How do we target molecules?

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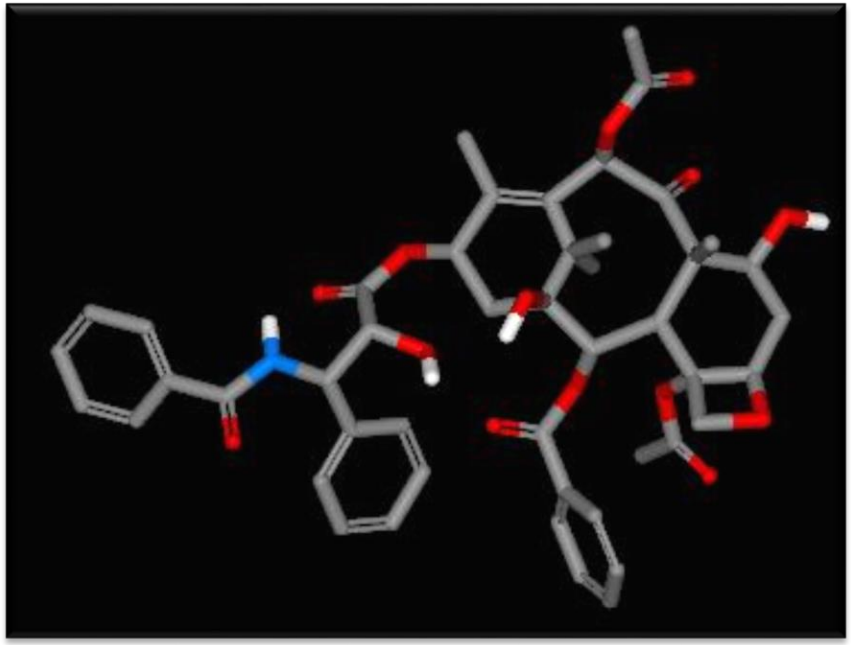
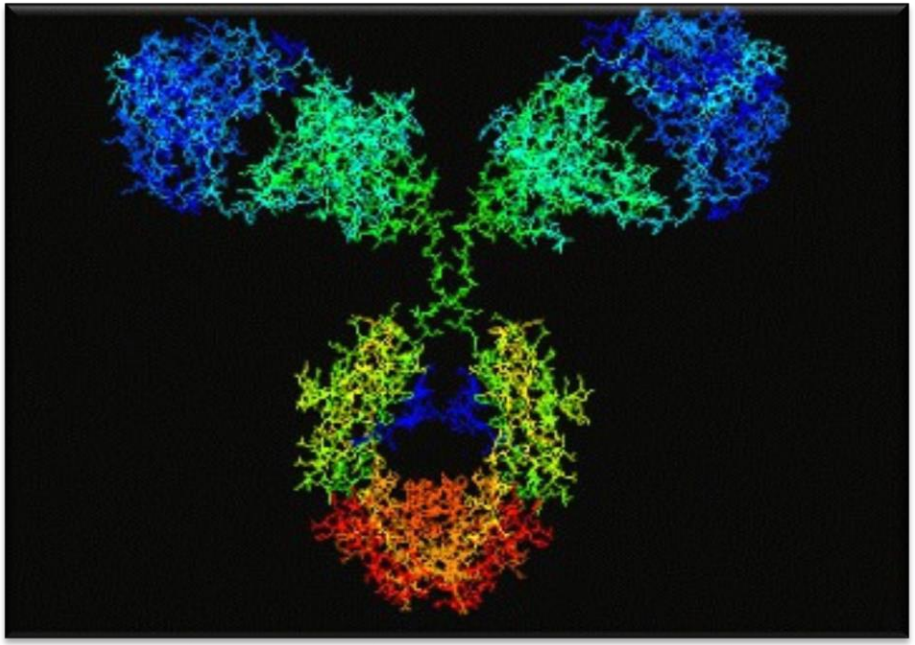
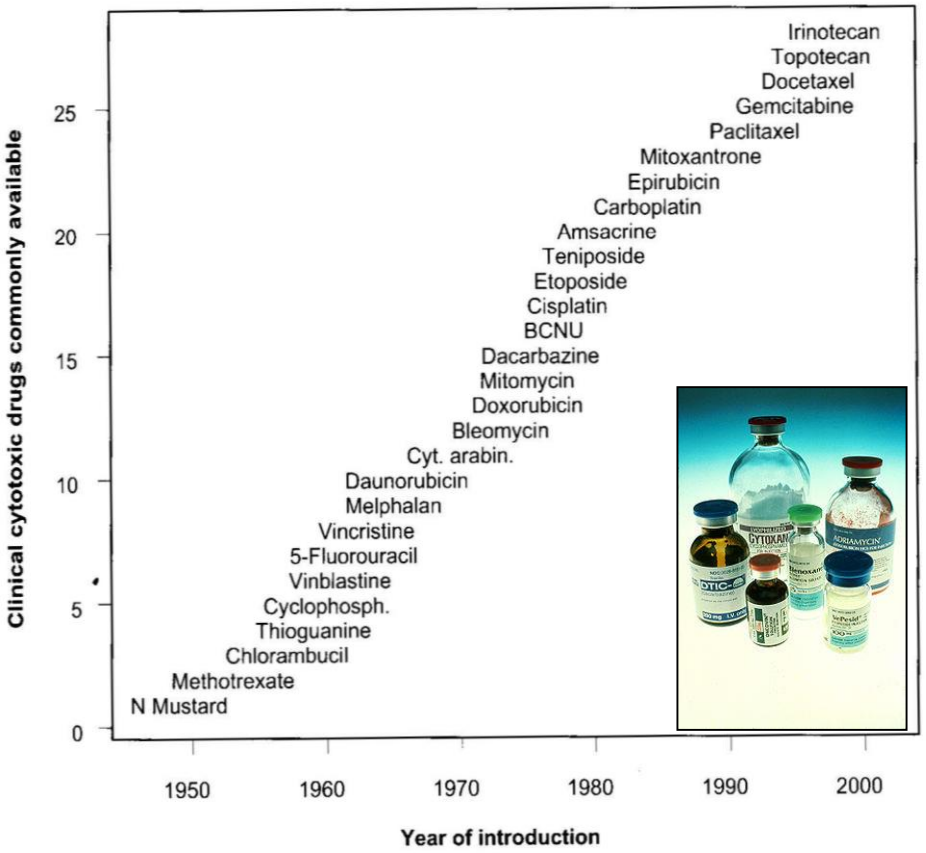


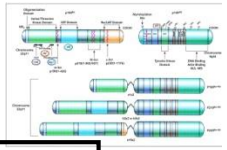


Overview

- Therapeutic Window and Oncogene Addiction
- Kinases as prototypes for targeted molecules
- Antibodies
- Small Molecular Compounds
- Resistance Mechanisms



2001



Classic Cytotoxic Agents

Molecular Targeting Agents
Anti-Signaling Agents

CML: chronic myelogenous leukemia

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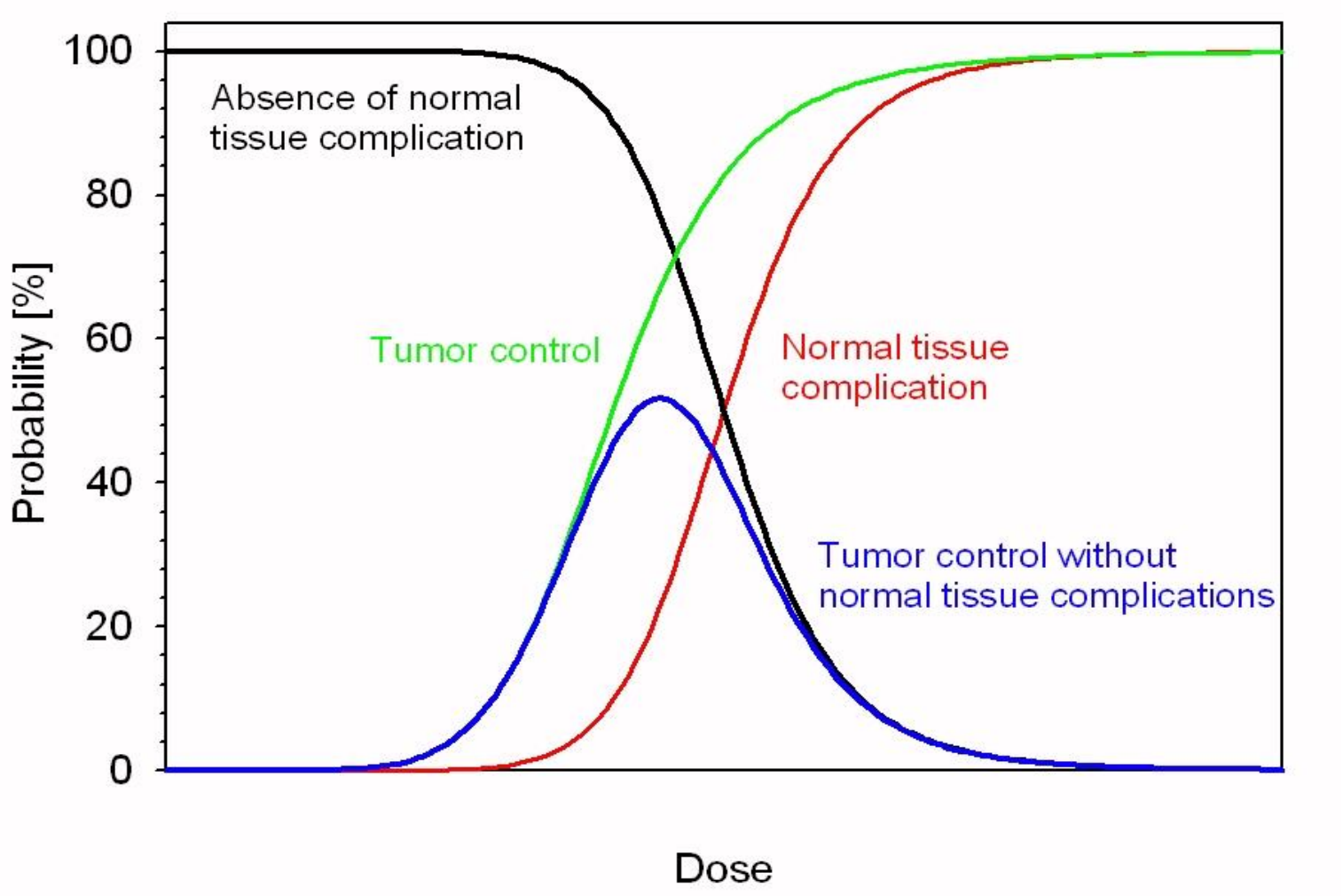
How do we target molecules ? antibodies and small molecules



The Therapeutic Window

Merck pipeline

Phase I

Tepotinib – c-Met kinase inhibitor
Solid tumors

M2698 – p70S6K & Akt inhibitor
Solid tumors

M3814 – DNA-PK inhibitor
Solid tumors

M9831 (VX-984) – DNA-PK inhibitor
Solid tumors

Beigene-283 – BRAF inhibitor
Solid tumors

M7583 – BTK inhibitor
Hematological malignancies

M66207[7] (VX-970) – ATR inhibitor
Solid tumors

M4344 (VX-803) – ATR inhibitor
Solid tumors

Avelumab – Anti-PD-L1 mAb
Solid tumors

Avelumab – Anti-PD-L1 mAb
Hematological malignancies

M9241 (NHS-IL12)
Cancer immunotherapy
Solid tumors

M7824 - Bifunctional immunotherapy
Solid tumors

M1095 (ALX-0761)
Anti-IL-17 A/F nanobody
Psoriasis

Phase II

Tepotinib
c-Met kinase inhibitor
Non-small cell lung cancer

Tepotinib
c-Met kinase inhibitor
Hepatocellular cancer

Avelumab – Anti-PD-L1 mAb
Merkel cell carcinoma 1L[1]

Sprifermin
Fibroblast growth factor 18
Osteoarthritis

Atacicept
Anti-Blys/anti-APRIL fusion protein
Systemic lupus erythematosus

M2951
BTK inhibitor
Rheumatoid arthritis

M2951
BTK inhibitor
Systemic lupus erythematosus

Abituzumab
anti-CD 51 mAb
Systemic sclerosis with interstitial lung disease

Phase III

Avelumab – Anti-PD-L1 mAb
Non-small cell lung cancer 1L[1]

Avelumab – Anti-PD-L1 mAb
Non-small cell lung cancer 2L[2]

Avelumab – Anti-PD-L1 mAb
Gastric cancer 1L[1]

Avelumab – Anti-PD-L1 mAb
Gastric cancer 3L[3]

Avelumab – Anti-PD-L1 mAb
Urothelial cancer 1L[1]

Avelumab – Anti-PD-L1 mAb
Ovarian cancer platinum resistant/refractory

Avelumab – Anti-PD-L1 mAb
Ovarian cancer 1L[1]

Avelumab - Anti-PD-L1 mAb
Renal cell cancer 1L[1]

Avelumab - Anti-PD-L1 mAb
Locally advanced head and neck cancer

MSB11022
Proposed biosimilar of Adalimumab
Chronic plaque psoriasis

Registration

Cladribine[4] Tablets –
Lymphocyte targeting agent
Relapsing-remitting multiple sclerosis

Avelumab[5] – Anti-PD-L1 mAb
Merkel cell carcinoma

Avelumab[6] – Anti-PD-L1 mAb
Urothelial cancer 2L[2]

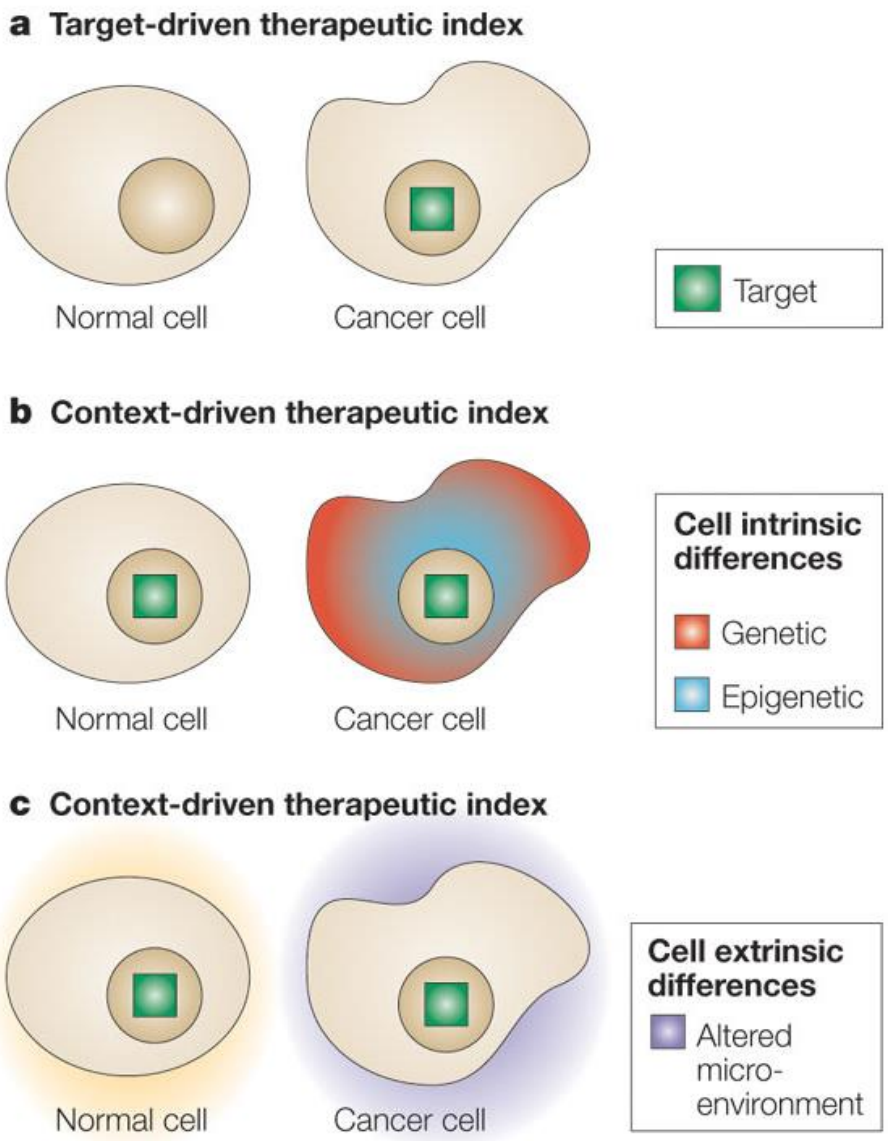
- Neurodegenerative Diseases
- Oncology
- Immunology
- Immuno-Oncology
- Biosimilars

Pipeline as of March 1st, 2017
Pipeline products are under clinical investigation and have not been proven to be safe and effective.
There is no guarantee any product will be approved in the sought-after indication.

[1] 1st line treatment; [2] 2nd line treatment; [3] 3rd line treatment; [4] European Medicines Agency (EMA) accepted Merck's Marketing Authorization Application (MAA) in July 2016;
[5] EMA accepted Merck's MMA in July 2016 and the US Food and Drug Administration (FDA) has accepted for Priority Review the Biologics License Application (BLA);
[6] FDA accepted for Priority Review the BLA; [7] Includes expansion cohorts in non small cell lung cancer, small cell lung cancer and triple negative breast cancer

MERCK

Increasing the Therapeutic Window: Exploiting Cancer Specific Features



e.g. BRAF in melanomas

e.g. cell cycle checkpoints corrupted in cancer cells; high rate of proliferation

e.g. tumor hypoxia

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Oncogene-Addiction: Achilles‘ Heel of the Tumor

- Plethora of genetic alterations in a tumor

though: dependence of a single pathway for its sustained proliferation and/or survival!

- trivial

though: inactivation of normal counterpart of such oncogenic proteins in normal tissues often tolerated

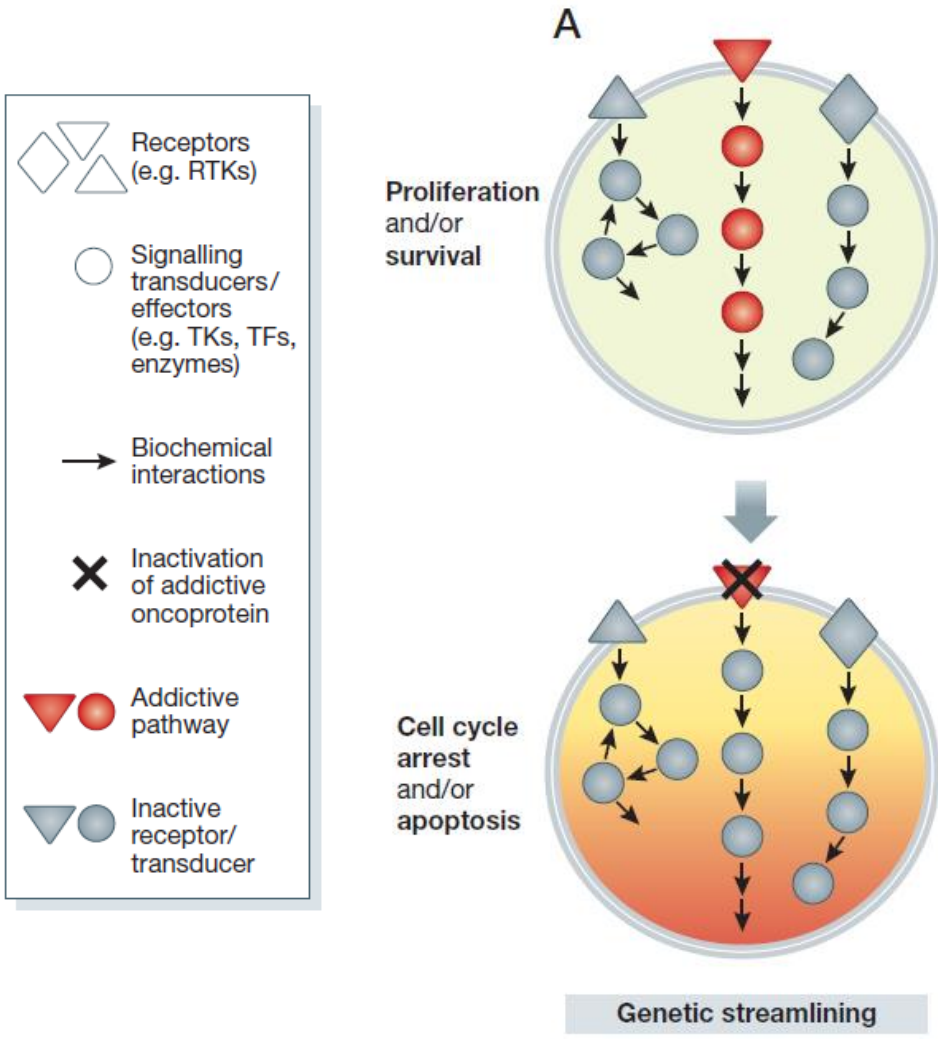
➢ basis for effective cancer therapeutic approach

Oncogene-Addiction: Achilles‘ Heel of the Tumor

		Oncogene addiction and oncogenic shock		
Oncogene	Cancer	Cell lines	Mouse models	Clinical (approved)
MYC	Lymphoma, leukemia	RI (Yokoyama and Imamato 1987; Loke et al. 1988)	IE (Felsher and Bishop 1999; Wu et al. 2007)	
RAS	Pancreatic, thyroid, colon, NSCLC	RI (Mukhopadhyay et al. 1991; Tokunaga et al. 2000) SMI (Kohl et al. 1994; Liu et al. 1998)	H-RAS (Chin et al. 1999); K-RAS (Fisher et al. 2001)	
HER2	Breast, ovarian, NSCLC	Ab (Hudziak et al. 1989) RI (Brysch et al. 1994; Colomer et al. 1994)	Ab (Shepard et al. 1991; Ohnishi et al. 1995; Tokuda et al. 1996) SMI (Xia et al. 2002; Rabindran et al. 2004; Wong et al. 2006)	**Trastuzumab/Herceptin** (*Breast cancer*); **Lapatinib/ Tykerb** (*Herceptin refractory breast cancer*)
BRAF	Melanoma, thyroid, colorectal	RI (Hingorani et al. 2003; Sumimoto et al. 2004) SMI (Karasarides et al. 2004)	SMI (Karasarides et al. 2004; Sharma et al. 2005)	**Sorafenib/Nexavar** (*Renal cell carcinoma*)
EGFR	NSCLC, glioblastoma, colon, pancreas	RI (Yamazaki et al. 1998; Halatsch et al. 2000; Sordella et al. 2004) Ab (Luwor et al. 2001)	SMI (Ji et al. 2006a,b; Politi et al. 2006) Ab (Luwor et al. 2001)	**Gefitinib/Iressa** (NSCLC); **Erlotinib/Tarceva** (*NSCLC, pancreatic cancer*); **Cetuximab/Erbitux** (*head and neck, colorectal cancer*); **Pantiumumab/ Vectibix** (*colorectal cancer*)
MET	Gastric, NSCLC	RI (Stabile et al. 2004; Ma et al. 2005) SMI (Sattler et al. 2003; Ma et al. 2005; Smolen et al. 2006)	RI (Stabile et al. 2004); SMI (Puri et al. 2007; Zou et al. 2007) Ab (Cao et al. 2001; Burgess et al. 2006)	
ABL	CML	SMI (Druker et al. 1996; Carroll et al. 1997; Deininger et al. 1997; Golas et al. 2003) RI (Smetsers et al.	RI (Skorski et al. 1994) SMI (Golas et al. 2003)	**Imatinib/Gleevec** (*Ph* CML; Ph* ALL*)

Oncogene Addiction: 2 models

a) genetic streamlining theory

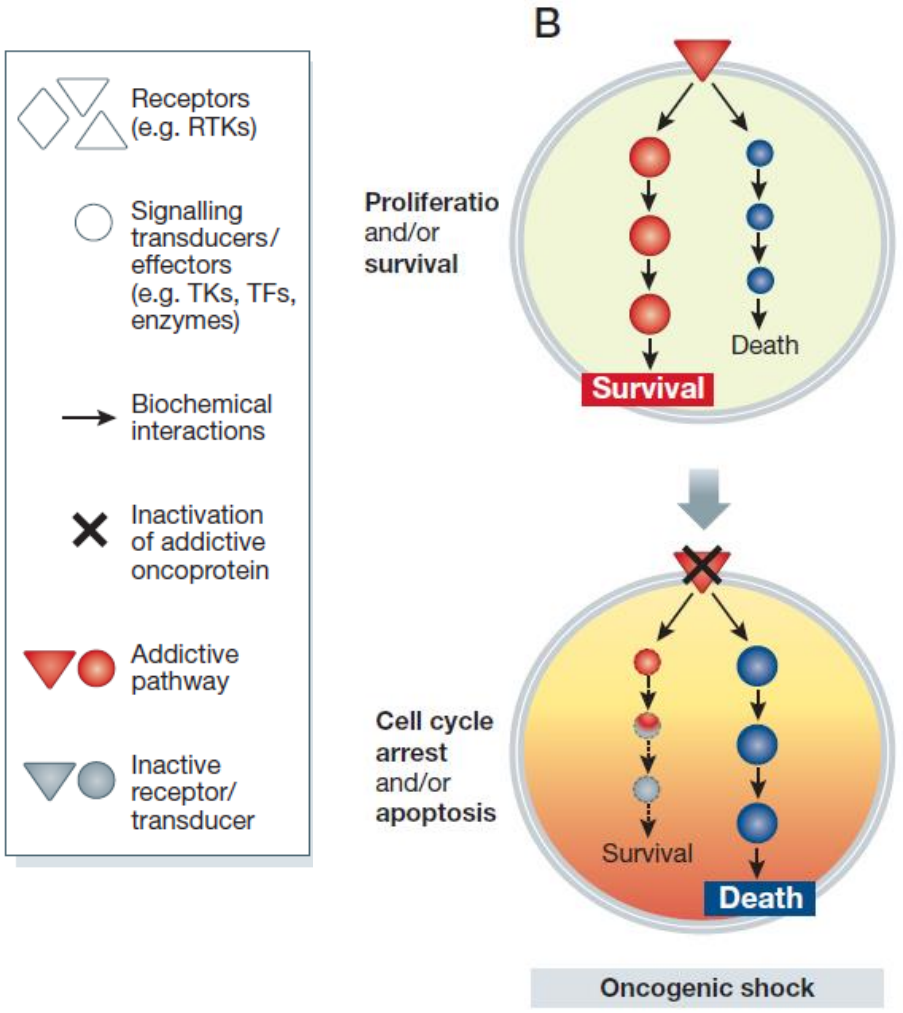


The 'genetic streamlining' theory postulates that non-essential pathways (top, light grey) are inactivated during tumour evolution, so that dominant, addictive pathways (red) are not surrogated by compensatory signals. Upon abrogation of dominant signals, there is a collapse in cellular fitness and cells experience cell-cycle arrest or apoptosis (bottom, red to yellow shading).

Torti and Trusolino, 2011

Oncogene Addiction: 2 models

b) oncogenic shock model



In the 'oncogenic shock' model, addictive oncoproteins (e.g. RTKs, red triangle) trigger at the same time pro-survival and pro-apoptotic signals (top, red and blue pathway, respectively). Under normal conditions, the pro-survival outputs dominate over the pro-apoptotic ones (top), but following blockade of the addictive receptor, the rapid decline in the activity of survival pathways (dashed lines, bottom) subverts this balance in favour of death-inducing signals, which tend to last longer and eventually lead to apoptotic death.

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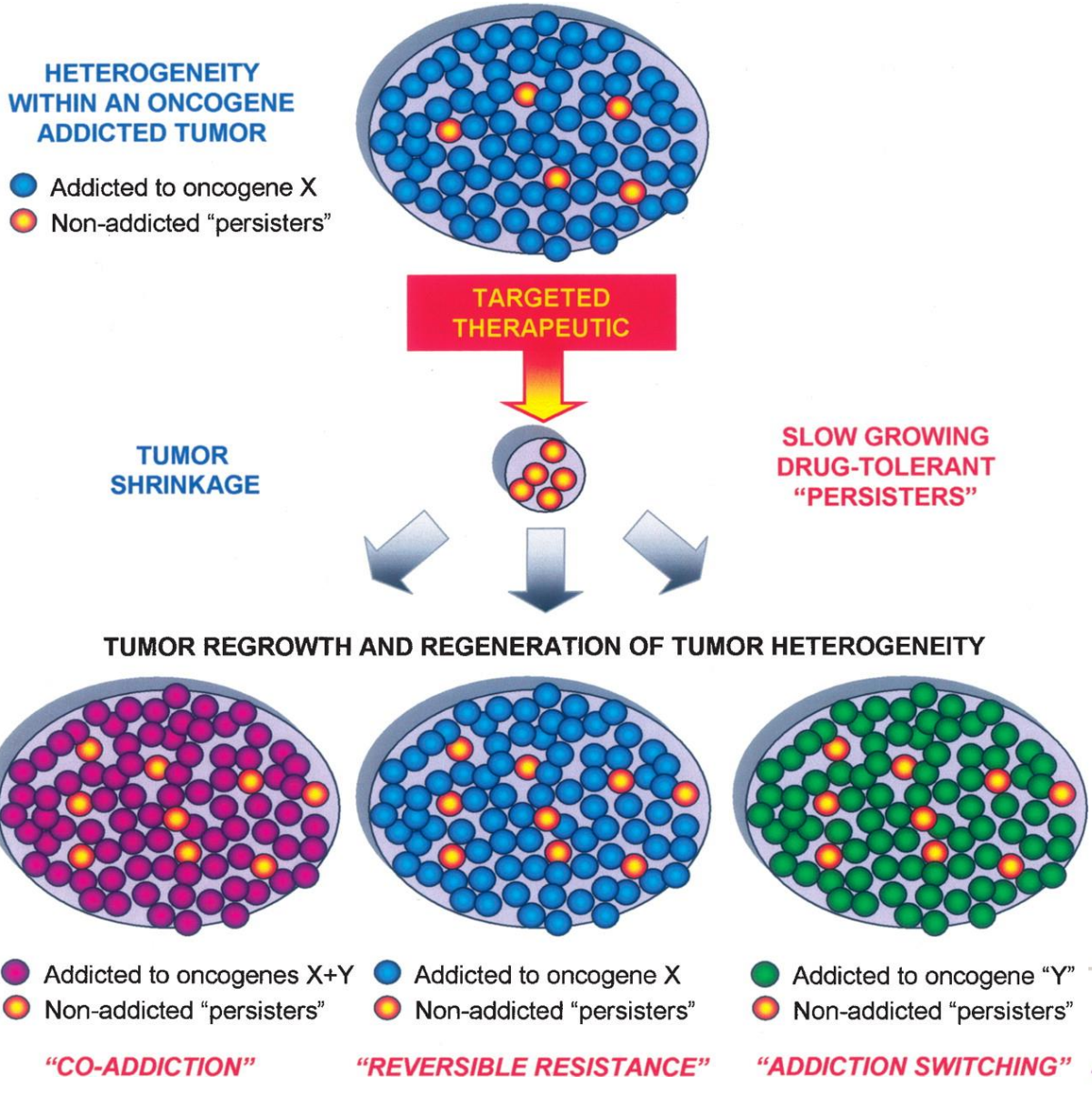
Heterogeneity of tumor cell dependency as the basis for resistance to therapeutics targeting



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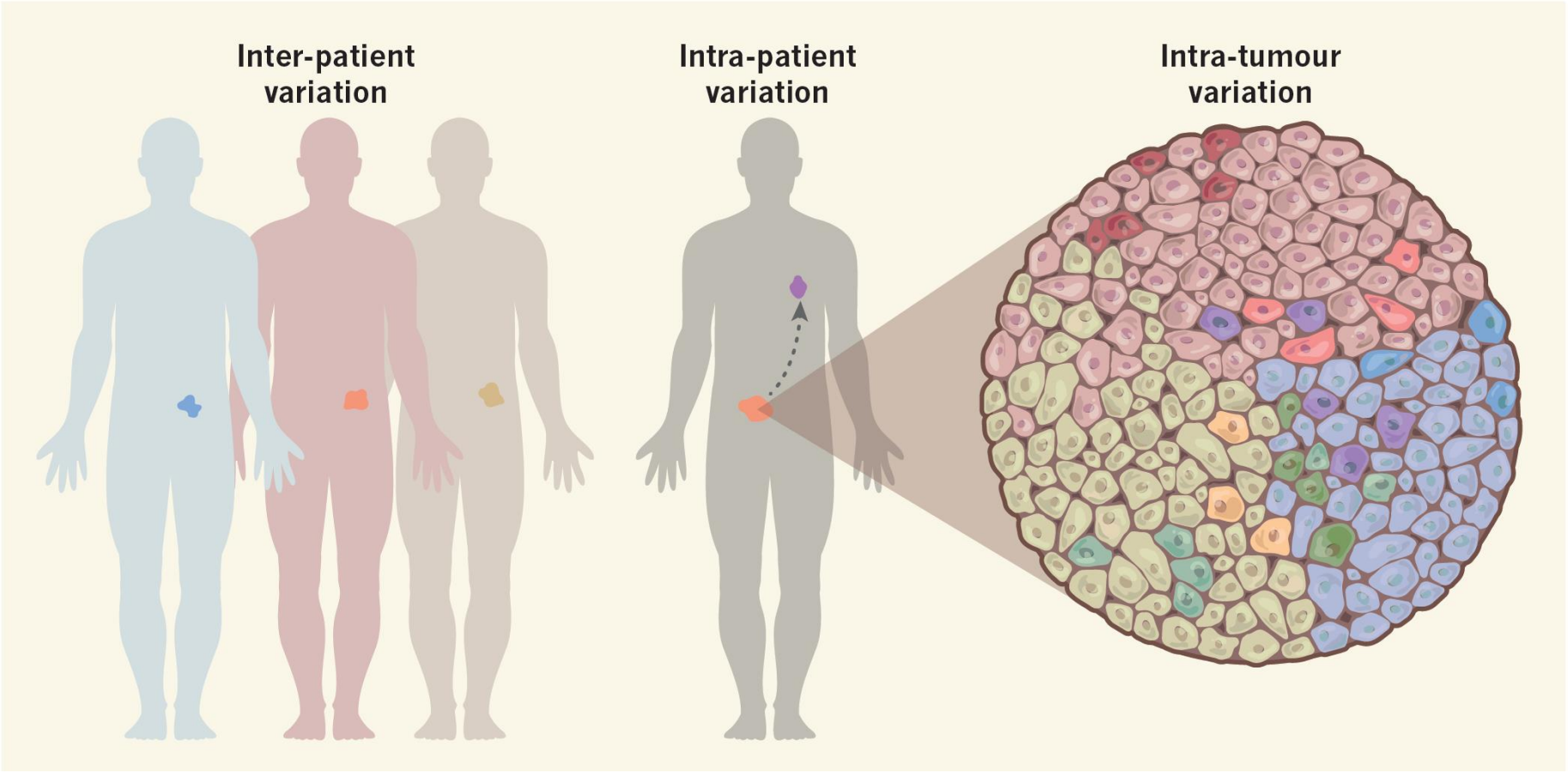
Inter- and intra-tumour heterogeneity



Nature 512:143-144, 2014

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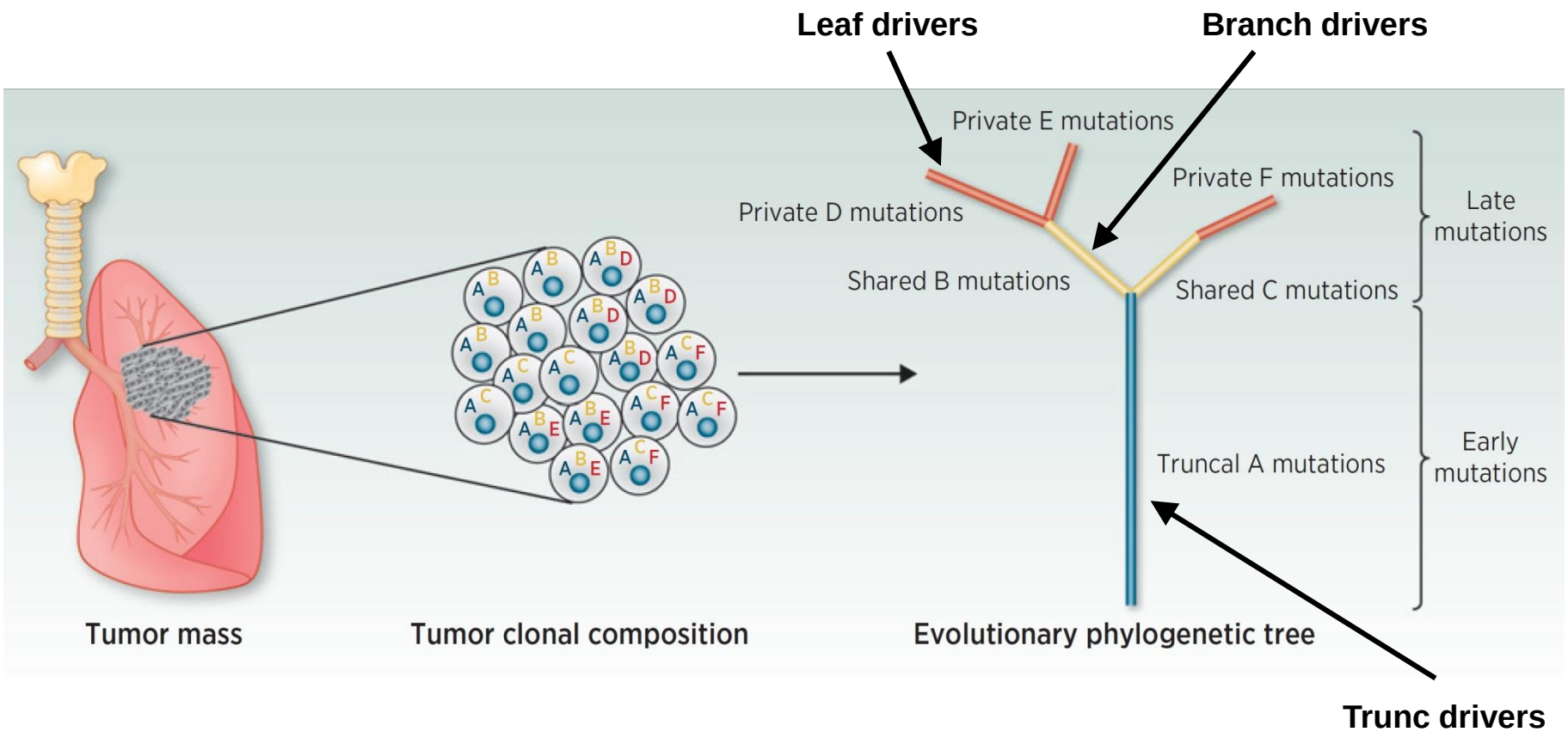
Intra-tumour heterogeneity



Clin Cancer Res 21:1258–66, 2015

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Relevant Questions::

Molecular evolution of resistance to treatment:

- Acquired during therapy?
- ➢ As a result of continuing mutagenesis?

- Already present in a clonal subpopulation within the tumours *prior* to the initiation of therapy?
- ➢ Is resistance therefore a fait accompli—the time to recurrence is simply the interval required for the subclone to repopulate the lesion.?
- ➢ Is the short time interval of recurrence due to the rapid expansion of the resistant subclone immediately following treatment initiation?
- ➢ Required:

Combination therapies targeting at least two different “processes” or “pathways”.

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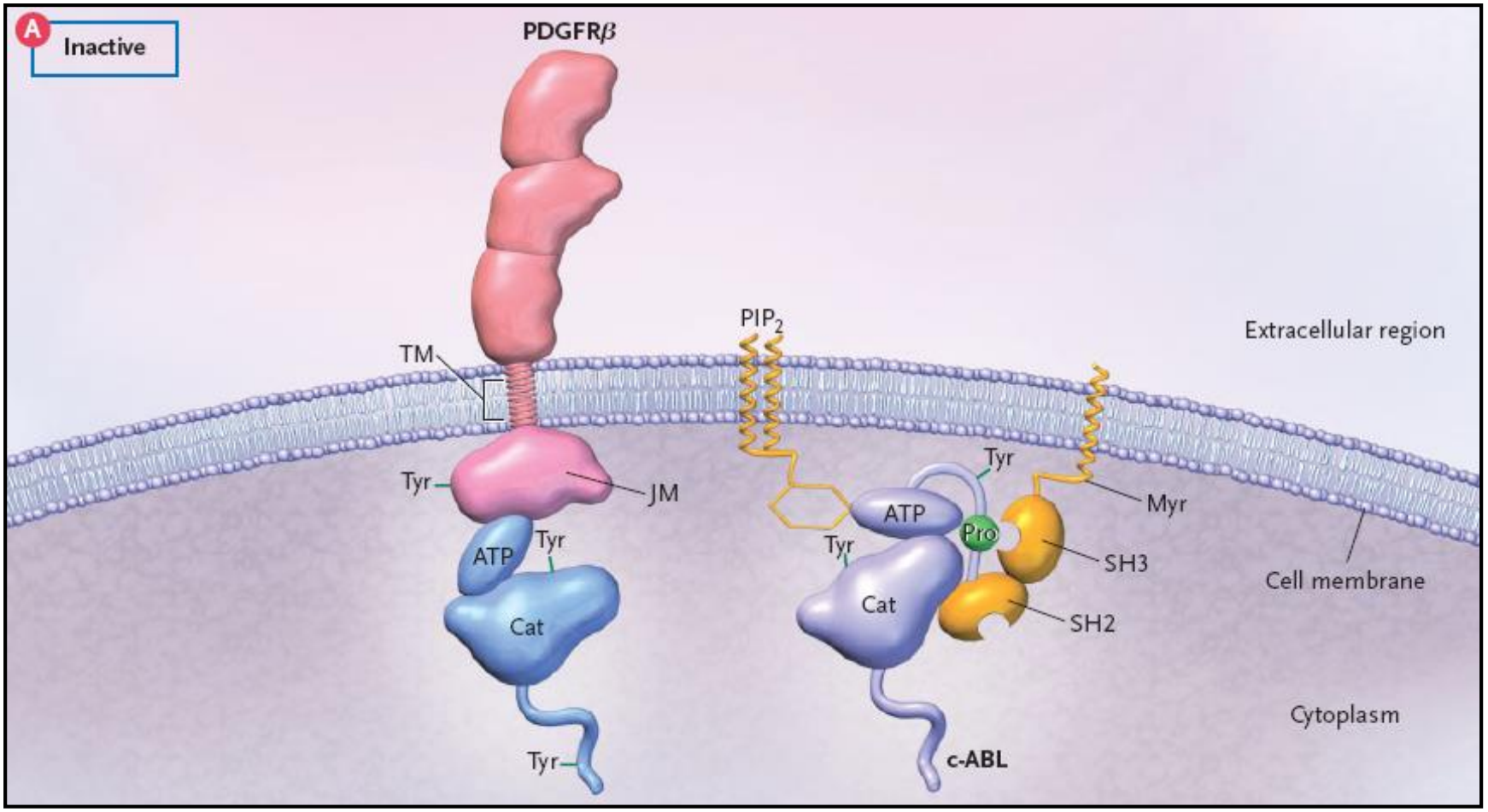
Kinases in Oncology

- Kinases are involved in processes leading to cell proliferation and survival

- Kinases are popular targets
  - virtually every signal transduction process is wired through phosphotransfer cascade
  - despite high degree of conservation highly specific agents can be developed
  - inhibition of kinase in normal tissue can often be tolerated (therapeutic window)
  - to date approx. 80 inhibitors advanced to some stage of clincial evaluation

Regulation of Normal Tyrosine Kinase Activity I



2 classes:

- Receptor tyrosine kinases
- Non-receptor tyrosine kinases

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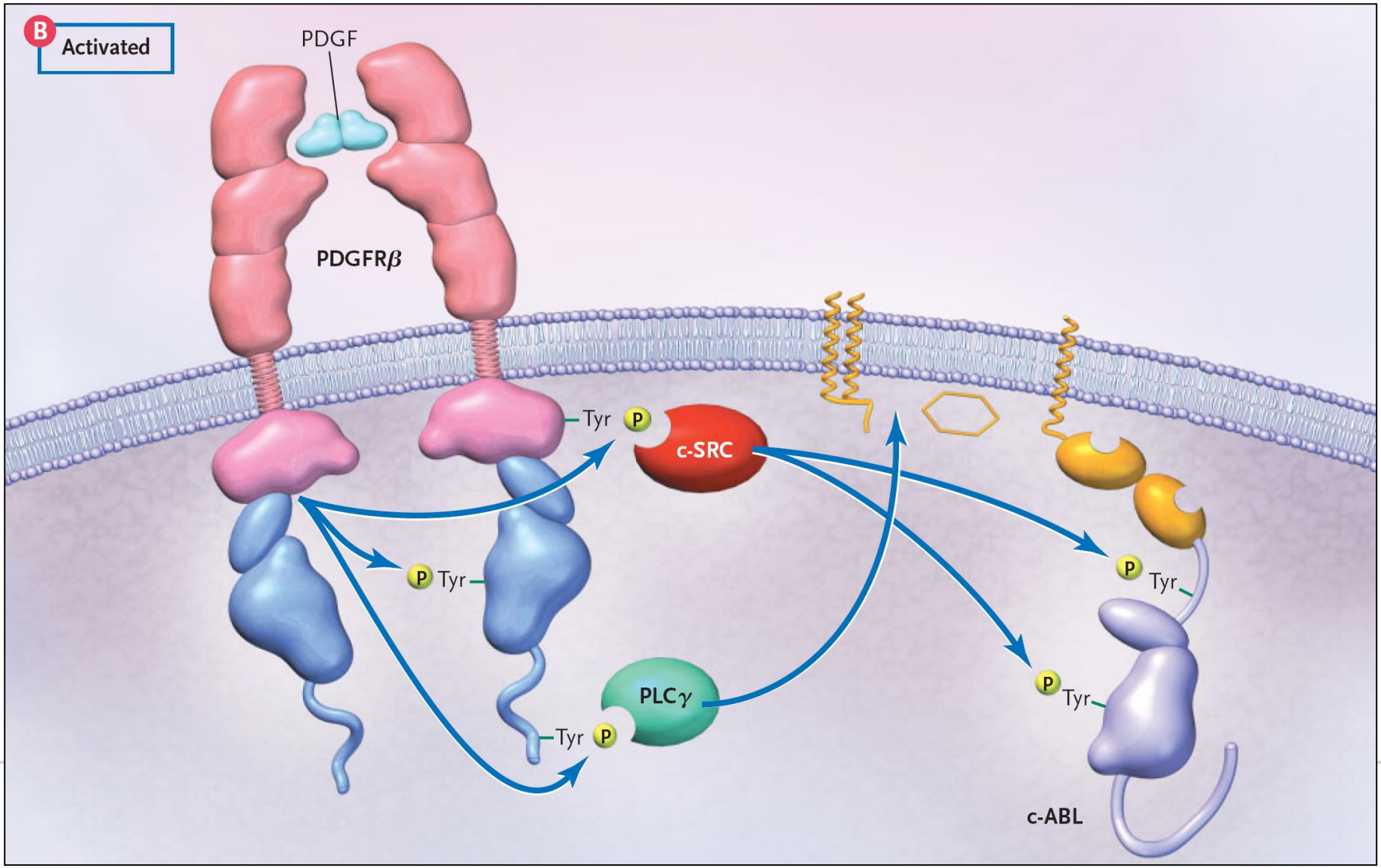
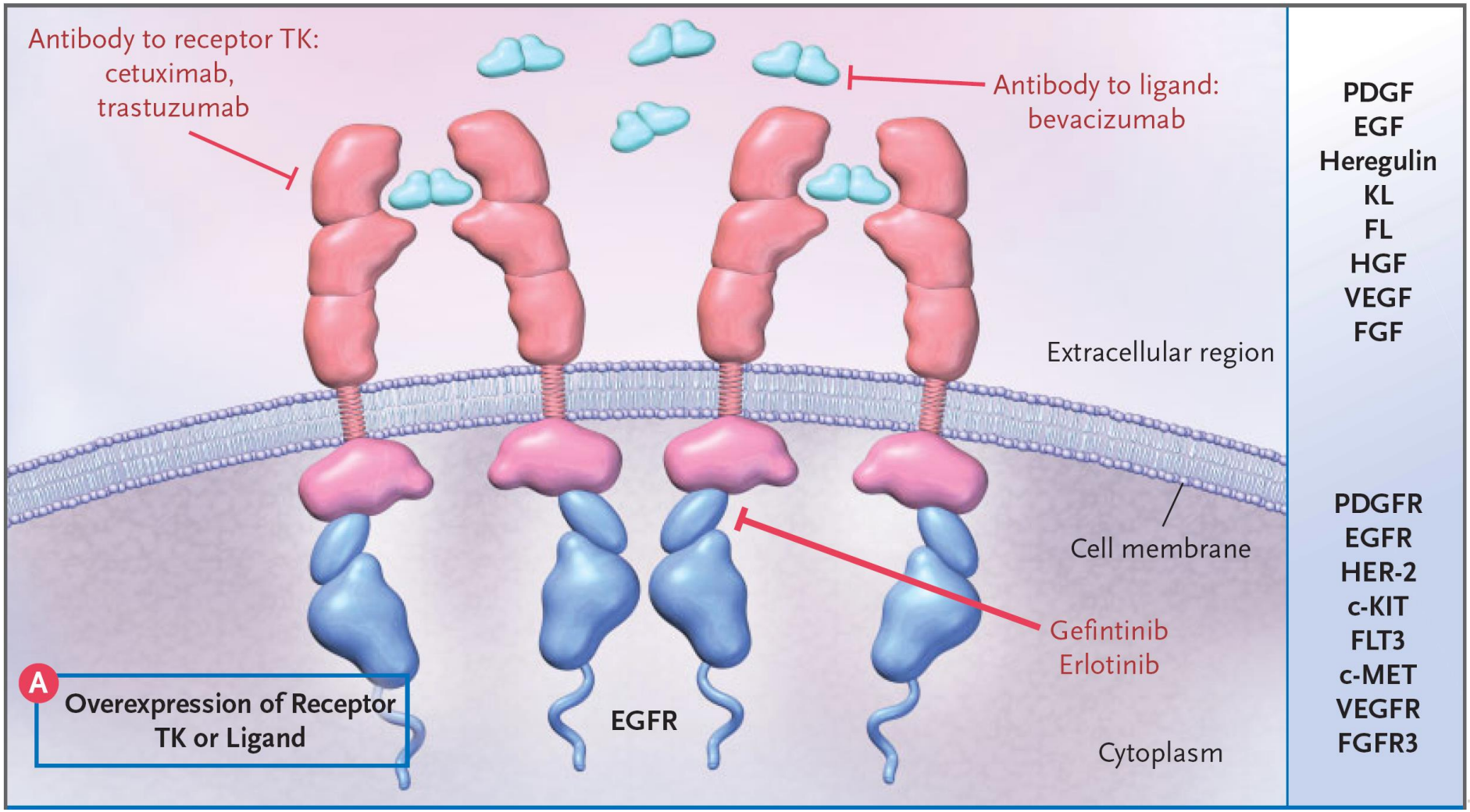
Regulation of Normal Tyrosine Kinase Activity II



Mechanisms of RTK Disregulation I



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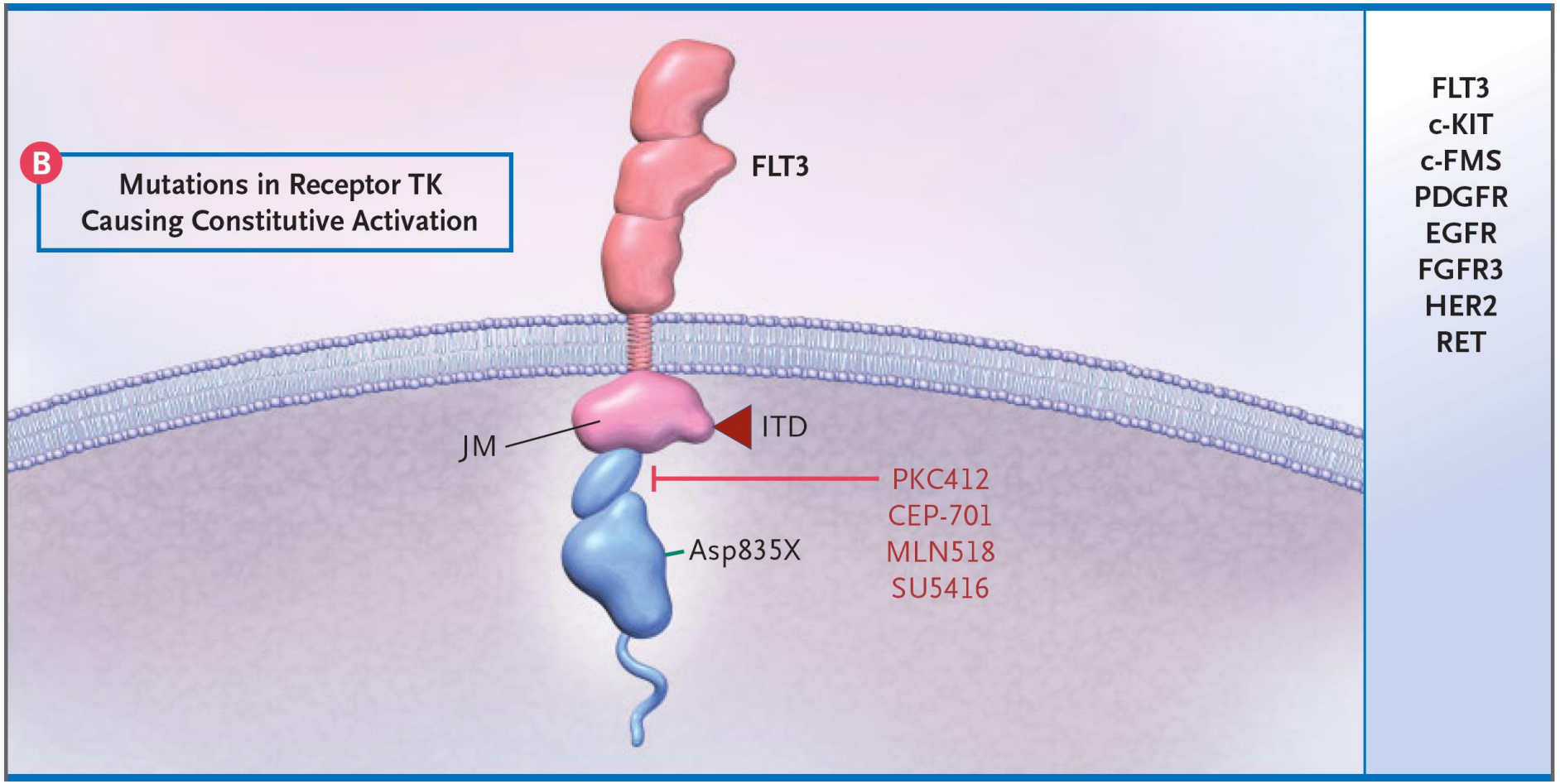
Mechanisms of RTK Disregulation II



Tyrosine kinase GF receptors altered in human tumors[a]

Name of receptor	Main ligand	Type of alteration	Types of tumor
EGF-R/ErbB1	EGF, TGF-α	overexpression	non-small cell lung cancer; breast, head and neck, stomach, colorectal, esophageal, prostate, bladder, renal, pancreatic, and ovarian carcinomas; glioblastoma
EGF-R/ErbB1		truncation of ectodomain	glioblastoma, lung and breast carcinomas
ErbB2/HER2/Neu	NRG, EGF	overexpression	30% of breast adenocarcinomas
ErbB3, 4	various	overexpression	oral squamous cell carcinoma
Flt-3	FL	tandem duplication	acute myelogenous leukemia
Kit	SCF	amino acid substitutions	gastrointestinal stromal tumor
Ret		fusion with other proteins, point mutations	papillary thyroid carcinomas, multiple endocrine neoplasias 2A and 2B
FGF-R3	FGF	overexpression; amino acid substitutions	multiple myeloma, bladder and cervical carcinomas

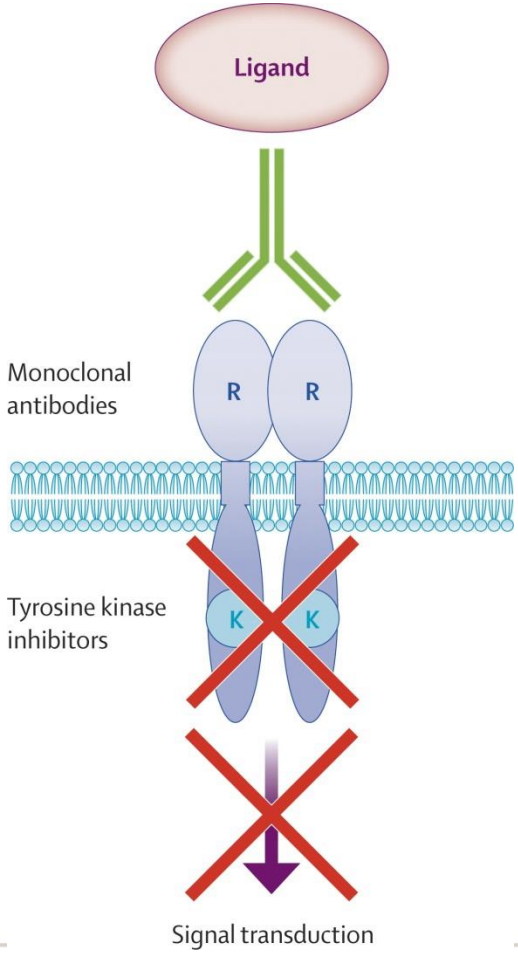
Examples of human tumors making autocrine growth factors

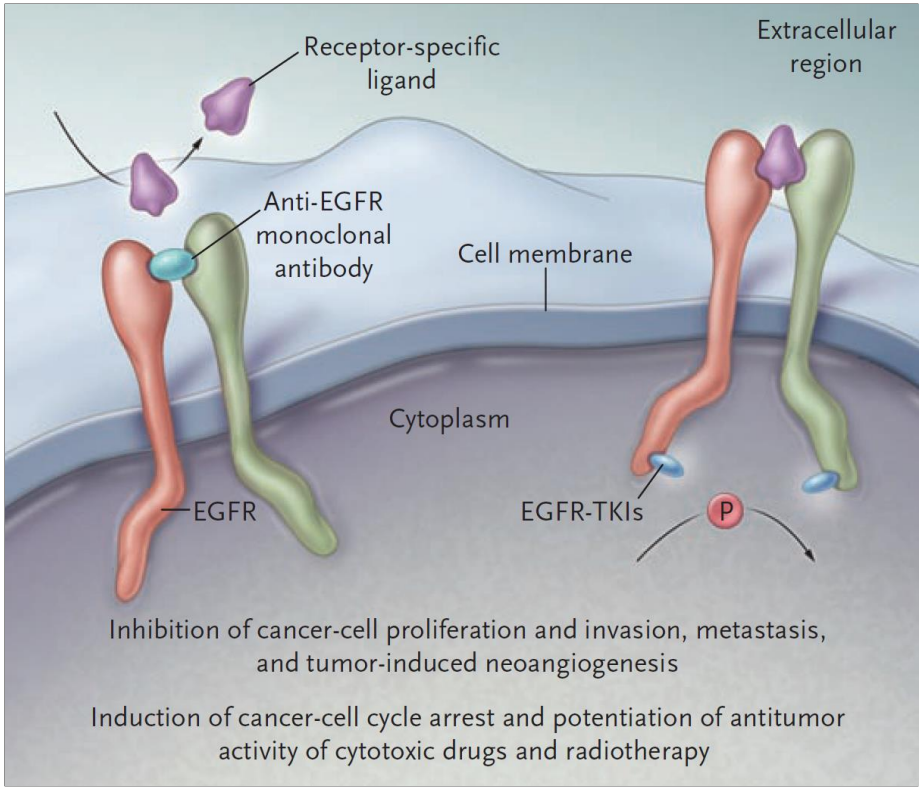
Ligand	Receptor	Tumor type(s)
HGF	Met	miscellaneous endocrinal tumors, invasive breast and lung cancers, osteosarcoma
IGF-2	IGF-1R	colorectal
IL-6	IL-6R	myeloma, HNSCC
IL-8	IL-8R A	bladder cancer
NRG	ErbB2[a]/ErbB3	ovarian carcinoma
PDGF-BB	PDGF-Rα/β	osteosarcoma, glioma
PDGF-C	PDGF-α/β	Ewing's sarcoma
PRL	PRL-R	breast carcinoma
SCF	Kit	Ewing's sarcoma, SCLC
VEGF-A	VEGF-R (Flt-1)	neuroblastoma, prostate cancer, Kaposi's sarcoma
TGF-α	EGF-R	squamous cell lung, breast and prostate adenocarcinoma, pancreatic, mesothelioma
GRP	GRP-R	small-cell lung cancer

[a]Also known as HER2 or Neu receptor.

How do we target key structures?

Monoclonal antibodies





Small molecules
(e.g. tyrosine kinase inhibitors)

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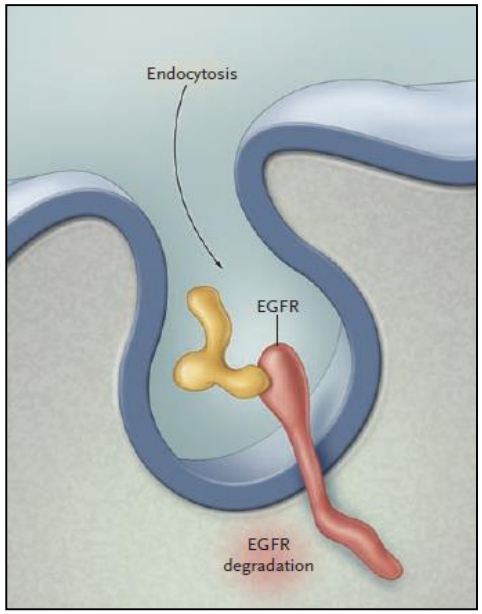
Mechanisms of mAB Action

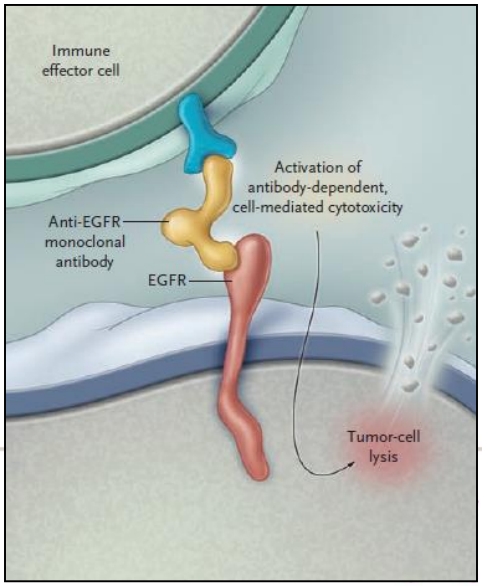
Interaction with immune system
- Antibody-dependent cellular cytotoxicity*
- Complement-dependent cytotoxicity

Delivery of cytotoxic payloads
- Radioisotops
- Toxins

*Combined mechanism of action

Signal transduction changes
- Ligand-receptor interaction*
- Receptor internalization*
- Clearance of ligand





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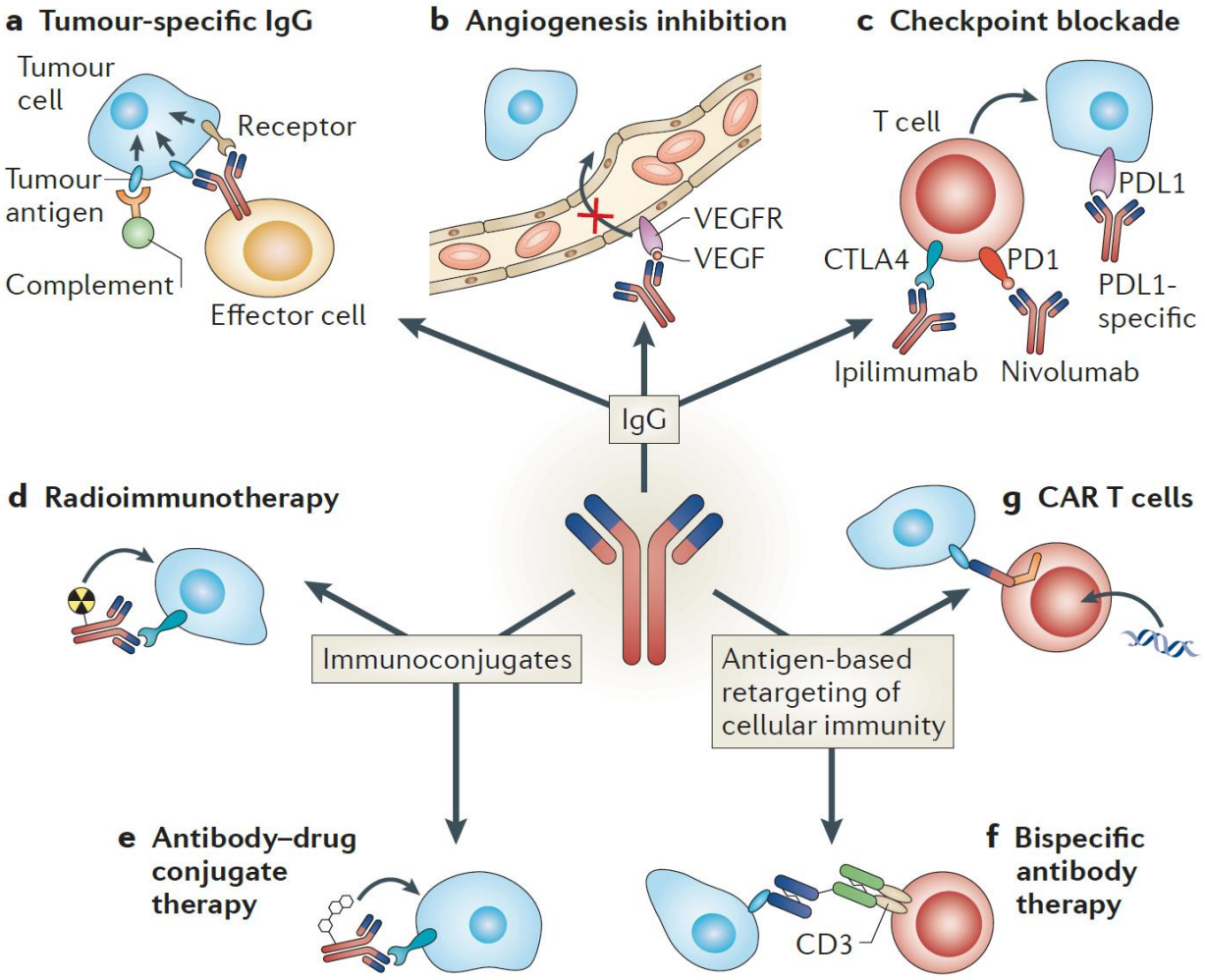
Antibody as anticancer drug candidate



- tumor-associated blood vessels
- chemokines; cytokines
- soluble growth factors
- diffuse malignant cells
- tumor cells within solid tumor
- tumor-associated stroma
- elements of immune response

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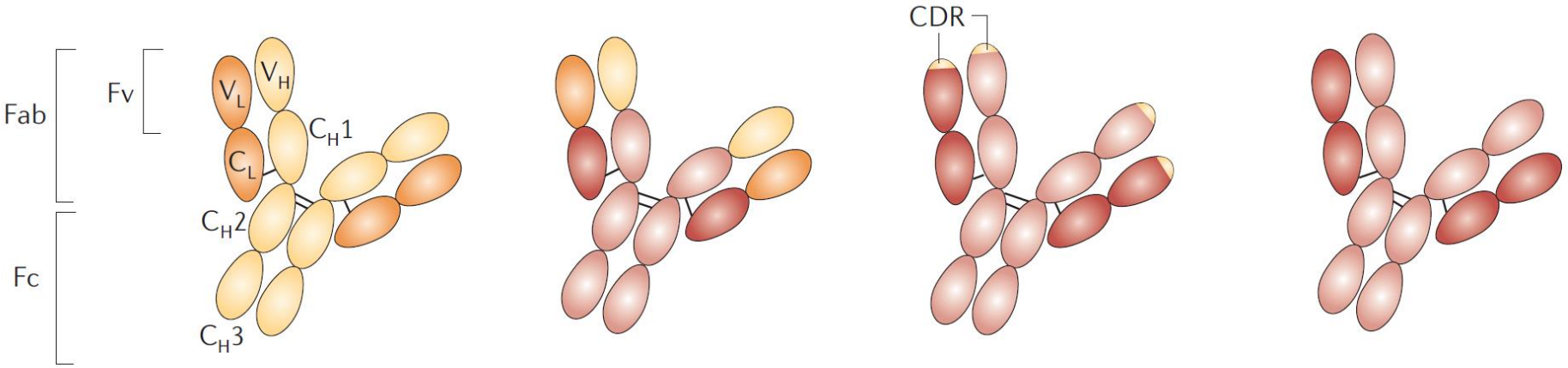
Generation of Chimeric (Humanized) Antibodies



Type of mAb	Murine	Chimeric	Humanized	Human
	Ibritumomab tiuxetan (CD20); IgG1κ*	Cetuximab (EGFR); IgG1κ	Trastuzumab (ERBB2); IgG1κ	Panitumumab (EGFR); IgG2
	Tositumomab-I^{131} (CD20); IgG2aλ*	Rituximab (CD20); IgG1κ	Bevacizumab (VEGF); IgG1	
			Alemtuzumab (CD52); IgG1κ	
			Gemtuzumab ozogamicin (CD33); IgG4κ*	

Reduction of Immunogenicity

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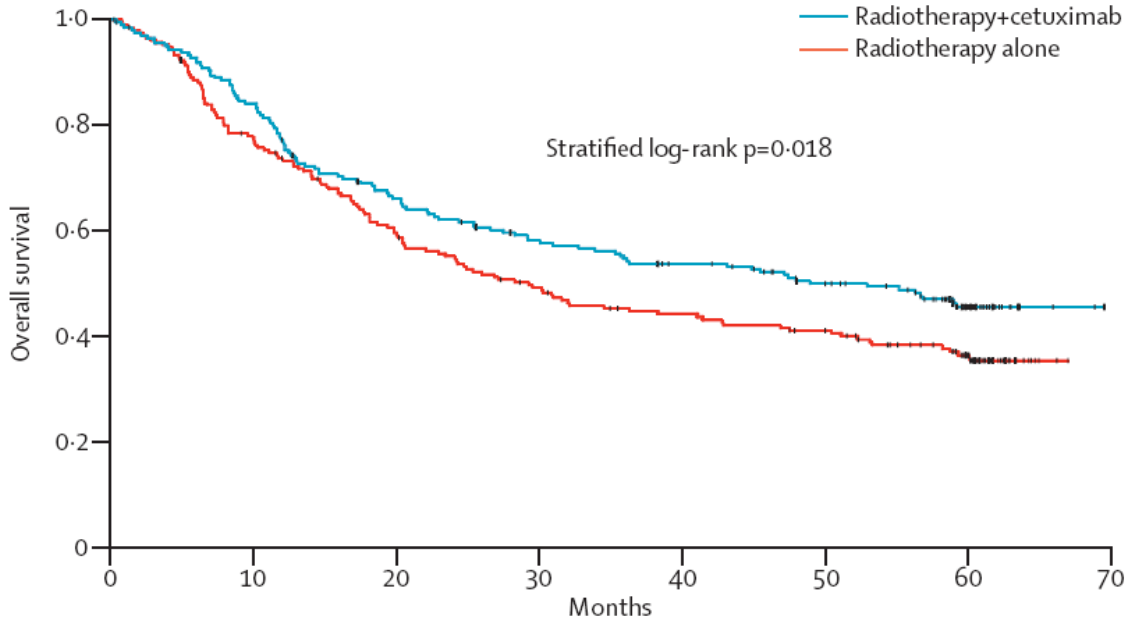
Radiotherapy ± EGFR-I: Prototype of monoclonal antibody

Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival

James A Bonner, Paul M Harari, Jordi Giralt, Roger B Cohen, Christopher U Jones, Ranjan K Sur, David Raben, Jose Baselga, Sharon A Spencer, Junming Zhu, Hagop Youssoufian, Eric K Rowinsky, K Kian Ang

www.thelancet.com/oncology Vol 11 January 2010

Bonner et al.,NEJM; 354; 567ff, 2006



Number at risk								
Radiotherapy+ cetuximab	211	177	136	117	105	90	49	..
Radiotherapy alone	213	162	122	98	85	77	49	..

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EGFR overexpression in human tumors

Tumors showing high EGFR expression

NSCLC	40-80%
Prostate	40-80%
Gastric	33-74%
Breast	14-91%
Colorectal	25-77%
Pancreatic	30-50%
Ovarian	35-70%
Bladder	31-48%
Renal cell	50-90%
H&N	80-100%
Glioma	40-63%
Esophageal	43-89%

High expression generally associated with

- Invasion
- Metastasis
- Late-stage disease

- Chemo-/Radiotherapy resistance
- Poor outcome

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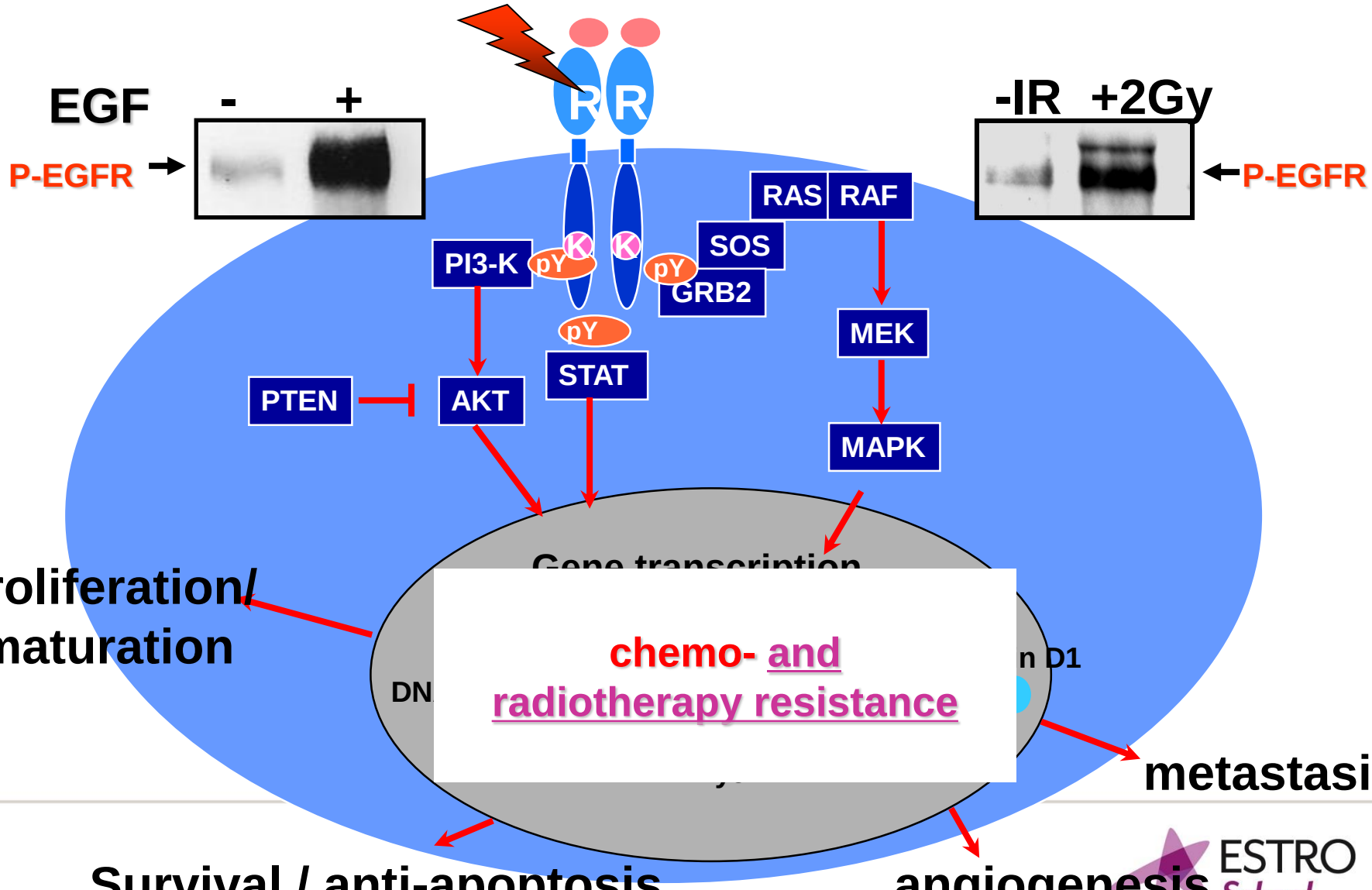
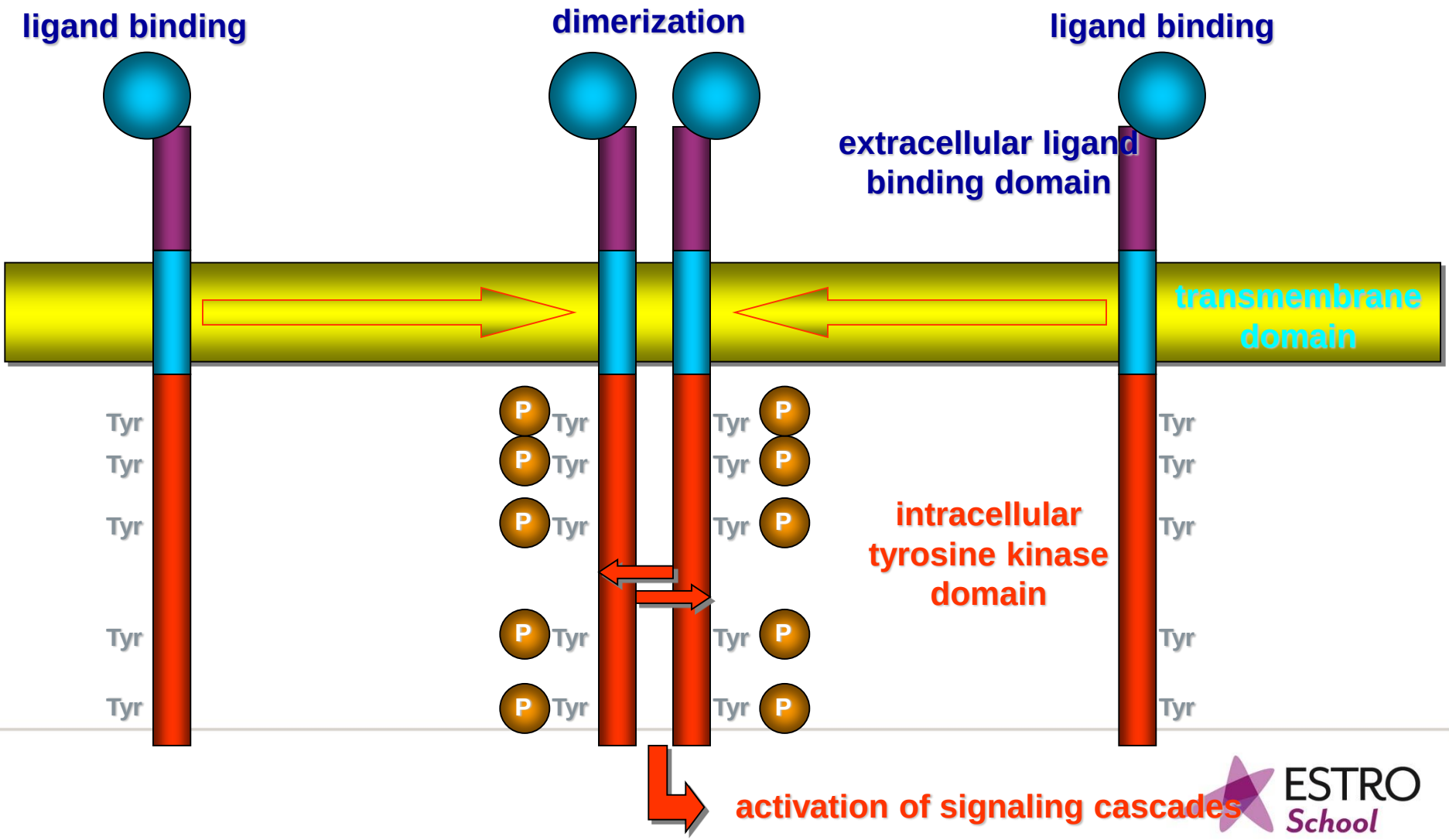
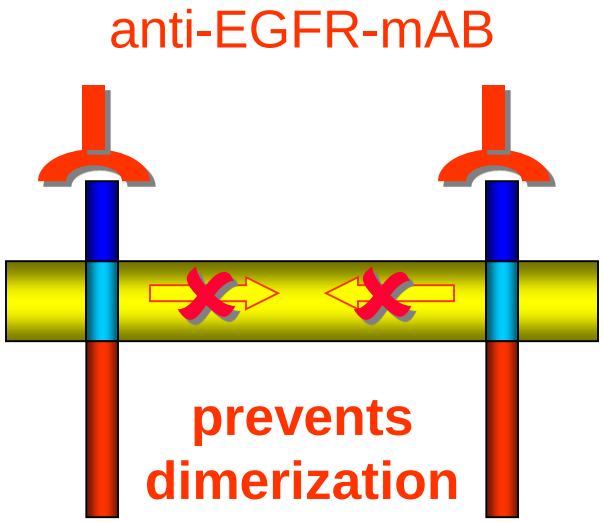
EGFR as an example



Activation of signaling cascade



C225 should prevent EGFR-signaling



DNA-repair (NHEJ, BER)

PI3K-AKT survival pathway

JAK-STAT pathway regulating gene transcription

Pro-proliferative RAS-MAPK pathway

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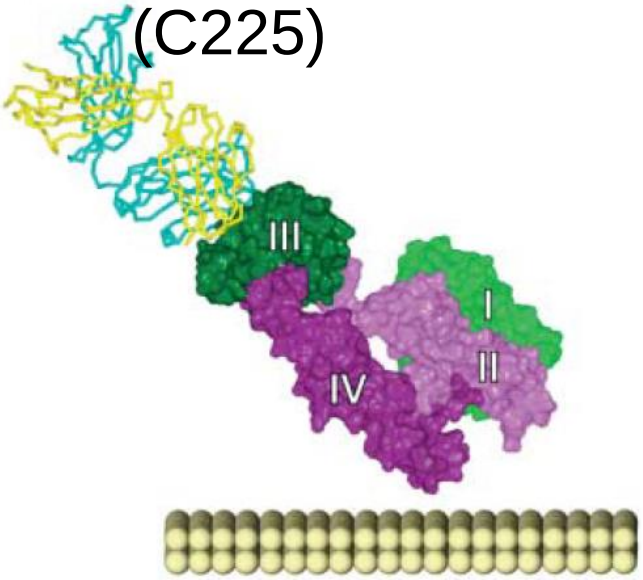
DIFFERENT BINDING SITES – DIFFERENT MECHANISMS

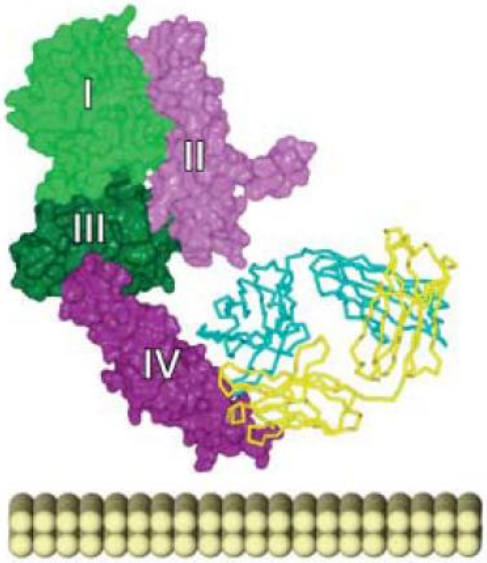
EXTRACELLULAR DOMAIN OF PROTEIN AS TARGET STRUCTURES!

Cetuximab (C225)



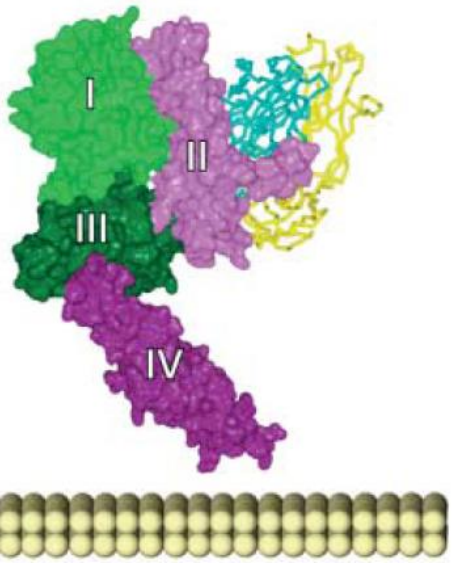
Competition to EGF-binding
Inhibition of Dimerization

Trastuzumab



Stimulation of endocytosis

Pertuzumab

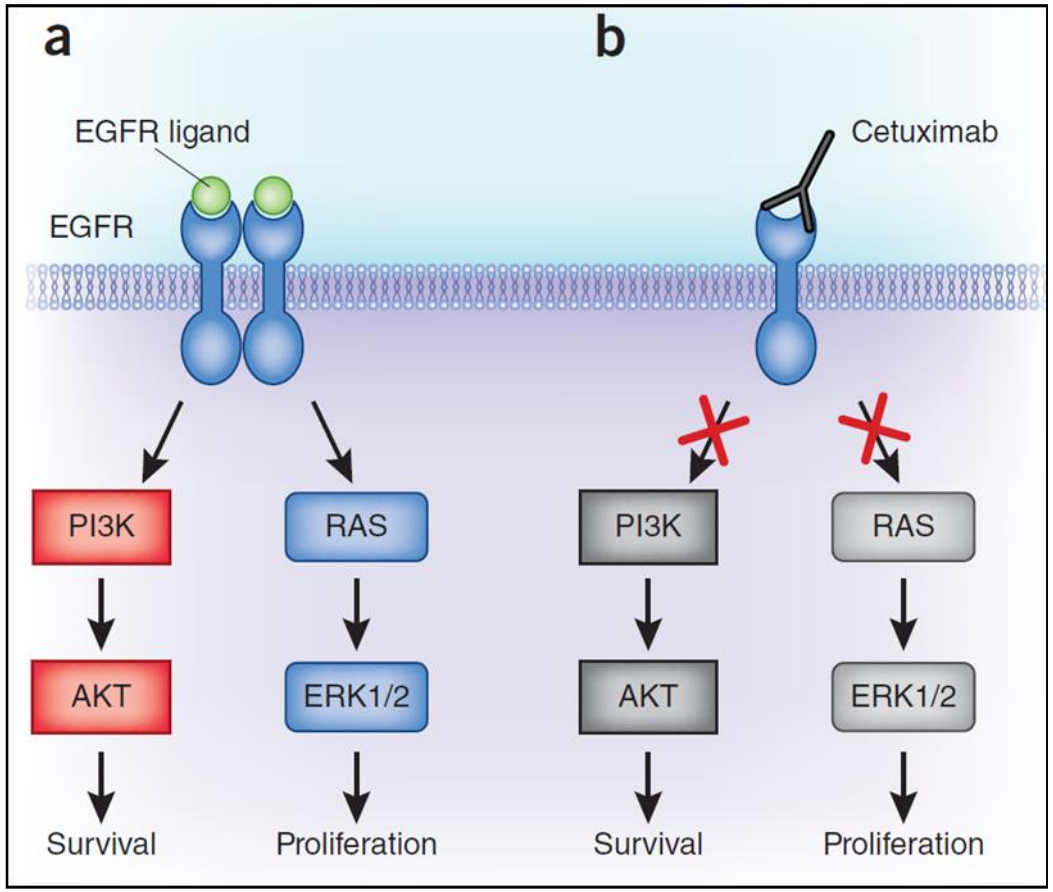


No heterodimerization

Multiple downstream mechanisms leading to e.g. radiosensitization

Mechanisms of Resistance to mAB

Cetuximab sensitivity



a) EGFR ligands bind the extracellular domain of the EGFR, induce receptor dimerization and activate downstream signaling pathways that are crucial for cell survival and proliferation
b) Cetuximab prevents ligand binding to EGFR, thus blocking EGFR signaling

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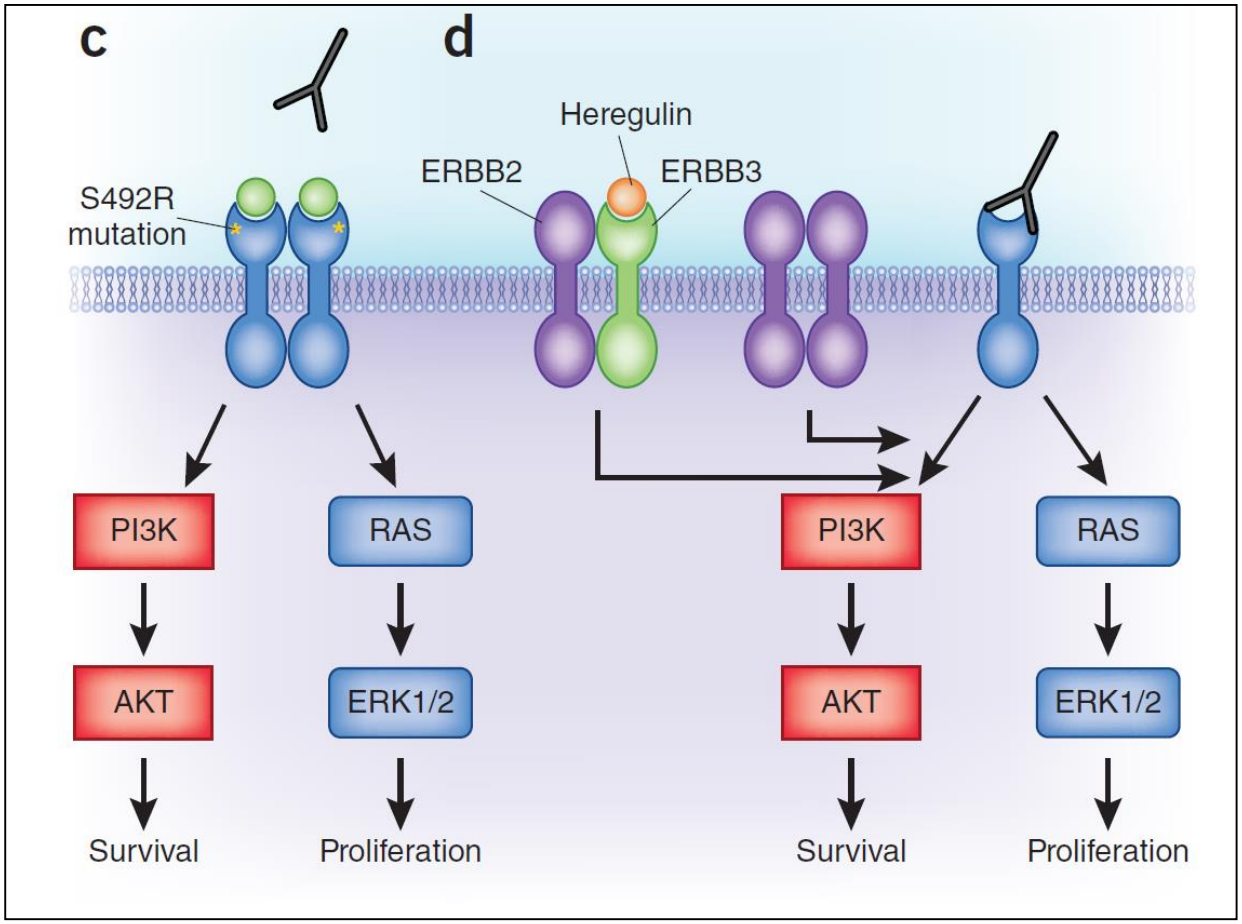
Mechanisms of Resistance to mAB

Cetuximab resistance



c) EGFR mutations in extracellular binding site inhibit cetuximab but not EGFR-ligand binding to EGFR
d) Cetuximab resistance can be mediated by activation of alternative signaling pathways

Mechanisms of Resistance to mAB

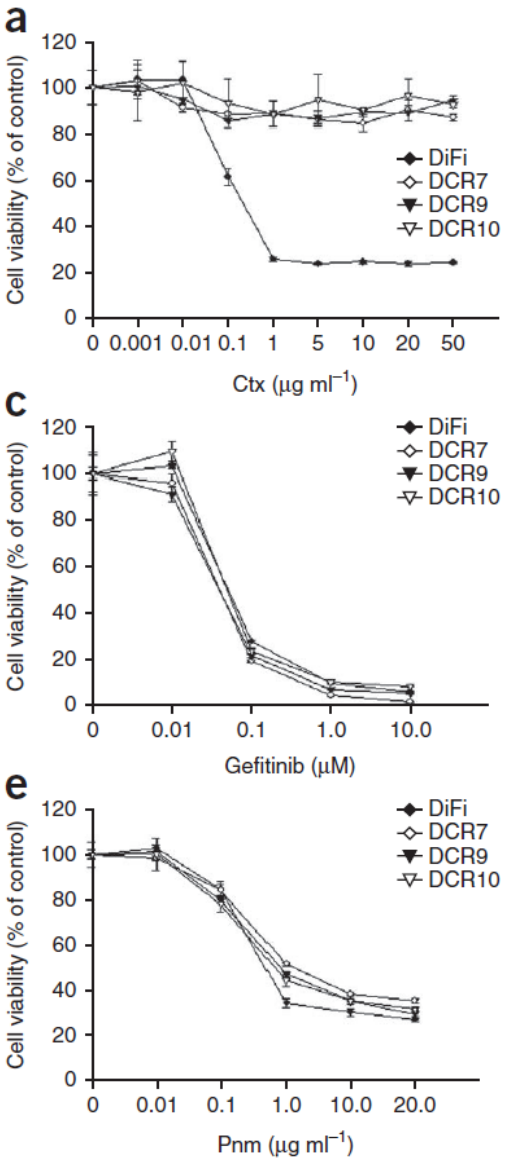
Identification of a mutation in the extracellular domain of the Epidermal Growth Factor Receptor conferring cetuximab resistance in colorectal cancer

Clara Montagut[1,2,9], Alba Dalmases[1,2,9], Beatriz Bellosillo[2,3], Marta Crespo[4], Silvia Pairet[2,3], Mar Iglesias[3,5], Marta Salido[3], Manuel Gallen[1,2], Scot Marsters[6], Siao Ping Tsai[6], André Minoche[7], Seshagiri Somasekar[6], Sergi Serrano[2,3,5], Heinz Himmelbauer[7], Joaquim Bellmunt[1,2,8], Ana Rovira[1,2], Jeff Settleman[6,9], Francesc Bosch[4,9] & Joan Albanell[1,2,5,9]

Nature Med. January, 2012

Cetuximab-resistant cells are still sensitive to EGFR-TKI Gefitinib and mAB Panitumumab

Cells from the DiFi human colorectal cancer cell line were made resistant to cetuximab by continuous exposure to cetuximab



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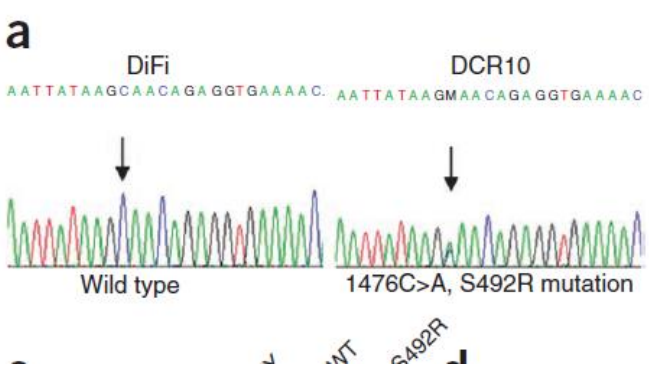
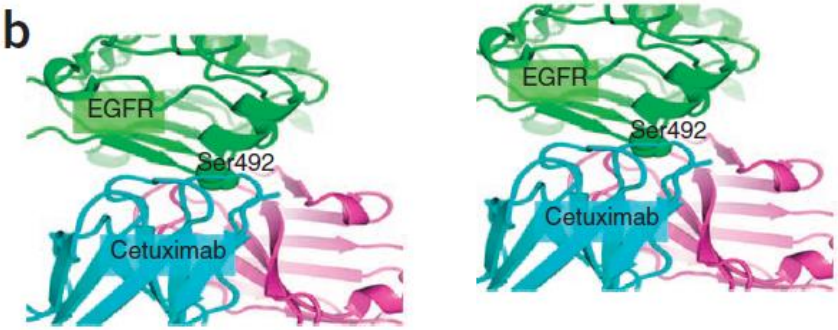
Mechanisms of Resistance to mAB





Supplementary Table 1. Clinical and mutational characteristics of subjects with metastatic colorectal cancer with paired biopsies before and after receiving treatment with cetuximab. The EGFR S492R mutation was detected in post-cetuximab tumor samples from subjects 3 and 9.

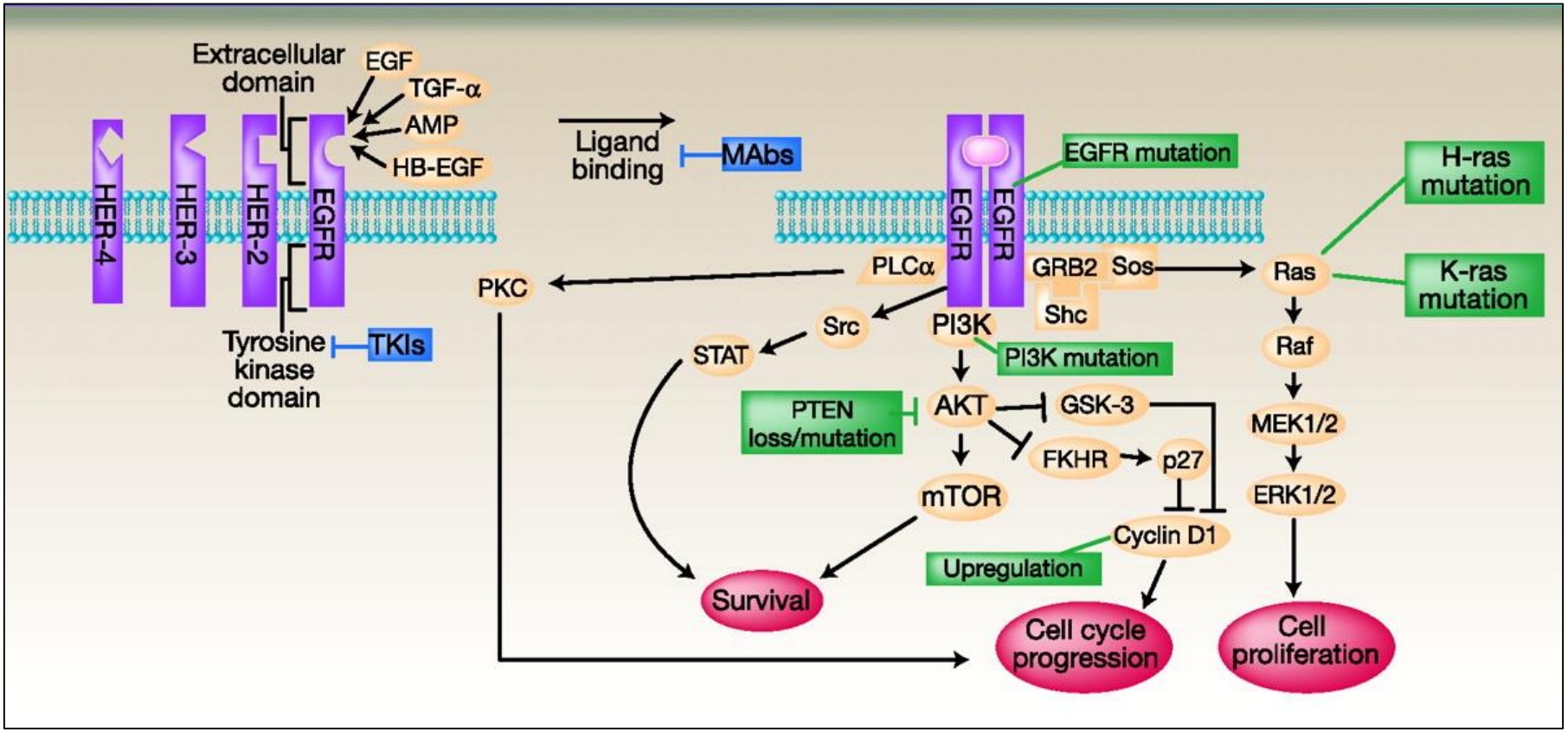
Subject No.	Sex	Age	Pre-cetuximab mutation status				Post-cetuximab mutation status			
			KRAS	*BRAF*	*PIK3CA*	*EGFR*	*KRAS*	*PIK3CA*	*BRAF*	*EGFR*
1	M	55	wt	wt	wt	wt	G12V	wt	wt	wt
2	F	42	wt	wt	wt	wt	wt	wt	wt	wt
3	M	64	wt	wt	wt	wt	wt	wt	wt	***S492R***
4	F	54	wt	wt	wt	wt	wt	wt	wt	wt
5	M	59	wt	wt	wt	wt	wt	wt	wt	wt
6	M	54	wt	wt	wt	wt	wt	wt	wt	wt
7	M	62	wt	wt	wt	wt	wt	wt	V600E	wt
8	M	79	wt	wt	wt	wt	wt	wt	wt	wt
9	M	52	wt	V600E	wt	wt	wt	wt	V600E	***S492R***
10	M	61	wt	wt	wt	wt	wt	wt	wt	wt

wt, wild-type

Nature Med. January, 2012

TRO ool

Secondary and Downstream Mutations



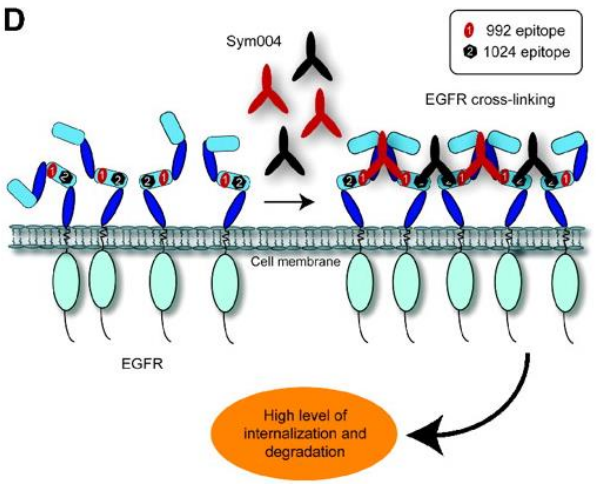
Next Generation Antibodies

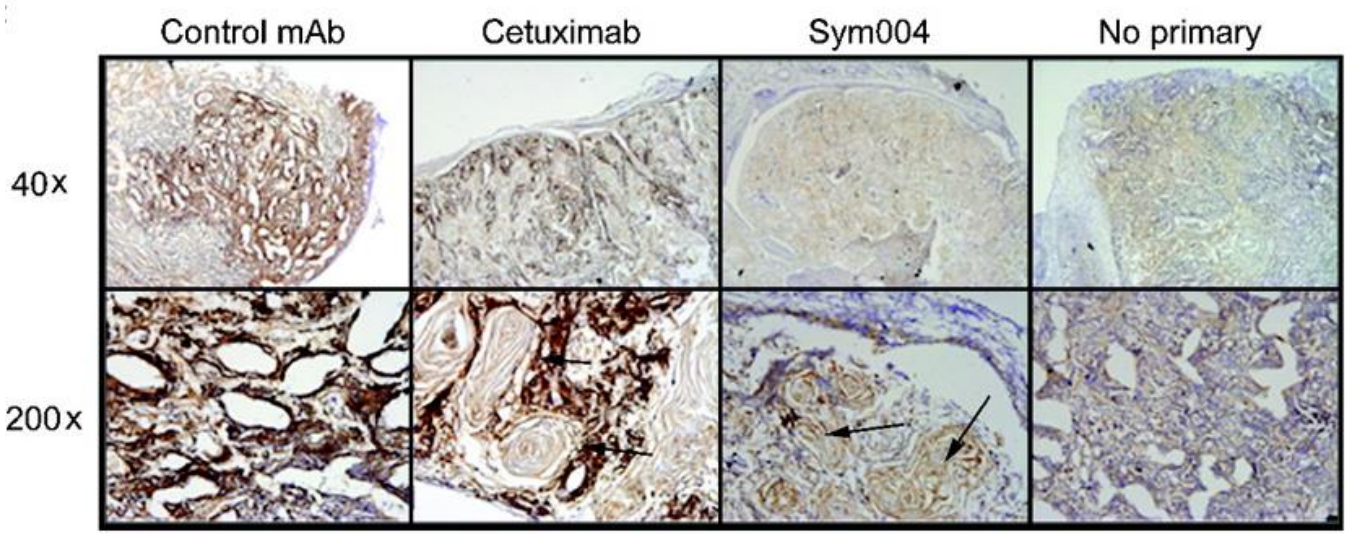
Published OnlineFirst January 12, 2010; DOI: 10.1158/0008-5472.CAN-09-1417

Therapeutics, Targets, and Chemical Biology

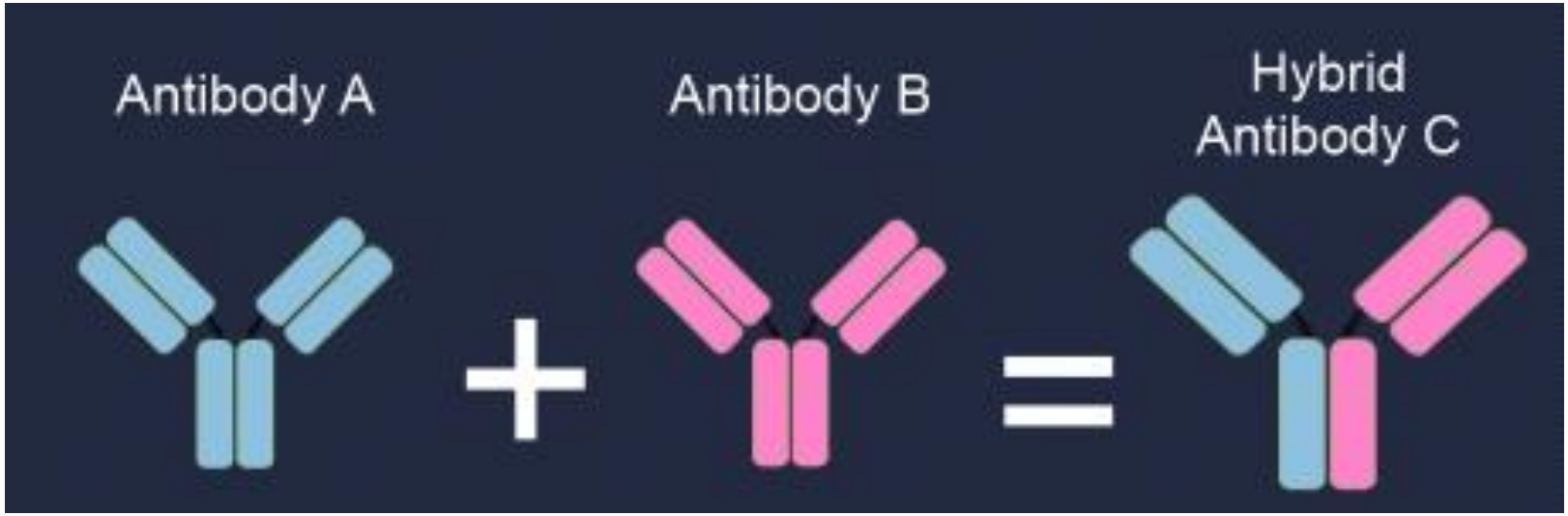
Sym004: A Novel Synergistic Anti–Epidermal Growth Factor Receptor Antibody Mixture with Superior Anticancer Efficacy

Mikkel Wandahl Pedersen, Helle Jane Jacobsen, Klaus Koefoed, Adam Hey, Charles Pyke, John Sørensen Haurum, and Michael Kragh





THE FUTURE ?

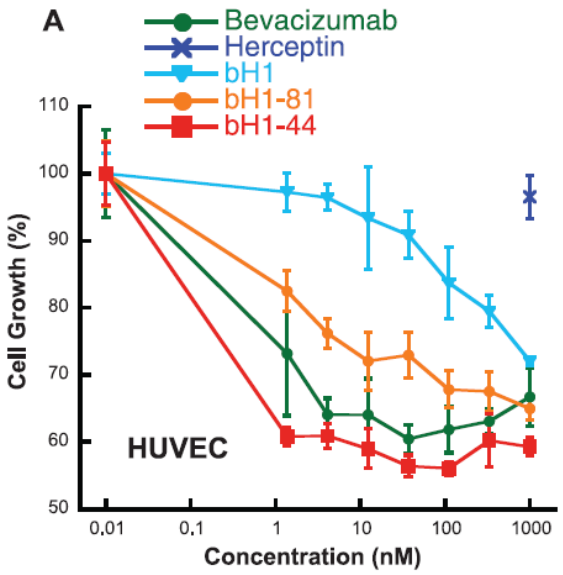


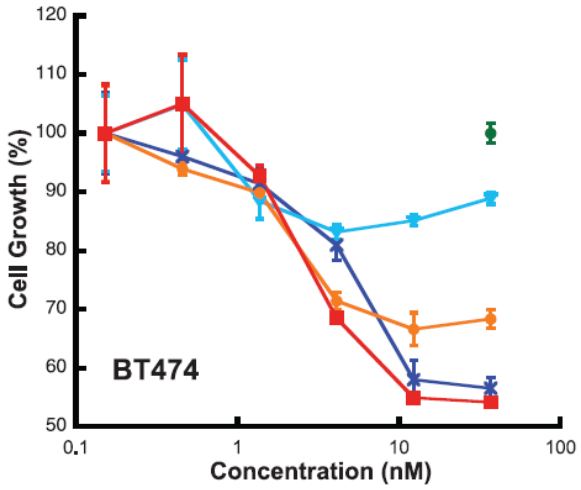
Dual specific antibodies?

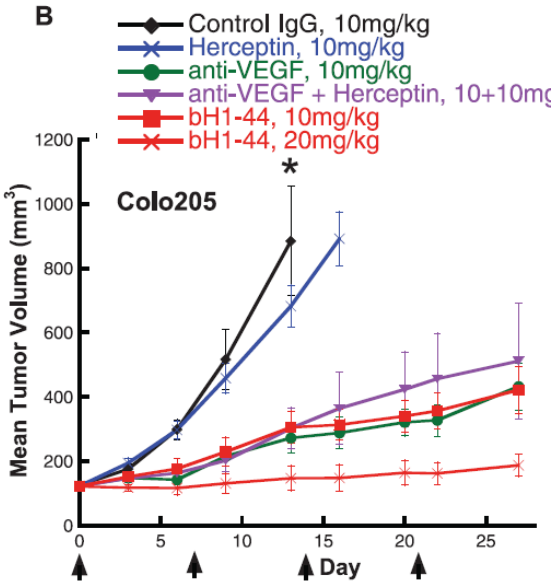
Variants of the Antibody Herceptin That Interact with HER2 and VEGF at the Antigen Binding Site

Jenny Bostrom,[1,2] Shang-Fan Yu,[3] David Kan,[3] Brent A. Appleton,[1] Chingwei V. Lee,[1,2]
Karen Billeci,[4] Wenyan Man,[1] Franklin Peale,[5] Sarajane Ross,[3]
Christian Wiesmann,[1] Germaine Fuh[1,2]*

„two-in-one“-antibody: challenge the monoclonal antibody paradigm of one binding site one antigen





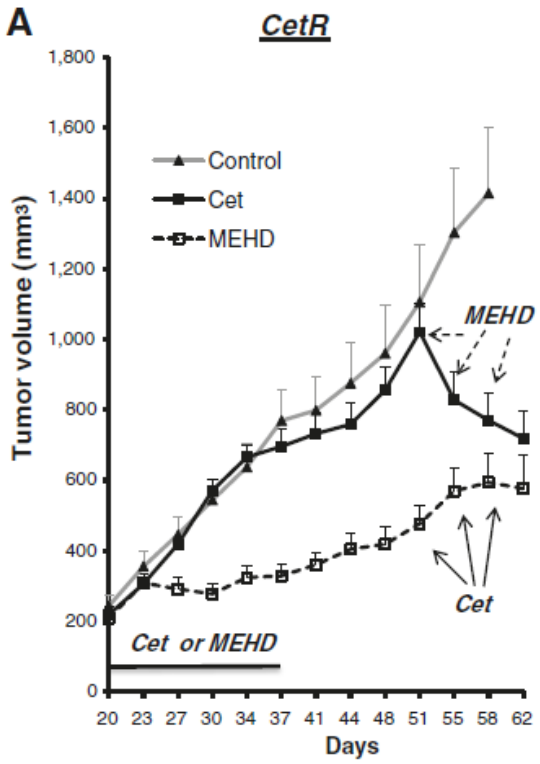


A Two-in-One Antibody against HER3 and EGFR Has Superior Inhibitory Activity Compared with Monospecific Antibodies

MEHD7945A

Gabriele Schaefer,[1,7] Lauric Haber,[2,7] Lisa M. Crocker,[3] Steven Shia,[4] Lily Shao,[1] Donald Dowbenko,[1] Klara Totpal,[3] Anne Wong,[5] Chingwei V. Lee,[2] Scott Stawicki,[2] Robyn Clark,[3] Carter Fields,[1] Gail D. Lewis Phillips,[1] Rodney A. Prell,[6] Dimitry M. Danilenko,[6] Yvonne Franke,[4] Jean-Philippe Stephan,[5] Jiyoung Hwang,[4] Yan Wu,[2] Jenny Bostrom,[2] Mark X. Sliwkowski,[1,*] Germaine Fuh,[2,*] and Charles Eigenbrot[2,4,*]

Cancer Cell *20*, 472–486, October 18, 2011



- Several clinical trials ongoing with duligotuzumab!

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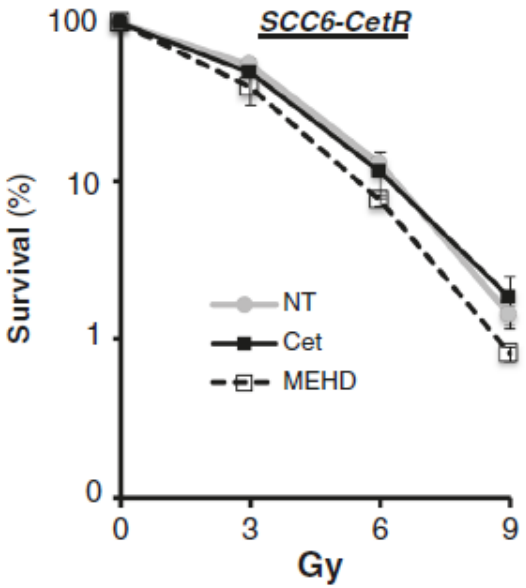
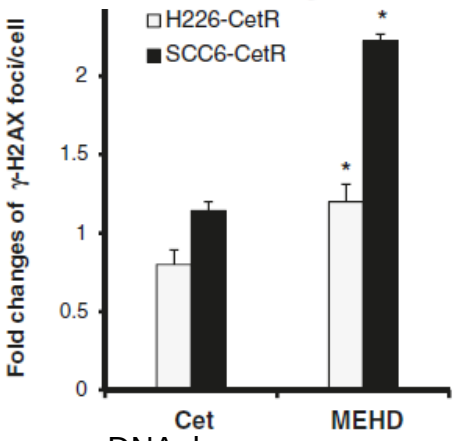
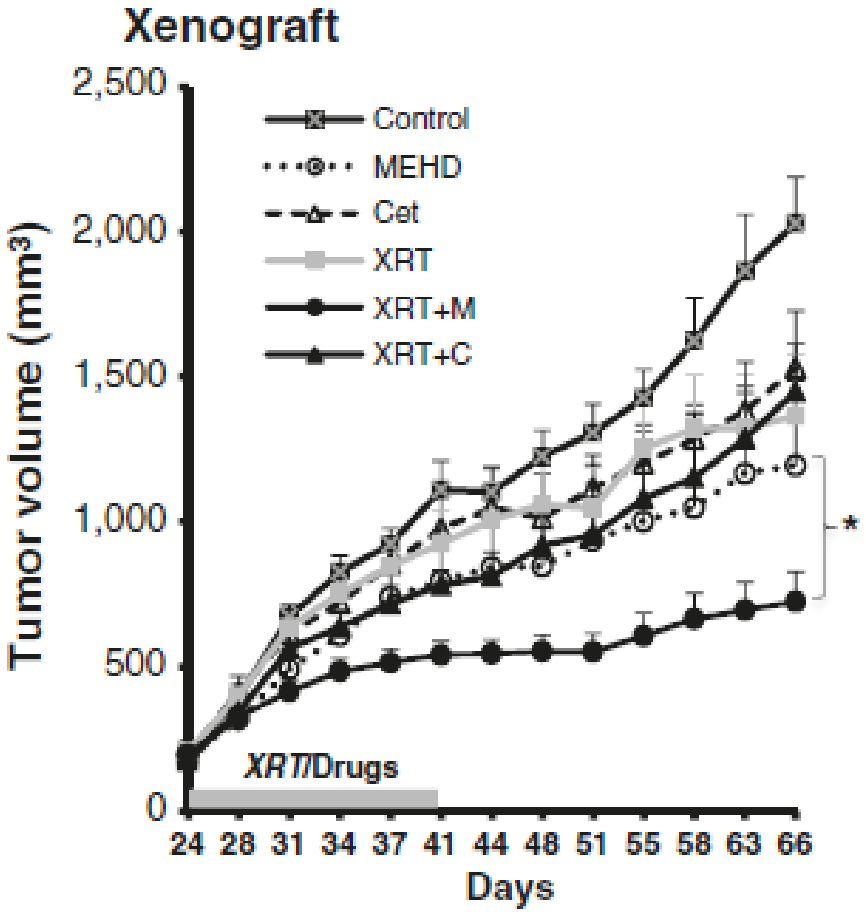
Dual Targeting of EGFR and HER3 overcomes Acquired Resistance to EGFR-Inhibitors and Radiation





DNA damage



Shyhmin Huang[1], Chunrong Li[1], Eric A. Armstrong[1], Chimera R. Peet[1], Jarob Saker[1], Lukas C. Amler[2], Mark X. Sliwkowski[2], and Paul M. Harari[1]

Cancer Res; 73(2) January 15, 2013

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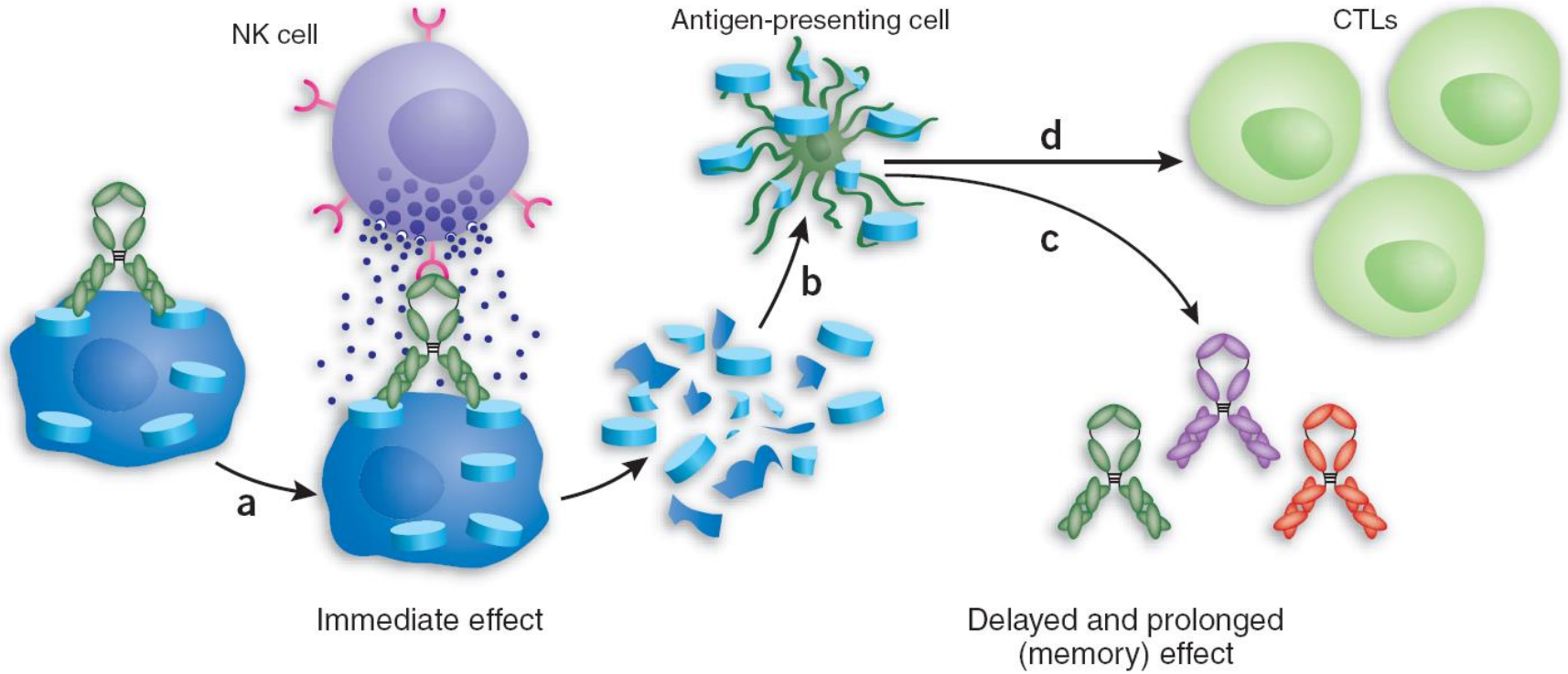
Antibody-Dependent Cellular Cytotoxicity Mediated by mABs , e.g. Cetuximab



ADCC: enhancement of antibody-based tumor therapy ↔ small molecular agents

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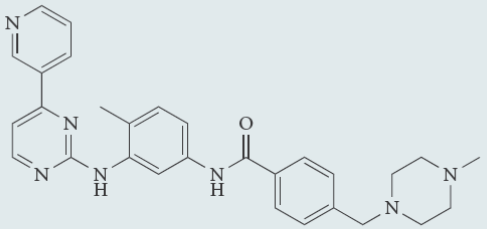
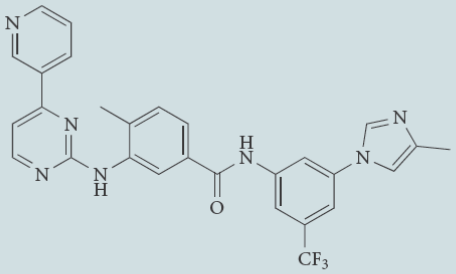
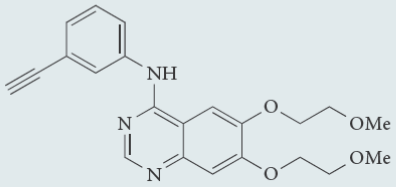
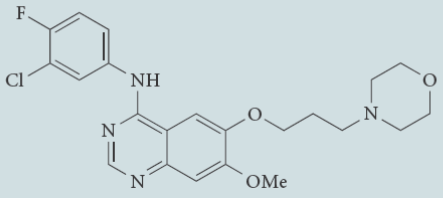
Chemical Structures of some clinically approved kinase inhibitors

Structure	Name	Known targets	Indication
	Imatinib (Gleevec; Novartis)	Bcr-Abl, c-Abl, PDGFR, c-KIT, DDR1	CML, GIST, HES
	Nilotinib (Tasigna; Novartis)	Bcr-Abl, c-Abl, PDGFR, c-KIT, DDR1	Imatinib-resistant CML
	Erlotinib (Tarceva; OSI Pharmaceuticals/ Genentech/Roche)	EGFR, ERBB2 (HER2)	NSCLC, pancreas cancer
	Gefitinib (Iressa; AstraZeneca)	EGFR, ERBB2, HER4	NSCLC

Mechanisms of small molecule action (TK-inhibitors) I

Initial concerns: well conserved ATP-binding sites in between the family of kinases: can we get specificity?

Using protein cristallography and NMR-spectroscopy sophisticated structure-based design of specific kinase-inhibitors are now feasible

Kinase inhibitors were developed with the goal of highest selectivity, however, several clinically approved kinases inhibitors are potent inhibitors of multiple kinases: reason for potency?

Potential to target multiple distinct processes (hallmarks) associated with tumor growth, but might be more toxic

Several preclinical studies demonstrate (supra-) additive effect by combined treatment modalities mAB plus TK-inhibitors (complementary effects)

Kinase inhibitor binding sites

- Type I inhibitors
  - constitutes majority of ATP-competitive inhibitors and recognizes the so called active conformation of the kinase
  - e.g. sorafenib, dasatinib, sutent
- Type II inhibitors
  - recognize the inactive conformation of the kinase
  - e.g. imatinib
- Allosteric Inhibitors
  - bind outside of ATP-binding site; at an allosteric site
  - exhibit highest degree of kinase selectivity
- Covalent inhibitors
  - require low concentrations
  - concern about potential toxicity by modification of unanticipated targets

Iressa - Gefitinib

The first selective inhibitor that targets the mutant proteins in malignant cells

Used to treat lung cancer

Only ~10% of non-small cell lung cancer patients response to Iressa

Toxicities include acne, diarrhea, nausea, vomiting and skin reactions

chemical class: quinazoline

orally bioavailable (compliance)

selective inhibitor of EGFR tyrosine kinase

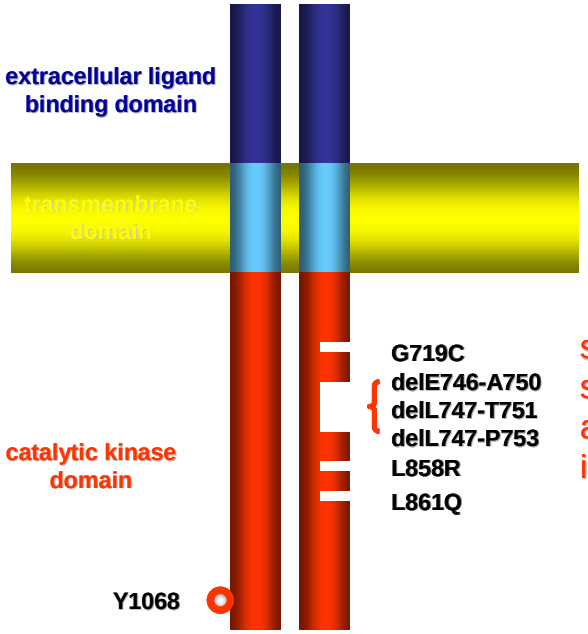
- EGFR IC50 = 0.023-0.079 μM
- erbB2 IC50 = 1.2-3.7 μM

competitive inhibitor of ATP-binding

inhibits ligand-induced cell growth

- IC50 = 0.08 μM

EGFR Mutation



specific mutations confer sensitivity of EGFR-TK activity to gefitinib/iressa in NSCLC patients !

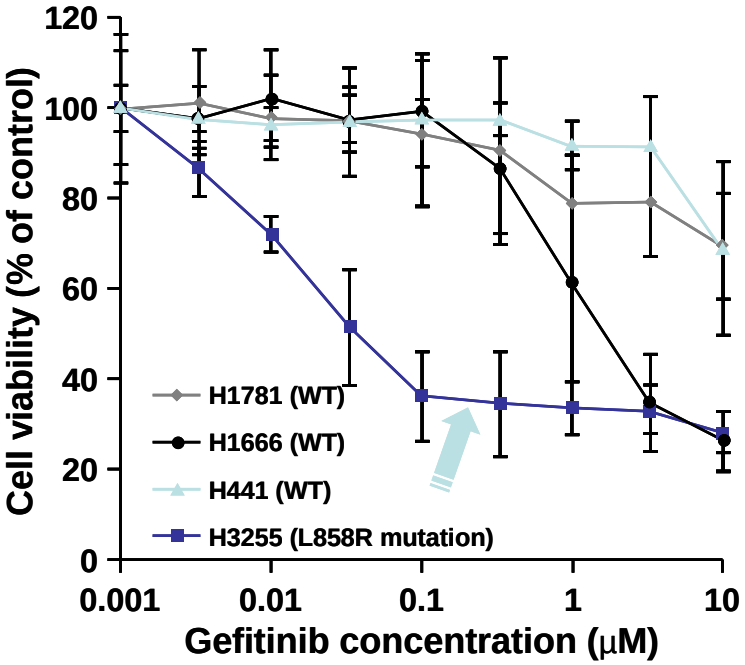
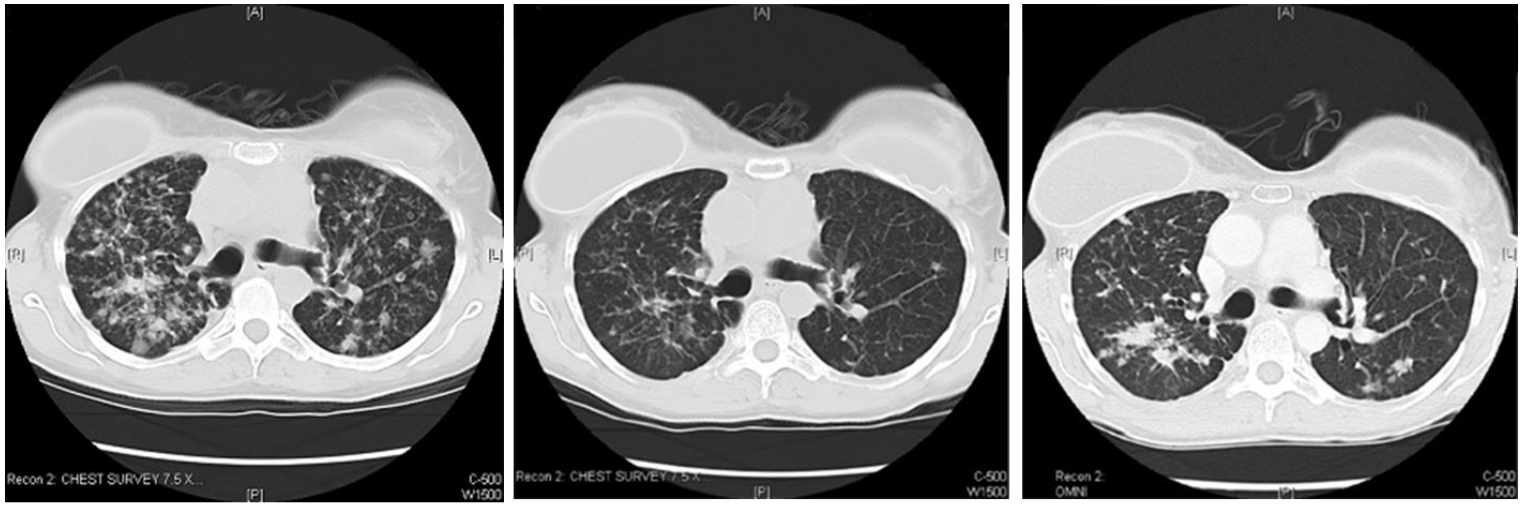


Table 1. The current state of knowledge of *EGFR* mutations in patients with NSCLC

Known	Unknown
EGFR mutations are associated with responses to gefitinib and erlotinib	The etiology of the *EGFR* mutations
EGFR mutations are somatic	The relative oncogenic properties of the different *EGFR* mutations
EGFR mutations are more common in women, nonsmokers, in adenocarcinomas, and East Asians	The outcome of patients with different *EGFR* mutation treated with different EGFR-TKIs
Secondary *EGFR* mutations are associated with resistance to gefitinib and erlotinib in patients and *in vitro*	The mechanisms of resistance to gefitinib and erlotinib in the patients who do not have the identified T790M secondary *EGFR* mutation

Acquired Resistance of Lung Adenocarcinomasto Gefitinib or Erlotinib Is Associated with a Second Mutation in the EGFR Kinase Domain

Patient 2.
This 55-y-old woman with a nine pack-year history of smoking underwent two surgical resections within 2 y (right lower and left upper lobectomies) for bronchioloalveolar carcinoma with focal invasion. Two years later, her disease recurred with bilateral pulmonary nodules and further progressed on systemic chemotherapy. Thereafter, the patient began erlotinib, 150 mg daily. A baseline CT scan of the chest demonstrated innumerable bilateral nodules (Figure S1B, left panel), which were markedly reduced in number and size 4 mo after treatment (Figure S1B, middle panel). After 14 mo of therapy, the patient's dose of erlotinib was decreased to 100 mg daily owing to fatigue. At 23 mo of treatment with erlotinib, a CT scan demonstrated an enlarging sclerotic lesion in the thoracic spine. The patient underwent CT-guided biopsy of this lesion and the erlotinib dose was increased to 150 mg daily. After 25 mo of treatment, she progressed within the lung (Figure S1B, right panel). Erlotinib was discontinued, and a fluoroscopically guided core needle biopsy was performed at a site of progressive disease in the lung.



Day 0 | **4 months** | **25 months**

del L747–E749;A750P; Kras Wild-type | del L747–E749;A750P; T790M Kras Wild-type

Pao et al., Plos Med., 2005

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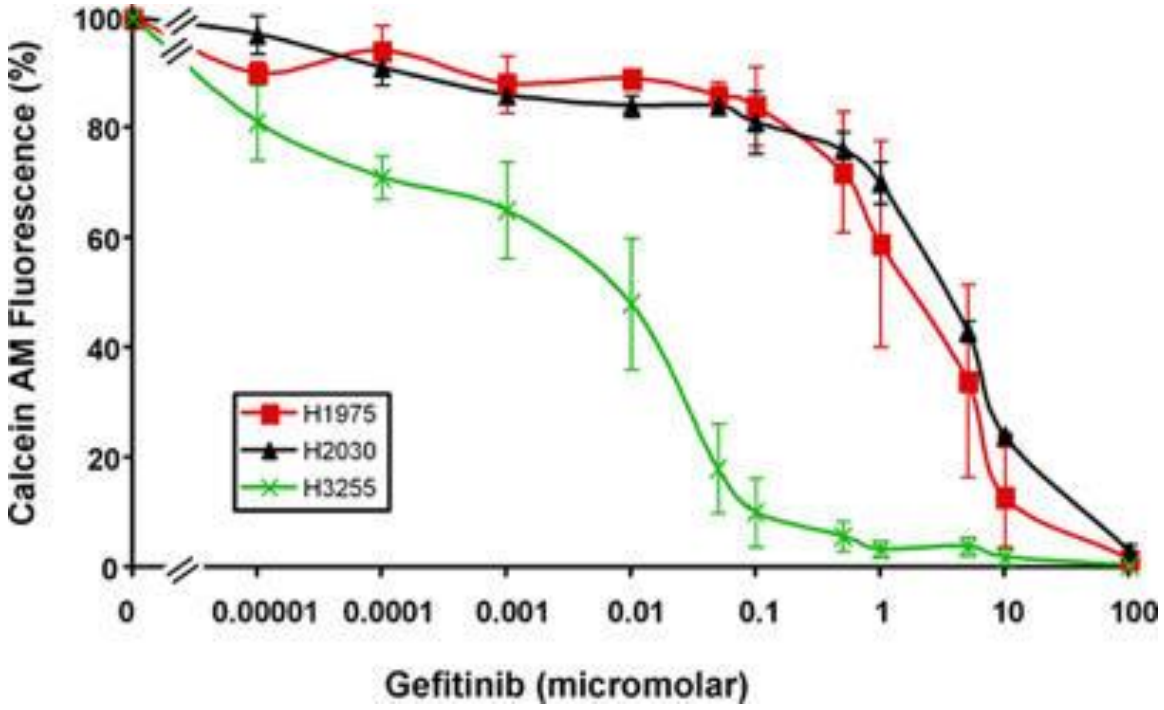
Secondary and Downstream Mutations



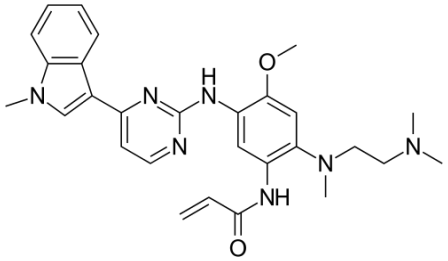
Kobayashi, PLoS Med, 2, e73

Sensitivity to Gefitinib Differs Among NSCLC Cell Lines Containing Various Mutations in *EGFR* or *KRAS*

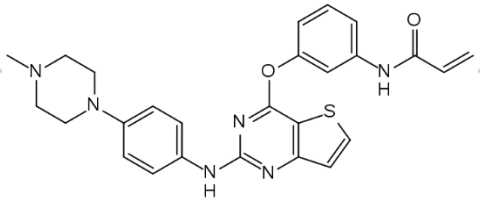
The three indicated NSCLC cell lines, H3255 (L858R mutation), H1975 (both T790M and L858R mutations), and H2030 (wild-type *EGFR,* mutant *KRAS*), were grown in increasing concentrations of gefitinib, and the density of live cells after 48 h of treatment was measured

Targeting EGFR T790M mutation in NSCLC: From biology to evaluation and treatment

Osimertinib (AstraZeneca) is a potent, irreversible EGFR tyrosine kinase inhibitor that is selective for EGFR tyrosine kinase inhibitor–sensitizing mutations and the T790M resistance mutation with an excellent therapeutic index because its activity is poor towards the wild-type EGFR



Olmutinib (HM 61713)(Boehringer Ingelheim) is an irreversible tyrosine-kinase inhibitor, selective for mutant EGFR. Its molecule structure contains a Michael acceptor that covalently binds a cysteine residue near the kinase domain of mutant EGFR



Resistances: Secondary and Downstream Mutations

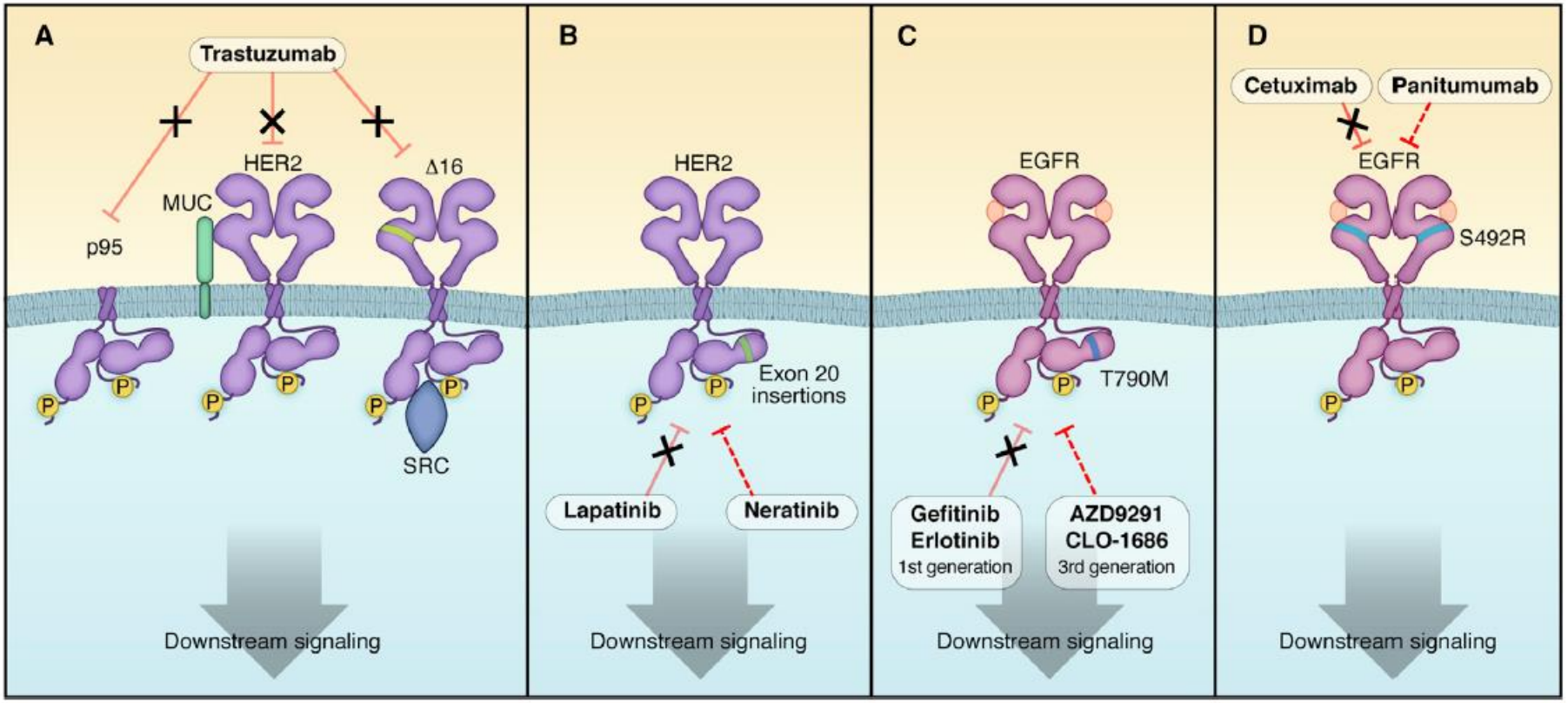


Figure 1. Schema Depicting Intragenic Alterations Leading to Resistance to HER2 and EGFR Inhibitors

(A) HER2 truncations (p95) and splice variants (Δ16) are not inhibited by trastuzumab. In addition, expression of specific mucin isoforms can prevent trastuzumab from binding HER2 (Price-Schiavi et al., 2002). Not shown in the figure, pertuzumab and T-DM1 cannot recognize p95 either.

(B) HER2s harboring exon 20 insertions are not inhibited by lapatinib, but may be sensitive to irreversible HER2 inhibitors afatinib and neratinib. They are also resistant to trastuzumab.

(C) The EGFR T790M gatekeeper mutation leads to acquired resistance to first generation EGFR inhibitors, but is effectively inhibited by third-generation EGFR inhibitors.

(D) An EGFR mutation in the extracellular domain is associated with acquired resistance to cetuximab, but may still be sensitive to another anti-EGFR antibody, panitumumab. Dashed lines indicate inhibition via alternative antibodies and inhibitors.

Arteaga, Cancer Cell, 25, 2015

Resistances: Secondary and Downstream Mutations

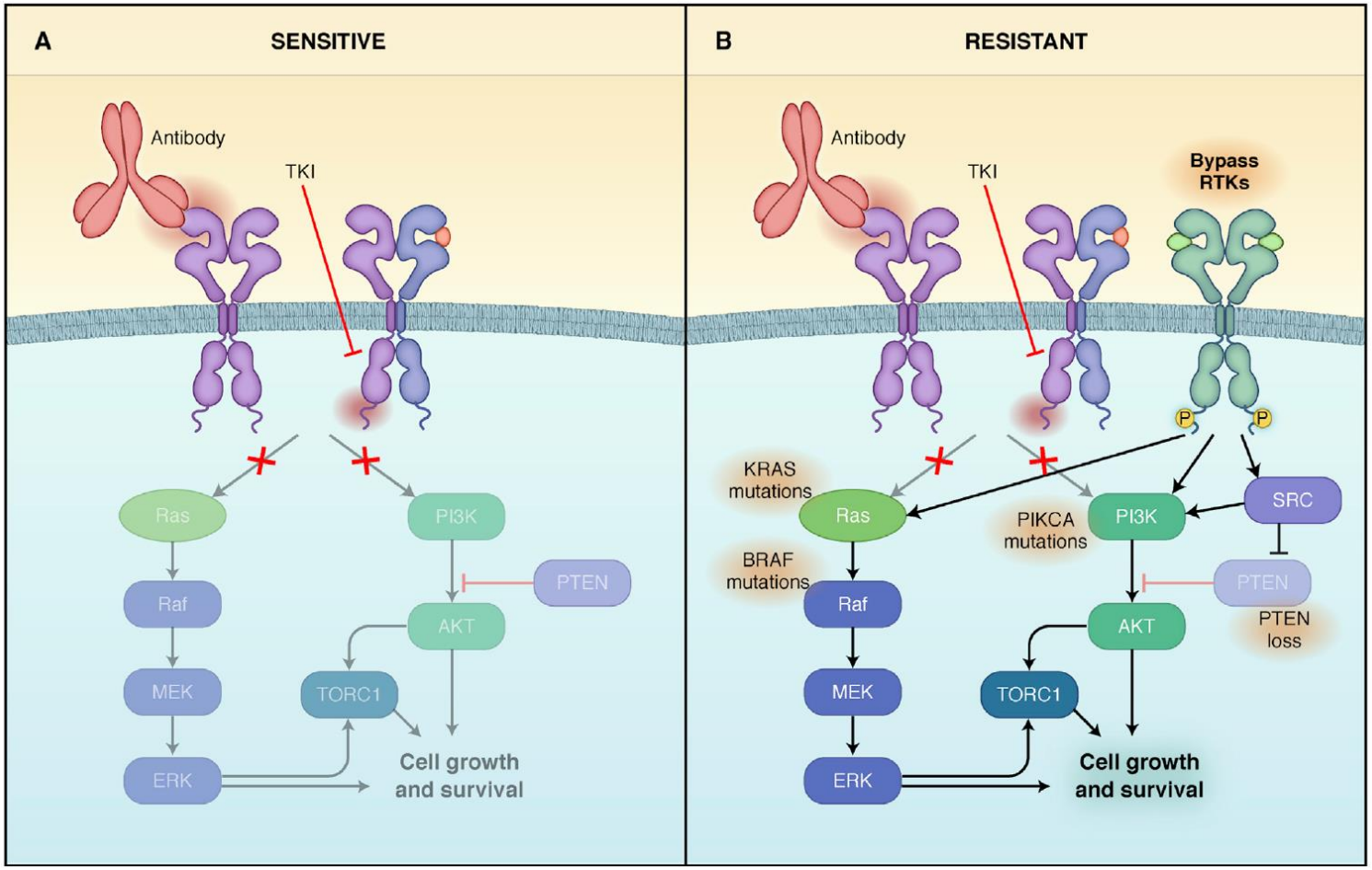


Figure 2. Schematic Depicting Resistance to EGFR and HER2 Inhibitors due to Activation of Bypass Track Signaling

(A) Model of a sensitive EGFR or HER2-addicted cancer treated with an ERBB small-molecule inhibitor or antibody resulting in suppression of downstream signaling. EGFR or HER2 homodimers and heterodimers are shown.

(B) Model of a EGFR mutant or *HER2*-amplified cancer with resistance due to maintenance of downstream signaling in the presence of the EGFR or HER2 inhibitors. Activation of signaling can be caused by activation of other RTKs or mutational activation of downstream signaling.

Arteaga, Cancer Cell, 25, 2015

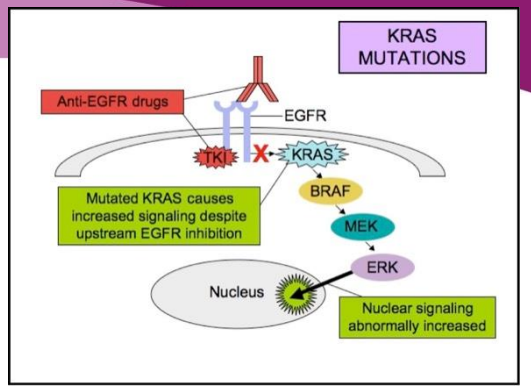
ESTRO School

The NEW ENGLAND JOURNAL of MEDICINE

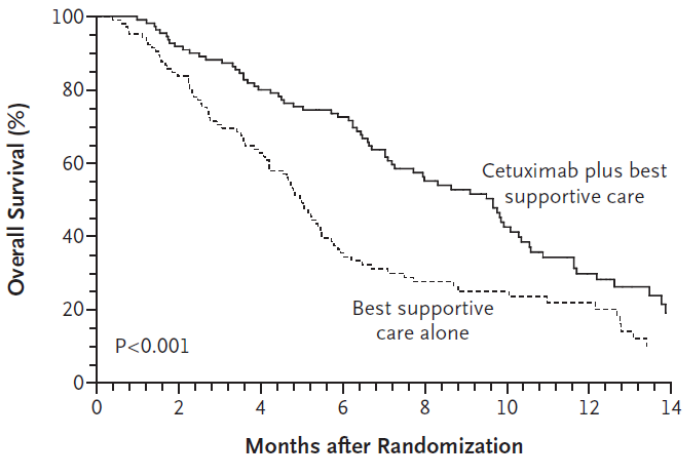
ESTABLISHED IN 1812 OCTOBER 23, 2008 VOL. 359 NO. 17

K-ras Mutations and Benefit from Cetuximab in Advanced Colorectal Cancer

Christos S. Karapetis, M.D., Shirin Khambata-Ford, Ph.D., Derek J. Jonker, M.D., Chris J. O'Callaghan, Ph.D., Dongsheng Tu, Ph.D., Niall C. Tebbutt, Ph.D., R. John Simes, M.D., Haji Chalchal, M.D., Jeremy D. Shapiro, M.D., Sonia Robitaille, M.Sc., Timothy J. Price, M.D., Lois Shepherd, M.D.C.M., Heather-Jane Au, M.D., Christiane Langer, M.D., Malcolm J. Moore, M.D., and John R. Zalcberg, M.D., Ph.D.*

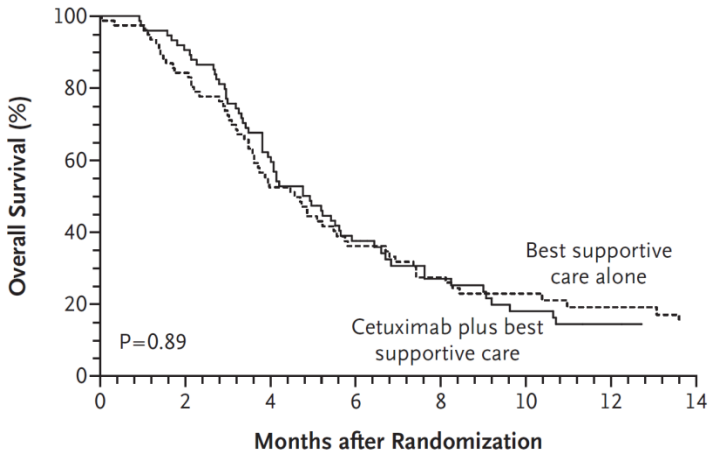


B Wild-type *K-ras*



No. at Risk								
Cetuximab plus best supportive care	110	101	88	75	48	31	19	8
Best supportive care alone	105	88	65	34	23	17	12	5

A Mutated *K-ras*



No. at Risk								
Cetuximab plus best supportive care	75	67	45	26	15	10	7	4
Best supportive care alone	76	64	39	26	19	12	10	7

Key Points

Molecularly targeted agents are less toxic than cytotoxic agents (antibodies/small molecular

resistances

Molecularly targeted agents work by targeting the genetic changes(s) in cancer cells

- Chromosomal translocation
- Gene duplication
- Gene mutation

Risk for secondary mutations high

Risk for paraxodical activation of pro-tumorigenic wildtype-signal transduction cascade exists (Raf-inhibitors)

To improve cancer treatment, we need to better understand the differences between cancer and normal cells

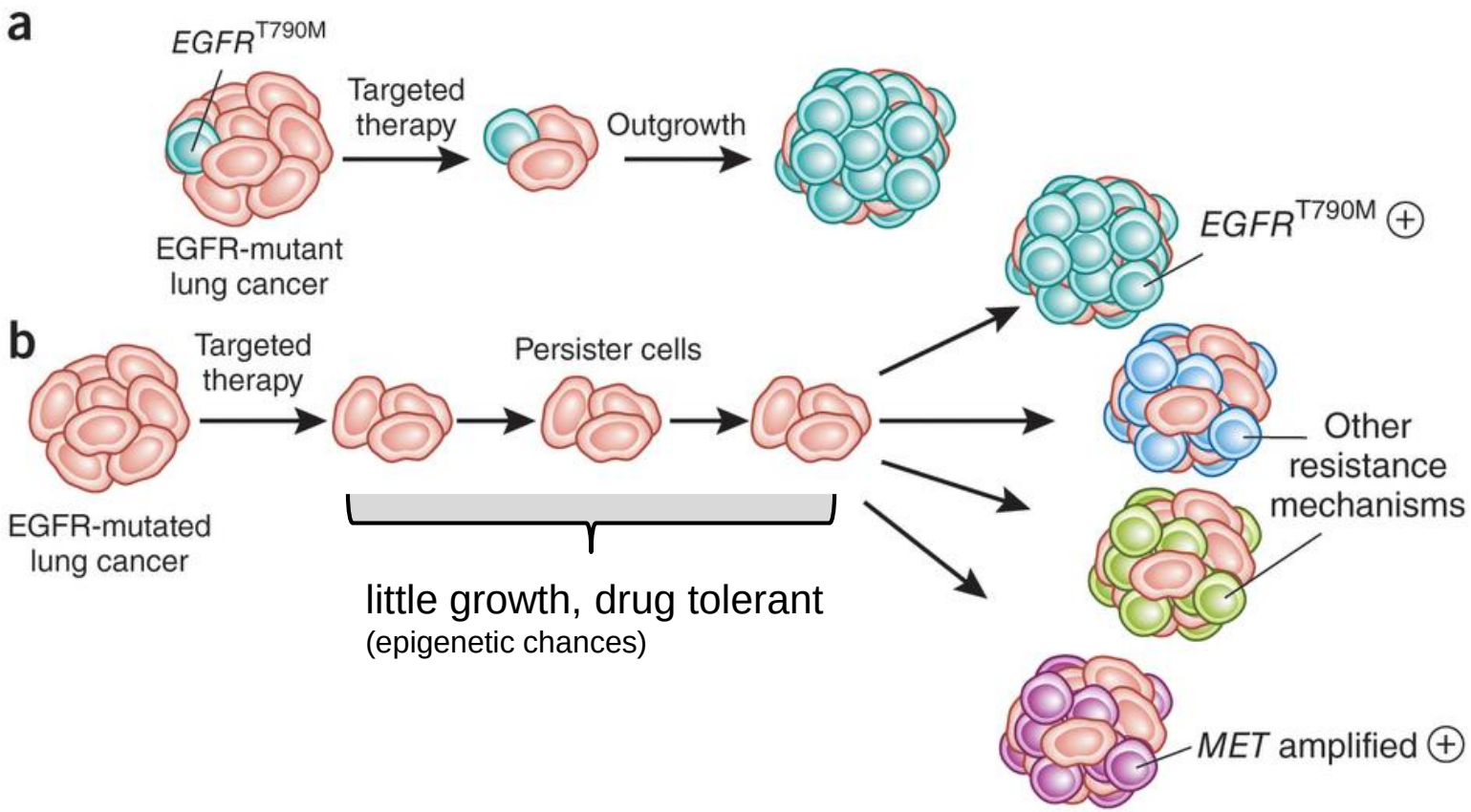
Major Callenges: Resistances

- de novo/ intrinsic resistance: do not exhibit an initial response

- acquired resistance: develops after an initial, often marked and durable clinical response

- same molecular mechanisms may cause both types of resistance

Cellular Origins of Drug Resistance in Cancer



a) Preexisting subclones

b) Induction of durable drug-tolerable state followed by aquisition of a variety of resistance mechanisms

Hata et al., Ramirez et al, 2016

ESTRO School

Relevant Questions:

- Molecular evolution of resistance to treatment:
  - acquired during therapy?
  - Already present in a clonal subpopulation within the tumours *prior* to the initiation of therapy?

- Is resistance is therefore a fait accompli—the time to recurrence is simply the interval required for the subclone to repopulate the lesion.?
- Is the short time interval of recurrence due to the rapid expansion of the resistant subclone immediately following treatment initiation?

- Required:

Combination therapies targeting at least two different pathways - processes.

IEO
Istituto Europeo di Oncologia

Personalized cancer therapy

Giuseppe Curigliano MD, PhD
Breast Cancer Program
Division Experimental Cancer Medicine

Changing nature of early development trials

- Enrichment strategies: by subtype of by genomic alterations
- Novel dose escalation methods applied
- Research biopsies
- Driving go-no-go decisions based on their ability to provide proof of concept
- Trends in increase in the sample size of phase I trials
- Expanding cohorts being conducted for multiple purposes

Evidence-Based Medicine

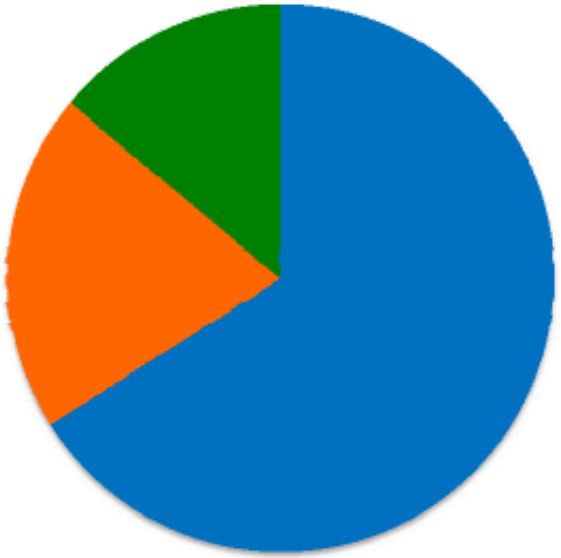
Cancer treatment is based on trials that were large, rigorous, and provided level I evidence.

Challenges to meaningful clinical trials in the ‘omic era:

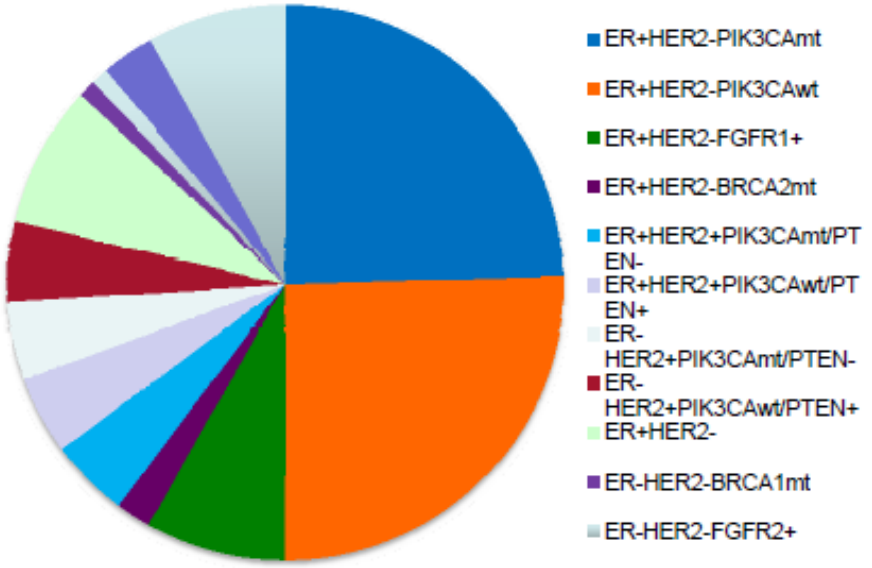
1. “Cancer” doesn’t exist, is now a fragmented group of biologically distinct entities.
2. Cancer outcomes are globally better (good for patients, bad for event rates)

Breast cancer as an orphan disease

Breast Cancer 2015

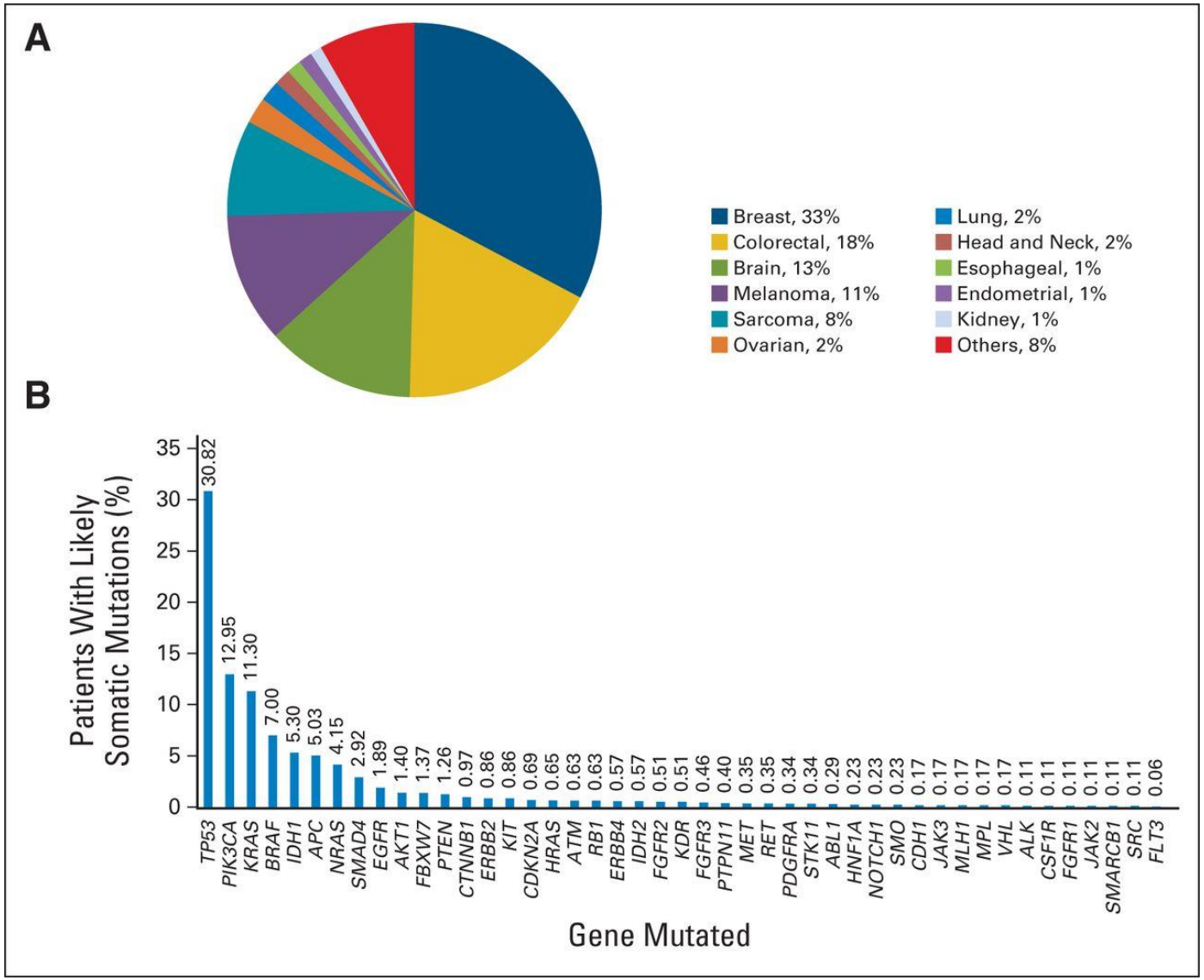


Breast Cancer 2023



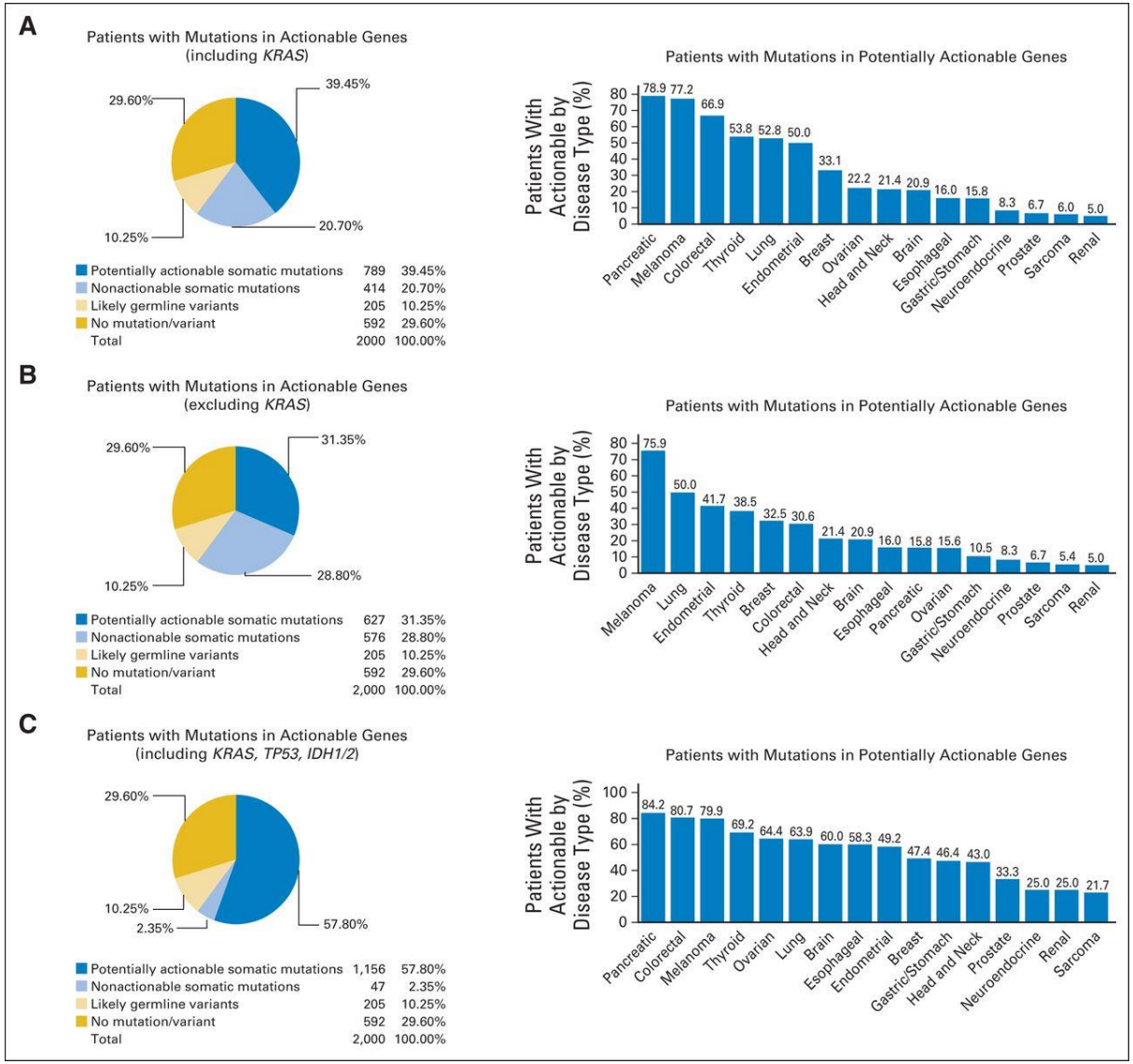
Each molecular segment is very rare
and presents a specific biological feature

The most common somatic mutations for patients who underwent genomic testing



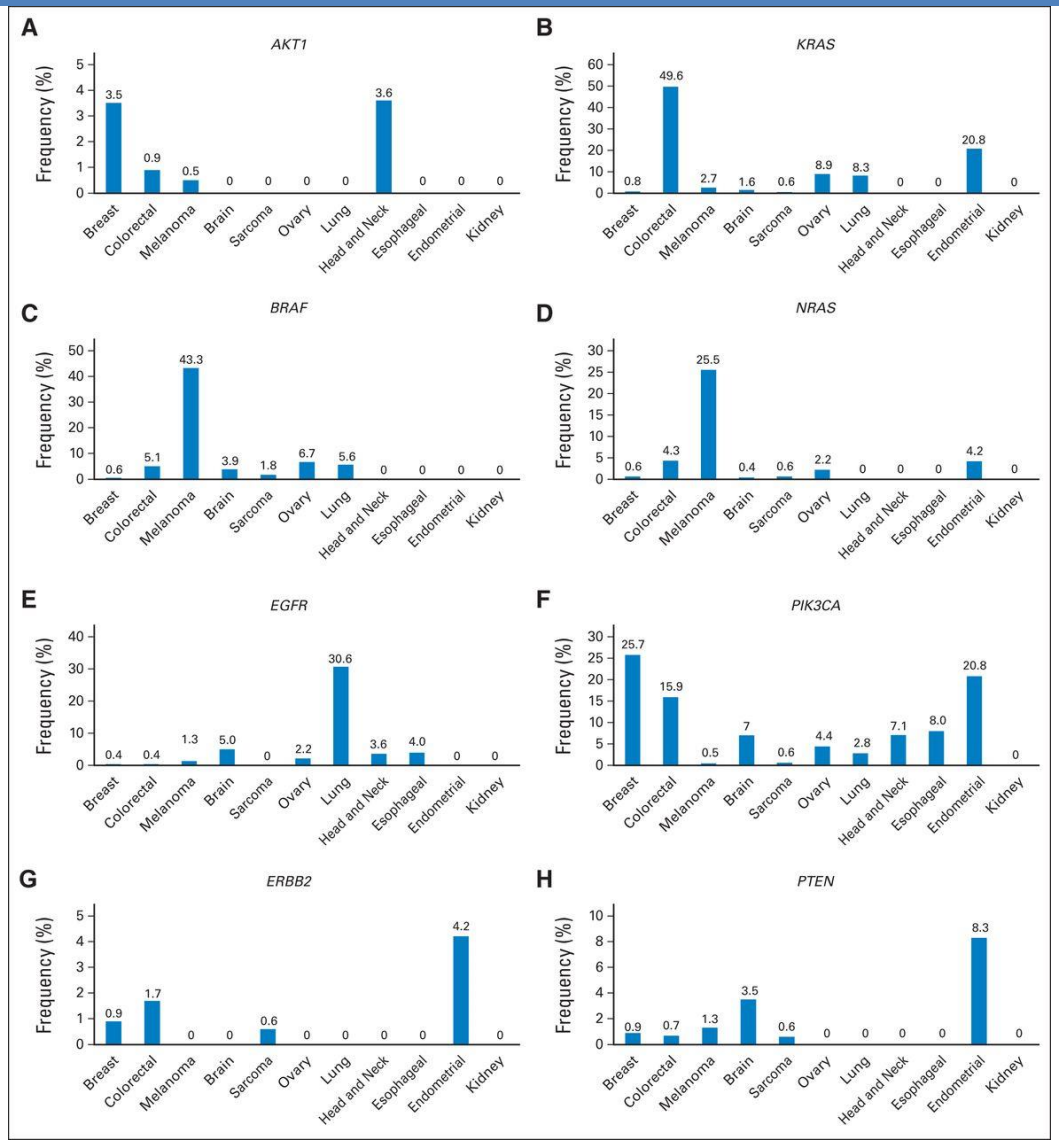
Funda Meric-Bernstam et al. JCO 2015;33:2753-2762

Frequency of actionable alterations



Funda Meric-Bernstam et al. JCO 2015;33:2753-2762

Frequency of selected alterations in different tumor types

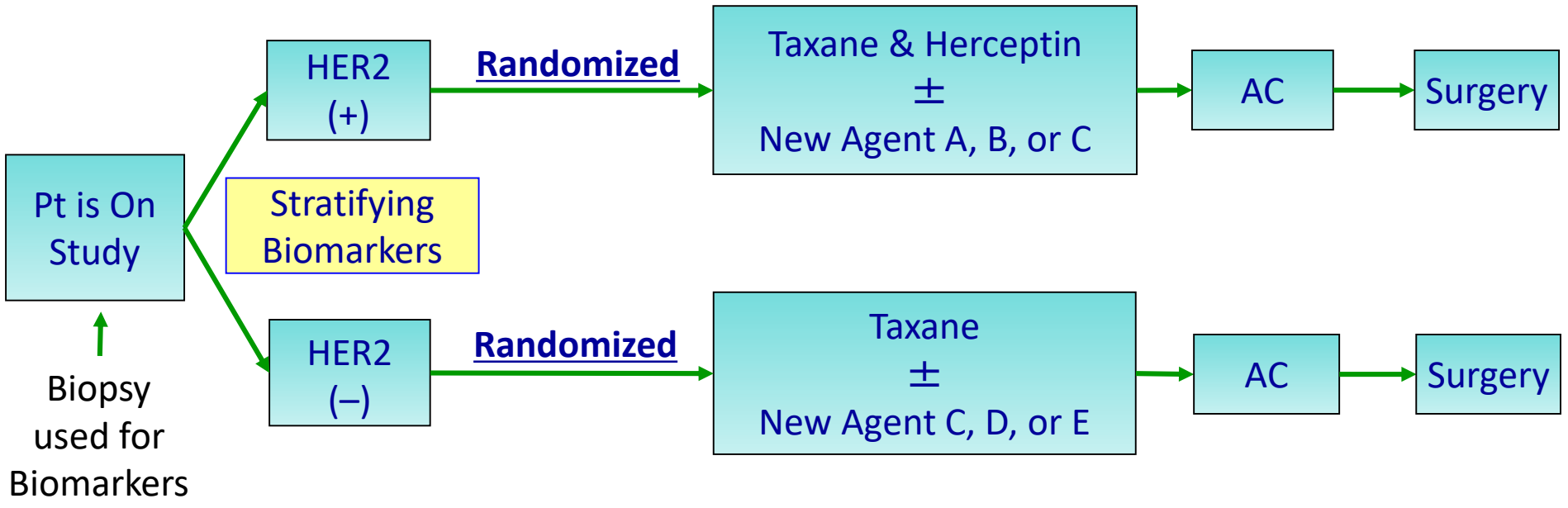


Funda Meric-Bernstam et al. JCO 2015;33:2753-2762

Why drug development is changing?

- Knowledge of molecular biology is accumulating and technology is rapidly evolving
- Molecularly targeted agents and immuno-oncology agents are becoming important
- Patients and infrastructure resources are limited
- Accelerated drug approval is possible with compelling results
- Desire to accelerate drug development process to bring active compunds to the clinic and improve cancer cures have fueled these changes

I-SPY 2 TRIAL



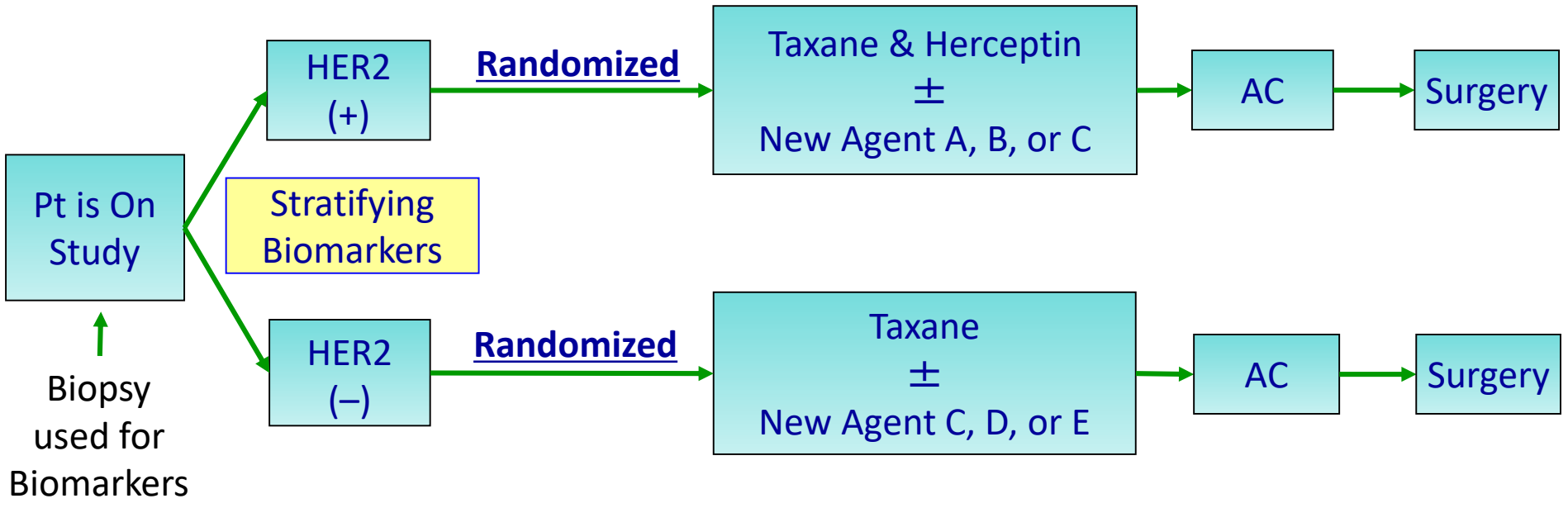
Stratifying Biomarkers (Established/Approved/IDE)

ER, PR

HER2 (IHC, FISH, RPMA, 44K-microarray)

MammaPrint 44K microarray

I-SPY 2 TRIAL



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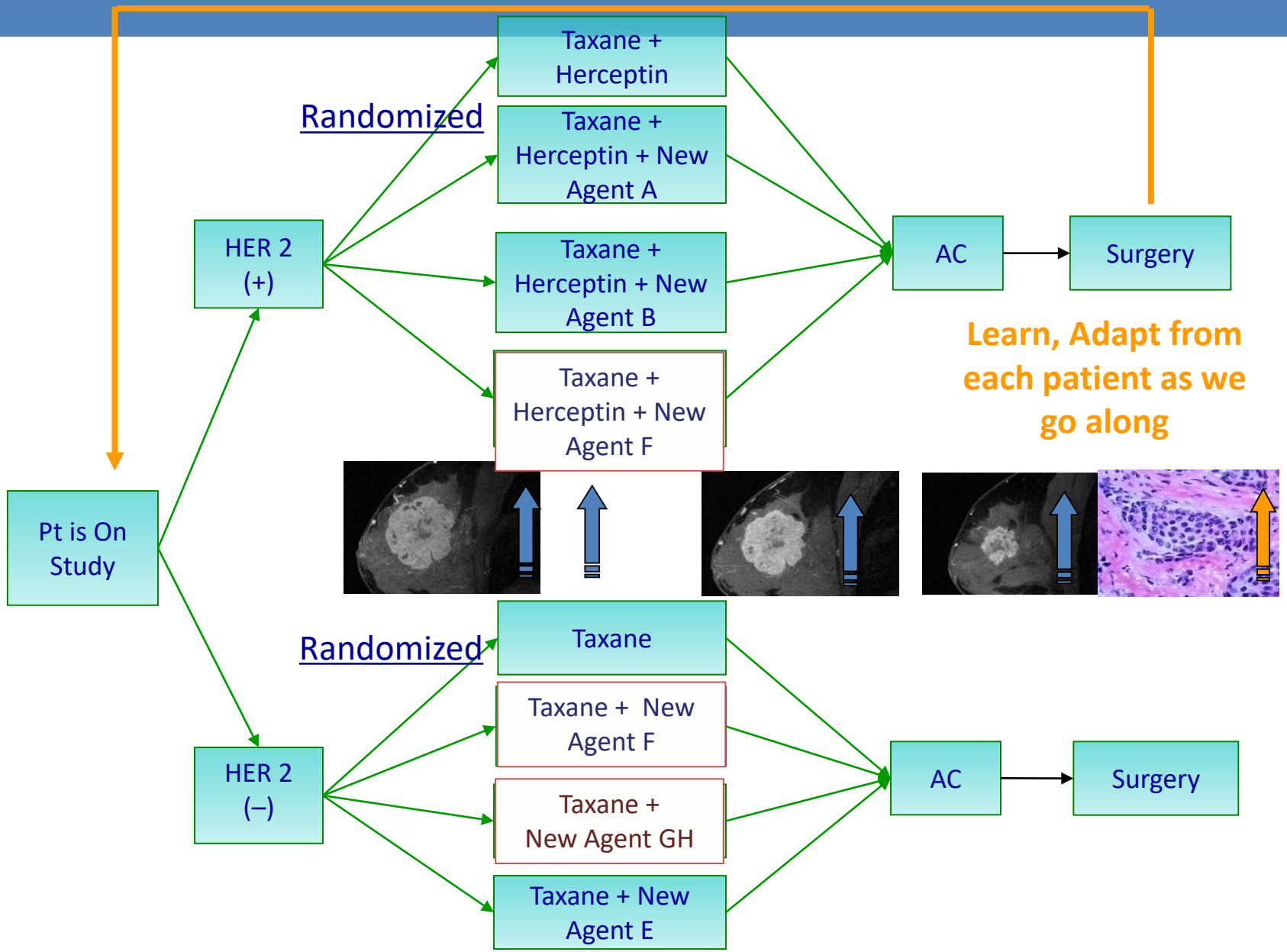

Taxane + Herceptin
Randomized
Taxane + Herceptin + New Agent A
HER 2 (+)
Taxane + Herceptin + New Agent B
AC
Surgery
Taxane + Herceptin + New Agent F
Learn, Adapt from each patient as we go along
Pt is On Study
Randomized
Taxane
Taxane + New Agent F
HER 2 (–)
Taxane + New Agent GH
AC
Surgery
Taxane + New Agent E

I-SPY 2 TRIAL

- HER2 (HSP90, HER2, HER3)
- IGFR
- PI3K
- Macrophage
- AKT
- AKT + MAPK, ERBB2, or PI3K+MEK inhibitors
- Death Receptor
- c-MET
- mTOR + X
- Angiogenesis + X

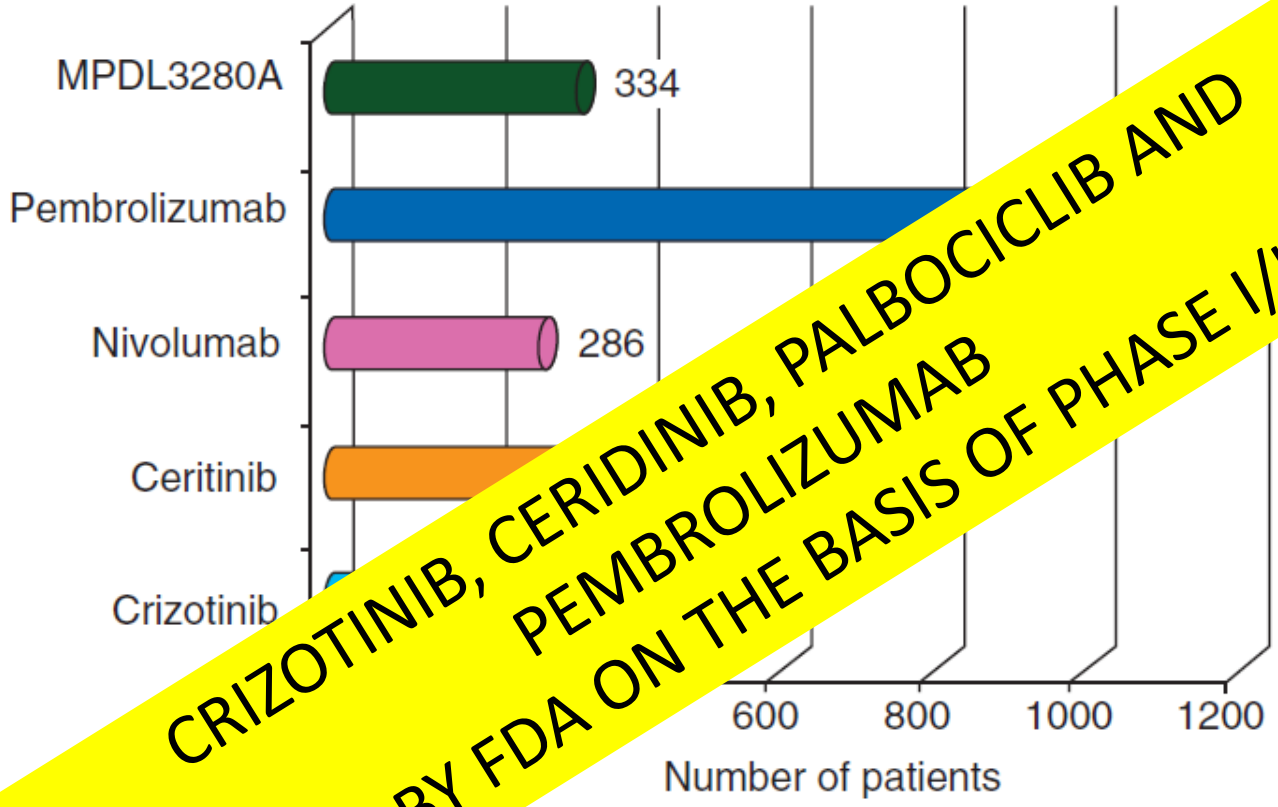
The traditional drug development paradigm

Phase I	Phase II	Phase III
Safety	Efficacy in selected tumors	Meaningful benefit in a randomized setting against existing standard
Tolerability	ORR	OS
Pharmacokinetics	TTP	
Pharmacodynamics	PFS	
Preliminary antitumor activity		

The current drug development paradigm

Proof of mechanism	Proof of concept	
	Early	Late
Safety, tolerability, on target and off target effects	Predictive biomarkers explored	Predictive biomarkers confirmed
Preliminary antitumor activity	Antitumor activity seen using surrogate endpoints	Proof of concept using a validated clinical endpoint
Evidence of target engagement in valid pharmacodynamic biomarkers	ORR TTP PFS	OS

New trend in Oncology Drug development



CRIZOTINIB, CERIDINIB, PALBOCICLIB AND PEMBROLIZUMAB APPROVED BY FDA ON THE BASIS OF PHASE I/II TRIALS

F ...patients enrolled in recent phase 1 trials having led to con... ...oval or breakthrough designations (based on www.

Postel-Vinay S Annals of Oncology 2014

Neoadjuvant Trials

Newly diagnosed pt
Tumor in place

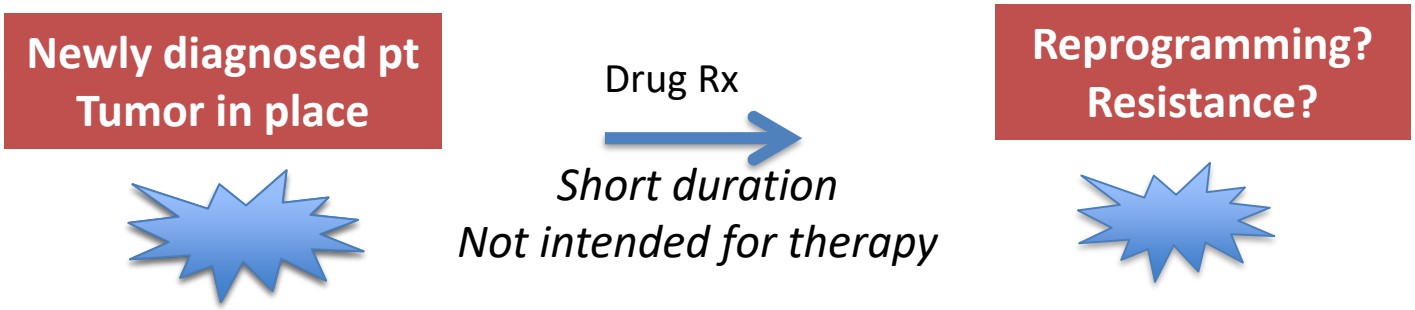
DRUG RX

Therapeutic intent and duration

Post-treatment clinical and correlative data

- Good ☺:
  - Small, fast
  - Pick-a-winner
  - pCR is a good surrogate endpoint (FDA registrational option)
  - DFS/OS can be collected in same cohort
- Bad ☹:
  - pCR only validated endpoint. Irrelevant in many (ER+)
  - Quantitative relationship pCR to DFS/OS not established
    - Trials underpowered for these endpoints
  - Macromet = micromet?
  - Drugs must be well known

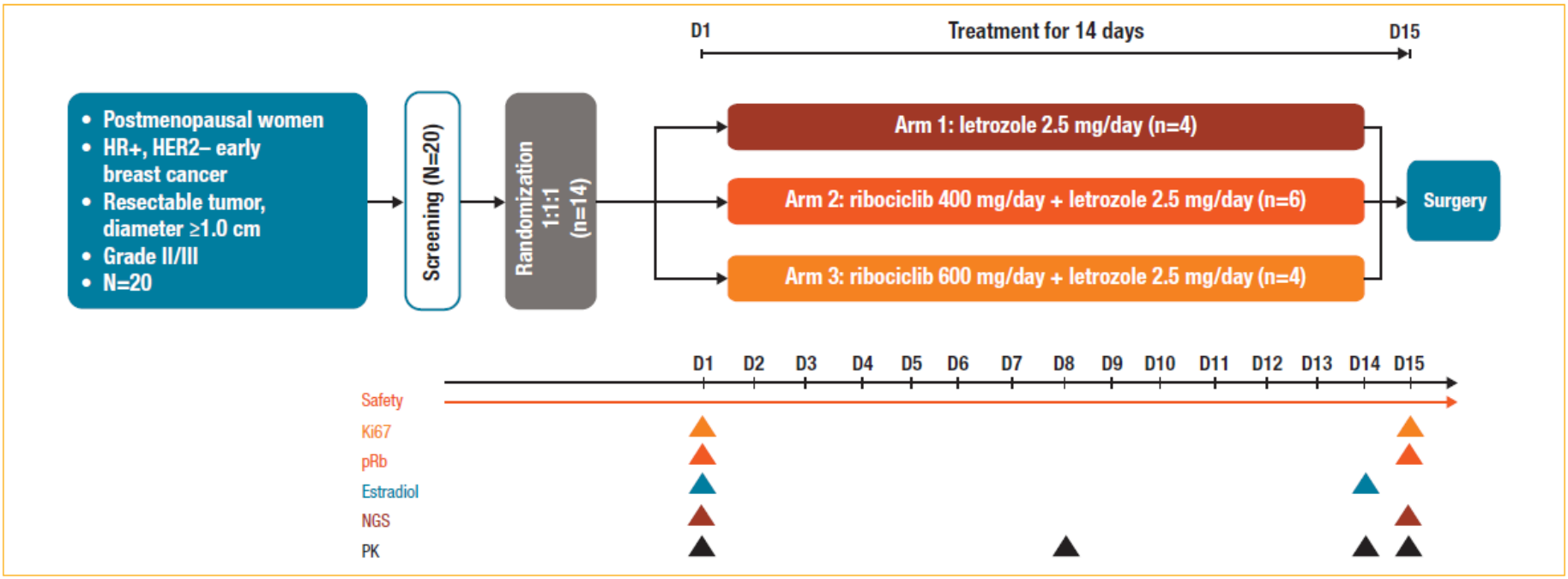
"Window of Opportunity" Trials



- Good for:
  - Discovery
  - Proof of principle (e.g. Johnson presentation)
- Bad for:
  - Unknown agents
  - ? Testing combinatorial strategies
    - Doses?
    - Toxicity issues

These contribute to scientific knowledge and therapeutic hypotheses, not clinical care

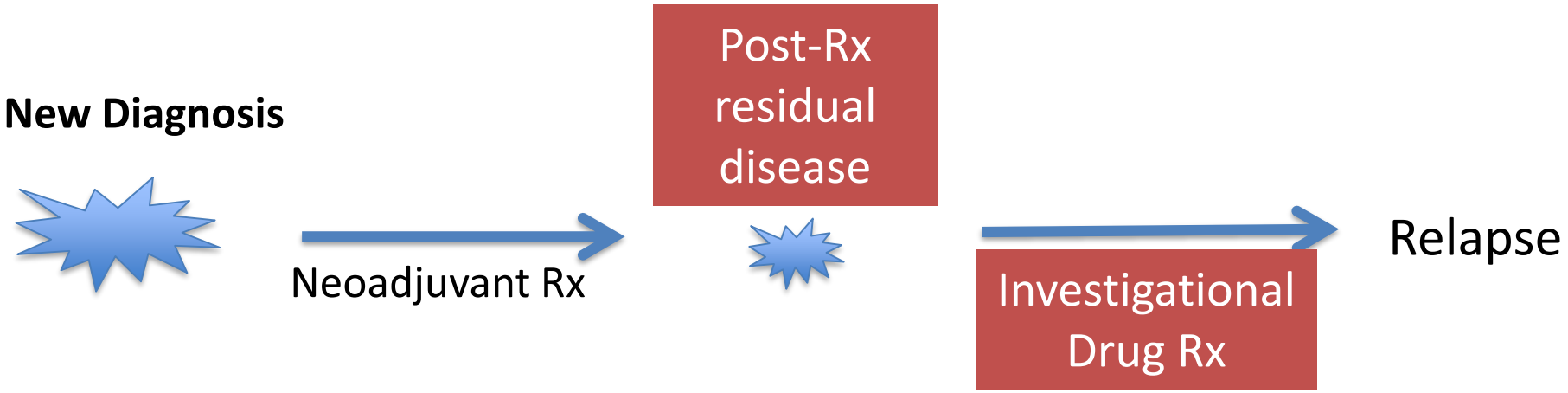
“Window of Opportunity” Trials: Monaleesa-1



D, Day; ER+, estrogen receptor-positive; HER2–, human epidermal growth factor receptor 2-negative; NGS, next-generation sequencing; PK, pharmacokinetics; pRb, phosphorylated Rb.

G. Curigliano et al. Submitted

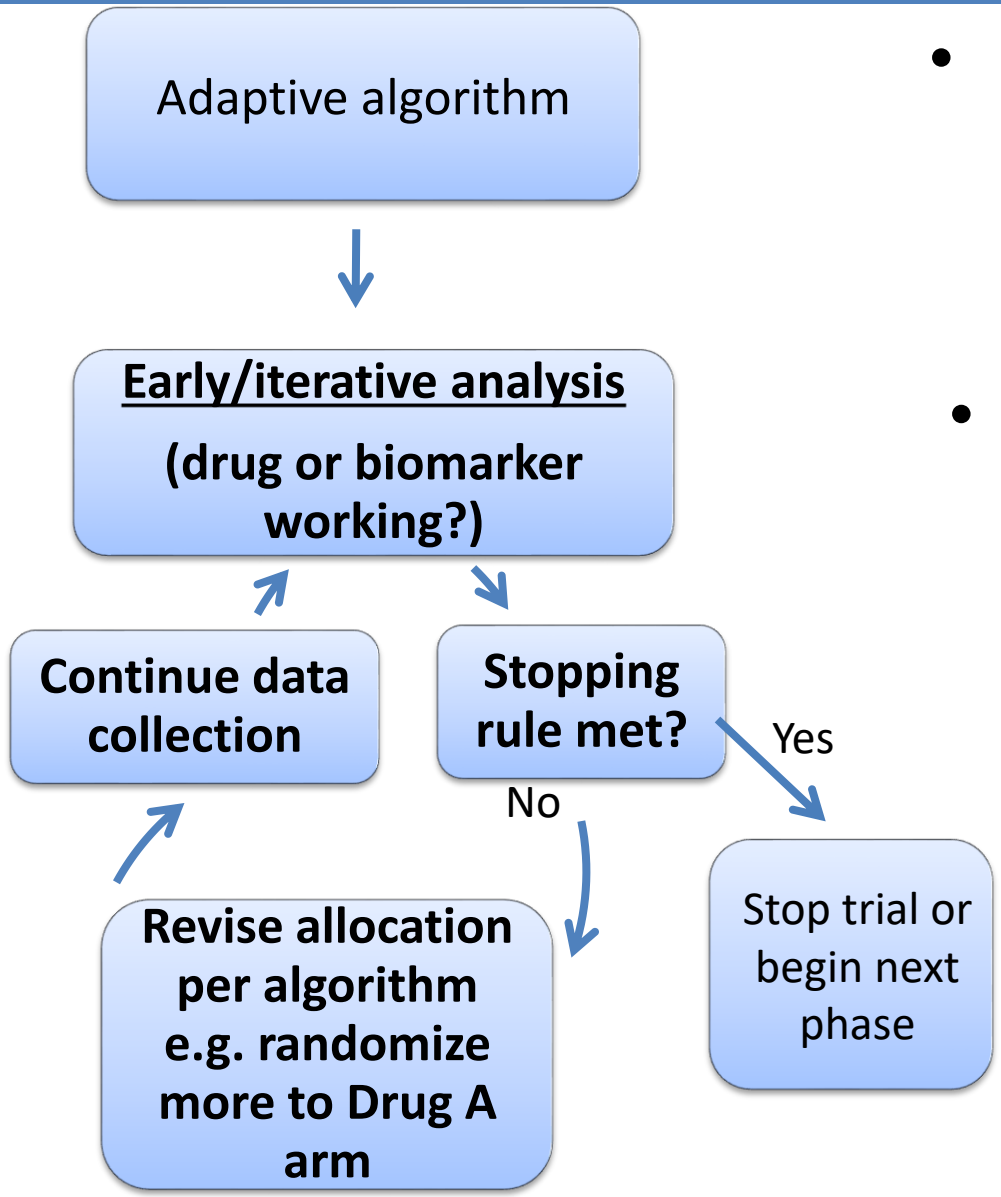
Residual Disease Trials



- Good ☺:
  - Tissue available
  - Resistant tumors
  - High risk population
- Bad ☺:
  - Adjuvant-size trial
  - Cannot assess response (event = relapse)

Example: PENELOPE – palbociclib in residual ER+ disease

Adaptive Trials

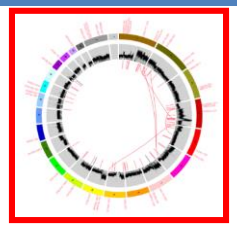


- Good ☺:
  - Pick-a-winner
  - Can adapt on drug or biomarker
  - Smaller, conserve resources
- Bad ☹:
  - Interim estimates= ↑error risk
  - Complicated! Continuously collecting response data
  - If biomarker-based
    - Must be validated.
    - Need real-time results
    - Cannot do discovery

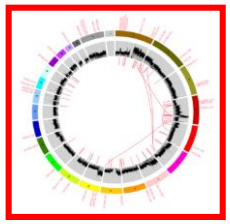
Example: ISPY2 - novel biologics in combination with chemotherapy

“Genome-Forward” Trials

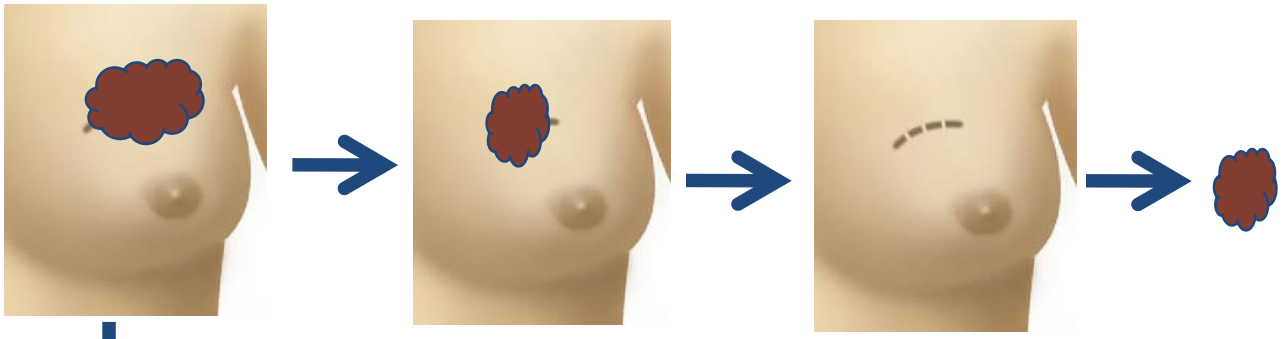
2 baseline frozen cores
70%+ tumor cellularity
DNA extracted

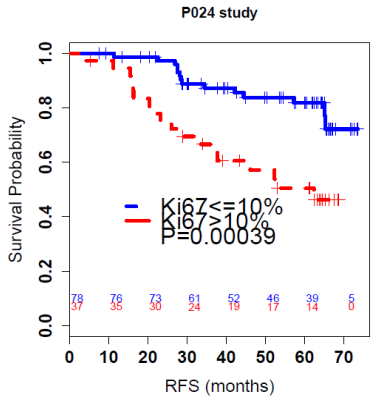


Ki67 in surgical sample
Greater that 10% = Unfavorable



16 to 18 weeks of aromatase inhibition





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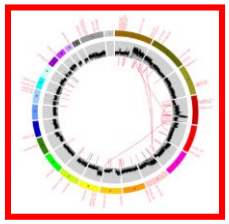
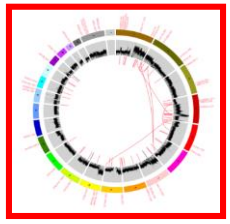


Ki67 in surgical sample
Less than10% = Favorable



BCRF, NHGRI, NCI

"Genome-Forward" Trials

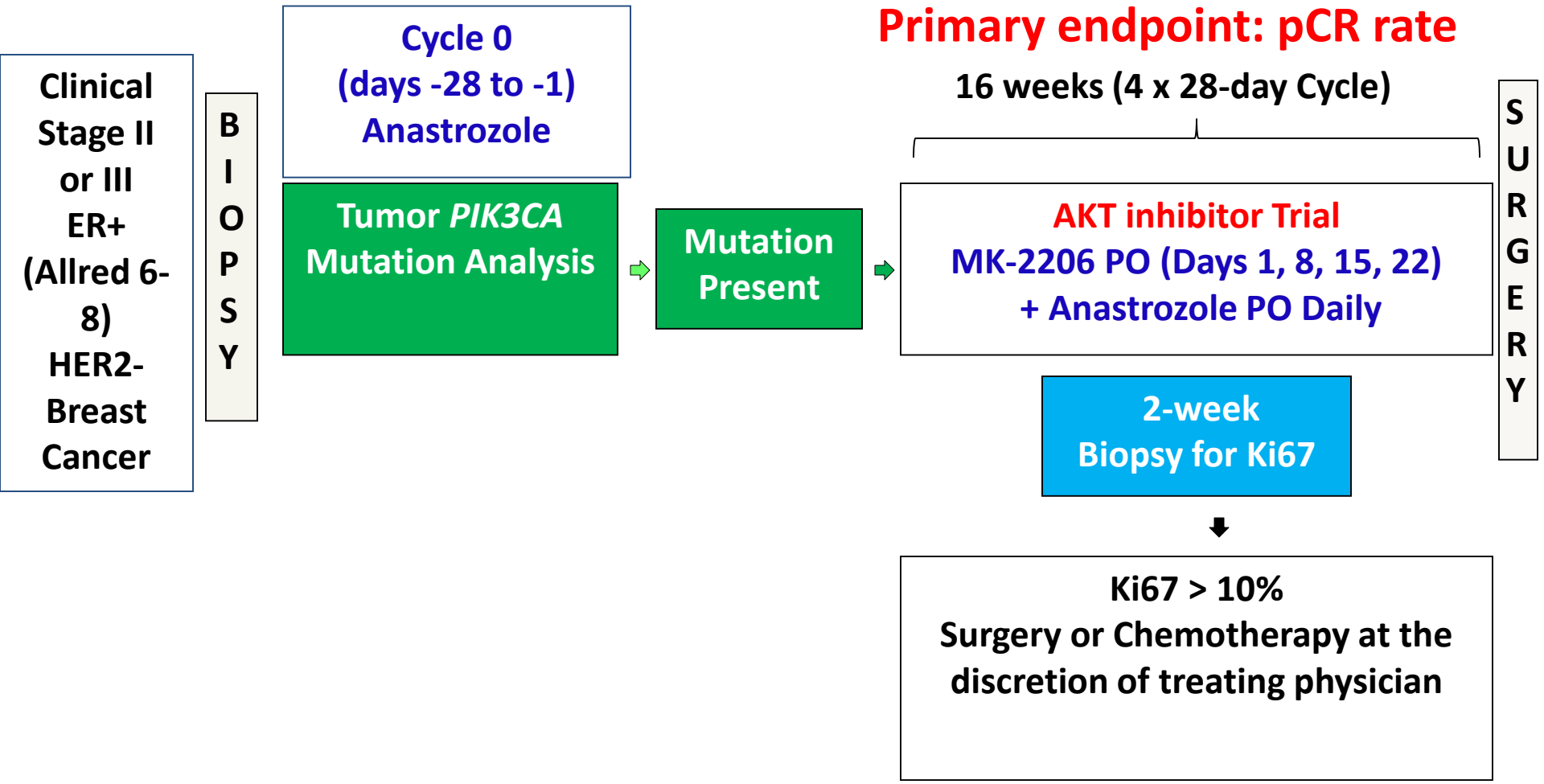
ARTICLE

doi:10.1038/nature11143

Whole-genome analysis informs breast cancer response to aromatase inhibition

Matthew J. Ellis[1,2,3]*, Li Ding[4,5]*, Dong Shen[4,5]*, Jingqin Luo[3,6], Vera J. Suman[7], John W. Wallis[4,5], Brian A. Van Tine[1], Jeremy Hoog[1], Reece J. Goiffon[8,9,10], Theodore C. Goldstein[11], Sam Ng[11], Li Lin[1], Robert Crowder[1], Jacqueline Snider[1], Karla Ballman[7], Jason Weber[1,8,12], Ken Chen[13], Daniel C. Koboldt[4,5], Cyriac Kandoth[4,5], William S. Schierding[4,5], Joshua F. McMichael[4,5], Christopher A. Miller[4,5], Charles Lu[4,5], Christopher C. Harris[4,5], Michael D. McLellan[4,5], Michael C. Wendl[4,5], Katherine DeSchryver[1], D. Craig Allred[3,14], Laura Esserman[15], Gary Unzeitig[16], Julie Margenthaler[2], G. V. Babiera[13], P. Kelly Marcom[17], J. M. Guenther[18], Marilyn Leitch[19], Kelly Hunt[13], John Olson[17], Yu Tao[6], Christopher A. Maher[1,4], Lucinda L. Fulton[4,5], Robert S. Fulton[4,5], Michelle Harrison[4,5], Ben Oberkfell[4,5], Feiyu Du[4,5], Ryan Demeter[4,5], Tammi L. Vickery[4,5], Adnan Elhammali[8,9,10], Helen Piwnica-Worms[8,12,20,21], Sandra McDonald[2,22], Mark Watson[6,14,22], David J. Dooling[4,5], David Ota[23], Li-Wei Chang[3,14], Ron Bose[2,3], Timothy J. Ley[1,2,4], David Piwnica-Worms[8,9,10,12,24], Joshua M. Stuart[11], Richard K. Wilson[2,4,5] & Elaine R. Mardis[2,4,5]

"Genome-Forward" Trials

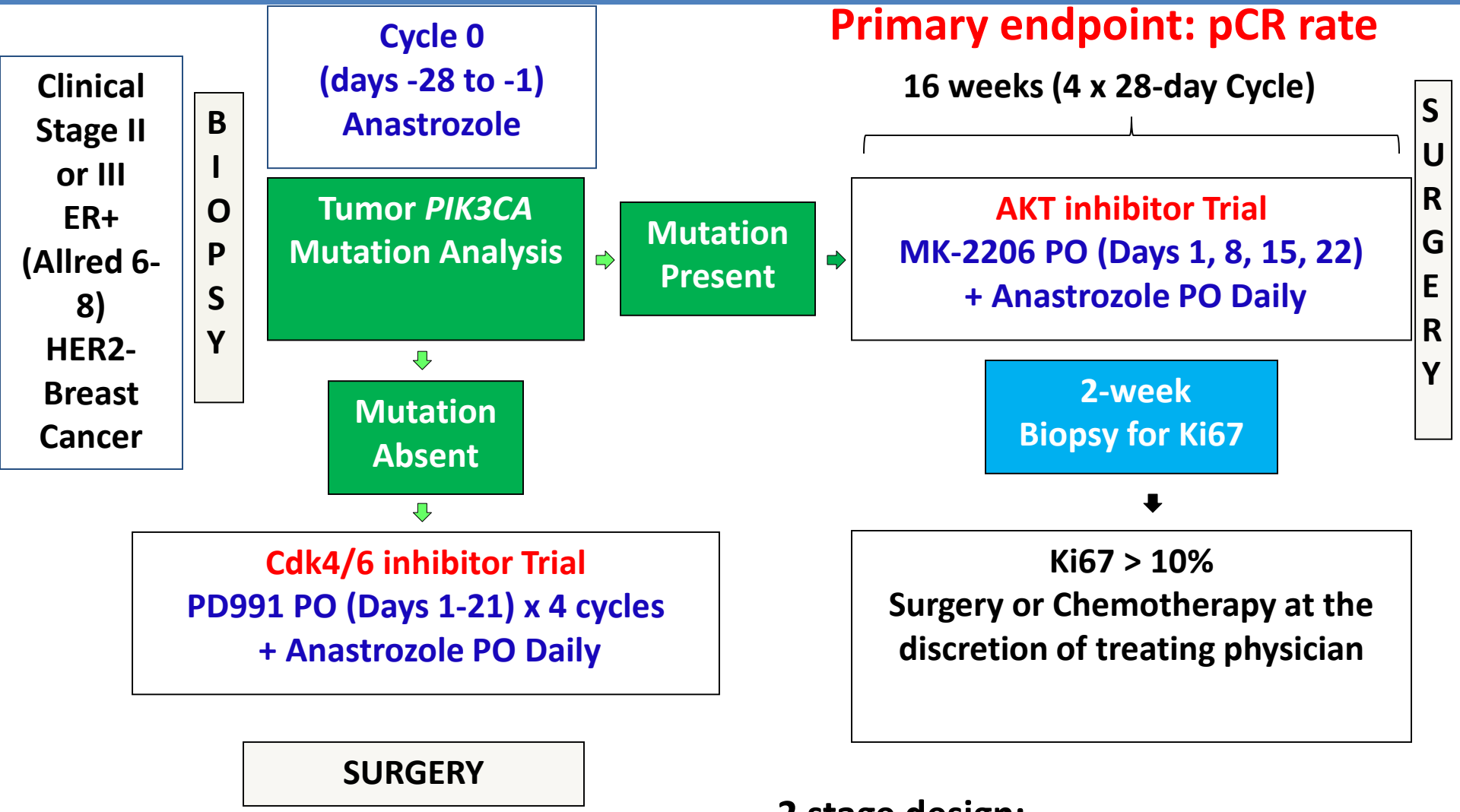


2 stage design:

1st stage: n=13

2nd stage: n=16

"Genome-Forward" Trials

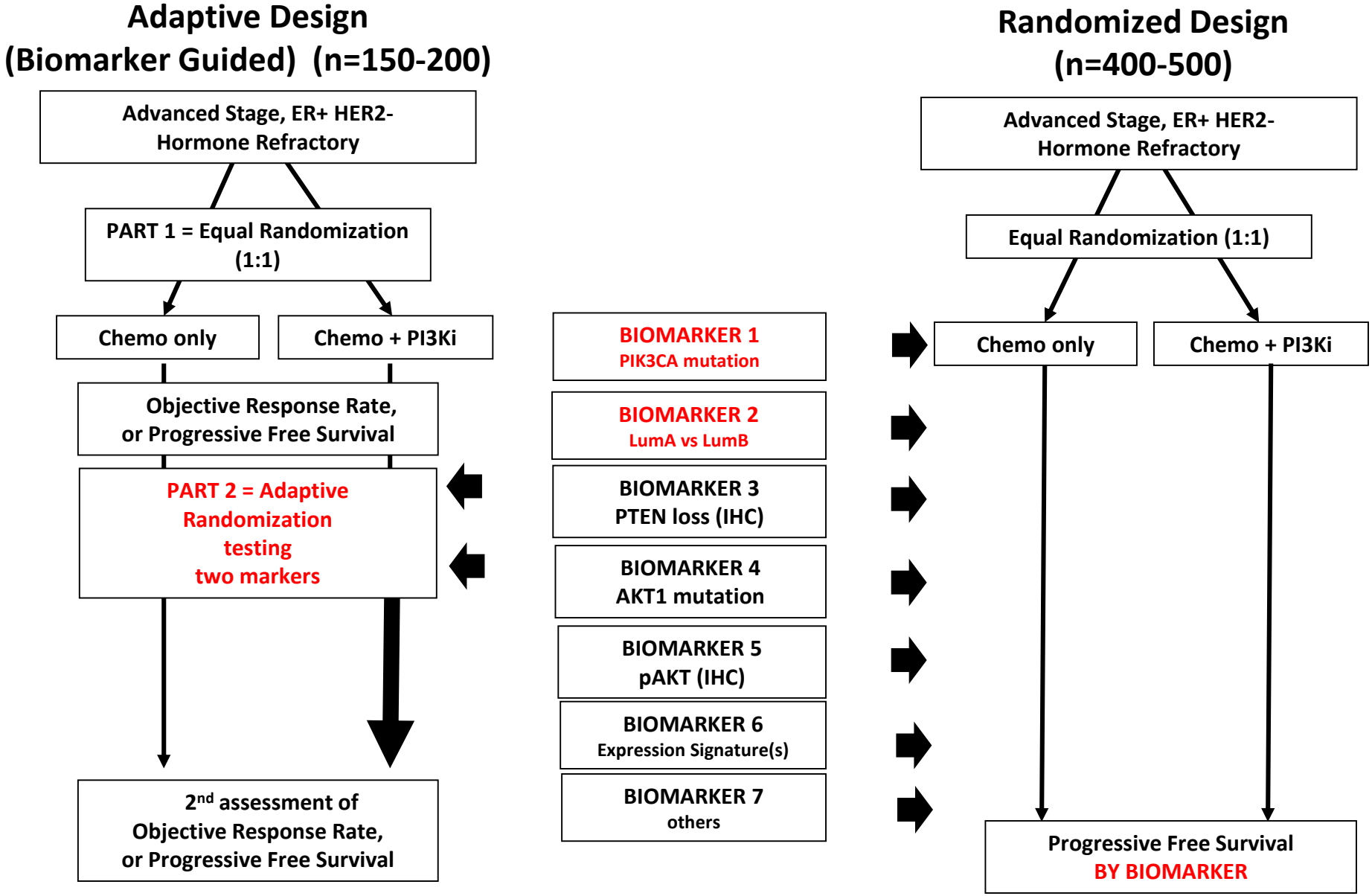


2 stage design:

1st stage: n=13

2nd stage: n=16

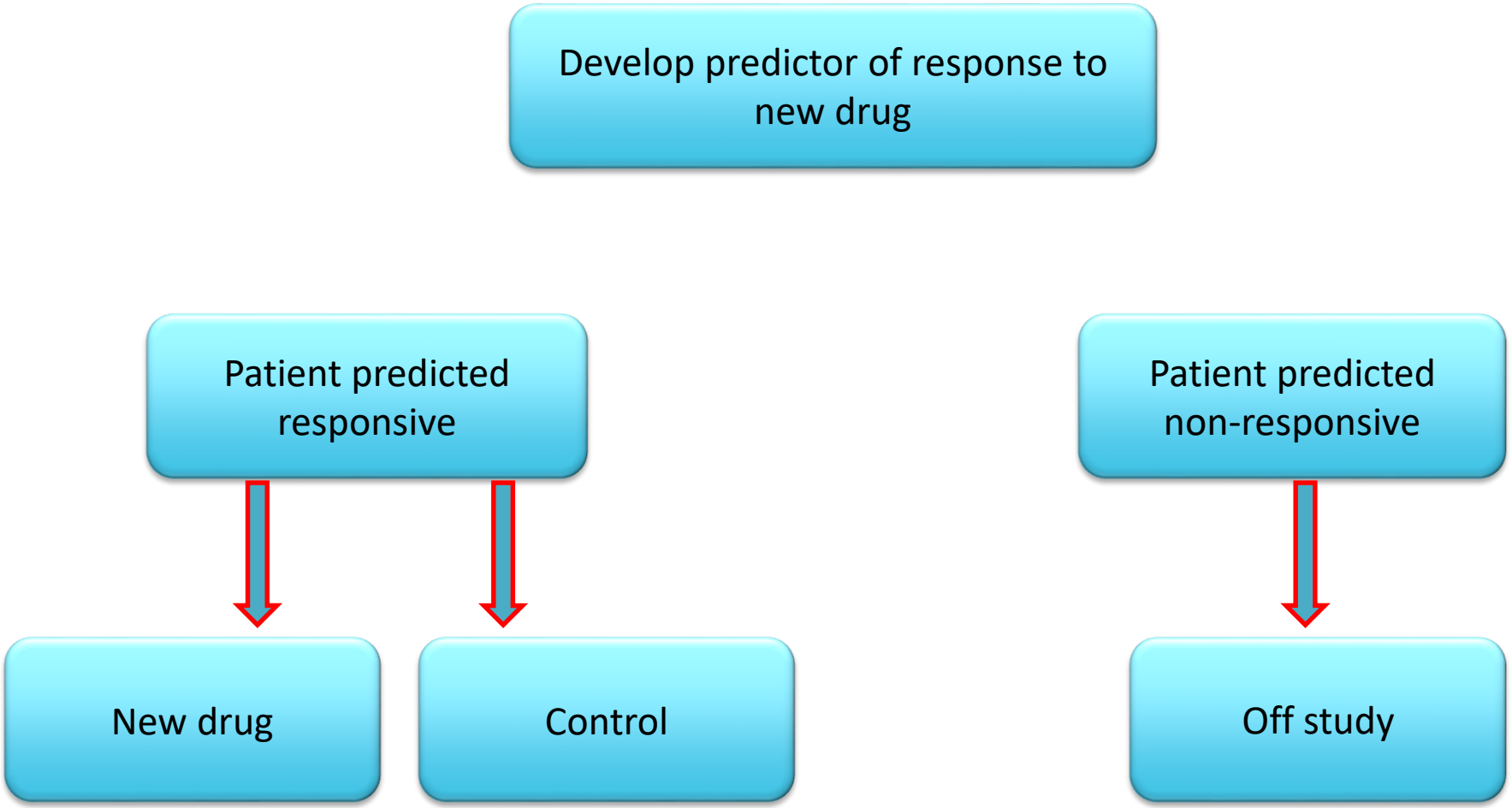
Testing A Predictive Biomarker?



Enrichment Design

- Restrict entry to the phase III trial based on the binary predictive classifier, i.e. targeted design

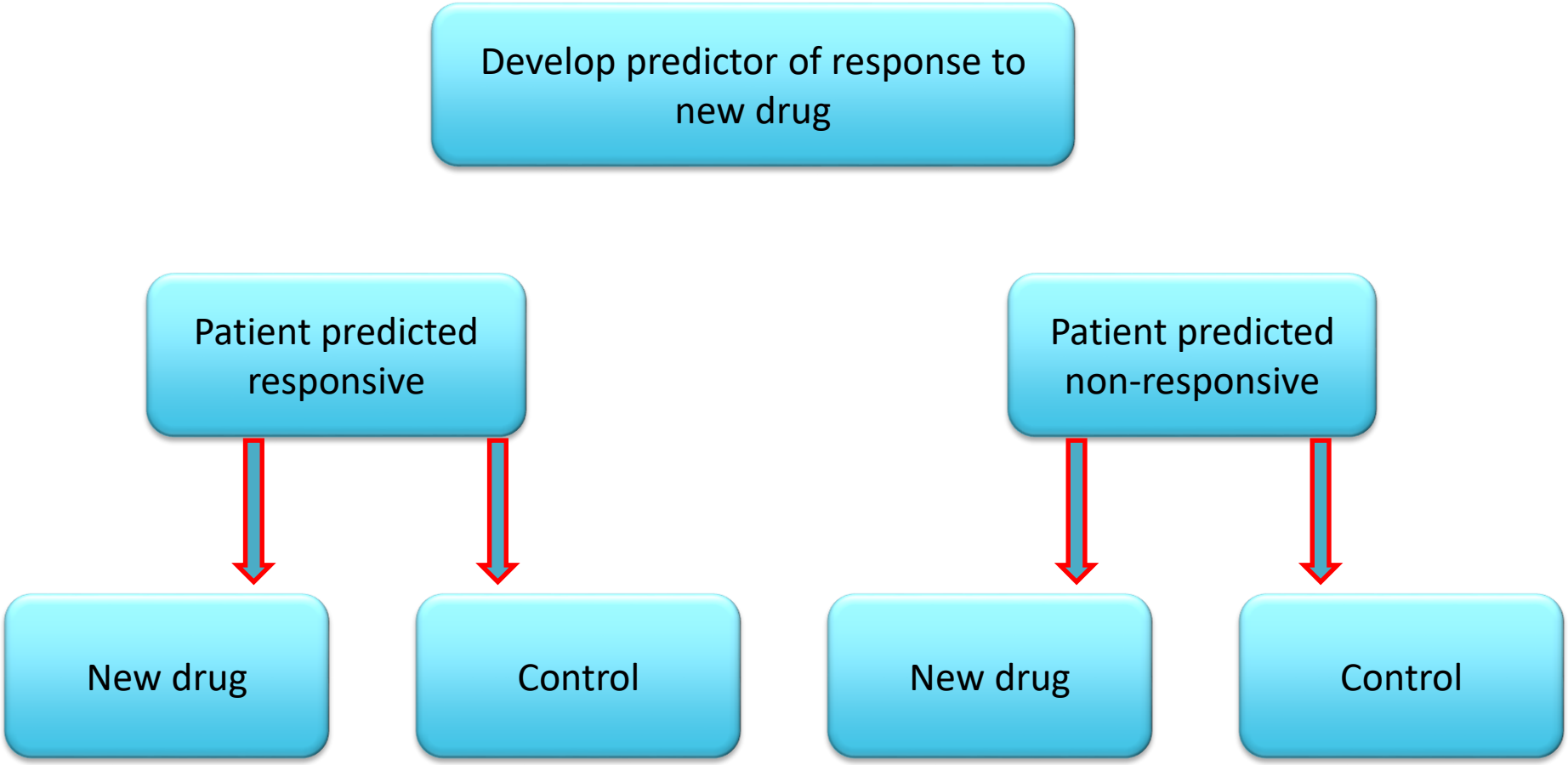
Enrichment Design



Enrichment Design

- Primarily for settings where the classifier is based on a single gene whose protein product is the target of the drug
  - eg trastuzumab
- Analytical validation, biological rationale and phase II data provide basis for regulatory approval of the test
- Phase III study focused on test + patients to provide data for approving the drug

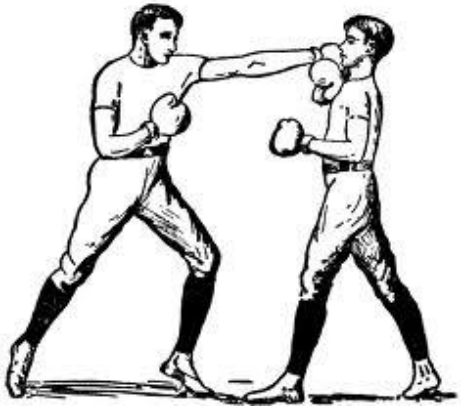
Stratification design



Stratification Design

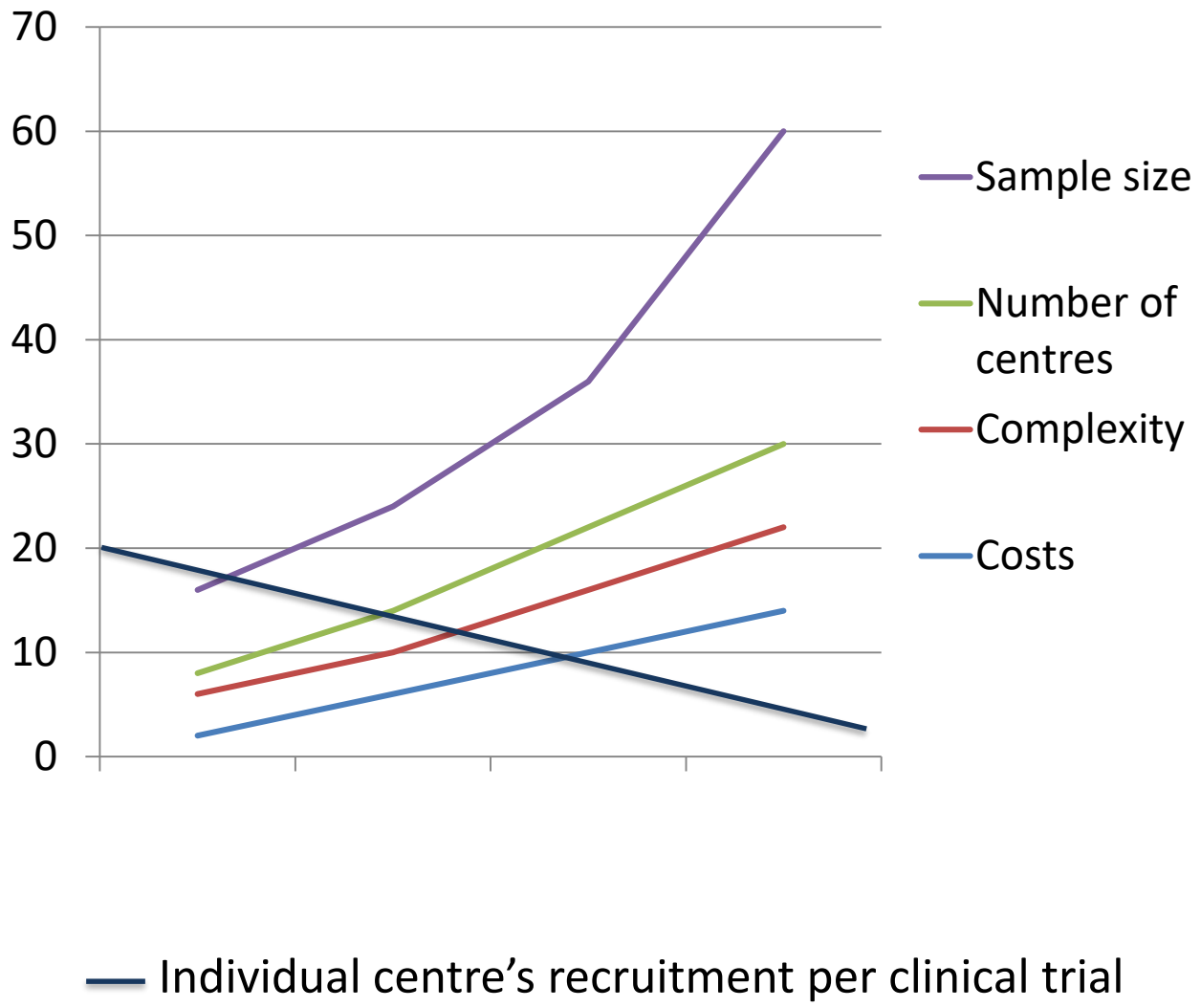
- Do not use the diagnostic to restrict eligibility, but to structure a prospective analysis plan
- Having a prospective analysis plan is essential
- "Stratifying" (balancing) the randomization is useful to ensure that all randomized patients have tissue available but is not a substitute for a prospective analysis plan
- The purpose of the study is to evaluate the new treatment overall and for the pre-defined subsets; not to modify or refine the classifier
- The purpose is not to demonstrate that repeating the classifier development process on independent data results in the same classifier

Later Stage Trials
Biomarkers: Enrich or Stratify?



- Enrich = “integral”
  - Certainty about biomarker
  - Certainty that you do not wish to test others
  - Assay clinically valid (FDA is watching you!)
- Stratify = “integrated”
  - Bigger than no-biomarker trial
  - Assay clinically valid (less scrutiny)

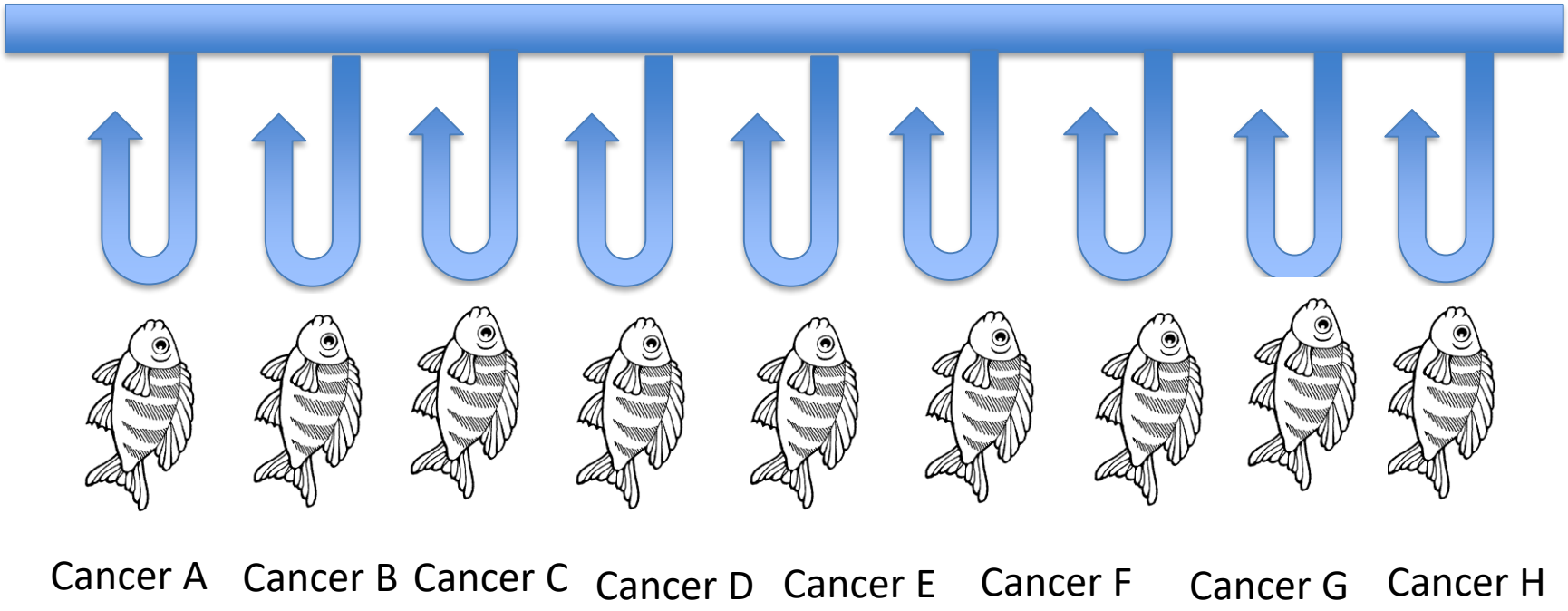
Economics and logistics of personalized medicine trials



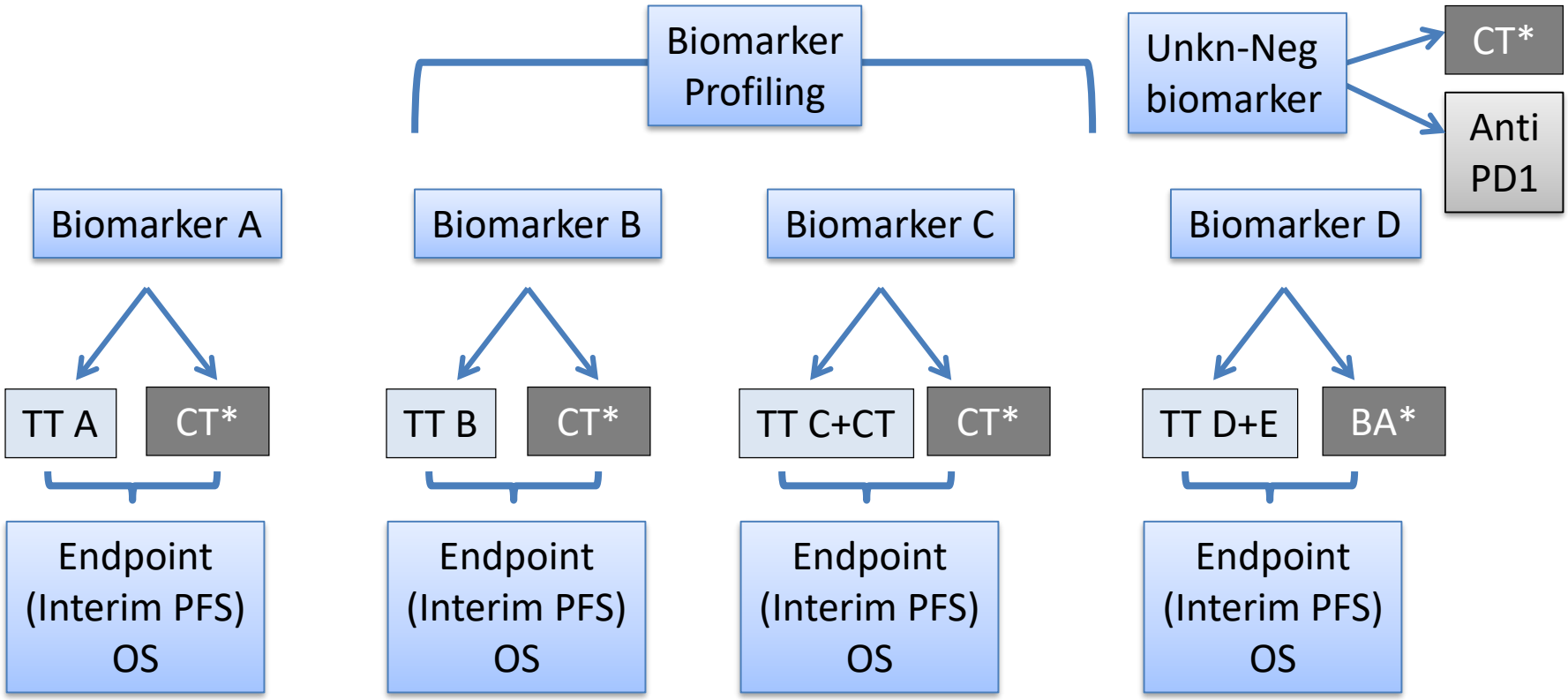
Economics and logistics of personalized medicine trials

- Each center needs to open multiple studies to be economically viable
- Greater regulatory burden (protocols emendments, SUSARs)
- Cost per case increased
- Limited experience accumulated per centre
- Collection of trial data by sponsor with sharing of toxicity data by grade and frequency on a regular basis throught protocol conduct

Single protocol: Multiple cohorts signal finding trials

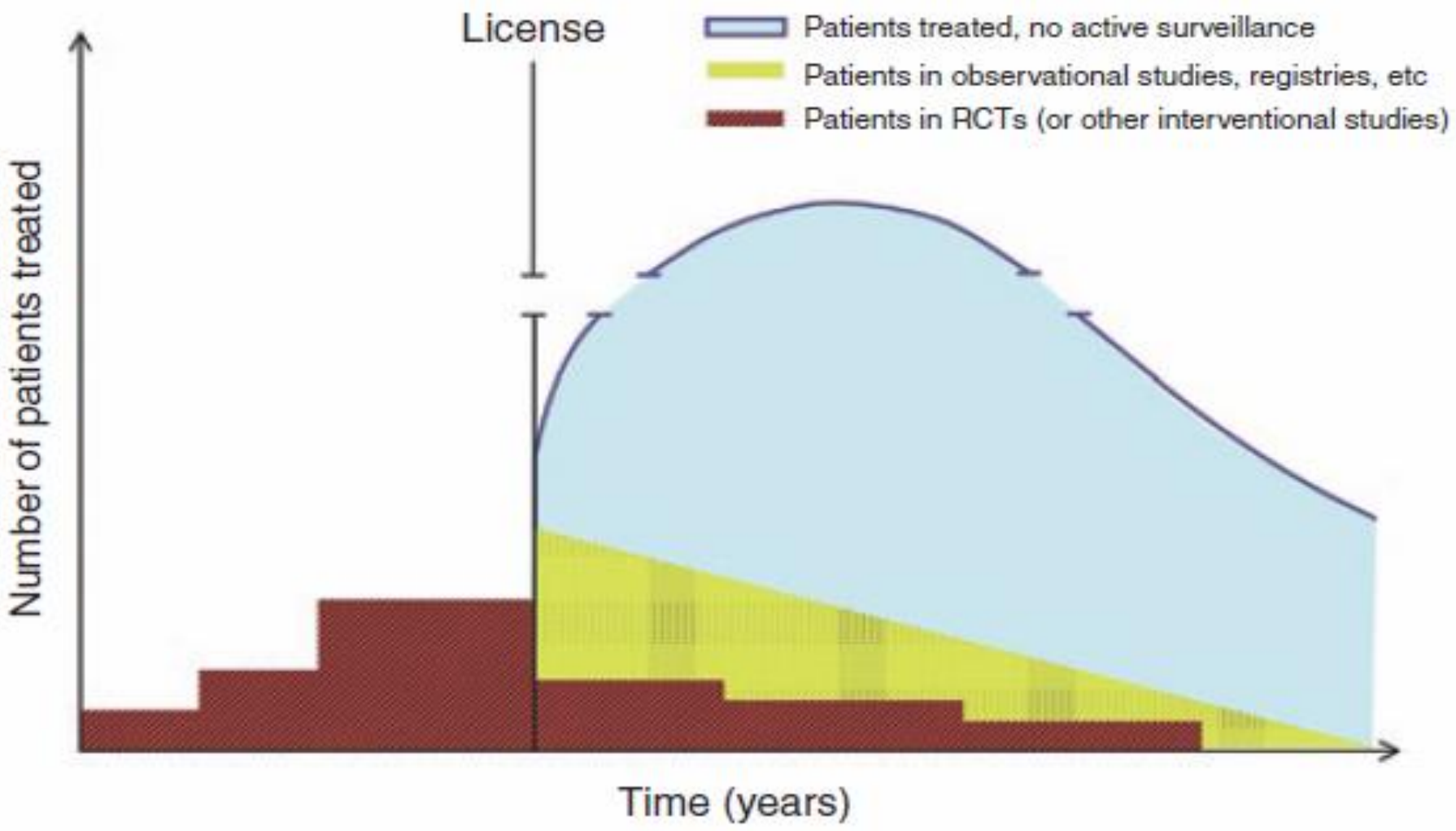


Master Protocol



TT=Targeted therapy, CT=chemotherapy; BA=Biological Agent

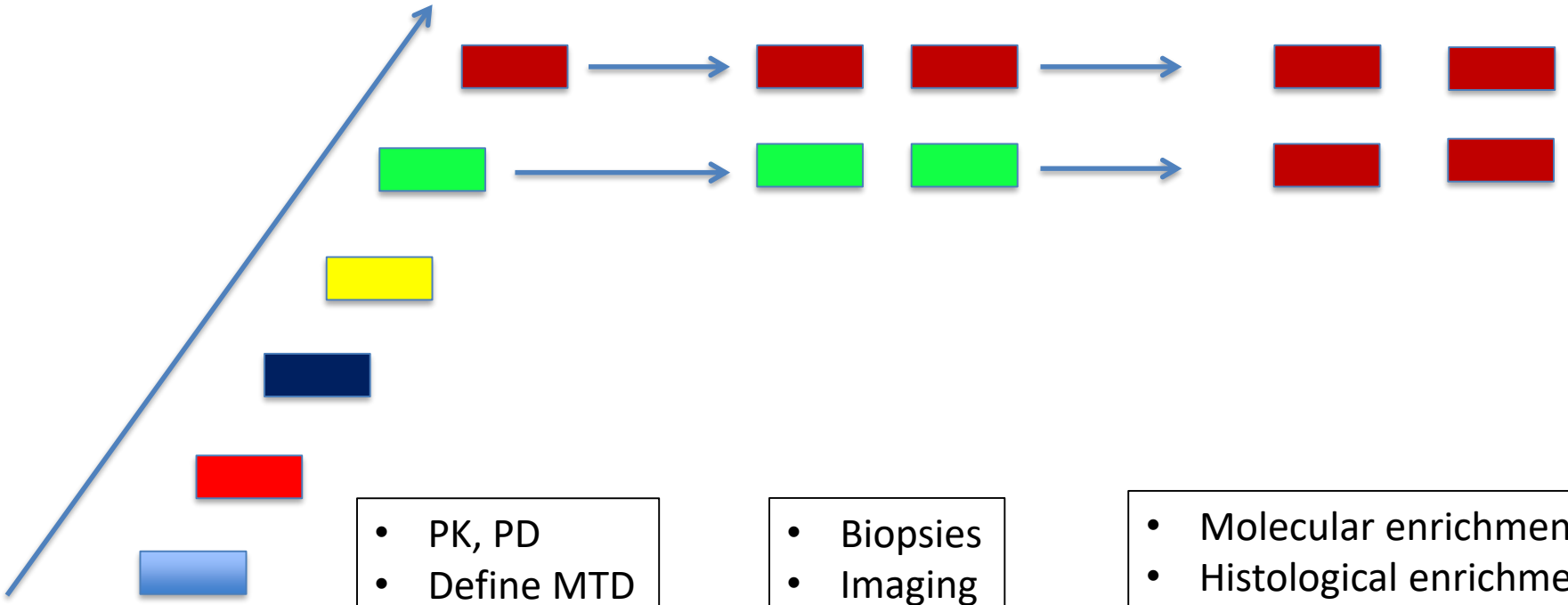
Observational data



Eichler H-G, et al: Clin. Pharm. Ther. Vol 91, 91:426–437, March, 2012

Unselected patients with expansion cohort in enriched population

Dose Escalation	Expansion cohort Pharmacodynamics Targeted tumors types



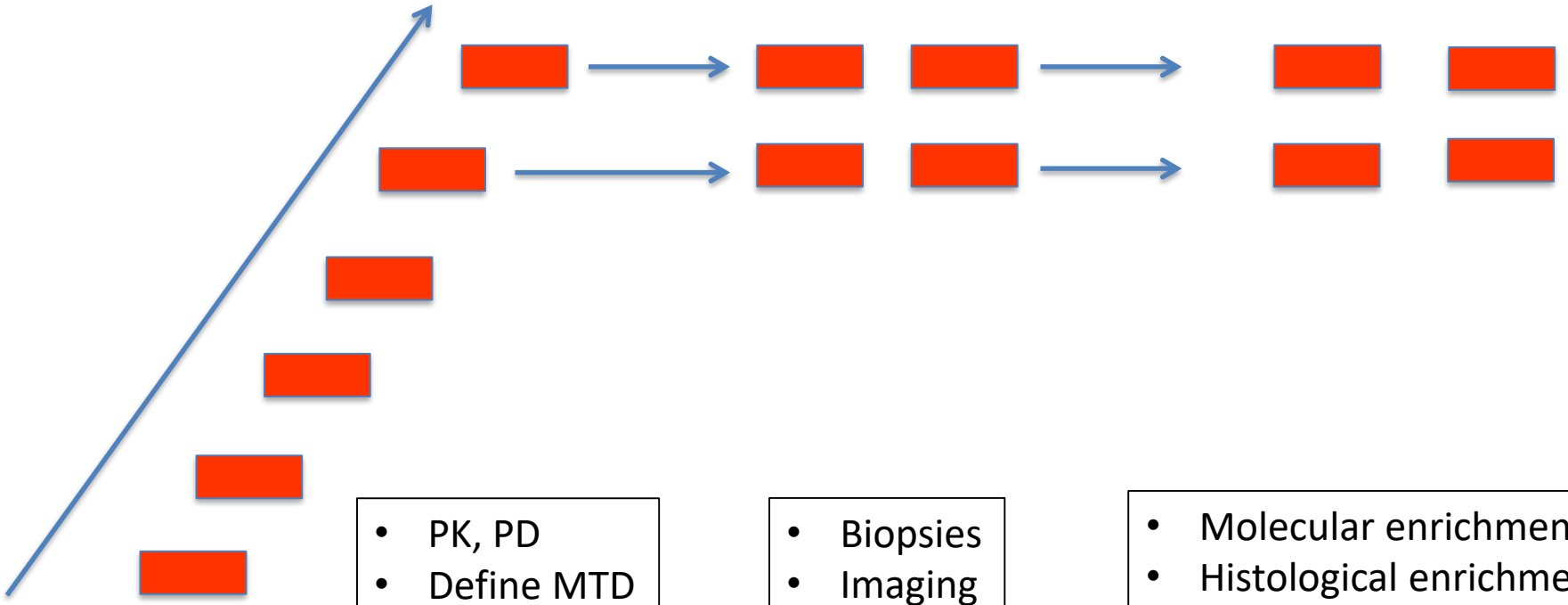
- PK, PD
- Define MTD

- Biopsies
- Imaging

- Molecular enrichment
- Histological enrichment

Molecular enriched population

Dose Escalation	Expansion cohort Pharmacodynamics Targeted tumors types

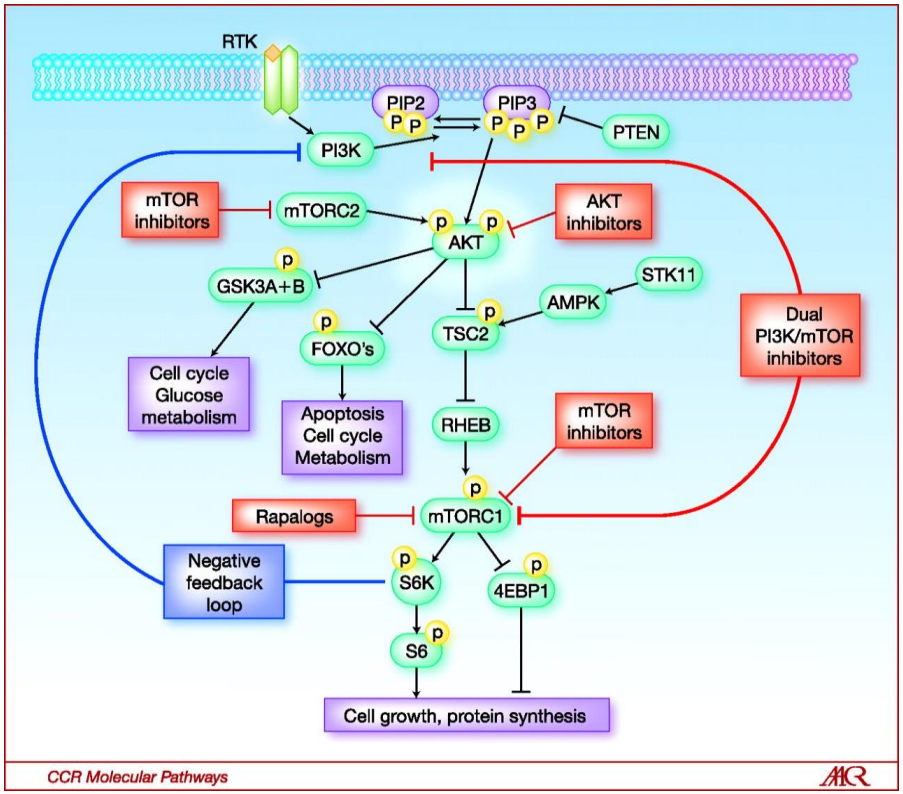


- PK, PD
- Define MTD

- Biopsies
- Imaging

- Molecular enrichment
- Histological enrichment

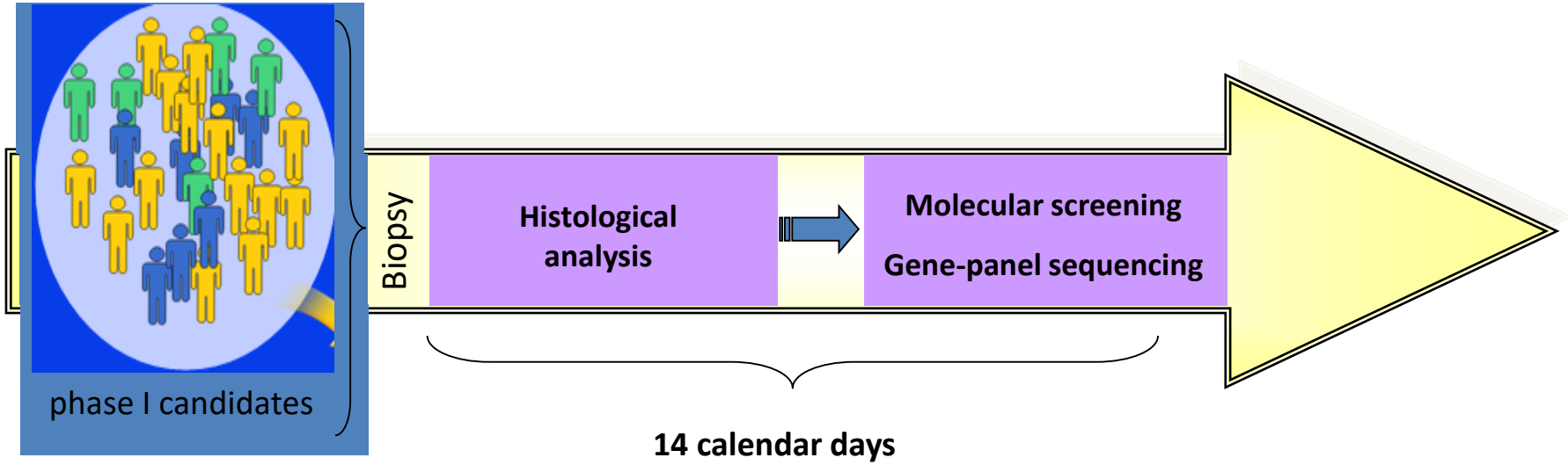
Examples



- Inclusion criteria

1. PIK3CA mutation or amplification
2. PTEN loss of function
3. cMET activation or HER2 amplification/IHC 3+
4. Endometrial cancer not selected for molecular status

Molecular enrichment



- Complex PK and PD, cardiokinetics
- Dedicated staff (research nurses, data managers, pathologists, interventional radiologists, MDs)
- Time to reaction

Biomarker-Driven Clinical Research

NNS = Number needed to screen

$$\frac{1}{\text{(fraction with biomarker X assay specificity X fraction trial-eligible X fraction giving informed consent)}}$$

Example: HER2+ in BC= 1/(0.25 X 0.9 X 0.5 X 0.5) = 17.8 patients screened/1 patient entered into trial

Example: ALKtx in NSCLC = 1/(0.05 X 0.9 X 0.5 X 0.5) = 88 patients screened/1 patient entered into trial

Example: PIK3CA mut in BC = 1/(**0.03** X 0.9 X 0.5 X 0.5) = 148 patients screened/ 1 patient entered into trial

Example: FGFR in BC = 1/(**0.08** X 0.9 X 0.5 X 0.5) = 55 patients screened/ 1 patient entered into trial

Enrichment and patient selection

Element	Challenges	Solutions
Molecular selection	Central screening • Archived tumor samples requested • Return of molecular information • Turnaround time variable Local screening • Local screening not reimbursed • Assay may not be validated in CLIA lab	Activate molecular screening programs national based or locally supported using validated multiplexed assays (funding remain an issue)
Identification of rare subset of patients	↑Screening costs while ↓ number of eligible patients with financial challenges to keep many trial open with less patients recruited	Support for screening Multiplexed screening Umbrella or basket protocols

Umbrella trials matching patients to therapies based on molecular profiles

Program name	Lead organization	Design	Histology	Indication	# Expected to accrue	Primary outcome measure(s)	Clinicaltrials.gov identifier
ALCHEMIST	US National Cancer Institute	Enrichment, research	Stage IB–IIIA lung adenocarcinoma	Screening	8,000	Feasibility, genotyping for placement on adjuvant trials	NCT02194738
	ECOG-ACRIN	R	Stage IB–IIIA adenocarcinoma of lung, with ALK fusion	Adjuvant	378	OS	NCT02201992
	ALLIANCE	R	Stage IB–IIIA adenocarcinoma of lung, with activating EGFR mutation	Adjuvant	450	OS	NCT02193282
BATTLE-2	MD Anderson	A–R	NSCLC	Metastatic	450	8-Week DCR	NCT01248247
FOCUS 4	Cancer Research UK	R	Colorectal	Metastatic	Variable (maximum 2,329)	PFS	EudraCT# 2012-005111-12 (37)

Umbrella trials matching patients to therapies based on molecular profiles

Program name	Lead organization	Design	Histology	Indication	# Expected to accrue	Primary outcome measure(s)	Clinicaltrials.gov identifier
GEMM	Yale University	R	Advanced non-V600–mutated metastatic melanoma	Metastatic	96	BORR	NCT02094872
ISPY-2	**Quantum Leap Healthcare Collaborative**	**A–R**	**Locally advanced breast cancer**	**Neo-Adjuvant**	**800**	**pCR**	**NCT01042379**
LUNG-MAP	SWOG and NCTN	R	Squamous	Metastatic	10,000 (screening)	PFS	NCT02154490
SAFIR-02 breast	**UNICANCER**	**R**	**Metastatic non-HER2^{+} breast cancer**	**Metastatic**	**400 (screening) 210 (randomized)**	**PFS**	**NCT02299999**
SAFIR-02 lung	UNICANCER	R	NSCLC	Metastatic	650 (screening) + 220 (treatment)	PFS	NCT02117167

Basket trials matching patients to therapies based on molecular profiles

Program name	Lead organization	Design	Histology	Indication	# Expected to accrue	Primary outcome measure(s)	Clinicaltrials.gov identifier
CREATE	EORTC	NR	ALK/MET activated advanced solid tumors	Metastatic	582	ORR	NCT01524926
IMPACT II	MD Anderson	R	Advanced solid tumors	Metastatic	1,362	PFS	NCT02152254
My Pathway	Genentech	NR	Advanced solid tumors	Metastatic	500	ORR	NCT02091141
SHIVA	Institut Curie	R	Advanced solid tumors	Metastatic	1,000	PFS	NCT01771458

Basket trials matching patients to therapies based on molecular profiles

Program name	Lead organization	Design	Histology	Indication	# Expected to accrue	Primary outcome measure(s)	Clinicaltrials.gov identifier
SIGNATURE	Novartis	NR	PI3K-activated solid tumors and/or hematologic malignancies	Metastatic	145	CBR	NCT01833169
			$BRAF^{V600}$-mutated solid tumors and/or hematologic malignancies	Metastatic	12	CBR	NCT01981187
			PTCH1 or SMO mutated	Metastatic	10	CBR	NCT02002689
			RAS/RAF/MEK activated	Metastatic	110	CBR	NCT01885195
			CDK4/6 pathway activated	Metastatic	90	CBR	NCT02187783
			FGFR mutated	Metastatic	70	CBR	NCT02160041

Basket trials matching patients to therapies based on molecular profiles

Program name	Lead organization	Design	Histology	Indication	# Expected to accrue	Primary outcome measure(s)	Clinicaltrials.gov identifier
SIGNATURE	Novartis	NR	ALK or ROS1 mutated solid tumors and/or hematologic malignancies	Metastatic	70	CBR	NCT02186821
			Solid tumors and/or hematologic malignancies with aberrations in FGFR, PDGFR, VEGF, cKIT, FLT3, CSFR1, Trk, or RET	Metastatic	80	CBR	NCT01831726

Basket trials matching patients to therapies based on molecular profiles

Program name	Lead organization	Design	Histology	Indication	# Expected to accrue	Primary outcome measure(s)	Clinicaltrials.gov identifier
Dabrafenib and trametinib in BRAFV600E-mutated rare cancers	GlaxoSmithKline	NR	BRAFV600E mutation–positive tumor: including anaplastic thyroid cancer, biliary tract cancer, gastrointestinal stromal tumor	Advanced disease without standard treatment options	135	ORR	NCT02034110
			Nonseminomatous germ cell tumor/nonseminomatous germ cell tumor, hairy cell leukemia, WHO grade 1 or 2 glioma, WHO grade 3 or 4 (high-grade) glioma, multiple myeloma, and adenocarcinoma of the small intestine	Advanced disease without standard treatment options		ORR	

Basket trials matching patients to therapies based on molecular profiles

Program name	Lead organization	Design	Histology	Indication	# Expected to accrue	Primary outcome measure(s)	Clinicaltrials.gov identifier
SPECTA	EORTC	NR	Advanced colorectal cancer	Metastatic	2,600	TMA (screening)	NCT01723969
			Thoracic tumors	Any stage	3,500	TMA (screening)	NCT02214134
			Brain neoplasms	Any stage	300	TMA (screening)	NCT02307604
VE-BASKET	Hoffmann-La Roche	NR	$BRAF^{V600E}$-mutated advanced solid tumors	Metastatic	160	ORR	NCT01524978

Basket trials matching patients to therapies based on molecular profiles

Program name	Lead organization	Design	Histology	Indication	# Expected to accrue	Primary outcome measure(s)	Clinicaltrials.gov identifier
WINTHER	WIN Consortium	NR	Advanced solid tumors	Metastatic	200	PFS	NCT01856296

Basket trials matching patients to therapies based on molecular profiles

Program name	Lead organization	Design	Histology	Indication	# Expected to accrue	Primary outcome measure(s)	Clinicaltrials.gov identifier
NCI-MATCH	NCI	NR	Advanced solid tumors and lymphomas	Metastatic	3,000	ORR	NCT02465060
	ECOG-ACRIN and NCTN						
NCI-MPACT	NCI	R	Advanced solid tumors	Metastatic	700	ORR or PFS	NCT01827384

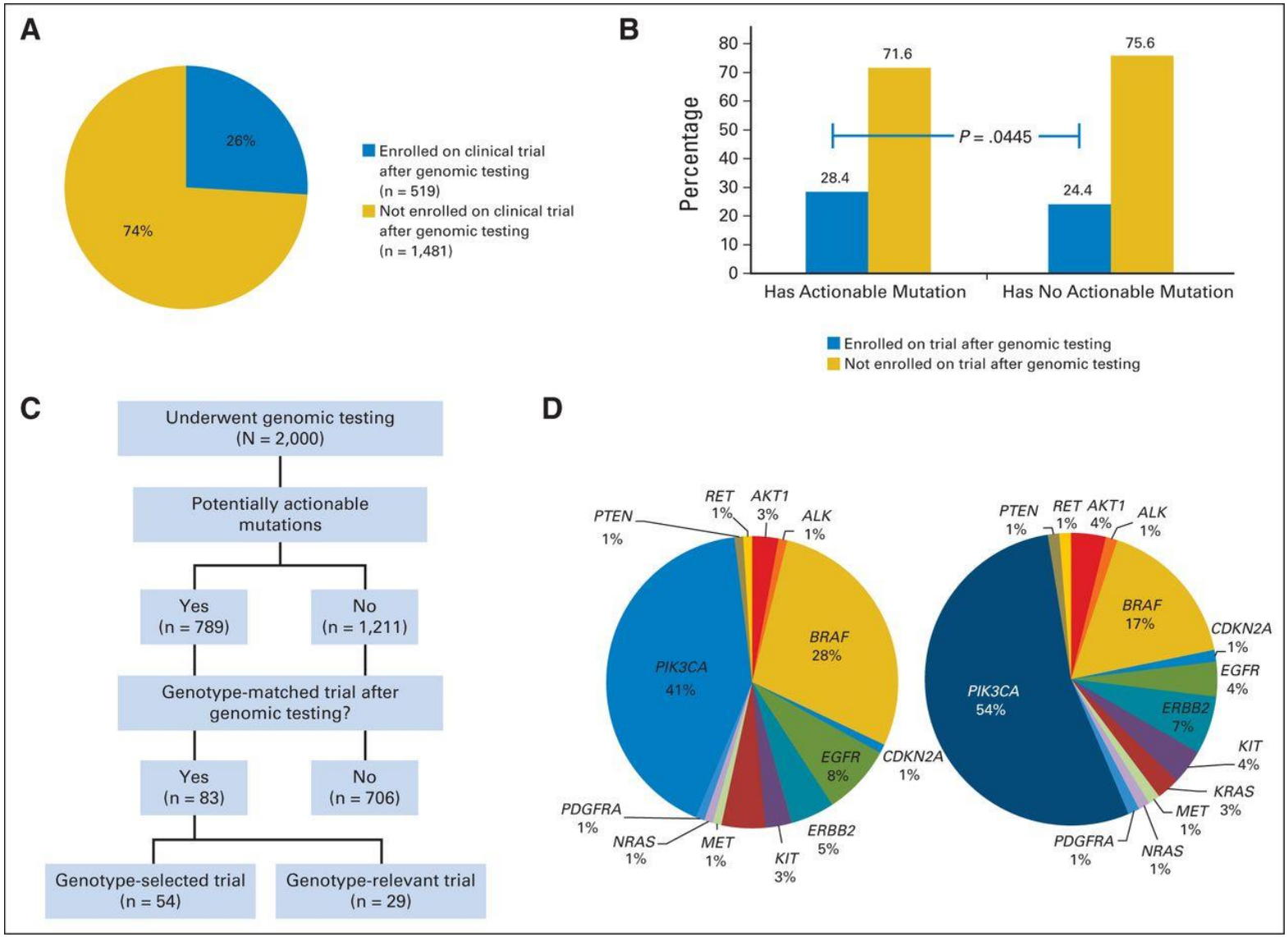
Enrollment in Therapeutic Trials

Tumor Type	Patients Accrued	Patients Profiled	% profiled enrolled on trials	% profiled enrolled on genotype matched trials
Gynecological	430	405	20%	5%
Breast	341	319	13%	6%
Lung	339	256	16%	7%
Colorectal	326	299	13%	6%
Pancreatobiliary	151	104	9%	1%
Upper Aerodigestive	115	102	8%	2%
Genitourinary	92	74	12%	5%
Other	99	81	21%	2%
Totals	**1893**	**1640**	**15%**	**5%**

*median follow-up 18 months

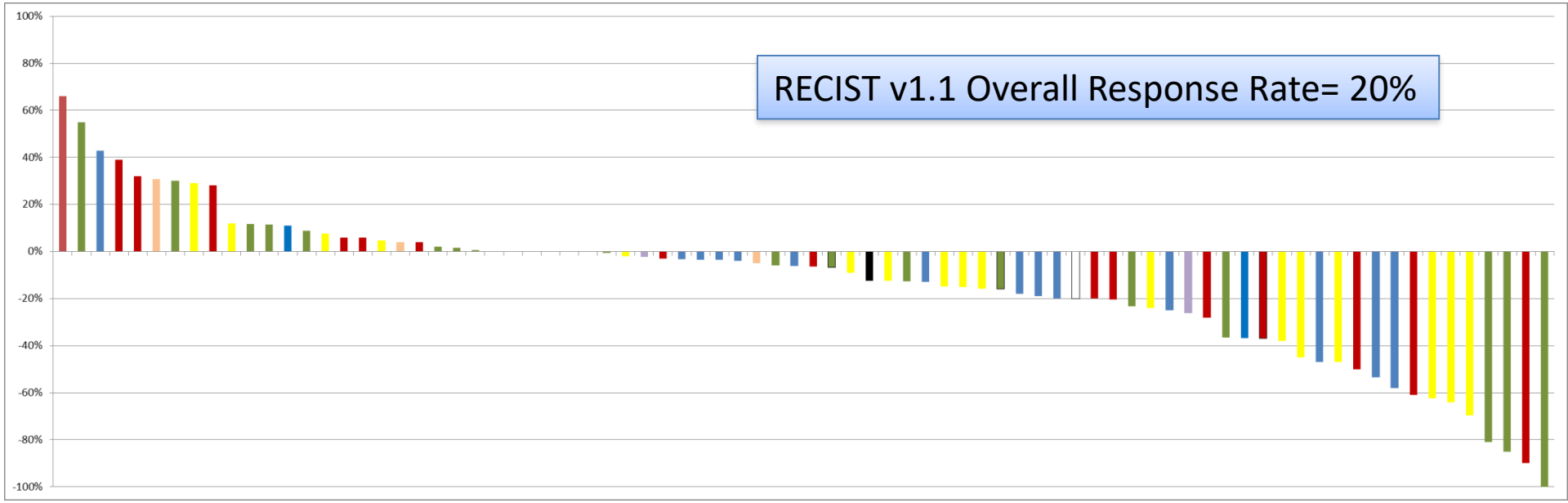
P. Bedard et al. AACR 2015

Enrollment in Therapeutic Trials



Funda Meric-Bernstam et al. JCO 2015;33:2753-2762

Best Tumor Shrinkage of Patients Enrolled in Genotype-Matched Trials



Disease Sites	Genotype Matched Trials	Most Common Mutations
Breast	22	PIK3CA (18)
Colorectal	18	BRAF (8), KRAS (5)
Lung	21	KRAS (11), EGFR (8)
Gynecological	22	KRAS (12), PIK3CA (6)

Breast
Colorectal
Lung
Gynecological
Genitourinary
Pancreatobiliary
Upper Aerodigestive
Other

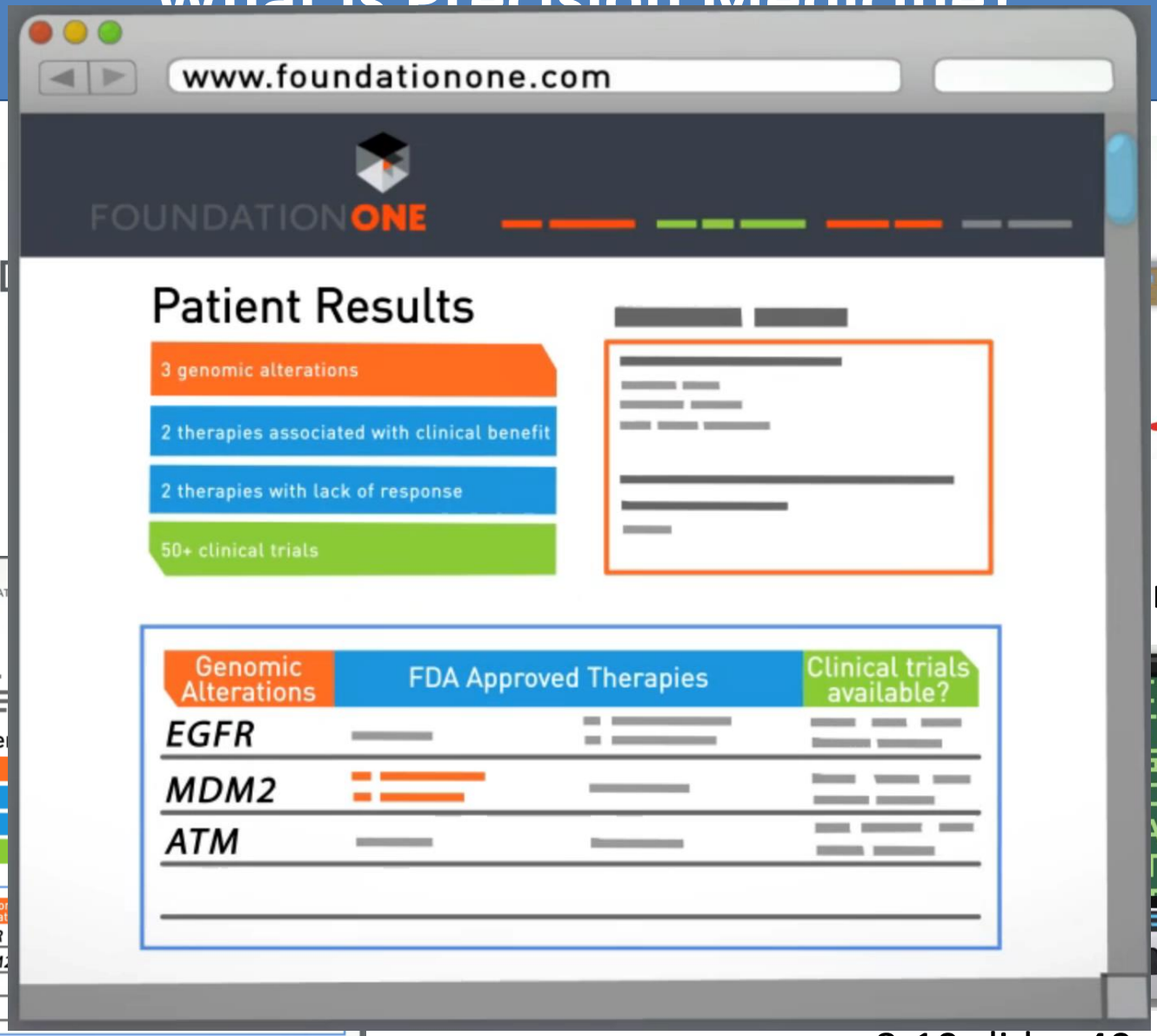
P. Bedard et al. AACR 2015

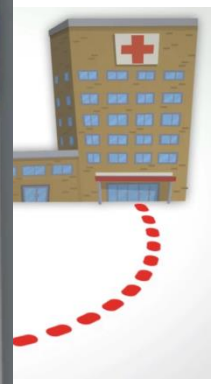
Trials in the 21st Century

- Small
- Fast (collaboration is key)
- Rational

- Careful!

What is Precision Medicine?





8-10 slides 40µm
20% tumor cells

National or institutional molecular screening programs in breast cancer and other advanced solid tumors predictive biomarker

Institution or National Program	Platform	Cancer(s)	Archival vs Biopsy	Timeframe	Additional Details
Massachusetts General Hospital	SNaP Shot	NSCLC, CRC, Melanoma, Breast	Archival	Ongoing	Includes somatic mutations in 14 oncogenes. In NSCLC, additional FISH panel for ALK rearrangements. Plan to integrate NGS technology in near future.
Dana Farber Cancer Institute	OncoMap (Sequenom)	All solid tumors	Archival	Ongoing	$43 million investment over 5 years. Currently tests ~470 mutations in 41 genes.
MD Anderson Cancer Centre	Sequenom	All	Archival	Ongoing	“T9 Program”. Customized Sequenom Panel (40+ genes) with Sanger confirmation. Plan to screen “Ten Thousand Tumors”.

National or institutional molecular screening programs in breast cancer and other advanced solid tumors predictive biomarker

Institution or National Program	Platform	Cancer(s)	Archival vs Biopsy	Timeframe	Additional Details
Vanderbilt-Ingram Cancer Center	SNaPshot	NSCLC, melanoma, and breast	Archived	Ongoing	SNaPshot profiling of ~40 mutations in NSCLC and melanoma. Recently launched "PI3K" panel for breast cancer.
Michigan University	Illumina HiSeq	Solid Tumors	Fresh Biopsies	Ongoing	Plan to perform whole exome sequencing for 100 patients per year.
Princess Margaret Hospital	Sequenom	Breast, CRC, Ovarian, NSCLC, and phase I	Archival	1Q2012	Customized Sequenom panel (~277 mutations in 25 genes). Plan to integrate NGS technology in near future.

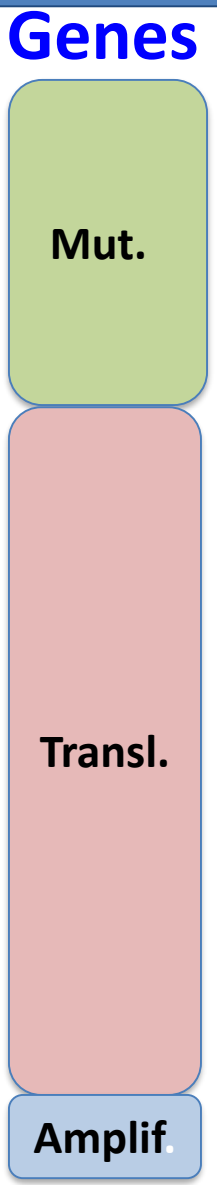
National or institutional molecular screening programs in breast cancer and other advanced solid tumors predictive biomarker

Institution or National Program	Platform	Cancer(s)	Archival vs Biopsy	Timeframe	Additional Details
Cancer Research UK	Unknown	Breast, Melanoma, Prostate, Ovarian, CRC, and NSCLC	Archival	4Q2011	Stratified Medicine Program. To include 9,000 patients in 7 cancer centres across UK.
Institut Gustav Roussy	aCGH Sanger	Breast, Phase I	Biopsy	Ongoing	MOSCATO (phase I; 600 patients) and SAFIR (breast; 400 patients)
Dutch (Amsterdam, Rotterdam, Utrecht)	Targeted exome sequencing (?HiSeq)	Phase I	Biopsy	Ongoing	1200 patients over 3 years with 2000 genes/patient

European Institute of Oncology

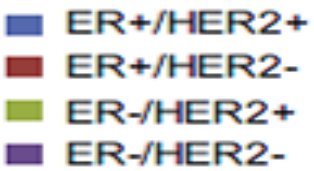
The IEO Mini-Chip

	Genes	Kb
Mutations	43	149.244,00
Translocations	91	18.200,00
Amplification	11	4.950,00
Total of Kb		172.394,00

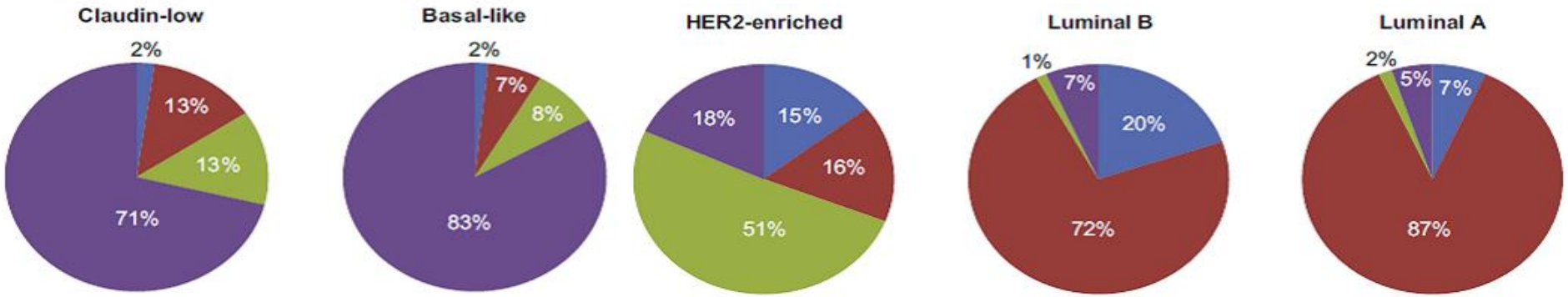


Confounding by Biologic Heterogeneity: Clinical Subsets ≠ Molecular Entities

Clinical assay:



Molecular assay:



Prat and Perou, Mol Oncol 2011

Introduces unmeasured variables into clinical trials.

Understanding Tumor Evolution

Detection of Tumor *PIK3CA* Status in Metastatic Breast Cancer Using Peripheral Blood

Michaela J. Higgins, Danijela Jelovac, Evan Barnathan, et al.

Clin Cancer Res 2012;18:3462-3469. Published OnlineFirst March 15, 2012.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Analysis of Circulating Tumor DNA to Monitor Metastatic Breast Cancer

N Engl J Med 2013;368:1199-209.
DOI: 10.1056/NEJMoa1213261

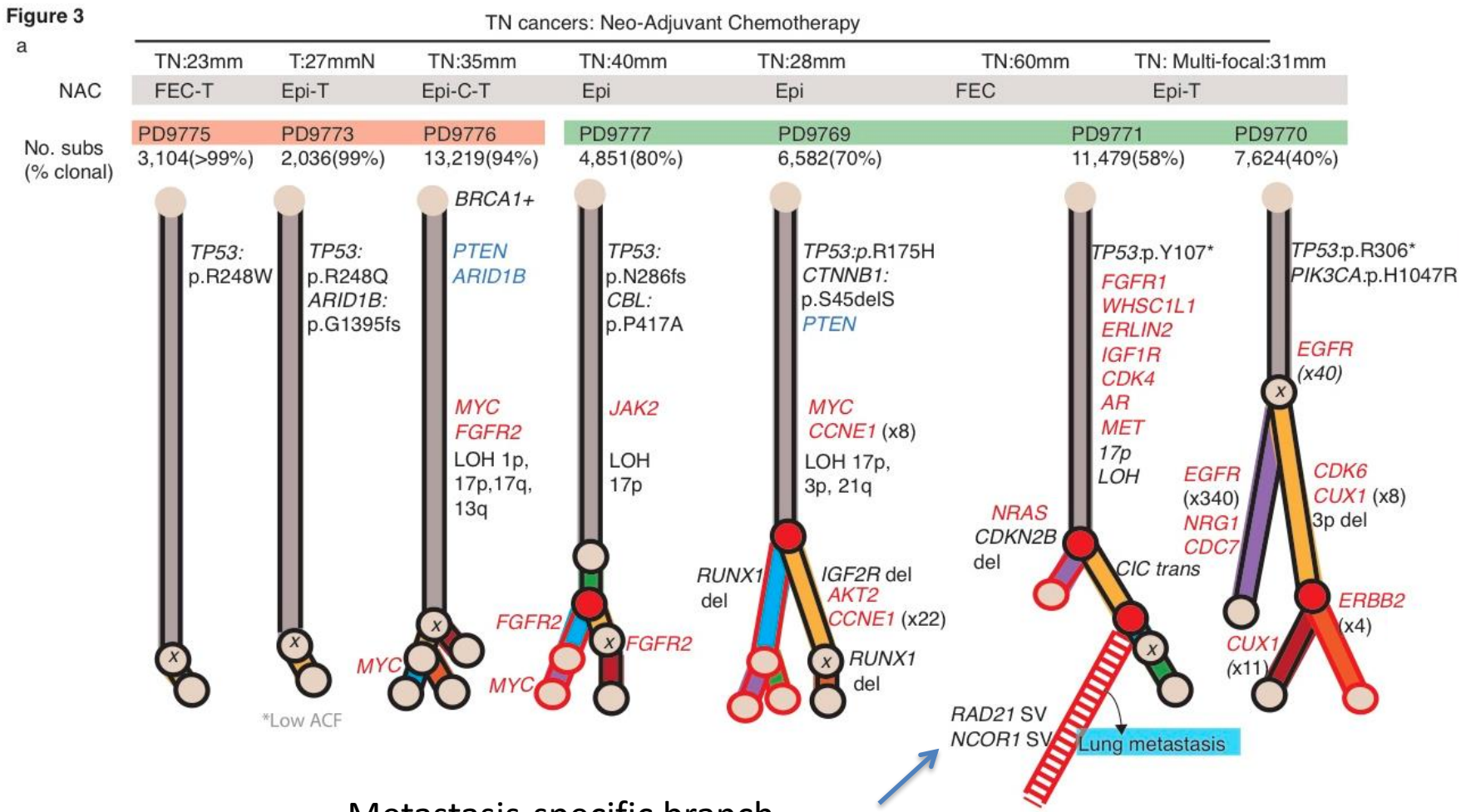
LETTER

doi:10.1038/na

Non-invasive analysis of acquired resistance to cancer therapy by sequencing of plasma DNA

Muhammed Murtaza[1]*, Sarah-Jane Dawson[1,2]*, Dana W. Y. Tsui[1]*, Davina Gale[1], Tim Forshew[1], Anna M. Piskorz[1], Christine Parkinson[1,2], Suet-Feung Chin[1], Zoya Kingsbury[3], Alvin S. C. Wong[4], Francesco Marass[1], Sean Humphray[3], James Hadfield[1], David Bentley[3], Tan Min Chin[4,5], James D. Brenton[1,2,6], Carlos Caldas[1,2,6] & Nitzan Rosenfeld[1]

Tumor Evolution in Neoadjuvant setting



Metastasis-specific branch

Courtesy P. Campbell

The future drug development paradigm?

Histology and molecular selection	Proof of concept
Safety and tolerability	Substancially efficacy in selected patients uding innovative trial designs and endpoints
Functional target selection	Trial design accounting for interpatient and intratumor heterogeneity
Pharmacology	
Antitumor activity	

Summary

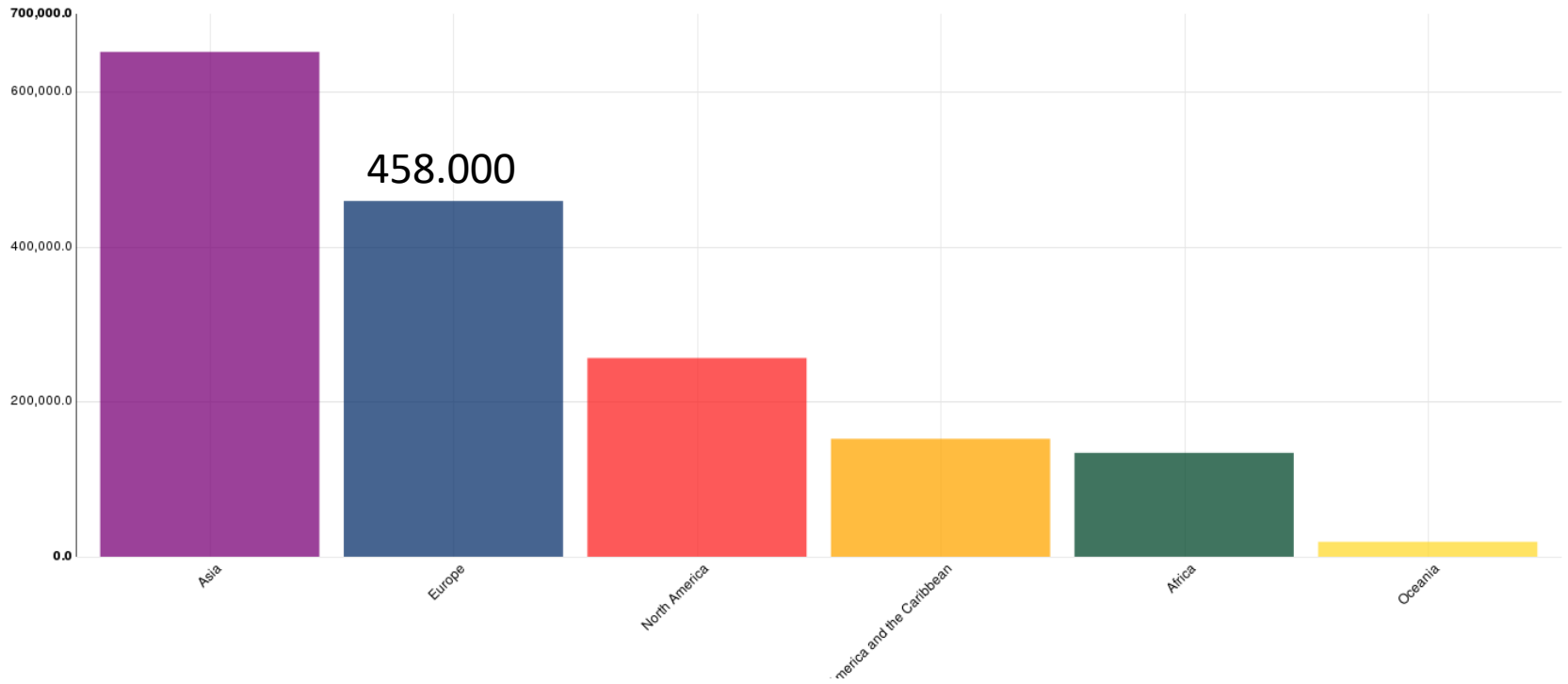
- What we can't do
  - 8000 pt trials in unselected breast cancer
- What we can do –
  - New continuum for genome-forward approaches
    - Representative model systems in parallel +
    - Small hypothesis-driven trials
  - New strategies for biomarker-driven clinical trials
    - Start broadly (relatively unselected) and learn
    - Be as critical about assays as you are of drugs
  - Novel strategies are good, but so are traditional endpoints – Overall survival
- Embrace your lab colleagues, molecular pathologists, and statisticians!

Thank you

Breast: Medical Oncology View

Giuseppe Curigliano MD, PhD
Istituto Europeo di Oncologia

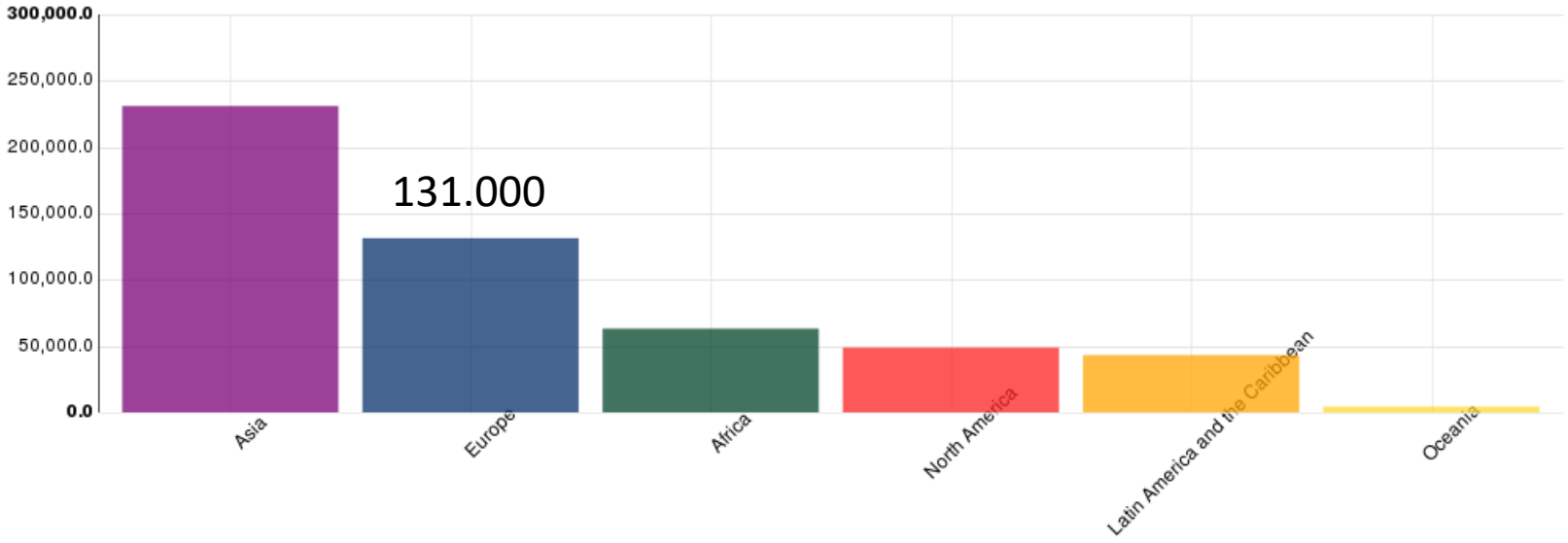
Epidemiology: Europe



Data source: GLOBOCAN 2016
Graph production: Cancer Today (http://gco.iarc.fr/today)

International Agency for Research on Cancer
World Health Organization

Epidemiology: Mortality

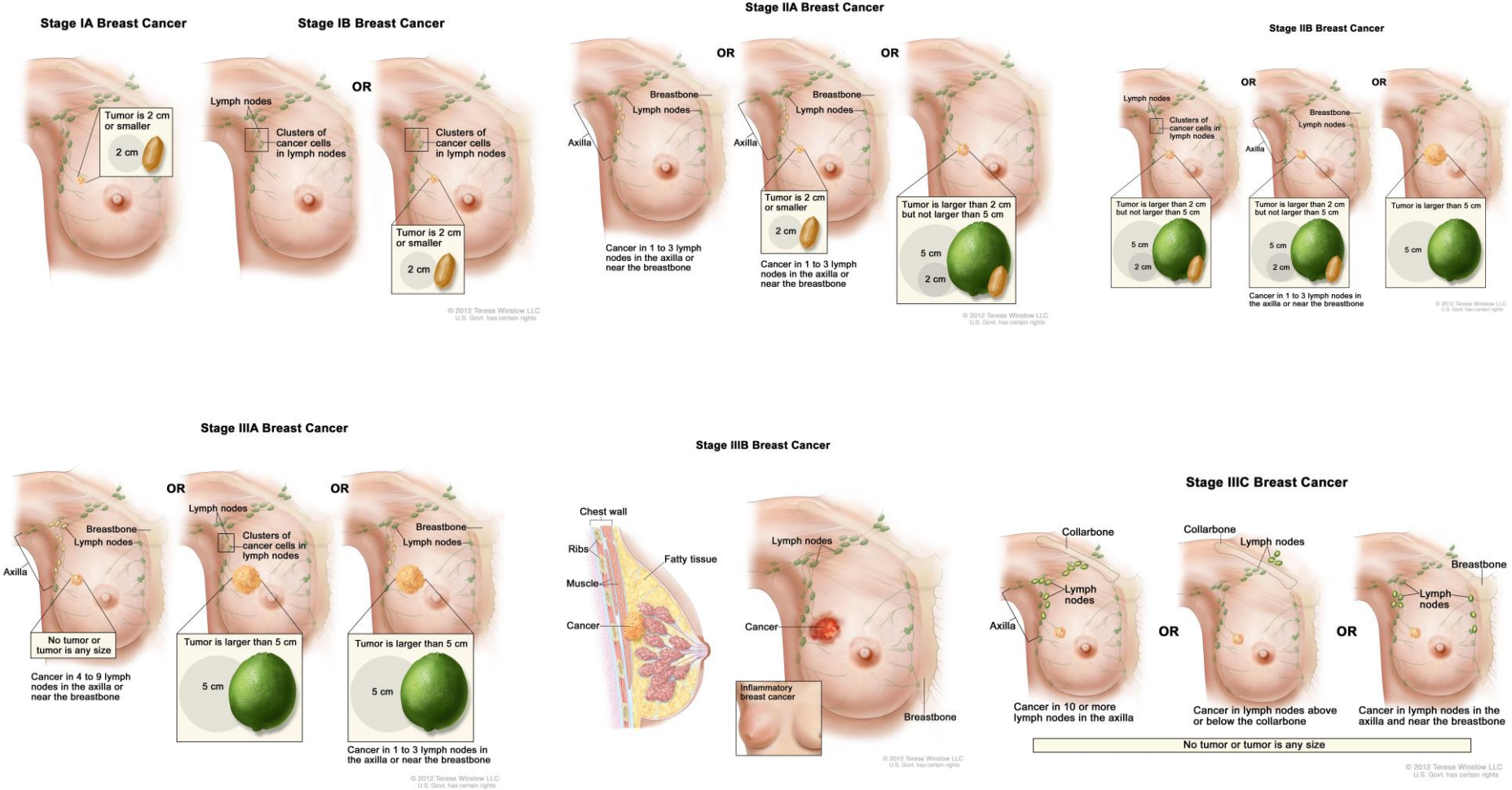


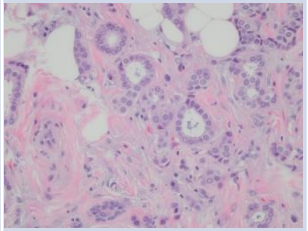
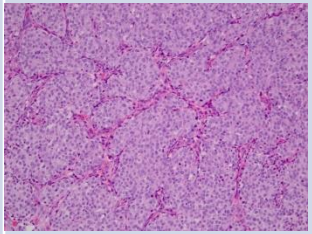
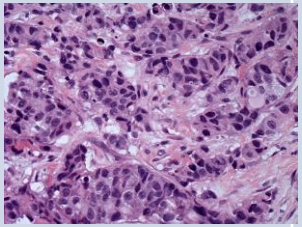
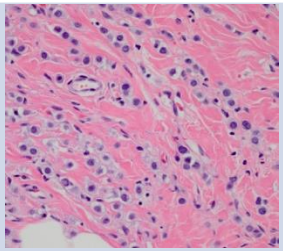
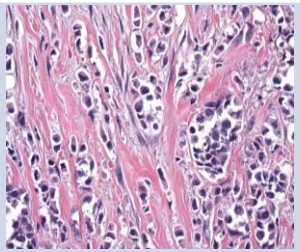
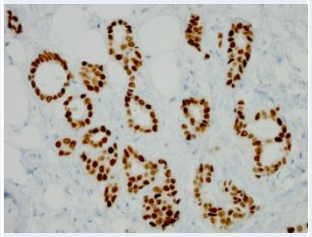
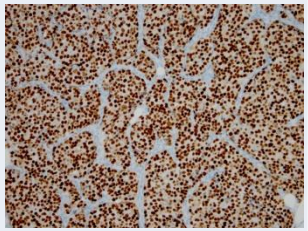
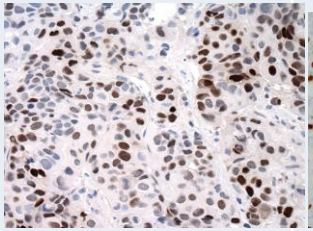
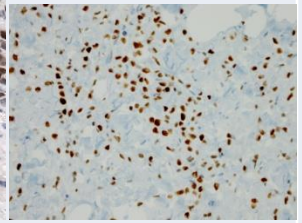
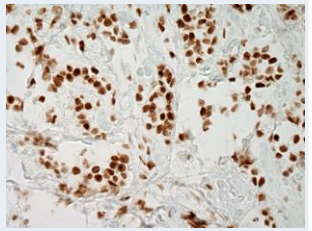
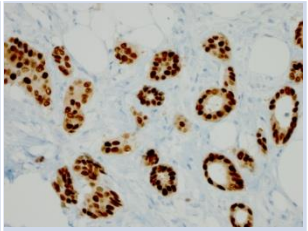
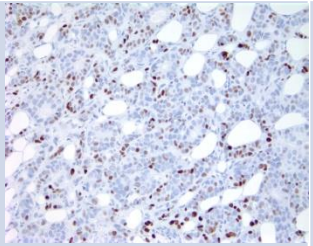
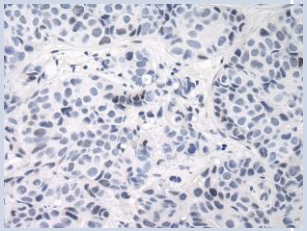
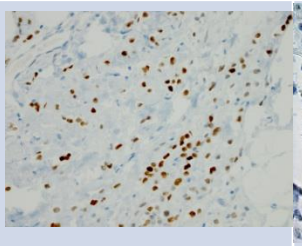
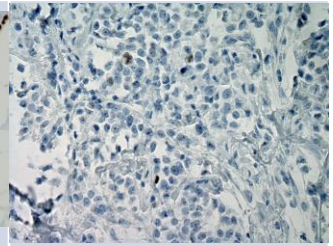
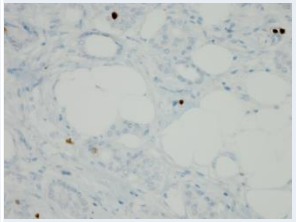
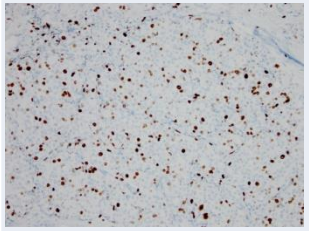
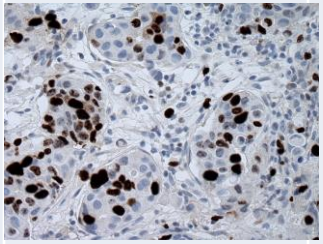
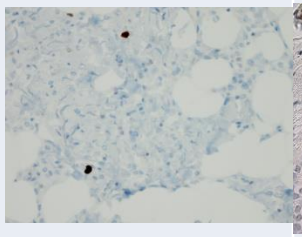
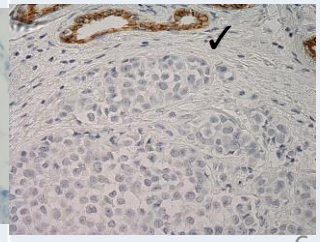
Data source: GLOBOCAN 2016
Graph production: Cancer Today (http://gco.iarc.fr/today)

Prognostic and predictive factors

- Stage (TNM)
- Menopausal status (pre and post-menopausal)
- Proliferative index and grading
- Estrogen (ER) and progestinic receptor (PgR) expression
- Hyperexpression or amplification di Human epidermal growth factor type 2 receptor (HER2/neu)
- Molecular tests

Stage


Stage IA Breast Cancer
Tumor is 2 cm or smaller
2 cm
Stage IB Breast Cancer
Lymph nodes
Clusters of cancer cells in lymph nodes
OR
Clusters of cancer cells in lymph nodes
Tumor is 2 cm or smaller
2 cm
Stage IIA Breast Cancer
Breastbone
Lymph nodes
Axilla
OR
Breastbone
Lymph nodes
Axilla
Tumor is 2 cm or smaller
2 cm
Cancer in 1 to 3 lymph nodes in the axilla or near the breastbone
OR
Tumor is larger than 2 cm but not larger than 5 cm
5 cm
2 cm
Cancer in 1 to 3 lymph nodes in the axilla or near the breastbone
Stage IIB Breast Cancer
Lymph nodes
Clusters of cancer cells in lymph nodes
Tumor is larger than 2 cm but not larger than 5 cm
5 cm
2 cm
OR
Breastbone
Lymph nodes
Axilla
Tumor is larger than 2 cm but not larger than 5 cm
5 cm
2 cm
Cancer in 1 to 3 lymph nodes in the axilla or near the breastbone
OR
Tumor is larger than 5 cm
5 cm
Stage IIIA Breast Cancer
Breastbone
Lymph nodes
Axilla
No tumor or tumor is any size
Cancer in 4 to 9 lymph nodes in the axilla or near the breastbone
OR
Lymph nodes
Clusters of cancer cells in lymph nodes
Tumor is larger than 5 cm
5 cm
OR
Breastbone
Lymph nodes
Tumor is larger than 5 cm
5 cm
Cancer in 1 to 3 lymph nodes in the axilla or near the breastbone
Stage IIIB Breast Cancer
Chest wall
Ribs
Fatty tissue
Muscle
Cancer
Lymph nodes
Cancer
Inflammatory breast cancer
Breastbone
Stage IIIC Breast Cancer
Collarbone
Lymph nodes
Axilla
Cancer in 10 or more lymph nodes in the axilla
OR
Collarbone
Lymph nodes
Cancer in lymph nodes above or below the collarbone
OR
Breastbone
Lymph nodes
Cancer in lymph nodes in the axilla and near the breastbone
No tumor or tumor is any size

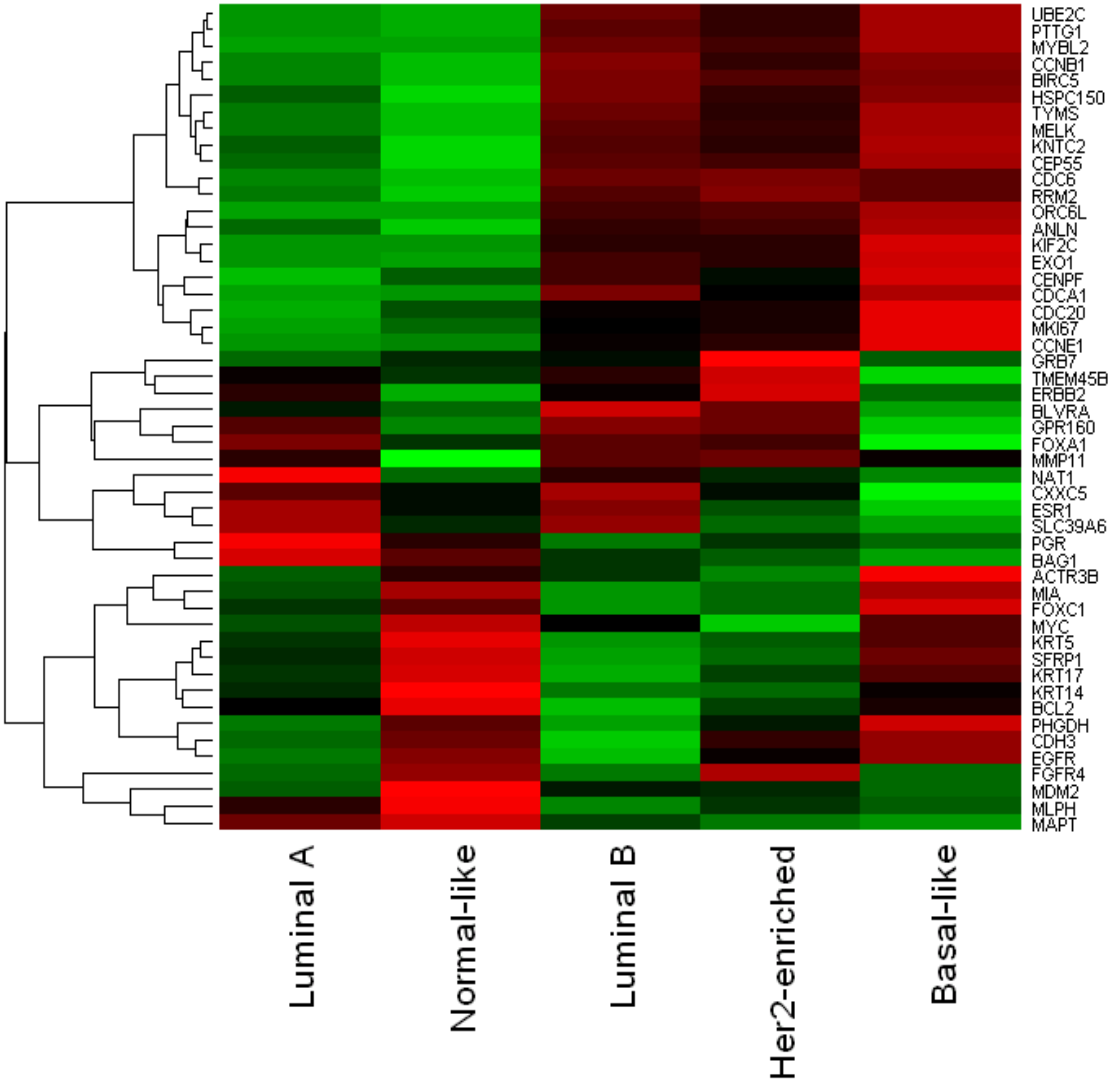
	A. DIC G1 ER 100% PR 100% HER2: 0	B. DIC G2 ER 95% PR 60% HER2: 2+	C. DIC G3 ER 70% PR <1% HER2 3+	D. LIC G1 ER 100% PR 100% HER2: 1+	E. LIC G2 ER 100% PR <1% HER2: 1+
H&E					
ER					
PR					
HER2					

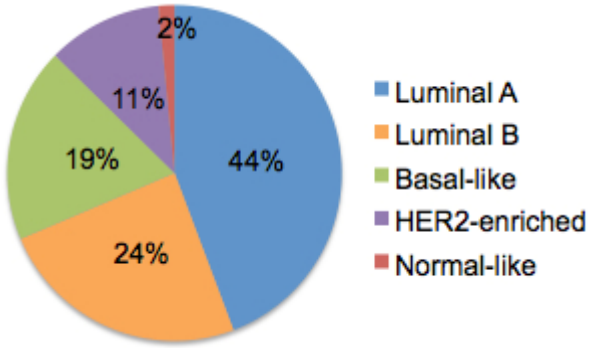
Prognostic factors

Molecular tests

- Oncotype Dx
- Mammaprint
- Predictor Analysis of Microarray 50 [PAM50] Risk of Recurrence [ROR] score
- EndoPredict
- Breast Cancer Index

Molecular classification





Classification: St Gallen 2017

Clinical grouping	Notes*
Triple negative	Negative ER, PR and HER2
Hormone receptor-negative & HER2-positive	ASCO/CAP guidelines
Hormone receptor-positive & HER2-positive	ASCO/CAP guidelines
Hormone receptor-positive & HER2-negative :a spectrum	ER and/or PgR positive >= 1%
High receptor, low proliferation, low grade ("luminal A-like")	Multi-parameter molecular marker "good" if available. High ER/PR and clearly low Ki-67 or Grade.
Intermediate	Multi-parameter molecular marker "intermediate" if available. Uncertainty persists about degree of risk and responsiveness to endocrine and cytotoxic therapies.
Low receptor, high proliferation, high grade ("luminal B-like")	Multi-parameter molecular marker "bad" if available. Lower ER/PR with clearly high Ki-67, histological grade 3.

Subtypes

Classification and pathology assessment	Definition
Luminal tumors: ER positive/HER2 negative	
• **Luminal like-A: High ER, high PgR, low proliferative index and low grade**	Low risk tumors. No “genomic testing”
• **Luminal A/B like**	
• **A spectrum : low-intermediate expression of ER and PgR, intermediate grade, intermediate proliferative index**	Recommended use of “genomic testing”
• **Luminal B-like: low expression of ER and PgR, high grade, high proliferative index**	High risk

St Gallen 2017

Integrate pathology and biology

Histologic Grade		**Low (I of III)**	**Intermediate (II of III)**	**High (III of III)**
Biomarkers	ER expression	**+++**	**++ to +++**	**+ to ++**
	PR expression	**++ to +++**	**0 to +++**	**0 to ++**
	Proliferation (Ki-67 / S phase fraction)	**Low (<10%)**	**Intermediate (10-20%)**	**High (>20%)**
	HER2 Overexpression	**Never**	**Occasional**	**Occasional**
Genetic / Genomic / multipanel markers	21-gene recurrence score	**Low (< 18)**	**Intermediate (18-25)**	**High (>25)**
	Intrinsic subtype	**Luminal A**	**Luminal B**	
	Genomic Grade	**Lower**		**Higher**
	IHC4	**Lower**		**Higher risk**
	MammaPrint	**Low**		**High**
	Tumor DNA ploidy	**Mostly diploid**		**Mostly aneuploid**

St Gallen 2017

Medical treatment

Neoadjuvant therapy

Adjuvant therapy

Neoadjuvant therapy

We advice neoadjuvant therapy in:

- Locally advanced breast cancer
- Breast cancer with predictive factors of response to neoadjuvant chemotherapy or targeted therapy (triple negative or HER2 positive BC)

Neoadjuvant therapy

- Increasing rate of conservative surgery
- Increasing rate of radical surgery.
- In vivo monitoring of tumor response.

Neoadjuvant therapy

Newly diagnosed tumor

THERAPY

Curative intent

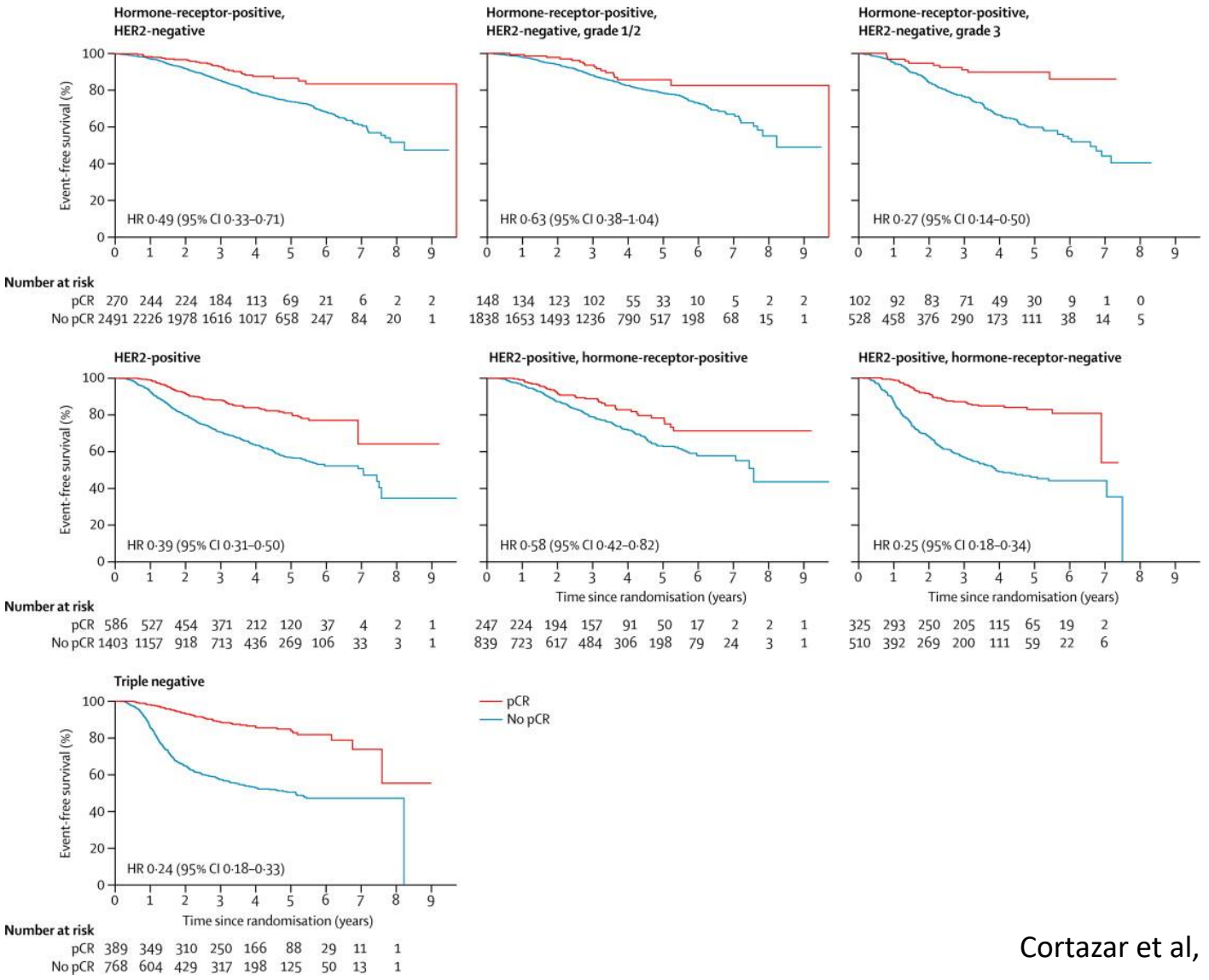
Residual tumor

- Pro:
  - Increasing rate of BCT
  - Pathological complete response
  - Drug develomment
- Contras:
  - Low rate of pCR (ER+)
  - Select subgroups
  - Implication for surgeons and radiation oncologists

Preferred option in some subtypes (triple negative ed HER2 positive)

pCR as surrogate for survival

(N=11,955)



Cortazar et al, Lancet 2014

Increase in pCR

74%

65%

48%

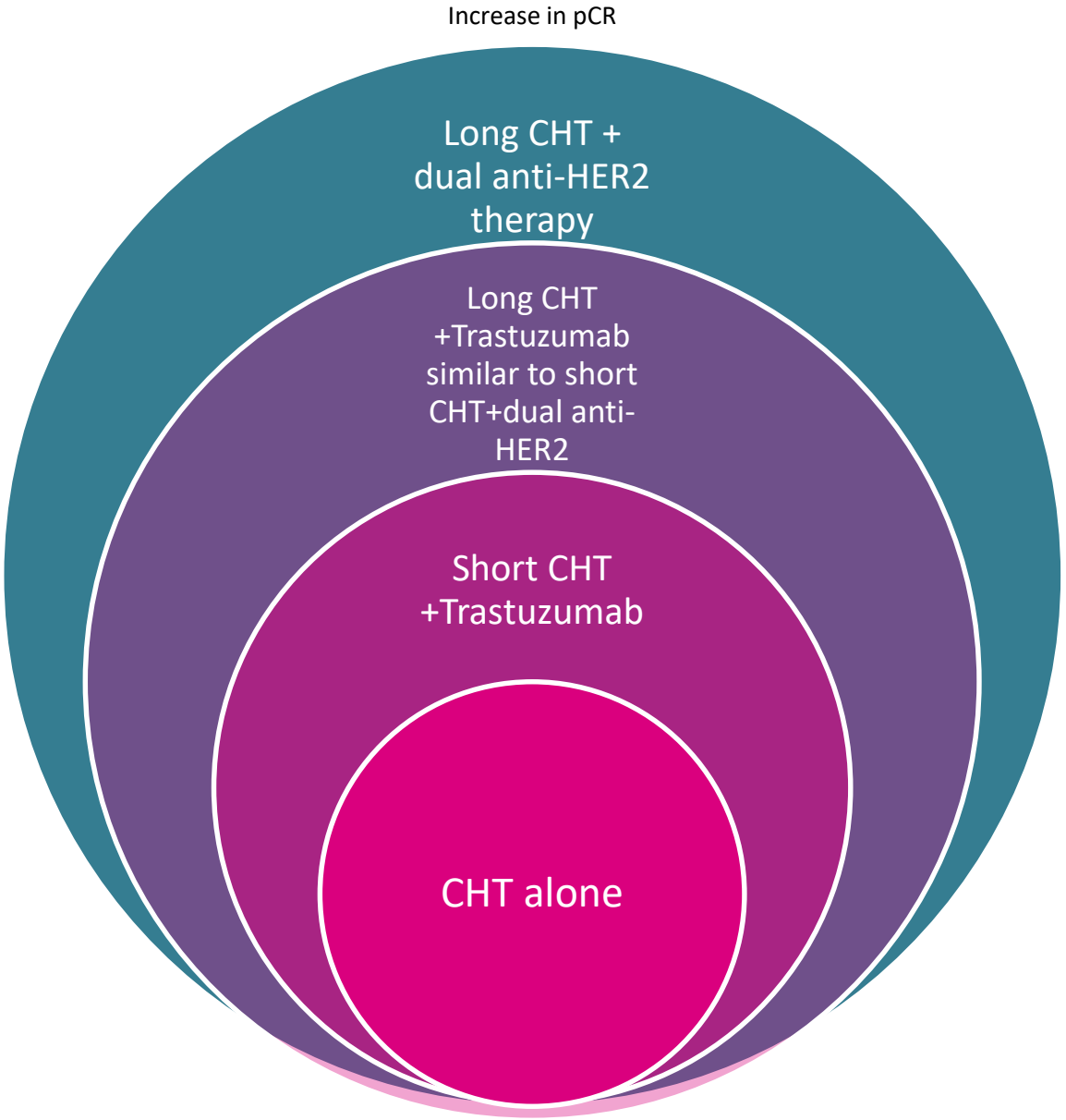
45%

38%

25%

20%

15%



Pathological complete response

- Absence of infiltrating carcinoma in breast and nodes

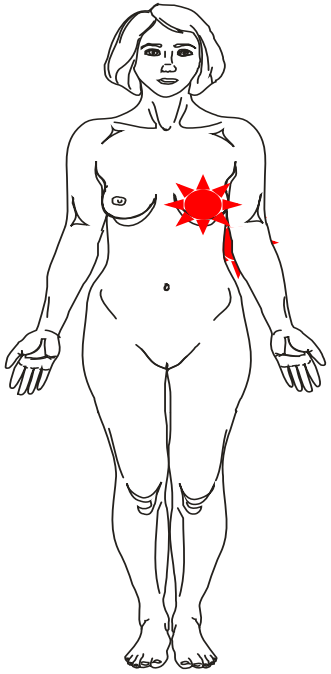
- Absence of infiltrating carcinoma (T and N) with residual *in situ* carcinoma.

Adjuvant therapy

- Reduce the risk of distant relapse.

- Adjuvant therapy (endocrine, chemotherapy or biology): duration and intensity to be decided according to stage and biological features of disease, balancing risk and benefits for the individual patient.

Adjuvant therapy

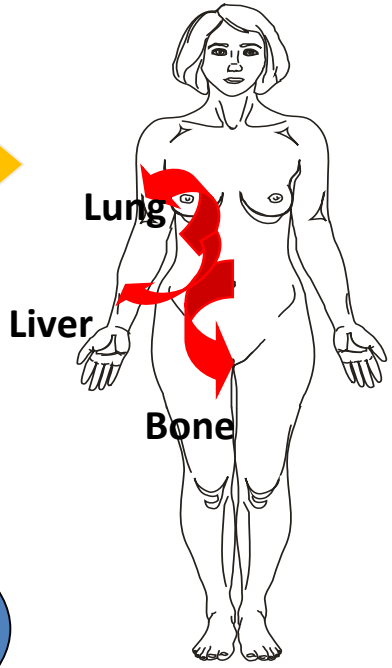


Early stage

Curable disease

Adjuvant therapy

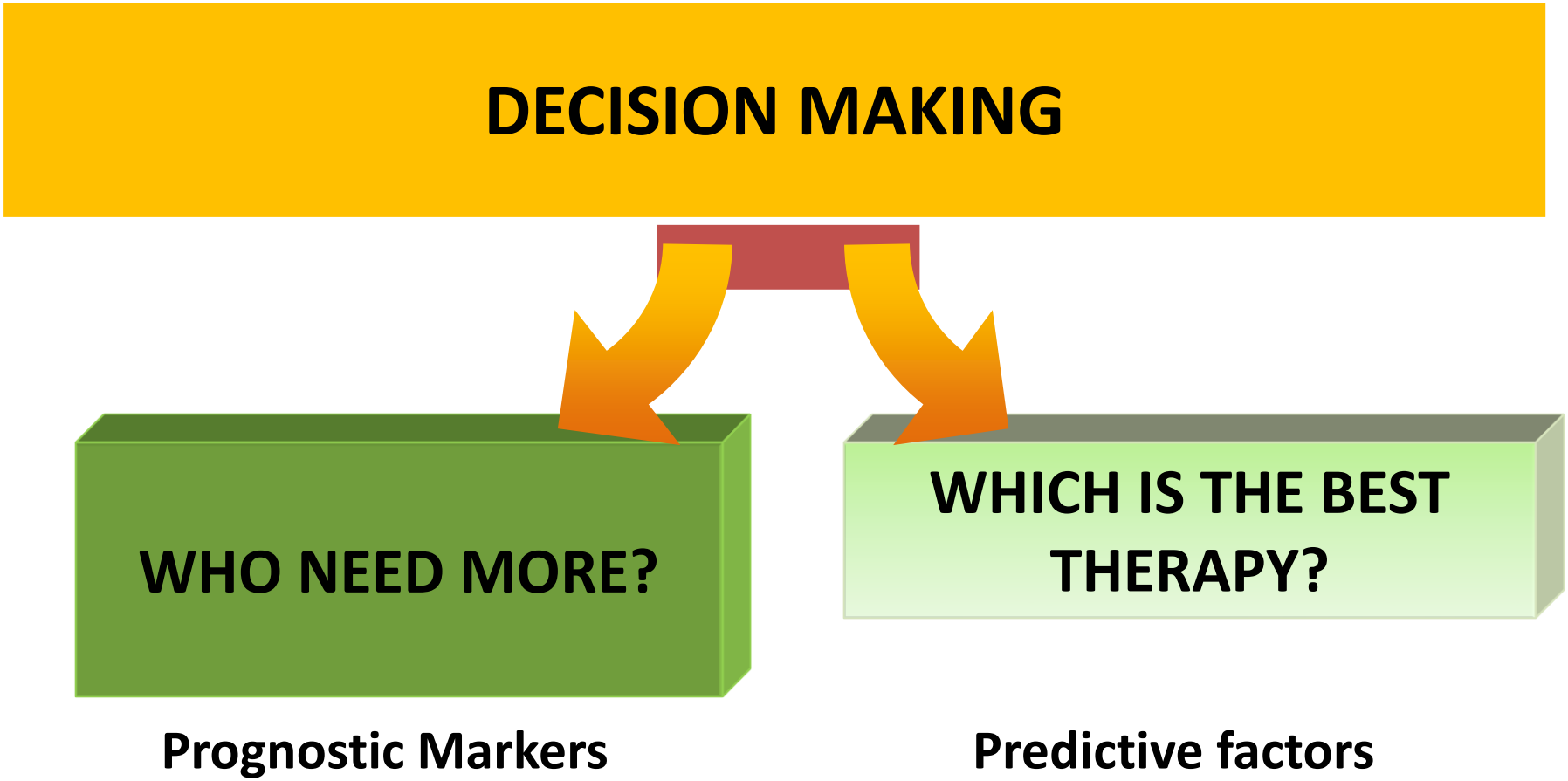
Risk of:
- Overtreatment
- Undertreatment
- Wrong treatment
- Suboptimal treatment



Mestatatic disease

Chronic disease

Adjuvant therapy



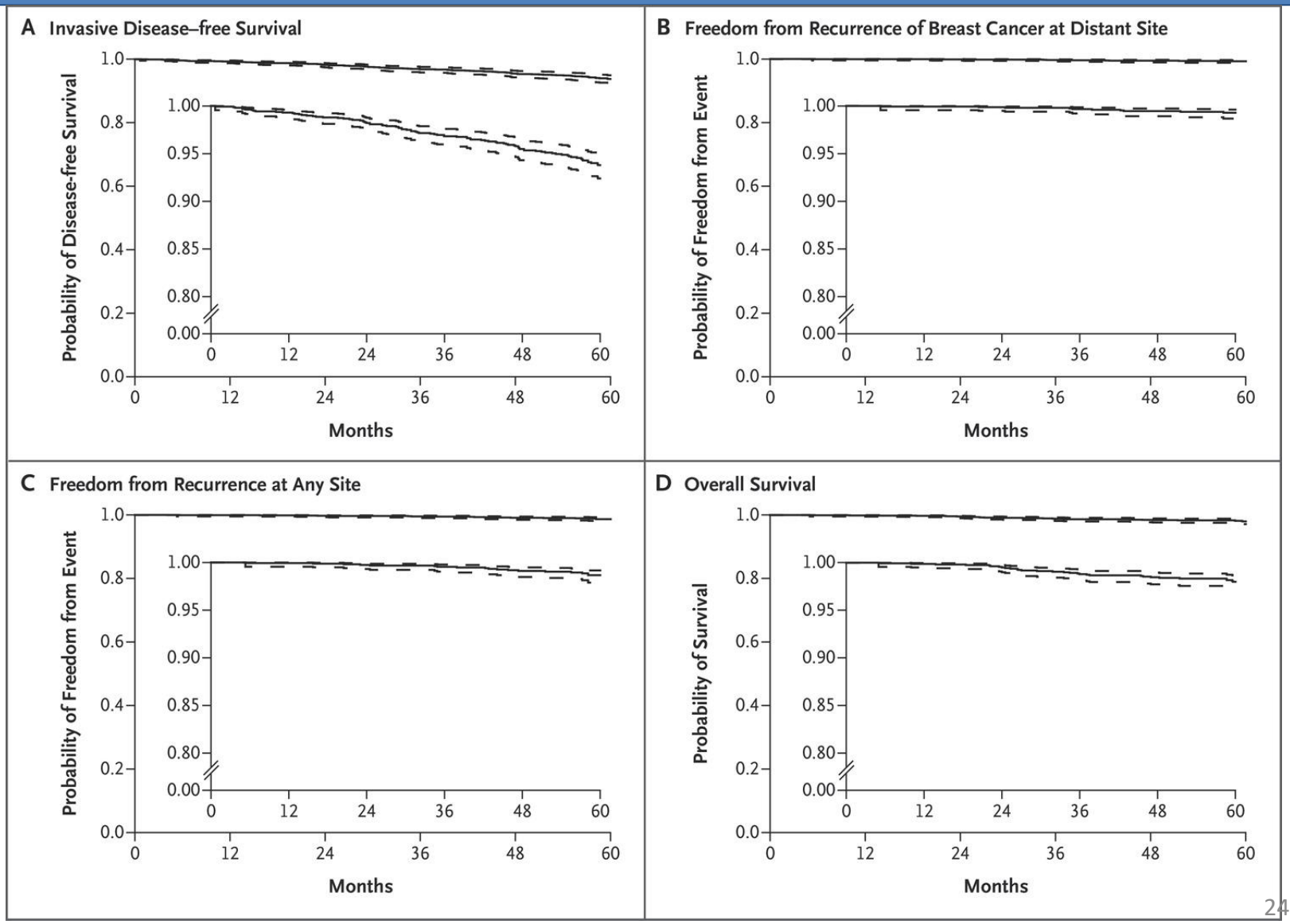
Adjuvant therapy

Relative Indications for chemotherapy in addition to endocrine therapy	Area of uncertainty for indication to chemotherapy in addition to endocrine therapy	Relative Indications for endocrine therapy alone
Histological Grade 3 **High or intermediate "genomic risk"**	Histological Grade 2 Intermediate "genomic risk"	Histological Grade 1 Low "genomic risk"
High proliferation[a]	Intermediate proliferation	Low proliferation
Lower ER and PgR level	High/Intermediate degree of ER and PgR expression	Higher ER and PgR level
Node positive (4 or more involved nodes)	Node positive (1-3 involved nodes)	Node negative
Presence of extensive peritumoral vascular invasion		Absence of extensive peritumoral vascular invasion
pT > 5 cm	pT 2.1 – 5 cm	pT ≤ 2cm

ER positive/HER2 negative

Subtypes according to clinical-pathological and genomic risk assessment	Treatment recommendation	De-escalation	Escalation
ER positive & HER2-negative			
High receptor, low tumour burden (pT1a, pT1b), no nodal involvement (pN0), low proliferation, low grade or low "genomic risk"	Endocrine therapy alone according to menopausal status		
Premenopausal	Tamoxifen 5 years	No role for extended adjuvant tamoxifen beyond 5 years No OFS	
Postmenopausal	Tamoxifen 5 year Consider AI as an option if tamoxifen is contraindicated or not tolerated	The majority of the panel recommended against extended adjuvant endocrine therapy beyond 5 years	

DFS and OS

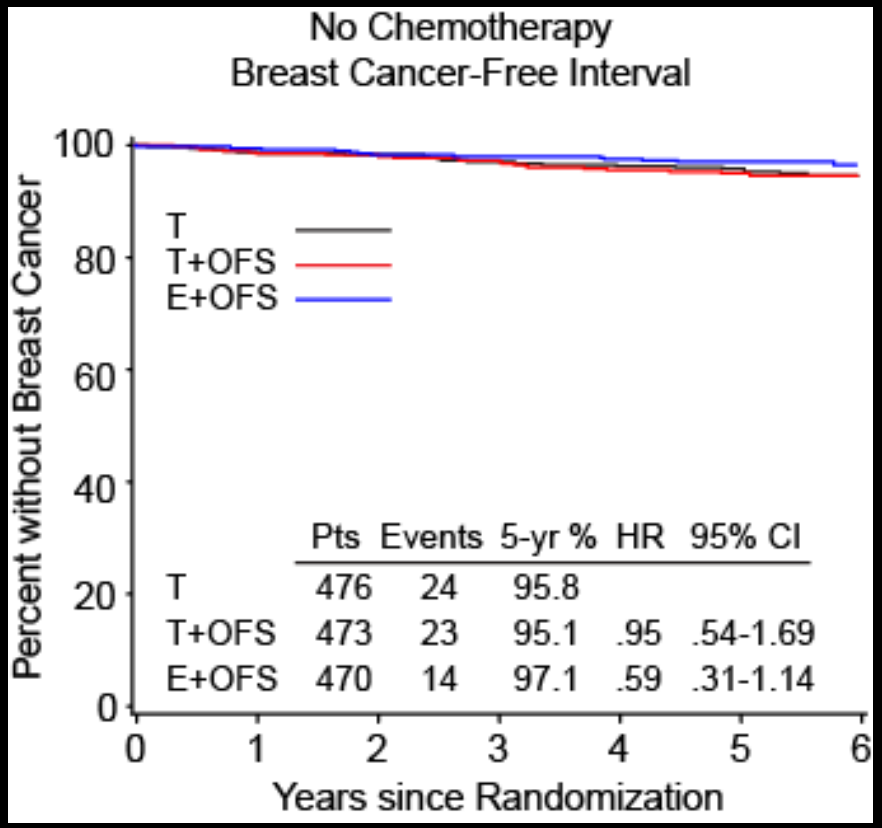


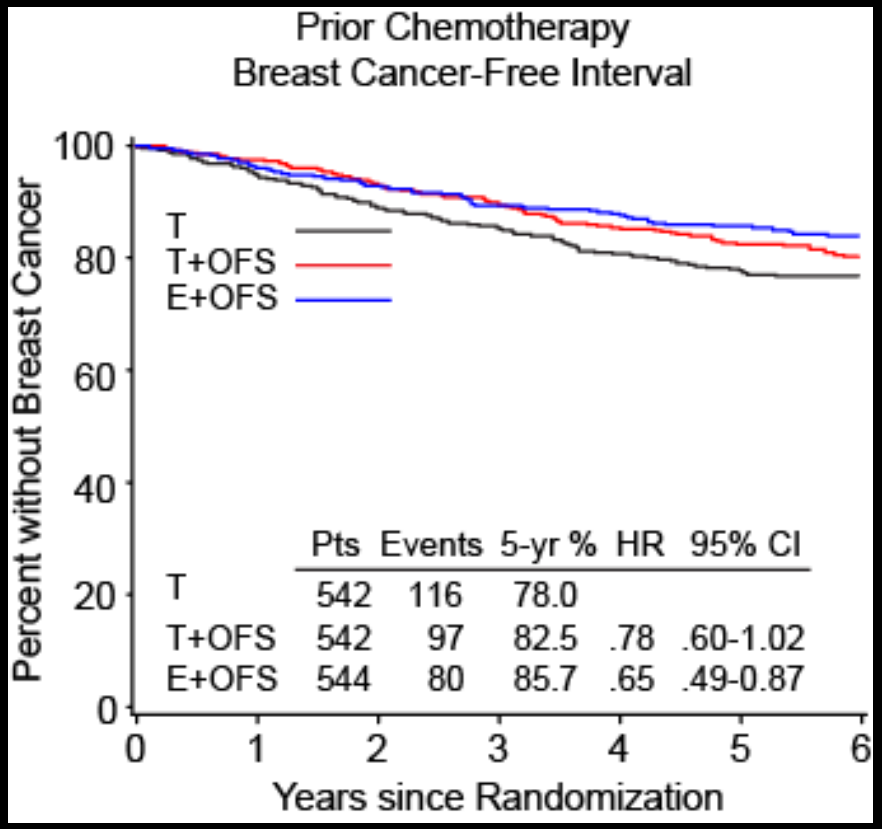
Sparano JA et al. N Engl J Med 2015;373:2005-2014.

ER positive/HER2 negative

Subtypes according to clinical-pathological and genomic risk assessment	Treatment recommendation	De-escalation	Escalation
ER positive & HER2-negative			
High/Intermediate degree of ER and PgR expression, intermediate tumour burden pT1c, pT2, pN0 or pN1 (1-3), intermediate or high proliferation or grade, and/or intermediate "genomic risk"	Endocrine therapy according to menopausal status plus adjuvant chemotherapy		
Premenopausal Uncertain "clinical risk" (node negative) "intermediate genomic risk"	OFS plus tamoxifen or OFS plus exemestane		Consider addition of chemotherapy in selected cases Extended adjuvant endocrine therapy with tamoxifen in some cases
Premenopausal intermediate/high "clinical risk" (node positive) "intermediate/high genomic risk"	OFS plus exemestane plus adjuvant chemotherapy in many cases		Chemotherapy Extended adjuvant endocrine therapy with tamoxifen
Post-menopausal Uncertain "clinical risk" (node negative) "intermediate genomic risk"	AI up front Chemotherapy in many cases		Bisphosphonates
Postmenopausal "intermediate/high genomic risk" and intermediate/high "clinical risk" (node positive)	Chemotherapy AI as first endocrine therapy for at least 3-5 years		Extended adjuvant AI according to risk and tolerability Bisphosphonates Denosumab has been shown to reduce bone-health related events in breast cancer patients

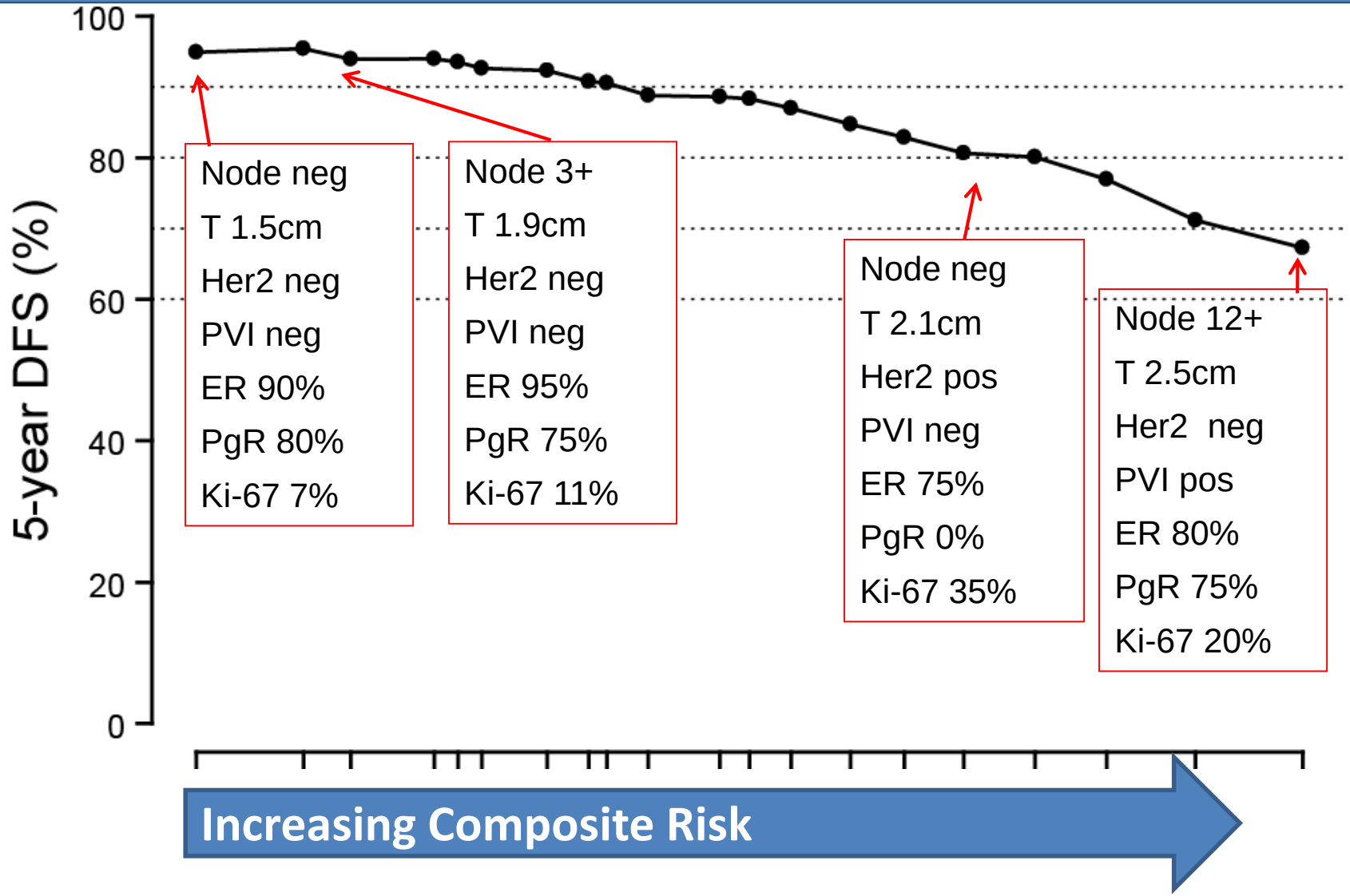
Premenopausal





Francis P, et al. NEJM 2015

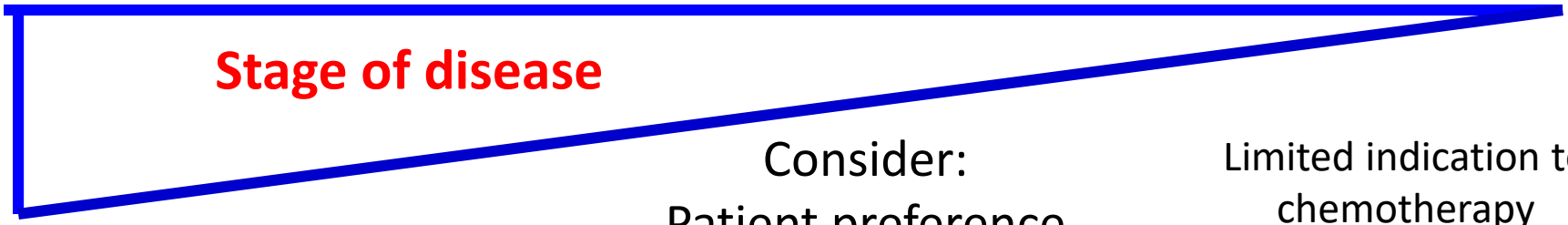
Post-menopausal



Viale G et al, JCO 2011

Chemotherapy

YES		NO
High grade	M A Y	Low grade
High Ki67		Low Ki67
Low ER and PR	B E	High ER e PR
High genomic risk		Low genomic risk
Luminal B like		Luminal A or surrogate
Risk of early recurrence		Risk of late recurrence



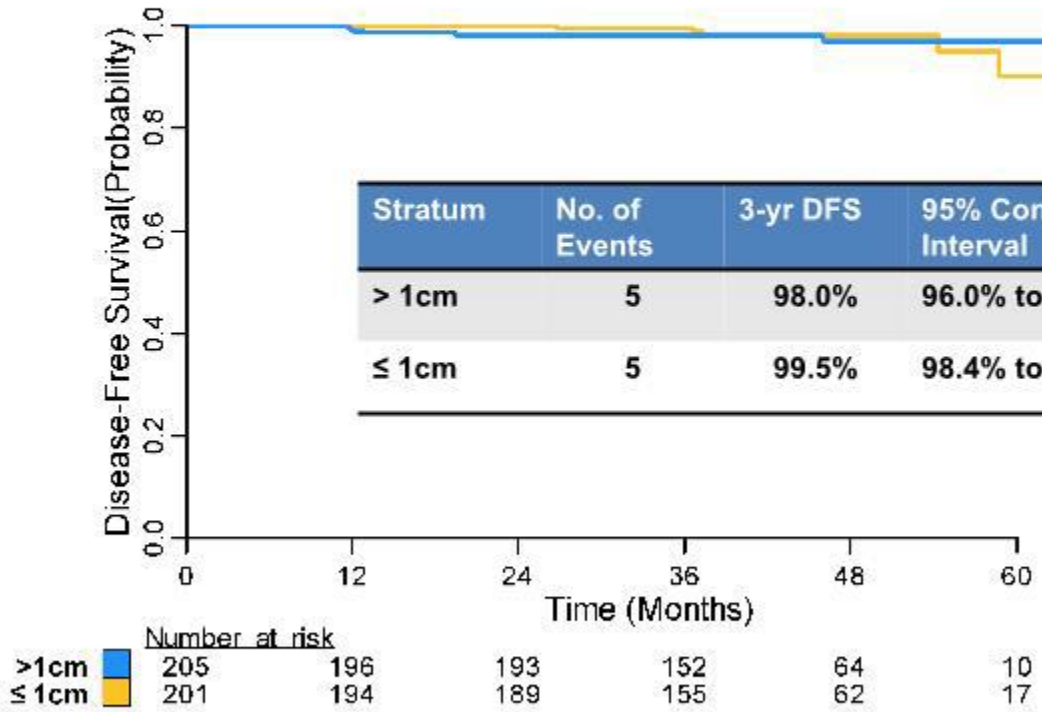
HER2 positive

Subtypes according to clinical-pathological and genomic risk assessment	Treatment recommendation	De-escalation	Escalation
ER negative & HER2-positive			
pT1a node negative	No systemic therapy	No systemic therapy	
pT1 b,c node negative	Chemotherapy plus trastuzumab	Consider paclitaxel plus one year trastuzumab without anthracyclines	Dual blockade with pertuzumab and trastuzumab improves outcome among patients who are at higher risk for relapse because of lymph-node involvement or hormone-receptor negativity [92]*
Higher T or N stage	Neoadjuvant therapy for stage II or III is the preferred initial treatment approach. Anthracycline followed by taxane with concurrent trastuzumab continued to 12 months	Patients may be treated with TCH regimen	Dual anti-HER2 therapy with pertuzumab and trastuzumab with chemotherapy as the preferred option in the neoadjuvant setting Dual blockade with pertuzumab and trastuzumab improves outcome among patients who are at higher risk for relapse because of lymph-node involvement or hormone-receptor negativity [92]*
ER positive & HER2-positive	As above plus endocrine therapy appropriate to menopausal status		Extended adjuvant therapy with neratinib after one year of trastuzumab may reduce recurrence in ER positive subgroup*.

Small HER2 positive

San Antonio Breast Cancer Symposium- Cancer Therapy and Research Center at UT Health Science Center- December 10-14, 2013

Disease-Free Survival by Tumor Size

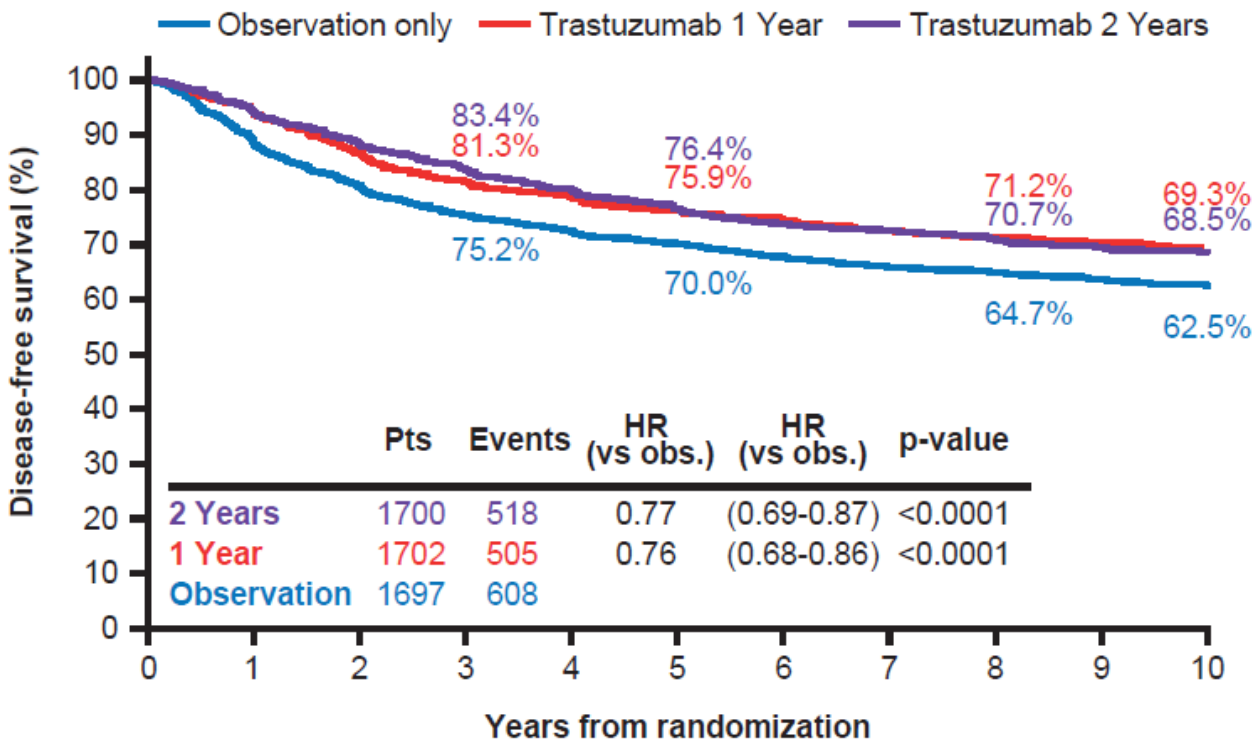


Stratum	No. of Events	3-yr DFS	95% Conf. Interval
> 1cm	5	98.0%	96.0% to >99.9%
≤ 1cm	5	99.5%	98.4% to >99.9%

Tolaney S, NEJM 2015

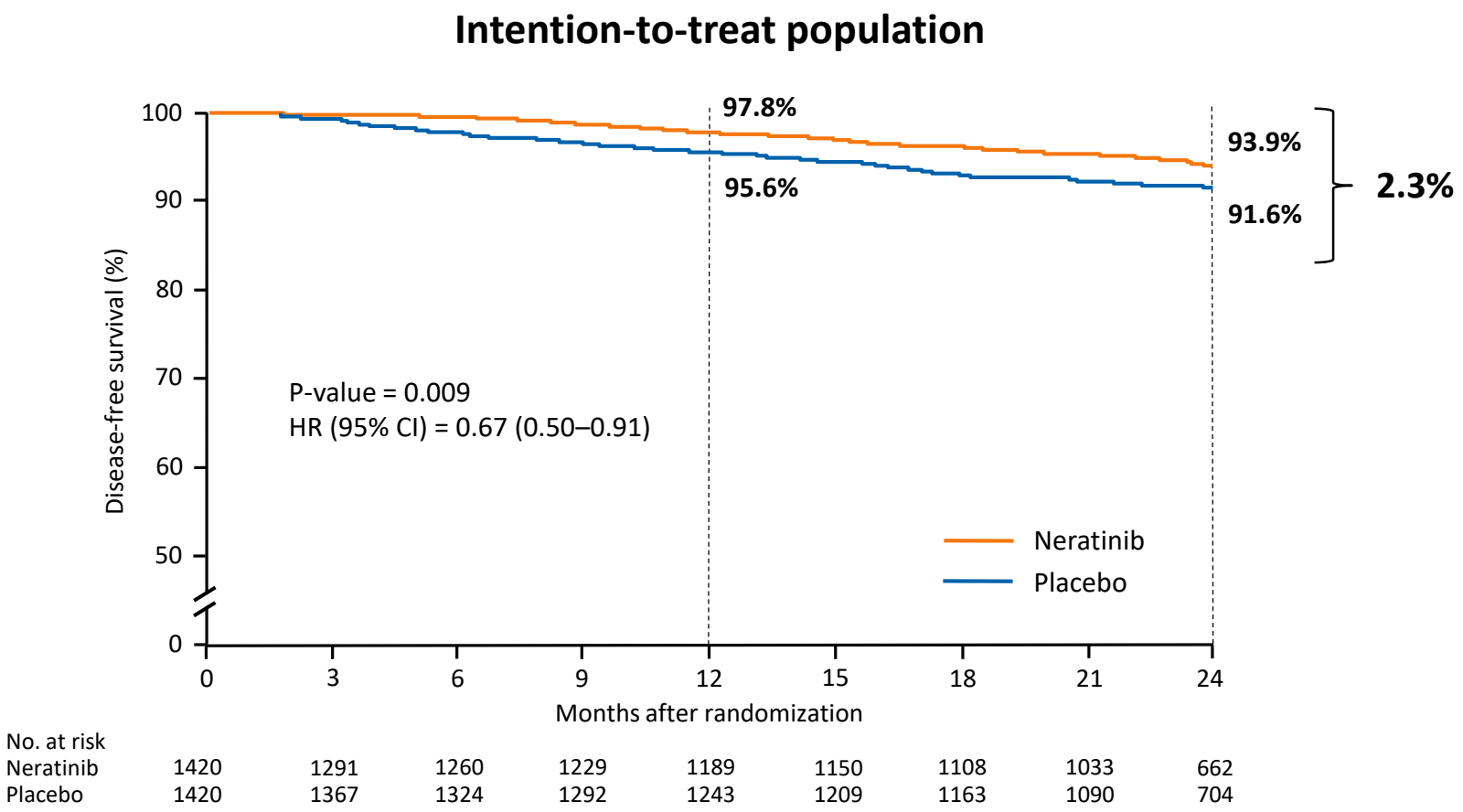
HERA trial

HERA Trial 11 Year Update



Cameron D, Lancet Oncol 2017

Extended adjuvant therapy

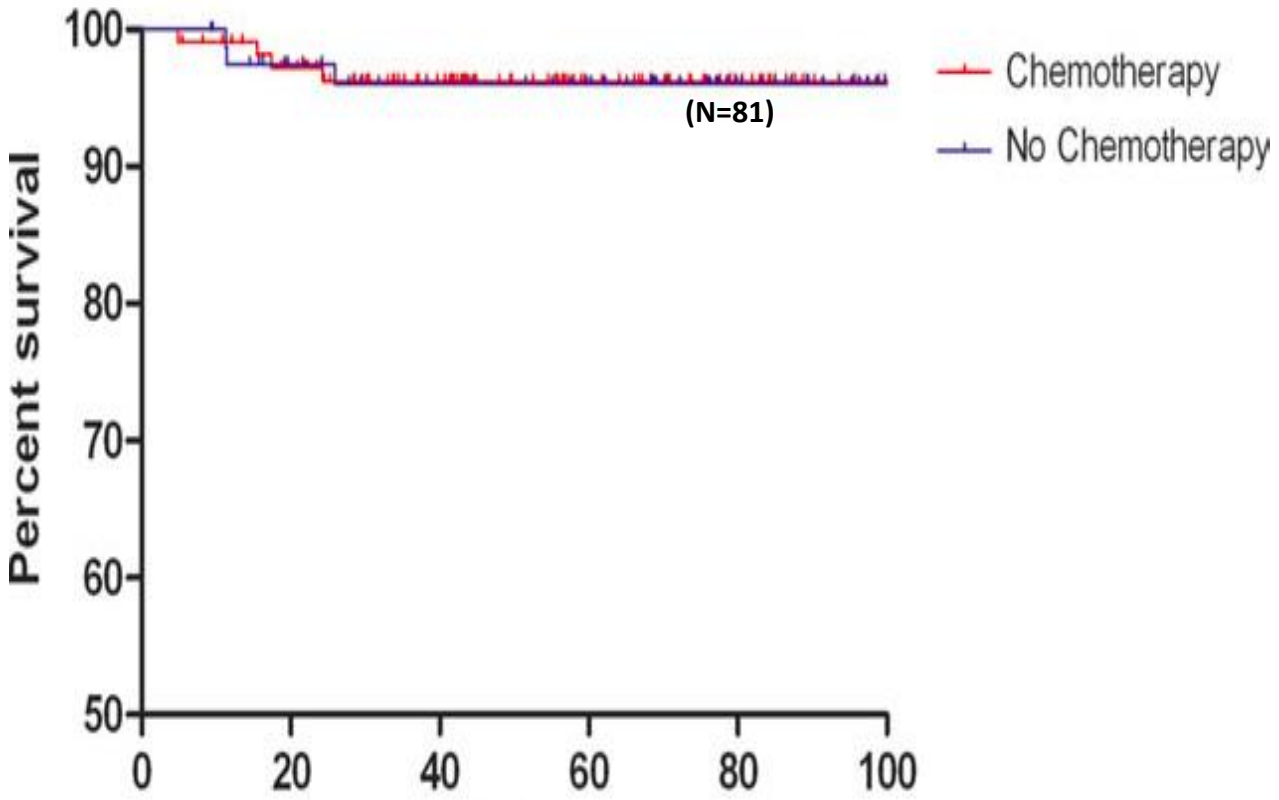


Chan et al. Lancet Oncol 2016

Triple negative

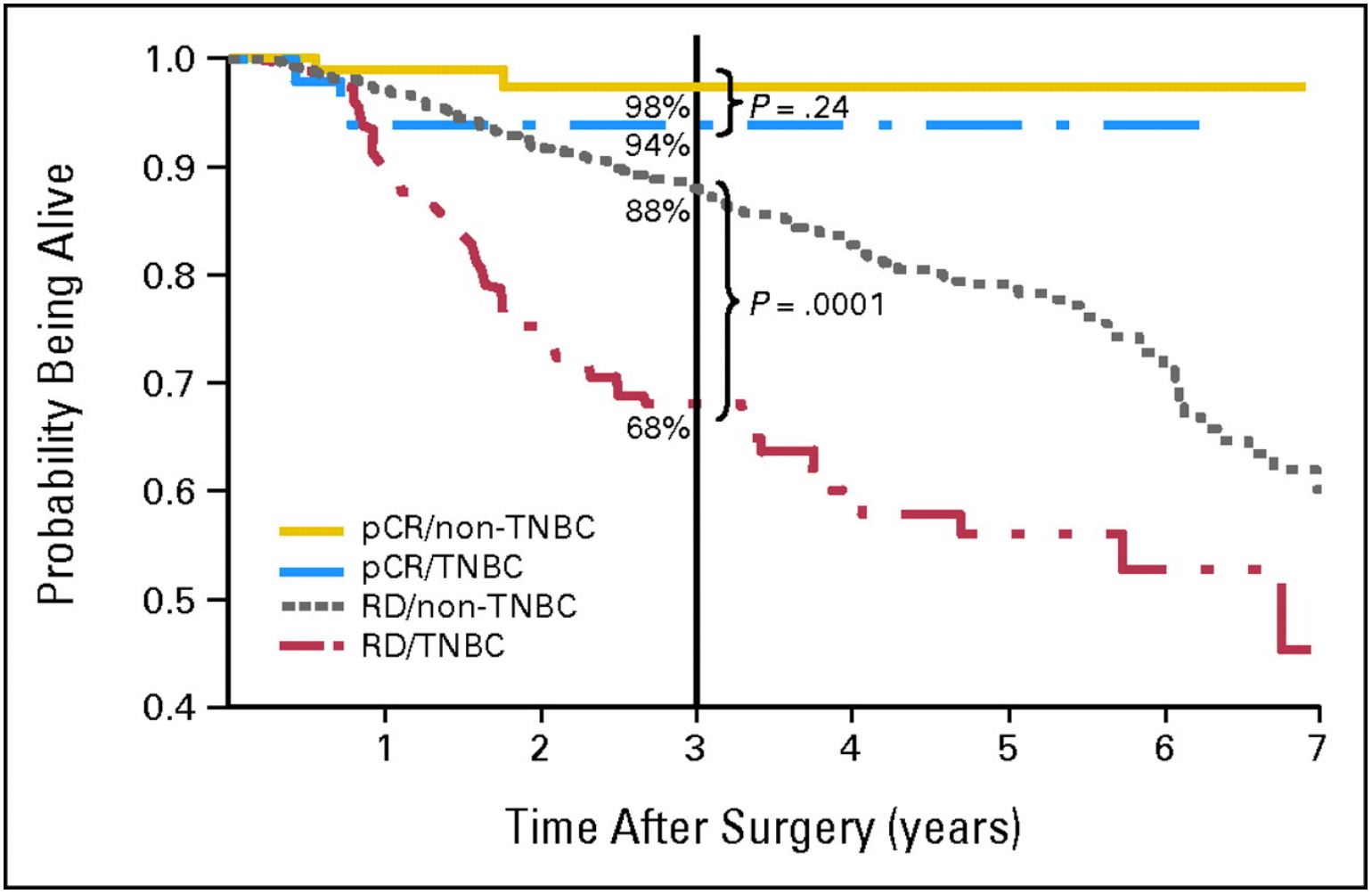
Subtypes according to clinical-pathological and genomic risk assessment	Treatment recommendation	De-escalation	Escalation
Ductal triple negative			
pT1a node negative		No routine adjuvant chemotherapy for stage pT1a pN0.	
Higher T and N stage	Neoadjuvant therapy for stage II or III is suggested as initial treatment approach. Chemotherapy should include anthracycline and taxanes	Dose-dense adjuvant chemotherapy preferred by only a minority of the consensus panel	No consensus on post-neoadjuvant treatment in case of residual disease. In BRCA1/2 associated cancers, the Panel was evenly split on whether to recommend (neo)-adjuvant platinum chemotherapy though agreed that such patients should receive alkylating chemotherapy.

Small triple negative



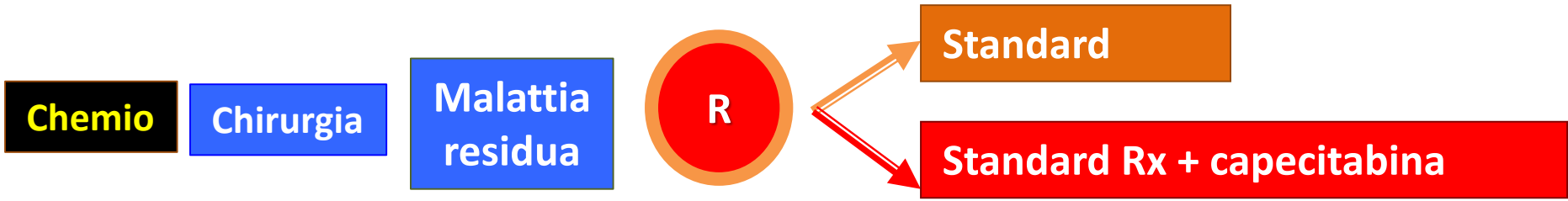
Vaz-Luis I et al.
J Clin Oncol 2014

Residual disease after neoadjuvant CT

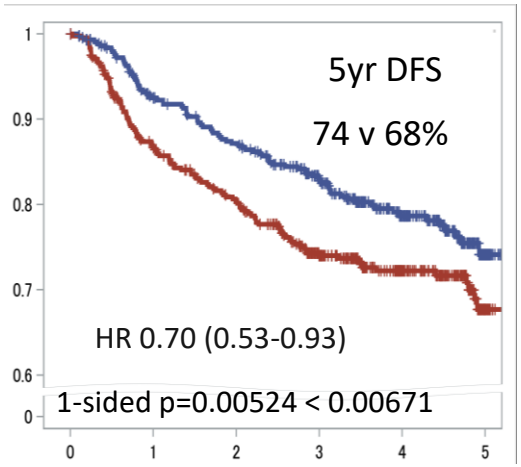


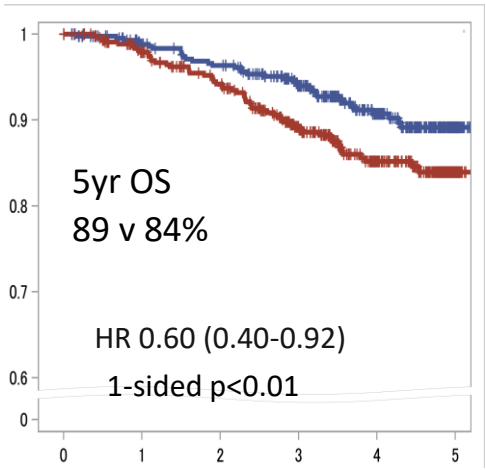
C. Liedtke JCO, 26, 8, 2008: pp. 1275-1281

Residual disease after neoadjuvant CT



(n=900, 296 TNBC)

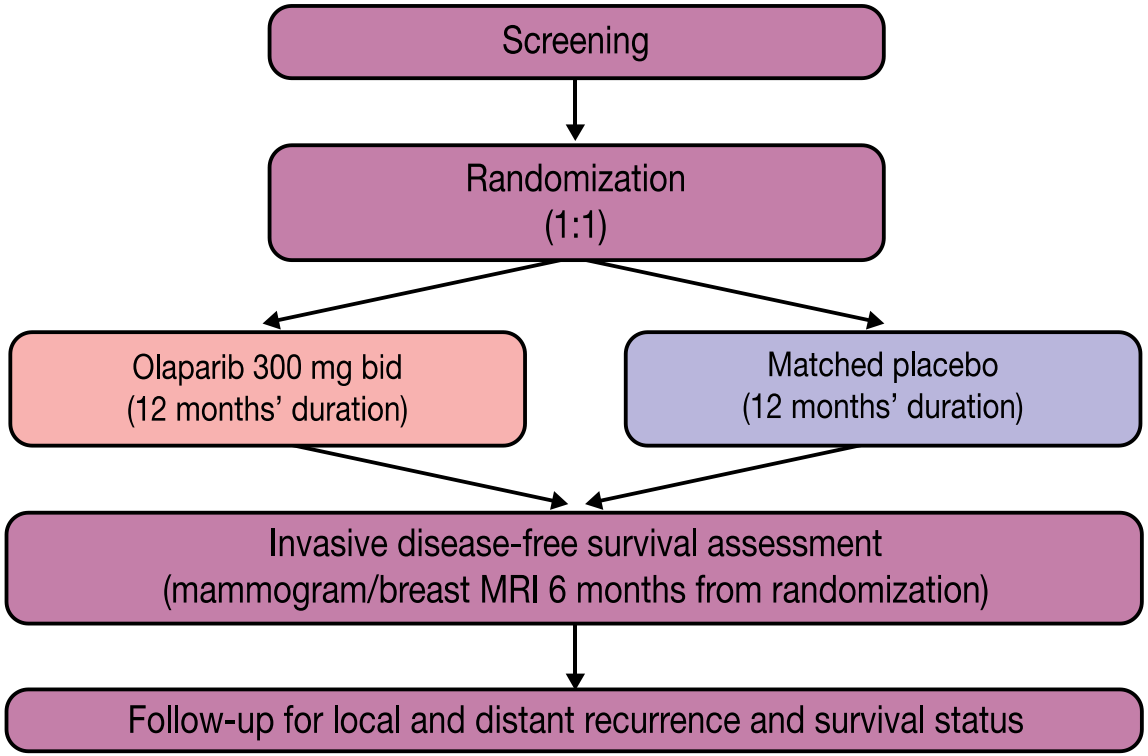




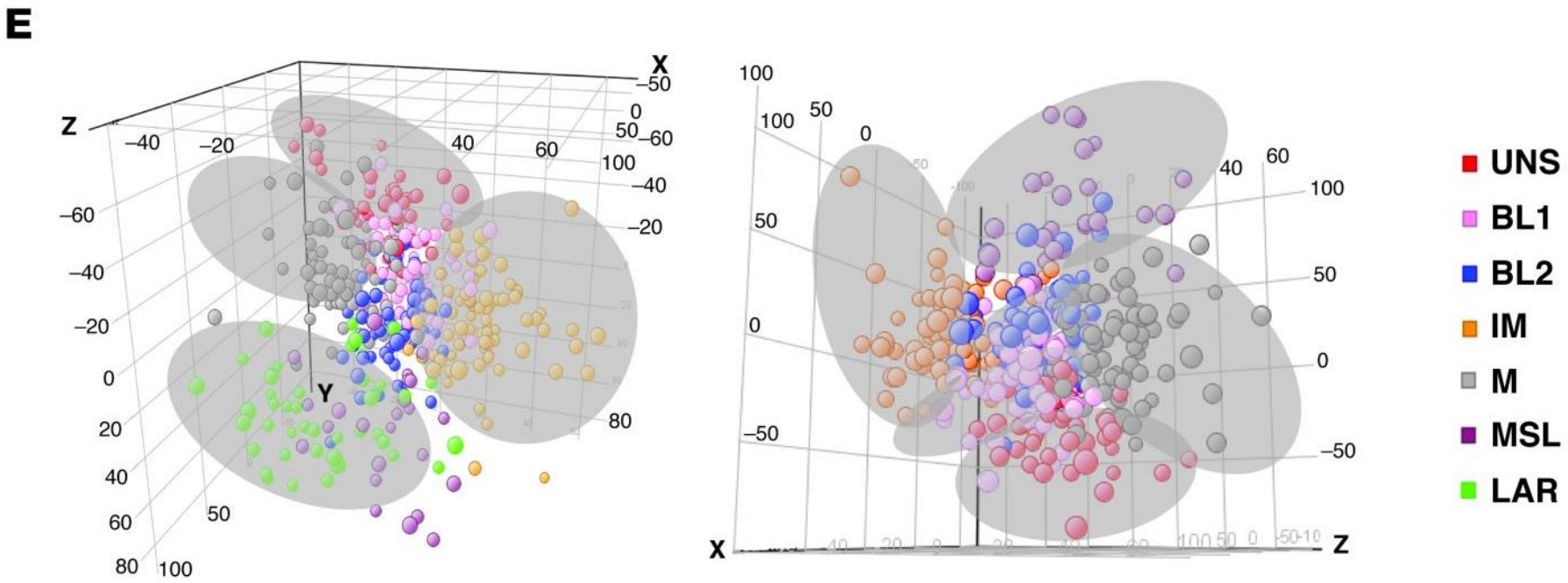
All patients

BRCA mutated

Figure 1. OlympiA study design



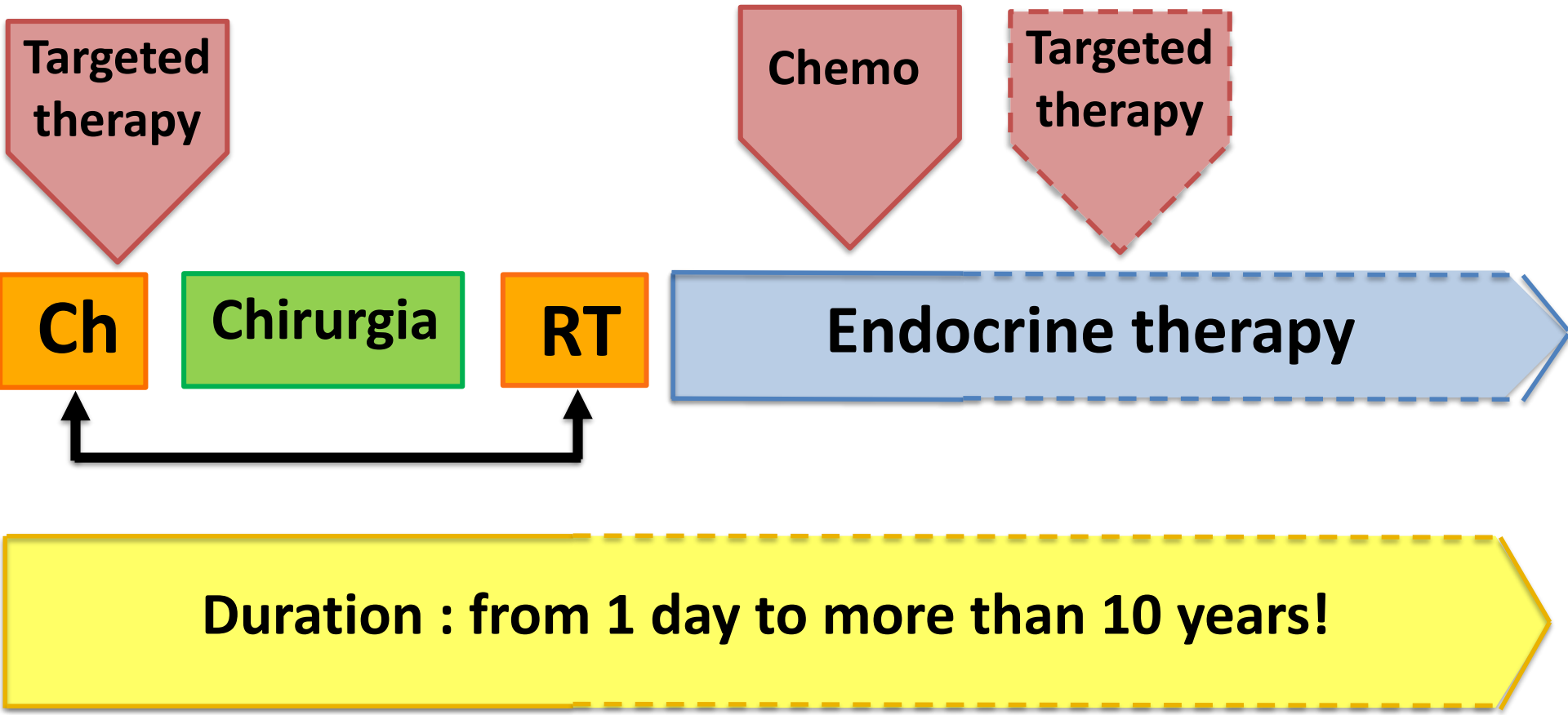
Triple negative: a spectrum



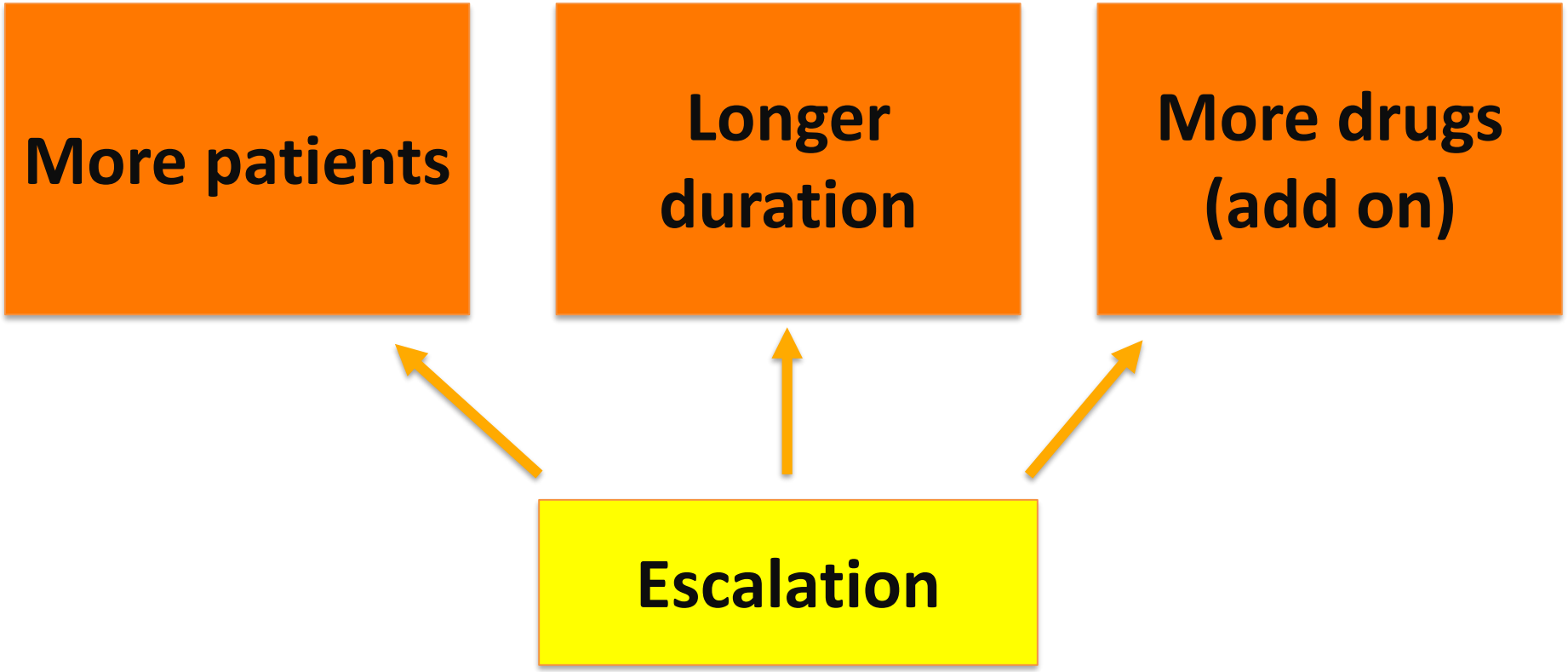
Subtype	Gene expression profile	Clinical
Basal-like 1	high Ki-67; DNA damage response	BRCA-associated
Basal-like 2	GF pathways	Higher pCR
Immunomodulatory	Immune genes	
Mesenchymal	Cell motility	Lower DDFS
Mesenchymal stem-like	Cell motility; claudin-low	
Luminal androgen receptor	Steroid pathways	Apocrine features, higher LRF; PI3Kmut

Lehman BD, et al. J Clin Invest 2011;121:2750-67.

Dove siamo


Targeted therapy
Chemo
Targeted therapy
Ch
Chirurgia
RT
Endocrine therapy
Duration : from 1 day to more than 10 years!

Escalation


More patients
Longer duration
More drugs (add on)
Escalation

De-Escalation: Surgery

1890

1993

1993

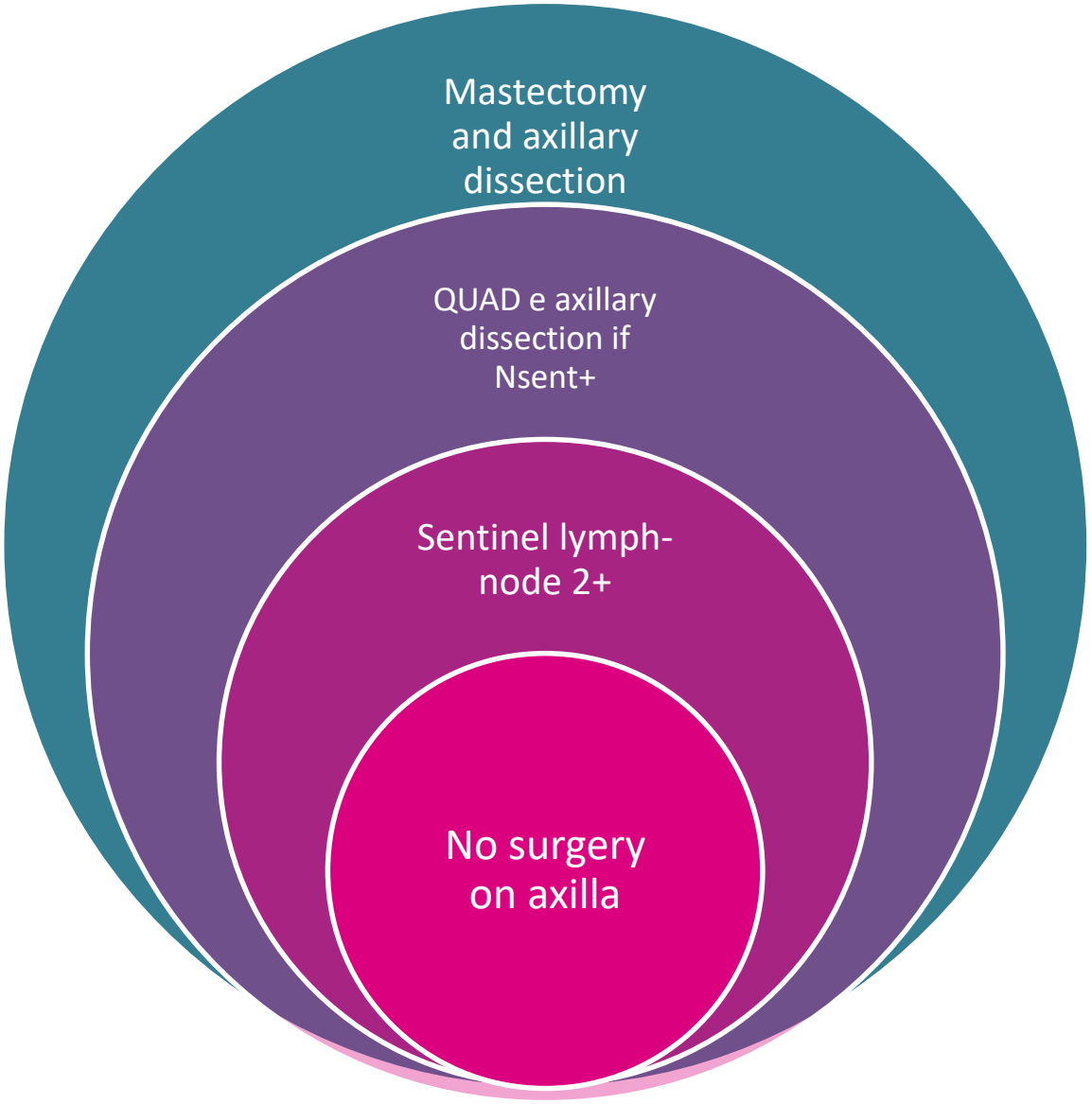
2009

2009

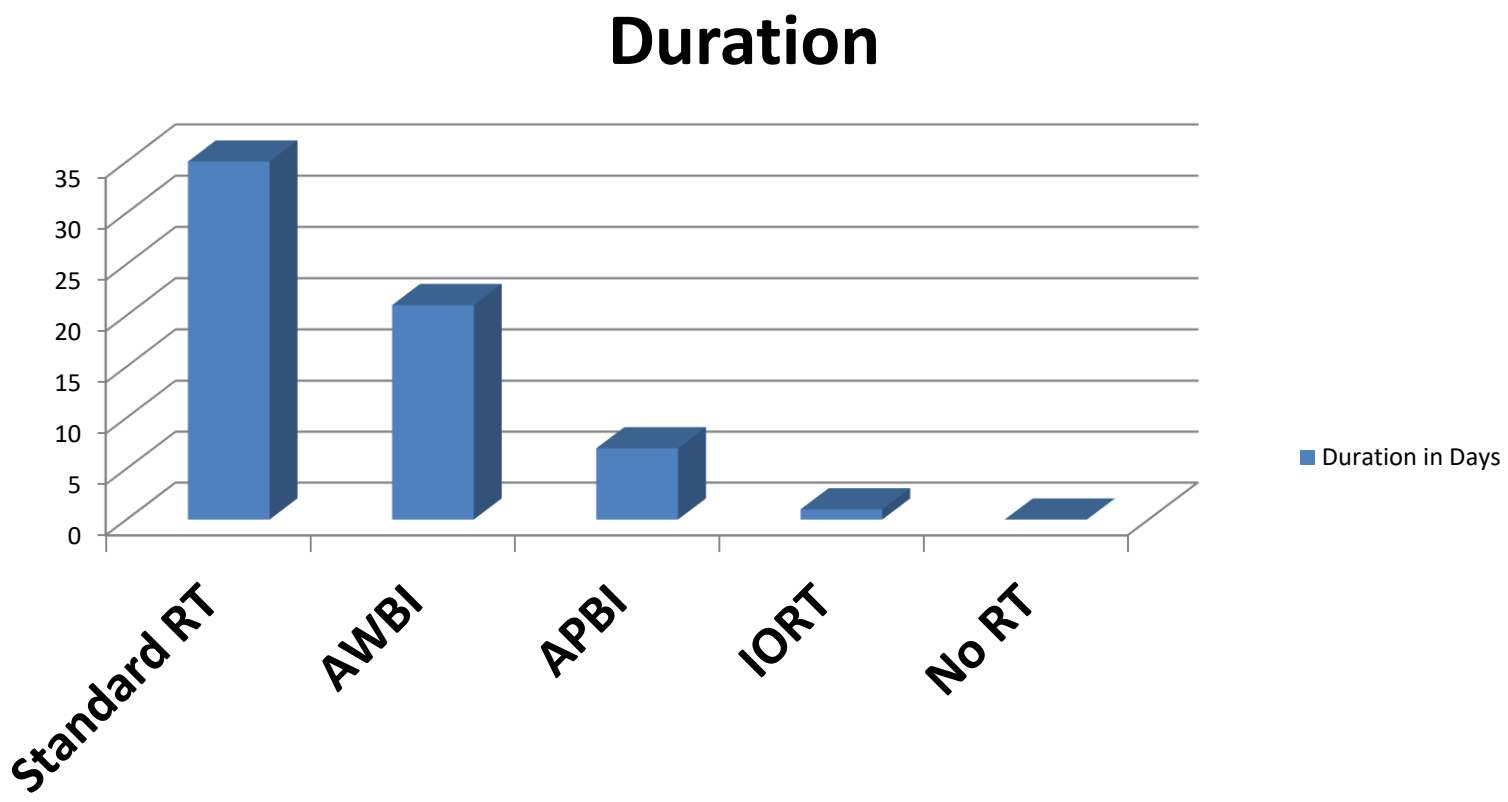
2016

2016

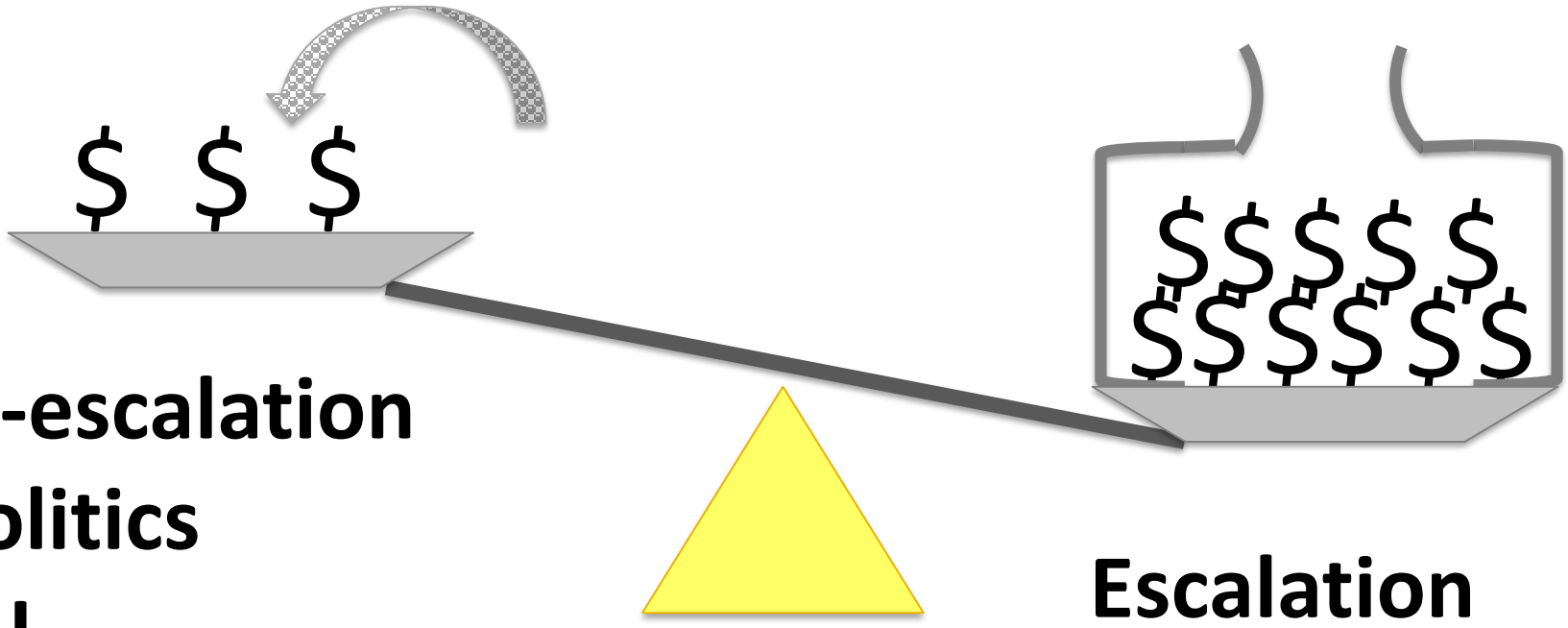
????



De-Escalation: Radiotherapy



Escalation and de-escalation



De-escalation

- **Politics**
- **EU**
- **[Charities]**

Escalation

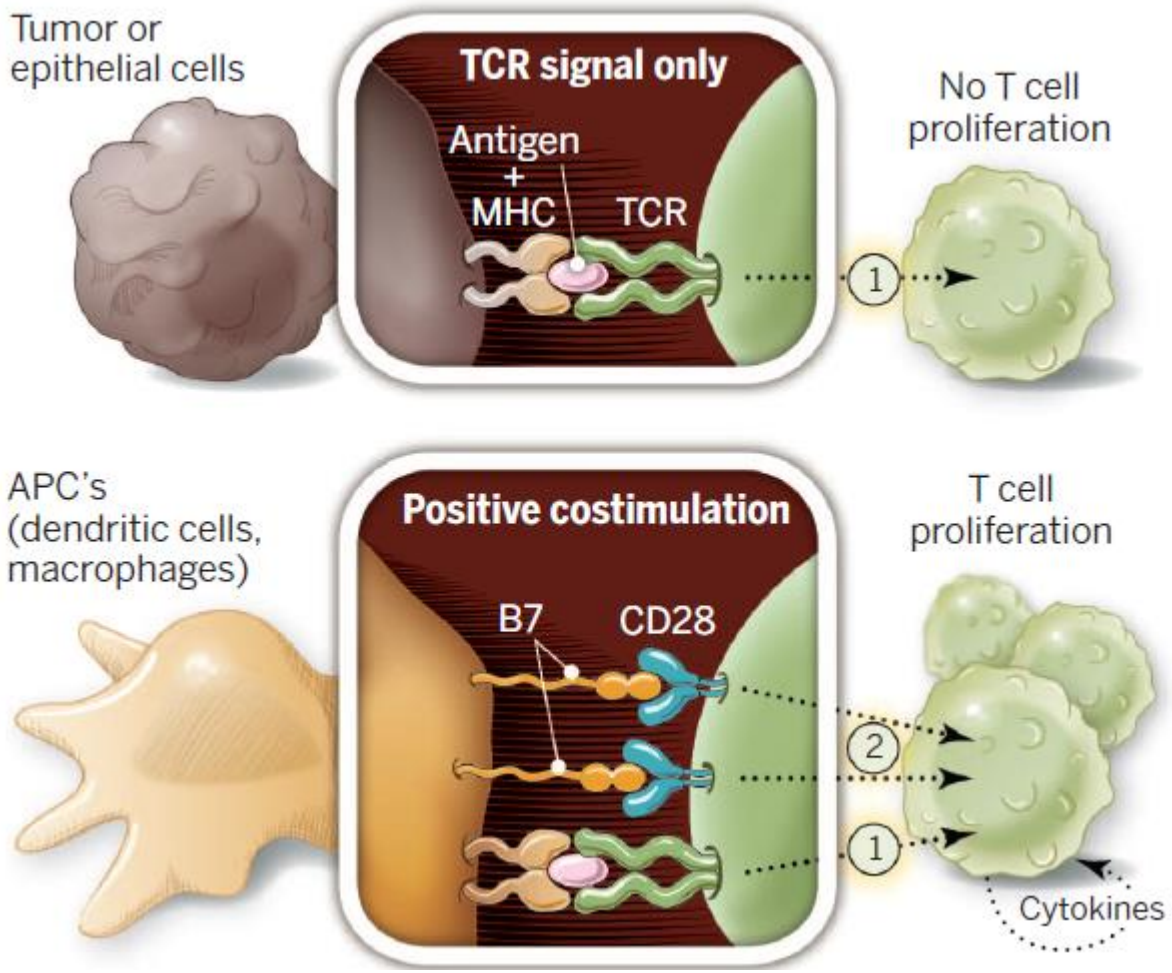
- **Pharma**

Thanks

Immunotherapeutics

Giuseppe Curigliano MD PhD
Istituto Europeo di Oncologia
Division of Early Drug Development

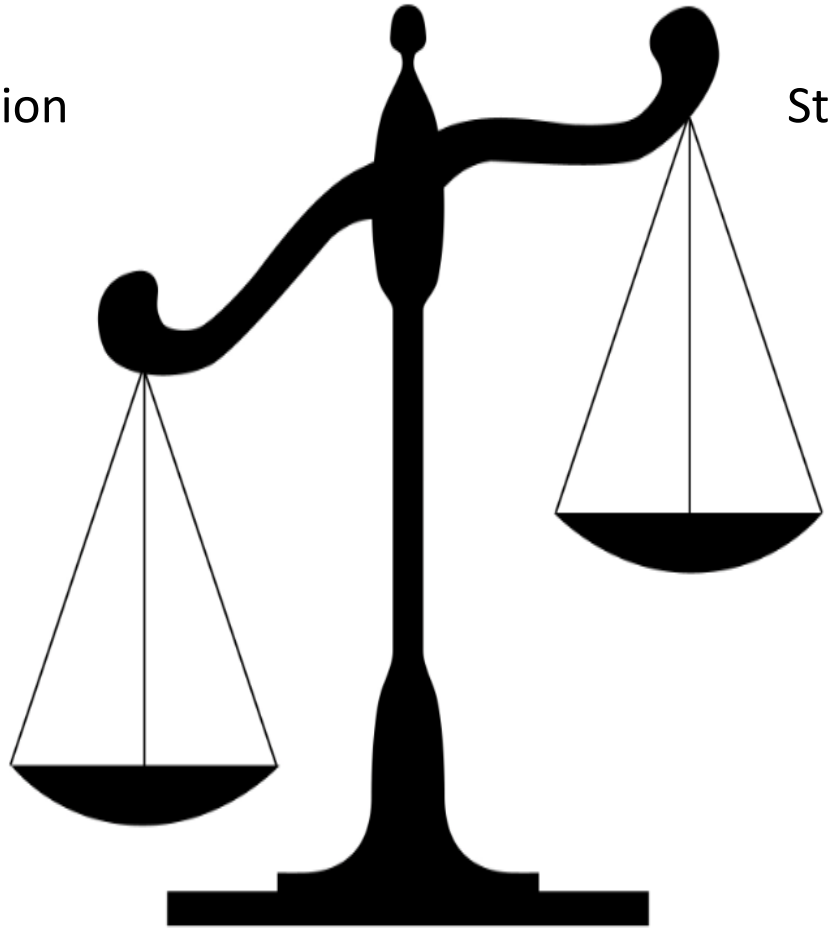
Activation of T cells requires two signals



Science 3 APRIL 2015 • VOL 348 ISSUE 6230

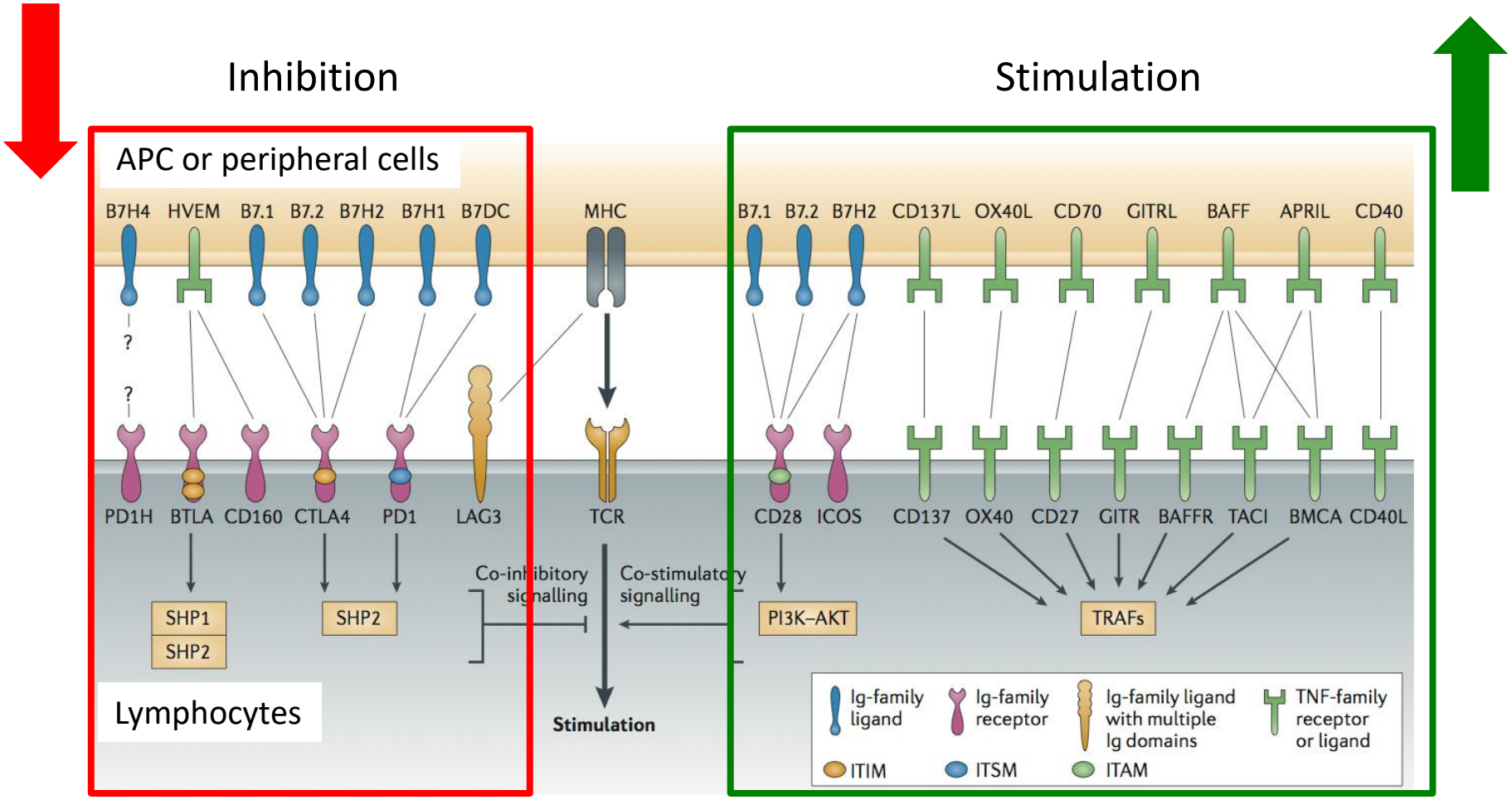
Finely tuning of the immune response

Inhibition



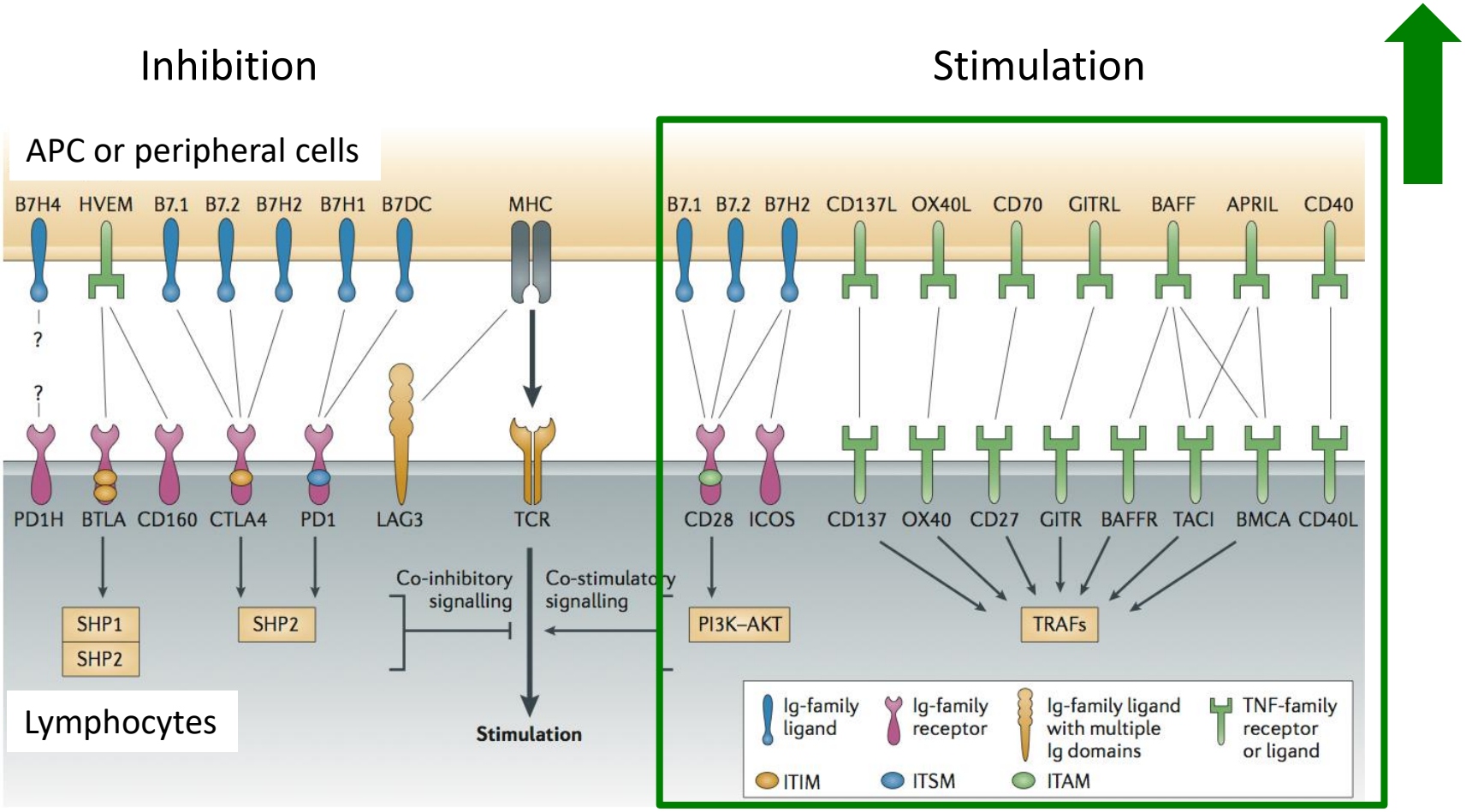
Stimulation

Finely tuning of the immune response
Immune checkpoints



Nature Reviews Drug Discovery 12, 130-146 (February 2013)

Finely tuning of the immune response
Immune checkpoints



Nature Reviews Drug Discovery 12, 130-146 (February 2013)

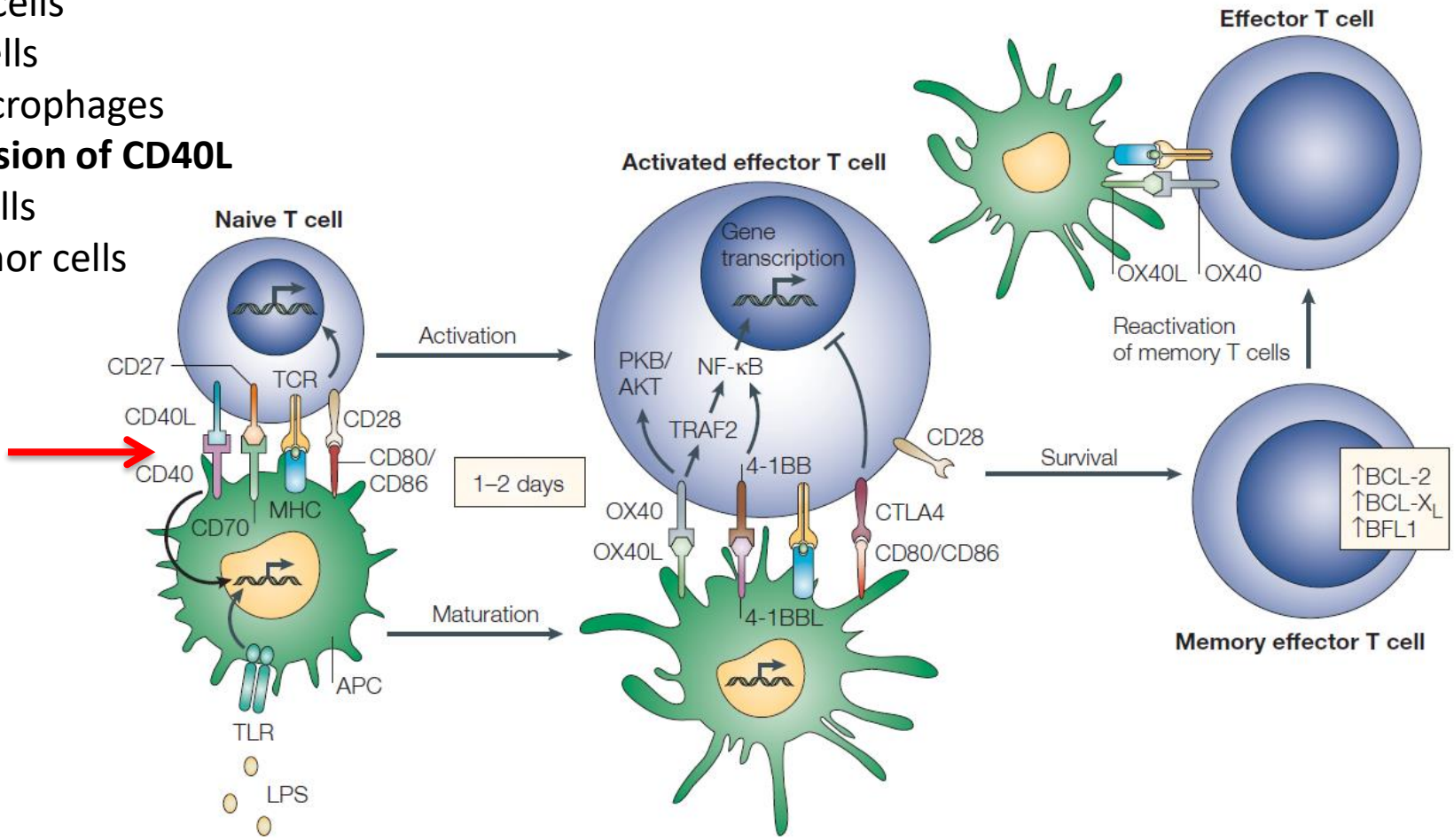
CD40/CD40L

Expression of CD40

- DC cells
- B cells
- Macrophages

Expression of CD40L

- T cells
- Tumor cells

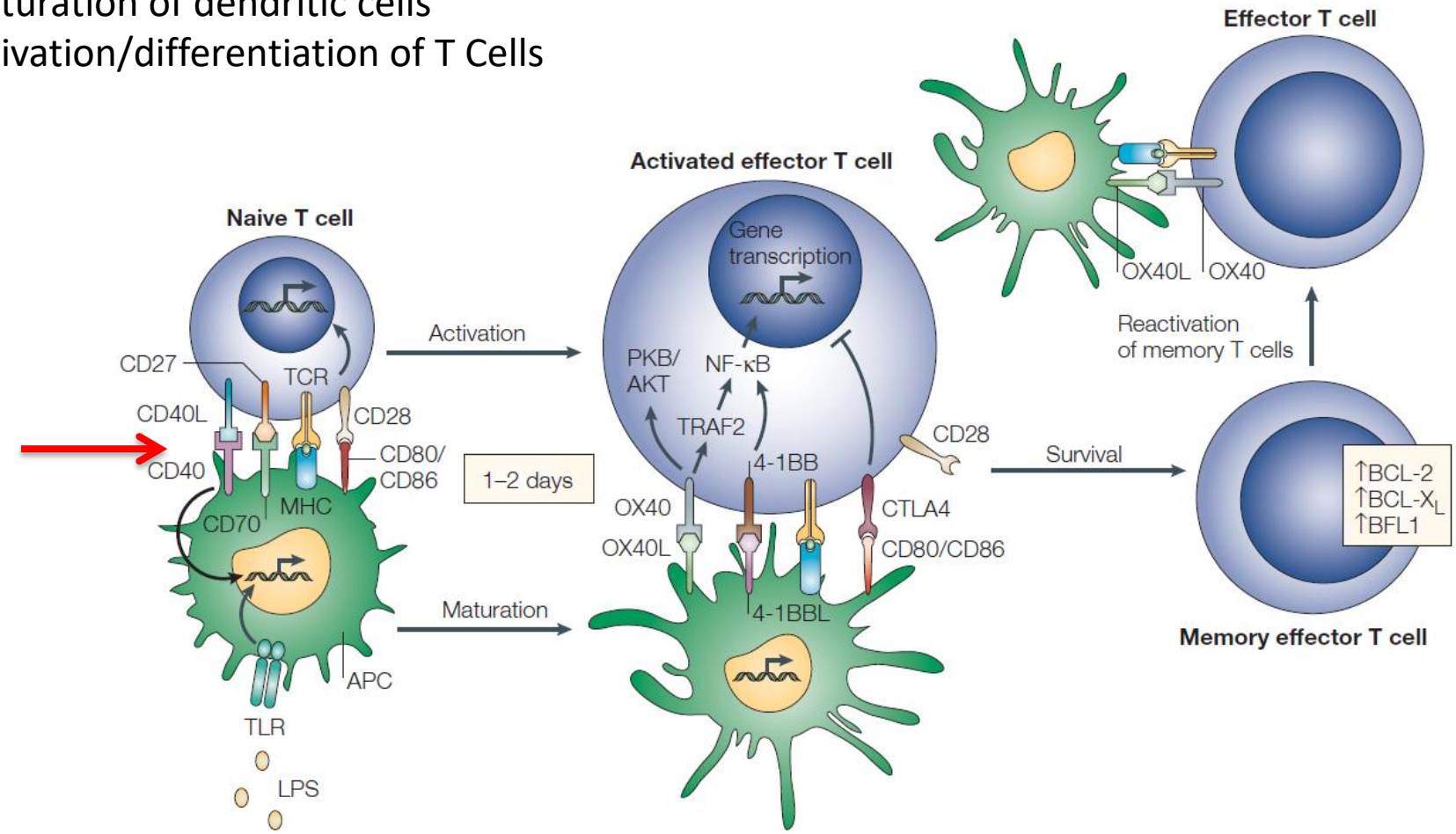


Nature Rev Immunol. 4:420 (2004)

CD40/CD40L

Function

- Maturation of dendritic cells
- Activation/differentiation of T Cells

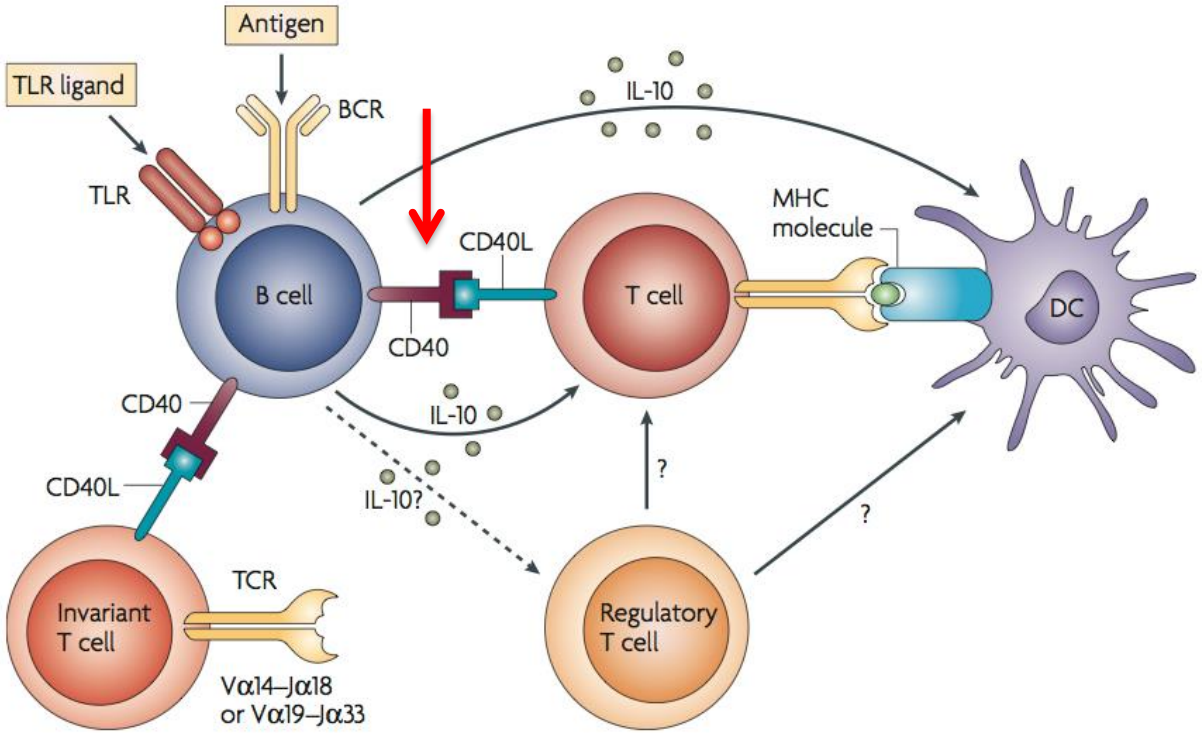


Nature Rev Immunol. 4:420 (2004)

CD40/CD40L

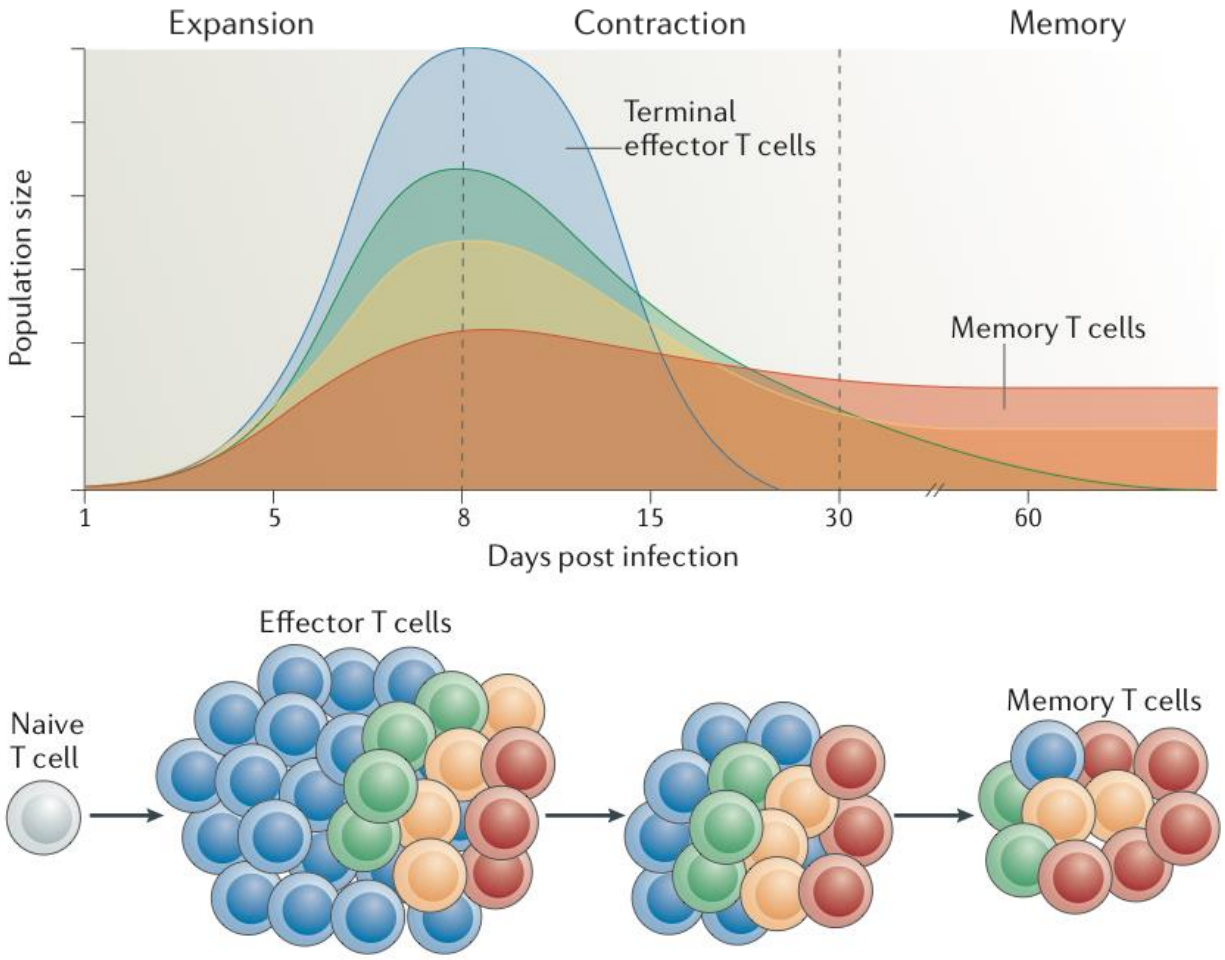
Function (B cells)

- Activation
  - immunoglobulin switching
  - antibody secretion
- Rescue from apoptosis
- Development of germinal centres
- Survival of memory B cells



Nature Reviews Immunology 8, 391-397 (May 2008)

OX40/OX40L:
three phases after antigen stimulation



Nature Reviews Immunology 12, 749-761 (November 2012)

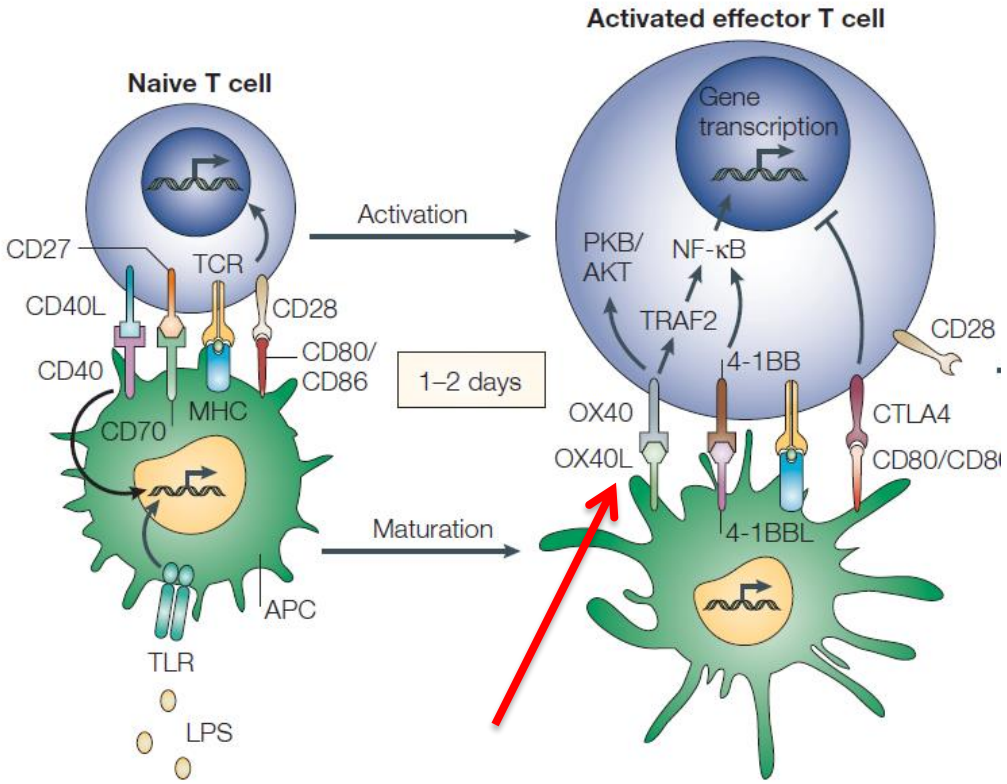
OX40/OX40L

Expression of OX40

- Following antigen stimulation on activated naïve CD4 and CD8 T cells
- Activated regulatory T cells, NKT cells, NK cells, and neutrophils

Expression of OX40L

- Following antigen stimulation on APCs
- Following recognition of antigen on T cells

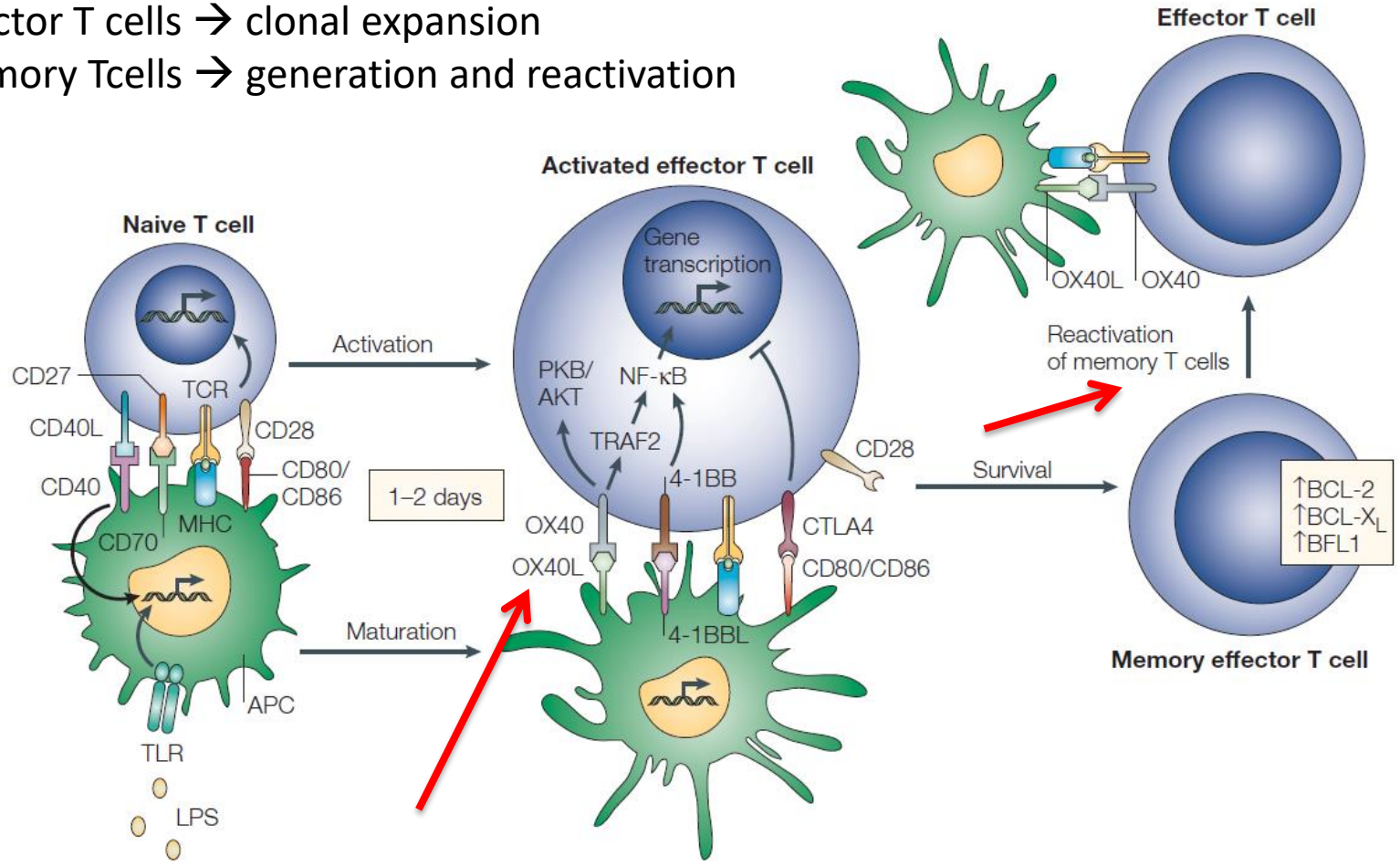


Nature Rev Immunol. 4:420 (2004)

OX40/OX40L
determine the size of effector and memory T cell pools

Function

- Effector T cells → clonal expansion
- Memory Tcells → generation and reactivation

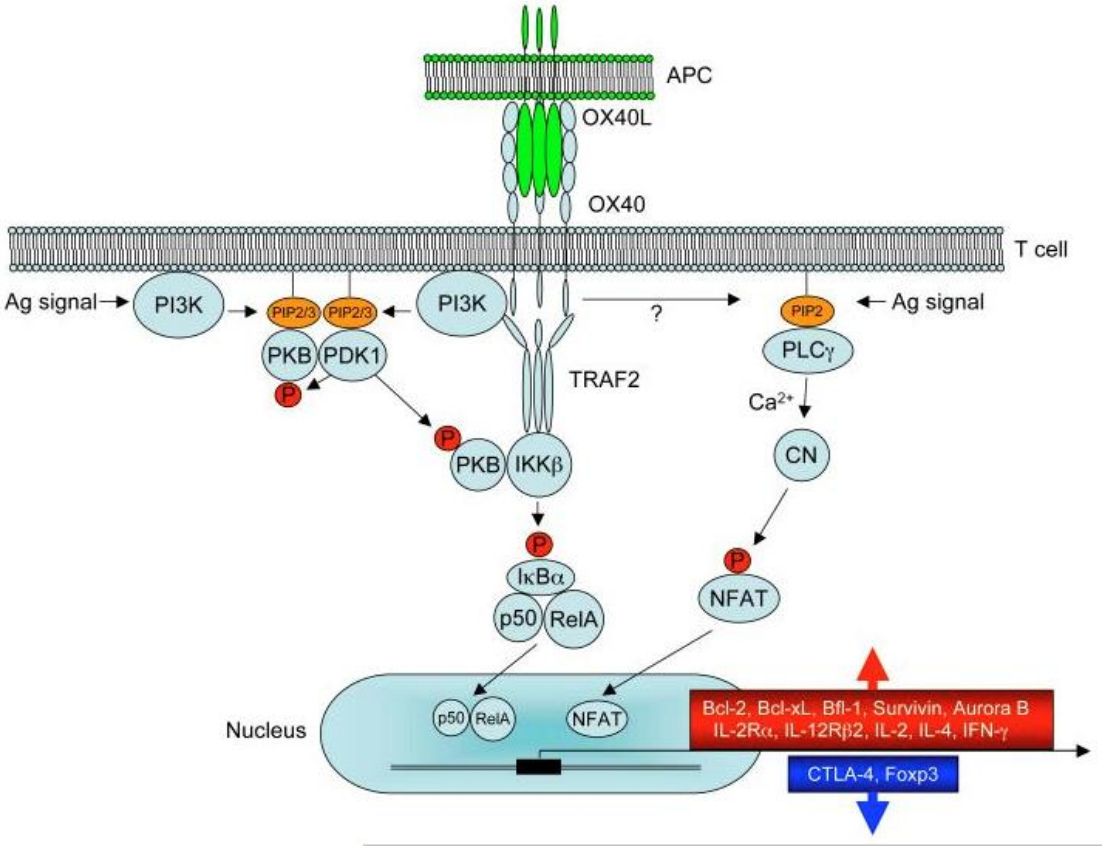


Nature Rev Immunol. 4:420 (2004)

OX40/OX40L

Function

- Effector T cells → clonal expansion
- Memory Tcells → generation and reactivation
- Regulatory T cells → inhibition by downregulation of CTLA4 and FoxP3



Immunol Rev. 2009 May; 229(1): 173–191

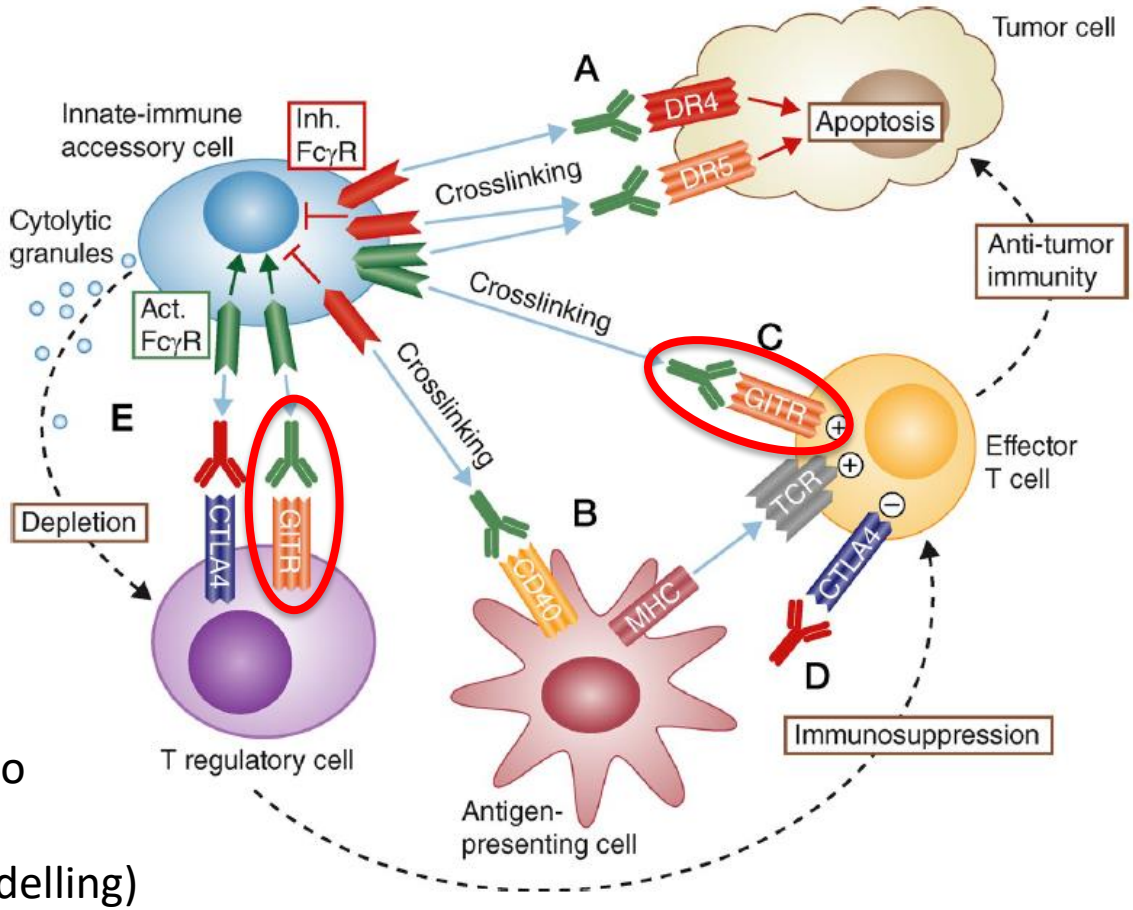
GITR

Expression of GITR

Cell type		
	Naïve	**Activated**
Regulatory T cells	High	Very high
T cells (CD4/CD8)	Intermediate	High
NK cells	Intermediate	High
Granulocytes	Intermediate	High
Mast cells	Intermediate	Intermediate
Eosinophils	Intermediate/low	
Basophils	Intermediate/low	
Monocytes	Low	Intermediate

GITR

Function:



On T regs:
Diverts the cells to Th9 phenotype (chromatin remodelling)

On T eff cells:
Increases survival (protection from activation-induced cell death (AICD) and function

Boosts the effect of CD4 helpers

CA009-002: for solid tumors alone or in combination with Nivolumab

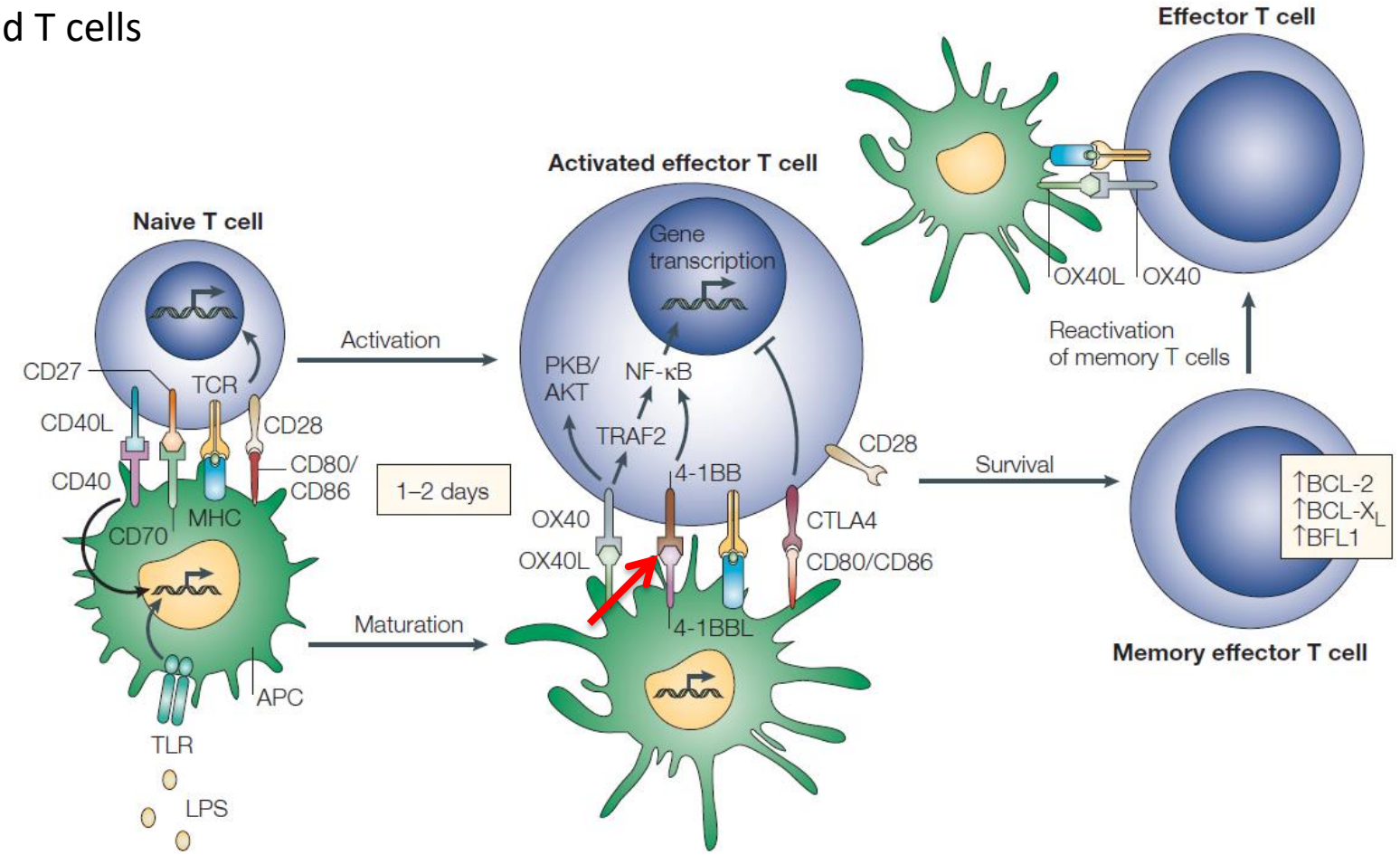
uncleal role

J Ex Med; 210(9), 1695–1710

CD137 (4-1BB): CD137 (4-1BB)L

Expression of CD137:

- stimulated T cells
- T regs
- DCs
- NK cells



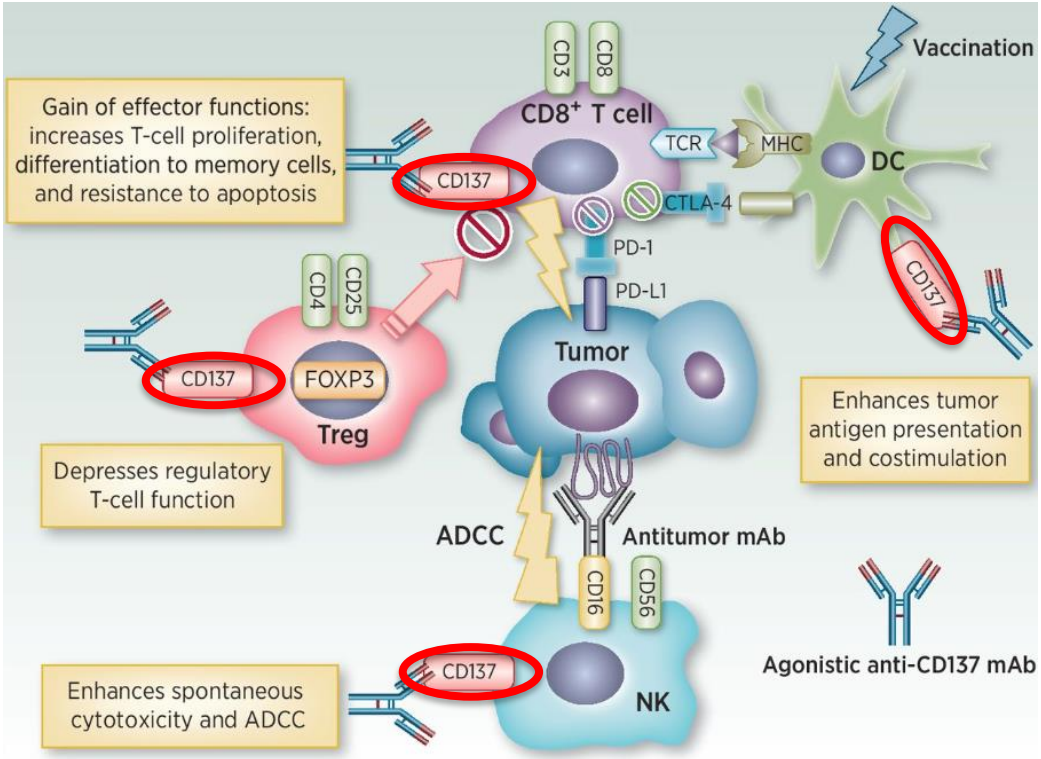
Nature Rev Immunol. 4:420 (2004)

CD137: CD137L

Function:

On T cells increasing:
proliferation, resistance to apoptosis, IFNγ secretion
→ increase in tumor-selective cytolytic T-cell activity

On T reg:
Reduction of T regs infiltration



On DC
Enhancing co-stimulation

On NK
Enhanced ADCC (antibody-dependent cell-mediated cytotoxicity)

Clin Cancer Research July 2015 Volume 21, Issue 14

Clinical trials with Abs targeting CD137

The experience with Urelumab

Phase I, NCT00309023:
- low grade fatigue
- grade 2+ neutropenia, leukopenia, thrombocytopenia, increased in AST and ALT

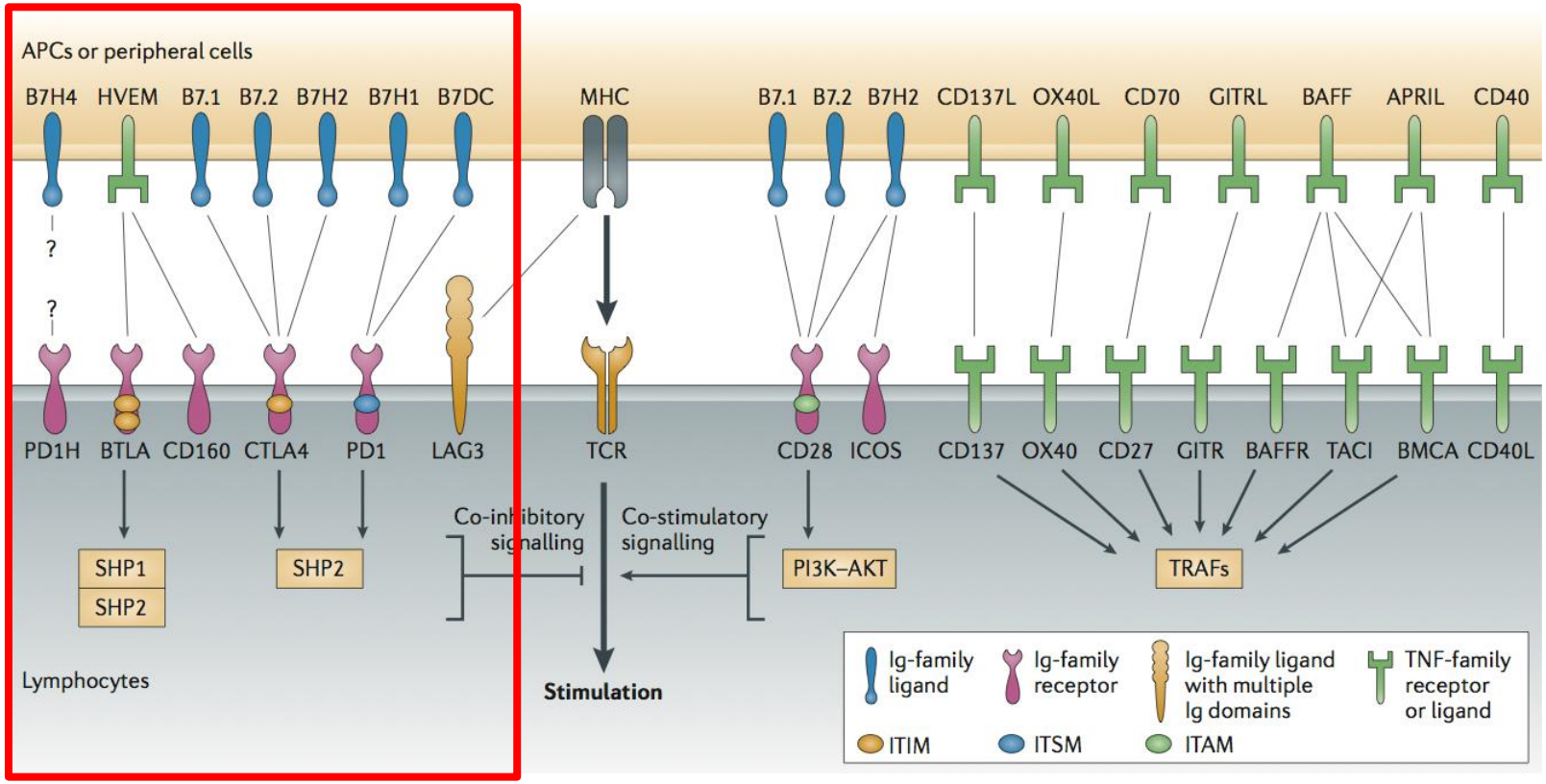
Phase II NCT00612664:
- terminated due to high incidence of Grade IV, potentially fatal, hepatitis

Ab	Trial number	Combination	Indication
Urelumab	NCT01471210		solid tumors and NHL
Urelumab	NCT02110082	Cetuximab	CRC and HN cancer
Urelumab	NCT01775621	Rituximab	Lymphoma
Urelumab	NCT02253992	Nivolumab	solid tumors and NHL
PF-05082566	NCT02179918	Pembrolizumab	solid tumors
PF-05082566	NCT01307267	Rituximab	NHL

Co-stimulatory molecules, treatments in development

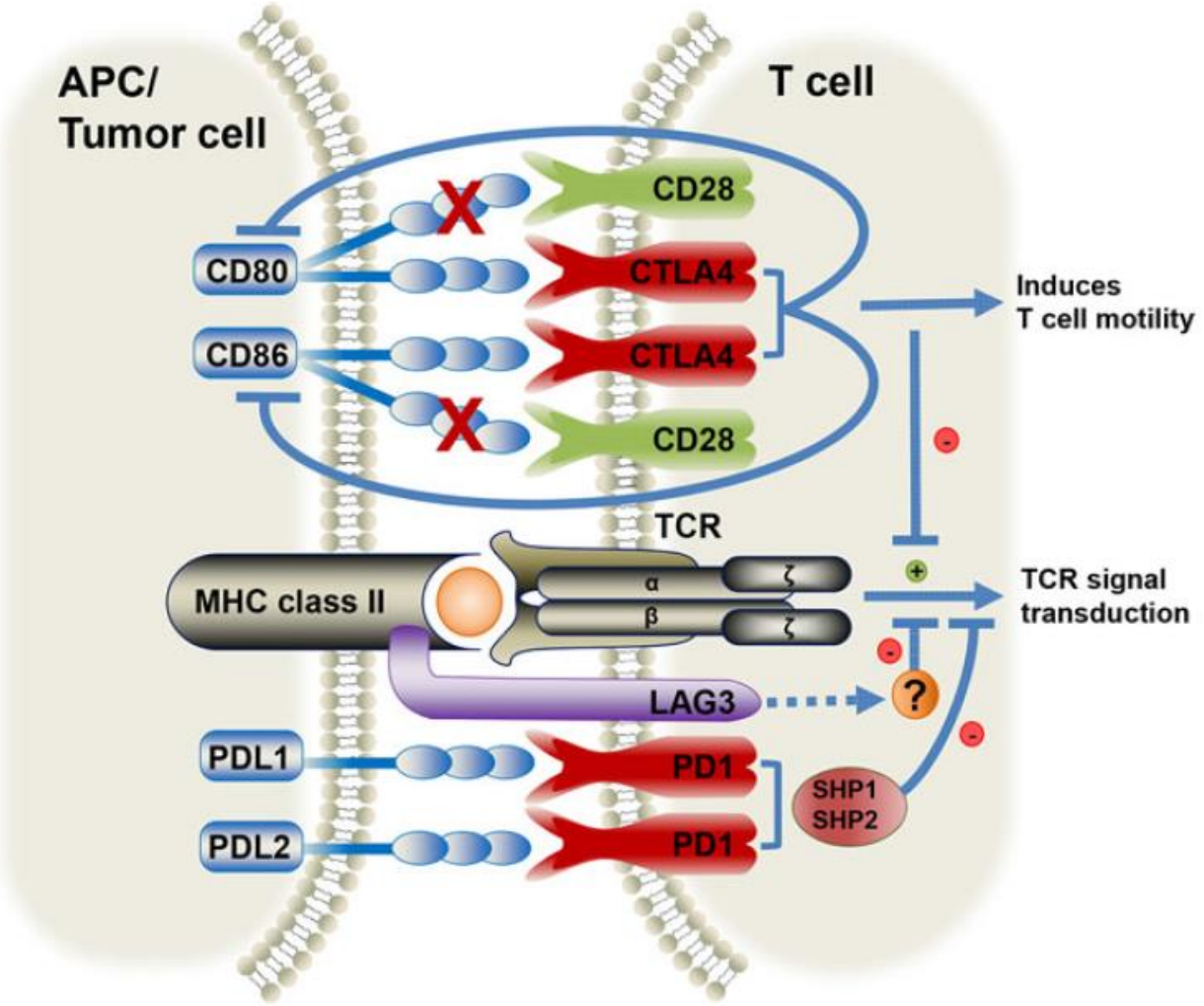
Name	Treatment
CD28:CD80/86	TAB08
CD27:CD70	Varilumab
CD40:CD40L	CP870, 893, ChiLob7/4
OX40:OX40L	MEDI0562, 6469, 6383, MOXR0916
GITR:GITRL	TRX518 GWN323 MEDI1873 INCAGN01876
CD137: CD137L	Urelumab, PF-05082566

Co-inhibition and co-stimulation determine the quality of the T cell response



Nature Reviews Drug Discovery 12, 130-146 (February 2013)

Co-inhibitory molecules

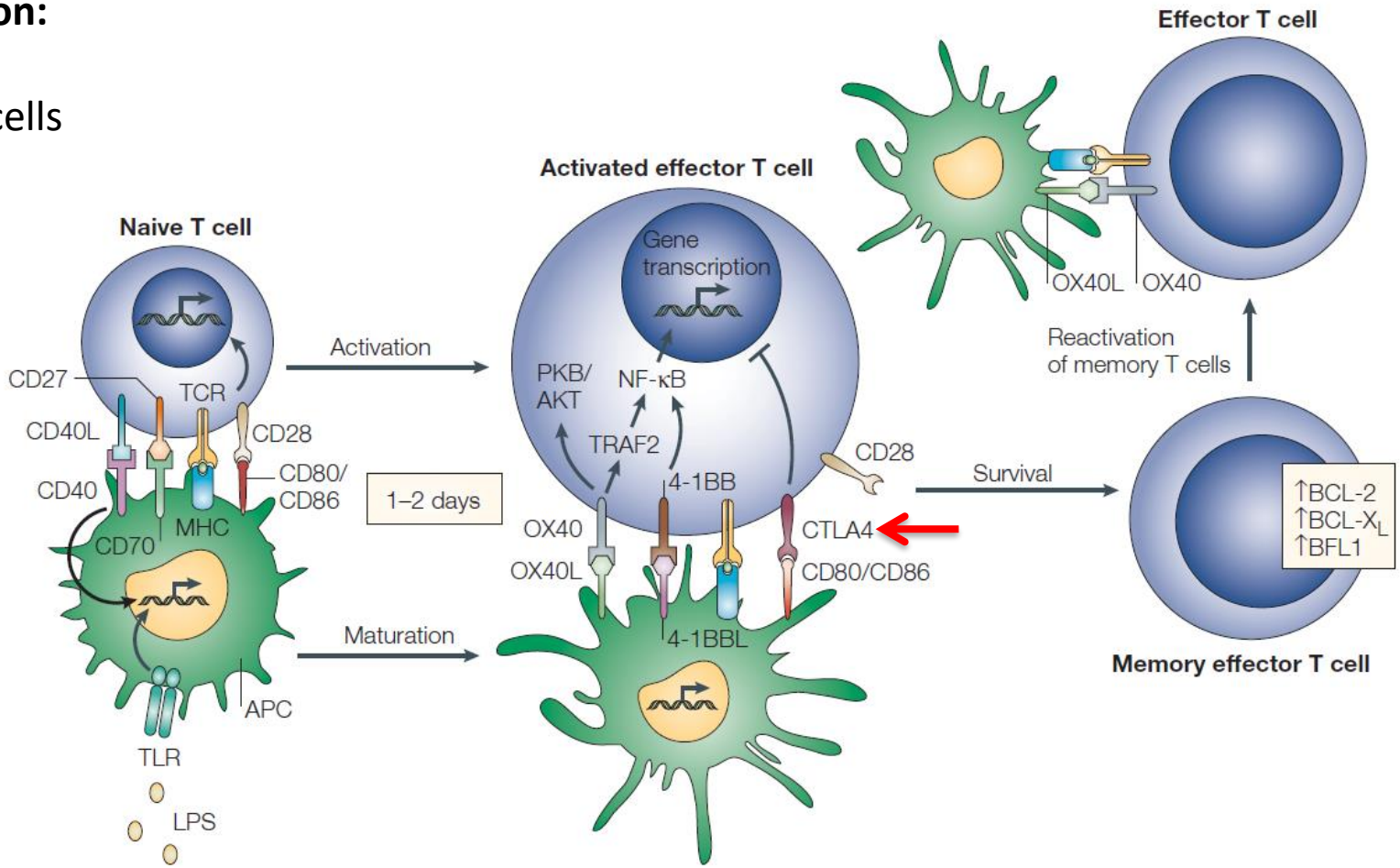


Eur. J. Immunol. 2015. 45: 1892–1905

CTLA4

Expression:

- T regs
- T eff cells

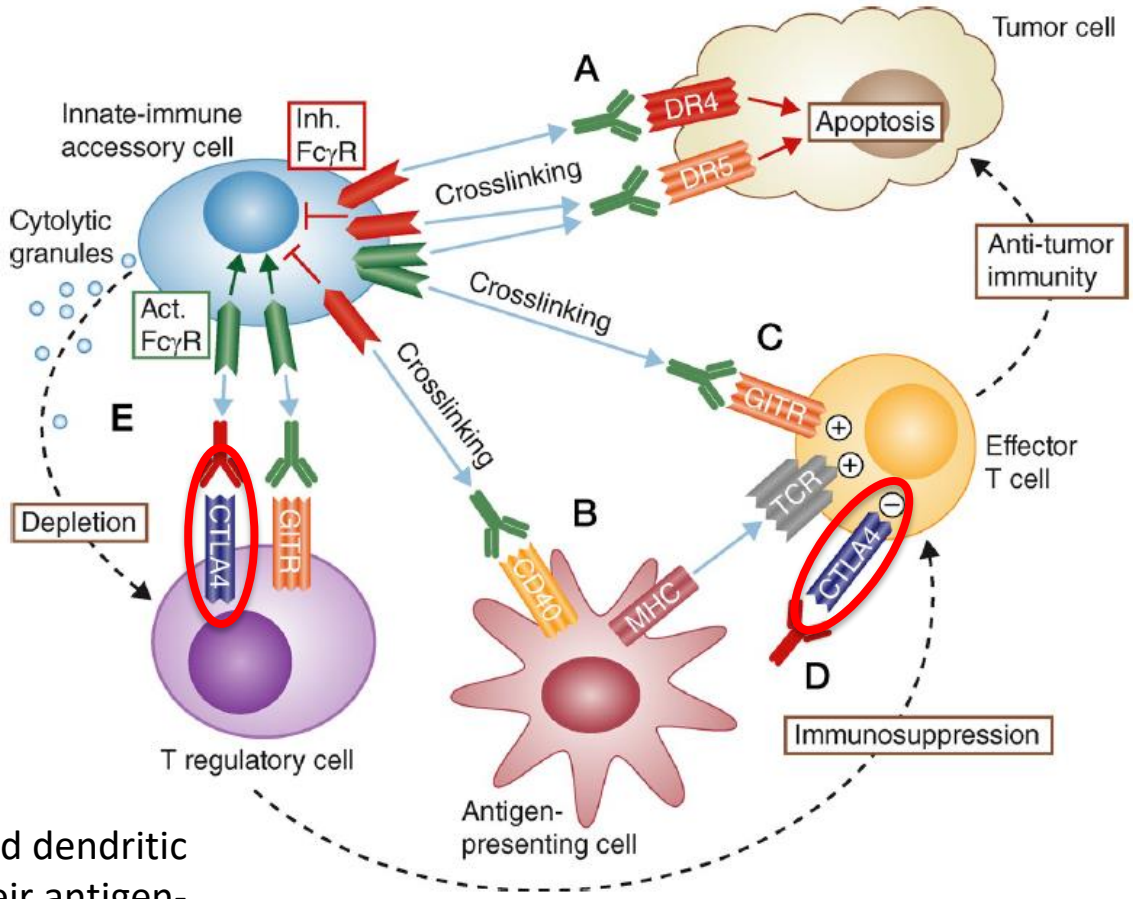


Activation of T cells → proliferation and functional differentiation
→ **inhibitory program → stop proliferation**

Nature Rev Immunol. 4:420 (2004)

CTLA4

Function:



On T eff cells:
as a negative feedback regulator

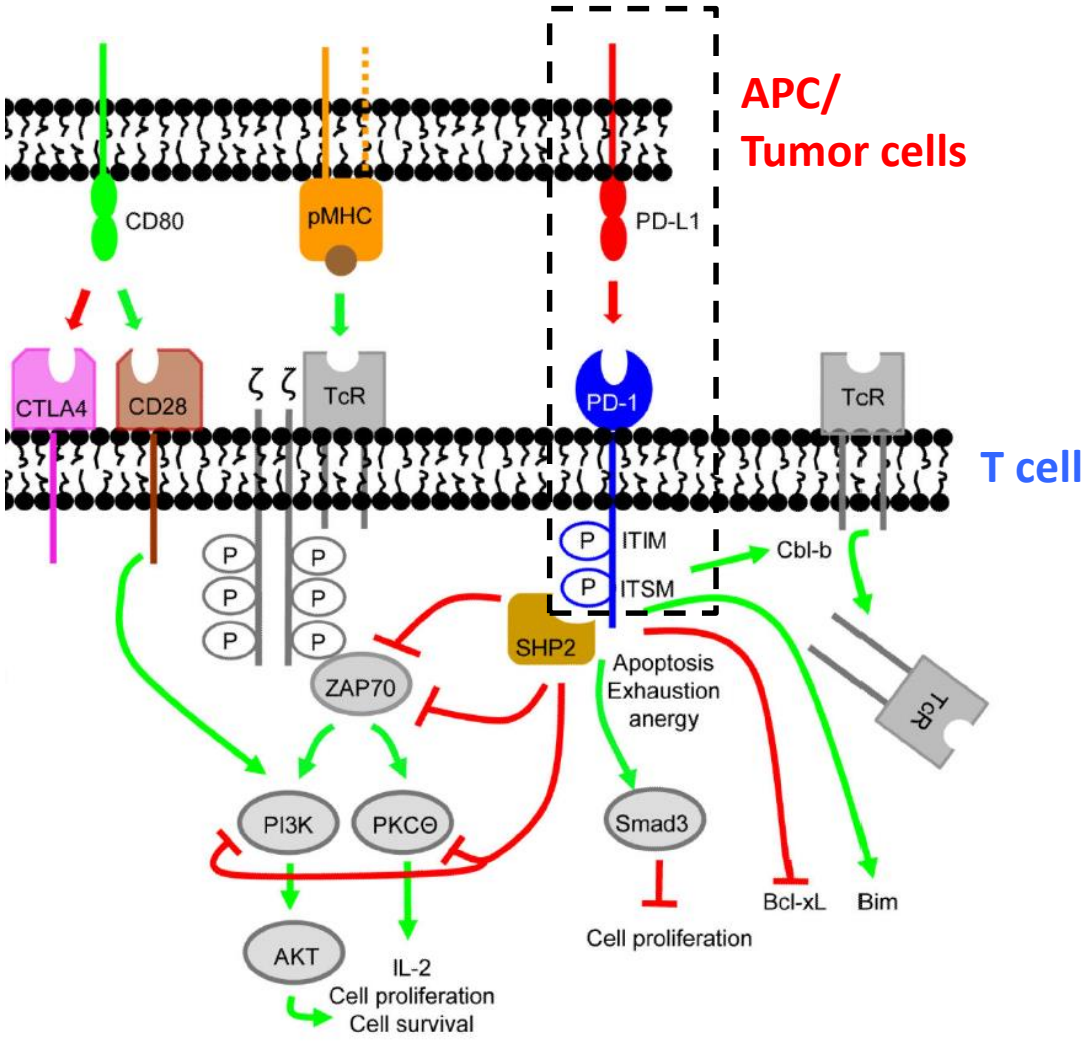
On T regs:
to aggregate around dendritic cells and inhibit their antigen-presenting activity

J Ex Med; 210(9), 1695–1710

The PD-L1/PD1 pathway leads to:

Function

- T cell death
- Down-regulation of activated T cells
- Reduction of T cells to kill tumor cells



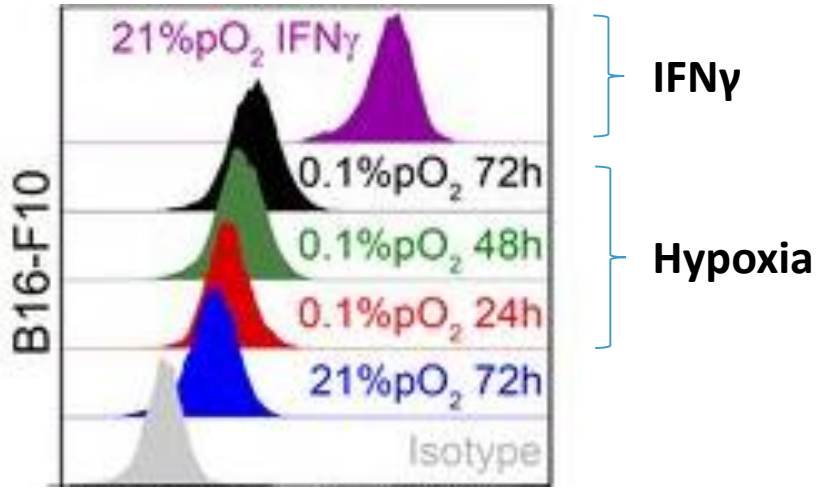
Adapted from J. Immunology 2014, 193(8): 3835–3841

The PD-L1 molecule

PD-L1 is expressed on:
Activated T cells, NK cells, macrophages, myeloid DCs, B cells, epithelial cells, vascular endothelial cells; tumor cells

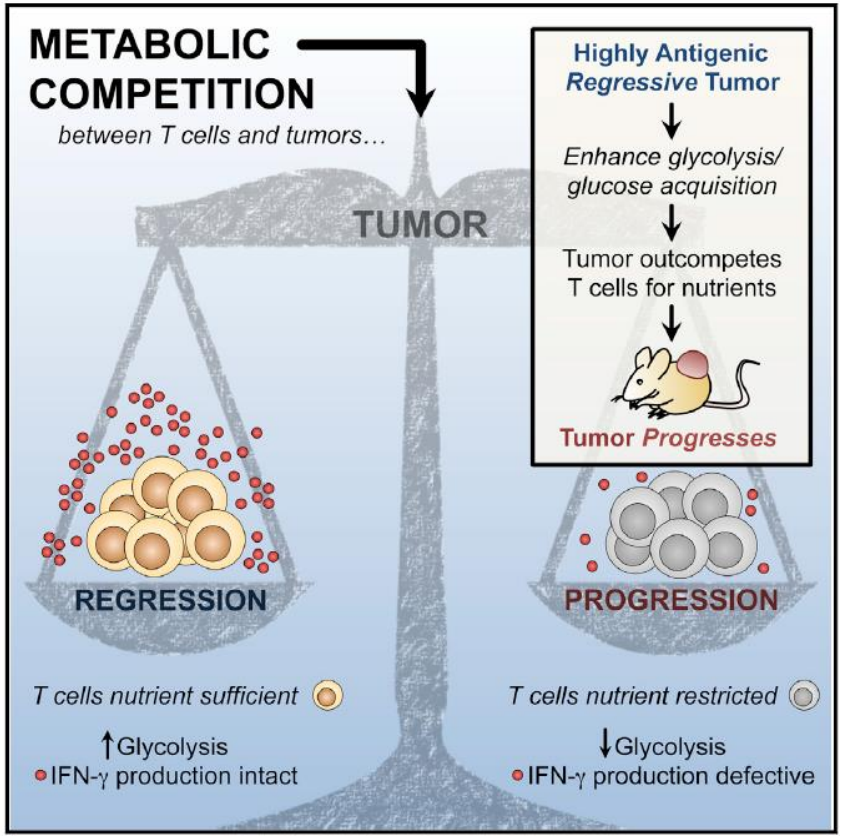
Expression of PD-L1 is induced by :
Type 1 and Type 2 IFNs, TNFα, LPS, GM-CSF, VEGF, IL-10, IL4

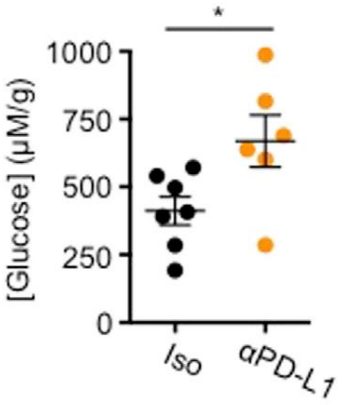
Expression of PD-L1 can be downregulated by:
downregulation of PI3K; ALK/STAT3 ; NF-kB; miRNA513;wtPTEN



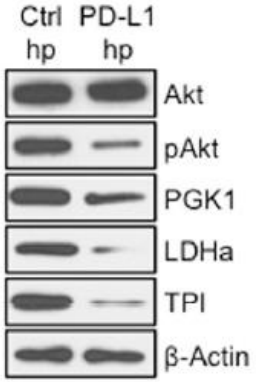
Adapted from J Exp Med 2014;211:781-790

PD-L1 has also a direct tumor activity





PD-L1 enhances tumor cell glycolysis and thus depletes glucose from immune cells in the tumor microenvironment



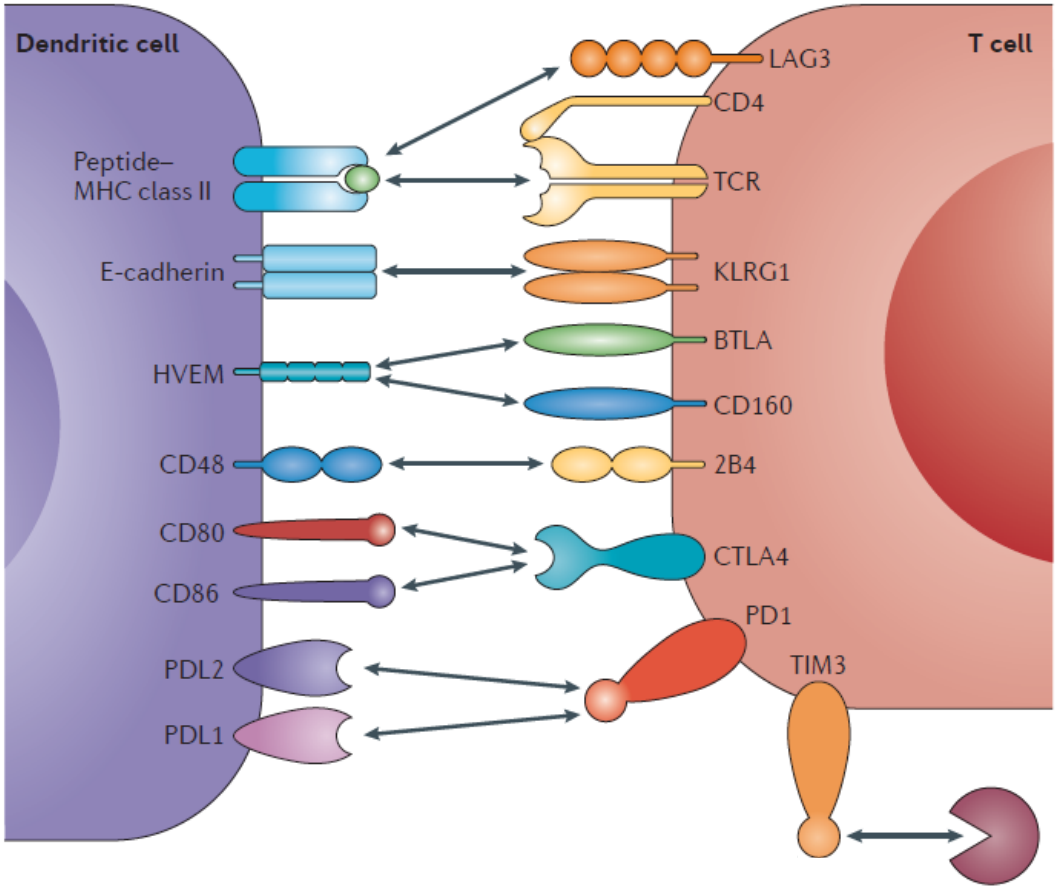
PD-L1 is important for Akt/mTOR signaling in tumors.

Cell 2015; 162: 1229–1241

LAG3: CD4 homologue, binding MHC II

Expression

- On exhausted T cells
- On TIL
- On T regs
- On NK



Function

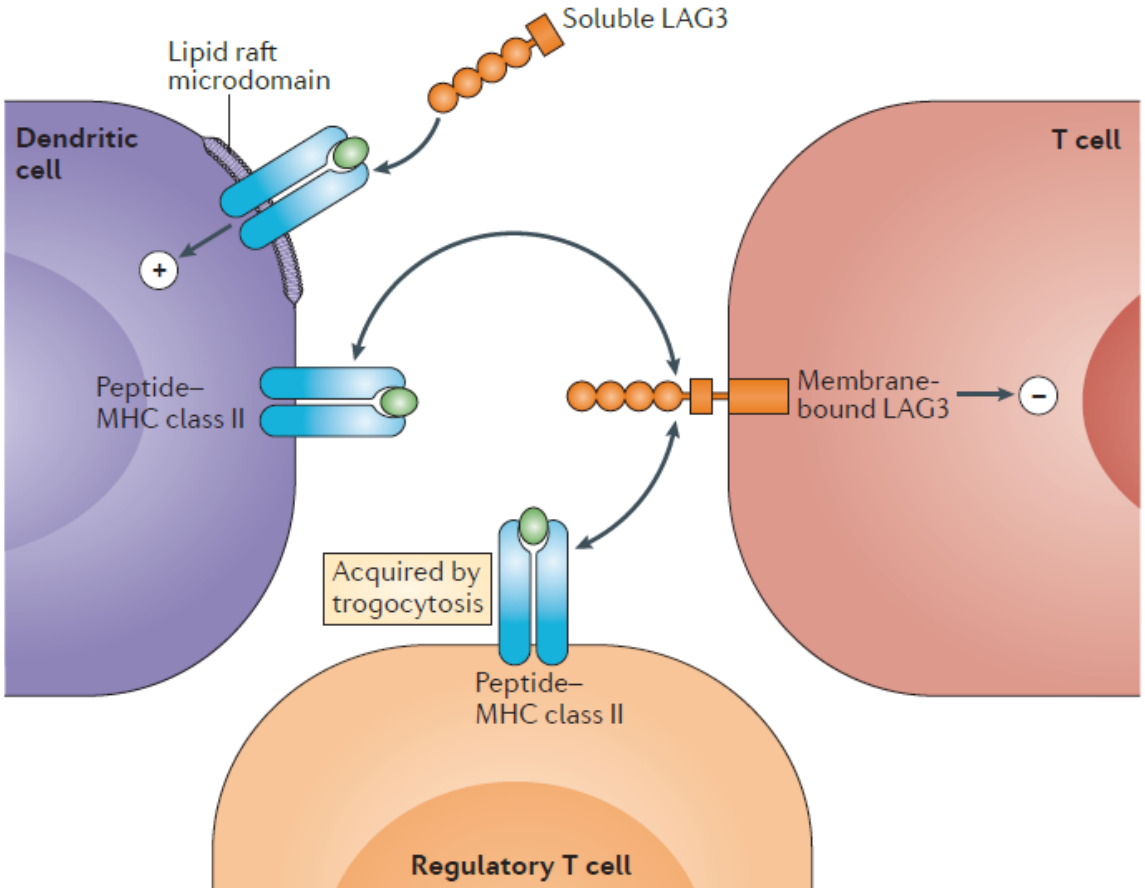
- Confers a Treg function on CD4 naïve T cells

LAG3 negatively regulates

- T-cell activation
- Proliferation
- Homeostatic expansion

Adapted from Nature Reviews Immunology 15; 2015: 45-56

Soluble LAG3 is an immunoadjuvant

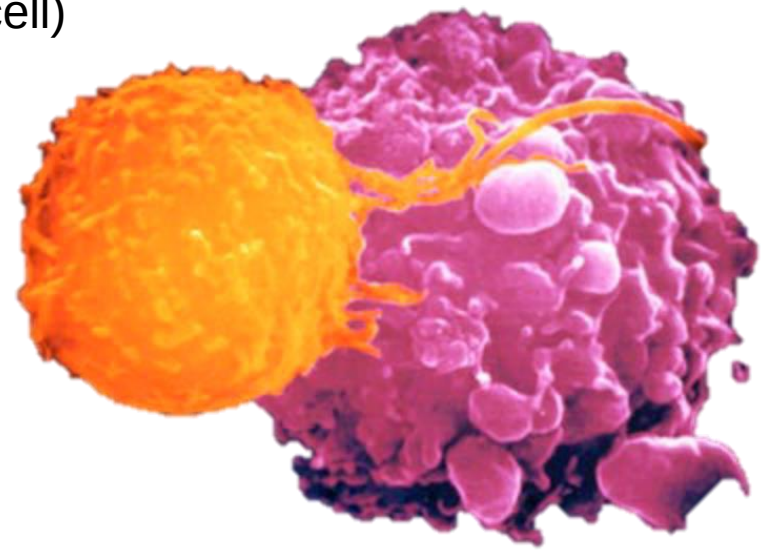


Adapted from Nature Reviews Immunology 15; 2015: 45-56

Adoptive Cell Therapy

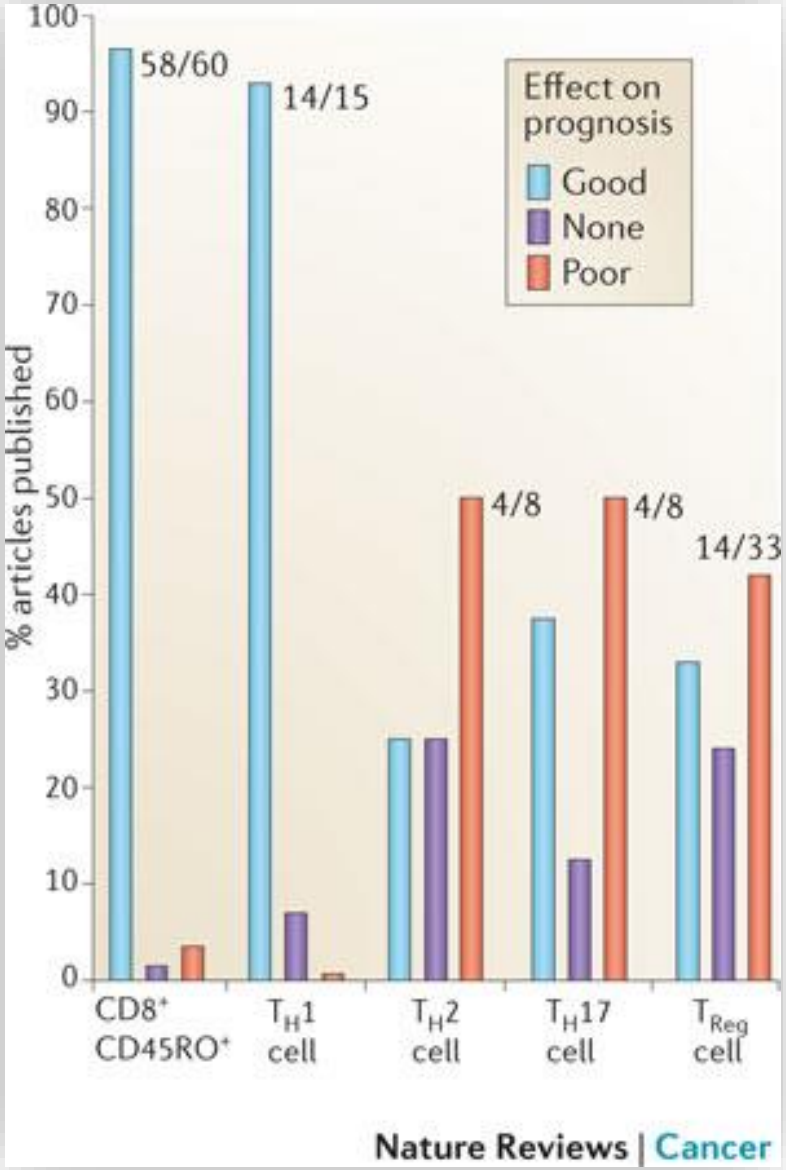
T lymphocyte
(T cell)

Tumor cell



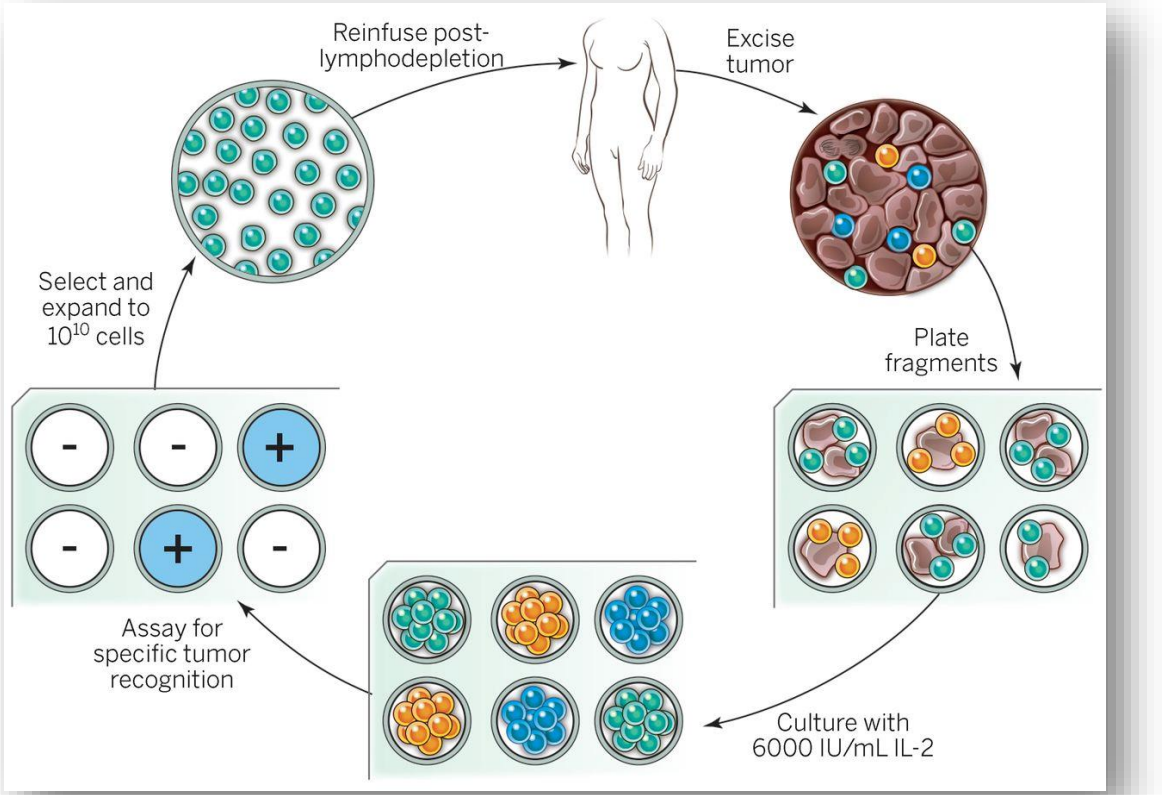
We need More T cells
We need them functional (Armed and Activated)
We need them Powerful and Persistent
We want them to reach tumor site
We need them targeted and specific

TILs and prognosis



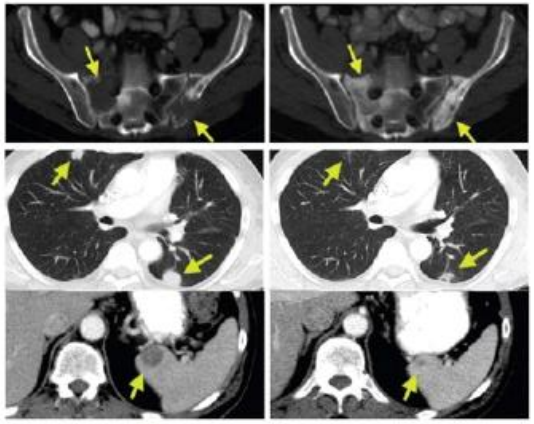
Fridman et al, Nature Review Cancer, 2012

OPTION 1: Adoptive Immunotherapy Using Natural T Cells

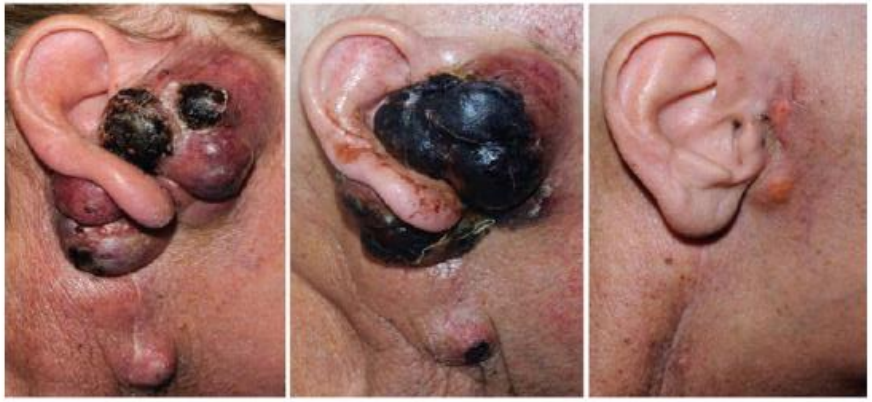


Rosenberg & Restifo Science 03 Apr 2015

TILS are powerful: Compelling Results in Late Stage Disease



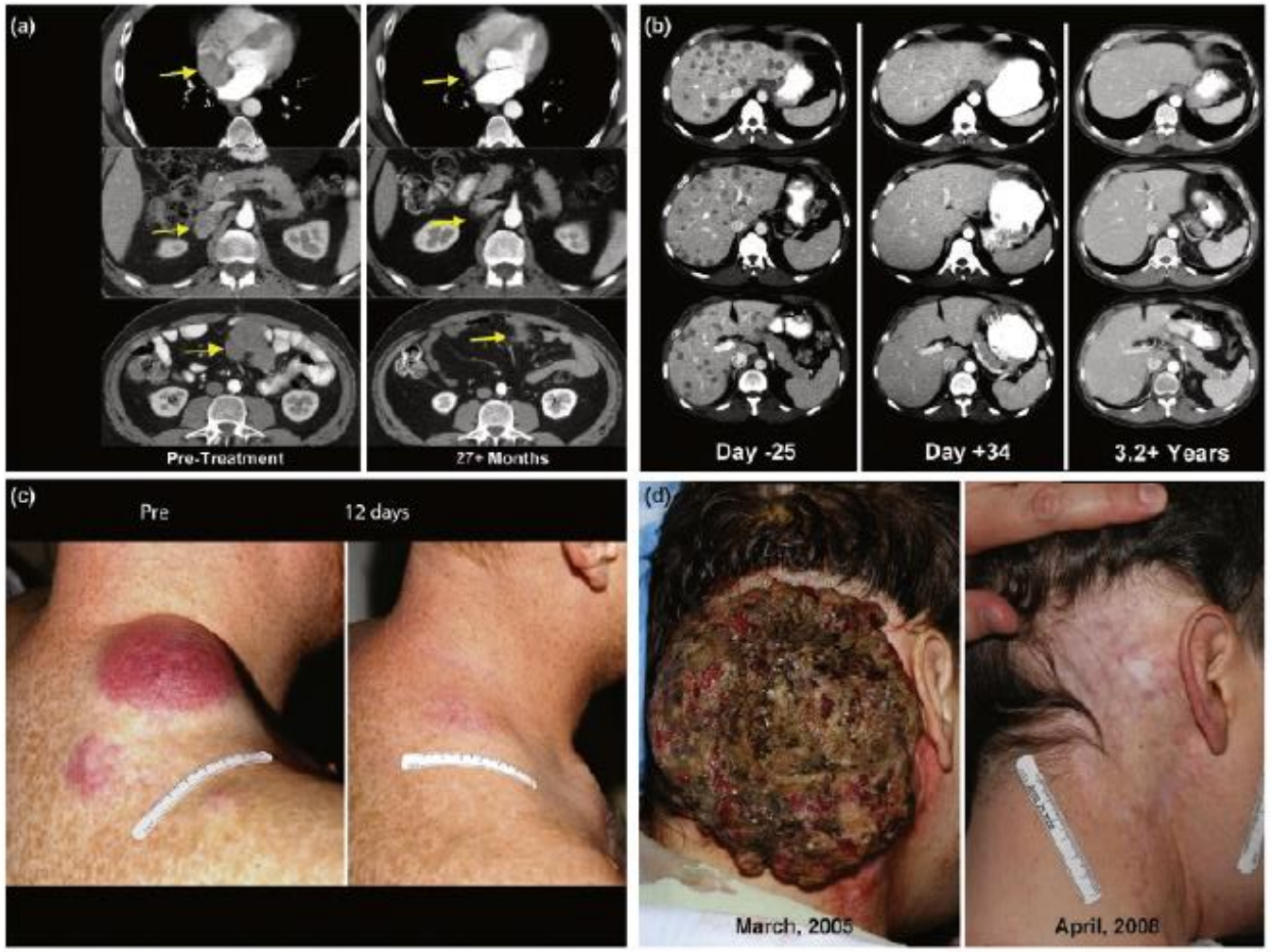
Pretreatment 2 months posttreatment



Day –9 Day +11 Day +76

Clinical Cancer Research December 15, 2010 16: 6122

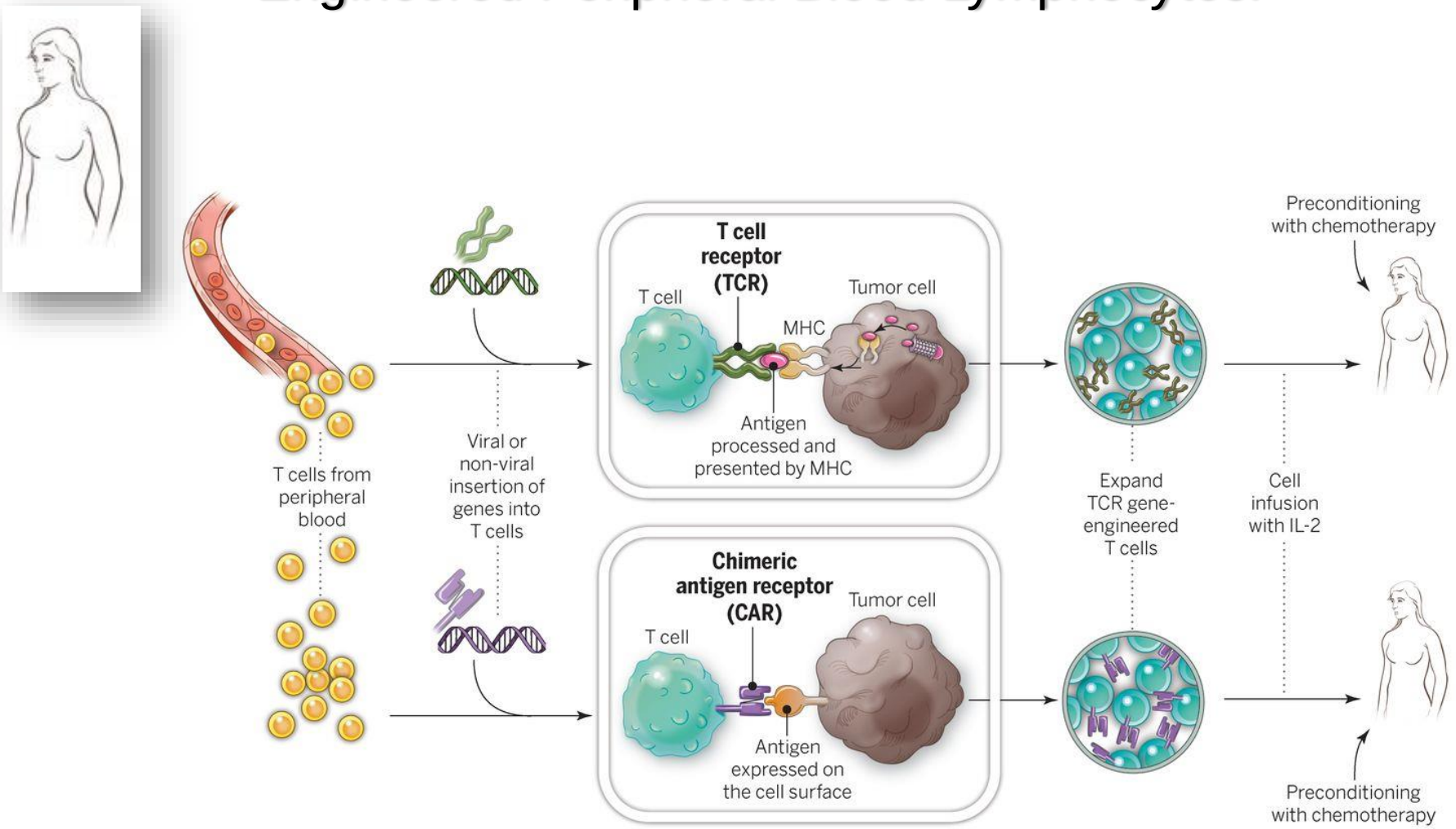
TILs: Regressions in Late-Stage Disease



Current Opinion in Immunology 2009, 21:233–240

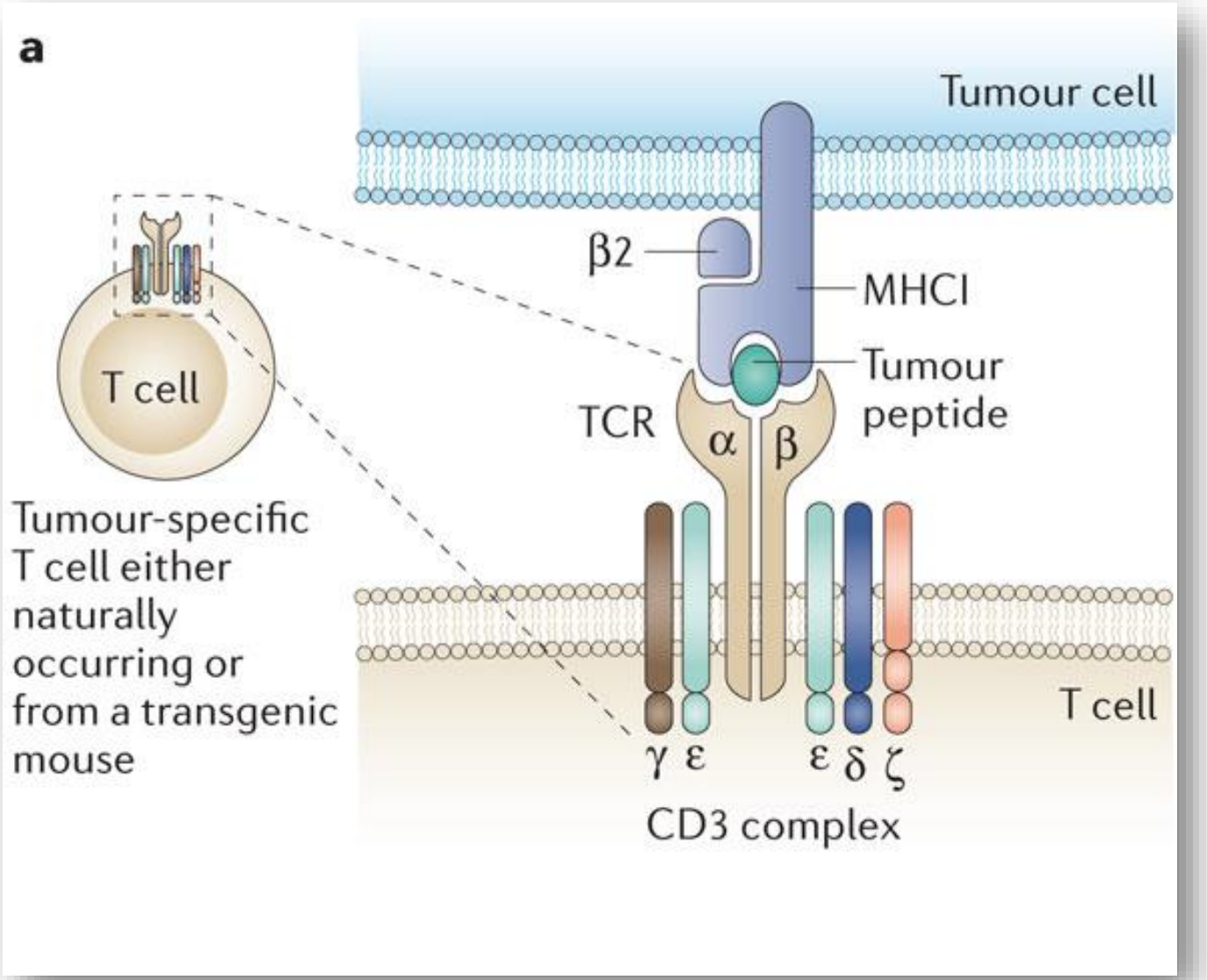
Current Opinion in Immunology 2009, 21:233–240

OPTION 2: Adoptive T cell Therapy with Genetically Engineered Peripheral Blood Lymphocytes.

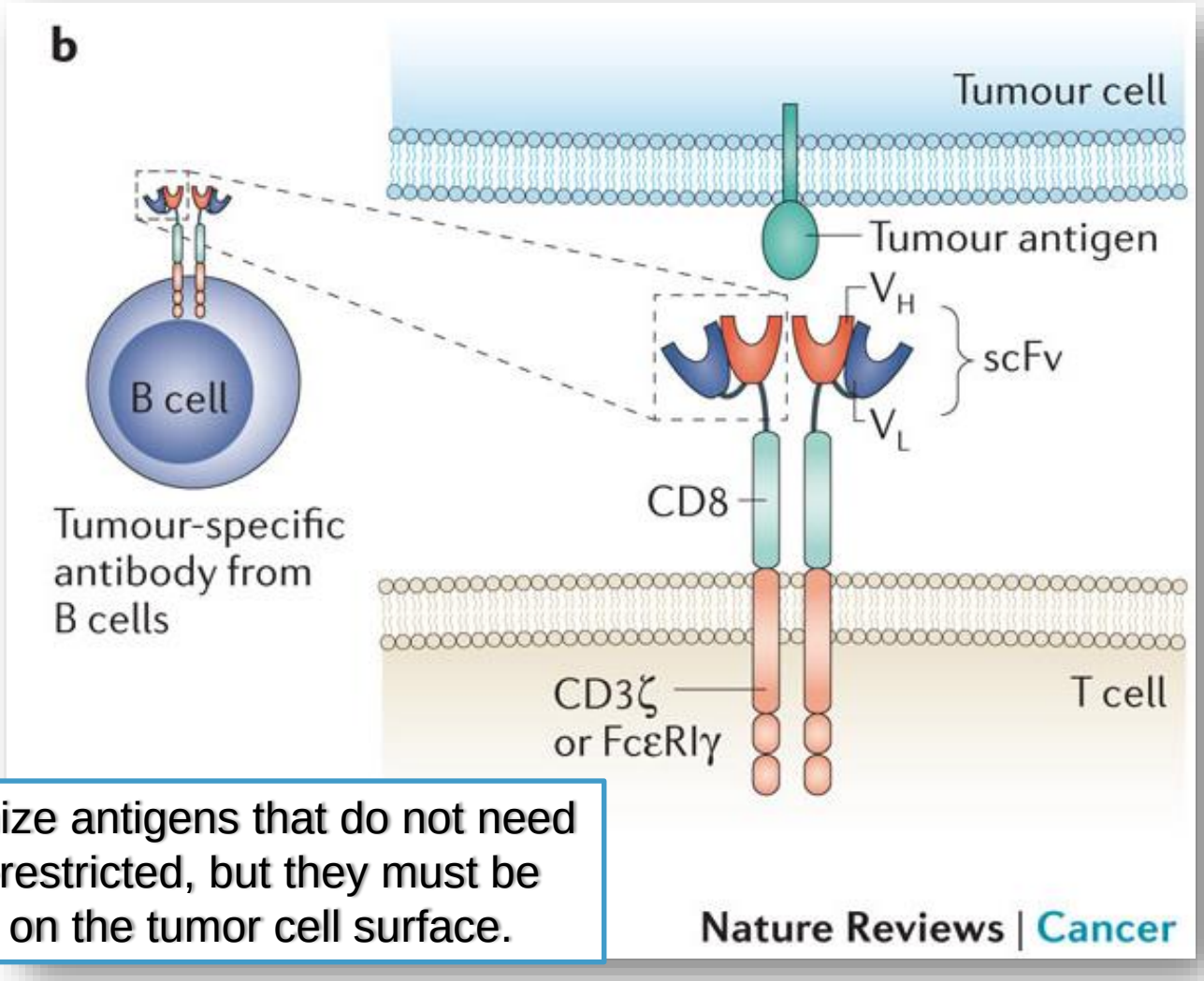


Steven A. Rosenberg, and Nicholas P. Restifo Science 2015;348:62-68

TCRs are composed of one α chain and one β chain, and they recognize antigens that have been processed and presented by one of the patient's own MHC molecules.

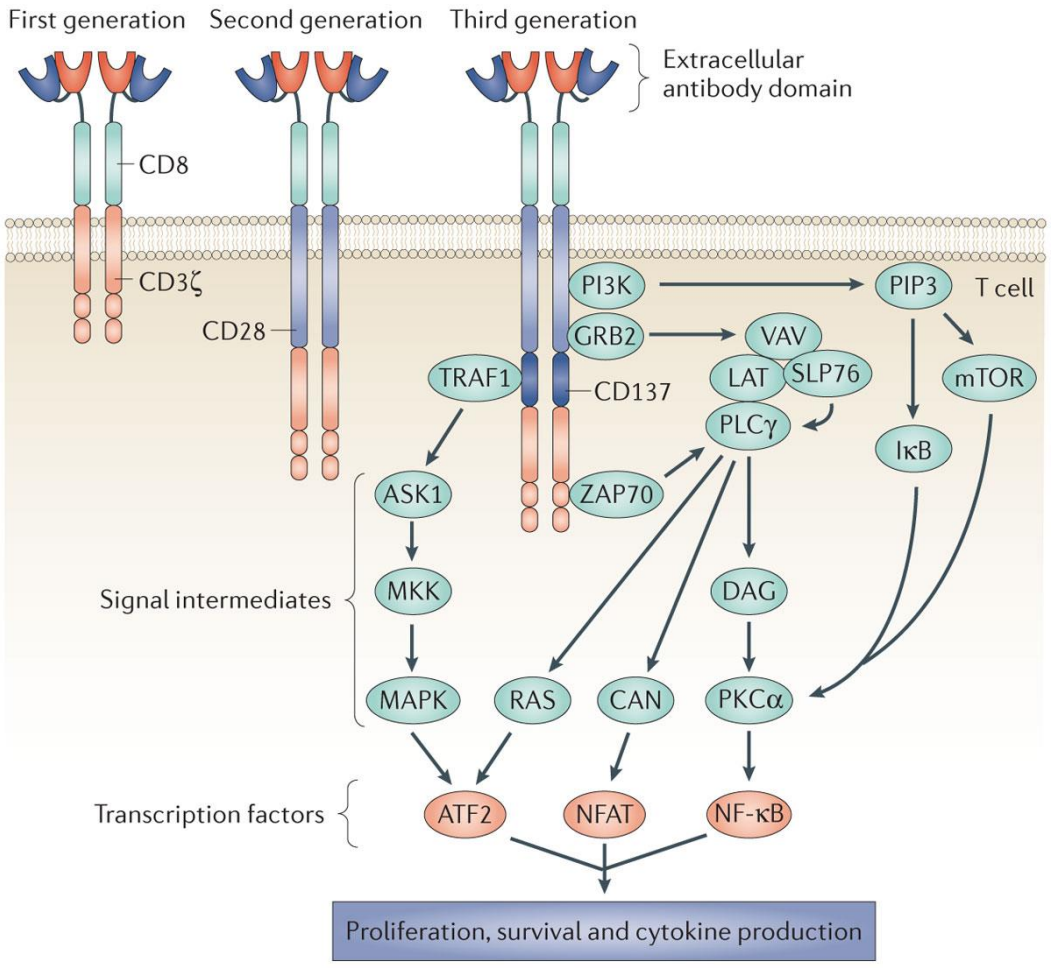


CARs are artificial receptors that can be constructed by linking the variable regions of the antibody heavy and light chains to intracellular signaling chains (such as CD3-zeta, CD28, 41BB) alone or in combination with other signaling moieties.



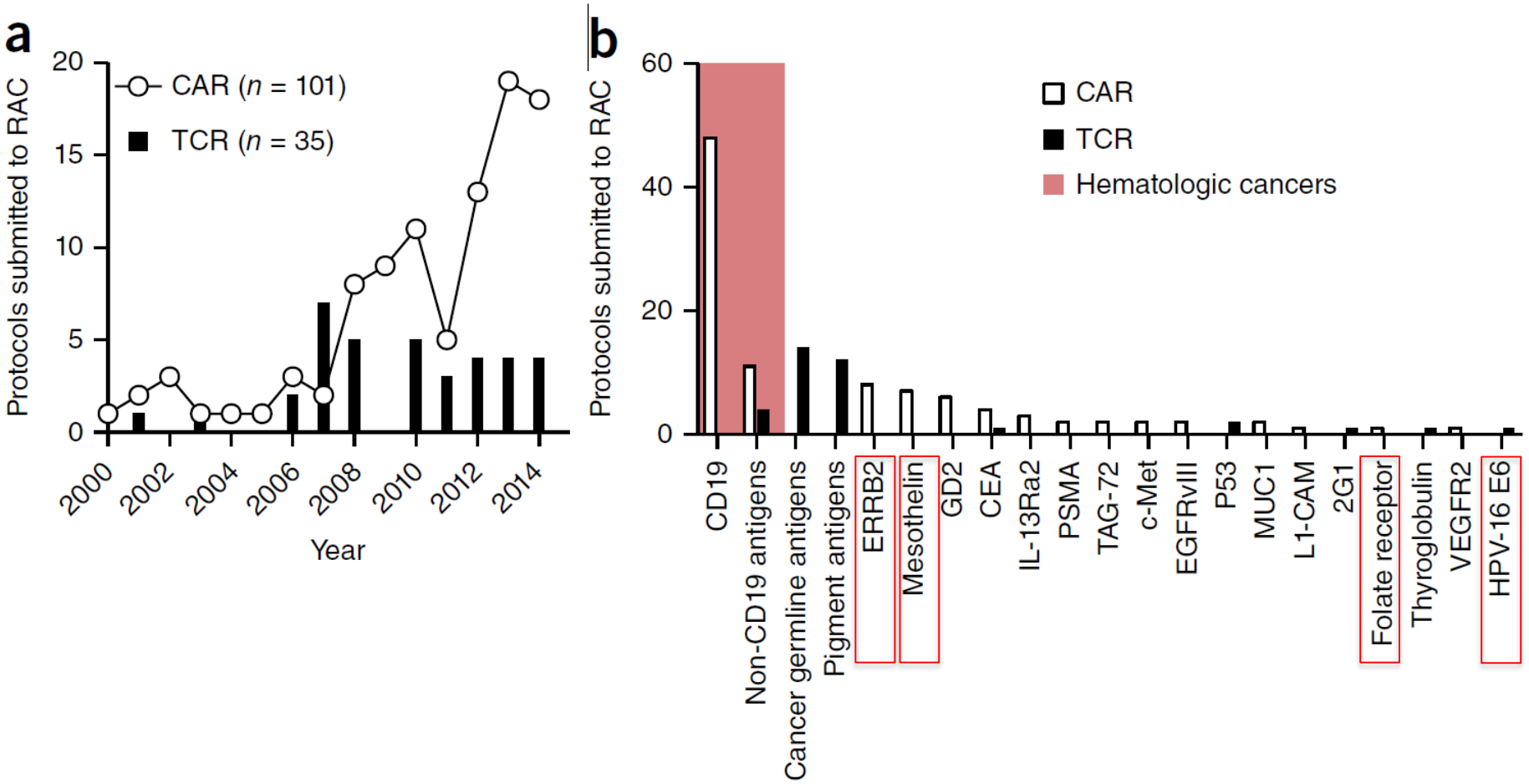
CARs recognize antigens that do not need to be MHC-restricted, but they must be presented on the tumor cell surface.

Generations of CARRs



Nature Reviews | Cancer

CAR and TCR Cancer Clinical Trials in the US 1994 - 2014



Klebanoff CA, Rosenberg SA, Restifo NP. Prospects for gene-engineered T cell immunotherapy for solid cancers. Nat Med. 2016 Jan;22(1):26-36

The CD19 CAR T Cell Success Story for relapsed ALL and CLL

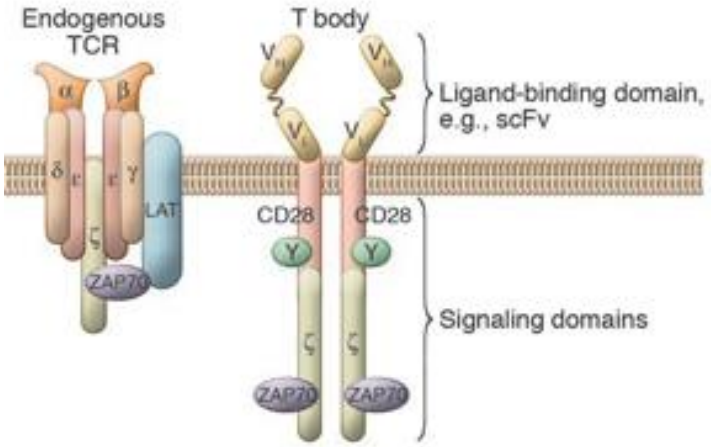
Emily Whitehead

- Complete remission and long-term responses in up to 90% of acute lymphoblastic leukemia (ALL) patients (both adult and pediatric)
- And in > 50% of chronic lymphocytic leukemia (CLL) patients.

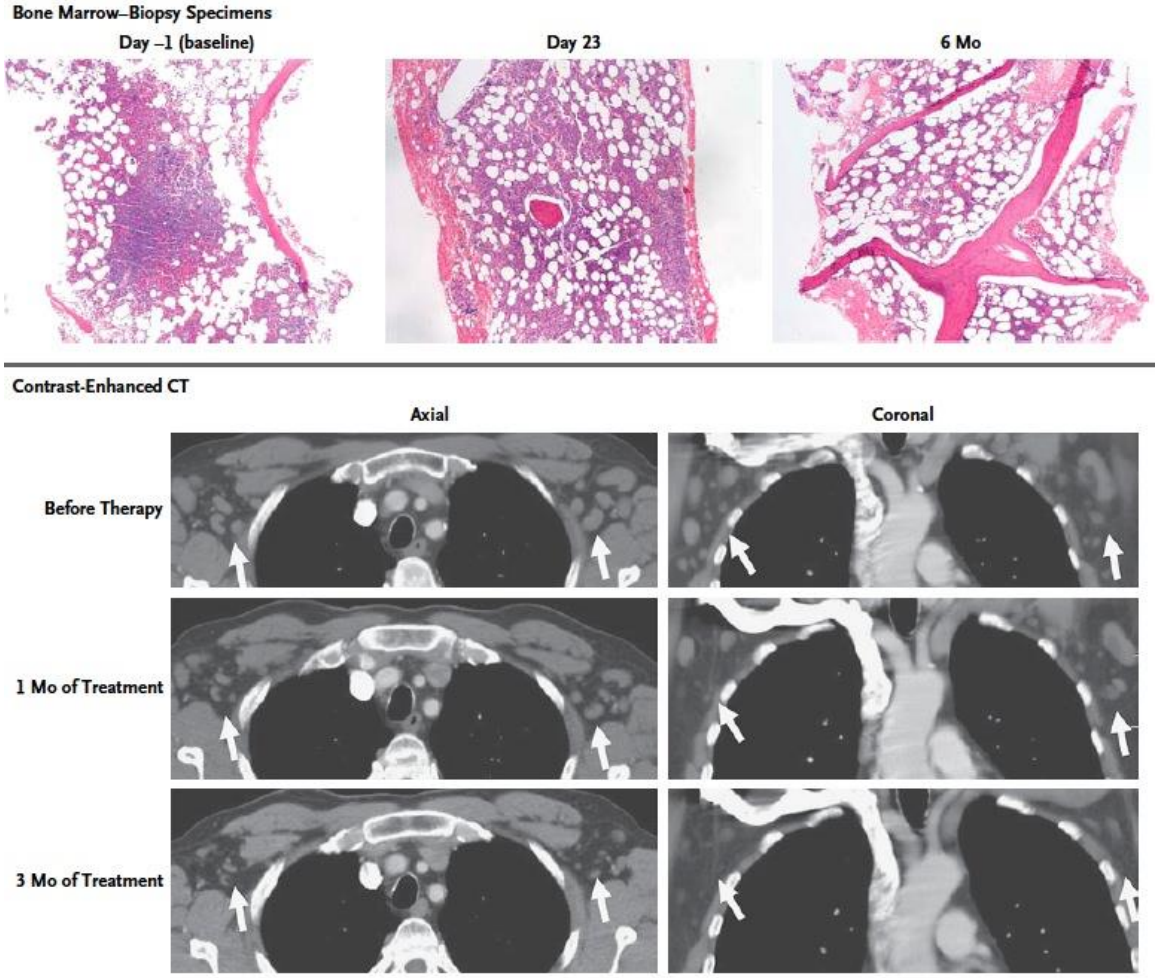
- On target side effects include B cell aplasia and cytokine release syndrome.

Maud et al, NEJM 2015 & Blood 201

Tumor Therapy with Engineered T Cells



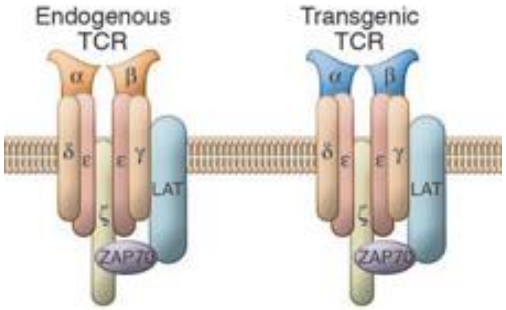
2017

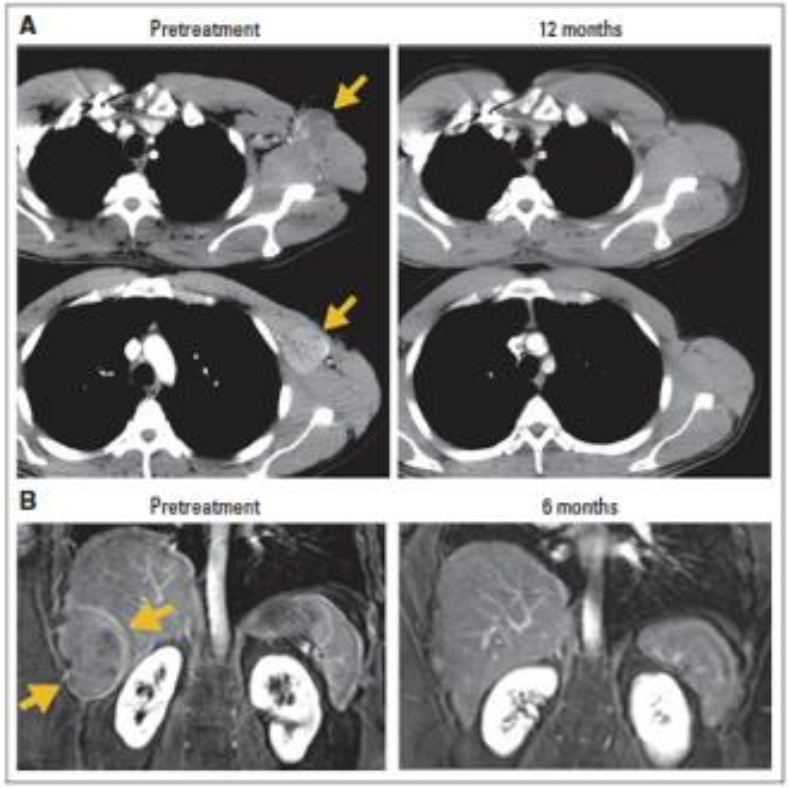


Porter *NEJM* 2011

Adoptive transfer of TCR-transferred T cells

NYESO-1 TCR
Sarcoma Patient





2017

Robbins *JCO* 2011

Challenges for CAR Therapy

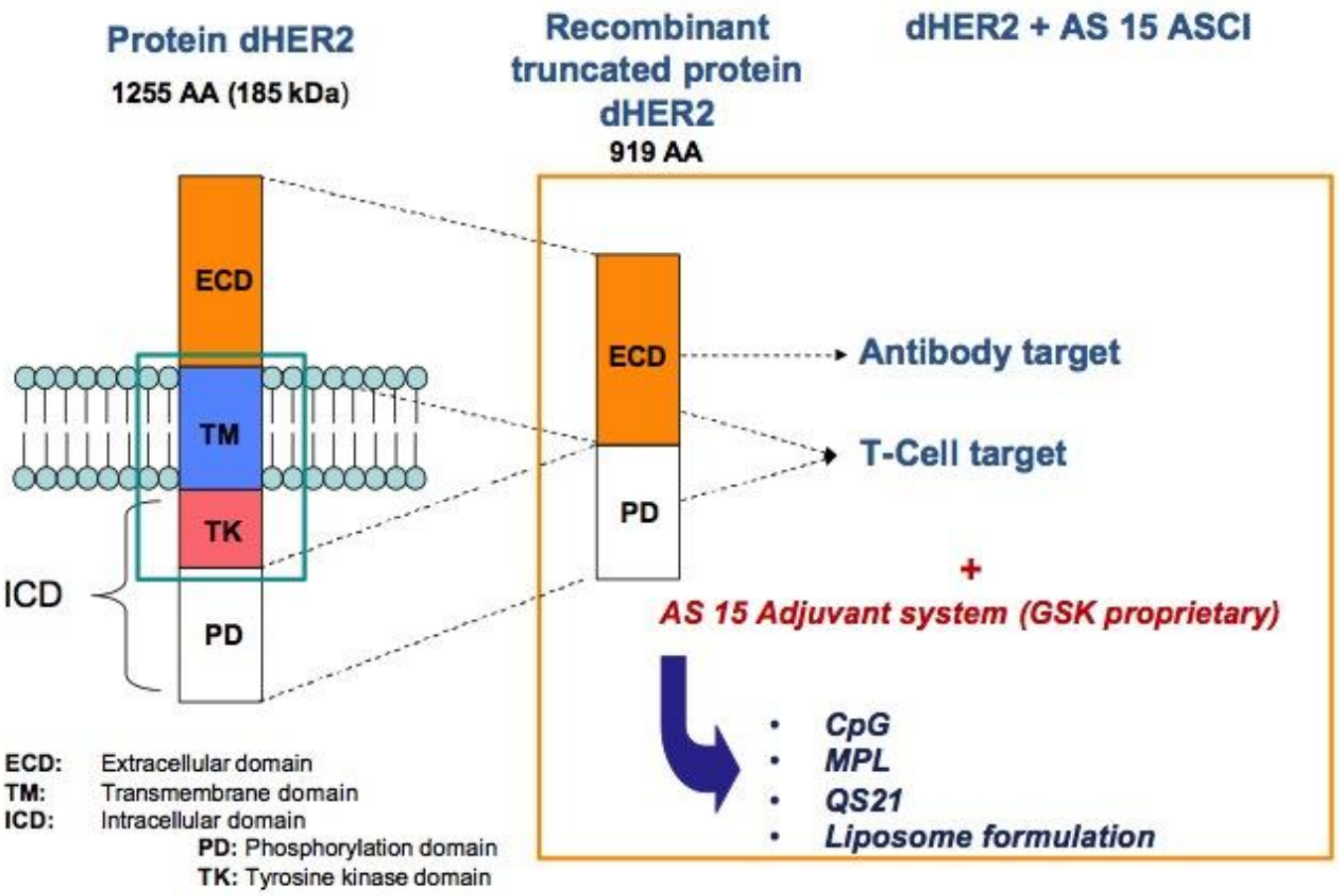
- Limitation: Antigen targets with surface expression are often not specific
- More specific targets are intracelullar (NYESO-1)
- Heterogenous expression of tumor antigen in solid tumors
- Suppressive tumor microenvironment factors
- Highly TOXIC
- Expensive (personalized) and infrastructure is required

Future Approaches

- Armored CARs
  - IL-12 secreting
- Combination Therapy
  - PD-1/PDL-1
- Suicide Switch : Abrogate CRS
- Finding cleaner Targets
  - To avoid on target toxicities

VACCINES

Phase I open-label dose-escalation vaccine trial of dHER2 protein with AS15 adjuvant in HER2-overexpressing patients with high-risk breast cancer



G. Curigliano et al. 2016

Endpoints

- Primary:

  Safety

- Secondary:

  Humoral immunogenicity

  Cell-mediated immunogenicity

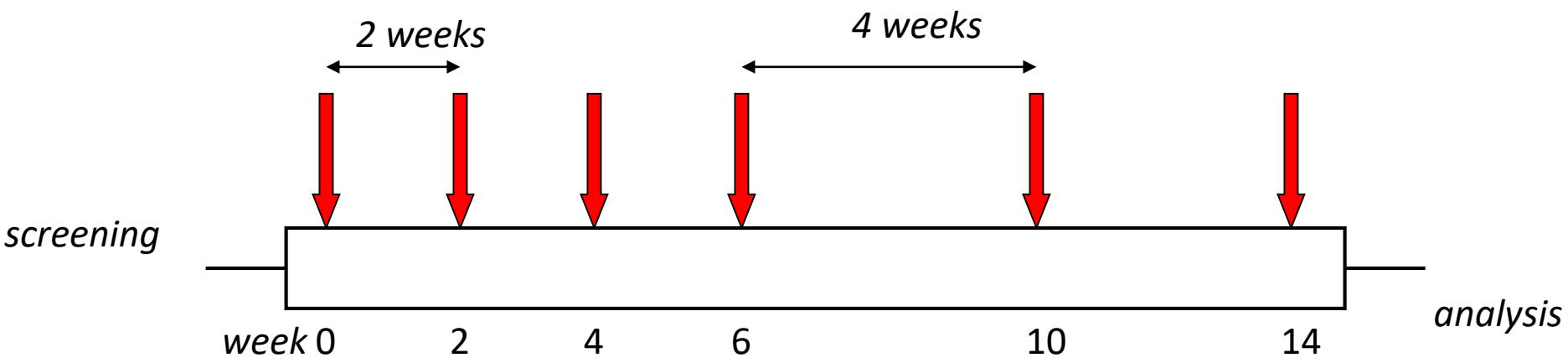
  Impact of escalating doses of HER2

G. Curigliano et al. 2016

Study design

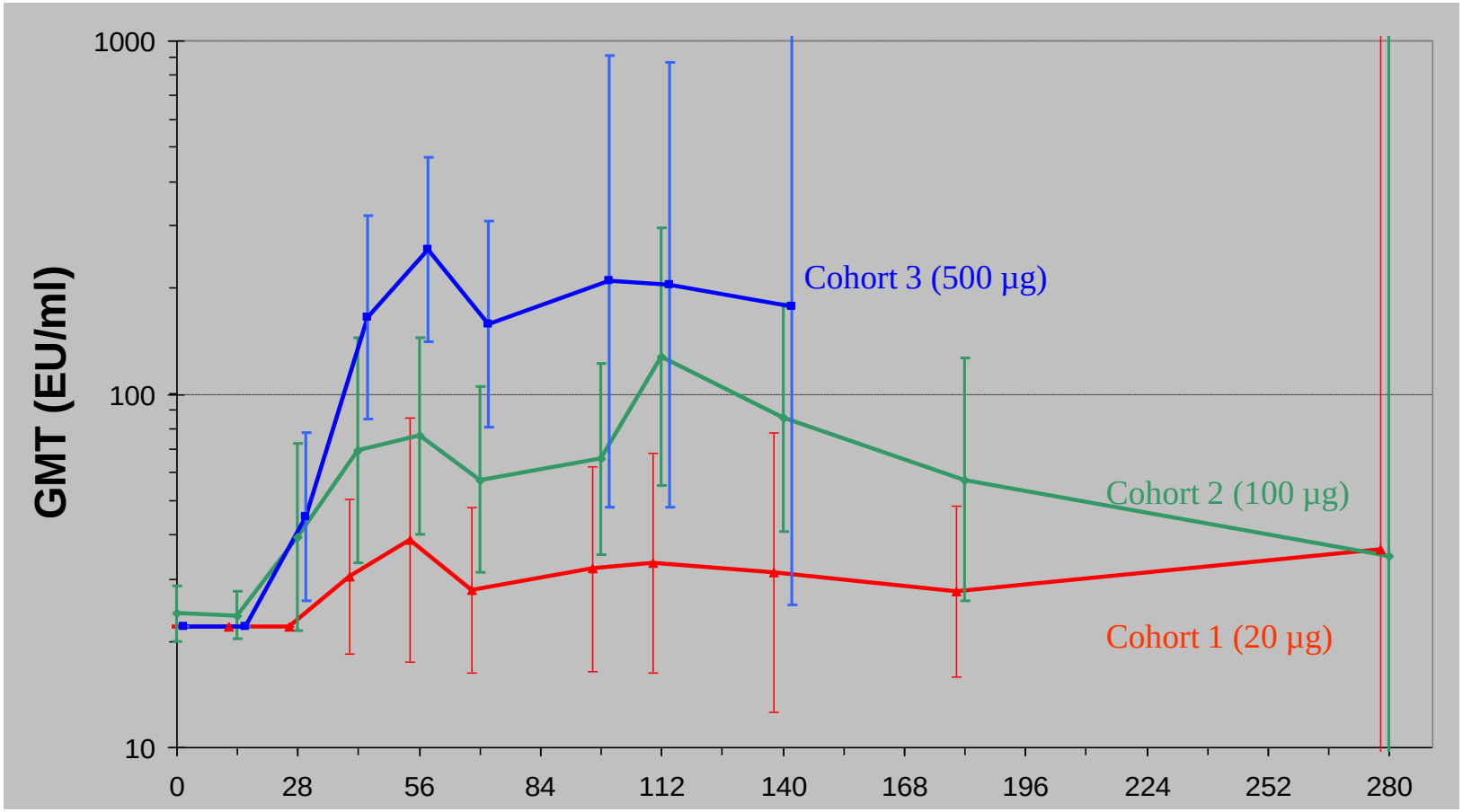
Cohorts	N	Dose (Route: IM)	Timing
Cohort 1	15	20 µg dHER2/AS15	D 0, 14, 28, 42
			(70 & 98)
Cohort 2	15	100 µg dHER2/AS15	D 0, 14, 28, 42
			(70 & 98)
Cohort 3	15	500 µg dHER2/AS15	D 0, 14, 28, 42

Study design: Treatment



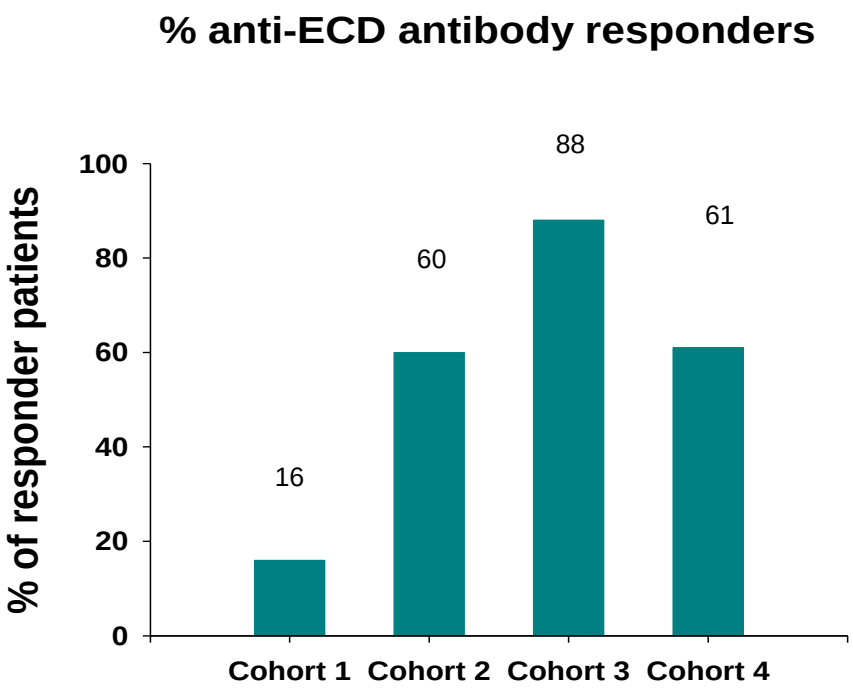
	week 0	2	4	6	10	14	analysis
PBMC	X			X			X
Ab	X X	X	X	X	X X	X X X	X
MUGA	X			X			X

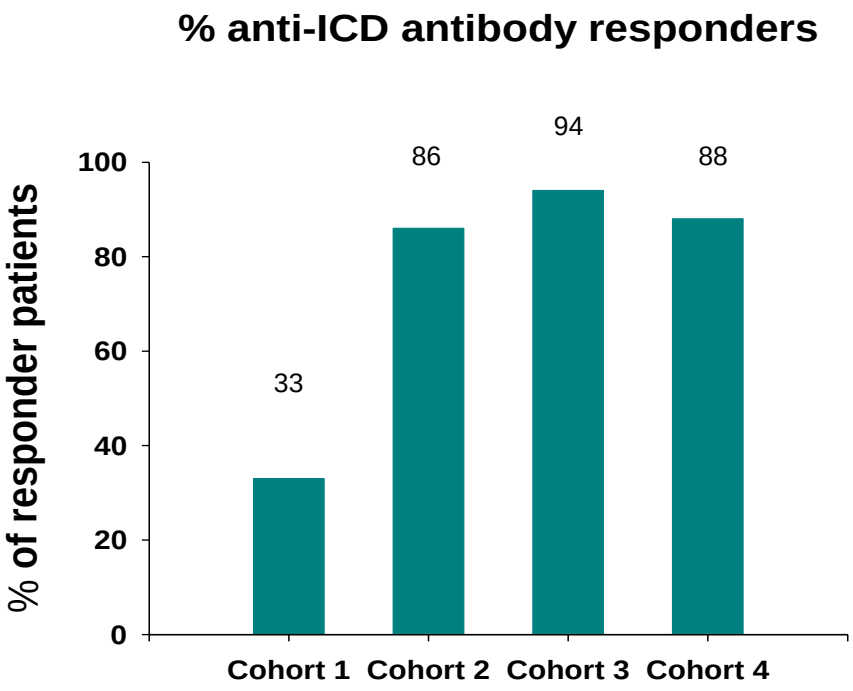
Immunogenicity



G. Curigliano et al. 2016

Responders anti ECD and anti ICD

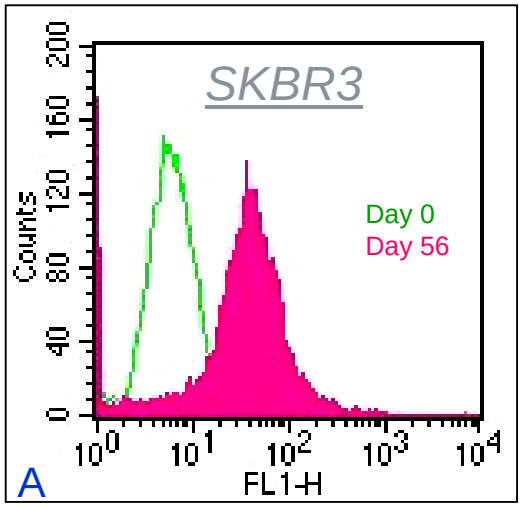


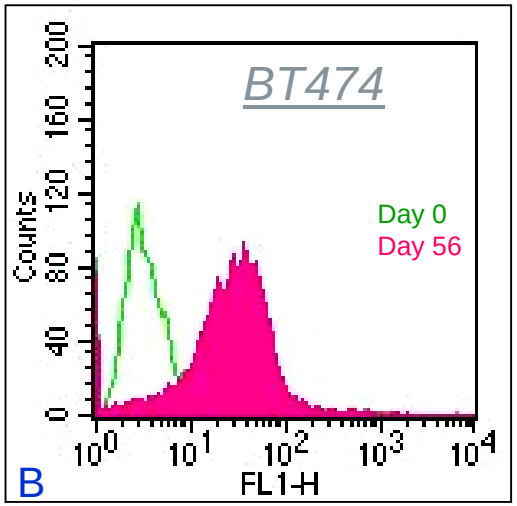


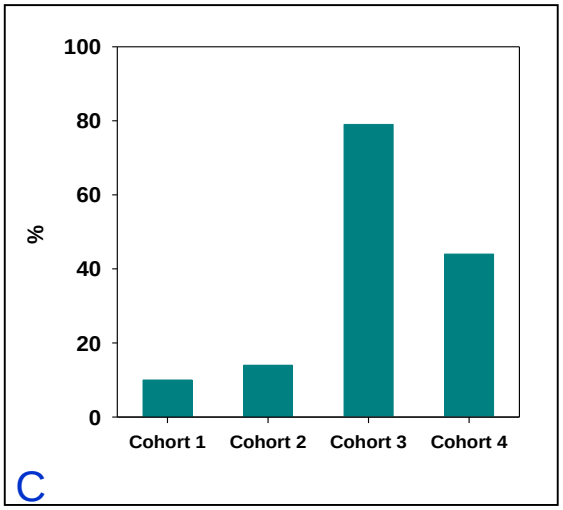
G. Curigliano et al. 2016

d-HER2 induces antibodies that specifically bind the native HER2 receptor

- The ECD binding ratio seems to increase with the dose of HER2 protein when assessed after the administration of four dHER2 + AS15 doses.







G. Curigliano et al. 2016

Thank you for your attention

Concomitant Chemoradiotherapy of esophageal carcinomas

C. Hennequin,
Hôpital Saint-Louis, Paris

Esophageal cancer

- Two main histological types:
  - Squamous cell carcinoma (SCC)
    - Tobacco, alcohool
    - Incidence decreasing
  - Adenocarcinoma (Adk)
    - Biliary and acid gastroesophageal reflux
    - Incidence dramatically increasing

Enzinger, NEJM, 2003: 349: 2241-52

Gastro-Oesophageal Junction (GOJ) adenocarcinoma

Siewert Classification

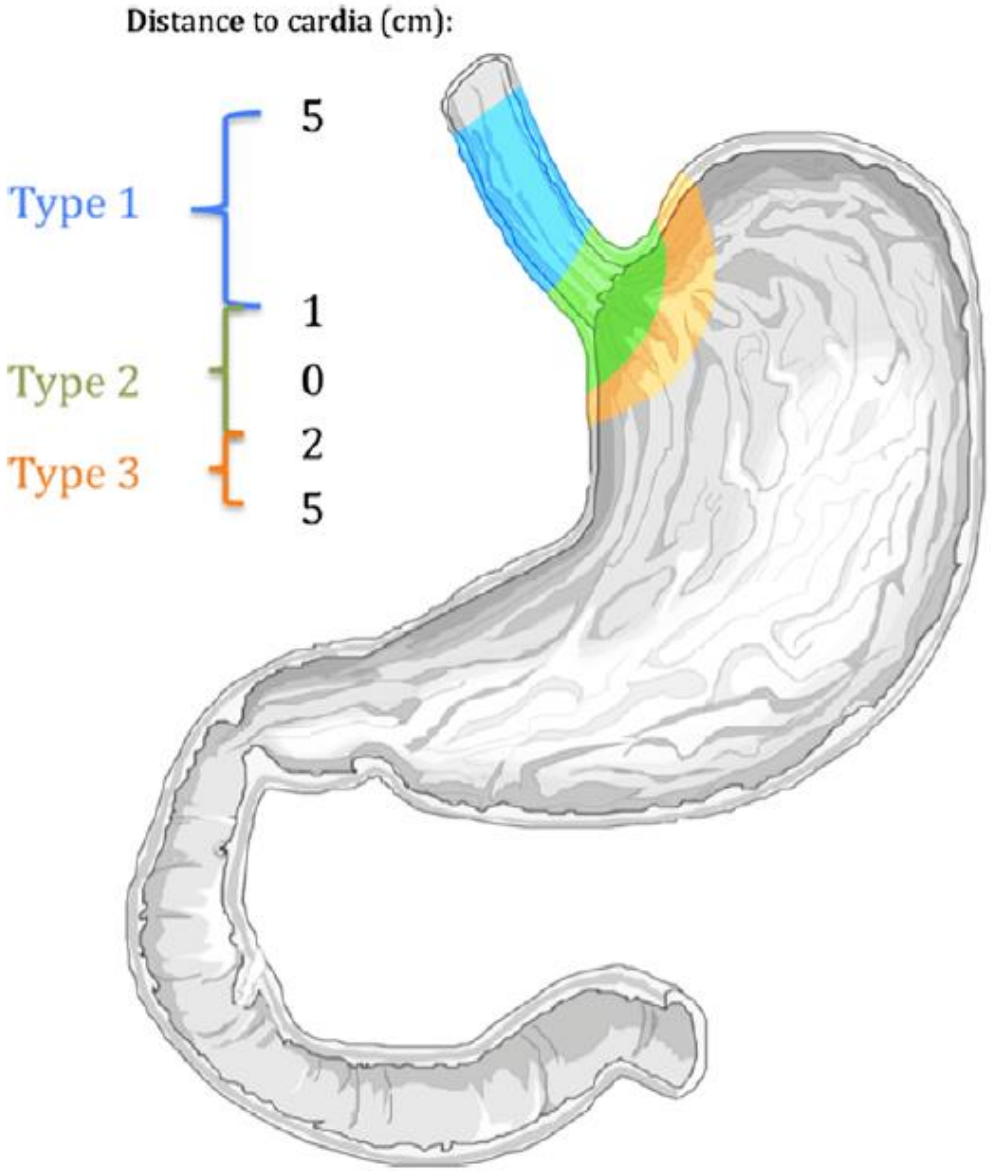


Figure 5–1. Classification of gastroesophageal junction tumors. (Adapted from Siewert JR, Stein HJ. Classification of adenocarcinoma of the oesophagogastric junction. Br J Surg 1998;85:1457–9.)

Outcome of esophageal cancer

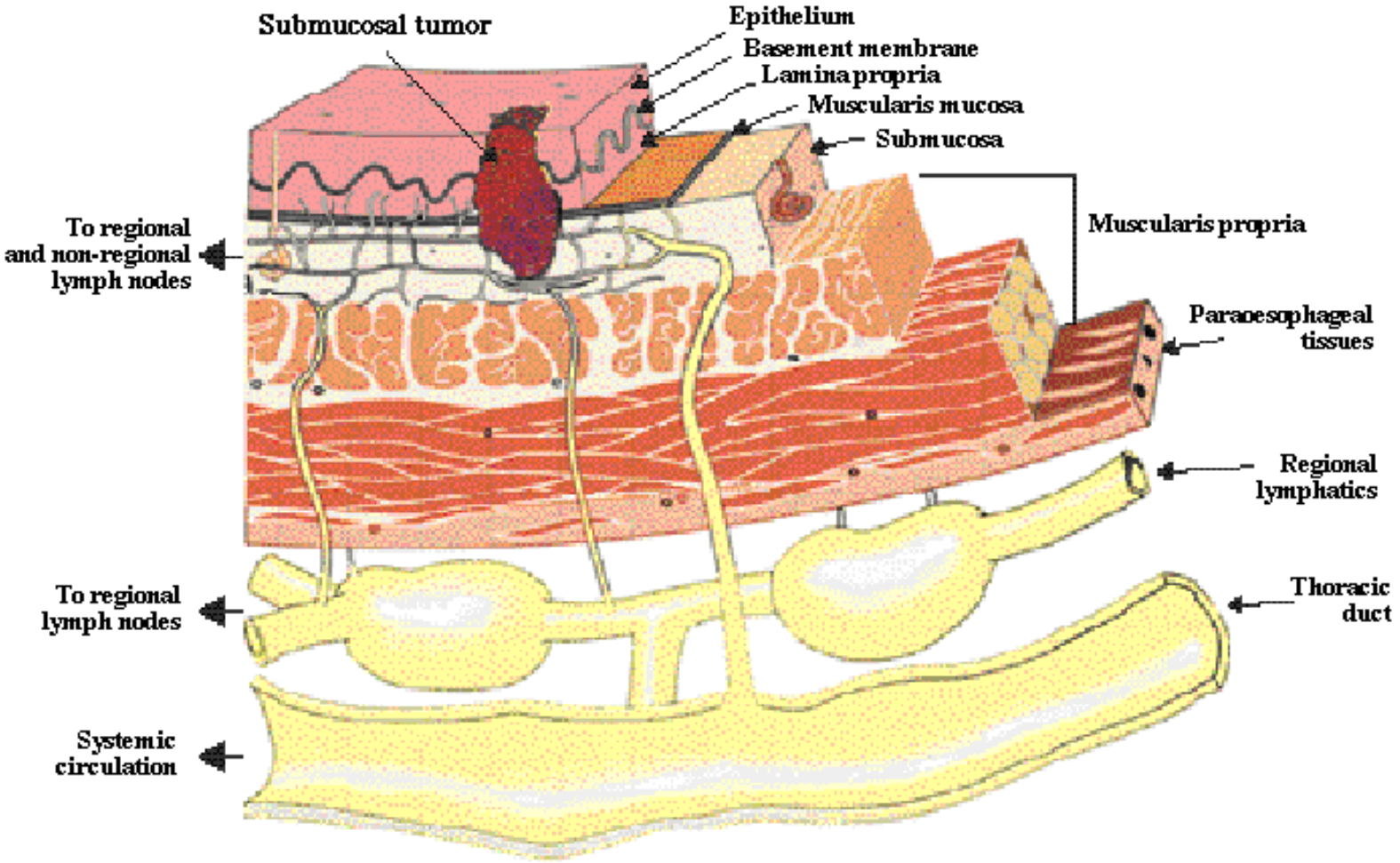
	1976-1990	1991-1996	1996-2002
3 yr Survival (%)	6.8	10.4	7.2

Bouvier, Eur J Cancer, 2006, 42: 228-233

Historical approach:
Surgery is the cornerstone of the treatment
Modern questions

- Is a pre-or post-operative treatment useful? ?
- If yes, chemo or chemoradiotherapy?
- Must all the resectable patients be resected?
- What are the best modalities of CT-RT:
  - Doses
  - Volumes
  - Drugs

Esophageal wall



Lymphatic anatomy of the oesophagus
There are three routes of lymphatic flow and potential lymphatic and systemic metastases.

Lymph nodes involvement

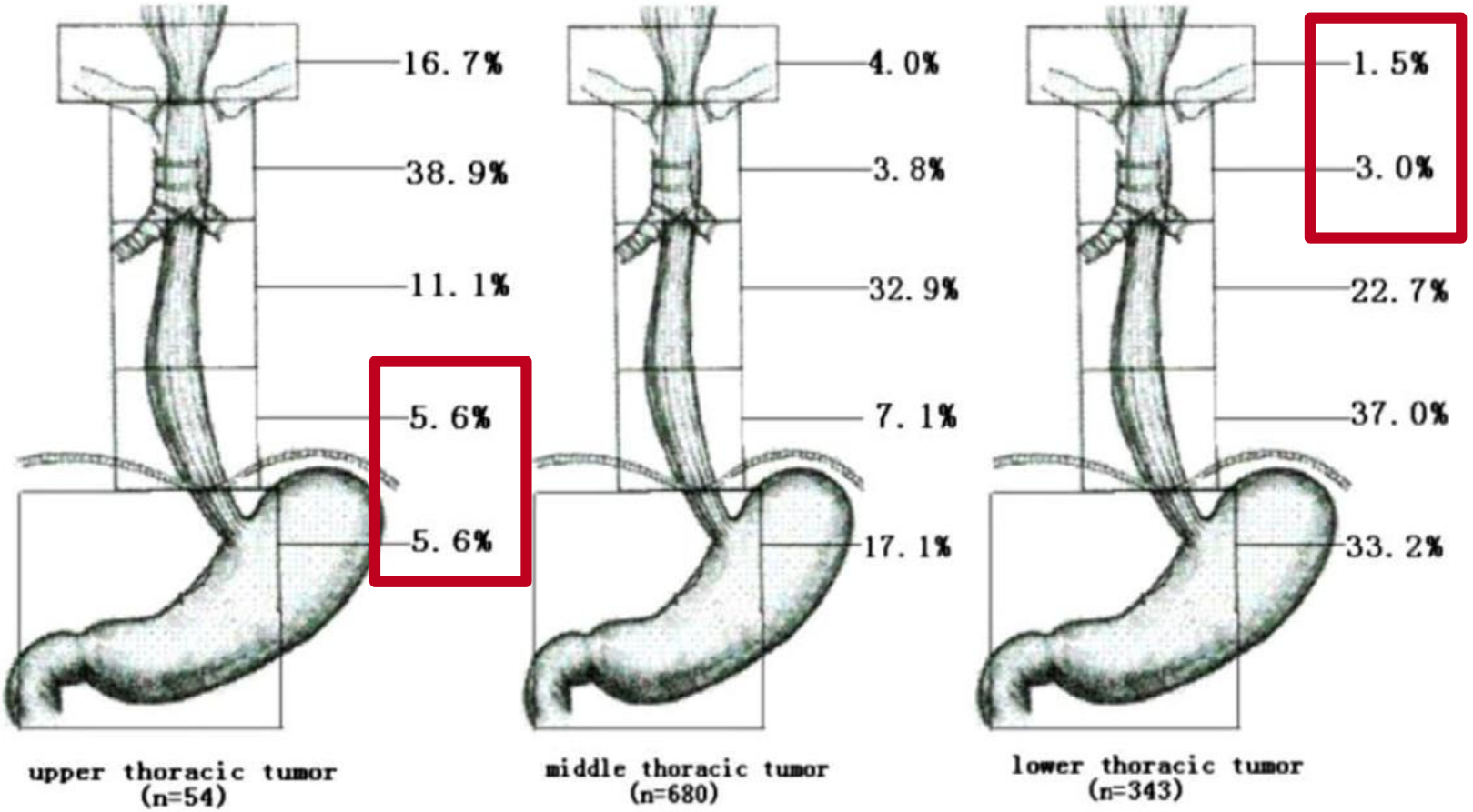


Fig. 1. Rate of LNM to different regions according to the location of the primary tumor.

1077 cases – China, Huang, Radioth. Oncol., 95: 229-233, 2010

Evolution of surgical results

Hofstetter, Ann Surg, 2002 (MD Anderson, Houston)

	1970-1985 (n= 246)	1986-1996 (n=465)	1997-2001 (n=283)
Post-op mortality (%)	12	5	6
R0 (%)	78	87	94
3-yr Survival (%)	27	34	46

Evolution of surgical results

Hofstetter, Ann Surg, 2002 (MD Anderson, Houston)

	1970-1985 (n= 246)	1986-1996 (n=465)	1997-2001 (n=283)
AdenoK. (%)	29	68	83
Stage 0-1 (%)	15	14	43
Stage IIa	32	22	25
Stage IIb	11	12	7
Stage III	25	38	18
Stage IV	18	14	7
Pre-op. CT	2	33	5
Pre-op. RT	51	3	1
Pre-op. CT/RT	2	10	59

Adenocarcinomas of the cardia: Results of Surgery

Mariette, Br J Surg., 2002

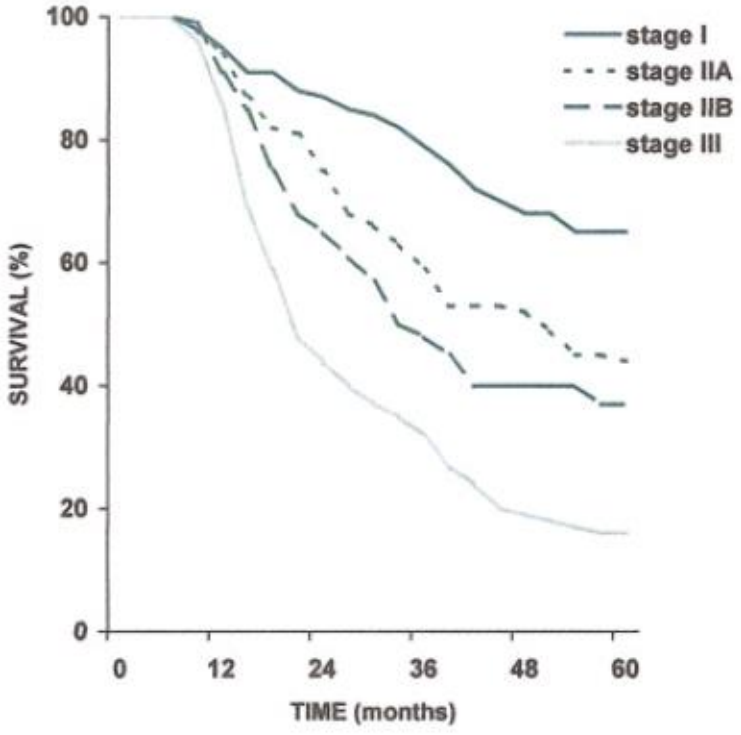
	Type I	Type II
N° pts	56	44
N+ (%)	68	70
R0 (%)	76.8	75
Survival:		
- 3 yrs	46.8	42.1
- 5 yrs	28.2	25.7

Post-operative mortality: 4.8%

Adenocarcinomas of the cardia: Results of Surgery

- 5-year survival rates < 40%
  - Siewert, Ann Surg, 2000: 232: 353-61
  - Orringer, Ann Surg, 1999: 230: 392-400
  - Mariette, Cancer, 2003, 97: 1616-23
  - Lerut, Hepatogastroenterol, 1999, 46: 717-725
  - Hulscher, J Am Coll Surg, 2000; 191: 143-148

Survival according to stage



Stage I	107	101	78	52	32	23
Stage IIA	114	108	75	52	43	33
Stage IIB	76	66	39	22	16	10
Stage III	142	127	57	35	20	14

FIGURE 1. Overall survival following discharge for 439 patients undergoing R0 resection for esophageal carcinoma according to the TNM stage. The number of subjects at risk at each interval is shown in the table at the bottom of the graph.

Stage I: TIS-T1 N0
Mucosal/sub-mucosal

Stage IIA: pT2-pT3 N0
Muscularis (pT2)
Adventice (pT2)

Stage IIB: pT1-pT2, N1

Stage III: pT3, N1 ou pT4Nx

Mariette, Cancer, 2003

Value of Post-operative treatments

- Radiotherapy: Only one positive randomized trial
- Chemotherapy:
  - A few data; no clear benefit
- Chemoradiotherapy:
  - A few data
  - Feasibility to demonstrate

Pre-operative treatments

- YES or NO ??
- Radiotherapy or Chemotherapy or Chemoradiotherapy ??

Pre-operative radiotherapy

- No benefit

TABLE I. Randomized Trials of Preoperative Radiotherapy

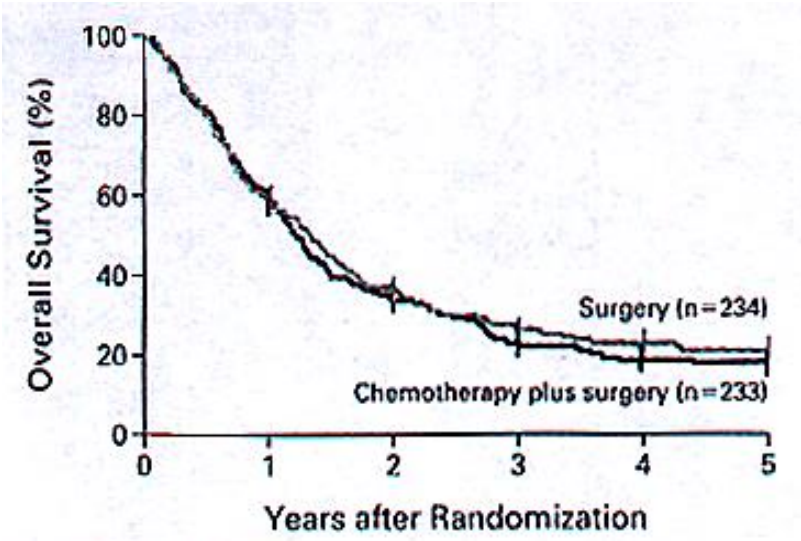
Refs.	Year	Histology	Therapy	Patients	Total dose (Gy)	% Resectable	% Local failure	% 5-year survival
Launois et al. [20]	1981	Squam	Surgery	47		70	NR	11.5
			Radiation + surgery	67	40	75	NR	9.5
Gignoux et al. (EORTC) [19]	1987	Squam	Surgery	114		58	49	8
			Radiation + surgery	115	33	47	31	10
Wang et al. [22]	1989	NR	Surgery	102		85	12	30
			Radiation + surgery	104	40	93	13	35
Arnott et al. [18]	1992	Squam/adeno	Surgery	86		NR	NR	17 ($P = 0.4$)
			Radiation + surgery	90	20	NR	NR	9
Nygaard et al. [21]	1992	Squam	Surgery	41		37	NR	9[a]
			Chemo + surgery	50		44	NR	3[a]
			Radiation + surgery	48	35	40	NR	21[a]
			XRT + chemo + surgery	47	35	55	NR	17[a]

Squam, squamous cell cancer; NR, not reported; Adeno, adenocarcinoma; XRT, radiation.
[a]Thirty-six-month survival.

Cochrane review 2005: same conclusion

Neo-adjuvant chemotherapy

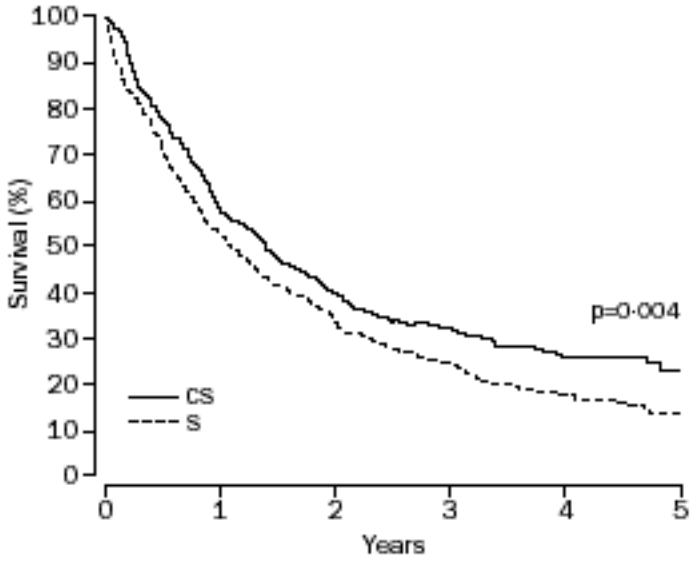
Kelsen et al.,
N Engl J Med, 1998,
339: 1979-84



No. of Patients at Risk

Chemotherapy plus surgery	136	73	42	28	15
Surgery	138	81	45	27	16

MRC,
Lancet, 2002,
359: 1727-1733



Patients at risk (events)

CS	400 (164)	231 (73)	143 (26)	81 (13)	36 (2)	14
S	402 (185)	212 (76)	124 (32)	70 (18)	28 (5)	10

Figure 2: **Kaplan-Meier curve showing survival from date of randomisation**
Two CS patients died after 5 years.

Comparison of the two trials of neo-adjuvant chemoth.

	USA		GB	
	Control	CT	Control	CT
Chemoth.	Cisplatin: 100 mg/m2 5FU: 1000 mg/m2 D1-5 3 cycles		Cisplatin: 80 mg/m2 5FU: 1000 mg/m2 D1-4 2 cycles	
AdenoK. (%)	53		66	
R0 (%)	59	62	54	60
Post-operative mortality (%)	6	6	10	10
2-yr survival (%)	37	35	34	43
3-yr survival (%)	26	23	25	32

Local relapses after surgery

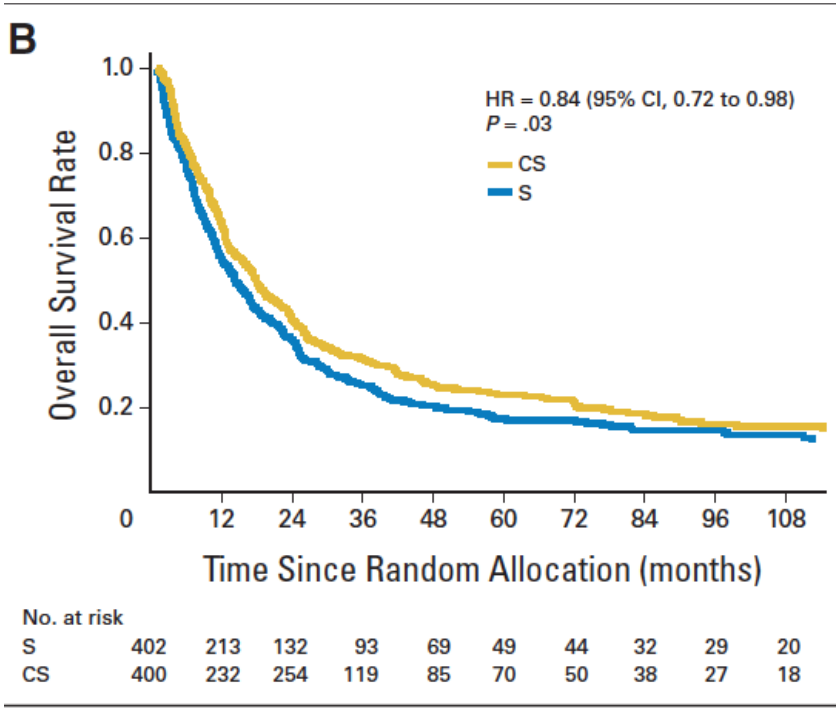
Kelsen		Surgery	Surg. + CT
	Local	31%	32%
	Distant	50%	41%

Huscher	Transhiatal	Thoracic
Local relapses	32%	31%

Urba*	Surgery	Surgery et RT/CT pré-op.
Local relapses	42%	19%

* No effect on distant metastasis

MRC Study -update



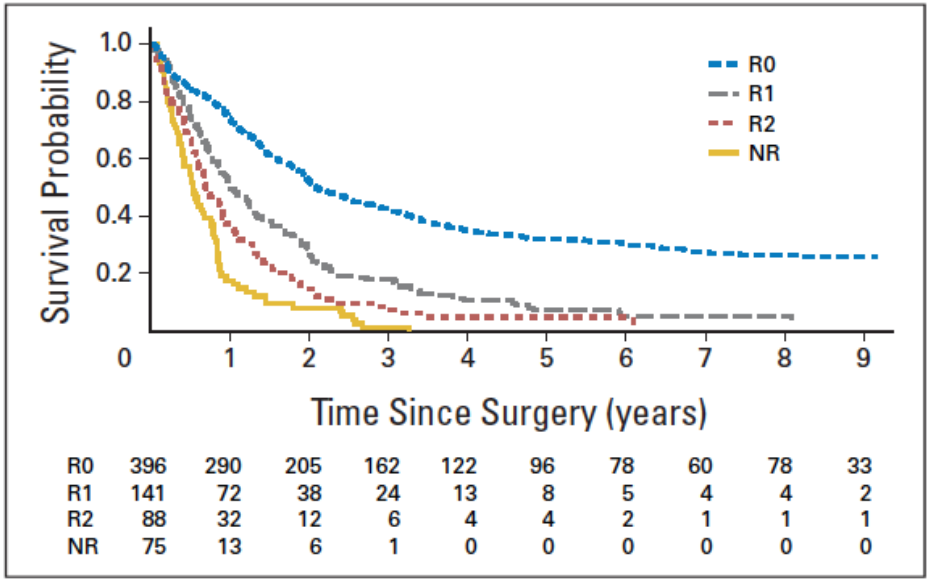


Fig 4. Survival by type of resection for all patients. An R0 resection was defined as all margins histologically free of tumor, R1 resection as macroscopically complete with microscopically positive margins, and R2 resection as macroscopically incomplete. NR, not resected.

Allum, JCO, 27:5062-5067, 2009

Pre-operative chemo-radiotherapy

Pre-operative Chemo-Radiotherapy

	N° pts	CT	RT	pCR (%)
Le Prisé, 1984	35	5FU/CDDP	20 Gy/10fr	11
Gignoux, 1989	111	CDDP	18.5 Gy/5 fr	22
Bedenne, 1993	80	5FU/CDDP	15 Gy/ 5 fr	24
Poplin, 1987	71	5FU/CDDP	30 Gy/15 fr	25
Gill, 1992	46	5FU/CDDP	36 Gy/ 18 fr	22
Forastiere, 1993	41	5FU/CDDP	37.5 Gy/15 fr	24
Hennequin, 2001	39	5FU/CDDP	40 Gy/20 fr	24
Malhaire, 1996	56	5FU/CDDP	37 Gy/10 fr	37.5
Ganem, 1997	36	5FU/CDDP/Hydroxyur.	40 Gy/20fr	44
Bates, 1996	35	5FU/CDDP	45 Gy/25 fr	51
Kim, 2001	53	5FU/CDDP	48 Gy/40fr	49

Pre-operative Chemo-Radiotherapy : Randomized trials

Le Prisé

Nygaard

Walsh

Bosset

Urba

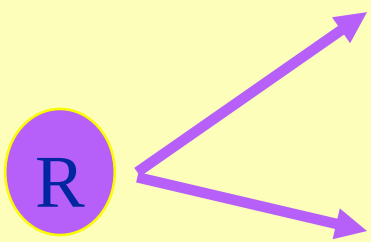
Burmeister

Tepper

Conflicting results:
- Low number of pts
- Old combinations
- Various stages and histology

Chemoradiotherapy before surgery

Bosset et al., N Engl J Med, 1997; 337: 161-7



ChemoRadiotherapy
then Surgery (143 pts)

Immediate Surgery (139 pts)

Radioth.: 5 x 3.7 Gy - 2 weeks - 5 x 3.7 Gy (37 Gy)
Chemoth.: Cisplatin (80 mg/m2) before RT

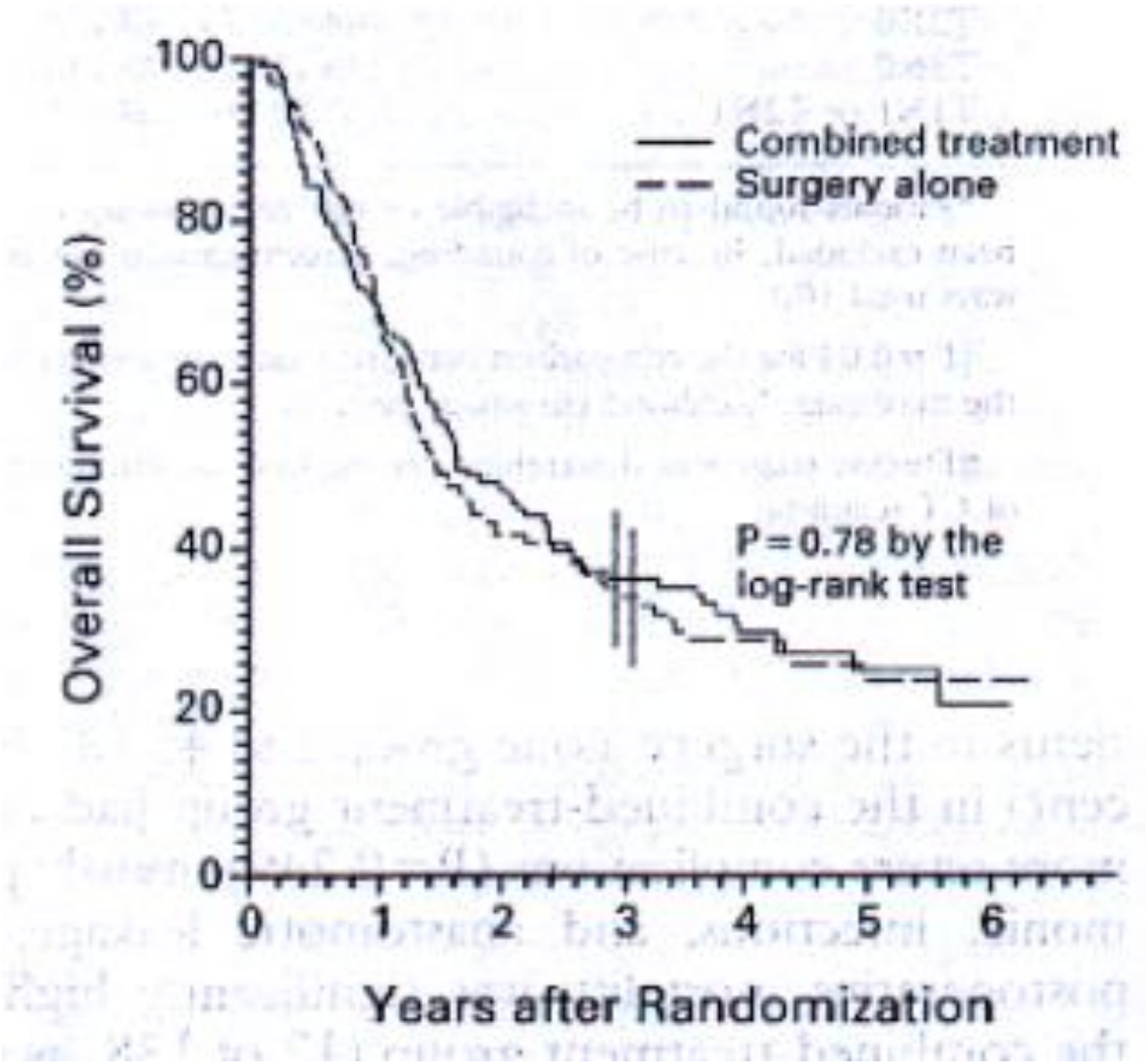
Stages: T1NO: 17%; T2N0: 33%; T3N0: 27%
T1-T2 N1: 23%

Chemoradiotherapy before surgery

Bosset et al.,

N Engl J Med,
1997; 337: 161-7

Overall Survival

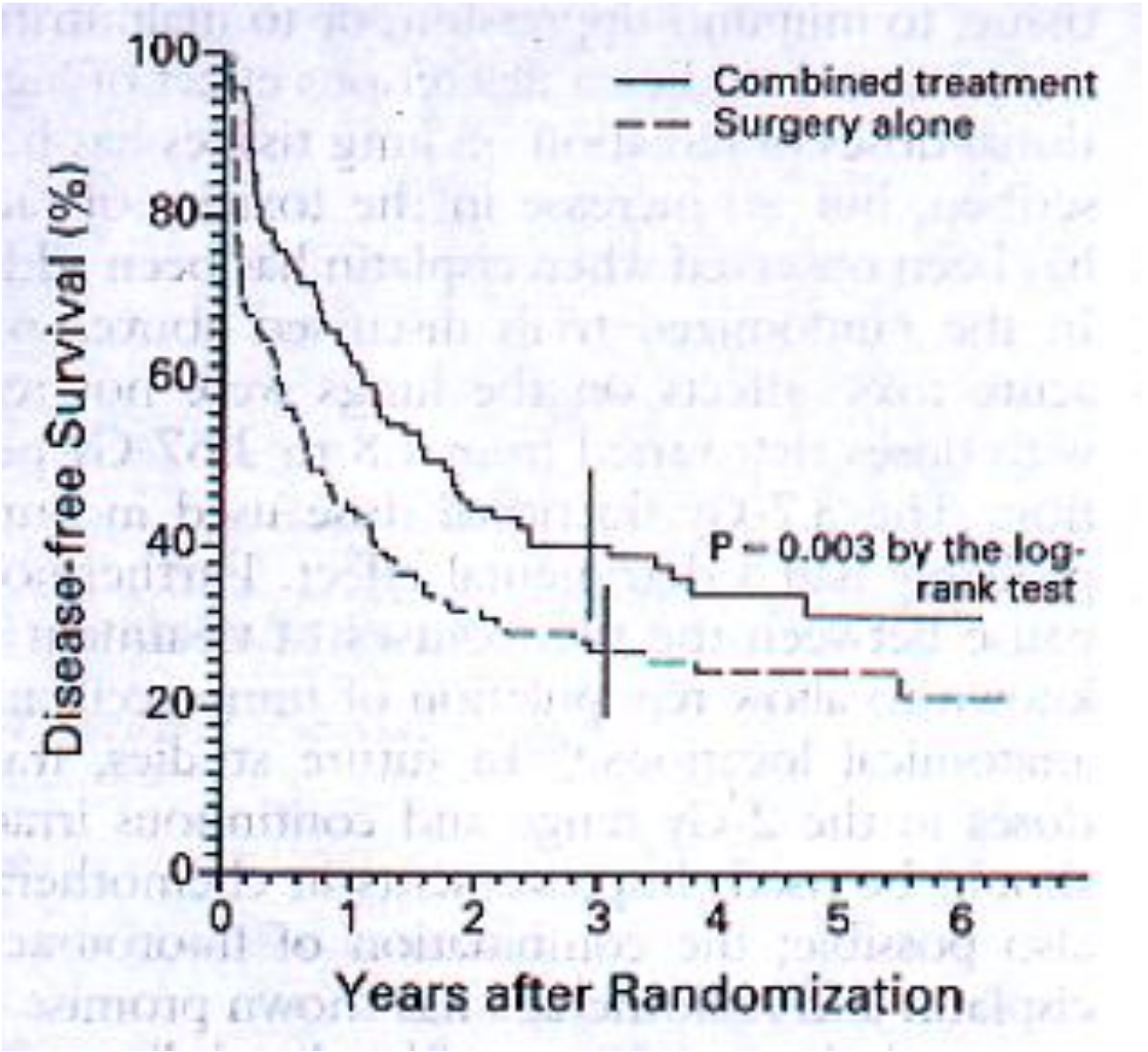


Chemoradiotherapy before surgery

Bosset et al.,

N Engl J Med,
1997; 337: 161-7

Disease-free Survival



Chemoradiotherapy before surgery

Bosset et al.,

N Engl J Med, 1997

Causes of Death according to treatment group

	Surgery alone (%)	Combined Treatment (%)
Esophageal cancer *	86.1	67.6
Postoperative complications **	5	16.7
Secondary tumor	2	8.8
Cardiovascular disease	2	1
Anastomotic leakage	1	1
Autre	1	2.9
Unknown	3	1

* p= 0.002; ** p = 0.012

Pre-operative chemoradiotherapy: Australian trial

(Burmeister, Lancet Oncol, 2005, 6:659-68)

Resectable Oesophageal carcinomas T1-3, N0-1

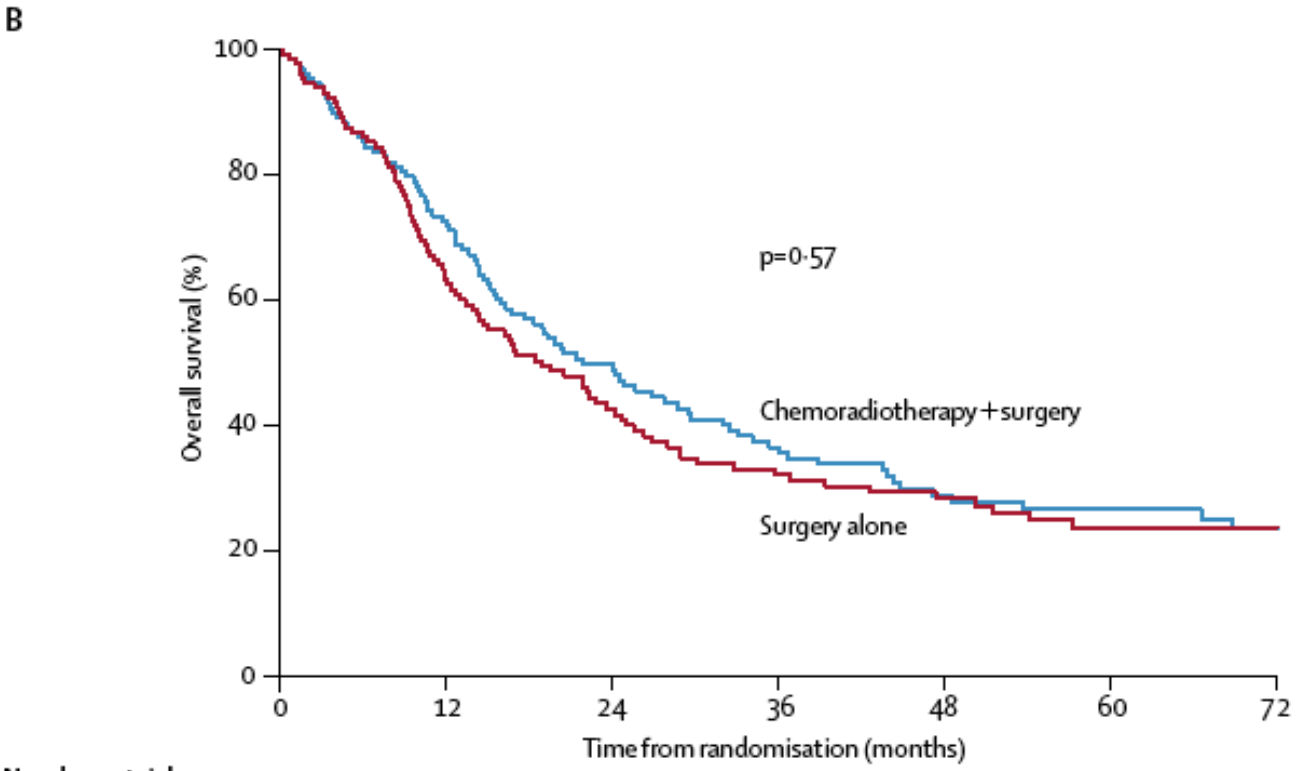
Surgery

Pre-op. RT-CT pré-op.
35 Gy/ 15 fr/ 2.3 Gy/fr
5FU-CDDP: 1 cycle

Population		RT-CT	Surgery
	SCC	35%	39%
	N1	16%	15%

Pre-operative chemoradiotherapy: Australian trial

(Burmeister, Lancet Oncol, 2005, 6:659-68)



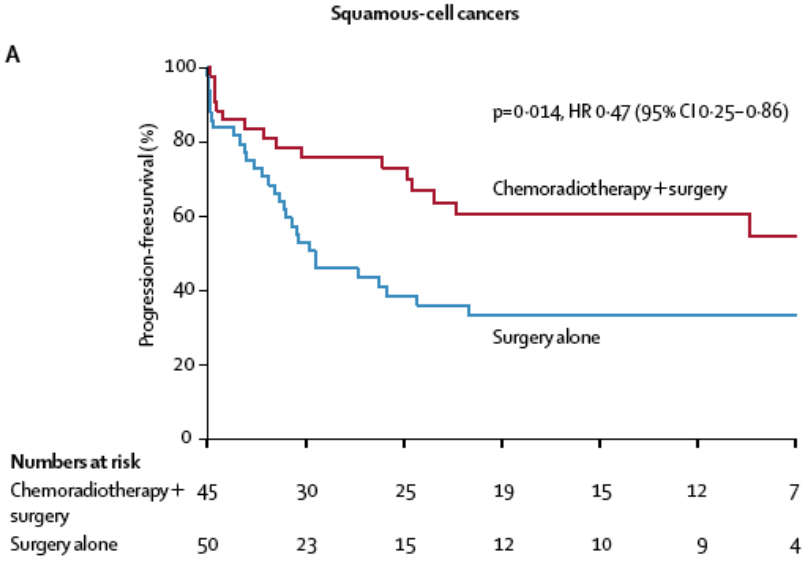
Numbers at risk

Chemoradiotherapy + surgery	128	95	58	42	28	21	15
Surgery alone	128	81	51	36	30	19	10

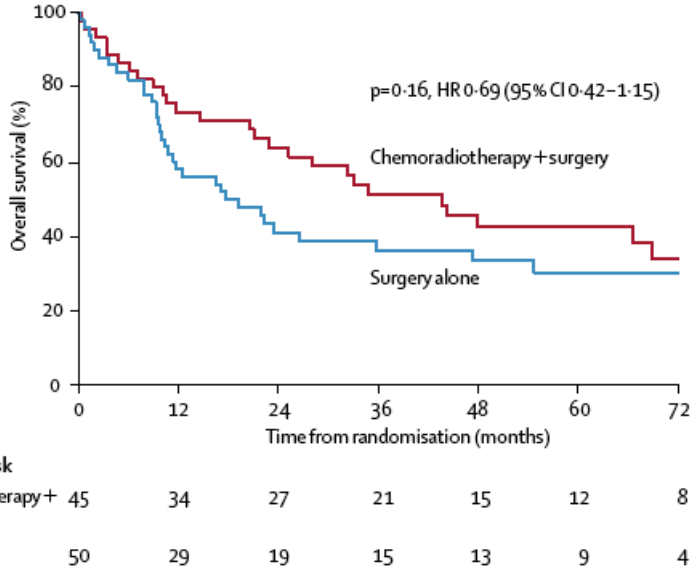
Pre-operative chemoradiotherapy: Squamous cell carcinomas

(Burmeister, Lancet Oncol, 2005, 6:659-68)

Disease-free survival

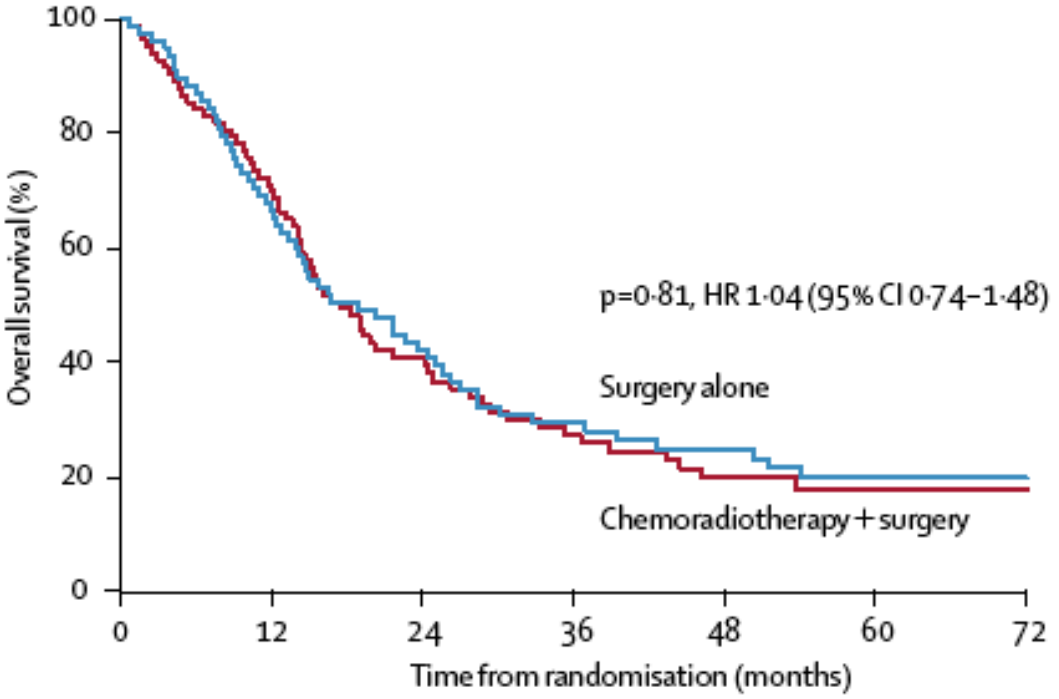


Survival



Pre-operative chemoradiotherapy: Adenocarcinomas

(Burmeister, Lancet Oncol, 2005, 6:659-68)

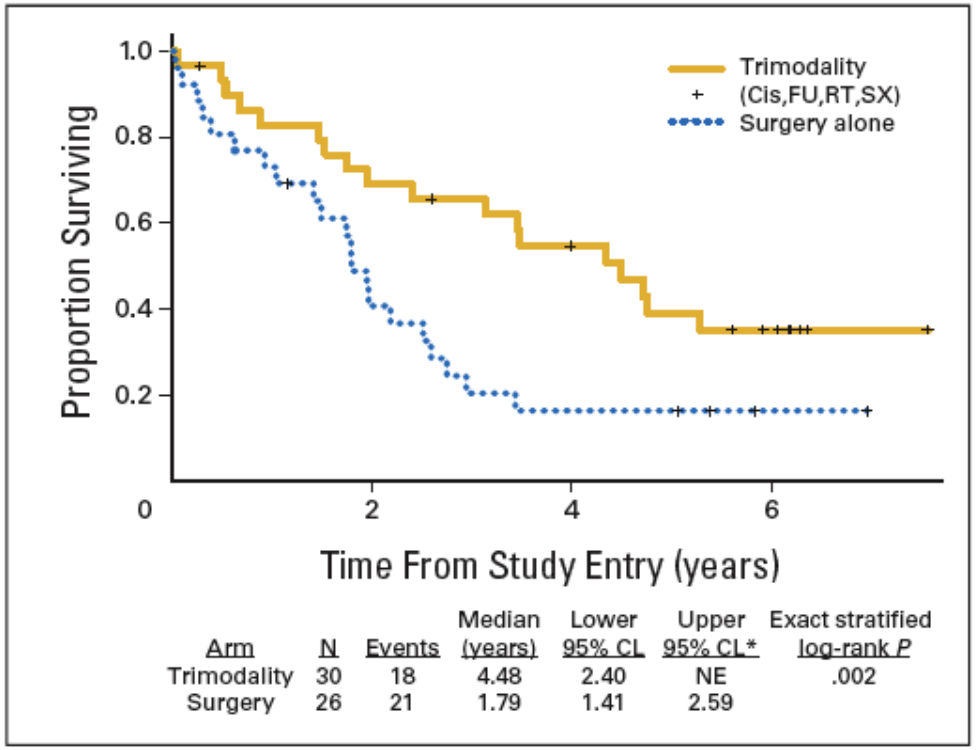


Numbers at risk							
Chemoradiotherapy + surgery	78	51	31	20	16	9	5
Surgery alone	83	60	30	20	12	8	6

Pre-operative chemoradiotherapy: CALGB 9781 trial

- Early closure because of poor accrual
- 56 pts
- 5FU-Cisplatine

+ 50.4 Gy



Arm	N	Events	Median (years)	Lower 95% CL	Upper 95% CL*	Exact stratified log-rank *P*
Trimodality	30	18	4.48	2.40	NE	.002
Surgery	26	21	1.79	1.41	2.59	

Fig 2. Kaplan-Meier estimates of overall survival (OS) by treatment arm measured from study entry until death from any cause. (*) NE, not estimable. †Asymptotic results for OS were comparable to those obtained using the exact method.

Tepper,
J Clin Oncol, 2008
26: 1086-1092

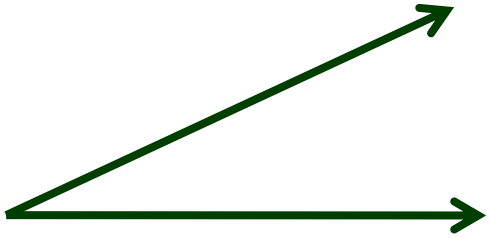
Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer

P. van Hagen, M.C.C.M. Hulshof, J.J.B. van Lanschot, E.W. Steyerberg,

CROSS Trial

Population: T1N1 or T2-T3-N0-1 and Tumour size between 5 and 8 cm

Oesophageal or gastro-oesophageal junction tumours



Surgery n=188

RT/CT then Surgery n=178

Adenocarcinoma: 75% +++

Carbo AUC2 and Taxol 50 mg/m2 D1, 8, 15, 22, 29

RT: 41.4 Gy / 1.8 Gy by fraction

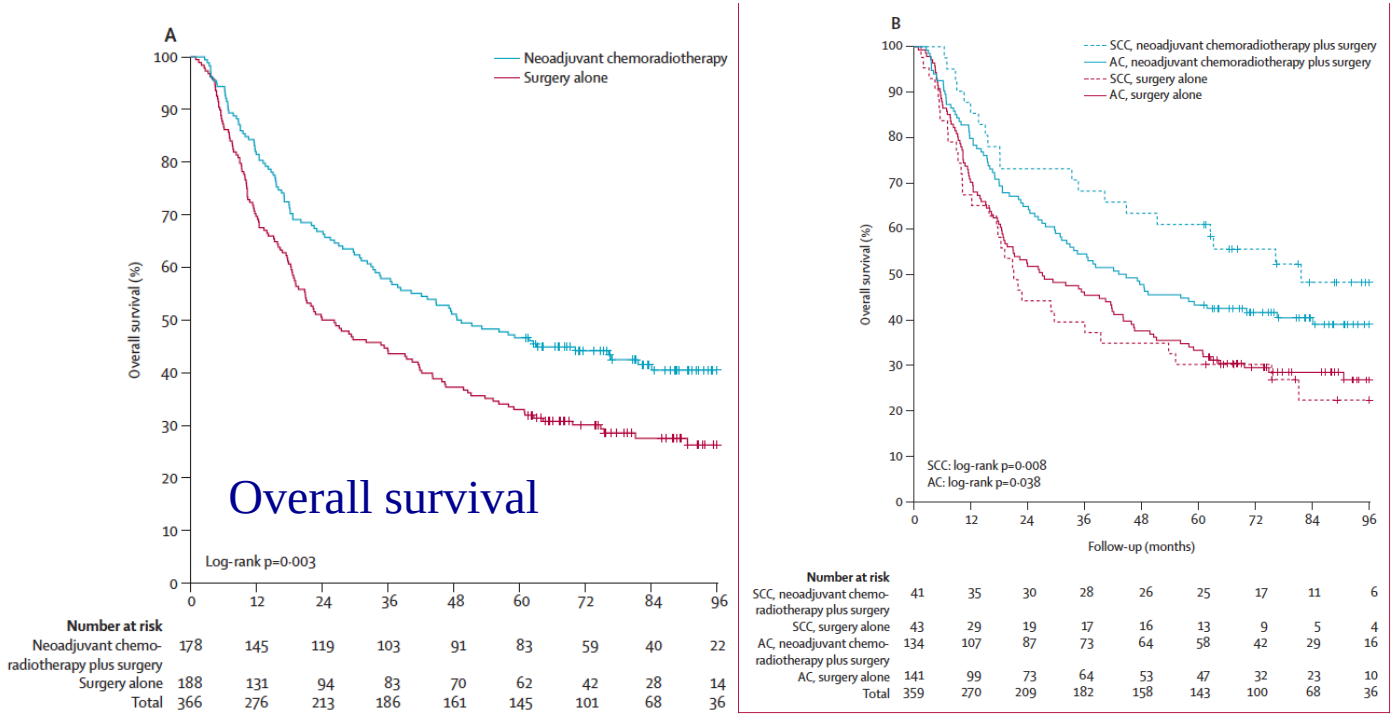
Better tolerated than 5FU-Cisplatin (?)

N Engl J Med 2012;366:2074-84

Shapiro, Lancet Oncol 2015; 16: 1090–98

CROSS Trial

A significant improvement in favor of pre-op. RT-CT



Overall survival According to histology

OS improvement for both histologies

pCR: 29%

R0: 92 vs 65%

Post-op mortality: 4% in both groups

Shapiro, Lancet Oncol 2015; 16: 1090–98

FFCD 9901 trial

Surgery alone versus chemoradiotherapy followed by surgery for localized esophageal cancer :

Early stages: Stage I&II (T1-T1, N0-1, T3N0)

cN1: #25%; cT3: #18%

5FU-CDDP/ RT: 45 Gy

	RT-CT	Surg alone	
Nbre pts	98	97	
Post-op Mortality (%)	11.1	3.4	0.049
5-yr survival (%)	41.1	33.8	NS
Local recurrences (%)	22.1	28.9	0.02
R0 resection (%)	93.8	92.1	

Per-op. RT-CT is not useful for early stages

Mariette, J Clin Oncol, 32:2416-2422, 2014

Preoperative Chemoradiotherapy vs Surgery: meta-analyses

Urschel, Am J Surg, 185, 538-543, 2003

Fiorica, Gut, 53: 925-930

Gebski, Lancet Oncol, 8: 226-234, 2007
Updated Sjoquist, Lancet Oncol, 2011, 12: 681-92

Jin, World J Gastroenterol, 15: 5983-91, 2009

Benefit for pre-operative RT-CT

Meta-analysis: Preop. RT-CT

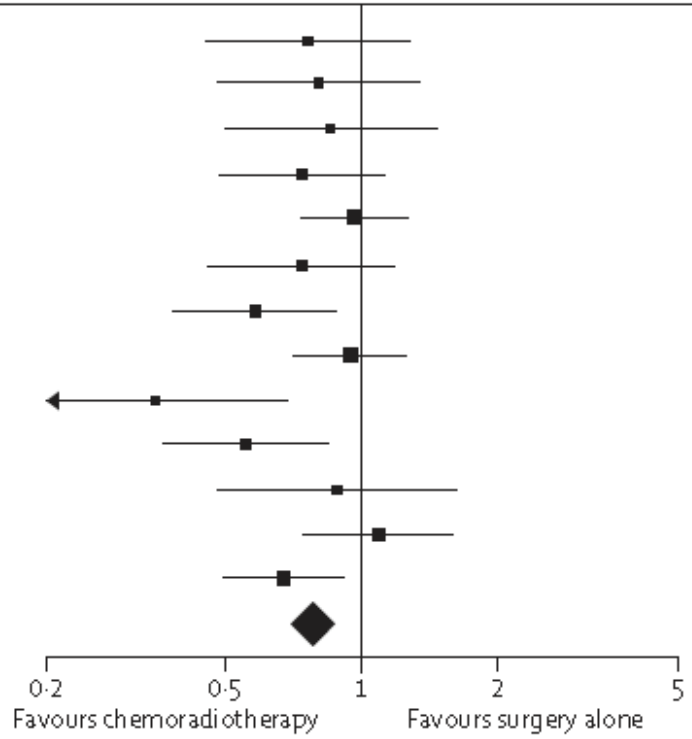
Sjoquist, Lancet Oncol, 2011, 12: 681-92

A

	Chemoradiotherapy (total)	Surgery alone (total)	Hazard ratio (95% CI)
Nygaard[9]	53	25	0·76 (0·45–1·28)
Apinop[39]	35	34	0·80 (0·48–1·34)
Le Prise[10]	45*	41	0·85 (0·50–1·46)
Urba[40]	50	50	0·74 (0·48–1·12)
Bosset[12]	148	145	0·96 (0·73–1·27)
Walsh (SCC)[13]	29	32	0·74 (0·46–1·18)
Walsh (adenocarcinoma)[14]	58	55	0·58 (0·38–0·88)
Burmeister[22]	128†	128‡	0·94 (0·70–1·26)
Tepper[43]	30	26	0·35 (0·18–0·68)
Lv[41]	80	80	0·55 (0·36–0·84)
Lee[17]	51	50	0·88 (0·48–1·62)
Mariette[11]	97	98	1·09 (0·74–1·59)
van der Gaast[42]	176	188	0·67 (0·49–0·91)
Total	**980**	**952**	**0·78 (0·70–0·88)**

Heterogeneity: χ^2=18·04, df=12 (p=0·11); I^2=33%

Test for overall effect: Z=4·28 (p<0·0001)



HR: 0.78; p <0.0001

Meta-analysis: Pré-op. CT

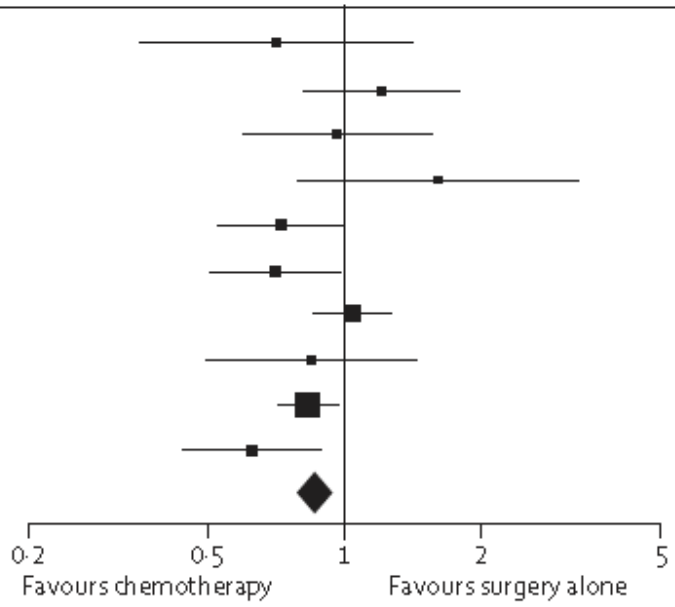
Sjoquist, Lancet Oncol, 2011, 12: 681-92

A

	Chemotherapy (total)	Surgery alone (total)	Hazard ratio (95% CI)
Roth[23]	19	20	0·71 (0·36–1·43)
Nygaard[9]	56	25	1·22 (0·82–1·81)
Schlag[19]	22	24	0·97 (0·60–1·57)
Maipang[24]	24	22	1·61 (0·79–3·27)
Law[20]	74	73	0·73 (0·53–1·00)
Boonstra[37]	85	84	0·71 (0·51–0·98)
Kelsen[8]	233*	234	1·05 (0·86–1·28)
Ancona[21]	48	48	0·85 (0·50–1·44)
Allum[1]	400†	402*	0·84 (0·72–0·98)
Ychou[7]	85	84	0·63 (0·45–0·89)
Total	**1046**	**1016**	**0·87 (0·79–0·96)**

Heterogeneity: χ^2=15·77, df=9 (p=0·07); I^2=43%

Test for overall effect: Z=2·83 (p=0·005)



HR: 0.87; p = 0.005

Meta-analysis

Sjoquist, Lancet Oncol, 2011, 12: 681-92

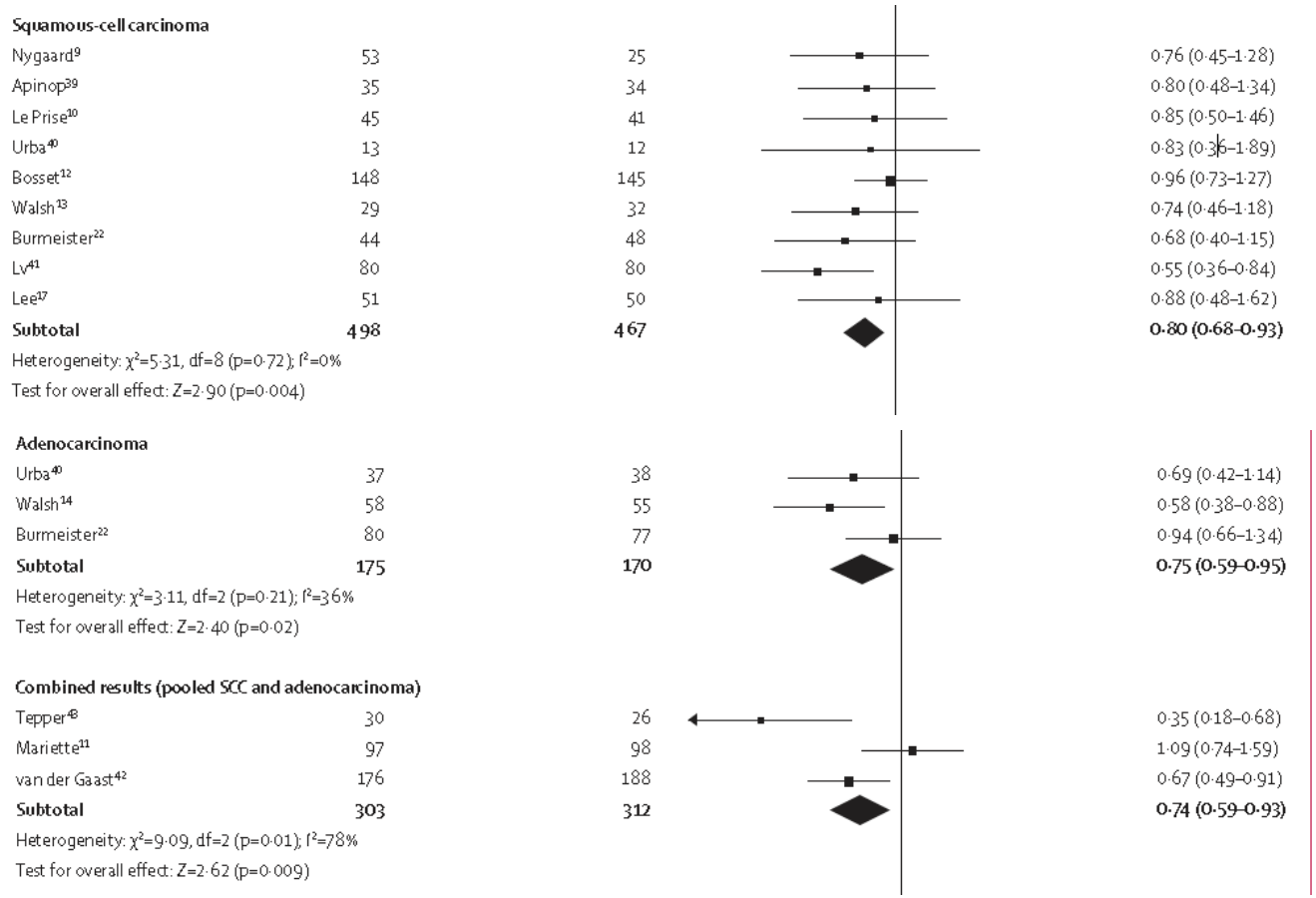
Absolute benefit in Survival:

- Pre-operative chemoradiotherapy: 8.7%
- Pre-operative chemotherapy: 5.1%

Effect of pre-operative RT-CT according to histology

Sjoquist, Lancet Oncol, 2011, 12: 681-92

Benefit of pre-operative RT- CT for both types



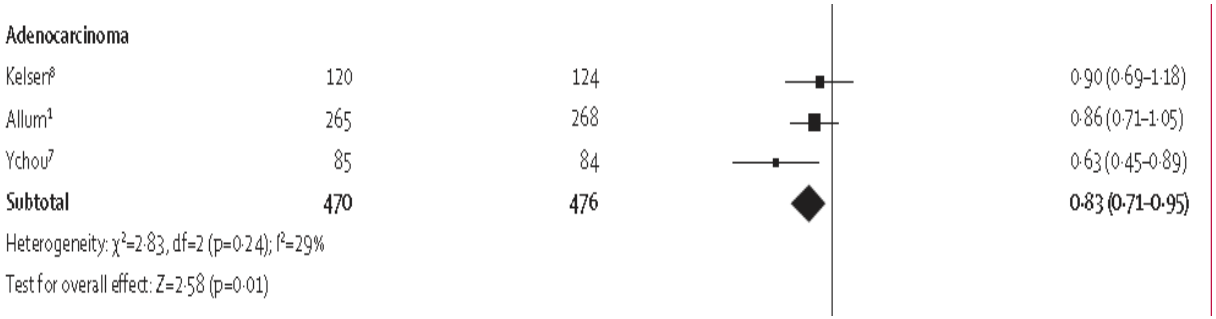
SCC
P=0.004

ADK
P=0.02

Effect of preoperative CT according to histology

Sjoquist, Lancet Oncol, 2011, 12: 681-92

No benefit of pre-op. CT in case of SCC

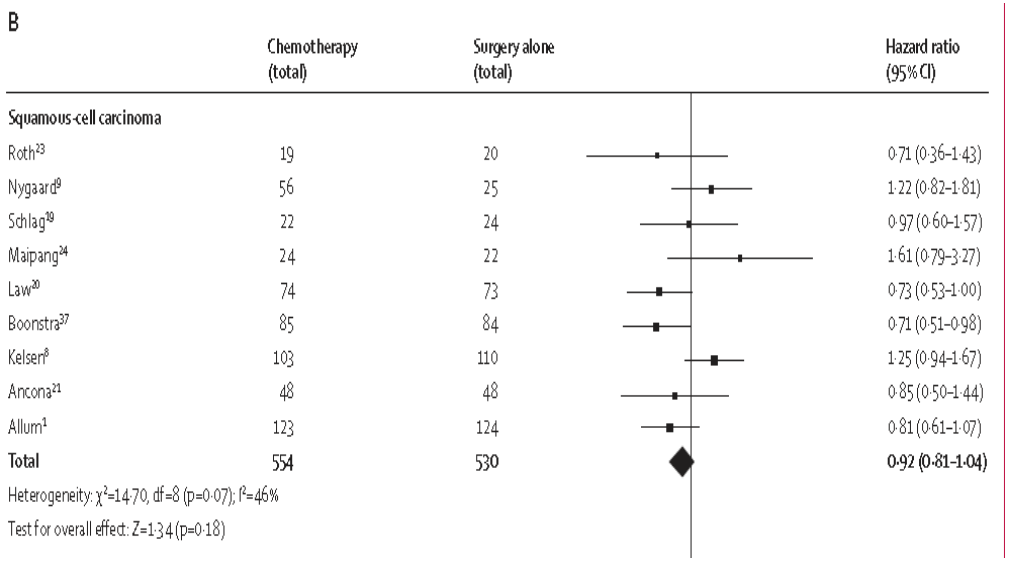


Adenocarcinoma			
Kelsen[8]	120	124	0·90 (0·69–1·18)
Allum[1]	265	268	0·86 (0·71–1·05)
Ychou[7]	85	84	0·63 (0·45–0·89)
Subtotal	**470**	**476**	**0·83 (0·71–0·95)**

Heterogeneity: χ^2=2·83, df=2 (p=0·24); I^2=29%

Test for overall effect: Z=2·58 (p=0·01)

ADK
P=0.01



B

	Chemotherapy (total)	Surgery alone (total)	Hazard ratio (95% CI)
Squamous-cell carcinoma			
Roth[23]	19	20	0·71 (0·36–1·43)
Nygaard[9]	56	25	1·22 (0·82–1·81)
Schlag[19]	22	24	0·97 (0·60–1·57)
Maipang[24]	24	22	1·61 (0·79–3·27)
Law[20]	74	73	0·73 (0·53–1·00)
Boonstra[37]	85	84	0·71 (0·51–0·98)
Kelsen[8]	103	110	1·25 (0·94–1·67)
Ancona[21]	48	48	0·85 (0·50–1·44)
Allum[1]	123	124	0·81 (0·61–1·07)
Total	**554**	**530**	**0·92 (0·81–1·04)**

Heterogeneity: χ^2=14·70, df=8 (p=0·07); I^2=46%

Test for overall effect: Z=1·34 (p=0·18)

SCC
P=0.18

Pre-operative chemo or chemoRT for adenocarcinomas?

German trial, prematurely closed
126 pts randomized between : CT vs CT+RT-CT before surgery

	CT	CT-RT
3 yr OS (%)	27.7	47.4

P=0.07

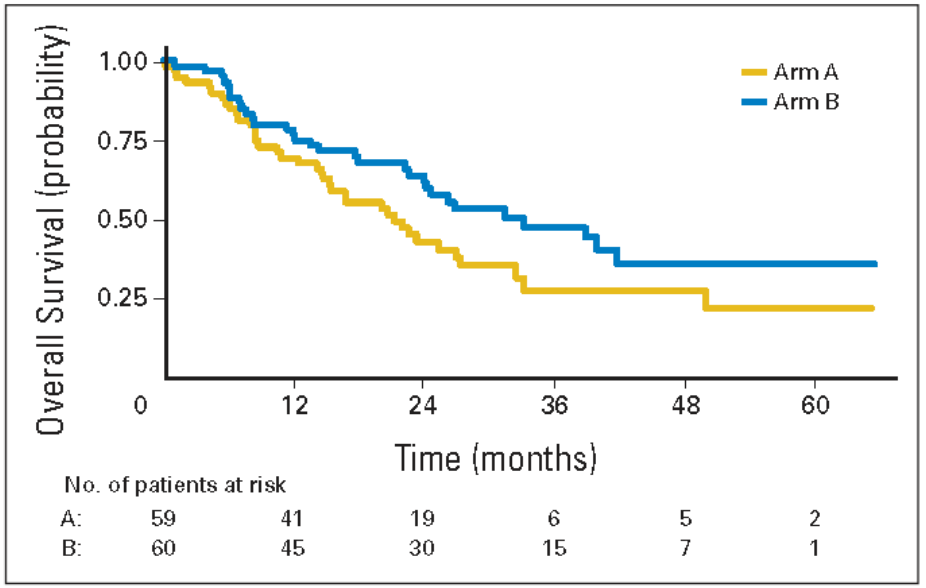
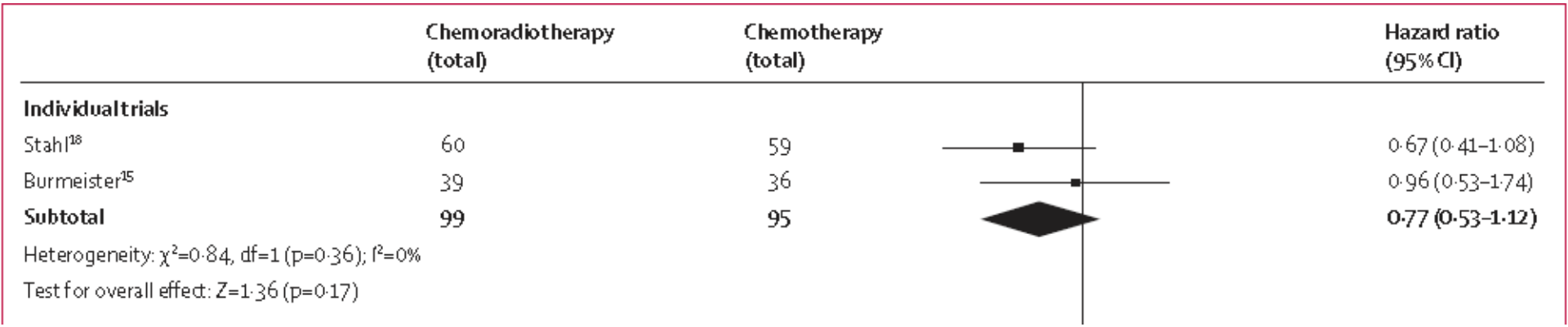


Fig 2. Overall survival (intent to treat). Arm A, n = 59 (chemotherapy and surgery): median survival time 21.1 months, 3-year survival rate 27.7%. Arm B, n = 60 (chemoradiotherapy and surgery): median survival time 33.1 months, 3-year survival rate 47.7%.

Stahl, JCO, 2009, 851-856

Pre-operative chemo or chemoRT for adenocarcinomas?

Sjoquist, Lancet Oncol, 2011, 12: 681-92



	Chemoradiotherapy (total)	Chemotherapy (total)	Hazard ratio (95% CI)
Individual trials			
Stahl[18]	60	59	0·67 (0·41–1·08)
Burmeister[15]	39	36	0·96 (0·53–1·74)
Subtotal	**99**	**95**	**0·77 (0·53–1·12)**
Heterogeneity: χ^2=0·84, df=1 (p=0·36); I^2=0%			
Test for overall effect: Z=1·36 (p=0·17)			

Two trials

Closed prematurely

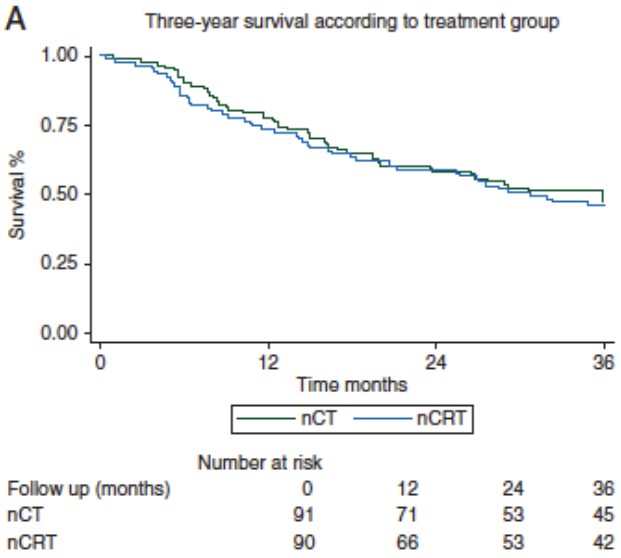
No benefit – p=0.17

Pre-operative CT or RT-CT?

- Swedish randomized trial
- 3 cycles of Cisplatin/5FU
- ± Radiotherapy: 40 Gy

	CT	RT-CT	
N pts	91	90	
90-day mortality (%)	3	8	0.12
Post-op complications (%)	35	38	0.28
pCR (%)	9	28	0.002
R0 resection (%)	74	87	0.042
pN1	62	35	0.001

Overall survival



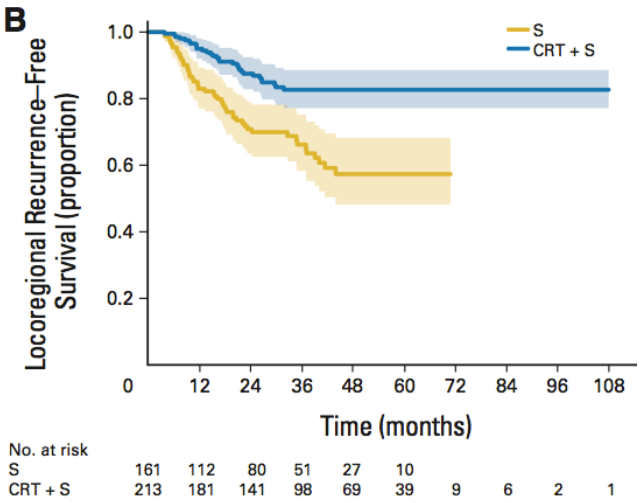
On Going trials:

- Irish neo-AGIS: MAGIC vs CROSS
- Japan

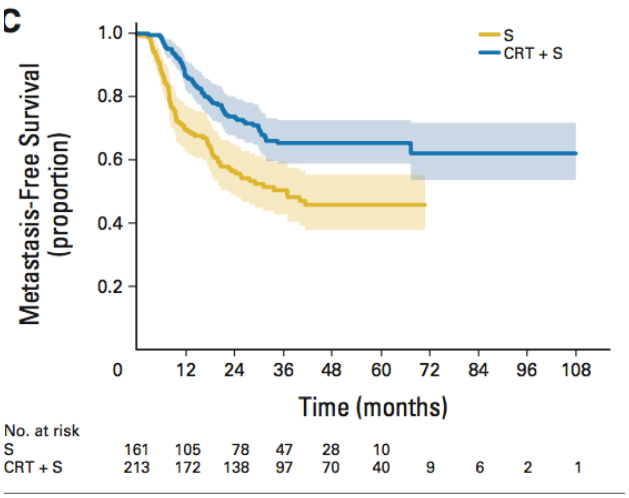
Klevebro, Ann Oncol, 2016, 27: 660-667

CROSS study: patters of failure

LocoRegional control



Distant metastasis



Site of Recurrence	S Arm (n = 161) No.	S Arm (n = 161) %	CRT + S Arm (n = 213) No.	CRT + S Arm (n = 213) %
Anastomosis	14	8.7	6	2.8
Mediastinum	33	20.5	15	7.0
Supraclavicular	7	4.3	9	4.2
Celiac axis	11	6.9	8	3.8
Para-aortic	17	10.6	14	6.6
Peritoneal carcinomatosis	22	13.7	9	4.2
Hematogenous	57	35.4	61	28.6

Oppedijk, JCO, 2014, 32: 385=91

Conclusion:
Pre-operative treatments for locally advanced oesophageal cancers (T3 and/or N+)

- SCC: RT-CT
  - Advantage well demonstrated
    - Meta-analysis, CROSS, etc…
- Adenocarcinomas of the Gastro-oesophageal junction
  - A neo-adjuvant treatment is required
  - CT or RT-CT ?
  - CT: MRC trial, MAGIC, FFCD trial, meta-analysis
  - RT-CT: CROSS, trial meta-analysis
    - Maybe better for large tumors
- Trial in progress: MAGIC vs CROSS study

Locally advanced oesophageal carcinomas

Definition: T3-T4 and/or N+

Results of surgery:

5-yr survival:10 - 30%

Could Chemoradiotherapy be used instead of surgery?

Locally advanced oesophageal carcinomas: Is surgery useful?

2 Randomized trials:

Stahl, JCO, 23: 2310-17, 2005

Bedenne, JCO, 25: 1160-68, 2007

Same design:

After concomitant chemo-radiotherapy

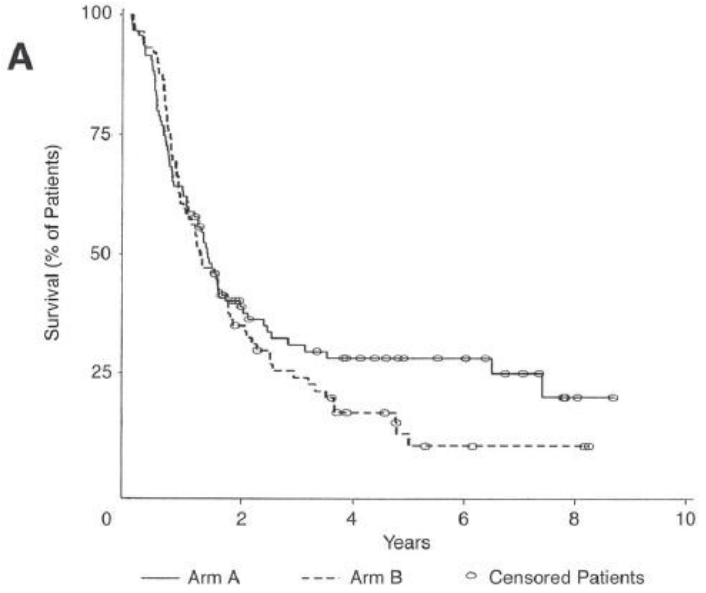
And a « good » response

Randomisation: Surg. or continuation of CT-RT

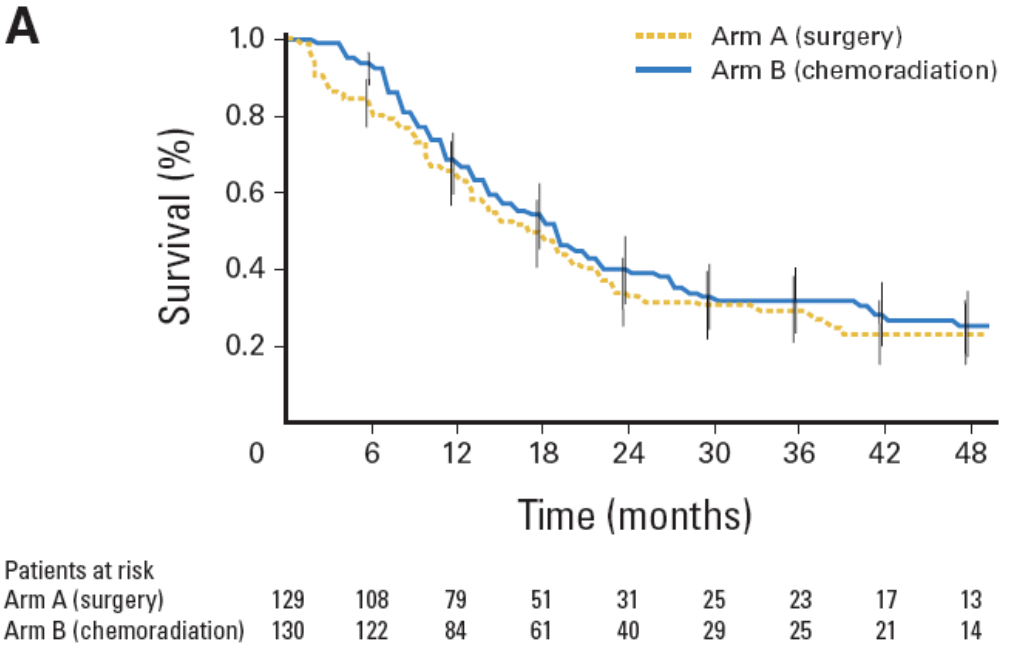
Locally advanced oesophageal carcinomas: Is surgery useful?

	German trial		French trial	
	RT/CT	RT/CT + Chir.	RT/CT	RT/CT + Chir.
N° pts	86	86	130	129
AdénoK. (%)	0	0	11.5	10.9
pCR (%)		35		23
2-yr survival (%)	**35.4**	**39.9**	**39.8**	**33.6**
	Freedom from local progression (%)		Locoregional relapses (%)	
	40.7	64.3	43	33.6

German trial:
A: Surgery
B: RT-CT



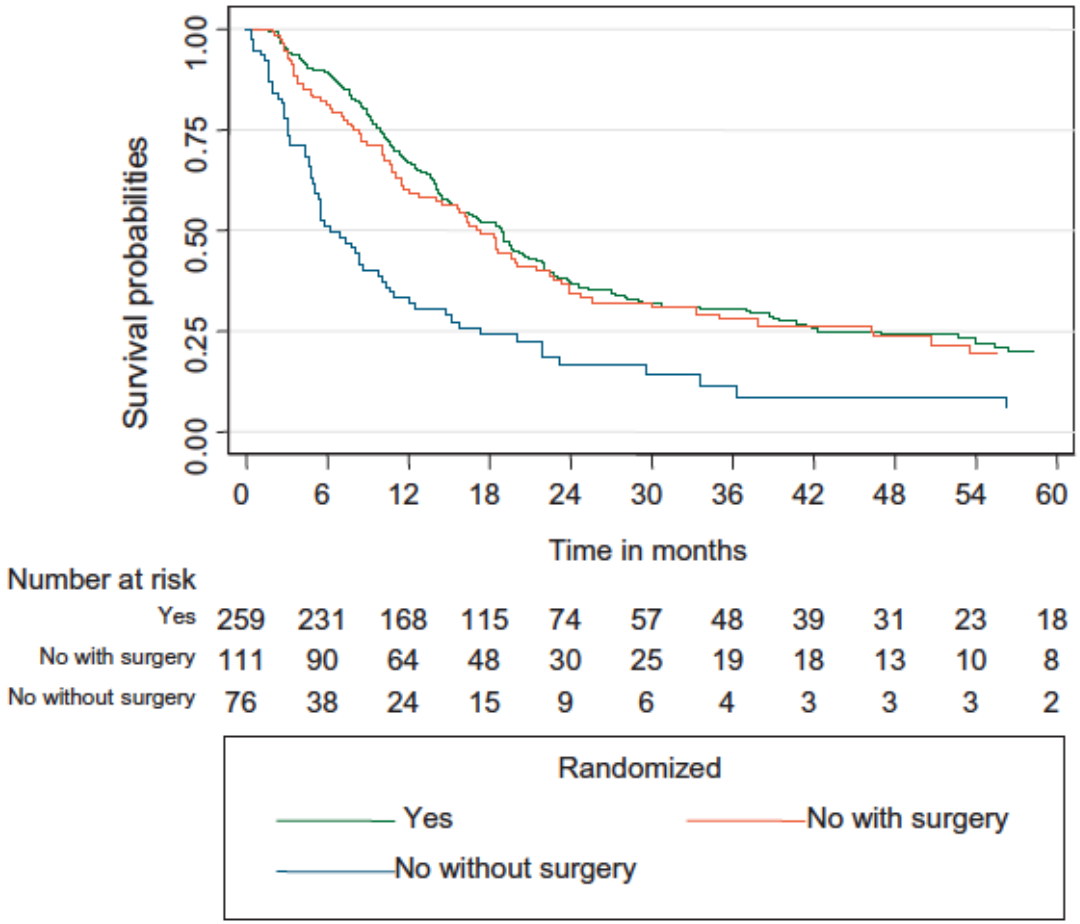
French trial:
A: Surgery
B: RT-CT



Surgery: a salvage modality?

FFCD trial: what happen to the non-randomized pts (non-responders, mainly) ?

- 451 pts registered
- 192 pts not randomized because of
  - A less than partial response
  - Contraindication for surgery
  - Patient's refusal
  - Death
- 112 pts underwent salvage surgery



Non-responders pts who are operated Have the same survival that randomized pts !

Vincent, EJC, 2015, 51:1683– 1693

Salvage Surgery

Large multicenter retrospective study

Salvage surgery vs Planned surgery

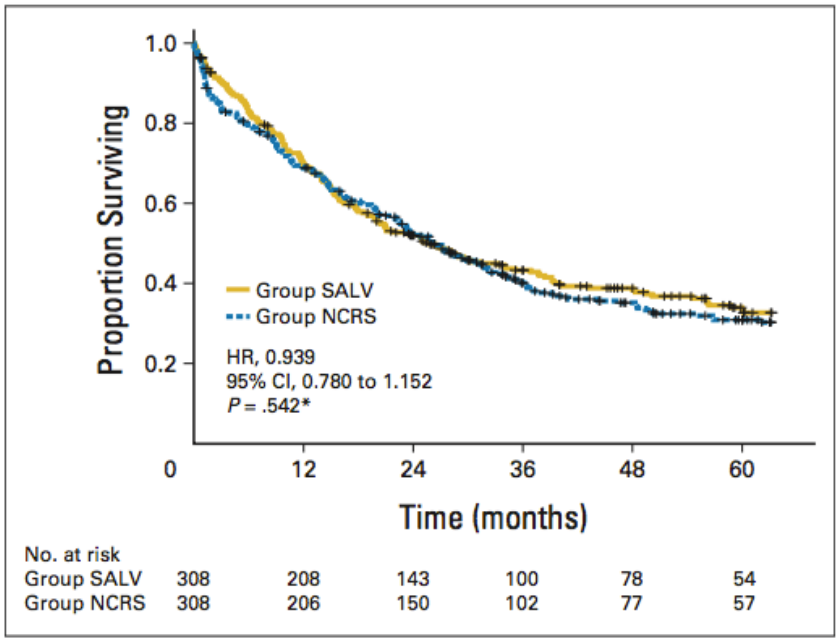


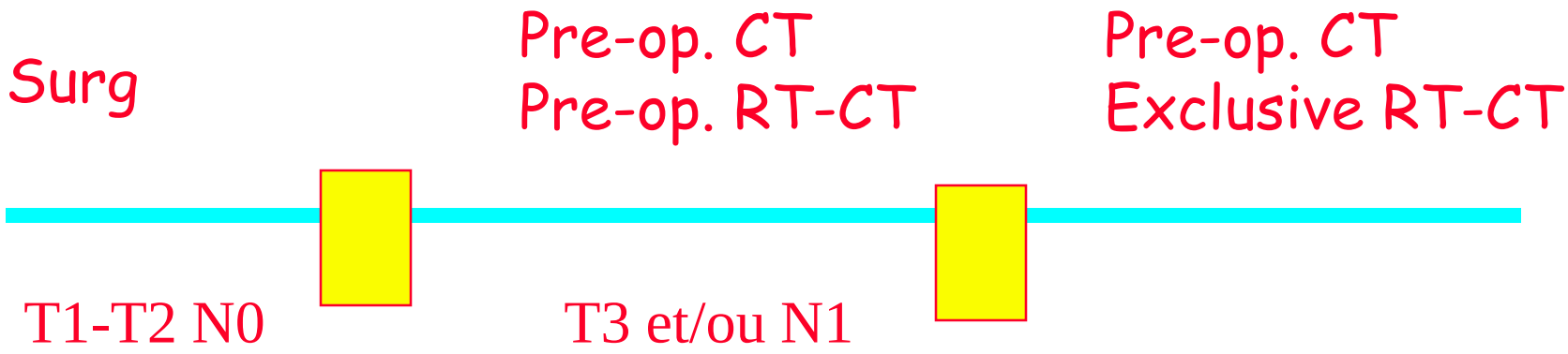
Fig 1. Comparison of overall survival in propensity-matched salvage esophagectomy after definitive chemoradiotherapy (SALV) and neoadjuvant chemoradiotherapy followed by planned esophagectomy (NCRS) groups. No. of patients at risk in each interval is shown in table at bottom of graph. HR, hazard ratio. (*) *P* value and HR calculated using Cox regression model for matched data set.

No difference
In long-term outcome

A viable option ?

Markar, JCO, 33: 3866-73, 2015

Conclusion:
« Resectable » oesophageal carcinomas
Big heterogeneity



Stage
Resectability (surgeon)
Histology (+++)
Tumour volume
Patient (Age, comorbidities, …)

Role of surgery in locally advanced oesophageal carcinomas

Who benefit from surgery ?

Improving the results of concomitant Chemo-Radiotherapy

- Predictive factors of chemosensitivity
- Evaluation of response to chemo/radiotherapy
- "Neo-adjuvant" Chemotherapy
- New drugs for chemo-radiation schedules
- Endoluminal brachytherapy
- Altered fractionnation schedules
- Conformal radiotherapy

Predictive factors of chemo-radiosensitivity

- Apoptosis: p53, p21, Survivin, bcl2
- Tumour proliferation: NF-κB, COX-2, cyclins
- EGFR, HER-2
- DNA repair: ERCC1
- Tumour hypoxia
- Thymydylate synthase (5FU)
- Metallothionein, GST-Π, P-glycoprotein (cisplatin)
- Gene expression arrays
- SNPs for AKT, PTEN, …

Prognostic value of NF-κB

37 pts
Preoperative RT-CT
Then surgery
NF-κB evaluated by immunochemistry

pCR according to NF-kB

NF-kB +	NF-kB -
1/10 (10%)	13/27 (48%)

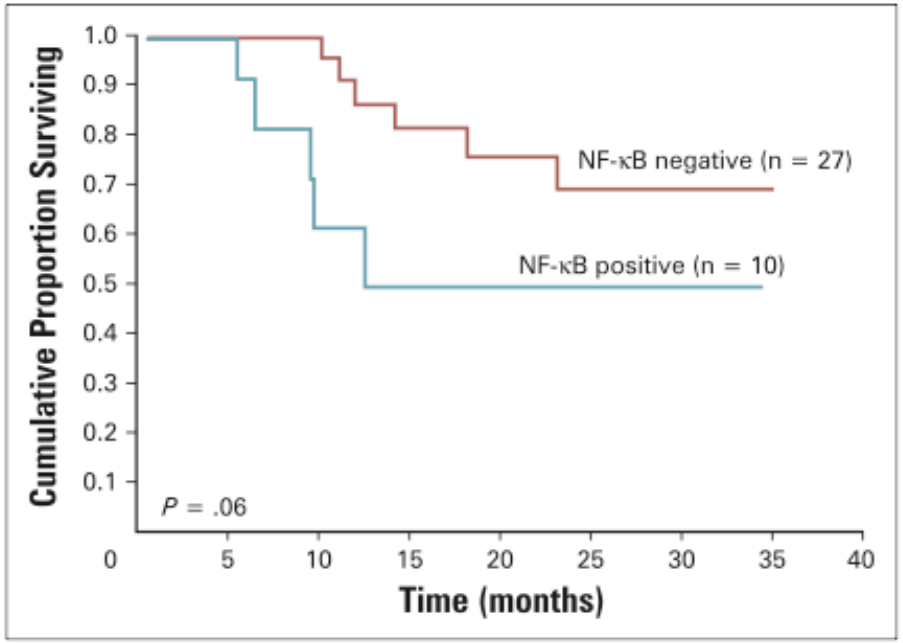


Fig 4. Kaplan-Meier curve and overall survival by pretreatment nuclear factor κB (NF-κB) expression status for esophageal cancer patients treated with preoperative chemoradiotherapy.

Izzo, JCO, 24:748-754, 2006

Impact of surgery in locally advanced oesophageal carcinomas

Population:

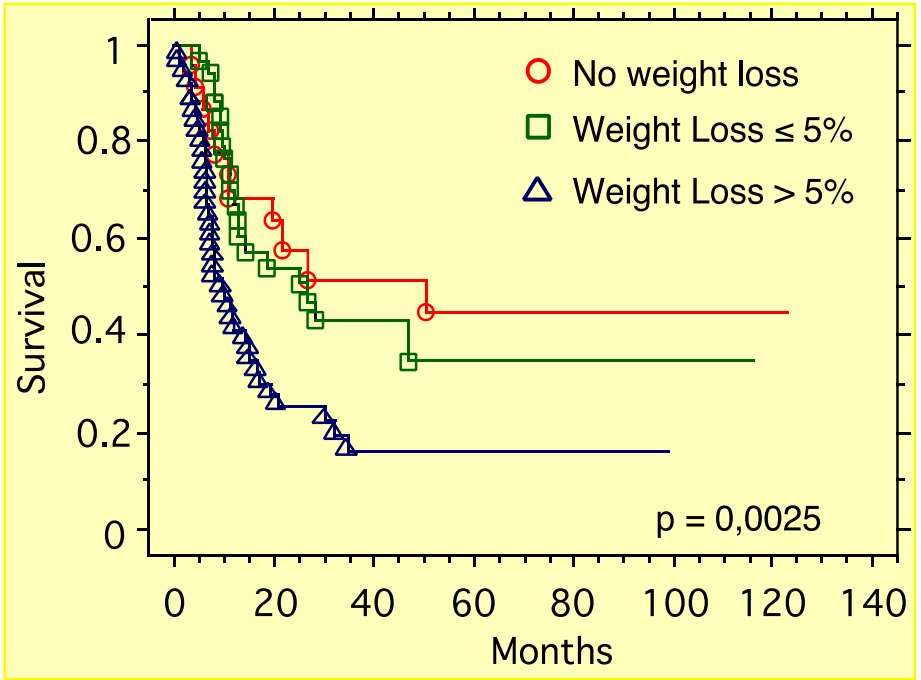
-112 patients with a T3 and/or N+ tumor

- Concomitant chemoradiotherapy
- 2 cycles of 5FU-CDDP then 40 Gy
- Reevaluation

-Then Surgery or continuation of RT-CT

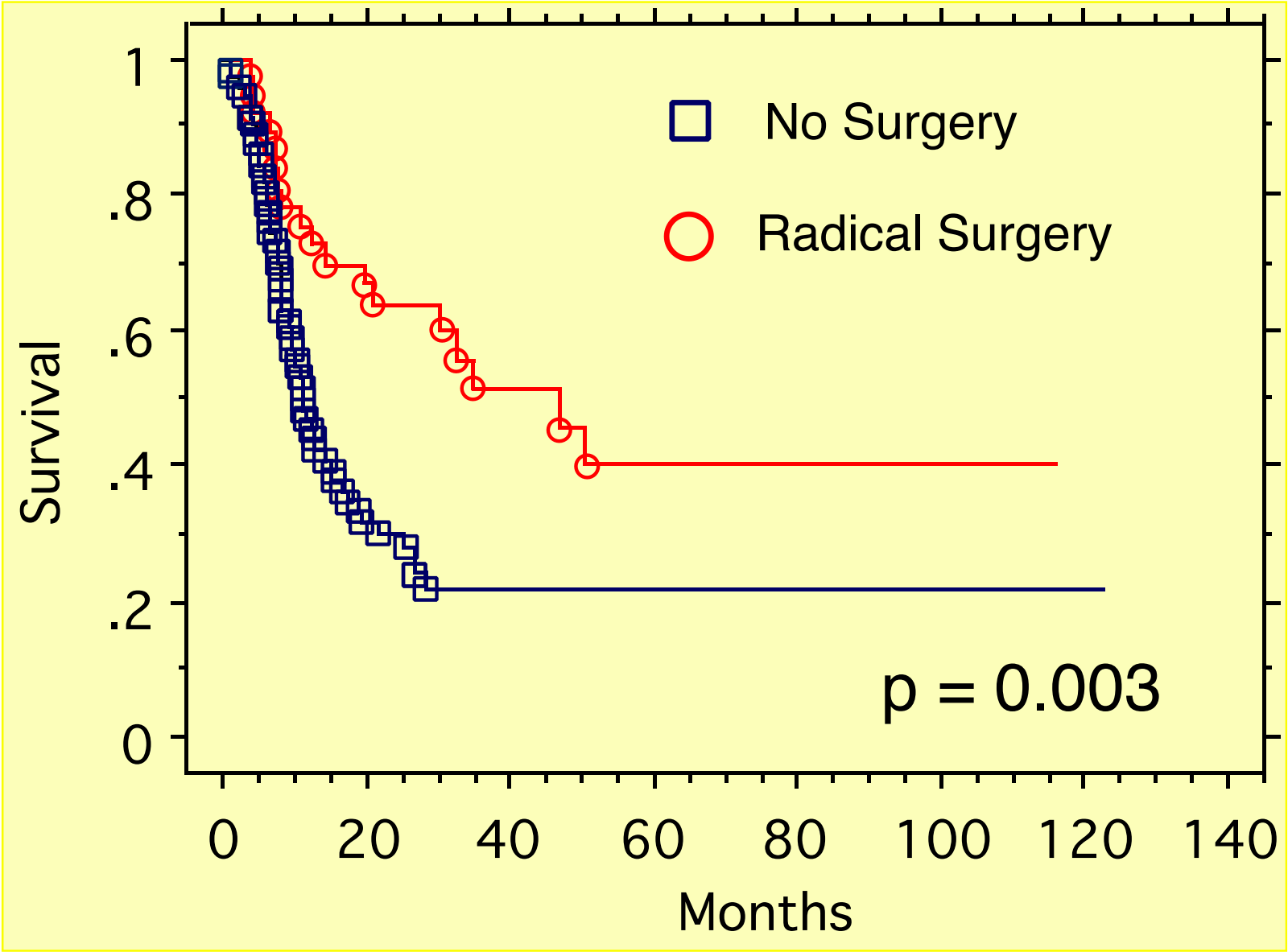
Prognostic factors (Univariate):

- Karnofsky index
- Weight loss
- Response to RT-CT
- Surgery



Hennequin et al, IJROBP, 2001

Survival according to Surgery



Five-year survival rate for the 78 responders according to surgery and clinical response

Clinical response	Esophagectomy	No surgery	P
Complete response, n (%)	7 (35.7%)	21 (42.2%)	NS
Partial response, n (%)	28 (49.1%)	22 (23.5%)	0.003

(%) : 5-year survival rates

Evaluation of response

- Endoscopy: could not assessed intra-parietal tumor residual

- Echo-endoscopy (Giovannini, Ital J Gastro, 1999)

Overestimation of residual tumour because of oedema

- CT –IV contrast (Griffith, Br J Radiol, 1999) +++

- PET-scan (Brucher, Ann Surg, 2001)
- Inflammation due to radiation

Prognostic value of metabolic response

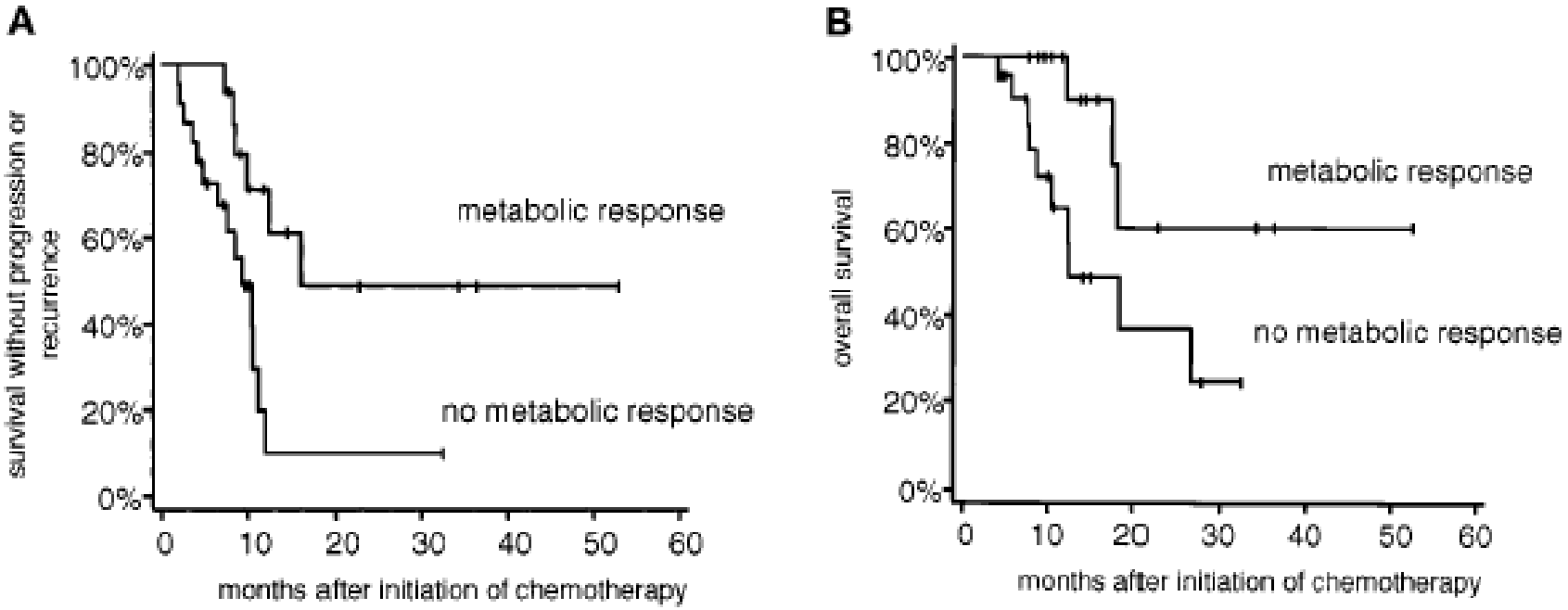


Fig 3. Kaplan-Meier plots showing (A) survival without disease progression or recurrence and (B) overall survival. For both parameters there is a statistically significant difference between patients with and without a metabolic response ($P = .01$ and $P = .04$, respectively).

Weber, JCO, 2001

Time Course of Tumor Metabolic Activity During Chemoradiotherapy of Esophageal Squamous Cell Carcinoma and Response to Treatment

Wieder, JCO, 22: 900-908, 2004

N =38 pts

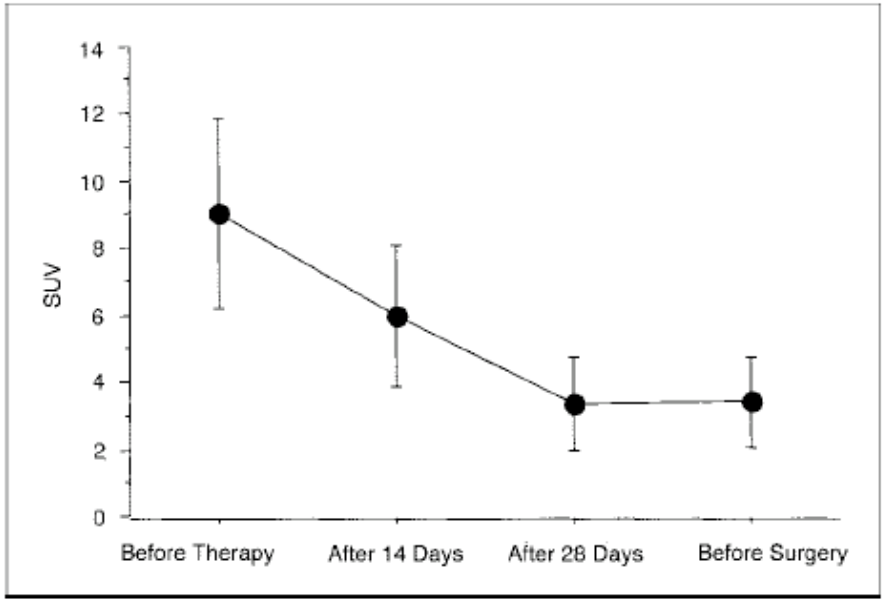


Fig 1. Time course of tumor fluorodeoxyglucose uptake during chemoradiotherapy. Error bars denote 1 standard deviation. SUV, standardized uptake value.

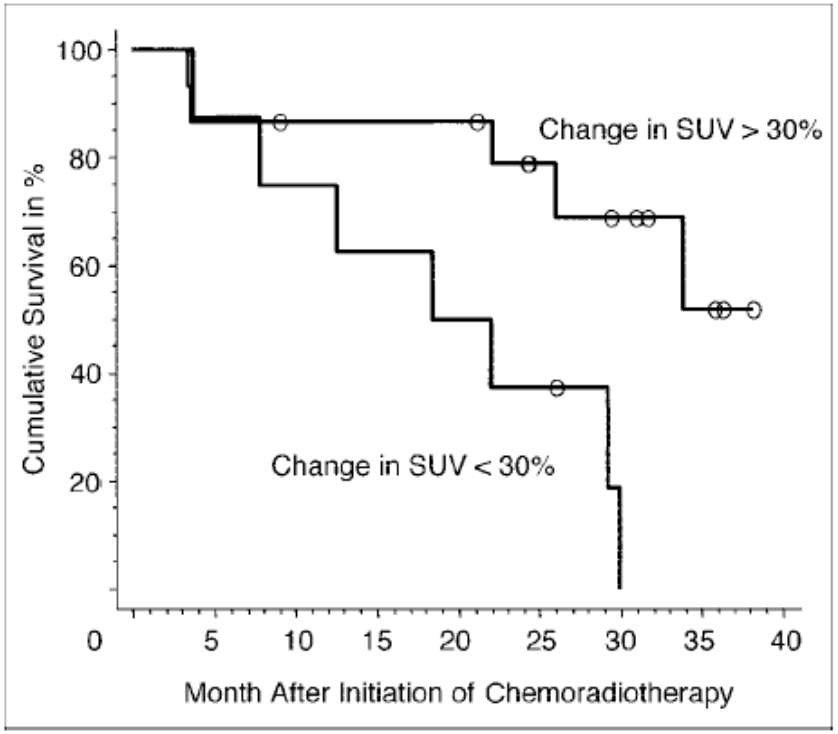
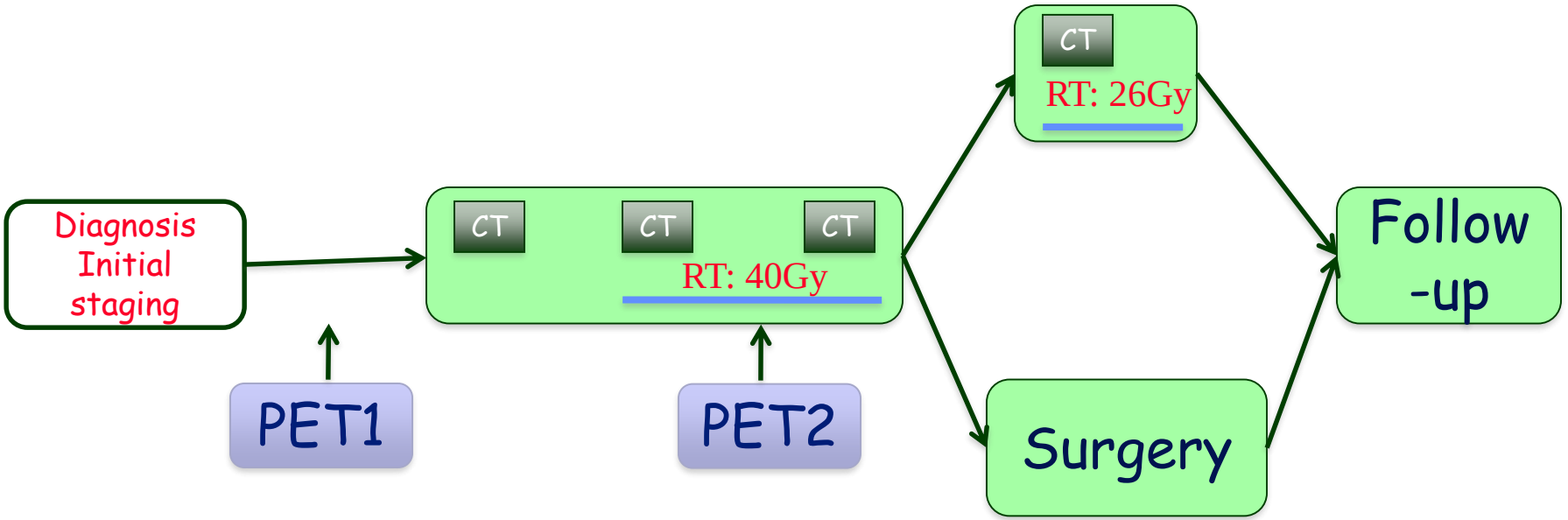


Fig 6. Reduction of tumor fluorodeoxyglucose uptake 14 days after initiation of chemoradiotherapy versus patient survival. SUV, standardized uptake value.

Evaluation of response to RT-CT by 18-FDG-PET-CT



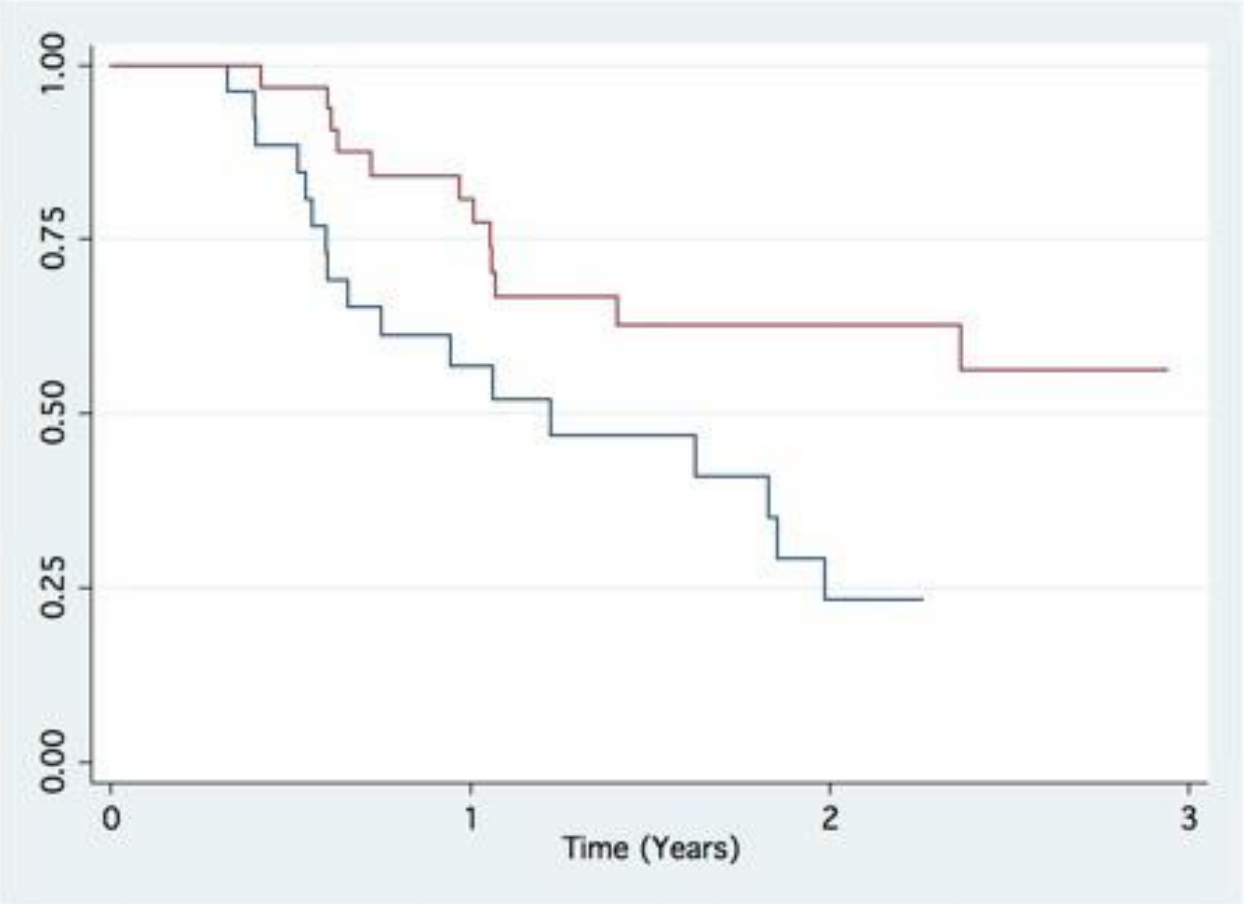
Included:
72 pts

Second PET-CT:
N=59 pts

No Second PET-CT:
n=13

Cuenca, Hennequin, …Eur J Nucl Med Mol Imaging. 2013 Apr;40(4):477-85

Evaluation of response to RT-CT by 18-FDG-PET-CT



Log-rank : p=0.016

Numbers of patients at risk:

Months	0	6	12	18	24	30	36
Good Response	33	32	25	16	12	8	5
Poor Response	26	23	13	8	4	2	_

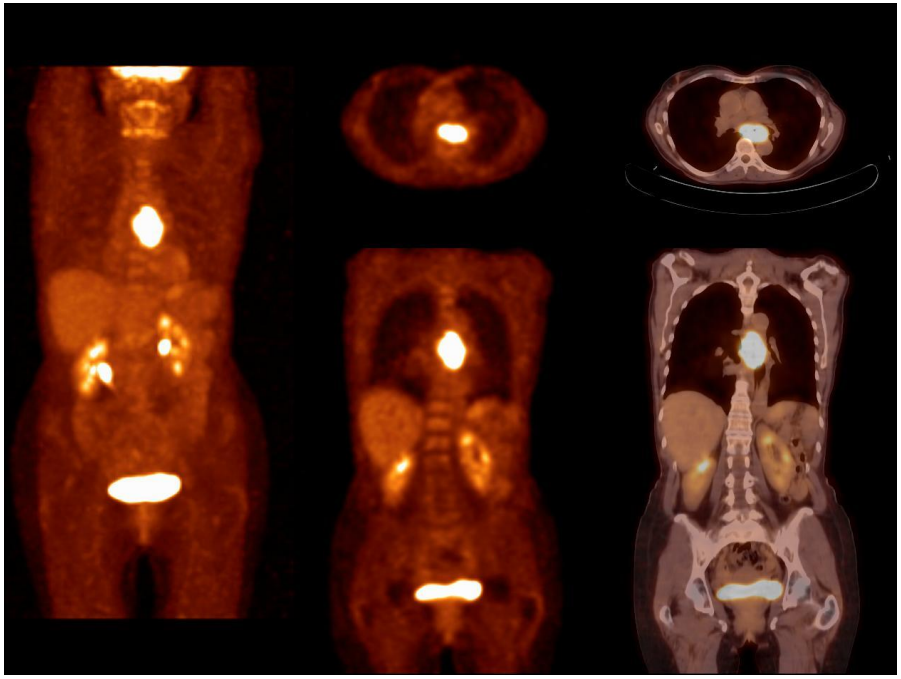
Overall survival according to metabolic response (>50% decline in SUV)

Cuenca, EJNM, 2013

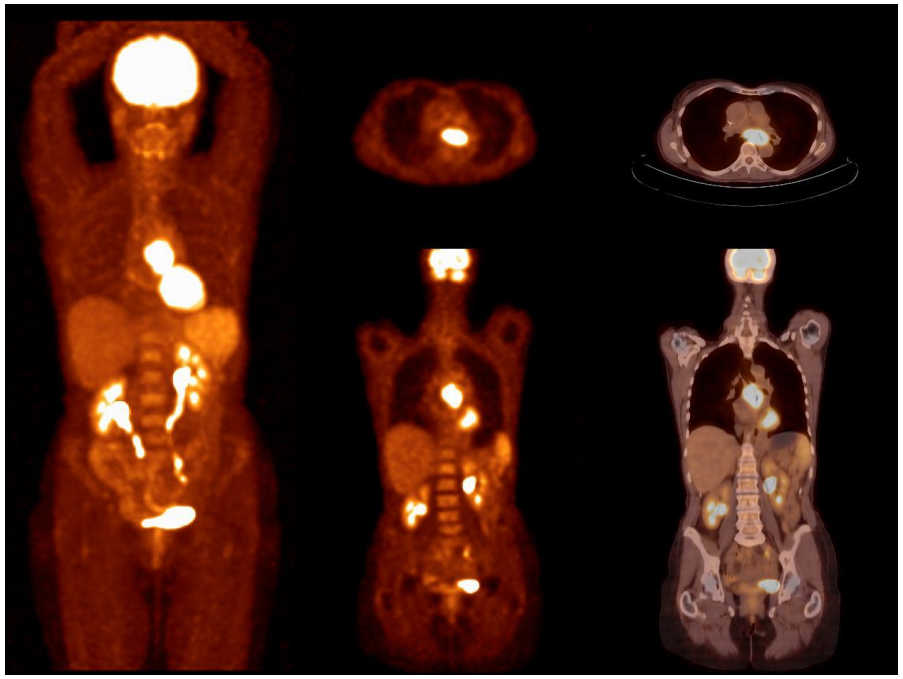
- Exemple N° 1

- 72 yr-old; T3N1 middle third of the oeso.

Primary TEP: SUVmax=14



TEP at 20 Gy: SUVmax=12



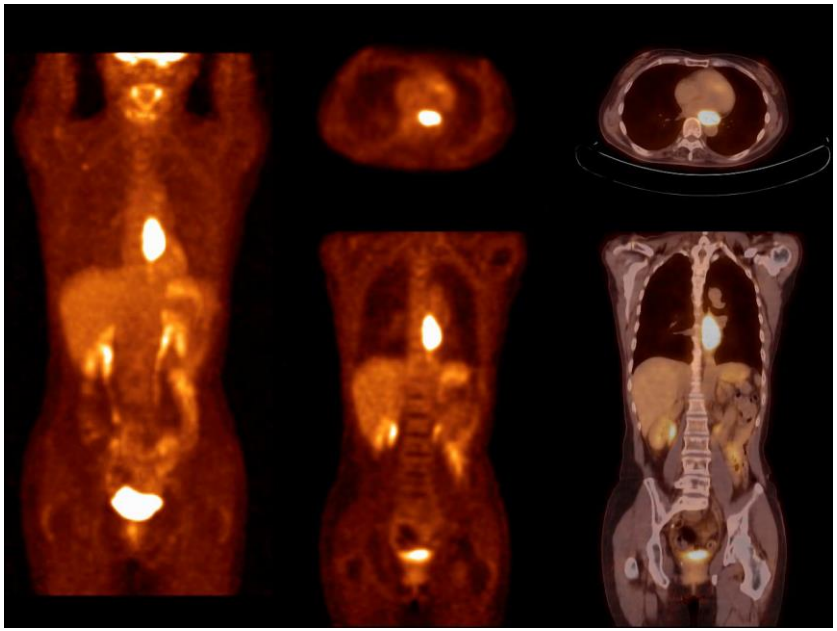
Conclusion: No metabolic response

Surgery : No tumour down staging
No sign of tumour regression

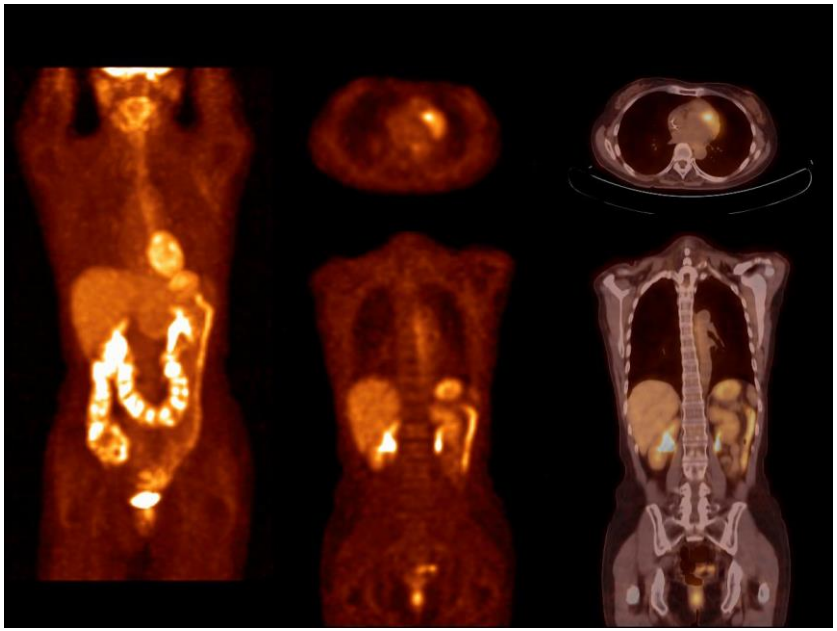
- Exemple N° 2

- 55 yrs old; SCC T3N0 lower third

First TEP : SUVmax=19.3



TEP à 20 Gy: SUVmax=2.3



Conclusion: Complete metabolic response

Surgery: pathologic metabolic response

New drugs

Taxanes: Taxol, Taxoter

Oxaliplatine

Targeted therapies

- EGFR inhibitors (cetuximab, panitunimab)
- Anti-angiogenic drugs
- HER2 inhibitors (for Her2 ADK tumours)

FolFox vs 5FU/CDDP

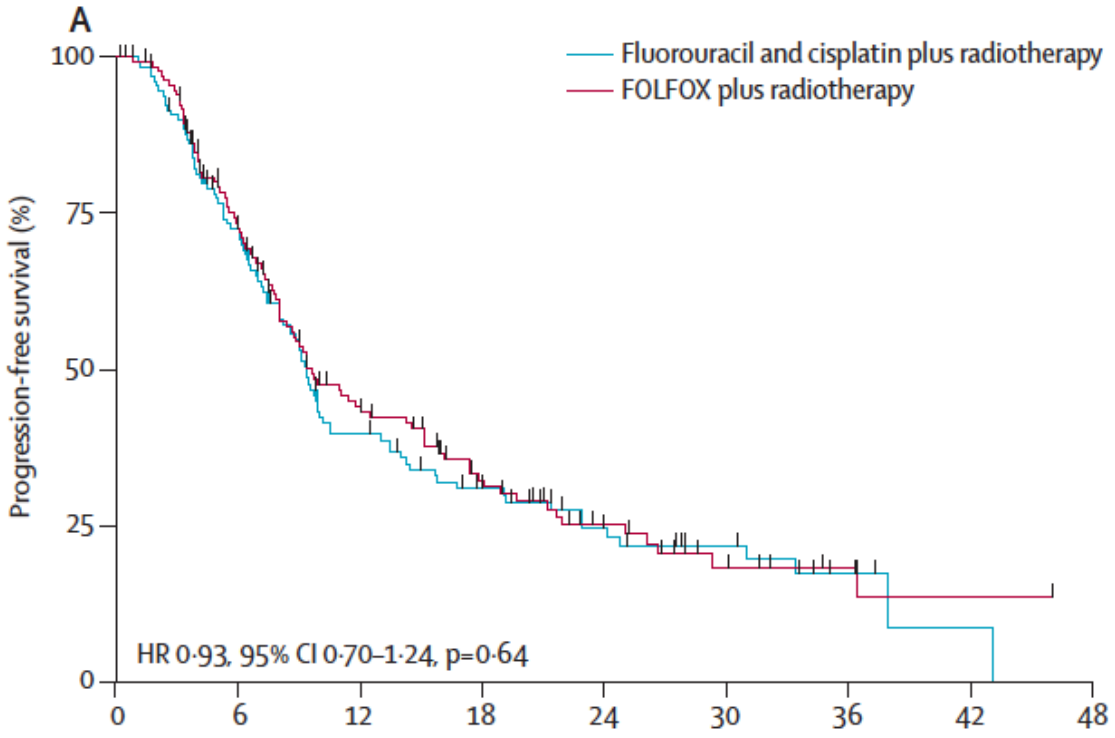
Phase III trial
267 pts – SCC: 85.8% - Stage III-IV: 61%

	FolFOx RT	5FU/CDDP/RT
Grade ¾ toxicities (%)	30.6	31.3
3-yr PFS (%)	18.2	17.4
OS (%)	20.2	17.5

No difference – better tolerated?

Conroy, T., Lancet Oncol. 2014 Mar;15(3):305-14

FolFox vs 5FU/CDDP



Number at risk									
Fluorouracil and cisplatin plus radiotherapy	133	89	44	29	18	11	5	1	0
FOLFOX plus radiotherapy	134	90	50	29	17	8	4	3	2

No difference

But this is not an non-inferiority trial

Conroy, T., Lancet Oncol. 2014 Mar;15(3):305-14

5FU/CDDP ± Cetuximab: SCOPE Trial

Phase II/III trial:

RT-CT: Cisplatin 60 mg/m2 D1+ capecitabine: 625mg/m2 twice daily
4 cycles – RT 50 Gy during cycles 3&4
± Cetuximab: 400 mg/m2 D1 then 250 mg/m2 weekly

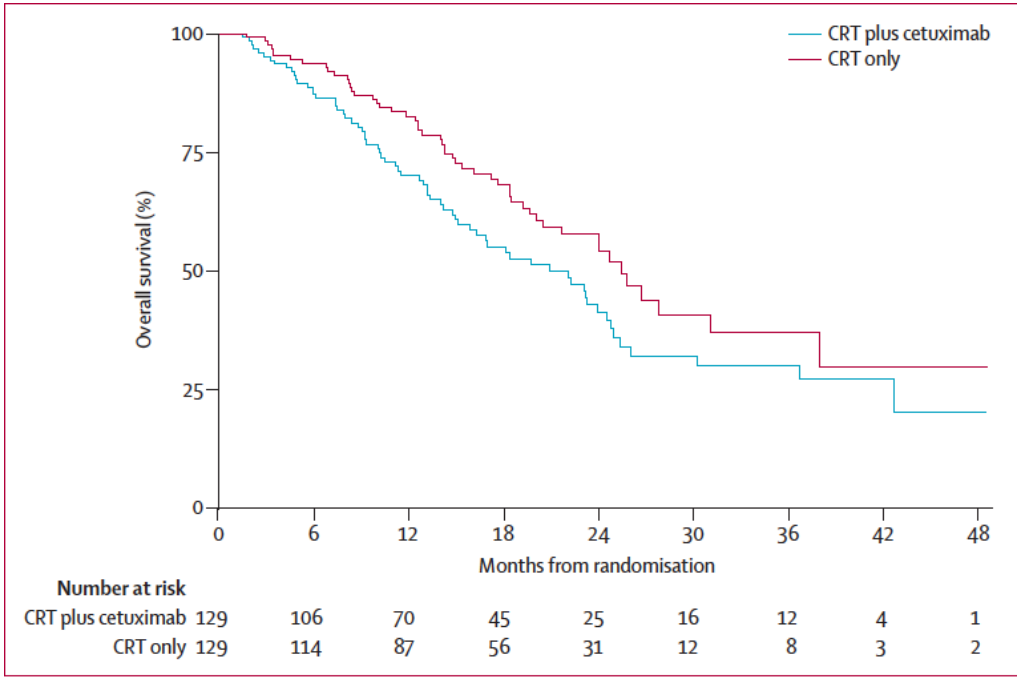
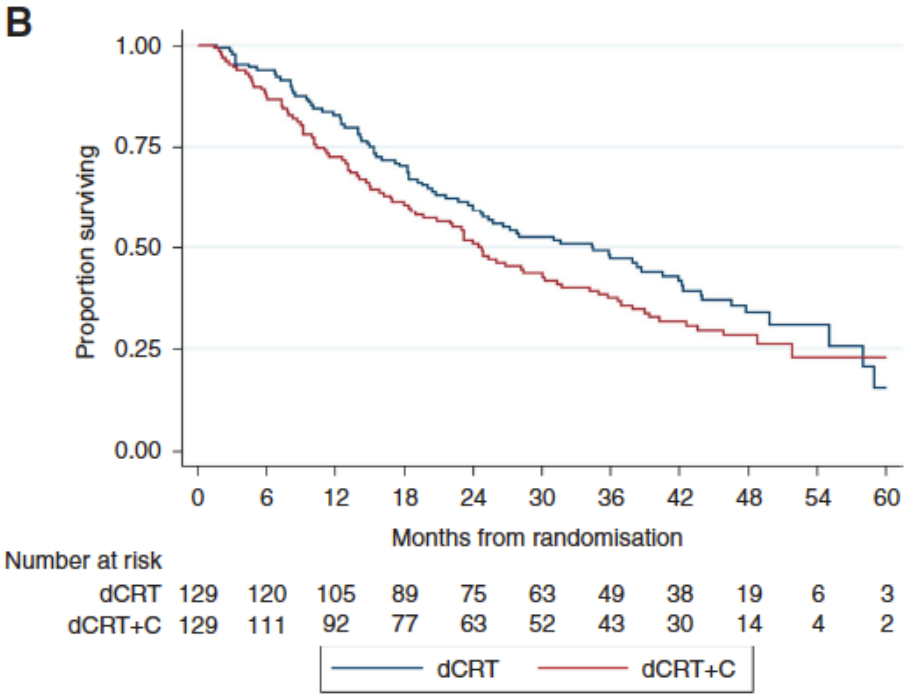


Figure 2: Kaplan-Meier curves of overall survival by treatment group

Crosby, Lancet Oncol 2013; 14: 627–37

Scope trial: update



Exclusive RT-CT
(contemporary series)
3-yr OS: 47.2%

Prognostic factors:
- Radiation dose
- Cisplatin intensity

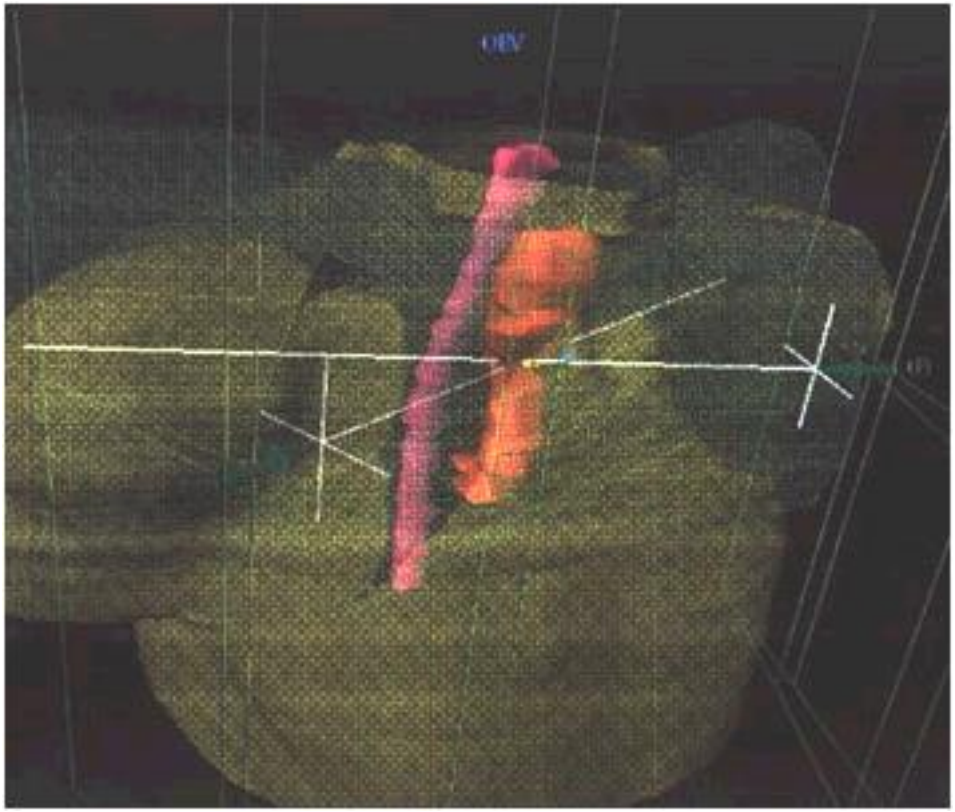
Crosby, BJC, 2017, 116: 709-716

Improving radiotherapy

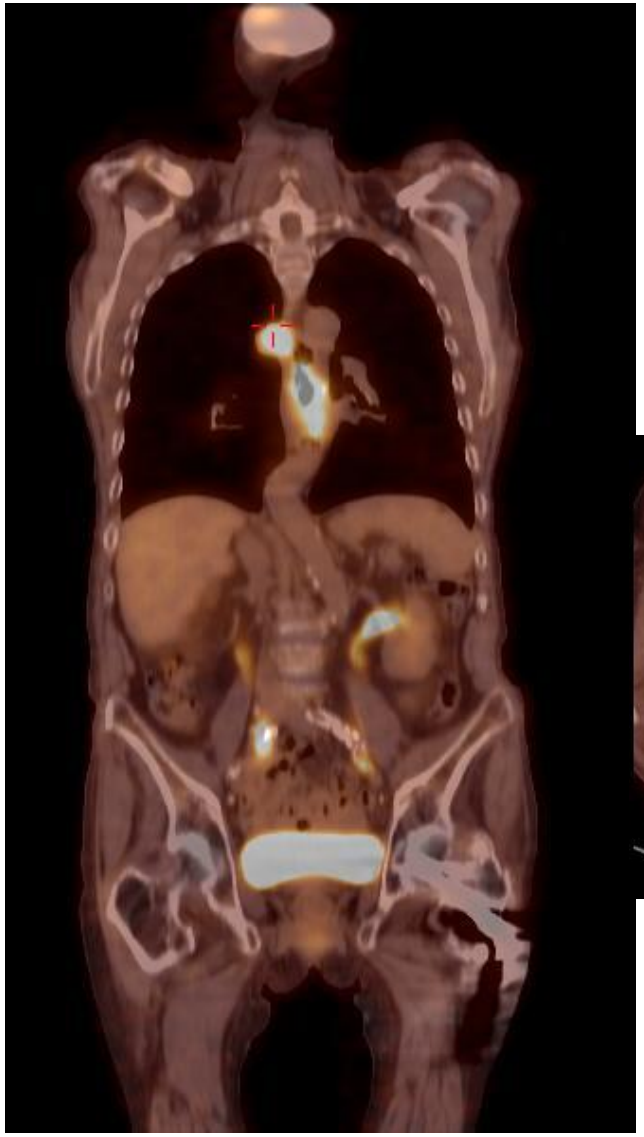
- Conformal RT/IMRT

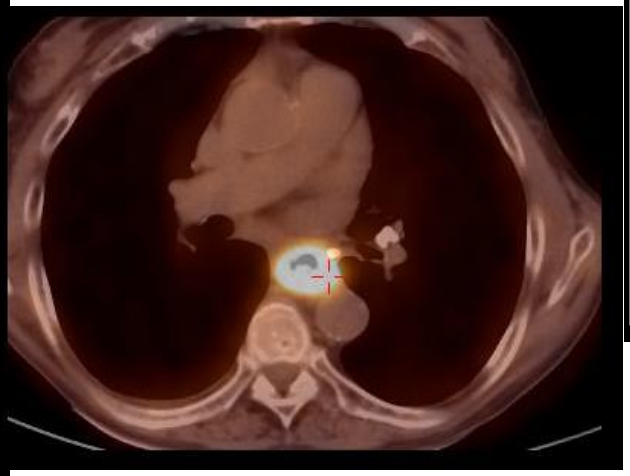
- Definition of target volumes: PET-scan

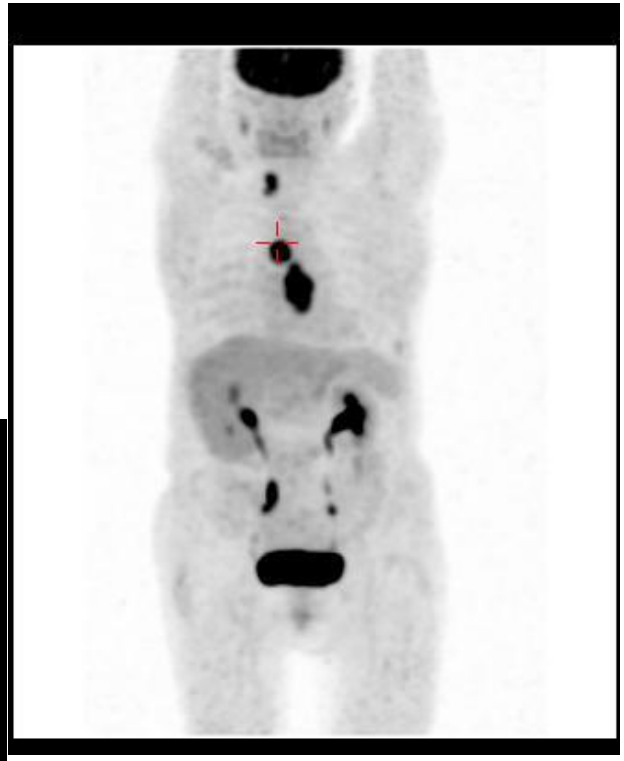
- Dose:
50 or 66 Gy ++++



PET-scan for staging







Dose-effect of chemoradiotherapy in oesophageal carcinomas

Intergroup Trial INT 0123

R → 5FU-CDDP- **50.4 Gy (n = 109)**

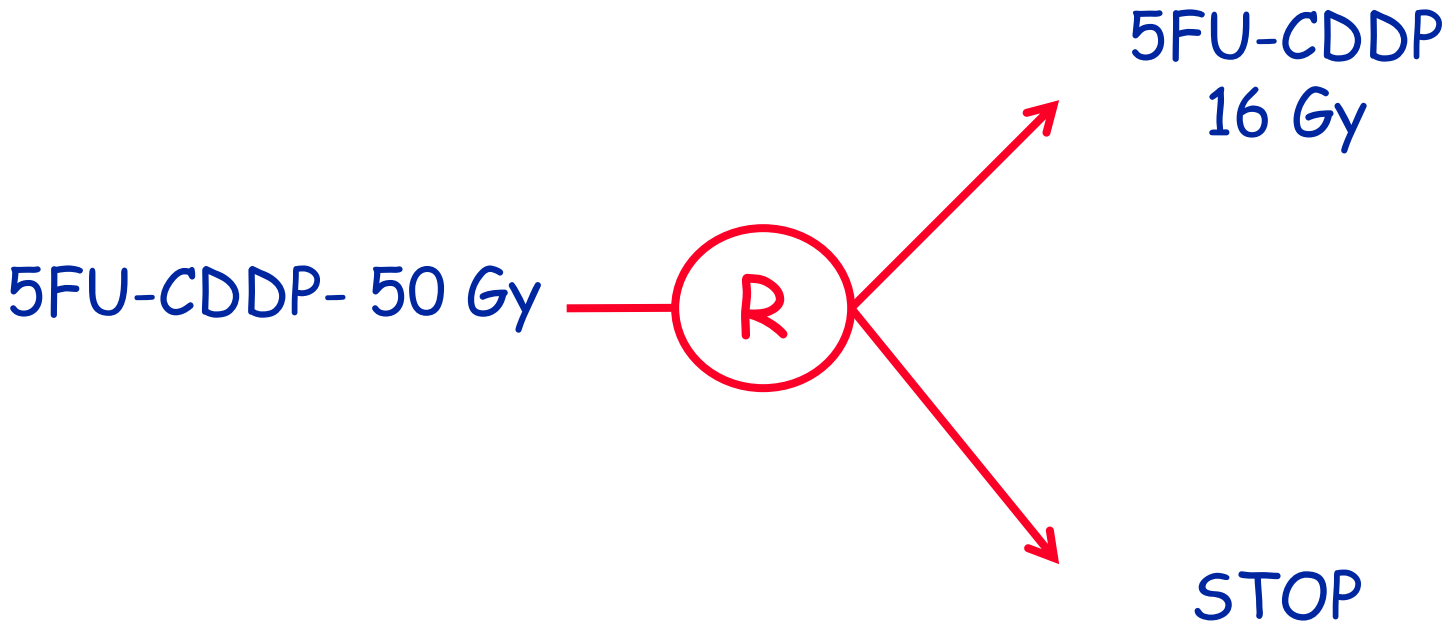
R → 5FU-CDDP- **64.8 Gy (n = 109)**

Minsky, JCO, 20:1167-1174, 2002

Intergroup Trial INT 0123

	High dose (64.8 Gy)	Standard dose (50.4 Gy)
No pts	109	109
Treatment-related deaths	10%	2%
2-yr survival (%)	31%	40%

New french trial: CONCORDE



Chemo-radiotherapy in oesophageal carcinomas: Take-home messages

1. For T3-T4 or N1 tumours, pre-op RT-CT is required

2. For T3-T4 or N1 tumours, after pre-op RT-CT, the role of surgery is not well defined

3. For inoperable locally advanced tumours, RT-CT could cure #25% of the patients

4. The best chemotherapy regimen to be used with RT:
- 5FU-CDDP
- FolFox
- Taxol/carboplatine

Mr Abid

55 ans

Alcohool + smoking

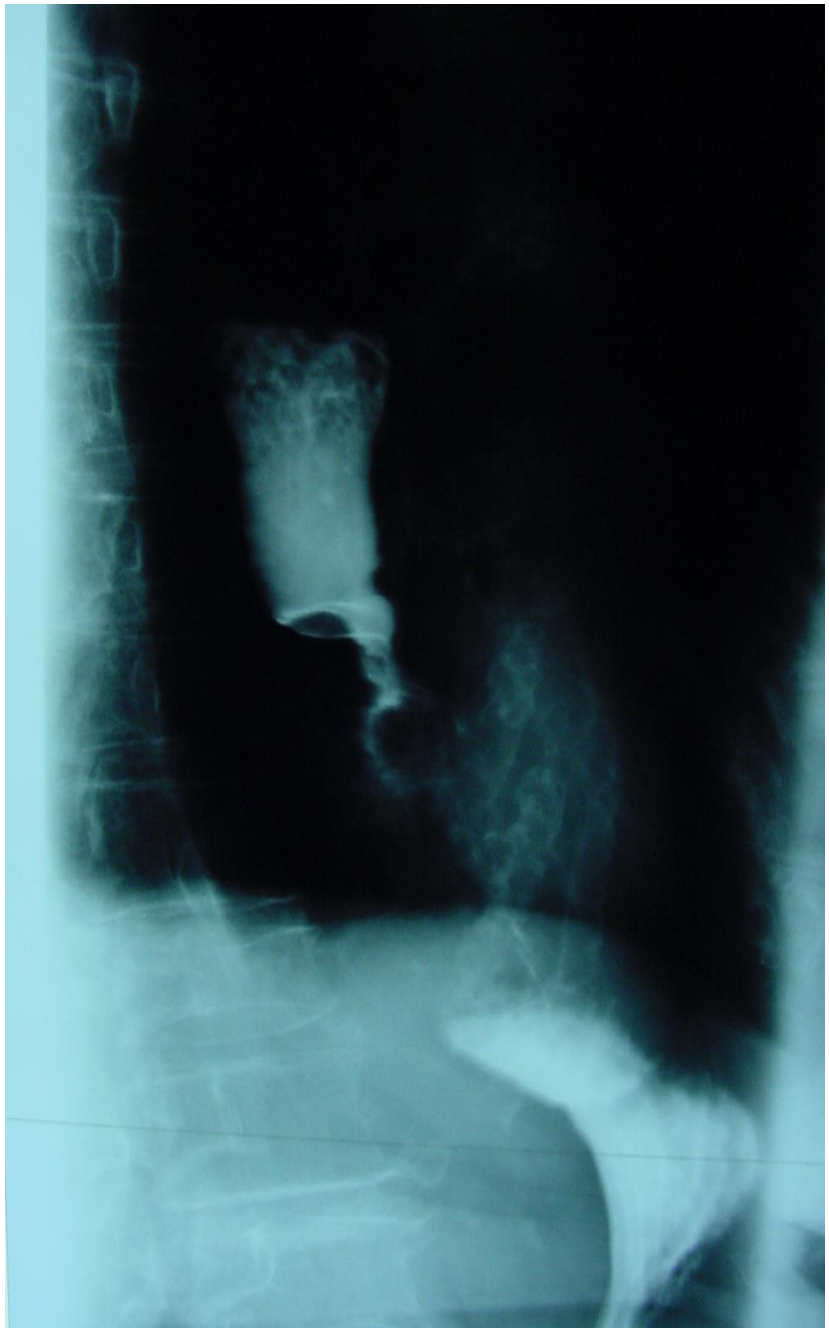
Dysphagia

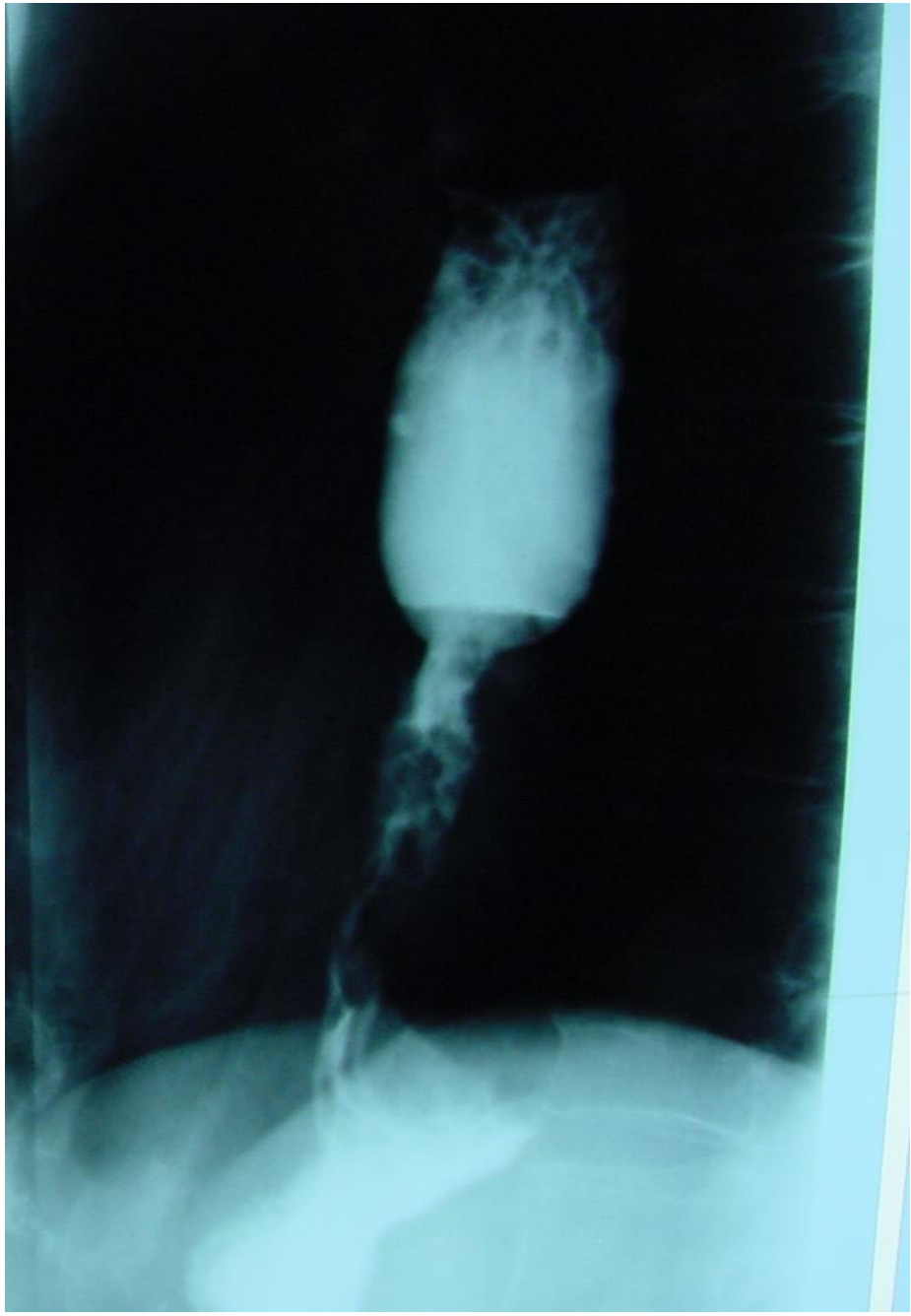
Endoscopy: ulcerating disease

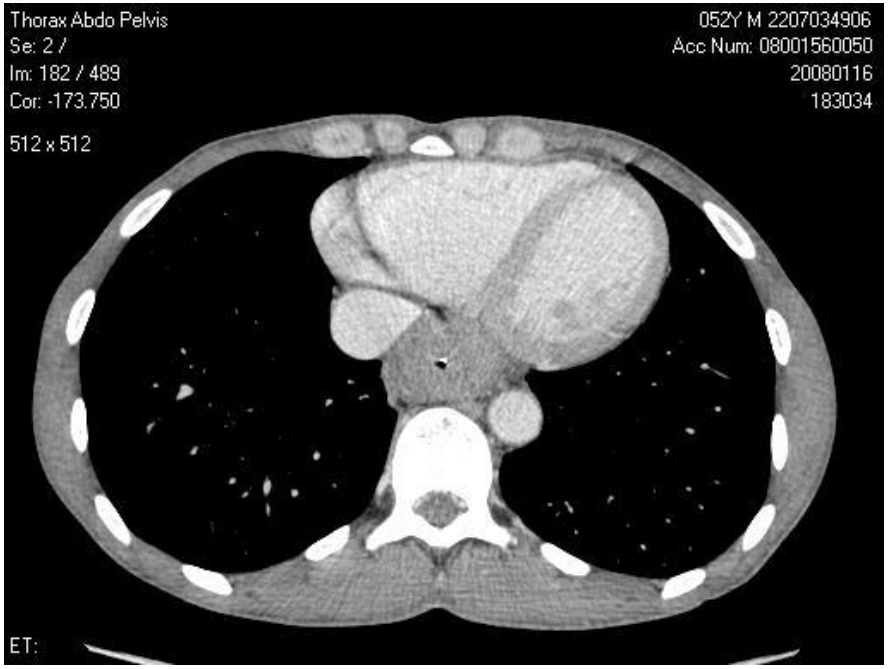
30 ----> 35 cm from D.A.

Squamous cell carcinoma

Endoscopic ultrasound impossible



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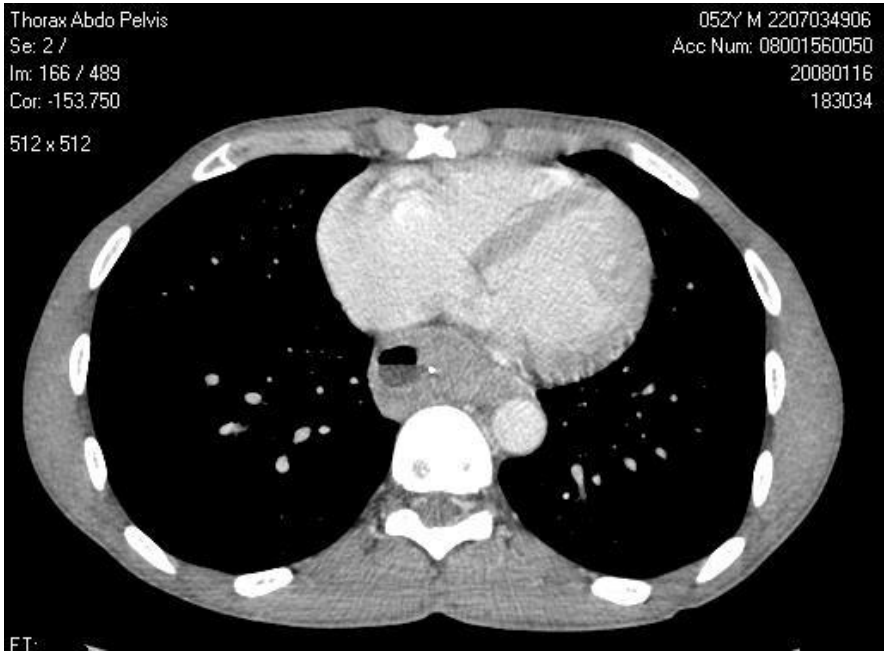
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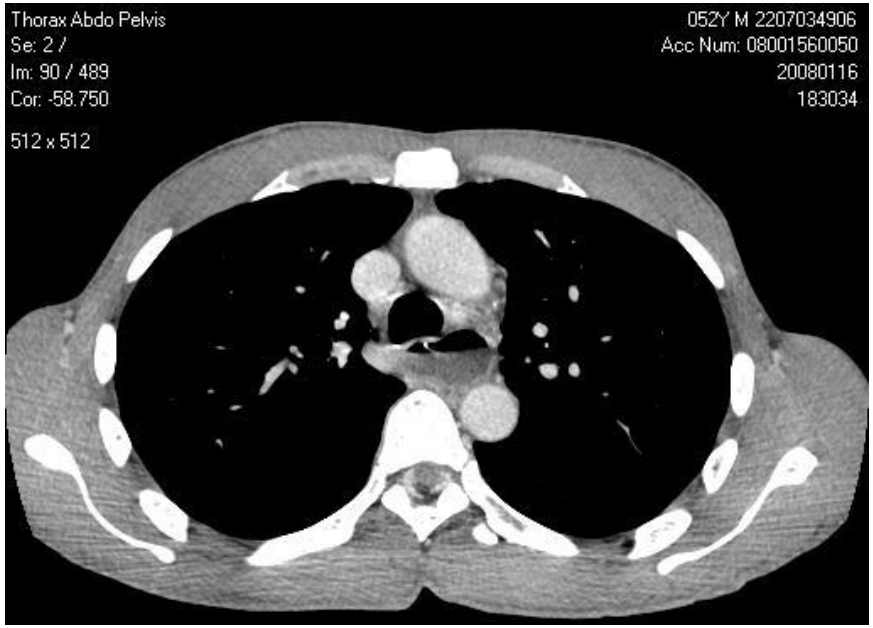
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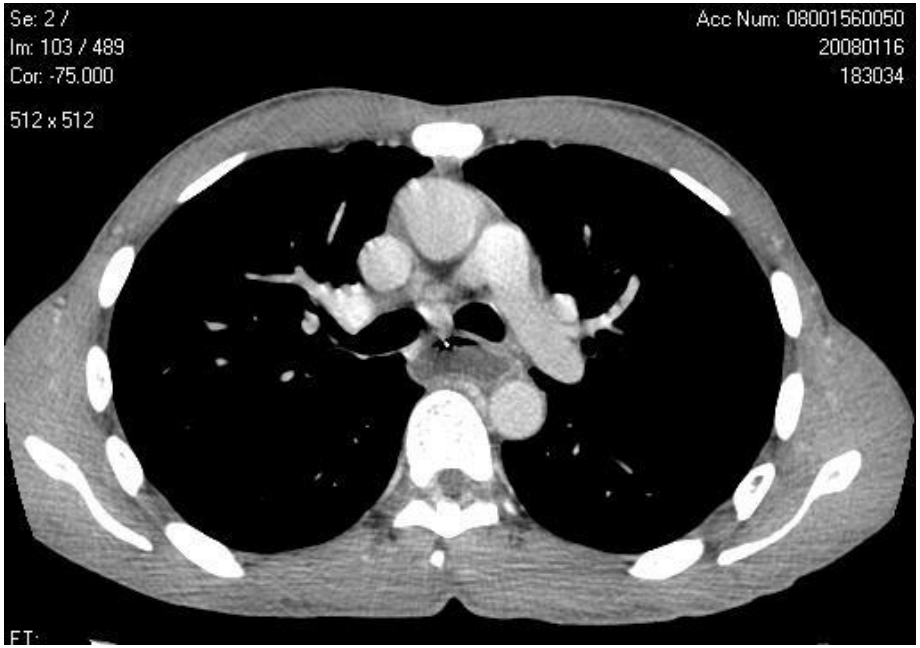
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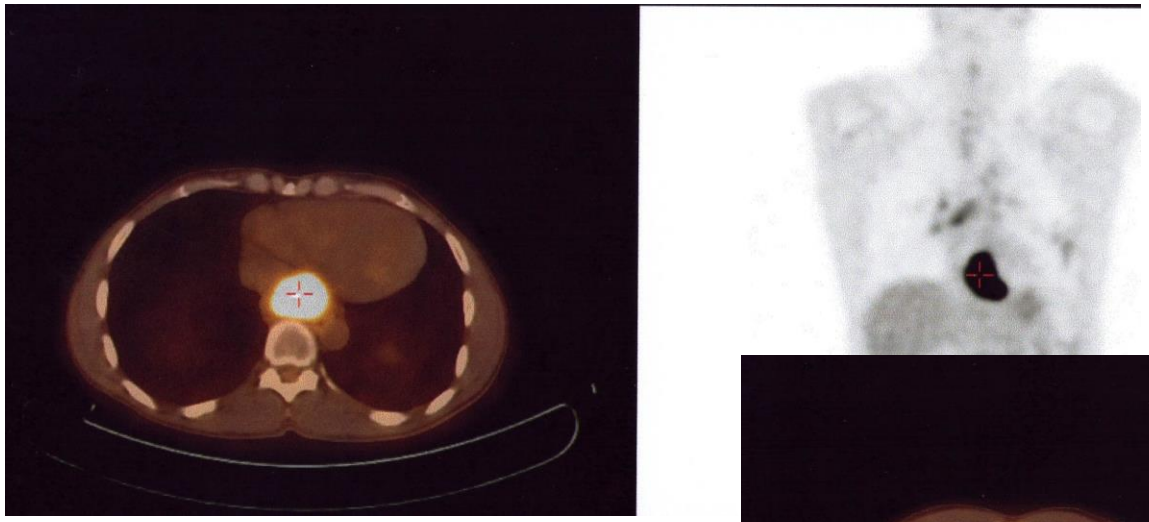
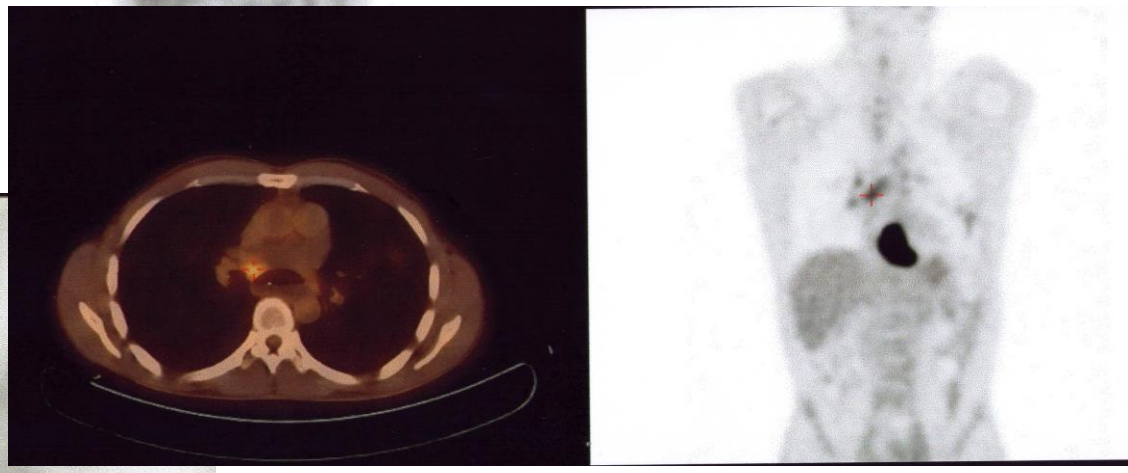
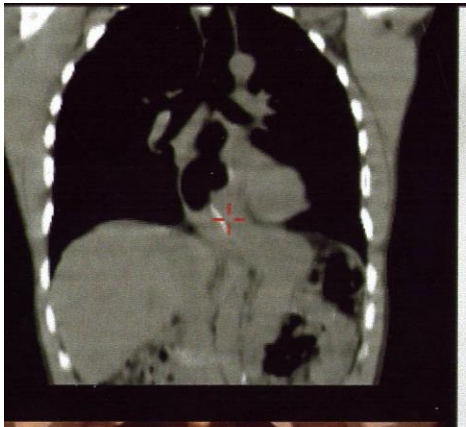
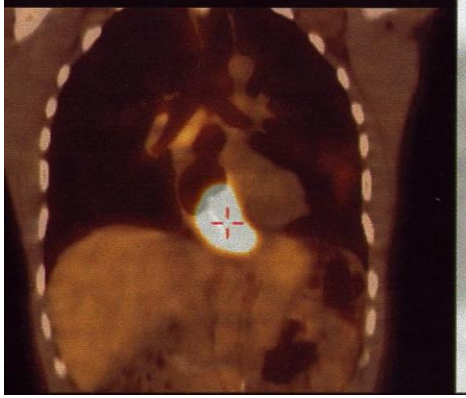
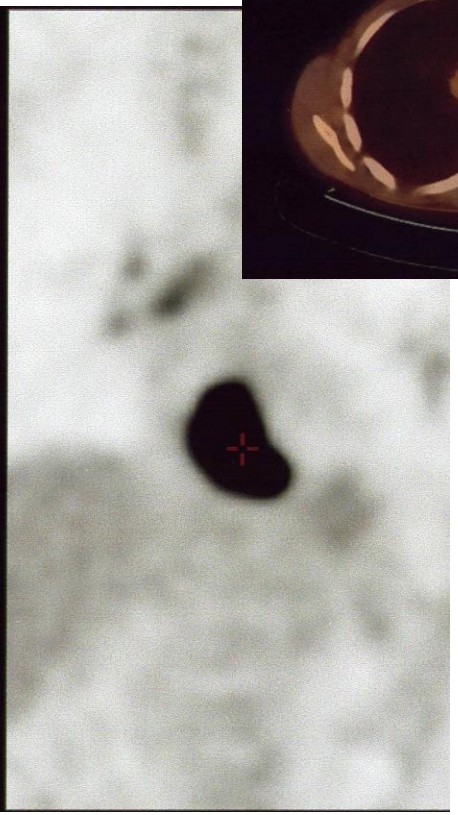




What stage ?

1. T2 N0
2. T3 N0
3. T2 N1
4. T3 N1
5. T3 M1

What do you proposed ?

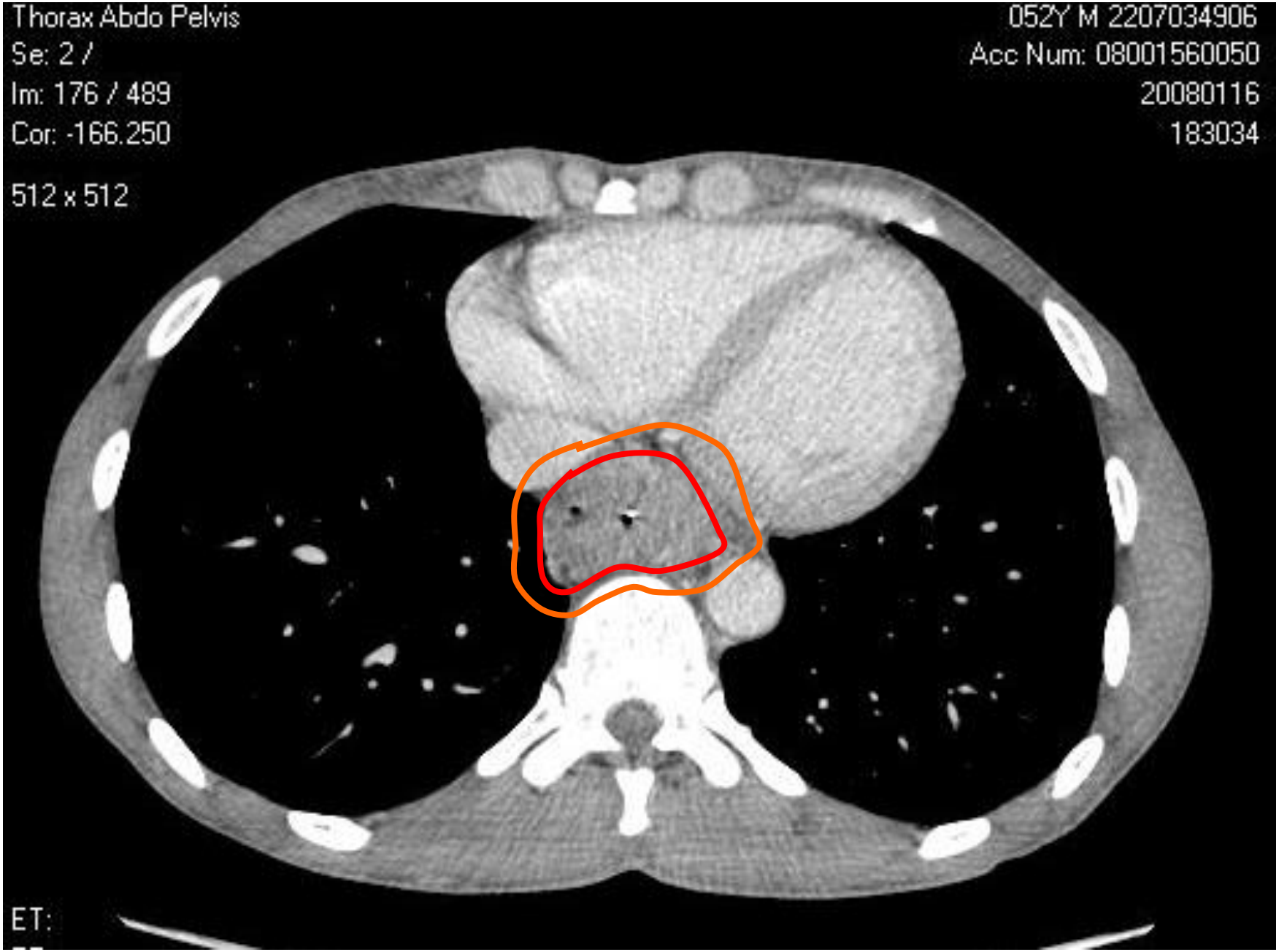
1. Front-line surgery
2. Chemotherapy then reevaluation for surgery
3. Chemoradiotherapy then reevaluation for surgery
4. Exclusive chemoradiation

Exclusive chemoradiotherapy

- Target-volumes:
  - First step: GTV
  - Then defining CTV1:
    - GTV + 5 cm below and behind GTV
    - Including peri-oesophageal spaces and lymph nodes stations
  - PTV1 = CTV1 + 0.5 cm
  - Eventually: CTV2: GTV + 2 cm longitudinal margins + circumferential margins: 5 mm

Target volumes in CROSS trial

- GTV: Primary T and positive nodes
- No CTV
- PTV:
  = 4 cm margins up and down
  = Circumferential margins: 1.5 cm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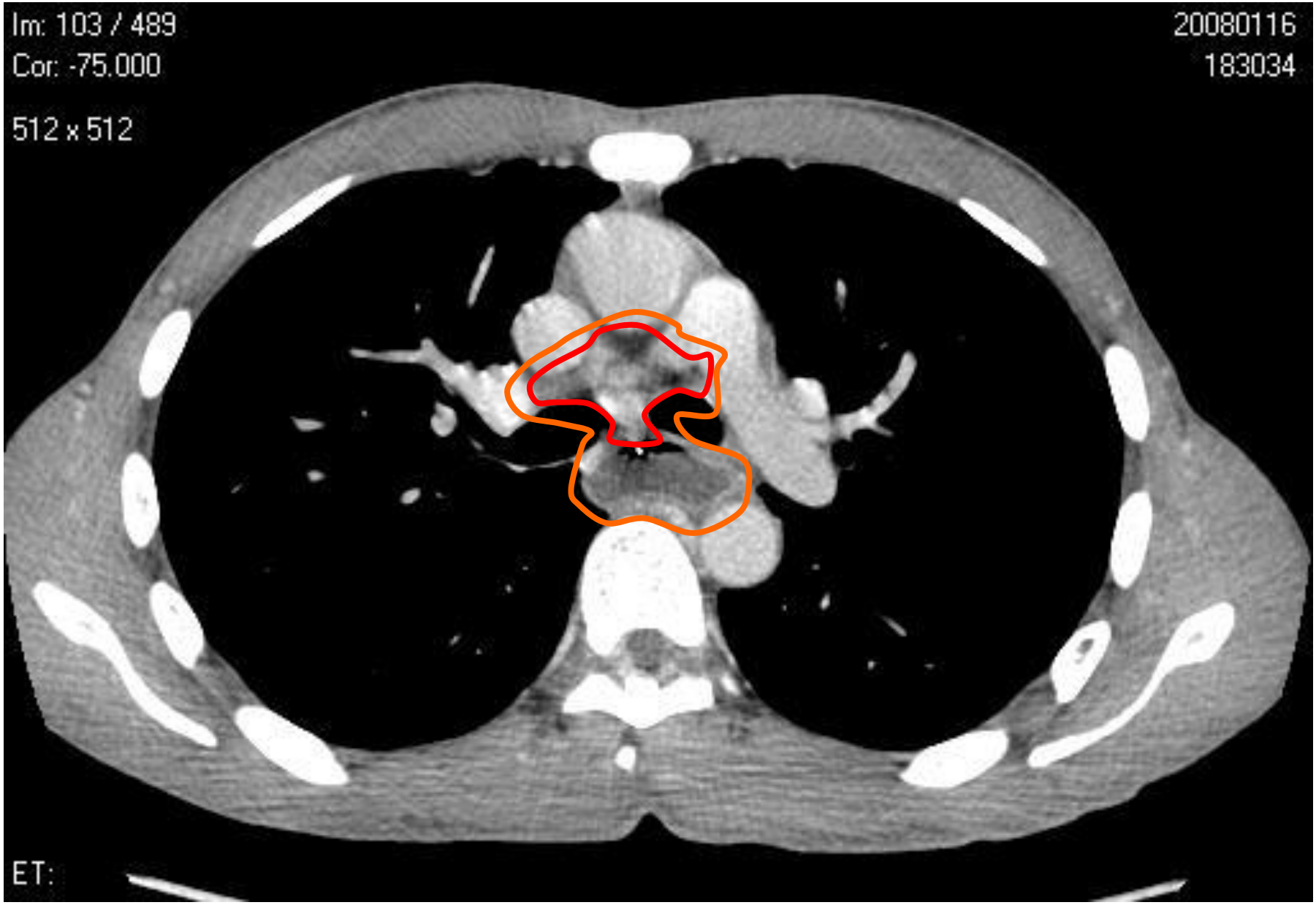
183034
ET: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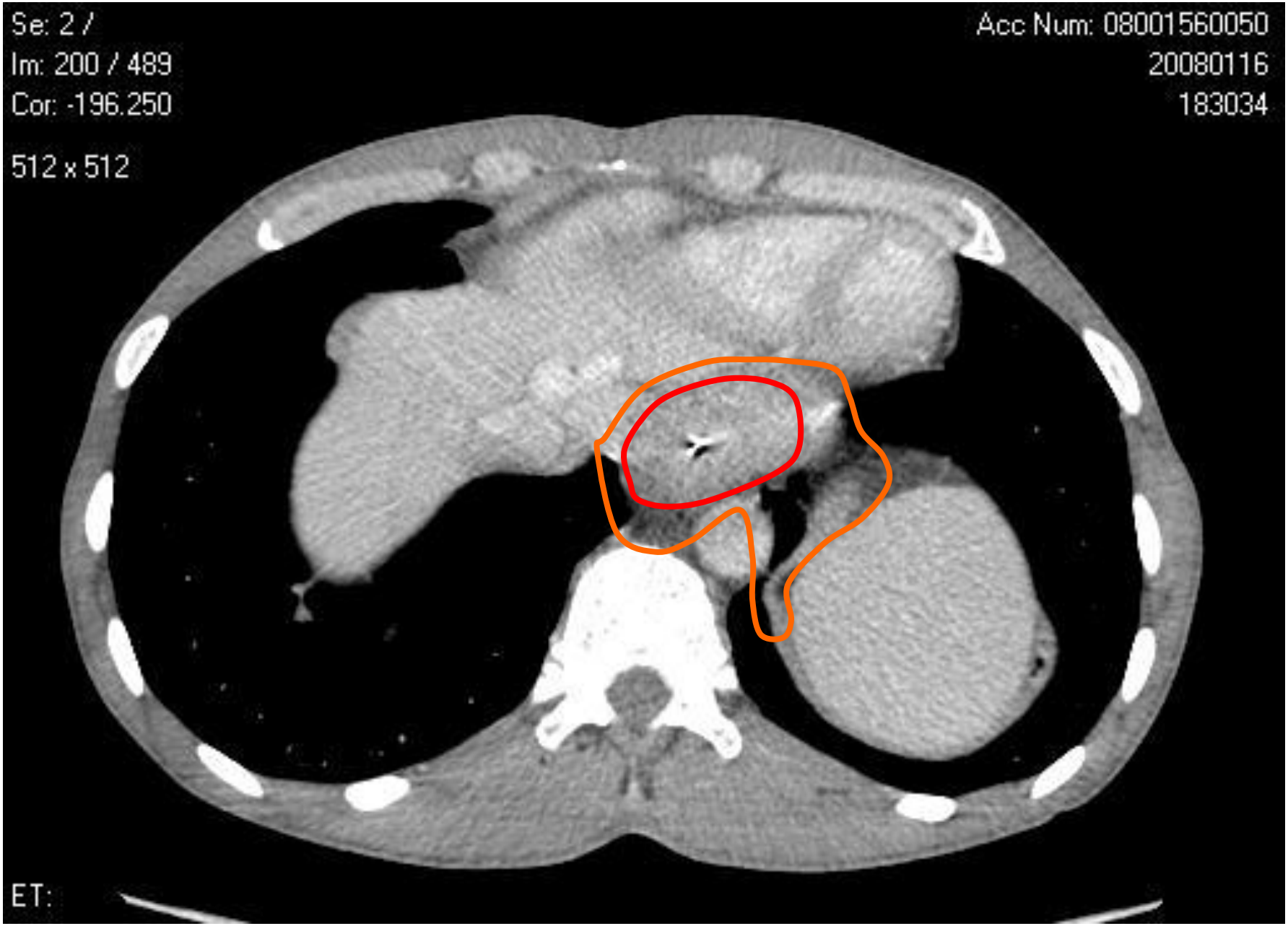
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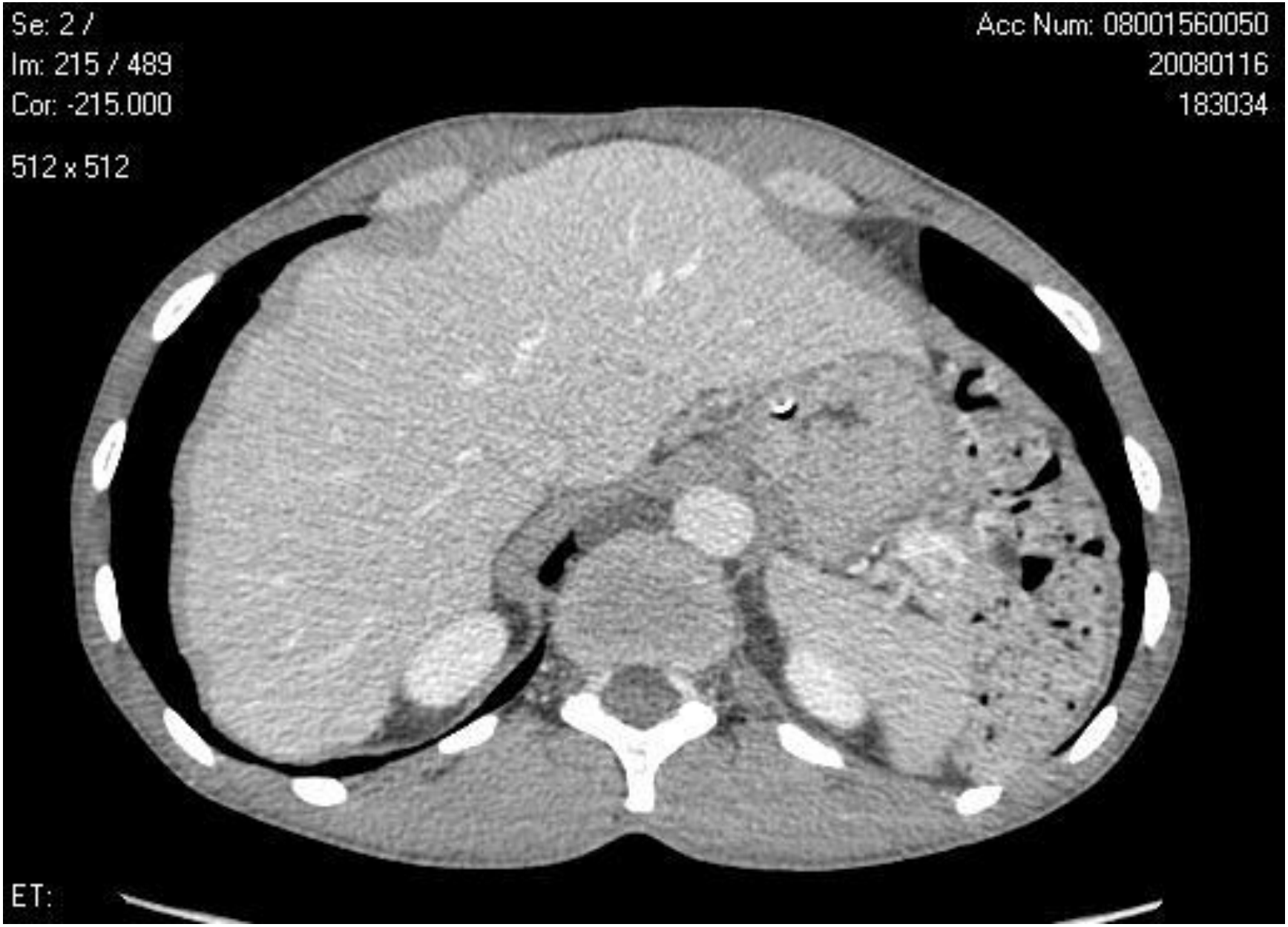
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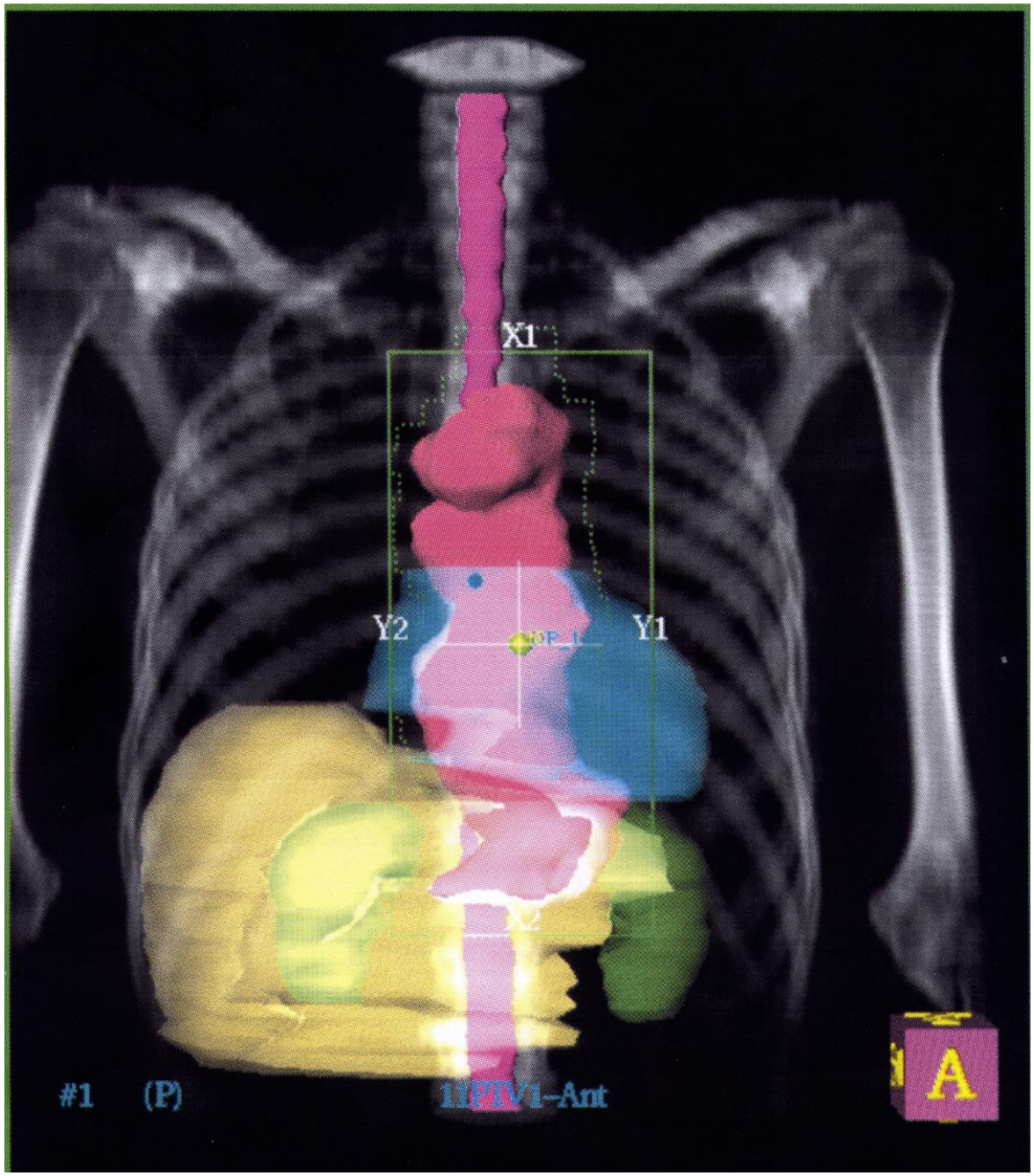
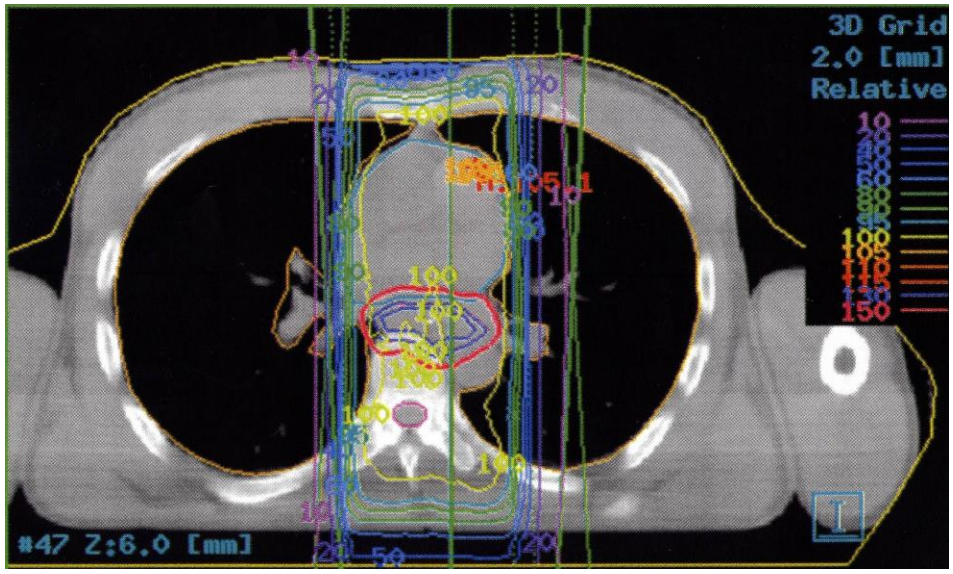

X1
Y2
Y1
X2
#1 (P)
11PTV1-Ant
A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2.0 [mm]
Relative
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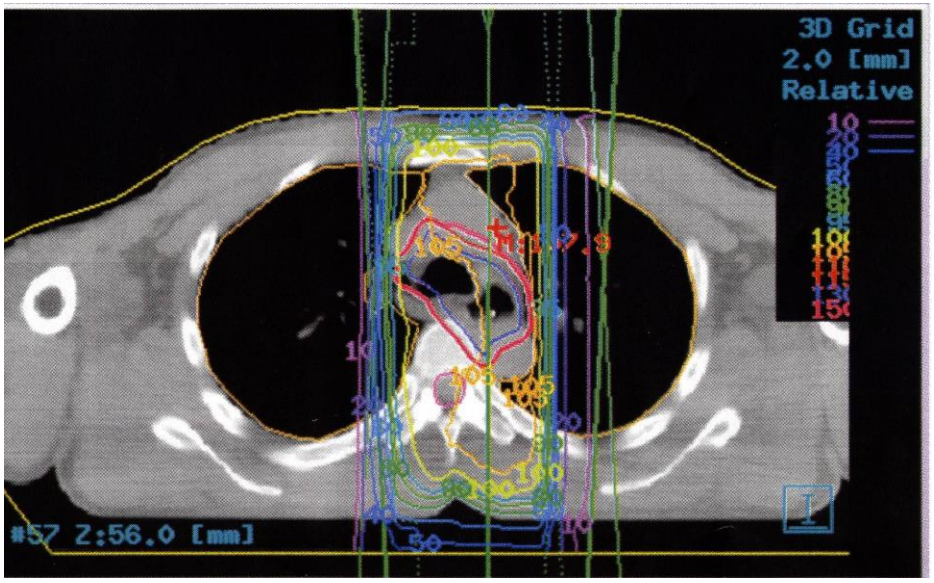
20
40
50
60
80
90
95
100
105
110
115
130
150
#47 Z:6.0 [mm]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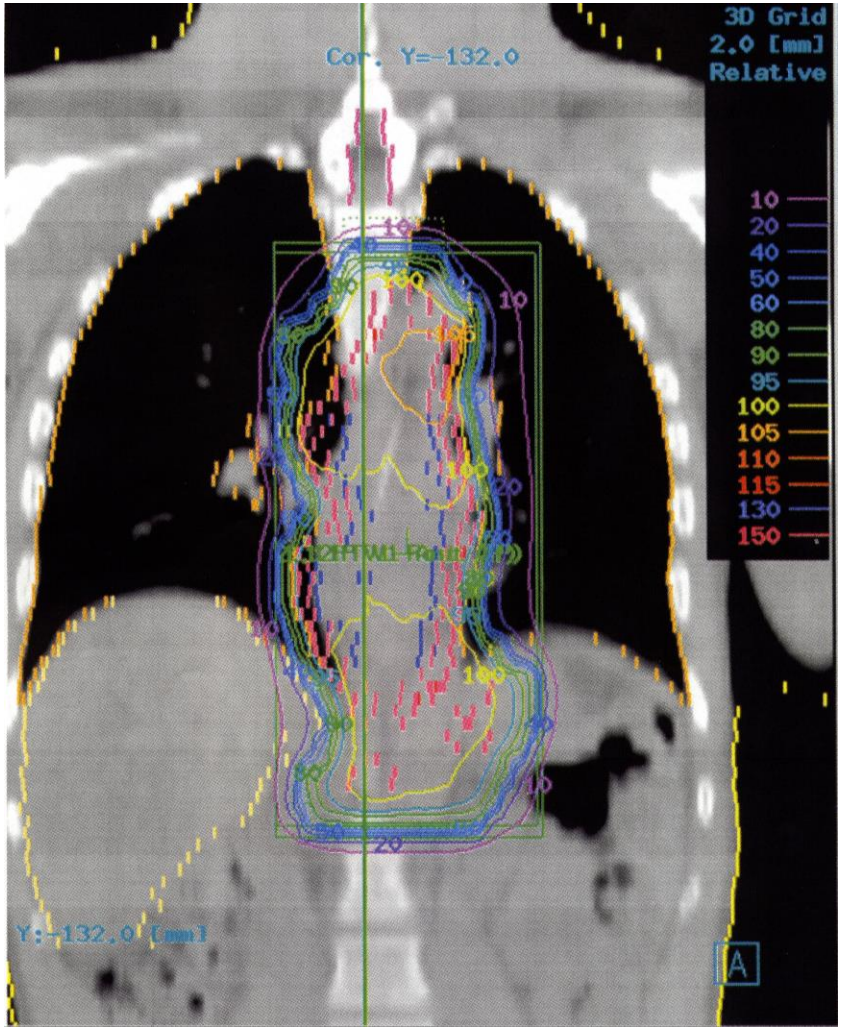
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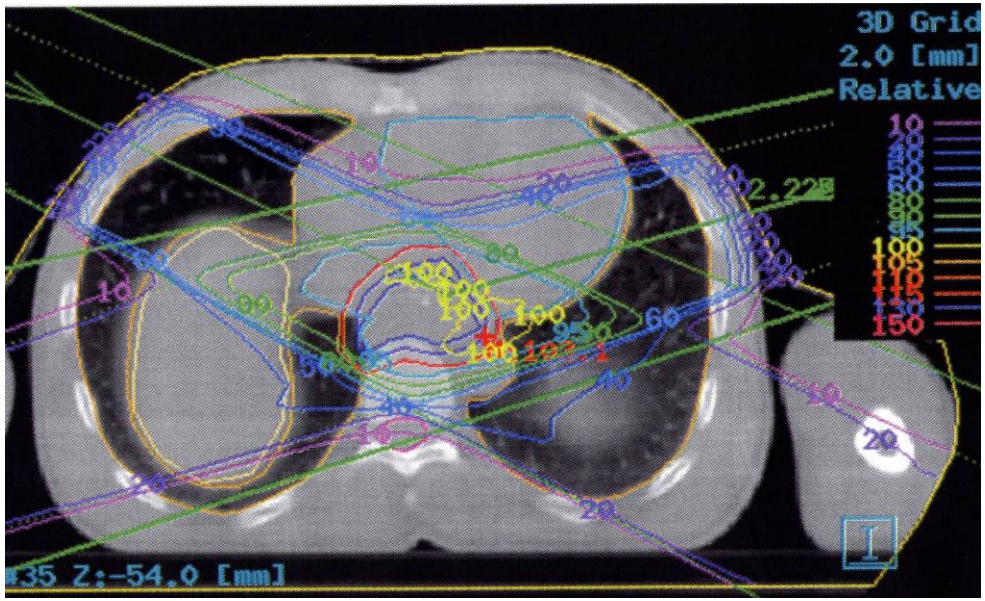
Y:-132.0 [mm]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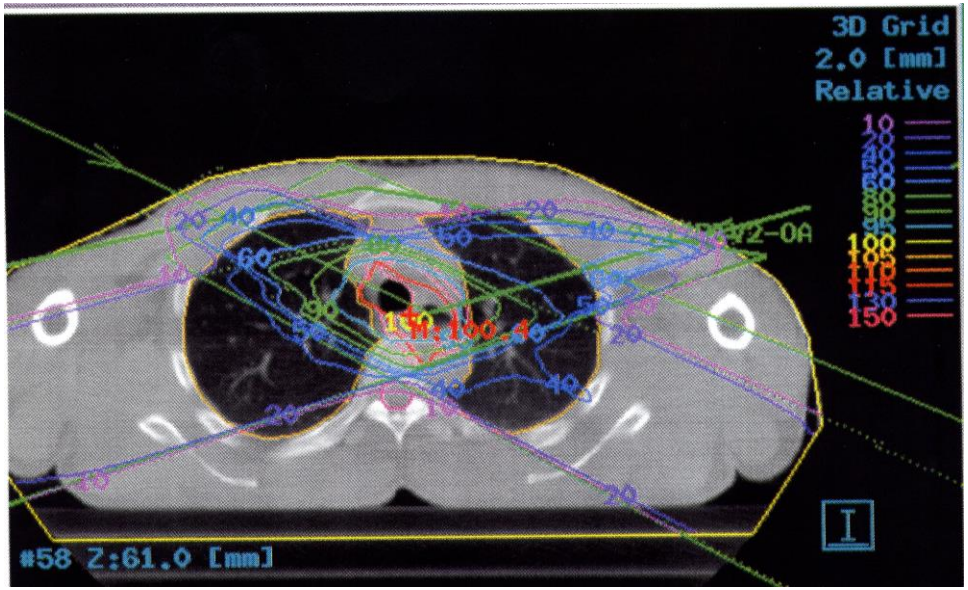
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Relative
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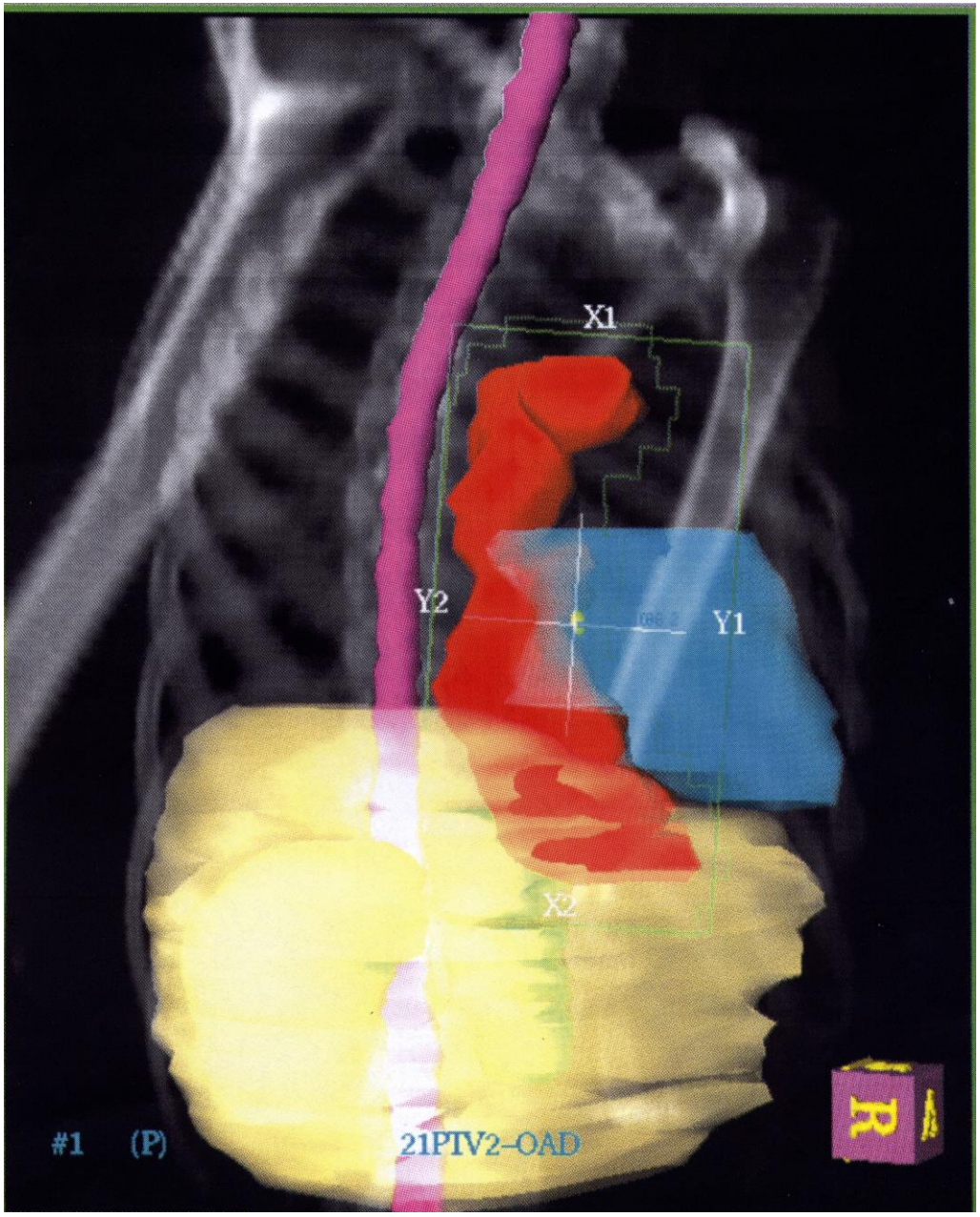
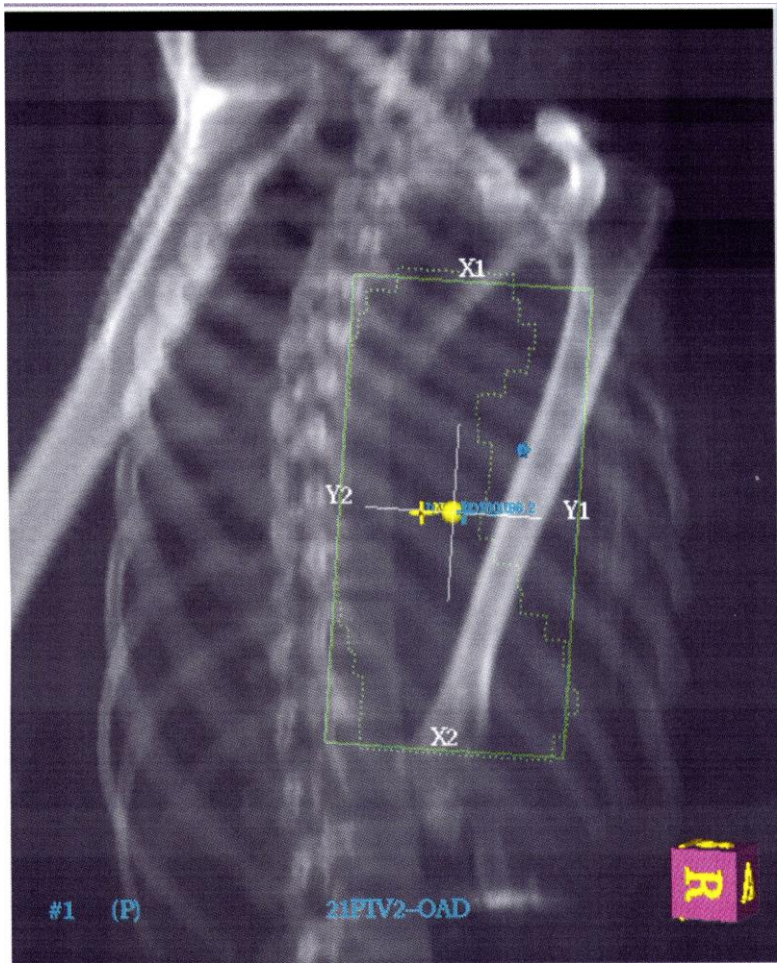
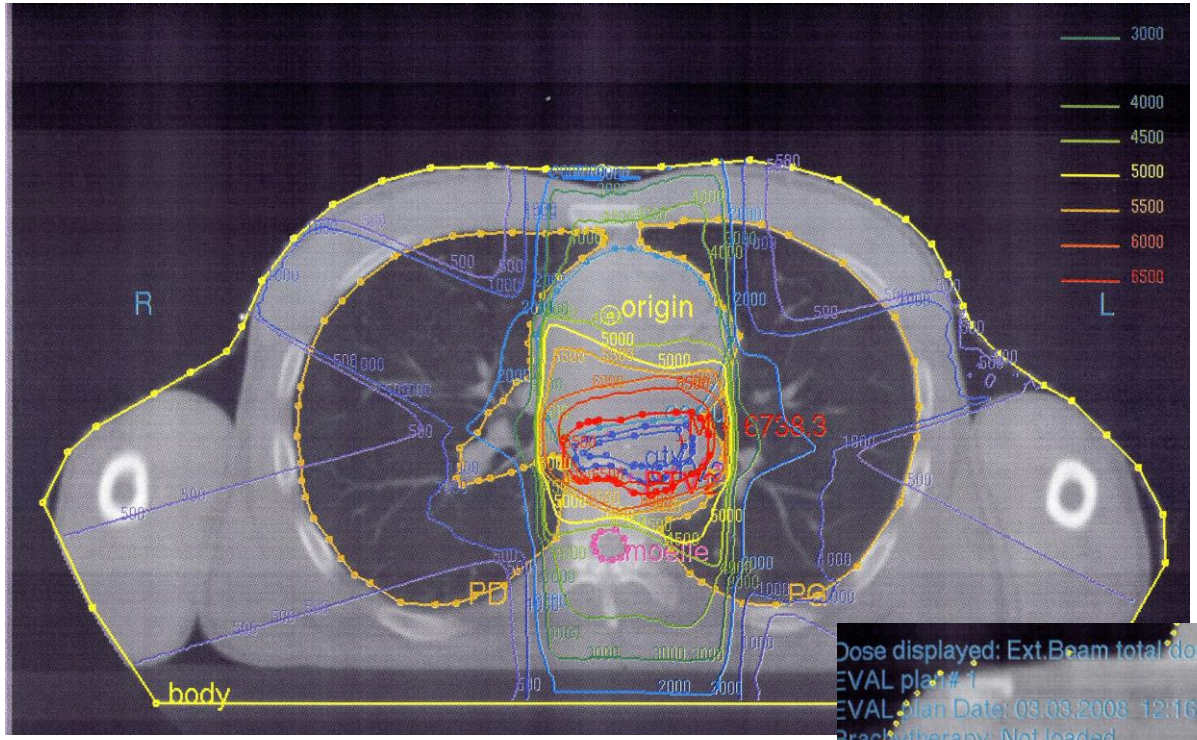
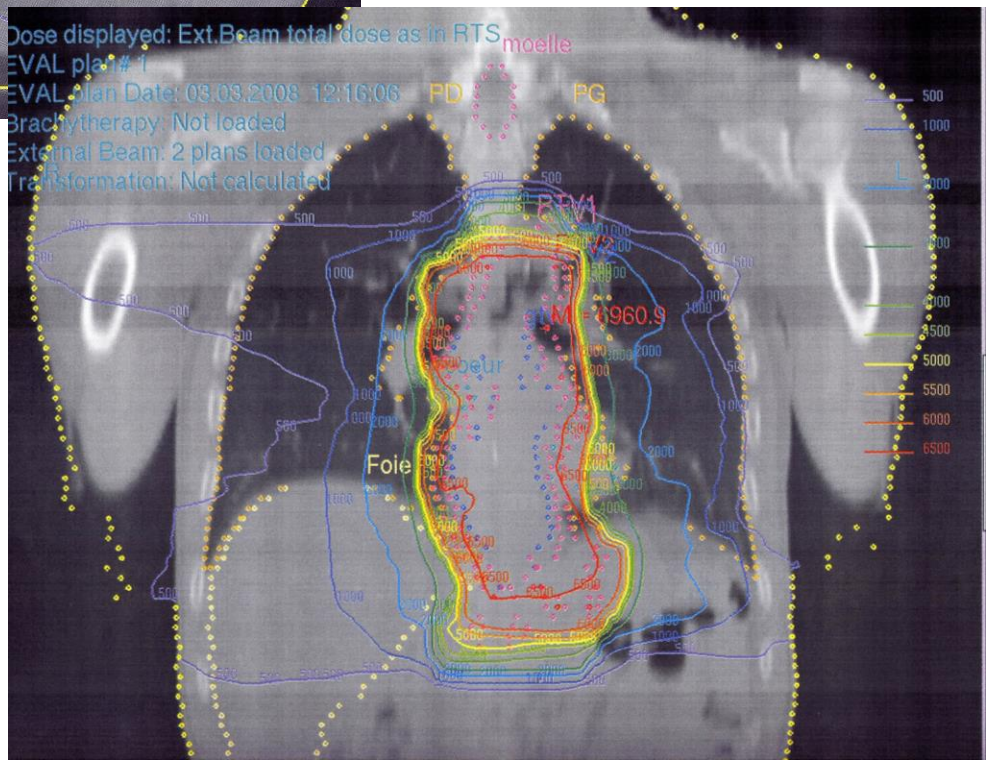
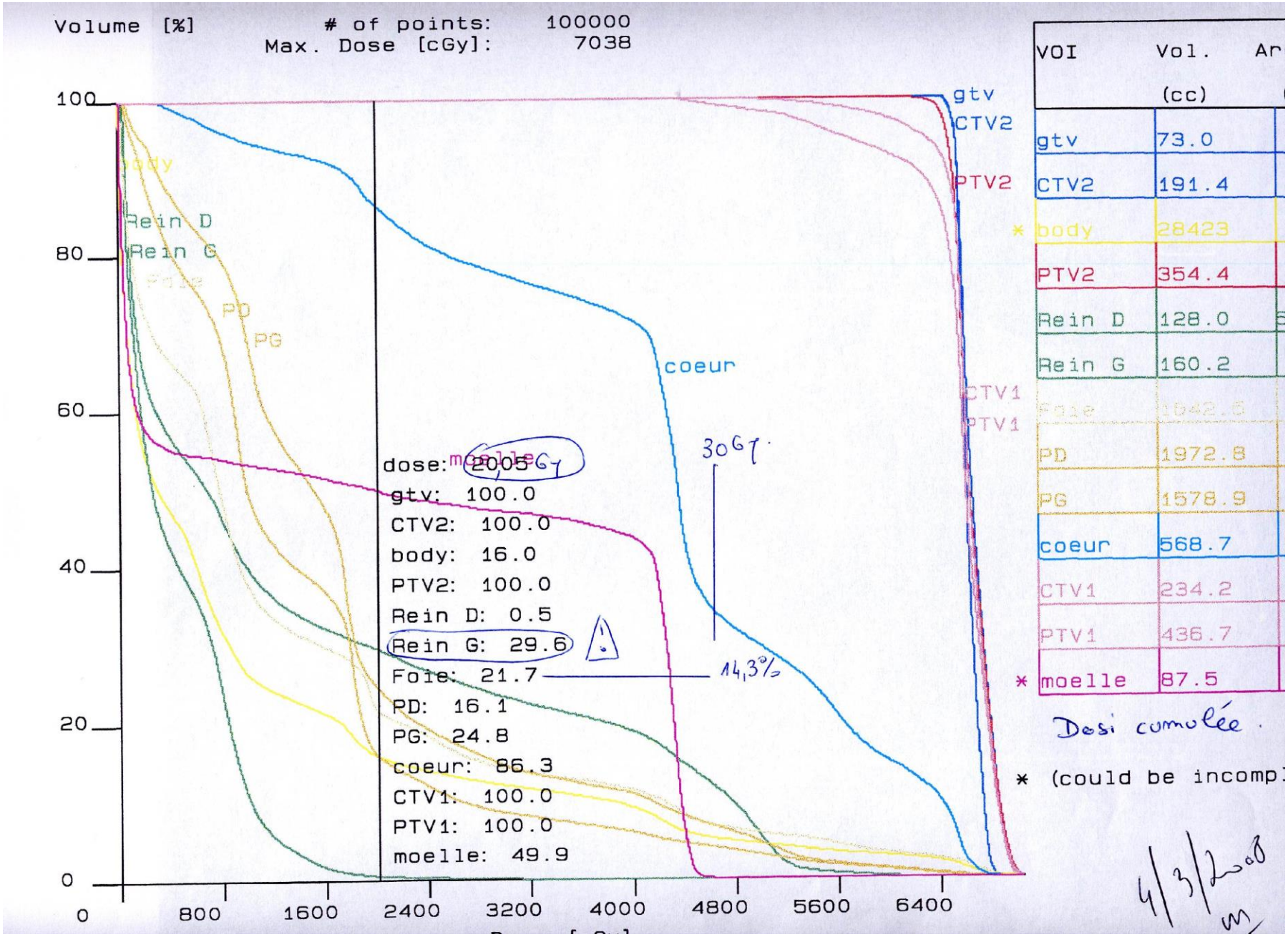

X1
Y2
Y1
X2
#1 (P)
21PTV2–OAD
R


X1
Y2
Y1
X2
#1 (P)
21PTV2–OAD
R


3000
4000
4500
5000
5500
6000
6500
R
L
origin
6738.3
moelle
PD
PG
body


Dose displayed: Ext.Beam total dose as in RTS
EVAL plan# 1
EVAL plan Date: 03.03.2008 12:16:06
Brachytherapy: Not loaded
External Beam: 2 plans loaded
Transformation: Not calculated
moelle
PD
PG
PTV1
7960.9
Foie
500
1000
1500
2000
2500
3000
4000
4500
5000
5500
6000
6500



VOI	Vol. (cc)
gtv	73.0
CTV2	191.4
* body	28423
PTV2	354.4
Rein D	128.0
Rein G	160.2
Foie	1042.6
PD	1972.8
PG	1578.9
coeur	568.7
CTV1	234.2
PTV1	436.7
* moelle	87.5

Analyse des HDV

	Vol (cc)	Min (Gy)	Max (Gy)	Avg (Gy)
CTV1	234	45	70	66
PTV1	436	42	70	65
CTV2	191	63	70	66
PTV2	354	55	70	66
Kydney R	128	2.5	31	4.6
Kydney L	160	3.5	60	15.3

Lung
- V10: 58.4%
- V20: 20%
- V30: 11.4%

Heart
V40: 71.4%

OAR constraints

Lung: V20 < 35%

Heart : V40 < 30%
50% < 25 Gy

Kidney: V20 < 70%

Liver: V30 < 40%

Rationale for altered fractionation and combining radiation with chemo/bio-therapy

Jesper Grau Eriksen

Dept. Of Oncology
Odense University Hospital, Denmark

jesper@oncology.au.dk

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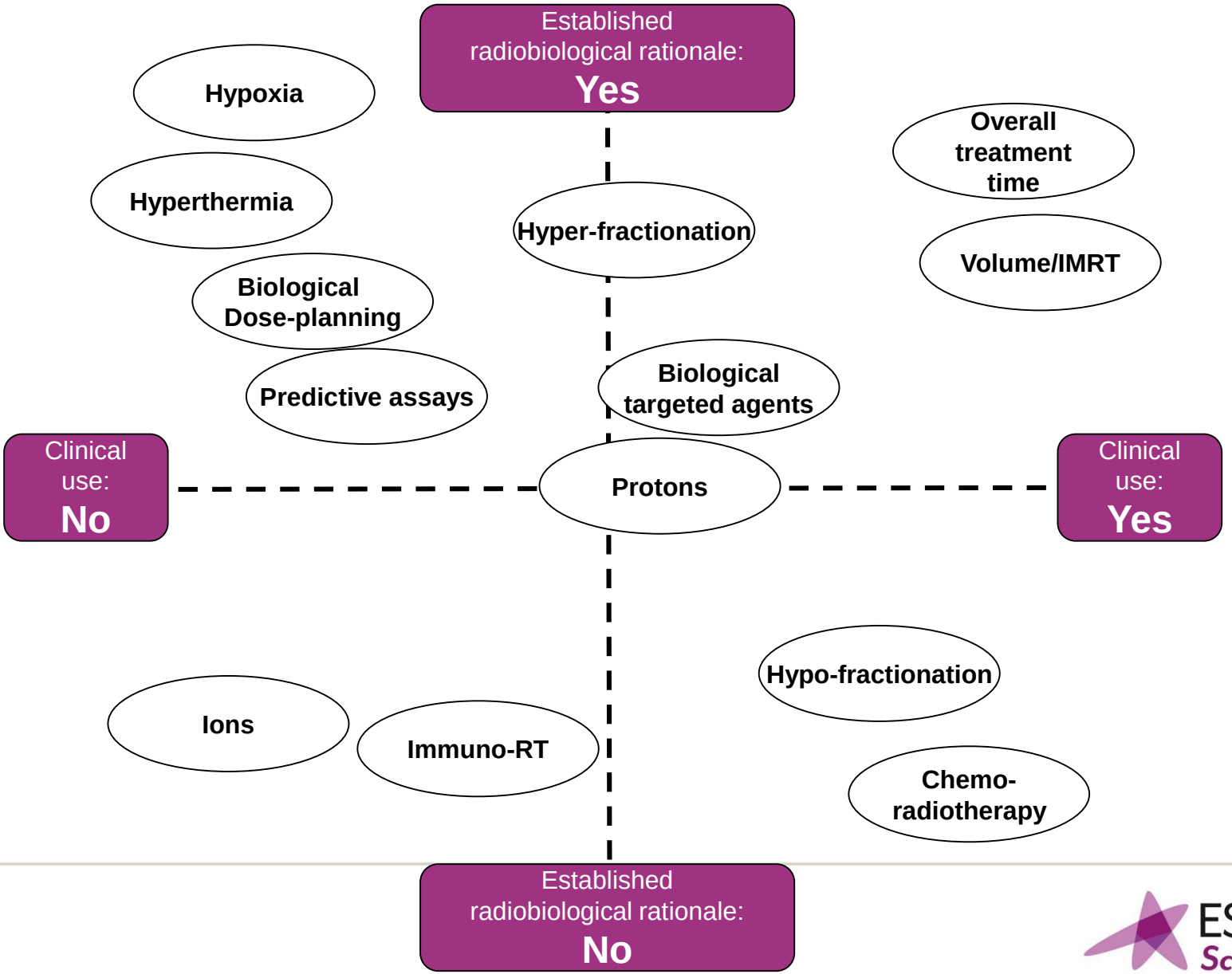
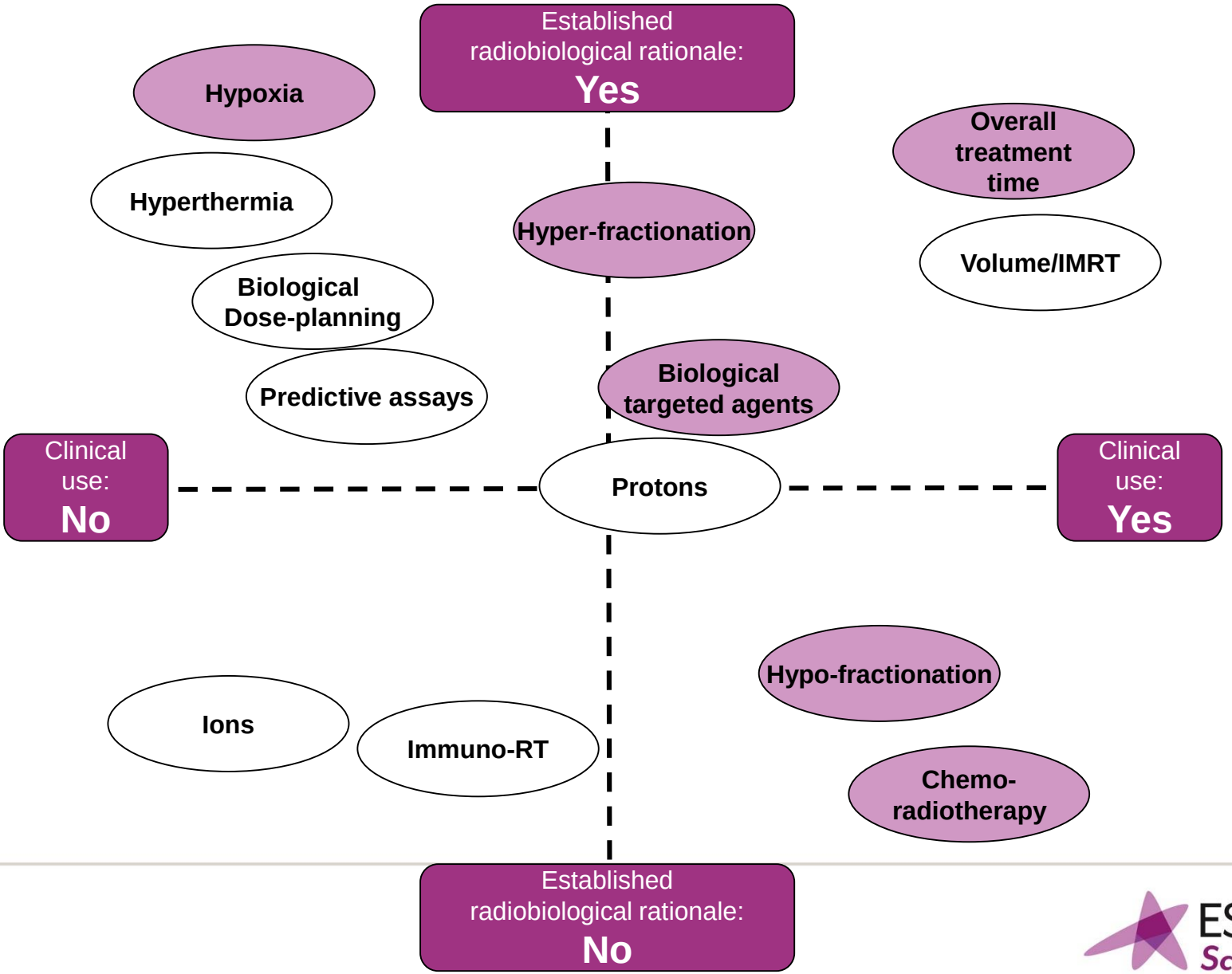
The landscape of evidence and practice



The landscape of evidence and practice



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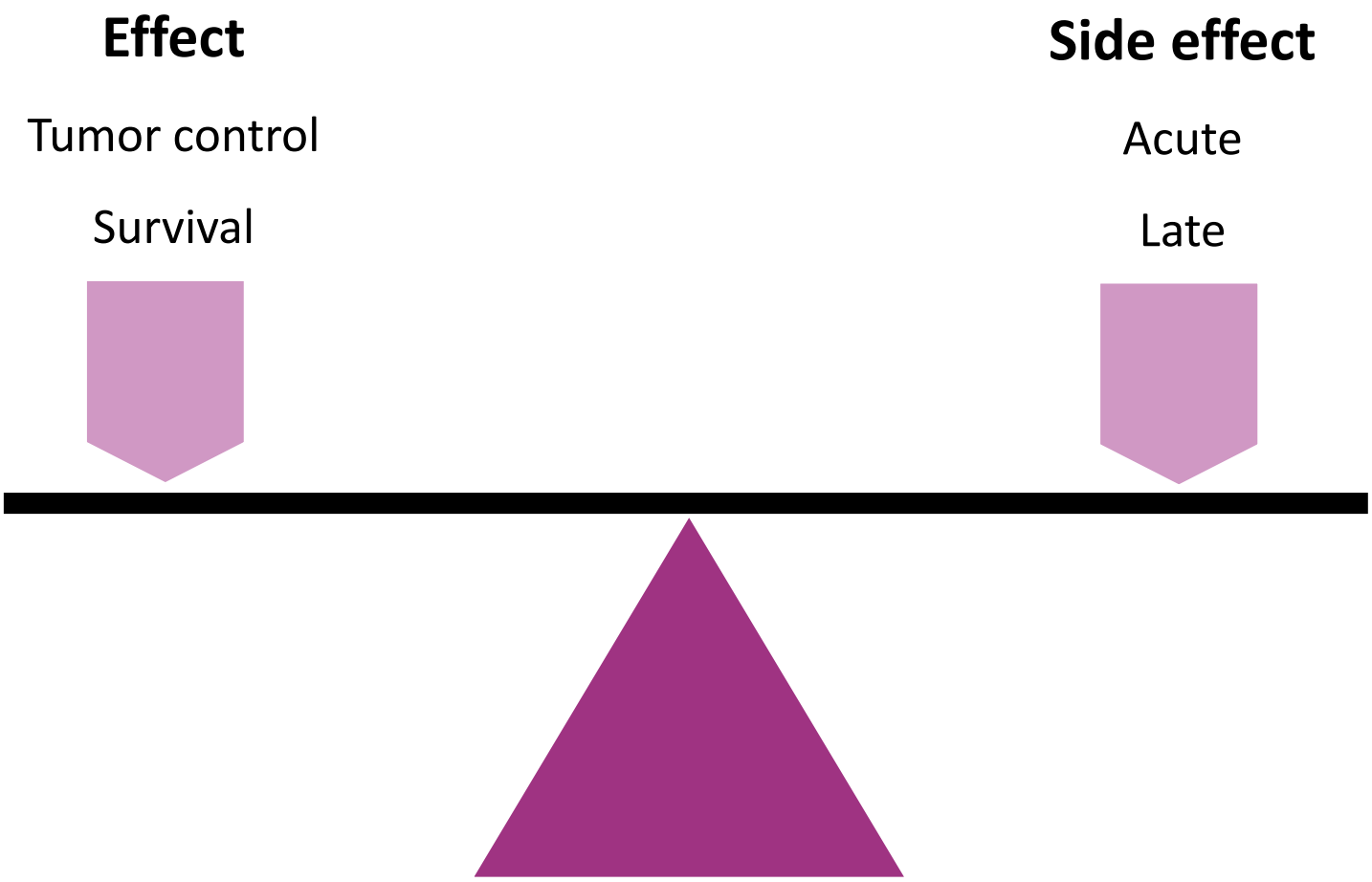
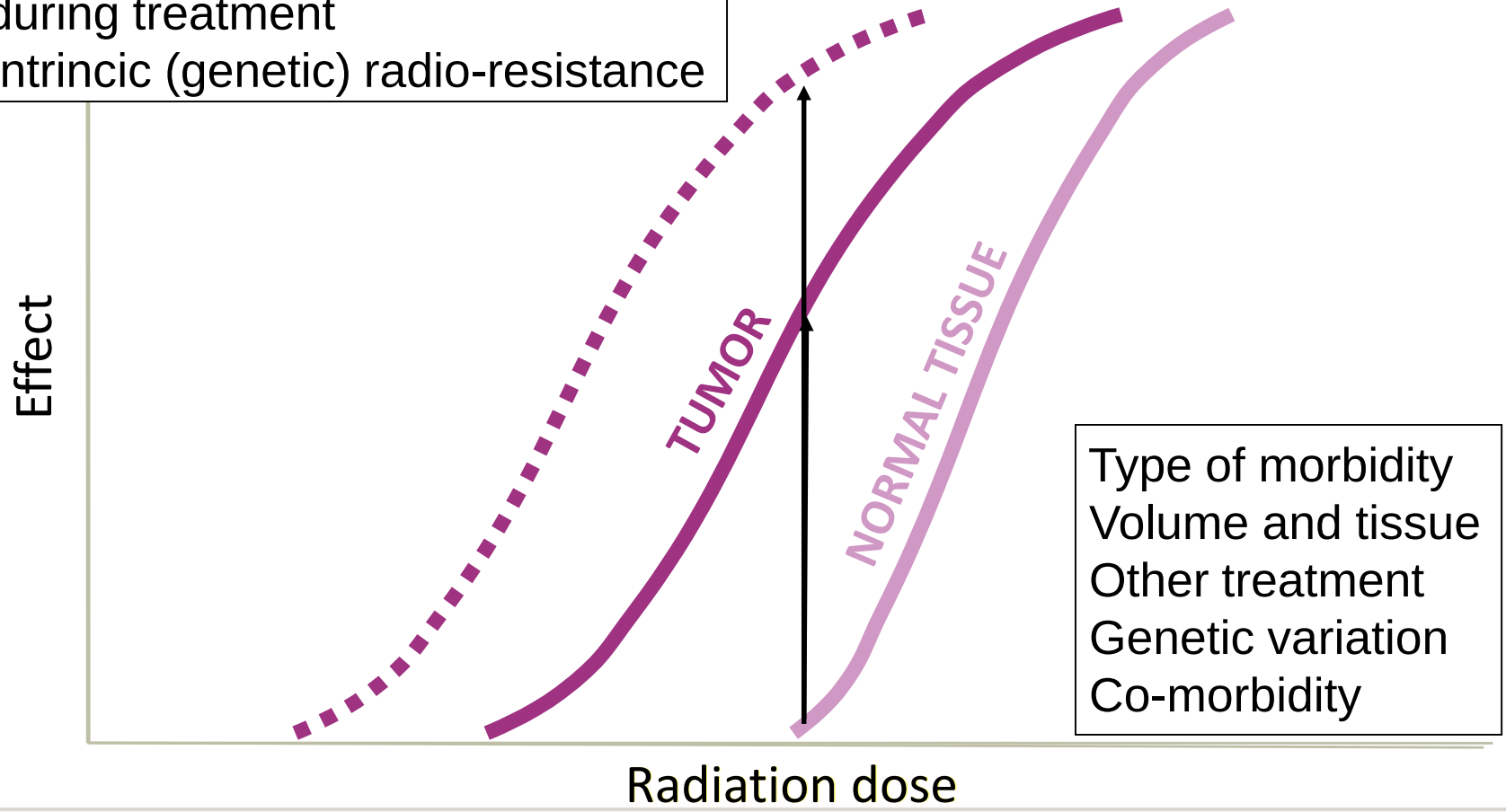
Therapeutic ratio



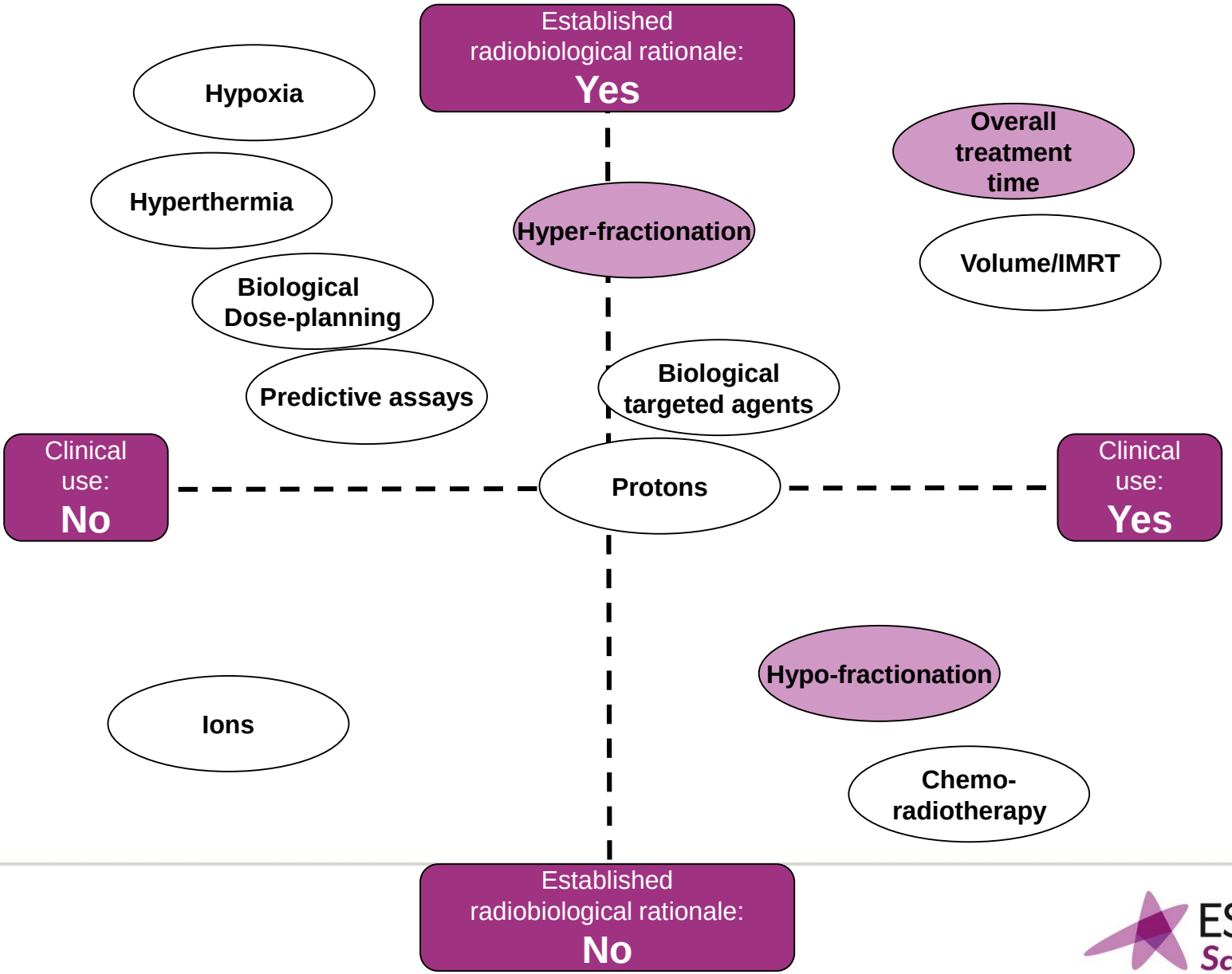
Therapeutic ratio

Tumor enviroment (hypoxia)
Proliferation of tumor stem cells during treatment
Intrincic (genetic) radio-resistance



Type of morbidity
Volume and tissue
Other treatment
Genetic variation
Co-morbidity

Altered fractionation



Altered fractionation

Conventional fractionation: 1.8-2 Gy/fx - 5fx per week

Split-course fractionation: a break (weeks long) during treatment resulting in prolonged overall treatment time

Hyperfractionation: small doses per fraction (<1.8-2 Gy/fx)

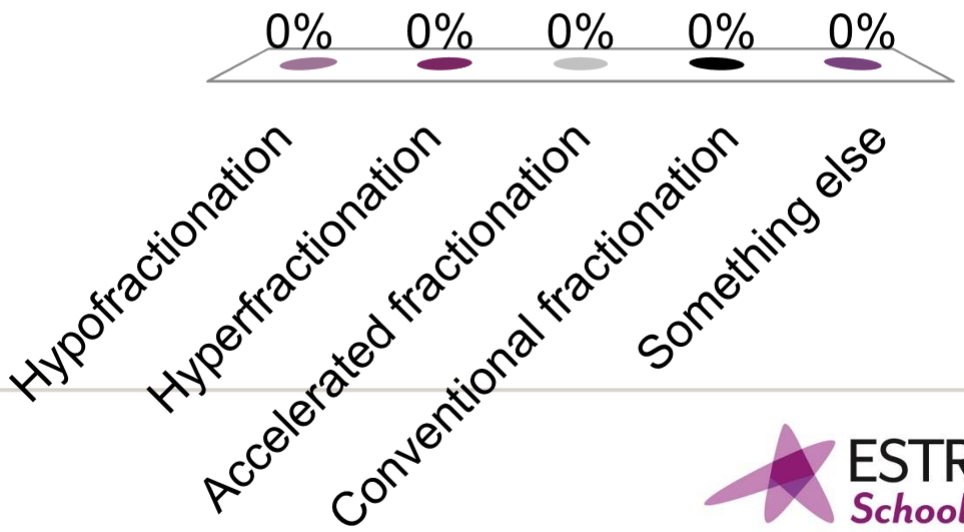
Hypofractionation: large doses per fraction (>2 Gy/fx)

Accelerated fractionation: reduced overall treatment time

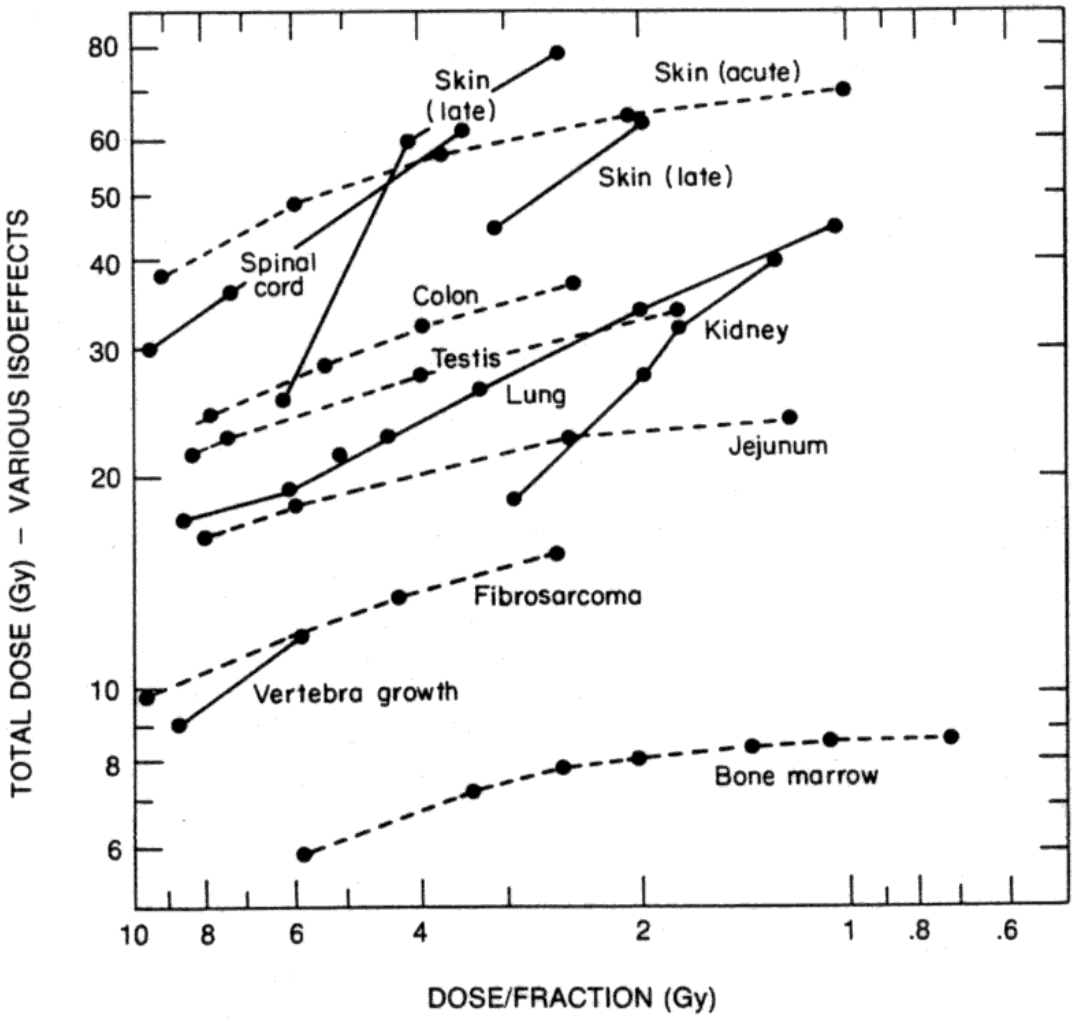
- and any combination of the different principles

For treatment of curative H&N cancer we *mainly* use:

A. Hypofractionation
B. Hyperfractionation
C. Accelerated fractionation
D. Conventional fractionation
E. Something else



Fractionation sensitivity - The spaghetti plot



Withers Cancer 1985

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Fractionation sensitivity

Early reacting normal tissues

- Low fractionation sensitivity
- Small increase in tolerance with decreasing dose per fraction
- High alpha-beta (8-30 Gy)
- Time factor (repopulation)

Late reacting normal tissues

- High fractionation sensitivity
- Large increase in tolerance with decreasing dose per fraction
- Low alpha-beta (2-4 Gy)
- No time factor

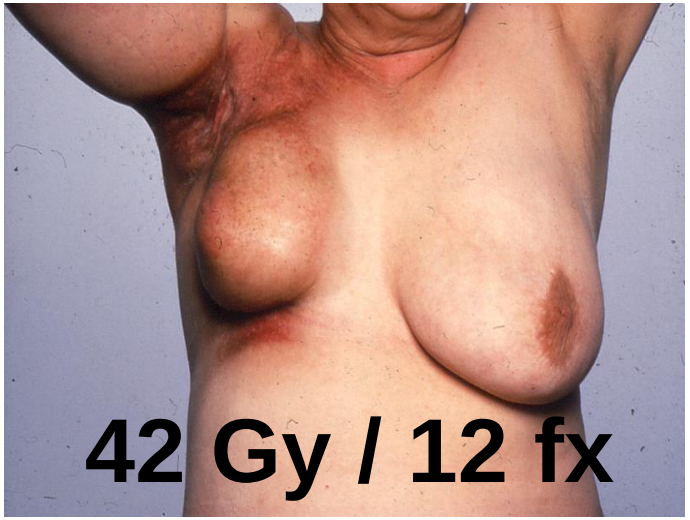
Hypofractionation: Palliative radiotherapy

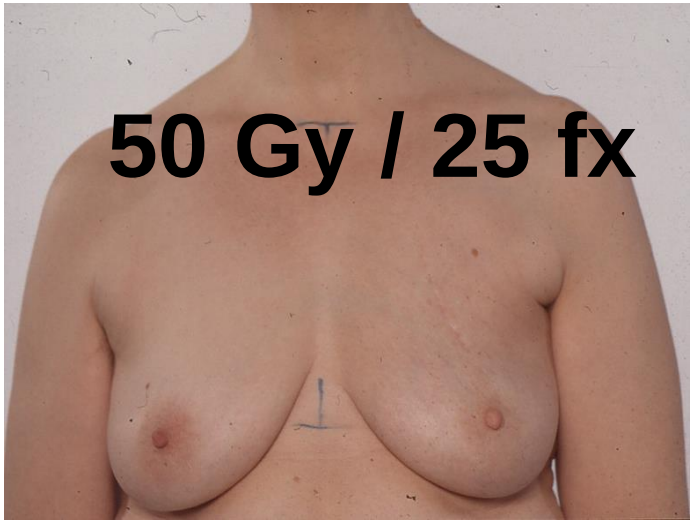
PAIN RELIEF AFTER LOCAL RADIOTHERAPY

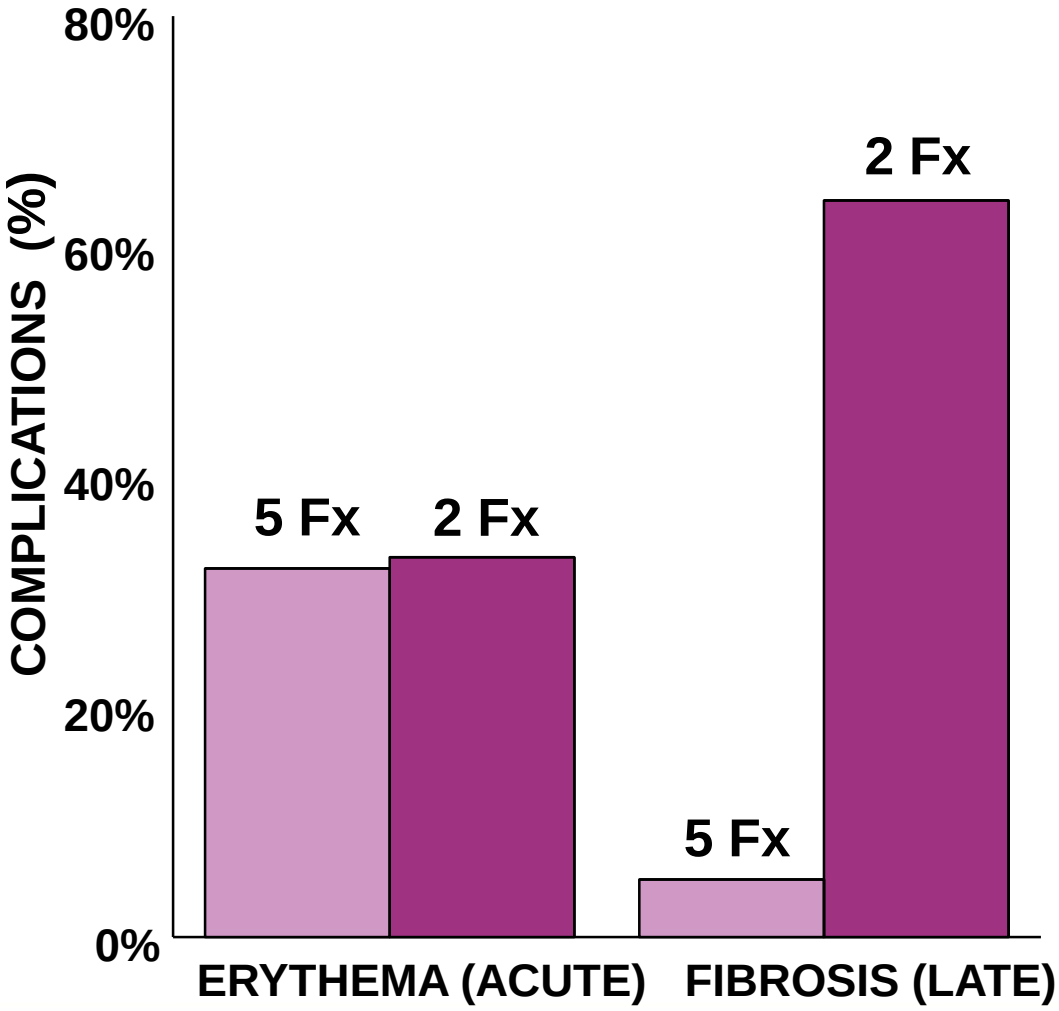
Randomized studies with > 100 patients

Study	Number of patients	Treatment #1	Treatment #2	Pain relief (CR+PR)
Tong 1982	146	4 Gy x 5	2.7 Gy x 15	90%/92%
Price 1986	288	8 Gy x 1	3 Gy x 10	85%/85%
Hoskin 1992	270	4 Gy x 1	8 Gy x 1	44%/69%
Rasmusson 1995	217	5 Gy x 3	3 Gy x 10	69%/66%
Nielsen 1998	241	8 Gy x 1	5 Gy x 4	80%/82%
BPTWP 1999	765	8 Gy x 1	4 Gy x 5 or 3 Gy x 10	78%/78%
Steenland 1999	1171	8 Gy x 1	4 Gy x 6	72%/69%

High dose per fx increase late radiation damage







Overgaard M et al. 1987

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The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial

1999-2001, 23 UK centres: Tumor <5 cm and ≤3 N+ in axillae
(92% lumpectomy, 74% pN0, 64% T<2 cm, 72% only Tam, 15% Tam+CT, 7% RT to axillae)

2215 pts

- **40 Gy/15 fX, 2.67 Gy/fx**
- **50 Gy/25 fX, 2.0 Gy/fx**

Endpoints: local control and morbidity
Median follow-up 6.0 years

Yarnold et al Lancet, 2008

START TRIAL B, local relapse

	Events/total (%)	Estimated % with event by 5 years (95% CI)	Crude hazard ratio (95% CI)	Log-rank test p value
Local relapse*				
50 Gy	34/1105 (3·1)	3·3 (2·2–4·4)	1	
40 Gy	25/1110 (2·2)	2·0 (1·1–2·8)	0·72 (0·43–1·21)	0·21
Local-regional relapse				
50 Gy	36/1105 (3·2)	3·3 (2·2–4·5)	1	
40 Gy	29/1110 (2·6)	2·2 (1·3–3·1)	0·79 (0·48–1·29)	0·35
Distant relapse				
50 Gy	122/1105 (11·0)	10·2 (8·4–12·1)	1	
40 Gy	87/1110 (7·8)	7·6 (6·0–9·2)	0·69 (0·53–0·91)	0·01
Any breast cancer-related event†				
50 Gy	164/1105 (14·8)	14·1 (12·0–16·2)	1	
40 Gy	127/1110 (11·4)	10·6 (8·7–12·4)	0·75 (0·60–0·95)	0·02
All-cause mortality				
50 Gy	138/1105 (12·5)	11·0 (9·1–12·9)	1	
40 Gy	107/1110 (9·6)	8·0 (6·4–9·7)	0·76 (0·59–0·98)	0·03

*Local relapse defined as ipsilateral local tumour relapse in breast parenchyma/breast skin/chest wall skin. †Local, regional, or distant relapse, breast cancer death, contralateral breast cancer ("disease-free survival").

Yarnold et al Lancet, 2008

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START TRIAL B, morbidity

	α/β = 2 Late damage	α/β = 5	α/β = 10 Acute damage
50Gy/25fx	50	50	50
40Gy/15fx	**EQD_{2Gy} 46.7**	**EQD_{2Gy} 43.8**	EQD_{2Gy} 42.2

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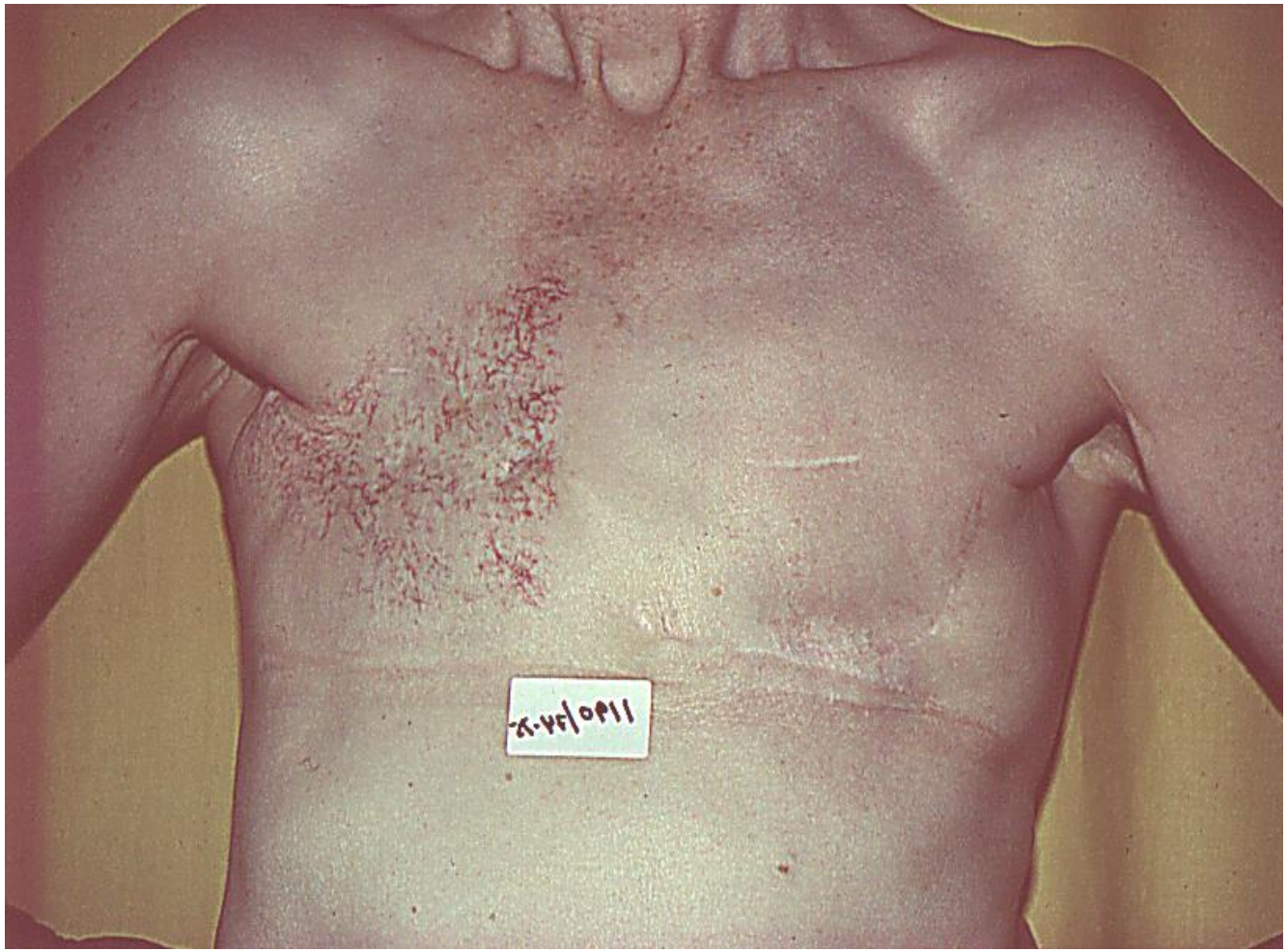
Dose per fraction and late morbidity in breast cancer



12 fx (5 years) **24 fx (9 years)**

From Marie Overgaard

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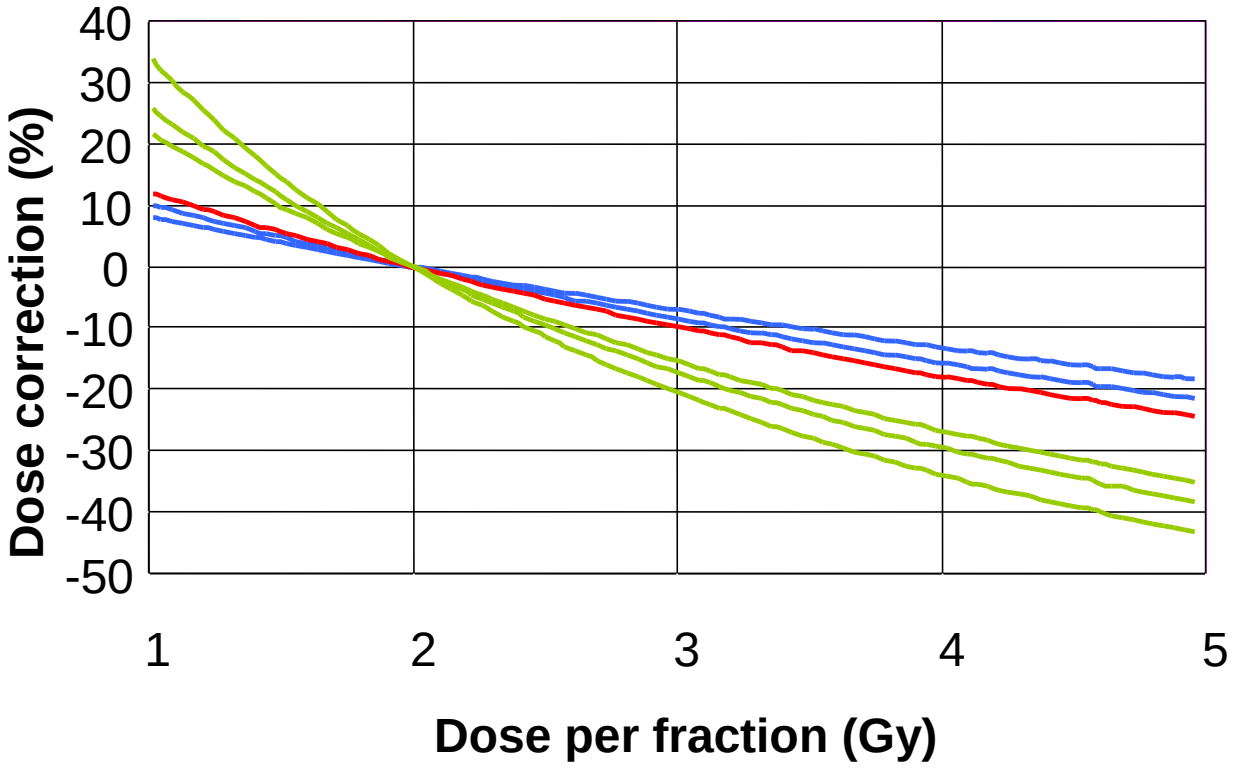
Fractionation sensitivity for human endpoints



Moist desquamation
Erythema
SCC head and neck
Telangiectasia
Frozen shoulder
Fibrosis

Modified from Bentzen 2007

Fractionation studies in head and neck cancer

CONVENTIONAL 66-70 Gy 2 Gy x 33-35 6.5-7 wks.

HYPERFRACT. (EORTC) 80.5 Gy 1.15 Gy x 70 7 wks.

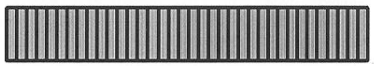
CONCOMITANT BOOST 69 Gy 1.5-1.8 Gy x 38 6 wks.

DAHANCA 6 & 7 66 Gy 2 Gy x 33 5.5 wks.

DAHANCA 9 76 Gy 1.36 Gy x 56 5.5 wks.

ACC. SPLIT COURSE (EORTC) 72 Gy 1.6 Gy x 45 5 wks.

CHART 54 Gy 1.5 Gy x 36 2 wks.



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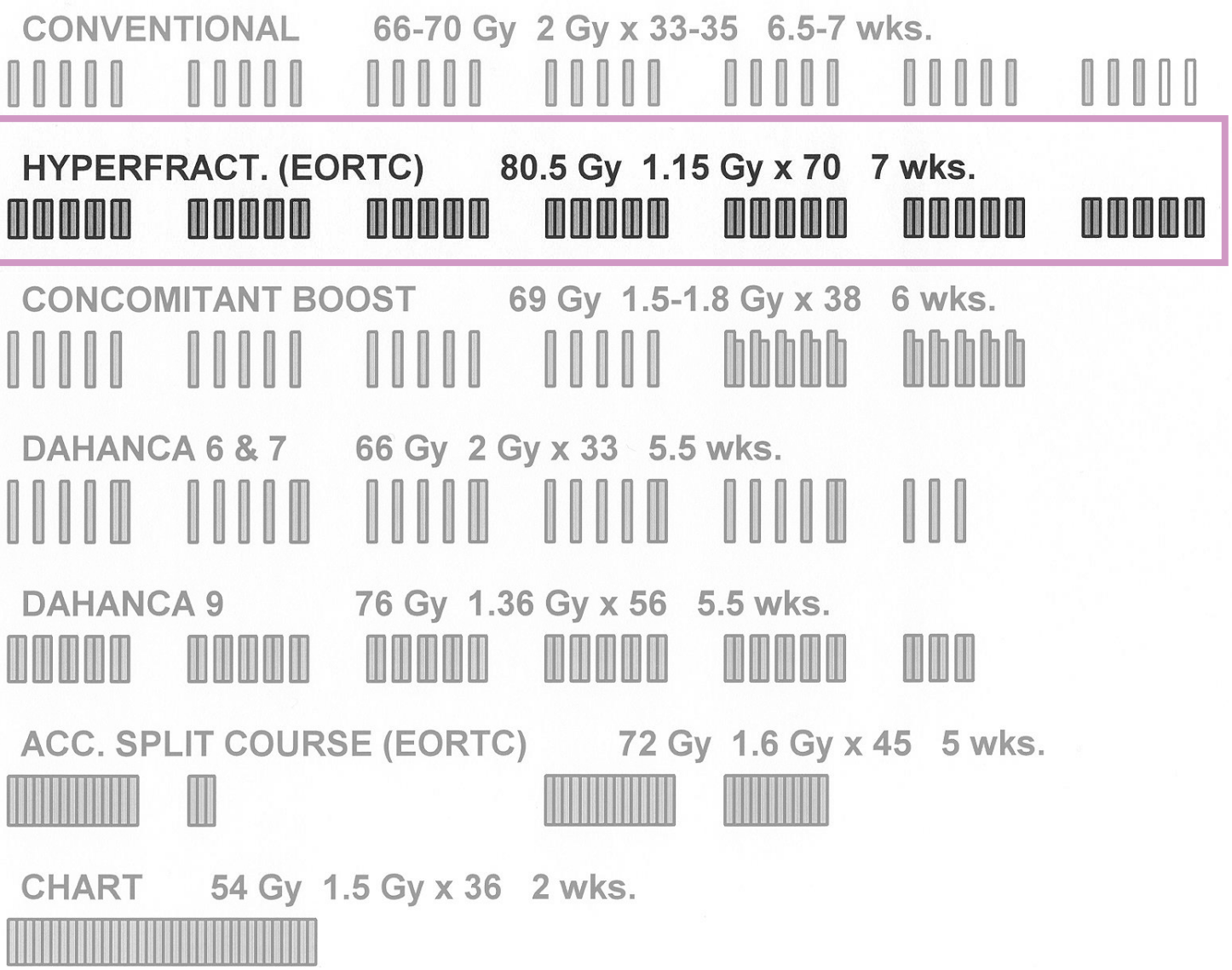
Fractionation studies in head and neck cancer



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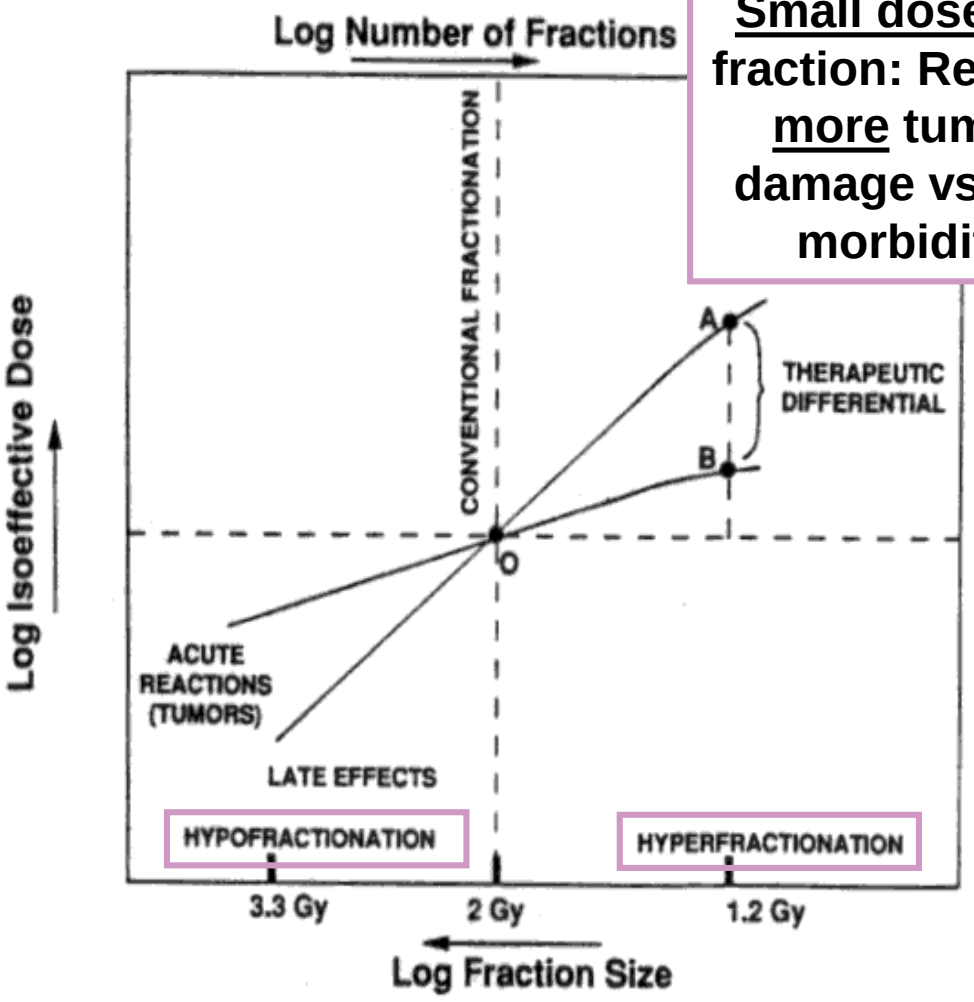
Rationale for hyperfractionation

Therapeutic ratio
vs
dose per fraction



Small dose per fraction: Relative more tumor damage vs late morbidity

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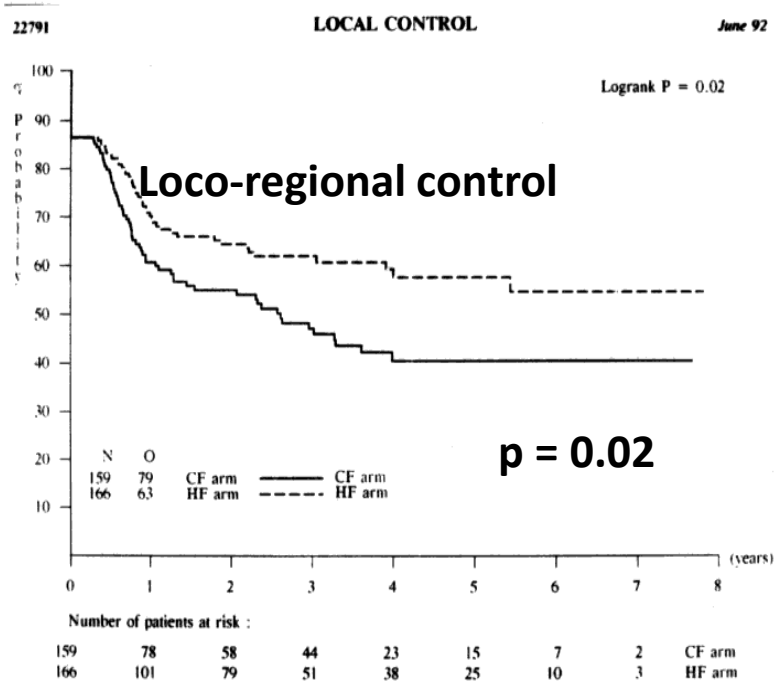
Hyperfractionation

EORTC 22791: 356 ptt. T2-T3 N0-N1 oropharynx



Scheme of trial EORTC 22791: hyperfractionation versus conventional fractionation in oropharyngeal carcinoma.

OROPHARYNGEAL CARCINOMA

T_2T_3,

N_0, $N_1 < 3$ cm

M_0

RANDOMIZATION

- Single daily fraction of 2 Gy 70 Gy/35 fractions/7 weeks
- Twice daily fractions of 1.15 Gy each 80.50 Gy/70 fractions/7 weeks

Improved Terapeutic Ratio:
Increase in tumor control with same late morbidity

Horiot 1992

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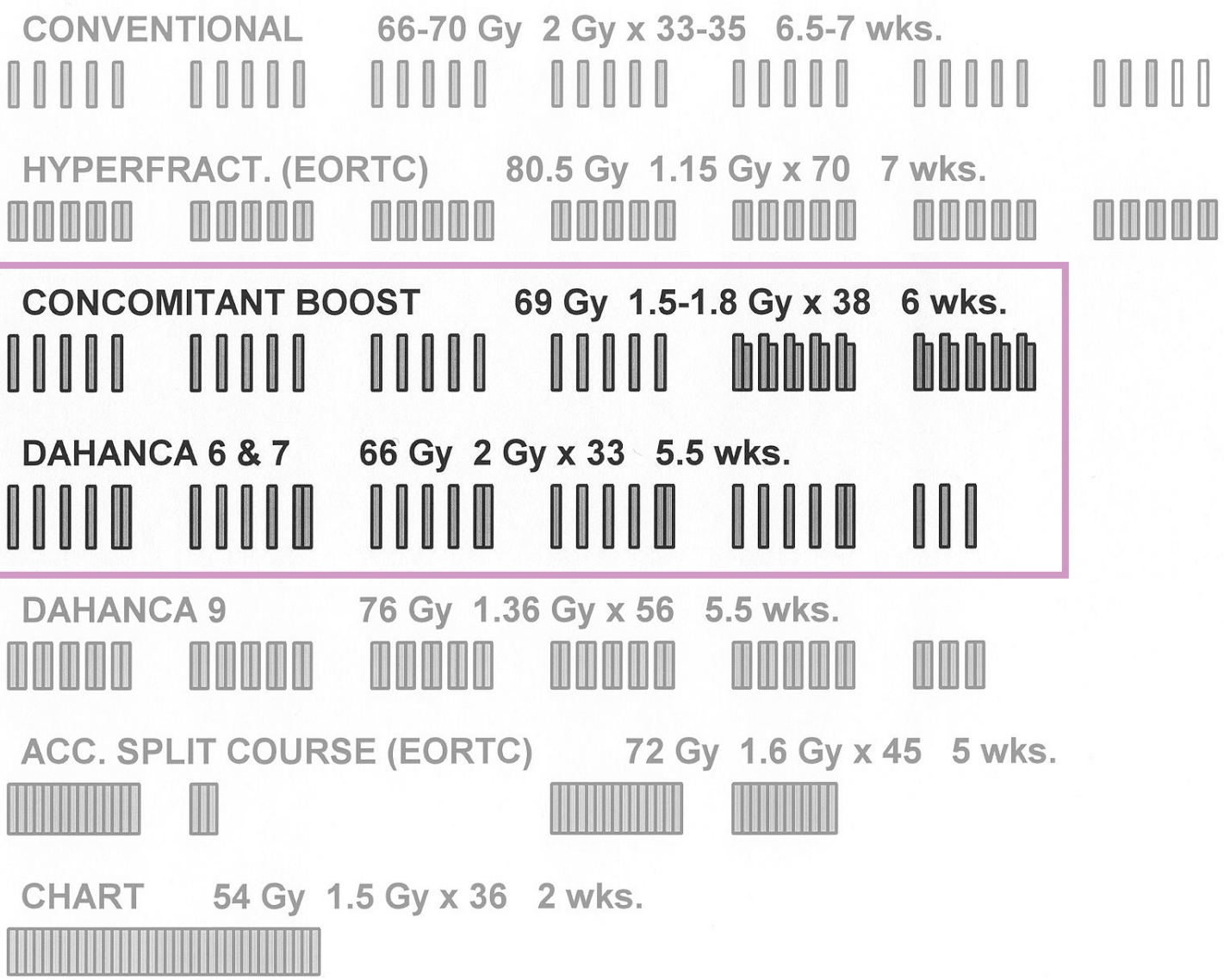
Fractionation studies in head and neck cancer



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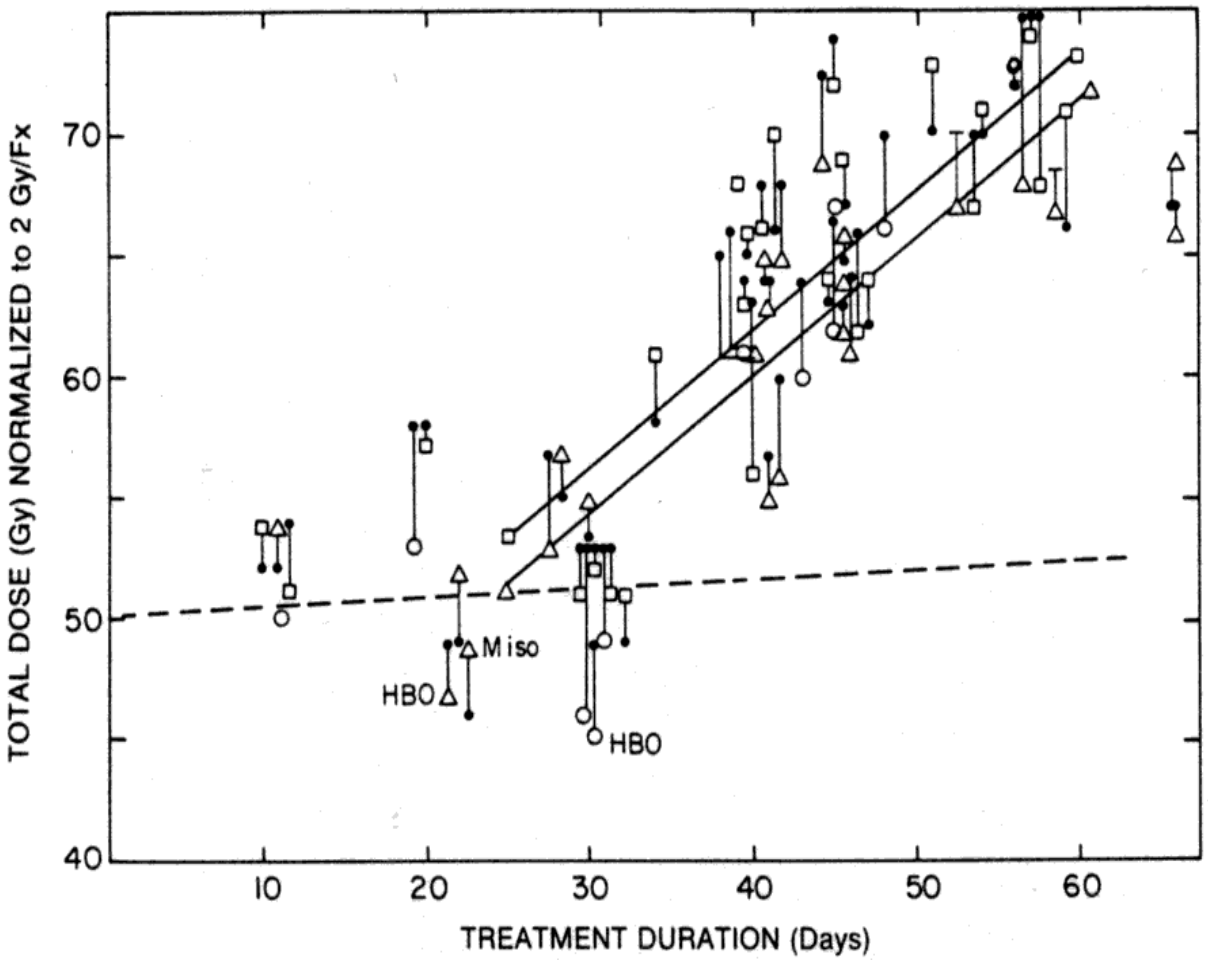
Accelerated repopulation



Withers 1988

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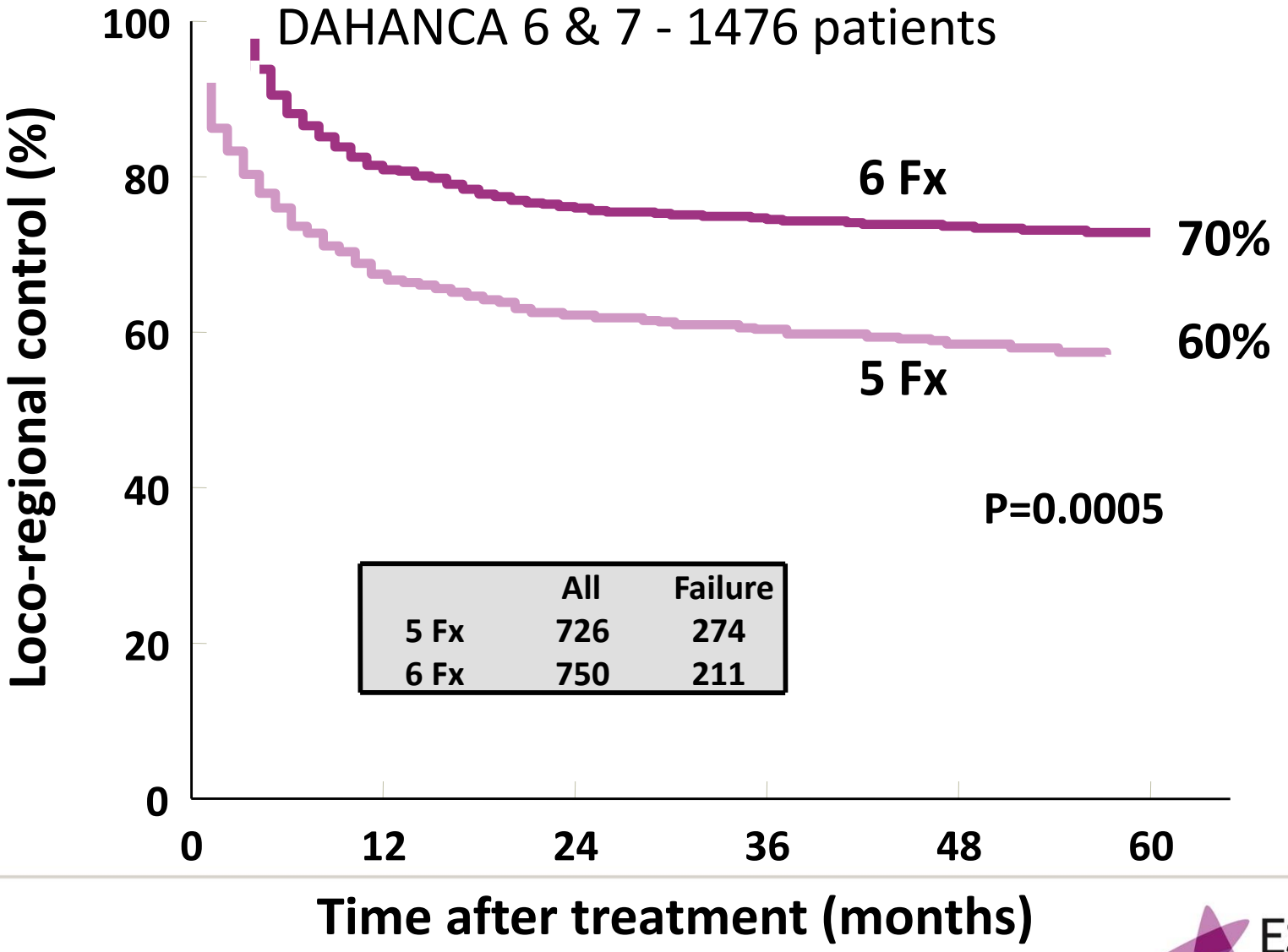
Accelerated Radiotherapy



Overgaard 2003

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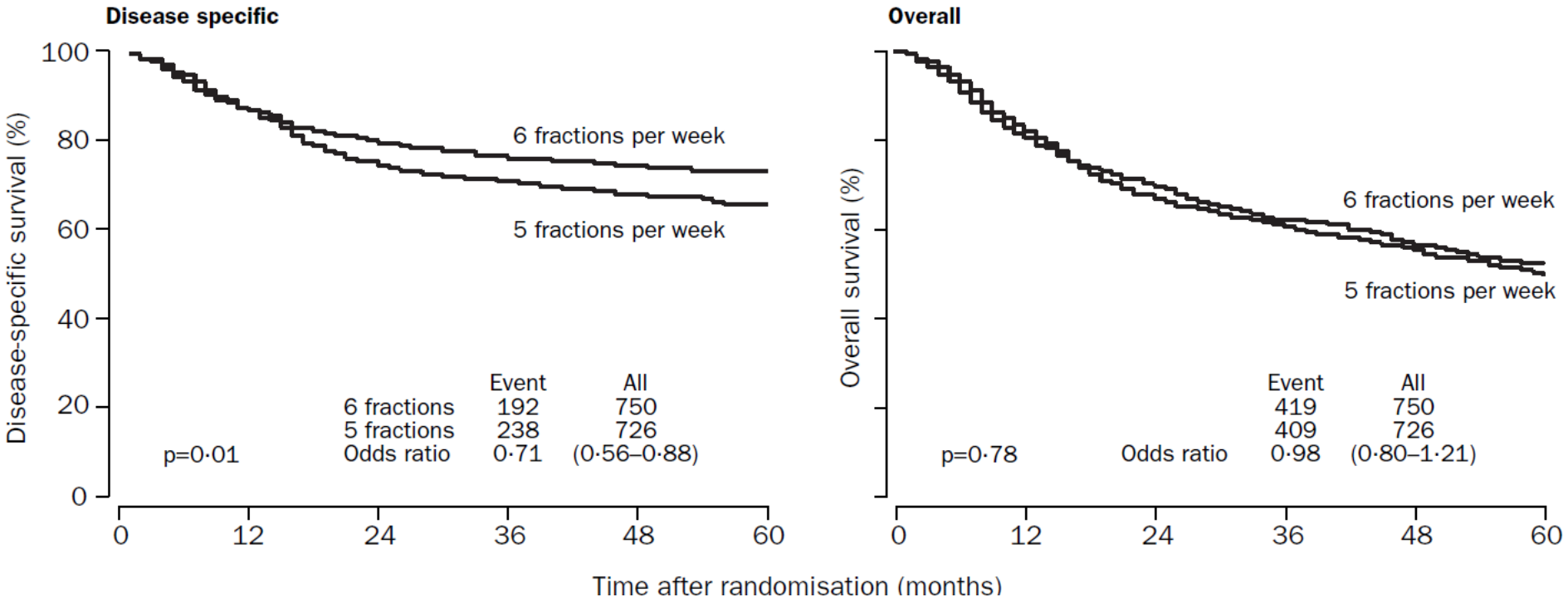
Accelerated Radiotherapy

DAHANCA 6&7 survival



Overgaard 2003

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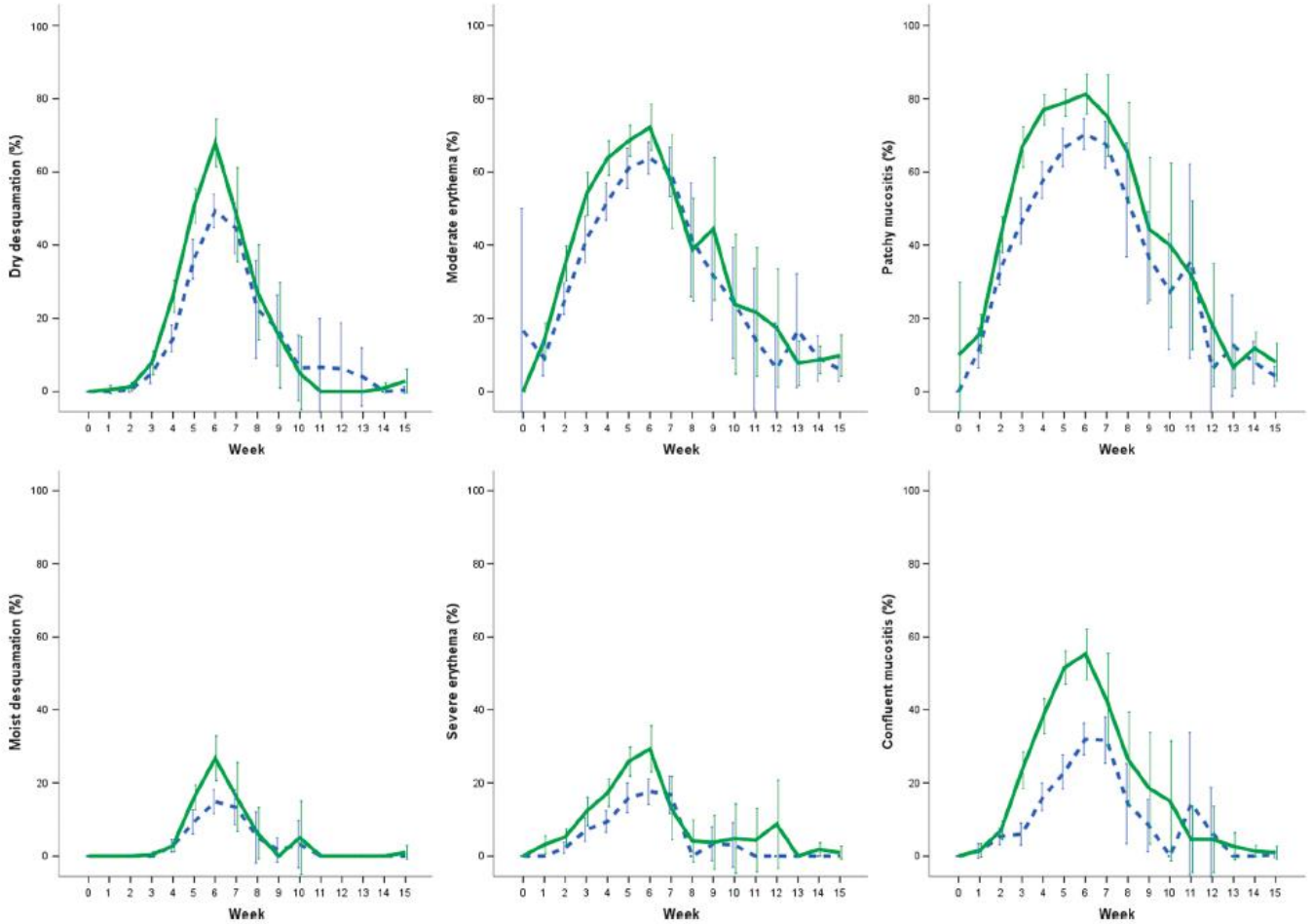
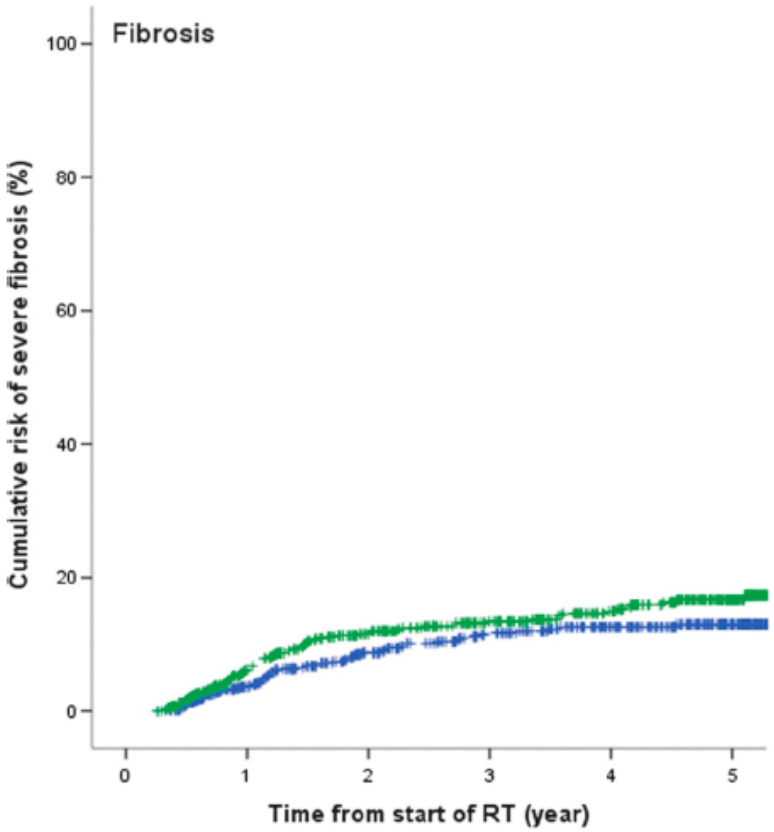
Acute morbidity - DAHANCA 6 & 7

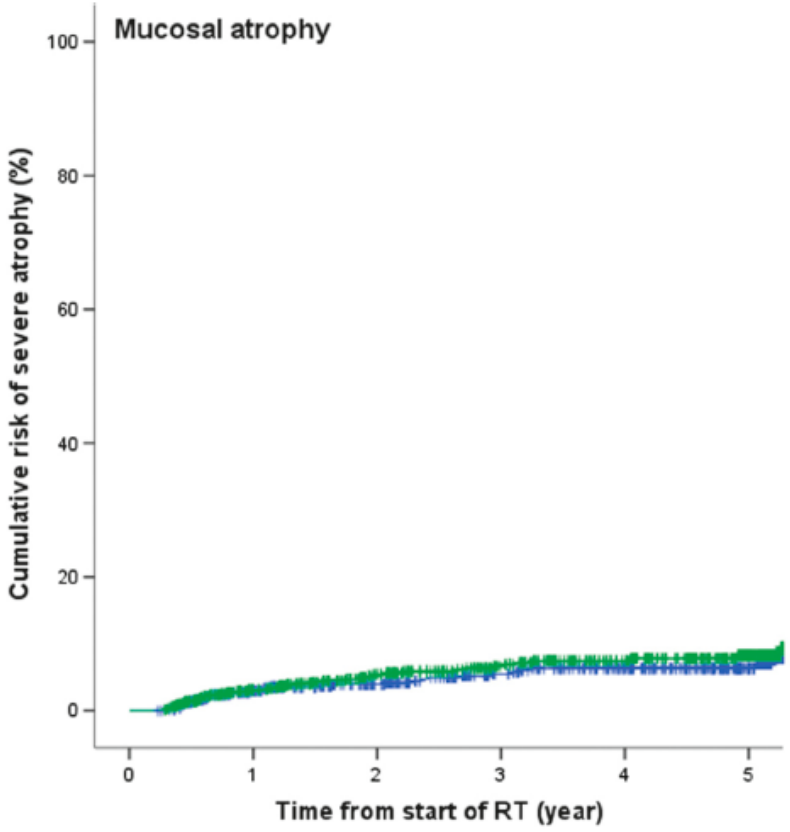


Mortensen et al 2012

ESTRO School

Late morbidity - DAHANCA 6 & 7





Mortensen et al 2012

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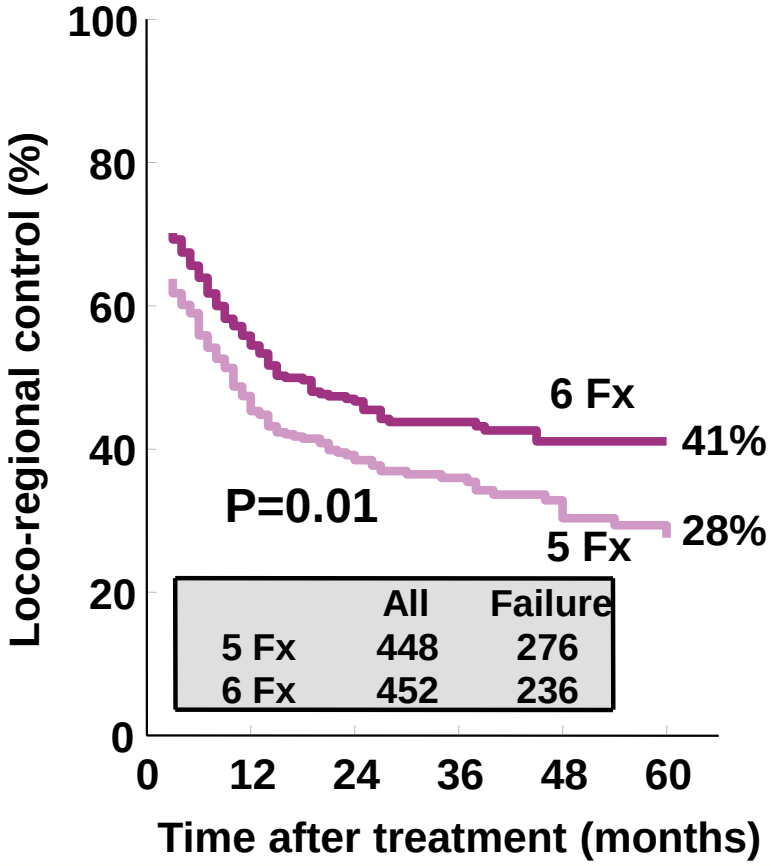
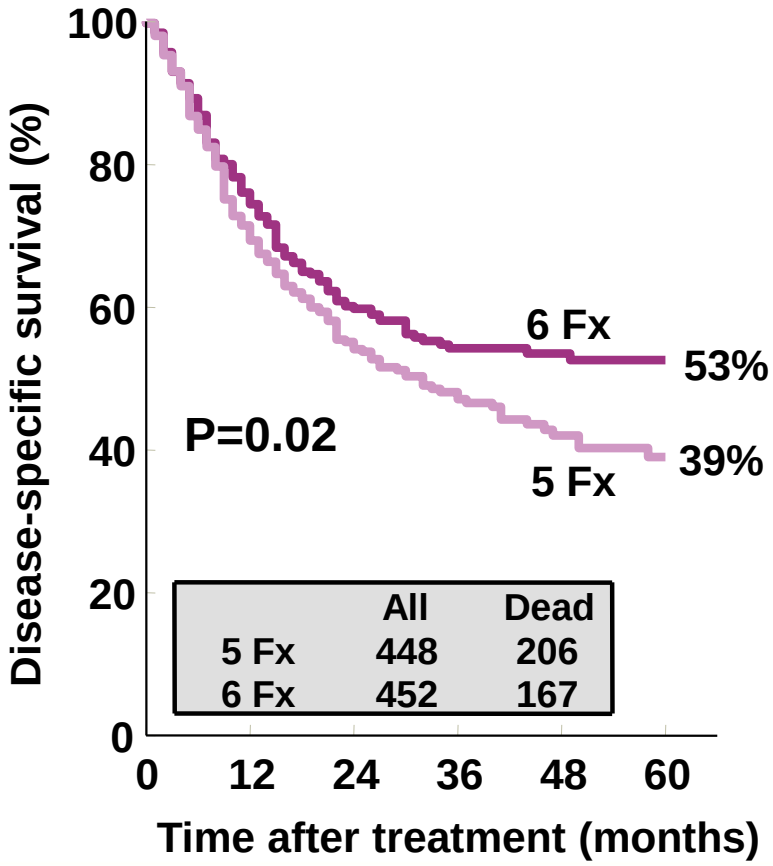
The IAEA-ACC Study

900 pts with head and neck carcinoma.

Loco-regional control



Disease-specific survial



Overgaard et al. 2010

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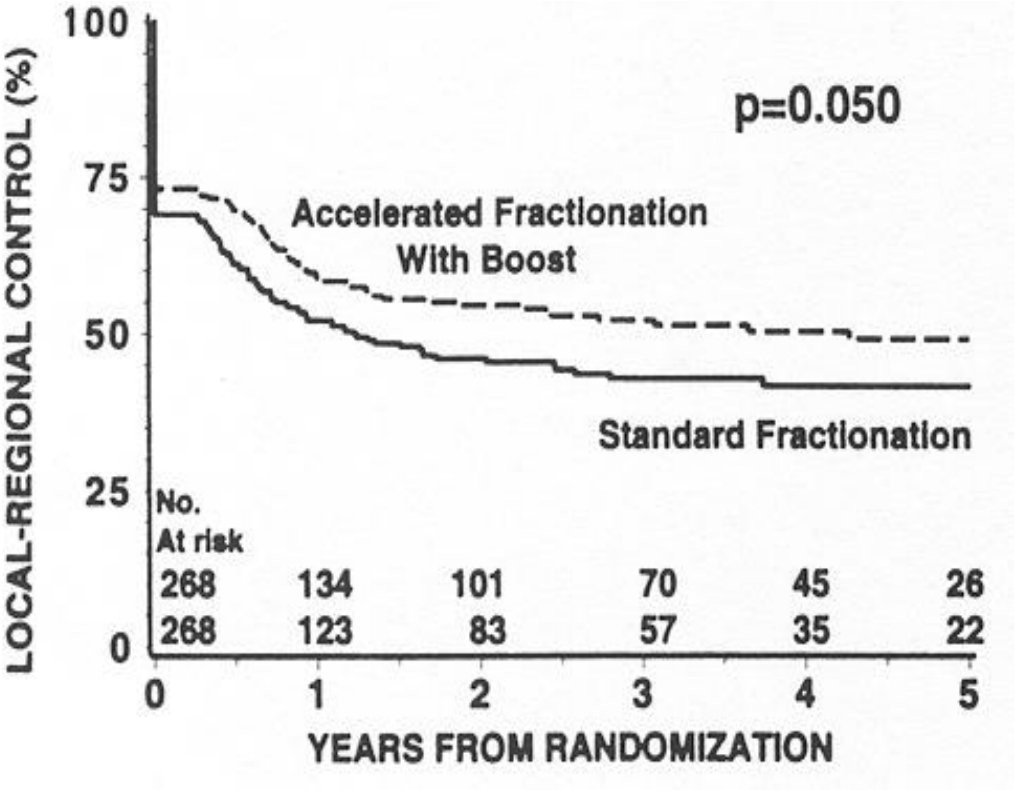
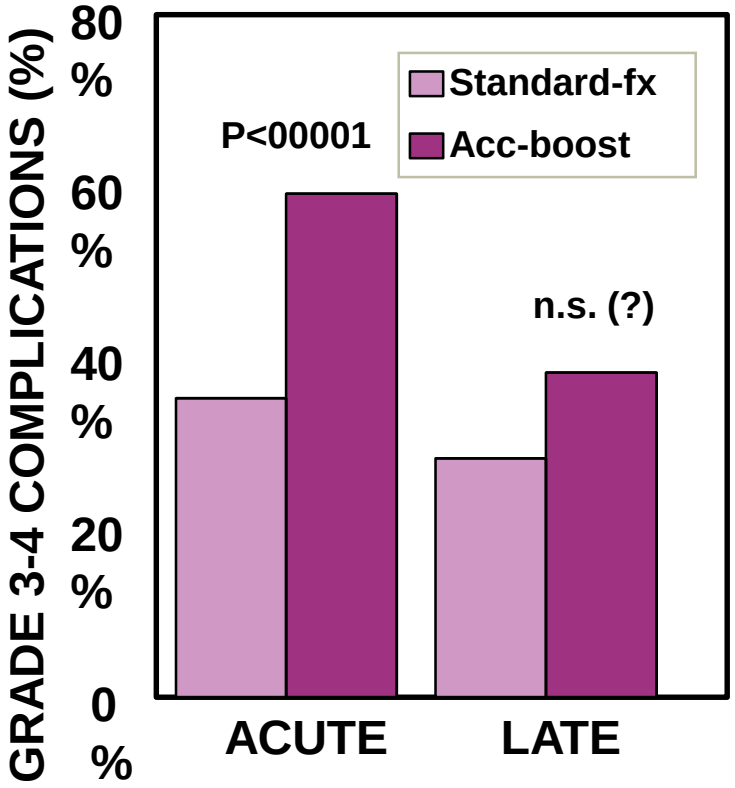
Acc. fractionation with concomitant boost

RTOG 9003: (70Gy/35fx/7w vs. 72 Gy/42fx/6w) - 532 pts.





Fu et al. 2000

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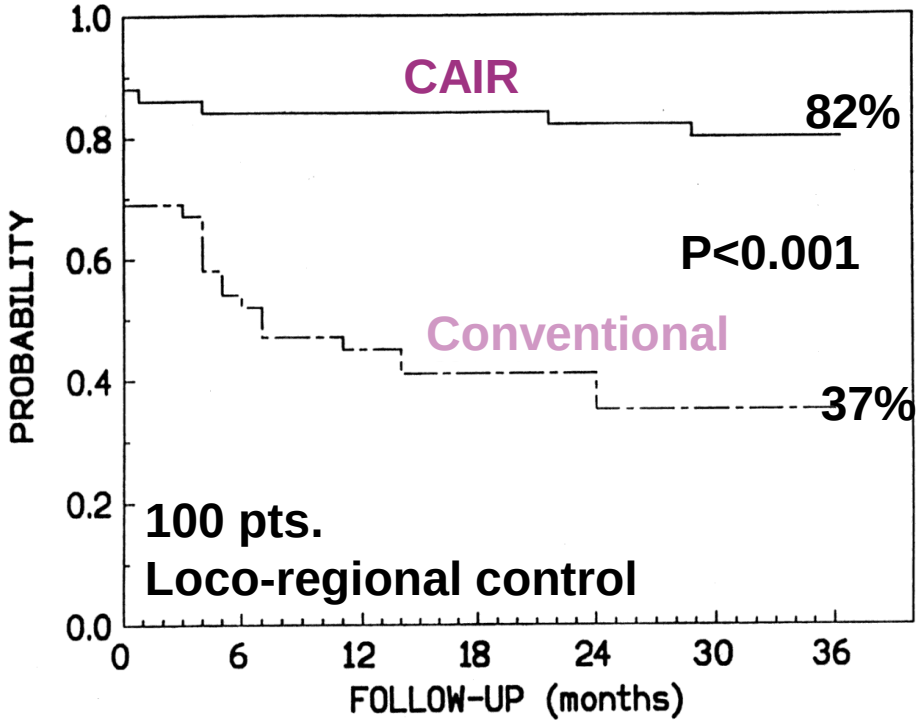
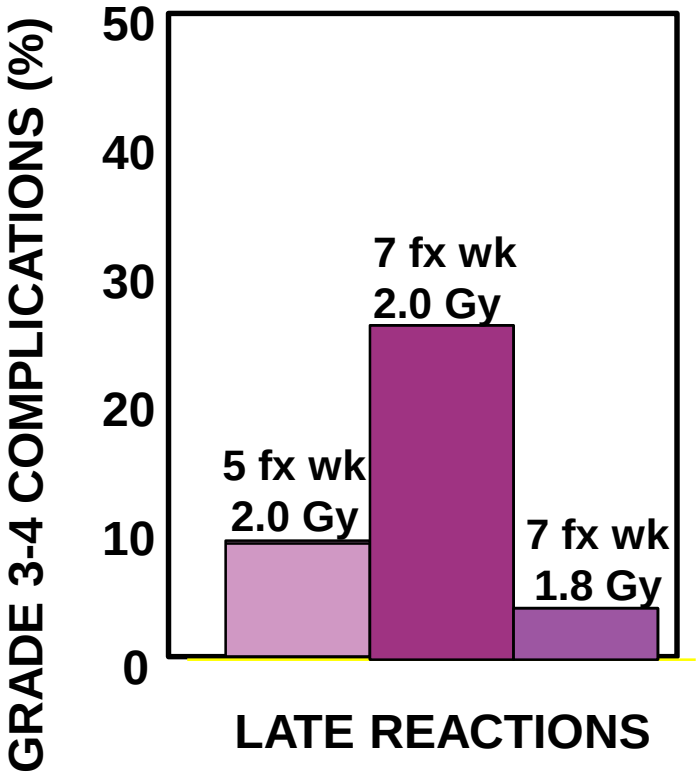
CAIR: Continuous accelerated fractionation

5 vs 7 Fx / week (66-70 Gy/ 33-35 fx)





Skladowski al. 2000.

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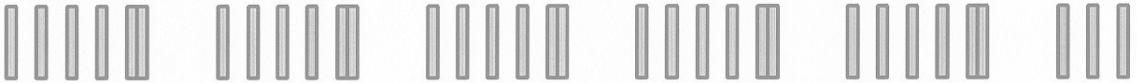
Fractionation studies in head and neck cancer

CONVENTIONAL 66-70 Gy 2 Gy x 33-35 6.5-7 wks.

HYPERFRACT. (EORTC) 80.5 Gy 1.15 Gy x 70 7 wks.

CONCOMITANT BOOST 69 Gy 1.5-1.8 Gy x 38 6 wks.

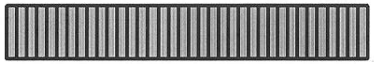
DAHANCA 6 & 7 66 Gy 2 Gy x 33 5.5 wks.



DAHANCA 9 76 Gy 1.36 Gy x 56 5.5 wks.

ACC. SPLIT COURSE (EORTC) 72 Gy 1.6 Gy x 45 5 wks.

CHART 54 Gy 1.5 Gy x 36 2 wks.



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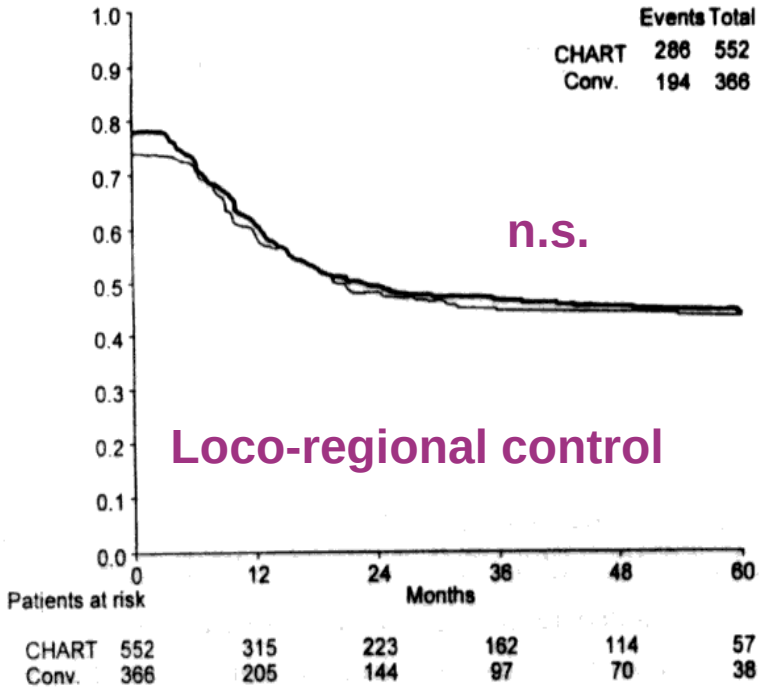
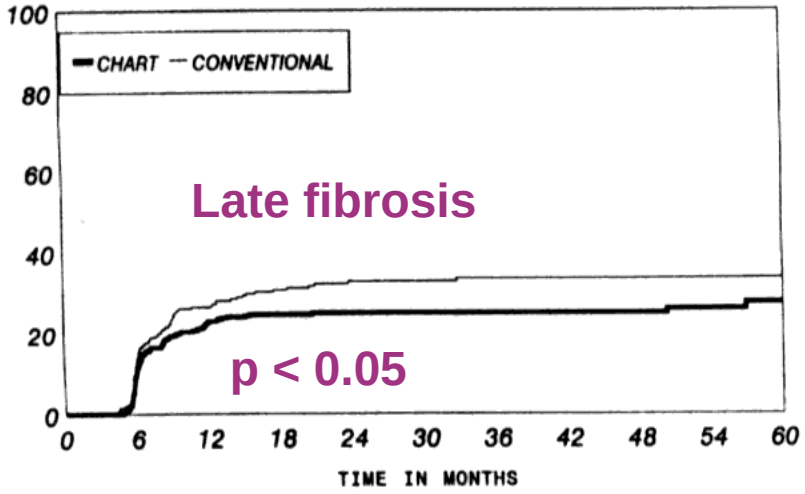
MRC-CHART

54 Gy/36 fx / 12 days vs. 66 Gy/ 33 fx/ 6.5 wks





Dische et al. 1997.

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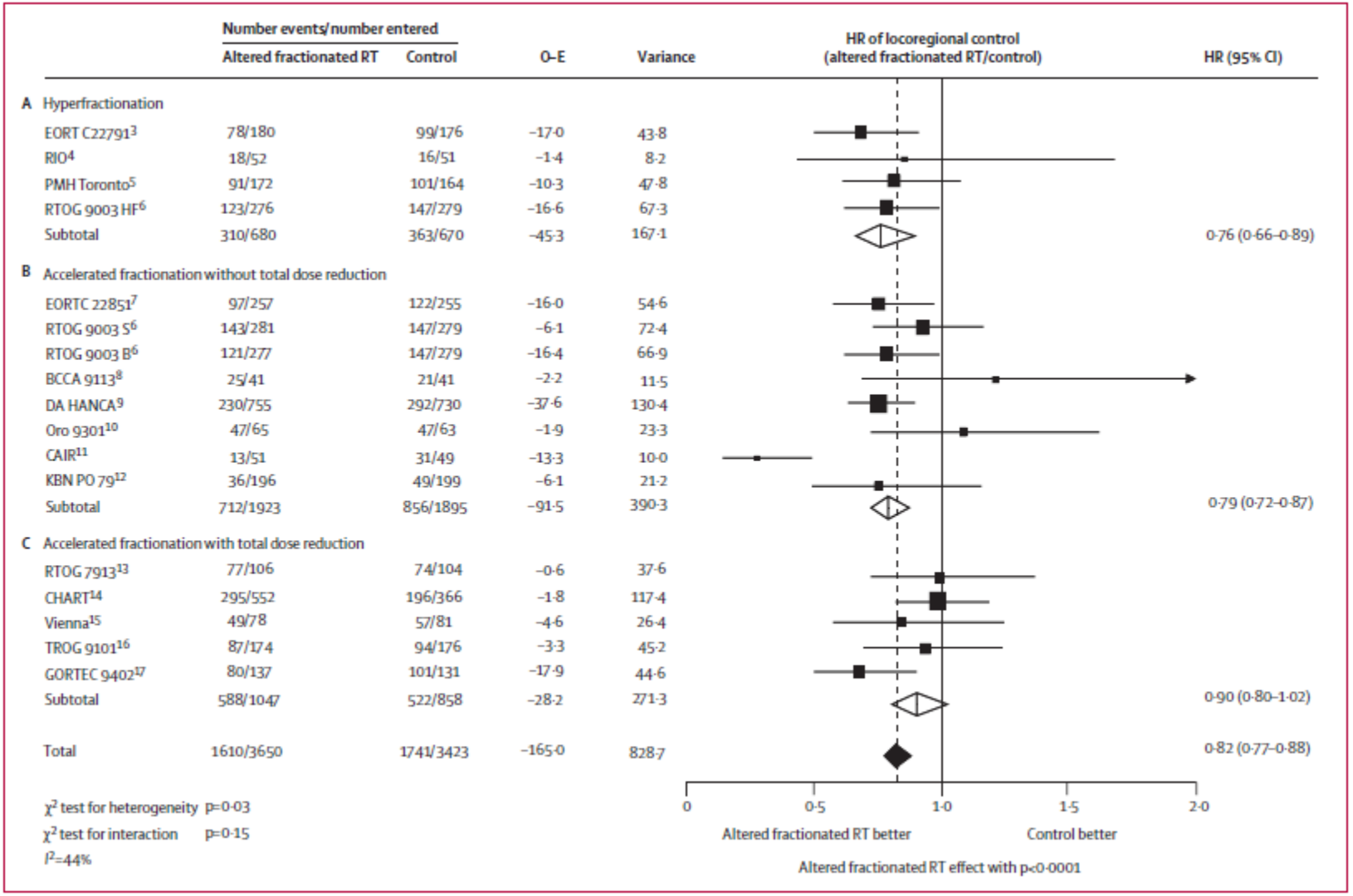
Meta-analysis

Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis

Jean Bourhis, Jens Overgaard, Hélène Audry, Kian K Ang, Michele Saunders, Jacques Bernier, Jean-Claude Horiot, Aurélie Le Maître, Thomas F Pajak, Michael G Poulsen, Brian O'Sullivan, Werner Dobrowsky, Andrzej Hliniak, Krzysztof Skladowski, John H Hay, Luiz H J Pinto, Carlo Fallai, Karen K Fu, Richard Sylvester, Jean-Pierre Pignon, on behalf of the Meta-Analysis of Radiotherapy in Carcinomas of Head and neck (MARCH) Collaborative Group*

Meta-analysis: loco-regional control



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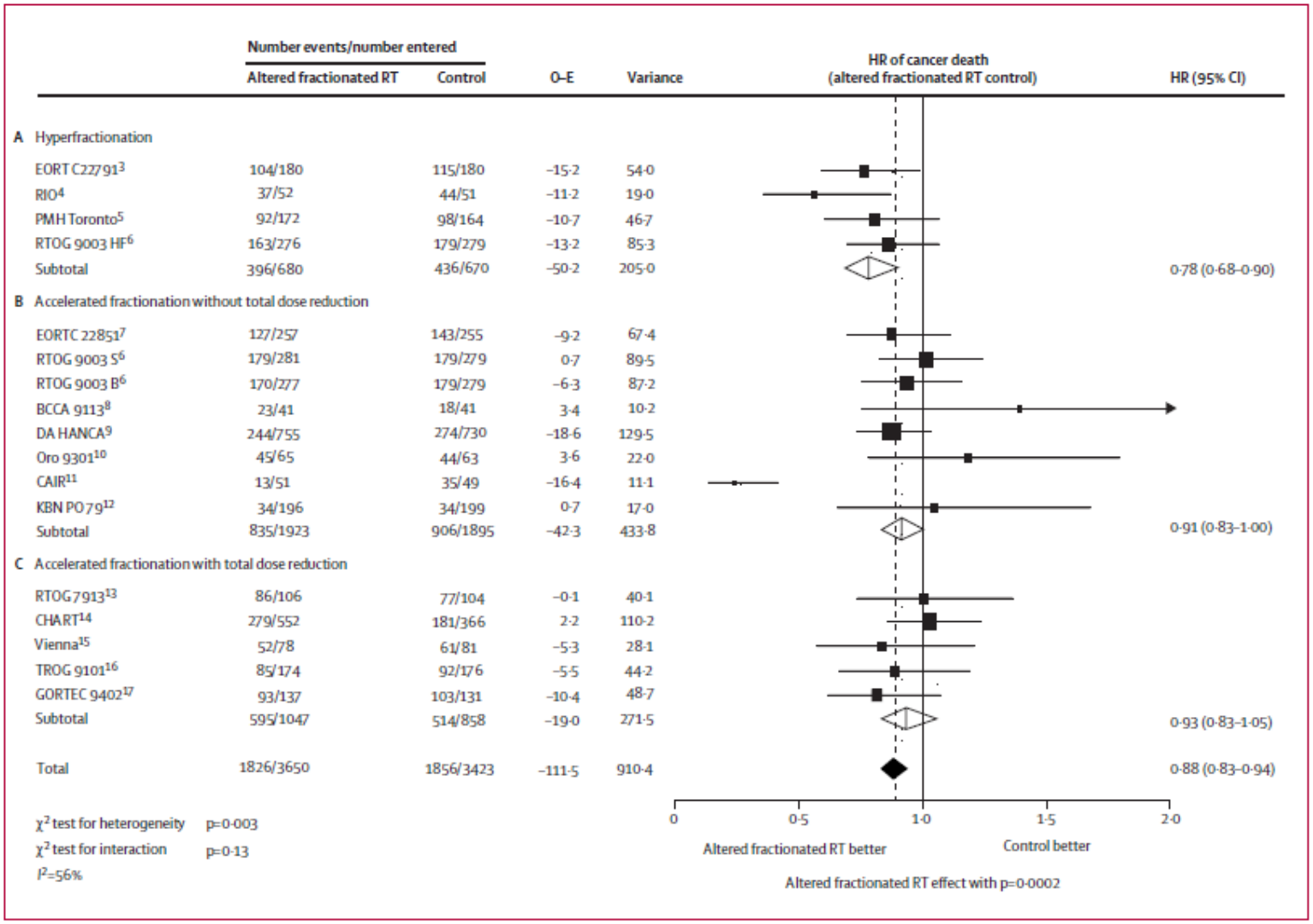
Meta-analysis: disease-specific survival



Lancet 2006; 368: 843–54

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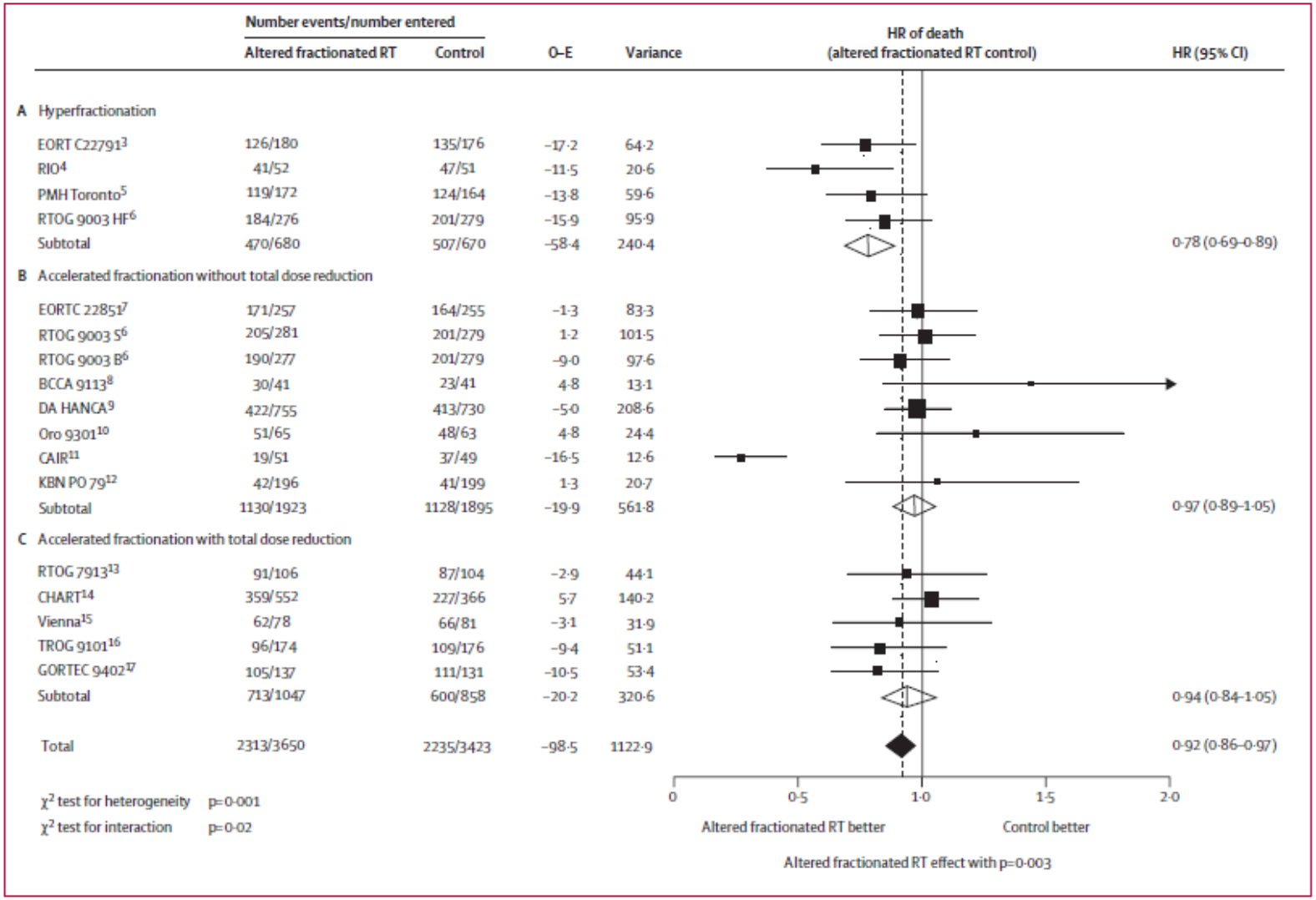
Meta-analysis: overall survival



Lancet 2006; 368: 843–54

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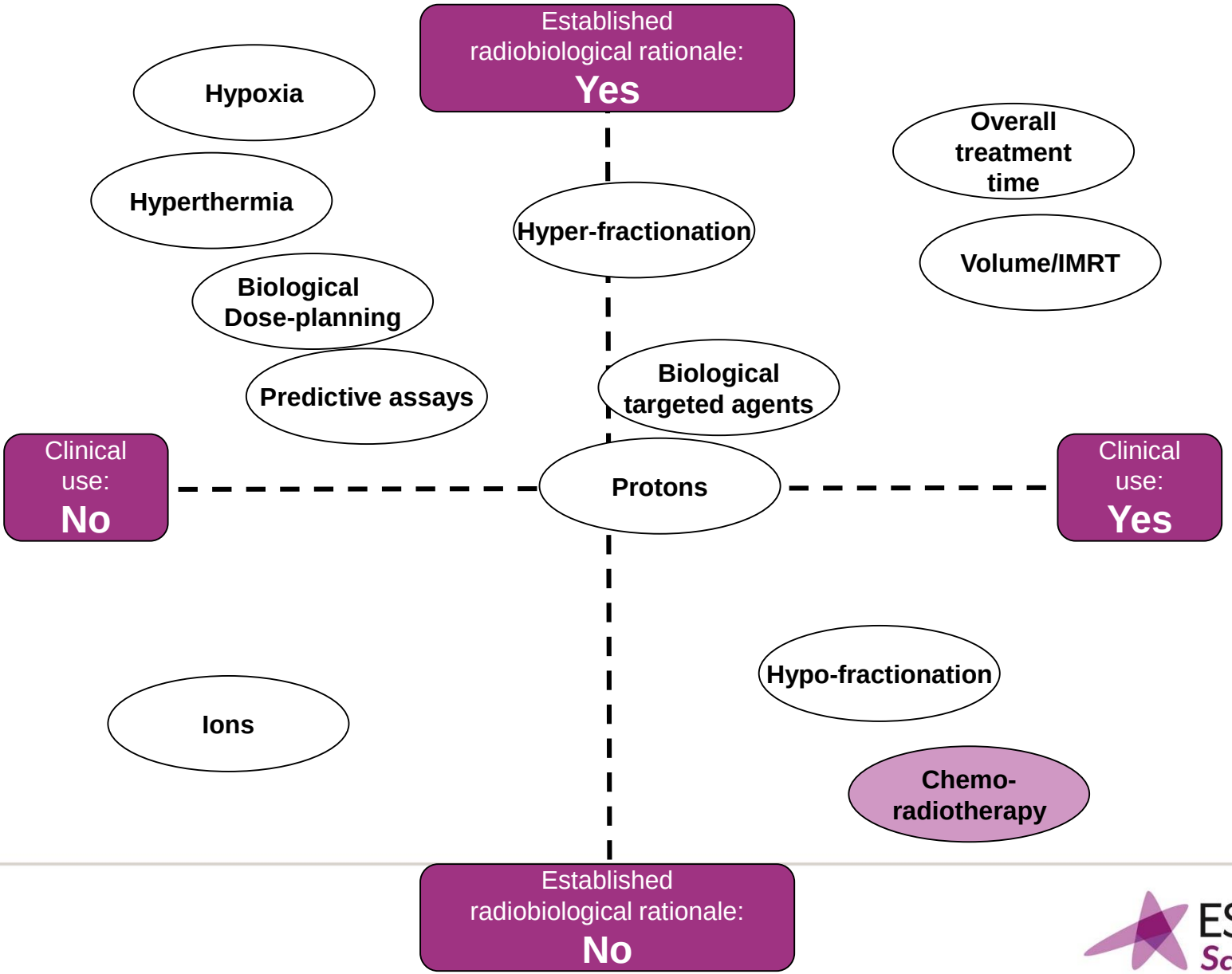
Conclusion - fractionation

- Awareness of the fractionation sensitivity of tumors and normal tissues is critical
- Clinical studies and meta-analysis have shown that moderately accelerated radiotherapy improves loco-regional control
- Hyperfractionated RT improves loco-regional control and survival
- Altered fractionation is thus recommended for primary radiotherapy of head and neck cancer

The landscape of evidence and practice



First clinical success with C-RT

Sidney Farber,
Brigham and Women's hospital
Boston, 1958

- Wilms' tumour
- Actinomycin D, RT,
- Followed by surgery
- DSS: 40%-85%

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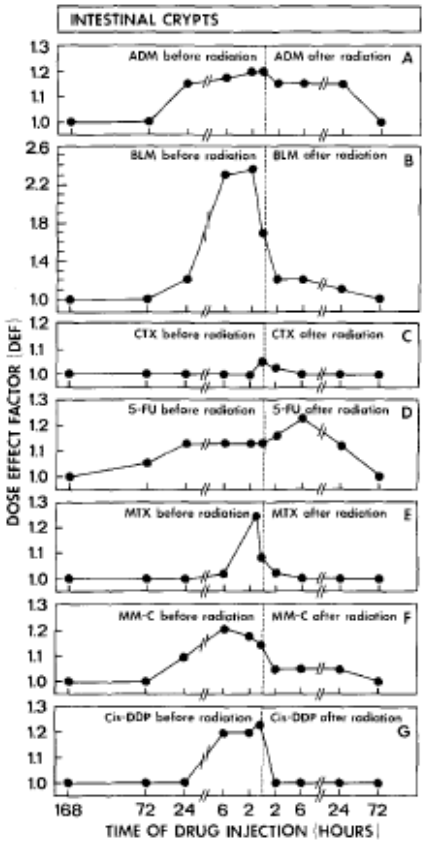
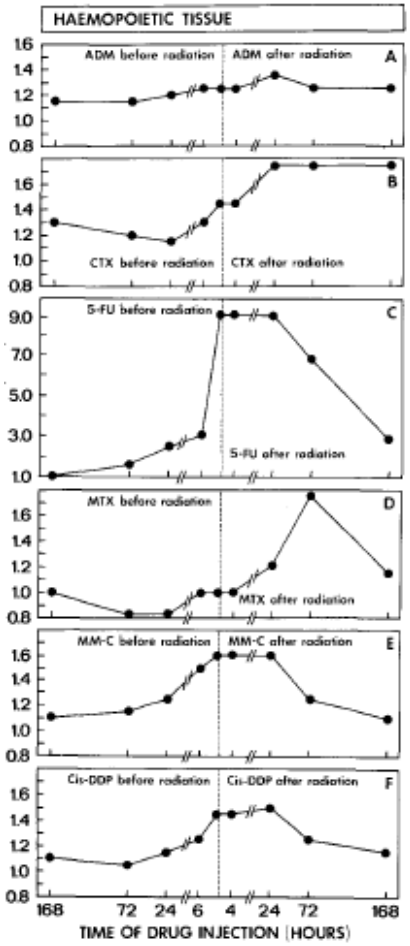
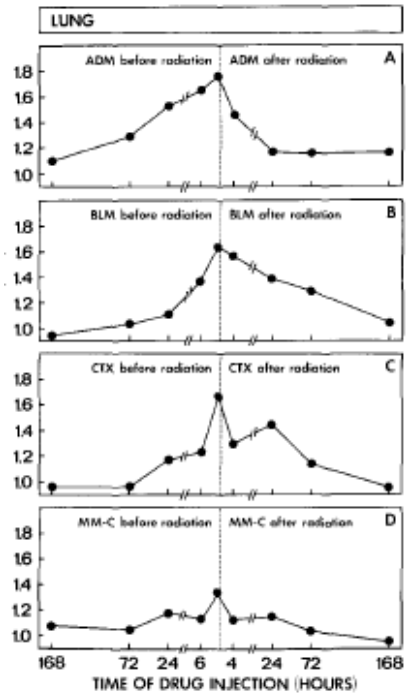
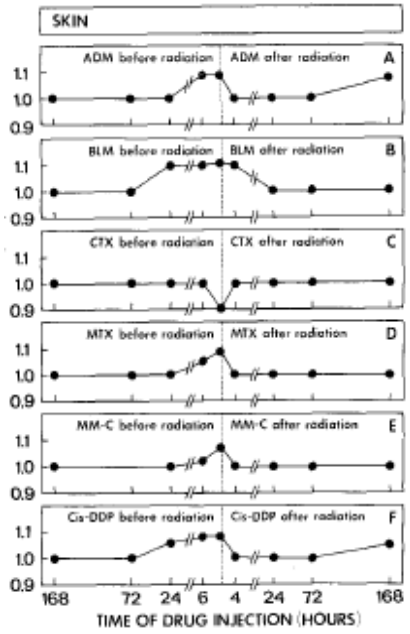
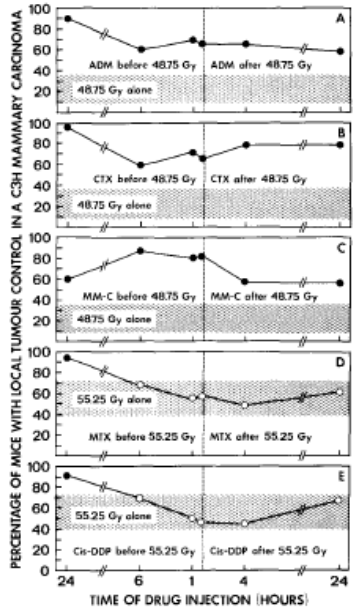
Preclinical data











vdMaase 1986

Why combine chemotherapy with radiotherapy?

Two purposes:

- To increase the effect of radiotherapy

- To remove micrometastases outside the RT-field

- But preferably without increase in morbidity

How to combine chemotherapy with radiotherapy?

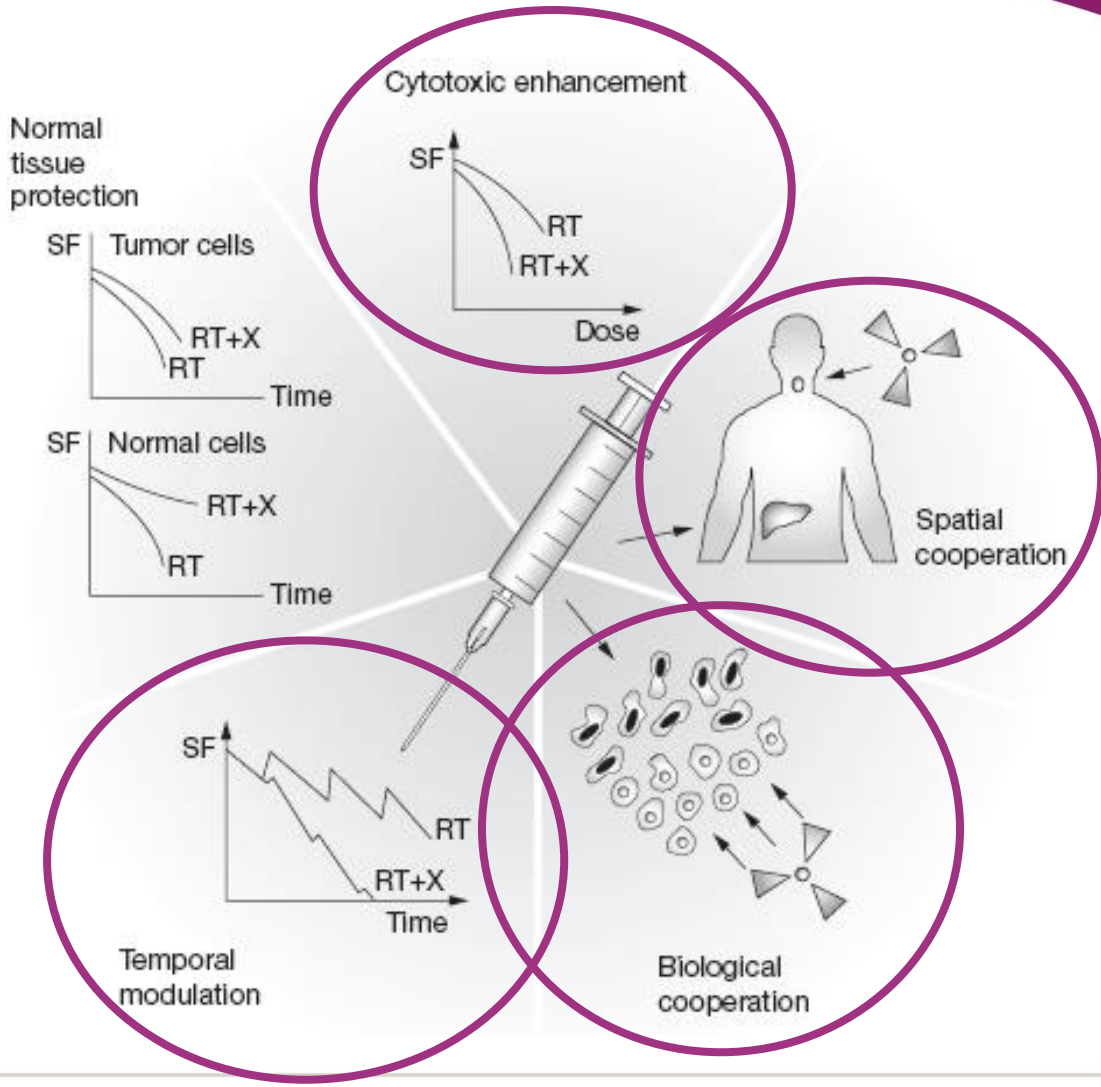
Spatial cooperation

Cytotoxic enhancement

Biological cooperation

Temporal modulation

Normal tissue protection



Bentzen SM 2007

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Evidence for effect of a combined approach

Disease	Induction	Concomitant	Adjuvant
GBM	÷	+(Level II)	+ (Level II)
HNSCC	÷/+ (Level I)	+++ (Level I)	÷ (Level II)
NSCLC	+(Level I)	+++ (Level I)	÷
SCLC	+++ (Level I)	+++ (Level I)	+++ (Level I)
CCU	÷/+ (Level I)	+++ (Level I)	÷
Oesophagus	÷	+++ (Level I)	÷
Rectum	÷	+++ (Level II)	÷
Anal	÷	+++ (Level II)	÷

Cisplatin

Barnett Rosenberg,
Michigan State University
1965

1890: Cisplatin discovered

1965: Inhibits bacteria cell division

1969: First cure of a solid tumour

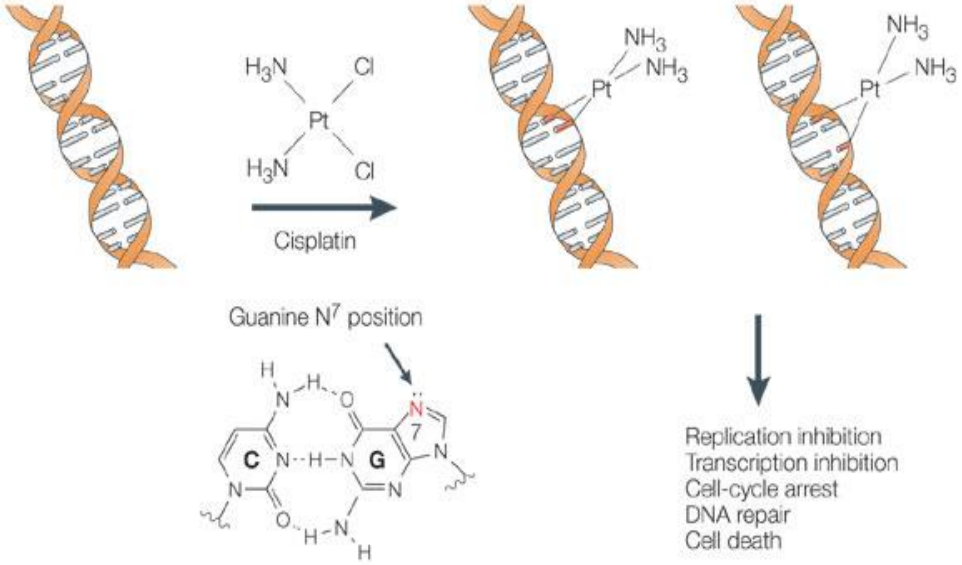
1976: First clinical trials

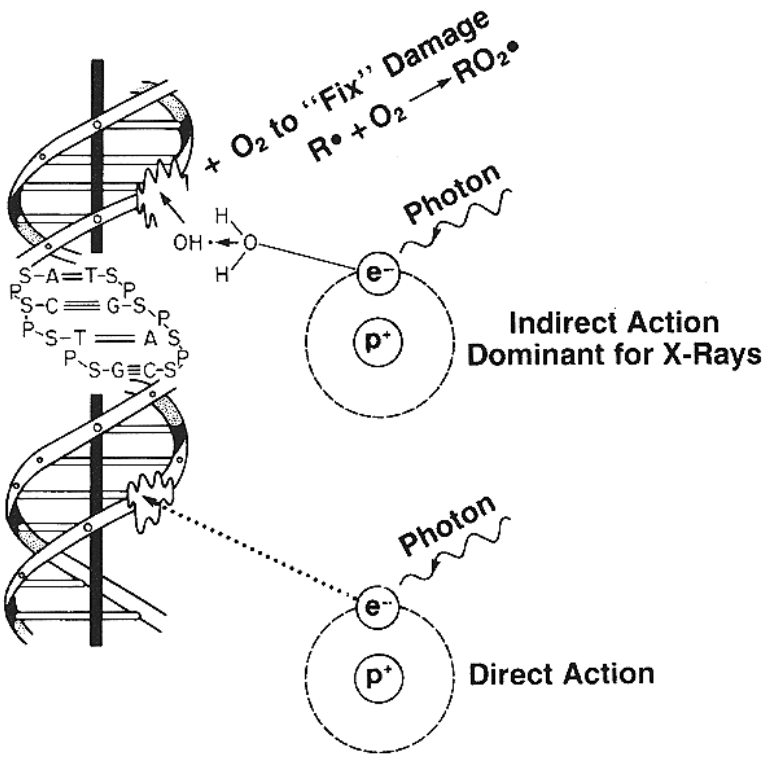
1978: FDA approval

1999: First data of C-RT

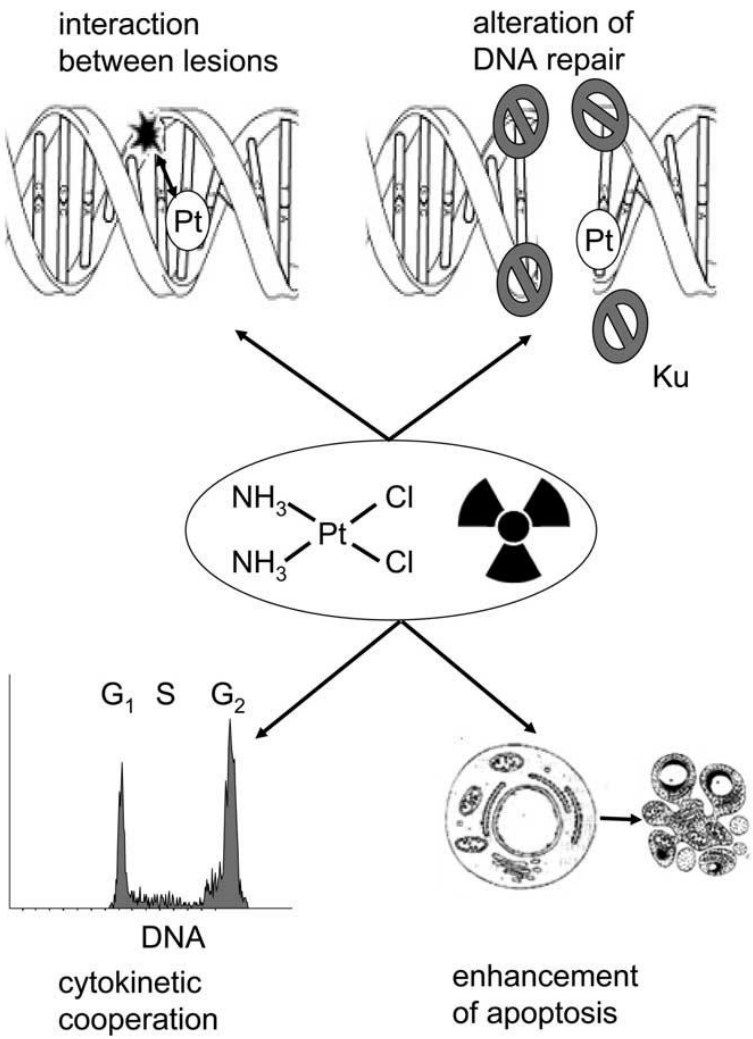
Cisplatin RT

- Intra/inter-strand crosslinks
- Cyklus uspecific





Cisplatin and RT

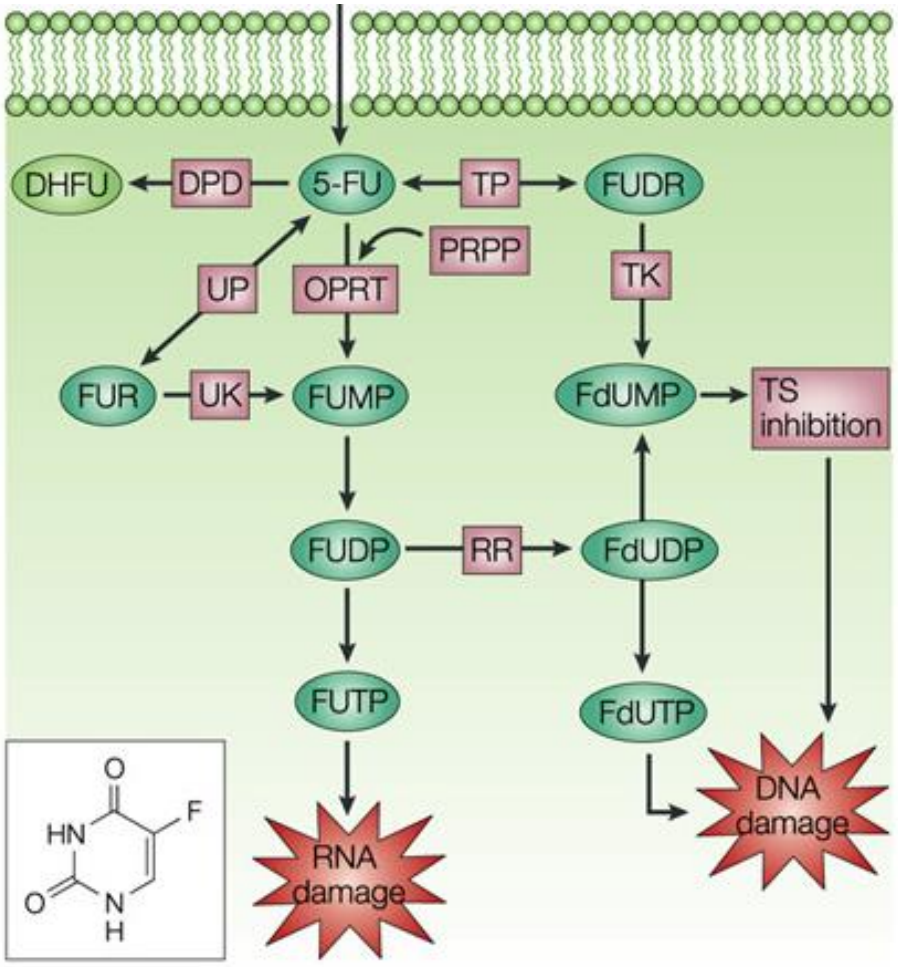


- Increase in toxic platin-derivatives
- Cisplatin blocks DNA-ends
- RT increase cellular uptake of cisplatin
- Stop cells in the G2-phase
- Impaired repair of DNA

Wilson GD 2006

ESTRO School

5-FU and RT



- Thymidin 5-tri-P analogue
- Inhibition of TS
- Deplete Thymidine 5 mono-P and Thymidine 5 tri-P
- Inhibition of DNA synthesis
- Interference with DNA repair.
- S-phase specific (RT-resistent)
- Inhibit S-phase entry

Longley DB 2003

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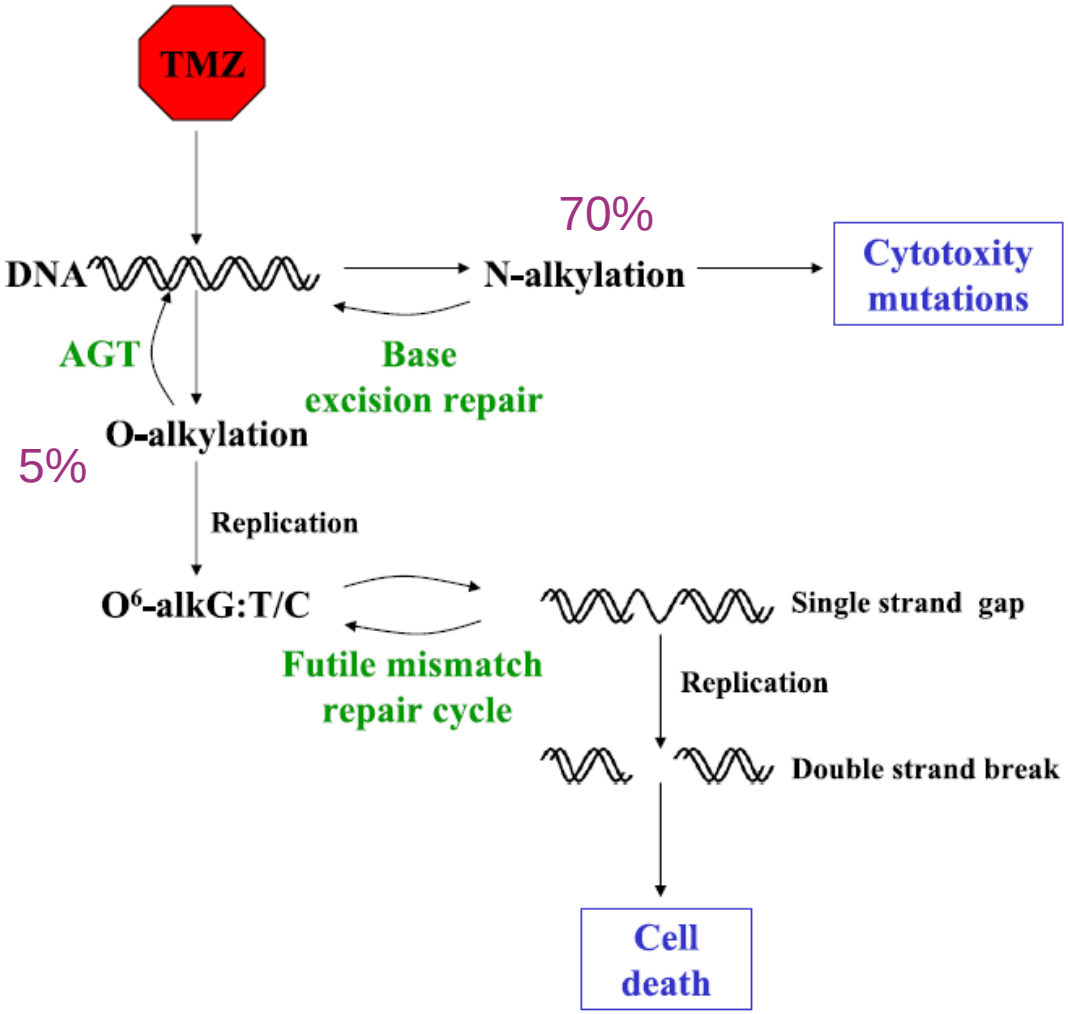
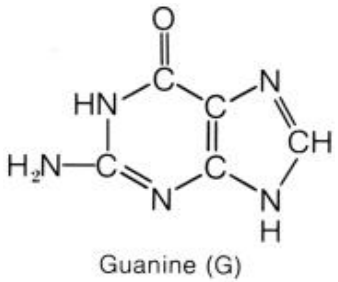
Temozolomide and RT



- Alkylating drug (Guanine)
- Ireversible
- AGT/MGMT



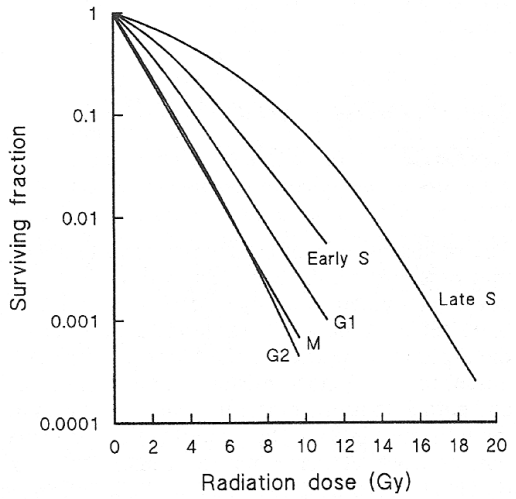
Guanine (G)

Zhang M 2006

”New drugs”

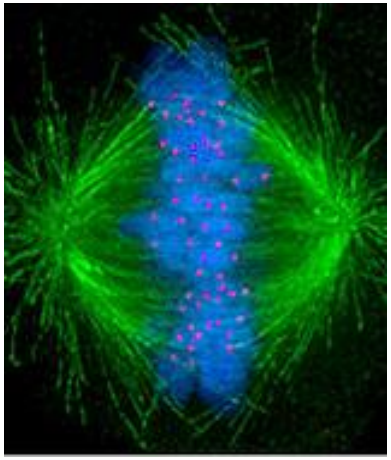
Gemcitabine:

- Pyrimidin-analogue - interferes with DNA and inhibits DNA synthesis and repair
- S-phase specific?

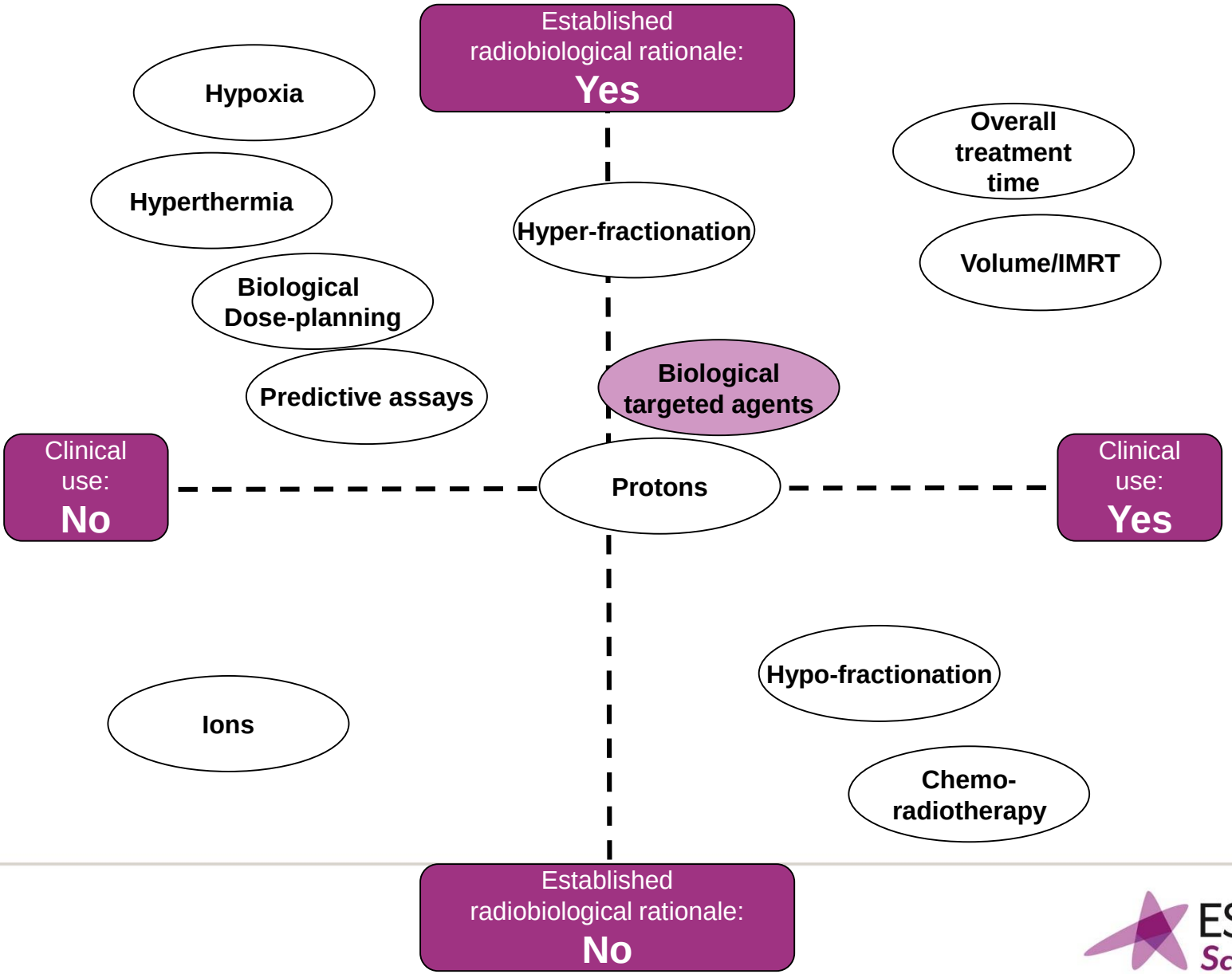


Taxanes:

- Interferes with microtubuli - cell cycle stops in G2/M-phase
- Synchronizing (only seen *in vitro*)
- Reoxygenation through tumour reduction?



The landscape of evidence and practice

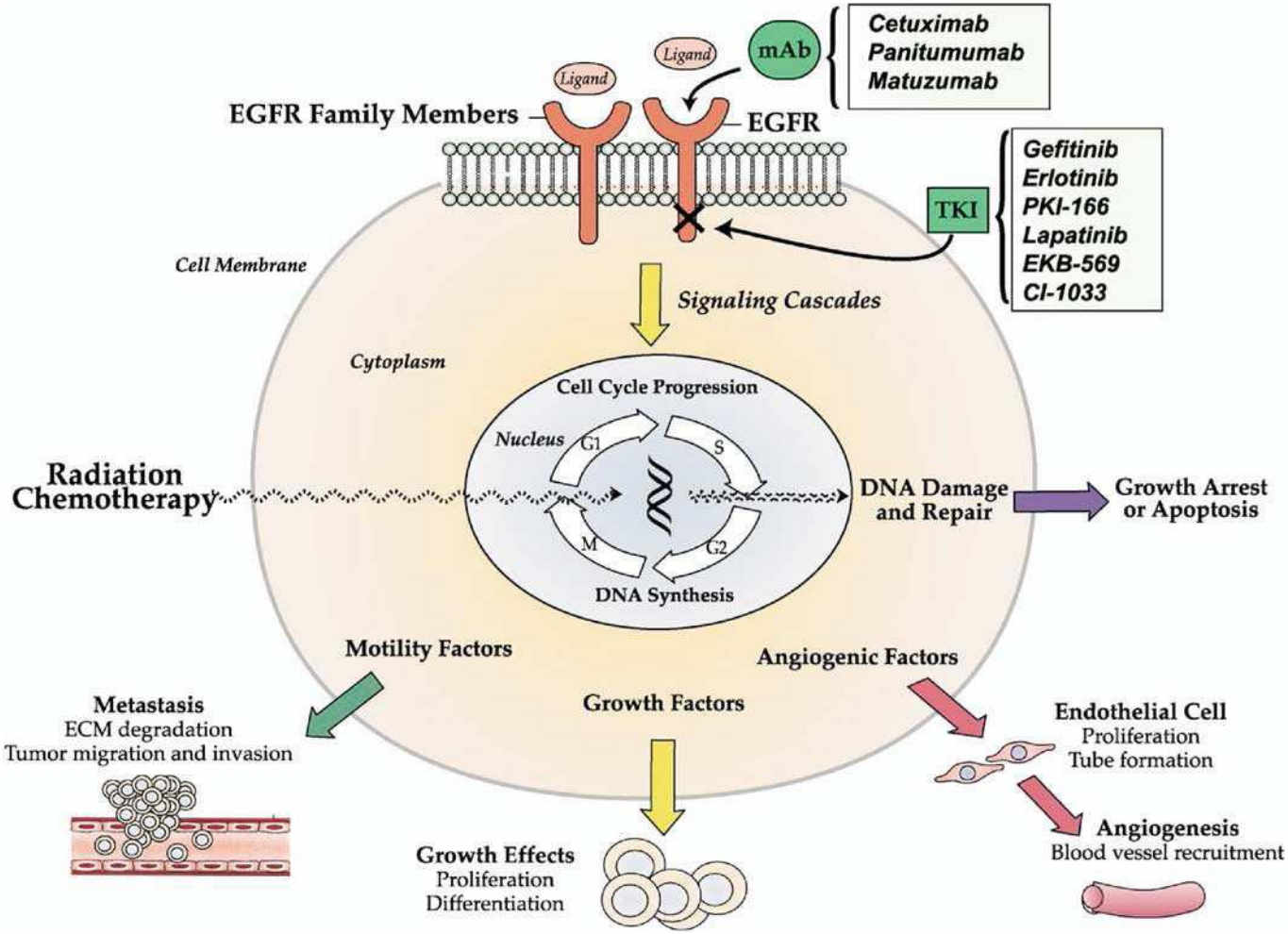


The Ideal biological target

- Selective inhibition of a specific target
- Present in tumour cells
- Only present in tumour cells….or…..
- The function of the target is not essential for normal tissue
- Only one or a few activation pathways (little redundacy)
- Good preclinical models that shows tumour efficacy

After Grandis 2008

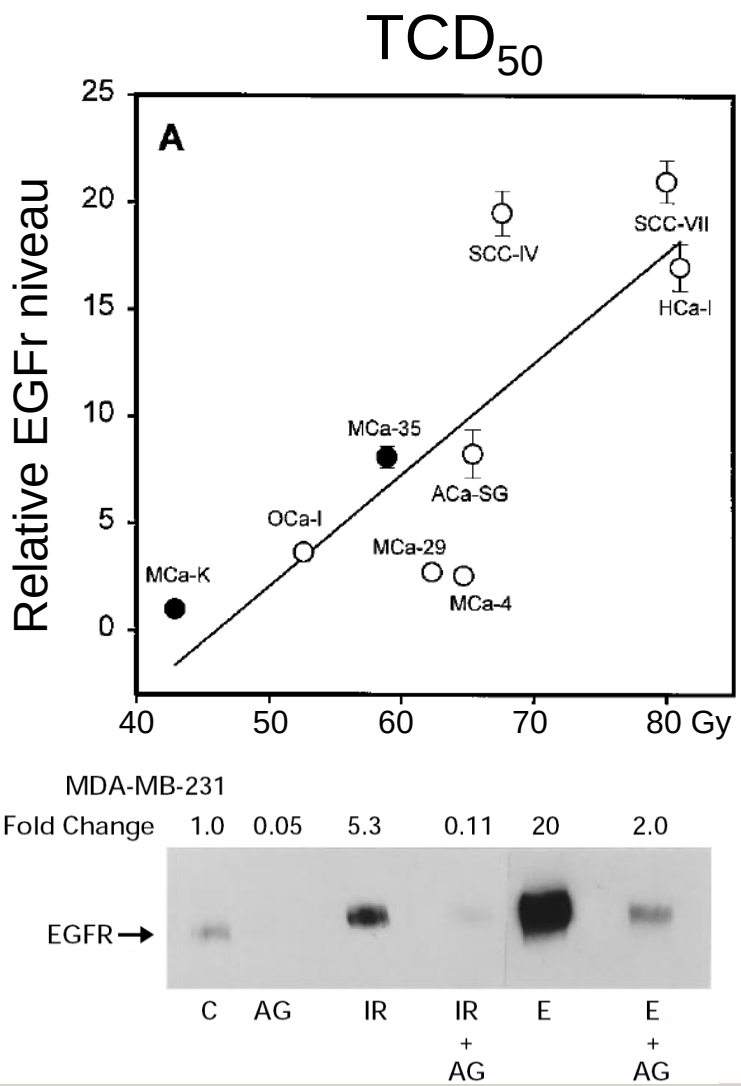
Epidermal Growth Factor Receptor

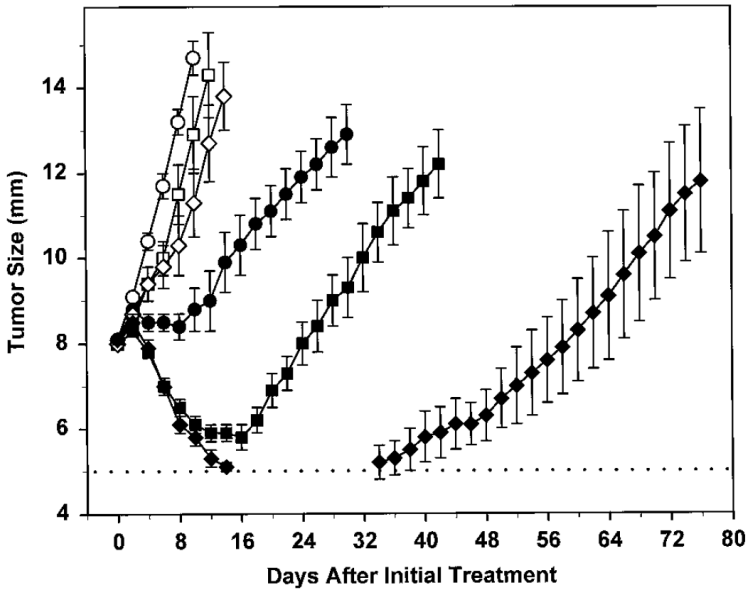


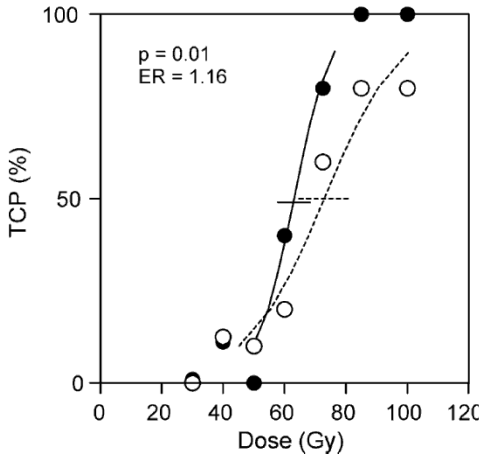
Harari PM 2006

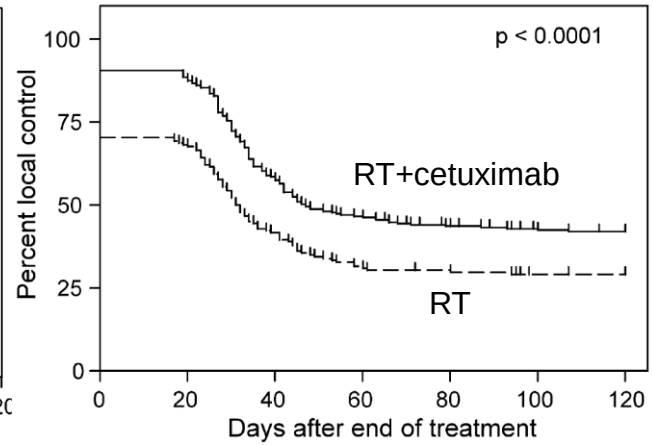
ESTRO School

Preclinical data





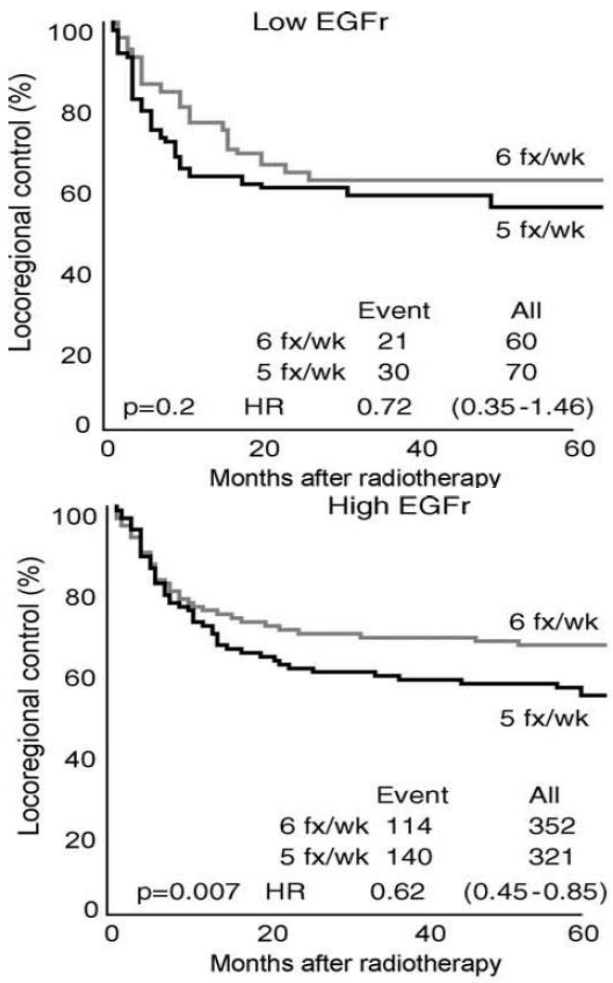


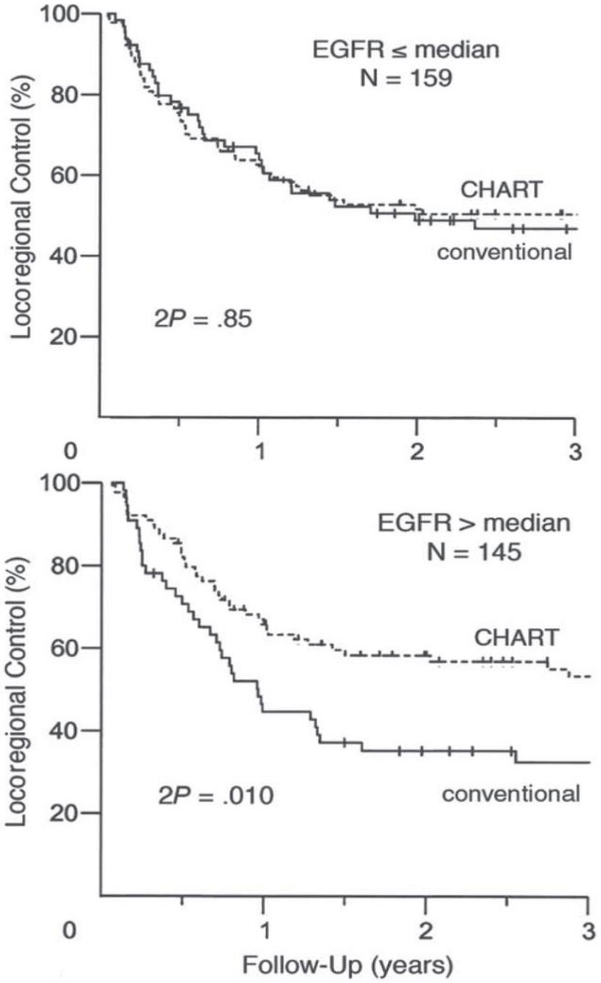


Akimoto T 1999;Schmidt-Ullrich 1997
Milas L 2000; Krause M 2005

ESTRO School

EGFR and accelerated repopulation





Eriksen JE 2005; Bentzen SM 2005;

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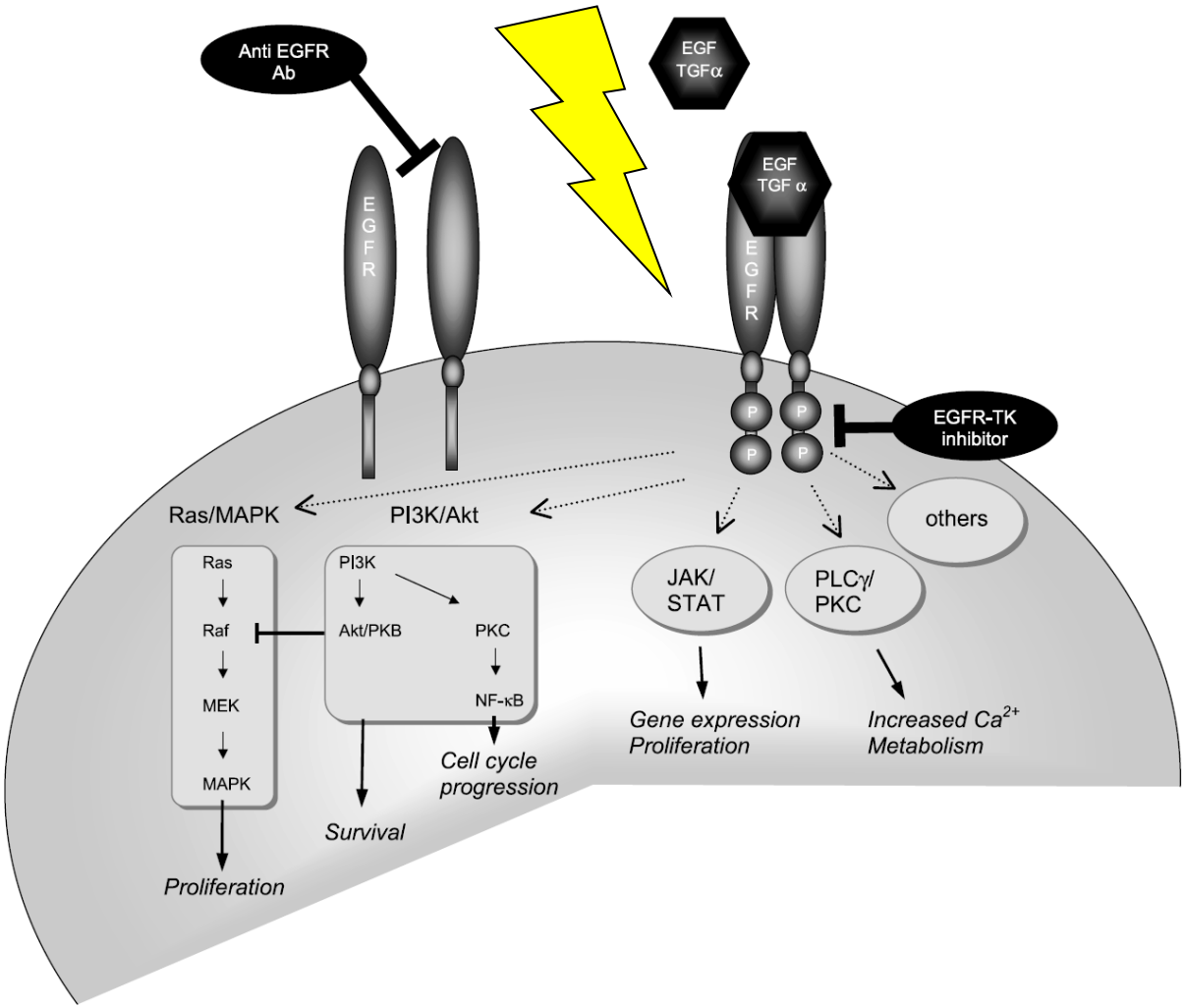
Synergy between EGFR and RT?



Baumann M 2004

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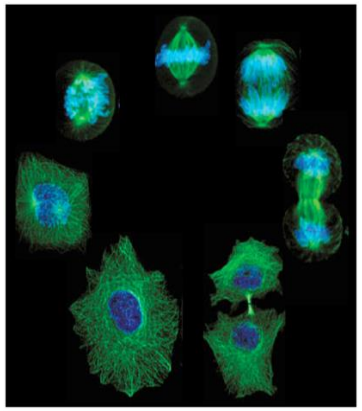
Antiproliferation

Ionising radiation → G2/M-stop

EGFR-I → G1-stop

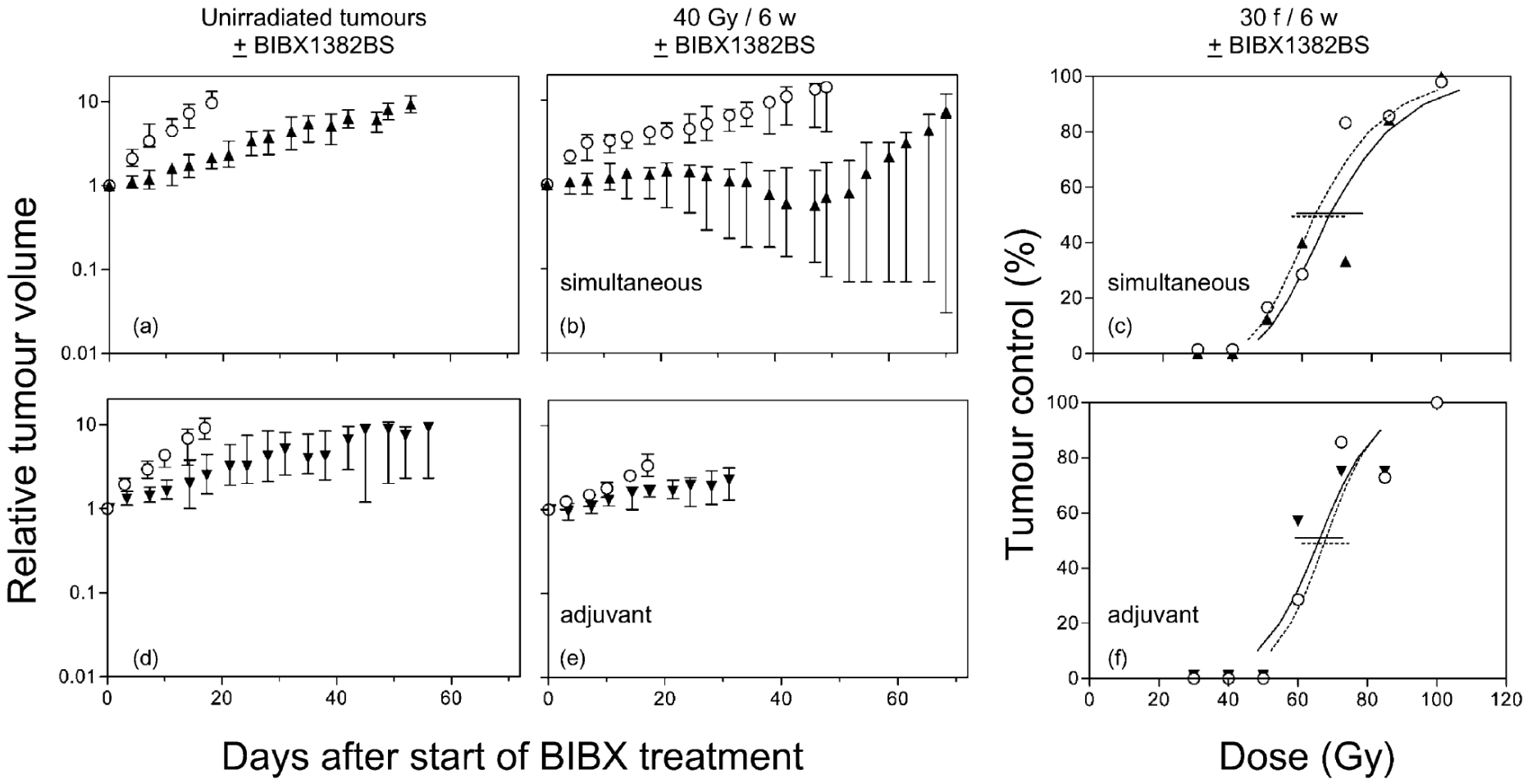
- Cell cycle checkpoint deregulation and apoptosis
- Fewer cells in the relatively radioresistent S-phase
- More cells in the relatively radiosensitive G1-phase



Huang SM 1999; Harari PM 2001;

Nyati MK 2004

Tumour volume vs. tumour control?



Baumann M 2004; Krause M 2009

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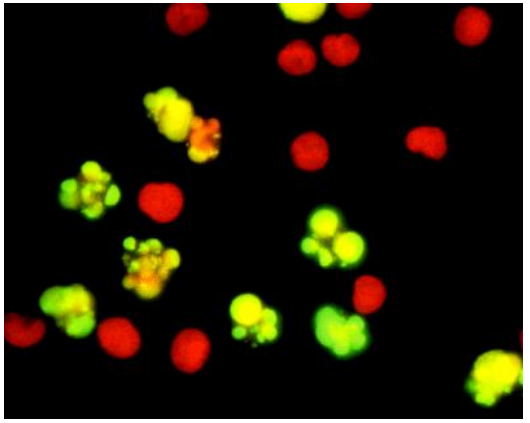
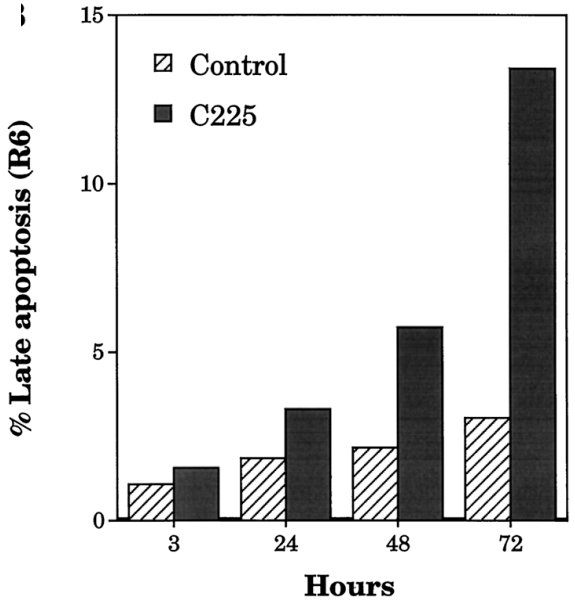
Apoptosis

- EGFr-I induce apoptosis (~ 2 fold)
- RT induce apoptosis (6 Gy – 2 fold)
- RT and EGFr-I induce (5-6 fold)



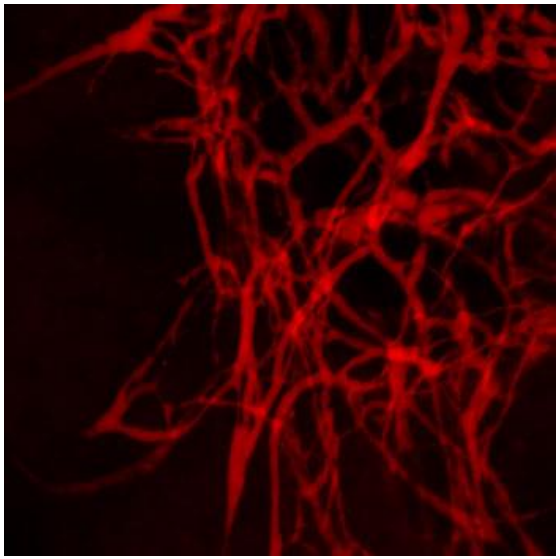


Huang SM 1999

Anti-angiogenesis

Ionising radiation → Increased VEGF

EGFr-I → Reduced VEGF



RT+EGFr-I

- Decreased vascular density
- More organised/better? flow
- Reoxygenation

Gorski DH 1999; Milas 2000; Krause M 2005

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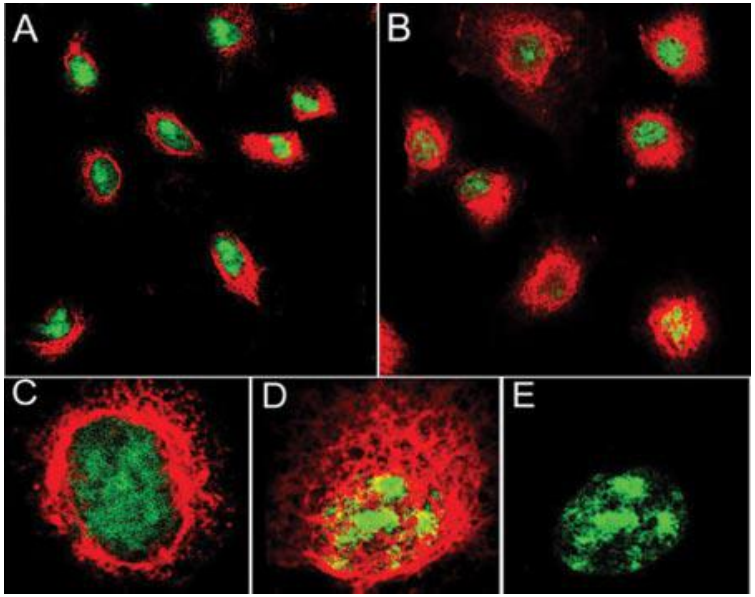
DNA repair

- RT-induced cell damage activate repair
  - Increased PI3-K and DNA-PK
  - EGFR enters nucleus bound to KU70/80 and increases DNA-DNA-PK complex and repair



- EGFR-I inhibits EGFR enucleation
- Interaction between EGFR-I bound to EGFR and DNA-PK increases sequestration of DNA-PK

Lieber 1999; Dittmann K 2000 etc..

Important to know biology for understanding the clinical reality

mTor inhibitors

EGFr inhibitors

HER2 inhibitors

Multikinase inhibitors

VEGF/r inhibitors

PARP inhibitors

PD1/PD-L1 inhibitors

BRAF inhibitors

What -so-ever inhibitors

MEK inhibitors

CTLA4 inhibitors

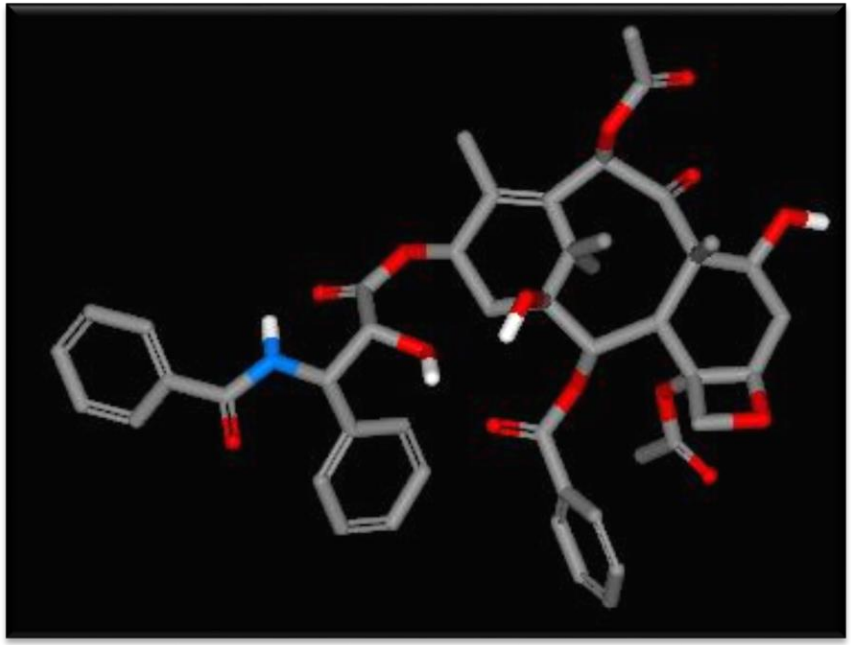
How do we target molecules?

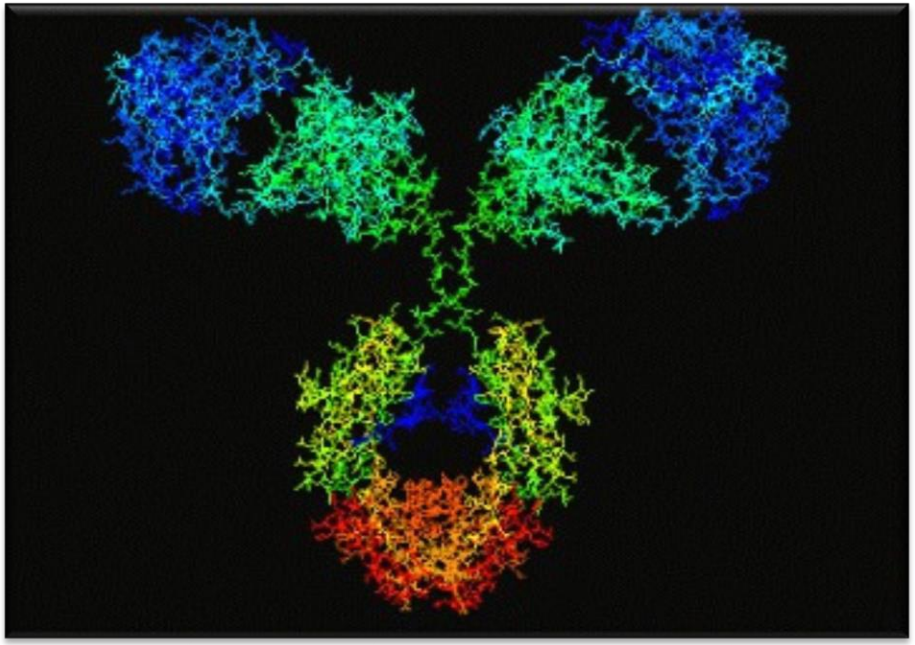
Martin Pruschy

Dept. of Radiation Oncology
University Hospital Zurich, Switzerland

martin.pruschy@usz.ch

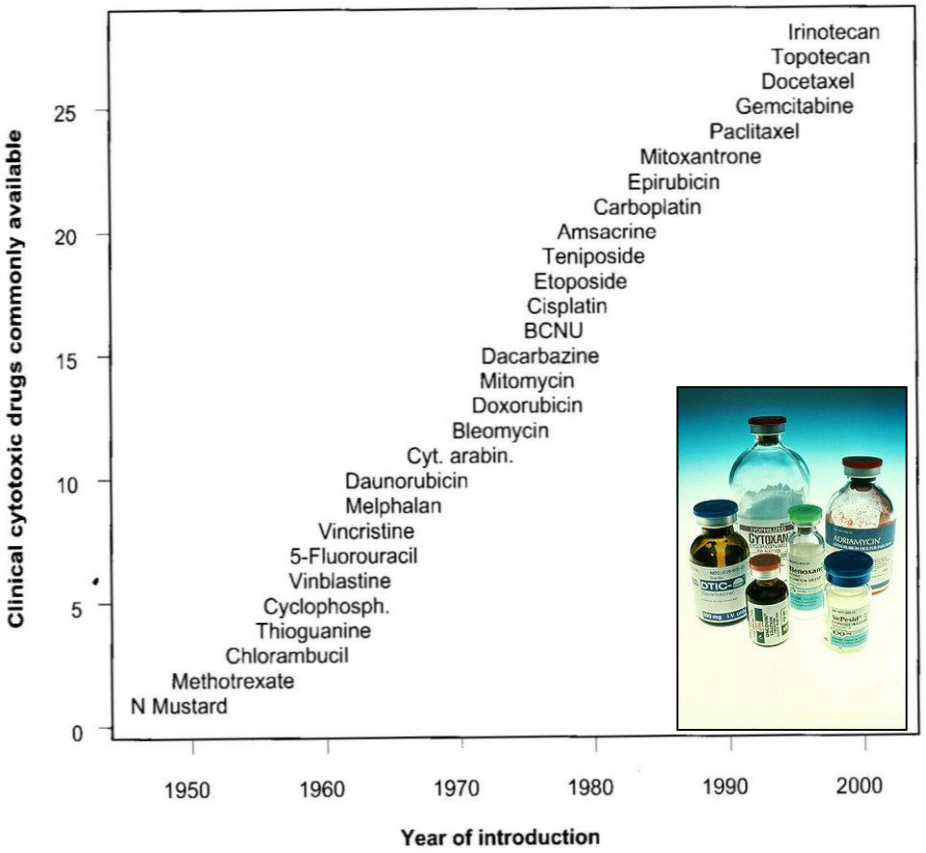
How do we target molecules ?



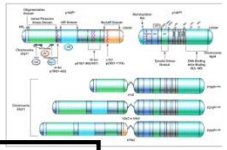


Overview

- Therapeutic Window and Oncogene Addiction
- Kinases as prototypes for targeted molecules
- Antibodies
- Small Molecular Compounds
- Resistance Mechanisms



2001



Classic Cytotoxic Agents

Molecular Targeting Agents
Anti-Signaling Agents

CML: chronic myelogenous leukemia

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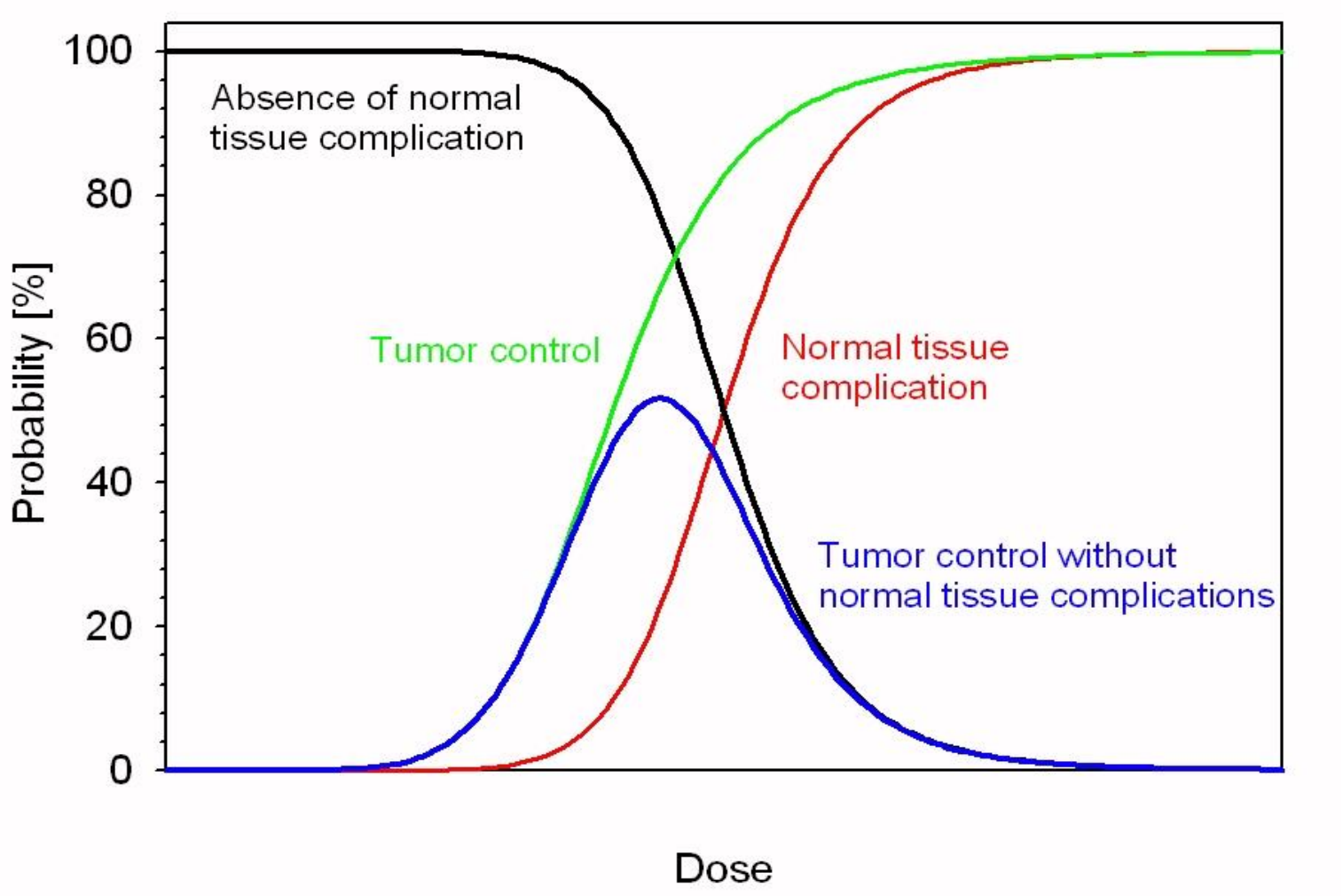
How do we target molecules ? antibodies and small molecules



The Therapeutic Window

Merck pipeline

Phase I

Tepotinib – c-Met kinase inhibitor
Solid tumors

M2698 – p70S6K & Akt inhibitor
Solid tumors

M3814 – DNA-PK inhibitor
Solid tumors

M9831 (VX-984) – DNA-PK inhibitor
Solid tumors

Beigene-283 – BRAF inhibitor
Solid tumors

M7583 – BTK inhibitor
Hematological malignancies

M66207[7] (VX-970) – ATR inhibitor
Solid tumors

M4344 (VX-803) – ATR inhibitor
Solid tumors

Avelumab – Anti-PD-L1 mAb
Solid tumors

Avelumab – Anti-PD-L1 mAb
Hematological malignancies

M9241 (NHS-IL12)
Cancer immunotherapy
Solid tumors

M7824 - Bifunctional immunotherapy
Solid tumors

M1095 (ALX-0761)
Anti-IL-17 A/F nanobody
Psoriasis

Phase II

Tepotinib
c-Met kinase inhibitor
Non-small cell lung cancer

Tepotinib
c-Met kinase inhibitor
Hepatocellular cancer

Avelumab – Anti-PD-L1 mAb
Merkel cell carcinoma 1L[1]

Sprifermin
Fibroblast growth factor 18
Osteoarthritis

Atacicept
Anti-Blys/anti-APRIL fusion protein
Systemic lupus erythematosus

M2951
BTK inhibitor
Rheumatoid arthritis

M2951
BTK inhibitor
Systemic lupus erythematosus

Abituzumab
anti-CD 51 mAb
Systemic sclerosis with interstitial lung disease

Phase III

Avelumab – Anti-PD-L1 mAb
Non-small cell lung cancer 1L[1]

Avelumab – Anti-PD-L1 mAb
Non-small cell lung cancer 2L[2]

Avelumab – Anti-PD-L1 mAb
Gastric cancer 1L[1]

Avelumab – Anti-PD-L1 mAb
Gastric cancer 3L[3]

Avelumab – Anti-PD-L1 mAb
Urothelial cancer 1L[1]

Avelumab – Anti-PD-L1 mAb
Ovarian cancer platinum resistant/refractory

Avelumab – Anti-PD-L1 mAb
Ovarian cancer 1L[1]

Avelumab - Anti-PD-L1 mAb
Renal cell cancer 1L[1]

Avelumab - Anti-PD-L1 mAb
Locally advanced head and neck cancer

MSB11022
Proposed biosimilar of Adalimumab
Chronic plaque psoriasis

Registration

Cladribine[4] Tablets –
Lymphocyte targeting agent
Relapsing-remitting multiple sclerosis

Avelumab[5] – Anti-PD-L1 mAb
Merkel cell carcinoma

Avelumab[6] – Anti-PD-L1 mAb
Urothelial cancer 2L[2]

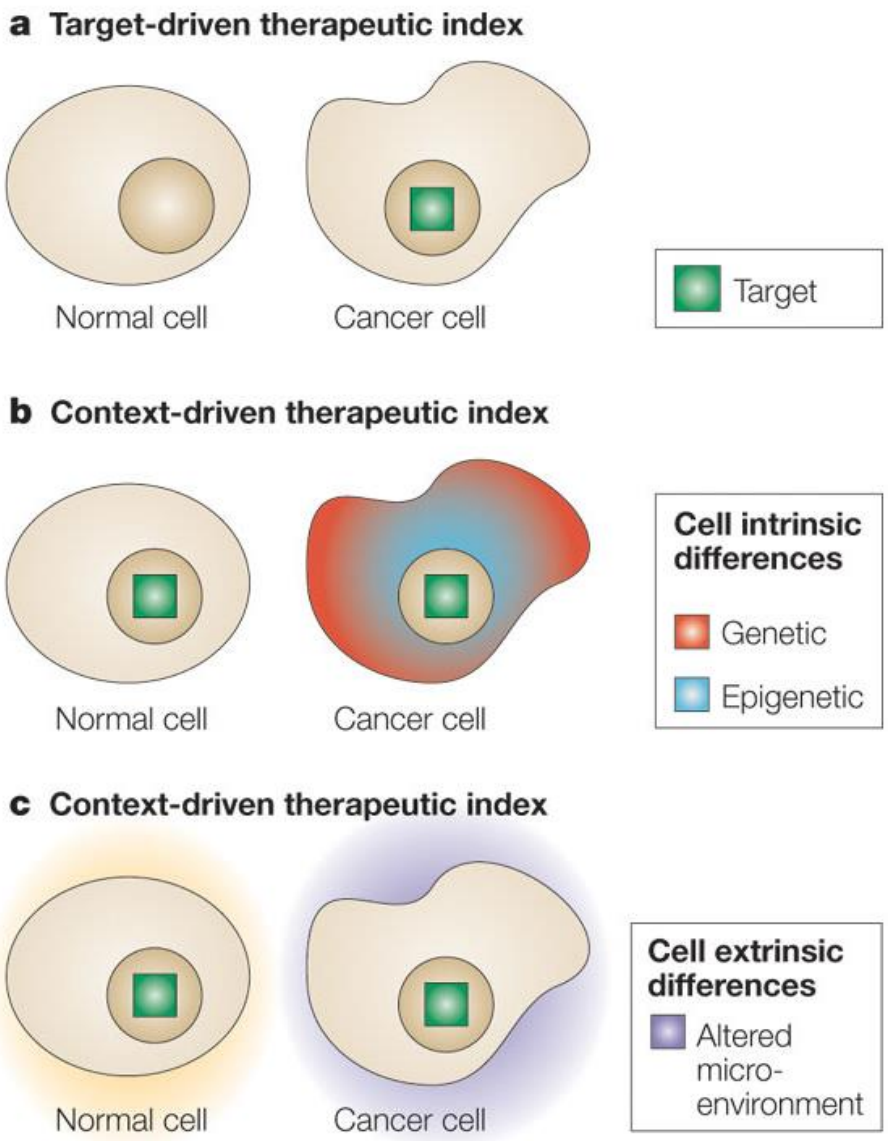
- Neurodegenerative Diseases
- Oncology
- Immunology
- Immuno-Oncology
- Biosimilars

Pipeline as of March 1st, 2017
Pipeline products are under clinical investigation and have not been proven to be safe and effective.
There is no guarantee any product will be approved in the sought-after indication.

[1] 1st line treatment; [2] 2nd line treatment; [3] 3rd line treatment; [4] European Medicines Agency (EMA) accepted Merck's Marketing Authorization Application (MAA) in July 2016;
[5] EMA accepted Merck's MMA in July 2016 and the US Food and Drug Administration (FDA) has accepted for Priority Review the Biologics License Application (BLA);
[6] FDA accepted for Priority Review the BLA; [7] Includes expansion cohorts in non small cell lung cancer, small cell lung cancer and triple negative breast cancer

MERCK

Increasing the Therapeutic Window: Exploiting Cancer Specific Features



e.g. BRAF in melanomas

e.g. cell cycle checkpoints corrupted in cancer cells; high rate of proliferation

e.g. tumor hypoxia

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Oncogene-Addiction: Achilles‘ Heel of the Tumor

- Plethora of genetic alterations in a tumor

though: dependence of a single pathway for its sustained proliferation and/or survival!

- trivial

though: inactivation of normal counterpart of such oncogenic proteins in normal tissues often tolerated

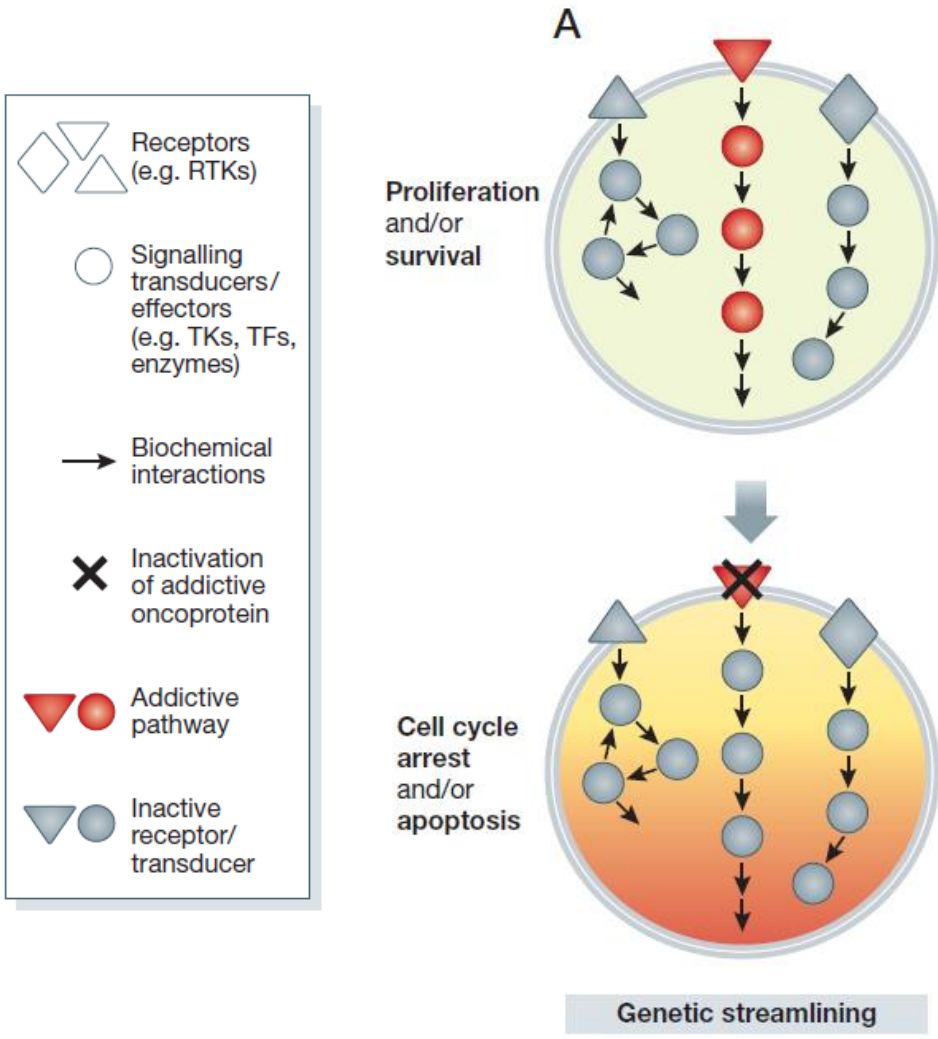
➢ basis for effective cancer therapeutic approach

Oncogene-Addiction: Achilles‘ Heel of the Tumor

		Oncogene addiction and oncogenic shock		
Oncogene	Cancer	Cell lines	Mouse models	Clinical (approved)
MYC	Lymphoma, leukemia	RI (Yokoyama and Imamato 1987; Loke et al. 1988)	IE (Felsher and Bishop 1999; Wu et al. 2007)	
RAS	Pancreatic, thyroid, colon, NSCLC	RI (Mukhopadhyay et al. 1991; Tokunaga et al. 2000) SMI (Kohl et al. 1994; Liu et al. 1998)	H-RAS (Chin et al. 1999); K-RAS (Fisher et al. 2001)	
HER2	Breast, ovarian, NSCLC	Ab (Hudziak et al. 1989) RI (Brysch et al. 1994; Colomer et al. 1994)	Ab (Shepard et al. 1991; Ohnishi et al. 1995; Tokuda et al. 1996) SMI (Xia et al. 2002; Rabindran et al. 2004; Wong et al. 2006)	**Trastuzumab/Herceptin** (*Breast cancer*); **Lapatinib/ Tykerb** (*Herceptin refractory breast cancer*)
BRAF	Melanoma, thyroid, colorectal	RI (Hingorani et al. 2003; Sumimoto et al. 2004) SMI (Karasarides et al. 2004)	SMI (Karasarides et al. 2004; Sharma et al. 2005)	**Sorafenib/Nexavar** (*Renal cell carcinoma*)
EGFR	NSCLC, glioblastoma, colon, pancreas	RI (Yamazaki et al. 1998; Halatsch et al. 2000; Sordella et al. 2004) Ab (Luwor et al. 2001)	SMI (Ji et al. 2006a,b; Politi et al. 2006) Ab (Luwor et al. 2001)	**Gefitinib/Iressa** (NSCLC); **Erlotinib/Tarceva** (*NSCLC, pancreatic cancer*); **Cetuximab/Erbitux** (*head and neck, colorectal cancer*); **Pantiumumab/ Vectibix** (*colorectal cancer*)
MET	Gastric, NSCLC	RI (Stabile et al. 2004; Ma et al. 2005) SMI (Sattler et al. 2003; Ma et al. 2005; Smolen et al. 2006)	RI (Stabile et al. 2004); SMI (Puri et al. 2007; Zou et al. 2007) Ab (Cao et al. 2001; Burgess et al. 2006)	
ABL	CML	SMI (Druker et al. 1996; Carroll et al. 1997; Deininger et al. 1997; Golas et al. 2003) RI (Smetsers et al.	RI (Skorski et al. 1994) SMI (Golas et al. 2003)	**Imatinib/Gleevec** (*Ph* CML; Ph* ALL*)

Oncogene Addiction: 2 models

a) genetic streamlining theory

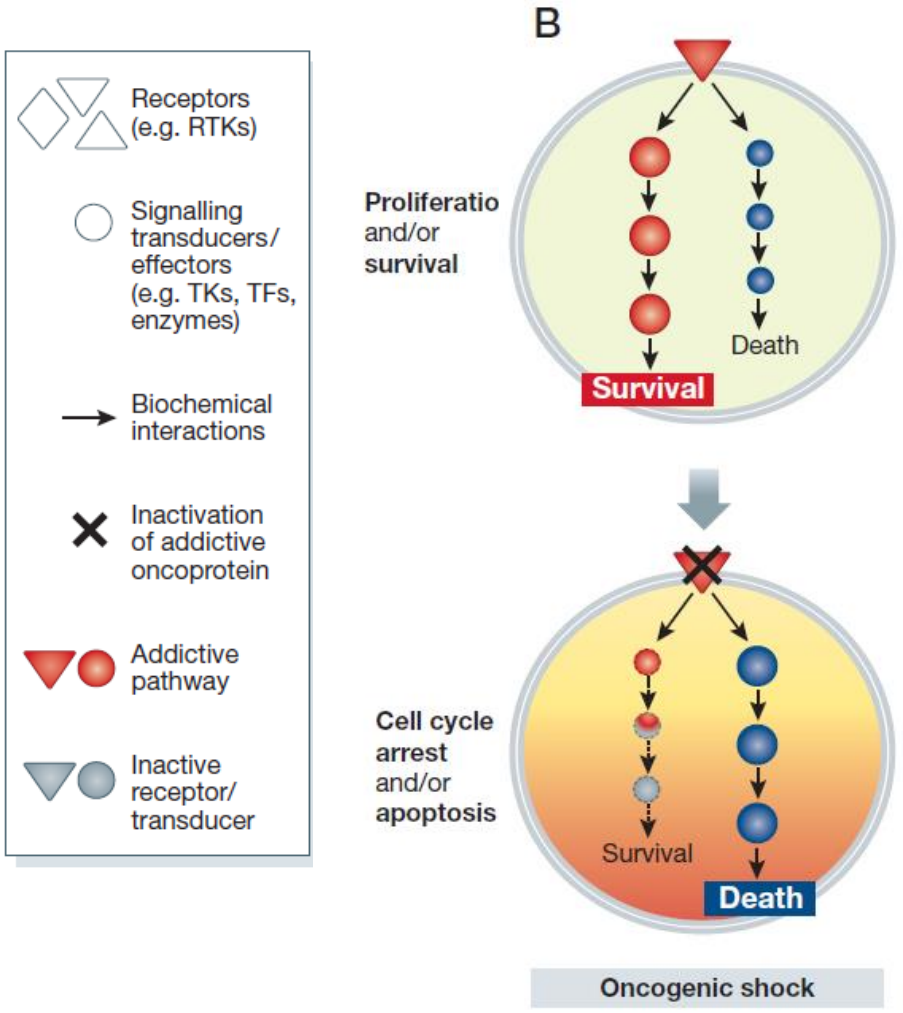


The 'genetic streamlining' theory postulates that non-essential pathways (top, light grey) are inactivated during tumour evolution, so that dominant, addictive pathways (red) are not surrogated by compensatory signals. Upon abrogation of dominant signals, there is a collapse in cellular fitness and cells experience cell-cycle arrest or apoptosis (bottom, red to yellow shading).

Torti and Trusolino, 2011

Oncogene Addiction: 2 models

b) oncogenic shock model



In the 'oncogenic shock' model, addictive oncoproteins (e.g. RTKs, red triangle) trigger at the same time pro-survival and pro-apoptotic signals (top, red and blue pathway, respectively). Under normal conditions, the pro-survival outputs dominate over the pro-apoptotic ones (top), but following blockade of the addictive receptor, the rapid decline in the activity of survival pathways (dashed lines, bottom) subverts this balance in favour of death-inducing signals, which tend to last longer and eventually lead to apoptotic death.

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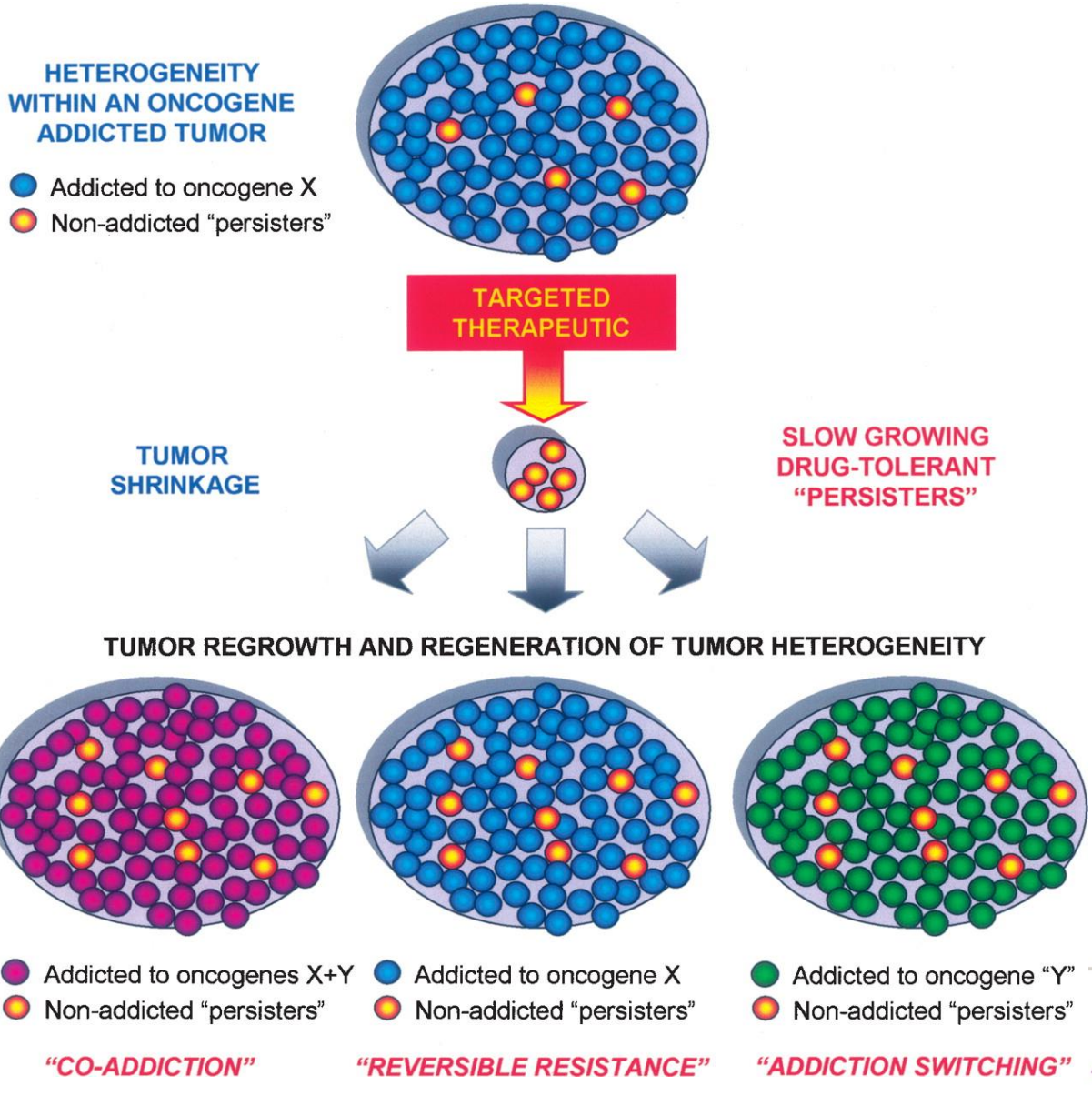
Heterogeneity of tumor cell dependency as the basis for resistance to therapeutics targeting



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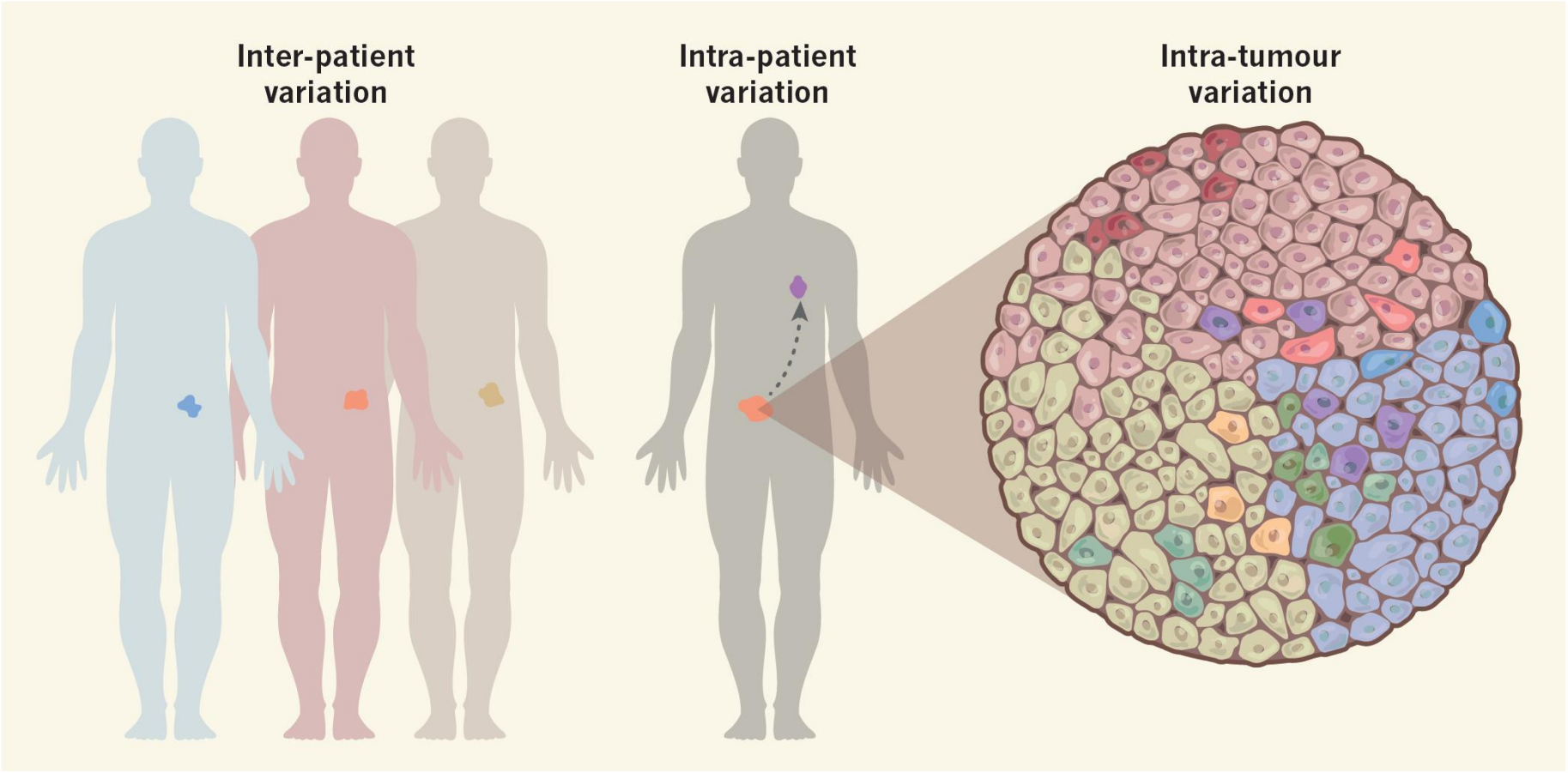
Inter- and intra-tumour heterogeneity



Nature 512:143-144, 2014

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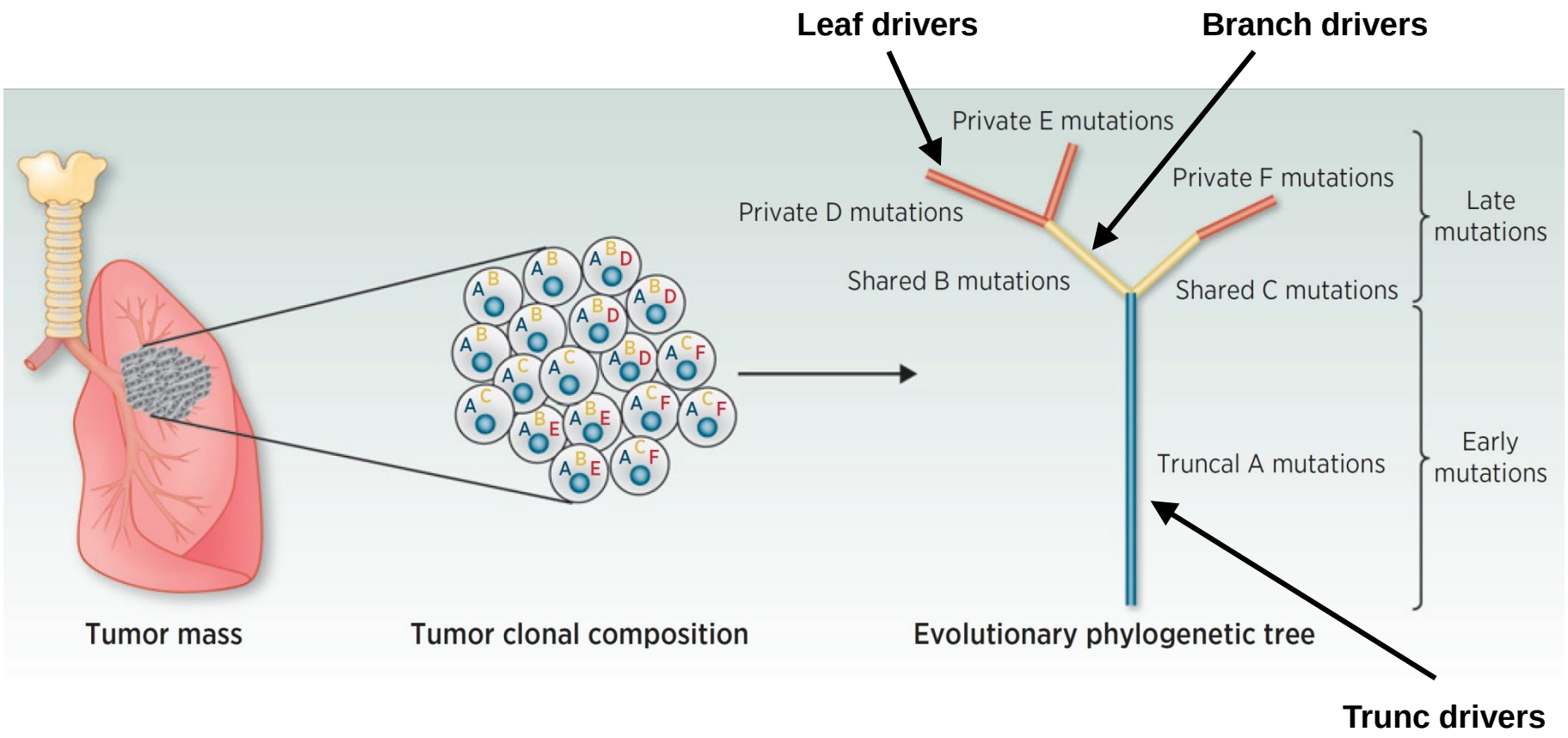
Intra-tumour heterogeneity



Clin Cancer Res 21:1258–66, 2015

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Relevant Questions::

Molecular evolution of resistance to treatment:

- Acquired during therapy?
- ➢ As a result of continuing mutagenesis?

- Already present in a clonal subpopulation within the tumours *prior* to the initiation of therapy?
- ➢ Is resistance therefore a fait accompli—the time to recurrence is simply the interval required for the subclone to repopulate the lesion.?
- ➢ Is the short time interval of recurrence due to the rapid expansion of the resistant subclone immediately following treatment initiation?
- ➢ Required:

Combination therapies targeting at least two different “processes” or “pathways”.

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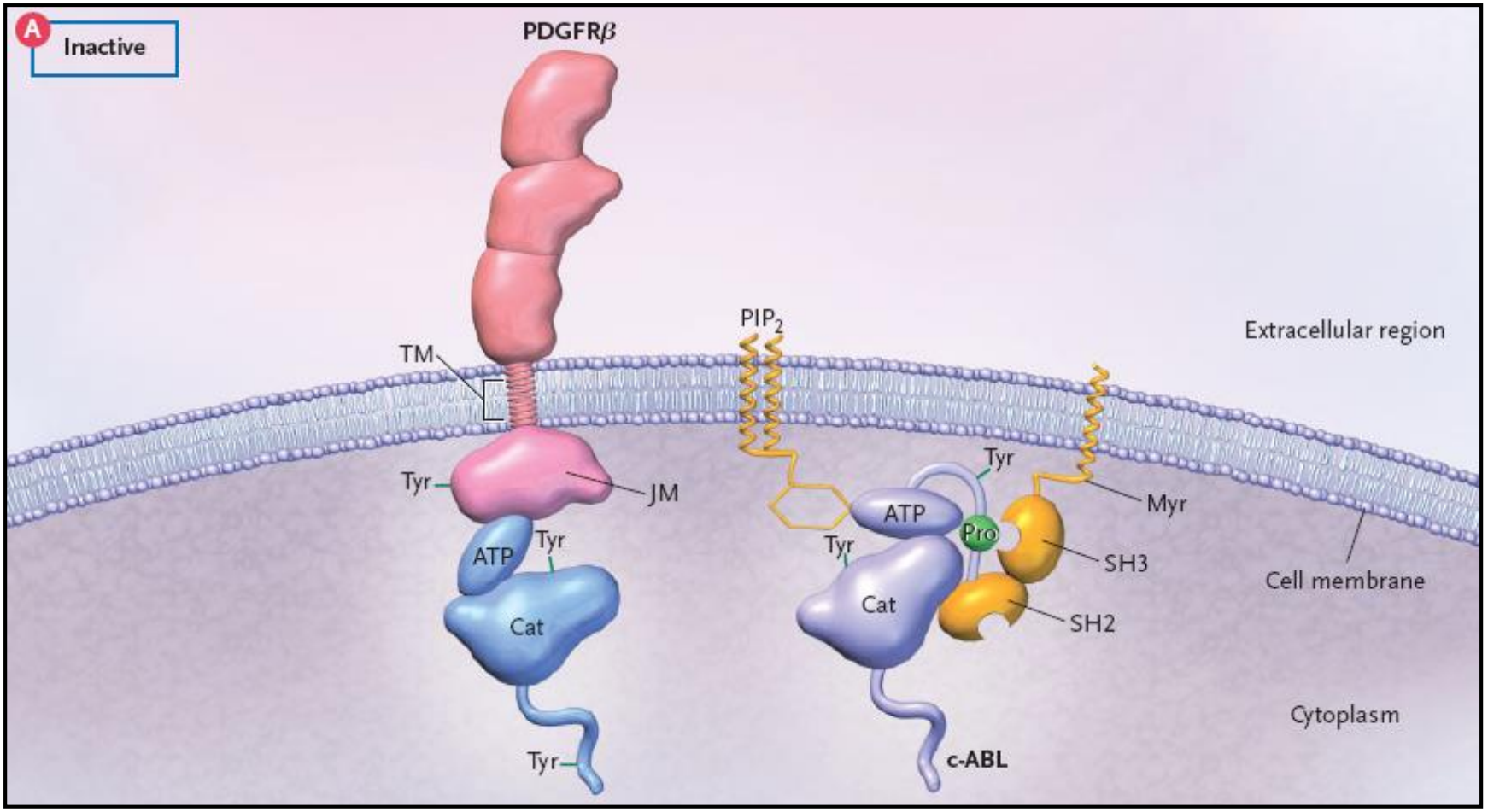
Kinases in Oncology

- Kinases are involved in processes leading to cell proliferation and survival

- Kinases are popular targets
  - virtually every signal transduction process is wired through phosphotransfer cascade
  - despite high degree of conservation highly specific agents can be developed
  - inhibition of kinase in normal tissue can often be tolerated (therapeutic window)
  - to date approx. 80 inhibitors advanced to some stage of clincial evaluation

Regulation of Normal Tyrosine Kinase Activity I



2 classes:

- Receptor tyrosine kinases
- Non-receptor tyrosine kinases

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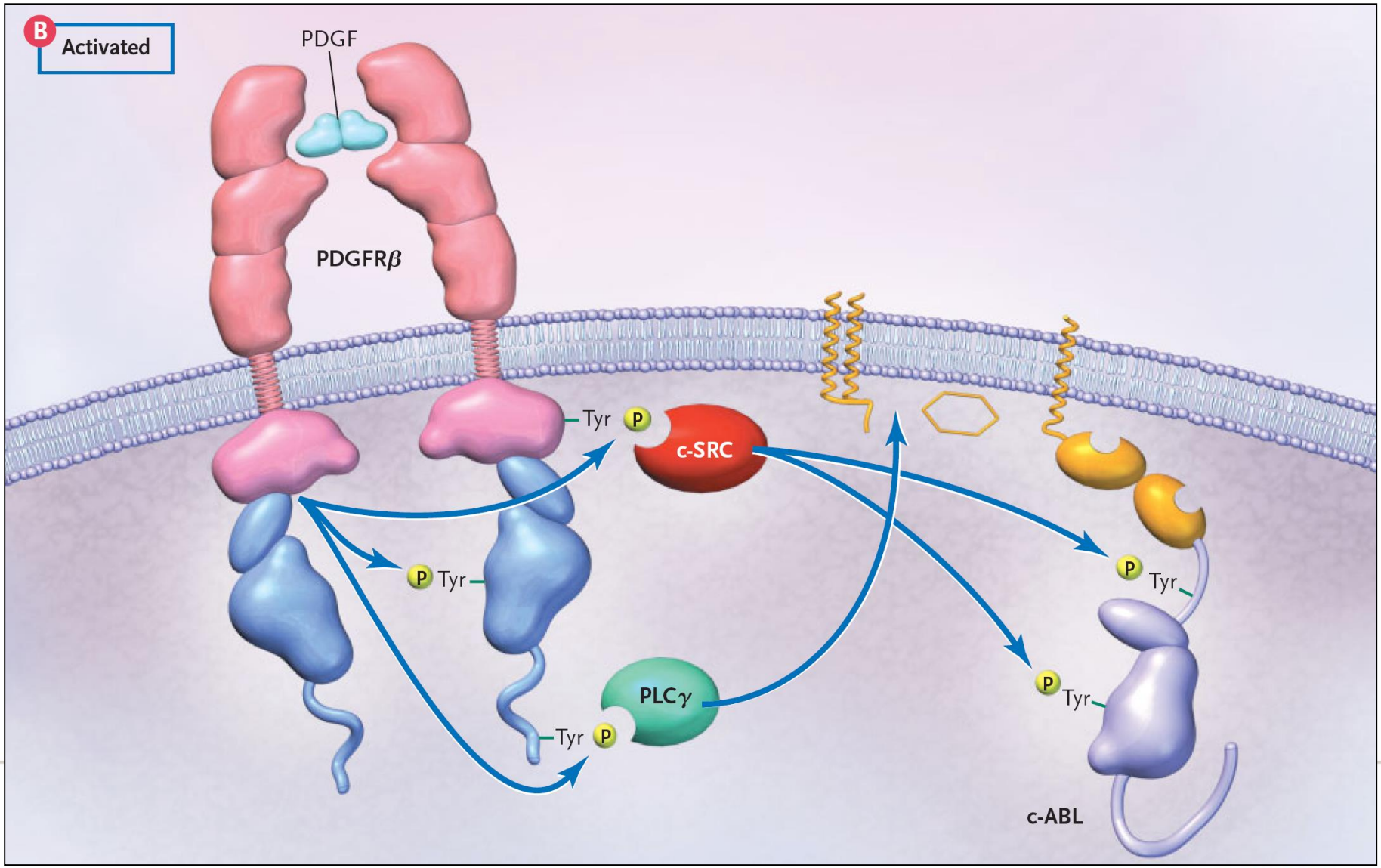
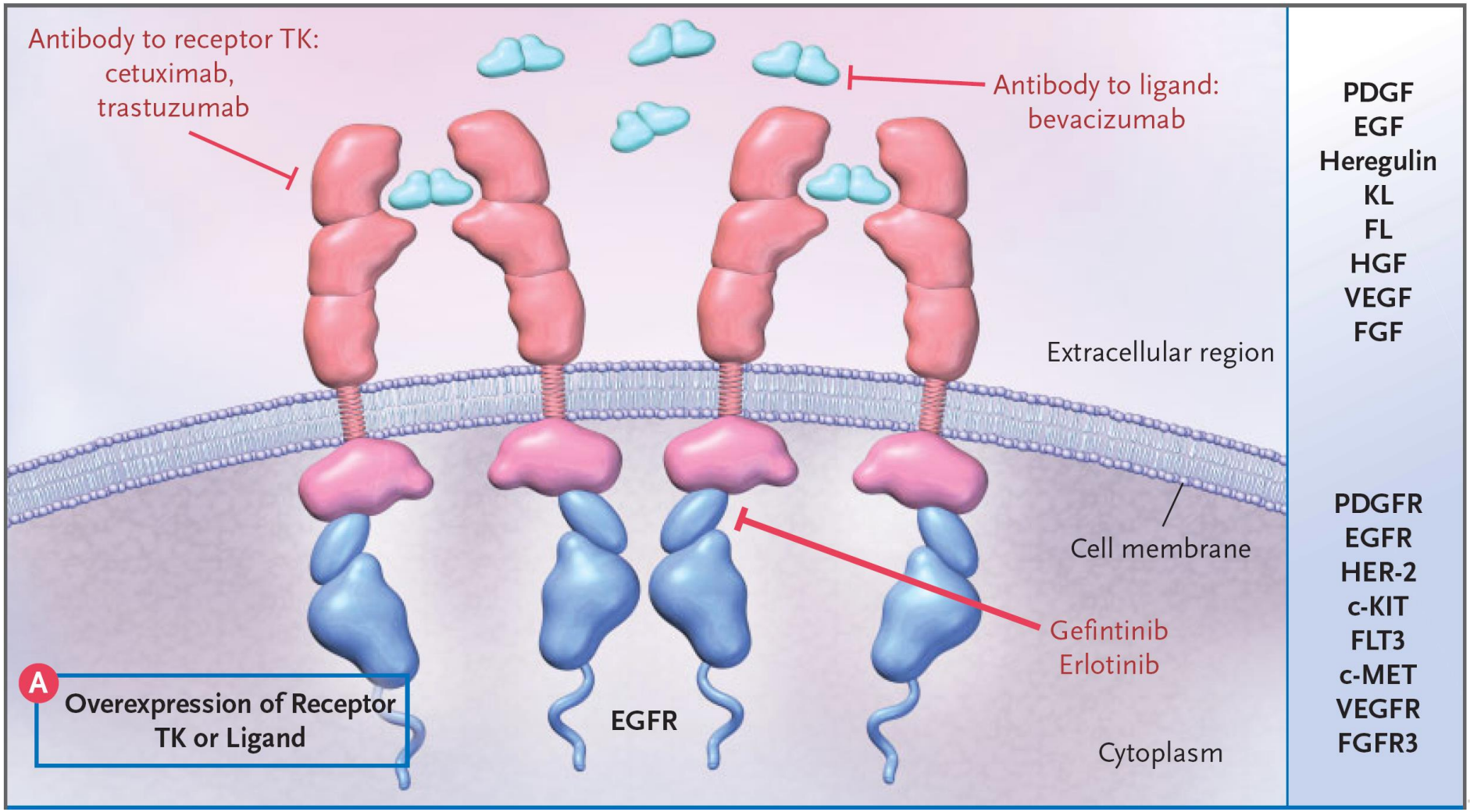
Regulation of Normal Tyrosine Kinase Activity II



Mechanisms of RTK Disregulation I



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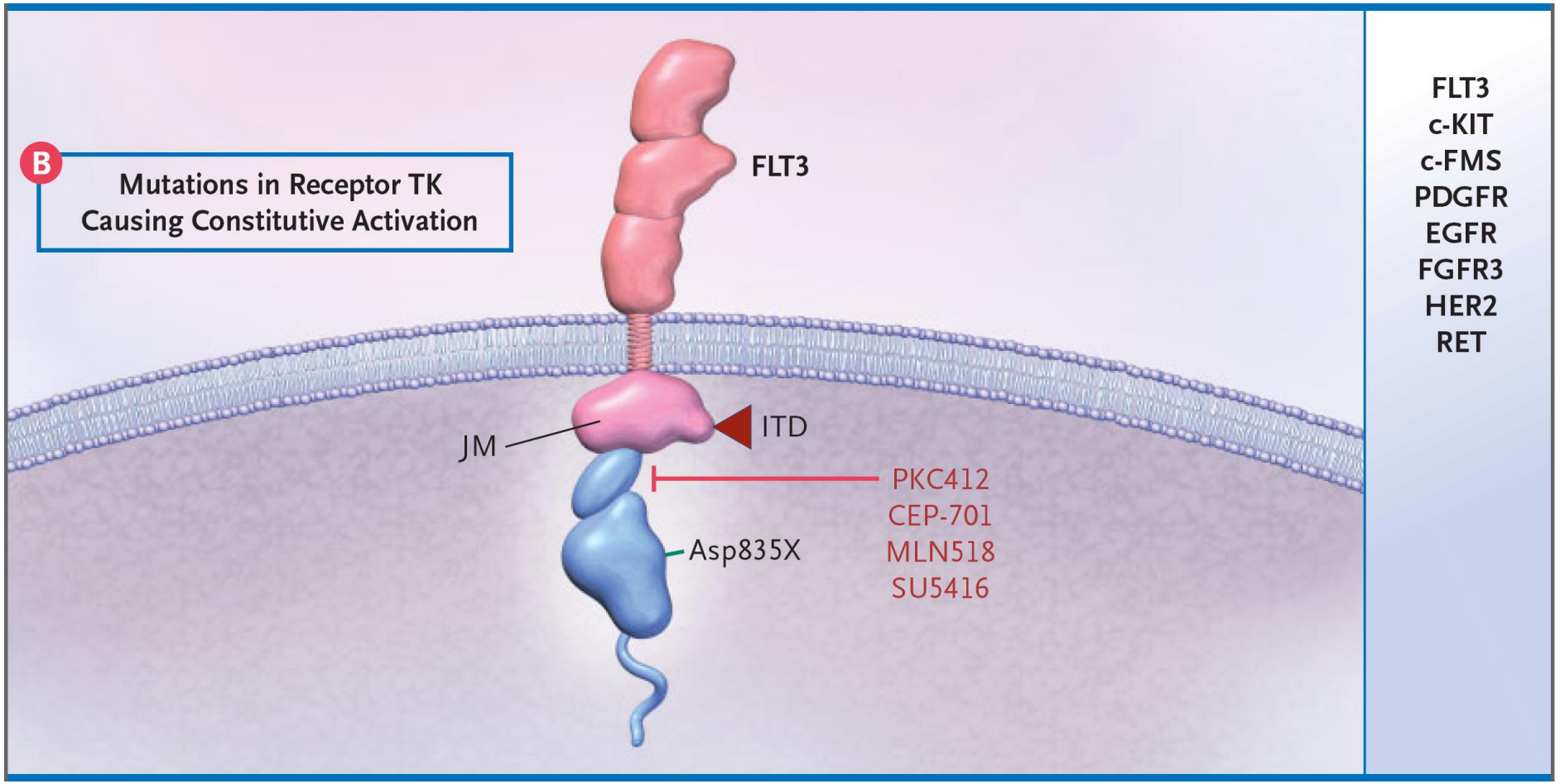
Mechanisms of RTK Disregulation II



Tyrosine kinase GF receptors altered in human tumors[a]

Name of receptor	Main ligand	Type of alteration	Types of tumor
EGF-R/ErbB1	EGF, TGF-α	overexpression	non-small cell lung cancer; breast, head and neck, stomach, colorectal, esophageal, prostate, bladder, renal, pancreatic, and ovarian carcinomas; glioblastoma
EGF-R/ErbB1		truncation of ectodomain	glioblastoma, lung and breast carcinomas
ErbB2/HER2/Neu	NRG, EGF	overexpression	30% of breast adenocarcinomas
ErbB3, 4	various	overexpression	oral squamous cell carcinoma
Flt-3	FL	tandem duplication	acute myelogenous leukemia
Kit	SCF	amino acid substitutions	gastrointestinal stromal tumor
Ret		fusion with other proteins, point mutations	papillary thyroid carcinomas, multiple endocrine neoplasias 2A and 2B
FGF-R3	FGF	overexpression; amino acid substitutions	multiple myeloma, bladder and cervical carcinomas

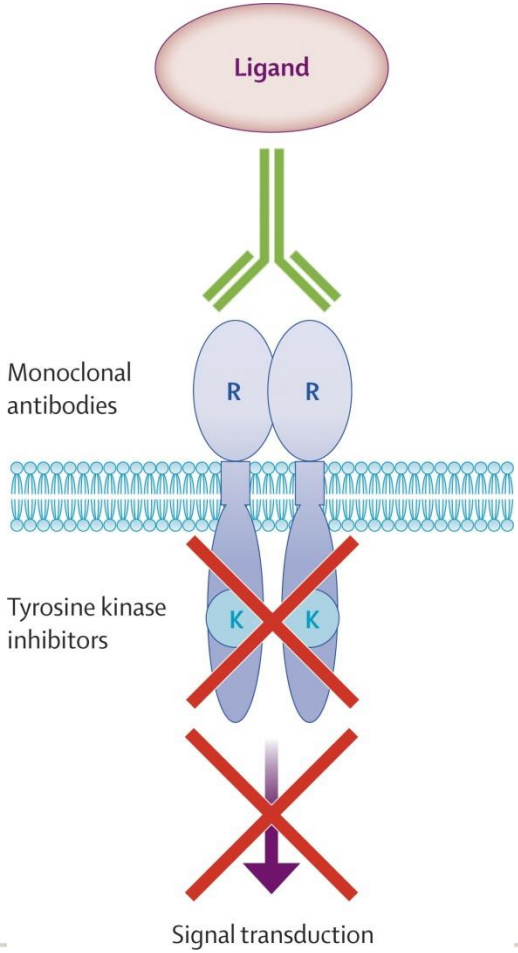
Examples of human tumors making autocrine growth factors

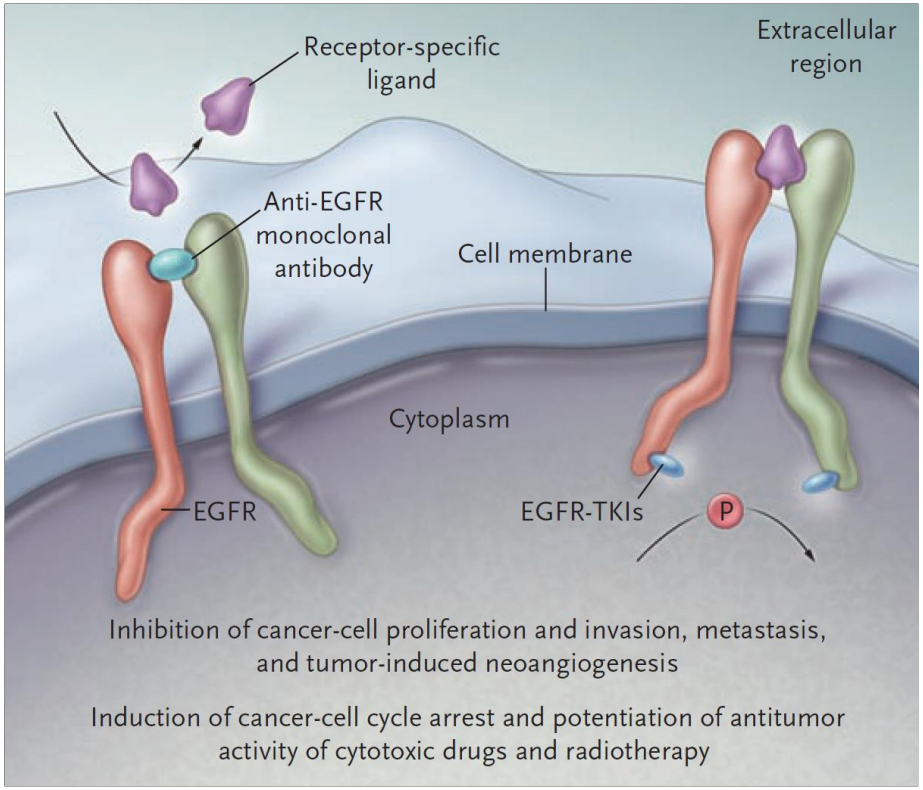
Ligand	Receptor	Tumor type(s)
HGF	Met	miscellaneous endocrinal tumors, invasive breast and lung cancers, osteosarcoma
IGF-2	IGF-1R	colorectal
IL-6	IL-6R	myeloma, HNSCC
IL-8	IL-8R A	bladder cancer
NRG	ErbB2[a]/ErbB3	ovarian carcinoma
PDGF-BB	PDGF-Rα/β	osteosarcoma, glioma
PDGF-C	PDGF-α/β	Ewing's sarcoma
PRL	PRL-R	breast carcinoma
SCF	Kit	Ewing's sarcoma, SCLC
VEGF-A	VEGF-R (Flt-1)	neuroblastoma, prostate cancer, Kaposi's sarcoma
TGF-α	EGF-R	squamous cell lung, breast and prostate adenocarcinoma, pancreatic, mesothelioma
GRP	GRP-R	small-cell lung cancer

[a]Also known as HER2 or Neu receptor.

How do we target key structures?

Monoclonal antibodies





Small molecules
(e.g. tyrosine kinase inhibitors)

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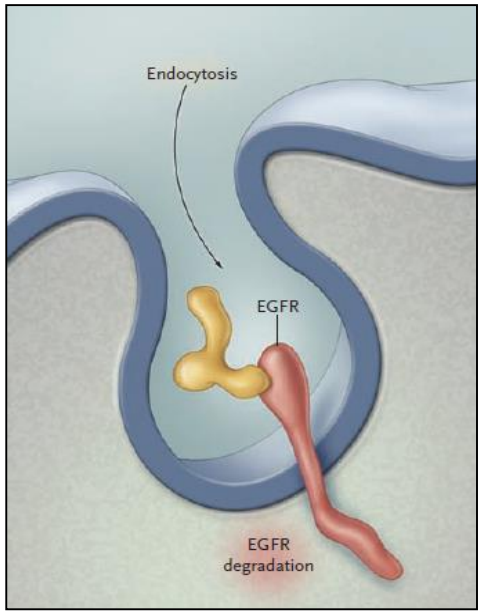
Mechanisms of mAB Action

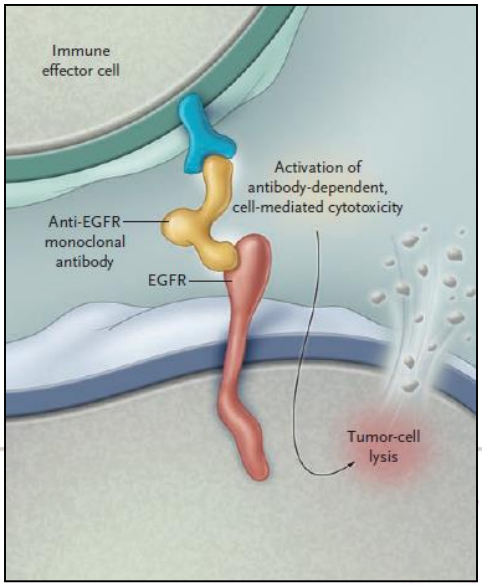
Interaction with immune system
- Antibody-dependent cellular cytotoxicity*
- Complement-dependent cytotoxicity

Delivery of cytotoxic payloads
- Radioisotops
- Toxins

*Combined mechanism of action

Signal transduction changes
- Ligand-receptor interaction*
- Receptor internalization*
- Clearance of ligand





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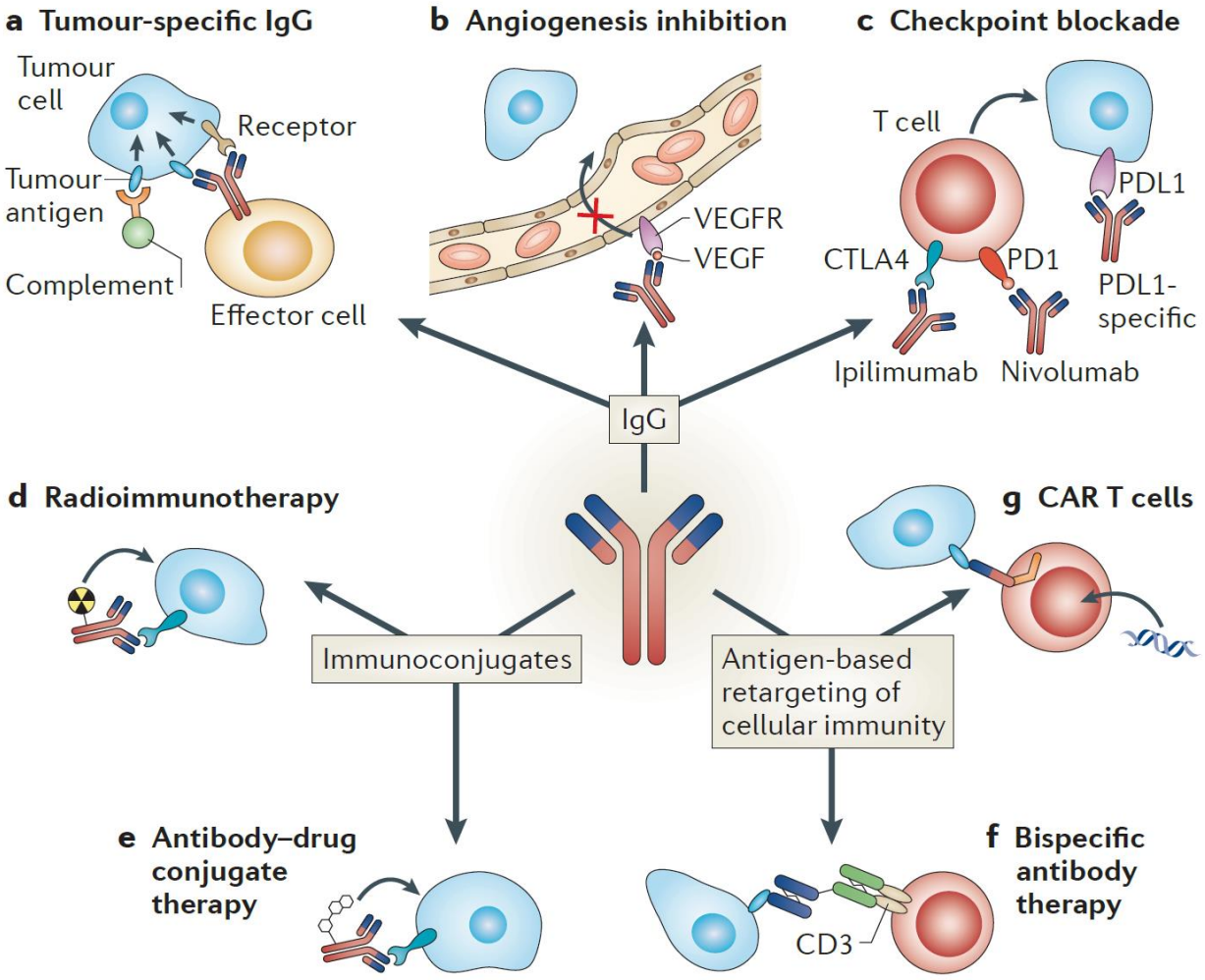
Antibody as anticancer drug candidate



- tumor-associated blood vessels
- chemokines; cytokines
- soluble growth factors
- diffuse malignant cells
- tumor cells within solid tumor
- tumor-associated stroma
- elements of immune response

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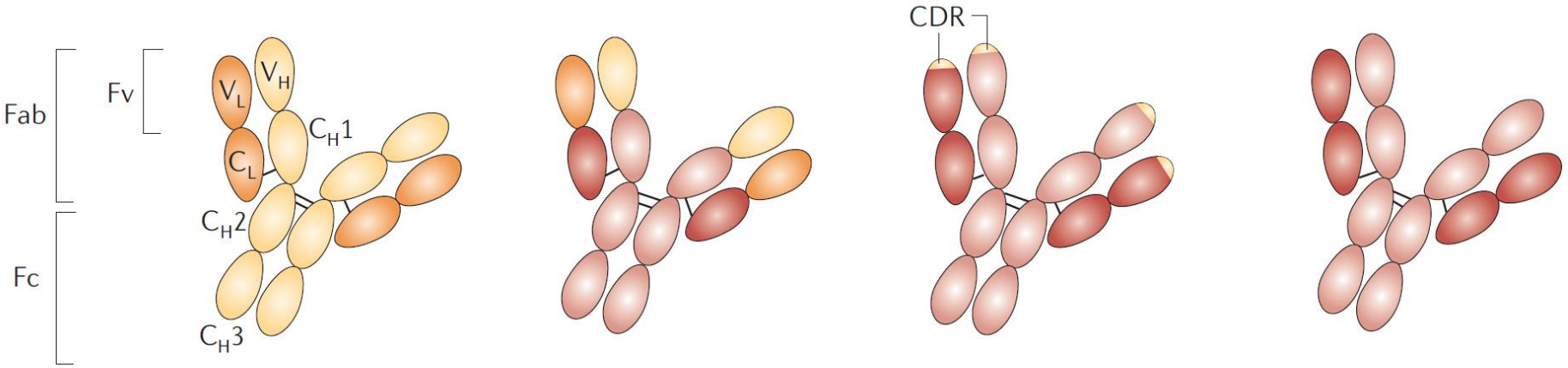
Generation of Chimeric (Humanized) Antibodies



Type of mAb	Murine	Chimeric	Humanized	Human
	Ibritumomab tiuxetan (CD20); IgG1κ*	Cetuximab (EGFR); IgG1κ	Trastuzumab (ERBB2); IgG1κ	Panitumumab (EGFR); IgG2
	Tositumomab-I^{131} (CD20); IgG2aλ*	Rituximab (CD20); IgG1κ	Bevacizumab (VEGF); IgG1	
			Alemtuzumab (CD52); IgG1κ	
			Gemtuzumab ozogamicin (CD33); IgG4κ*	

Reduction of Immunogenicity

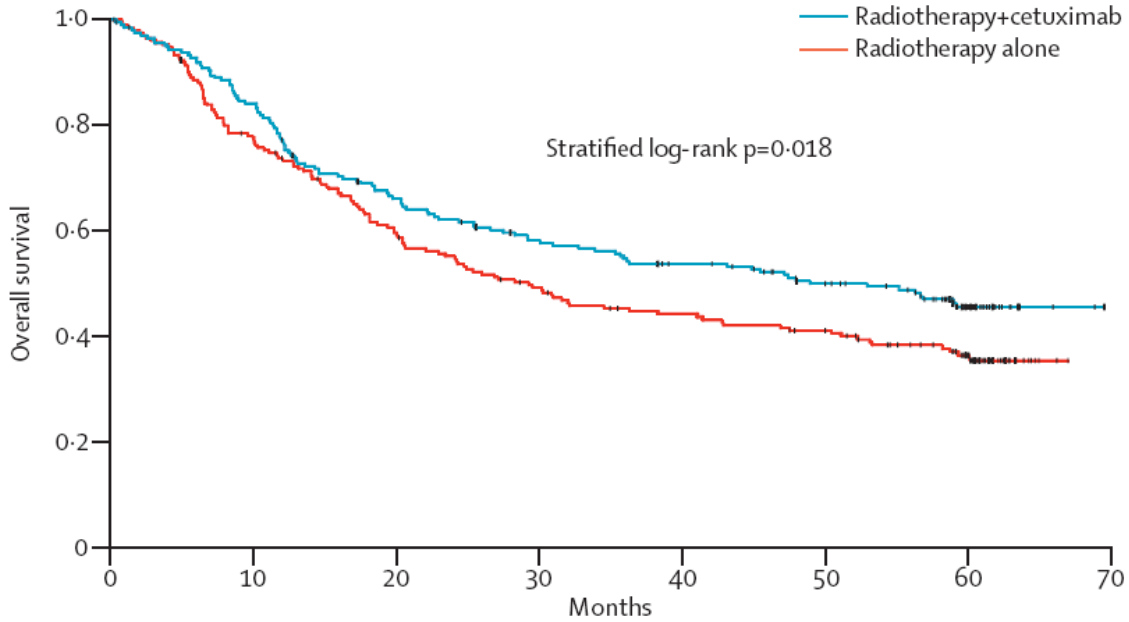
Radiotherapy ± EGFR-I: Prototype of monoclonal antibody

Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival

James A Bonner, Paul M Harari, Jordi Giralt, Roger B Cohen, Christopher U Jones, Ranjan K Sur, David Raben, Jose Baselga, Sharon A Spencer, Junming Zhu, Hagop Youssoufian, Eric K Rowinsky, K Kian Ang

www.thelancet.com/oncology Vol 11 January 2010

Bonner et al.,NEJM; 354; 567ff, 2006



Number at risk								
Radiotherapy+ cetuximab	211	177	136	117	105	90	49	..
Radiotherapy alone	213	162	122	98	85	77	49	..

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EGFR overexpression in human tumors

Tumors showing high EGFR expression

NSCLC	40-80%
Prostate	40-80%
Gastric	33-74%
Breast	14-91%
Colorectal	25-77%
Pancreatic	30-50%
Ovarian	35-70%
Bladder	31-48%
Renal cell	50-90%
H&N	80-100%
Glioma	40-63%
Esophageal	43-89%

High expression generally associated with

- Invasion
- Metastasis
- Late-stage disease

- Chemo-/Radiotherapy resistance
- Poor outcome

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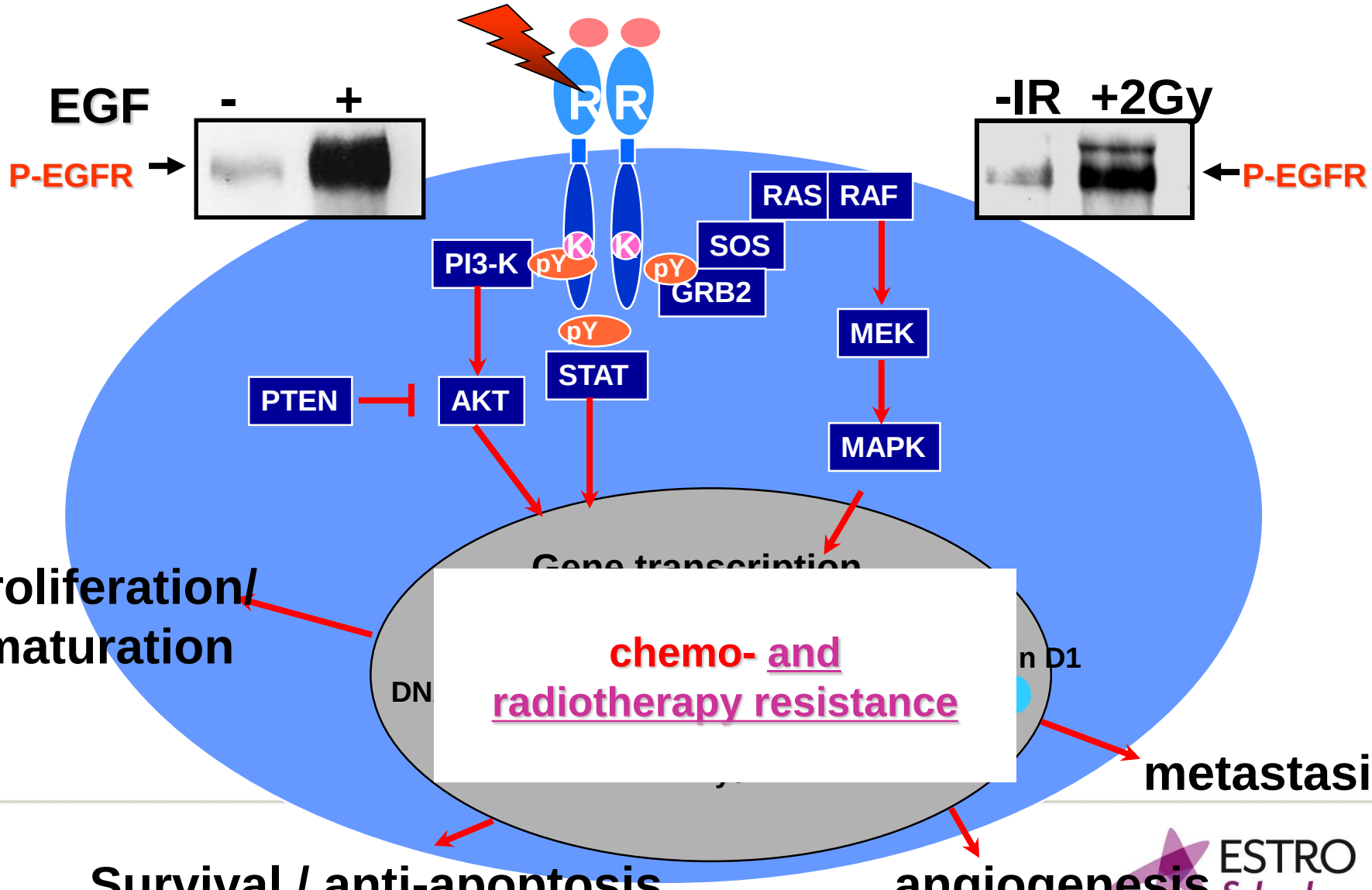
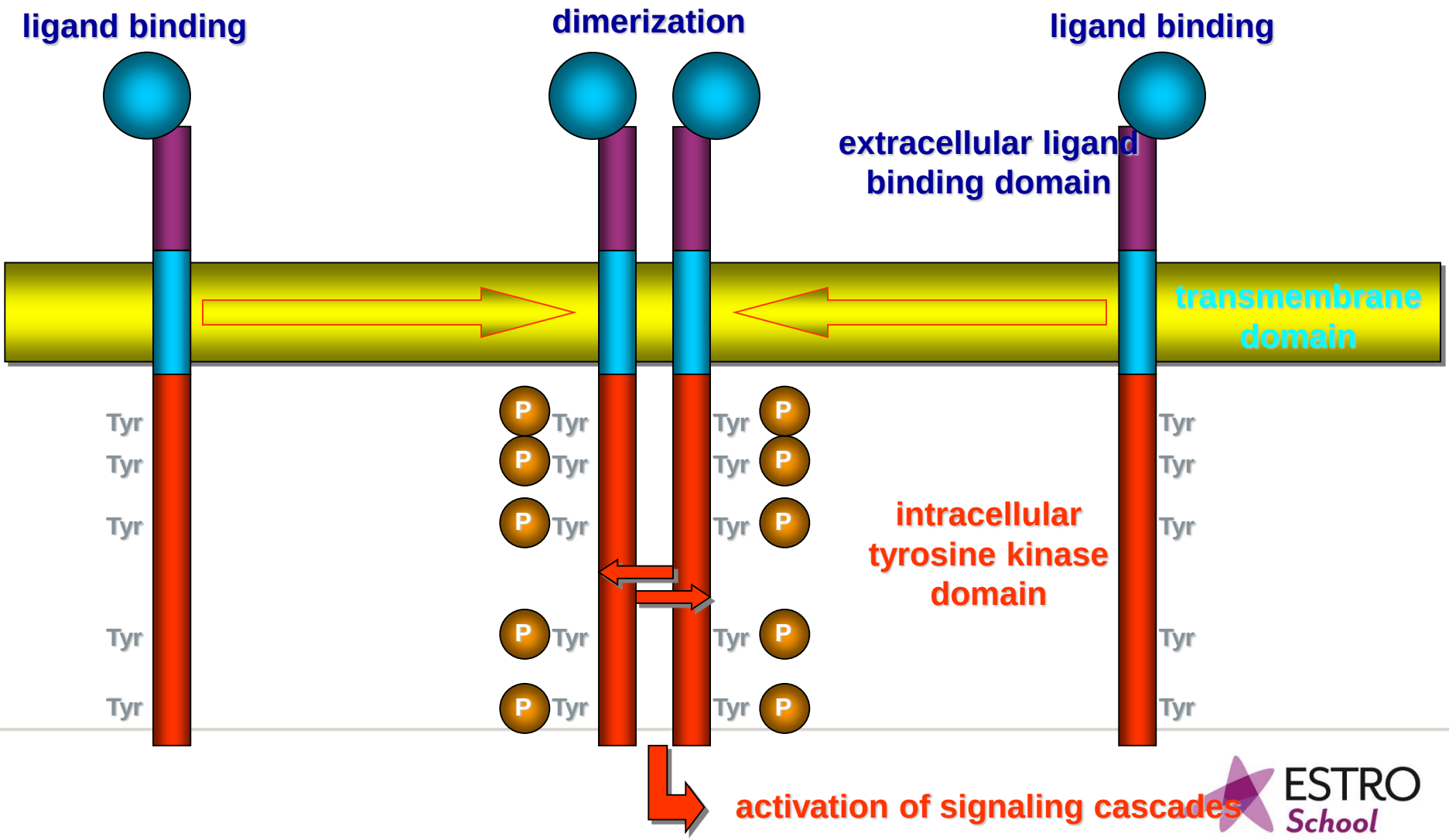
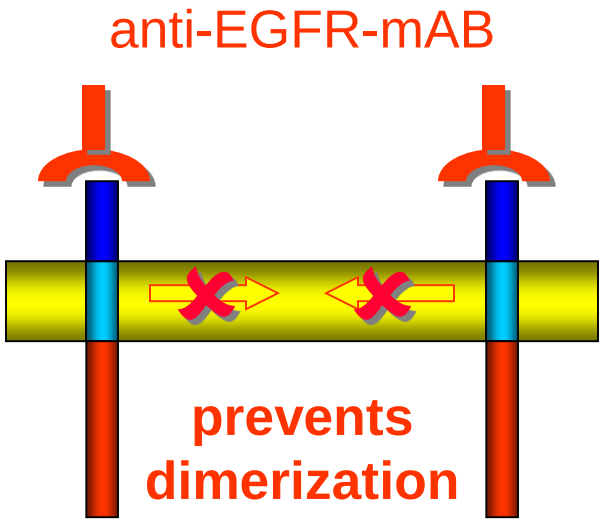
EGFR as an example



Activation of signaling cascade



C225 should prevent EGFR-signaling



DNA-repair (NHEJ, BER)

PI3K-AKT survival pathway

JAK-STAT pathway regulating gene transcription

Pro-proliferative RAS-MAPK pathway

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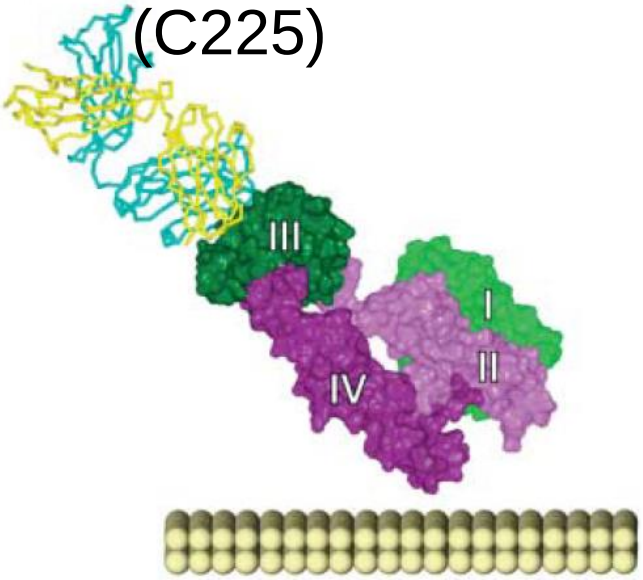
DIFFERENT BINDING SITES – DIFFERENT MECHANISMS

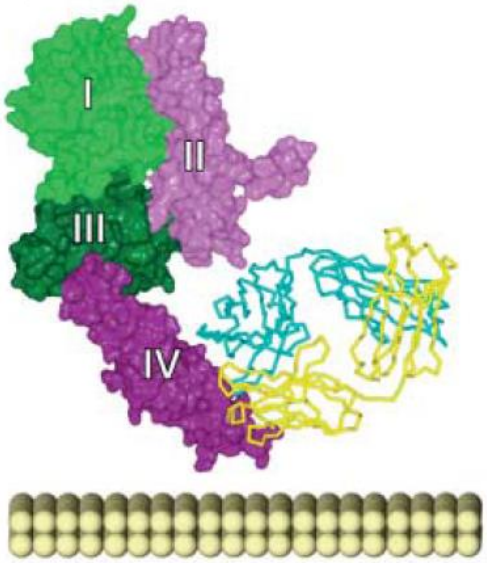
EXTRACELLULAR DOMAIN OF PROTEIN AS TARGET STRUCTURES!

Cetuximab (C225)



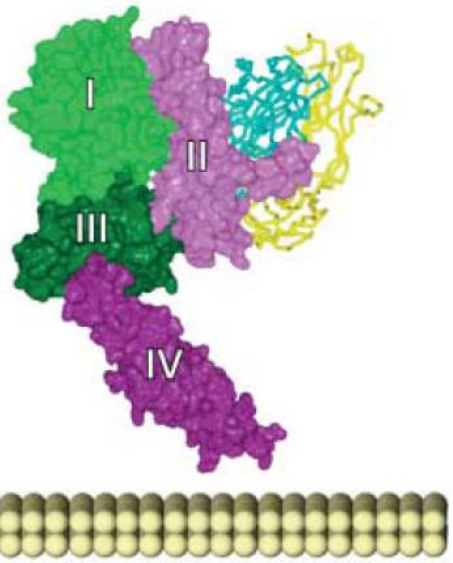
Competition to EGF-binding
Inhibition of Dimerization

Trastuzumab



Stimulation of endocytosis

Pertuzumab

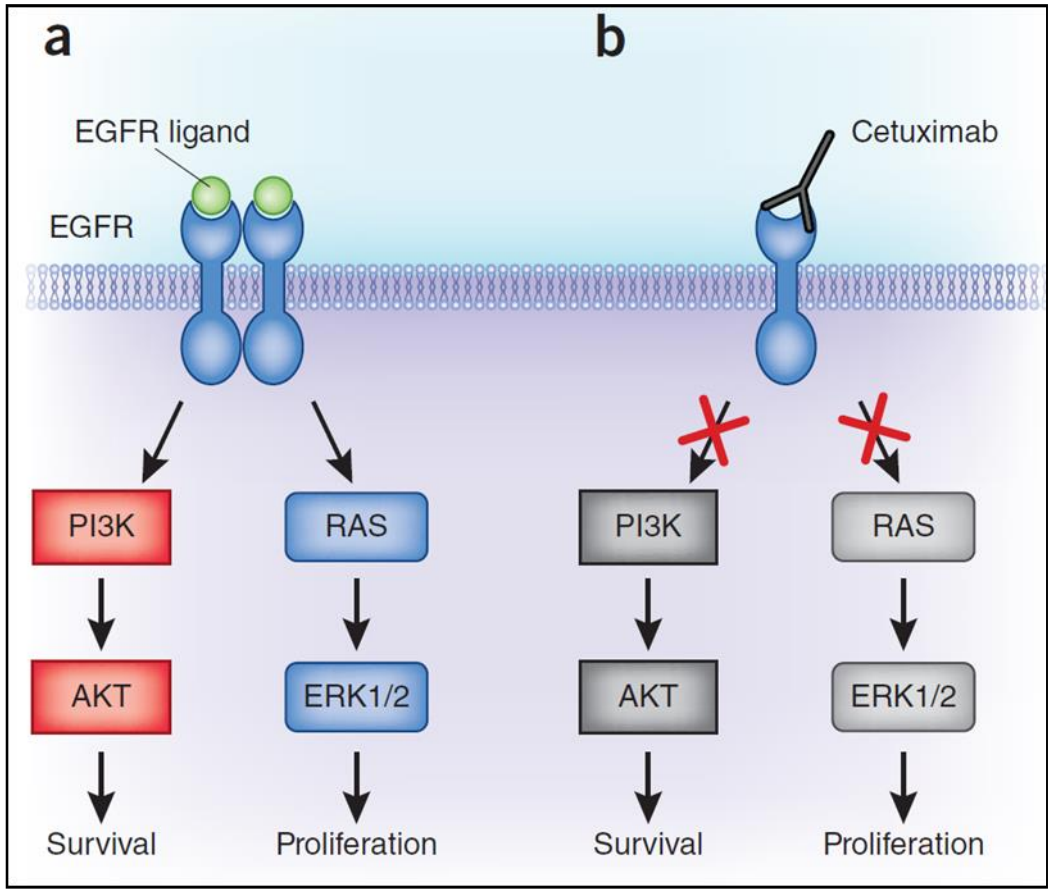


No heterodimerization

Multiple downstream mechanisms leading to e.g. radiosensitization

Mechanisms of Resistance to mAB

Cetuximab sensitivity



a) EGFR ligands bind the extracellular domain of the EGFR, induce receptor dimerization and activate downstream signaling pathways that are crucial for cell survival and proliferation
b) Cetuximab prevents ligand binding to EGFR, thus blocking EGFR signaling

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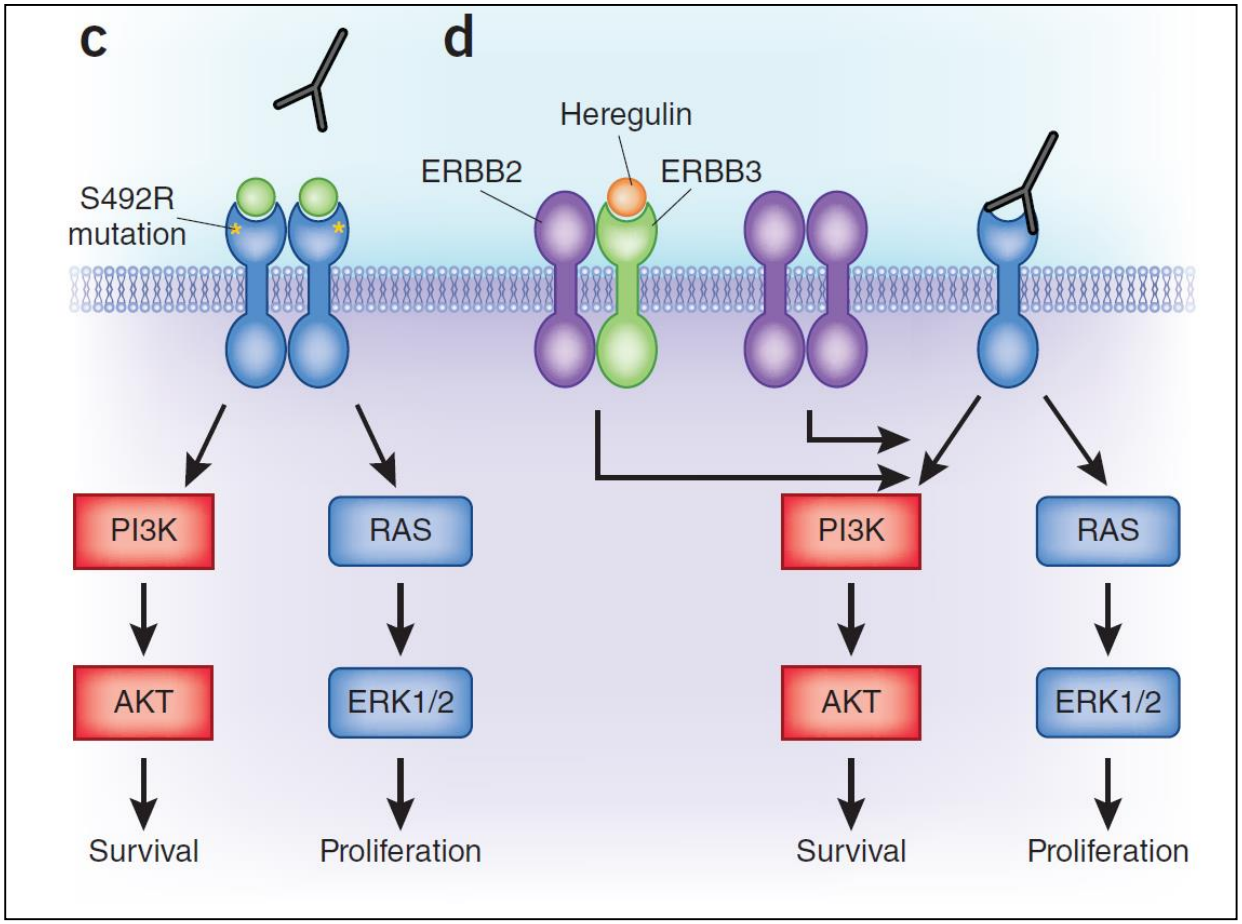
Mechanisms of Resistance to mAB

Cetuximab resistance



c) EGFR mutations in extracellular binding site inhibit cetuximab but not EGFR-ligand binding to EGFR
d) Cetuximab resistance can be mediated by activation of alternative signaling pathways

Mechanisms of Resistance to mAB

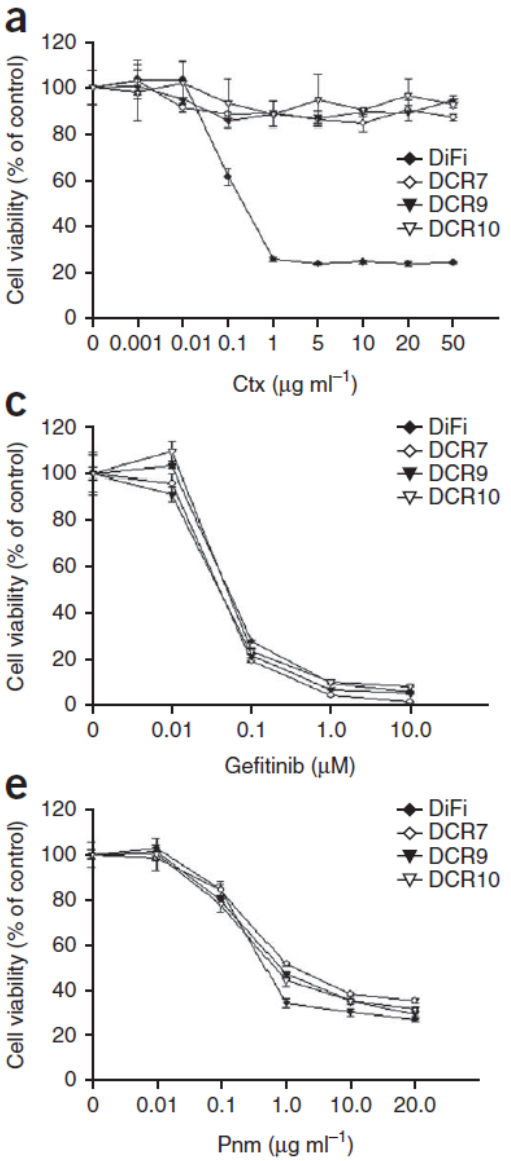
Identification of a mutation in the extracellular domain of the Epidermal Growth Factor Receptor conferring cetuximab resistance in colorectal cancer

Clara Montagut[1,2,9], Alba Dalmases[1,2,9], Beatriz Bellosillo[2,3], Marta Crespo[4], Silvia Pairet[2,3], Mar Iglesias[3,5], Marta Salido[3], Manuel Gallen[1,2], Scot Marsters[6], Siao Ping Tsai[6], André Minoche[7], Seshagiri Somasekar[6], Sergi Serrano[2,3,5], Heinz Himmelbauer[7], Joaquim Bellmunt[1,2,8], Ana Rovira[1,2], Jeff Settleman[6,9], Francesc Bosch[4,9] & Joan Albanell[1,2,5,9]

Nature Med. January, 2012

Cetuximab-resistant cells are still sensitive to EGFR-TKI Gefitinib and mAB Panitumumab

Cells from the DiFi human colorectal cancer cell line were made resistant to cetuximab by continuous exposure to cetuximab



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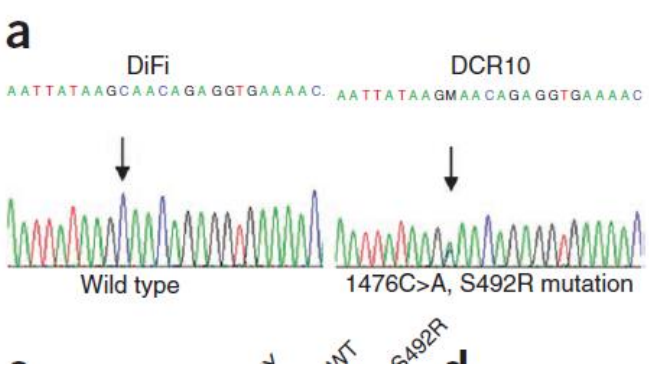
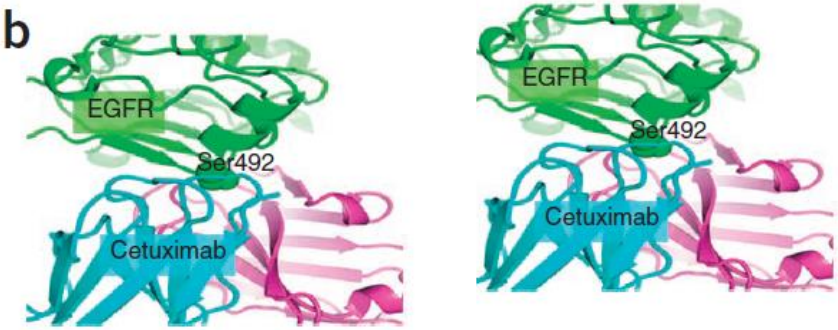
Mechanisms of Resistance to mAB





Supplementary Table 1. Clinical and mutational characteristics of subjects with metastatic colorectal cancer with paired biopsies before and after receiving treatment with cetuximab. The EGFR S492R mutation was detected in post-cetuximab tumor samples from subjects 3 and 9.

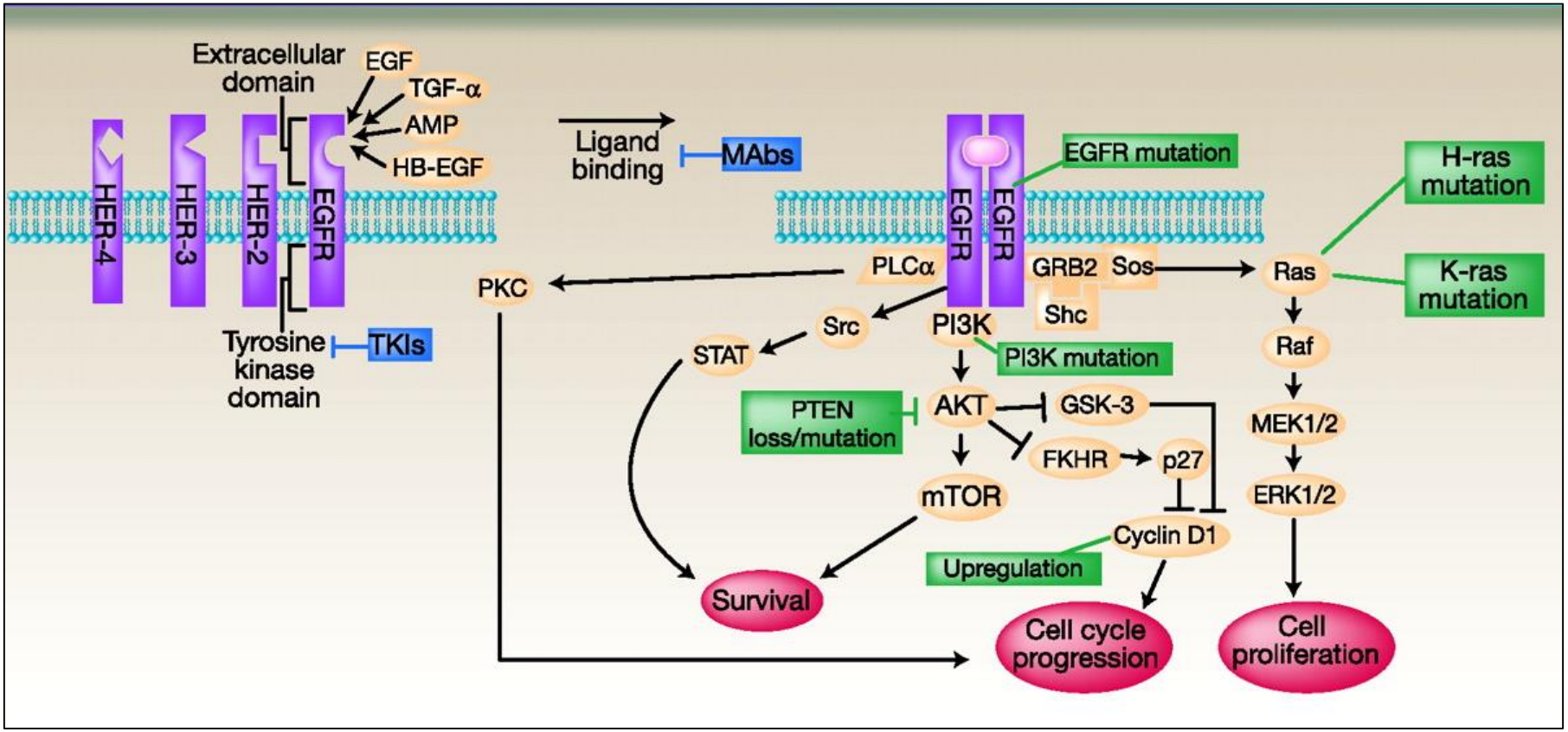
Subject No.	Sex	Age	Pre-cetuximab mutation status				Post-cetuximab mutation status			
			KRAS	*BRAF*	*PIK3CA*	*EGFR*	*KRAS*	*PIK3CA*	*BRAF*	*EGFR*
1	M	55	wt	wt	wt	wt	G12V	wt	wt	wt
2	F	42	wt	wt	wt	wt	wt	wt	wt	wt
3	M	64	wt	wt	wt	wt	wt	wt	wt	***S492R***
4	F	54	wt	wt	wt	wt	wt	wt	wt	wt
5	M	59	wt	wt	wt	wt	wt	wt	wt	wt
6	M	54	wt	wt	wt	wt	wt	wt	wt	wt
7	M	62	wt	wt	wt	wt	wt	wt	V600E	wt
8	M	79	wt	wt	wt	wt	wt	wt	wt	wt
9	M	52	wt	V600E	wt	wt	wt	wt	V600E	***S492R***
10	M	61	wt	wt	wt	wt	wt	wt	wt	wt

wt, wild-type

Nature Med. January, 2012

TRO ool

Secondary and Downstream Mutations



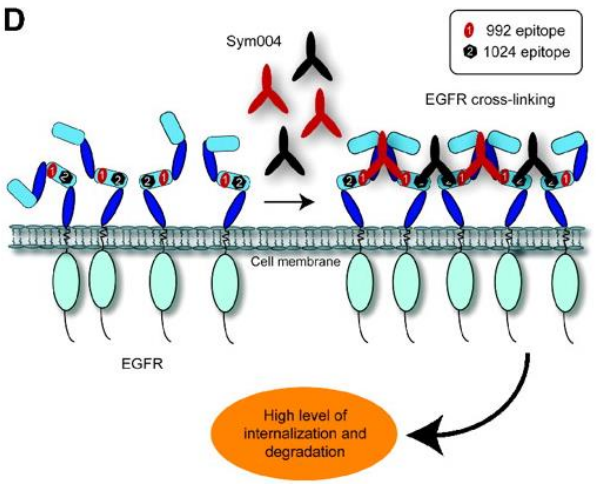
Next Generation Antibodies

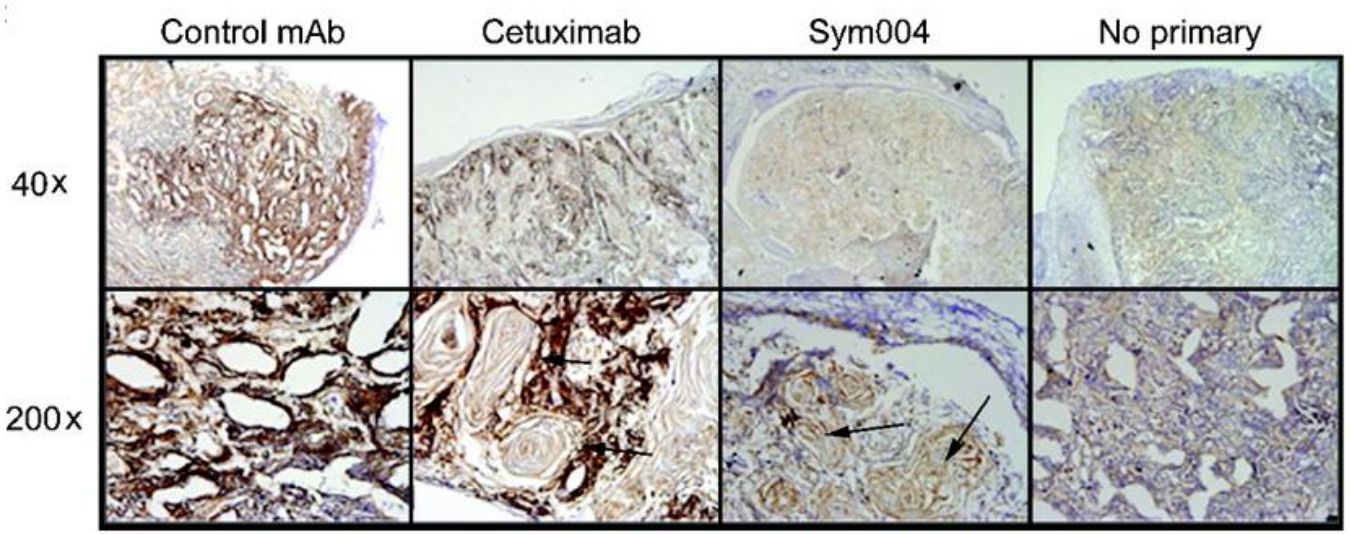
Published OnlineFirst January 12, 2010; DOI: 10.1158/0008-5472.CAN-09-1417

Therapeutics, Targets, and Chemical Biology

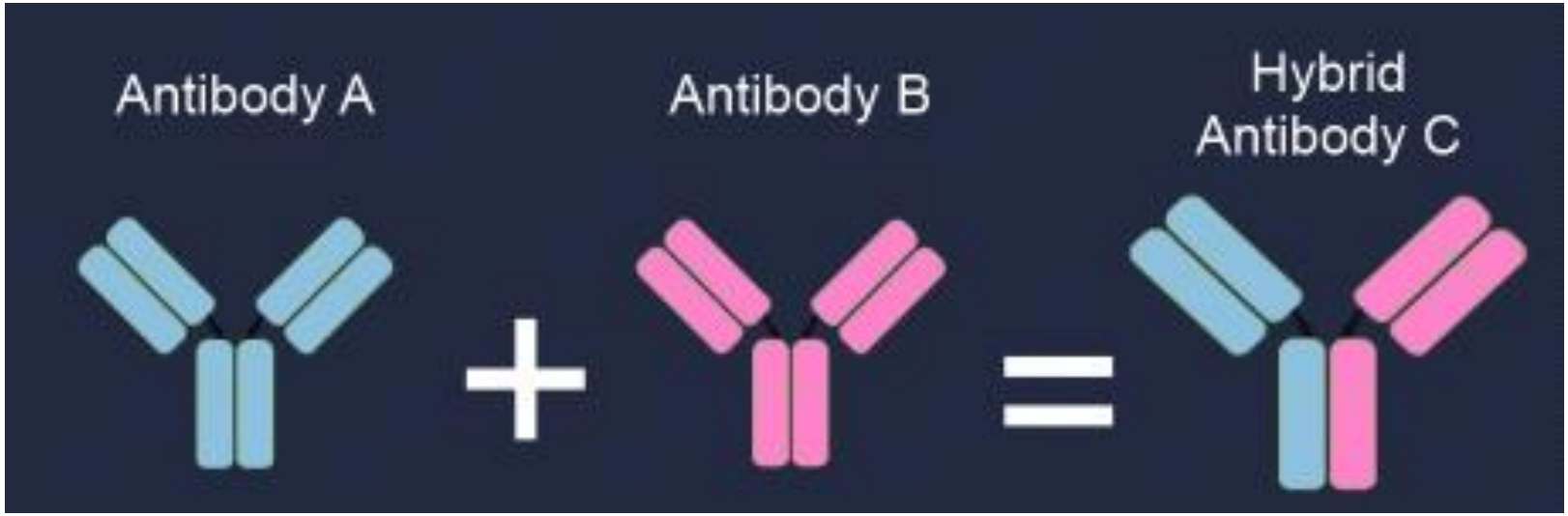
Sym004: A Novel Synergistic Anti–Epidermal Growth Factor Receptor Antibody Mixture with Superior Anticancer Efficacy

Mikkel Wandahl Pedersen, Helle Jane Jacobsen, Klaus Koefoed, Adam Hey, Charles Pyke, John Sørensen Haurum, and Michael Kragh





THE FUTURE ?

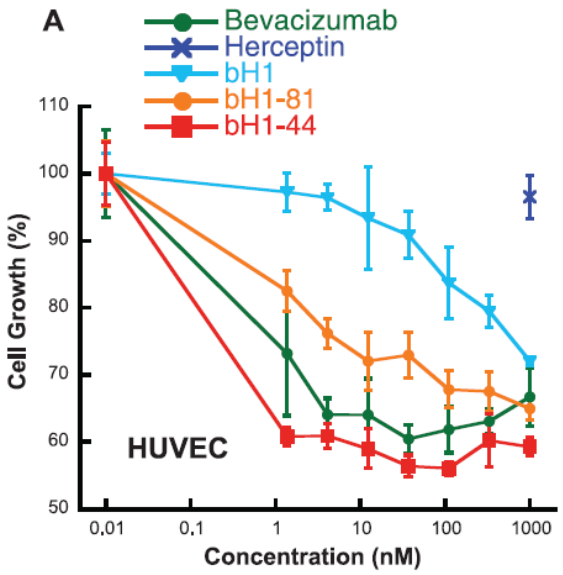


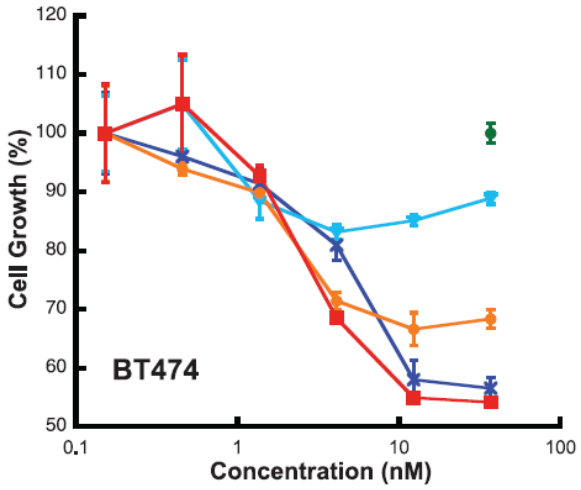
Dual specific antibodies?

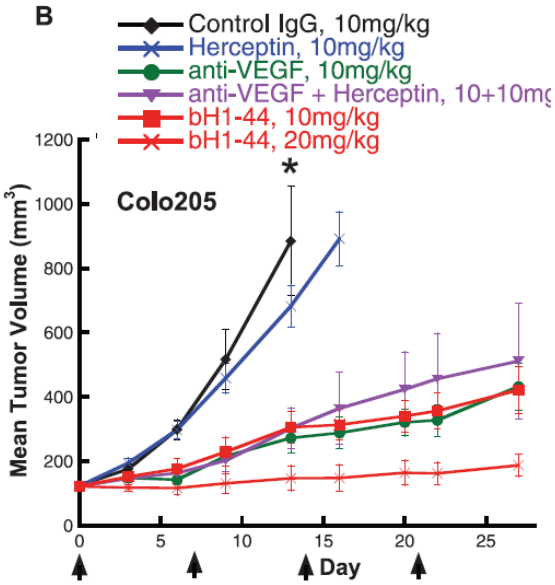
Variants of the Antibody Herceptin That Interact with HER2 and VEGF at the Antigen Binding Site

Jenny Bostrom,[1,2] Shang-Fan Yu,[3] David Kan,[3] Brent A. Appleton,[1] Chingwei V. Lee,[1,2]
Karen Billeci,[4] Wenyan Man,[1] Franklin Peale,[5] Sarajane Ross,[3]
Christian Wiesmann,[1] Germaine Fuh[1,2]*

„two-in-one“-antibody: challenge the monoclonal antibody paradigm of one binding site one antigen





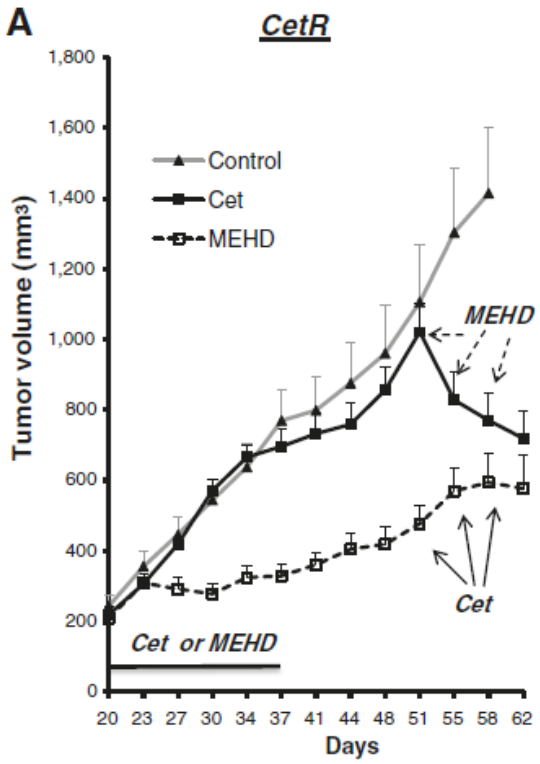


A Two-in-One Antibody against HER3 and EGFR Has Superior Inhibitory Activity Compared with Monospecific Antibodies

MEHD7945A

Gabriele Schaefer,[1,7] Lauric Haber,[2,7] Lisa M. Crocker,[3] Steven Shia,[4] Lily Shao,[1] Donald Dowbenko,[1] Klara Totpal,[3] Anne Wong,[5] Chingwei V. Lee,[2] Scott Stawicki,[2] Robyn Clark,[3] Carter Fields,[1] Gail D. Lewis Phillips,[1] Rodney A. Prell,[6] Dimitry M. Danilenko,[6] Yvonne Franke,[4] Jean-Philippe Stephan,[5] Jiyoung Hwang,[4] Yan Wu,[2] Jenny Bostrom,[2] Mark X. Sliwkowski,[1,*] Germaine Fuh,[2,*] and Charles Eigenbrot[2,4,*]

Cancer Cell *20*, 472–486, October 18, 2011



- Several clinical trials ongoing with duligotuzumab!

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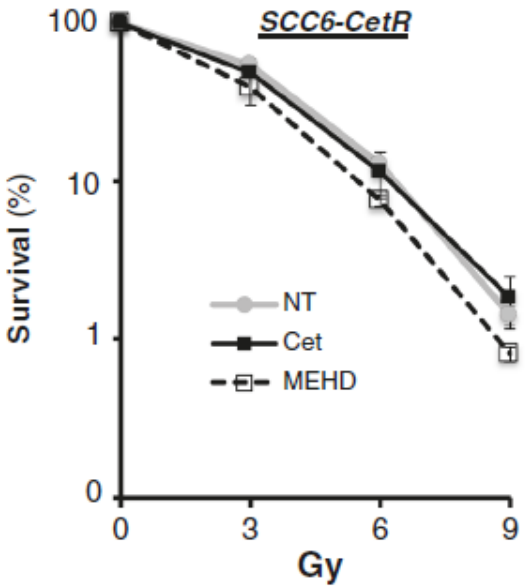
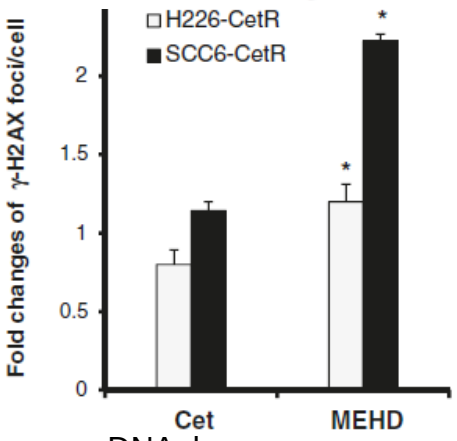
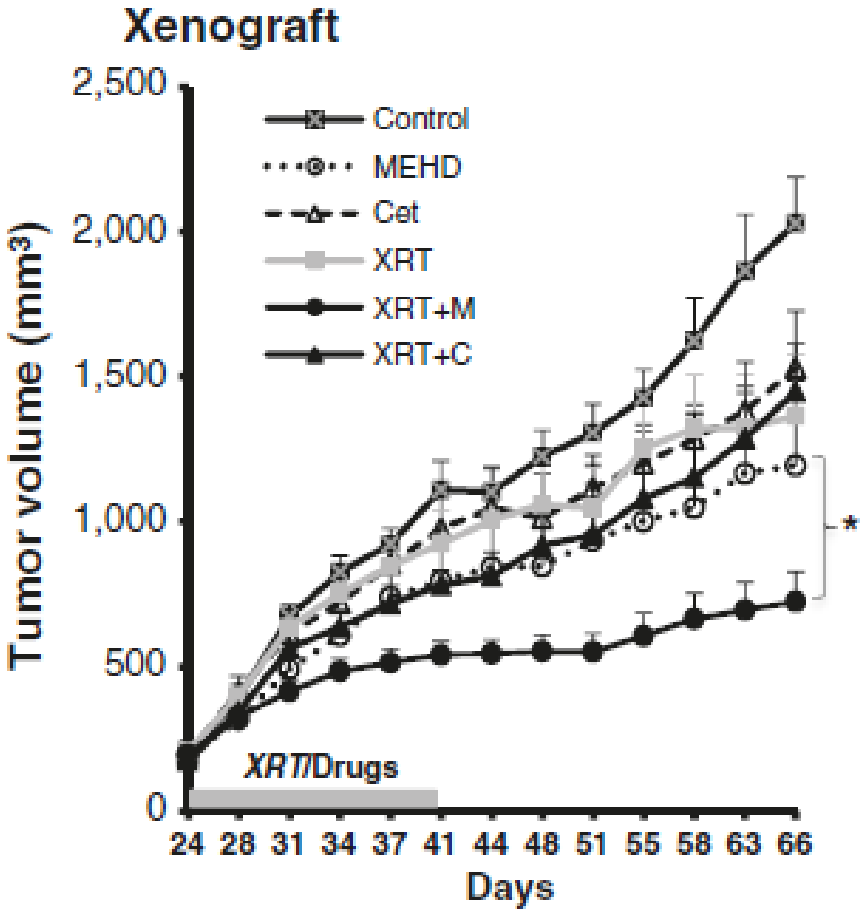
Dual Targeting of EGFR and HER3 overcomes Acquired Resistance to EGFR-Inhibitors and Radiation





DNA damage



Shyhmin Huang[1], Chunrong Li[1], Eric A. Armstrong[1], Chimera R. Peet[1], Jarob Saker[1], Lukas C. Amler[2], Mark X. Sliwkowski[2], and Paul M. Harari[1]

Cancer Res; 73(2) January 15, 2013

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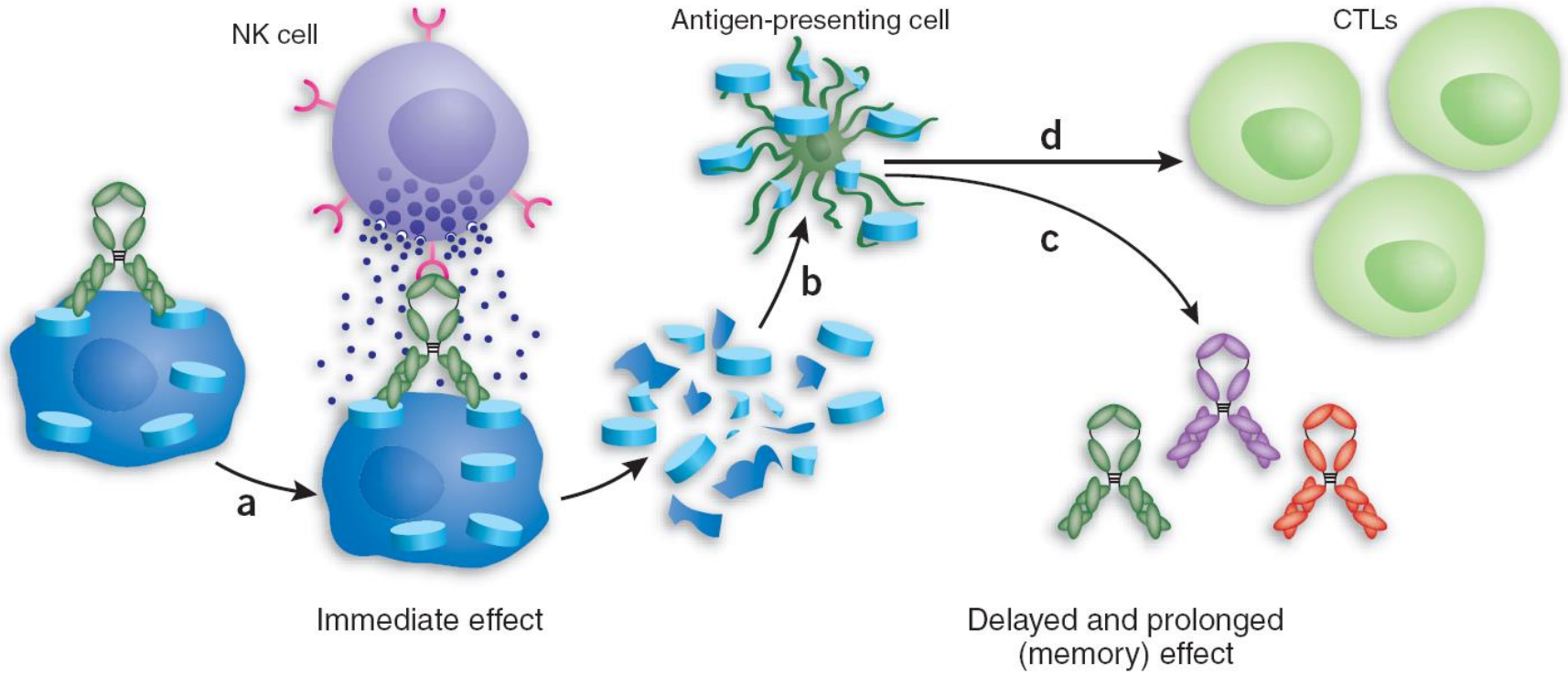
Antibody-Dependent Cellular Cytotoxicity Mediated by mABs , e.g. Cetuximab



ADCC: enhancement of antibody-based tumor therapy ↔ small molecular agents

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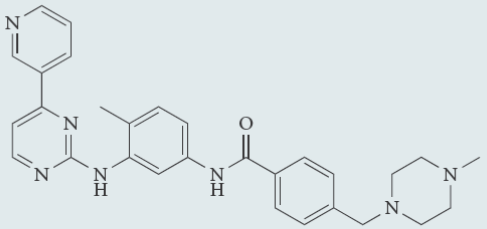
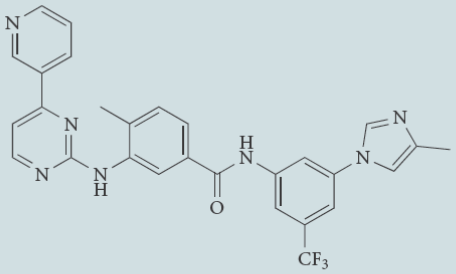
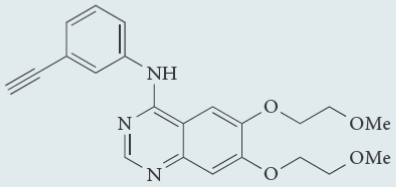
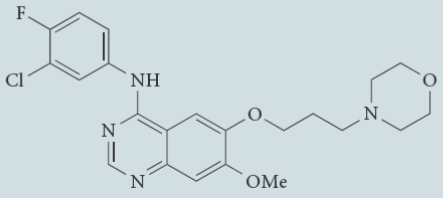
Chemical Structures of some clinically approved kinase inhibitors

Structure	Name	Known targets	Indication
	Imatinib (Gleevec; Novartis)	Bcr-Abl, c-Abl, PDGFR, c-KIT, DDR1	CML, GIST, HES
	Nilotinib (Tasigna; Novartis)	Bcr-Abl, c-Abl, PDGFR, c-KIT, DDR1	Imatinib-resistant CML
	Erlotinib (Tarceva; OSI Pharmaceuticals/ Genentech/Roche)	EGFR, ERBB2 (HER2)	NSCLC, pancreas cancer
	Gefitinib (Iressa; AstraZeneca)	EGFR, ERBB2, HER4	NSCLC

Mechanisms of small molecule action (TK-inhibitors) I

Initial concerns: well conserved ATP-binding sites in between the family of kinases: can we get specificity?

Using protein cristallography and NMR-spectroscopy sophisticated structure-based design of specific kinase-inhibitors are now feasible

Kinase inhibitors were developed with the goal of highest selectivity, however, several clinically approved kinases inhibitors are potent inhibitors of multiple kinases: reason for potency?

Potential to target multiple distinct processes (hallmarks) associated with tumor growth, but might be more toxic

Several preclinical studies demonstrate (supra-) additive effect by combined treatment modalities mAB plus TK-inhibitors (complementary effects)

Kinase inhibitor binding sites

- Type I inhibitors
  - constitutes majority of ATP-competitive inhibitors and recognizes the so called active conformation of the kinase
  - e.g. sorafenib, dasatinib, sutent
- Type II inhibitors
  - recognize the inactive conformation of the kinase
  - e.g. imatinib
- Allosteric Inhibitors
  - bind outside of ATP-binding site; at an allosteric site
  - exhibit highest degree of kinase selectivity
- Covalent inhibitors
  - require low concentrations
  - concern about potential toxicity by modification of unanticipated targets

Iressa - Gefitinib

The first selective inhibitor that targets the mutant proteins in malignant cells

Used to treat lung cancer

Only ~10% of non-small cell lung cancer patients response to Iressa

Toxicities include acne, diarrhea, nausea, vomiting and skin reactions

chemical class: quinazoline

orally bioavailable (compliance)

selective inhibitor of EGFR tyrosine kinase

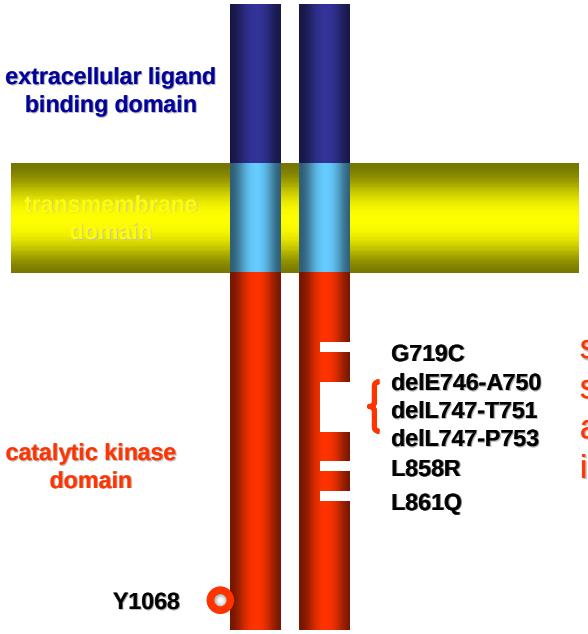
- EGFR IC50 = 0.023-0.079 μM
- erbB2 IC50 = 1.2-3.7 μM

competitive inhibitor of ATP-binding

inhibits ligand-induced cell growth

- IC50 = 0.08 μM

EGFR Mutation



specific mutations confer sensitivity of EGFR-TK activity to gefitinib/iressa in NSCLC patients !

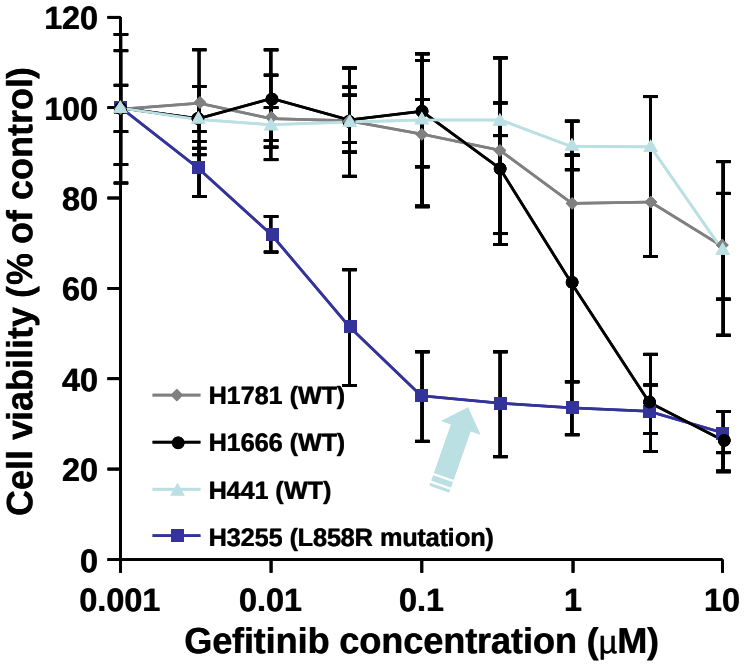
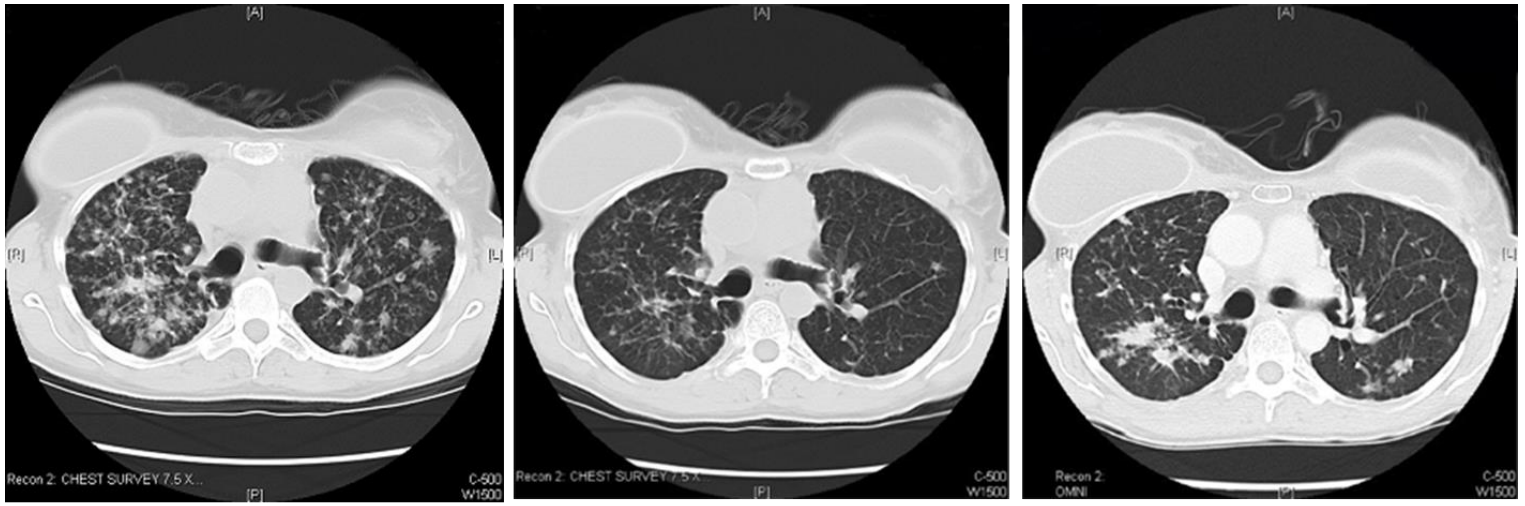


Table 1. The current state of knowledge of *EGFR* mutations in patients with NSCLC

Known	Unknown
EGFR mutations are associated with responses to gefitinib and erlotinib	The etiology of the *EGFR* mutations
EGFR mutations are somatic	The relative oncogenic properties of the different *EGFR* mutations
EGFR mutations are more common in women, nonsmokers, in adenocarcinomas, and East Asians	The outcome of patients with different *EGFR* mutation treated with different EGFR-TKIs
Secondary *EGFR* mutations are associated with resistance to gefitinib and erlotinib in patients and *in vitro*	The mechanisms of resistance to gefitinib and erlotinib in the patients who do not have the identified T790M secondary *EGFR* mutation

Acquired Resistance of Lung Adenocarcinomasto Gefitinib or Erlotinib Is Associated with a Second Mutation in the EGFR Kinase Domain

Patient 2.
This 55-y-old woman with a nine pack-year history of smoking underwent two surgical resections within 2 y (right lower and left upper lobectomies) for bronchioloalveolar carcinoma with focal invasion. Two years later, her disease recurred with bilateral pulmonary nodules and further progressed on systemic chemotherapy. Thereafter, the patient began erlotinib, 150 mg daily. A baseline CT scan of the chest demonstrated innumerable bilateral nodules (Figure S1B, left panel), which were markedly reduced in number and size 4 mo after treatment (Figure S1B, middle panel). After 14 mo of therapy, the patient's dose of erlotinib was decreased to 100 mg daily owing to fatigue. At 23 mo of treatment with erlotinib, a CT scan demonstrated an enlarging sclerotic lesion in the thoracic spine. The patient underwent CT-guided biopsy of this lesion and the erlotinib dose was increased to 150 mg daily. After 25 mo of treatment, she progressed within the lung (Figure S1B, right panel). Erlotinib was discontinued, and a fluoroscopically guided core needle biopsy was performed at a site of progressive disease in the lung.



Day 0 | **4 months** | **25 months**

del L747–E749;A750P; Kras Wild-type | del L747–E749;A750P; T790M Kras Wild-type

Pao et al., Plos Med., 2005

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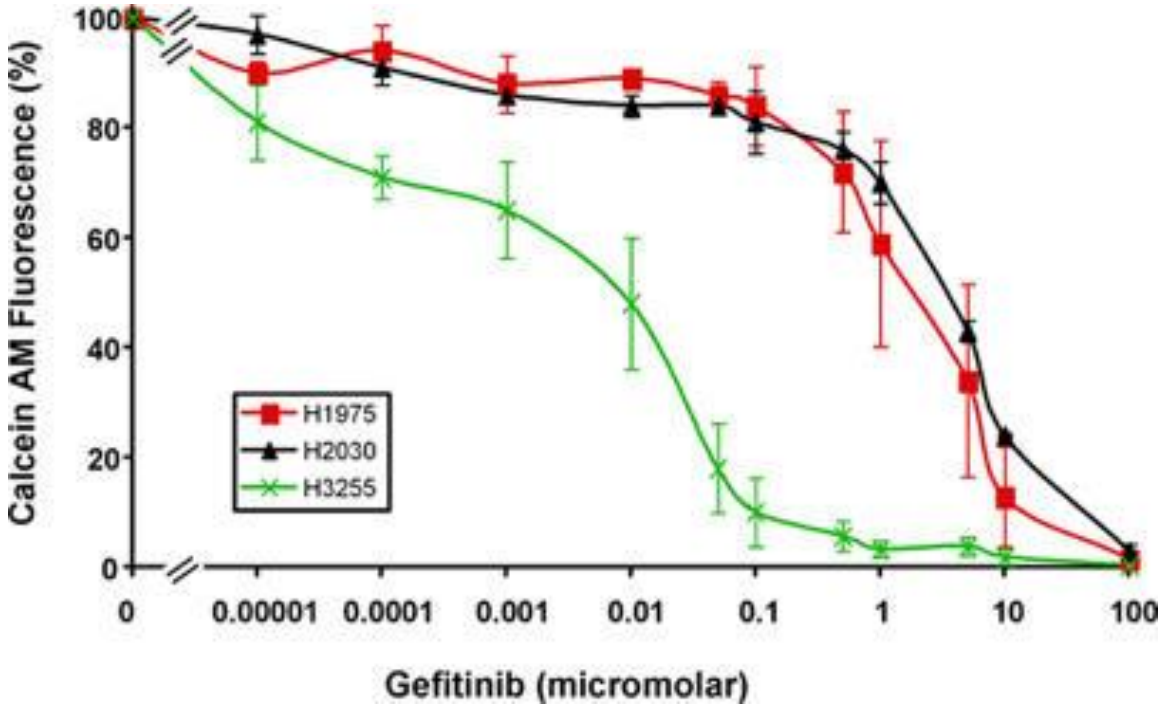
Secondary and Downstream Mutations



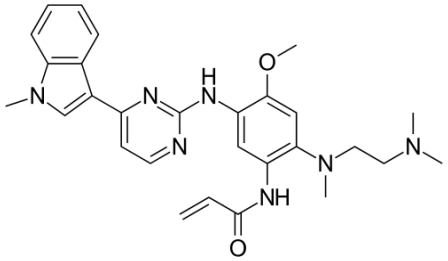
Kobayashi, PLoS Med, 2, e73

Sensitivity to Gefitinib Differs Among NSCLC Cell Lines Containing Various Mutations in *EGFR* or *KRAS*

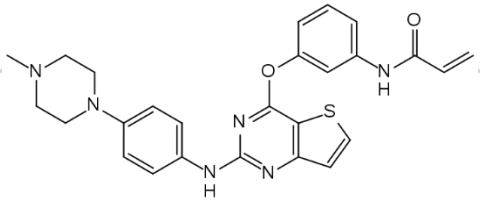
The three indicated NSCLC cell lines, H3255 (L858R mutation), H1975 (both T790M and L858R mutations), and H2030 (wild-type *EGFR,* mutant *KRAS*), were grown in increasing concentrations of gefitinib, and the density of live cells after 48 h of treatment was measured

Targeting EGFR T790M mutation in NSCLC: From biology to evaluation and treatment

Osimertinib (AstraZeneca) is a potent, irreversible EGFR tyrosine kinase inhibitor that is selective for EGFR tyrosine kinase inhibitor–sensitizing mutations and the T790M resistance mutation with an excellent therapeutic index because its activity is poor towards the wild-type EGFR



Olmutinib (HM 61713)(Boehringer Ingelheim) is an irreversible tyrosine-kinase inhibitor, selective for mutant EGFR. Its molecule structure contains a Michael acceptor that covalently binds a cysteine residue near the kinase domain of mutant EGFR



Resistances: Secondary and Downstream Mutations

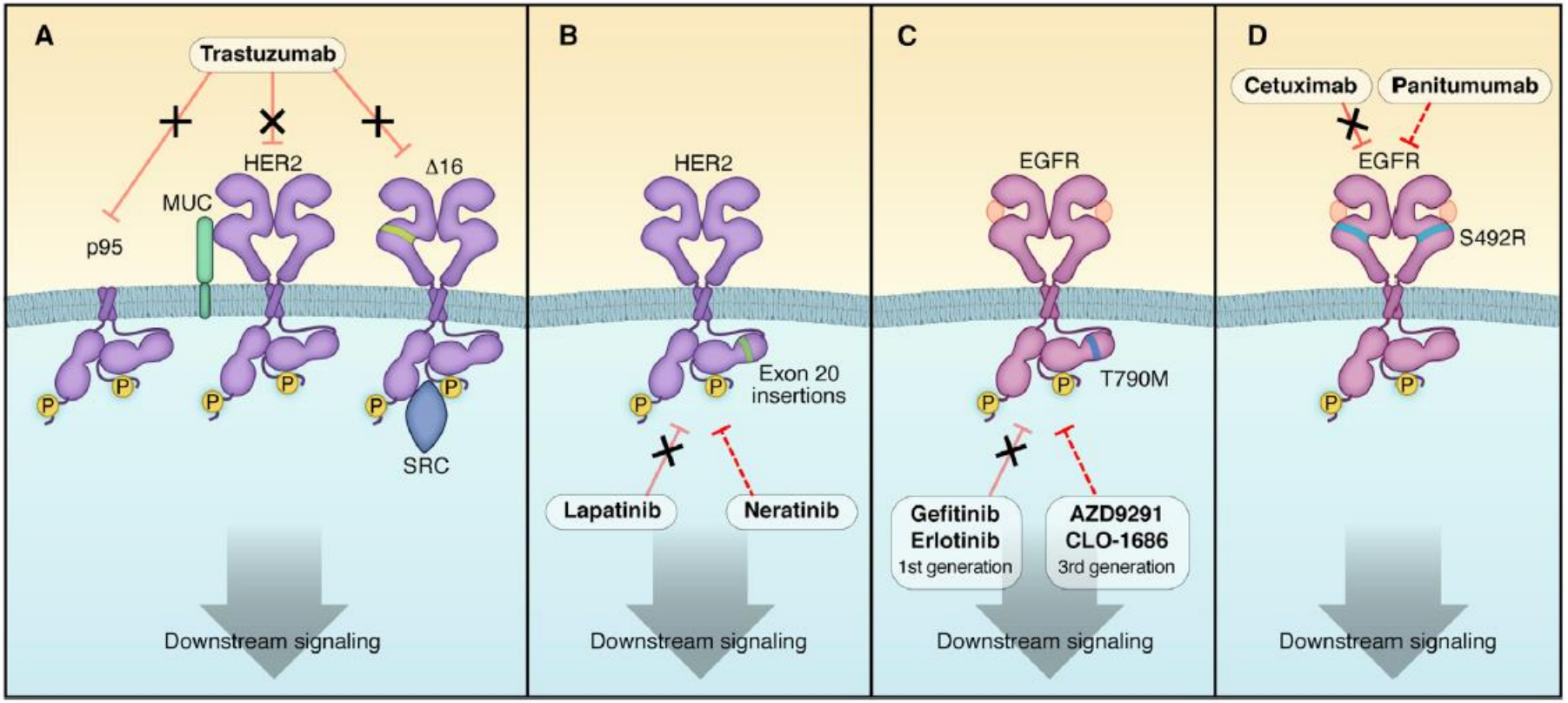


Figure 1. Schema Depicting Intragenic Alterations Leading to Resistance to HER2 and EGFR Inhibitors

(A) HER2 truncations (p95) and splice variants (Δ16) are not inhibited by trastuzumab. In addition, expression of specific mucin isoforms can prevent trastuzumab from binding HER2 (Price-Schiavi et al., 2002). Not shown in the figure, pertuzumab and T-DM1 cannot recognize p95 either.

(B) HER2s harboring exon 20 insertions are not inhibited by lapatinib, but may be sensitive to irreversible HER2 inhibitors afatinib and neratinib. They are also resistant to trastuzumab.

(C) The EGFR T790M gatekeeper mutation leads to acquired resistance to first generation EGFR inhibitors, but is effectively inhibited by third-generation EGFR inhibitors.

(D) An EGFR mutation in the extracellular domain is associated with acquired resistance to cetuximab, but may still be sensitive to another anti-EGFR antibody, panitumumab. Dashed lines indicate inhibition via alternative antibodies and inhibitors.

Arteaga, Cancer Cell, 25, 2015

Resistances: Secondary and Downstream Mutations

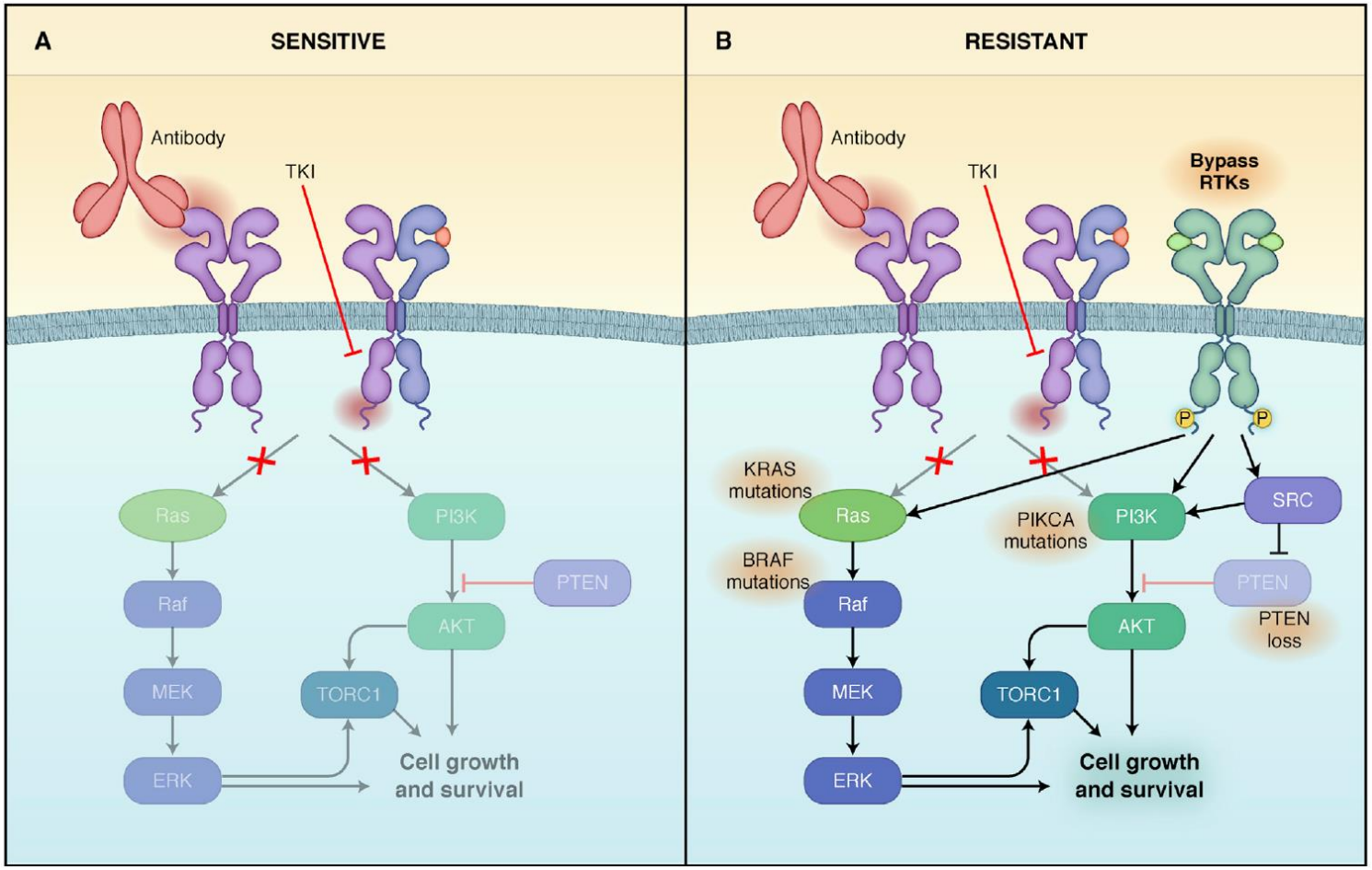


Figure 2. Schematic Depicting Resistance to EGFR and HER2 Inhibitors due to Activation of Bypass Track Signaling

(A) Model of a sensitive EGFR or HER2-addicted cancer treated with an ERBB small-molecule inhibitor or antibody resulting in suppression of downstream signaling. EGFR or HER2 homodimers and heterodimers are shown.

(B) Model of a EGFR mutant or *HER2*-amplified cancer with resistance due to maintenance of downstream signaling in the presence of the EGFR or HER2 inhibitors. Activation of signaling can be caused by activation of other RTKs or mutational activation of downstream signaling.

Arteaga, Cancer Cell, 25, 2015

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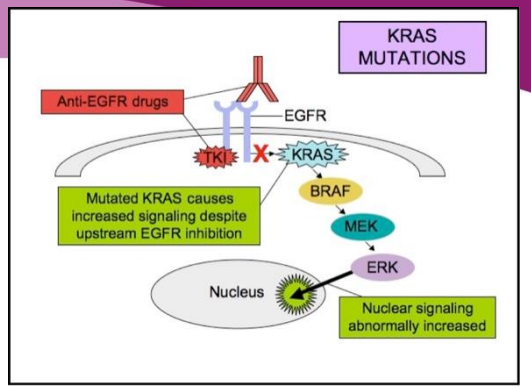
The NEW ENGLAND JOURNAL of MEDICINE

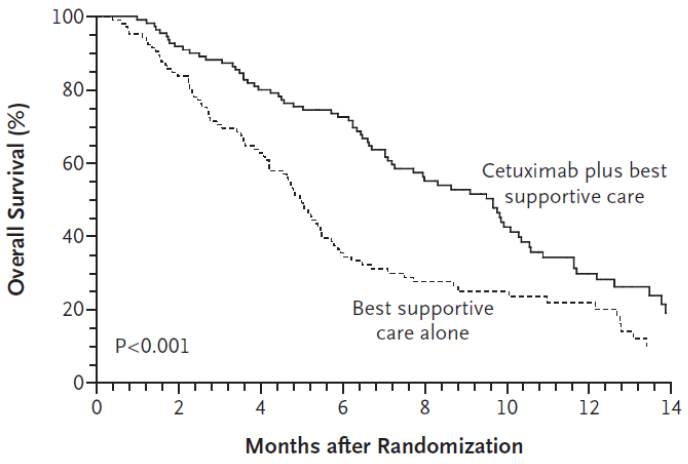
ESTABLISHED IN 1812 OCTOBER 23, 2008 VOL. 359 NO. 17

K-ras Mutations and Benefit from Cetuximab in Advanced Colorectal Cancer

Christos S. Karapetis, M.D., Shirin Khambata-Ford, Ph.D., Derek J. Jonker, M.D., Chris J. O'Callaghan, Ph.D., Dongsheng Tu, Ph.D., Niall C. Tebbutt, Ph.D., R. John Simes, M.D., Haji Chalchal, M.D., Jeremy D. Shapiro, M.D., Sonia Robitaille, M.Sc., Timothy J. Price, M.D., Lois Shepherd, M.D.C.M., Heather-Jane Au, M.D., Christiane Langer, M.D., Malcolm J. Moore, M.D., and John R. Zalcberg, M.D., Ph.D.*

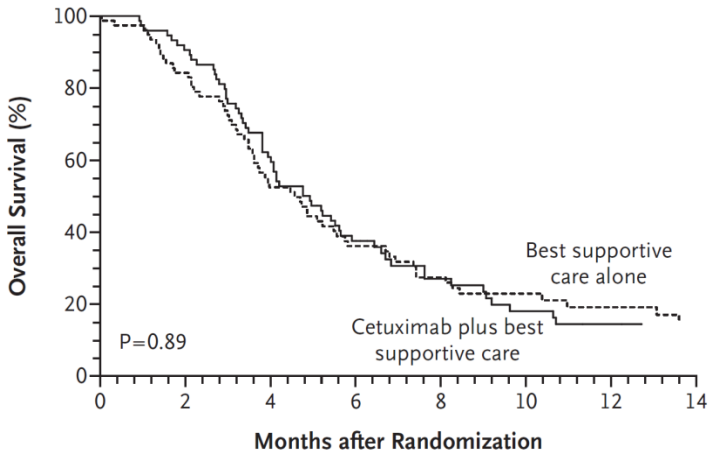


B Wild-type *K-ras*



No. at Risk								
Cetuximab plus best supportive care	110	101	88	75	48	31	19	8
Best supportive care alone	105	88	65	34	23	17	12	5

A Mutated *K-ras*



No. at Risk								
Cetuximab plus best supportive care	75	67	45	26	15	10	7	4
Best supportive care alone	76	64	39	26	19	12	10	7

Key Points

Molecularly targeted agents are less toxic than cytotoxic agents (antibodies/small molecular

resistances

Molecularly targeted agents work by targeting the genetic changes(s) in cancer cells

- Chromosomal translocation
- Gene duplication
- Gene mutation

Risk for secondary mutations high

Risk for paraxodical activation of pro-tumorigenic wildtype-signal transduction cascade exists (Raf-inhibitors)

To improve cancer treatment, we need to better understand the differences between cancer and normal cells

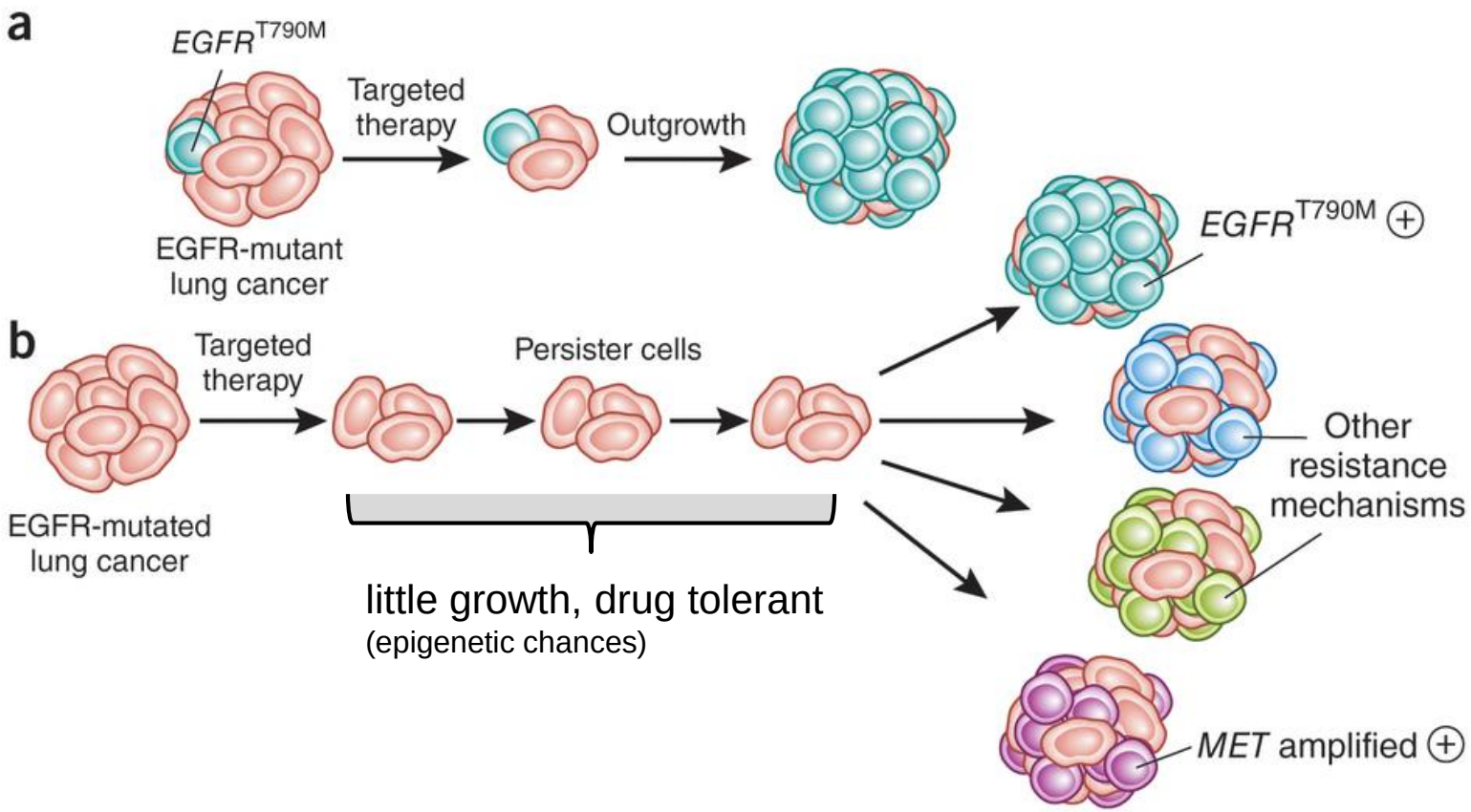
Major Callenges: Resistances

- de novo/ intrinsic resistance: do not exhibit an initial response

- acquired resistance: develops after an initial, often marked and durable clinical response

- same molecular mechanisms may cause both types of resistance

Cellular Origins of Drug Resistance in Cancer



a) Preexisting subclones

b) Induction of durable drug-tolerable state followed by aquisition of a variety of resistance mechanisms

Hata et al., Ramirez et al, 2016

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Relevant Questions:

- Molecular evolution of resistance to treatment:
  - acquired during therapy?
  - Already present in a clonal subpopulation within the tumours *prior* to the initiation of therapy?

- Is resistance is therefore a fait accompli—the time to recurrence is simply the interval required for the subclone to repopulate the lesion.?
- Is the short time interval of recurrence due to the rapid expansion of the resistant subclone immediately following treatment initiation?

- Required:

Combination therapies targeting at least two different pathways - processes.

Hypoxia: The view of a ~~biologist~~ ~~and~~ radiation oncologist

Jesper Grau Eriksen

Dept. Of Oncology
Odense University Hospital, Denmark

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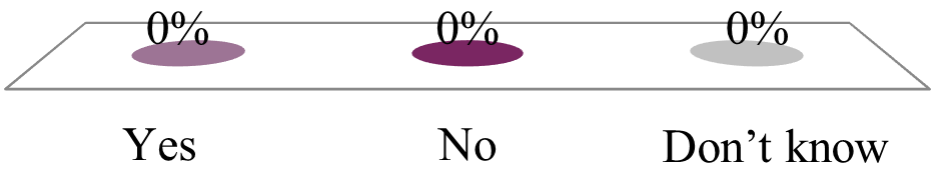
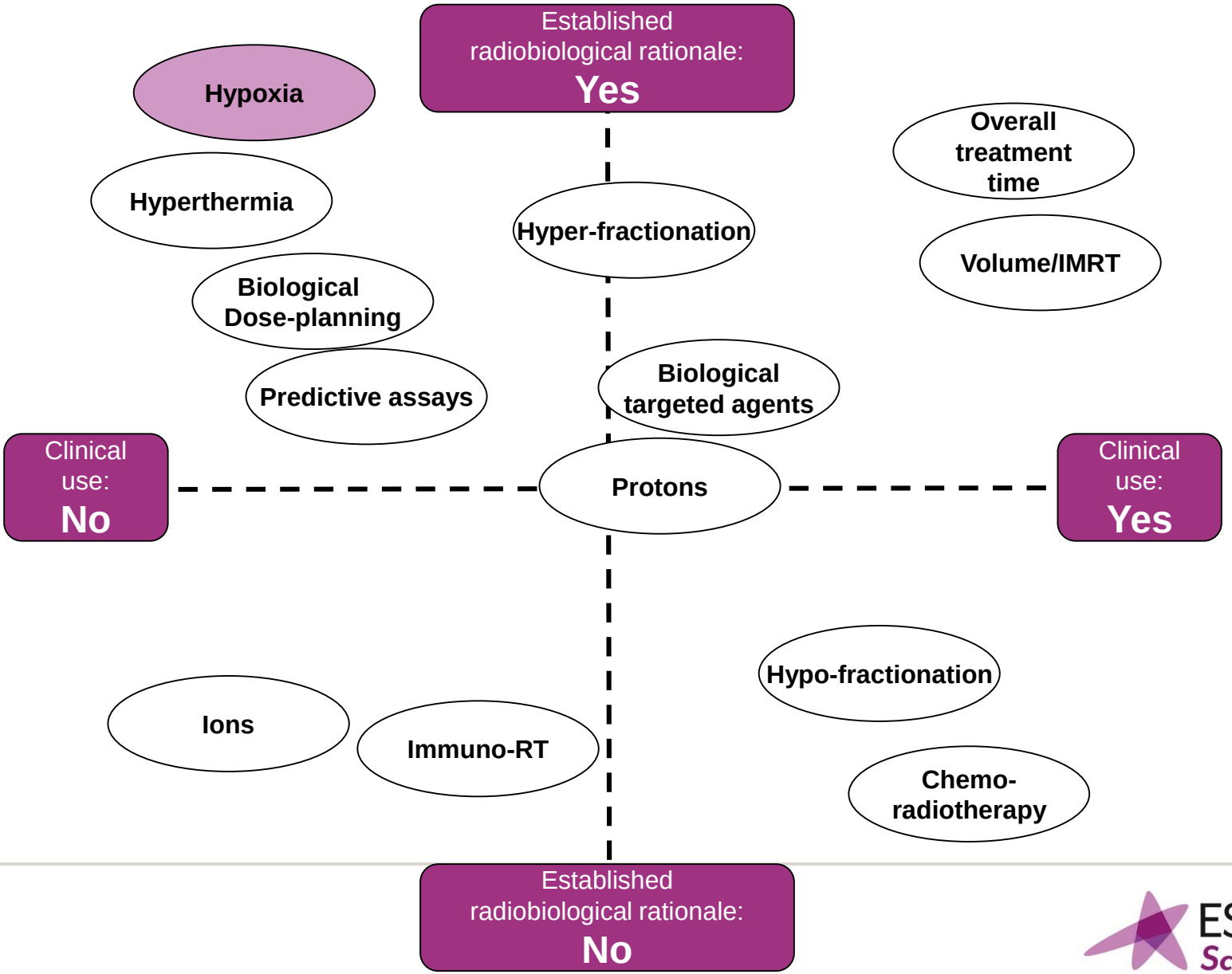
There is a radiobiological rationale for hypoxic modification

A. Yes
B. No
C. Don’t know



The landscape of evidence and practice



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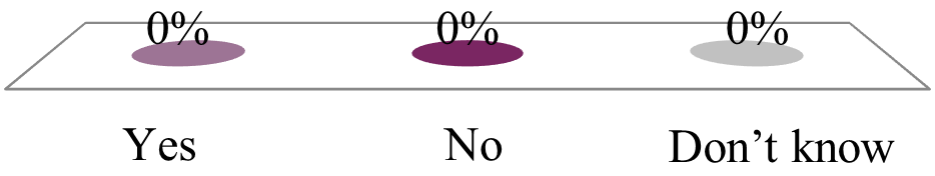
I use hypoxic modification in the treatment of some tumour types:

A. Yes
B. No
C. Don’t know



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Modification of hypoxic radioresistance

Increased oxygen delivery by the blood

- Hyperbaric oxygen
- Carbogen breathing
- Nicotinamide
- Blood transfusion, Erythropoetin

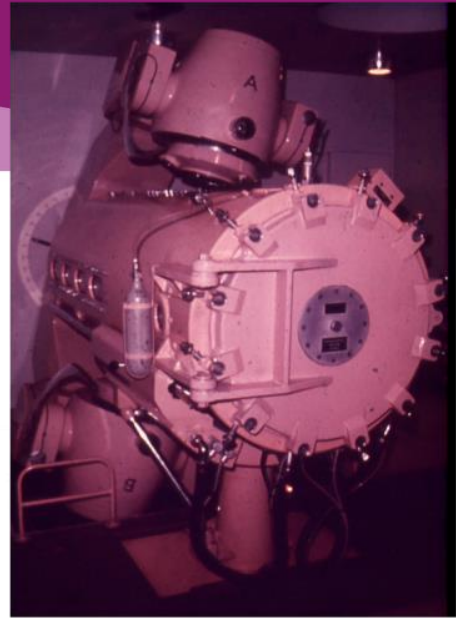
Mimic of oxygen in the radiochemical process

- Nitroimidazoles

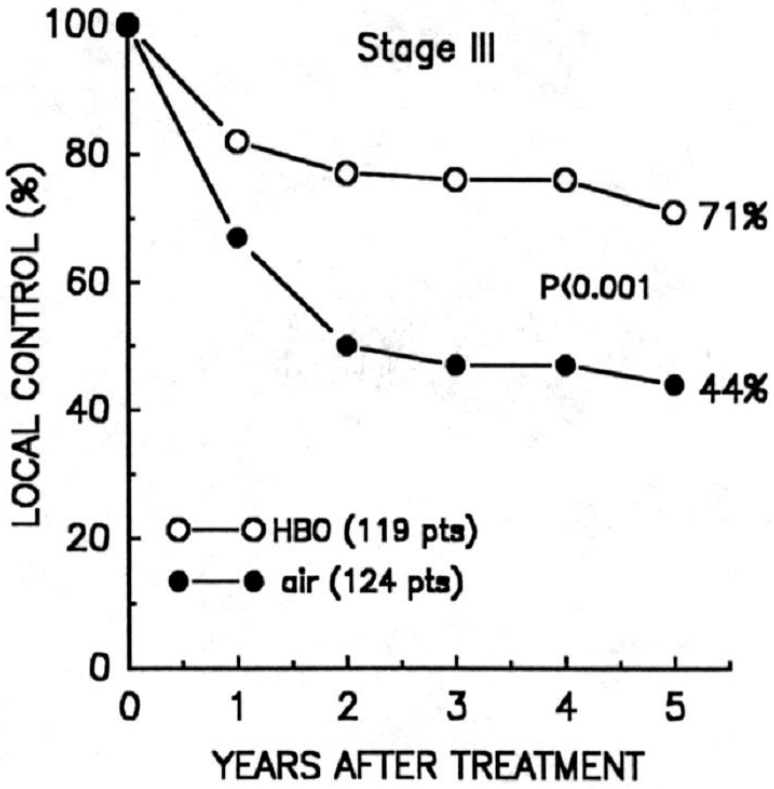
Destruction of hypoxic cells

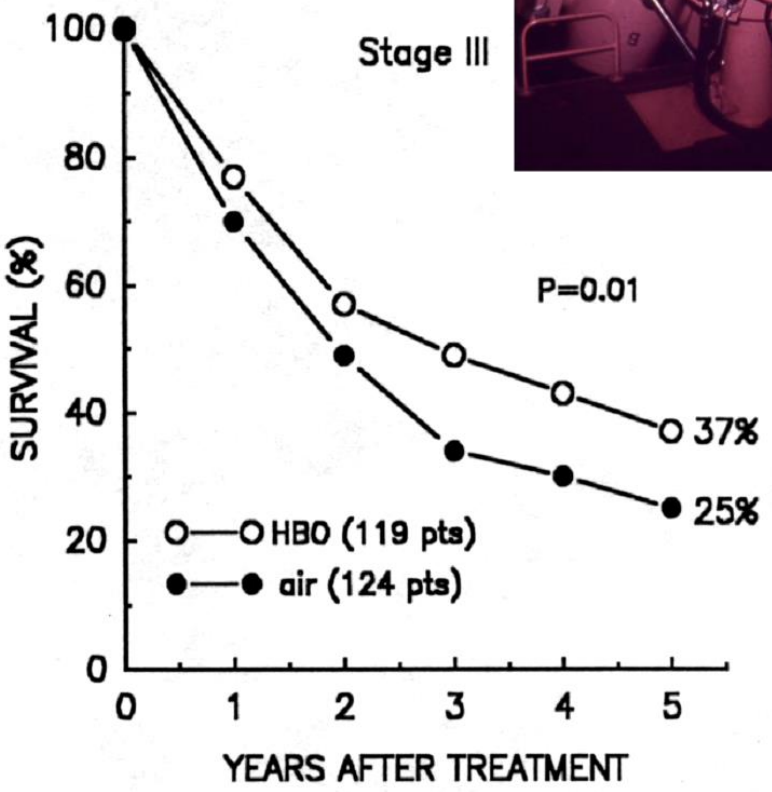
- Hypoxic cytotoxins
- Hyperthermia

Hyperbaric oxygen



MRC Trial in Carcinoma of the Uterine cervix





Watson et al 1978

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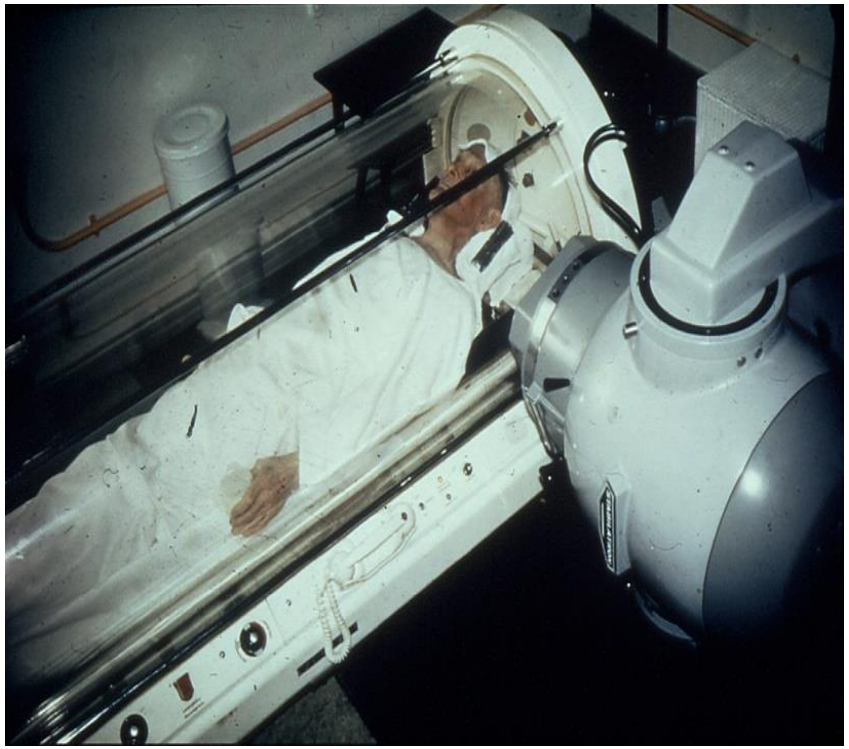
Hyperbaric oxygen

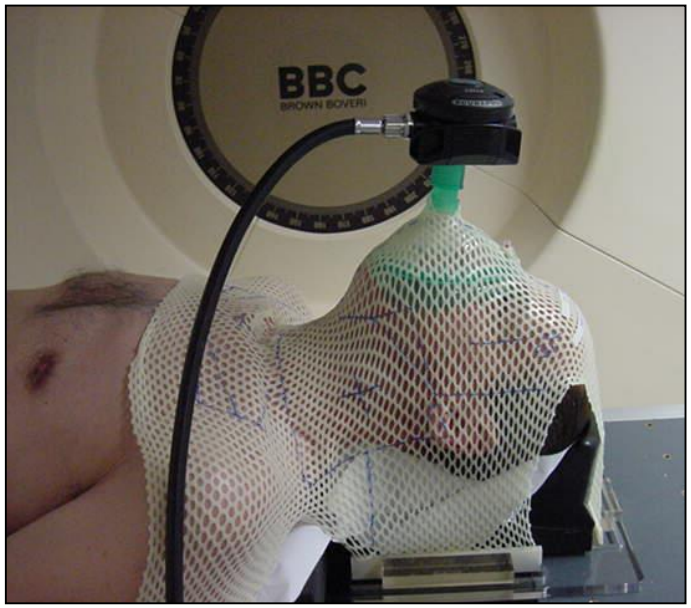
“...the project was prematurely and violently terminated by an explosive decompression of the chamber.....which left the cobalt room in shambles.

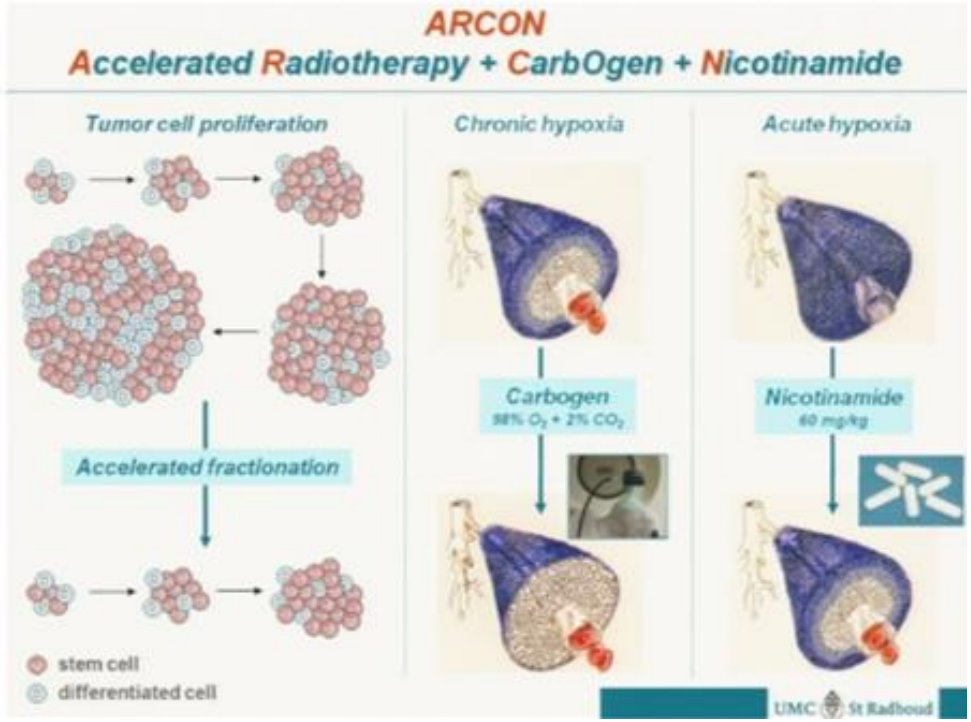
Although both the patient and the senior author survived the accident, the project was not continued....”

Tobin & Vermund AJR 1971



Carbogen and Nicotinamide

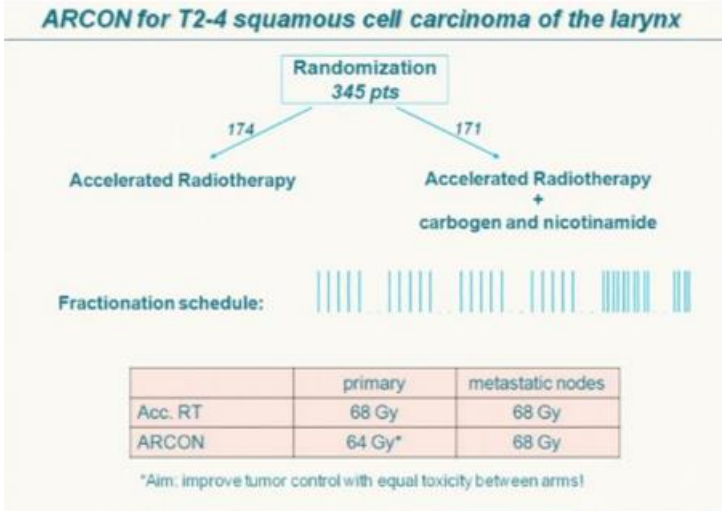


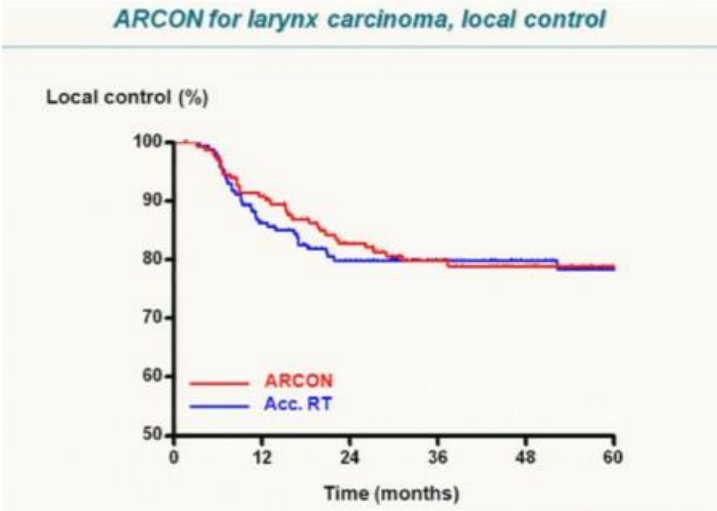


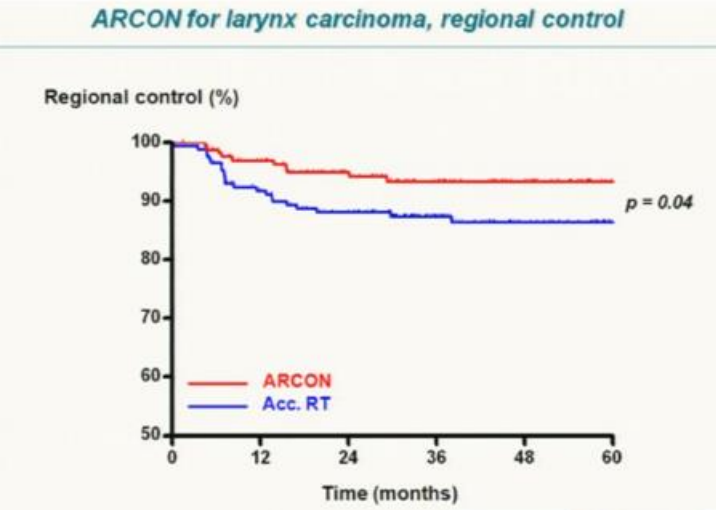
Carbogen: a gas mixture of 95% O2 and 5% CO2, increase blood oxygen levels and reduce diffusion-limited hypoxia.
Nicotinamide: increase vascular perfusion

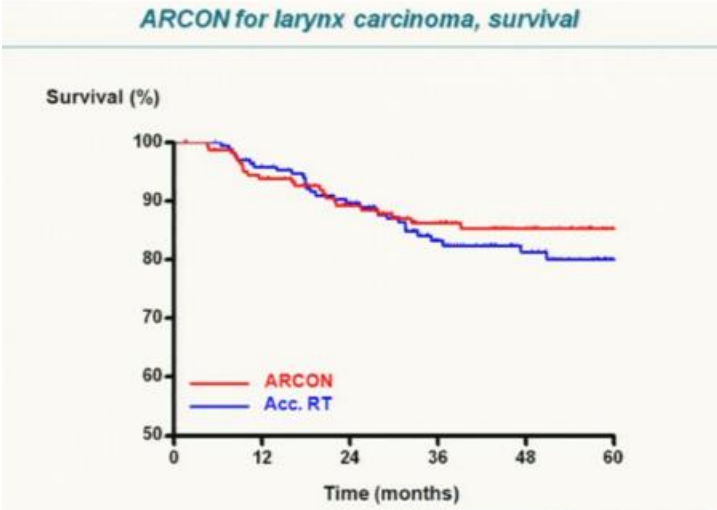
Adapted from Kaanders et al ICHNO 2011

ARCON phase III









Adapted from Kaanders et al ICHNO 2011

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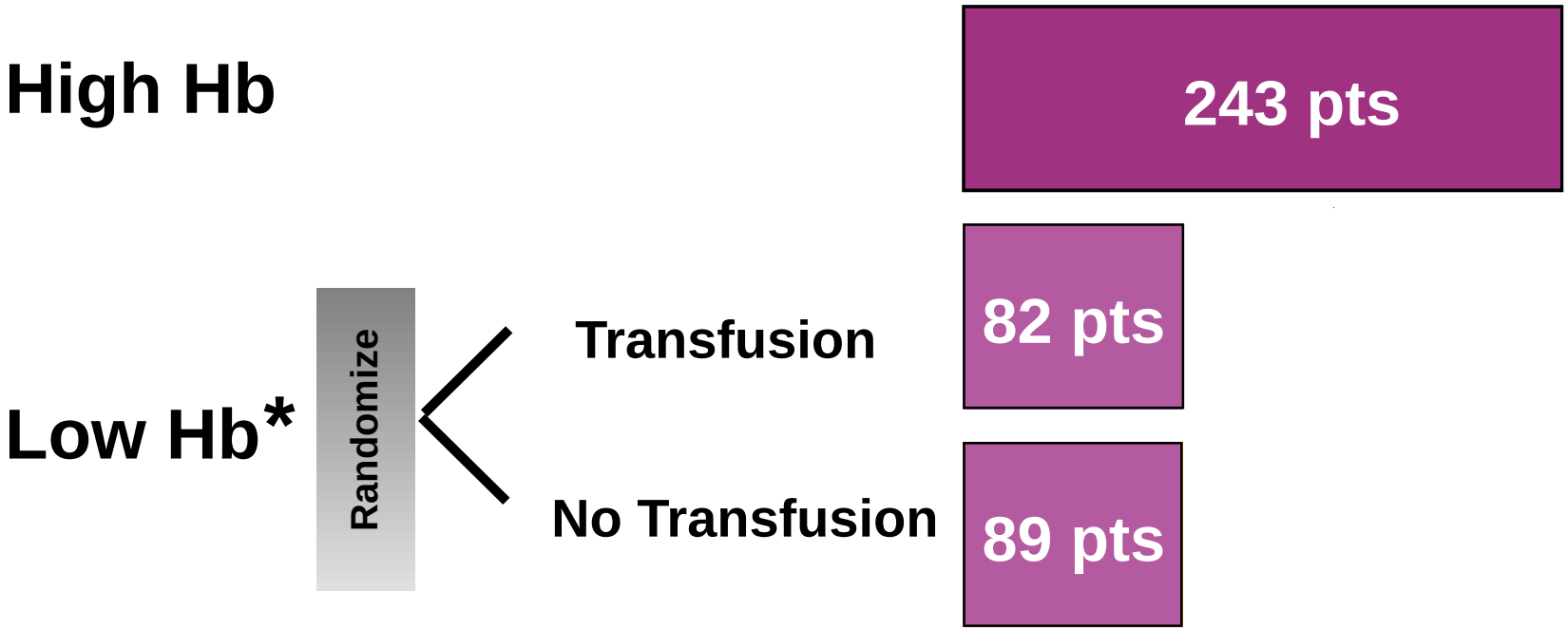
DAHANCA 5 - Blood transfusion and RT in HNSCC

Hemoglobin and randomization

414 evaluable pts. with supraglottic and pharynx carcinoma



***Low Hb: Male < 9 mmol/L (14.5 g/L), Female < 8 mmol/L (13 g/L)**

Hoff CM 2011

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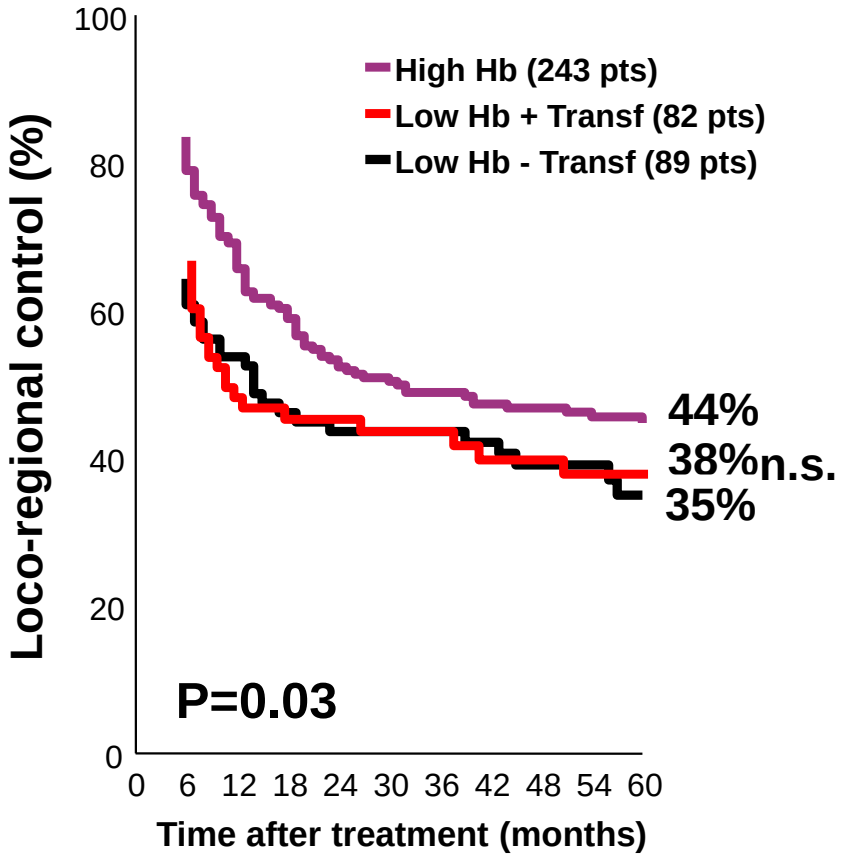
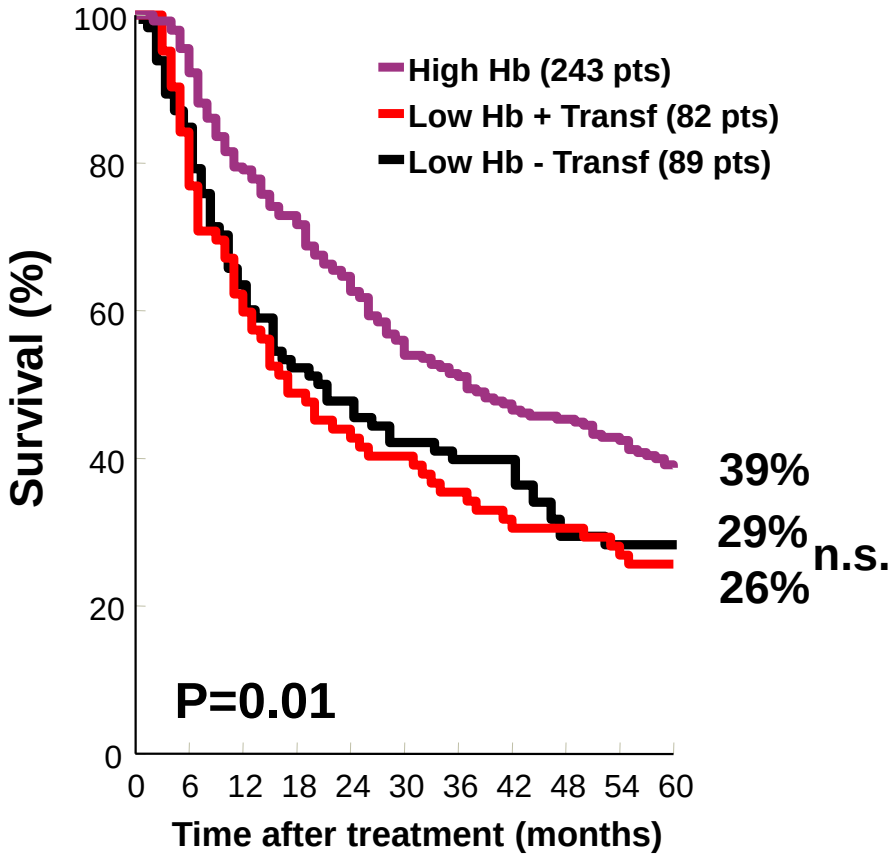
DAHANCA 5 - Blood transfusion and RT in HNSCC





Hoff CM 2011

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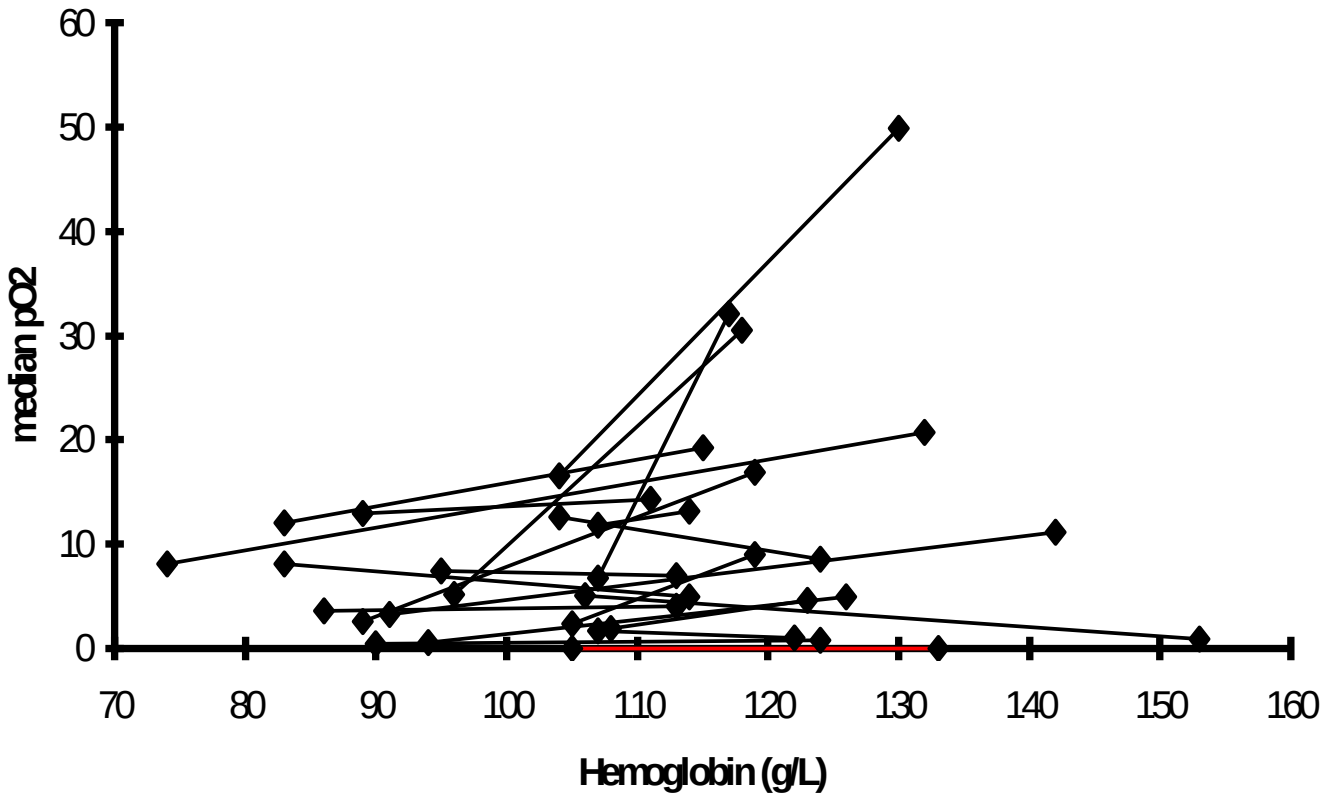
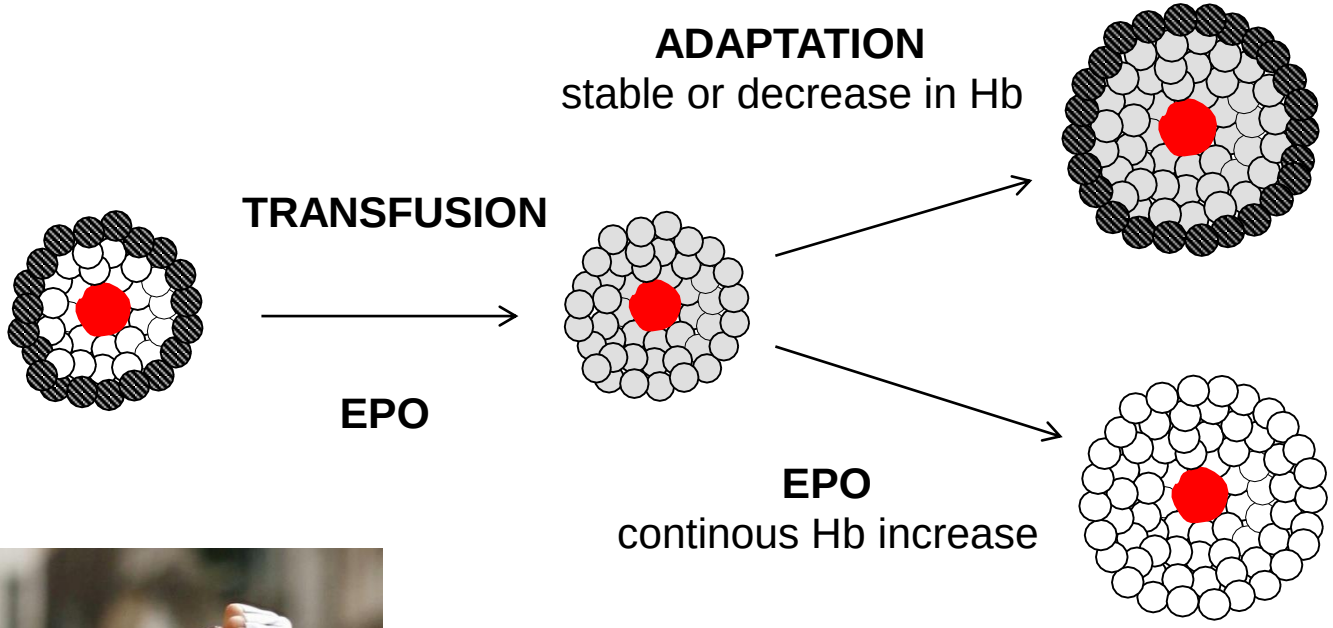
Change in intratumoral pO2 with transfusion in CCU



Aquino-Parsons et al. 1999

EPO



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DAHANCA 10 randomized phase III

LARYNX, PHARYNX* and ORAL CAVITY

T1-4,N0-3, M0 (not st 1 glottic larynx)

* Except NPC

Low hemoglobin value: ≤ 9.0 mmol/l (14.5 g/dl).

Stratify by:

Gender
Site
T&N stage
WHO perf.
Institution

RANDOMIZE

Acclerated RT (6 fx/week) (66-68 Gy/33-34 fx)
+ Hypoxic sensitizer: Nimorazol

Acclerated RT (6 fx/week) (66-68 Gy/33-34 fx)
+ Hypoxic sensitizer: Nimorazol

+

Aranesp® (darbepoetin alpha) **Weekly subcutaneously injection**

Overgaard et al ICHNO 2013

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DAHANCA 10 randomized phase III

Recruitment and number of patients

Estimated gain: 12% in loco-regional

Due to the outcome of a planned interim analysis the trial was stopped in October 2006

522 patients included

Overgaard et al ICHNO 2013

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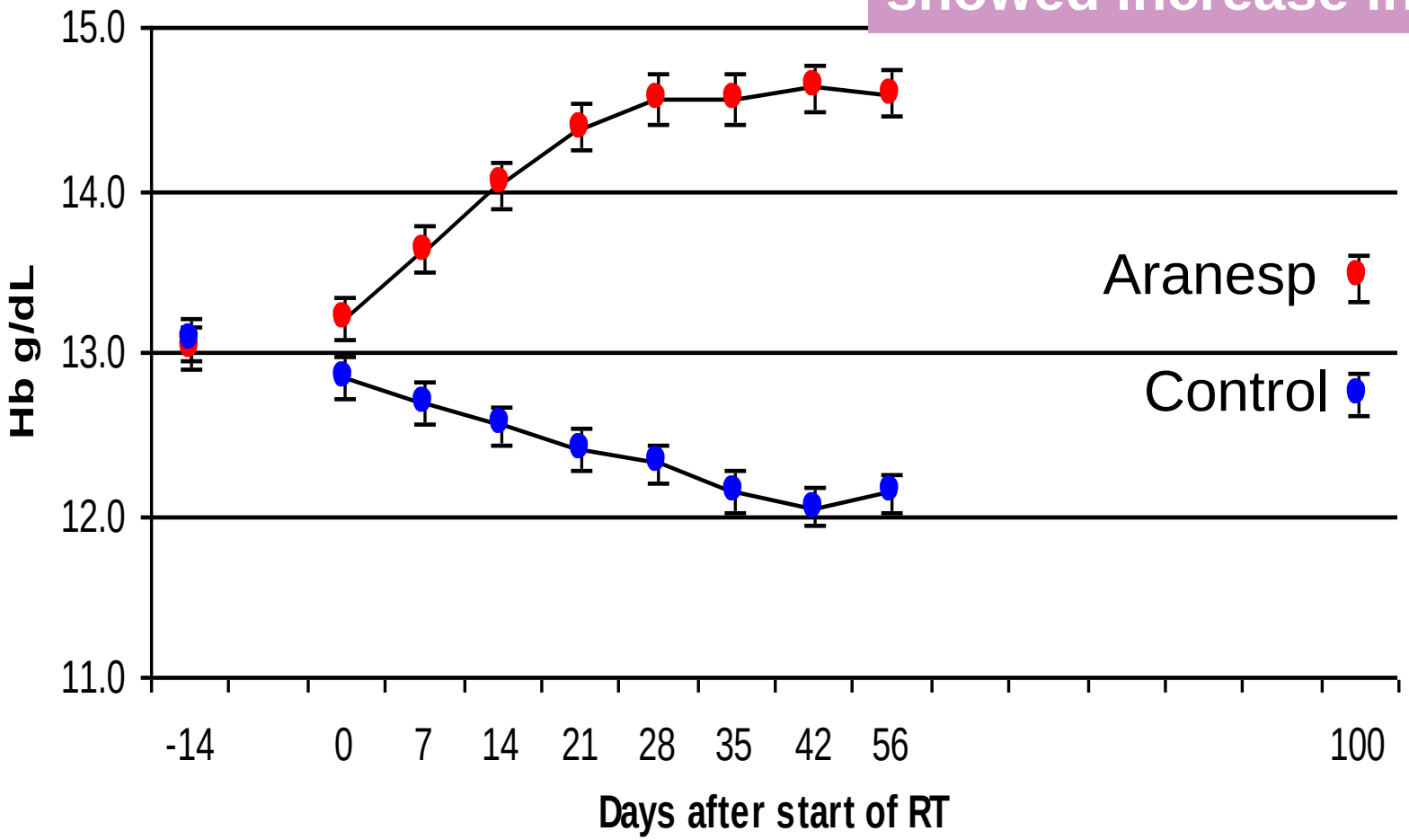
Effect of Aranesp during Radiotherapy

81% of the patients showed increase in Hb



Overgaard et al ICHNO 2013

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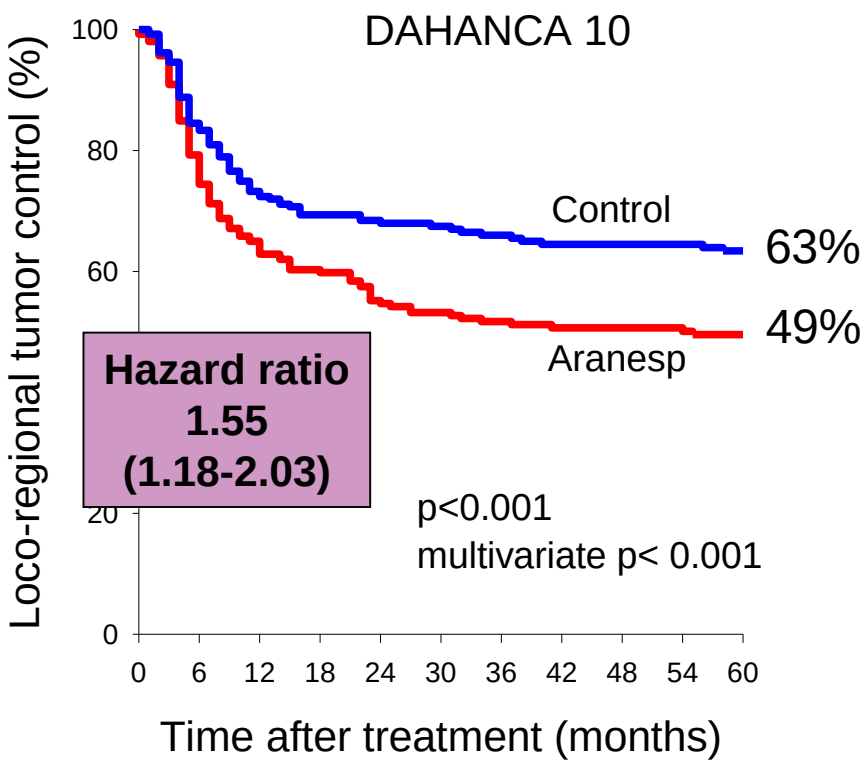
DAHANCA 10 – Loco-regional control



Overgaard et al ICHNO 2013

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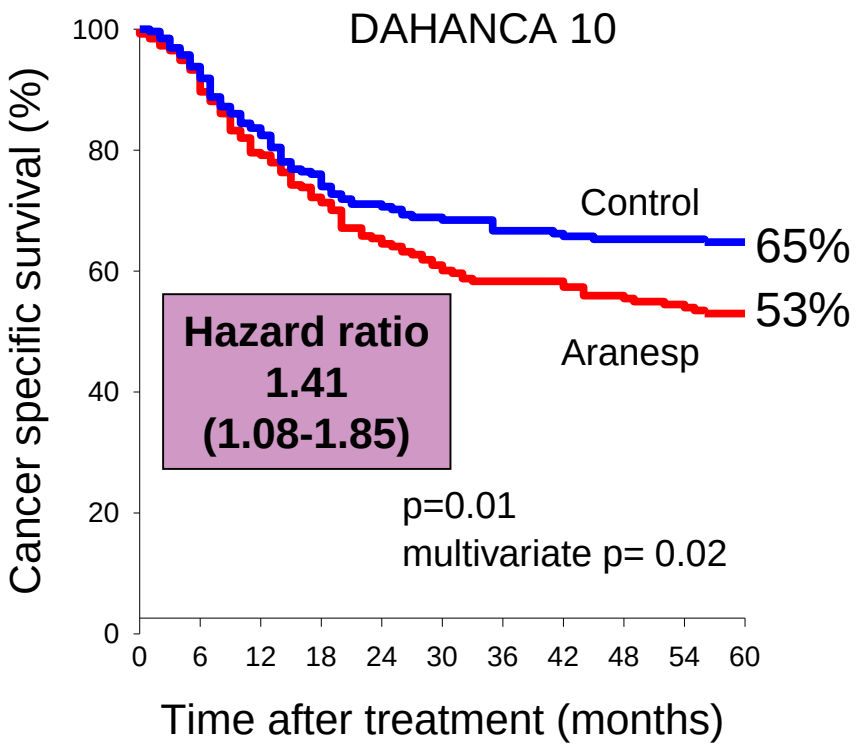
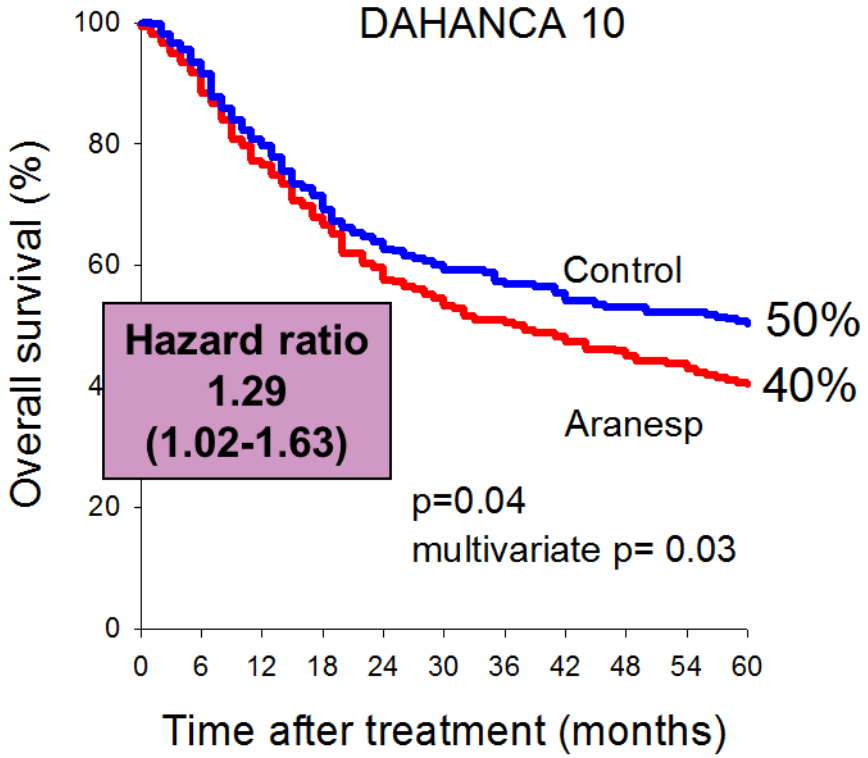
DAHANCA 10 – Cancer-specific and overall survival





Overgaard et al ICHNO 2013

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DAHANCA 10 - multivariate analyses

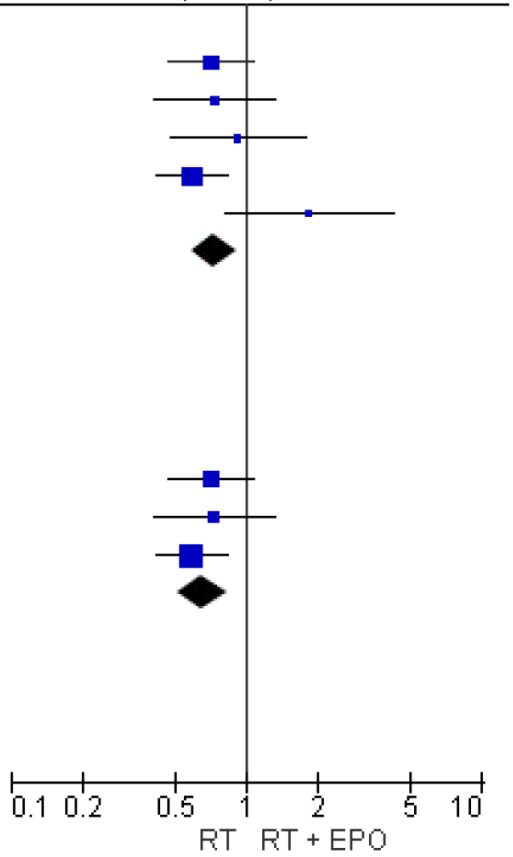
Variable	Loco-regional failure		Overall death		Disease specific survival	
	P-value	HR	P-value	HR	P-value	HR
T1-2 vs T3-4	<0.0001	2.44 (1.83-3.26)*	<0.0001	2.18 (1.73-2.759	<0.0001	2.57 (1.92-3.45)
No vs N+	0.57		0.07		0.02	1.44 (1.04-1.98)
Aranesp	0.0007	1.60 (1.22-2.10)	0.03	1.26 (1.01-1.57)	0.008	1.44 (1.10-1.909
Gender (male)	0.007	1.55 (1.11-2.17)	0.0001	1.67 (1.27-2.18)	0.0007	1.75 (1.24-2.46)
Performance, WHO	0.09		<0.0001	1.32 (1.18-1.47)	0.001	1.29 (1.13-1.46)

* 95% cf.l.

Overgaard et al ICHNO 2013

Epo - Cochrane review

Study or Subgroup	RT + EPO Events	RT + EPO Total	RT Events	RT Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.1.1 Overall survival						
Henke 2003	71	180	82	171	27.5%	0.71 [0.46, 1.08]
Hoskin 2004	122	151	127	149	13.5%	0.73 [0.40, 1.33]
Machtay 2007	37	72	37	69	11.3%	0.91 [0.47, 1.77]
Overgaard 2007	97	255	133	260	40.5%	0.59 [0.42, 0.83]
Rosen 2003	28	47	19	43	7.2%	1.84 [0.81, 4.19]
Subtotal (95% CI)		**705**		**692**	**100.0%**	**0.73 [0.58, 0.91]**
Total events	355		398			
Heterogeneity: Chi² = 6.79, df = 4 (P = 0.15); I² = 41%						
Test for overall effect: Z = 2.82 (P = 0.005)						
1.1.2 Without studies supplementing iron to intervention group only						
Henke 2003	71	180	82	171	33.7%	0.71 [0.46, 1.08]
Hoskin 2004	122	151	127	149	16.6%	0.73 [0.40, 1.33]
Overgaard 2007	97	255	133	260	49.7%	0.59 [0.42, 0.83]
Subtotal (95% CI)		**586**		**580**	**100.0%**	**0.65 [0.51, 0.83]**
Total events	290		342			
Heterogeneity: Chi² = 0.62, df = 2 (P = 0.73); I² = 0%						
Test for overall effect: Z = 3.46 (P = 0.0005)						



Lambin et al 2009

THE COCHRANE COLLABORATION®

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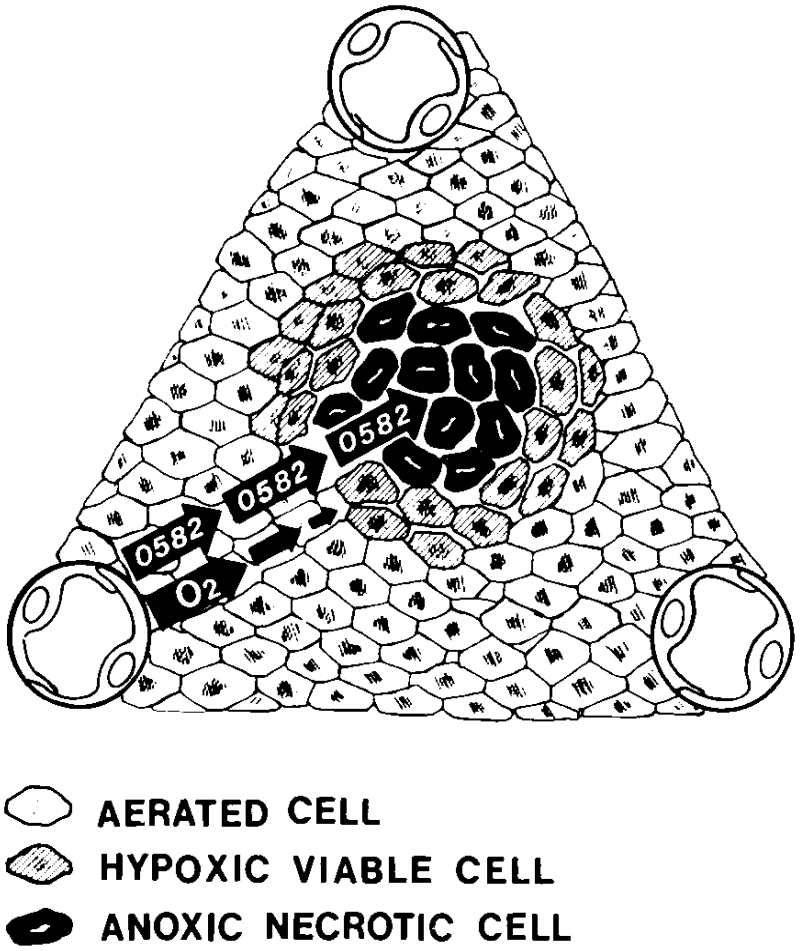
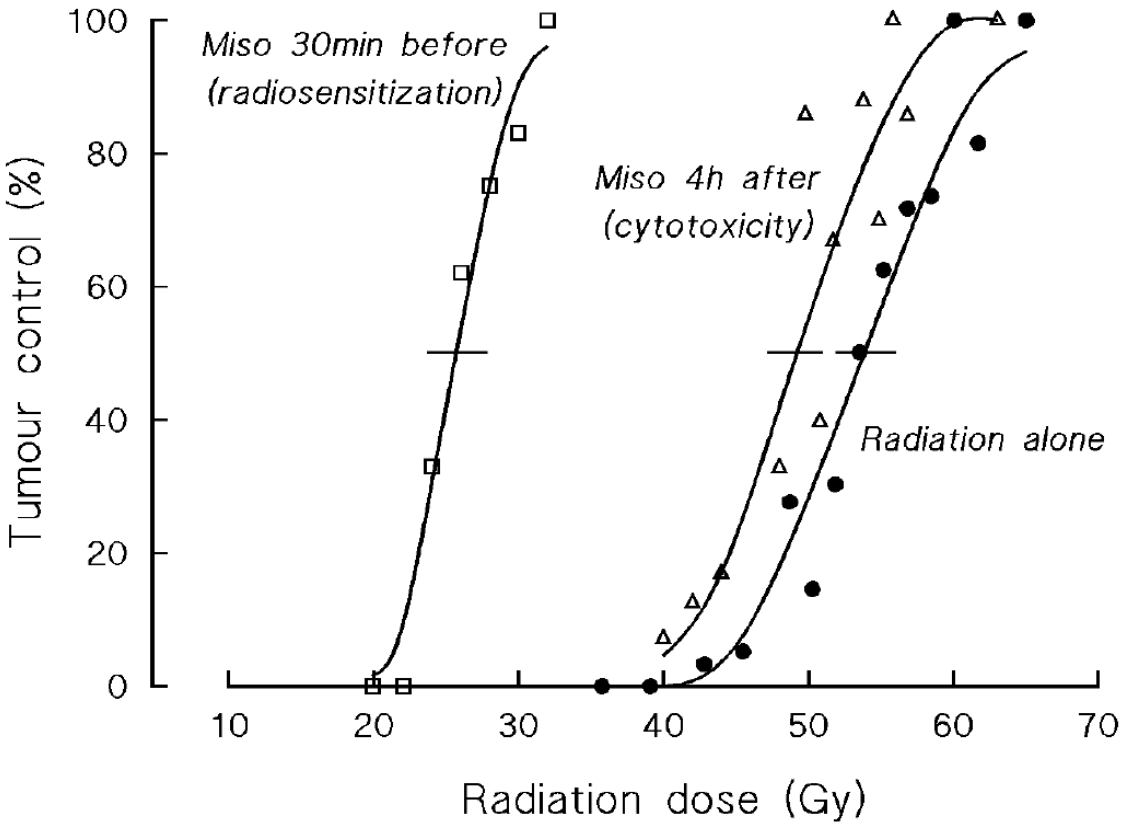
Hypoxic cell radiosensitizers

A drug which selectively sensitizes hypoxic cells to the effect of ionizing irradiation by mimicking the role of oxygen in radiation damage fixation



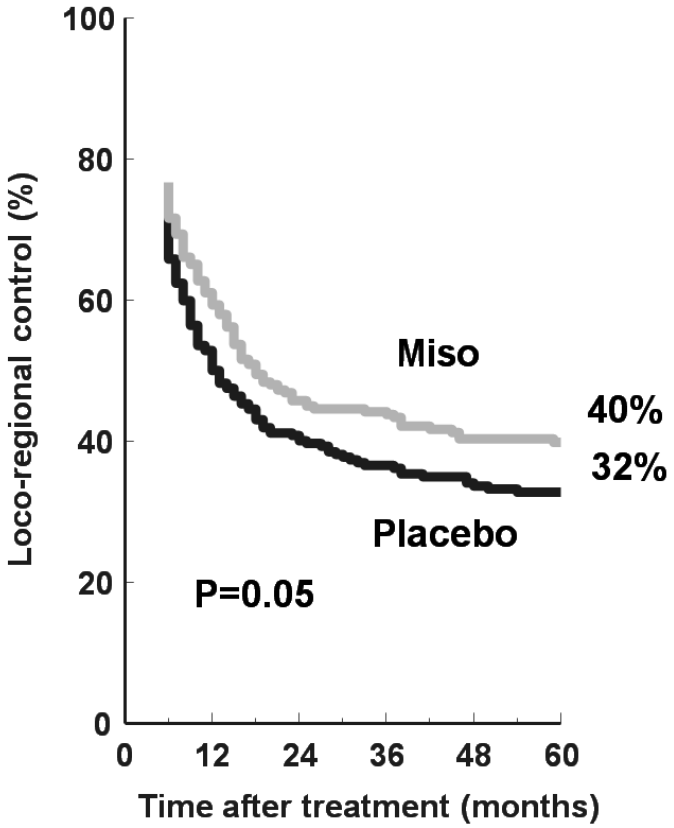
Hypoxic cell radiosensitizers:misonidazole

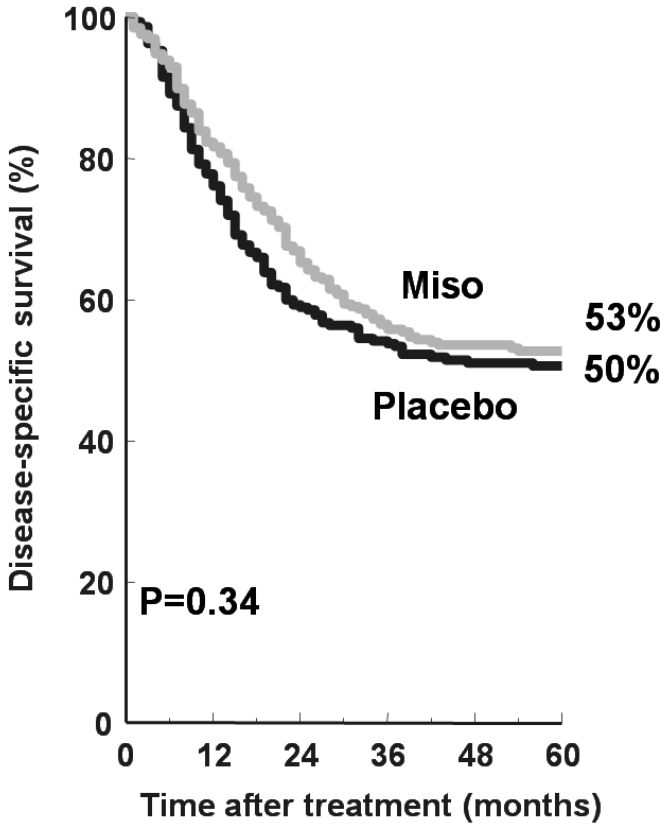


DAHANCA 2: +/-misonidazole

LARYNX AND PHARYNX - 622 pts.

MISONIDAZOLE vs PLACEBO (66 Gy/ 33 fx - 9.5 wk, split-course)





Overgaard et al 1989

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DAHANCA 2: +/-misonidazole

UNACCEPTABLE MISONIDAZOLE RELATED TOXICITY

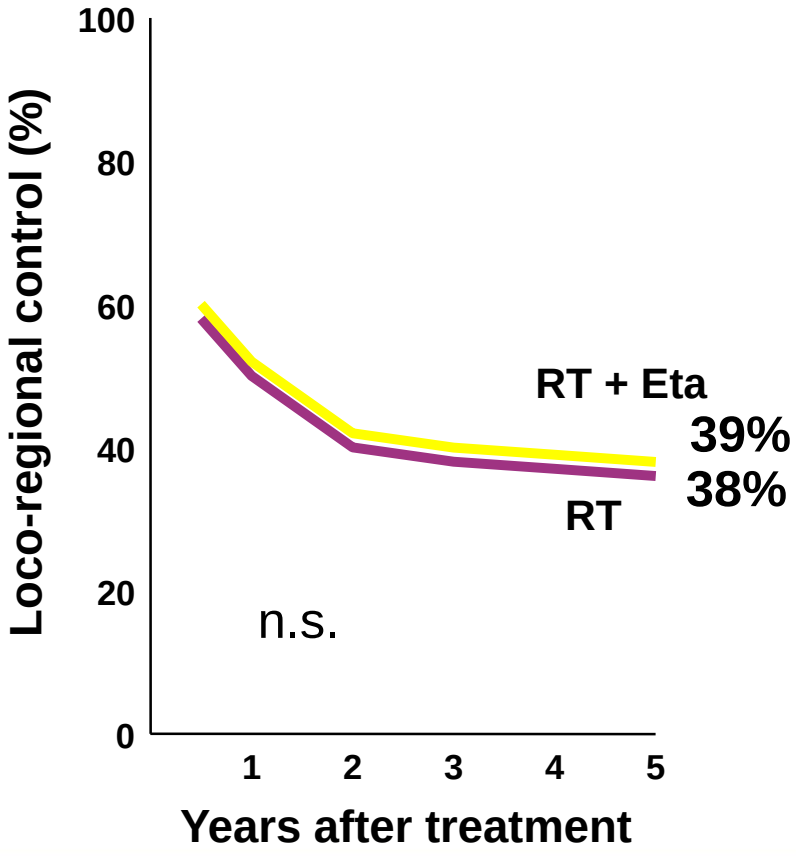
Symptom	Misonidazole (330 pts)	Placebo (296 pts)
Nausea	20%	13%
Skin rash	12%	3%
Neuropathy	**26%**	2%

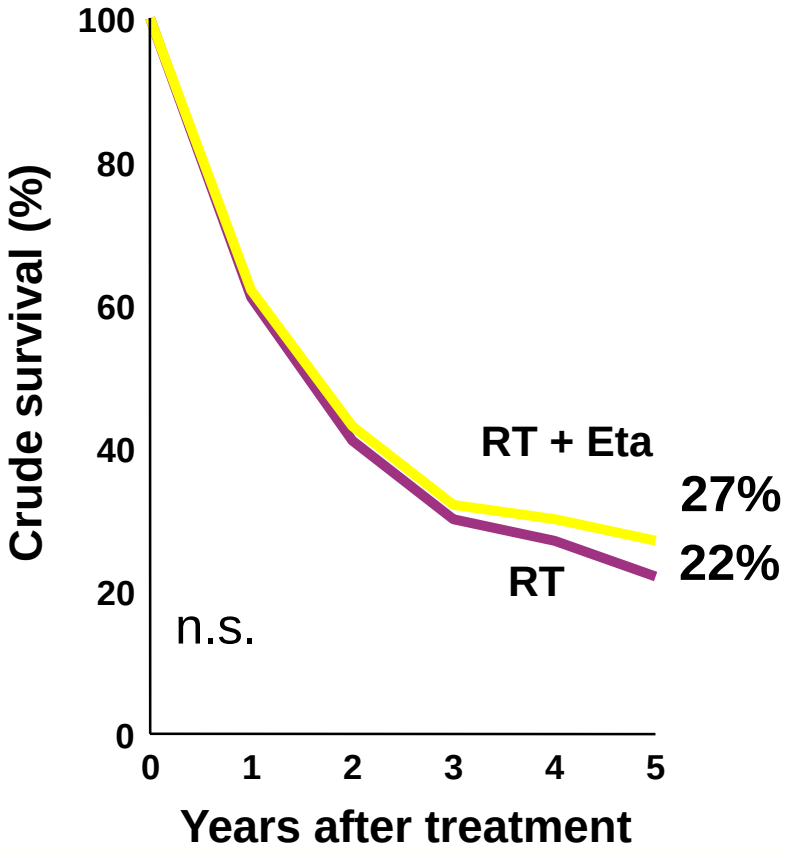
Overgaard et al 1989

ESTRO School

Etanidazole

RTOG 85-27, 504 H&N patients





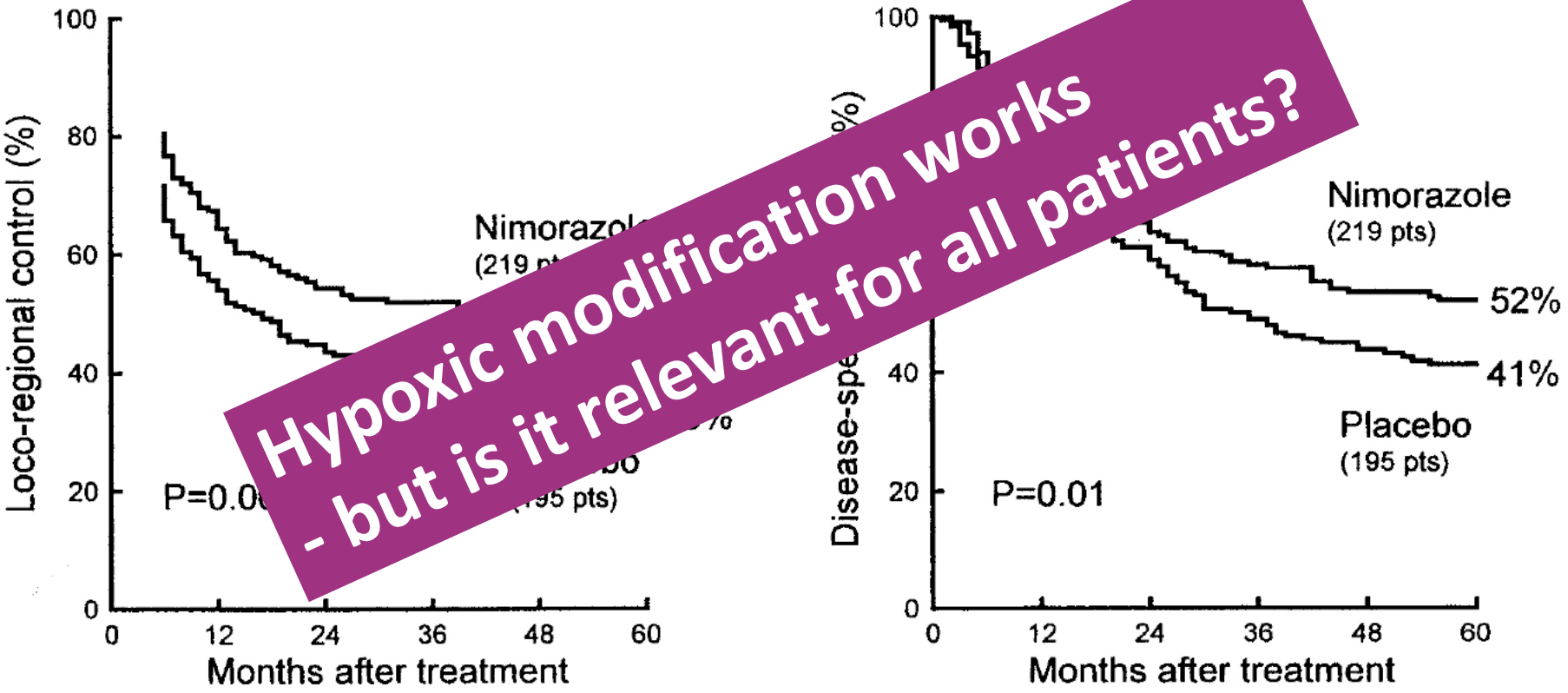
Lee et al. 1995

ESTRO School

DAHANCA 5: RT +/- nimorazole

SUPRAGLOTTIC AND PHARYNX - 414 pts.

NIMORAZOLE vs PLACEBO (66 Gy/ 33 fx - 6.5 wk)

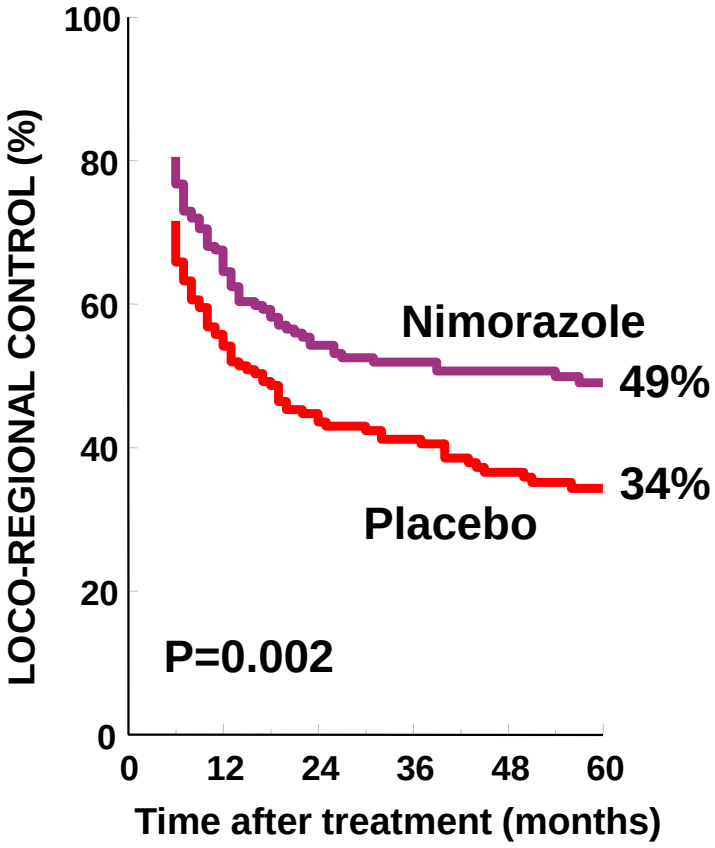


Hypoxic modification works - but is it relevant for all patients?

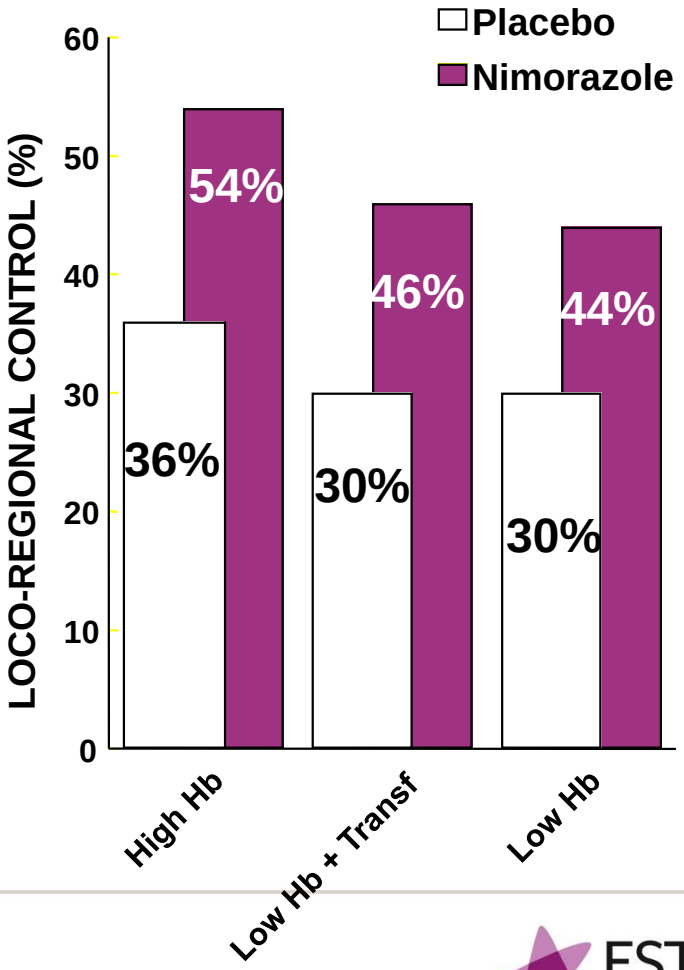
Overgaard et al 1998

ESTRO School

Effect of Nimorazole and blood transfusion



5-years actuarial value



Hoff CM 2011

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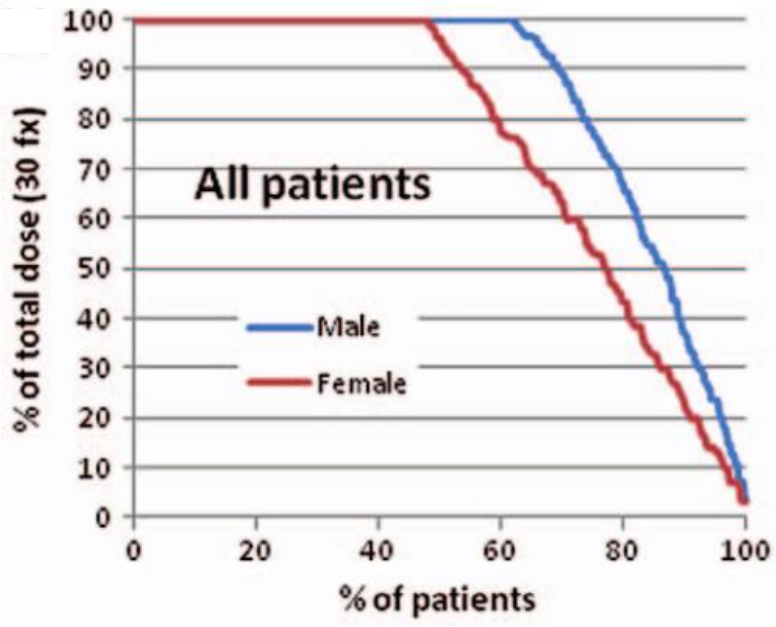
Effect of hypoxic modification with Nimorazole

Endpoint	Loco- regional failure	Dead of disease
Relative Risk Reduction	26%	27%
Absolute Risk Reduction	16%	12%
Number of patients needed to treat (to achive benefit)	6	6

Side-effect of hypoxic modification with Nimorazole

- 1049 patients
- 58% received full prescribed dose
- 260 had dose reductions due to side effects

Side-effect	%
Nausea/vomiting	87 %
Skin rash	10 %
Fushing	2 %
Unknown	23%

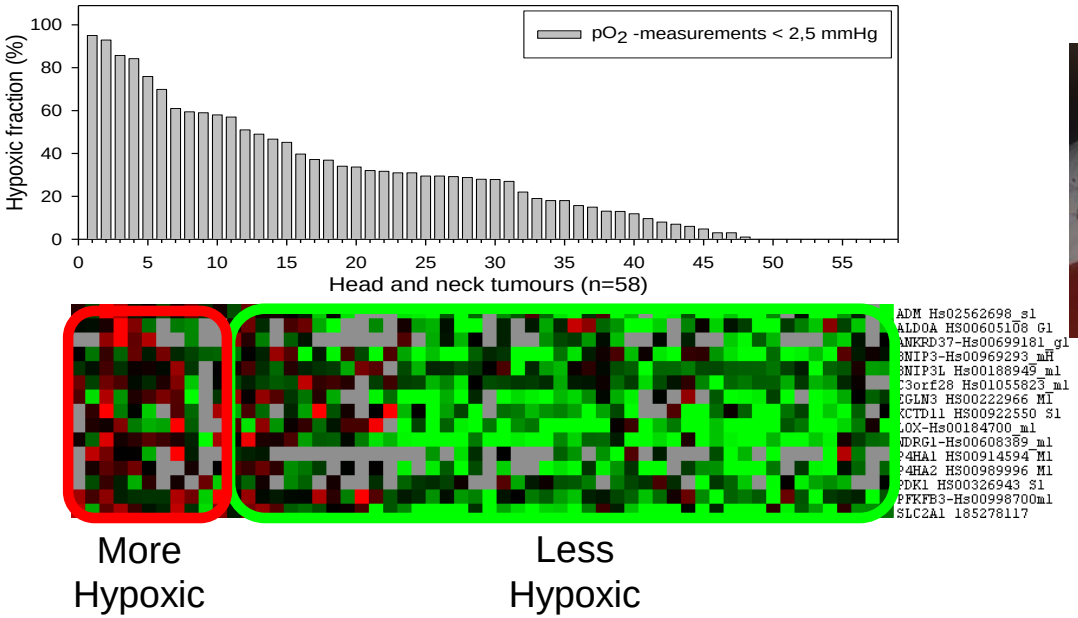


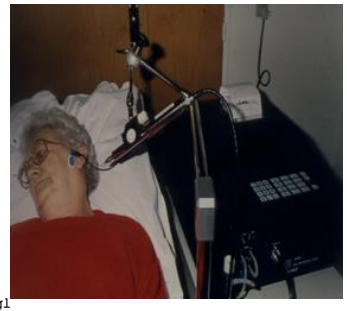
Metwally MAH et al, 2013

ESTRO School

Hypoxia-classification: 15-gene hypoxia classifier

- Based on hypoxia induced genes (in vitro/in vivo validated)
- Classification based on gene expression similarity to either ”more” or ”less” hypoxic tumours as estimated with pO_2-electrode in an independent trainingset of 58 H&N cancer patients





Toustrup K et al, 2011

ESTRO School

Validating the hypoxia classifier: Independent dataset

414 patients enrolled in the DAHANCA 5 trial

219 randomly assigned to radiotherapy and nimorazole

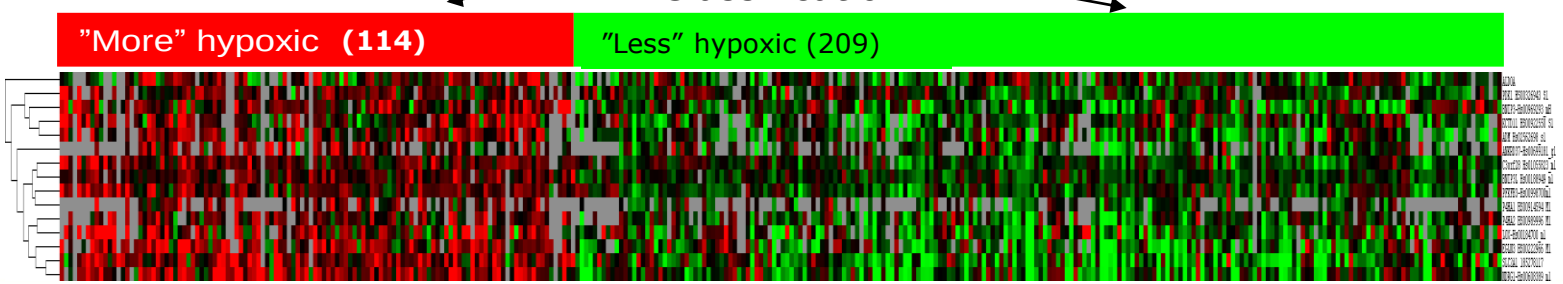
195 randomly assigned to radiotherapy and placebo

52 excluded from classification (2 failed in PCR, 50 did not have tumour tissue for PCR)

39 excluded from classification (1 failed in PCR, 38 did not have tumour tissue for PCR)

323 tumour samples for classification

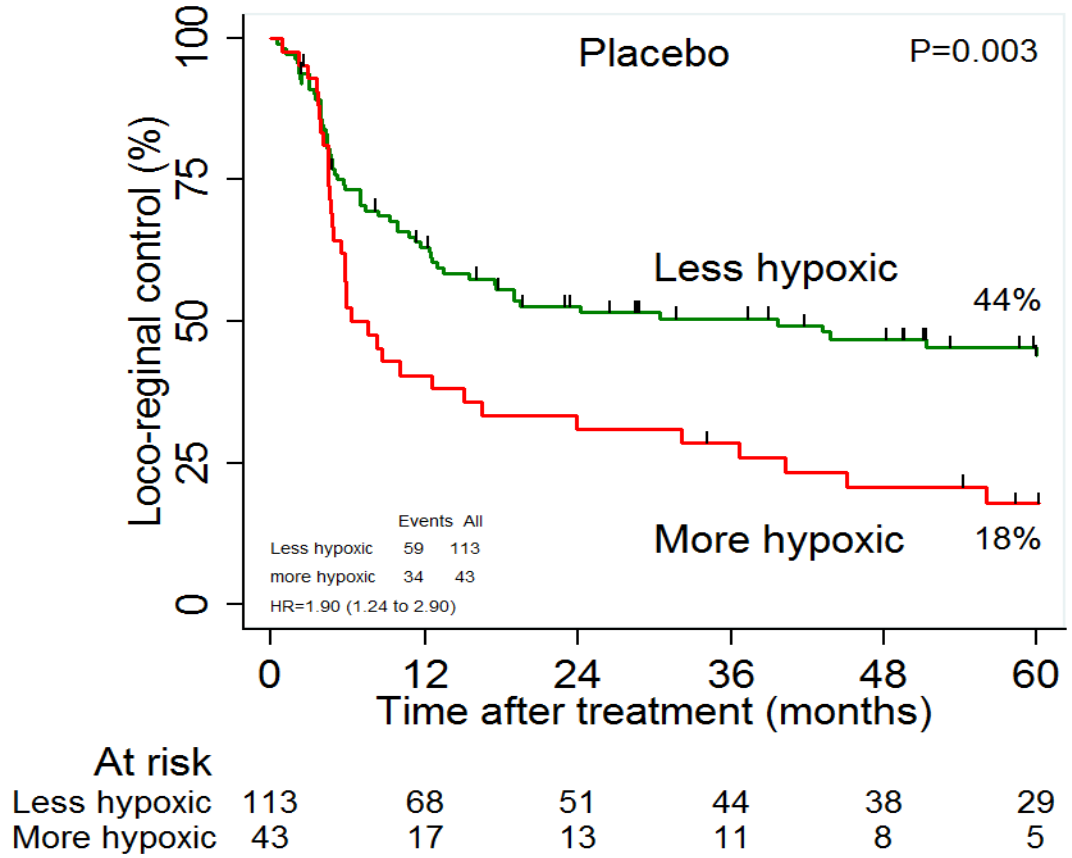
Classification



Toustrup K et al, 2012

ESTRO School

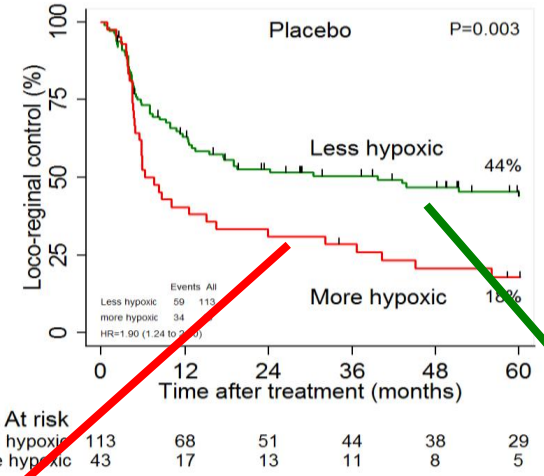
Validating the hypoxia classifier: Independent dataset

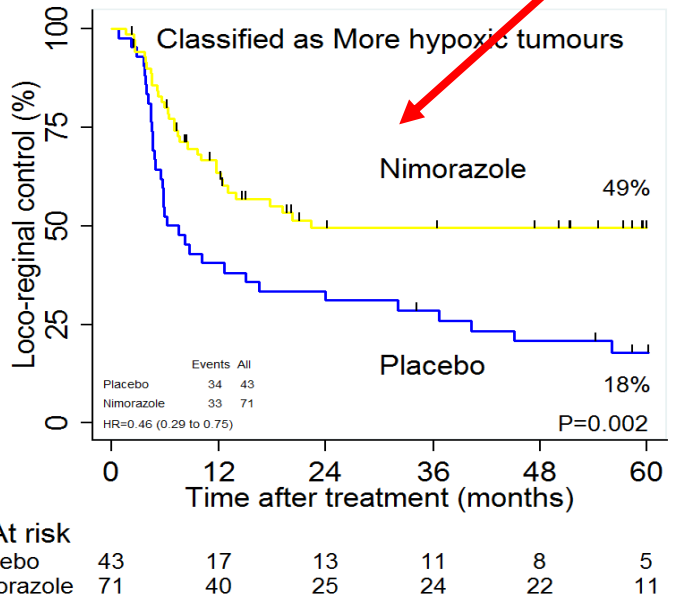


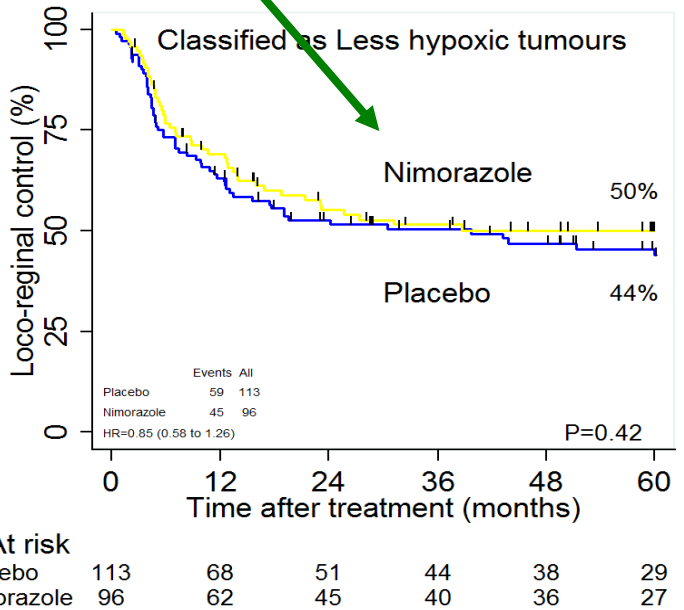
Toustrup K et al, 2012

ESTRO School

Validating the hypoxia classifier: Independent dataset







Toustrup K et al, 2012

ESTRO School

EORTC/DAHANCA 29 randomized phase III

Role of Nimorazole in chemo-radiation of HPV neg HNSCC

LARYNX, PHARYNX* * Except NPC

HPVneg (p16); Stage 3-4 (T2-4,N0-3)

Stratify:

Stage
Site
Inst.
Hypox.
Gene profile
(retro-spective)

RANDOMIZE

Accl RT(6 fx/wk) +cisPl

640 patients – (>200 with positive hypoxic gene profile).

Pivotal trial to establish the true indication of Nimorazole in Chemoradiotherapy of advanced HNSCC and the value of the hypoxic gene profile

Accl RT(6 fx/wk) +cisPl
+ Nimorazole (1.2 g/m2)

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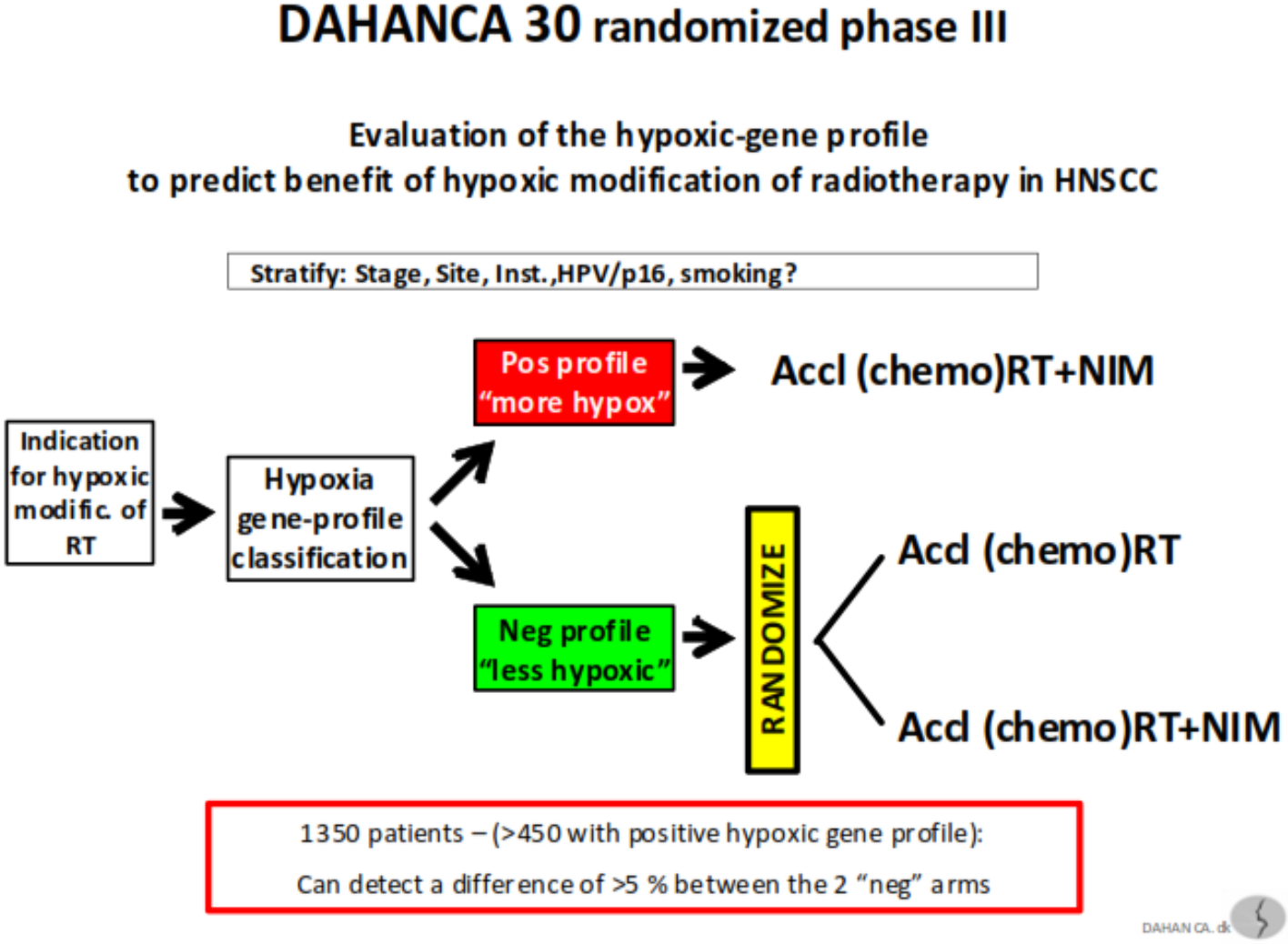
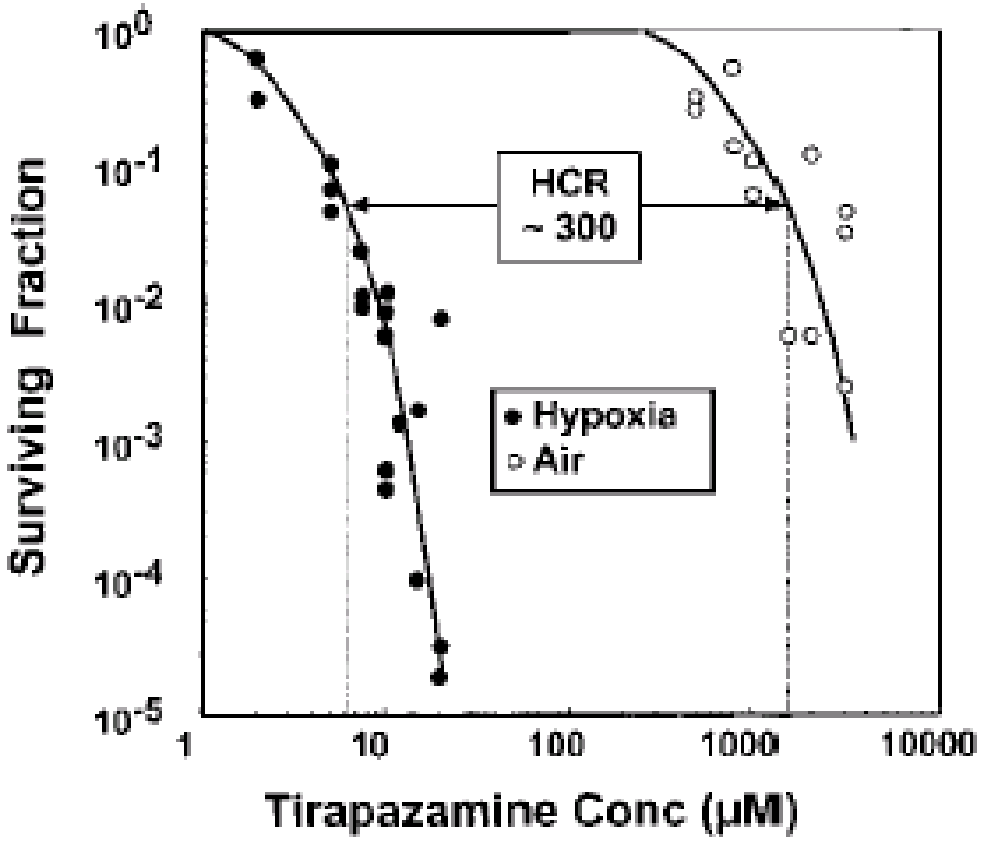
DAHANCA 30 randomized phase III trial



Hypoxic cytotoxins



Quinone antibiotics

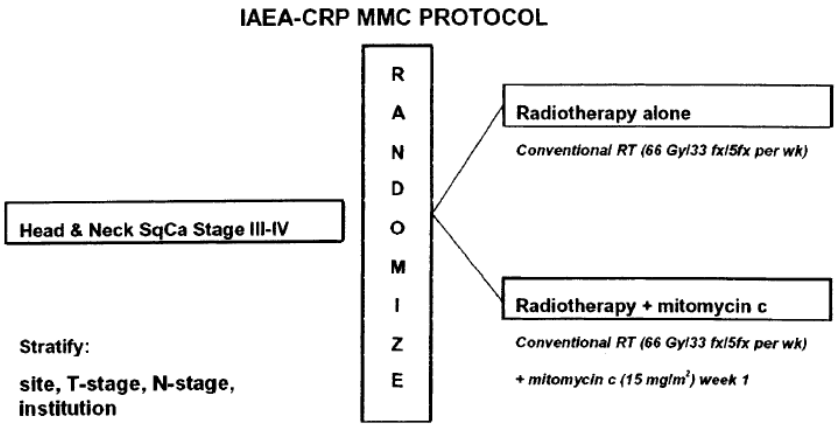
- Mitomycin C

N-oxides

- Tirapazamine

Brown 2000

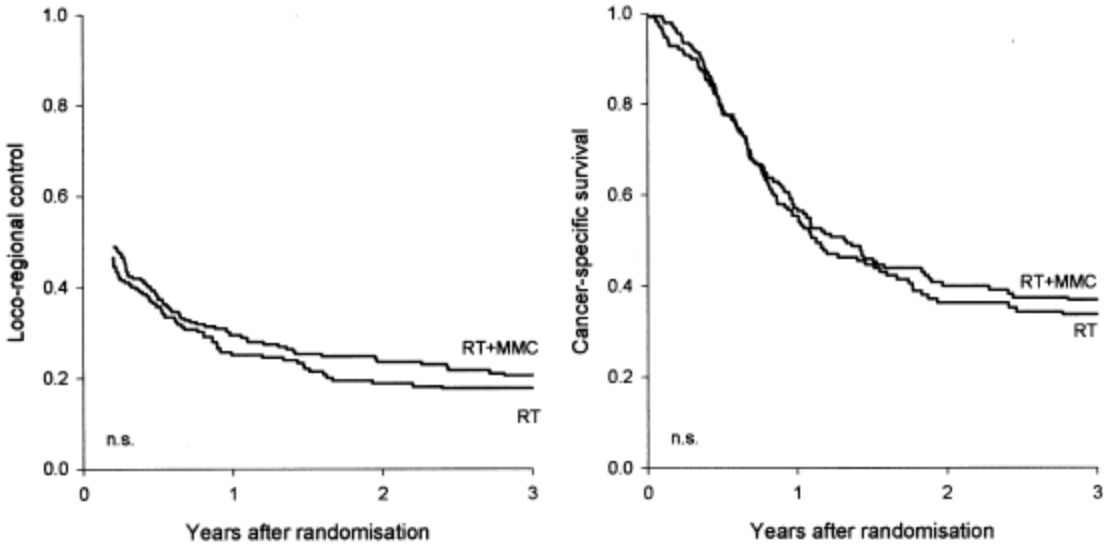
Mitomycin C chemoradiation in HNSCC



Radiotherapy with or without mitomycin c in the treatment of locally advanced head and neck cancer: results of the IAEA multicentre randomised trial

Cai Grau[a,*], Jai Prakash Agarwal[b], Kaukab Jabeen[c], Abdul Rab Khan[d], Sarath Abeyakoon[e], Tatiana Hadjieva[f], Ibrahim Wahid[g], Sedat Turkan[h], Hideo Tatsuzaki[i], Ketayun A. Dinshaw[b], Jens Overgaard[a]

N=558; 478 elegible
66Gy/ 33, 5fx/w +/-a single injection
(15 mg/m²) of MMC
the first week of RT

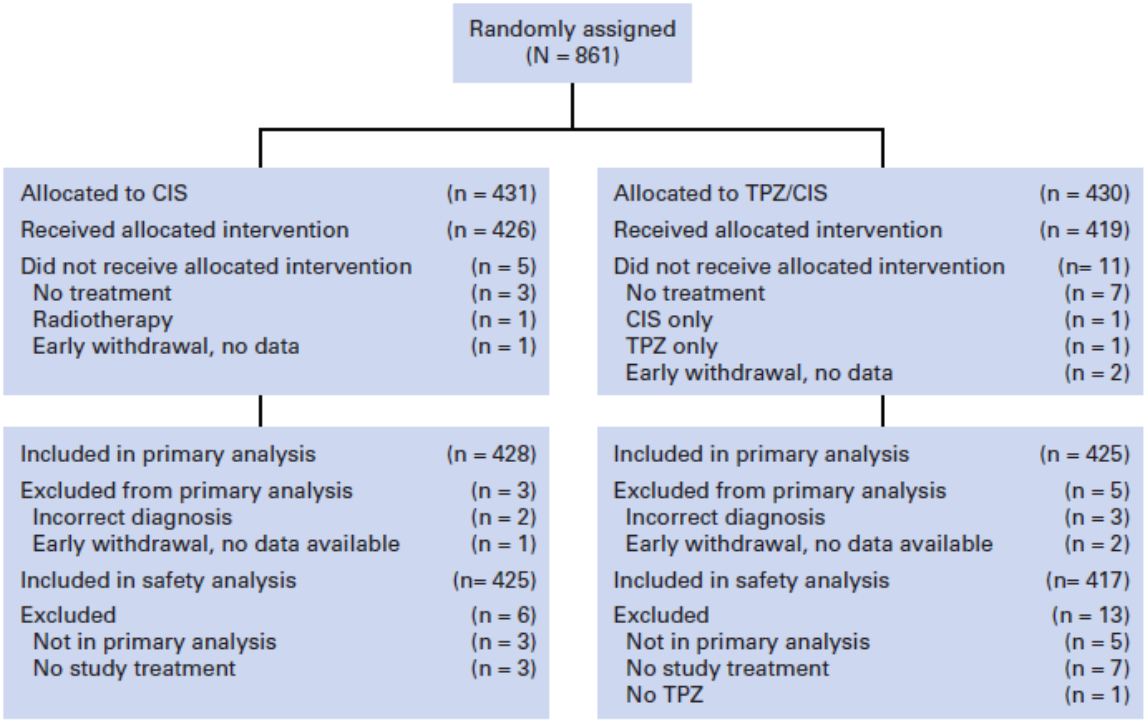


Grau et al 2003

ESTRO School

Tirapazamine

Tirapazamine, Cisplatin, and Radiation Versus Cisplatin and Radiation for Advanced Squamous Cell Carcinoma of the Head and Neck (TROG 02.02, HeadSTART): A Phase III Trial of the Trans-Tasman Radiation Oncology Group



89 sites

16 countries

Tirapazamine is a bioreductively activated, hypoxia-selective antitumor agent of the benzotriazine series that can potentiate both radiation and CIS cytotoxicity.

Rischin et al 2010;

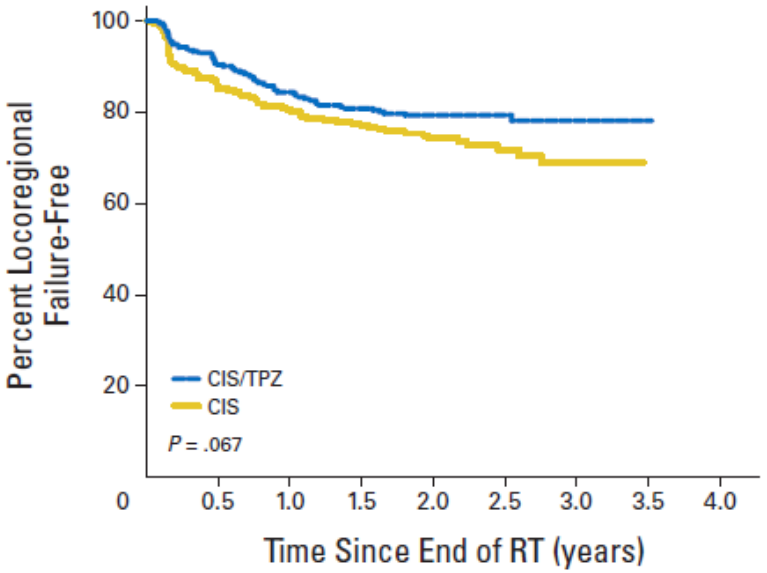
Tirapazamine

Tirapazamine, Cisplatin, and Radiation Versus Cisplatin and Radiation for Advanced Squamous Cell Carcinoma of the Head and Neck (TROG 02.02, HeadSTART): A Phase III Trial of the Trans-Tasman Radiation Oncology Group

Table 3. Investigator Factors (country and enrollment bracket) Analyzed for Adverse Impact on Tumor Control Probability After Secondary Review (n = 818)

Factor	No. of Patients	Number With Major Adverse Impact	%
Country			
Western Europe C	39	0	0.0
Oceania A	154	8	5.2
North America A	101	6	5.9
Eastern Europe A	48	5	10.4
South America A	54	6	11.1
Western Europe B	67	8	11.9
Western Europe E	25	3	12.0
Oceania B	16	2	12.5
Western Europe A	127	17	13.4
South America B	42	6	14.3
Eastern Europe B	28	4	14.3
North America B	63	10	15.9
Western Europe D	30	5	16.7
Western Europe F	6	2	33.3
Western Europe G	4	2	50.0
Eastern Europe C	14	13	92.9
Enrollment bracket			
1-4 (26 centers)	57	17	29.8
5-9 (22 centers)	130	28	21.5
10-19 (22 centers)	279	33	11.8
≥ 20 (11 centers)	352	19	5.4

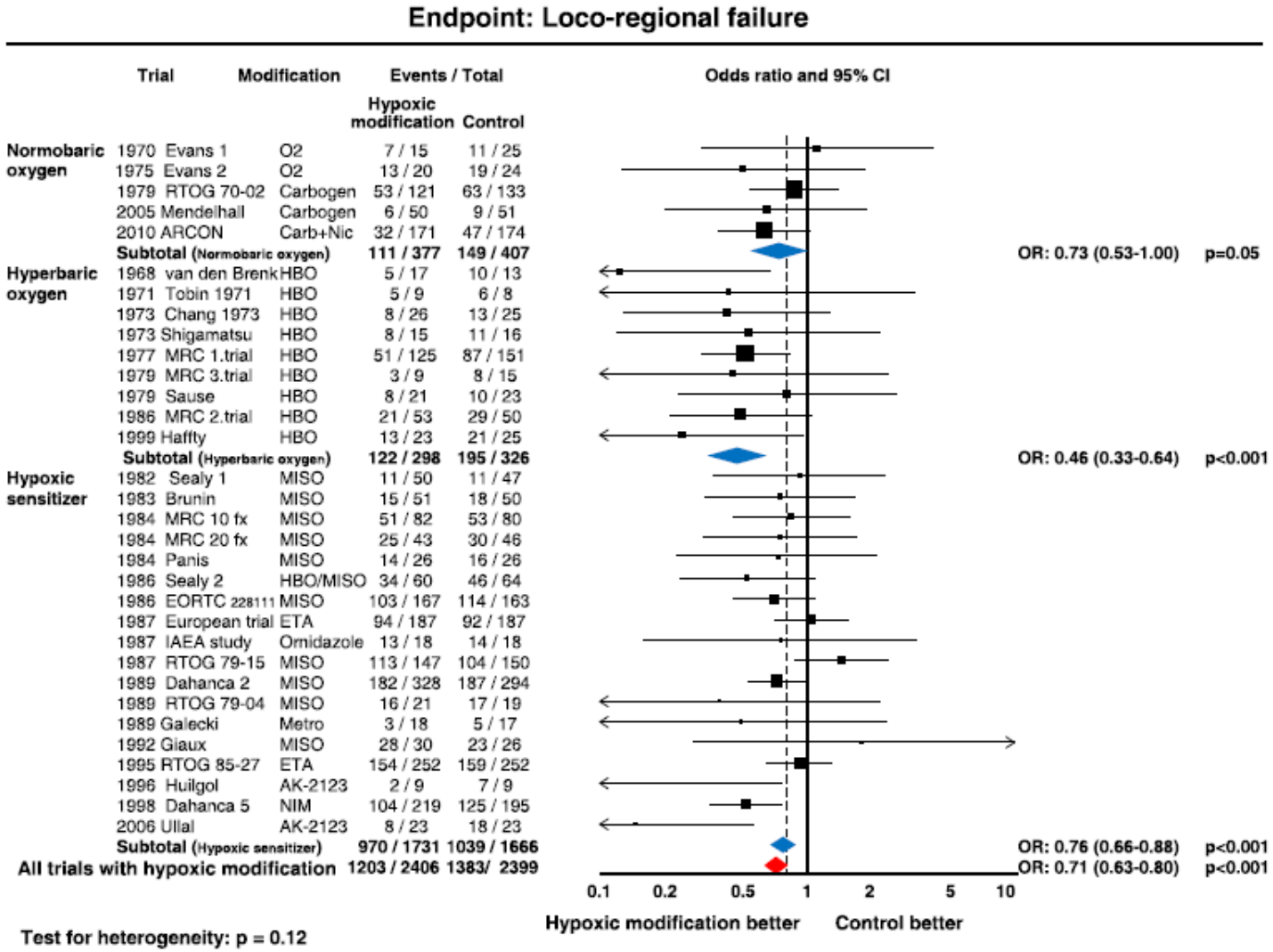
NOTE. $P < .001$ for country and enrollment bracket. Letters refer to countries in each region ranked in order of number of patients enrolled.



Rischin et al 2010; Peters et al 2010

ESTRO School

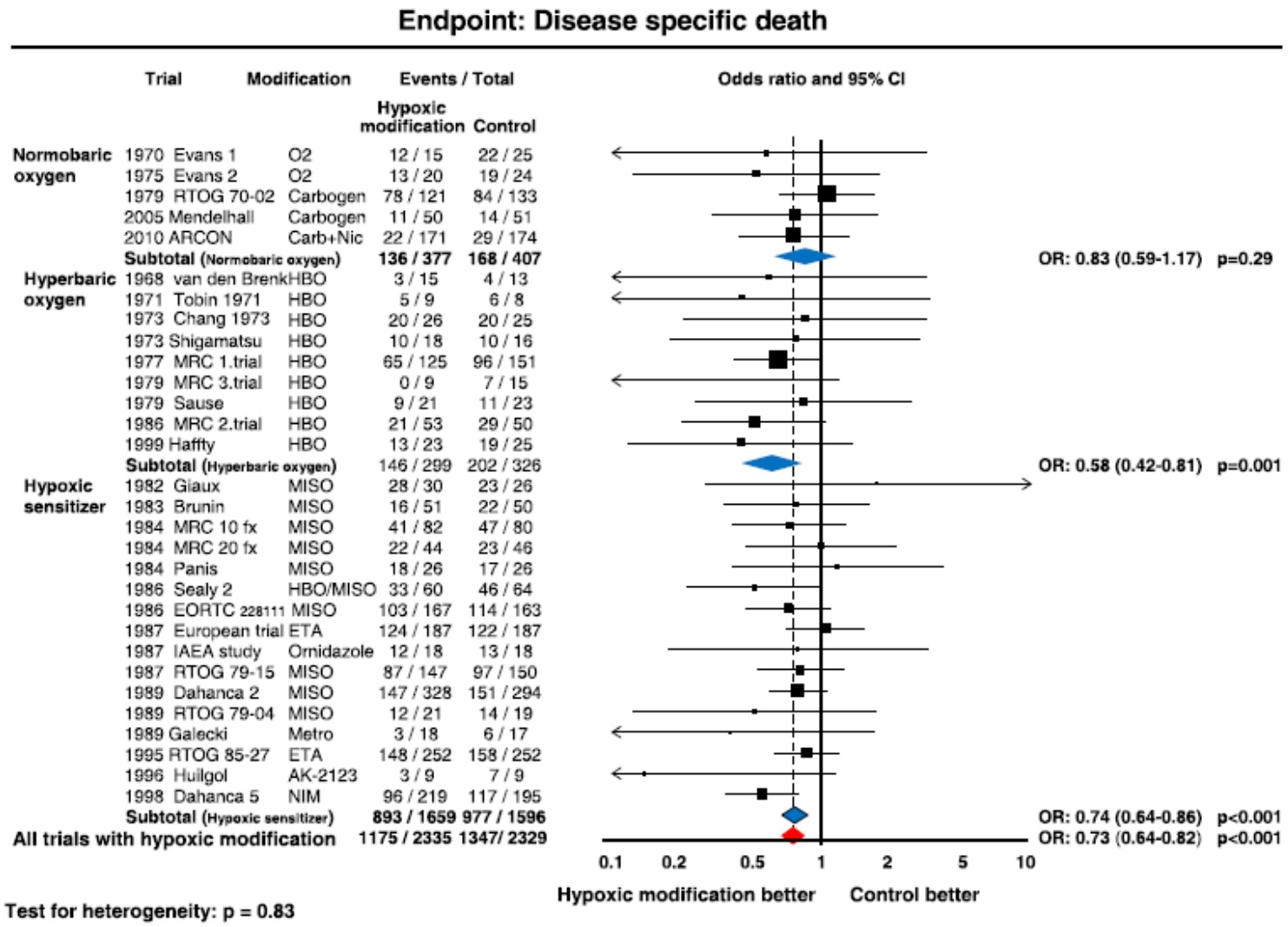
Metaanalysis of hypoxic modification



Overgaard et al 2011

ESTRO School

Metaanalysis of hypoxic modification



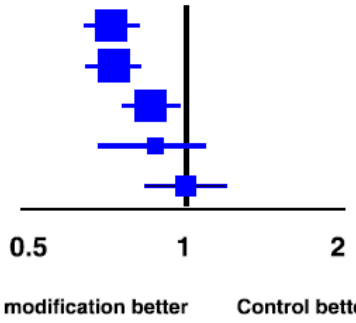
Overgaard et al 2011

ESTRO School

Metaanalysis of hypoxic modification

Head and neck cancer - meta analysis - summary

Endpoint	Events / Total		Odds ratio and 95% CI			
	Hypoxic modification	Control		Odds ratio	Risk Reduction	NNT**
Loco-regional control	1203 / 2406	1383 / 2399		0.71 (0.63-0.80)*	8% (5-10%)*	13
Disease specific survival	1175 / 2335	1347 / 2329		0.73 (0.64-0.82)	7% (5-10%)	14
Overall survival	1450 / 2312	1519 / 2305		0.87 (0.77-0.98)	3% (0-6%)	31
Distant metastasis	159 / 1427	179 / 1391		0.87 (0.69-1.09)	2% (-1-4%)	57
Radiotherapy complications	307 / 1864	297 / 1822		1.00 (0.82-1.23)	0% (-3-2%)	>>



Meta Analysis - Hypoxic modification of radiotherapy in HNSCC

* 95% CI.
** Numbers of patients Needed to Treat to achieve benefit in one patients.

Overgaard et al 2011

ESTRO School

Conclusive remarks

- Hypoxia can be modulated in HNSCC and CCU
- Influences LRC, DSS and OS
- But still “adored in lab, ignored in the clinic”.
- Success’es as well as dissapointments
- A few really ugly ones
- New trials of imidazoles in Asia, UK and EORTC
- Gene-test

Combined drug-radiation treatment: cervix cancer

Dr Li Tee Tan

Cambridge University Hospitals NHS
NHS Foundation Trust

Outline

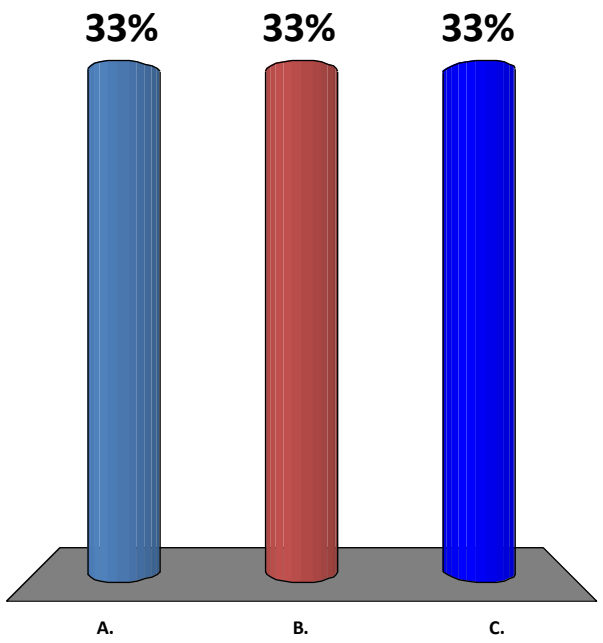
- Concomitant chemotherapy
- Neoadjuvant chemotherapy
- Adjuvant chemotherapy
- Targeted agents
- Personalised medicine
- Clinical cases

Outline

- **Concomitant chemotherapy**
  - **Evidence**
  - Questions
- Neoadjuvant chemotherapy
- Adjuvant chemotherapy
- Targeted agents
- Personalised medicine
- Clinical cases

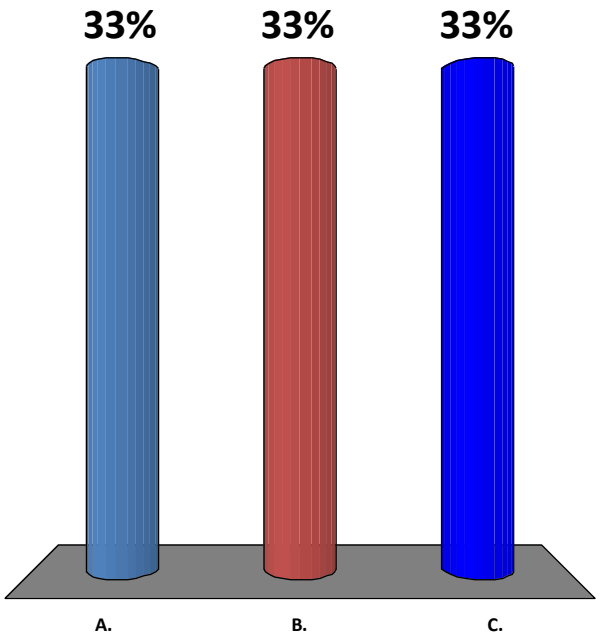
Is concomitant chemotherapy routinely given with radiotherapy for cervix cancer at your centre?

A. Yes
B. No



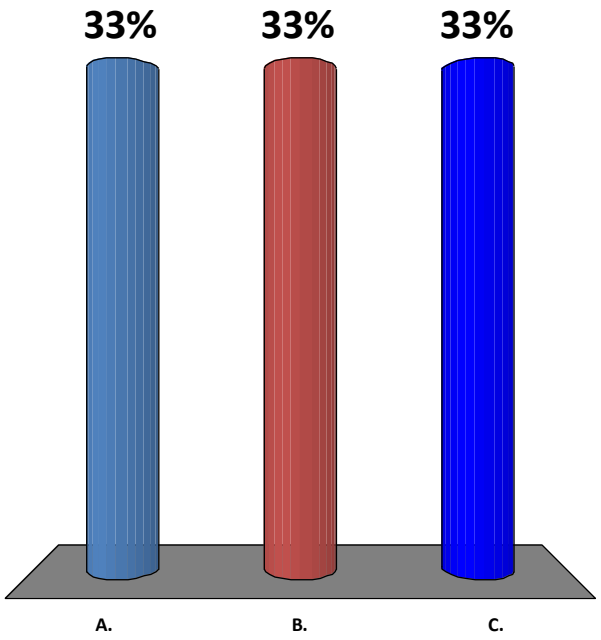
Which concomitant chemotherapy regimen is used at your centre?

A. Weekly cisplatin only
B. Weekly cisplatin and cisplatin-5FU
C. Both platinum and non-platinum regimens



Which FIGO stage would you treat with concomitant chemo-RT?

A. All stages
B. Not Ib1 patients
C. Not IIIb or IVa patients



NCI clinical alert 1999

NIH NEWS ADVISORY

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

EMBARGOED FOR RELEASE
Monday, February 22, 1999
10 a.m. EST

NCI Press Office
(301) 496-6641

NCI Issues Clinical Announcement on Cervical Cancer: Chemotherapy Plus Radiation Improves Survival

UK survey 2000

96% (46/48) respondents had begun using chemo-RT for cervical cancer

Tan LT, et al. Clin Oncol (R Coll Radiol). 2004.

Evidence

Trial	Publication
GOG 85	Whitney CW, *et al*. J Clin Oncol 1999; 17(5):1339-1348
RTOG 9001	Morris M, *et al*. N Engl J Med 1999; 340(15):1137-1143
GOG 120	Rose PG, *et al*. N Engl J Med 1999; 340(15):1144-1153
SWOG 8797	Peters WA, III, *et al*. J Clin Oncol 2000; 18(8):1606-1613
GOG 123	Keys HM, *et al*. N Engl J Med 1999; 340(15):1154-1161

Benefit

Trial	Patients	Survival gain	*p* value
GOG 85	388	10% at 3 years	0.02
RTOG 9001	403	15% at 5 years	0.004
GOG 120	767	18% at 3 years	0.004
SWOG 8797	268	10% at 4 years	0.007
GOG 123	374	9% at 3 years	0.008

Comparison

Trial	Control	Experimental
GOG 85	RT + HU	CRT
RTOG 9001	EFRT	CRT
GOG 120	RT + HU	CRT ± HU
SWOG 8797	S + RT	S + CRT + CT
GOG 123	RT + S	CRT + S

Chemotherapy

Trial	Regimen
GOG 85	Cisplatin 50 mg/m^2 + 5-FU 4000 mg/m^2
RTOG 9001	Cisplatin 75 mg/m^2 + 5-FU 4000 mg/m^2
GOG 120	Cisplatin 40 mg/m^2 Cisplatin 50 mg/m^2 + 5-FU 4000 mg/m^2 + HU 2 g/m^2
SWOG 8797	Cisplatin 70 mg/m^2 + 5-FU 4000 mg/m^2
GOG 123	Cisplatin 40 mg/m^2

Chemotherapy

Trial	Regimen
GOG 85	Cisplatin 50 mg/m^2 + 5-FU 4000 mg/m^2
RTOG 9001	Cisplatin 75 mg/m^2 + 5-FU 4000 mg/m^2
GOG 120	Cisplatin 40 mg/m^2 Cisplatin 50 mg/m^2 + 5-FU 4000 mg/m^2 + HU 2 g/m^2
SWOG 8797	Cisplatin 70 mg/m^2 + 5-FU 4000 mg/m^2
GOG 123	Cisplatin 40 mg/m^2

Chemotherapy

Trial	Regimen
GOG 85	Cisplatin 50 mg/m^2 + 5-FU 4000 mg/m^2
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GOG 120	Cisplatin 40 mg/m^2 Cisplatin 50 mg/m^2 + 5-FU 4000 mg/m^2 + HU 2 g/m^2
SWOG 8797	Cisplatin 70 mg/m^2 + 5-FU 4000 mg/m^2
GOG 123	Cisplatin 40 mg/m^2
Pearcey 2002	Pelvic RT ± Cisplatin 40 mg/m^2, 259 pat, ns for OS/LC

Meta-analyses

- **2001 (2005)**

  Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis.

  *Lancet 2001;**358**:781–6*

- **2002**

  Concurrent cisplatin-based chemotherapy plus radiotherapy for cervical cancer--a meta-analysis.

  *Clin Oncol (R Coll Radiol). 2002;**14**:203-12*

- **2008**

  Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials.

  *J Clin Oncol. 2008;**26**:5802-12*

Conclusion 1

- Addition of chemotherapy to radiotherapy significantly improves 5-year survival

5-year survival

Metaanalysis	Trials	Patients	Increase	HR	*p* value
2001 (2005)	24	4921	10% (7 to 13%)	0.69 (0.61 to 0.77)	<0.00001
2002	8	1065		0.74 (0.64 to 0.86)	0.00006
2008	13	3104	6%	0.81 (0.71 to 0.91)	0.0006

Other measures

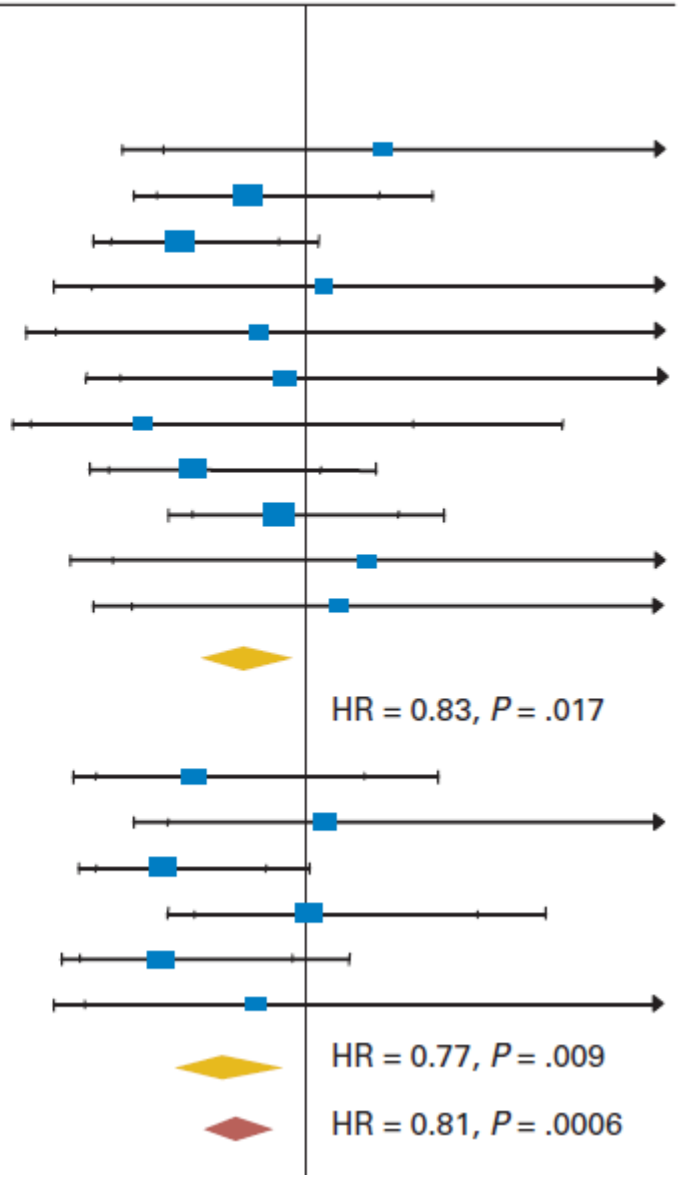
Survival Measure	HR	95% CI	*P*	Absolute 5-Year Survival Benefit (%)
Overall disease-free survival	0.78	0.70 to 0.87	.000005	8
Locoregional disease-free survival	0.76	0.68 to 0.86	.000003	9
Metastases-free survival	0.81	0.72 to 0.91	.0004	7
Locoregional disease-free interval	0.74	0.64 to 0.86	.00009	6
Metastases-free interval	0.83	0.71 to 0.99	.037	4

*J Clin Oncol. 2008;**26**:5802-12*

Conclusion 2

- Significant survival benefit for both
  - Platinum-based
  - Non-platinum based

Trial ID	CTRT events	CTRT pts.	Control events	Control pts.	O-E	Variance
Trials of Chemoradiation *v* radiotherapy						
(a) Platinum-based CTRT						
Onishi[44] (CDDP or CDBCA)	16	26	15	23	1.52	7.59
Pearcey[43] (CDDP)	53	130	60	129	-5.00	28.20
GOG0123[6] (CDDP)	49	185	69	189	-12.90	29.38
Chen[23] (a) (CDDP FU VCR)	8	30	8	30	0.21	4.00
Chen[23] (b) (CDDP FU VCR)	6	30	7	30	-0.45	3.25
Pras (CDBCA FU)	17	28	16	26	-0.47	8.15
GOG0165[26] (a) (CDDP)	8	26	12	24	-3.03	4.92
Cikaric[47] (CDDP)	37	100	48	100	-8.02	21.12
Leborgne (CDDP FU)	75	170	85	170	-3.07	39.91
Gariapagaoglu[48] (CDDP)	9	22	8	22	0.70	4.23
Lal[50] (CDDP)	14	94	12	86	0.62	6.49
Sub-total	292	841	340	829	-29.89	157.23
(b) Non–platinum-based CTRT						
Thomas[24] (a) (FU)	24	57	32	58	-5.16	13.83
Thomas[24] (b) (FU)	26	58	25	60	0.71	12.74
Lorvidhaya[25] (a) (MMC FU)	40	233	59	242	-12.52	24.57
Lorvidhaya[25] (b) (MMC FU)	54	230	49	221	0.31	25.67
Roberts[49] (MMC)	25	124	39	124	-8.39	15.92
GOG0165[26] (b) (FU)	11	27	12	24	-0.82	5.55
Sub-total	180	729	216	729	-25.87	98.28
Total	472	1,570	544	1,534	-54.56	251.54



*J Clin Oncol. 2008;**26**:5802-12*

Conclusion 3

- No difference in the size of benefit by
  - Radiotherapy dose
  - Chemotherapy dose
  - Chemotherapy scheduling

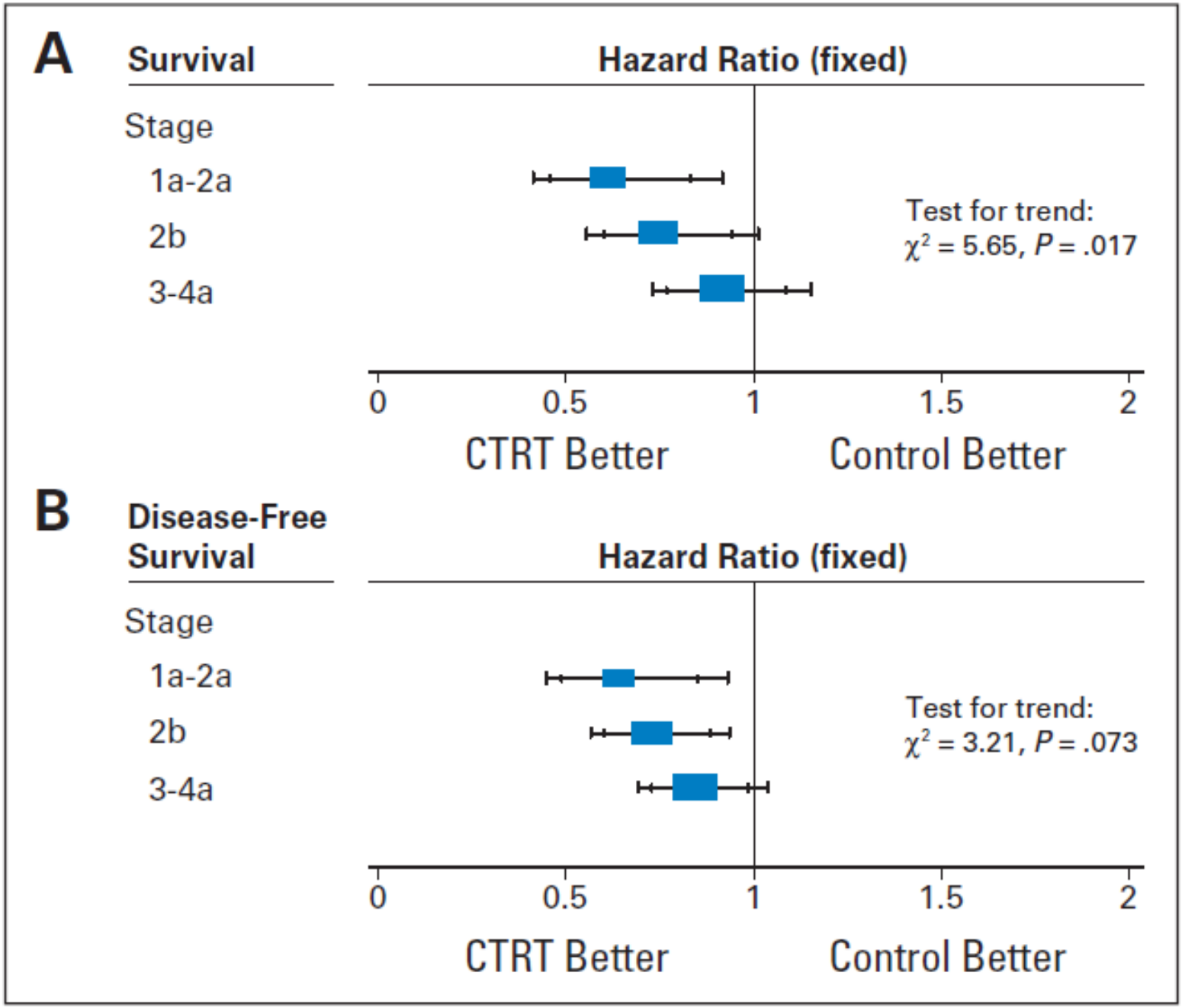
Variable	Main Analysis (13 trials)		
	HR	95% CI	Interaction *P*
Planned radiotherapy dose			
≥ 45 Gy + BRT	0.78	0.68 to 0.89	
< 45 Gy + BRT	0.93	0.70 to 1.24	.26
Planned radiotherapy duration, weeks			
≤ 8	0.83	0.72 to 0.96	
> 8	0.73	0.57 to 0.93	.35
Planned chemotherapy cycle length, weeks*			
≤ 1	0.74	0.60 to 0.92	
> 1	0.95	0.72 to 1.25	.16
Planned cisplatin dose-intensity, mg/m^2/wk*			
≤ 25	0.93	0.70 to 1.24	
> 25	0.76	0.62 to 0.96	.25
Cisplatin regimen*			
Single agent	0.76	0.62 to 0.93	
Combination	0.93	0.70 to 1.24	.25
Chemotherapy regimen			
Single agent	0.75	0.63 to 0.88	
Combination	0.86	0.71 to 1.04	.29

*J Clin Oncol. 2008;**26**:5802-12*

Conclusion 4

- Suggestion of difference in size of benefit with tumour stage

*J Clin Oncol. 2008;**26**:5802-12*

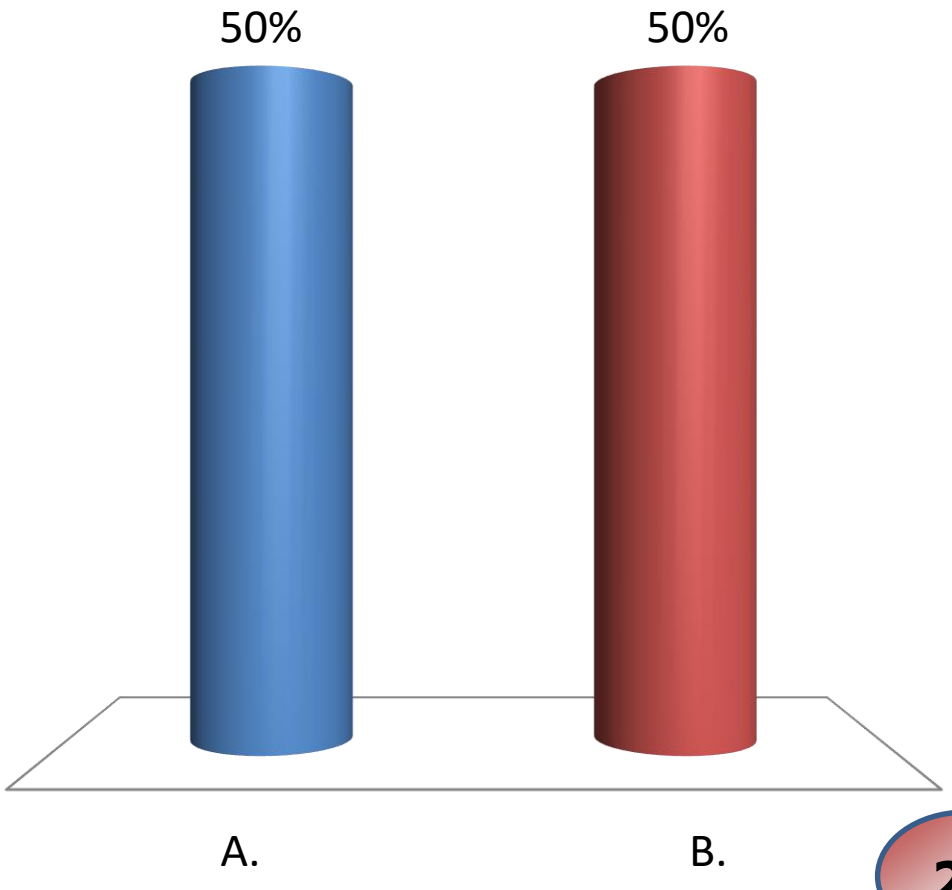


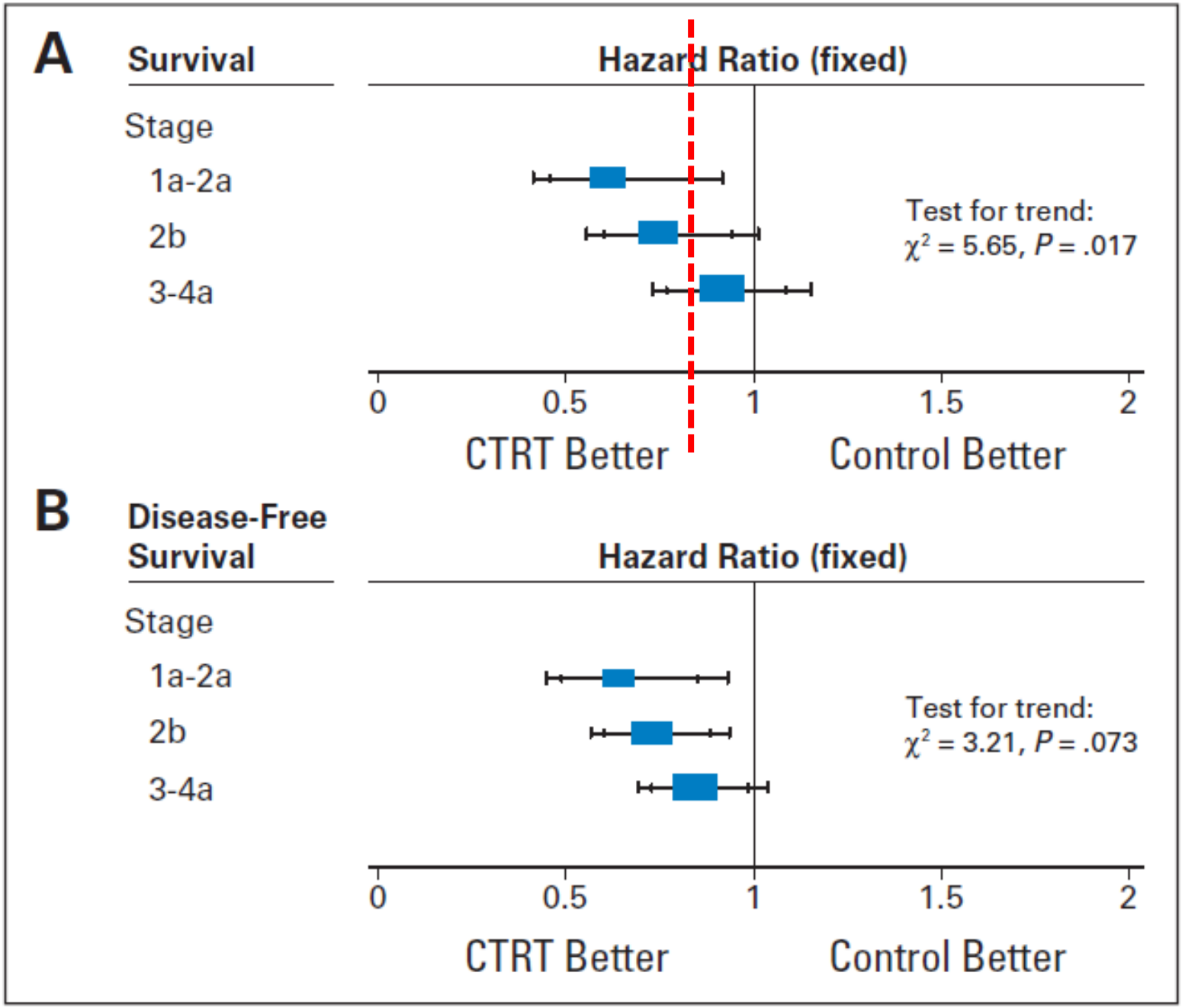
*J Clin Oncol. 2008;**26**:5802-12*

Would you stop offering concomitant chemo Stage III and IVa patients based on these results?

A. Yes

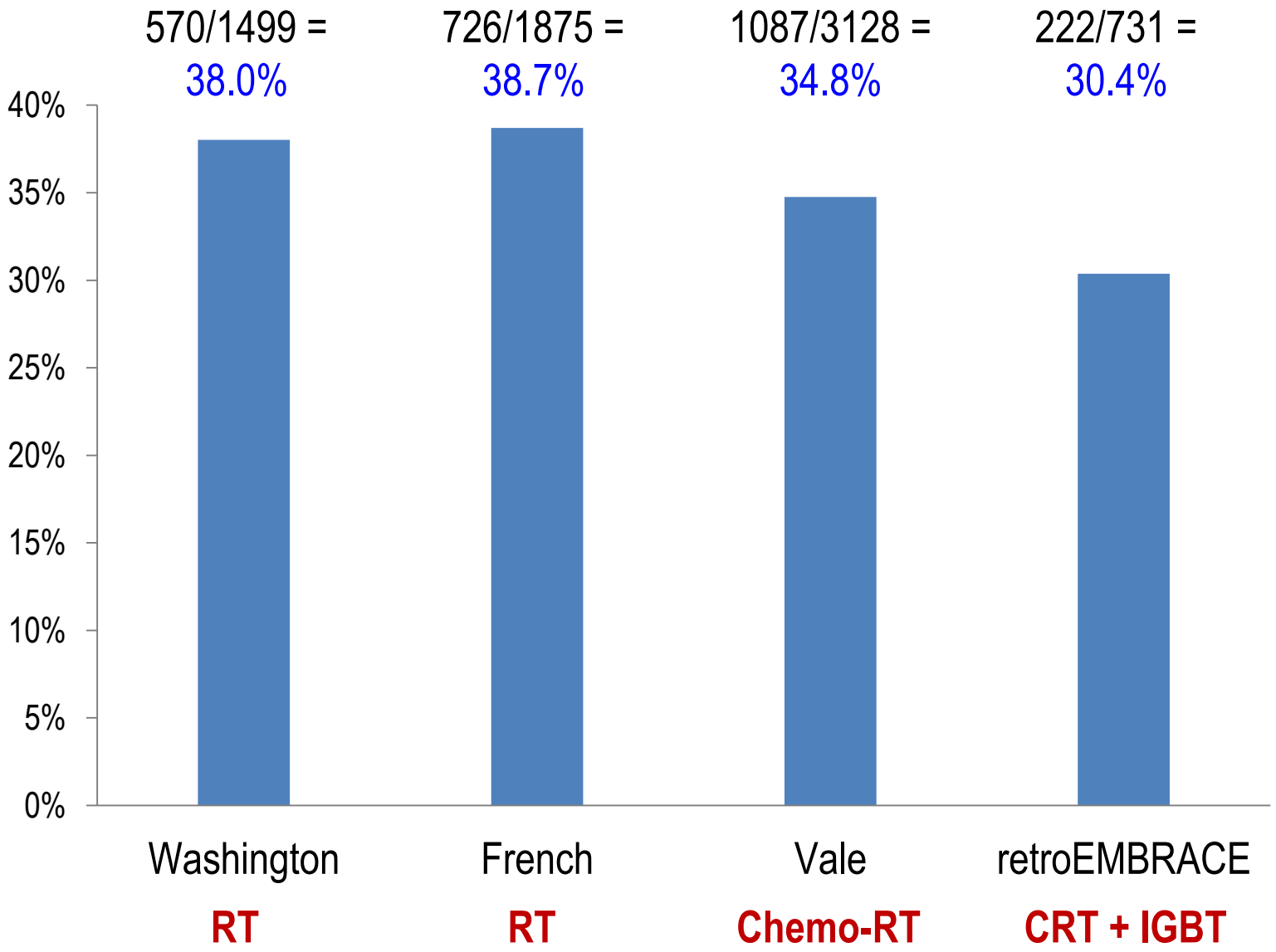
B. No



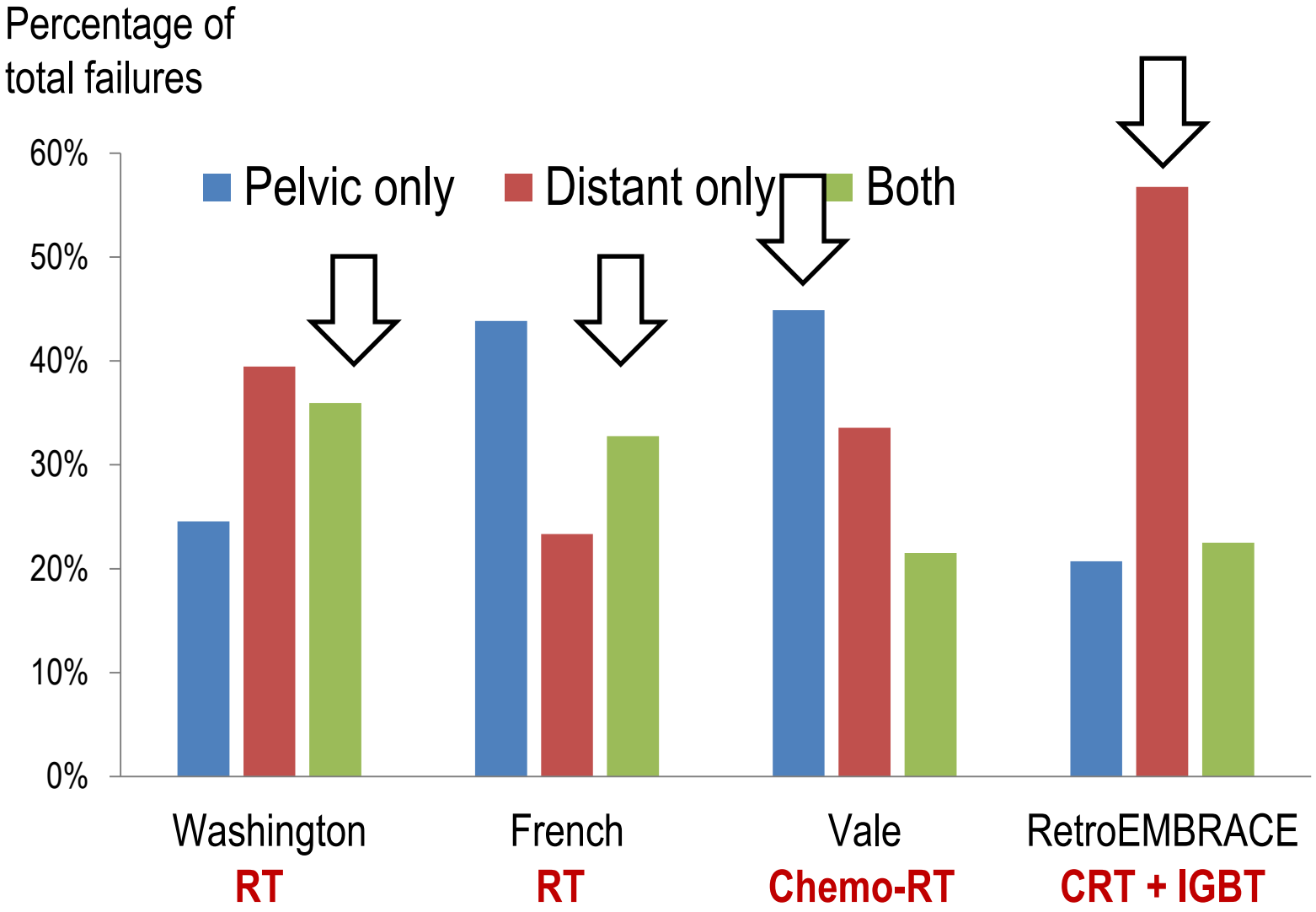


*J Clin Oncol. 2008;**26**:5802-12*

Total failures



Patterns of spread



Toxicity

- Acute toxicity
  - Serious haematologic toxicity increased by ~2 to 10-fold in individual trials
  - Significant increase in serious GI toxicity

Toxicity

- Late toxicity
  - Not recorded in majority of trials
    - Rectal 7 trials
    - Bladder 5 trials
    - Intestinal/vaginal 4 trials
  - Substantial missing data within these trials

Outline

- **Concomitant chemotherapy**
  - Evidence
  - **Questions**
- Neoadjuvant chemotherapy
- Adjuvant chemotherapy
- Targeted agents
- Personalised medicine
- Clinical cases

Questions

- Number of cycles
- Drugs
  - Carboplatin
  - Paclitaxel
  - Gemcitabine
- Scheduling
  - Weekly
  - 3-weekly
- Timing
  - Before or after chemo?
  - Gap?
  - Day of the week?

Korean phase II trial

- Cisplatin
  - Weekly 40 mg/m^2 weekly x 6 cycles
  - 3-weekly 75 mg/m^2 x 3 cycles
- 104 patients, Stage IIB-IVA
- Results
  - Compliance (weekly 86%, 3-weekly 93%, $p > 0.05$)
  - G3-4 neutropenia (weekly 39%, 3-weekly 23%, $p = 0.03$)
  - 5-y OS (weekly 67%, 3-weekly 89%, $p = 0.03$)

Ryu SY, et al. Int J Radiat Oncol Biol Phys. 2011

Summary

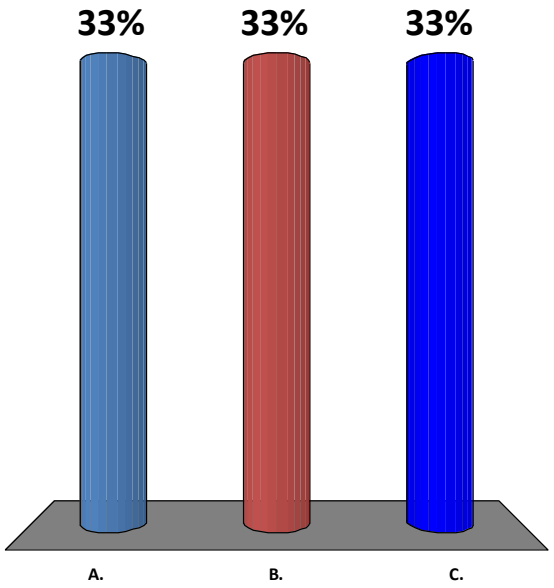
- Benefit of concomitant chemo-RT irrefutable
- Questions
  - Optimal drugs?
  - Optimal schedule?

Outline

- Concomitant chemotherapy
- **Neoadjuvant chemotherapy**
- Adjuvant chemotherapy
- Targeted agents
- Personalised medicine
- Clinical cases

Do you give neoadjuvant chemotherapy before radiotherapy for cervix cancer?

A. Yes
B. No
C. Don’t know

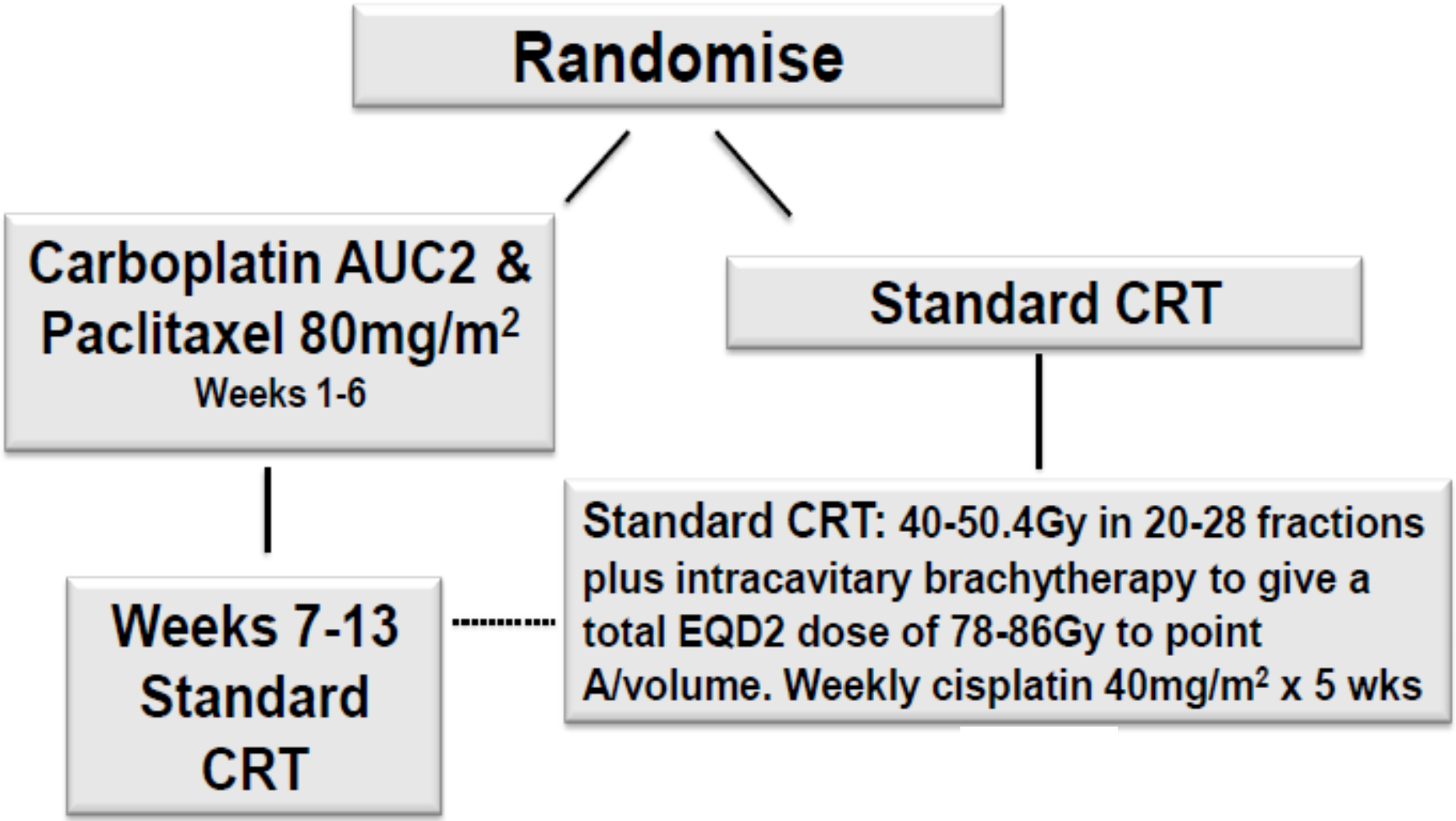


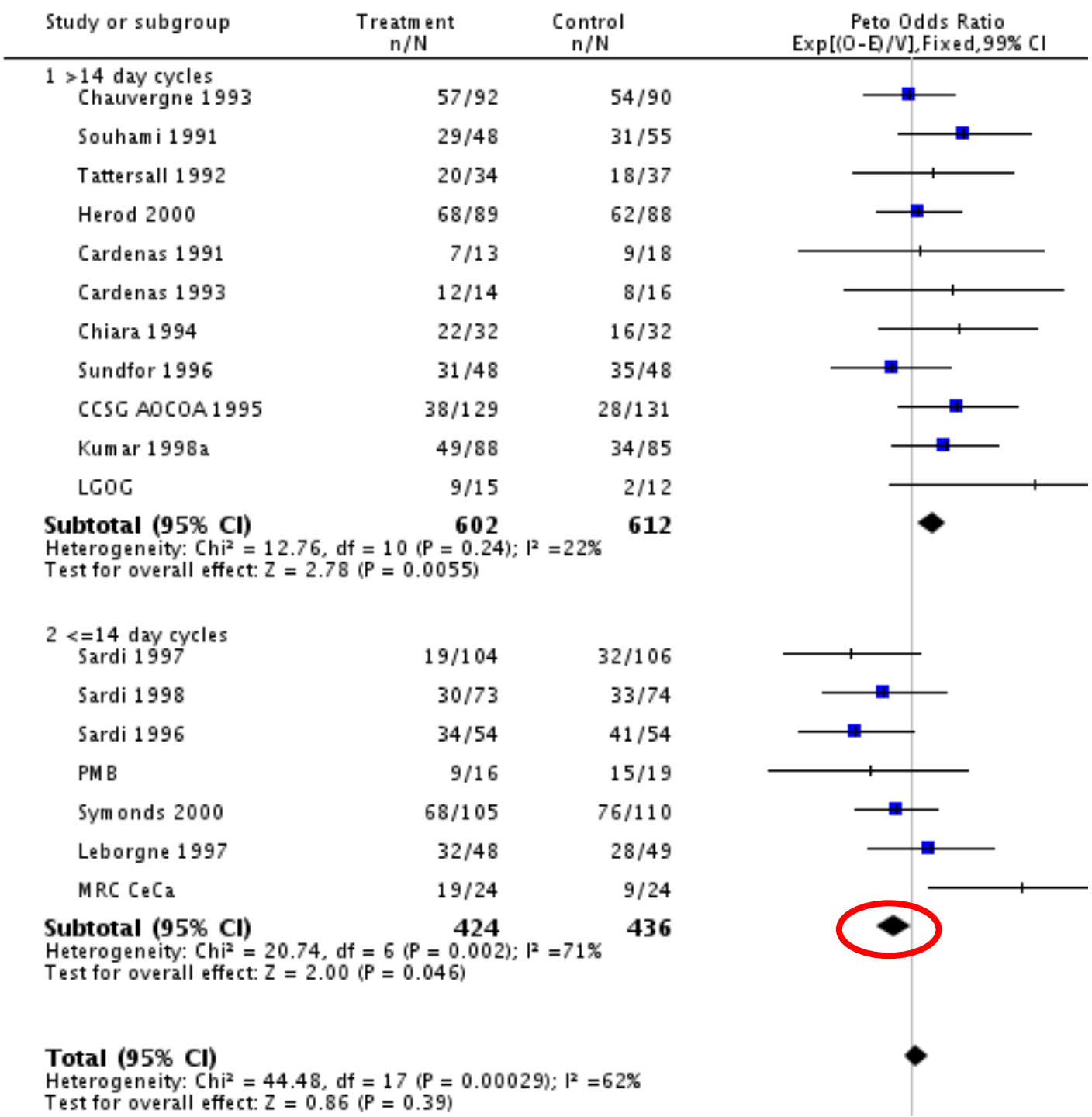
Cochrane review 2004

- 1975-2006
- 18 trials, 2074 patients
- No survival benefit (p = 0.4)
- Benefit varies depending on cycle length and cisplatin dose intensity?

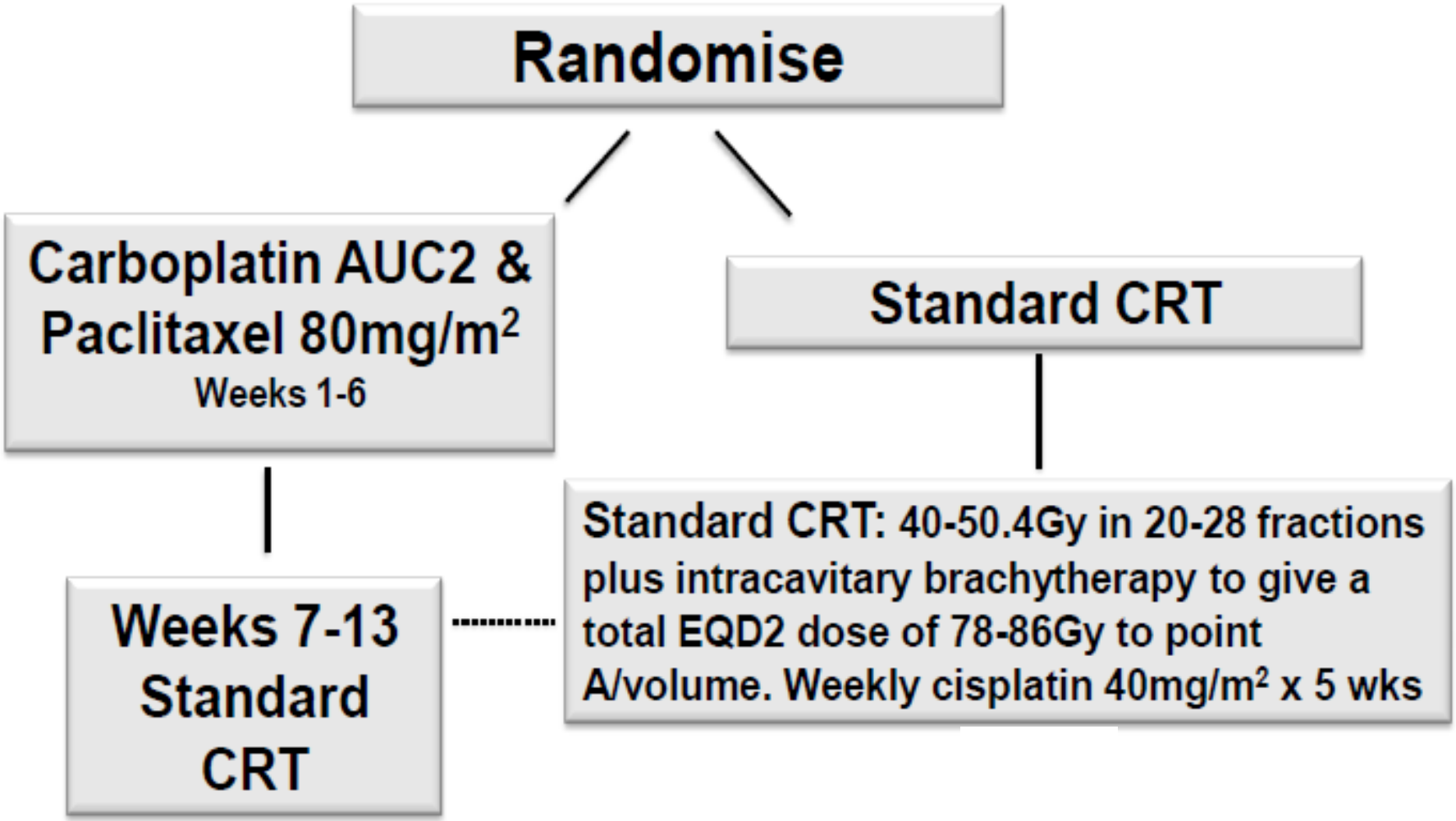
Tierney J. Cochrane Database of Systematic Reviews 2004

UK INTERLACE




Study or subgroup
Treatment n/N
Control n/N
Peto Odds Ratio Exp[(O-E)/V],Fixed,99% CI
1 >14 day cycles
Chauvergne 1993 57/92 54/90
Souhami 1991 29/48 31/55
Tattersall 1992 20/34 18/37
Herod 2000 68/89 62/88
Cardenas 1991 7/13 9/18
Cardenas 1993 12/14 8/16
Chiara 1994 22/32 16/32
Sundfor 1996 31/48 35/48
CCSG ADCOA 1995 38/129 28/131
Kumar 1998a 49/88 34/85
LGOG 9/15 2/12
Subtotal (95% CI) 602 612
Heterogeneity: Chi² = 12.76, df = 10 (P = 0.24); I² =22%
Test for overall effect: Z = 2.78 (P = 0.0055)
2 <=14 day cycles
Sardi 1997 19/104 32/106
Sardi 1998 30/73 33/74
Sardi 1996 34/54 41/54
PMB 9/16 15/19
Symonds 2000 68/105 76/110
Leborgne 1997 32/48 28/49
MRC CeCa 19/24 9/24
Subtotal (95% CI) 424 436
Heterogeneity: Chi² = 20.74, df = 6 (P = 0.002); I² =71%
Test for overall effect: Z = 2.00 (P = 0.046)
Total (95% CI)
Heterogeneity: Chi² = 44.48, df = 17 (P = 0.00029); I² =62%
Test for overall effect: Z = 0.86 (P = 0.39)

UK INTERLACE

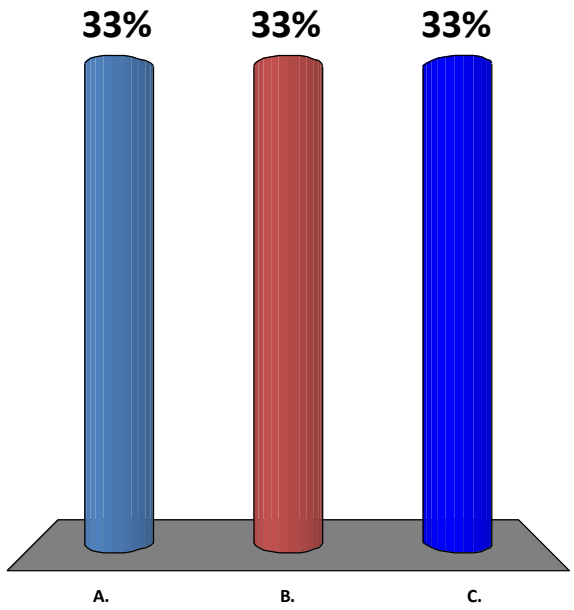


Outline

- Concomitant chemotherapy
- Neoadjuvant chemotherapy
- **Adjuvant chemotherapy**
- Targeted agents
- Personalised medicine
- Clinical cases

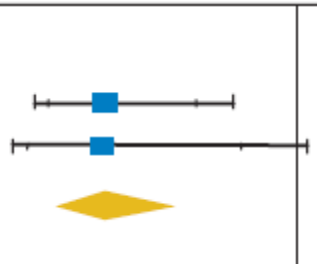
Do you give adjuvant chemotherapy after radiotherapy for cervix cancer?

A. Yes
B. Sometimes
C. No



2008 meta-analysis

Trial ID	CTRT events	CTRT pts.	Control events	Control pts.	O-E	Variance
Trials of CTRT + adjuvant chemotherapy *v* radiotherapy						
SWOG8797[8,46] (CDDP FU)	28	135	54	133	-15.61	20.36
Kantardzic[45] (CDDP BLM)	15	40	25	40	-7.74	9.74
Sub-total	43	175	79	173	-23.35	30.10



= absolute benefit of 19% at 5 years

*J Clin Oncol. 2008;**26**:5802-12*

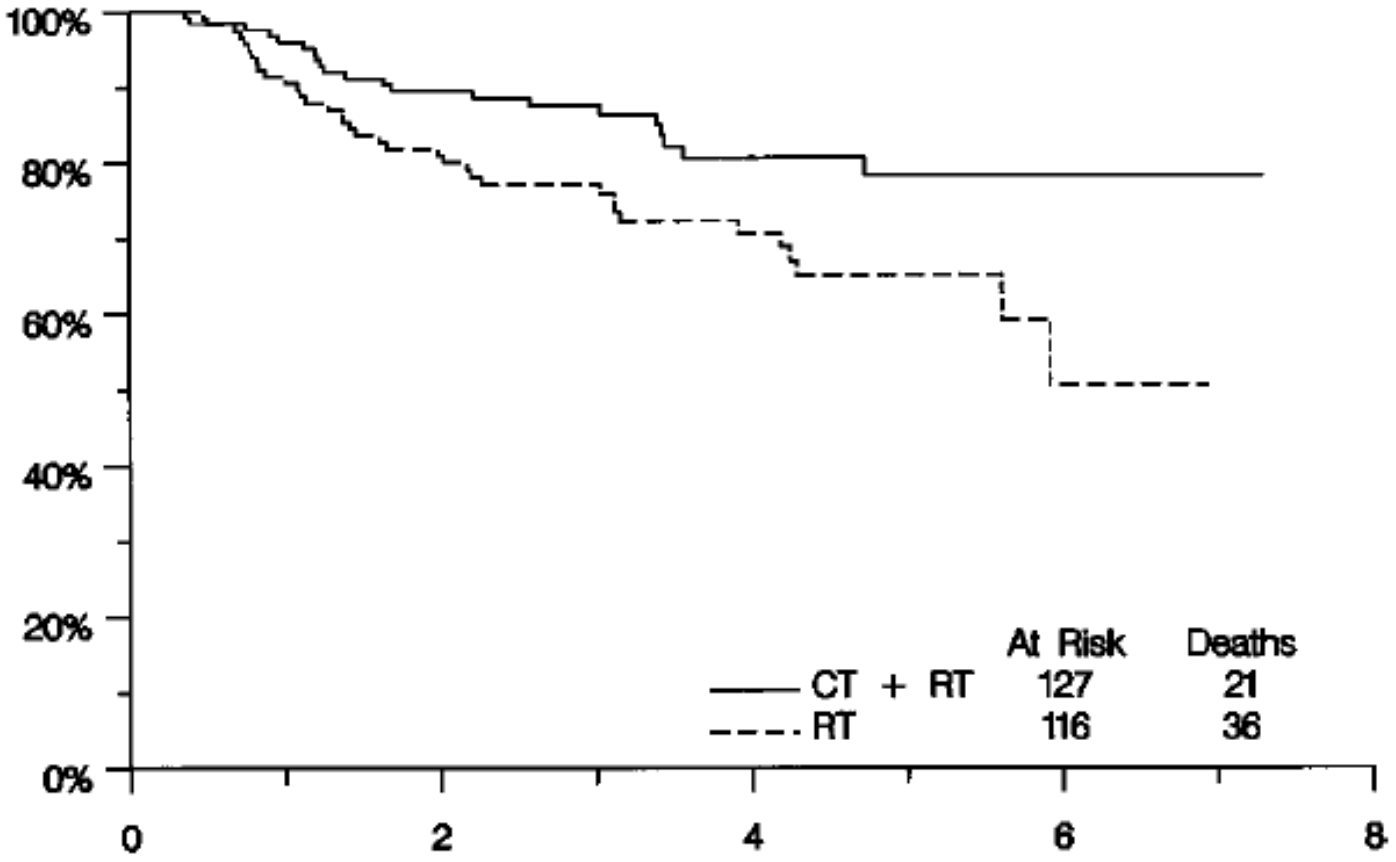
SWOG 7897

- 268 patients - IA2, IB, IIA
- Radical hysterectomy + PLND
- RT to pelvis (49.3 Gy in 29#) for
  - Positive LN
  - Positive margins
  - Parametrial disease
- 4 cycles of cisplatin 70 mg/m^2 + 5-FU 1000 mg/m^2/d x 4 days

Peters, et al. JCO 2000; ***18****:1606-13*

SWOG 7897

- 4-year survival
  - 81% for CT + RT vs 71% for RT only (p = 0.007)



SWOG 7897

- Acute toxicity
  - 21 G4 toxicity for CT + RT vs 4 for RT alone

- Late toxicity not reported

SWOG 7897

No. of Cycles Received	Patients (n = 127) No.	%
0 (refused)	10	8
1	8	6
2	19	15
3	14	11
4	76	60

Dueñas-González 2011

- 515 patients - IIB - IVA
- Treatment
  - RT to pelvis (50.4 Gy in 28#) + BT 30 Gy to point A
  - Standard 4-field box or opposed fields
  - Weekly cisplatin 40 mg/m^2 + gemcitabine 125 mg/m^2
  - 2 cycles cisplatin 80 mg/m^2 + gemcitabine 1000 mg/m^2 (d1 + d8) q21

*J Clin Oncol. 2011;**29**:1678-85*

Dueñas-González 2011

- 9% improvement in 3-year PFS (p = 0.03)
- OS not analysed
- No difference in local failure - 11% and 16%

Toxicity

- Acute
  - G3-4 haematological toxicity 72% vs 24%
  - More G3-4 non-haematological toxicity (p = 0.002)
  - 3 deaths within 60 days
  - 30 patients hospitalised vs 11 (p = 0.003)
- Late
  - G3-4 toxicity 4.1% vs 1.4%
  - Data for 1 year only (median FU 47 months)
  - 15% missing

Table 6 — Comparison of rates of serious morbidity in published reports

Reference	Patients	Treatment	Morbidity
Clatterbridge [13]	223	Radiotherapy alone	5.0%
Cookridge, Leeds [14]	371	Radiotherapy alone	19.0%
Bristol [15]	270	Radiotherapy alone	32.5%
French Co-operative Study [16]	1383	Radiotherapy alone	27.6%
Washington University [17]	970	Radiotherapy alone	18.4%
Addenbrooke's	71	Chemoradiotherapy	18.3%
Birmingham [9]	79	Chemoradiotherapy	12.7%
China Medical University, Taiwan [10]	70	Chemoradiotherapy	14.3%
Albert Einstein College of Medicine, New York [11]	77	Chemoradiotherapy	6.0%
RTOG 90-01 [7]	191	Chemoradiotherapy	12.6%
GOG 120* [6]	215	Chemoradiotherapy	2.8%

Tan LT, et al. Clin Oncol (R Coll Radiol). 2008.

ANZGOG OUTBACK

- Pelvic RT 45-50.4 Gy in 25-28#
- Weekly cisplatin 40 mg/m^2
- 4 cycles of carboplatin AUC5 + paclitaxel 155 mg/m^2
- 780 patients over 3 years to detect 10% improvement in OS
- IGBT not allowed

Outline

- Concomitant chemotherapy
- Neoadjuvant chemotherapy
- Adjuvant chemotherapy
- **Targeted treatments**
- Personalised medicine
- Clinical cases

Targeted treatments

- Anti-angiogenesis
  - **Bevacizumab**
- Tyrosine kinase inhibitors
  - Sunitinib, sorafenib, imatinib, pazopanib, cediranib
- EGFR inhibitors
  - Gefitinib, erlotinib, cetuximab, lapatinib, trastuzumab, panitumumab
- Ribonucleotide reductase inhibitor
  - Triapine
- Immunotherapy
  - Adoptive T-cell therapy
  - **ADXS11-001 (axamilogene)**

ADXS11-001 immunotherapy

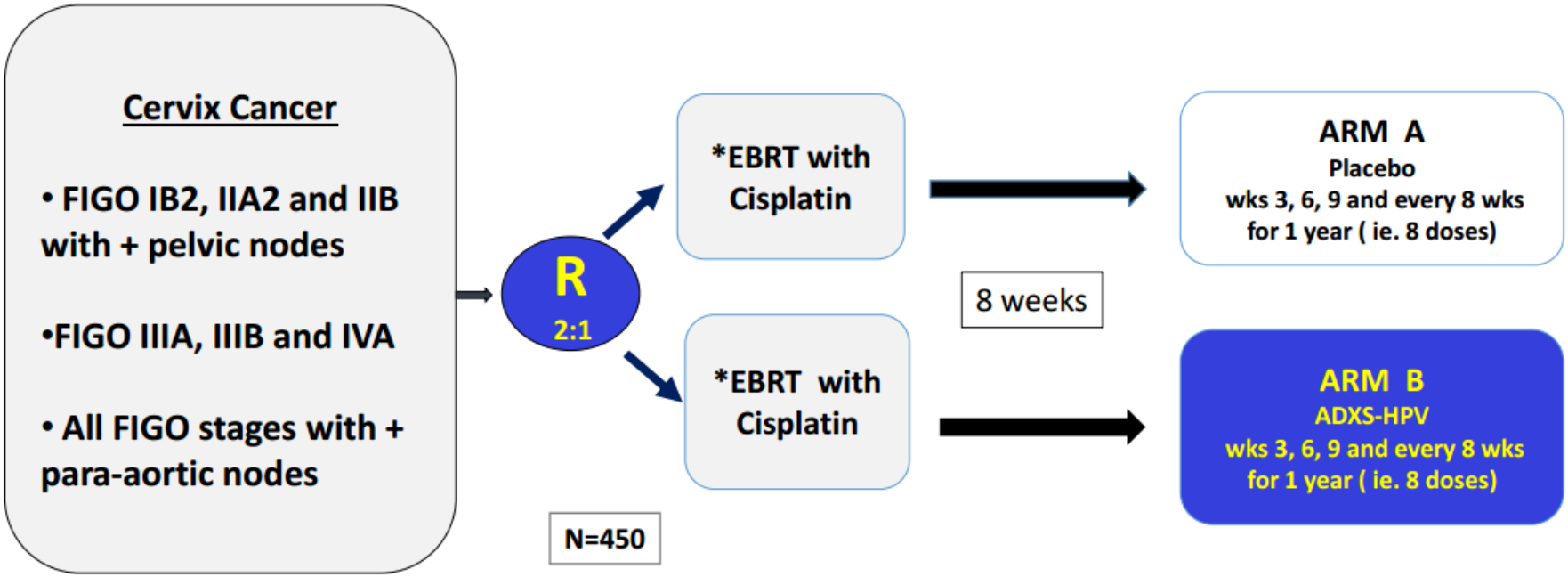
- Utilizes listeria monocytogenes (gram positive bacteria) which selectively infects antigen presenting cells
- Targets HPV-transformed cells, inducing antitumor T-cell immunity
- Activity observed across all HPV types

GOG 0265

- Phase II study
  - Persistent or recurrent cervical Ca
  - One prior line of systemic therapy
  - 3 doses of ADXS

- 12-month OS = 38.5% in 26 patients

AIM2CERV



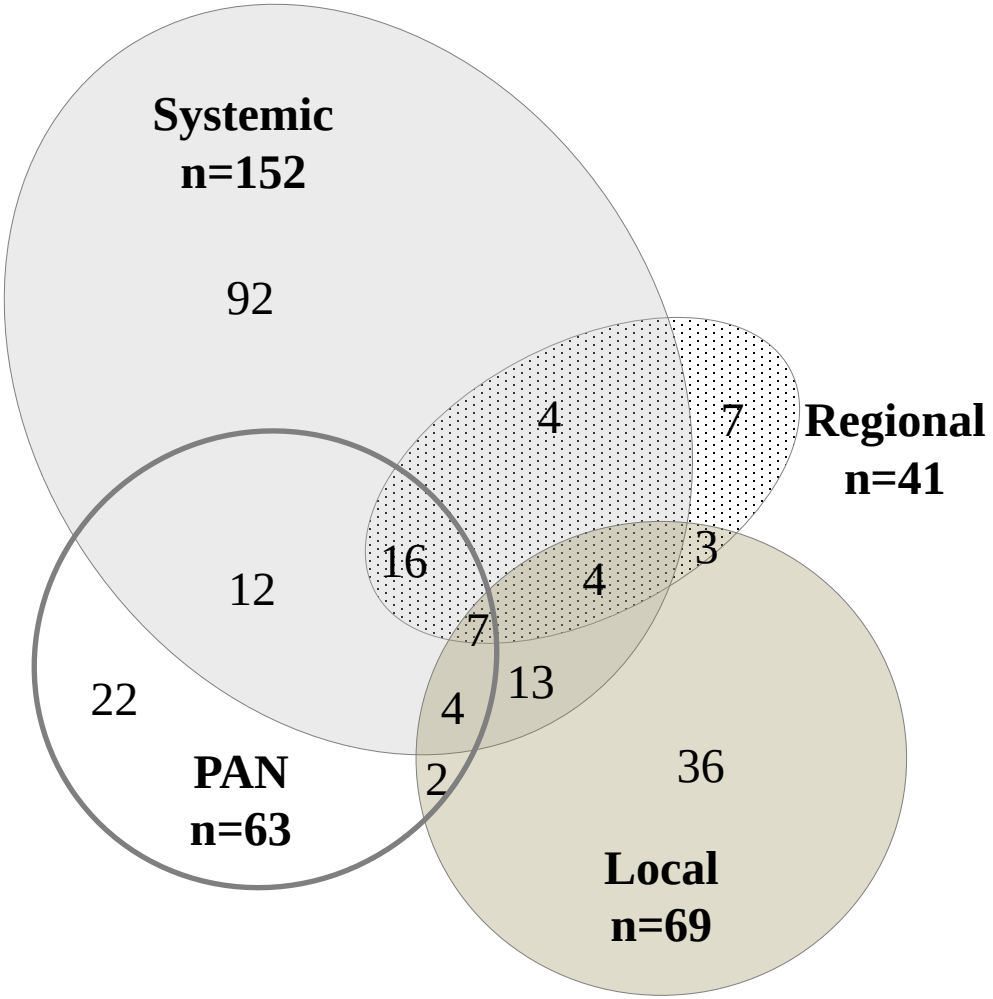
1° endpoint: Progression Free Survival
2° endpoint: Overall Survival

*Concurrent chemo radiation therapy administered with curative intent according to national/institutional guidelines

Outline

- Concomitant chemotherapy
- Neoadjuvant chemotherapy
- Adjuvant chemotherapy
- Targeted agents
- **Personalised medicine**
- Clinical cases

RetroEMBRACE patterns of spread



RetroEMBRACE

		Single type of failure			
Stage	n	L only	R only	PAN only	S only
1A	2				
1B1	84		1	4	7
1B2	39				4
2A	42	1		2	3
2B	368	14	4	7	41
3A	23	1		1	5
3B	145	19	2	8	22
4A	23	1			9
4B	5				1
		157			
		70.7%			

Predictive biomarkers

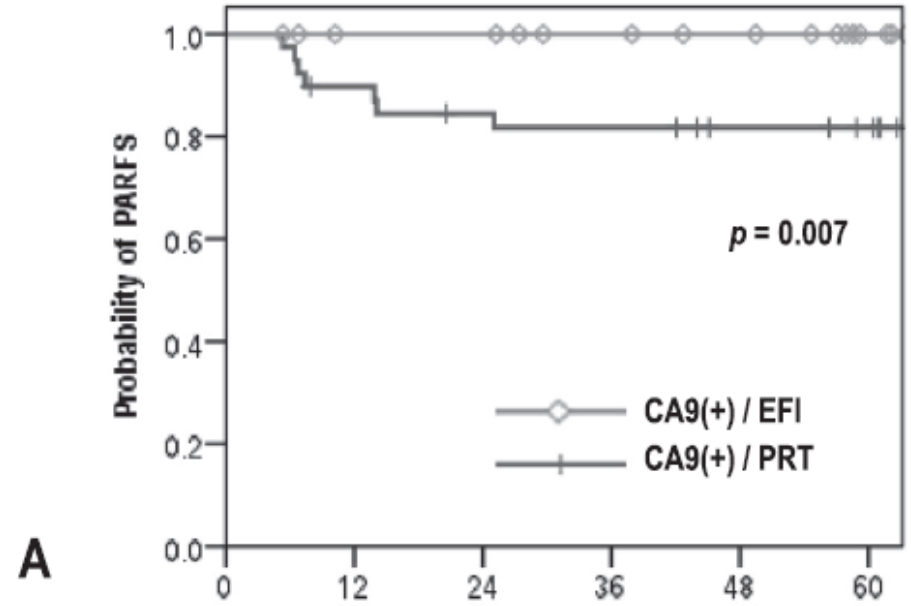
- Imaging
  - DWI MRI, DCE-MRI, CT-PET
- Immunohistochemistry
  - CA9, CK19, SCC-Ag
- Serum
  - SCC-Ag

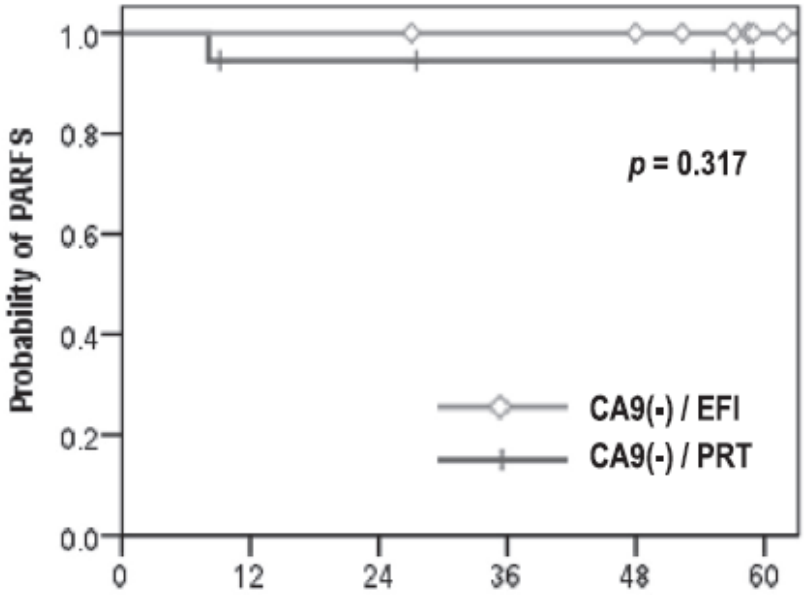
KROG 07-01

- Phase II study
- 79 = CA9-positive, 37 = CA9-negative
- Randomised to pelvic vs. extended field RT + chemo

Kim JH, et al. Radiother Oncol. 2016;120(3):383-9

KROG 07-01



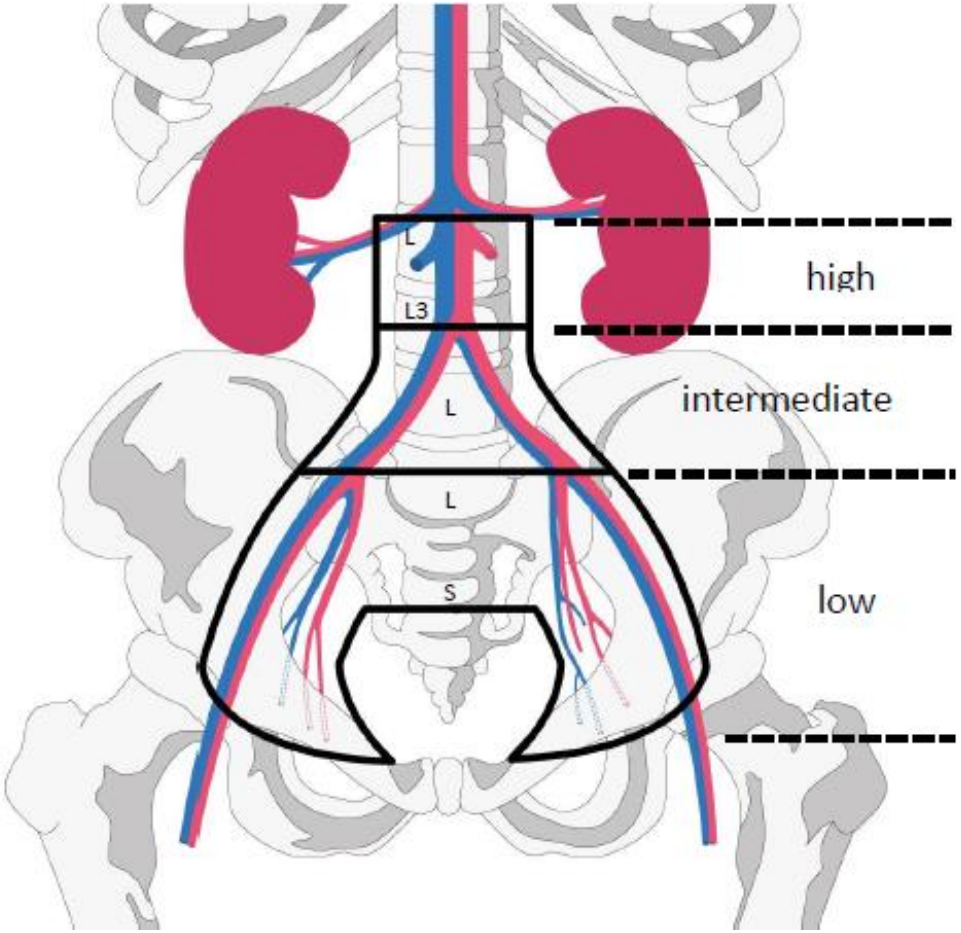


Number at risk						
CA9(+) / EFI	38	38	38	38	38	38
CA9(+) / PRT	38	34	32	30	30	30

Number at risk						
CA9(-) / EFI	38	37	37	37	37	37
CA9(-) / PRT	38	34	32	30	29	29

Kim JH, et al. Radiother Oncol. 2016;120(3):383-9

EMBRACE-II IMRT + IGBT



- Imaging
  - DWI-MRI, DCE-MRI
- Immunohistochemistry

Immuno-radiotherapy

Jesper Grau Eriksen

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Odense University Hospital, Denmark

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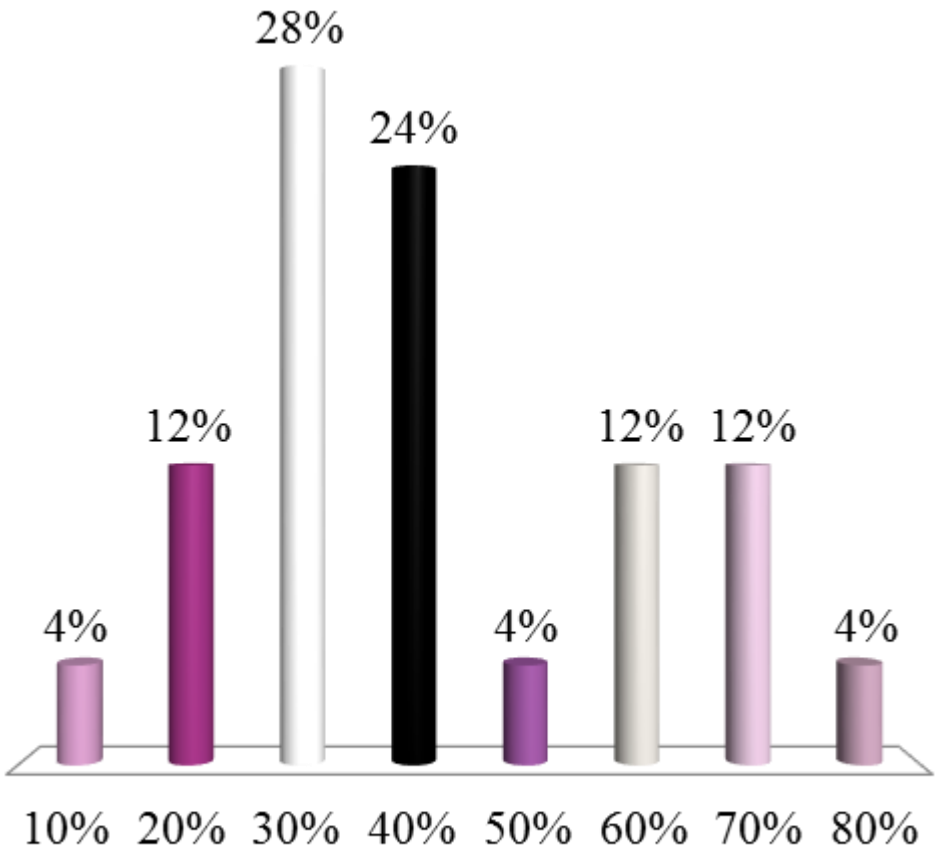
What overall response rates can be expected with check-point inhibitors as single agent in MMM

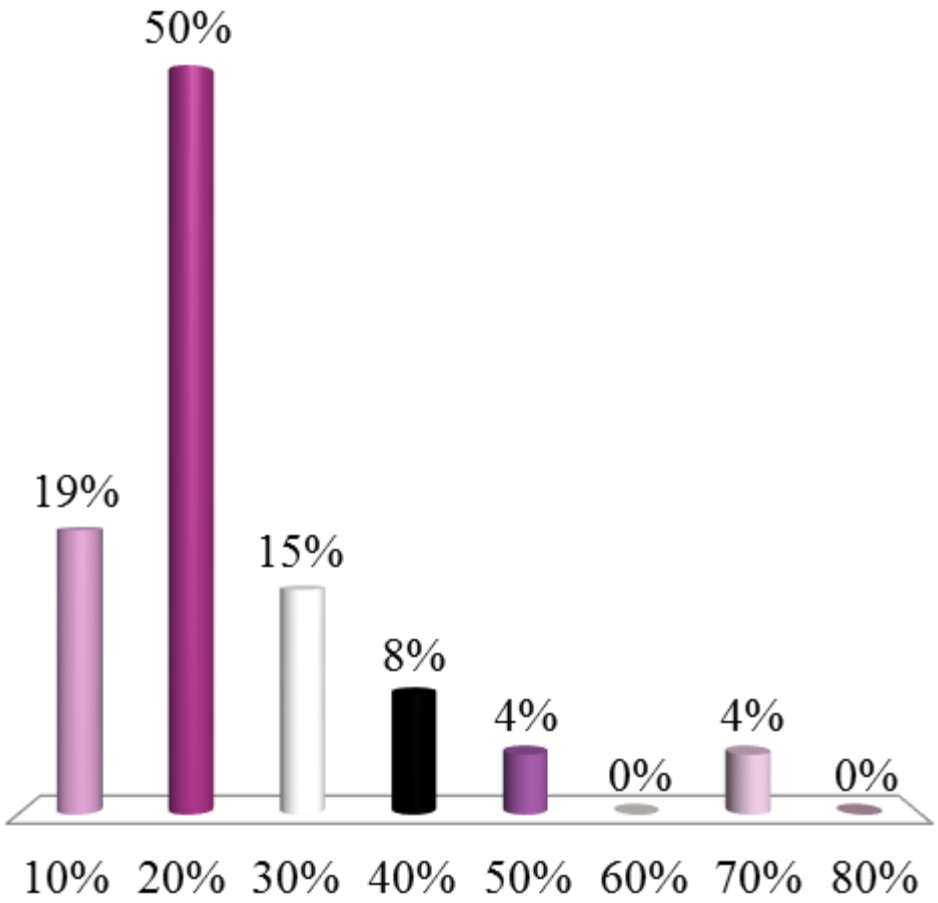
A. 10%
B. 20%
C. 30%
D. 40%
E. 50%
F. 60%
G. 70%
H. 80%



ESTRO School

What is the ORR for HD Interleukin-2/Interferony?

A. 10%
B. 20%
C. 30%
D. 40%
E. 50%
F. 60%
G. 70%
H. 80%



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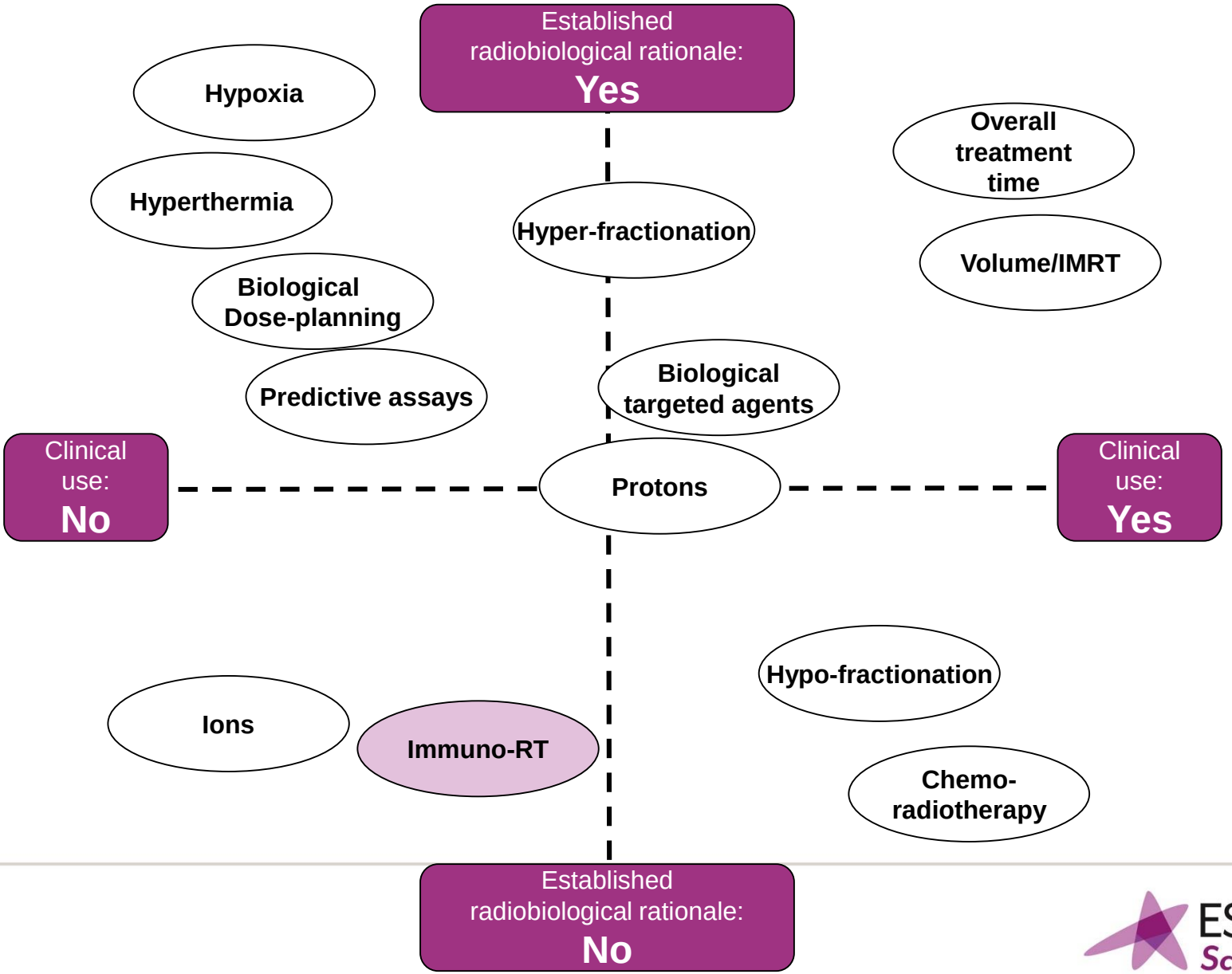
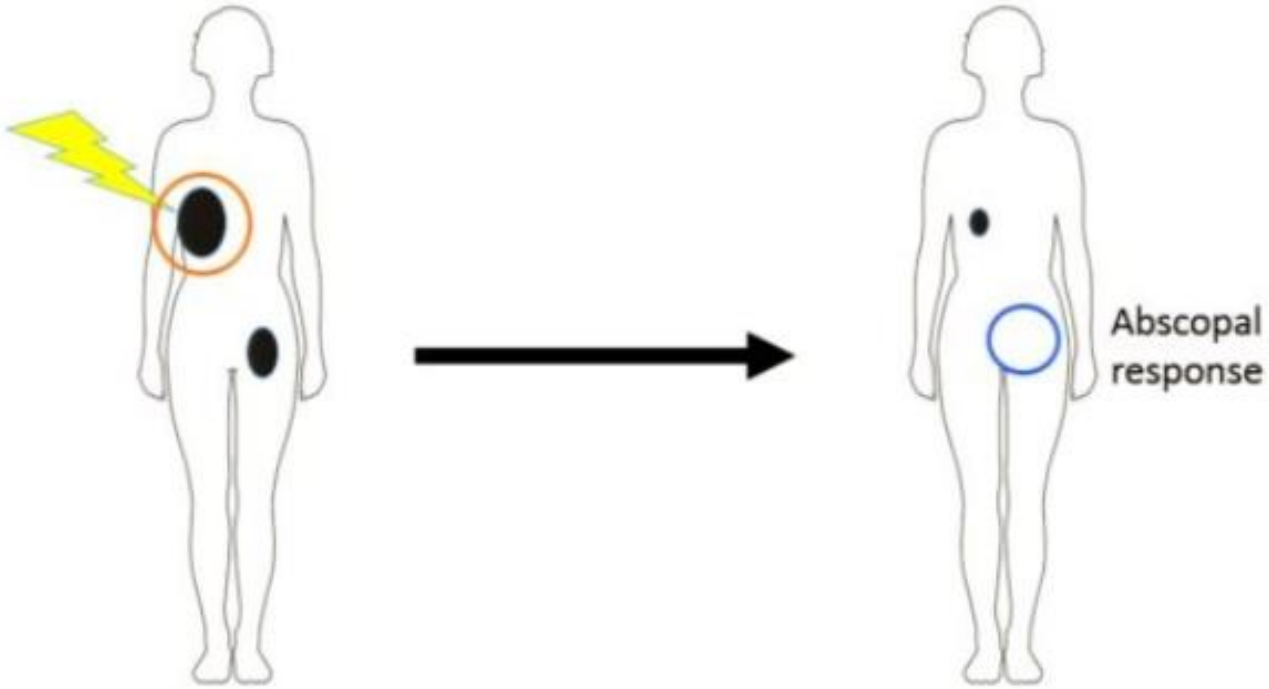
The landscape of evidence and practice



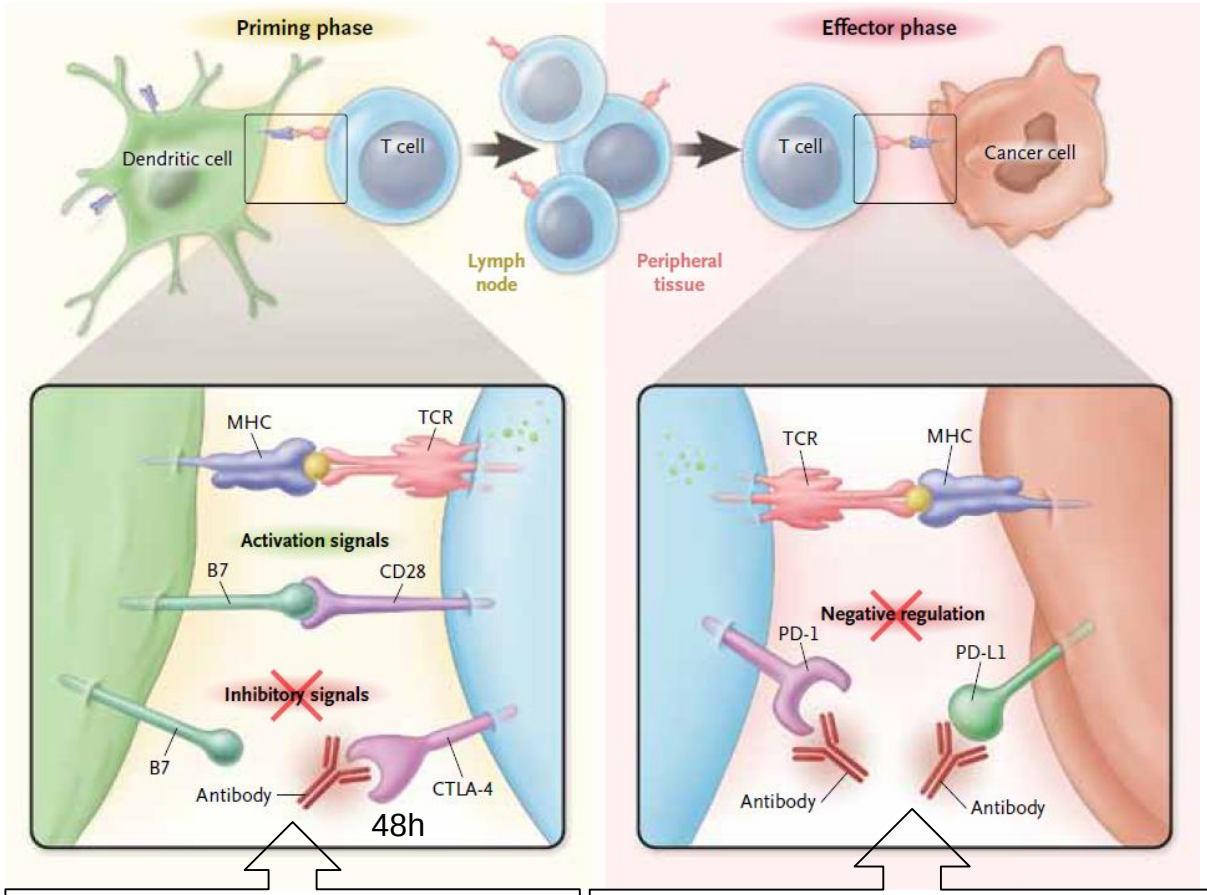
Not one word about abscopal effect!



Treatment of cancer by harnessing immune responses

Adapted from Kevin Harrington

Checkpoint blocade



CTLA-4 inhibition
Ipilimumab/Tremelimumab

PD-L1 inhibition
Pembrolizumab/Nivolumab/
Duravulumab/Avelumab

Ribas NEJM 2012

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Approved antibodies for the treatment of cancer

FDA approved antibodies for the treatment of cancer.

Generic name (trade name)	Origin	Isotype (conjugate)	Target	Approved uses/trials	Initial approval
Unconjugated MAbs					
Rituximab (Rituxan)	Chimeric	IgG1	CD20	Various leukemias and lymphomas	1997
Ofatumumab (Arzerra)	Human (XenoMouse)	IgG1	CD20	CLL/NHL	2009
Obinutuzumab (Gazyva)	Humanized	IgG1	CD20	CLL/NHL	2013
Alemtuzumab (Campath-1H)	Humanized	IgG1	CD52	CLL (no longer in clinical use)	2001
Trastuzumab (Herceptin)	Humanized	IgG1	HER2	Breast and gastric cancer/esophageal	1998
Pertuzumab (Perjeta)	Humanized	IgG1	HER2	Breast/esophageal, neuroendocrine, gastric	2012
Cetuximab (Erbitux)	Chimeric	IgG1	EGFR	Colorectal, HNSCC, lung	2004
Panitumumab (Vectibix)	Humanized	IgG2	EGFR	Colorectal/pancreatic	2006
Bevacizumab (Avastin)	Humanized	IgG1	VEGF-A	Colorectal, NSCLC, glioblastoma, RCC, cervical, ovarian	2004
Denosumab (Xgeva)	Human	IgG2	RANKL	GCTB	2010
Ipilumimab (Yervoy)	Human	IgG1	CTLA-4		
Nivolumab (Opdivo)	Human	IgG4	PD-1		
Pembrolizumab (Keytruda)	Humanized	IgG4	PD-1		
Immunoconjugates					
Ibritumomab Tiuxetan (Zevalin)	Murine	IgG1 (^{90}Y)	CD20	Non-Hodgkin's lymphoma	2002
Brentuximab vedotin (Adcetris)	Chimeric	IgG1 (MMAE)	CD30	Hodgkin's lymphoma, SALCL	2011
Ado-trastuzumab emtansine (Kadcyla)	Humanized	IgG1 (DM1)	HER2	Breast cancer	2013
Gemtuzumab ozogamicin (Mylotarg)	Humanized	IgG1 (calicheamicin)	CD33	AML	2000[a]

MAb, monoclonal antibody; IgG, immunoglobulin-G; CLL, Chronic Lymphocytic Leukemia; NSCLC, Non-Small Cell Lung Cancer; ^{90}Y, yttrium-90; ^{131}I-Iodine-131; MMAE, monomethyl auristatin E; DM1, Mertansine; HNSCC, head and neck squamous cell carcinoma; SRE, skeletal-related event; GTCB, giant cell tumor of bone; SALCL, Systemic Anaplastic Large Cell Lymphoma.

[a] Withdrawn in 2010, currently reentered clinical trials for AML in France.

Redman et al Mol Immun 2015

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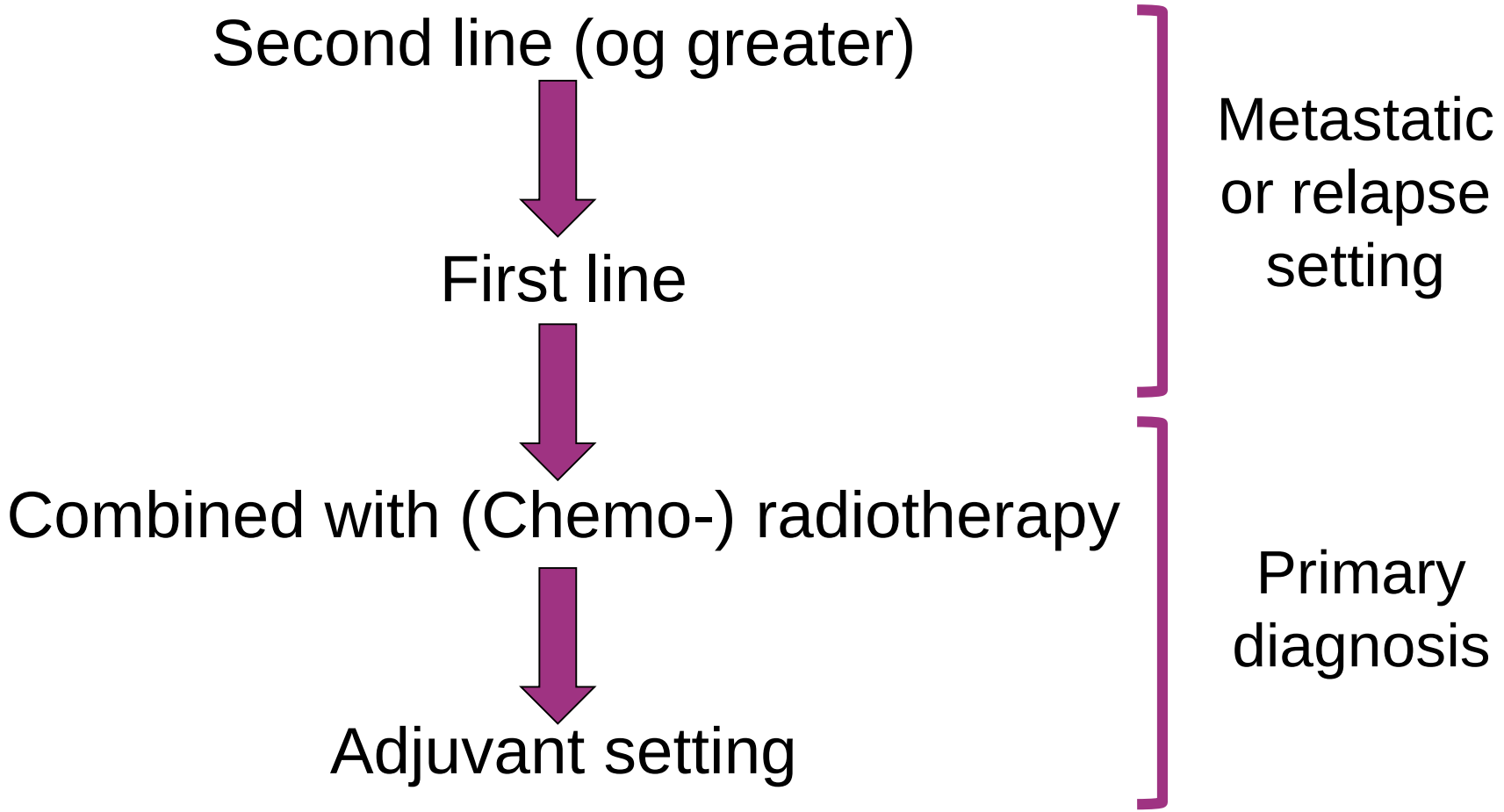
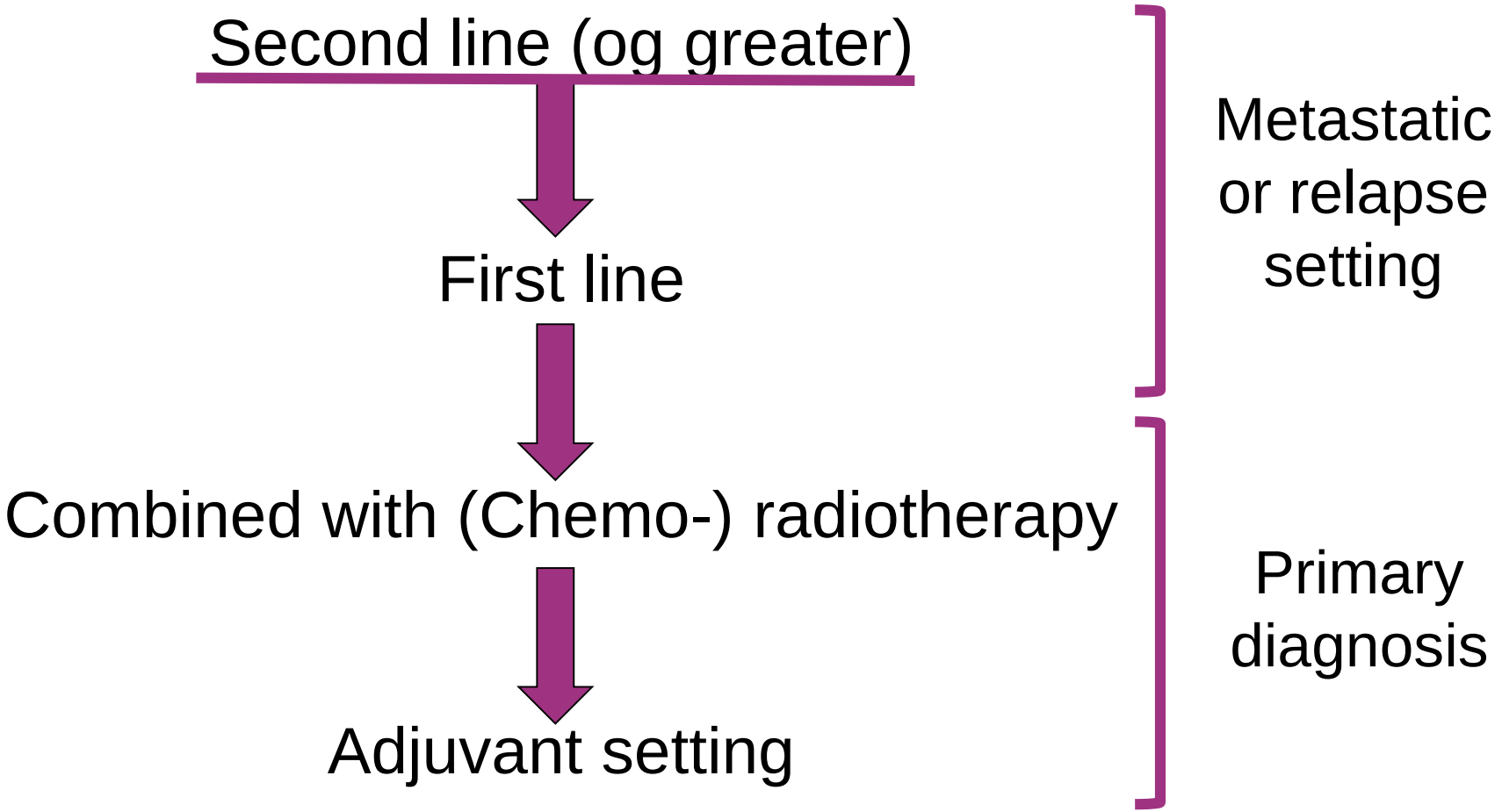
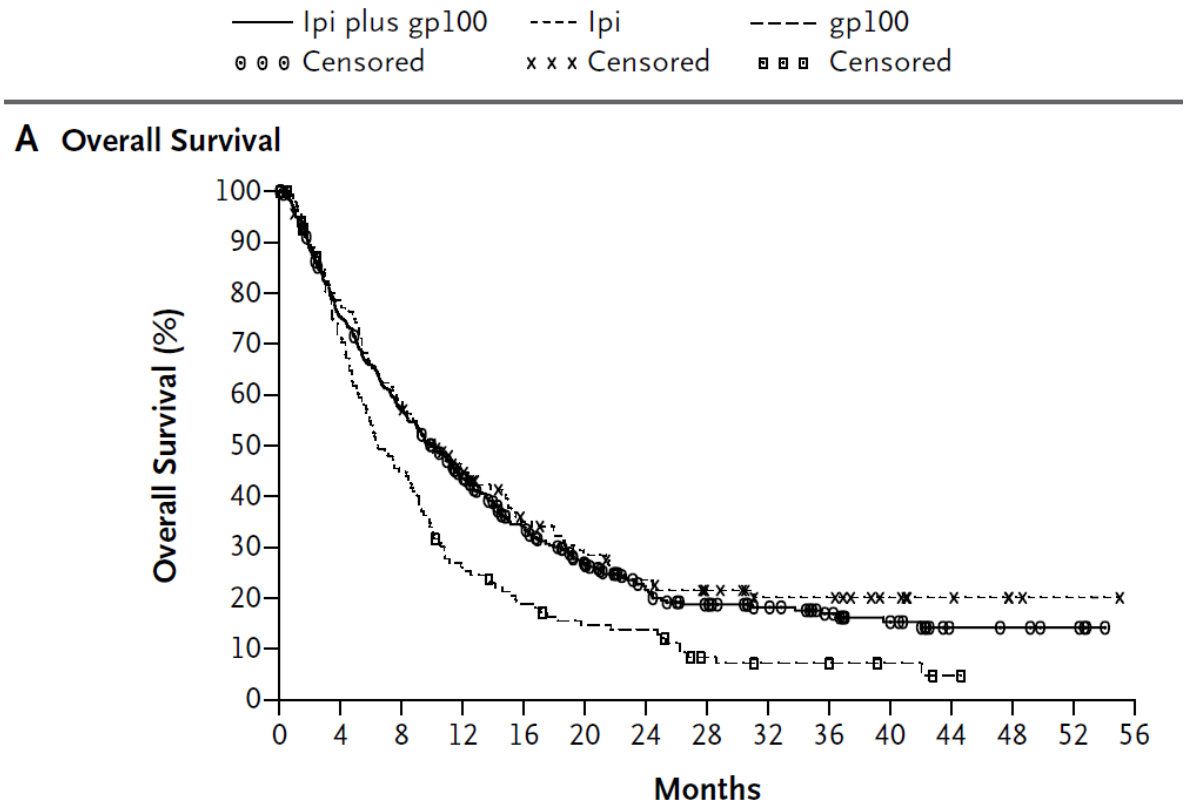
The landscape of treatment development



The landscape of treatment development



Previously treated MMM - Ipilimumab

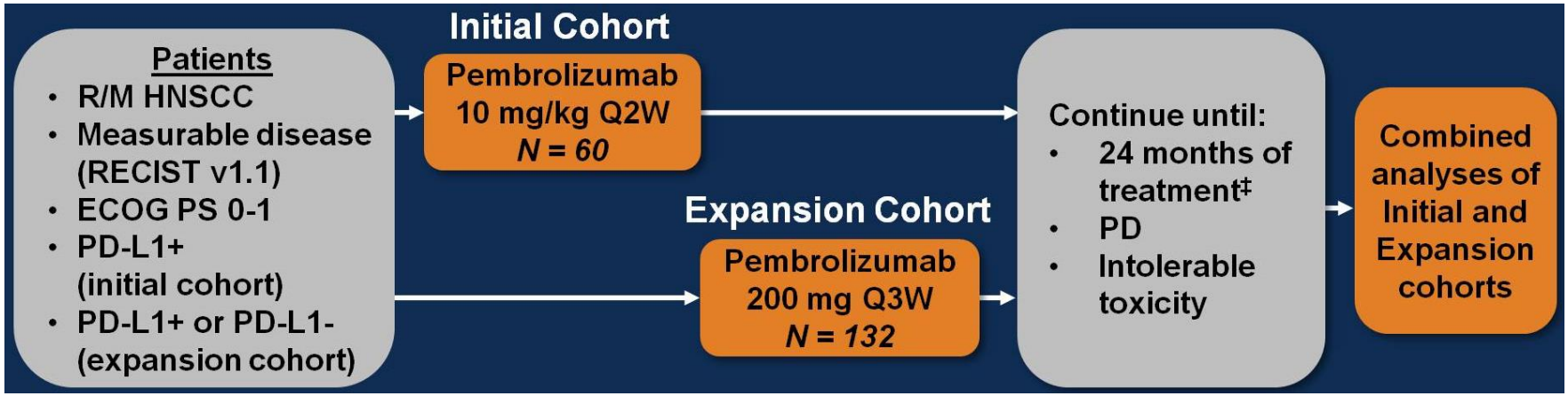


No. at Risk

Ipi plus gp100	403	297	223	163	115	81	54	42	33	24	17	7	6	4	0
Ipi	137	106	79	56	38	30	24	18	13	13	8	5	2	1	0
gp100	136	93	58	32	23	17	16	7	5	5	3	1	0	0	0

Hodi et al NEJM 2010

HNSCC: KEYNOTE-012 Phase 1a+b trial



Seiwert et al ASCO 2017 and Lancet Oncol 2016

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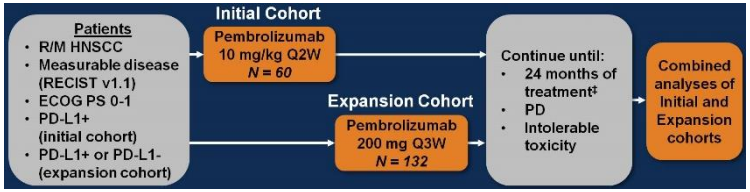
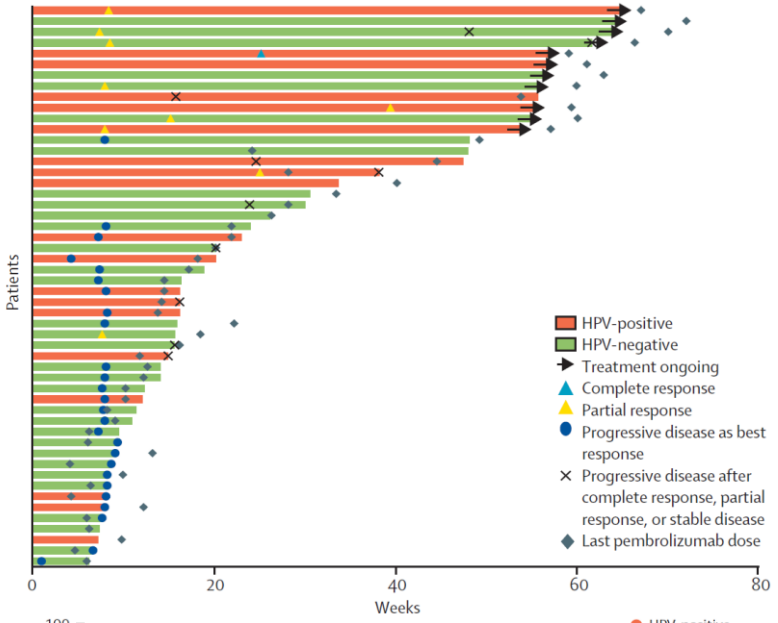
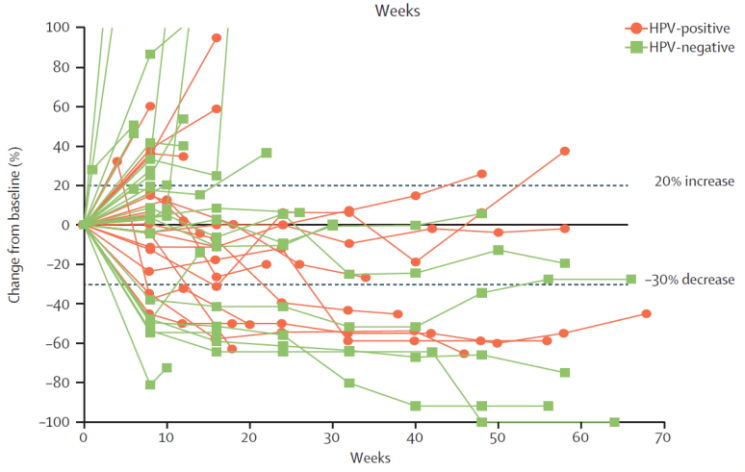
HNSCC: KEYNOTE-012 Phase 1a+b trial







Seiwert et al ASCO 2017 and Lancet Oncol 2016

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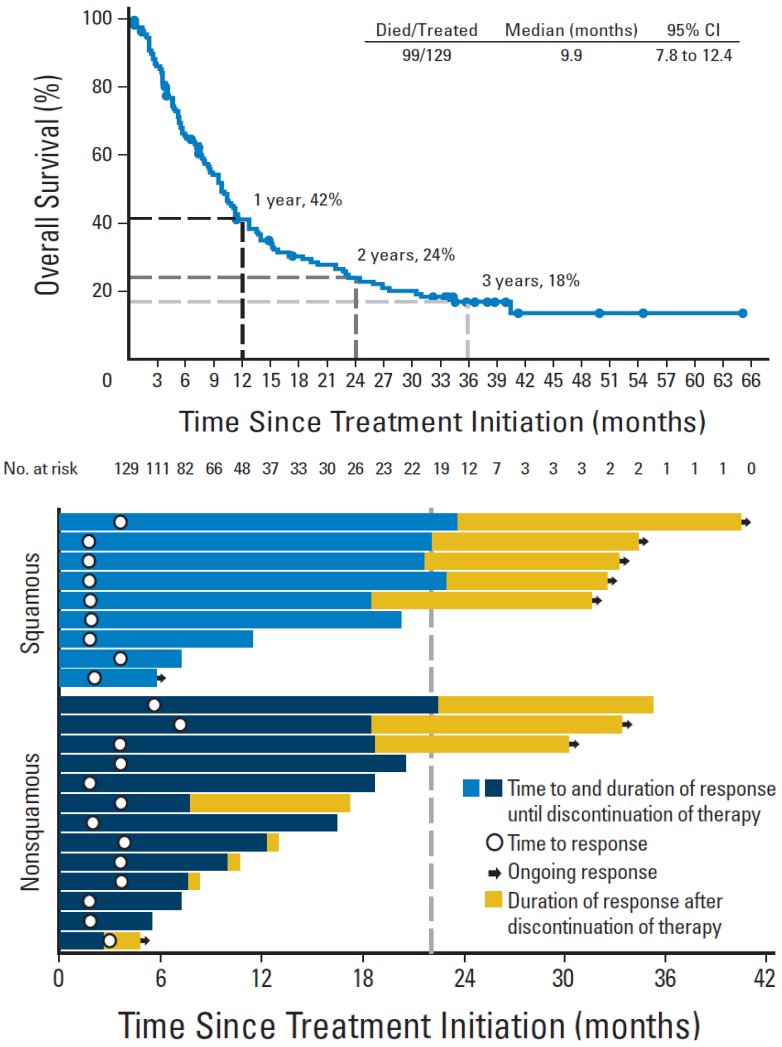
Previously heavily treated lung cancer

Characteristic	All Treated Patients (N = 129) No.	%
Age, years		
Median	65	
Range	38-85	
Sex		
Male	79	61.2
Female	50	38.8
Tumor cell histology		
Squamous	54	41.9
Nonsquamous	74	57.4
Unknown	1	0.8
ECOG performance status[17]		
0 or 1	127	98.4
2*	2	1.6
No. of prior systemic treatment regimens		
1-2	59	45.7
≥ 3	70	54.3
Nature of prior therapy		
Platinum-based chemotherapy	128	99.2
Tyrosine kinase inhibitor	36	27.9
Surgery†	85	65.9
Radiotherapy†	75	58.1
Hormonal, immunologic, or biologic therapy	16	12.4
Other	9	7.0
EGFR tumor mutation status		
Mutant	12	9.3
Wild type	56	43.4
Unknown‡	61	47.3
KRAS tumor mutation status		
Mutant	21	16.3
Wild type	36	27.9
Unknown‡	72	55.8



Gettinger et al JCO 2015

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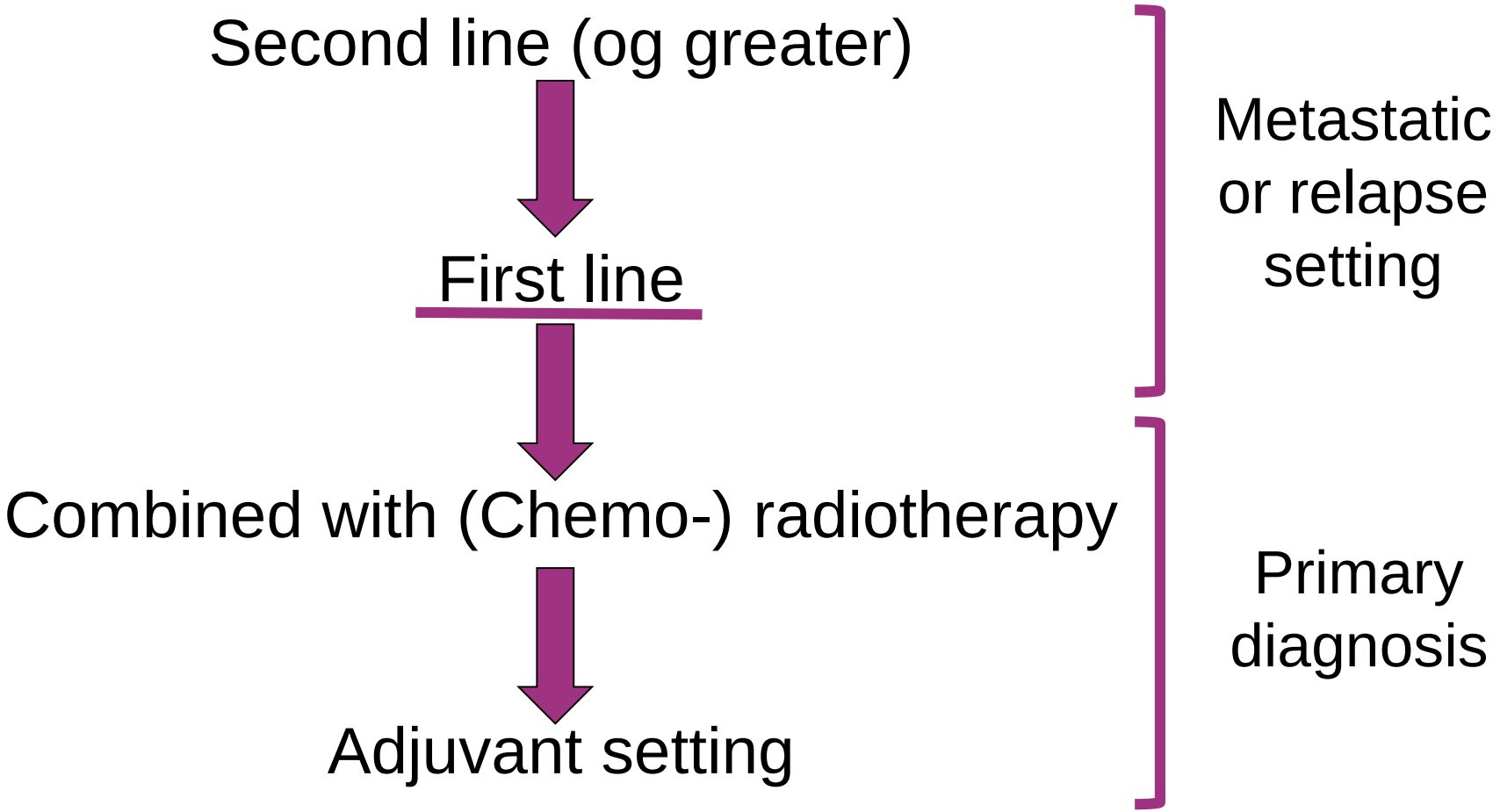
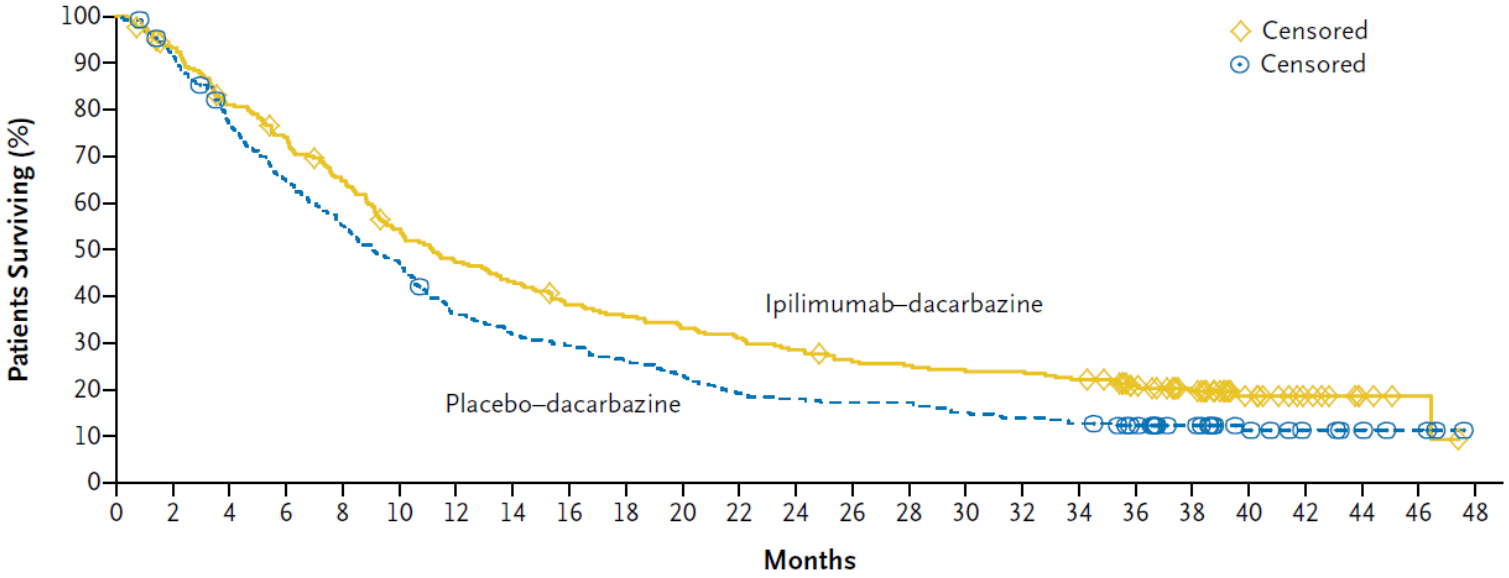
The landscape of treatment development



Ipilimumab as first-line treatment for MMM



No. at Risk

Ipilimumab–dacarbazine	250	230	199	181	157	131	114	104	91	85	79	74	68	61	59	56	56	52	41	31	17	10	4	2	0
Placebo–dacarbazine	252	229	190	160	136	116	89	78	72	64	56	47	44	42	42	37	34	31	26	19	11	7	5	3	0

Roberts et al NEJM 2011

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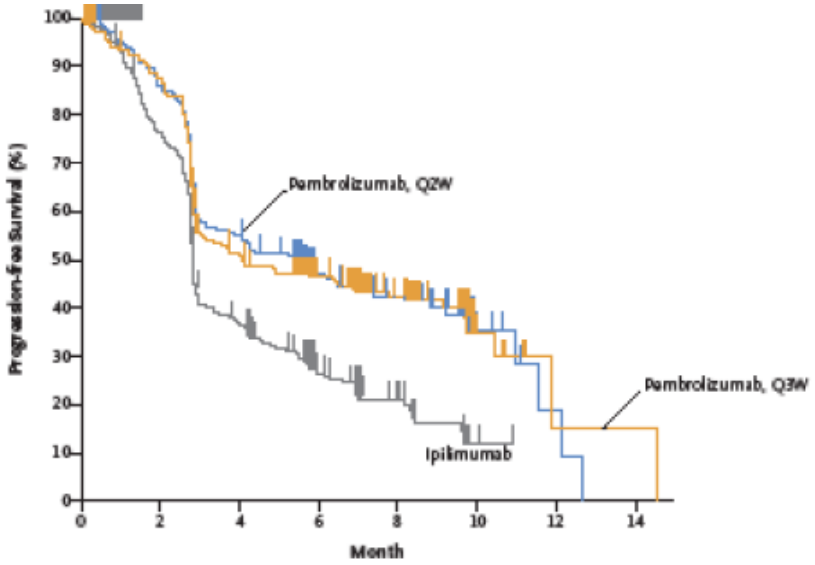
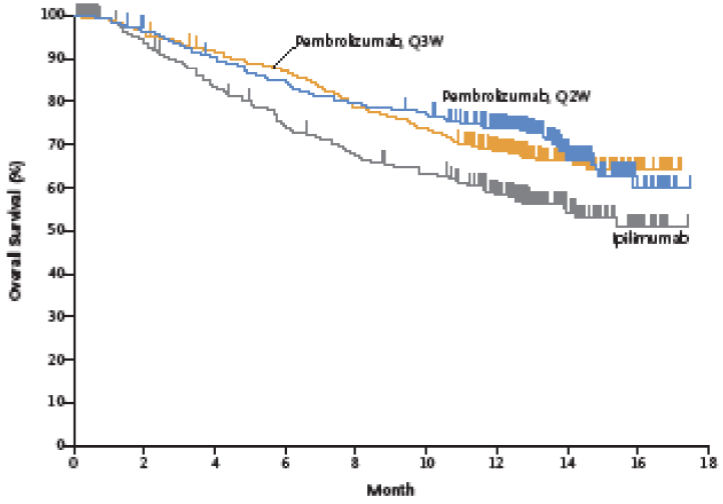
Ipilimumab vs. pembrolizumab first-line MMM



No. at Risk								
Pembrolizumab, Q2W	279	231	147	98	49	7	2	0
Pembrolizumab, Q3W	277	235	133	95	53	7	1	1
Ipilimumab	278	186	88	42	18	2	0	0



No. at Risk										
Pembrolizumab, Q2W	279	266	248	233	219	212	177	67	19	0
Pembrolizumab, Q3W	277	266	251	238	215	202	158	71	18	0
Ipilimumab	278	242	212	188	169	157	117	51	17	0

Roberts et al NEJM 2015

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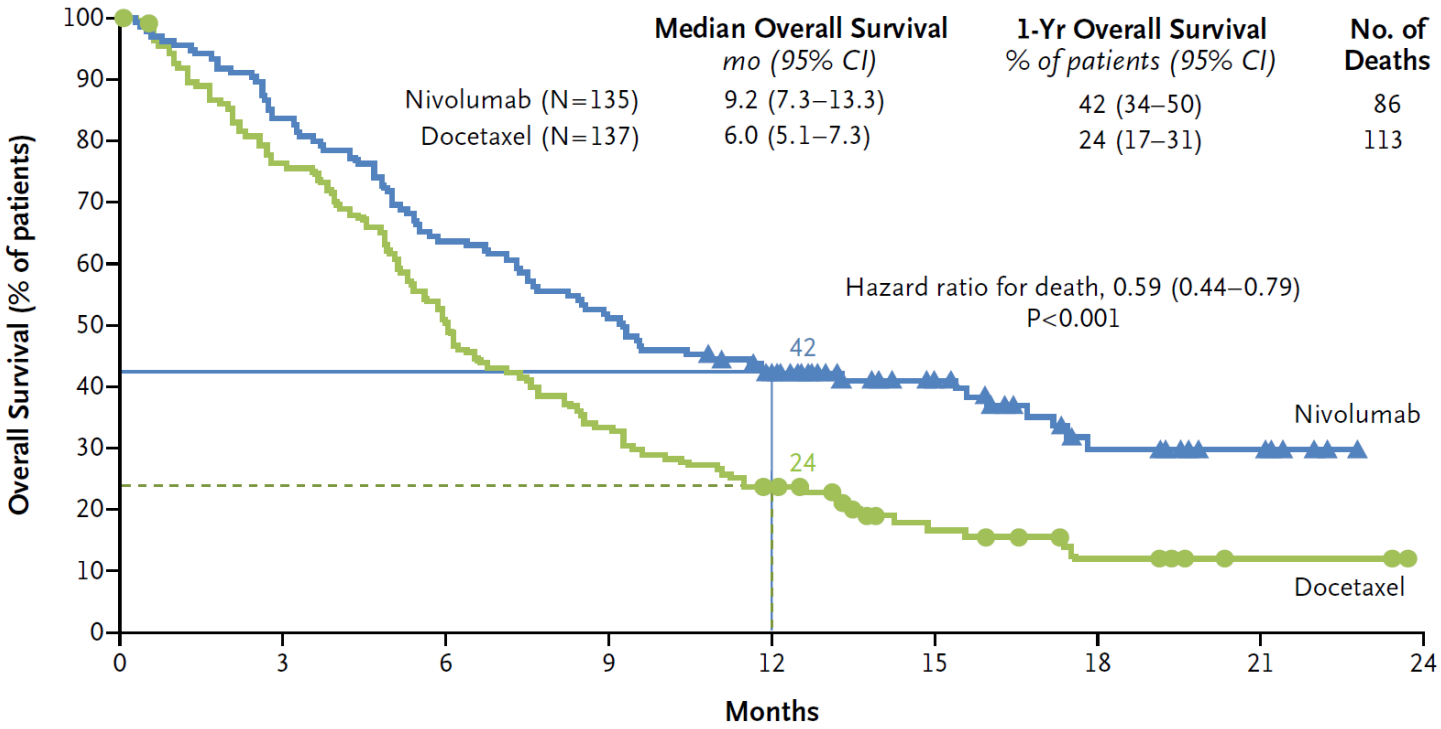
Nivolumab vs. docetaxel for advanced NSCLC



Brahmer et al NEJM 2015

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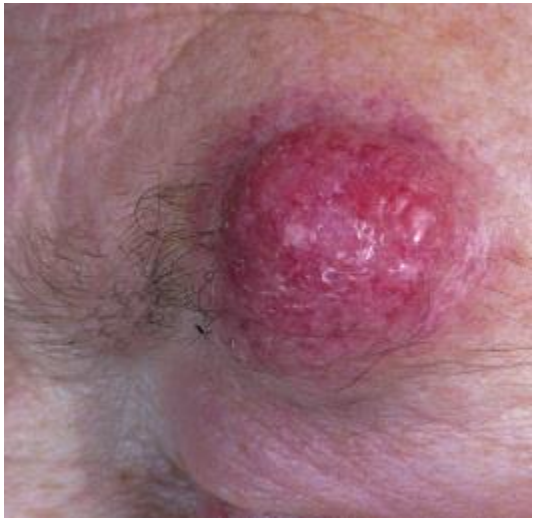
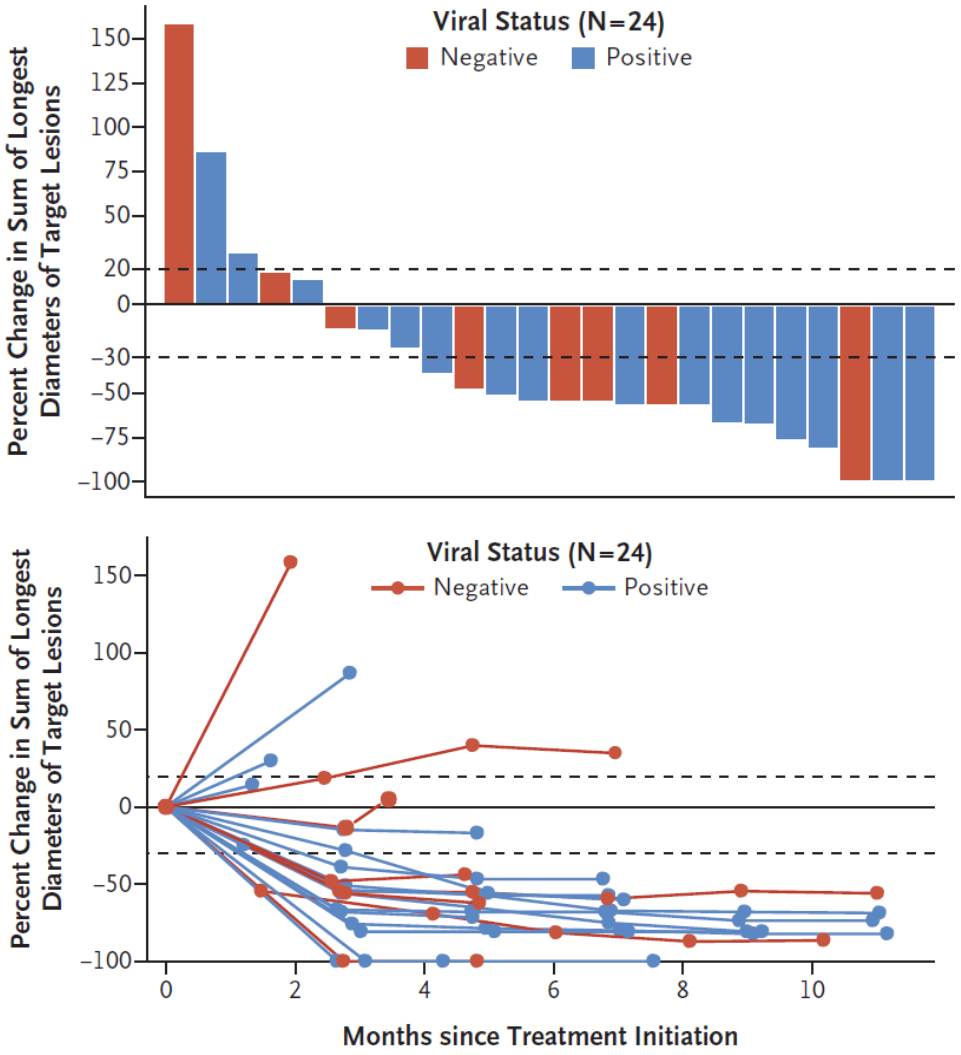
Merkel cell carcinoma of the skin

- Phase 2, study
- Advanced MCC
- N=26 (24 eval.)
- ≥ 1 serie Pembro





Nghiem NEJM 2016

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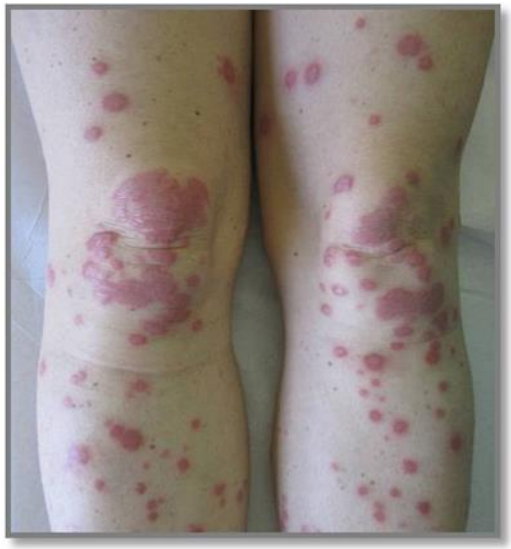
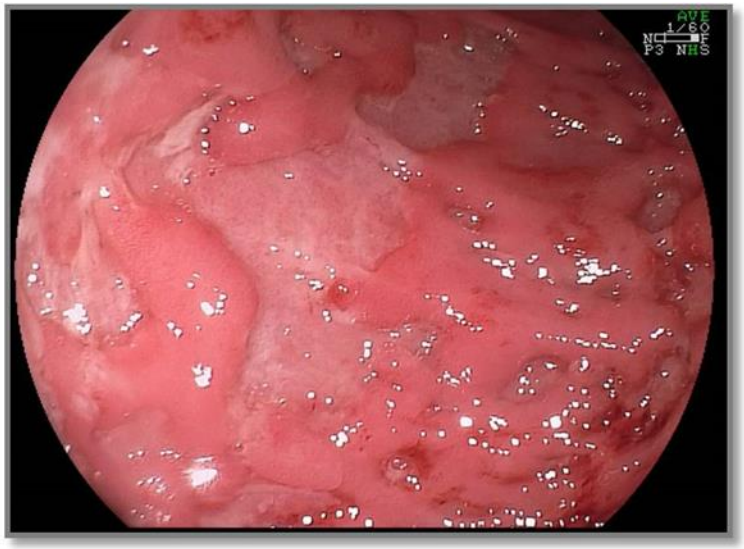
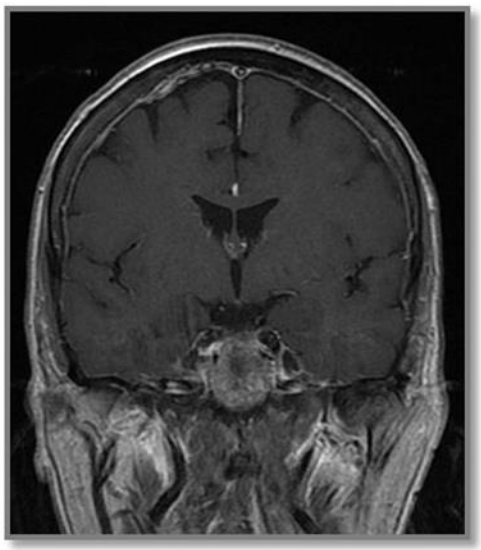
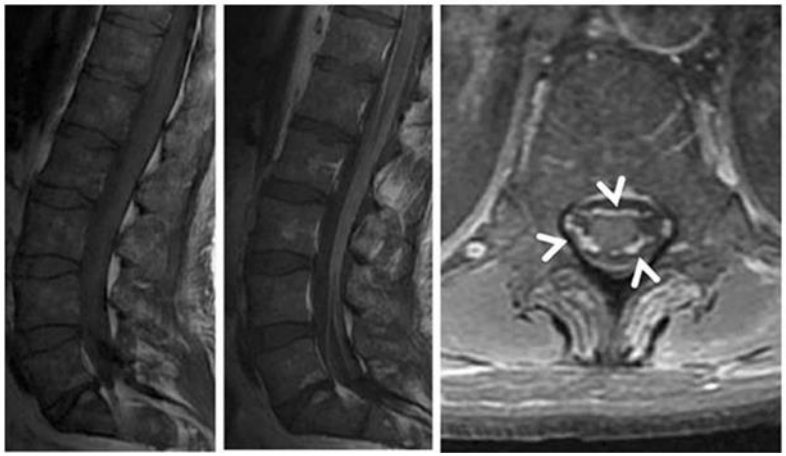
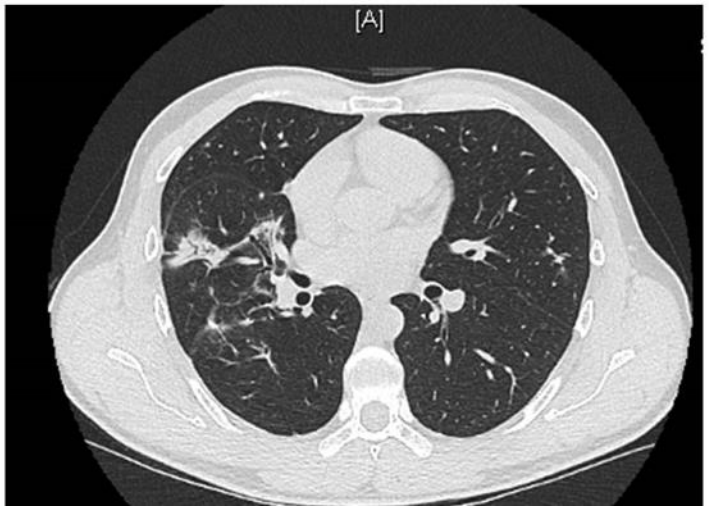
New drugs – new toxicities











Robert ASCO 2017

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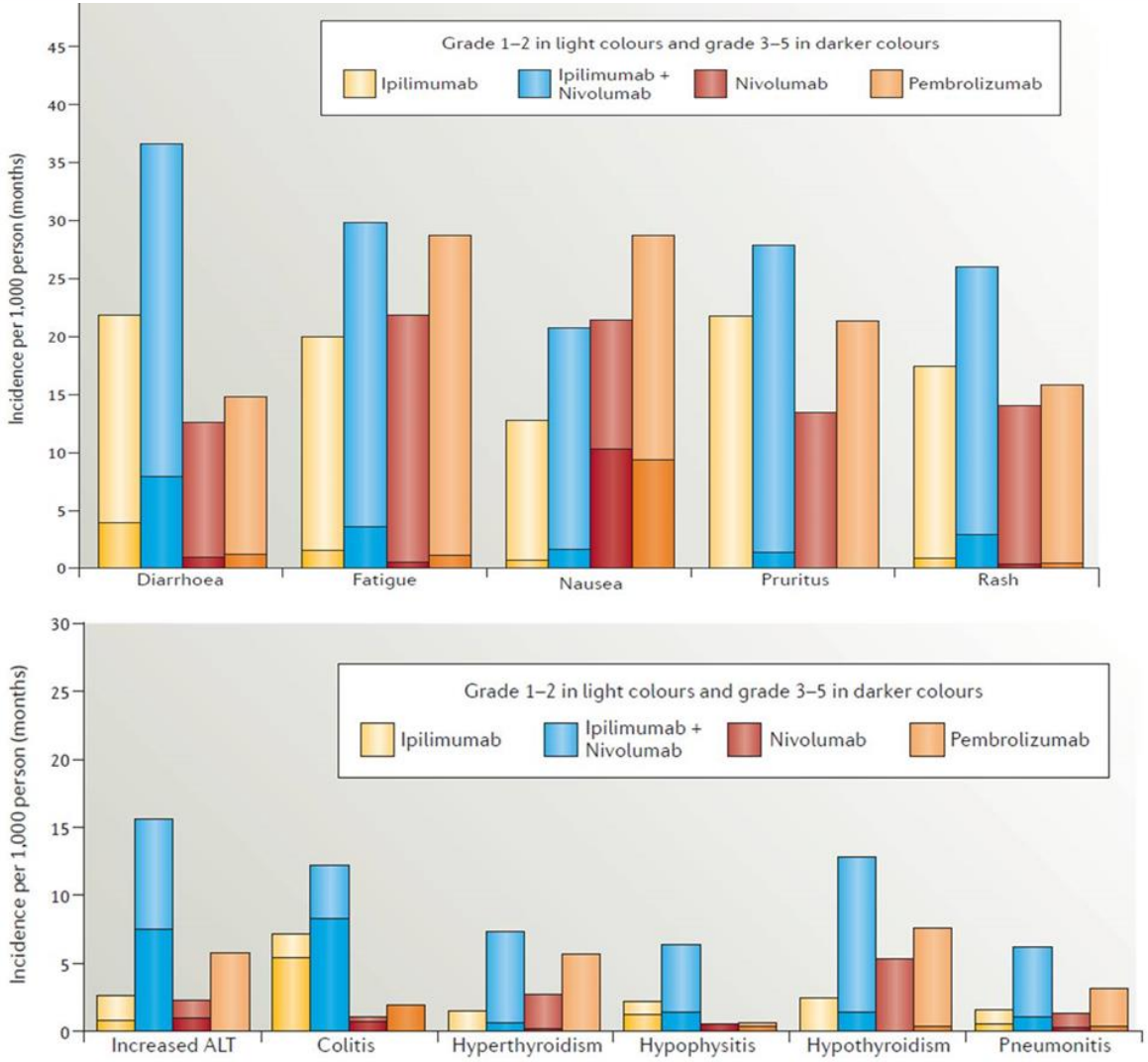
New drugs – new toxicities



Boutros et al, Nat Clin Pract Oncol 2016

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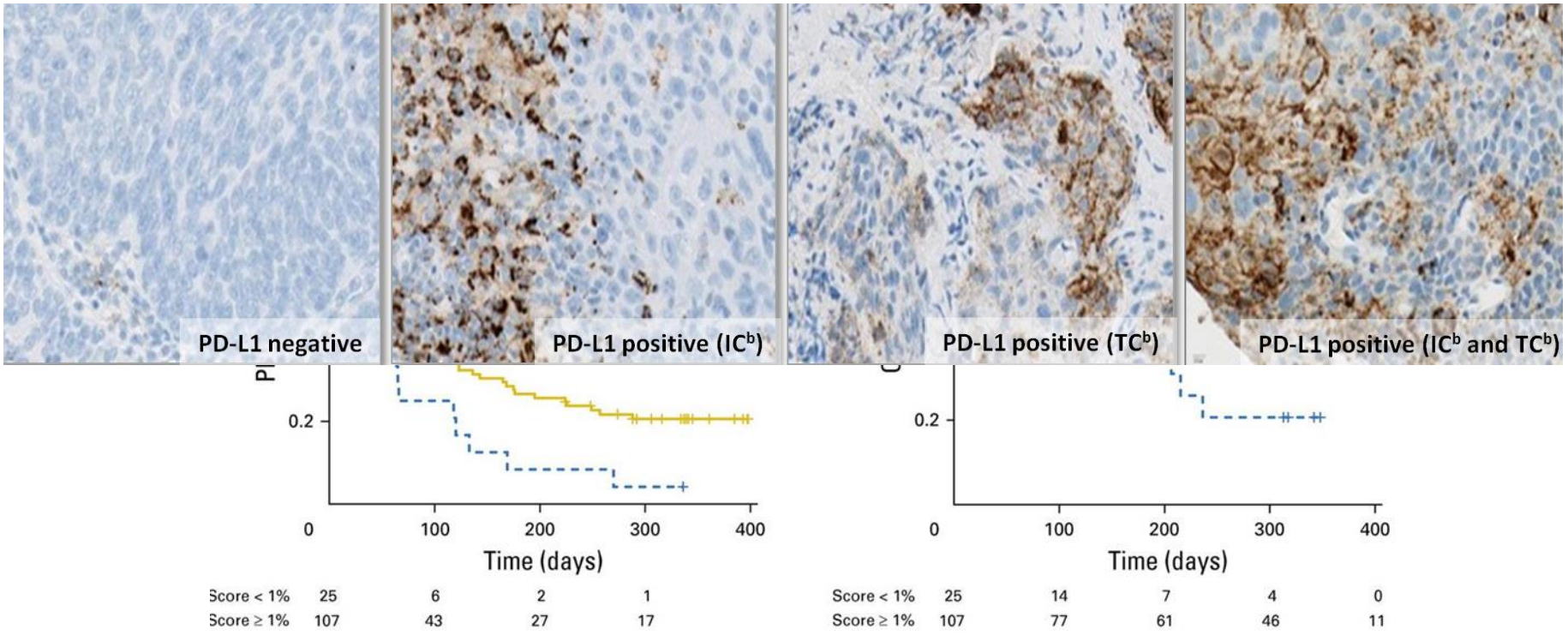
Personalised immunotherapy

PD-L1 Status	Tumor and Immune Cells			Tumor Cells Only		
	Nonresponders, No.	Responders, No.	Response, % (95% CI)	Nonresponders, No.	Responders, No.	Response, % (95% CI)
Negative (< 1%)	24	1	4 (0.1 to 20)	36	7	16 (7 to 31)
Positive (≥ 1%)	84	23	22 (14 to 31)	72	17	19 (12 to 29)



Cohen ASCO 2017 and Seiwert Lancet Oncol 2016

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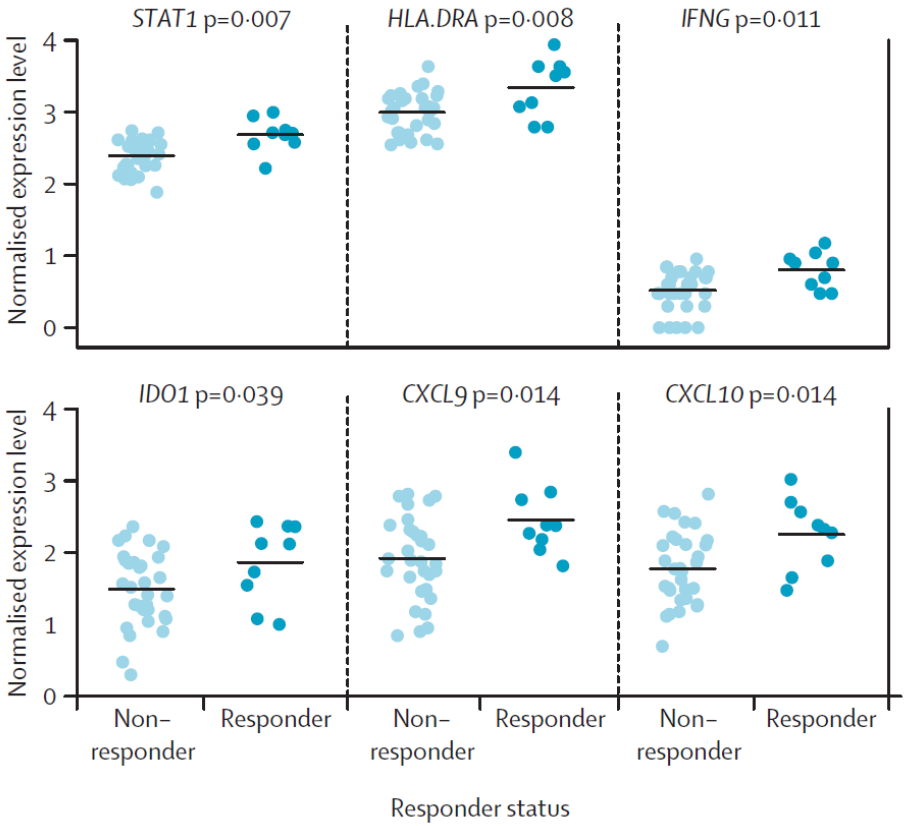
Personalised immunotherapy



Seiwert Lancet Oncol 2016

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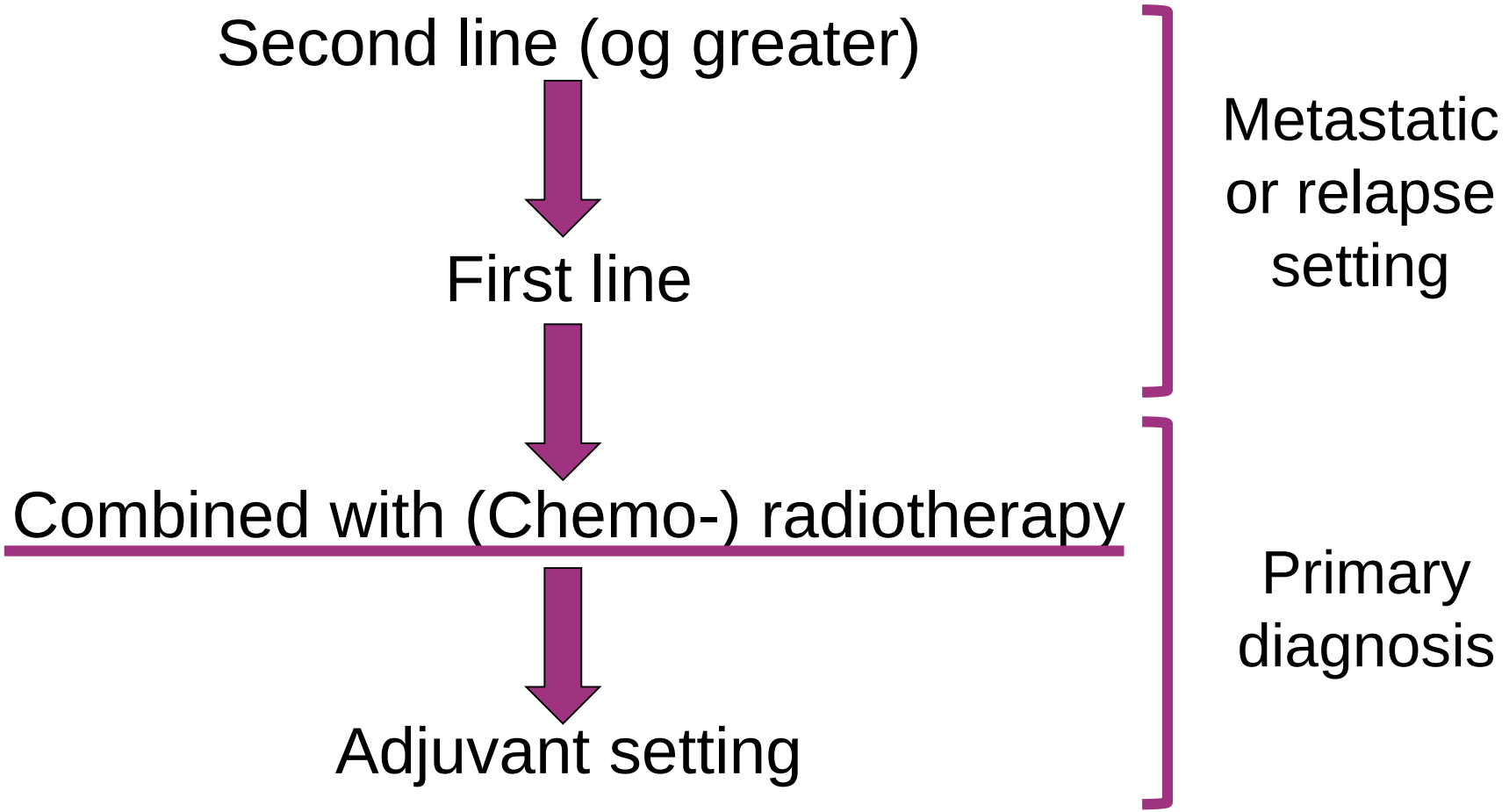
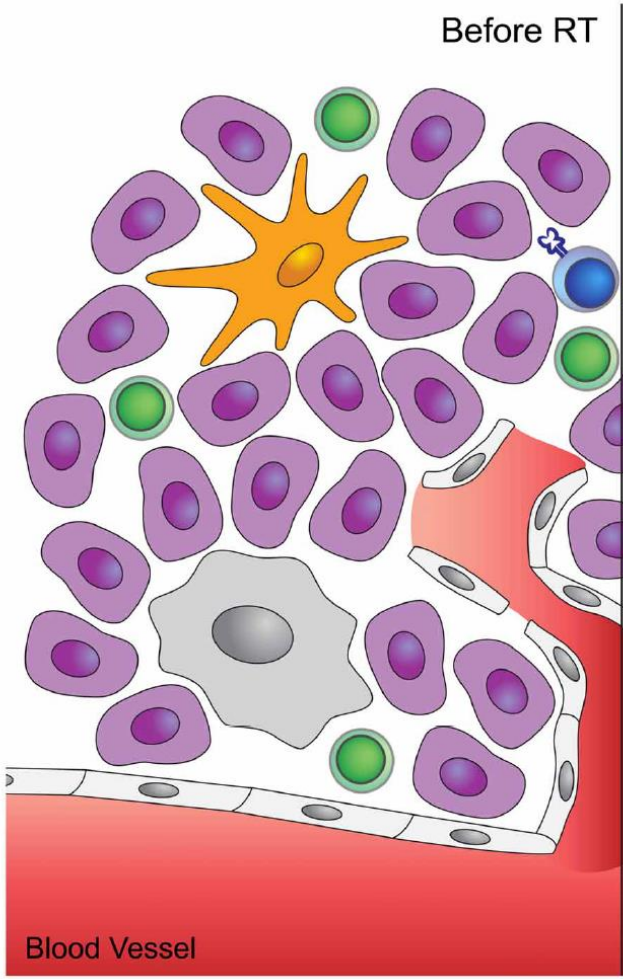
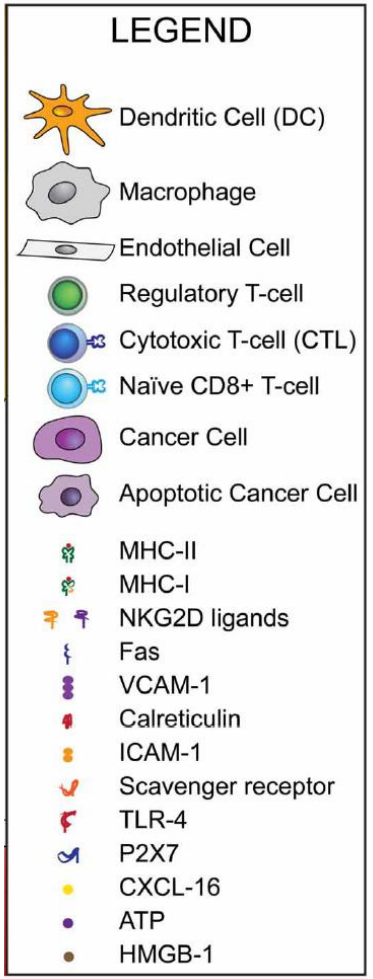
The landscape of treatment development



Biological rationale





Demaria S et al Frontir Oncol 2012

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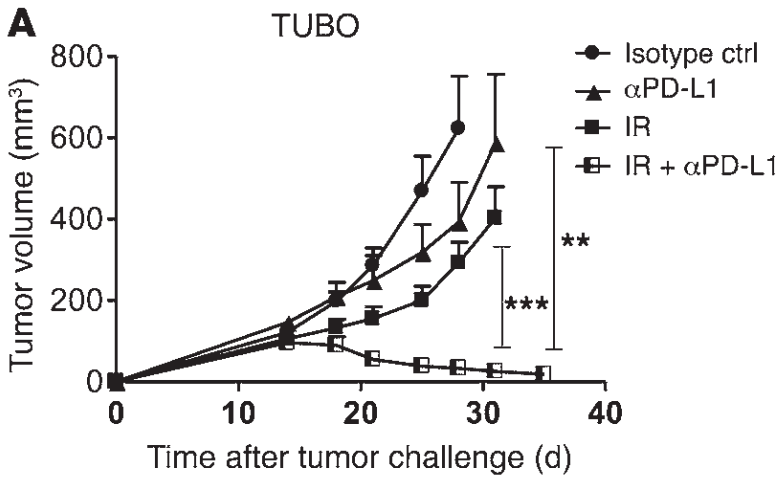
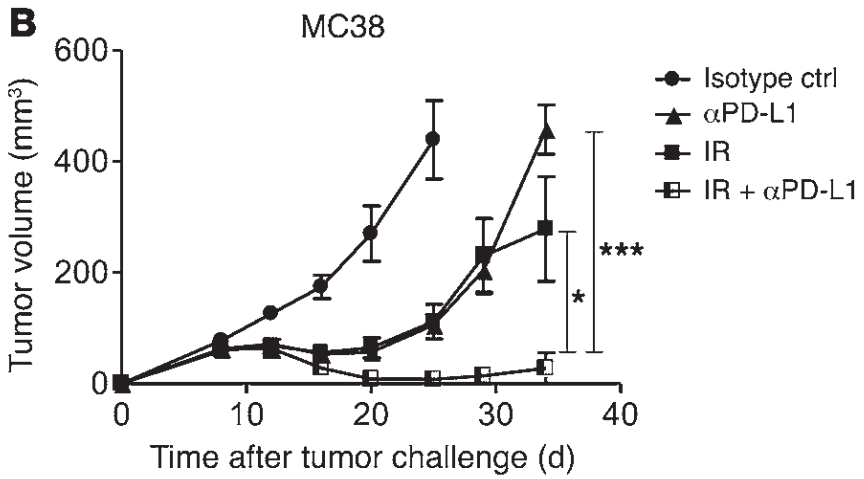
PD-L1 inhibition is synergistic with radiation





Deng et al J Clin Invest 2014

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Ongoing clinical studies

ClinicalTrials.gov

Example: "Heart attack" AND "Los Angeles"

Search for studies: Search

Advanced Search | Help | Studies by Topic | Glossary

IMPORTANT: Listing of a study on this site does not reflect endorsement by the National Institutes of Health. Talk with a trusted healthcare professional before volunteering for a study. Read more...

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52 studies found for: PD-L1 and radiation | Interventional Studies | Phase 2, 3

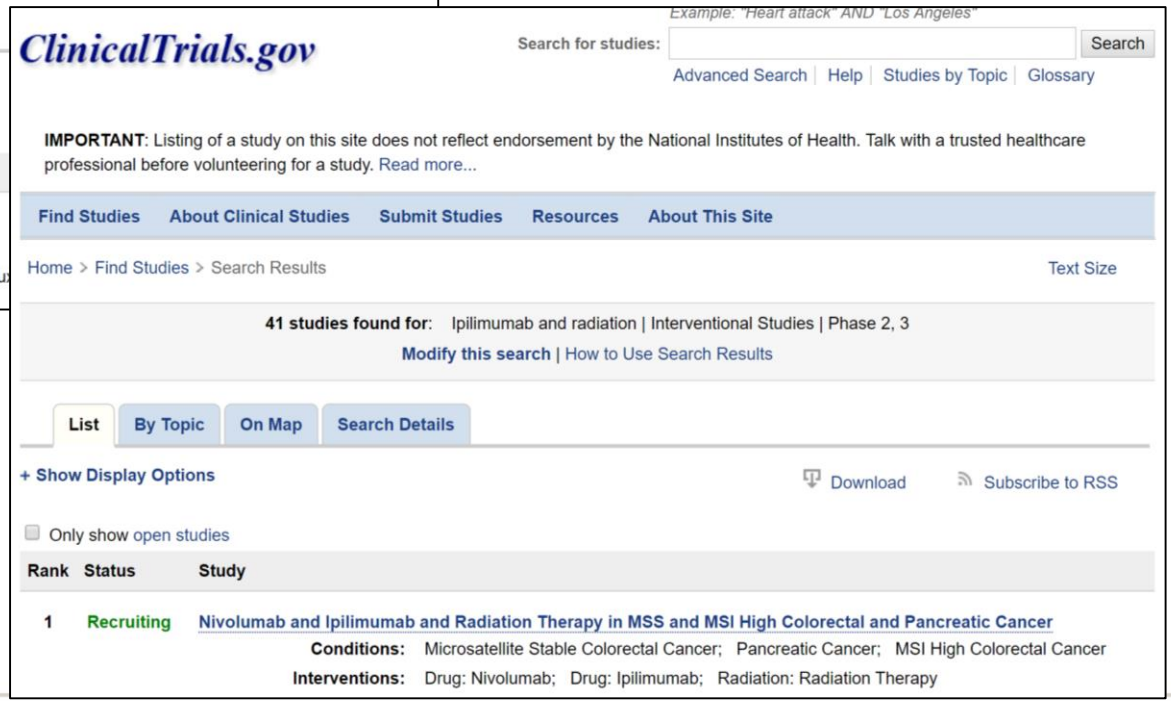
Modify this search | How to Use Search Results

List | By Topic | On Map | Search Details

+ Show Display Options

Only show open studies

Rank	Status	Study
1	Not yet recruiting	Durvalumab, Cetuximab and Radiotherapy in Head Neck Cancer **Condition:** Head and Neck Neoplasms **Interventions:** Biological: Durvalumab; Biological: Cetu therapy (IMRT)



ClinicalTrials.gov

Example: "Heart attack" AND "Los Angeles"

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41 studies found for: Ipilimumab and radiation | Interventional Studies | Phase 2, 3

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Only show open studies

Rank	Status	Study
1	Recruiting	Nivolumab and Ipilimumab and Radiation Therapy in MSS and MSI High Colorectal and Pancreatic Cancer **Conditions:** Microsatellite Stable Colorectal Cancer; Pancreatic Cancer; MSI High Colorectal Cancer **Interventions:** Drug: Nivolumab; Drug: Ipilimumab; Radiation: Radiation Therapy

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Palliative RT in combination with ipilimumab

- 22 pts
- St. IV melanoma
- Pall. RT + ipilimumab x4
- RT to 1-2 sites
- Initiated within 5 days after start of ipilimumab

	Grade 2	Grade 3	Grade 4
Colitis*	2 (9%)	1 (5%)	1 (5%)
Hypophysitis*	2 (9%)	1 (5%)	NR
Rash*	3 (14%)	NR	NR
Anemia*	2 (9%)	NR	NR
Nausea**	2 (9%)	NR	NR
Radiation Dermatitis**	4 (19%)	NR	NR

*: primarily immunotherapy-related
**: primarily radiation-related

Hiniker et al IJROBP 2016

ESTRO School

C-RT + Pembrolizumab – a safety study

Safety of Pembrolizumab with Chemoradiation (CRT) in Locally Advanced Squamous Cell Carcinoma of the Head and Neck (LA-SCCHN).

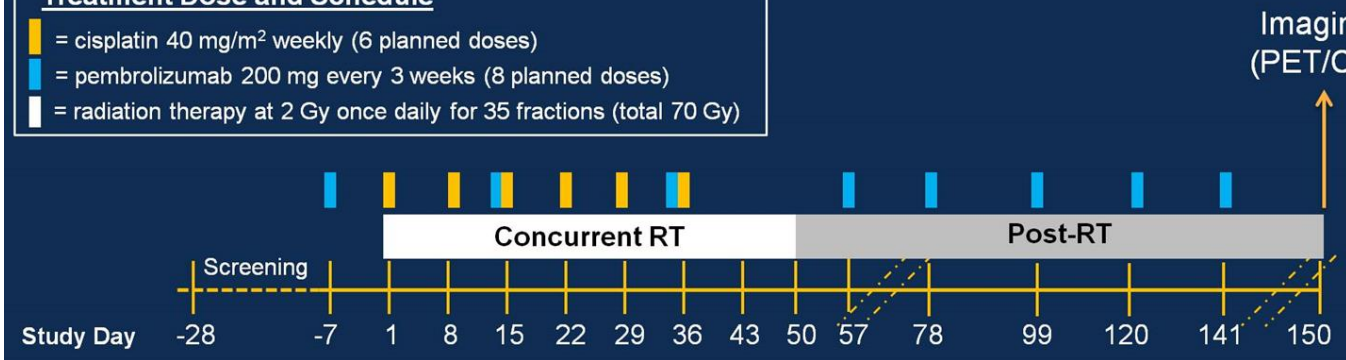
Steven F. Powell[1], Mark M. Gitau[2], Christopher J. Sumey[1], John T. Reynolds[3], Andrew M. Terrell[2], Michele M. Lohr[1], Steven C. McGraw[1], Ryan K. Nowak[1], Ashley W. Jensen[2], Miran J. Blanchard[2], Christie A. Ellison[1], Lora J. Black[1], Paul A. Thompson, PhD[1], Kathryn A. Gold[4], Ezra E.W. Cohen[4], John H. Lee[1,5], William C. Spanos[1]

[1]Sanford Health, Sanford Cancer Center, Sioux Falls, SD; [2]Sanford Health, Roger Maris Cancer Center, Fargo, ND; [3]Sanford Health, Sanford Cancer Center, Bismarck, ND, [4]University of California, San Diego, Moores Cancer Center, La Jolla, CA, [5]NantKwest, Inc., Culver City, CA

PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17

Treatment Dose and Schedule

- = cisplatin 40 mg/m² weekly (6 planned doses)
- = pembrolizumab 200 mg every 3 weeks (8 planned doses)
- = radiation therapy at 2 Gy once daily for 35 fractions (total 70 Gy)



Primary end points:

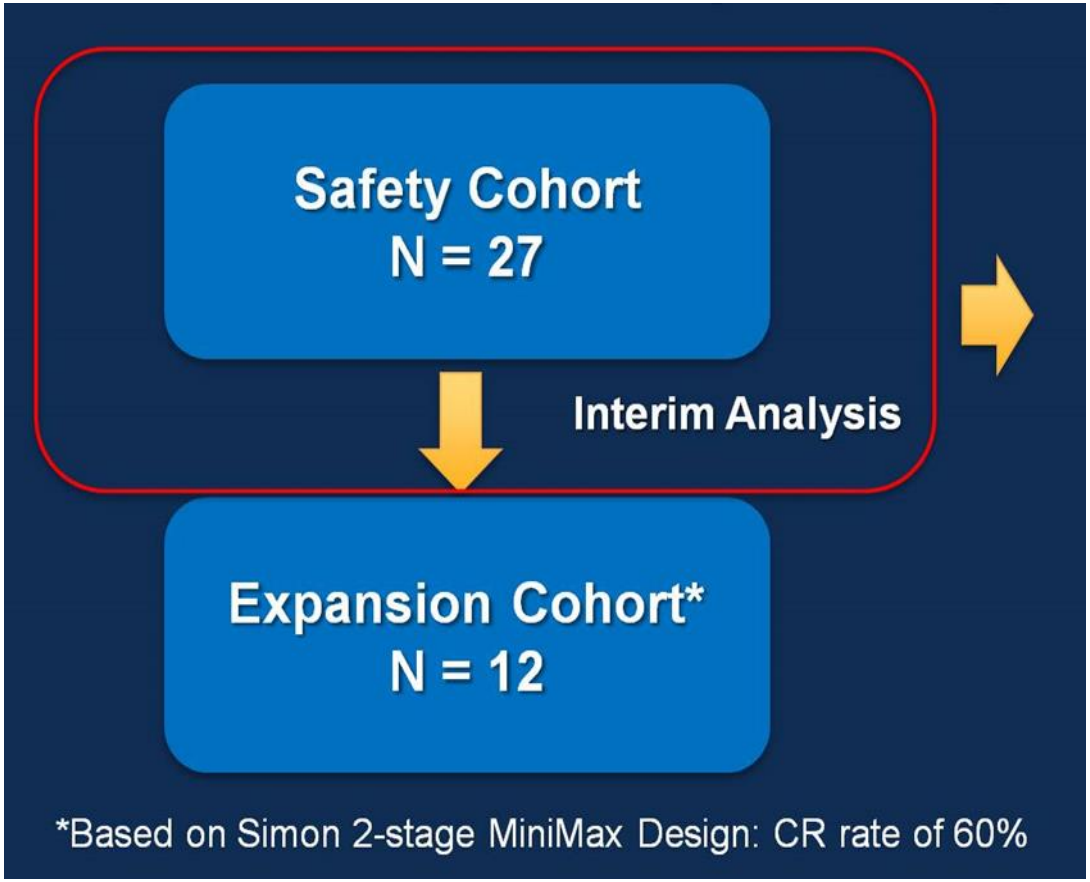
- Safety - dose-limiting adverse events (AEs) and immune-related AEs (irAEs)
- Efficacy - complete response (CR) rate on imaging or salvage surgery at day 150

Secondary end points: PFS, OS, locoregional control, distant metastasis rate, quality-of-life (FACT H&N)

Powell ASCO 2017

ESTRO School

C-RT + Pembrolizumab – a safety study



All Patients n = 27		
Age (median, range)		61.7 yrs (36-80 yrs)
Sex (% male)		23 (85%)
Primary site:		
	Oropharynx	22 (81.5%)
	Larynx	4 (14.8%)
	Hypopharynx	1 (3.7%)
Stage		
	III	1 (3.7%)
	IVA	25 (92.6%)
	IVB	1 (3.7%)
T stage		
	T1-3	19 (70%)
	T4	8 (30%)
N Stage		
	N0-1	2 (7%)
	N2	24 (89%)
	N3	1 (4%)
Tobacco use (>10 PYH)		21 (78%)
Prophylactic feeding tube		22 (82%)

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C-RT + Pembrolizumab – a safety study

Pembrolizumab – Discontinuations and irAEs

Pembrolizumab (8 planned doses)	N (%)
<3 doses (CRT)	2 (7.4%)
>3 but <8 doses (post-CRT)	4 (15%)
All 8 doses	21 (78%)

- 3 discontinuations due to irAEs (11%)
  - Grade 3 AST increase
    - Resolved with corticosteroids
  - Grade 2 peripheral motor neuropathy
  - Grade 1 Lhermitte-like syndrome
- No other irAEs requiring discontinuation or treatment
- 3 discontinuations due to protocol reasons
  - Early neck dissection (N = 2)
  - Prolonged hospitalization

C-RT + Pembrolizumab – a safety study

Selected Adverse Events - CRT

AE	All Grades	Grade 3	Grade 4
Dysphagia	26 (96%)	12 (44%)	None
Mucositis (oral/pharyngeal)	26 (96%)	8 (30%)	
Dermatitis radiation	22 (81%)	4 (15%)	
Weight loss	22 (81%)	4 (15%)	
Neutropenia	17 (63%)	9 (33%)	1(4%)
Anemia	25 (93%)	4 (15%)	None
Thrombocytopenia	11 9(41%)	2 (7%)	
Hyponatremia	20 (74%)	5 (19%)	None
Hypomagnesemia	17 (63%)	1 (4%)	
Hypophosphatemia	12 (44%)	4 (15%)	1 (4%)

23 (85%) completed ≥ 200 mg cisplatin/m²
27 (100%) completed 70Gy of radiation

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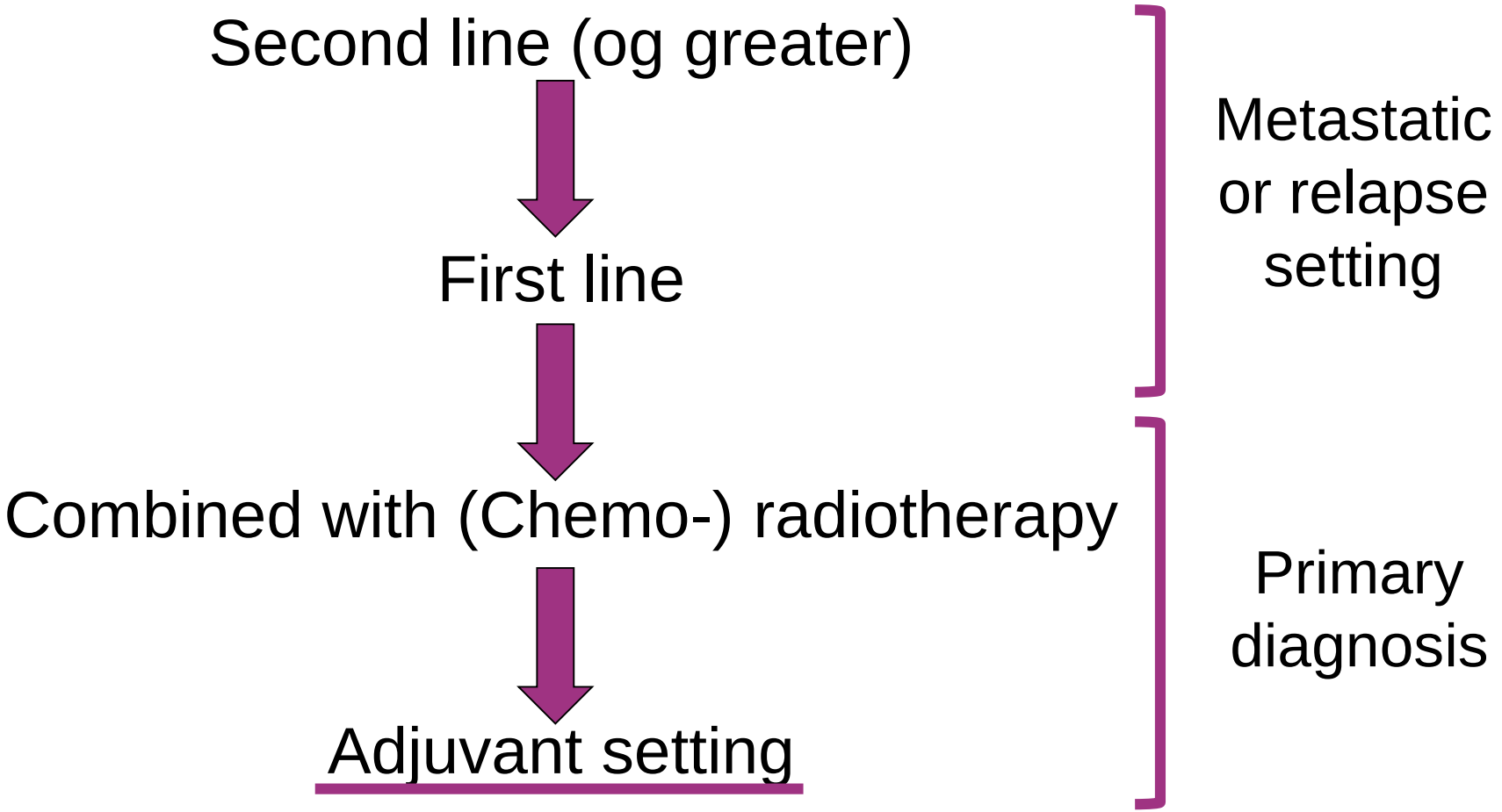
The landscape of treatment development

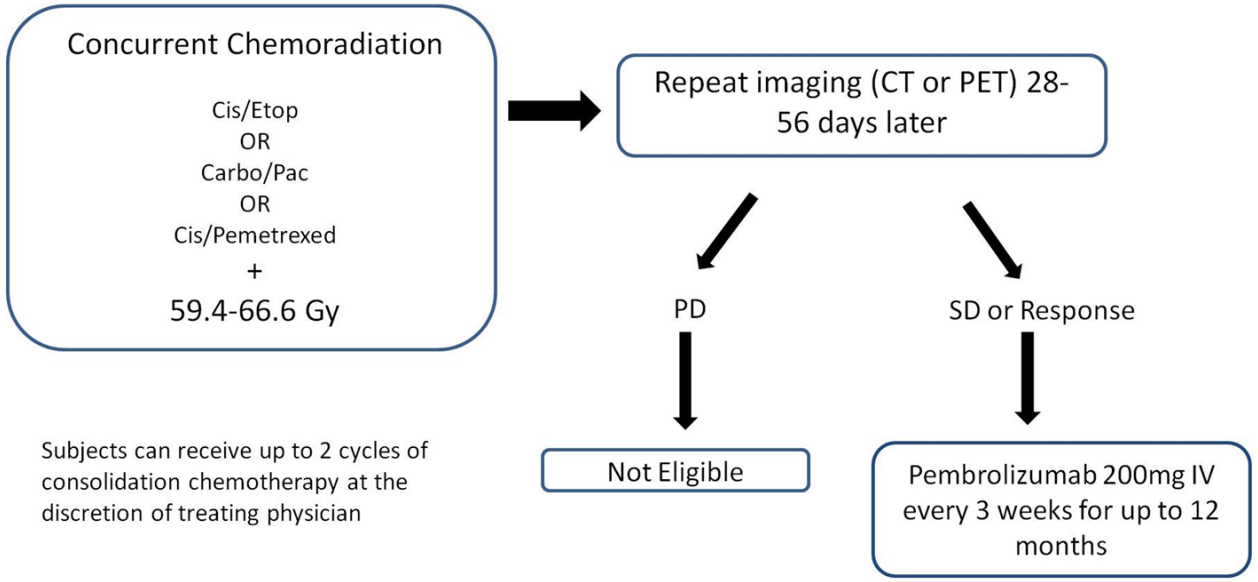


Adjuvant Pembrolizumab after C-RT to st. III NSCLC

Safety and Feasibility of Consolidation Pembrolizumab following Concurrent Chemoradiation for Unresectable Stage III Non-Small Cell Lung Cancer: Hoosier Cancer Research Network LUN14-179

Greg Durm, Cynthia Calley, Shadia Jalal, Ahad Sadiq, Salma Jabbour, Robin Zon, Goetz Kloecker, Karen Reckamp, William Fisher, and Nasser Hanna

SCHOOL OF MEDICINE



Adjuvant Pembrolizumab after C-RT to st. III NSCLC

Feasibility of Receiving 4 Cycles of Pembrolizumab Consolidation

- 76/93 (81.7%) eligible patients were able to receive 4 cycles of therapy
- Reasons for dropout or withdrawal:
  - Adverse events-7 (pneumonitis (4), recurrent colitis, pulmonary embolus, pneumothorax)
  - Disease progression- 4
  - Patient withdrawal- 3
  - Death- 2
  - Unknown-1

Conclusion

- Biological basis for combining RT with check-point inhibitors
- In mice models there seems to be synergy
- Different toxicity profile
- Apparently not synergy re. side effects
- Trials are ongoing
- No immuno-RT treatments can be considered standard – everything should be done in controlled trials


LUNG CANCER PATIENTS
UMBRELLA TRIAL
DIFFERENT MEDICINES SAME TARGET

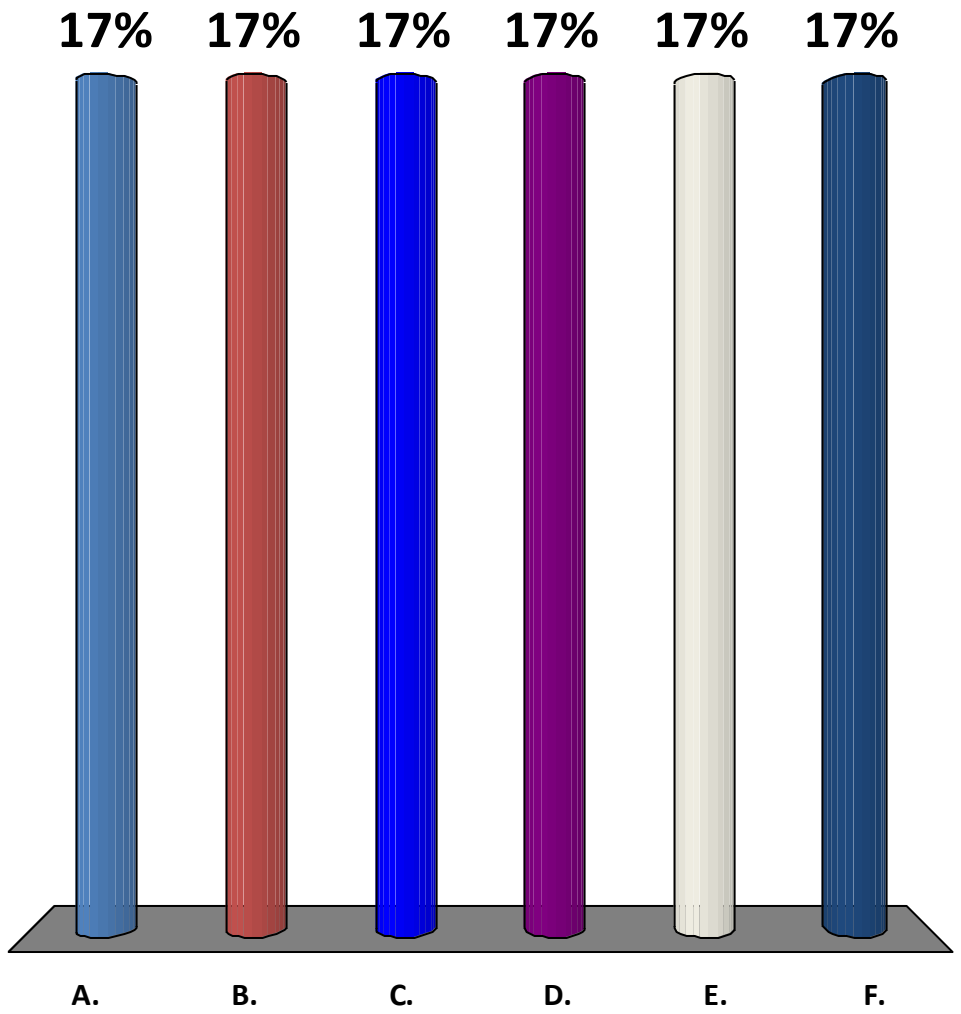
Decision-making in oncology

Dr Li Tee Tan

Cambridge University Hospitals NHS
NHS Foundation Trust

Do you find decision-making in your clinical practice difficult?

A. Consultant - often
B. Consultant - sometimes
C. Consultant - rarely
D. Trainee - often
E. Trainee - sometimes
F. Trainee - rarely



What is decision-making?

- Decision-making is the act of choosing between two or more courses of action.

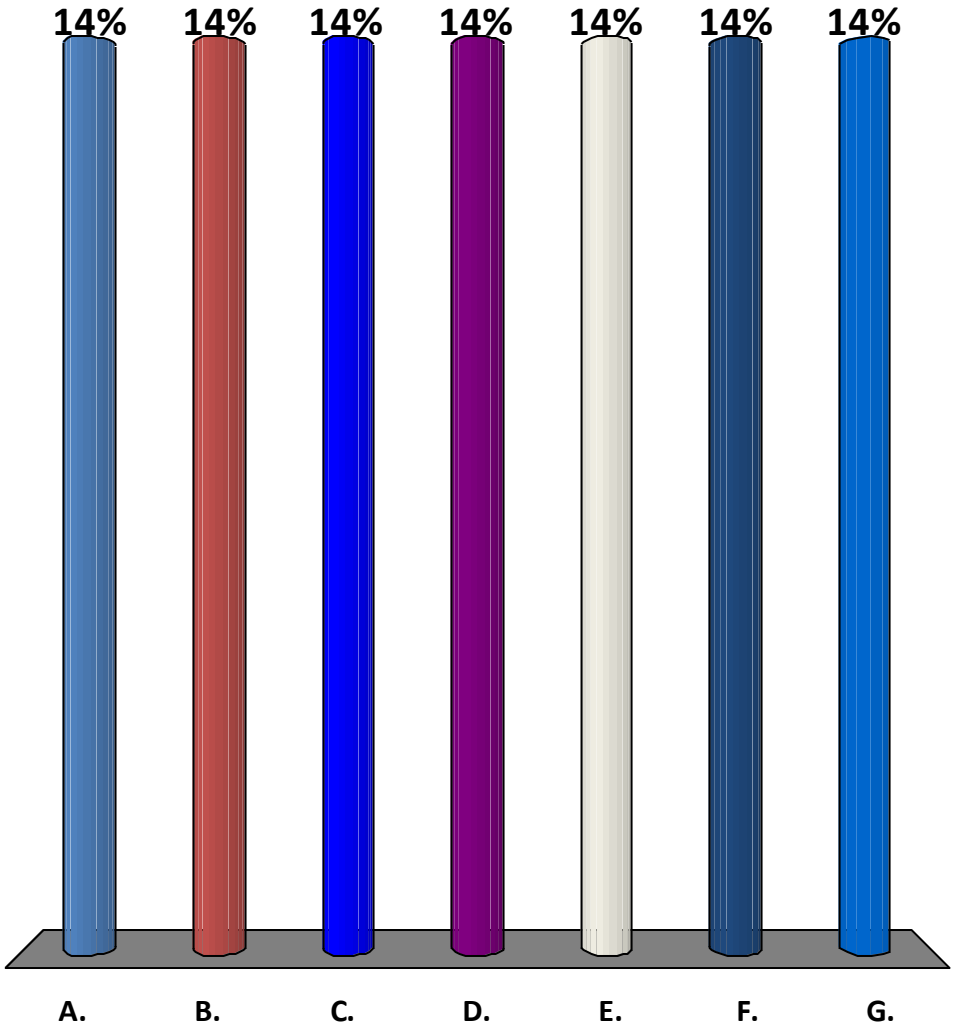
https://www.skillsyouneed.com/ips/decision-making.html

Decision-making in oncology

- To decide on the best treatment for the **individual** patient

What do you find challenging in oncology decision-making? (Select one or more)

A. Knowing the latest evidence
B. Applying the evidence to the individual patient
C. Presence of conflicting or little evidence
D. Deciding on treatment intent
E. Modifying treatment plan according to tumour and patient factors
F. Helping patients to make a choice
G. Giving consistent and unbiased advice to different patients



What can prevent effective decision-making?

- Not enough information
- Too much information
- Too many people
- Vested interests
- Emotional attachments
- No emotional attachment

- Some people put off making decisions by endlessly searching for more information or getting other people to offer their recommendations.
- Others resort to decision-making by taking a vote, sticking a pin in a list or tossing a coin.

https://www.skillsyouneed.com/ips/decision-making.html

What can prevent effective decision-making?

- Not enough information
- Too much information
- Too many people
- Vested interests
- Emotional attachments
- No emotional attachment

"Many of these issues can be overcome by using a structured decision-making process."

https://www.skillsyouneed.com/ips/decision-making.html

How are decisions made?

- Decisions can be made through either an intuitive or reasoned process, or a combination of the two.
- Intuition is using your ‘gut feeling’ about possible courses of action.
- Reasoning is using the facts and figures in front of you to make decisions.

https://www.skillsyouneed.com/ips/decision-making.html

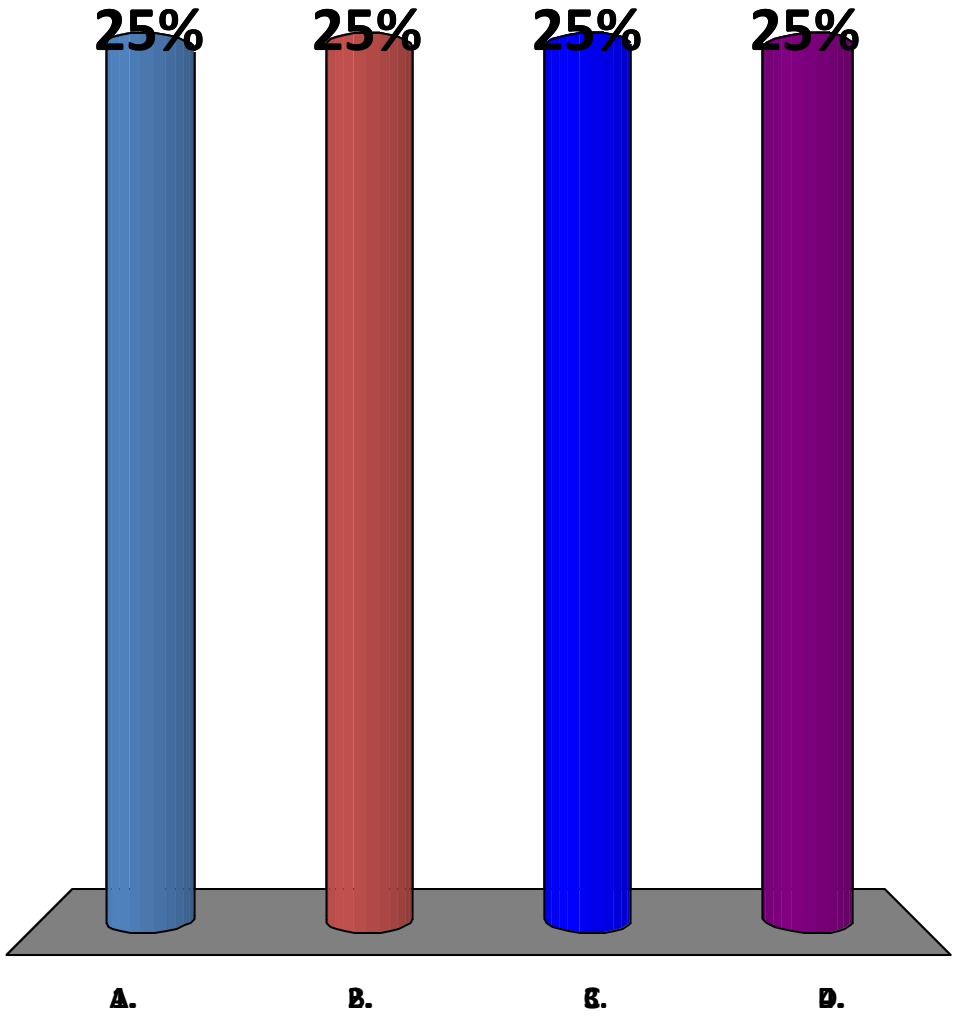
Intuition

- Intuition is a combination of past experience and your personal values.
- It is worth taking your intuition into account, because it reflects your learning about life.
- In oncology, intuition can be considered the same as clinical judgement.

https://www.skillsyouneed.com/ips/decision-making.html

Evidence-based medicine has replaced the need for clinical judgement.

A. Consultant - agree
B. Consultant - disagree
C. Trainee - agree
D. Trainee - disagree



Intuition

- Intuition is a combination of past experience and your personal values.
- It is worth taking your intuition into account, because it reflects your learning about life.
- It is not always based on reality, only your perceptions, many of which may have started in childhood and may not be very mature as a result.
- It is worth examining your gut feeling closely, especially if you have a very strong feeling against a particular course of action, to see if you can work out why, and whether the feeling is justified.

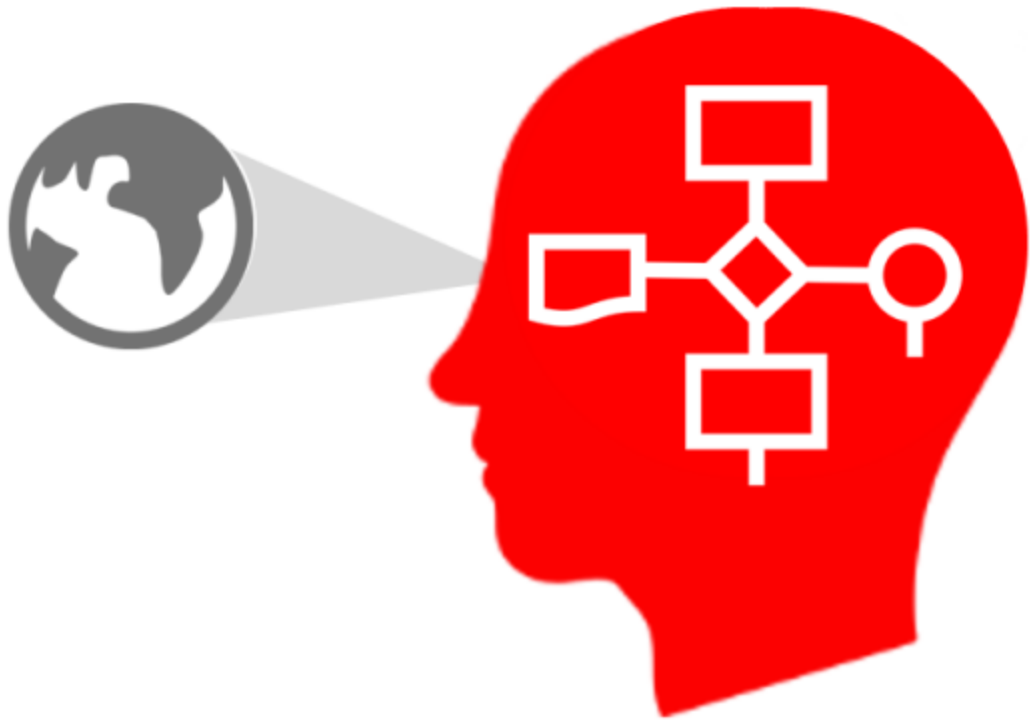
https://www.skillsyouneed.com/ips/decision-making.html

RE-FRAMING

A **mental model** is:

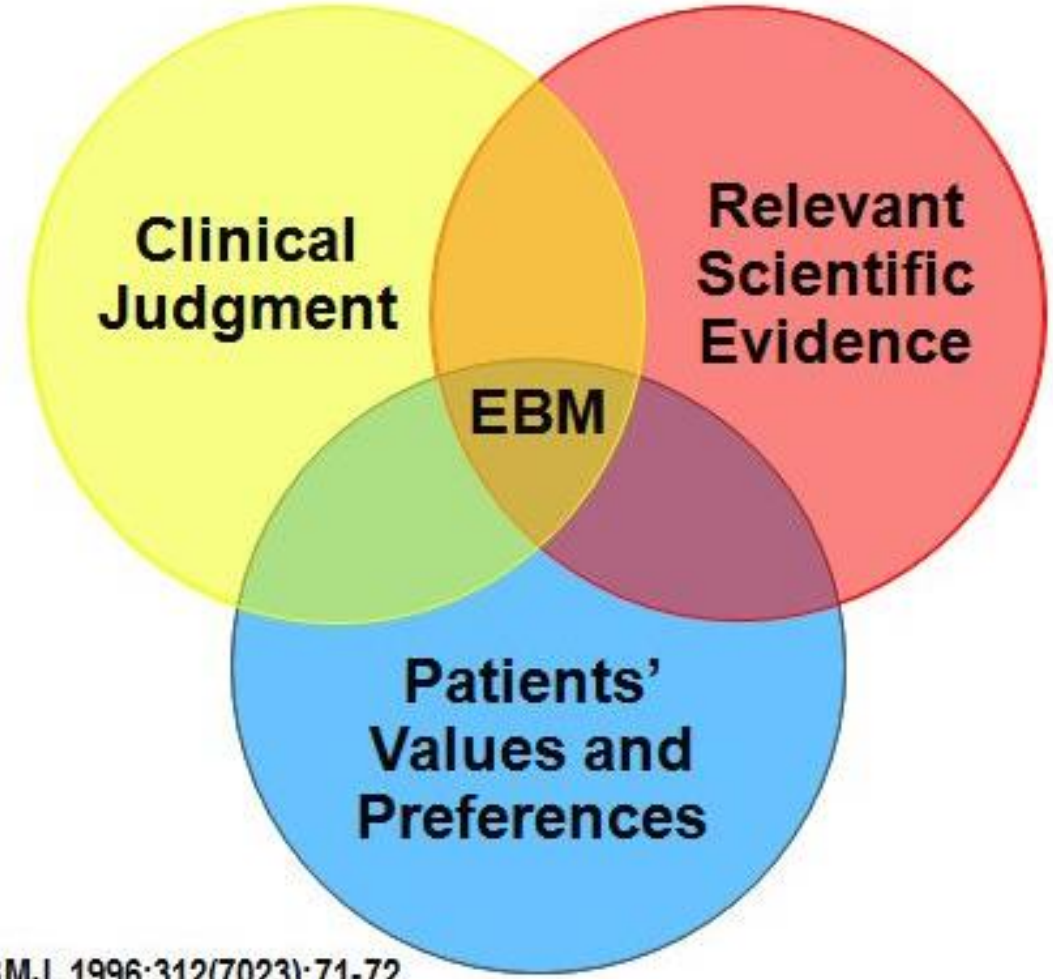
‘an explanation of someone's thought process about how something works in the real world’.

Wikipedia



STRATEGY PitStop

Evidence-based medicine



Sackett DL, et al. BMJ. 1996;312(7023):71-72.

Outline

- Treatment intent
- Decision-making process
- Patient values

Aim of treatment

- Maximise therapeutic index

$$\frac{\text{Benefit}}{\text{Side-effects}}$$

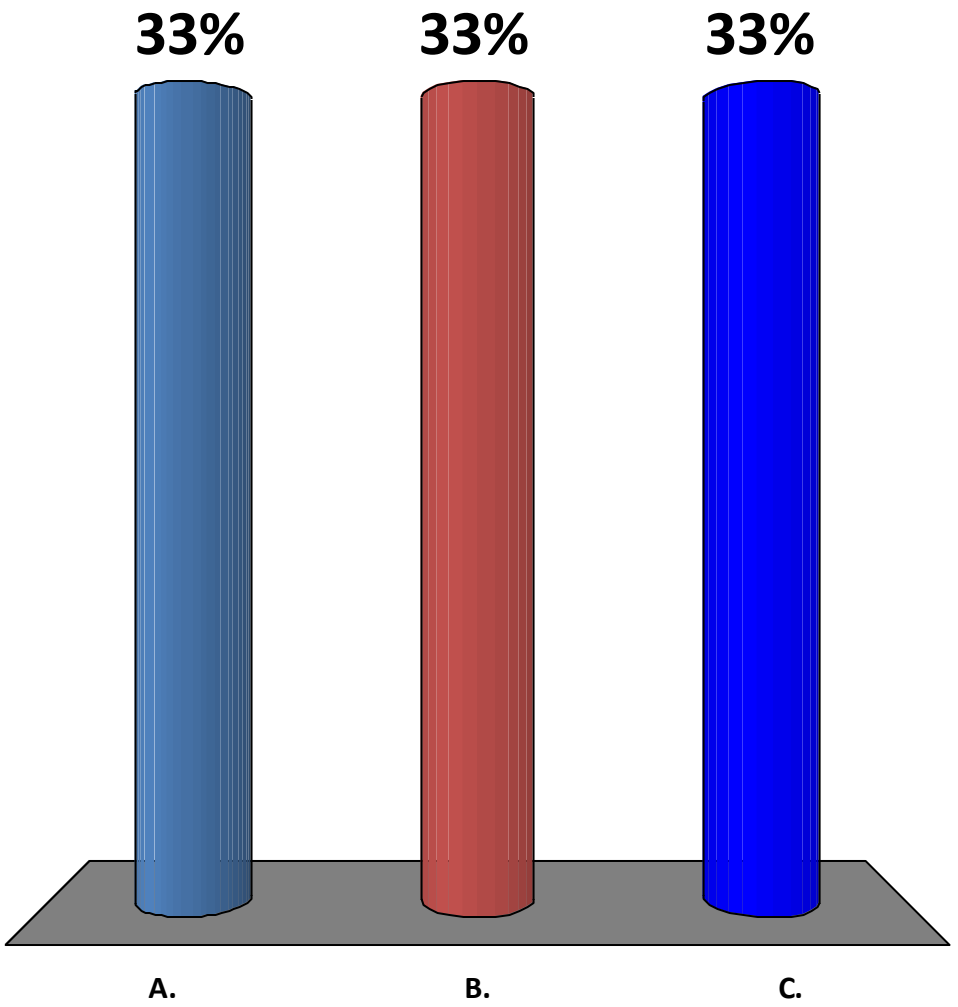
Terminology

- Radical
- Adjuvant
- Palliative

- Curative
- Non-curative
- Neo-adjuvant
- Concomitant
- Concurrent
- Synchronous
- Disease modification
- Terminal

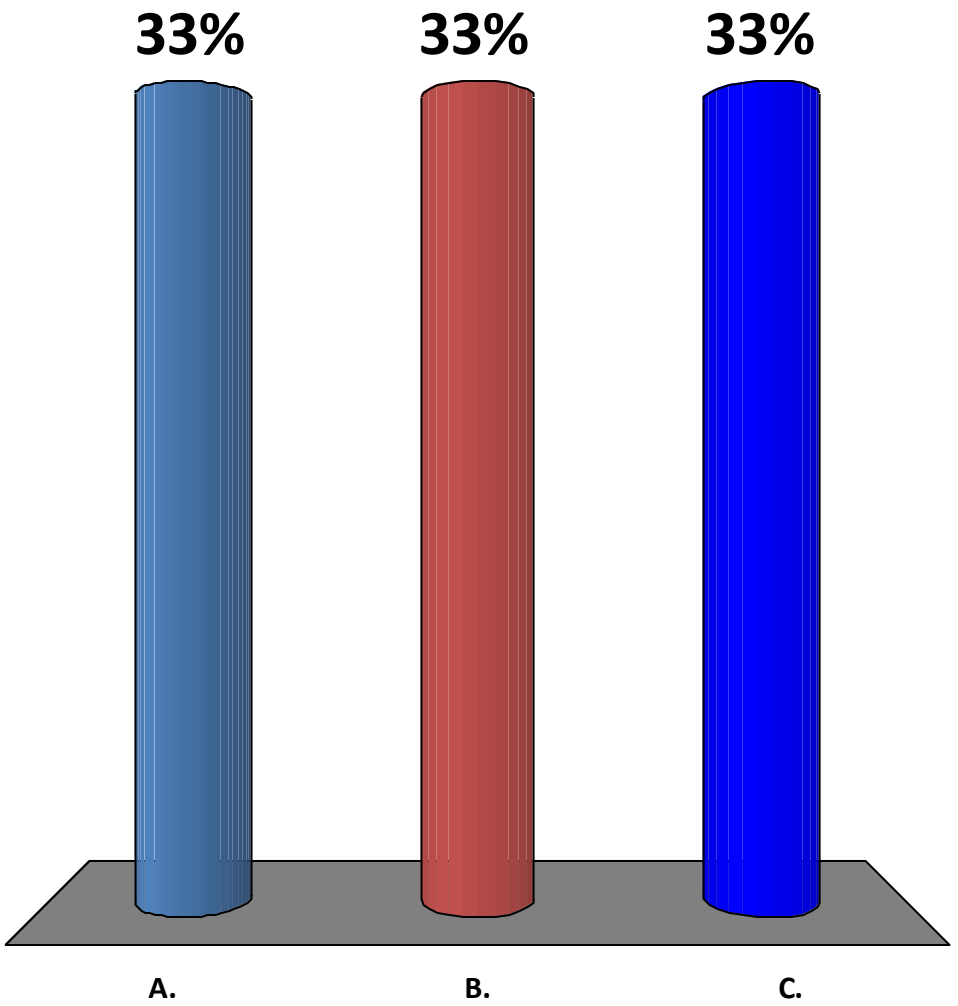
Cure means that the disease will never return.

A. Mostly agree
B. Neither agree nor disagree
C. Mostly disagree



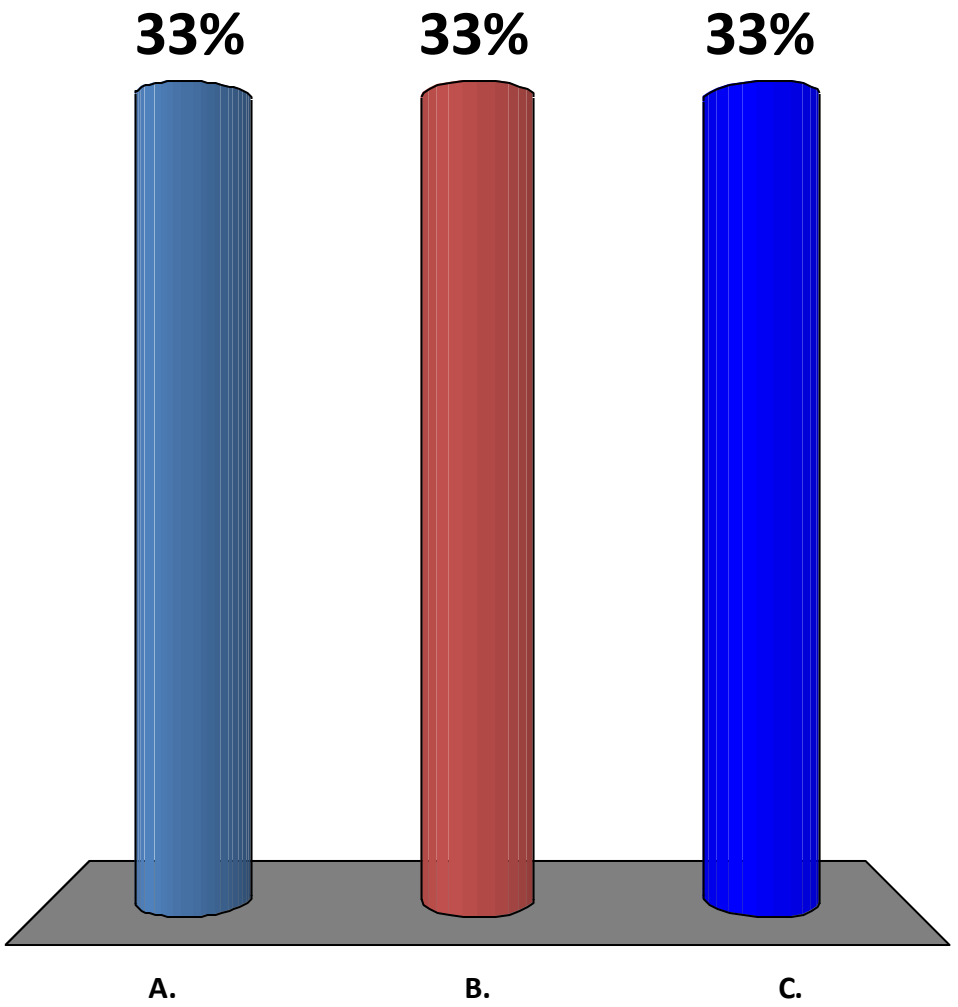
M0 disease should be regarded as curable.

A. Mostly agree
B. Neither agree nor disagree
C. Mostly disagree



M1 disease should be regarded as incurable.

A. Mostly agree
B. Neither agree nor disagree
C. Mostly disagree

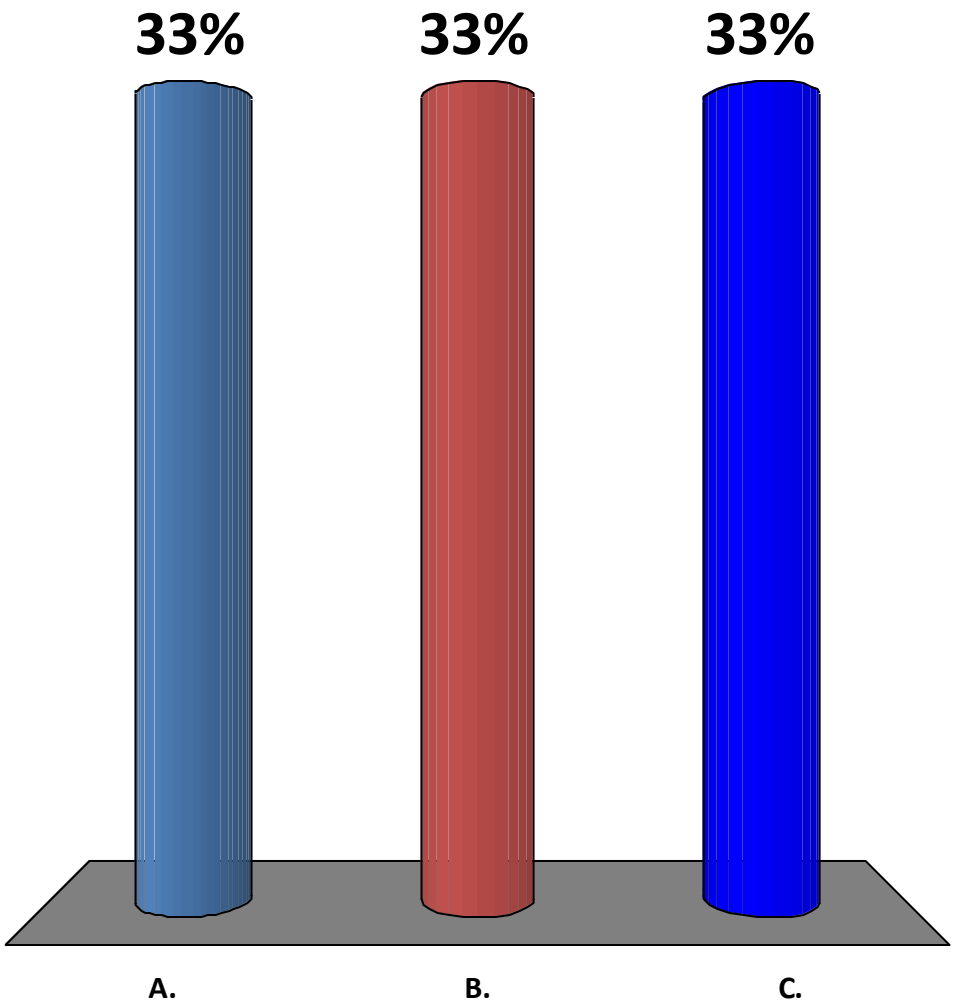


Norms vs exceptions

- Liver metastases in colorectal cancer are potentially curable.
- Liver metastases in breast cancer are potentially curable.
- Blood supply to liver from bowel is via portal circulation.
- Should liver metastases in breast cancer be resected?

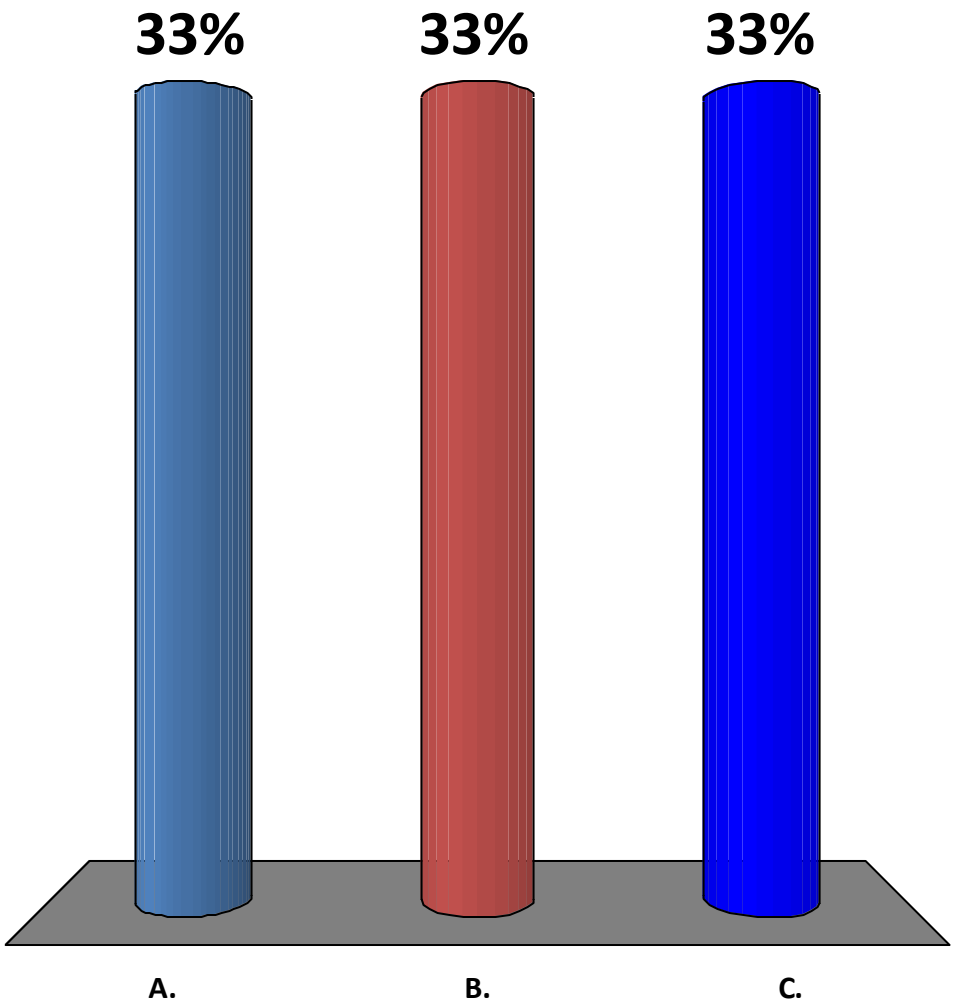
Adjuvant treatment on its own can be curative.

A. Mostly agree
B. Neither agree nor disagree
C. Mostly disagree



Neo-adjuvant treatment on its own can be curative if there is complete remission at the end of treatment.

A. Mostly agree
B. Neither agree nor disagree
C. Mostly disagree



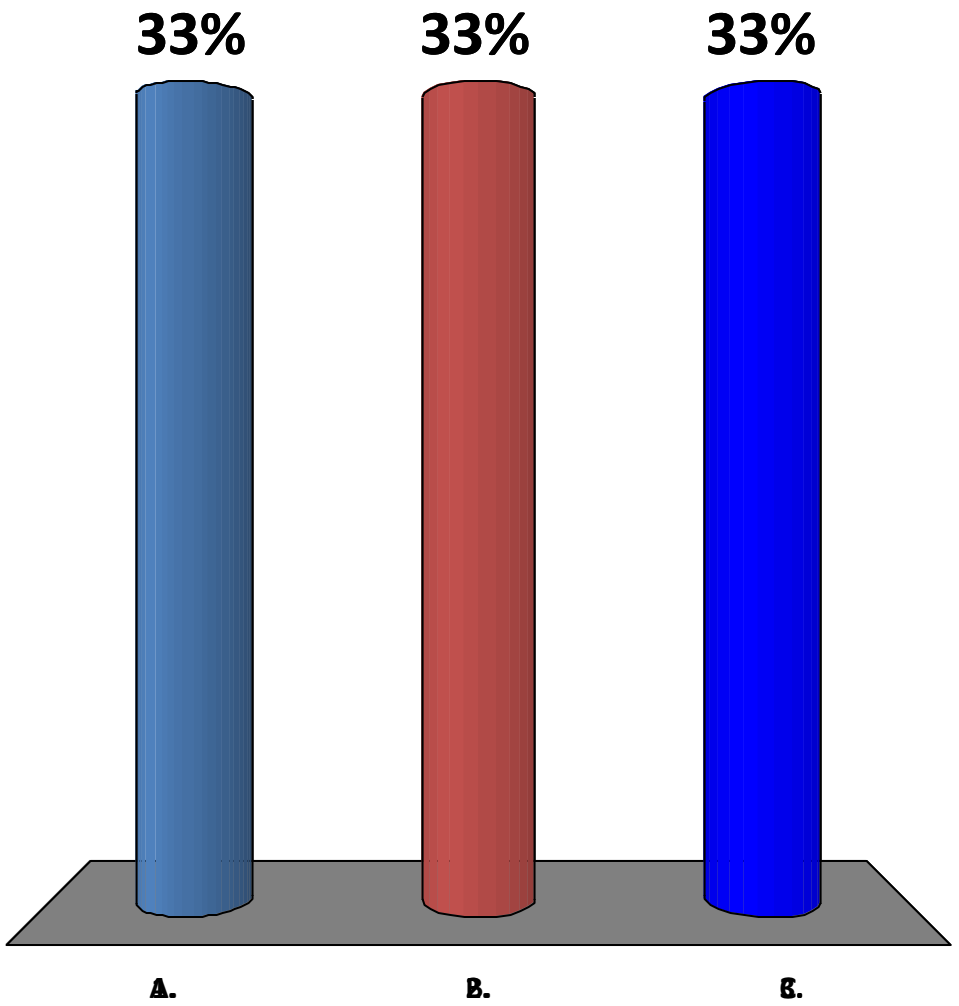
Response is not necessarily an indicator of prognosis

- Examples
  - Small cell carcinoma of lung
  - Ovarian carcinoma

Be wary of switching strategy halfway through treatment based on response.

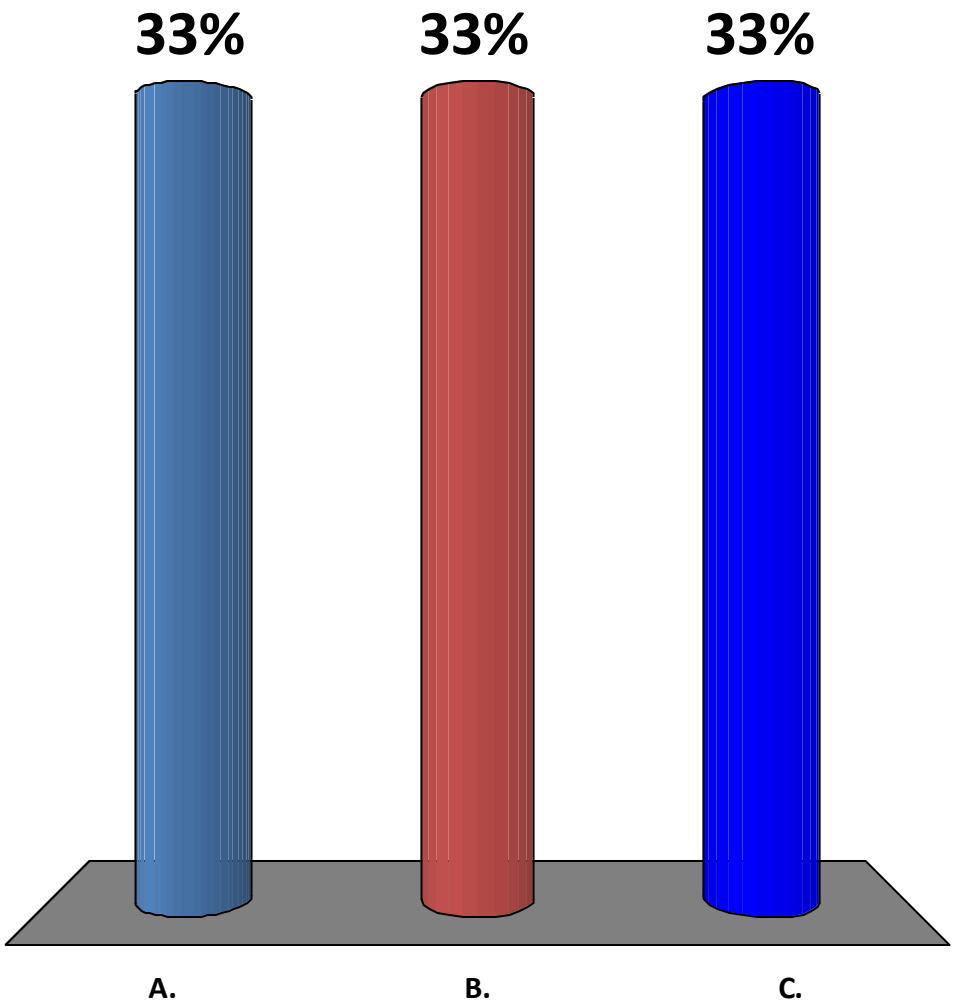
The term palliative is the same as incurable.

A. Mostly agree
B. Neither agree nor disagree
C. Mostly disagree



Radical treatment should only be offered for curable disease.

A. Mostly agree
B. Neither agree nor disagree
C. Mostly disagree

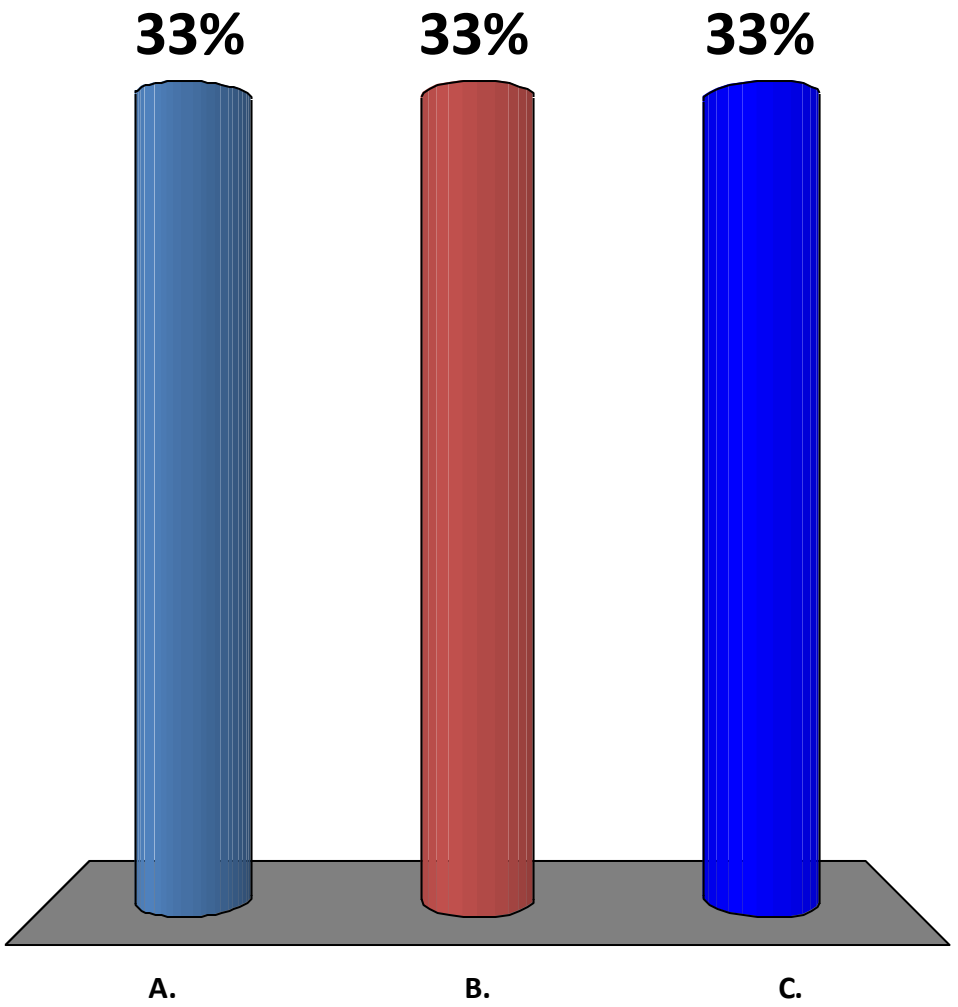


Intent vs. treatment

- “Radical with palliative intent”
- “Radical dose with palliative intent”

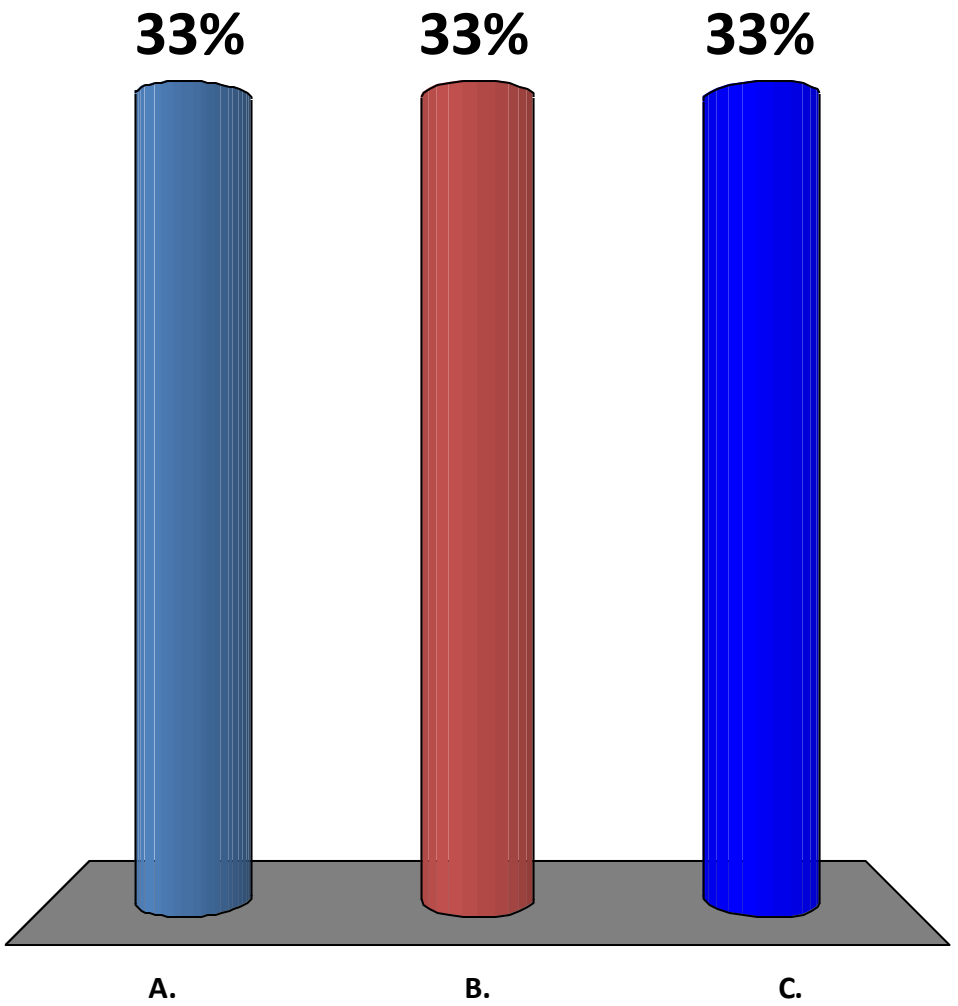
The treatment intent can be changed during the course of treatment.

A. Mostly agree
B. Neither agree nor disagree
C. Mostly disagree



The treatment intent can be changed from curative to palliative during treatment.

A. Mostly agree
B. Neither agree nor disagree
C. Mostly disagree



The treatment intent can be changed palliative to curative during treatment.

A. Mostly agree
B. Neither agree nor disagree
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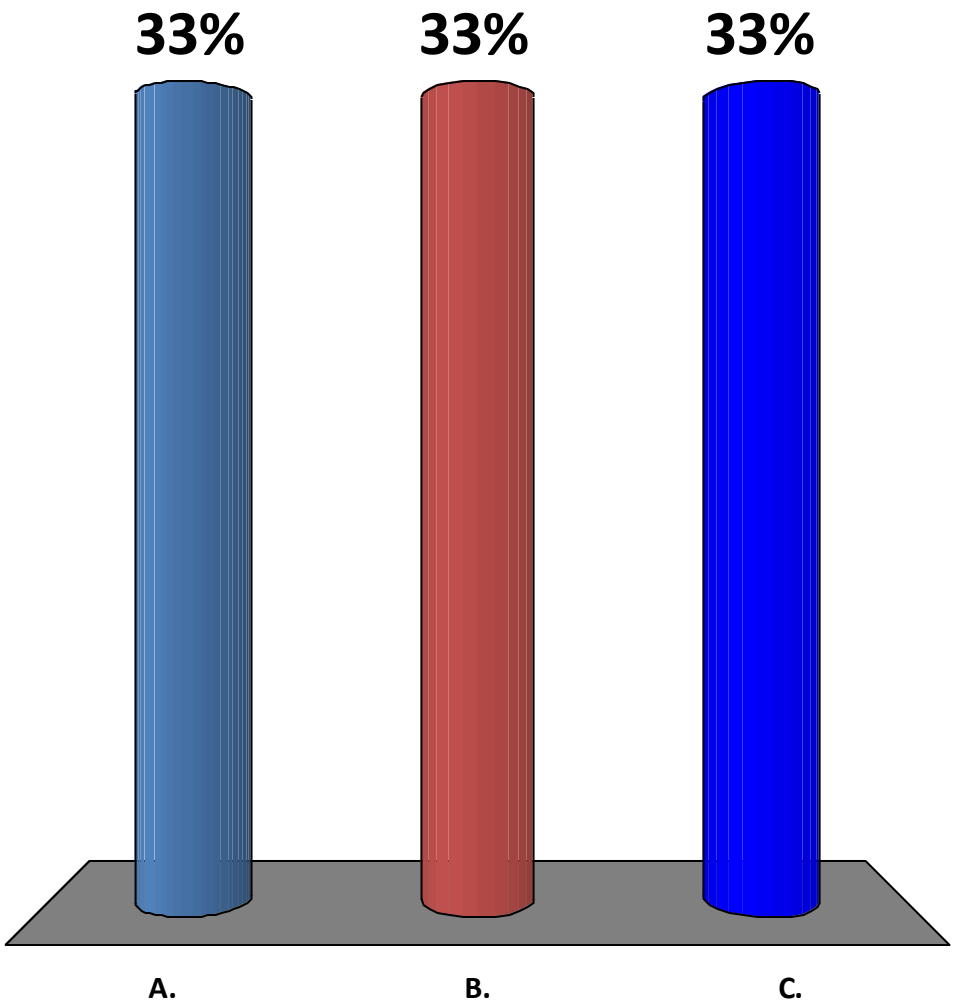


Treatment intent - tips

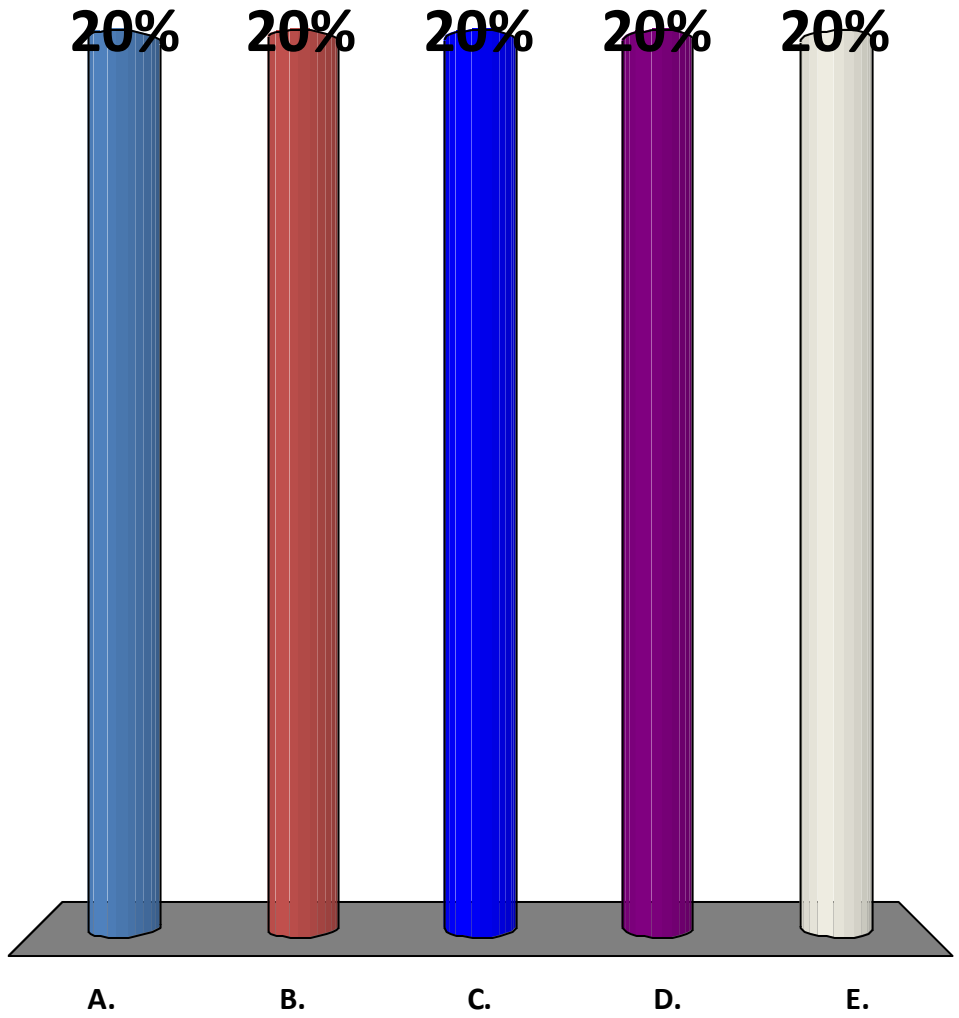
- Decide on treatment intent at the start of treatment
  - Possible to switch from curative to palliative (e.g. if metastatic disease develops or patient unable to tolerate curative treatment)
  - Not possible to switch from palliative to curative
- Think of the norms rather than exceptions

Outline

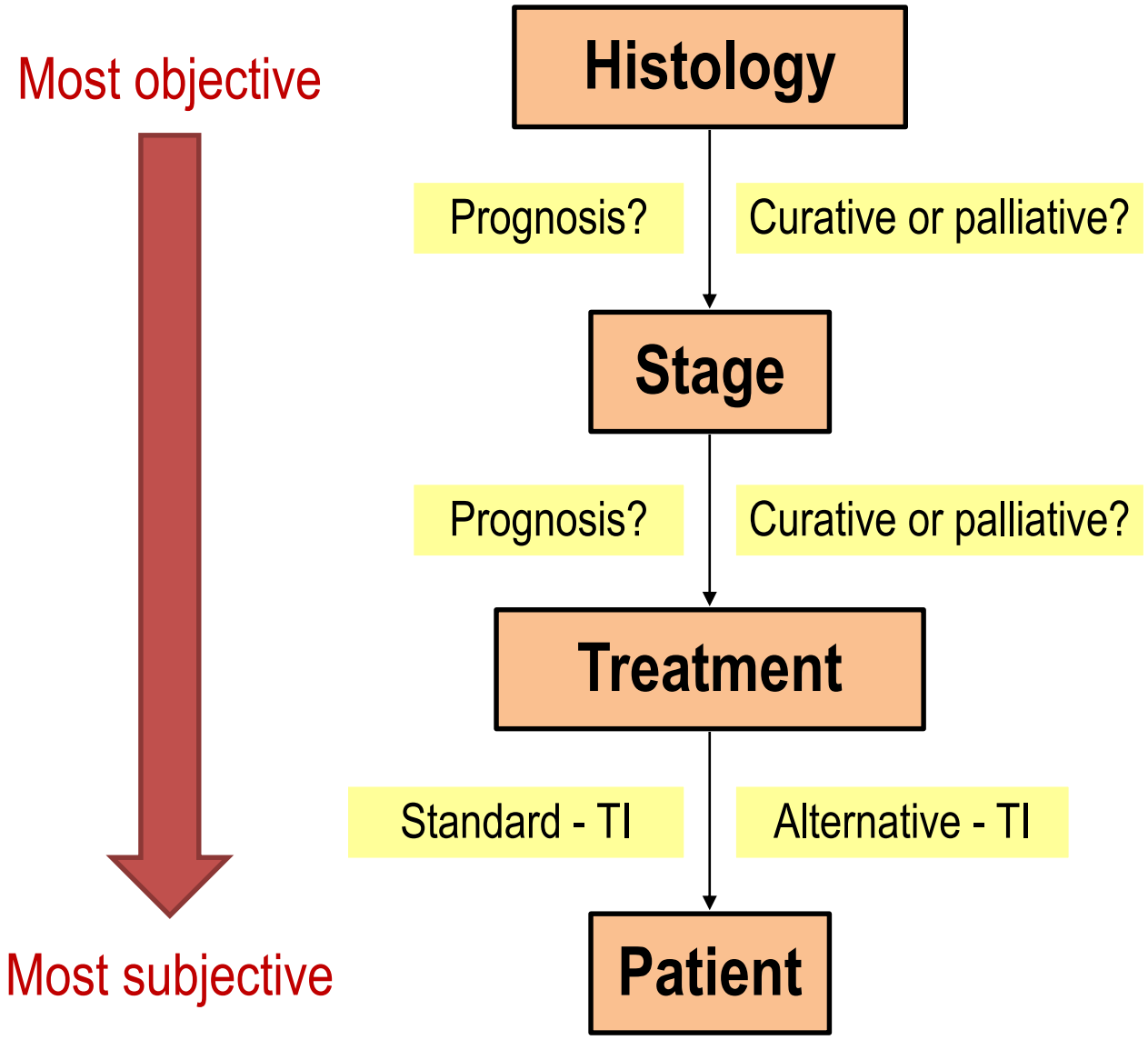
- Treatment intent
- Decision-making process
- Patient values and expectations

When deciding how to treat a patient, what do you consider first?

A. Economic factors
B. Patient factors – age, co-morbidity
C. Treatment factors – options, benefits, side-effects
D. Tumour factors – histology, stage
E. It depends

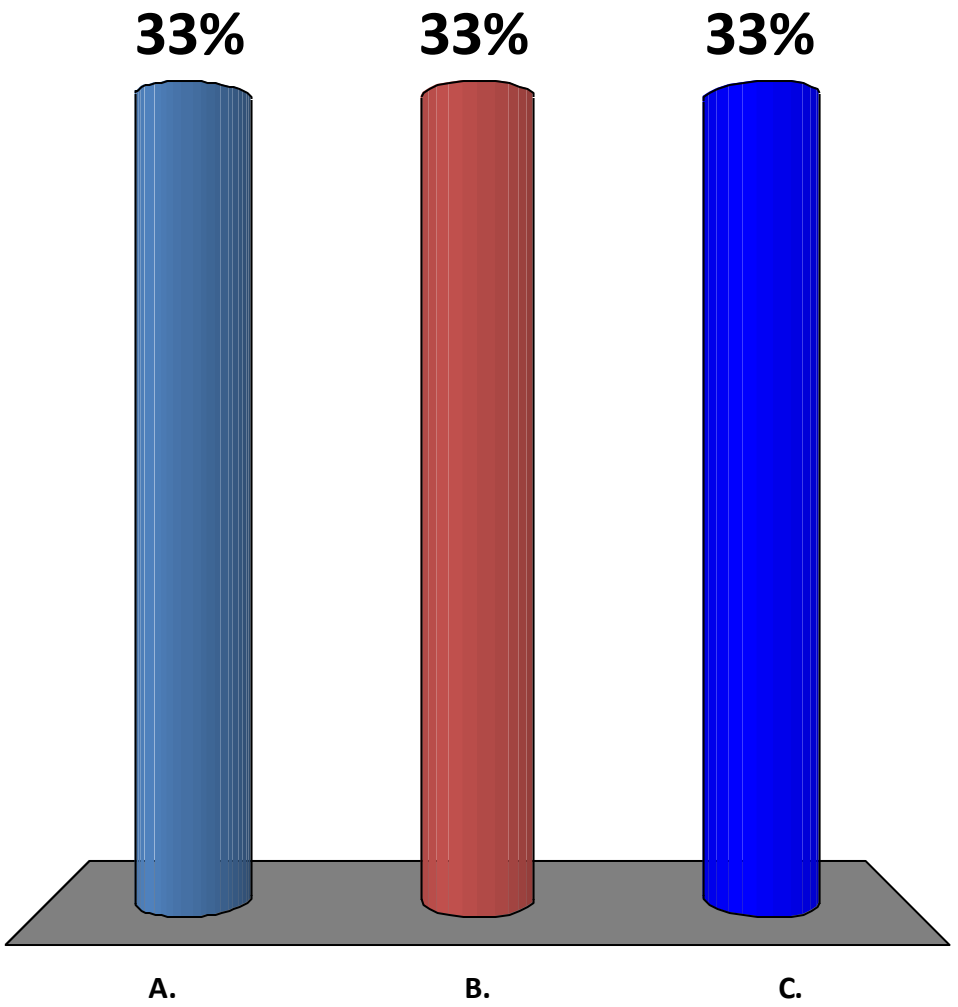


Decision-making - curative



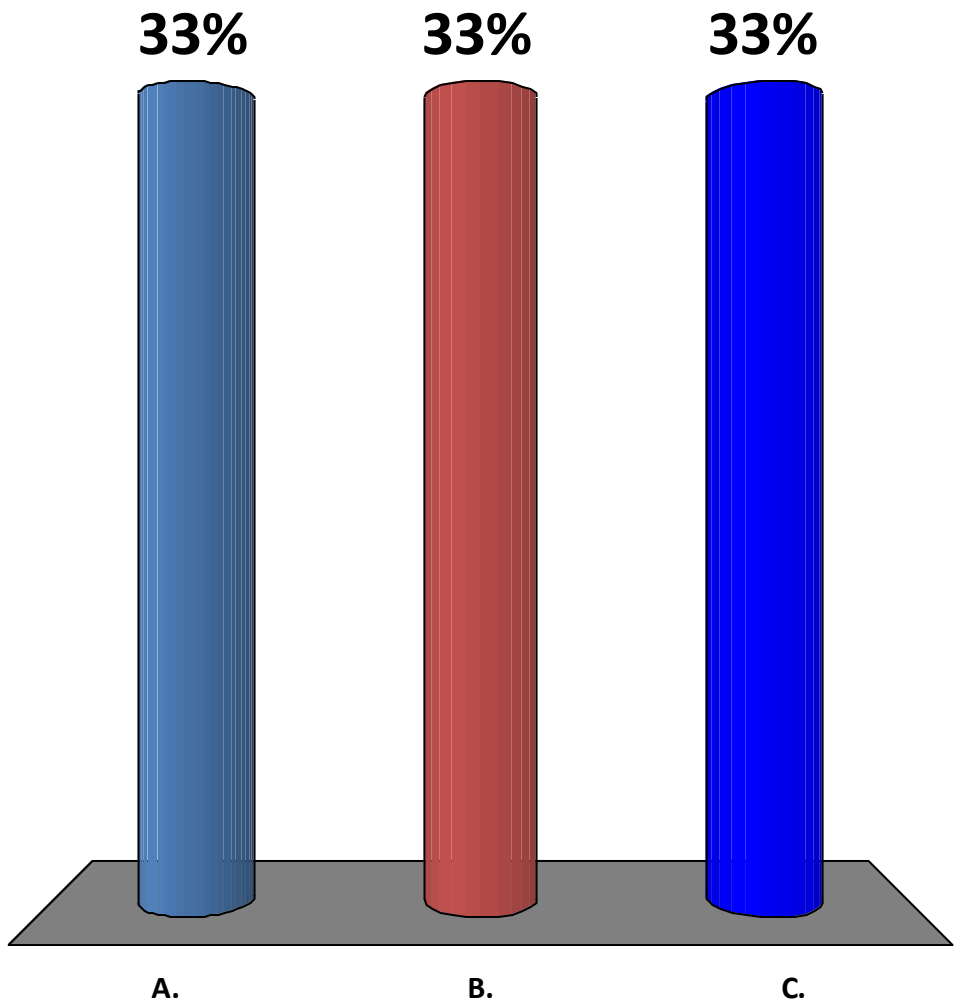
AdenoCa of cervix has worse prognosis than squamous cell Ca cervix

A. Mostly agree
B. Neither agree nor disagree
C. Mostly disagree

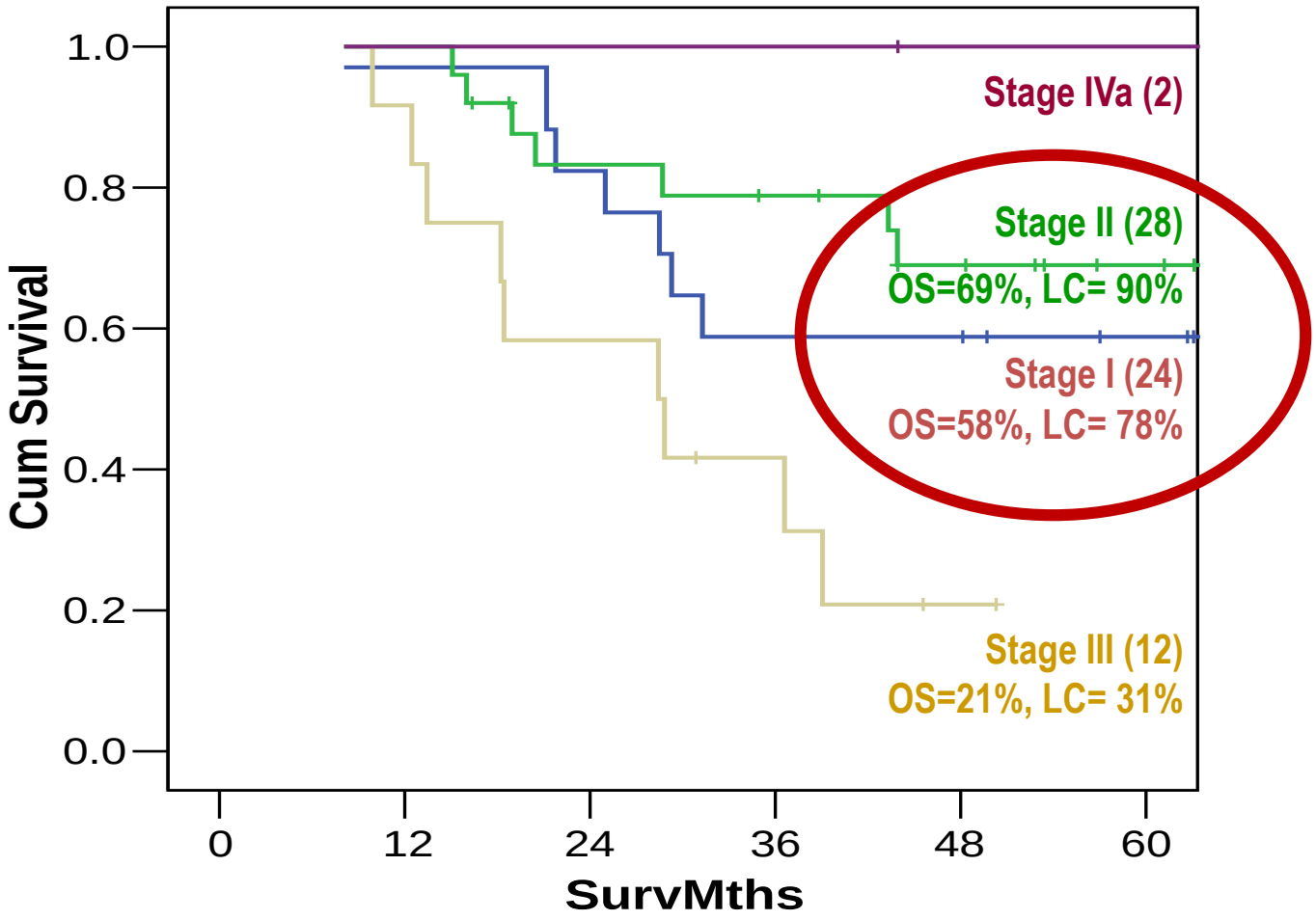


Stage Ib2 adenoCa cervix has worse prognosis than Stage IIb squamous cell Ca cervix.

A. Mostly agree
B. Neither agree nor disagree
C. Mostly disagree



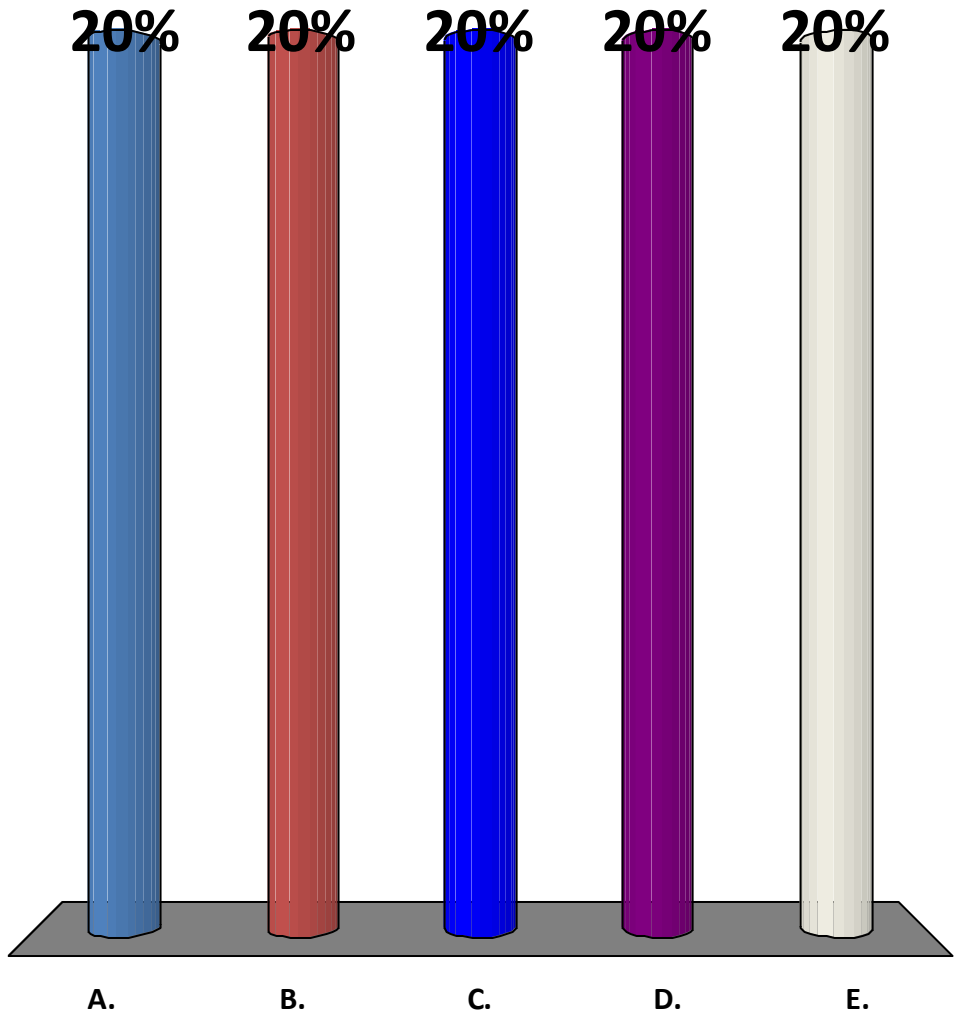
Addenbrooke's 1999–2003



Tan LT, Zahra M. Clin Oncol (R Coll Radiol) 2008;20(5):358-64

What is the standard treatment for a 5 cm Stage Ib2 adenoCa cervix?

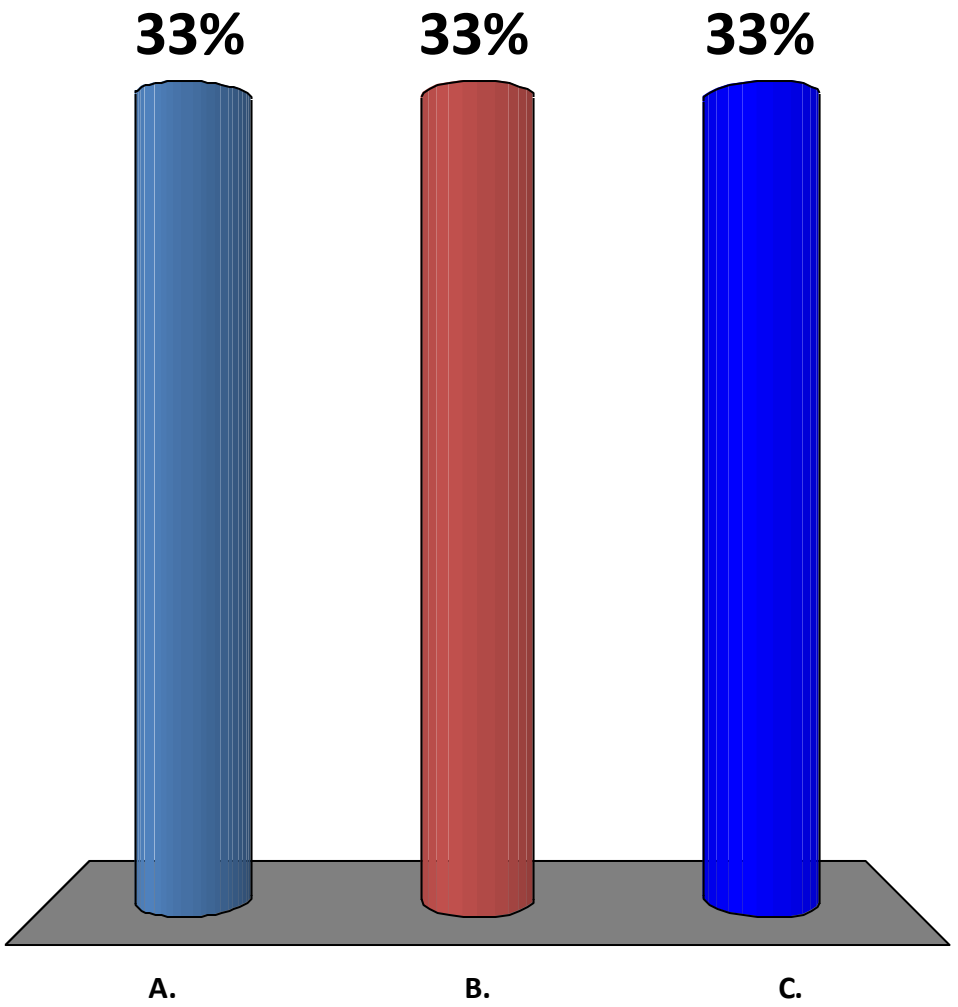
A. Radical surgery
B. Chemo-RT
C. Neoadjuvant chemo + chemo-RT
D. Neoadjuvant chemo + surgery
E. Chemo-RT + surgery



What is standard treatment?

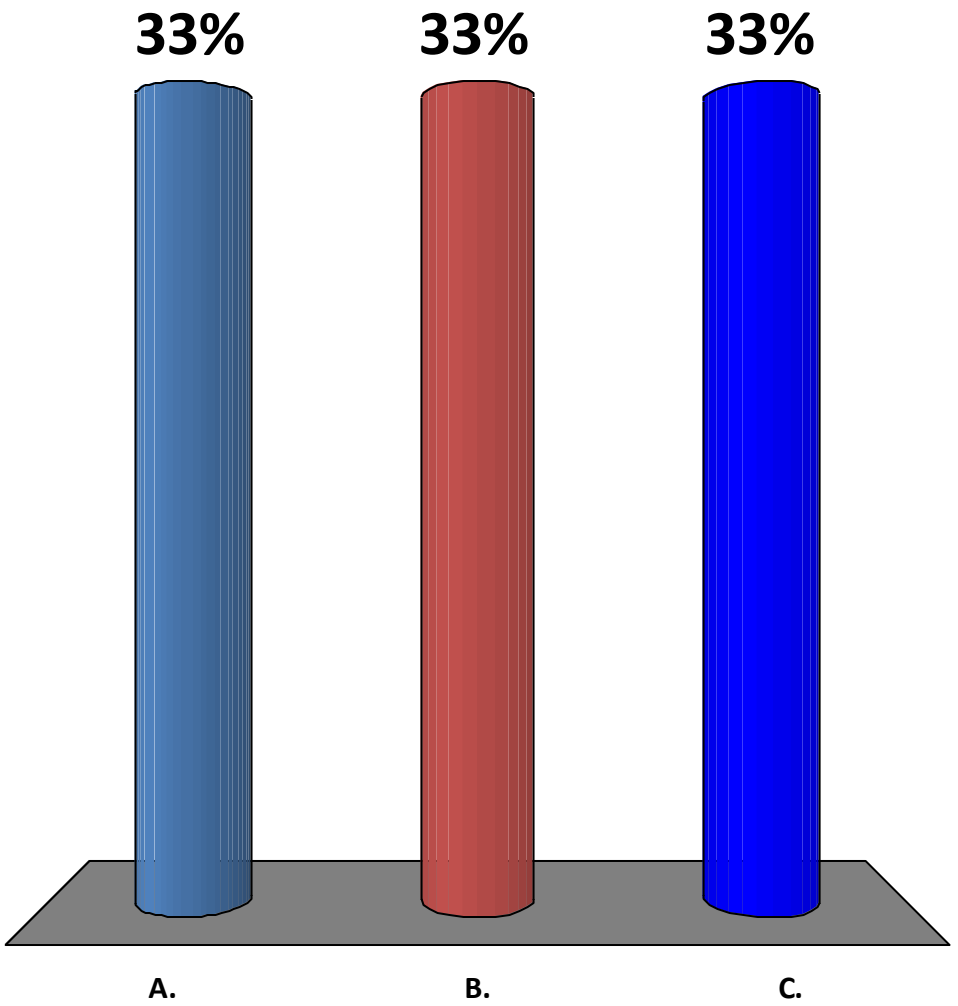
It is the treatment most commonly given to a group of patients with the same tumour and patient factors.

A. Mostly agree
B. Neither agree nor disagree
C. Mostly disagree



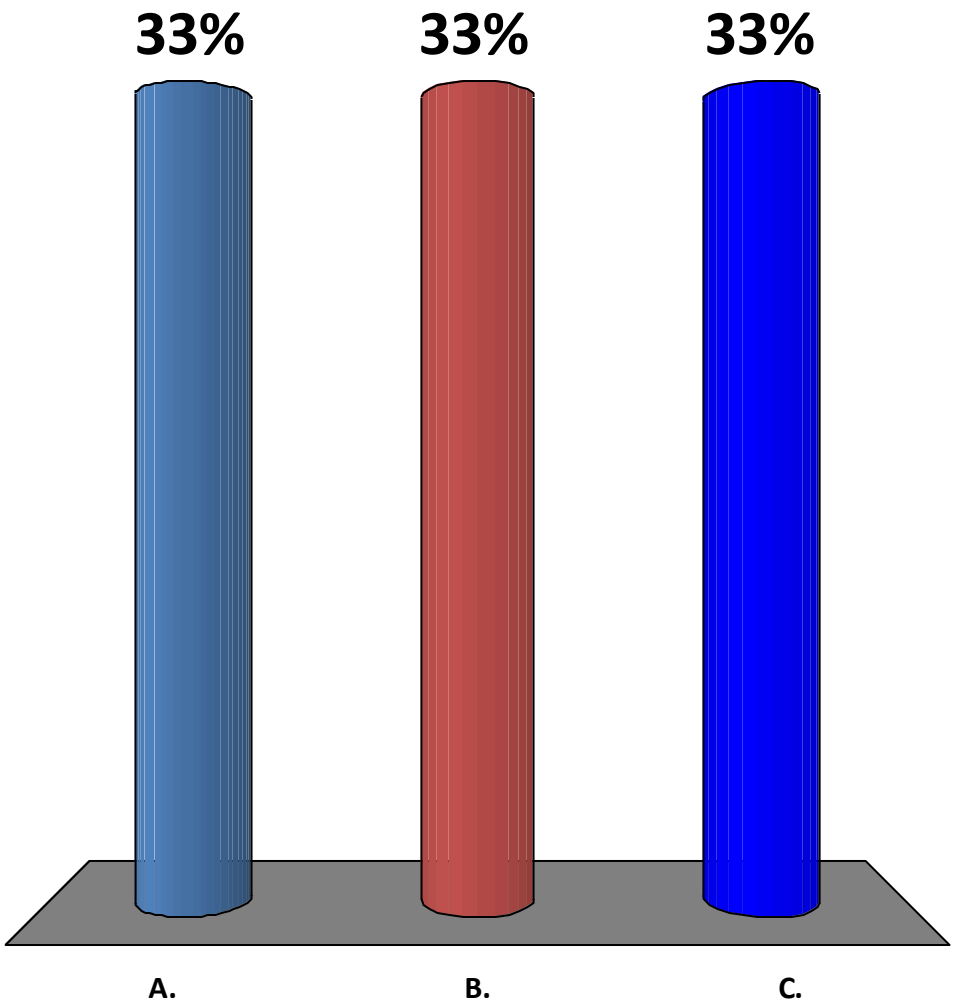
It is the most appropriate treatment for an individual patient.

A. Mostly agree
B. Neither agree nor disagree
C. Mostly disagree



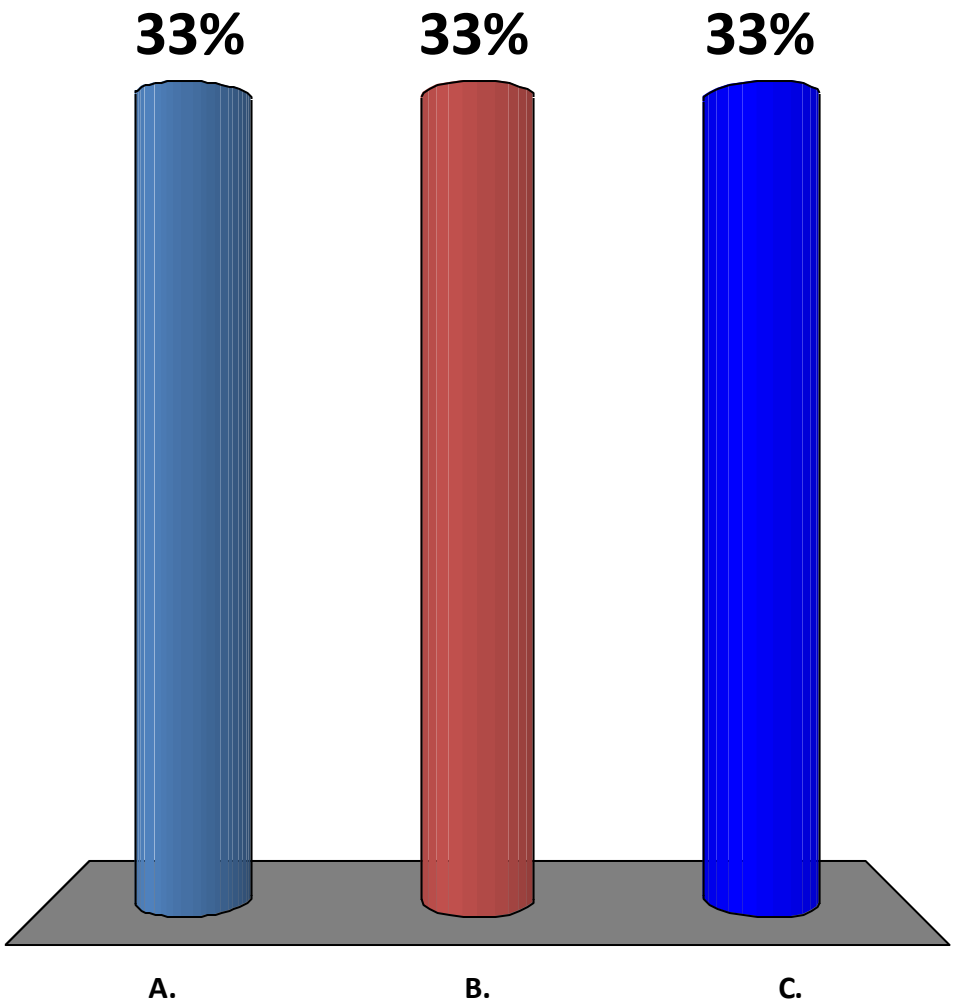
It is the treatment that gives the best chance of cure.

A. Mostly agree
B. Neither agree nor disagree
C. Mostly disagree



It must be accepted by the majority of experts.

A. Mostly agree
B. Neither agree nor disagree
C. Mostly disagree



Guidelines may recommend alternative treatments instead of standard treatment for patients with the same characteristics.

Cervical Cancer Treatment (PDQ®)–Health Prof Version

Go to Patient Version

Stages IB and IIA Cervical Cancer Treatment

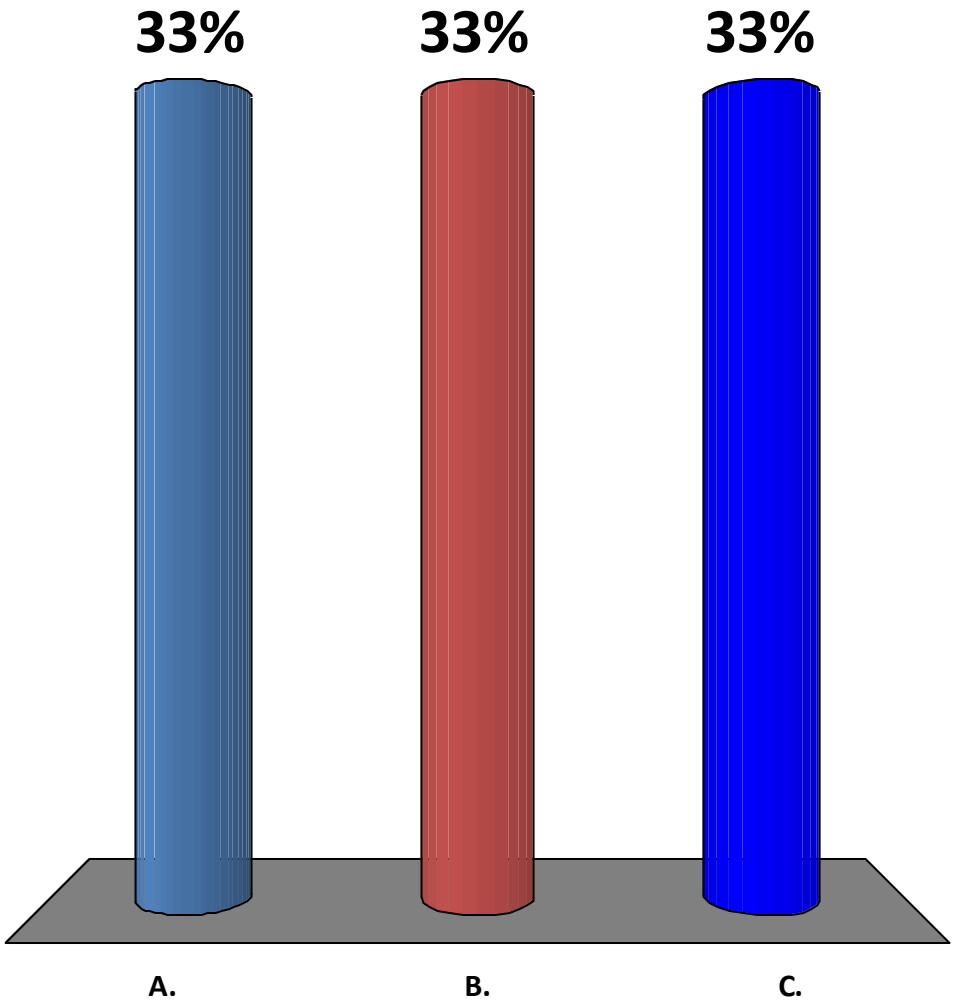
- Standard Treatment Options for Stages IB and IIA Cervical Cancer
  - Radiation therapy with concomitant chemotherapy
  - Radical hysterectomy and bilateral pelvic lymphadenectomy with or without total pelvic radiation therapy plus chemotherapy
- Other Treatment Options
  - Radical trachelectomy
  - Neoadjuvant chemotherapy
  - Radiation therapy alone
  - IMRT

Which of the following statements about the therapeutic index (benefit over toxicity) of the alternative treatment is true?

A. The therapeutic index of the alternative treatment is usually larger than that of the standard treatment.

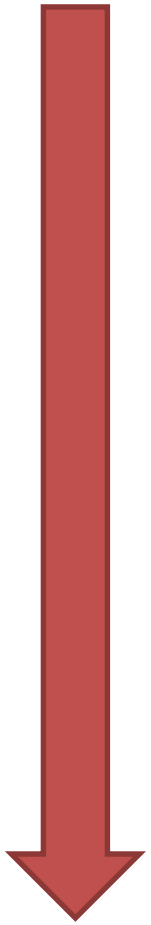
B. The therapeutic index of the alternative treatment is usually similar to that of the standard treatment.

C. The therapeutic index of the alternative treatment is usually smaller than that of the standard treatment.

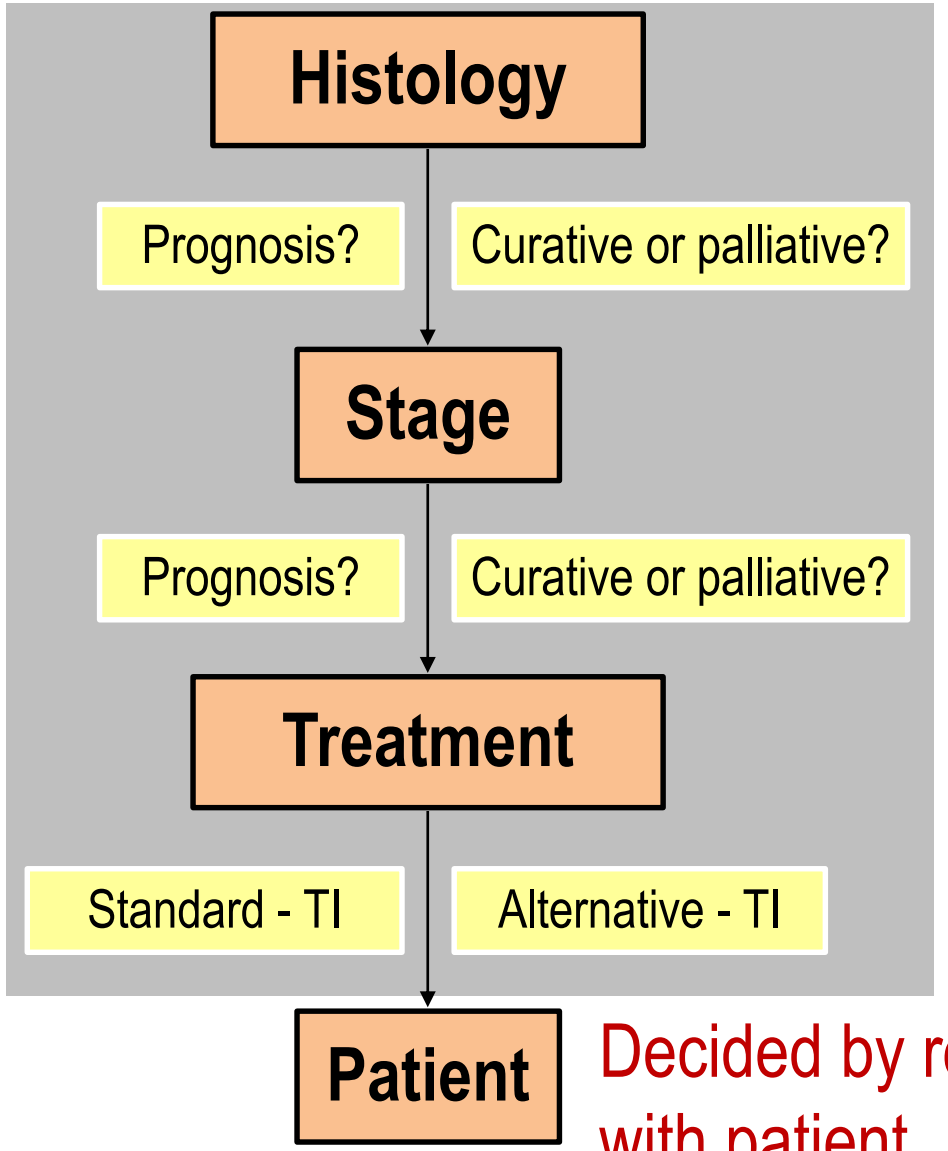


Decision-making - curative

Most objective



Most subjective



Decided by MDT

Decided by responsible clinician with patient

Decision-making for cure - tips

- Standard treatments have the largest therapeutic index.
- Alternative treatments have similar or smaller therapeutic index compared to standard treatment.

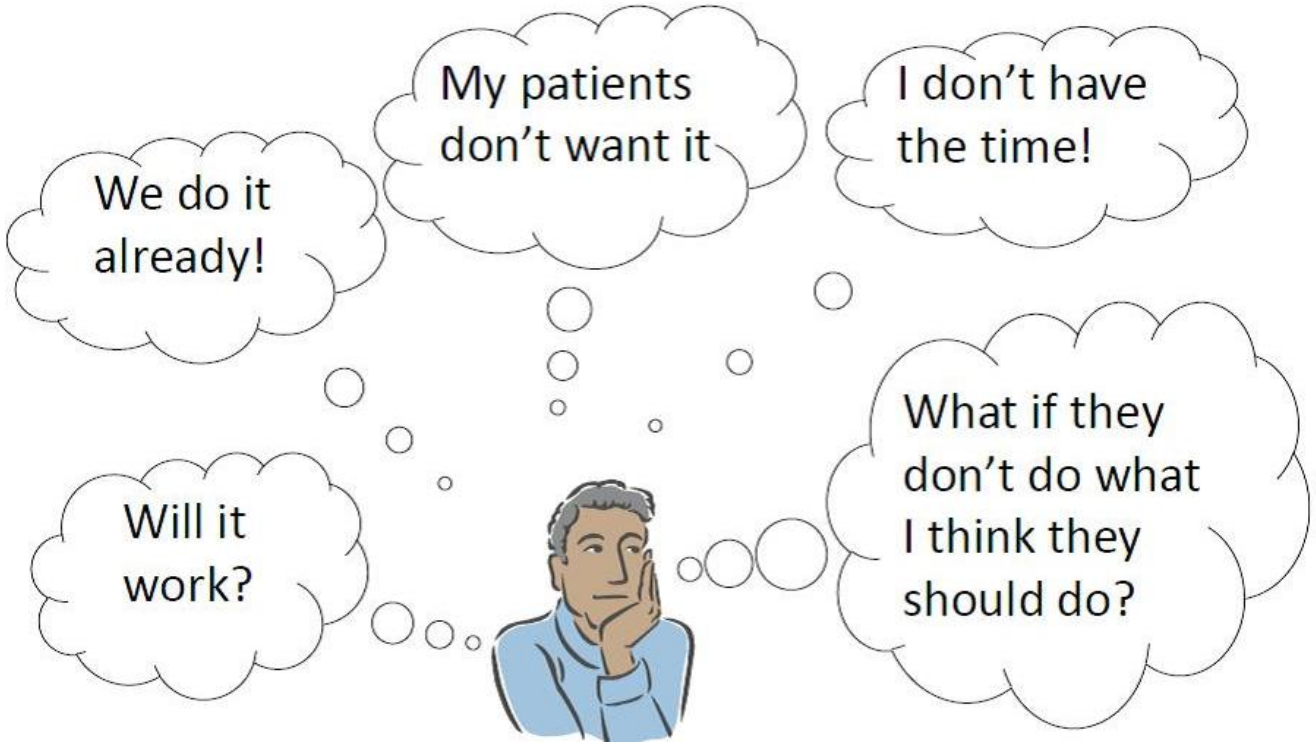
Be wary of recommending "more" than standard treatment.

Outline

- Treatment intent
- Decision-making process
- **Patient values**

Shared decision making cancer

- 23320 publications



Attitudes to chemotherapy

Mild

- Slight nausea/vomiting
- No hair loss
- Occasional use of needles/drips
- Some tiredness/weakness
- Hospital admission 1/month

Intensive

- Severe nausea/vomiting
- Hair loss
- Frequent needles/drips
- Frequent tiredness/weakness
- Admission 3-4/month
- Possible infertility

Slevin ML, et al. BMJ. 1990 Jun 2;300(6737):1458-60.

1% chance of cure

	Mild	Intensive
Controls (100)	35%	19%
Cancer Nurses (300)	39%	14%
GPs (790)	44%	12%
Clin oncologists (88)	27%	5%
Med oncologists (60)	52%	20%
Patients (96)	67%	53%

Slevin ML, et al. BMJ. 1990 Jun 2;300(6737):1458-60.

Prolong life by 3 months, 1% chance of symptom relief

	Mild	Intensive
Controls (100)	19%	10%
Cancer Nurses (300)	26%	6%
GPs (790)	21%	2%
Clin oncologists (88)	2%	0%
Med oncologists (60)	12%	10%
Patients (96)	60%	42%

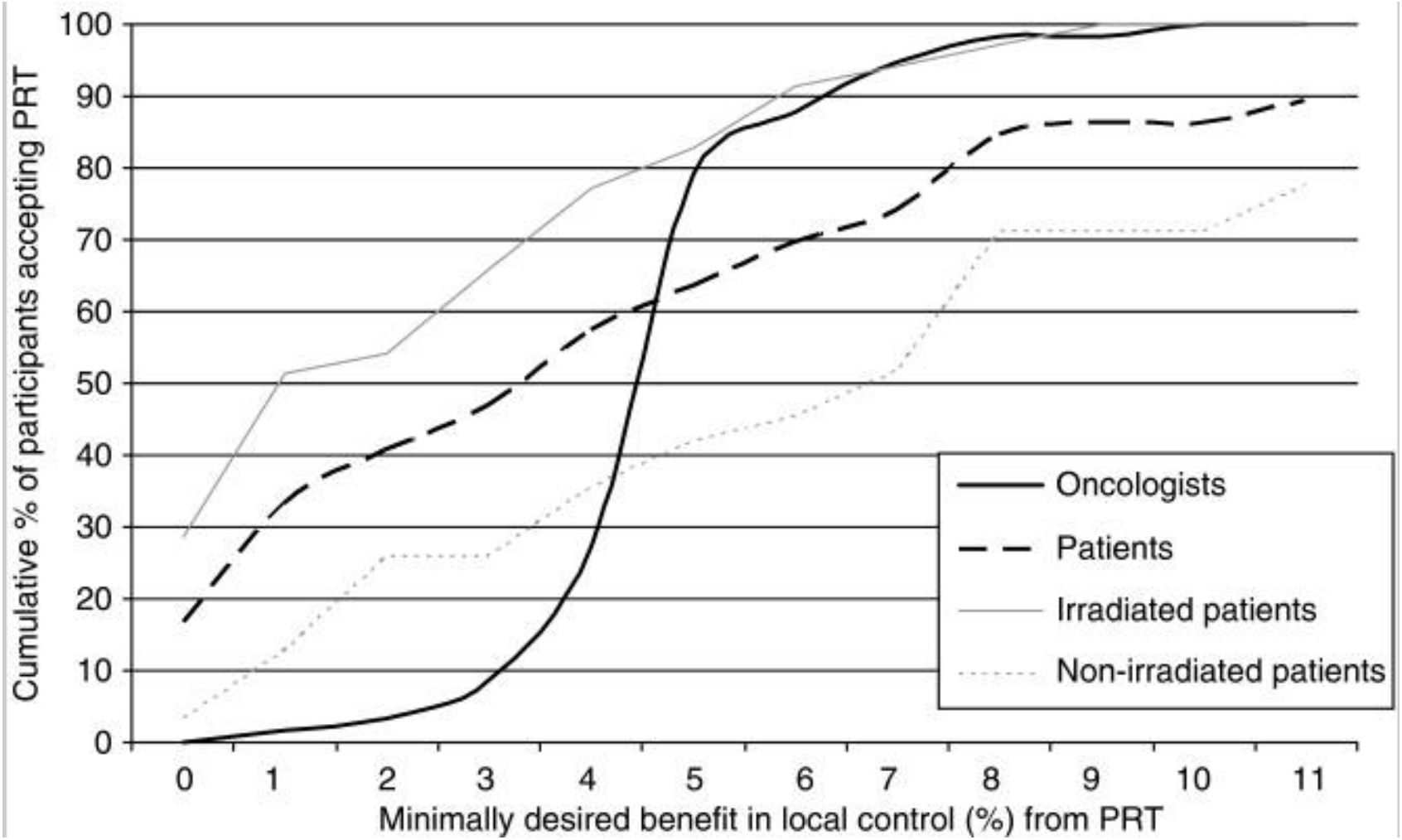
Slevin ML, et al. BMJ. 1990 Jun 2;300(6737):1458-60.

Pre-op RT for rectal cancer

- Interview
  - 66 disease-free patients
  - 60 oncologists (surgical, radiation, medical)
- Outcome measures
  - Survival
  - Local control
  - Faecal incontinence
  - Sexual dysfunction

Pieterse AH, et al. Br J Cancer. 2007;97(6):717-24

Pre-op RT for LC



Pieterse AH, et al. Br J Cancer. 2007;97(6):717-24

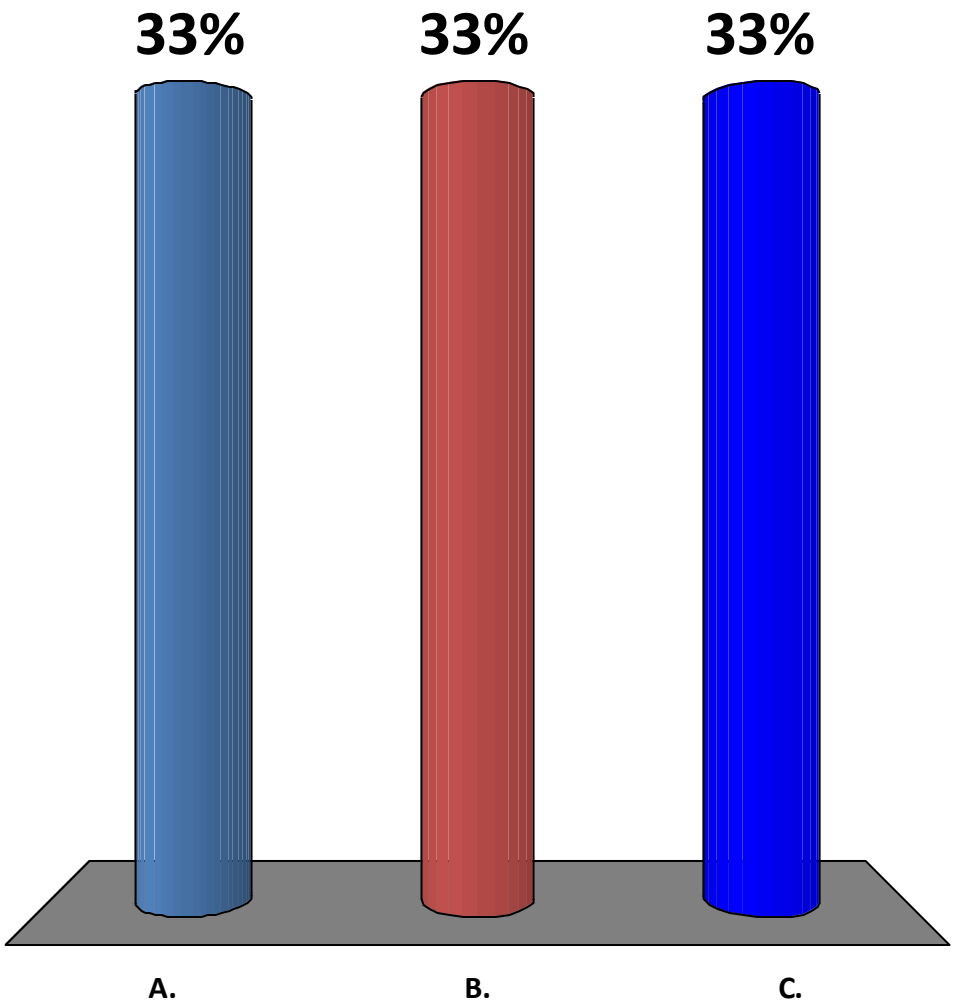
Pre-op RT for LC

- One medical oncologist would not advise PRT to male patients, and only for a 7% benefit to female patients.
- One surgical oncologist would advise PRT to male patients for 6% benefit, but could not decide for female patients.

Pieterse AH, et al. Br J Cancer. 2007;97(6):717-24

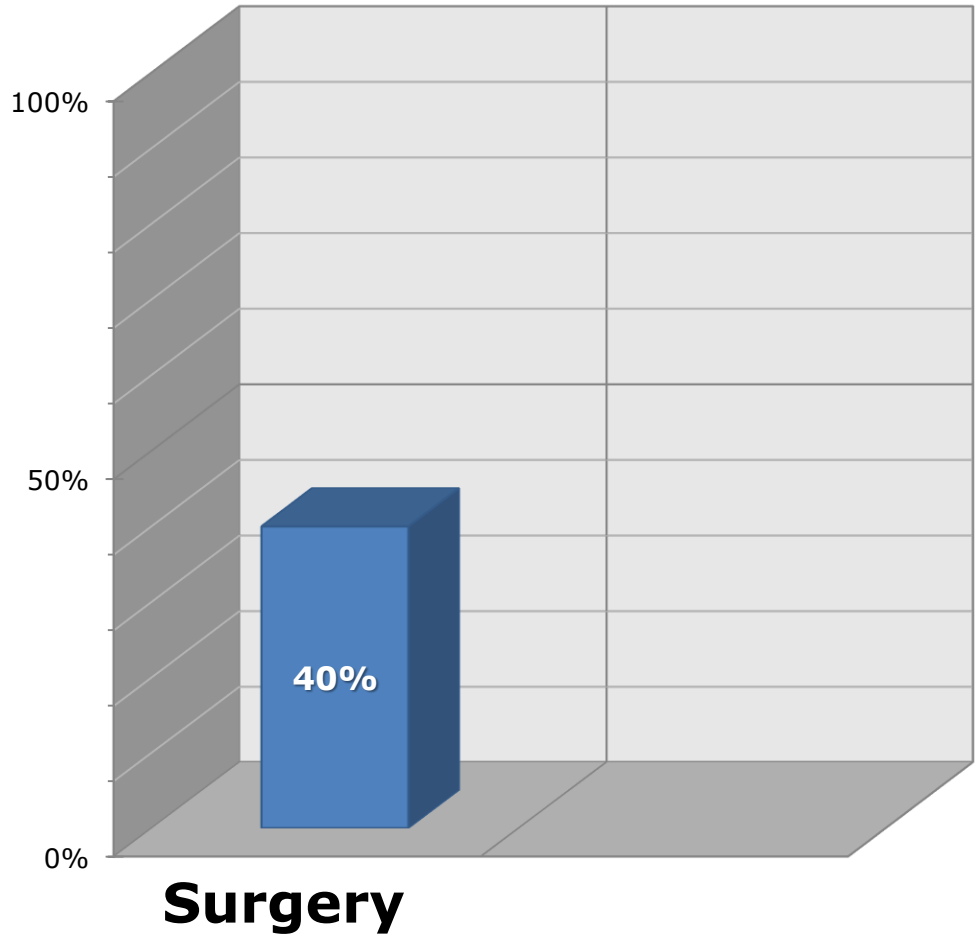
Which type of treatment do you find most difficult to explain to patients?

A. Radical (curative)
B. Adjuvant
C. Palliative

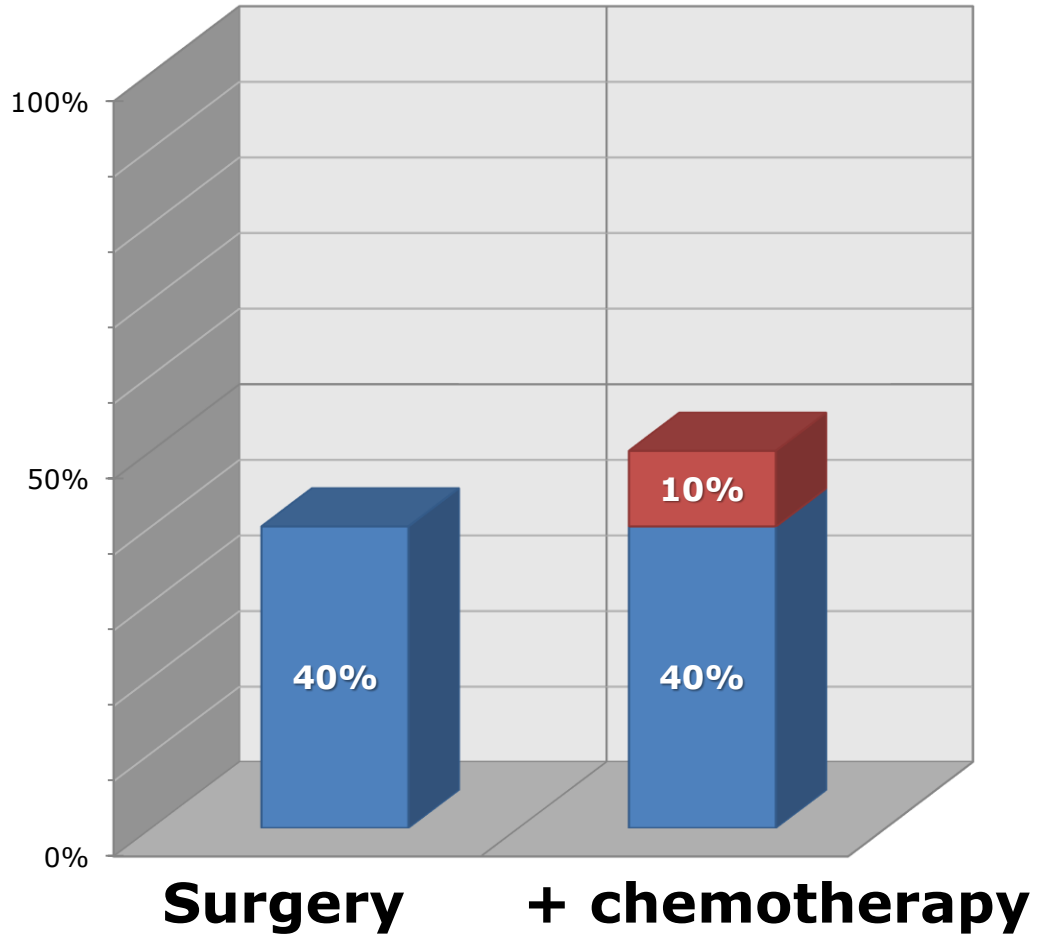


Number needed to treat

Dukes' C colon



Dukes' C colon



10 patients

10 patients

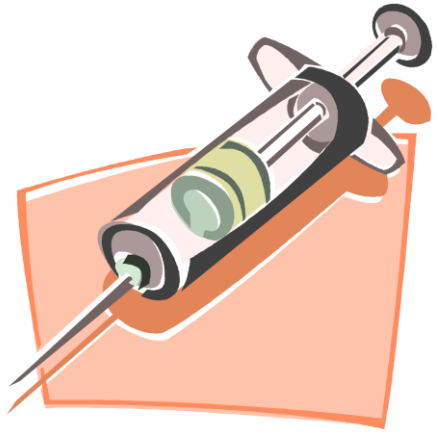
Cured

10 patients

Cured

Not cured

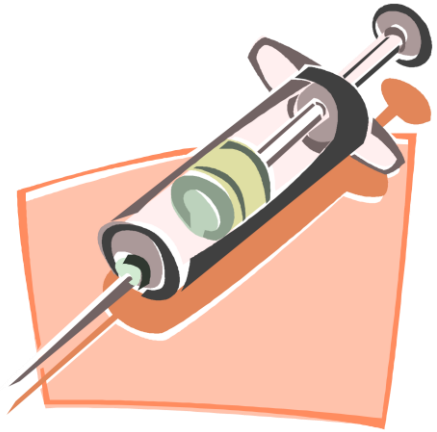
Give chemotherapy



Cured

Not cured

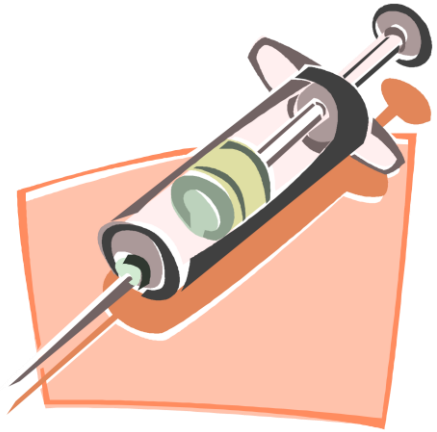
Give chemotherapy



Cured

Not cured

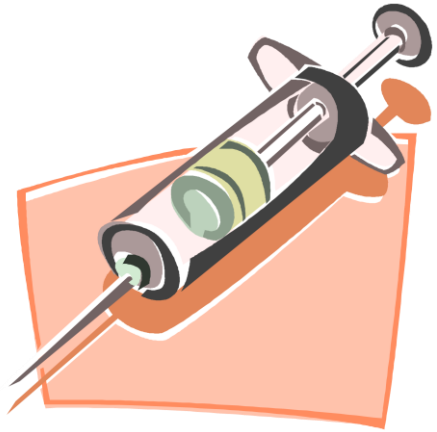
Give chemotherapy



Cured

Not cured

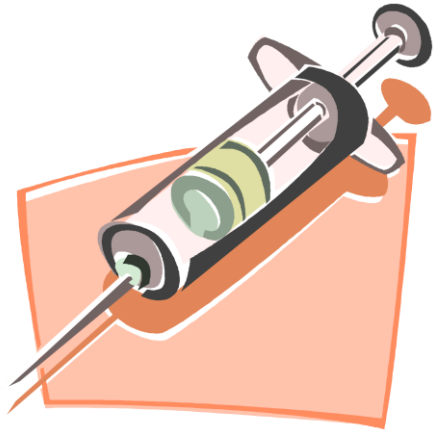
Give chemotherapy



Cured

Not cured

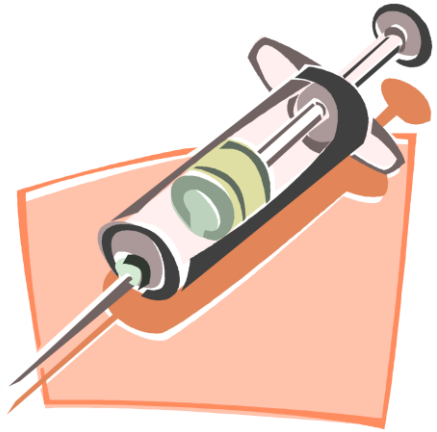
Give chemotherapy

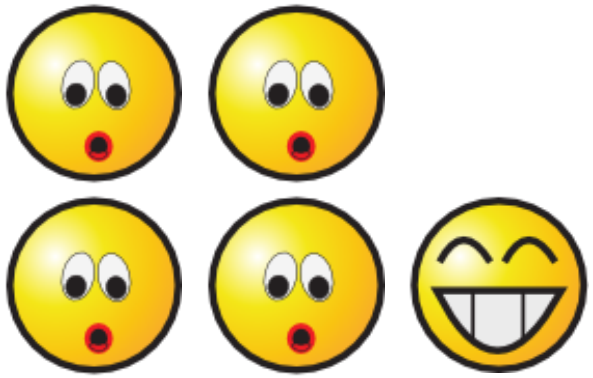


Cured

Not cured

Give chemotherapy

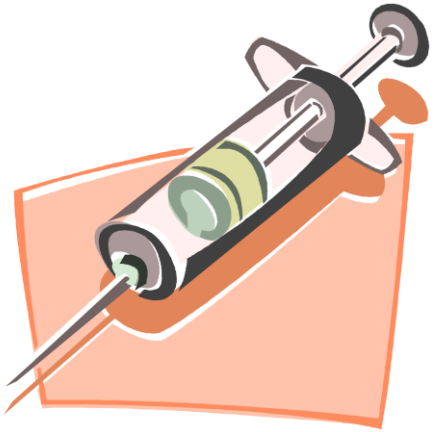


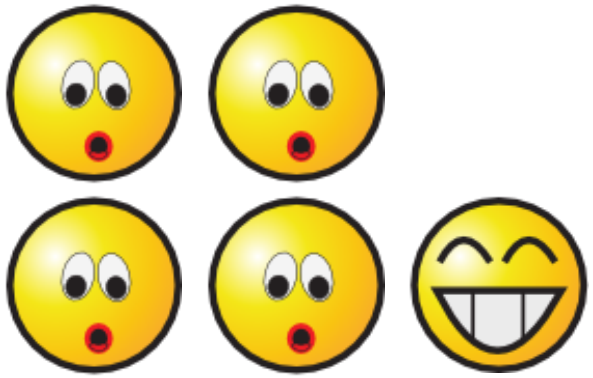


Cured

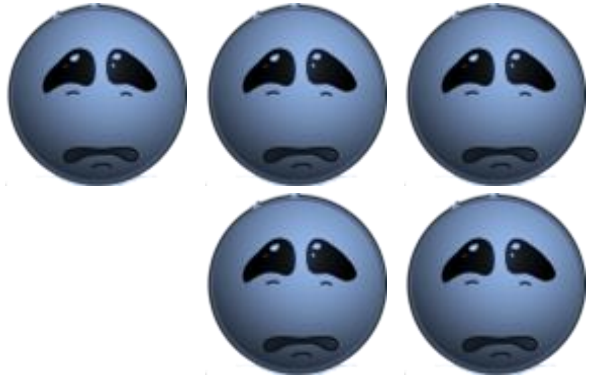
Not cured

Give chemotherapy



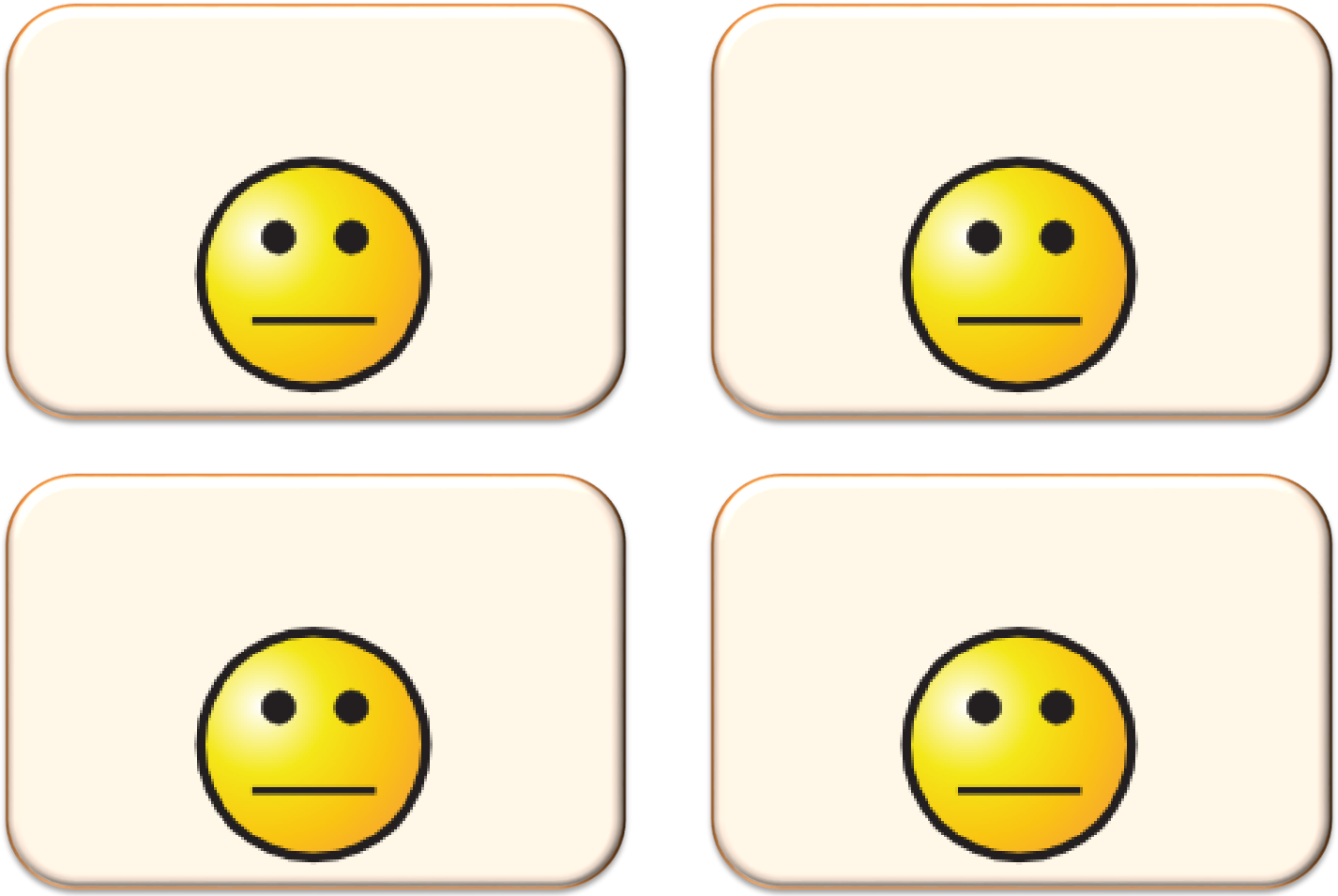


Cured



Not cured

Outcome



Outcome

Cured
No side-effects

Outcome

Cured
No side-effects

Cured
Has side-effects

Outcome

Cured
No side-effects

Cured
Has side-effects

Not cured
No side-effects

Outcome

Cured
No side-effects

Cured
Has side-effects

Not cured
No side-effects

Not cured
Has side-effects

Future

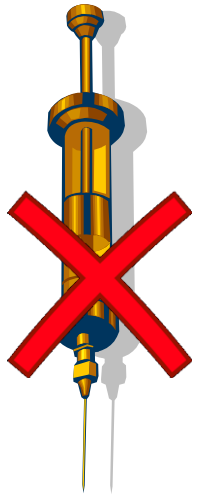
Not cured
Has side-effects

Future

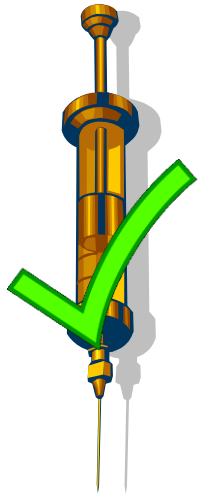
Future

Now

I wish
I hadn't
bothered



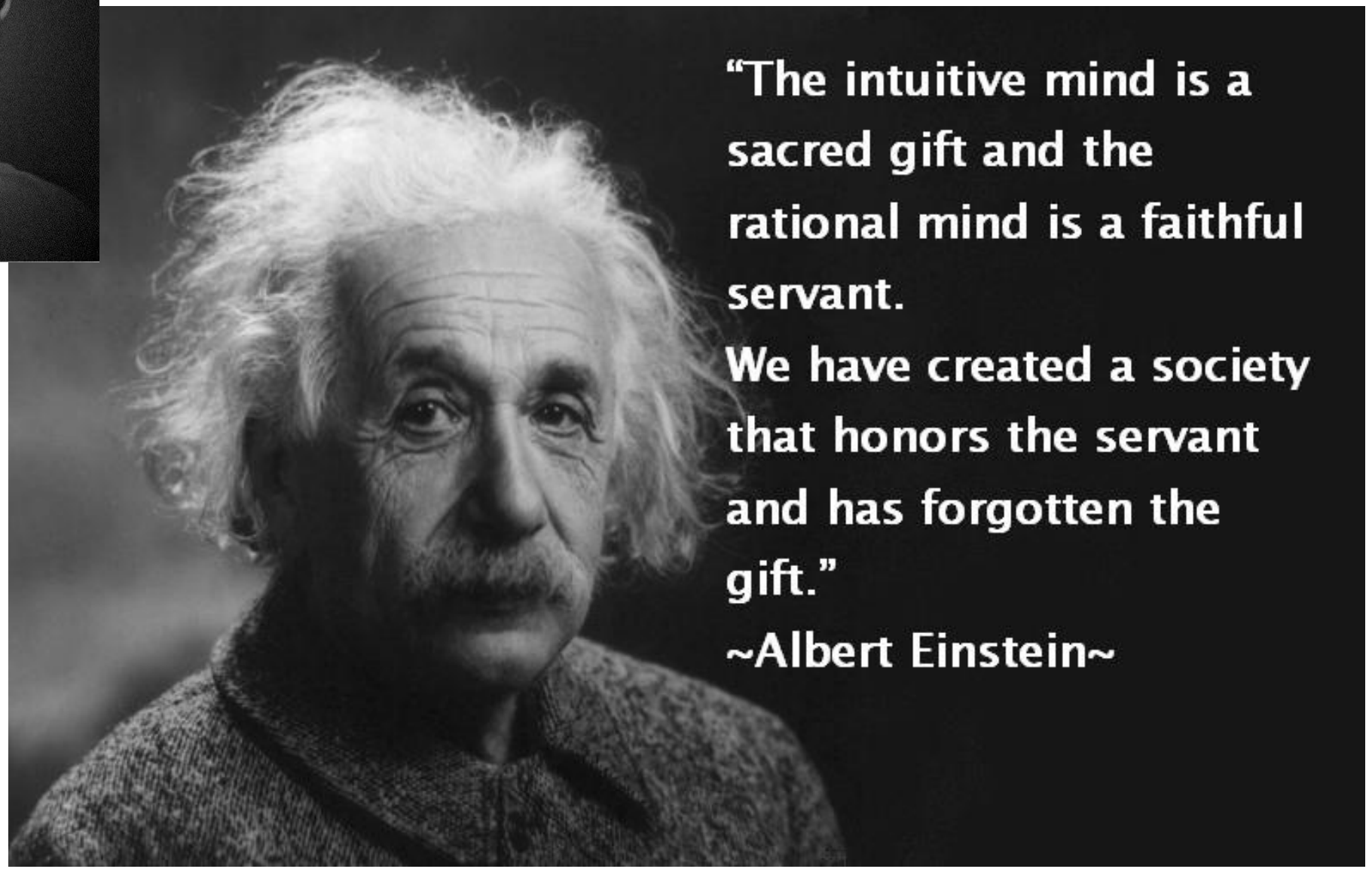
At least
I've tried



Future

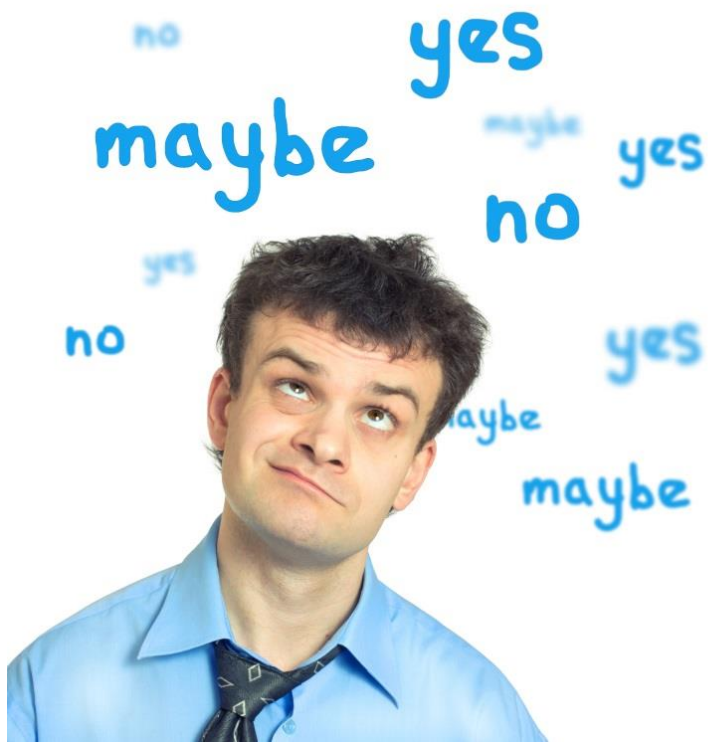
Decisional regret

- Factors most frequently associated with decision regret in multivariate analyses included
  - Higher decisional conflict
  - Lower satisfaction with the decision
  - Adverse physical health outcomes
  - Greater anxiety levels
- If we measure that success of decision-making in terms of conflict and regret, we may favour easy decisions over rational ones.


“The intuitive mind is a sacred gift and the rational mind is a faithful servant.
We have created a society that honors the servant and has forgotten the gift.”
~Albert Einstein~

Tips for decision-making

- Begin with objective factors
- Be clear about treatment intent
- If evidence is lacking, have plausible explanations



State of the art multimodal treatment of anal cancer

ESTRO Chemoradiation Course
Bruxelles, June 2017

Rob Glynne-Jones
Mount Vernon Centre for Cancer Treatment

Disclosures: last 5 years

- **Speaker:** Roche, Merck Serono, Sanofi Aventis, Pfizer
- **Advisory Boards:** Roche, Merck Serono, Sanofi Aventis, Astra Zeneca, BMS
- **Funding to attend meetings**: Roche, Merck Serono, Sanofi Aventis,
- **Research funding**: Roche, Merck Serono, Sanofi Aventis

Incidence and risk factors

- Rare disease
  - Annual incidence: 1-2/100 000 (USA)
  - Incidence is increasing over the last 25 years

- 5 year survival: +/- 60%

- Risk factors:
  - HPV (in 90% of the patients), HIV, (HSV)
  - Immune suppression (transplant recipients)
  - Cigarette smoking
  - Previous malignancies (gynaecological, lymphoma, leukemia)

Squamous carcinoma of anus

- HPV heavily implicated
- ?as in HNSCCC modified by smoking

HPV-Prevalence in Anal SCC

Author	HPV total (%)	HPV16 (%)
Koerber	83.3	76.6
Mai	67.9	n.a.
Rödel	95.8	78.9
Serup-Hansen	87.5	79.8
Baricevic	95	89

Koerber S, Radiother Oncol 2014; Mai S, Int J Radiat Oncol Biol Phys 2015; Rödel F, Int J Cancer 2015; Baricevic I, Eur J Canc 2015; Serup-Hansen E, J Clin Oncol 2014

Squamous carcinoma of anus

- HPV heavily implicated ?as in HNSCCC modified by smoking
- Usually loco-regional disease at presentation
- 30% -40% will have nodal spread at diagnosis
- Primary T stage based mainly on size

TNM Staging of anal canal cancer

- Tx cannot assess primary
- T0 no evidence of tumour
- Tis Carcinoma in situ
- T1 <2cm
- T2 2-5cm
- T3 >5cm
- T4 adjacent organ invasion
- M0 no distant metastases
- M1 distant metastases

- Nx cannot be assessed
- N1 perirectal nodes
- N2 unilateral internal iliac/inguinal nodes
- N3 perirectal and inguinal or bilateral internal iliac and/or inguinal nodes

Site of relapse after CRT from ACT II (940 patients)

Primary Inguinal/pelvic nodes Metastases/oligometastases	Number	% total relapses
Pelvic - no metastases	133	64%
Pelvic - with metastases	30	14%
Distant metastases only	46	22%
Total crude pelvic failure (with or without metastases)	163	78%
Total relapses	209	

Data from ACT II – Sebag-Montefiore D et al ASCO 2012

Prognostic factors
ACT I validated against ACT II

- Prognostic for LRF and OS
- Clinically palpable nodes
- Male sex

- Prognostic for ACD and OS
- Haemoglobin

Glynne-Jones R et al., Cancer 2013 Feb 15;119(4):748-55.

$P16^{INK4A}$

- In UK 90% patients mod/strongly + for $p16^{INK4A}$ (Gilbert 2013)

- p16+ 37/137(27%) relapsed
- P16 - 10/16 (63%) relapsed (Gilbert 2013) p=0.0076

Prognostic relevance of TILs

Author	Patients (n)	Results
Grabenbauer	38	CD3/CD4: decreased 3 years NED
Rubio	277	CD3/CD8: increased 15 years survival
Hu	40	intratumoral CD8: increased DFS peritumoral CD8: increased OS
Gilbert	153	increased relapse-free survival

High levels of TILs, especially CD8(+) cells, are associated with a favourable clinical response and survival

Squamous cell carcinoma of the Anus

- The standard of care is chemoradiation with 5FU and MMC
- Standard of care for radiation is IMRT

Diagnosis and staging

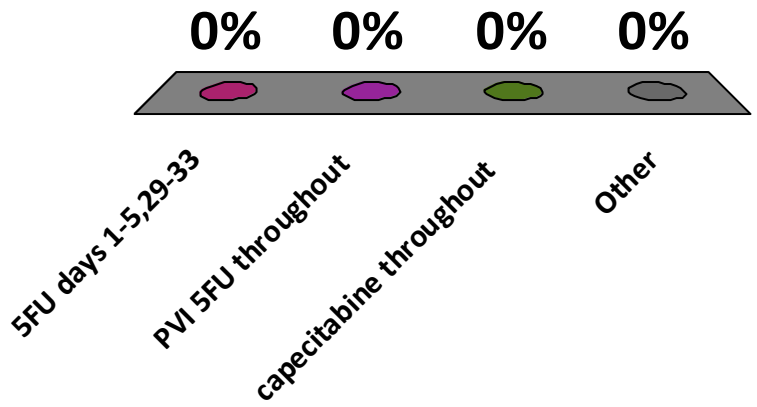
- A 48 years old male with a 4cm anal mass.
- Biopsy: Squamous cell carcinoma.
- Positive HPV 16 and HPV 53. HIV test:Negative
- MRI: mass 3.6 cm. No involvement of external sphincter. No enlarged inguinal or pelvic lymph nodes detected.
- CT scan/PET scan: No metastases.

Squamous cell carcinoma of the anal canal
cT2 cN0M0. Stage II.

What to do next?

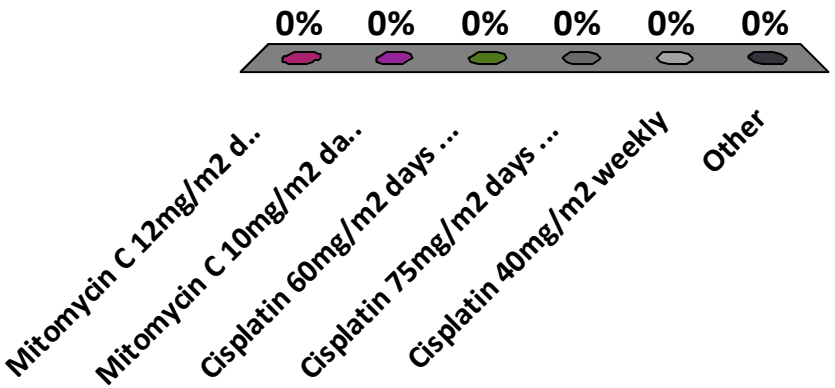
Chemoradiation- what fluoropyrimidine?

A. 5FU days 1-5,29-33
B. PVI 5FU throughout
C. capecitabine throughout
D. Other



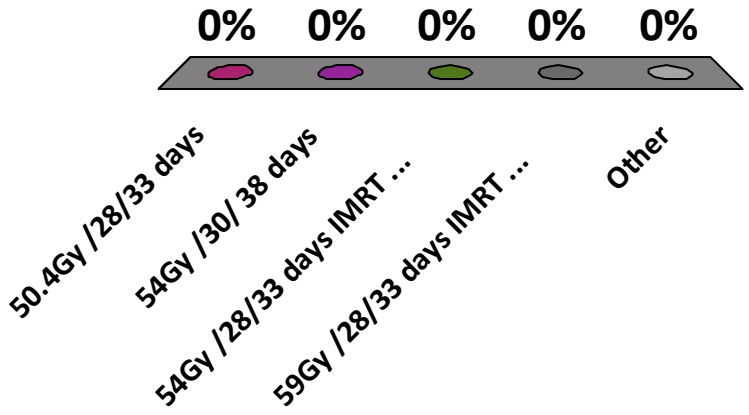
Chemoradiation- what partner?

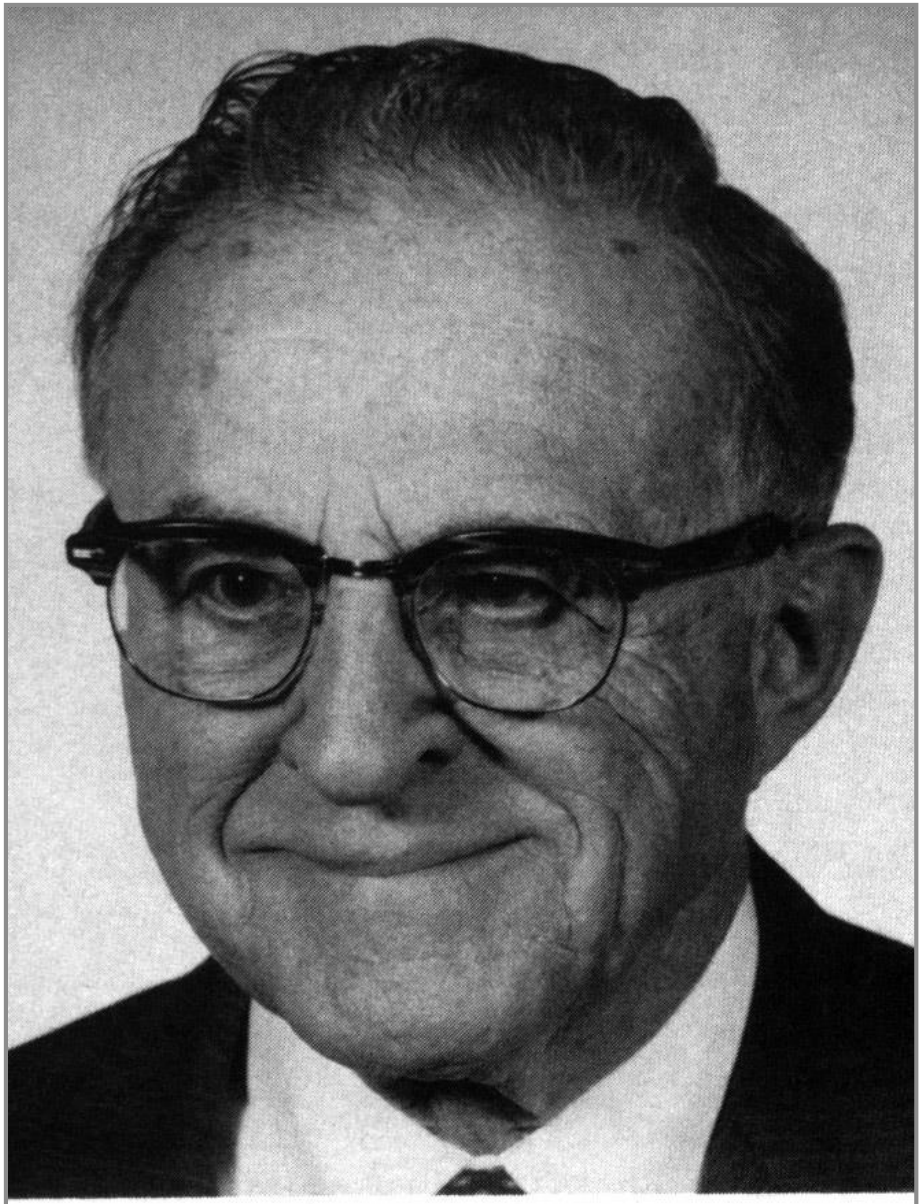
A. Mitomycin C 12mg/m2 day 1 only
B. Mitomycin C 10mg/m2 days 1 and 29
C. Cisplatin 60mg/m2 days 1 and 29
D. Cisplatin 75mg/m2 days 1 and 29
E. Cisplatin 40mg/m2 weekly
F. Other



Chemoradiation- what dose to primary PTV?

A. 50.4Gy /28/33 days
B. 54Gy /30/ 38 days
C. 54Gy /28/33 days IMRT /VMAT simultaneous integrated boost
D. 59Gy /28/33 days IMRT /VMAT simultaneous integrated boost
E. Other





Nigro suggested that CTRT

- Low doses of RT - 30Gy could achieve path CR in tumours 5cm or less
- Response is sustained
- Failure to respond is usually associated with rapid systemic relapse

Results: Nigro et al.,1983

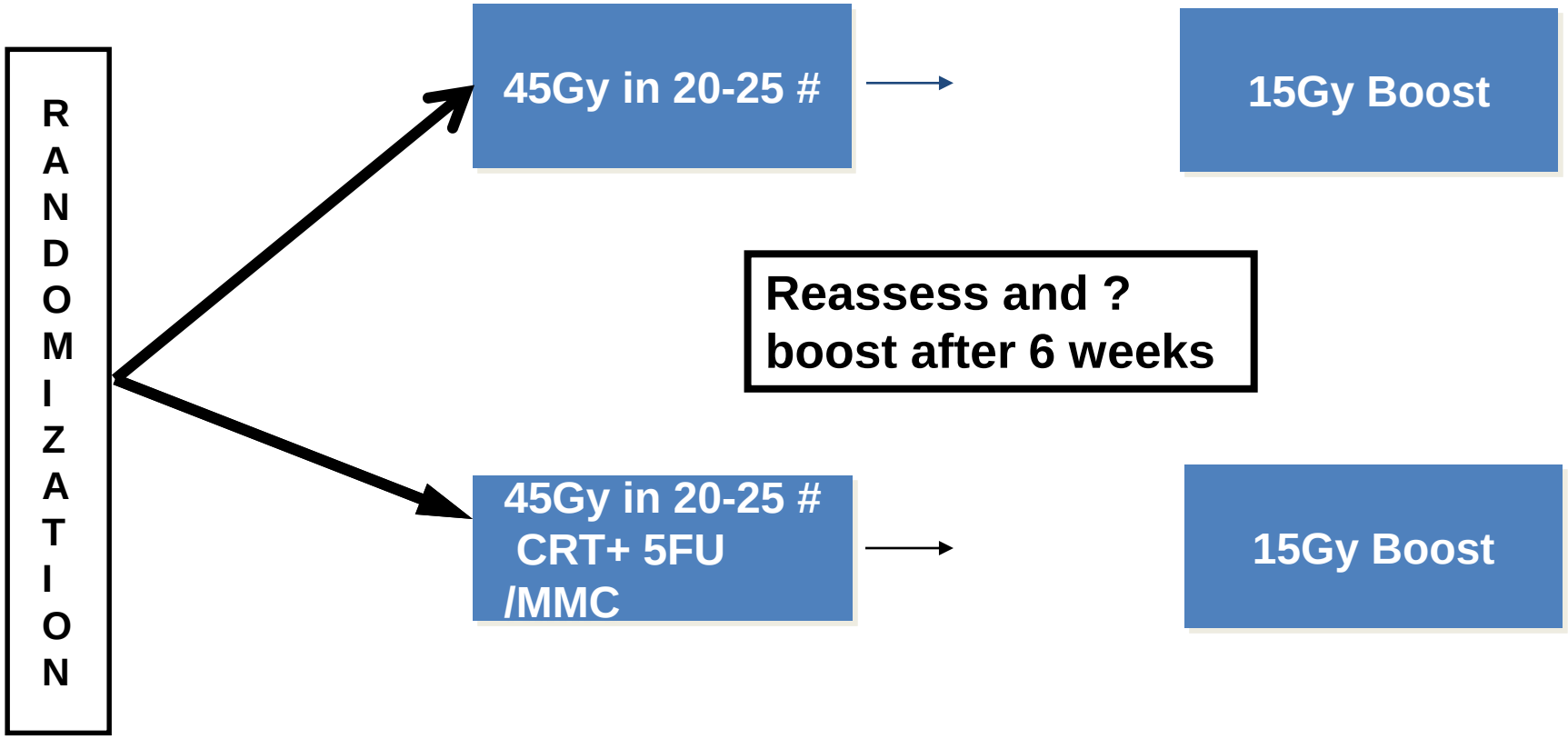
- 28 patients 4 persistent tumour
  24 clinical CR

12 had APER (7/12 path CR)
14 excision of scar (100% path CR)
2 refused surgery
Failure to control 5/9 tumours of 6cm

Anal canal squamous cell carcinoma should not be treated by the same procedure as adenocarcinoma of the lower rectum, because both these diseases differ markedly.

ACT I Trial

N = 585 patients



Squamous carcinoma of anus

- **Three phase III trials 1987– 1994**
  - **UKCCCR ACT 1 n=585**
  - **EORTC 22861 n=110**
  - **RTOG 87-04/ECOG 1289 n=310**

- **Three phase III trials 1998– 2008**
  - **UKCCCR ACT II n=940**
  - **RTOG 9811 n=644**
  - **ACCORD-03 n=307**

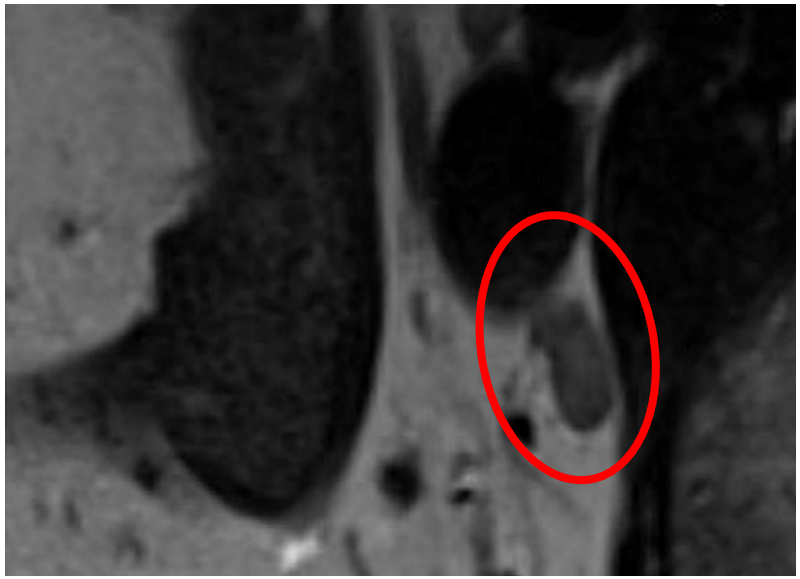
Work-up and diagnosis

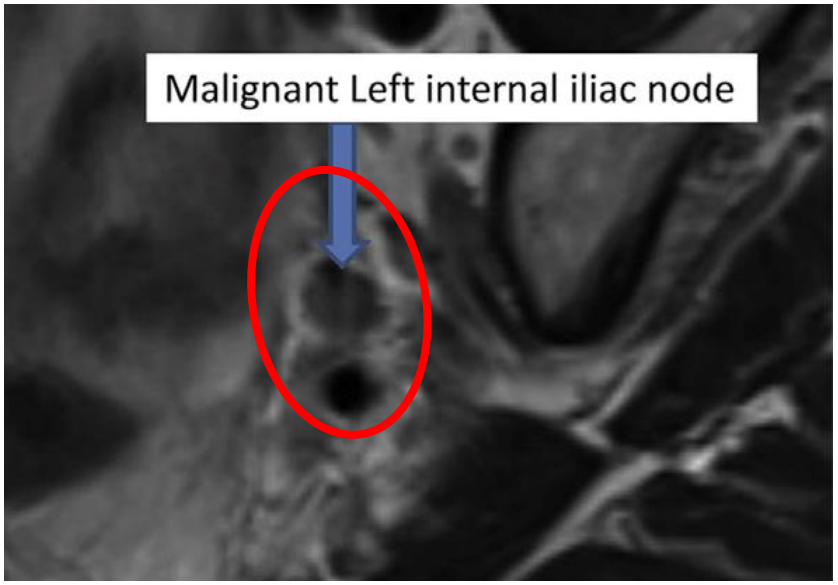
- Standard work up includes proctoscopy
- Examination under anaesthetic (EUA) is necessary on occasions in anal cancer to inspect and obtain biopsy
- Pelvic MRI mandatory for loco-regional staging
- TRUS if MRI not available but difficult in advanced anal lesions
- Whole body CT to determine if metastatic disease
- Positron emission tomography (PET/CT) scan

Anal cancer pelvic nodes

- Size not accurate because > 50% LN+ smaller than 5 mm

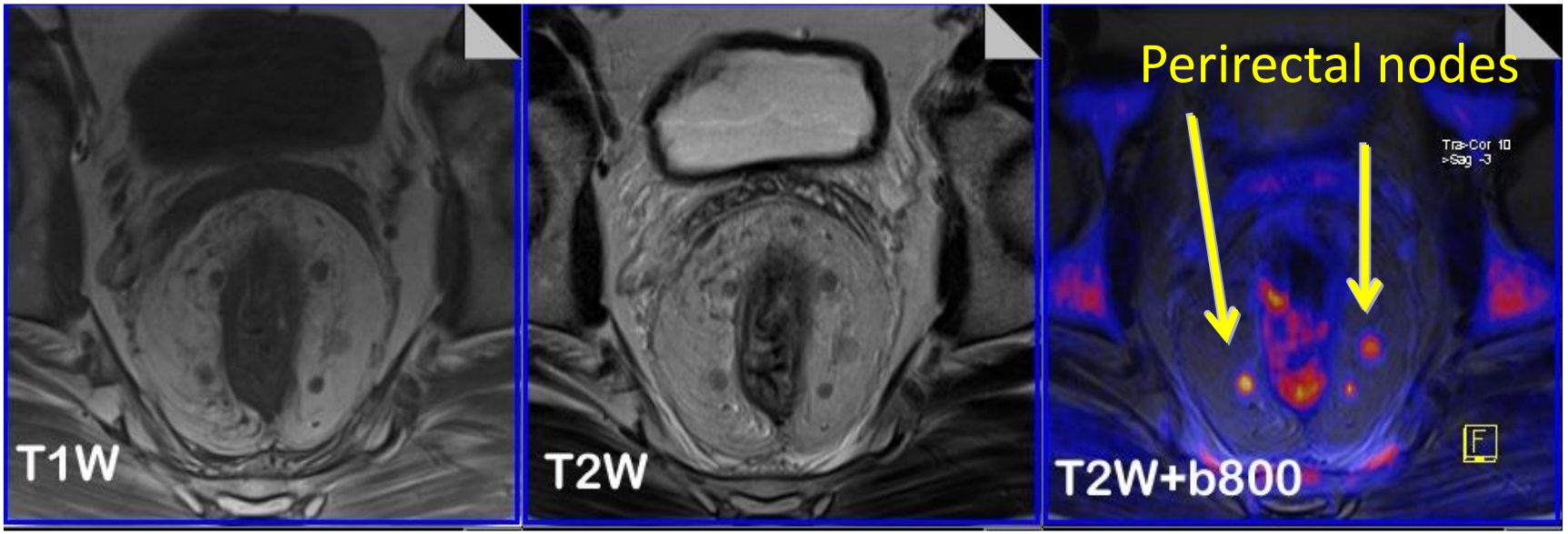
→ overestimation of node positivity in large nodes

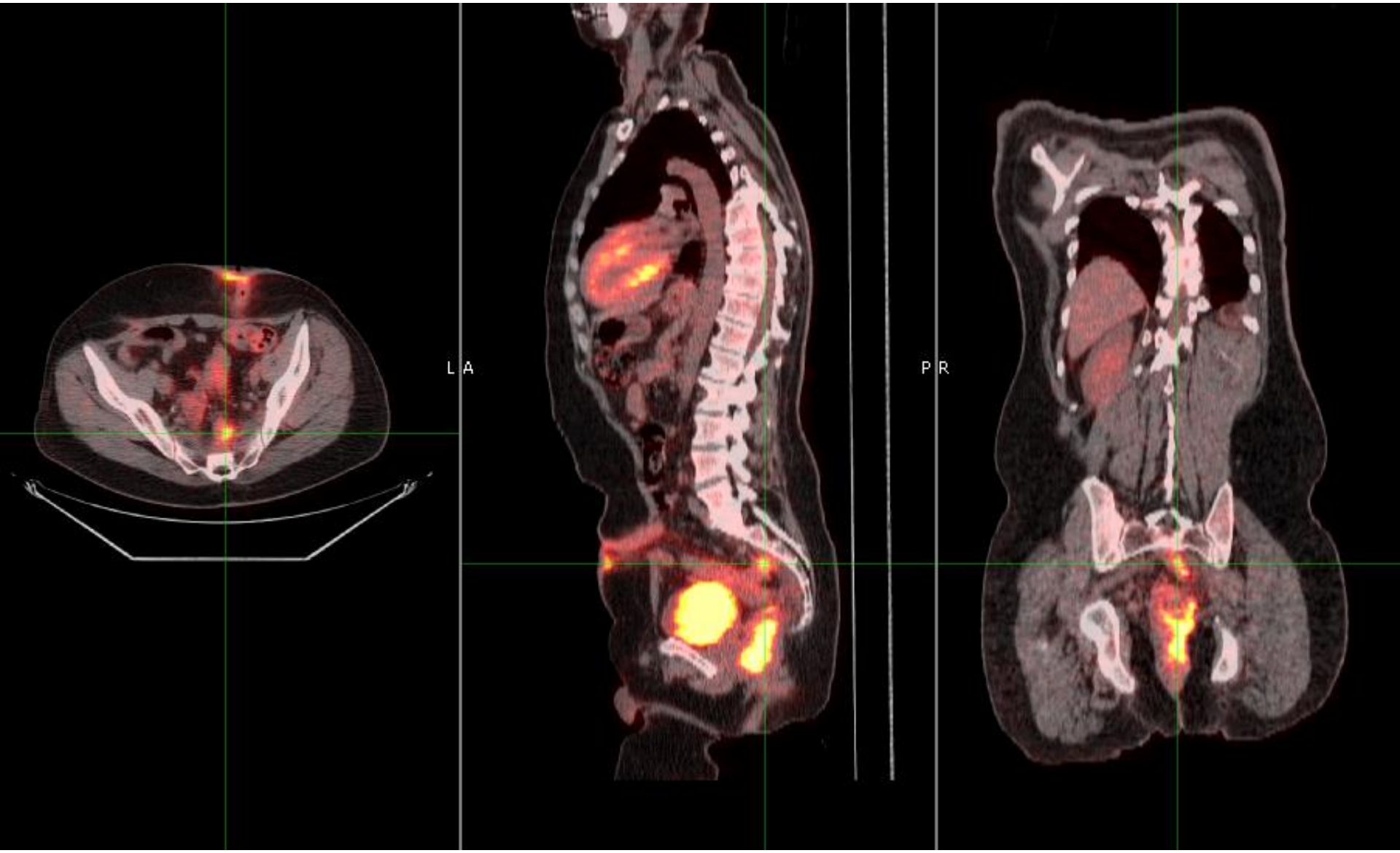




Ciombor et al. Surg Oncol Clin N Am 2017

N1 Stage




L A
P R

We investigated Chemotherapy Options

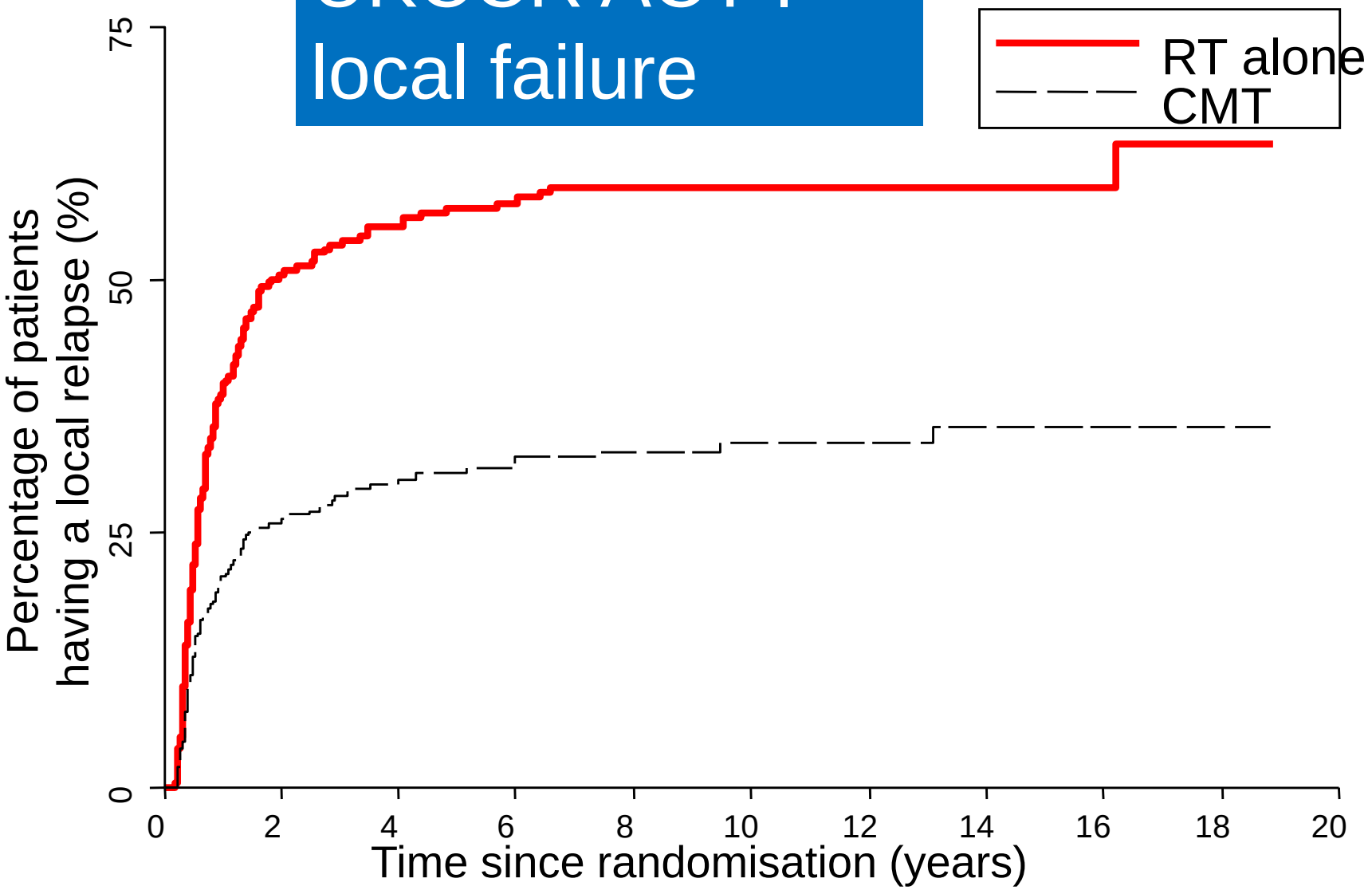
- Induction chemotherapy prior to CRT
- Different concurrent chemotherapy in CRT
- Consolidation chemotherapy after CRT

Concurrent Chemoradiation

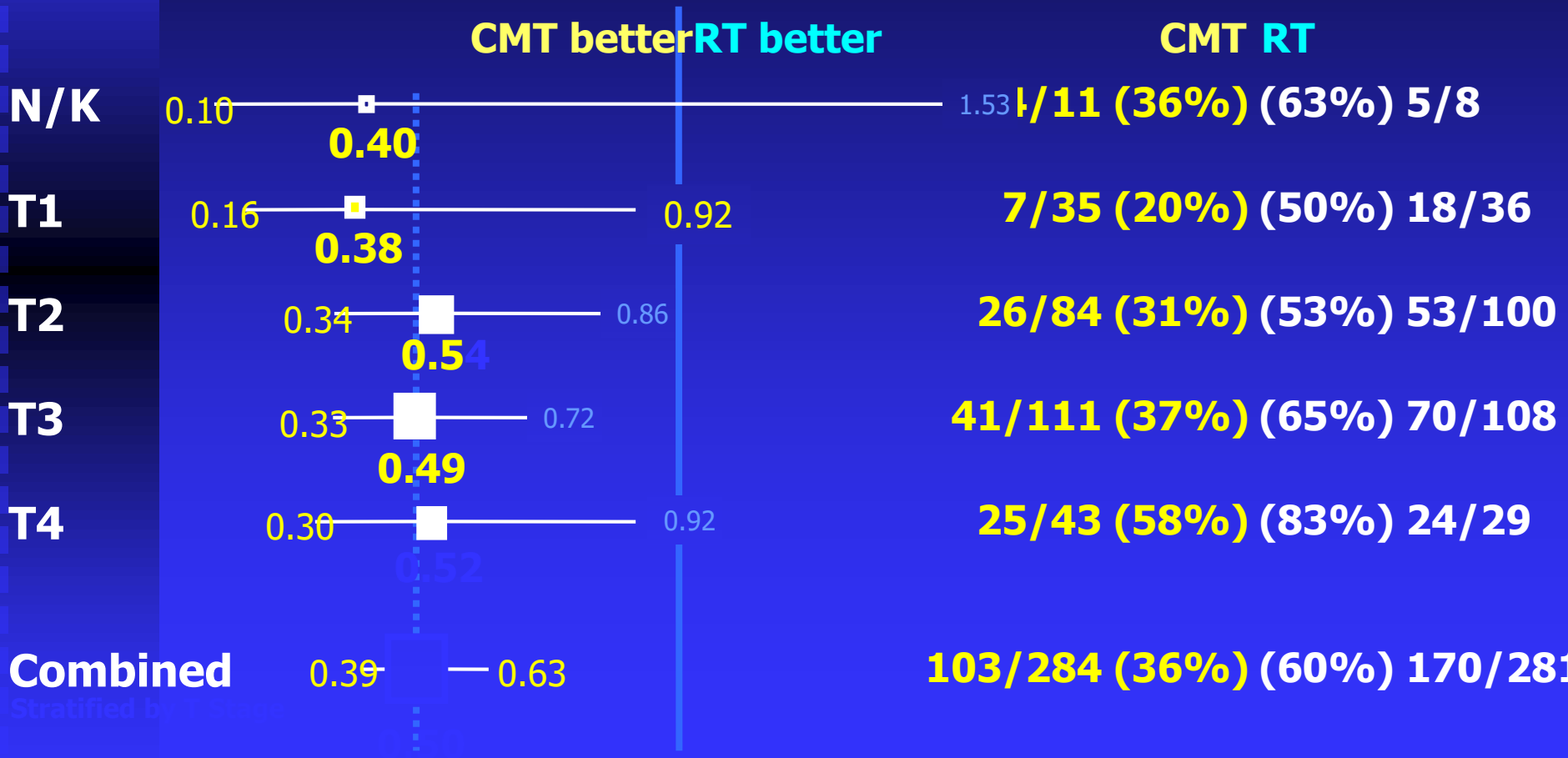
Mid eighties first phase III trials

	Arm A	Arm B
EORTC 22861	RT	RT + 5 FU-Mito C
UKCCCR ACT I	RT	RT + 5 FU-Mito C
US RTOG 8704	RT+ 5 FU	RT + 5 FU-Mito C

UKCCR ACT I local failure

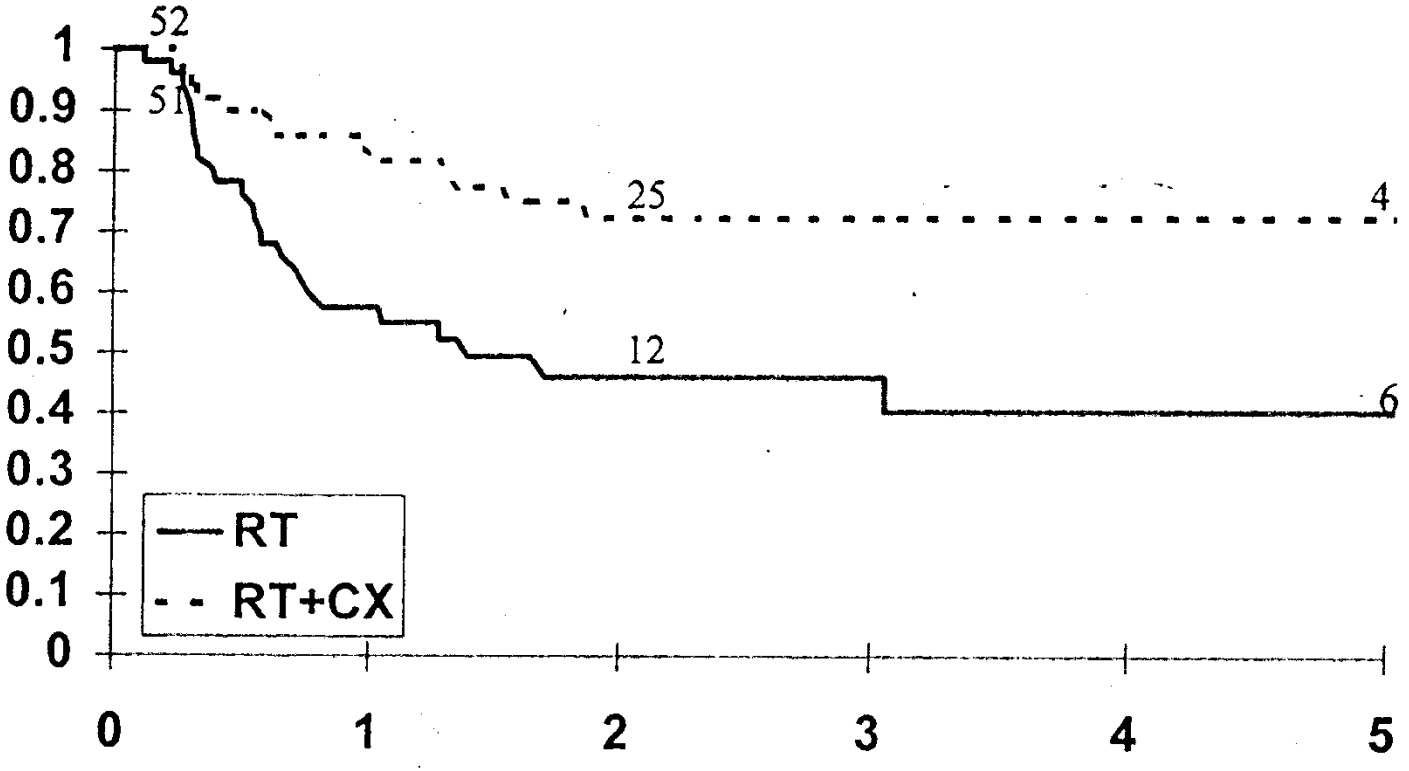


ACT I Phase III Trial
Time to Disease by T Stage



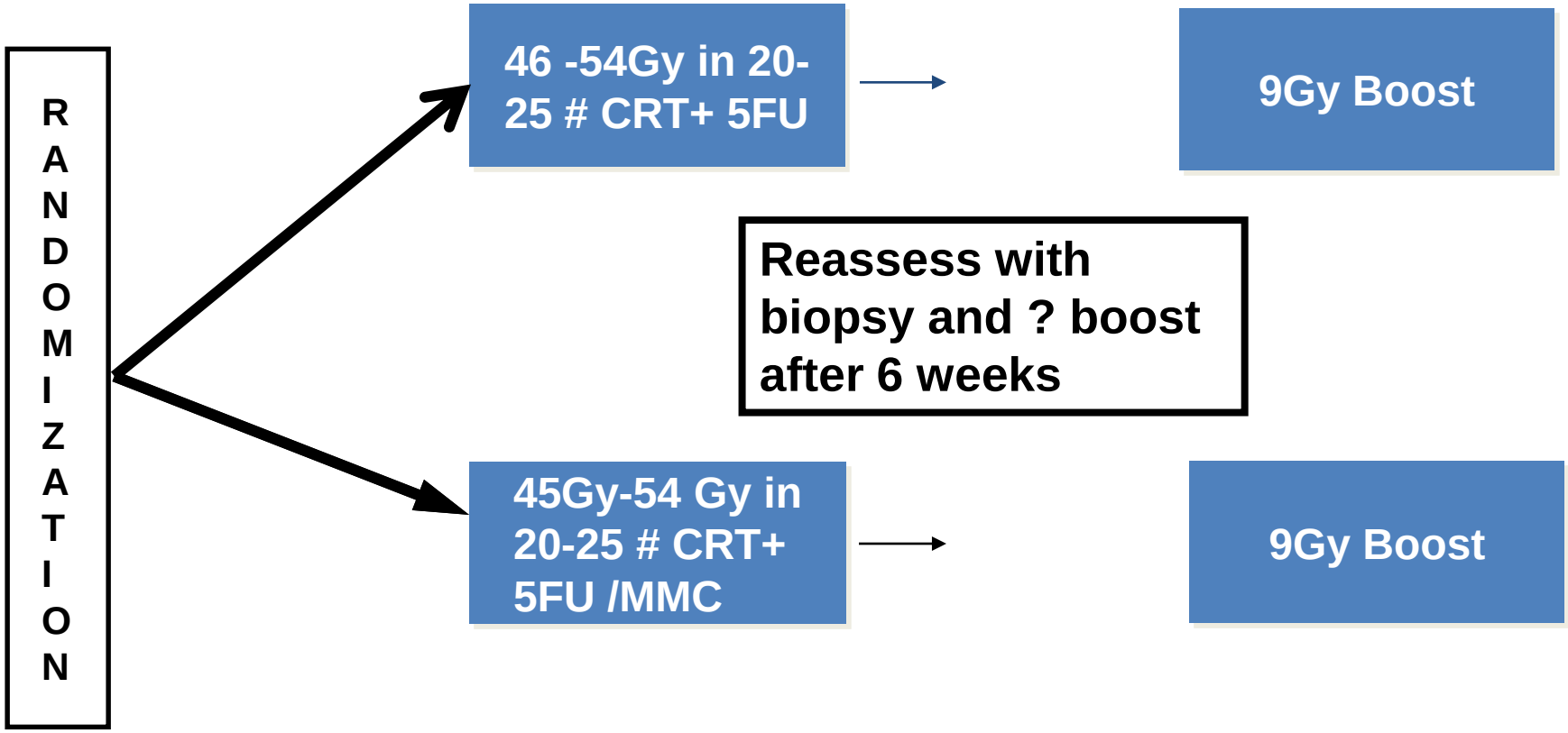
EORTC trial

- DFS 68 vs 55 % at 3 years p = 0,03
- Colostomy FS 72 vs 47 % at 3 years p = 0.002



RTOG 87-04 Trial

N = 291 patients

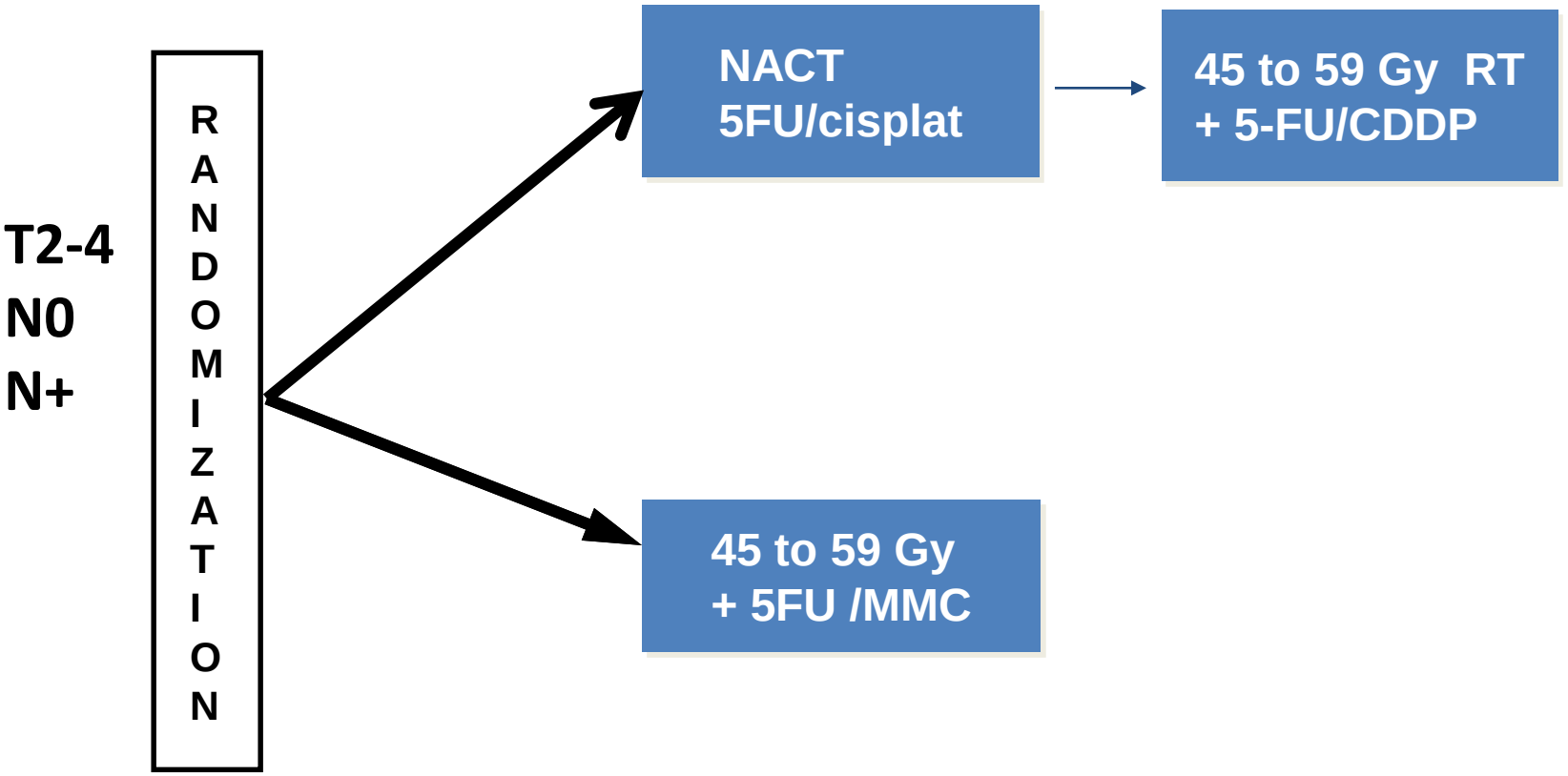


RTOG 87-04 trial

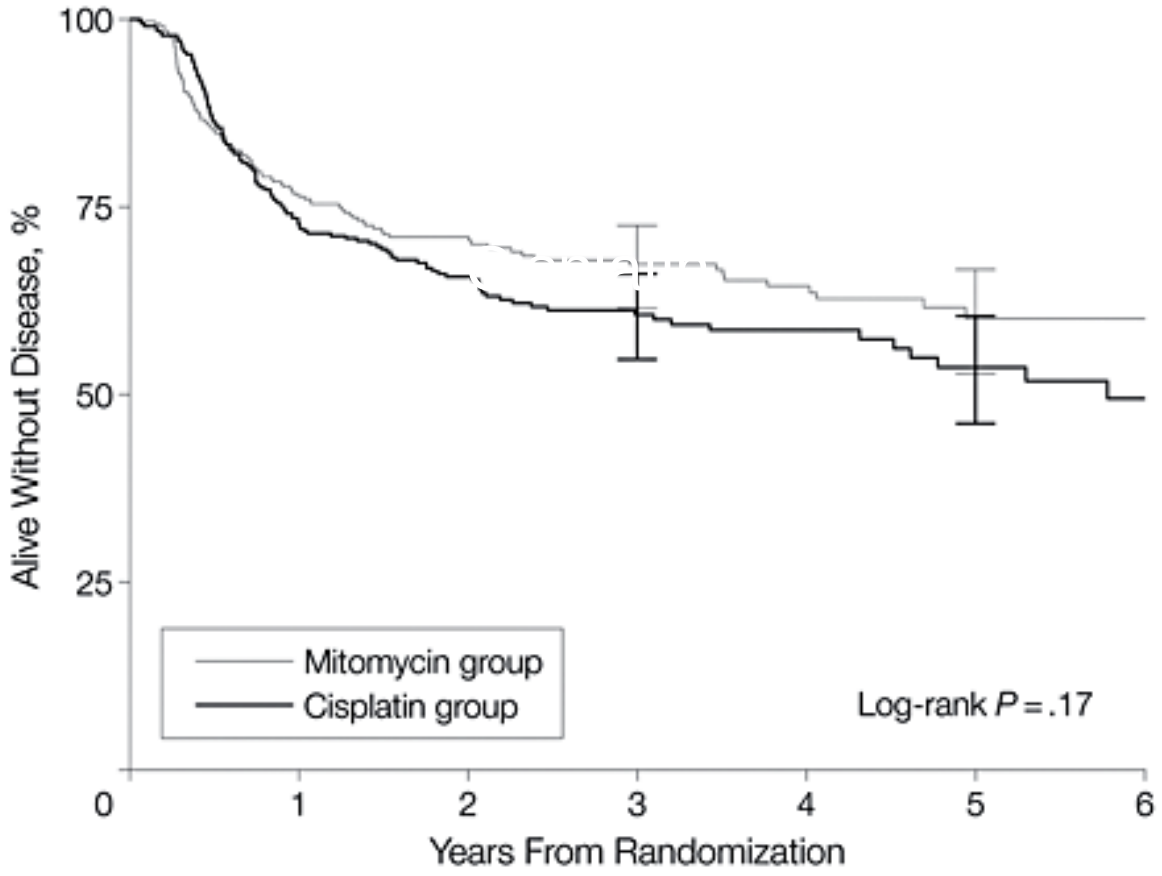
	XRT+ 5 FU	XRT + 5 FU-MMC	p value
Complete response	86%	92.2%	NS
Colostomy- free survival	59%	71%	0.014
Colostomy rate	22%	9%	0.002
DFS	51%	73%	**0.003**
OS	71%	78%	0.1

Intergroup RTOG 98-11

N = 644 patients



Disease Free Survival RTOG 9811

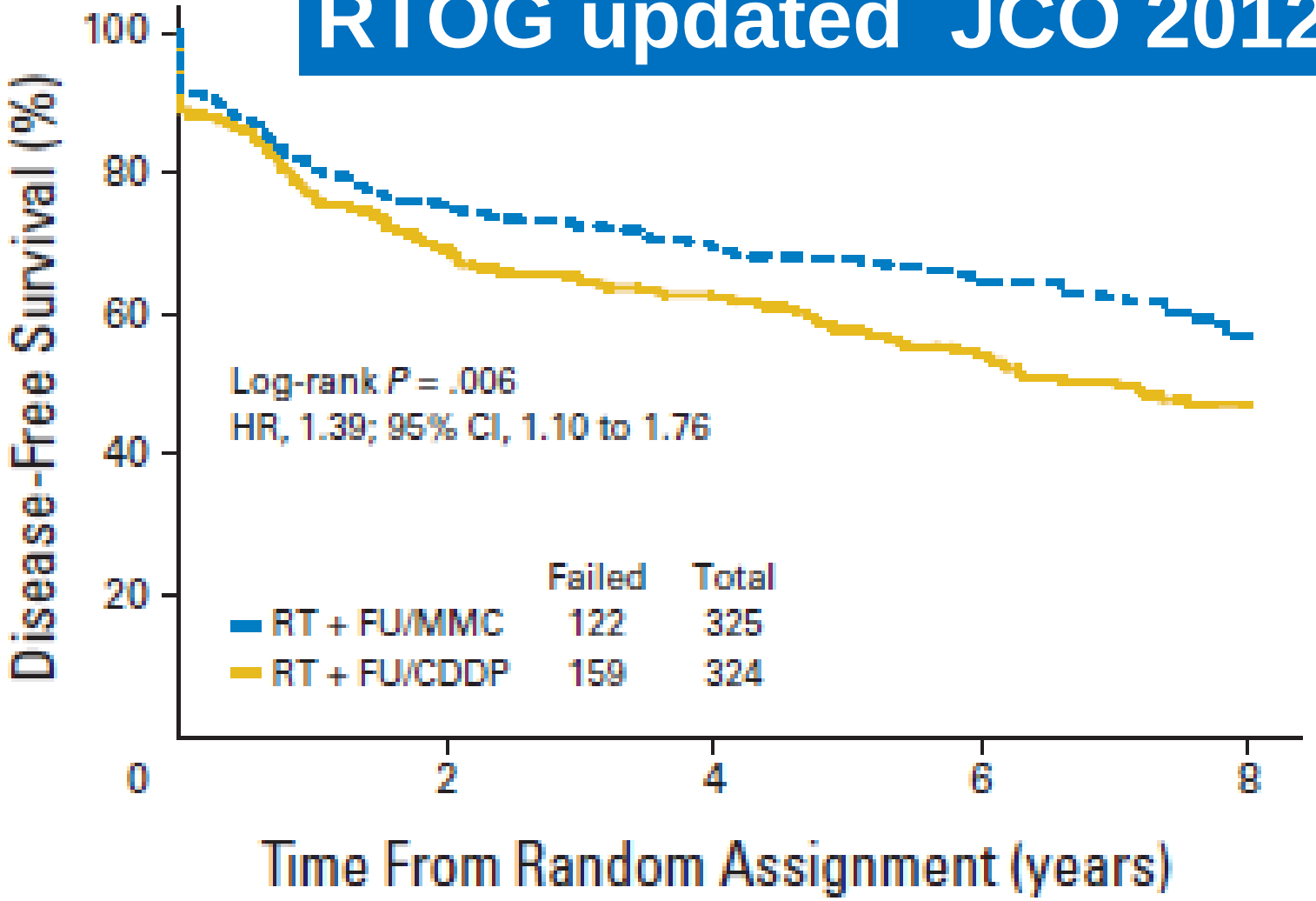


No. at risk							
Mitomycin group	324	226	150	114	76	34	10
Cisplatin group	320	223	160	104	62	34	18

RTOG 9811 Ajani JA et al JAMA 2008

A

RTOG updated JCO 2012

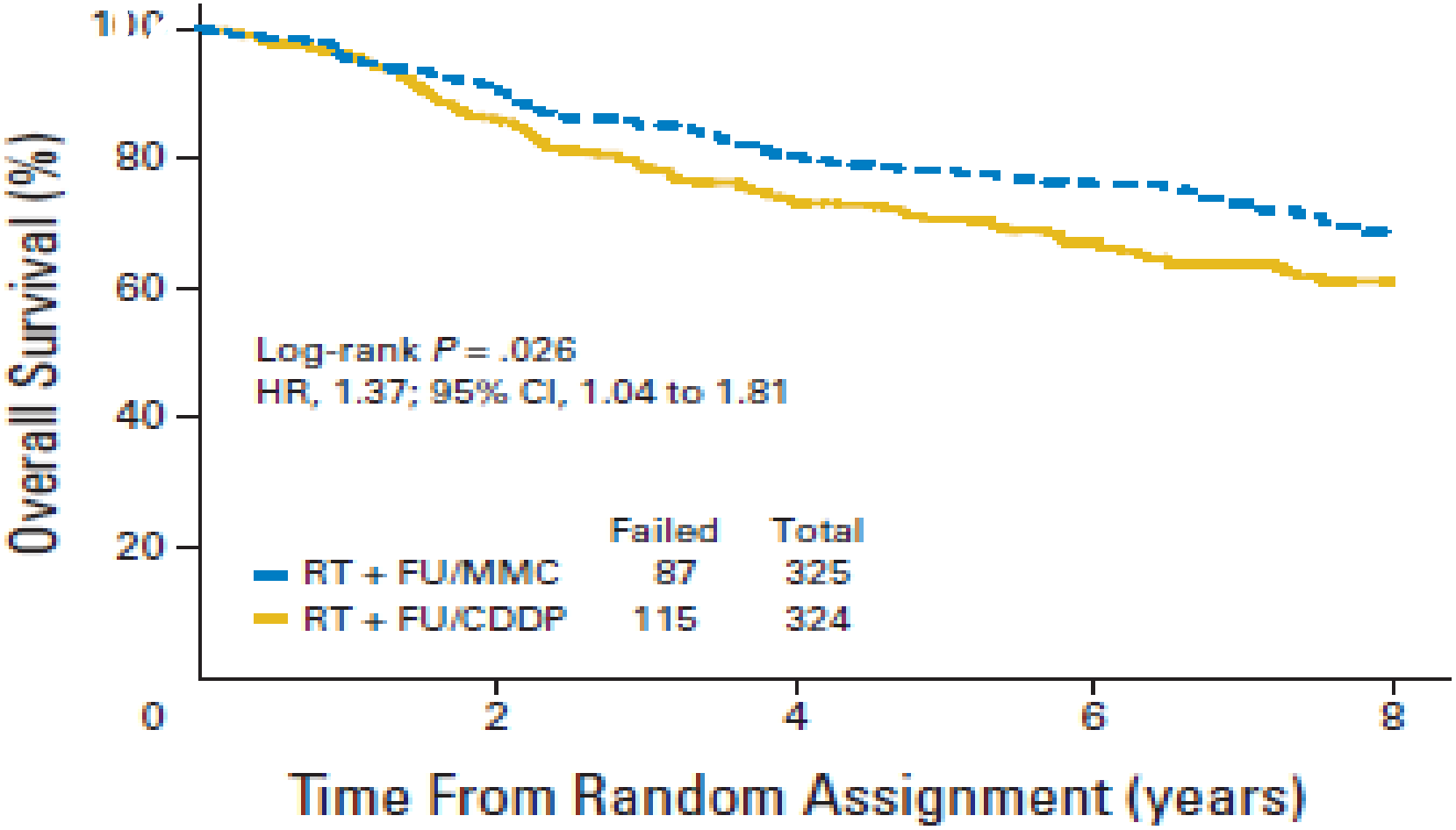


No. at risk

RT + FU/MMC	325	234	204	144	59
RT + FU/CDDP	324	218	181	121	57

RTOG 9811 Gunderson et al

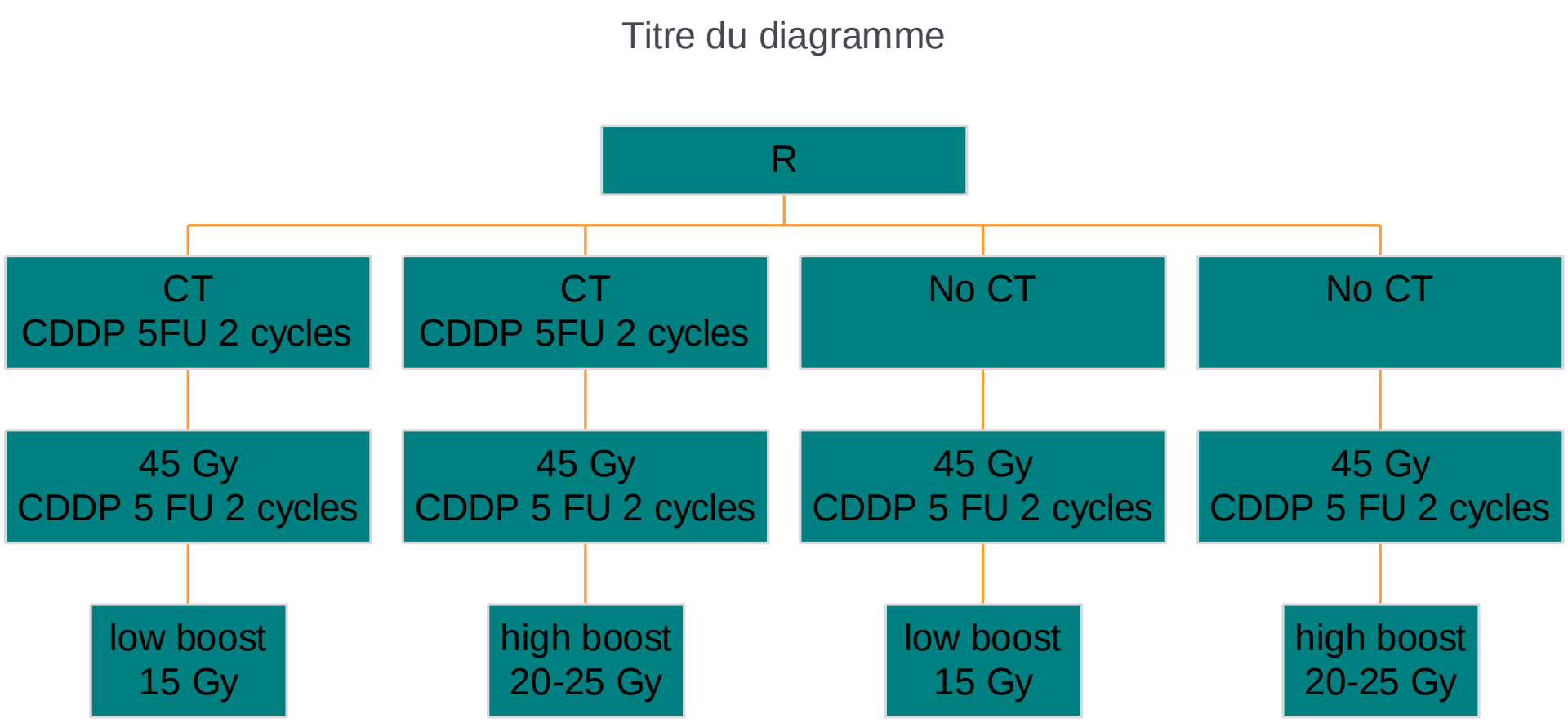
B



No. at risk

RT + FU/MMC	325	283	235	168	68
RT + FU/CDDP	324	271	213	151	76

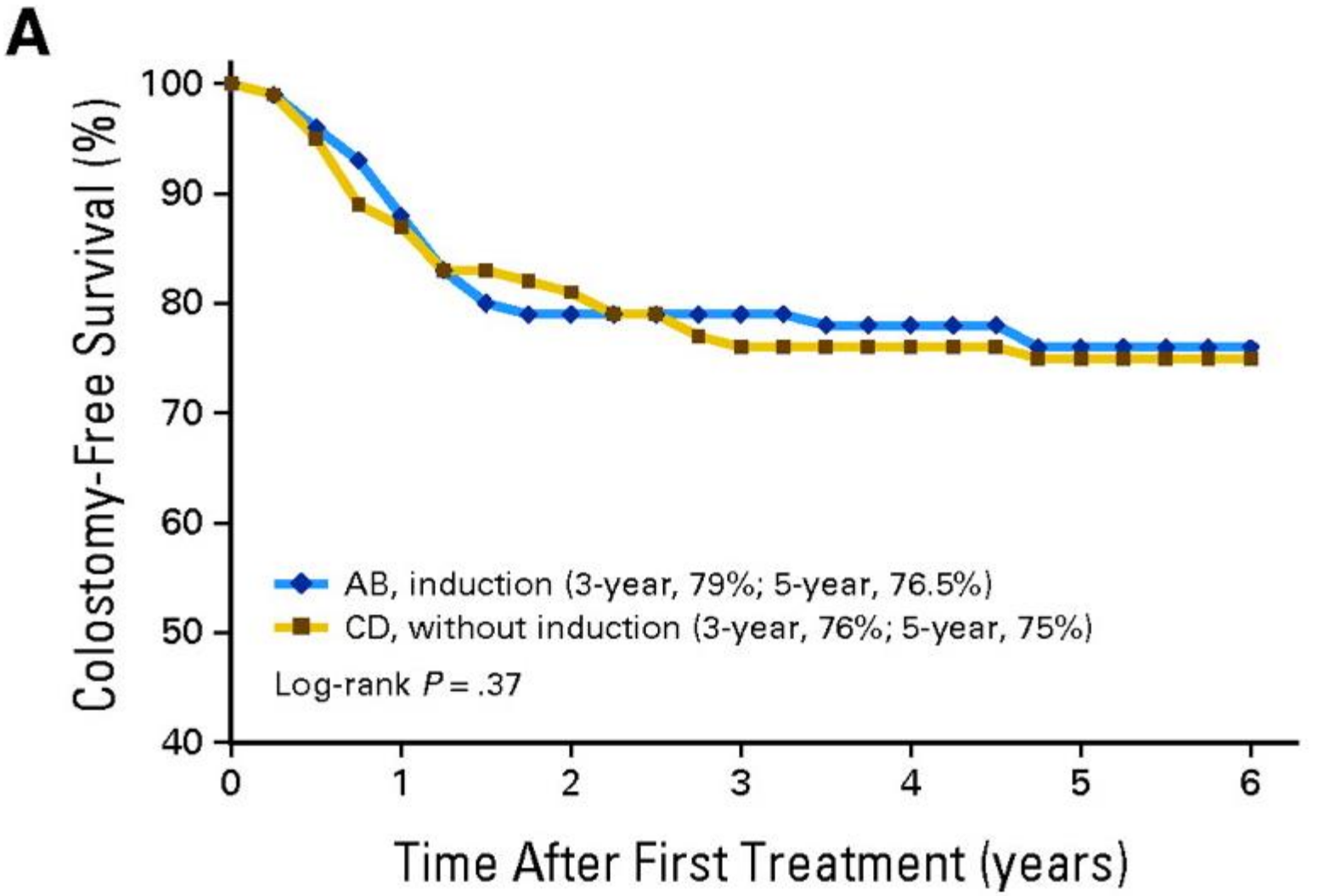
ACCORD 03


Titre du diagramme
R
CT
CDDP 5FU 2 cycles
CT
CDDP 5FU 2 cycles
No CT
No CT
45 Gy
CDDP 5 FU 2 cycles
45 Gy
CDDP 5 FU 2 cycles
45 Gy
CDDP 5 FU 2 cycles
45 Gy
CDDP 5 FU 2 cycles
low boost
15 Gy
high boost
20-25 Gy
low boost
15 Gy
high boost
20-25 Gy

ACCORD- 03

- Therapeutic intensification
  - **Induction chemotherapy (CRT cisplatin)**
  - **High dose radiotherapy (CRT cisplatin)**
- Primary endpoint: colostomy-free-survival(CFS).

ACCORD CFS : induction versus no induction



2 Trials

- No advantage to induction chemotherapy prior to CRT

  (actually worse in RTOG 9811)

Why has induction chemotherapy not worked?

Any initial beneficial response to chemo may be lost owing to

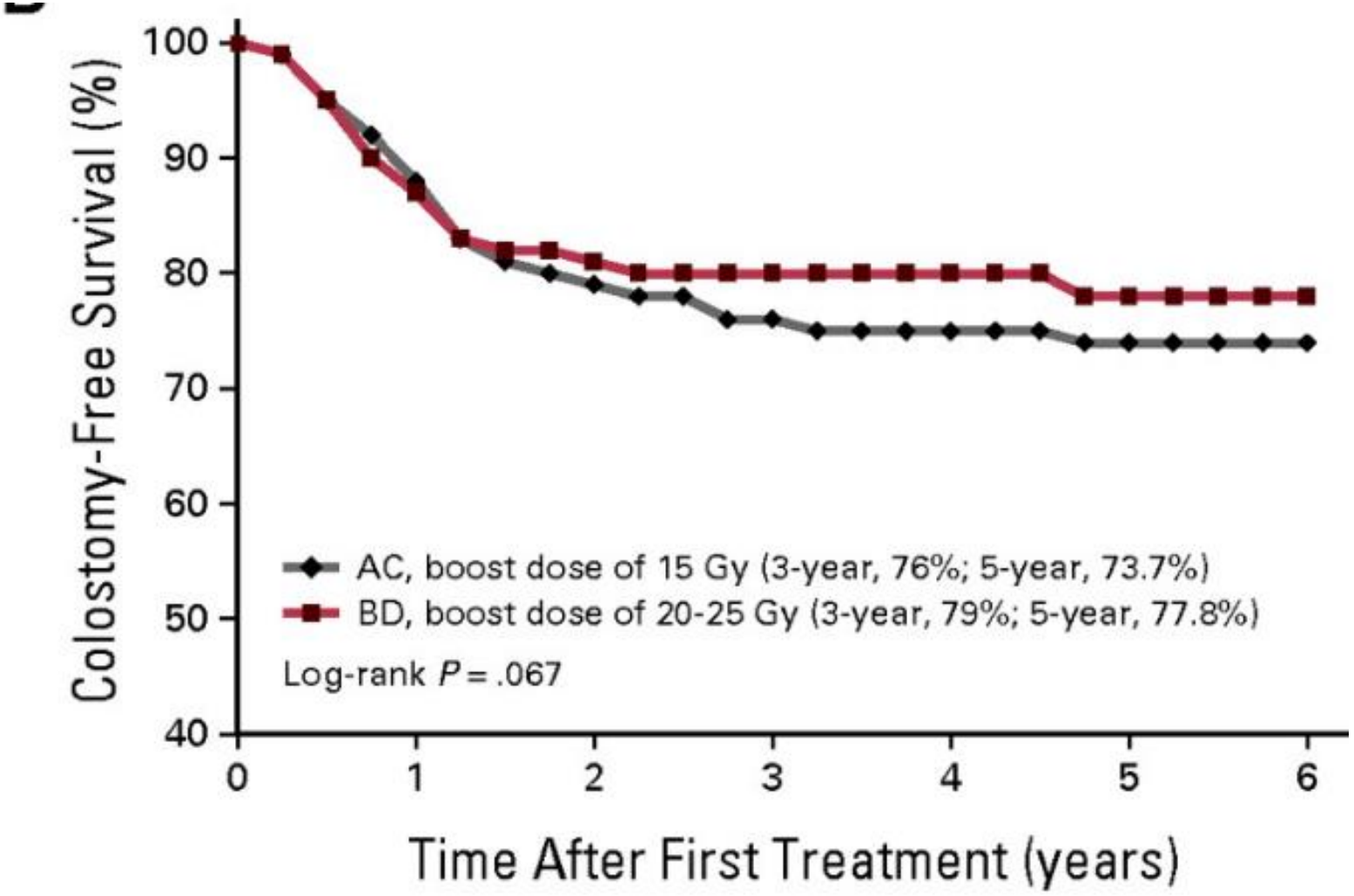
- More proliferation prior to start of CRT.
- Acute toxicity causing delay to CRT
- ? Impacted on compliance to CRT
- Development of resistance mechanisms.
- Creating inherent bias in terms of smaller dose/field size

- De Ruysschers Principle of SER

(the interval between the start of treatment and the end of radiotherapy should be as short as possible)

De Ruysscher D, et al., Time between the first day of chemotherapy and the last day of chest radiation is the most important predictor of survival in limited-disease small-cell lung cancer. **J Clin Oncol 2006;24(7):1053-63**

ACCORD CFS : boost versus no boost

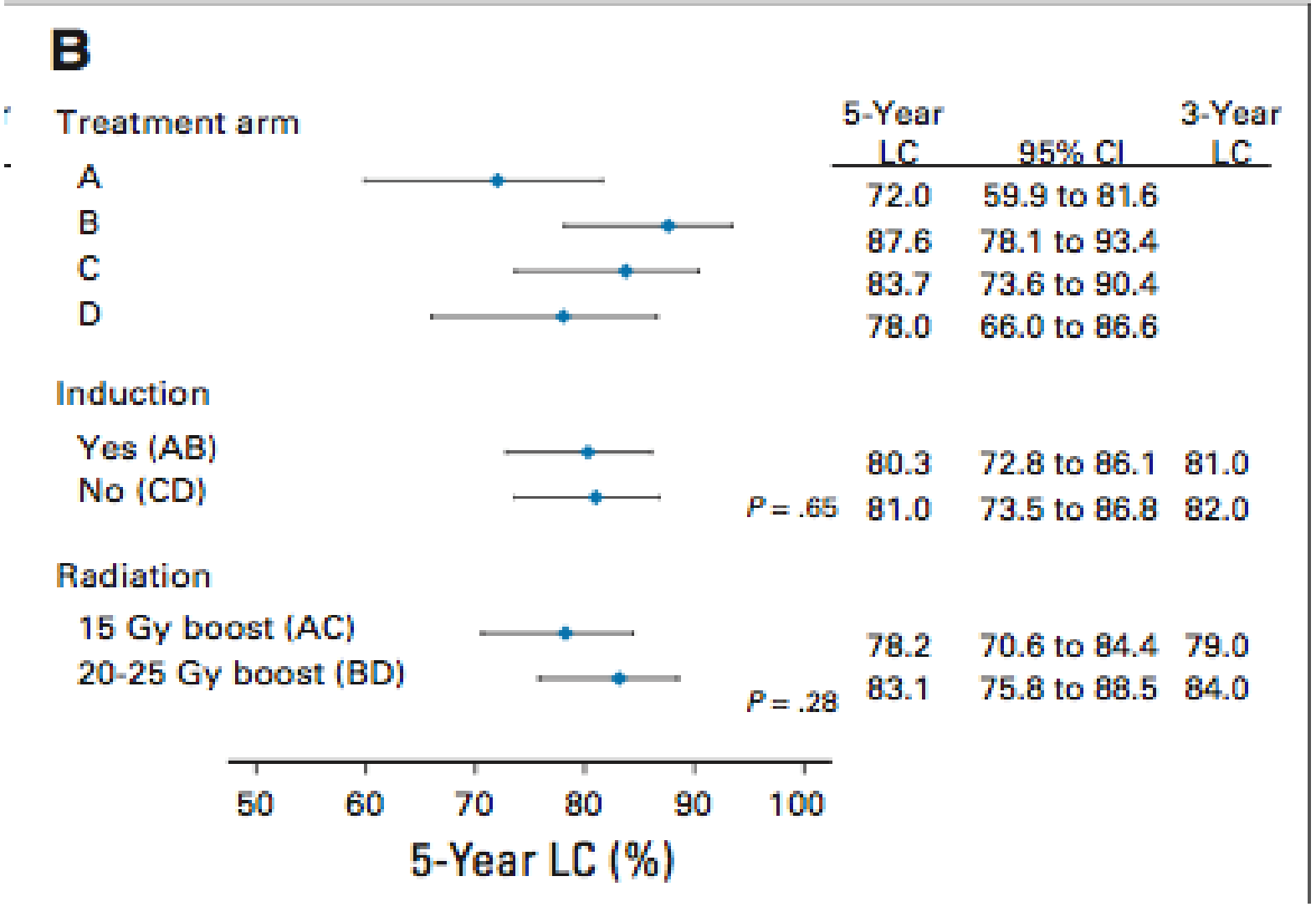


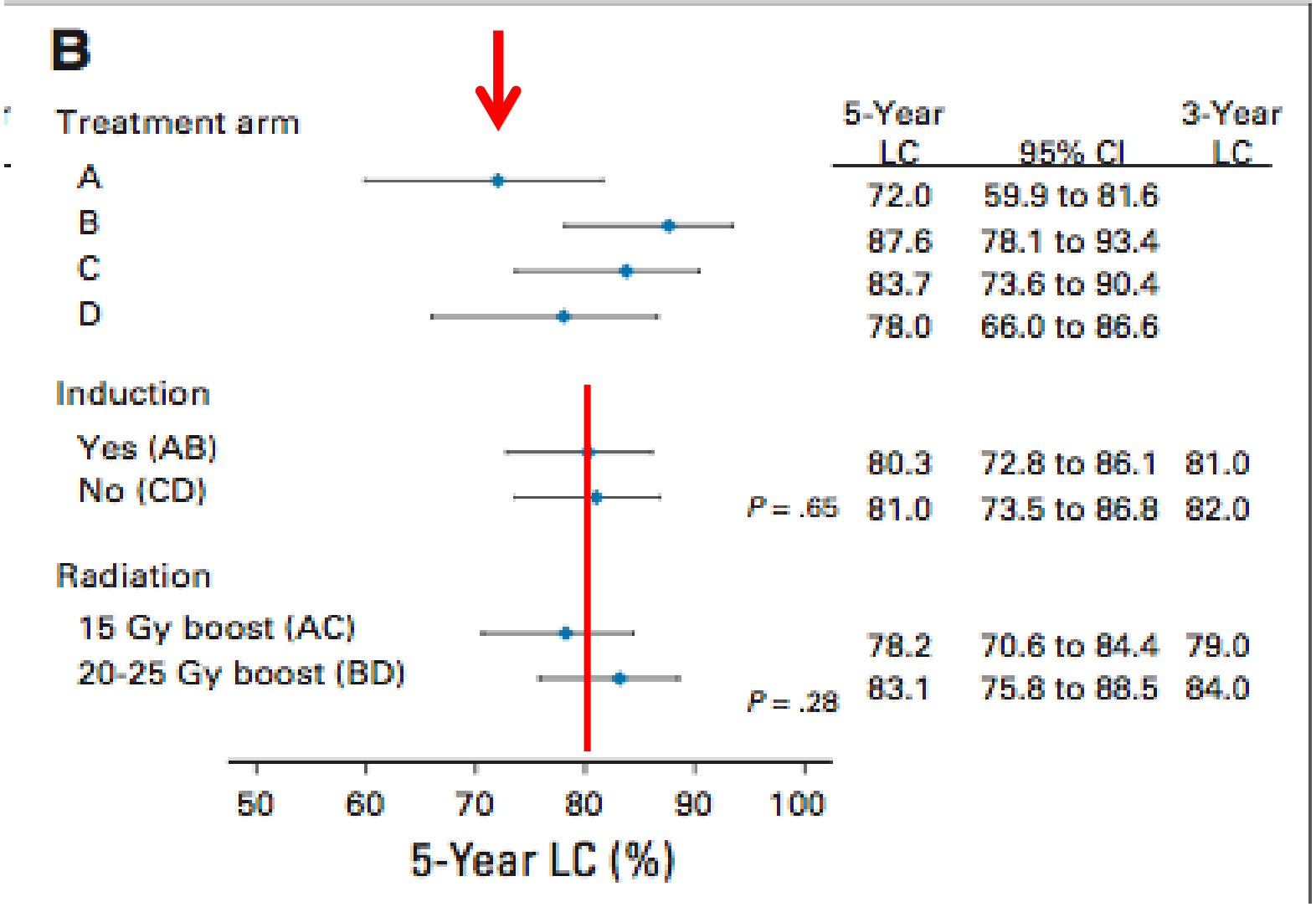
No. at risk							
AC	157	123	103	90	51	52	21
BD	150	127	106	93	73	53	26

ACCORD -03 Peiffert 2012

- Additional dose to compensate for a 3 week gap (0.7Gy per day) may facilitate repopulation further, if induction chemotherapy is added

- Outcomes for the induction (Arm A) appear inferior to standard RT boost alone arm


B
Treatment arm
5-Year LC
95% CI
3-Year LC
A
72.0
59.9 to 81.6
B
87.6
78.1 to 93.4
C
83.7
73.6 to 90.4
D
78.0
66.0 to 86.6
Induction
Yes (AB)
80.3
72.8 to 86.1
81.0
No (CD)
P = .65
81.0
73.5 to 86.8
82.0
Radiation
15 Gy boost (AC)
78.2
70.6 to 84.4
79.0
20-25 Gy boost (BD)
P = .28
83.1
75.8 to 88.5
84.0
50
60
70
80
90
100
5-Year LC (%)

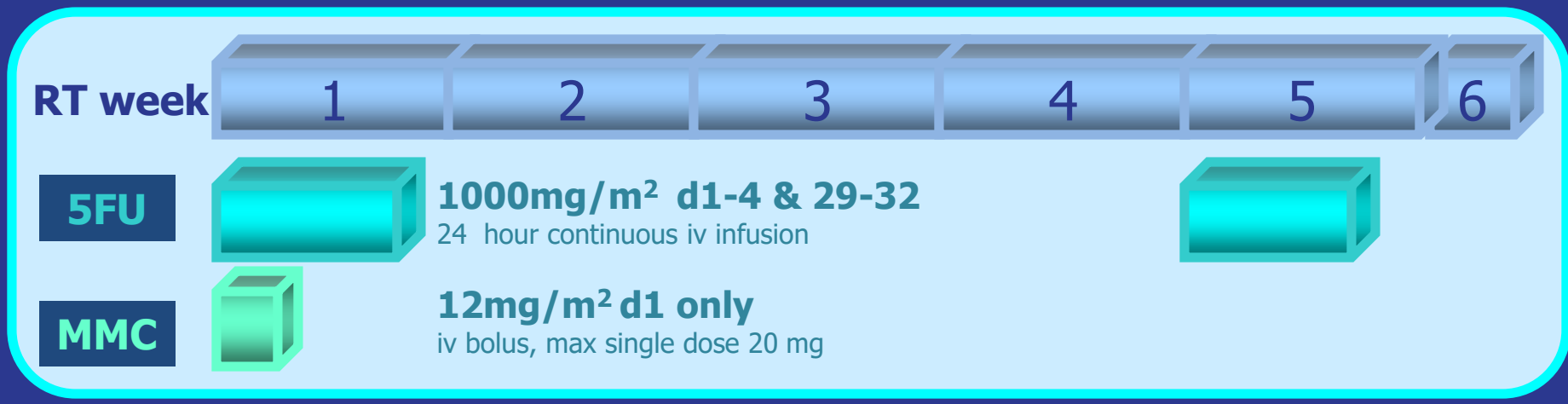

B
Treatment arm
A
B
C
D
Induction
Yes (AB)
No (CD)
Radiation
15 Gy boost (AC)
20-25 Gy boost (BD)
P = .65
P = .28
5-Year LC
95% CI
3-Year LC
72.0 59.9 to 81.6
87.6 78.1 to 93.4
83.7 73.6 to 90.4
78.0 66.0 to 86.6
80.3 72.8 to 86.1 81.0
81.0 73.5 to 86.8 82.0
78.2 70.6 to 84.4 79.0
83.1 75.8 to 88.5 84.0
50
60
70
80
90
100
5-Year LC (%)

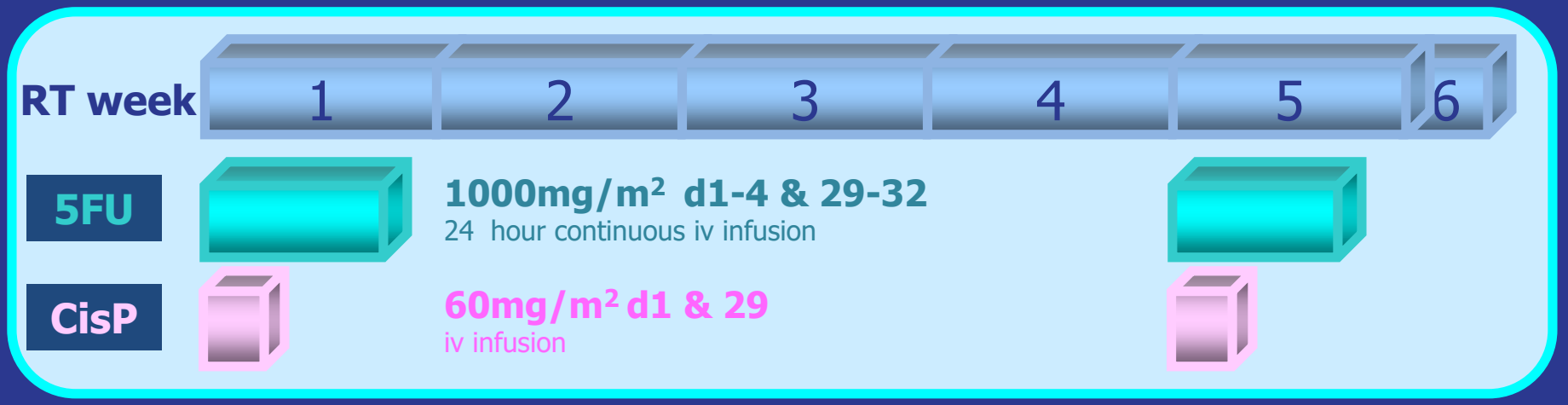
ACT II Trial Design

n=940 - Recruitment 2001-2008

Arm 1	**MMC** 5FU 50.4Gy	
Arm 2	**MMC** 5FU 50.4Gy	→ **CisP 5FU x 2**
Arm 3	**CisP** 5FU 50.4Gy	
Arm 4	**CisP** 5FU 50.4Gy	→ **CisP 5FU x 2**

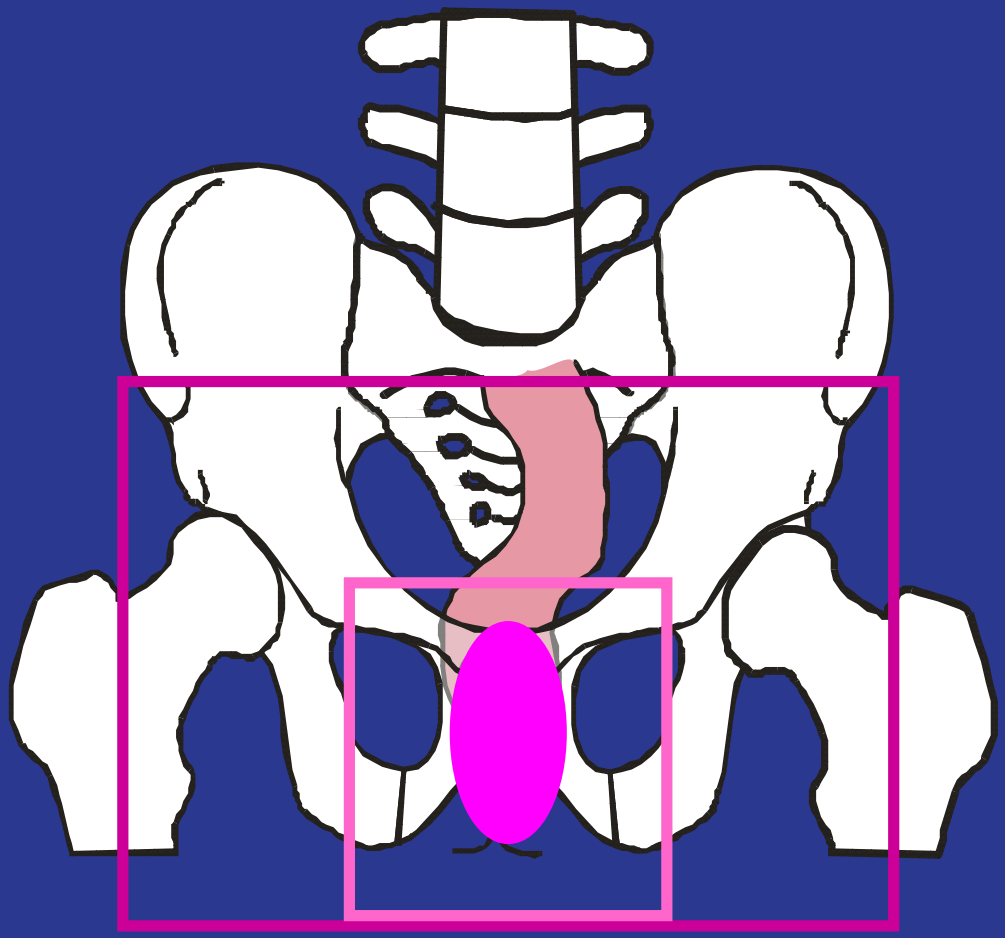
ACT II Chemoradiation Treatment





ACT II Radiotherapy

- 50.4 Gy
- 28 daily fractions
- 5 ½ weeks
- *Two-phase technique*
- *Both phases planned simultaneously*



ACT II CR at 26 weeks

MMC	CisP	Difference (95% CI)	P value
90.5% (391/432)	**89.6%** (386/431)	+0.9% (-4.9 to 3.1)	p =0.64
Progressive disease			
5.1% (22/432)	**3.5%** (13/431)		

ACT II Progression free survival

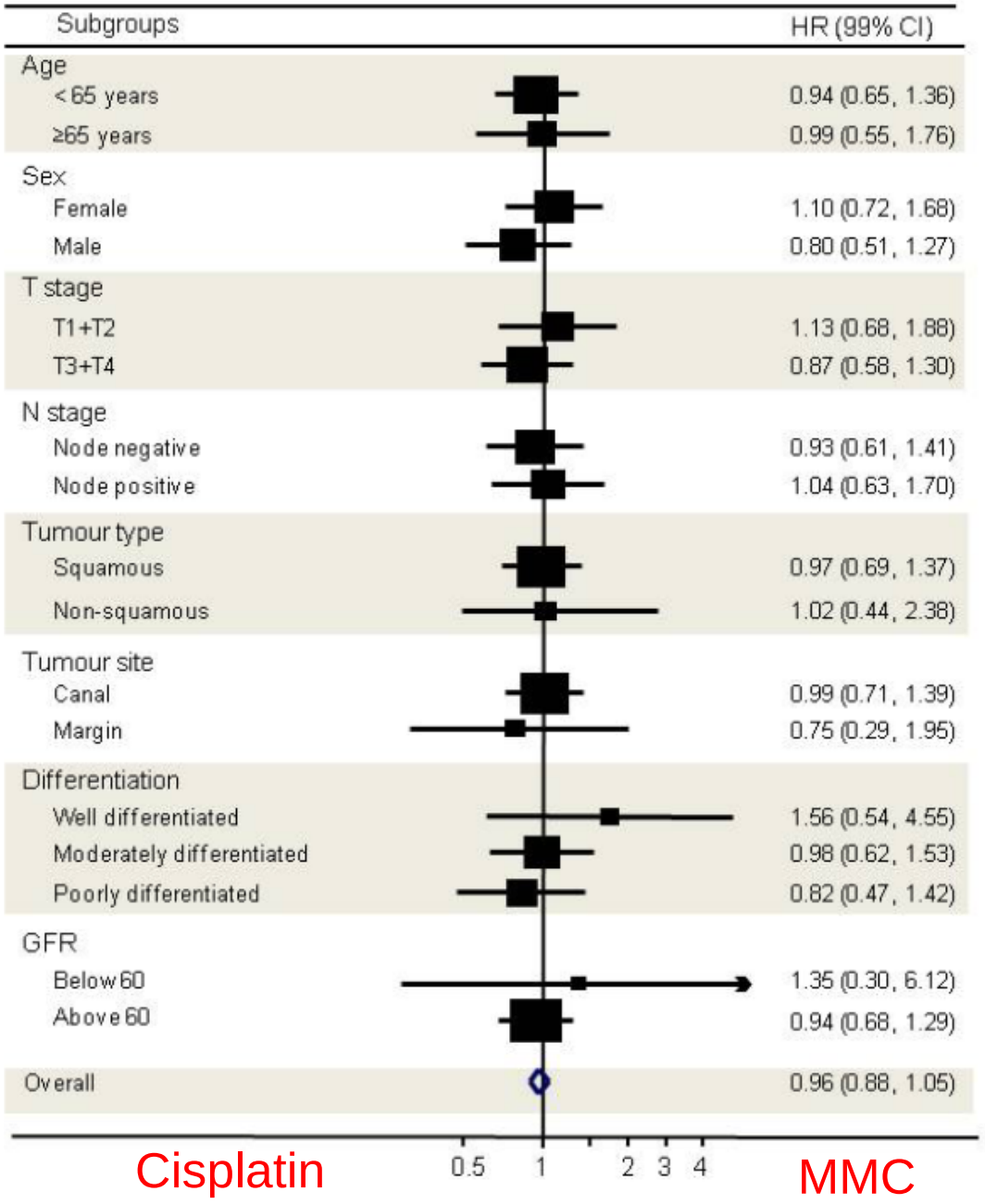
Comparison group	3-year rate, % (95%CI)	5-year rate , % (95% CI)	HR (95% CI), p value
MMC	73 (69 to 77)	69 (65 to 73)	
CisP	74 (69 to 77)	69 (64 to 73)	0.95 (0.75 to 1.19), p= 0.63
No-maint	73 (68 to 77)	69 (64 to 73)	
Maint	74 (69 to 77)	70 (65 to 74)	0.95 (0.75 to 1.21), p=0.70

ACT II Progression free survival

	According to T stage	3-year rate, % (95% CI)	5-year rate , % (95% CI)
	T1/T2	81 (78 to 85)	77 (73 to 81)
	T3/T4	64 (59 to 68)	60 (55 to 64)
	According to N stage		
	Negative	76 (72 to 79)	72 (68 to 76)
	Positive	68 (62 to 73)	62 (56 to 68)

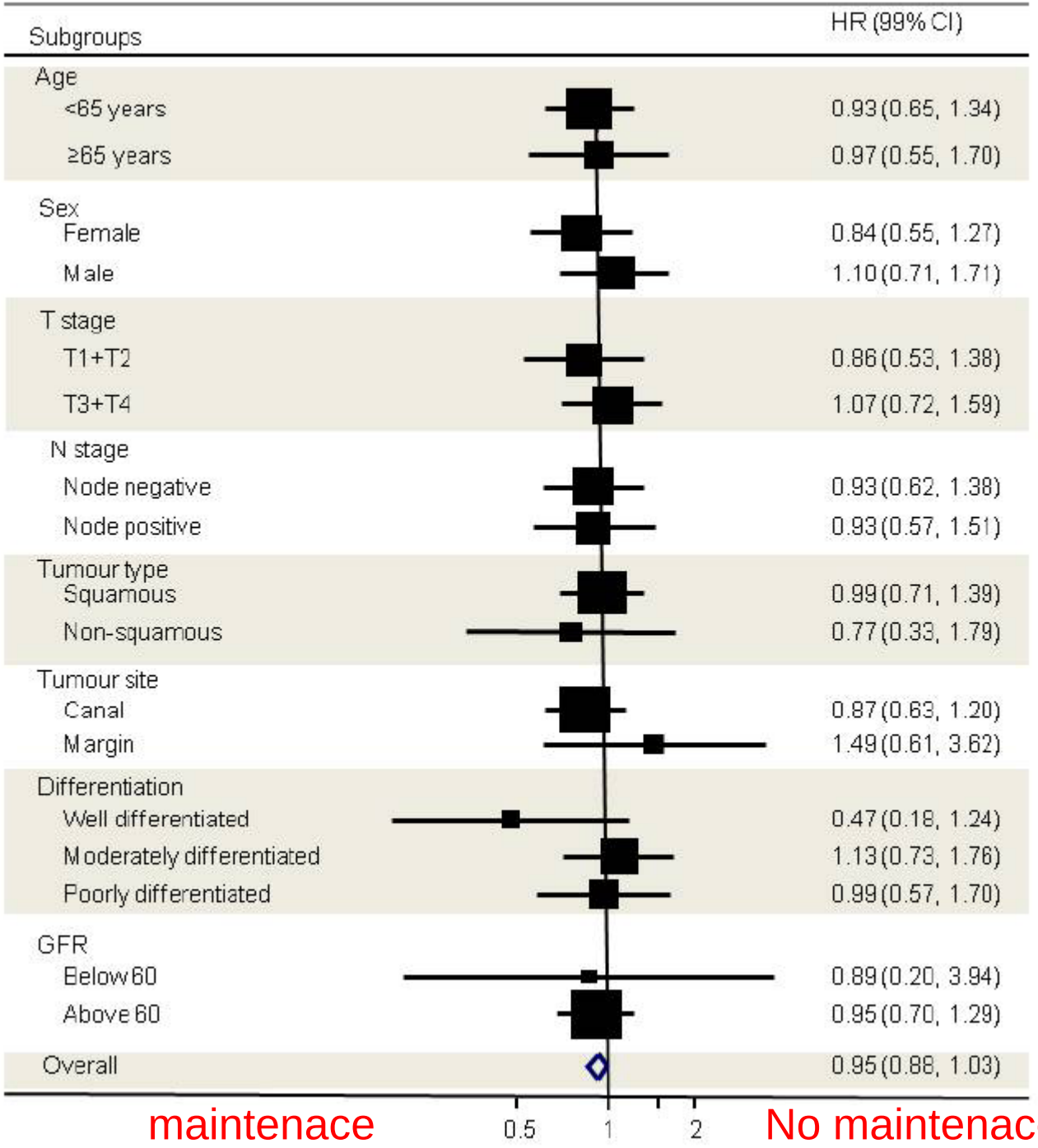
ACT II Overall survival

Comparison group	3-year rate, % (95%CI)	5-year rate , % (95% CI)	HR (95% CI), p value
MMC	84 (80 to 87)	79 (74 to 82)	
CisP	84 (80 to 87)	77 (73 to 81)	1.05 (0.80to 1.38), p=0.70
No-maint	85 (81 to 88)	79 (75 to 83)	
Maint	83 (79 to 86)	76 (72 to 80)	1.07 (0.81 to 1.41). p=0.65



Online Figure 5. Forest plot for progression-free survival: CisP vs. MMC (left)

Forrest Plot
Cisplatin
versus MMC



Forrest Plot maintenace versus no maintenance

Conclusions from ACT II

- MMC/cisplatin no difference
- Maintenance chemo no benefit
- Majority of survivors with morbidity

Doses of Mitomycin/Cisplatin

Trial	Day 1	Day 29	Total
ACT I	MMC 12mg/m2	none	MMC 12mg/m2
EORTC	MMC 12mg/m2	none	MMC 12mg/m2
RTOG 8704	MMC 10mg/m2	MMC 10mg/m2	MMC 20mg/m2
RTOG 9811	MMC 10mg/m2	MMC 10mg/m2	MMC 20mg/m2
	Cisp 75mg/m2	Cisp75mg/m2	Cisp 150mg/m2
ACCORD-03	Cisp 80mg/m2	Cisp 80mg/m2	Cisp 160mg/m2
ACT II	MMC 12mg/m2 Max 20mg	none	MMC 12mg/m2
	Cisp 60mg/m2	Cisp 60mg/m2	Cisp 120mg/m2

MMC - Comparison 1 versus 2 doses

no difference

- PFS (HR 0.85, 95% CI 0.37–1.92),
- CFS (HR 0.91, 95% CI 0.31–2.67) between the MMC1 and MMC2 groups.
- Acute grade ⩾2 toxicities were worse in the MMC2 group.
- 3 treatment-related deaths, all in the MMC2 group

- **White et al Chemoradiotherapy for squamous cell carcinoma of the anal canal: Comparison of one versus two cycles mitomycin-C. Radiother Oncol 2015;117 (2):240–245**

Question 1

- Do you need 2 doses of MMC?
- ie 10mg/m2 X 2
- Or 12mg/m2 X 1 (max 20mg)

Question 2

60 mg/m2 X **2**

compared with **100 mg/m2**
used commonly in head and neck cancer
(Where it is important to ensure 3rd dose is applied)

Other options for concurrent CRT

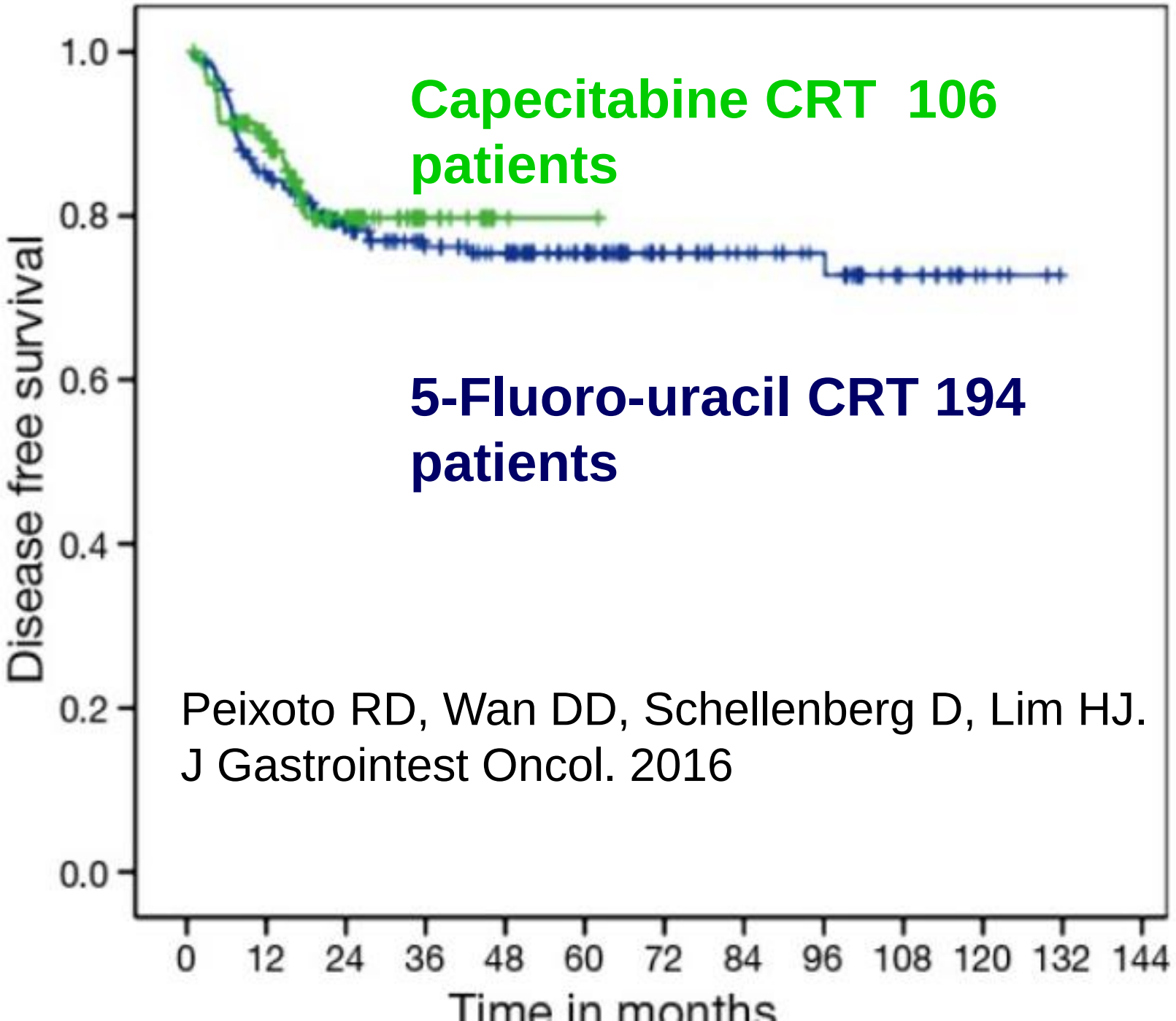
- Cisplatin versus MMC
- 5FU/MMC versus Cisplatin/MMC (EORTC)
- 2 drugs versus 3 drugs (ACT II pilot)

- Carboplatin/taxol

- EGFR inhibition

Capecitabine integrated into CRT in anal cancer

Study	RT	MMC	Capecitabine
Glynne-Jones 2008	50.4 Gy in 28 fractions in 2 phases	Single dose of MMC 12mg/m2 max 20mg	825 mg/m^2 b.i.d on radiation days
Deenen 2013	59.4 Gy in 33 fractions with SIB-IMRT	Single dose of MMC 10mg/m2 max 15mg	825 mg/m^2 b.i.d on radiation days
Goodman 2014 Retrospective	50-54 Gy	Mitomycin 10 mg/m2 day 1,29	825 mg/m^2 b.i.d on radiation days
Oliveira 2016 phase II	54 -59Gy	mitomycin 15 mg/m2 IV day 1	825 mg/m^2 b.i.d on radiation days
Peixoto 2016	50-54 Gy	Mitomycin 10 mg/m2 day 1,29	825 mg/m^2 b.i.d on radiation days



Peixoto RD, Wan DD, Schellenberg D, Lim HJ. J Gastrointest Oncol. 2016

Trials with Panitumumab/RT in anal cancer

Trial	N of patients	IMRT	Regimen	Toxicity	Efficacy
Feliu et al, ASCO 2014 GEMCAD 09-02	**58**	**No** **45 Gy** + boost of 10-15 Gy	**5-FU/MMC +RT + panitumumab**	**High** 33/36 (92%) G3/4 AE	At 24 weeks 55% had CR

Study	Stage I/II/III-IV %	2 Year LocRegional Failure Rate	2 Year Overall Survival
RTOG 9811 control: MMC + 5-FU	47/19/31	25 %	91%
RTOG 9811*: 5-FU + Cis	48/17/31	28 %	85%
ECOG 3205	**11/50/39**	**13%**	**93 %**
AMC 045	**24/42/34**	**7%**	**89 %**

Trials with Cetuximab in anal cancer

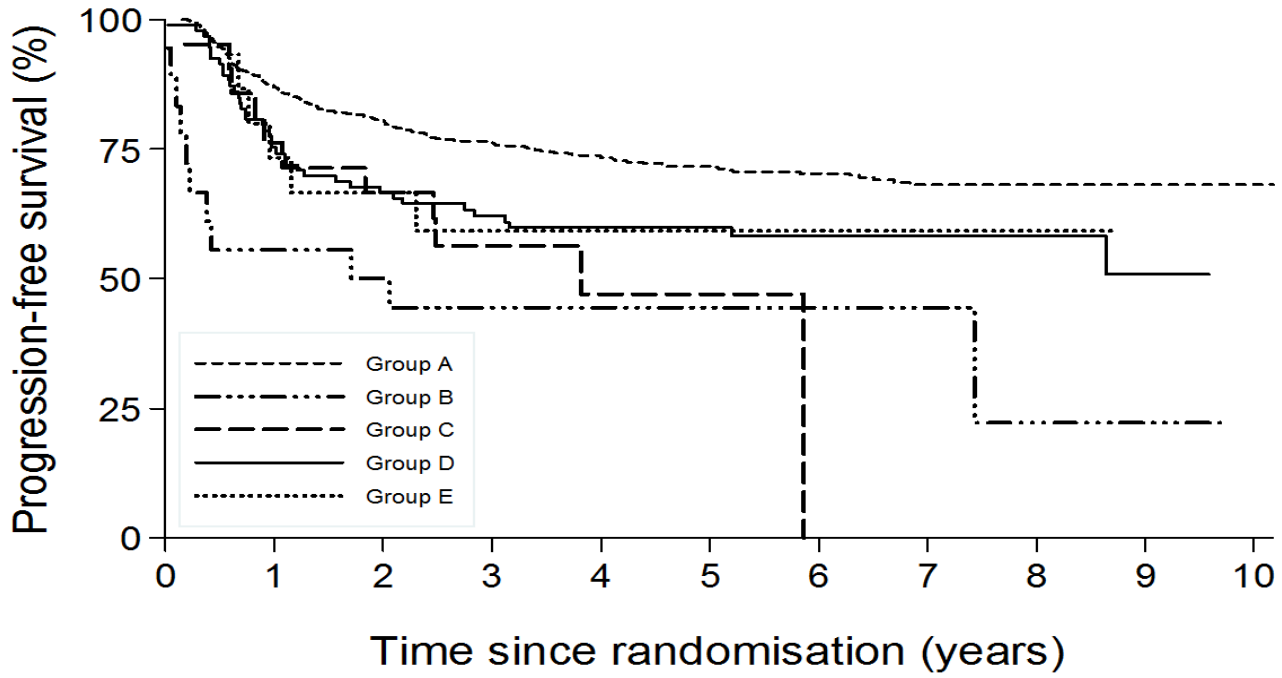
Trial	N of patients	IMRT	Regimen	Toxicity	Efficacy
ECOG 3205	**61**	**some**	**5-FU/CisP +RT + cetuximab**	**32% G4 5% G5**	**The 3-year LRF 23%**
AMC045 HIV+	**45**	**some**	**NACT + 5-FU/CisP +RT + cetuximab**	**26% G4 4% G5**	**LRF 16%**

Garg MK, et al., J Clin Oncol. 2017 Jan 9: [Epub ahead of print]
Garg MK, et al., J Clin Oncol 34, 2016 (suppl; abstr 3522)

Impact of RT Compliance on PFS n=933

Group	Total events	3 year PFS	Treatment adjusted HR (95% CI)	P value
A. 50.4Gy per protocol	221/786 (28%)	76%	1.00	
B. ≤ 40Gy	11/18 (61%)	44%	3.71 (2.01-6.82)	
C. >40–48.6Gy in 23-27F	11/21 (52%)	56%	2.26 (1.23-4.14)	0.0001
D. 50.4Gy in > 42 days	39/93 (42%)	62%	1.62 (1.15-2.28)	
E. >52Gy compensated	6/15 (40%)	59%	1.60 (0.7-3.61)	

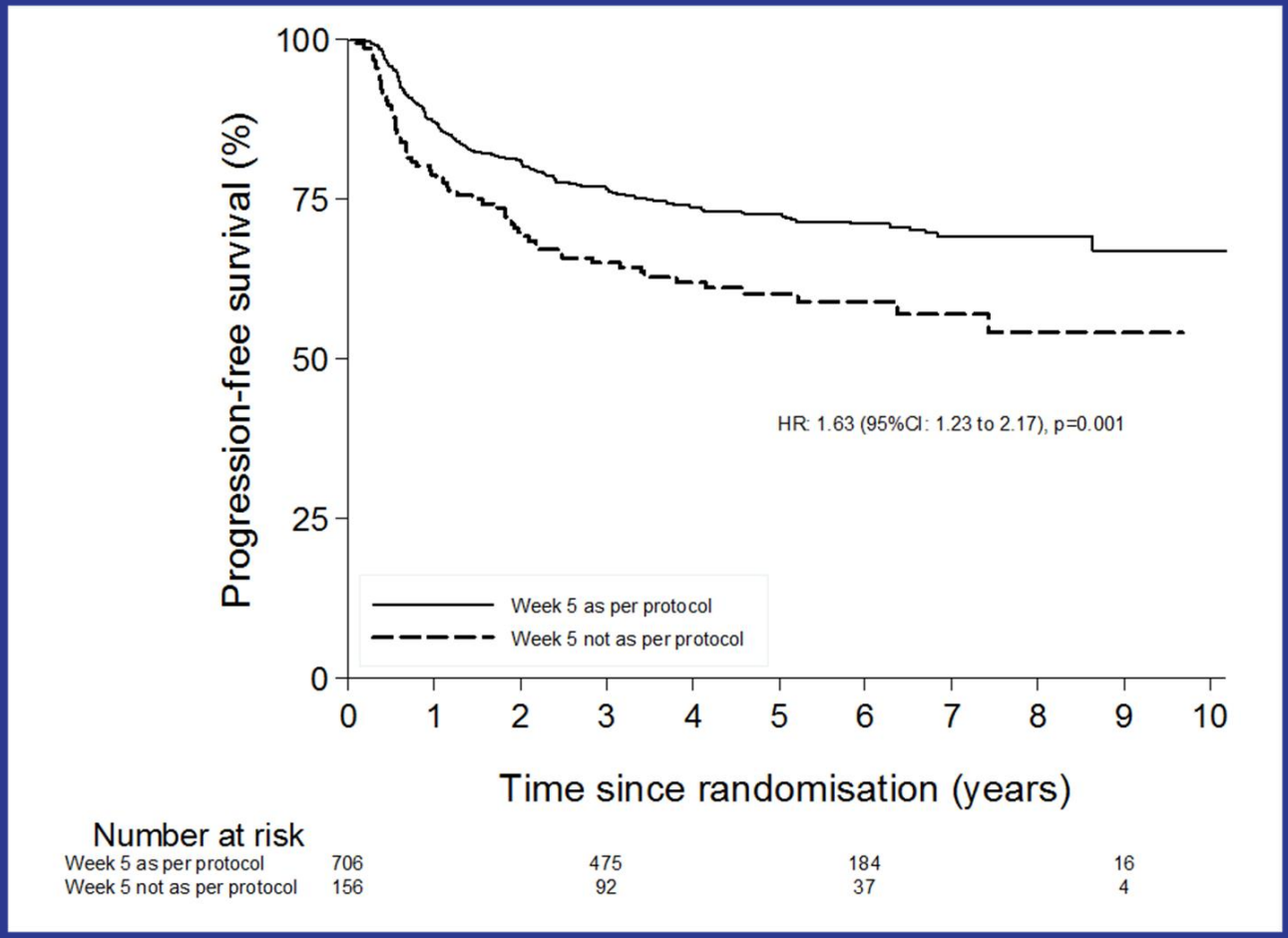
Impact of RT Compliance on PFS n=933



Number at risk

Group A	786	528	205	17
Group B	18	5	3	1
Group C	21	9	0	0
Group D	93	54	24	3
Group E	15	7	3	0

Impact of CT Compliance on PFS n=862



OXFORD JOURNALS Annals of Oncology

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Published online 2017 Feb 7. doi: 10.1093/annonc/mdx029

Safety and antitumor activity of the anti-PD-1 antibody pembrolizumab in patients with recurrent carcinoma of the anal canal

P. A. Ott,[✉1] S. A. Piha-Paul,[2] P. Munster,[3] M. J. Pishvaian,[4] E. M. J. van Brummelen,[5] R. B. Cohen,[6] C. Gomez-Roca,[7] S. Ejadi,[8] M. Stein,[9] E. Chan,[10] M. Simonelli,[11] A. Morosky,[12] S. Saraf,[12] K. Emancipator,[12] M. Koshiji,[12] and J. Bennouna[13]

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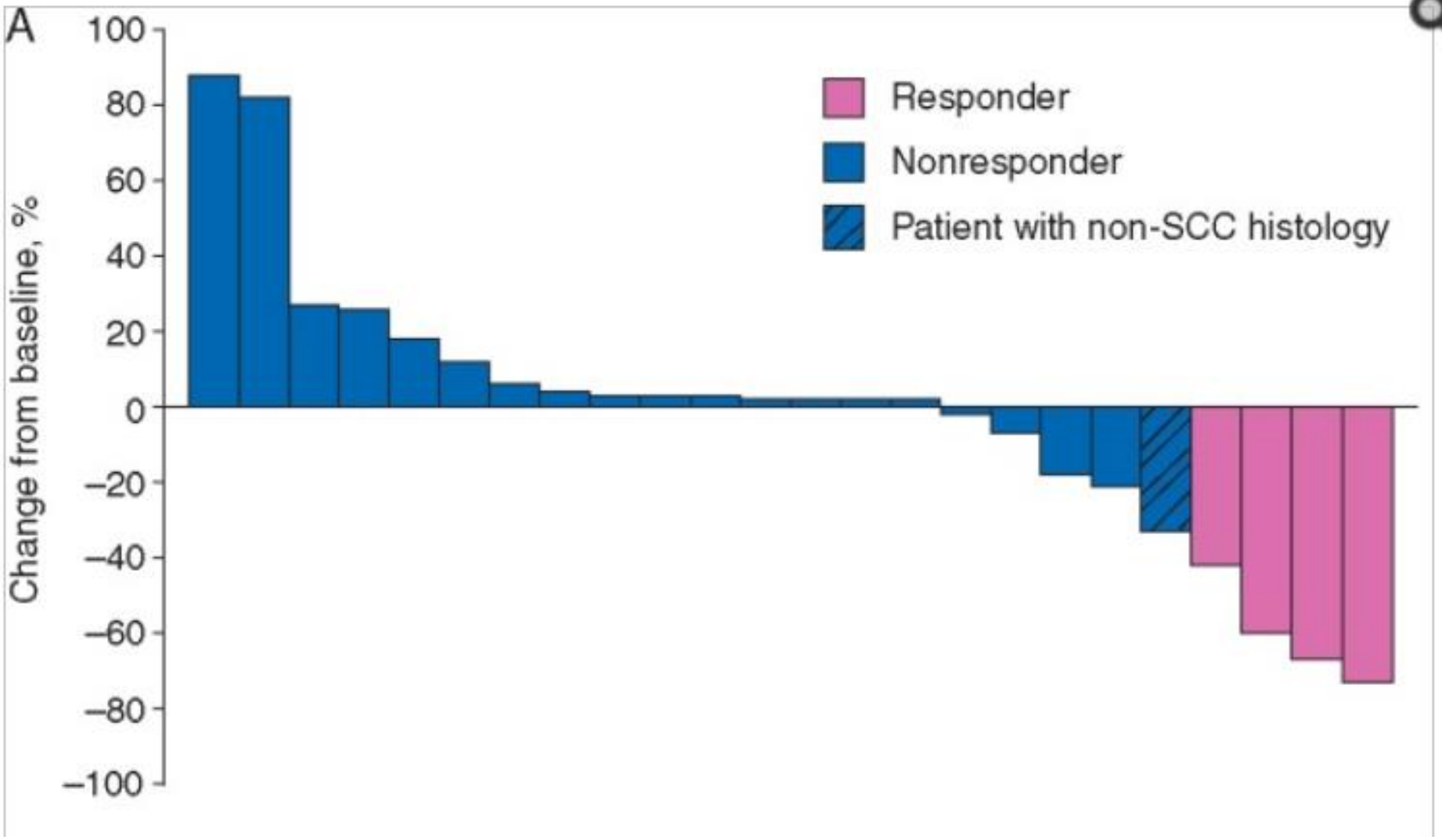
Abstract

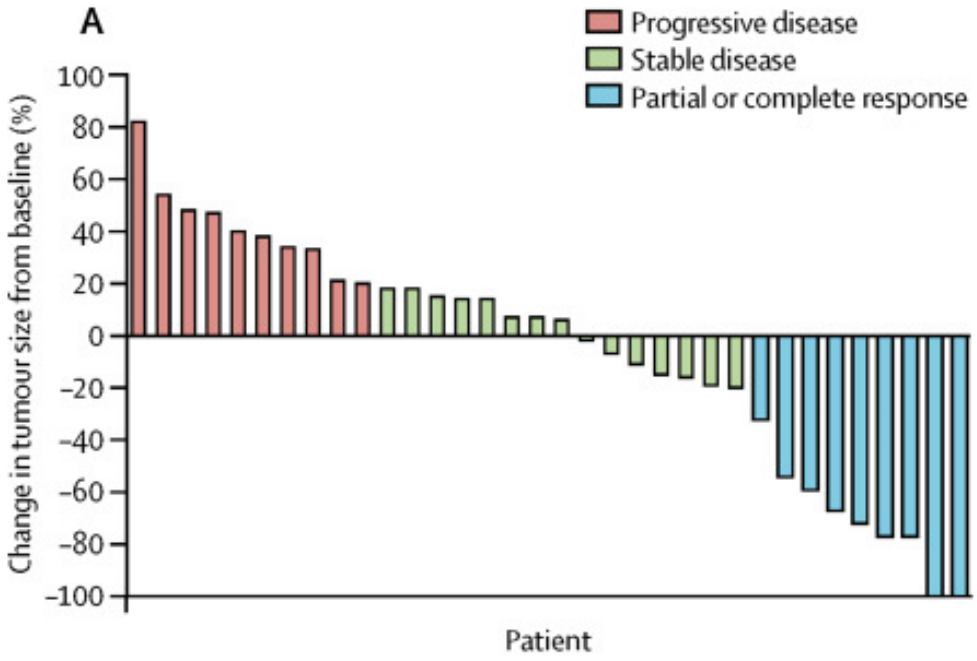
Go to:

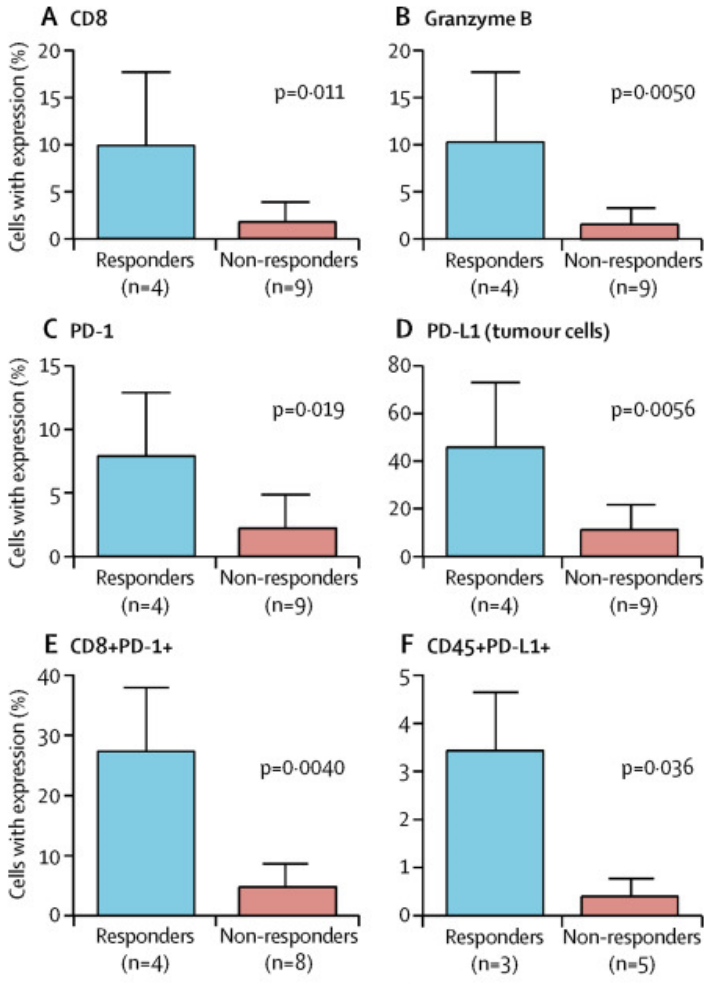
Background

Safety and efficacy of pembrolizumab, a humanized programmed death 1 monoclonal antibody, was assessed in KEYNOTE-028, a multicohort, phase Ib trial for patients with programmed death ligand 1 (PD-L1)-positive advanced solid tumors. We report results for the cohort of patients with advanced anal carcinoma.


A
100
80
60
40
20
0
–20
–40
–60
–80
–100
Change from baseline, %
Responder
Nonresponder
Patient with non-SCC histology

Nivolumab for previously treated unresectable metastatic anal cancer



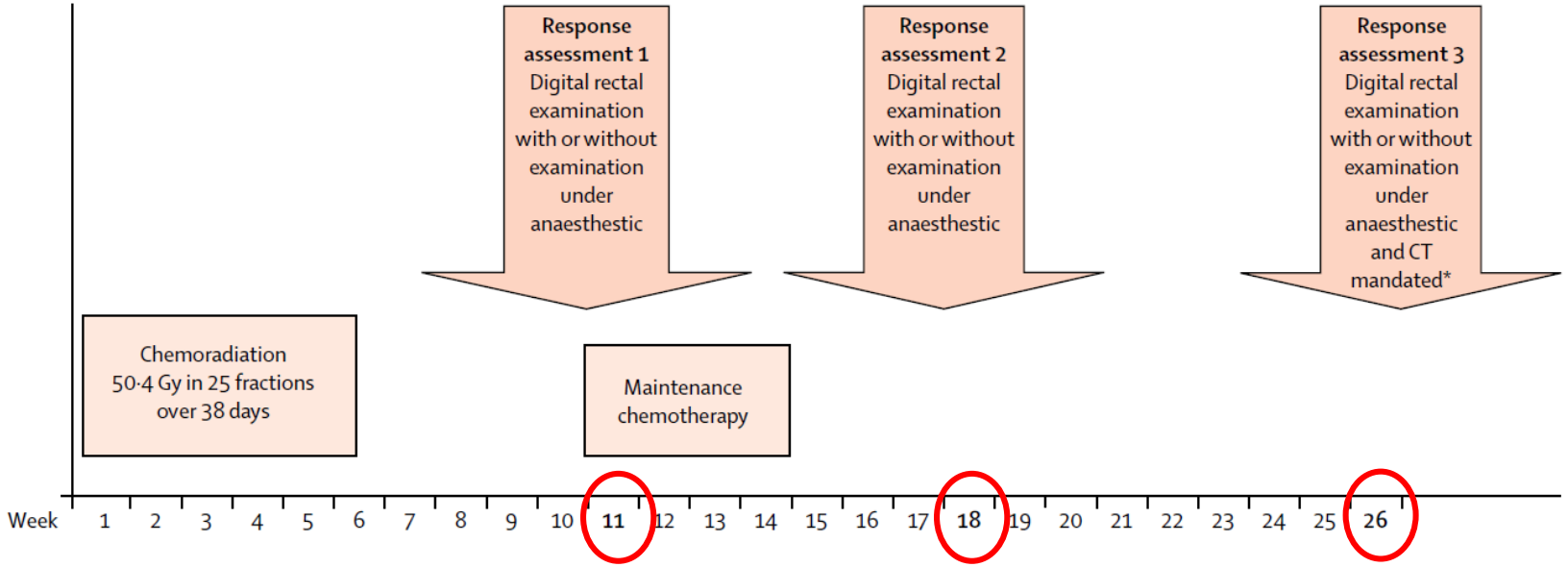


Higher immunogenicity → Better response

ACT II –how long is it safe to wait ? Conclusions

- Excellent CR rate at 6 months - 83% v 84%
- 151/209 (72%) patients not in cCR at Assessment 1 (11 weeks) achieved cCR at 18 or 26 weeks.
- Assessment safe at 26 weeks

Best time to assess complete clinical response (cCR) after CRT in Anal-Ca: ACTII data



- n=691 attended all three assessments
- cCR: 64%, 80% and 85% at assessments 1, 2 and 3, respectively
- 72%: no cCR at assessment 1; cCR by assessment 3
- 5-year OS (at assessment 3): cCR=87%; non-cCR=48%

- **Can the classical 5Rs of Radiobiology explain the delayed tumor response over a period of weeks?**

ADXS11-001 immunotherapy

- live attenuated Listeria monocytogenes (Lm)
- bioengineered to secrete a HPV-16-E7 fusion protein targeting HPV transformed cells.

- Anal cancer cells infected with HPV have the tumour associated antigen HPV E7.

- So ADXS11-001 causes antigen presenting cells to be stimulated to facilitate immune cells to attach to cancer cells expressing HPV E7

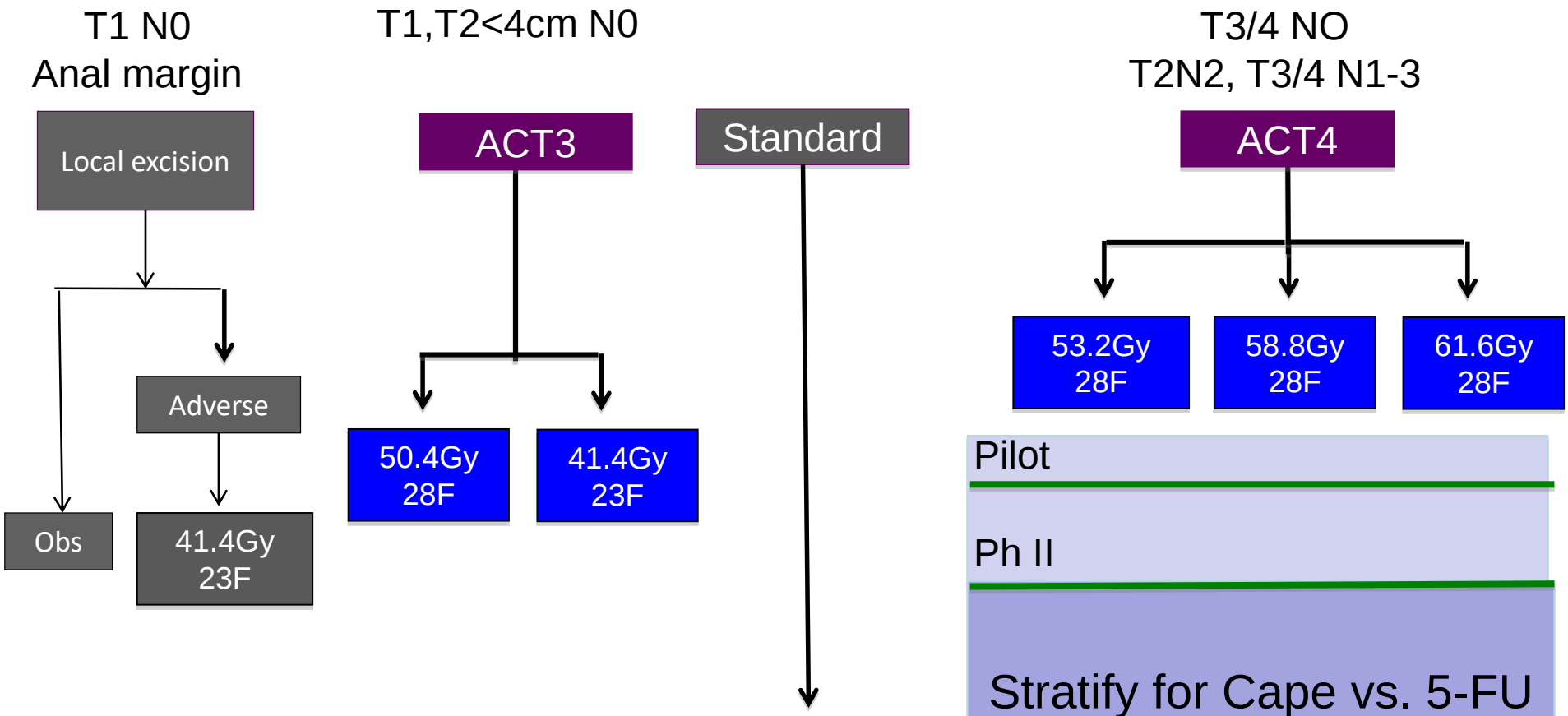
IRCI anal cancer metastatic trial

InterAACT

An Open Label Phase II **Inter**national Multicentre Randomized **A**dvanced **A**nal **C**ancer **T**rial Comparing Cisplatin plus 5-fluorouracil (5-FU) versus Carboplatin plus Weekly Paclitaxel in Patients with Relapsed or Metastatic Disease

Clinical Protocol Version 1.0 Dated 01.02.2013

PLATO – PERSONALISING RADIOTHERAPY DOSE FOR ANAL CANCER



Courtesy of David Sebag-Montefiore

Phase II trial

Phase II/III trial

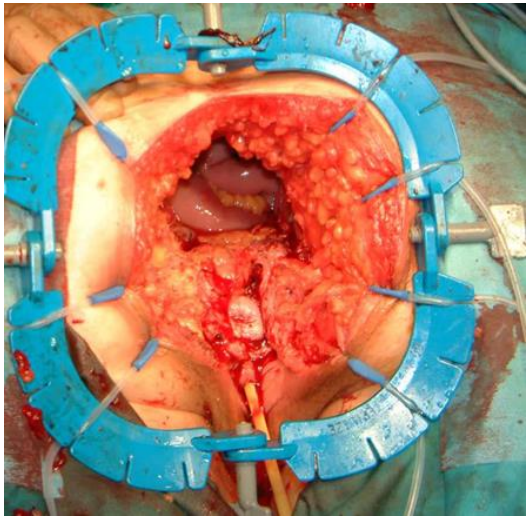
Conclusions

- Ideally patients should be treated in specialist units
- Imaging with CT and MRI ? PET
- Advice re smoking
- Limited local excisions
- CRT with 5FU and MMC
- IMRT better for toxicity and compliance
- RT dose open
- Can assess CCR up to 6 months
- Need to explore immunotherapy
- Surveillance an open question


Thank you for listening

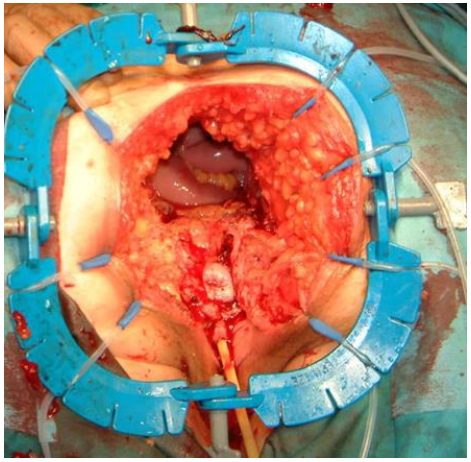
Surgical Salvage

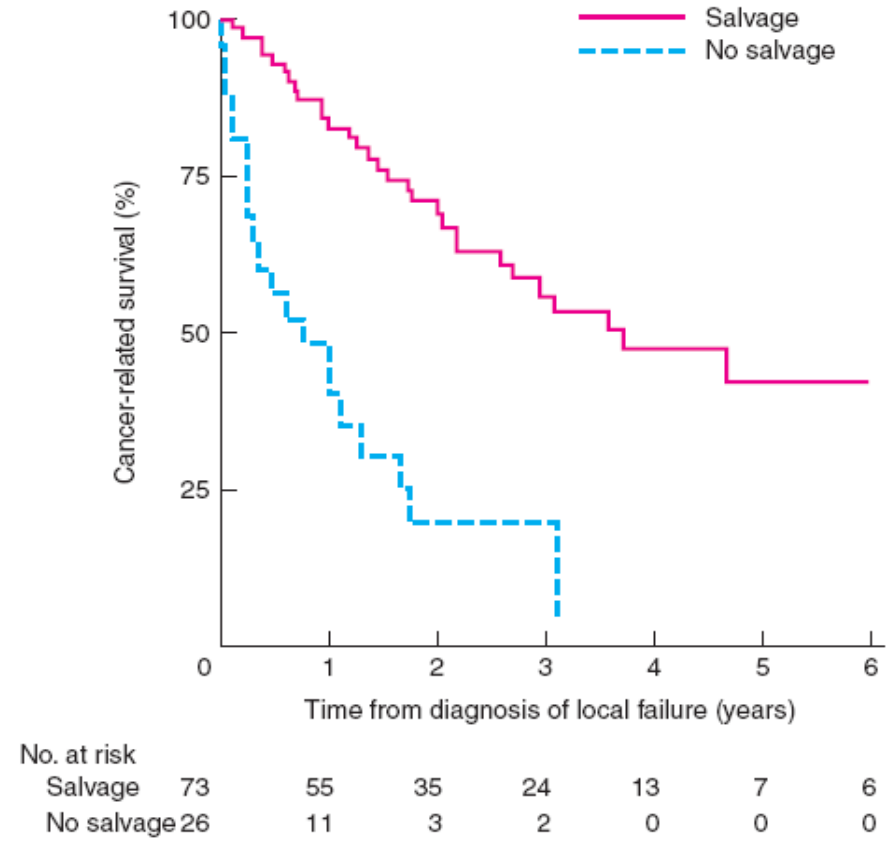
- Not the same as APER in rectal cancer
- Often late effects of radiotherapy
- En bloc resection of adjacent viscera more common
- Need for reconstruction
- R0 important for survival



Surgical Salvage: Prognosis

- Post salvage
  - 40-60% at 5years
- No salvage
  - 5% at 3 years





Renehan et al. BJS 2005

Prognosis

- Post salvage
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- No salvage
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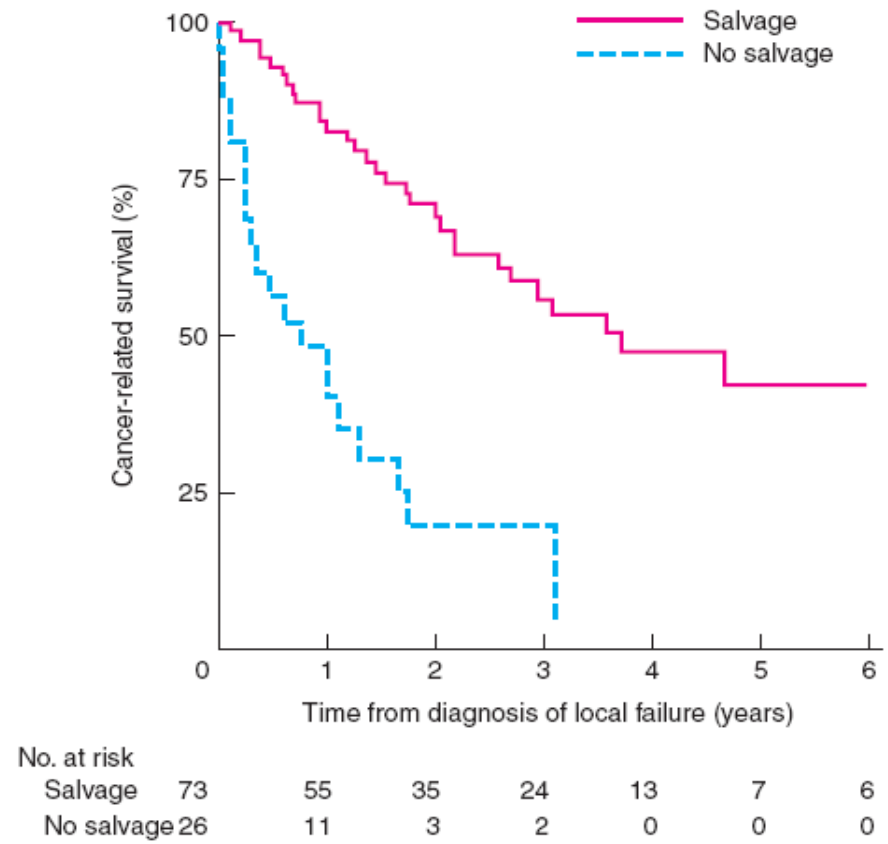

Renehan et al. BJS 2005

Summary of IMRT

- Dosimetric studies and clinical trials have shown reduced dosing and toxicity to normal structures with the use of IMRT.
- No decreases in treatment effectiveness or local control rates have been detected.
- Limited sample sizes and duration of follow-up minimize the ability to detect small variations in local control rates.

Comparison of trials (Not Accord – Brachtherapy)

Factor	RTOG 8704 RT + FU + MMC (n = 146)	RTOG 9811 RT + FU + MMC (n = 324)	Combined RTOG 8704 9811 RT + FU + MMC (n = 472)	ACT II RT + FU + MMC (n = 472)
Median age	62 (29-85)	55 (25-83)	57 (25-85)	58 (25 – 81)
RT OTT in days	Not stated	Median 49 days (Kachnic)	Median 45 days (range 1-158)	Median 38 days (range 5-54)
Median Total primary central axis dose in Gy	Between 41.76 and 47.25Gy	55Gy (range 9- 69Gy)	50.4Gy (range 0 - 79.4Gy)	50.4 Gy (range 9 – 54 Gy)
RT intensity	Not possible to calculate	1.12	1.15 (Range 0-2.25)	1.29

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COMBINED DRUG-RADIATION TREATMENT: BIOLOGICAL BASIS APPLICATIONS AND PERSPECTIVES

15-18 June, 2017
Brussels, Belgium

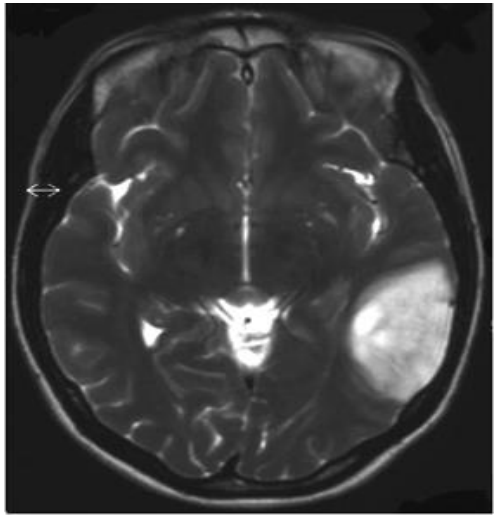
BRAIN

Mario Levis
Radiation Oncologist
University of Torino, Italy

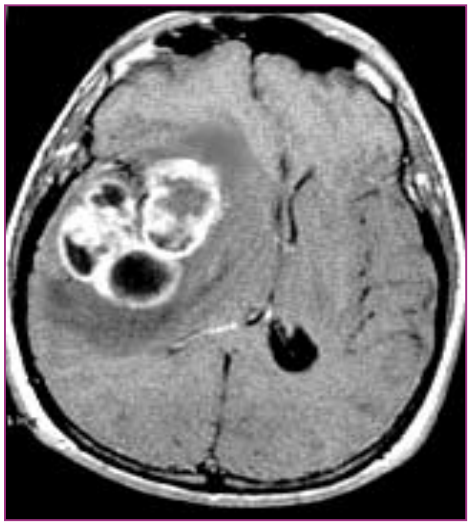
ESTRO School

Combined modality treatment in brain tumors

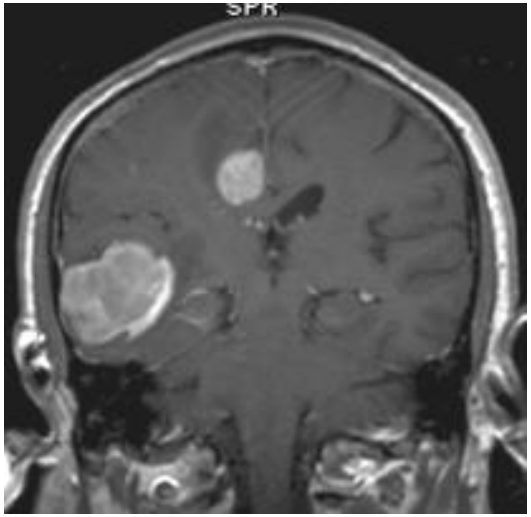
Low grade gliomas



High grade gliomas



PCNSL



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LGG: Introduction and Background

- LGG are hetrogeneous
- Surgery plays a key role
- RT improves PFS, but total dose is not clearly defined
- Target RT volumes are not easy
- Chemotherapy may be useful in high-risk patients
- Biology has changed our vision

LGG: classical prognostic factors

Prognostic Factors for Survival in Adult Patients With Cerebral Low-Grade Glioma

Pignatti F. et al. JCO 2002;20

Prognostic factors for OS: multivariate model

Variable		HR	p value
❑ **Age**	≥40 vs <40 y	1.26	0.0077
❑ **Pre-surgical Neurologic deficit**	Yes vs No	1.35	0.0013
❑ **Largest diameter**	≥6 cm vs <6 cm	1.39	0.0003
❑ **Histology subtype**	Astro vs Oligo	1.30	0.0050
❑ **Tumor crossing the midline**	Yes vs No	1.37	0.0005

New validated prognostic models and prognostic calculators in patients with low-grade gliomas diagnosed by central pathology review: a pooled analysis of EORTC/RTOG/NCCTG phase III clinical trials

Gorlia T. et al. Neuro-Oncol 2013;15

Prognostic factors for OS: multivariate model

Variable		HR	p value
❑ **Neurologic deficit**	Worse baseline neurologic status	1.5	<0.0001
❑ **Largest diameter**	<5 cm vs ≥5 cm	1.7	<0.0001
❑ **Histology subtype**	Astro vs Oligo	1.9	<0.0001
❑ **Shorter time since first symptoms**	>30 weeks vs <30 weeks	0.67 (only EORTC)	0.009

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LGG Definition of «High Risk patient»

- Age >40 years
- Radiologically proven tumor progression
- New or worsening symptoms
- Tumor diameter > 6 cm
- Tumor crossing midline

- Age<40, with partial resection biopsy (by surgeon)
- Age>40

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CLINICAL CASE #1 - LGG

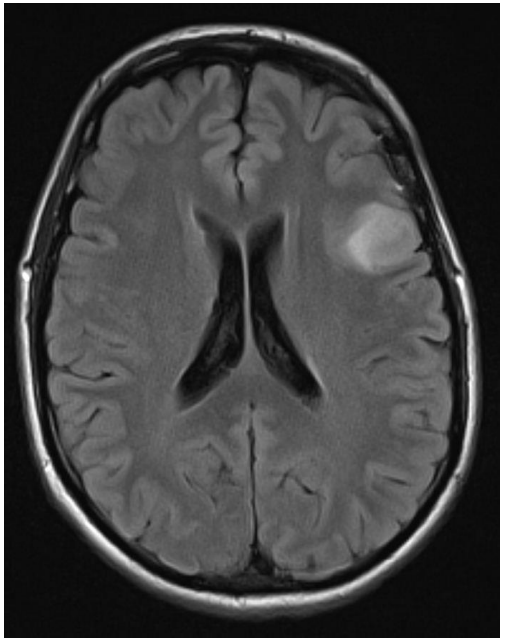
- Male patient
- 43 years old
- Seizures for 2 months

- Craniotomy – frontal debulking

- Histology: GII glioma, NOS

- KPS after surgery: 90

- MRI 30 days after surgery: complete resection



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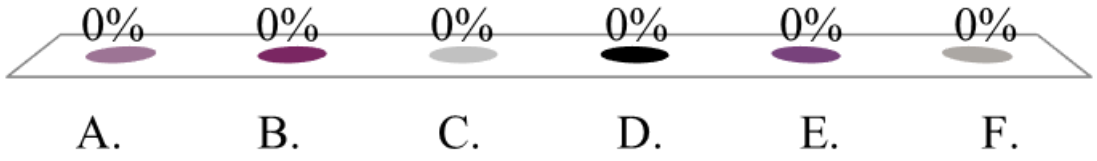
What to do now?

A. Watchful waiting
B. Adjuvant RT (45 Gy)
C. Adjuvant RT (50-54 Gy)
D. Adjuvant RT (50-54 Gy) followed by PCV chemotherapy
E. TMZ chemotherapy alone
F. Require further histopathological and molecular details



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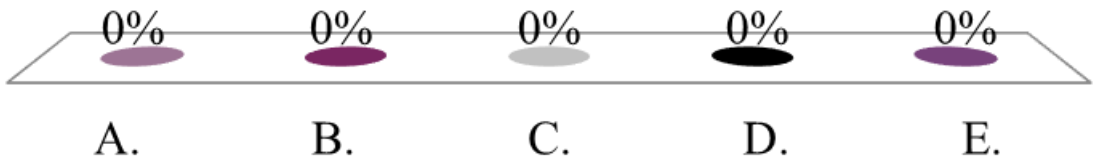
Your pathologist accept to revise the case… What are we looking for?

A. Definition of the histology (Astrocytoma vs Oligodendroglioma)
B. MGMT methylation
C. 1p/19q codeletion status
D. IDH1 mutation
E. Definition of the histology + 1p/19q codeletion + IDH1 mutation



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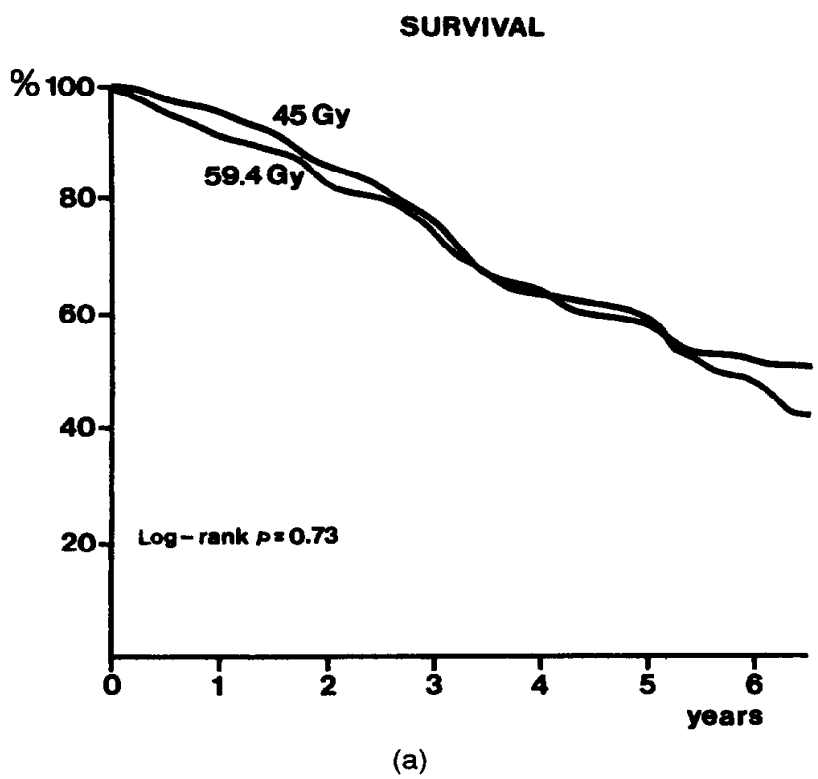
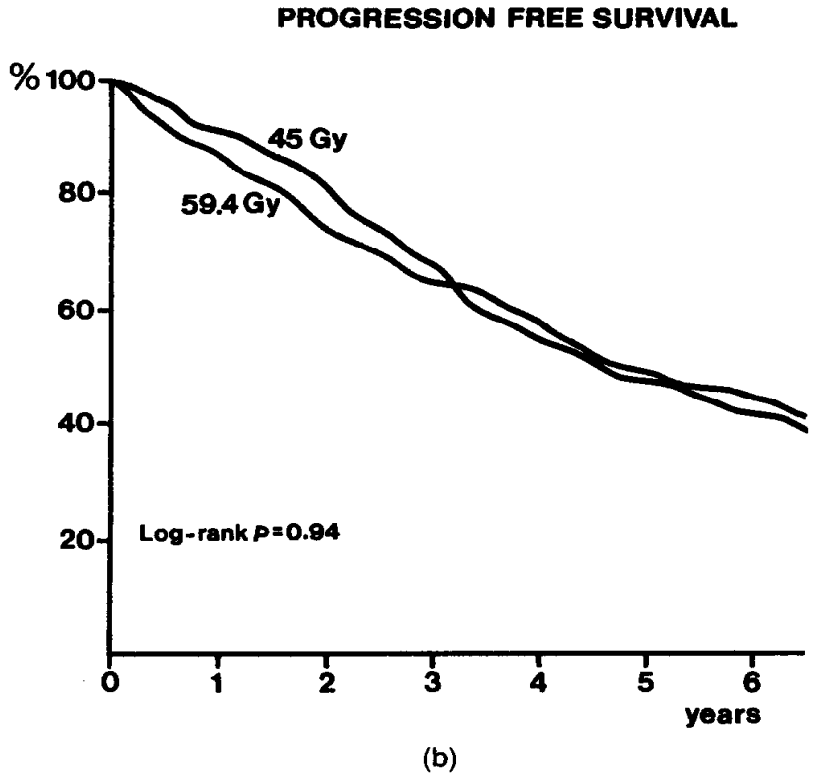
A RANDOMIZED TRIAL ON DOSE–RESPONSE IN RADIATION THERAPY OF LOW-GRADE CEREBRAL GLIOMA: EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT OF CANCER (EORTC) STUDY 22844

RT dose: EORTC 22844





No evidence for a dose-response relationship in LGG

Karim AB at al IJROBP 1996;36

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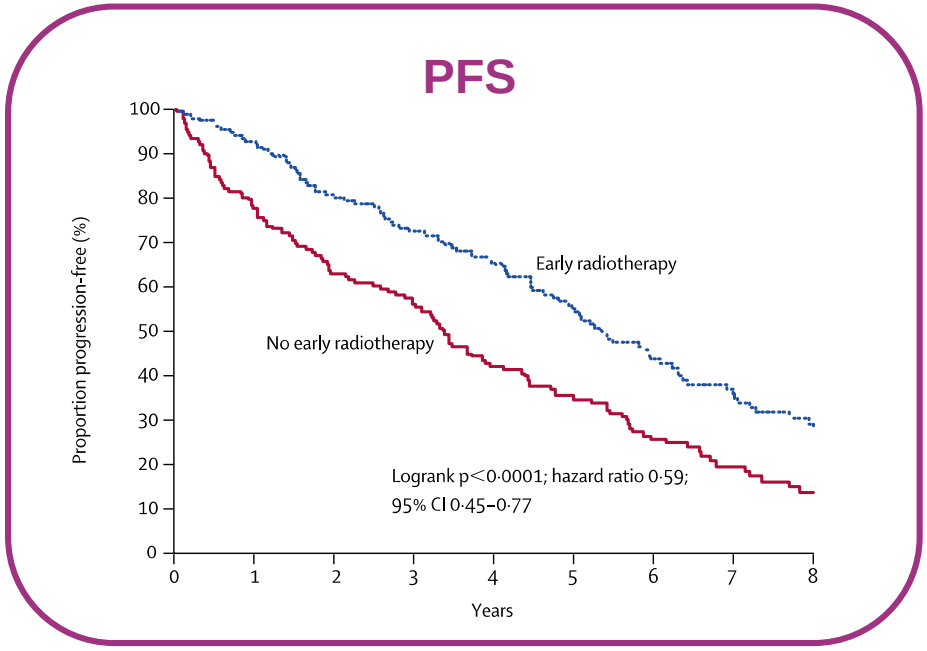
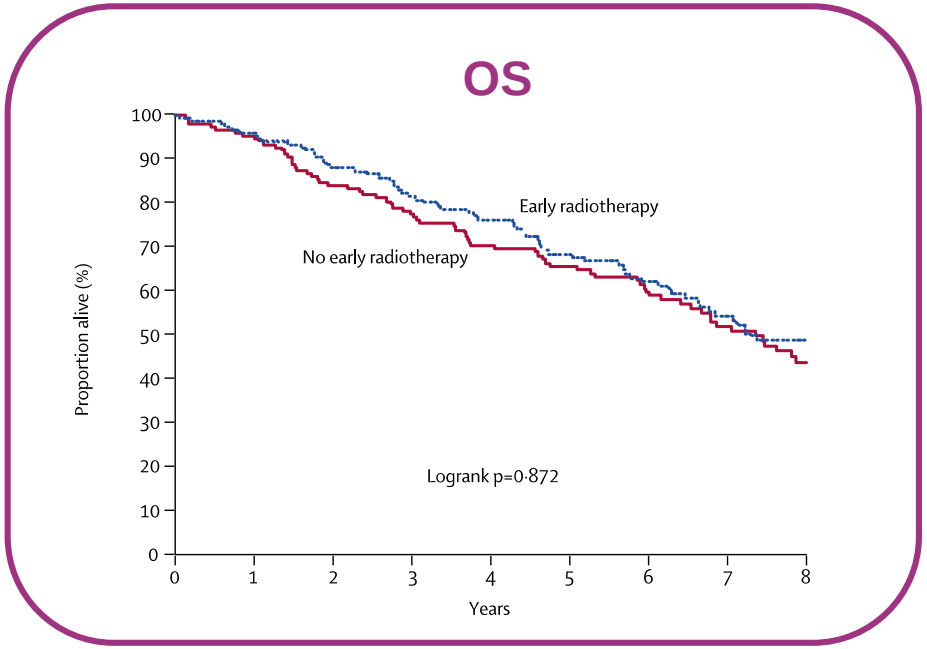
Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC22845 randomised trial

RT timing: EORTC 22845





314 pts with LGG	mOS	5y-OS	mPFS	5y-PFS		Seizure control @1 y	
Early RT (54 Gy)	7.4 y	68.4%	5.3 y	55%	p = 0.003	75%	p = 0.03
Delayed RT	7.2 y	65.7%	3.4 y	35%		59%	

Van den Bent MJ et al. Lancet 2005

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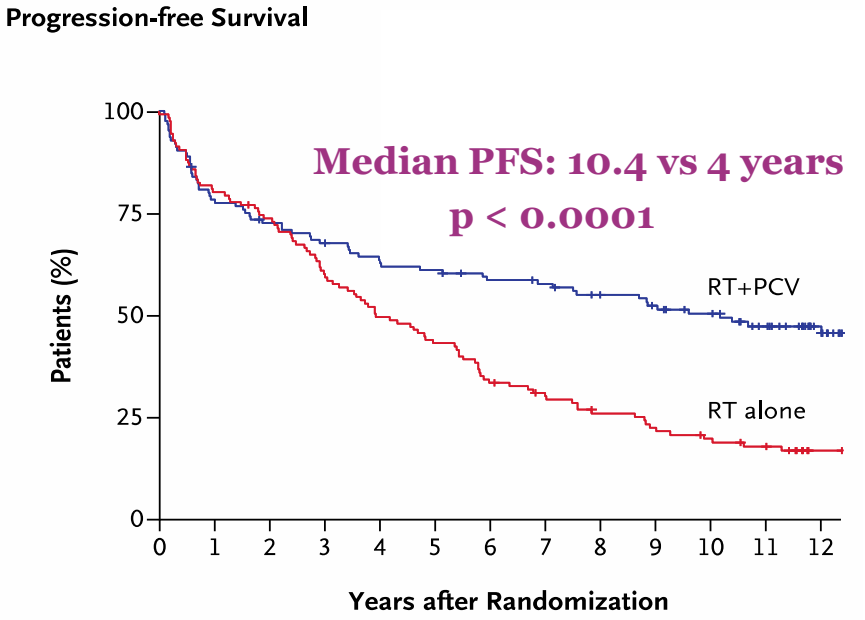
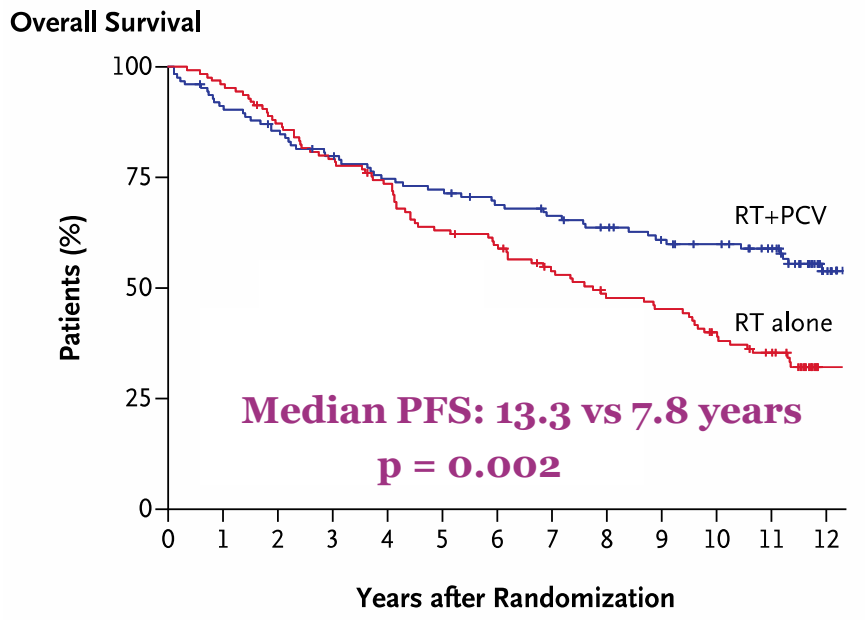
The NEW ENGLAND JOURNAL of MEDICINE

Radiation plus Procarbazine, CCNU, and Vincristine in Low-Grade Glioma

RT+CT in HR LGG: RTOG 98-02

- 251 patients randomly assigned to receive 54 Gy RT alone (126) or 54 Gy RT + adjuvant PCV x 6 (125)
- High risk patients according to RTOG criteria:
  - Age<40, with partial resection or biopsy
  - Age>40





Buckner JC et al. NEJM 2016;374

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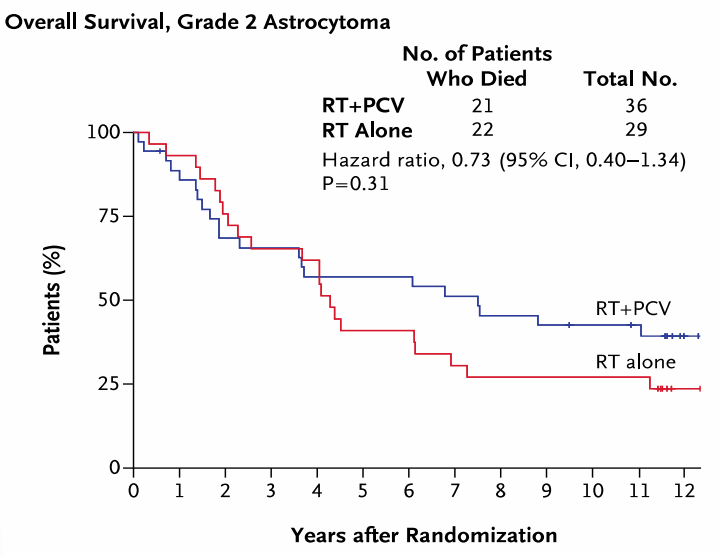
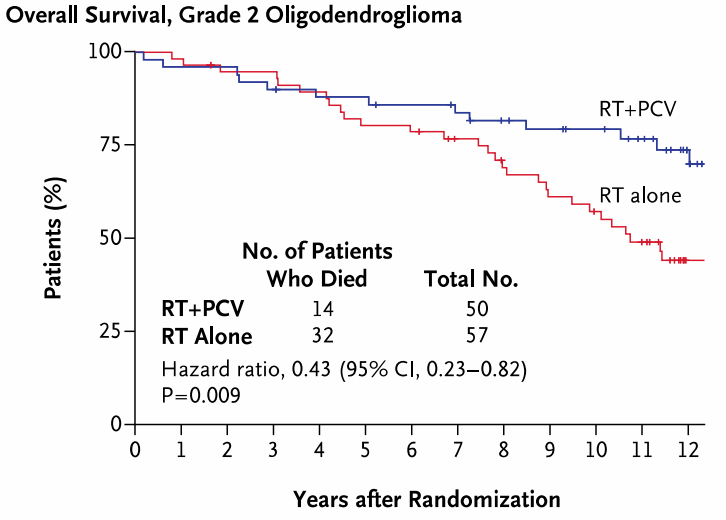
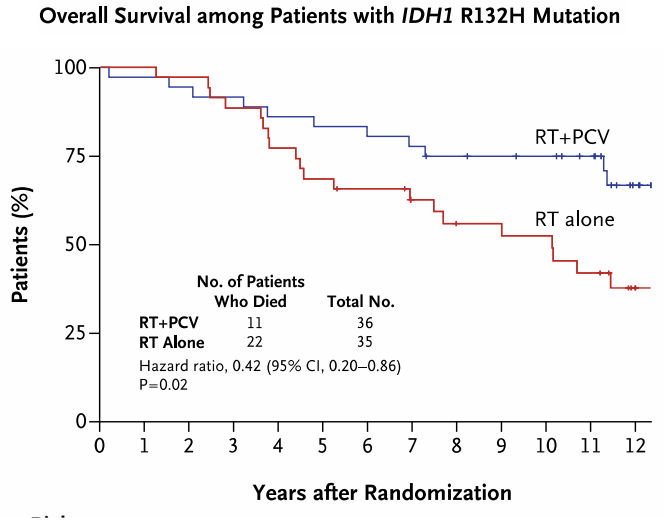
The NEW ENGLAND JOURNAL of MEDICINE

Radiation plus Procarbazine, CCNU, and Vincristine in Low-Grade Glioma

RT+CT in HR LGG: RTOG 98-02
(subgroup analysis)







Buckner JC et al. NEJM 2016;374

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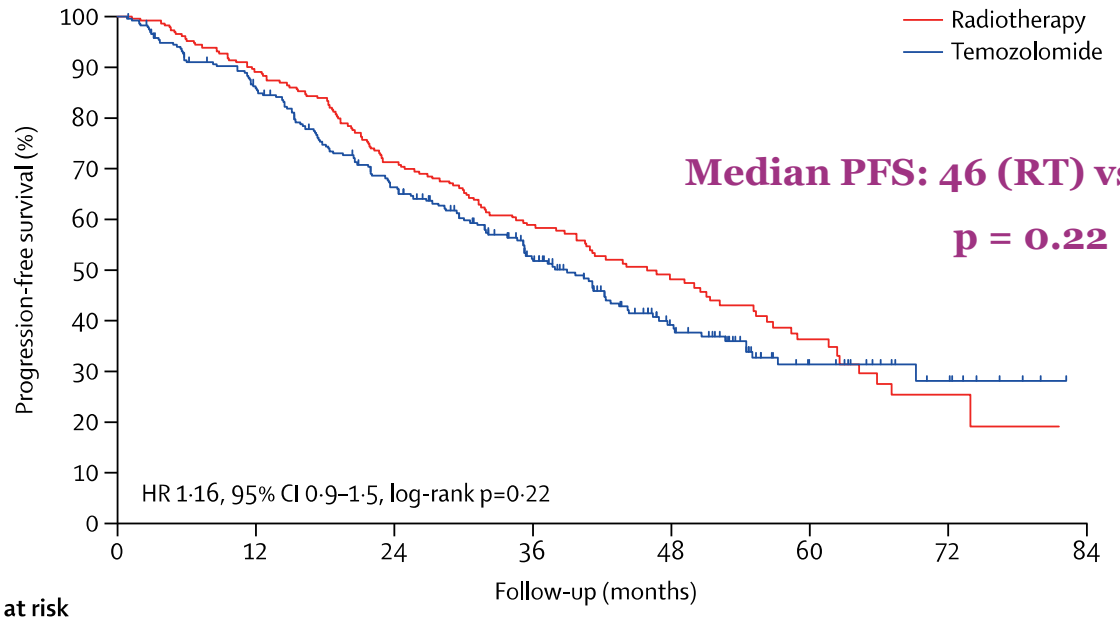
Temozolomide chemotherapy versus radiotherapy in high-risk low-grade glioma (EORTC 22033-26033): a randomised, open-label, phase 3 intergroup study

RT vs TMZ in HR LGG: EORTC 22033

- "High Risk" LGG according to European criteria
- 477 patients were randomly assigned to receive either 50.4 Gy RT (240) or TMZ (237)



Median PFS: 46 (RT) vs 39 (TMZ) months

p = 0.22

Number at risk (censored)							
Radiotherapy	240 (12)	203 (19)	156 (39)	110 (73)	60 (96)	25 (110)	5 (114)
Temozolomide	237 (7)	197 (12)	148 (31)	100 (59)	51 (83)	19 (93)	8 (101)

Baumert BG et al. Lancet Oncol 2016;17

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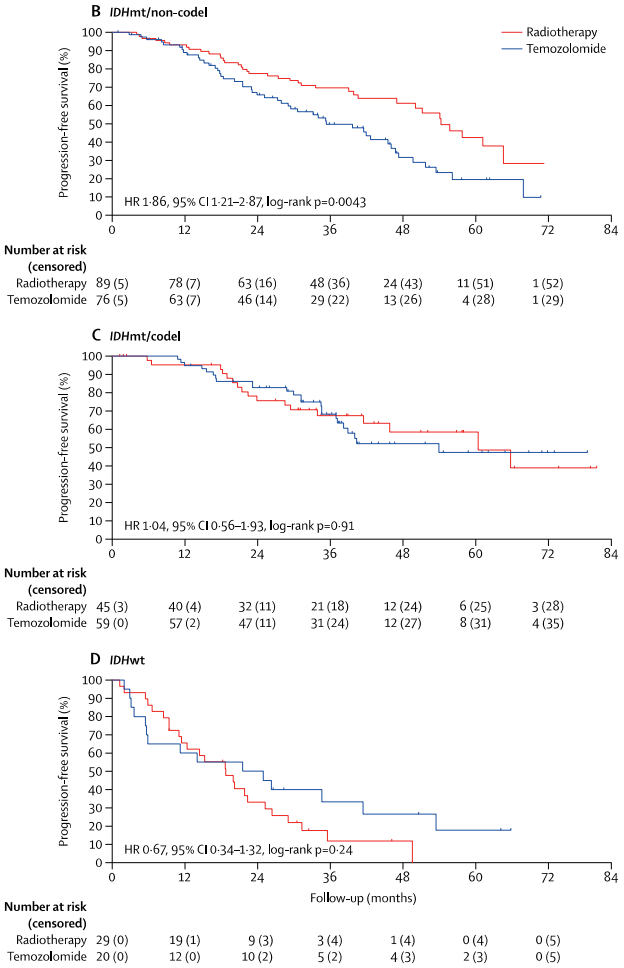
Temozolomide chemotherapy versus radiotherapy in high-risk low-grade glioma (EORTC 22033-26033): a randomised, open-label, phase 3 intergroup study

RT vs TMZ in HR LGG: EORTC 22033
(molecular analysis)



IDHmut/1_p19_q intact

- Median PFS:
  - ❑ RT 55.4 months
  - ❑ TMZ 36 months

p = 0.0043

IDHmut/1_p19_q codel

- Median PFS:
  - ❑ RT 61.6 months
  - ❑ TMZ 55 months

p = n.s.

IDHwt

- Median PFS:
  - ❑ RT 19.1 months
  - ❑ TMZ 23.7 months

p = n.s.

CONCLUSION

Our results might support the option of initial TMZ alone in good-prognosis tumors (IDHmut/1_p19_q codel), in order to minimize the potential risk of late toxicity by postponing RT (if TMZ could be used instead) in a patient population who might live for more than 10–20 years.

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Health-related quality of life in patients with high-risk low-grade glioma (EORTC 22033-26033): a randomised, open-label, phase 3 intergroup study

QoL → 50.4 Gy RT vs TMZ: EORTC 22033

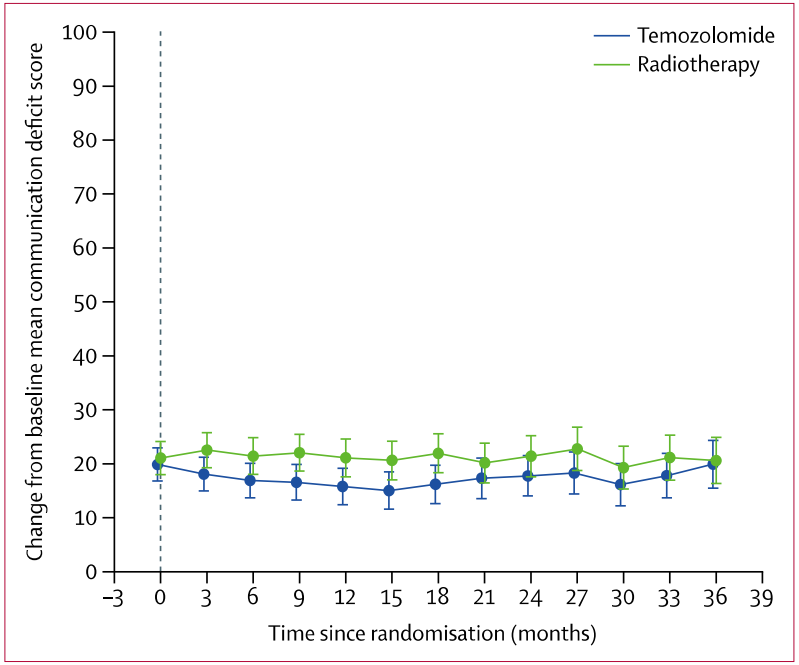

Figure 2: **Changes from baseline in communication deficit scores**
Error bars are SDs. 0 months is the baseline. A higher communication deficit score means more symptoms.

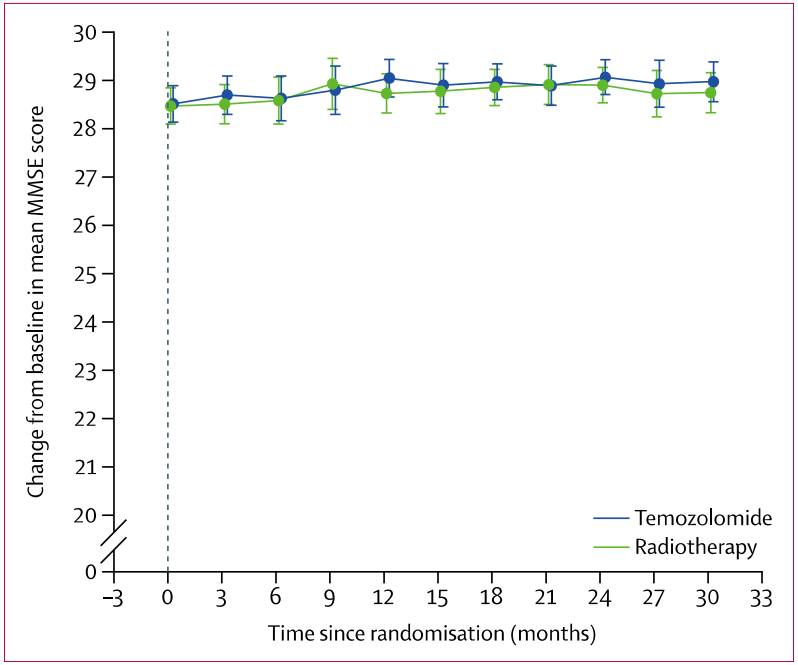

Figure 3: **Changes from baseline in MMSE scores**
Error bars are 99% CIs. No significant difference was found between radiotherapy and temozolomide in the longitudinal and overall analysis or at any timepoint (p=0·47). 0 months is the baseline. MMSE=Mini-Mental State Examination.

QoL or global cognitive funtioning did not differ between RT or TMZ in patients with LGG.
Our results do not support the choice of TMZ alone over RT alone in patients with "high-risk" LGG.

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Reijneveld JC et al. Lancet Oncol 2016;17

CRUCIAL POINT

"The current evidence supports that in future trials, **grades II and III tumors with similar molecular backgrounds should be combined**, and trials should focus on molecular glial subtype regardless of grade"

Van den Bent, Neuro Oncol 2014

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Comprehensive, Integrative Genomic Analysis of Diffuse Lower-Grade Gliomas

The Cancer Genome Atlas Research Network*

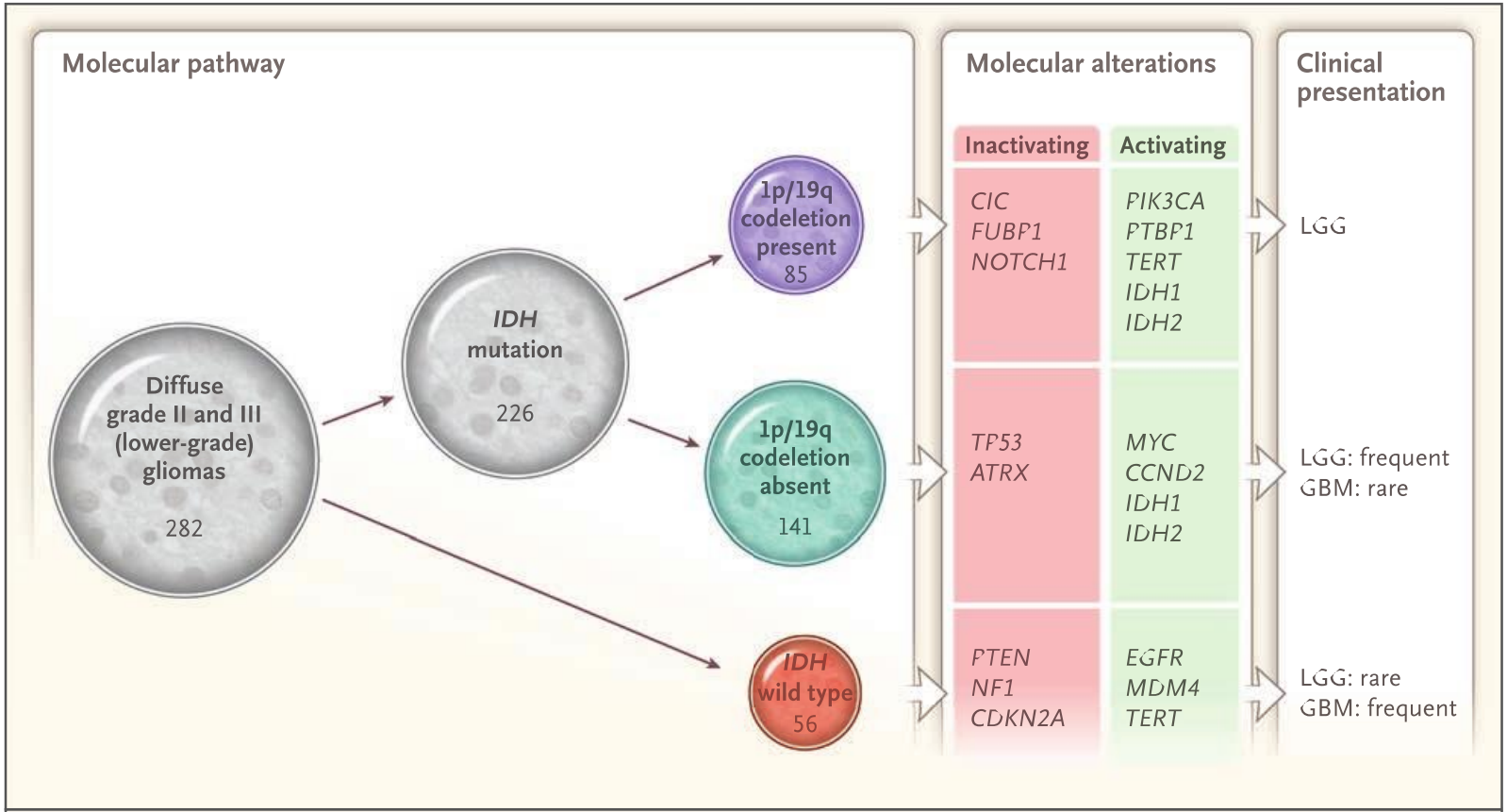
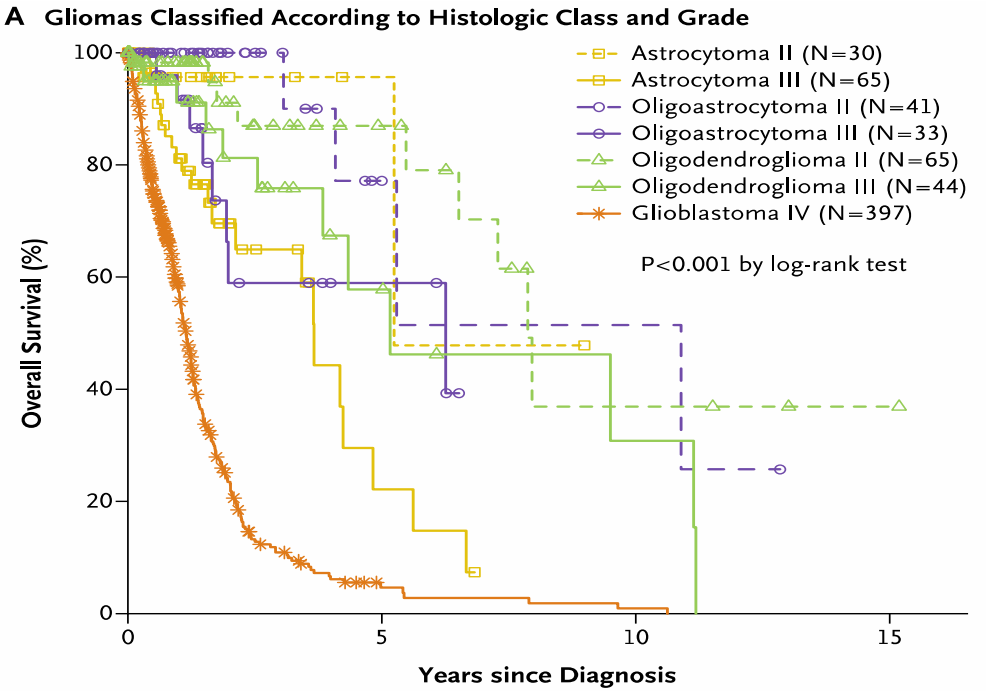


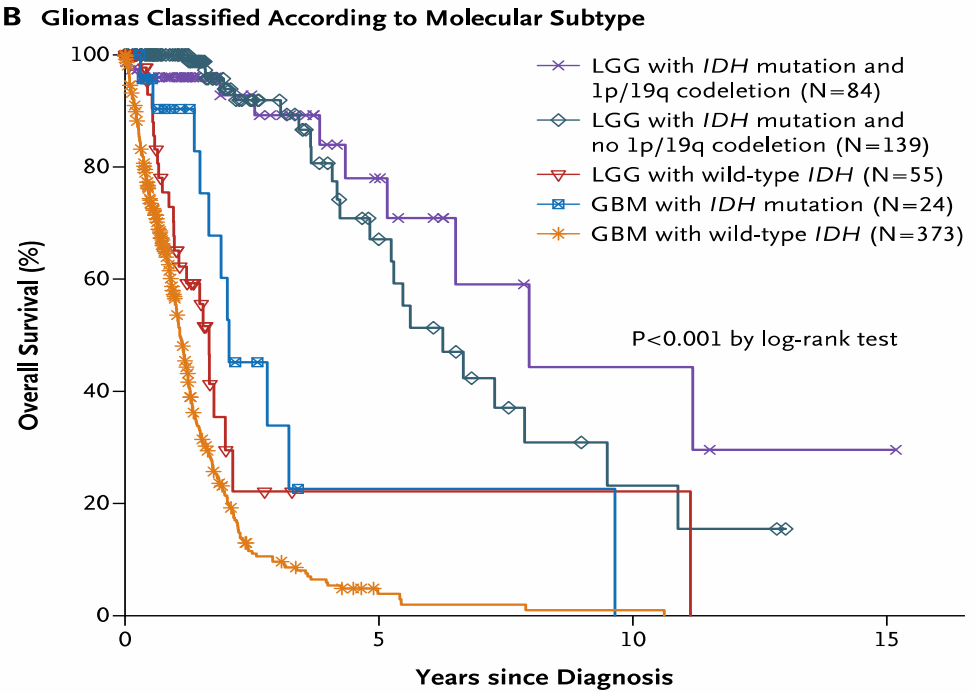
Figure 4. Summary of Major Findings.

Shown is a schematic representation that summarizes the major molecular findings and conclusions of our study: consensus clustering yielded three robust groups that were strongly correlated with *IDH* mutation and 1p/19q codeletion status and had stereotypical and subtype-specific molecular alterations and distinct clinical presentations. GBM denotes glioblastoma, and LGG lower-grade glioma.

Brat DJ et al. NEJM 2015;372

Prognostic Role according to traditional classification and to molecular subtype

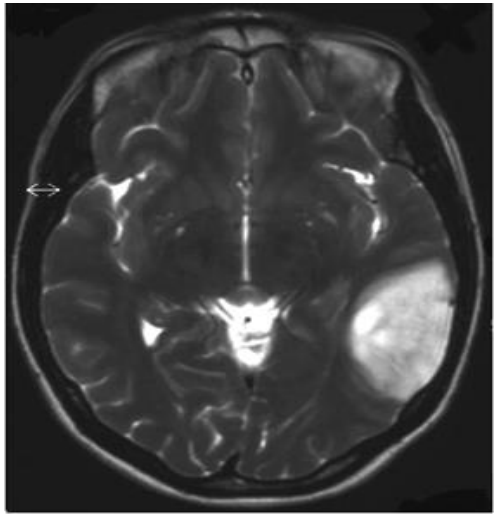




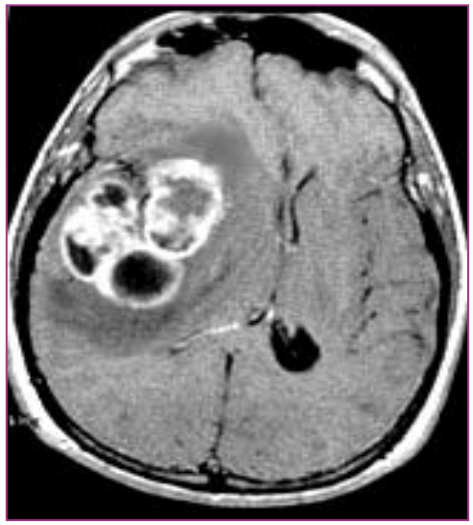
Brat DJ et al. NEJM 2015;372

Combined modality treatment in brain tumors

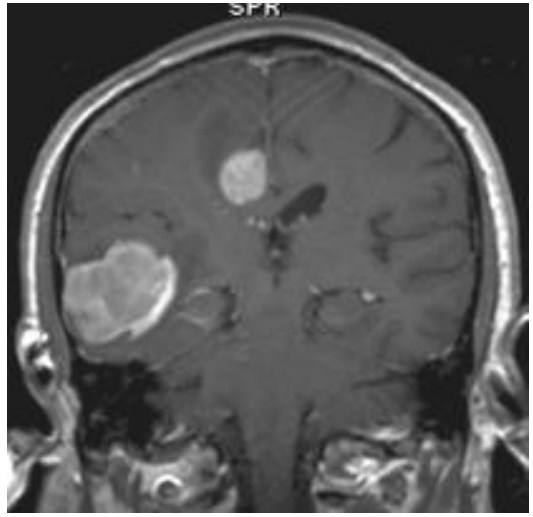
Low grade gliomas



High grade gliomas



PCNSL



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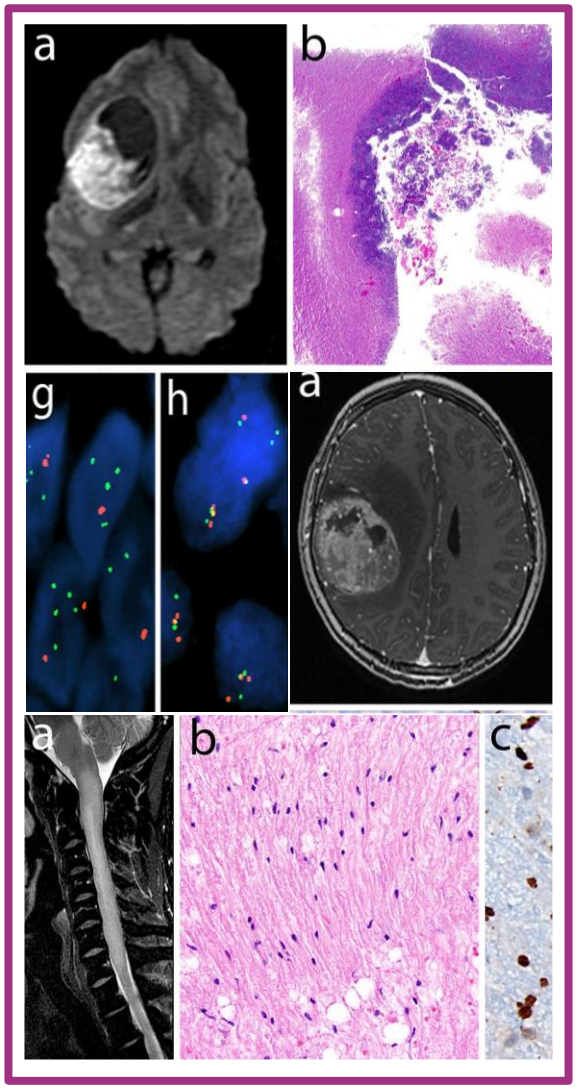
Grade III gliomas: WHO 2016



- Anaplastic astrocytoma, IDH-mutant
- Anaplastic astrocytoma, IDH-wild type
- Anaplastic astrocytoma, NOS

- Anaplastic oligodendroglioma, IDH-mutant, 1p/19q-codeleted
- Anaplastic oligodendroglioma, NOS

- Oligoastrocytoma: this diagnosis is strongly discouraged. Nearly all tumors with histological features suggesting both astrocytic and oligodendroglial component can be more properly classified by using genetic testing

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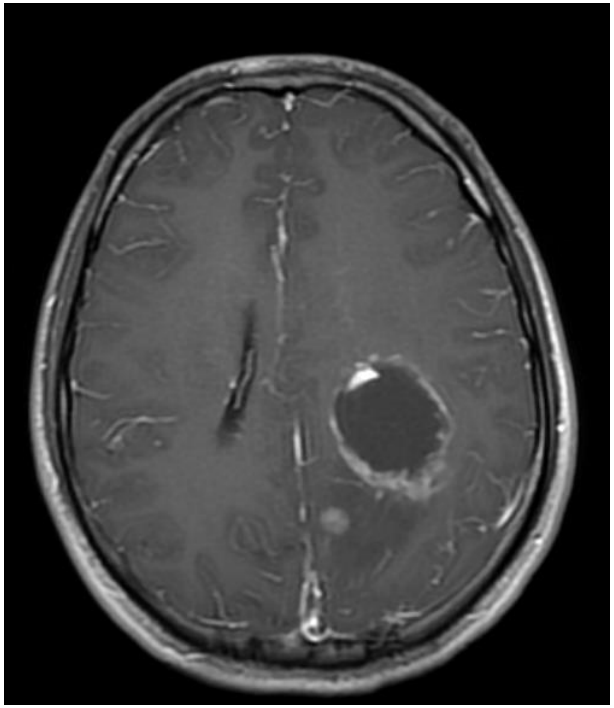
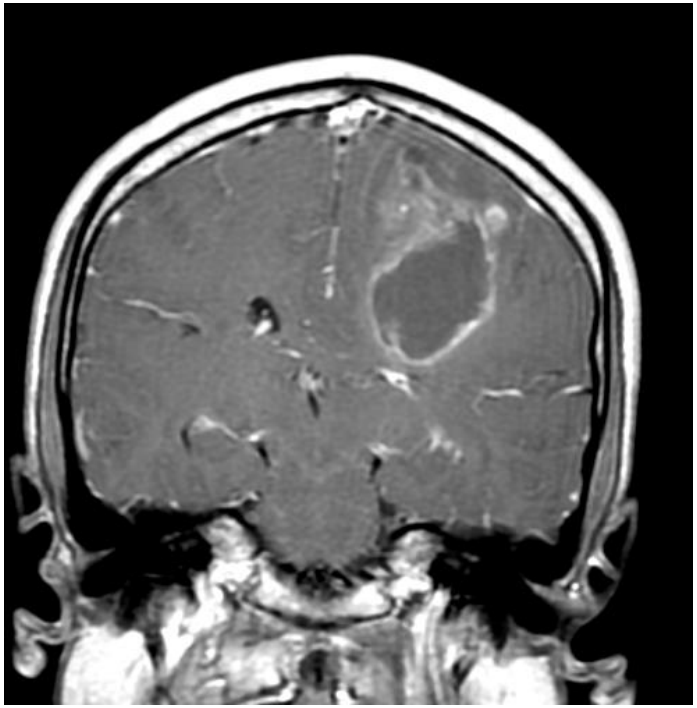
CLINICAL CASE #2 – Anaplastic glioma (G III WHO)

- T.P. MALE, 23 years old
- Headache for 1 month, seizures requiring hospitalization
- MRI: brain mass in the left parietal lobe
- Craniotomy – debulking

- Histology: GIII oligoastrocytoma, IDH1 mutated, 1p/19q non codeleted, MGMT methylated





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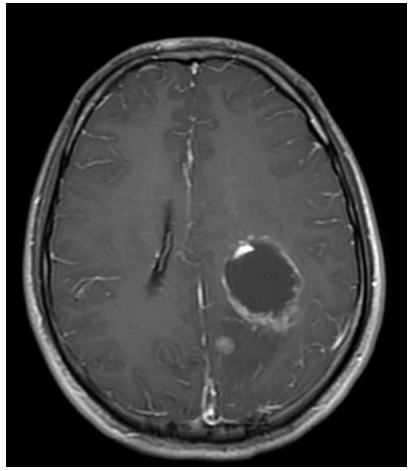
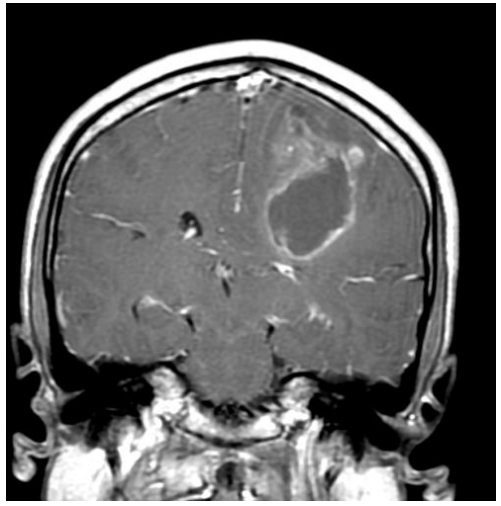
CLINICAL CASE #2 – Anaplastic glioma (G III WHO)

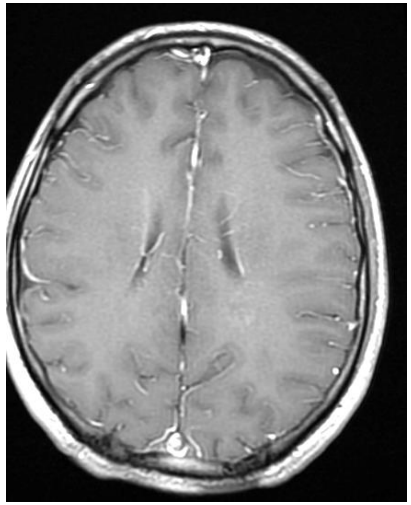
- KPS after surgery
- MRI 30 days after surgery: nearly total resection

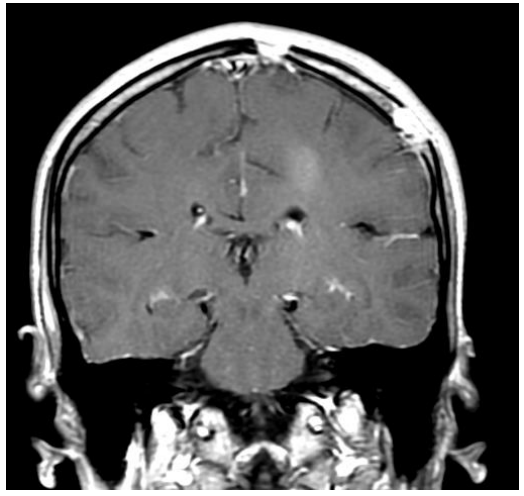
Before surgery





After surgery





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What to do now ?

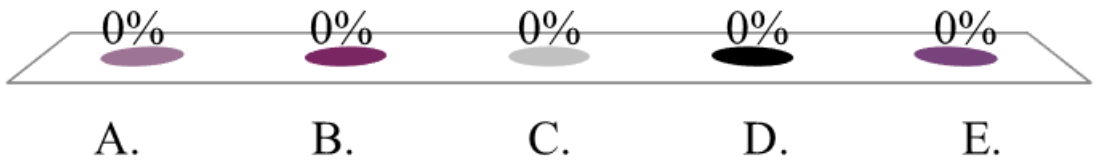
A. **RT alone (59.4 Gy/33 fractions**

B. **RT (59.4 Gy/33 fractions) followed by adjuvant PCV**

C. **PCV chemotherapy followed by RT (59.4 Gy/33 fractions)**

D. **PCV chemotherapy alone**

E. **RT (59.4 Gy/33 fractions) followed by adjuvant TMZ**



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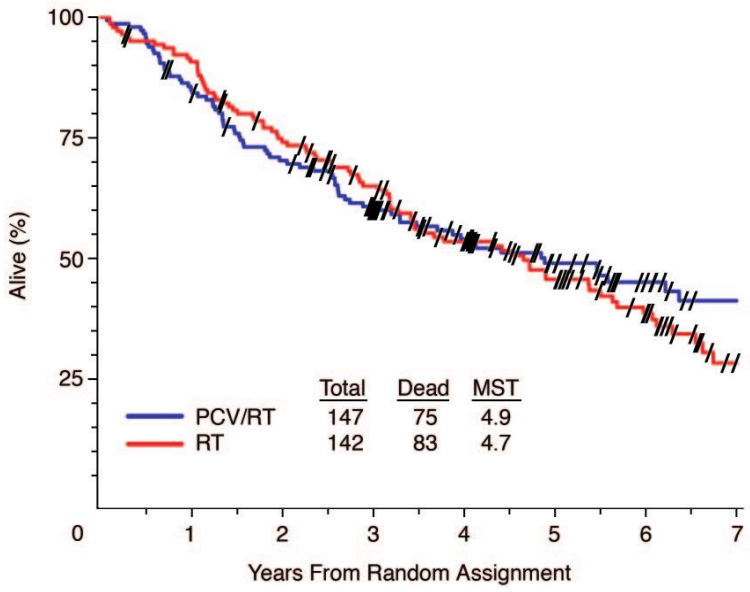
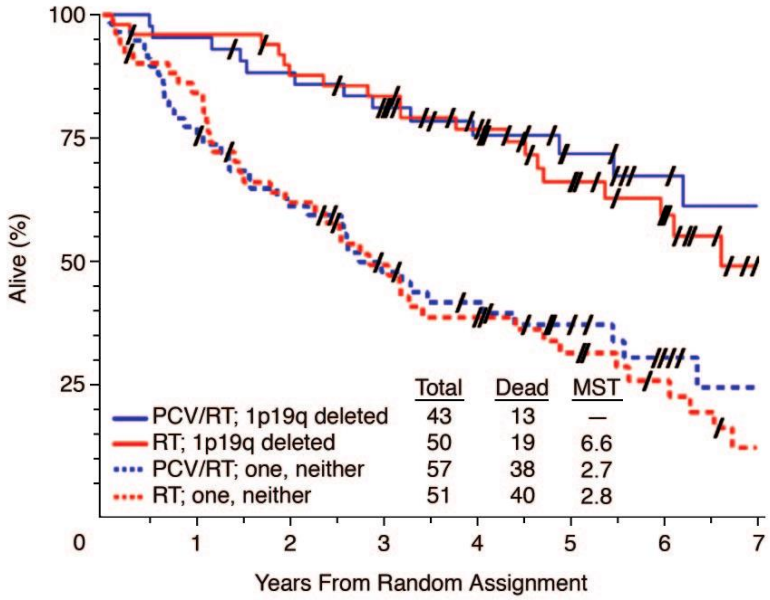
JOURNAL OF CLINICAL ONCOLOGY

Phase III Trial of Chemotherapy Plus Radiotherapy Compared With Radiotherapy Alone for Pure and Mixed Anaplastic Oligodendroglioma: Intergroup Radiation Therapy Oncology Group Trial 9402

PCV x 4 + RT vs RT alone: RTOG 9402





- 289 AA or AOA patients
- Randomization to receive either 4 PCV (procarbazine, lomustine, vincristine) followed by RT 59.4 Gy/33 fr or RT alone
- **No differences in term of median OS between the 2 arms** (4.9 vs 4.7 years)
- PFS benefit for patients receiving PCV + RT (2.6 vs 1.7 years)
- Higher rates of G3-G4 toxicity in patients receiving PCV+RT (65%), with at least 1 fatal event.
- **1p/19q codeletion is a favorable prognostic factor** (median OS >7 vs 2.8 years)

Cairncross G. et al. JCO 2006;24

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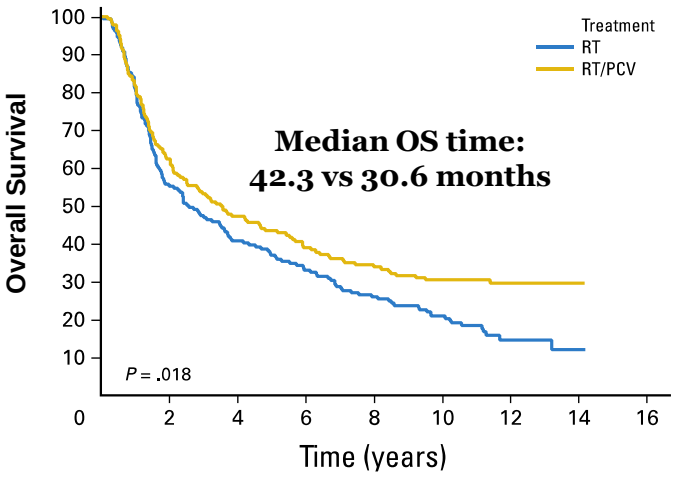
JOURNAL OF CLINICAL ONCOLOGY

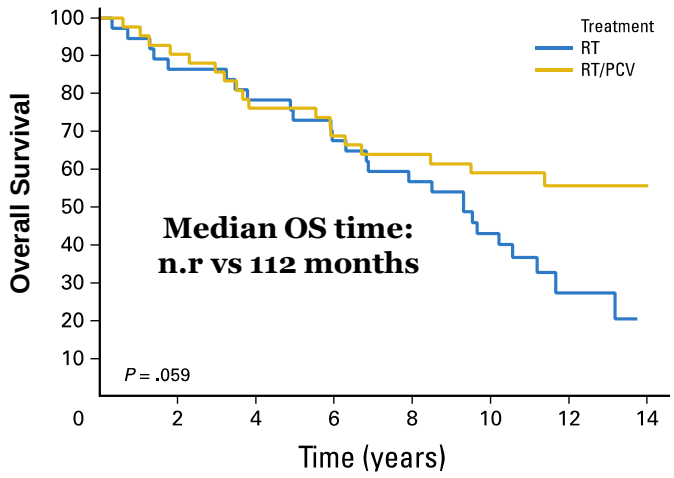
Adjuvant Procarbazine, Lomustine, and Vincristine Chemotherapy in Newly Diagnosed Anaplastic Oligodendroglioma: Long-Term Follow-Up of EORTC Brain Tumor Group Study 26951

RT + adjuv PCV vs RT alone: EORTC 26951

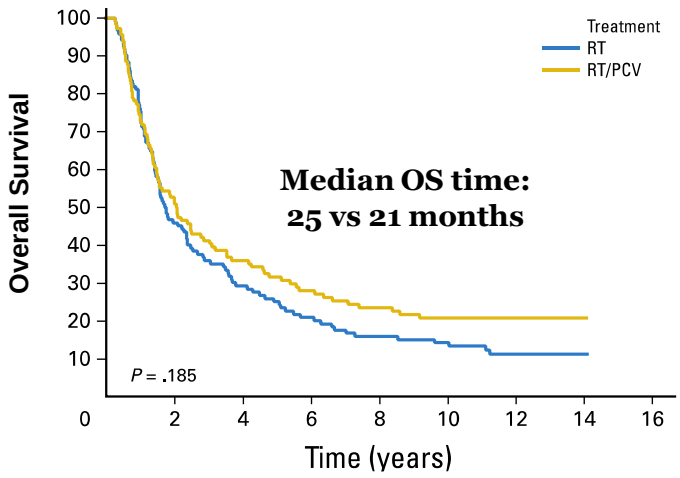
Overall population



1p/19q CODELETED



non CODELETED



- 368 AO or AOA randomly assigned to receive RT 59.4 Gy/33 fr + adjuvant PCV x 6 vs RT alone
- Long term results: increased OS and PFS in favor of patients receiving PCV in the overall population
- After molecular stratification **1p/19q codeleted tumors derived major benefit** from adjuvant PCV, whereas **non codeleted tumors has derived NO benefit from PCV**

Van den Bent MJ. et al. JCO 2013;31

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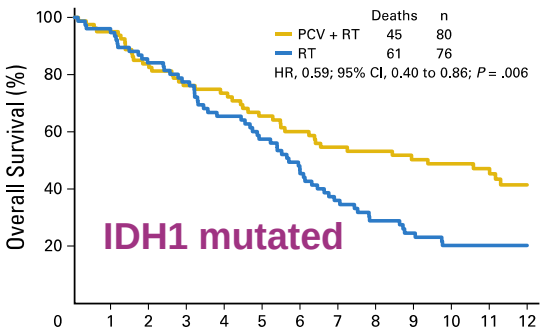
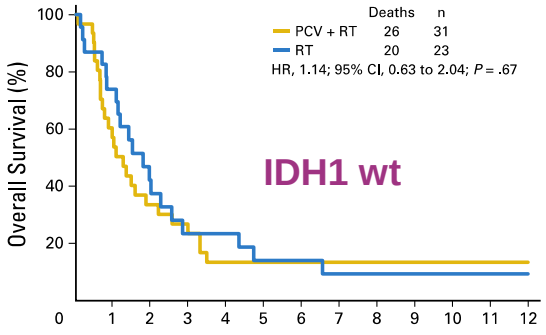
Molecular “status” overcomes treatment strategy…

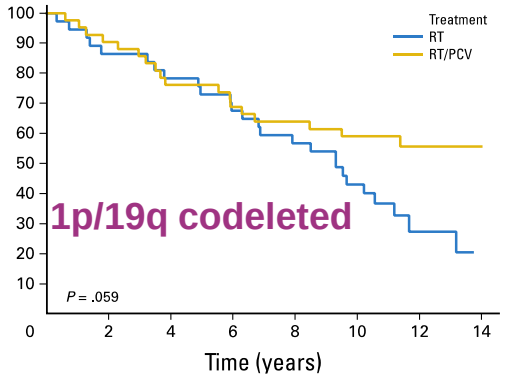
Favourable ***Unfavourable***

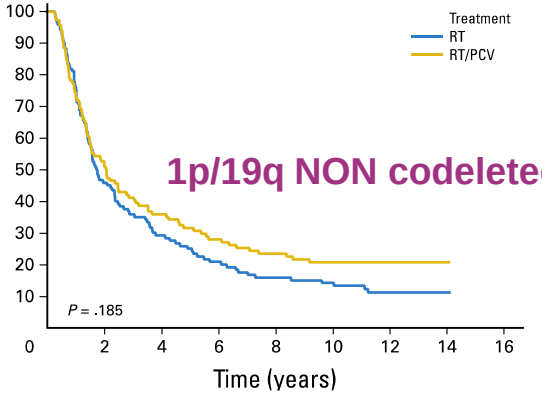




RTOG 9402

Cairncross JG. et al. JCO 2014;32





EORTC 26951

Van den Bent MJ. et al. JCO 2013;31

…can we consider RT + PCV as standard of care ?

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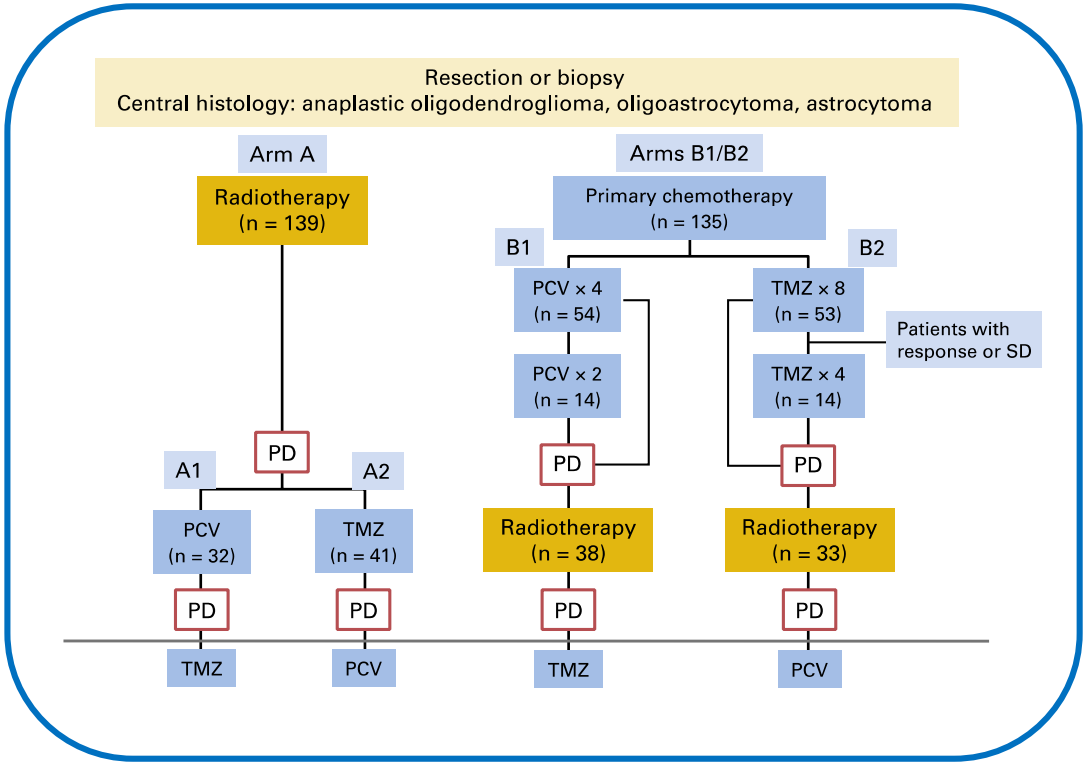
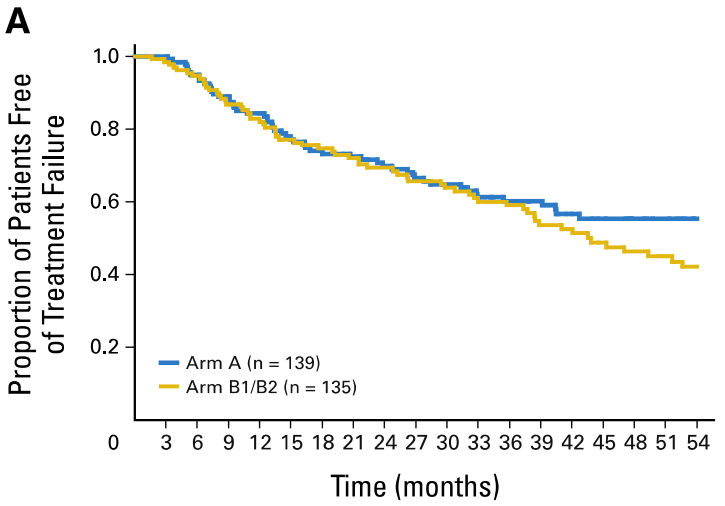
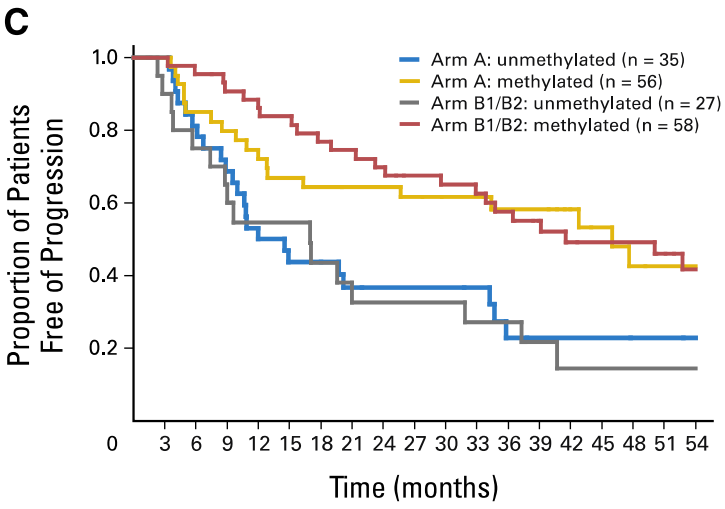
JOURNAL OF CLINICAL ONCOLOGY

NOA-04 Randomized Phase III Trial of Sequential Radiochemotherapy of Anaplastic Glioma With Procarbazine, Lomustine, and Vincristine or Temozolomide

Alternative approaches: NOA trial







- **Initial RT or CT achieved comparable results in patients with anaplastic gliomas**

Wick W. et al. JCO 2009;27

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Prognostic factors

Clinical

- Age
- Extent of surgical resection
- Performance status

Pathological

- Histology and grade

Molecular

- IDH1 mutation
- 1p/19q codeletion
- MGMT promoter methylation

Table 4. Complete Model of Major Prognostic Factors As Determined in a Multivariate Cox Regression Analysis for the Primary End Point of Time to Treatment Failure

Variable	Hazard Ratio	95% CI	*P*
Anaplastic astrocytoma *v* anaplastic oligoastrocytoma/ anaplastic oligodendroglioma	1.95	1.1 to 3.5	.0237
IDH1, wild-type *v* mutated	2.0	1.2 to 3.3	.0128
1p/19q retained *v* 1p/19q deleted	1.8	0.9 to 3.4	.0718
MGMT promoter, unmethylated *v* methylated	1.9	1.1 to 3.4	.0172
Age, > 50 *v* ≤ 50 years	2.6	1.5 to 4.3	.0004
Extent of resection			
Incomplete *v* complete resection	1.6	0.9 to 3.0	
Biopsy *v* incomplete resection	2.1	1.1 to 4.0	.0006
Biopsy *v* complete resection	3.5	1.8 to 7.0	

Wick W. et al. JCO 2009;27

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The NEW ENGLAND JOURNAL of MEDICINE

IDH1 and *IDH2* Mutations in Gliomas

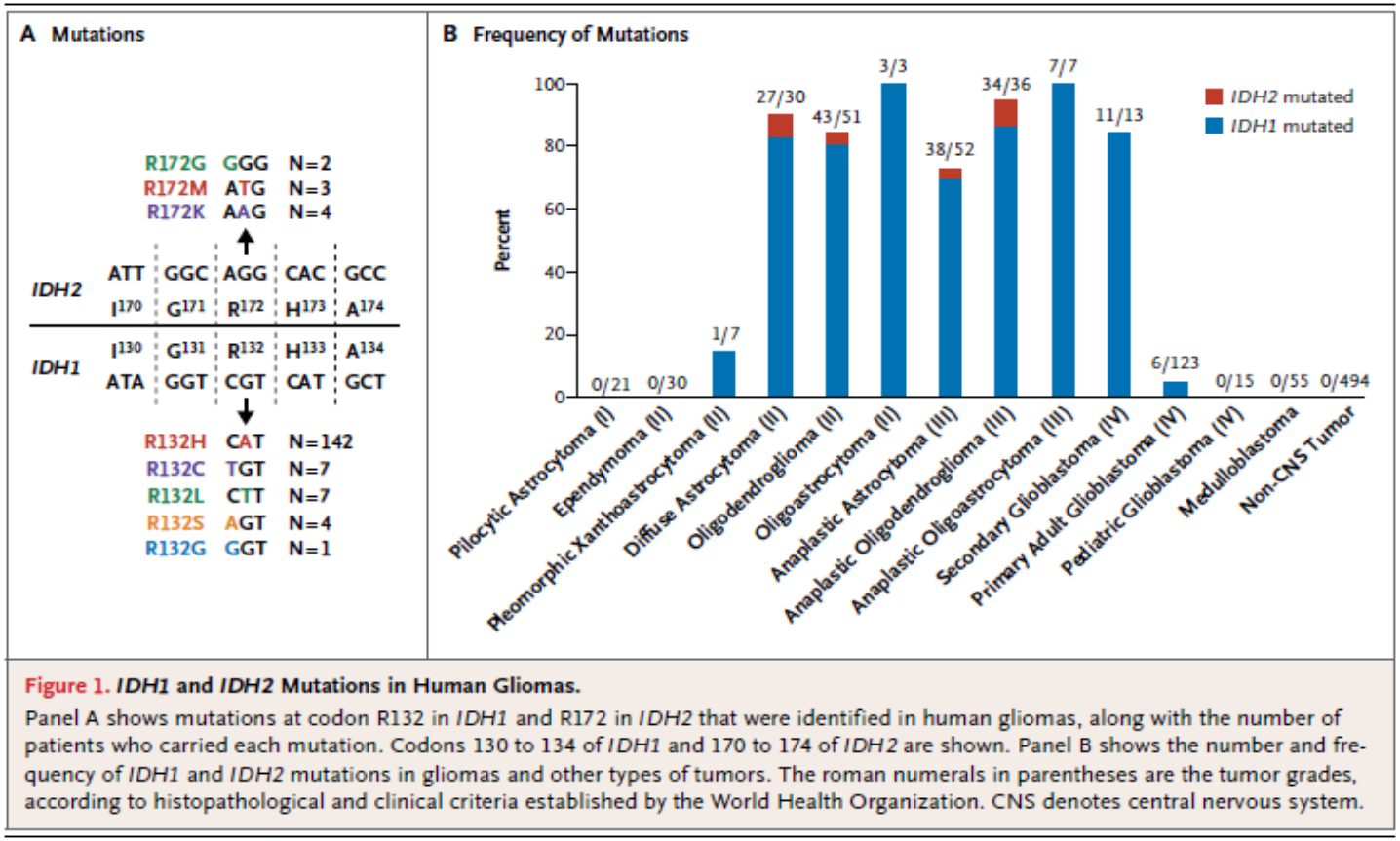


Figure 1. *IDH1* and *IDH2* Mutations in Human Gliomas.

Panel A shows mutations at codon R132 in *IDH1* and R172 in *IDH2* that were identified in human gliomas, along with the number of patients who carried each mutation. Codons 130 to 134 of *IDH1* and 170 to 174 of *IDH2* are shown. Panel B shows the number and frequency of *IDH1* and *IDH2* mutations in gliomas and other types of tumors. The roman numerals in parentheses are the tumor grades, according to histopathological and clinical criteria established by the World Health Organization. CNS denotes central nervous system.

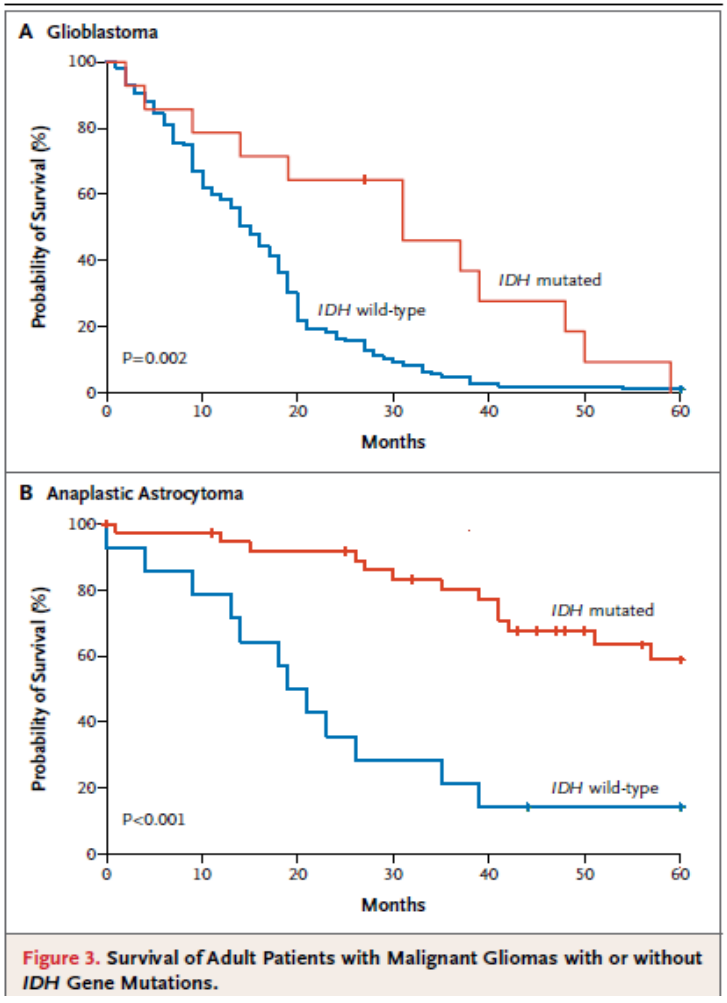
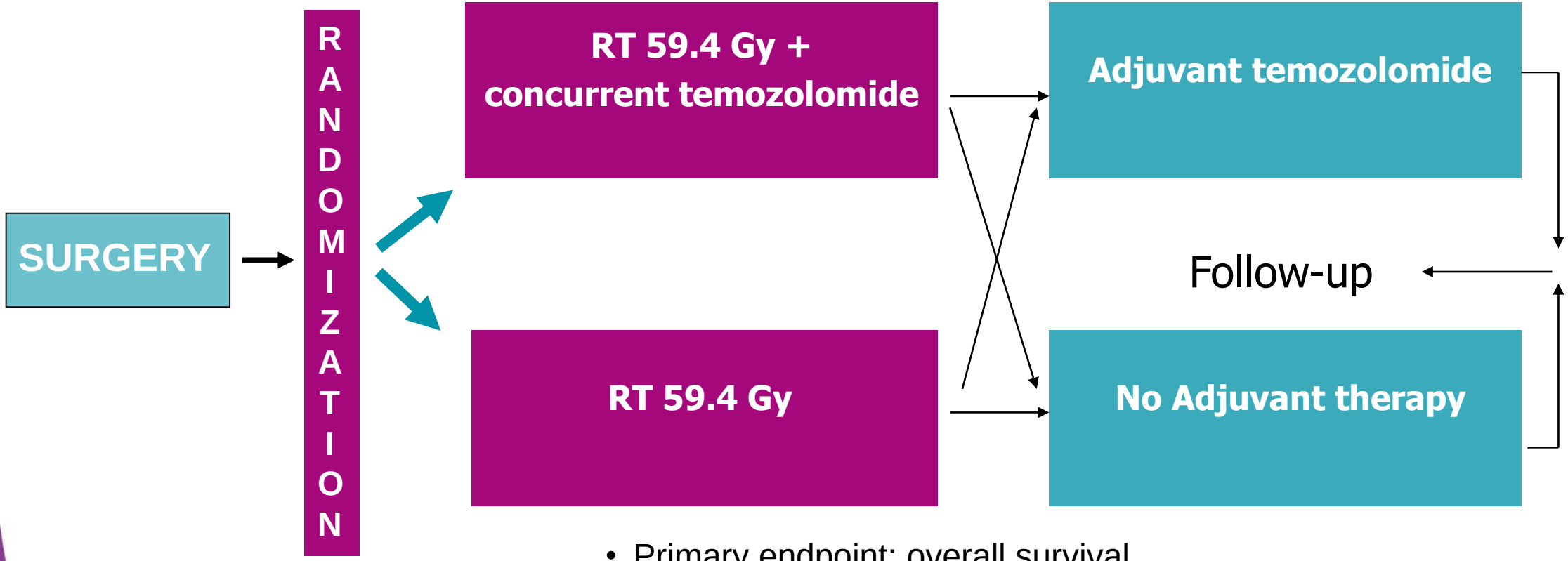


Figure 3. Survival of Adult Patients with Malignant Gliomas with or without *IDH* Gene Mutations.

Yan H. et al. NEJM 2009;370

EORTC 26053-22054/NCI-C/RTOG 0834 (CATNON) study on Anaplastic Gliomas without 1p/19q loss: 2 x 2 design



- Pre-study 1p/19q testing
- Stratification:
  - Methylation status

- Primary endpoint: overall survival
- Secondary endpoints:
  - Progression-free survival
  - Quality of life
  - Neurological deterioration free survival

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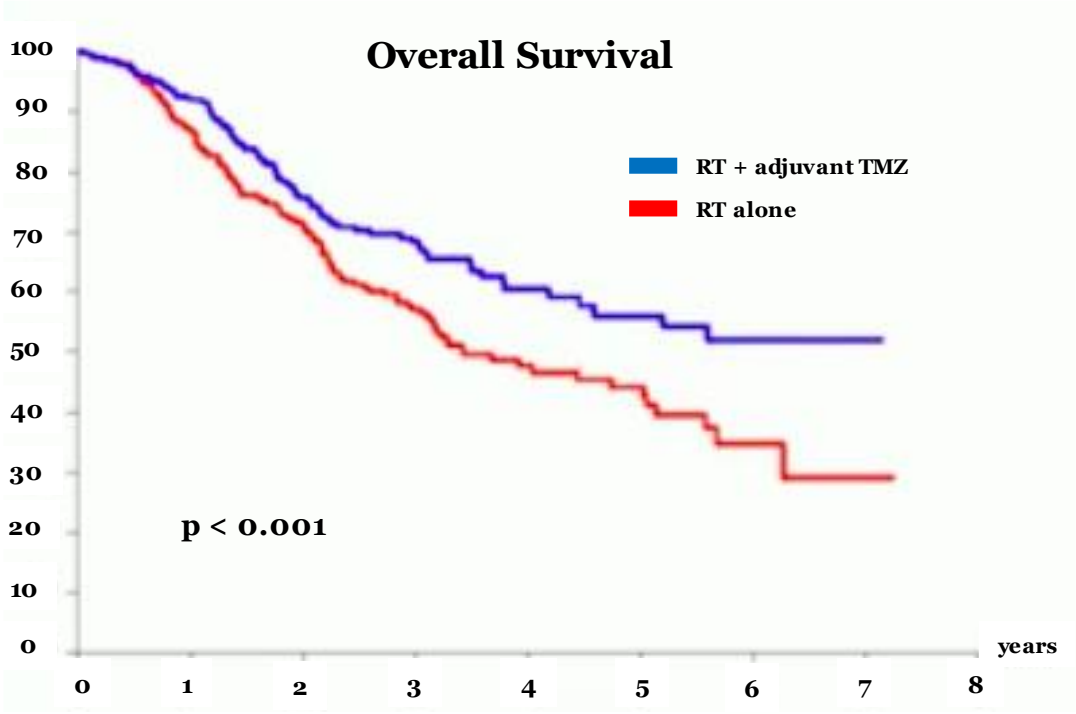
CATNON trial:
New standard regimen for non-codeleted anaplastic glioma ?



- 748 patients randomized
- 12 cycles TMZ improve OS in anaplastic glioma without 1p/19q codeletion.
- MGMT methylation was prognostic for OS, but did not predict improved outcome to adjuvant TMZ

	OS		PFS
Adjuvant temozolomide	Median	% 5 year	Median
No (n = 372)	41.1 months	44.1%	19.0 mo
Yes (n = 373)	Not reached	55.9%	42.8 mo

Van den Bent MJ. et al. presented at ASCO 2016 annual meeting, Chicago

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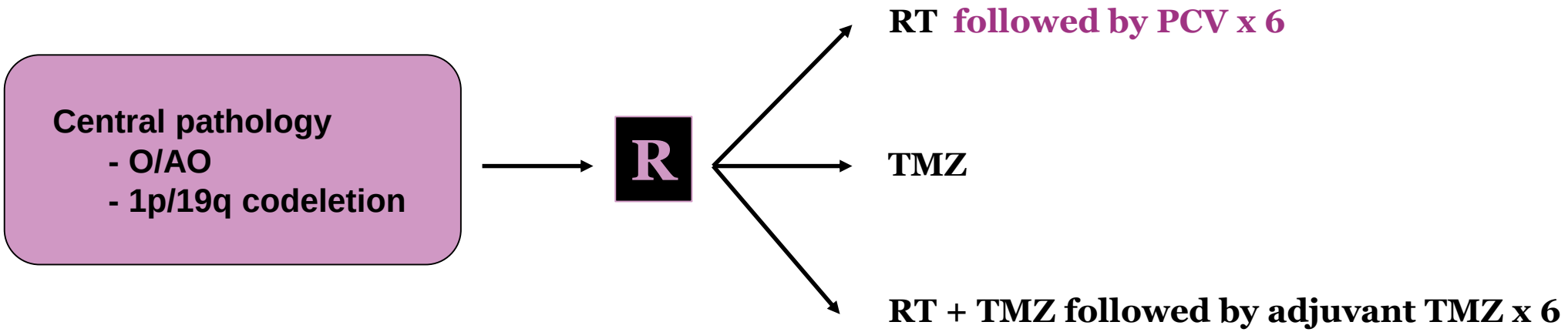
CODEL: Phase III study of RT+ concomitant and adjuvant TMZ vs RT + adjuvant PCV in patients with 1p/19q codeleted anaplastic glioma or Low grade glioma

PROPOSED DESIGNED OF REVITALIZED TRIAL



Estimated enrollment: 520
Study start date: October 2009
Estimated primary completion date: December 2018

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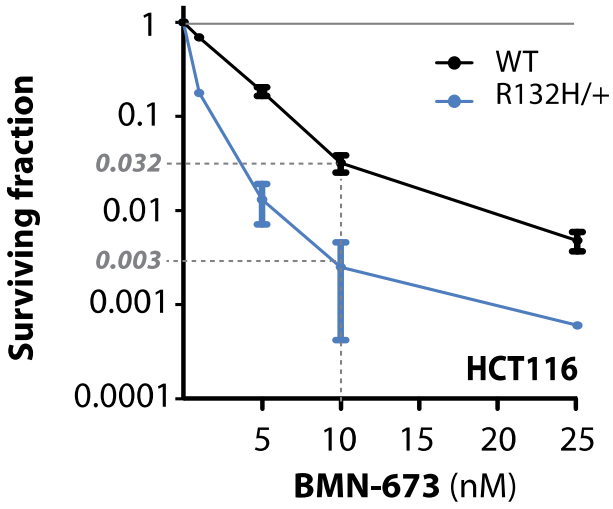
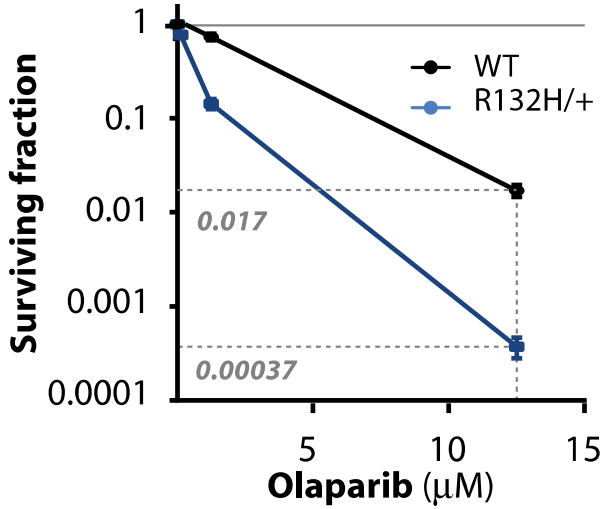
CANCER

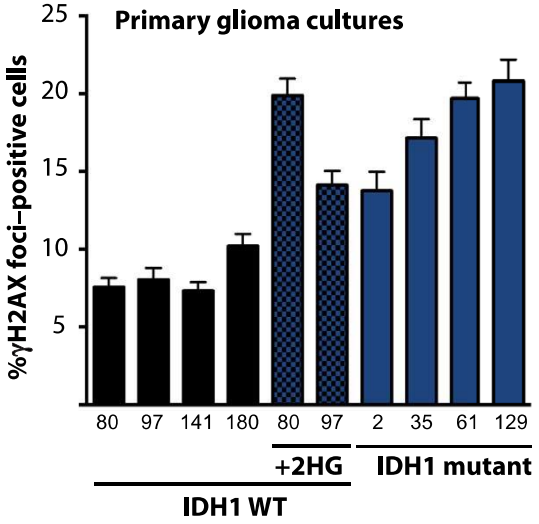
2-Hydroxyglutarate produced by neomorphic IDH mutations suppresses homologous recombination and induces PARP inhibitor sensitivity

FUTURE DIRECTION:
combination of molecular signatures with new drugs

IDH mutant tumor cells are sensitive to PARP inhibitors







Sulkowski PL. et al. Sci Transl. Med. 2017;9

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Take Home Message (Anaplastic gliomas)

A) 1p/19q CODELETED TUMORS

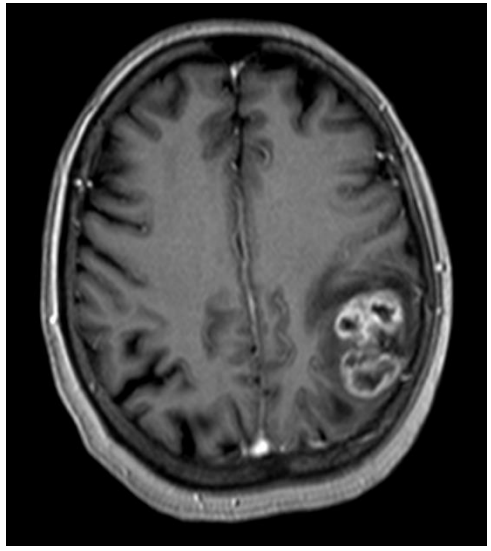
- ❑ Median survival >10 years
- ❑ Benefit from “upfront” sequential RT and CT (PCV regimen)
- ❑ RT→PCV or PCV→RT are both feasible options
- ❑ TMZ instead of PCV? No final answer so far (waiting for results from CODEL trial)

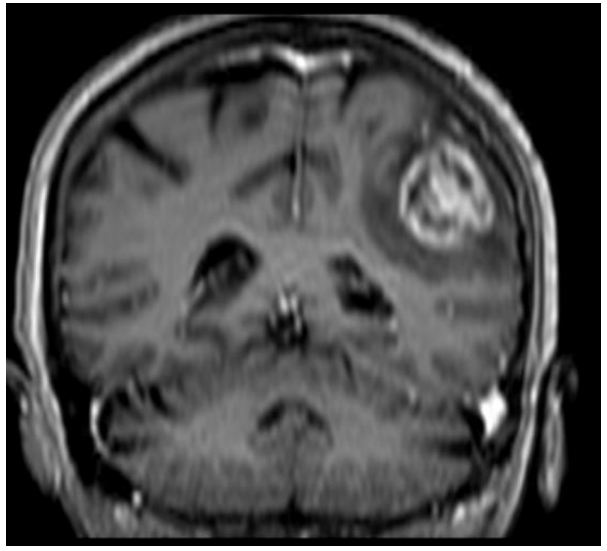
B) NON-CODELETED TUMORS

- ❑ Median survival 2-7 years
- ❑ RT as current standard for newly diagnosed cases.
- ❑ Benefit from adjuvant TMZ (CATNON trial)

CLINICAL CASE #3 – GLIOBLASTOMA

- F.E. woman, aged 52
- Seizures, for 3 months
- Craniotomy – debulking of the lesione in the left parietal lobe
- Histology – glioblastoma, Ki67 30%





- Post-operative KPS: 90
- Post-op MR: nearly GTR

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How would you treat this patient ?

A. **RT alone 60 Gy/30 fractions**

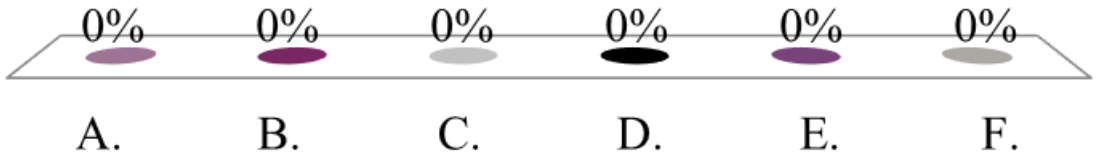
B. **RT (60 Gy/30 fractions) + concomitant TMZ followed by adjuvant TMZ x 6**

C. **RT (60 Gy/30 fractions) + concomitant TMZ**

D. **RT (60 Gy/30 fractions) + adjuvant TMZ x 6**

E. **Hypofractionated RT alone (40-42 Gy)**

F. **TMZ alone**



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What if the same patient was 74 years old ?

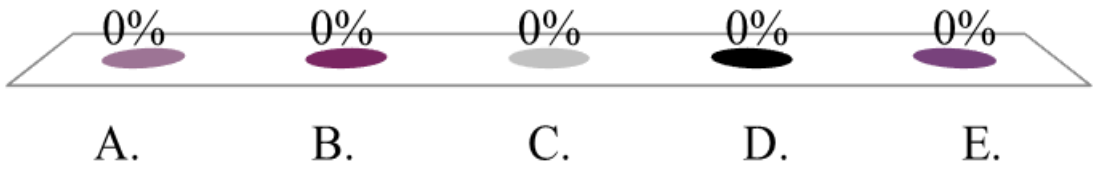
A. **RT 60 Gy/30 fractions alone**

B. **Hypofractionated RT alone (40-42 Gy)**

C. **RT 60 Gy/30 fractions + concomitant TMZ followed by adiuvant TMZ x 6**

D. **TMZ alone**

E. **Hypofractionated RT (40-42 Gy) + concomitant TMZ followed by adjuvant TMZ**



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Survival has not improved between ’70 and 2005

RANDOMIZED COMPARISONS OF RADIOTHERAPY AND NITROSOUREAS FOR THE TREATMENT OF MALIGNANT GLIOMA AFTER SURGERY

Walker MD et al. NEJM 1980;303

- **Median OS = 12 months (arm RT + BCNU)**

Cancer

survival of 8%. The study also demonstrated that a modified histologic classification of anaplastic astrocytoma *versus* glioblastoma provided better prognostic information than the astrocytoma grading system of Kernohan. Patients with anaplastic astrocytoma had a median survival of 27 months as compared to 8 months for patients with glioblastoma. In further evaluation of any beneficial effect of chemotherapy, it was identified that only among the 40–60-year-old groups, BCNU treated patients appeared to have significantly increased survival than patients in the control groups ($P = 0.01$, one-sided). Similarly, methyl-CCNU + DTIC was suggestively better than the control ($P = 0.08$, one-sided).

Chang CH et al. Cancer 1983;52

- **Median OS = 10 months (arm RT + BCNU)**

JOURNAL OF CLINICAL ONCOLOGY

Randomized Trial of Procarbazine, Lomustine, and Vincristine in the Adjuvant Treatment of High-Grade Astrocytoma: A Medical Research Council Trial

Medical Research Council Brain Tumor Working Party. JCO 2001;19

- **Median OS = 10 months (arm RT + adjuvant PCV x 12)**

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The ’90s… advent of TMZ has changed the paradigm

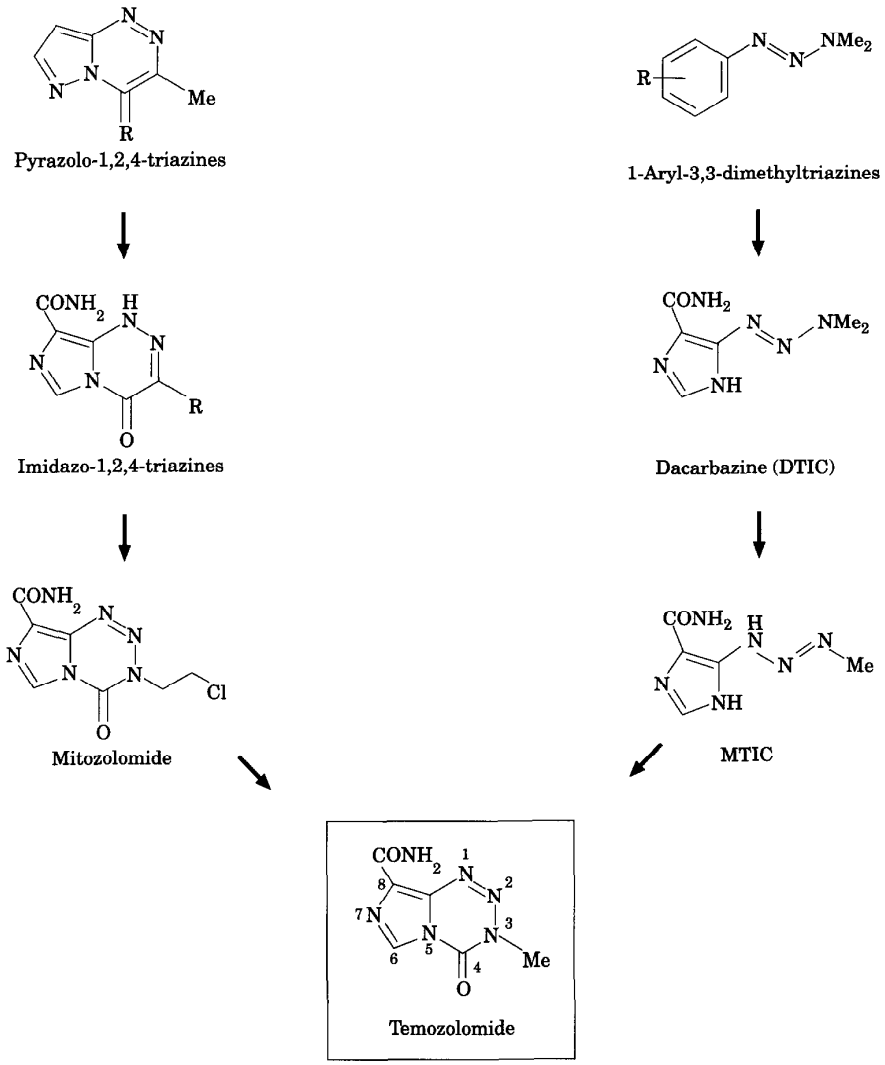

Figure 1. The chemical ancestry of temozolomide.

- **Oral alkylating agent**
- **Rapidly and completely adsorbed after oral administration**
- **Spontaneous conversion into the active metabolite without the need for liver demethylation (Advantage over dacarbazine)**
- **Excellent penetration into all body tissues, including the brain**
- **Mechanism of resistance to TMZ is mediated through O^6-methylguanine-DNA methyltransferase (MGMT). Many brain tumors express low concentrations of this enzyme.**

Newlands ES. et al. Canc Treat Rev 1997;23

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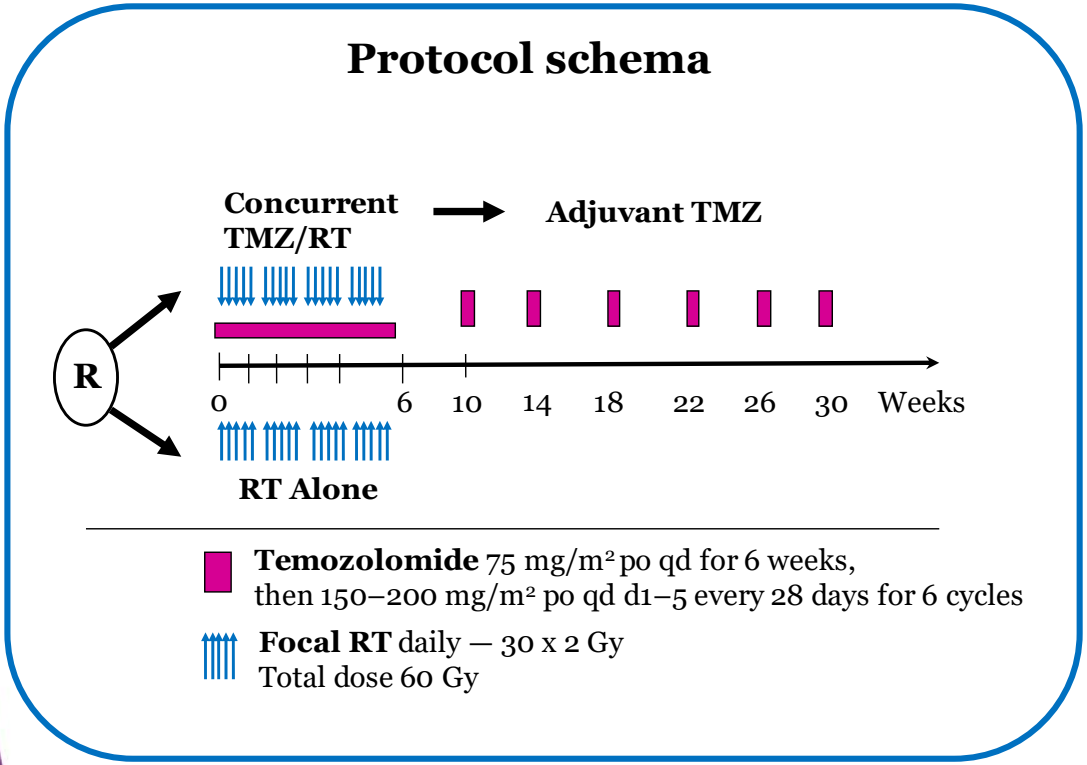
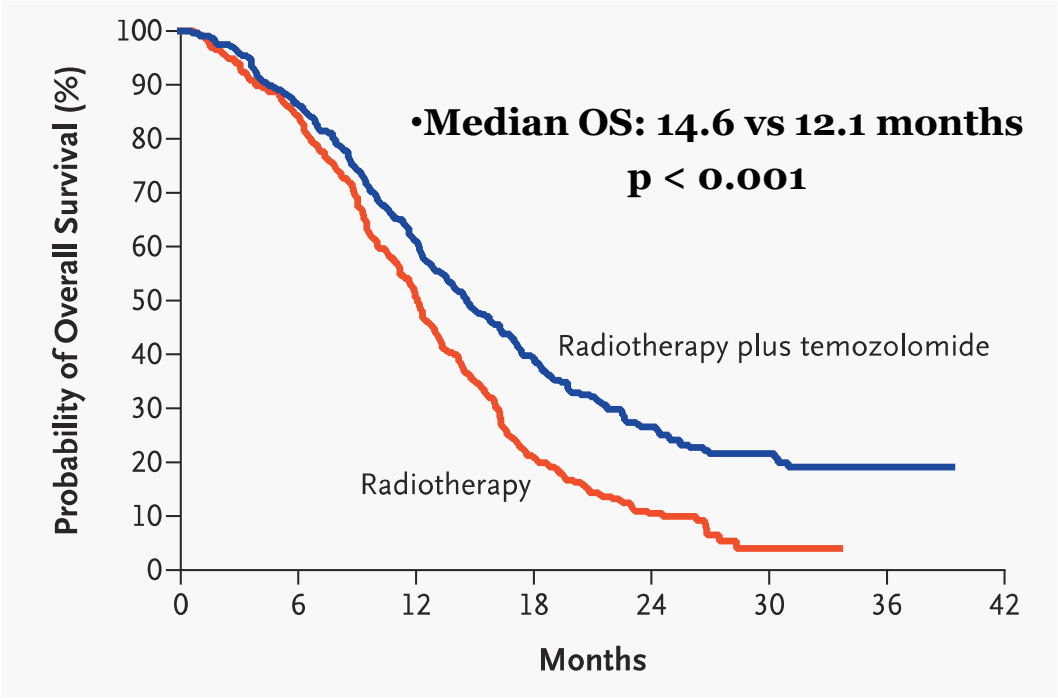
The NEW ENGLAND JOURNAL of MEDICINE

Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

Stupp Regimen: EORTC/NCIC trial – beneficial role of TMZ



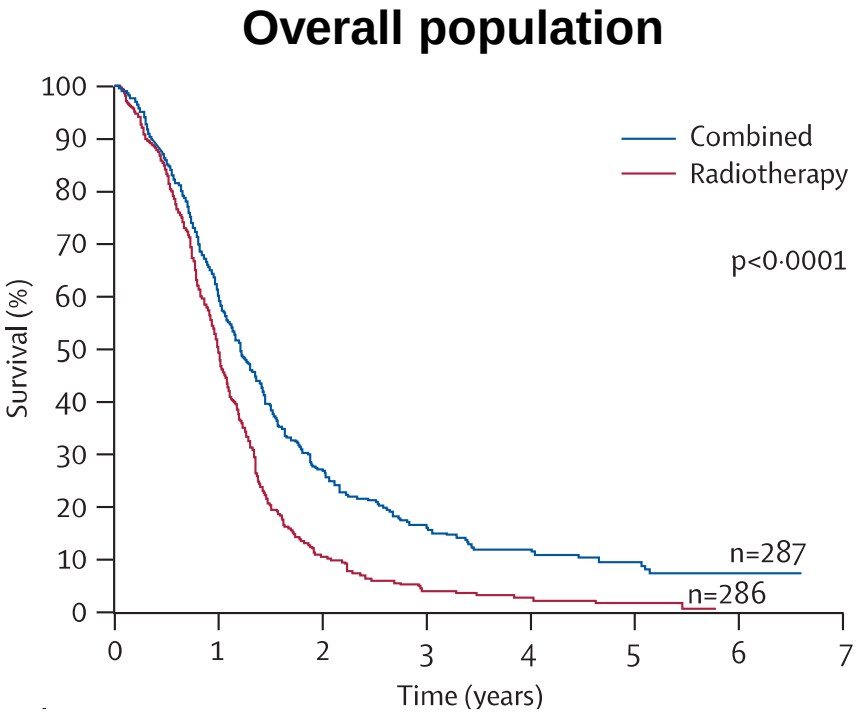


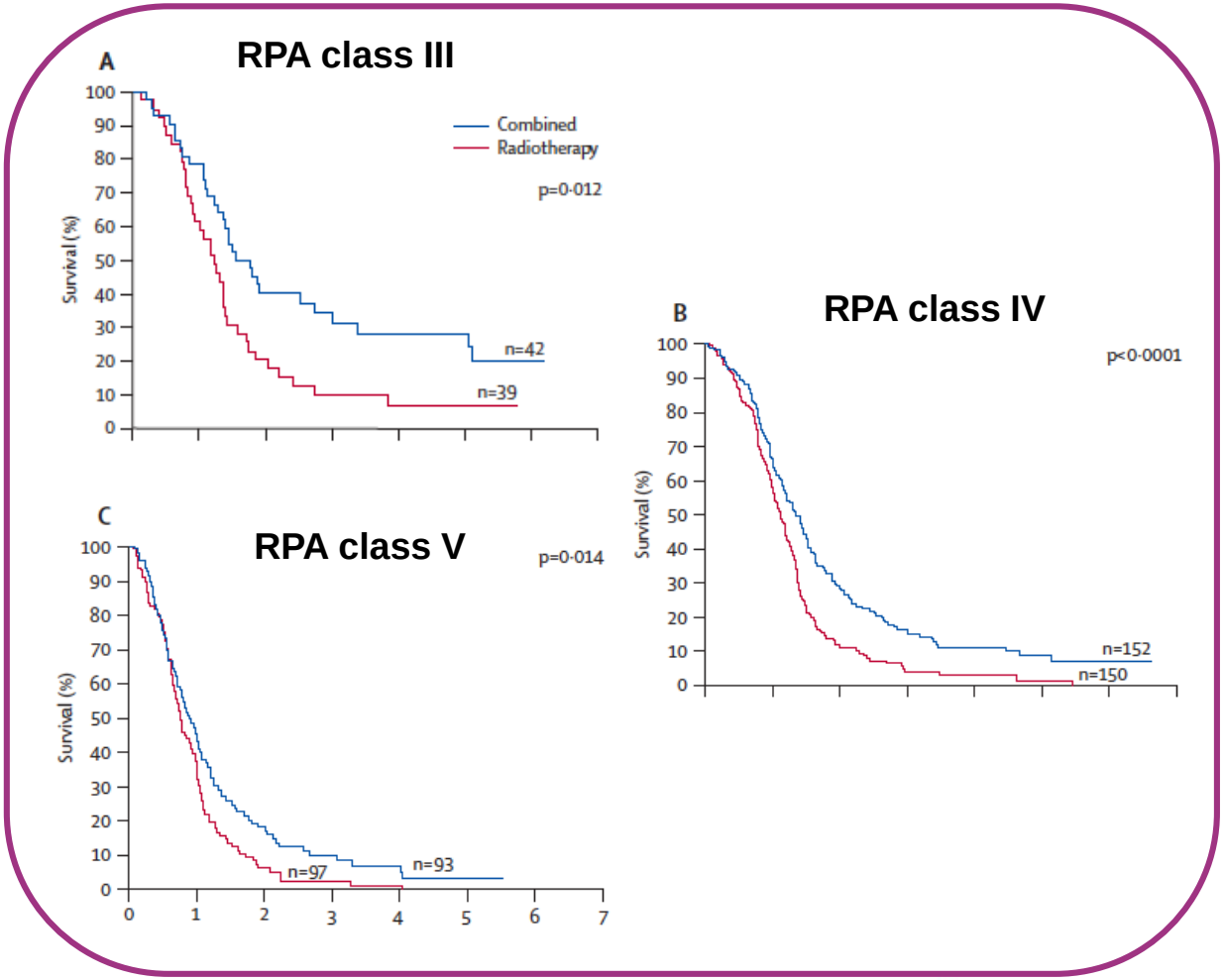
Stupp R. et al. NEJM 2005;352

THE LANCET Oncology

Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial

Stupp Regimen: benefit confirmed after 5 years





Stupp R. et al. Lancet Oncol 2009;10

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THE LANCET Oncology

Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial

Stupp Regimen: benefit maintained across age groups

	Deaths/ patients	Hazard ratio (95% CI)	Median (months; 95% CI)	2 years (%)	3 years (%)	4 years (%)	5 years (%)
Overall							
Radiotherapy	278/286	1·0	12·1 (11·2–13·0)	10·9 (7·6–14·8)	4·4 (2·4–7·2)	3·0 (1·4–5·7)	1·9 (0·6–4·4)
Combined	254/287	0·6 (0·5–0·7)	14·6 (13·2–16·8)	27·2 (22·2–32·5)	16·0 (12·0–20·6)	12·1 (8·5–16·4)	9·8 (6·4–14·0)
Age <50 years							
Radiotherapy	83/88	1·0	13·6 (11·6–15·6)	14·8 (8·3–23·0)	6·5 (2·5–13·1)	4·9 (1·5–11·3)	4·9 (1·5–11·3)
Combined	79/95	0·6 (0·4–0·8)	17·4 (15·3–21·5)	34·7 (25·3–44·3)	25·4 (17·0–34·7)	20·1 (12·4–29·1)	17·0 (9·8–25·9)
Age ≥50 years							
Radiotherapy	195/198	1·0	11·9 (10·6–12·6)	9·1 (5·6–13·7)	3·4 (1·4–6·7)	2·3 (0·8–5·2)	0·7 (0·1–3·5)
Combined	175/192	0·7 (0·5–0·8)	13·6 (11·8–15·1)	23·5 (17·7–29·7)	11·4 (7·3–16·5)	8·2 (4·7–12·9)	6·4 (3·2–11·0)
Age 50–60 years							
Radiotherapy	109/111	1·0	12·0 (10·0–14·2)	11·8 (6·6–18·6)	4·2 (1·5–9·4)	2·1 (0·4–6·6)	1·1 (0·1–5·1)
Combined	101/109	0·7 (0·5–0·9)	14·6 (13·6–17·9)	24·8 (17·1–33·2)	11·0 (6·0–17·7)	8·0 (3·8–14·2)	6·4 (2·6–12·6)
Age >60 years							
Radiotherapy	86/87	1·0	11·8 (10·4–12·7)	5·7 (2·1–12·0)	2·3 (0·4–7·2)	2·3 (0·4–7·3)	0
Combined	74/83	0·7 (0·5–0·97)	10·9 (8·9–14·9)	21·8 (13·5–31·2)	12·3 (6·1–20·8)	8·8 (3·6–16·9)	6·6 (2·1–14·7)

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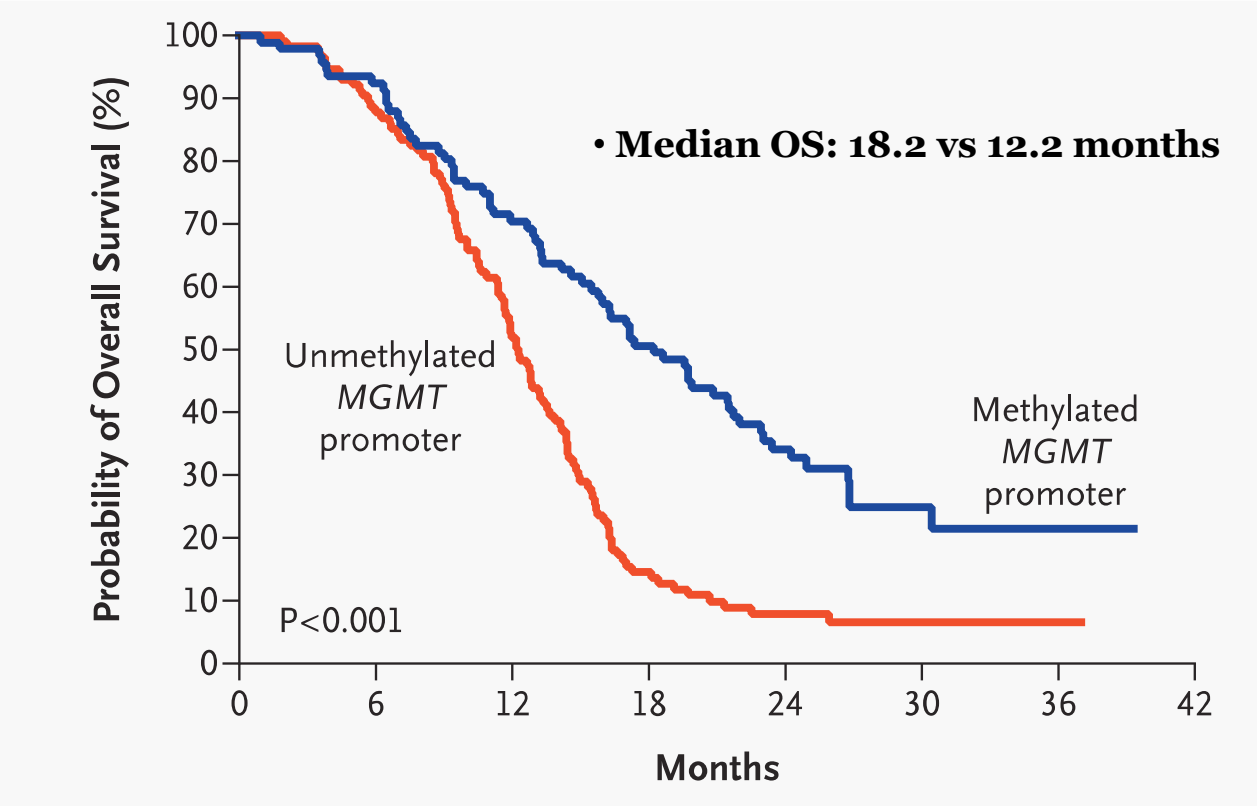
The NEW ENGLAND JOURNAL of MEDICINE

MGMT Gene Silencing and Benefit from Temozolomide in Glioblastoma

Positive prognostic role of MGMT methylation



- Overall, MGMT promoter methylated in 45% of patients
- MGMT promoter was an independent favorable prognostic factor, irrespective of treatment.

Hegi M. et al. NEJM 2005;352

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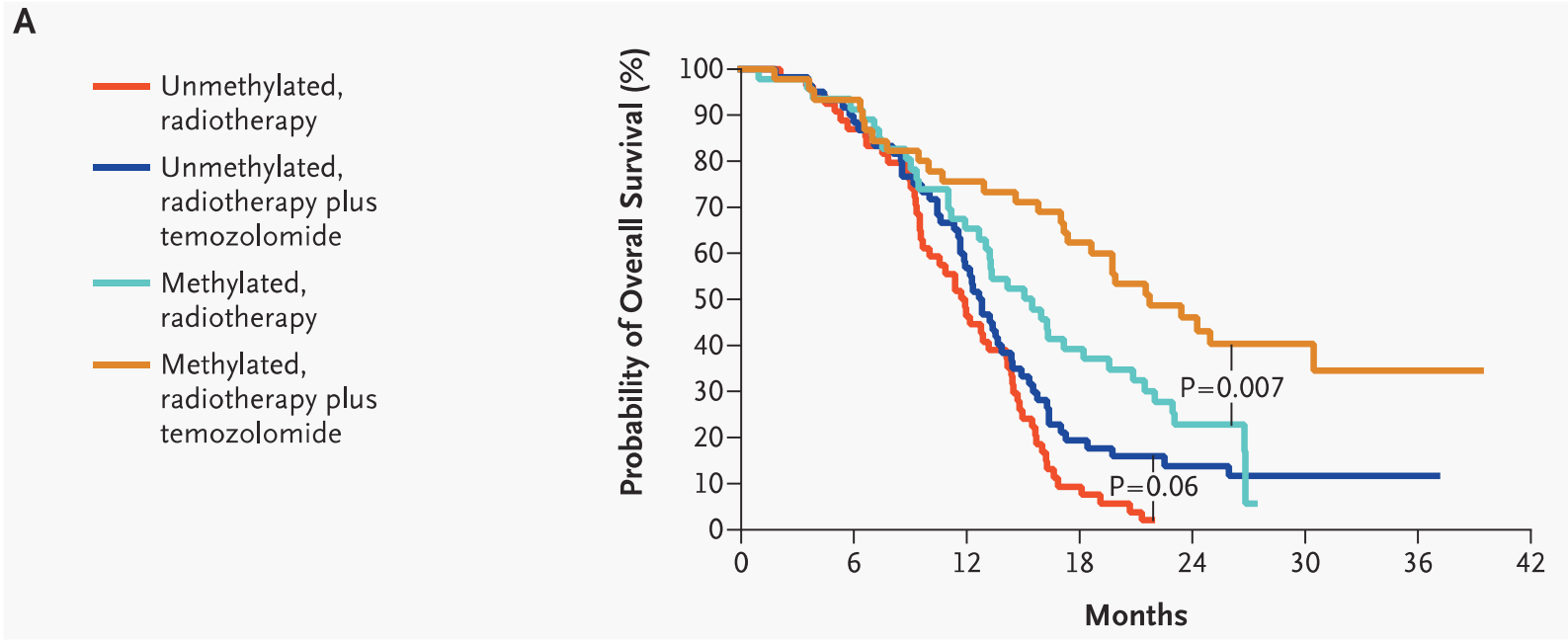
The NEW ENGLAND JOURNAL of MEDICINE

MGMT Gene Silencing and Benefit from Temozolomide in Glioblastoma

Stupp Regimen: major benefit seen in methylated patients



- **Patients with GBM containing a methylated MGMT promoter benefited from TMZ**
- **Unmethylated patients did not have such a benefit; for these patients alternative treatments with different mechanisms of action or methods of inhibiting MGMT shoulf be investigated**

• Can we "somehow" overcome TMZ resistance...?

Hegi M. et al. NEJM 2005;352

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Alternative TMZ post-radiation dosing regimens

Regimen	Dose and schedule	Drug exposure
Standard monthly	**150-200mg/m² x 5d q28d**	**1**
Continuous daily	50mg/m²/d	1.8
Continuous (42-49/56-63)	75mg/m²/d x 7d/wk for 6 wk	2.1
Alternating (21/28)	85-100 mg/m²/d x 21d q 28d	2.6
Alternating weekly (7/14)	135-150 mg/m²/d x 7d qow	3.2
Twice daily	200 mg/m² (1st dose), 90-100 mg/m² q12h x 9 doses	---

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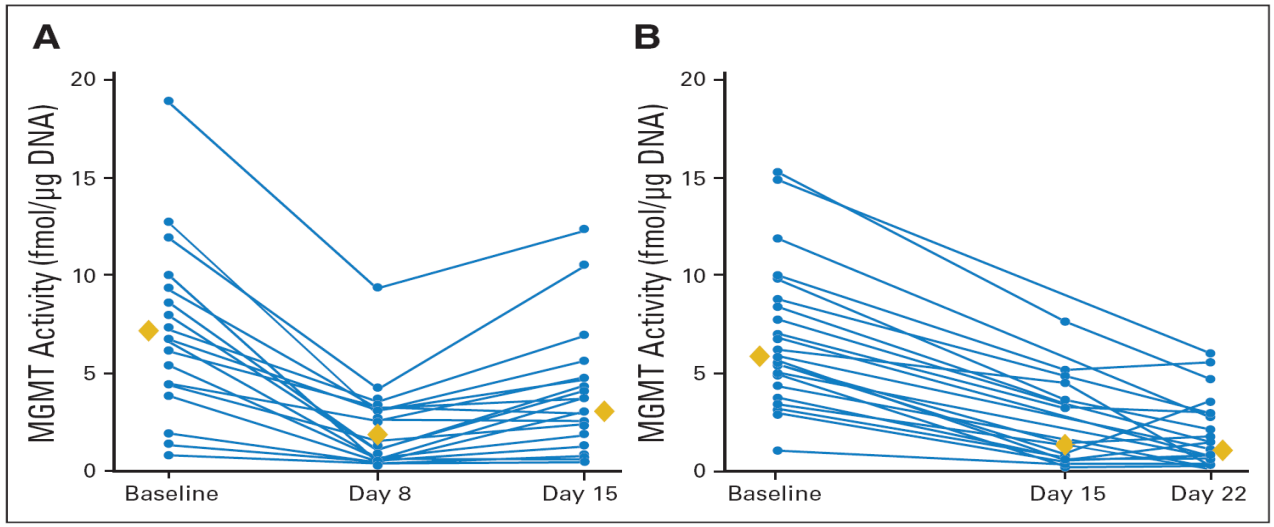
Marked inactivation of O^6-alkylguanine-DNA alkyltransferase activity with protracted temozolomide schedules

Alternative regimens: Alternating TMZ



A MGMT activity in PBMC after treatment with temozolomide 7 days on/7days off schedule

B MGMT activity in PBMC after treatment with temozolomide 21/28 day schedule

Dose and schedule	Average decrease in MGMT activity		
	DAY 7	DAY 14-15	DAY 21
50 to 175 mg/m²/day x 7 days every other week	**72%**	**55%***	
50 to 150 mg/m²/day x 21 days with 1 week rest		**63%**	**73%**

*After 7-day treatment free period

Tolcher AW. et al. Br J Cancer 2003;88

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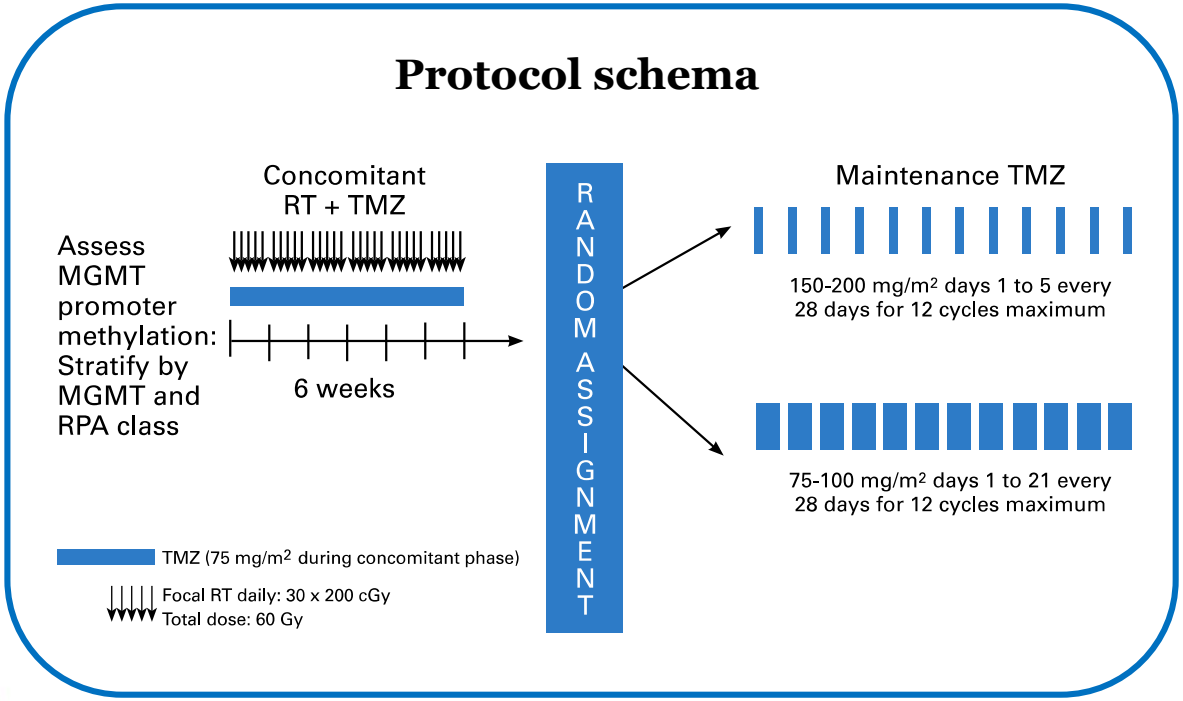
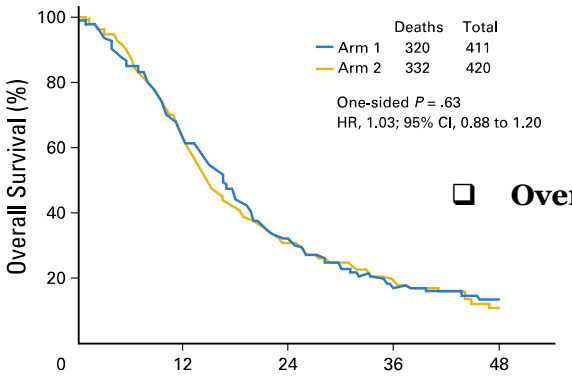
JOURNAL OF CLINICAL ONCOLOGY

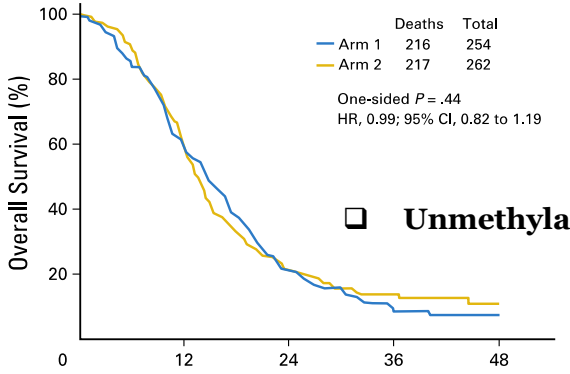
Dose-Dense Temozolomide for Newly Diagnosed Glioblastoma: A Randomized Phase III Clinical Trial

Dose-dense TMZ: RTOG 0525

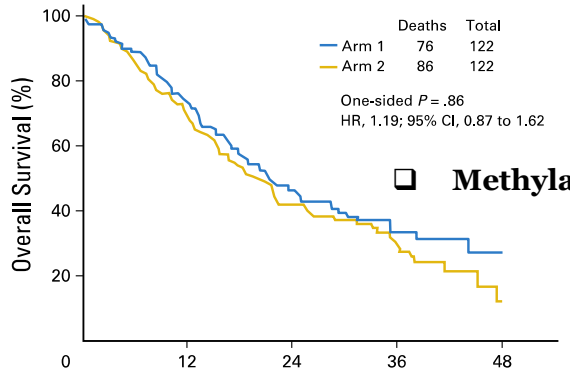




❑ **Overall population**



❑ **Unmethylated MGMT promoter**



❑ **Methylated MGMT promoter**

This study did not demonstrate improved efficacy for DD – TMZ for newly diagnosed GBM, regardless of methylation status

Gilbert MR. et al. JCO 2013;31

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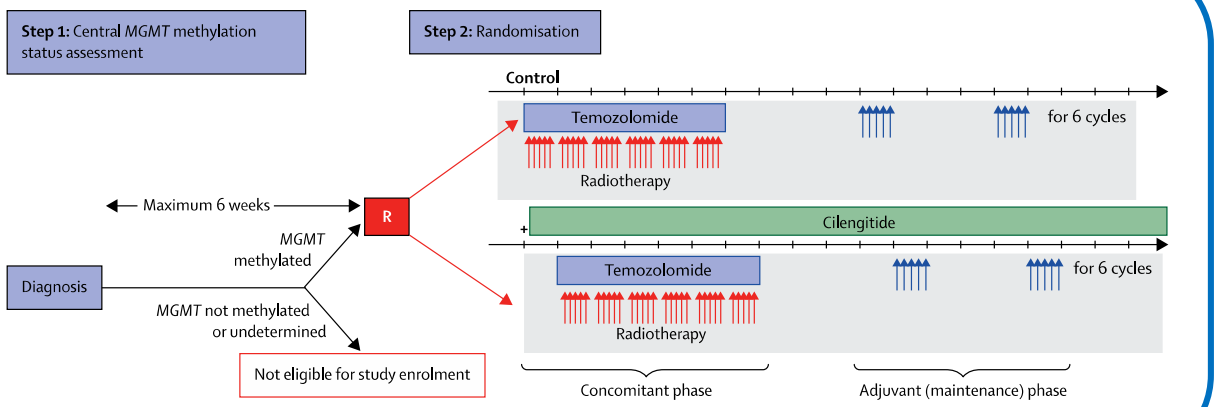
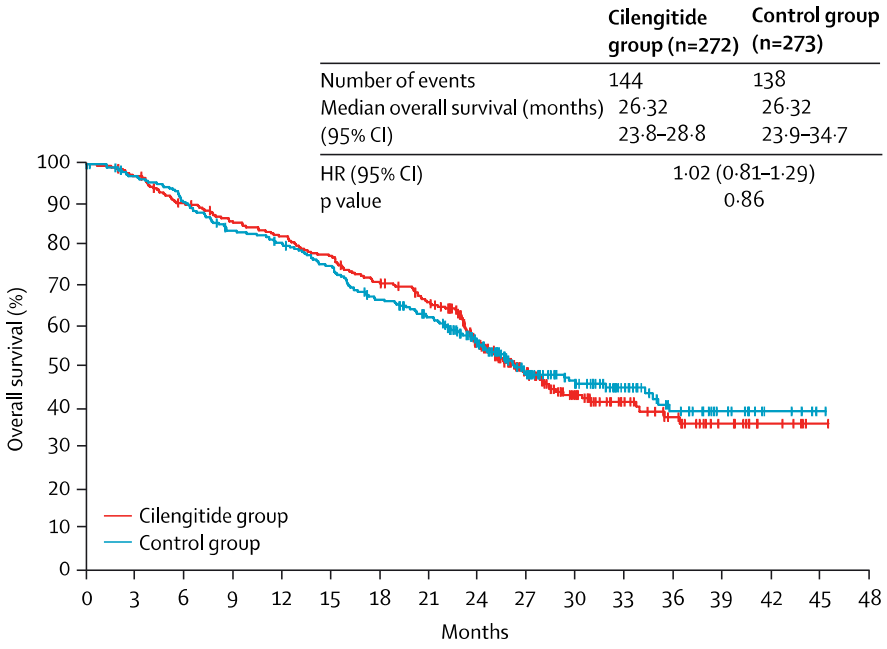
THE LANCET Oncology

Cilengitide combined with standard treatment for patients with newly diagnosed glioblastoma with methylated *MGMT* promoter (CENTRIC EORTC 26071-22072 study): a multicentre, randomised, open-label, phase 3 trial

Alternative drugs: CILENGITIDE (CENTRIC/EORTC 26071)





- **Cilengitide is a selective integrin inhibitor**
- Data from phase I-II studies suggest that it has antitumor activity in association with TMZ (particularly in tumors with methylated MGMT promoter).
- **545 patients randomized** to receive either CILENGITIDE (272) or PLACEBO (273) in addition to Stupp regimen

"The addition of Cilengitide to Stupp regimen did not improve outcomes"

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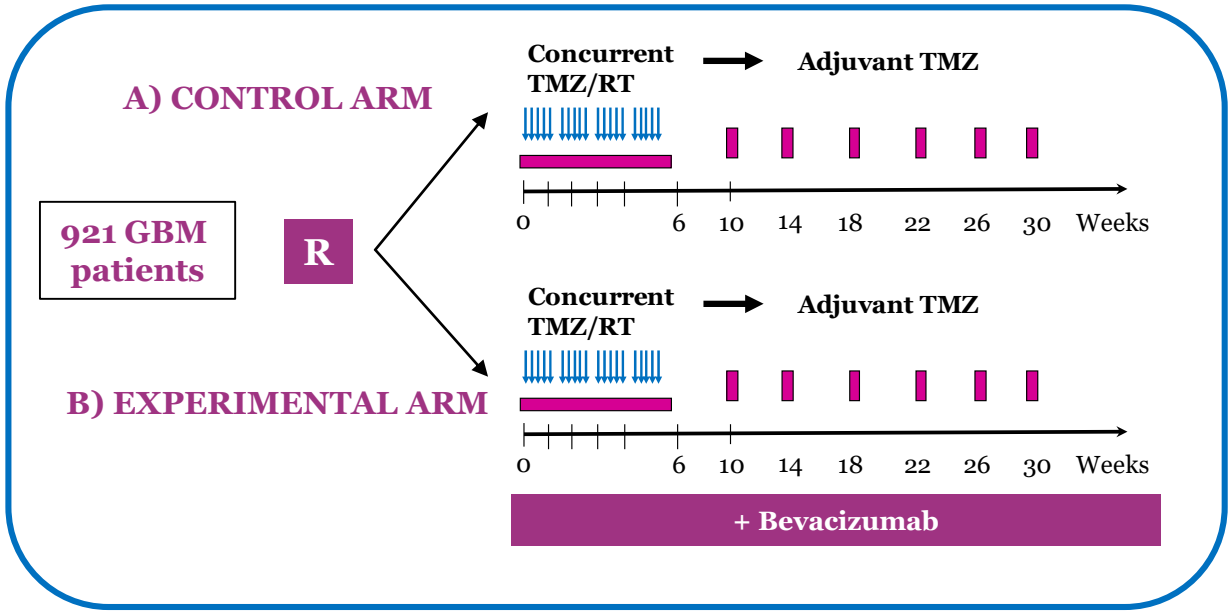
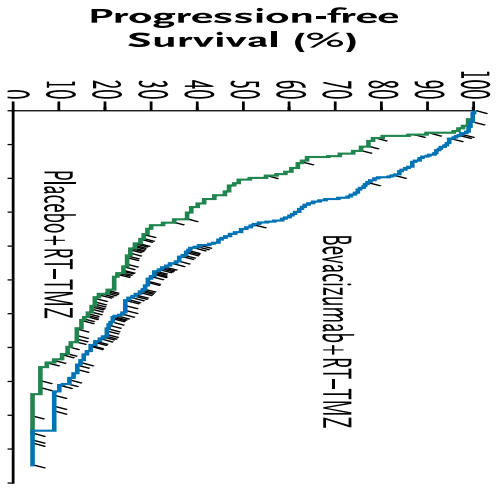
Stupp R. et al. Lancet Oncol 2014;15

The NEW ENGLAND JOURNAL of MEDICINE

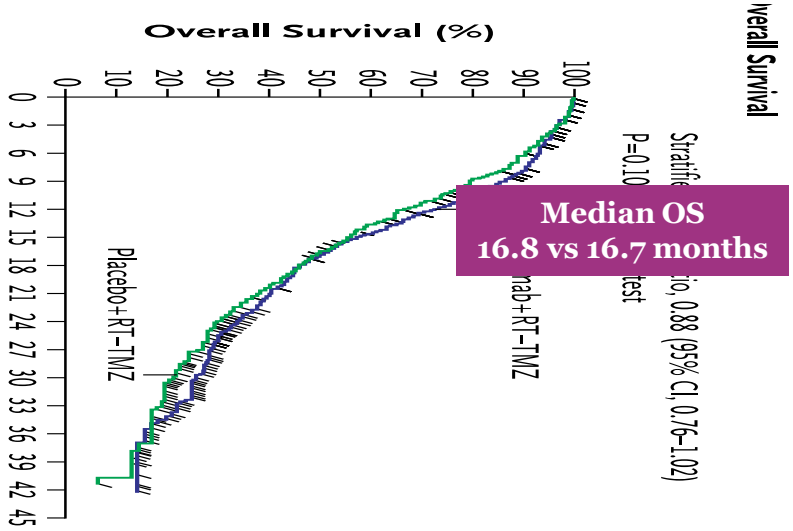
Bevacizumab plus Radiotherapy–Temozolomide for Newly Diagnosed Glioblastoma

Alternative drugs: Bevacizumab (AVAglio)





Median PFS
10.6 vs 6.2 months



Median OS
16.8 vs 16.7 months

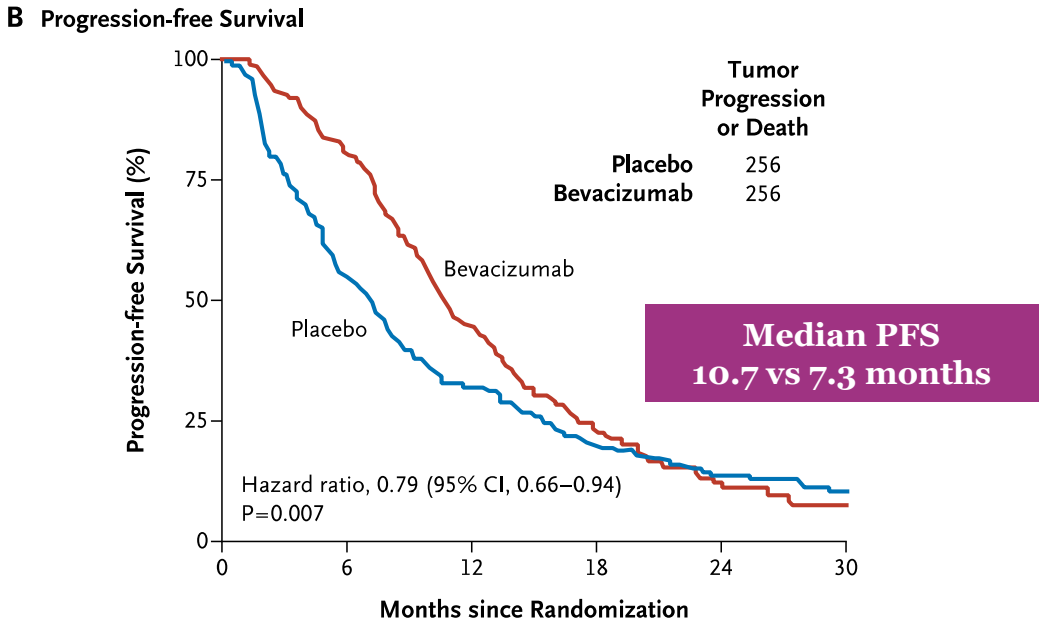
- The addition of Bevacizumab to TMZ-radiotherapy did not improve OS.
- Improved PFS and KPS were observed with Bevacizumab
- Rate of adverse events was higher with Bevacizumab (G3 related: 32% vs 15%)

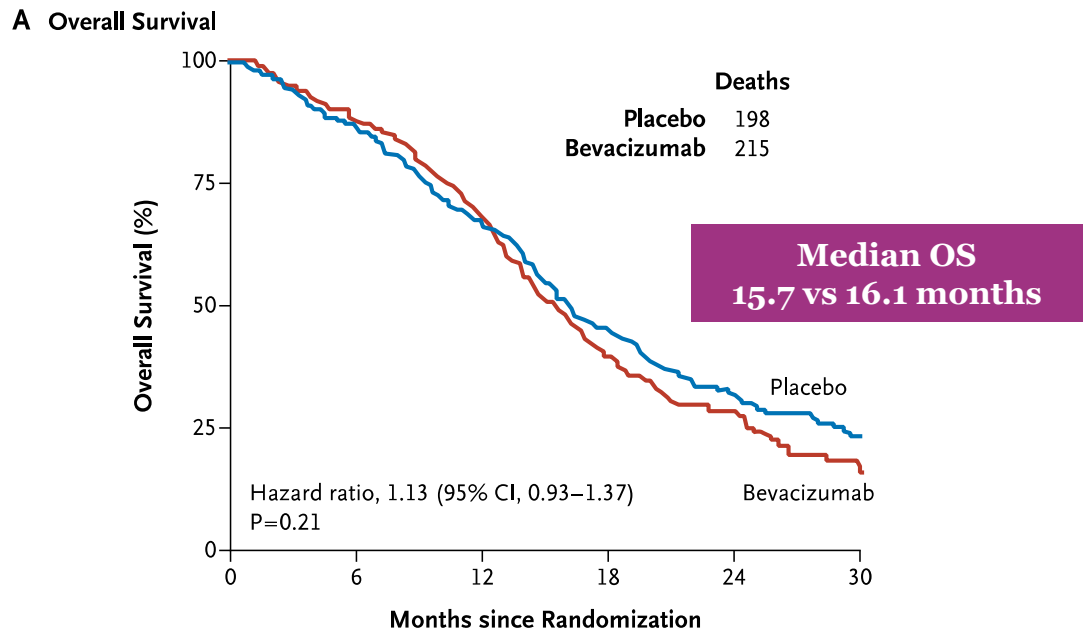
Chinot OL. et al. NEJM 2014;370

The NEW ENGLAND JOURNAL of MEDICINE

A Randomized Trial of Bevacizumab for Newly Diagnosed Glioblastoma

Alternative drugs: Bevacizumab (RTOG 0825)





- ❑ **First-line use of Bevacizumab did not improve OS**
- ❑ **PFS was prolonged, but did not reach the prespecifiec improvement target (-30% reduction)**

Gilbert MR. et al. NEJM 2014:370

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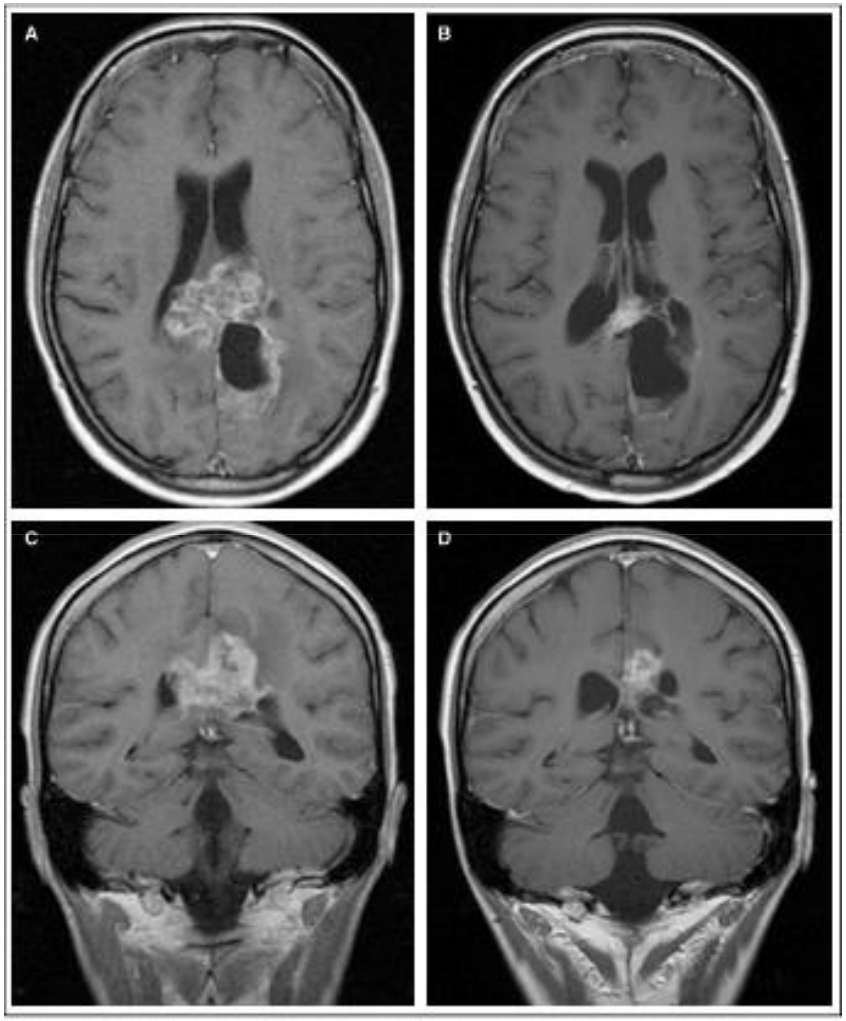
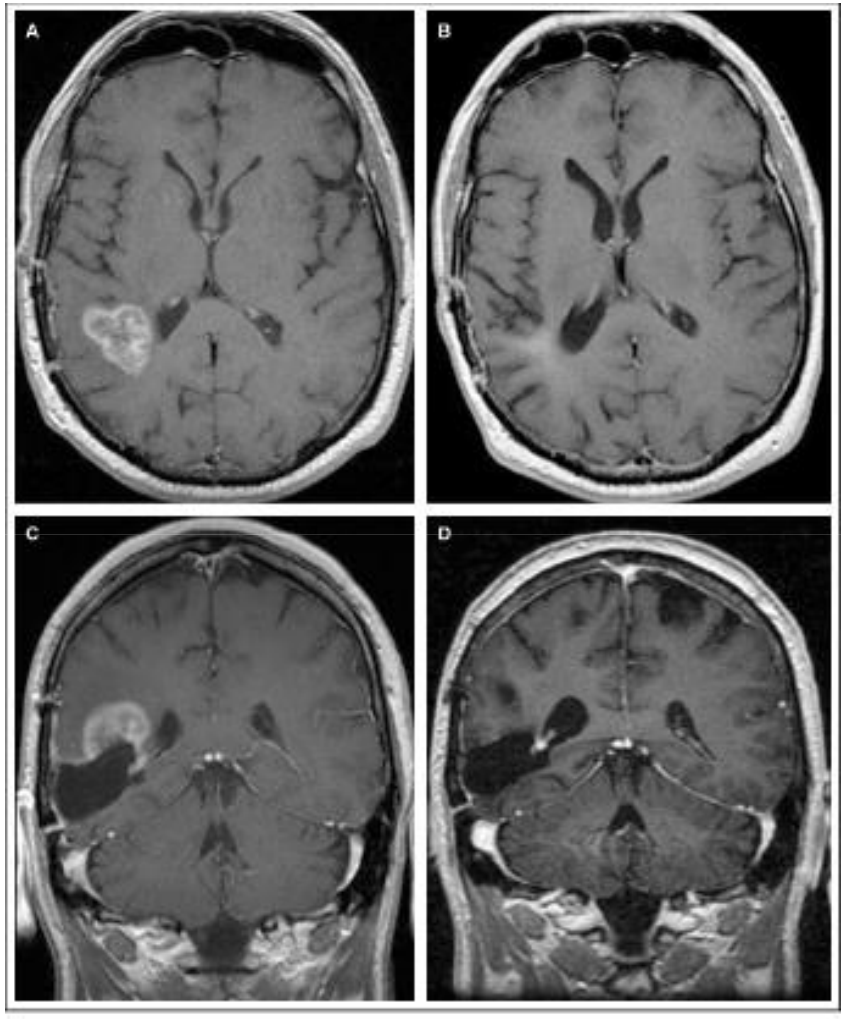
Crucial point when administering Bevacizumab…





Is it a RESPONSE or a PSEUDORESPONSE ?

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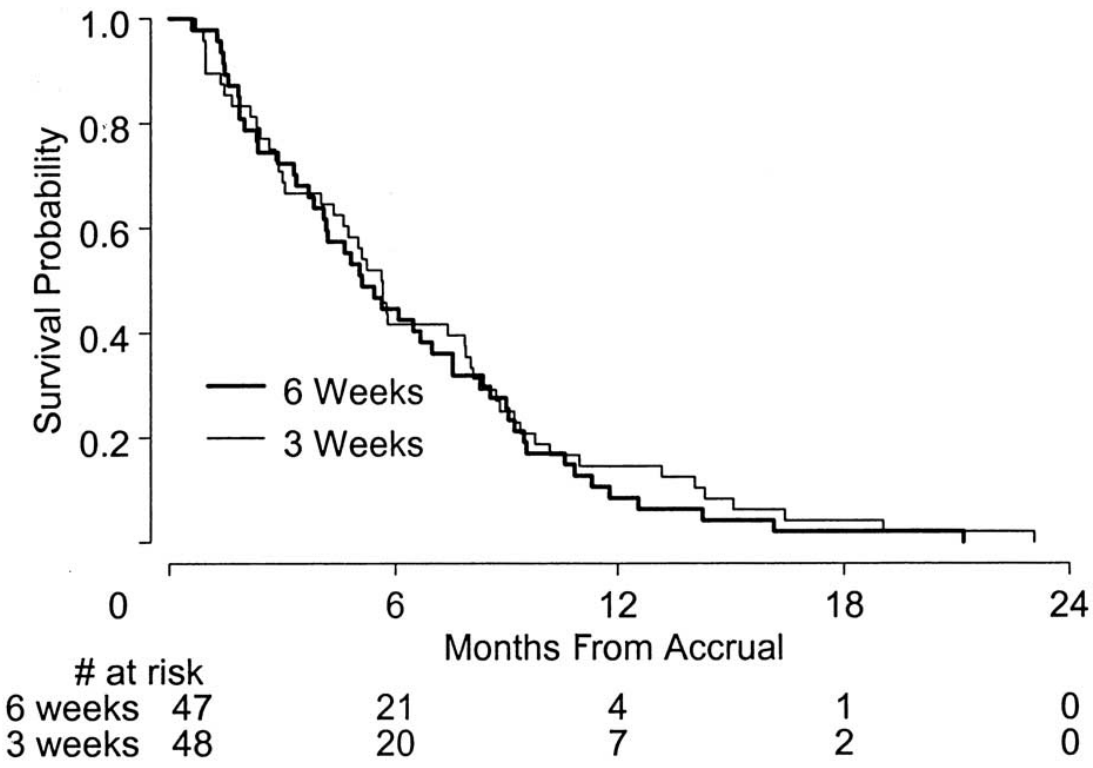
JOURNAL OF CLINICAL ONCOLOGY

Abbreviated Course of Radiation Therapy in Older Patients With Glioblastoma Multiforme: A Prospective Randomized Clinical Trial

Elderly patients: Short course RT



- **100 patients**
- **Short course = 40 Gy/15 fr**
- **Standard course = 60 Gy/30 fr**

- **There is no difference in OS between patients receiving standard or short-course RT**
- **The short course of RT seems a reasonable treatment option for older patients with GBM**

ROA W. et al. JCO2004;22

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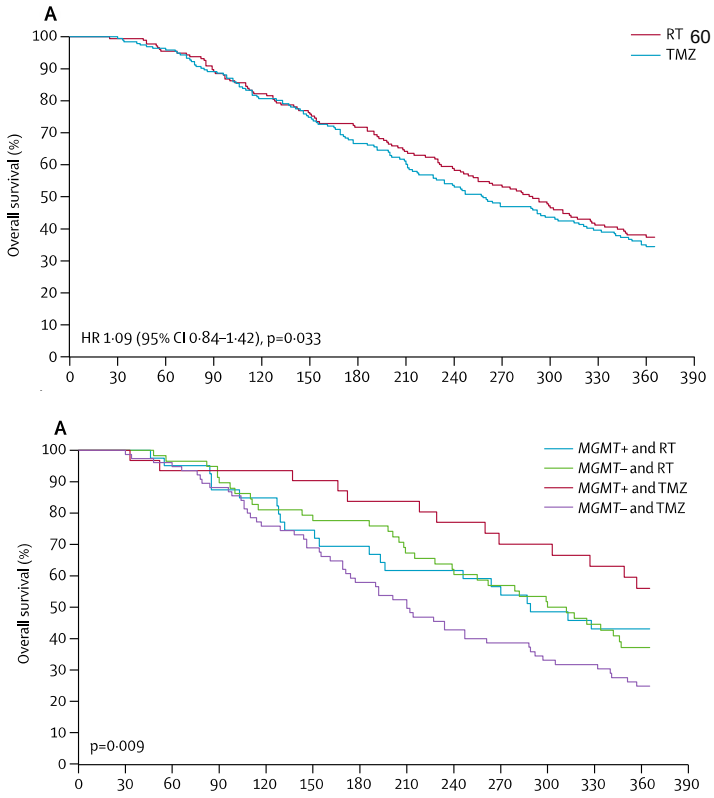
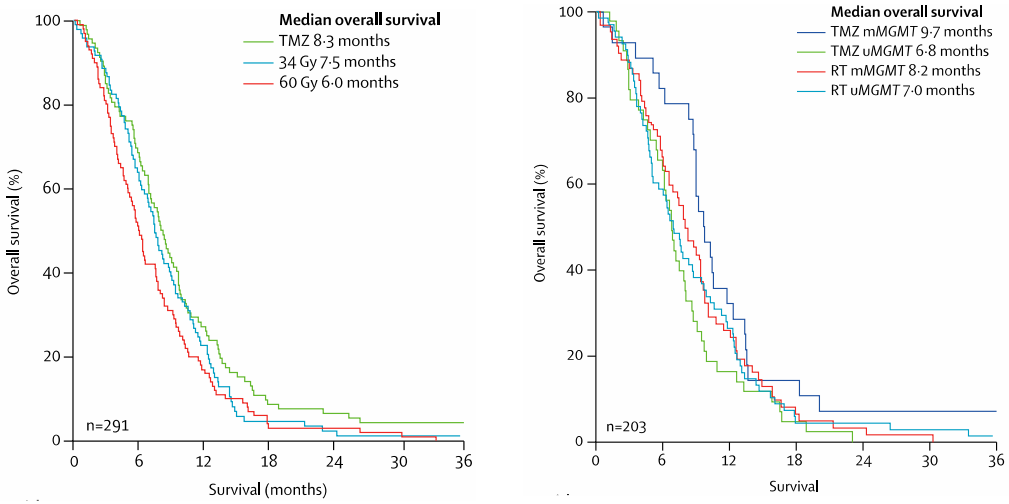
Elderly patients: TMZ vs RT (NORDIC and NOA-08)

Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial



Wick W. et al. Lancet Oncol 2012;13

Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial



Malmstrom A. et al. Lancet Oncol 2012;13

- **TMZ alone is not inferior to RT alone in the treatment of Elderly GBM.**
- **MGMT promoter methylation seems to be a useful biomarker and could aid decision-making**

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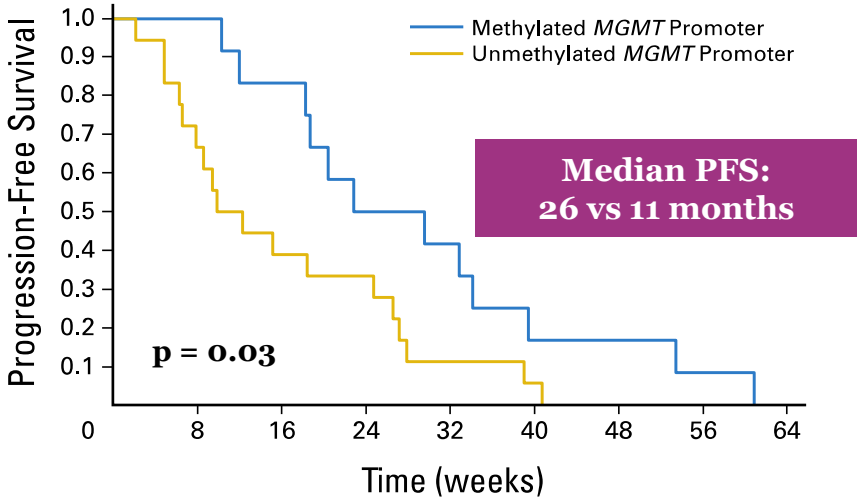
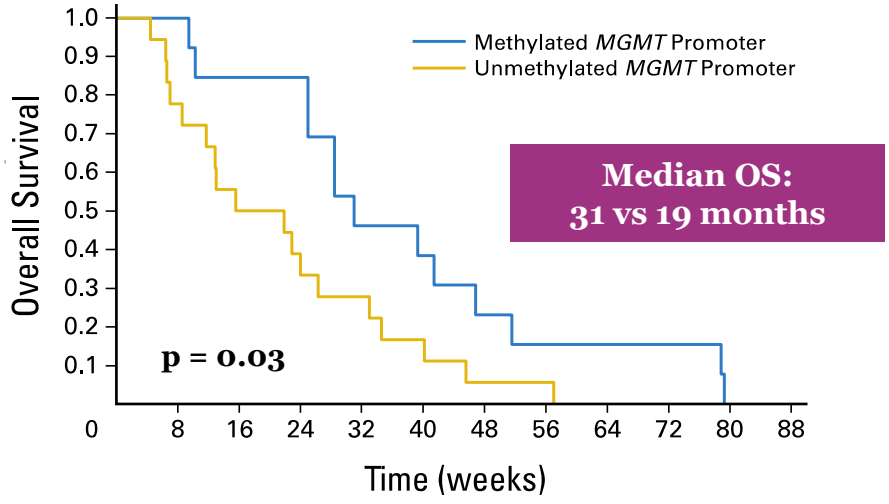
JOURNAL OF CLINICAL ONCOLOGY

Temozolomide in Elderly Patients With Newly Diagnosed Glioblastoma and Poor Performance Status: An ANOCEF Phase II Trial

Elderly with poor KPS: TMZ alone is an option (ANOCEF study)





- **TMZ alone has an acceptable tolerance in elderly GBM patients with low KPS (<70) and increases survival compared with supportive care alone, especially in those with methylated MGMT promoter**

Perez-Larraya JG. et al. JCO 2011;29

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The NEW ENGLAND JOURNAL of MEDICINE

Short-Course Radiation plus Temozolomide in Elderly Patients with Glioblastoma

TMZ + "short-course" RT in Elderly: New standard regimen ?

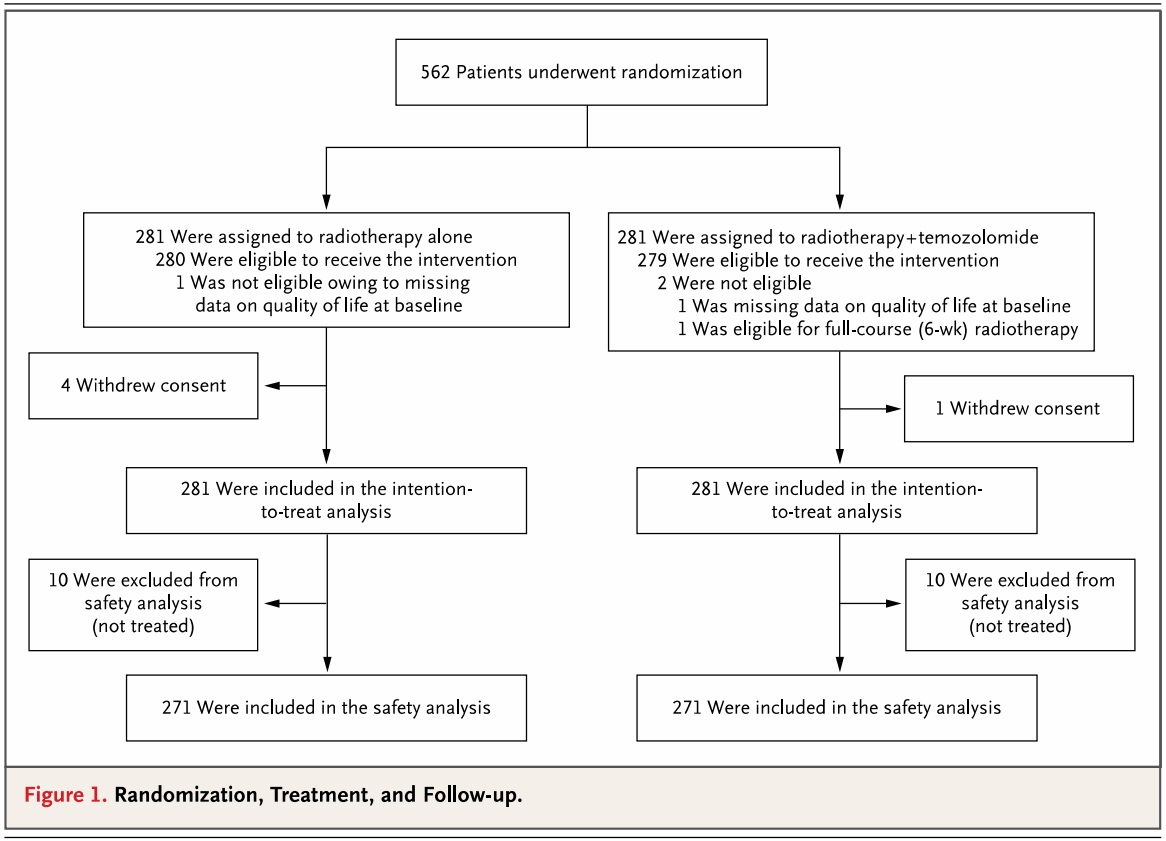

Figure 1. Randomization, Treatment, and Follow-up.

- Newly diagnosed Glioblastoma
- Patients 65 years of age or older (median age 73)
- RT dose: 40 Gy/15 fractions
- Concurrent TMZ: 75 mg/m^2/day for 21 consecutive days
- Adjuvant TMZ: 150-200 mg/m^2/day for 5 consecutive days out of 28 for up to 12 cycles or until progression

Perry JR et al, NEJM 2017;376

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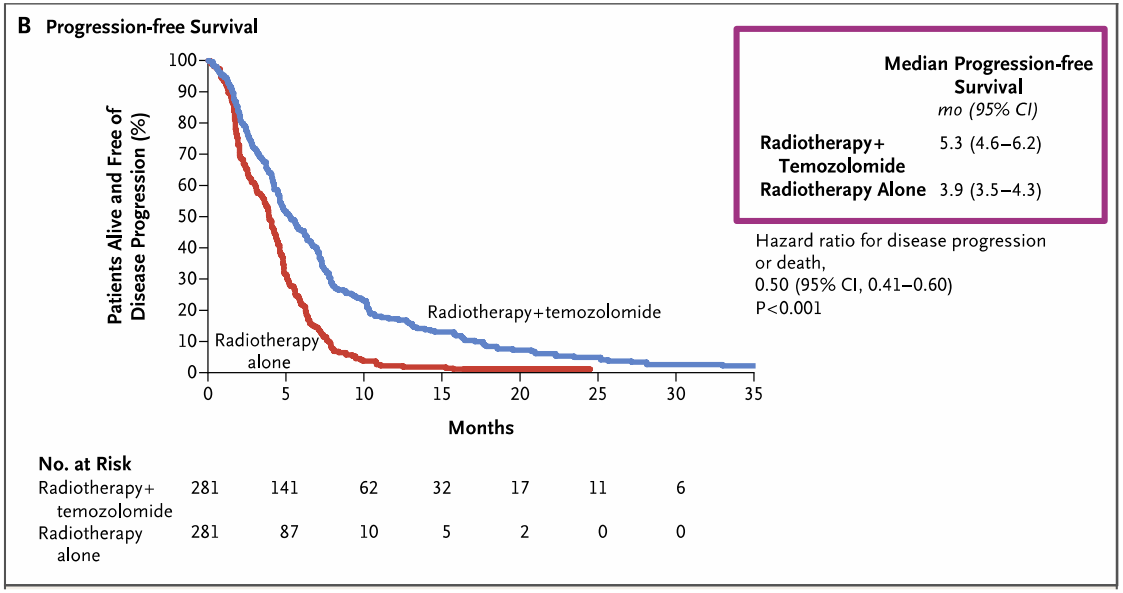
The NEW ENGLAND JOURNAL of MEDICINE

Short-Course Radiation plus Temozolomide in Elderly Patients with Glioblastoma



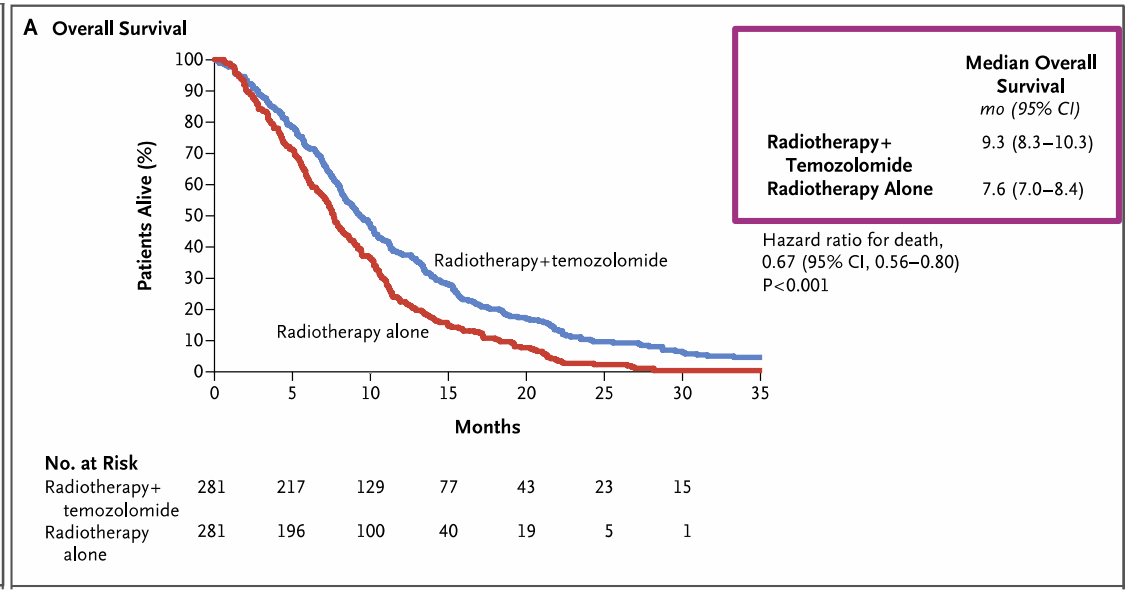


Table 3. Exploratory Analyses of Overall Survival Rate at 12, 18, and 24 Months According to Treatment Group and MGMT Status.

Population	At 12 Months	At 18 Months	At 24 Months
	percent (95% confidence interval)		
All patients			
Radiotherapy alone	22.2 (17.5–27.3)	10.8 (7.4–14.8)	2.8 (1.2–5.4)
Radiotherapy plus temozolomide	37.8 (32.1–43.6)	20.0 (15.5–24.9)	10.4 (7.1–14.5)
Patients with unmethylated MGMT			
Radiotherapy alone	21.3 (13.7–30.0)	12.7 (6.9–20.3)	3.8 (1.1–9.6)
Radiotherapy plus temozolomide	32.3 (23.0–42.0)	13.4 (7.3–21.2)	6.7 (2.7–13.1)
Patients with methylated MGMT			
Radiotherapy alone	29.9 (19.9–40.5)	13.6 (7.0–22.4)	4.1 (1.1–10.4)
Radiotherapy plus temozolomide	55.7 (44.7–65.3)	34.1 (24.4–44.0)	17.8 (10.5–26.7)

Perry JR et al, NEJM 2017;376

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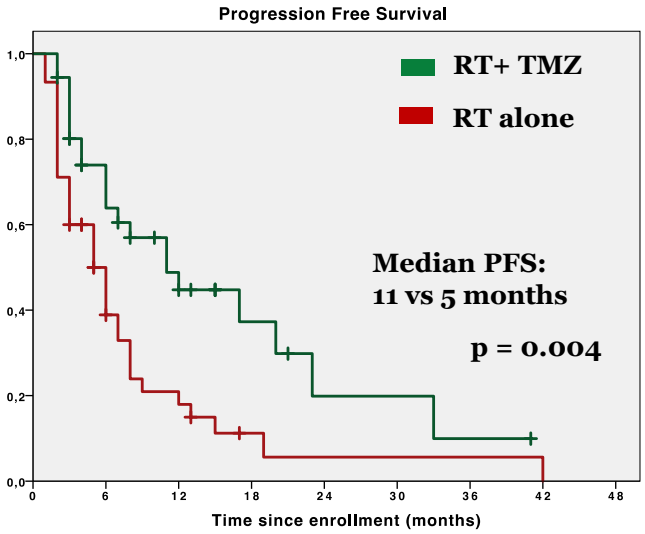
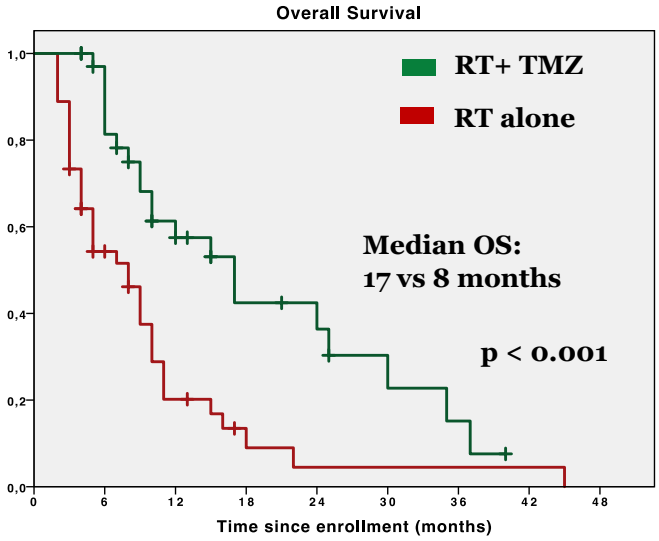
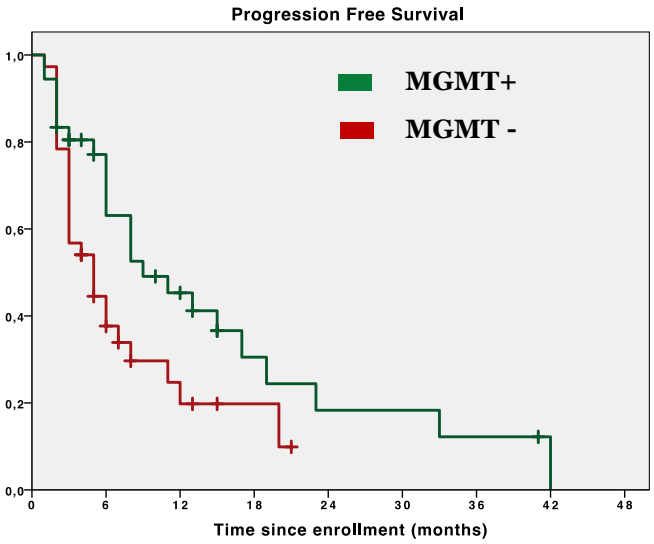
Experience @ University of Torino

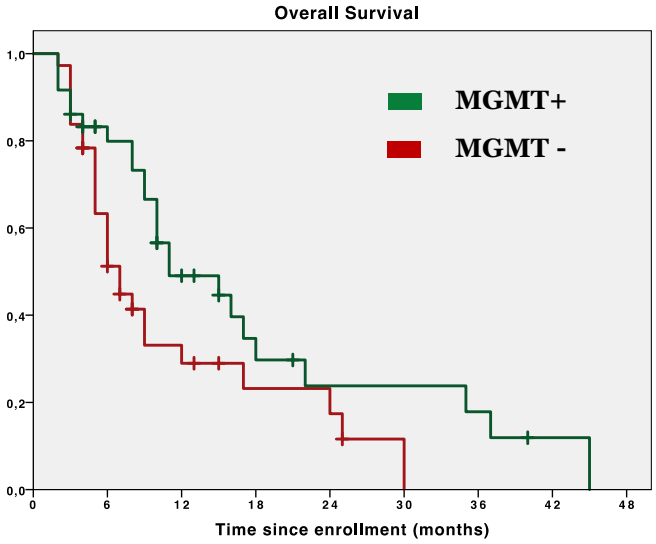




- 81 patients affected with glioblastoma
- Median age: 66 years (range 34-81)
- Median KPS before RT: 70 (range 50-90)

- Outcomes (overall population):
  - ✓ Median PFS: 6 (±7.8) months
  - ✓ Median OS: 10 (±8.6) months





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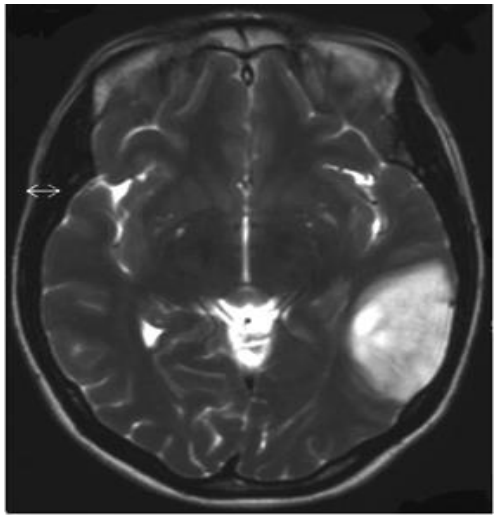
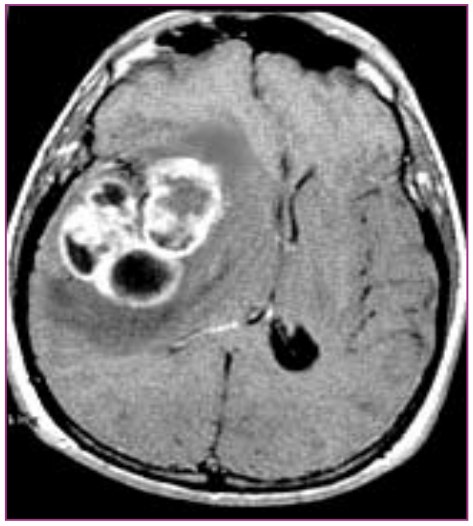
Combined modality treatment in brain tumors

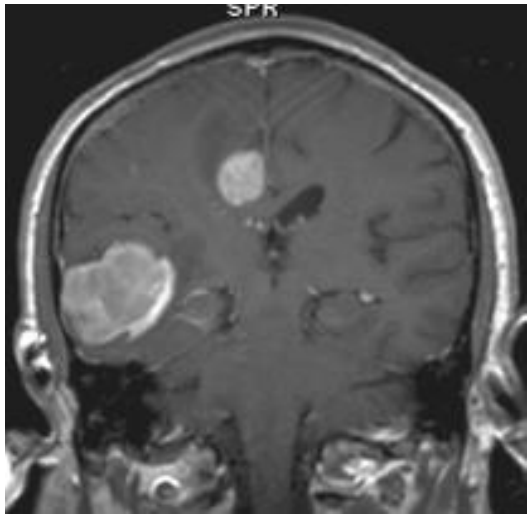
Low grade gliomas



High grade gliomas



PCNSL



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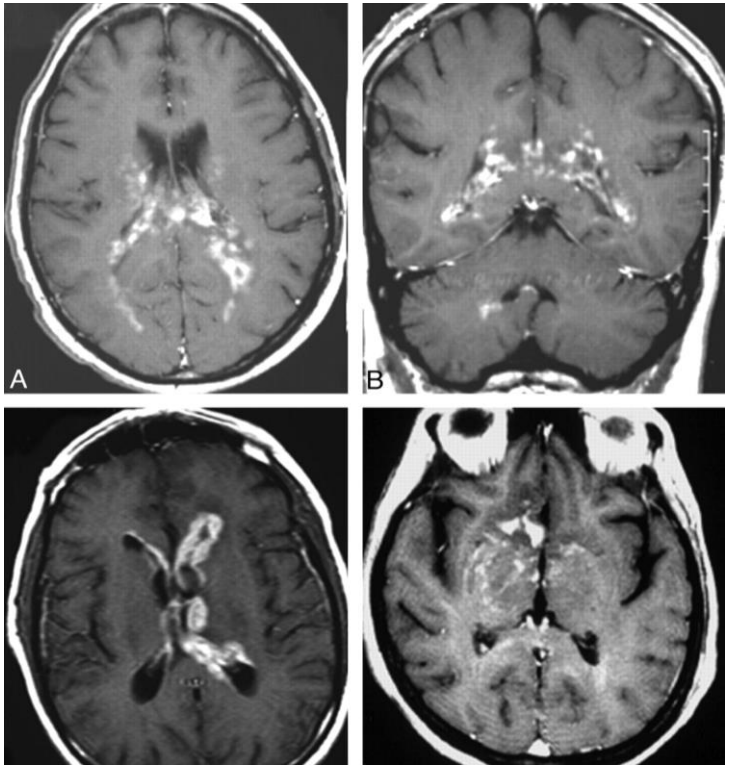
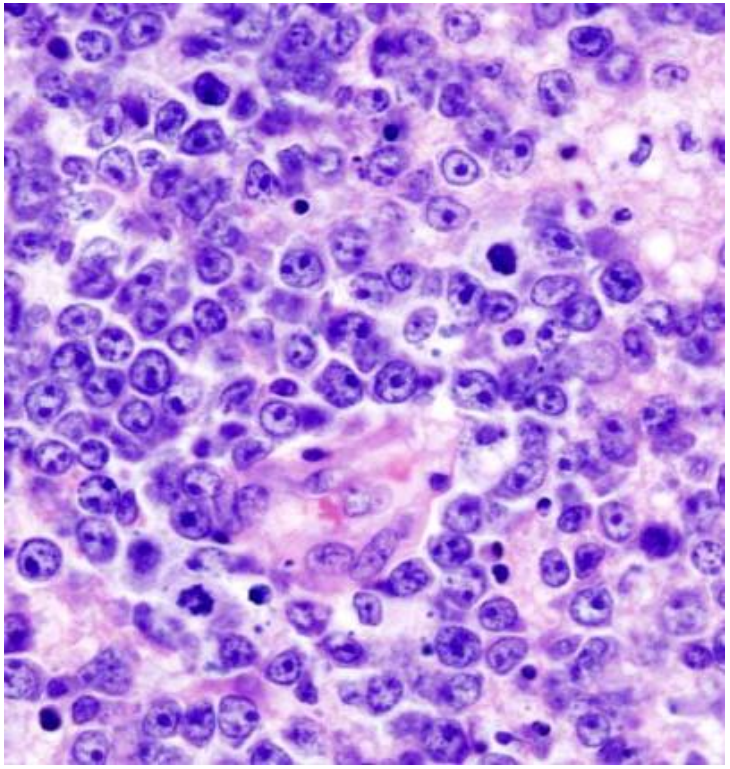
Primary CNS lymphoma (PCNSL)





- Rare (but progressively increasing incidence), aggressive brain tumor
- 4-6% of all extranodal NHLs
- 90-95% DLBCL

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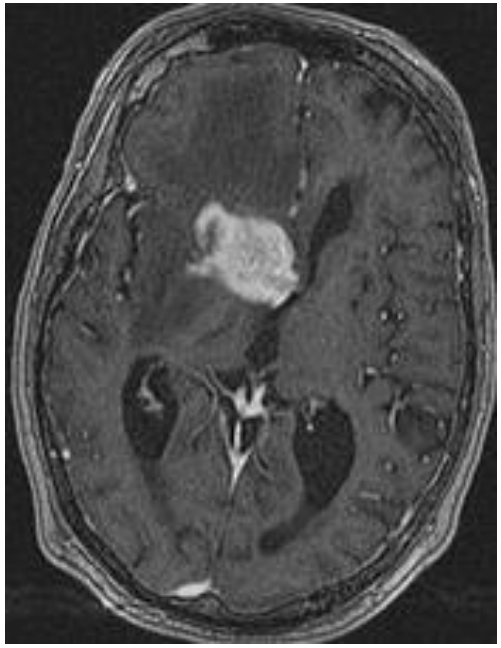
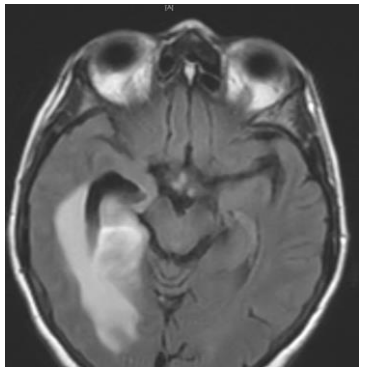
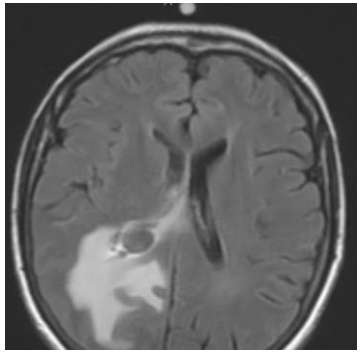
Clinical features

- **Sites of presentation**
  - Brain
  - Leptomeninges
  - Eye (PIOL)
  - Spinal cord
- **Mean age = 60**
- **Gender**: M/F = 1:1
- 23% ocular involvement
- 17% positive CSF cytology
- **Symptoms**
  - 51% behavioral/personality
  - 28% hemiparesis
  - 13% seizure







- **Chemo-radiotherapy is the most commonly used strategy**
- Efficacy of chemo: limited by special functional and micro-environmental characteristics of the CNS (BBB)
- Consolidation after chemotherapy represents the best role for radiotherapy (whole brain RT due to infiltrative nature of PCNSL)

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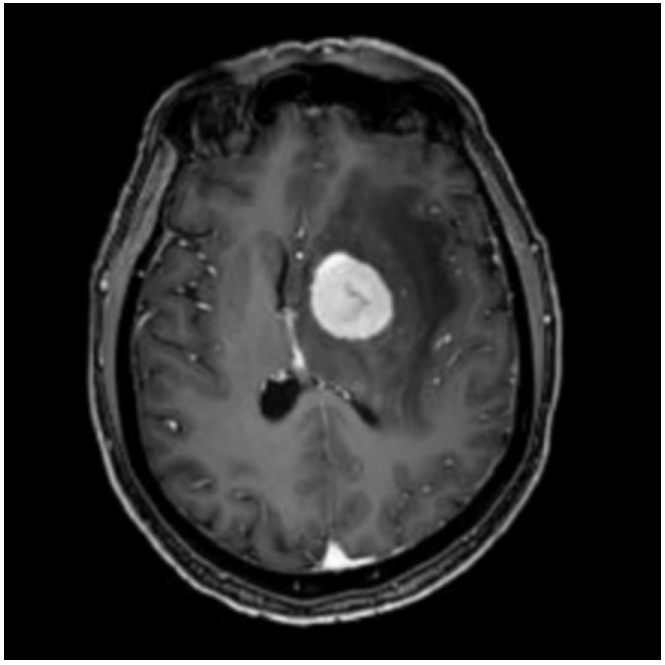
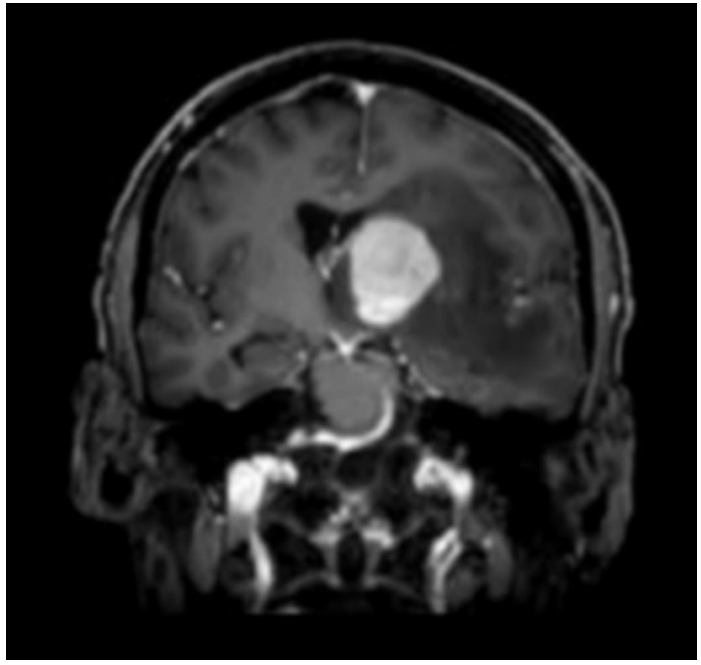
CLINICAL CASE #4 – PRIMARY CNS LYMPHOMA

- R.V. 59 years
- Headache and neurocognitive decline
- MRI: suspicion for PCNSL
- Stereotactic biopsy: confirmed PCNSL, DLBCL, CD20+, Ki67 80%
- PET-CT and Bone Marrow biopsy: no evidence of extracranial dissemination of lymphoma
- KPS: 70





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How would you treat this patients ?

A. **High dose Methotrexate**

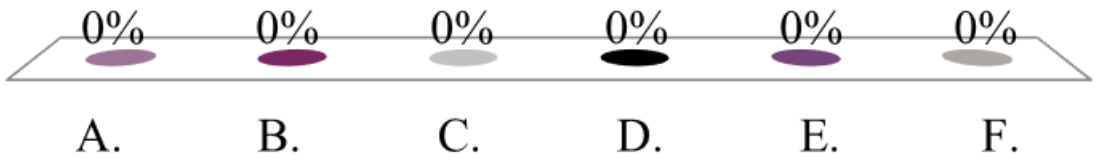
B. **High dose Methotrexate + ARA-C**

C. **Rituximab + High dose Methotrexate + ARA-C + Thiotepa**

D. **Rituximab + High dose Methotrexate + Procarbazine + Vincristine + ARA-C**

E. **R-CHOP**

F. **Upfront Whole Brain RT**



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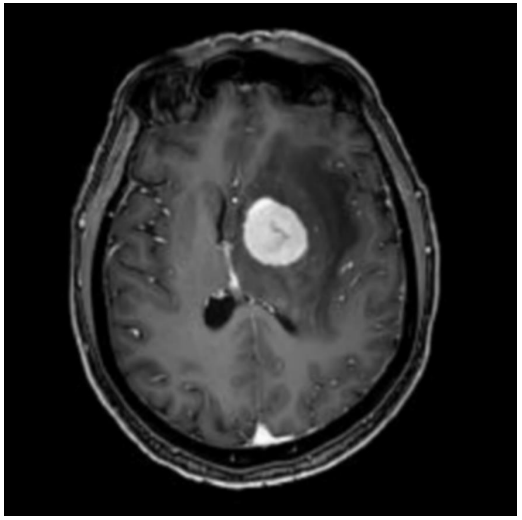
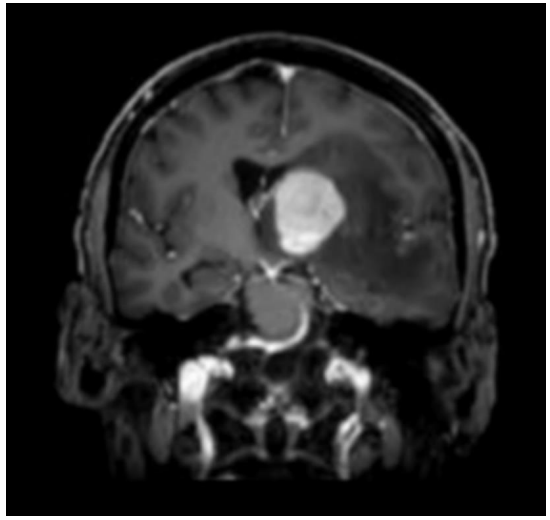
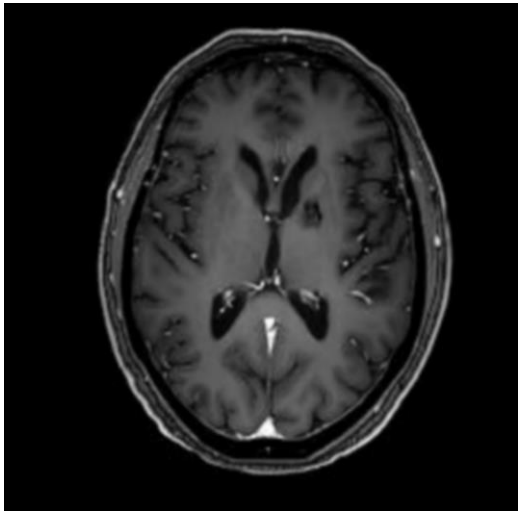
- The patient was treated according to the MATRix regimen x 4 (**M**ethotrexate + **A**RA-C + **T**hiotepa + **Ri**tu**x**imab)
- Complete response after CT

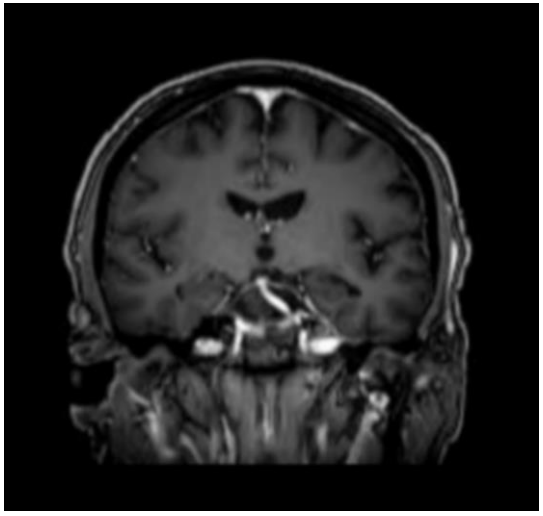
Before MATRix CT





After MATRix CT





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Indication for consolidative treatment ?

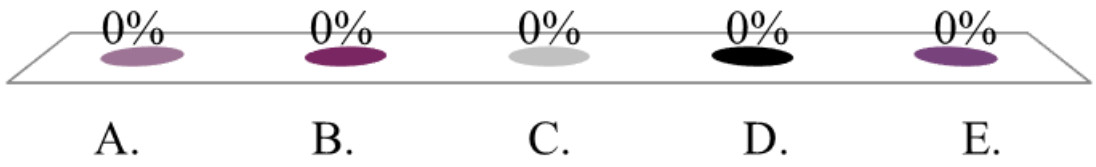
A. **NO**

B. **WBRT (30-36 Gy)**

C. **WBRT (40-45 Gy)**

D. **Autologous stem cell transpantation**

E. **Reduced Dose WBRT (23.4 Gy)**



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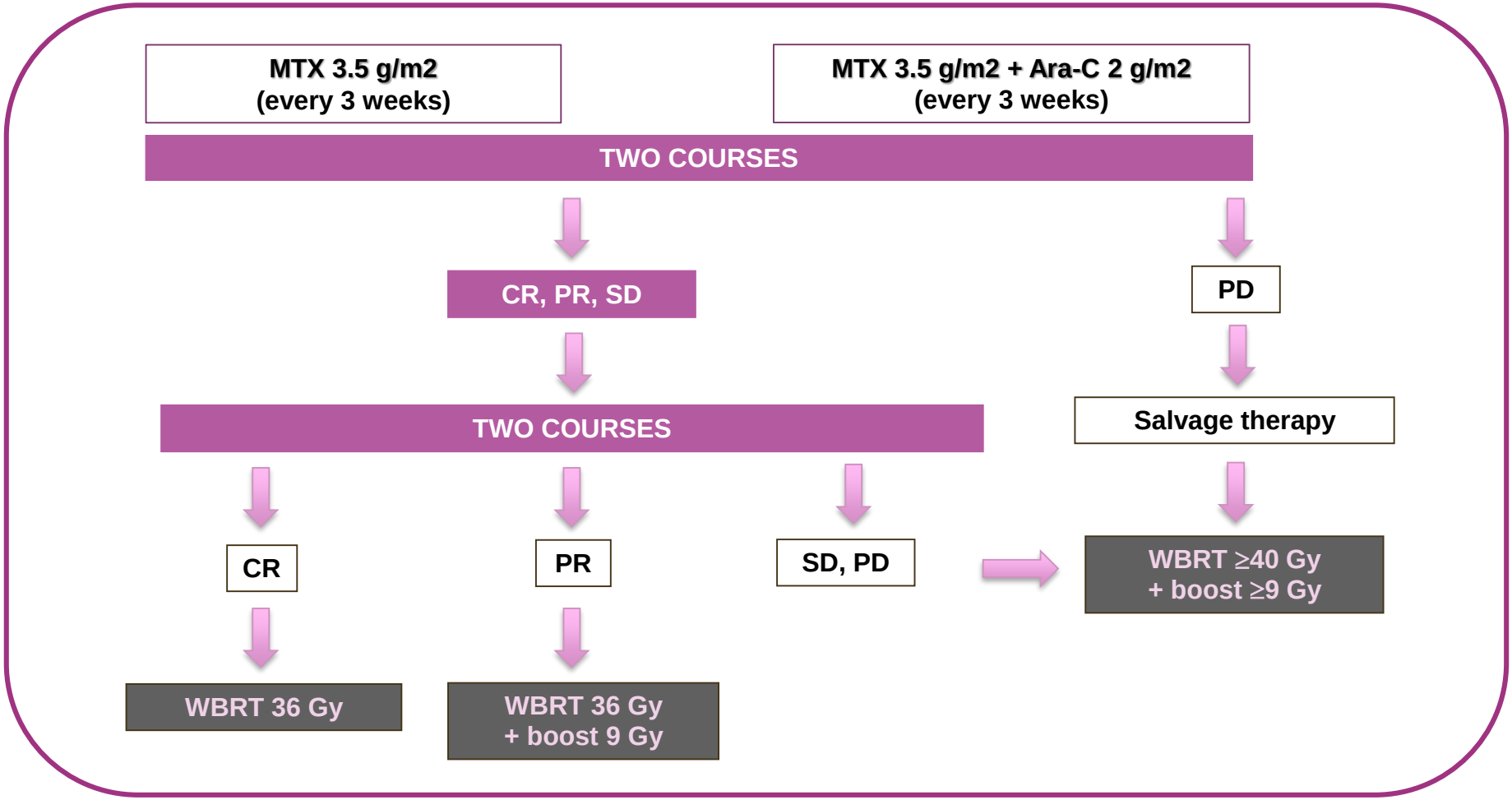
High-dose cytarabine plus high-dose methotrexate versus high-dose methotrexate alone in patients with primary CNS lymphoma: a randomised phase 2 trial

High dose MTX+ARA-C: IELSG20 trial



Ferreri AJ et al, Lancet 2009; 374

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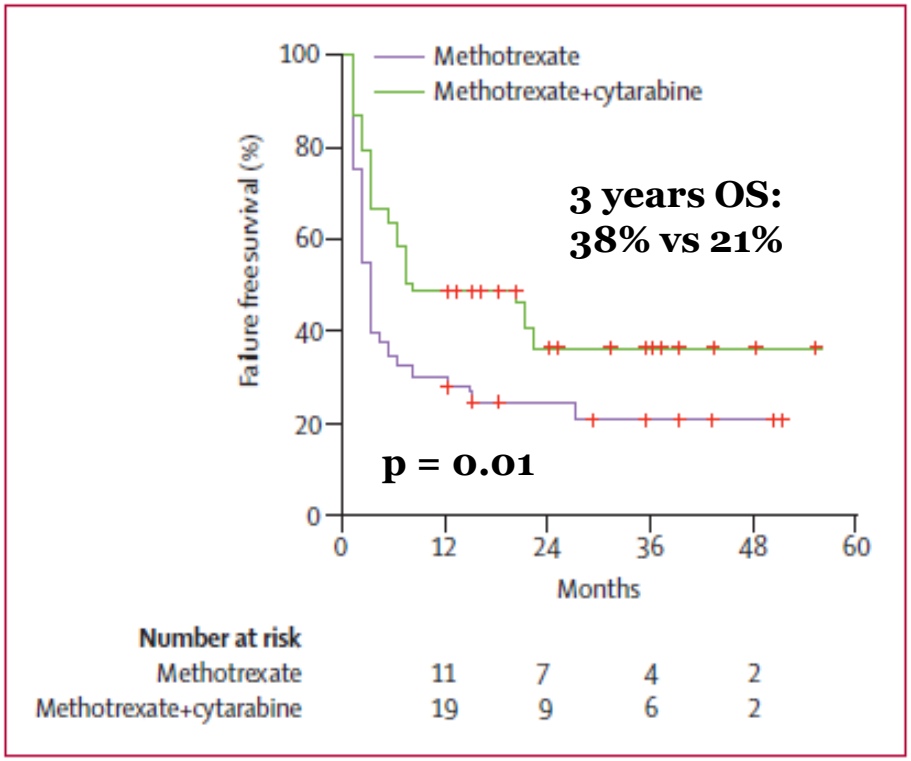
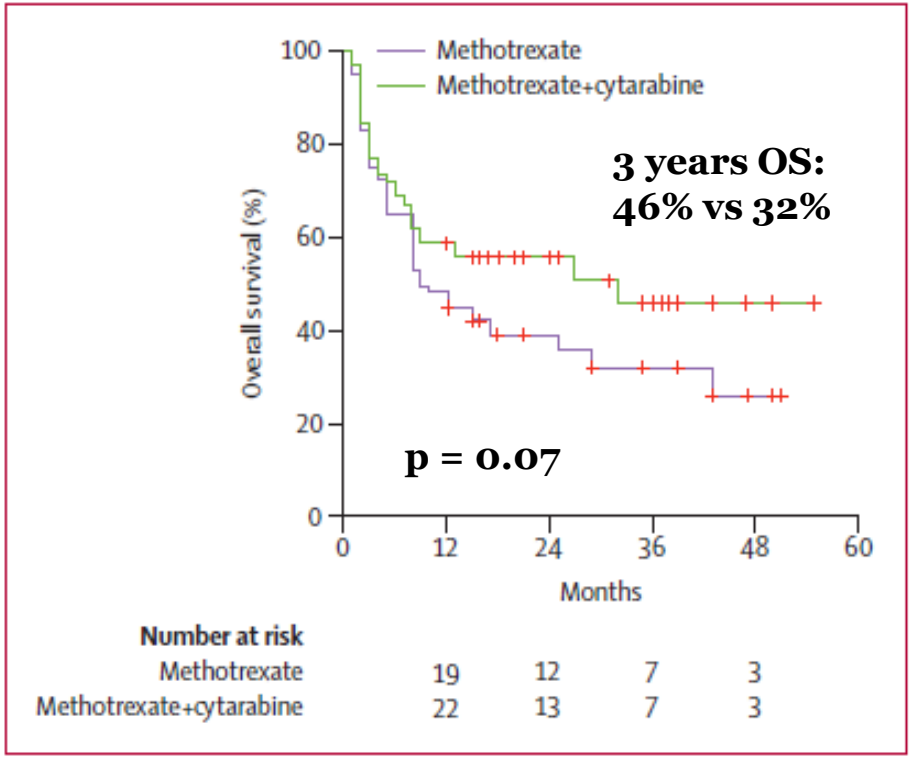
High-dose cytarabine plus high-dose methotrexate versus high-dose methotrexate alone in patients with primary CNS lymphoma: a randomised phase 2 trial

PFS



OS



CONCLUSION: High dose MTX-Cytarabine is the new standard chemotherapeutic approach

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Ferreri AJ et al, Lancet 2009; 374

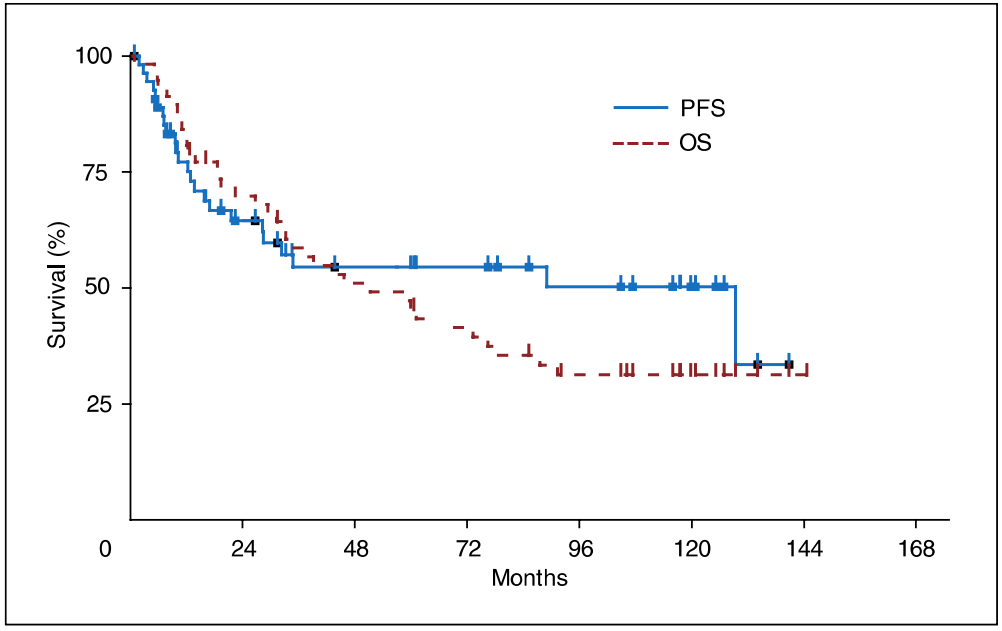
VOLUME 24 · NUMBER 28 · OCTOBER 1 2006

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Long-Term Follow-Up of High-Dose Methotrexate-Based Therapy With and Without Whole Brain Irradiation for Newly Diagnosed Primary CNS Lymphoma

Igor T. Gavrilovic, Adília Hormigo, Joachim Yahalom, Lisa M. DeAngelis, and Lauren E. Abrey

Overall population



- **TREATMENT:**
  1. **HD-MTX + Procarbazine + Ara-C**
  2. **Eventual WBI: 45 Gy**
- 30% of patients developed treatment-related neurotoxicity after WBI.
  1. Pts >60 years: 75% (9/12).
  2. Pts <60 years: 26% (5/19).
- Only one patient developed neurotoxicity after chemotherapy alone; this patient had an initial KPS of 40 with poor recovery of function and possible MTX- induced leukoencephalopathy.
- The median survival from diagnosis of neurotoxicity was 23 months.

N.B. formal neuropsychological testing was not performed

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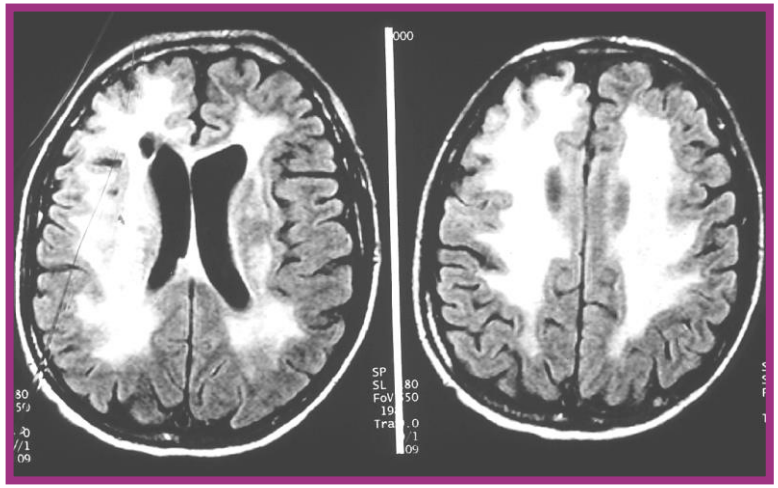
Cognitive functions in primary central nervous system lymphoma: literature review and assessment guidelines

D. D. Correa[1]*, L. Maron[2], H. Harder[3], M. Klein[4], C. L. Armstrong[5], P. Calabrese[6], J. E. C. Bromberg[3], L. E. Abrey[1], T. T. Batchelor[7] & D. Schiff[8]

Annals Oncol. 2007;18

Neurotoxicity: the big problem…

- **WBRT ± chemotherapy is associated with more pronounced cognitive impairment than chemotherapy alone**
- Long term impairment in the areas of attention, executive function, memory and psychomotor speed



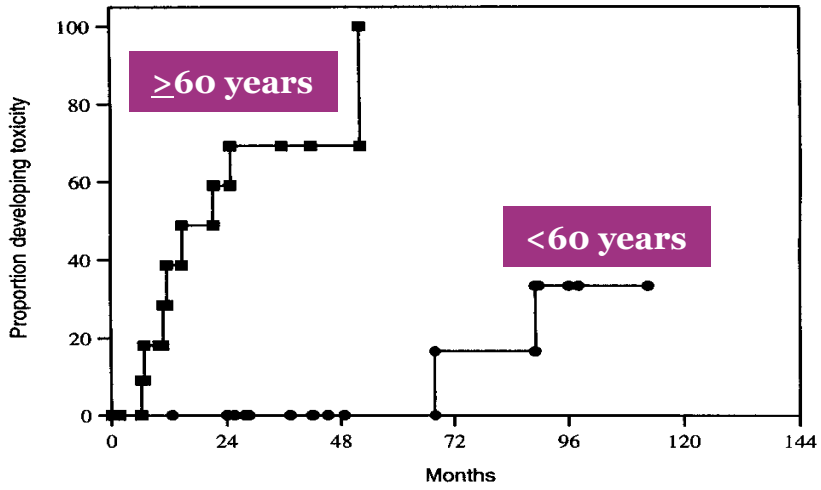


Fig 1. Proportion of patients who developed neurotoxicity with increasing duration of follow-up. Patients less than 60 years of age (circles) are compared with patients aged more than 60 years (squares); $P < .0001$ (Mantel-Cox method).

- High incidence of neurotoxicity particulary in patients > 60 years

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The Million Dollar Question…

Can we reduce RT-induced neuropsychological impairment, without compromising the clinical outcome ?

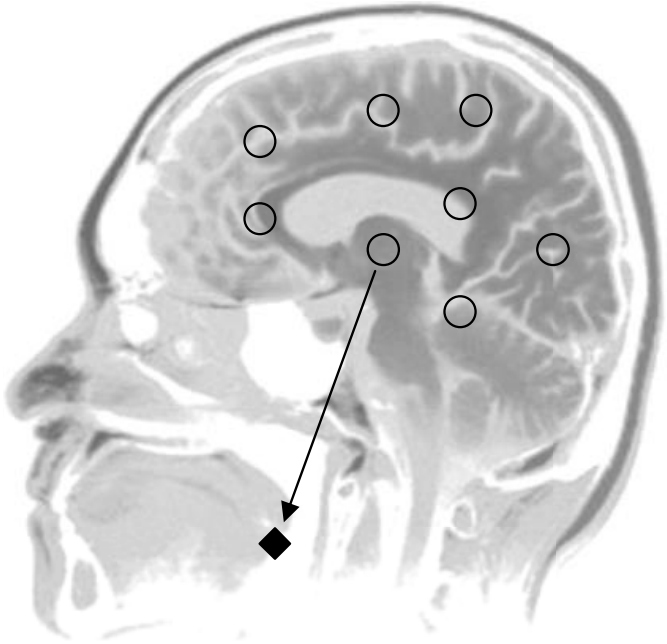
Reducing RT-related neurotoxicity
(moving points)

- To optimize (dose and volume) consolidative RT
- To avoid consolidative RT
- To replace RT with other strategies

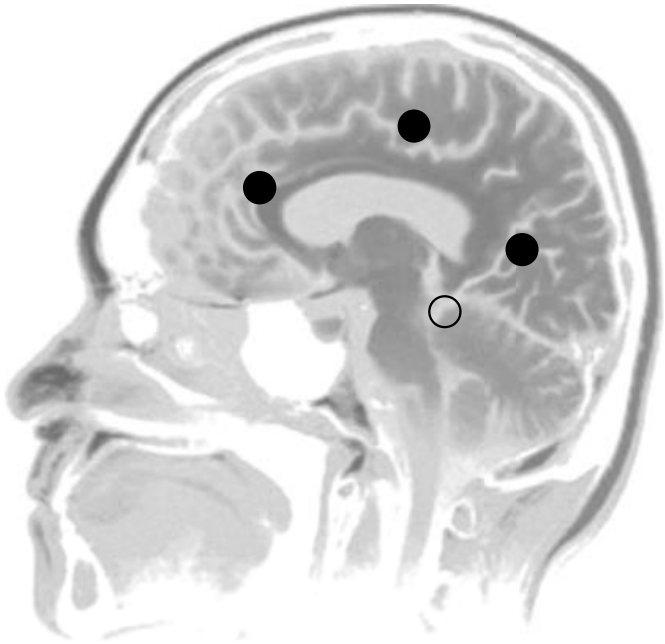
CONSOLIDATION RADIOTHERAPY IN PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMAS: IMPACT ON OUTCOME OF DIFFERENT FIELDS AND DOSES IN PATIENTS IN COMPLETE REMISSION AFTER UPFRONT CHEMOTHERAPY

Consolidation WBRT: optimal dose

WB dose 30-36 Gy



WB dose 40-45 Gy



Ferreri AJ et al, IJROBP 2011; 80

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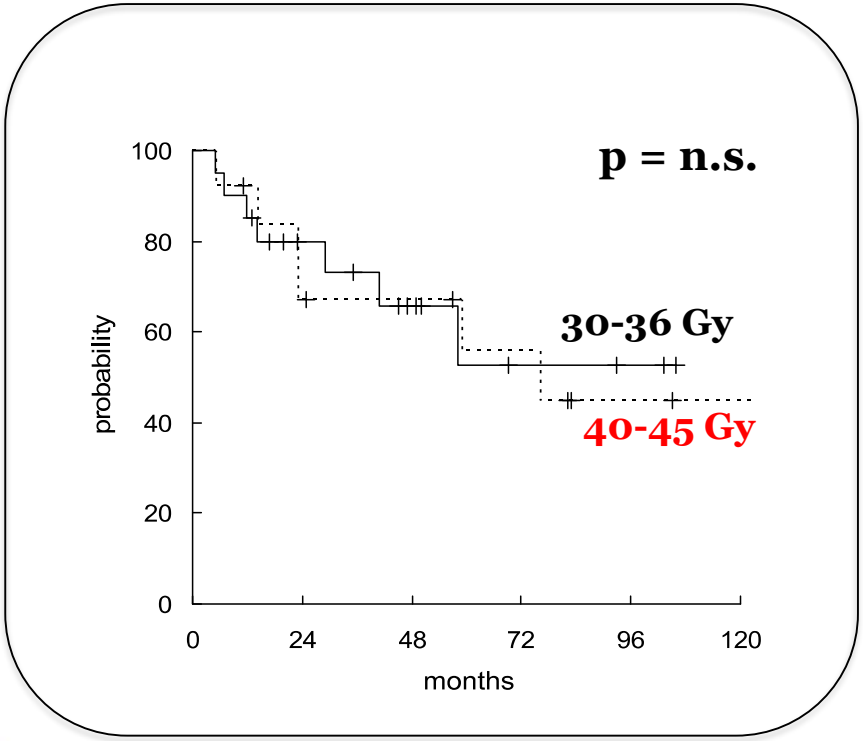
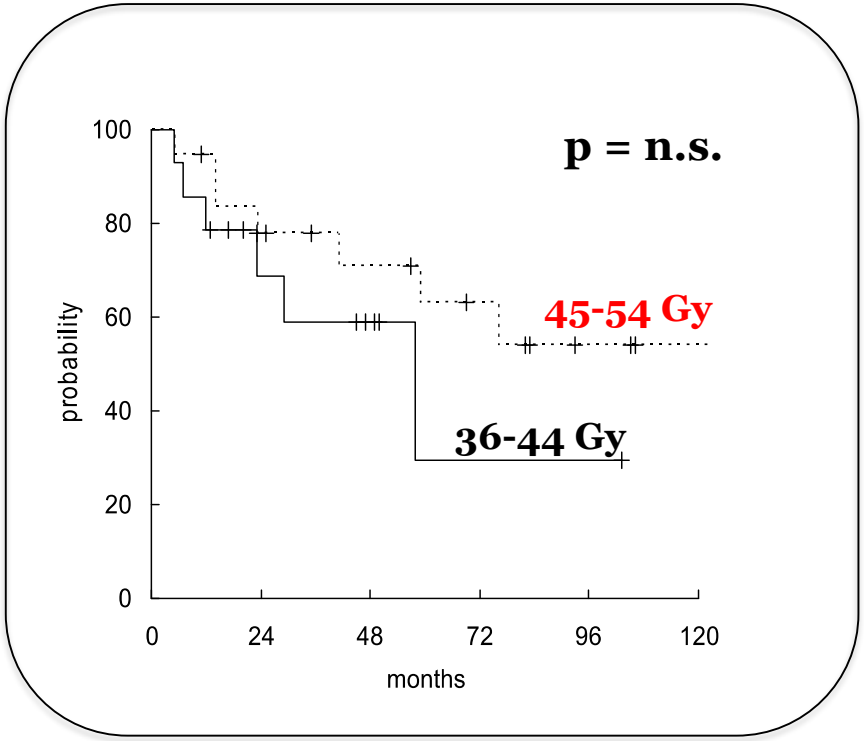
CONSOLIDATION RADIOTHERAPY IN PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMAS: IMPACT ON OUTCOME OF DIFFERENT FIELDS AND DOSES IN PATIENTS IN COMPLETE REMISSION AFTER UPFRONT CHEMOTHERAPY

Consolidation WBRT: optimal dose

OS according to **WBI dose**



OS according to **TUMOR BED dose**



Ferreri AJ et al, IJROBP 2011; 80

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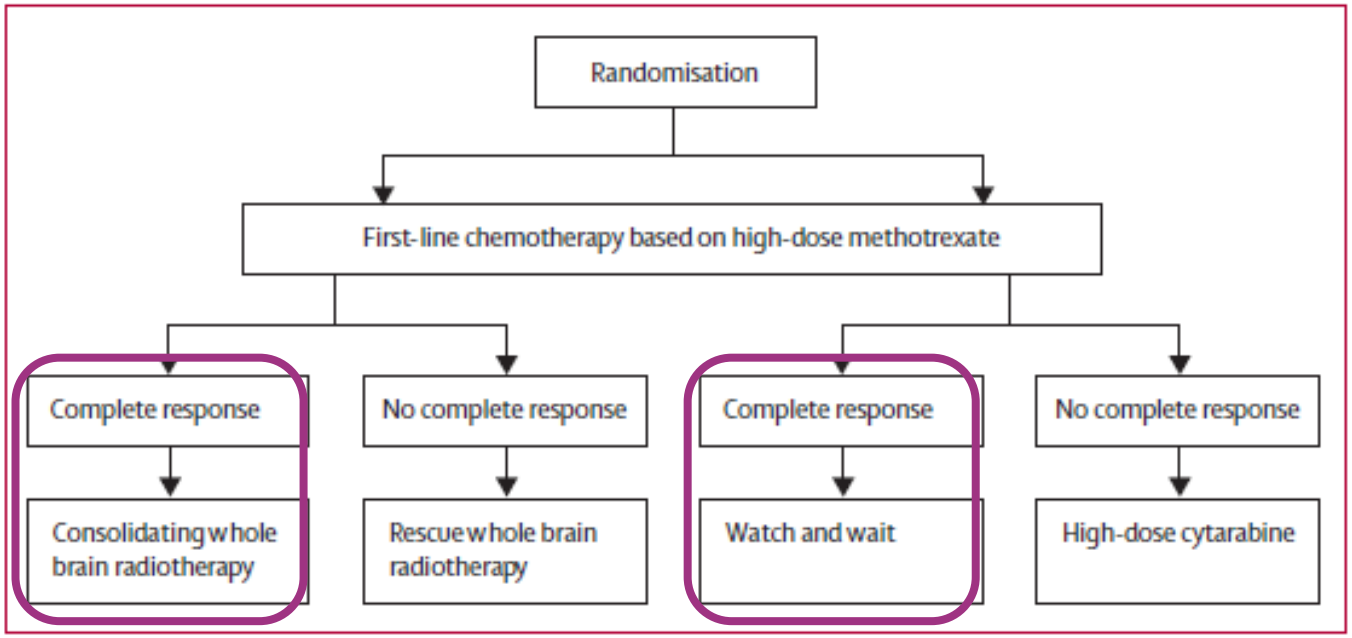
High-dose methotrexate with or without whole brain radiotherapy for primary CNS lymphoma (G-PCNSL-SG-1): a phase 3, randomised, non-inferiority trial

Omission of consolidation WBRT: is it a feasible option ?

- **Randomized trial designed to establish whether first-line chemotherapy based on high-dose MTX is non-inferior to the same chemotherapy regimen followed by whole brain radiotherapy**



Thiel E. et al. Lancet Oncol 2010;11

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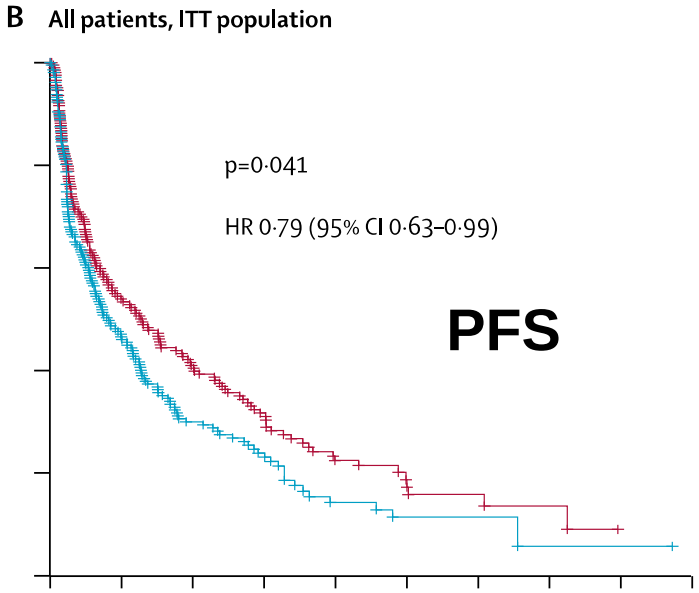
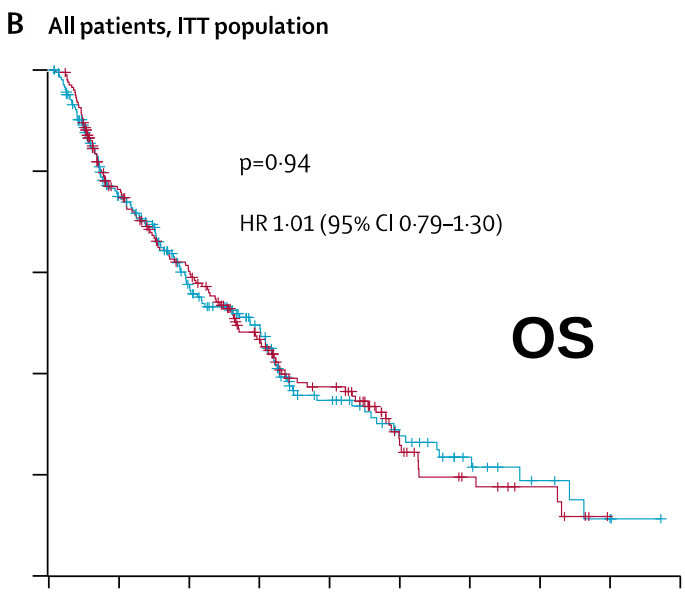
Omission of consolidation WBRT: is it a feasible option ?





"Although whole brain radiotherapy has a role in disease control, the absence of a survival benefit in this study could justify its omission from first-line treatment in primary CNS lymphoma."

Thiel E. et al. Lancet Oncol 2010;11

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High-dose methotrexate with or without whole brain radiotherapy for primary CNS lymphoma (G-PCNSL-SG-1): a phase 3, randomised, non-inferiority trial

Omission of consolidation WBRT: is it a feasible option ?

	First-line chemotherapy with whole brain radiotherapy			First-line chemotherapy without whole brain radiotherapy		
	Patients	Events	Median time (months; 95% CI)	Patients	Events	Median time (months; 95% CI)
All patients						
Progression-free survival	154	113	18·3 (11·6–25·0)	164	124	11·9 (7·3–16·5)
Overall survival	154	97	32·4 (25·8–39·0)	164	96	37·1 (27·5–46·7)
Patients with complete response						
Progression-free survival	56	33	36·3 (19·3–53·3)	96	62	21·5 (12·5–30·5)
Overall survival	56	32	38·8 (23·2–54·4)	96	46	39·4 (20·7–58·0)
Patients without complete response						
Progression-free survival	98	80	5·6 (1·6–9·5)	68	62	3·0 (2·7–3·3)
Overall survival	98	65	24·3 (12·2–36·3)	68	50	18·6 (8·3–29·0)

Table 3: Progression-free and overall survival (per-protocol population)

Thiel E. et al. Lancet Oncol 2010;11

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Whole-brain radiotherapy in primary CNS lymphoma

Andrés J M Ferreri*, Lisa DeAngelis, Gerald Illerhaus, Brian P O'Neill, Michele Reni, Carole Soussain, Joachim Yahalom

The study did not meet many standards… in design, undertaking, and interpretation.

- **Poor protocol adherence** (318/551 = 57.7%)
- **Low statistical power** because of exclusion of patients with protocol violations from the denominator in various analyses (PP vs ITT analyses)
- **Long accrual period** (2000-2009, 75 centers)
- **Involvement of many centers with little experience in PCNSL** (high rates of erroneous response assessment, patients lost to follow-up, and toxic deaths).
- **Inconsistent data for iatrogenic neurotoxicity** (exclusively assessed by MRI)

The G-PCNSL-SG-1 trial is compromised by several flaws and failed to prove its primary hypothesis.

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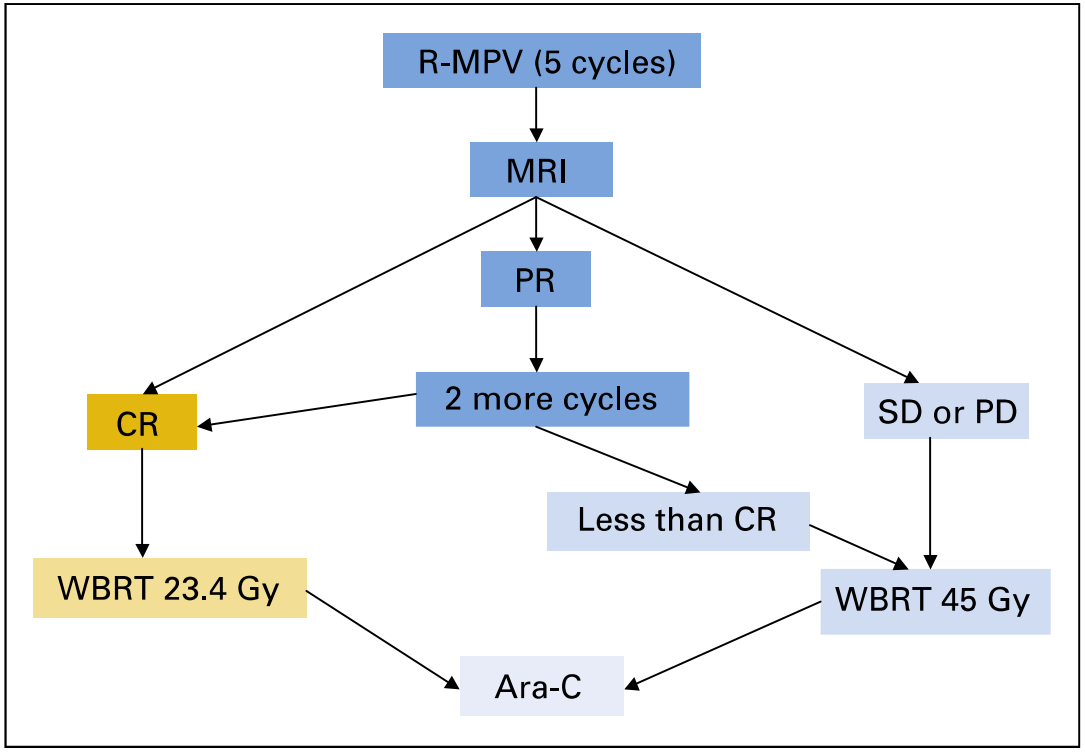
JOURNAL OF CLINICAL ONCOLOGY

Combined Immunochemotherapy With Reduced Whole-Brain Radiotherapy for Newly Diagnosed Primary CNS Lymphoma

Feasibility of ”reduced dose” WBRT



The primary end points were:

a) 2-year progression-free survival (PFS)
57% in the entire population
79% in the patients who received rdWBRT

b) acute treatment-related toxicity.
No evidence of neurocognitive decline within the 12-month post-**rdWBRT** follow-up period. One case of grade 4 neutropenia

Shah et al. JCO 2007;25

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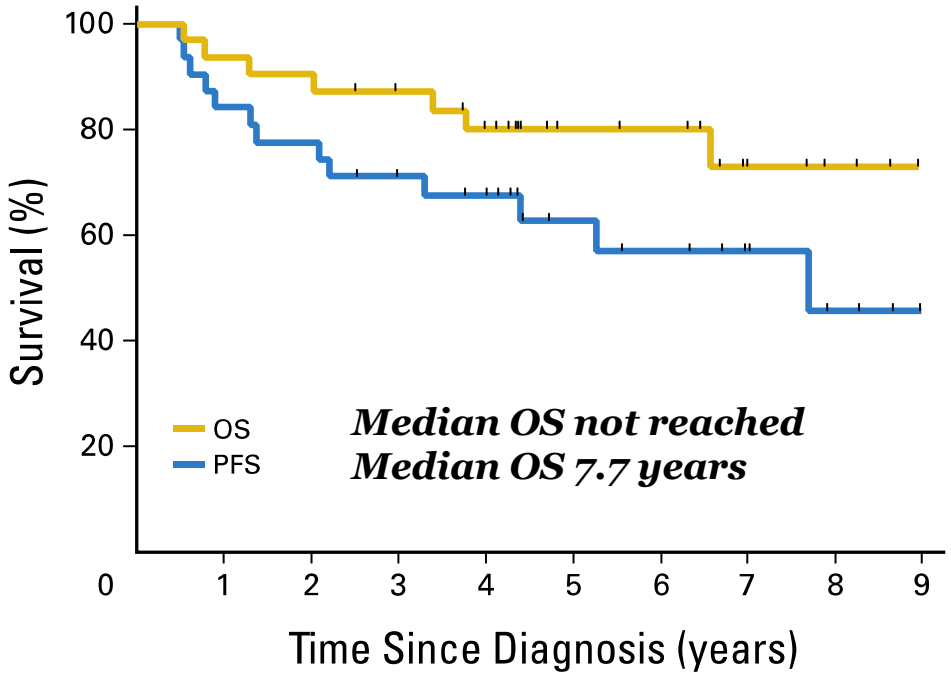
Rituximab, Methotrexate, Procarbazine, and Vincristine Followed by Consolidation Reduced-Dose Whole-Brain Radiotherapy and Cytarabine in Newly Diagnosed Primary CNS Lymphoma: Final Results and Long-Term Outcome

Feasibility of ”reduced dose” WBRT

- **Chemotherapy schedule R-MVP x 5-7 cycles**
  - Rituximab
  - Methotrexate
  - Vincristine
  - Procarbazine
- **WBRT**
  - rdWBRT (23.4 Gy/13 fr) in patients who achieved CR
  - Standard WBI (45 Gy/25 fr) in patients with PR-SD-PD
- **Consolidative CT**
  - High dose ARA-Cx 2 cycles

CR rate: 47%
ORR rate: 95%

Outcomes of patients receiving rdWBRT



Morris PG et. al JCO 2013;31

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Rituximab, Methotrexate, Procarbazine, and Vincristine Followed by Consolidation Reduced-Dose Whole-Brain Radiotherapy and Cytarabine in Newly Diagnosed Primary CNS Lymphoma: Final Results and Long-Term Outcome

Toxicity profile of ”reduced dose” WBRT

- **Prospective comprehensive neuropsychological evaluations were conducted:**
  - At baseline
  - After induction chemotherapy (before rdWBRT)
  - At 6-month intervals after completion of rdWBRT (up to 48 months)

- **Three cognitive domains were evaluated:**
  - Executive (Trail Making Test; Brief Test of Attention)
  - Verbal memory (Hopkins Verbal Learning Test)
  - Motor speed (Grooved Pegboard Test)

- **RESULTS**
  - At baseline, cognitive impairment was present in several domains.
  - After CT, there was a significant improvement in executive ($P<0.01$) and verbal memory ($P<0.05$)
  - There was ***no evidence of significant cognitive decline***, except for motor speed ($P<0.05$).
  - Self-reported ***quality of life remained stable*** during the follow-up period

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Morris PG et. al JCO 2013;31

Rituximab, Methotrexate, Procarbazine, and Vincristine Followed by Consolidation Reduced-Dose Whole-Brain Radiotherapy and Cytarabine in Newly Diagnosed Primary CNS Lymphoma: Final Results and Long-Term Outcome

Toxicity profile of ”reduced dose” WBRT

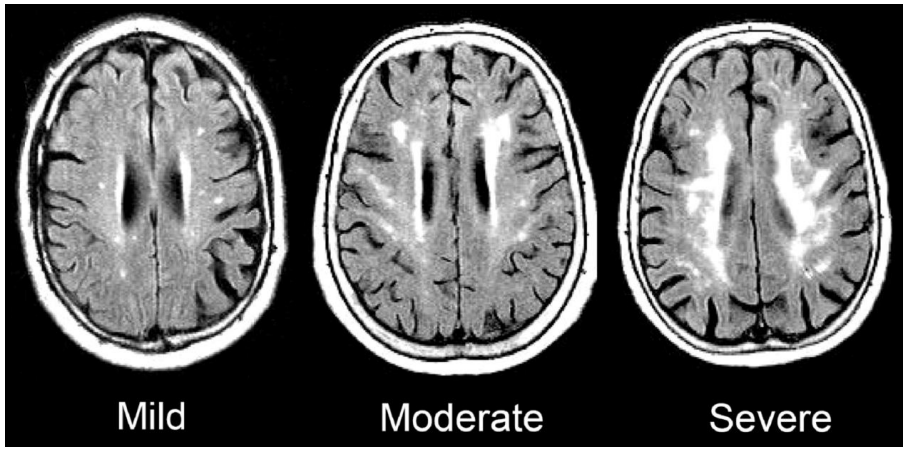
WHITE MATTER CHANGES (Fazekas scale)

Table 2. White Matter Changes in Patients Undergoing Neuropsychological Evaluation After Receiving Reduced-Dose Whole-Brain Radiotherapy (Fazekas Scale; n = 12)[20]

Grade	Baseline	Post R-MPV (prior to rdWBRT)	1 Year	2 Years	3 Years	4 Years
0	2	0	0	0	0	0
1	5	11	8	8	5	5
2	3	1	3	3	5	5
3	2	0	1	1	2	2
4	0	0	0	0	0	0
5	0	0	0	0	0	0

NOTE. Grades are defined as follows: grade 0, no white matter change; grade 1, minimal patchy white matter foci; grade 2, start of confluence of white matter disease; grade 3, large confluent areas; grade 4, confluence of white matter changes with cortical and subcortical involvement; grade 5, leukoencephalopathy.

Abbreviations: rdWBRT, reduced-dose whole-brain radiotherapy; R-MPV, rituximab, methotrexate, procarbazine, and vincristine.



- At baseline, five of 12 patients had grade ≥ 2 white matter disease, which decreased to one of 12 after chemotherapy.
- At the 4-year evaluation, the proportion of patients with white matter changes increased:
  - G2 changes → 5 patients
  - G3 changes → 3 patients
  - G4-G5 changes → 0 patients

Morris PG et. al JCO 2013;31

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PROMISING STUDIES

RTOG 1114 ***Phase II Randomized Study of Rituximab, Methotrexate, Procarbazine, Vincristine, and Cytarabine With and Without Low-Dose Whole-Brain Radiotherapy for Primary Central Nervous System Lymphoma***

IELSG 32 ***Randomized phase II trial on primary chemotherapy with high-dose methotrexate and high-dose cytarabine with or without thiotepa, and with or without rituximab, followed by brain irradiation vs. high-dose chemotherapy supported by autologous stem cells transplantation for immunocompetent patients with newly diagnosed primary CNS lymphoma***

ONGOING STUDY
(enrollment closed)

RTOG 1114

PHASE II RANDOMIZED STUDY OF RITUXIMAB, METHOTREXATE, PROCARBAZINE, VINCRISTINE, AND CYTARABINE WITH AND WITHOUT LOW-DOSE WHOLE-BRAIN RADIOTHERAPY FOR PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

SCHEMA

STRATIFY

RPA Class

Class 1: age ≤ 50

Class 2: age > 50 and KPS ≥ 70

Class 3: age >50 and KPS < 70

RANDOMIZE

Arm A (chemo only)	R-MPV Cycle 1	R-MPV Cycle 2	R-MP Cycle 3 (no vincristine)	R-MP Cycle 4 (no vincristine)		Ara-C Cycle 1	Ara-C Cycle 2
Arm B (chemo + low-dose WBRT)	R-MPV Cycle 1	R-MPV Cycle 2	R-MP Cycle 3 (no vincristine)	R-MP Cycle 4 (no vincristine)	Low-Dose WBRT (13 fx)	Ara-C Cycle 1	Ara-C Cycle 2

1 cycle = 28 days
(8 MTX doses total)

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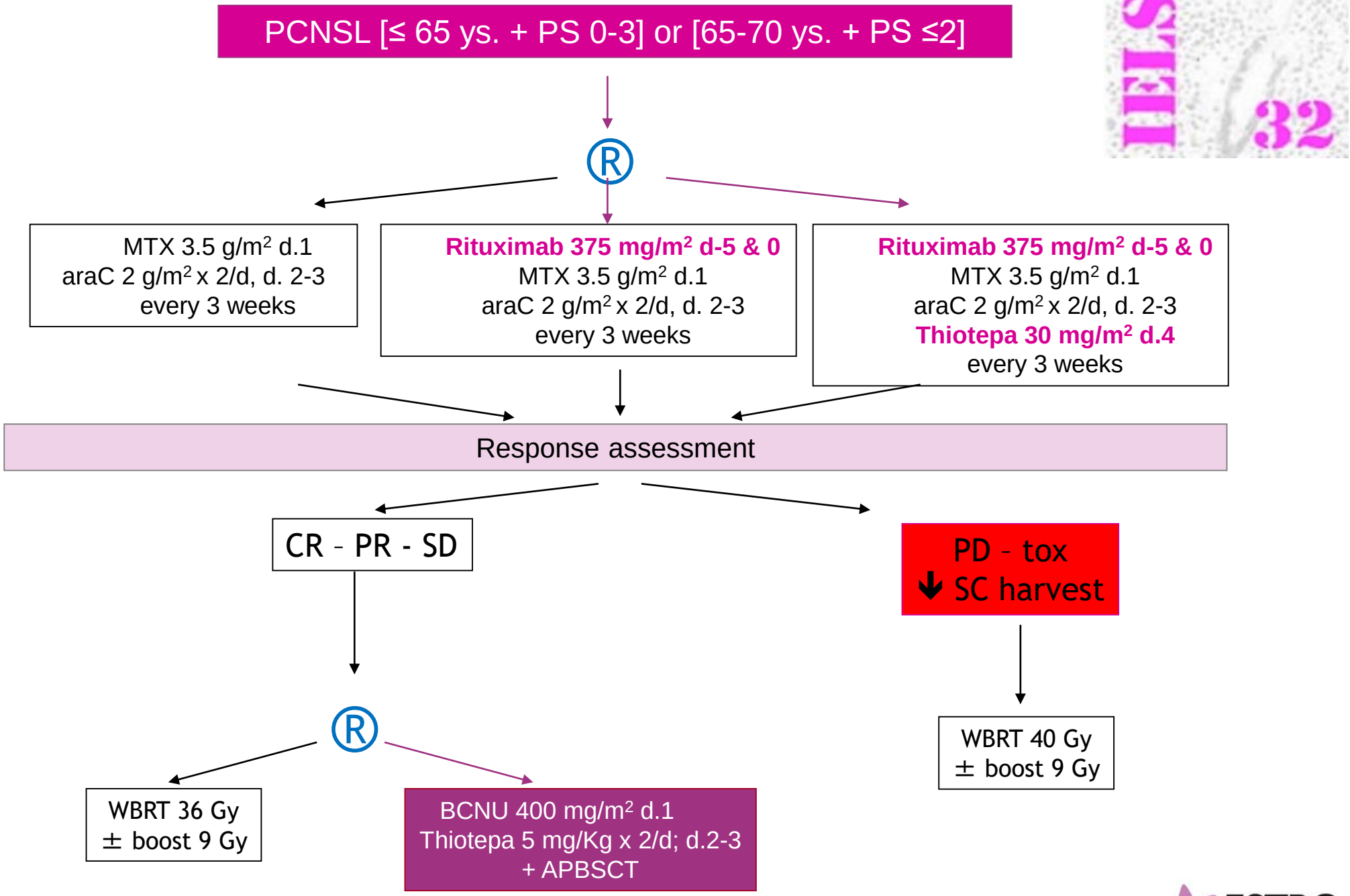

PCNSL [≤ 65 ys. + PS 0-3] or [65-70 ys. + PS ≤2]
R
MTX 3.5 g/m² d.1
araC 2 g/m² x 2/d, d. 2-3
every 3 weeks
Rituximab 375 mg/m² d-5 & 0
MTX 3.5 g/m² d.1
araC 2 g/m² x 2/d, d. 2-3
every 3 weeks
Rituximab 375 mg/m² d-5 & 0
MTX 3.5 g/m² d.1
araC 2 g/m² x 2/d, d. 2-3
Thiotepa 30 mg/m² d.4
every 3 weeks
Response assessment
CR - PR - SD
PD - tox
SC harvest
R
WBRT 36 Gy
± boost 9 Gy
BCNU 400 mg/m² d.1
Thiotepa 5 mg/Kg x 2/d; d.2-3
+ APBSCT
WBRT 40 Gy
± boost 9 Gy

Chemoimmunotherapy with methotrexate, cytarabine, thiotepa, and rituximab (MATRix regimen) in patients with primary CNS lymphoma: results of the first randomisation of the International Extranodal Lymphoma Study Group-32 (IELSG32) phase 2 trial

ORR:

Arm A: 53% (CR 23%)

Arm B: 74% (CR 30%)

Arm C: 87% (CR 49%)

OS @ 2 years:

Arm A: 40%

Arm B: 58%

Arm C: 66%

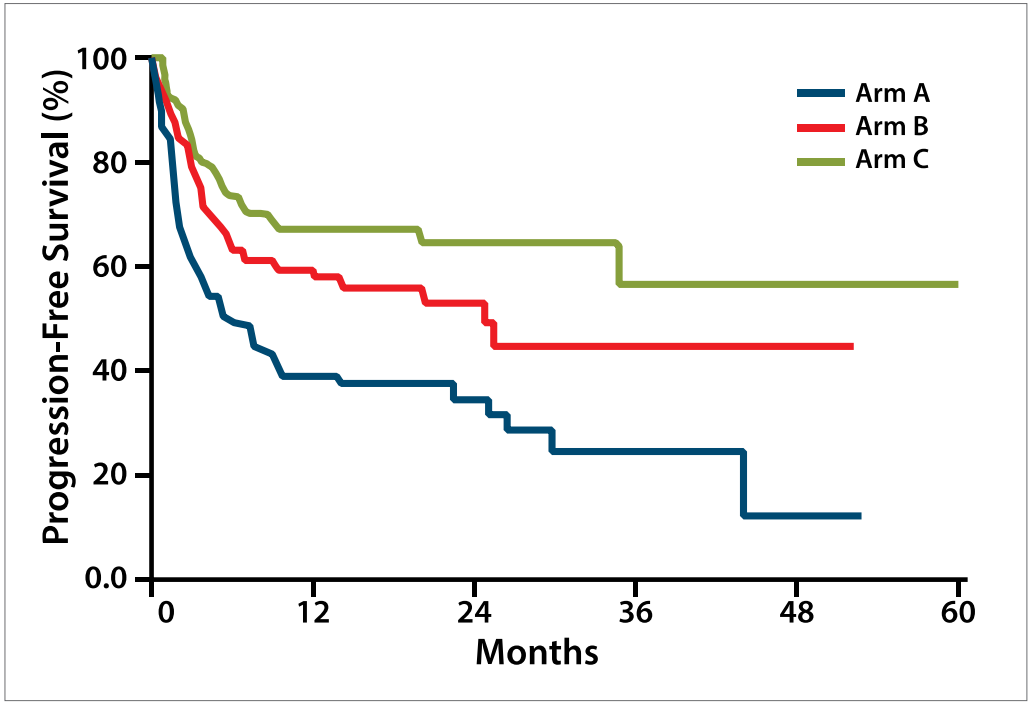


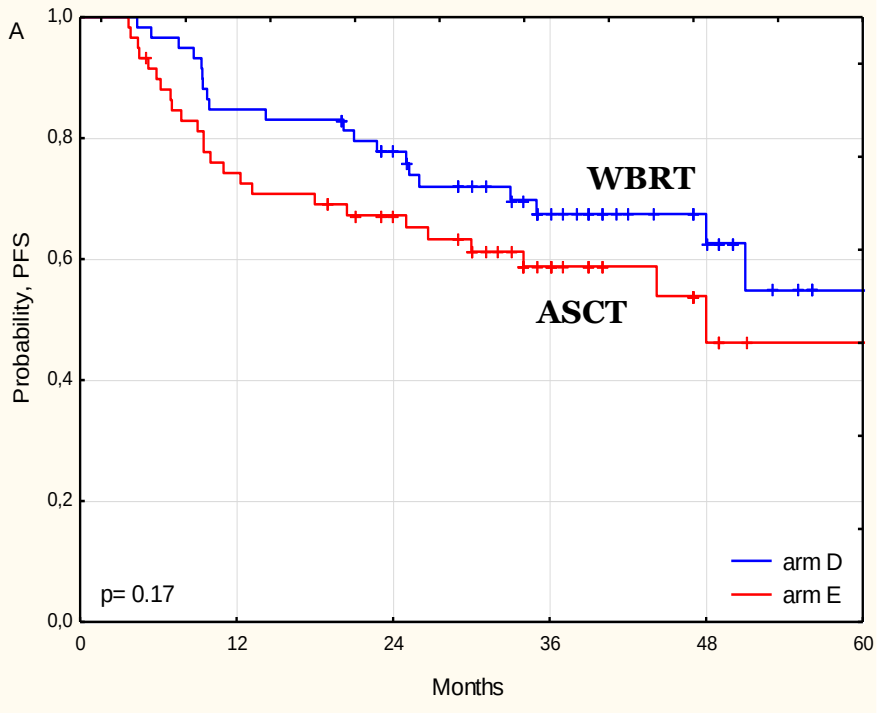
Figure 4. Progression-free survival in a trial evaluating the addition of thiotepa and rituximab to antimetabolites in patients with primary central nervous system lymphoma. Arm A: methotrexate and cytarabine. Arm B: methotrexate, cytarabine, and rituximab. Arm C: methotrexate, cytarabine, rituximab, and thiotepa. Adapted from Ferreri AJ et al. Addition of thiotepa and rituximab to antimetabolites significantly improves outcome in primary CNS lymphoma: first randomization of the IELSG32 trial [ICML abstract 009]. *Hematol Oncol.* 2015;33(suppl 1):103.[2]

Ferreri AJM. et al. Lancet Hematol 2016;3

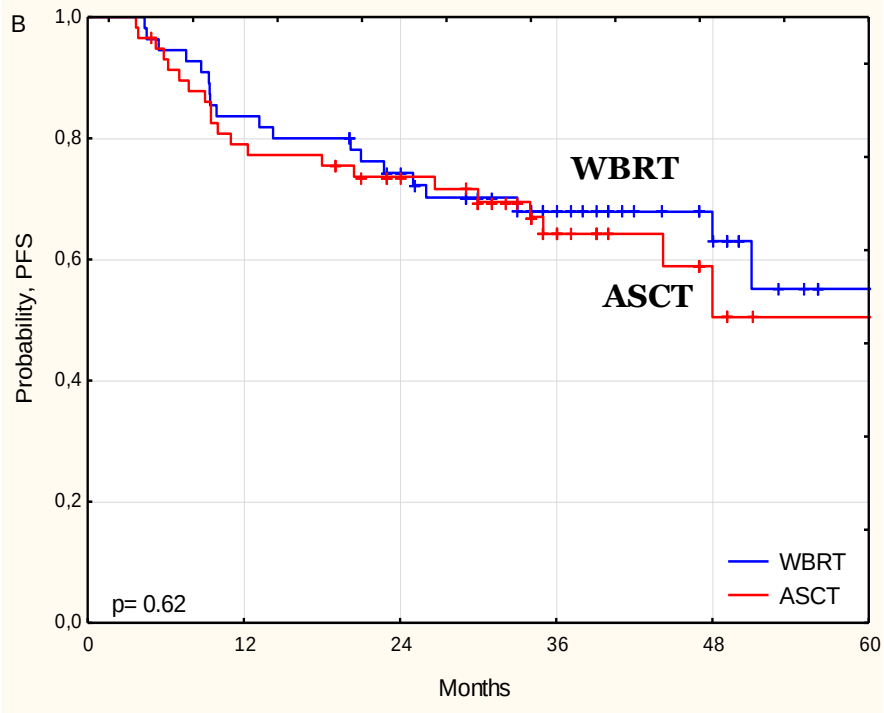
ASH | 58th Annual Meeting & Exposition
San Diego, CA · December 3-6, 2016

Effects on Survival and Neurocognitive Functions of Whole-Brain Radiotherapy (WBRT) and Autologous Stem Cell Transplantation (ASCT) as Consolidation Options After High-Dose Methotrexate-Based Chemoimmunotherapy in Patients with Newly Diagnosed Primary CNS Lymphoma (PCNSL): Results of the Second Randomization of the IELSG32 Trial

PFS – Intention to treat



PFS – Per protocol



Ferreri AJM. et al. Blood; abstract book ASH 2016

Neuropsycological tests

WBRT

ASCT

- ***A significant impairment of some attention/executive functions among patients treated with WBRT was recorded****, while results of tests addressing language and memory were stable after this therapy.*
- Patients treated with ASCT exhibited improved functions at most of the performed test, and both consolidation therapies were associated with improved QoL figures.
- **BUT… 2 toxic deaths (out of 40 patients, 5%) in the arm of Consolidative ASCT.**

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Ferreri AJM. et al. Blood; abstract book ASH 2016

Conclusions – PCNSL

- **MTX + Rituximab containing regimen** is significantly more active and effective than the other combinations leading to high rates of CR (≃50%) and ORR (85-90%), and should be considered the new standard induction for PCNSL

- **A Consolidative therapy is strongly recommended** after induction chemotherapy for PCNSL

- **WBRT and ASCT are both active and effective**, as consolidation therapies after high-dose-methotrexate-based chemoimmunotherapy with a 95% CR rate, and 75-80% progression-free survivors at 2 years

- **The best consolidative approach** should be selected “case by case” and tailored to the patients within a multidisciplinary tumor board, taking into account the toxicity profile of each strategy.

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Role of WBI in PCNSL

"Don't throw the baby out with the bathwater…!"

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Abscopal Effects -Combining Radiotherapy with Immunotherapy

Martin Pruschy

Dept. of Radiation Oncology
University Hospital Zurich, Switzerland

martin.pruschy@usz.ch

Overview

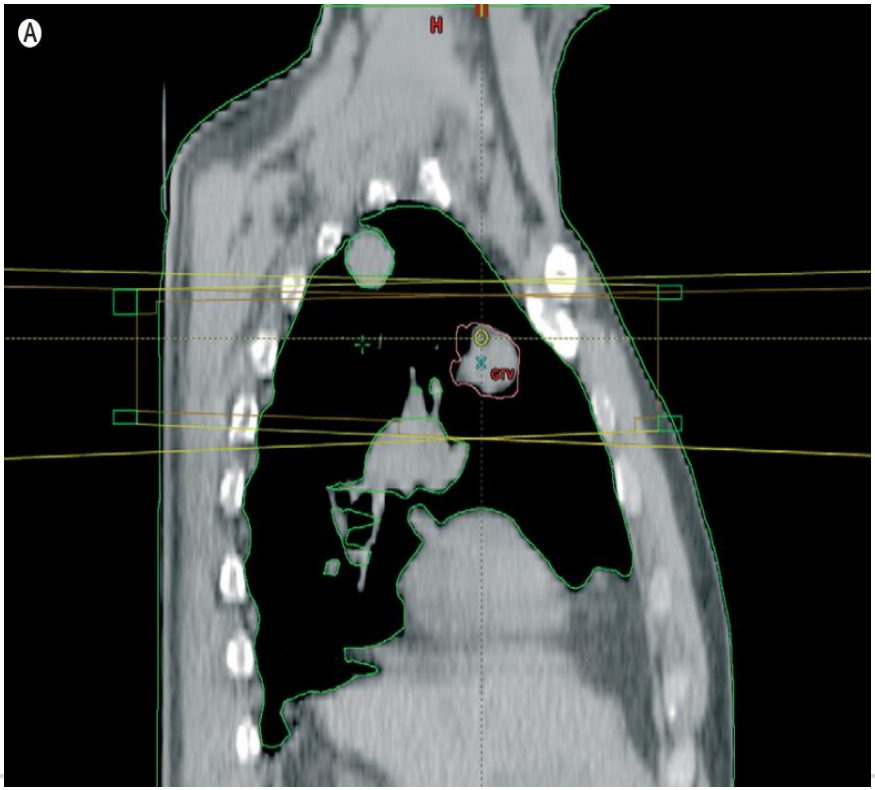
- Clinical situation
- Immunogenic cell death
- Preclinical examples

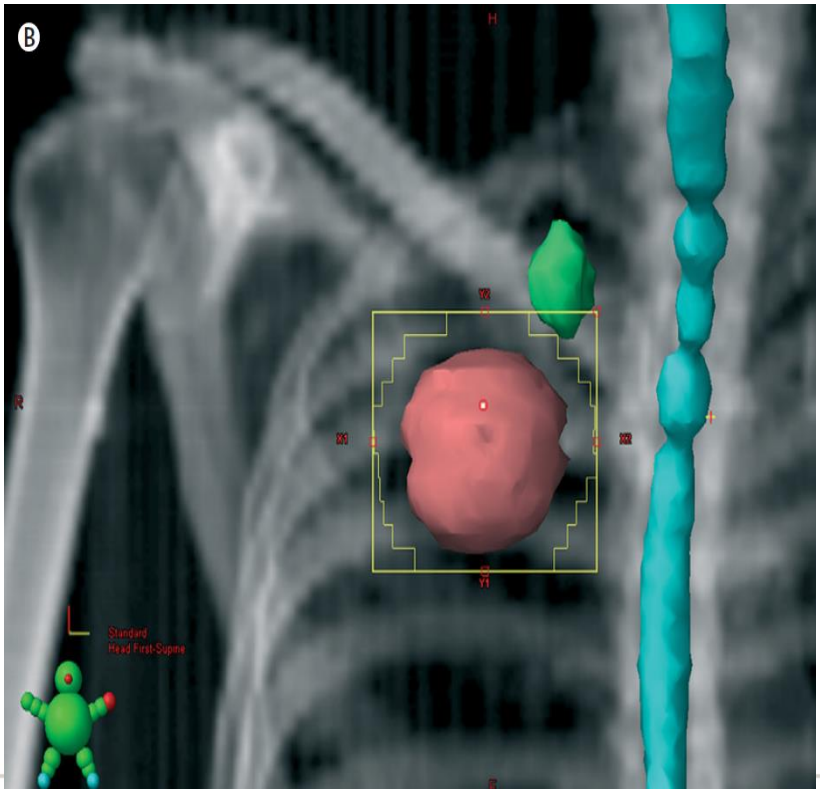
- Radiotherapy and immune checkpoint inhibitors
- Resistance mechanisms

Systemic effects of local radiotherapy

Silvia C Formenti, Sandra Demaria Lancet Oncol 2009; 10: 718–26

- Patient with thymic carcinoma
- 2 lung lesions, one irradiated, one not irradiated





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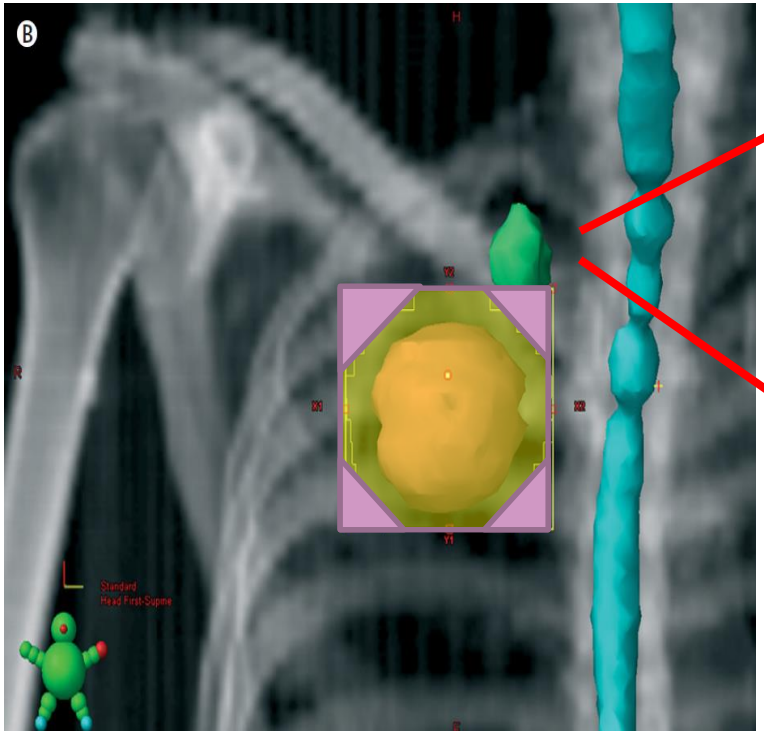
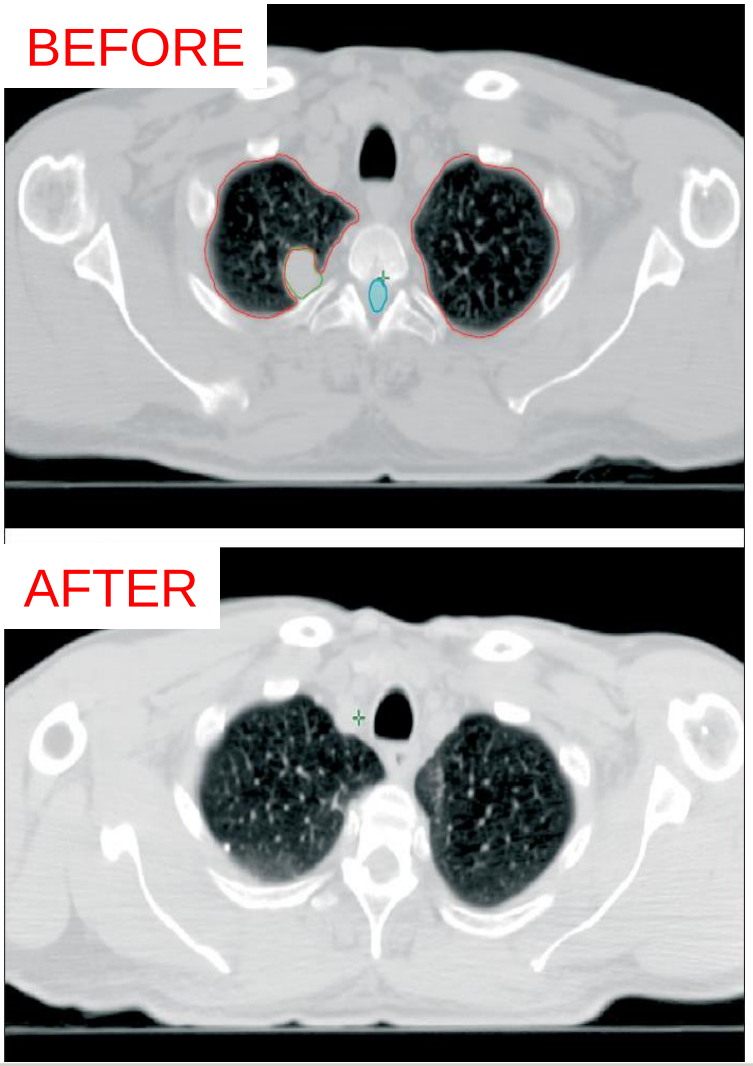
Tumor regression in non-irradiated, distant tumor sites





Abscopal response in unirradiated lesion
Ab = away from Scopus = the target

First described in 1953: Mole R; Br. J. Radiol, 26:234-241)

Reported clinical cases (1960-2014):51 patients (23 case reports after RT alone)

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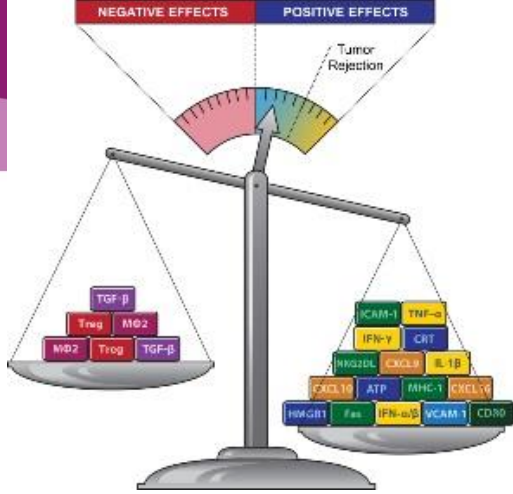
Radiotherapy and Immune Response



- Radiation is cytotoxic through the induction of non-repairable, double-stranded DNA breaks.

- It has long been believed that radiation is immunosuppressive. (normal hematopoietic cells and hematologic malignancies appear to be very sensitive to low radiation; release of immunosuppressive factors)

- However, the effects of RT are multifaceted and may serve as an immune stimulus: primary tumor site; abscopal site

Radiotherapy and Abscopal Effect

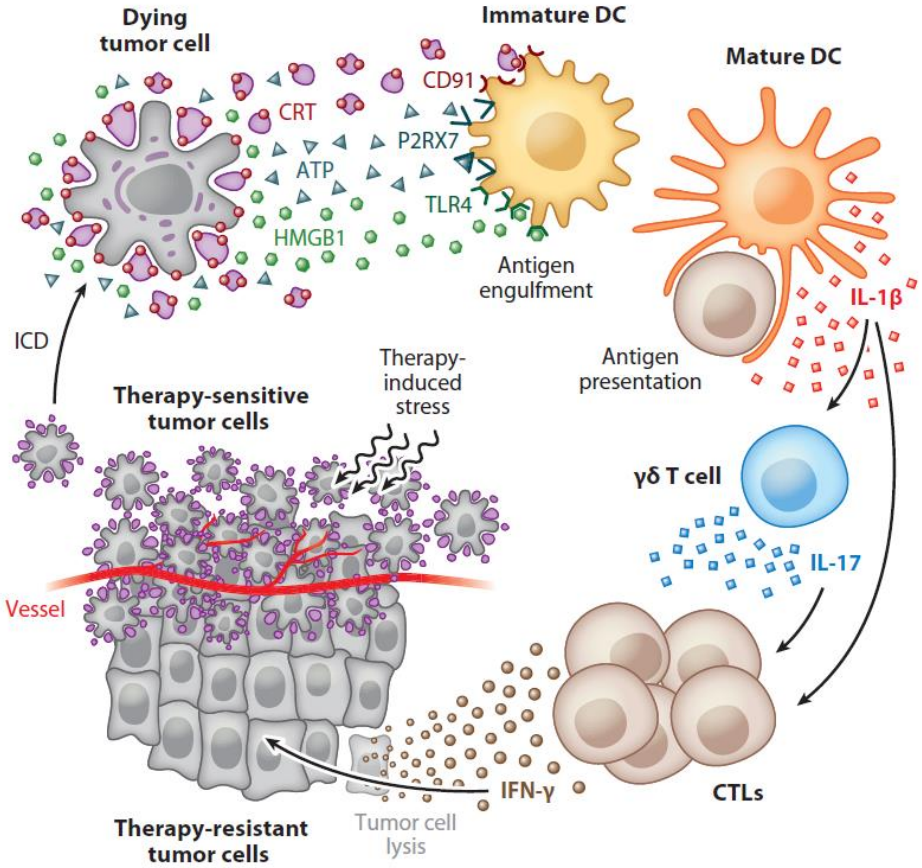
- «True» abscopal effect does not include the effect of systemic therapies
- Preclinical research fails to consistently reproduce abscopal effects by RT *alone*

➢ Is abscopal effect coincidental representation of spontaneous regression?

- New enhanced systemic responses after RT described in patients progressing through immunotherapy

➢ We need more controlled (pre-)clinical studies

Radiotherapy meets Immunology: Immunogenic Cell Death induced by RT



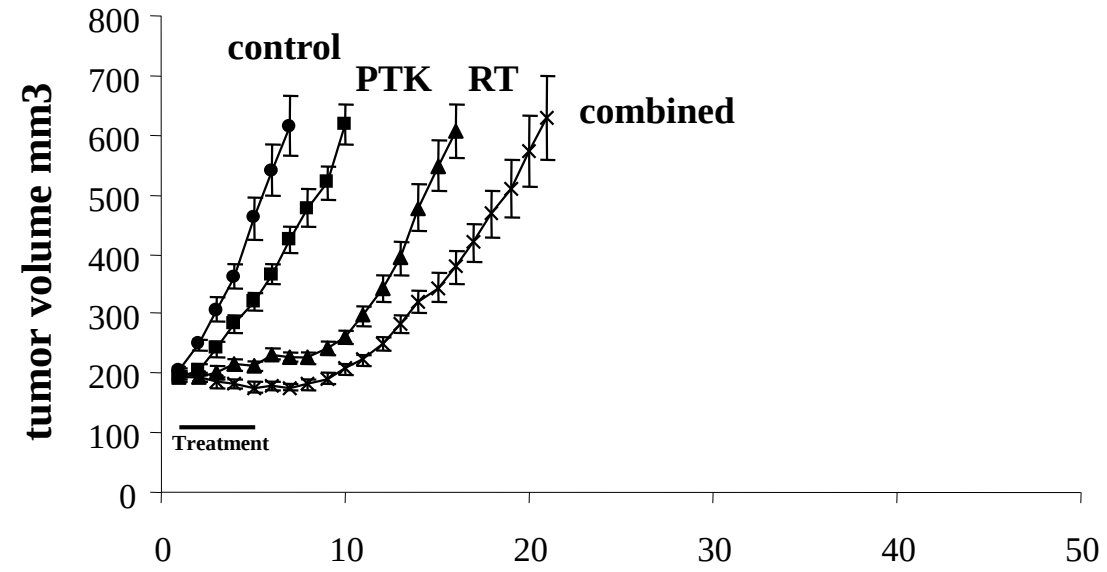
Properties of Immunogenic Cell Death:

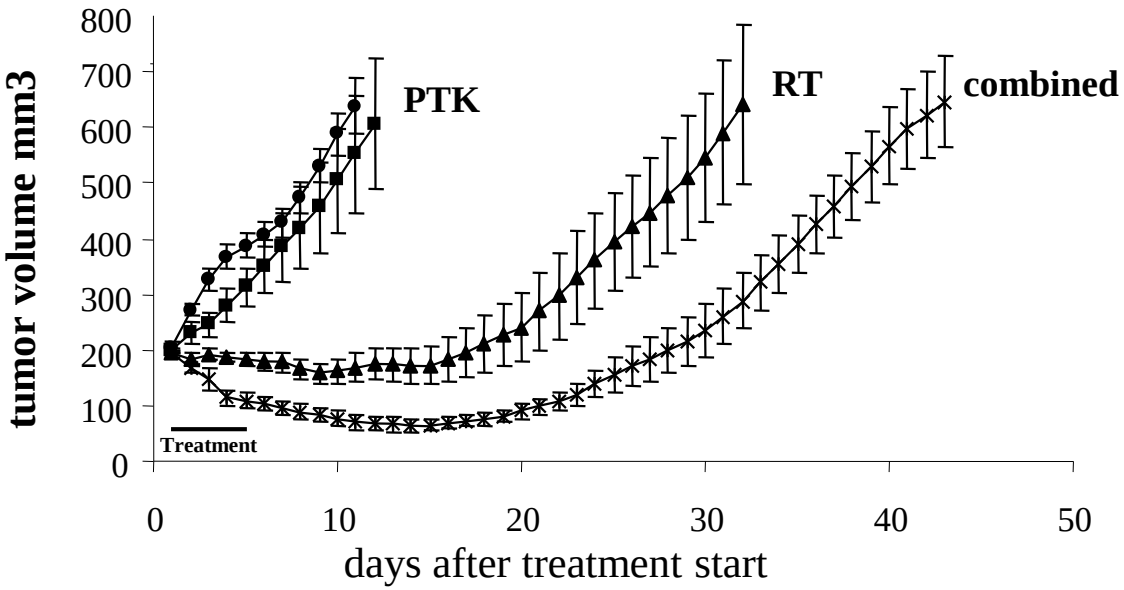
a) Exposure of calreticulin, secretion of ATP, release of HMGB1

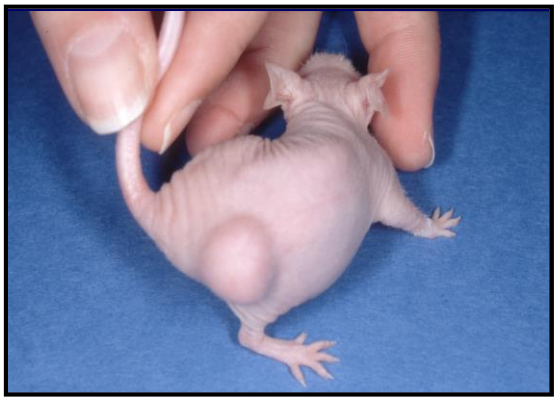
b) Recruitment of dendritic cells into tumor bed, optimal antigen presentation to T cells

c) Followed by potent immune-response

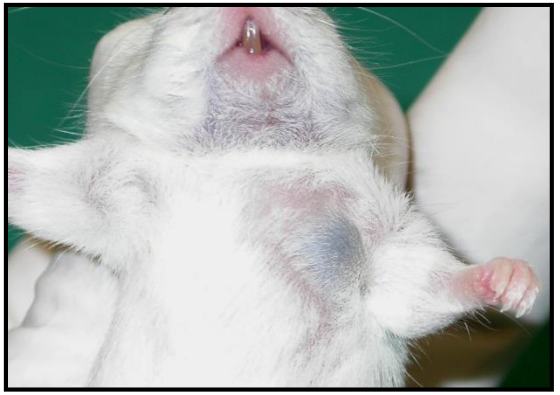
Relevance of Immune System for Treatment Response







Tumor in
immune compromised mice

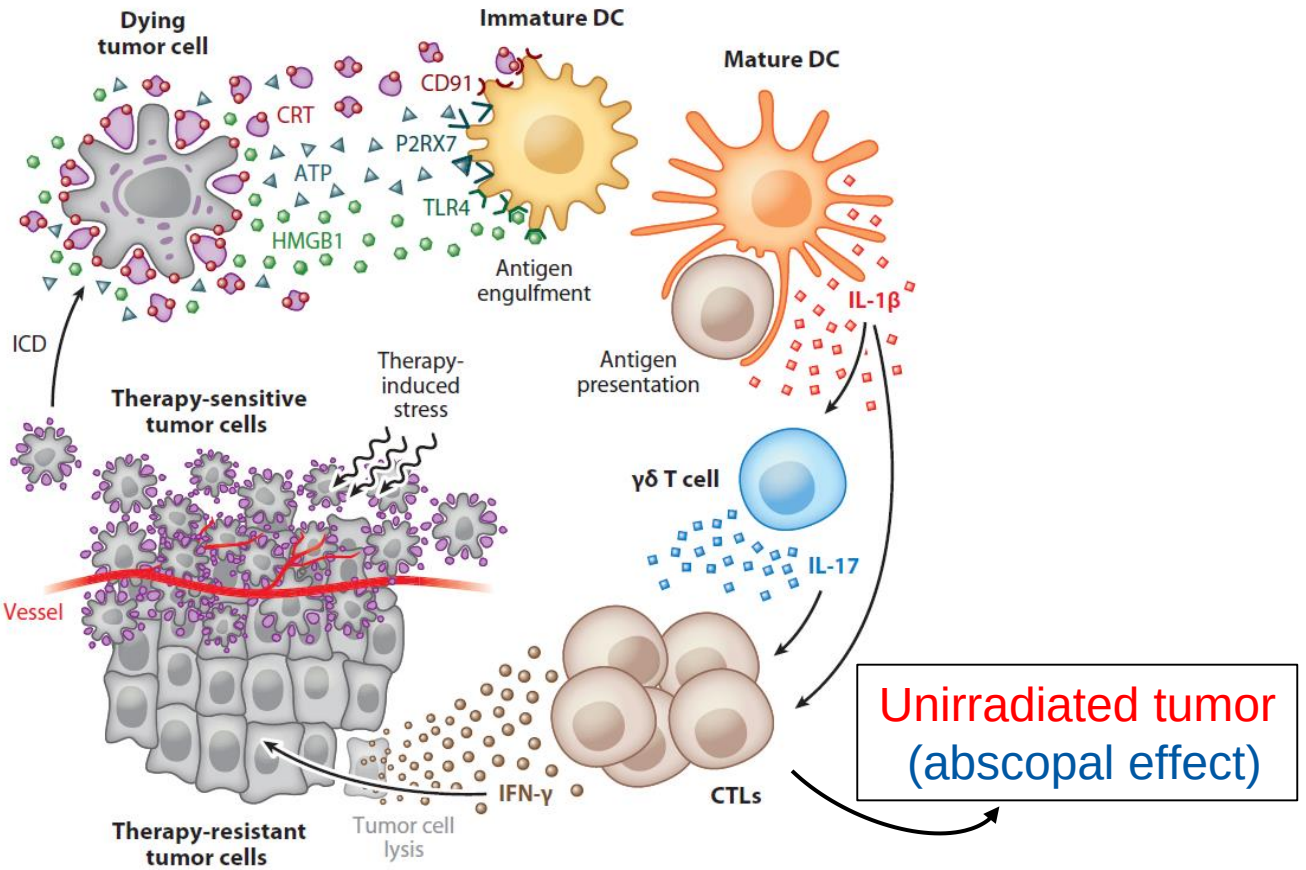


Tumor in
immune-competent mice

Minimal Treatment Schedule:
4 x 3 Gy + 4 x 100 mg/kg PTK787

Riesterer et al., 2007, 2011

Radiotherapy meets Immunology: Immunogenic Cell Death induced by RT



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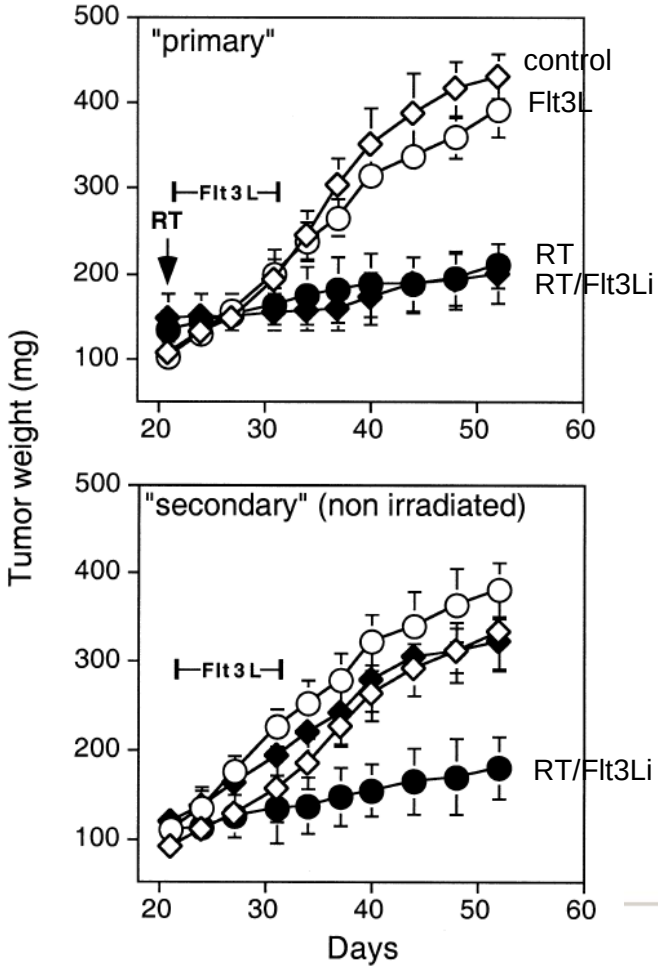
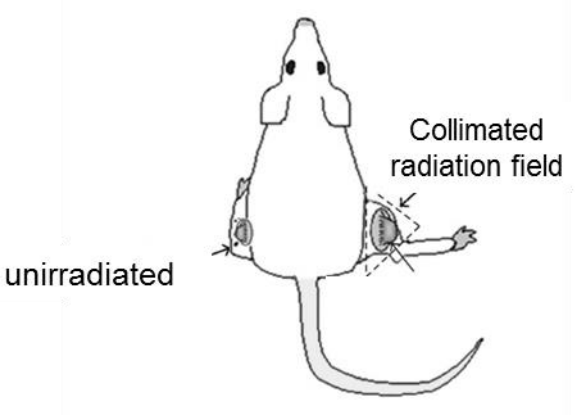
b) Recruitment of dendritic cells into tumor bed, optimal antigen presentation to T cells

c) Followed by potent immune-response

IONIZING RADIATION INHIBITION OF DISTANT UNTREATED TUMORS (ABSCOPAL EFFECT) IS IMMUNE MEDIATED





Flt-3Li: DC growth factor

Demaria et al., 2004

Int. J. Radiation Oncology Biol. Phys., Vol. 58, No. 3, pp. 862–870, 2004

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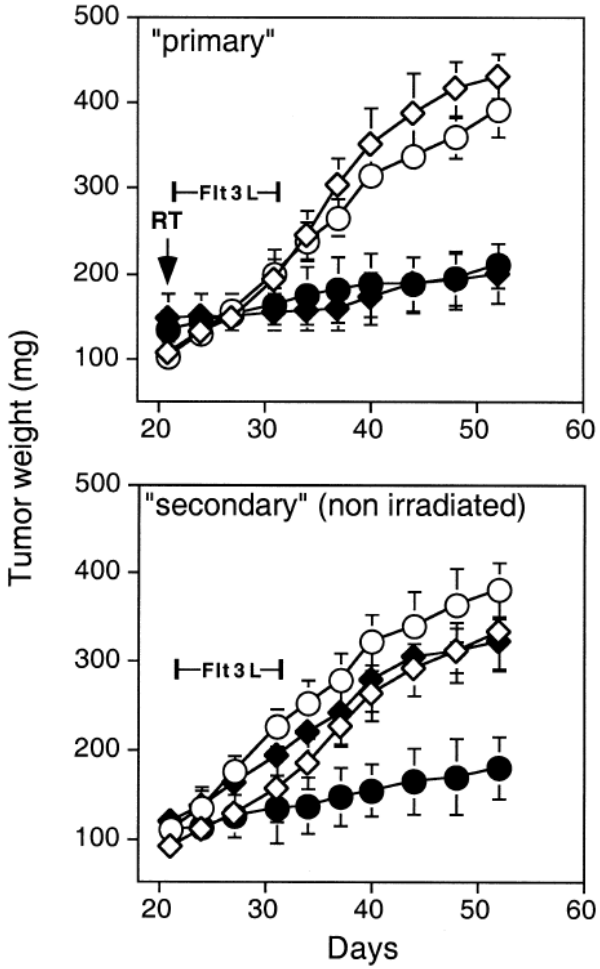

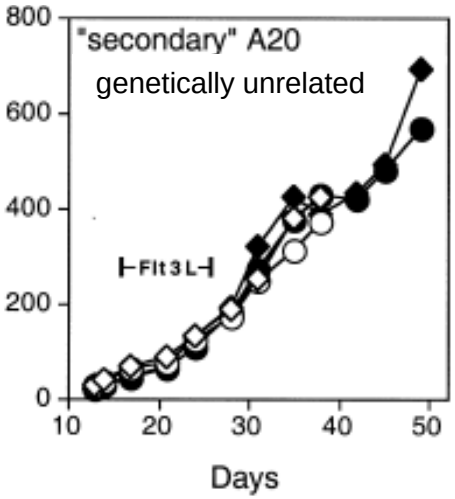

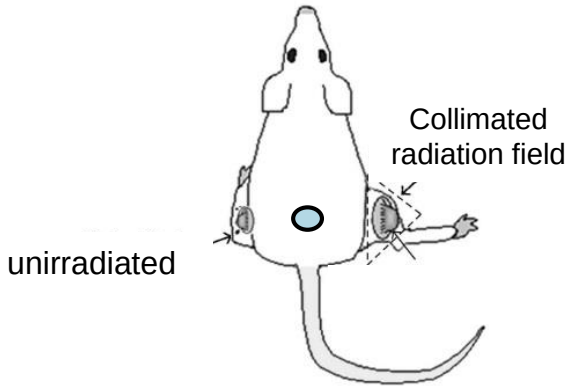

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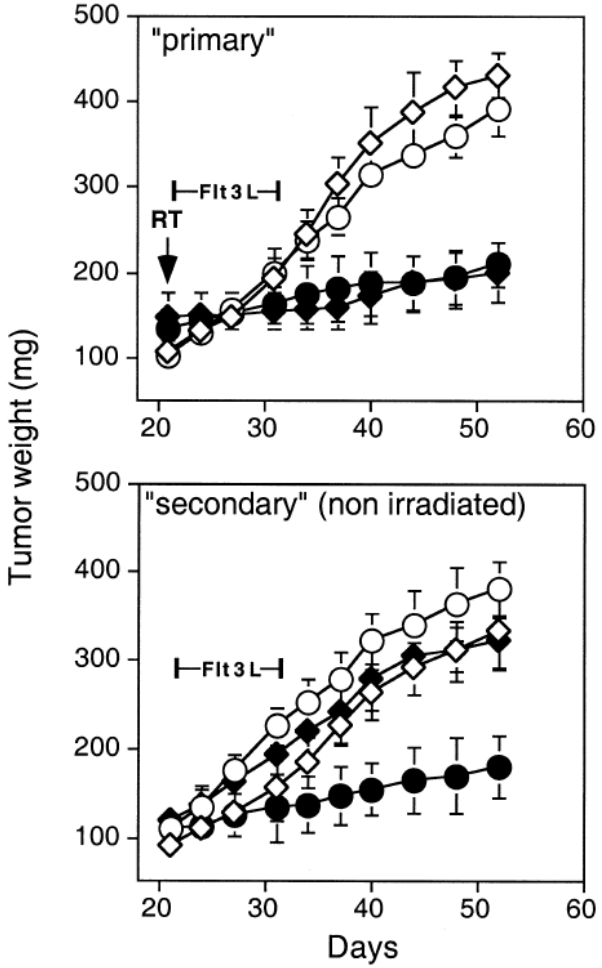
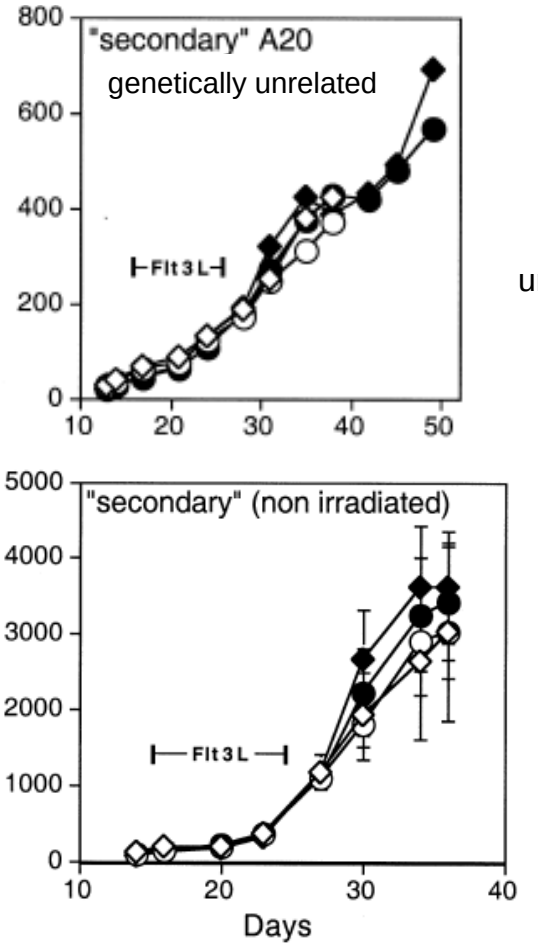
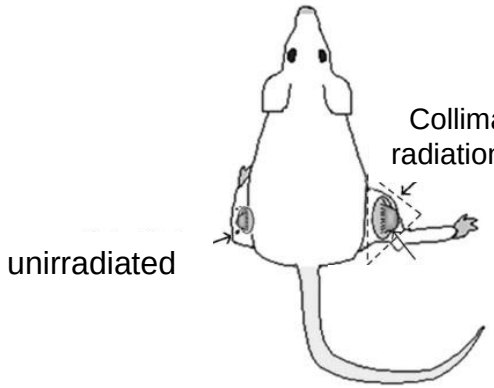






Nude mice: immuno-compromised

Flt-3L: DC growth factor

Demaria et al.,

Int. J. Radiation Oncology Biol. Phys., Vol. 58, No. 3, pp. 862–870, 2004

Local radiotherapy and granulocyte-macrophage colony-stimulating factor to generate abscopal responses in patients with metastatic solid tumours: a proof-of-principle trial

Encouse B Golden, Arpit Chhabra, Abraham Chachoua, Sylvia Adams, Martin Donach, Maria Fenton-Kerimian, Kent Friedman, Fabio Ponzo, James S Babb, Judith Goldberg, Sandra Demaria, Silvia C Formenti

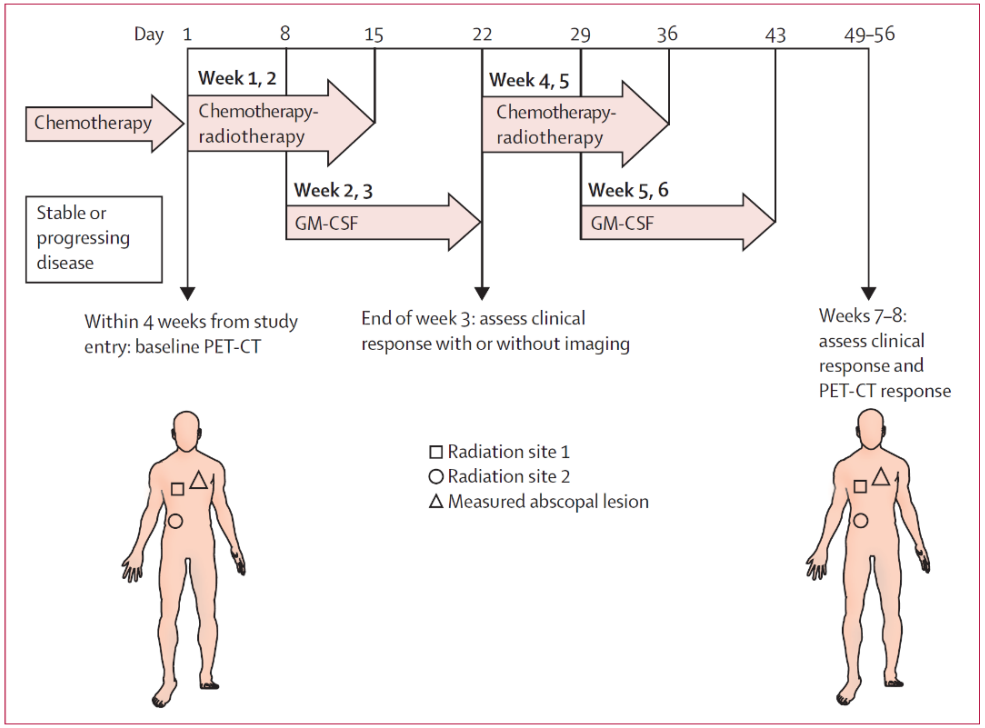


Figure 1: **Treatment and assessment schema for induction and determination of abscopal responses**

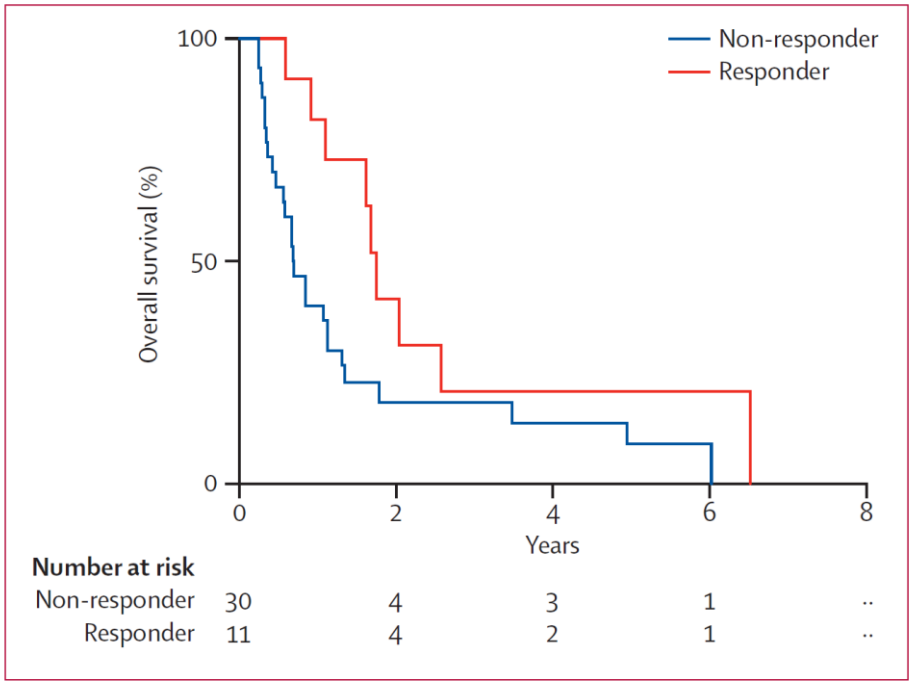
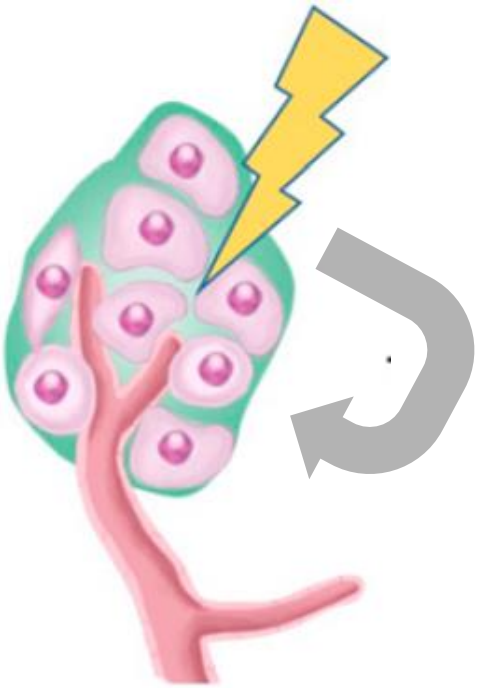


Figure 3: **Overall survival for abscopal responders and non-responders in an intention-to-treat analysis**

- primary endpoint: proportion of patients with an abscopal response
- in chemotherapy and hormone therapy refractory metastatic patients
- in combination with GM-CSF: DC stimulation

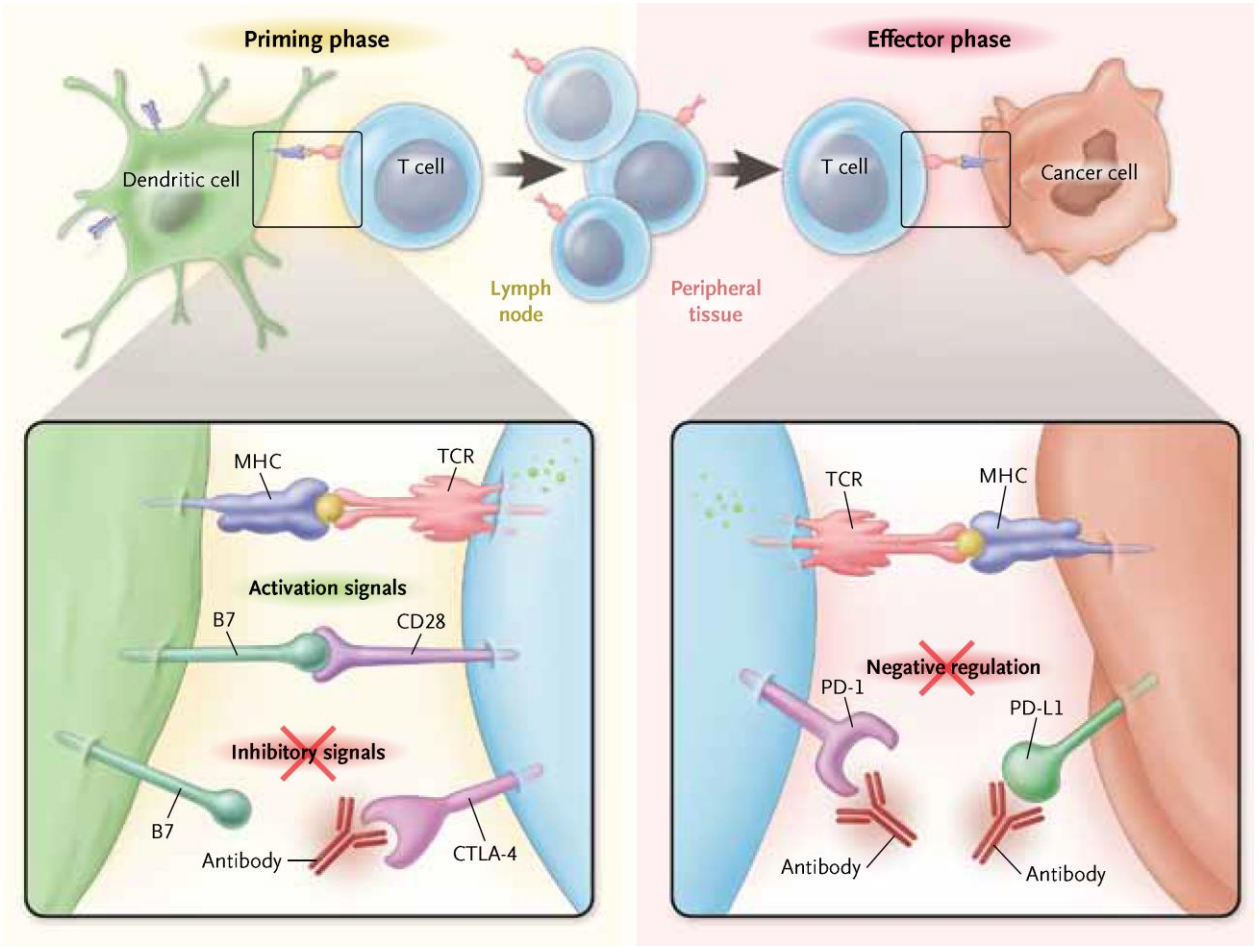
Lancet Oncol 2015; 16: 795–803

Radiotherapy in Combination with Immunotherapy



Radiotherapy to the local tumour site

Immune Checkpoint Inhibitors



- Boosting RT-induced Immunogenic Cell Death Effect
- Overcoming Immune Response Thresholds

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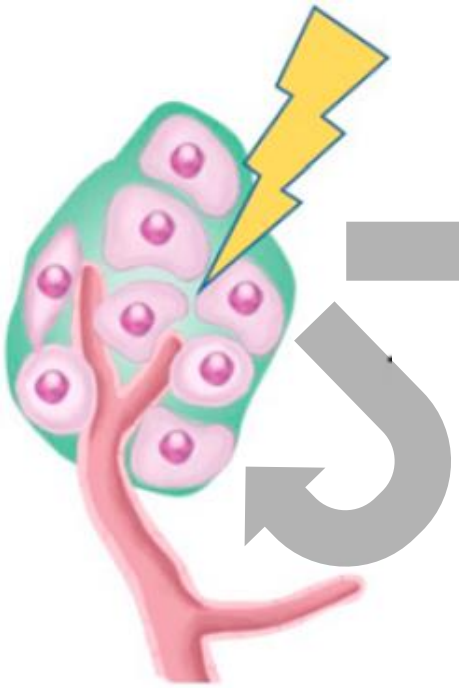
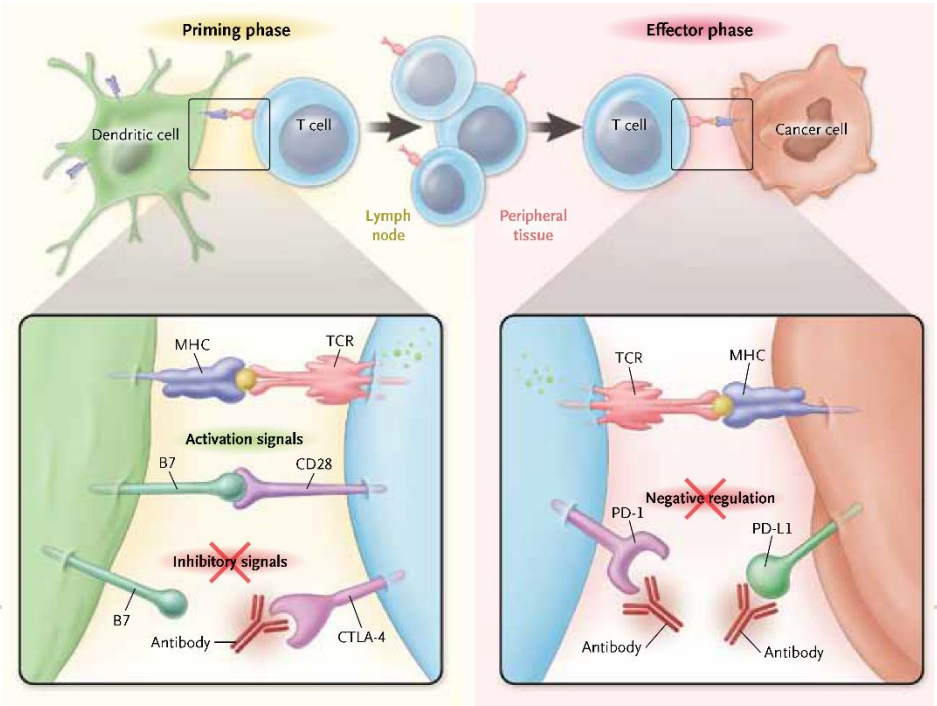
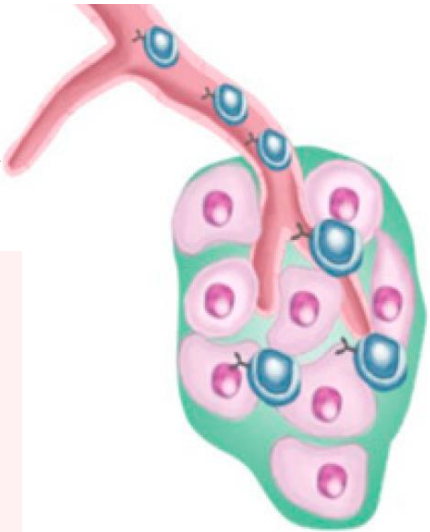
Increasing the Abscopal Effect by Immunotherapy



Immune Checkpoint Inhibitors





Radiotherapy to the local tumour site

Abscopal effect to a distant tumour site

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Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: a secondary analysis of the KEYNOTE-001 phase 1 trial

Narek Shaverdian*, Aaron E Lisberg*, Krikor Bornazyan, Darlene Veruttipong, Jonathan W Goldman, Silvia C Formenti, Edward B Garon†, Percy Lee†

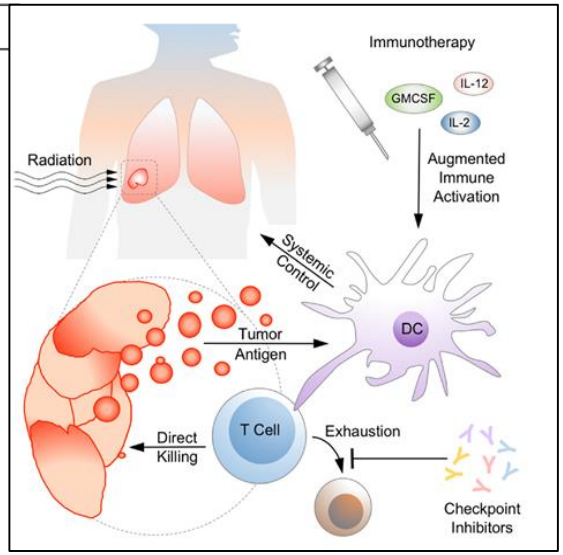
Previous RT extends PFS and OS in NSCLC patients treated with αPD-1 antibody

Lancet Oncol, 2017

Table 1 Ongoing trials combining immunotherapy with radiation in NSCLC

NCT#	Phase	Description
Metastatic disease		
NCT02318771	I	Use of anti-PD-1 + RT in patients with metastatic or recurrent solid tumor
NCT02303990	I	RADVAX: use of pembrolizumab + hypofractionated RT in metastatic melanoma or NSCLC
NCT02400814	I	Use of MPDL3280A (anti-PD-1) with stereotactic ablative radiotherapy in patients with stage IV NSCLC
NCT02444741	I/II	Use of dose escalated ipilimumab and SBRT in patients with metastatic solid tumors
NCT02221739	II	Use of ipilimumab and RT in patients with metastatic NSCLC
NCT02831933	II	ENSIGN: use of SBRT and gene therapy prior to nivolumab in patients with metastatic NSCLC
NCT02658097	II	Use of pembrolizumab following SBRT in patients with previously treated stage IV NSCLC
NCT02492568	II	Use of pembrolizumab following SBRT in patients with previously treated stage IV NSCLC
NCT02407171	II	Use of anti-PD1 MK-3475 (pembrolizumab) and stereotactic body radiotherapy in patients with metastatic melanoma or NSCLC
Oligometastatic/oligoprogressive disease		
NCT02621398	I	Use of pembrolizumab with chemoradiation in stage II/III NSCLC
NCT00828009	II	Use of bevacizumab and BLP25 vaccine in patients with stage III SNCLC who have received chemoradiation
NCT02434081	II	NiCOLAS: use of nivolumab consolidation after standard first line chemoradiation in locally advanced NSCLC
NCT02125461	III	PACIFIC: use of anti-PD1 MEDI4736 (AstraZeneca) following chemoradiation in patients with unresectable stage III NSCLC
NCT02768558	III	RTOG 3505: use of chemoradiation with adjuvant nivolumab in patients with locally advanced NSCLC

NSCLC, non-small cell lung cancer; PD-1, programmed death 1; SBRT, stereotactic body radiation therapy.



Campbell et al., 2017, Transl Lung Cancer Res 2017;6(2):220-229

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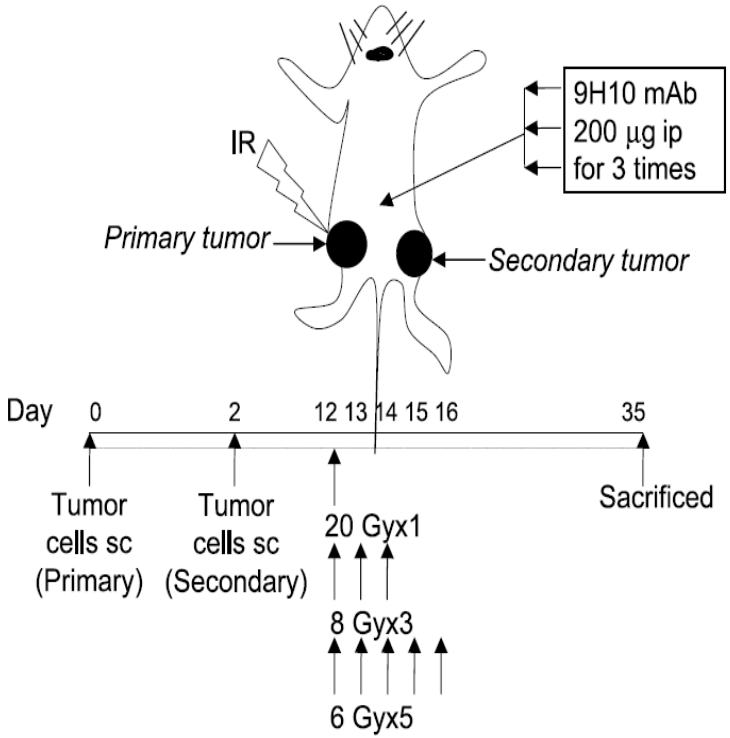
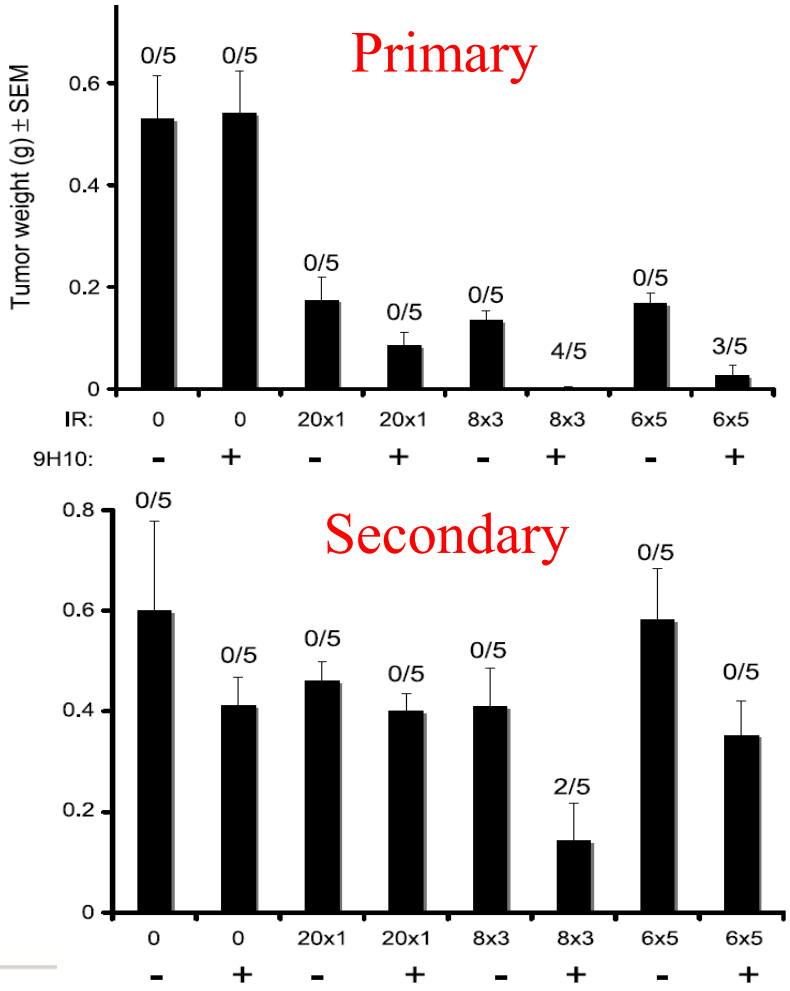
Fractionated but Not Single-Dose Radiotherapy Induces an Immune-Mediated Abscopal Effect when Combined with Anti–CTLA-4 Antibody

M. Zahidunnabi Dewan,[1] Ashley E. Galloway,[1] Noriko Kawashima,[1] J. Keith Dewyngaert,[3] James S. Babb,[2] Silvia C. Formenti,[3] and Sandra Demaria[1]





9H10mAb: mouse Ipi

(Clin Cancer Res 2009;15(17):5379–88)

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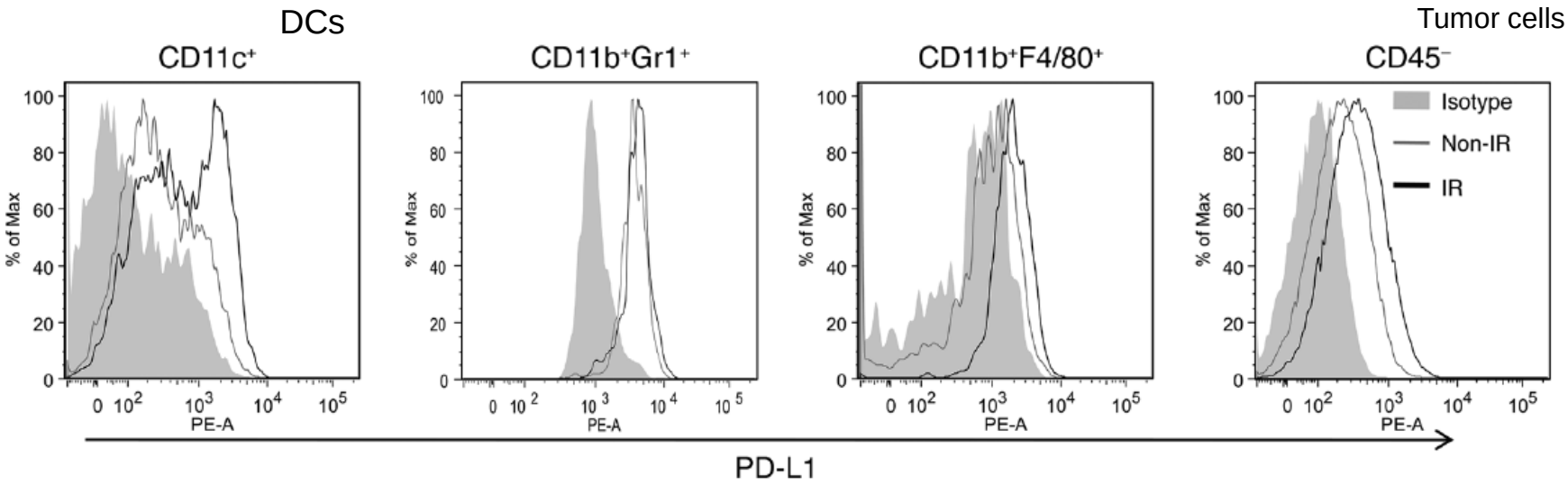
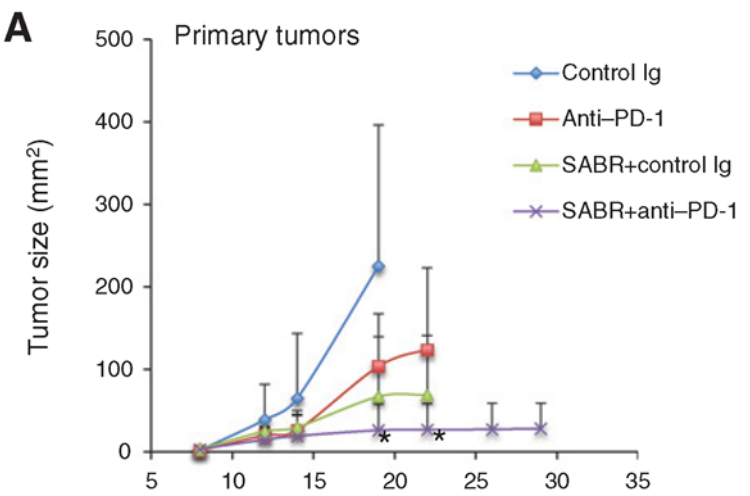
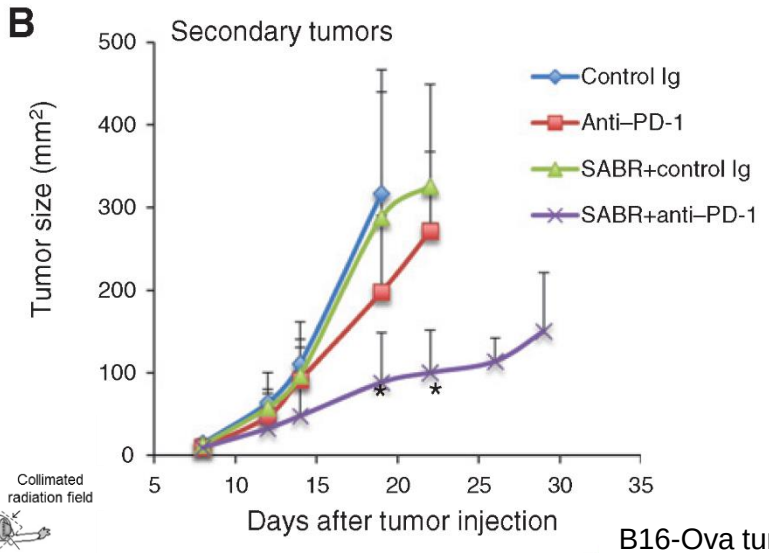
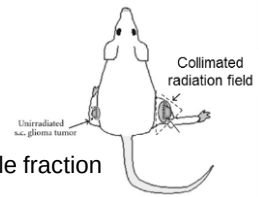
Radiotherapy combined with αPD-1-blockage









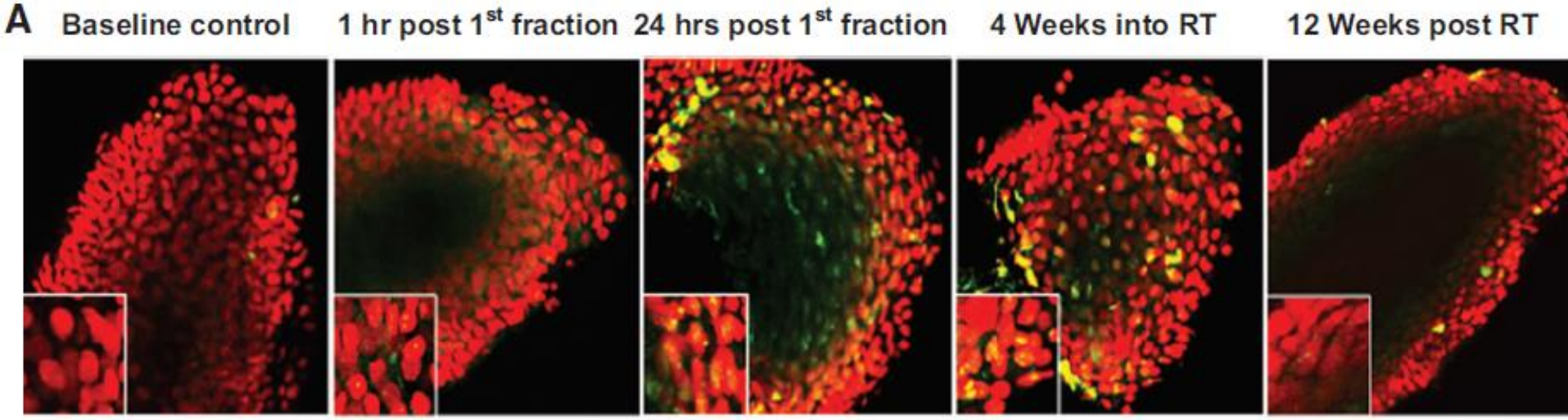
15 Gy single fraction

B16-Ova tumor model

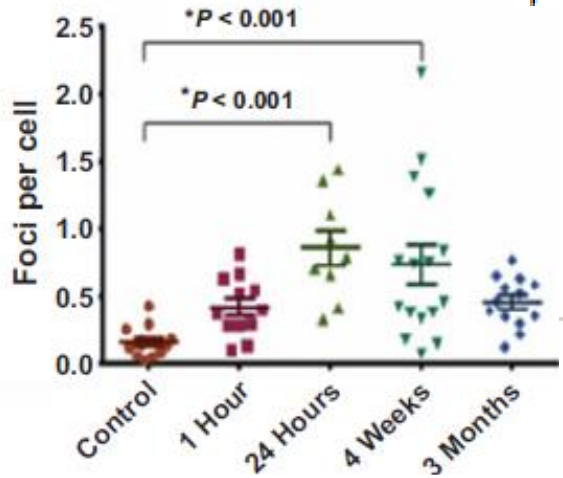
Park et al., Cancer Immunol. Res., 2015
Deng et al., JCI, 2014

see also Twyman et al., Nature, 2015, 520, 373ff

Radiotherapy for Non–Small Cell Lung Cancer Induces DNA Damage Response in Both Irradiated and Out-of-field Normal Tissues



γ-H2AX foci in out-of-irradiated volume eyebrow hair follicles

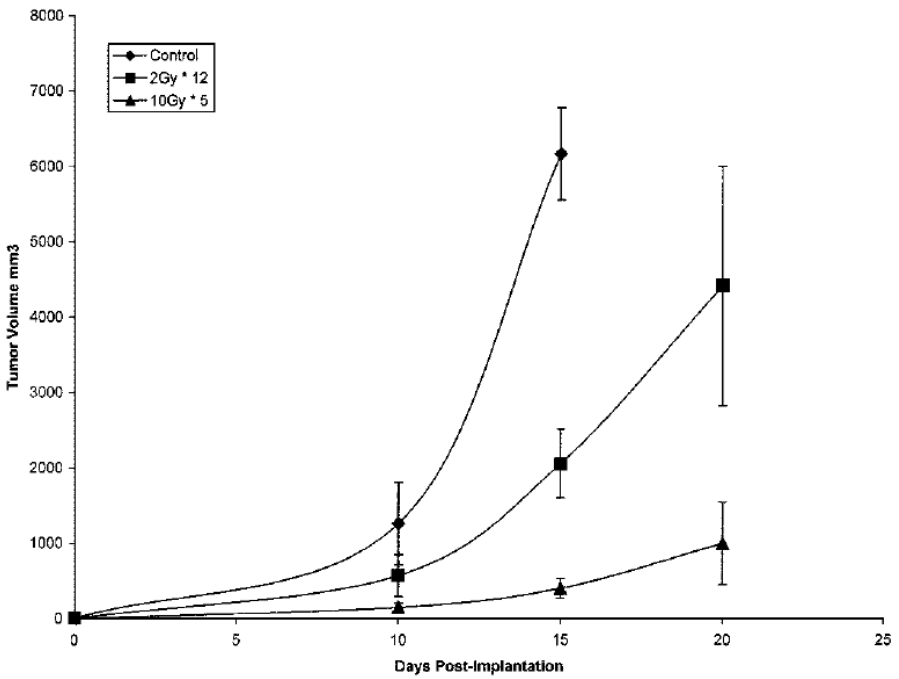


Siva et al., 2016

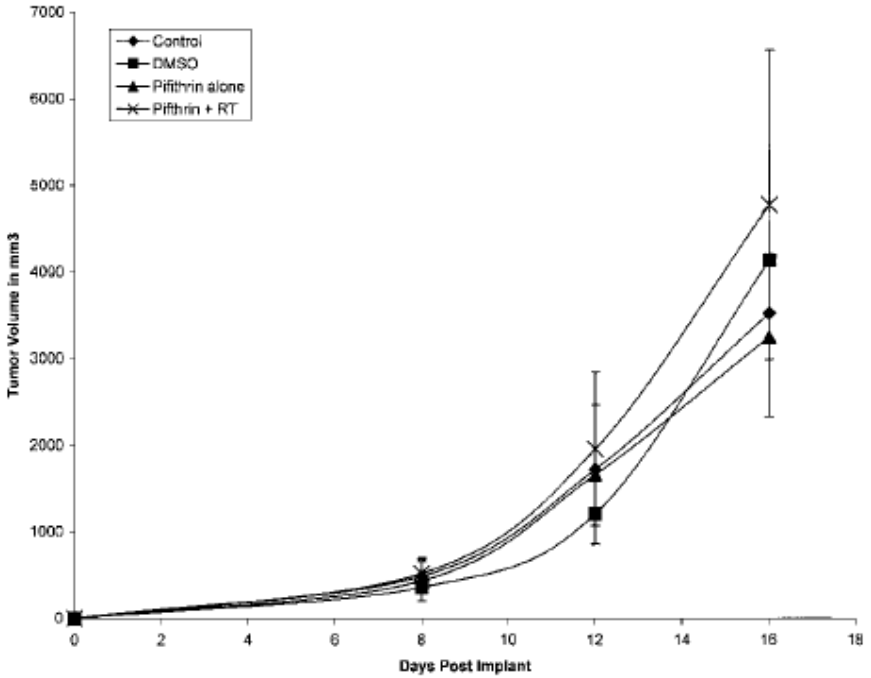
Multiple Open Questions: Influence of Genetic Background

[CANCER RESEARCH 63, 1990–1993, April 15, 2003]

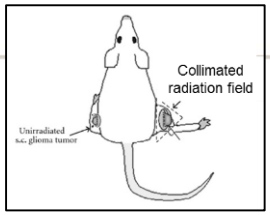
Radiation Abscopal Antitumor Effect Is Mediated through p53[1]



LLC and T124 tumors
in p53wt animals



LLC and T124 tumors
in p53-def animals
or +Pifithrin



Camphausen et al., 2004

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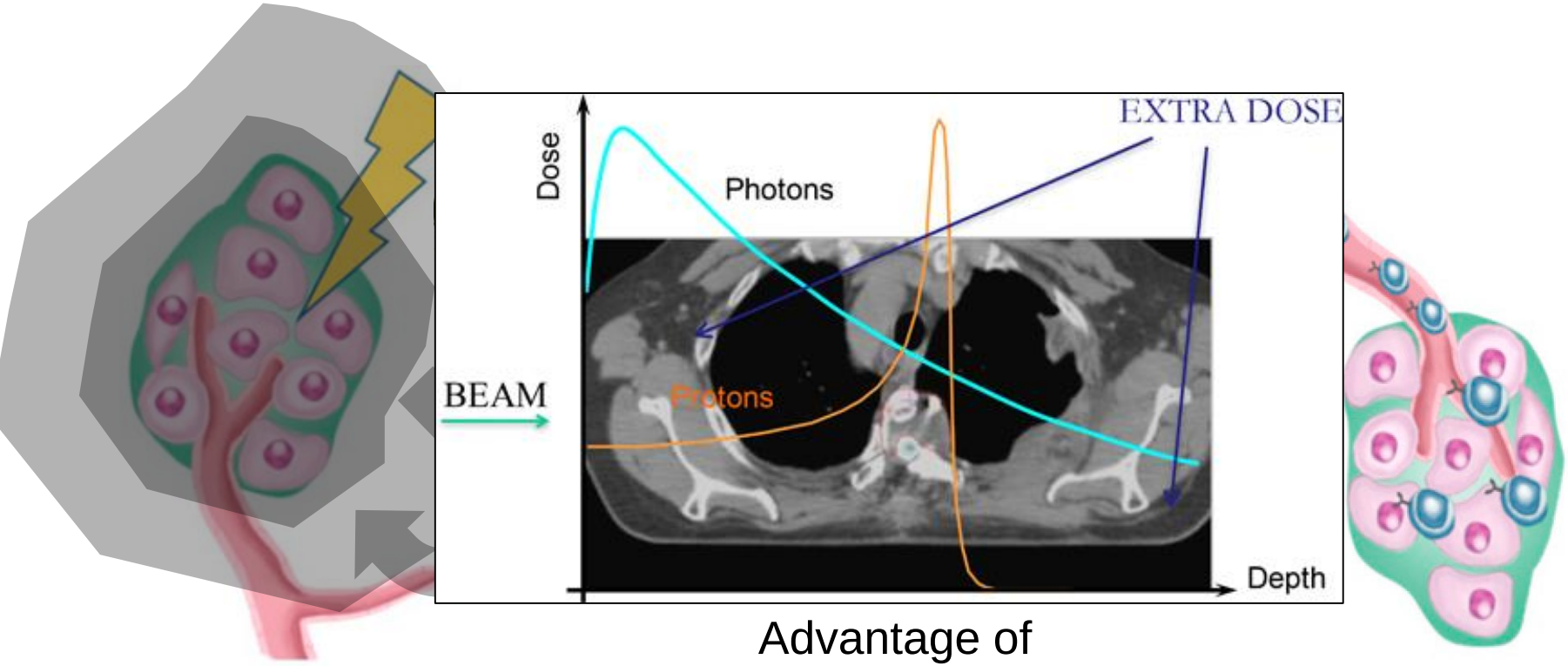
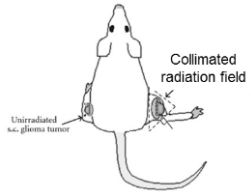
Open Question: Will Margins and Low Dose Bath of IR affect Impact of Immune Response

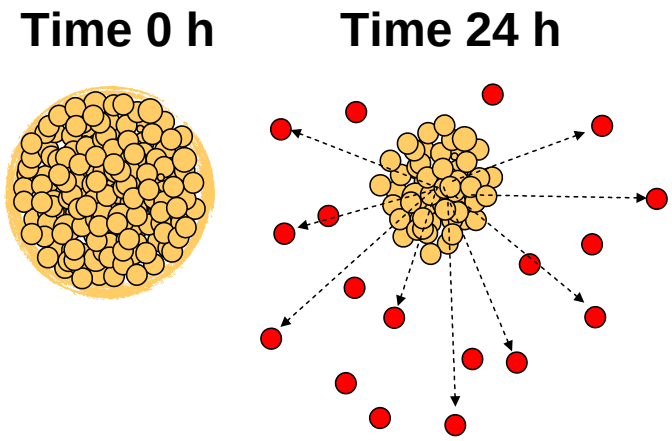


Advantage of
Proton versus Photon Radiotherapy

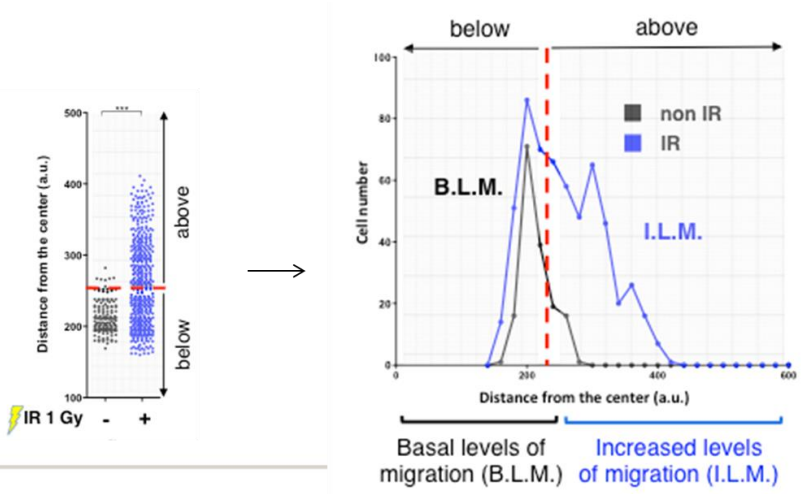
Radiotherapy to the local tumour site

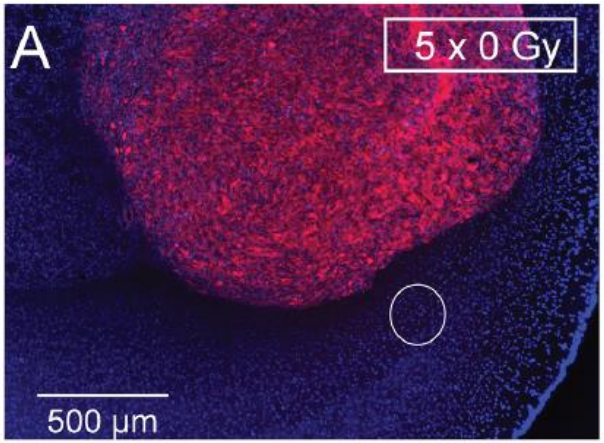


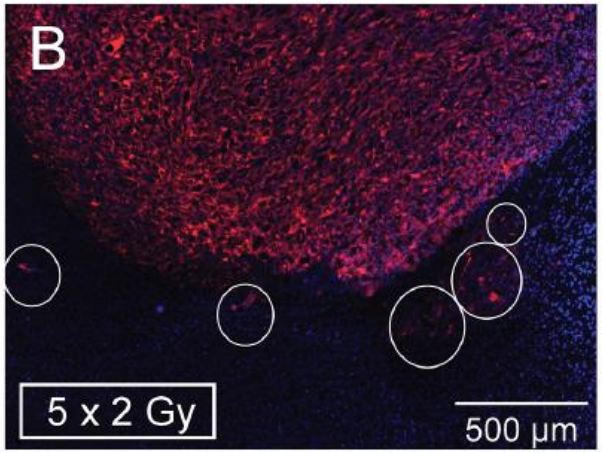
Radiotherapy-induced Motility and Invasiveness



Spheroid Invasion Assay







Glioblastoma tumor model,
Edalat et al., Oncotarget, 2016

Preliminary own results

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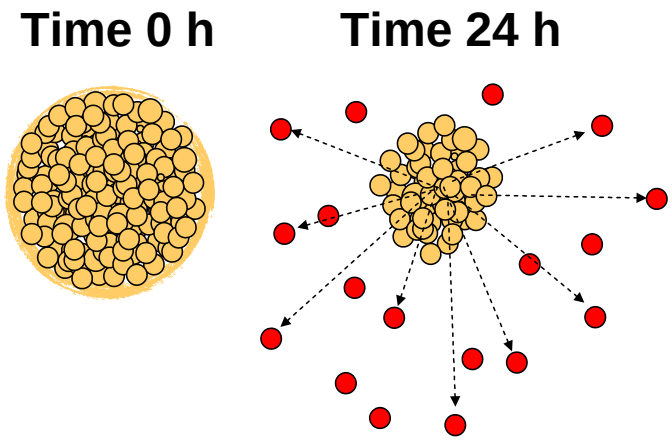
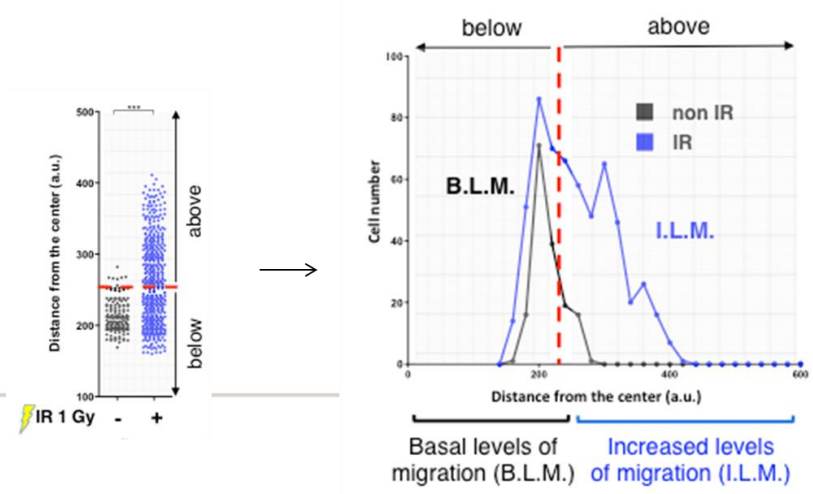
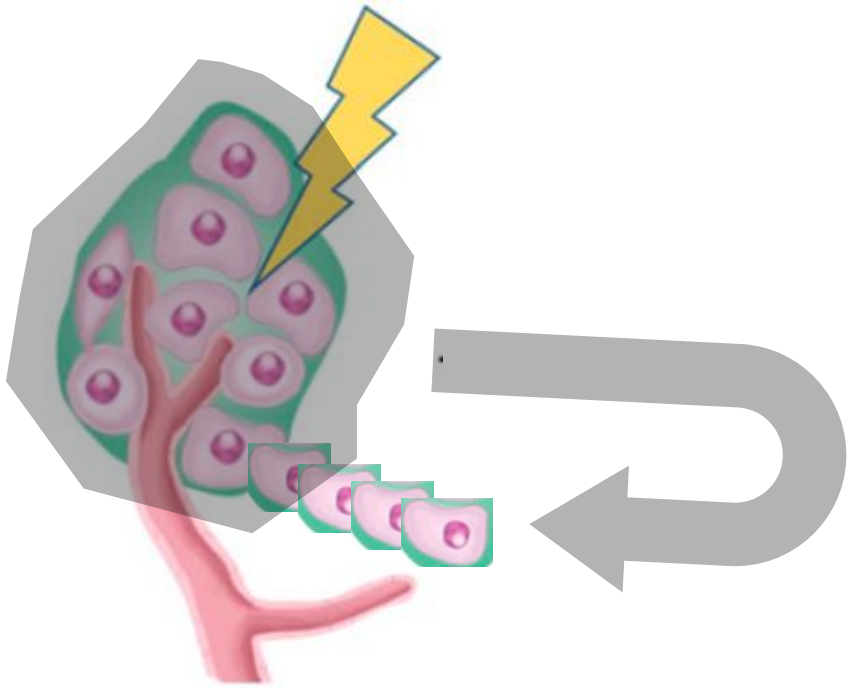
Radiotherapy-induced Motility and Invasiveness



Spheroid Invasion Assay





Radiotherapy to the local tumour site

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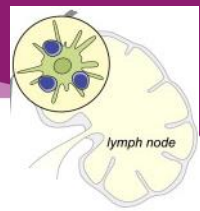
Radiotherapy and Immune Response



Radiotherapy

Radiotherapy to the local tumour site

Immunogenic cell death

Upregulation of surface molecules

T-cell attracting cytokines

Antigen uptake and activation of dendritic cells

Priming and activation of T-cells

Effector T-cells

Abscopal effect to a distant tumour site

adapted from Van Limbergen et al., BJR 2017

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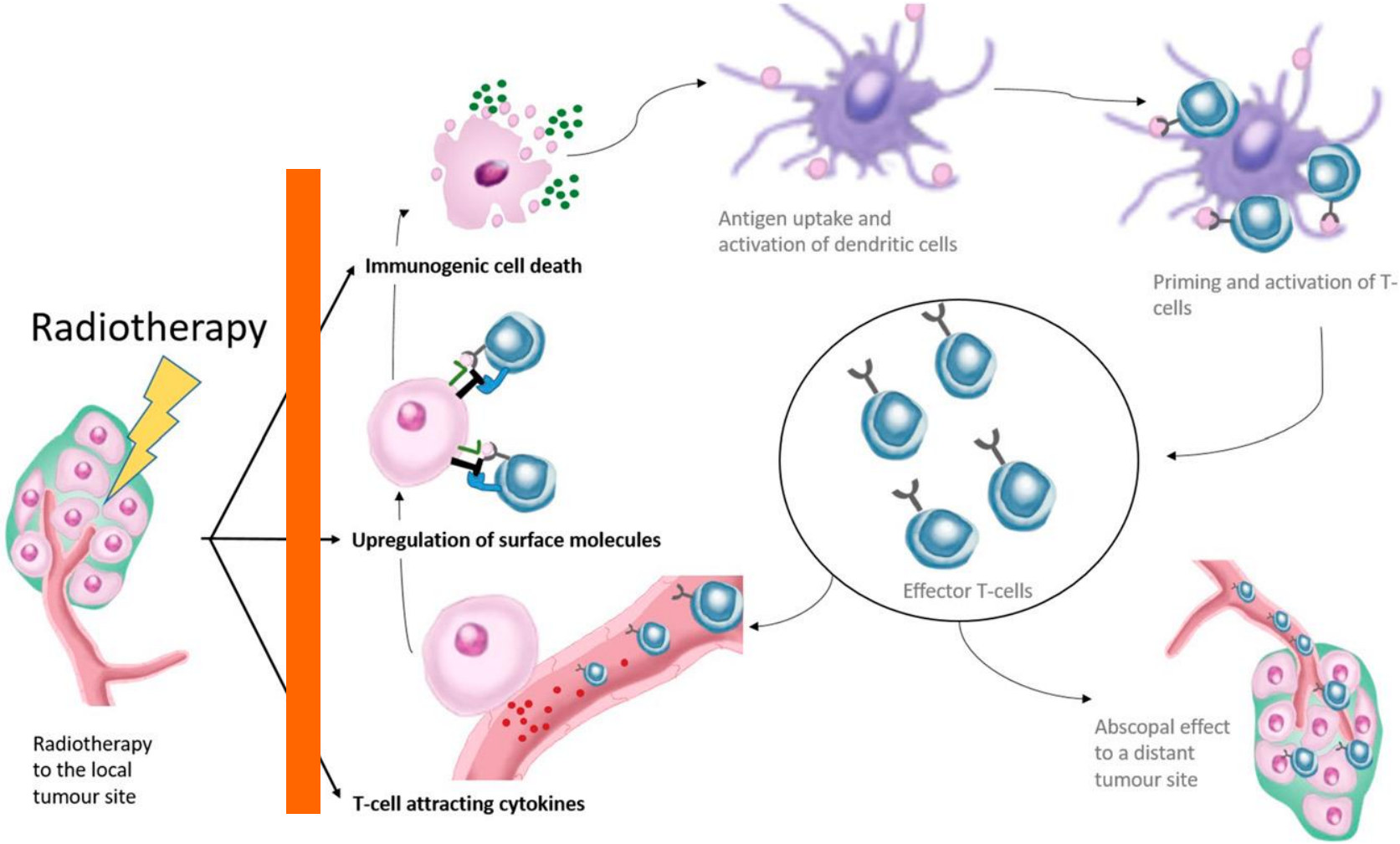
Open Questions: Mechanisms of Resistance



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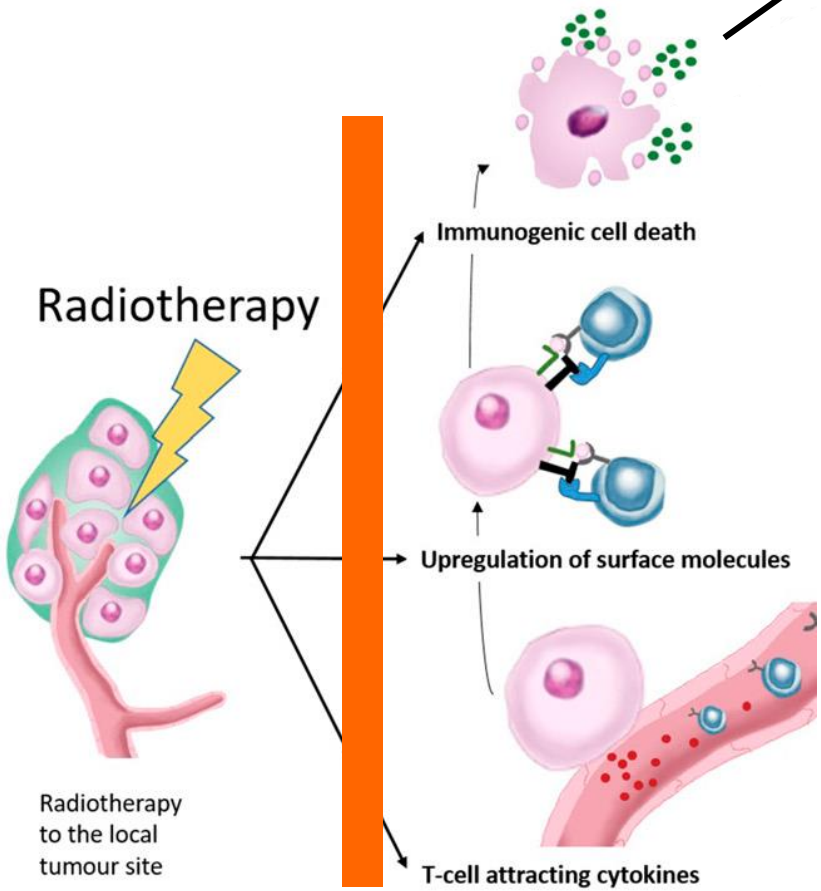
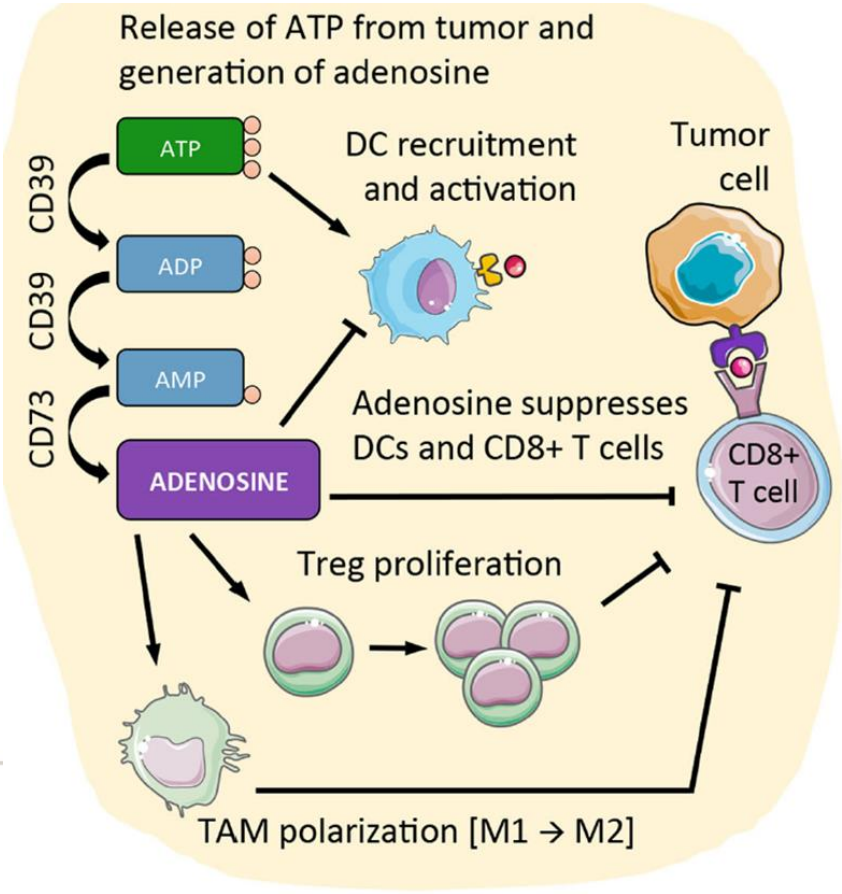
Immunosuppressive Pathways enhanced by RT

Release of DAMPs:
Calreticulin, HMGB1, ATP

- Activation of Dendritic Cells





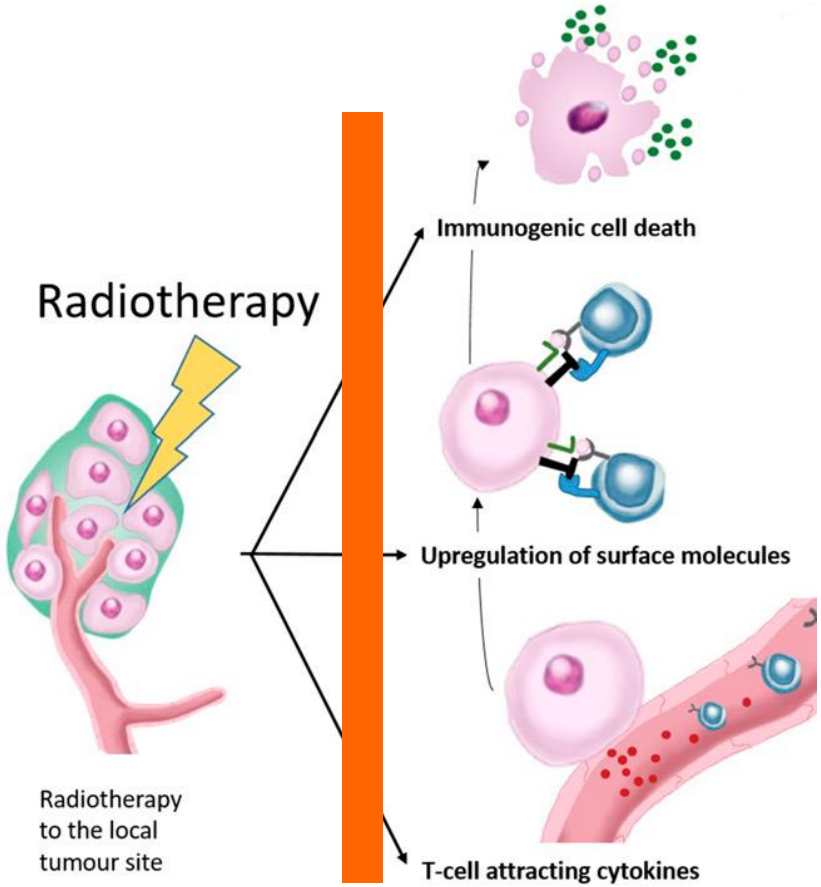
adapted from Wennerberg et al., 2017

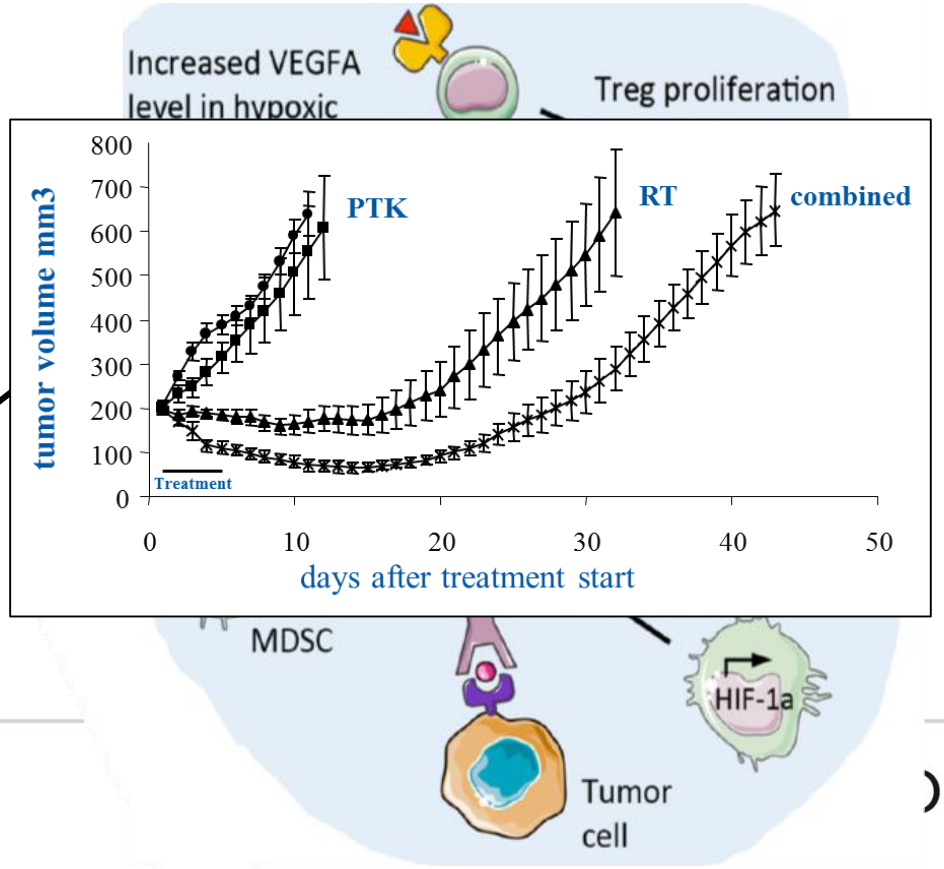
Immunosuppressive Pathways enhanced by RT

- Hypoxia-induced PDL-1-expression
- Hypoxia fine-tuned M2-phenotype tumor-associated Macrophages

- Hypoxia-induced VEGF-secretion

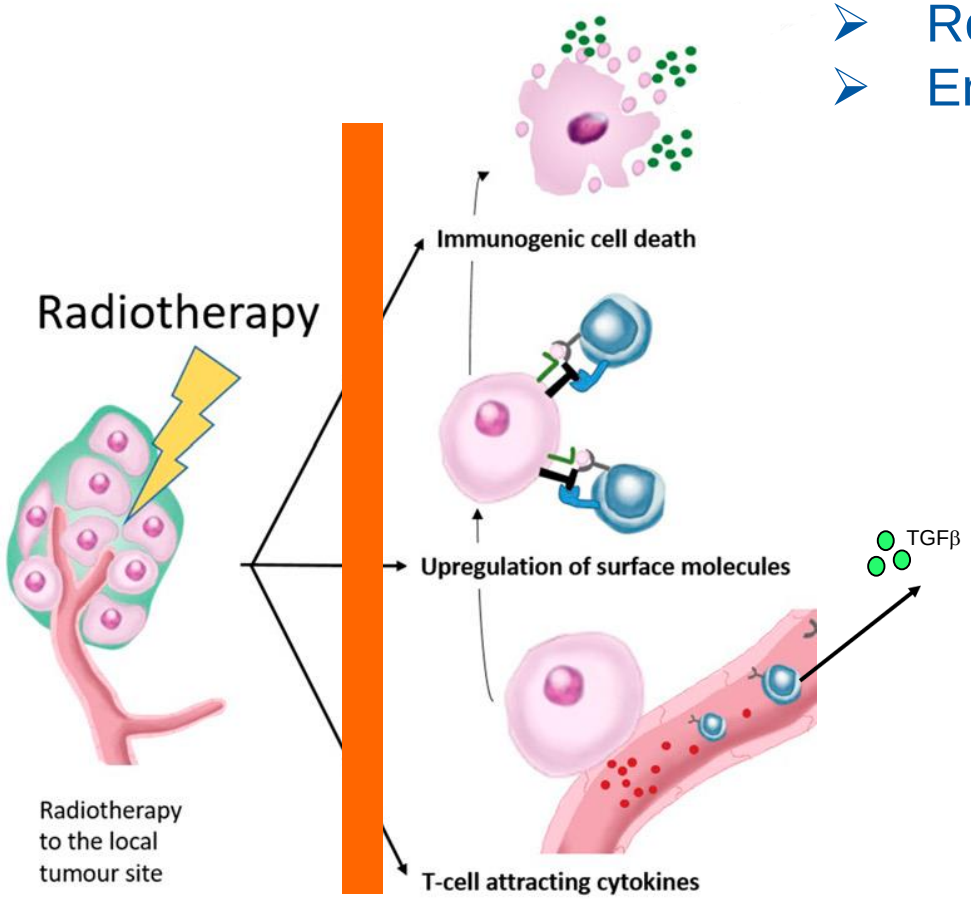
➢ VEGF-mediated Treg proliferation

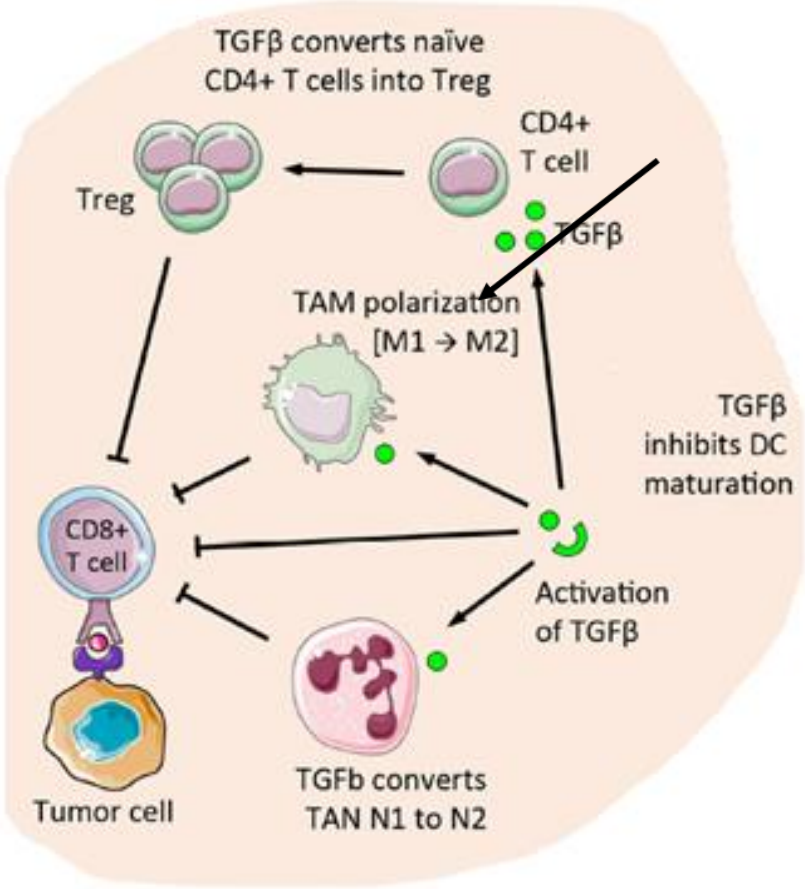




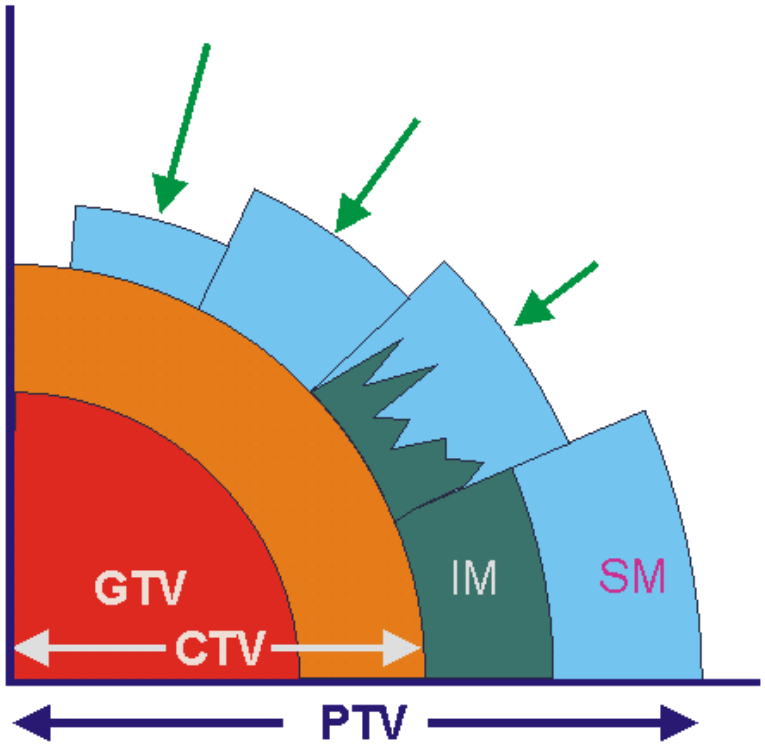
Immunosuppressive Pathways enhanced by RT

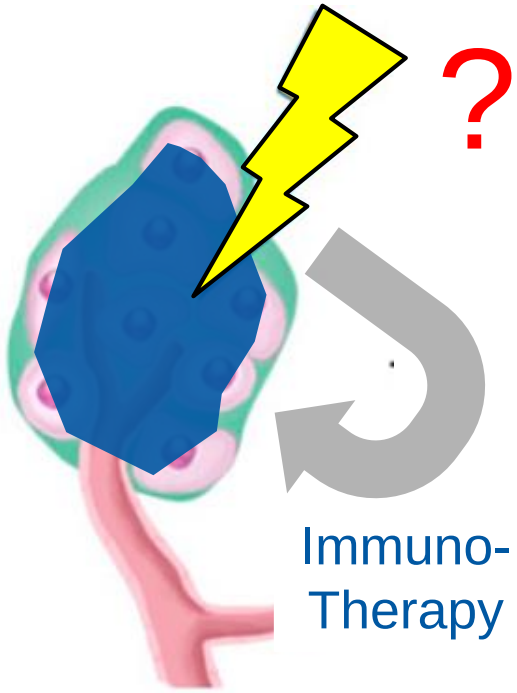
- RT-induced TGFβ-release and activation
  - Reduced $CD8^+$ T cell differentiation
  - Enhanced Treg population





In an Ideal World: Exploting IR-Induced ICD and Immunotherapy at the Site of the Primary Tumor





Radiotherapy to the local tumour site

Reduced Normal Tissue Toxicity ?

Reduced Requirement for Conformal Radiotherapy ?

Summary

True RT-induced abscopal effects exist, are rare, are immune-mediated (irradiated tumor as immunogenic hub)

- Novel immunomodulatory agents have the potential to maximise RT-induced anti-tumor immune responses
- Radiotherapy can enhance antitumor immune response

Multiple questions exist:

Relation between dose/fraction and the immune effects of radiation; additional resistance mechanisms

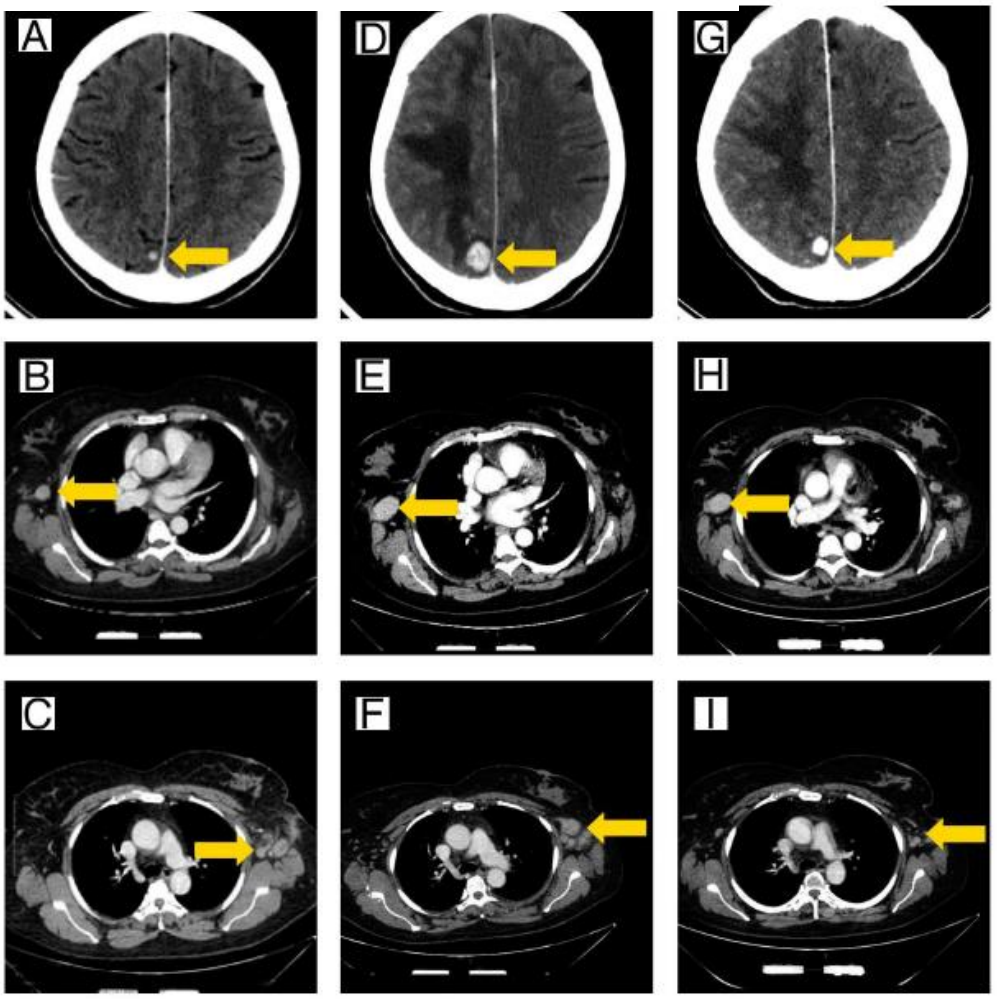
Timing of immune therapy with radiotherapy is crucial

Is Rejection of neoplastic lesions by immune system a novel «R»?

Abscopal effect and brain metastases

Figure 3. Patient Case 2. (**A–I**) A 52-y-old female patient received 4 cycles of ipilimumab 3 mg/kg (May to August 2012) followed by palliative whole-brain radiotherapy (WBRT) in August to September 2012 for symptomatic brain metastases. Whole body 128-slice CT scans (1 mm thickness) were performed at baseline, post-ipilimumab and post-RT. (**A–C**) Baseline, pre-ipilimumab scans from May 2012. (**D–F**) Post-ipilimumab scans from August 2012 showing representative brain metastasis (**D**) and lymphnodal (**E–F**) metastases. (**G–I**) Post-RT follow-up scan from september 2012 showing a local response (**G**) and reduction of lymphnodal (**H–I**) metastases indicative of abscopal response.

Does RT «just» enhance Ipilimumab-effect ?



Baseline | Post-ipilimumab | Post-RT

Grimaldi et al., Oncoimmunology, 2014
See also, e.g. Postow et al., NEJM, 2012:

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COMBINED DRUG-RADIATION TREATMENT: BIOLOGICAL BASIS APPLICATIONS AND PERSPECTIVES

15-18 June, 2017
Brussels, Belgium

NSCLC

Mario Levis
Radiation Oncologist
University of Torino, Italy

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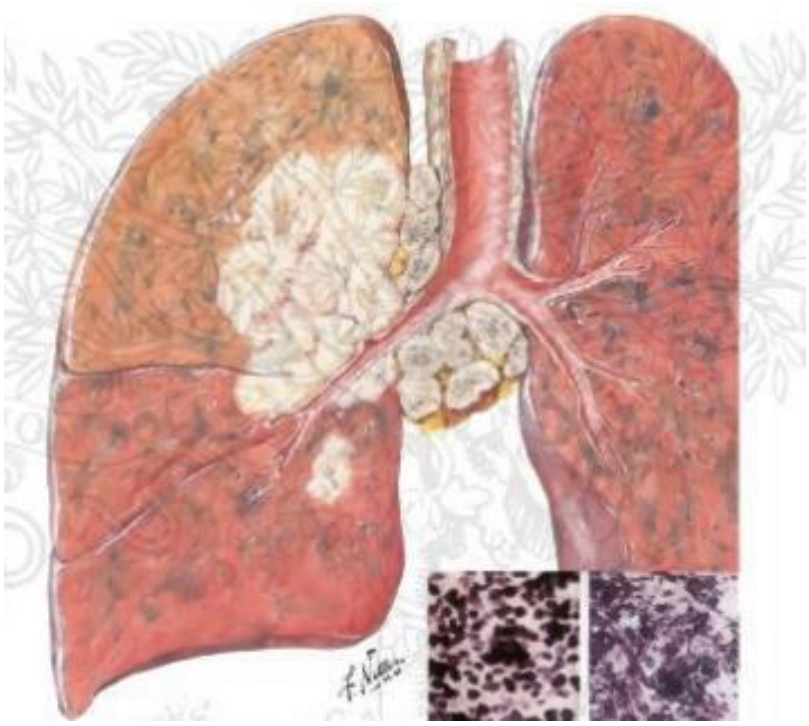
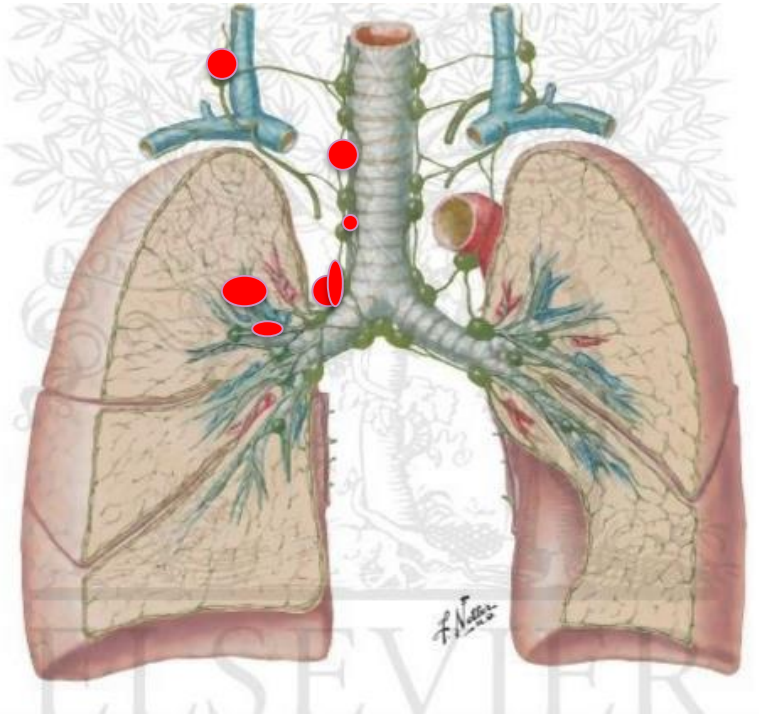
- **Locally advanced NSCLC (IIIA-IIIB)**
- **Oligometastatic NSCLC**

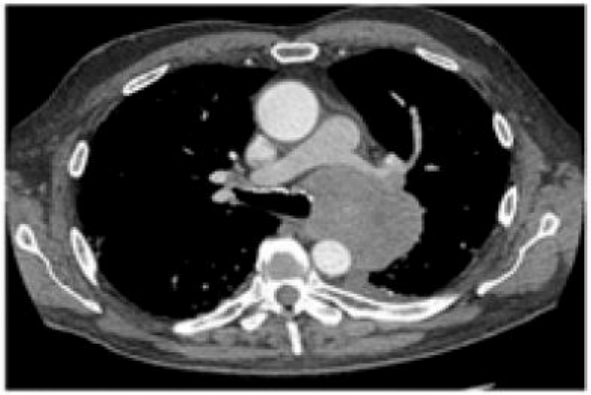
The problem of stage III heterogeneity

T3/T4

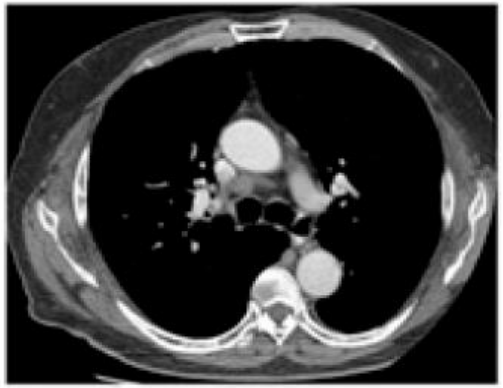


N2/N3

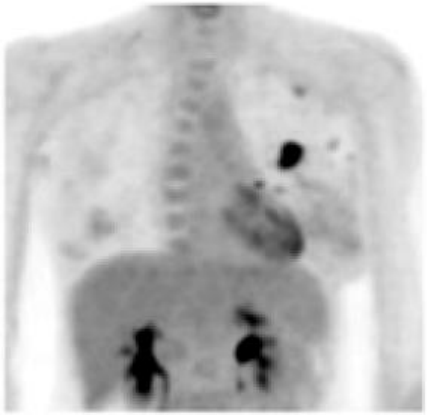




Mediastinal Infiltration

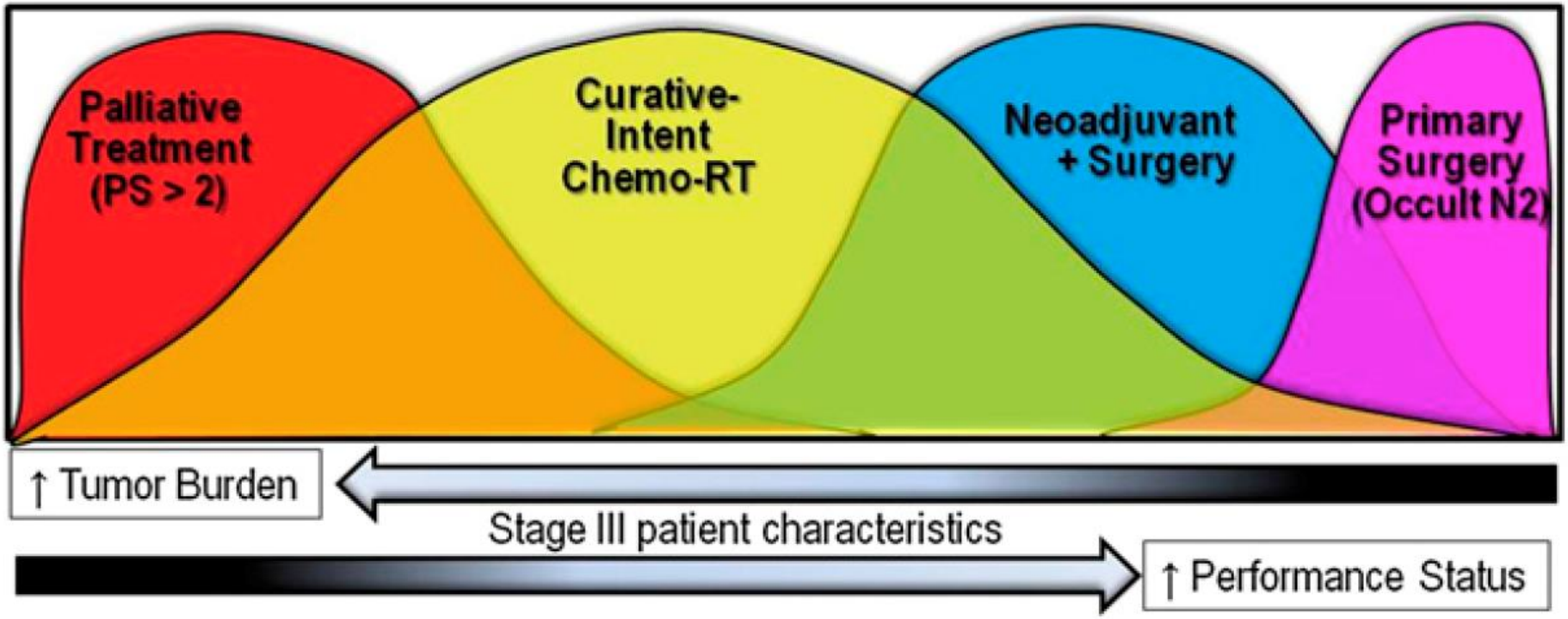


Discrete node enlargement



Clinically occult N2

Schematic of types of patients included in studies using different treatment approaches



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clinical practice guidelines

Annals of Oncology 24 (Supplement 6): vi89–vi98, 2013
doi:10.1093/annonc/mdt241
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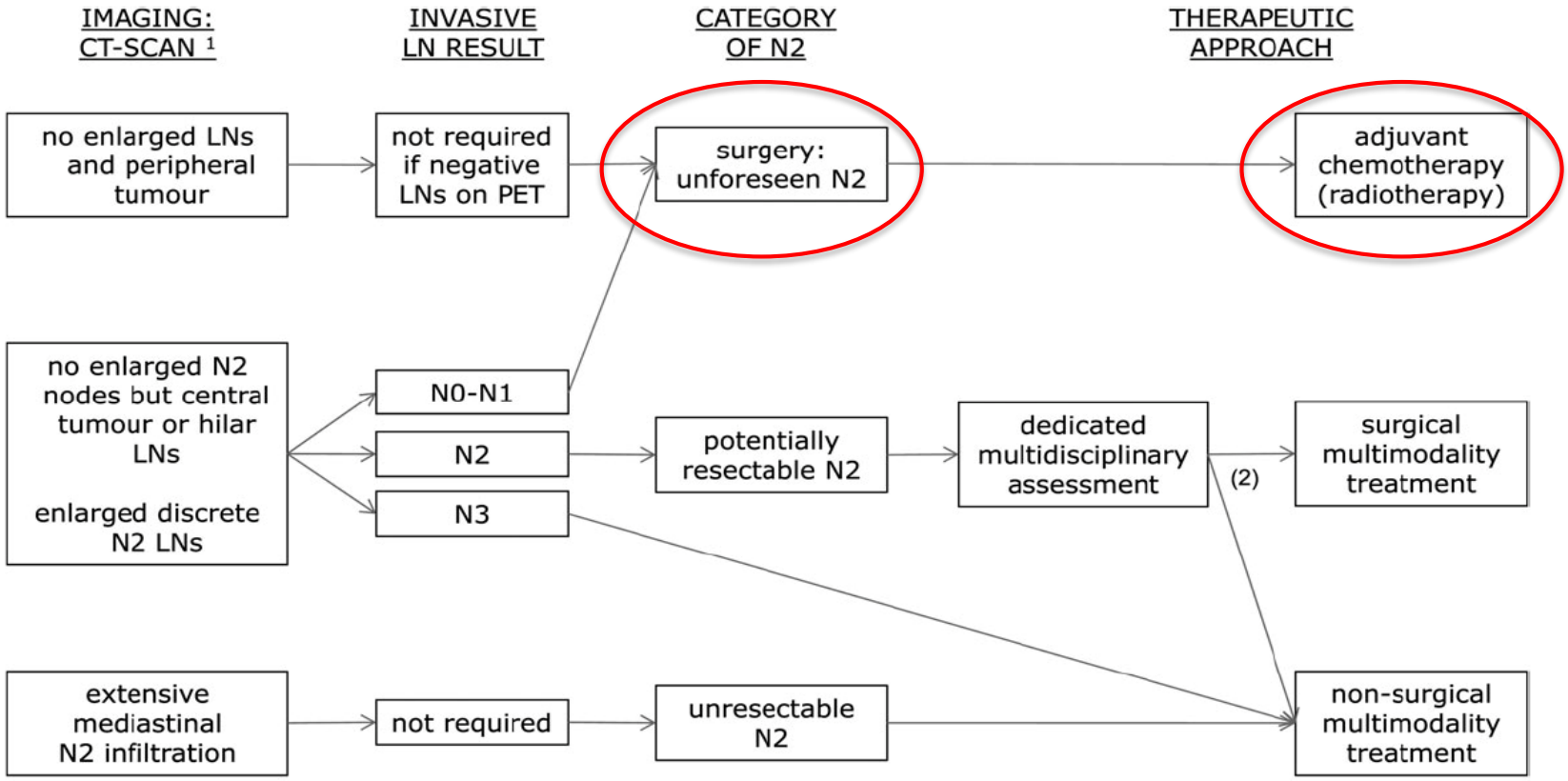
Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†



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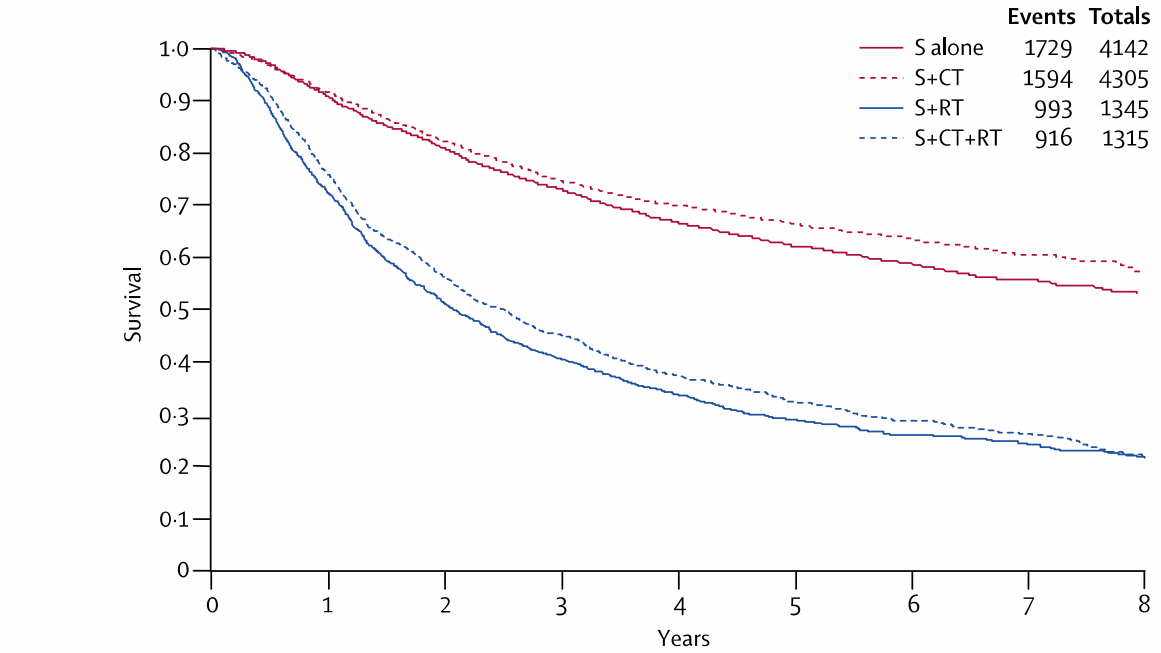
Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data

Adjuvant CT provides survival benefit



Number at risk									
S alone	4142	3648	3102	2584	2083	1601	841	407	148
S+CT	4305	3809	3261	2746	2278	1785	936	473	165
S+RT	1345	956	660	503	376	282	202	141	85
S+CT+RT	1315	977	711	532	385	279	203	143	84

- **Benefit of adding CT after surgery** with an absolute increase in survival of **4% at 5 years** (64% vs 60%)
- **Benefit of adding CT to surgery + RT** with an absolute increase in survival, again, of **4% at 5 years** (33% vs 29%)
- **Adjuvant CT improves survival, irrespective of the addition of RT.**

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Burdett S. et al. (NSCLC Meta-analyses Collaborative Group) Lancet 2010;375

THE LANCET

Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials

PORT Meta-analysis

Trial	Number of events/ number entered PORT	No PORT	O-E	Variance
Belgium (10)	88/98	80/104	16·04	40·67
LCSG 773 (11)	84/110	81/120	4·77	41·02
CAMS (12)	83/153	100/164	1·07	44·88
Lille (13)	59/81	45/82	10·87	25·66
EORTC 08861	26/52	20/54	5·53	11·20
MRC LU11 (14)	116/154	123/154	-2·48	59·39
GETCB 04CB86	69/99	59/90	4·95	31·59
Slovenia (15)	30/35	33/39	-2·56	15·63
GETCB 05CB88	152/274	120/265	25·13	67·08
Total	707/1056	661/1072	63·32	337·12

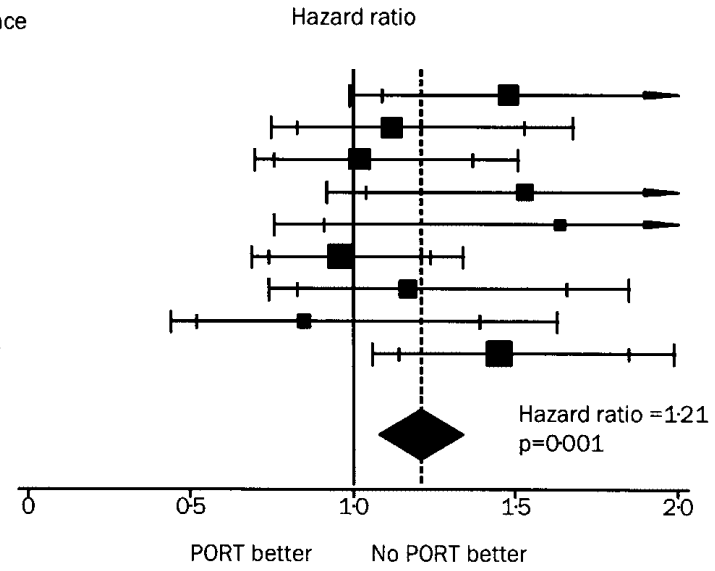

Figure 1: **Hazard ratio plot for survival**

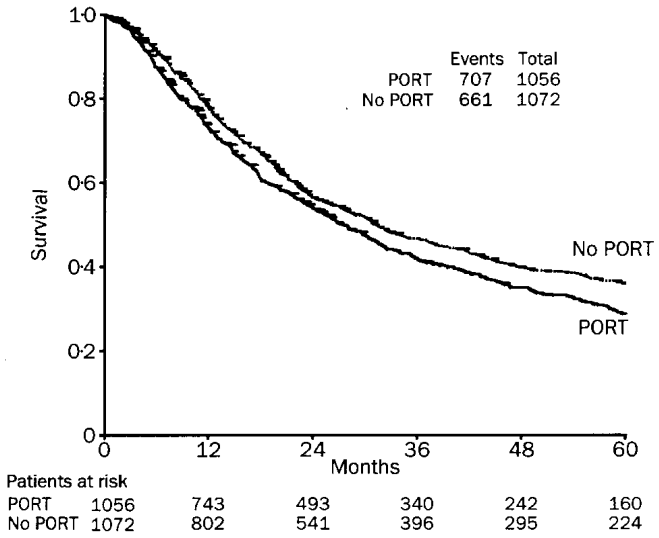

Figure 2: **Kaplan-Meier curve for survival**

Stewart LA. et al. Lancet 1998;352

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THE LANCET

Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials

PORT Meta-analysis

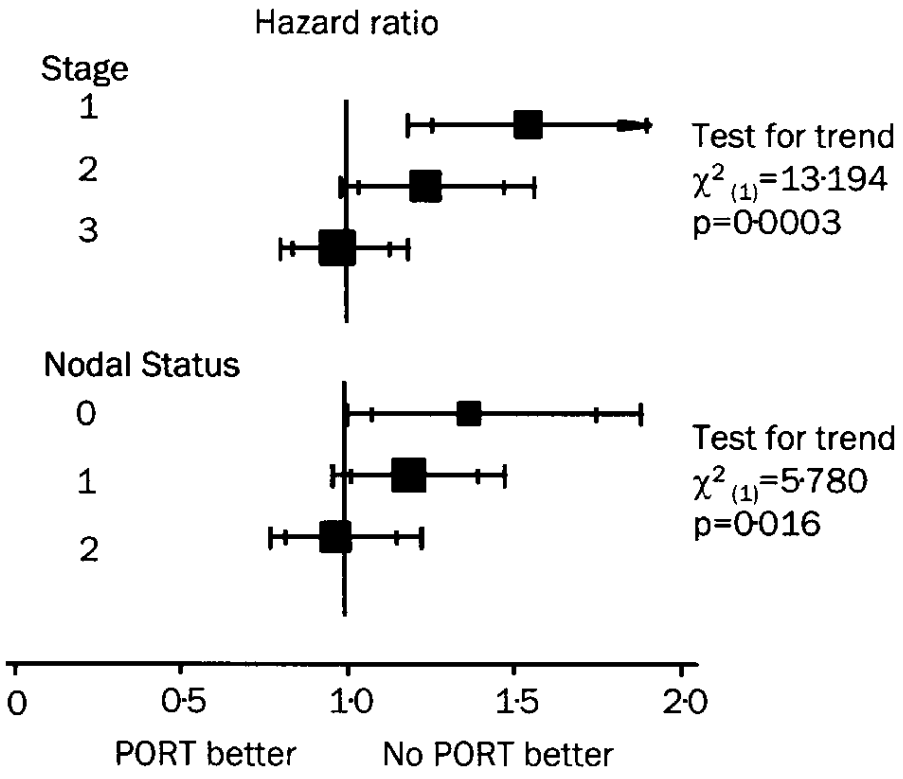

Figure 6: **Stage and nodal status subgroup analysis for survival**

Interpretation

- **PORT is detrimental to patients with early stage completely resected NSCLC and should not be used routinely for such patients**
- **The role of post-operative radiotherapy in the treatment of N2 tumors is not clear and may warrant further research.**

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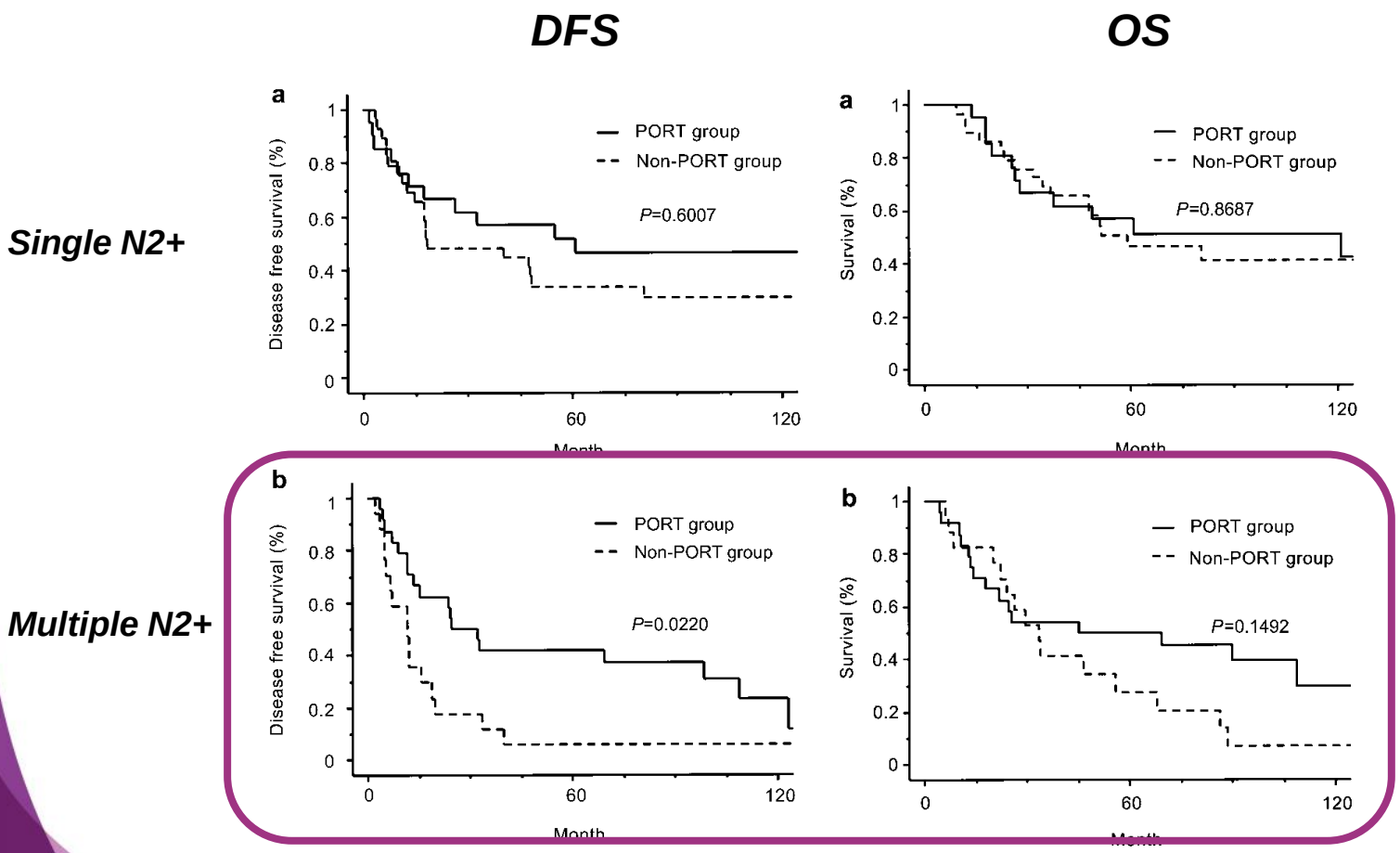
Stewart LA. et al. Lancet 1998;352

Postoperative radiotherapy for patients with completely resected pathological stage IIIA-N2 non-small cell lung cancer: focusing on an effect of the number of mediastinal lymph node stations involved

PORT utility according to N2 status (Single vs Multiple nodes)



- **Retrospective study**
- **91 patients**
- **Enrollment: 1986-2003**
- **PORT more effective in multiple station than single station metastasis**
- **Prospective randomized phase III trial is warranted**

Matsugama H. et al. Interact Cardiovasc Thorac Surg 2008;7

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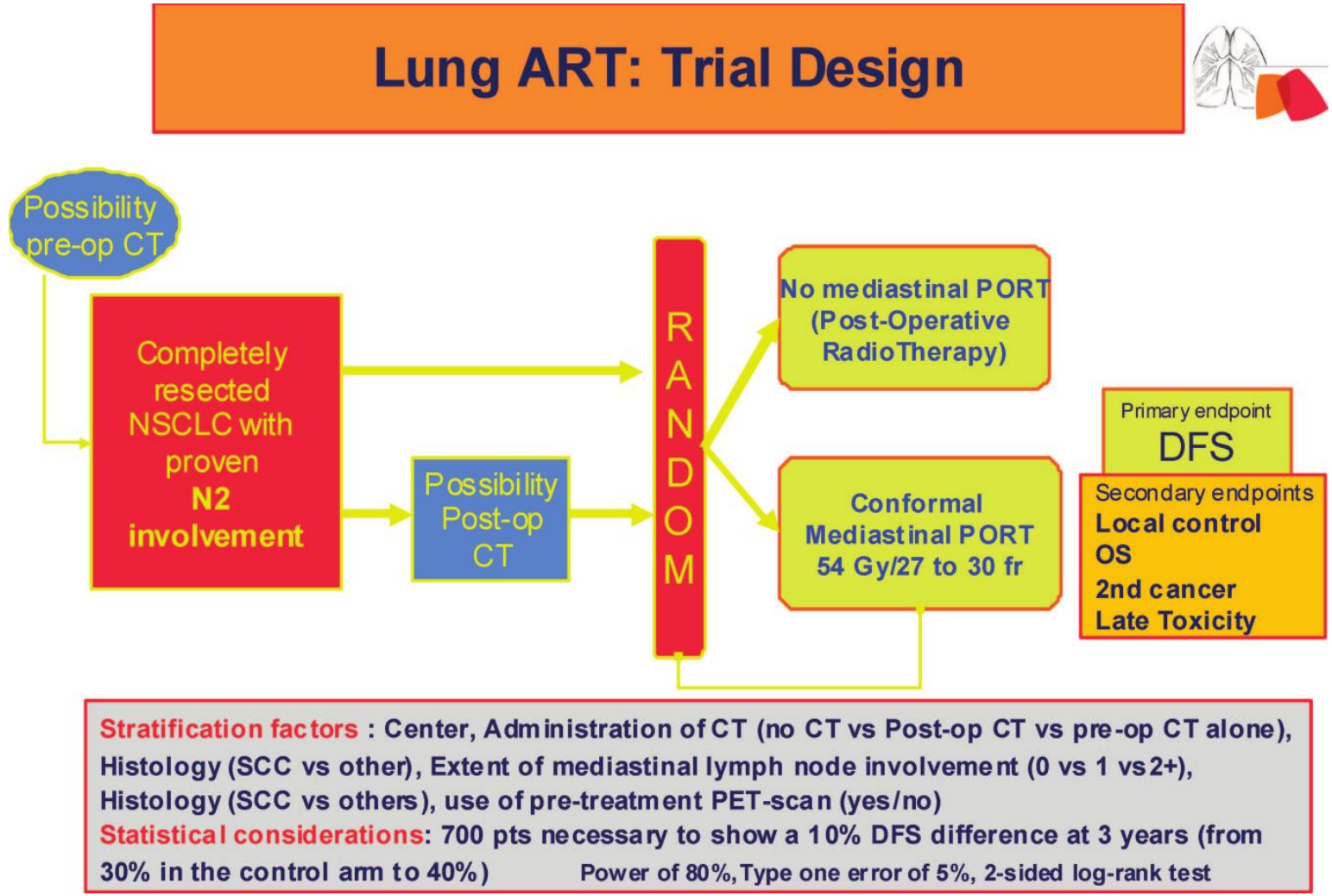
Ongoing study on the role of adjuvant RT: LUNG ART trial (Collaborative Intergroup)



clinical practice guidelines

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- PORT may be considered for fit patients with completely resected NSCLC with **N2 nodal involvement**, preferably after completion of adjuvant chemotherapy. This may **reduce local recurrences** (**25-30% gain**), although no survival benefit has been demonstrated [III, B]
- A **randomised clinical trial to assess the effect on survival is ongoing** (LUNGART, NCT00410683)
- PORT **can be indicated in case of a R1 or R2 resection**, although survival in these patients remains poor [III, B]

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Vansteenkiste J, et al. Ann Oncol. 2013;24

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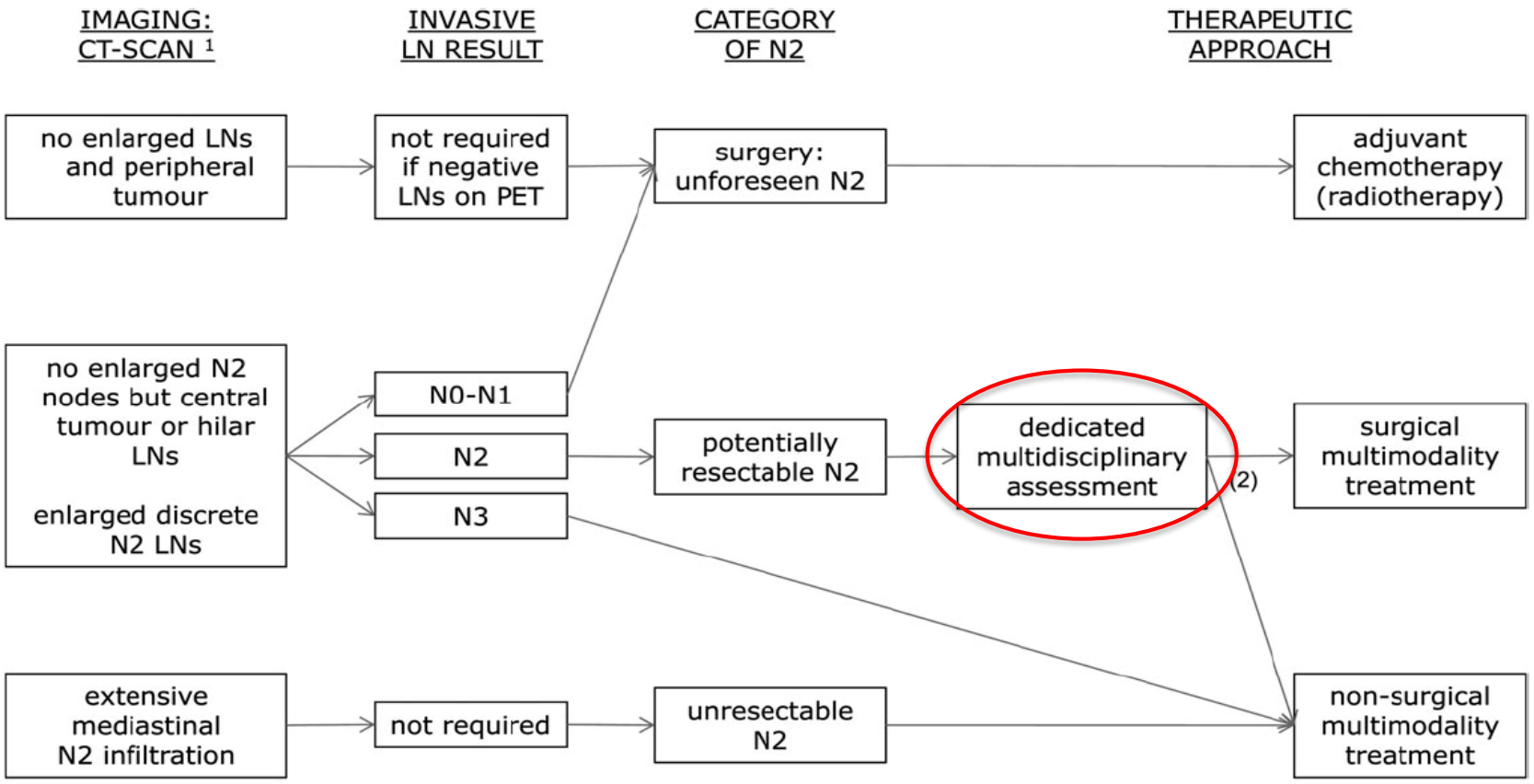

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Vansteenkiste J, et al. Ann Oncol. 2013;24

CLINICAL CASE #1 – Locally advanced NSCLC

- **A 55-year-old, otherwise healthy man (ECOG PS = 0)**
- Former smoker (quit 10 years ago)
- Suspicious 5-cm mass in right upper lobe (RUL) at the chest X-ray
- Chest **CT scan**: 5x4-cm spiculated lesion in RUL and suspicious 1.7-cm mediastinal lymph node (LN) at the 4R region
- **PET-CT**: 5-cm fluorodeoxyglucose (FDG) avid mass in RUL (mSUV 16.4), right hilum, 4R node (SUV4)

- Bronchoscopy and Endobronchial Ultrasound (EBUS):
  Biopsy of lung lesion and 4R LN; both show adenocarcinoma (CK7+, CK20-TTF1+)

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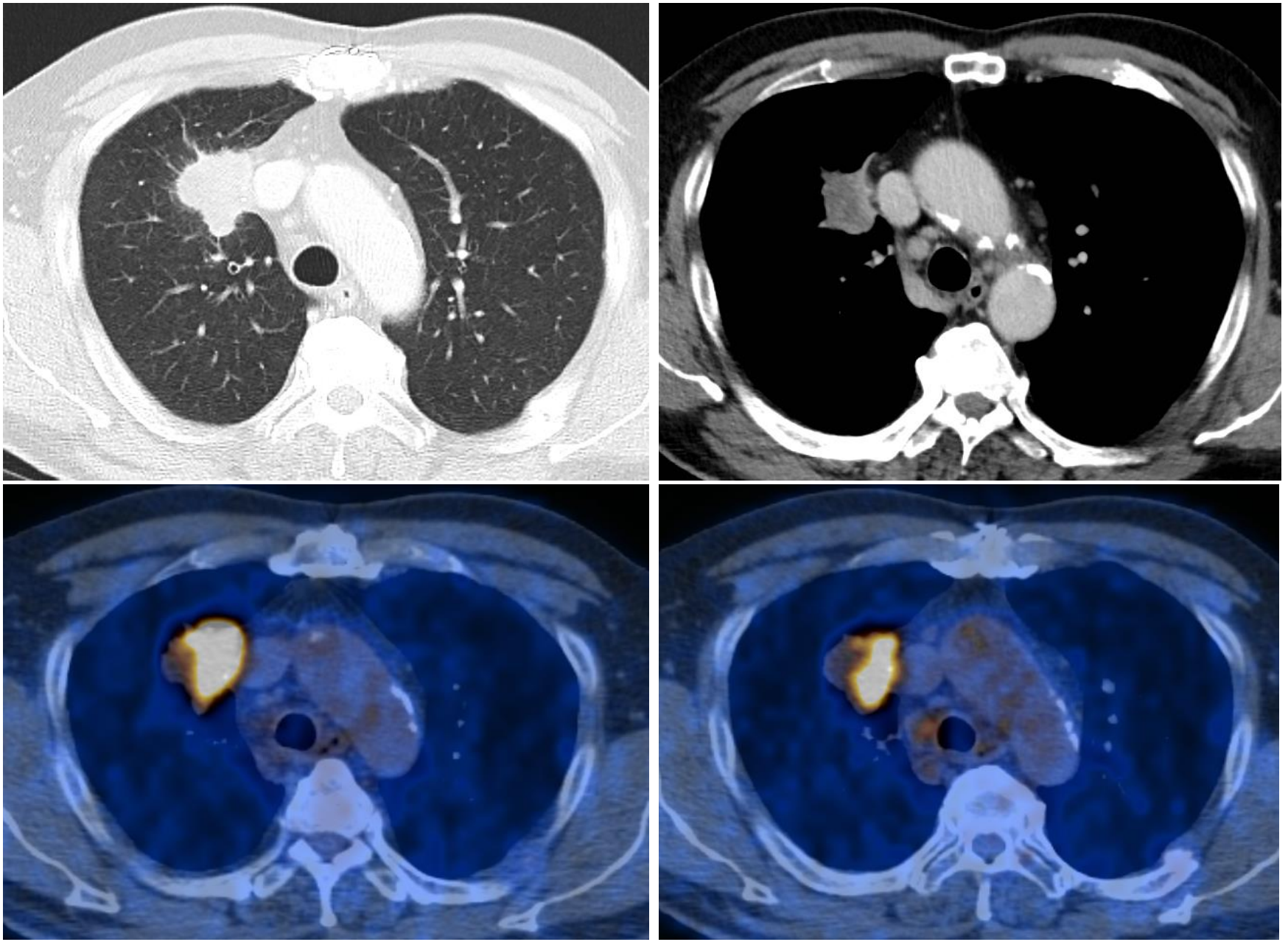


Additional Evaluations:

- ❑ Adequate pulmonary function tests (PFTs) and cardiac function, results from laboratory tests are normal
- ❑ Brain MRI: Negative
- ❑ Molecular Analysis (biopsy of the Lung Tumor): ***EGFR* mutation (deletion 19)**

Clinical Stage: **T2bN2M0 (IIIA-N2)**

Patient was presented and discussed at a multidisciplinary thoracic tumor board

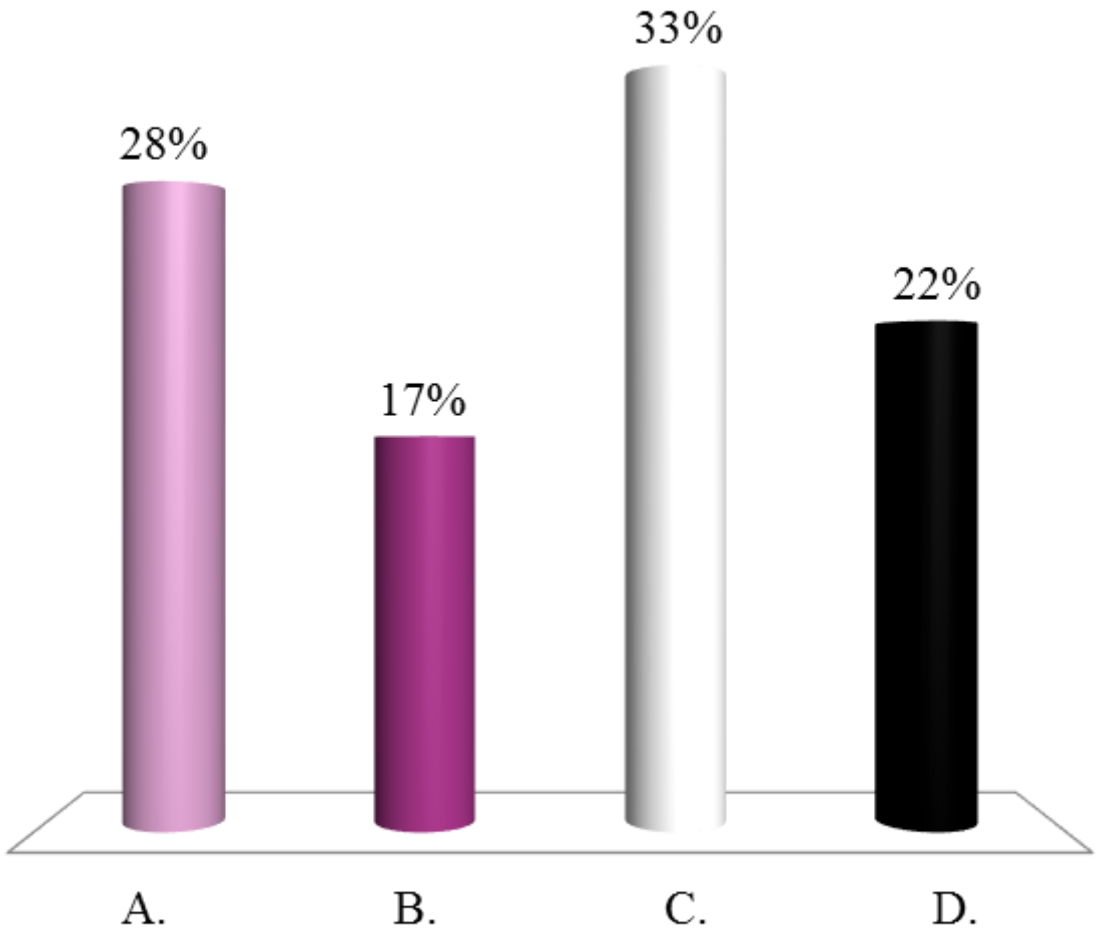
What treatment approach would you suggest for this patient with clinical stage IIIA-N2 (single node 1.7-cm) NSCLC?

A. Surgical resection with mediastinal LN dissection → chemotherapy +/- radiotherapy

B. Neoadjuvant systemic therapy → surgery if no progression

C. Induction chemoradiotherapy (CRT) → surgery if no progression

D. Definitive concurrent CRT



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Which Patients Are Candidates for Surgery?

- **Is a complete resection possible?**
- Does the patient tolerate pulmonary resection?
- What is the mortality/morbidity?

➔ **Risk-benefit ratio**

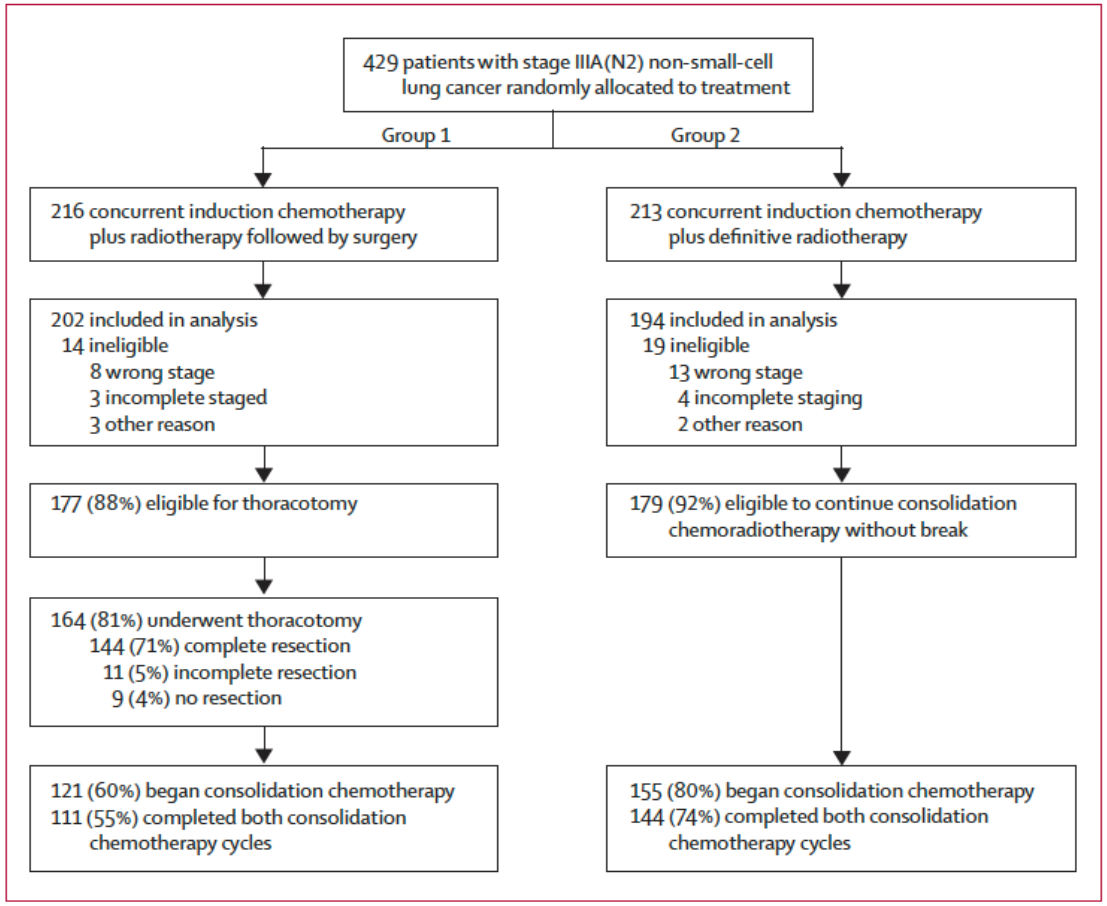
Complete Resection in Lung Cancer Surgery

- Free resection margins (proved microscopically)
- No extra-capsular nodal extension
- Highest mediastinal LN removed is negative

Rami-Porta R, et al. (IASLC Staging Committee). *Lung Cancer.* 2005;49

Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial

Role of Induction CT-RT: Lung Intergroup Trial 0139



- 429 Stage IIIA (**pN2**) patients

- **Group 1:**
  - Cisplatin + Etoposide x 2
  - RT 45 Gy
  - Surgery
  - 2 additional CT cycles

- **Group 2:**
  - Cisplatin + Etoposide x 2
  - RT 61 Gy
  - 2 additional CT cycles

Albain KS. et al. Lancet 2009;374

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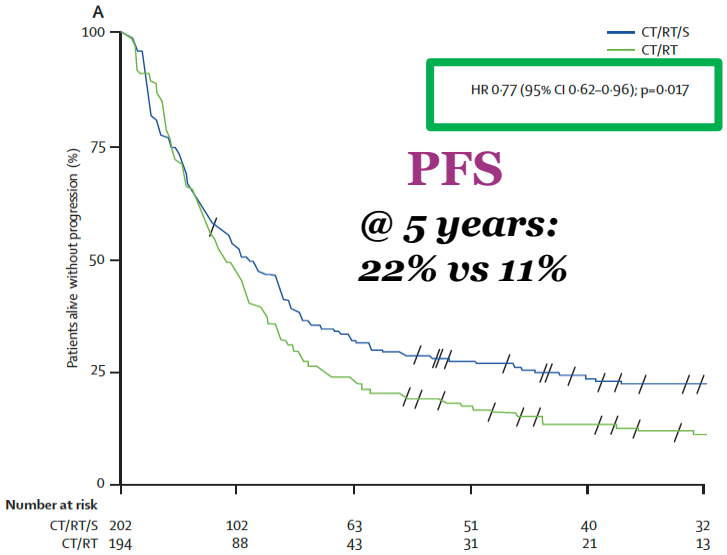
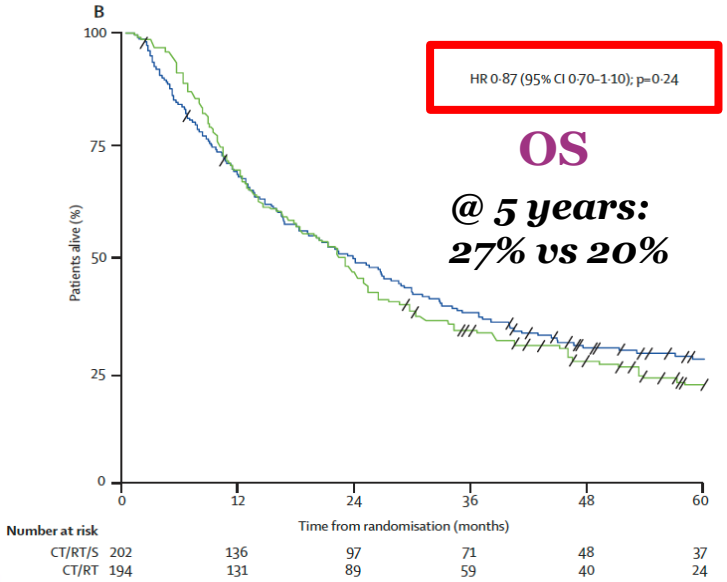
Role of Induction CT-RT: Lung Intergroup Trial 0139



PFS

@ 5 years: 22% vs 11%



OS

@ 5 years: 27% vs 20%

Toxicity profile

	CT/RT/S (group 1, n=202)			CT/RT (group 2, n=194)		
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
Leucopenia	82 (41%)	15 (7%)	0	76 (39%)	31 (16%)	0
Neutropenia	54 (27%)	23 (11%)	0	47 (24%)	33 (17%)	0
Anaemia	25 (12%)	1 (<1%)	0	42 (22%)	5 (3%)	0
Thrombocytopenia	10 (5%)	4 (2%)	0	12 (6%)	11 (6%)	0
Worst haematological toxicity per patient	89 (44%)	28 (14%)	0	75 (39%)	50 (26%)	0
Nausea or emesis, or both	27 (13%)	2 (1%)	0	22 (11%)	4 (2%)	0
Neuropathy	10 (5%)	0	0	4 (2%)	3 (2%)	0
Oesophagitis*	17 (8%)	3 (1%)	0	37 (19%)	7 (4%)	0
Stomatitis or mucositis, or both	6 (3%)	0	0	4 (2%)	1 (<1%)	0
Pulmonary	17 (8%)	1 (<1%)	13 (6%)	24 (12%)	4 (2%)	3 (2%)
Other gastrointestinal or renal	6 (3%)	4 (2%)	0	5 (3%)	2 (1%)	0
Cardiac	4 (2%)	3 (1%)	3 (1%)†	7 (4%)	2 (1%)	0
Miscellaneous infection	5 (2%)	1 (<1%)	0	8 (4%)	0	0
Haemorrhage	0	0	1 (<1%)	0	1 (<1%)	0
Fatigue	11 (5%)	0	0	9 (5%)	0	0
Anorexia	3 (1%)	0	0	4 (2%)	3 (2%)	0
Allergy	1 (<1%)	0	0	3 (2%)	0	0

CT=chemotherapy. RT=radiotherapy. S=surgery. *Only toxicity that was significantly (p=0·0006) different between groups 1 and 2. †One patient also included in grade 5 pulmonary toxicity.

Table 2: **Overall worst toxicities**

Albain KS. et al. Lancet 2009;374

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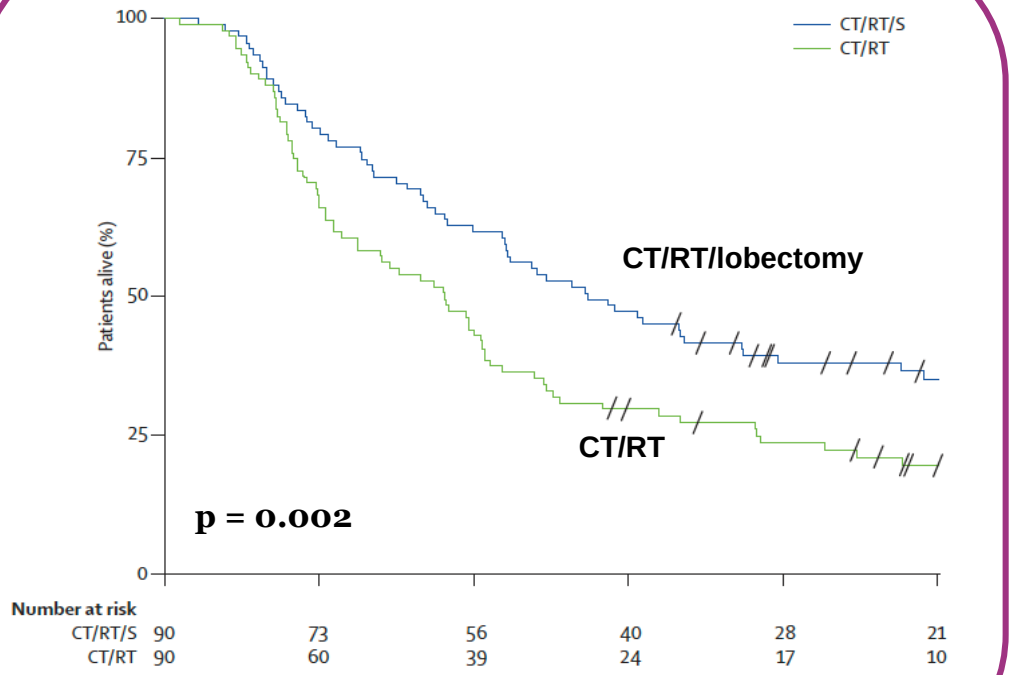
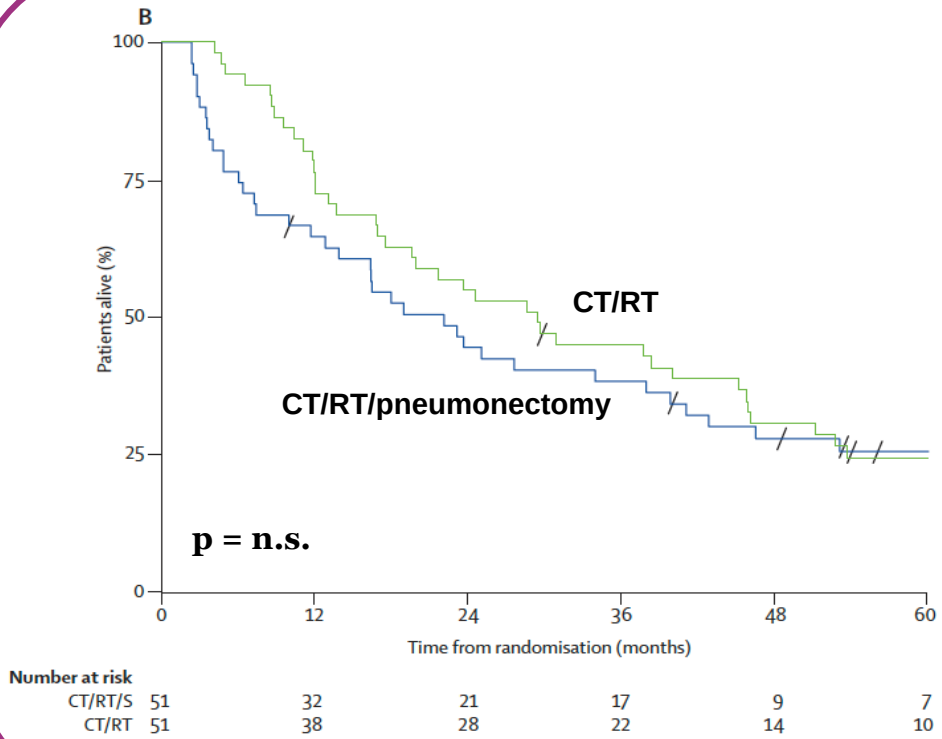
Role of Induction CT-RT: Lung Intergroup Trial 0139

OS
Lobectomy



OS
Pneumonectomy



- **OS was improved for patients who underwent lobectomy, but not pneumonectomy, versus chemotherapy + radiotherapy**

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Albain KS. et al. Lancet 2009;374

clinical practice guidelines

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- Patients are defined as having **potentially resectable LA-NSCLC when** a dedicated multidisciplinary assessment—including an experienced thoracic surgeon—judges **a complete resection (R0) may be feasible after induction treatment**
- The optimal treatment plan is to be discussed in a **multidisciplinary tumour board**, taking into account the local treatment expertise
- Both **definitive chemoradiotherapy and induction therapy followed by surgery** (preferably lobectomy) **are options**

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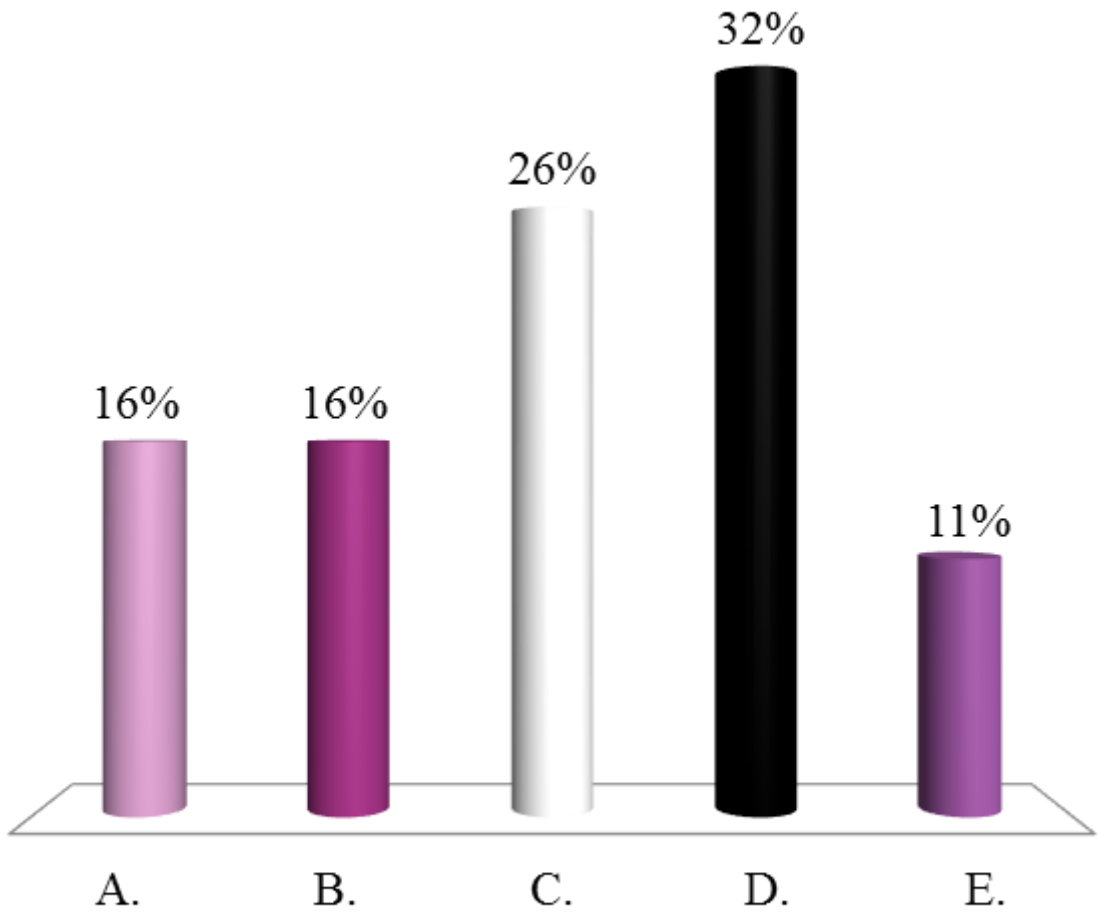
Vansteenkiste J, et al. Ann Oncol. 2013;24

Again a question on our patient: which of the following treatment strategies would you recommend if the same patient were to have multiple sites N2 disease (size of the lymph nodes 1.5-3.5 cm)?

A. Neoadjuvant chemotherapy → surgery (if PET/CT restaging = No-1) +/-radiotherapy
B. Induction concurrent CRT (45-50 Gy) → surgery
C. Definitive concurrent CRT (60-74 Gy)
D. Definitive concurrent CRT → consolidation chemotherapy
E. Induction chemotherapy → concurrent CRT



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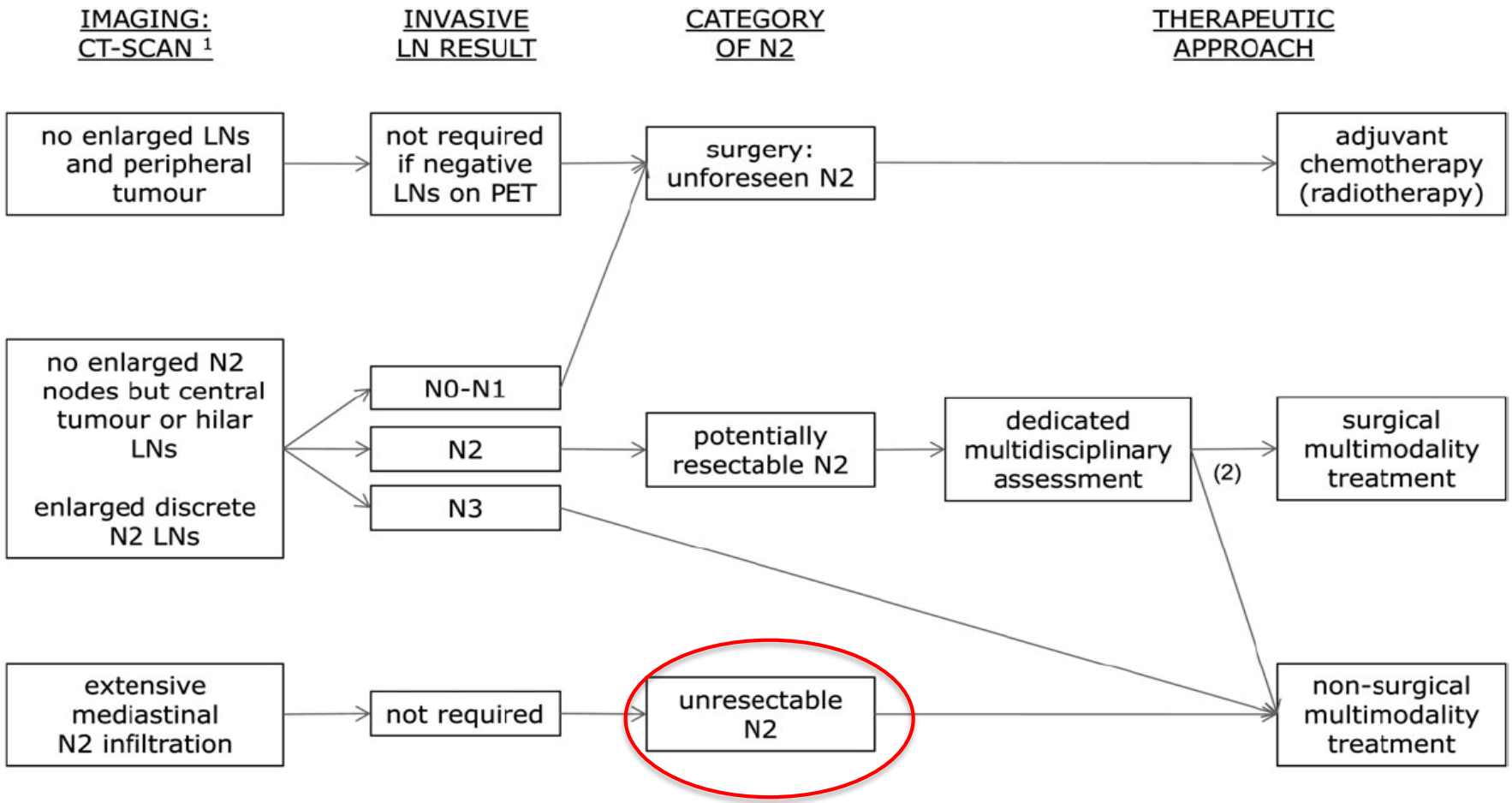

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Vansteenkiste J, et al. Ann Oncol. 2013;24

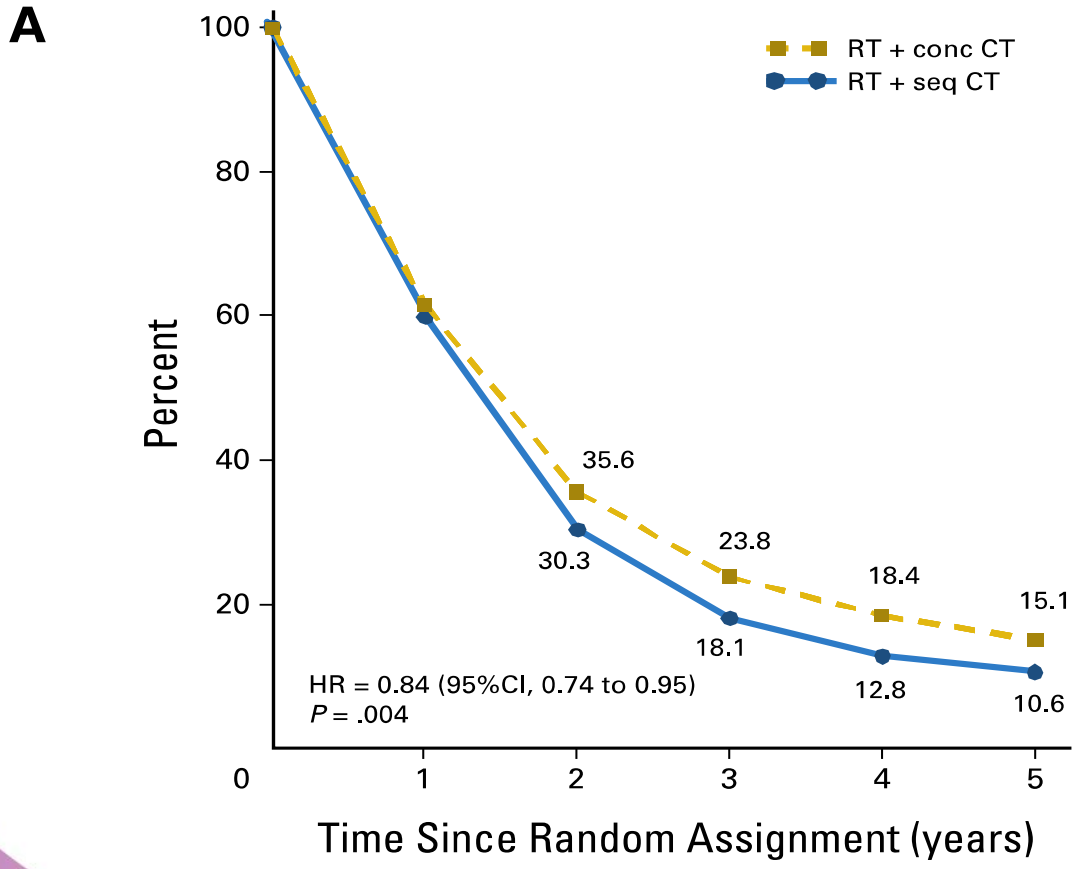
Good PS Stage III NSCLC
What positive Level 1 Evidence is there?

- **Chemo-RT:**
  - Better survival than RT alone
- **Concurrent chemo-RT:**
  - Better survival than sequential chemo-RT

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Meta-Analysis of Concomitant Versus Sequential Radiochemotherapy in Locally Advanced Non–Small-Cell Lung Cancer

"Concomitant" is better than "Sequential" Radio-Chemotherapy



- **Absolute survival benefit with concomitant radio-chemotherapy:**
  - **5.7% at 3 years**
  - **4.5% at 5 years**

- **Concomitant radio-chemotherapy increased acute esophageal toxicity (Grade 3-4) from 4% to 18% with a relative risk of 4.9 (p < 0.001). There was no significant difference regarding acute pulmonary toxicity**

Aupérin A, et al. *JCO* 2010;28

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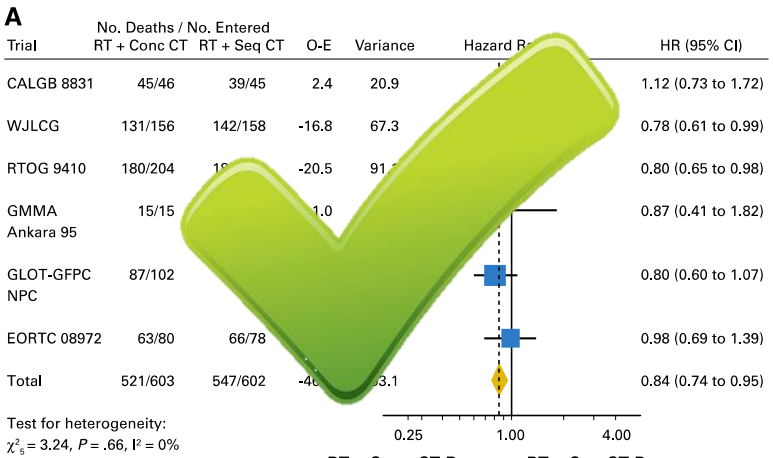
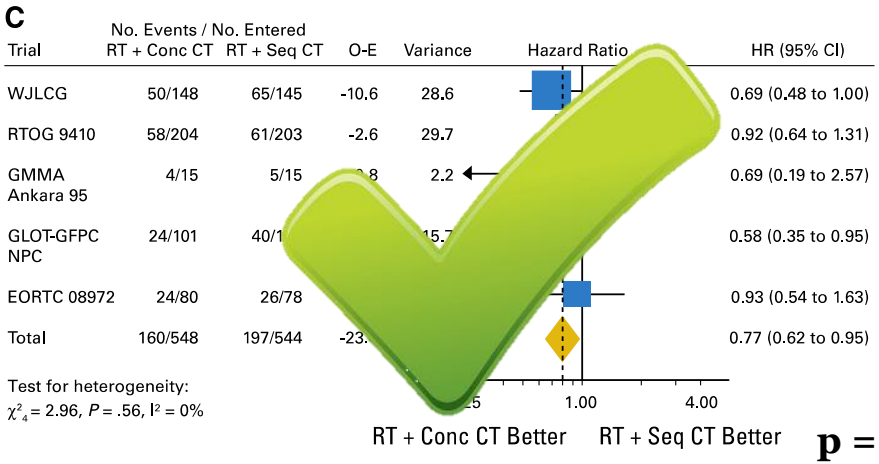
“Concomitant” is better than “Sequential” Radio-Chemotherapy

Overall Survival



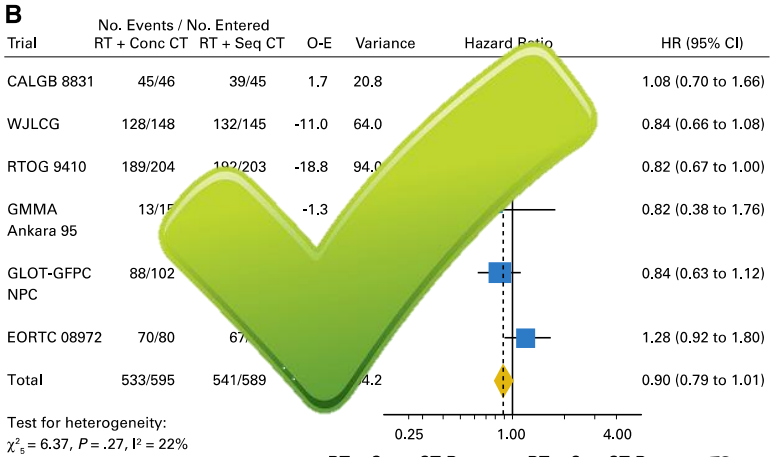
p = 0.004

Local Progression



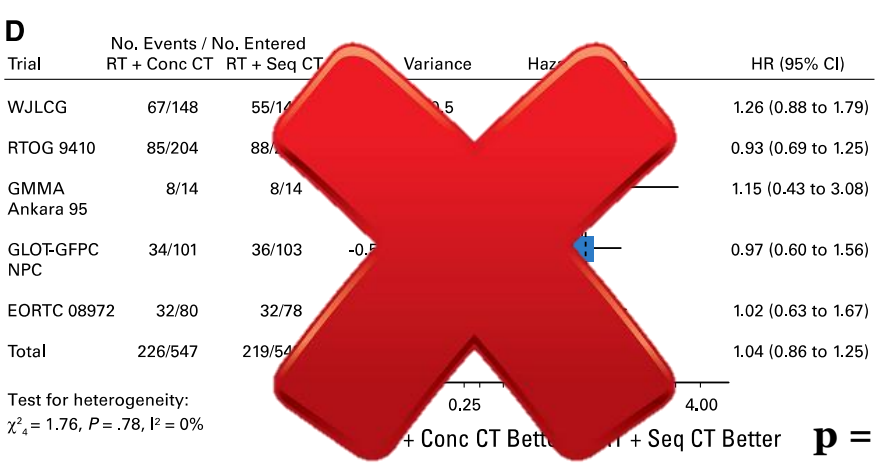
p = 0.01

Progression Free Survival



p = 0.07

Distant Progression



p = 0.69

- **Concomitant radiochemotherapy improved survival of patients with locally advanced NSCLC, primarily because of a better locoregional control**

Aupérin A, et al. *JCO* 2010;28

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- The preferred treatment of **unresectable LA-NSCLC is definitive concurrent chemotherapy and radiotherapy** [I, A].
- Definitive **thoracic radiotherapy should be no less than** the biological equivalent of **60 Gy in 2.0 Gy fractions** [I, A].
- In patients who are **unfit to receive concurrent** chemotherapy and radiotherapy, the **sequential approach** should be offered as an **alternative treatment with curative intent** [I, A].

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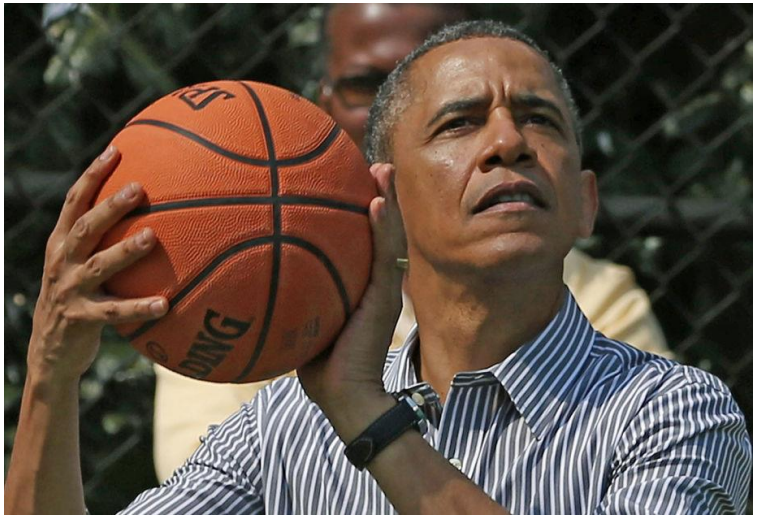
Vansteenkiste J, et al. Ann Oncol. 2013;24

Is concurrent CT-RT the Standard Treatment in Locally Advanced NSCLC in the real life… ?

Expectation



55 years

Reality

50 years

… only when we treat "Highly FIT" patients

- ❑ Age
- ❑ Performance status
- ❑ Weight loss
- ❑ Pulmonary function tests
- ❑ Stage/Tumor burden
- ❑ Dose to critical organs

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EDITORIAL

Dutch Statistics on Lung Cancer

Sobering Experience for a New Approach

Matjaz Zwitter, MD, PhD

- **50% of patients** with NSCLC **did not receive** treatment according to the well **accepted guidelines**
- **EBM is based on selected series** of patients and is **not applicable** to an average patient in clinical practice
- **Stage III** NSCLC: **the gap** between an ideal patient from the guidelines and the average patient from clinical practice **is especially wide**
- Vast **majority** of patients present **bulky tumors** and/or suffer from significant **comorbidity**

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Zwitter M. *J Thorac Oncol.* 2012;7

Good PS Stage III NSCLC: What Negative/Null Evidence Do We Have?

- **Induction chemotherapy:**
  - No advantage when added to concurrent chemo-RT
- **Consolidation chemotherapy**
  - No advantage when added to concurrent chemo-RT

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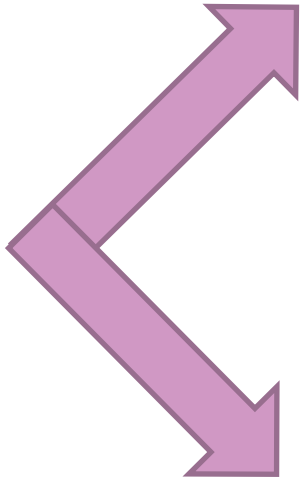
Induction CT: CALGB 39801 – Trial Design

R E G I S T E R



A (Concurrent Chemo/RT)

Paclitaxel 50 mg/m^2 IV/1h/week
Carboplatin AUC 2 IV/30 min/wk
XRT 6600 cGy (total)

B (Induction→ Concurrent Chemo/RT)

Paclitaxel 200 mg/m^2 IV/3h
Carboplatin AUC 6 IV/30 min
q 21 days for a total of 2 cycles

Paclitaxel 50 mg/m^2 IV/1h/week
Carboplatin AUC 2 IV/30 min/wk
XRT 6600 cGy (total) (d 43)

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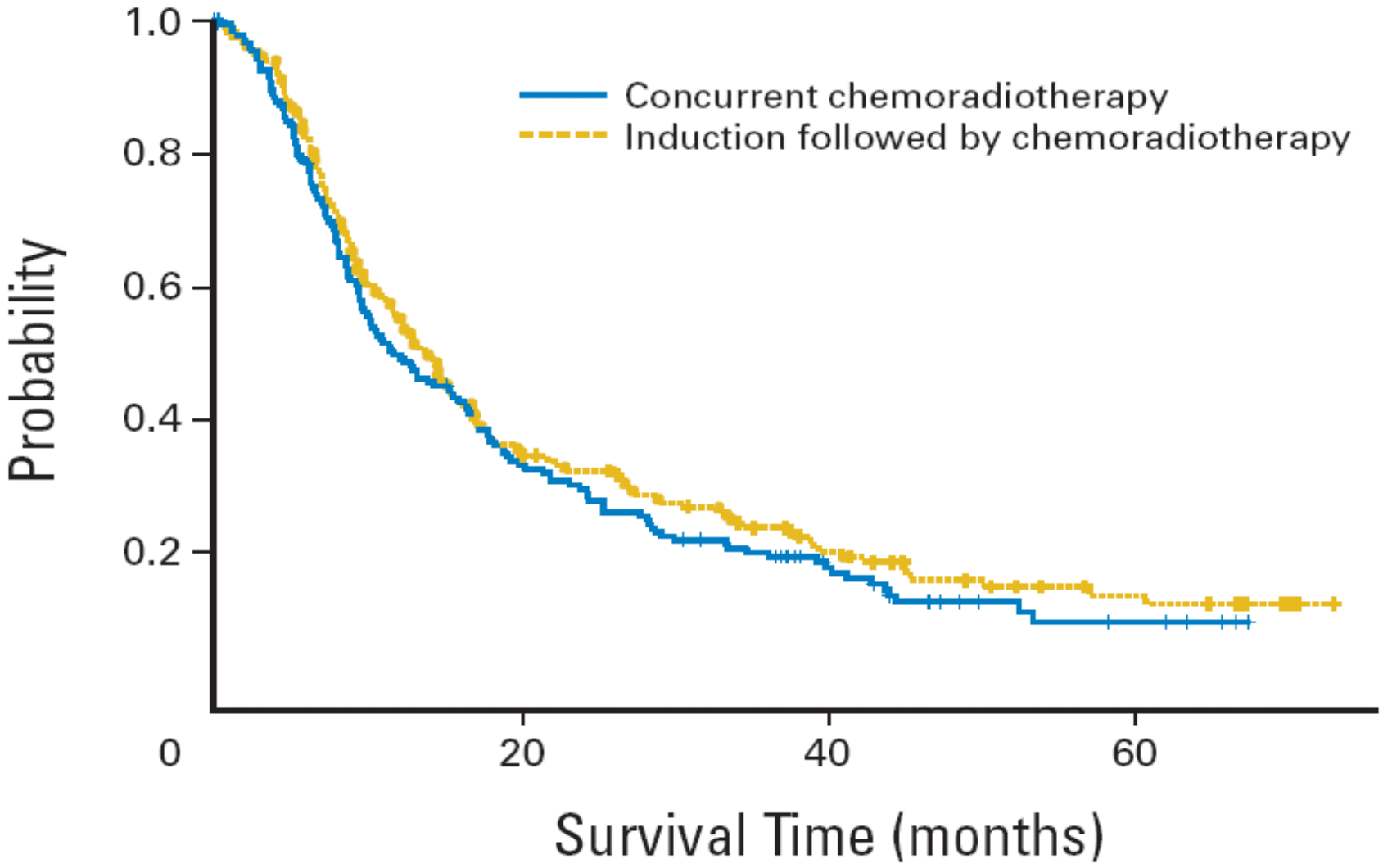
Vokes EE, et al. J Clin Oncol. 2007;25

CALGB 39801: Overall Survival

Intent-to-Treat (ITT)



Vokes EE, et al. J Clin Oncol. 2007;25

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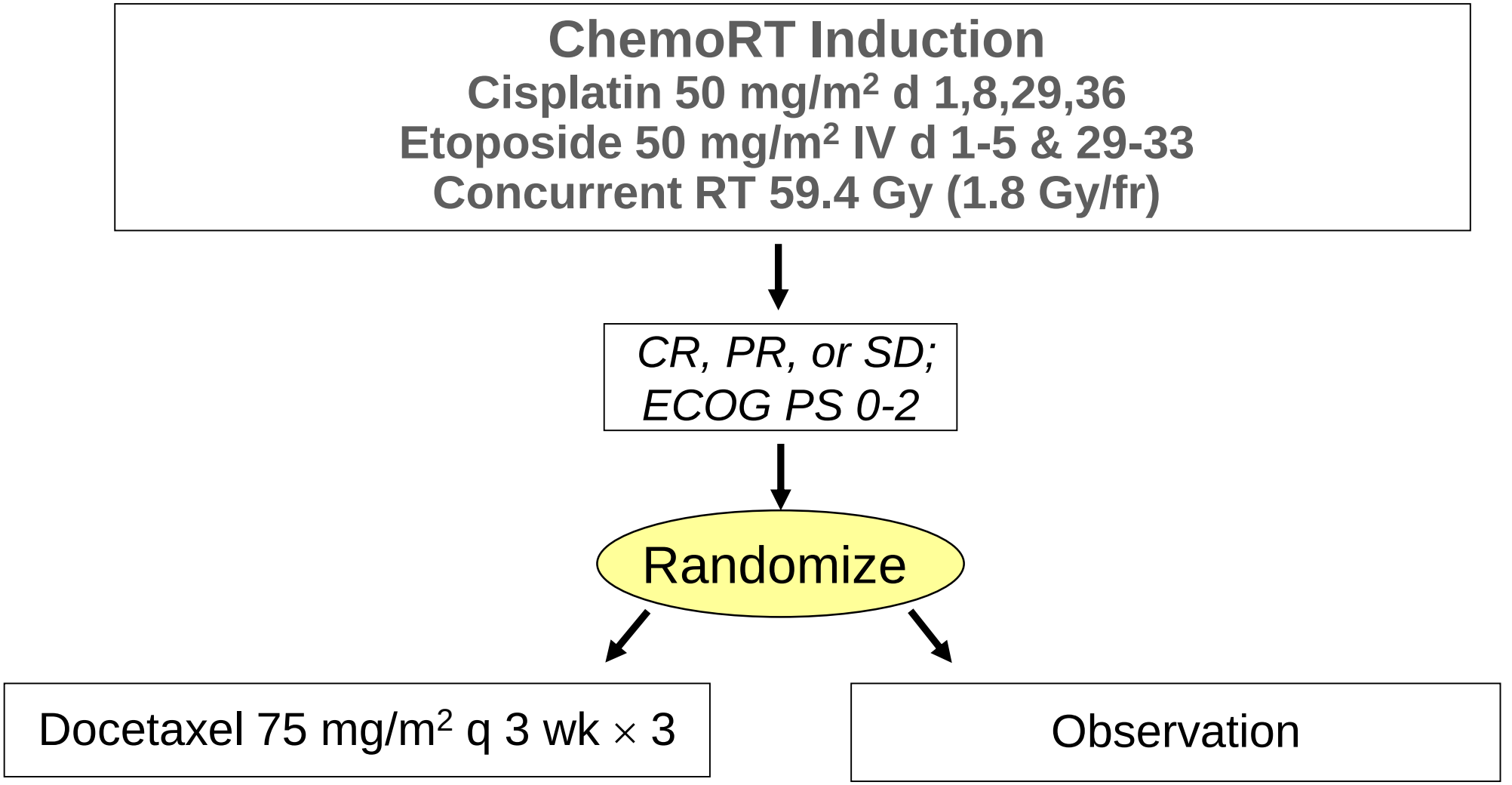
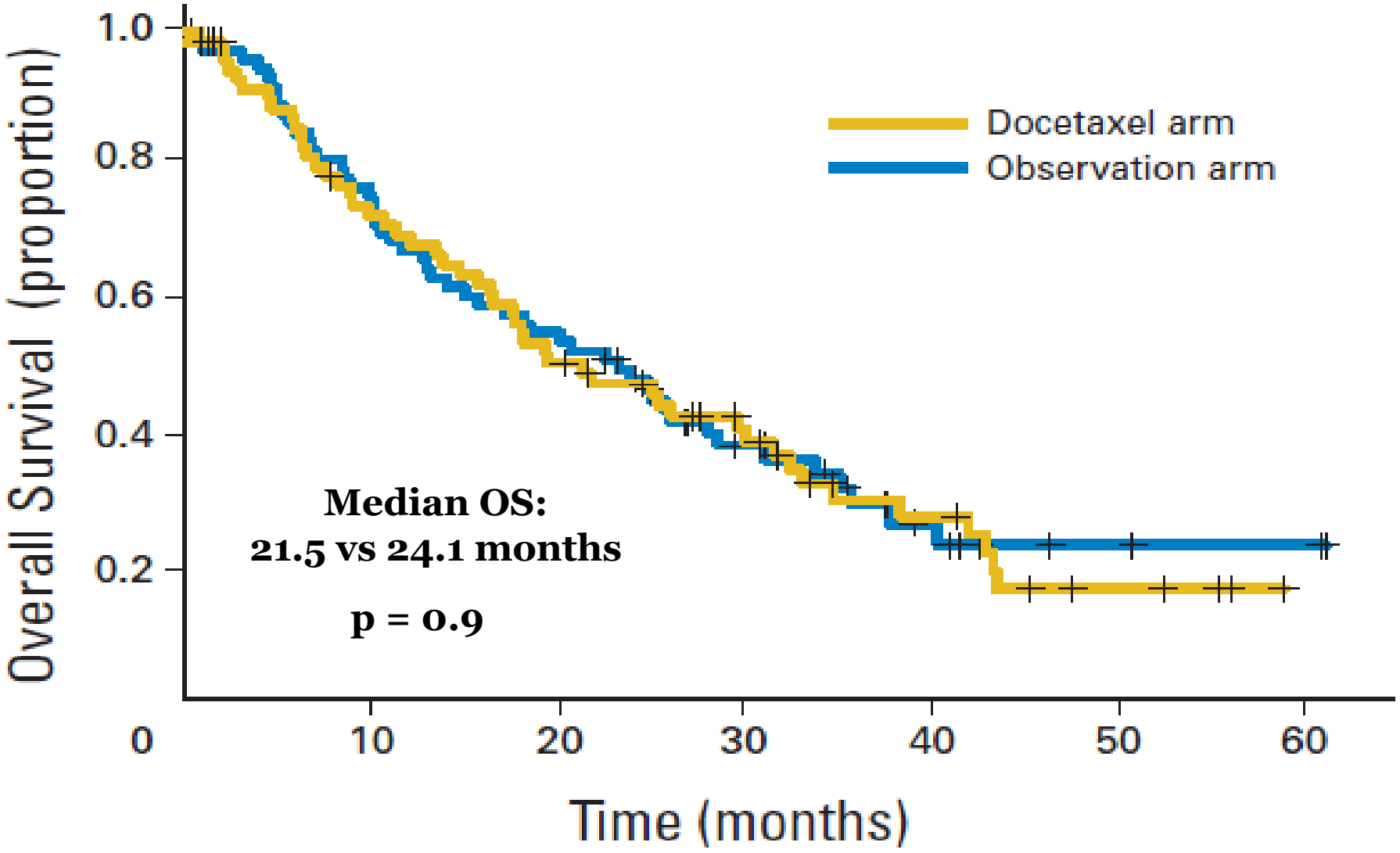
Consolidative Docetaxel after Concurrent CT-RT:
Hoosier Oncology Group (HOG LUN 01-24)



Hanna N, et al. *J Clin Oncol.* 2008;26

LUN 01-24: Overall Survival (ITT)

Randomized Patients (n=147)

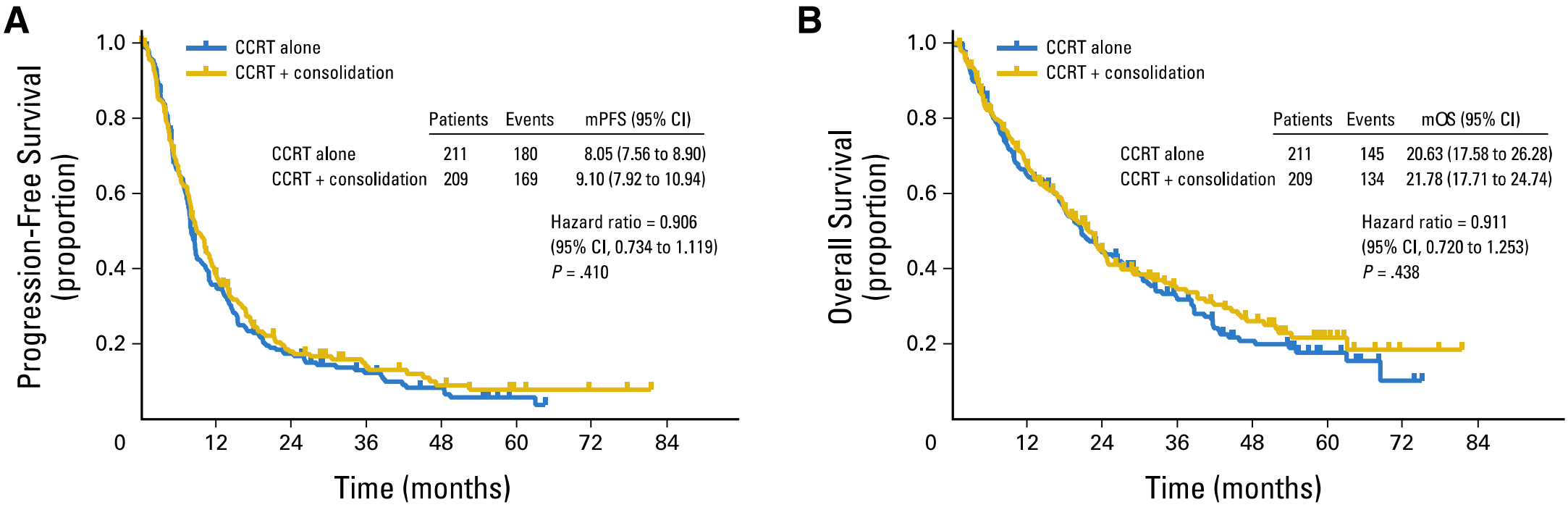


Hanna N, et al. *J Clin Oncol.* 2008;26

JOURNAL OF CLINICAL ONCOLOGY

Multinational Randomized Phase III Trial With or Without Consolidation Chemotherapy Using Docetaxel and Cisplatin After Concurrent Chemoradiation in Inoperable Stage III Non–Small-Cell Lung Cancer: KCSG-LU05-04

Consolidative Docetaxel + Cisplatin after Concurrent CT-RT:
Korean Cancer Study Group (KCSG LU 05-04)



❑ ***Consolidative chemotherapy with DP after concurrent CT-RT failed to further prolong PFS and OS***

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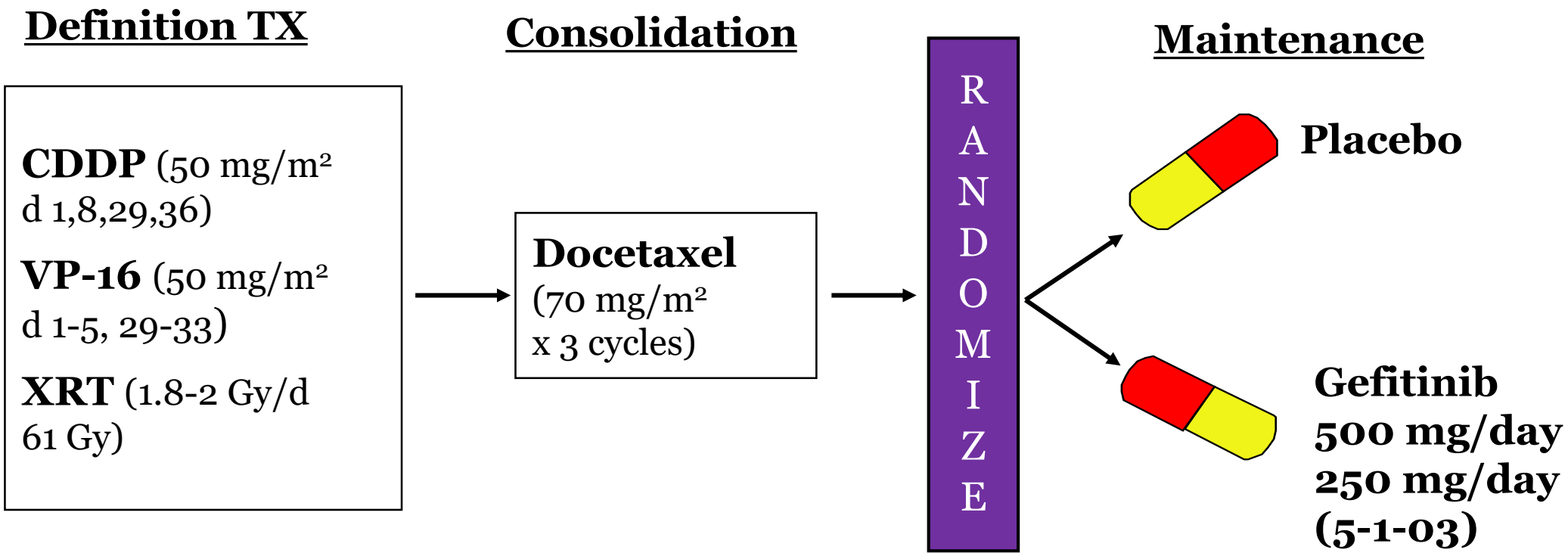
Ahn JS, et al. JCO 2015;33

SWOG 0023: Gefitinib vs Placebo After Chemoradiation Followed by Docetaxel in Stage IIIA (N2) or IIIB

Study Schema



1° Endpoint: overall survival
2° Endpoint: PFS, toxicity and correlative science

Maintenance therapy could continue for a maximum of 5 years.
Stratification factors: IIIA vs IIIB; measurable vs non-measurable disease; squamous vs nonsquamous.

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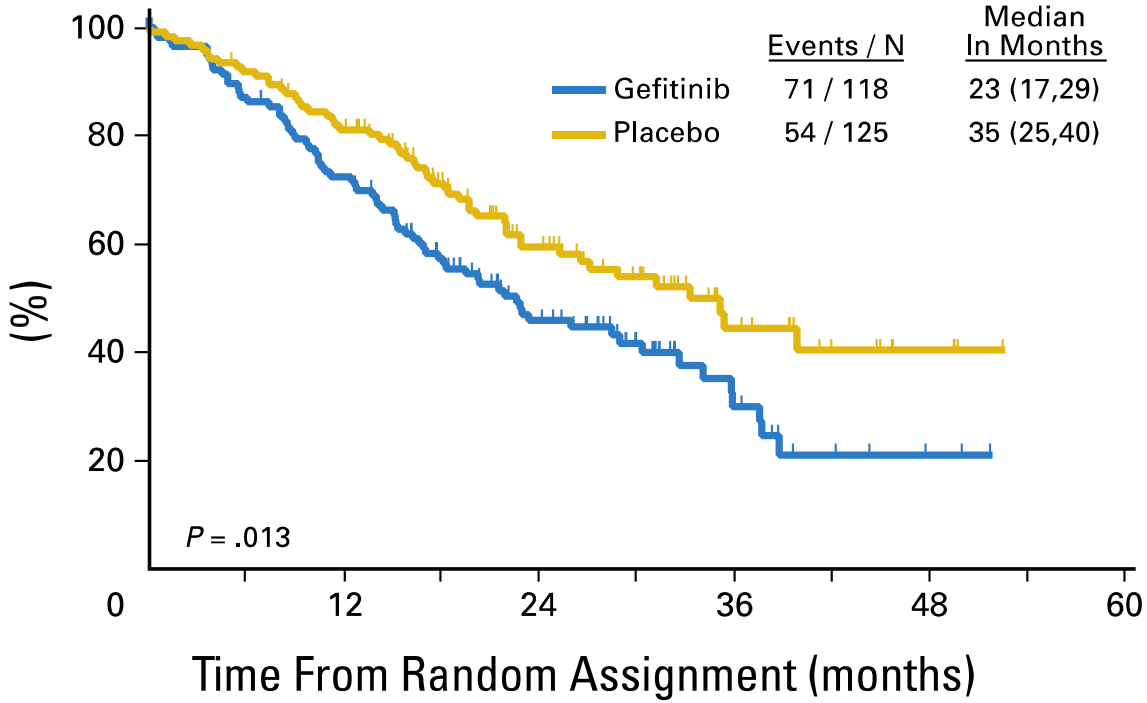
Kelly K, et al. JCO 2008;26

JOURNAL OF CLINICAL ONCOLOGY

Phase III Trial of Maintenance Gefitinib or Placebo After Concurrent Chemoradiotherapy and Docetaxel Consolidation in Inoperable Stage III Non–Small-Cell Lung Cancer: SWOG S0023

SWOG 0023: Decreased OS for patients receiving maintenance Gefitinib



- **Decreased OS was a result of tumor progression and not Gefitinib toxicity**

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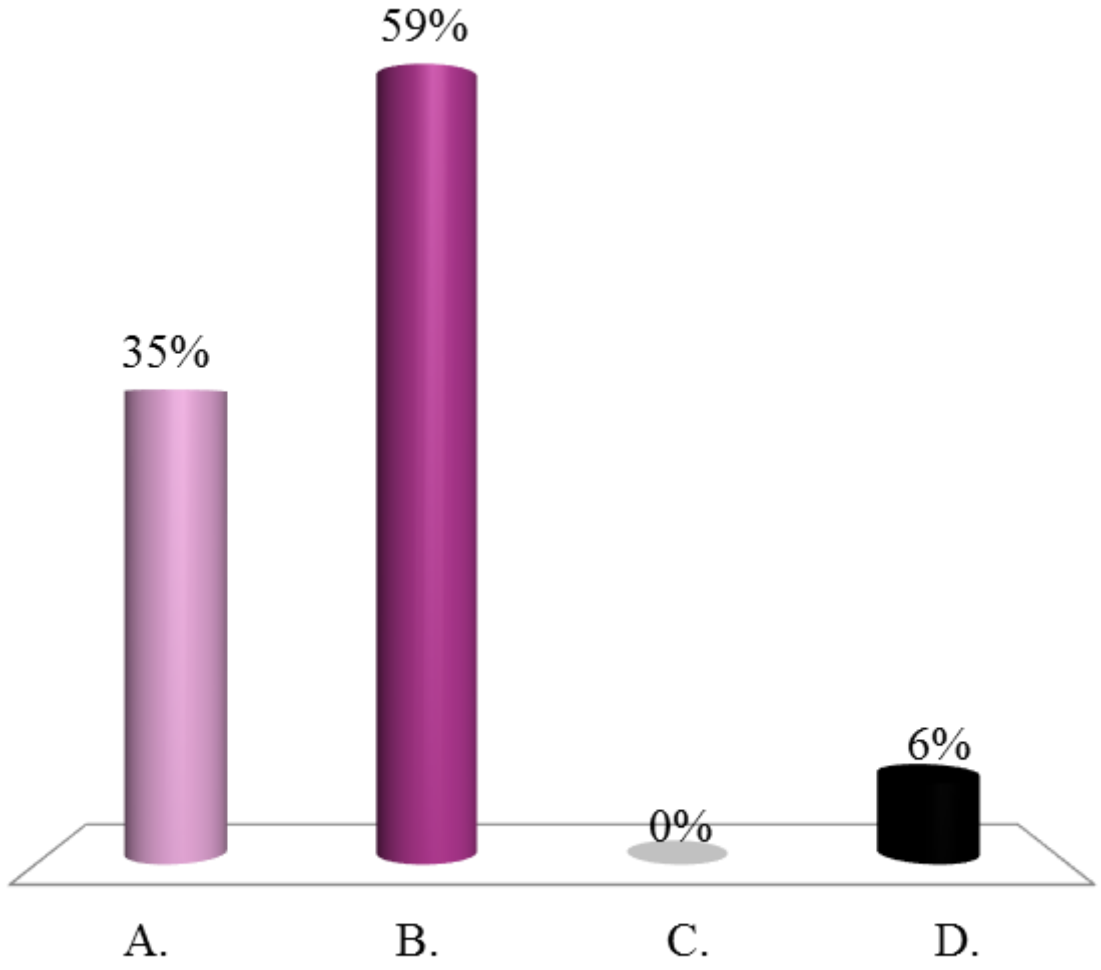
Kelly K, et al. JCO 2008;26

Good PS Stage III NSCLC: Lack of Evidence

- Selection of **best CT** to give concurrently with RT
- Use of **targeted agents** concurrent with chemo-RT
- Role of **Rx dose intensification** and use of any advanced technology RT tools

Which of the following systemic therapy options would be your first choice for use with radiotherapy?

A. Cisplatin/etoposide q3 weeks
B. Cisplatin/pemetrexed q3 weeks
C. Weekly carboplatin/paclitaxel
D. Clinical trial of concurrent radiation with targeted agent +/- chemotherapy



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Geographic differences in the combined-modality treatment of stage III unresectable non-small cell lung cancer

	North America (N=330) n (%)	Australia (N=43) n (%)	Western Europe (N=609) n (%)	Eastern Europe (N=394) n (%)	Latin America (N=86) n (%)	Asia (N=51) n (%)
Carboplatin-based doublet therapy						
Gemcitabine	11 (3.3)	0	**43 (7.1)**	12 (3.0)	3 (3.5)	2 (3.9)
Paclitaxel	106 (32.1)	21 (48.8)	**97 (15.9)**	16 (4.1)	13 (15.1)	8 (15.7)
Vinorelbine	8 (2.4)	1 (2.3)	**61 (10.0)**	55 (14.0)	3 (3.5)	2 (3.9)
Cisplatin-based doublet therapy						
Docetaxel	5 (1.5)	3 (7.0)	**63 (10.3)**	4 (1.0)	1 (1.2)	14 (27.5)
Etoposide	164 (49.7)	19 (44.2)	**57 (9.4)**	46 (11.7)	28 (32.6)	3 (5.9)
Gemcitabine	3 (0.9)	0	**83 (13.6)**	42 (10.7)	11 (12.8)	3 (5.9)
Vinorelbine	22 (6.7)	0	**187 (30.7)**	211 (53.6)	11 (12.8)	7 (13.7)

Thatcher N, WCLC-IASLC 2013

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Background

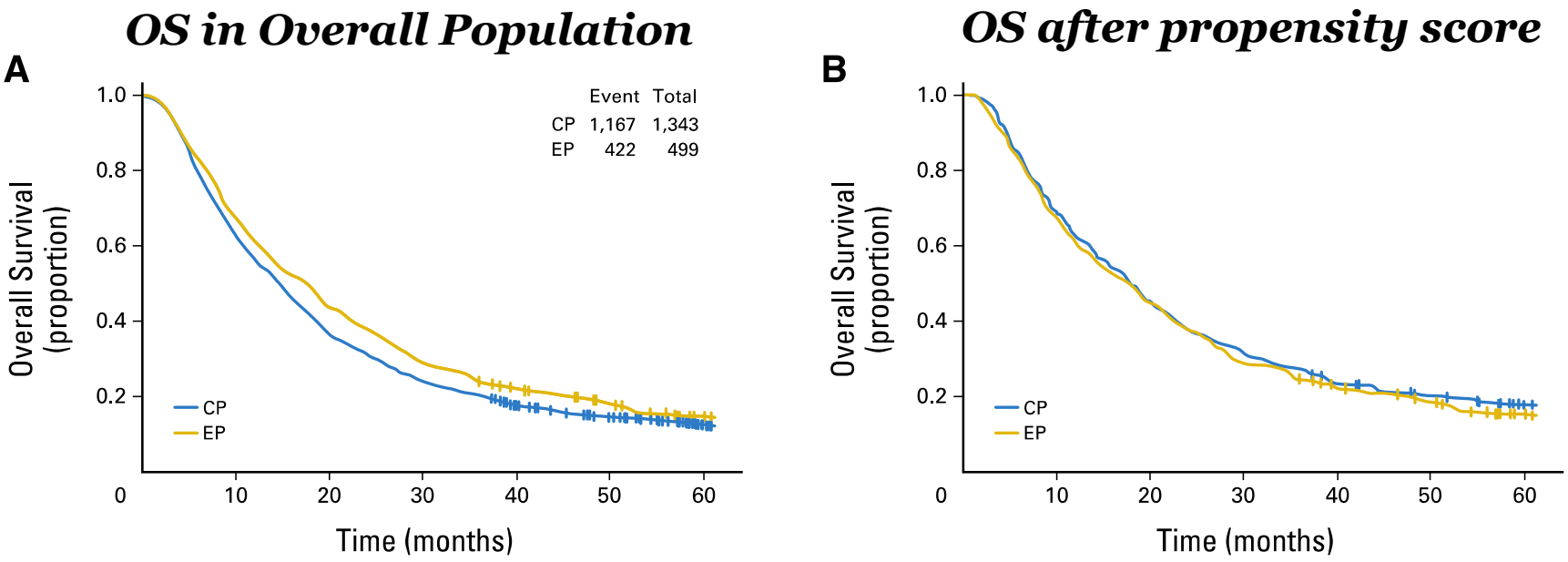
- **Cisplatin/Etoposide** (CE) and **Carboplatin/Paclitaxel** (CP) are two of the most commonly utilized regimens for the treatment of stage III non-small cell lung cancer (NSCLC)

JOURNAL OF CLINICAL ONCOLOGY

Cisplatin and Etoposide Versus Carboplatin and Paclitaxel With Concurrent Radiotherapy for Stage III Non–Small-Cell Lung Cancer: An Analysis of Veterans Health Administration Data

Cisplatin + Etoposide vs Carboplatin + Paclitaxel:

NO OS DIFFERENCE but INCREASE TOXICITY wit Cisplatin + Etoposide



Patients treated with Cisplatin + Etoposide had:

- ***More hospitalizations (p <0.001)***
- ***Infectious complications (p = 0.002)***
- ***Acute kidney disease (p < 0.001)***
- ***Mucositis/esophagitis (p = 0.02)***

Santana-Davila R, et al, JCO, 2015;33

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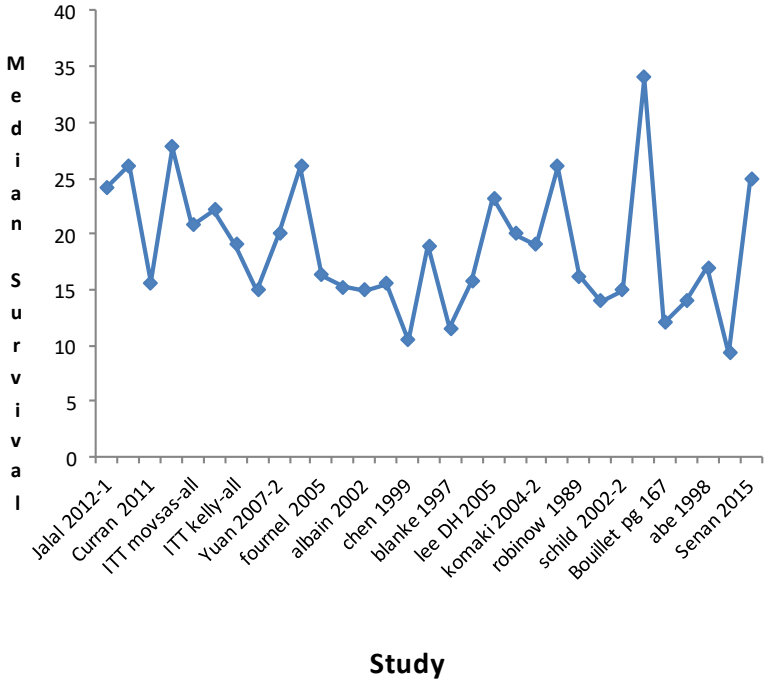
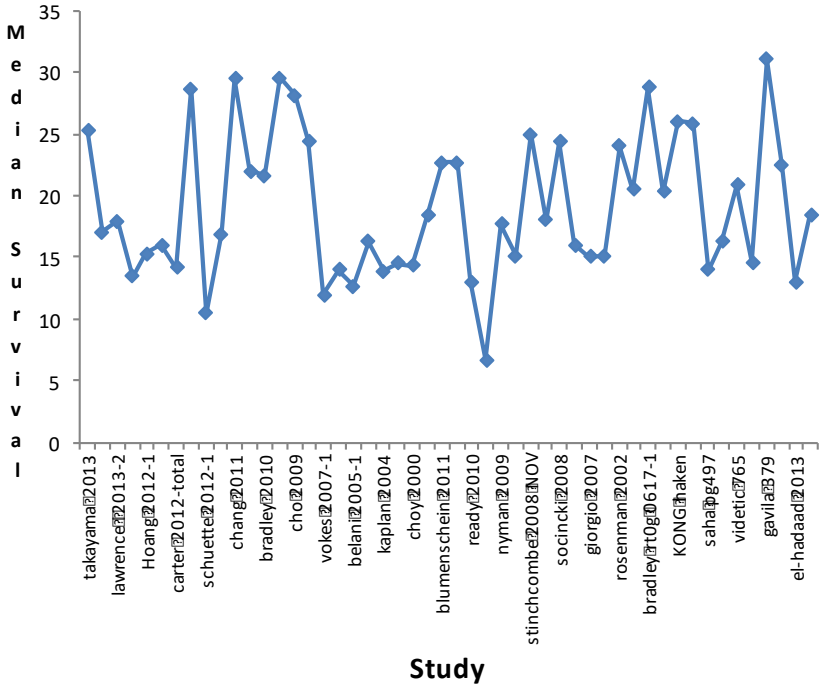
JAMA Oncology | Review

Comparison of Concurrent Use of Thoracic Radiation With Either Carboplatin-Paclitaxel or Cisplatin-Etoposide for Patients With Stage III Non–Small-Cell Lung Cancer

A Systematic Review

Overall Survival





p=0.35

Cisplatin/Etoposide

Weighted median survival = **19.4 months** (N=2770)

Carboplatin/Paclitaxel

Weighted median survival = **18.4 months** (N=3602)

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Steuer CE. et al. JAMA 2016;4280

Comparison of Concurrent Use of Thoracic Radiation With Either Carboplatin-Paclitaxel or Cisplatin-Etoposide for Patients With Stage III Non–Small-Cell Lung Cancer

A Systematic Review

Table 3. Patient Characteristics

Characteristic	% Cisplatin and Etoposide (n = 3090)	% Carboplatin and Paclitaxel (n = 3728)
Median age, y	61	63
Sex		
Men	65	65
Women	35	35
Histology		
Adenocarcinomas	36	37
Squamous	40	40
Stage IIIA/IIIB	45/54	46/54
Performance status (0/1)	49/49	48.5/51.5
Median radiation dose	63 Gy	64.6 Gy
Median chemotherapy dose	Cisplatin: 50 mg/m^2 Etoposide: 50 mg/m^2	Carboplatin: AUC 2 Paclitaxel: 50 mg/m^2
Induction therapy	3	51
Consolidation therapy	46	39

Abbreviation: AUC, area under the curve.

Table 4. Clinical Outcomes and Toxic Effects in 6818 Patients

Outcome	% Cisplatin and Etoposide (n = 3090)	% Carboplatin and Paclitaxel (n = 3728)	*P* Value
ORR	58	56	.26
OS (weighted median)	19.6 m	18.4m	.40
1-Year survival	65	65	.80
3-Year survival	30	25	.50
PFS (weighted median)	12 m	9.3m	.24
Locoregional relapse	38	37	.63
Distant metastasis	44	46	.50
Pneumonitis	12	9	.12
Esophagitis	23	21	.27
Nausea and/or vomiting	20	11	.03
Anemia	14	9	.15
Thrombocytopenia	14	8	<.001
Neutropenia	54	23	<.001

Abbreviations: ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

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Steuer CE. et al. JAMA 2016;4280

Conclusions

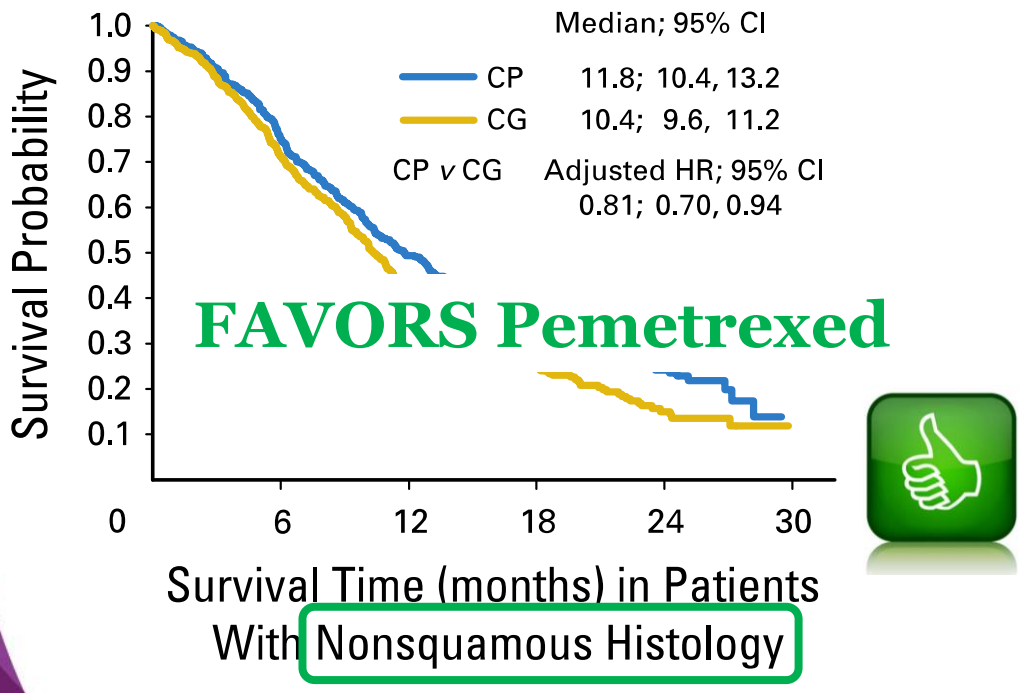
- **No significant differences** were seen in efficacy between Cisplatin-Etoposide (CE) and Carboplatin-Paclitaxel (CP)
- There was no difference in pneumonitis or esophagitis rates between CE and CP. However, **hematologic toxicities and N/V were significantly higher in the CE arm**
- Both **CE and CP with XRT are acceptable standards of care** to treat stage III NSCLC, and prospective data is needed to determine the optimum regimen

Phase III Study Comparing Cisplatin Plus Gemcitabine With Cisplatin Plus Pemetrexed in Chemotherapy-Naive Patients With Advanced-Stage Non–Small-Cell Lung Cancer

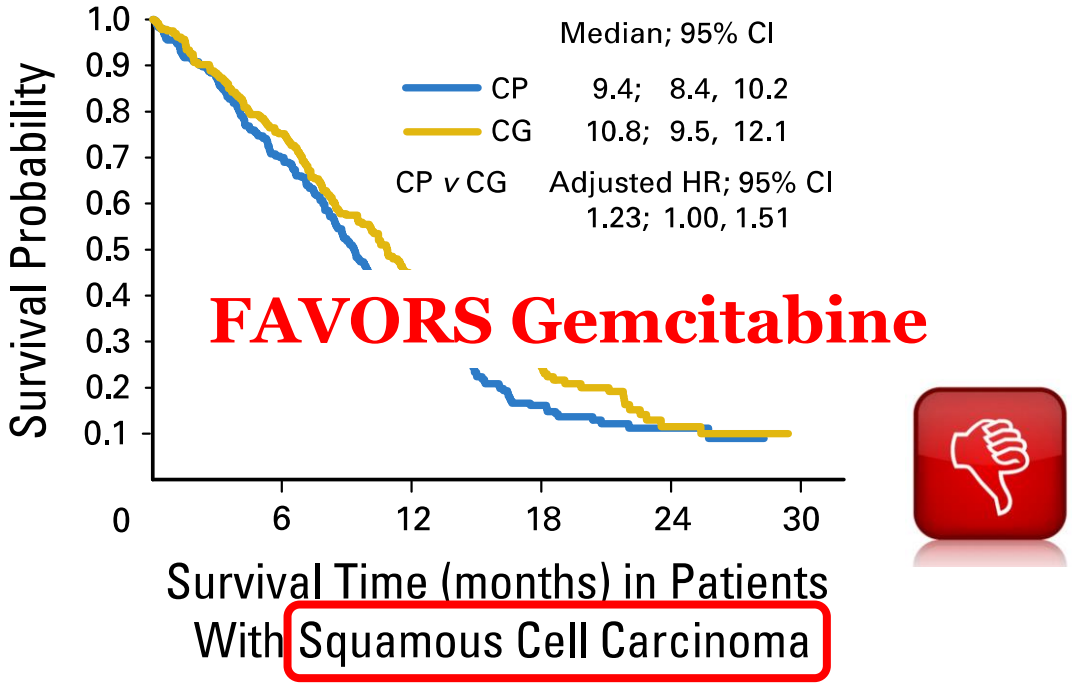
Cisplatin/Pemetrexed:

a valuable option for Stage IIIB/IV NON-squamous NSCLC

OS



OS



Scagliotti GV. et al. JCO 2008;26

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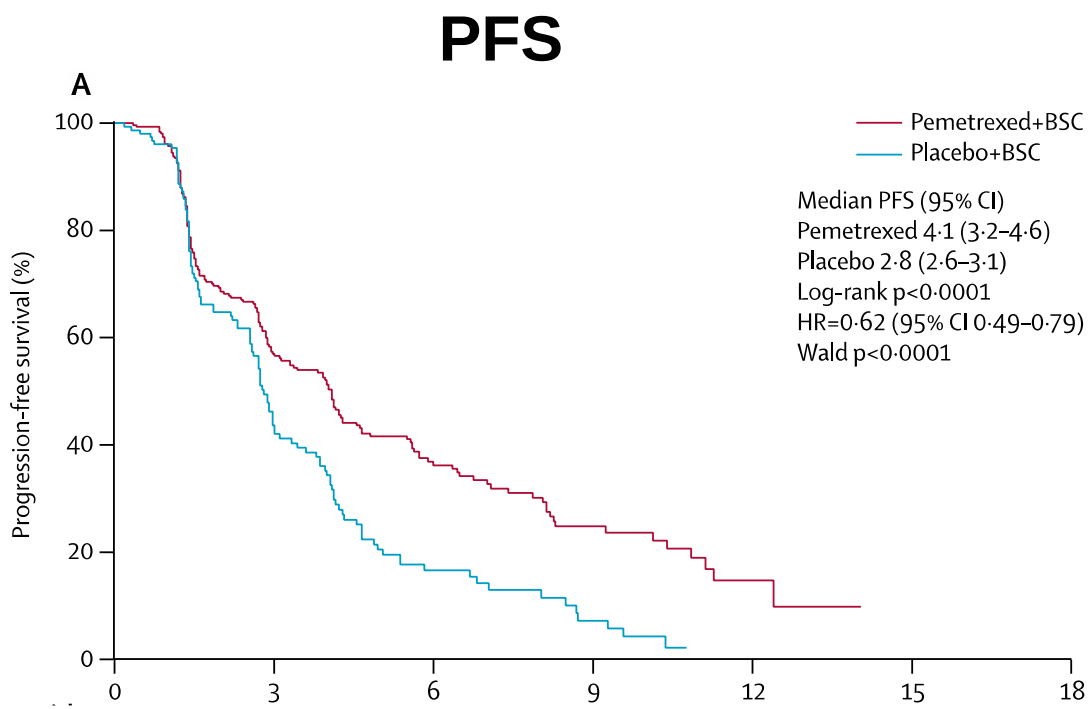
Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial

Maintenance with Pemetrexed: an effective strategy



- 90% stage IV NSCLC
- Induction: Cisplatin + Pem x 4
- Maintenance with PEM is an effective treatment option (for stage IV NSCLC)

Paz-Ares L. et al. Lancet Oncol 2012;13

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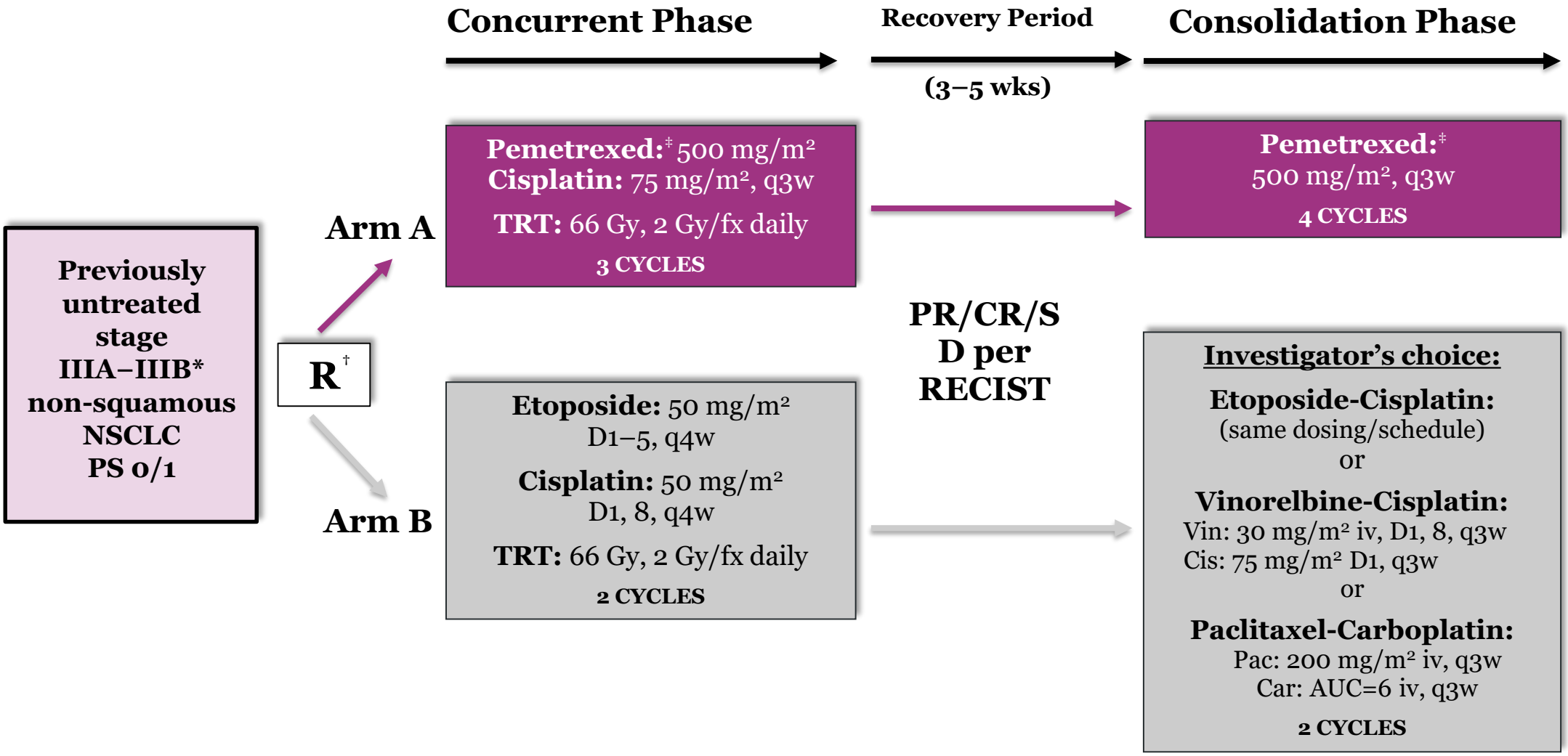
PROCLAIM trial: Study design



***Stratified for: ECOG PS (0 *vs* 1); PET scan staging (yes *vs* no); gender; and disease stage (IIIA *vs* IIIB).**

† AJCC Cancer Staging Manual (ed 6), 2002. ‡ Folic acid, vitamin B_{12}, and dexamethasone administered in Arm A. TRT=thoracic radiotherapy.

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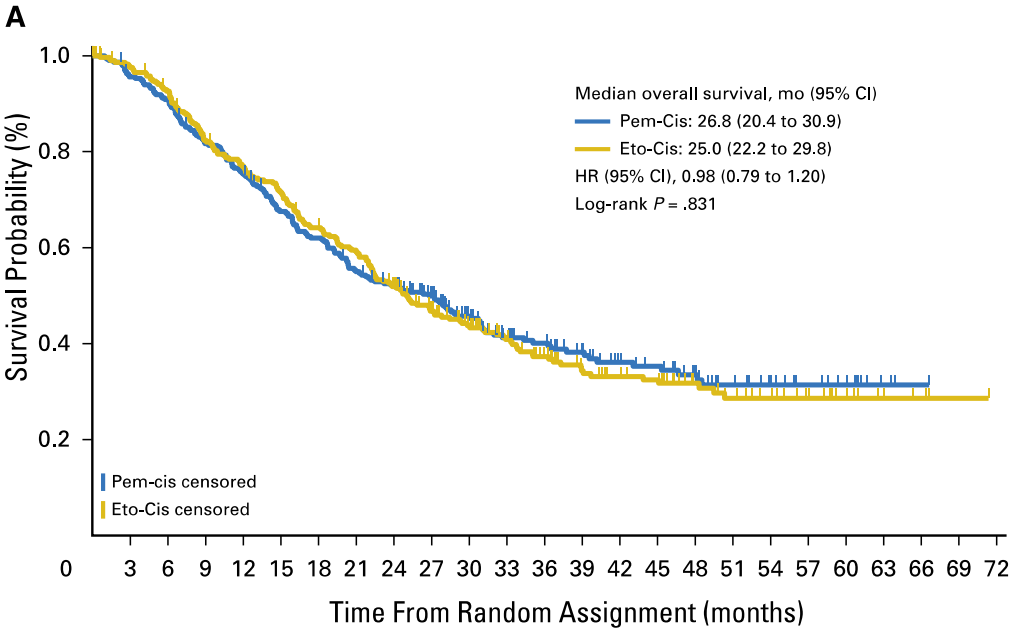
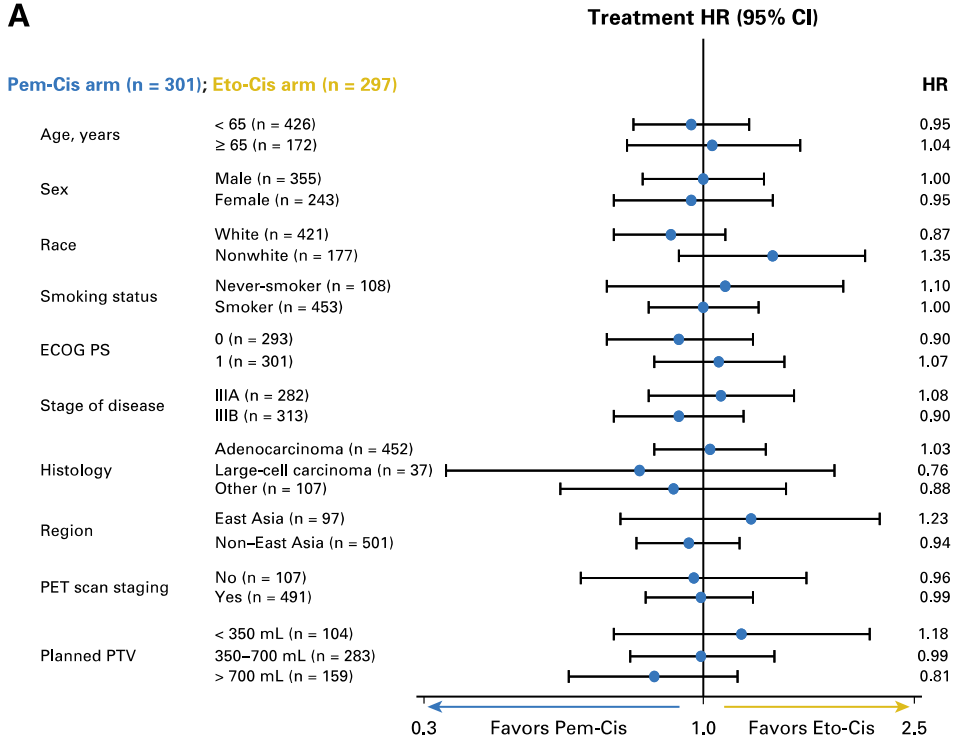
PROCLAIM: Randomized Phase III Trial of Pemetrexed-Cisplatin or Etoposide-Cisplatin Plus Thoracic Radiation Therapy Followed by Consolidation Chemotherapy in Locally Advanced Nonsquamous Non–Small-Cell Lung Cancer

PROCLAIM trial: early stopping for futility

Overall Survival



Overall Survival



- **PEM arm less toxic both during the concurrent administration with RT and in the consolidation phase**

Senan S. et al. JCO 2016;34

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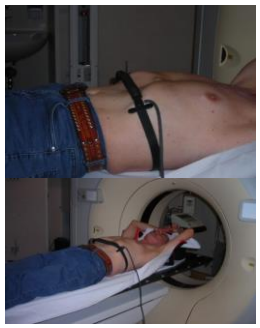
Radiotherapy for Locally Advanced NSCLC

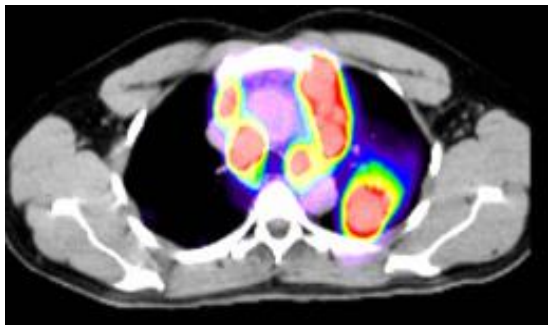
- ***Objectives of XRT for lung cancer***
  - Optimize local control
  - Reduce toxicity

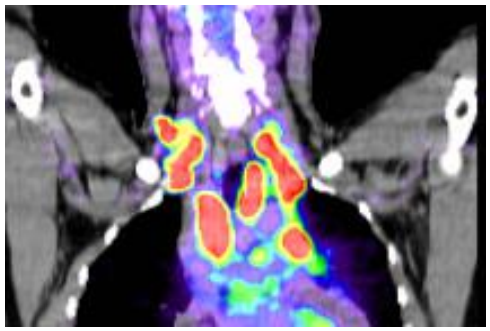
- ***Technical advances that improve UTCP (uncomplicated tumor control probability) rates***
  - Incorporate **PET-CT** into radiation planning
  - **4D-CT** to account for tumor motion (ITV)
  - Advanced planning solutions (**IMRT**)
  - **IGRT** to limit PTV margins

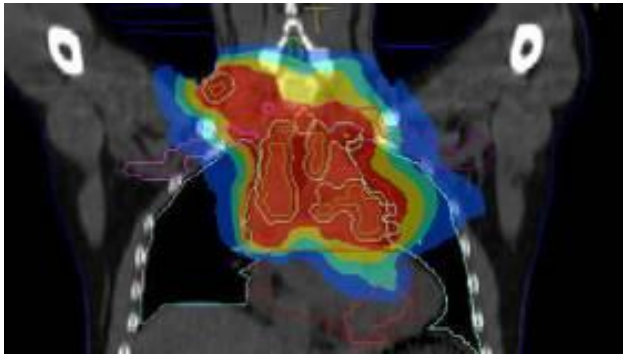
Cutting edge Radiotherapy in Lung Cancer

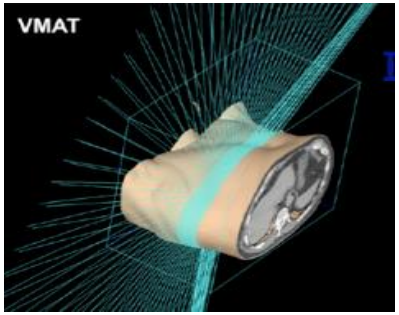
1. **Use of 4D-CT**: accounting for tumor motion during breathing
2. **GTV-Definition**: minimization based on functional Imaging (PET-CT) and shift to smaller CTV volumes

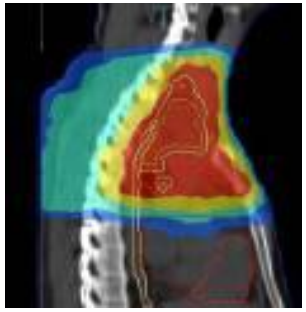




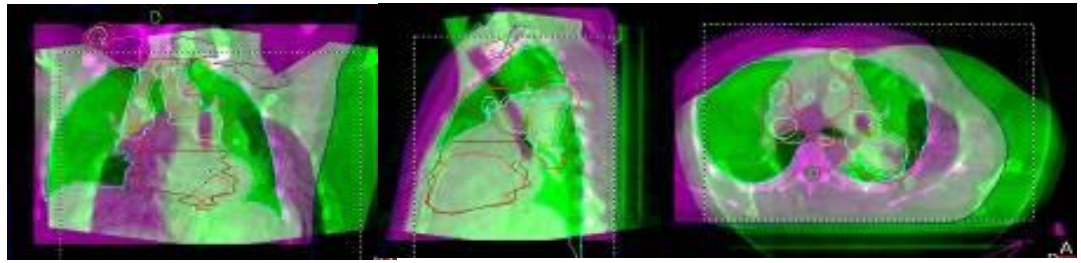




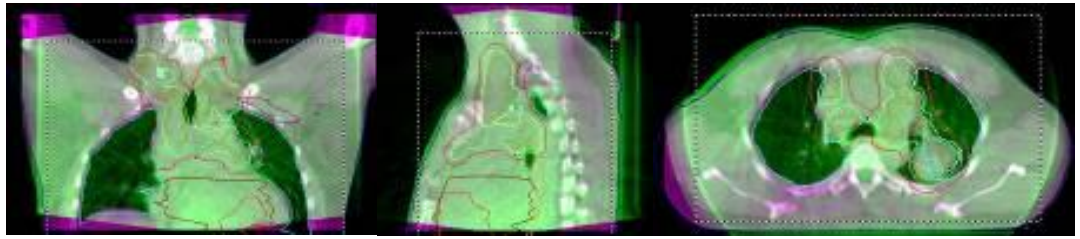




2. Treatment Planning: IMRT based on Monte-Carlo Dose calculation (dose-painting)



Suboptimal Positioning



Optimal Positioning

3. Image Guided Radiotherapy Treatment with Cone-Beam-CT at Linac for margins reduction

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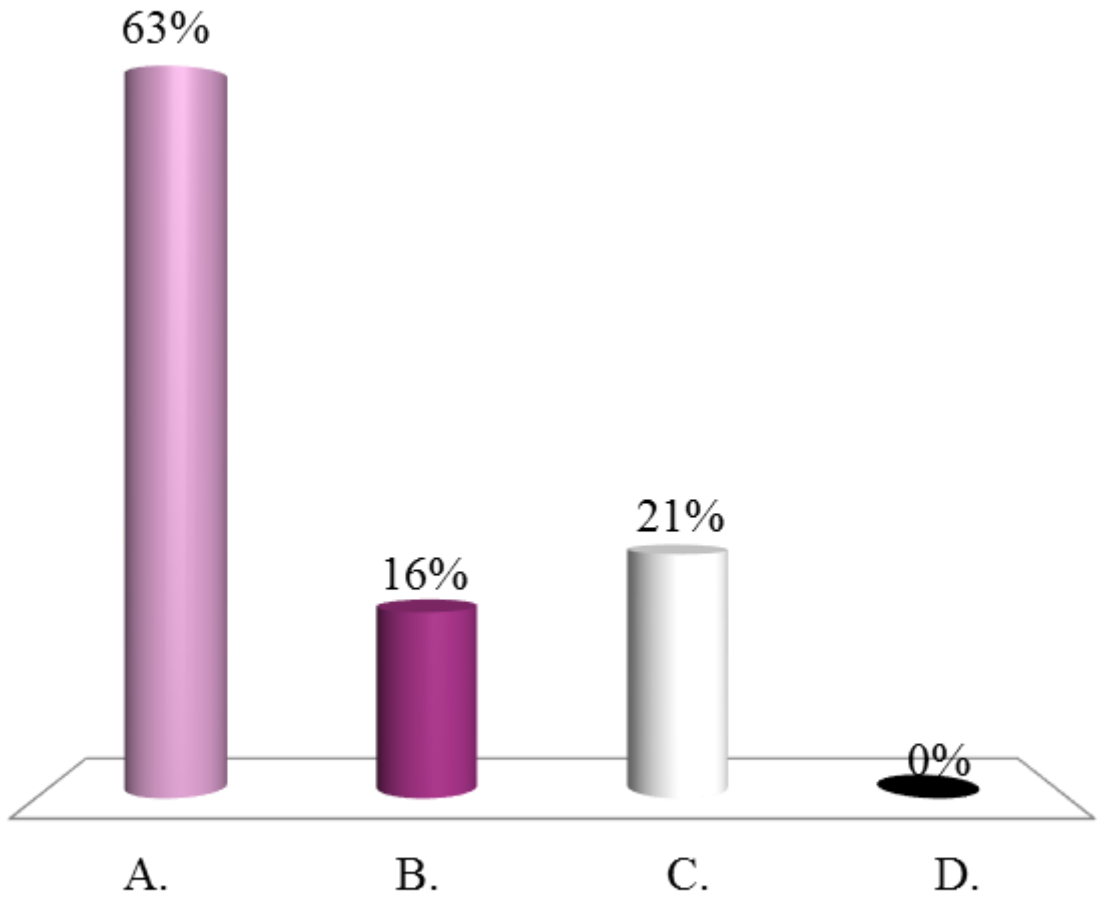
Let's Move back for a while to our patient… He obtained a partial response after Carboplatin/Paclitaxel chemotherapy. Which is now the best RT schedule in a sequential approach ?

A. Thoracic RT 60 Gy/30 fractions

B. Thoracic RT 74 Gy/37 fractions

C. Hypofractionated RT 66 Gy/24 fractions (2.75 Gy/day)

D. Hyperfractionated accelerated RT 60 Gy/40 fractions/tid (4.5 Gy/day in 3 fractions)



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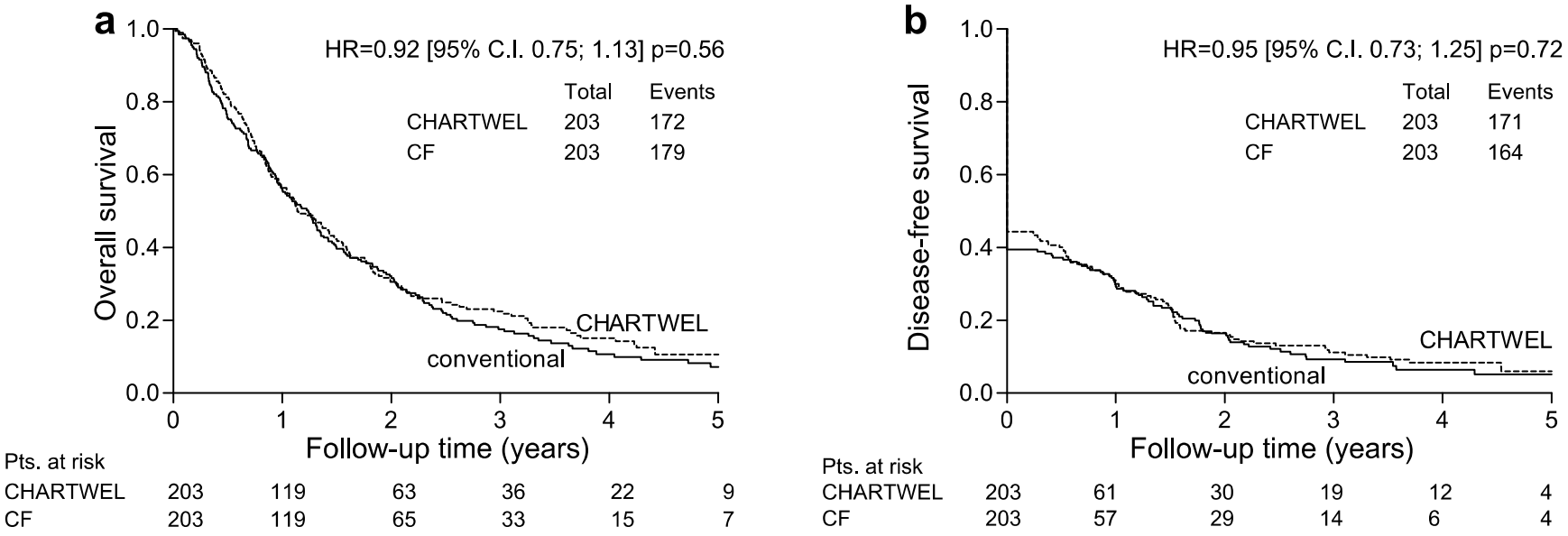
Phase III randomised trial

Final results of the randomized phase III CHARTWEL-trial (ARO 97-1) comparing hyperfractionated-accelerated versus conventionally fractionated radiotherapy in non-small cell lung cancer (NSCLC)

Hyperfractionated-accelerated RT



- Standard arm: 66 Gy/33 fr.
- Experimental arm: 60 Gy/40 fractions, 3 fractions per day (weekend-less)
- N.B. not all patients received neoadjuvant chemotherapy before RT

- ***"Outcome after CHARTWEL or conventional fractionation was not different"***

Baumann M. et al. Radiot Oncol 2011;100

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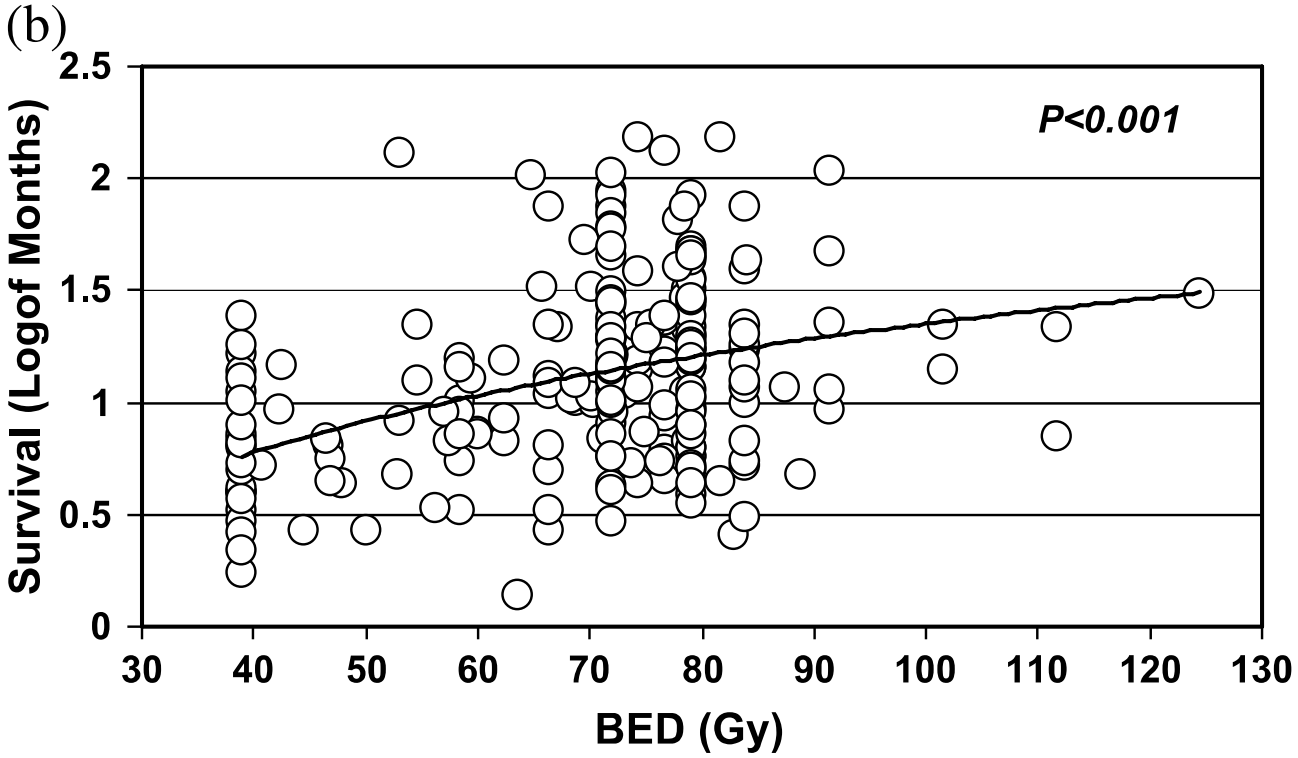
THE EFFECT OF RADIATION DOSE AND CHEMOTHERAPY ON OVERALL SURVIVAL IN 237 PATIENTS WITH STAGE III NON–SMALL-CELL LUNG CANCER

Dose response relation



- Retrospective study
- Median RT dose:
  - **60 Gy** (range 30-102.9)
- Median BED:
  - **72 Gy** (range 39-124.5)
- **RT dose** is an independent **predictor od OS** in stage III NSCLC

Wang L. et al. IJROBP 2009;73

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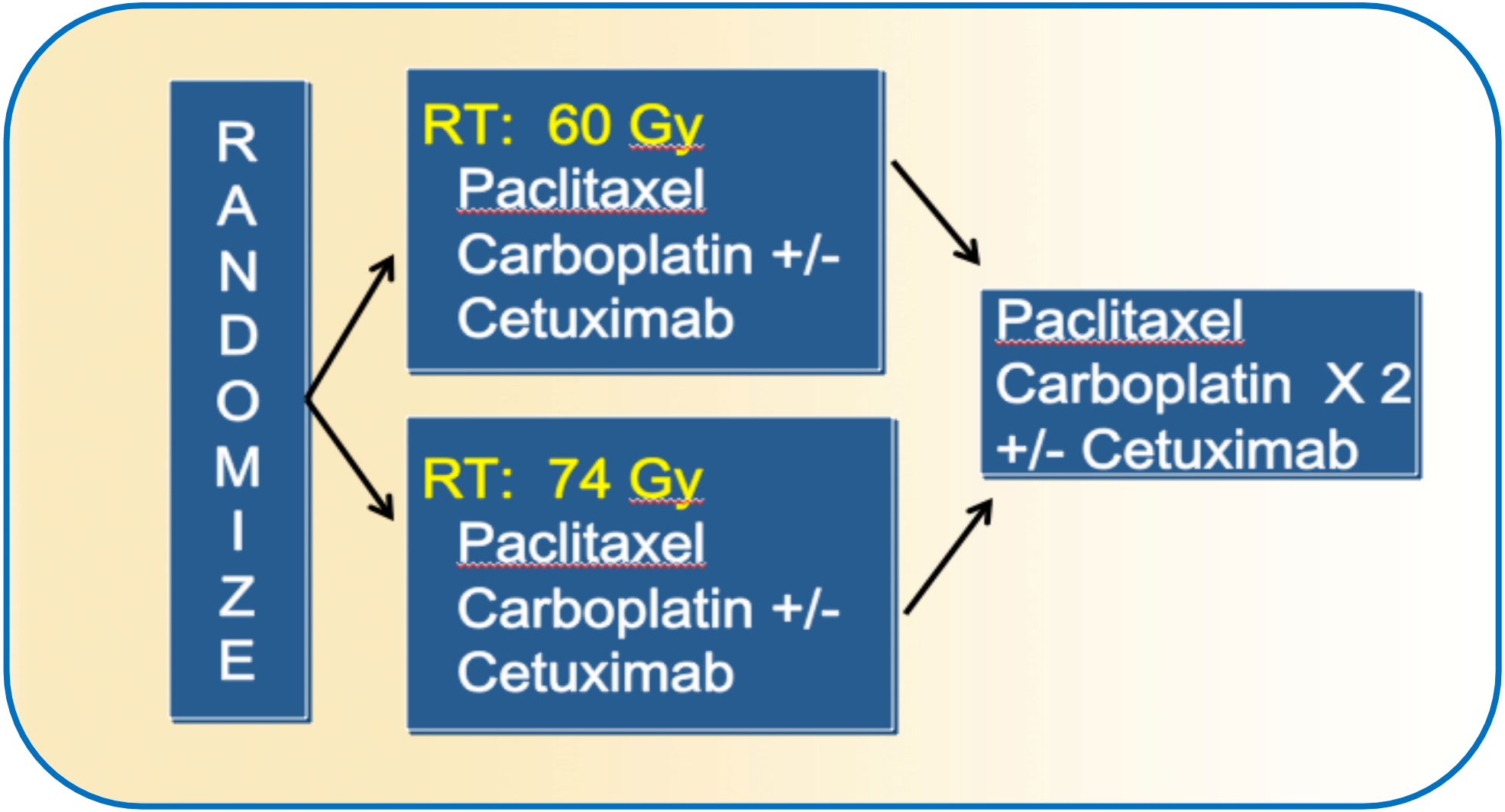
Unresectable Stage III NSCLC
Optimal radiation dose

- **Indirect evidence suggests that radiation dose-escalation may improve survival also in the context of chemo-radiation**

Table – Phase I and II Trials establishing safety and potential efficacy of 74 Gy

Study	Radiation dose (Gy)	Chemotherapy	Median survival time (months)
RTOG 0117	74	Carboplatin/paclitaxel	21.6
NCCTG 0028	74	Carboplatin/paclitaxel	37
North Carolina	74	Carboplatin/paclitaxel	24
Wake Forest	74	Gemcitabine	18
CALGB 30105	74	Carboplatin/paclitaxel	24

RTOG 0617 Trial:
Conventional Vs High Dose RT



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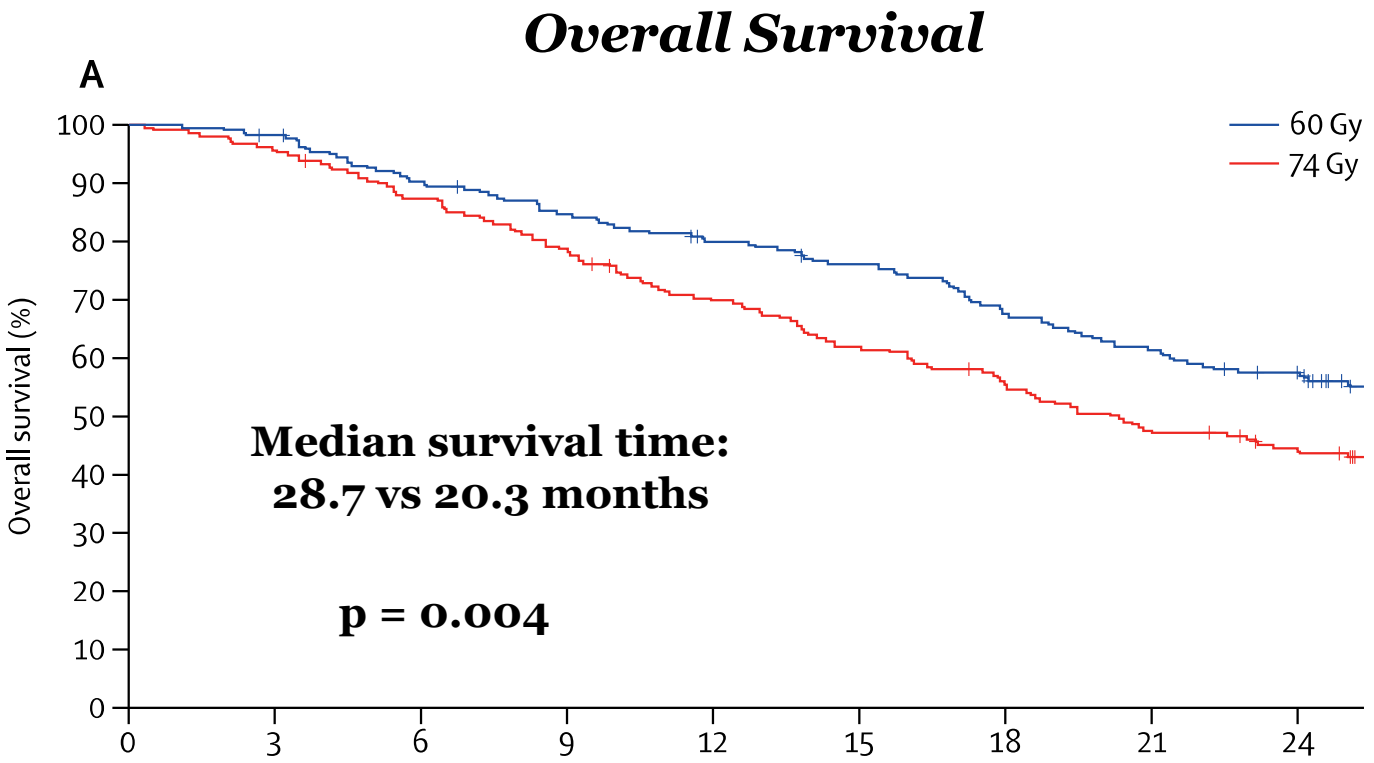
THE LANCET Oncology

Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study

RTOG 0617 Trial



- **N.B. Local failure rates at 18 months:**
  - 25.1% in standard arm (60 Gy)
  - 34.3% in high dose arm (74 Gy)

→ **p < 0.05**

Bradley JD. et al. Lancet Oncol 2015;16

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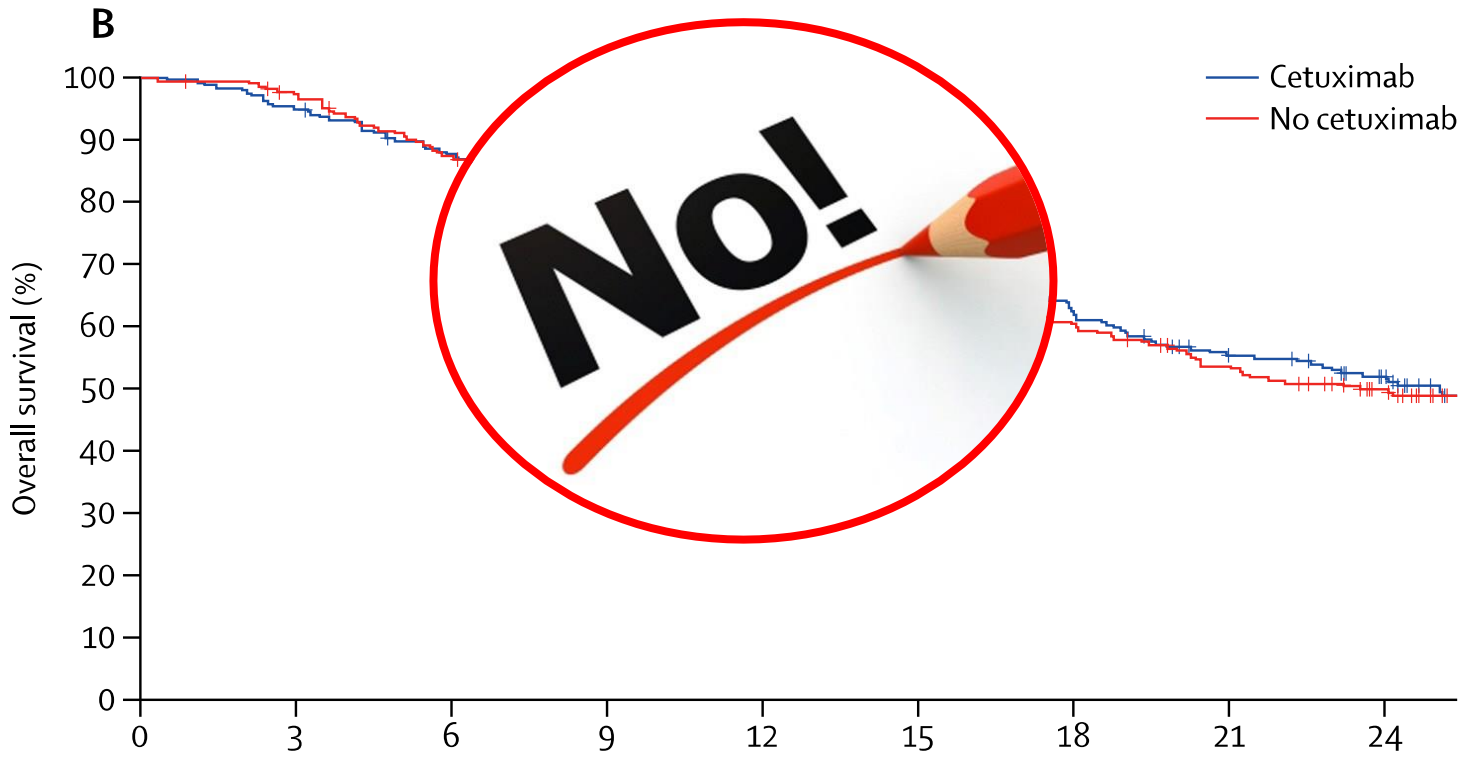
THE LANCET
Oncology

Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study

RTOG 0617 Trial – Any role for Cetuximab ?



Bradley JD. et al. Lancet Oncol 2015;16

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RTOG 0617 – Conclusions

- **"Positive" of RTOG 0617**
  - Excellent median survival of 28.7 months in the 60-Gy study arms when compared with prior cooperative group studies in stage III NSCLC.
  - May reflect PET scan use for staging (used in ~ 90% of pts)

- **"Negative" of RTOG 0617**
  - 74 Gy radiation with concurrent CT was not better than 60 Gy for patients with stage III NSCLC, and might be potentially harmful.
  - Addition of Cetuximab to concurrent CR-RT and consolidation treatment provided no benefit in OS for these patients, but increased overall grade 3-5 toxicity (85% vs 69%, $p < 0.0001$)

RTOG 0617…

Why results poor in higher RT dose arm? NOT YET KNOWN

- Higher rate of treatment-related deaths?
- Higher dose of radiation to the heart (V_{40})?
- Unreported side effects?
- Higher dose scheduled compromising overall treatment time?
- RT delivery?

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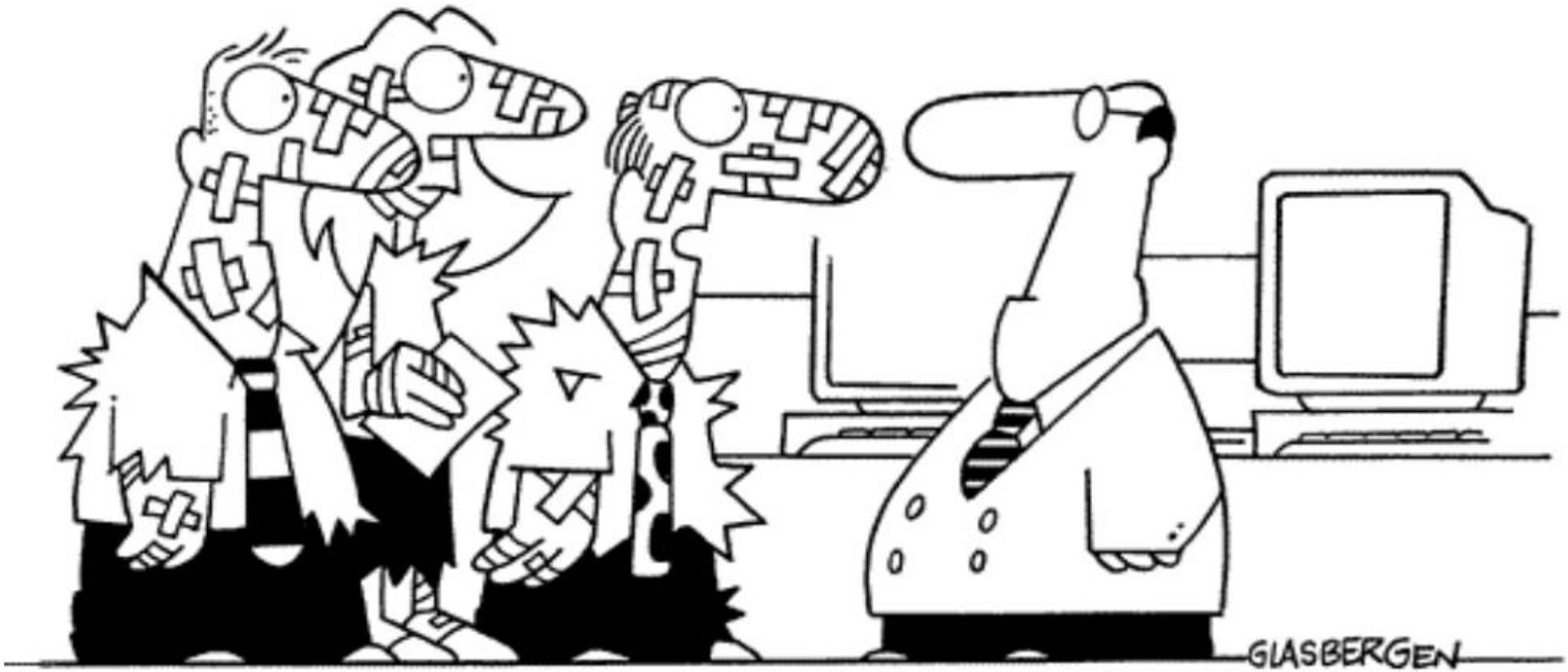
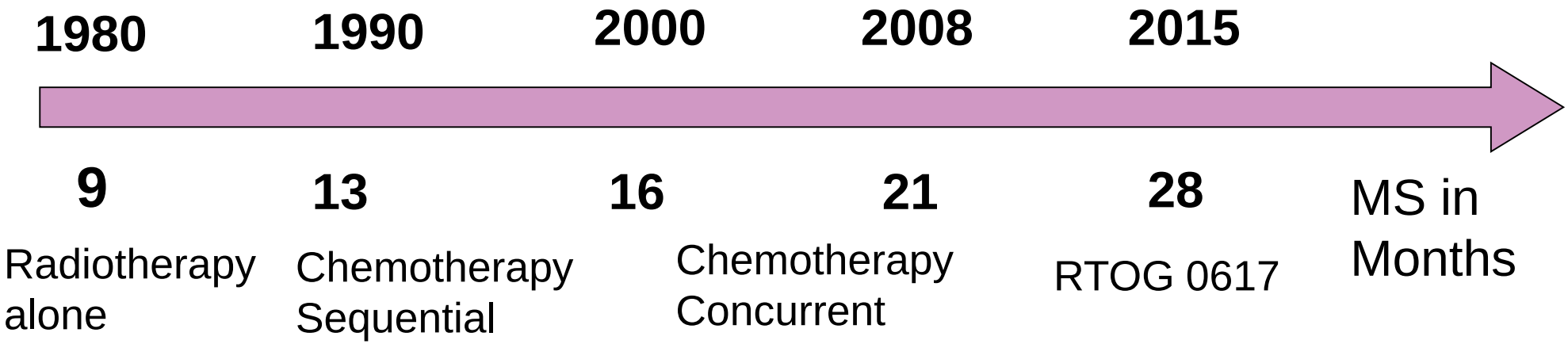


“Frankly sir, we’re tired of being on the cutting edge of technology.”

Survival of Stage III NSCLC:



1. Stage Migration
2. Concurrent Chemo-radiation Therapy
3. Improved Radiation Technology

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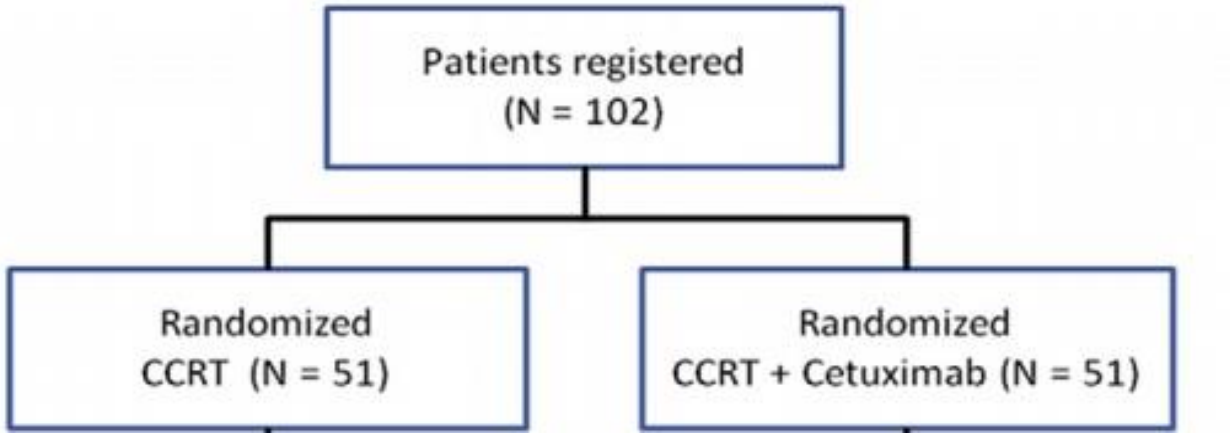
Dutch Phase II trial "RADITUX":
Concurrent CT/RT using a hypofractionated scheme

To investigate 60-month OS in LA-NSCLC patients treated in Raditux trial: concurrent chemoradiotherapy +/- cetuximab, using a hypofractionation scheme of 24 x 2.75 Gy



- RT schedule: 24 x 2.75 Gy
- CT schedule: daily low dose cisplatin (6 mg/m²) +/- weekly cetuximab

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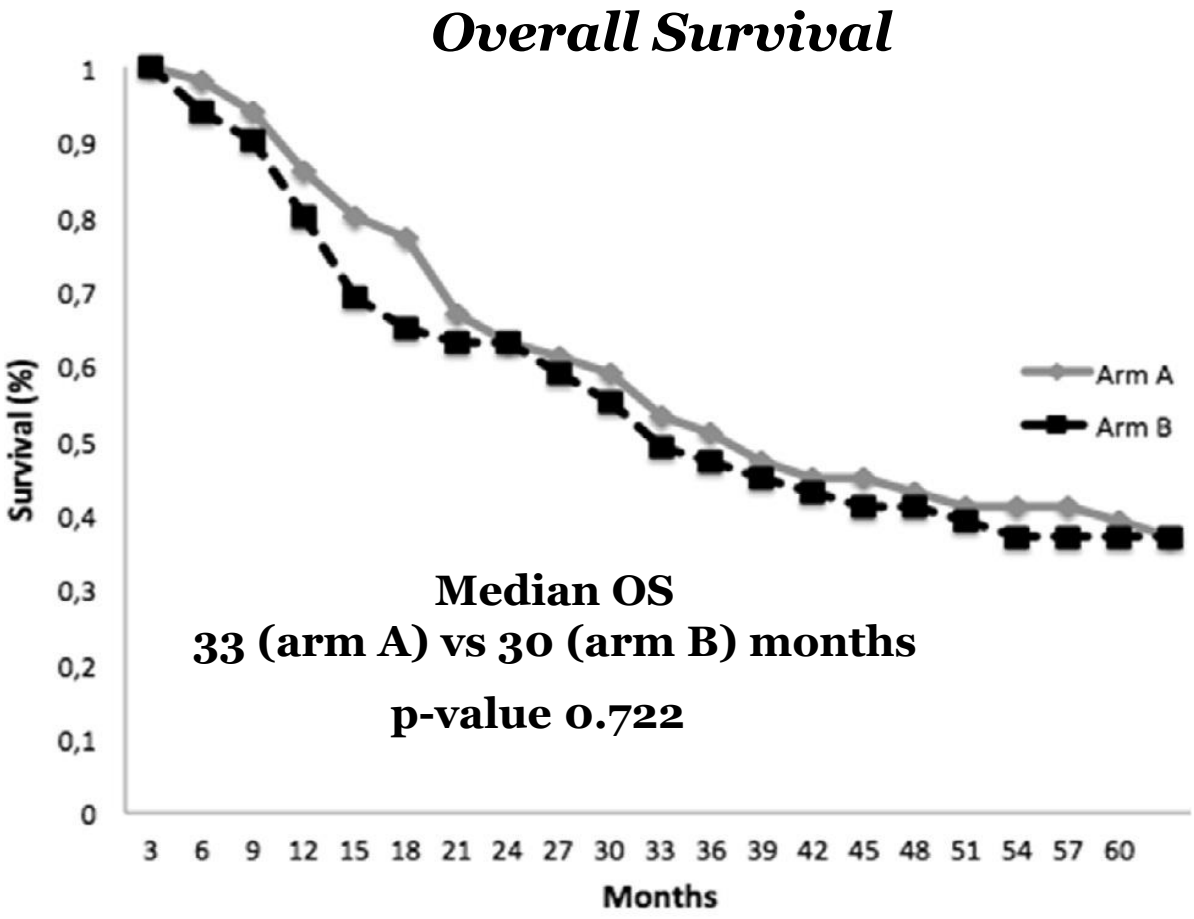
Phase II randomised trial

Long-term follow-up of patients with locally advanced non-small cell lung cancer receiving concurrent hypofractionated chemoradiotherapy with or without cetuximab

RADITUX trial: final results



- **OS** was remarkably **high** (37% @ 5 years)
- **Hypofractionated RT + daily** might contribute to **increase OS** in locally advanced NSCLC
- **No positive** results for **Cetuximab and RT** in stage III NSCLC so far

Walraven I. et al. Radiot Oncol 2016;116

Overall survival
RTOG 0617 vs RADITUX

	Raditux trial	RTOG 0617 60 Gy	RTOG 0617 74 Gy
Mortality	64%*	58%[a]	67%[a]
1-year OS (%)	75%	78%	69%
2-year OS (%)	60%	53%	42%
5-year OS (%)	37%	-	-
Median OS (months)	32 months	29 months	20 months

*based on 5-years of follow-up
[a]based on 2-years of follow-up

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Baseline characteristics
RTOG 0617 vs RADITUX

	Raditux trial 66 Gy	RTOG 0617 60 Gy	RTOG 0617 74 Gy
Age	62 years	64 years	64 years
Stage II	8%	-	-
Stage IIIA	52%	66%	63%
Stage IIIB	40%	34%	37%
GTV	119 cc	93 cc	110 cc
PTV	499 cc	481 cc	478 cc
PET staged	92%	90%	90%

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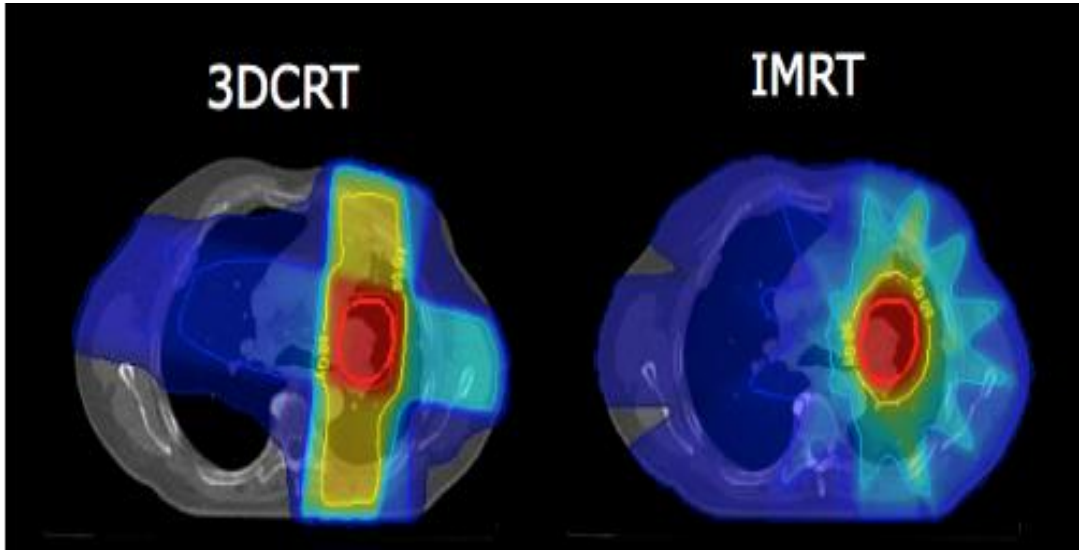
JOURNAL OF CLINICAL ONCOLOGY

Impact of Intensity-Modulated Radiation Therapy Technique for Locally Advanced Non–Small-Cell Lung Cancer: A Secondary Analysis of the NRG Oncology RTOG 0617 Randomized Clinical Trial

Impact of IMRT compared to 3D-CRT:
Secondary analysis of RTOG 0617



Compared RT technique in Univariate and Multivariate Analyses

•Stratified: 3D-CRT 53%, IMRT 47% in both RT dose arms

•Endpoints of secondary analysis
- Survival – overall, progression free, local control
- Grade 3+ toxicity
- Amount of chemotherapy administered

Chun SG. et al. JCO 2017;35

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JOURNAL OF CLINICAL ONCOLOGY

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Impact of IMRT compared to 3D-CRT:
Secondary analysis of RTOG 0617

"Deck Stacked against IMRT"

Characteristic	3D-CRT	IMRT	P-value
Stage IIIB	30%	39%	0.056
PTV	427 mL	486 mL	0.005
PTV:lung ratio	0.13	0.15	0.013

Multivariate analysis
3D-CRT (reference) vs IMRT

Outcome	OR (95% CI)	P-value
Overall survival	1.01 (0.8, 1.28)	0.95
Progression free survival	1.12 (0.91, 1.39)	0.28
Local control	0.91 (0.67, 1.23)	0.54
Distant metastasis free	0.92 (0.71, 1.19)	0.52

❑ Overall and progression-free survival **similar**, in spite of more unfavorable tumors in IMRT group

Chun SG. et al. JCO 2017;35

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Impact of Intensity-Modulated Radiation Therapy Technique for Locally Advanced Non–Small-Cell Lung Cancer: A Secondary Analysis of the NRG Oncology RTOG 0617 Randomized Clinical Trial

Impact of IMRT compared to 3D-CRT:

Radiation Induced pneumonitis

RESULTS

Benefits of IMRT

Outcome	3D-CRT	IMRT	P-value
Grade 3+ pneumonitis	8%	3.5%	0.0462
Heart V40	11.4%	6.8%	0.0026
Full consolidative chemotherapy	29%	37%	0.05

Esophagitis, weight loss, cardiovascular, neurologic adverse effects similar in IMRT and 3D-CRT

RESULTS

Multivariate Predictors of Grade 3+ pneumonitis

Co-variate	Comparison	OR (95% CI)	P-value
Technique	3D-CRT vs IMRT	0.44 (0.18, 1.04)	0.0621
Stage	IIIA vs. IIIB	2.35 (1.05, 5.29)	0.0385
Lung V20	Continuous	1.081 (1.02, 1.146)	0.009

Low dose bath bigger with IMRT

Lung V5 – IMRT 62% vs. 3D-CRT 55% ($P < 0.0001$)

Lung V5 did not predict pneumonitis, P = 0.14, OR 1.02, 95% CI (0.994, 1.04)

MLD did not predict pneumonitis

Chun SG. et al. JCO 2017;35

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JOURNAL OF CLINICAL ONCOLOGY

Impact of Intensity-Modulated Radiation Therapy Technique for Locally Advanced Non–Small-Cell Lung Cancer: A Secondary Analysis of the NRG Oncology RTOG 0617 Randomized Clinical Trial

Impact of IMRT compared to 3D-CRT:

Heart dose

Heart Doses

Heart Doses	3D-CRT	IMRT	P-value
V20	23.5%	19.3%	0.049
V40	11.4%	6.8%	0.003
V60	2.4%	1.4%	0.045

Overall survival univariate analysis

Co-variate	HR	95% CI	P-value
Heart V20	1.008	1.004, 1.013	0.0005
Heart V40	1.013	1.006, 1.021	0.0005
Heart V60	1.023	1.007, 1.039	0.0051

Overall survival multivariate analysis

Co-variate	HR	95% CI	P-value
Heart V40	1.013	1.005, 1.02	0.0008

- **CONCLUSION**: in RTOG 0617 trial, **IMRT** was associated with **lower** rates of **severe pneumonitis and cardiac doses**, which supports **routine use** of IMRT for locally advanced NSCLC

Chun SG. et al. JCO 2017;35

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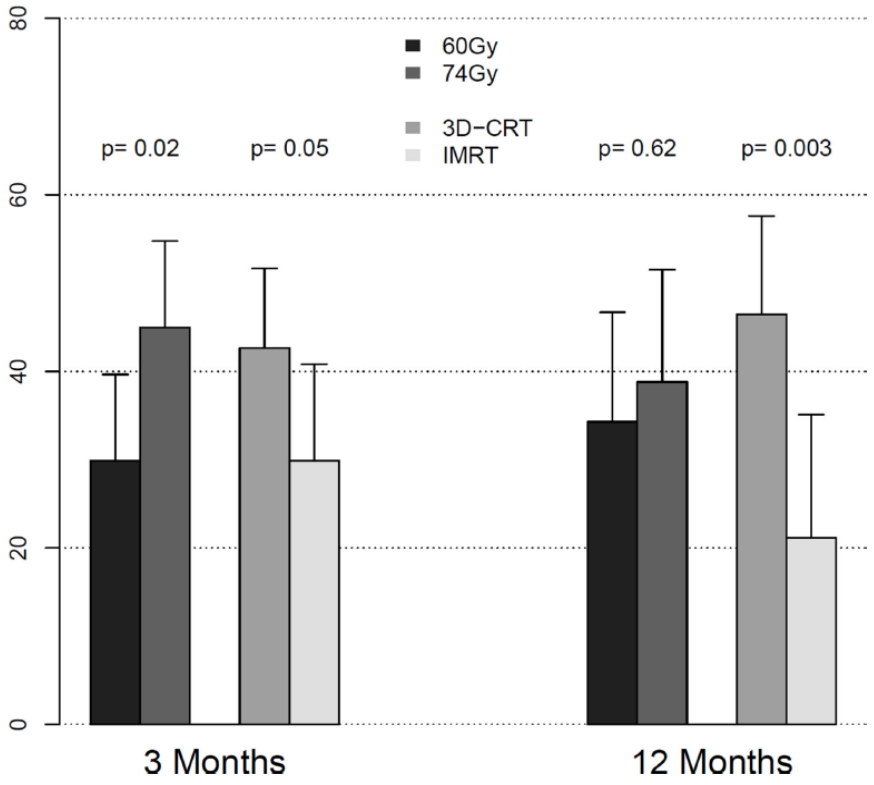
Quality of Life Analysis of a Radiation Dose–Escalation Study of Patients With Non–Small-Cell Lung Cancer
A Secondary Analysis of the Radiation Therapy Oncology Group 0617 Randomized Clinical Trial

Impact of IMRT compared to 3D-CRT:
Quality of Life

FACT-LCS decline



- QoL evaluated with the **FACT-LCS** scale (Fuctional Assessment of Cancer Therapy – Lung Cancer Subscale) at baseline (313 pts), 3 (219 pts) and 12 months (137 pts)
- Significantly **more patients** on **74Gy arm** had clinically meaningful **decline** in FACT-LCS at 3 months than on the 60Gy arm (45% vs. 30%, p=0.02)
- At 12 months, **fewer patients** who received **IMRT** (vs 3DCRT) had clinically meaningful **decline** in FACT-LCS (21% vs 46%, p=0.003)

Movsas B. et al., JAMA Oncol 2016;2

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SBRT with concurrent chemoradiation in stage III NSCLC: first results of the phase I Hybrid trial

- H. Peulen, J.-J. Sonke, E. van der Bijl, E. Damen, J. Belderbos
- ESTRO 2016: poster discussion

DUTCH CANCER SOCIETY

NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

Courtesy of J. Belderbos

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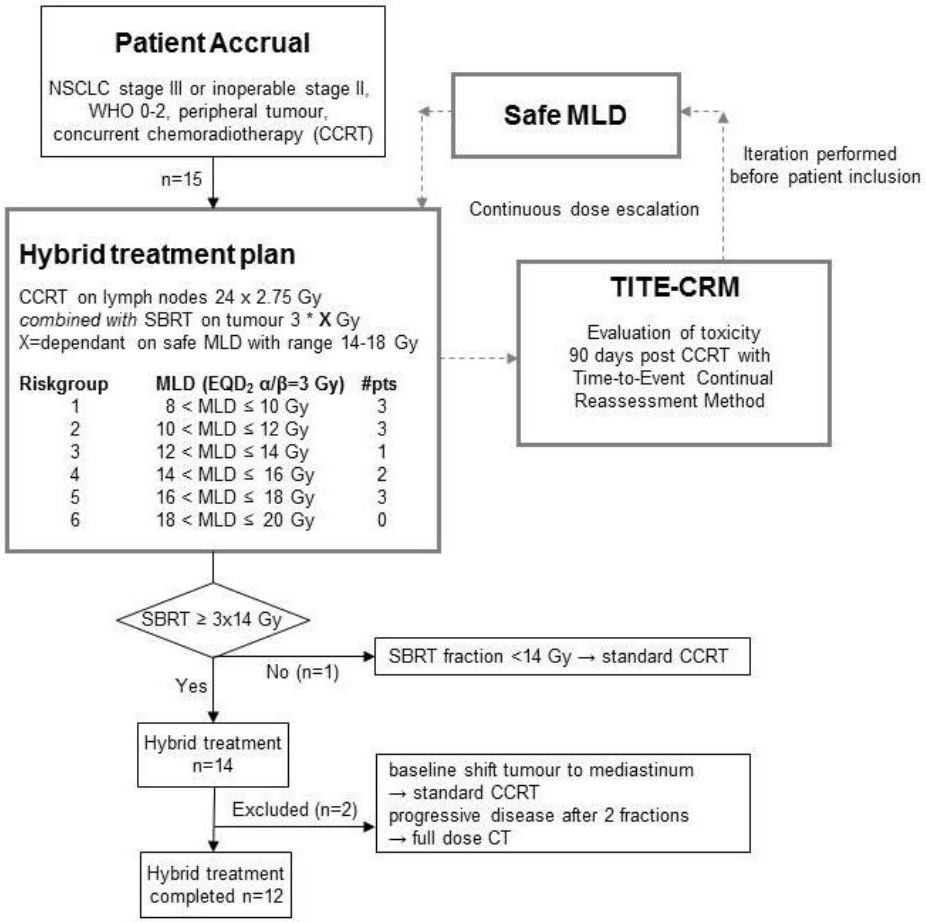
Hybrid study:
SBRT with concurrent chemoradiation

Study design



Endpoints

- **Primary endpoint:**
  - The Mean-lung dose (MLD) associated with 15% chance on radiation pneumonitis ≥G3 and dyspnea ≥G3

- **Secondary endpoints**:
  - Overall toxicity
  - Disease control

Courtesy of J. Belderbos

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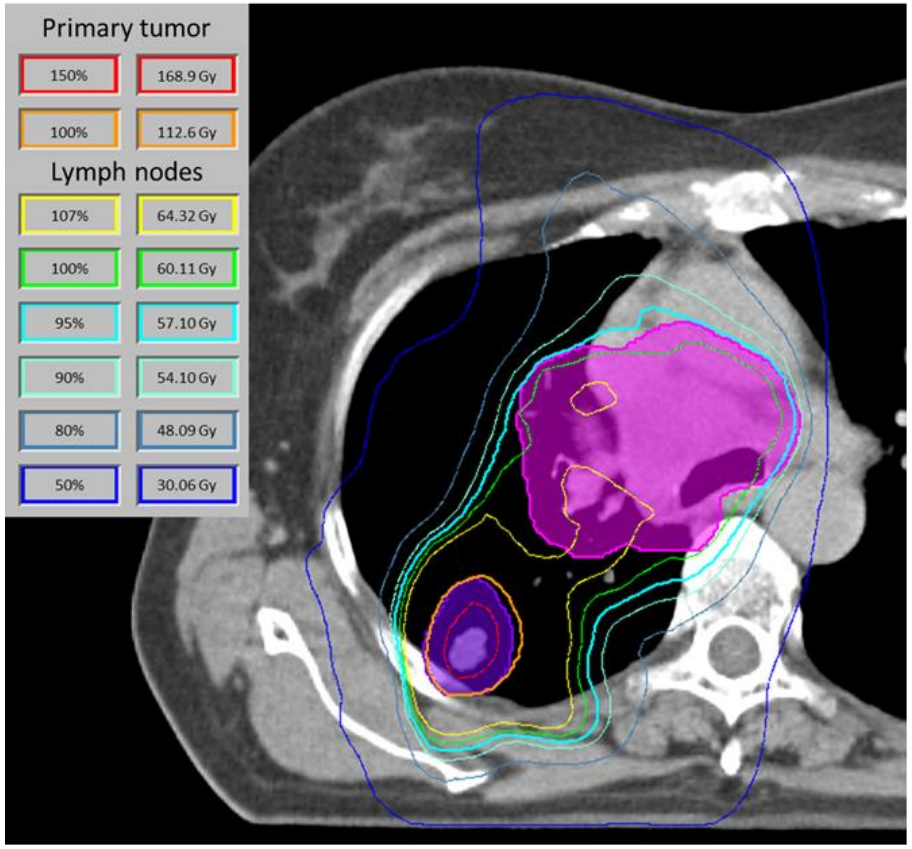
Hybrid study:
SBRT with concurrent chemoradiation

Treatment planning and delivery

- 2 isocentres and 2 dual VMAT arcs
- Compensation for indirect lymph node (LN) dose to primary tumour (PT): the biological equivalent of the minimal dose (D99) to the PT PTV from LN irradiation was subtracted from the biological prescribed dose to the PTV.
- Chemotherapy consisted of daily low dose Cisplatinum 6 mg/m²



PT: 3 x 18 Gy (purple)

LN: 24 x 2.42 Gy (pink)

Courtesy of J. Belderbos

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Hybrid study:
SBRT with concurrent chemoradiation

Toxicity profile using CTCAE v4

Toxicity grade– RT related*	# G1	# G2	# G3-5
Bronchopulmonary hemorrhage	1	1	-
Chest wall pain	-	1	-
Cough	4	2	-
Dyspnea	2	-	-
Fracture	-	1	-
Peripheral sensory neuropathy	-	1	-
Pleural effusion	1	-	-
Pneumonitis	1	2	-
Toxicity grade- RT AND CT related			
Radiation dermatitis	2	-	-
Dysphagia	4	6	-
Fatigue	4	3	-
Nausea	3	1	-
Vomiting	-	1	-
Weight loss	2	1	-
Toxicity grade - CT related			
Anorexia	-	1	-
Dysgeusia	2	-	-
Platelets count decreased	-	1	-

DVH parameters

Organ	Parameter	Constraint	α/β (Gy)	Results n=12 median (range)
Lung	Mean-lung dose	Dose escalation	3	12.2 (8.1-18.0)
Spinal cord	Dmax	≤50 Gy	2	41.0 (17.8-46.0)
Oesophagus	Dmax V35Gy	<66Gy <65%	Physical 10 Gy	63.6 (28.3-68.4) 25.2 (0-58.4)
Heart	Dmax	≤94 Gy	3	58.5 (1.5-79.0)
mediastinal envelope PRV*	Dmax	≤94 Gy	3	83.4 (68.6-92.6)
Brachial plexus	Dmax	≤94 Gy	3	1.3 (0.1-59.4)

Conclusions

- A Hybrid treatment of SBRT of the primary tumor combined with fractionated radiotherapy on the lymph nodes with concurrent chemotherapy is feasible.
- This phase I trial (NCT01933568) is currently accruing and no unexpected toxicity has been observed thus far.

Courtesy of J. Belderbos

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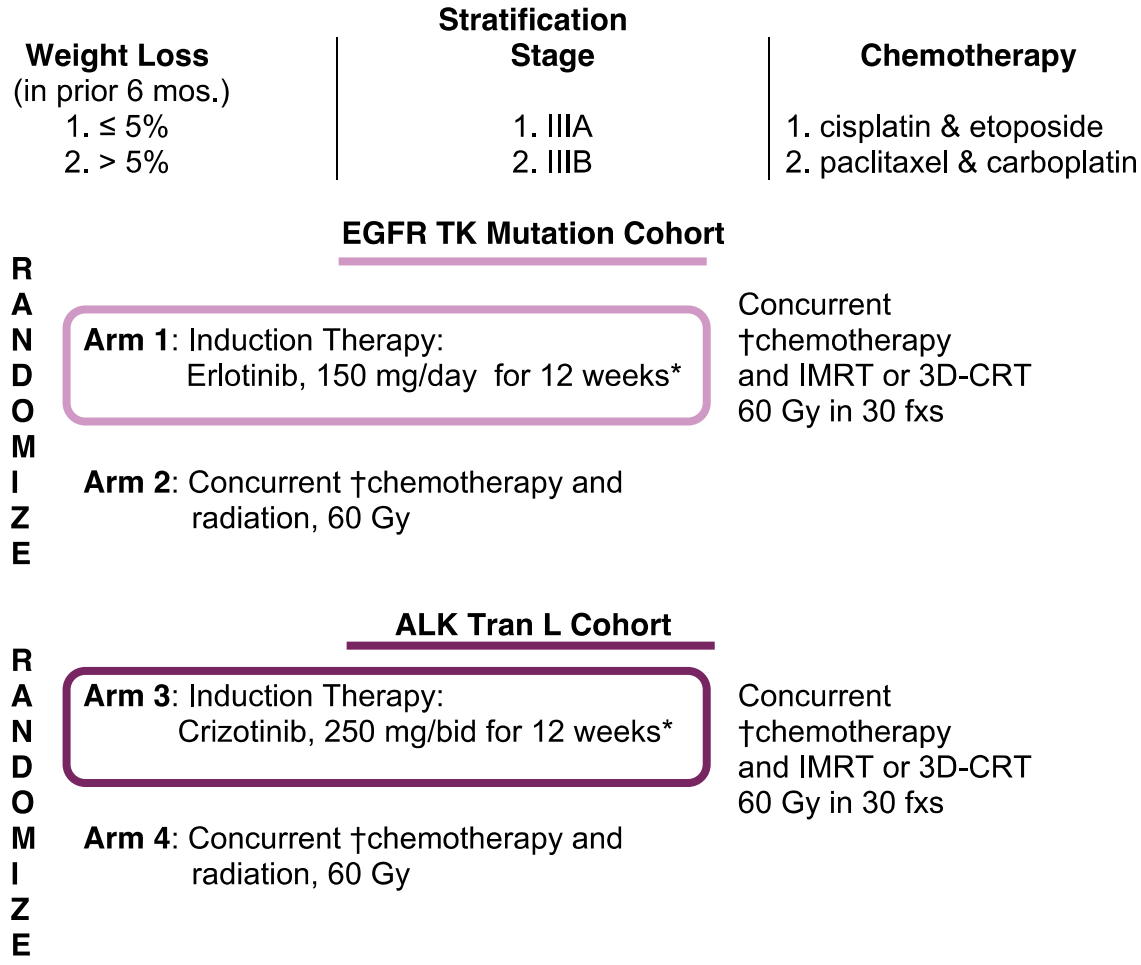
Future Perspectives…

RTOG 1306 trial – “ALLIANCE”

Induction therapy with TKIs in “oncogene addicted” NSCLC



Patient population

- ❑ *Histologically confirmed non-squamous NSCLC*
- ❑ *Unresectable stage IIIA-IIIB disease*
- ❑ *Surgically staged to confirm N2 or N3 disease*

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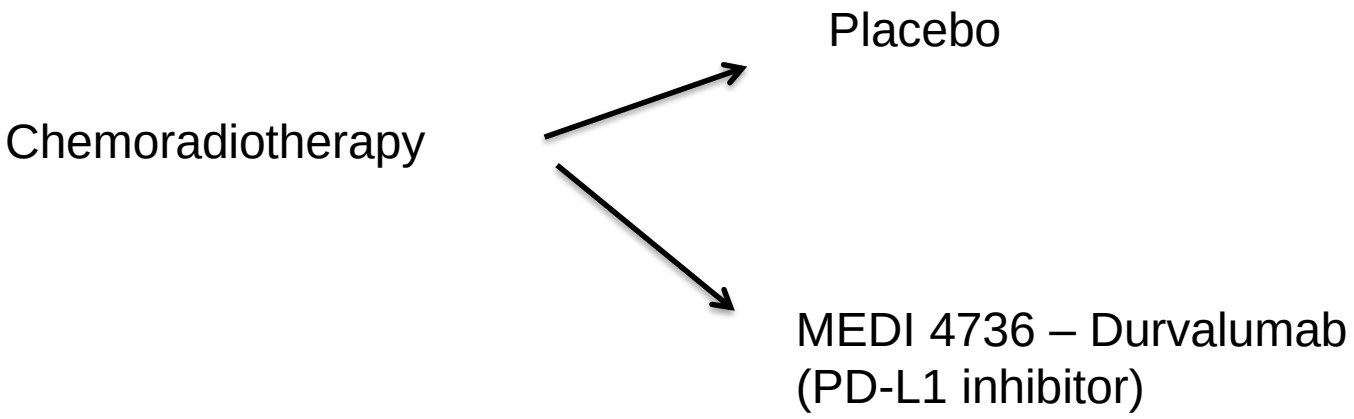
Future Perspectives…

PACIFIC PD-L1 Phase III Trial

Consolidative therapy with Durvalumab vs Placebo



Planned accrual: 702 pts, >100 sites
Endpoints: PFS, OS

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Conclusion (CMT in Stage III)

- Current standard regimens remain Carbo-tax and Cis-etoposide
- Testing of **targeted agents** in appropriate populations is long **overdue** – no clear indication to date
- Promising **immune-therapy** approaches are **under investigation**
- Prognostic and predictive factors are needed

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clinical practice guidelines

Annals of Oncology 24 (Supplement 6): vi89–vi98, 2013
doi:10.1093/annonc/mdt241
Published online 16 July 2013

Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

- Stage III NSCLC: the **gap** between an **ideal patient** from the guidelines and the **average patient** from clinical practice is especially wide

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Vansteenkiste J, et al. Ann Oncol. 2013;24

- **Locally advanced NSCLC (IIIA-IIIB)**
- **Oligometastatic NSCLC**

Categories of Oncology Care and Historical Outcomes

1) Local (limited to the site of origin)

- Highest cure rates (especially with more extensive surgery)
- Non-surgical treatments woefully inadequate
- Relapse is predominantly distant

2) Local-regional (spread to lymph nodes and adjacent organs)

- Mediocre cure rates, 30-50%
- Concurrent chemo added to improve radiotherapy
- Most patients will relapse either locally or distant

3) Metastatic (spread to distant sites)

- Dismal cure rates, <5%
- Surgery only helpful in small percentage
- Most patients first relapse in original sites of disease burden

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Moving Forward……

1) **Local**
   - Need an effective NON-SURGICAL treatment option
2) **Local-regional**
   - Need to “break the stalemate” of concurrent chemoradiotherapy by finding a potent local therapy
3) **Metastatic**
   - Even “targeted” systemic therapies fail first in sites of initial gross disease
   - Need to add a potent but tolerable local therapy

The Oligometastatic State

In a 1995 JCO Editorial, clinical evidence led Hellmann and Weichselbaum to coin the term "oligometastases"

It was a proposal for a new clinical concept :

- **Intermediate** biologic state of restricted metastatic capacity between truly locoregionally-confined and widely –metastatic cancer
- **Limited** number and organ sites of metastases
- **Transitional** state to dissemination (not yet achieved a widespread dissemination)

*Oligometastatic state (by "arbitrary definition"): limited number of metastases (**usually ≤ 5**), all amenable to radical local therapies*

Weichselbaum & Hellmann. J Clin Oncol 1995;13
Weichselbaum & Hellmann. Nat Rev Clin Oncol 2011;8

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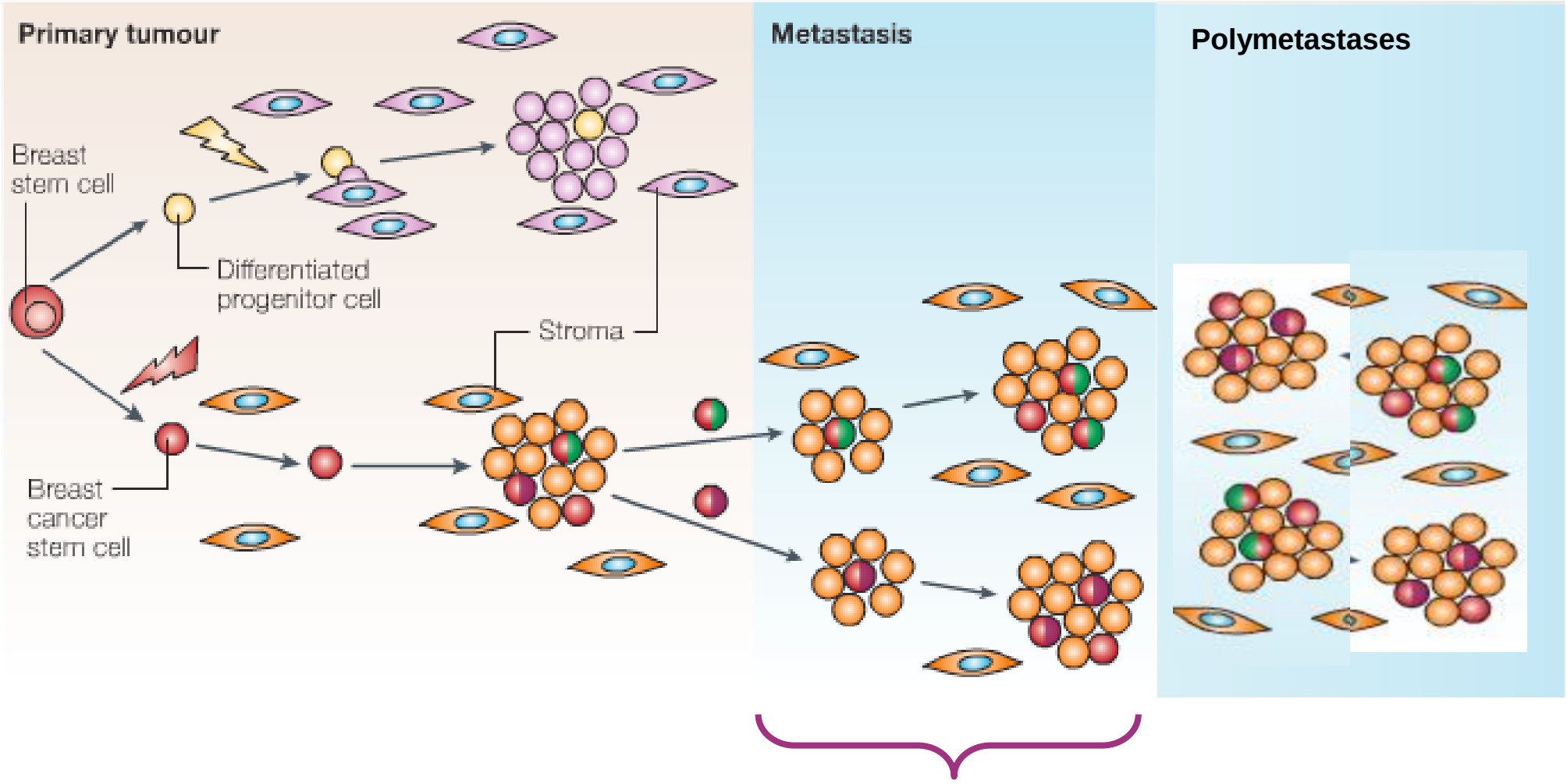
Terminology and definition



Oligometastases → *Patients with **one to five metastases** may be at a continuum between truly local disease and widely disseminated cancer*

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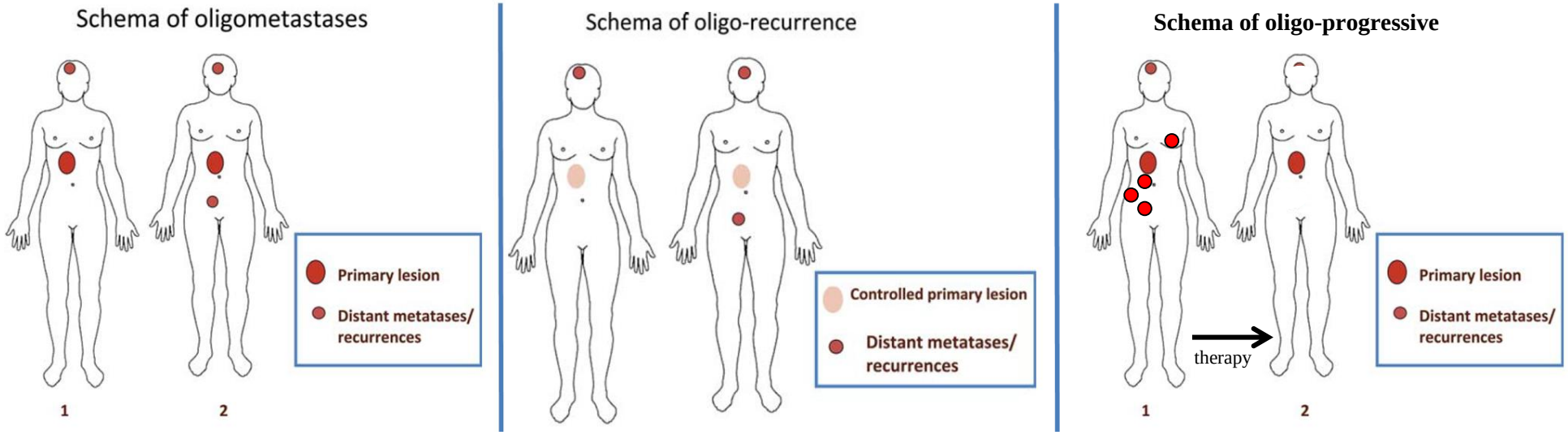
Distinct cohorts of oligometastatic disease

‘**oligometastases**’ = diagnosed with oligometastatic disease
‘**oligorecurrence**’ = relapsed oligometastatic disease
‘oligoprogressive’ = status after cytoreductive therapy



❑ ***These cohorts have probably different prognoses***

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The Oligometastatic State

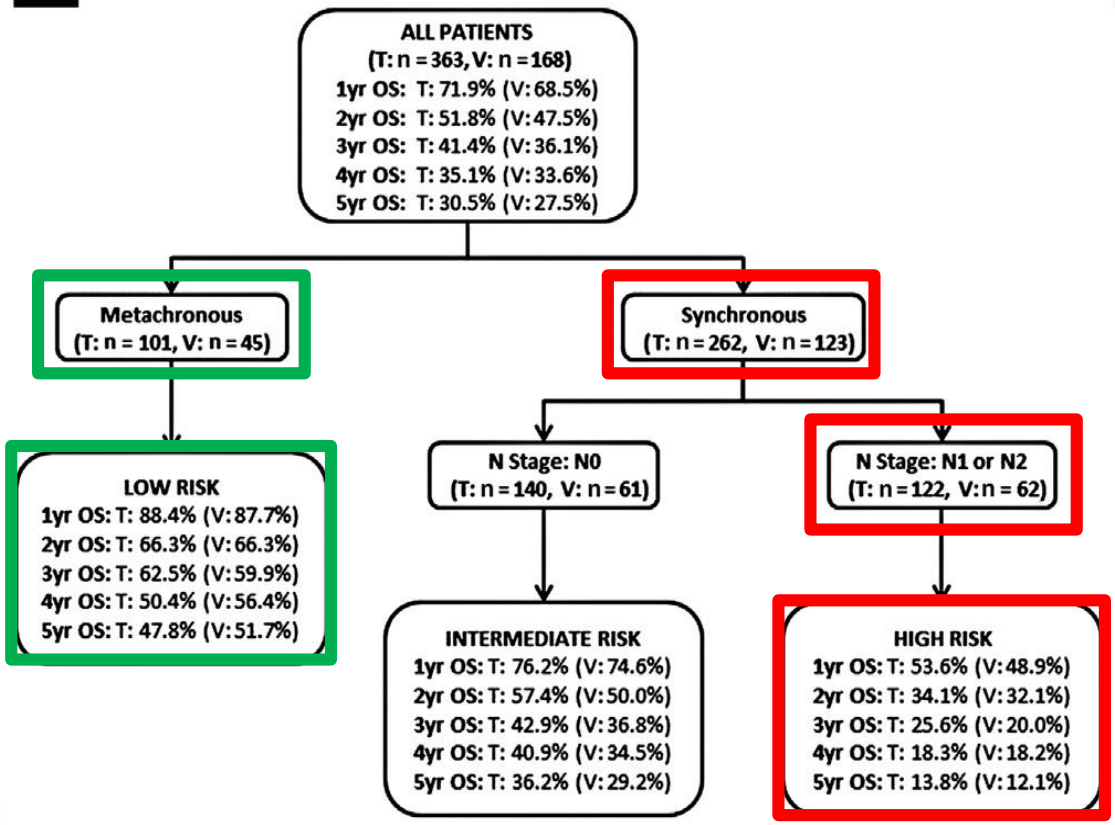
- In such a state of limited disease burden (≤ 5 mts), the **eradication of all sites** of metastatic disease with a **local therapy** (either surgery or radiotherapy) could result in **long-term survival** or even **cure** in a subgroup of pts
- This hypothesis is **based on long-term survival following** surgical **resection** of limited lung and liver metastases in some tumors
- Extracranial oligometastases are **different from intracranial oligometastases**, which represent an **established clinical entity** where surgery, radiotherapy, radiosurgery have defined roles supported by phase III RCT and detailed outcome analyses

An Individual Patient Data Metaanalysis of Outcomes and Prognostic Factors After Treatment of Oligometastatic Non–Small-Cell Lung Cancer

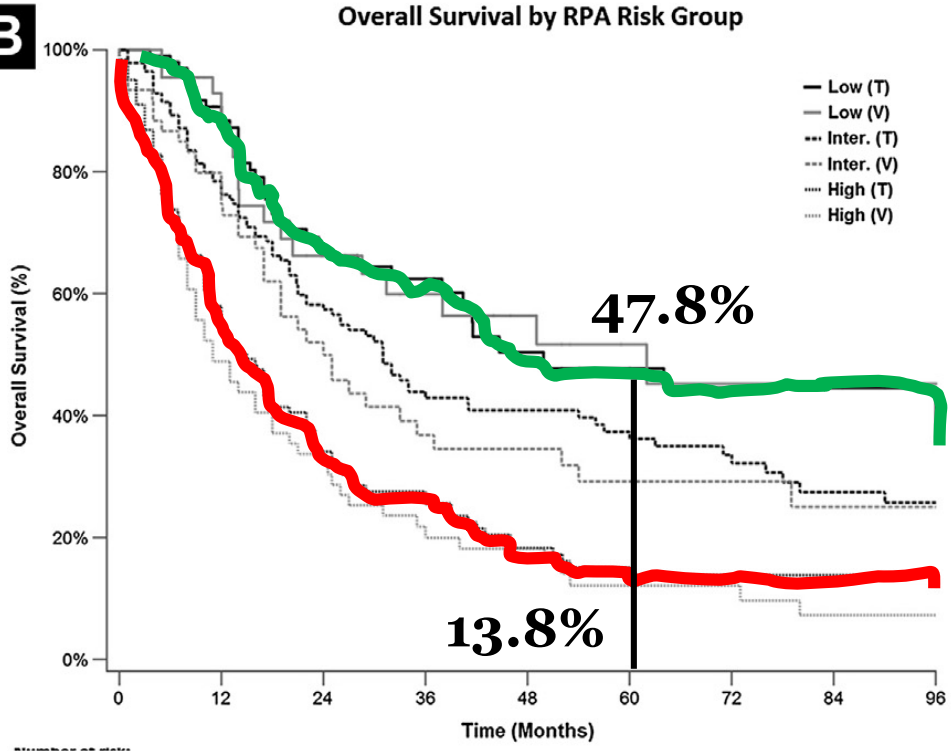
RPA OVERALL SURVIVAL

- 757 oligometastatic patients
- Training and validation cohorts
- Surgery to primary tumors: 83.9%
- Surgery to metastatic patients: 62.3%

A



B



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Ashworth A et al, Clin Lung Cancer 2014;15

Clinical applications of stereotactic radiation therapy for oligometastatic cancer patients: a disease-oriented approach

Umberto Ricardi*, Serena Badellino and Andrea Riccardo Filippi

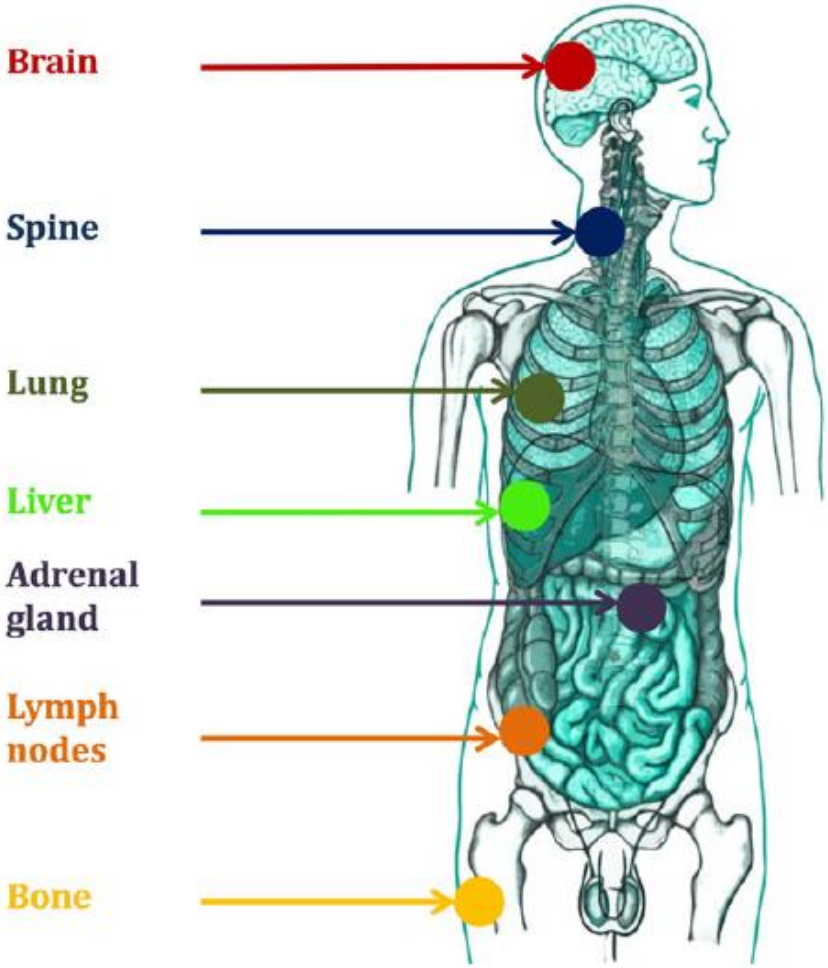
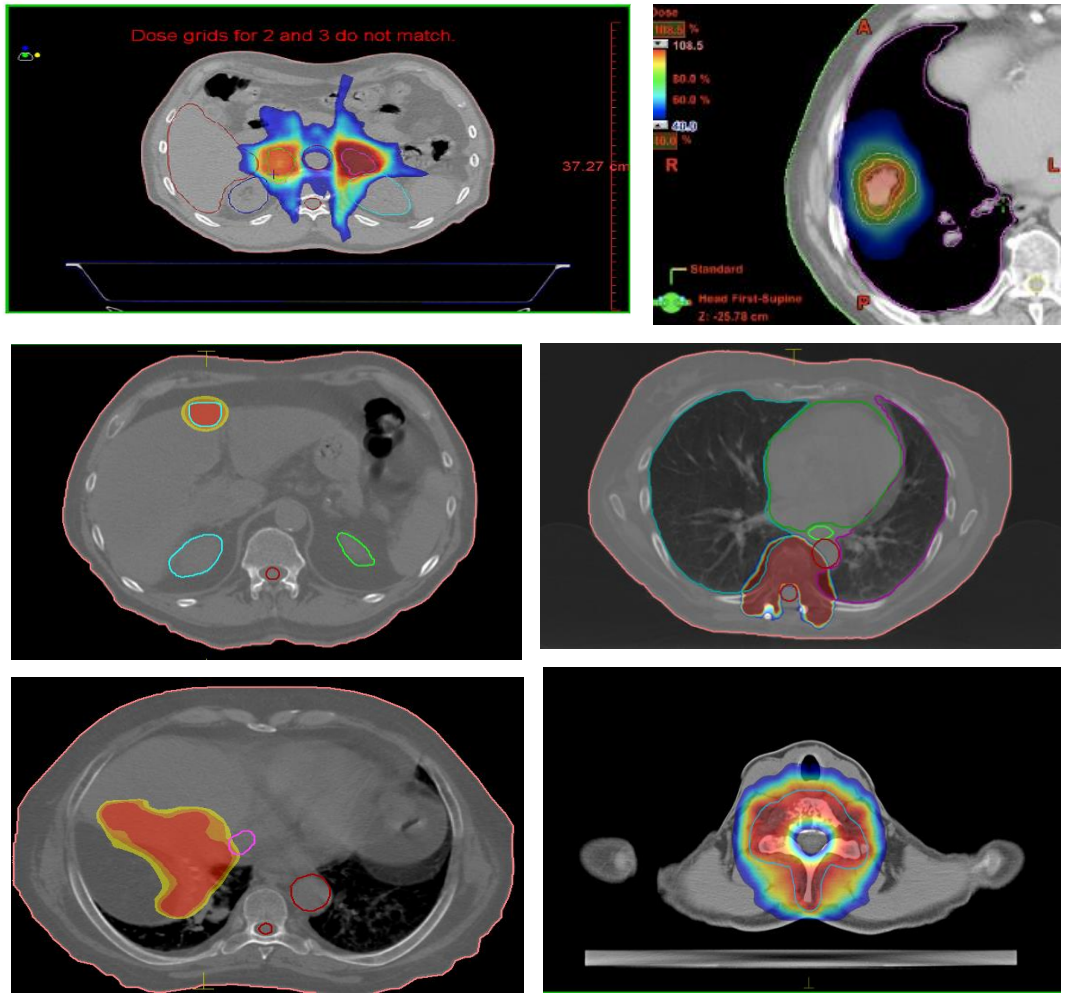


Fig. 1. Metastatic sites treatable with stereotactic radiotherapy.



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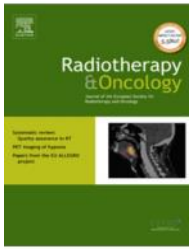
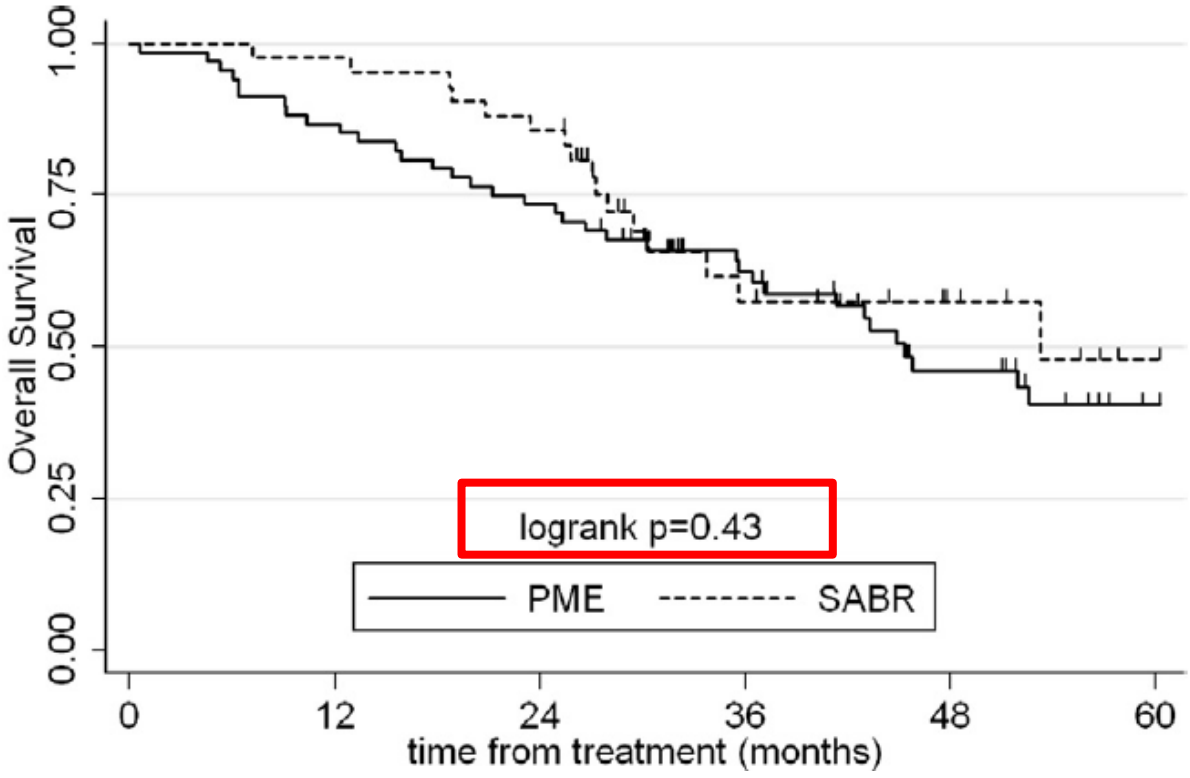
Pulmonary oligometastases: Metastasectomy or stereotactic ablative radiotherapy? ☆



SBRT vs Surgery: both equally (highly) effective in Oligometastatic disease



- 110 Consecutive patients
- 2007 and 2010
- *PME: first choice (68 pts)*
- *SABR: second best alternative (42 pts)*

- **3-ys OS years after SABR: 60%**
- **3-ys OS after PME: 62%**

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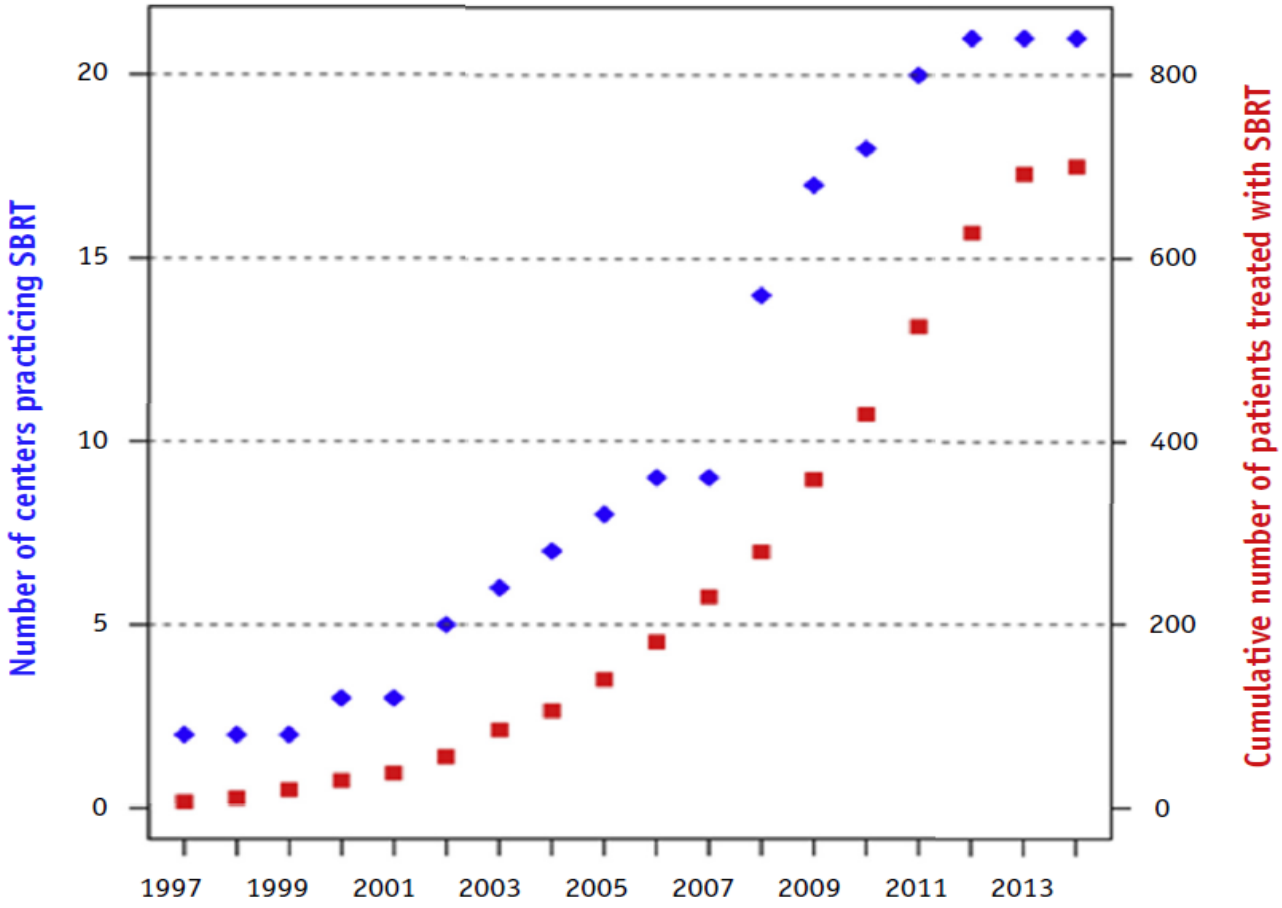
Widder et al. Radiot Oncol 2013

International Journal of Radiation Oncology biology • physics

www.redjournal.org

Influence of Institutional Experience and Technological Advances on Outcome of Stereotactic Body Radiation Therapy for Oligometastatic Lung Disease



- 700 patients
- All treated with SBRT
- 20 German centers
- 1997-2014

Rieber J et al, IJROBP 2017

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Oligometastatic NSCLC

- About **50%** of all patients with **NSCLC** present with **metastatic** disease at the time of **diagnosis**
- Platinum-based doublet **chemotherapy can improve** quality of life and extend **survival**, **but the prognosis** of patients with metastatic NSCLC remains **extremely poor**, with MST from 8 to 11 months
- Moreover, the **predominant pattern of failure** in patients with **localized NSCLC is distant** metastatic spread

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Oligometastatic NSCLC

- For patients with **NSCLC** and molecular **mutations or rearrangements** targeted with systemic therapy, metastatic **progression** **frequently** occurs in **limited number and location**

subgroup of patients who can enjoy significantly longer treatment responses and prolonged survival

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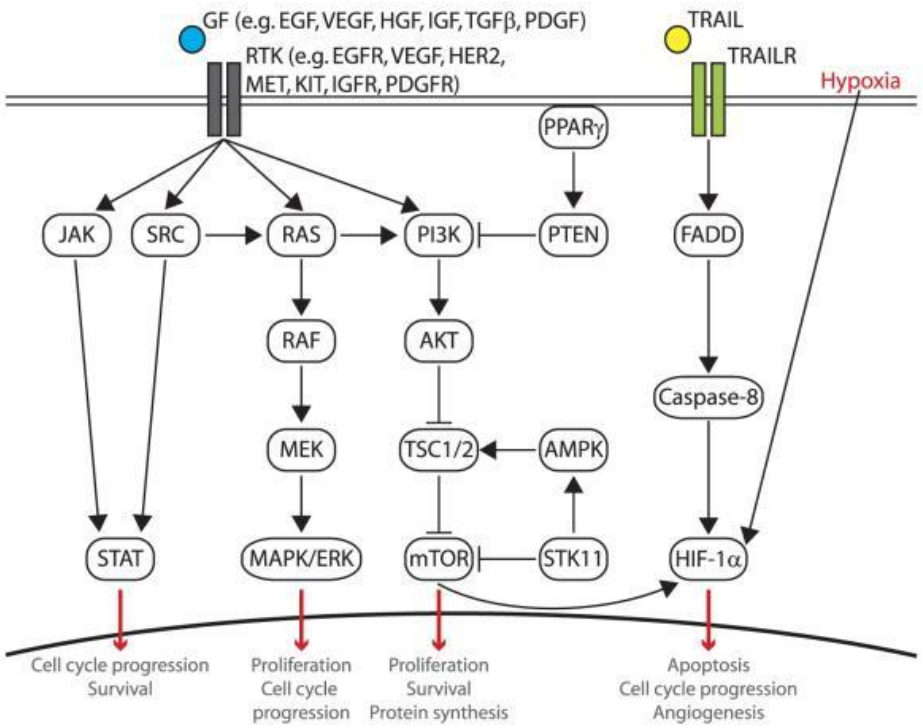
Targeted agents: Molecular vs Spatial



Larsen J, Cancer 2011

Great if you find an Achilles heel pathway
Eventually, some resistant cells emerge

Radiation Therapy:
Spatially targeted

All cells susceptible, given enough dose
Nearby normal tissue tolerance

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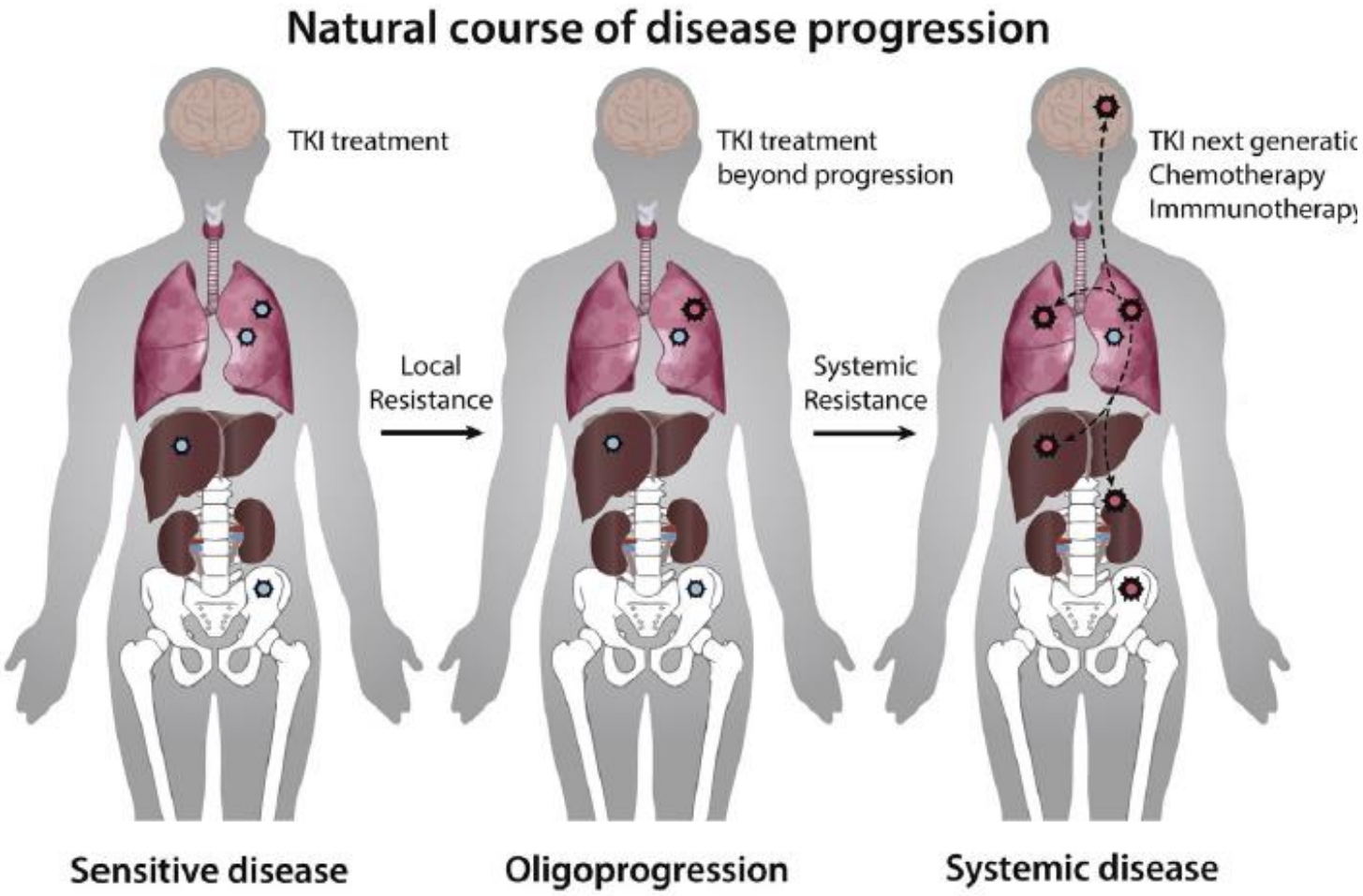
SBRT for oligoprogressive “oncogene addicted” NSCLC



Basler L et al, Lung Cancer 2017

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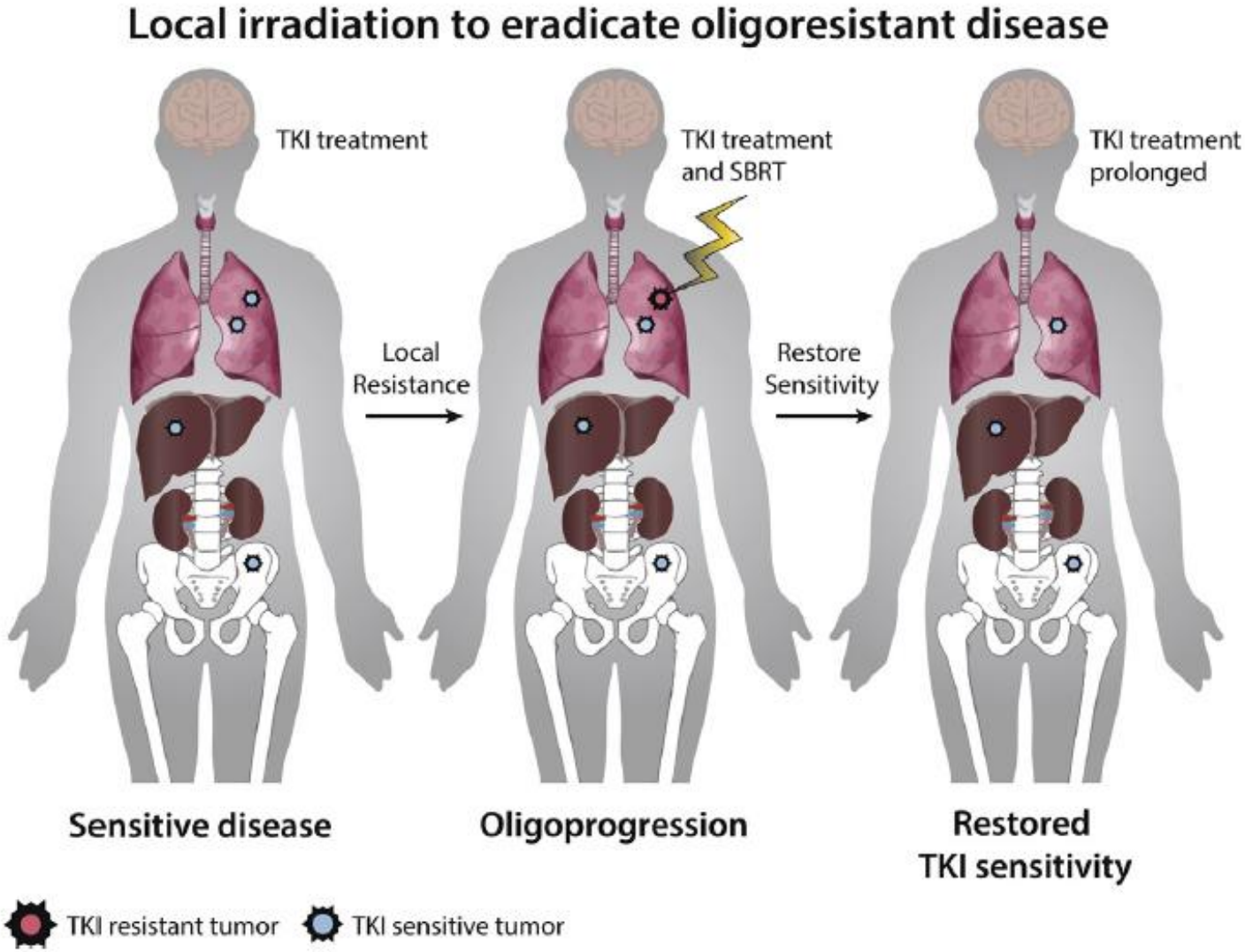
SBRT for oligoprogressive "oncogene addicted" NSCLC



Basler L et al, Lung Cancer 2017

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THE LANCET Oncology

Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study

- Phase II **randomized trial**, 49 patients enrolled
- Stage IV NSCLC, **3 or fewer metastases**
- Primary Endpoint: **PFS**
- First line therapy with 4+ platinum based doublet or 3+ months of EGFR or ALK inhibitors (if mutated)
- Patients randomly assigned to:

A. Local therapy →
- Hypofx RT or SBRT 48%
- Surgery and RT 24%
- Chemo-beam 8%
- Hypofx RT and chemo-beam 12%
- Surgery 4%

} **20% received Chemo-radiation**

B. Maintenance →
- Pemetrexed 67%
- Erlotinib 8%
- Afatinib 4%
- Bevacizumab 4%
- Observation 17%

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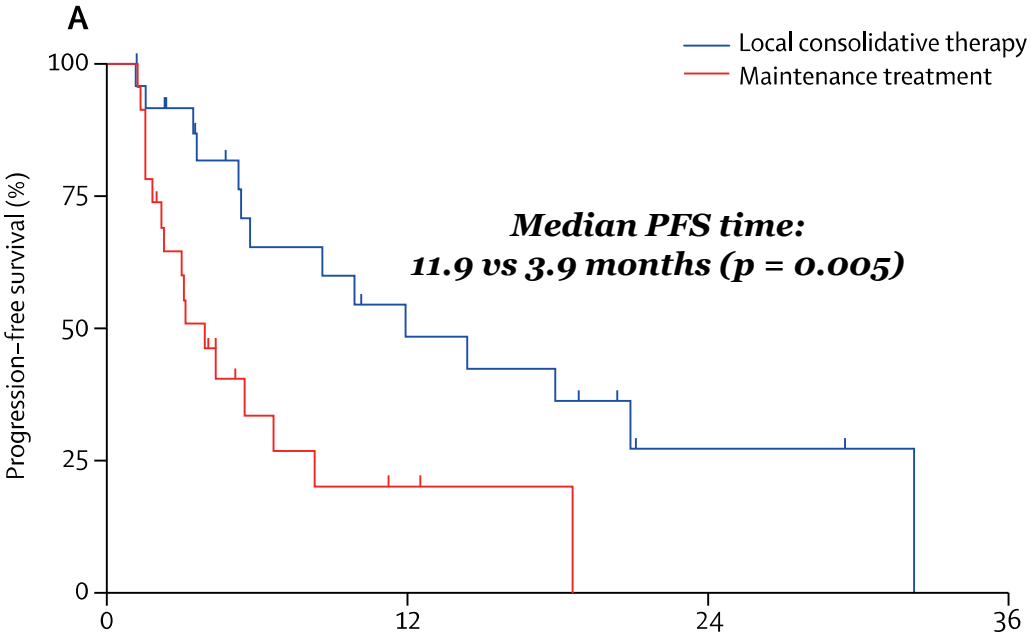
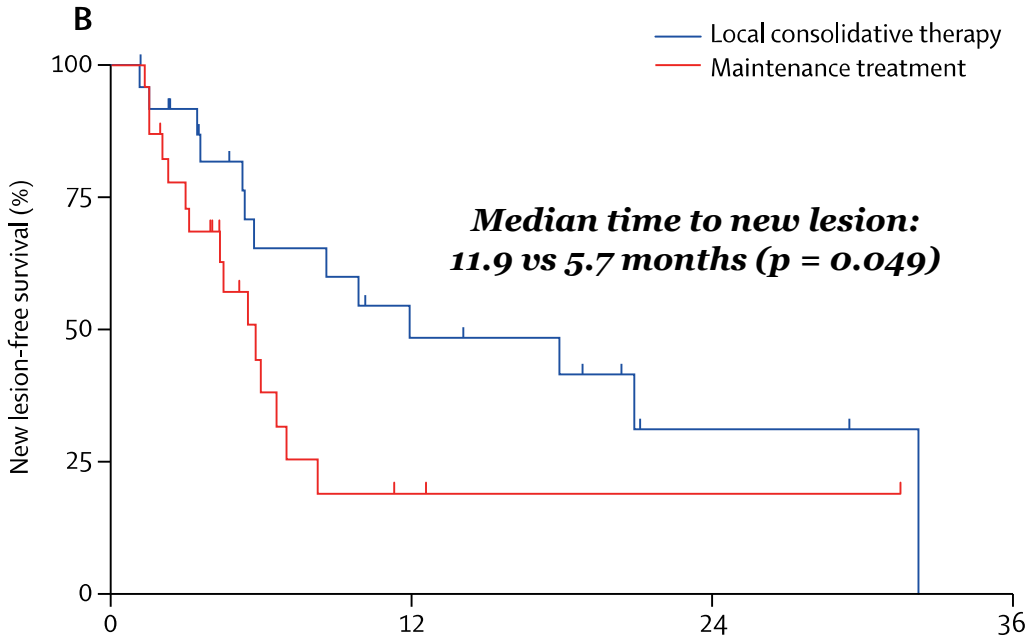
Gomez DR. et al. Lancet Oncol 2016

THE LANCET Oncology

Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study





- Local **consolidative therapy** with or without maintenance therapy for patients with **3 or fewer metastases** from NSCLC **improved PFS** compared with maintenance therapy alone.
- These findings suggest that **aggressive local therapy** should be **further explored in phase III trials** as a standard treatment option in this scenario

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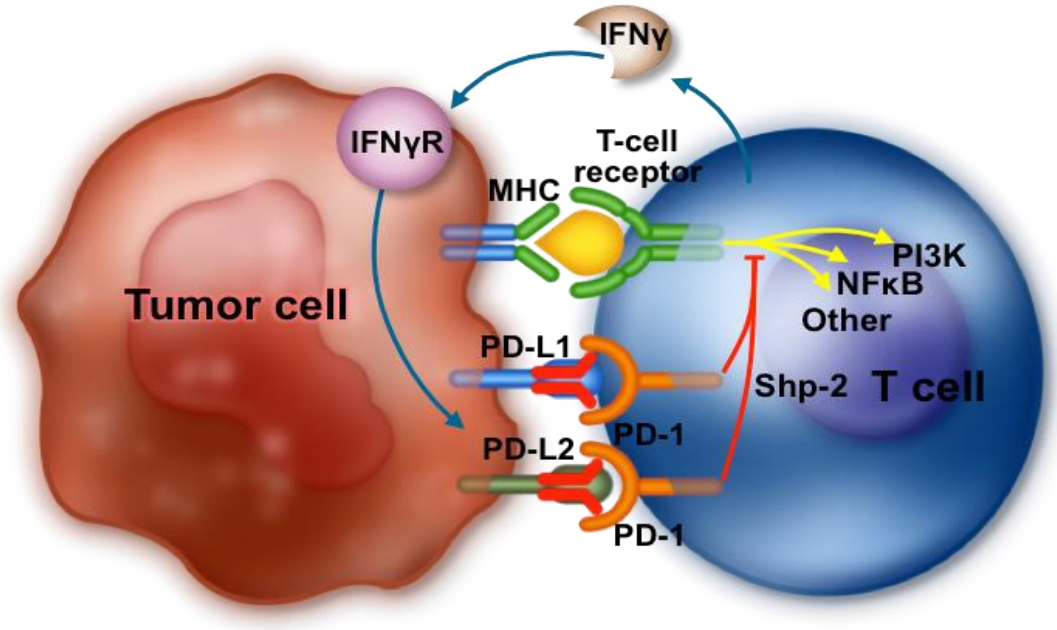
Gomez DR. et al. Lancet Oncol 2016

New agents: PD-1 Blockade:

- PD-1 engagement by its ligands results in transient down-regulation of T-cell function (T-cell exhaustion).
- Nivolumab (BMS) and Pembrolizumab (MSD) fully human/humanized anti-PD-1 antibody selectively blocking the PD-1 and PD-L1/PD-L2 interaction.



- PD-1 blockade through monoclonal antibody therapy has single-agent activity in a range of solid tumors

Brahmer et al, NEJM 2012;366 *Topalian et al, NEJM 2012;366*

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IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER
16TH WORLD CONFERENCE ON LUNG CANCER
SEPTEMBER 6–9, 2015 → DENVER, COLORADO, USA

Efficacy of Chemo-Radiotherapy in Stage III Non-Small Cell Lung Cancer (NSCLC) and PD-L1 expression

J. Adam, A. Boros, B. Lacas, L. Lacroix, J.-P. Pignon, C. Caramella, D. Planchard, A. Levy, B. Besse, C. Le Pechoux

Gustave Roussy, Villejuif, France

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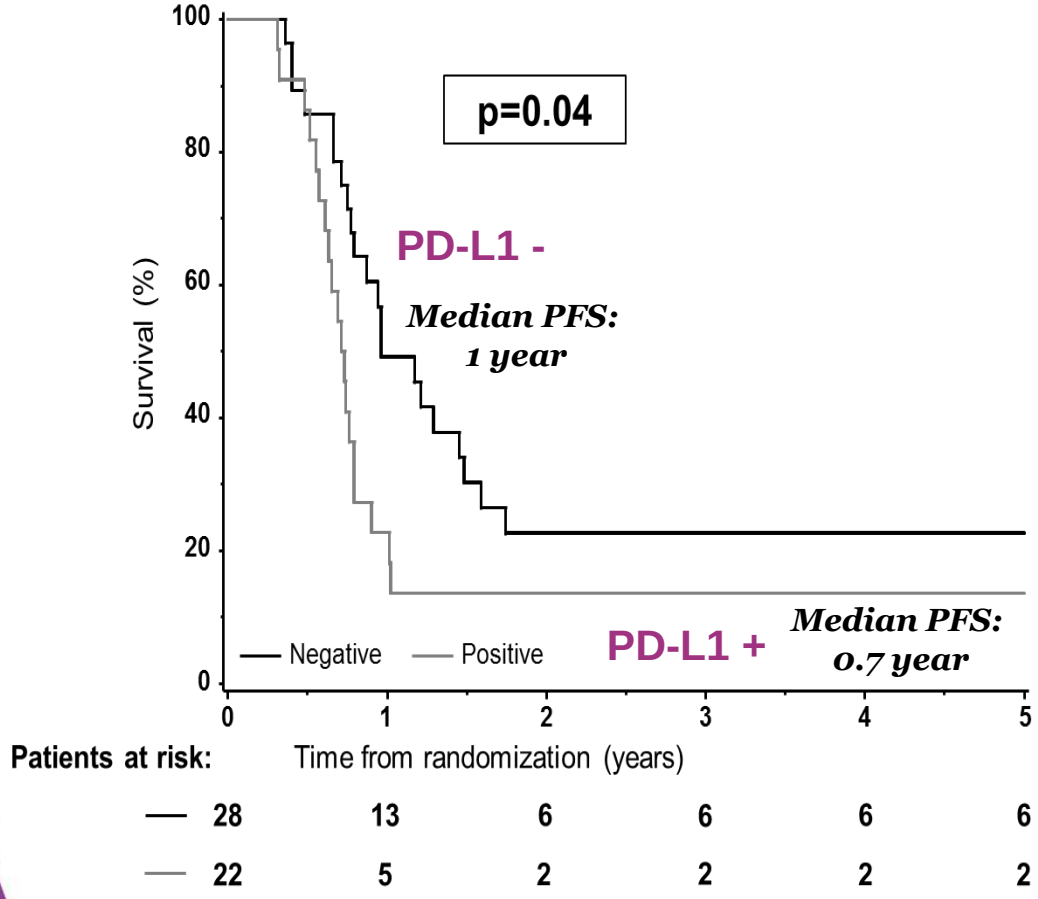
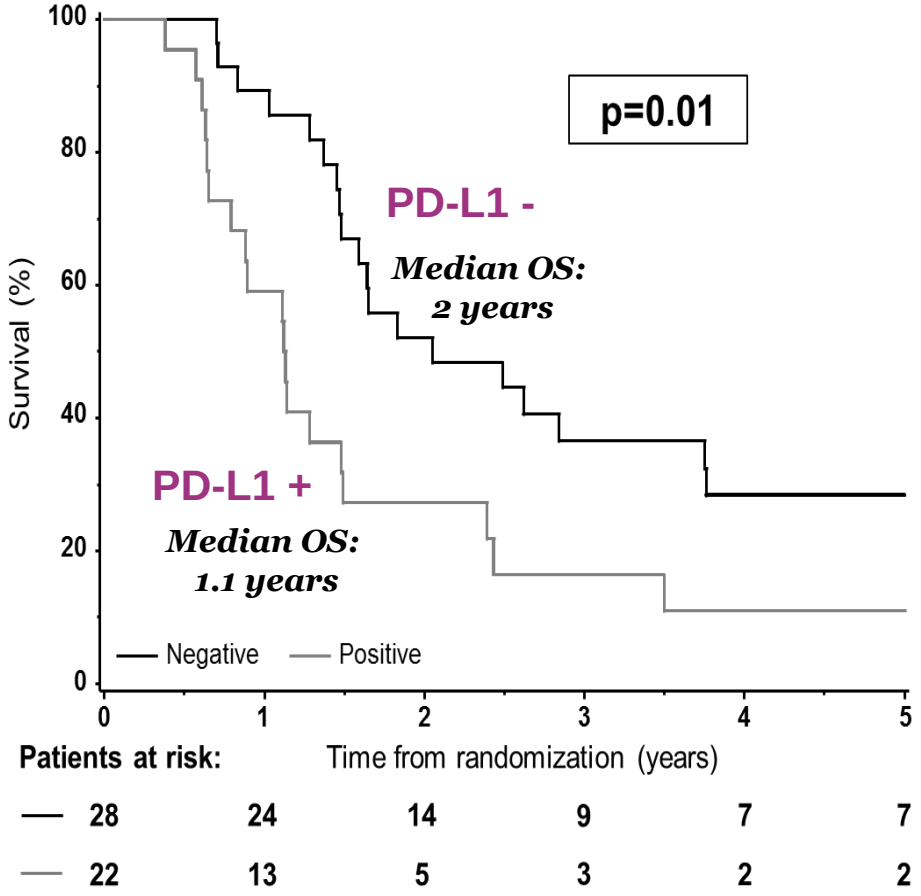
Efficacy of Chemo-Radiotherapy in Stage III Non-Small Cell Lung Cancer and PD-L1 expression

J Adam, A. Boros, B. Lacas, L. Lacroix, J.-P. Pignon, C. Caramella, D. Planchard, A. Levy, B. Besse, C. Le Pechoux

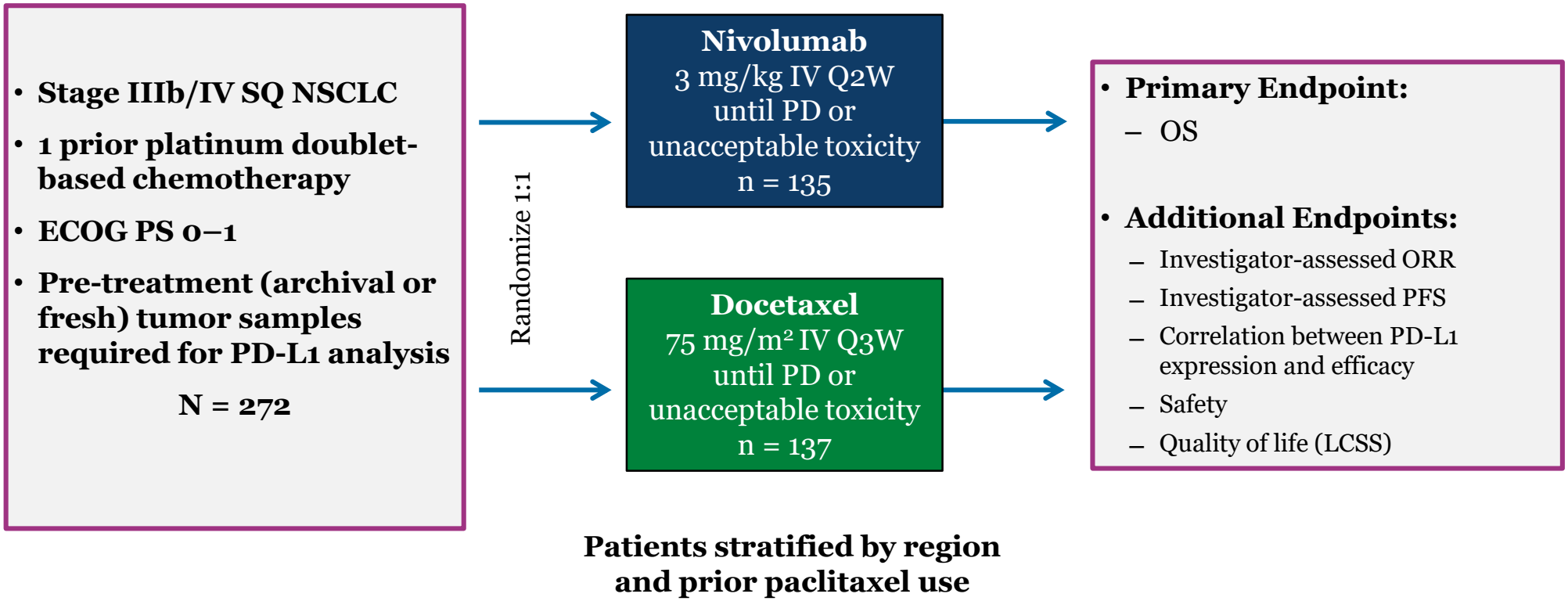
Progression free survival (PFS)



Overall survival (OS)



CheckMate 017 (NCT01642004) - Study Design



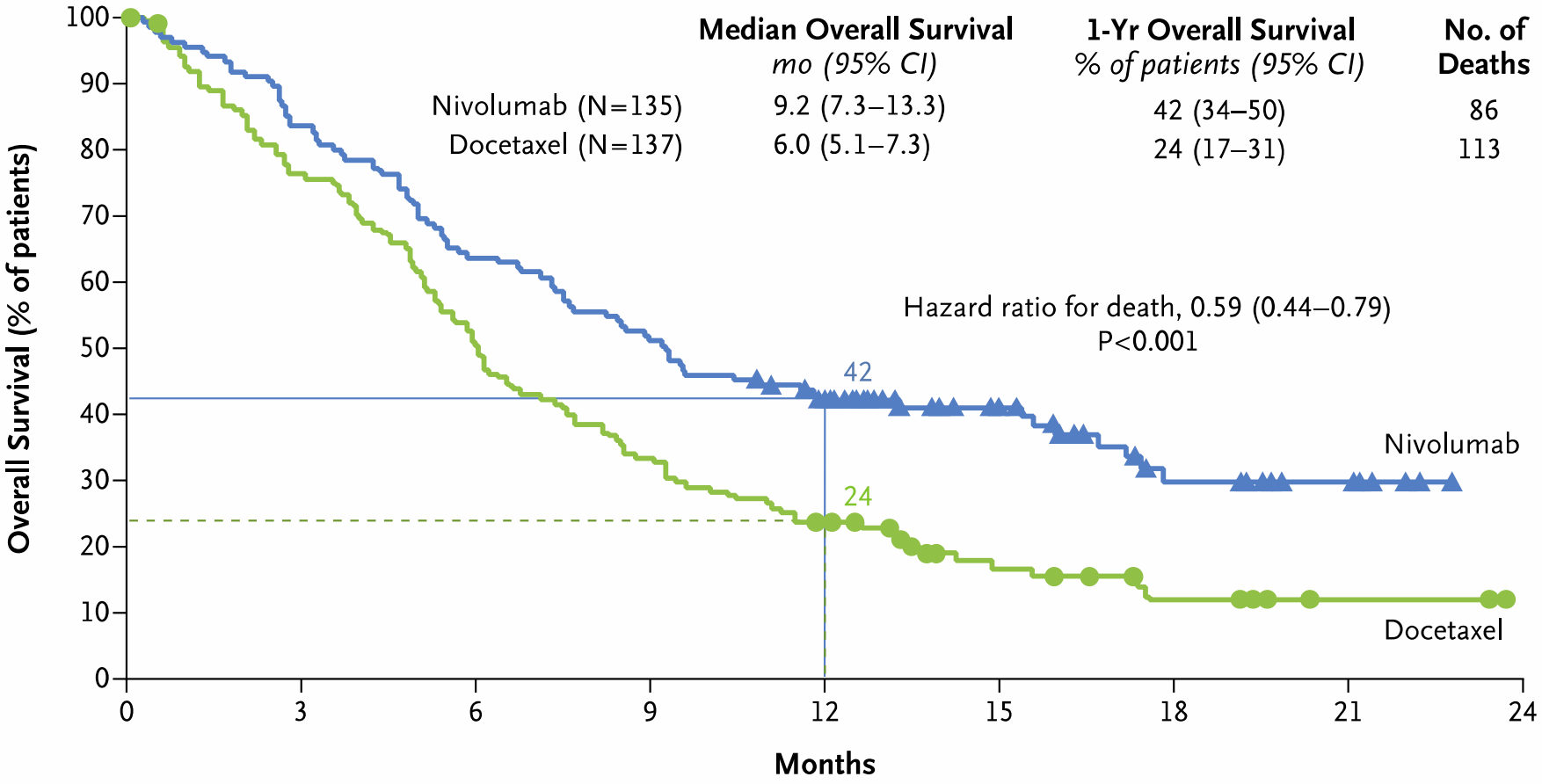
- One pre-planned interim analysis for OS
- At time of DBL (December 15, 2014), 199 deaths were reported (86% of deaths required for final analysis)
- The boundary for declaring superiority for OS at the pre-planned interim analysis was $P < 0.03$

LCSS = Lung cancer symptom scale

The NEW ENGLAND JOURNAL of MEDICINE

Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer

Nivolumab vs Chemotherapy in relapsed/refractory NSCLC



Brahmer J. et al. NEJM 2015,373

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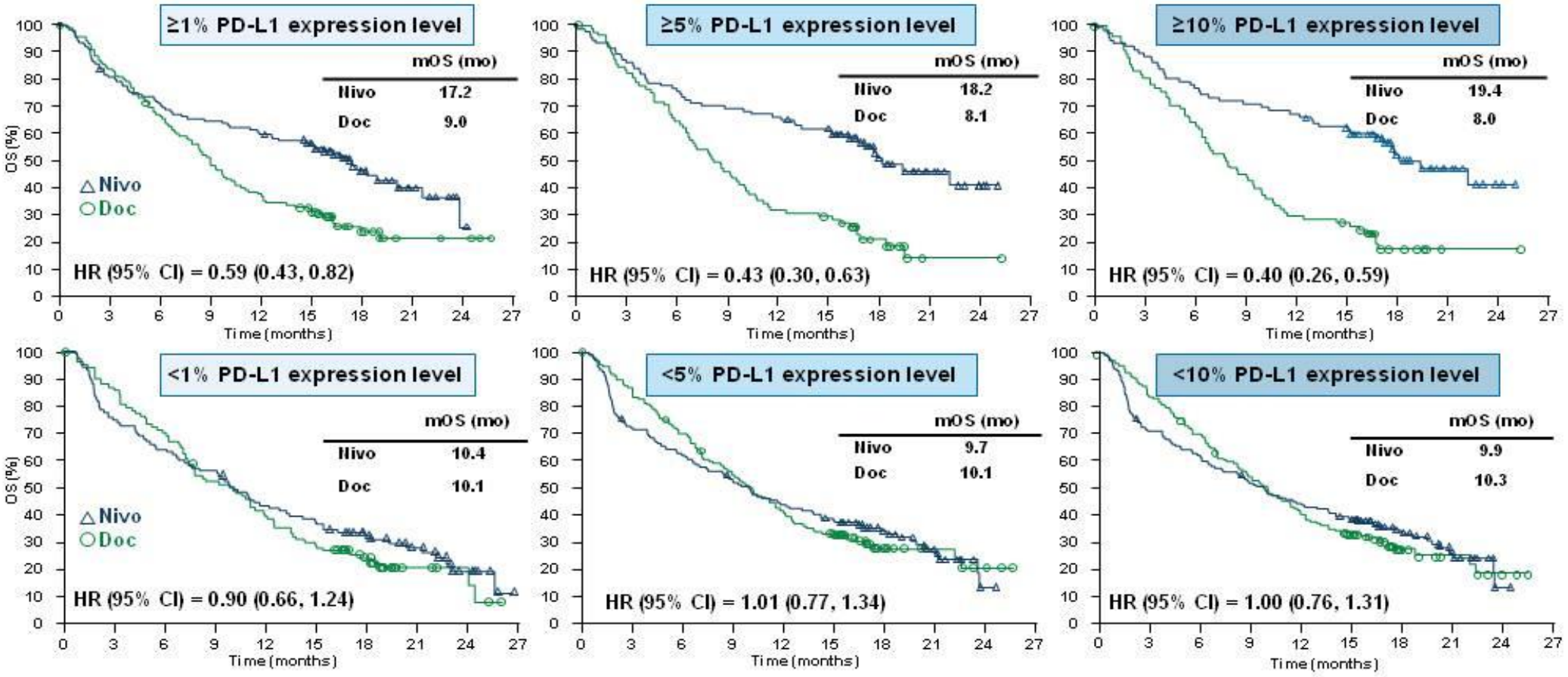
OS by PD-L1 Expression



Symbols represent censored observations.

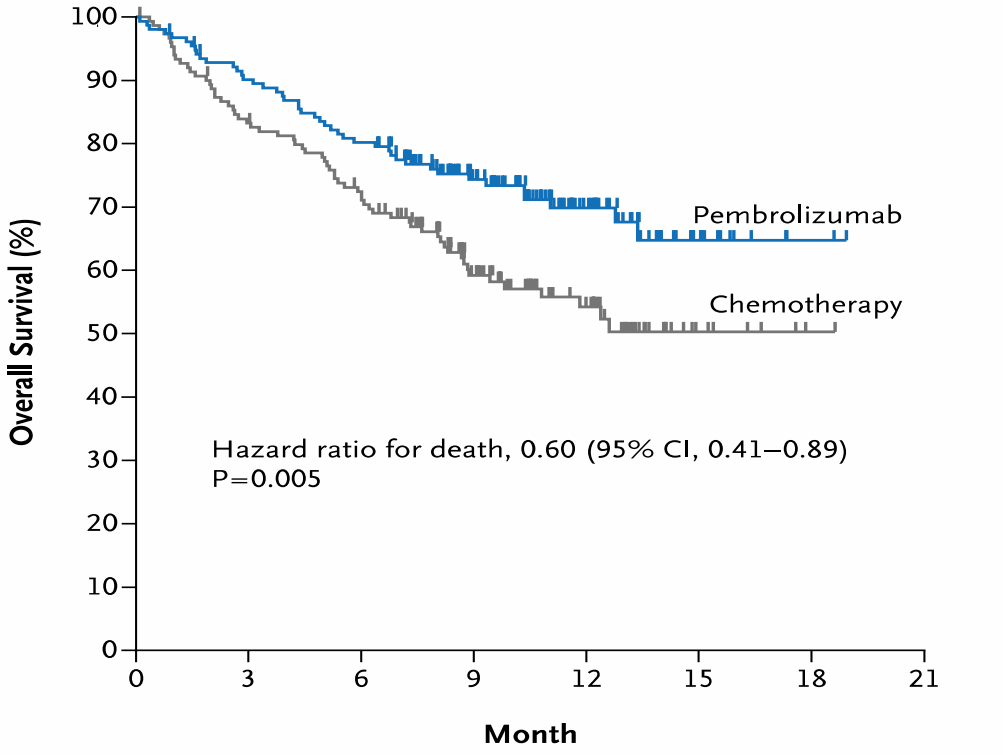
PRESENTED AT: ASCO Annual '15 Meeting

The NEW ENGLAND JOURNAL of MEDICINE

Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer

Keynote-024:

Pembrolizumab vs Chemotherapy as first line therapy in stage IV NSCLC



- Phase III trial
- Pembrolizumab vs Platinum based doublet
- 305 patients enrolled
- All patients had a **PD-L1 expression on at least 50% of the tumor cells**

Reck M. et al. NEJM 2016

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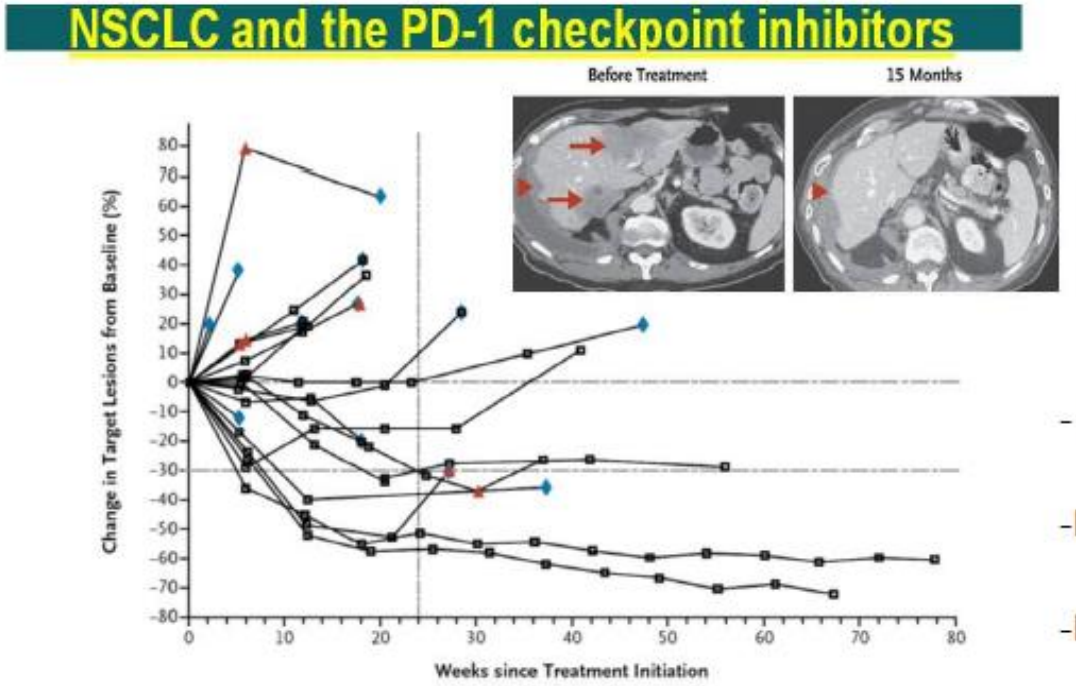
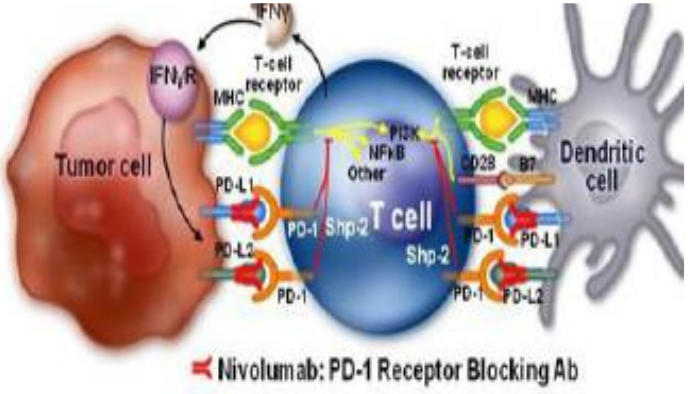
Immunotherapy: a less toxic approach
To increase treatment success rates in NSCLC



Topalian, S et.al. NEJM 2012, Brahmer J et al. NEJM 2012



- Biomarker?

-Role in first line?

-Role as adjuvant treatment?

- Combination with chemo?

- Combination with anti-CTLA4?

-Combination with radiotherapy ?

PD-1 inhibitors and RT

- **PD-L1** expression is a **prognostic factor** in resected NSCLC and a **predictive factor for efficacy** of therapies targeting PD-1 and PD-L1 in metastatic NSCLC.
- The **prognostic value of PD-L1** expression in patients with NSCLC treated with radiotherapy **(RT) and** chemotherapy **(CT)** has **not been explored**.
- Tumor **immune microenvironment is involved** in mechanisms underlying **efficacy of RT and CT**, suggesting that PD-L1 expression may modulate response to these treatments.

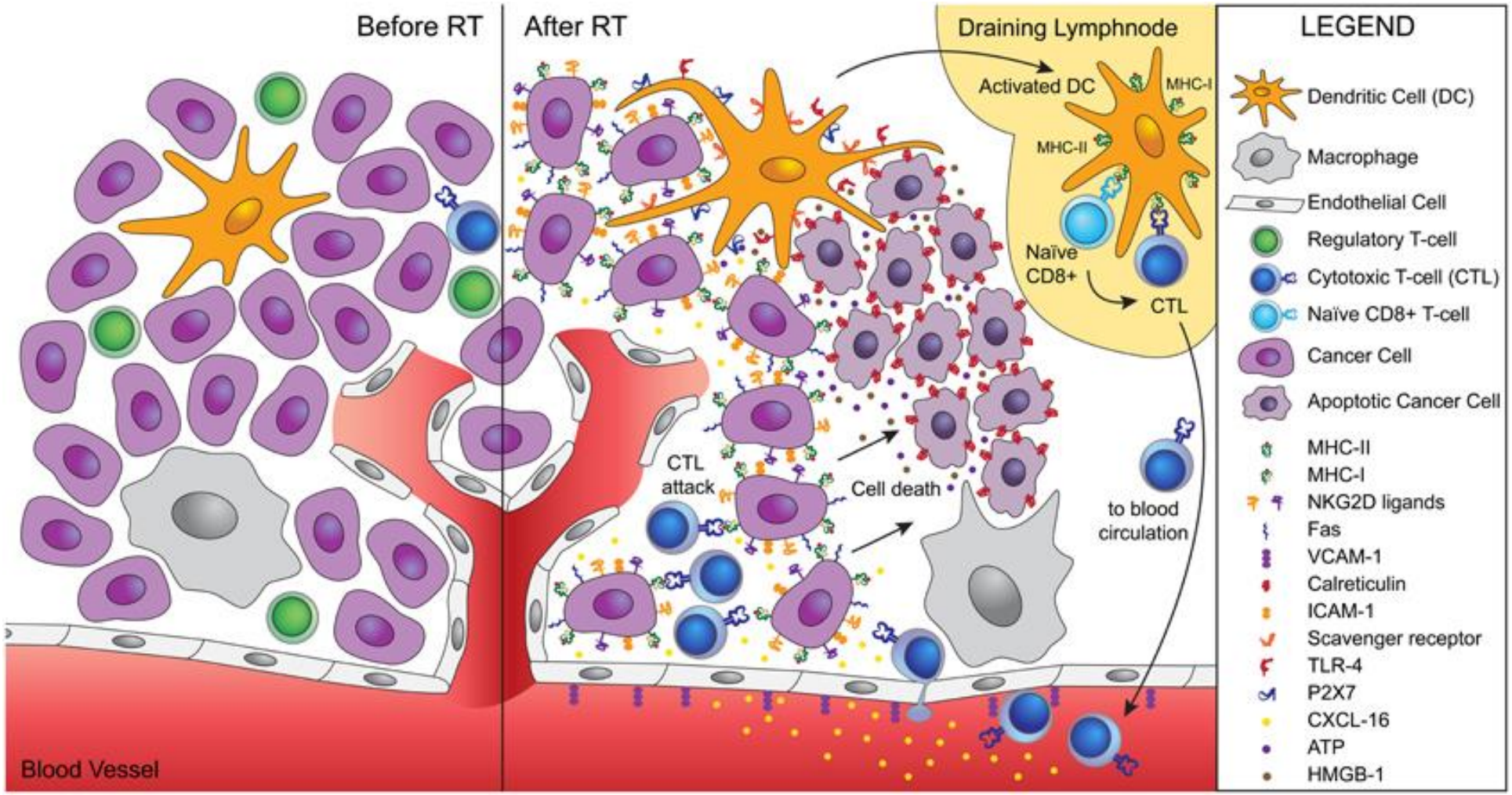
Randomized data needed due to lack of historical baseline and recent stage migration

Rationale for combining RT and immunotherapy

- **Mechanism: spatial and biologic cooperation , temporal modulation**

  - RT induced release of tumor antigens leading to activation of the immune system
  - RT induced expression of PDL1
  - RT induced bystander (abscopal) effect
  - RT+IT increases CD8+ T cells

Ionizing radiation acts as a modifier of the tumor microenvironment converting the tumor into an "*in situ* vaccine".



De Maria & Formenti, Front Oncol 2012

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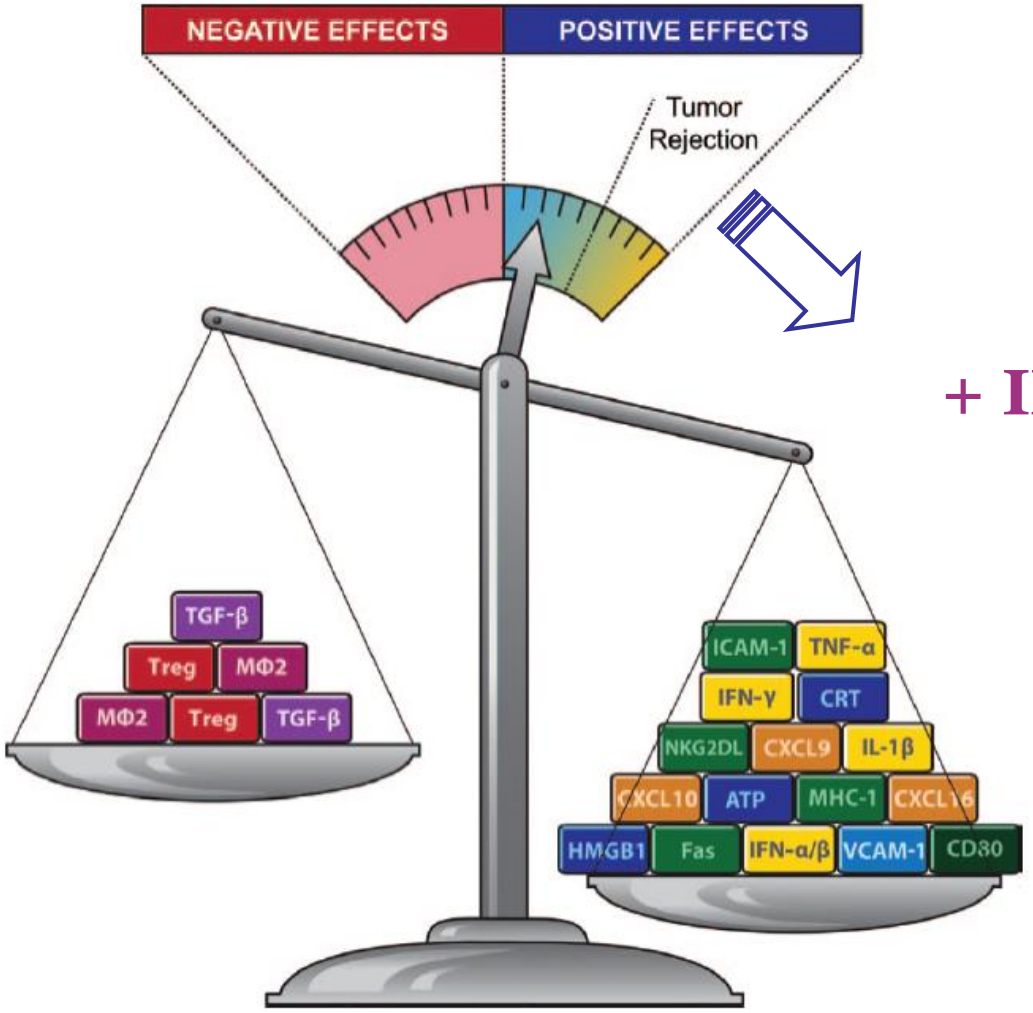
Harnessing Radiation to Improve Responses to Immunotherapy



+ IMMUNOTHERAPY

Formenti et al, JNCI 2012

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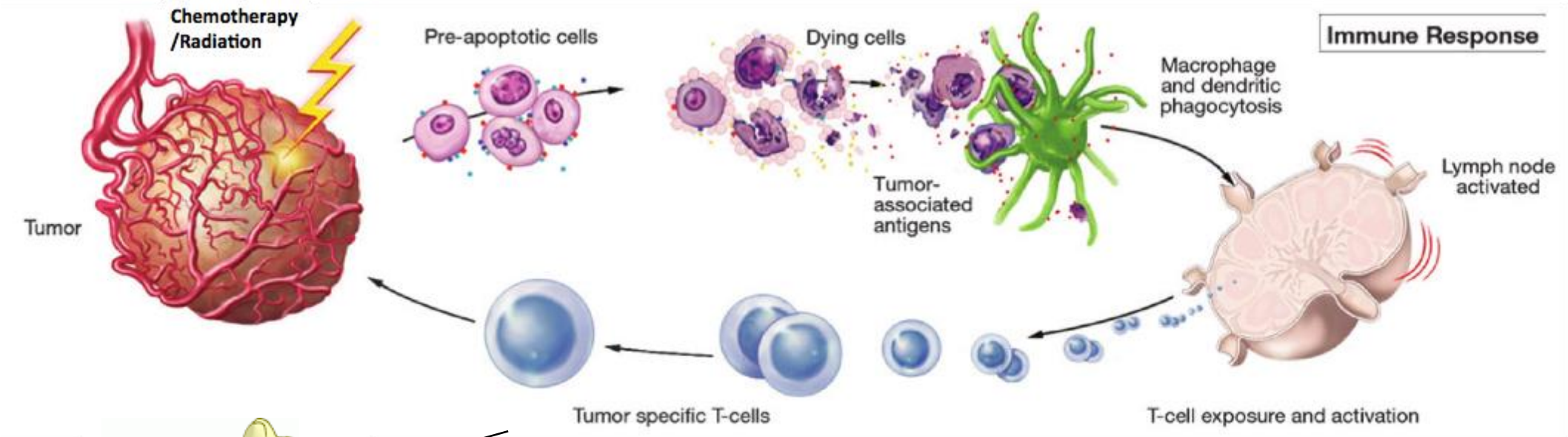
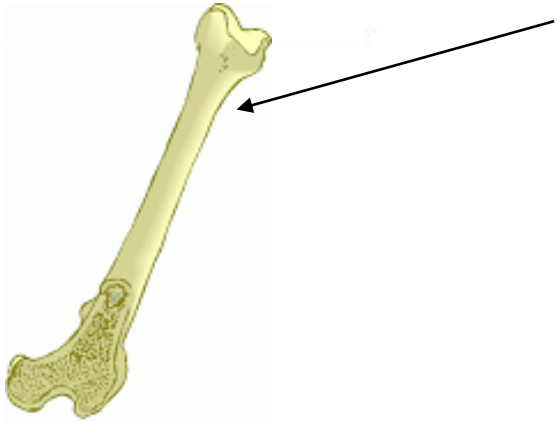
The “vaccine role” of RT may induce the abscopal effect





Bone metastases

Modified from Kamrava et al, Molecular BioSystems 2009

Take Home Message for Oligometastatic NSCLC

- A **combination** of chemo or immunotherapy + local therapies could **probably improve patients outcome** in this setting, at least in selected subgroups
- **Phase III trials are warranted** to confirm the effectiveness of a multimodality approach in this setting.
- In the meantime…

Unity Makes Strength…!

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WWW.ESTRO.ORG/SCHOOL

COMBINED DRUG-RADIATION TREATMENT: BIOLOGICAL BASIS APPLICATIONS AND PERSPECTIVES

15-18 June, 2017
Brussels, Belgium

SCLC

Mario Levis
Radiation Oncologist
University of Torino, Italy

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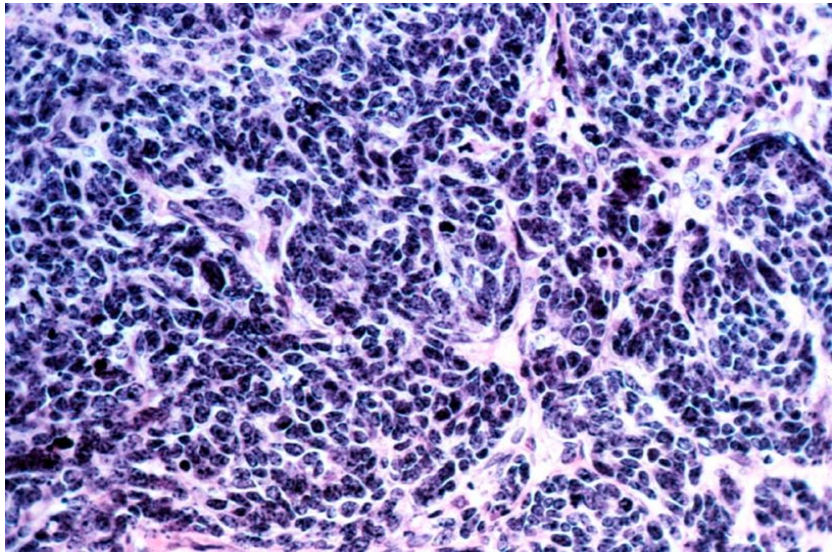
Small Cell Lung Cancer (SCLC)

- Reduced incidence (from 25-30 to 13-15%)
- Strongly associated with cigarette smoking
- Neuroendocrine features
- High frequency of *TP53* and *RB* gene mutations
- Highly responsive to CT and RT
- High rate of early relapse/PD
- Highly aggressive
- Often metastasized at the time of diagnosis
- Poor cure-rate (10-20%) and overall
- prognosis (MS 9-12 months)



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Neuroendocrine tumors of the lung

	Carcinoid	Atypical Carcinoid	LCNEC	SCLC
Mitoses/2mm² (10 HPF)	<2	2-10	>10	>10
Smoking	33% (general population)	64%	98%	**97%**
5 YR OS	92-100%	61-88%	13-57%	**5%**
Prevalence	1-2%	0.1-0.2%	1.6-3%	15%
TP53 mutation	6%	-	74%	**90%**
RB1 down-regulation	0%	21%	68%	**87%**
MEN mutation	18%	36%	0%	0%

Beasley et al. *Human Pathol*, 2003
Haruki et al. *Jpn J can cer* Res, 2000
Adapted from Swarts et al. *BBA-Rev on Cancer*,2012

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SCLC/LCNEC: State of the art treatment

- **Platinum** (either cis or carbo) **combination chemotherapy** (i.e cis/carbo-etoposide) x 4-6 courses q 3 weeks **"standard of care"** 1st line therapy for **both LD and ED**
- **Combined chemotherapy** and thoracic **radiotherapy** (preferably early concurrent) **standard of care for LD**
- **Possible** role of upfront **surgery** in very limited disease
- Second line therapy: Topotecan o CAV or PE-rechallenge based on treatment-free interval (refractory vs sensitive disease)
- **PCI** for pts with both **LD or ED** with **good response** to 1st line therapy
- **Thoracic irradiation in ED** ?

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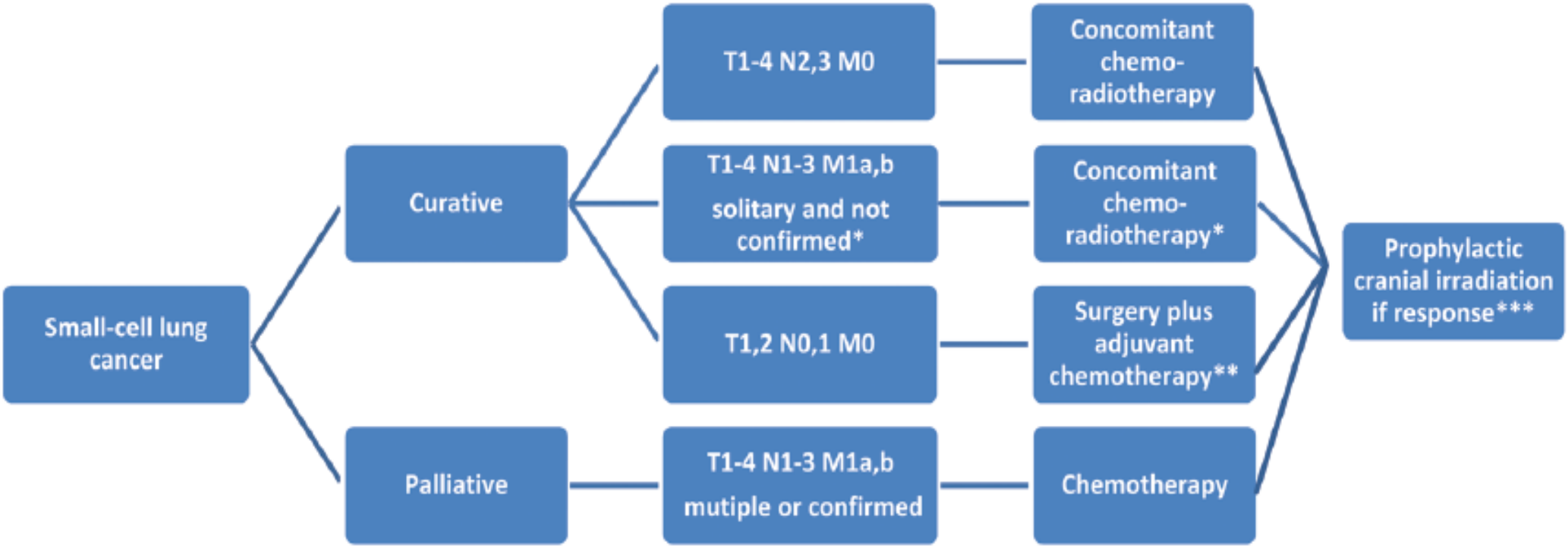
Annals of Oncology 00: 1–7, 2013
doi:10.1093/annonc/mdt178

Small-cell lung cancer (SCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

M. Früh[1], D. De Ruysscher[2], S. Popat[3], L. Crinò[4], S. Peters[5] & E. Felip[6], on behalf of the ESMO Guidelines Working Group*

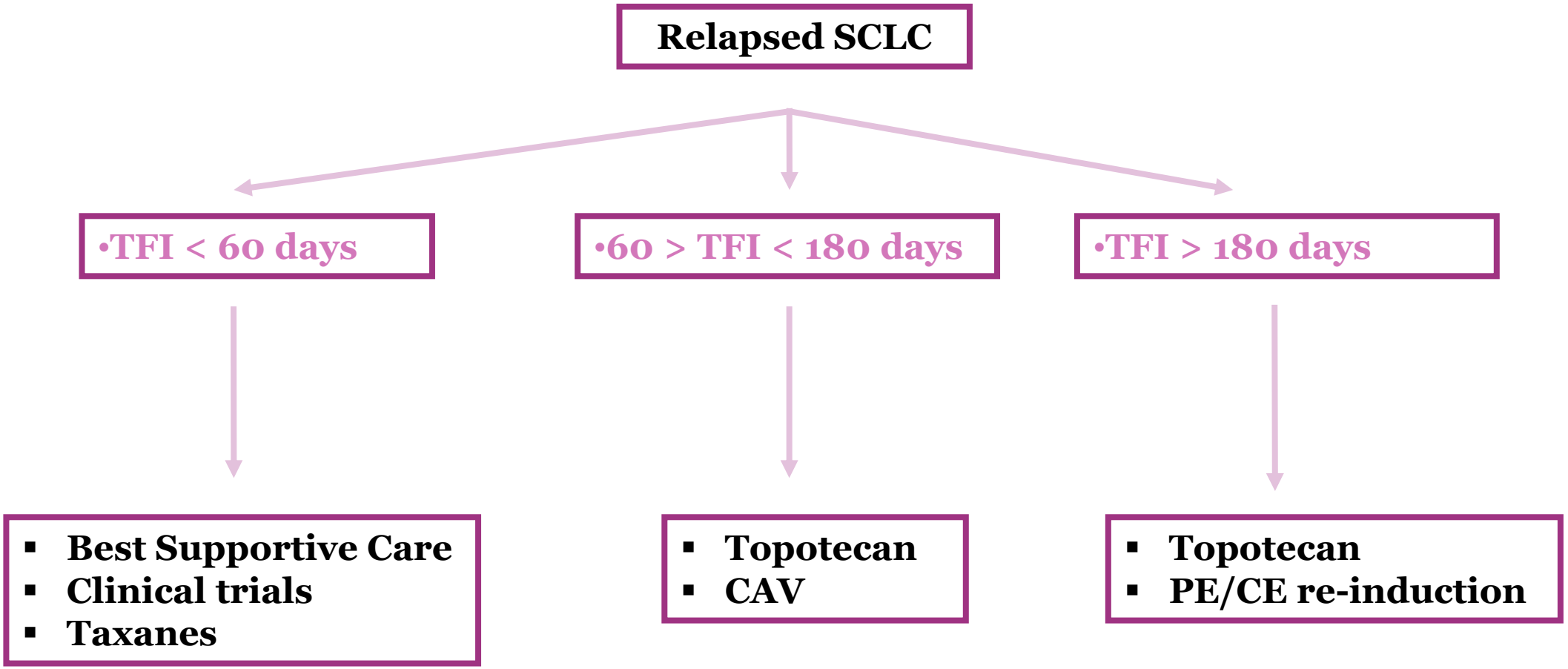


***if no confirmation of solitary metastasis is obtained, radiotherapy may be added after first response evaluation and is omitted in case of obvious metastatic involvement**

**** concomitant chemoradiotherapy as an alternative option**

***** or stable disease in case of localised disease**

Standard treatment of relapsed SCLC



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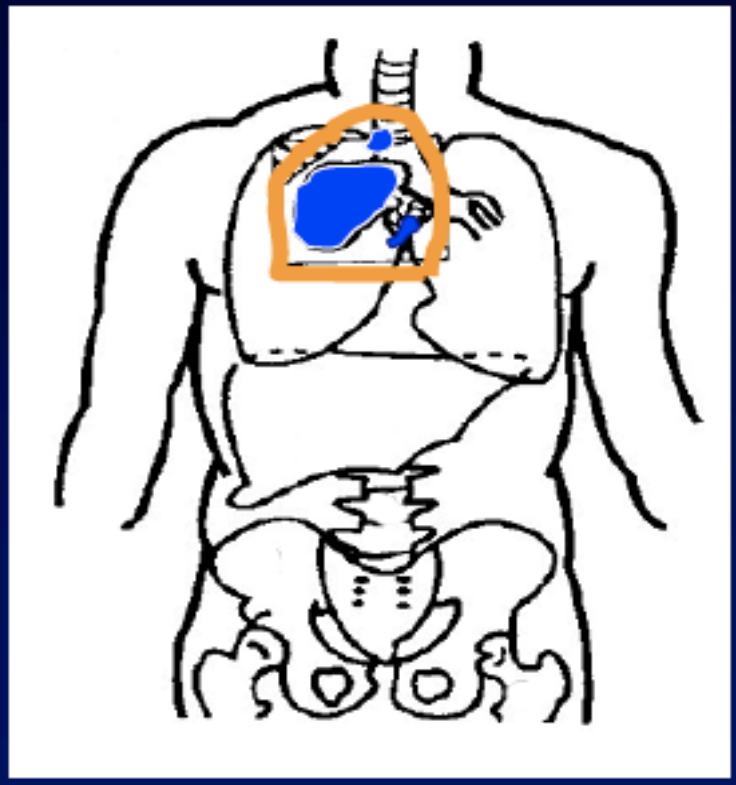
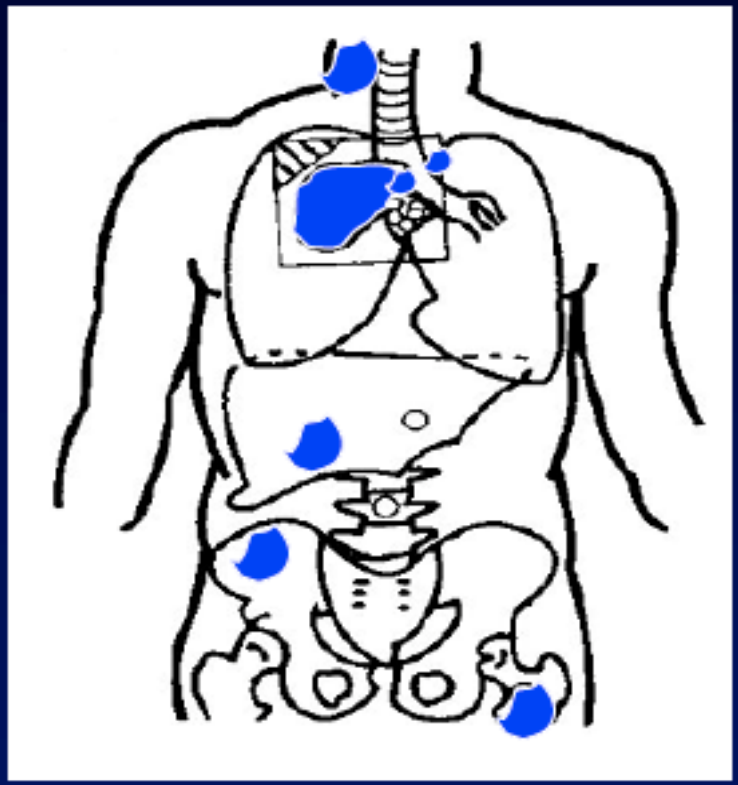
SCLC: staging



Limited disease (LD)



Extensive disease (ED)

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SCLC and radiation therapy

- **LIMITED DISEASE:** disease limited to the chest and capable of inclusion with a reasonable radiotherapeutic portal

- **EXTENDED DISEASE:** disease outside the chest or not capable of inclusion with a reasonable radiotherapeutic portal

LIMITED DISEASE

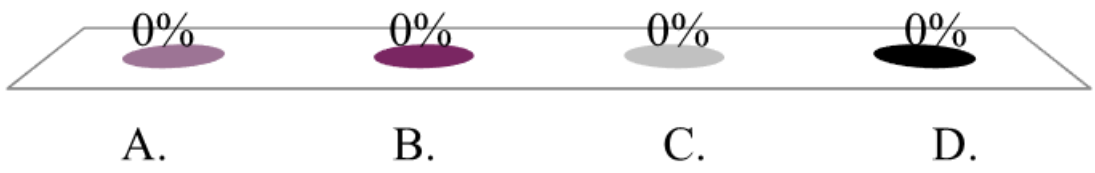
A colleague has referred to you a 62 year old male patient in excellent clinical conditions (ECOG PS 0) affected with LD-SCLC.
No comorbities. Which is the best treatment strategy for this patient ?

A. **Chemotherapy alone (Cisplatin + Etoposide x 4-6 cycles)**

B. **Chemotherapy (Cisplatin + Etoposide) + thoracic RT (60 Gy)**

C. **Chemotherapy (Cisplatin + Etoposide x 4 cycles) + thoracic RT (60 Gy) + Prophylactic cranial irradiation if patients responds to CMT.**

D. **Chemotherapy (Cisplatin + Paclitaxel x 4 cycles) + thoracic RT (60 Gy) + Prophylactic cranial irradiation if patients responds to CMT.**



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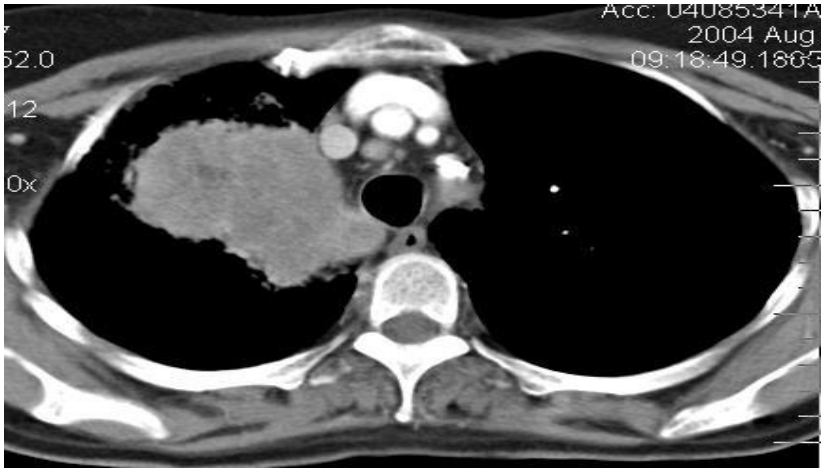
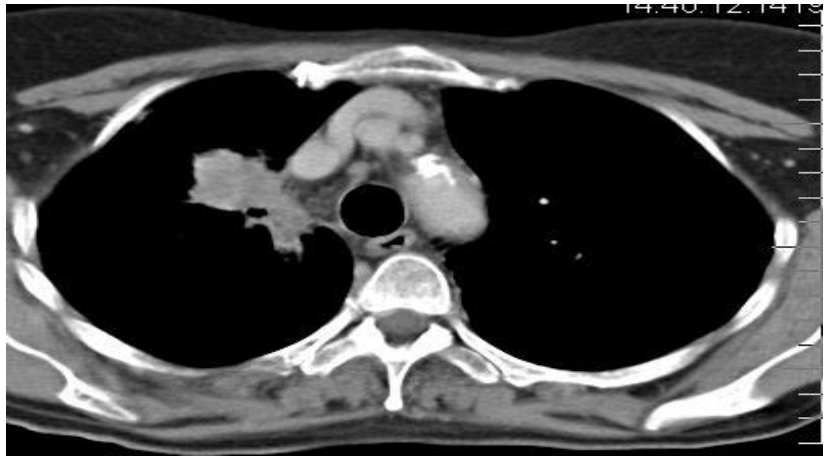
LD-SCLC

- The disease is “limited” in 20% of patients (TNM IASLC classification probably better)
- Is a systemic disease
- Surgery has a limited role
- CT is the mainstay of treatment and RT is the most important local therapy

Before treatment
(Chemo-radiotherapy)



After treatment
(Chemo-radiotherapy)



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Chemotherapy Regimens

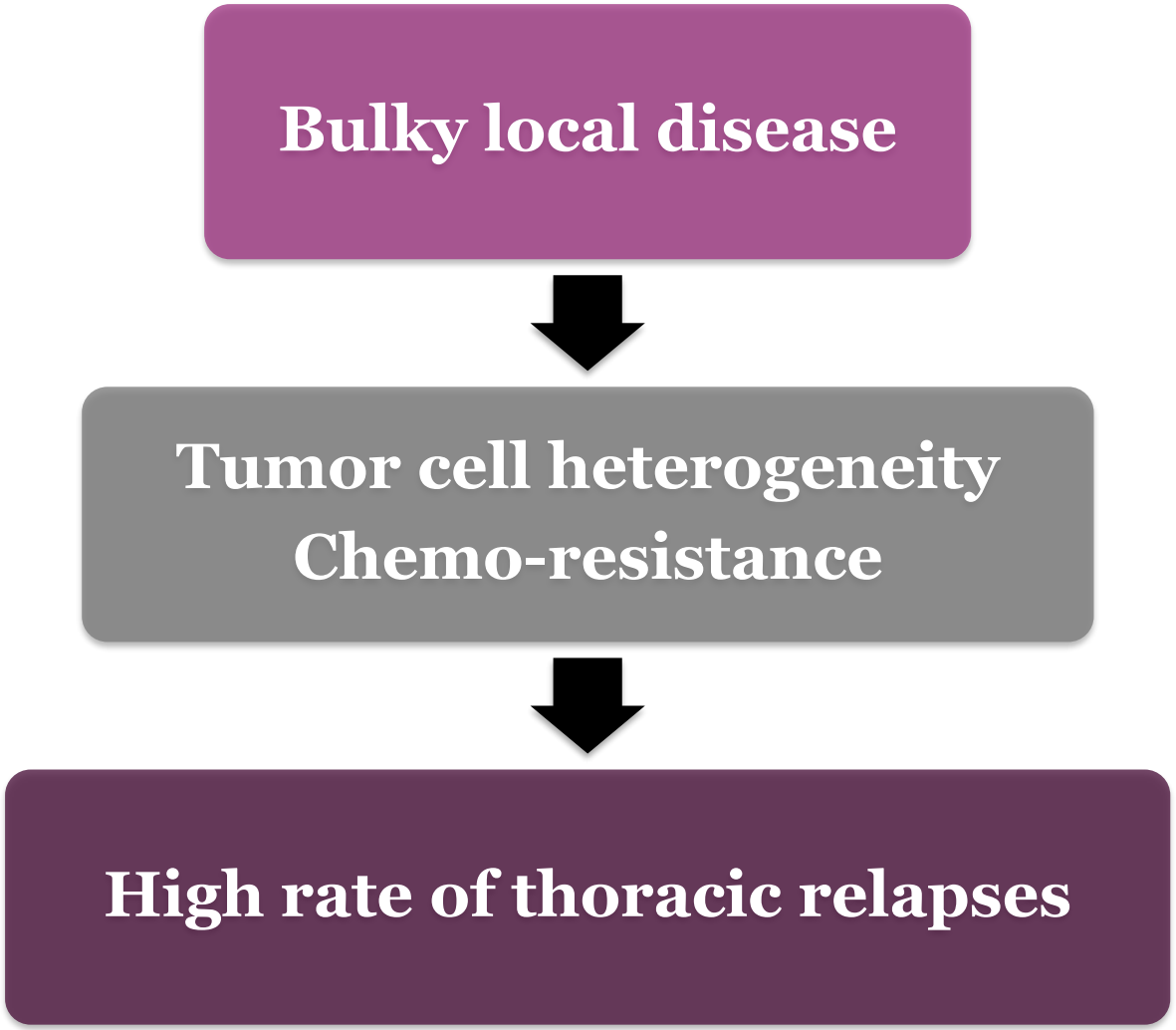
- **EP** (Etoposide Cisplatin)
- **CAV** (Cyclophosphamide/Doxorubicin/Vincristine)
- **IP** (Irinotecan/Cisplatin)

All these regimens are considered standard therapies, but EP is largely preferred because can easily be integrated with TRT

Small cell lung cancer: treatment outcomes

	LD	ED
Response rate (CR + PR)	80-90%	70-80%
Complete response	50-60%	20-30%
Median survival	12-16 mos.	8-10 mos.
Long-term survival	5-10%	<1%

LD-SCLC: rationale for thoracic irradiation (TRT)



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Metanalysis of 13 studies on the role of thoracic RT in LD-SCLC

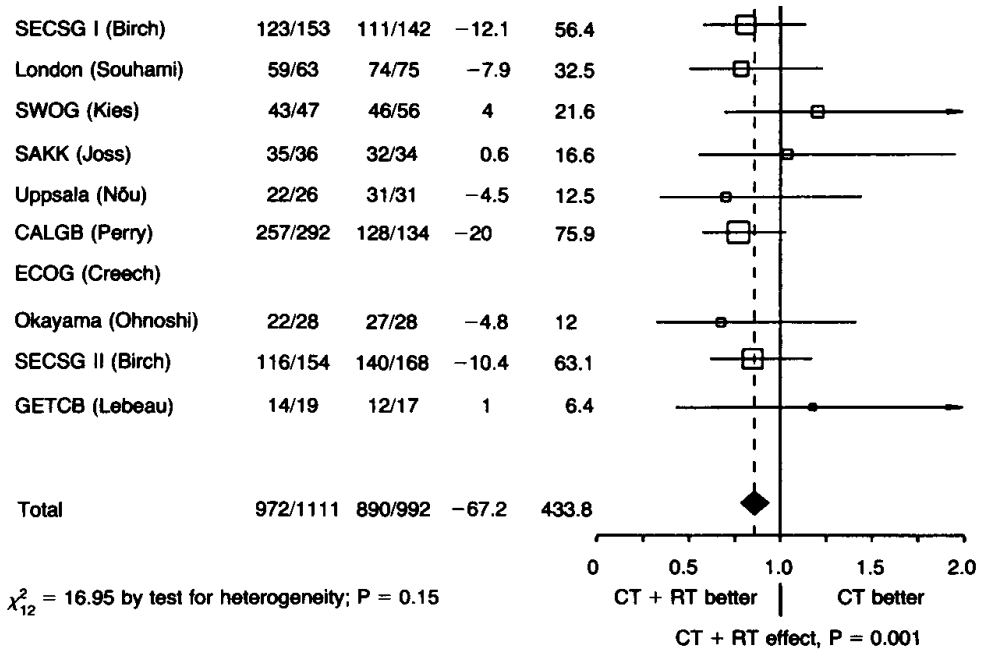

Figure 1. Relative Risk of Death among Patients Receiving Both Chemotherapy and Radiotherapy (CT + RT) as Compared with Patients Receiving Chemotherapy Alone (CT).

Each open square represents the relative risk for the trial, and each horizontal line its 99 percent confidence interval; the area of each square is proportional to the amount of information from the corresponding trial. The broken line and the solid diamond represent the pooled relative risk and its 95 percent confidence interval (see the Statistical Analysis section for details). The percentage reduction in the pooled relative risk

5.4% gain in OS @ 3 years (14.3% vs 8.9%)

p = 0.001

Pignon JP et al. NEJM 1992;327

Approaches to increase the efficacy of Thoracic RT

1) **Early administration**
2) **Increasing total dose**
3) **Altered fractionation schedules**
4) **Optimal radiation volumes**

1) “Early” irradiation in LD-SCLC: arguments for and against

FOR:

- ❑ Earlier tumor regression
- ❑ Decreased risk of resistant clones appearance

AGAINST:

- ❑ No selection of patients
- ❑ Increased toxicity
- ❑ Larger irradiated volumes

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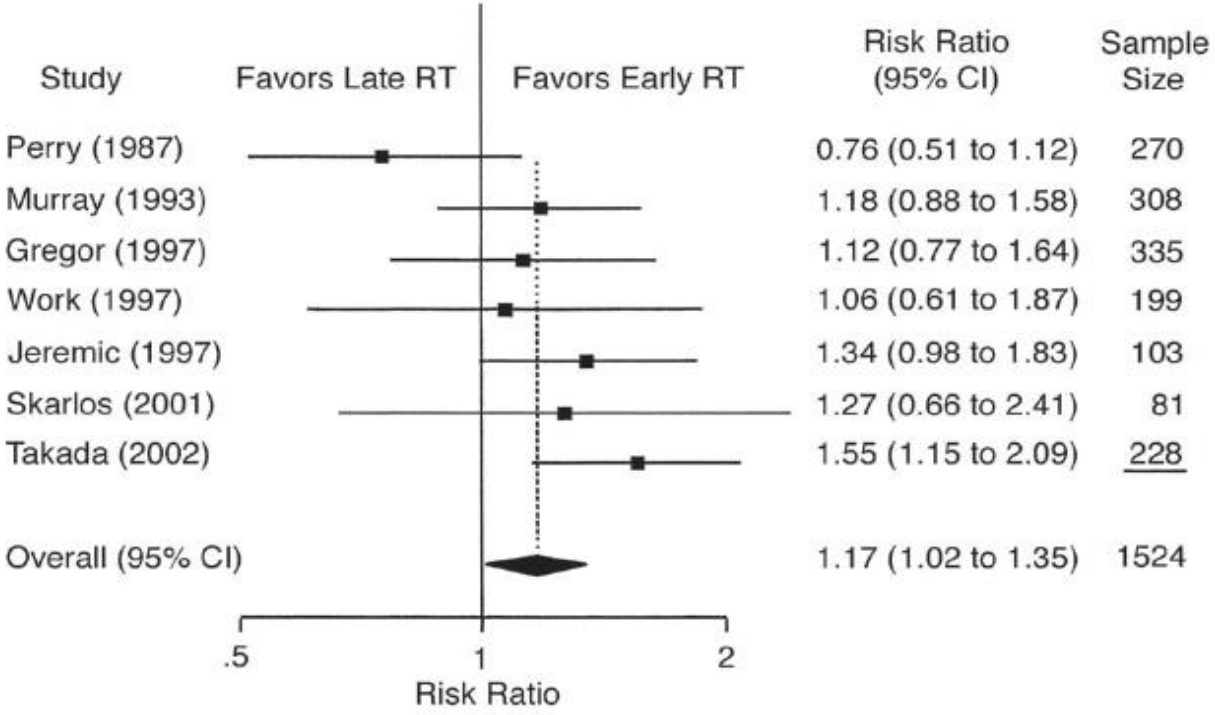
1) “Early” vs. “Late” thoracic RT in LD-SCLC

Overall Survival @ 2 years



- **Early RT** = beginning of RT **within 9 weeks** after the initiation of chemotherapy and **before the third cycle** of chemotherapy

- **Late RT** = beginning of RT **9 weeks or more** after the initiation of chemotherapy or **after** the beginning of **the third cycle** of chemotherapy

Fried DB et al, JCO 2004;22

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The concept of SER in LD-SCLC (Start of any treatment to the End of Radiotherapy)

Time Between the First Day of Chemotherapy and the Last Day of Chest Radiation Is the Most Important Predictor of Survival in Limited-Disease Small-Cell Lung Cancer

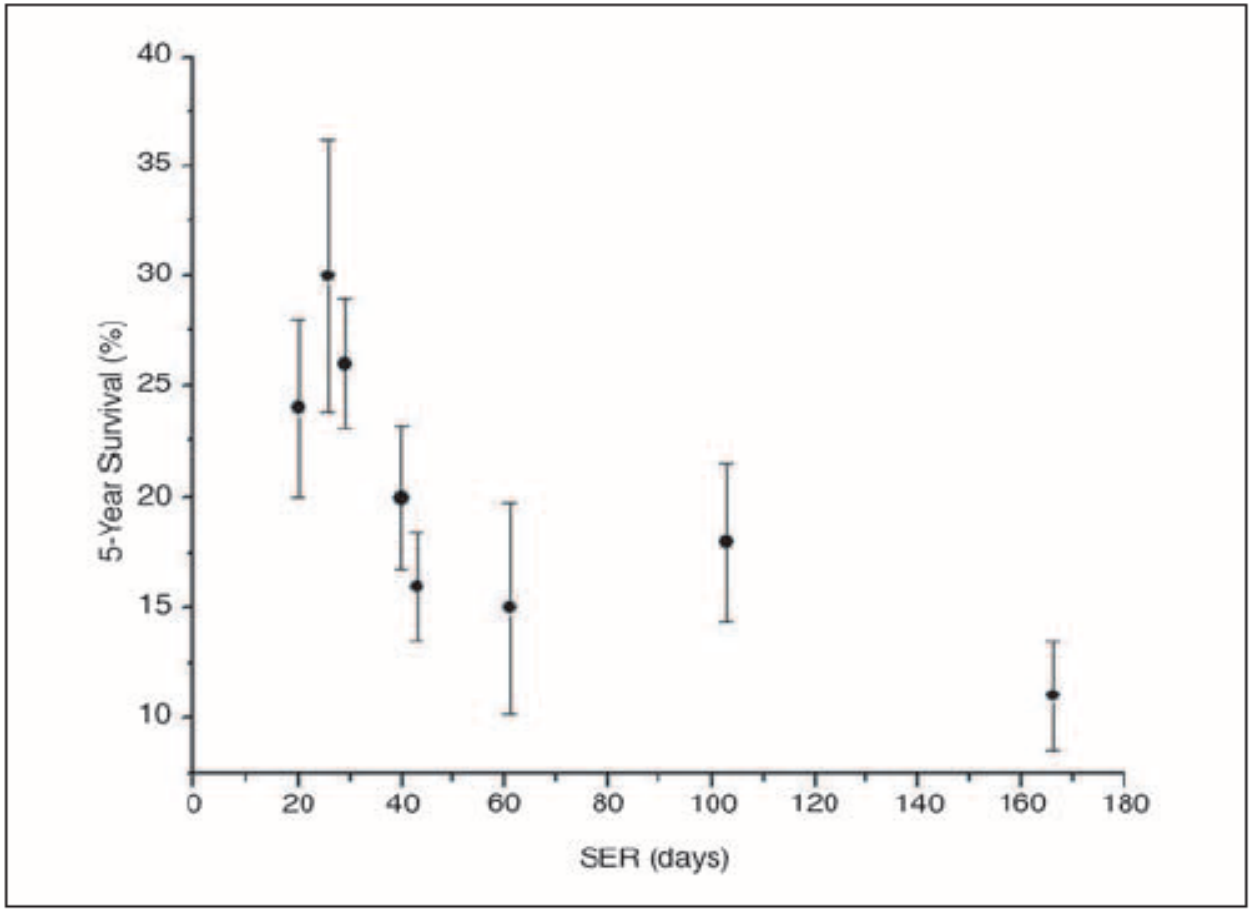

Fig 5. The survival at 5 years as a function of the time from the start of any treatment and the end of radiotherapy (SER). Each dot represents a single trial ± SE.

De Ruysscher D. et al JCO 2006;24

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2) Rationale for RT dose escalation in LD-SCLC

- Better **local control** with **higher RT doses** in some retrospective series
- Trend towards **better survival** with **higher RT doses** in some retrospective series
- Possibility of **dose-escalation** with **modern radiotherapy**

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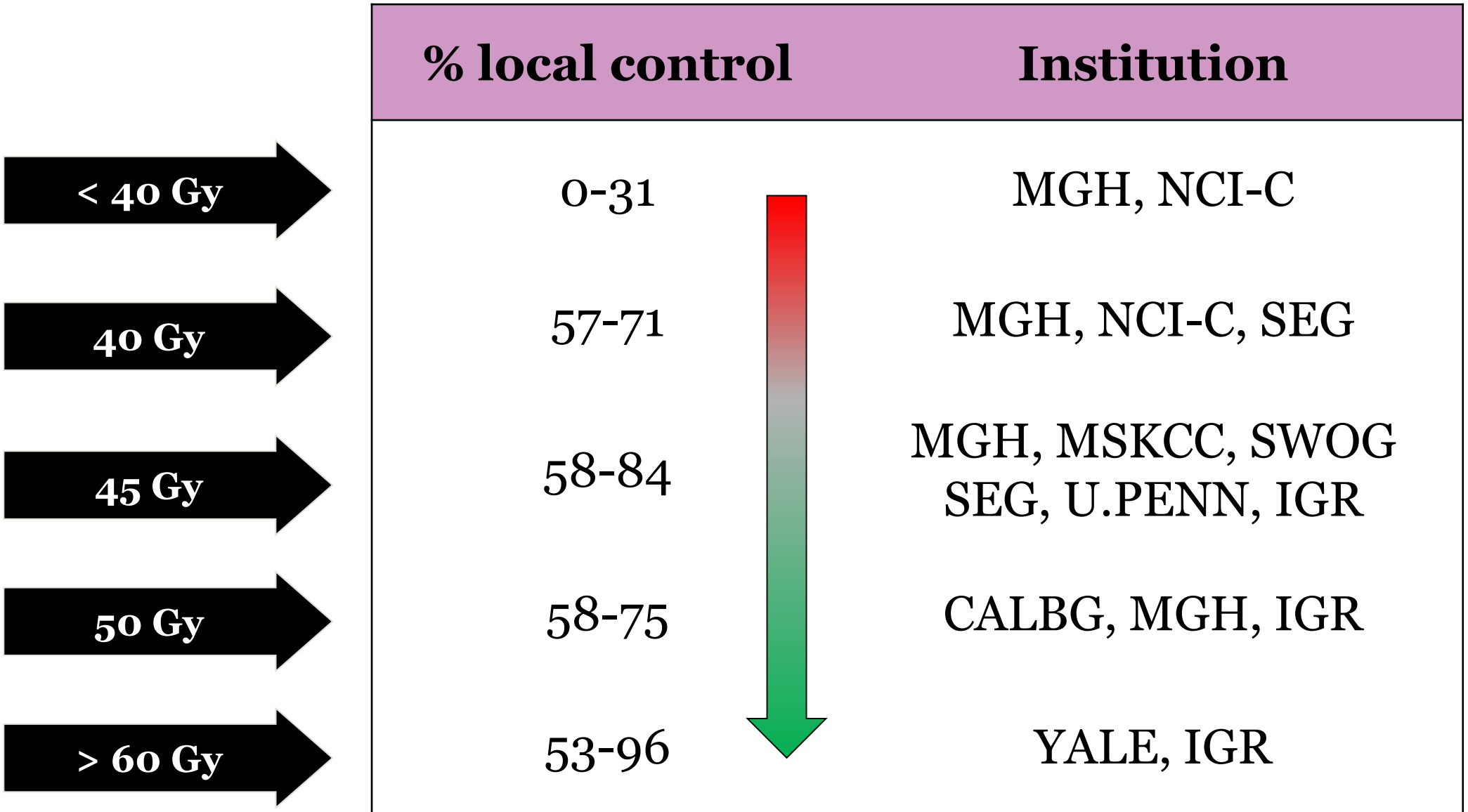
Local control as a function of RT dose



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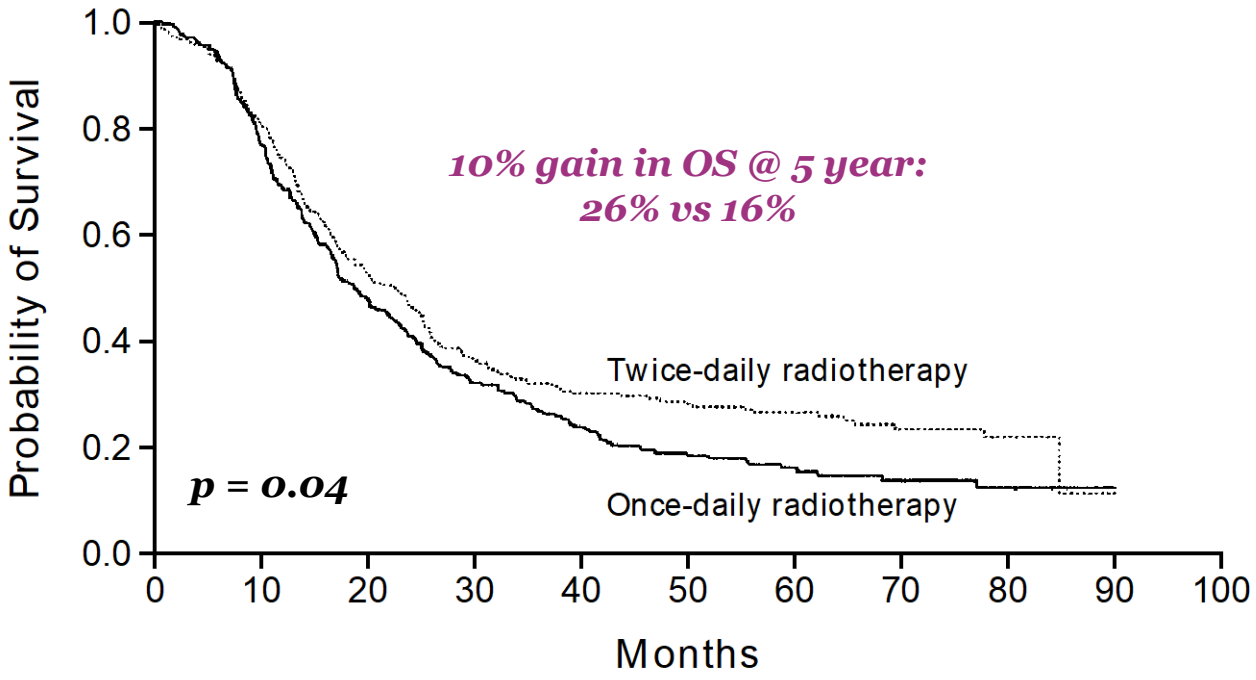
TWICE-DAILY COMPARED WITH ONCE-DAILY THORACIC RADIOTHERAPY IN LIMITED SMALL-CELL LUNG CANCER TREATED CONCURRENTLY WITH CISPLATIN AND ETOPOSIDE

3) Altered fractionation - Intergroup trial 0096:
the current standard in LD-SCLC?

Overall Survival



- 417 Patients
- All patients received 4 x Cis+Etoposide
- Randomly assigned to receive either 45 Gy twice daily (1.5 Gy/bid) or once daily (1.8 Gy/die)
- Higher rates of G3+ esophageal toxicity in the accelerated arm

The schedules were not biologically equivalent!

Turrisi AT et al NEJM 1999;340

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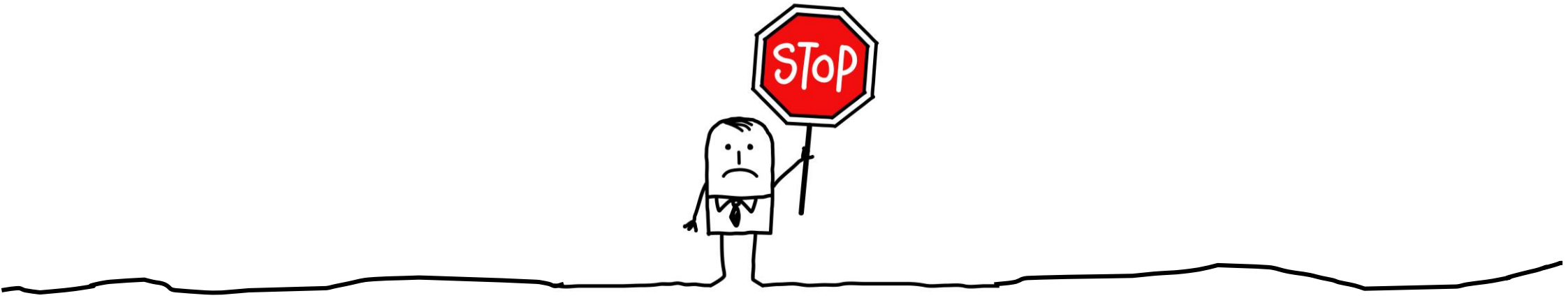
Why 45 Gy BID failed to adopt ?

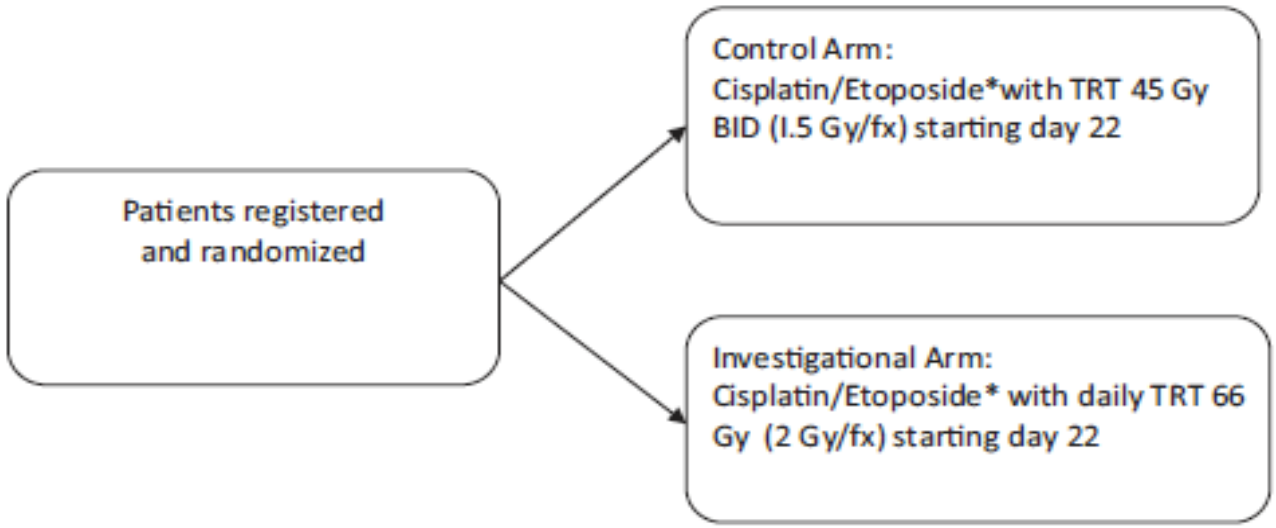


- Inconvenience of twice daily treatment
- Increased rate of esophagitis
- Suboptimal control arm in “Turrisi” trial
- **Lack of phase III trial comparing hyperfractionation with “high-dose” conventionally fractionated treatment**

BMJ Open

Protocol for the CONVERT trial––Concurrent ONce-daily VErsus twice-daily RadioTherapy: an international 2-arm randomised controlled trial of concurrent chemoradiotherapy comparing twice-daily and once-daily radiotherapy schedules in patients with limited stage small cell lung cancer (LS-SCLC) and good performance status

3) Ongoing study on the role of altered fractionation: the CONVERT trial



- Phase III randomized trial
- 447 patients enrolled, accrual closed, results expected very soon.
- The **results will be crucial** in determining the best standard regimen for LD-SCLC
- **Higher dose of radiation** in the "once-daily" arm, compared to the hyperfractionated one (66 Gy vs 45)
- Primary endpoint: OS

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Faivre-Finn C. et al. BMJ 2016;6

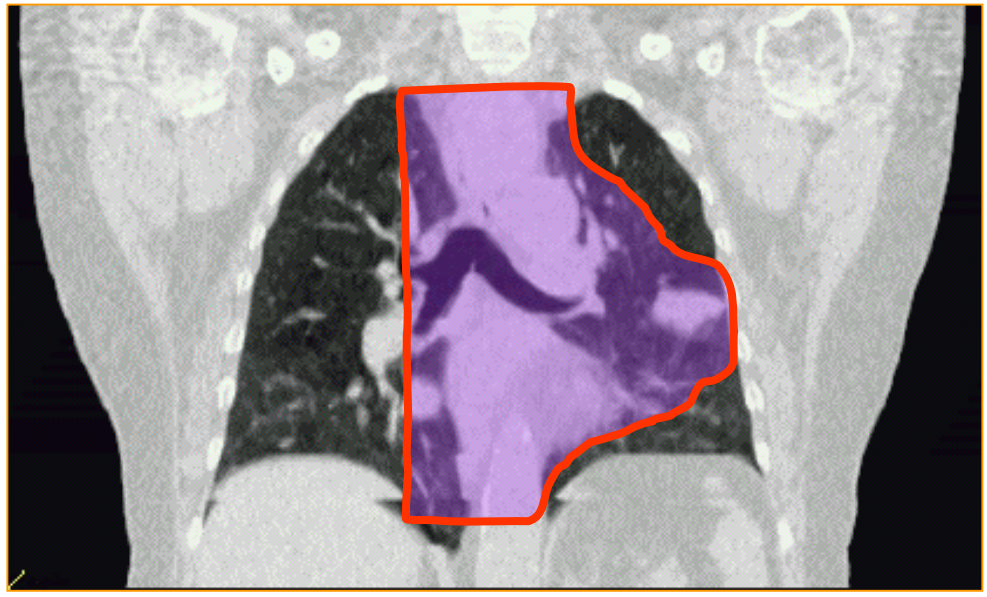
4) Radiation Therapy Volume in LD-SCLC

- Defining the radiotherapy target in limited stage SCLC is evolving
- In NSCLC selective nodal irradiation widely replaced elective nodal irradiation
- In SCLC the role of ENI is still controversial

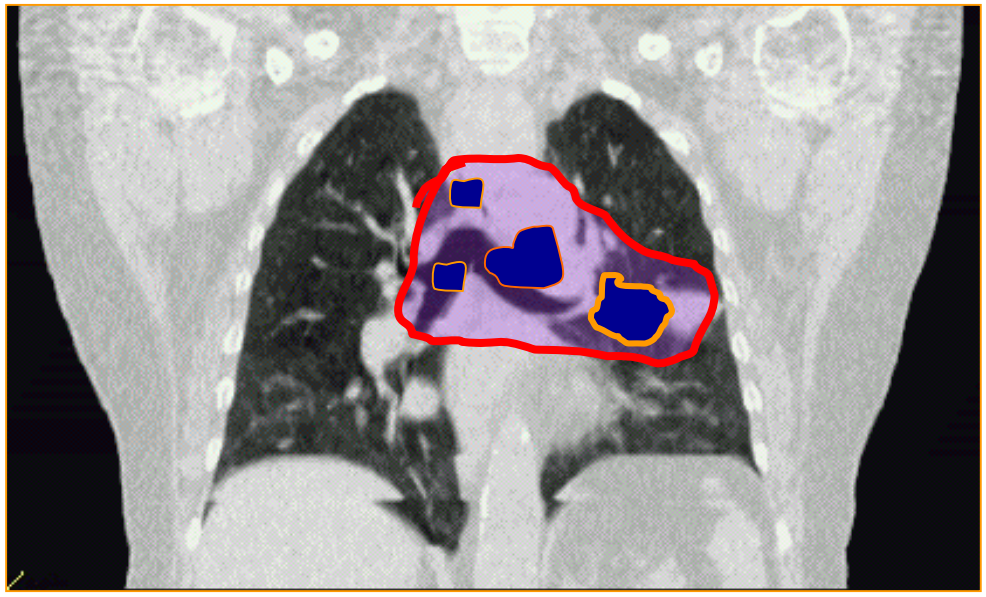
4) Changes in radiotherapy fields:

From Elective Nodal Irradiation (ENI) to Involved Field Irradiation

Elective nodal RT



Involved-field RT



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4) Radiation Therapy Volume in LD-SCLC

- **Elective Fields**: classical management, used in most studies
  - Advantage: inclusion of potential micromets
  - Disadvantage: increased toxicity

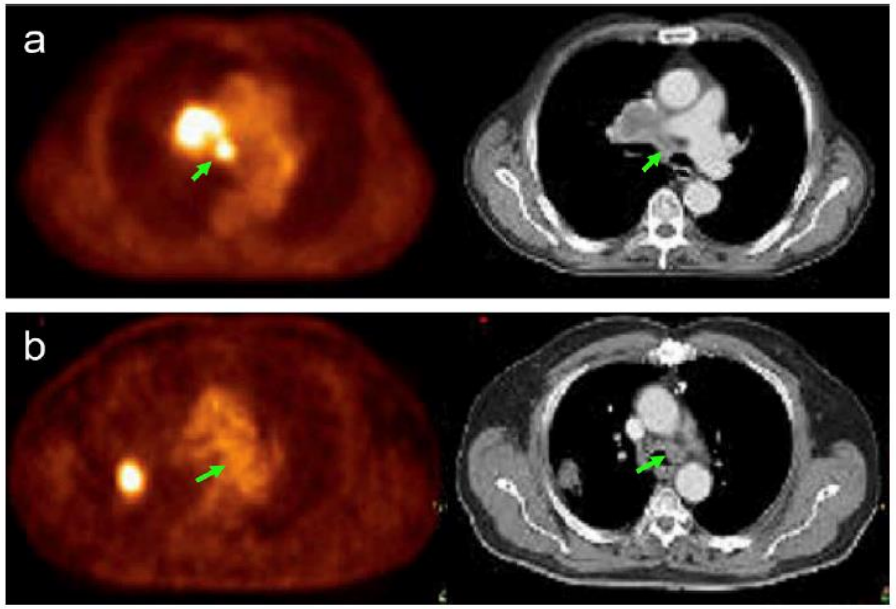
- **Involved Fields**: omission of ENI
  - Advantage: dose-escalation
  - Disadvantage: increased risk of regional nodal relapse

Involved Field RT: phase II studies

Author	Pts	CT	RT dose	RT timing	Local/Regional relapse	Distant relapse
Baas et al	37	CPE	45/25	2-3 cycle	6 (16%)	19
Lievens et al	34	EP	50/25	2 cycle	2 (6%)	NR
De Ruysscher et al	27	EC	45/50 BID	1-2 cycle	7 (33%) + 2 supraclav LN	11

PET-guided nodal contouring definitely supports the use of Involved Fields RT

Recurrence	Patients (n)
None	**21 (35)**
Local	**9 (15)**
In field	3 (5.0)
Out of field	4 (6.7)
Both in field and out of field	2 (3.3)
Isolated local	2 (3.3)
Local and distant/nodal	7 (11.7)
Nodal	**20 (33.3)**
In field	8 (13.3)
Out of field	7 (11.7)
Both in field and out of field	5 (8.0)
Isolated nodal	2 (3.3)
Nodal and distant/local	18 (30.0)
Distant	**34 (56.7)**
Isolated distant	19 (31.7)
Distant and local/nodal	15 (25.0)
Isolated brain	9 (15.0)



3% of isolated nodal relapse in PET-staged SCLC patients receiving IF-RT

Van Loon J et al. IJROBP2010;77

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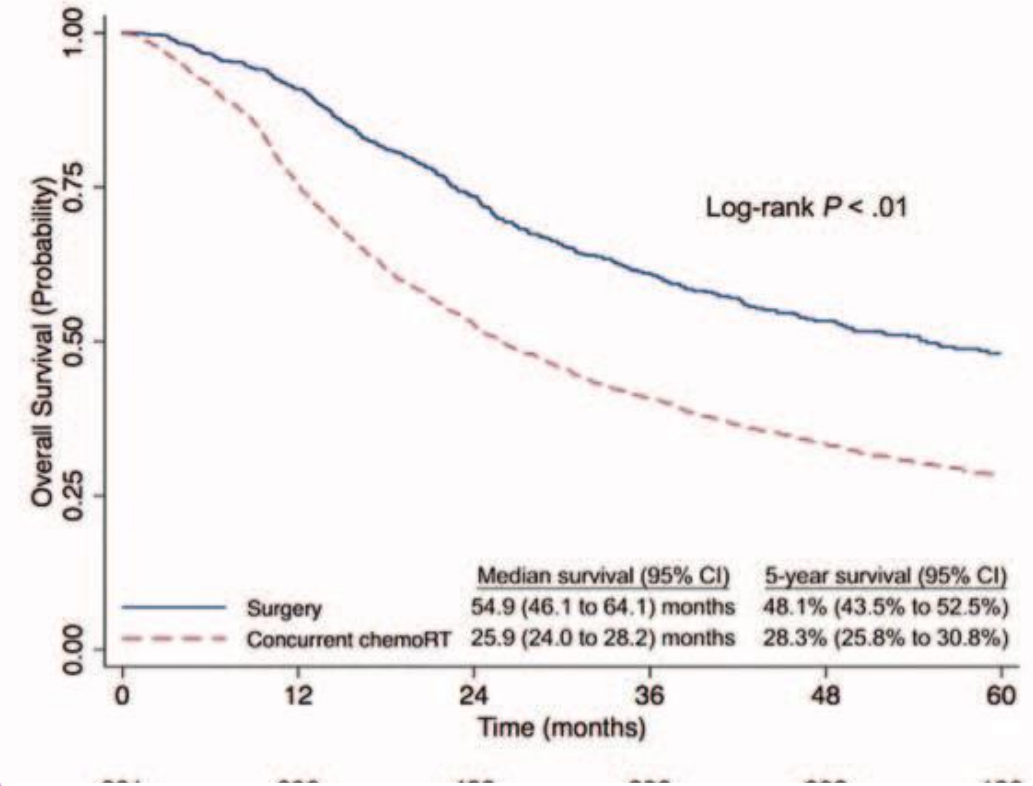
Long-term Survival After Surgery Compared With Concurrent Chemoradiation for Node-negative Small Cell Lung Cancer

Surgery is a feasible option in “very limited” disease (N0M0)

OS after propensity score analysis



- NCDB analysis (2003-2011)
- 1002 patients identified after propensity score analysis (501 vs 501)
- Group 1: Concurrent CT/RT
- Group 2: Surgery + adjuvant CT
- 5 years OS: **47.6% vs 29.8% (p < 0.01)**

Yang CJ. et al. Ann Surg 2017

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Rationale for Prophylactic Cranial Irradiation in SCLC

- Brain metastases are very common (50-75% at 2 years)
- Insufficient drugs supply in brain (BBB)
- Relative increase of brain relapse in long-term survivors
- Response rate in brain disease < 50%

PROPHYLACTIC CRANIAL IRRADIATION FOR PATIENTS WITH SMALL-CELL LUNG CANCER IN COMPLETE REMISSION

SCLC and Prophylactic Cranial Irradiation:

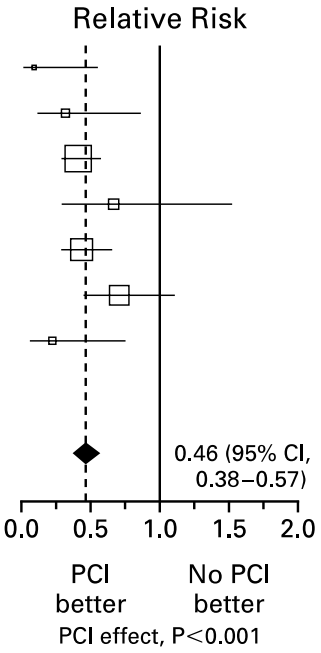
Benefit on Brain Metastases

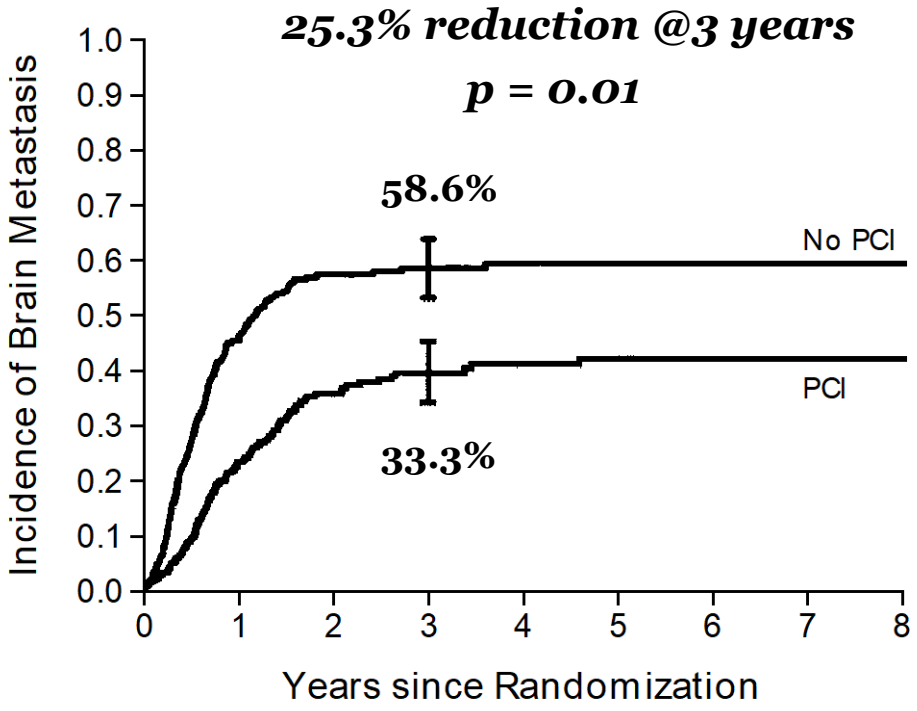
B

Brain Metastasis

Study	No. of Events/No. Enrolled PCI	No. of Events/No. Enrolled No PCI	O−E	Variance
UMCC	0/14	5/12	−2.9	1.2
Okayama	5/23	11/23	−4.4	3.8
PCI-85	46/149	87/151	−28.7	32.5
Danish–NCI	10/27	13/25	−2.3	5.7
UKCCCR–EORTC	46/194	54/120	−18.7	22.8
PCI-88	32/100	44/111	−6.4	18.9
ECOG–RTOG	4/17	8/15	−3.9	2.6
Total	143/524	222/457	−67.2	87.6

Test for heterogeneity: $\chi^2_6 = 9.71$, P=0.14





Auperin A. et al. NEJM 1999;341

PROPHYLACTIC CRANIAL IRRADIATION FOR PATIENTS WITH SMALL-CELL LUNG CANCER IN COMPLETE REMISSION

SCLC and Prophylactic Cranial Irradiation:

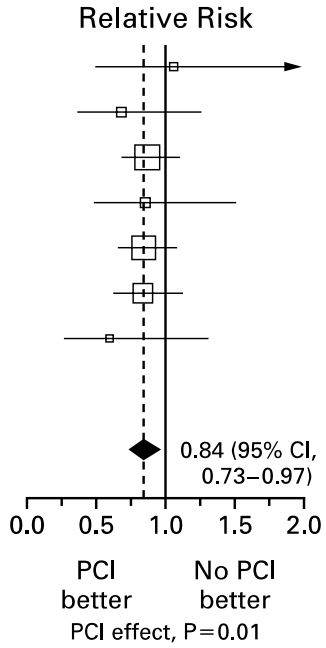
Benefit on Overall Survival

A

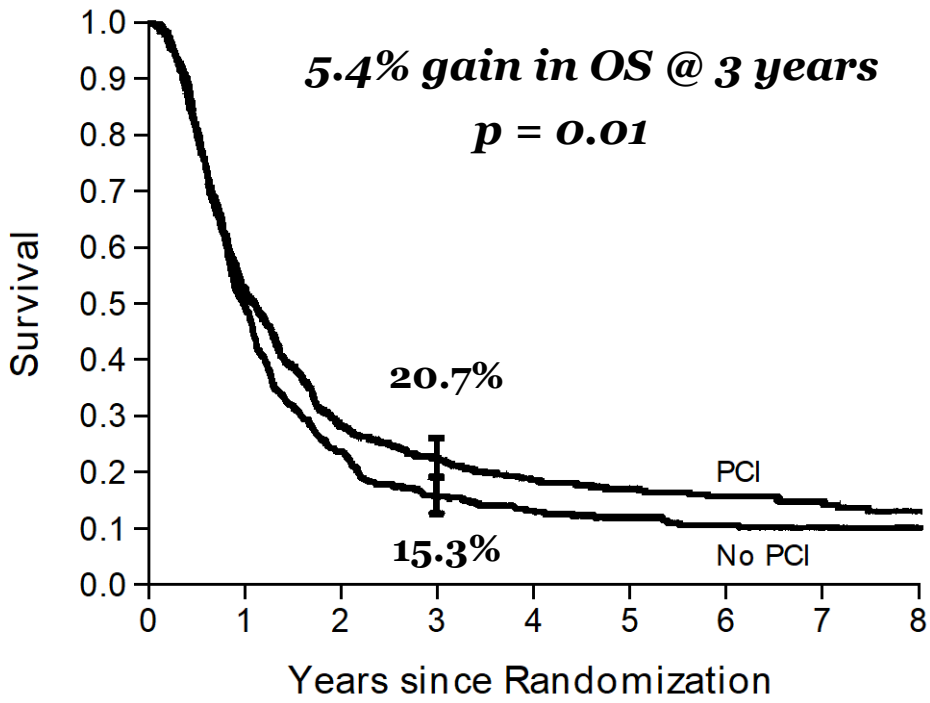
Death

Study	No. of Events/No. Enrolled PCI	No. of Events/No. Enrolled no PCI	O−E	Variance
UMCC	14/15	13/14	0.4	6.7
Okayama	21/23	21/23	−3.8	10.1
PCI-85	133/149	135/151	−8.9	66.5
Danish–NCI	24/28	24/27	−1.8	11.8
UKCCCR–EORTC	154/194	106/120	−10.1	60.3
PCI-88	80/100	94/111	−7.6	43.1
ECOG–RTOG	14/17	13/15	−3.2	6.1
Total	440/526	406/461	−35.0	204.4

Test for heterogeneity: $\chi^2_6 = 1.62$, P=0.95



A



Auperin A. et al. NEJM 1999;341

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Meta-analysis of PCI in SCLC : RT doses

	Relative risk of death (95% CI)	*p value*	Relative risk of brain mets (95% CI)	*p value*
Total dose				
8 Gy	0.69 (0.35-1.37)		0.76 (0.28-2.10)	
24-25 Gy	0.88 (0.75-1.04)		0.52 (0.41-0.67)	
30 Gy	0.81 (0.59-1.12)	NS	0.34 (0.19-0.59)	**0.02**
36-40 Gy	0.81 (0.54-1.20)		0.27 (0.14-0.51)	
Timing (between start of induction CT and randomization to PCI)				
< 4 mo	0.92 (0.66-1.29)		0.27 (0.16-0.46)	
4-6 mo	0.79 (0.61-1.02)	NS	0.50 (0.35-0.72)	**0.01**
> 6 mo	1.01 (0.74-1.38)		0.69 (0.44-1.08)	

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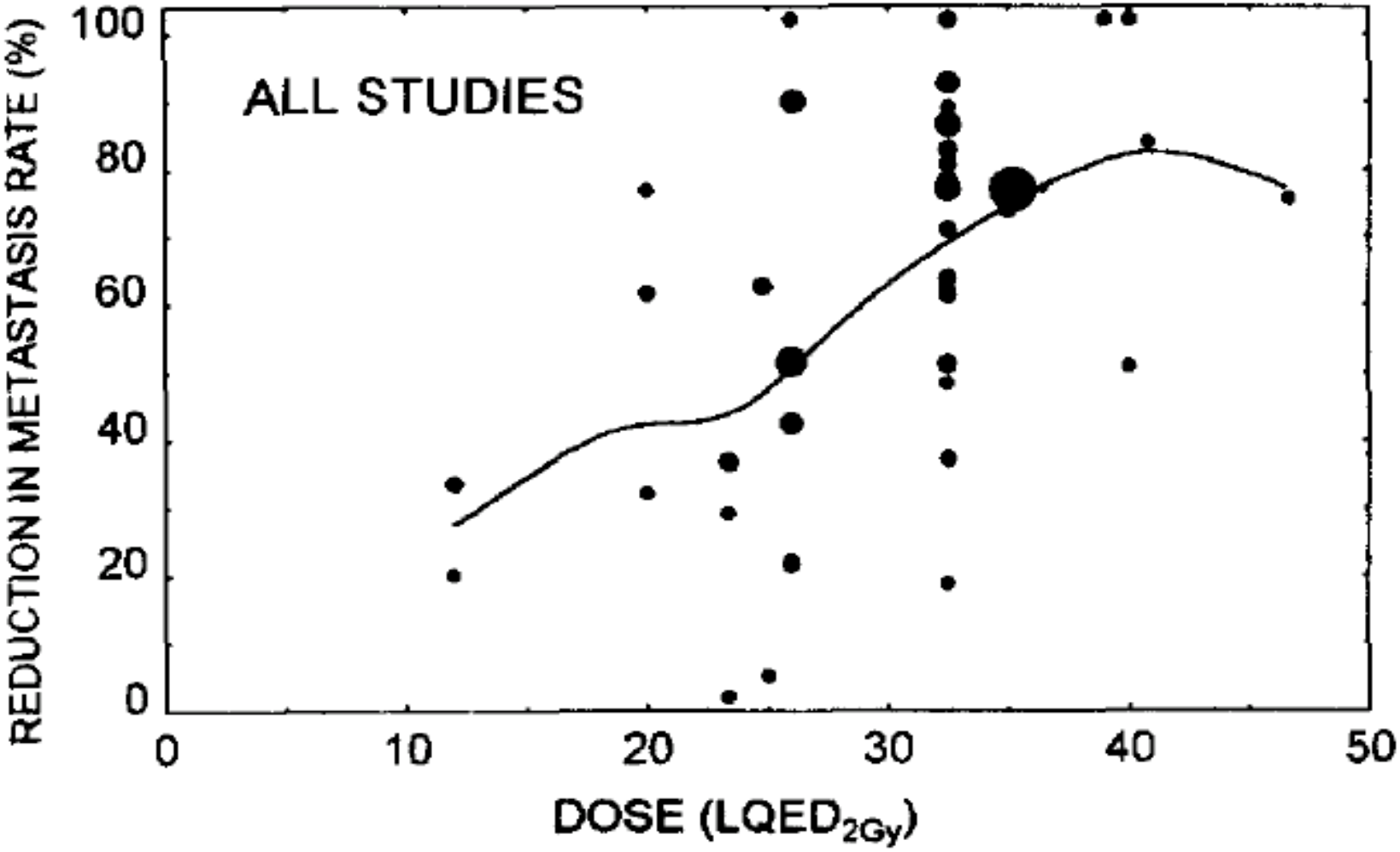
Auperin A. et al. NEJM 1999;341

PCI dose vs. Brain Mets Control



Suwinski et al, IJROBP 1998

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EORTC 22003-08004

IFCT 99-01

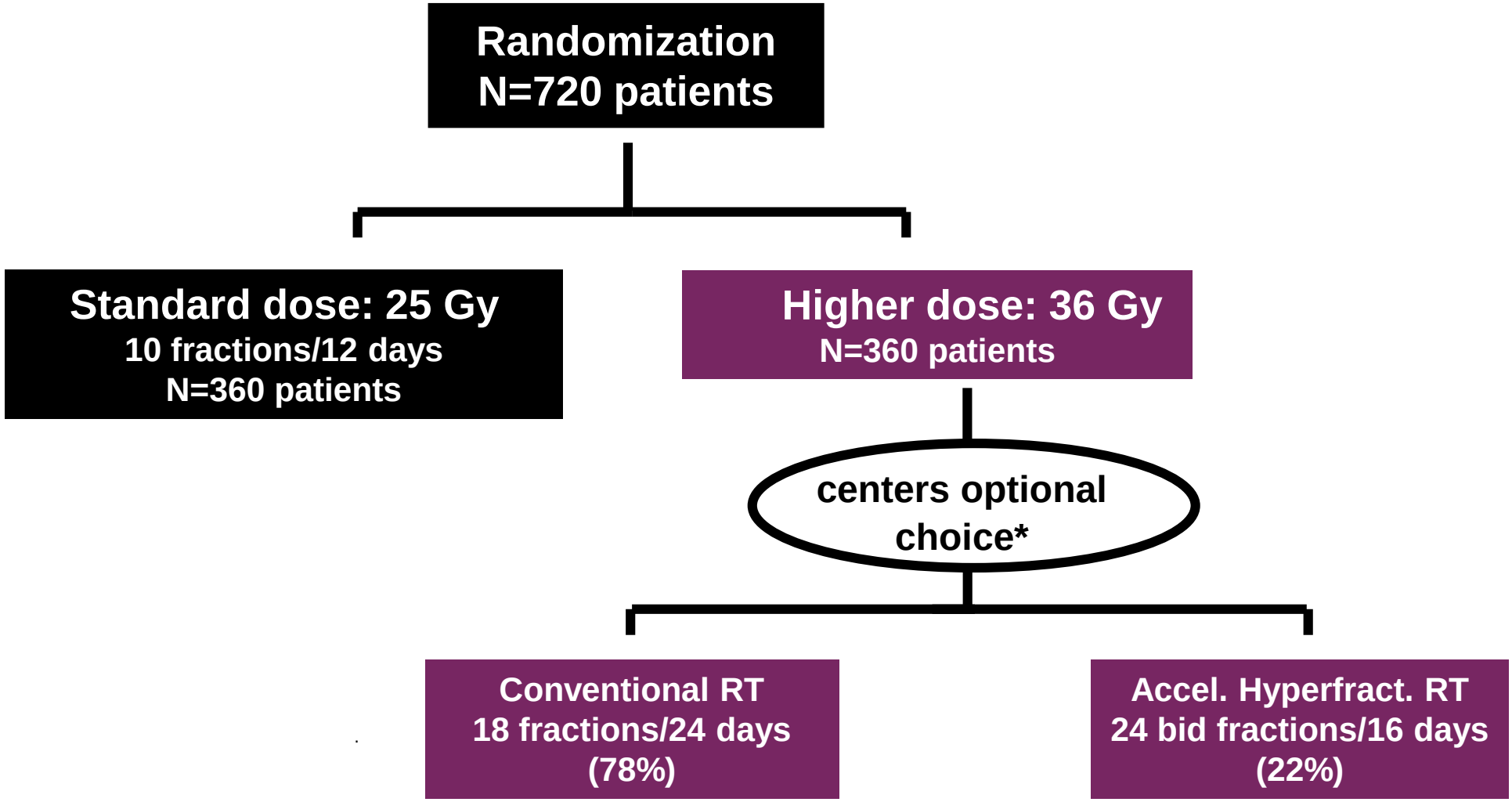
RTOG 0212

Randomized trial of standard dose to a higher dose prophylactic cranial irradiation (PCI) in limited-stage small cell cancer (SCLC) complete responders (CR): Primary end-point analysis

(PCI99-01, IFCT 99-01, EORTC 22003-08004, RTOG 0212)

Le Pechoux C. et al., Lancet 2012

Standard vs High-Dose PCI: Study design



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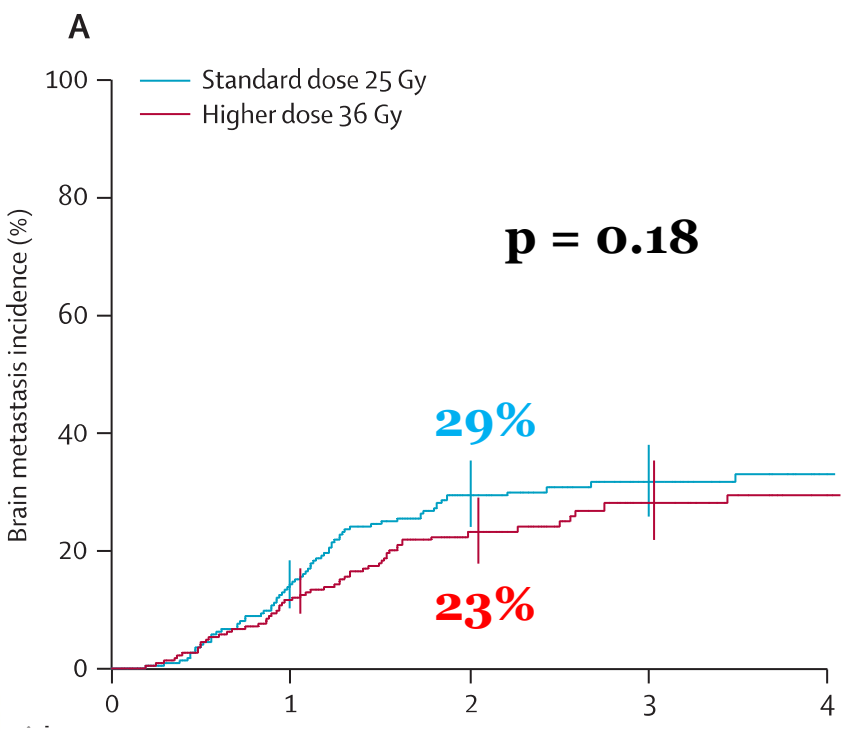
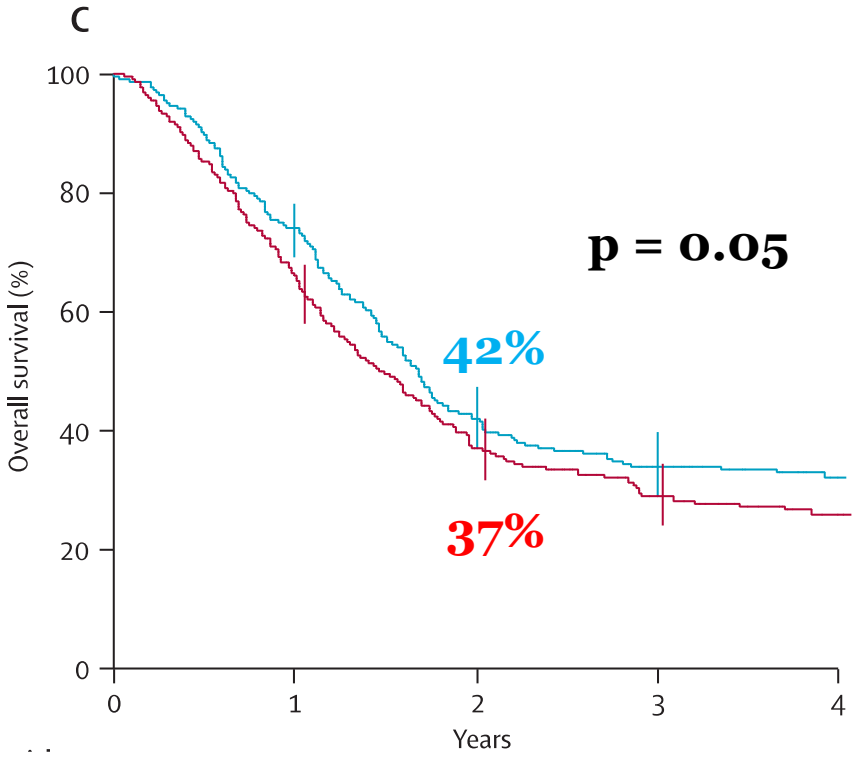
Standard-dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic radiotherapy (PCI 99-01, EORTC 22003-08004, RTOG 0212, and IFCT 99-01): a randomised clinical trial

Brain metastasis incidence



Overall survival



Le Pechoux C. et al. Lancet Oncol 2009;10

Standard-dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic radiotherapy (PCI 99-01, EORTC 22003-08004, RTOG 0212, and IFCT 99-01): a randomised clinical trial

Standard vs High-Dose PCI: CONCLUSION

- **No significant reduction in the total incidence of brain metastases was observed after higher-dose PCI, but there was a significant increase in mortality.**
- **PCI at 25 Gy should remain the standard of care in limited-stage SCLC.**

Le Pechoux C. et al. Lancet Oncol 2009;10

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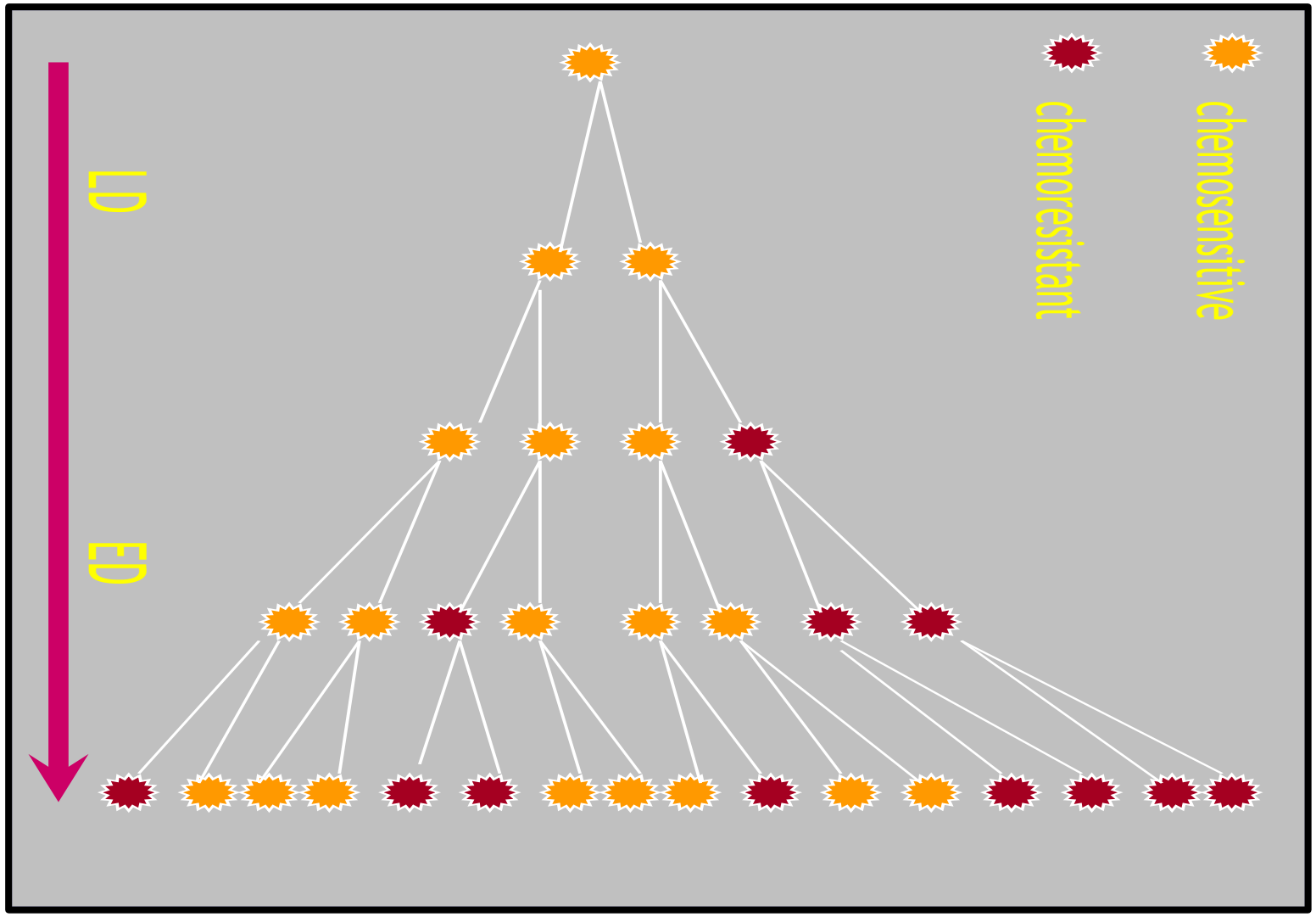
EXTENDED DISEASE

“Chemoresistance” raises with growing extension of the disease



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A 59 years old female patient affected with ED-SCLC has obtained a PR after 6 cycles of Cisplatin-Etoposide. Would you consider this patient for further therapies?

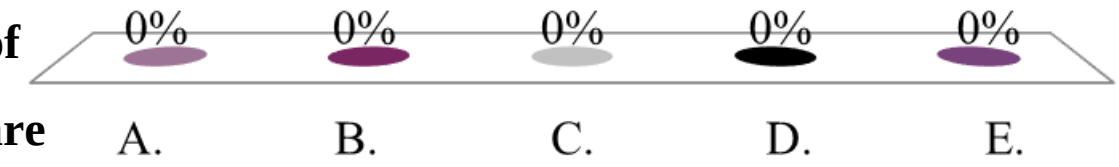
A. NO

B. Yes, she deserves 2 more cycles of chemotherapy

C. Yes, I would consider her for PCI (if no evidence of brain mets at least at the CT scan), followed by thoracic RT (30 Gy/10 fractions)

D. Yes, I would consider her for PCI (if no evidence of brain mets at least at the CT scan)

E. I would refer the patient for WBI in case of brain mets at MRI. No PCI if brain mets are excluded at the MRI



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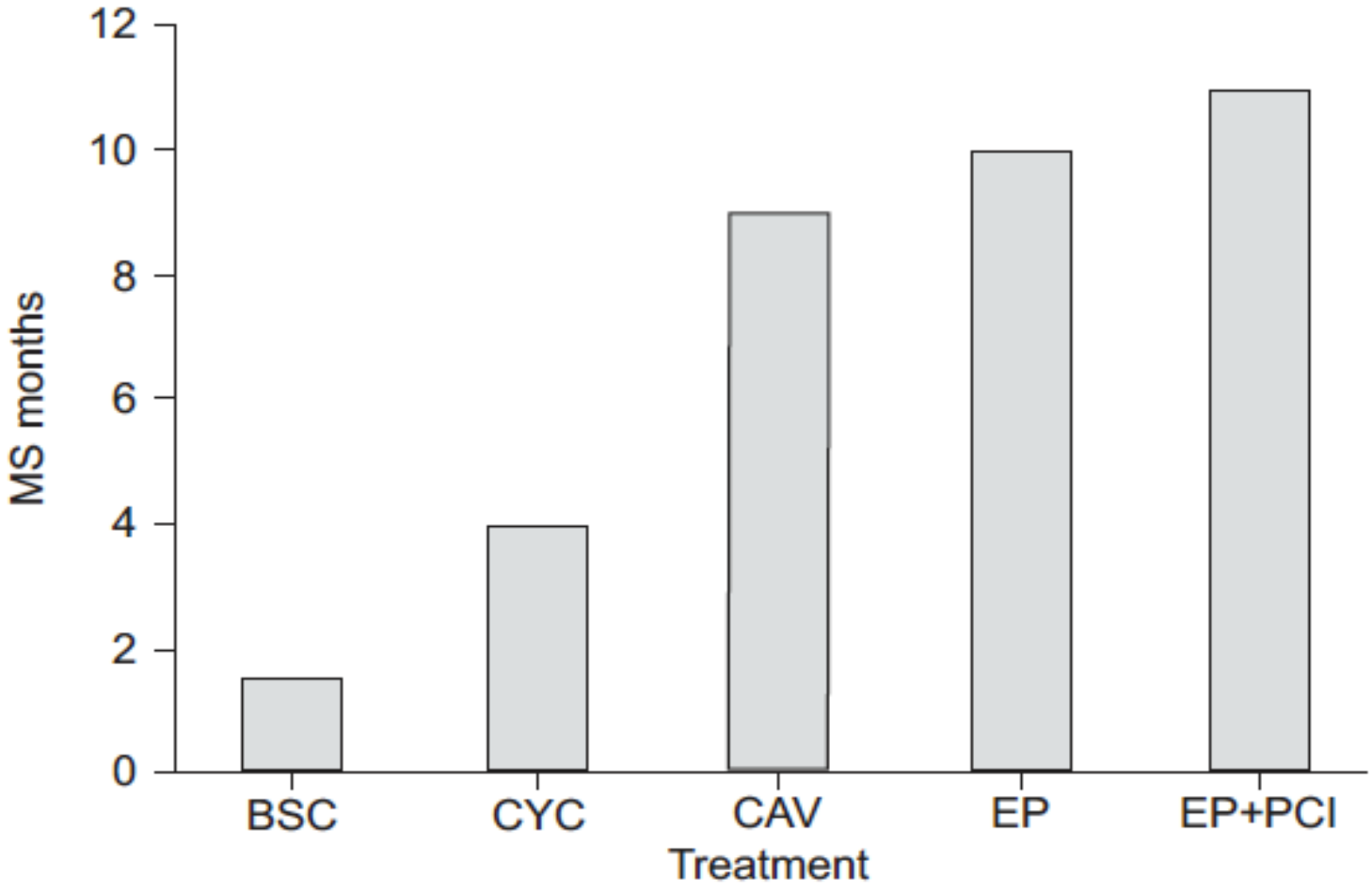
Treatment strategy for ED-SCLC

- Chemotherapy: the mainstay of treatment

- Adjunctive role of radiotherapy
  - PCI ?
  - Thoracic irradiation ?

Median Survival in ED-SCLC with various regimens developed since the 1960's.



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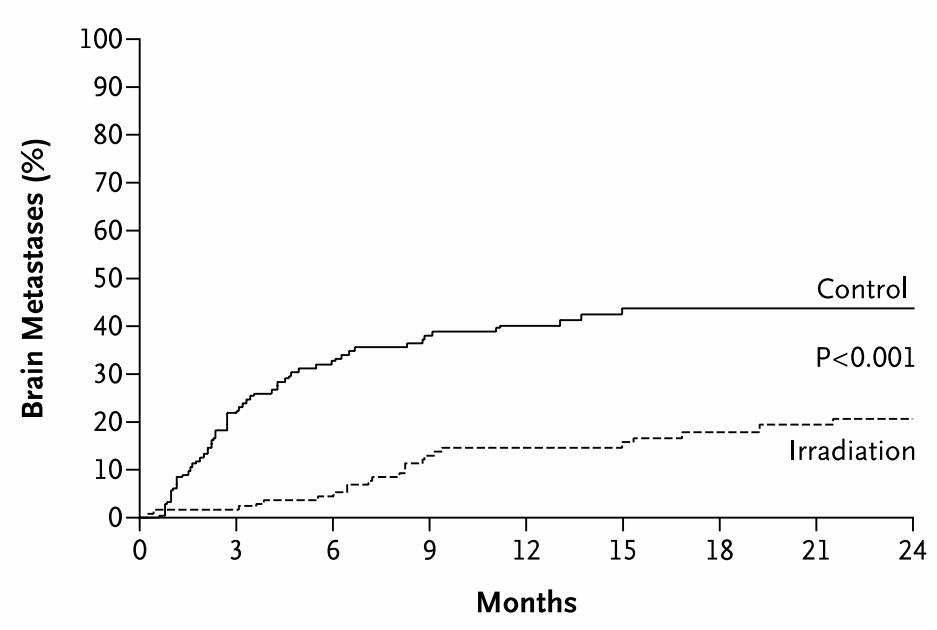
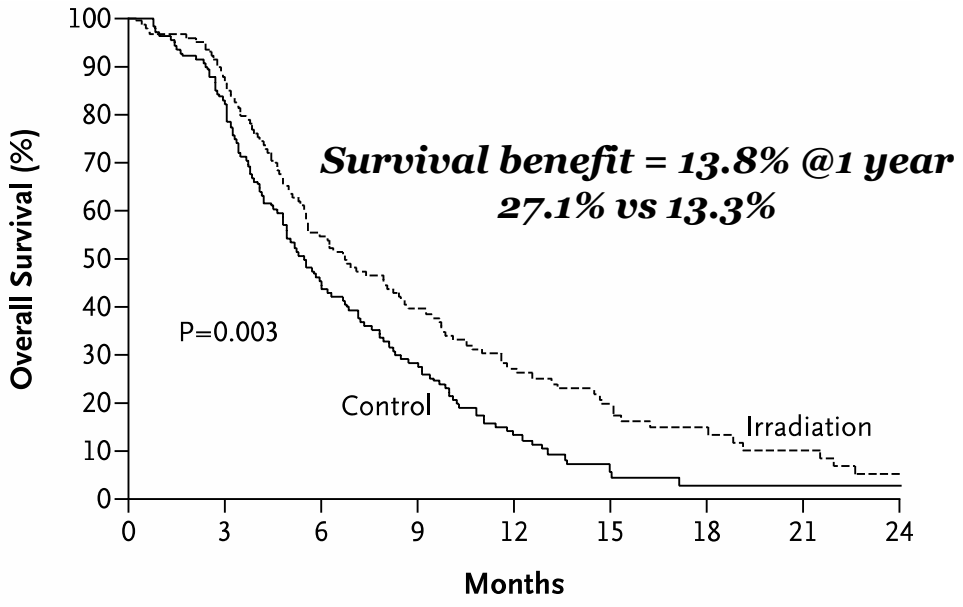
The NEW ENGLAND JOURNAL of MEDICINE

Prophylactic Cranial Irradiation in Extensive Small-Cell Lung Cancer

Role of PCI in ED-SCLC: EORTC 22993 trial

- **N.B. response to chemotherapy (4-6 cycles) mandatory to enter this study**





- Prophylactic cranial irradiation reduces the incidence of symptomatic brain metastases and prolongs disease-free and overall survival

Slotman B. et al. NEJM 2007;357

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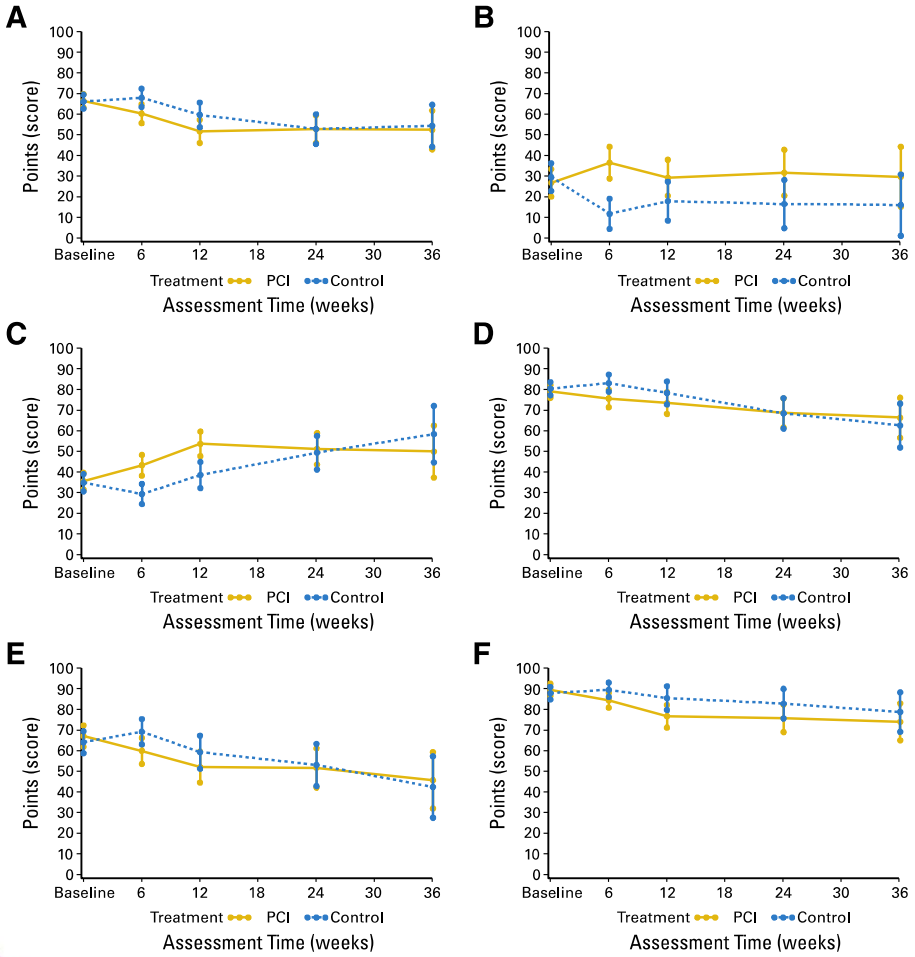
JOURNAL OF CLINICAL ONCOLOGY

Prophylactic Cranial Irradiation in Extensive Disease Small-Cell Lung Cancer: Short-Term Health-Related Quality of Life and Patient Reported Symptoms—Results of an International Phase III Randomized Controlled Trial by the EORTC Radiation Oncology and Lung Cancer Groups

QoL after PCI in ED-SCLC



A. Global health status

B. Hair loss

C. Fatigue

D. Role functioning

E. Cognitive Functioning

F. Emotional functioning

- The **largest mean difference** between the two arms was observed for **fatigue** and **hair loss**.
- For global health status, the observed mean difference was eight points on a scale 0 to 100 at 6 weeks (P=.018) and 3 months (P = .055).

Slotman B. et al. JCO 2009;27

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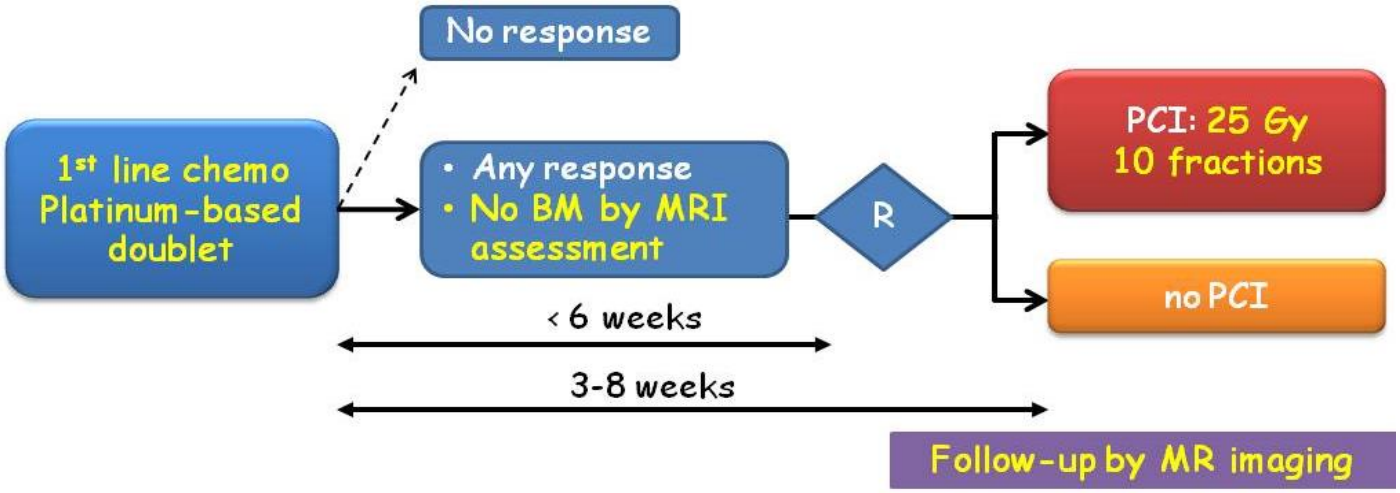
Japanese trial on the role of PCI in ED-SCLC: Study design



Stratification by Age (70≦ / <70), PS (0-1 / 2), Response (CR / PR+MR), Institutions

Primary endpoint:	Overall Survival
Secondary endpoints:	Time to BM (evaluated every 3 months) Progression-Free Survival (PFS) Safety Mini Mental State Examination (MMSE)

N.B. patients randomized to receive PCI only if brain metastases were excluded by MRI assessment

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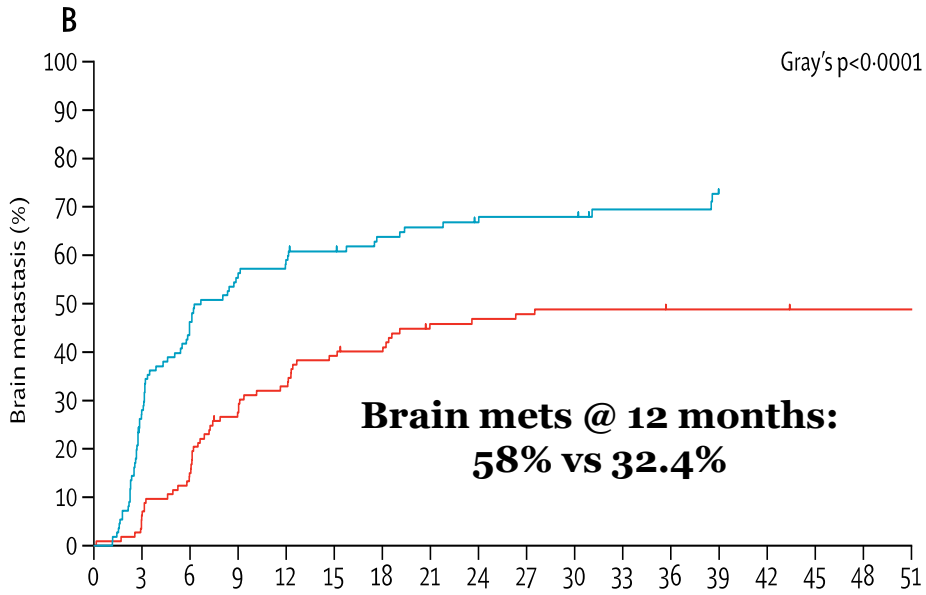
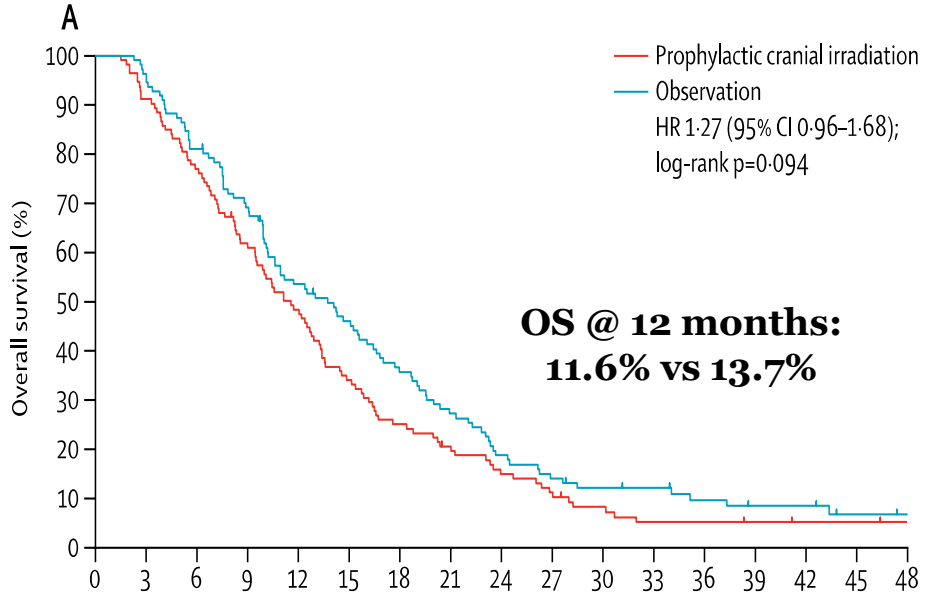
Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial

Japanese trial: futility of PCI when mets are excluded by MRI





- **Study early terminated because of futility after 1st interim analysis**
- **PCI did not result in longer OS compared with observation in patients with any response to initial chemotherapy and a confirmed absence of brain metastases when patients receive periodic MRI examination during follow-up.**

Takahashi T. et al. Lancet Oncol 2017

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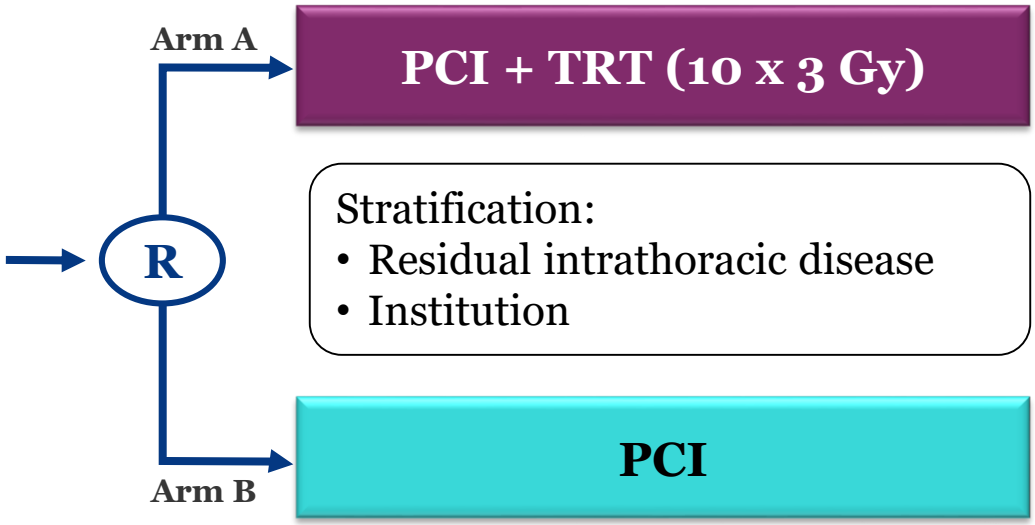
Is there a role for thoracic RT in ED-SCLC ?
CREST trial – Study design

Chest
Radiotherapy
Extensive
Stage
Trial

ED-SCLC

- ❑ No brain- /leptomeningeal mets
- ❑ No pleural mets
- ❑ No previous RTX brain/thorax
- ❑ Any response after 4-6 cycles of platinum-based chemotherapy
- ❑ WHO 0-2
- ❑ Age 18+
- ❑ Encompassable volume



Study treatment should start between 2 and 7 weeks after last chemotherapy

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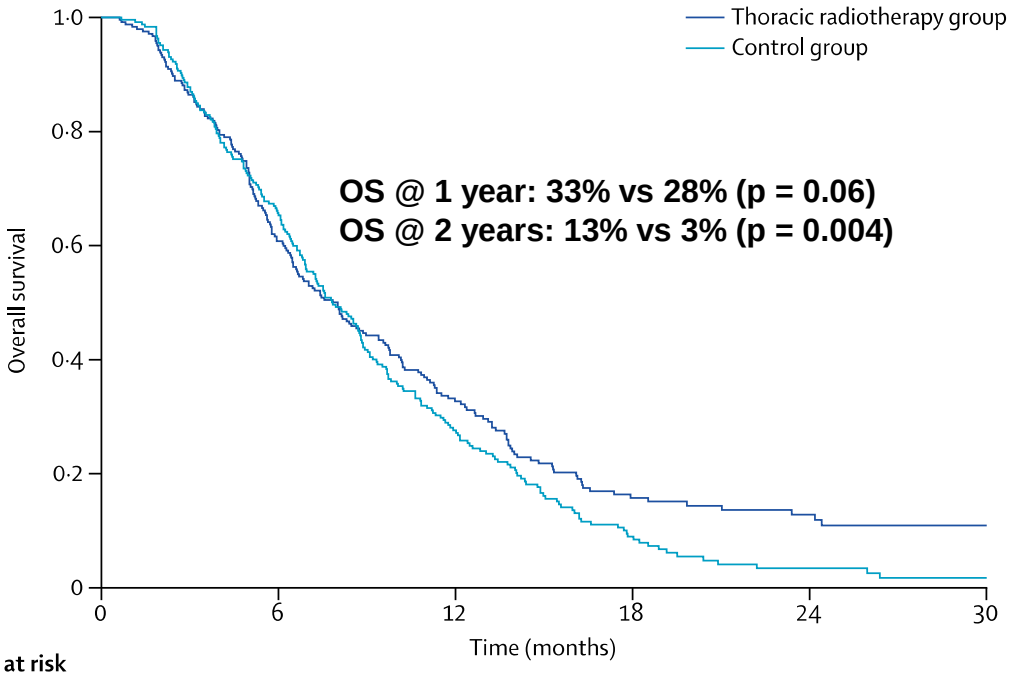
Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial

Is there a role for thoracic RT in ED-SCLC ? CREST trial

Overall Survival



Number at risk						
Thoracic radiotherapy group	247	147	67	26	14	7
Control group	248	160	61	17	5	1

- Progression was less likely to occur in patients treated with thoracic RT (**PFS @ 6 months = 24% vs 7%, p = 0.001**)
- No differences in grade 3 or higher toxic effects
- **Many patients have relapse outside the thorax and the brain**
- **Thoracic RT** in addition to PCI should be considered **for all ED-SCLC patients who respond to chemotherapy**

Slotman B. et al. Lancet 2015;385

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Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial

Pattern of failure in the CREST trial:

Many patients have relapse outside the thorax and the brain

	Thoracic radiotherapy group (n=247)	Control group (n=248)
Any site	213 (86·2%)	223 (89·9%)
Thorax only	49 (19·8%)	114 (46·0%)
Thorax and brain	5 (2·0%)	3 (1·2%)
Thorax and other sites	50 (20·2%)	77 (31·0%)
Thorax, brain, and other sites	4 (1·6%)	4 (1·6%)
Brain only	10 (4·0%)	6 (2·4%)
Brain and other sites	5 (2·0%)	0 (0·0%)
Other sites only	90 (36·4%)	19 (7·6%)

Progression occurring at different organ sites within 30 days was considered as occurring simultaneously.

Table 3: **Recurrences**

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Paradigm shifts in the management of SCLC: significant contribution from RT

❑ LD-SCLC

Socinski M. and Bogart J, JCO 2007;25

Study	Regimen	Impact on Survival
Pignon et al,[25] Warde and Payne[26]	Chemotherapy versus chemotherapy + TRT	+5.4% at 3 years
Turrisi et al[29]	Standard TRT versus intensified TRT	+10% at 5 years
Fried et al[40]	Early concurrent versus delayed or sequential TRT	+5% at 2 years
Auperin et al[86]	Prophylactic cranial irradiation	+5.4% at 3 years

❑ ED-SCLC:

Study	Regimen	Impact on Survival
Slotman et al. (NEJM 2007)	Prophylactic cranial irradiation	+13.8% at 1 year
Slotman et al. (Lancet 2015)	CT + PCI vs CT+ PCI + Thoracic RT	+5% at 1 year

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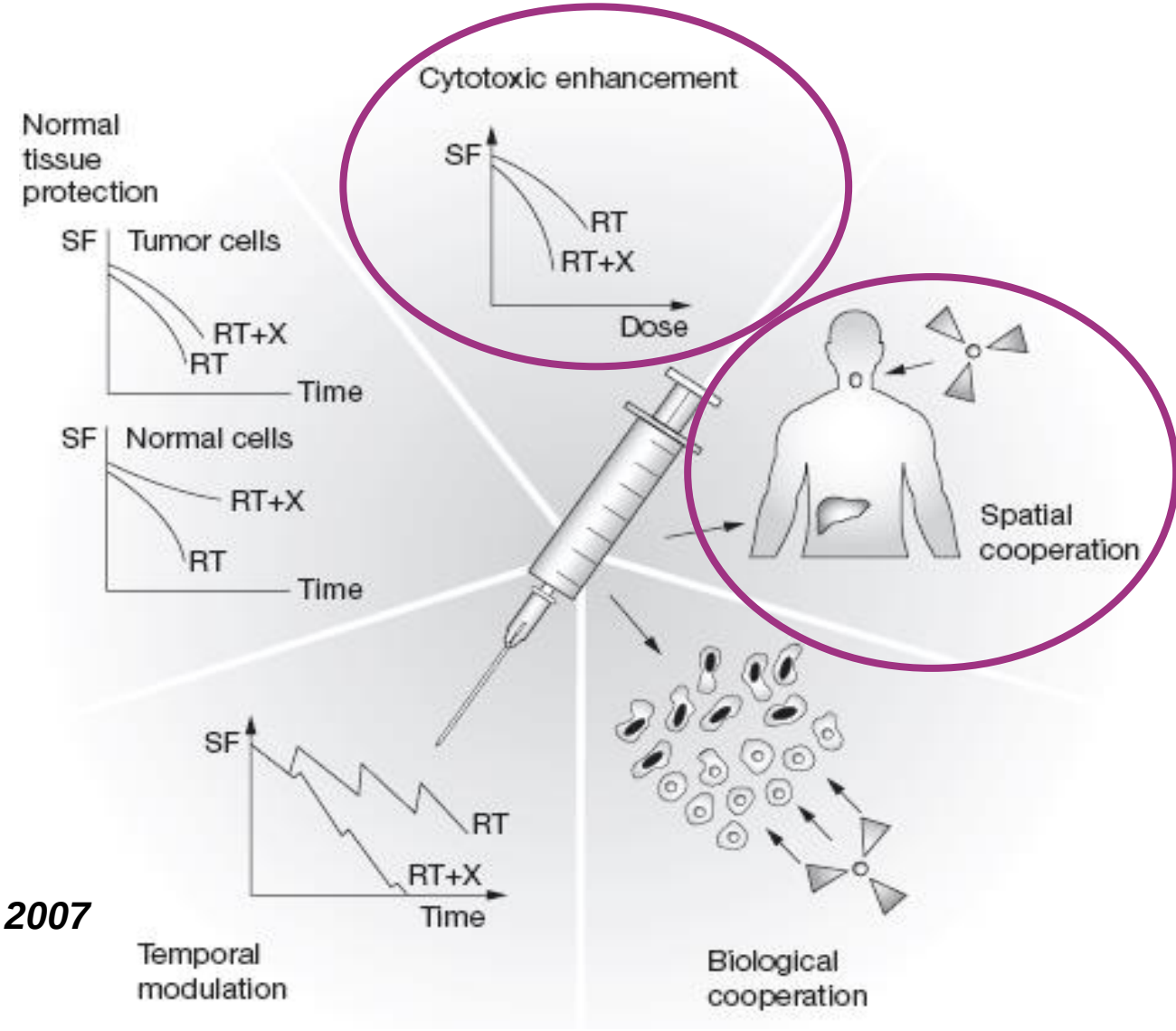
How to combine chemotherapy with radiotherapy?

- Spatial cooperation
- Cytotoxic enhancement
- Biological cooperation
- Temporal modulation
- Normal tissue protection



Bentzen SM 2007

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New perspectives and future directions:

Is there a role for RT in oligometastatic SCLC ?

RANDOMIZED PHASE II STUDY COMPARING PROPHYLACTIC CRANIAL IRRADIATION ALONE TO PROPHYLACTIC CRANIAL IRRADIATION AND CONSOLIDATIVE EXTRA-CRANIAL IRRADIATION FOR EXTENSIVE DISEASE SMALL CELL LUNG CANCER (ED-SCLC)

RTOG 0937 – STUDY DESIGN

S	**Response to Treatment**	**R**	**Arm 1: Prophylactic Cranial Irradiation**
T	1. Complete Response (CR)	**A**	2.5 Gy per fraction for a total of 25 Gy
R	2. Partial Response (PR)	**N**	
A		**D**	**Arm 2: Prophylactic Cranial Irradiation**
T		**O**	2.5 Gy per fraction for a total of 25 Gy
I	**Number of Metastatic Lesions**	**M**	and
F	1. 1	**I**	**Consolidative Radiation to**
Y	2. 2-4	**Z**	**Locoregional and Residual Metastatic Disease**
	Age	**E**	45 Gy at 3 Gy per fraction*
	1. <65		
	2. ≥65		*Acceptable alternative regimens: 30-40 Gy in 10 fractions

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RANDOMIZED PHASE II STUDY COMPARING PROPHYLACTIC CRANIAL IRRADIATION ALONE TO PROPHYLACTIC CRANIAL IRRADIATION AND CONSOLIDATIVE EXTRA-CRANIAL IRRADIATION FOR EXTENSIVE DISEASE SMALL CELL LUNG CANCER (ED-SCLC)

RTOG 0937 – Preliminary results (study prematurely closed for futility)

OS @ 1 year:

- 60.1% for PCI arm
- 50.8% for PCI+ RT arm

p = 0.21

PFS @ 3 months:

- 46.7% for PCI arm
- 85.5% for PCI+ RT arm

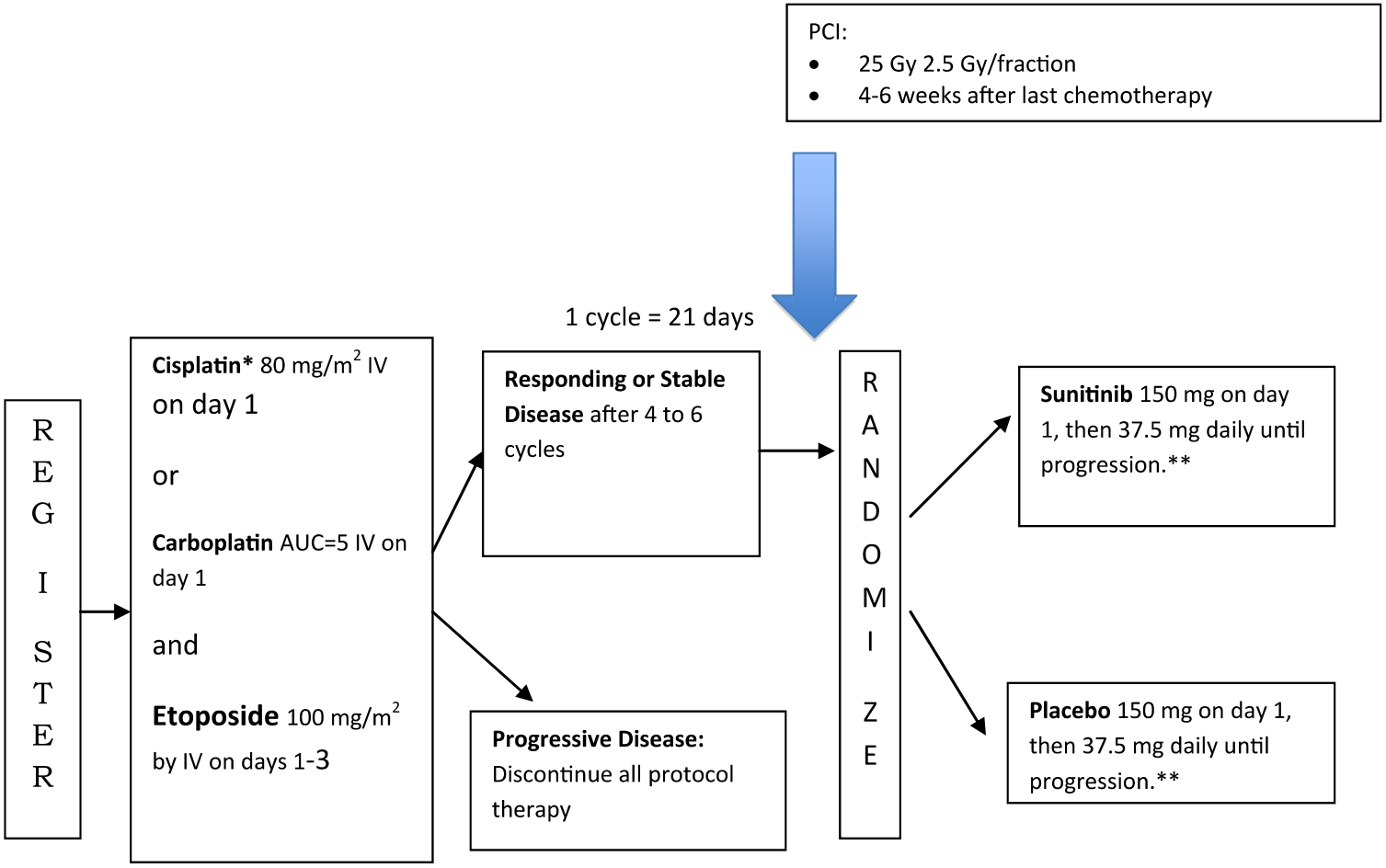
p = 0.01

❑ *Excessive deaths and increased toxicity (G4-5) in the experimental arm*

Gore E.M. et al. Astro Meeting 2015

New perspectives and future directions:
Combination of PCI + maintenance Sunitib?

CALGB 30504 (Alliance) – Study Design



Rationale for integrating Sunitinib and PCI in ED-SCLC

- The potential for synergy between PCI and sunitinib is supported by both preclinical and clinical reports.
- It has previously been established that **small cell lung cancer expresses** vascular endothelial growth factor (**VEGF**) **receptors** and that **VEGF is required** for the development of **brain metastases**.
- In **murine models**, the delivery of **antiangiogenic agents** alone to the brain has been shown to **slow the growth of brain metastases**. Sunitinib seems to have a "single-agent activity" against brain metastases also in human models.

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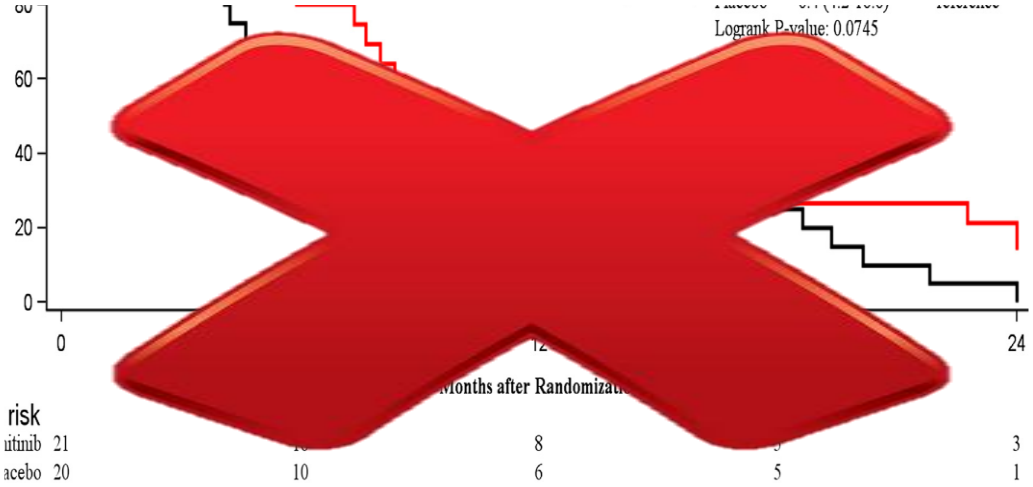
Positive Interaction between Prophylactic Cranial Irradiation and Maintenance Sunitinib for Untreated Extensive-Stage Small Cell Lung Cancer Patients After Standard Chemotherapy: A Secondary Analysis of CALGB 30504 (ALLIANCE)

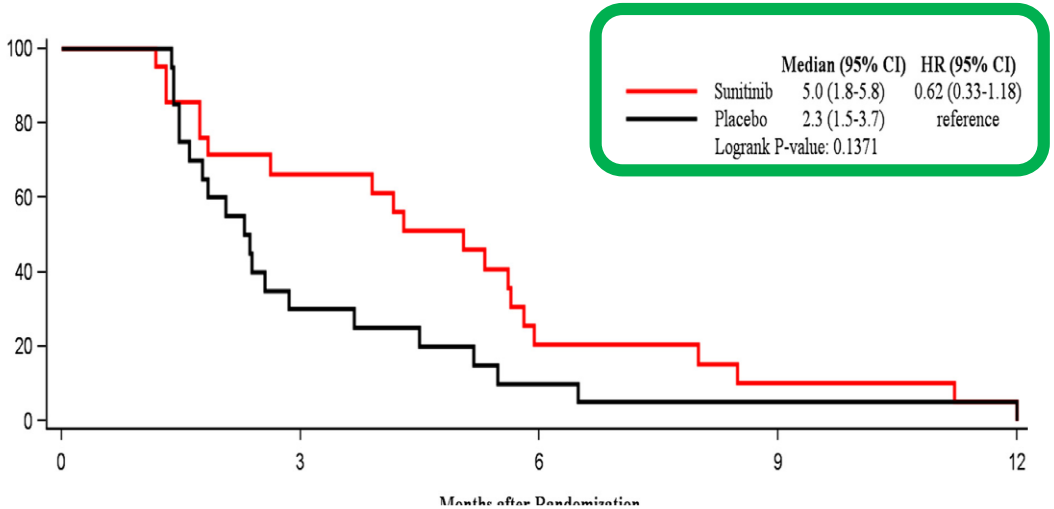
New perspectives and future directions:

Combination of PCI + maintenance Sunitib?

Progression Free Survival



Overall Survival



- Trends toward improved OS were seen in patients receiving PCI and Sunitinib
- These results support the need for further prospective studies evaluating the integration of maintenance systemic therapy and PCI in ED-SCLC

Salama JK. et al. J Thor Oncol 2015;11

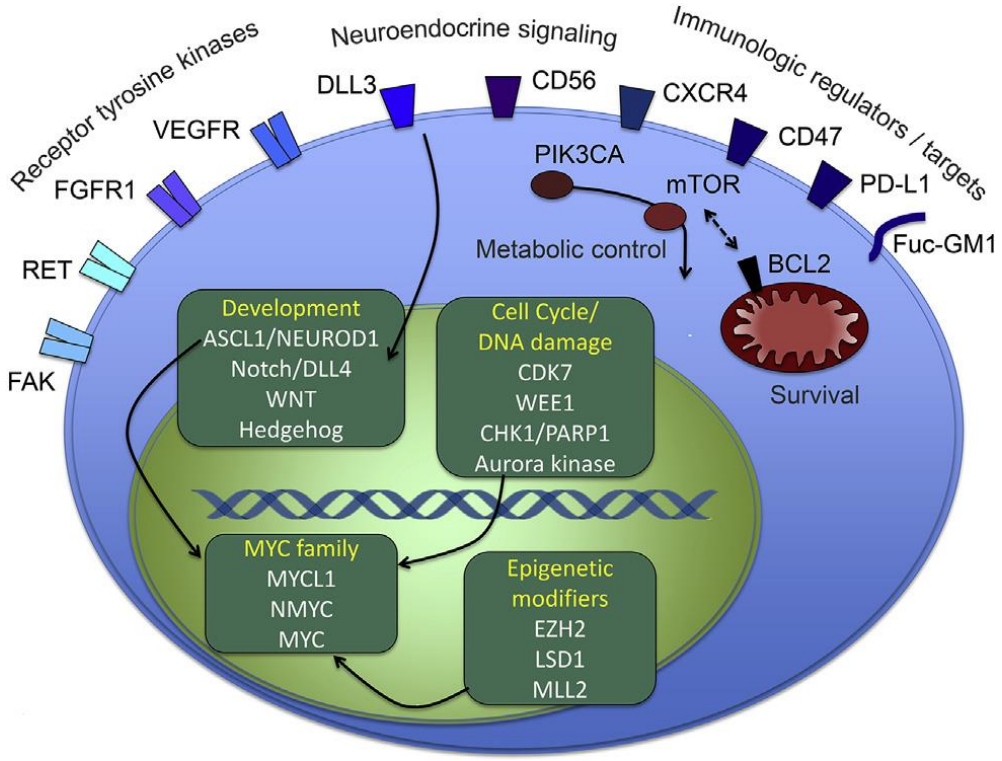
IASLC

Small Cell Lung Cancer: Can Recent Advances in Biology and Molecular Biology Be Translated into Improved Outcomes?

CrossMark

New perspectives and future directions:

Is there a role for "mAbs" and immunotherapy in SCLC ?



Potential "targets of treatment":

- ❑ Notch
- ❑ FGFR
- ❑ PI3KCA
- ❑ RET
- ❑ FAK
- ❑ CXCR4
- ❑ PARP
- ❑ PD-L1
- ❑ VEGFR

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Bunn Jr PA. et al. J Thor Oncol 2016;11

Most important suggestion:

Don’t smoke!

Don’t smoke!

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Head and neck and lung tumors The view from the biologist's point of view

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University Hospital Zurich, Switzerland

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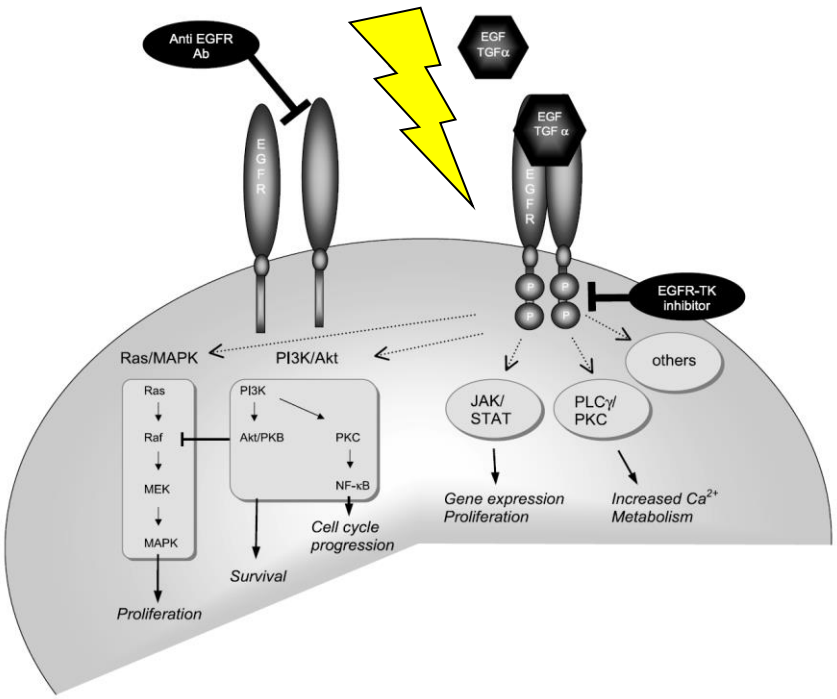
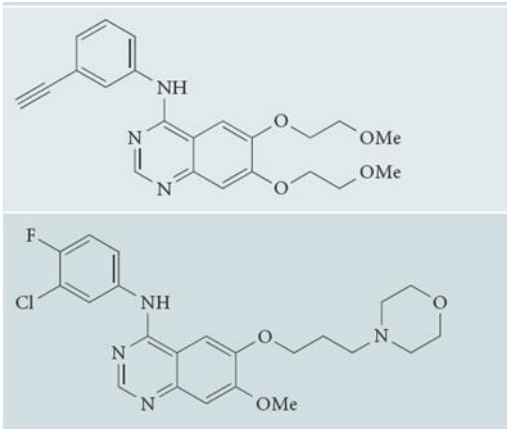
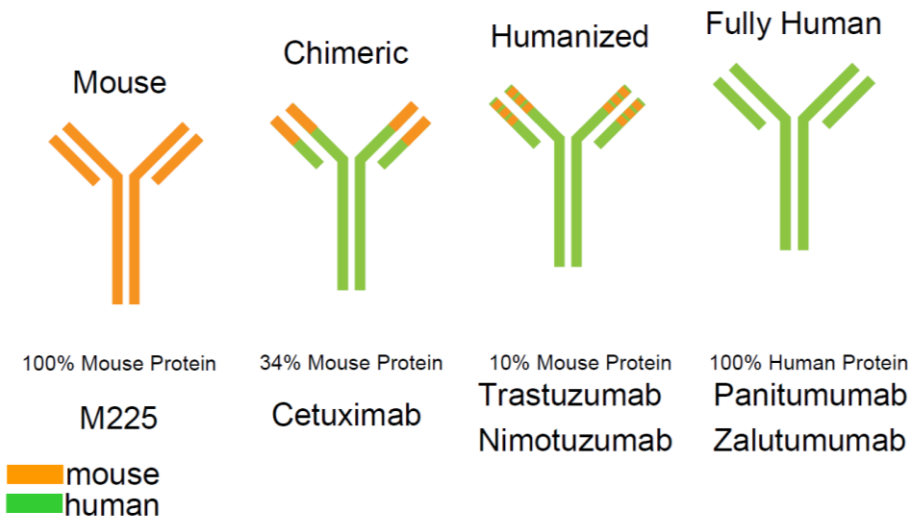
Overview

- Mechanism of Radiosensitization: EGFR
- Novel Target: AXL, Immune response and RT
- Own approach: Secretome as Target

Targeting with EGFR-directed Inhibitors

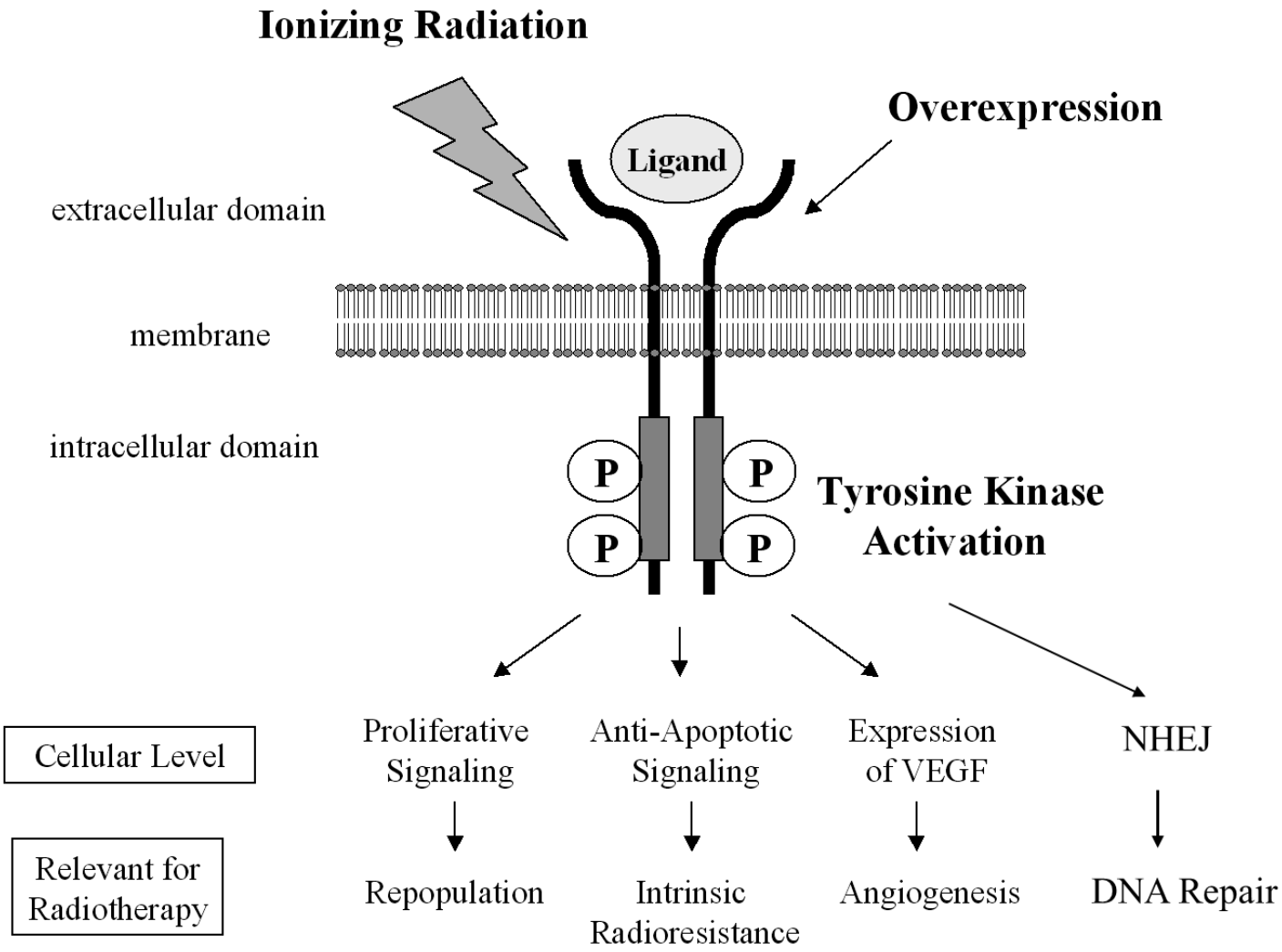






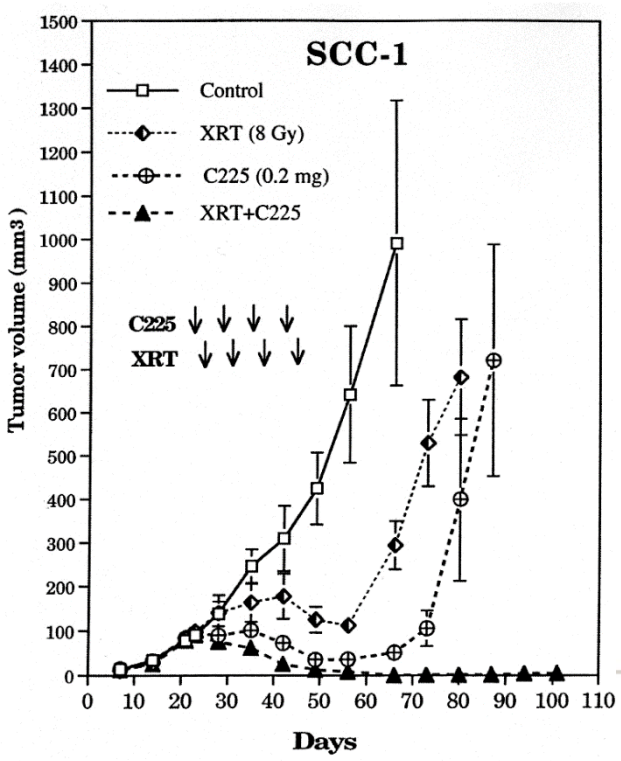
Multiple downstream mechanisms leading to radiosensitization

Multiple Role of Activated RTKs



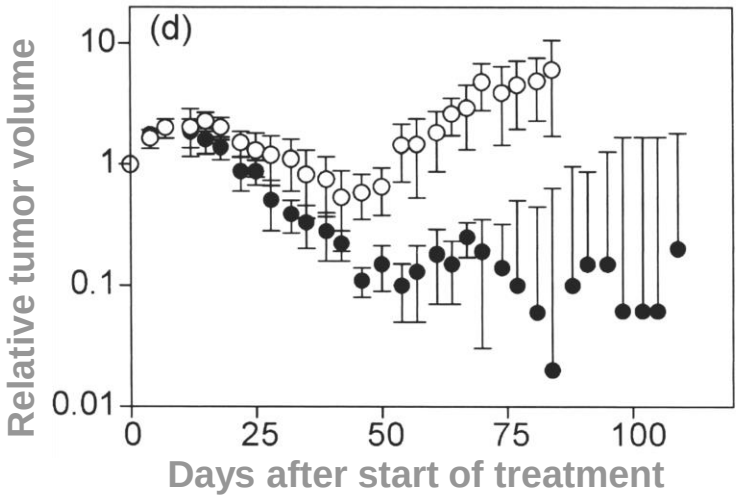
Cetuximab mediates tumor growth delay and enhances tumor control in vivo

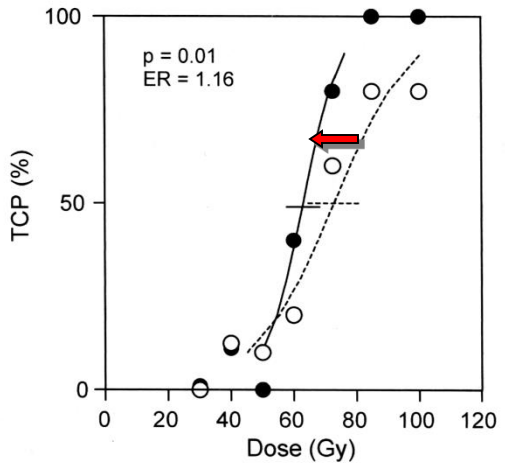
Huang et al., Clin. Cancer Res., 6, 2166ff, 2002



Krause et al. Radiother. Oncol. 2005

FaDu tumor xenograft model





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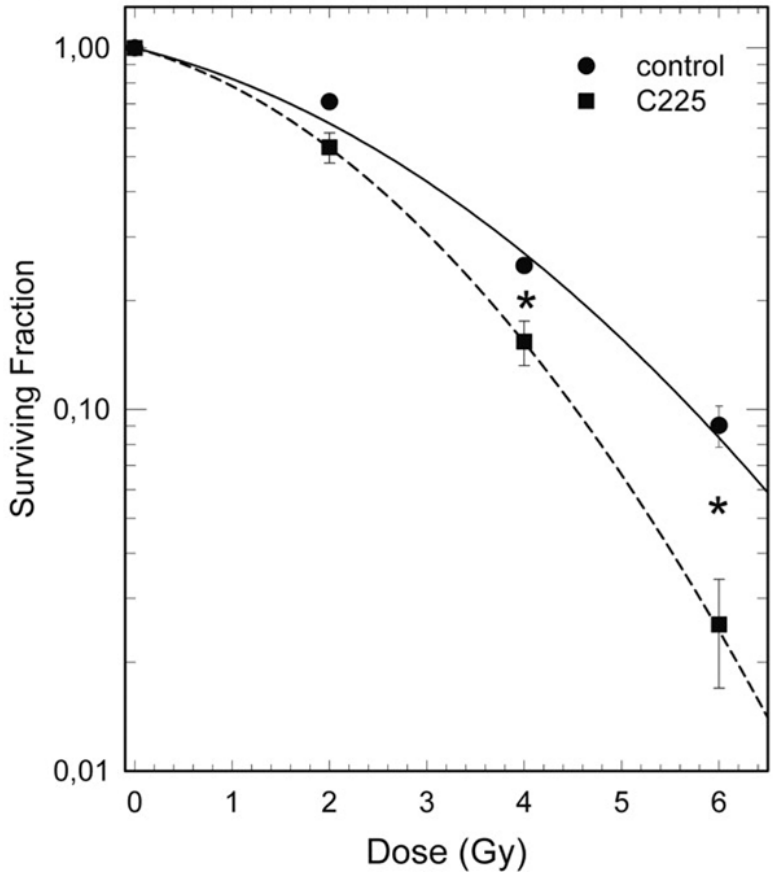
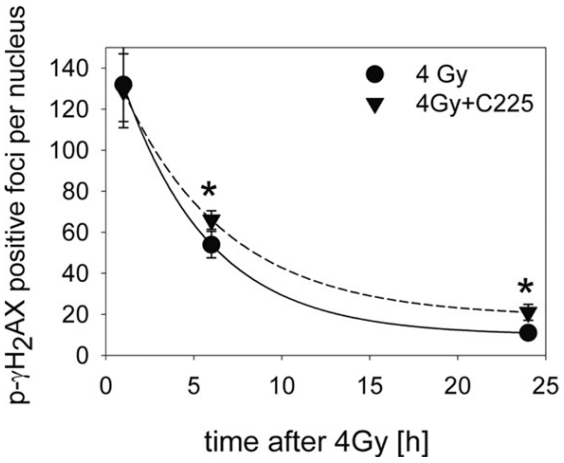
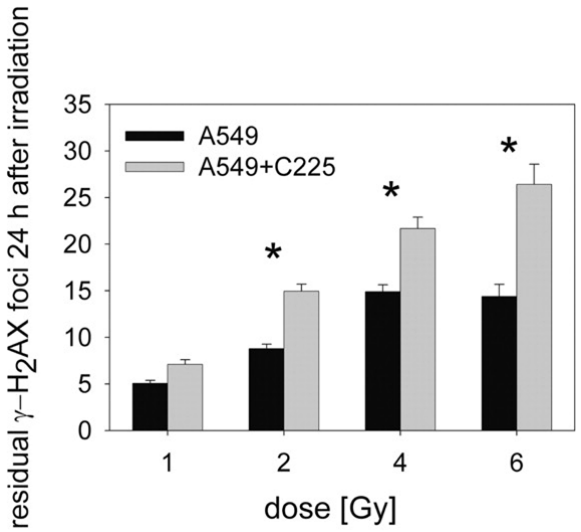
Effect of EGFR blockage on DNA repair and cell survival after irradiation

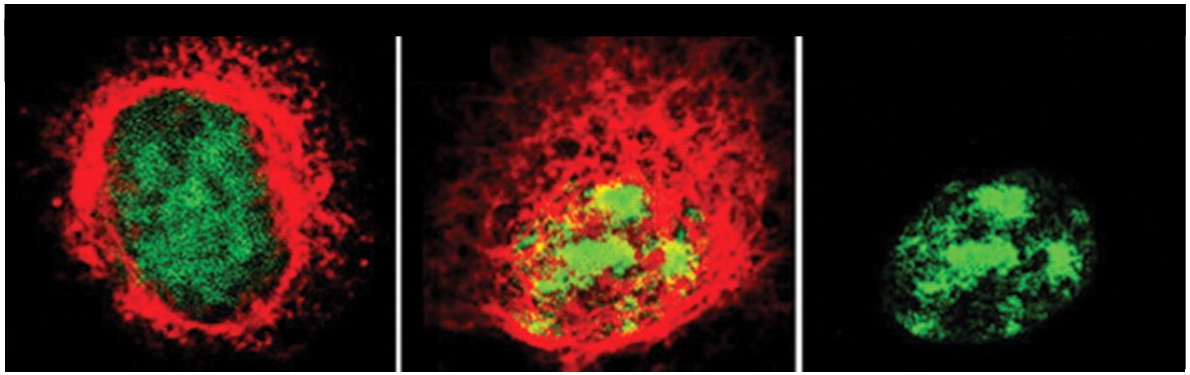


Radiosensitization in vitro (A549)

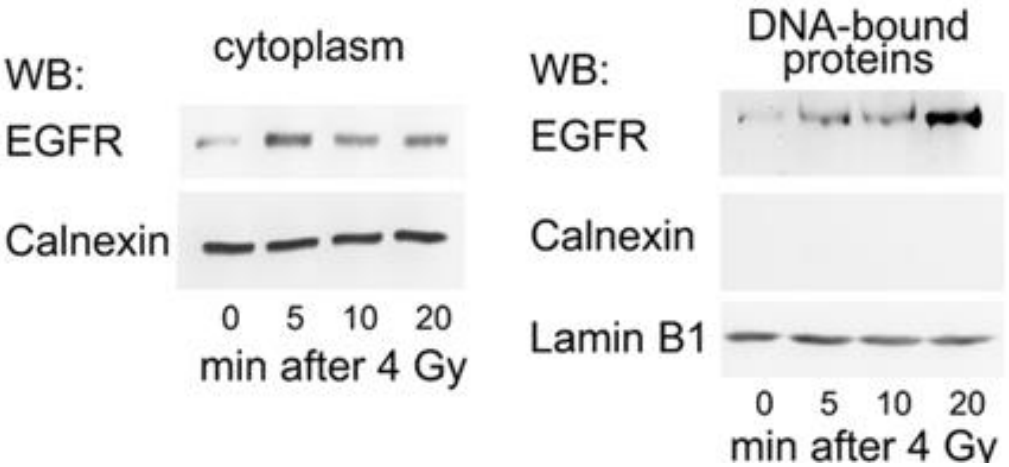


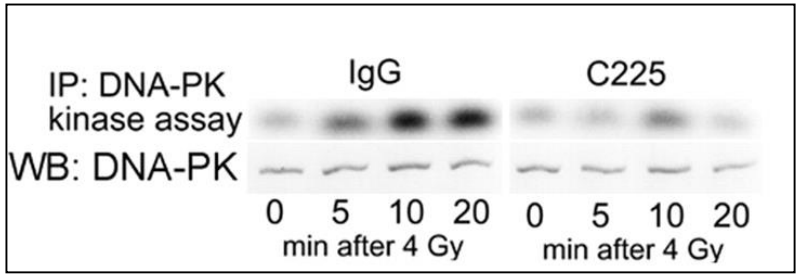


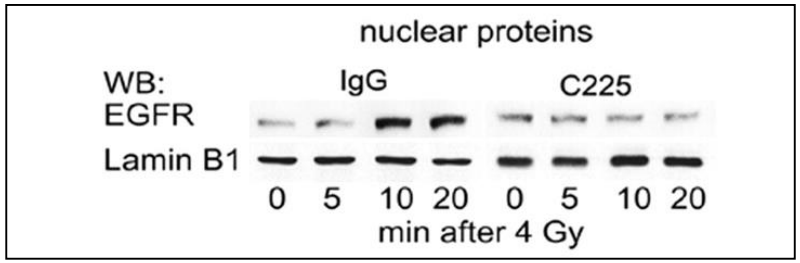
POTENTIAL ROLE OF EGFR IN THE NUCLEUS



Nuclear localization of the EGFR after treatment with ionizing radiation (EGFR, in red after 4 Gy)







Dittmann et al., JBC, 280, 31182ff, 2005

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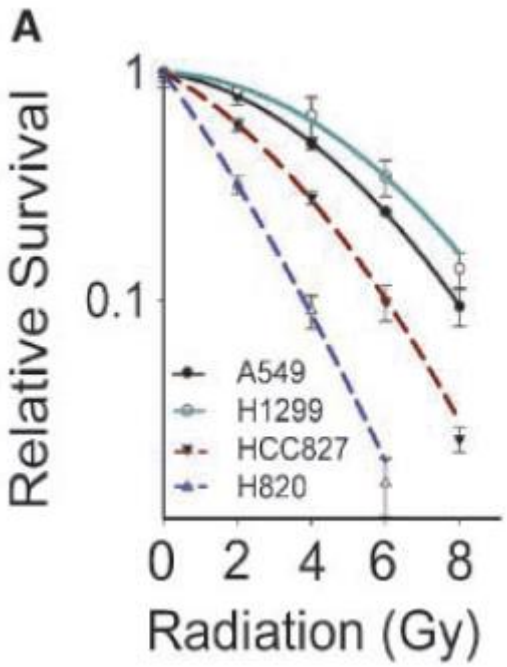
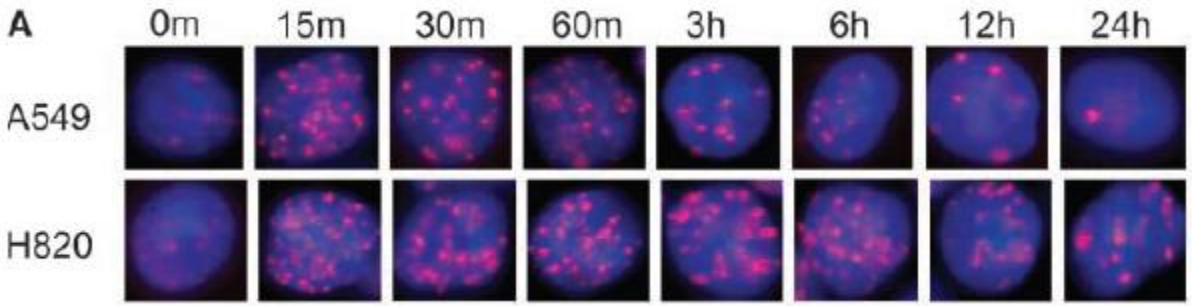
NSCLC: EGFR TKD Mutations and Radiation Sensitivity



A549: wildtype
H820: in-frame deletion
mt EGFR TKR
show a radiation sensitive phenotype
delayed DSB repair
disturbed cell-cycle control



EGFR TKD wt

dE746-750 mtEGFR TKD

Das AK et al. Cancer Res 2006, 66:9601-9608

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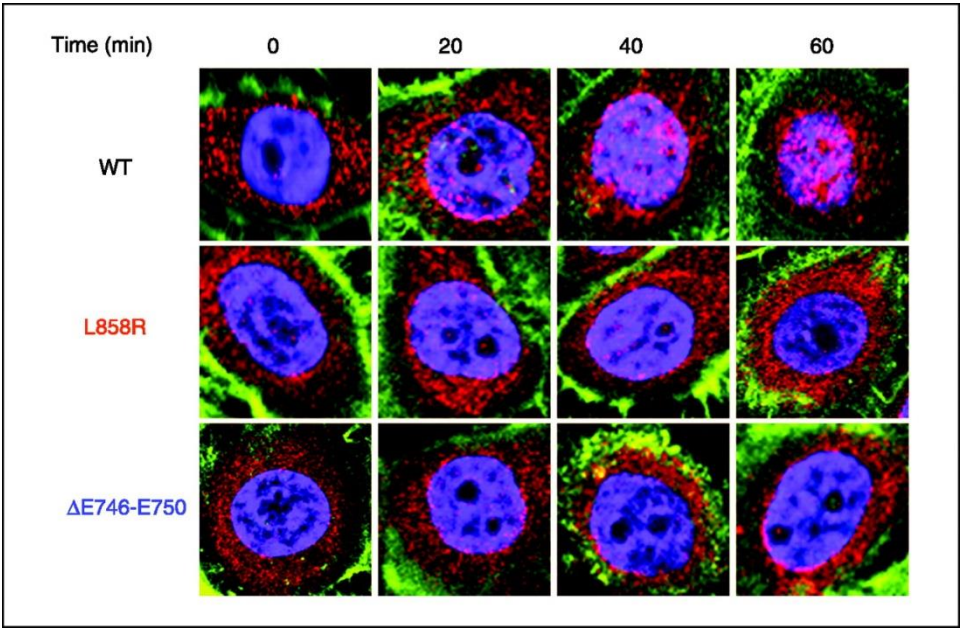
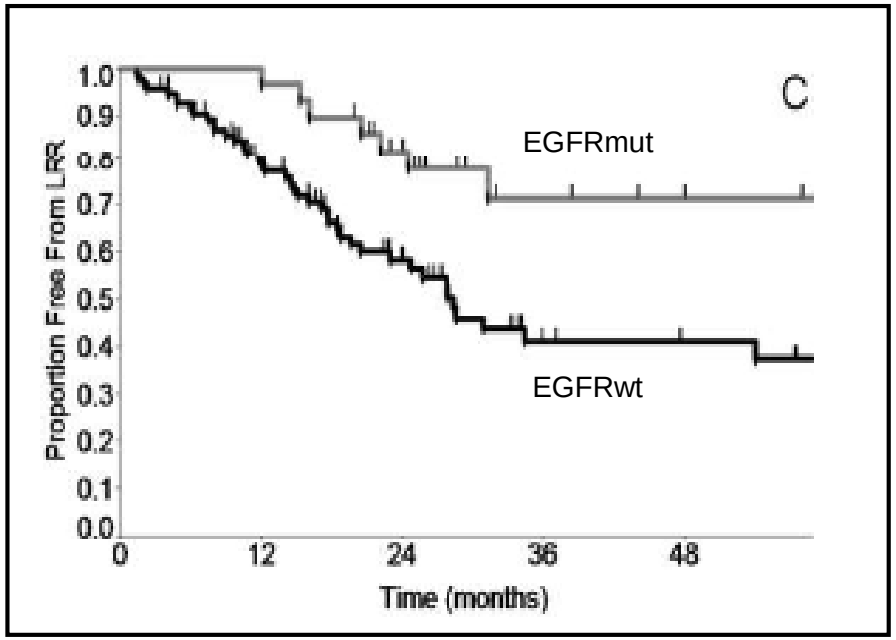
NSCLC: EGFR TKD Mutations and Radiation Sensitivity



IR-induced Nuclear Translocation of WT but not TKD-mutated EGFR

Das A K et al. Cancer Res 2007;67:5267-5274



Locoregional control for EGFR mut vs wt stage III NSCLC; retrospective

Mak et al. *The Oncologist* 2011, 16:886-895.

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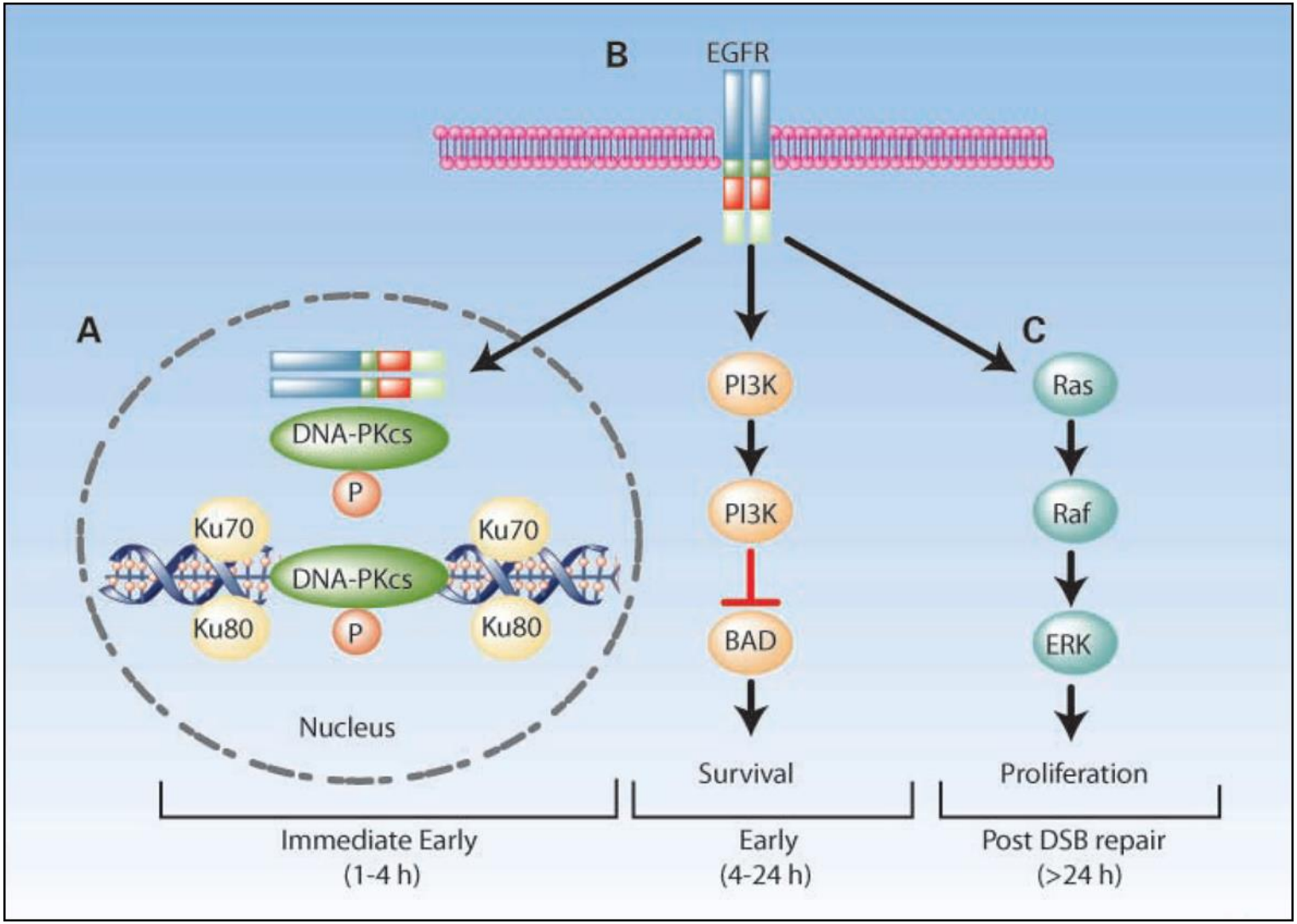
A model for EGFR-mediated Radioprotection



Chen D J , and Nirodi C S Clin Cancer Res 2007;13:6555-6560

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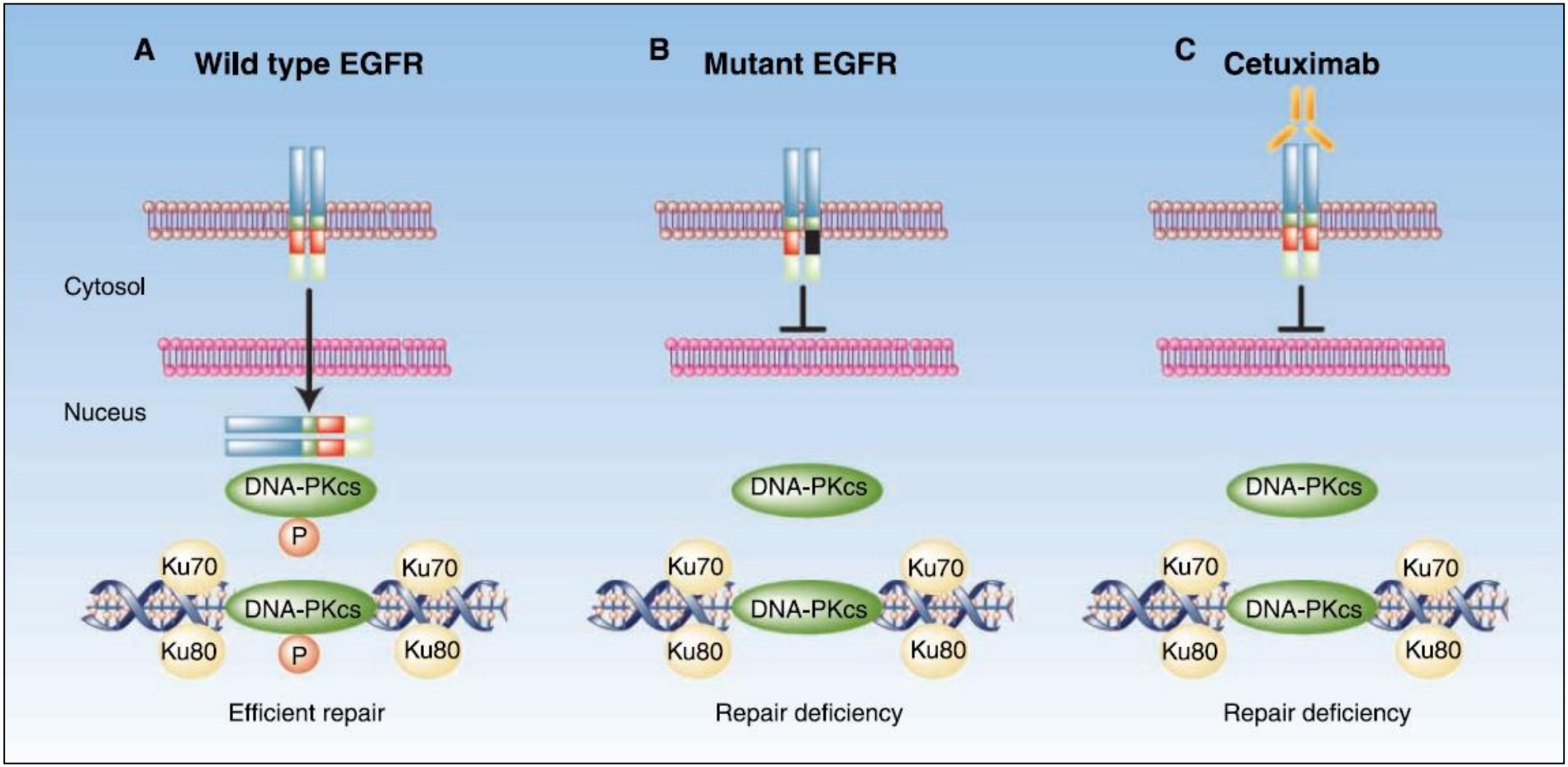
Blockade of EGFR-mediated DNA Repair



Chen D J , and Nirodi C S Clin Cancer Res 2007;13:6555-6560

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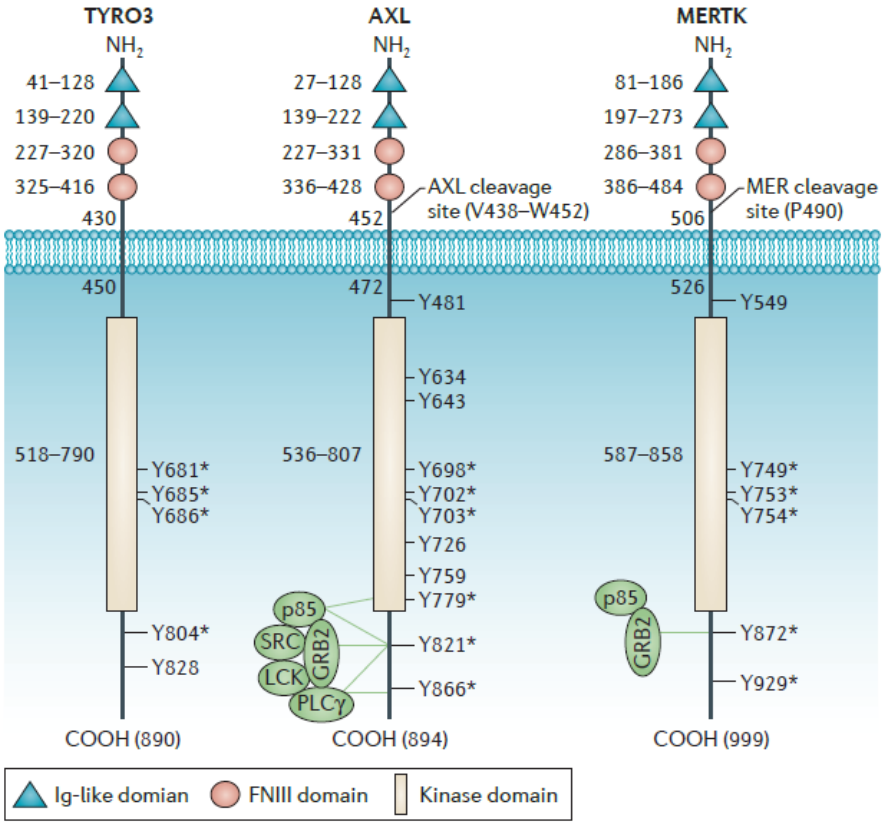
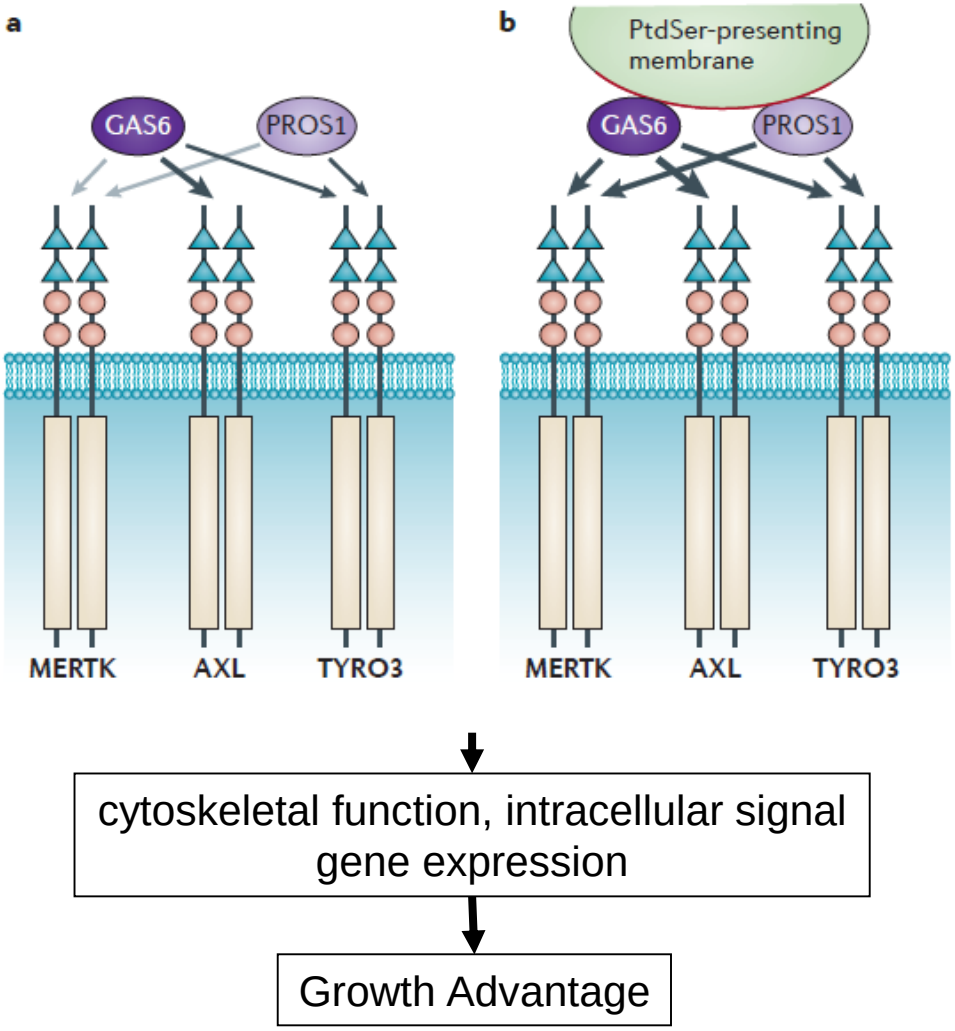
We need new targets!

The AXL-axis





Abberantly expressed in multiple cancer entities
(lung, mamma, HNSCC, glioblastoma etc.; correlates with worse prognosis)
(Graham et al., Nature Cancer Reviews, 2014)

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AXL-Axis: Additional Modes of Action

AXL immunosuppresses innate immune cells

AXL is expressed in immunosuppressive cells

AXL drives immunosuppressive cytokine release

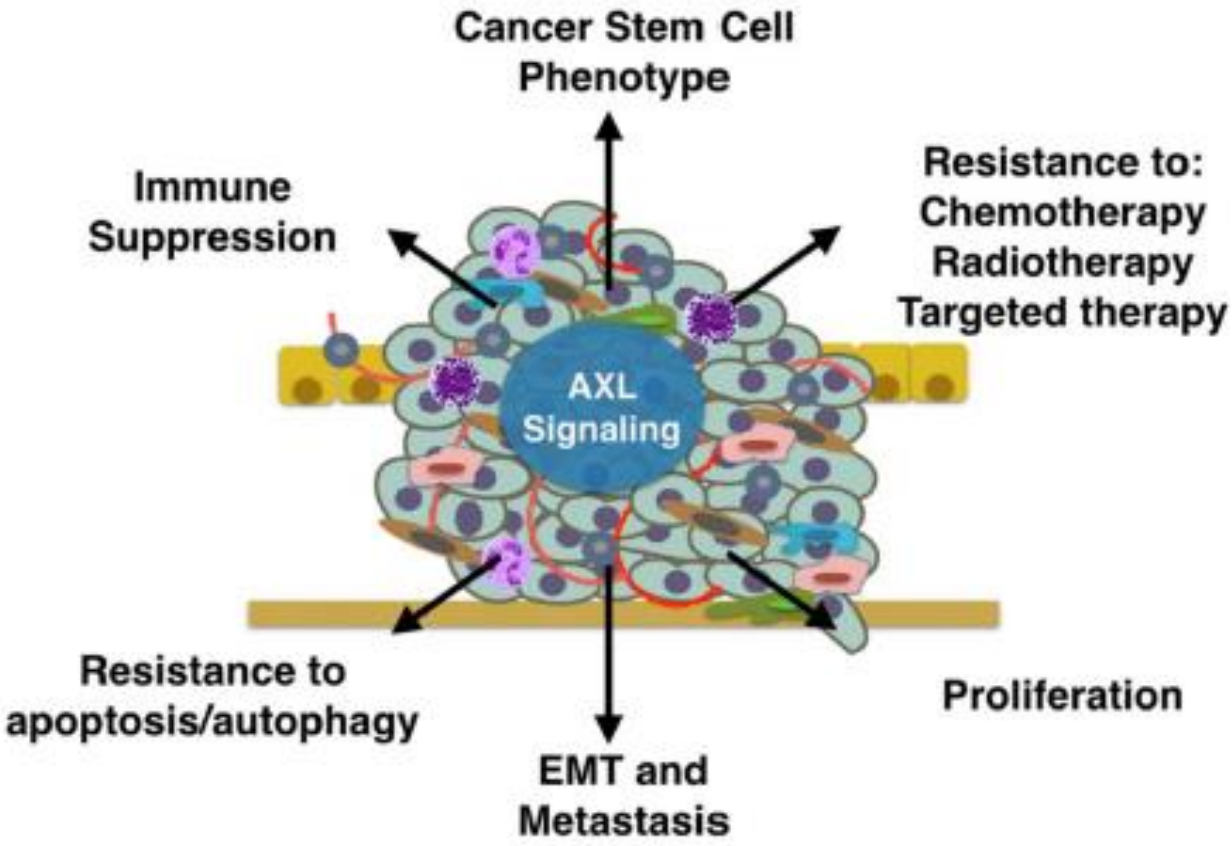
AXL expression inhibits NK cell mediated anti-metastatic effects

AXL promotes vasculogenesis

AXL is overexpressed in EGFR-treatment resistant tumors

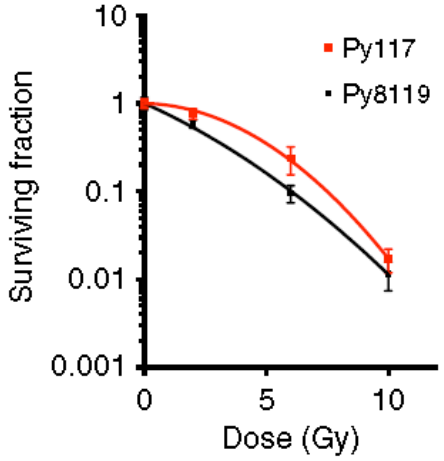
(Several Met inhibitors inhibit AXL)

Axl and Treatment Resistance

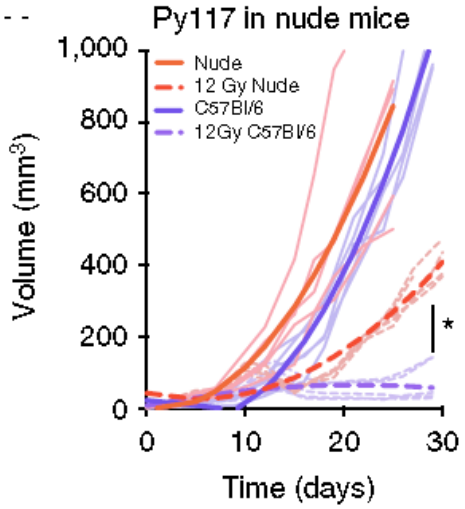


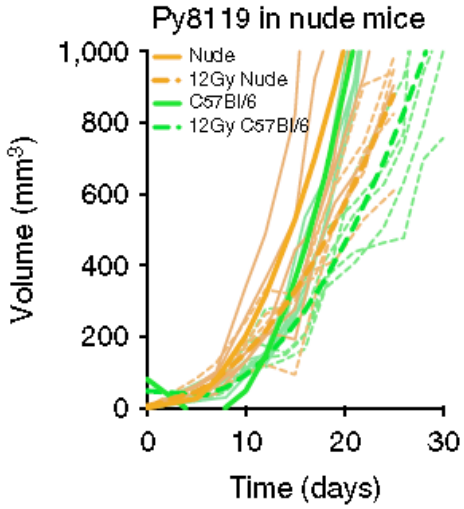
AXL suppresses MHC-I surface expression (reduced antigen presentation)

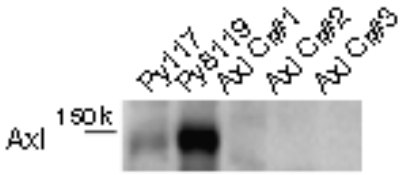
2 mammary tumor cells: in vitro

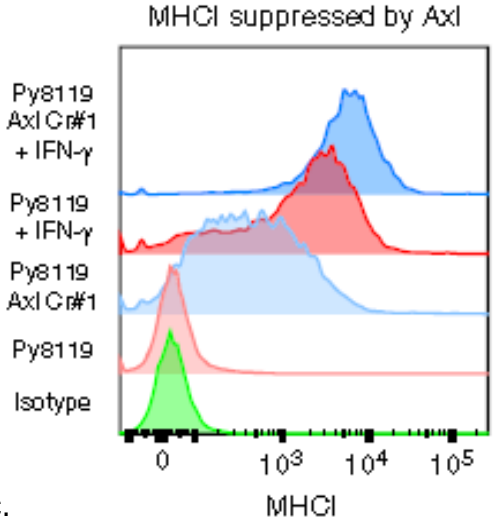


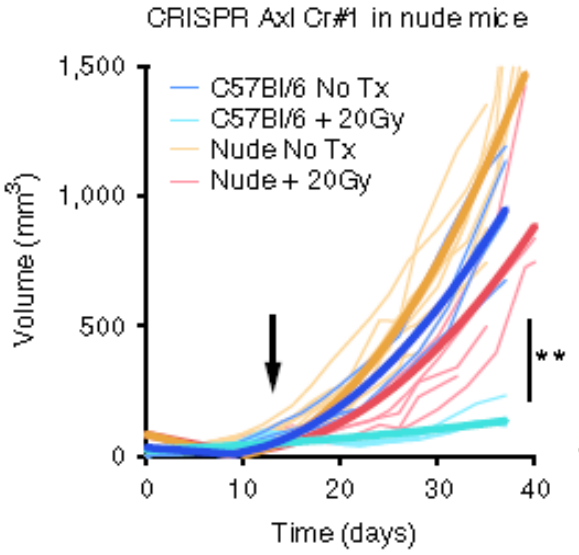
allografts derived thereof in vivo





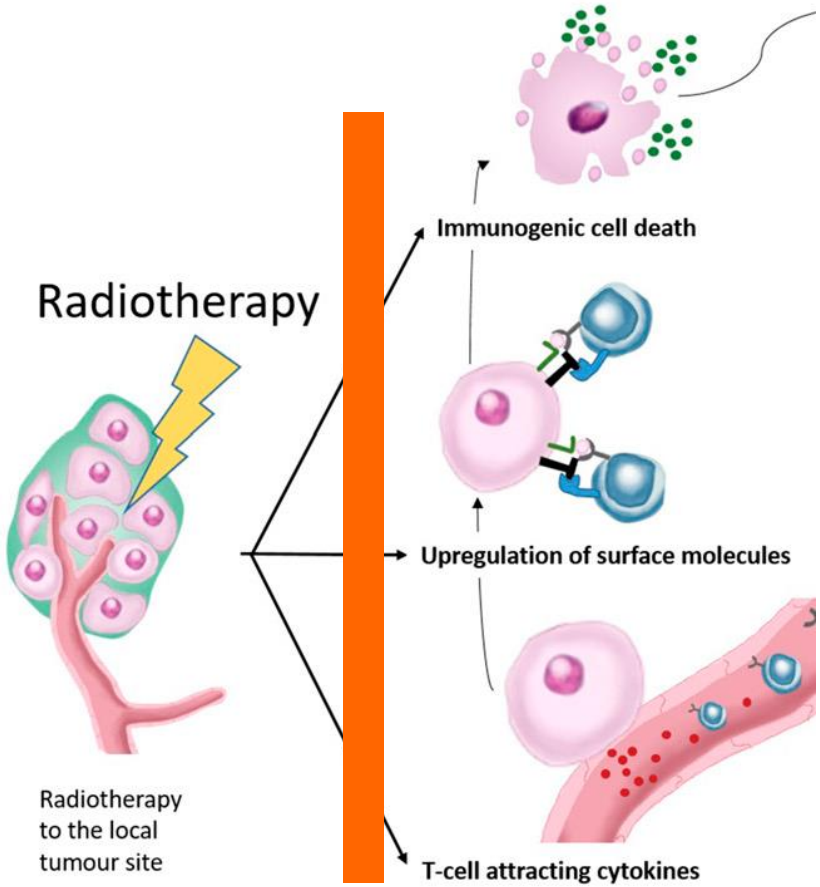






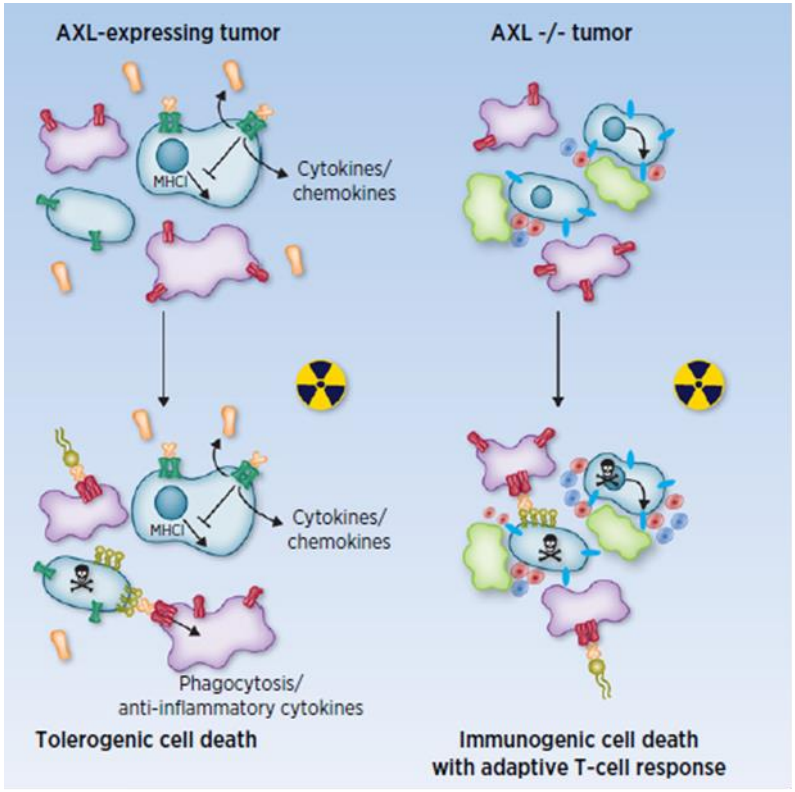
Aguilera et al., 2016 Nature Communic.

AXL, Immune Response and RT

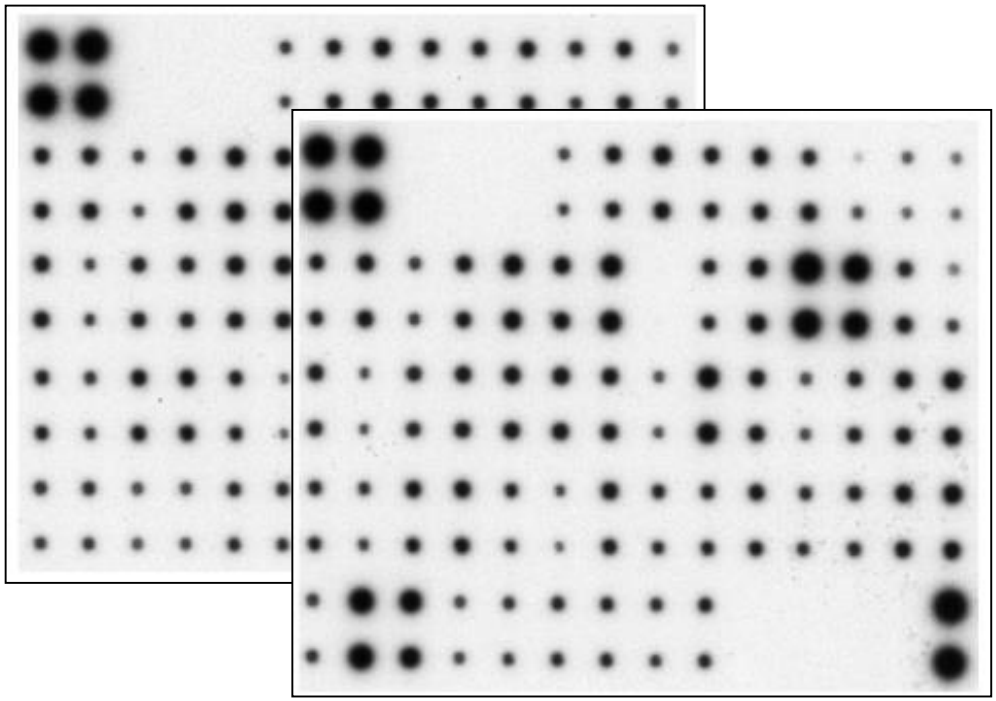


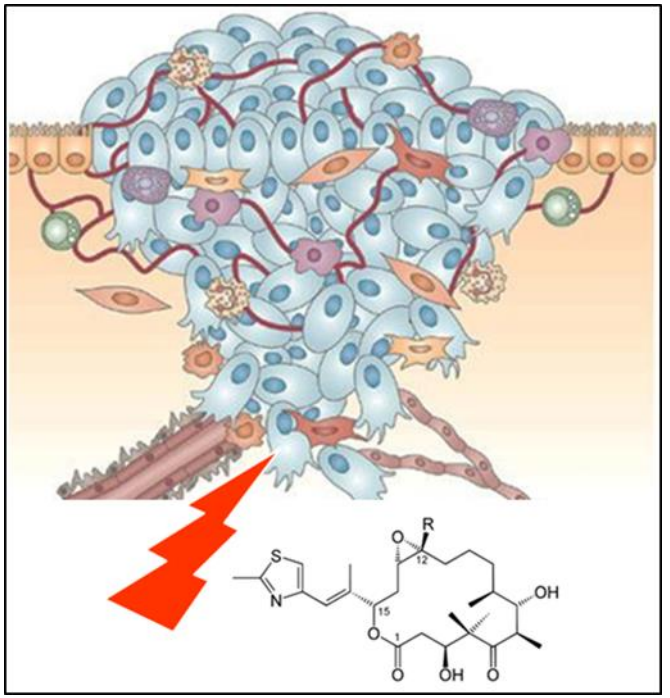
Inhibition of AXL: MHCI-increase

- Increase of adaptive T-cell response
- RT boosts ICD plus immune response



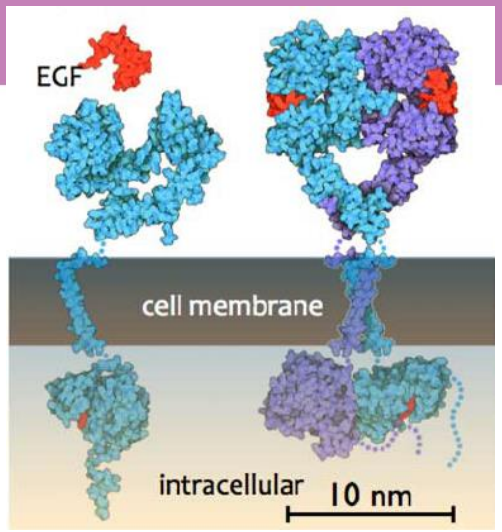
Secretome as novel target for lung cancer





Secretome:

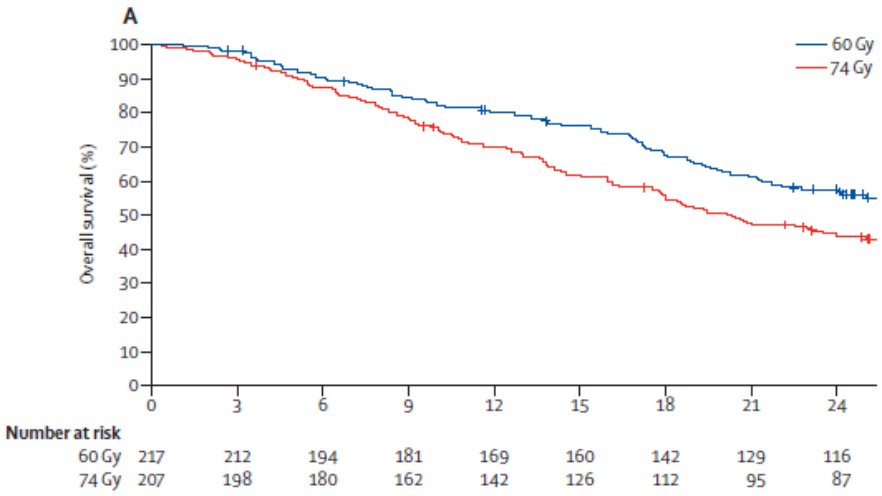
- easy accessible biomaterial
- multiple, serial samples
- as diagnostic tool
- as biomarker for treatment response
- as target

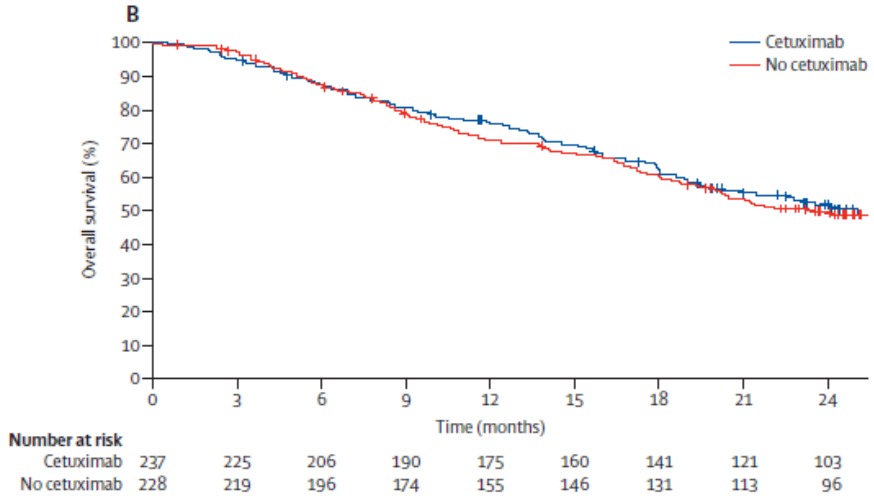


Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study

Jeffrey D Bradley, Rebecca Paulus, Ritsuko Komaki, Gregory Masters, George Blumenschein, Steven Schild, Jeffrey Bogart, Chen Hu, Kenneth Forster, Anthony Magliocco, Vivek Kavadi, Yolanda I Garces, Samir Narayan, Puneeth Iyengar, Cliff Robinson, Raymond B Wynn, Christopher Koprowski, Joanne Meng, Jonathan Beitler, Rakesh Gaur, Walter Curran Jr, Hak Choy

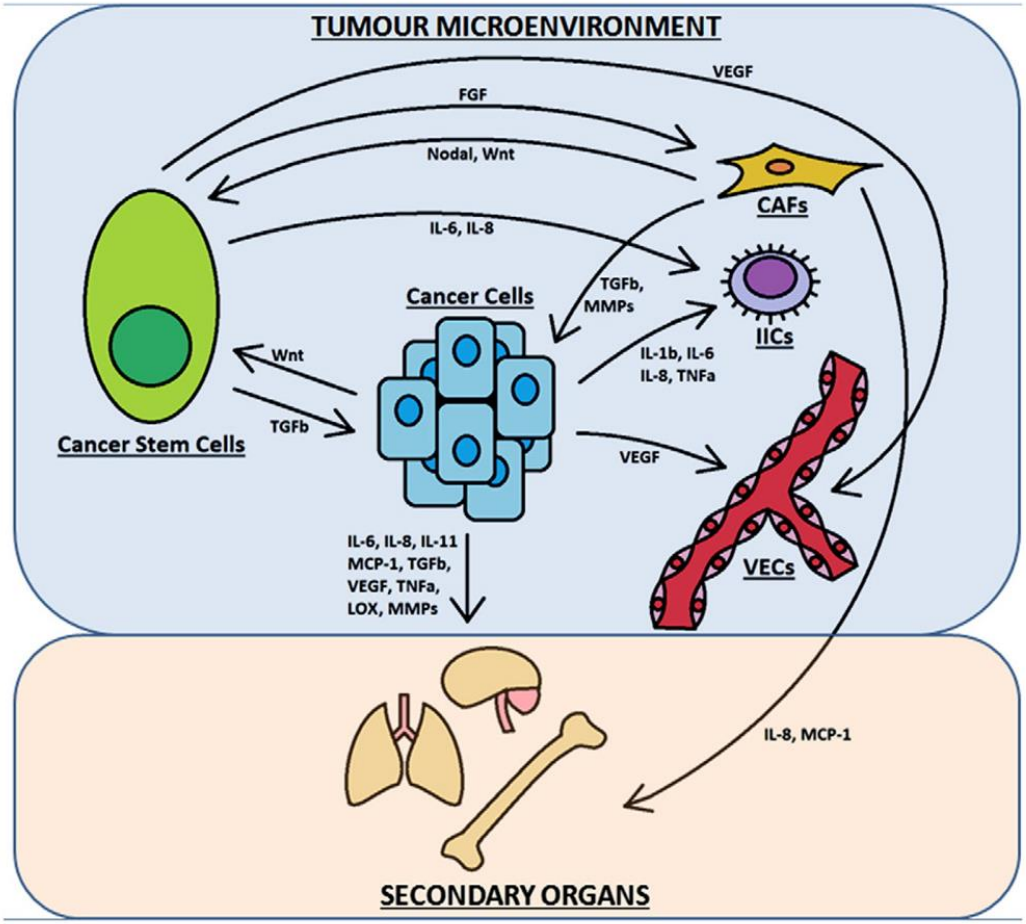
Lancet Oncol 2015; 16: 187–99





- many open questions:e.g. targeting multiple instead of single factor

Elements and interactions of the tumor secretome



Paltridge et al., BBA, 1834, 2233ff, 2013

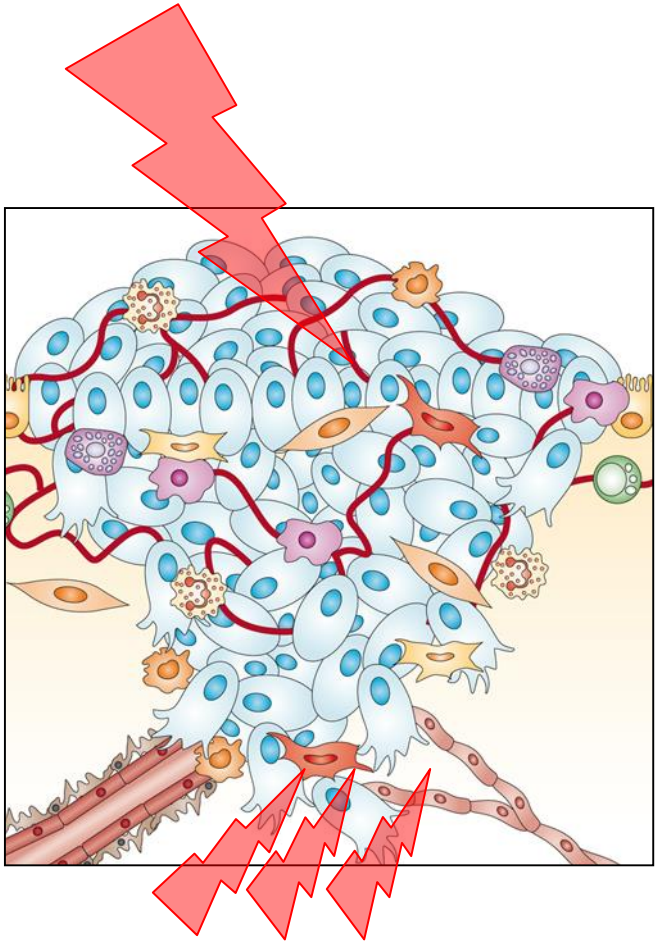
in vitro - cellular level:
Supernatants
Co-culturing of multiple cell types

in vivo - tumor models:
Tumor interstitial fluid
Pleural effusion
Blood serum

patients – clinical level:
Tumor interstitial fluid
Pleural effusion
Blood serum

Tumor Secretome and Radiation Resistance

Growth- and resistance-modulatory factors (EGF, IGF, etc)



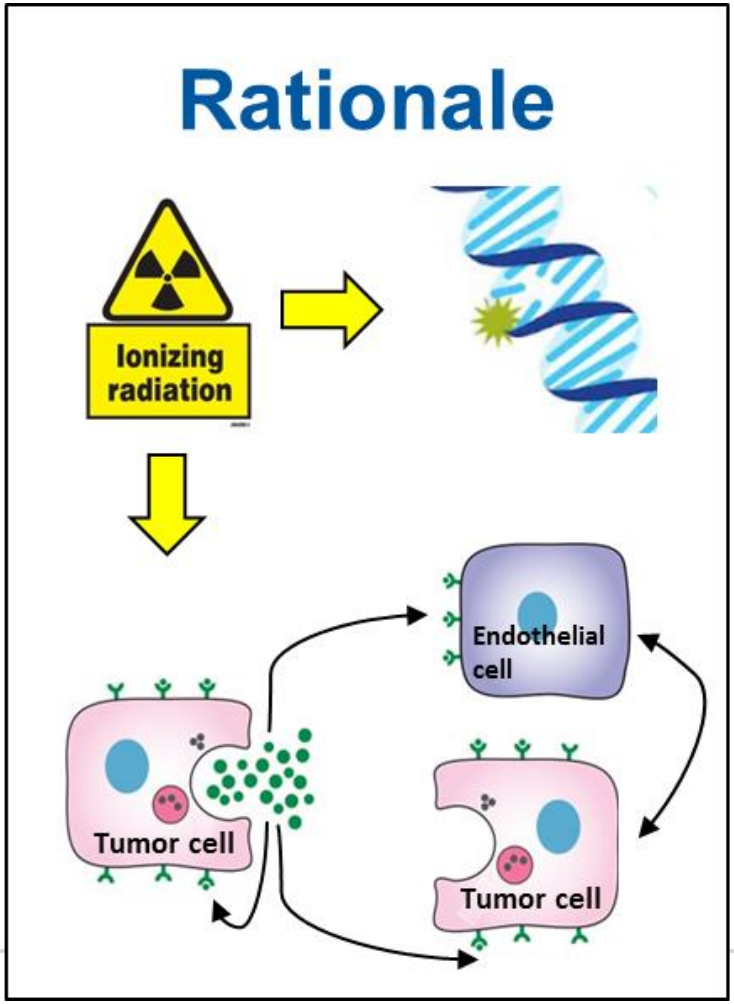
Immun-modulatory factors (IL-2,6, IFNβ, etc)

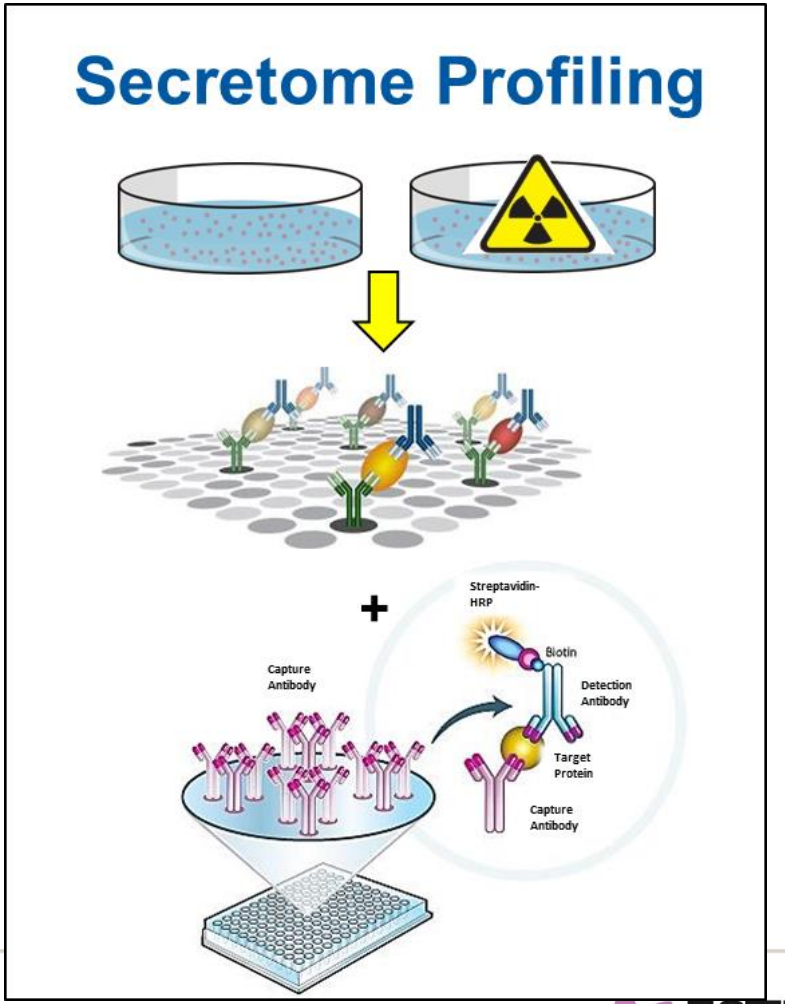
ECM- and dissemination-modulatory factors (TIMPs, LOX, PAI-1, etc)

Vasculature- and hypoxia-modulatory factors (VEGF, PLGF, Osteopontin etc.

Identification of Biomarkers for Relevant Processes (basal, under treatment)

Detection of IR-Induced Secretome from Tumor Cells (antibody array, Bioplex, ELISA)



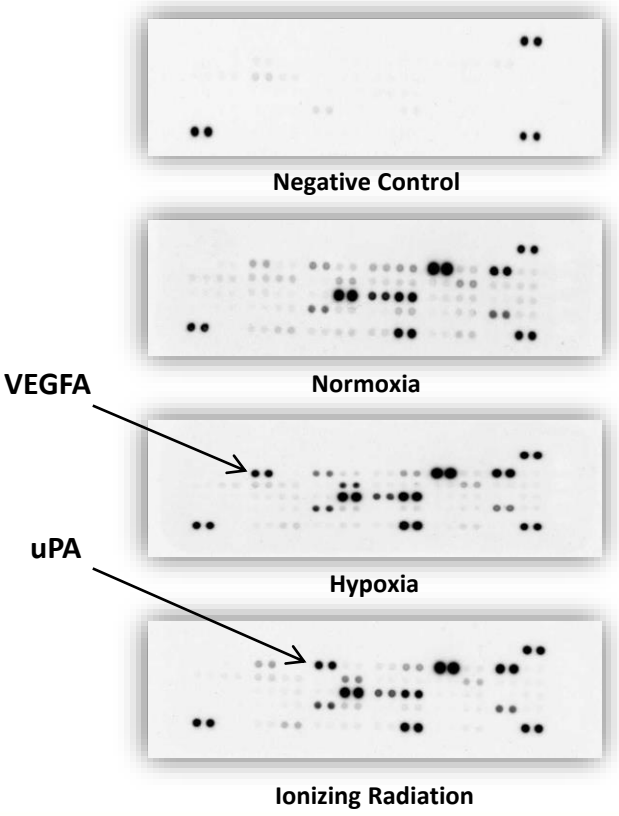


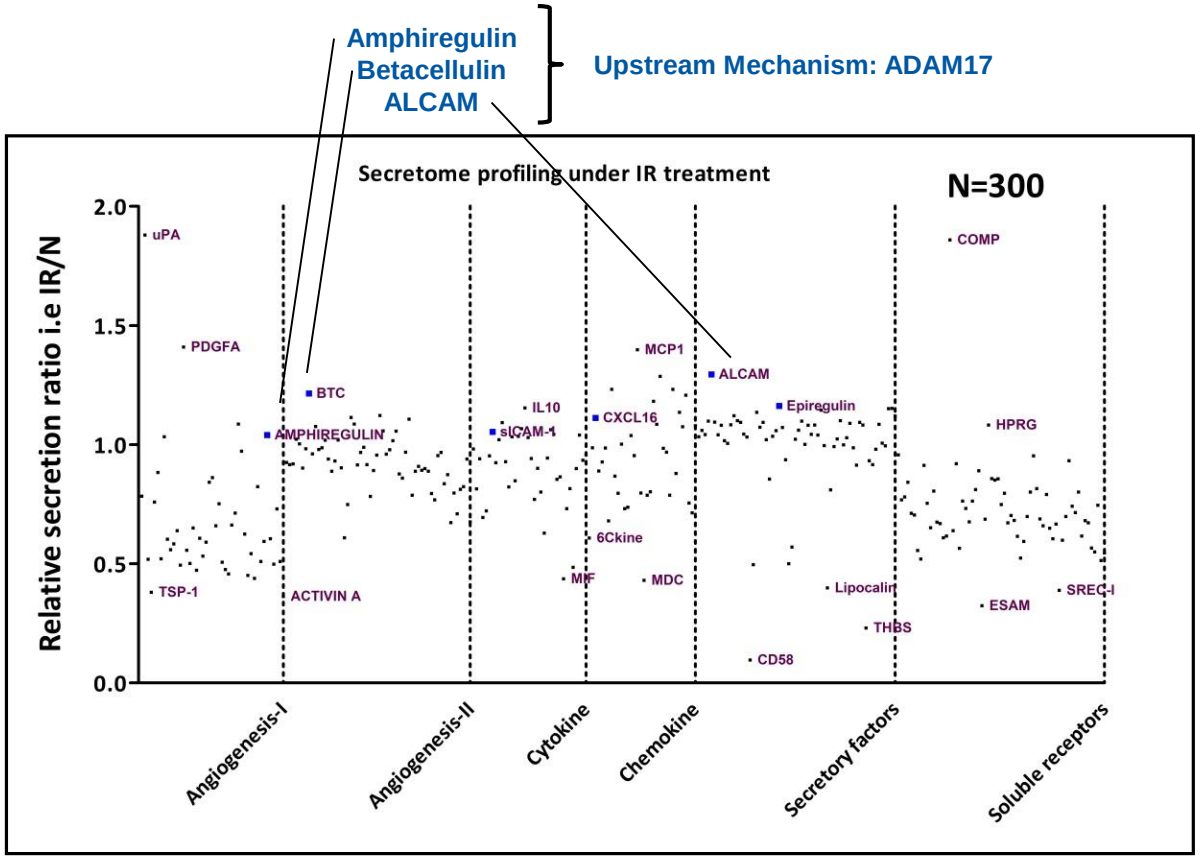
Broggini et al., JNCI, 2015

ESTRO School

Ionizing Radiation (IR) induces the secretion of multiple ADAM substrates *in vitro* and *in vivo*

(A549 adenocarcinoma cells)

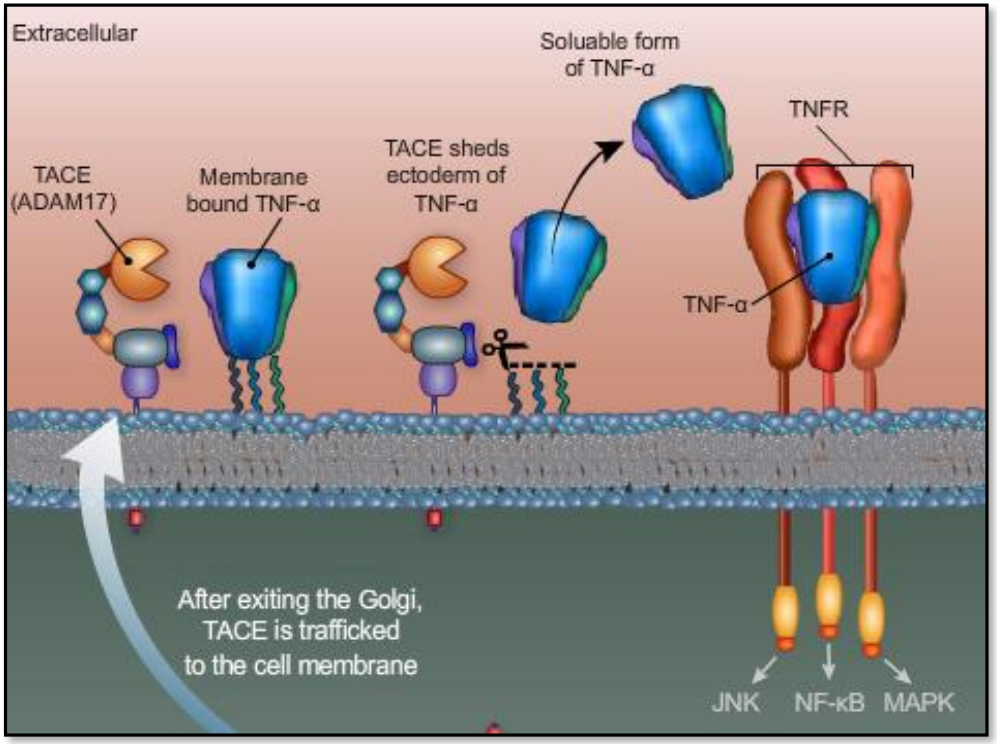




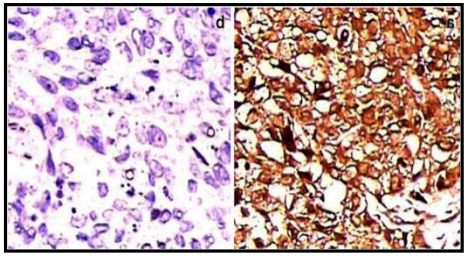
(In parallel: Screening of patient serum as part of clinical trials)

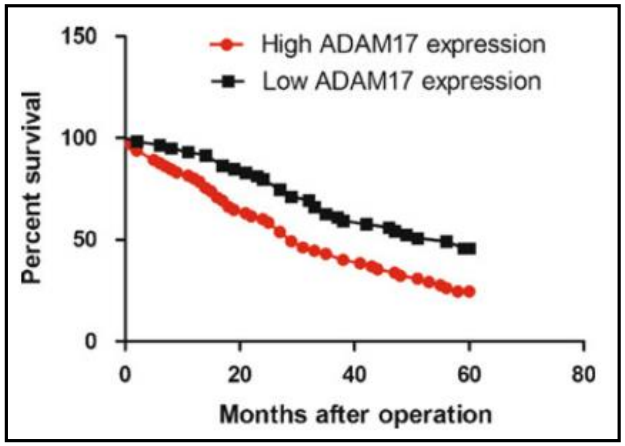
Sharma A *et al*. Clin. Cancer Research (2016)

ADAM17 (A Disintegrin and Metalloprotease 17) - Signaling Scissors



https://mutagenetix.utsouthwestern.edu/phenotypic/phenotypic_rec.cfm?pk=370



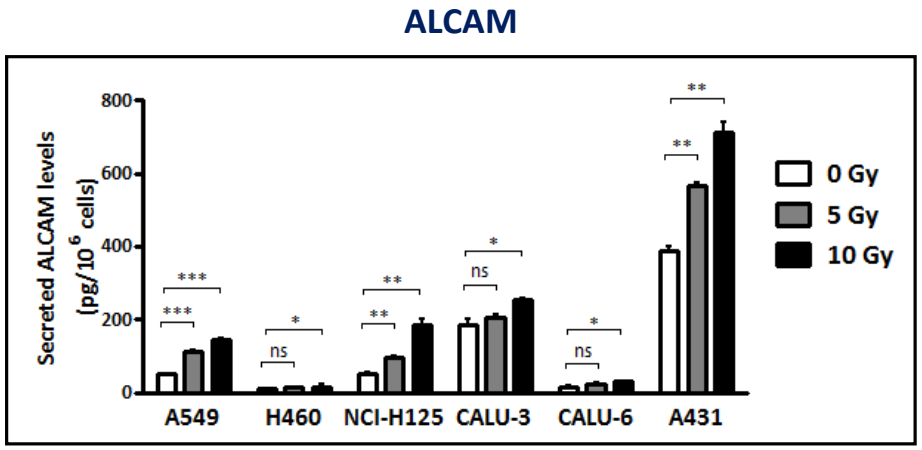


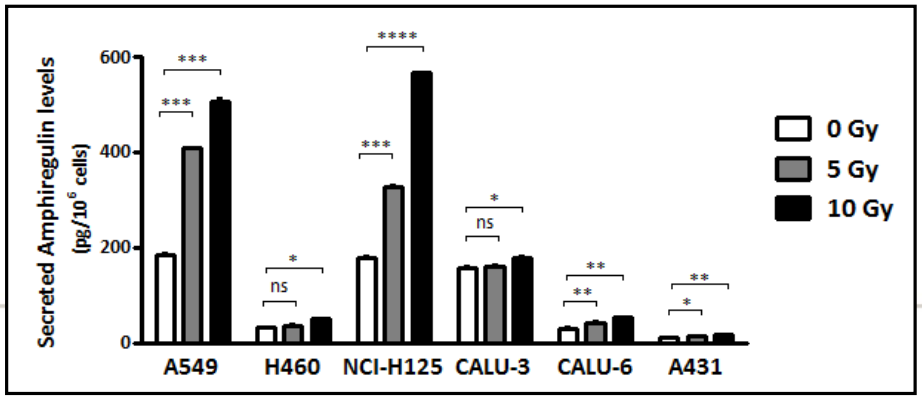
Tumour Biol. 2013 Jun;34(3):1813-8.

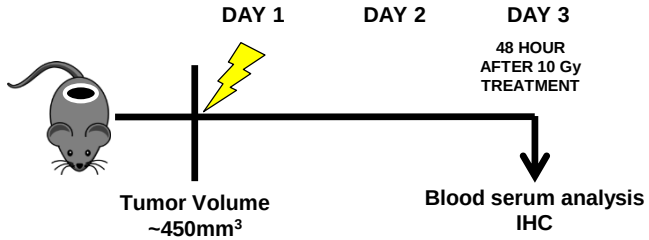
- ADAM 17 also called TACE (tumor necrosis factor-α-converting enzyme)
- Present at the trans-Golgi-network and plasma membrane
- ADAM17 is overexpressed in NSCLC and correlates with poor patient survival

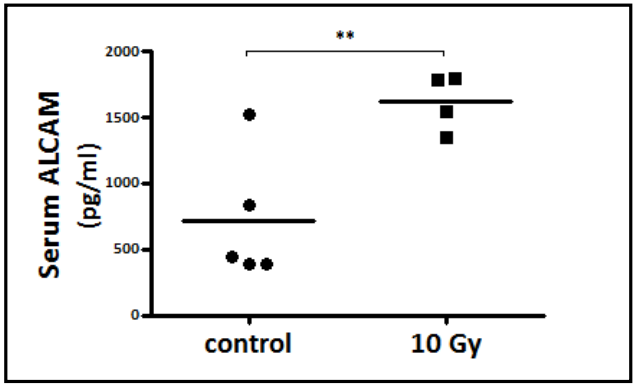
ESTRO School

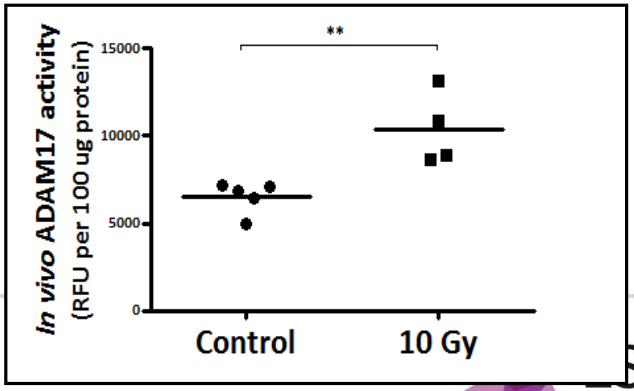
Ionizing Radiation (IR) induces the secretion of multiple ADAM substrates *in vitro* and *in vivo* (ELISA)





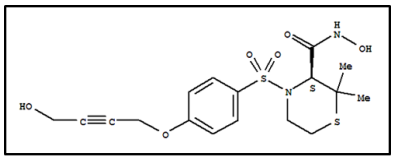




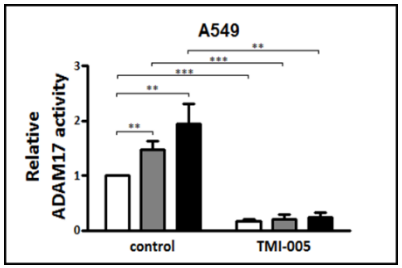


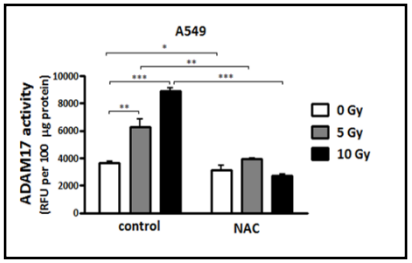
Sharma A *et al*. Clin. Cancer Research (2016)

Targeting of ADAM17 activity sensitizes NSCLC cells for ionizing radiation – in an EGFR-independent way

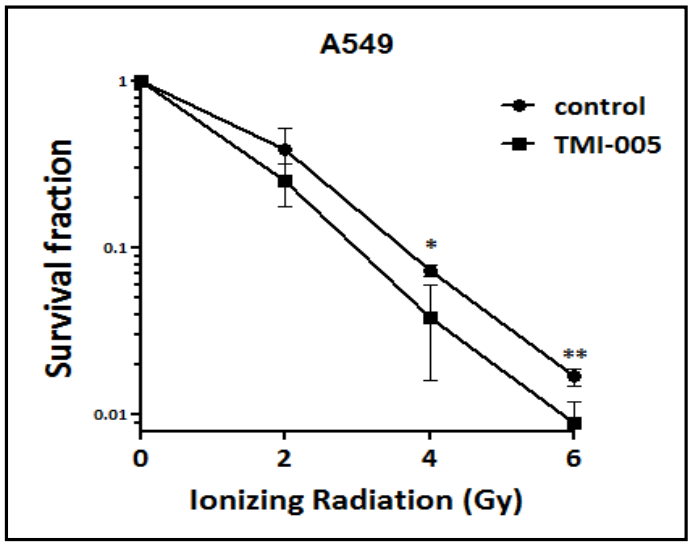


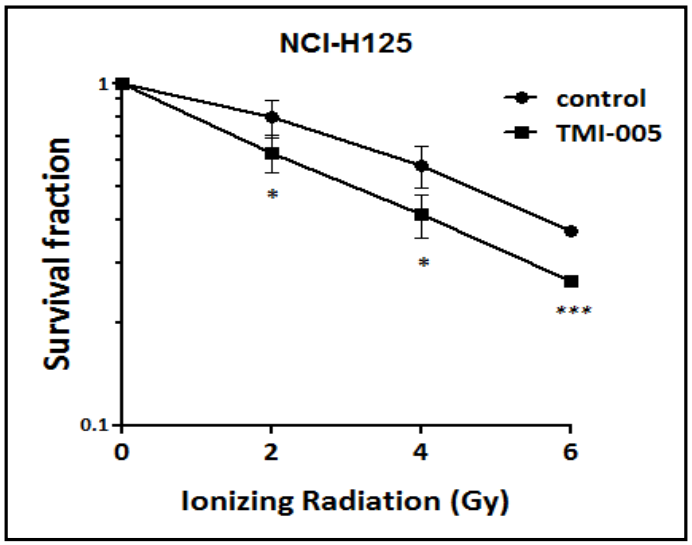
TMI-005

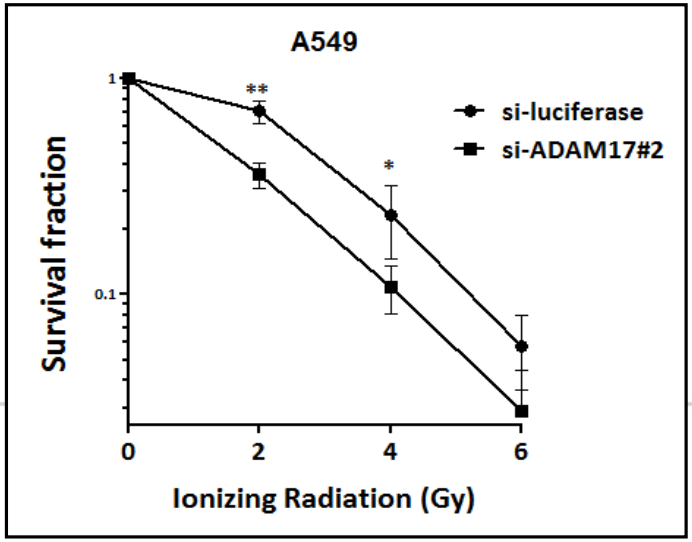


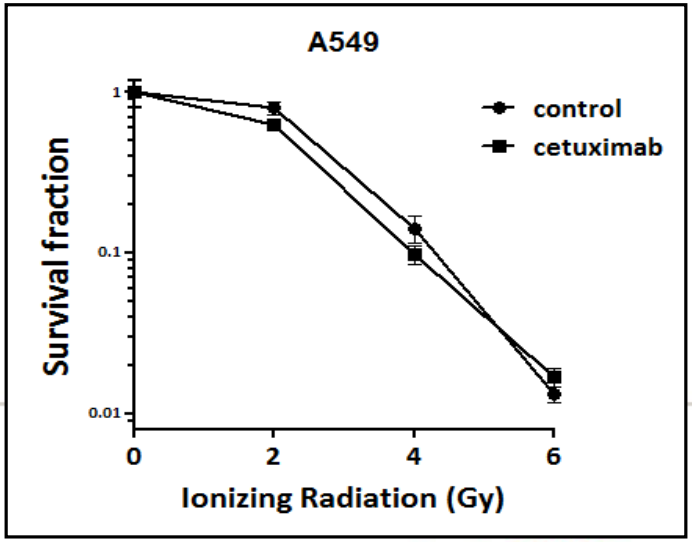


Clonogenic Cell Survival Assays

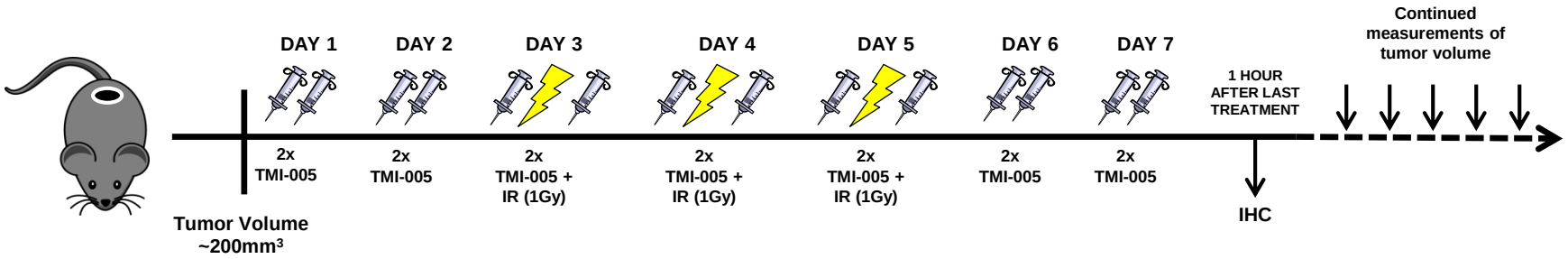


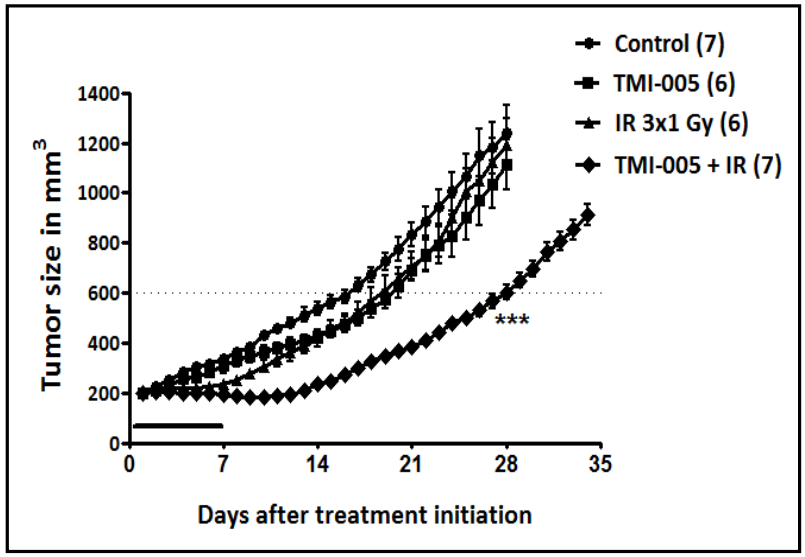


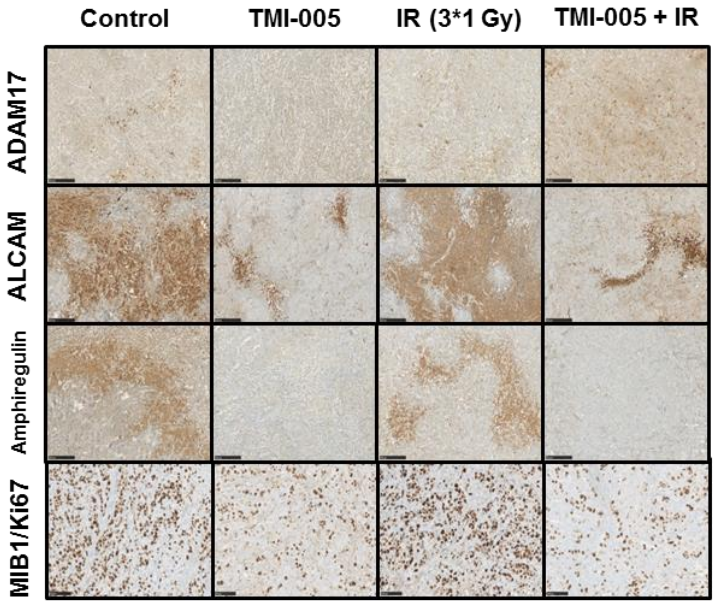




Effect of TMI-005 and IR alone and in combination on the growth of A549-derived tumor xenografts

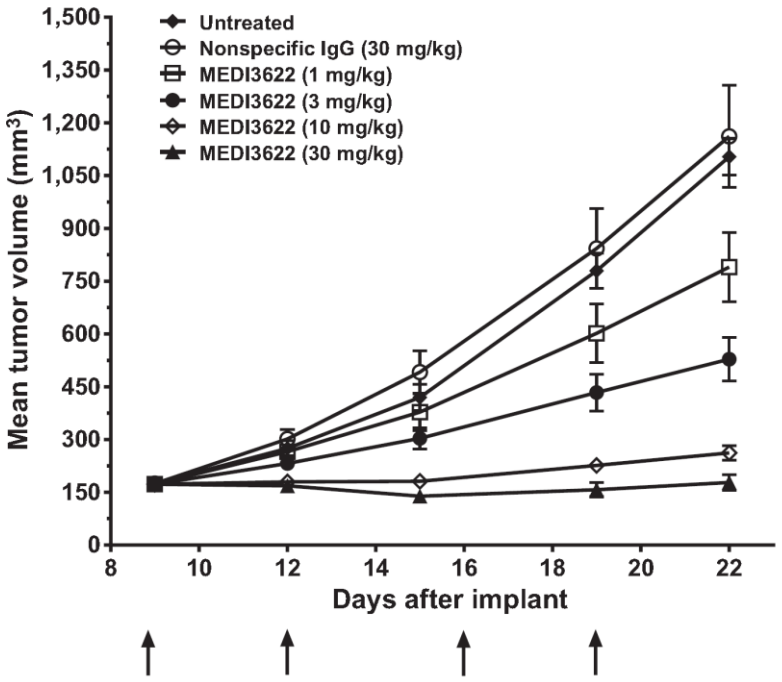


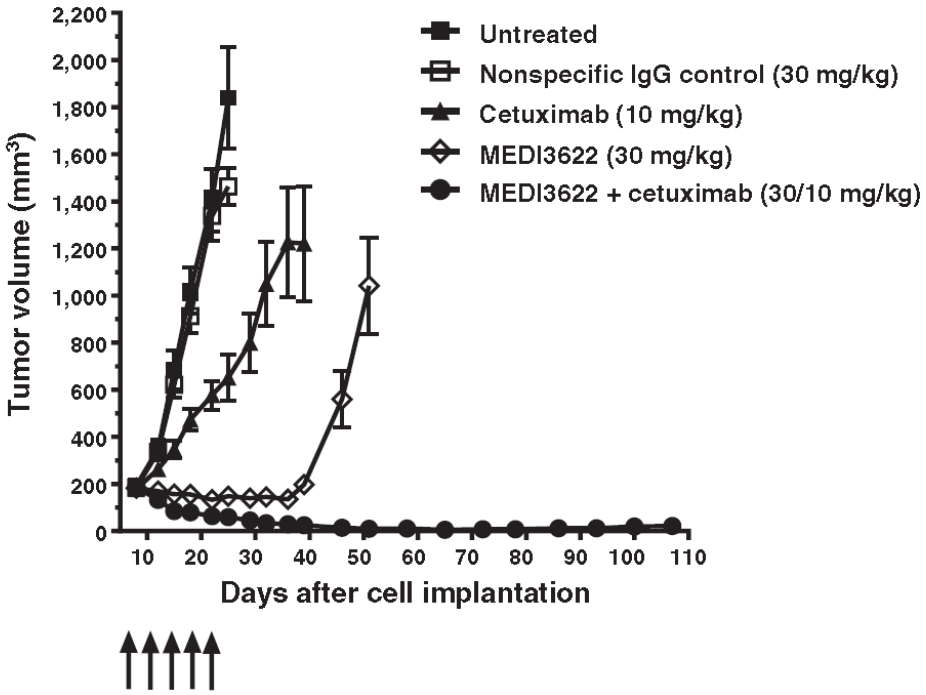




Combined treatment of TMI-005 and IR exerts a supra-additive tumor growth delay in A549-derived tumor xenografts

A Monoclonal Antibody to ADAM17 Inhibits Tumor Growth by Inhibiting EGFR and Non–EGFR-Mediated Pathways





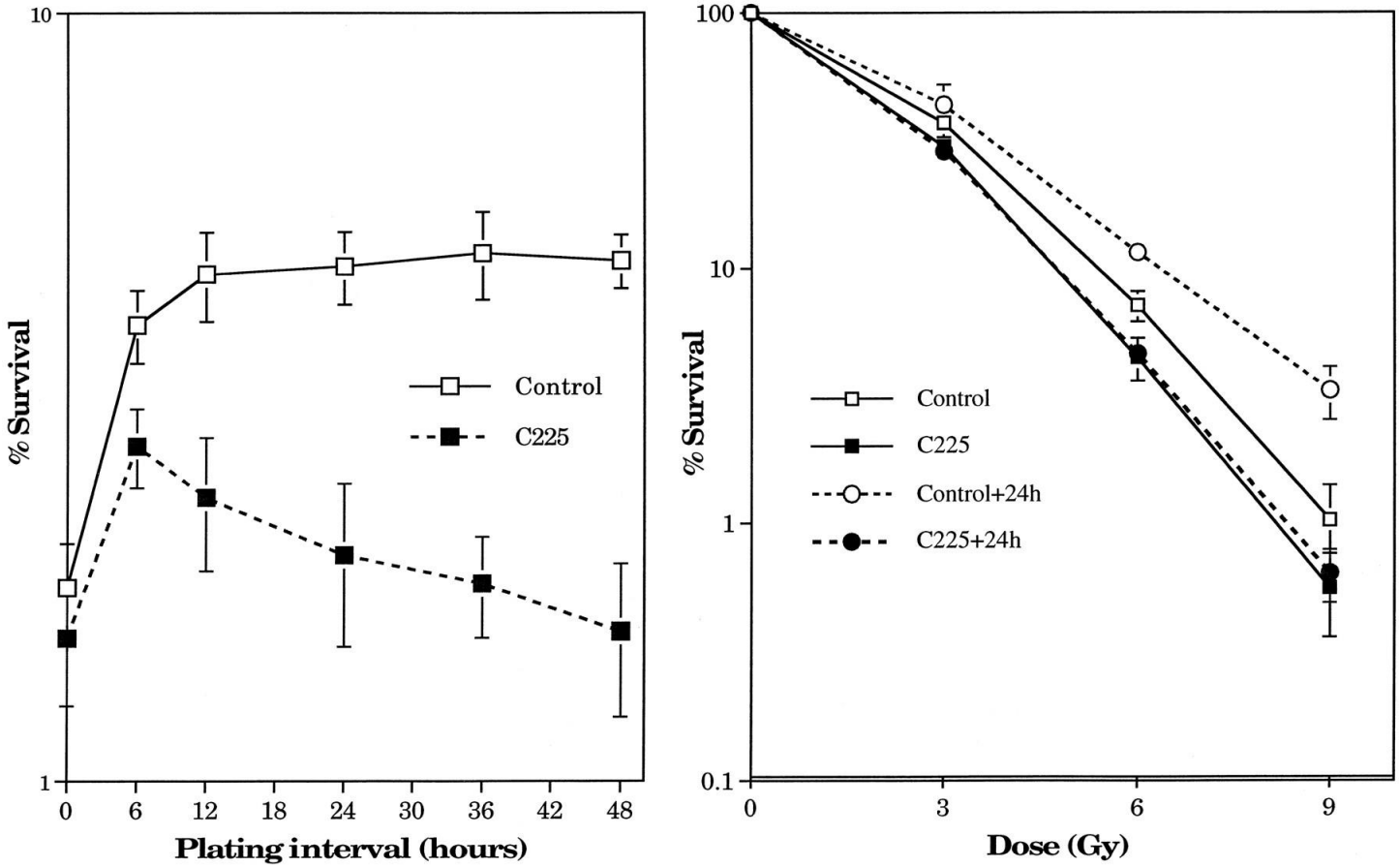
Jonathan Rios-Doria et al., 2015

ESTRO
Mol Cancer Ther; 14(7) July 2015

Summary

- Inhibition of EGFR in combination with RT
  - multiple mechanisms contribute to enhanced radiosensitivity
  - From DDR to Repopulation
- Secretome is as mediator of treatment resistance
- AXL is a promising target for combined radiochemotherapy
- Differential secretome analysis is a promising approach to identify predictive markers and novel targets for radiosensitization.
- Novel ADAM17 inhibitors are promising agents to improve the radiotherapy outcome of NSCLC.

Cetuximab compromises the capacity of SCCs to accomplish effective repair after radiation-induced damage

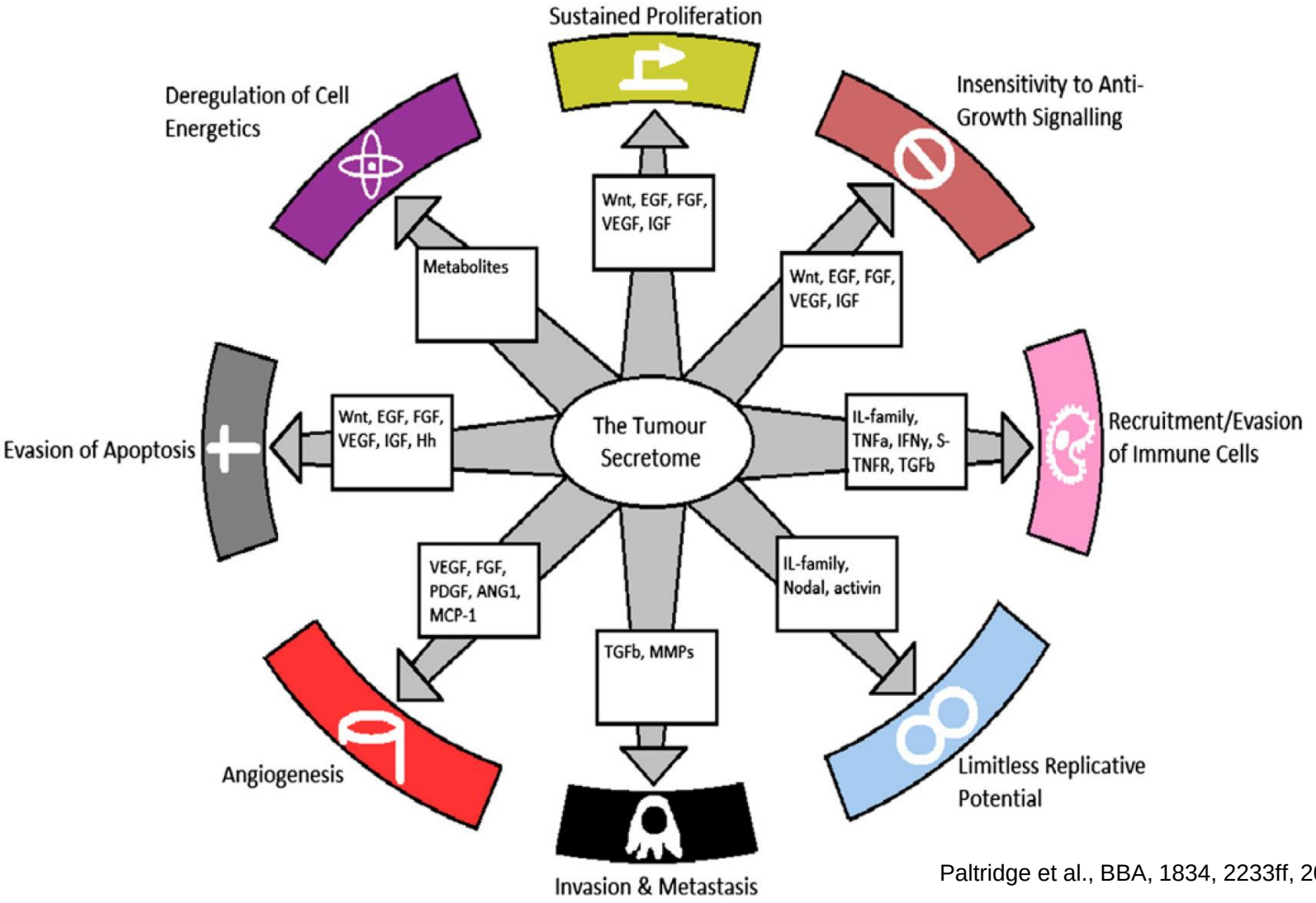


PLDR was examined using single-dose irradiation of **confluent** cultures. Irradiation, cells were either immediately subcultured for colony formation (0 h) or were returned to the incubator for delayed plating at specified time intervals.

Inhibition of Potentially Lethal Damage Repair by Cetuximab

ESTRO School

Tumor Secretome and the Hallmarks of Cancer



Paltridge et al., BBA, 1834, 2233ff, 2013

Tumor Secretome as Mediator of Treatment Resistance

Chemo/bio-radiotherapy in Head and Neck Cancer

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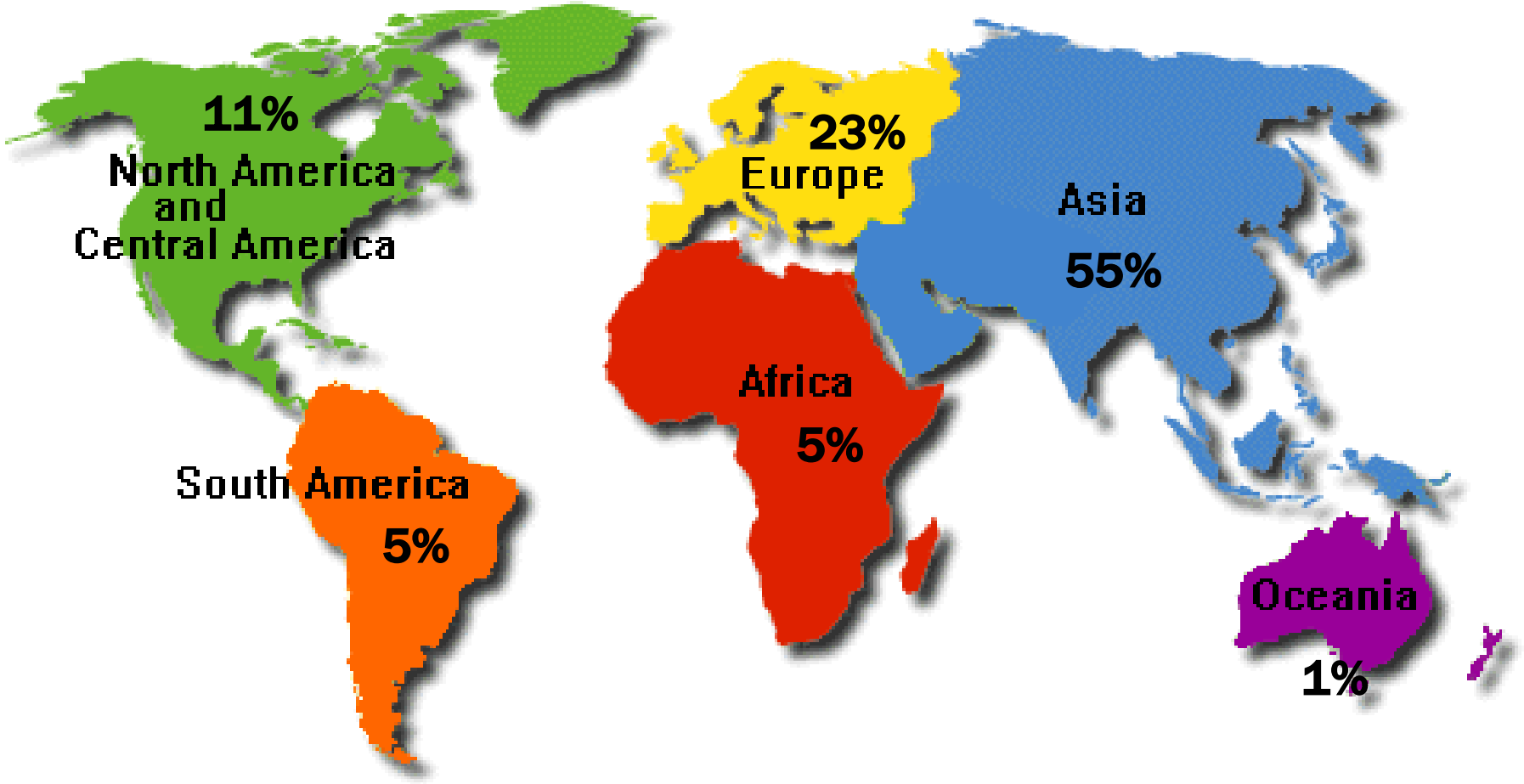
Dept. of Oncology
Odense Universityhospital, Denmark

jesper@oncology.au.dk

Estimated global distribution of HNSCC (IARC)



7% of all cancer – but with huge variation due to aetiology

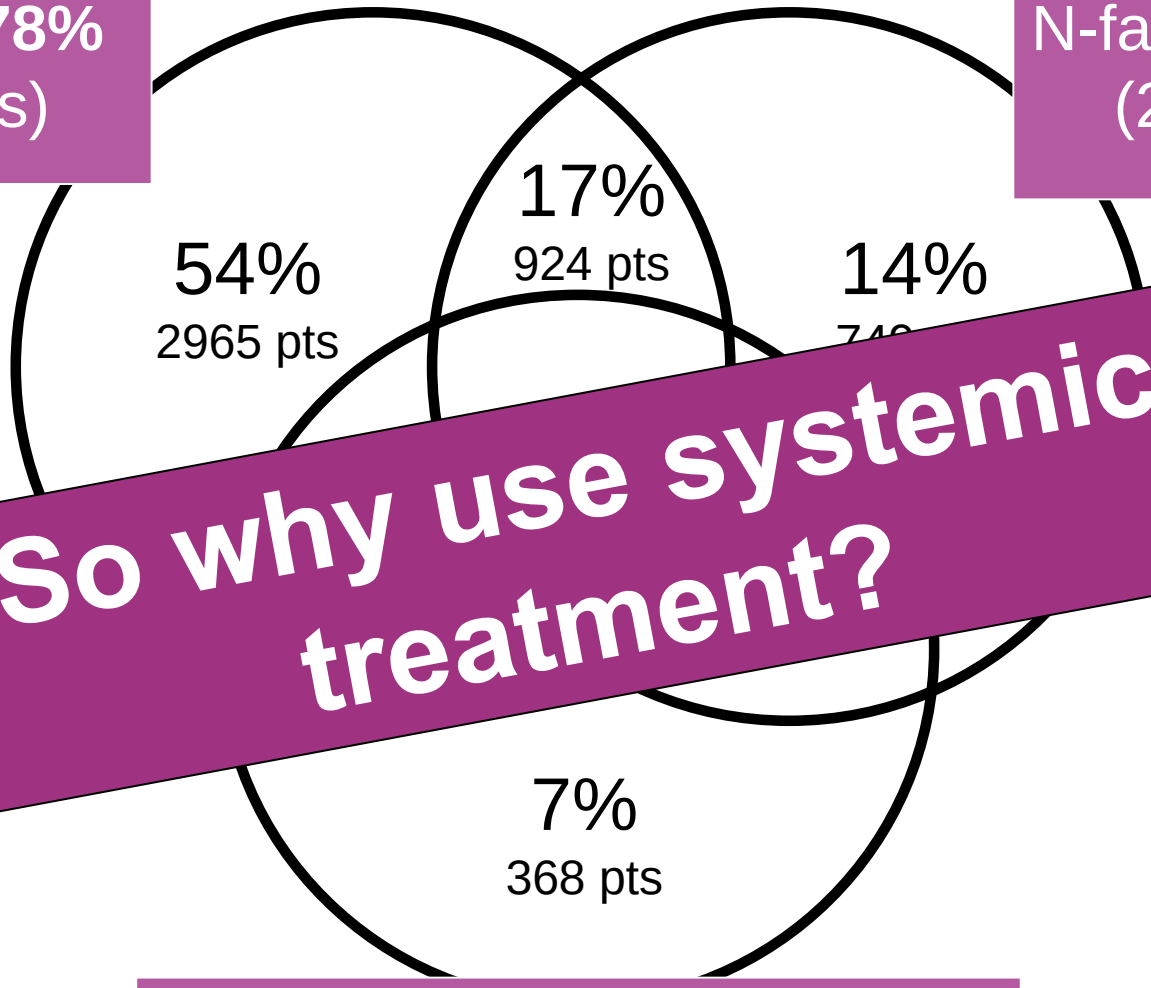
HNSCC is predominantly a loco-regional disease, where distant metastasis mainly is a consequence of local failure.

The treatment must therefore aim towards control of primary tumor and the regional lymph nodes.

Patterns of failure* of 5.506 recurrences in 15.146 patients from the DAHANCA database

T-failure: **78%** (4216 pts)

N-failure: **37%** (2014 pts)



So why use systemic treatment?

M-failure: **16%** (868 pts)

*5-year values

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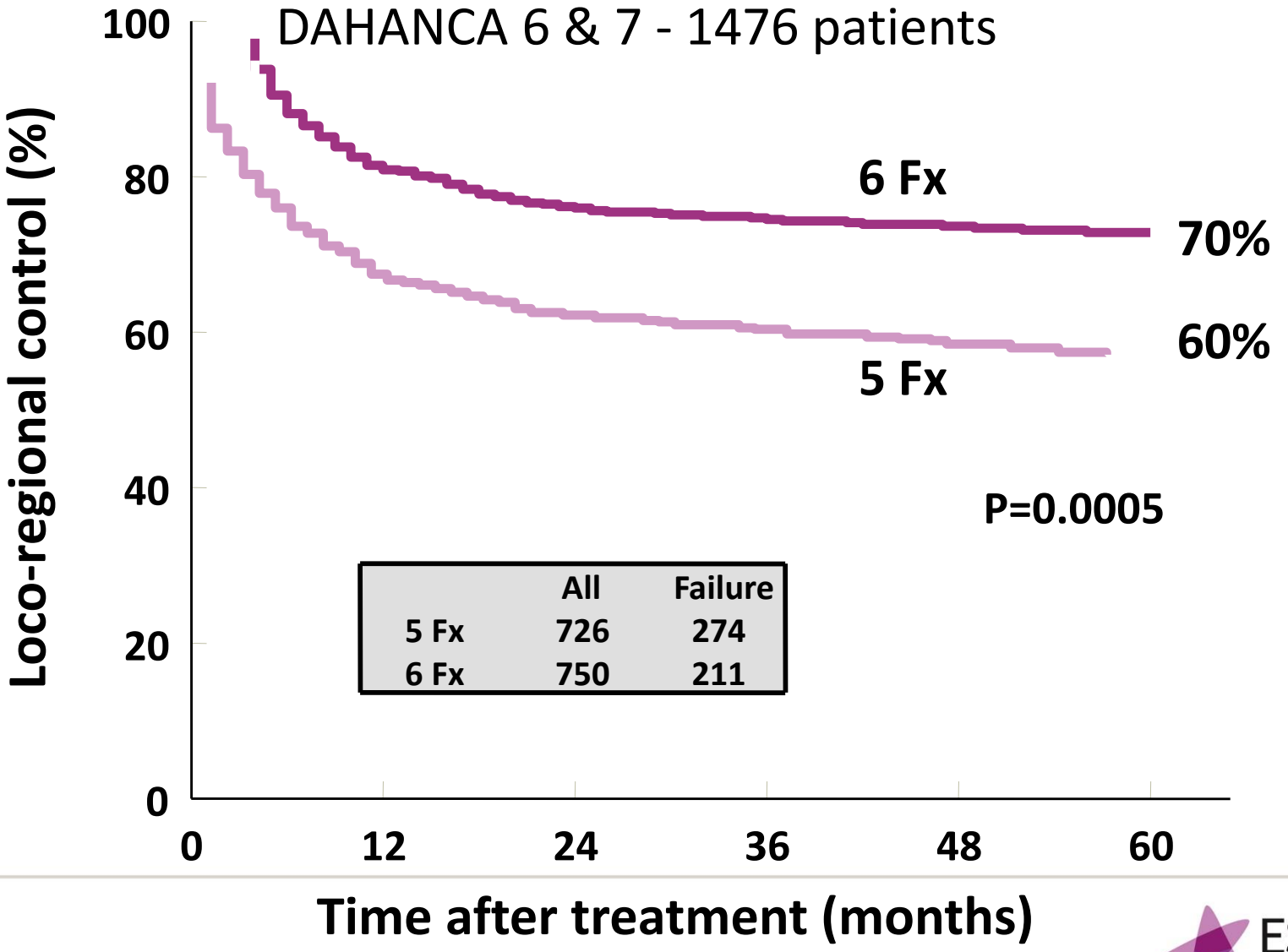
Accelerated Radiotherapy



Overgaard 2003

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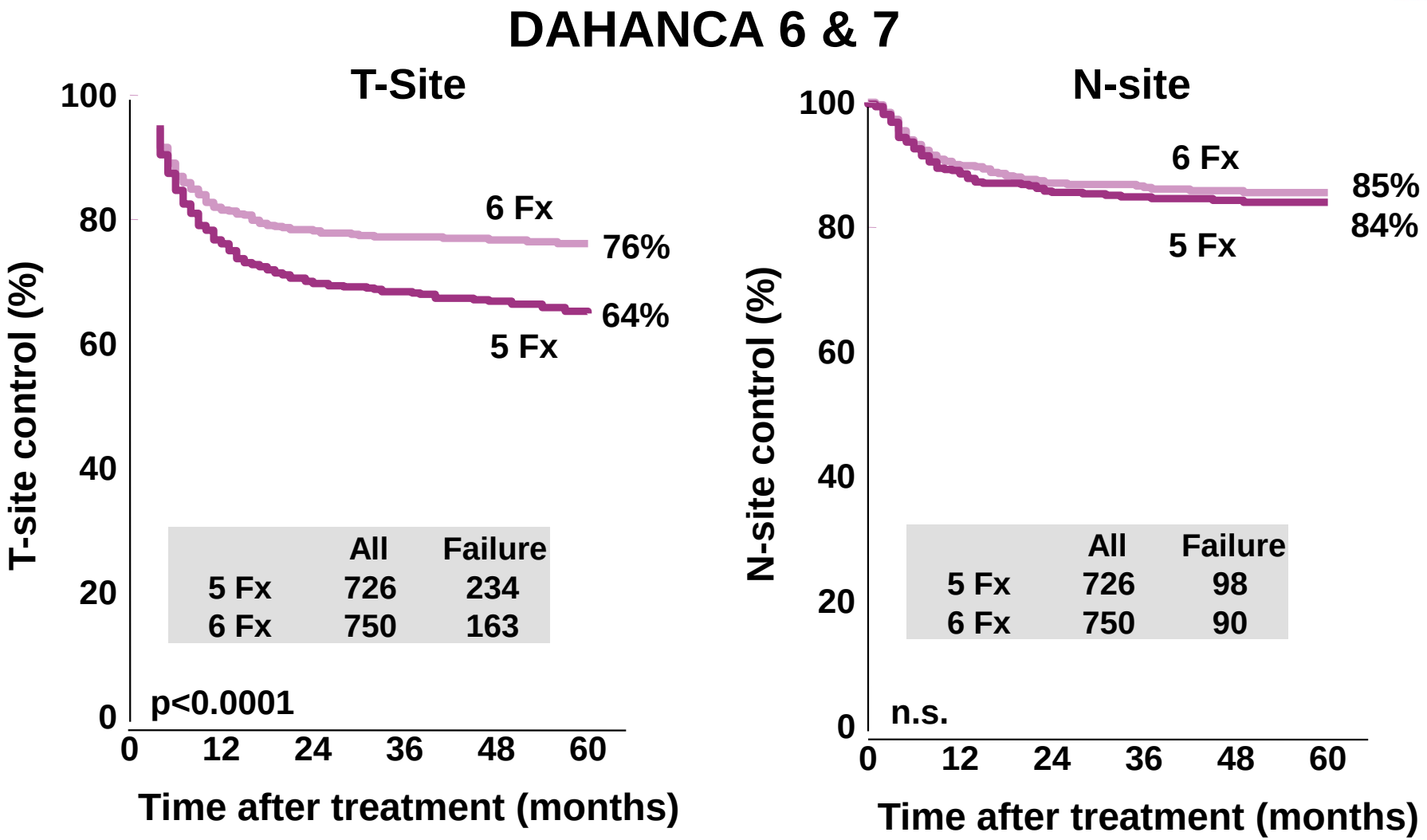
Effect of acceleration in T-site but not in N-site



Overgaard 2003

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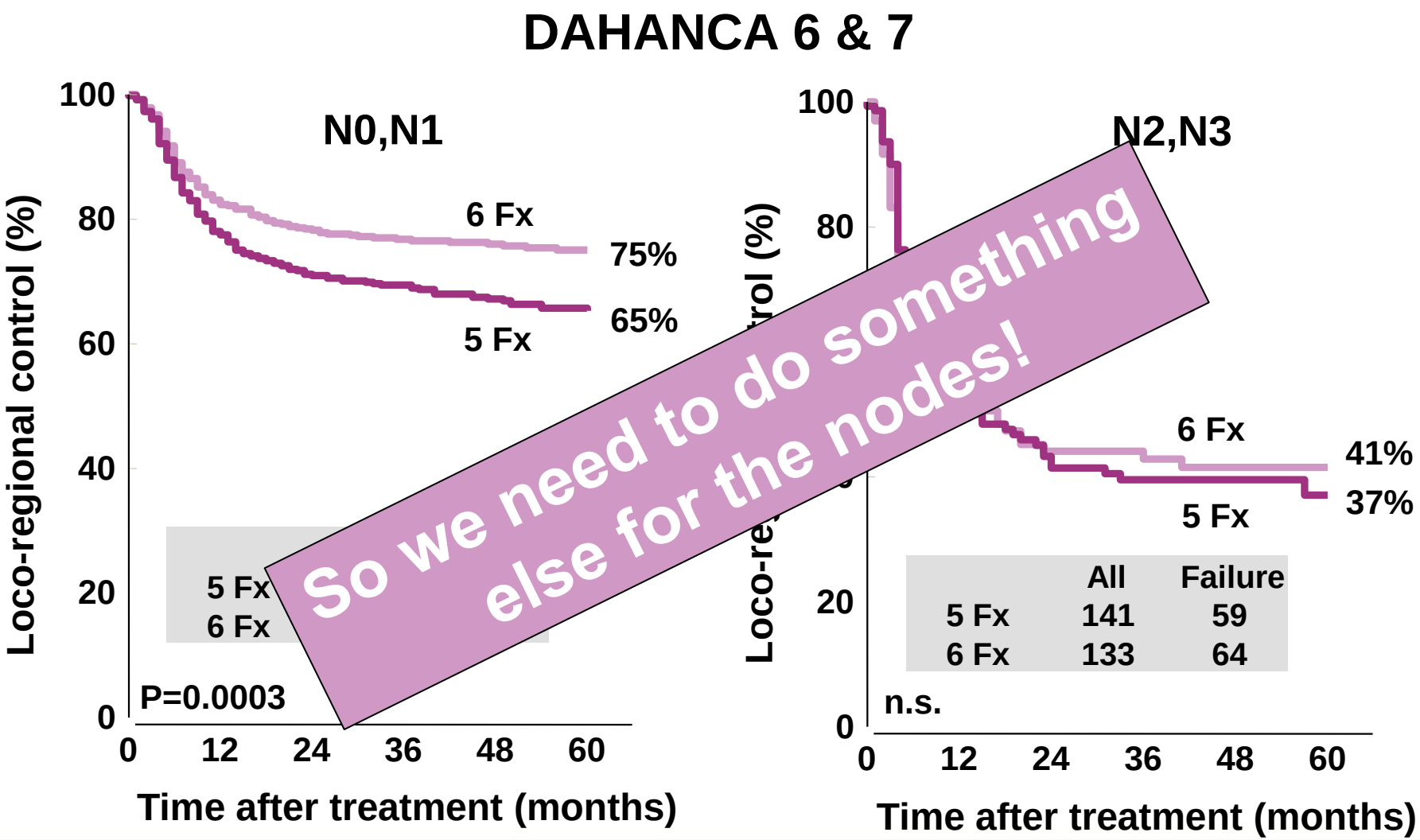
Effect of N-status on loco-regional control



Questions to be discussed (by you!) in this session

- When to deliver chemotherapy?
- What sites?
- Which drugs?
- How much and how often?
- To all patients?
- ART or CRT (conventional fx)?
- BRT or CRT?
- De-escalation strategies

Meta-analysis on C-RT

Original article

Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients

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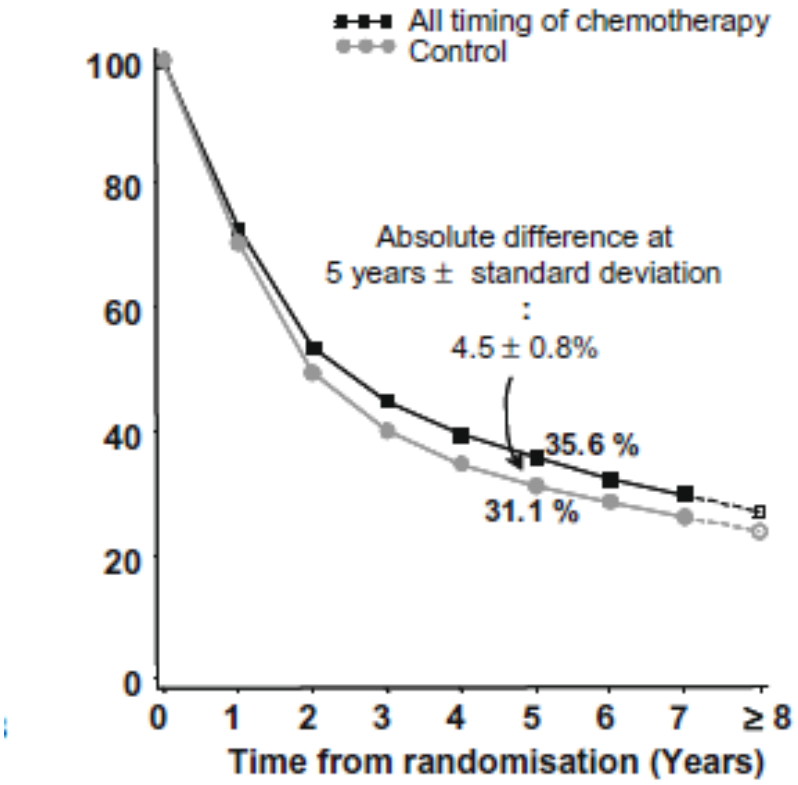
ABSTRACT

Background: Our previous individual patient data (IPD) meta-analysis showed that chemotherapy improved survival in patients curatively treated for non-metastatic head and neck squamous cell carcinoma (HNSCC), with a higher benefit with concomitant chemotherapy. However the heterogeneity of the results limited the conclusions and prompted us to confirm the results on a more complete database by adding the randomised trials conducted between 1994 and 2000.
Methods: The updated IPD meta-analysis included trials comparing loco-regional treatment to loco-regional treatment + chemotherapy in HNSCC patients and conducted between 1965 and 2000. The log-rank-test, stratified by trial, was used to compare treatments. The hazard ratios of death were calculated.
Results: Twenty-four new trials, most of them of concomitant chemotherapy, were included with a total of 87 trials and 16,485 patients. The hazard ratio of death was 0.88 ($p < 0.0001$) with an absolute benefit for chemotherapy of 4.5% at 5 years, and a significant interaction ($p < 0.0001$) between chemotherapy timing (adjuvant, induction or concomitant) and treatment. Both direct (6 trials) and indirect comparisons showed a more pronounced benefit of the concomitant chemotherapy as compared to induction chemotherapy. For the 50 concomitant trials, the hazard ratio was 0.81 ($p < 0.0001$) and the absolute benefit 6.5% at 5 years. There was a decreasing effect of chemotherapy with age ($p = 0.003$, test for trend).
Conclusion: The benefit of concomitant chemotherapy was confirmed and was greater than the benefit of induction chemotherapy.
 Radiotherapy and Oncology xxx (2009) xxx–xxx

Pignon et al 2009

Overall survival RT vs. CRT regardless of timing

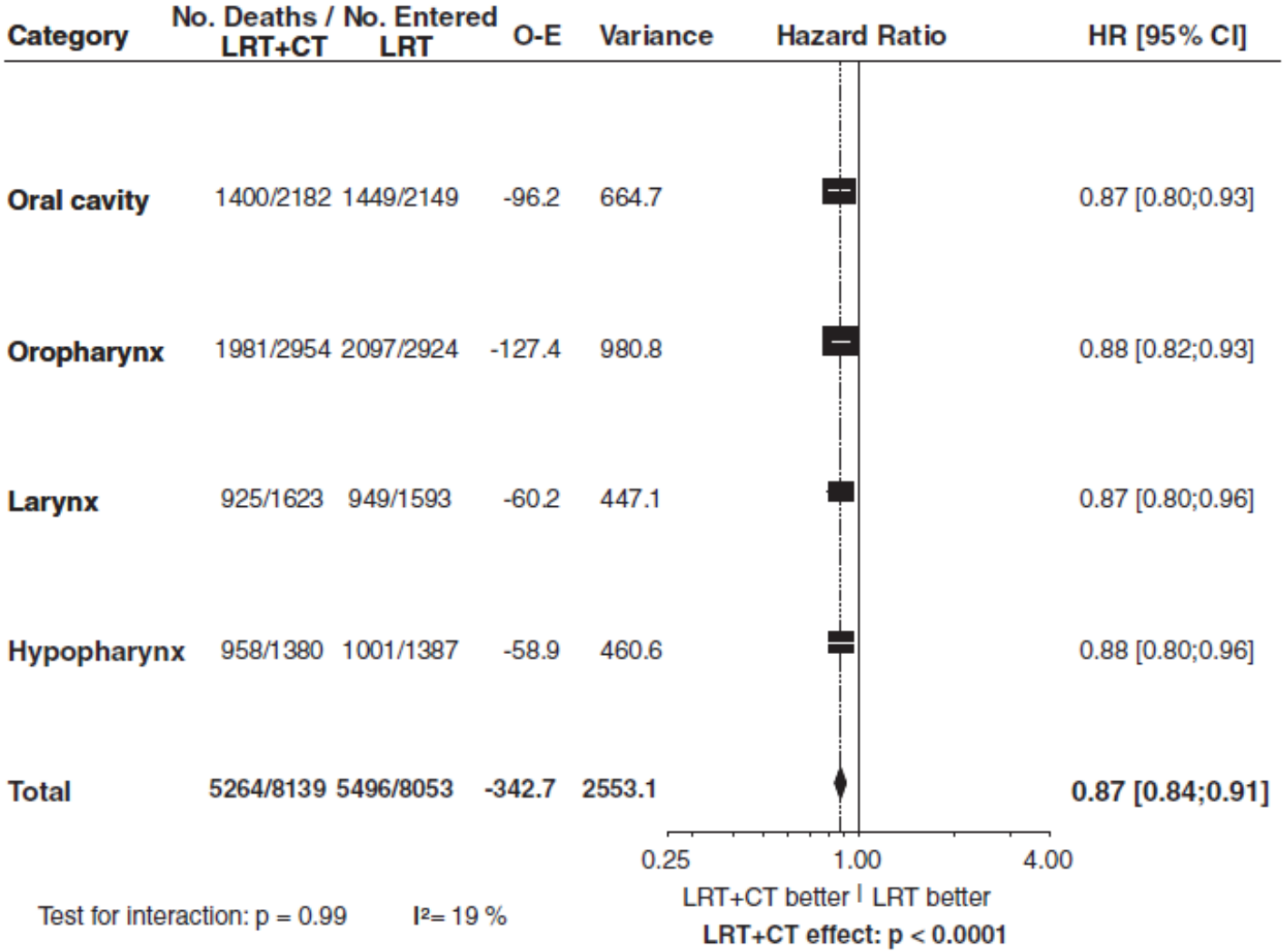


Death/person-years by period

Years 0-2	Years 3-5	Years ≥ 6
4200/11939	1246/7587	417/4633
3908/12425	1256/8712	515/5443

Pignon et al 2009

Site vs. effect of C-RT



Blanchard et al 2011

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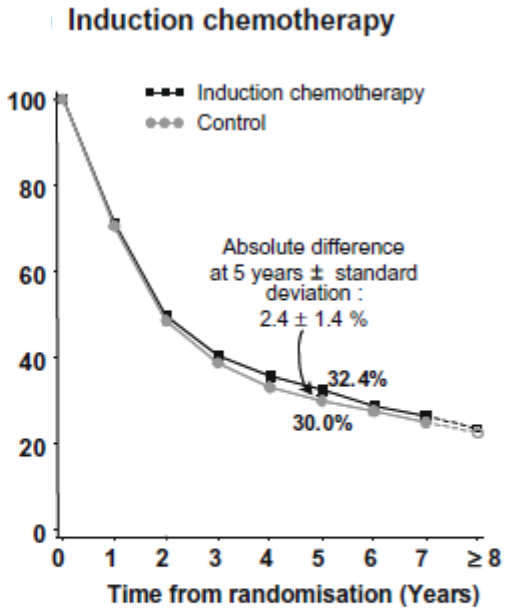
RT vs. CRT and influence of timing

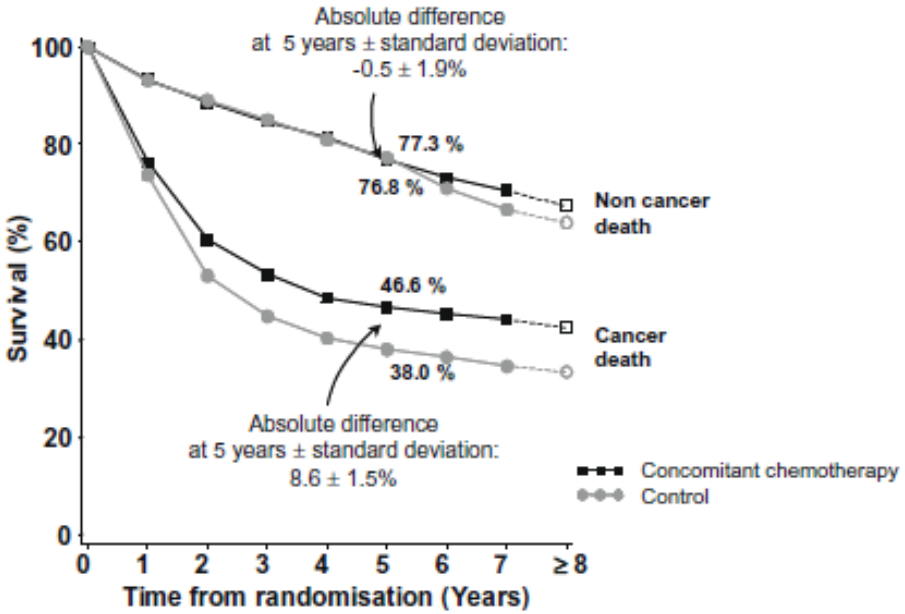


Death/person-years by period

	Years 0-2	Years 3-5	Years ≥ 6
	1283/3535	393/2276	137/1417
	1318/3820	392/2608	167/1530

Pignon et al 2009

Non-cancer death and cancer death; C-RT vs. RT



Non cancer death/person-years by period

	Years 0-2	Years 3-5	Years ≥ 6
Control	187/2985	86/1769	37/544
Chemotherapy	201/3301	106/2330	34/727

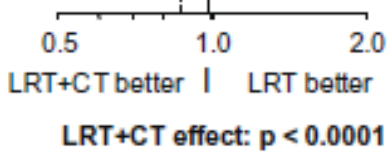
Cancer death by period

	Years 0-2	Years 3-5	Years ≥ 6
Control	1268	290	32
Chemotherapy	1049	278	28

Pignon et al 2009

Hazard ratio for recurrence or death

Timing	No. Events / No. Entered LRT+CT	LRT	O-E	Variance	Hazard Ratio	HR [95% CI]
Concomitant	3447/4824	3735/4791	-401.7	1742.6		**0.79 [0.76;0.83]**
Induction	2036/2740	1924/2571	-13.3	956.7		0.99 [0.93;1.05]
Adjuvant	703/1244	762/1323	-4.2	360.9		0.99 [0.89;1.10]
Total	**6186/8808**	**6421/8685**	**-419.3**	**3060.2**		**0.87 [0.84;0.90]**



Test for heterogeneity: $\chi^2_{107} = 187.7$ $p < 0.0001$ $I^2 = 43\ \%$

Test for interaction: $\chi^2_2 = 35.40$ $p < 0.0001$

LRT+CT effect: p < 0.0001

Pignon et al 2009

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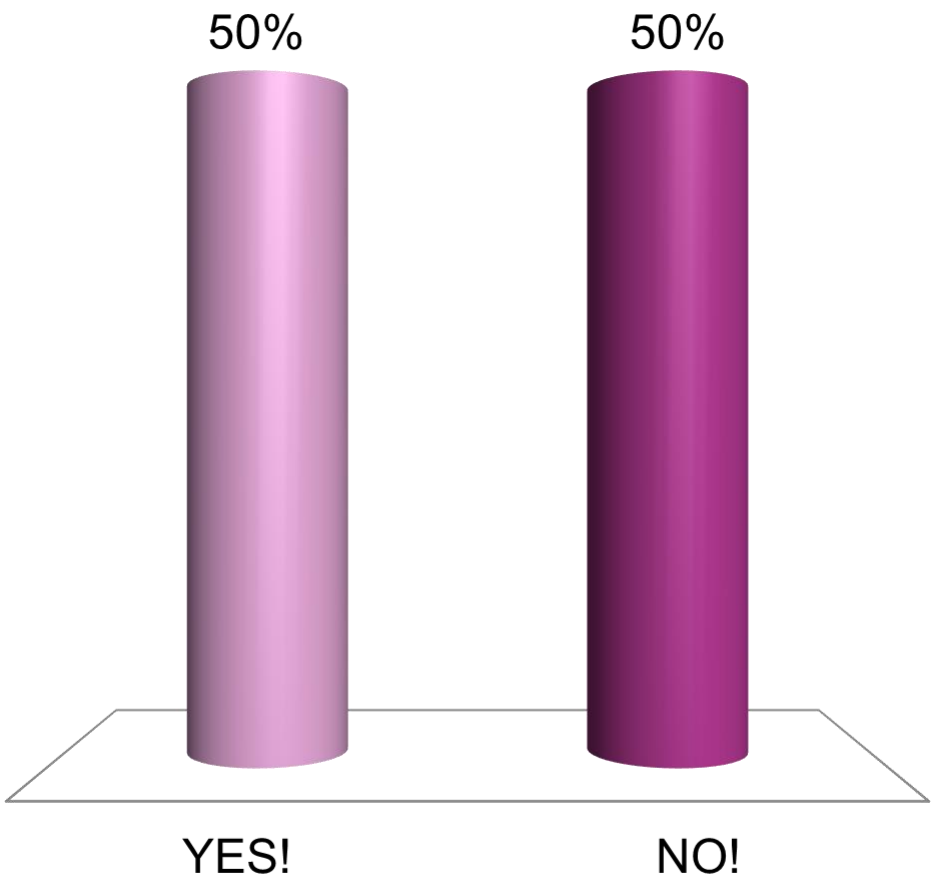
Metastatic micro-deposits - a reason for induction?

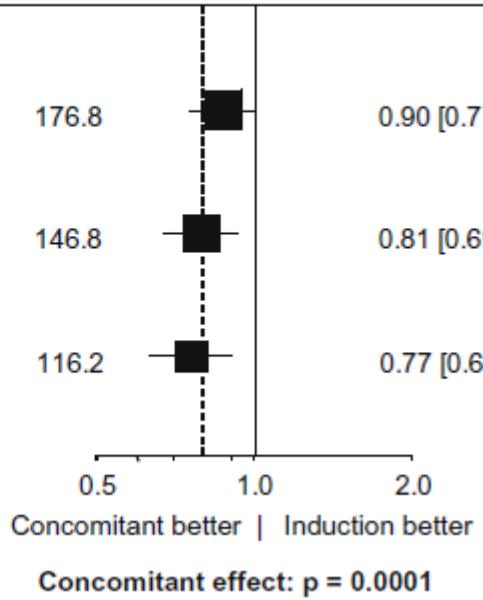
Metastatic micro-deposits - a reason for induction?

A. YES!
B. NO!

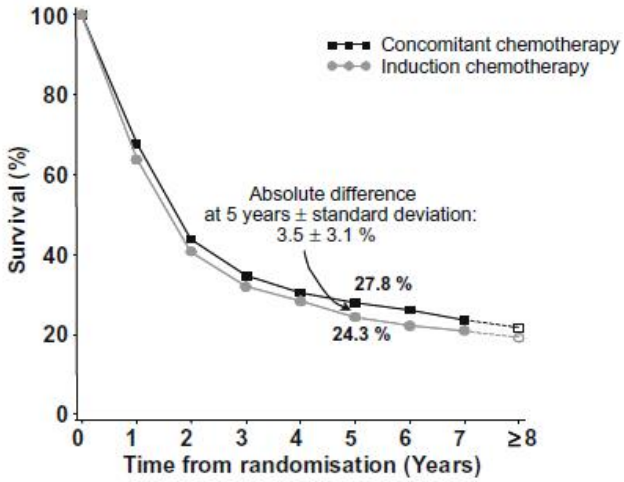


Induction versus concomitant

Endpoint	No. Events / No. Entered Concomitant	Induction	O-E	Variance	Hazard Ratio	HR [95% CI]
Overall Survival	349/430	368/431	-19.2	176.8		0.90 [0.77;1.04]
Event free survival	293/354	307/347	-30.1	146.8		0.81 [0.69;0.96]
Loco regional failure	218/343	254/339	-30.4	116.2		0.77 [0.64;0.92]



Concomitant effect: p = 0.0001



6 randomized trials; 861 pts

Death/Person-years by period

	Years 0-2	Years 3-5	Years ≥ 6
Concomitant	240/593	64/398	45/511
Induction	256/566	68/382	44/506

Pignon et al 2009

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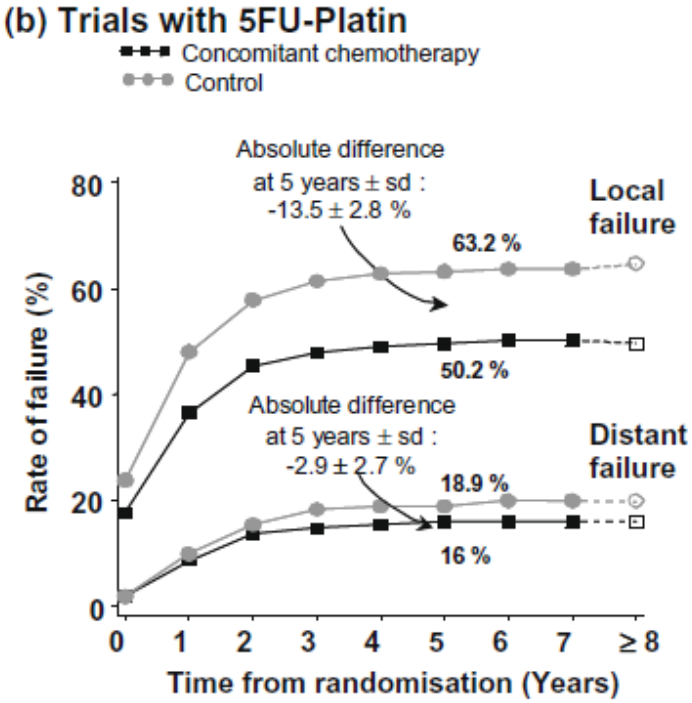
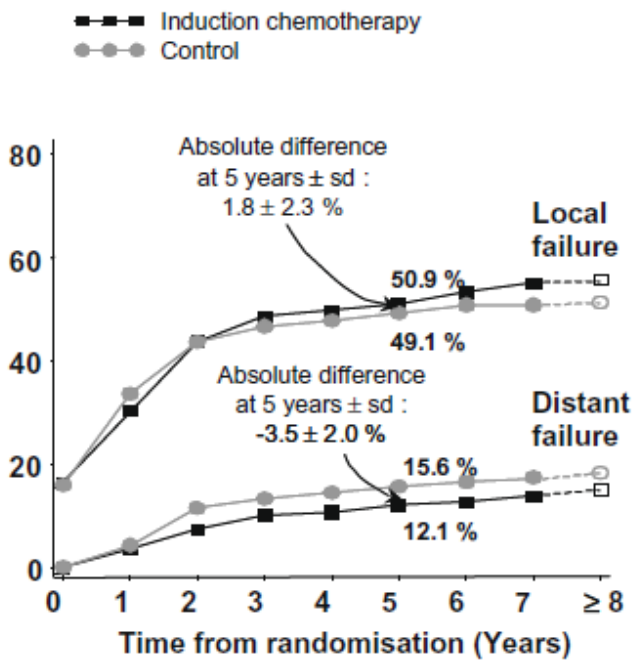
Pattern of failure: Induction vs. concomitant C-RT



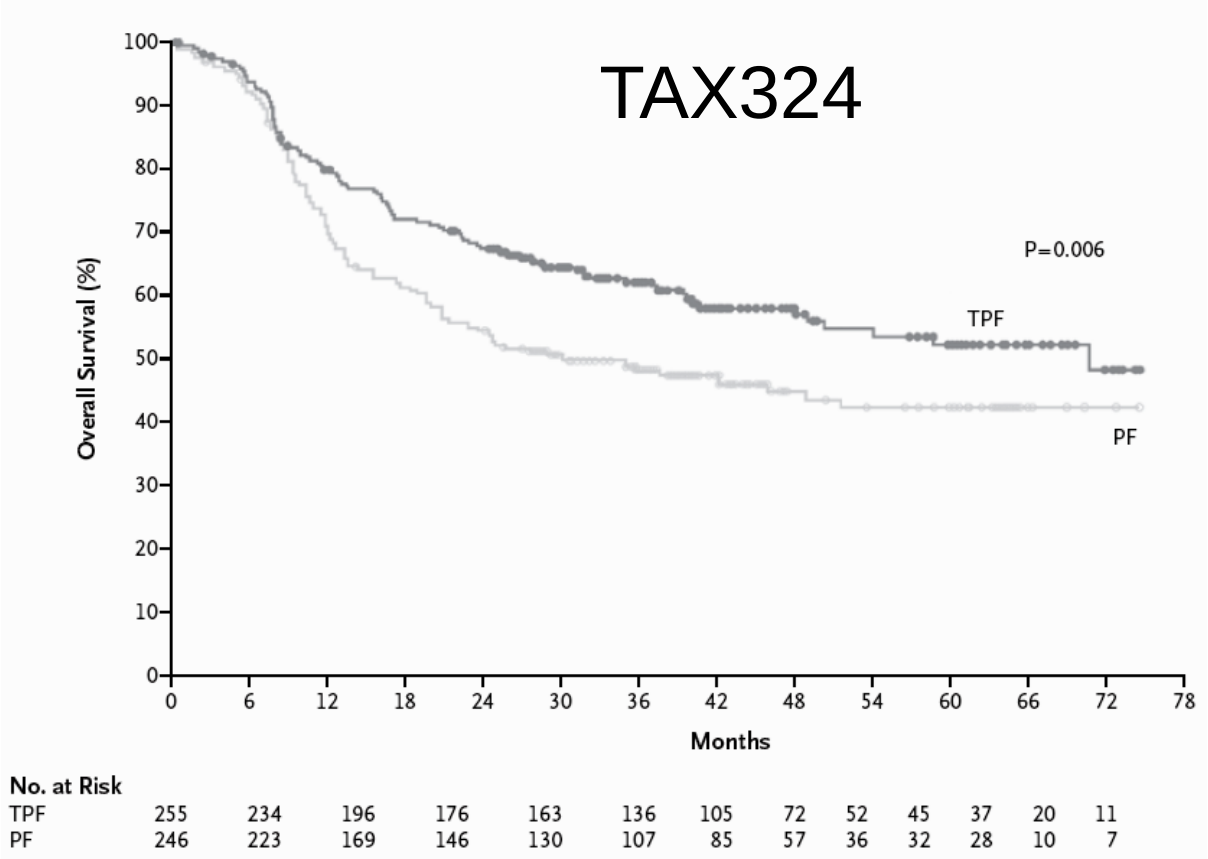


Local failure and distant failure /person-years by period

	Years 0-2	Years 3-5	Years ≥ 6	Years 0-2	Years 3-5	Years ≥ 6
Local failure						
Control	493/1648	22/406	2/165	497/2627	38/1073	10/684
Chemotherapy	373/1837	20/603	1/240	519/2749	58/1142	22/751
Distant failure						
Control	82/1756	8/416	1/166	90/2788	18/1116	8/711
Chemotherapy	83/1915	6/616	0/241	62/2929	23/1204	9/773

Pignon et al 2009

More cytotoxic chemotherapy?



- St. III/IV
- 3x I-CT
- 70Gy/35fx
- Carbo AUC 1.5
- 30% faliures
- No diff. in distant mets 5% vs. 9%

Posner MR 2007

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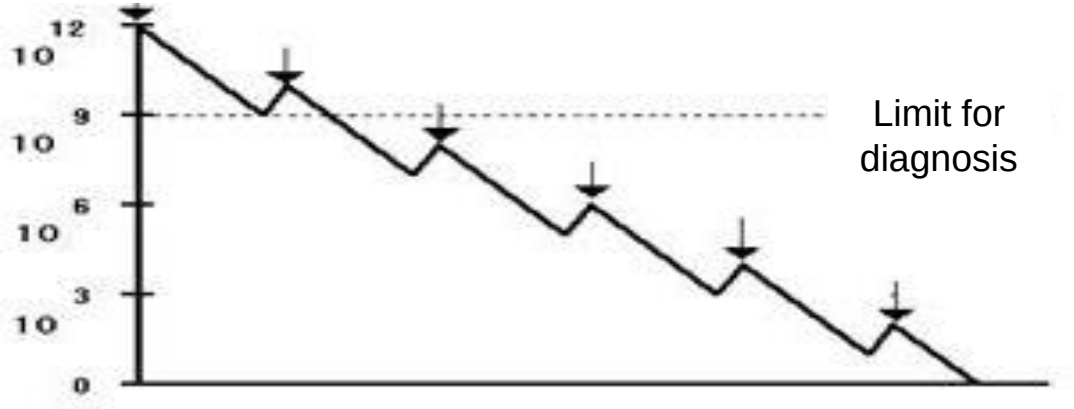
Micrometastases outside the field



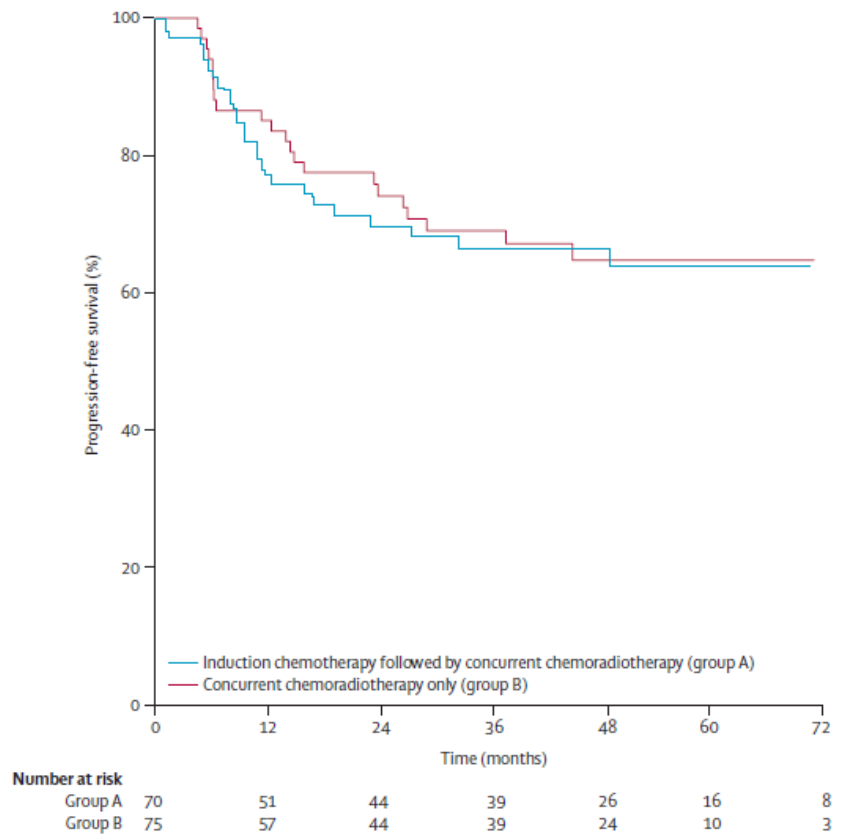
- Limit for detection of micro-deposits is ~10^8 -10^9 cells
- In solid tumours chemotherapy seldom achieves SF<10^{-6}
- Even metastatic deposits <0.1g may contain 10^7 -10^8 cells.
- If the majority of these are clonogenic, then standard CT may fail to control even small amounts of disseminated disease.

Concurrent chemotherapy ± Induction chemotherapy

	Induction chemotherapy followed by concurrent chemoradiotherapy (n=70)	Concurrent chemoradiotherapy only (n=75)
Any disease failure	17 (24%)	19 (25%)
Local or regional only	9 (13%)	6 (8%)
Distant only	3 (4%)	3 (4%)
Both	2 (3%)	5 (7%)
Unknown	3 (4%)	5 (7%)
Total local or regional	11 (16%)	11 (15%)
Total distant	5 (7%)	8 (11%)

Data are number of patients (%).

Table 2: **Pattern of disease failure (36 cancer failures)**



Paradigm

Haddad 2013

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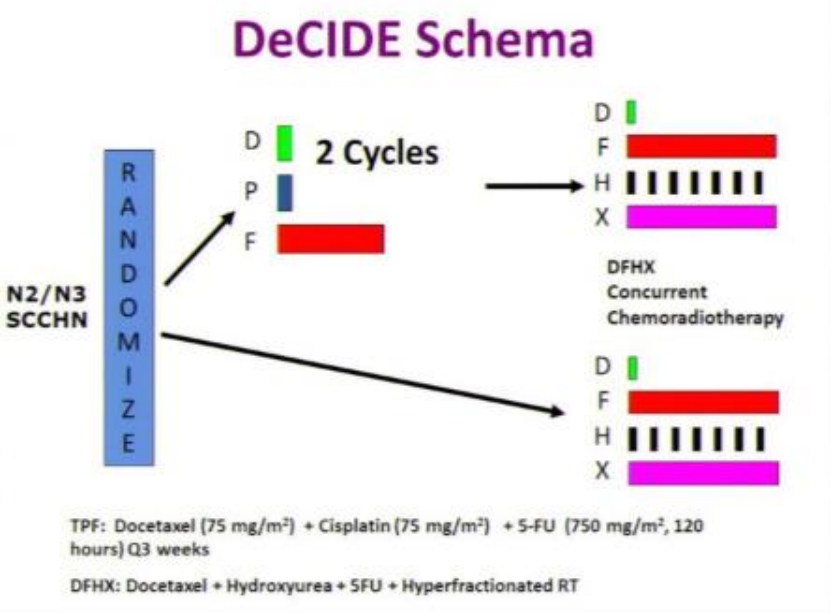
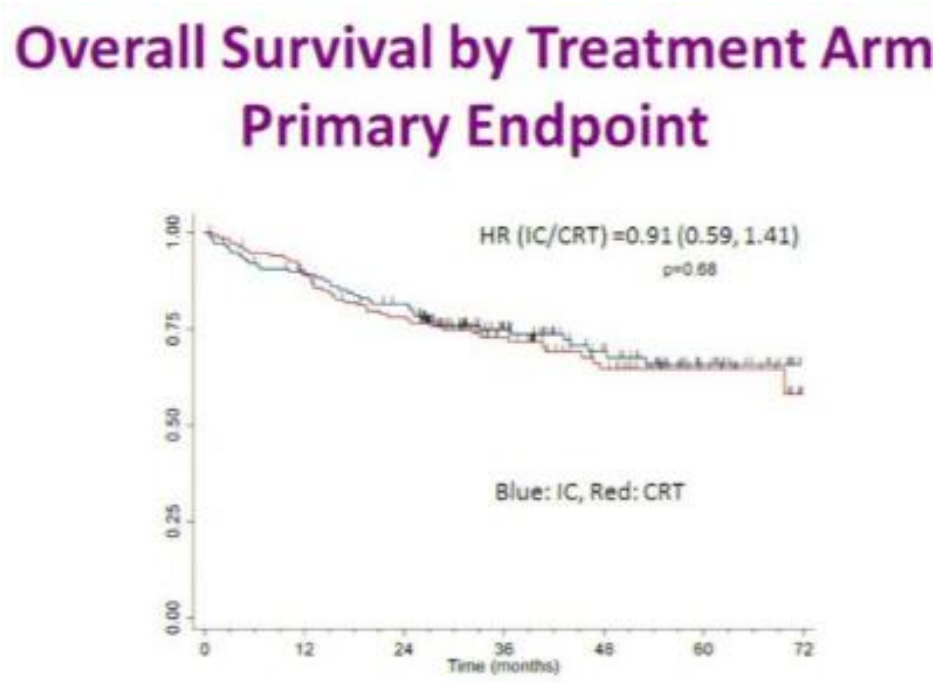
Concurrent chemotherapy ± Induction chemotherapy





Cohen 2014

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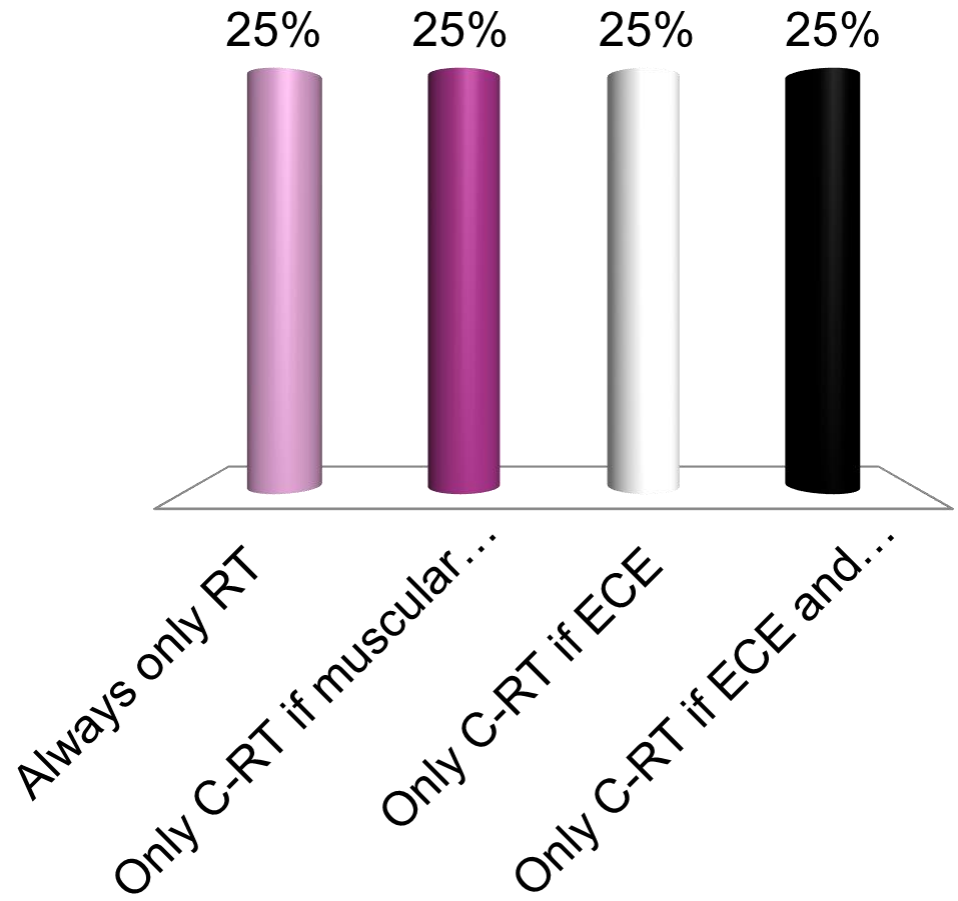
Adjuvant C-RT after surgery?

Adjuvant C-RT after surgery?

A. Always only RT
B. Only C-RT if muscular involvement
C. Only C-RT if ECE
D. Only C-RT if ECE and low differentiated tumours



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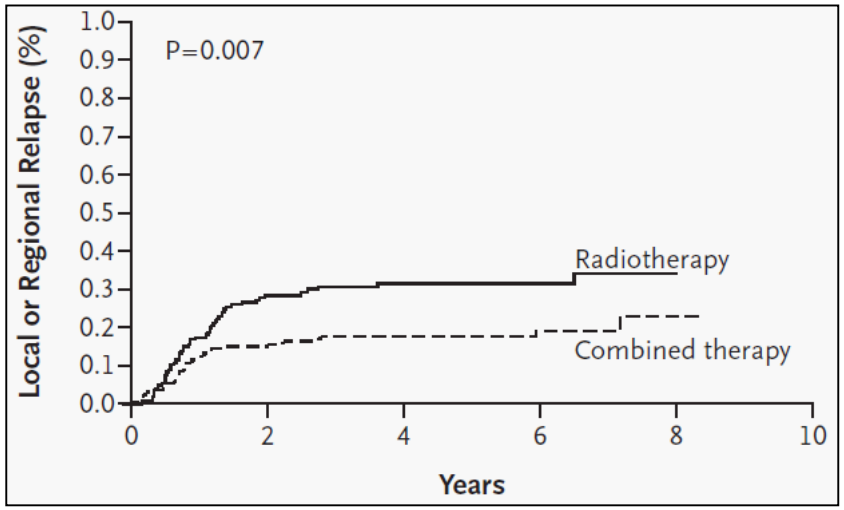
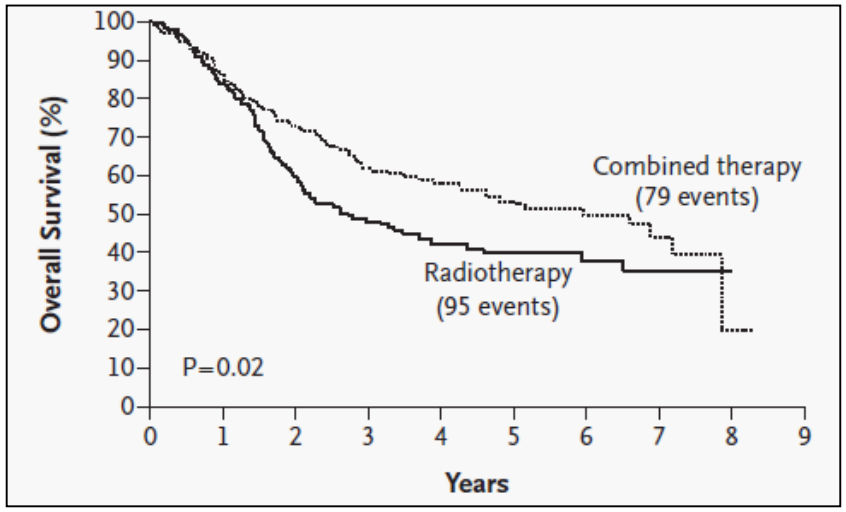
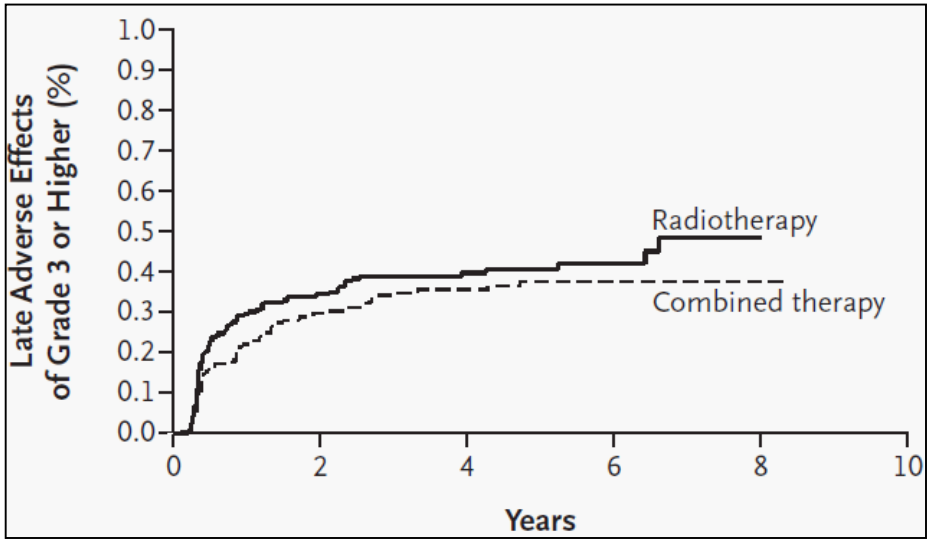
Adjuvant C-RT after surgery







334 ptt, st. III-IV, 66Gy conventional fx
+ cisplatin 100mg/m² , 3-weekly

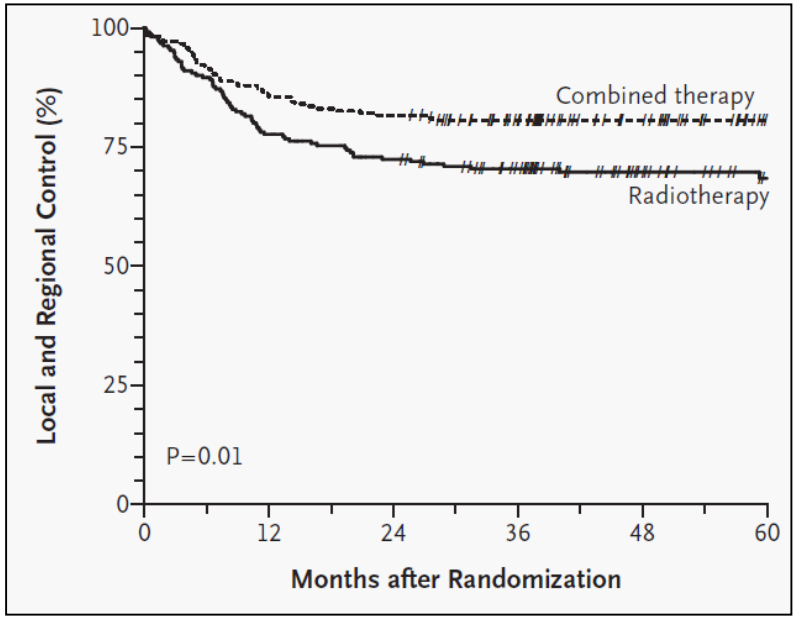
Bernier et al. 2004

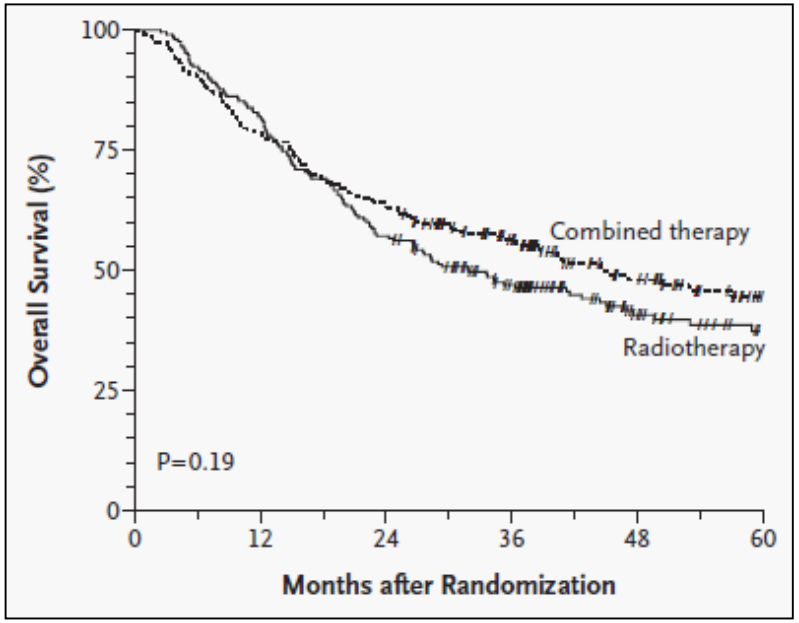
ESTRO School

Adjuvant C-RT after surgery

RTOG 9501 ECOG R9501 SWOG 9515

N=459, st. III-IV, 66Gy conventional fx + cisplatin 100mg/m², 3-weekly





Cooper et al.2004

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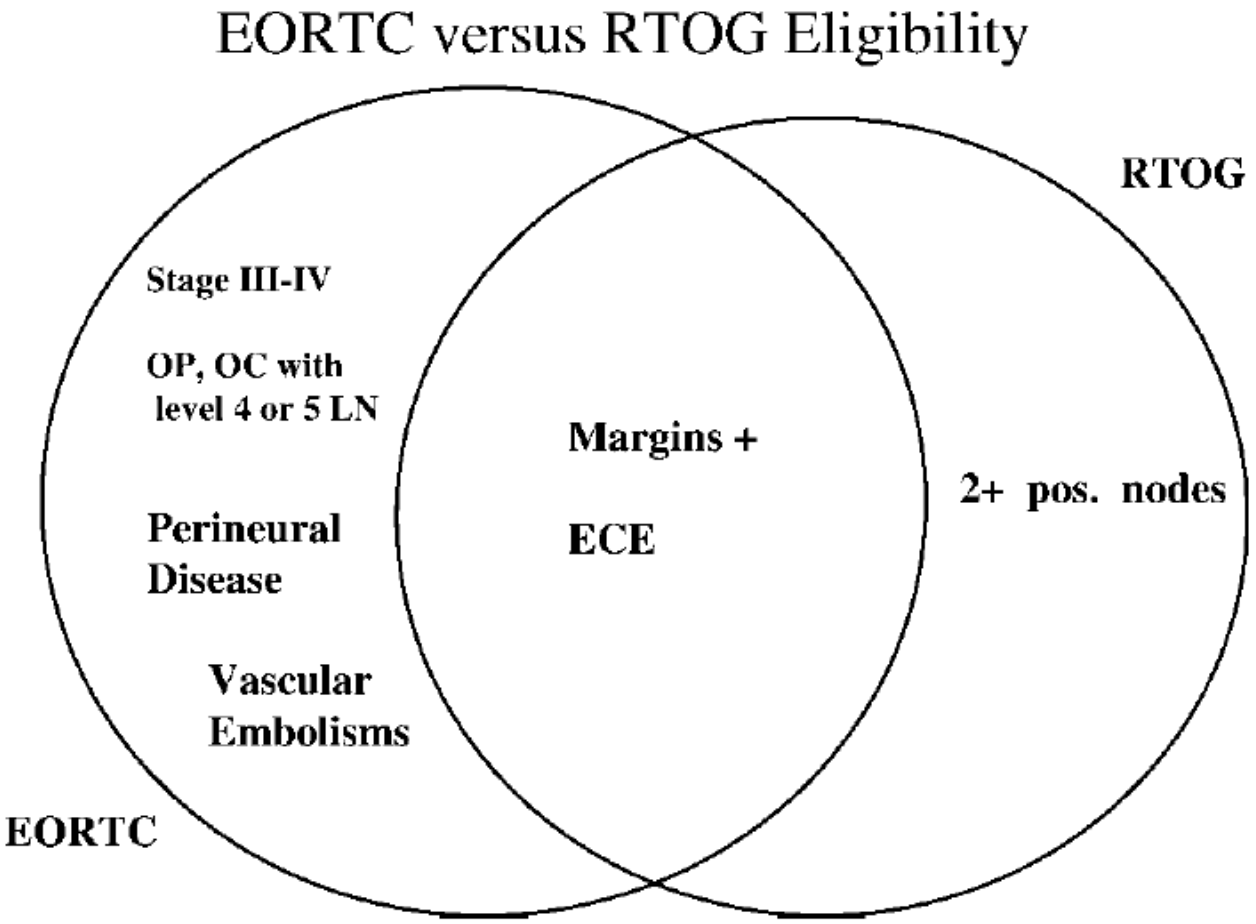
Postoperative C-RT - results of two phase III trials



Bernier Head&Neck 2005

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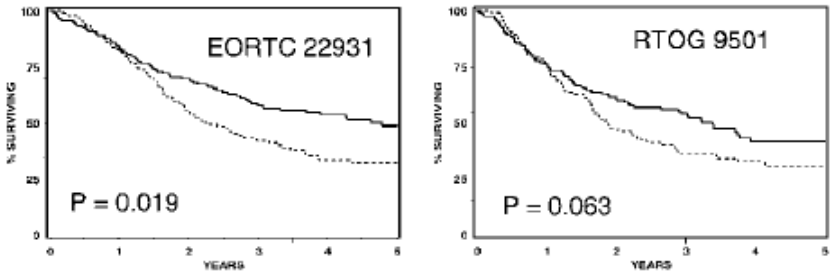
Postoperative C-RT - results of two phase III trials

Overall Survival
Patients with positive margin and/or ECE

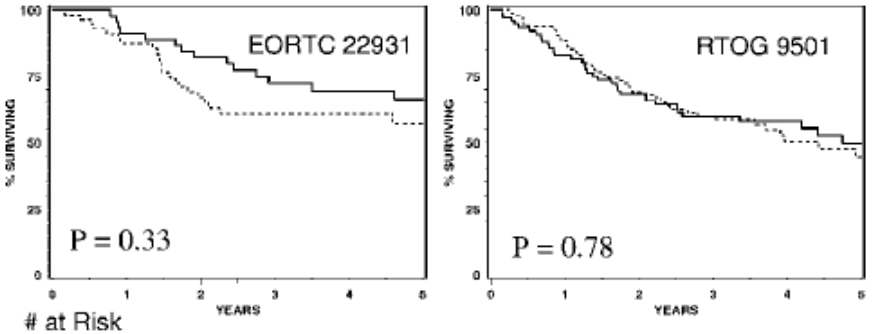


at Risk

Year	0	2	5	0	2	5
RCT ——	122	82	31	130	80	16
RT ---	111	59	16	116	55	11

13% **10%**

Overall Survival
Patients without positive margin and/or ECE



at Risk

Year	0	2	5	0	2	5
RCT ——	45	36	16	76	52	11
RT ---	56	34	15	94	65	14

Bernier 2005

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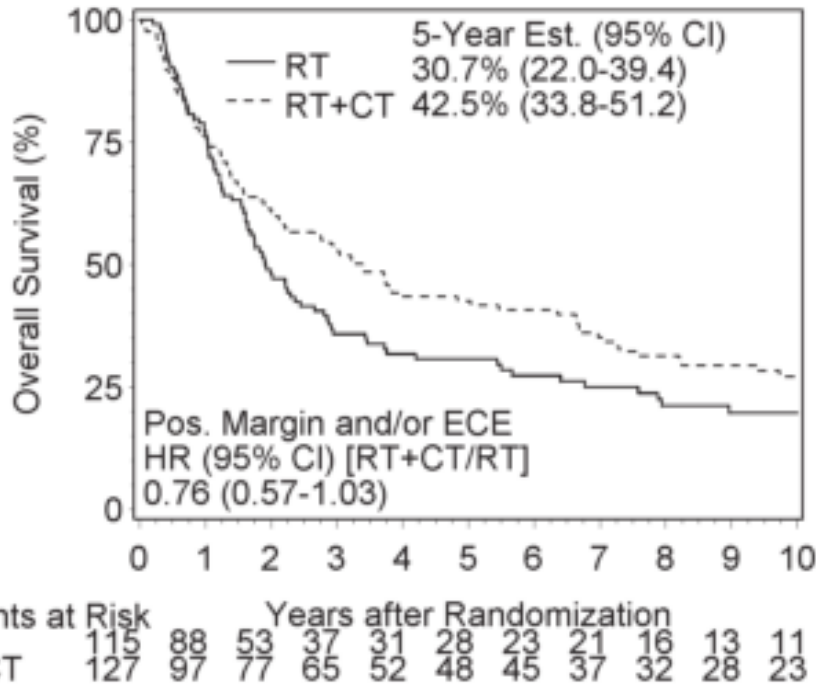
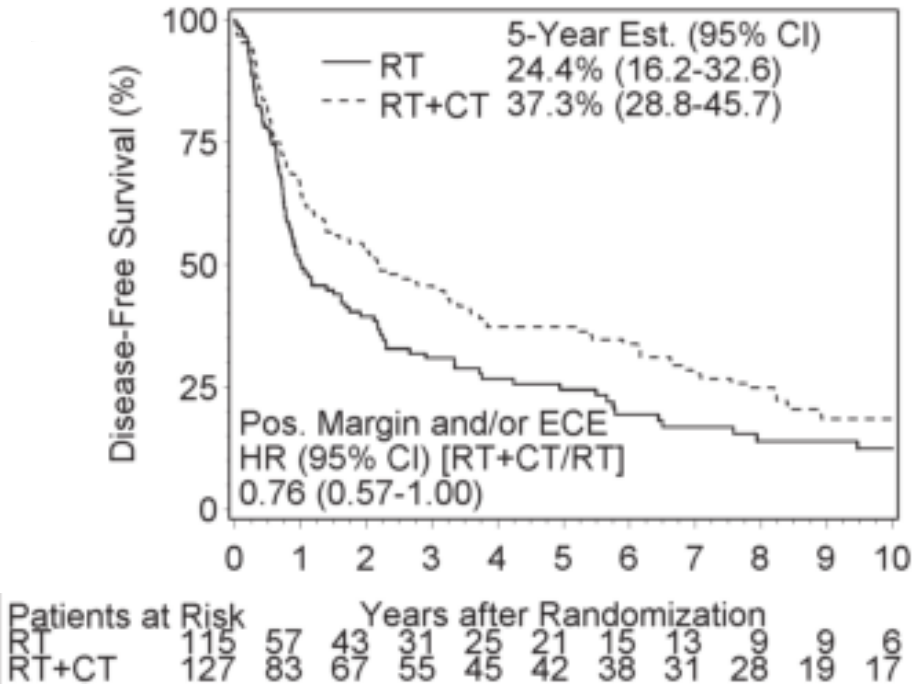
Long time follow-up on the combined trials





Cooper et al. 2012

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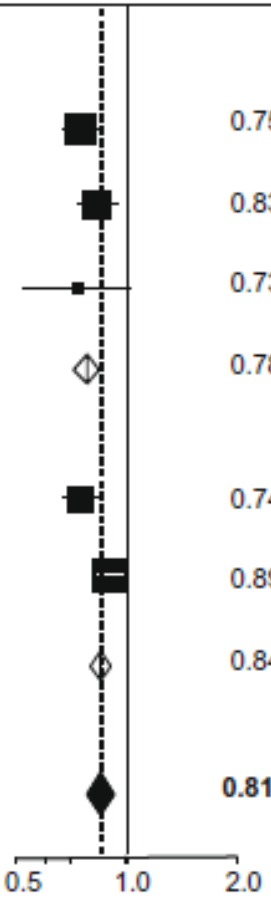
Which kind of concomitant chemotherapy?

Which type and combination of chemotherapy?

Type of chemotherapy	No. Deaths / No. Entered LRT+CT	LRT	O-E	Variance	Hazard Ratio	HR [95% CI]	p of interaction
(a) Poly chemotherapy							
5-FU and Platin	602/940	695/931	-92.2	317.6		0.75 [0.67;0.84]	p = 0.41
5-FU or Platin	495/743	543/795	-45.8	250.0		0.83 [0.74;0.94]	
Neither 5-FU nor Platin	62/115	85/129	-11.1	35.0		0.73 [0.52;1.01]	
Subtotal (a)	1159/1798	1323/1855	-149.0	602.6		0.78 [0.72;0.85]	
(b) Mono chemotherapy							
Mono Platin	703/1151	739/1059	-102.6	341.8		0.74 [0.67;0.82]	p = 0.006
Mono Other	1309/1875	1327/1877	-74.8	643.3		0.89 [0.82;0.96]	
Subtotal (b)	2012/3026	2066/2936	-177.4	985.1		0.84 [0.78;0.89]	
Total (a ... b)	**3171/4824**	**3389/4791**	**-326.4**	**1587.7**		**0.81 [0.78;0.86]**	



Test for heterogeneity: $\chi^2_1 = 1.69$ p = 0.19

Pignon et al 2009

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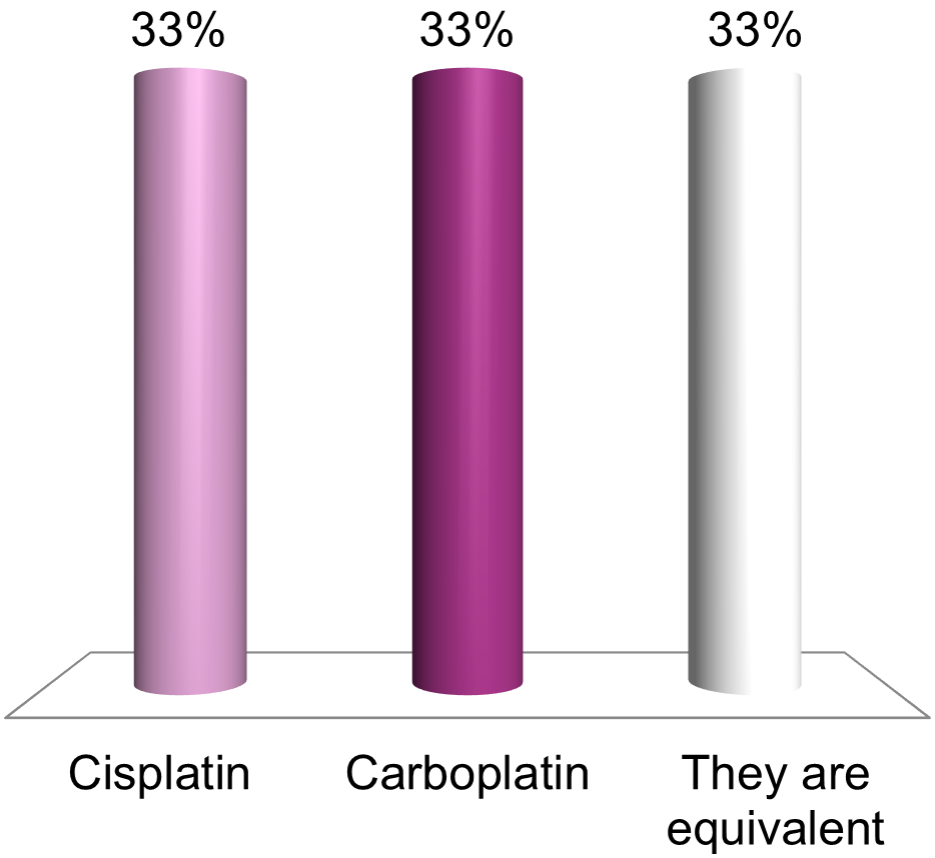
Cisplatin or carboplatin?

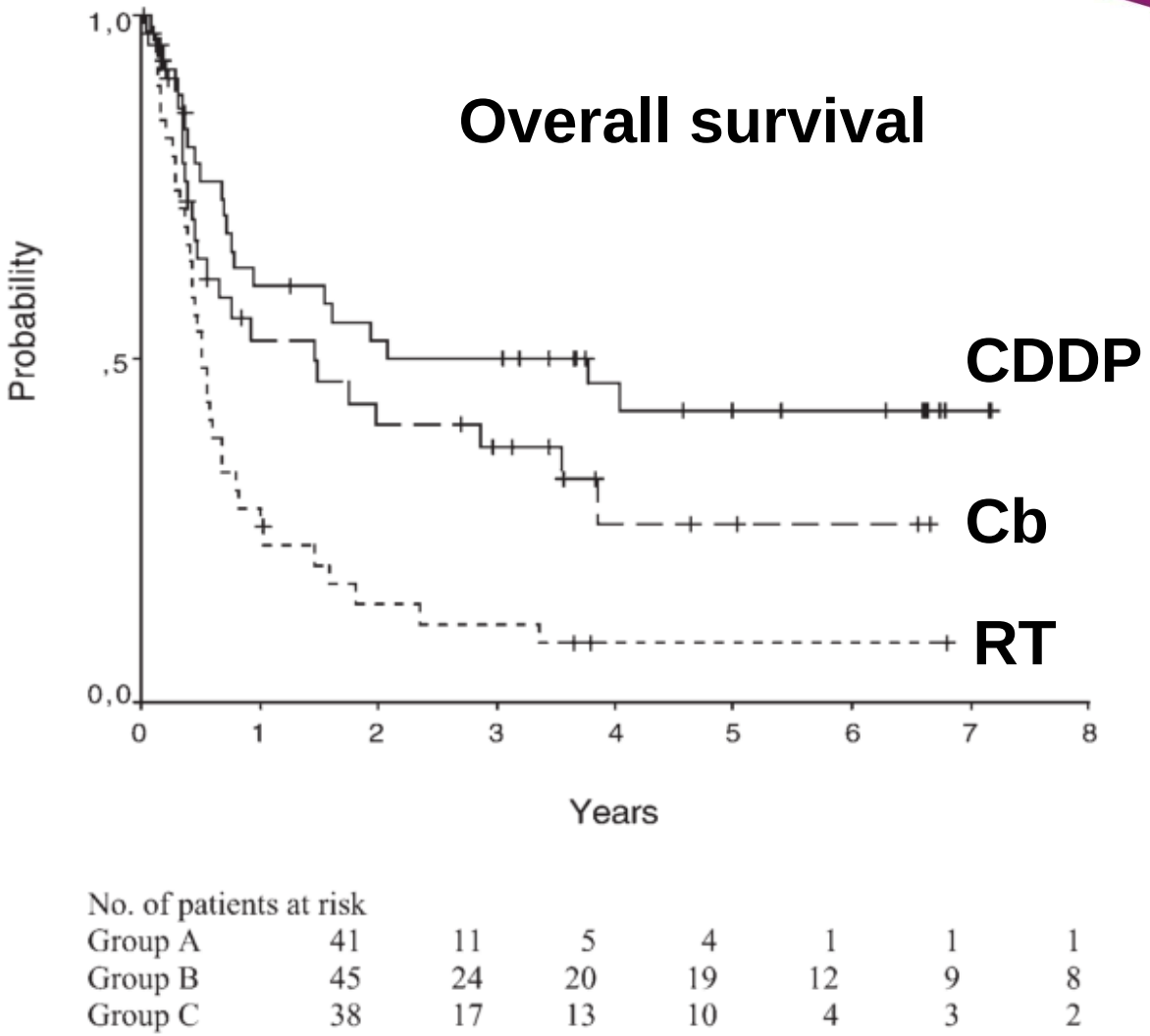
A. Cisplatin
B. Carboplatin
C. They are equivalent



Cisplatin-RT vs. Carboplatin-RT vs. RT alone

- Randomized trial
- N=124
- st. III and IV

- 70Gy/35 fx, 5 fx/wk
- CDDP 100mg/m^2
- Cb AUC7



Fountzilas G 2004

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Cisplatin or carboplatin?

	Carboplatin	Cisplatin
Age (years)		
Median (range)	59 (27–82)	58 (35–78)
Sex [n (%)]		
Male	49 (75)	54 (83)
Female	16 (25)	11 (17)
Stage [n (%)]		
III	11 (17)	13 (20)
IV	54 (83)	52 (80)
Smokers [n (%)]		
Yes	13 (20)	17 (26)
No	41 (63)	42 (65)
Ex	25 (38)	22 (34)
Never	16 (25)	13 (20)
Unknown	0	7 (11)
Unknown	11 (17)	6 (9)
Site [n (%)]		
Oropharynx	34 (52)	36 (55)
Larynx	9 (14)	10 (15)
Hypopharynx	7 (11)	6 (9)
Oral cavity	7 (11)	7 (11)
Paranasal sinuses	5 (8)	3 (5)
Unknown Primary	3 (5)	3 (5)
HPV status [n (%)] (oropharyngeal tumours)		
HPV positive	18 (53)	19 (53)
HPV negative	7 (21)	6 (17)
Unknown	9 (26)	11 (30)
Prior treatment [n (%)]		
PORT	18 (28)	18 (28)
Induction chemo	47 (72)	47 (72)

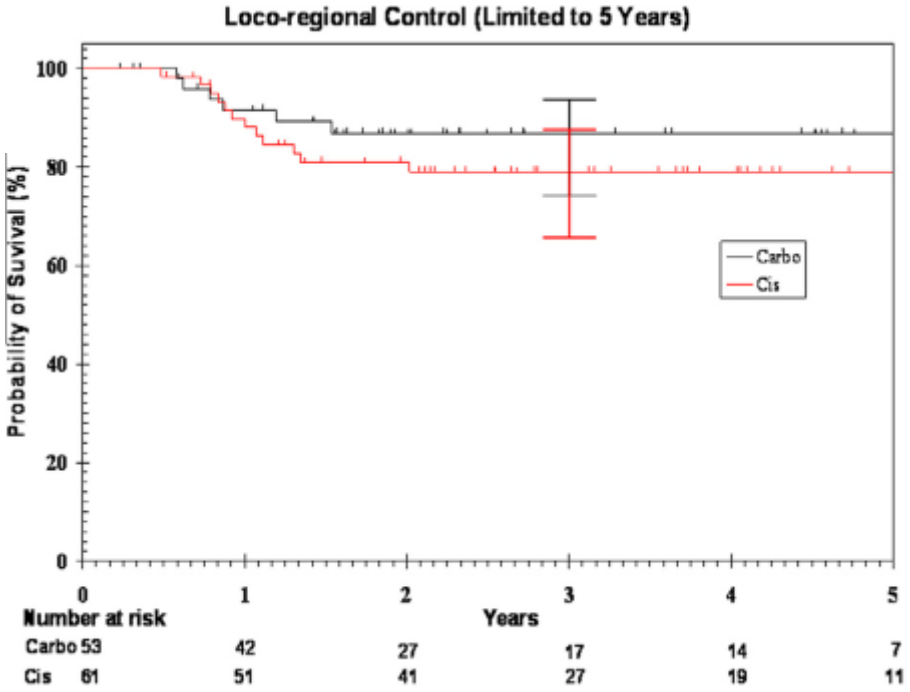
Matched pair analysis

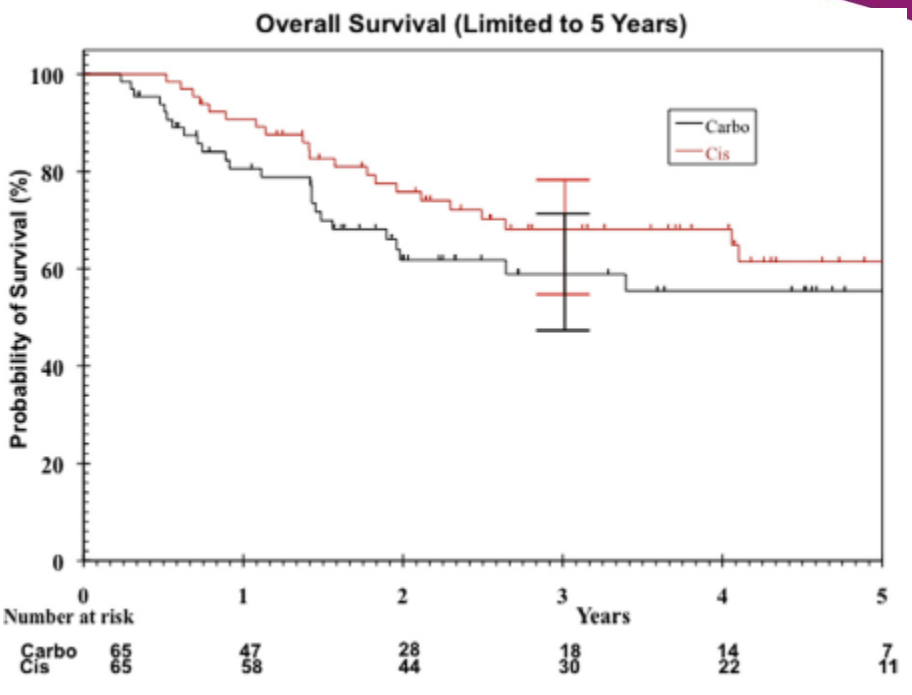
N= 2x65

Selected patients due to risk of nephro- , neuro- or oto-toxicity

Wilkins et al 2013

Cisplatin or carboplatin?





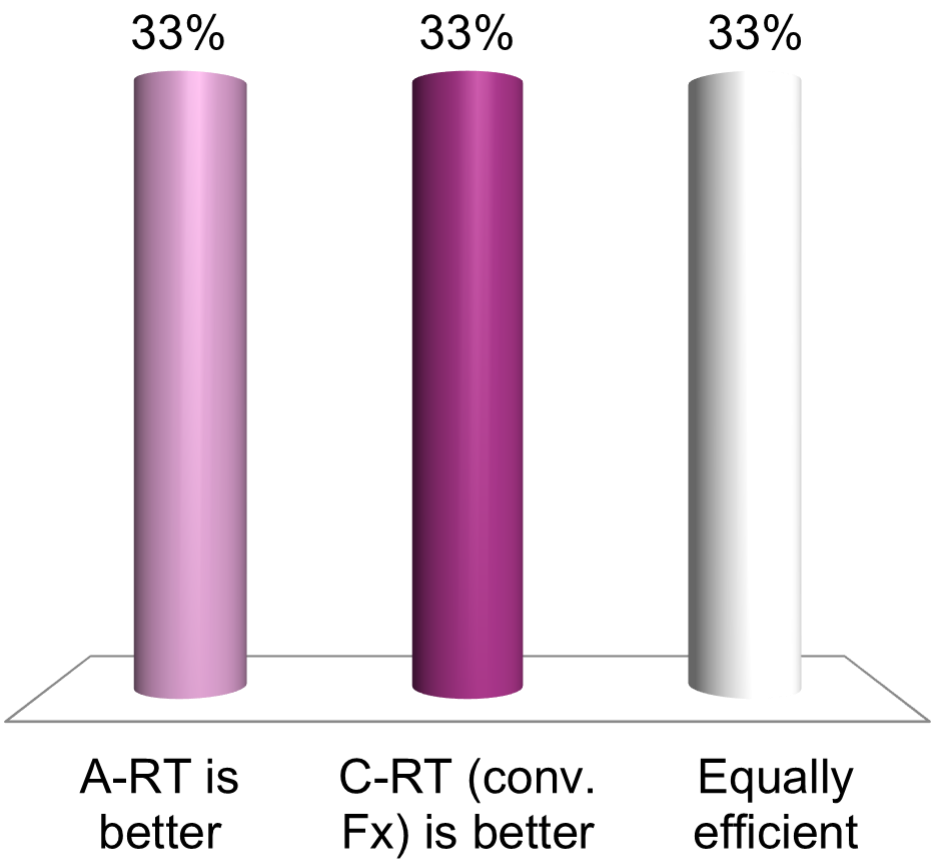
Toxicity grades 1-4 (CTCAE v 3.0).

	Carboplatin	Cisplatin	*p*-Value
	All grades [n (%)]		
Dermatitis	59 (100)	60 (97)	0.5
Mucositis	64 (99)	64 (99)	1
Dysphagia	62 (97)	61 (94)	0.68
Ototoxicity	4 (6.2)	3 (4.6)	0.71
N and V	11 (17)	24 (37)	0.012
Neurotoxicity	1 (1.5)	0 (0)	0.59
Anaemia	62 (95)	48 (73)	0.001
Neutropenia	27 (42)	33 (50)	0.3
Thombocytopenia	45 (70)	21 (32)	<0.001
Nephrotoxicity	19 (29)	20 (30)	0.84

Wilkins et al 2013

ART or CRT (concentional fractionation)?

A. A-RT is better
B. C-RT (conv. Fx) is better
C. Equally efficient



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RTOG 0129: Is AFX-C better than SFX-C?

Stage III & IV
larynx and pharynx
carcinomas
(-T1N+ and T2N1)

Statified by nodal
stage and KPS

Randomize

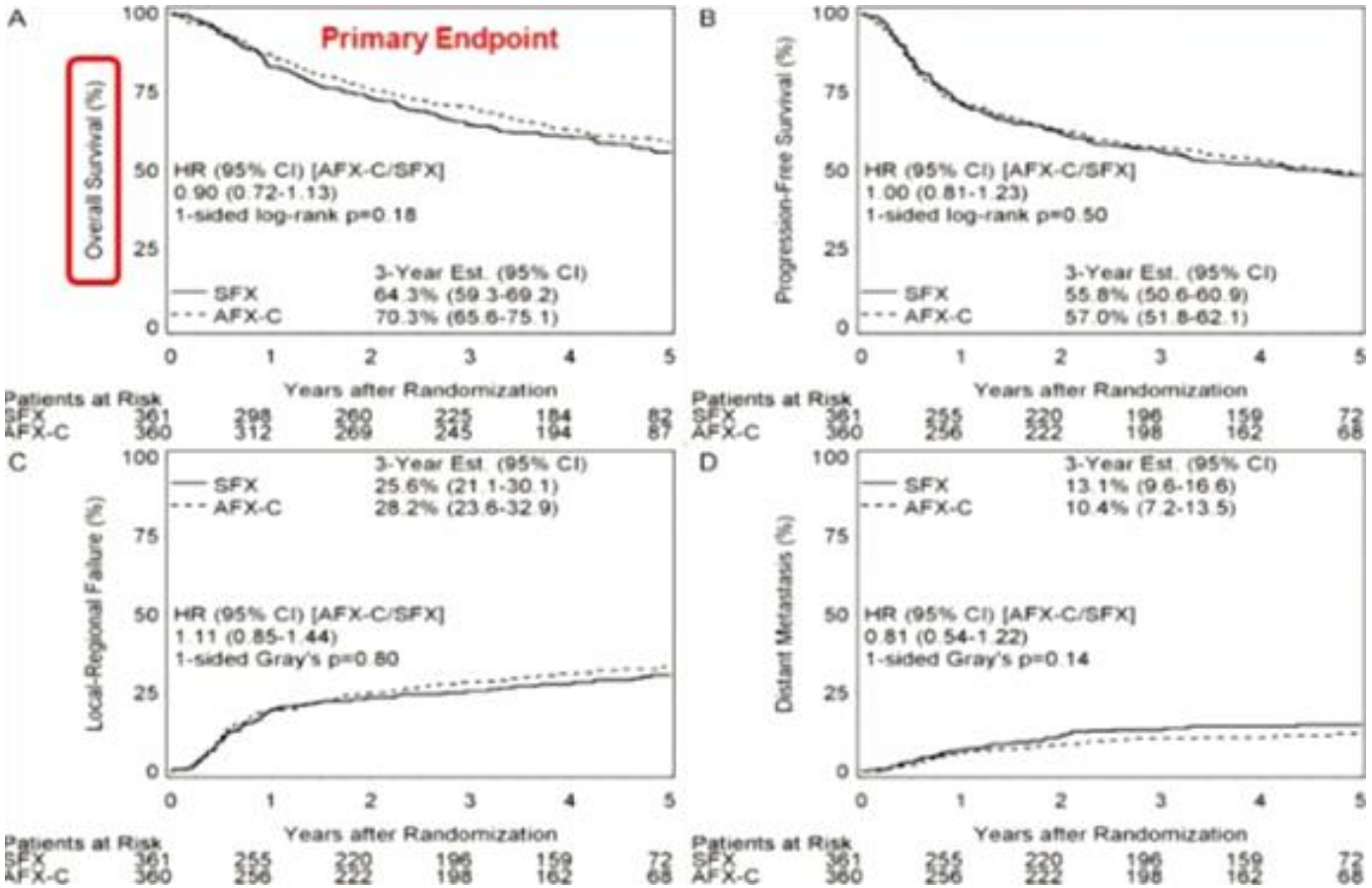
→ AFX-CB 72Gy/42fx, 6fx/w
+ CDDP 100mg/m² x 2

→ SFX 70Gy/35fx, 5fx/w
+ CDDP 100mg/m² x 3

N=721 for analysis

Ang 2010

RTOG 0129: Is AFX-C better than SFX-C?



Ang 2010

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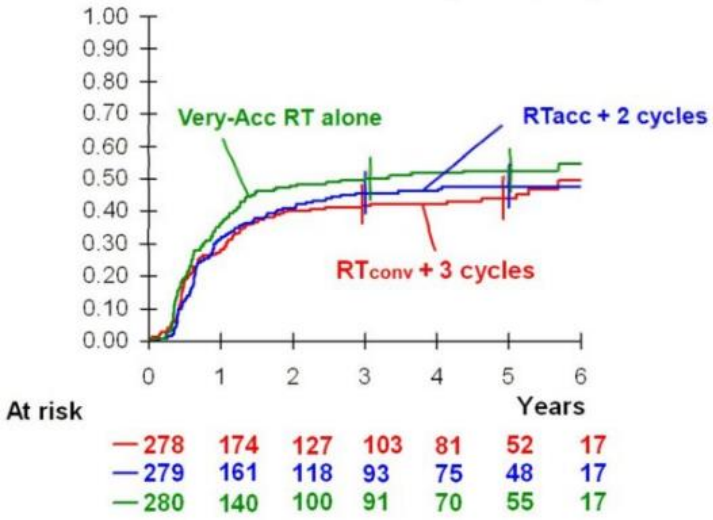
Importance of fractionation

GORTEC 99-02 randomized trial

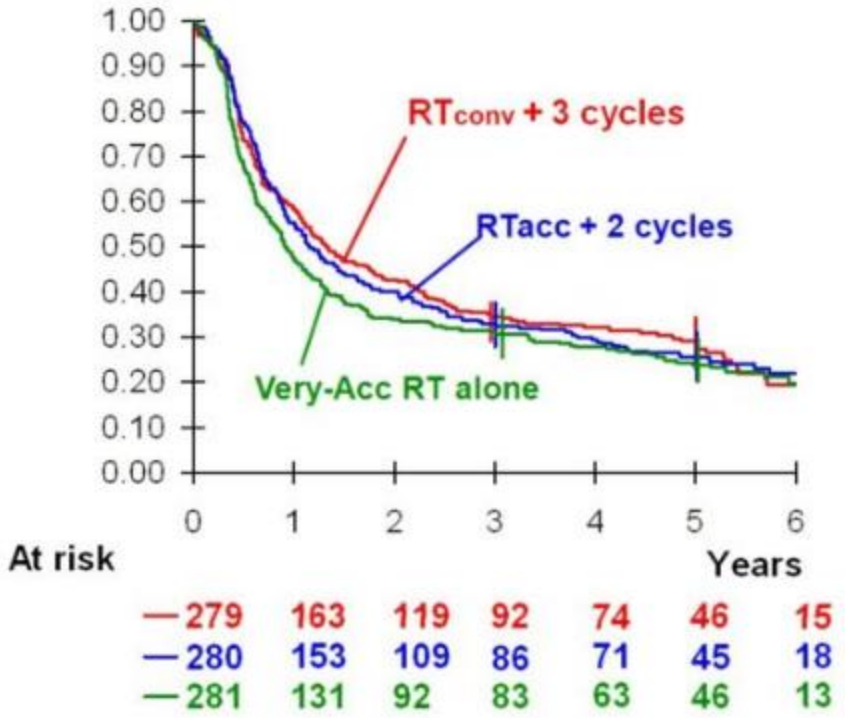
Randomisation

- 70 Gy / 7 weeks
  5FU / carboplatin concomitant (3 cycles)
- Accelerated concomitant boost RT
  70 Gy / 6 weeks
  5FU / carboplatin concomitant (2 cycles)
- Very accelerated RT 64.8 Gy / 3.5 weeks

GORTEC 9902 - Locoregional progression



Progression free survival (primary end point)



Bourhis 2012

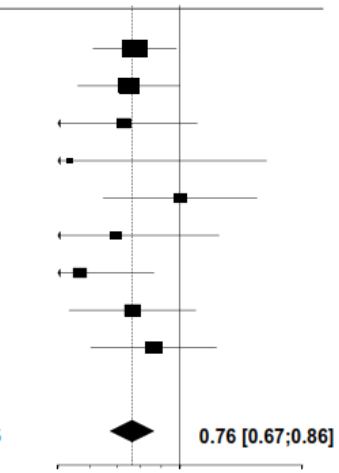
ESTRO School

So...what about combination of hyperfractionation and concomitant chemotherapy?

Altered fractionation ± concurrent chemotherapy

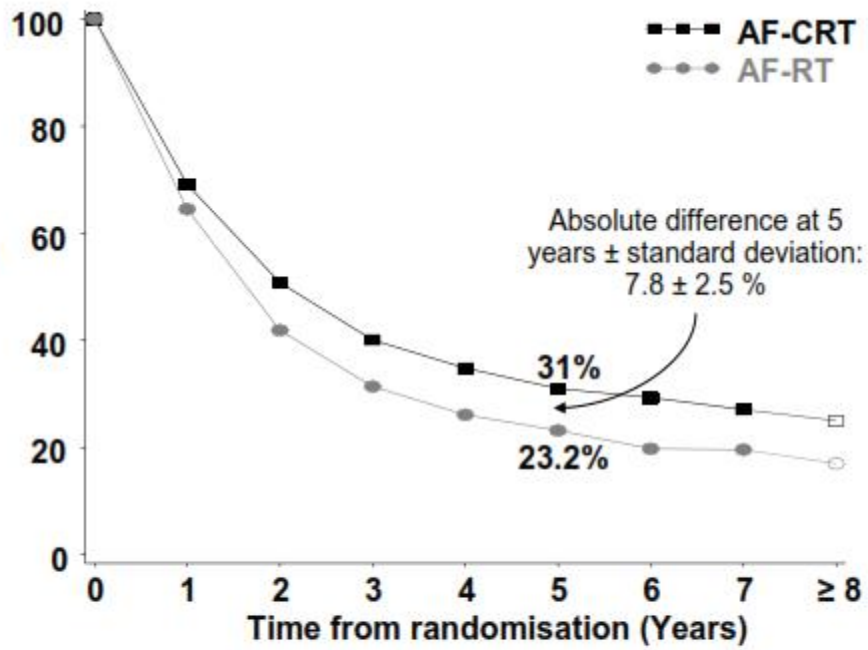
Trial	No. Deaths / No. Entered AF-CRT	AF-RT	O-	Variance
ARO 95-6	130/190	146/194	-17.5	68.5
Cologne 95	82/131	103/132	-13.3	45.9
Duke 90040	41/60	48/60	-7.0	21.9
EORTC 22962b	8/15	7/13	-1.9	3.1
GORTEC 9601	39/53	42/56	0.0	20.1
IAR 92	34/45	20/23	-4.1	11.2
Kragujevac2	38/65	51/65	-12.3	21.7
SAKK 10-94	54/112	66/112	-8.0	29.8
Vienna	61/80	62/78	-4.5	30.2
Total	**487/751**	**545/733**	**-68.6**	**252.5**

Hazard Ratio



Test for heterogeneity: $\chi^2_8 = 4.43$ p = 0.82 I^2 = 0 %

Overall survival



Number of deaths/person-years :

	Years 0-2	Years 2-5	Years ≥ 6
AF-CRT	353/1028	120/688	14/201
AF-RT	417/948	113/502	15/125

Blanchard 2011

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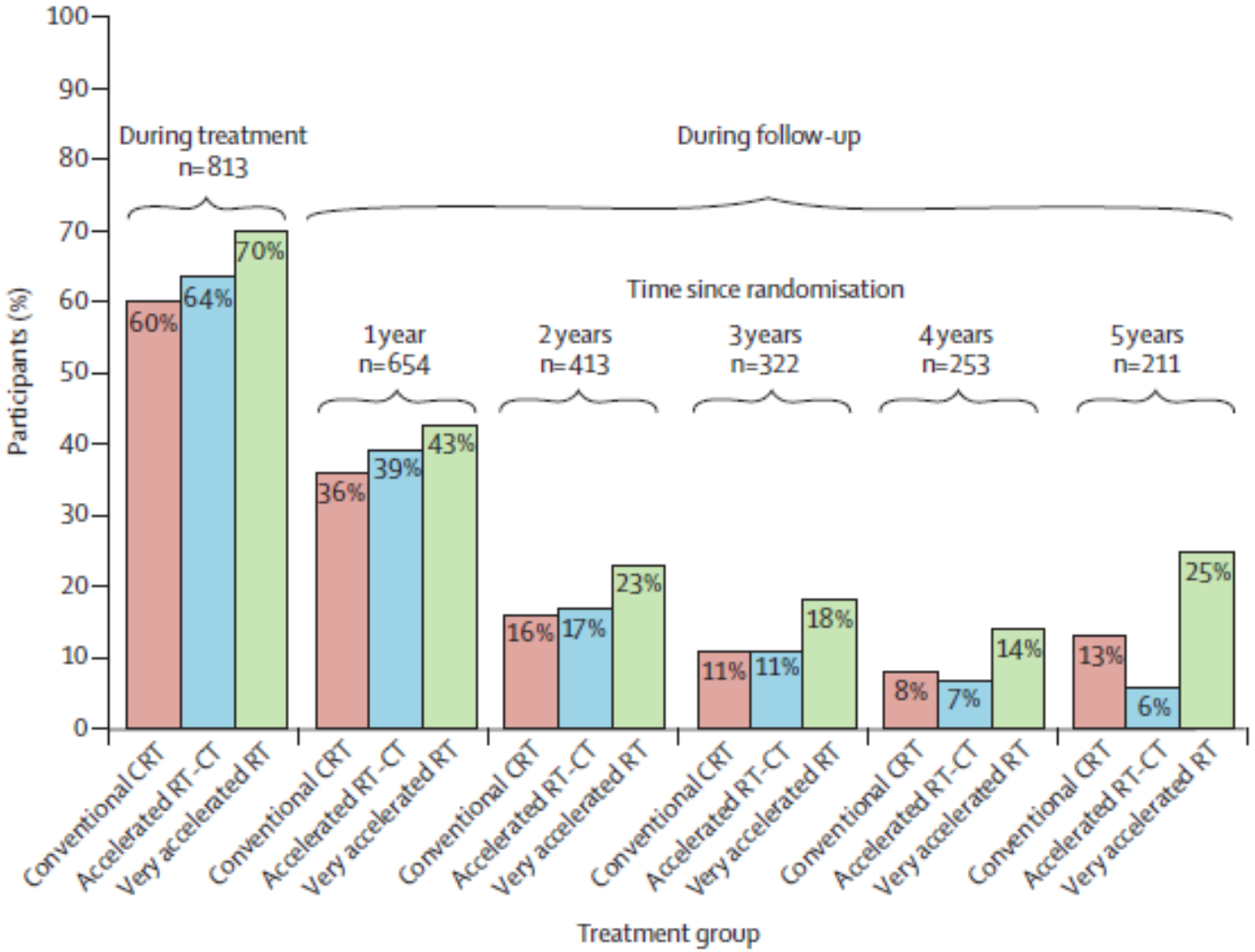
The prize to pay

GORETEC 99-02: PEG-tube dependency



Bourhis 2012

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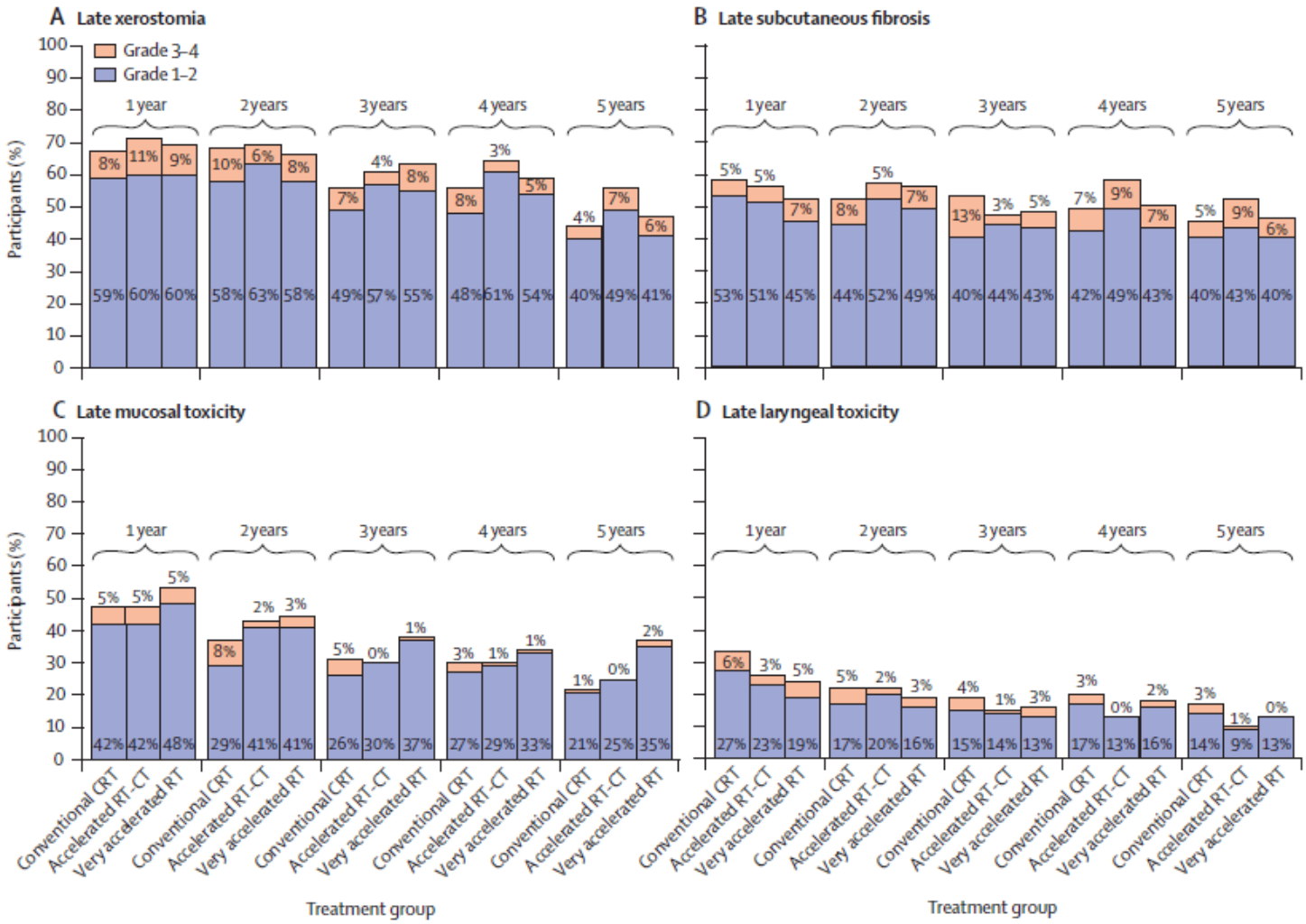
GORETEC 99-02: Late toxicity



Bourhis 2012

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ECOG/SWOG: Head and neck intergroup (295 pts.)

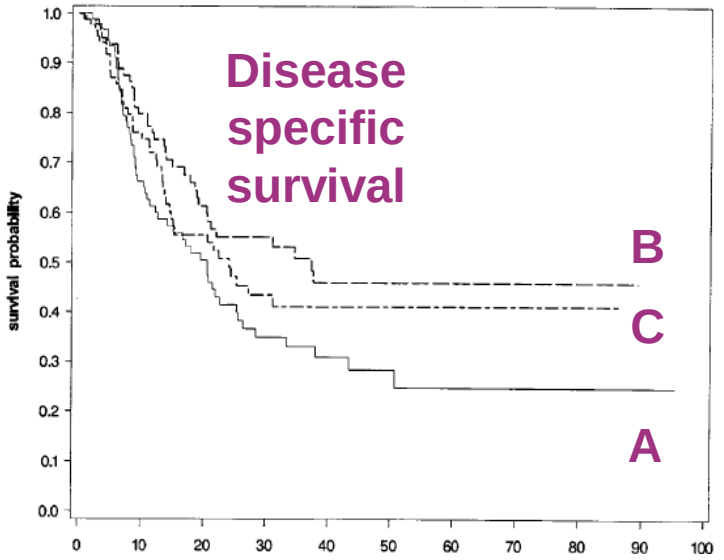
RANDOMIZE

Arm A : Radiotherapy Alone

Arm B : Radiotherapy plus Cisplatin

Arm C : Radiotherapy (split course) plus Cisplatin/5FU

(3 cycles of 100 mg/m2)



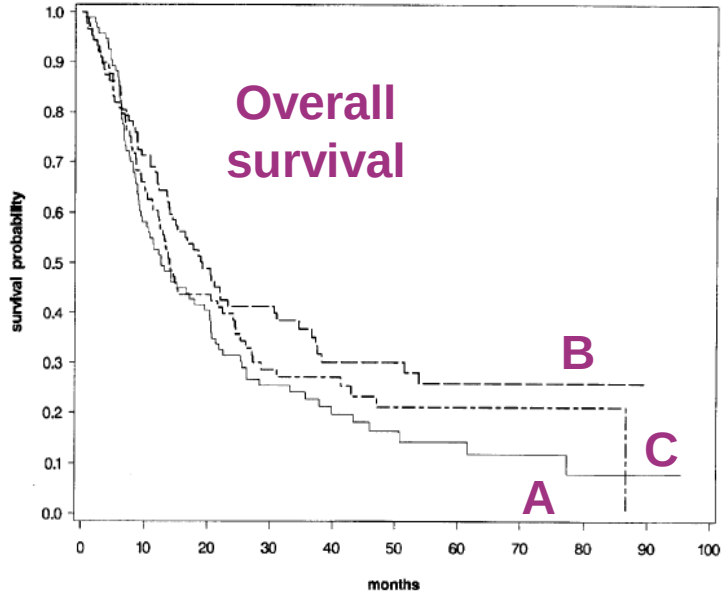


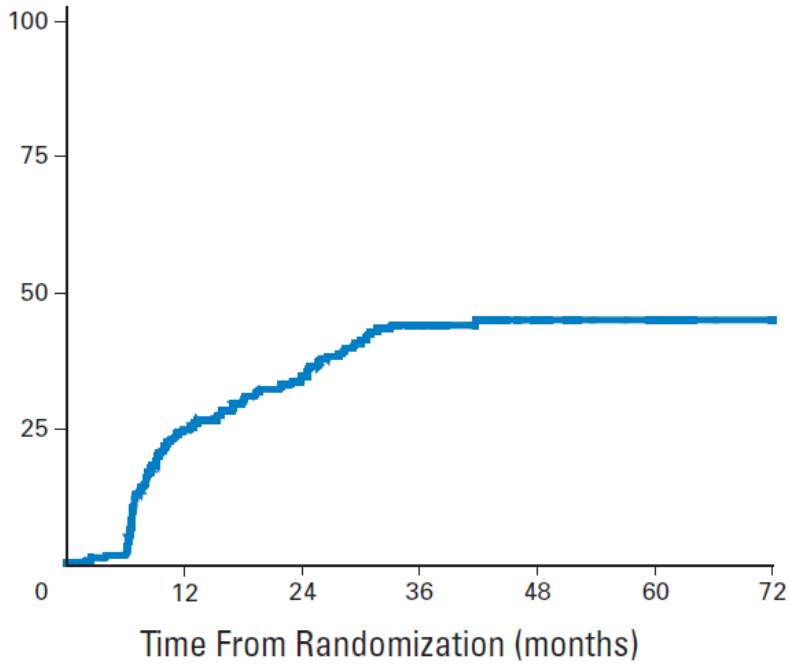
Table 4. Toxicity (grade 3-5)

Morbidity

	Arm			P		
	A (N = 98)	B (N = 95)	C (N = 94)	A versus B	A versus C	B versus C
Nausea/vomiting	6	15	8	.03		
Mucositis/dysphagia	32	43	44	.08	.06	
Leukopenia	1	40	29	< .001	< .001	< .001
Thrombocytopenia	0	3	3			
Anemia	0	17	18	< .001	< .001	
Renal	1	8	0	.01		.01
Skin	13	7	2		.005	
All grade 3-5	51	85	72	< .0001	< .001	.02

Adelstein et al. 2003

Late morbidity



Analysis of 3 RTOG trial with C-RT

(RTOG 91-11, 97-03, and 99-14)

In total 230 patients

- 43% severe late morbidity
- 40% larynx/pharynx dysfunction
- 13% tube feeding >2 Y after C-RT

Machtay M 2008

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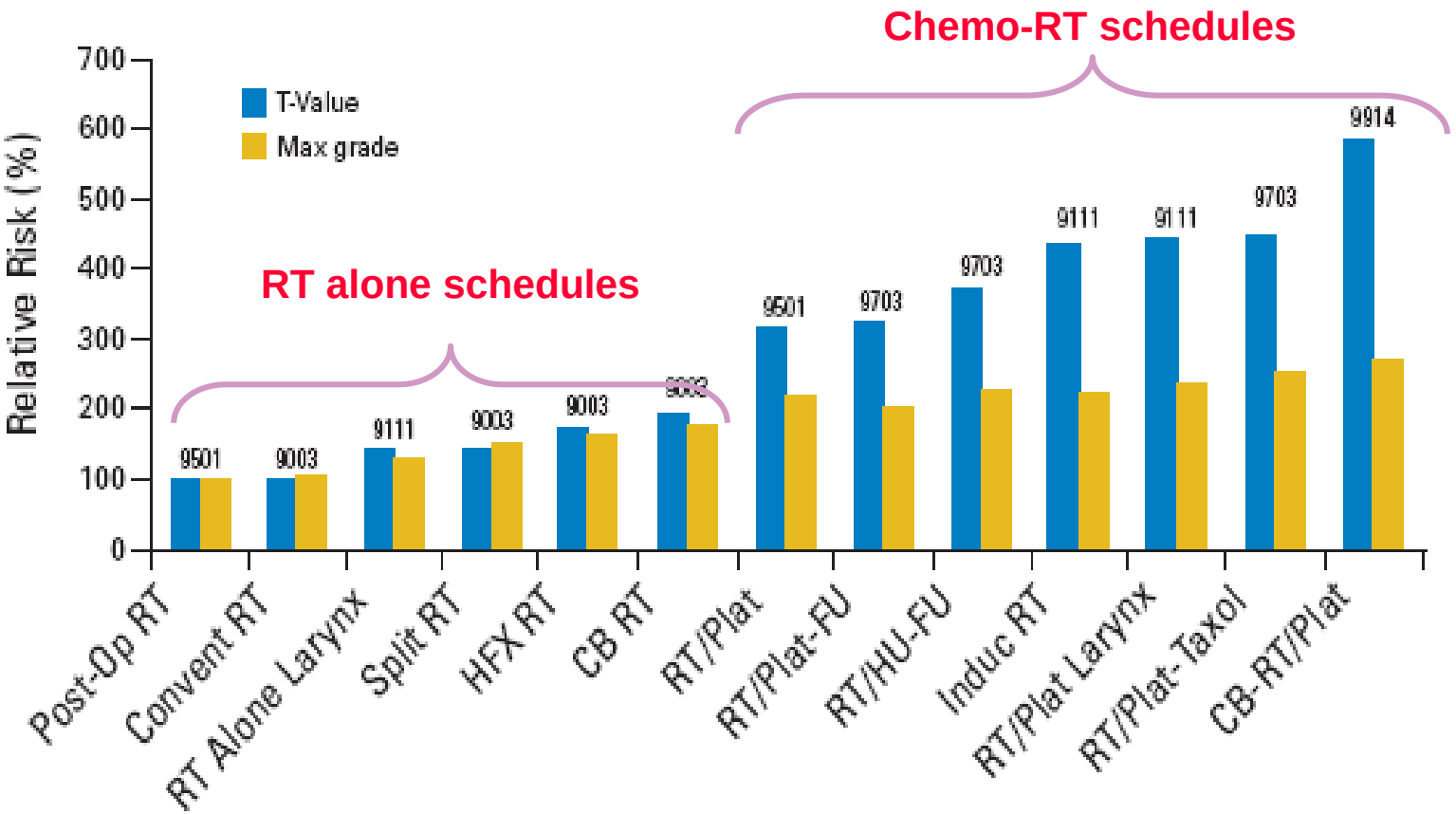
Chemo-radiation enhance late morbidity



Trotti 2007; Bentzen and Trotti 2007

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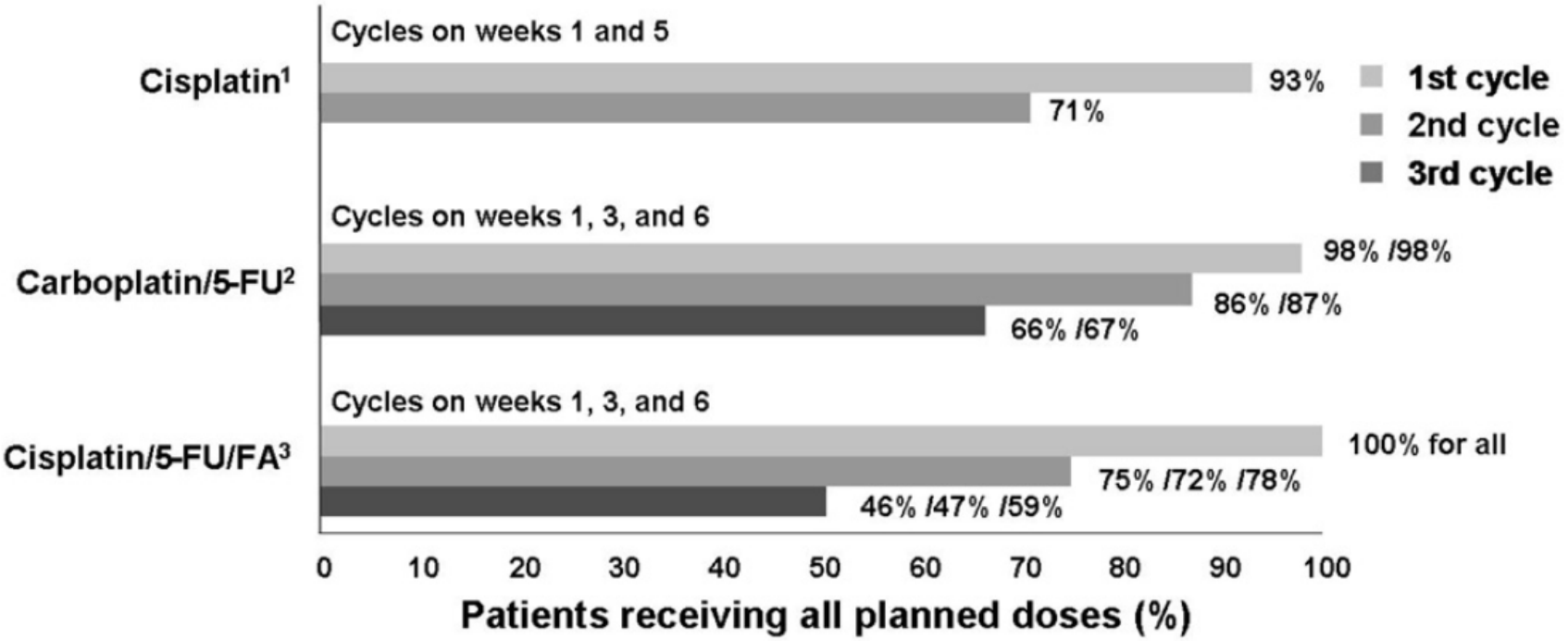
Compliance to concurrent C-RT



- 1/3 of pts. in trials do not receive the planned number of cisplatin cycles
- Compliance decreases over time
- C-RT regimens are affected by longer overall treatment times
- More frequent treatment interruptions than radiotherapy alone

Bernier J 2009

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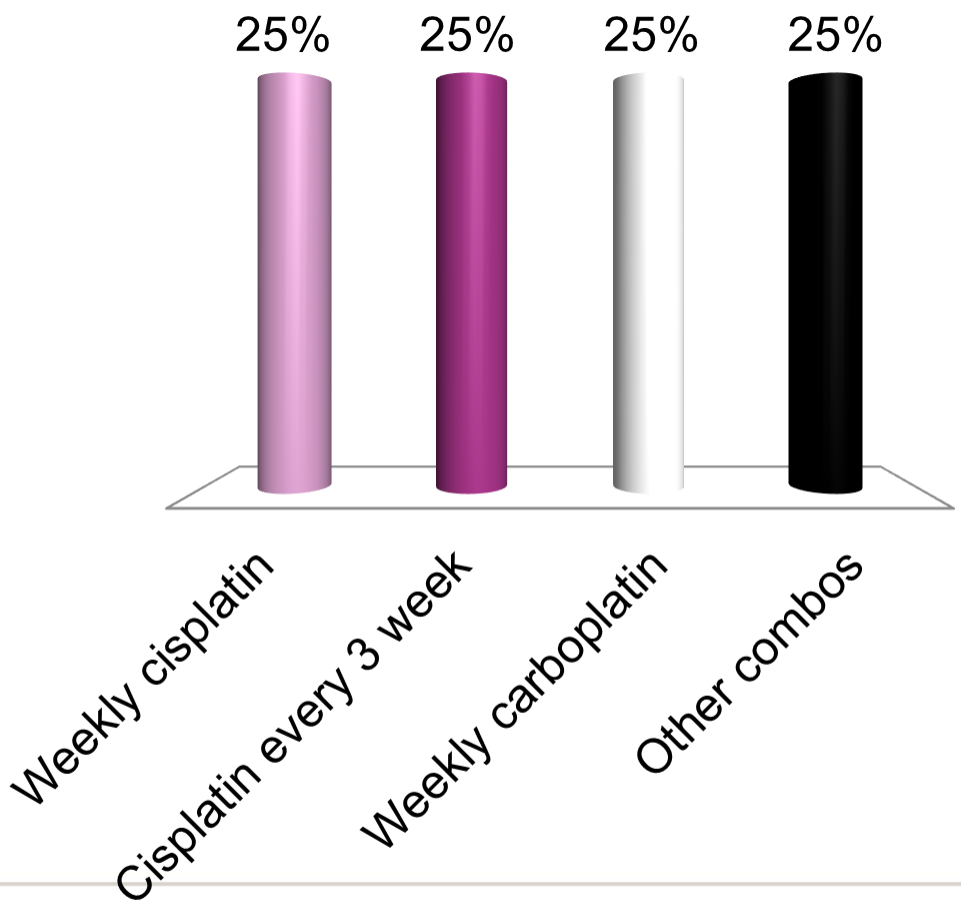
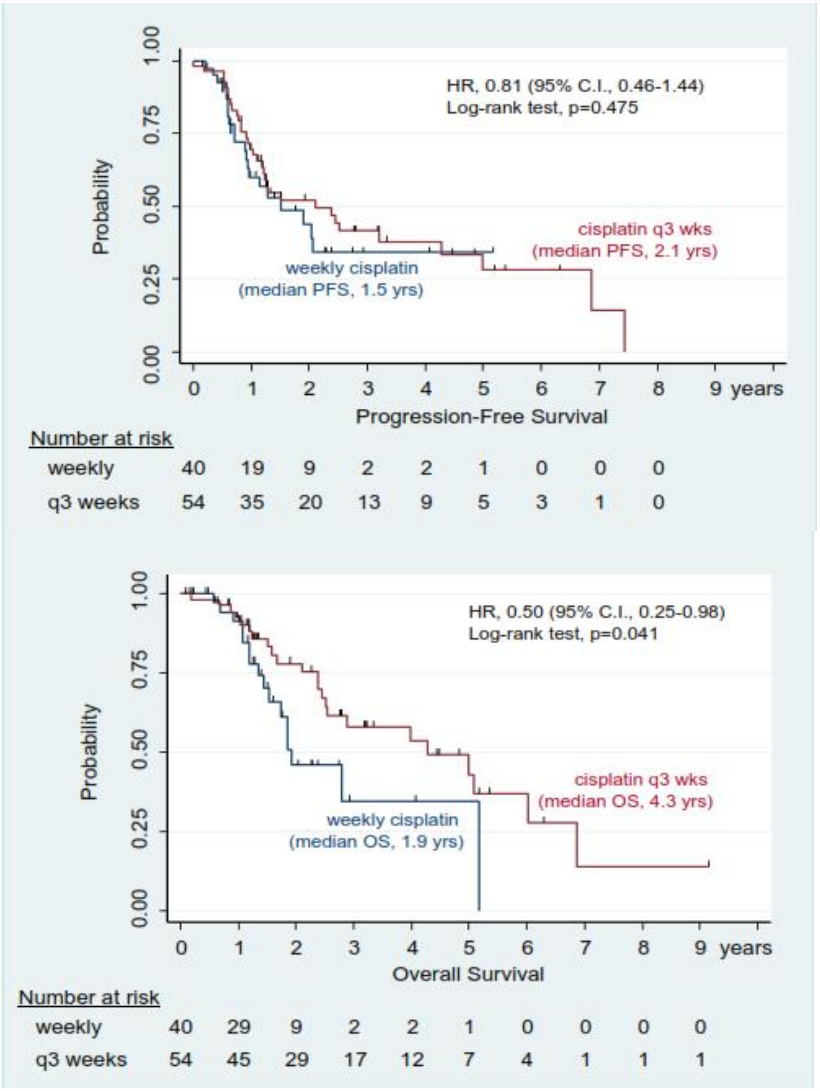
How much and how often?

How much and how often?

A. Weekly cisplatin
B. Cisplatin every 3 week
C. Weekly carboplatin
D. Other combos



Low-dose weekly or high-dose every 3 weeks?



- Retrospective
- N=94
- 40 vs. 100 mg/m^2
- Selection biased
- Sign. older in 40 mg group

	Total	Group A 3-weekly cisplatin (100 mg/m^2)	Group B weekly cisplatin (40 mg/m^2)	*P*-value
Acute renal failure	43 (46 %)	29 (53.7%)	14 (35%)	0.07
Chronic renal failure	21 (23%)	16 (29.6%)	5 (12.5%)	0.04
Mucositis	80 (85%)	45 (83.3%)	35 (87.5%)	
Grade 1–2	58 (62%)	36 (66.6%)	22 (55%)	
Grade 3–4	22 (23.5%)	9 (16.6%)	13 (32.5%)	0.08
Cutaneous toxicity	78 (83%)	44 (81.5%)	34 (85%)	
Grade 1	45 (58%)	24 (44.5%)	21 (52.5%)	
Grade 2–3	33 (42%)	20 (37%)	13 (32.5%)	0.5

Espeli 2012

ESTRO School

DAHANCA 18: Low-dose weekly cisplatin + RT

	All patients (n = 227)	
Patient/tumour data	n	(%)
Age (years)		
Median	57	
Range	(31–82)	
Gender		
Female	49	22
Male	178	78
Tumour site		
Larynx	28	12
Hypopharynx	26	12
Oropharynx	150	66
Cavum Oris	23	10
Tumour stage		
T1–2	144	63
T3–4	83	37
Nodal stage		
N0	5	2
N1–3	222	98
Disease stage		
I–II	47	21
III–IV	180	79

- 227 consecutive patients
- LAHNC
- Follow-up: 46 mo. (24-73 mo.)
- 66-68Gy, 33-34 fractions, 6fx/wk
- Weekly cisplatin 40mg/m^2

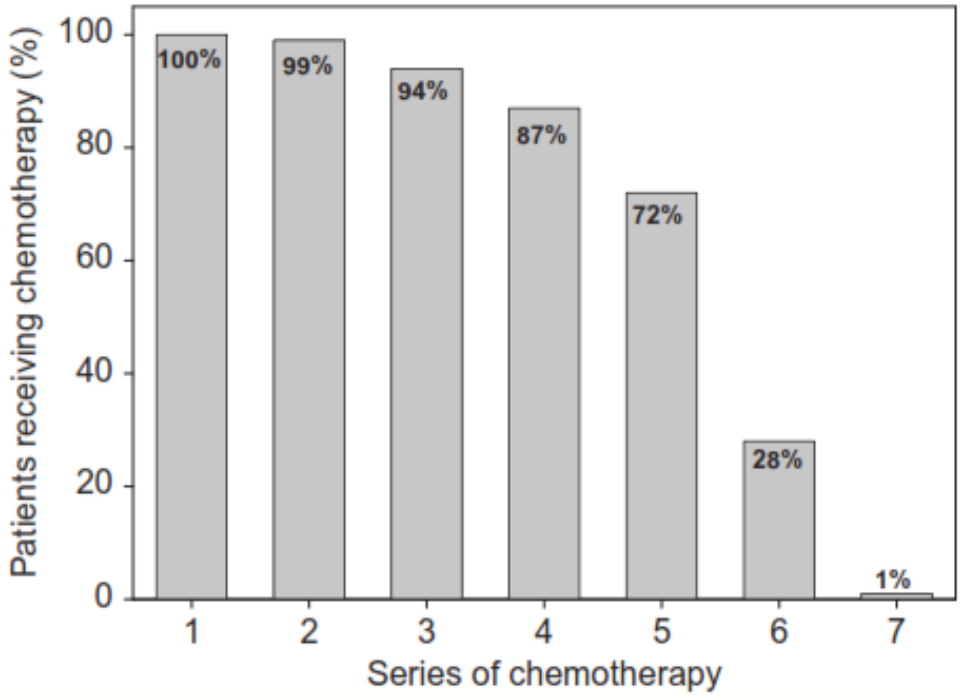
Benzten 2015

ESTRO School

DANANCA 18: compliance

Compliance Radiotherapy and Chemotherapy

Total dose Gy	59,7	60	64	66	68
Number	1	3	1	100	122



72% got 5 cycles of cisplatin or more

Benzten 2015

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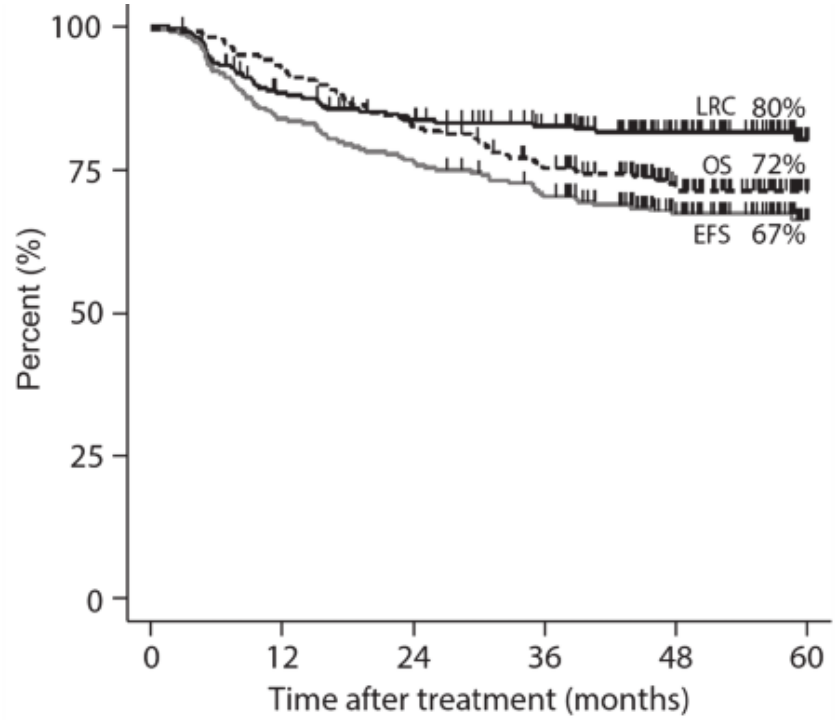
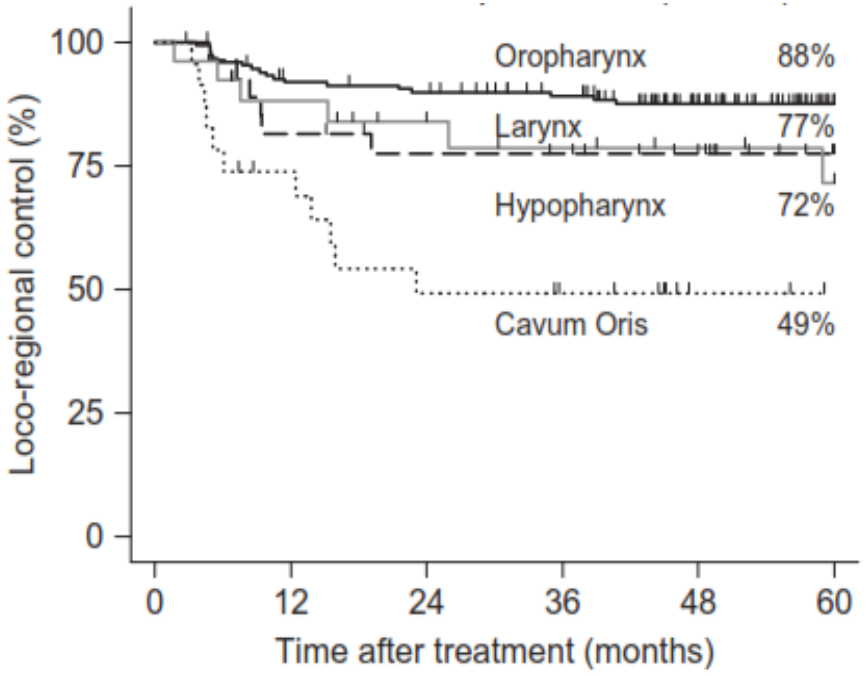
DAHANCA 18: outcome



At risk						
LRC	227	192	176	159	115	57
EFS	227	192	176	158	115	57
OS	227	211	189	167	122	60



At risk						
Larynx	28	22	19	18	14	5
Oropharynx	150	134	130	119	87	41
Hypopharynx	26	21	17	14	12	10
Cavum oris	23	15	10	8	2	0

Benzten 2015

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DAHANCA 18: morbidity

	Acute (during treatment) (n = 227)		Chronic 1 year after treatment (n = 200)		Chronic 2 years after treatment (n = 181)	
Side effect	n	%	n	%	n	%
Acute mucositis	173	76				
Need of feeding tube	146	64	11	6	6	3
Dysphagia, only fluid nutririon	168	74	17	9	17	9
Severe dryness of mouth/throat			32	16	35	19
Severe mucosal atrophy			2	1	4	12
Pronounced fibrosis of the neck			19	10	25	14

Benzten 2015

ESTRO School

Postoperative weekly C-RT in high risk HNSCC

PATIENTS AND TUMOR CHARACTERISTICS

Pts	A (No 35)	B (no 49)	p
Sex male/female	27/8	45/4	0,11
Age	58 (43-76)	59 (40-77)	0.96
Oral cavity	2(5,71%)	1 (2,04%)	
Oropharynx	8 (22,8%)	12 (24,48%)	P=0,53
Hipopharynx	3(8,57%)	6 (12,2%)	
Larynx	**22(62.84%)**	**30 (61,22%)**	
CS			
III	8 (22,8%)	9 (18.37%)	p=0,61
IV	**27 (77,14%)**	**40 (81,63%)**	
TNM			
T3	14 (40%)	15 (30,61%)	p=0,68
T4	**15 (42,86%)**	**20 (40,82%)**	
N2	**14 (40%)**	**20 (40,82%)**	
N3	5 (14,29%)	12 (24,49%)	
High risk features			
>2Lymph.nodes	**22 (62,86%)**	**26 (53,06%)**	p=0,37
ECS+	21 (60%)	26 (53,06%)	p=0,52
margins +	5 (14,29%)	4 (8,16%)	p=0,48
pT4	15(42,86%)	20(40,82%)	p-=0,53

High risk factors

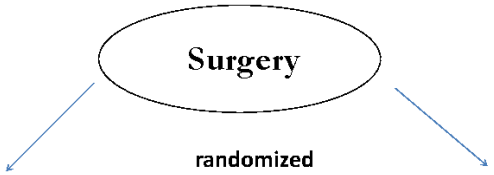
Extra capsular tumor spread

Microscopically involved surgical margins

pT4 with negative surgical margins

> 2 involved lymph nodes

perineural,lymphatic,venous invasion



Arm A
III cycles 100mg/m² CDDP 1,22,43d
TD 64Gy/32f/2Gy/d/6.5w

Arm B
VI cycles 40mg/m² CDDP weekly
TD 64Gy/32f/2Gy/d/6.5w

Korda et al ICHNO 2013

ESTRO School

Postoperative weekly C-RT in high risk HNSCC

TREATMENT COMPLIANCE

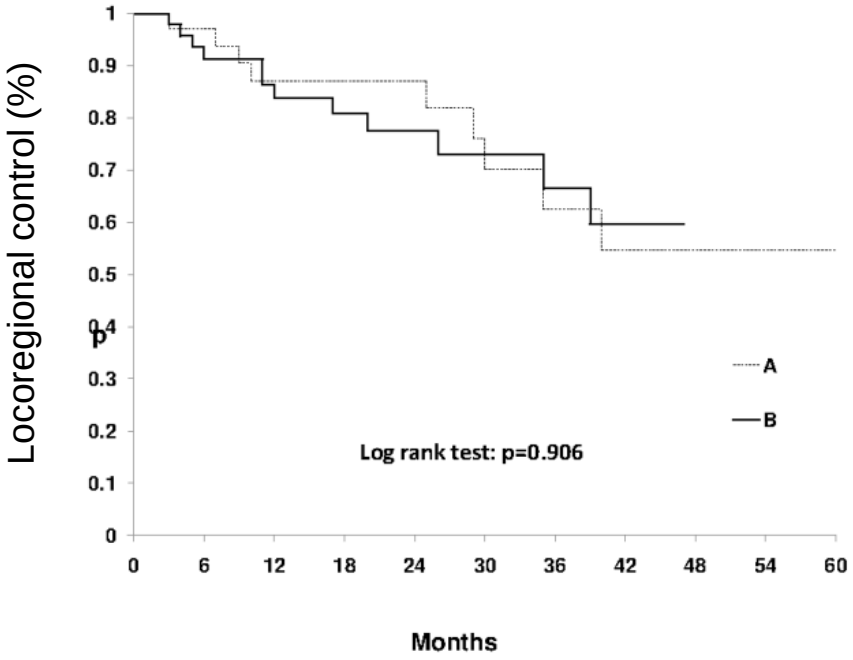
Chemoradiotherapy schedule	**A 100mg/m² (** 1,22,43d)
CHRT complete III cycles	13(37,14%)
CHRT complete II cycles	20(57,14%)
CTRT complete I cycle	2 (5,71%)
RT complete	33(94,28%)
Chemoradiotherapy schedule	B 40mg/m² weekly
CHRT complete VI cycles	39 (79,5%)
CHRT incomplete (<VI cycles)	9 (18,36%)
RT complete	49 (100%)

Korda et al ICHNO 2013

Postoperative weekly C-RT in high risk HNSCC

PATTERNS OF FAILURE

Relapse	A 100mg/m²	B 40mg/m²
Relapse	9 (25,71%)	12 (24,49%)
Locoregionally	6(17,14%)	9(18,36%)
Distant metastases	3 (8,57 %)	3 (6,12%)
Locoregionally + distant meta	1 (2,86 %)	2 (4,08%)
Second primary	0 (0%)	1 (2,04%)



Korda et al ICHNO 2013

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Cisplatin – LD weekly or HD every 3rd week

W3W

Phase III randomized trial comparing weekly versus 3-weekly (W3W) cisplatin in patients receiving chemoradiation for locally advanced head and neck cancer

Vanita Noronha, MD DM
On behalf of Medical Oncology Department
Head and Neck Disease Management Group
Tata Memorial Hospital, Mumbai, India

PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17

Trial Design-W3W

ELIGIBILITY CRITERIA

- Age ≤ 70 yrs
- SCC of oral cavity/ pharynx/ larynx/ cervical lymphadenopathy of unknown primary
- Stage III / IV, no distant mets
- Adjuvant or definitive CRT
- If postop: high-risk features: ECE, close or + margins, T4 primary, > 2 LNs +
- No induction chemotherapy
- Adequate organ function

Stratify

- **T-group** (T0,1,2 vs T3,4)
- **N-group** (N0,1 vs N2,3)
- **Therapy intent** (adjuvant vs definitive)

Randomized 1:1 Open Label

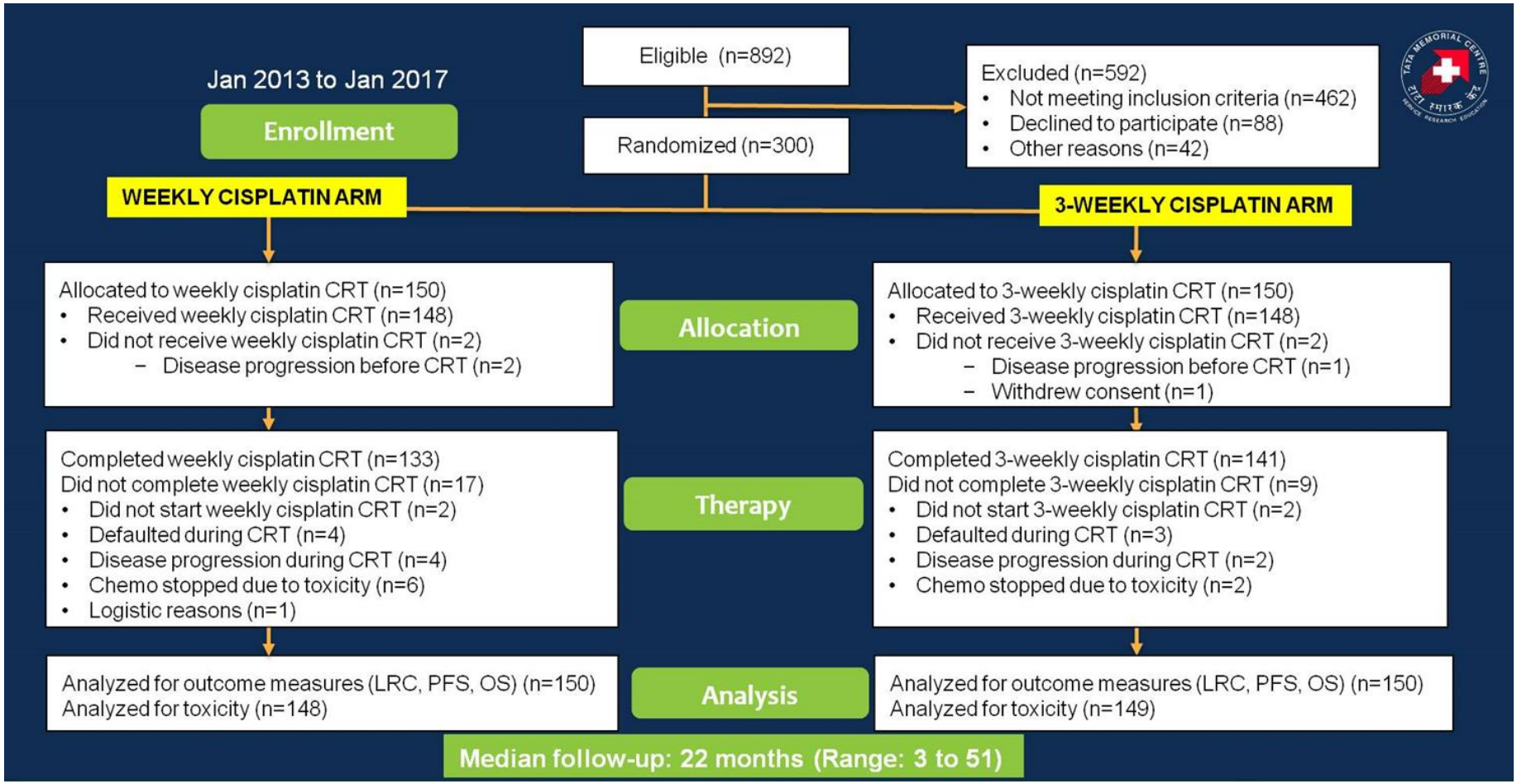
n=150 → **3-weekly cisplatin 100mg/m² D1,22,43 of RT**

n=150 → **Weekly cisplatin 30mg/m² with RT**

RT: 60 Gy/30 fr/6 wks (adj)
70 Gy/35 fr/7 weeks-(def)

Follow-up: Weekly during CRT, then Q3 mths x 2 yrs, then Q6 mths

Cisplatin – LD weekly or HD every 3rd week



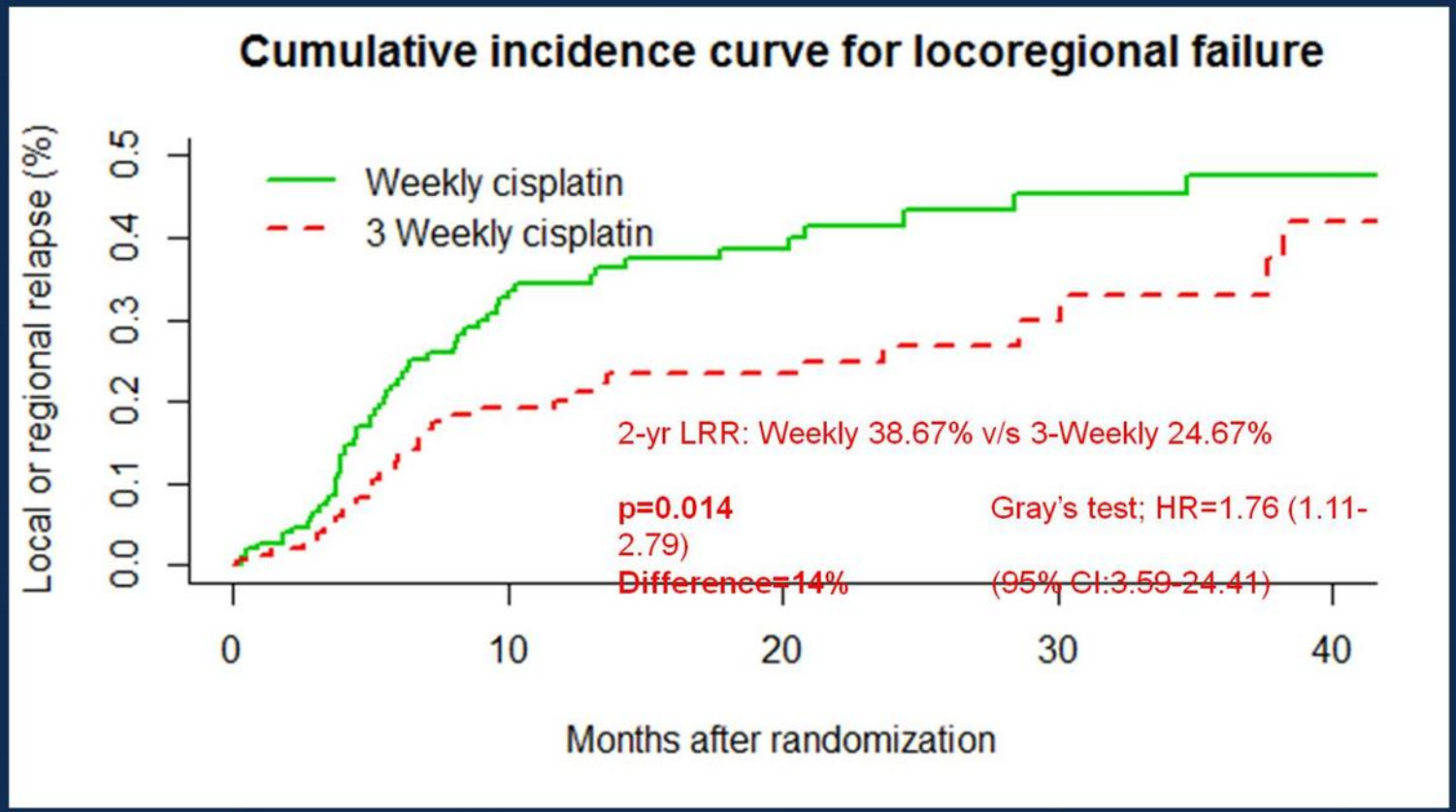
Cisplatin – LD weekly or HD every 3rd week

Chemotherapy Details	Weekly cisplatin (n=150)	3-wkly cisplatin (n=150)
Cycles of chemotherapy-no. (%)	< 5: 17 (11.3)	0/ 1: 7 (4.7)
	≥6: 133 (88.7) P=0.1	≥2: 143 (95.3)
Days from surgery to CRT start (n=276)-Median (IQR)	42 (36-50)	42 (35-49)
Total treatment time in days (n=276)-Median (IQR)	85 (79-96)	86 (79-95)
Dose reduction in chemotherapy-no. (%)		
Yes	14 (9.3)	12 (8)
No	136 (90.7)	138 (92)
Dose delay > 2 days-no. (%)		
Yes	37 (24.7)	42 (28)
No	113 (75.3)	108 (72)
Days between planned and actual chemo cycle-median (IQR)	0 (0-3)	0 (0-3)
Cumulative cisplatin dose in mg/m^2- Median (IQR)	210 (180-210)	300 (200-300)

Characteristic (Intention-to-treat)	Weekly Cisplatin (N=150)	3-weekly cisplatin (N=150)	All patients (N=300)
Age in years-Median (range)	41.5 (26 to 65)	47 (25-67)	44 (25-67)
Male sex-no.(%)	135 (90)	132 (88)	267 (89)
Tobacco use-no. (%)			
Smokeless tobacco	109 (72.7)	105 (70)	214 (71.3)
Smoking	27 (18)	32 (21.3)	59 (19.7)
ECOG performance status- no. (%)			
0	21 (14)	24 (16)	45 (15)
1	128 (85.3)	125 (83.3)	253 (84.3)
2	1 (0.7)	1 (0.7)	2 (0.7)
Primary			
Oral cavity- no. (%)	136 (90.7)	126 (84)	262 (87.3)
Buccal mucosa-no.	82	80	162
Tongue/ hard palate-no.	54	46	100
Pharynx- no. (%)	4 (2.6)	6 (4)	10 (3.4)
Larynx- no. (%)	3 (2)	8 (5.2)	11 (3.7)
Cervical lymphadenopathy, unk pr- no (%)	7 (4.7)	10 (6.7)	17 (5.7)

Cisplatin – LD weekly or HD every 3rd week

OUTCOMES



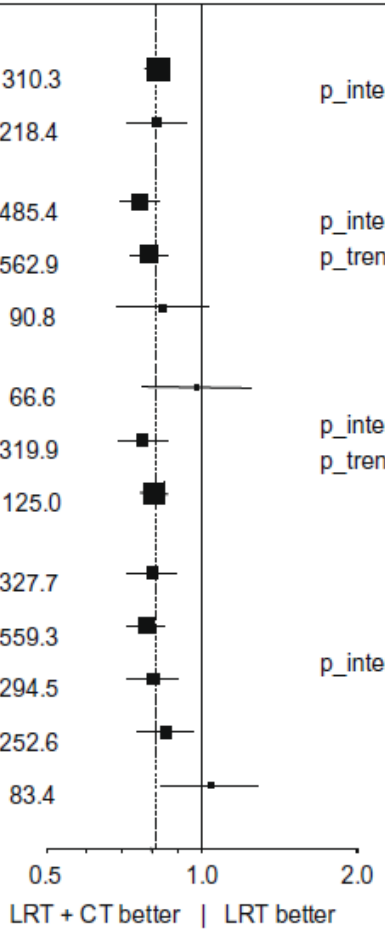
Number at risk					
Weekly Cisplatin	150	75	45	24	15
3 weekly Cisplatin	150	84	54	22	10

Who will benefit?

Who benefit from C-RT?

(a) by sex, performance status, stage and tumour site

Category	No. Deaths / No. Entered LRT + CT	LRT	O-E	Variance	Hazard Ratio	Interaction and trend tests
Sex						
Male	2635/3882	2807/3847	-259.2	1310.3		p_inter = 0.95
Female	483/788	508/788	-44.1	218.4		
Performance status						
0	923/1667	1084/1696	-135.1	485.4		p_inter = 0.59
1	1210/1680	1179/1538	-131.8	562.9		p_trend = 0.31
2 or 3	220/279	218/274	-15.8	90.8		
Stage						
I-II	133/251	155/286	-1.5	66.6		p_inter = 0.20
III	661/1140	699/1094	-83.7	319.9		p_trend = 0.60
IV	2268/3266	2430/3261	-240.9	1125.0		
Site						
Oral cavity	680/997	754/1020	-72.8	327.7		p_inter = 0.16
Oropharynx	1123/1723	1219/1681	-138.3	559.3		
Larynx	607/1013	644/1012	-64.0	294.5		
Hypopharynx	546/760	563/757	-40.5	252.6		
Others	187/264	183/256	3.2	83.4		



Pignon et al 2009

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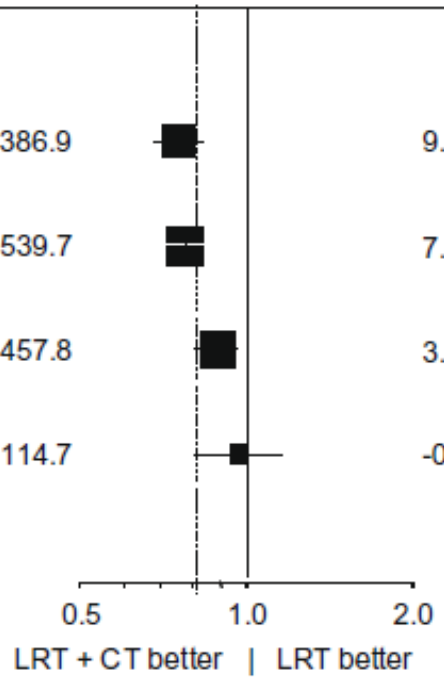
Age and benefit of C-RT

Category	No. Deaths / No. Entered LRT + CT	LRT	O-E	Variance	Absolute difference at 5 years ± sd
Age					
Less than 50	803/1296	860/1288	-107.6	386.9	9.8 ± 2.1
51-60	1069/1645	1198/1661	-136.4	539.7	7.8 ± 1.8
61-70	972/1368	988/1330	-56.2	457.8	3.0 ± 1.9
71 or over	273/356	260/336	-3.5	114.7	-0.7 ± 3.9



p_inter = 0.02

p_trend = 0.003

	Altered fractionated RT vs. standard RT			Concomitant CT + RT vs. RT		
Age (y)	No. of patients	Hazard ratio (95% CI)	Test for trend (p)	No. of patients	Hazard ratio (95% CI)	Test for trend (p)
≤50	1311	0.78 (0.65–0.94)	0.007	2584	0.76 (0.66–0.86)	0.003
51–60	2300	0.95 (0.83–1.09)		3306	0.78 (0.70–0.87)	
61–70	2346	0.92 (0.81–1.06)		2698	0.88 (0.78–1.00)	
≥71	1085	1.08 (0.89–1.30)		692	0.97 (0.76–1.23)	

Pignon et al 2009

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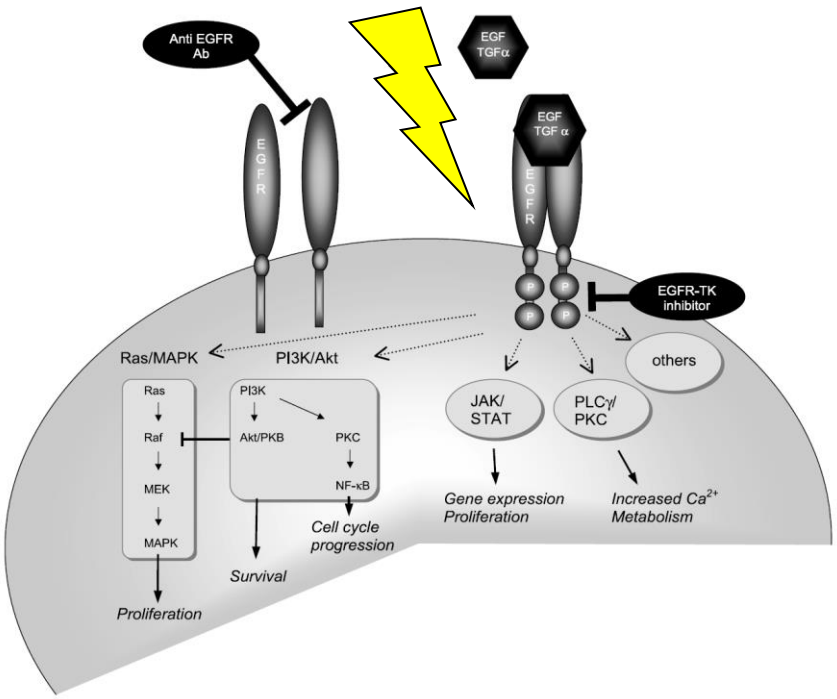
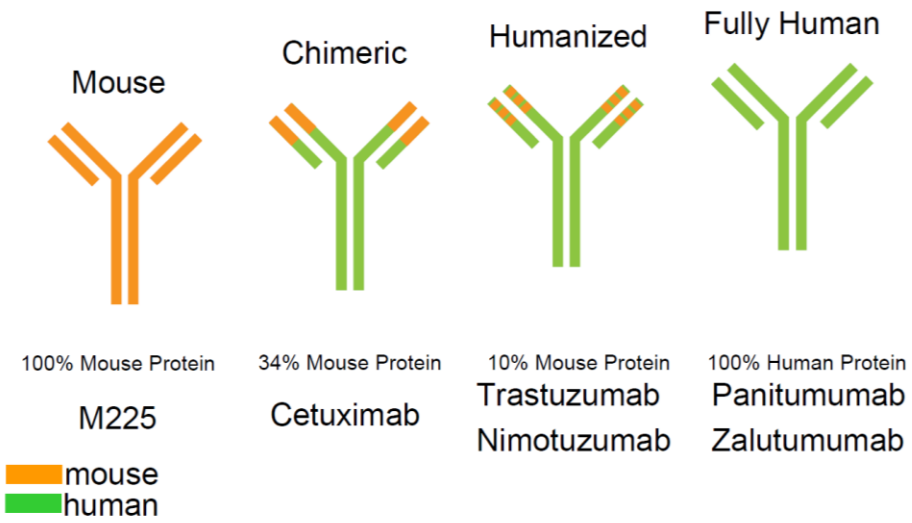
C-RT for the 70+ ???

Does the tumour sense that it is placed in an old body?

Bio-radiotherapy





The Ideal biological target

- Selective inhibition of a specific target
- Present in tumour cells
- Only present in tumour cells….or…..
- The function of the target is not essential for normal tissue
- Only one or a few activation pathways (little redundacy)
- Good preclinical models that shows tumour efficacy

After Grandis 2008

Radiotherapy ± EGFR-I

Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival

James A Bonner, Paul M Harari, Jordi Giralt, Roger B Cohen, Christopher U Jones, Ranjan K Sur, David Raben, Jose Baselga, Sharon A Spencer, Junming Zhu, Hagop Youssoufian, Eric K Rowinsky, K Kian Ang

STRATIFY:
T-stage
N-stage
KPS
Fractionation

RANDOMIZE

RT alone

208 ptt. each arm

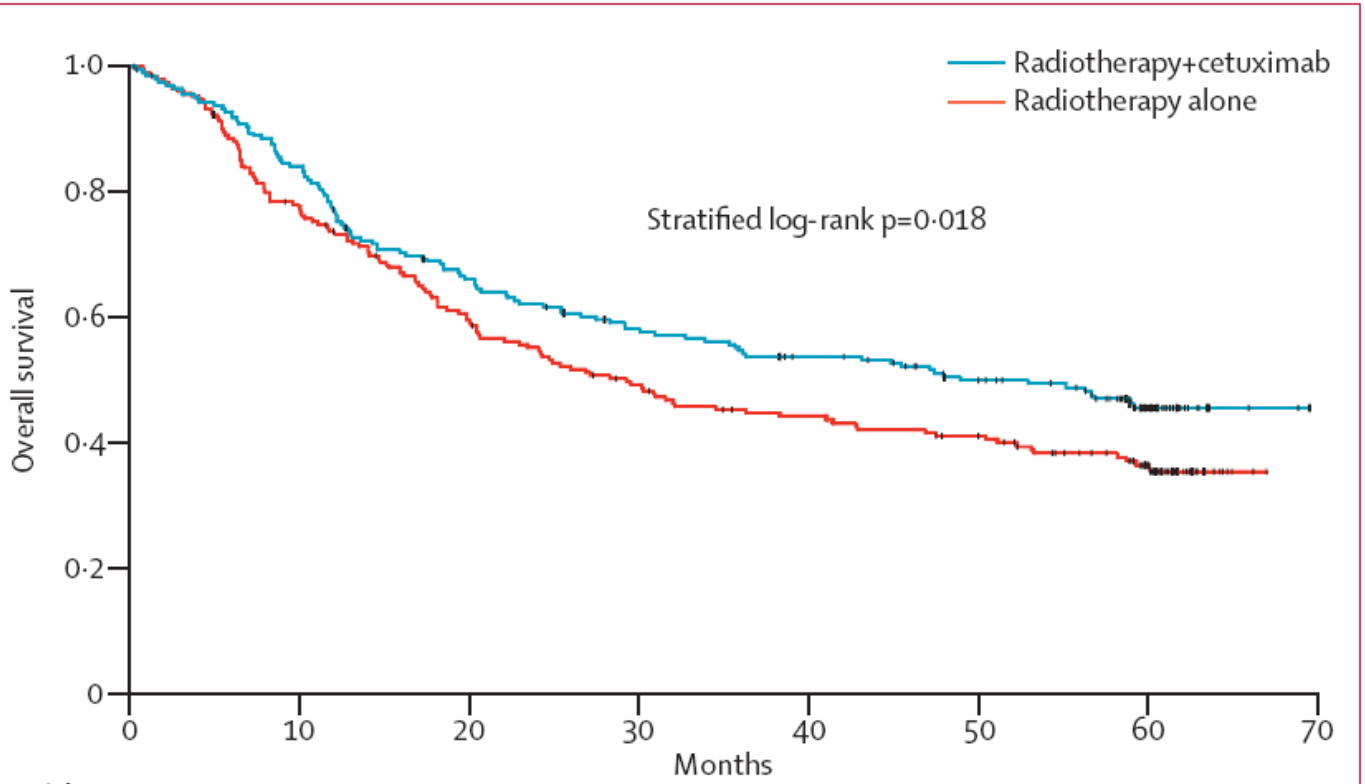
RT+cetuximab

Primary endpoint: Locoregional control

Bonner JA 2010

ESTRO School

Radiotherapy ± EGFR-I



Number at risk								
Radiotherapy+ cetuximab	211	177	136	117	105	90	49	..
Radiotherapy alone	213	162	122	98	85	77	49	..

Bonner JA 2010

ESTRO School

Radiotherapy ± EGFR-I

Acute toxic effects (WHO criteria)

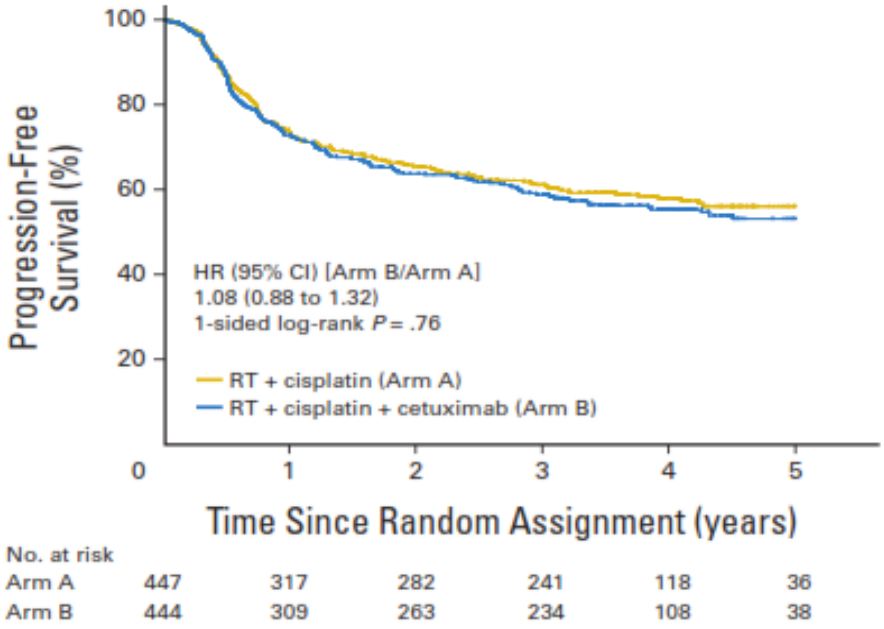
	RT alone	RT + cetuximab	*p* - value
Mucositis (grade 3-5)	52%	56%	N.S.
Skin rash (all grades)	10%	87%	< 0.001
Radiation dermatitis (grade 3-5)	18%	23%	N.S.
Weight loss (all grades)	72%	84%	0.005
Nausea (all grades)	37%	49%	0.02
Fever (all grades)	13%	26%	0.001
Anemia (all grades)	13%	3%	< 0.001

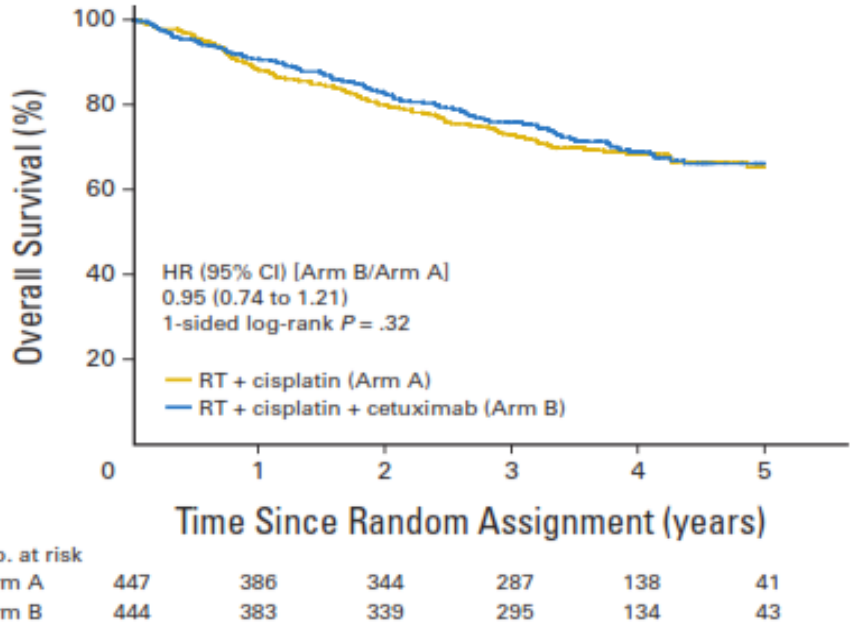
Late toxicity: no difference

Bonner JA 2010

RTOG 0522: C-RT ± cetuximab for stage III-IV HNSCC

- 940 pts with stage III-IV HNSCC of the larynx and pharynx
- No significant differences in PFS or OS
- Triplet patients had higher rates of grade 3-4 mucositis and skin reactions

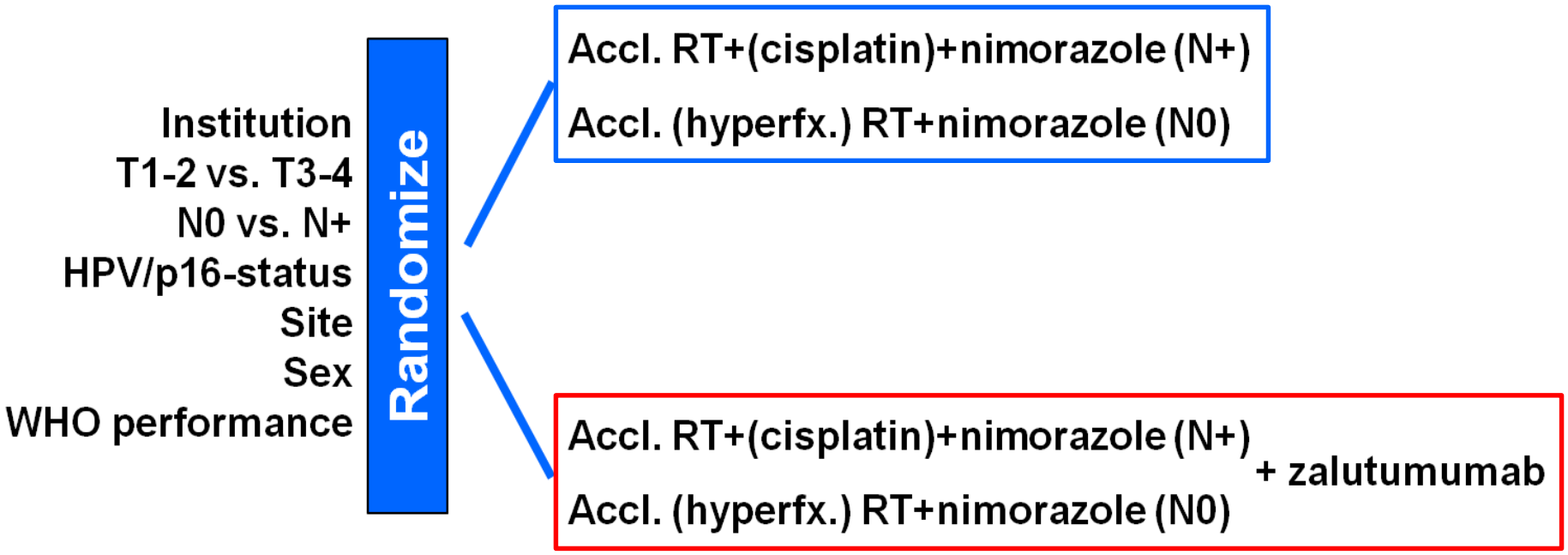




Ang, JCO 2014

ESTRO School

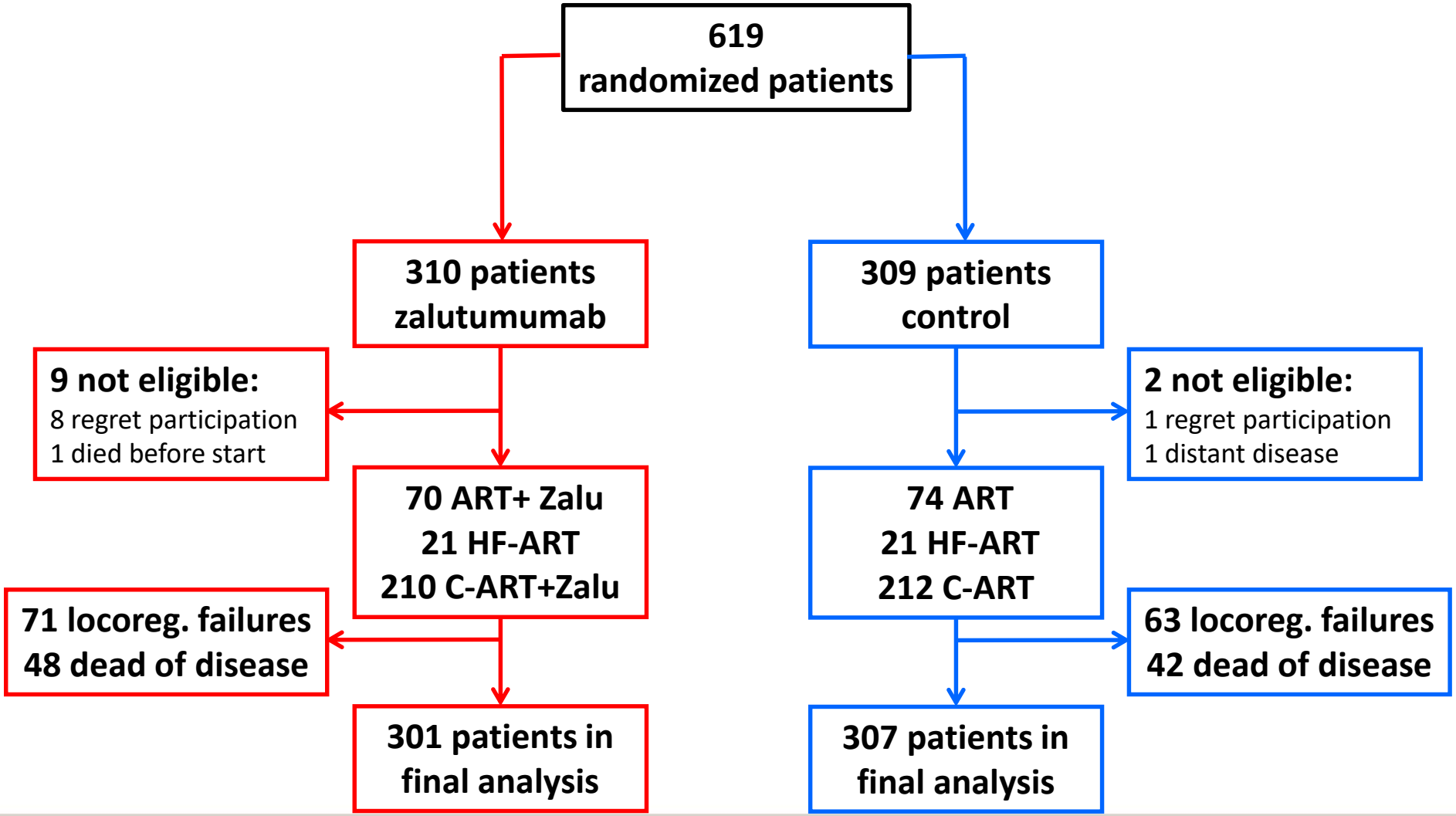
DAHANCA19: RT/CRT ± EGFR-I



Eriksen 2015

ESTRO School

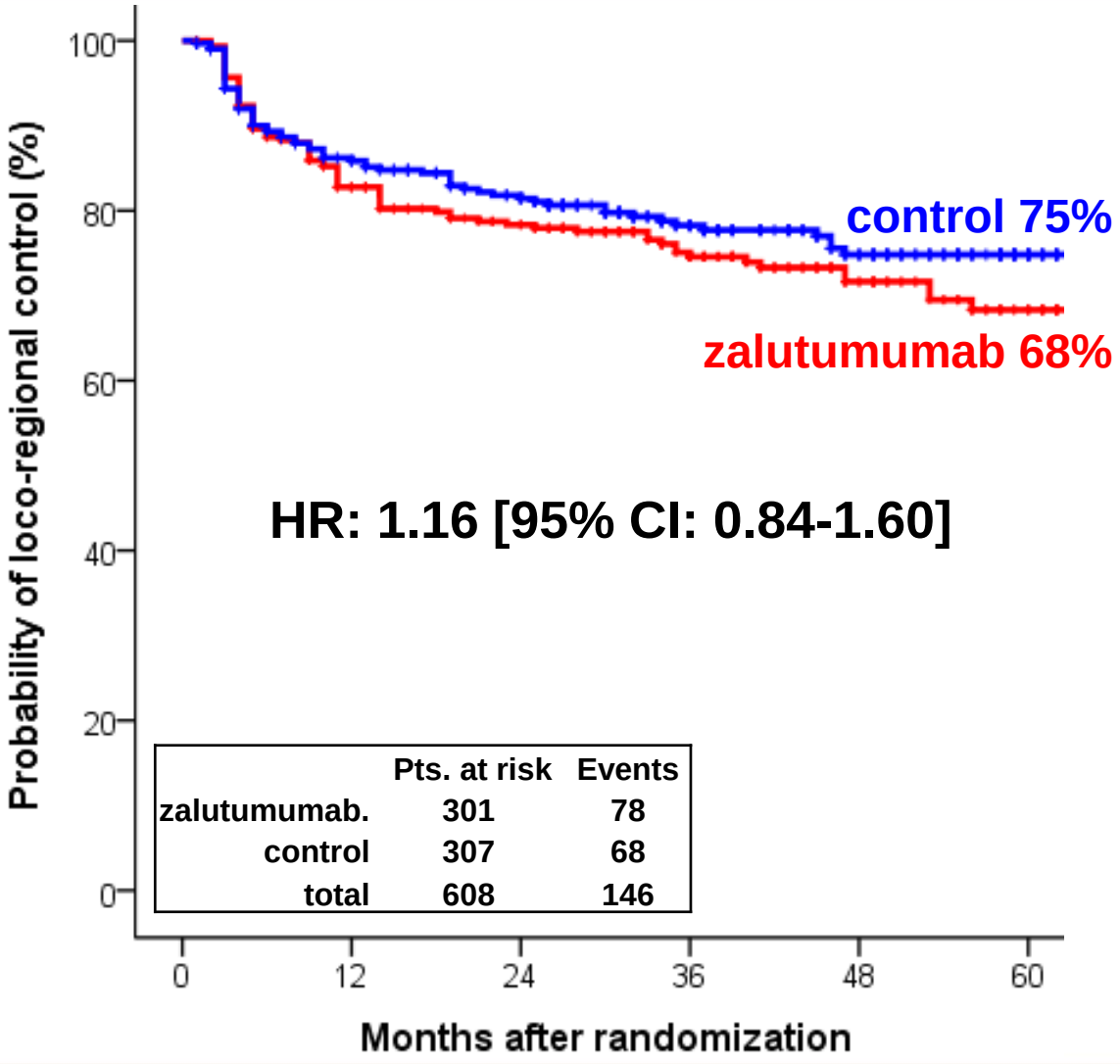
DAHANCA19: RT/CRT ± EGFR-I



Eriksen 2015

ESTRO School

DAHANCA19: Loco-regional control

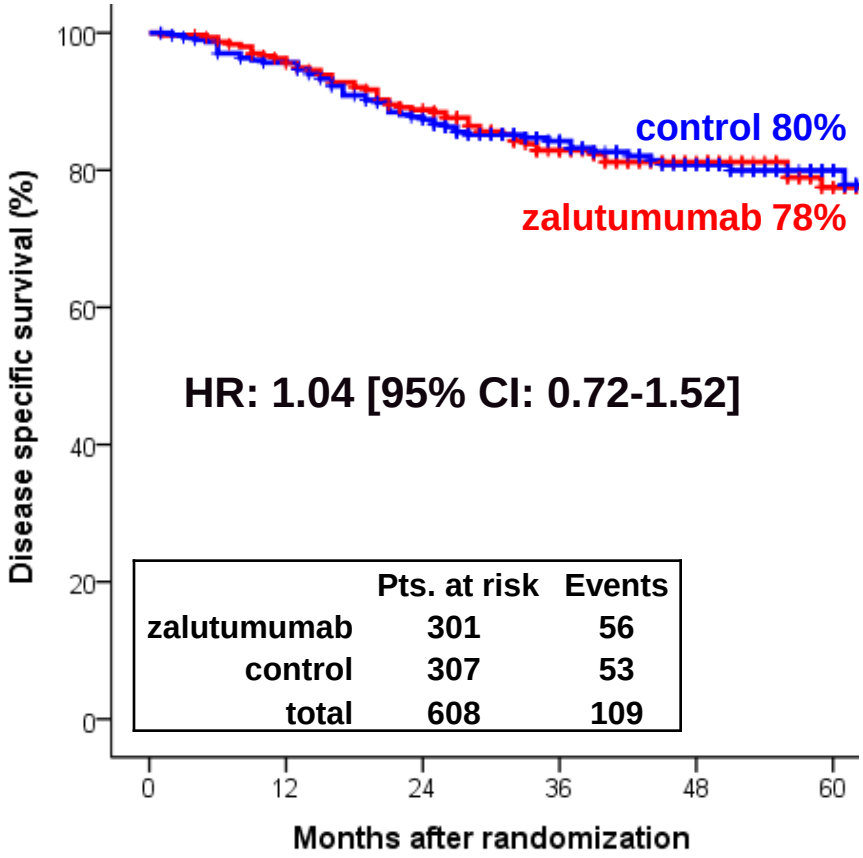


Eriksen, ICHNO 2015

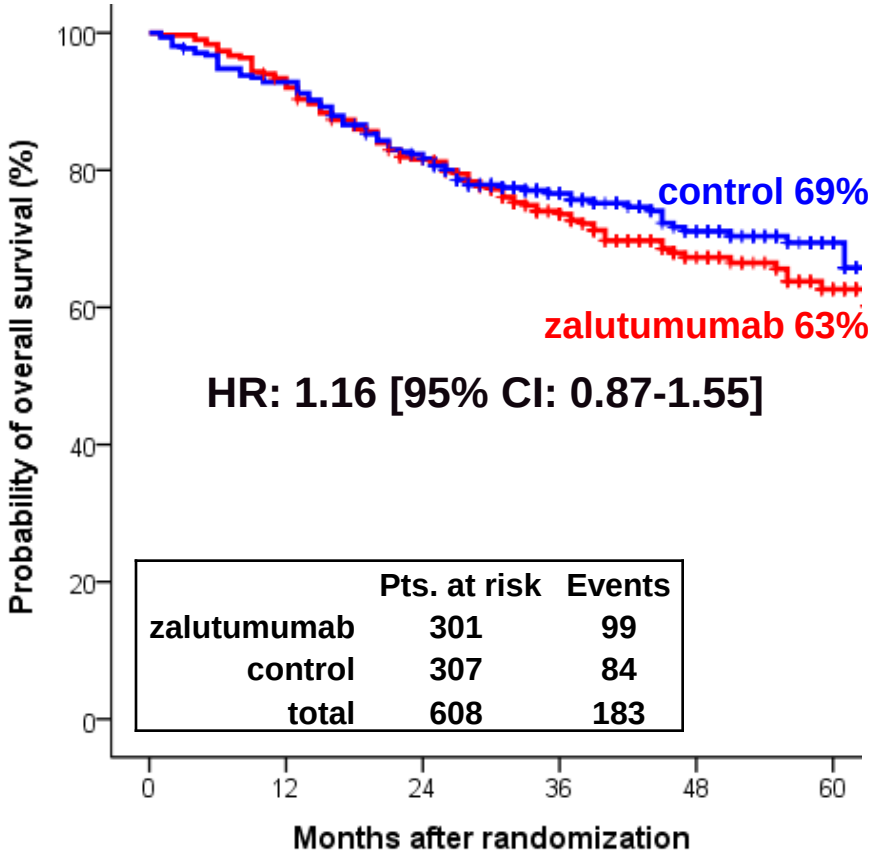
ESTRO School

DAHANCA19: Secondary endpoints

Disease specific



Overall survival



Eriksen, ICHNO 2015

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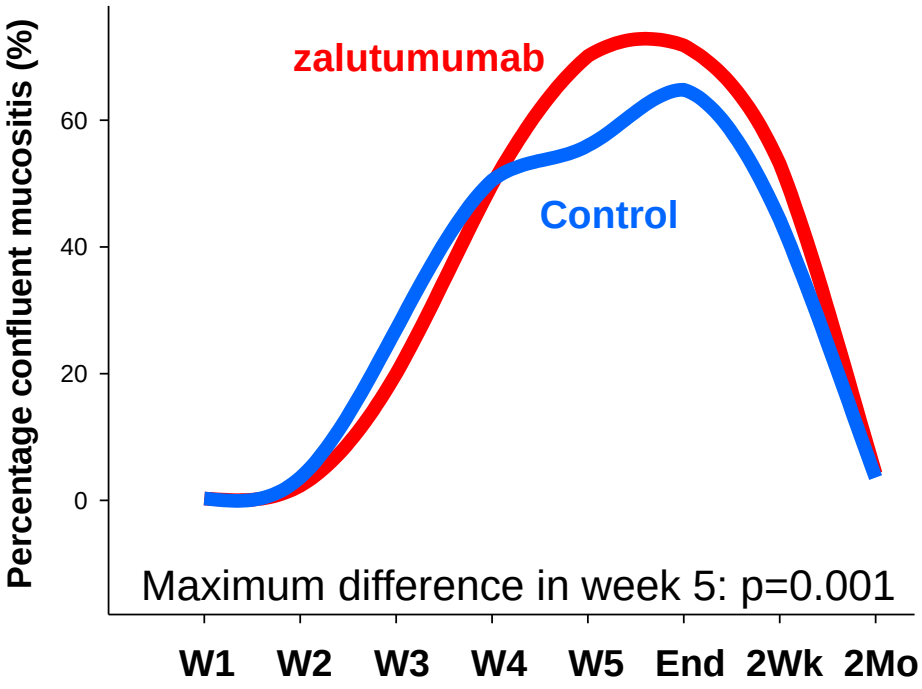
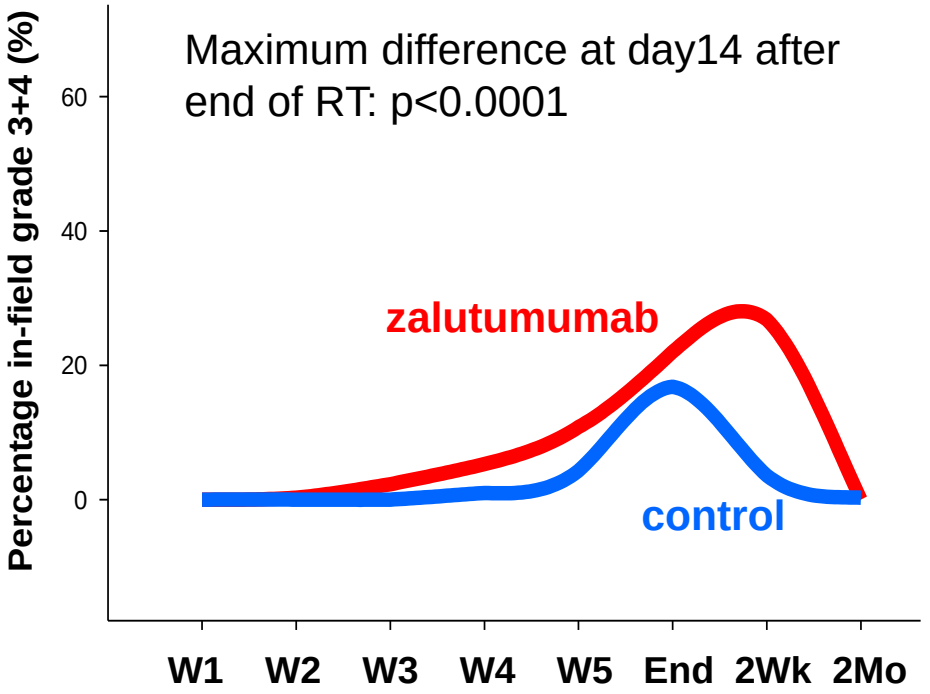
DAHANCA19: Acute morbidity

Confluent mucositis



Grade 3-4 in-field reaction



Need for tube-feeding at end of treatment:
No difference (50% vs. 50%)

Eriksen, ICHNO 2015

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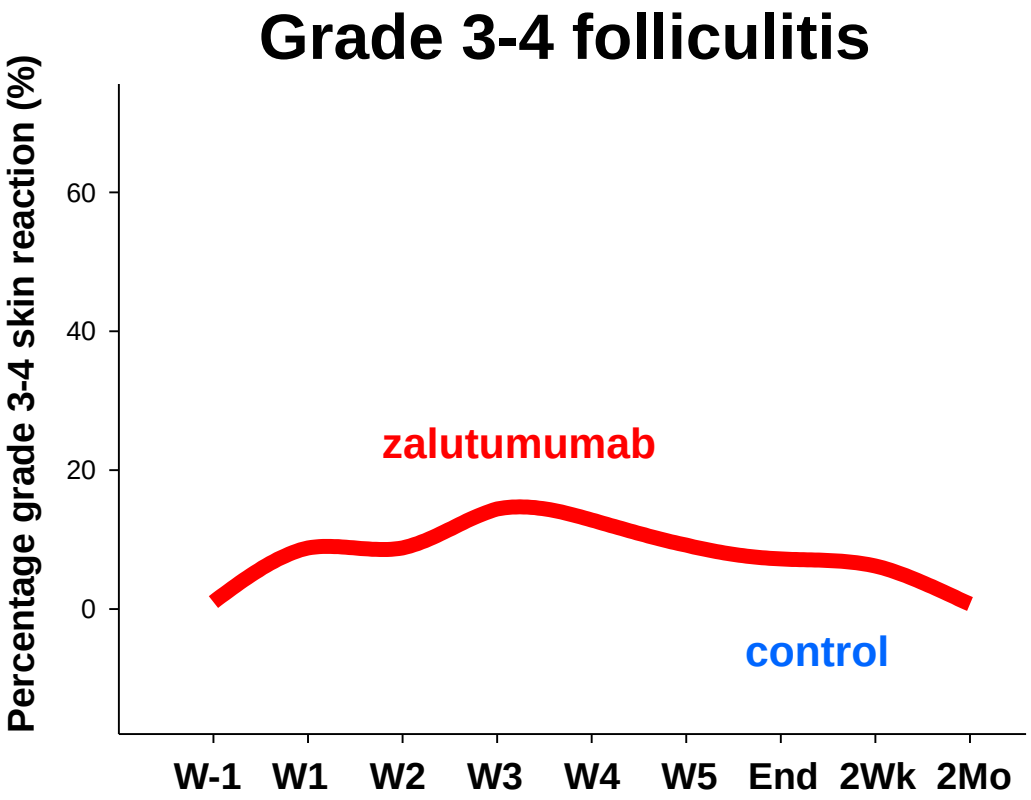
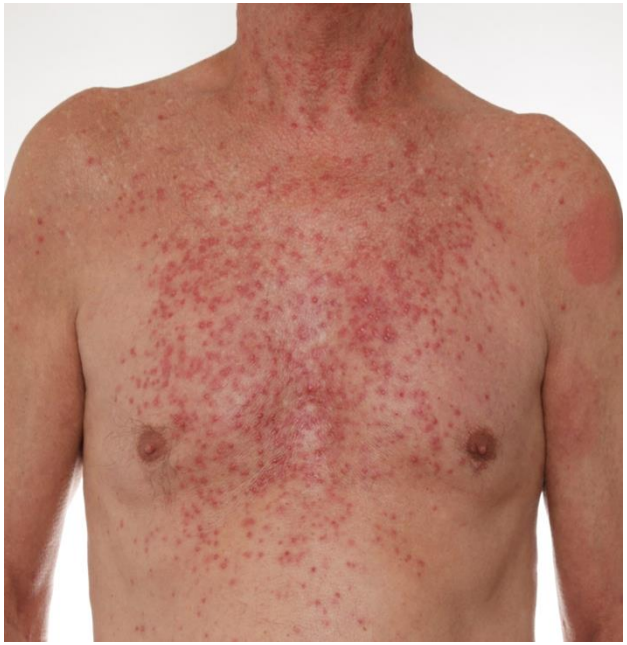
DAHANCA19: Acute morbidity





94% in the zalutumumab-arm developed a skin rash

29% experienced grade 3-4 rash

11% ceased zalutumumab due to rash

Eriksen, ICHNO 2015

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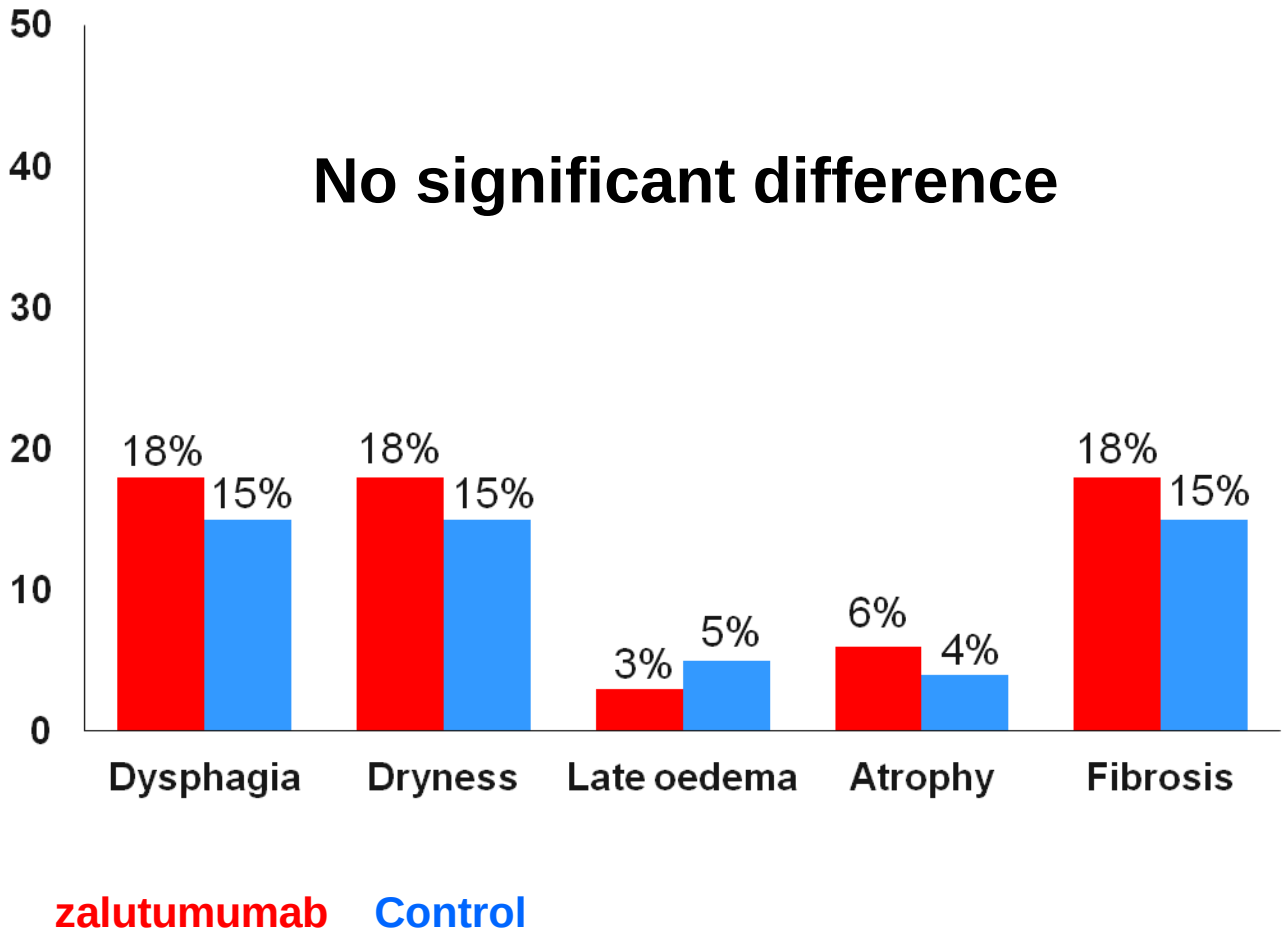
DAHANCA19: Late morbidity



Eriksen, ICHNO 2015

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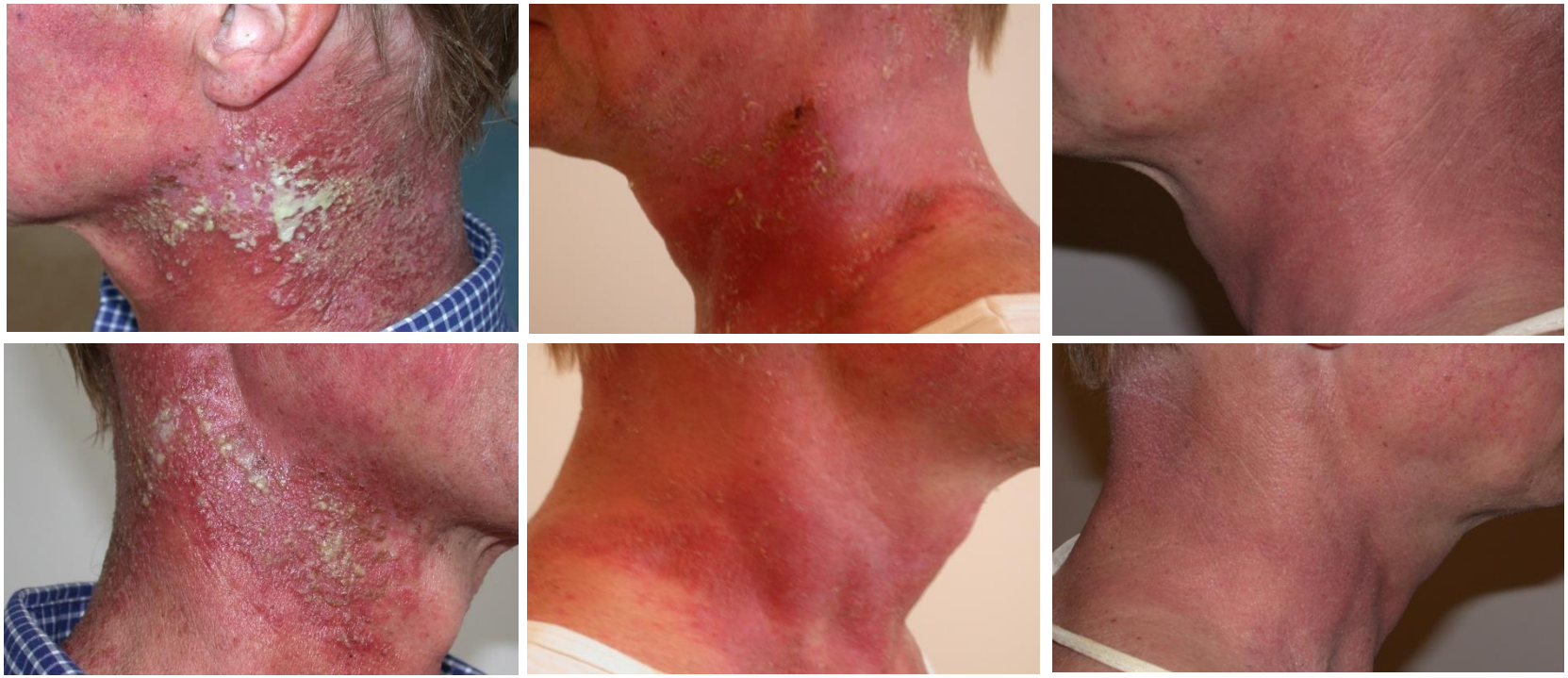
Bio-radiation toxicity



Eriksen 2009

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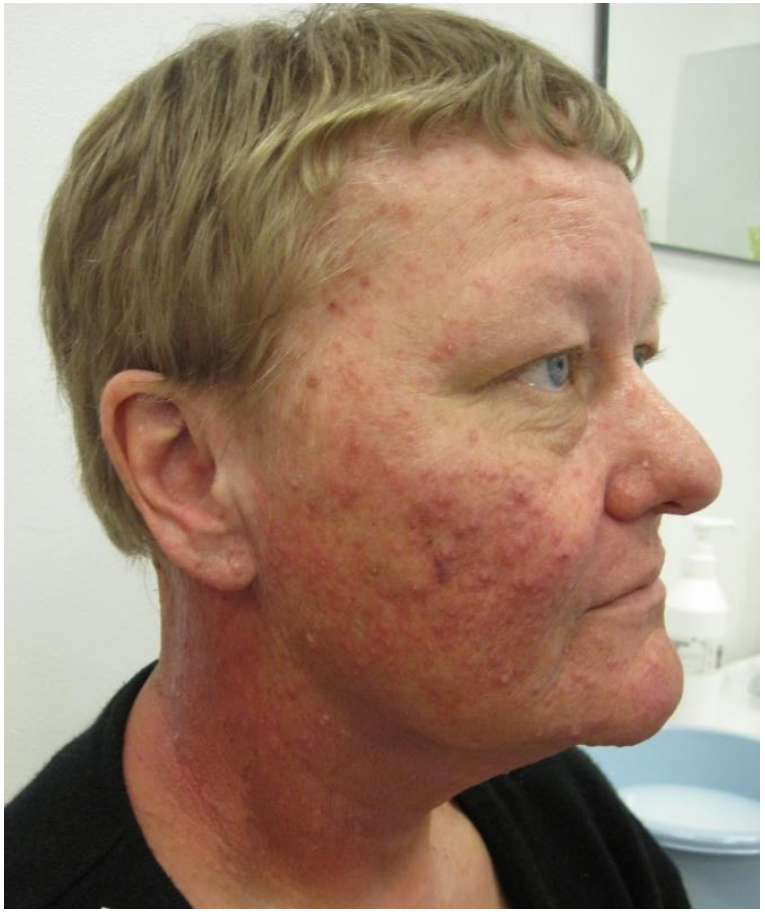
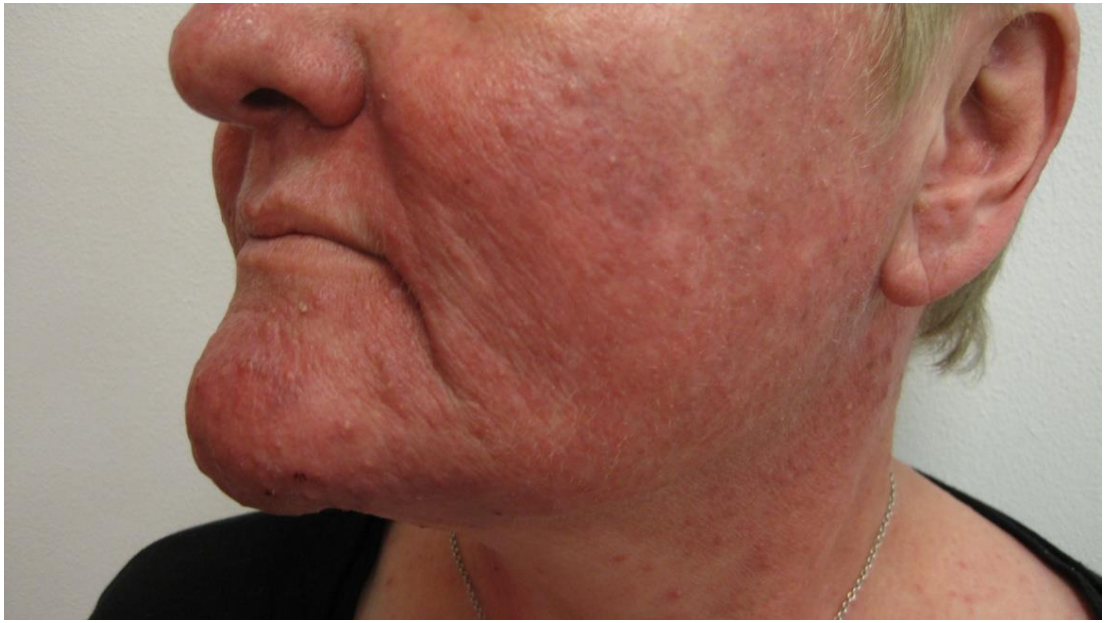
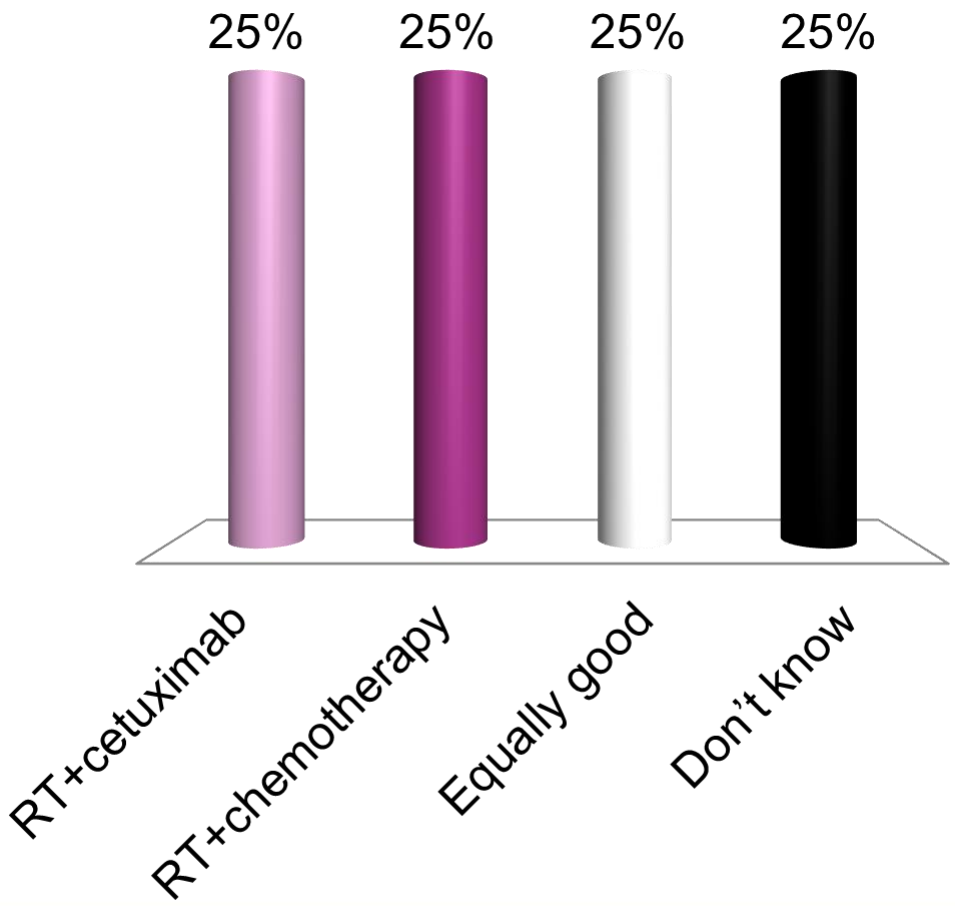
Long-time effects?





What is best? B-RT or C-RT ?

A. RT+cetuximab
B. RT+chemotherapy
C. Equally good
D. Don’t know



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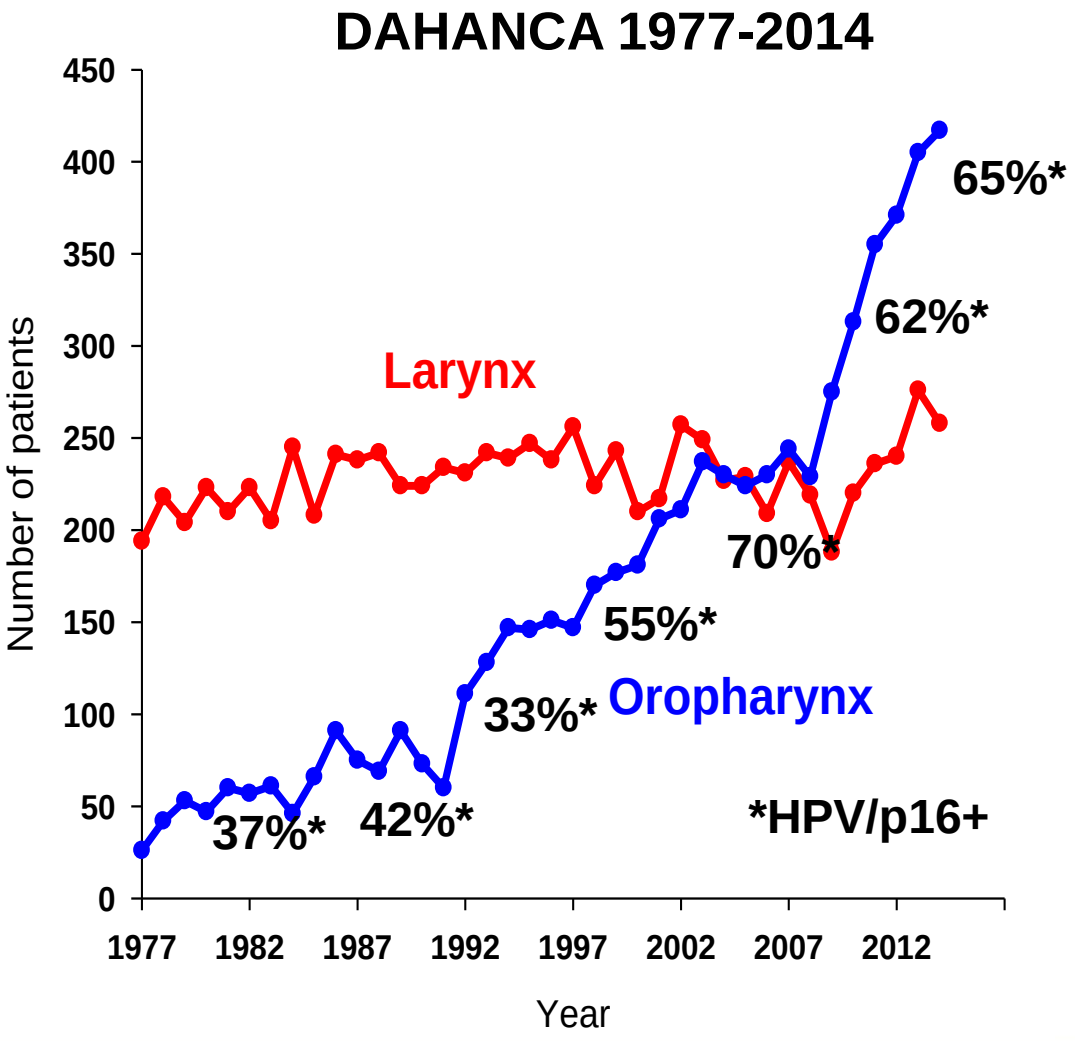
HNSCC is a disease in transition…….

HPV/p16 and HNSCC in the oropharynx

- Oropharynx cancer
- Increasing incidence

- Non-keratinizing SCC
- p16 expression, p53wt

- Younger age/more fit
- Less smoking
- Less alcohol
- N+ (advanced disease)
- Improved prognosis



Updated from Lassen 2010

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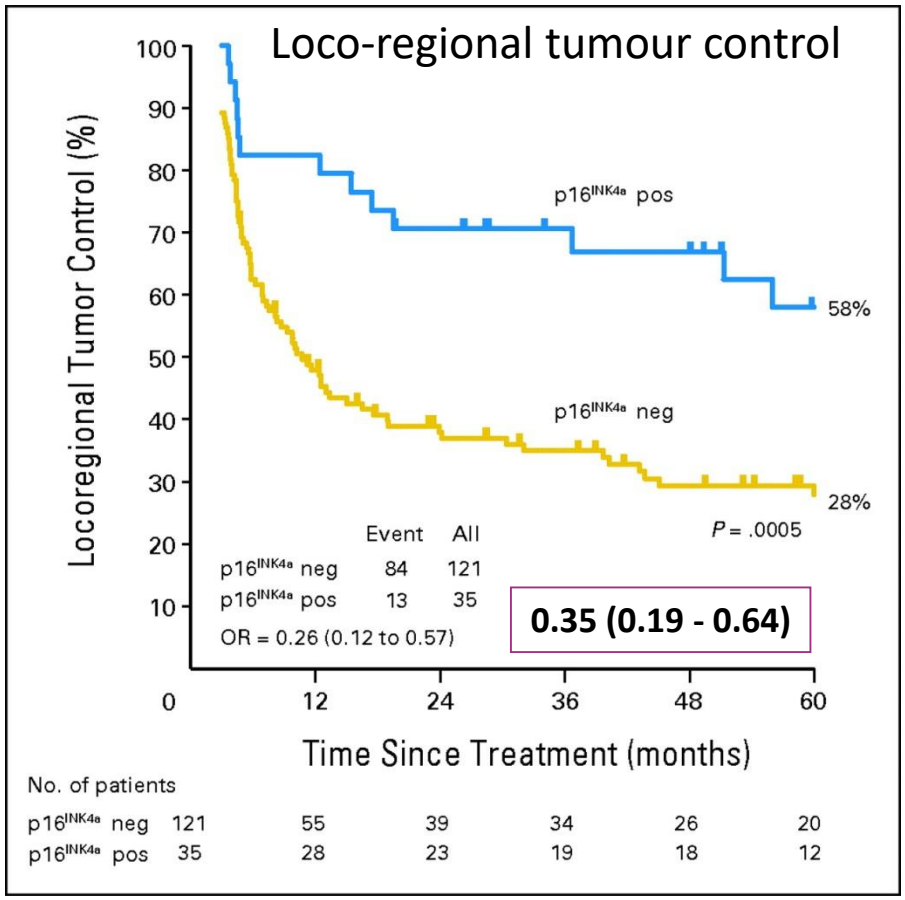
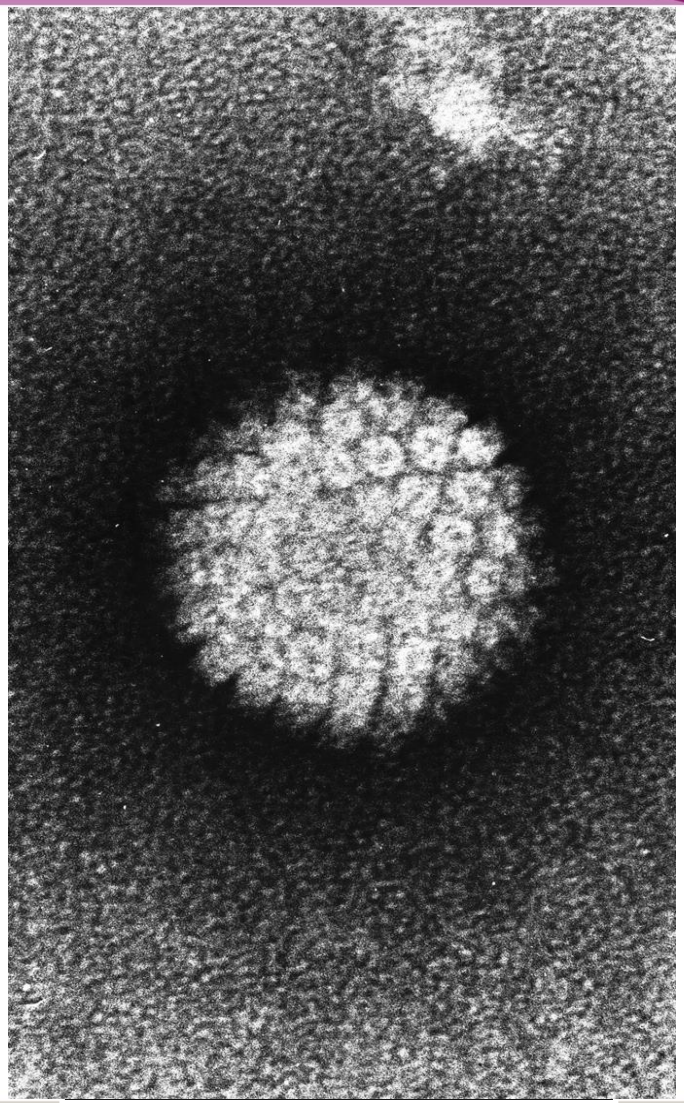
Influence of p16/HPV on RT outcome in HNSCC

DAHANCA 5 (N=156)





Lassen 2009

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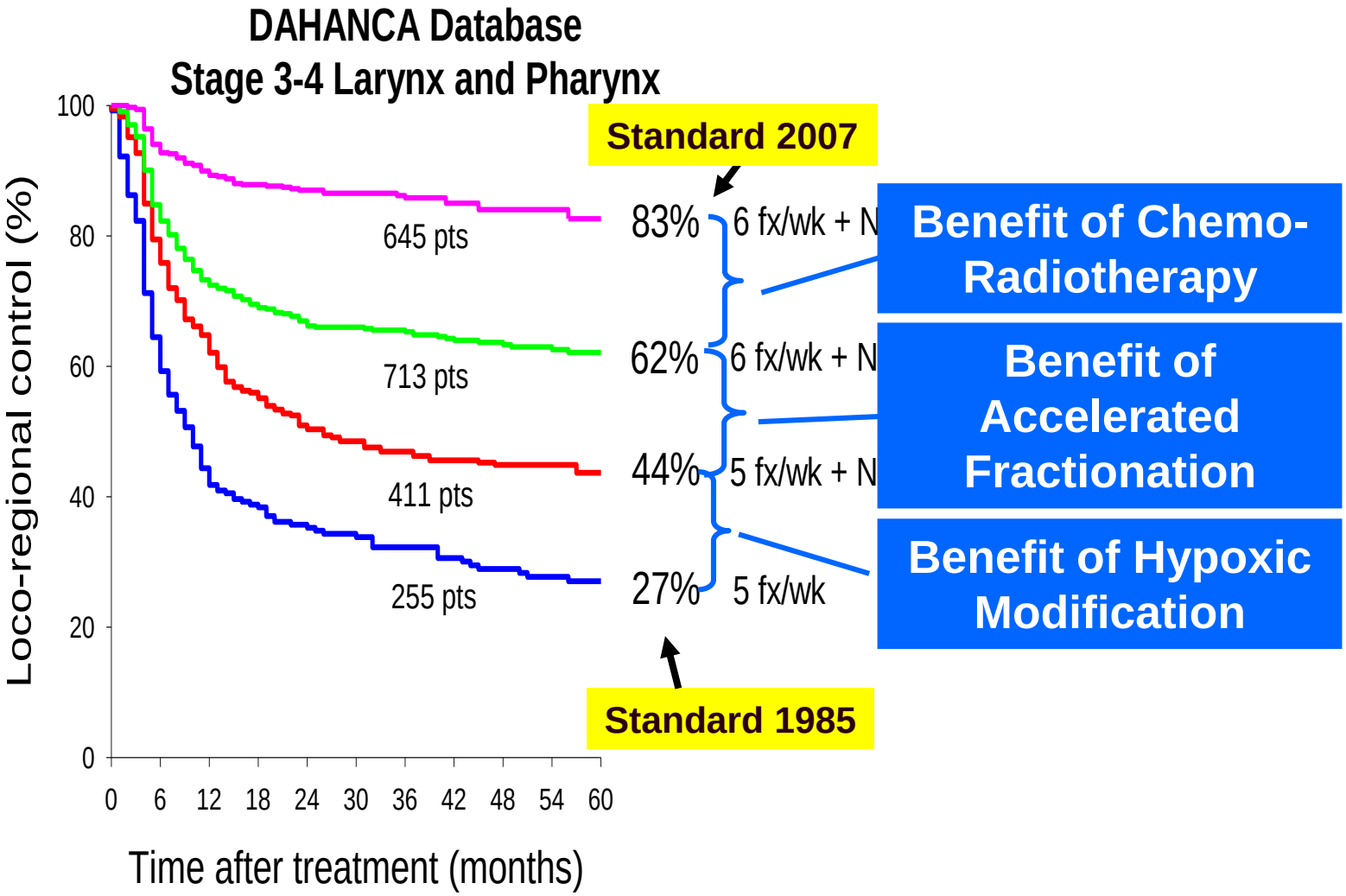
DAHANCA strategy: progression through clinical trials



Adapted from Overgard and Lassen 2015

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Clinical impact of HPV in H&N radiotherapy

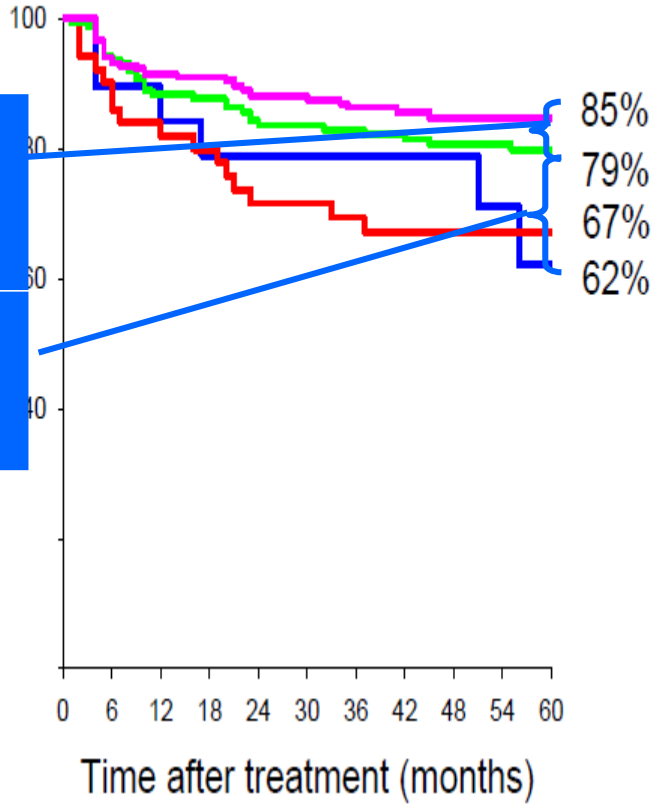
DAHANCA database stage III-IV oropharynx, hypopharynx, larynx
N=1604

Current standard of care:
Chemo-radiotherapy (accelerated fx)

Benefit of Chemo-Radiotherapy

Benefit of Accelerated Fract.

HPV/p16 positive oropharynx
N=480

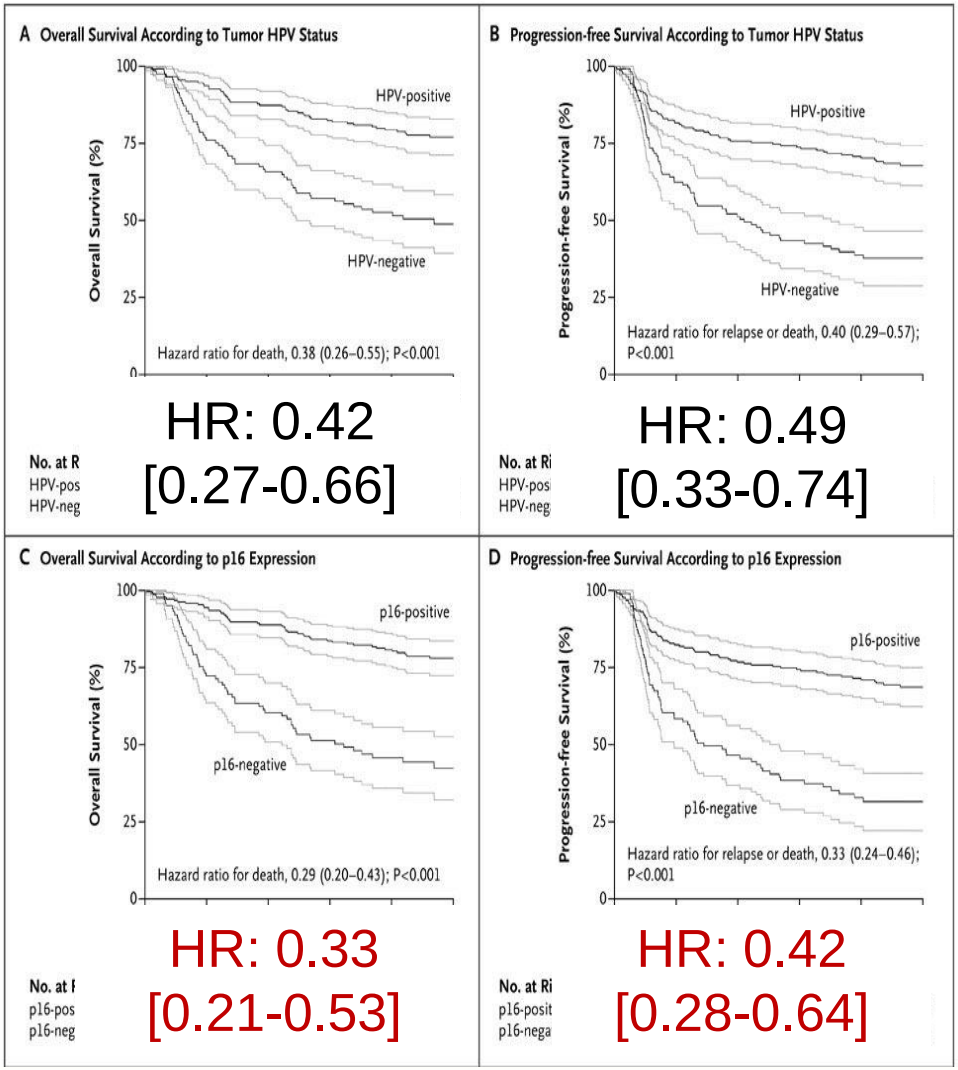


Adapted from Overgard and Lassen 2015

HPV and chemoradiation: RTOG0129
Subgroup analysis of oropharynx cancer (N=261)

HPV DNA
ISH

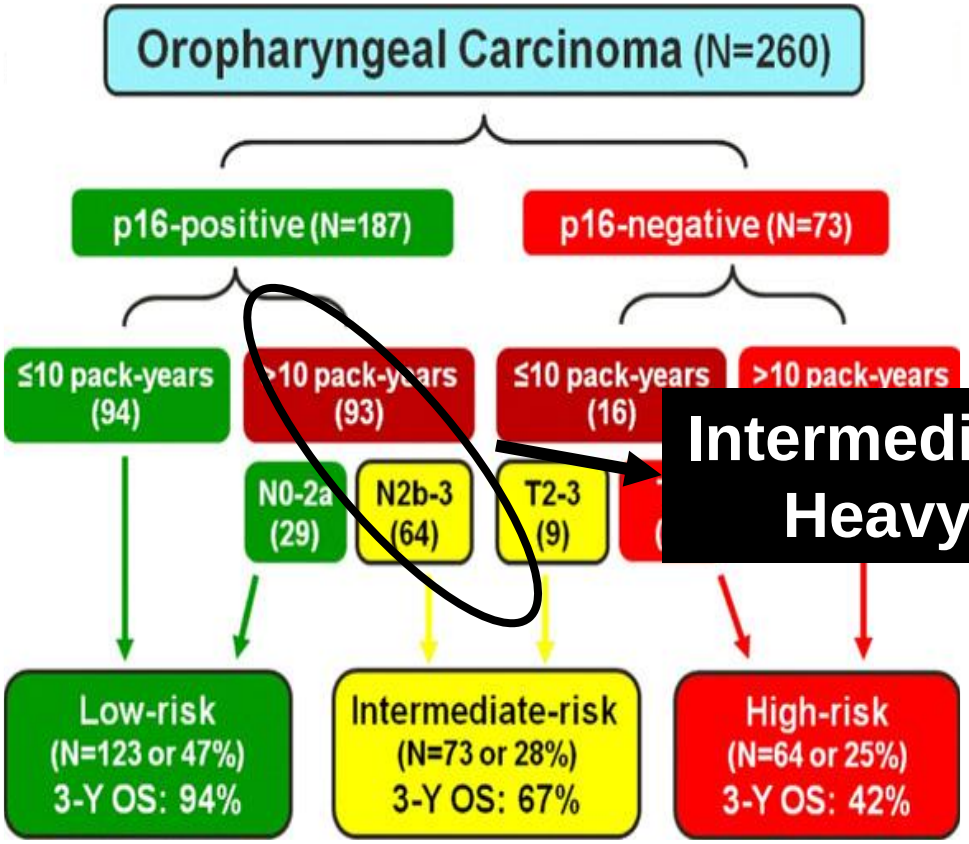
p16 IHC
>70%



Ang et al NEJM 2010

ESTRO School

HPV, smoking and risk groups in RTOG 0129

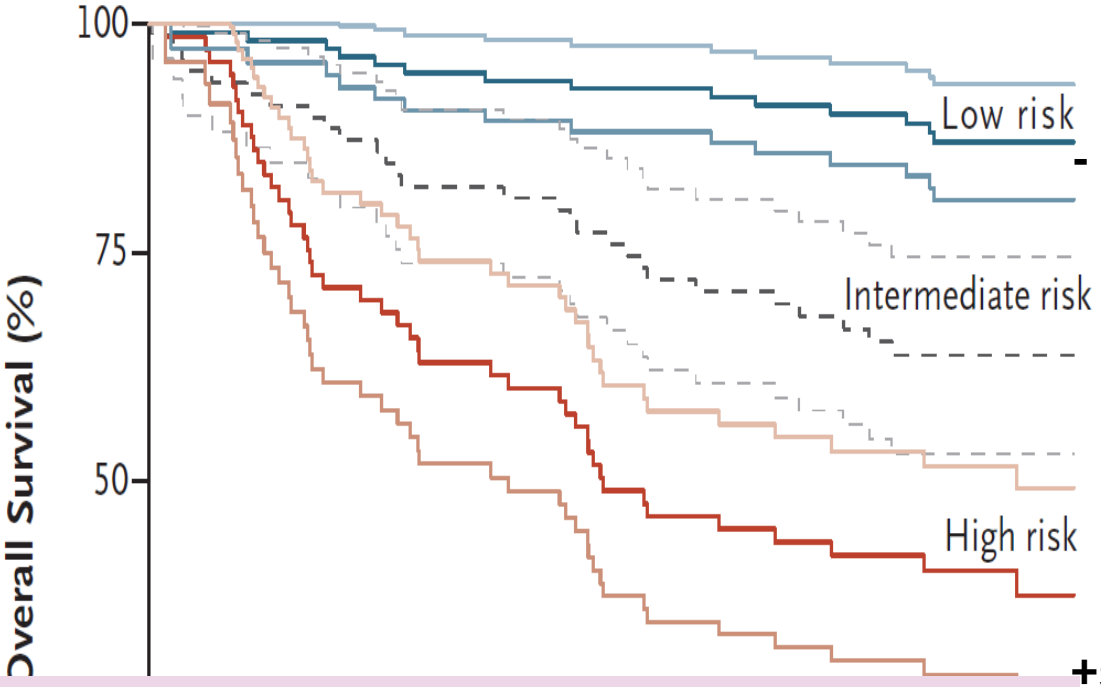


Intermediate-risk subset of p16+ OPC: Heavy smoking (>10pack years)

Ang 2012

ESTRO School

HPV, smoking and risk groups in RTOG 0129



p16pos - smoking

p16neg +smoking

Mixed etiology?

The "**pack year**" definition:

Probably covers a mixture of the influence of *current smoking*, and a potential *dual etiology* in patients with a smoking history

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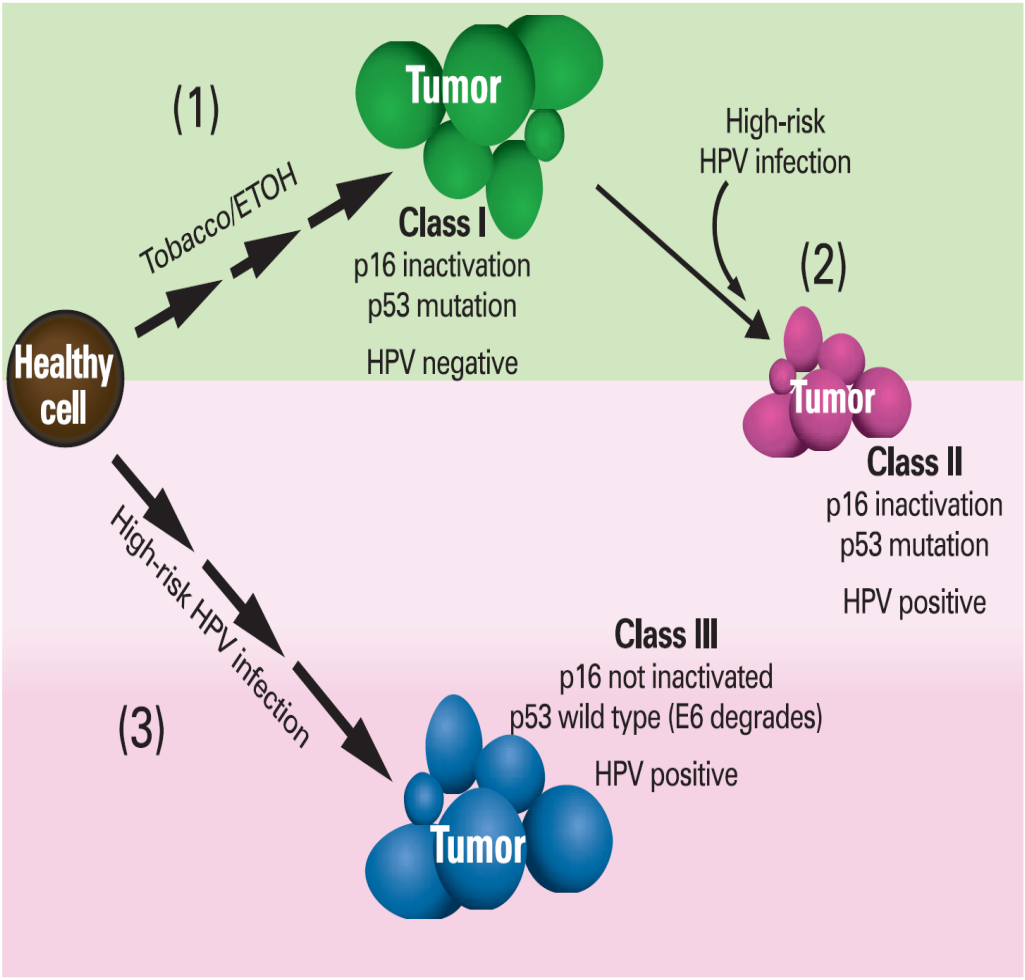
Molecular differences in OPC reflecting mixed etiology



Mixed etiology?

The link between tobacco exposure and tumour biology still remains to be clarified

De-escalation: RTOG 1016: phase III

p16+ oropharyngeal carcinomas

T1-2,N2a-3 or T3-4
any N

Stratify:
T 1-2
T3-4
N0-2a
N2b-c
Smoking
Zubrod 1-2

RANDOMIZE

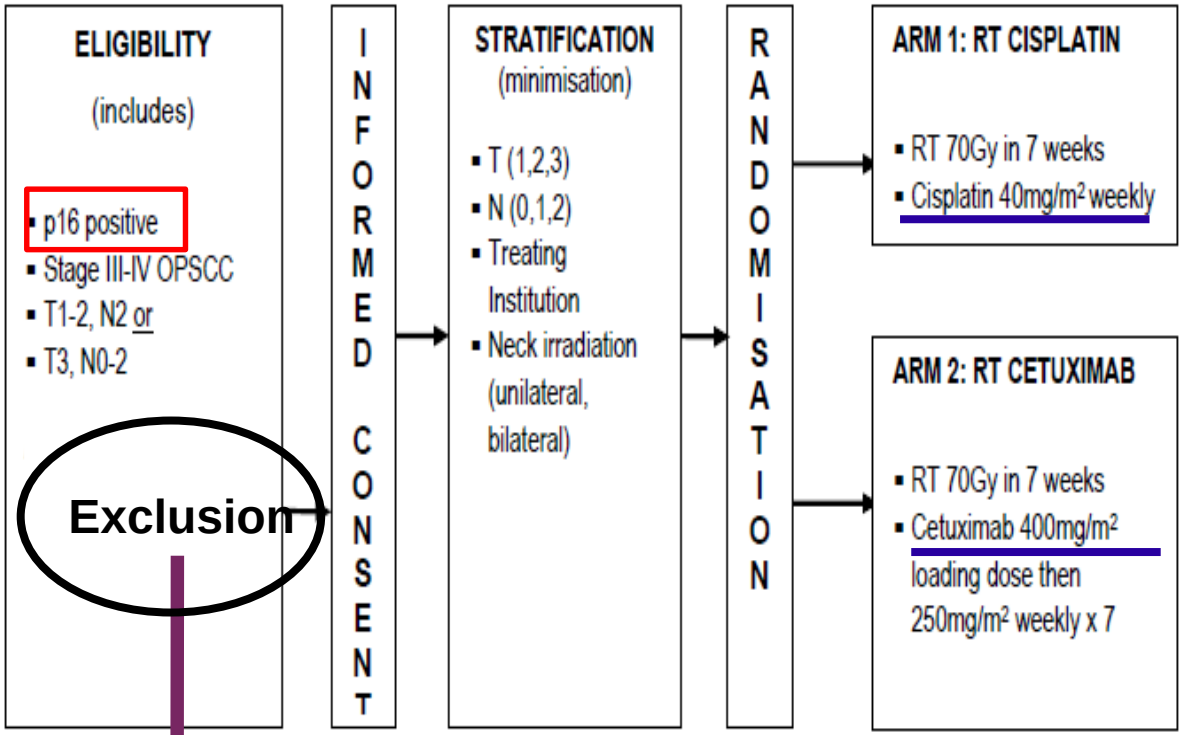
RT 70Gy/35f/6 wks + cisplatin 100mg/m² x 2

987 pts recruited before closure in July 2014

RT 70Gy/35f/6 wks + cetuximab for 8 weeks

Reducing toxicity by replacement of cisplatin with cetuximab ?

TROG 12.01 phase III CRT vs RT+Cetuximab



T4, N3 or distant metastases

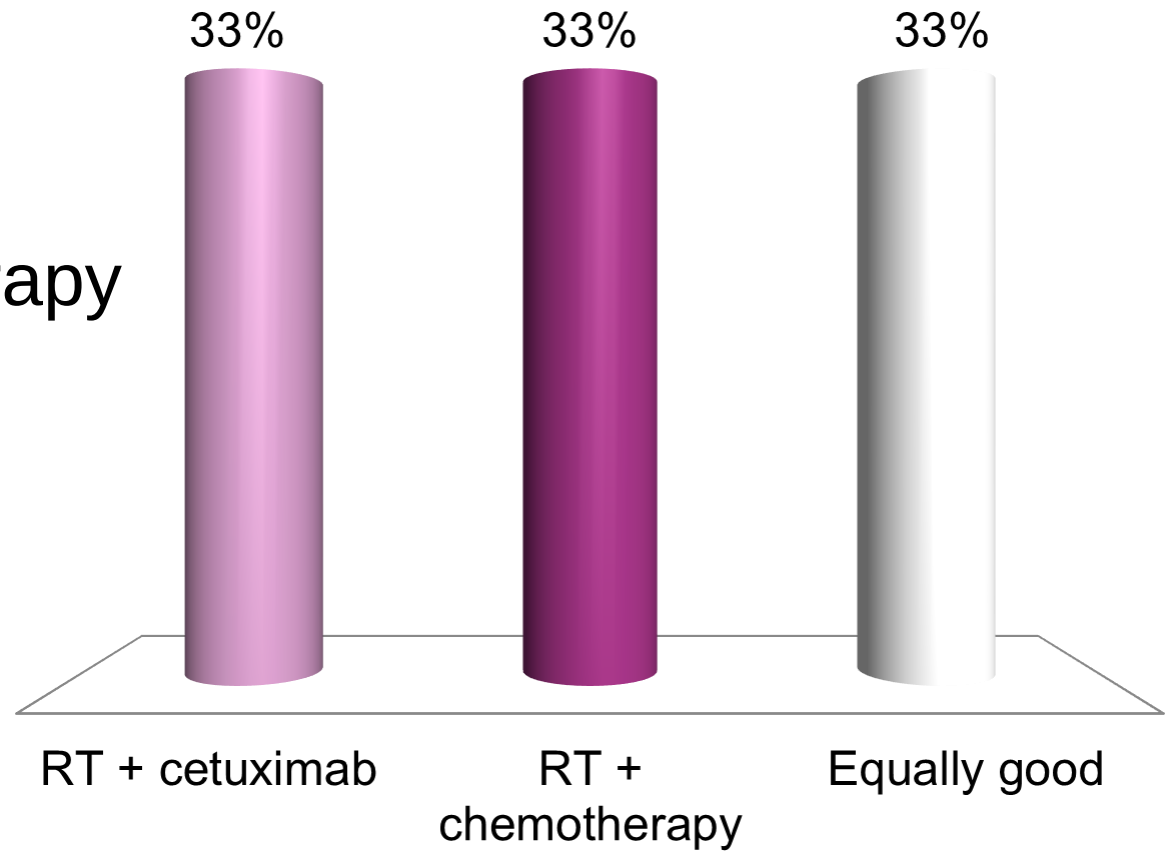
Smoking history >10 pack years with N2b or c nodal status

Intermediate-risk subset of p16+ OPC:
Heavy smoking (>10packyears)
Bulky nodal disease (>N2b)

ESTRO School

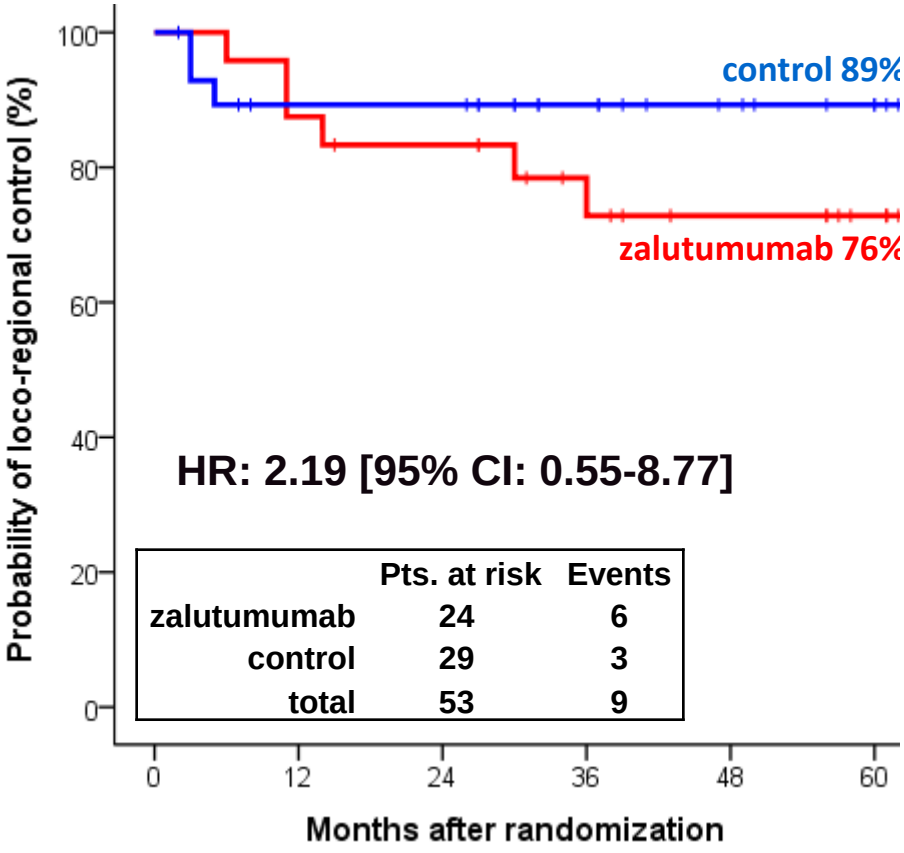
What is best? B-RT or C-RT for HPV/p16 patients?

A. RT + cetuximab
B. RT + chemotherapy
C. Equally good

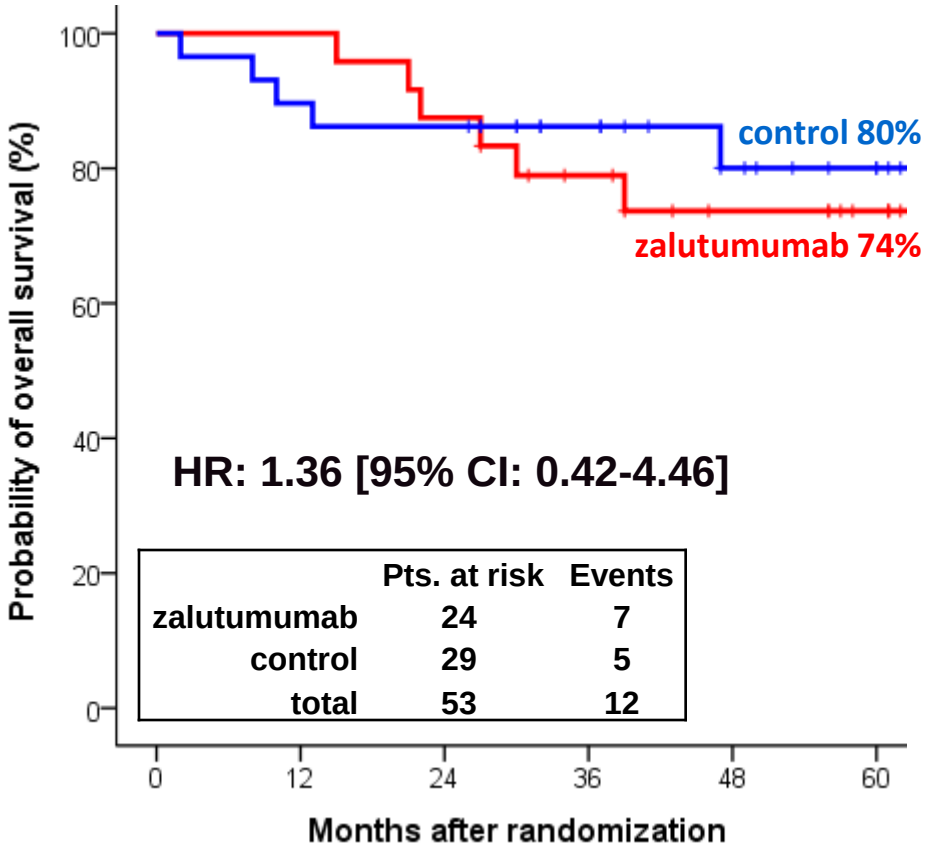


DAHANCA 19: ART only, oropharynx, HPV/p16+

Loco-regional control



Overall survival



Eriksen 2015

ESTRO School

Is EGFR-I and radiotherapy less toxic?

	RT-Z All Grades	RT-Z Grade 3-4	RT-Z Grade 4	C-RT All Grades	C-RT Grade 3-4	C-RT Grade 4
In-field reaction	88%	32%	8%	91%	3%	1%
Mucositis	90%	45%	0%	92%	45%	1%
Dysphagia	86%	22%	9%	79%	14%	7%
Xerostomia	88%	15%	0%	87%	15%	0%
EGFR-I rash	87%	17%	3%	-	-	-
Leukopenia	3%	0%	0%	29%	11%	1%
Hypo-Mg^{2+}	14%	6%	2%	2%	0%	0%

RT-Z: 78 pts; C-RT: 224 pts

Eriksen 2015

ESTRO School

HPV-neg., locally advanced, smoking HNSCC patient

DAHANCA 28a

P16 negativ SCC

Tumor i larynx, pharynx eller c. oris

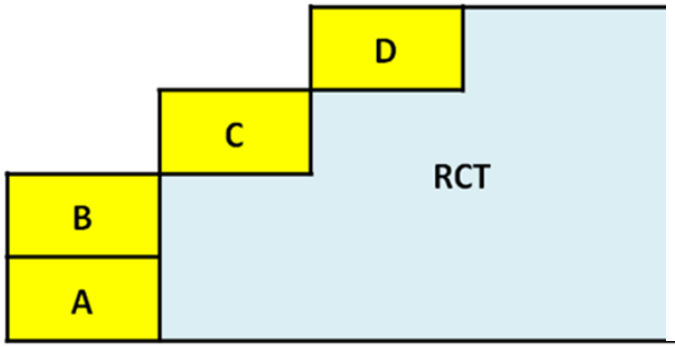
Opfylder inklusion

T1-4, N1-N3,M0

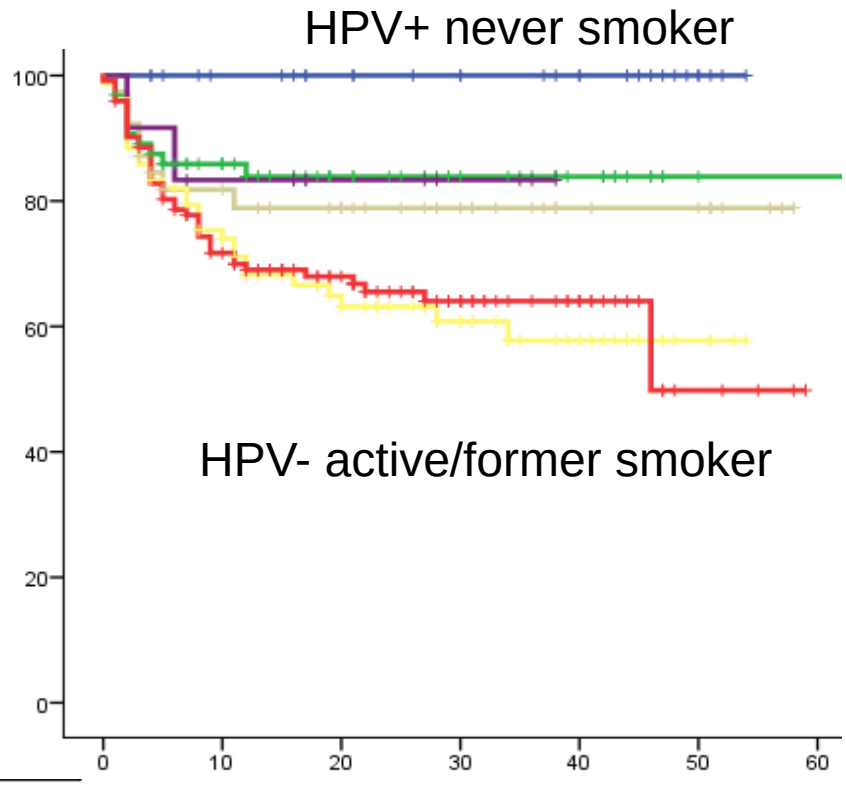
76Gy/56 fx, BID, 10fx/w

Cisplatin 40 mg/m²

Nimoral e. skema



Gruppe A: Patienter med PS 0-1, Charlson score = 0
Gruppe B: Patienter med PS 0-1, Charlson score = 1
Gruppe C: Patienter med PS 0-1, Charlson score ≥ 2
Gruppe D: Patienter med PS 2, uanset Charlson score



Head and Neck patient case

Jesper Grau Eriksen

Dept. Of Oncology
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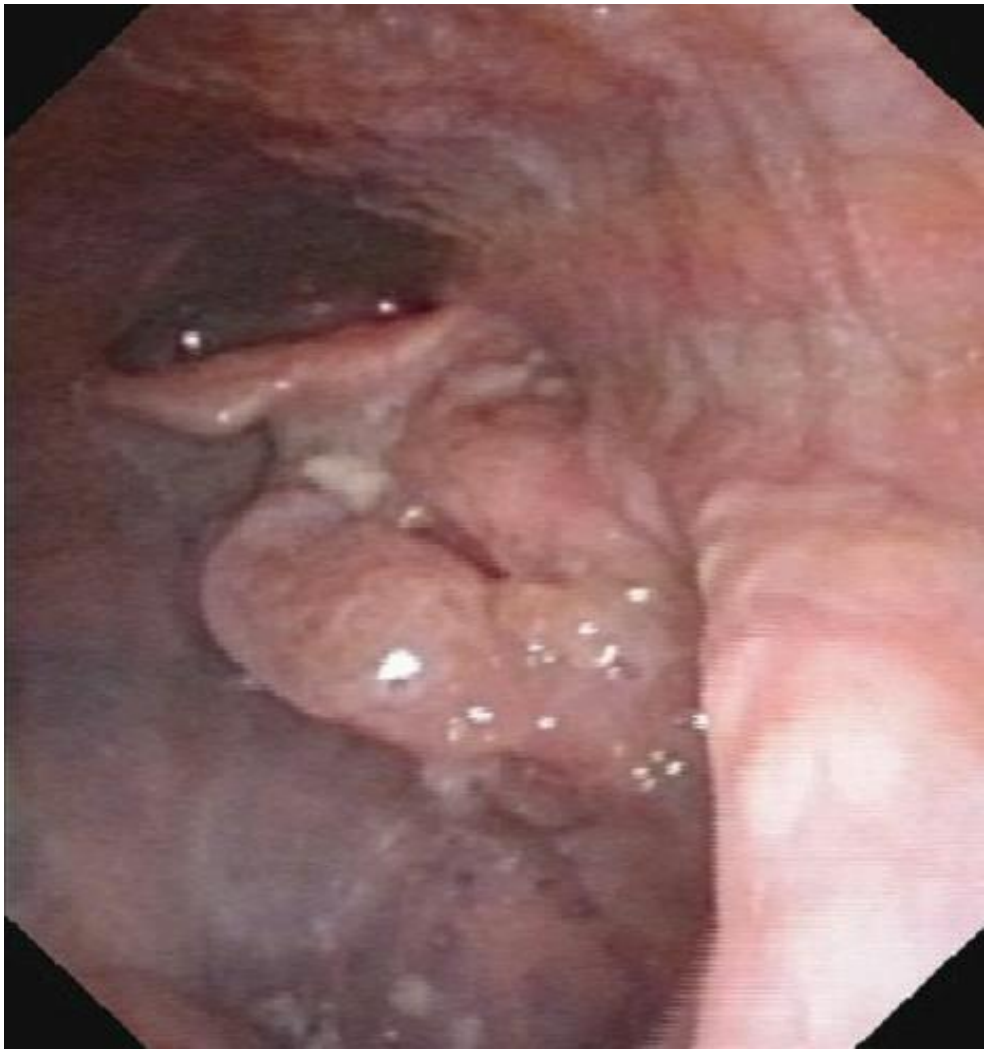
Patient history

- 60-year old man.
- 3 week history of nodal swelling, left side of the neck. No pain or dysphagia. No weight loss.
- No co-morbidity except from back pain.
- Ceased smoking in 1990, 16 pack-years.
- 1-2 glasses of alcohol a day.

Clinical examination

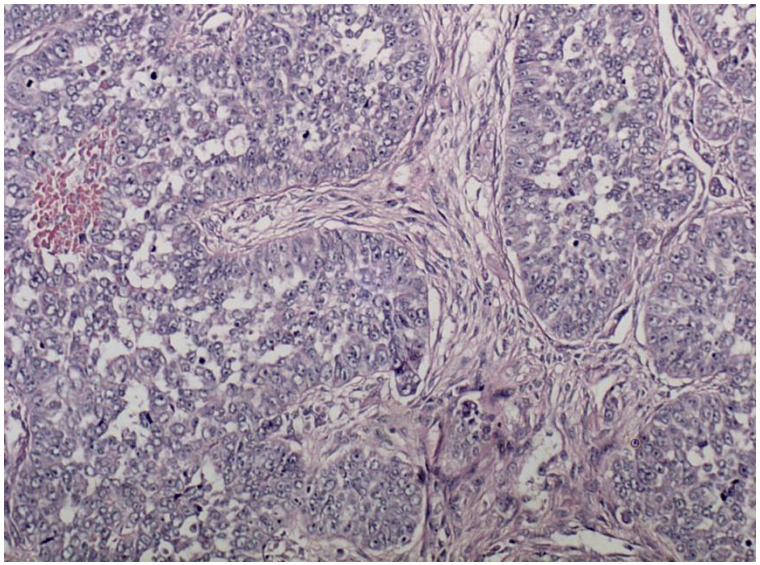
- Good performance (WHO PS 0).
- Base of tongue/vallecula area a 3x2x2 cm large tumour is seen. Proximal border of the tumour seems to be close to the lower pole of the left tonsil.
- Otherwise normal fiber optic examination.
- Palpable node in region II, left side.
- Contra-lateral side normal.

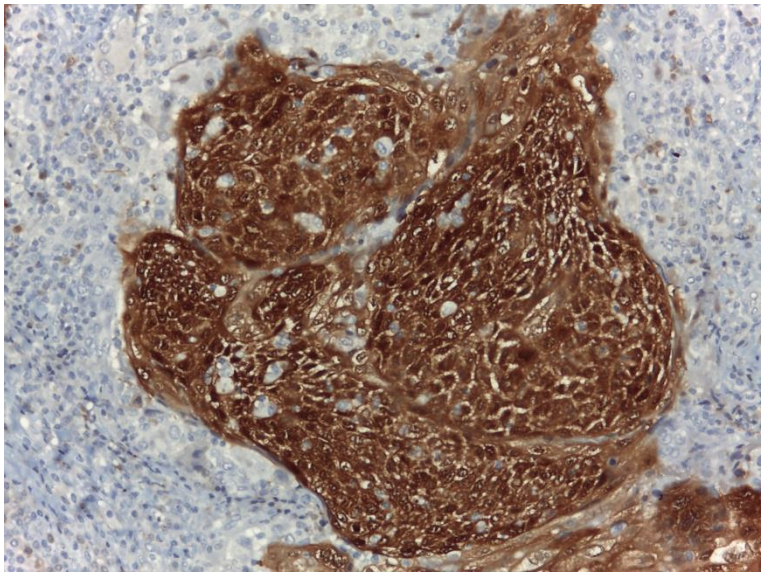
Fiber optic examination



Pathology

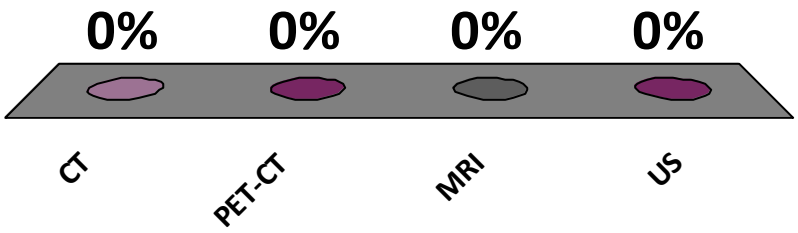
- Moderate differentiated squamous cell carcinoma (G2)
- p16 positive





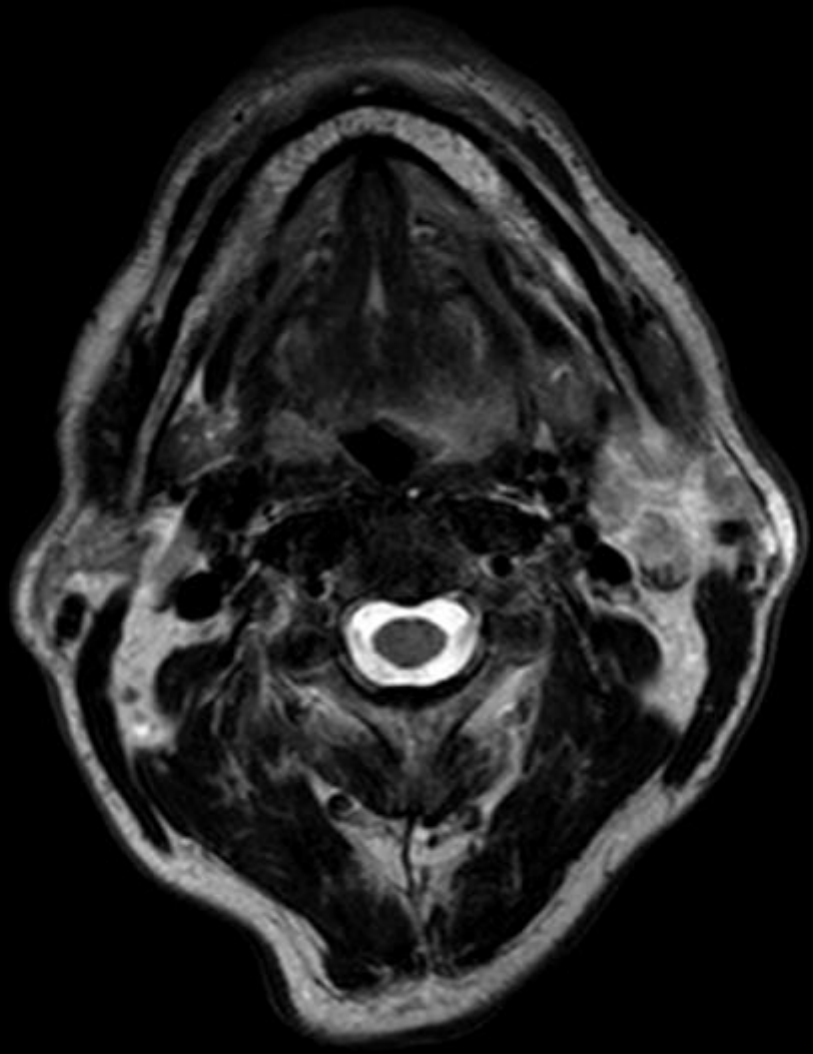
What Image-modality would you primarily choose?

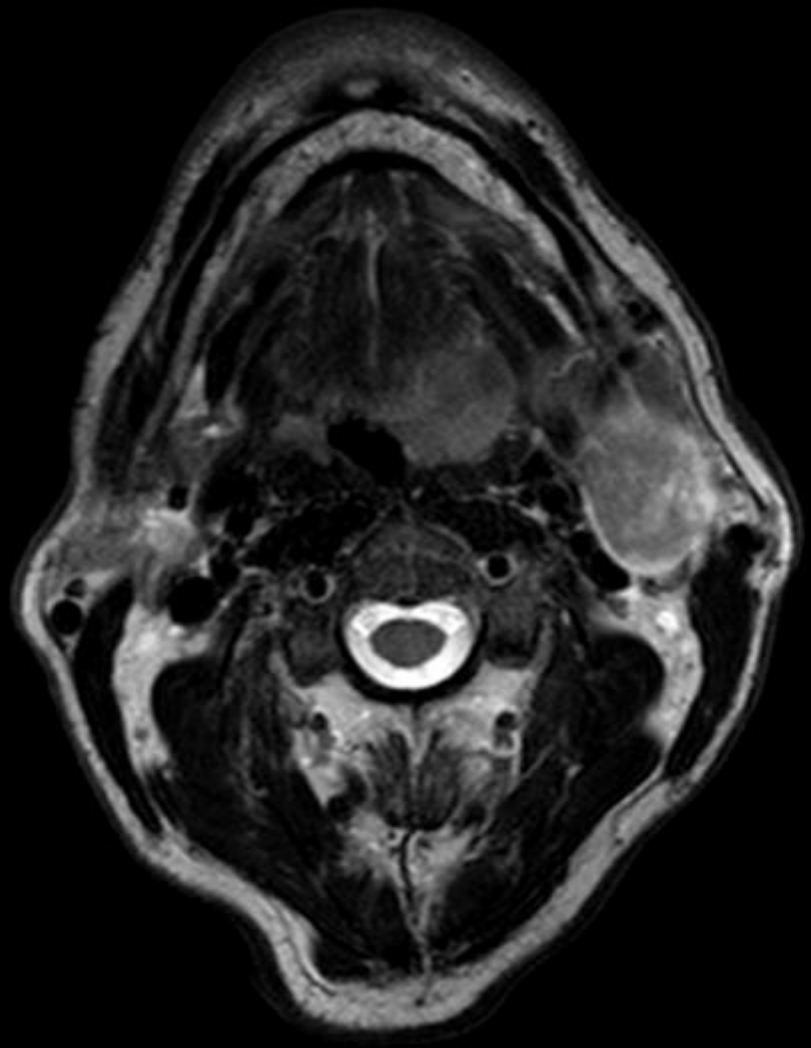
A. CT
B. PET-CT
C. MRI
D. US



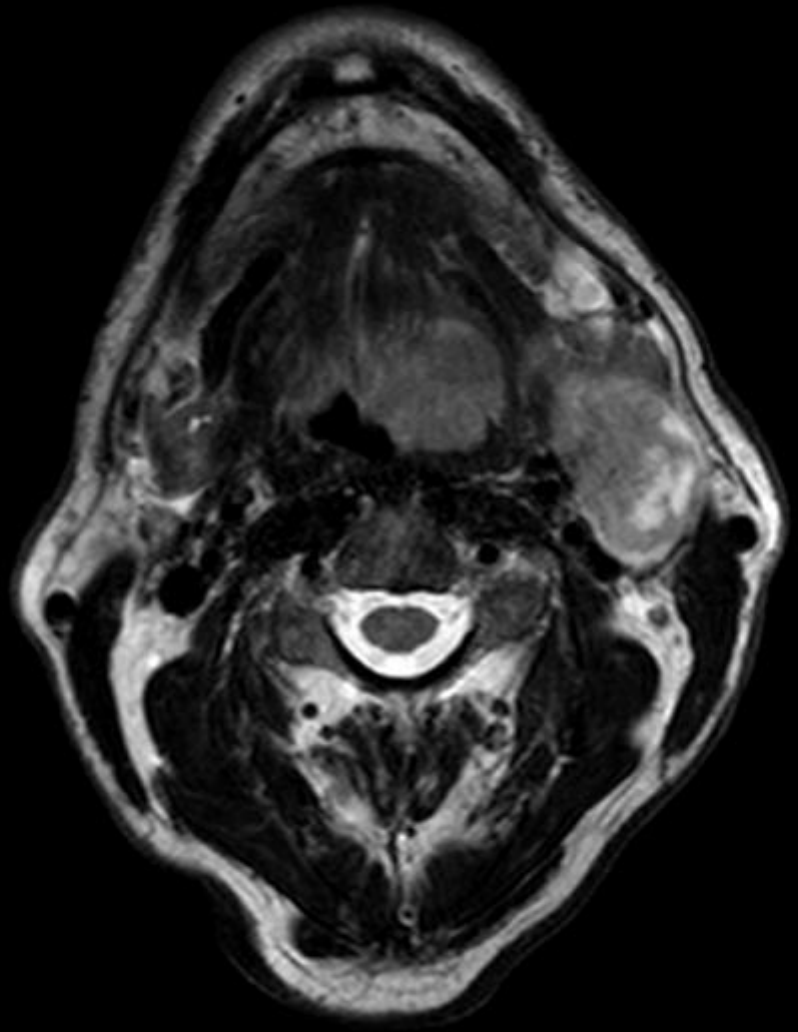
ESTRO School

MR
Axial view

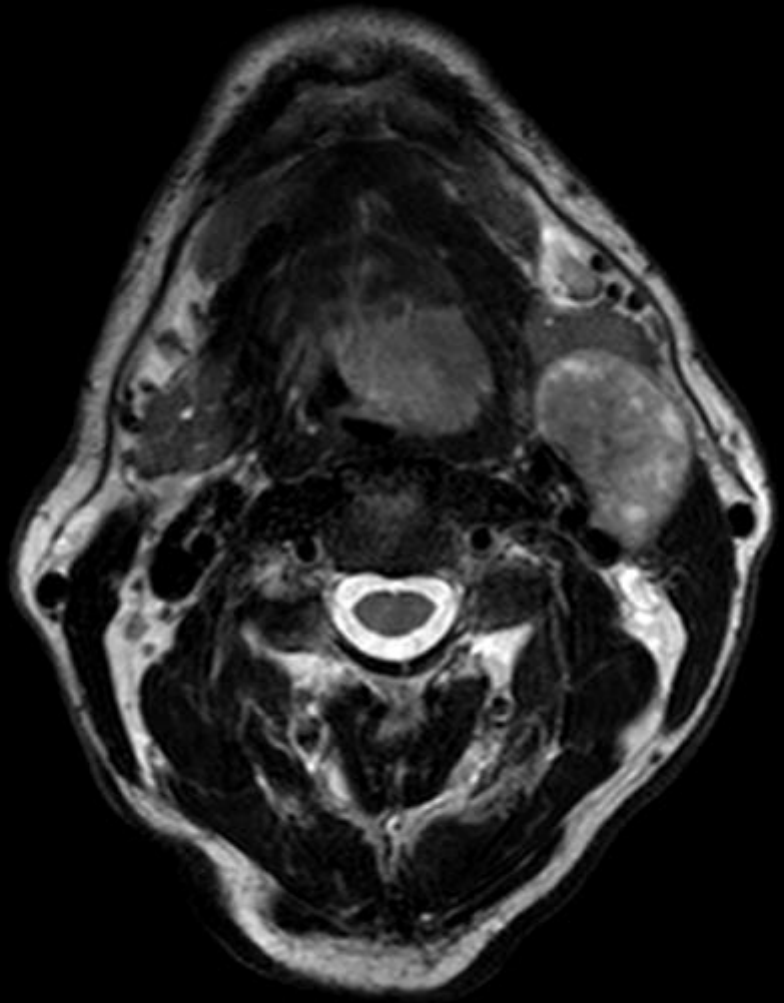




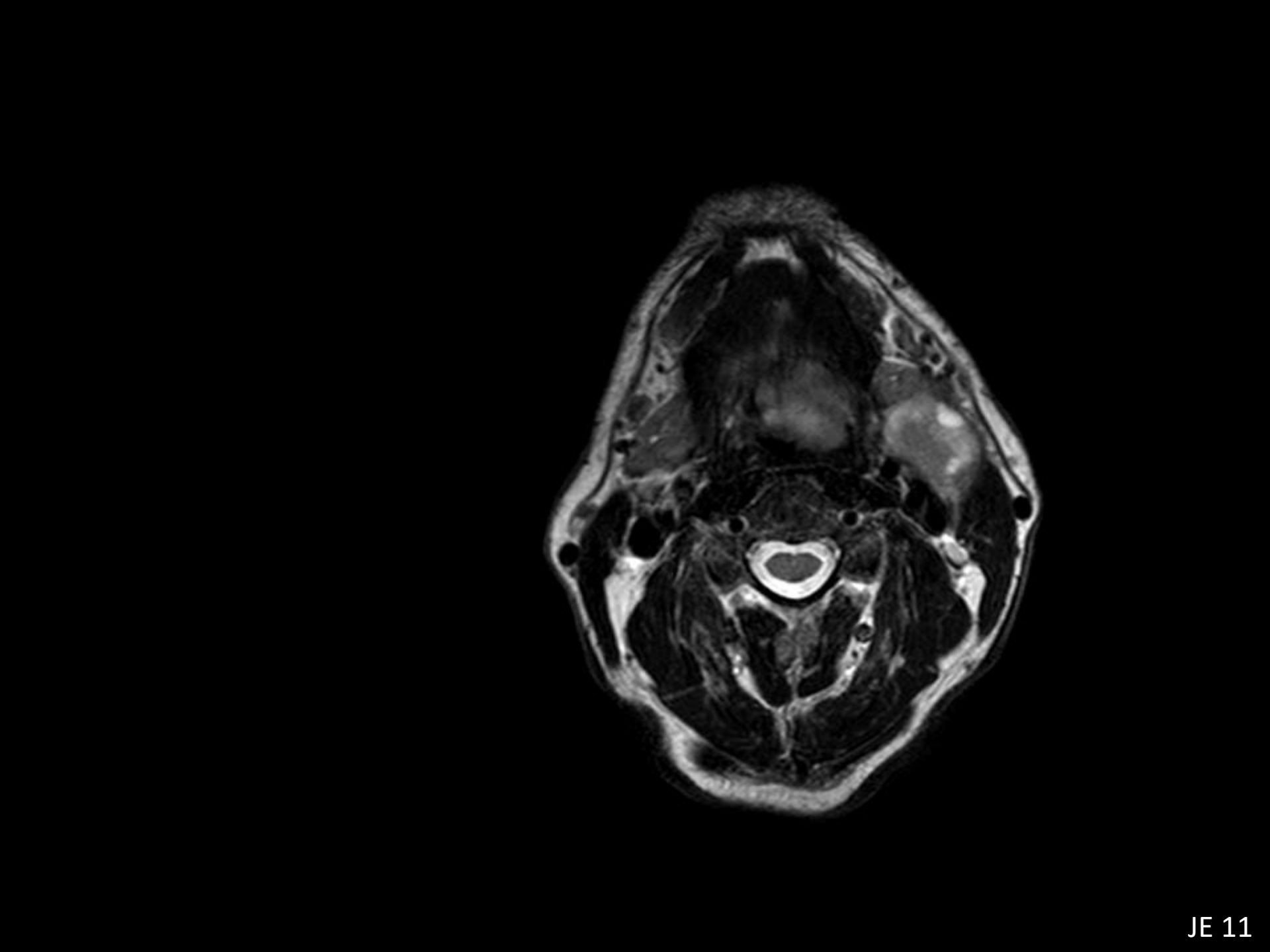
JE 8

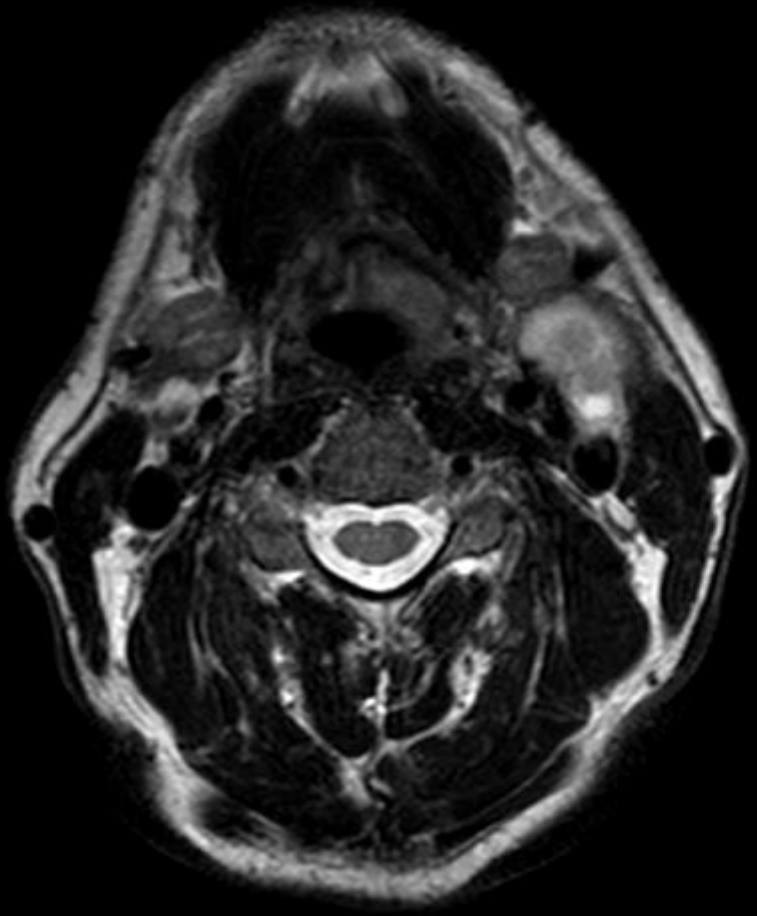


JE 9

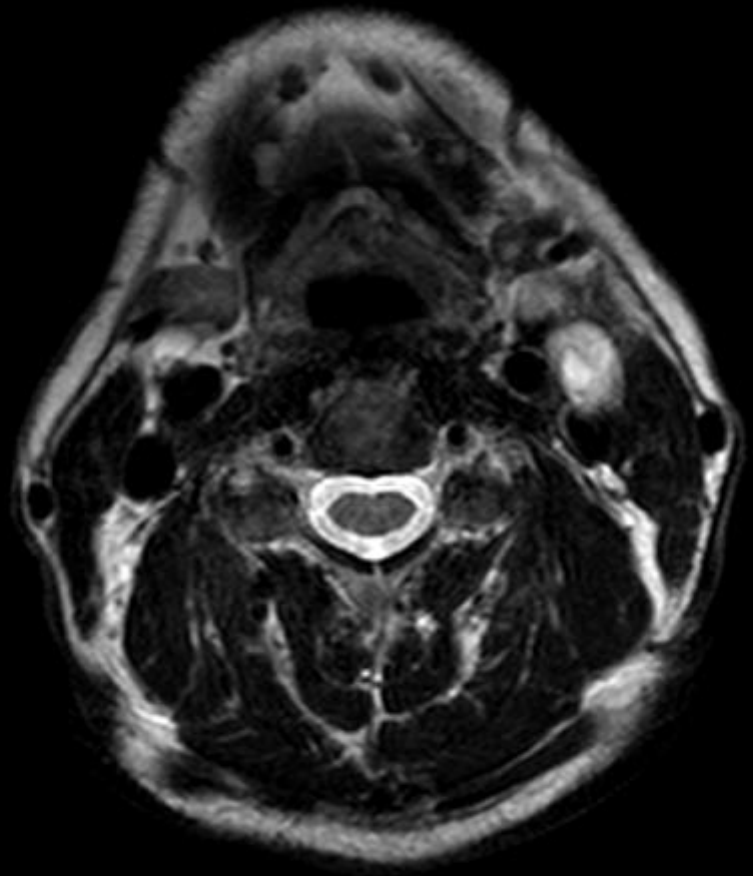


JE 10

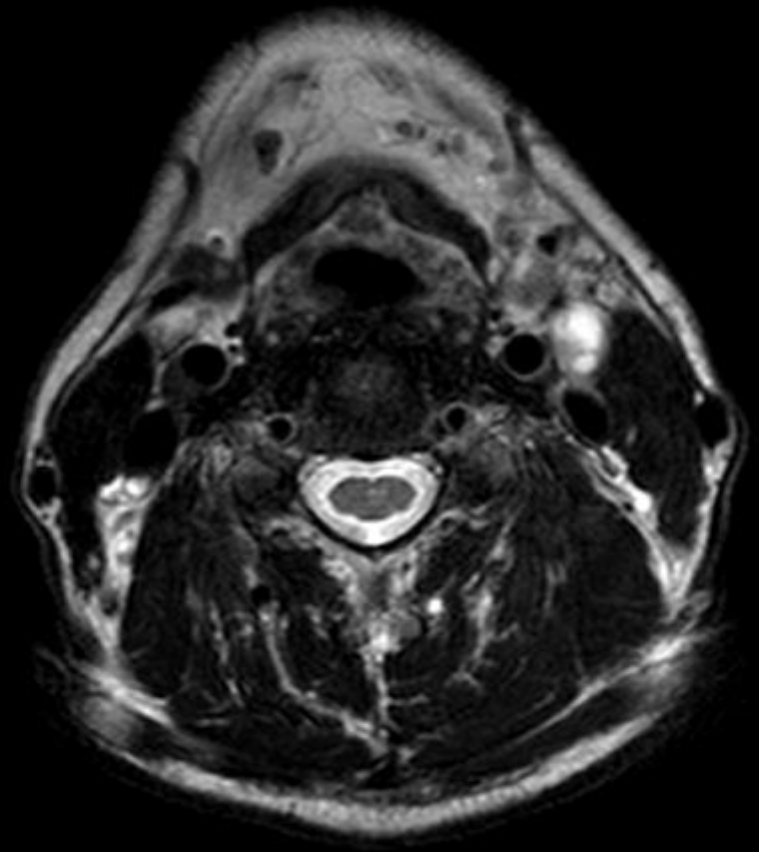

JE 11



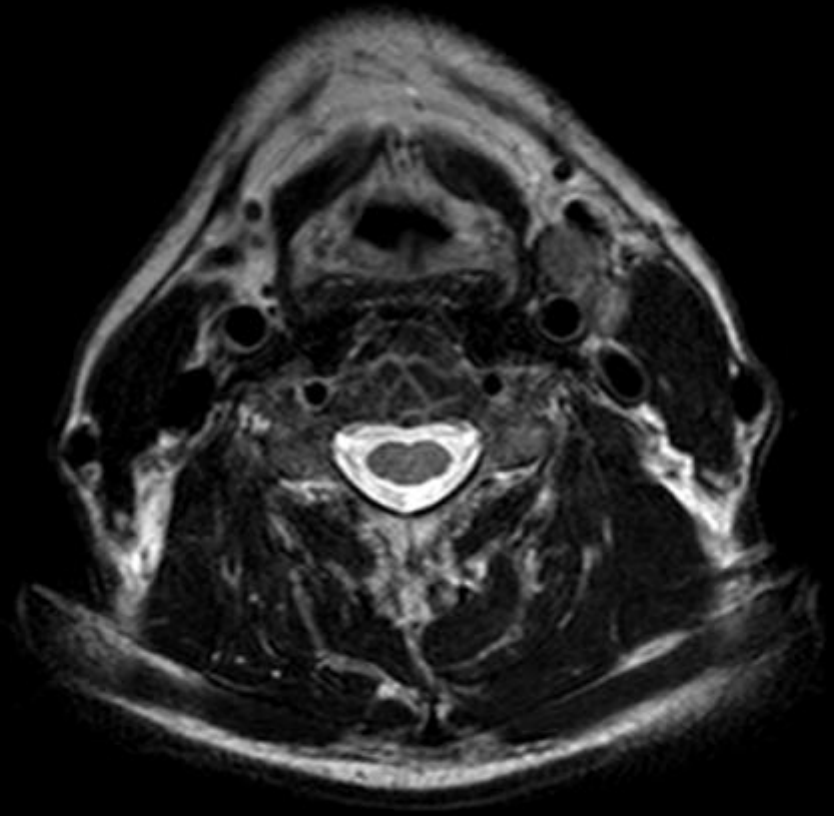
JE 12



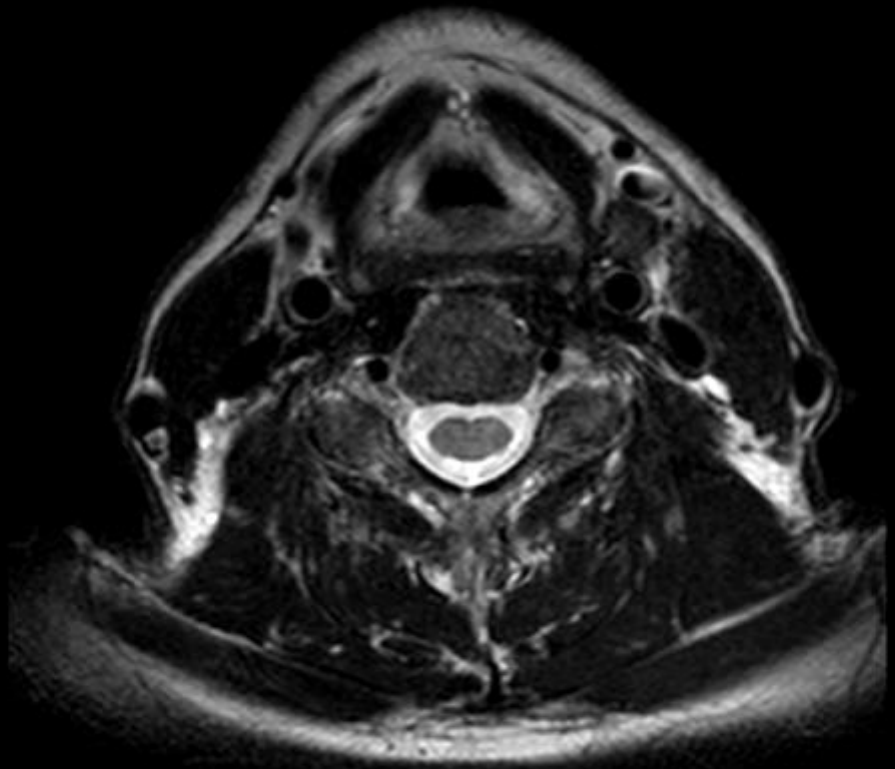
JE 13



JE 14

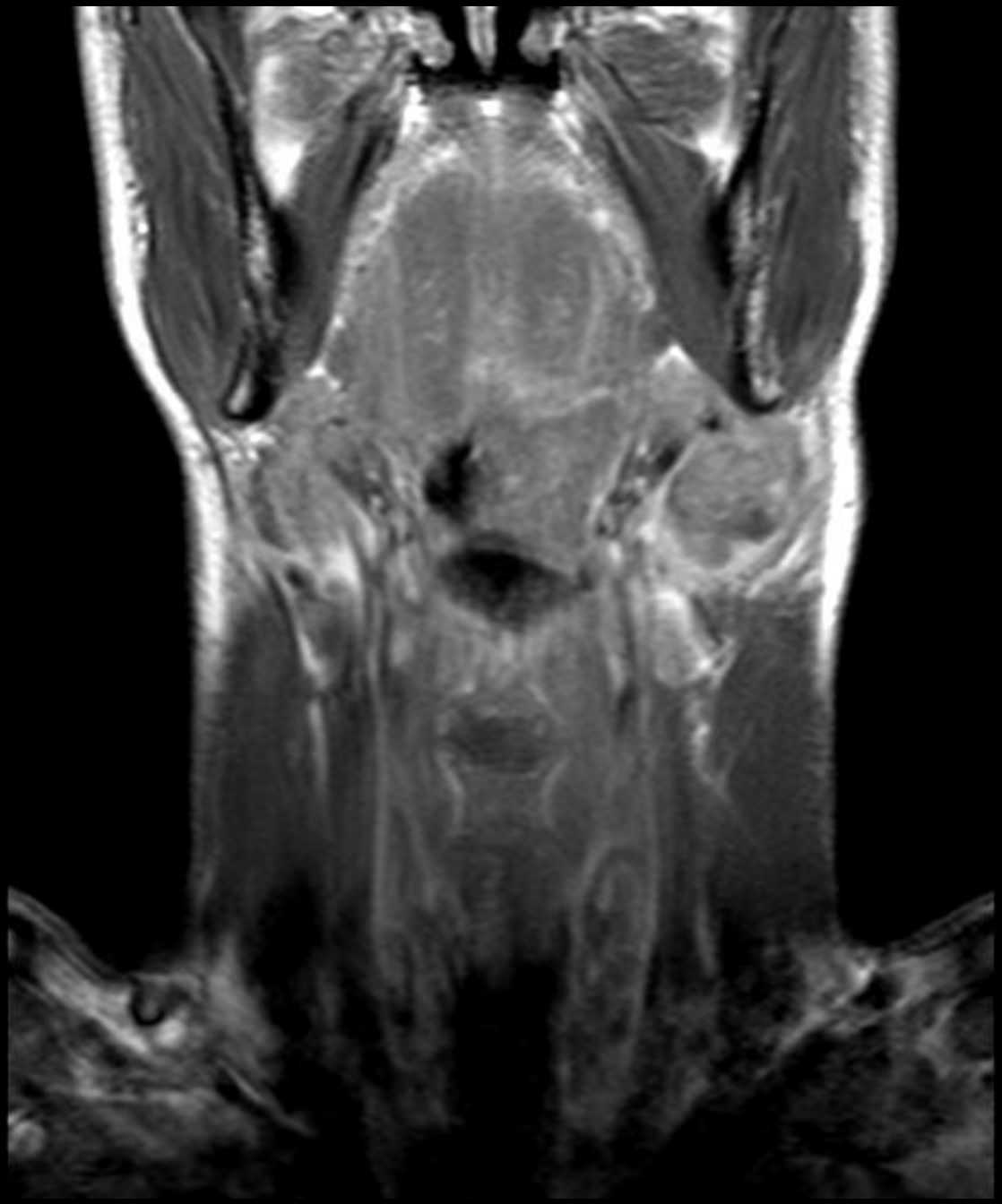


JE 15

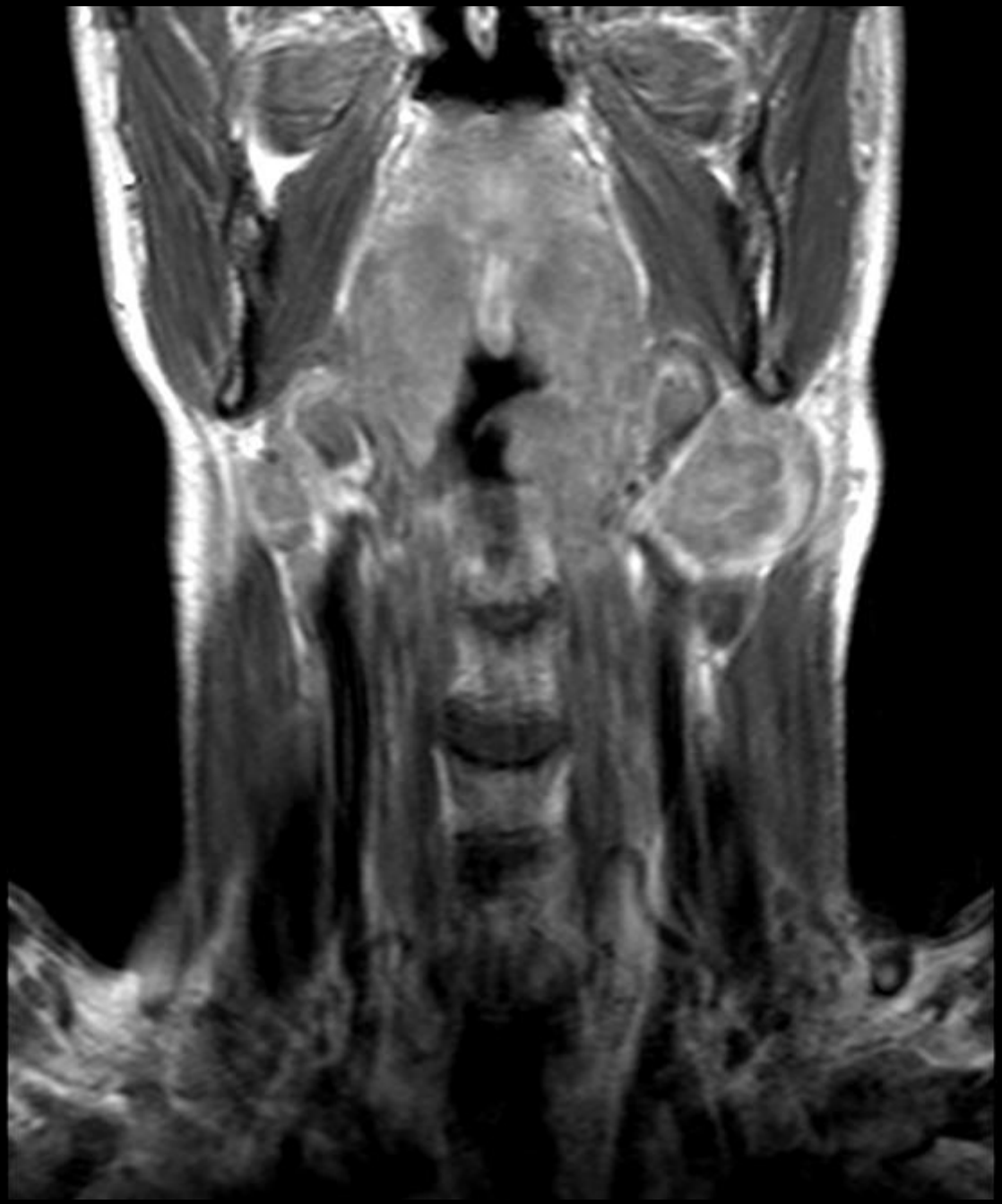


JE 16

MR
Coronal view

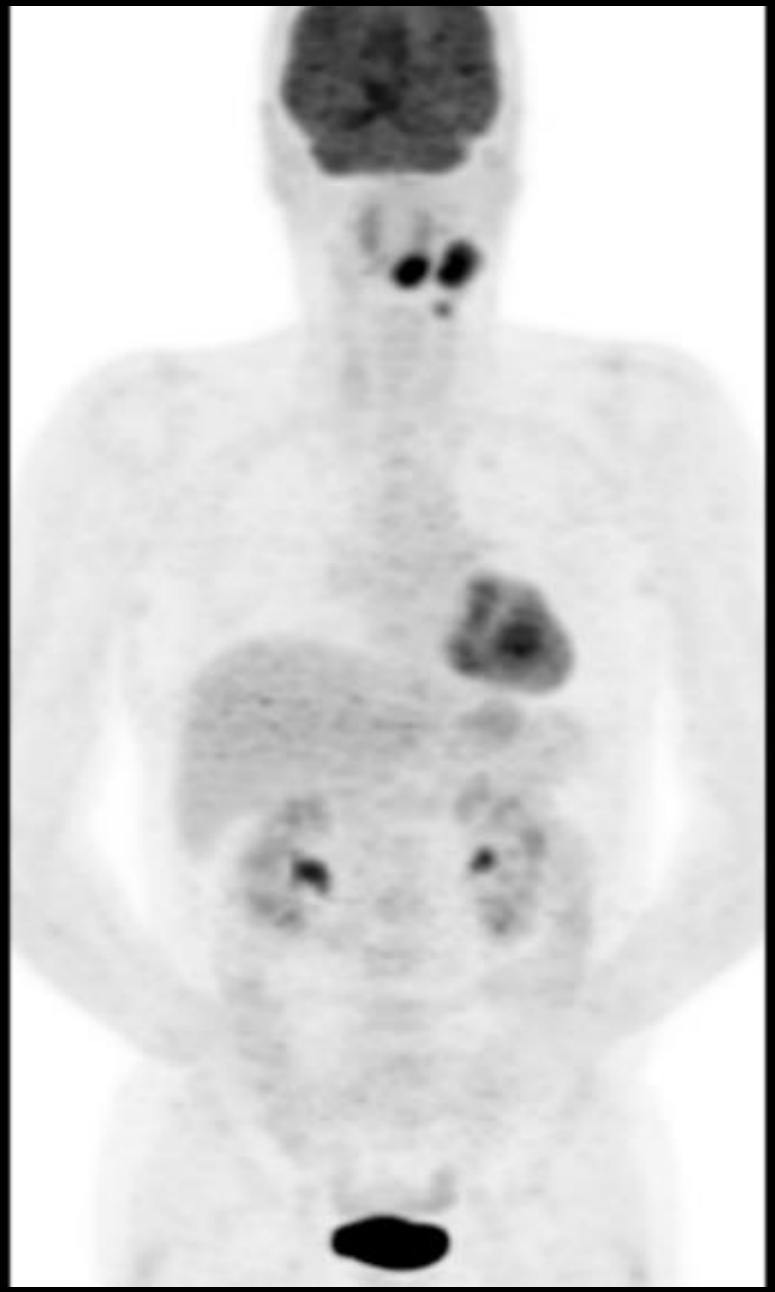


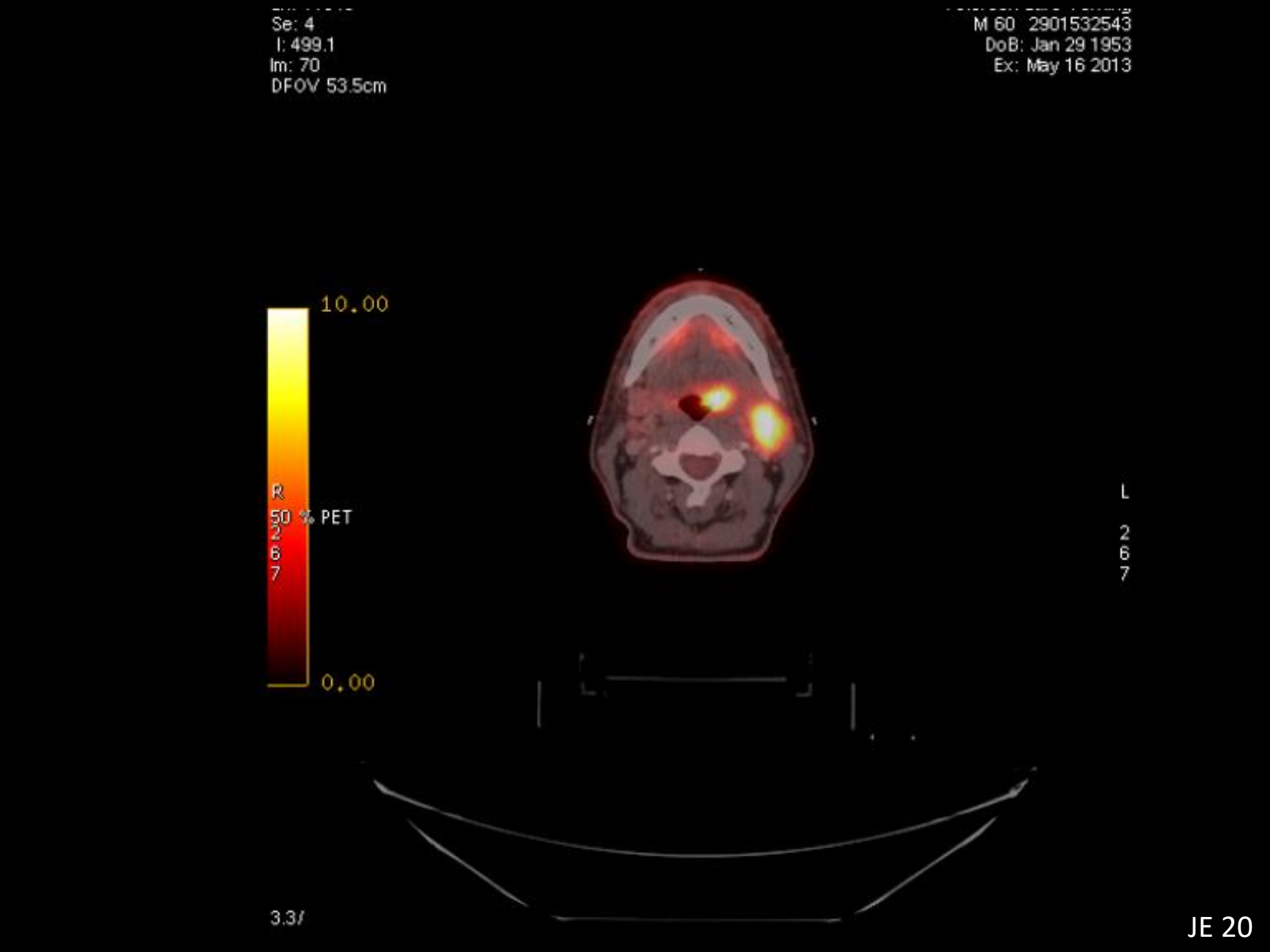
JE 17



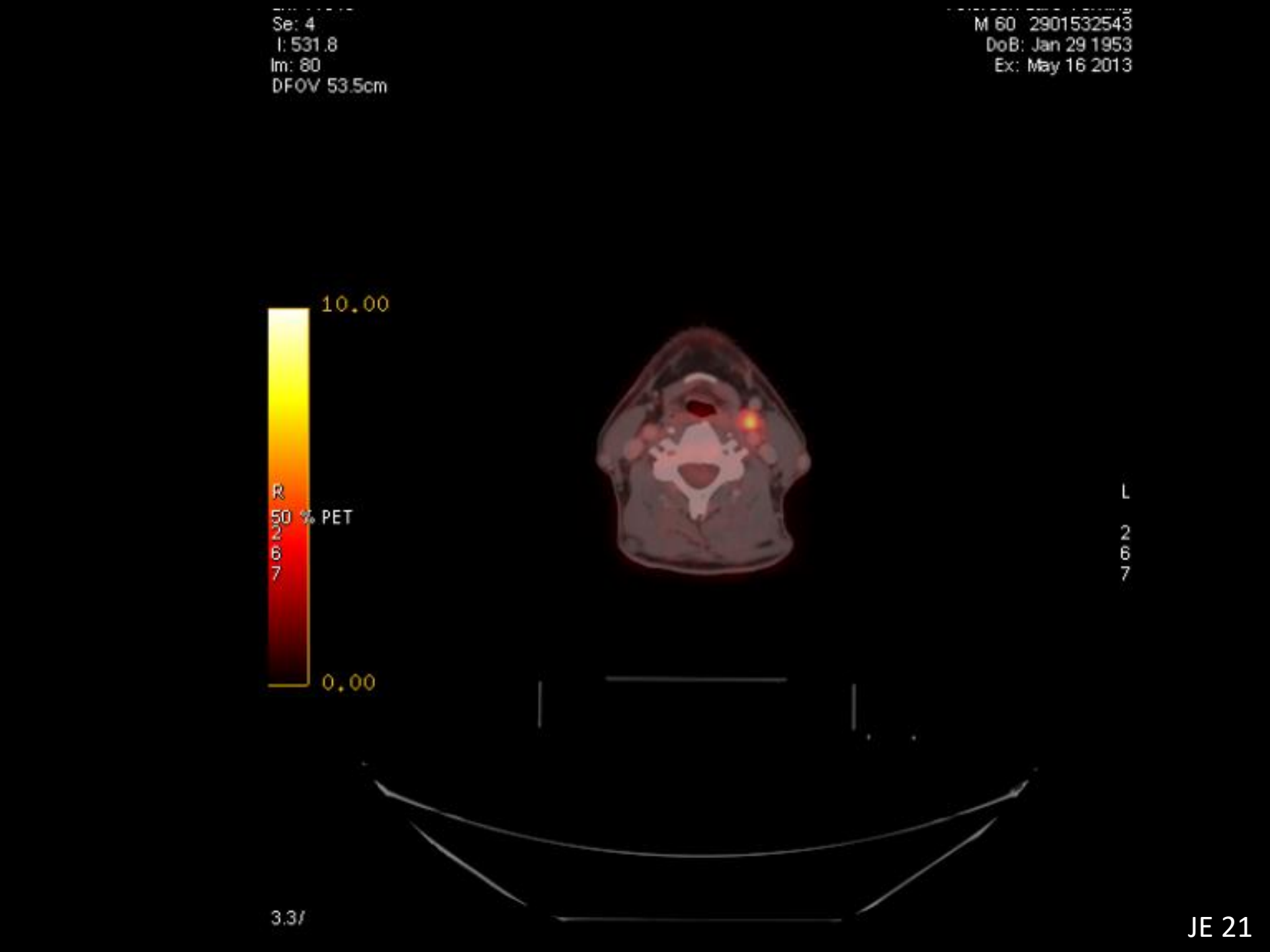
JE 18

FDG-PET-CT

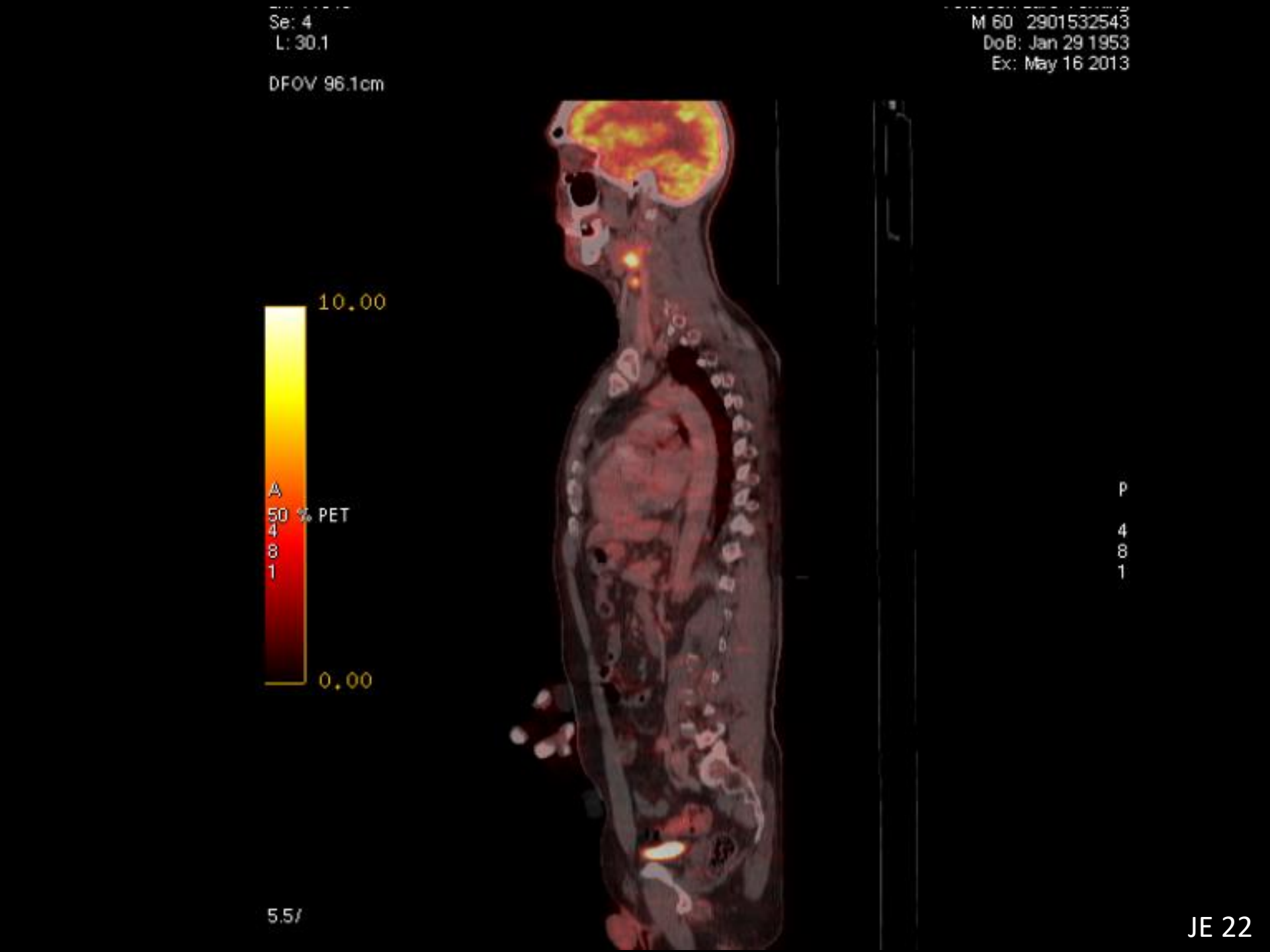



Se: 4
I: 499.1
Im: 70
DFOV 53.5cm
M 60 2901532543
DoB: Jan 29 1953
Ex: May 16 2013
10.00
R
50 % PET
2
6
7
0.00
L
2
6
7
3.3/

JE 20


Se: 4
I: 531.8
Im: 80
DFOV 53.5cm
M 60 2901532543
DoB: Jan 29 1953
Ex: May 16 2013
10.00
R
50 % PET
2
6
7
0.00
L
2
6
7
3.3/

JE 21


Se: 4
L: 30.1
DFOV 96.1cm
M 60 2901532543
DoB: Jan 29 1953
Ex: May 16 2013
10.00
A
50 % PET
4
8
1
0.00
P
4
8
1
5.5/

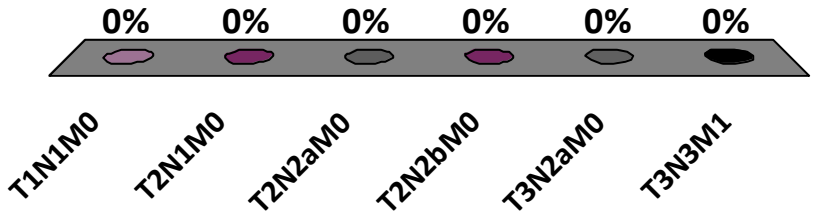
JE 22

Ultrasound of neck

- One necrotic node in the upper part of left region II close to the submandibular gland; 3.5x2x2 cm.
- One node in left region III, 1.5x1x1 cm without preserved hilar region.
- Right side of the neck is normal.

What stage

A. T1N1M0
B. T2N1M0
C. T2N2aM0
D. T2N2bM0
E. T3N2aM0
F. T3N3M1

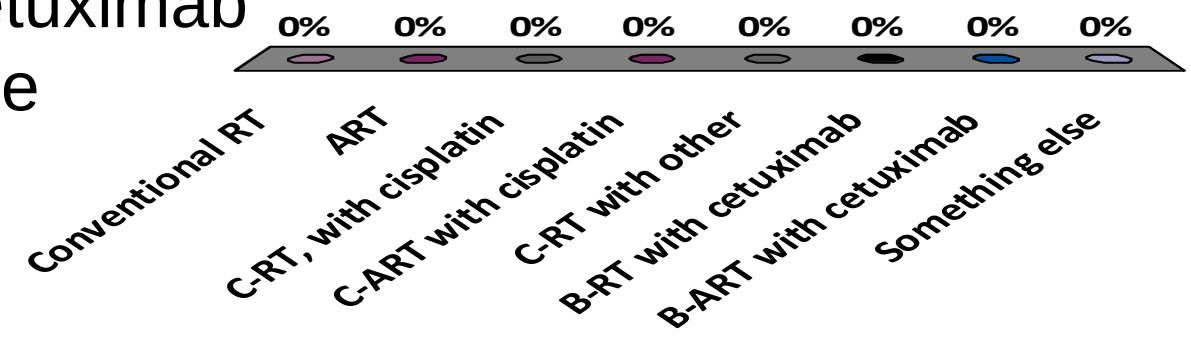


Conclusions after diagnostic workup

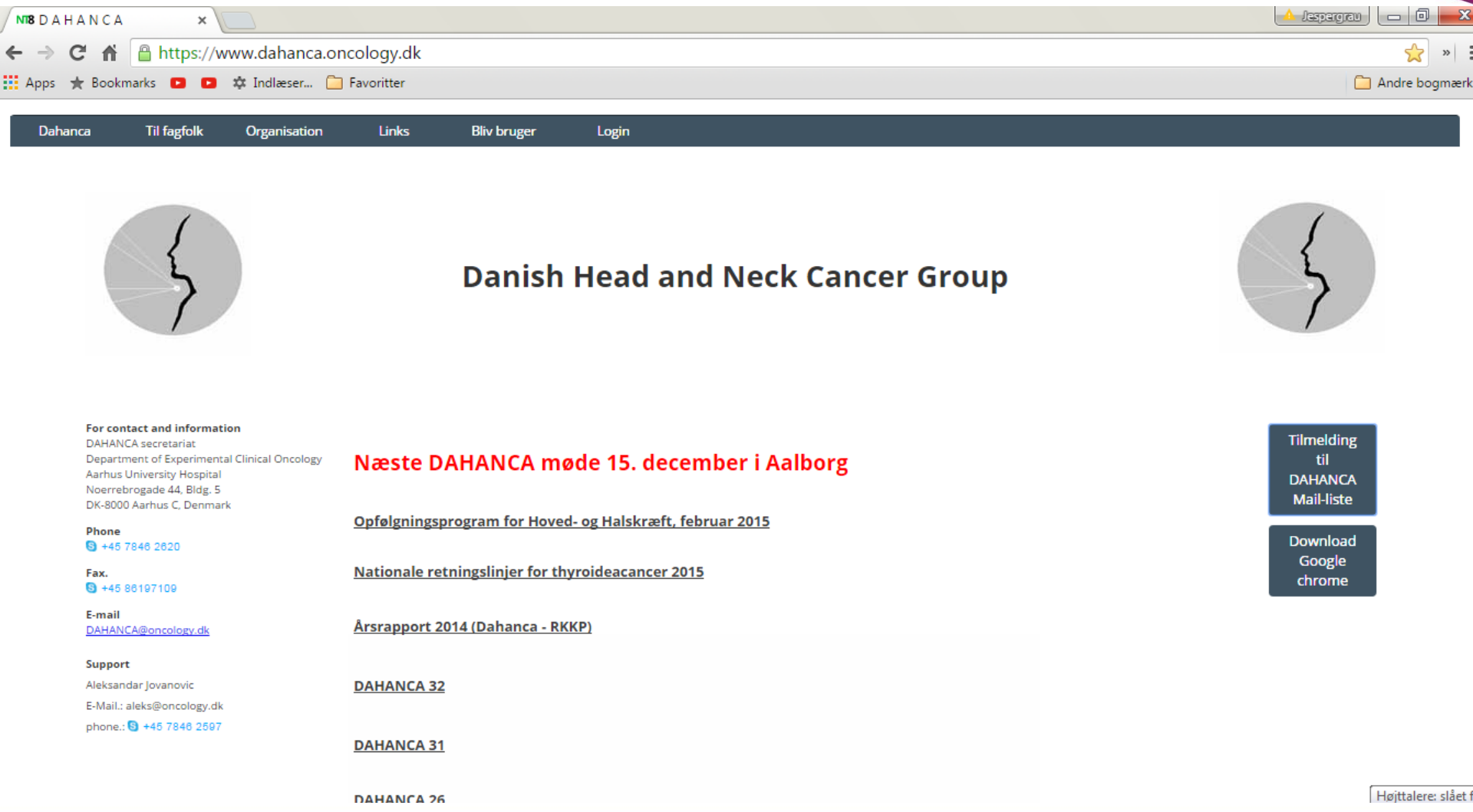
- T2N2bM0 (stage IVa) SCC oropharyngeal tumour.
- Patient in a good performance with no relevant comorbidity.

Treatment?

A. Conventional RT
B. ART
C. C-RT, with cisplatin
D. C-ART with cisplatin
E. C-RT with other
F. B-RT with cetuximab
G. B-ART with cetuximab
H. Something else



DAHANCA Treatment planning guide lines



ESTRO online FALCON course

ABOUT THE SCHOOL
COURSES
ONLINE WORKSHOPS
E-LEARNING
EUROPEAN TRAINING
PUBLICATIONS
GRANTS
FAQ

HEAD AND NECK CANCER – AUSTRALIAN EDITION

07-21 December, 2015

TARGET GROUP
These online delineation workshops are aimed at junior clinical or radiation oncologists who want to improve their contouring skills or at more senior specialists who want to refresh and validate their knowledge and skills in this field.
The workshop is limited to 30 people. Places are given on a first-come-first-serve basis.

FACULTY
Workshop Director
Jesper Eriksen

Cancer Specialist
Vincent Gregoire

WORKSHOP SESSIONS
7 December, 2015 - 18.00-19.00 AEDT (Australian Eastern Daylight Time)
14 December, 2015 - 18.00-20.00 AEDT (Australian Eastern Daylight Time)
21 December, 2015 - 18.00-19.30 AEDT (Australian Eastern Daylight Time)

COURSE AIM
The workshops will be conducted through 3 interactive web conference sessions that offer the opportunity to compare delineations from participants and experts and discuss the interobserver variability and the available guidelines.

< < Nov 2015 > >

Mo	Tu	We	Th	Fr	Sa	Su
26	27	28	29	30	31	1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29
30	1	2	3	4	5	6

NEWS

ESTRO SCHOOL GUIDES AND CALENDARS

- 2016 ESTRO GUIDE
- 2016 ESTRO School Calendar
- 2015 ESTRO Flip Guide
- 2015 ESTRO School Calendar
- ESTRO School Roadmap

2017 ESTRO Courses

- Sneak Peak on 2017 live courses

In training members	100 €
ESTRO members	150 €
Non-members	250 €

ESTRO School

Head and Neck patient case

Jesper Grau Eriksen

Dept. Of Oncology
Odense Universityhospital, Denmark

jesper@oncology.au.dk

Patient history

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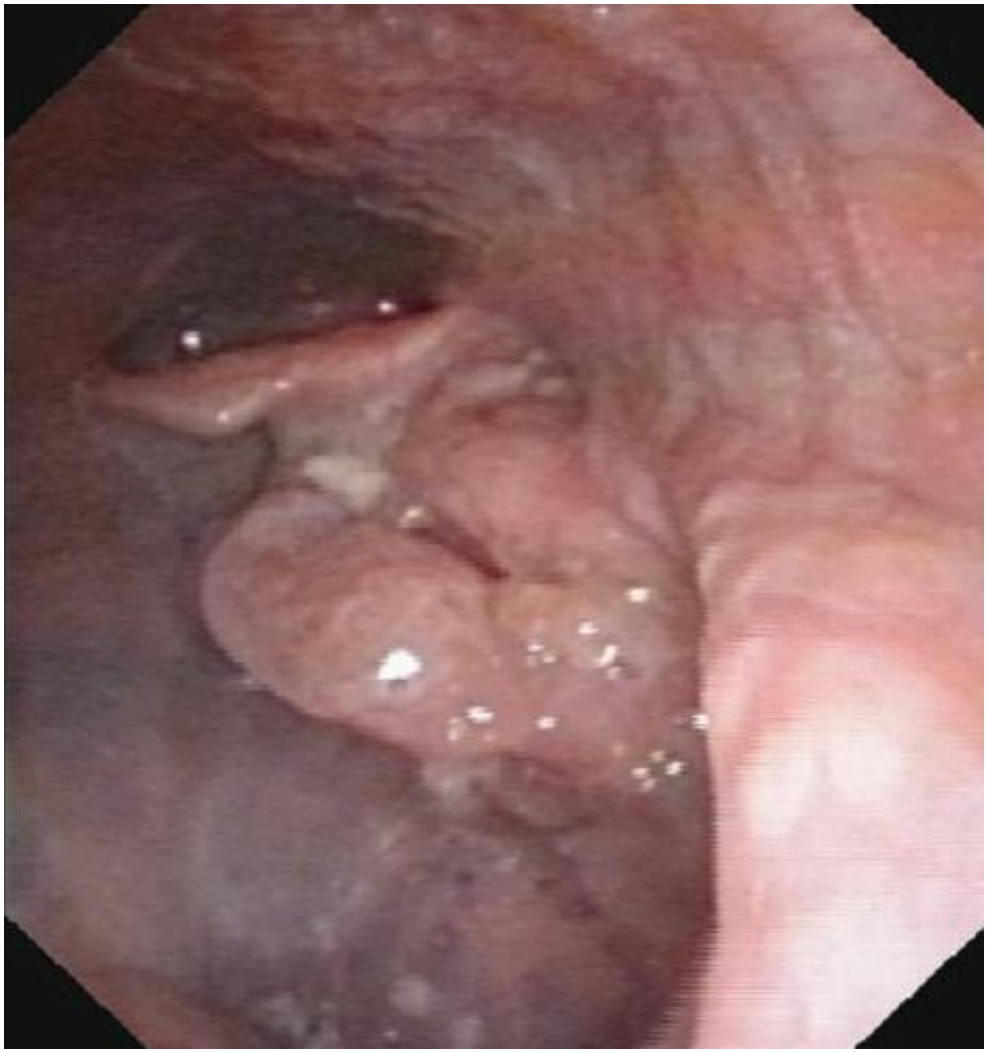
- No co-morbidity except from back pain.
- Ceased smoking in 1990, 16 pack-years.
- 1-2 glasses of alcohol a day.

Clinical examination

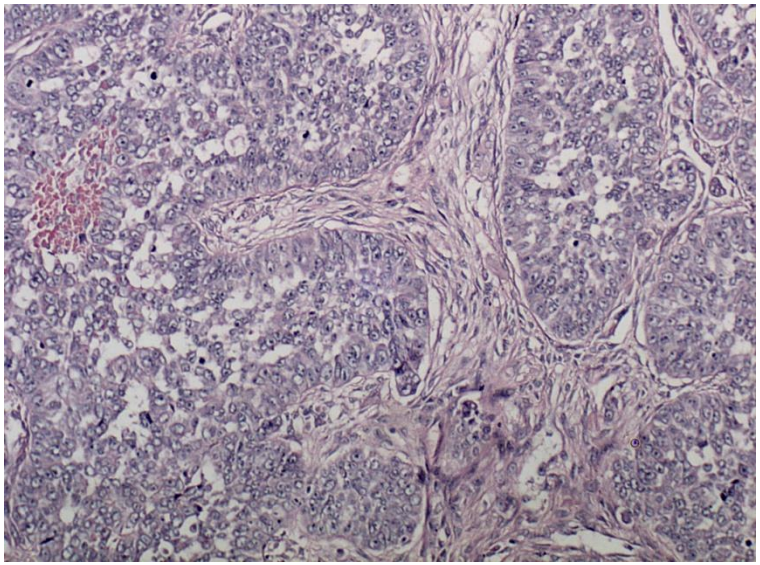
- Good performance (WHO PS 0).
- Base of tongue/vallecula area a 3x2x2 cm large tumour is seen. Proximal border of the tumour seems to be close to the lower pole of the left tonsil.
- Otherwise normal fiber optic examination.
- Palpable node in region II, left side.
- Contra-lateral side normal.

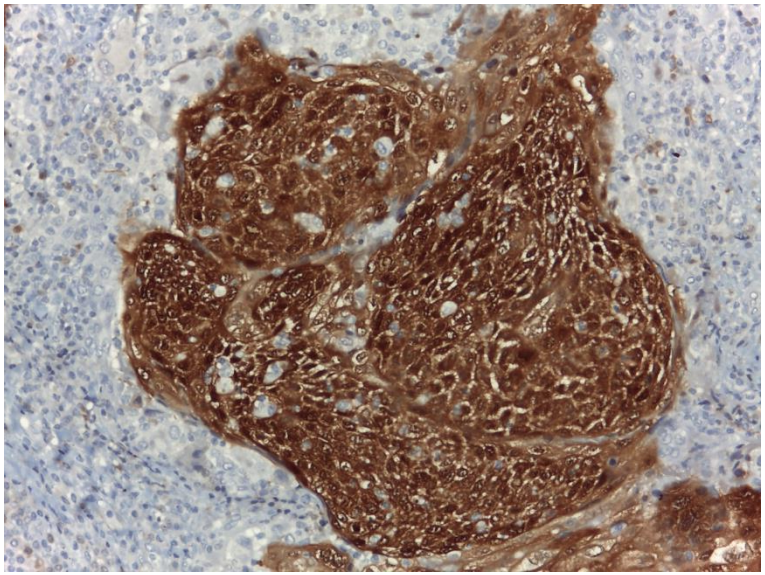
Fiber optic examination



Pathology

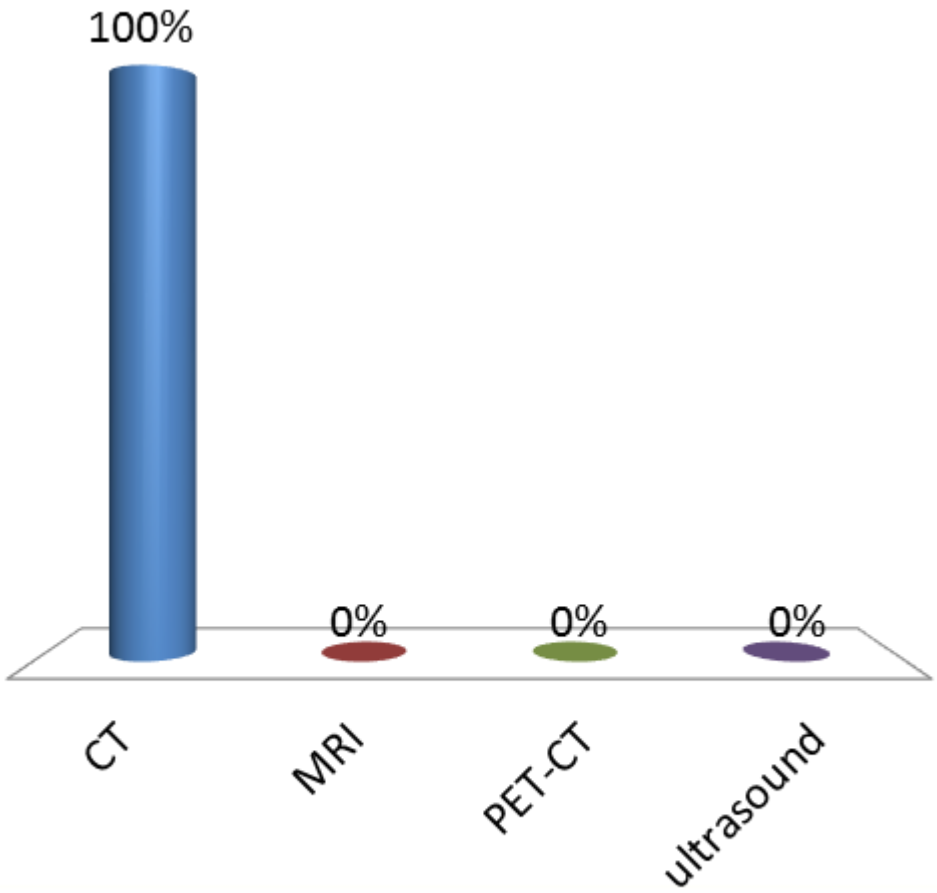
- Moderate differentiated squamous cell carcinoma (G2)
- p16 positive





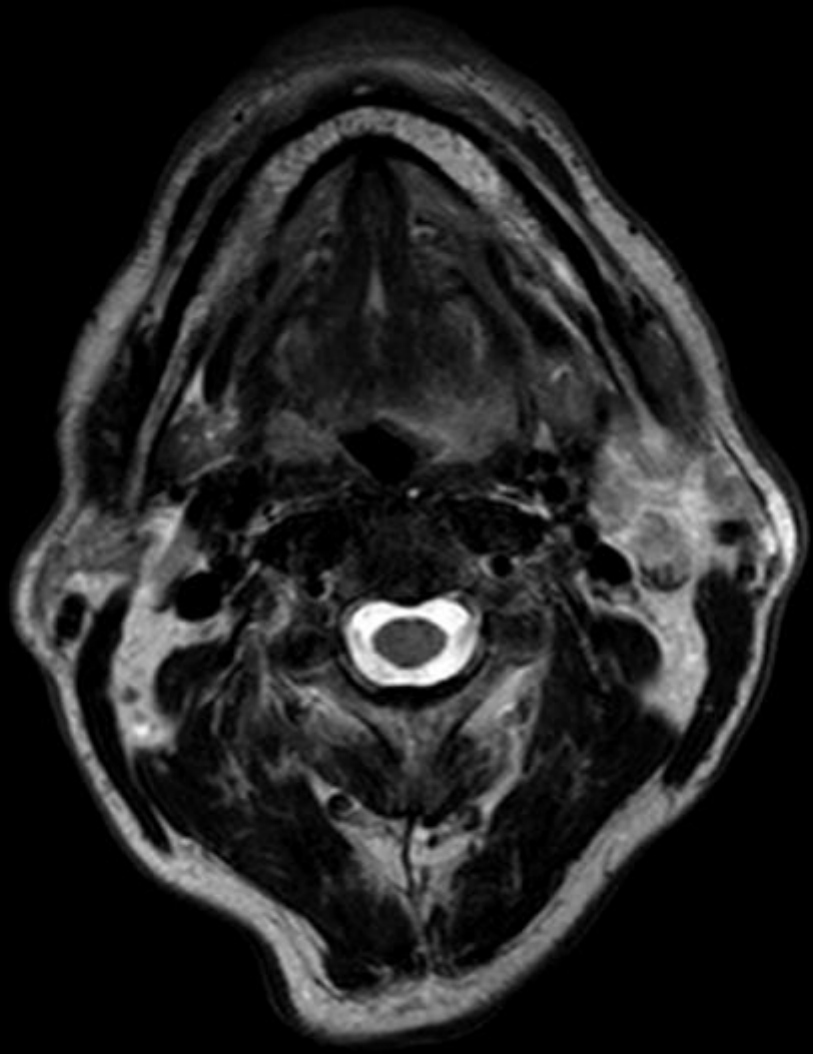
What Image-modality would you primarily choose?

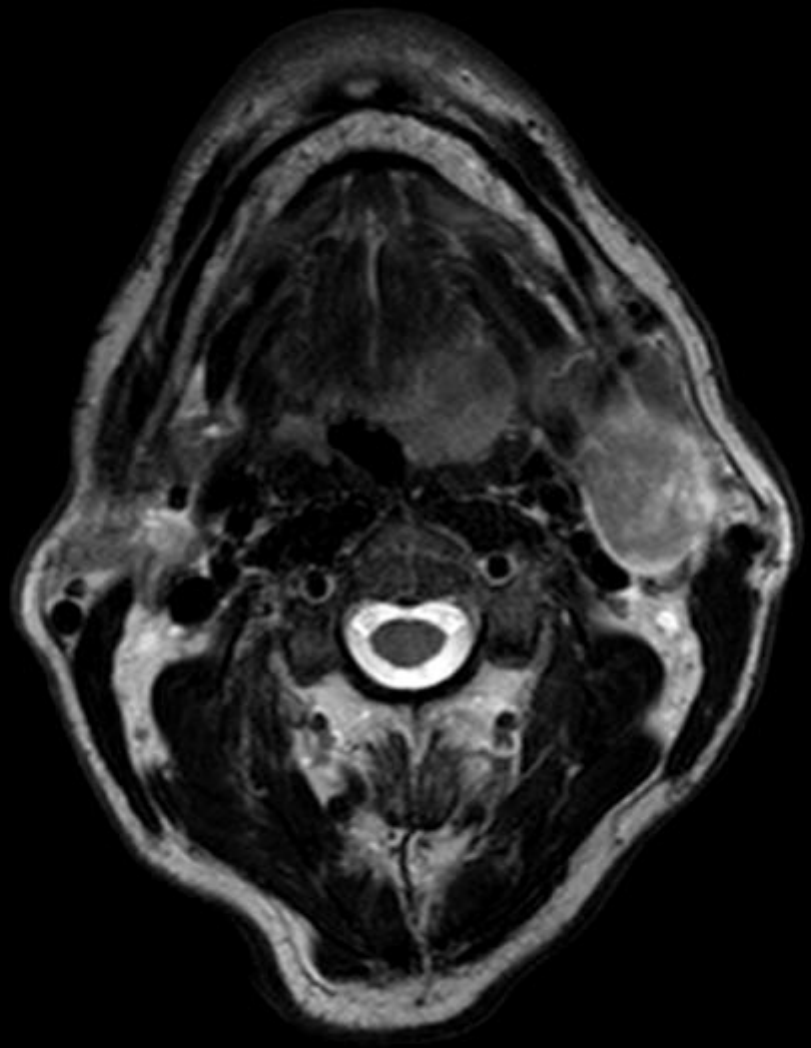
A. CT
B. MRI
C. PET-CT
D. ultrasound



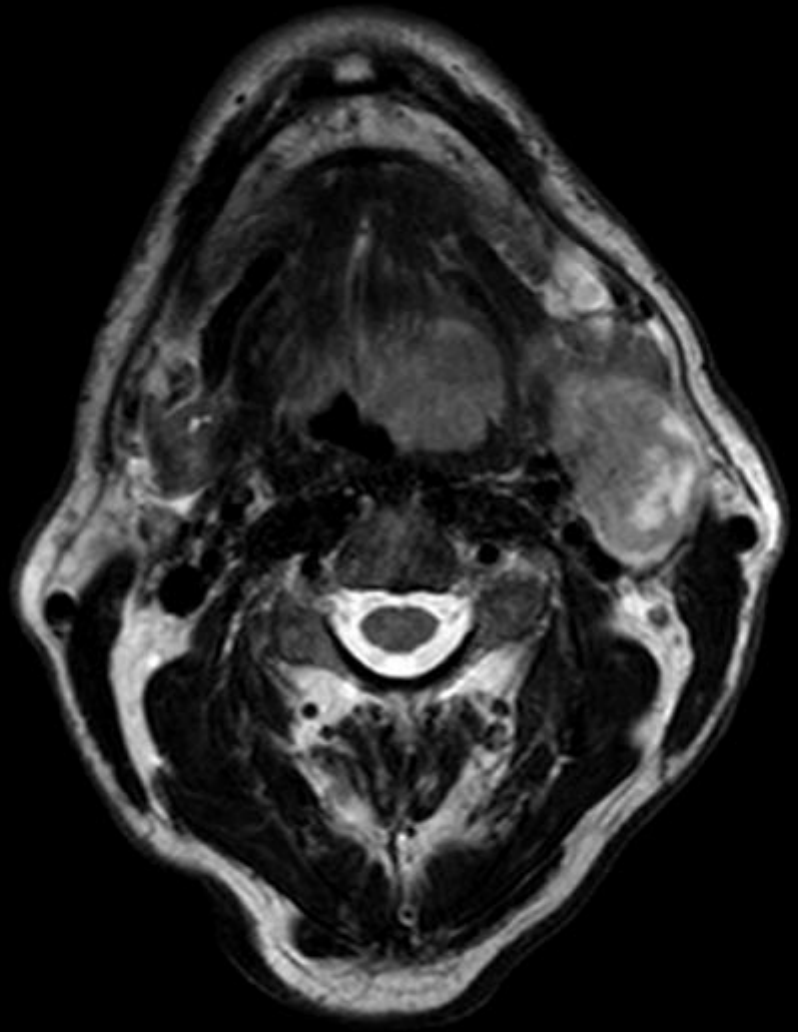
ESTRO School

MR
Axial view

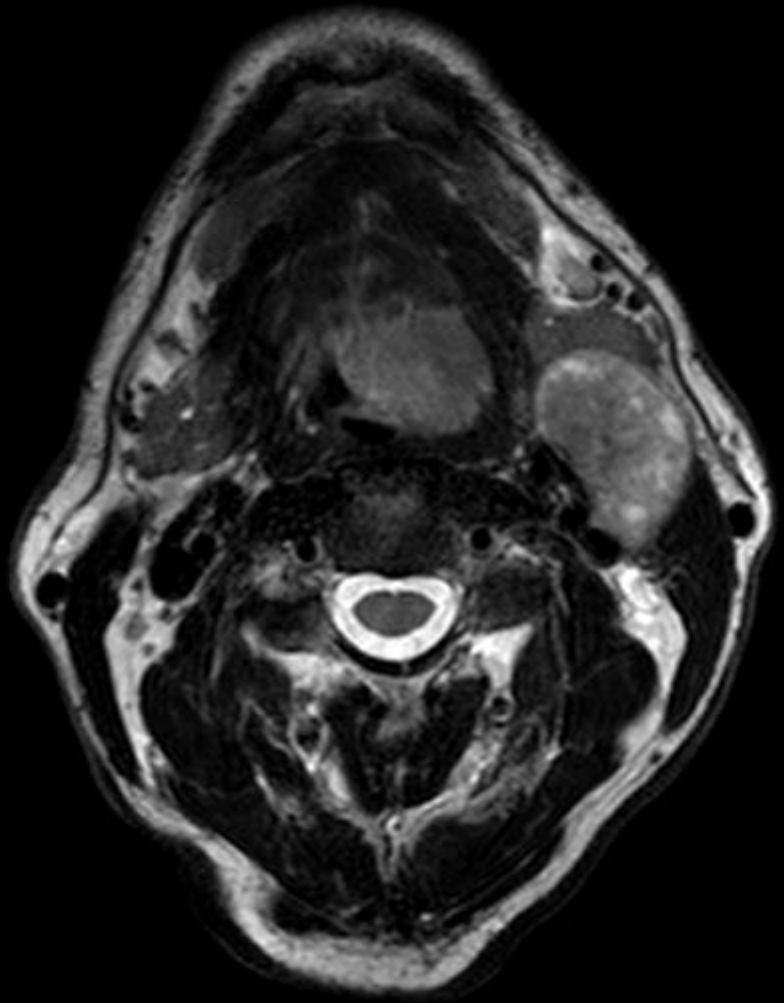




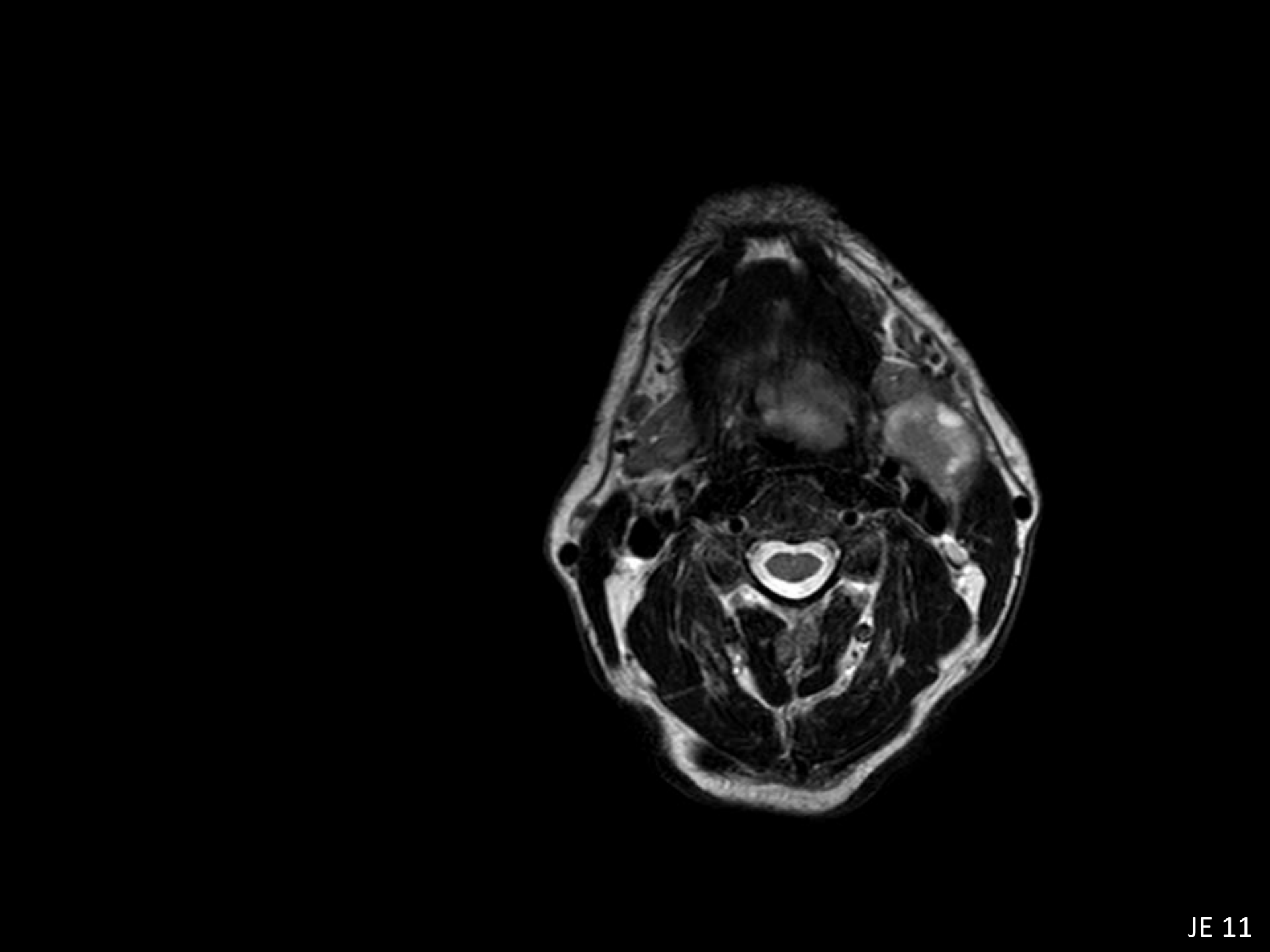
JE 8



JE 9



JE 10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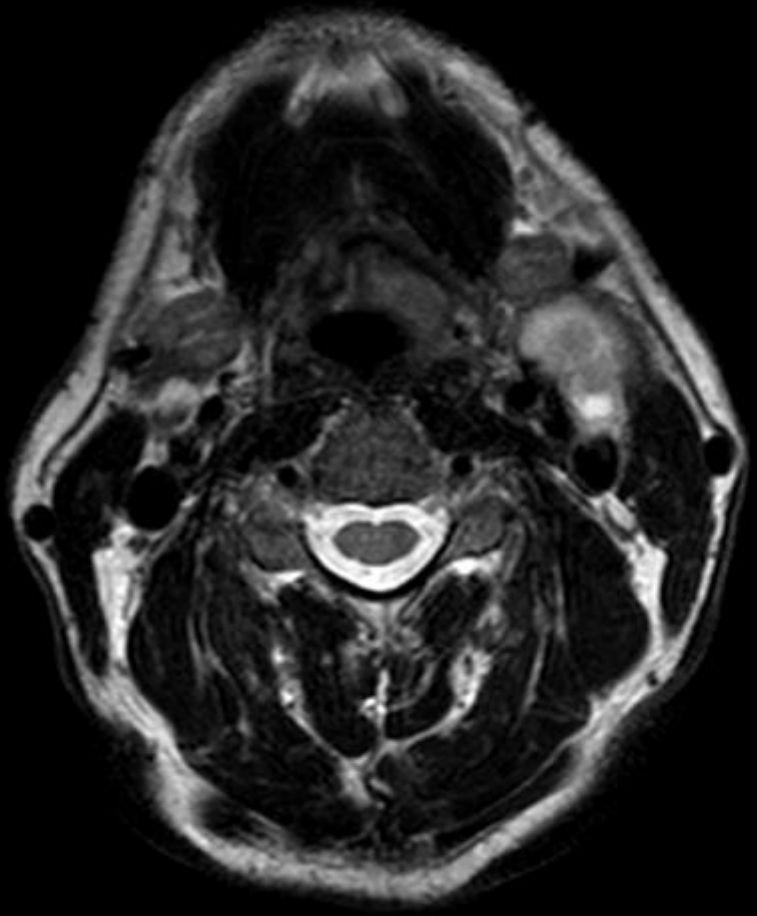

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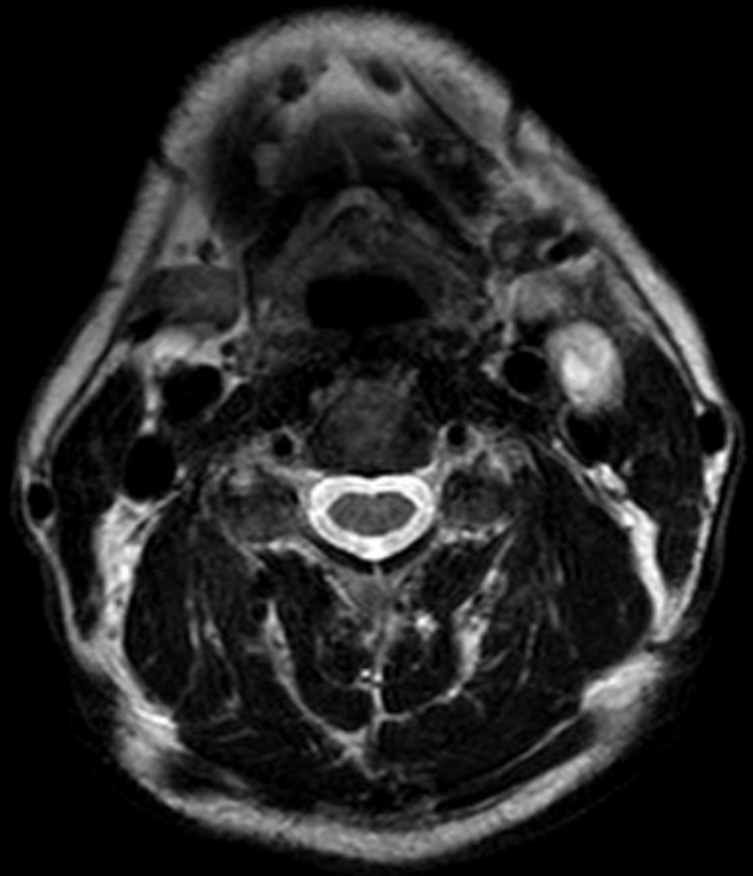
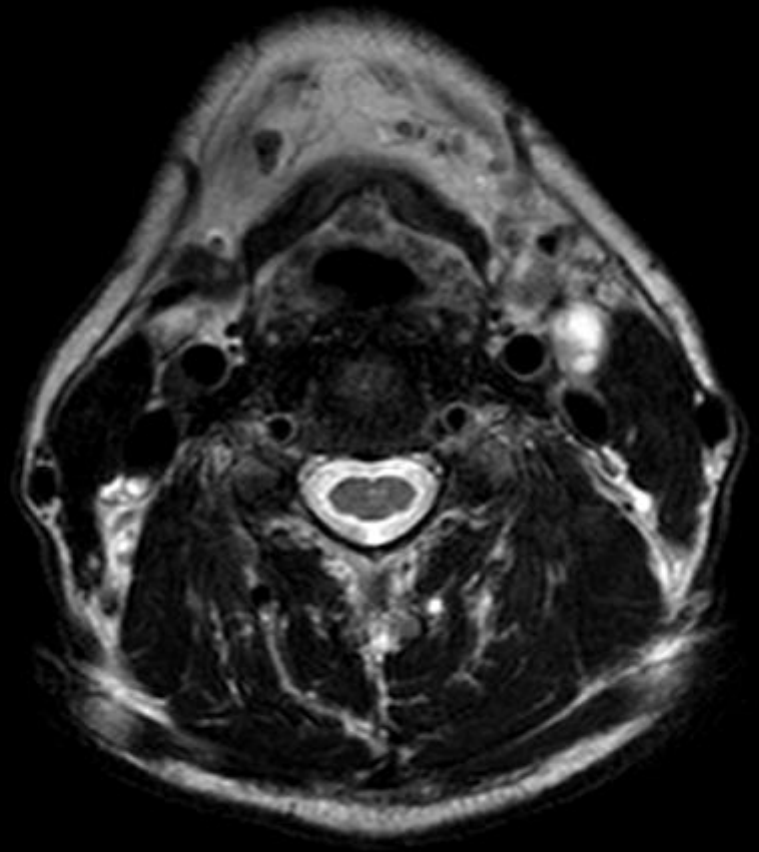
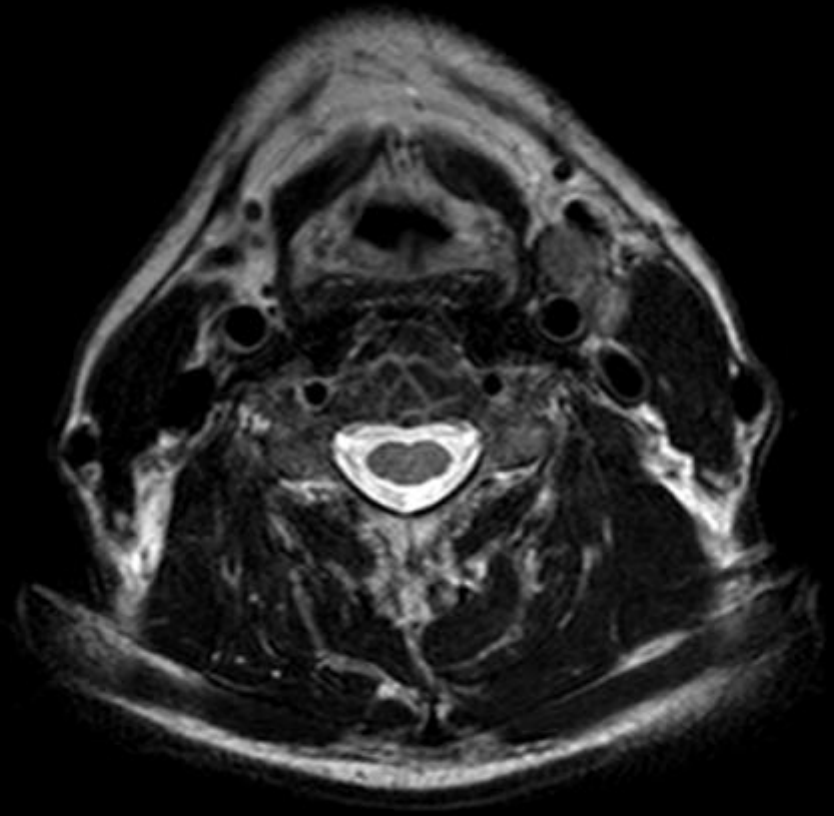


JE 13



JE 14



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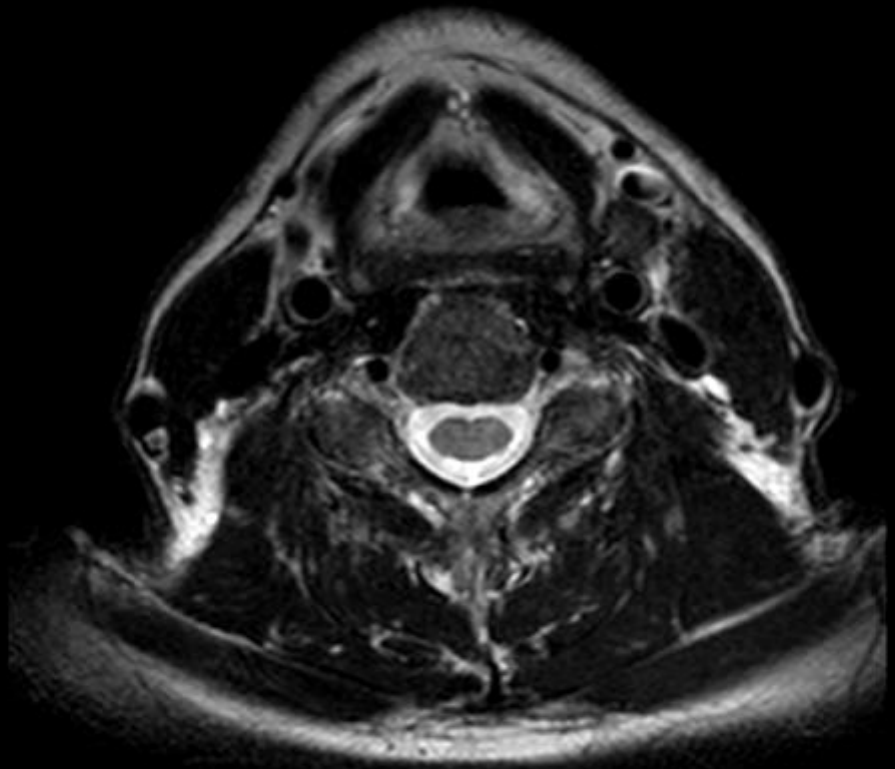
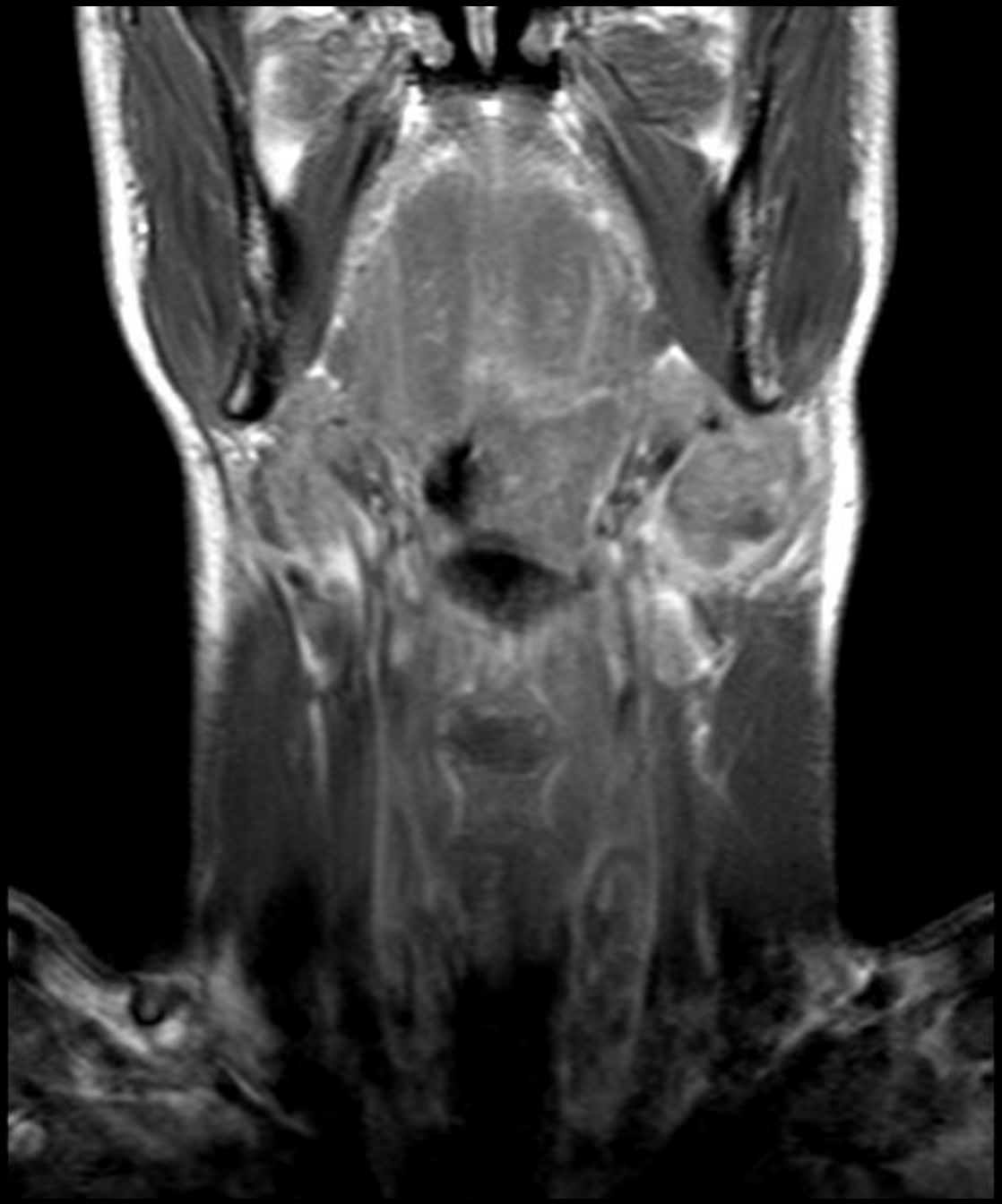


JE 16

MR
Coronal view



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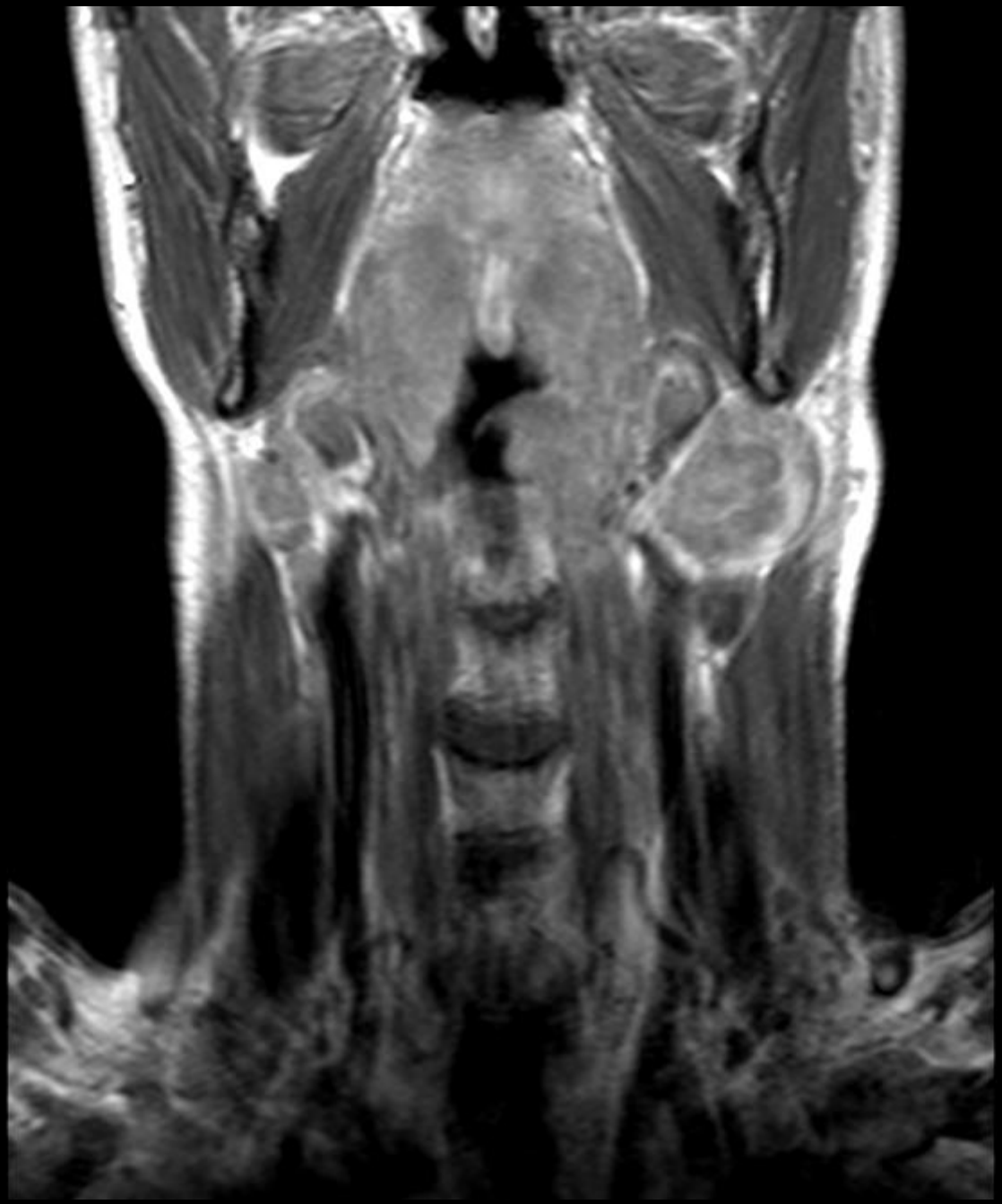
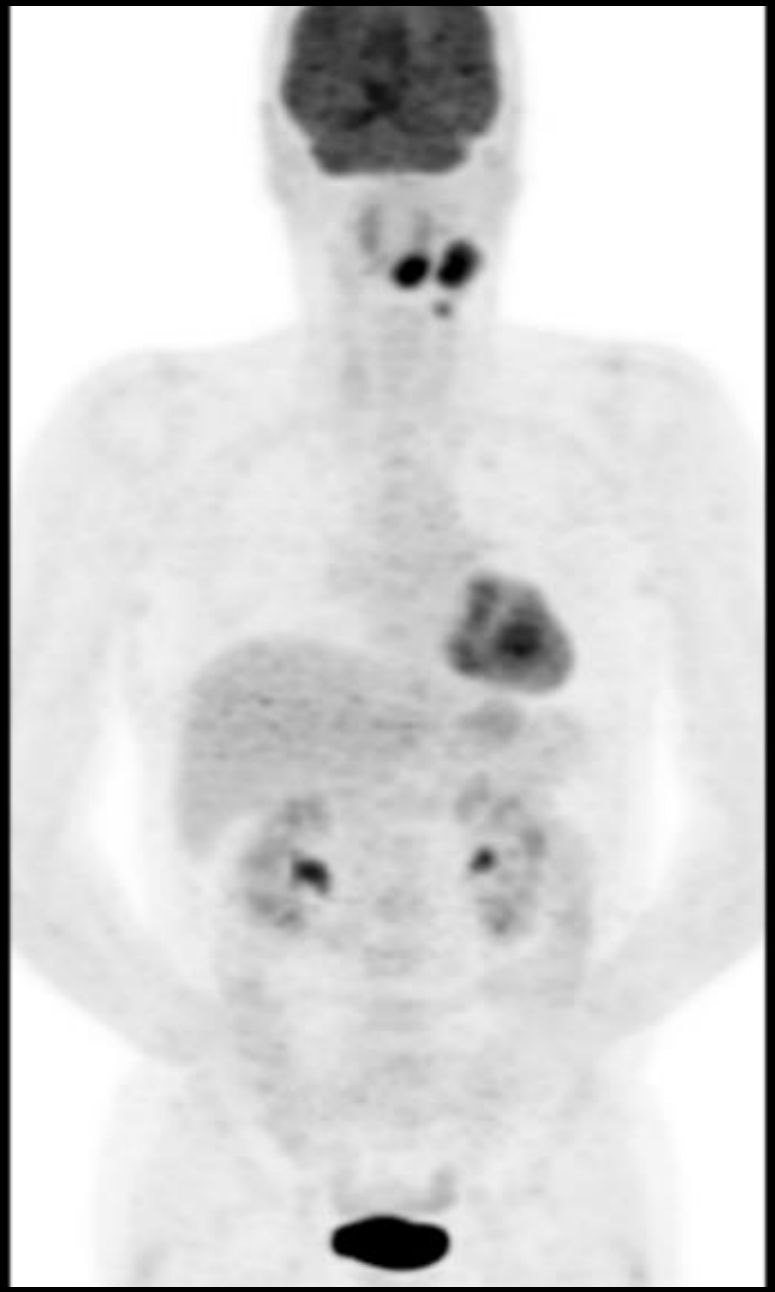
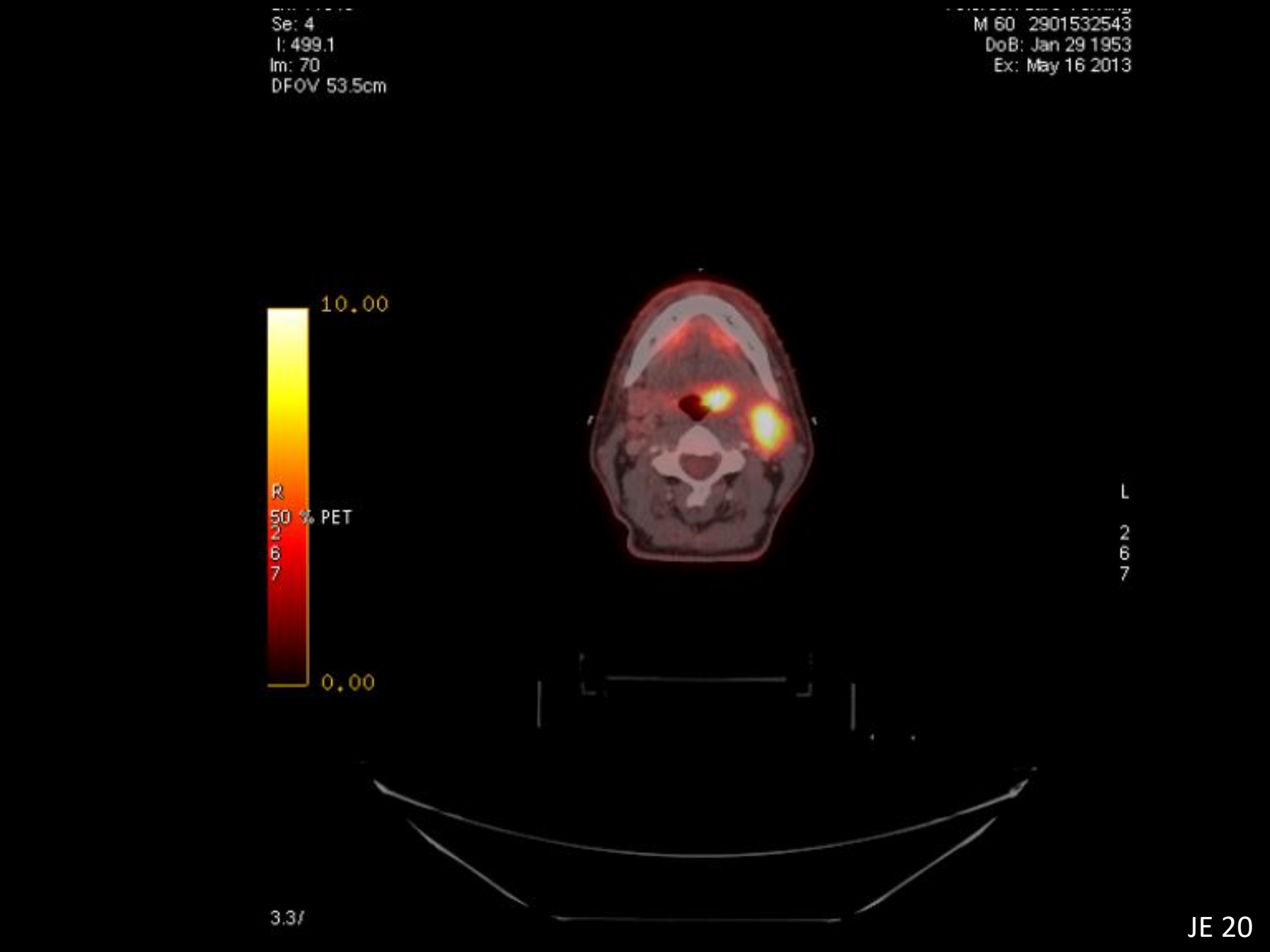


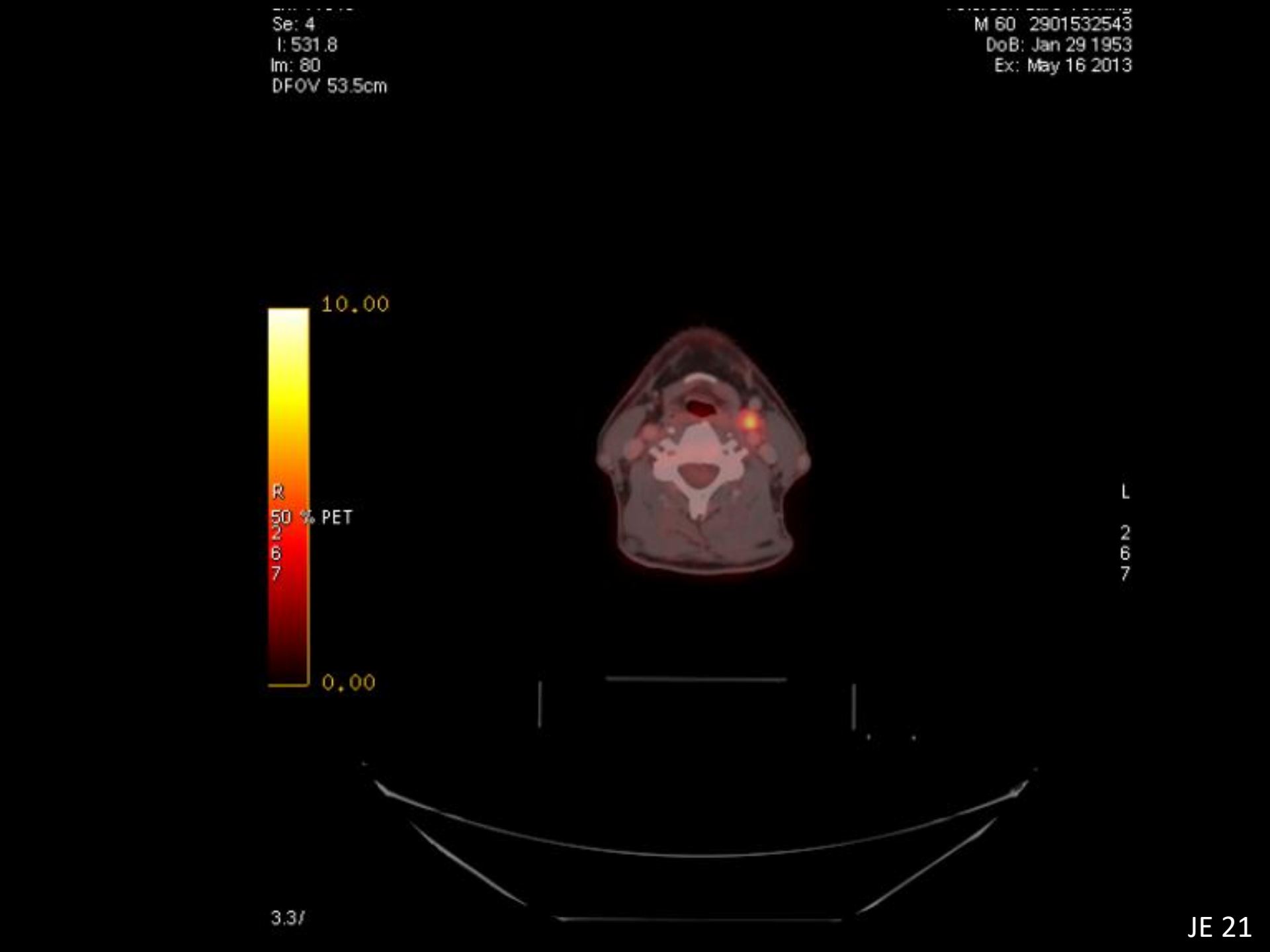
JE 18

FDG-PET-CT

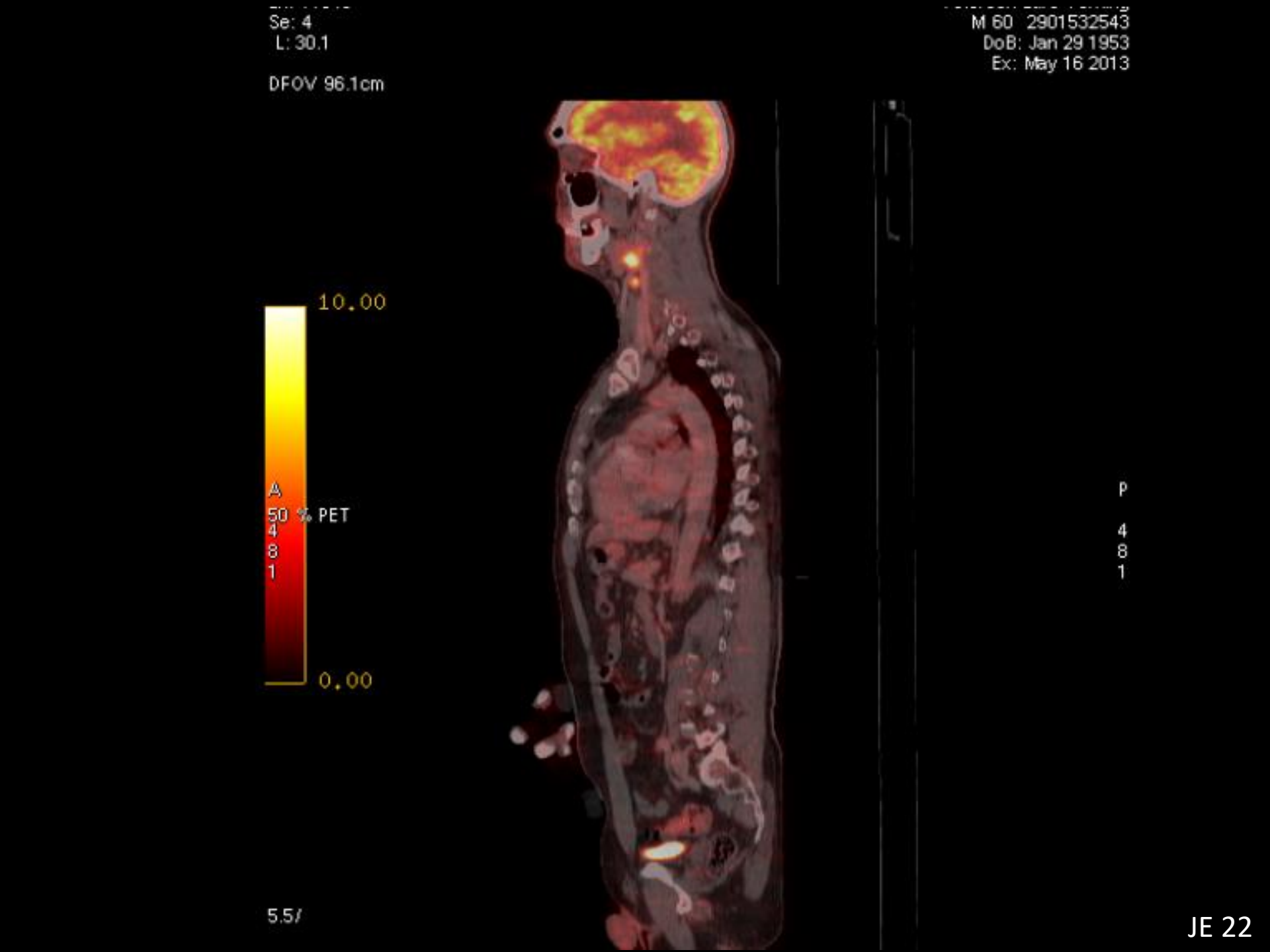



Se: 4
I: 499.1
Im: 70
DFOV 53.5cm
M 60 2901532543
DoB: Jan 29 1953
Ex: May 16 2013
10.00
R
50 % PET
2
6
7
0.00
L
2
6
7
3.3/

JE 20


Se: 4
I: 531.8
Im: 80
DFOV 53.5cm
M 60 2901532543
DoB: Jan 29 1953
Ex: May 16 2013
10.00
R
50 % PET
2
6
7
0.00
L
2
6
7
3.3/

JE 21


Se: 4
L: 30.1
DFOV 96.1cm
M 60 2901532543
DoB: Jan 29 1953
Ex: May 16 2013
10.00
A
50 % PET
4
8
1
0.00
P
4
8
1
5.5/

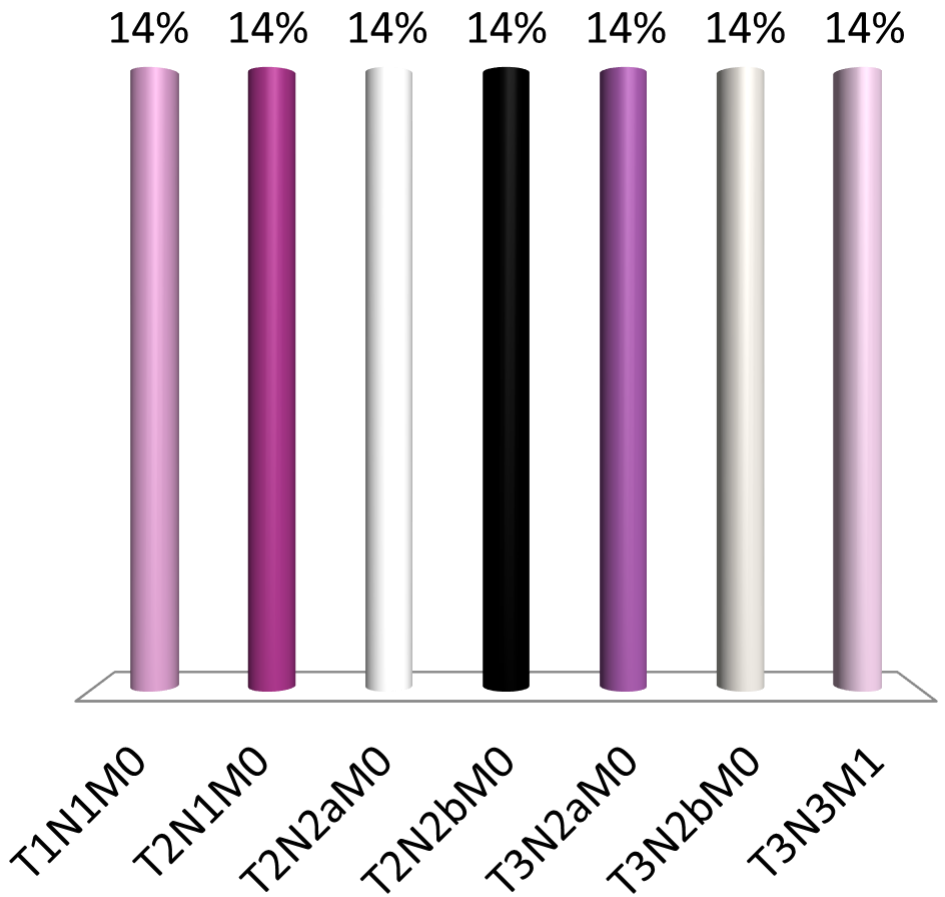
JE 22

Ultrasound of neck

- One necrotic node in the upper part of left region II close to the submandibular gland; 3.5x2x2 cm.
- One node in left region III, 1.5x1x1 cm without preserved hilar region.
- Right side of the neck is normal.

What stage

A. T1N1M0
B. T2N1M0
C. T2N2aM0
D. T2N2bM0
E. T3N2aM0
F. T3N2bM0
G. T3N3M1



Conclusions after diagnostic workup

- T2N2bM0 (stage IVa) SCC oropharyngeal tumour.
- Patient in a good performance with no relevant comorbidity.

Treatment?

ESTRO online FALCON course

ONLINE CONTOURING WORKSHOP SCHEDULE FOR 2017

Session Dates	Workshop Topic
7 March 2017 14 March 2017 29 March 2017	Lung Cancer
15 May 2017 22 May 2017 29 May 2017	Lymphoma
30 May 2017 6 June 2017 13 June 2017	Head and Neck Cancer
4 July 2017 11 July 2017 18 July 2017	APAC version Head and Neck Cancer
6 September 207 13 September 2017 20 September 2017	Rectal Cancer
4 October 2017 11 October 2017 18 October 2017	Breast Cancer
17 October 2017 24 October 2017 30 October 2017	Oesophageal Cancer
7 November 2017 14 November 2017 21 November 2017	Prostate Cancer
5 December 2017 12 December 2017 19 December 2017	Paediatic Oncology

ESTRO School

ESTRO course on
Chemoradiation
Bruxelles June 2017

Rectal and Anal cancer: use of clinical endpoints

Rob Glynne-Jones
Mount Vernon Cancer Centre

My Disclosures: last 5 years

- **Speaker:** Roche, Merck Serono, Sanofi Aventis, Pfizer, AIS
- **Advisory Boards:** Roche, Merck Serono, Sanofi Aventis, Astra Zeneca, BMS
- **Funding to attend meetings**: Roche, Merck Serono, Sanofi Aventis,
- **Research funding**: Roche, Merck Serono, Sanofi Aventis

Time-to-events endpoints (38)

As you can see there are many different time to event endpoints, with very subtle differences and different papers may even use different names for the same outcome:

	Results from systematic review of RCTs of systemic therapy for EBC				
	DFS	**RFS**	**EFS**	**TTR**	**Total**
LR + DR + CLB + NBSP + Death	**7**	**0**	**2**	**0**	**9**
LR + DR + CLB + DCIS + Death	**1**	**0**	**0**	**0**	**1**
LR + DR + CLB + DCIS + BC Death	**0**	**0**	**0**	**1**	**1**
LR + DR + CLB + Death	**3**	**0**	**0**	**0**	**3**
LR + DR + CLB + NBSP	**1**	**0**	**0**	**0**	**1**
LR + DR + CLB	**2**	**3**	**0**	**1**	**6**
LR + DR + Death	**6**	**1**	**1**	**1**	**9**
LR + DR	**3**	**3**	**0**	**1**	**7**
LR + DR + BC Death	**0**	**1**	**0**	**0**	**1**

Table: Lucy S Kilburn
Clinical Trials & Statistics Unit (ICR-CTSU),
The Institute of Cancer Research, London, UK

LR = local recurrence, DR =distant recurrence, CLB= contralateral breast, NBSP =National Breast Screening Programme

Starting points in breast cancer trials

Time from	DFS	RFS	EFS	TTR	Total
Randomisation	11	1	0	2	14
Surgery	3	3	0	0	6
Study entry	2	0	0	0	2
diagnosis	0	0	1	0	1
Treatment start	0	1	0	0	1
Undefined	7	3	2	2	14

Problems

- Huge variations in which endpoints are used
- and how they are defined
- And variable starting points (not always defined)

Imprecision/heterogeneity makes it difficult if not impossible to compare results among studies

The current randomised trials are slow – require decades!

? we need to drive them faster!

? We need….Early Clinical Endpoints

TRIAL	No	Median FU	Primary endpoint	Secondary endpoints
ACT 1 (UKCCR 1996)	585	42 months	Local treatment failure (composite of local failure and colostomy)	Overall survival
EORTC 22861 (Bartelink 1997)	110	42 months	Local failure	Event-free survival
RTOG 87-04/ECOG (Flam 1996)	291	3 years	Disease-free survival.	Overall survival Colostomy-free survival, Loco-regional control etc..
RTOG 98-11 (Ajani 2008)	644	2.51 years	Disease-free survival.	Overall Survival Cumulative incidence of Colostomy
ACCORD-03 (Conroy 2009)	307	43 months	Colostomy-free survival	Overall survival Cancer-specific survival Local control etc..
ACT II (CRUK) (James 2013)	940	61 months	**Complete response** Acute Toxicity Recurrence-free survival	Overall survival Cancer-specific survival Colostomy rate

Definition of composite disease-related endpoints used in Anal Cancer Trials

Trial	Endpoint	Loco-regional disease	Pelvic disease	Distant mets	Death	New tumour	Colostomy
ACT I[1]	Local Treatment Failure	✓	✓	✓	✓		✓
ACT II[6]	Progression -Free Survival*	✓	✓	✓	✓		✓
EORTC[7]	Event-Free Survival	✓			✓	✓	
ACCORD 03[5]	Event-Free Survival	✓		✓	✓		
RTOG 8704[8]	Disease-Free Survival	✓		✓	✓		
RTOG 9811[4]	Disease-Free Survival	✓		✓	✓		

Most meaningful clinical end points

Depend on

1. The disease stage

- primary only,
- adjuvant ie primary removed
- or advanced/metastatic

2. The individual tumour site
3. The natural history of that disease site
4. The target patient population
5. The type of treatment employed

Endpoints based on tumour assessments

- Overall response rate (ORR)
- Time to progression (TTP)
- Progression free survival (PS)
- Disease free survival (DFS)
- Time to treatment failure (TTF)

All time to event endpoints

Primary disease:Recurrence related endpoints

Most used recurrence endpoints

- Loco-regional failure–free survival
- Disease free survival
- Recurrence free survival
- Colostomy-free survival
- Event free survival
- Time to recurrence

Composite of the following events

- Local Recurrence (LR)
- Colostomy
- Distant recurrence (DR)
- Second primary (same disease site)
- Second primary (different disease site)
- Cancer specific survival
- Overall survival

Composite of the following events

- Local Recurrence (LR)
- Colostomy
- Distant recurrence (DR)
- Second primary (same disease site)
- Second primary (different disease site)
- Cancer specific survival
- Overall survival

What do you think is most appropriate?
Discuss for anal cancer

Local primary site

- Particular issues if chemoradiation rather than surgery is the standard of care

ACT I - Local tumour failure

defined as evidence of

- persistent local disease,
- local regrowth or local recurrence in the primary tumour after protocol therapy.
- Patients who never attained local control (after chemoradiotherapy) were counted as treatment failures at the first assessment post-treatment at 6 weeks.
- Requirement for colostomy

Discuss

- Higher RT doses give rise to higher risk of 2nd malignancy?
- Higher RT doses give rise to more likelihood of colostomy?
- Should there be an internationally agreed consensus?

RTOG-8704

Local failure-free-survival

patients who had

- a colostomy,
- local excision,
- abdominoperineal resection,
- or exenteration for any reason were considered treatment failures on the day of surgery – even if subsequent long-term local control was achieved

Second malignancies common in SCCA

In ACT II 20 patients died of other cancers - in total 6 who received mitomycin C (MMC) based CRT and 14 who received cisplatinum either as CRT or maintenance

Metastatic /advanced

- Few options in practice (OS or PFS)

Main primary endpoints used in advanced or metastatic various types of cancers

	Phase II	Phase III
Non-small cell lung cancer	response rate, progression free survival	overall survival, progression free survival
Small-cell lung cancer	response rate, progression free survival	overall survival, progression free survival
Mesothelioma	response rate	overall survival
Breast cancer	response rate, progression free survival	overall survival, progression free survival
Nasopharyngeal carcinoma	response rate, time to progression	overall survival, progression free survival
Thyroid cancer	response rate	progression free survival
Esophageal cancer	response rate	overall survival, progression free survival
Gastric cancer	response rate	overall survival
Colon rectal cancer	response rate, progression free survival	overall survival, progression free survival
Pancreatic cancer	response rate, progression free survival, overall survival	overall survival
Hepatocellular carcinoma	response rate, progression free survival	overall survival, time to progression
Biliary tract Cancer	response rate, progression free survival	overall survival
Cervical cancer	response rate	overall survival, progression free survival
Endometrial Cancer	response rate, progression free survival	overall survival, recurrence free survival
Ovarian cancer	response rate, progression free survival	overall survival, progression free survival
Prostate Cancer	time to PSA progression, progression free survival	overall survival, progression free survival
Renal cell carcinoma	response rate, progression free survival	overall survival, progression free survival
Glioblastoma	response rate, progression free survival	overall survival, progression free survival
Melanoma	response rate, relapse free survival, disease stabilization rate	overall survival, progression free survival

Kiba, J Cancer Sci Ther 2011, 3:7

Metastatic /advanced

- Few options in practice (OS or PFS)
- TFS: Time to Failure of Strategy
- TTP: Time To Progression
- TTTF: time to treatment failure (includes toxicity)

Progression free survival

- Do you think PFS is meaningful or simply measurable?

- Extending PFS does not always lead to longer overall survival

Please discuss

Convenience/Feasibility

size of a trial is determined by the number of "events"

- since recurrence/progression of cancer usually occurs before death
- PFS or DFS can be evaluated earlier and require less patients

Progression free survival

- Defining Disease Progression (when and how?)
- What does PFS mean for patients?
- Why do treatments that increase PFS fail to improve survival?
- Post-progression therapy debate (do you continue biologicals?)

Whose endpoint is it anyway?

- Important, relevant and meaningful to

- Pharma
- Investigators/clinicians
- Patients
- The FDA

Guidance for industry Clinical trials Endpoints for the approval of cancer drugs FDA, May 2007

“Overall survival is considered the most reliable cancer endpoint, and when studies can be conducted to adequately assess survival, it is usually the preferred endpoint.”

Endpoints in Drug Development

Early phase

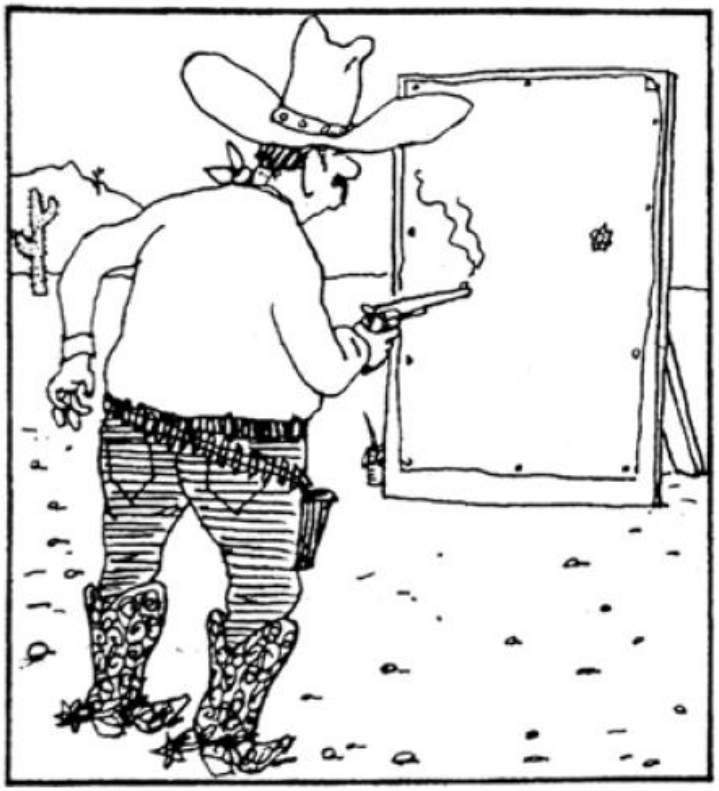
- Safety
- Evidence of activity
- Identifying potential indications

Late phase

- To confirm clinical benefit

The Texas sharpshooter

SHOOTS FIRST…



With thanks to Søren Laurberg

Outcomes

- Those that matter to HCPs/statisticians
- Those that matter to patients

"I won't mince words, Mrs. Horton, concerning your husband, we've had a negative patient-care outcome."

Outcomes can be positive or negative

- So should we poll patients to ask them to choose the most relevant endpoints?

Clinical Benefit

- Live longer (overall survival)
- Live longer without cancer (progression free siurvival)
- Live better (QOL)

- Safer
- Cheaper

Overall Survival (the "gold" standard for showing clinical benefit)

Definition	Time from randomisation to death from any cause (in ITT population)
Pros	• Measure of direct benefit • Easy to measure (unbiased) • Reliable and precise • Blinding not required
Cons	• May require large population and long follow-up • Includes deaths unrelated to cancer • Can be affected by crossover and subsequent treatment (eg checkpoint inhibitors) • Other endpoints may have intrinsic value
Censor	Last date subject was seen alive

Progression Free Survival

Definition	Time from randomisation to recurrence (in ITT population)
Pros	• Smaller population and shorter follow-up • Not affected by crossover or subsequent treatment (eg checkpoint inhibitors)
Cons	• ? Measure of direct benefit • Subject to assessment bias • Unreliable and imprecise • Blinding required • Need to balance radiological assessments
Censor	bias – if imbalanced withdrawal of patients who are censored prior to relapse or progression

Limitation of Progression free survival

- Focusses on a single line of treatment
- All that happens later is just ignored or considered as confounding factor

Disease Free Survival

Definition	Time from randomisation to recurrence (in ITT population)
Pros	• Smaller population and shorter follow-up • Not affected by crossover or subsequent treatment (eg checkpoint inhibitors)
Cons	• ? Measure of direct benefit • Subject to assessment bias • Unreliable and imprecise timing • Need to balance radiological assessments ie need standardized follow-up protocols
Censor	bias – if imbalanced withdrawal of patients who are censored prior to relapse or progression

Colostomy-free survival

- Primary outcome measure of the ACCORD-03 trial
- Secondary endpoint in ACT II and RTOG 9811

Colostomy-free survival

Definition	Time from randomisation to colostomy formation (in ITT population)
Pros	• Easy to define • Not affected by crossover or subsequent treatment (eg checkpoint inhibitors)
Cons	• ? Measure of direct benefit • Initial colostomy can be reversed but often not reversed • Colostomy can be formed both for recurrence and late effects
Censor	bias – if imbalanced withdrawal of patients who are censored prior to colostomy

Survival may depend on

- differences in risk factor prevalence
- adjustment for stage and other clinical factors
- adjustment for comorbidities, socioeconomic disadvantage and remoteness
- Adjustments for region
- Further treatments after progression
- Alternative medicines taken by large tranches of population (eg aspirin) -we don’t know about

Options for Survival

- Survival from all causes (masks the outcomes for cancer per se)

- Disease-specific /cancer specific survival (may be vulnerable to censoring bias)

  Unreliable information on cause of death.

  (Death certificates inaccurate).

- Relative survival

Relative Survival

<u>overall survival after diagnosis</u>

survival in a similar population (not diagnosed with that disease).

(A similar population is composed of individuals with at least age and gender similar to those diagnosed with the disease.)

Relative Survival

<u>overall survival after diagnosis</u>

survival in a similar population (not diagnosed with that disease).

(A similar population is composed of individuals with at least age and gender similar to those diagnosed with the disease.)

But requires credible life tables.

Options for Survival

- Survival from all causes (masks the outcomes for cancer per se)

- But if a treatment is toxic……and could cause deaths

Which do you think is the best option for Survival endpoint?

1. Survival from all causes (masks the outcomes for cancer per se)

2. Disease-specific survival (may be vulnerable to censoring bias)

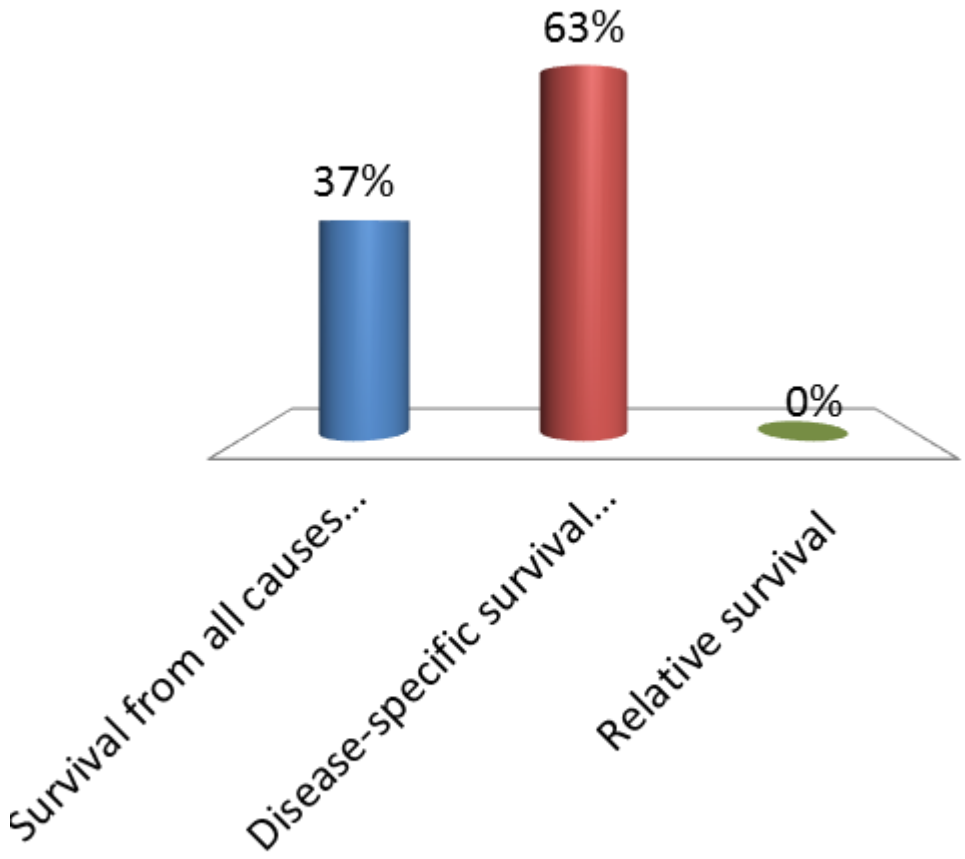
3. Relative survival

Which do you think is the best option for Survival endpoint?

A. Survival from all causes (masks the outcomes for cancer per se)

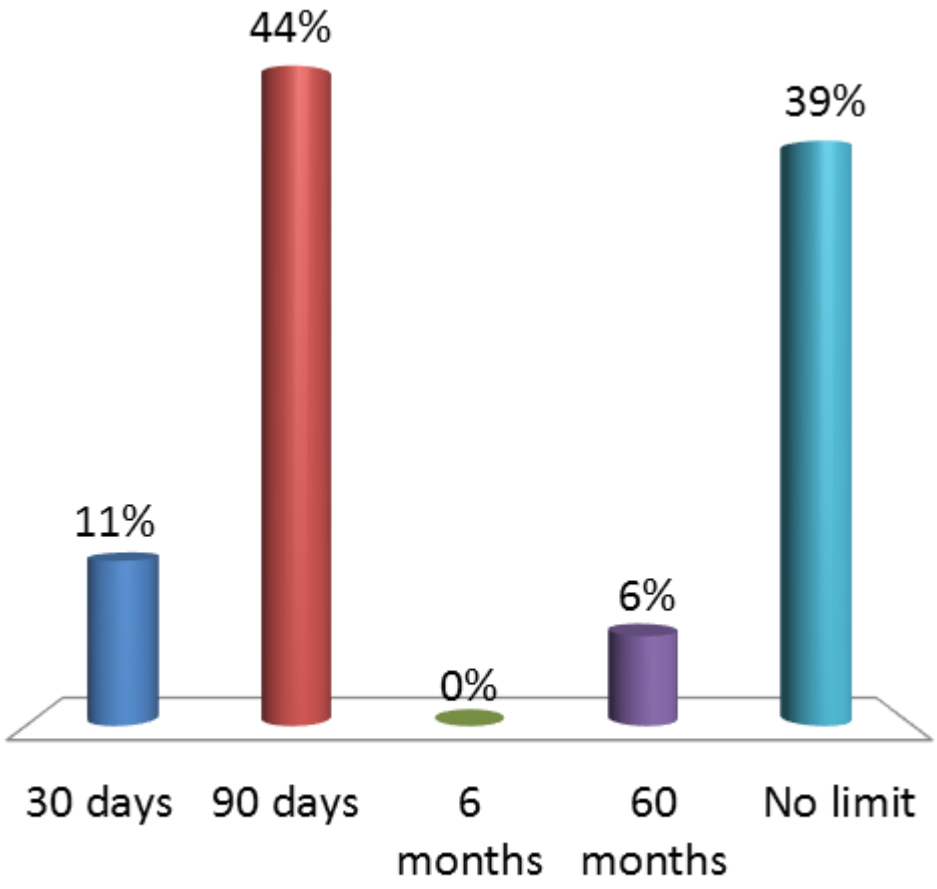
B. Disease-specific survival (may be vulnerable to censoring bias)

C. Relative survival



Should you have a time limit for death due to treatment after CRT?

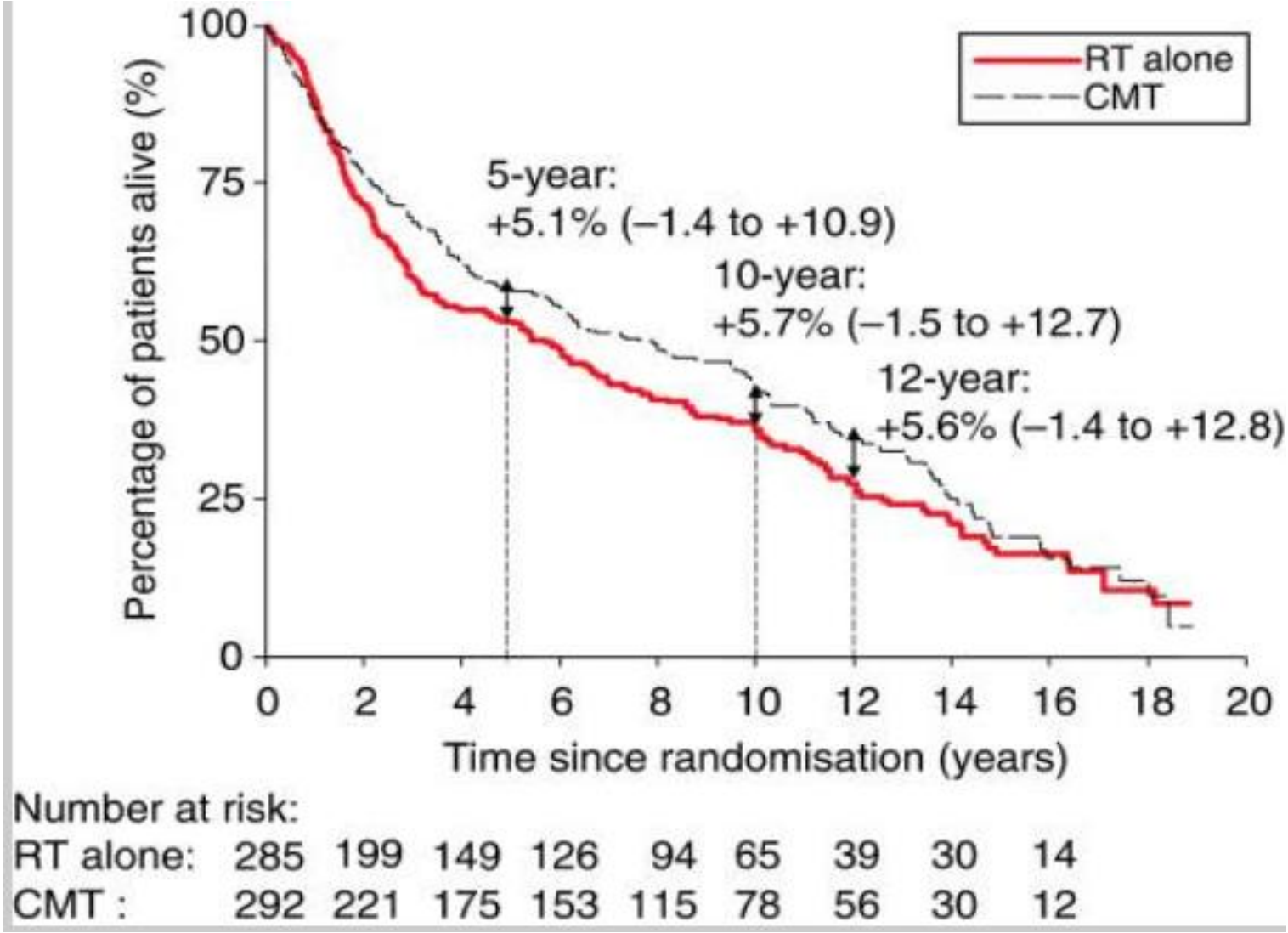
A. 30 days
B. 90 days
C. 6 months
D. 60 months
E. No limit



Options for Survival

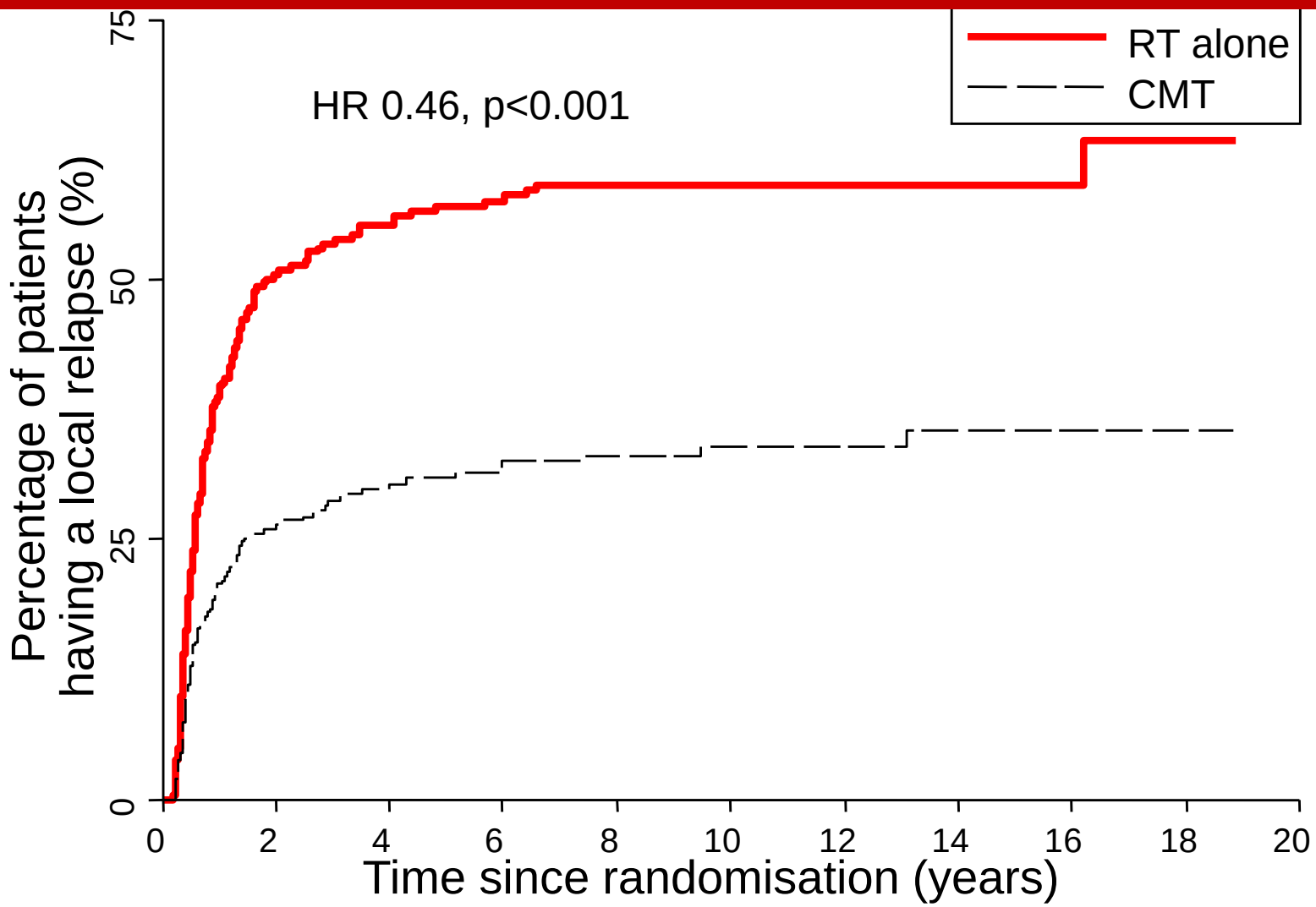
- Survival from all causes (masks the outcomes for cancer per se)
- Disease-specific survival (may be vulnerable to censoring bias)
- Relative survival

ACT I : Overall survival



Northover J et al Br J Cancer 2010;102(7):1123–8

ACT I :Time to first local relapse



Northover J et al Br J Cancer 2010;102(7):1123–8

- variable use of salvage treatments among centers or countries may have uncontrollable effects on overall survival benefits.

Why? competing risks

Needs to be adjusted

- for age,
- sex,
- year of diagnosis,
- Socio-economic status
- Remoteness
- Availability of surgical salvage/quality of hospitals

- Punt CJ et al., **Endpoints in adjuvant treatment trials: a systematic review of the literature in colon cancer and proposed definitions for future trials.** J Natl Cancer Inst. 2007 Jul 4;99(13):998-1003

Adjuvant treatment

- with the increasing number of effective salvage treatments available in many types of cancer,
- much longer follow-up is required to demonstrate that adjuvant treatments improve overall survival compared with other clinical endpoints

Adjuvant trials should include

- DFS
- RFS
- TTR
- TTF
- Cancer specific survival
- Overall survival

Punt CJ, **Endpoints in adjuvant treatment trials: a systematic review of the literature in colon cancer and proposed definitions for future trials**
J Natl Cancer Inst. 2007 Jul 4;99(13):998-1003

DFS

- Serves both as a surrogate endpoint
- and as an endpoint in itself

DFS

- Defined as the time from randomization to any event, (irrespective of cause)
- is the most informative endpoint for assessing the effect of treatment and therefore the most relevant to clinical practice.
- Accepted surrogate for OS in colon cancer adjuvant trials

- Not yet accepted in rectal cancer trials of CRT

DFS after CRT

DFS often counts the following as an event:

- non-complete response (nCR) (timed 4-18 weeks following CRT)
- New radiological local, nodal, pelvic or distant disease following a post CRT CR
- or death from any cause.

- ***Is this a meaningful endpoint for patients who have slow or no response, but are salvaged by surgery and thereafter have no clinical disease?***

Primary tumour

Surgery to recurrence is straightforward –tumour is removed - so definitely no tumour and first new evidence is event

Chemoradiation (CRT)

- Tumour disappears at some point
- Some never free from disease –so treatment failure - assume event occurs at randomisation
- Some disappears and then reappears

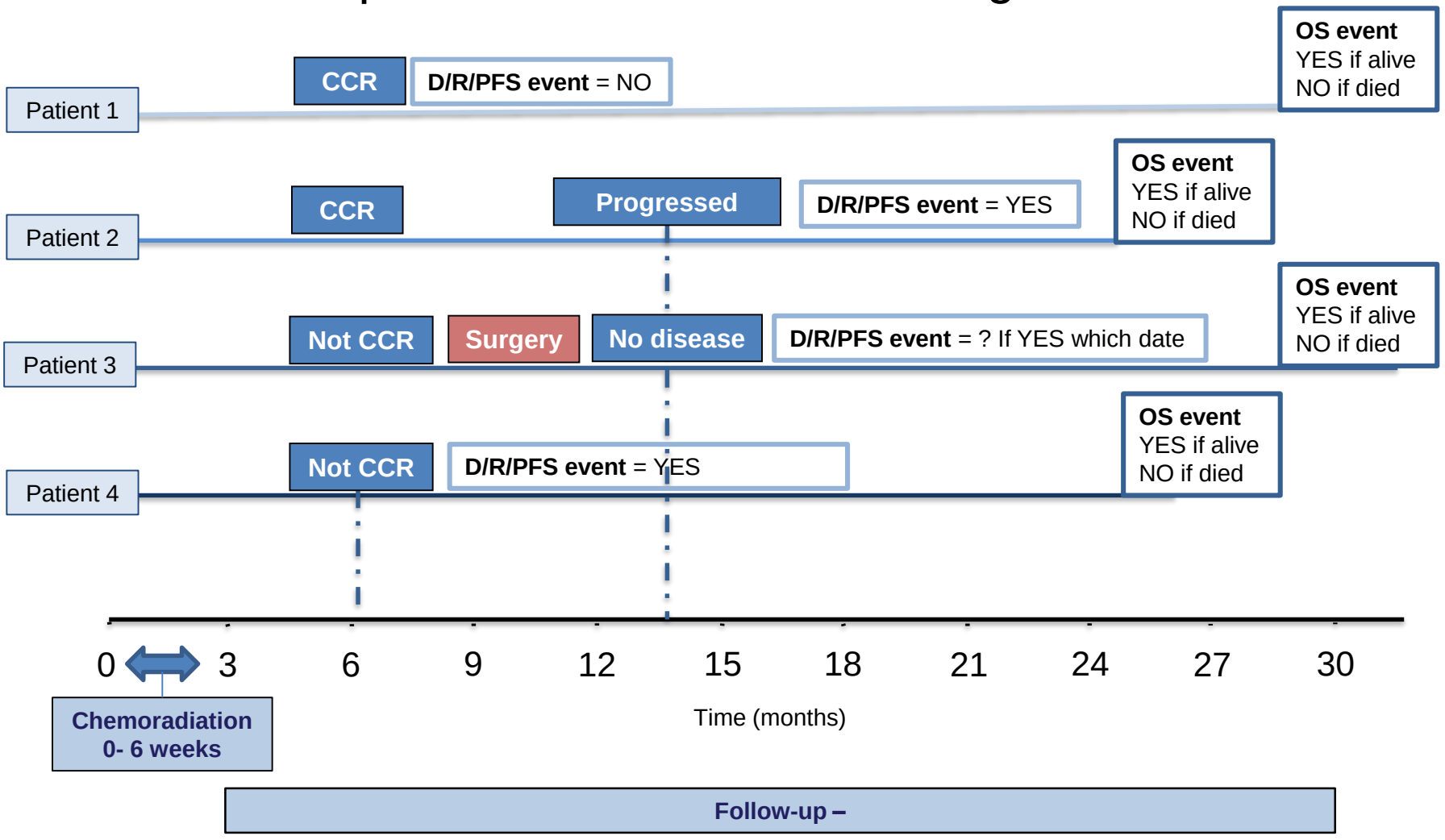
ie both an early and late pattern to loco-regional relapse /failure

DFS

- A positive biopsy may define the endpoint conclusively
- but a premature positive biopsy may indicate active tumour, which is actually destined to disappear if the tumour is observed for a longer period.

Glynne-Jones R et al. Lancet Oncology 2017; Mar;18(3):347-356.

Figure 1. Time-to-event outcomes in SCCA - possible outcomes for patients with SCCA following chemoradiation.



Surrogate endpoints

- Alternative early endpoint if validated
- Allows inference on the effect of an intervention on the long-term endpoint (survival)
- Rely on early response or growth of tumour (pCR etc..)

Prentice Criteria

- The treatment has an effect on survival time.
- The treatment has an effect on the surrogate.
- The surrogate is associated with survival time.
- The treatment effect on survival is captured by the surrogate.

ie a patient with a longer PFS/DFS will have a longer OS (correlation is insufficient)

PCR

- is almost immediately observable event, which dramatically reduces the time required until trial completion.

- An increase in the pCR rate objectively demonstrates efficacy of the agent against the primary tumour.

PCR

- The Radiation Therapy Oncology Group (RTOG) 0247 (A Randomized, Phase 2 Study of Neoadjuvant Radiation Therapy Plus Concurrent Capecitabine and Irinotecan or Capecitabine and Oxaliplatin for Patients With Locally Advanced Rectal Cancer)

PCR

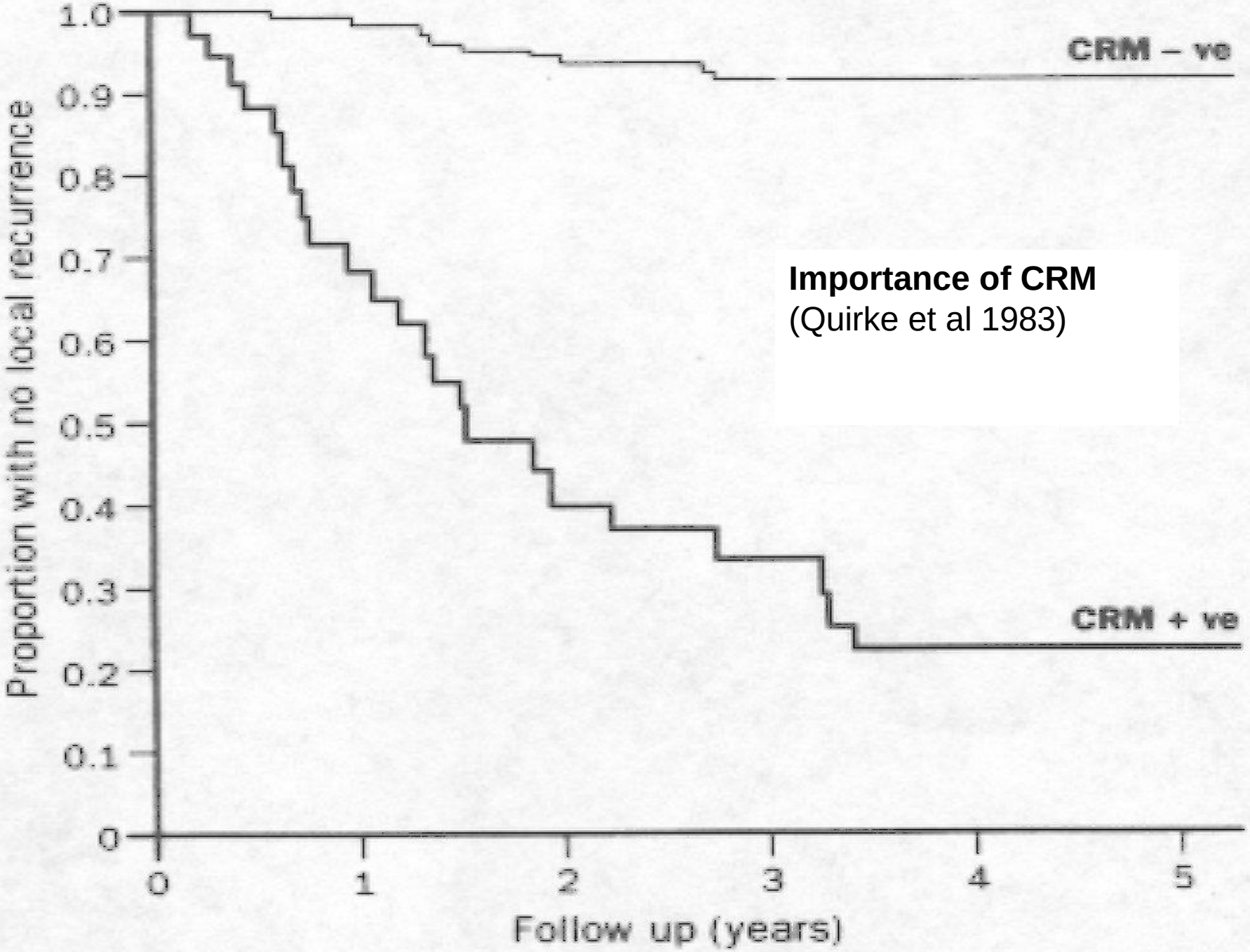
Capecitabine/oxaliplatin pCR = 21% (10/48)
capecitabine/irinotecan pCR = 10% (5/48)

so the irinotecan arm was rejected

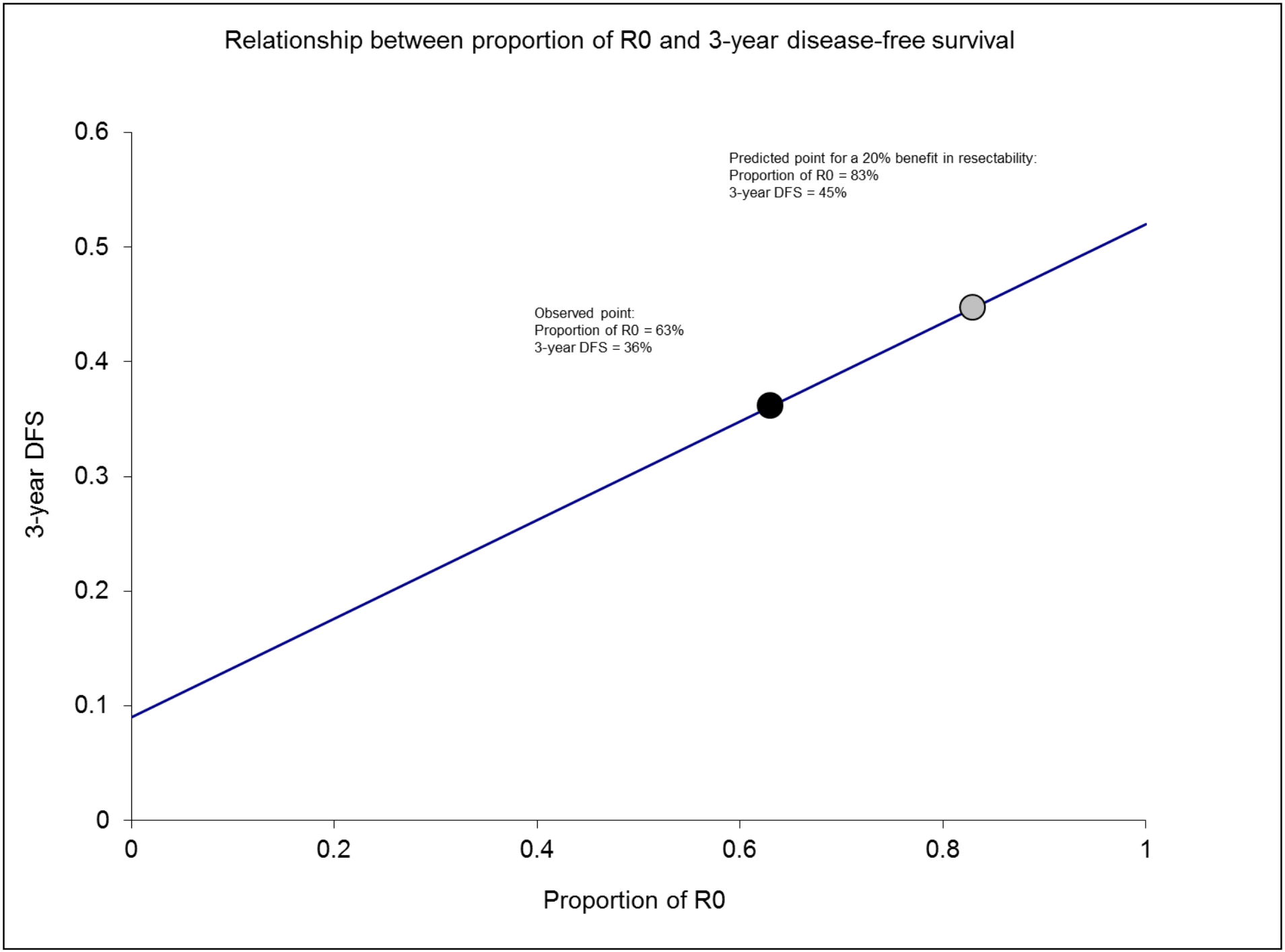
But long-term follow-up showed

- Numerically superior survival (4-year OS: 85% v 75%; P > .05)
- The 4-year DFS 68% versus 62%.

Wong SJ et al. IJROBP 2015; 91(1):116-123



Importance of CRM
(Quirke et al 1983)

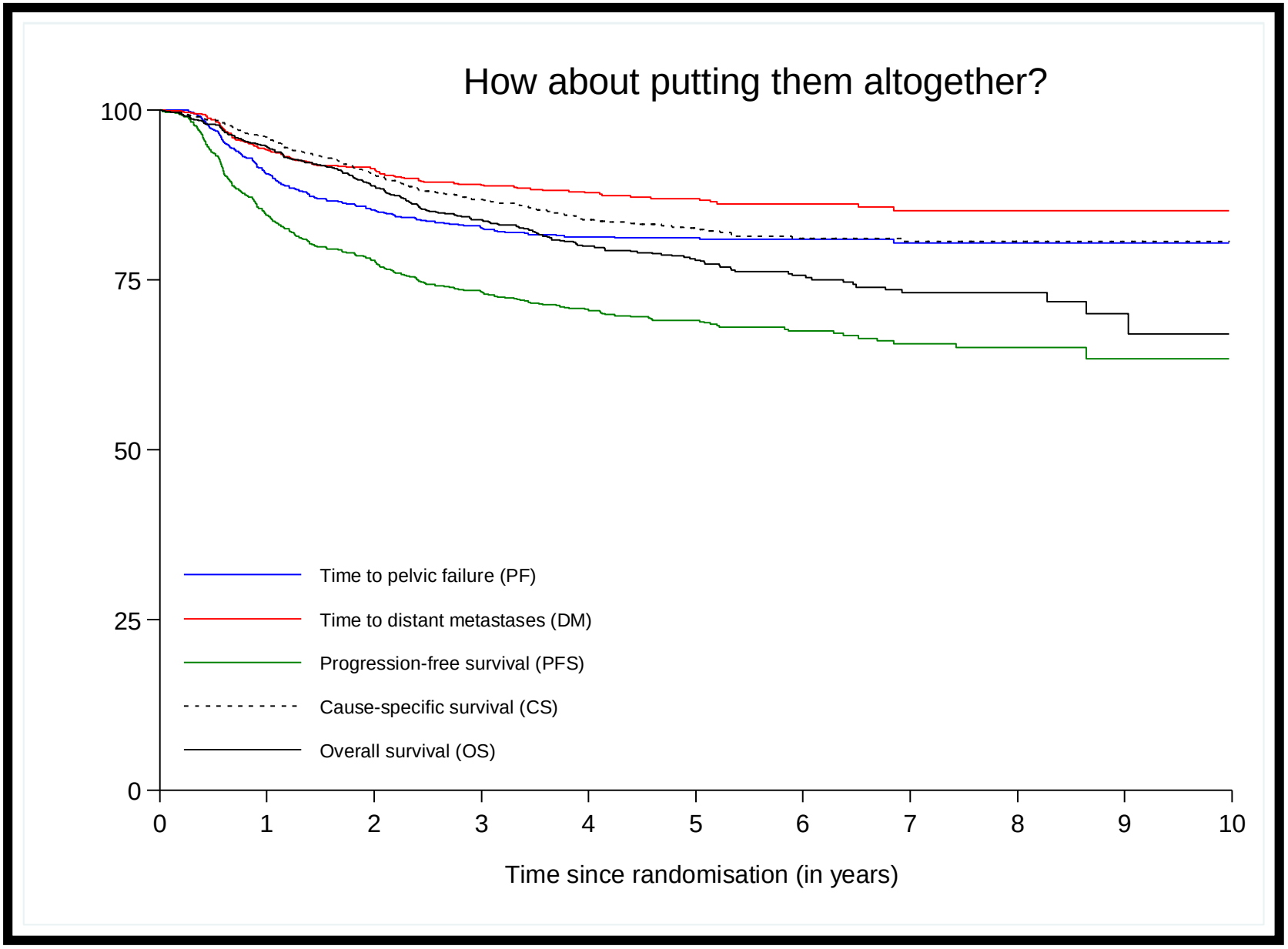

Relationship between proportion of R0 and 3-year disease-free survival
Predicted point for a 20% benefit in resectability:
Proportion of R0 = 83%
3-year DFS = 45%
Observed point:
Proportion of R0 = 63%
3-year DFS = 36%
3-year DFS
0.6
0.5
0.4
0.3
0.2
0.1
0
0
0.2
0.4
0.6
0.8
1
Proportion of R0

Novel endpoints

Imaging (mri TRG)

Imunological

- Immunoscore before and after treatment
- PD1
- TIL


How about putting them altogether?
100
75
50
25
0
0
1
2
3
4
5
6
7
8
9
10
Time since randomisation (in years)
Time to pelvic failure (PF)
Time to distant metastases (DM)
Progression-free survival (PFS)
Cause-specific survival (CS)
Overall survival (OS)

Conclusion

- The ideal objective for gauging success in future SCCA phase III trials should be anal dysfunction-free survival.

Conclusions /Recommendations

- Be wary of variations in named endpoints and what events they include
- Need a future consensus
- Editors of journals/clinicians/groups need to agree

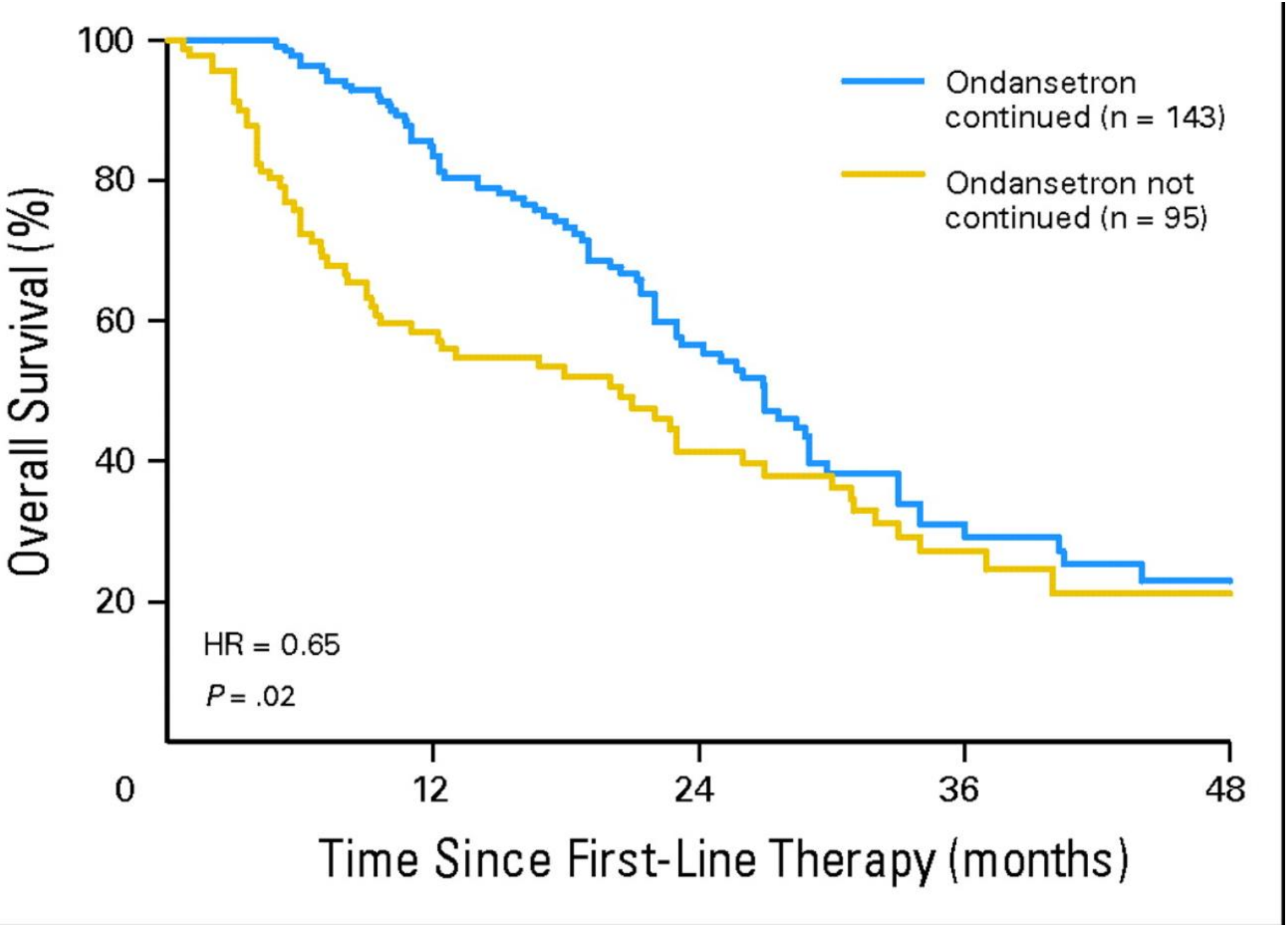

Thank you for listening

RTOG 9811 defined event free survival (EFS)

- time from date of registration to the date of death from any cause,
- first evidence of disease progression, evaluated as non-complete response (nCR) at the second evaluation after CR,
- undergoing colostomy
- or first evidence of second primary cancer,

whichever happens first.

- Axel Grothey No66c- bevacizumab trial continuing Bev post progression
- Criticized by Kopetz


100
80
60
40
20
0
12
24
36
48
Overall Survival (%)
Time Since First-Line Therapy (months)
Ondansetron continued (n = 143)
Ondansetron not continued (n = 95)
HR = 0.65
P = .02

HAZARD RATIOS

- OS, DFS and PFS report difference between experimental/control curves as Hazard Ratio (HR).

i.e. ratio between events occurring in any given time interval with experimental compared to control treatment is constant

- HR may not be meaningful if survival curves are not of similar shape
- If HR <1 and the 95% confidence interval excludes 1, there is a statistically significant effect of the experimental treatment as compared to control.

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Multidisciplinary set-up in Lymphomas

Haemato-pathology

Radiology,
Nuclear Medicine

Medical Oncology,
Haematology,
Clinical Oncology

Radiation Oncology,
Clinical Oncology

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How many new cancer patients in Europe will require radiotherapy by 2025? An ESTRO-HERO analysis

Josep M. Borras [a,*], Yolande Lievens [b], Michael Barton [c], Julieta Corral [d], Jacques Ferlay [e], Freddie Bray [e], Cai Grau [f]

≈ **3.4 million** new cancer patients in **2012**

≈ **4.0 million** new cancer patients in **2025** **(+15.9%)**

Radiotherapy "evidence-based" Optimal Utilization Proportion (OUP):

≈50%

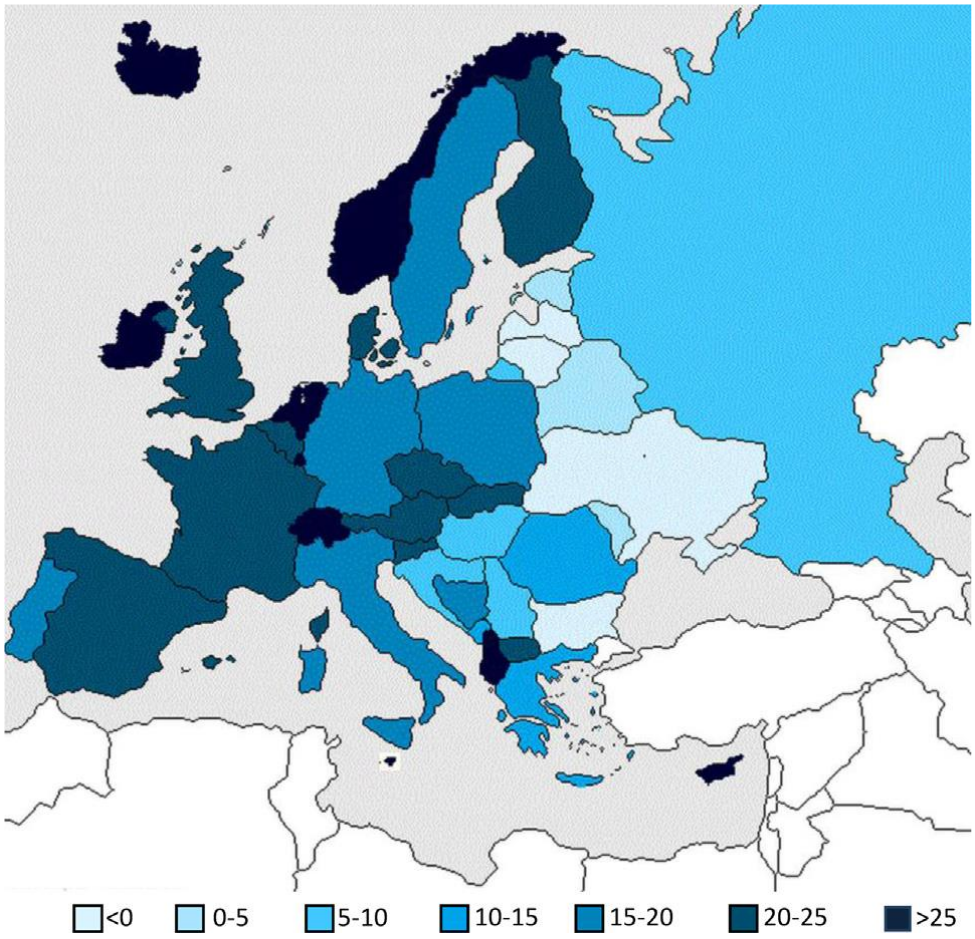

Fig. 1. Increase in new cancer patients that would require radiotherapy by 2025 by country (%).

Radiotherapy need for lymphoma patients

Cancer cases with an evidence based Indication for RT in 2012 and 2025 in Europe (most important tumor sites)

Tumor site	2012	2025
Breast	396.891	437.415 (+10.2%)
Lung	315.197	371.755 (+17.9%)
Prostate	243.669	303.162 (+24.4%)
Head&Neck	108.194	121.531 (+12.3%)
Rectum	99.493	117.807 (+18.4%)
Lymphoma	***74.852***	***84.723 (+13.2%)***

Top 5 ranking by absolute number of cancer patients requiring RT in 2025

Country	First	Second	Third	Fourth	Fifth
Belgium	Breast	Lung	Prostate	Bladder	Head&Neck
Czech Repubic	Breast	Lung	Prostate	Rectum	Head&Neck
France	Prostate	Breast	Lung	Head&Neck	Lymphoma
Germany	Breast	Prostate	Lung	Rectum	Head&Neck
Italy	Breast	Lung	Prostate	Rectum	Lymphoma
Poland	Lung	Breast	Prostate	Head&Neck	Bladder
Russia	Breast	Lung	Prostate	Head&Neck	Rectum
Spain	Lung	Breast	Prostate	Rectum	Head&Neck
Sweden	Prostate	Breast	Lung	Rectum	Lymphoma
Switzerland	Prostate	Breast	Lung	Lymphoma	Head&Neck
The Netherlands	Breast	Lung	Prostate	Rectum	Lymhpoma
United Kingdom	Breast	Lung	Prostate	Lymphoma	Rectum

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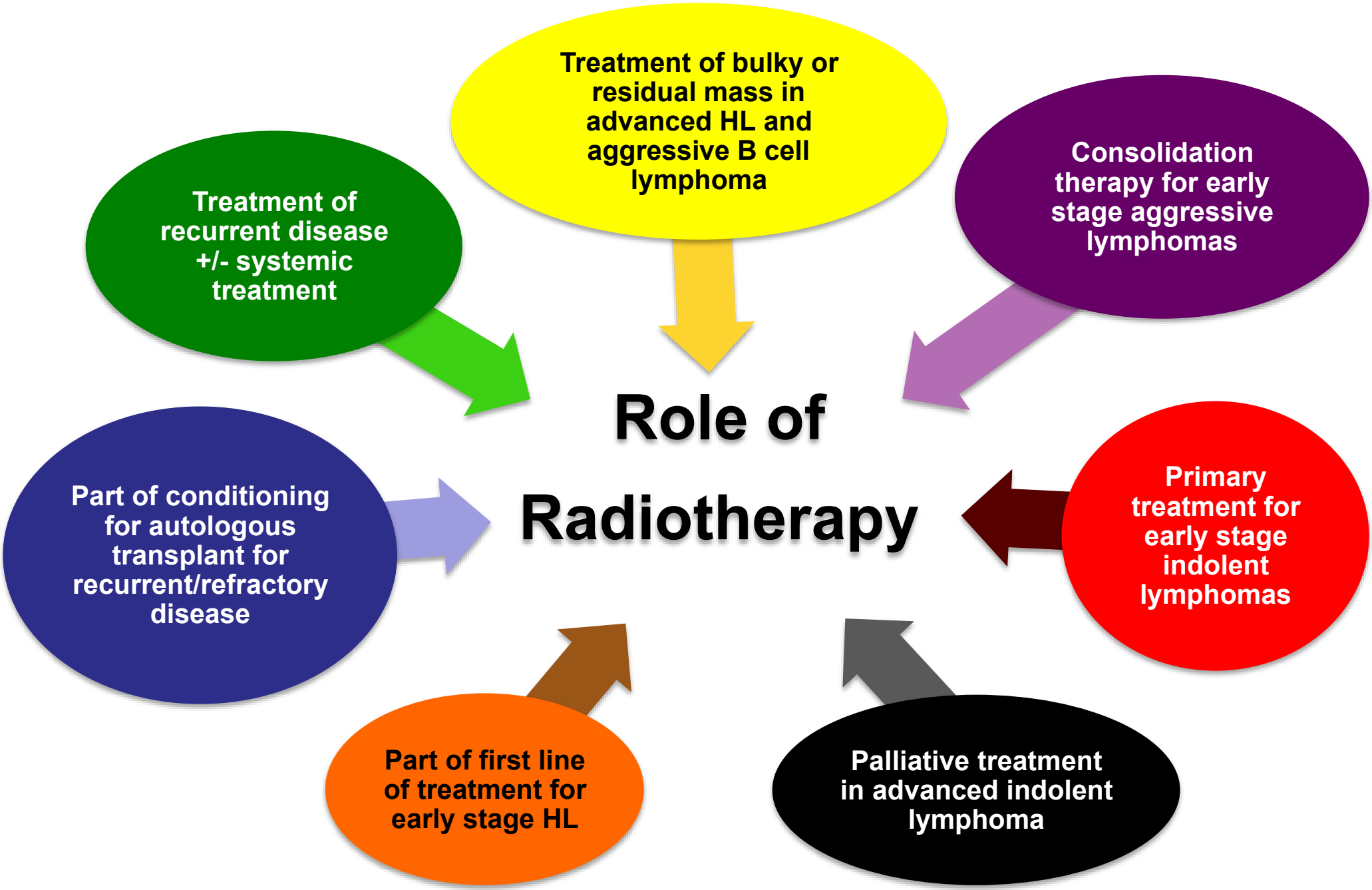
Borras JM. et al. Radiot & Oncol 2016



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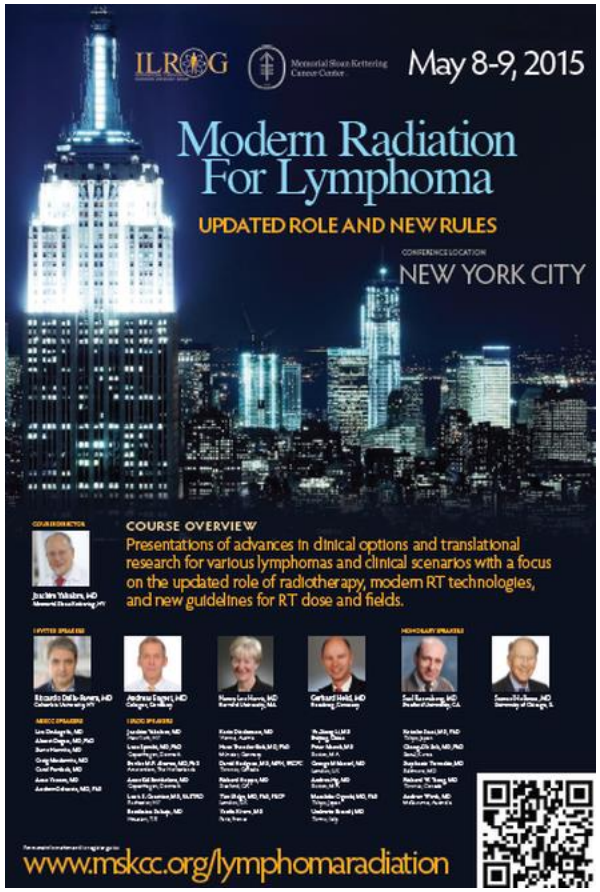
New York, USA
LENA SPECHT, M.D., PhD
Vice Chair, ILROG
Copenhagen, Denmark

ILROG
INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

- **Promoting Education and Collaboration on Radiotherapy for Lymphoma**
- **Worldwide organization, steering committee members from Europe, America, Asia, and Australia**
- **Webpage: www.ilrog.org**

• Developing guidelines for radiotherapy



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EDITORIAL

The Red Journal's Top Downloads of 2015

Anthony L. Zietman, MD, FASTRO

Editor-in-Chief

Table 1 Top Red Journal articles downloaded via ScienceDirect in 2015

Rank	Year	Article title	Reference
1	2015	Modern Radiation Therapy for Extranodal Lymphomas: Field and Dose Guidelines from the International Lymphoma Radiation Oncology Group	(7)
2	2015	Phase 3 Trials of Stereotactic Radiosurgery with or without Whole-Brain Radiation Therapy for 1 to 4 Brain Metastases: Individual Patient Data Meta-Analysis	(8)
3	2014	Modern Radiation Therapy for Hodgkin Lymphoma: Field and Dose Guidelines from the International Lymphoma Radiation Oncology Group (ILROG)	(9)
4	2008	Development and Validation of a Standardized Method for Contouring the Brachial Plexus: Preliminary Dosimetric Analysis Among Patients Treated with IMRT for Head-and-Neck Cancer	(18)
5	2015	Modern Radiation Therapy for Primary Cutaneous Lymphomas: Field and Dose Guidelines from the International Lymphoma Radiation Oncology Group	(10)
6	2011	Consensus Guidelines for Delineation of Clinical Target Volume for Intensity-Modulated Pelvic Radiotherapy for the Definitive Treatment of Cervix Cancer	(19)
7	2014	Modern Radiation Therapy for Nodal Non-Hodgkin Lymphoma—Target Definition and Dose Guidelines From the International Lymphoma Radiation Oncology Group	(11)
8	2015	Expert Consensus Contouring Guidelines for Intensity Modulated Radiation Therapy in Esophageal and Gastroesophageal Junction Cancer	(12)
9	2010	Use of Normal Tissue Complication Probability Models in the Clinic	(20)
10	2004	Review of Epidermal Growth Factor Receptor Biology	(21)

Modern RT in lymphoma

- Radiation therapy has **changed dramatically** over the last few decades in terms of both irradiated volumes and dose

- **Smaller** treatment volumes, **lower** radiation dose and **advanced** conformal radiotherapy can certainly allow a safer radiation delivery, when/if needed (!!!)

❑Early stage HL

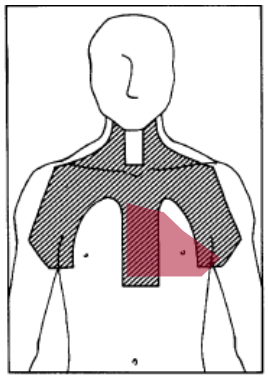
- Without risk factors (Favourable)
- With risk factors (Unfavourable or Intermediate)

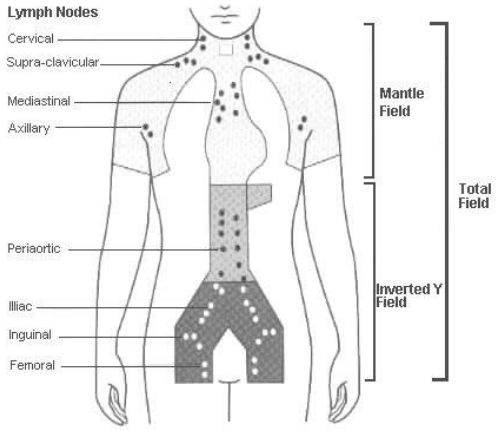
❑Advanced stage HL

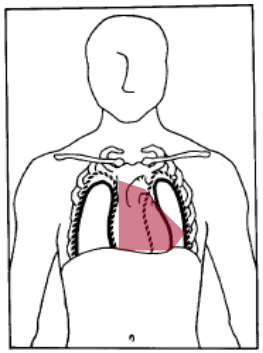
❑Relapsed/Refractory HL

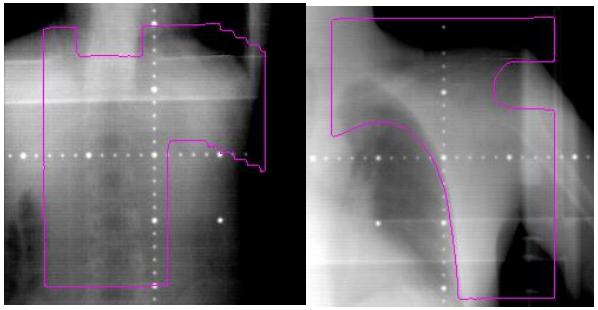
❑Non Hodgkin Lymphoma

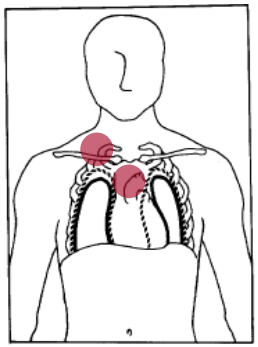
Timeline of major changes in RT in Hodgkin's Lymphoma

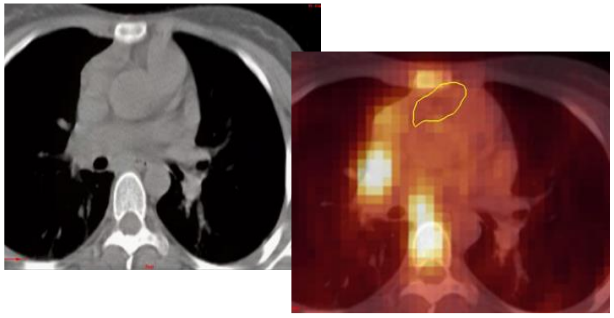












1960

Extended fields

DFT≈40 Gy

MOPP

Involved fields

DFT≈30 Gy

ABVD

Involved node(s)

DFT≈20 Gy

Now

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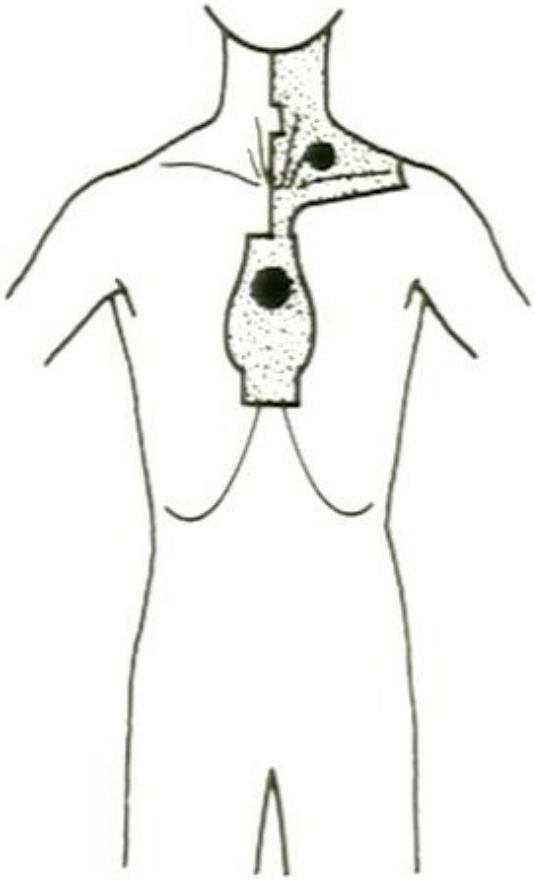
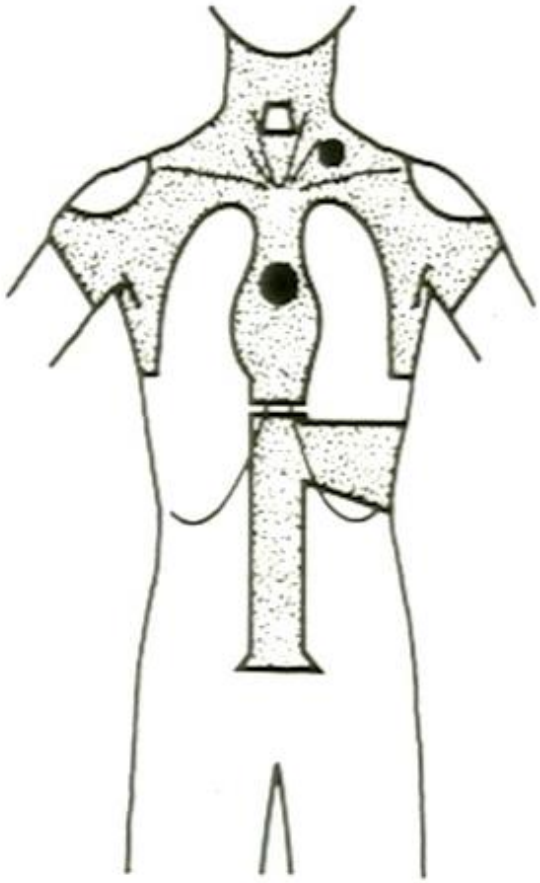
RT in classical Hodgkin Lymphoma

- In most HL patients, RT is used in combination with chemotherapy
- Chemotherapy has evolved with increasing efficacy to play a major role in the management of HL
- RT continues to have an important place in ensuring locoregional control and improving overall outcome in the combined modality treatment programs for HL

HODGKIN'S DISEASE
STANFORD RANDOMIZED CLINICAL TRIAL
CLINICAL STAGES I & II

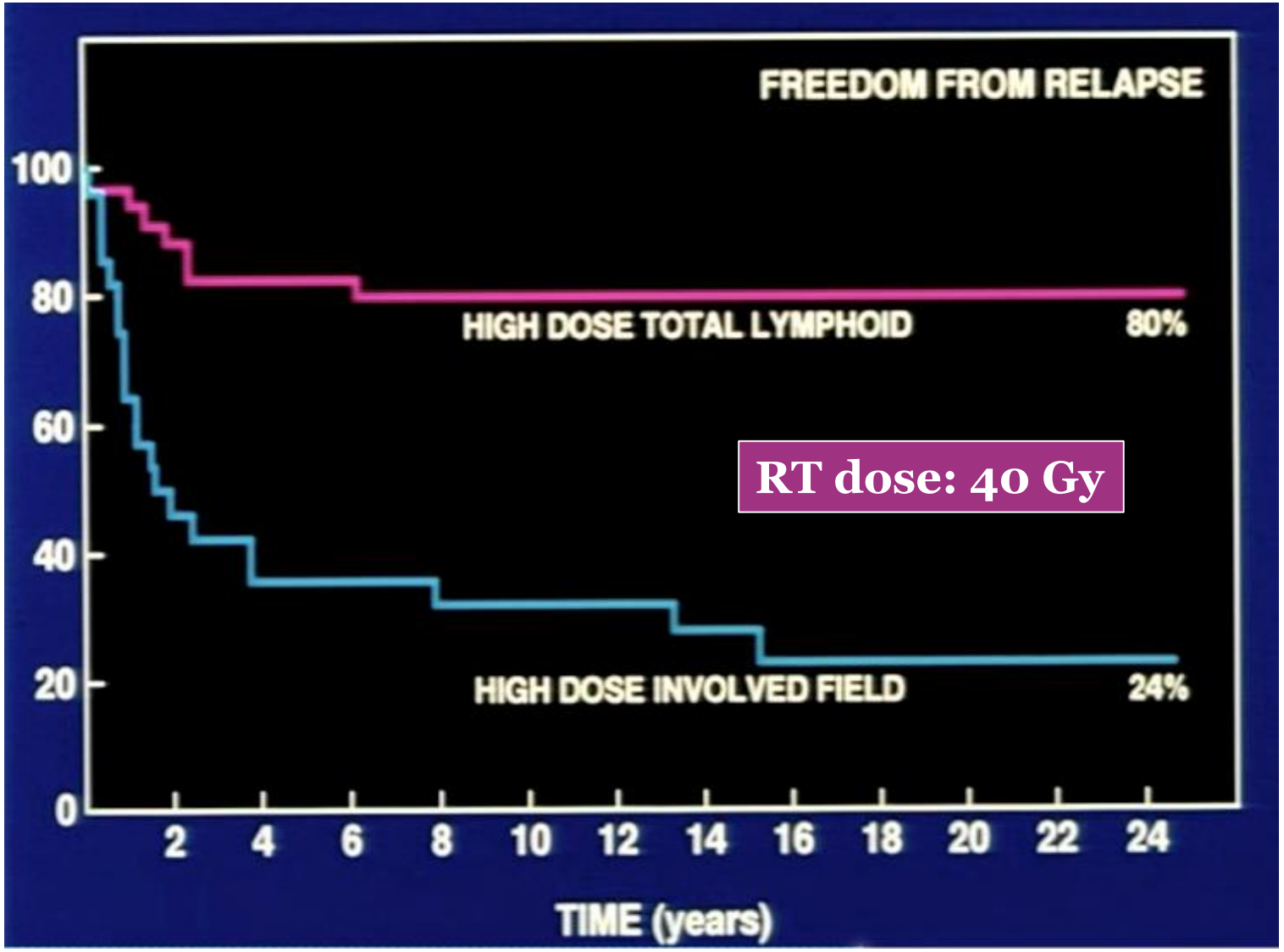


INVOLVED FIELD IRRADIATION
L-1-A



EXTENDED FIELD IRRADIATION
L-1-B

Hodgkin's Disease – Stanford Clinical Trial (late '60)
Stage I-IIA IF vs (S)TLI



RT dose: 40 Gy

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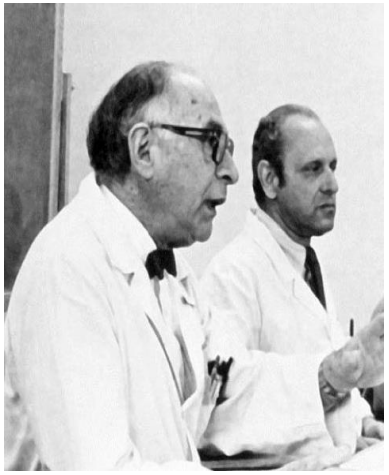
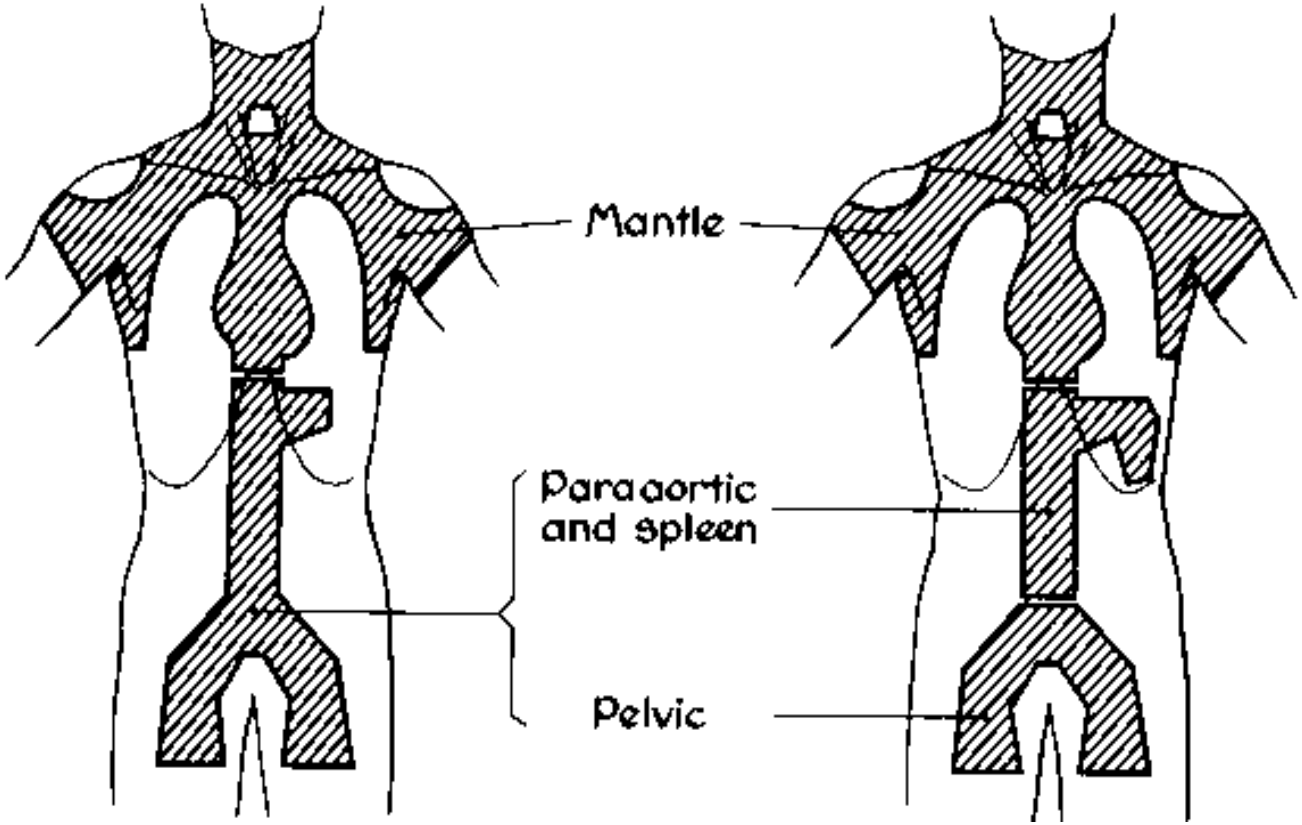
Prophylactic irradiation of clinically uninvolved regions → extended field RT



1960-1980



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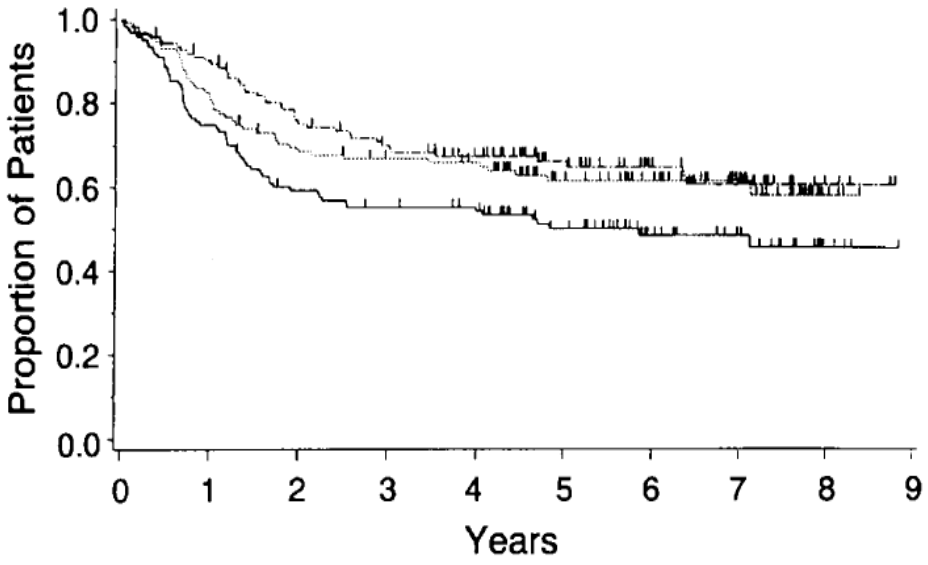
Effective chemotherapy was developed

FFS



Regimen	No. of Patients	No. (%) of Treatment Failures	Median Survival
MOPP	123	62 (50)	4.84
ABVD	115	44 (38)	None
MOPP–ABVD	123	43 (35)	None
All	361	149 (41)	—

Figure 1. Failure-free Survival According to Primary Chemotherapeutic Regimen.

OS

noted (P = 0.28). In the column for median years of survival, none indicates that the median survival has not yet been reached.

years old or who have Stage IV disease with two or more extranodal sites (five-year failure-free survival, 45 percent). The statistical power to detect a difference between regimens according to risk group was small (78 percent) because of the size of the sample. The failure rate for MOPP in the low-risk group was 36 percent (24 of 67 patients), as compared with 57 percent (38 of 67) in the high-risk group; the rates were 31 percent and 38 percent, respectively, for ABVD.

Toxicity

The short-term toxic effects of each regimen are summarized in Table 4. There were significant differences in the extent of hematologic toxicity noted with each regimen. In the two groups treated with

Canellos et al. NEJM 1992; 327:

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In the Era of Combined Modality therapy Bigger is not Better (Radiation Fields)

Milan Trial

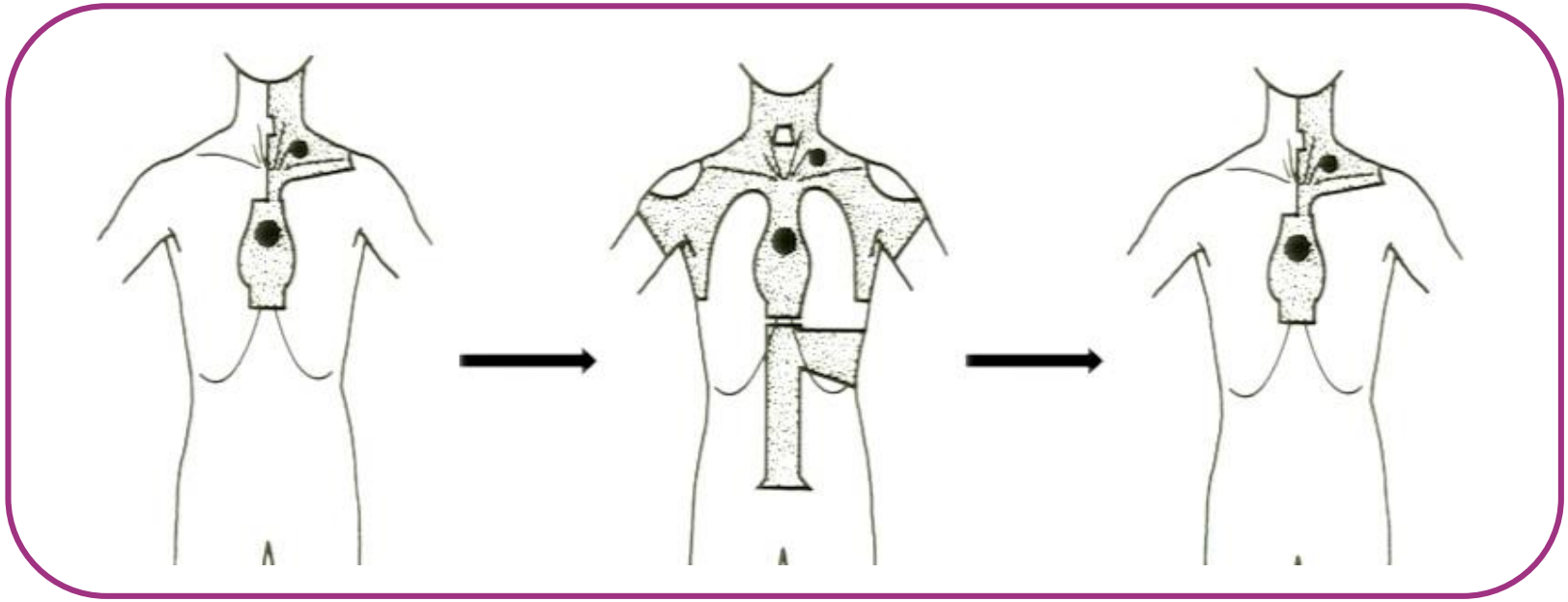
Bonadonna et al. J Clin Oncol 2004; 22(14):2835-2841

EORTC H8

Ferme et al. N Engl J Med. 2007; 357(19):1916-1927

GHSG HD8

Engert et al. J Clin Oncol 2003; 21(19):3601-3608



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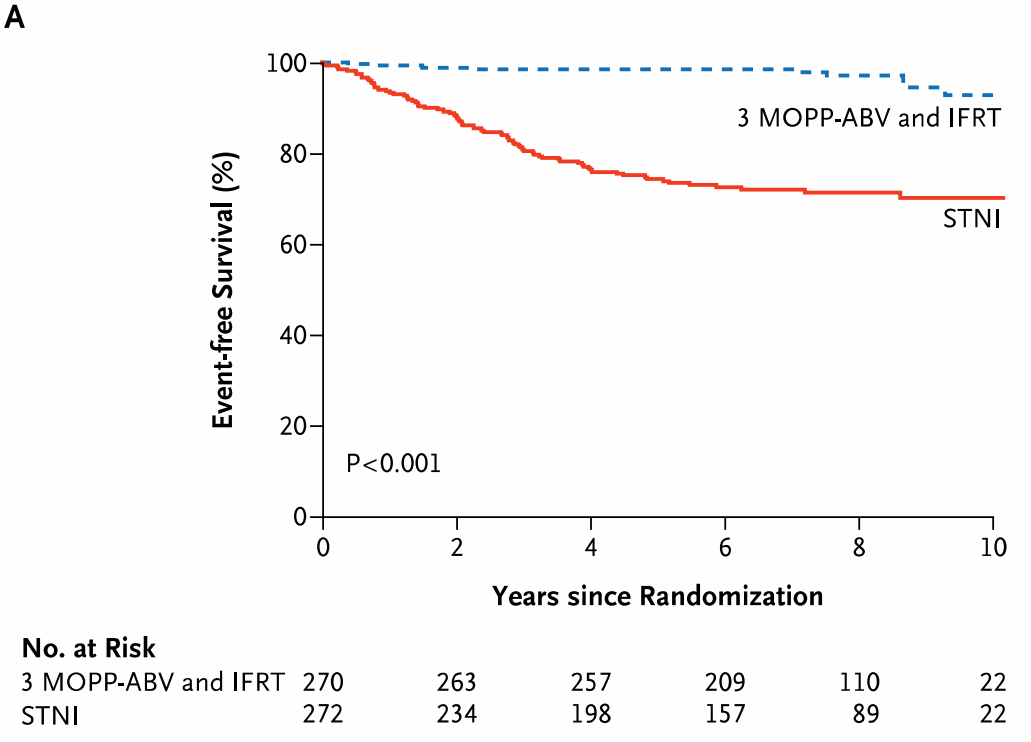
EORTC H8F trial

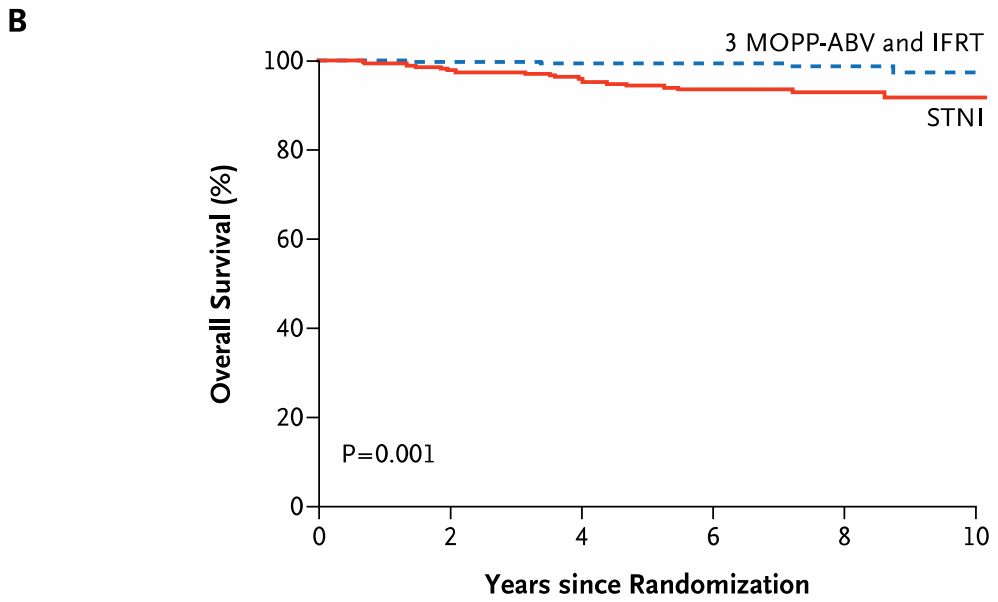
FFTF for pts with early favorable HL

EFS



No. at Risk						
3 MOPP-ABV and IFRT	270	263	257	209	110	22
STNI	272	234	198	157	89	22

OS



No. at Risk						
3 MOPP-ABV and IFRT	270	265	259	211	111	24
STNI	272	260	249	202	119	30

Ferme et al NEJM 2007

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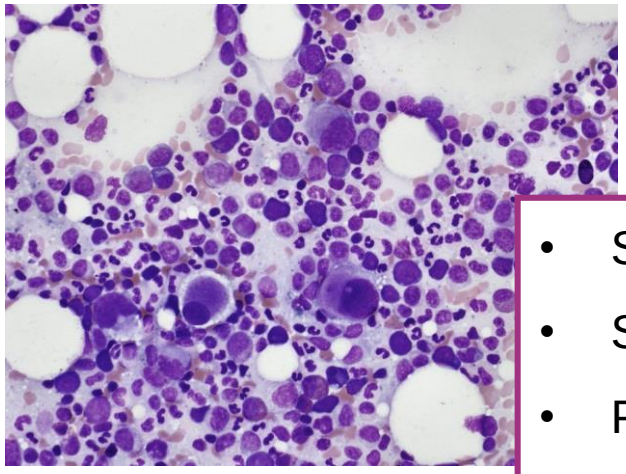
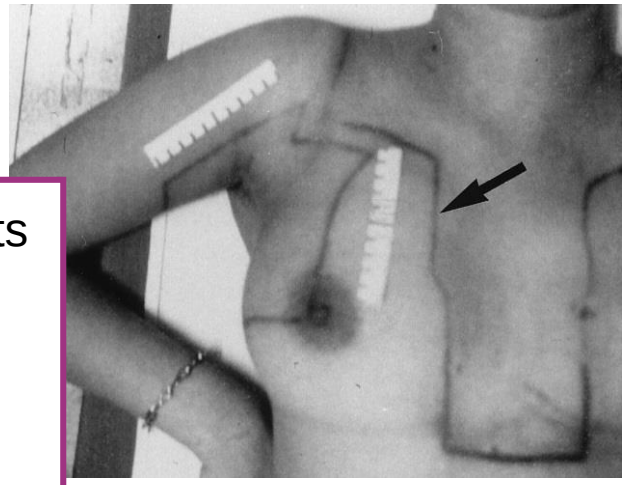
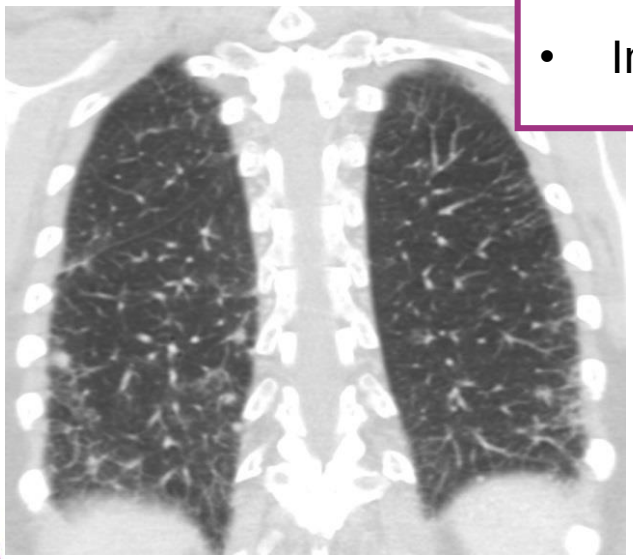
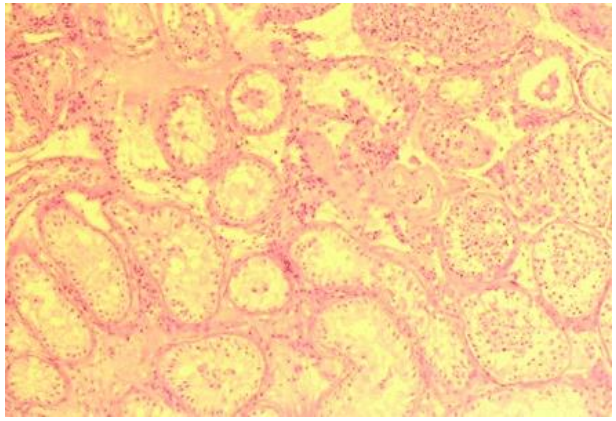
Late effects to avoid as cures increase

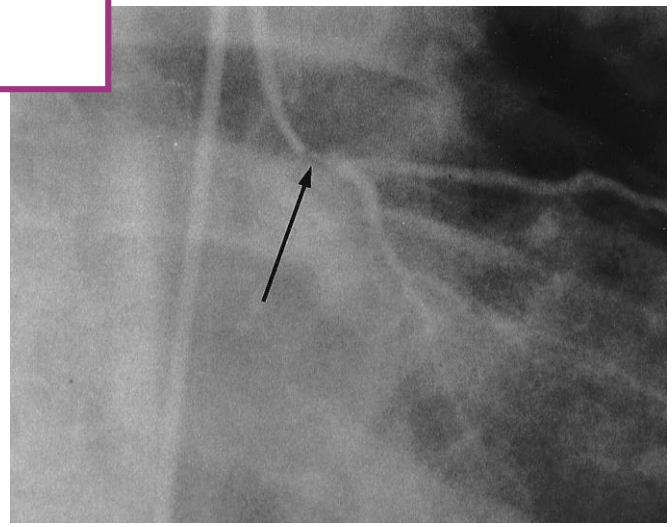




- Secondary MDS/AML from alkylating agents
- Solid tumours from extended field radiation
- Pulmonary fibrosis from bleomycin
- Heart disease from mediastinal irradiation and doxorubicin
- Infertility from alkylating agents







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Hypothesis: Is more dose better?

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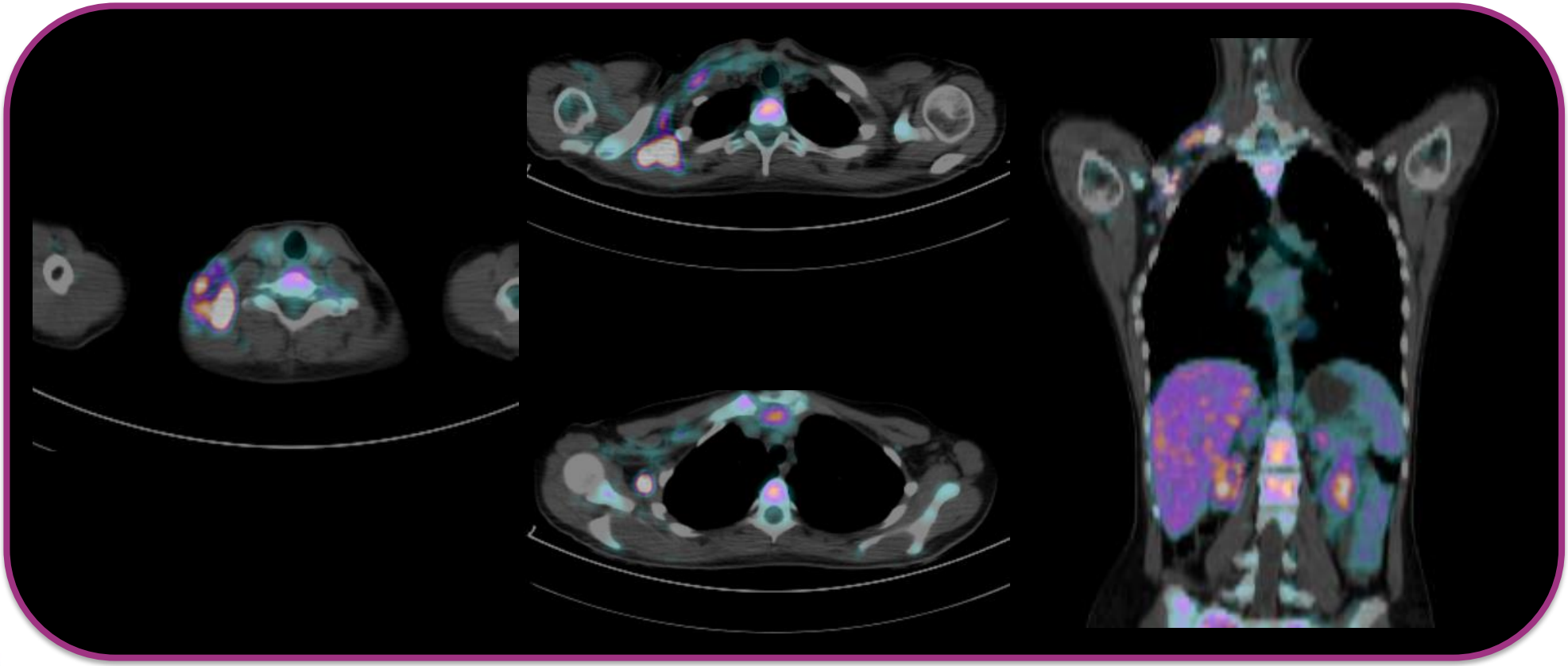
CLINICAL CASE #1 – Early stage HL

- N.M. 18 years old, female, no B symptoms reported
- Right neck, supraclavicular and right axillary lumps
- Excisional biopsy of a right neck lymph node: cHL, CD30+, CD20-
- Erythrocyte sedimentation rate (ESR) = 8



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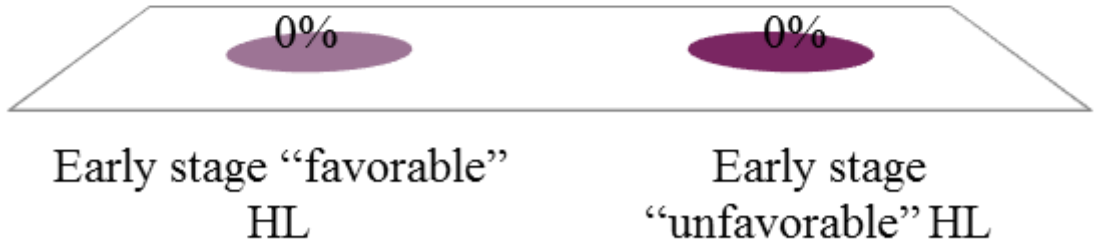
How do you classify this patient ?

A. Early stage “favorable” HL

B. Early stage “unfavorable” HL



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Early stage Hodgkin Lymphoma
RISK FACTORS

	GHSG	EORTC	NCIC and ECOG	Stanford
Risk factors	a) Large mediastinal mass b) Extranodal disease c) ESR ≥ 50 without B-symptoms or ≥30 with B-symptoms d) ≥ 3 nodal areas	a) Large mediastinal mass b) Age ≥50 years c) ESR ≥ 50 without B-symptoms or ≥ 30 with B-symptoms d) ≥ 4 nodal areas	a) Histology other than LP/NS b) Age ≥ 40 years c) ESR ≥ 50 d) ≥ 4 nodal areas	a) B-symptoms b) Large mediastinal mass
Favourable	CS I-II without risk factors	CS I-II without risk factors	CS I-II without risk factors	CS I-II without risk factors
Unfavourable	CS I or CS IIA with ≥ 1 risk factors CS IIB with c) or d) but without a) and b)	CS I-II with ≥ 1 risk factors	CS I-II with ≥ 1 risk factors	CS I-II with ≥ 1 risk factors

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How would you treat her ?

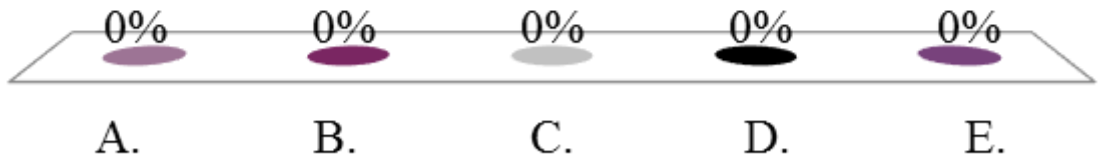
A. **ABVD x 4 followed by ISRT 30 Gy**

B. **ABVD x 2 followed by ISRT 20 Gy**

C. **BEACOPP x 2 + ABVD x 2 followed by ISRT 30 Gy**

D. **ABVD x 3**

E. **ABVD alone (3-4 cycles) in patients with "interim" PET –ve findings and ABVD + ISRT 30 Gy in patients with "interim PET +ve findings**



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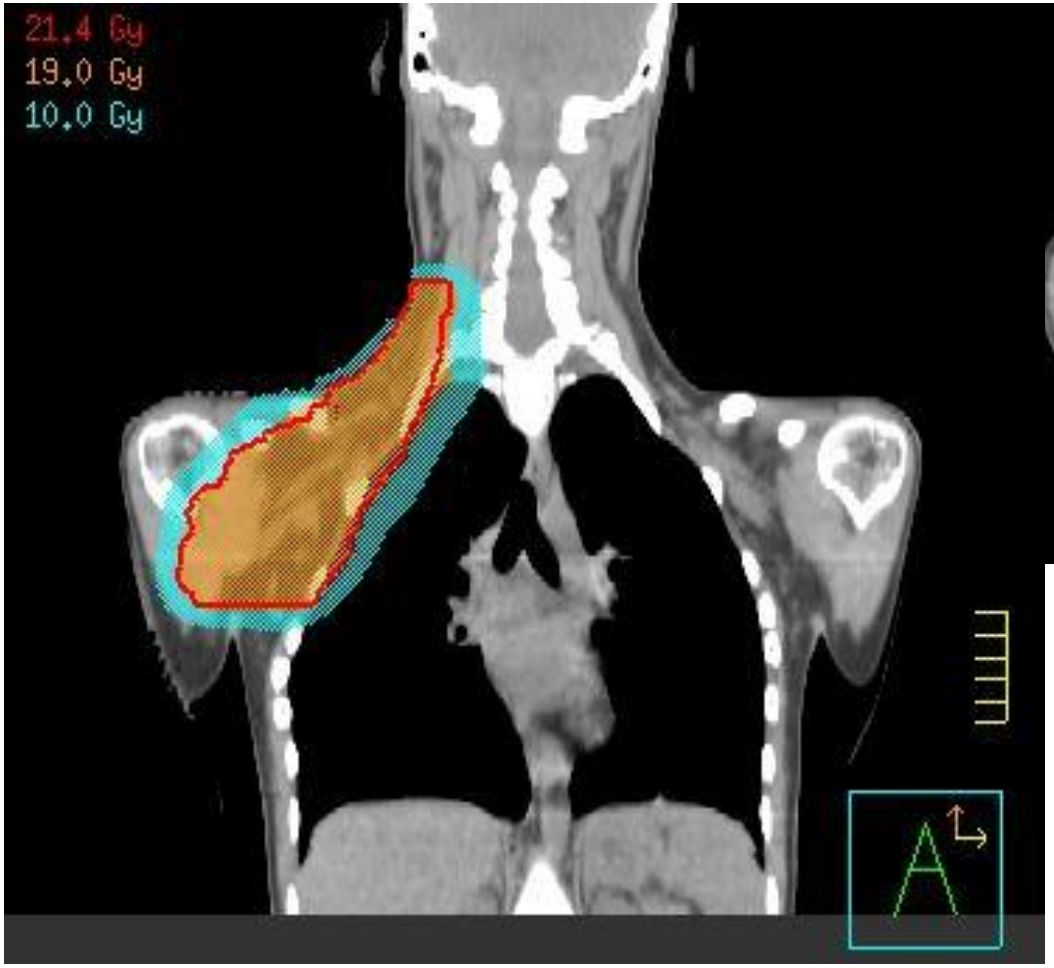
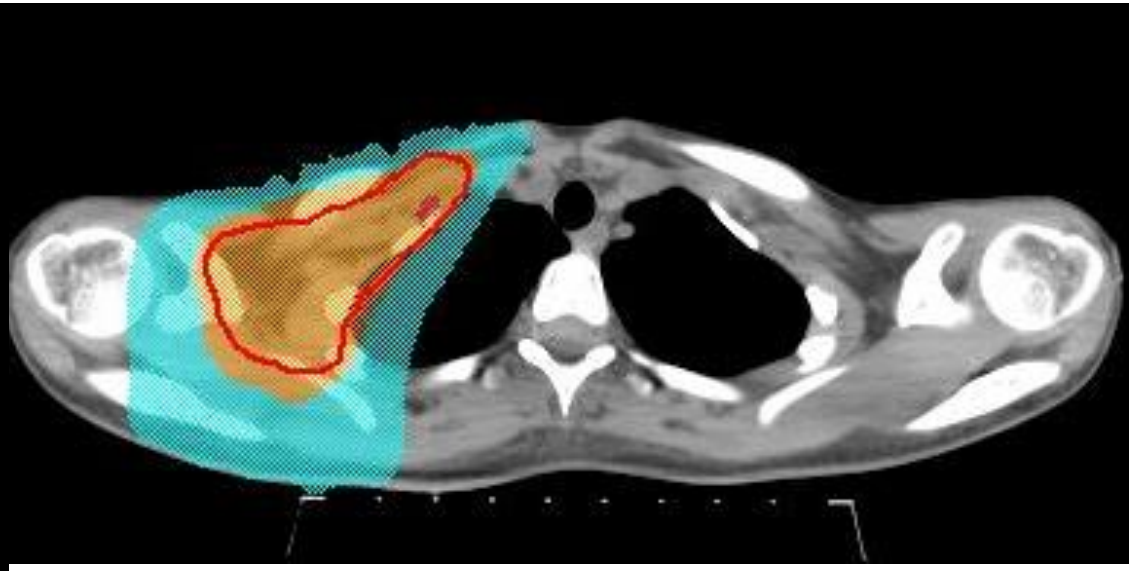
- **Stage IIA favorable** (VES 8)
- ABVD x 2 (completed 21.11.2016) → PET2: complete metabolic response (DS1)





ROI Statistics:

- **RT dose to PTV: 20 Gy/10 fractions**
- Right breast **MAX dose: 0.814 Gy**
- Left breast **MAX dose: 0.222 Gy**
- Thyroid gland **MAX dose: 6.590 Gy**
- Right lung **MEAN dose: 2.909 Gy**

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German HD 10 study:
reducing therapy in early favourable disease

- **1370 pts 1998-2003**
- **Early Favourable disease: I_A/II_A**

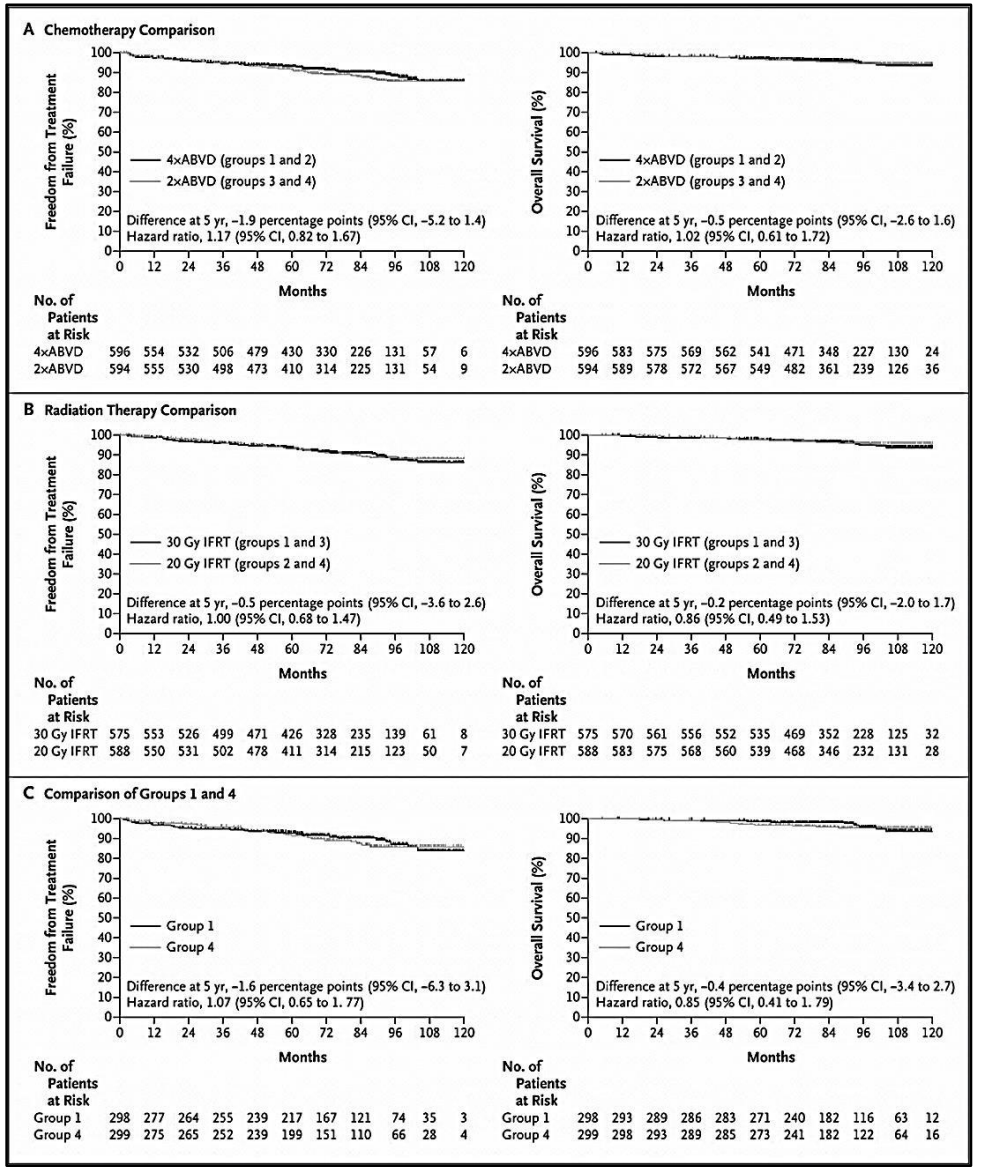
ABVD

2 cycles 4 cycles

Involved field RT

20 Gy 30 Gy

Results equivalent for all 4 arms: 5yr FFTF 92% OS 97%



Engert A et al. N Engl J Med 2010;363

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German HD 11 Study:
Lower threshold of therapy for early unfavourable disease

- **1395 pts 1998-2003**
- **Early Unfavourable disease**

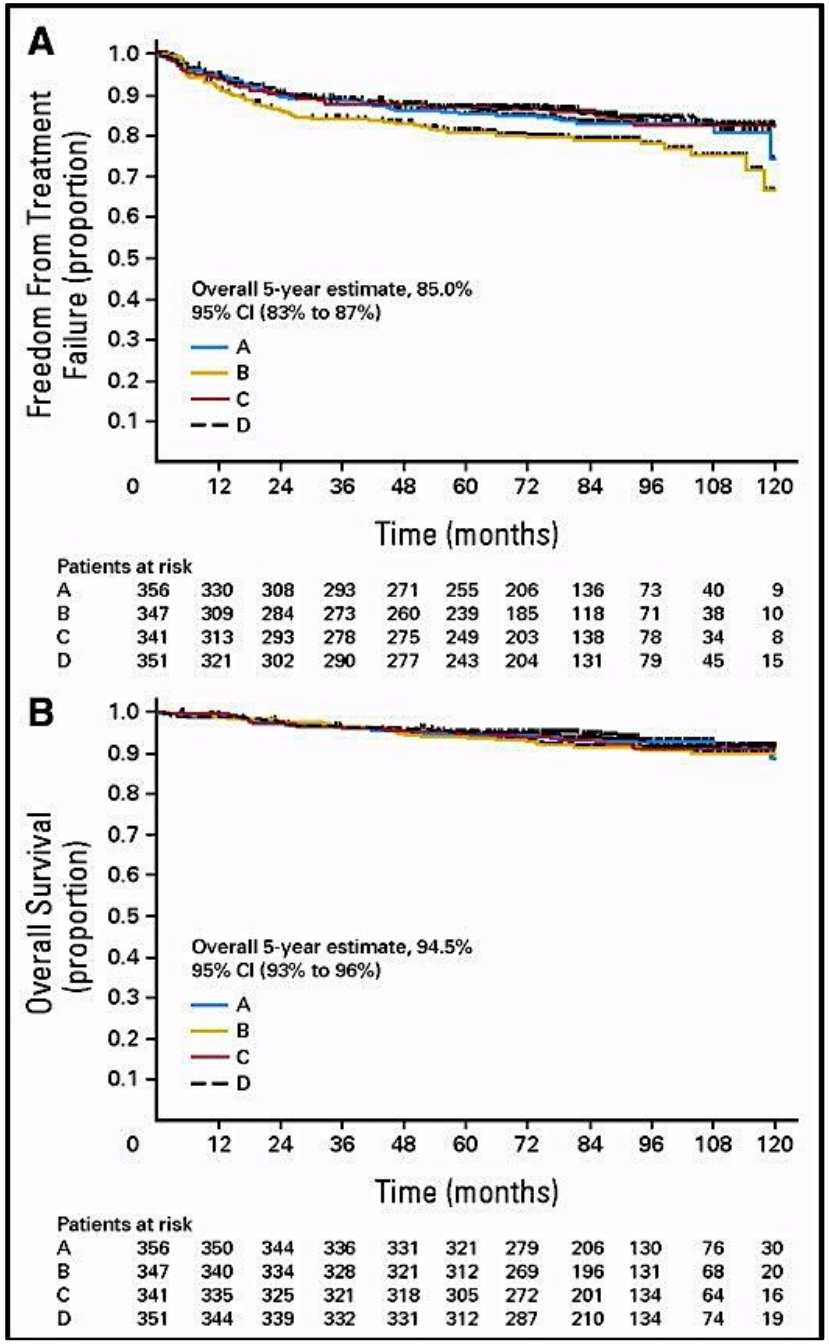
Chemotherapy

4 ABVD 4 BEACOPP

Involved field RT

20 Gy 30 Gy

ABVD + 20Gy inferior on FFTF



Eich H T et al. J Clin Oncol 2010;28

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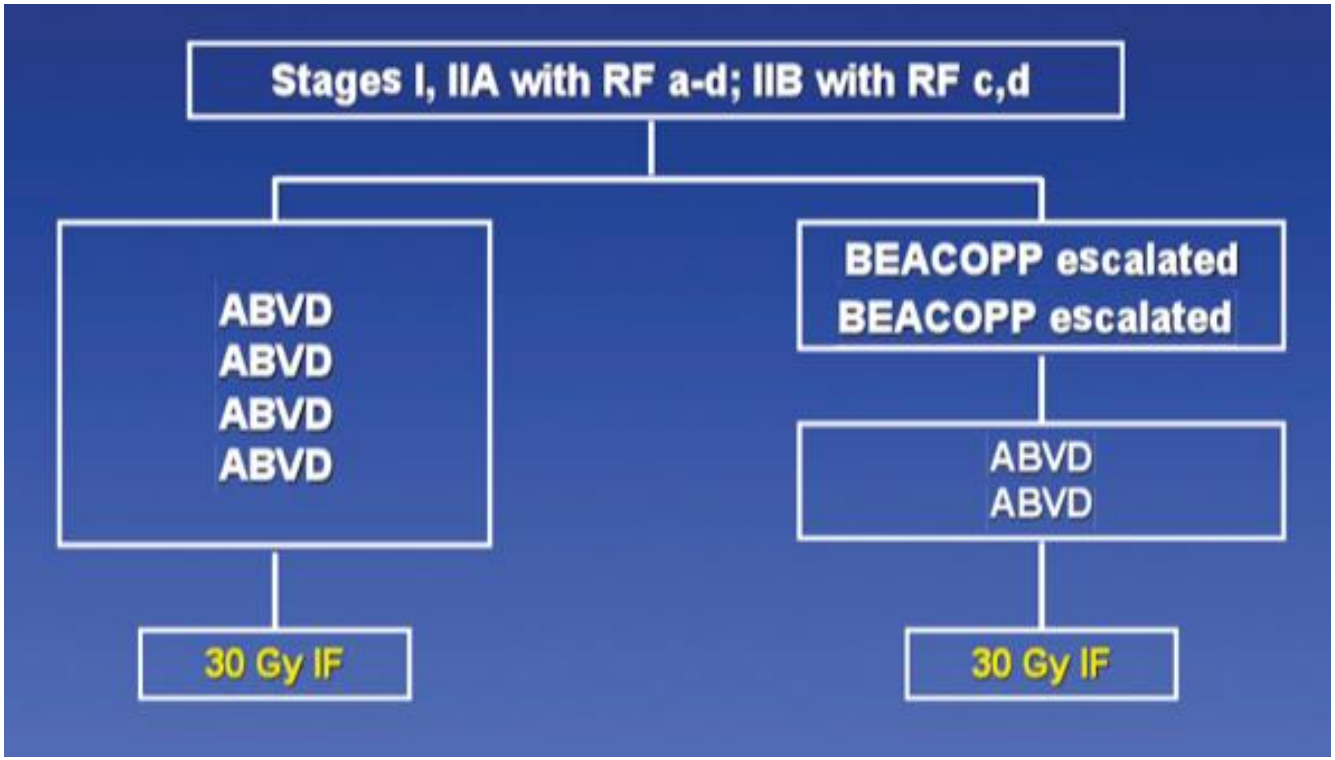
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Dose-Intensification in Early Unfavorable Hodgkin's Lymphoma: Final Analysis of the German Hodgkin Study Group HD14 Trial

Bastian von Tresckow, Annette Plütschow, Michael Fuchs, Beate Klimm, Jana Markova, Andreas Lohri, Zdenek Kral, Richard Greil, Max S. Topp, Julia Meissner, Josée M. Zijlstra, Martin Soekler, Harald Stein, Hans T. Eich, Rolf P. Mueller, Volker Diehl, Peter Borchmann, and Andreas Engert



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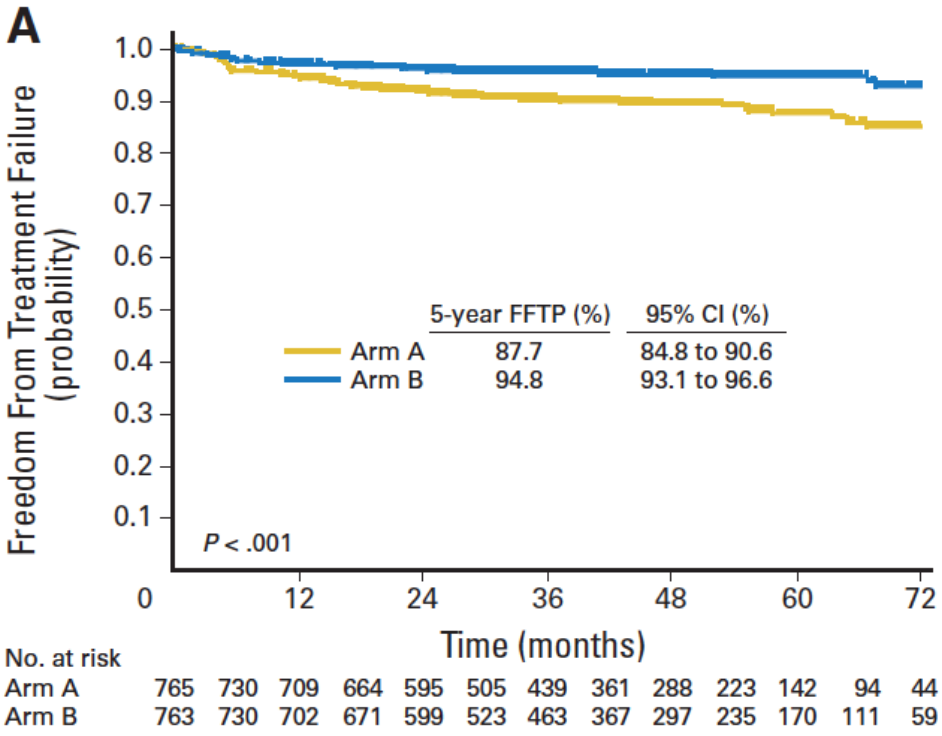

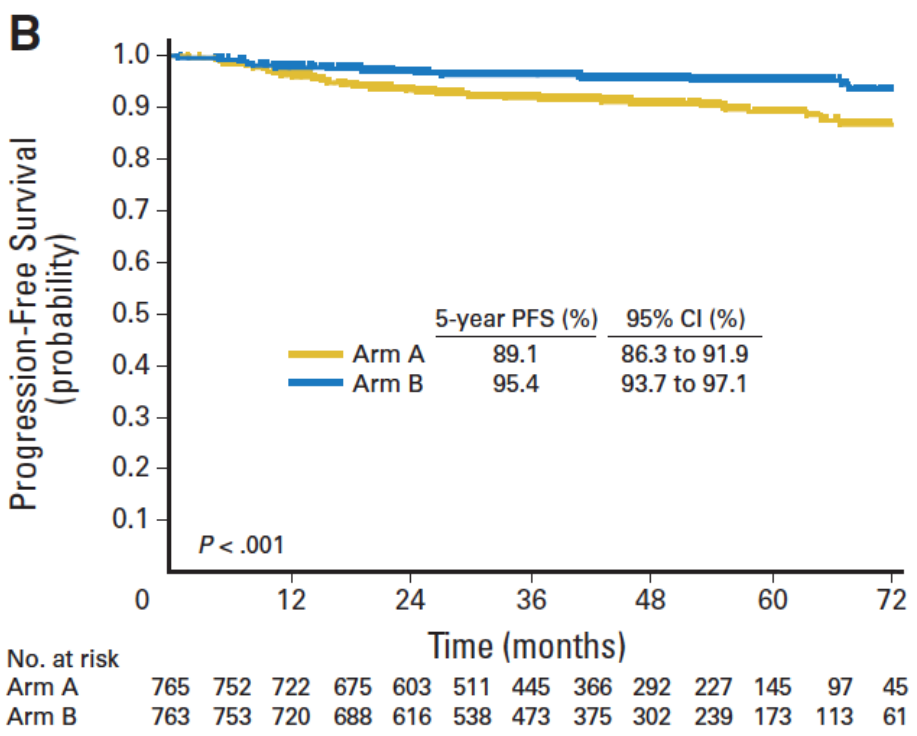

There was more acute toxicity associated with 2+2 than with ABVD, but there were no overall differences in treatment-related mortality or secondary malignancies

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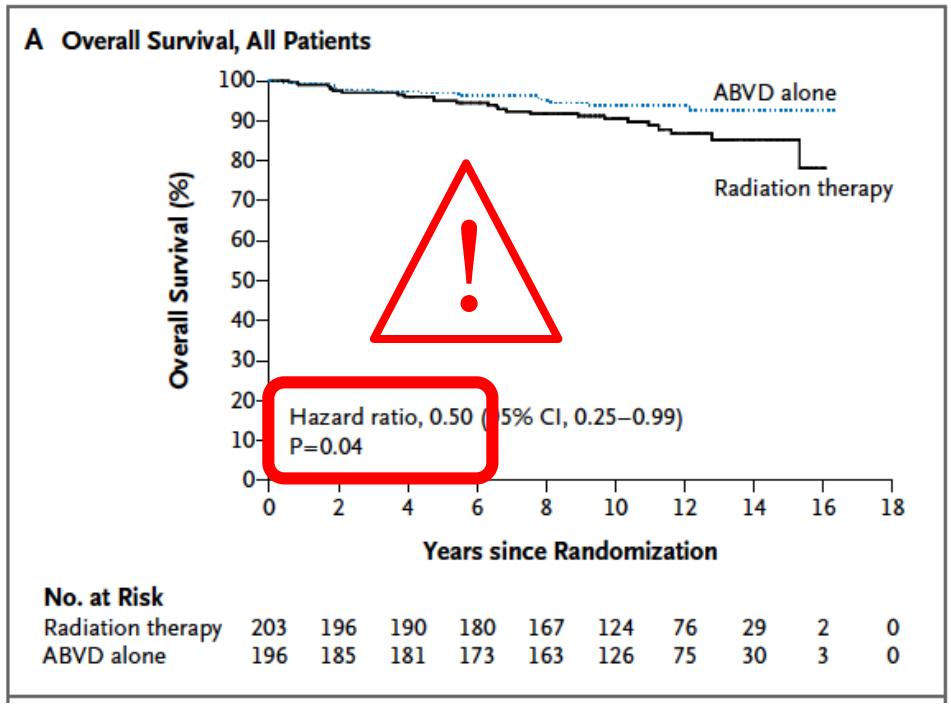
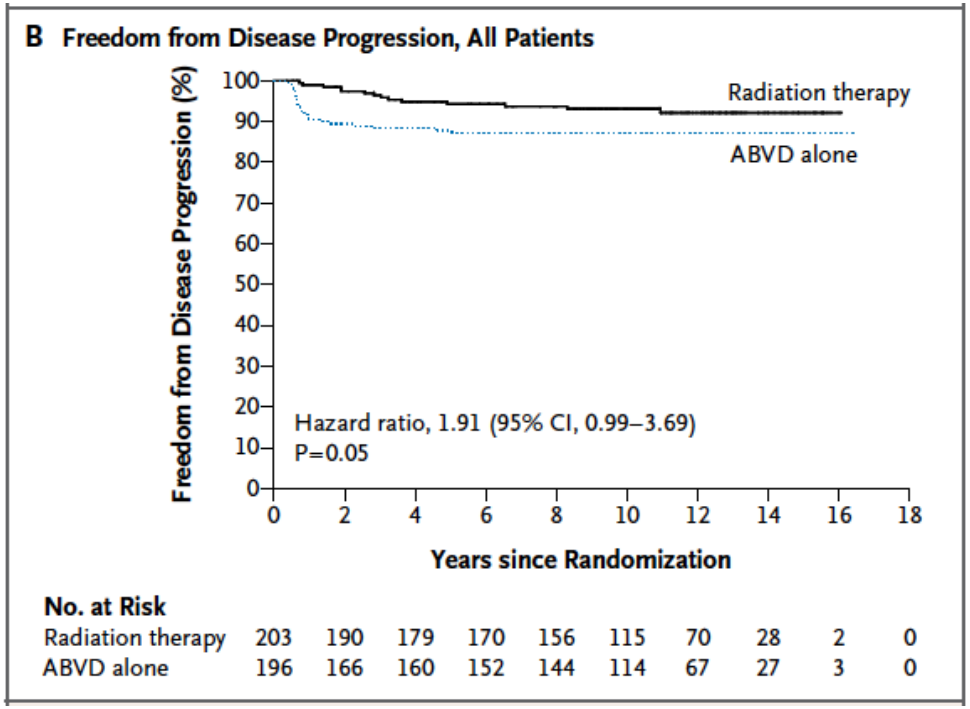
Can Radiotherapy be avoided altogether?

Canadian HD6 trial

ABVD Alone versus Radiation-Based Therapy in Limited-Stage Hodgkin's Lymphoma





CONCLUSION: ABVD therapy alone improves the rate of long-term overall survival in patients with stage IA or IIA nonbulky HL

Meyer RM et al. NEJM 2012

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Canadian HD6 trial: Why lower OS rates in the RT arm ?
The Unexpected Culprits…

Cause of death: Alzheimer disease (1), drowning (2), suicide (3), respiratory failure (4), unknown (5)

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Reading between the lines…

- RT fields → Subtotal lymphoid irradiation
- RT dose → 35 Gy
- Unrelated mortality events (Alzheimer, suicide, drowning) were considered in this analysis.

CONCLUSION: "This study serves as an excellent example how a small number of events, unrelated causes of death, and incomplete analysis of morbidity may distort the results, conclusion and interpretation" (Yahalom J – ASCO 2012)

"Could Interim PET-CT facilitate the use of chemotherapy alone in HL?"

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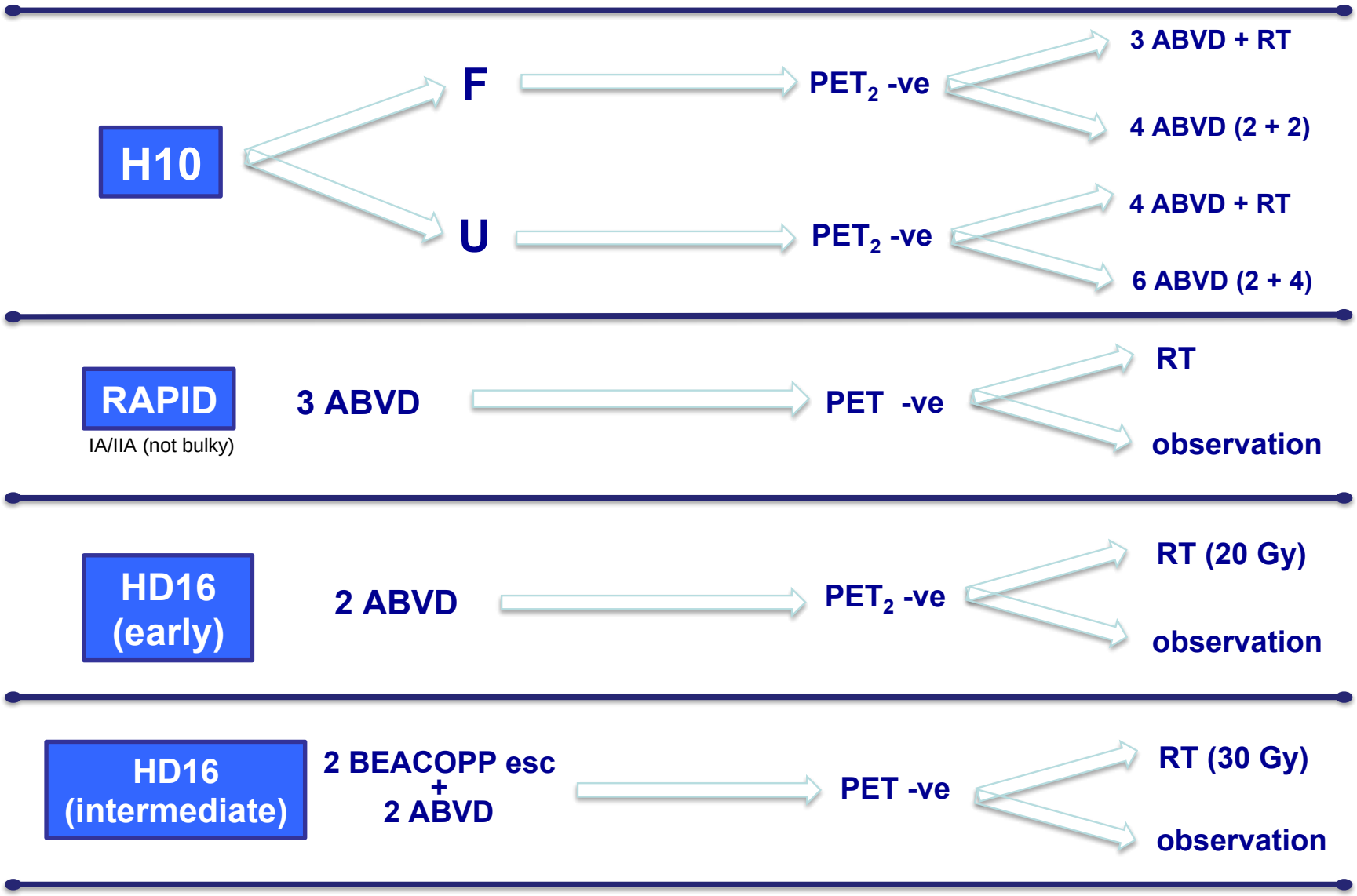
^{18}FDG-PET DRIVEN TRIALS IN EARLY STAGE HL



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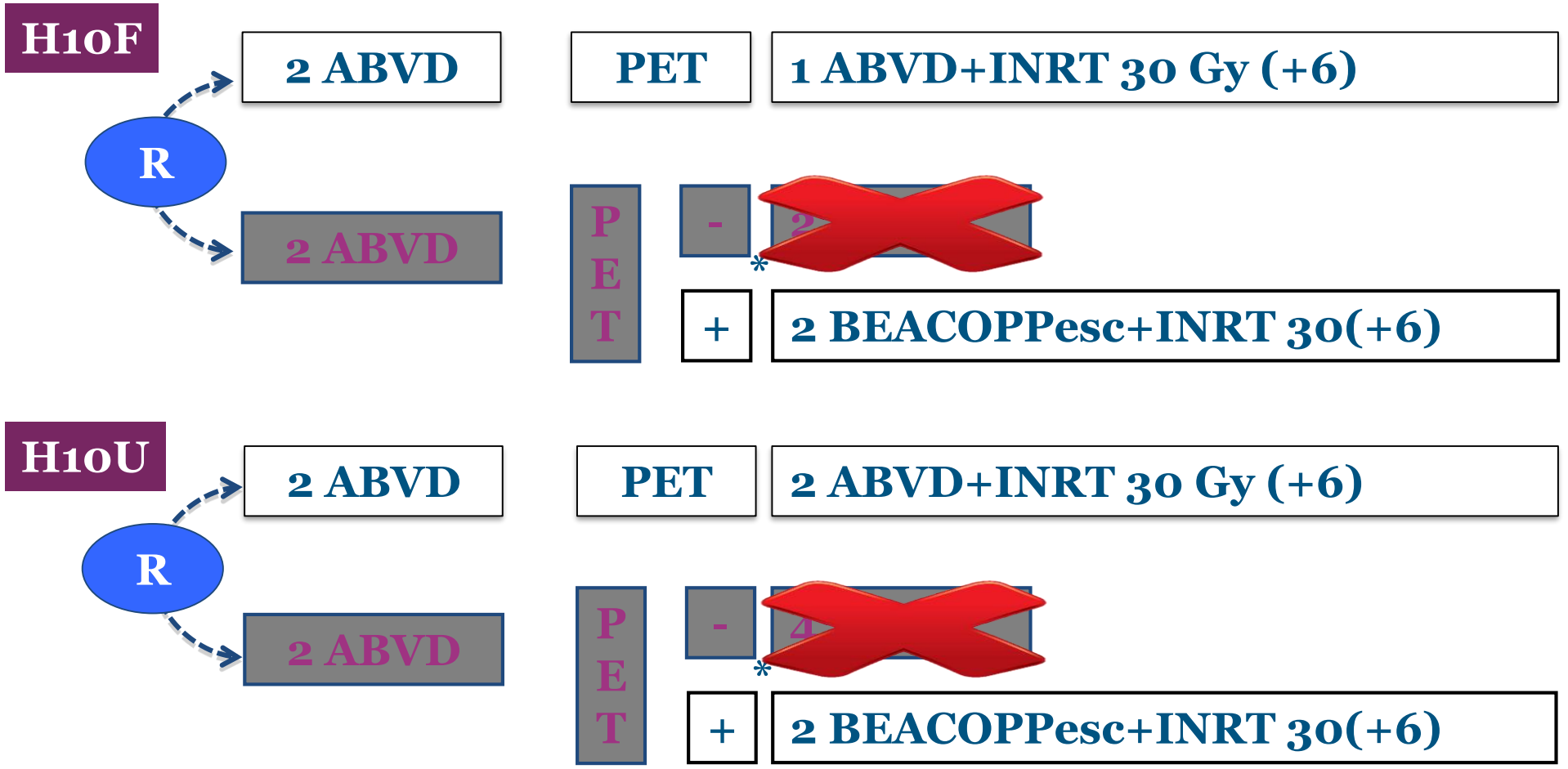
EORTC/GELA/IIL H10 Study

For early favorable and unfavorable HL

H10 (#20051): study design



*PET-/+ according to protocol criteria

Hodgkin - CS I/II – untreated - 15-70 yrs – supradiaphragmatic - no NLPHL

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Omitting Radiotherapy in Early Positron Emission Tomography–Negative Stage I/II Hodgkin Lymphoma Is Associated With an Increased Risk of Early Relapse: Clinical Results of the Preplanned Interim Analysis of the Randomized EORTC/LYSA/FIL H10 Trial

John M.M. Raemaekers, Marc P.E. André, Massimo Federico, Theodore Girinsky, Reman Oumedaly, Ercole Brusamolino,† Pauline Brice, Christophe Fermé, Richard van der Maazen, Manuel Gotti, Reda Bouabdallah, Catherine J. Sebban, Yolande Lievens, Allessandro Re, Aspasia Stamatoullas, Frank Morschhauser, Pieternella J. Lugtenburg, Elisabetta Abruzzese, Pierre Olivier, Rene-Olivier Casasnovas, Gustaaf van Imhoff, Tiana Raveloarivahy, Monica Bellei, Thierry van der Borght, Stephane Bardet, Annibale Versari, Martin Hutchings, Michel Meignan, and Catherine Fortpied

JOURNAL OF CLINICAL ONCOLOGY

Omitting Radiotherapy in Early Positron Emission Tomography–Negative Stage I/II Hodgkin Lymphoma Is Associated With an Increased Risk of Early Relapse: Clinical Results of the Preplanned Interim Analysis of the Randomized EORTC/LYSA/FIL H10 Trial

Table 2. Results of Interim Analysis in Patients With Early PET-Negative Disease

Subset	No. of Patients	No. of Observed Events	HR	Adjusted CI*	*P*†	1-Year PFS	
						%	Adjusted CI*
Favorable					.017		
Standard	188	1	1.00			100.00	
Experimental	193	9	9.36	2.45 to 35.73		94.93	91.89 to 96.85
Unfavorable					.026		
Standard	251	7	1.00			97.28	95.17 to 98.48
Experimental	268	16	2.42	1.35 to 4.36		94.70	92.11 to 96.46

Abbreviations: HR, hazard ratio; PET, positron emission tomography; PFS, progression-free survival.
*Confidence level adjusted to significance level used in interim test: 79.6% CI for favorable group and 80.4% CI for unfavorable group.
†One-sided Wald-test *P* value of superiority test.

Favorable: PET-negativity 85.8%

Unfavorable: PET-negativity 74.8%

CONCLUSION

Combined-modality treatment resulted in fewer early progressions in clinical stage I/II HL, although early outcome was excellent in both arms. The final analysis will reveal whether this finding is maintained over time

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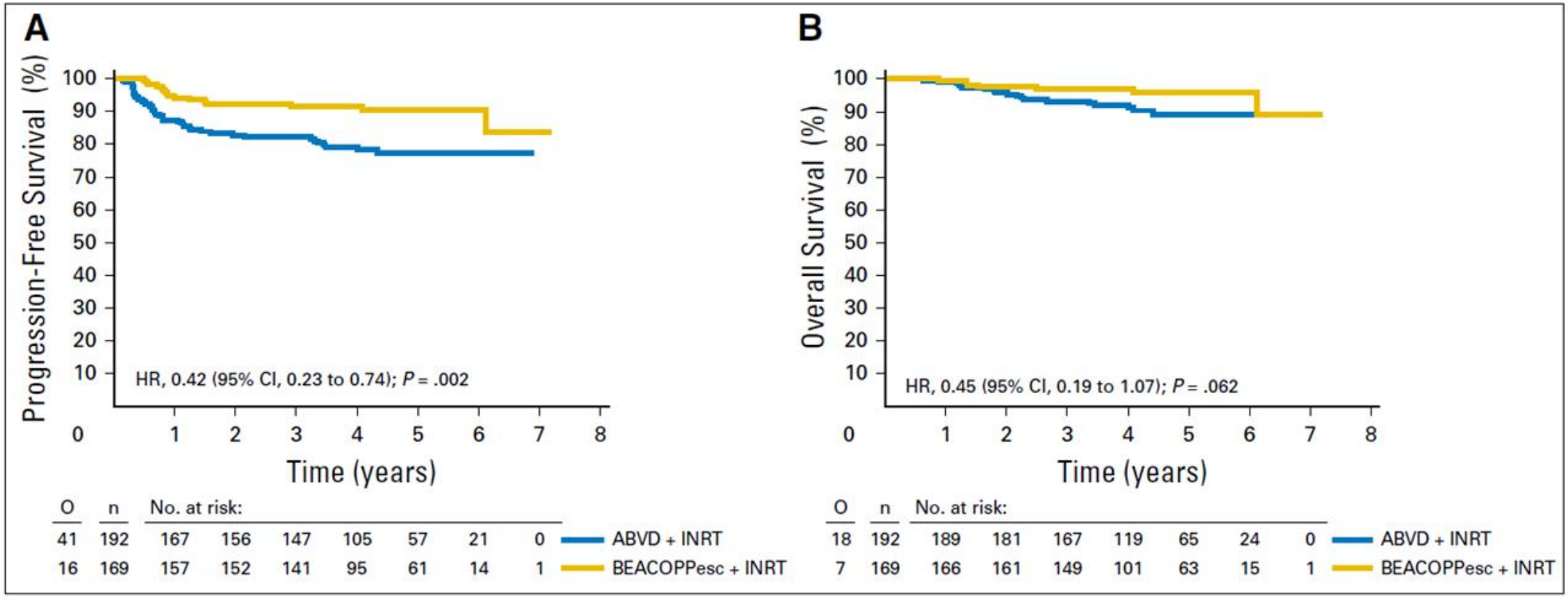
Raemaekers JM et al. J Clin Oncol. 2014

JOURNAL OF CLINICAL ONCOLOGY

Early Positron Emission Tomography Response–Adapted Treatment in Stage I and II Hodgkin Lymphoma: Final Results of the Randomized EORTC/LYSA/FIL H10 Trial

Interim-PET can potentially guide a "chemo-intensification" in the cohort of patients with a positive finding



Andrè M. et al. JCO 2017

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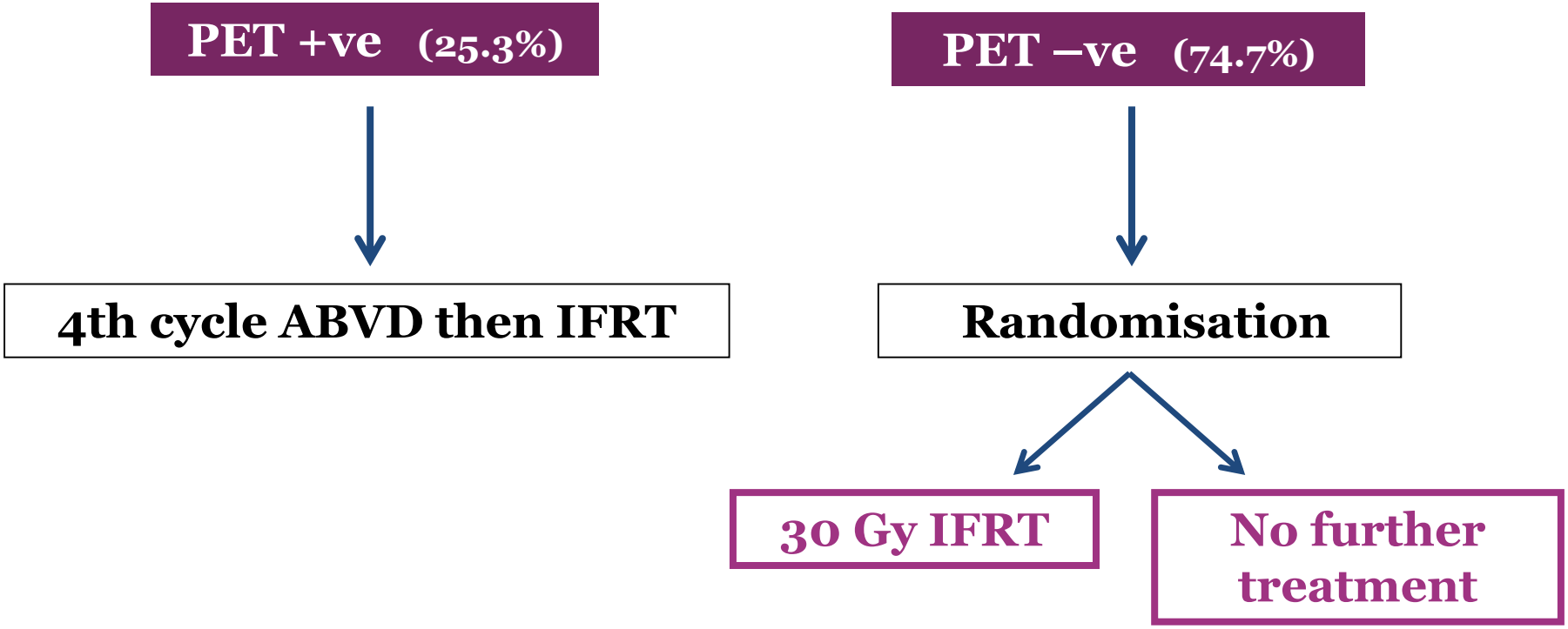
UK NCRI RAPID trial

- Initial treatment: 3 x ABVD
- Re-assessment: if response, PET scan performed



N.B. Favourable features according with GHSG criteria were present in 74% of patients randomized to "NFT" (65.1% in patients randomized to 30 Gy IFRT)

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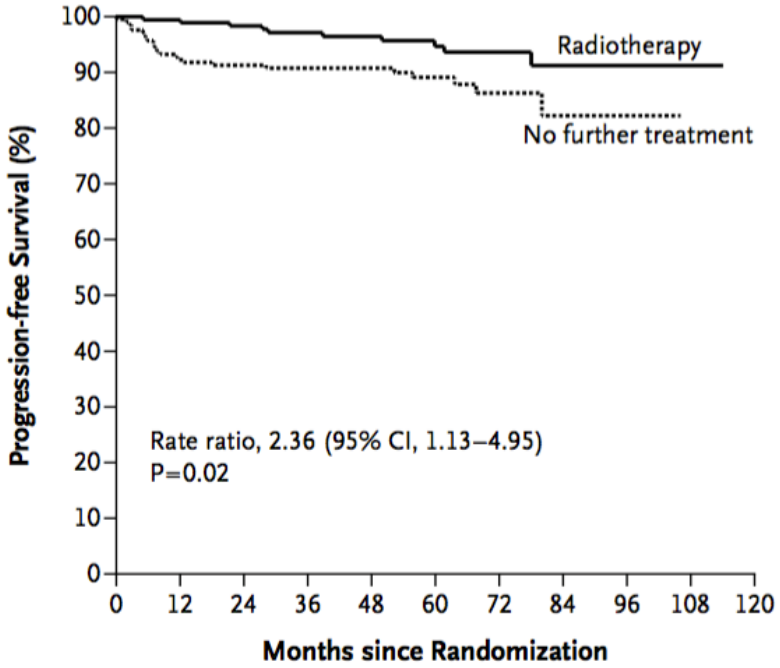
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

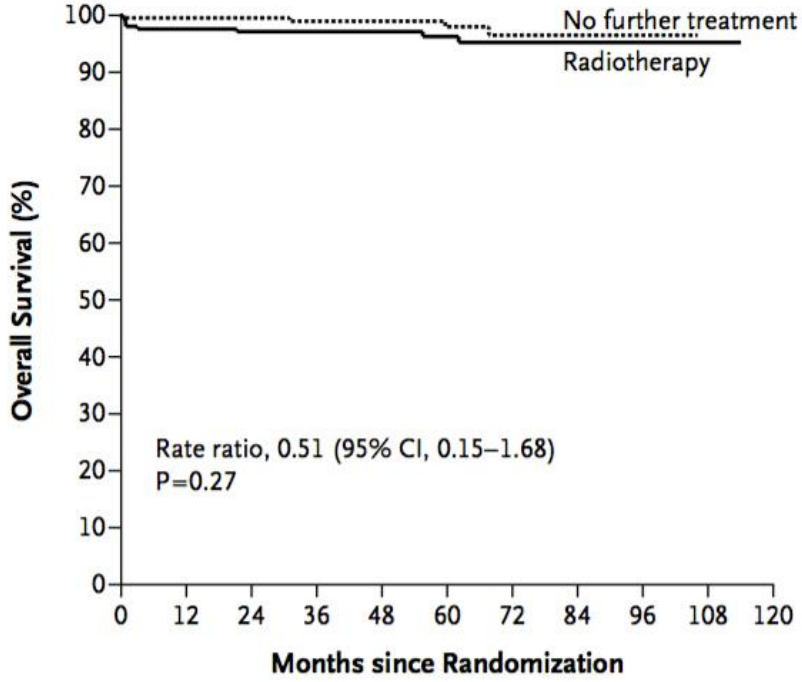
Results of a Trial of PET-Directed Therapy for Early-Stage Hodgkin's Lymphoma

B **Per-Protocol Analysis**



No. at Risk

Radiotherapy	183	180	172	161	130	99	58	33	13	2	0
No further treatment	209	202	194	165	139	97	56	18	6	0	0



No. at Risk

Radiotherapy	209	200	191	175	139	103	60	34	13	2	0
No further treatment	211	204	196	167	140	97	56	18	6	0	0

- ***The "noninferiority" of the strategy of no further treatment after chemotherapy in PET –ve patients was not demonstrable***

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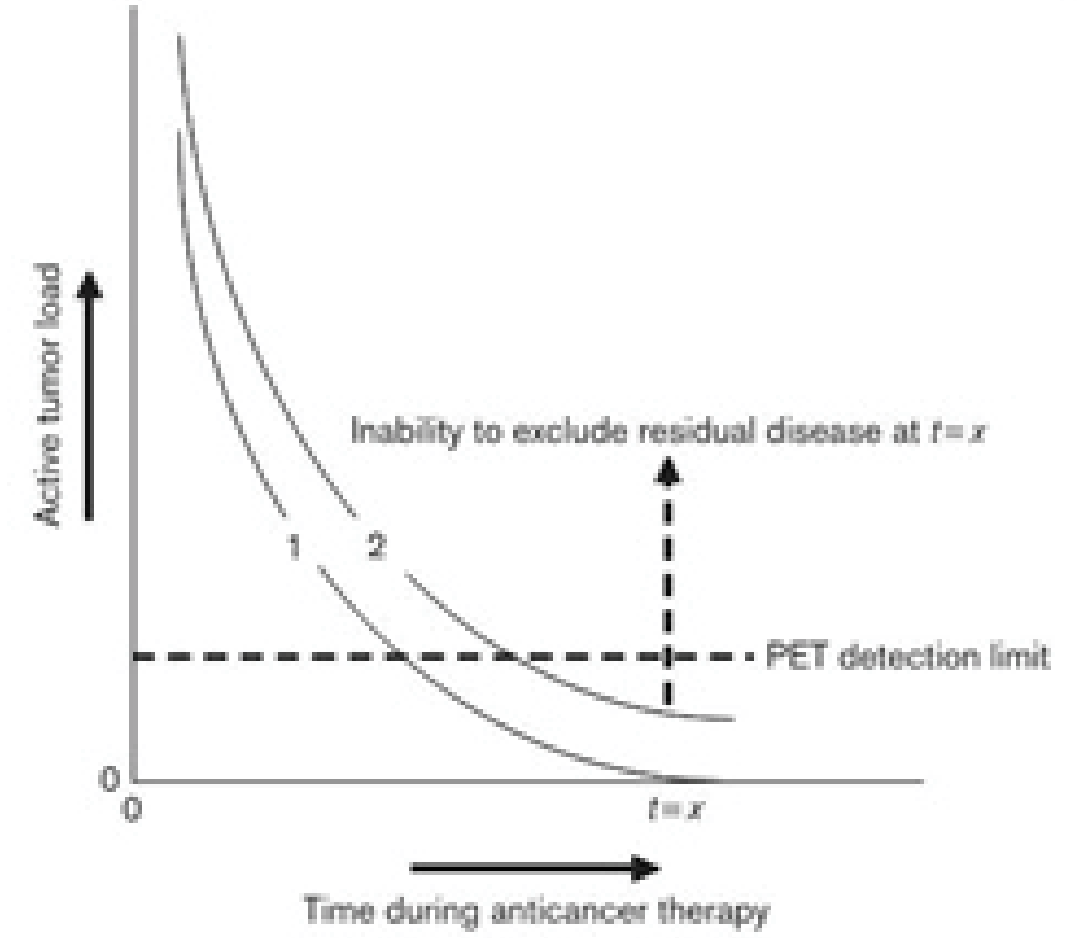
Radford J et al NEJM 2015

A negative 18FDG-PET scan can never exclude residual disease

Fig. 1



Adams and Kwee, Nucl Med Commun 2016

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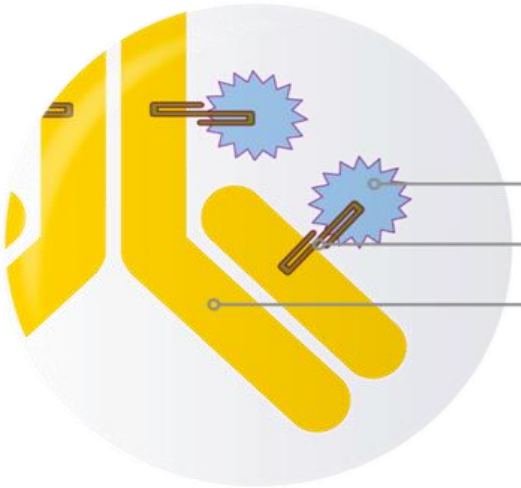
Role of Immunotherapy in Hodgkin Lymphoma

Brentuximab Vedotin (SGN-35)

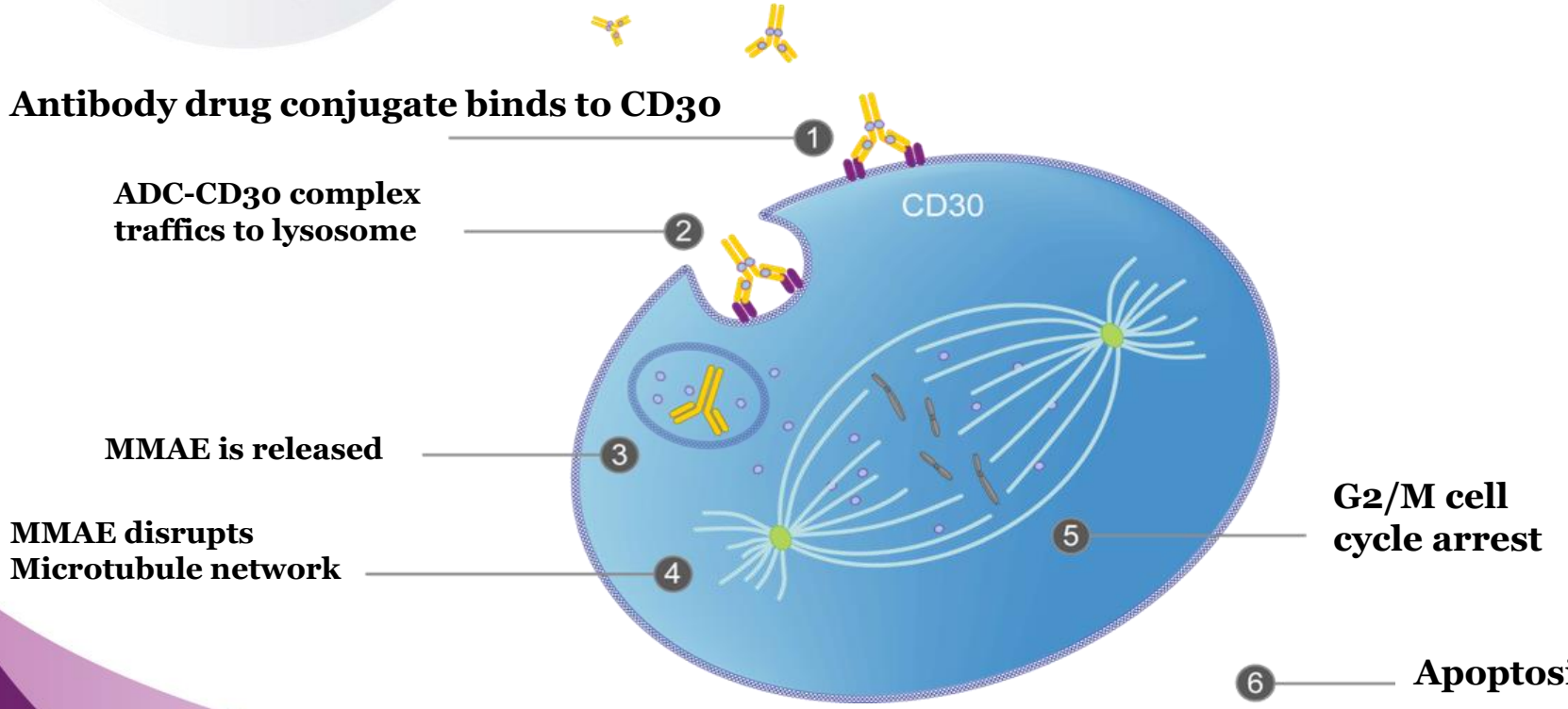
Mechanism of action



monomethyl auristatin E (MMAE), potent antitubulin agent

protease-cleavable linker

anti-CD30 monoclonal antibody



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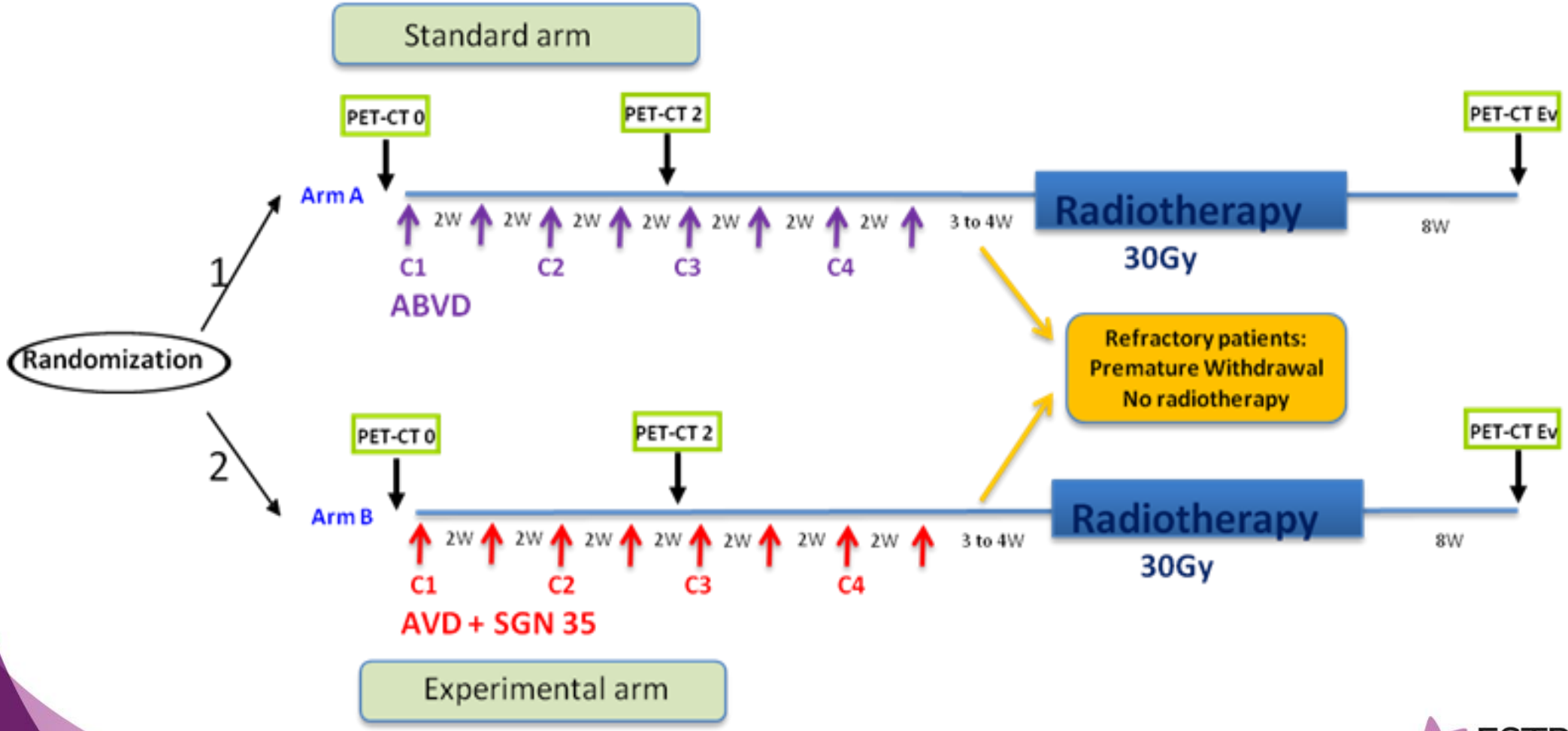
EORTC-20113-LYMG

Brentuximab vedotin associated with chemotherapy in untreated patients with stage I/II unfavourable Hodgkin's lymphoma. A randomized phase II LYSA-FIL-EORTC intergroup study

BREACH STUDY



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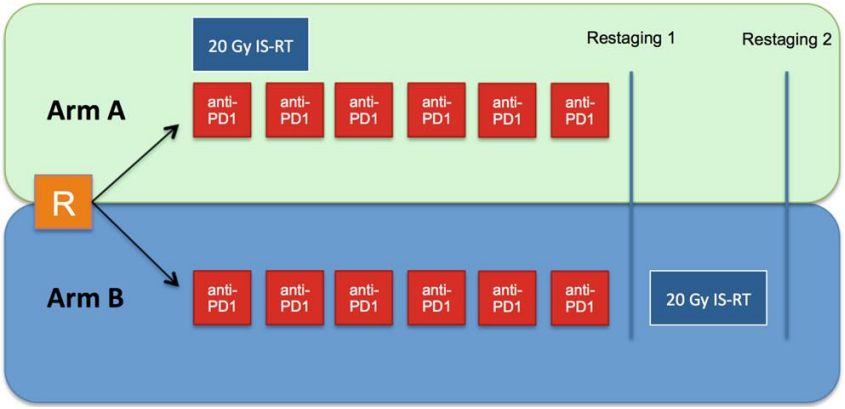
Checkpoint inhibitors and radiation treatment in Hodgkin's lymphoma

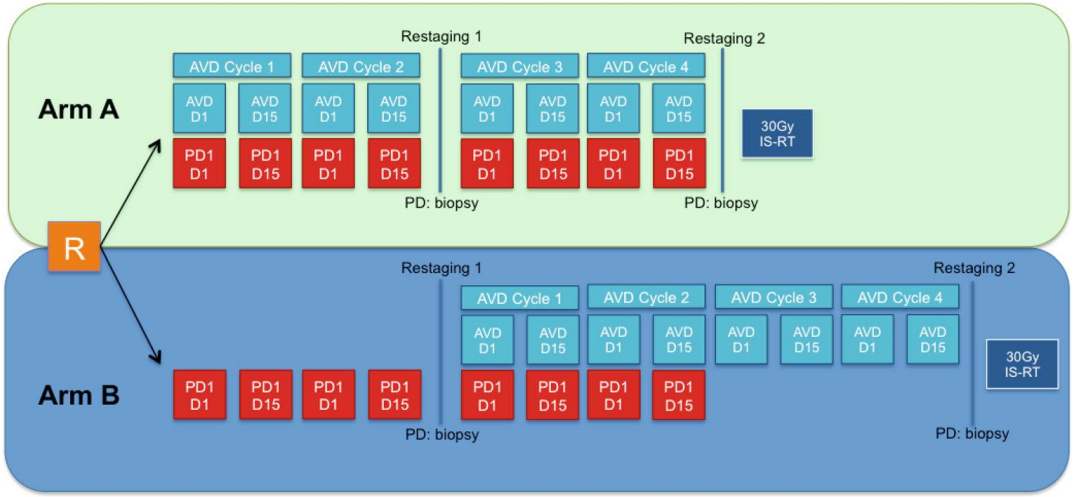
New study concepts of the German Hodgkin Study Group

FUTURE DIRECTIONS…



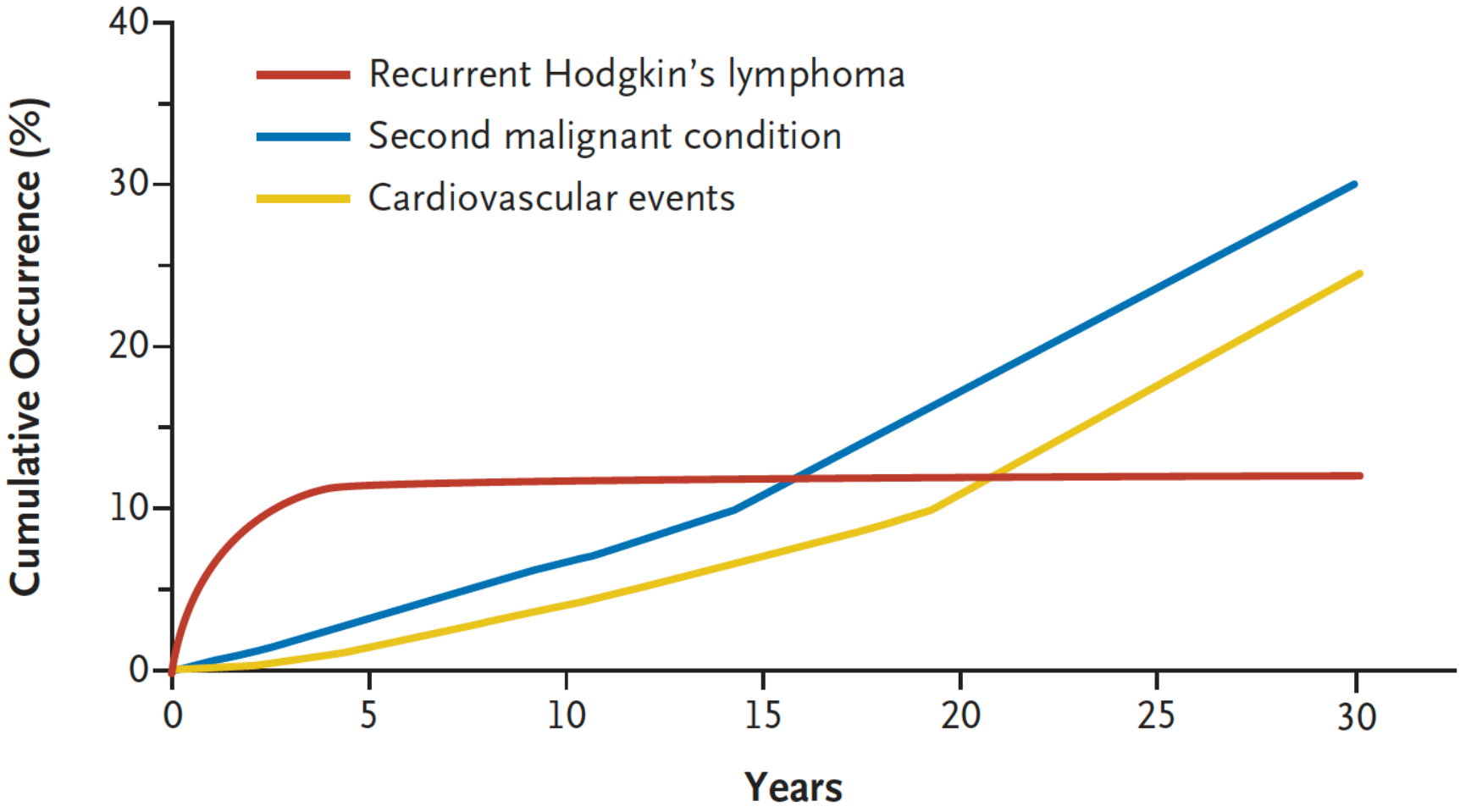
Early Stage FAVOURABLE

Early Stage UNFAVOURABLE



Baues C. et al. Strahlenther Onkol 2016

Which are the reasons to remove upfront RT ?
The Price of Success



Armitage J, NEJM 2010

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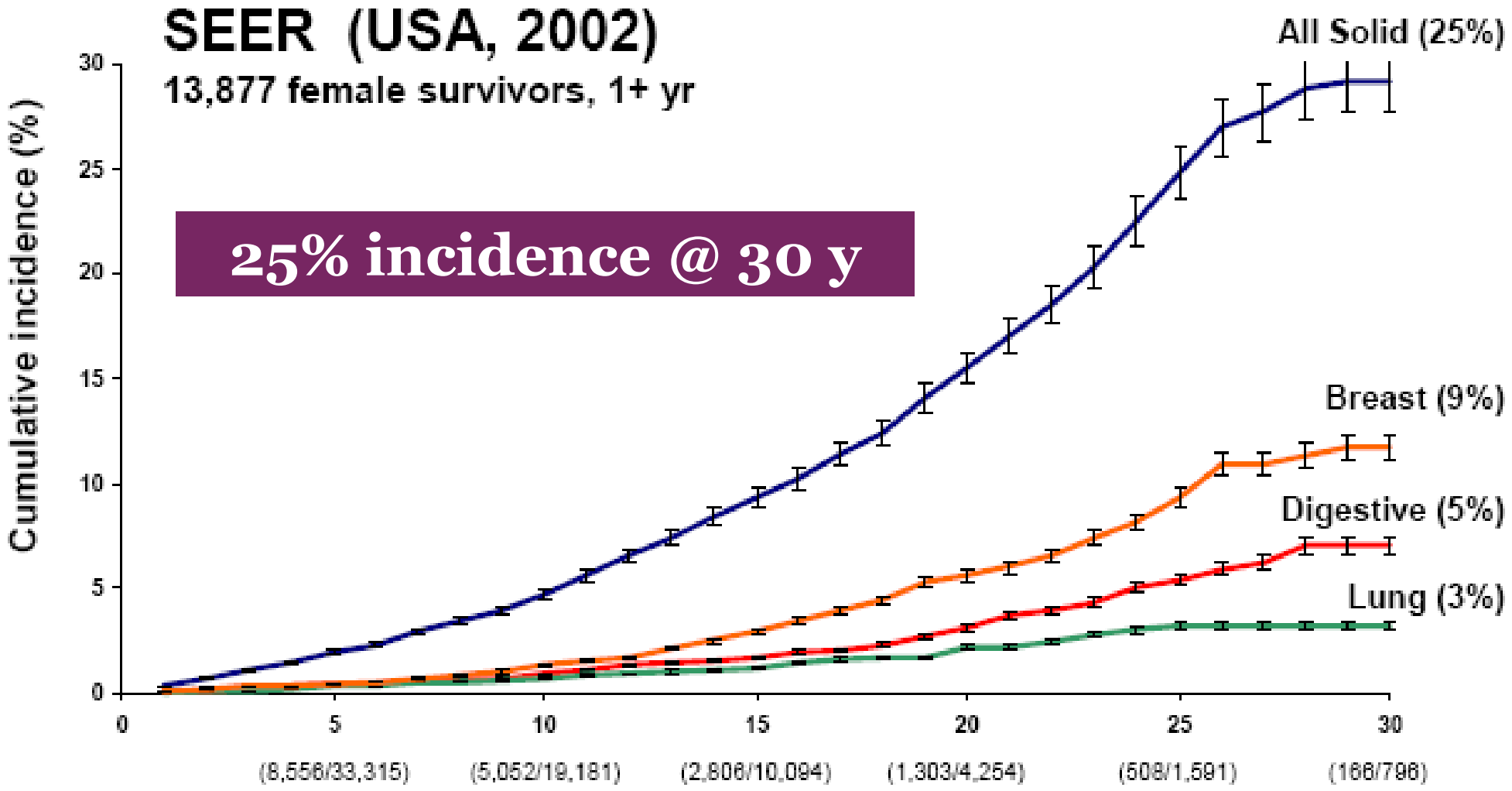
Second Cancer after Hodgkin Lymphoma



Dores et al JCO 20:3484, 2002

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Breast Cancer Risk After Supradiaphragmatic Radiotherapy for Hodgkin's Lymphoma in England and Wales: A National Cohort Study

Anthony J. Swerdlow, Rosie Cooke, Andrew Bates, David Cunningham, Stephen J. Falk, Dianne Gilson, Barry W. Hancock, Sarah J. Harris, Alan Horwich, Peter J. Hoskin, David C. Linch, T. Andrew Lister, Helen H. Lucraft, John A. Radford, Andrea M. Stevens, Isabel Syndikus, and Michael V. Williams

- 5.002 patients treated for HL with supradiaphragmatic RT at age <36 in UK
- 1956-2003
- Median RT dose 36 Gy
- Cumulative **risk at 40 years was 48%** for patients treated at **younger ages** with doses >40 Gy
- Breast cancer **risk** was **twice as great** in patients treated with **mantle RT** as in those who received different fields of supradiaphragmatic RT

Table 2. Risk of Breast Cancer in Relation to Treatment

Variable	Observed	Expected	SIR	95% CI*	AER	95% CI*
Age at first supradiaphragmatic RT, years						
0-9	1	0.2	5.4	0.8 to 38.2	7.5	−1.5 to 49.4
10-14	25	1.1	22.0	14.9 to 32.6	65.1	41.1 to 97.6
15-19	117	8.2	14.3	12.0 to 17.2	58.6	47.7 to 71.1
20-24	100	18.4	5.4	4.5 to 6.6	30.7	23.7 to 38.8
25-29	71	22.2	3.2	2.5 to 4.0	22.1	15.1 to 30.5
30-35	59	25.1	2.4	1.8 to 3.0	19.4	11.4 to 29.2
P heterogeneity			< .001		< .001	

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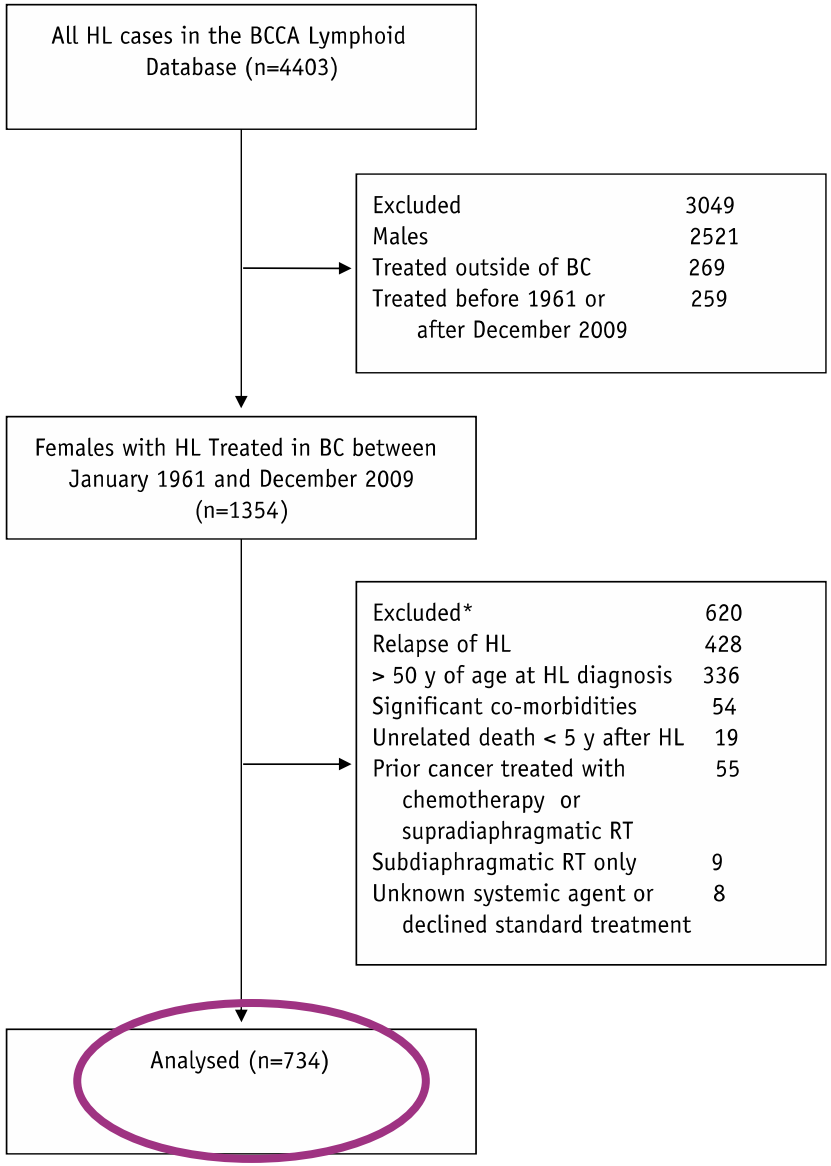
Swerdlow AJ. et al. JCO 2012

Secondary Breast Cancer Risk by Radiation Volume in Women With Hodgkin Lymphoma

Jessica L. Conway, MD,*,† Joseph M. Connors, MD,*
Scott Tyldesley, MD,*,† Kerry J. Savage, MD,*
Belinda A. Campbell, MD,‡ Yvonne Y. Zheng, MEng, MSc,§
Jeremy Hamm, MSc,§ and Tom Pickles, MD*,†

- ***Period of analysis: 1961-2009 (>5 years of follow up)***
- ***Median RT dose: 35 Gy***
- ***Median follow up: 18 years***
- ***Total population: 734 patients***
  - ***Mantle Field RT (MFR) = 231 pts***
  - ***Small Fields RT (SFRT) = 185 pts***
  - ***Chemotherapy only (CO) = 318 pts***
- ***N.B: SFRT = IFRT; ISRT; INRT***



Conway JL et al. IJROBP 2017

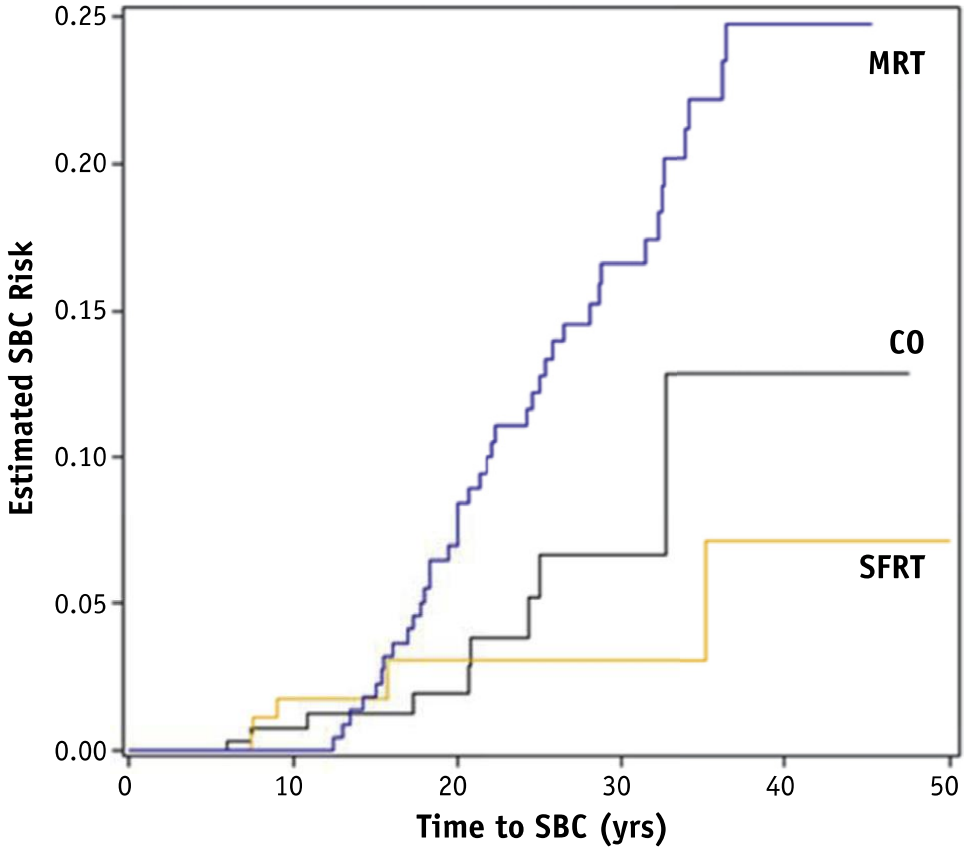
Secondary Breast Cancer Risk by Radiation Volume in Women With Hodgkin Lymphoma

Jessica L. Conway, MD,*,† Joseph M. Connors, MD,* Scott Tyldesley, MD,*,† Kerry J. Savage, MD,* Belinda A. Campbell, MD,‡ Yvonne Y. Zheng, MEng, MSc,§ Jeremy Hamm, MSc,§ and Tom Pickles, MD*,†

Table 3 Fine and Gray multivariable regression for the risk of SBC: competing risk model (stratified by age)

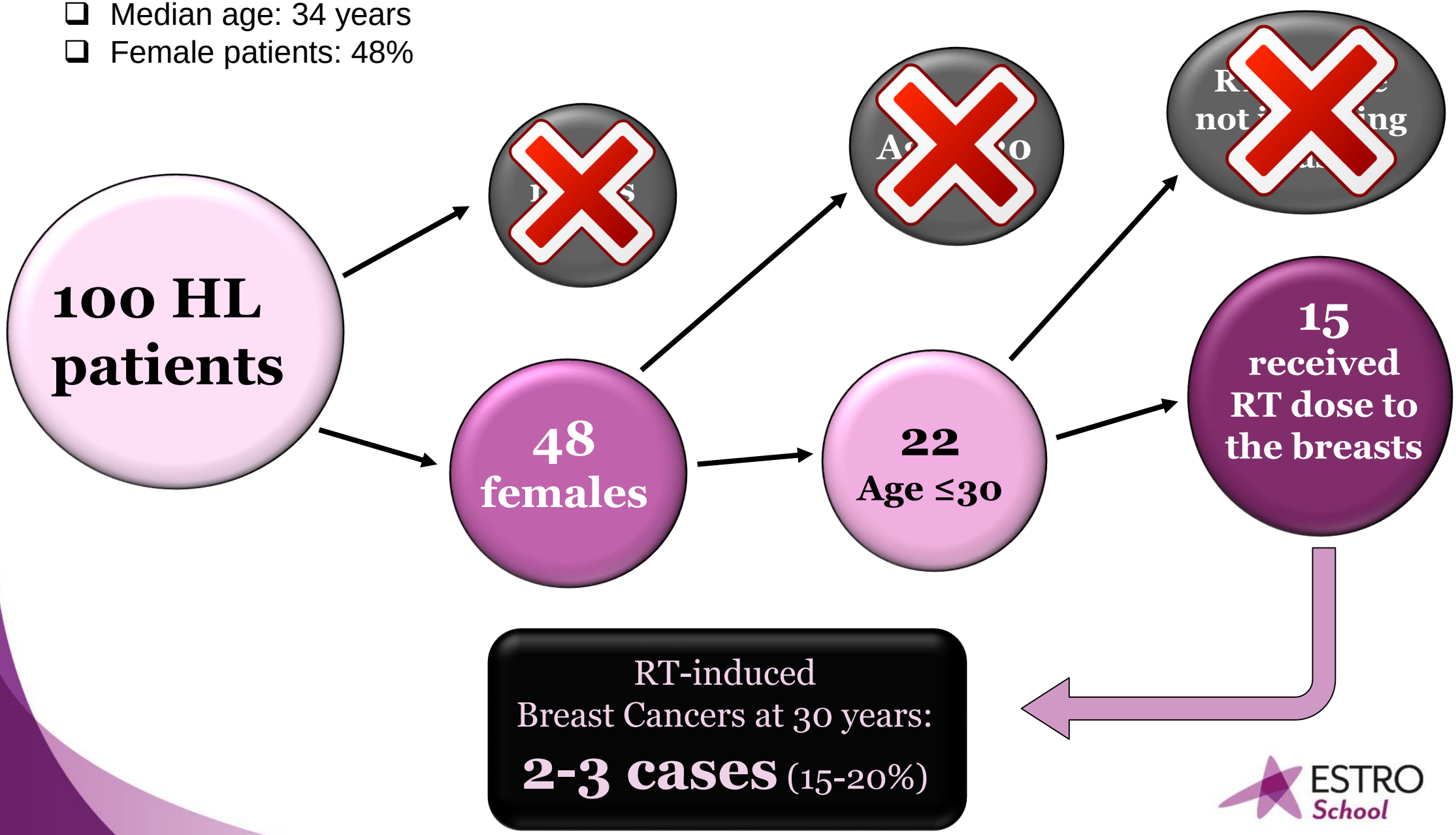
Factor	HR	95% CI	*P* value
Radiation field			
CO		1.00 (reference)	
MRT	2.90	1.41-5.97	.004
SFRT	0.87	0.28-2.66	.803
Radiation field			
SFRT		1.00 (reference)	
MRT	3.34	1.33-8.40	.01
Premature menopause risk			
Not at risk		1.00 (reference)	
At risk	1.18	0.61-2.27	.63

Abbreviations: CO = chemotherapy only; HR = hazard ratio; MRT = mantle field radiation; SBC = secondary breast cancer; SFRT = small field radiation.

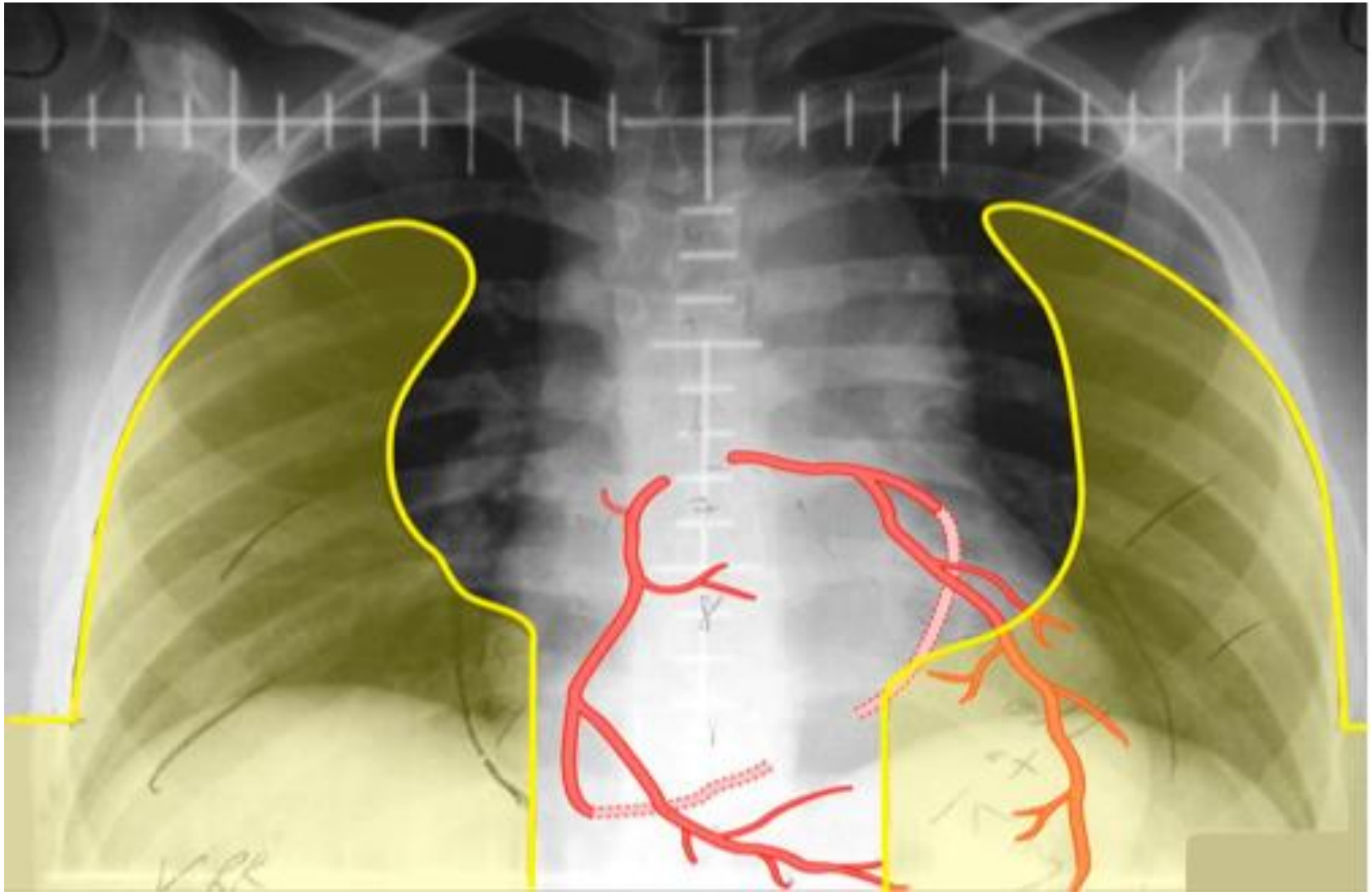


Risk of Secondary breast cancer (from GHSG trial)

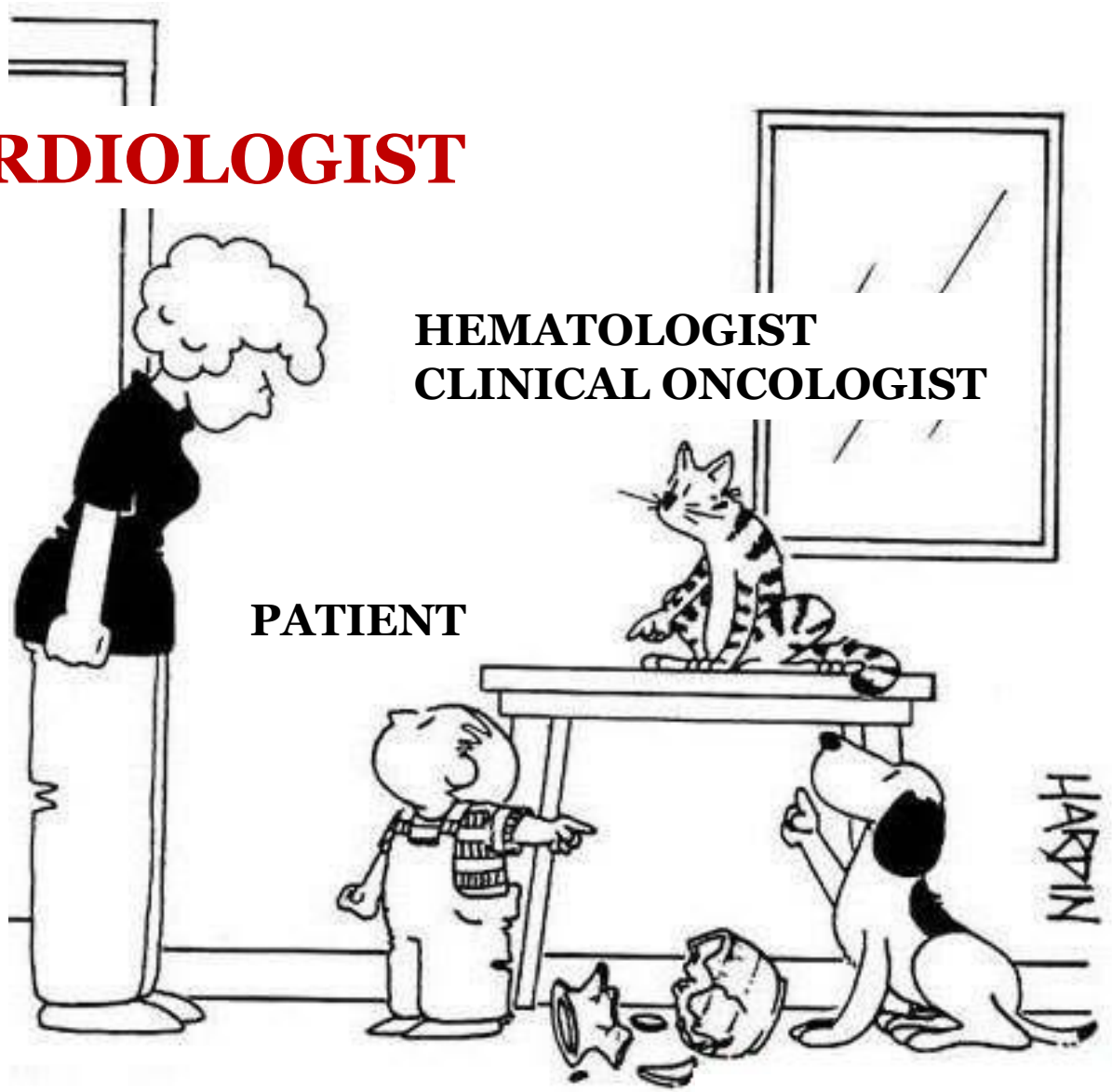
- 5804 early stage HL patients (GHSG trial HD7-HD8-HD10-HD11-HD14)
- Median age: 34 years
- Female patients: 48%



Cardiovascular Events after Hodgkin Lymphoma



TREATMENT RELATED ISCHEMIC DISEASE IN LONG TERM CANCER SURVIVORS: WHO IS THE GUILTY ONE?



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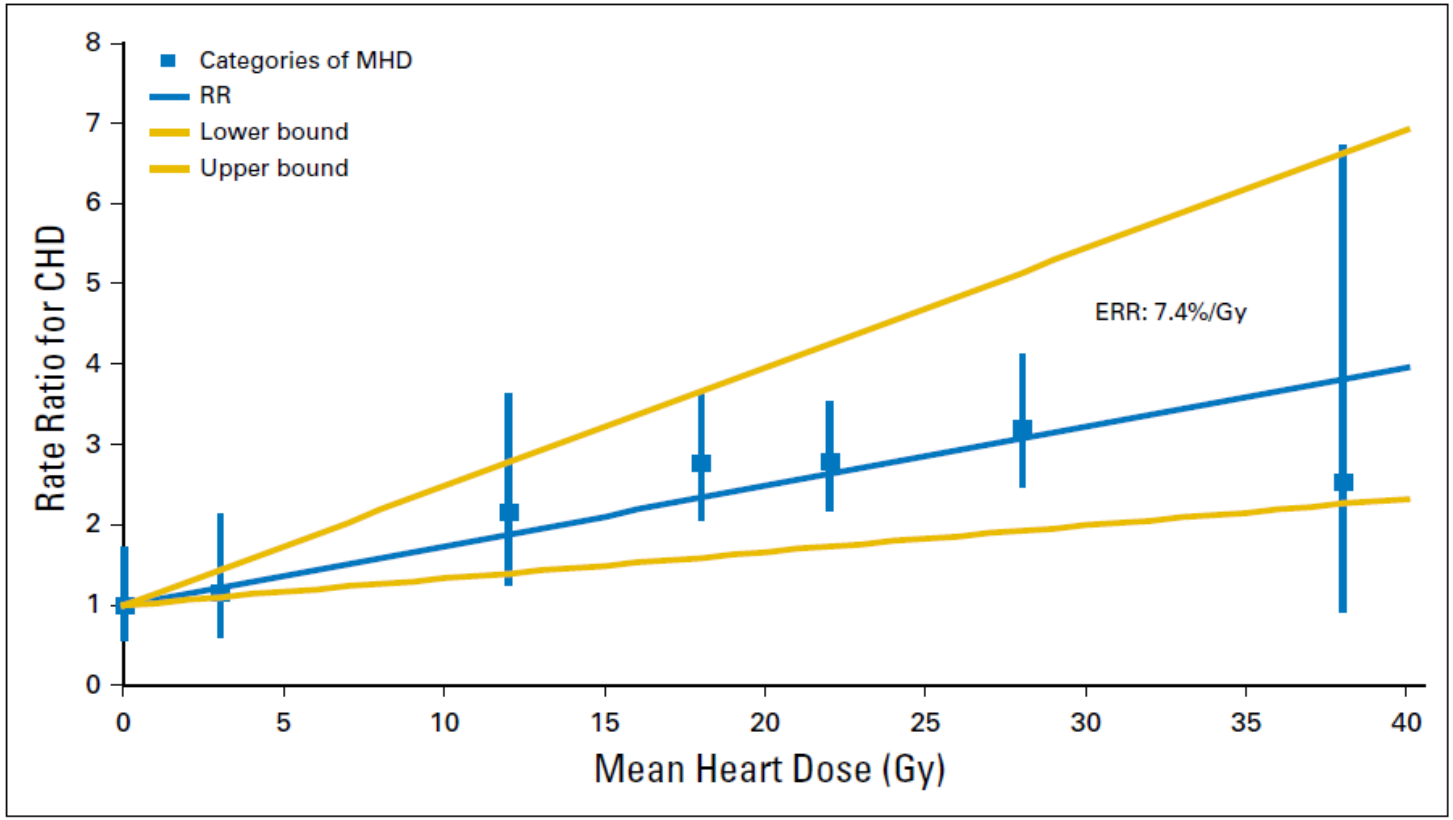
JOURNAL OF CLINICAL ONCOLOGY

Radiation Dose-Response Relationship for Risk of Coronary Heart Disease in Survivors of Hodgkin Lymphoma

Frederika A. van Nimwegen, Michael Schaapveld, David J. Cutter, Cècile P.M. Janus, Augustinus D.G. Krol, Michael Hauptmann, Karen Kooijman, Judith Roesink, Richard van der Maazen, Sarah C. Darby, Berthe M.P. Aleman, and Flora E. van Leeuwen

LINEAR "NO-THRESHOLD" CORRELATION BETWEEN MEAN HEART DOSE AND DEVELOPMENT OF CAD



Van Nimwegen et al JCO 2016

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Crucial Points

- **How to reduce radiation induced heart diseases ?**

↓

we need to reduce the RT dose received by the cardiac structures!

- **How to reduce the RT dose received by the cardiac structures ?**

↓

first of all, we have to define them in the treatment planning!

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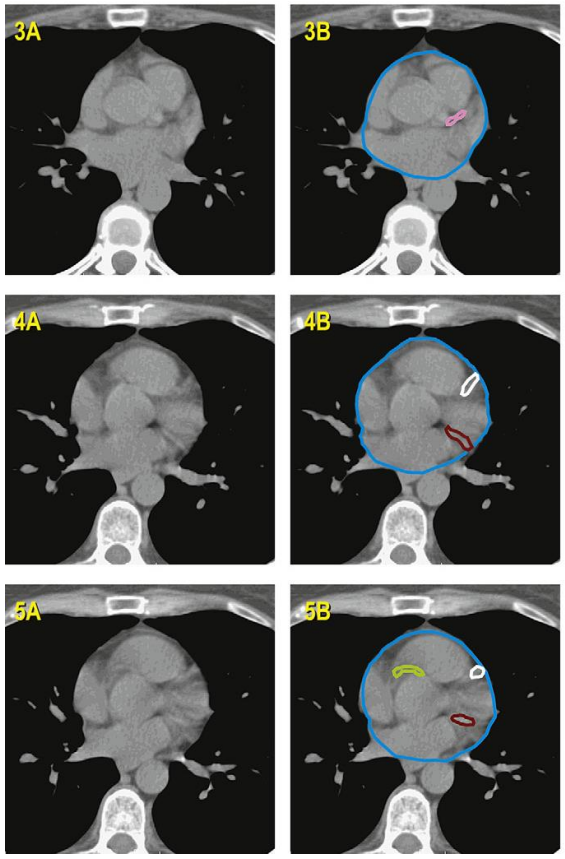
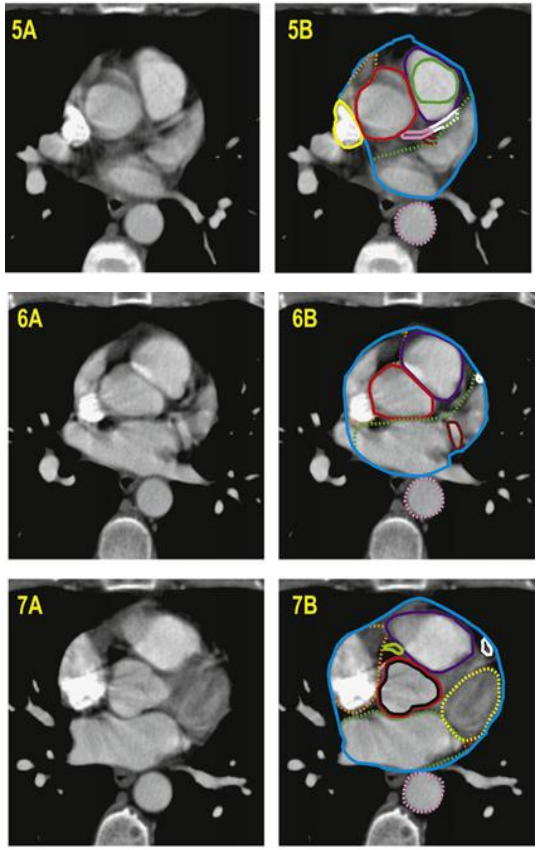
DEVELOPMENT AND VALIDATION OF A HEART ATLAS TO STUDY CARDIAC EXPOSURE TO RADIATION FOLLOWING TREATMENT FOR BREAST CANCER

CONTOURING OF THE HEART STRUCTURES

Basal CT scan



Contrast enhanced



Feng M et al. IJROBP 2011

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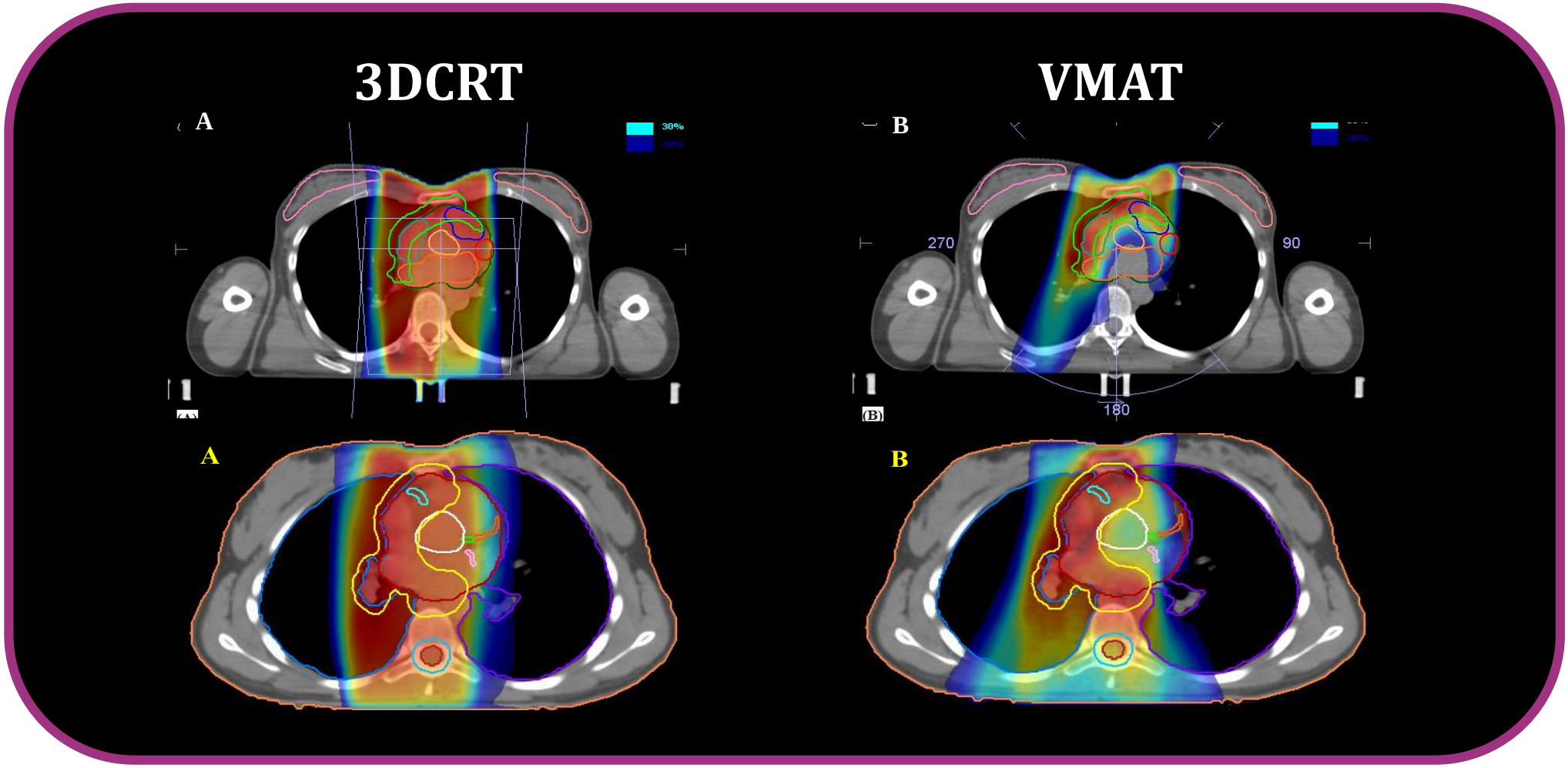
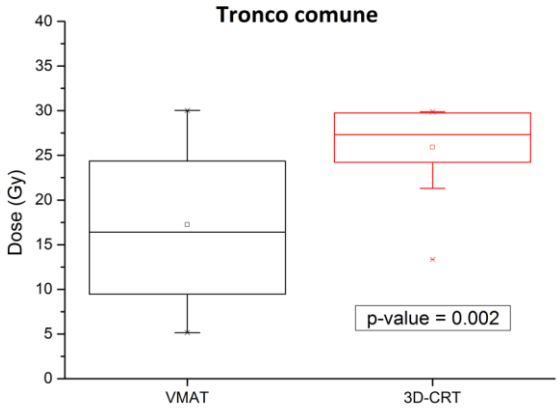
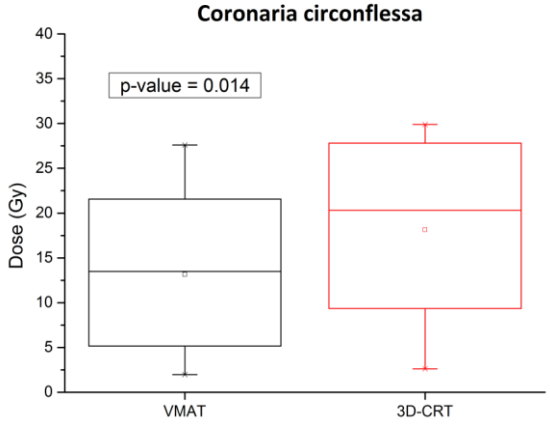
Heart structures sparing through Volumetric Modulated Arc Therapy (VMAT) in early stage Hodgkin lymphoma.

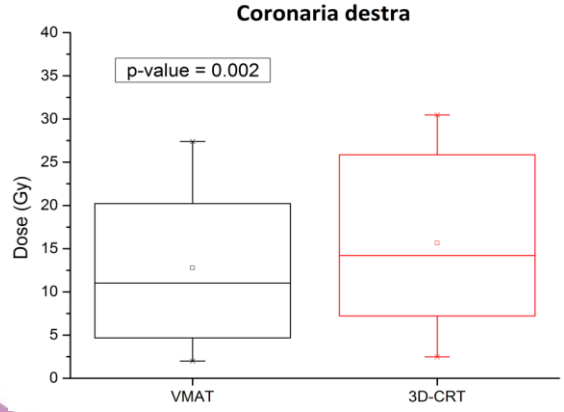
Filippi A.R.[1], Levis M. [1], Girardi A. [1], Fiandra C. [1], Cadoni F. [1], Papurello V. [1], Piva C. [1], Donegani I. [1], Ragona R. [1] and Ricardi U. [1]

[1] *Department of Radiation Oncology, University of Torino, Italy*



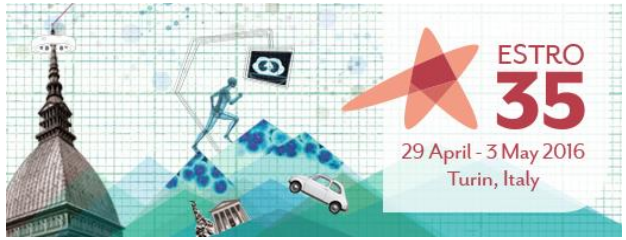






Mean doses to cardiac structures

Structure	VMAT	3D-CRT	p value
	Mean dose (Gy) ± SD	Mean dose (Gy) ± SD	
Heart	5.7 ± 3.4	7.2 ± 4.8	**0.032**
Aortic valve	12.7 ± 6.2	21.5 ± 5.8	**<0.001**
Pulmonary valve	19.7 ± 10.7	24.5 ± 8.2	**0.031**
Mitral valve	6.0 ± 5.2	10.9 ± 10.7	0.071
Tricuspid valve	7.3 ± 7.7	9.6 ± 11.8	**0.034**
Left main coronary trunk	17.2 ± 8.8	25.9 ± 5.2	**0.002**
Left interventricular coronary	17.0 ± 10.7	17.9 ± 9.1	0.42
Circumflex coronary artery	13.1 ± 9.3	18.1 ± 10.6	**0.014**
Right coronary artery	12.8 ± 9.0	15.6 ± 10.2	**0.002**
Right atrium	6.9 ± 5.4	8.8 ± 7.7	0.18
Left atrium	8.9 ± 5.1	14.2 ± 6.9	**0.005**
Right venctricle	4.5 ± 3.0	5.6 ± 4.8	0.15
Left ventricle	4.6 ± 3.7	5.2 ± 4.4	0.28
Interventricular septum	4.8 ± 3.4	5.6 ± 4.4	0.10
Left ventricular lateral wall	4.4 ± 4.5	4.1 ± 4.0	0.56



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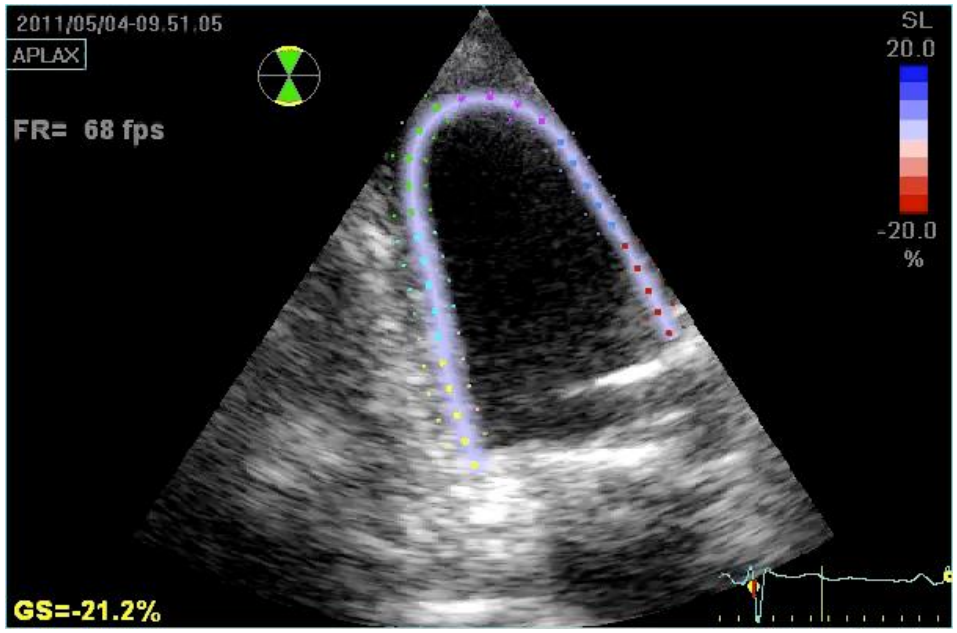
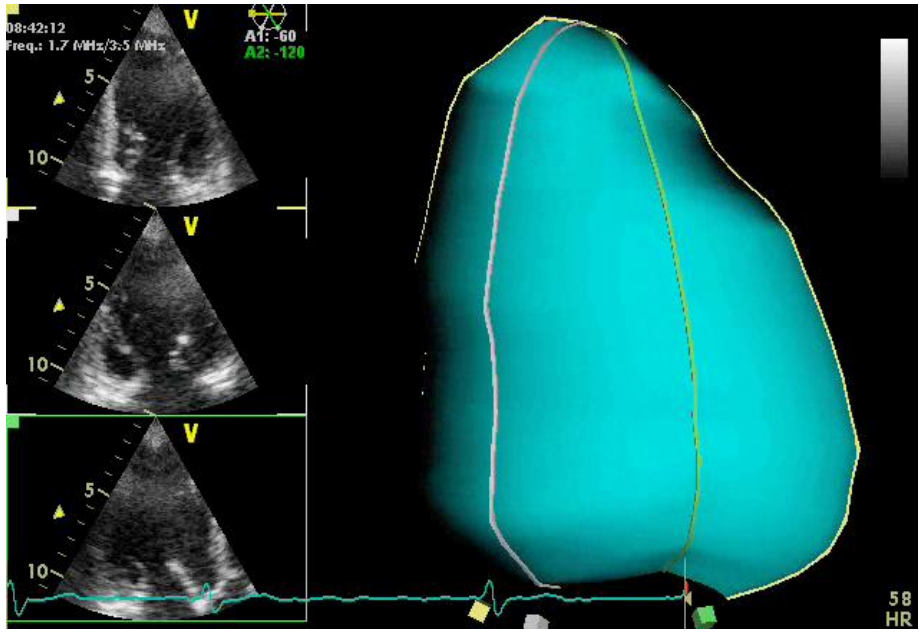
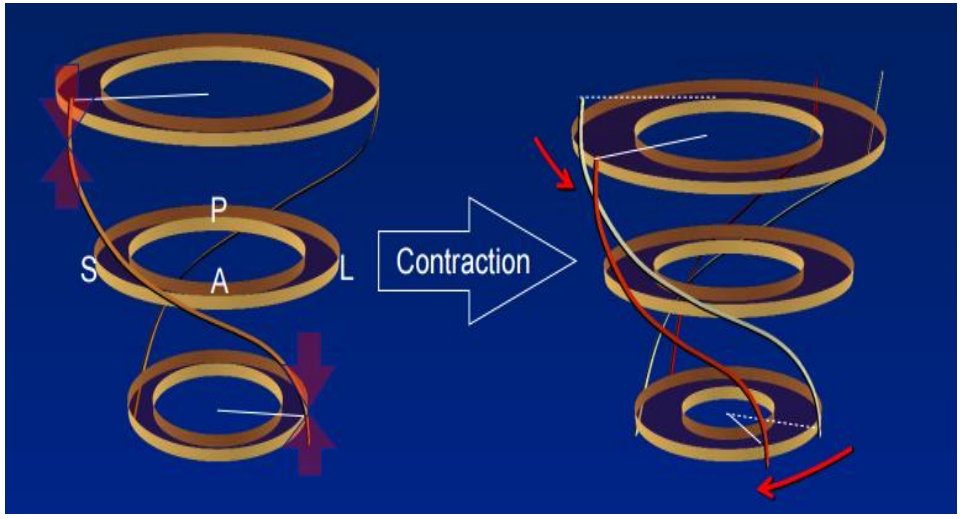
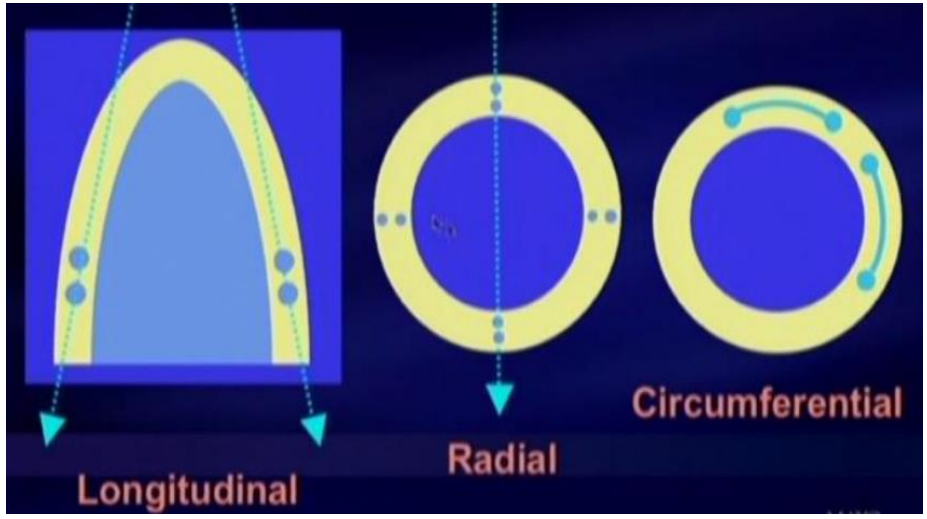
Advanced Ultrasound Imaging
STRAIN – “SPECKLE TRACKING”









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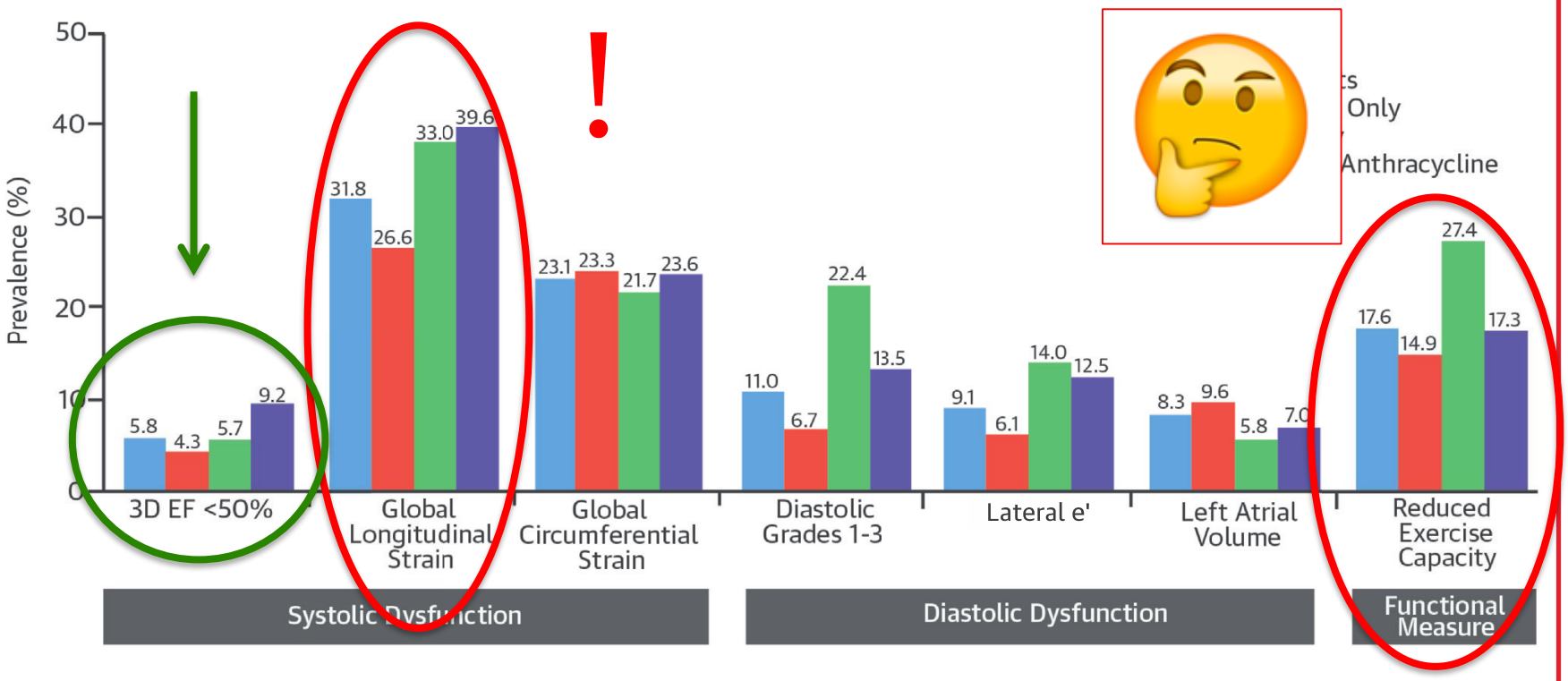
Comprehensive Echocardiographic Detection of Treatment-Related Cardiac Dysfunction in Adult Survivors of Childhood Cancer

Results From the St. Jude Lifetime Cohort Study

- 1820 adult patients (median age 31 years)
- Median time from diagnosis 23 years
- All patients underwent an ECHO-assessment

CENTRAL ILLUSTRATION **Prevalence of Cardiac Dysfunction and Reduced Exercise Capacity in Adult, 10-Year Survivors of Childhood Cancer**



Armstrong, G.T. et al. J Am Coll Cardiol. 2015; 65(23):2511–22.

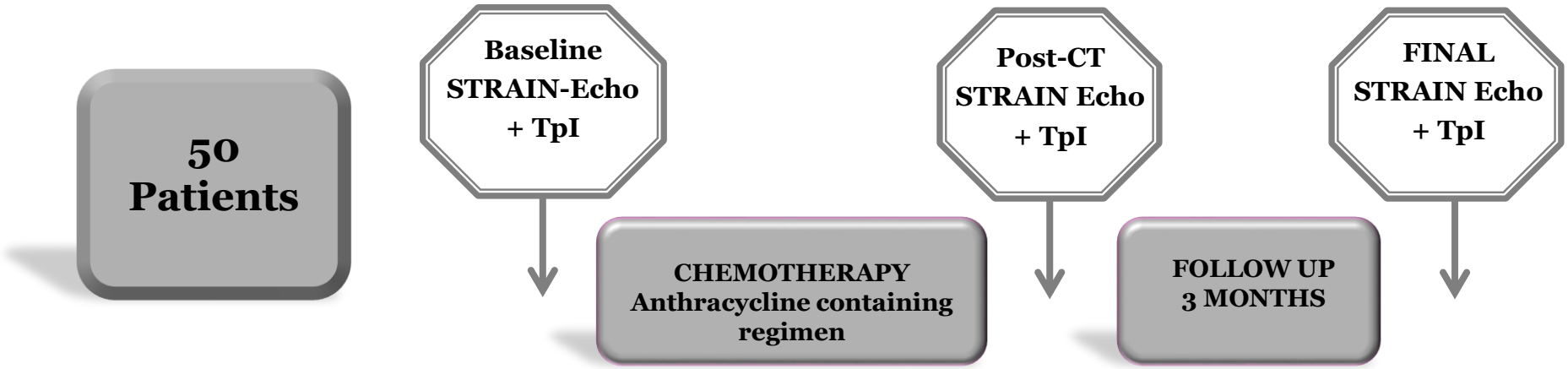
EF = ejection fraction; RT = radiotherapy; 3D = 3-dimensional.

Armstrong et al JACC 2015

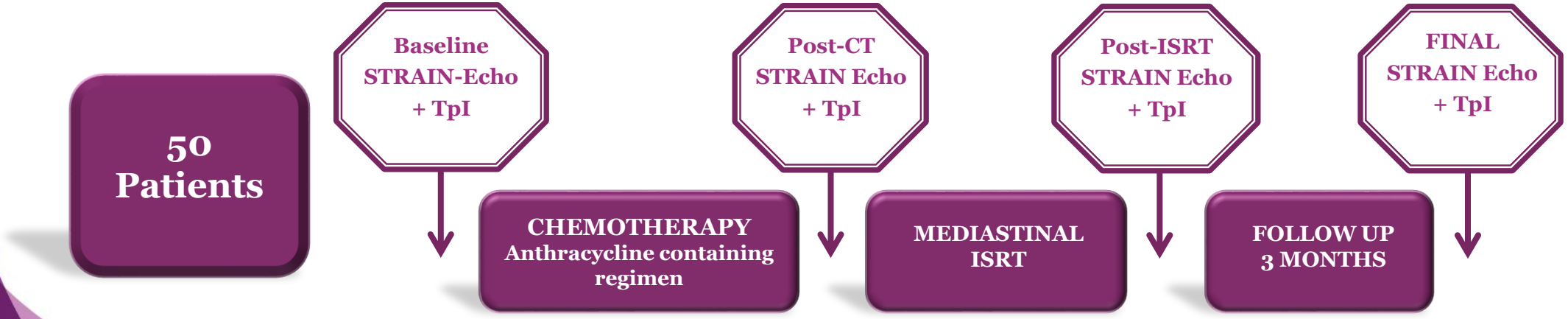
CARDIOCARE PROJECT @ Univerisity of Torino

"Subclinical Cardiotoxicity Detected By Strain Imaging After Chemotherapy And Mediastinal Rt In Lymphoma Patients (Hl – Dlcl –Pmbcl)"

Cohort A: CHEMOTHERAPY ALONE



Cohort B: COMBINED MODALITY TREATMENT



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RADIATION ONCOLOGY GROUP

A prospective, observational study evaluating early subclinical cardiotoxicity with global longitudinal strain imaging in lymphoma patients treated with chemotherapy +/- mediastinal radiotherapy: preliminary results of the CARDIOCARE project.

LEVIS Mario[1], **FILIPPI** Andrea Riccardo[1], **ORSUCCI** Lorella[2], **GIORGI** Mauro[3], **BOTTO** Barbara[2], **CHIAPPELLA** Annalisa[2], **FAVA** Antonella[3], **FERRERO** Simone[4], **PIVA** Cristina[1], **GAVAROTTI** Paolo[4], **LAPI** Simone[3], **FURFARO** Gabriella[1], **PREGNO** Patrizia[2], **VITOLO** Umberto[2] and **RICARDI** Umberto[1]

Author Affiliations:

[1]*Department of Oncology, Radiation Oncology, University of Torino, Italy*
[2]*Department of Hematology, A.O.U. Città della Salute e della Scienza, Torino, Italy*
[3]*Department of Cardiology, A.O.U. Città della Salute e della Scienza, Torino, Italy*
[4]*Department of Hematology, University of Torino, Italy*

- Preliminary results on the first 22 patients that completed the observation

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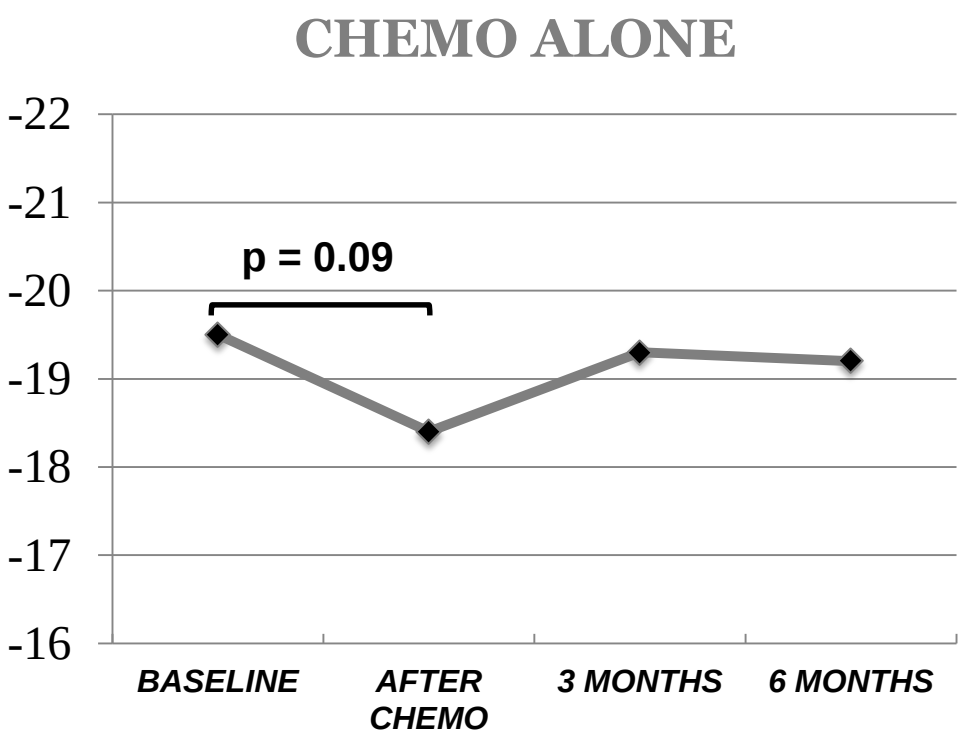
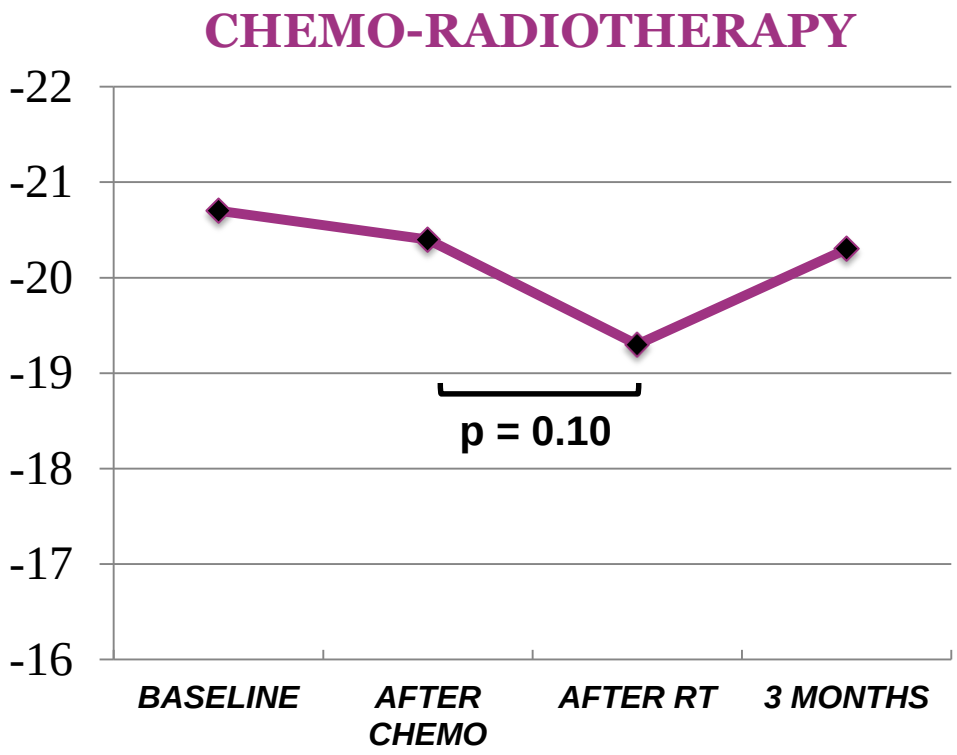
PRELIMINARY RESULTS

2D STRAIN (GLS)





Levis M. et al. Poster Session, ILROG meeting, Melbourne, 7-8 April 2017

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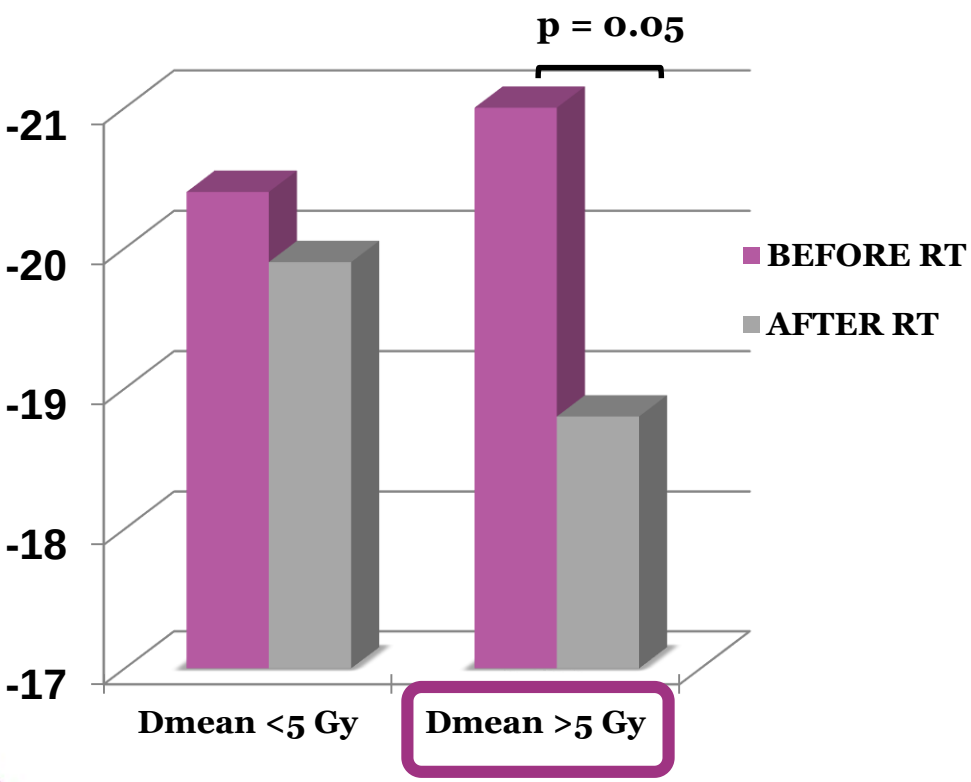
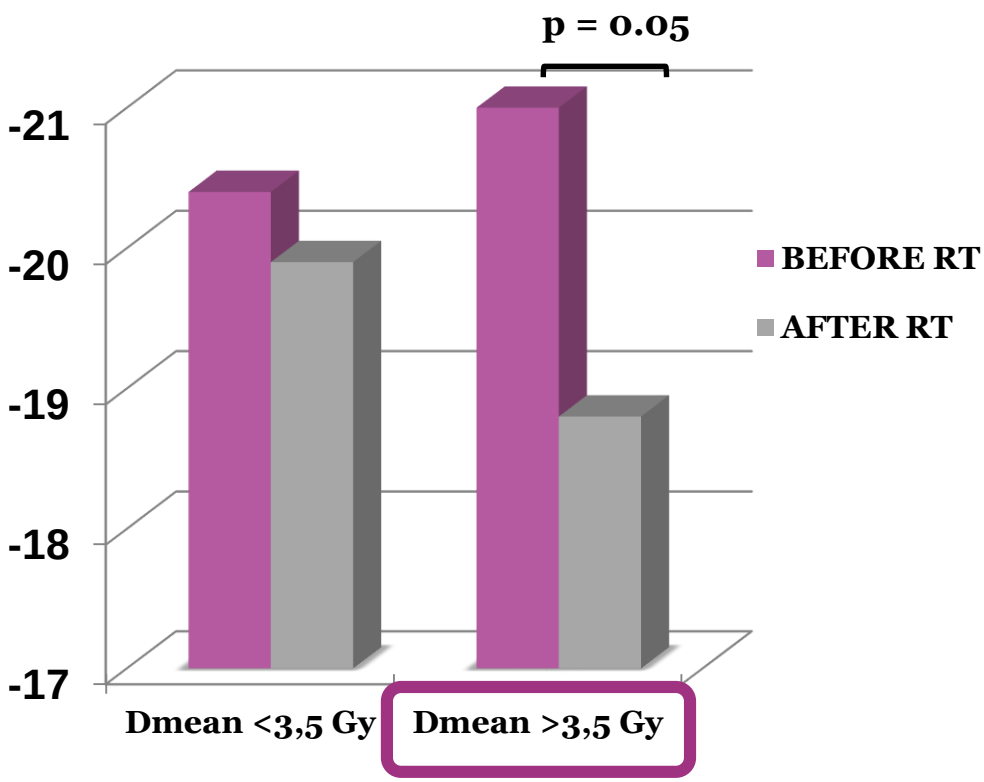
PRELIMINARY RESULTS

2D STRAIN (GLS)

MEAN HEART DOSE



MEAN LEFT VENTRICULAR DOSE



Levis M. et al. Poster Session, ILROG meeting, Melbourne, 7-8 April 2017

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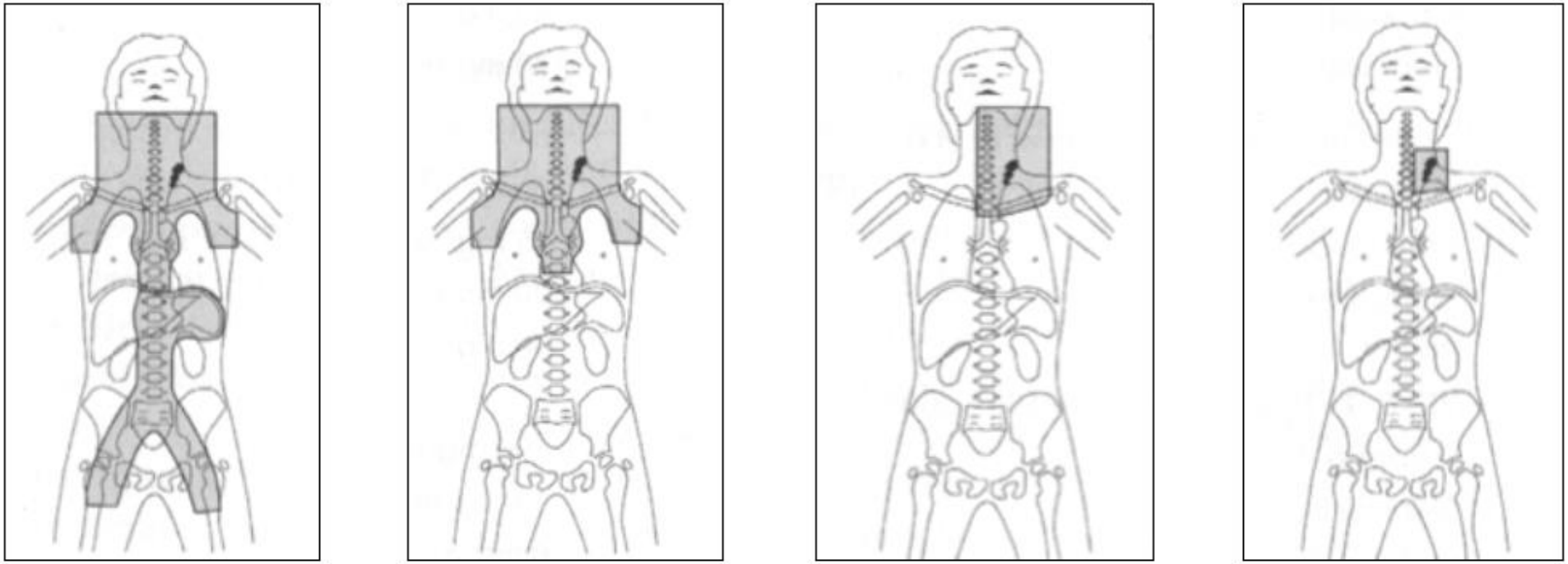
Radiotherapy Evolution in the treatment of HL: It's time to reap the fruits of our labor

1970-1980	1980-1990	1990-2005	2005 →
EXTENDED FIELD	REGIONAL NODAL	INVOLVED-FIELD	INVOLVED NODAL INVOLVED SITE



2D-RT → 3D-RT → IMRT/IGRT

Dose: 36-44 Gy → Dose: 20-30 Gy

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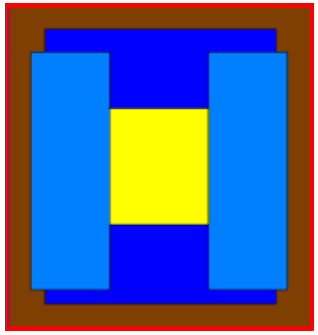
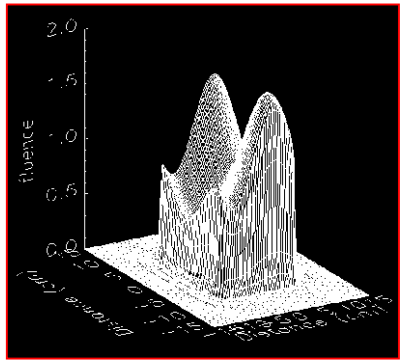
THE CONFORMALITY CONTINUUM

1980s | Late 1990s | 2000s | 2010s

TREND – Improving Precision

2D | 3D-CRT | IMRT/VMAT | IGRT





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Modern RT in Lymphoma: Volume delineation

- **Advances** in imaging, treatment planning, treatment delivery, have made it possible to better define and further **decrease RT volumes** in many situations

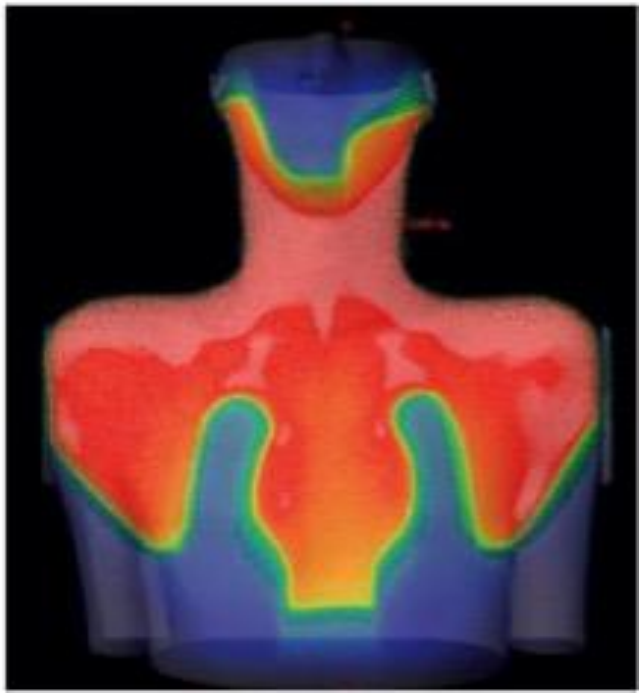
- The current **guidelines for involved field RT** based on **anatomic landmarks** and encompassing adjacent uninvolved lymph nodes **are no longer appropriate** for modern and more "targeted" RT delivery aimed at reducing normal tissue exposure

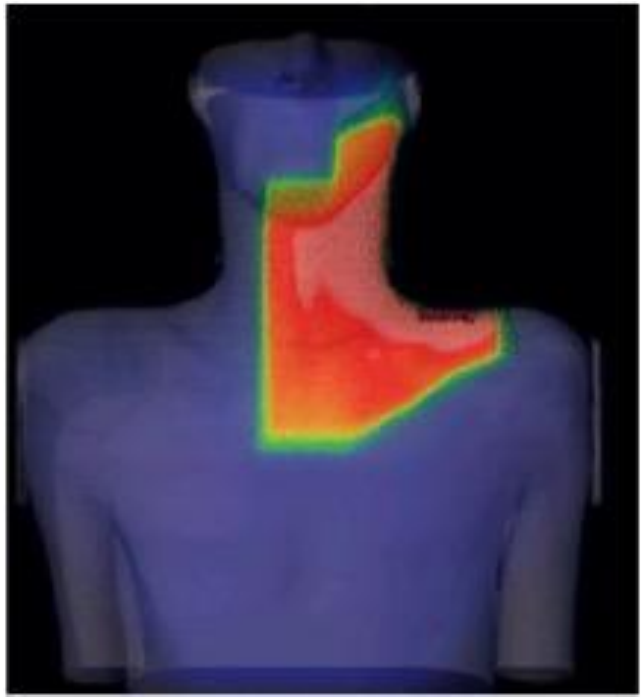
Radiotherapy Volumes for Lymphoma Patients

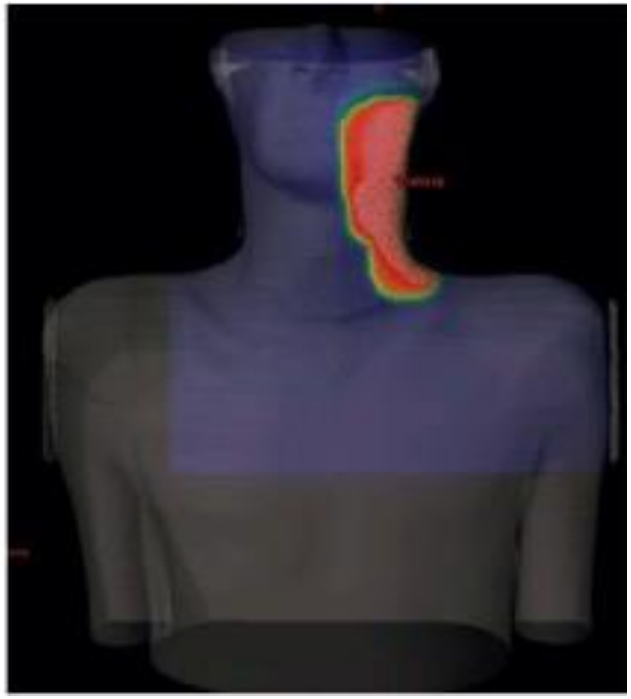
Mantle field

Involved field

Involved site
Involved node







Volume treated on the basis of anatomical borders

Targets of treatment are only lymph nodes and/or extranodal sites involved at baseline

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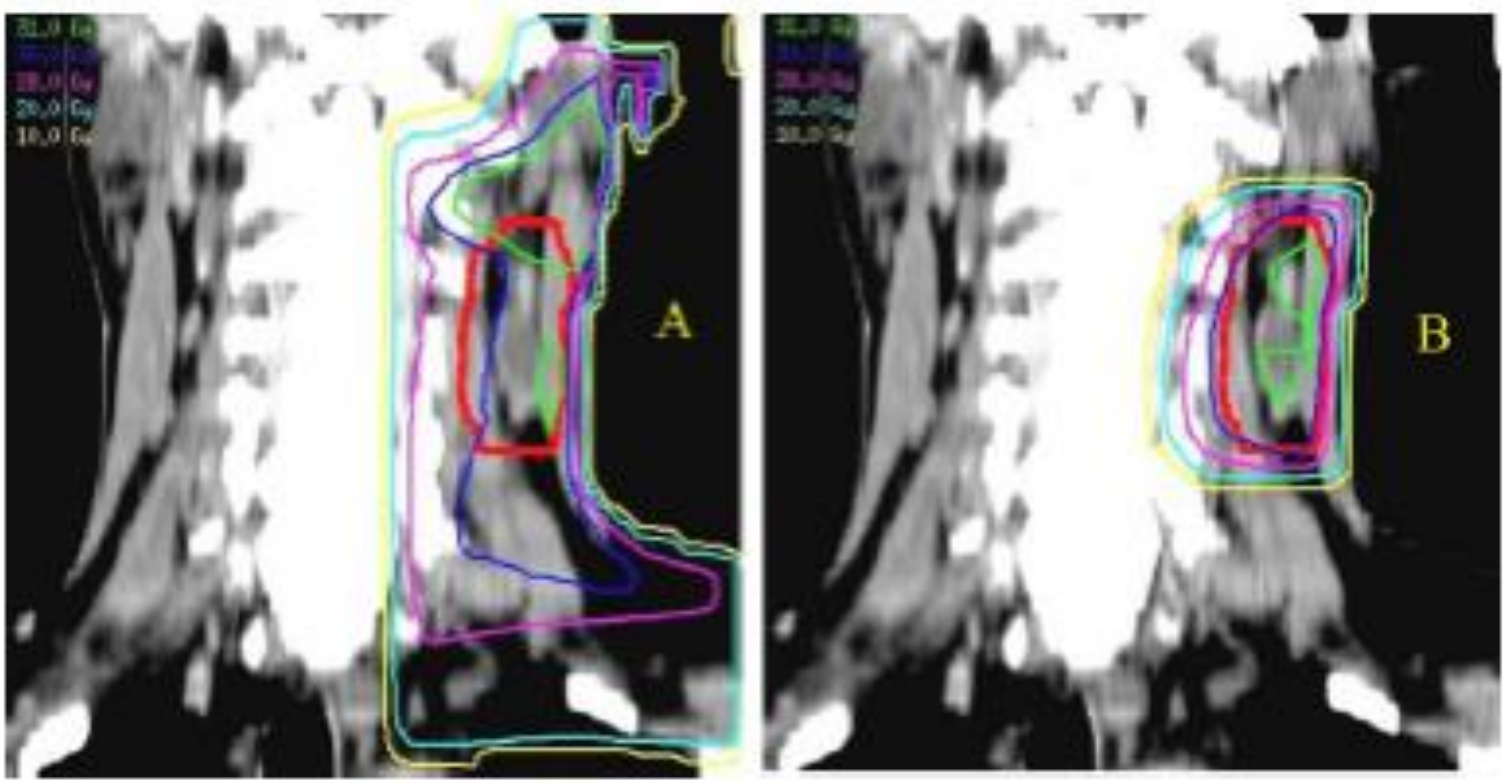
From IFRT to INRT or ISRT



- The concept of **IF-RT** which included the whole initially involved lymph node region can now be replaced by the concept of **involved-node RT**, which only includes the initially involved lymph node(s)

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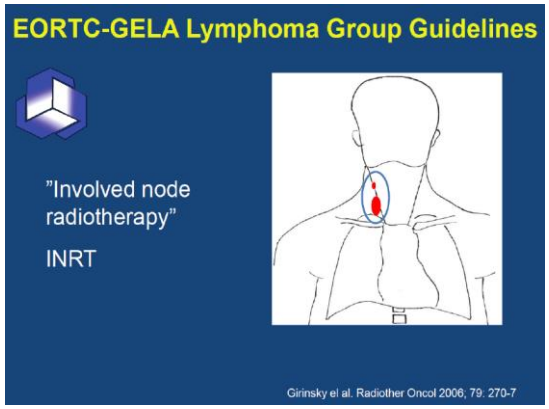
The concepts of INRT and ISRT

❑ Involved Node Radiotherapy (INRT)

- Good pre-chemo imaging with PET-CT in treatment position
- Image fusion with post-chemo planning CT
- Contouring target volume of tissue which contained lymphoma at presentation



❑ Involved Site Radiotherapy (ISRT)

- Detailed pre-chemo imaging is not always optimal (not in treatment position) in standard clinical practice
- Compared to INRT slightly larger volumes needed to ensure irradiation of all initially involved tissue volumes, but the same principles apply
- In most situations, ISRT includes significantly smaller volumes than IFRT

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The “Clinical” Role of the Radiation Oncologist

- ***Defining CTV relies upon:***

1. the quality and accuracy of imaging;

2. knowledge of the spread patterns of the disease, as well as potential subclinical extent of involvement, and adjacent organ at risk constraints

↓

All of which depend on clinical judgment and experience

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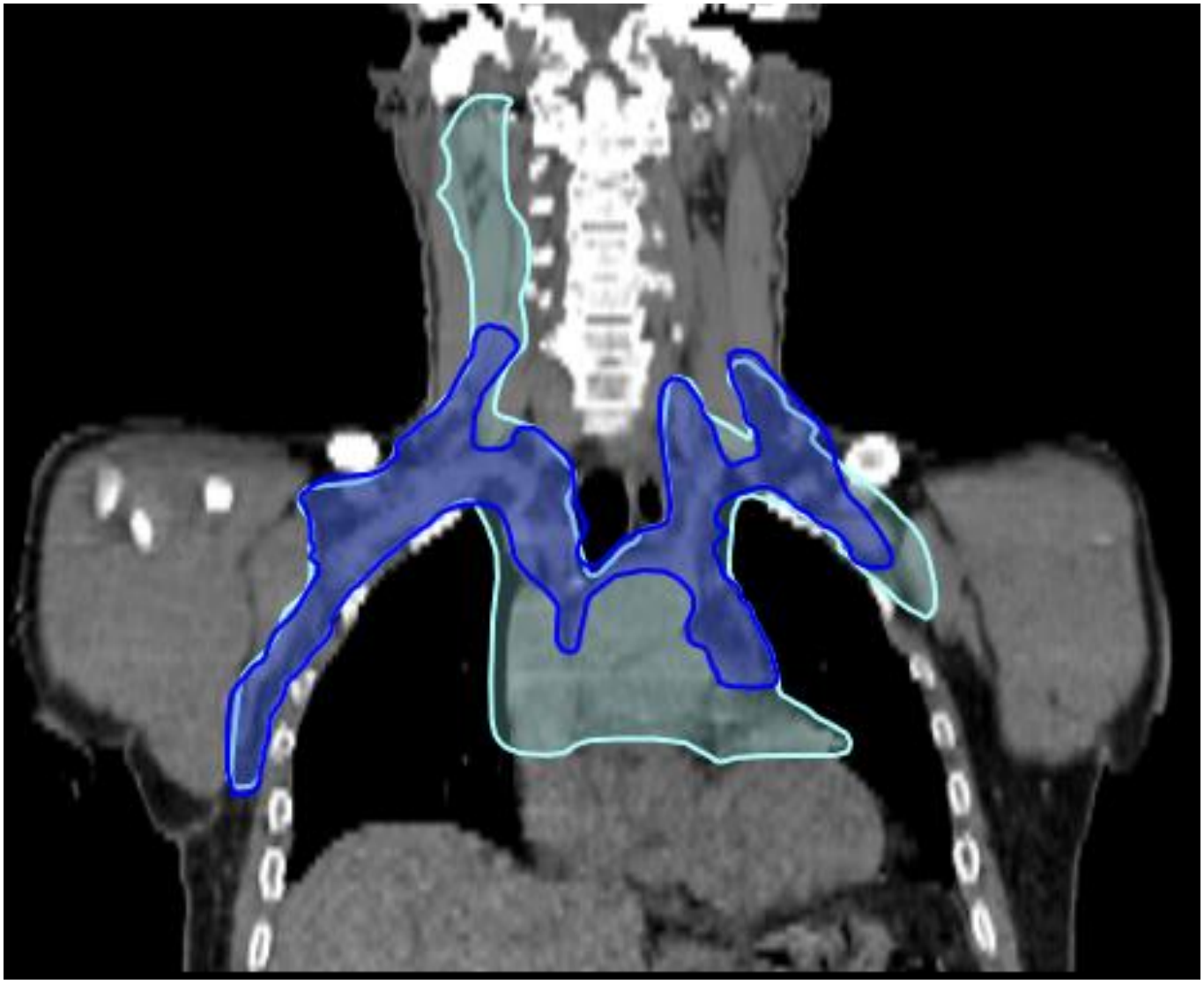
From IFRT to ISRT



“In most situations, ISRT will include significantly smaller volumes than IFRT"

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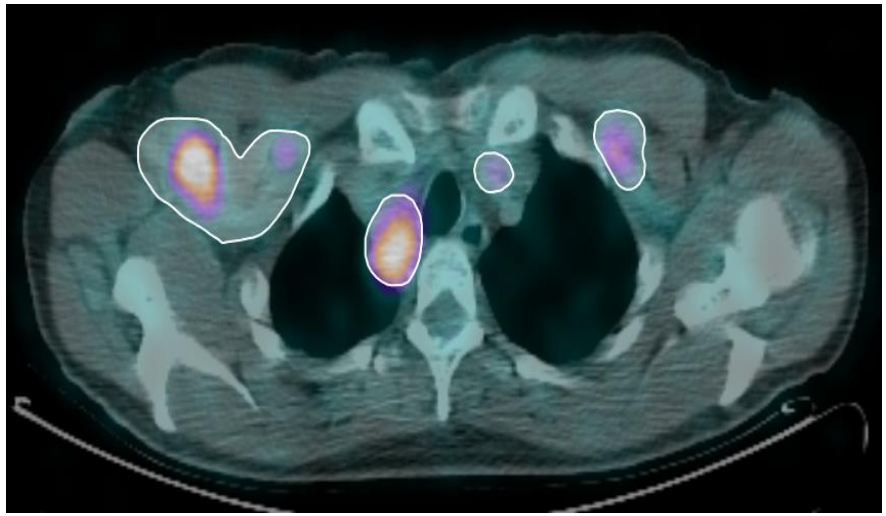
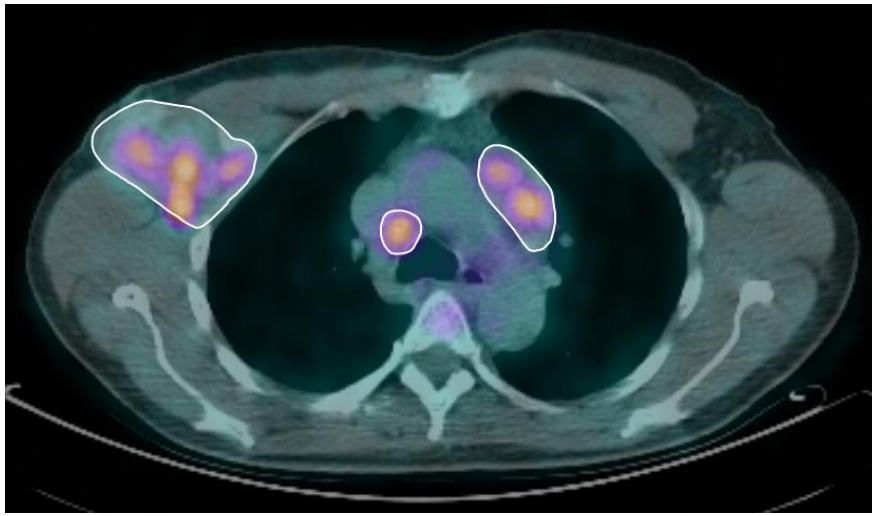
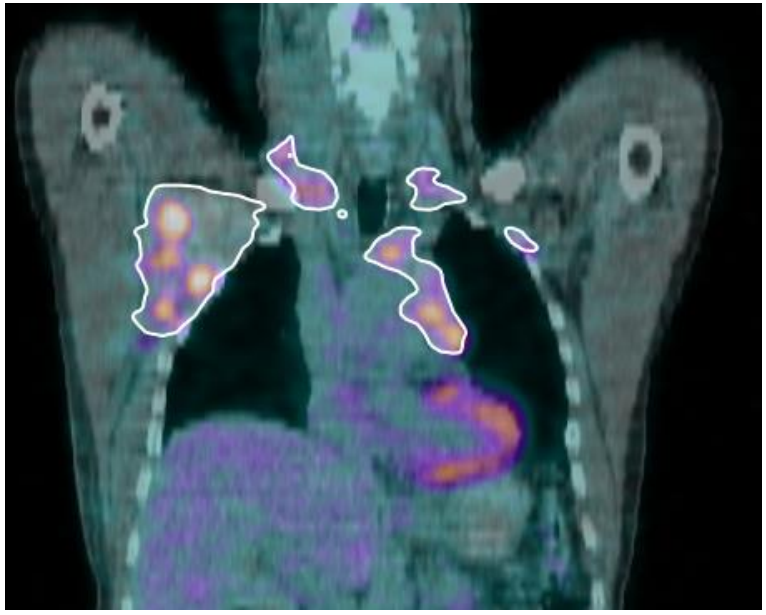
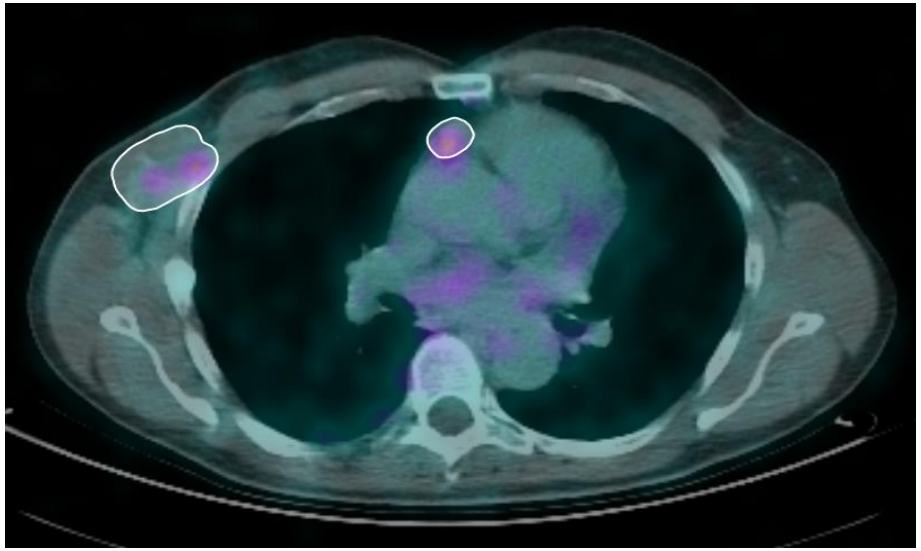
GTV on pre-chemotherapy PET









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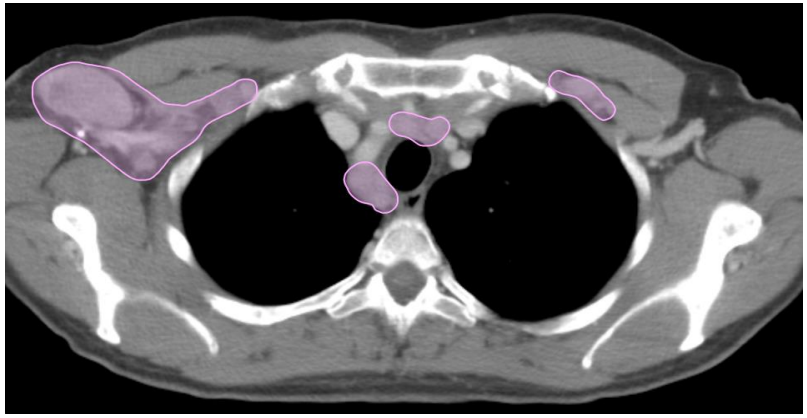
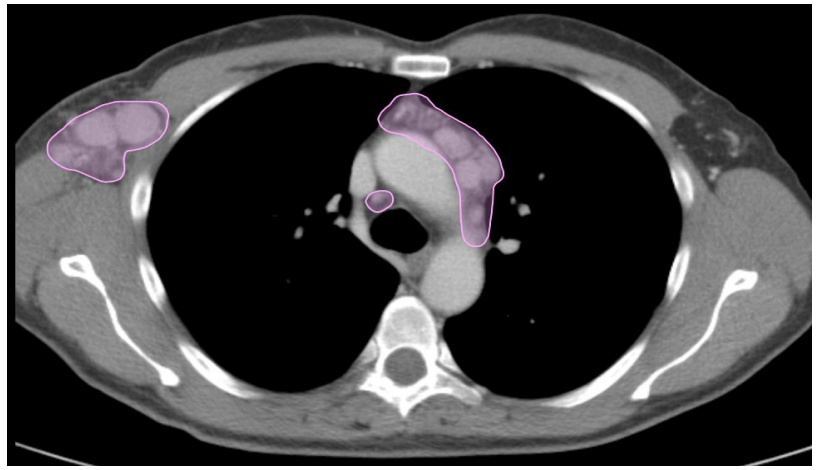
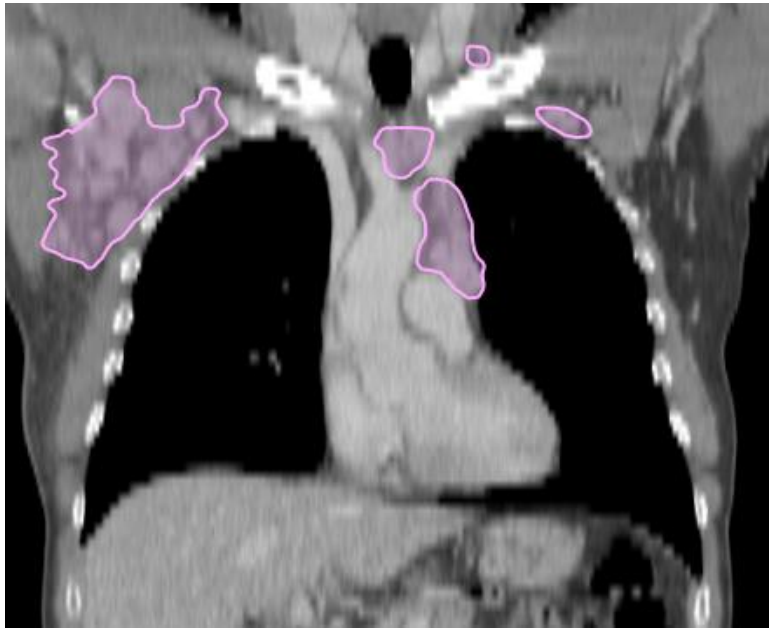
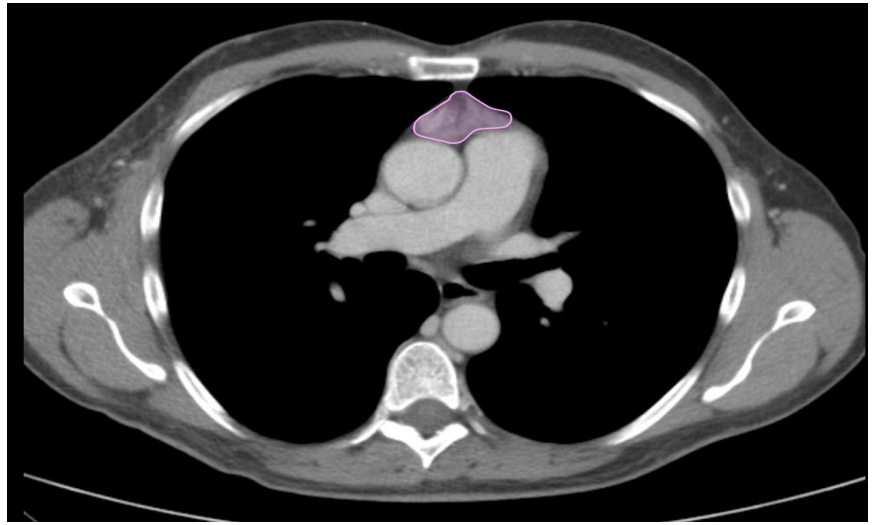
GTV on pre-chemotherapy CT scan









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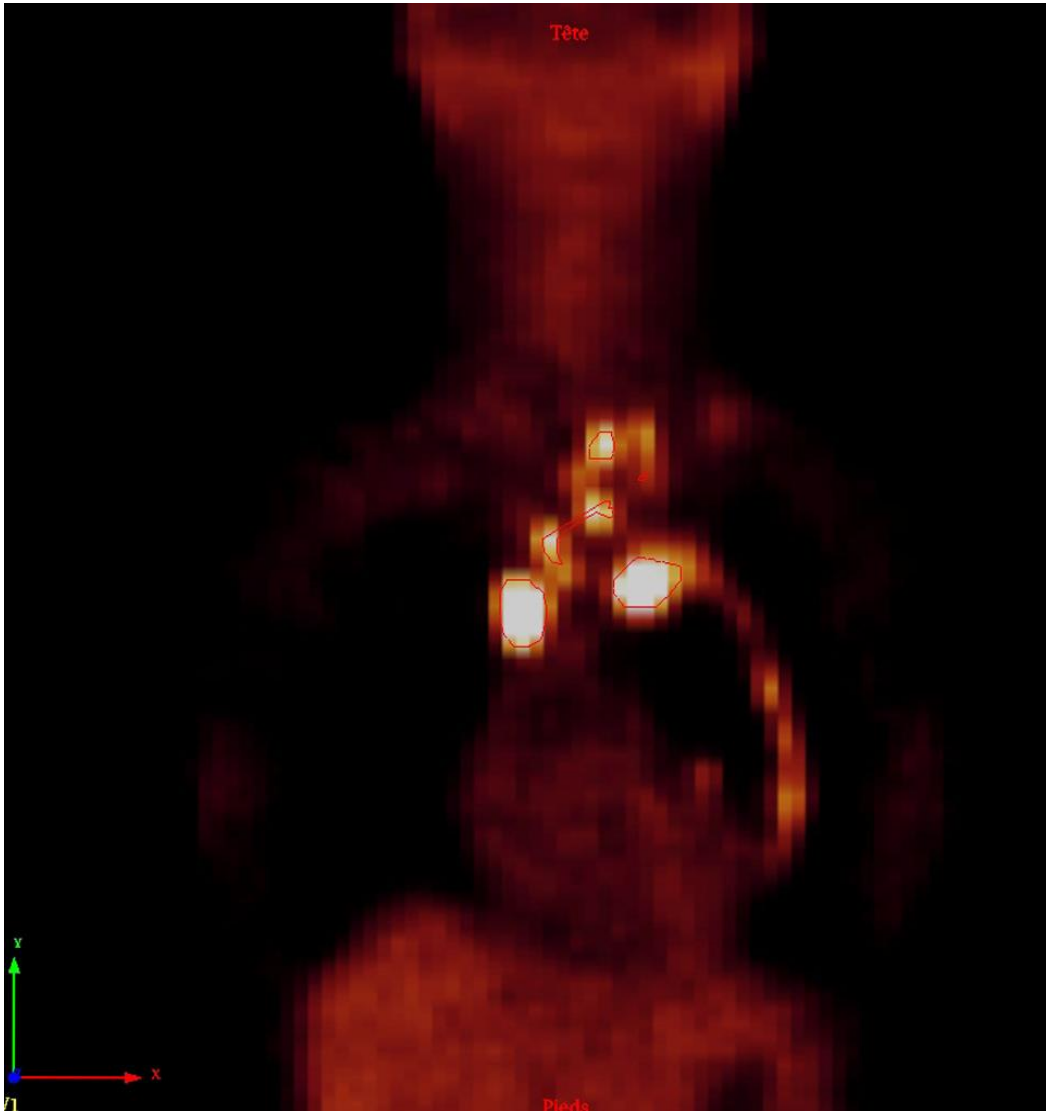
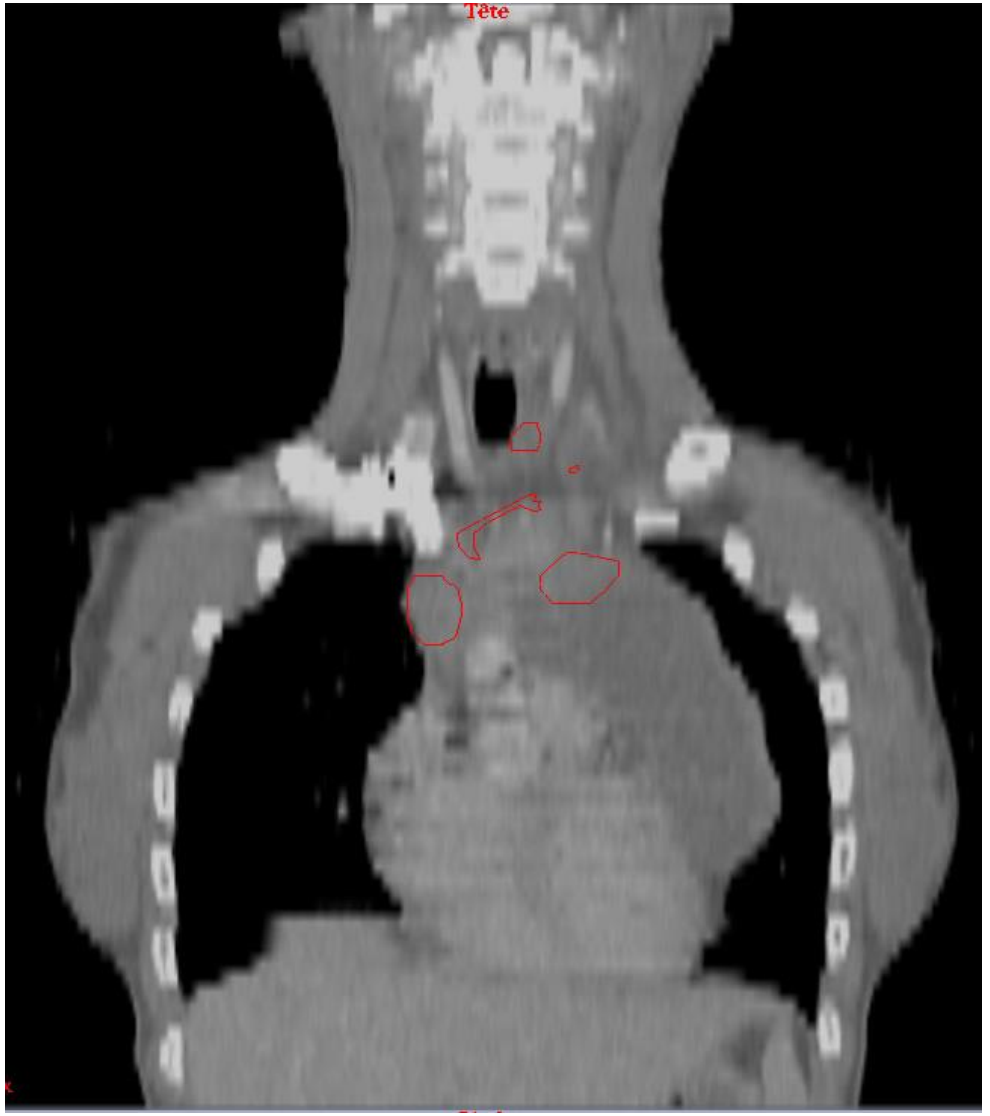
PET avidity often heterogeneous





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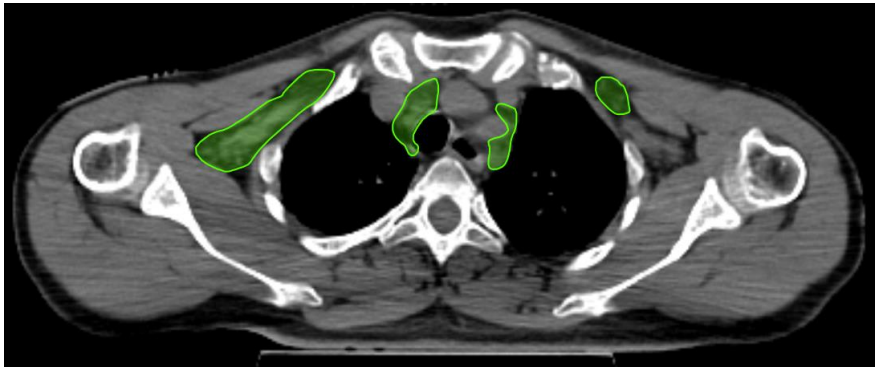
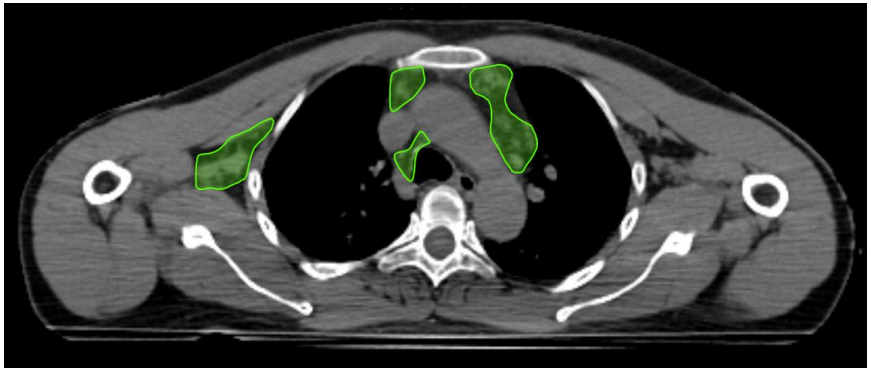
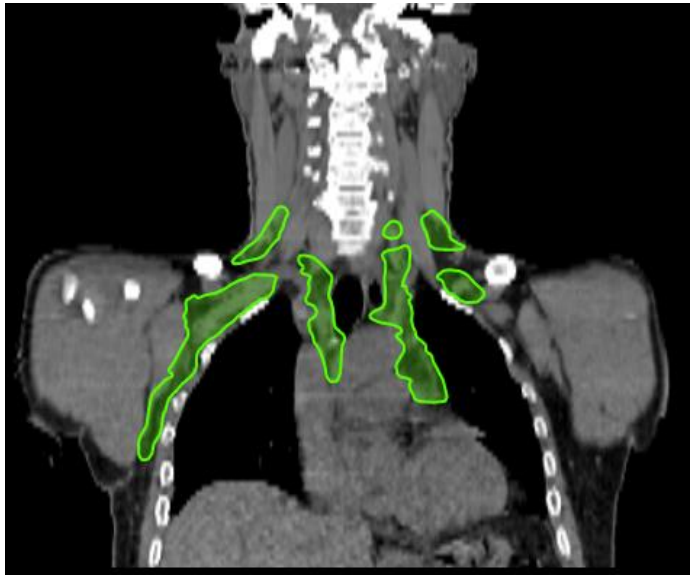
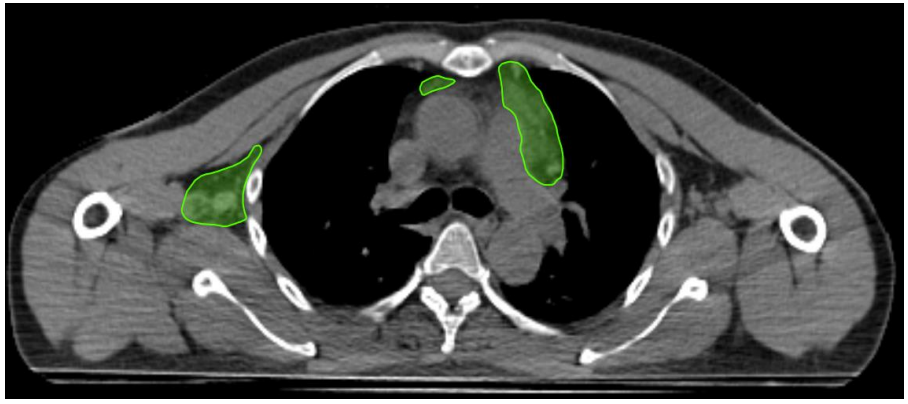
- GTV_{CT} and GTV_{PET} import on planning CT→
- CTV definition by modifying GTVs according to response and normal tissues displacement → INRT and ISRT









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3DCRT vs IMRT/VMAT
which technique is preferable ?

- ***There is no single proven best planning and delivery RT technique***

- No two lymphomas are the same with regard to localization and extent of disease

- ***The decision should be made at the individual patient level*** (i.e., what appears the optimal treatment plan for one patient may not be acceptable for another patient)

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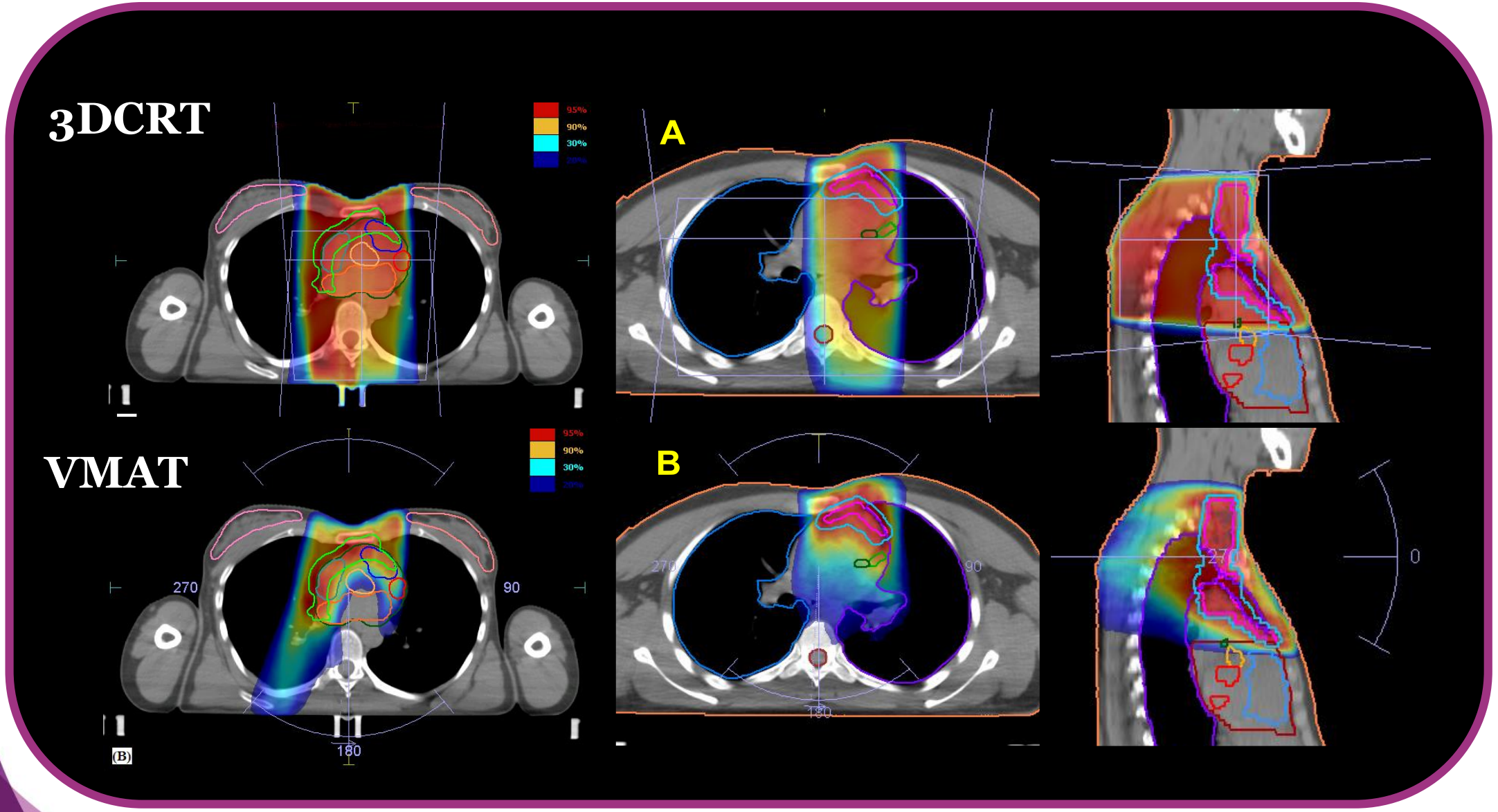
IMRT is probably better in mediastinal lymphomas



Take Home Message (Early Stage HL)

- ***Combined modality therapy still represents a standard*** for patients affected with early stage HL. Chemotherapy alone can be considered in some patients, after a discussion with a Radiation Oncologist to hear about PROs/CONs in his/her particular case

- Interim-PET studies confirmed that ***even PET-negative patients are more likely to fail without RT*** and modification of the treatment schedule according to PET-scan is experimental

- ***Radiation oncologists should be aware of the opportunity to minimize the risks*** of late toxicity by using smaller fields and most recent technological improvements in radiation planning and delivery.

- ***A balanced multi-disciplinary evaluation*** of individual patients should be ***encouraged*** for the proper selection of ***the best strategy*** according to age, disease extension, secondary cancer and heart diseases risk profile.

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❑Early stage HL

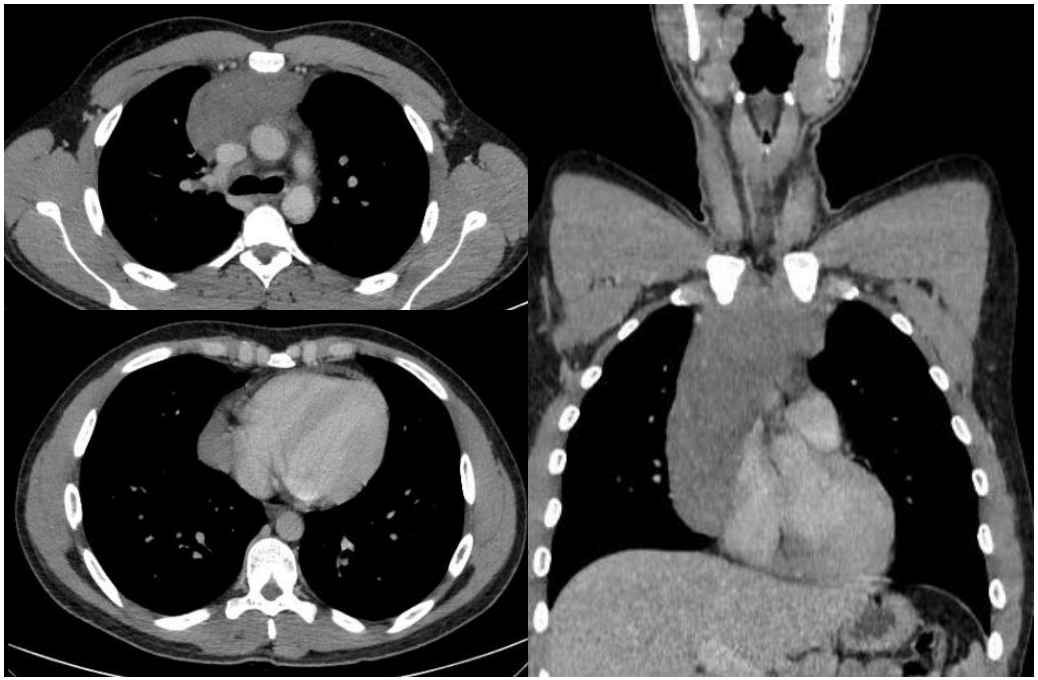
- Without risk factors (Favourable)
- With risk factors (Unfavourable or Intermediate)

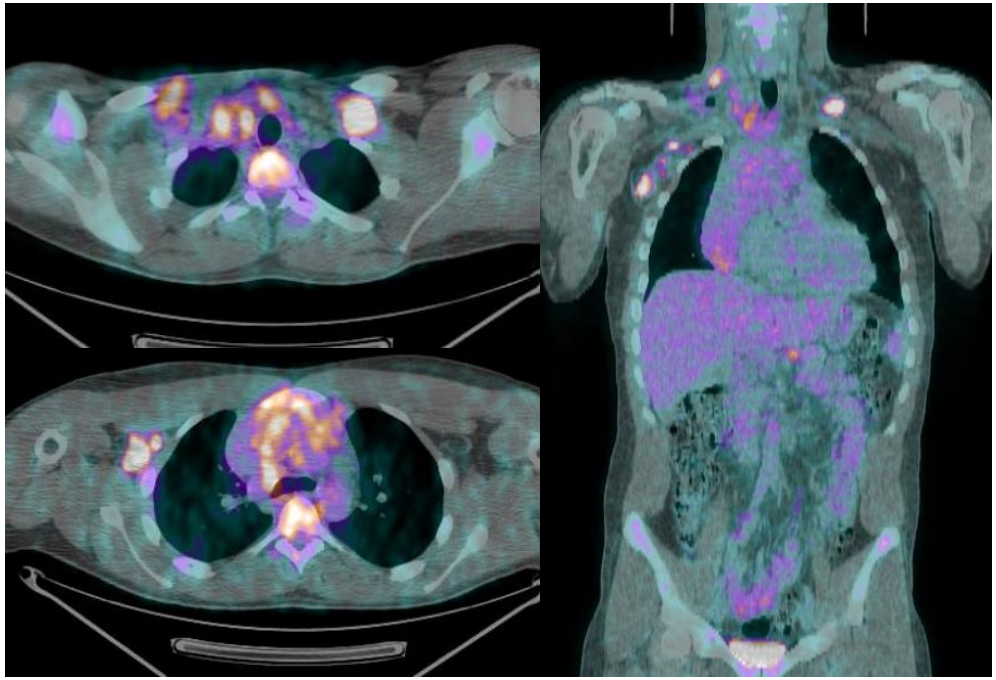
❑Advanced stage HL

❑Non Hodgkin Lymphoma

CLINICAL CASE #2 – Advanced stage HL

- G.R., 28 years old, male.
- April 2016: night sweats, fever (>38°C), left supraclavicular lymph node.
- Supraclavicular FNA: cHL scleronodular
- CT and PET-CT scans (May 2016): right neck, bilateral supraclavicular and left axillary involvement. **Mediastinal bulky lesion**, para-aortic abdominal adenopathy.
- **stage IIIBX.**





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How to treat this patient ?

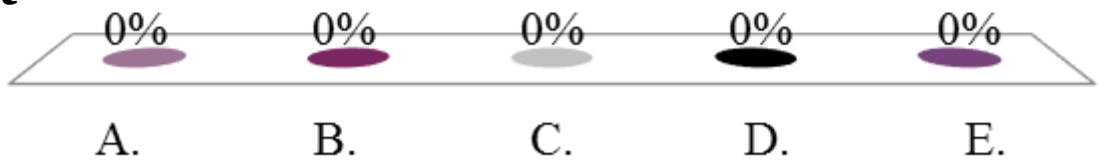
A. **ABVD x 6 alone**

B. **BEACOPPescalated x 6 alone**

C. **ABVD x 6 followed by consolidative ISRT 30 Gy to the bulky lesion**

D. **BEACOPPescalated x 6 + consolidative ISRT 30 Gy to PET+ residual disease after chemotherapy**

E. **ABVD x 6 or BEACOPPescalated alone; in case of PET+ residual disease, patient shifted to high dose chemo + ASCT**



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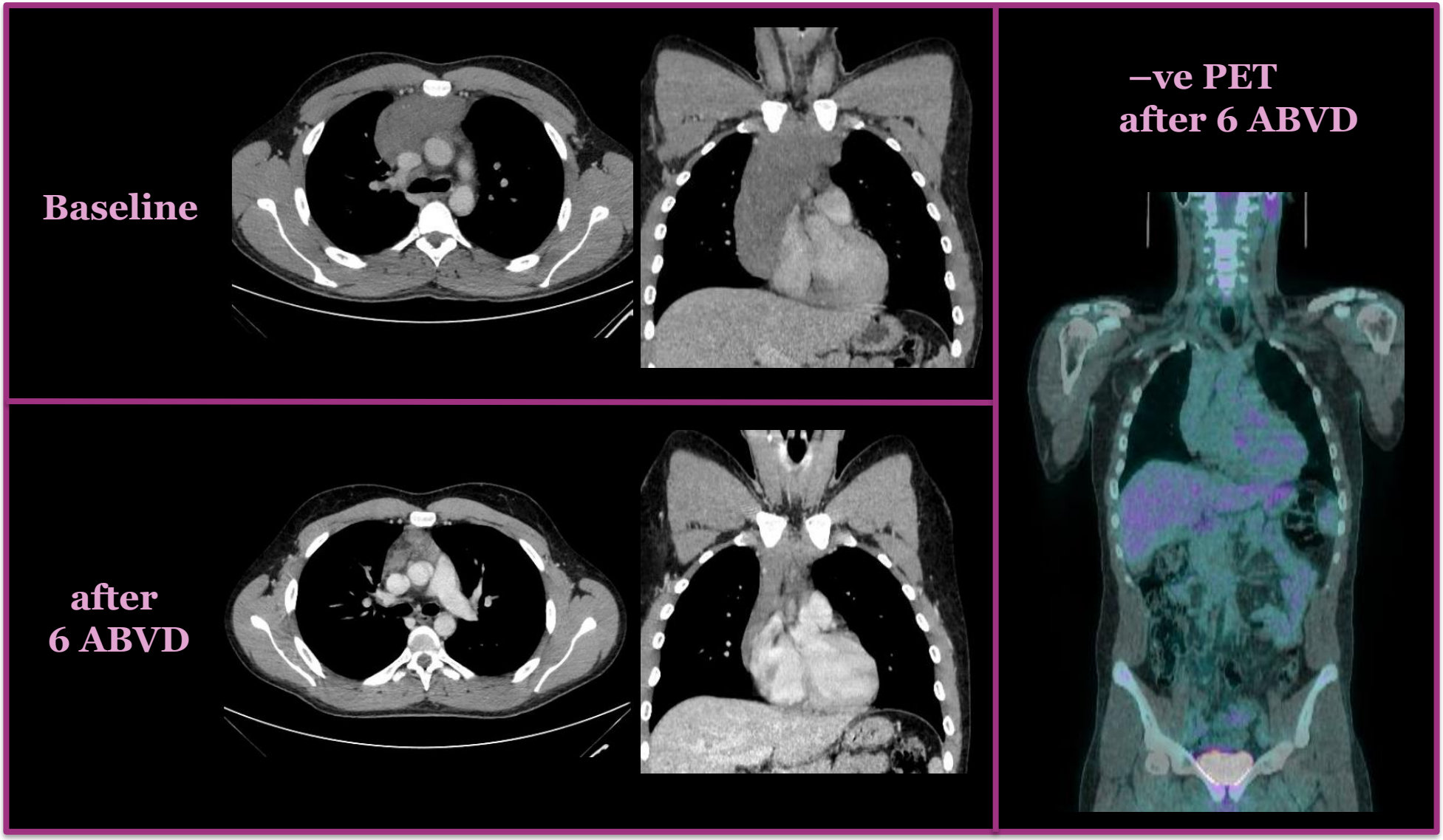
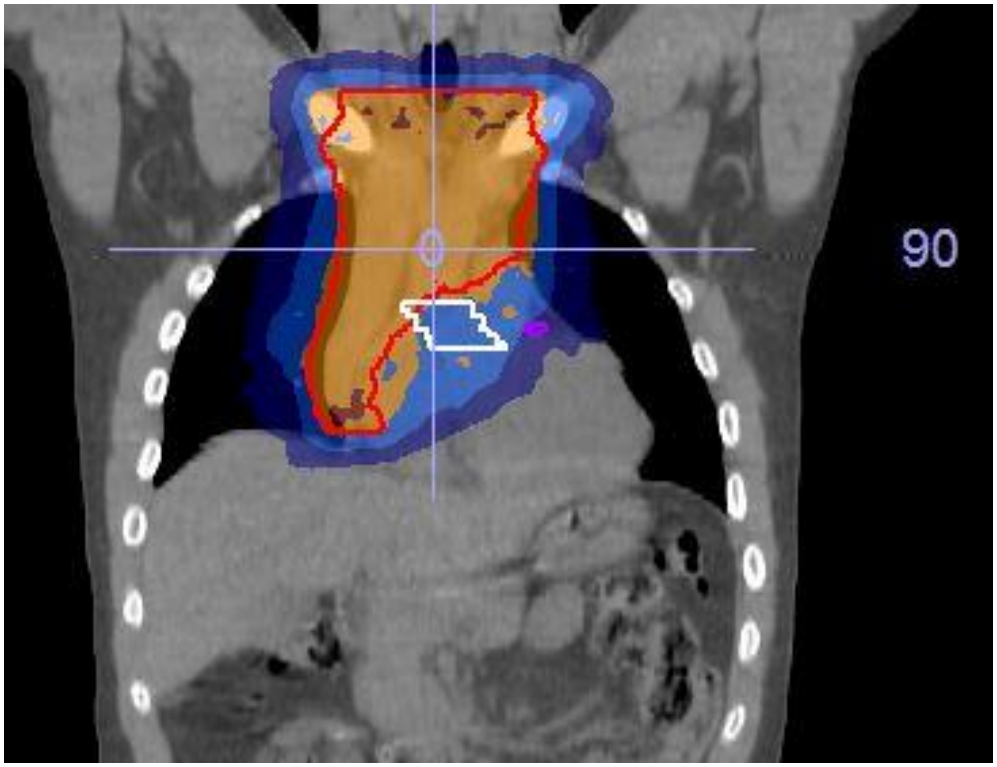
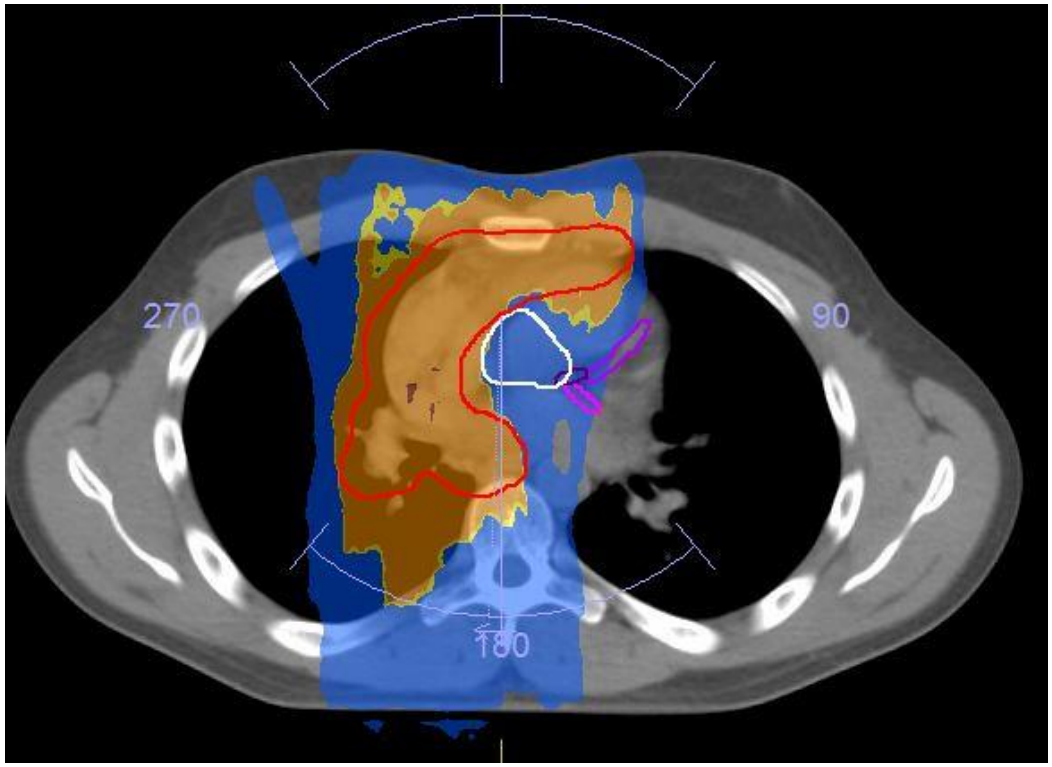
- Chemotherapy schedule: ABVD x 6
- PET2: complete metabolic response → Continued ABVD x 6
- PET6: confirmed complete metabolic response



- Treatments completed with consolidative RT to bulky lesion: 30 Gy/15 fractions
- IMRT approach (“butterfly VMAT)





Whole heart **MAX dose: 34.568 Gy**
Aortic valve **MAX dose: 30.404 Gy**
Left main trunk **MAX dose: 21.824 Gy**
Left descending **MAX dose: 21.850 Gy**
Circumflex **MAX dose: 20.163 Gy**
Lungs **MEAN dose: 9.559 Gy**

Whole heart **MEAN dose: 9.819 Gy**
Aortic valve **MEAN dose: 22.818 Gy**
Left main trunk **MEAN dose: 19.410 Gy**
Left descending **MEAN dose: 6.201 Gy**
Circumflex **MEAN dose: 11.639 Gy**
Lungs V20: **20.1% ---** Lungs **V5: 51.49%**

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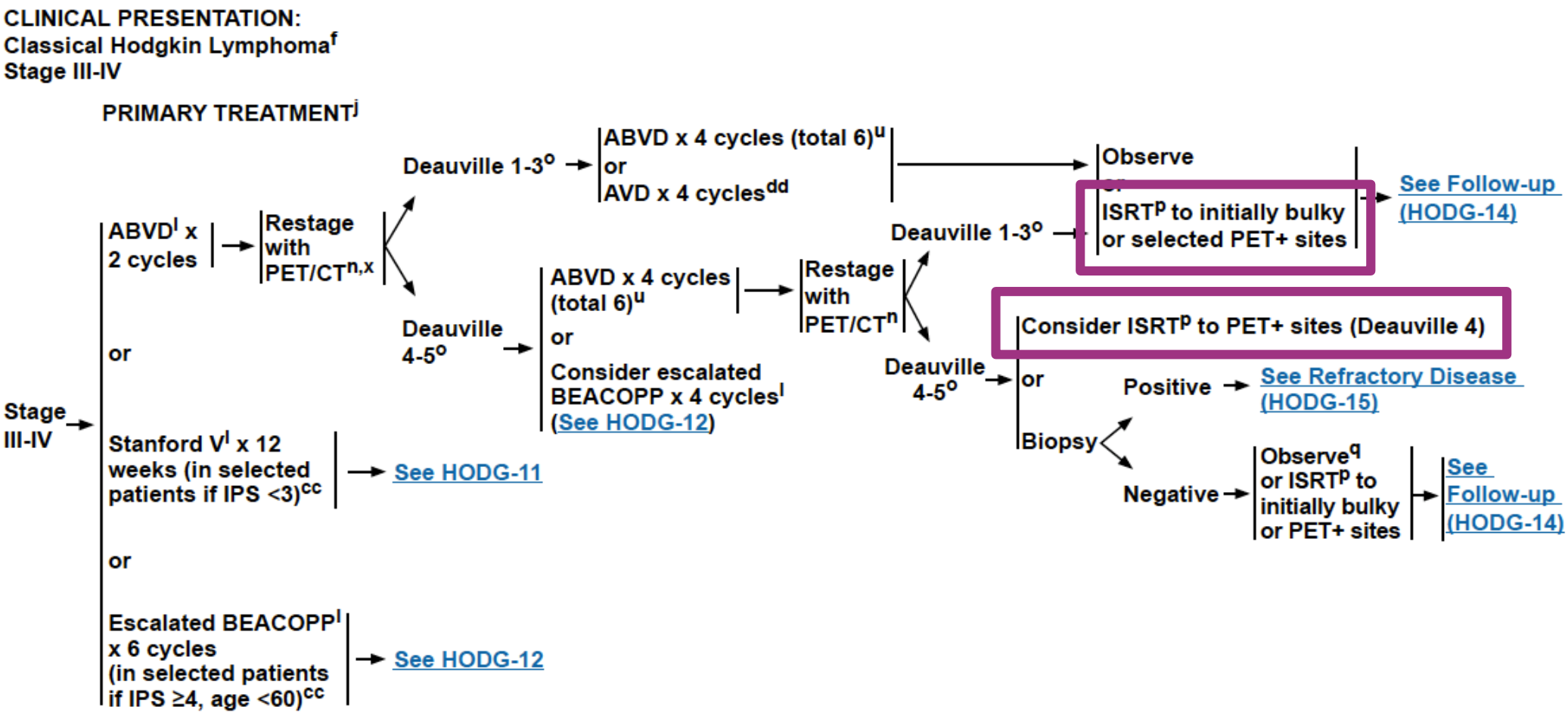
ROLE OF RADIATION THERAPY FOR ADVANCED STAGE HODGKIN LYMPHOMA



RADIATION ONCOLOGIST AND HEMATOLOGIST…
Different perspectives on the same story?!?

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Role of RT in Advanced stage HL

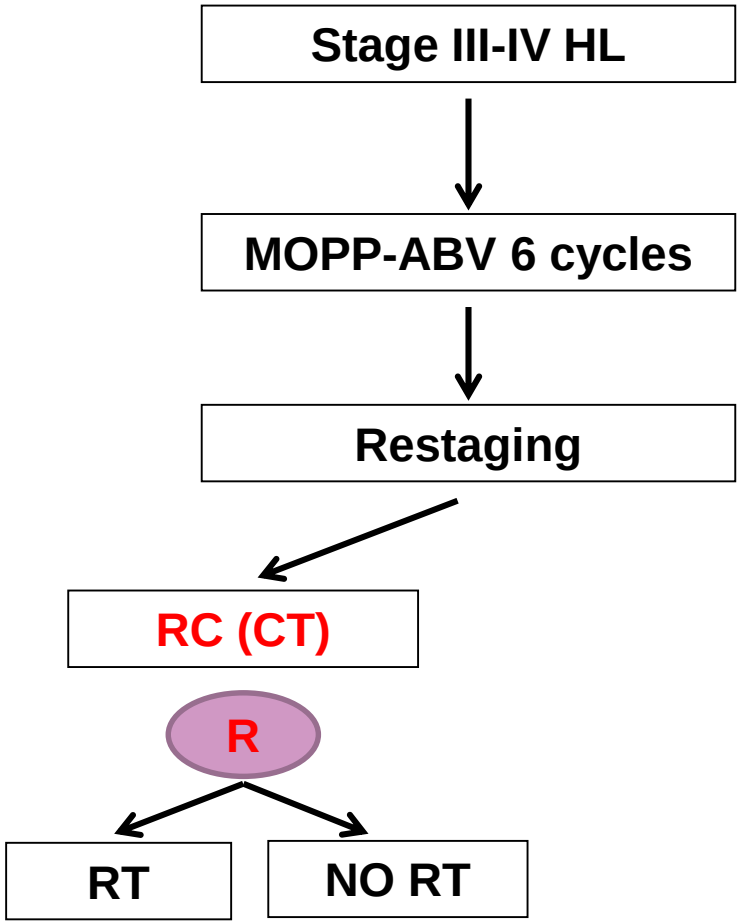
- The role of ***consolidative RT on bulky lesions*** for advanced stage Hodgkin disease is ***controversial***.

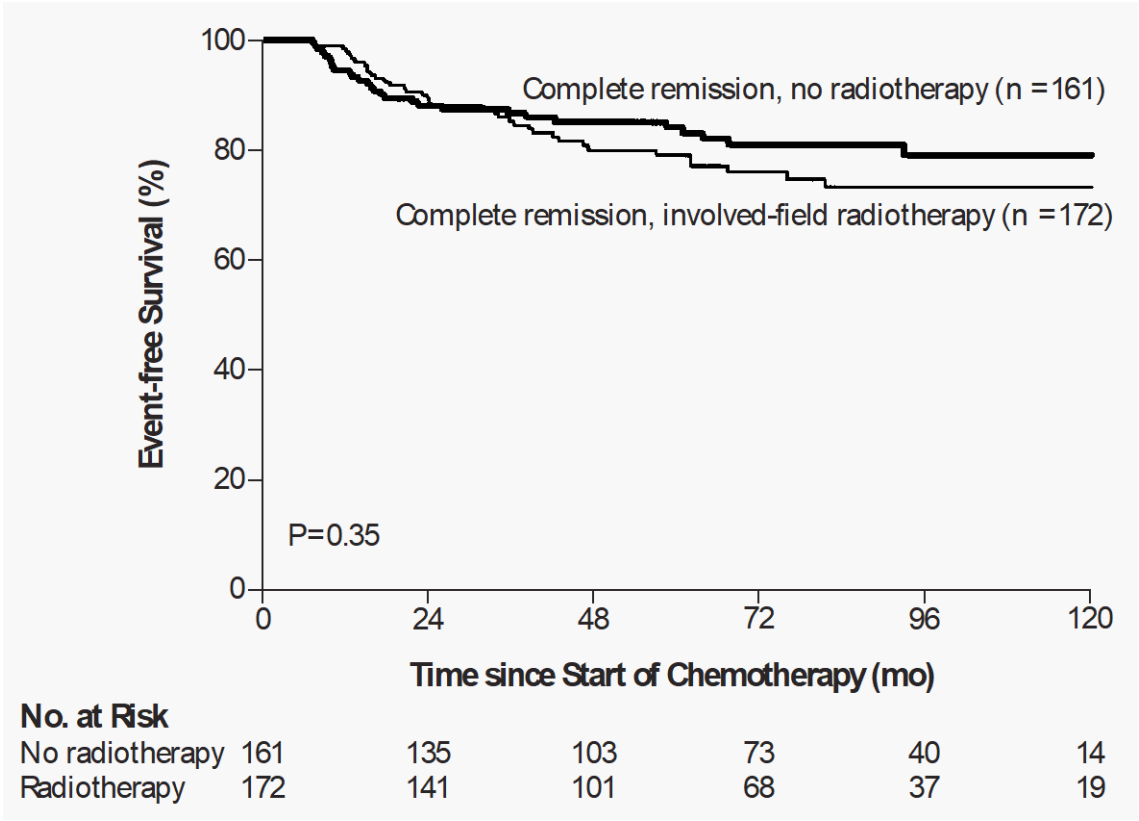
- Several studies have shown the ***beneficial role of consolidative RT*** in term of PFS (but not in term of OS). However these results were obtained with ***outdated RT*** (dose, fields and techniques) ***and CT*** (MOPP, Stanford V…) schedules.

- ***Nowadays*** consolidative **RT on bulky** lesions **is related** to the chemotherapy regimen and to the PET status at the end of it.

- Consolidative ***RT*** was not established, but ***left to the discretion*** of the treating physicians (bulky lesions or residual disease at the end of chemotherapy), by many ***recent randomized studies*** that tested the effect of ABVD regimen (e.g. RATHL study)

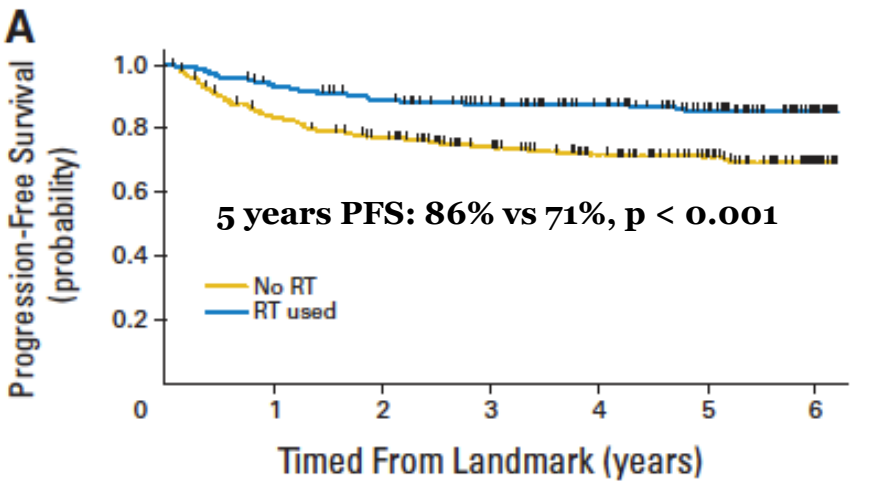
Involved-Field Radiotherapy for Advanced Hodgkin's Lymphoma

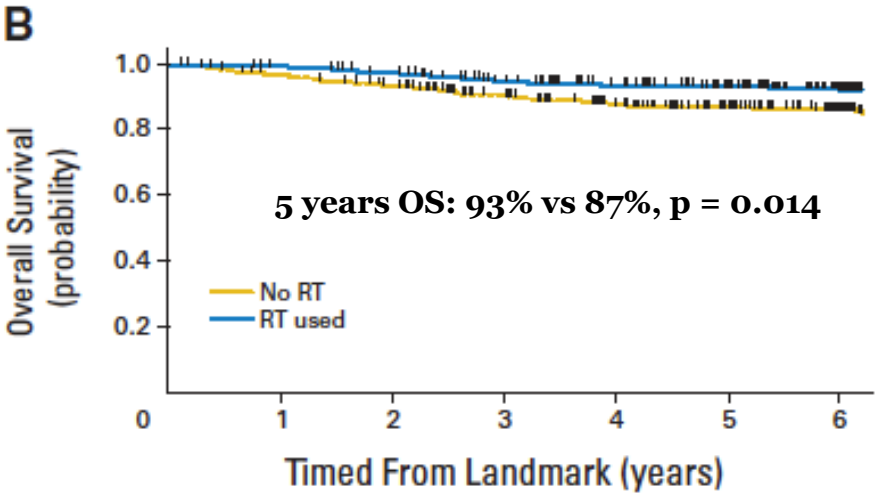


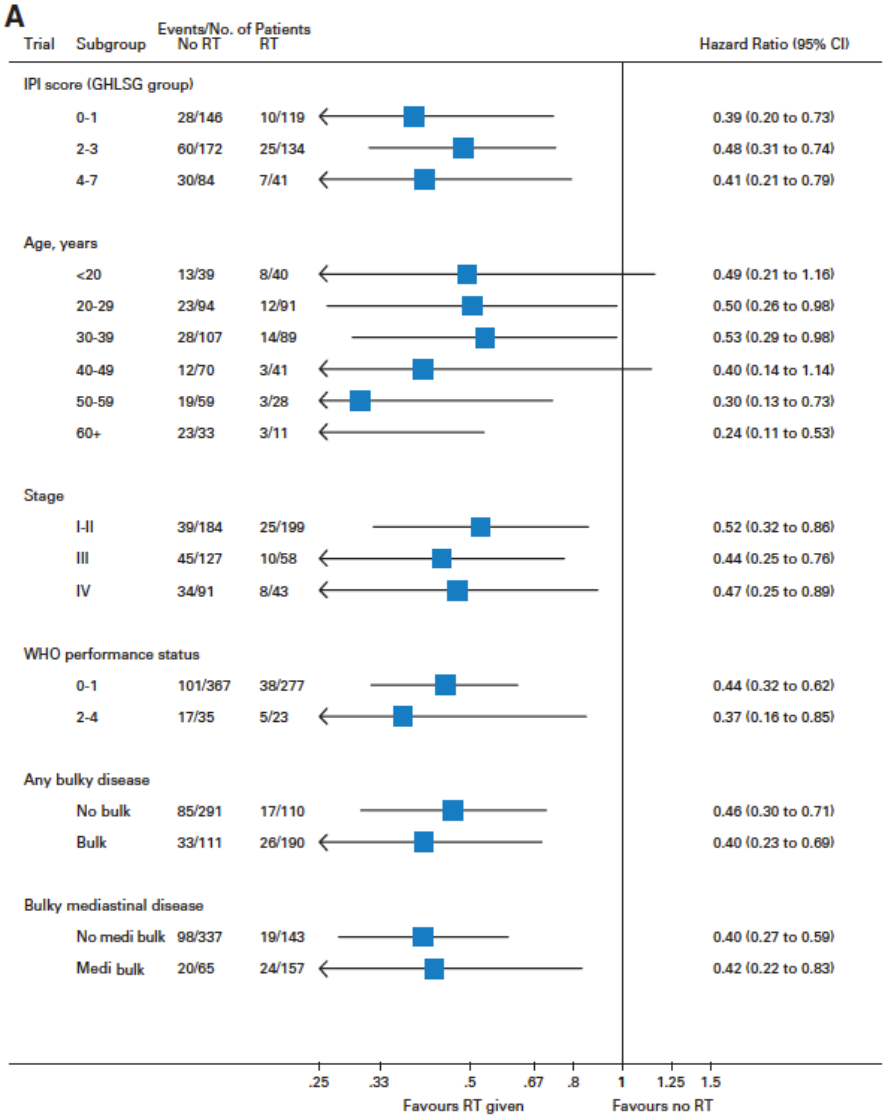


Aleman BM et al. NEJM 2003

Role of consolidative RT before "^{18}FDG-PET age" on bulky lesions or residual masses after chemotherapy – UKLG LY09 trial –





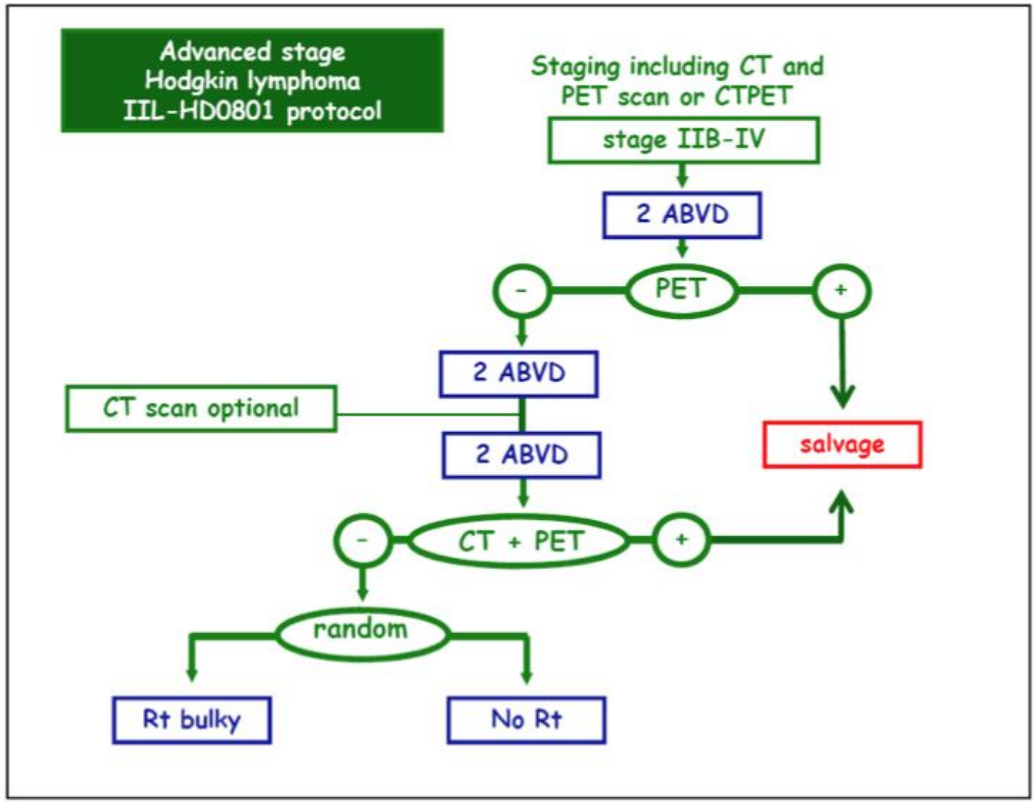


Johnson P. et al. JCO 2010;28

Role of consolidative RT to bulky lesions in the "^{18}FDG-PET AGE"

Two Italian trials are waiting for publication…

FIL HD 0801



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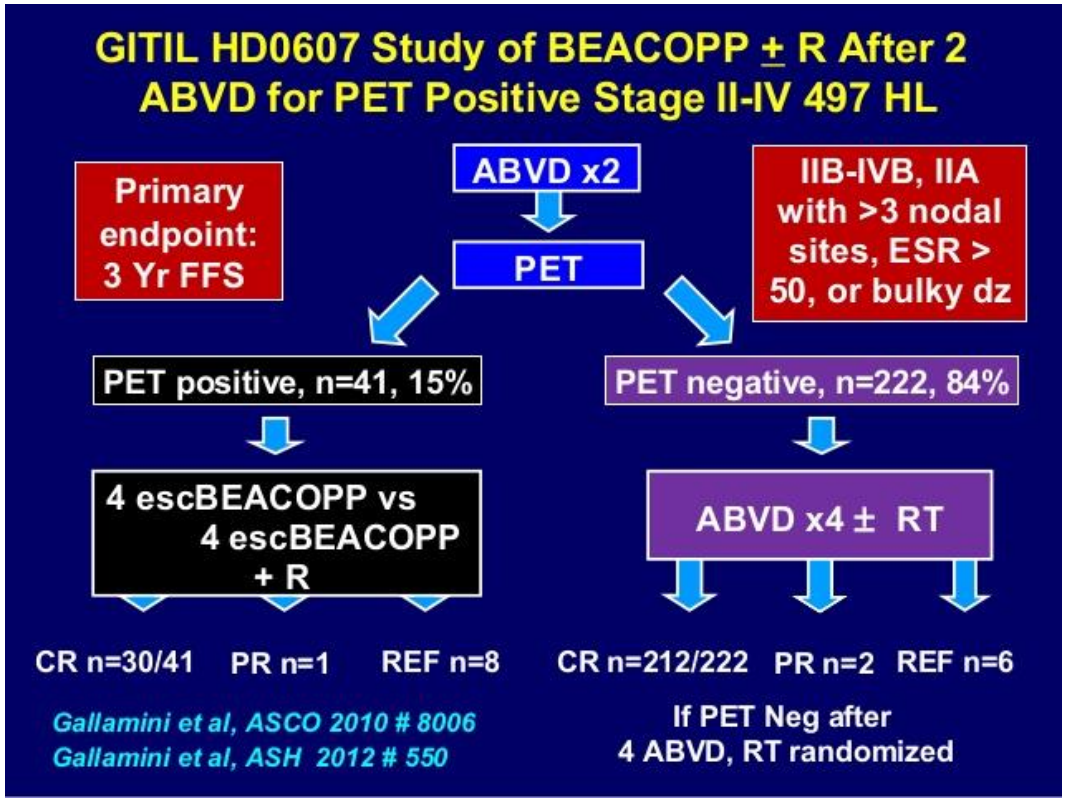

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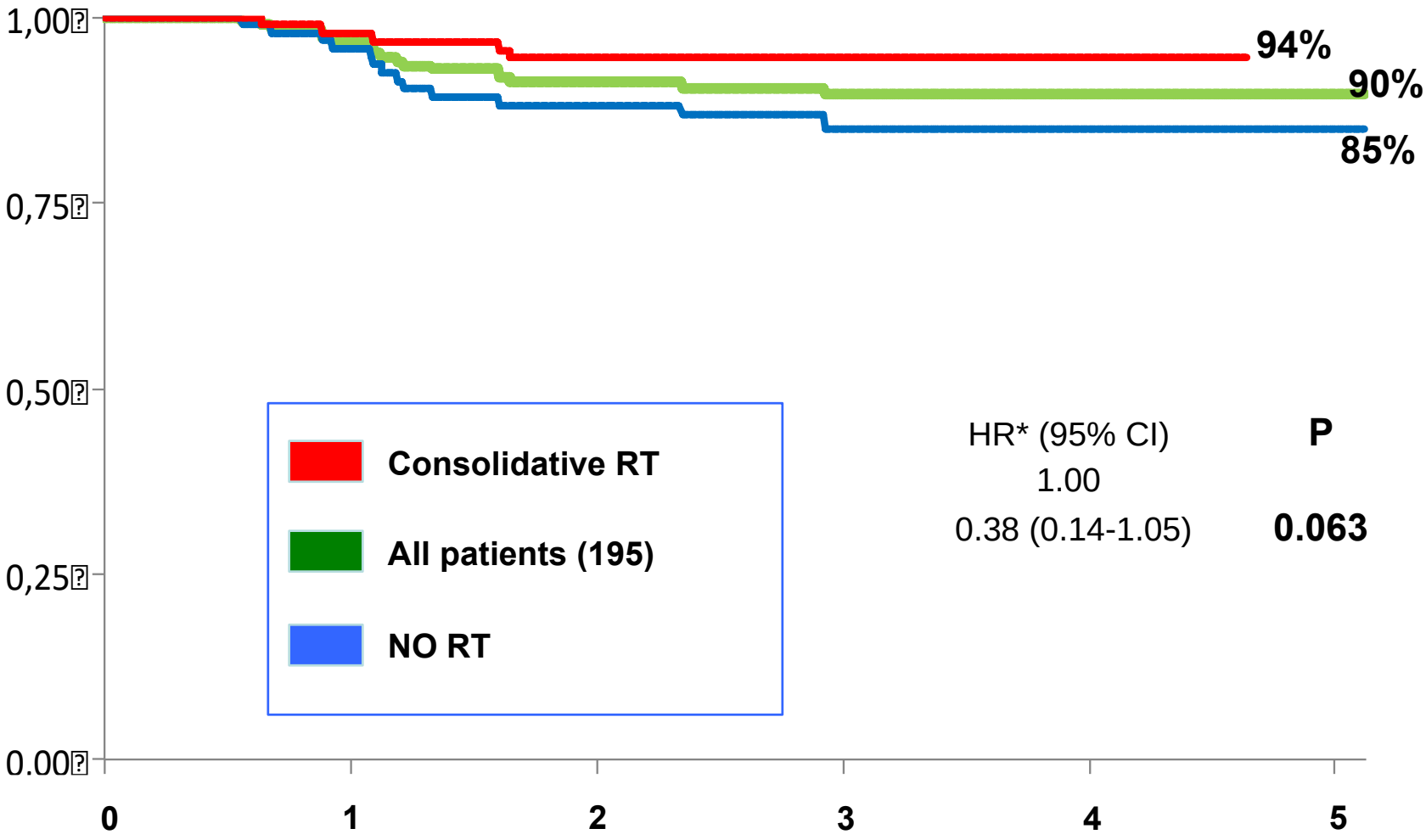
HD0607 FFS in PET2 NEG +/- Radiotherapy (N=195)

(interim analysis, presented at Lugano ICML 2015)



Gallamini et al, ICML (Lugano) 2015, abstract 118

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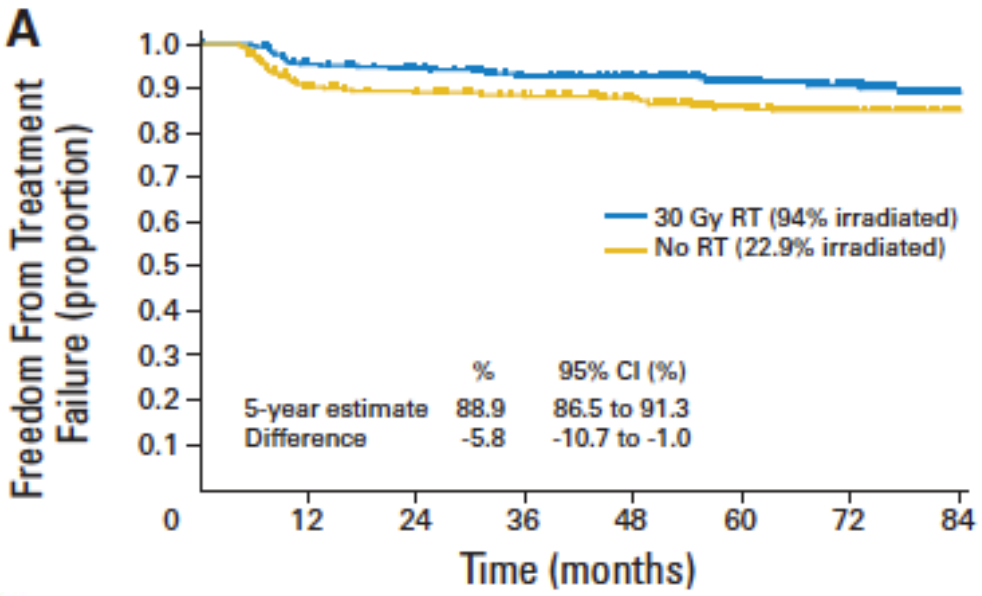
More aggressive chemotherapy regimen may relieve consolidative RT to bulky lesions

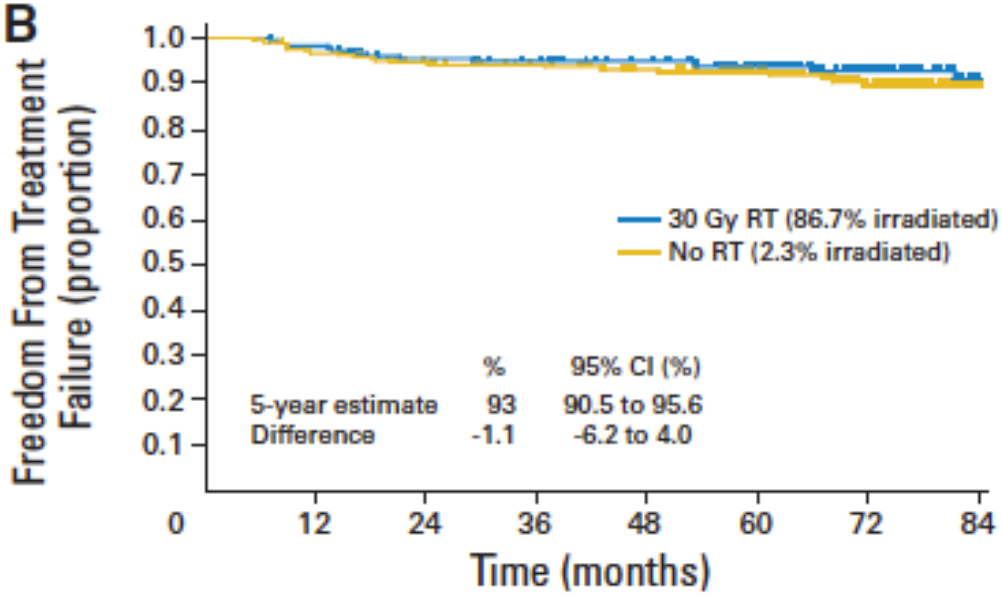
Eight Cycles of Escalated-Dose BEACOPP Compared With Four Cycles of Escalated-Dose BEACOPP Followed by Four Cycles of Baseline-Dose BEACOPP With or Without Radiotherapy in Patients With Advanced-Stage Hodgkin's Lymphoma: Final Analysis of the HD12 Trial of the German Hodgkin Study Group

Additional RT (30 Gy) given to:
- **residual disease > 1.5 cm on CT scan**
- **bulky lesion at baseline**

RESIDUAL DISEASE AFTER CT



BULKY LESIONS



Borchmann P. et al, JCO 2011

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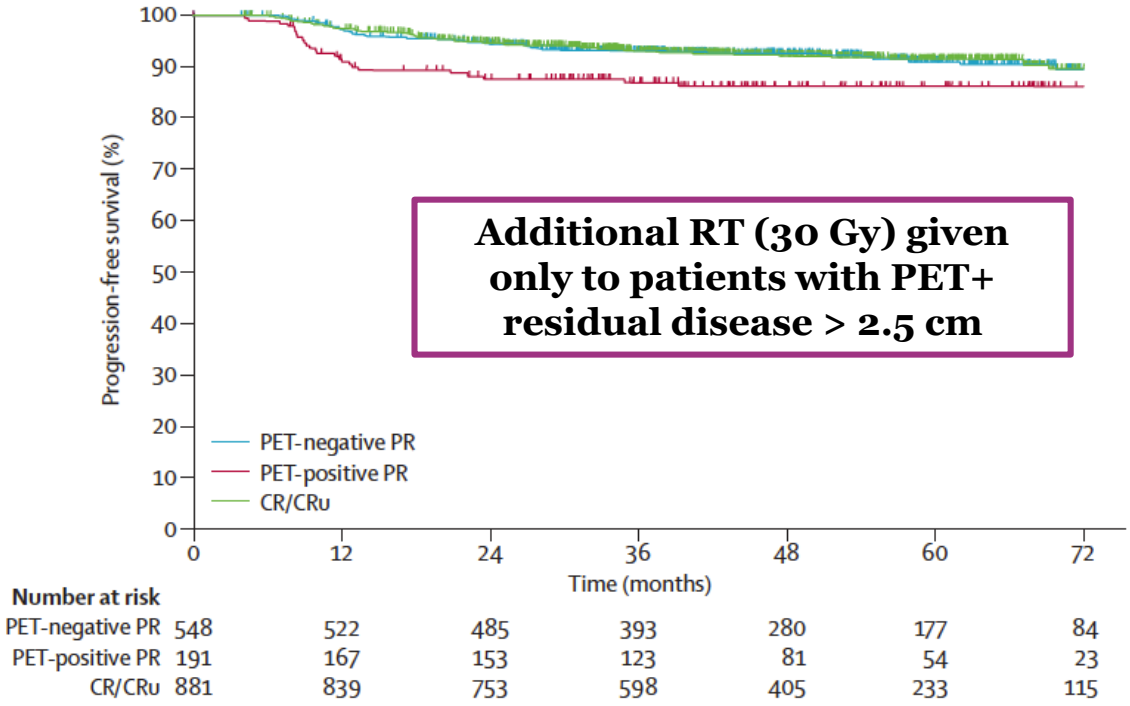
Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): a randomised, open-label, phase 3 non-inferiority trial

Reduced-Intensity Chemotherapy and PET-guided RT De-escalation TO REDUCE TOXICITY



Additional RT (30 Gy) given only to patients with PET+ residual disease > 2.5 cm

- **PET done after BEACOPP chemotherapy can guide the need for additional RT in this setting.**

HOWEVER:

- **Need for a careful extrapolation of this PET-guided approach to weaker regimens that might need more vigorous additional radiotherapy.**
- **PET-guided RT was not assessed in a randomised fashion.**

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Engert et al. Lancet 2012

Beacoppescalated Followed By Radiotherapy of Initial Bulk or Residual Disease in Advanced Stage Hodgkin Lymphoma: Long-Term Follow up of the HD9 and HD12 Trials of the German Hodgkin Study Group

Stefanie Kreissl, Bastian von Tresckow, Helen Goergen, Heinz Haverkamp, Stephanie Sasse, Volker Diehl, Andreas Engert and Peter Borchmann

Blood 2016 128:923;

Regarding the HD12 trial:

Amongst the patients with bulk

- **PFS in favor of RT arm** @ 10 years (88.6% vs 83.5%), HR 1.47
- **OS marginally in favor of RT arm** @ 10 years (93% vs 90.2%)

Amongst the patients with residual disease

- **PFS in favor of RT arm** @ 10 years (89.3% vs 83.4%)
- **OS in favor of RT arm** @ 10 years (94.4% vs 88.4%)

No significant difference in terms of second cancer @ 10 years (9.7% vs 6.4%)

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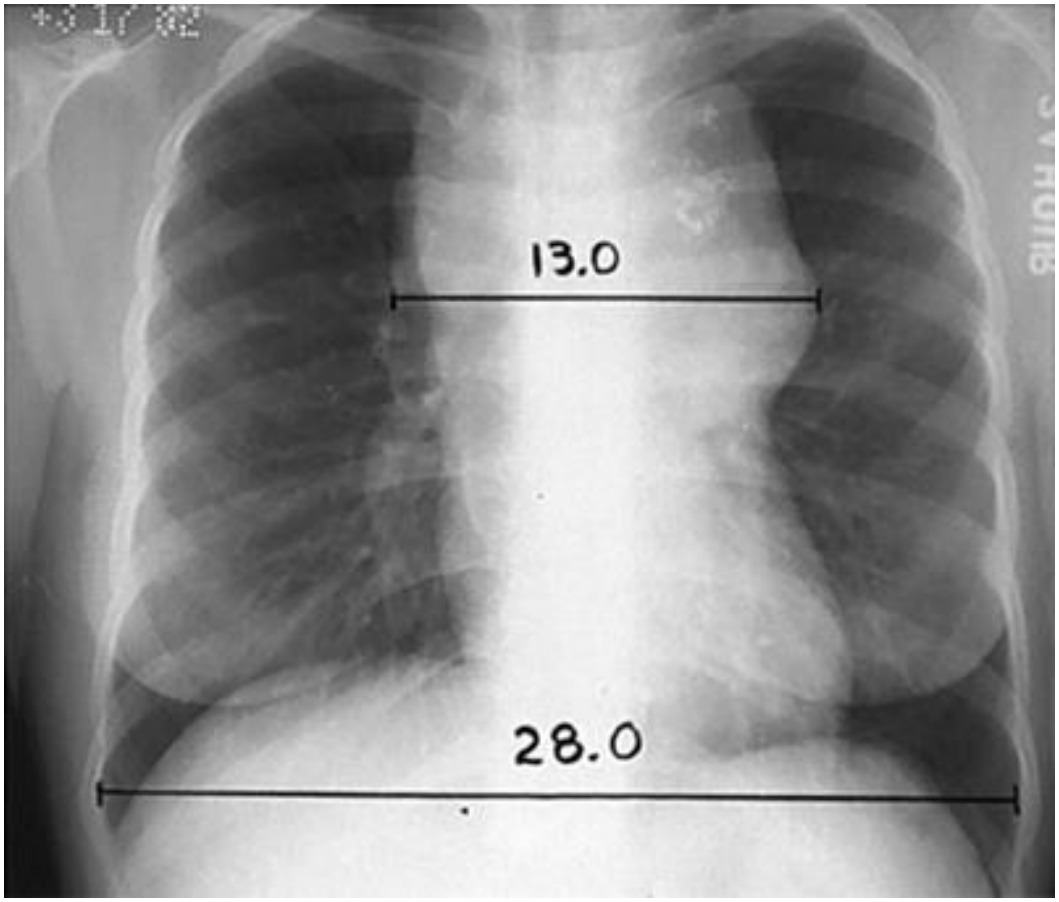
BULKY LESION DEFINITION



The definition of bulk has evolved as imaging modalities have changed.
The most common one is based on results of a chest X-ray, and bulky disease is defined based on the ratio of the maximum width of the mediastinal mass and the maximum intrathoracic diameter on standing posterior-anterior X-ray (mediastinal mass ratio [MMR] > 0.33)

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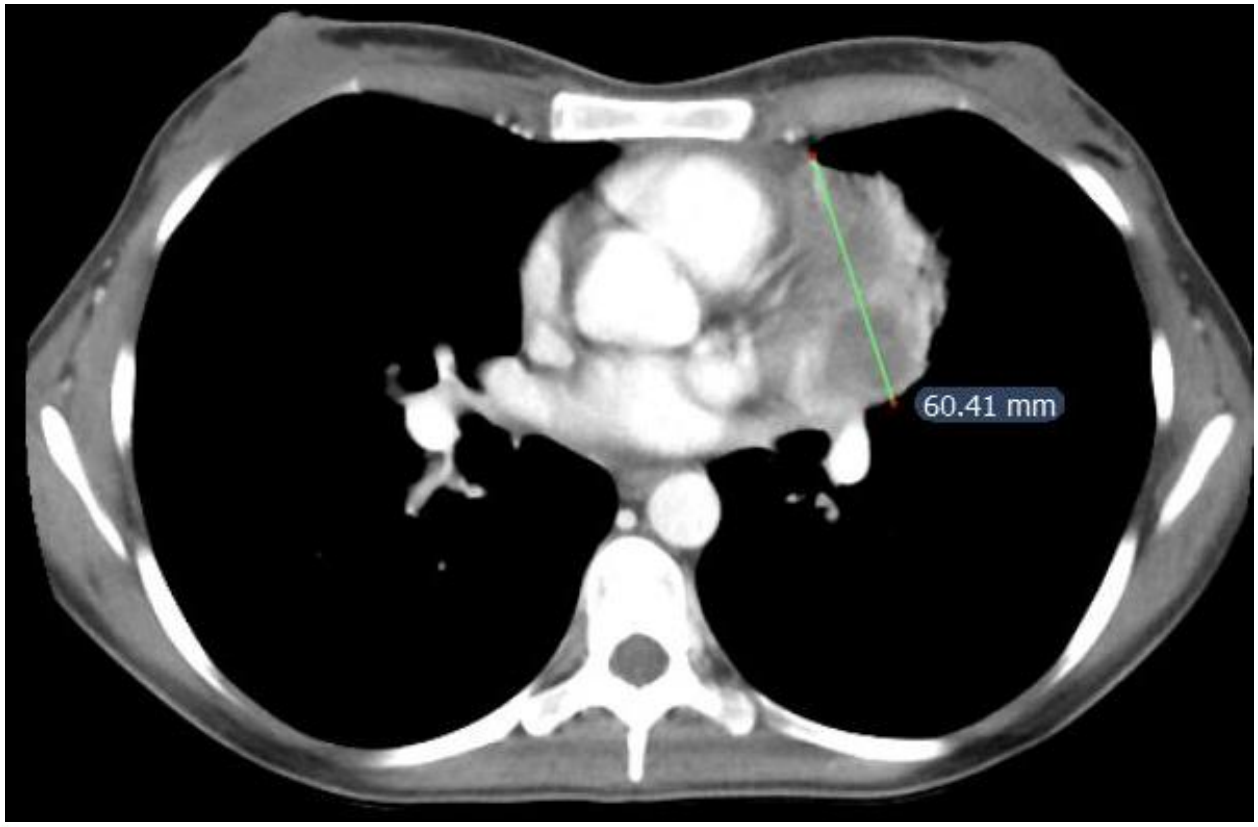
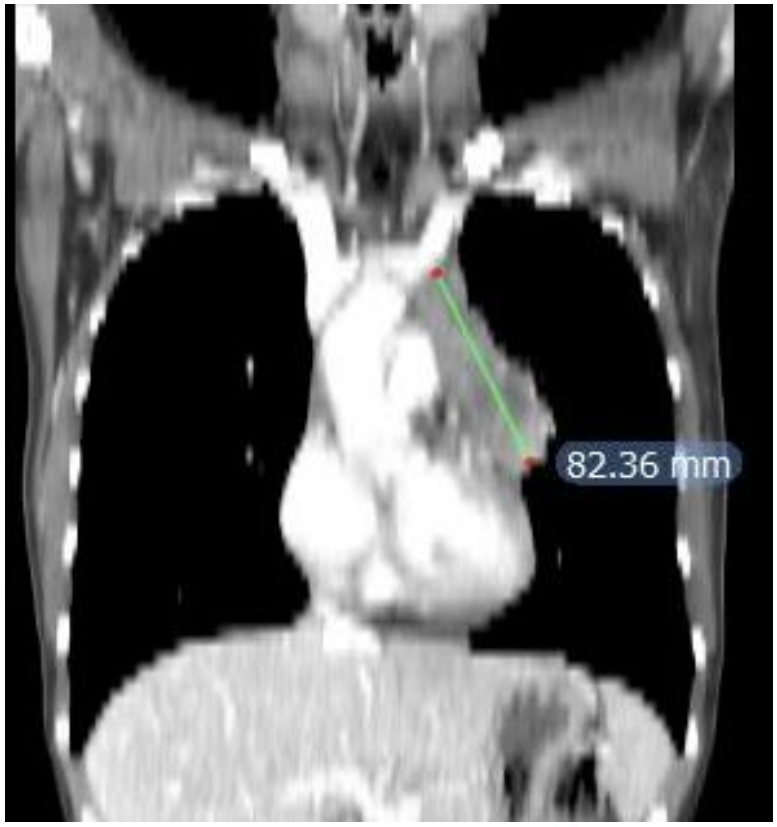
CLINICAL CASE #3 – Bulky definition

- E.F. 24 years old, female.
- Chest X-ray: mediastinal enlargement
- CT scan and PET-CT: mediastinal lesion. Maximum axial diameter: 6 cm.
- Mediastinal biopsy: cHL, CD30+.





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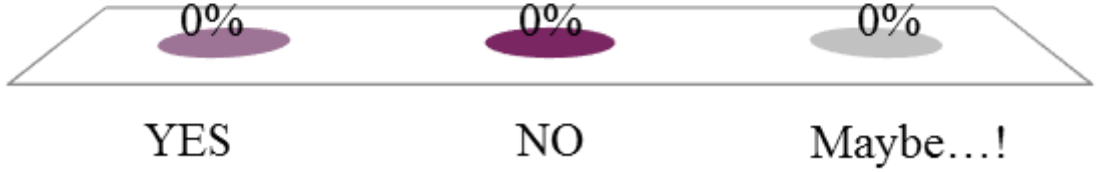
Is this a mediastinal “bulky” lesion ?

A. YES

B. NO

C. Maybe…!



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Definition of bulky disease in early stage Hodgkin lymphoma in computed tomography era: prognostic significance of measurements in the coronal and transverse planes

Anita Kumar,[1] Irene A. Burger,[2] Zhigang Zhang,[3] Esther N. Drill,[3] Jocelyn C. Migliacci,[1] Andrea Ng,[4] Ann LaCasce,[5] Darci Wall,[6] Thomas E. Witzig,[7] Kay Ristow,[7] Joachim Yahalom,[8] Craig H. Moskowitz,[1] and Andrew D. Zelenetz[1]

EUROPEAN HEMATOLOGY ASSOCIATION

- ***Training cohort***: (MSK) 185 early stage HL patients
- ***Validation cohort***: (MAYO/DANA FARBER) 38 patients

- **Aim**: to assess the **prognostic significance** of the **largest nodal mass** measured in either the **transverse and coronal** planes using CT scan

- A range of potential **cut-off points (in cm)** based upon the distribution of the data (between 10° and 90° percentiles) were identified and then examined to test their **significance level for RFS** using log rank test

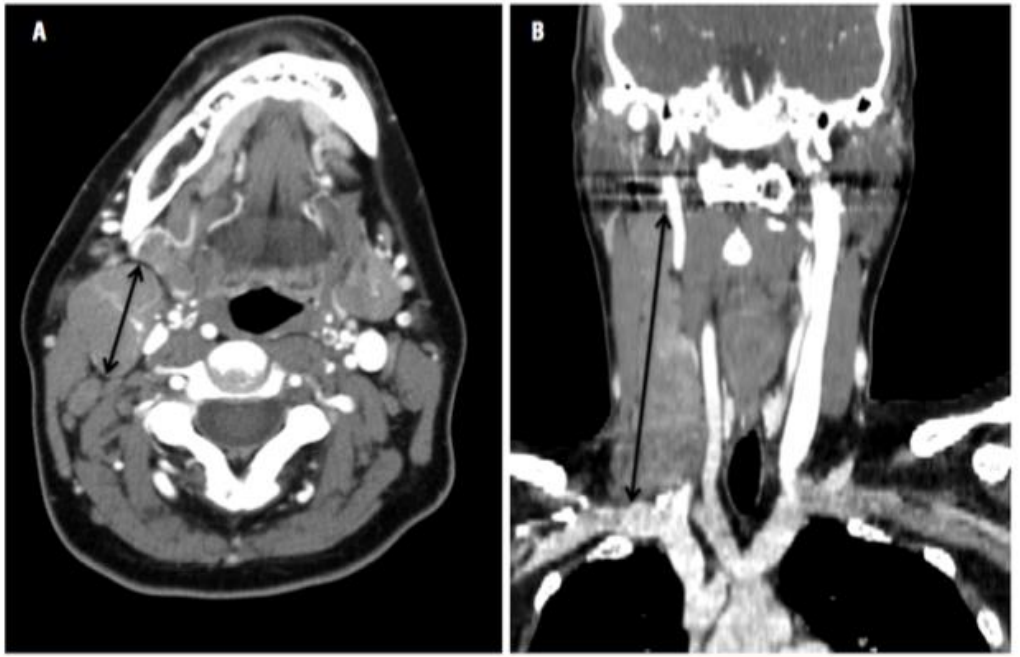

Figure 1. Representative images of the longest diameters measured using calipers of a right cervical mass in (A) transverse plane, 2.6 cm and (B) coronal plane, 12.1 cm.

Kumar A. et al. Hematologica 2016

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Roughly 30% of bulky patients were identified only using coronal reformations

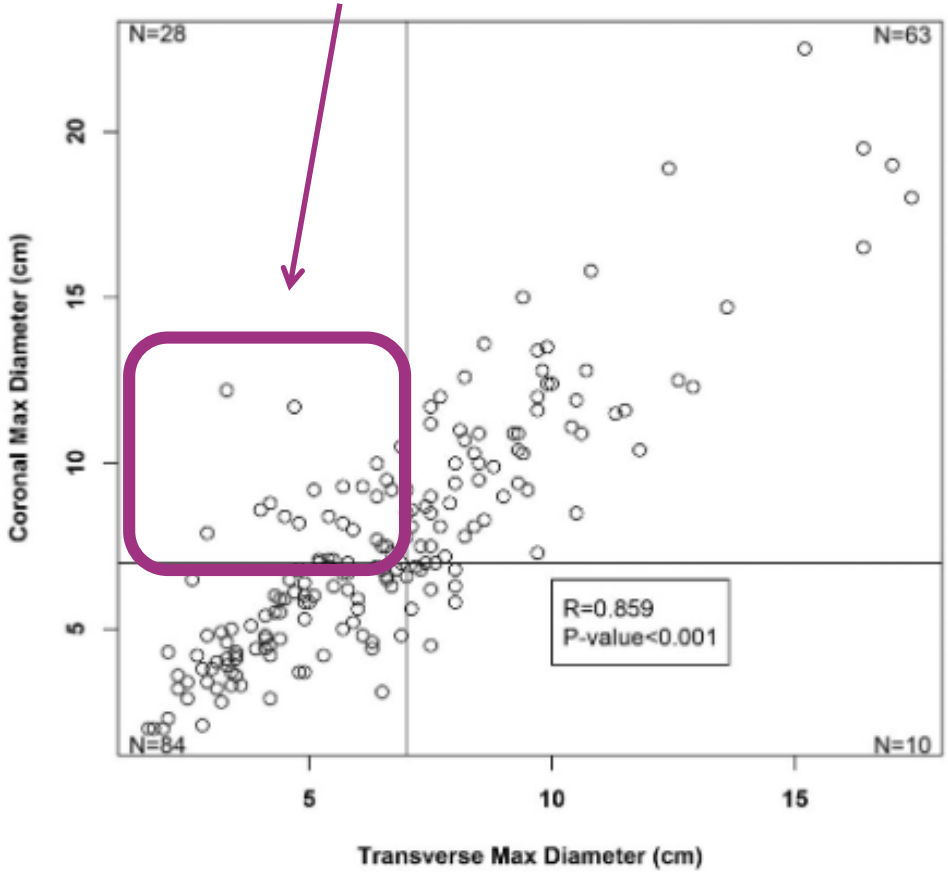
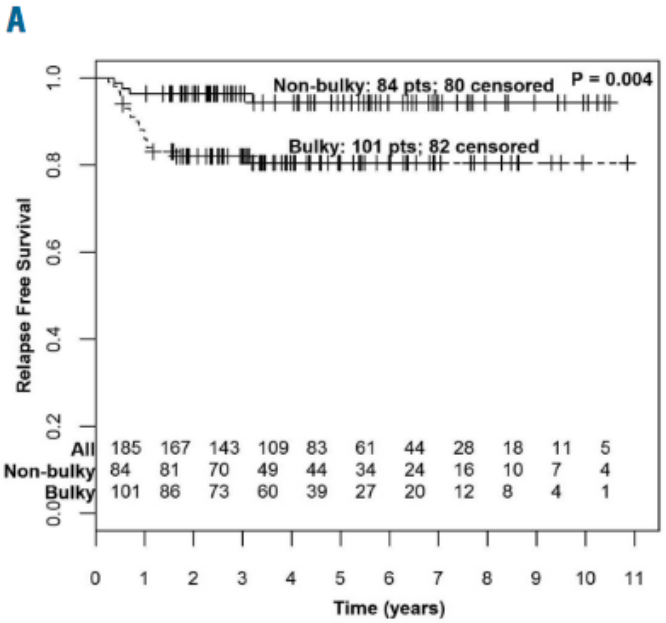
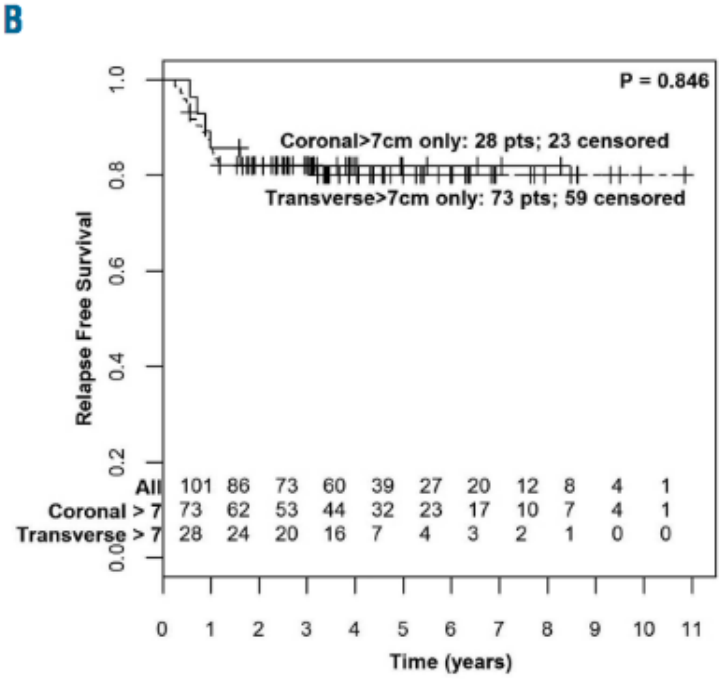


Figure 2. Correlation between maximal transverse and coronal measurements with lines for the 7 cm maximal transverse and coronal cut-offs for disease bulk.





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Kumar A. et al. Hematologica 2016

The prognostic role of bulky lesion is essential in patients treated with chemotherapy alone

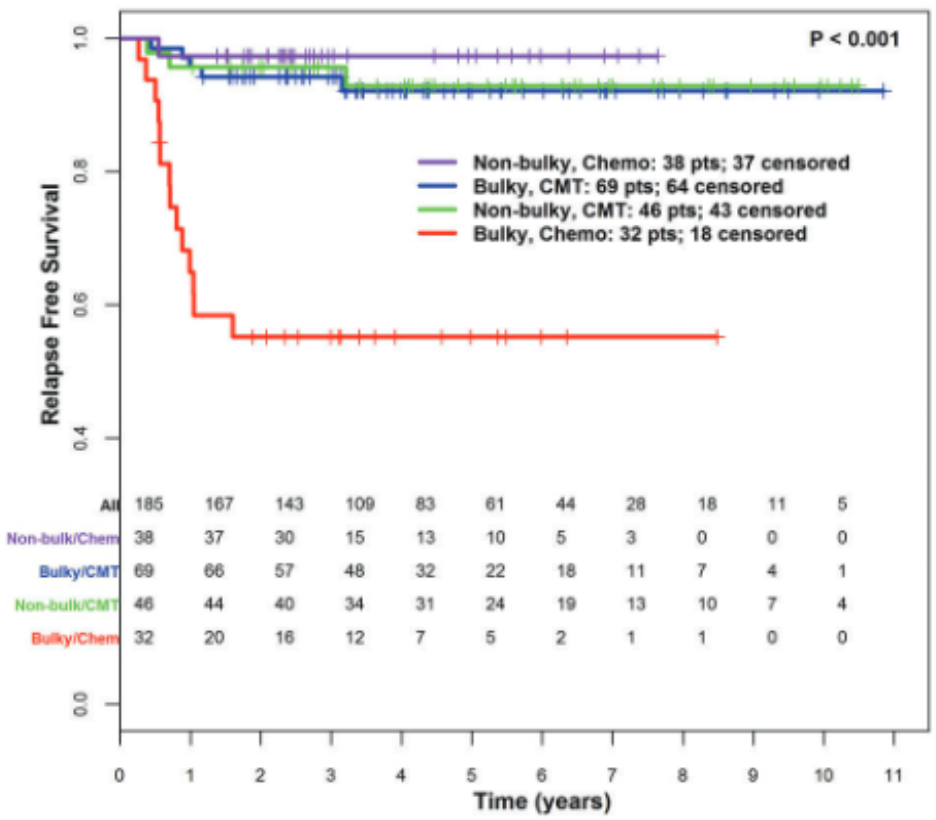

Figure 4. Relapse-free survival by presence of bulky disease (transverse or coronal max, diameter > 7cm) and treatment [chemotherapy alone (Chemo) *vs.* combined modality therapy (CMT)].

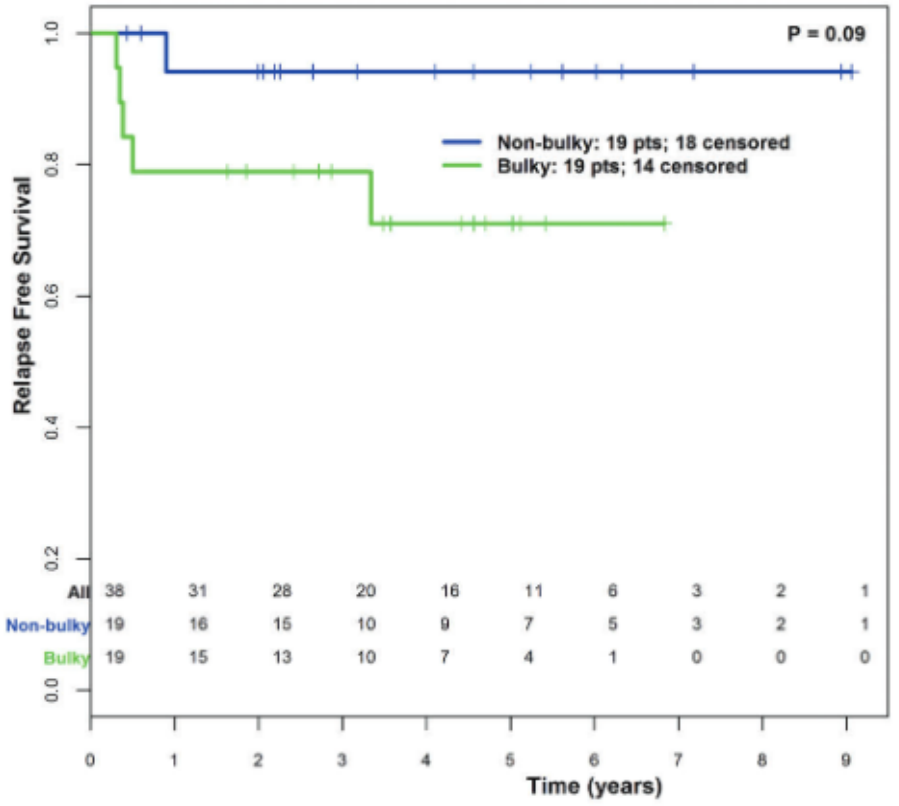

Figure 5. Relapse-free survival by presence of bulky disease (transverse or coronal max, diameter > 7cm) in validation cohort patients (n=38) treated with chemotherapy alone.

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Kumar A. et al. Hematologica 2016

Take Home Message (Advanced Stage HL)

- To date, waiting for definitive results of randomised studies (HD0607 and GD0801) patients ***treated with ABVD x 6 should receive consolidative ISRT to bulky site at baseline***

- Patients ***treated with more intensive chemotherapy*** **(**BEACOPPescalated x 6) need ***additional RT only to PET+ residual disease*** according to GHSG HD15.

- Patients with ***residual focal lesions*** after chemotherapy should be considered for ***a sequential ISRT***, with no regard to the chemotherapy schedule adopted (ABVD or BEACOPP)

- ***Multidisciplinary discussion*** is strongly recommended to offer the best treatment solution to each patient

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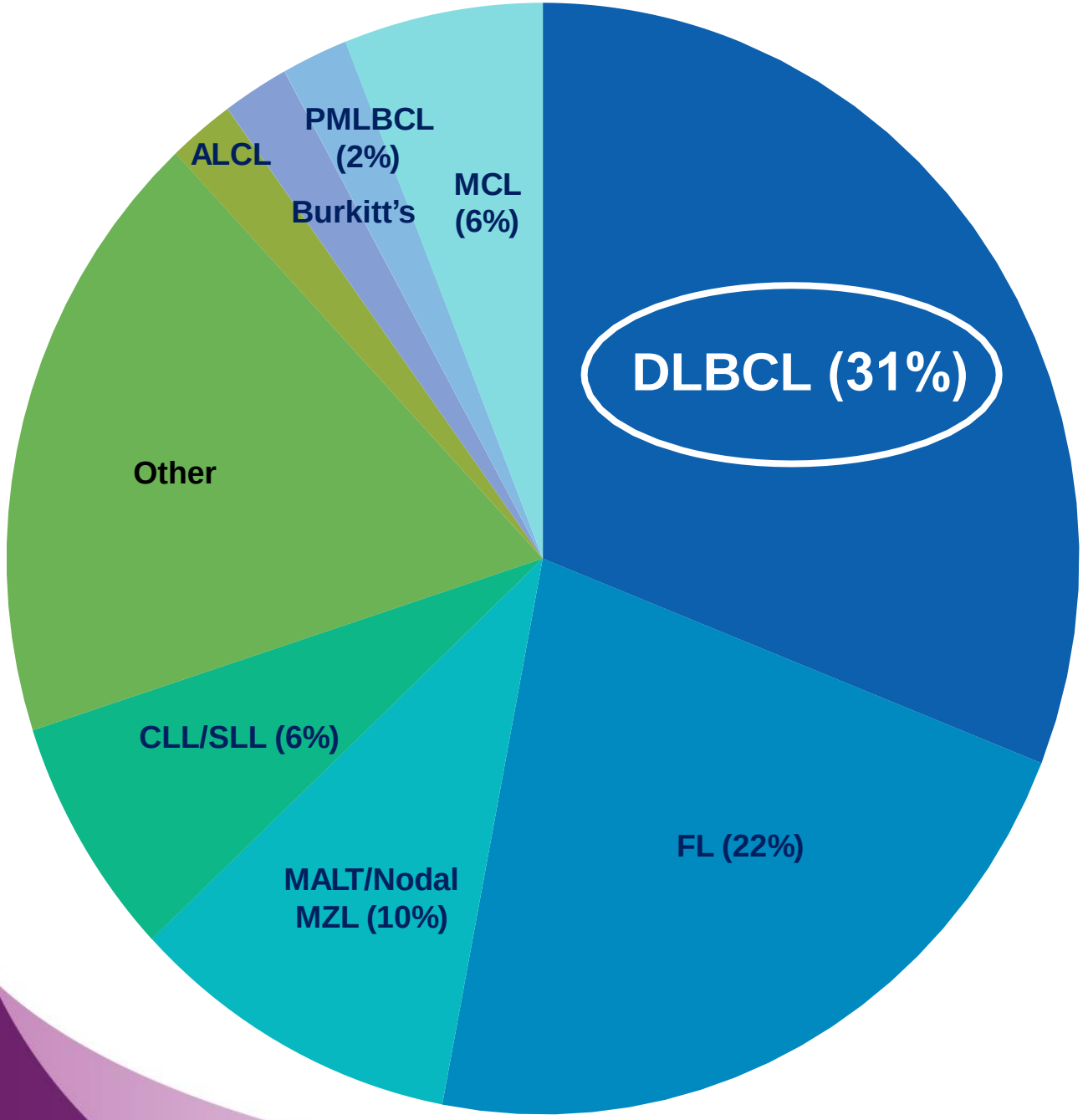
❑Early stage HL

- Without risk factors (Favourable)
- With risk factors (Unfavourable or Intermediate)

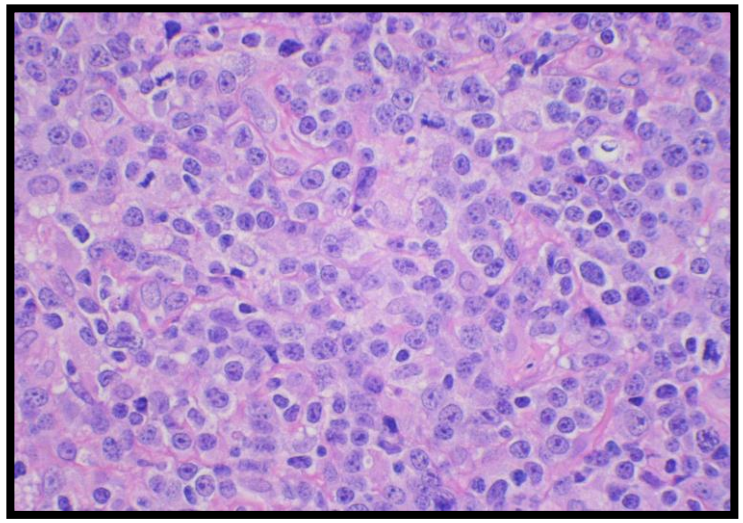
❑Advanced stage HL

❑Non Hodgkin Lymphoma

NHL: A Heterogeneous Disease



- 75% of aggressive NHL
- 40%: localized disease
- 40-50%: extranodal disease



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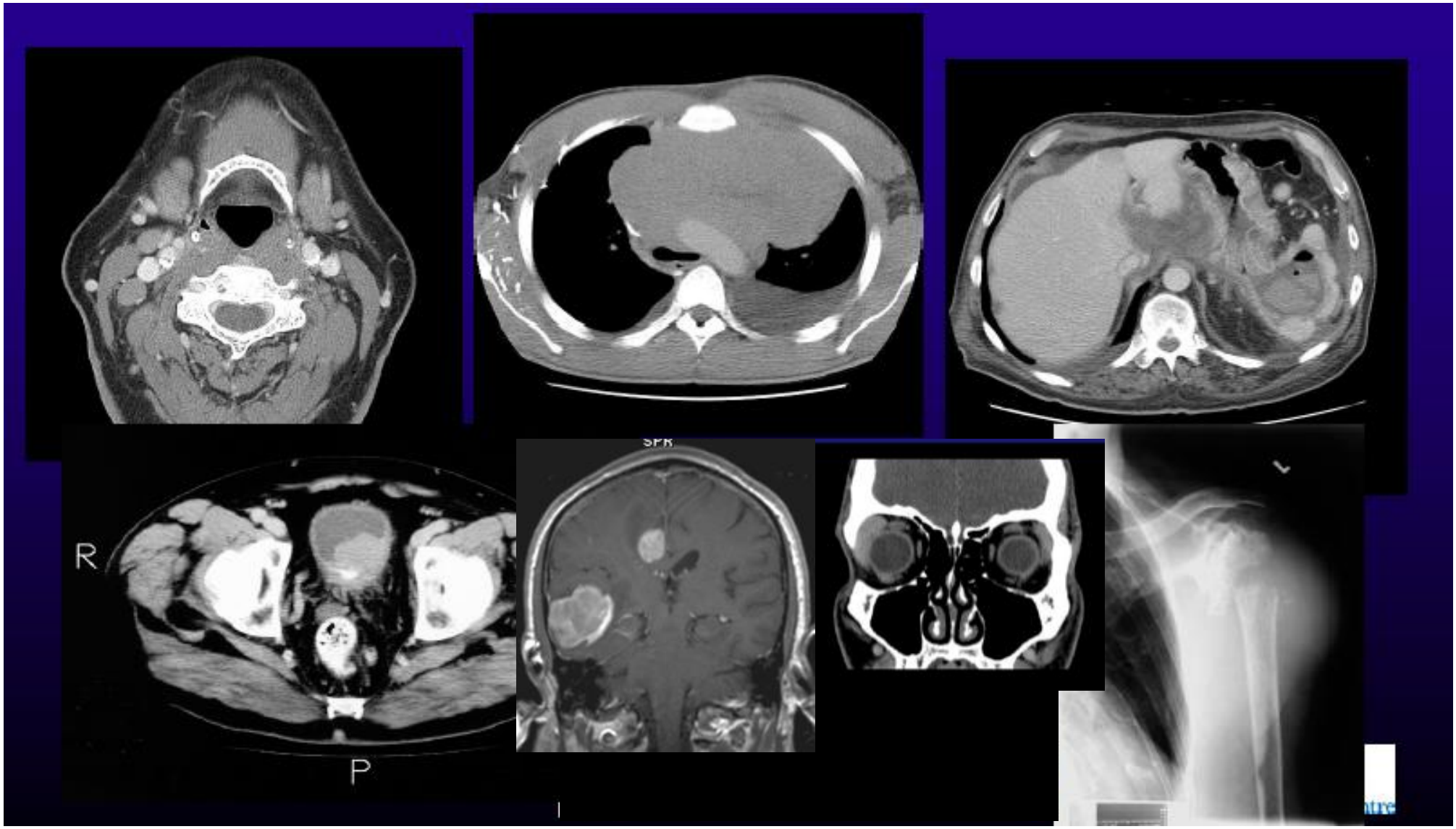
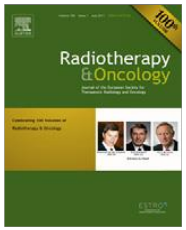
Extranodal sites

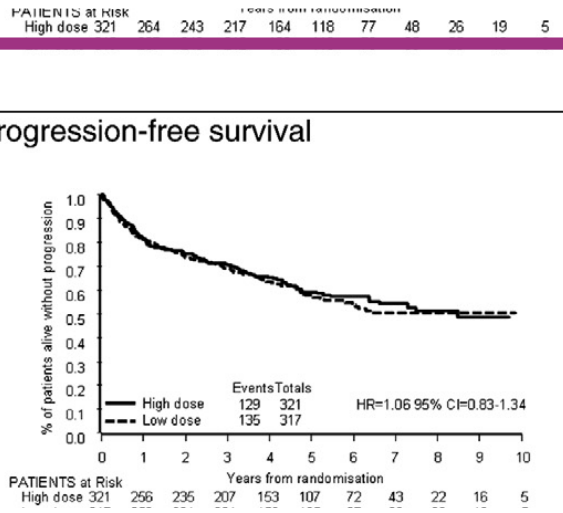


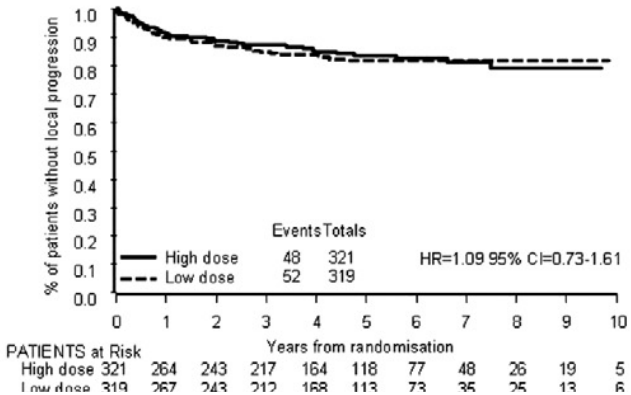


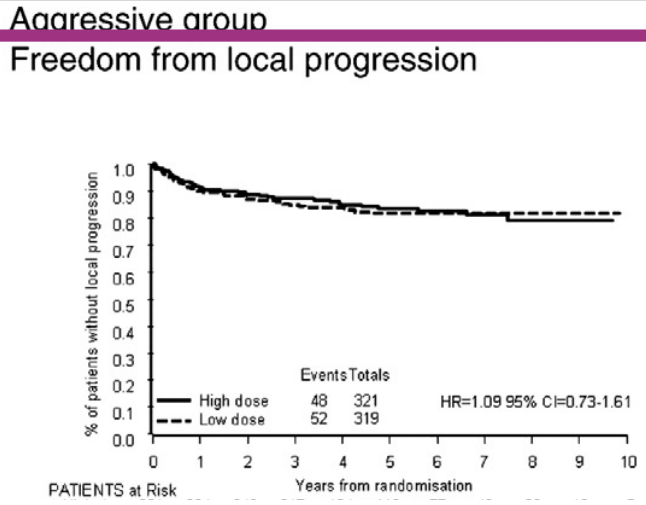
Phase III randomised trial

Reduced dose radiotherapy for local control in non-Hodgkin lymphoma: A randomised phase III trial ☆,☆☆

45 vs 30 Gy in aggressive B cell lymphoma







Conclusion: In a large, randomised trial, there was no loss of efficacy associated with radiotherapy doses of 24 Gy in indolent NHL and 30 Gy in aggressive NHL, compared with previous standard doses of 40–45 Gy.

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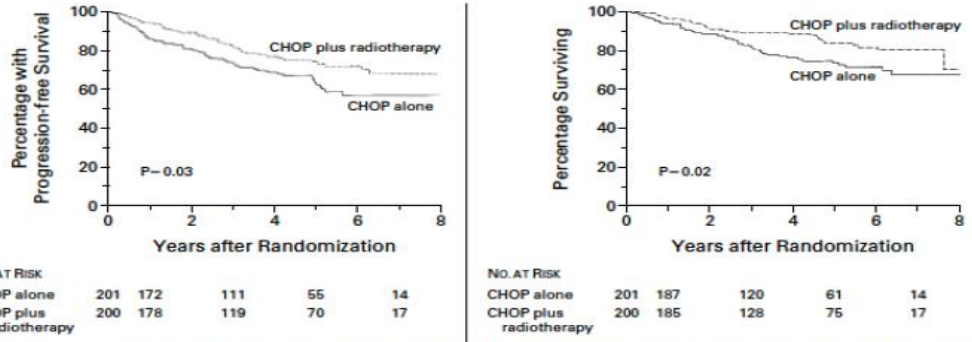
Lowry et al. Radiotherapy and Oncology 2011;100

Early stage (I-II) DLBCL
Trials in Favor of Chemoradiotherapy
(before Rituximab era)

CHEMOTHERAPY ALONE COMPARED WITH CHEMOTHERAPY PLUS RADIOTHERAPY FOR LOCALIZED INTERMEDIATE- AND HIGH-GRADE NON-HODGKIN'S LYMPHOMA

CHOP x 8 vs. CHOP x 3 + IFRT in Stage I/II DLBCL



NO. AT RISK

CHOP alone	201	172	111	55	14
CHOP plus radiotherapy	200	178	119	70	17

Figure 1. Progression-free Survival of 201 Patients Receiving Eight Cycles of CHOP Alone and 200 Patients Receiving Three Cycles of CHOP plus Radiotherapy.
Sixty-five patients in the CHOP-alone group died or had progression of their disease, as compared with 45 patients in the CHOP-plus-radiotherapy group. The estimated rates of progression-free survival at five years were 64 percent and 77 percent, respectively.

NO. AT RISK

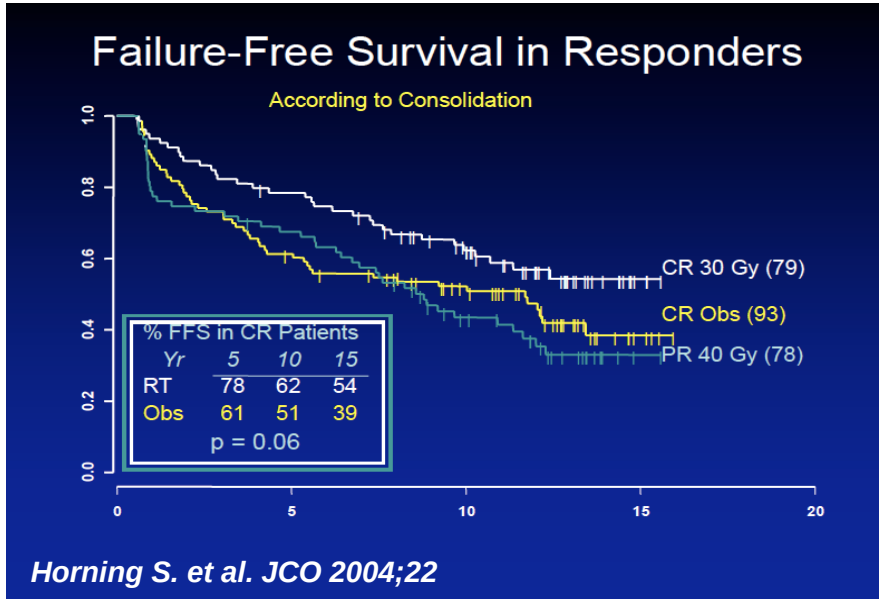
CHOP alone	201	187	120	61	14
CHOP plus radiotherapy	200	185	128	75	17

Figure 2. Overall Survival of 201 Patients Receiving Eight Cycles of CHOP and 200 Patients Receiving Three Cycles of CHOP plus Radiotherapy.
There were 51 deaths in the CHOP-alone group, and 32 in the CHOP-plus-radiotherapy group. The estimated rates of survival at five years were 72 percent and 82 percent, respectively.

Miller et al NEJM 1998; 339:21

Chemotherapy With or Without Radiotherapy in Limited-Stage Diffuse Aggressive Non-Hodgkin's Lymphoma: Eastern Cooperative Oncology Group Study 1484

Sandra J. Horning, Edie Weller, KyungMann Kim, John D. Earle, Michael J. O'Connell, Thomas M. Habermann, and John H. Glick



Horning S. et al. JCO 2004;22

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Early stage (I-II) DLBCL
Trials in Favor of Chemo alone
(before Rituximab era)

ACVBP versus CHOP plus Radiotherapy for Localized Aggressive Lymphoma

ACVBP vs CHOP + RT in Stage I/II aggressive Lymphoma

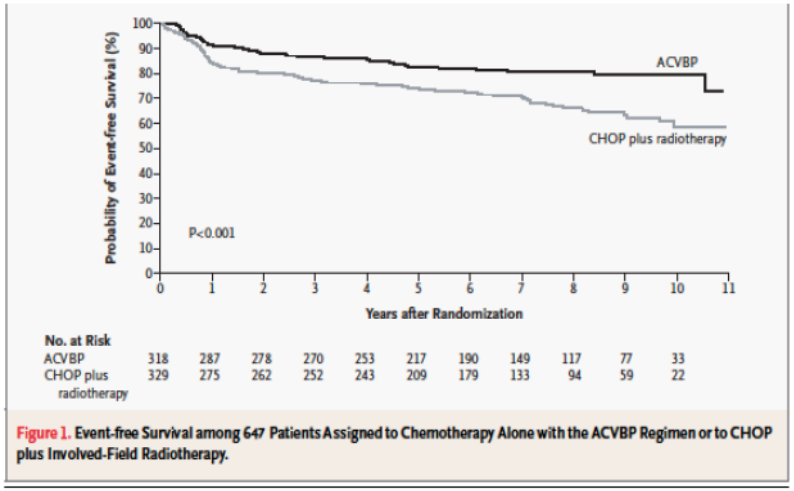


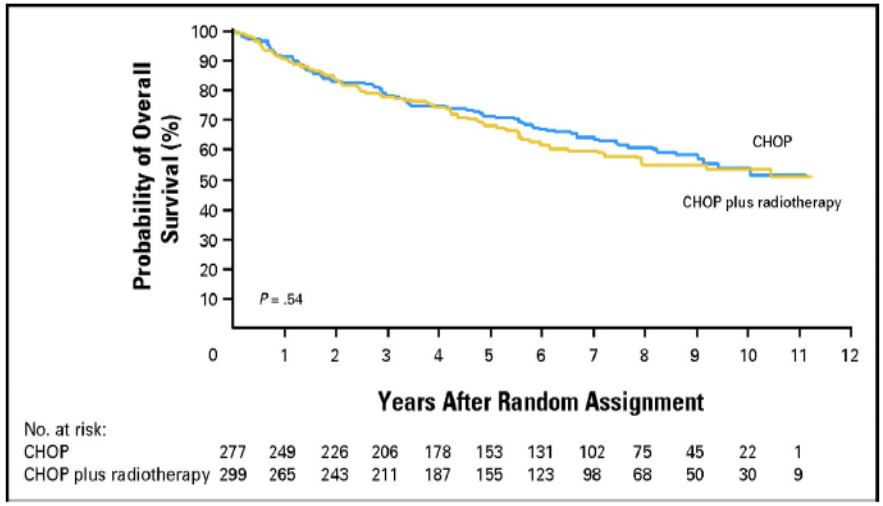
Figure 1. Event-free Survival among 647 Patients Assigned to Chemotherapy Alone with the ACVBP Regimen or to CHOP plus Involved-Field Radiotherapy.

GELA LNH 93-1

Reyes et al NEJM 2005; 352:1197

CHOP Alone Compared With CHOP Plus Radiotherapy for Localized Aggressive Lymphoma in Elderly Patients: A Study by the Groupe d'Etude des Lymphomes de l'Adulte

Christophe Bonnet, Georges Fillet, Nicolas Mounier, Gérard Ganem, Thierry Jo Molina, Catherine Thiéblemont, Christophe Fermé, Bruno Quesnel, Claude Martin, Christian Gisselbrecht, Hervé Tilly, and Félix Reyes†



GELA LNH 93-4

Bonnet C et al. JCO 2007;25:787-792

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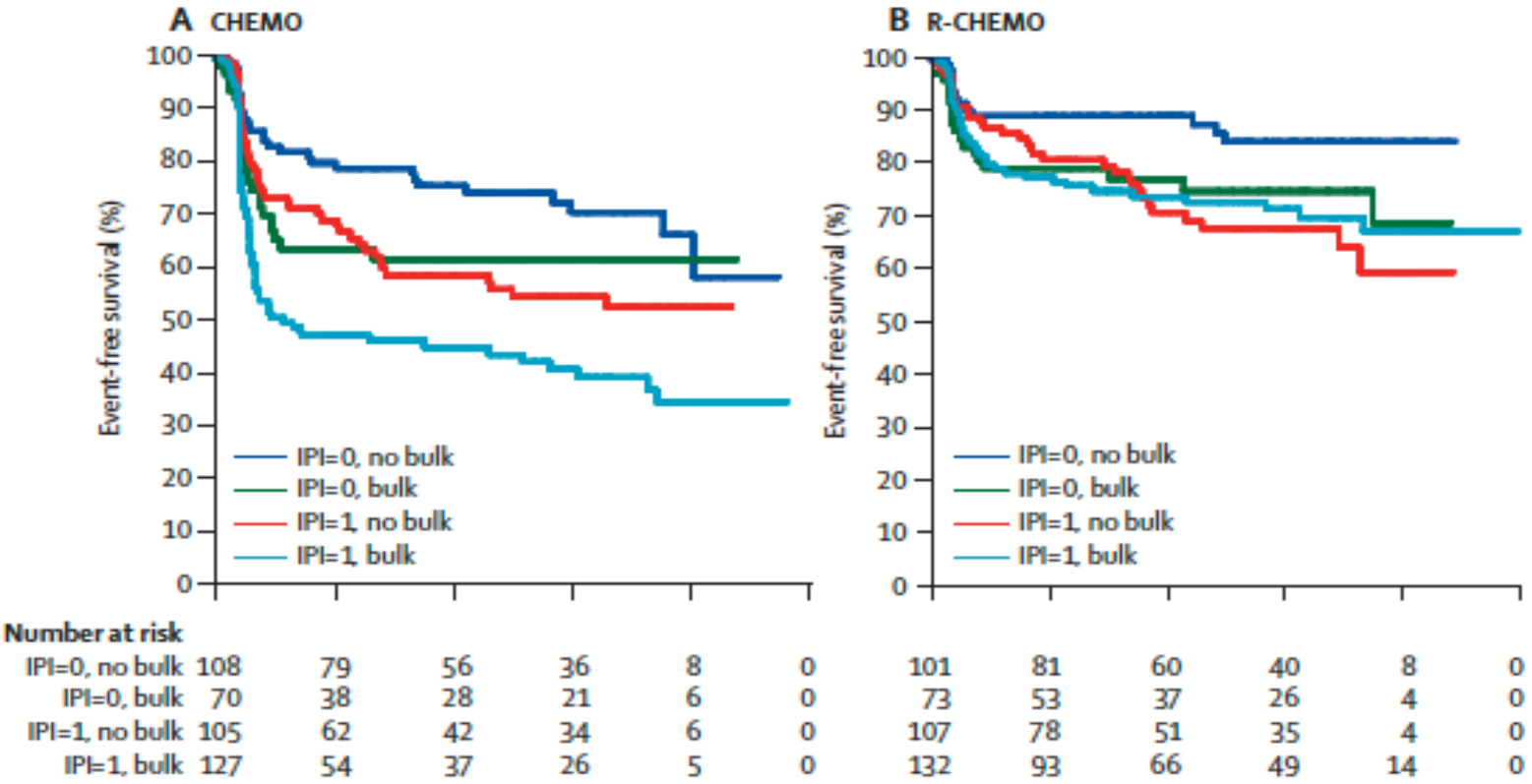
Will Rituximab markedly change the results of CHOP+RT?

CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomised study of the MabThera International Trial (MInT) Group

*Michael Pfreundschuh, Evelyn Kuhnt, Lorenz Trümper, Anders Österborg, Marek Trneny, Lois Shepherd, Devinder S Gill, Jan Walewski, Ruth Pettengell, Ulrich Jaeger, Pier-Luigi Zinzani, Ofer Shpilberg, Stein Kvaloy, Peter de Nully Brown, Rolf Stahel, Noel Milpied, Armando López-Guillermo, Viola Poeschel, Sandra Grass, Markus Loeffler, Niels Murawski, for the MabThera International Trial (MInT) Group**



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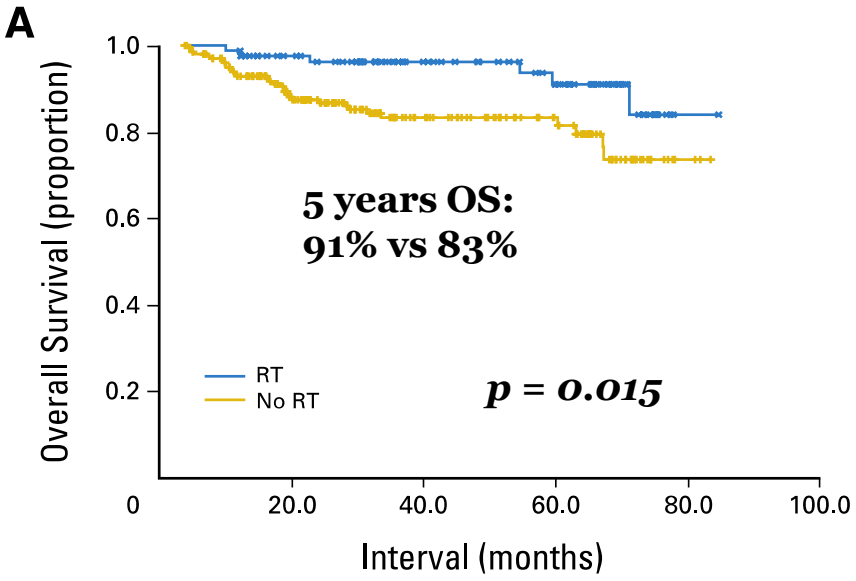
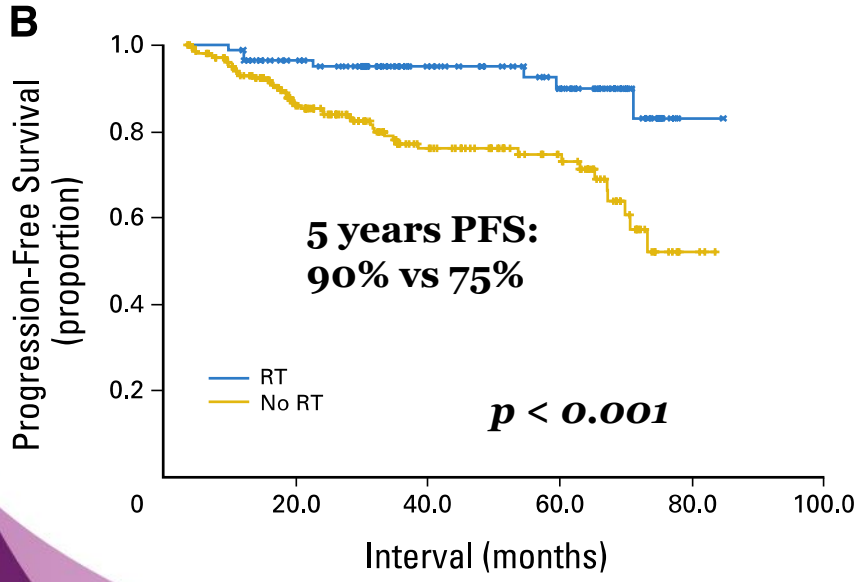
JOURNAL OF CLINICAL ONCOLOGY

Benefit of Consolidative Radiation Therapy in Patients With Diffuse Large B-Cell Lymphoma Treated With R-CHOP Chemotherapy





- 469 patients
- RT given to 30% patients after CR to R-CHOP
- Retrospective study

Table 5. Multivariate Analysis of Overall and Progression-Free Survival for All Patients

Variable	Hazard Ratio	95% CI	*P*	Hazard Ratio	95% CI	*P*
Age, years						
≤ 60	1.00		.051	1.00		.010
> 60	1.34	0.98 to 2.02		1.42	1.00 to 2.15	
Chemotherapy						
6-8 cycles of R-CHOP	0.42	0.27 to 0.65	< .0001	0.57	0.39 to 0.84	.0050
Other	1.00			1.00		
Radiotherapy						
No	1.00		< .0001	1.00		< .0001
Yes	0.19	0.10 to 0.38		0.32	0.17 to 0.51	
Triple negative						
No	1.00		.025	1.00		.038
Yes	0.16	0.03 to 0.79		0.24	0.06 to 0.92	
Triple positive						
No	1.00		.006	1.00		.037
Yes	4.96	1.58 to 15.61		1.39	1.58 to 9.87	
IPI score						
0	1.00			1.00		
1-2	2.53	1.32 to 4.84	.005	2.12	1.34 to 3.69	.001
≥ 3	5.41	2.24 to 8.28	.001	6.03	3.11 to 9.19	.001
Response						
No response	1.00			1.00		
Partial remission	1.96	0.91 to 2.05	< .0001	0.27	0.16 to 0.56	< .0001
Complete remission	3.35	2.33 to 4.59	< .001	0.42	0.33 to 0.72	.0055

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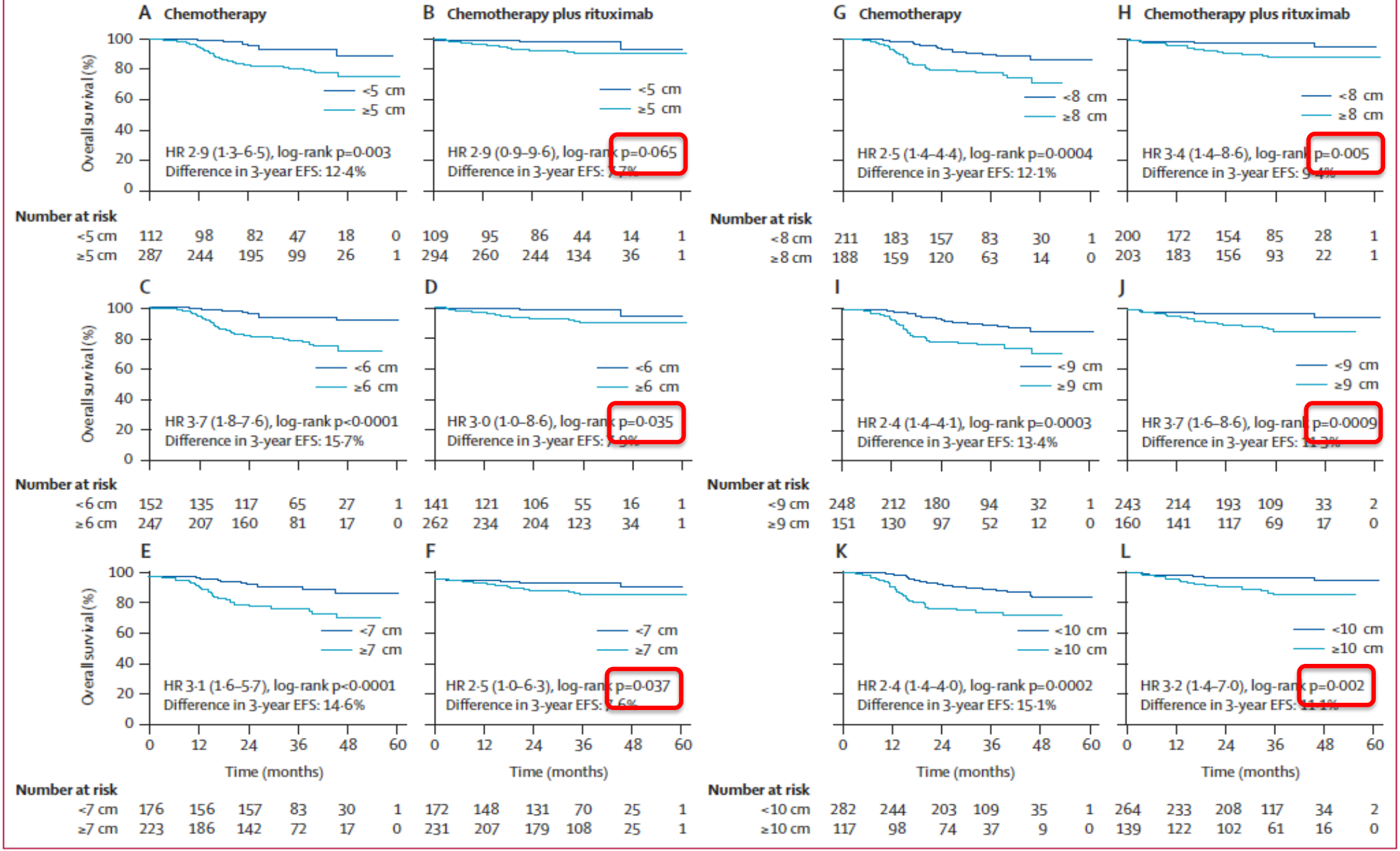
Phan J. et al. JCO 2010;28

Prognostic significance of maximum tumour (bulk) diameter in young patients with good-prognosis diffuse large-B-cell lymphoma treated with CHOP-like chemotherapy with or without rituximab: an exploratory analysis of the MabThera International Trial Group (MInT) study

Michael Pfreundschuh, Anthony D Ho, Eva Cavallin-Stahl, Max Wolf, Ruth Pettengell, Ingrid Vasova, Andrew Belch, Jan Walewski, Pier-Luigi Zinzani, Walter Mingrone, Stein Kvaloy, Ofer Shpilberg, Ulrich Jaeger, Mads Hansen, Claudia Corrado, Adriana Scheliga, Markus Loeffler, Evelyn Kuhnt, for the MabThera International Trial (MInT) Group

Lancet Oncol 2008; 9: 435–44

- Linear prognostic effect of tumor diameter on OS, which is decreased (but not eliminated) by the addition of rituximab



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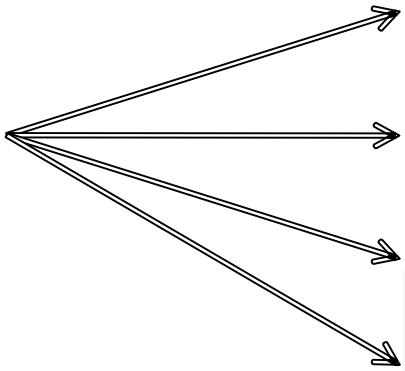
Role of Radiotherapy to Bulky Disease in Elderly Patients With Aggressive B-Cell Lymphoma (n=1,222)

RICOVER-60:



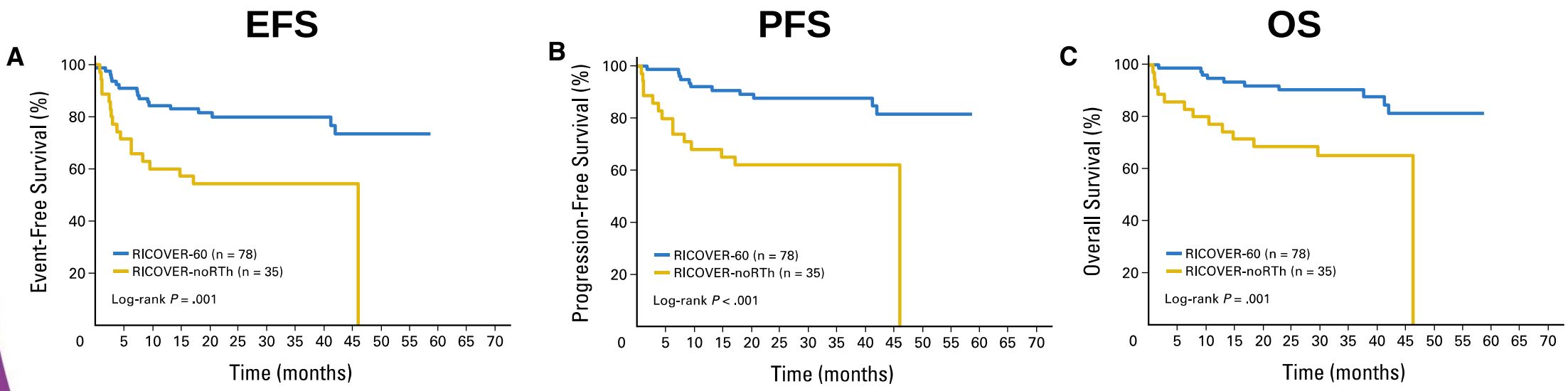
- CHOP- 14 x 8
- CHOP-14 x 6
- R-CHOP-14 x 8
- **R-CHOP-14 x 6**

Retrospective subgroup analysis of pts with bulky disease (≥7.5 cm) from the R-CHOP14 x 6 arm treated with or without RT

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Role of Radiotherapy to Bulky Disease in Elderly Patients With Aggressive B-Cell Lymphoma

RICOVER 60



Per protocol analysis

Held et al. JCO 2014;32(11):1112-1118

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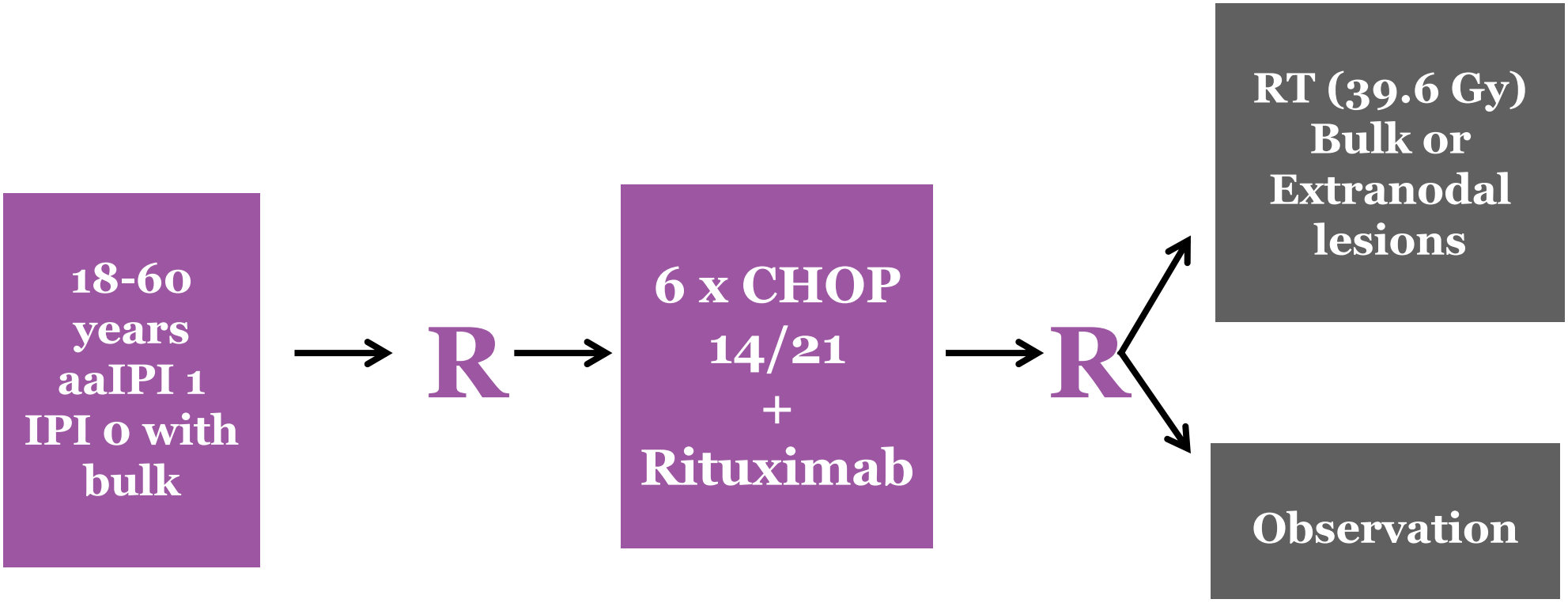
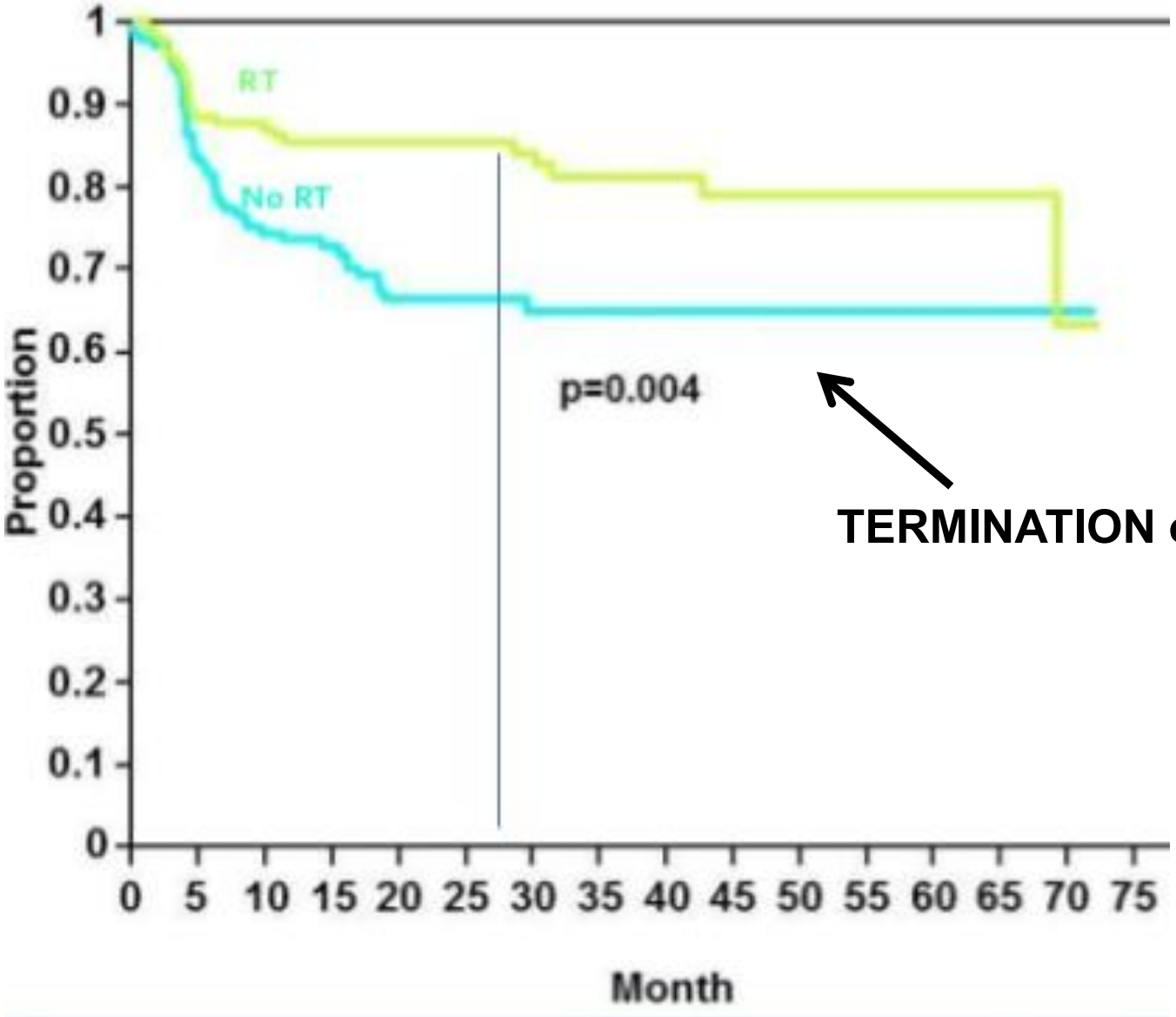
UNFOLDER trial



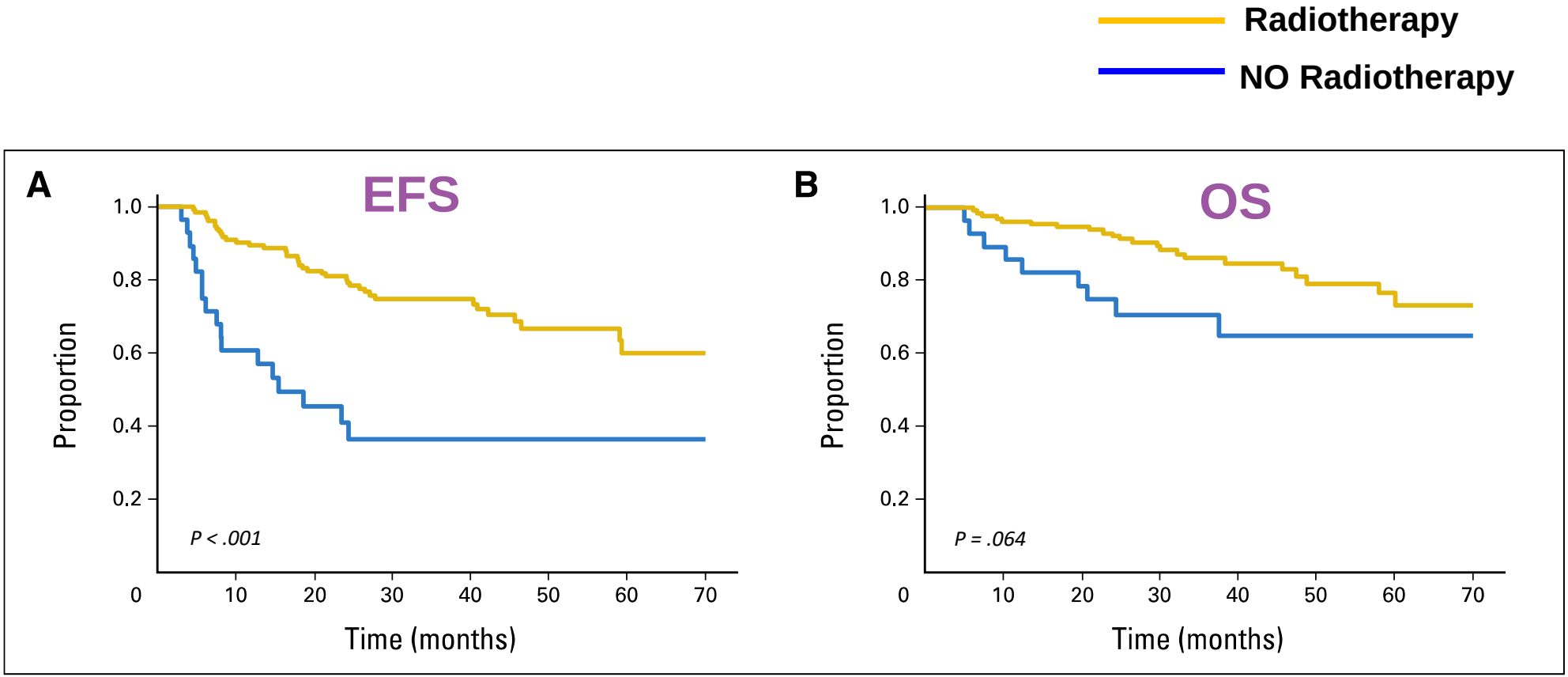
UNFOLDER trial



TERMINATION of "NO-RT" arm

Held. ICML RT Workshop, 2013

Impact of Rituximab and Radiotherapy on Outcome of Patients With Aggressive B-Cell Lymphoma and Skeletal Involvement



3-year EFS:

75% RT; 36% NO RT

3-year OS:

86% RT; 71% NO RT

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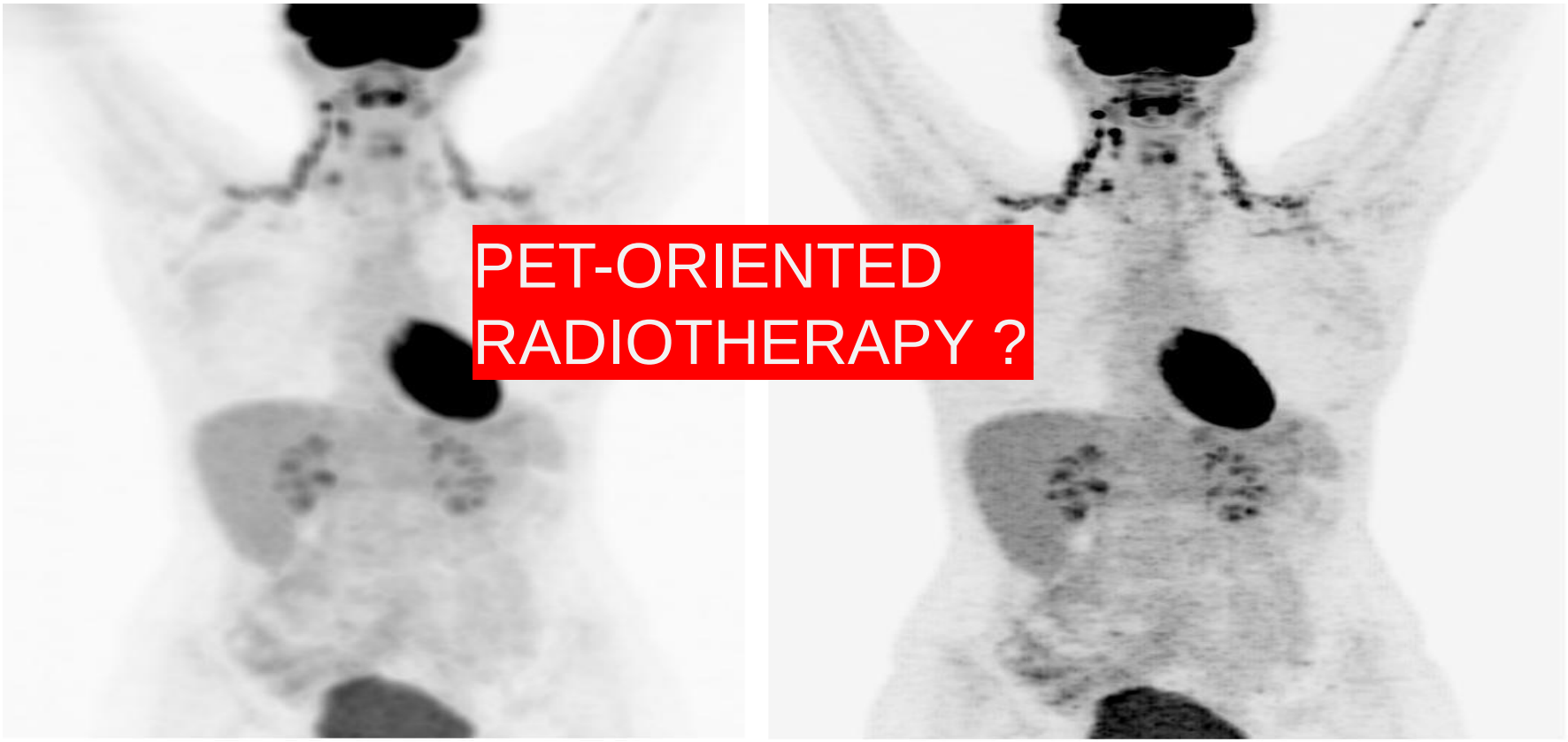
Held et al. JCO 2013;31(32):4115-4122

To irradiate or not to irradiate ?



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IELSG 37 – Study Design

PMBCL diagnosis
basal PET-CT 1

Standard therapy
R-Chemo

***RCHOP 14-21; R-V/MACOP-B**
DA-EPOCH-R; R-ACVBP;
R-CHO(E)P like

PET-CT 2
Central review

5-6 wks after R-Chemo

Positive not randomised pts will be followed for response, PFS and OS analysis of the chosen salvage strategy .

Positive

Negative

Random 1:1

8 wks after R-Chemo

Mediastinal RT
30 Gy

Observation

376 pts to randomize

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Is more of one modality better (and safer) than less of two?

CARDIAC MORTALITY IN PATIENTS WITH STAGE I AND II DIFFUSE LARGE B-CELL LYMPHOMA TREATED WITH AND WITHOUT RADIATION: A SURVEILLANCE, EPIDEMIOLOGY, AND END-RESULTS ANALYSIS

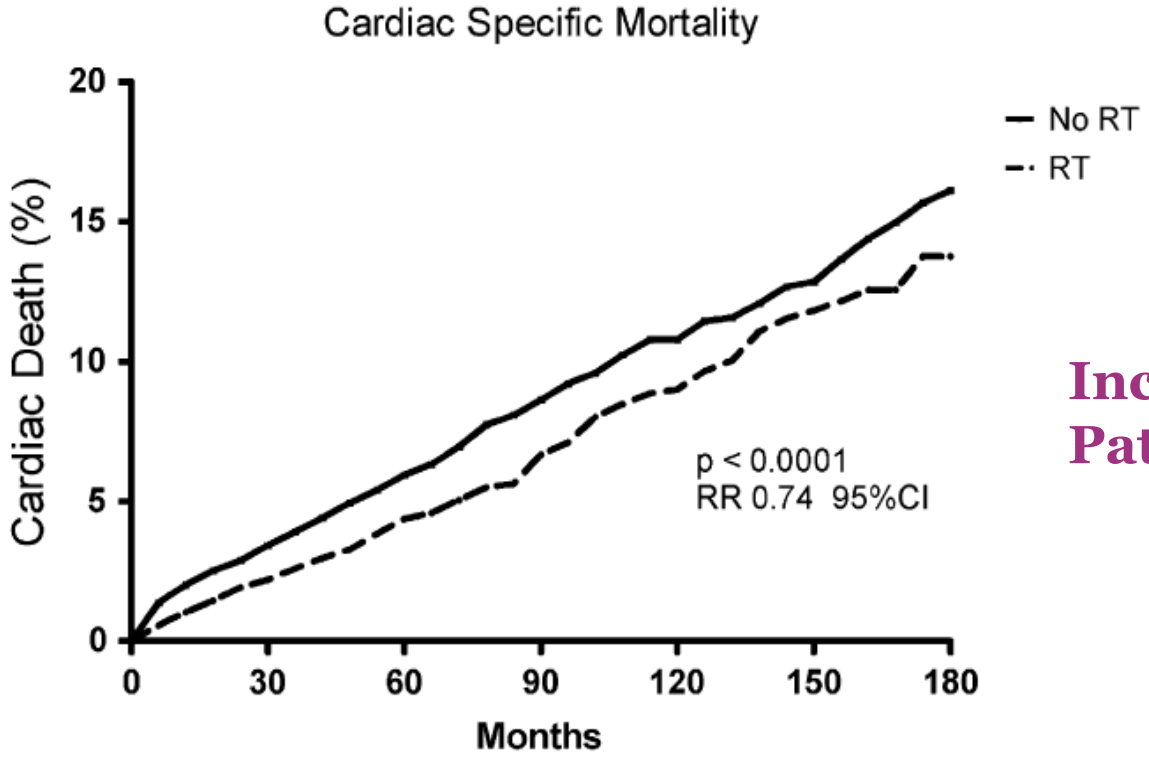
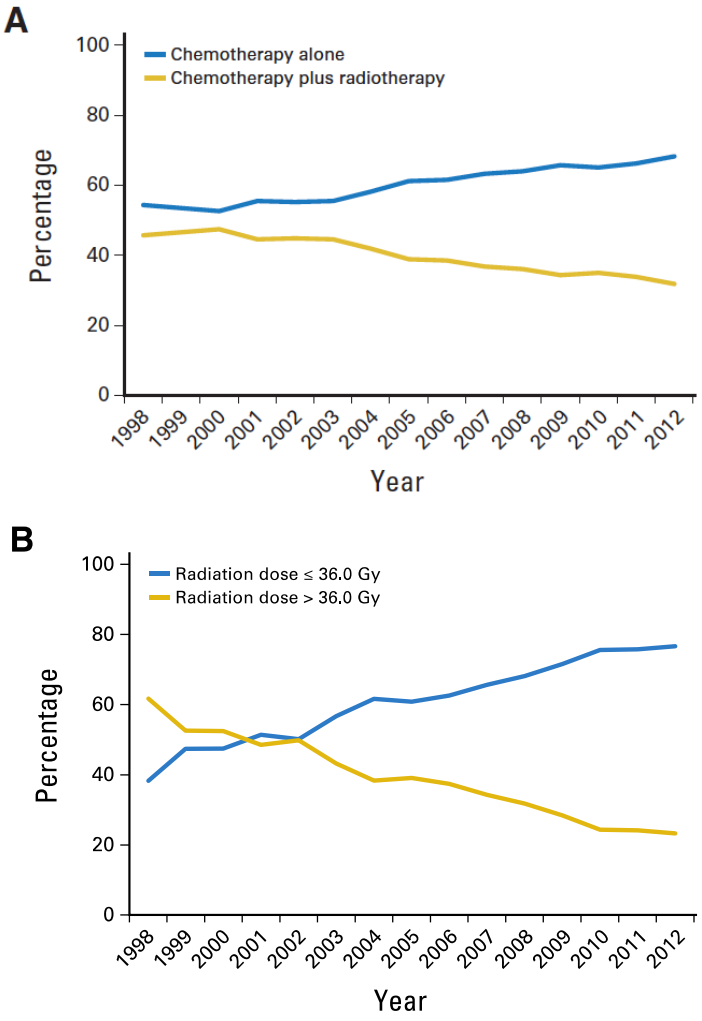
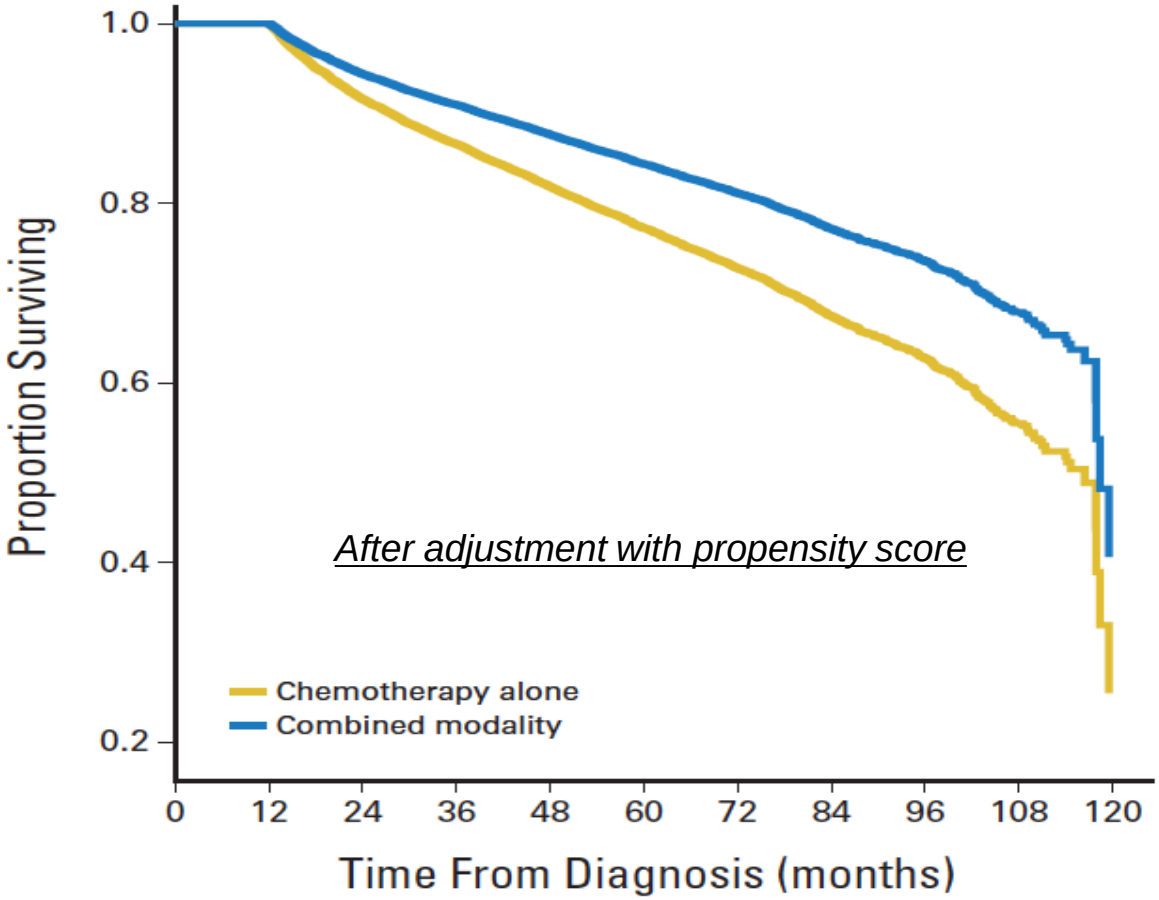


Fig. 1. Cardiac death in patients with stage I–II DLBCL. A comparison between patients treated with and without RT.

Increased Cardiac Death in Patients Treated without RT

Treatment Selection and Survival Outcomes in Early-Stage Diffuse Large B-Cell Lymphoma: Do We Still Need Consolidative Radiotherapy?





- **Abandonment of combined-modality therapy in favor of chemotherapy alone negatively affects patient survival.**

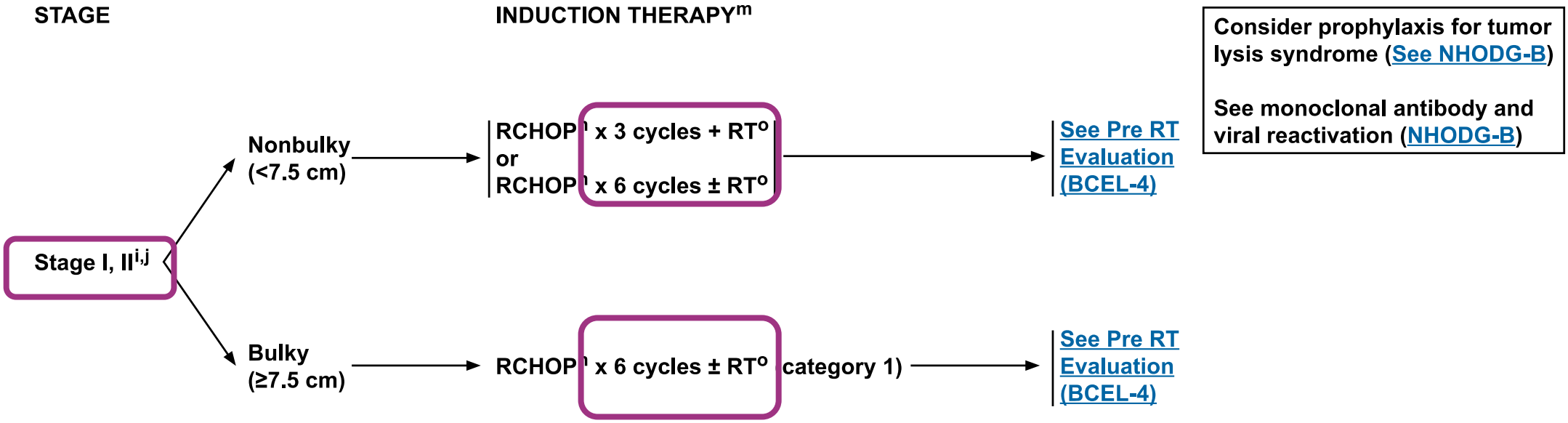
Vargo JA et al. JCO 2015;33

Radiotherapy role in Early stage DLBCL

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2015
Diffuse Large B-Cell Lymphoma

NCCN Guidelines Index
NHL Table of Contents
Discussion



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Radiotherapy role in advanced stage DLBCL

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2015
Diffuse Large B-Cell Lymphoma

NCCN Guidelines Index
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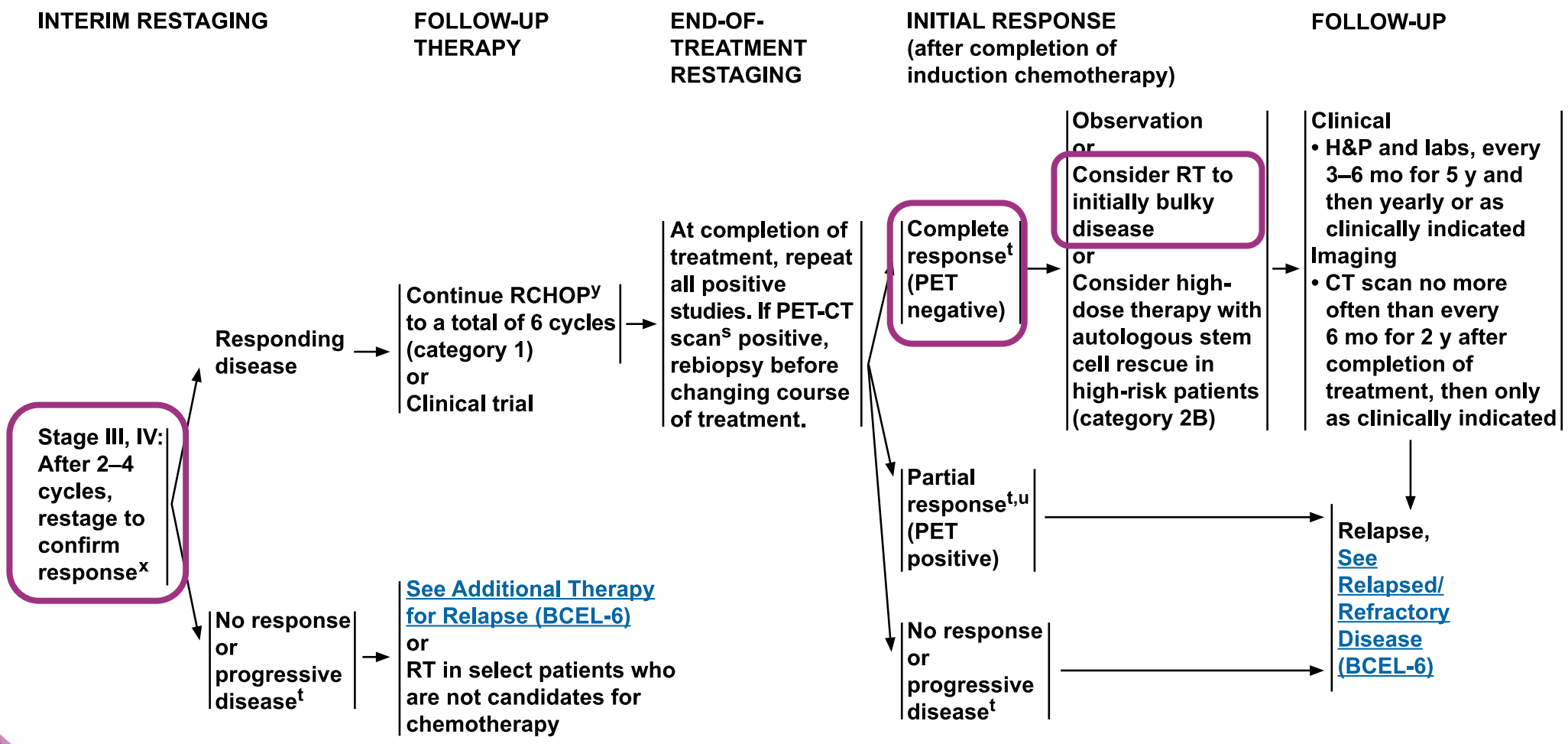
Discussion



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Take Home Message (DLBCL)

- The development of tailored therapy according to the relapse risk is warranted, rather than uniform treatment of all early-stage DLCL (bulky disease, PET-oriented treatment)

- Therapeutic burden: R-CHOP x 3 cycles followed by 30 Gy IF-RT probably better than R-CHOP x 6 cycles (less toxic and probably higher survival rates)

- Consolidative RT is strongly recommended, even after 6 R-CHOP and in advanced stage DLBCL, for patients with bulky lesions or skeletal involvement

”There is no doubt that radiation remains the most effective single agent in the treatment of most types of lymphoma”

James O. Armitage

“Combined modality treatment consisting of a fixed combination of a restricted number of ABVD courses followed by small-field radiotherapy remains the gold standard for early stage HL”

Andreas Engert & John Raemaekers

ESTRO School

Combined drug-radiation treatment: gynaecological cancers

Dr Li Tee Tan

Cambridge University Hospitals NHS
NHS Foundation Trust

Levels of evidence

IA	Meta-analysis of randomized controlled trials
IB	At least one randomized controlled trial
IIA	At least one controlled study without randomization
IIB	At least one quasi-experimental study
III	Non-experimental descriptive studies (comparative studies, correlation studies, case-control studies)
IV	Expert opinions

Grades of recommendation

A	Directly based on Level I evidence
B	Directly based on Level II evidence or extrapolated recommendations from Level I evidence
C	Directly based on Level III evidence or extrapolated recommendations from Level I or II evidence
D	Directly based on Level IV evidence or extrapolated recommendations from Level I, II, or III evidence

Levels of evidence

Levels of scientific evidence	
1++	High-quality meta-analyses, high-quality systematic reviews of clinical trials with very little risk of bias.
1+	Well-conducted meta-analyses, systematic review of clinical trials or well-conducted clinical trials with low risk of bias.
1-	Meta-analyses, systematic reviews of clinical trials or clinical trials with high risk of bias.
2++	High-quality systematic reviews of cohort or case and control studies; cohort or case and control studies with very low risk of bias and high probability of establishing a causal relationship.
2+	Well-conducted cohort or case and control studies with low risk of bias and moderate probability of establishing a causal relationship.
2-	Cohort or case and control studies with high risk of bias and significant risk that the relationship is not causal.
3	Non-analytical studies, such as case reports and case series.
4	Expert opinion.

Grades of recommendation

Grades of recommendations	
A	At least one meta-analysis, systematic review or clinical trial classified as 1++ and directly applicable to the target population of the guideline, or a volume of scientific evidence comprising studies classified as 1+ and which are highly consistent with each other.
B	A body of scientific evidence comprising studies classified as 2++, directly applicable to the target population of the guideline and highly consistent with each other, or scientific evidence extrapolated from studies classified as 1++ or 1+.
C	A body of scientific evidence comprising studies classified as 2+, directly applicable to the target population of the guideline and highly consistent with each other, or scientific evidence extrapolated from studies classified as 2++.
D	Level 3 or 4 scientific evidence, or scientific evidence extrapolated from studies classified as 2+.

Due to their high risk of bias, studies classified as 1- or 2- should not be used in compiling recommendations

Good Clinical Practice

√[1]	Practice recommended on the basis of clinical experience and consensus by the drafting team

Outline

- Endometrial cancer
- Vulva cancer
- Uterine sarcomas

Endometrial cancer

- Most common gynae cancer in western countries
- Confined to the uterus in 75%
  - High risk features in 30%
  - Occult metastatic disease in 15%
- Treatment of choice = surgery

Adjuvant treatment

- Radiotherapy
  - Who to treat?
  - How to treat?
- Role of chemotherapy?
- Future agents?

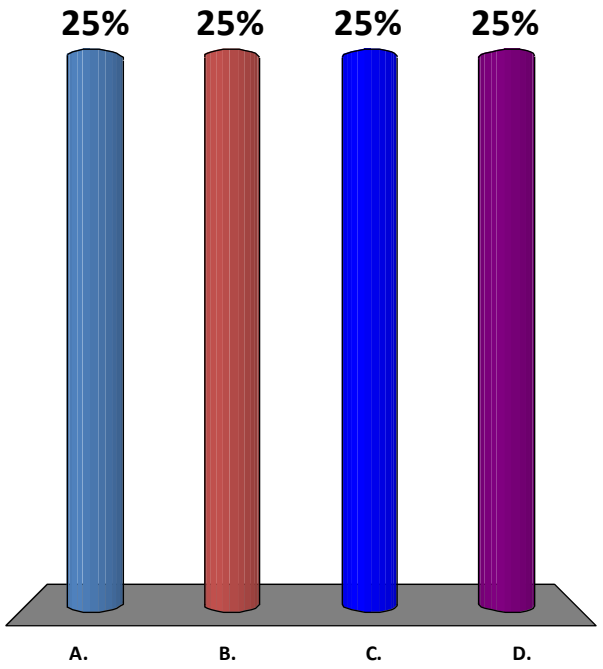
Patient

- Age 55
- LAVH + BSO (no LND) for IbG2 endometrioid ca
- Tumour invades into outer half of myometrium to within 3 mm of serosal surface
- No LVSI

What adjuvant RT would you recommend?

A. None
B. Vault BT
C. Pelvic RT
D. Don't know

- Age 55
- Stage IbG2 (no LND)
- No LVSI



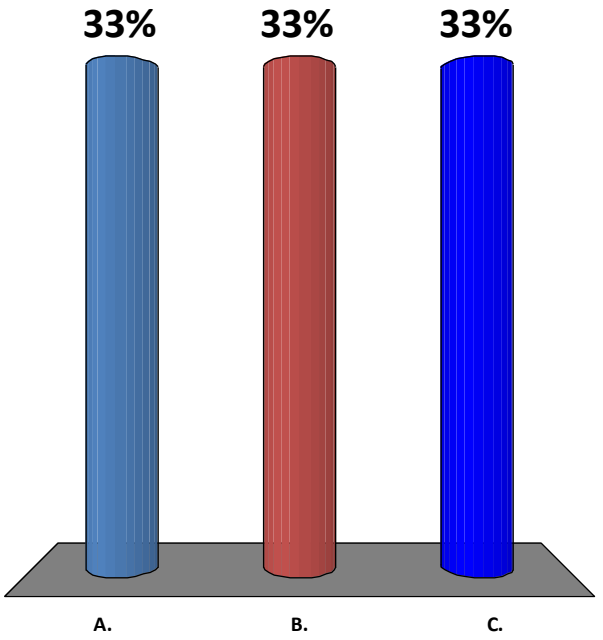
Would your recommendation be different if she was 65 instead of 55?

A. No

B. Yes – recommend more intensive RT

C. Yes – recommend less intensive RT

- Age **65**
- Stage IbG2 (no LND)
- No LVSI



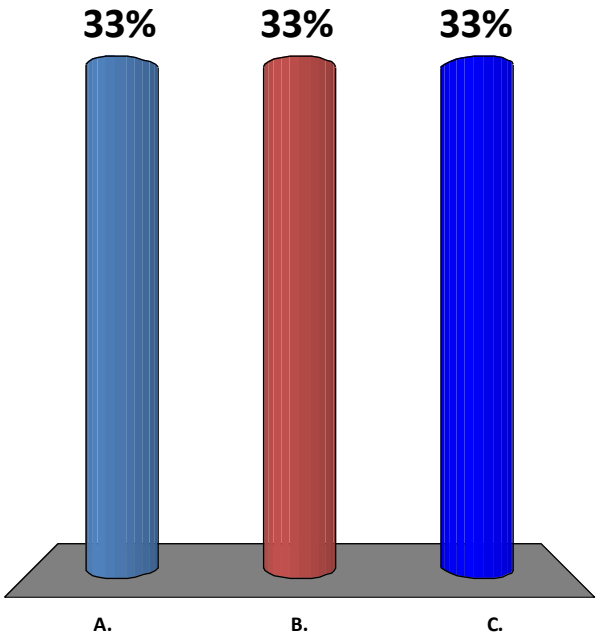
Would your recommendation be different if tumour was G3 instead of G2?

A. No

B. Yes – recommend more intensive RT

C. Yes – recommend less intensive RT

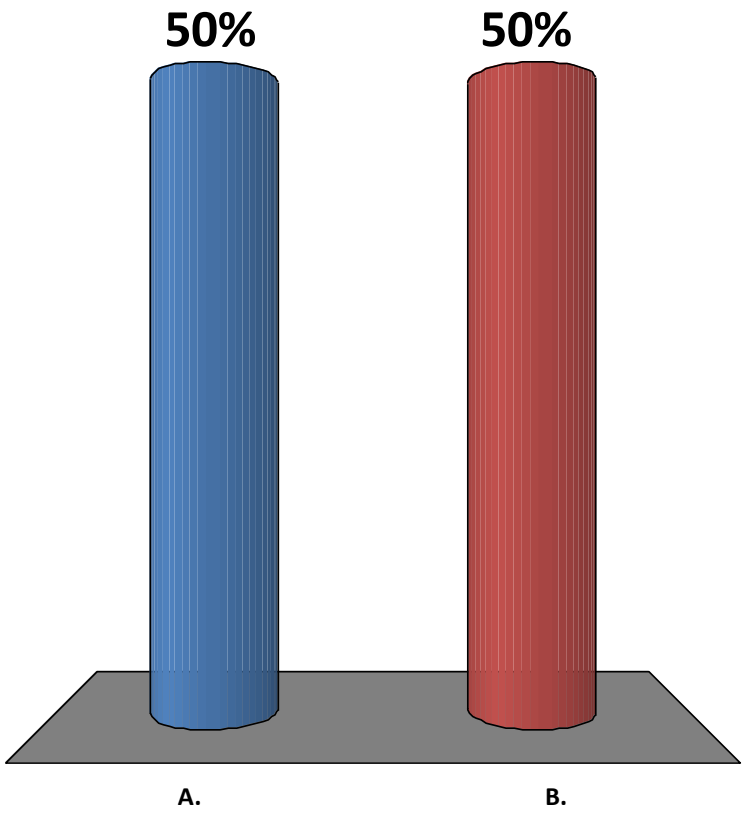
- Age 55
- Stage Ib**G3** (no LND)
- No LVSI



Would your recommendation be different if there was focal LVSI?

A. Yes
B. No

- Age 55
- Stage IbG2 (no LND)
- **Focal** LVSI



Adjuvant treatment

- Radiotherapy
  - **Who to treat?**
  - How to treat?
- Role of chemotherapy?

PORTEC-1

- Role of RT in Stage I disease (no LND)
- Whole pelvis RT vs. observation
- Inclusion criteria
  - G1, deep (≥50%) invasion (2009 Ib)
  - G2, superficial or deep invasion (2009 Ia + Ib)
  - G3, superficial (<50%) invasion (2009 Ia)

Creutzberg CL, et al. Lancet. 2000 22;355(9213):1404-11

PORTEC-1 results

	RT	Control	*p* value
Local recurrence	4%	14%	<0.001

RT recommended only if two adverse features present: age ≥ 60, deep myometrial invasion, G3.

Other RCTs

Trial	No of pts.	Surgery	Randomization	Local recurrence	Survival
Portec 1	714	TAH-BSO	Obs	14%	85%
2000	Stage IB, G2-3		EBRT	4%	81%
	Stage IC, G1-2			(p<.001)	(n.s.)
GOG-99	392	TAH-BSO &	Obs	12%	86%
2004	Stage IB, IC, IIA	LA	EBRT	3%	92%
				(p<.01)	(n.s.)
ASTEC/EN.5	789	TAH-BSO	Obs	6% (BT50%)	84%
2009	Stage IAB G3	LA optional	EBRT	3% (BT50%)	84%
	Stage IC	(30%)		(p<0.02)	(n.s.)

Adjuvant treatment

- Radiotherapy
  - Who to treat?
  - **How to treat?**
- Role of chemotherapy?

PORTEC-2

- Type of RT
- Vaginal BT vs. whole pelvis RT
- Inclusion criteria
  - 1C (deep invasion), G1 or 2, age ≥ 60 (Ib)
  - 1B (superficial invasion), G3 and age ≥ 60 (Ib)
  - 2A, any age, G1 or 2, deep or superficial invasion (Ia + Ib)
  - 2A, any age, G3, superficial invasion (Ia)

Nout RA, et al. Lancet. 2010 6;375(9717):816-23

PORTEC-2 results

	VBT	EBRT	*p* value
Vaginal recurrence	1.8%	1.6%	0.74
Pelvic recurrence	5.1%	2.1%	0.17
Acute GI toxicity	12.6%	53.8%	

VBT is adjuvant treatment of choice for patients with "high-intermediate risk" endometrial Ca

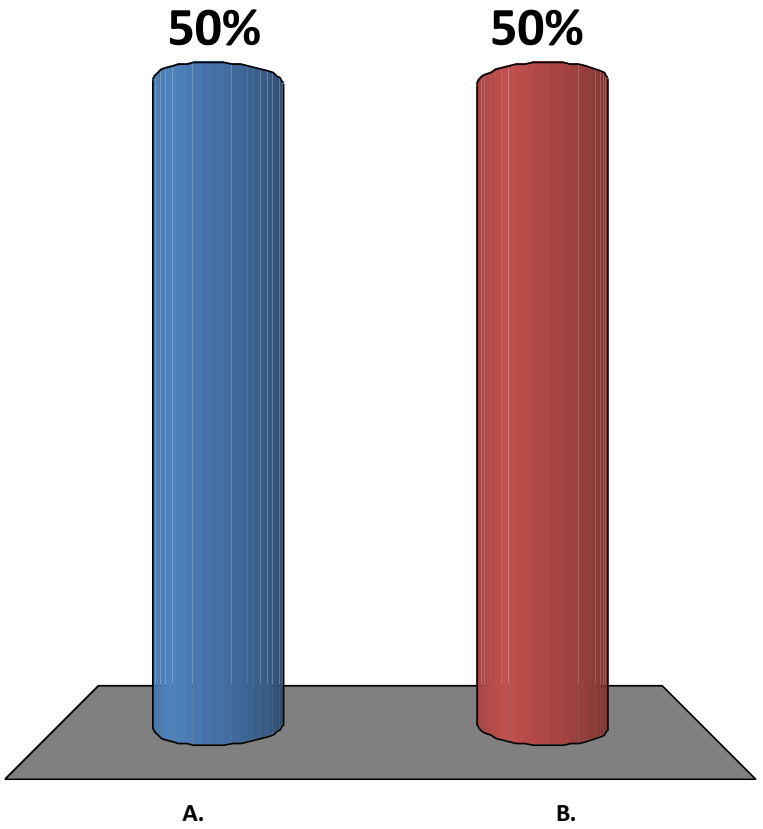
Adjuvant treatment

- Radiotherapy
  - Who to treat?
  - How to treat?
- **Role of chemotherapy?**

Do you offer adjuvant chemotherapy after radiotherapy for endometrial cancer patients outside clinical trials?

A. Yes

B. No



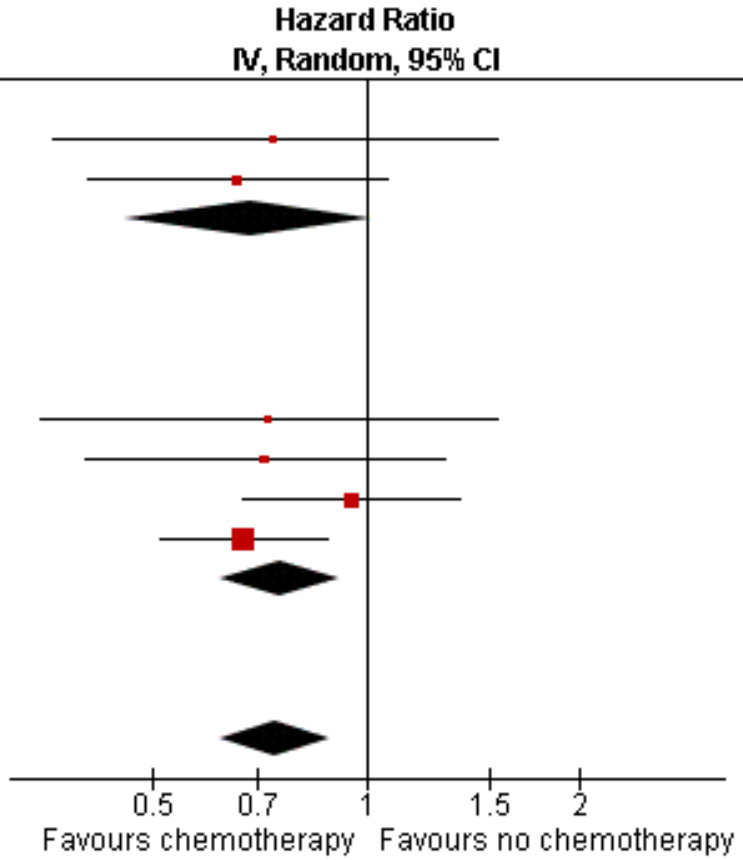
Adjuvant chemo studies

Study	Pats	Adv stage	Treatment	5-yr OS
NSGO-EORTC Hogberg 2007	382 Stage I-III	2%	RT RT+ A/P/T	74% 82%
J GOG 2033 Sagae 2005	385 Stage I-III	25%	RT CAP	86% 87%
GICOG Maggi 2006	340 Stage I-III	64%	RT CAP	69% 66%
GOG 122 Randall 2006	396 Stage III-IV	100%	WART AP	42% 55%

van Wijk FH, et al. Int J Gynecol Cancer. 2009;19(3):431-46

Meta-analysis

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
1.1.1 Chemotherpay versus no additional treatment (all receive EBRT+surgery)				
MaNGO	-0.3	0.37	5.9%	0.74 [0.36, 1.53]
NSGO & EORTC	-0.42	0.25	13.0%	0.66 [0.40, 1.07]
Subtotal (95% CI)			**18.9%**	**0.68 [0.45, 1.02]**
Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.79); I² = 0%				
Test for overall effect: Z = 1.85 (P = 0.06)				
1.1.2 Chemotherpay v Radiotherapy				
GOG 150	-0.32	0.38	5.6%	0.73 [0.34, 1.53]
J GOG 2033	-0.33	0.3	9.0%	0.72 [0.40, 1.29]
GICOG	-0.05	0.18	25.0%	0.95 [0.67, 1.35]
GOG 122	-0.4	0.14	41.4%	0.67 [0.51, 0.88]
Subtotal (95% CI)			**81.1%**	**0.76 [0.62, 0.92]**
Heterogeneity: Tau² = 0.00; Chi² = 2.41, df = 3 (P = 0.49); I² = 0%				
Test for overall effect: Z = 2.78 (P = 0.005)				
Total (95% CI)			**100.0%**	**0.74 [0.62, 0.89]**
Heterogeneity: Tau² = 0.00; Chi² = 2.68, df = 5 (P = 0.75); I² = 0%				
Test for overall effect: Z = 3.31 (P = 0.0009)				
Test for subgroup differences: Chi² = 0.20, df = 1 (P = 0.65), I² = 0%				



Cochrane Database of Systematic Reviews 2011

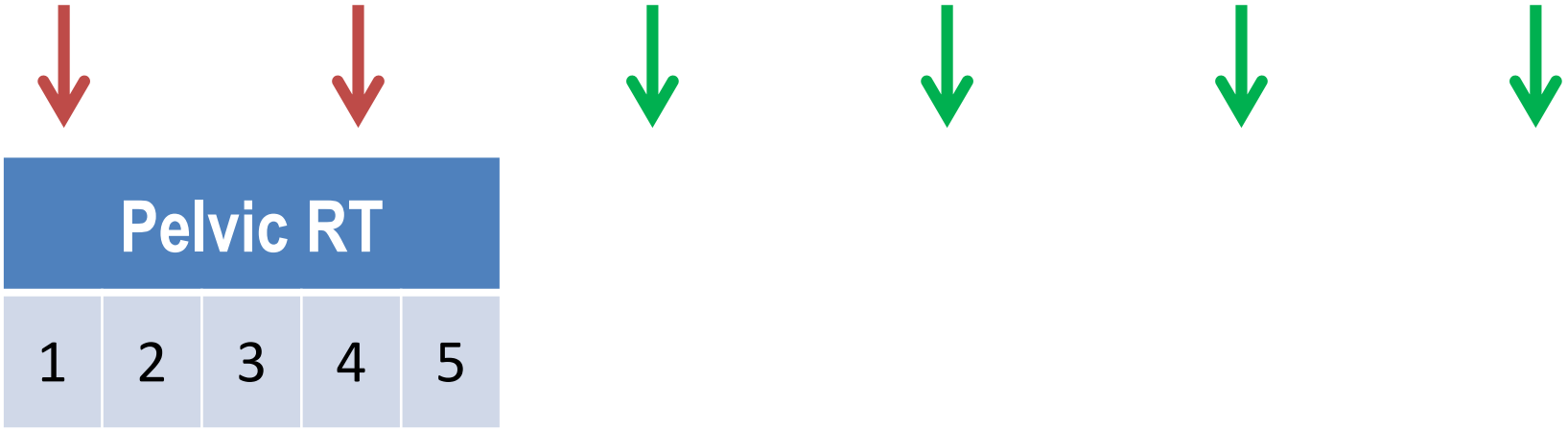
Meta-analysis - conclusions

- Post-op platinum-based chemotherapy is associated with small benefit in PFS and OS irrespective of RT.
  - Reduces risk of developing metastases
  - Could be alternative to RT
  - Has added value when used with RT

Cochrane Database of Systematic Reviews 2011

PORTEC-3

- EBRT ± 2# cisplatin (50 mg/m^2)
  4# carboplatin (AUC5) + Taxol 175 mg/m^2



PORTEC-3

- Criteria
  - IB G3 with LVSI
  - IC or IIA G3
  - IIB
  - IIIA* or IIIC (**IIIA on cytology alone must be G3)*
  - IB, IC, II or III with serous or clear cell histology
- Increase in 5-year OS of 12.5% (expected OS for RT: 50%). Target accrual = 500 over 5 years

Phase III Stage III + IVA EC

- Experimental arm

  RT + cisplatin 50 mg/m2 IV Days 1 and 29

  + Carboplatin AUC 5/6 + Paclitaxel 175 mg/m2 x 4 cycles

- “Active Comparator”

  Carboplatin AUC 6 + Paclitaxel 175 mg/m2 x 3 cycles

  + RT

  + Carboplatin AUC 5 or 6 + Paclitaxel 175 mg/m2 x 3 cycles

Phase III Stage III + IVA EC

- Primary endpoint
  - Recurrence-free survival
- Secondary endpoint
  - Overall survival
- Target accrual = 450
  - Study start March 2015
  - Study end date March 2023

GOG-0249

- Phase III study of pelvic RT vs. vaginal BT + 3# carbo-Taxol chemotherapy
- High-intermediate risk factors (GOG-99) - G2 or 3, LVSI, deep myometrial invasion:
  - Stage I, age ≥ 70, 1 risk factor
  - Stage I, age ≥ 50, 2 risk factors
  - Stage I, age ≥ 18, 3 risk factors
  - Stage II disease with or without risk factors
- Target accrual = 562

Preliminary results SGO 2014

- 601 patients randomized

	Pelvic RT	VBT + chemo
Vaginal recurrence	5	2
Pelvic recurrence	2	19
Distant failure	32	24
DFS	82%	84%
OS	93%	92%

- Acute toxicity more common with VBT + chemo

McMeekin, DS. SGO 2014 Abstract

ESMO-ESGO-ESTRO recommendations 2015

4 risk groups

Risk group	Histology	Adjuvant treatment
Low	Ia, G1-2, LVSI -ve	None

Colombo N. Radiother Oncol. 2015;117(3):559-81

ESMO-ESGO-ESTRO recommendations 2015

4 risk groups

Risk group	Histology	Adjuvant treatment
Low	Ia, G1-2, LVSI -ve	None
Intermediate	Ib, G1-2, LVSI -ve	BT or none if <60

Colombo N. Radiother Oncol. 2015;117(3):559-81

ESMO-ESGO-ESTRO recommendations 2015

4 risk groups

Risk group	Histology	Adjuvant treatment	
Low	Ia, G1-2, LVSI -ve	None	
Intermediate	Ib, G1-2, LVSI -ve	BT or none if <60	
		With LND	No LND
High-intermediate	Ib, G1-2, LVSI +ve Ia, G3	BT or none	BT if G3 and LVSI - EBRT if LVSI+

LVSI must be unequivocally positive (not focal)

Colombo N. Radiother Oncol. 2015;117(3):559-81

ESMO-ESGO-ESTRO recommendations 2015

4 risk groups

Risk group	Histology	Adjuvant treatment	
		With LND	No LND
High	Ib G3	EBRT or BT	EBRT (+ chemo)
	II G1-2, LVSI -ve II G3 or LVSI +ve	BT EBRT	EBRT EBRT (+ chemo)
	III	EBRT (+ chemo)	

Colombo N. Radiother Oncol. 2015;117(3):559-81

Take-home messages

- Younger patients have better prognosis.
- LVSI must be unequivocally positive (not focal) for RT

New agents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Cochrane Database of Systematic Reviews
PI3K/AKT/mTOR inhibitors for advanced or recurrent endometrial cancer
Protocol
Intervention
Julie Martyn, Felicia Roncolato, Melina L Willson, Kristina Lindemann, Linda Mileshkin
First published: 21 April 2016
Editorial Group: Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group
DOI: 10.1002/14651858.CD012160 View/save citation
Cited by (CrossRef): 0 articles Check for updates
Am score 1
Text size
Share
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Abstract
Background
Objectives
Methods
Acknowledgements
Appendices
Contributions of authors
Declarations of interest

New agents

- 4 main types
  - PI3K inhibitors e.g. BKM120
  - AKT inhibitors e.g. AZD5363, perfosine
  - mTOR complex 1/2 inhibitors e.g. everolimus, ridoforolimus, metformin, AZD8055
  - Dual mTOR/PI3K inhibitors, e.g. XL765

New agents


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Cochrane Database of Systematic Reviews
PI3K/AKT/mTOR inhibitors for advanced or recurrent endometrial cancer
Protocol
Intervention
Julie Martyn, Felicia Roncolato, Melina L Willson, Kristina Lindemann, Linda Mileshkin
First published: 21 April 2016
Editorial Group: Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group
DOI: 10.1002/14651858.CD012160 View/save citation
Cited by (CrossRef): 0 articles Check for updates
Am score 1
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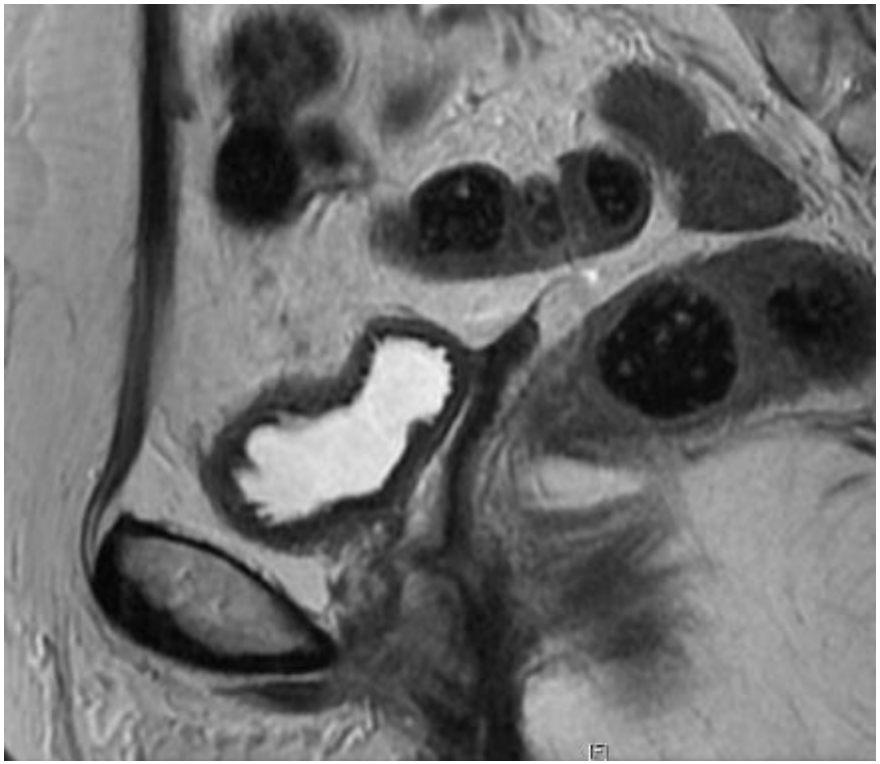
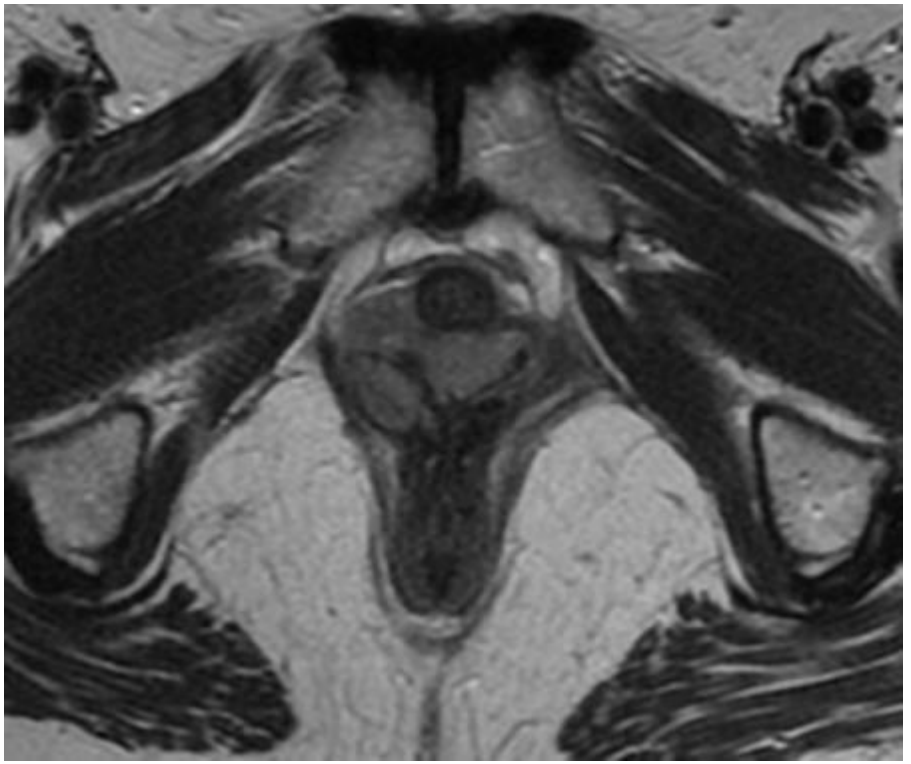
Background
Objectives
Methods
Acknowledgements
Appendices
Contributions of authors
Declarations of interest

Patient

- Age 55
- LAVH + BSO for IbG2 endometrioid ca
  - Tumour invades into outer half of myometrium to within 3 mm of serosal surface
  - No LVSI
- No post-operative RT
- Isolated vaginal recurrence at 12 months

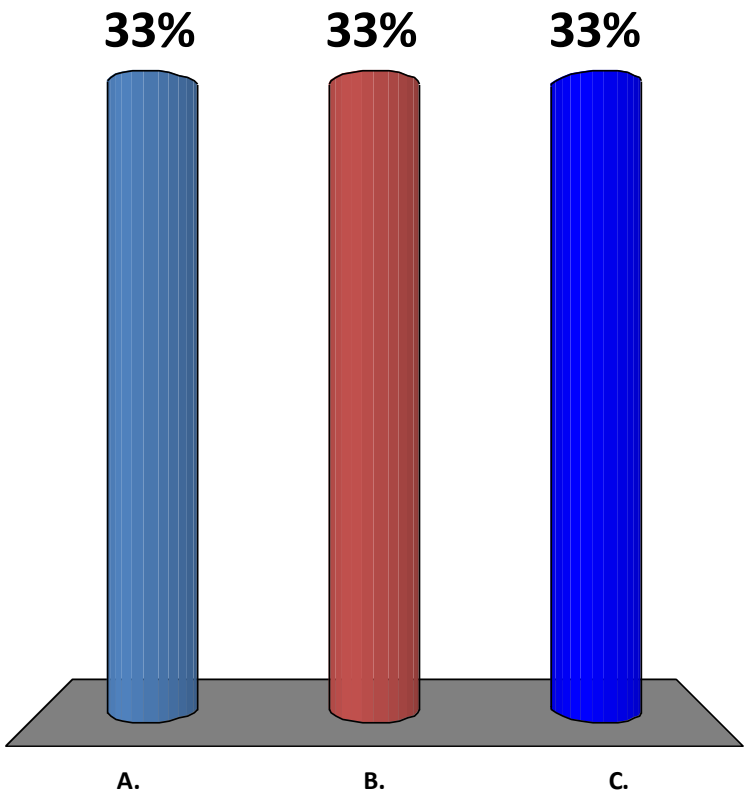
Patient





What treatment would you recommend for recurrence?

A. Surgery
B. Radiotherapy
C. Chemotherapy



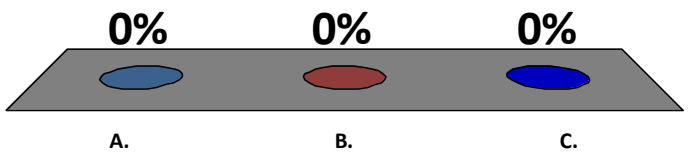
- Age 55
- Stage IbG2
- No LVSI
- No post-op RT

What local control rate would you expect after salvage RT for vault recurrence?

A. 20%

B. 50%

C. 80%

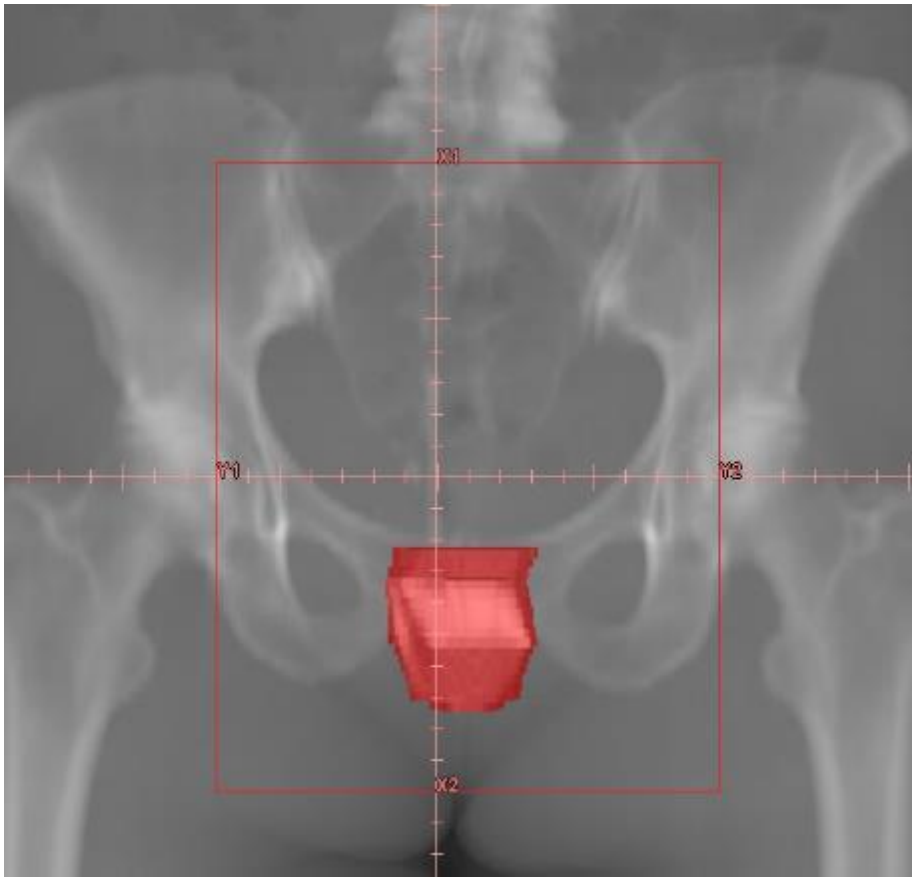


Vault recurrence

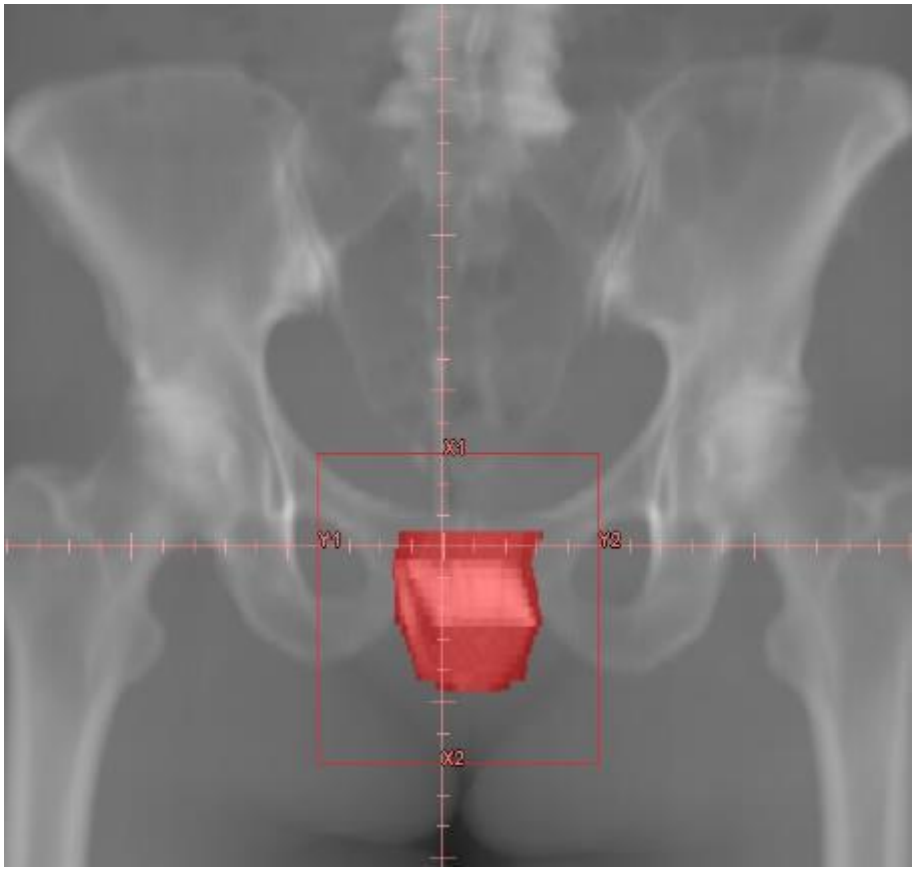
- Danish Endometrial Cancer Study
  - 1166 patients, surgery alone
  - Vaginal recurrence: low risk 6.3%, intermediate risk 22%
  - **Curative treatment: 100% CR, 74% cured**
- Must give sufficient dose (>65 Gy)
  - EBRT boost
  - Interstitial boost
  - IMRT

Ørtoft G, et al. Int J Gynecol Cancer. 2013; 23(8):1429-37

Patient

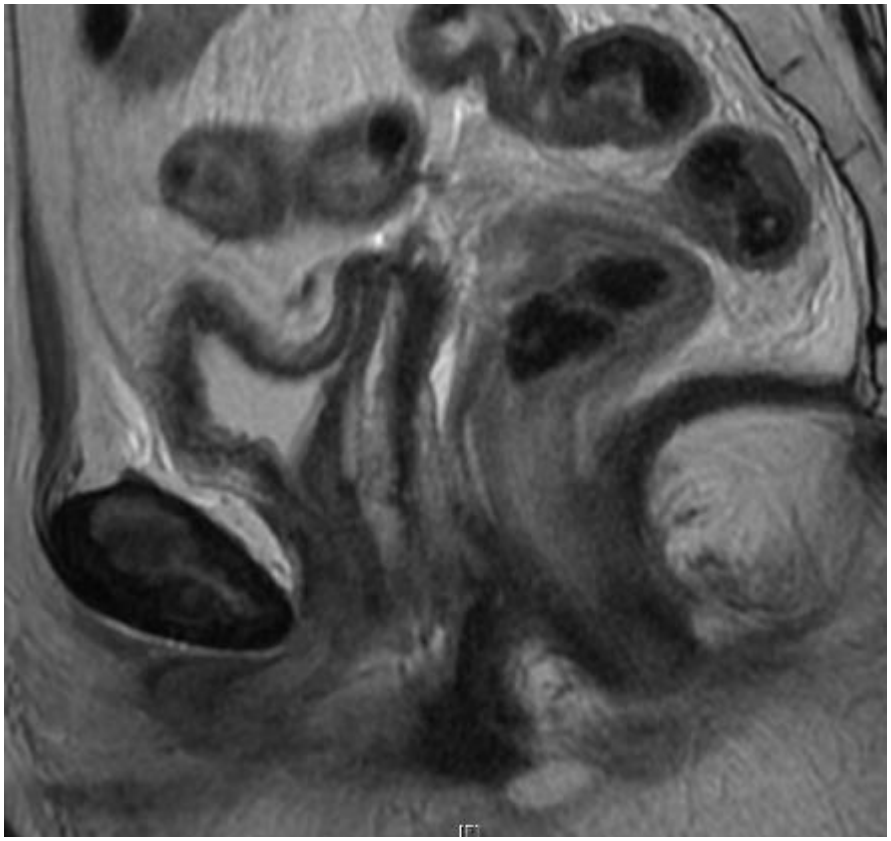


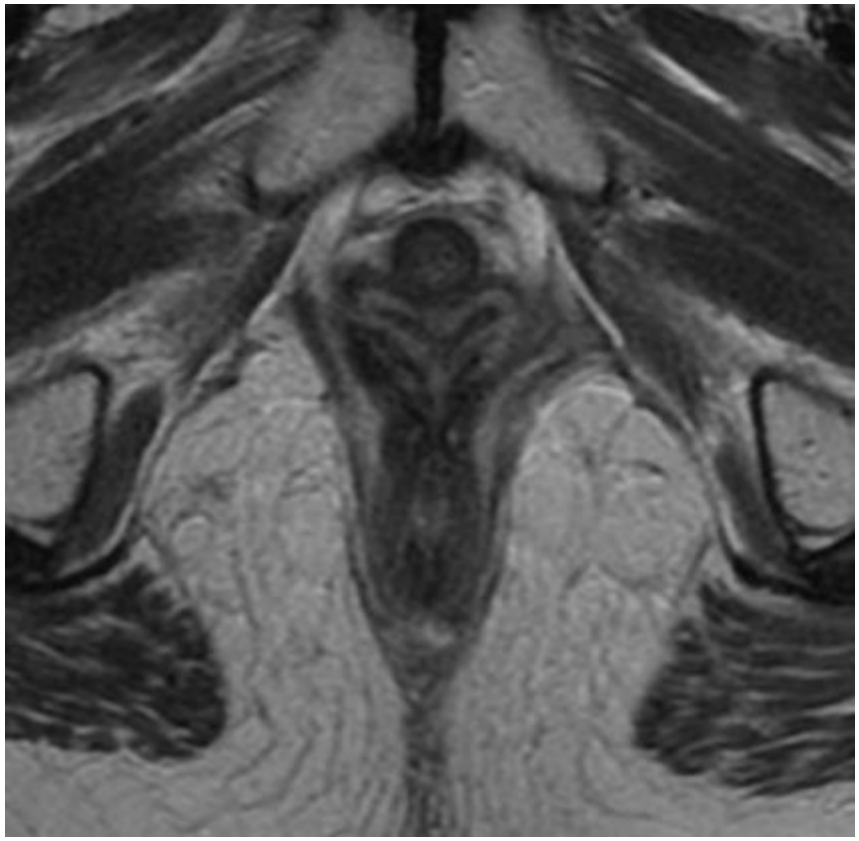
45Gy in 25#



20Gy in 10#

Patient





ESMO-ESGO-ESTRO recommendations 2015

- RT with curative intent is indicated in patients with isolated vaginal relapse after surgery.
- Use of systemic therapy or surgery before RT for vaginal or pelvic node recurrence could be considered in certain patients with more bulky disease.

Colombo N. Radiother Oncol. 2015;117(3):559-81

Outline

- Endometrial cancer
- **Vulva cancer**
- Uterine sarcomas

Epidemiology

- Rare - 3-5% of gynae cancers
- Squamous cell carcinoma in 85-90%
- Elderly patients
- Treatment of choice = surgery

Adjuvant treatments

- Post-operative
- Pre-operative

Post-operative radiotherapy

- Aims
  - Reduce local recurrence
  - Reduce regional recurrence
  - Improve survival
- Questions
  - Does it work?
  - Can it replace groin surgery?
  - Does adding chemotherapy help?

Reduce local recurrence

- 135 patients (observational study)
  - Stage I-II = 110
  - Stage III-IV = 25

Table 14–6. CORRELATION OF SURGICAL MARGIN WITH LOCAL RECURRENCE FOLLOWING SURGICAL THERAPY OF VULVAR CANCER

	Surgical Margin < 8 mm (N = 44)	Surgical Margin ≥ 8 mm (N = 91)
Local recurrence	21/44 (48%)	0/91

Heaps JM, et al. Gynecol Oncol. 1990;38(3):309-14

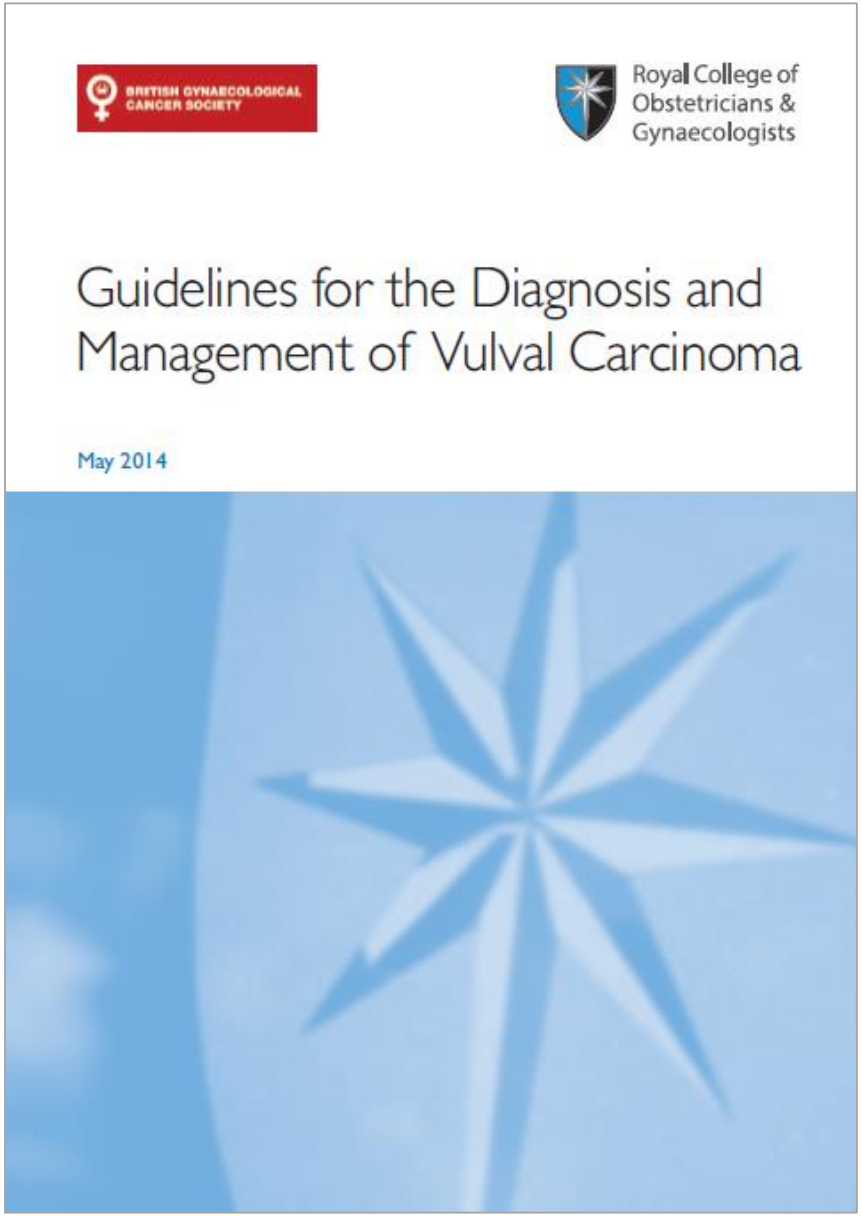
Would you offer post-op RT if margin is <8mm and further excision is not possible?

A. Yes

B. No

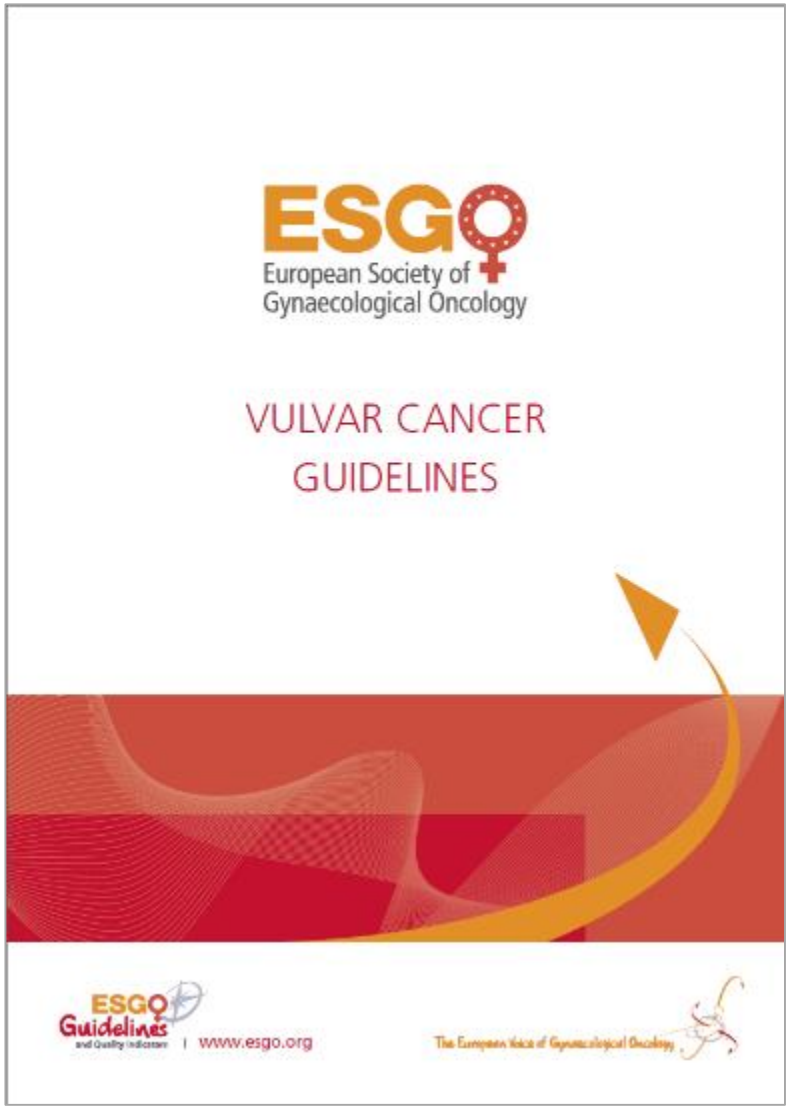
BGCS/RCOG guidelines 2014

"There is not enough evidence to recommend adjuvant local therapy routinely in patients with close surgical margins."



ESGO 2016

- In case of close but clear pathological margins, postoperative vulvar radiotherapy may be considered to reduce the frequency of local recurrences. There is no consensus for the threshold of pathological margin distance below which adjuvant radiotherapy should be advised.



Expert opinion

Reduce regional recurrence
Improve survival

- GOG-37 (RCT)
  - 114 patients
  - Positive inguinal nodes
- Pelvic node dissection vs pelvic RT

	Surgery	Radiotherapy
Regional recurrence	24%	5%
Survival	54%	68%

$p = 0.03$

Homesley HD, et al. Obstet Gynecol. 1986;68(6):733-40

Indications for post-operative RT

- 2 or more microscopic nodes
- 1 or more macroscopic node
- Extracapsular disease

Replace groin surgery

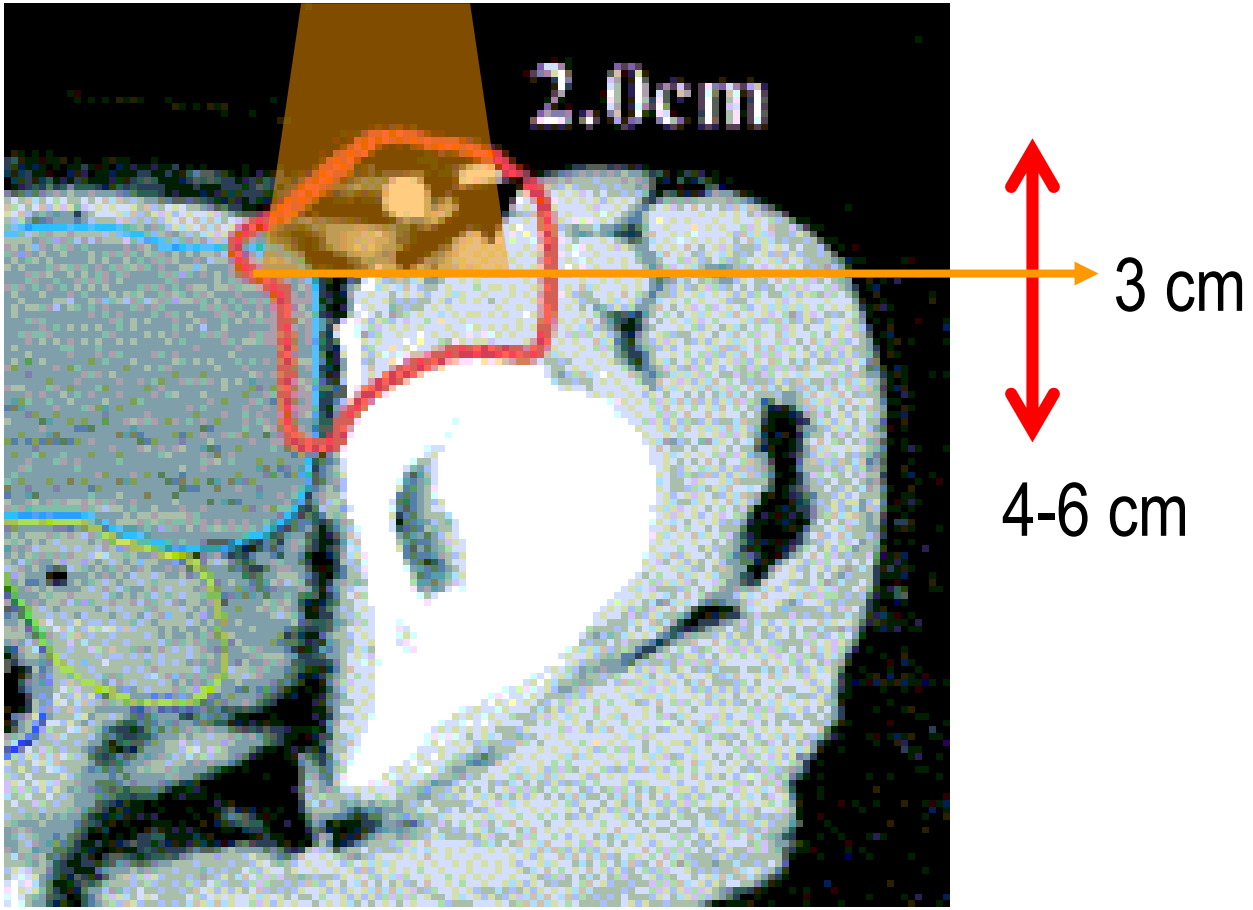
- GOG 88
  - RT vs inguinal node dissection
  - 58 patients
  - T1-3, N0-1, M0

	Surgery	Radiotherapy
Groin relapse	0%	18.5%

Stehman FB, et al. IJROBP 1992. 24:389-396

RT vs nodal dissection

- 50 Gy at 3 cm depth

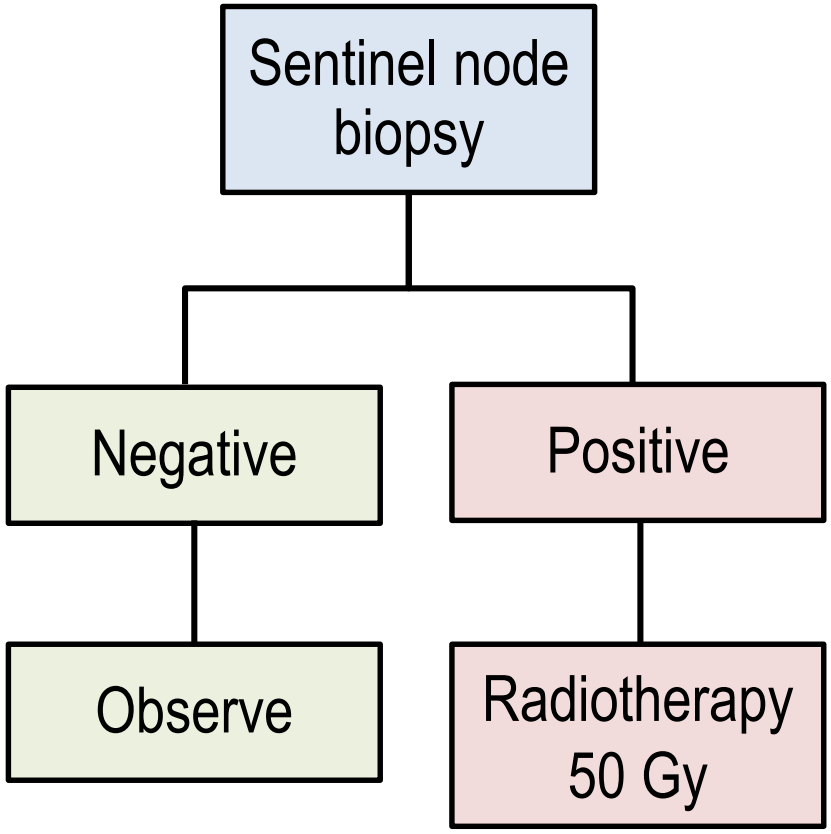


RCOG 2014

- Surgery is the cornerstone of therapy for the groin nodes in women with vulval cancer.
- Individual women who are not fit enough to withstand surgery, even when performed under regional anaesthesia, can be treated with primary radiotherapy.

GROINSS-V II

- Observational study
  - T1-T2 < 4 cm
  - No clinical/radiological involved nodes

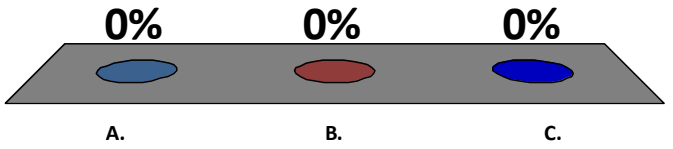


Do you offer concomitant chemotherapy with adjuvant radiotherapy for vulvar cancer?

A. Usually

B. Sometimes

C. No



GYNECOLOGIC CANCER INTERGROUP

An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

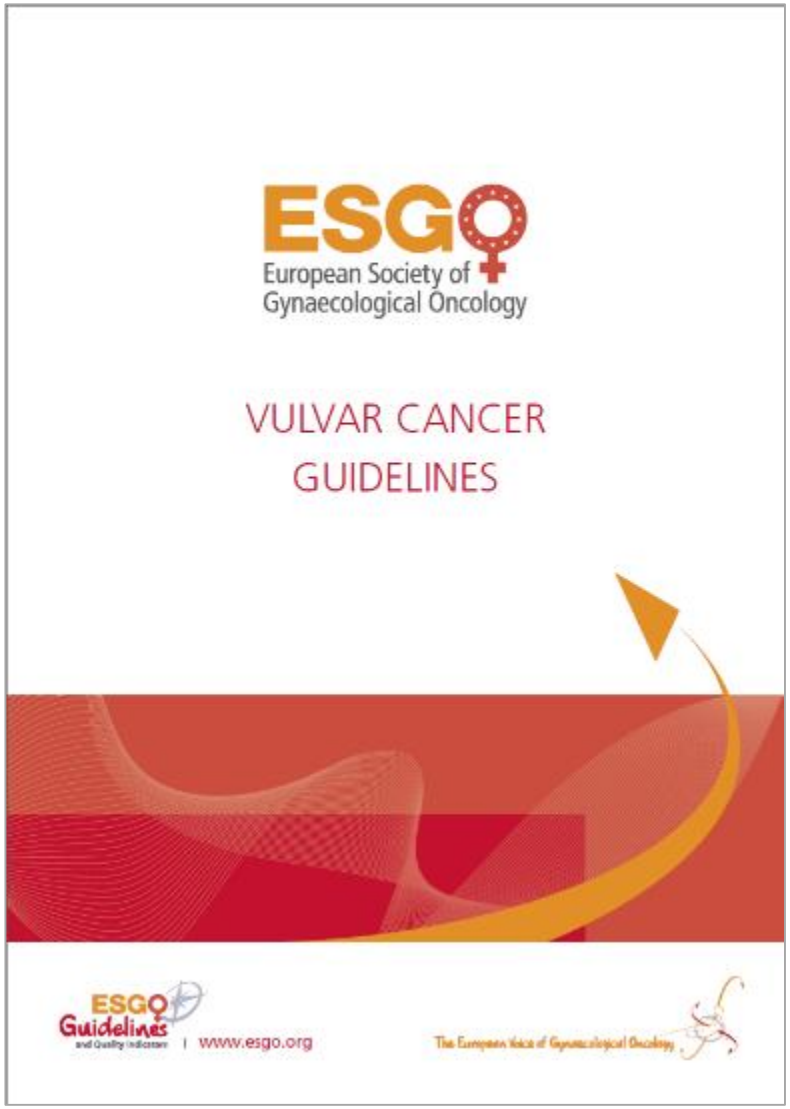
Patterns of Care for Radiotherapy in Vulvar Cancer: A Gynecologic Cancer Intergroup Study

- Use of concomitant chemotherapy
  - No = 50%
  - Yes = 50%
- Regimens
  - Cisplatin 70%
  - Cis + 5FU 20%
  - 5FU + MMC 10%

Gaffney DK, et al. Int J Gynecol Cancer. 2009;19:163-7

ESGO 2016

- Based on evidence from other squamous cell cancers such as cervical, head & neck, and anal cancer, the addition of concomitant, radiosensitising chemotherapy to adjuvant radiotherapy should be considered.



Grade C: Extrapolated evidence from studies rated as 2++

Adjuvant treatments

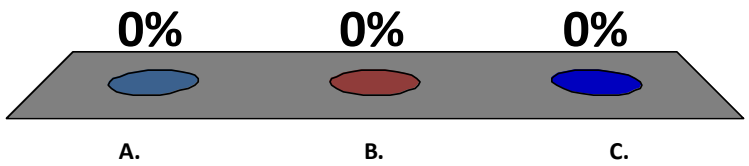
- Post-operative
- **Pre-operative**

Pre-operative

- Aims
  - Downstage disease
  - Avoid mutilating surgery
- Questions
  - Benefit of adding chemotherapy?
  - Avoid all surgery?

Do you offer neoadjuvant chemo-RT for vulvar cancer?

A. Usually
B. Sometimes
C. No



GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

Patterns of Care for Radiotherapy in Vulvar Cancer: A Gynecologic Cancer Intergroup Study

- Use of concomitant chemotherapy
  - No = 19%
  - Yes = 81%
- Regimens
  - Cisplatin 55%
  - Cis + 5FU 31%
  - 5FU + MMC 5%
  - Other 9%

Gaffney DK, et al. Int J Gynecol Cancer. 2009;19:163-7

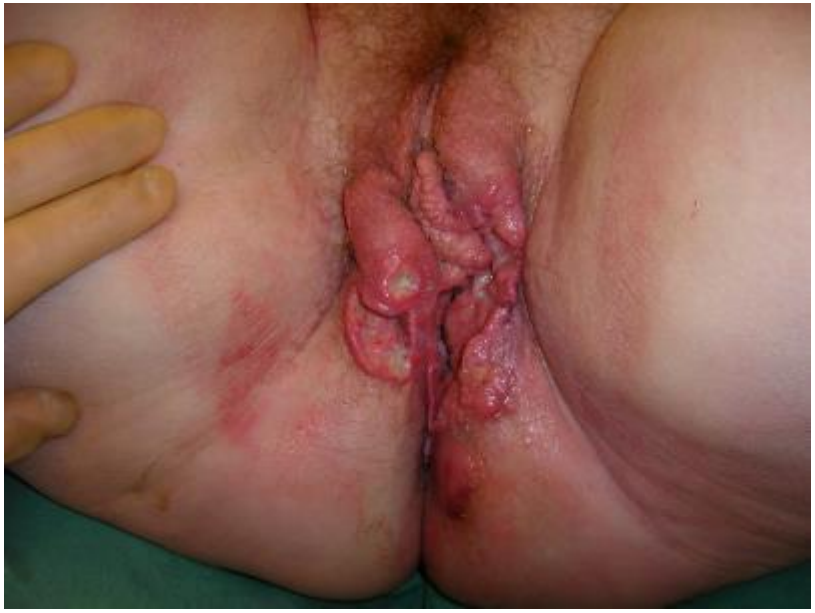
Concomitant chemotherapy

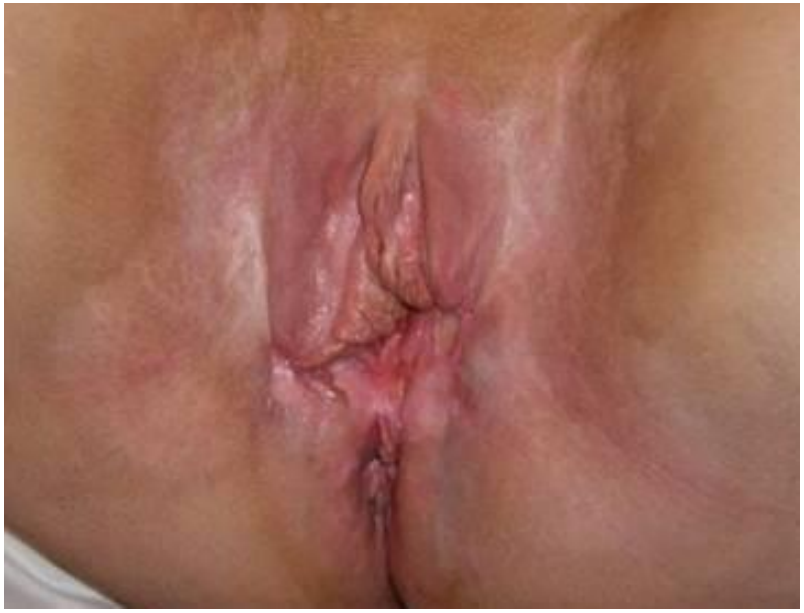
- RCT of neoadjuvant chemoRT vs. surgery
  - 68 patients
  - **Operable cancer**, FIGO Stage II-IV
  - Reported in abstract only (IJGC 2003; Vol. 13 Suppl 1:6)
  - No difference in 5-year survival or morbidity

Maneo A, et al. Cochrane Database of Systematic Reviews 2011

Avoid surgery

- Phase II studies
  - Operability achieved in 63-92% of cases with platinum-based regimens
  - Effective for both primary and nodes





Outcome

- 27-85% of patients died due to treatment-related causes or disease
- Toxicity substantial
  - Severe skin reactions
  - Avascular necrosis
- Different from cervical and anal cancers
  - Less responsive
  - Worse skin reaction c.f. anal Ca - vulva dystrophy?

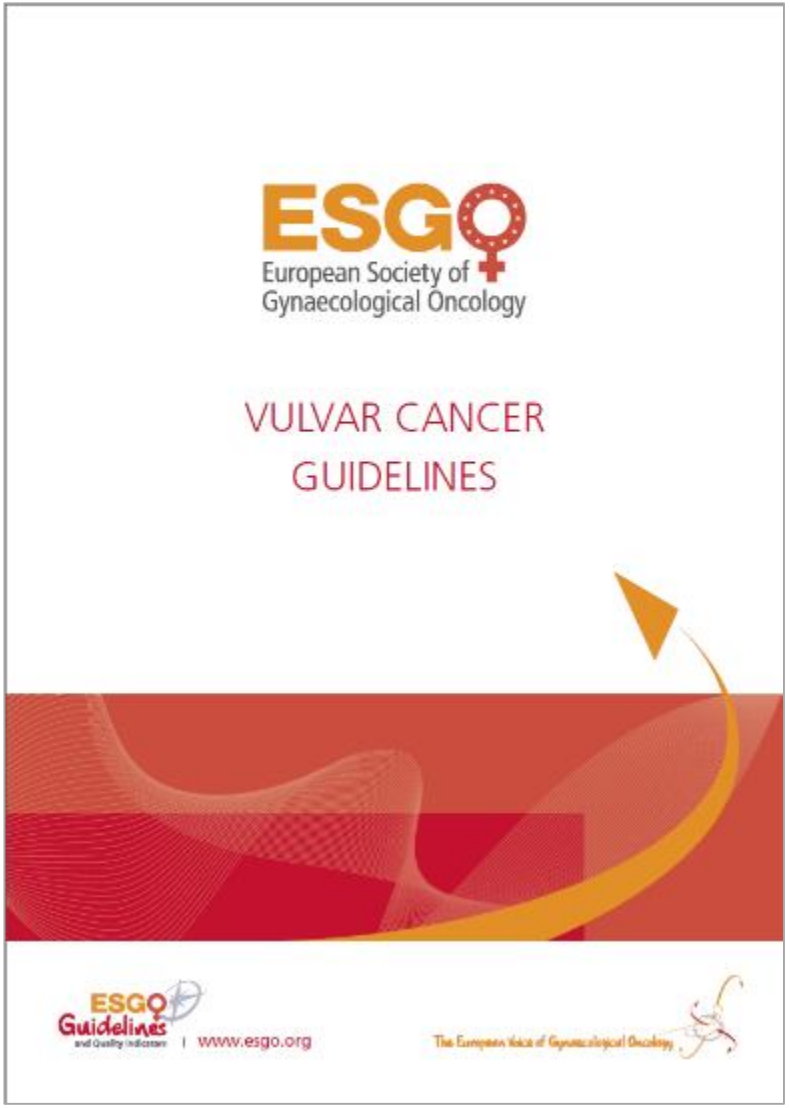
ESGO 2016

- Definitive chemoradiation (with radiation dose e[illegible]tion) is the treat[illegible]hoice in patient[illegible]ith unresectable disease.

Chemo?

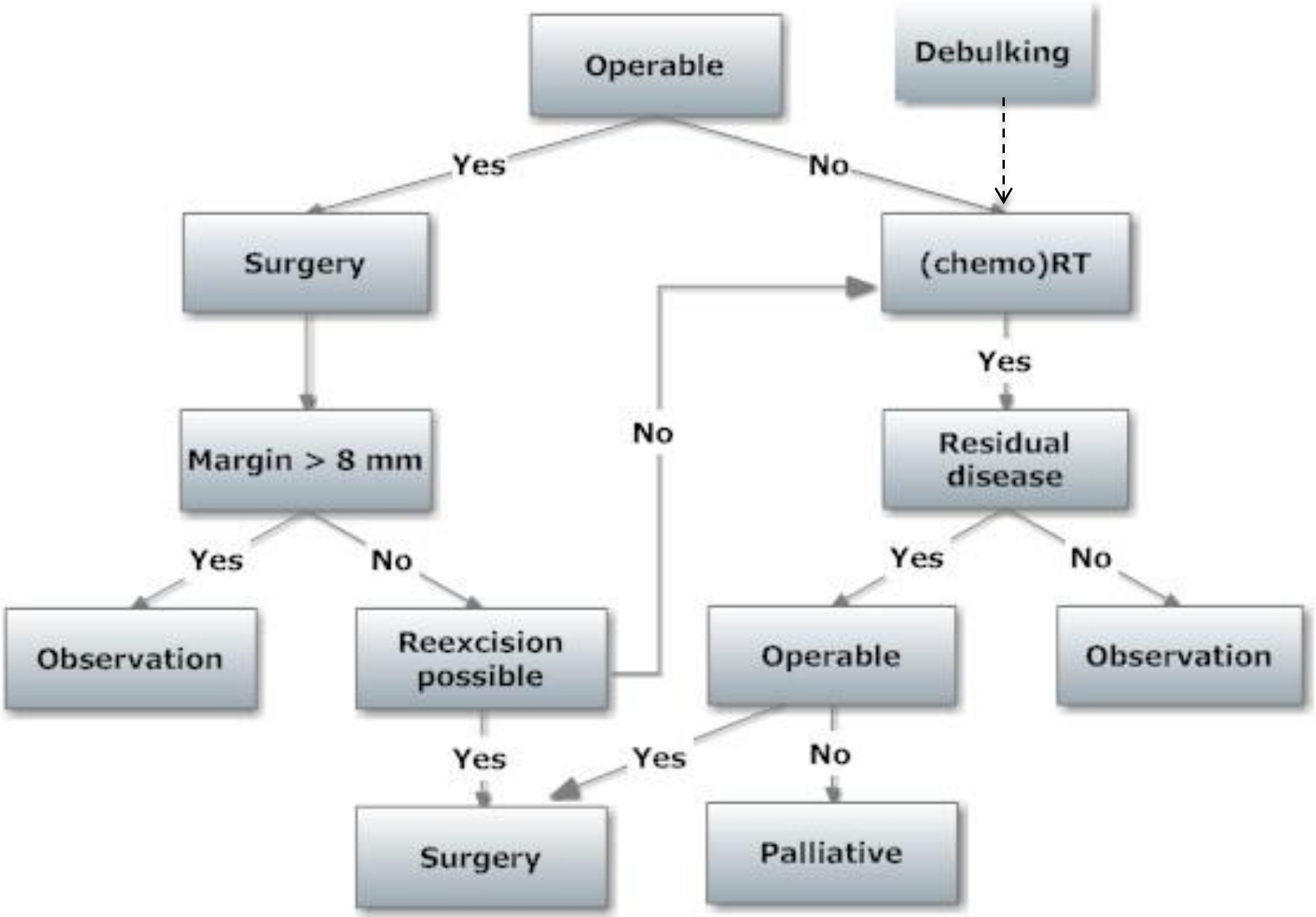
- In advanced [illegible] s[illegible] in order to [illegible]erative surgery.

Chemo?
Surgery with plastics + positive margins

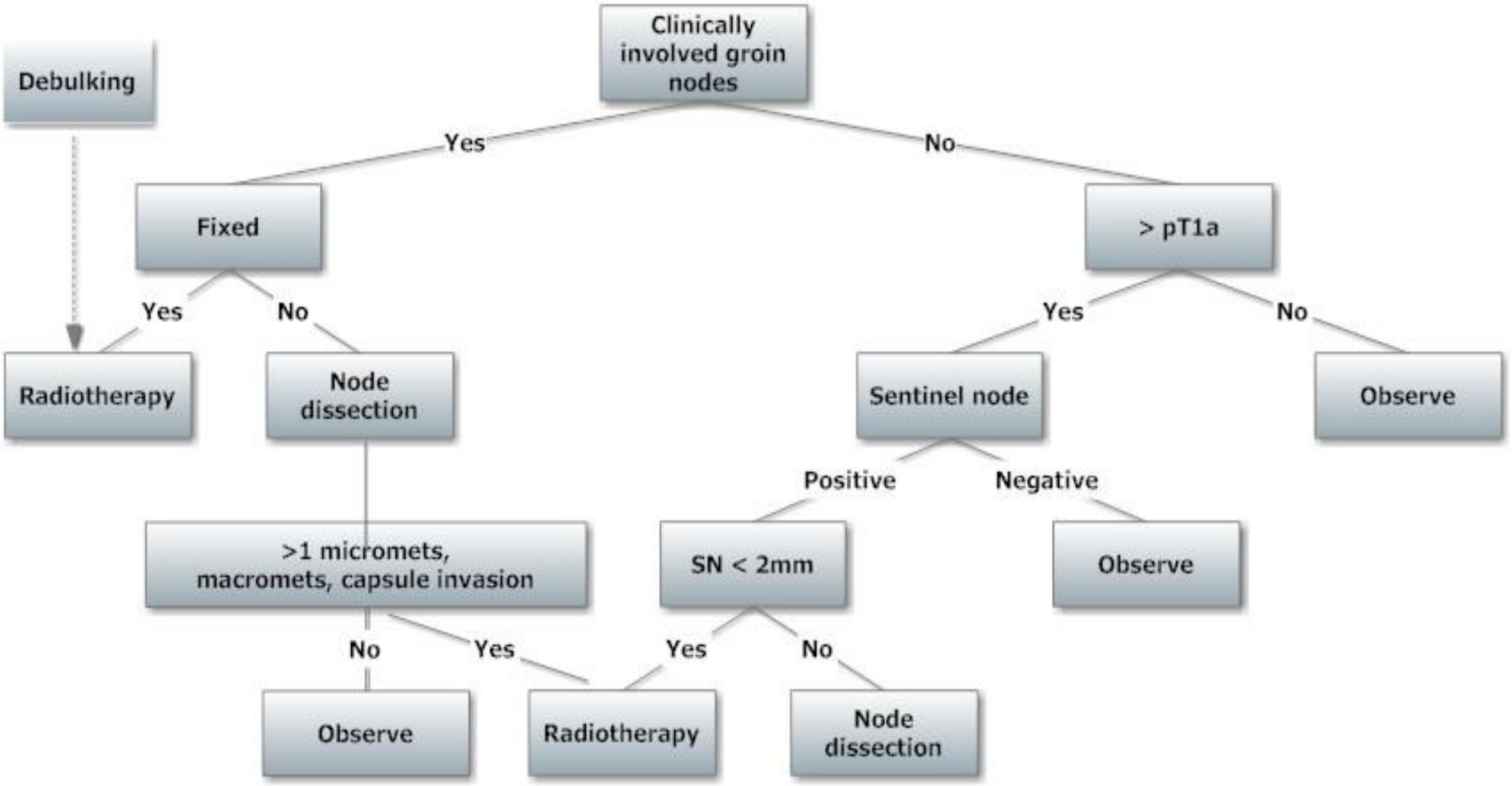


Grade C

Decision tree - vulva



Decision tree - groins



Outline

- Endometrial cancer
- Vulva cancer
- **Uterine sarcomas**

Epidemiology

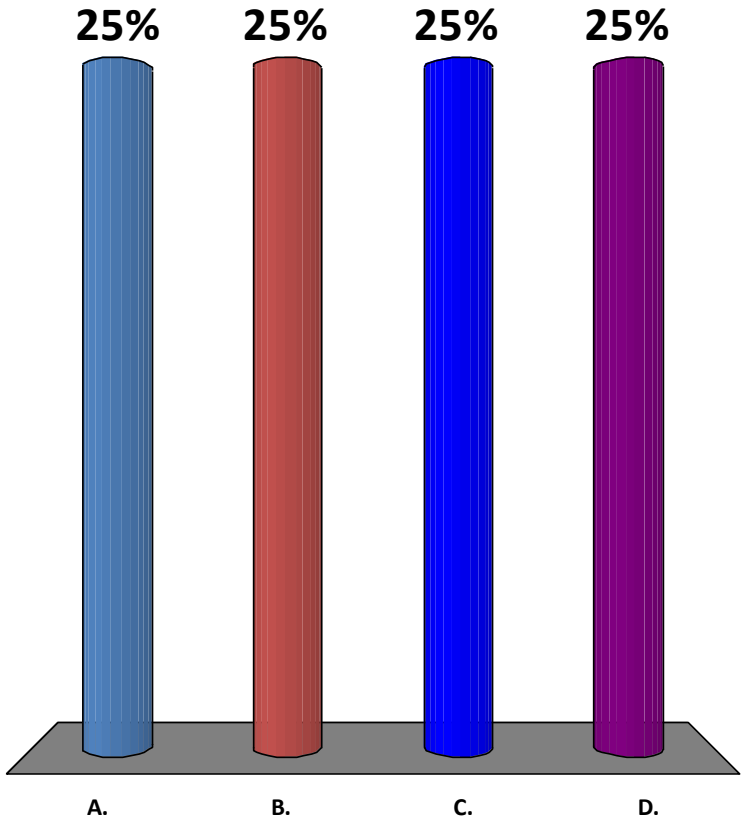
- Rare - ~4% of gynae cancers
- Histology
  - Stromal cell sarcoma
  - Leiomyosarcoma LG
  - Leiomyosarcoma HG
  - MMMT
- Low grade - local
- High grade - local and systemic problems

Adjuvant treatments

- Role of radiotherapy?
- Role of chemotherapy?

Do you offer adjuvant radiotherapy after surgery for patients with uterine sarcoma?

A. Yes - MMMT and LMS
B. Yes - MMMT only
C. Yes - LMS only
D. No



Role of RT - EORTC 55874

- 224 patients with HG uterine sarcoma
  - Stage I-II
  - Leiomyosarcoma 46%
  - MMMT 41%
  - Endometrial stromal sarcoma 13%
- Pelvic RT 50.4 Gy/28# vs. observation

Reed NS, et al. Eur J Cancer. 2008;44(6):808-18

EORTC 55874 - results

- Fewer local recurrences with RT - 3% vs. 18% (p = 0.0013)

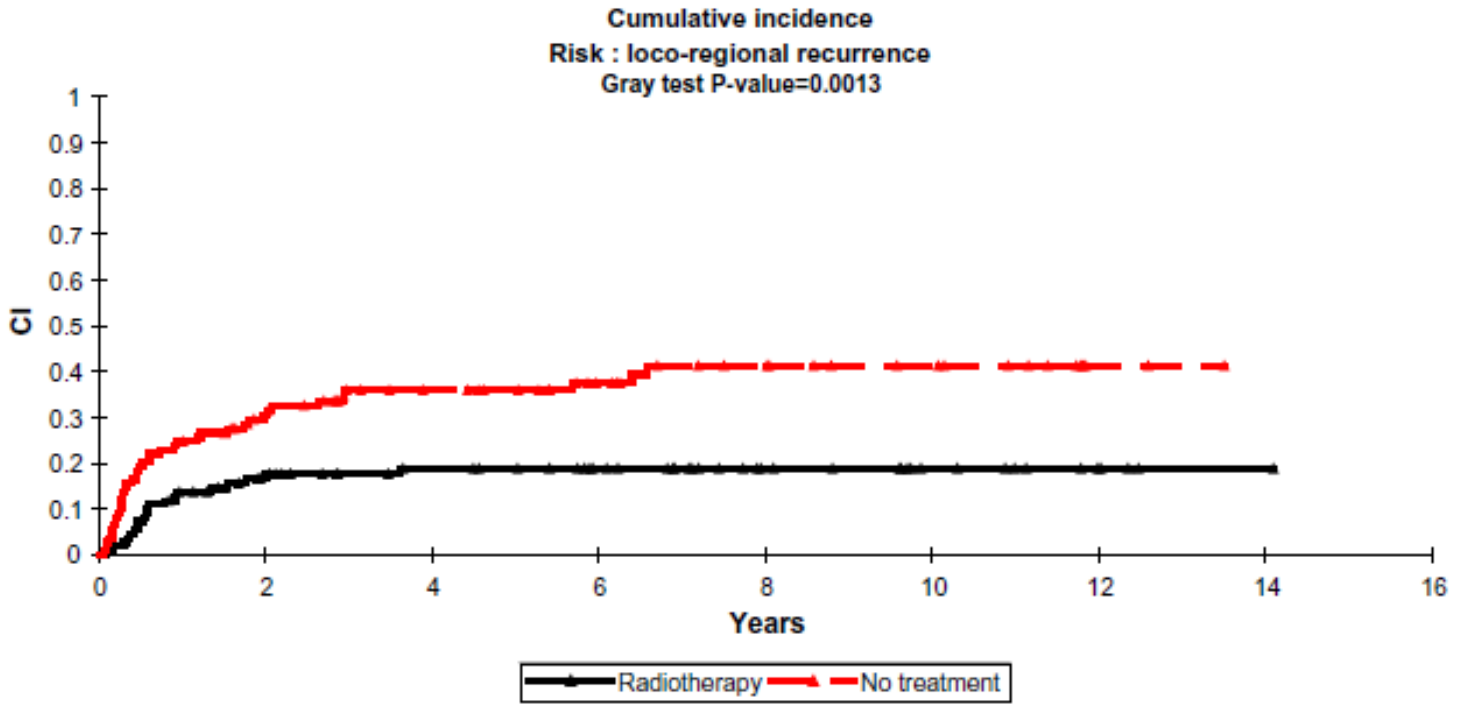
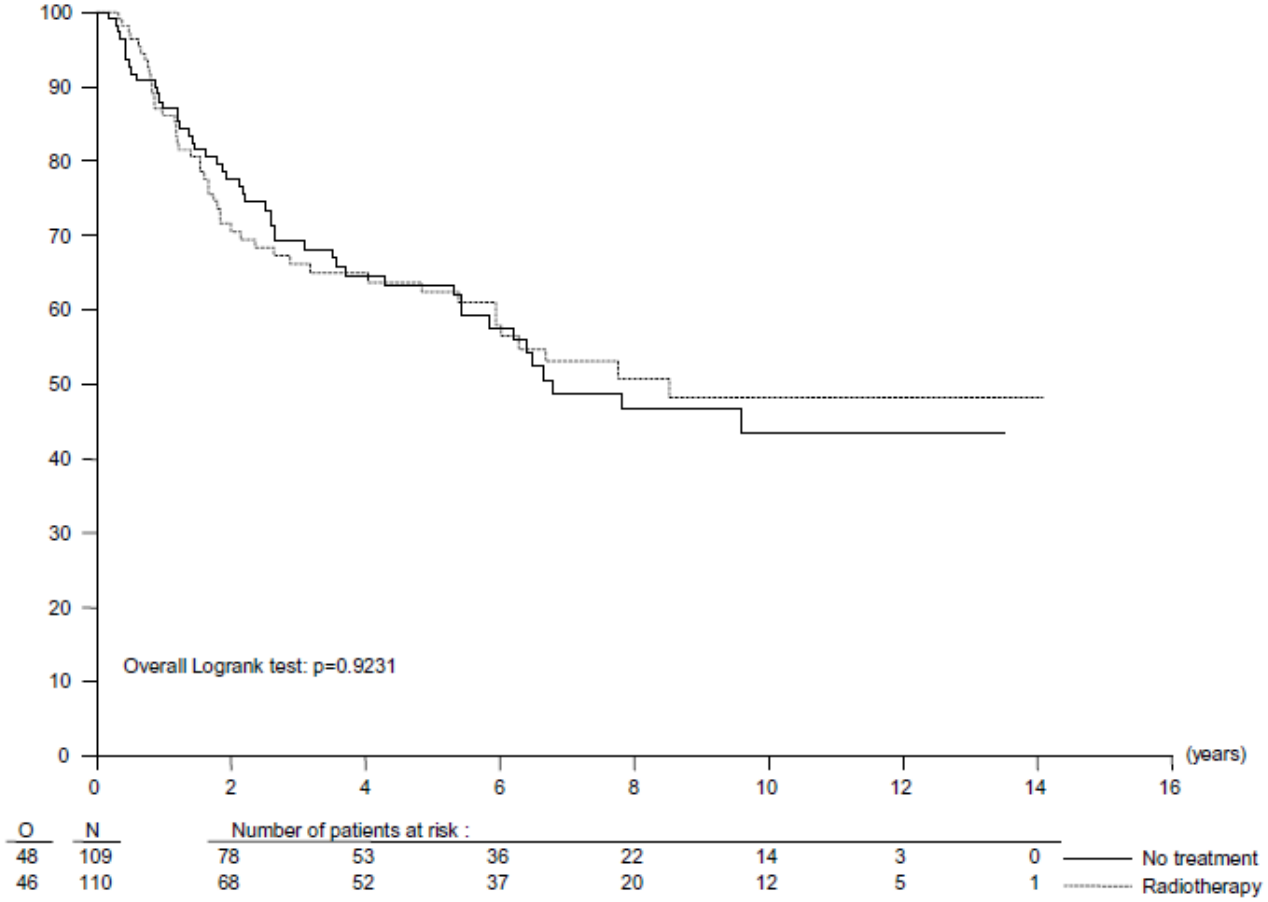


Fig. 3 – Cumulative incidence of local recurrence.

Reed NS, et al. Eur J Cancer. 2008;44(6):808-18

EORTC 55874 - results

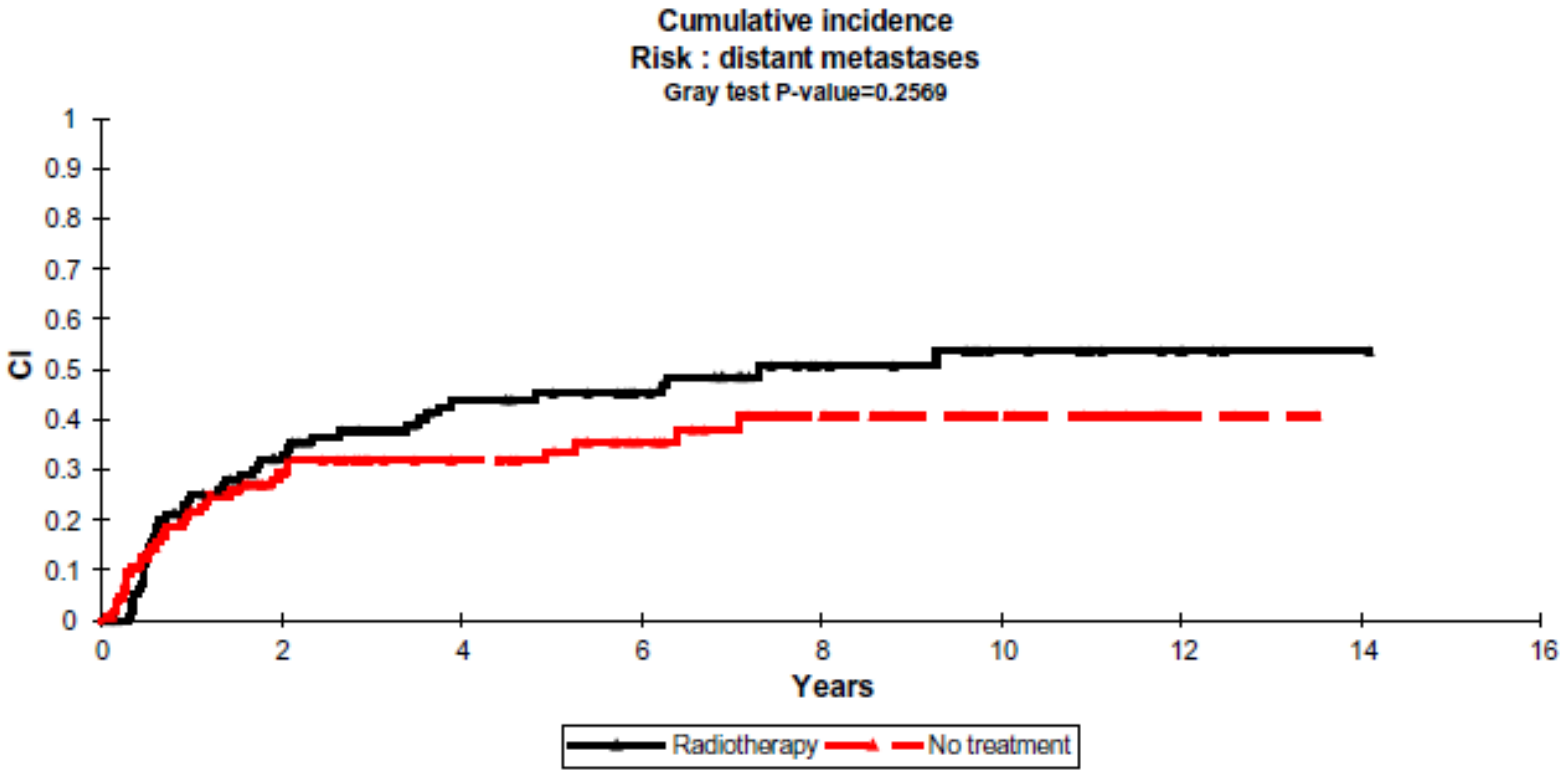
- No impact on PFS or OS



Reed NS, et al. Eur J Cancer. 2008;44(6):808-18

EORTC 55874 - results

- More metastases with RT - 25% vs. 10%



Reed NS, et al. Eur J Cancer. 2008;44(6):808-18

EORTC 55874

	MMMT n = 91		LMS n = 99	
	RT n = 46	Obs n = 45	RT n = 50	Obs n = 49
Local recurrence	24%	47%	20%	24%
Distant metastases	35%	29%	54%	33%

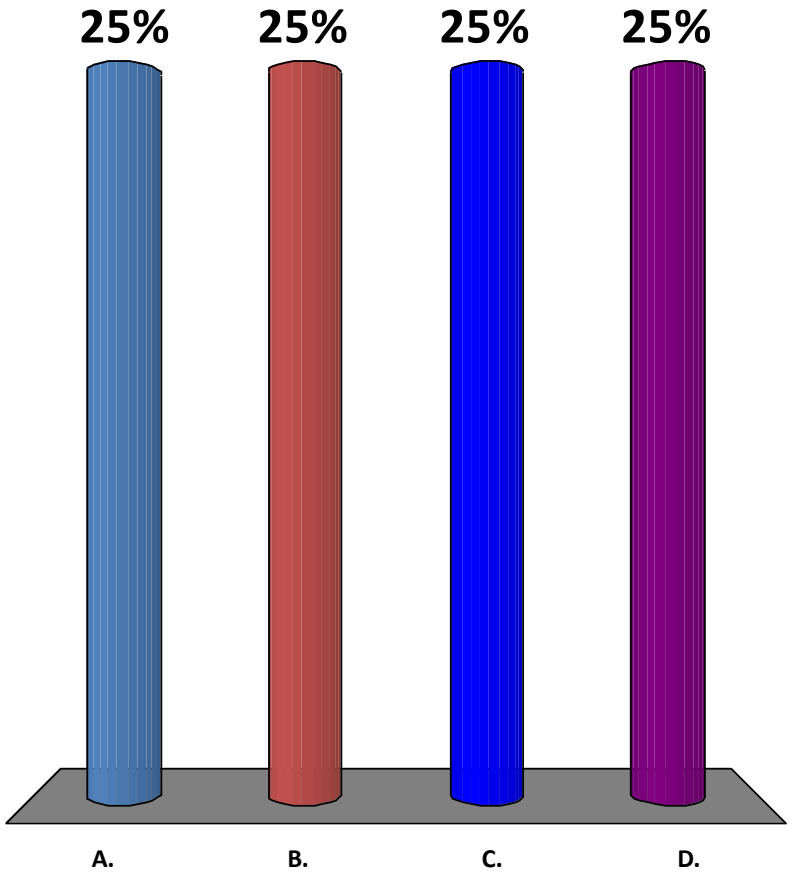
Reed NS, et al. Eur J Cancer. 2008;44(6):808-18

EORTC 55874 - conclusions

- No role for adjuvant RT in LMS
- ? Role in MMMT - reserve for salvage?

Do you offer adjuvant chemotherapy after surgery for patients with uterine sarcoma?

A. Yes - MMMT and LMS
B. Yes - MMMT only
C. Yes - LMS only
D. No



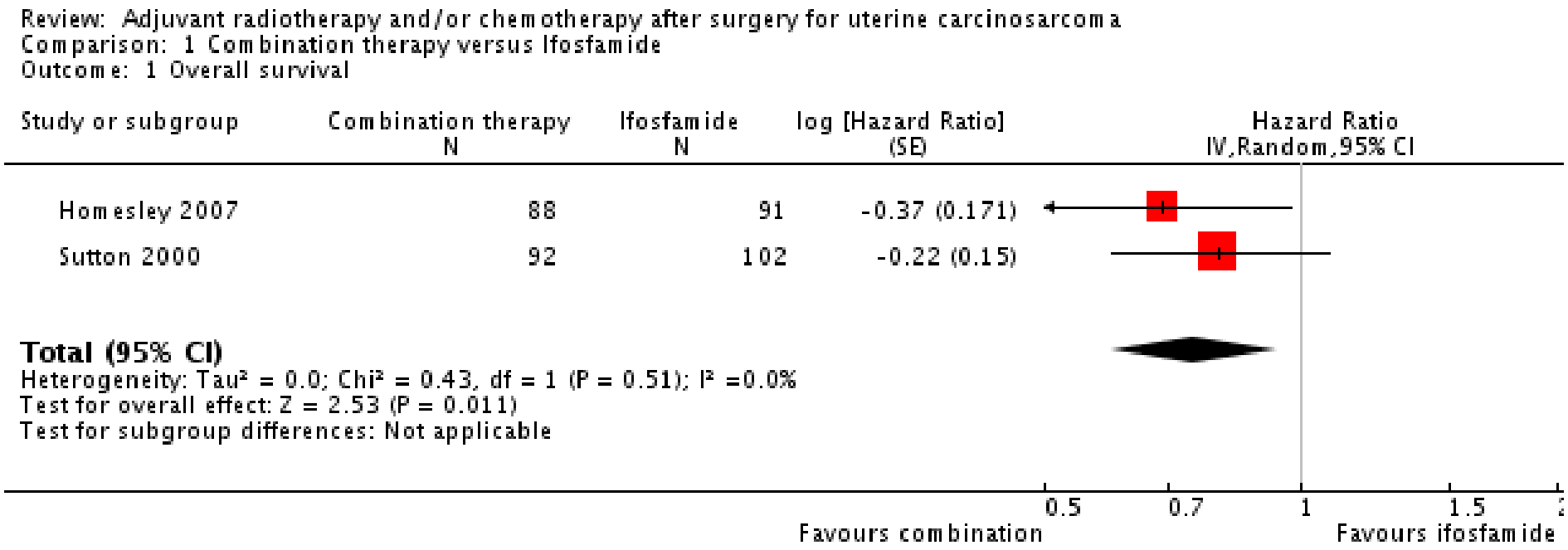
Chemo studies

3 randomised studies in MMMT

- 2 compared combination vs. single agent chemo
  - GOG 150 ifos + cisplatin vs. ifos
  - GOG 150 ifos + Taxol vs. ifos
- 1 compared chemo (ifos + cisplatin) vs. WART

Cochrane Database of Systematic Reviews 2013

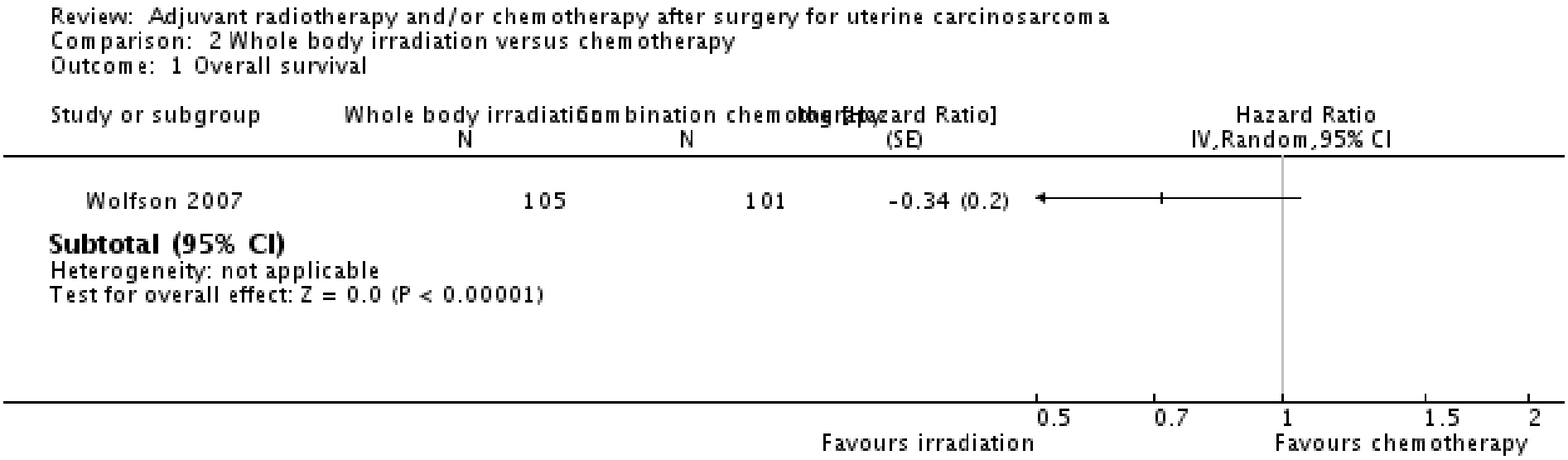
Combination vs. single agent



More toxicity with combination chemo

Cochrane Database of Systematic Reviews 2013

WART vs. chemo



More toxicity with combination chemo

Cochrane Database of Systematic Reviews 2013

Cochrane conclusions

- In advanced stage metastatic uterine carcinosarcoma as well as recurrent disease, adjuvant combination chemotherapy with ifosfamide should be considered.
- Combination chemotherapy with ifosfamide and paclitaxel is associated with lower risk of death compared with ifosfamide alone.
- In addition, radiotherapy to the abdomen is not associated with improved survival.

Cochrane Database of Systematic Reviews 2013

EORTC 62931

- 351 patients
- All macroscopically resected soft tissue sarcomas, including uterine
- Randomised to ifosfamide-doxorubicin vs. no chemo
- 73% received radiotherapy (equal in both arms)

Woll PJ, et al. Lancet Oncol. 2012;13(10):1045-54

EORTC 62931

- Results
  - No difference in 5-year OS (chemo 66·5%, control 67·8%)

- Conclusions

  "Future studies should focus on patients with larger, grade III, and extremity sarcomas"

Woll PJ, et al. Lancet Oncol. 2012;13(10):1045-54

Summary

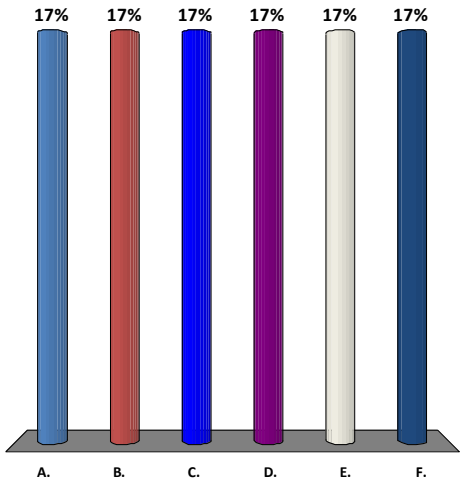
What if there is no evidence?

Patient

- Age 74
- 2 cm lump on vulva
- WLE
  - Mammary-type ductal carcinoma in situ with invasive component, strongly ER positive, margins >10mm
- Sentinel node biopsy
  - 3 nodes +ve on right, LVSI present

How would you manage this patient?

A. Bilat groin node dissection, no RT
B. Rt groin node dissection, no RT
C. Bilat groin node dissection + RT
D. Rt groin node dissection + RT
E. RT alone to bilat groins
F. RT alone to rt groin

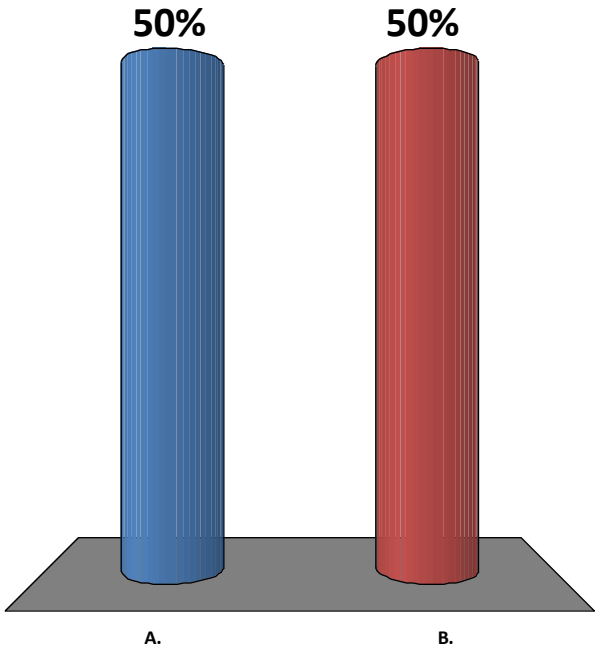


- Age 74
- 2 cm extra-mammary adenoCa
- ER +ve
- 3 right SN, LVSI +ve

Would you offer adjuvant tamoxifen?

A. No

B. Yes

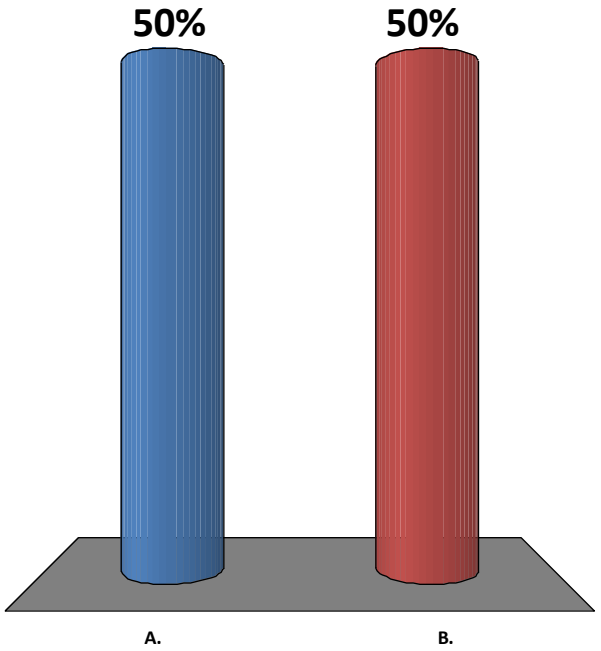


- Age 74
- 2 cm extra-mammary adenoCa
- ER +ve
- 3 right SN, LVSI +ve

If tumour was Her-2 +ve, would you offer Herceptin?

A. No

B. Yes



- Age 74
- 2 cm extra-mammary adenoCa
- ER +ve
- 3 right SN, LVSI +ve

Decision-making process

- Which site to extrapolate from?
- Breast or vulva or both?

Radiotherapy

- Indication – extrapolate from histology
  - Adjuvant RT given for adenoCa
- RT technique - extrapolate from location of tumour
  - Vulva
    - RT for close margins
    - SNB N+ - RT to both groins (even after LND)
  - Breast
    - RT regardless of margin
    - SNB N+ - RT to unilateral axilla (but not after LND)

Lymph node management

A. Bilateral groin node dissection, no RT
B. Right groin node dissection, no RT
C. Bilateral groin node dissection + RT
D. Right groin node dissection + RT
E. RT alone to both groins
F. RT alone to right groin

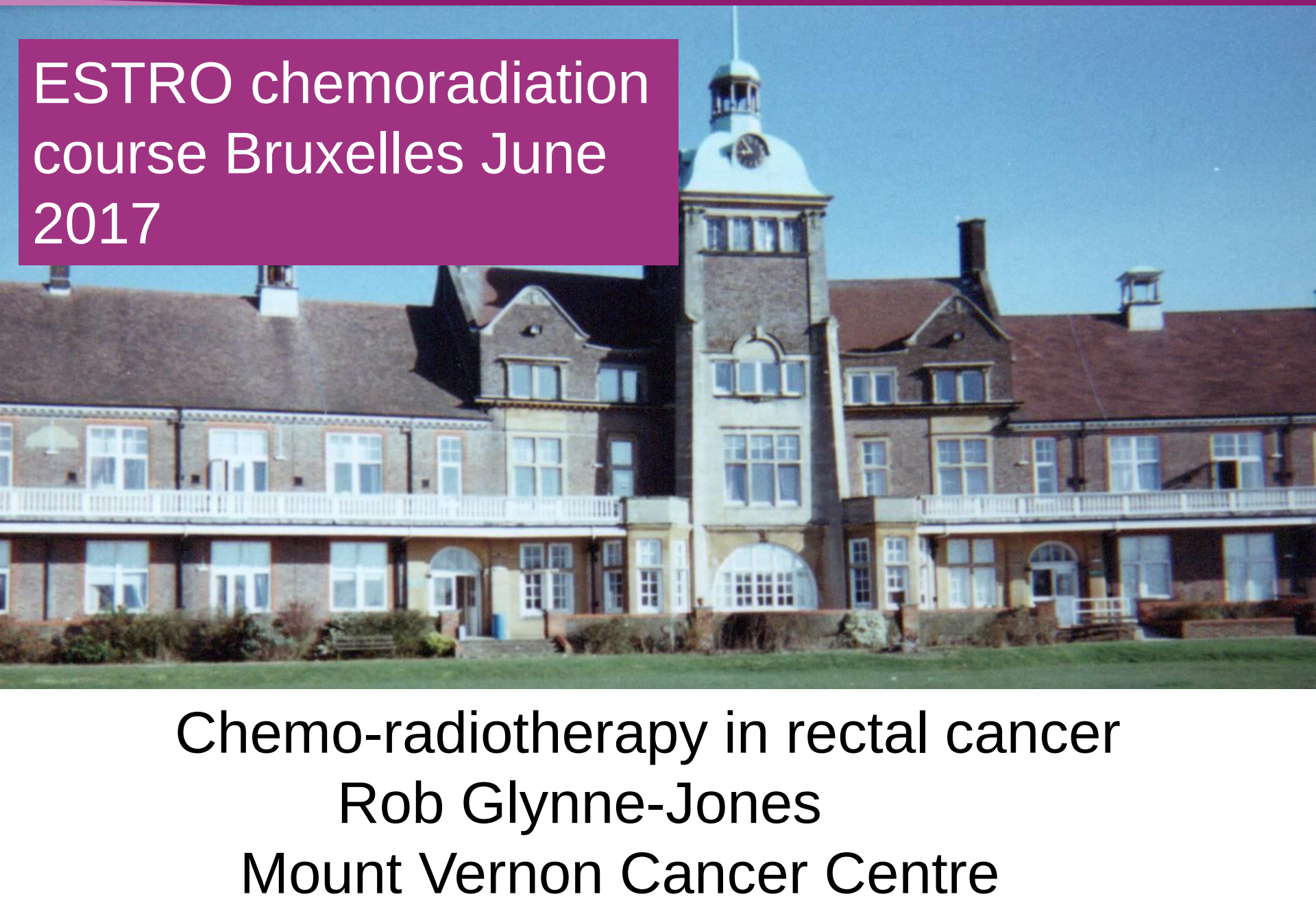
Systemic treatment

- Indication – extrapolate from histology (breast adenoCa)
  - N+, LVSI+ - in breast Ca, would offer systemic treatment
- What systemic treatment?
  - Consider therapeutic indices AND economic cost
  - ER positive - give tamoxifen (benefit U/K, toxicity low, cost low)
  - HER-2 positive – do not give Herceptin (benefit U/K, toxicity high, cost very high)
  - Chemo - ??? (benefit U/K, toxicity high, cost high)

Summary

- Indications for treatment – extrapolate from histology
- RT technique – extrapolate from location (lymphatic spread)
- For both, consider therapeutic index
  - Benefit unknown
  - Toxicity known
  - Cost known

Evidence-based medicine



ESTRO chemoradiation course Bruxelles June 2017

Chemo-radiotherapy in rectal cancer

Rob Glynne-Jones
Mount Vernon Cancer Centre

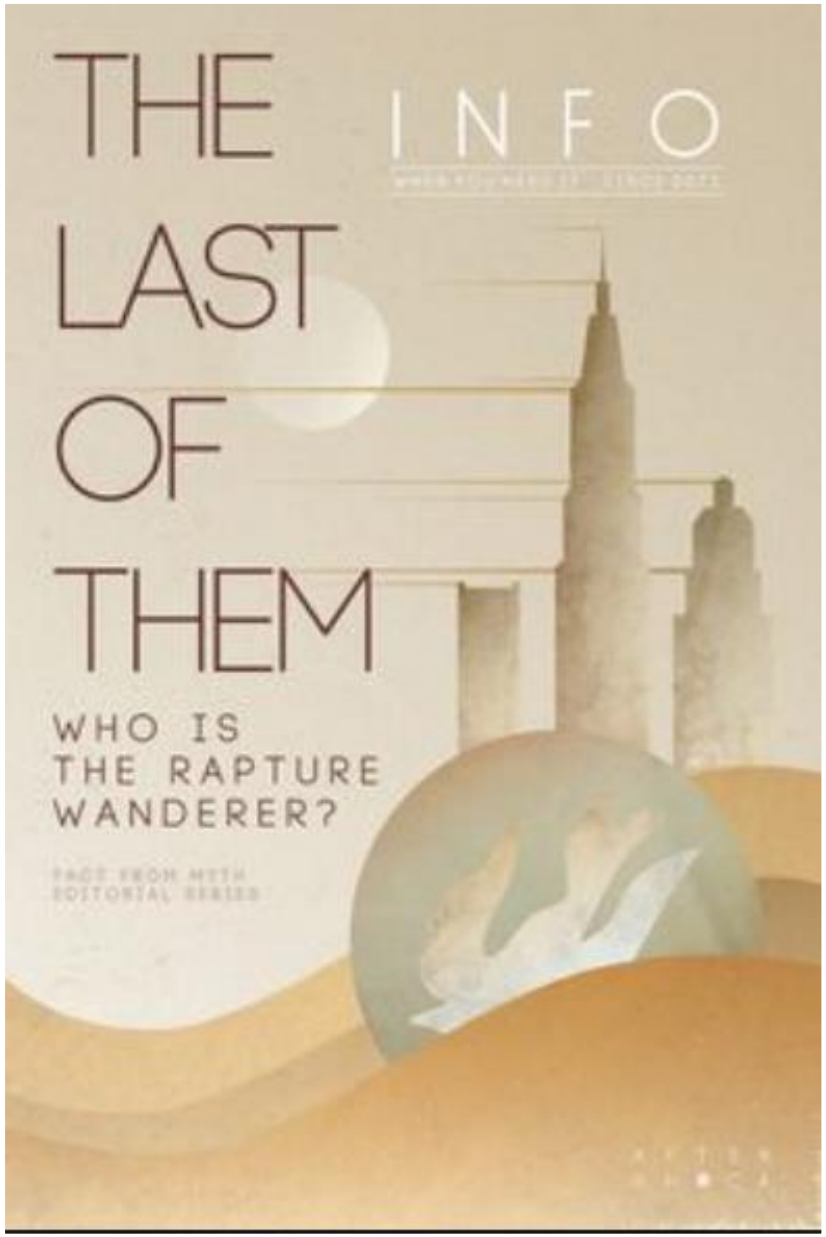
My Disclosures: last 5 years

Speaker: Roche, Merck Serono, Sanofi Aventis, Pfizer, AIS

Advisory Boards: Roche, Merck Serono, Sanofi Aventis, Astra Zeneca, Servier, BMS

Funding to attend meetings: Roche, Merck Serono, Sanofi Aventis,

Research funding: Roche, Merck Serono, Sanofi Aventis



ESTRO School

Do you treat?

Low risk Dukes B colon cancer patients with adjuvant chemo?

High Risk Dukes C colon cancer with adjuvant chemo?

FOLFOX or XELOX?

When do you want to start?

The European Society for Medical Oncology rectal cancer guidelines 2013 state

"Standard preoperative chemoradiotherapy means a dose of 45-50.4 Gy, 1.8 Gy/fraction, or alternatively 50 Gy, 2 Gy/fraction together with a fluoropyrimidine"

ESMO Guidelines

"An important aim is to treat so that the risk of residual disease in the pelvis, frequently causing a disabling local recurrence, is very low. This risk should preferably be less than about 5% in the population in whom curative treatment is intended"

Bengt Glimelius

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2017
Rectal Cancer

NCCN Guidelines Index
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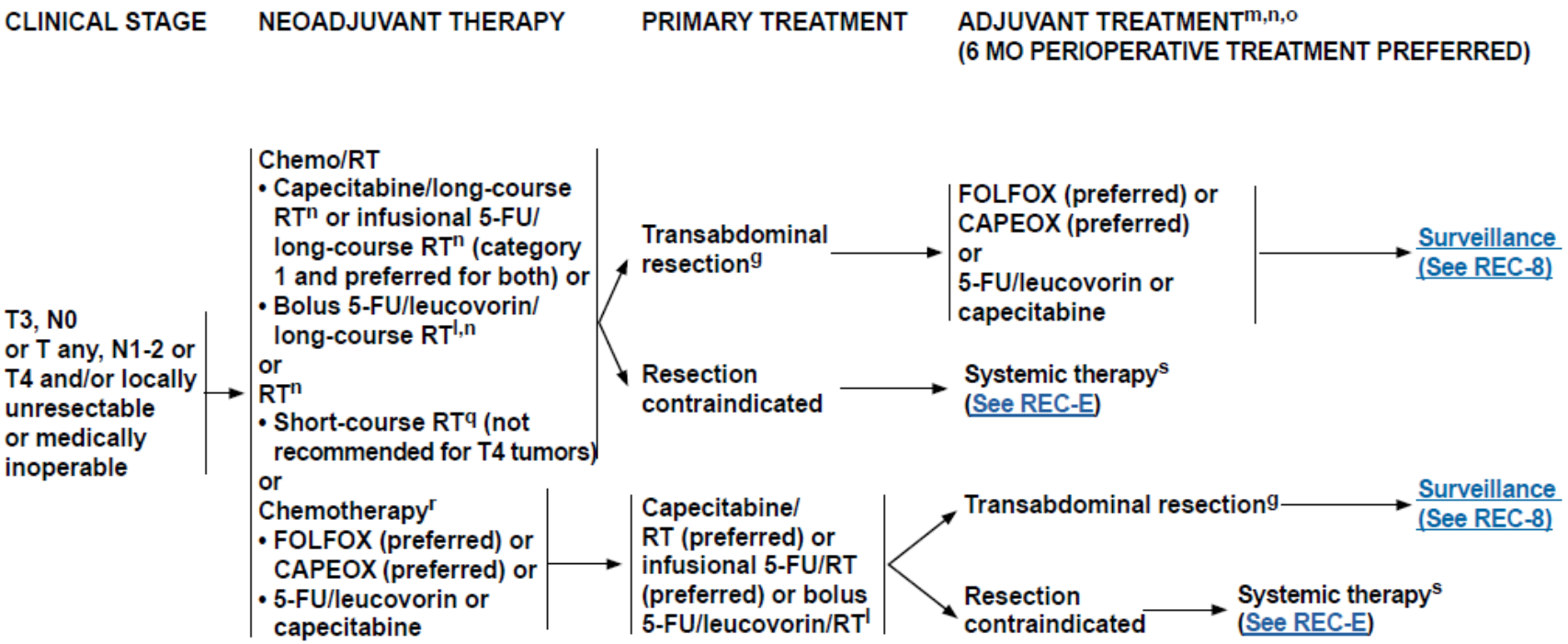
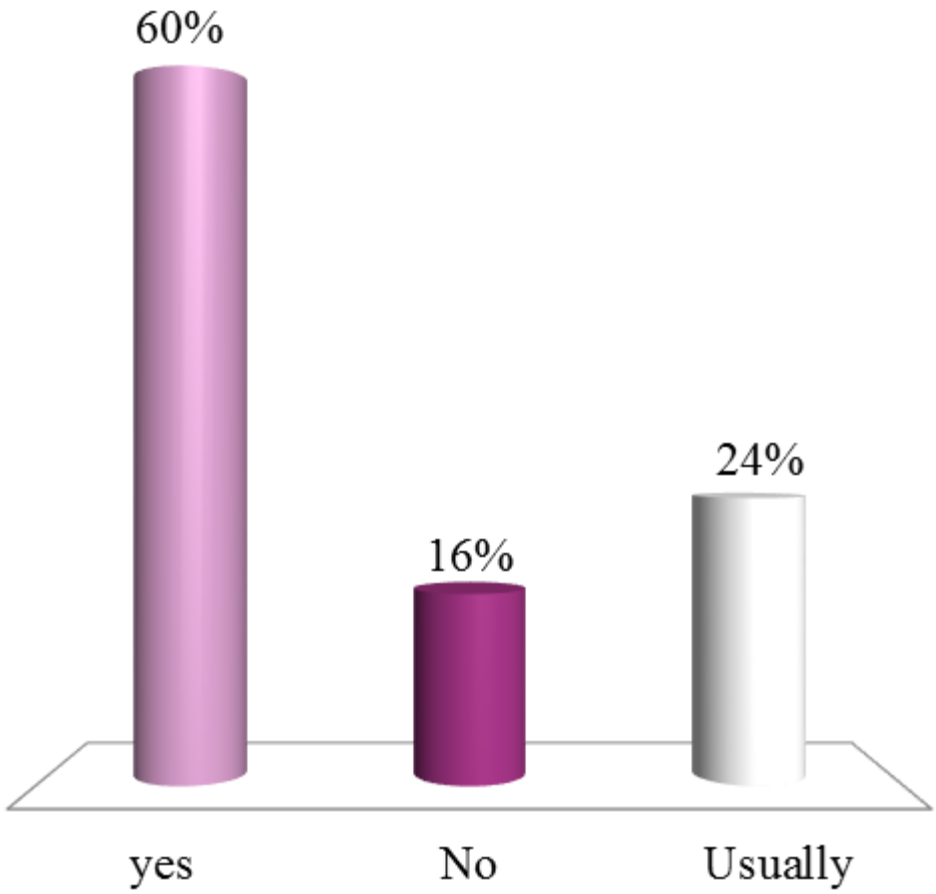
Discussion



[g] See Principles of Surgery (REC-B).
[l] Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.
[m] See Principles of Adjuvant Therapy (REC-C).
[n] See Principles of Radiation Therapy (REC-D).
[o] Imaging (Chest/Abdomen/Pelvic CT with contrast) to be performed prior to adjuvant treatment to assess response to primary therapy or resection.
[q] Evaluation for short-course RT should be in a multidisciplinary setting, with a discussion of the need for down-staging and the possibility of long-term toxicity.
[r] Fernandez-Martos C, Pericay C, Aparicio J, et al: Phase II, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging-defined, locally advanced rectal cancer: Grupo cancer de recto 3 study. J Clin Oncol 2010;28:859-865.
Cercek A, Goodman KA, Hajj C, et al. Neoadjuvant chemotherapy first, followed by chemoradiation and then surgery, in the management of locally advanced rectal cancer. J Natl Compr Canc Netw 2014;12:513-519.
[s] FOLFOXIRI is not recommended in this setting.

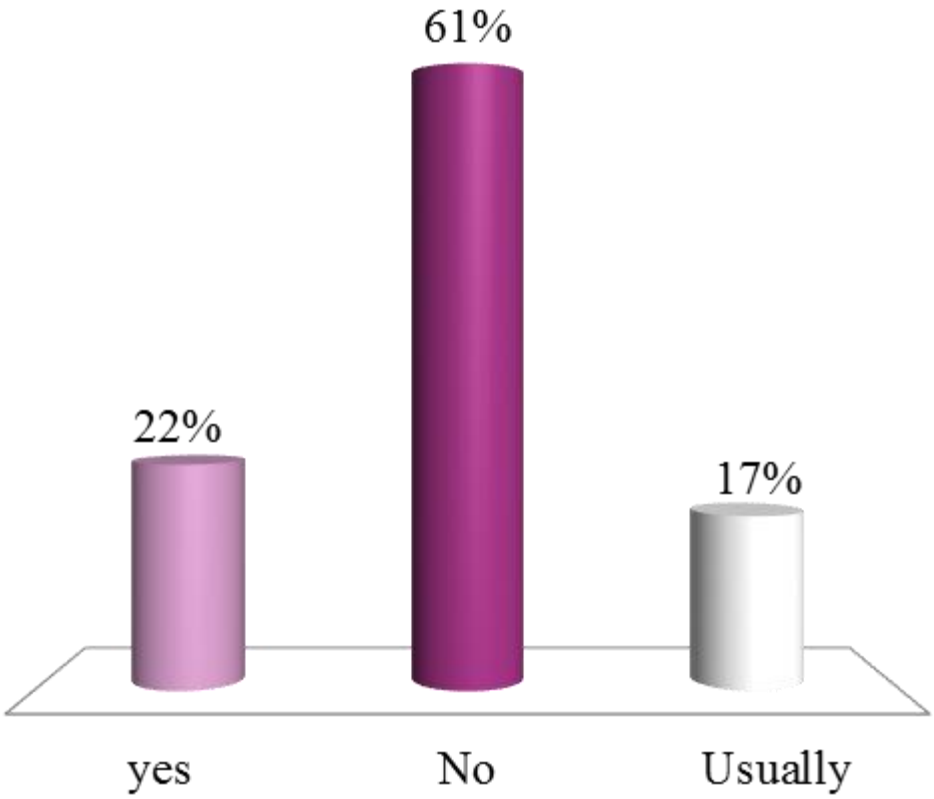
So do you treat all cT3cN1 with 5FU-based CRT?

A. yes
B. No
C. Usually



So do you treat all cT3cN1 with FOLFOX?

A. yes
B. No
C. Usually



I thought we had signed up to individualisation of treatment?

“Consistency is the last refuge of the unimaginative”

Oscar Wilde (1854-1900)

Preoperative Options to influence outcomes in rectal cancer

Chemoradiation (with fluoropyrimidine)

Radiotherapy (5 x 5Gy)

Neoadjuvant chemotherapy +/- Biologicals (Immunotherapy)

Different combinations and sequences of the above (4 x 3 x 2 x 1= 24)

Transcriptomic classification of four consensus molecular subtypes (CMS)

CMS1, called MSI-like, contains most microsatellite instable (MSI) tumors and enriched for tumors with a CpG-island methylator phenotype (CIMP) and mutations in the BRAF oncogene **(14%).**

CMS2, called canonical, with high chromosomal instability (CIN) and activation of the Wnt and MYC pathways **(37%).**

CMS3, called metabolic - enriched in *KRAS* mutations and shows a disruption of metabolic pathways **(13%).**

CMS4, called mesenchymal/stemlike, has a mesenchymal phenotype and frequent CIMP phenotype **(23%)**

stratifies CRC into intrinsic subtypes with different prognosis

Guinney J et al. The consensus molecular subtypes of colorectal cancer. Nat Med 2015;21:1350–1356.

CMS4 stemlike

Del Rio M, et al. Molecular subtypes of metastatic colorectal cancer are associated with patient response to irinotecan-based therapies. Eur J Cancer. 2017 May;76:68-75

87% response to FOLFIRI in CMS4

Song N, et al. Clinical Outcome From Oxaliplatin Treatment in Stage II/III Colon Cancer According to Intrinsic Subtypes: Secondary Analysis of NSABP C-07/NRG Oncology Randomized Clinical Trial. JAMA Oncol. 2016 Sep 1;2(9):1162-9

Lack of benefit from Oxaliplatin/poor prognosis in CMS4

Clinical Cancer Research

Prognostic and Predictive Values of the Immunoscore in Patients with Rectal Cancer

Maria-Gabriela Anitei[1,3], Guy Zeitoun[5], Bernhard Mlecnik[8], Florence Marliot[7,8,9], Nacilla Haicheur[7], Ana-Maria Todosi[1], Amos Kirilovsky[8], Christine Lagorce[11], Gabriela Bindea[8], Dan Ferariu[2], Mihai Danciu[1,4], Patrick Bruneval[6,9], Viorel Scripcariu[1,3], Jean-Marc Chevallier[5,9], Franck Zinzindohoué[5,9], Anne Berger[5,9], Jérôme Galon[8,10], and Franck Pagès[7,8,9]

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M.-G. Anitei, G. Zeitoun, and B. Mlecnik contributed equally to this work.

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Clin Cancer Res April 1, 2014 *20*; 1891

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  - Similar articles in this journal
  - Similar articles in PubMed

CD3 infiltration - immunoscore

The ypTNM downstaging and TRG were used as endpoints to evaluate response to pCRT

72% of the biopsies with high infiltration of $CD3^+$ cells responders to CRT (complete or partial response)

63% of the biopsies with a low infiltration of $CD3^+$ cells were non-responders to CRT

($P = 0.015$).

Anitei M-G Clin Cancer Res 2014;20:1891

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Glimelius
Radiother
Oncol 2017

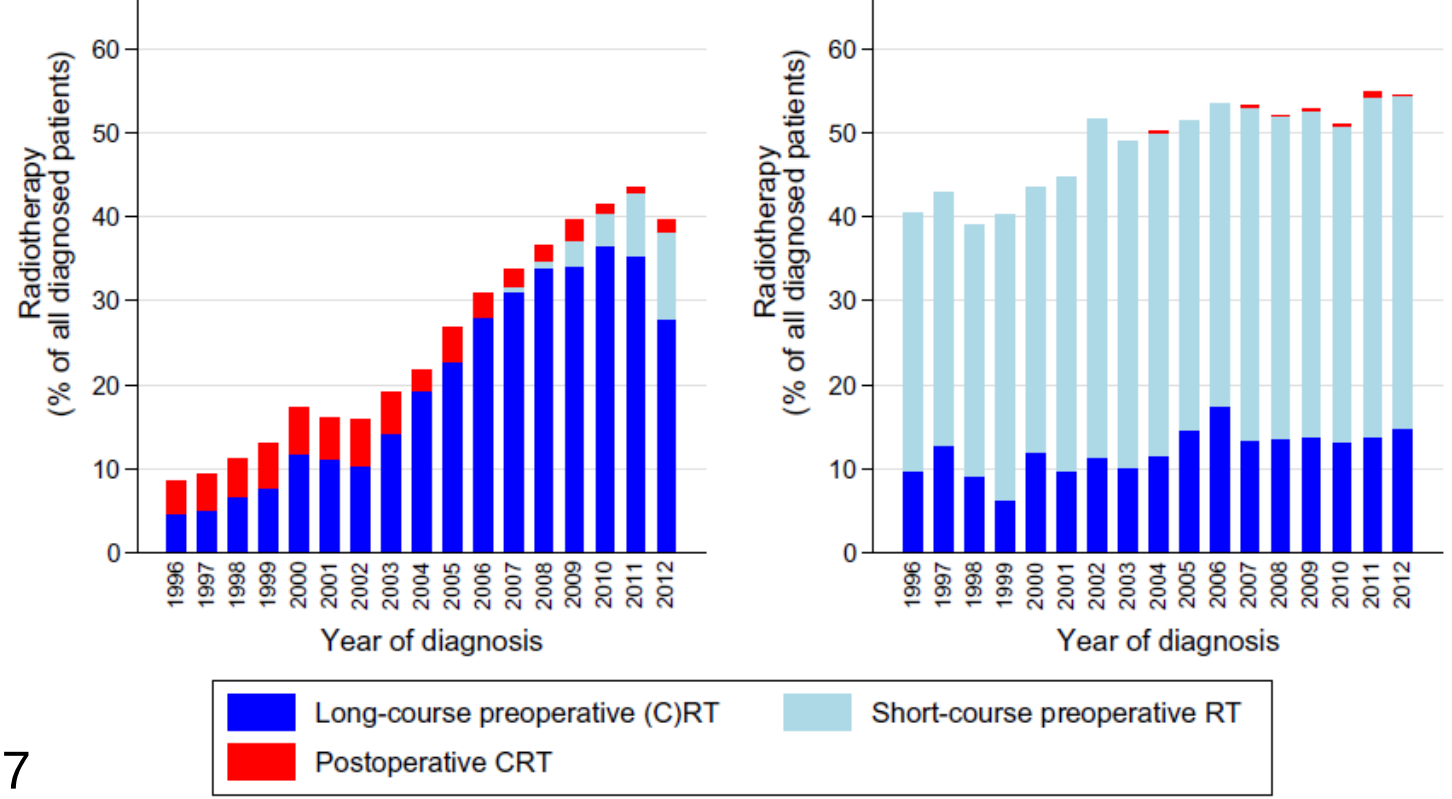
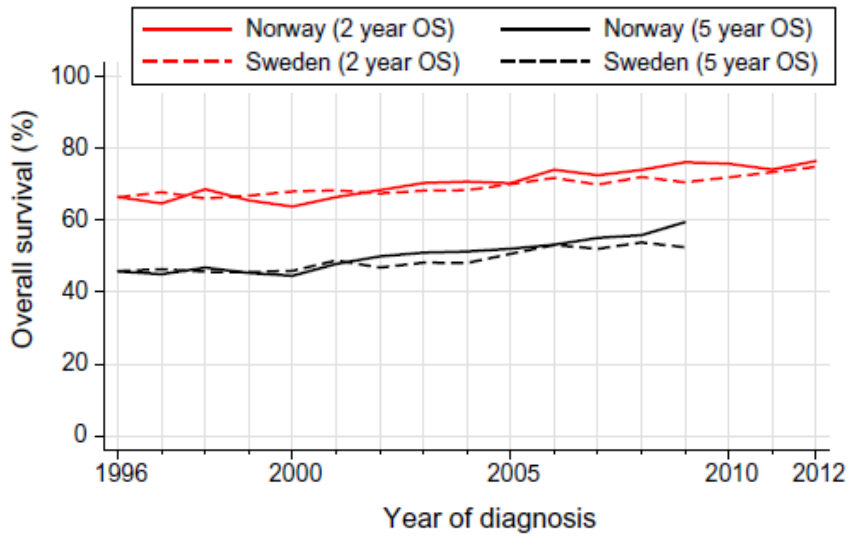


Fig. 2. Radiotherapy (RT) for all patients diagnosed with rectal cancer in Sweden and Norway from 1996 to 2012.



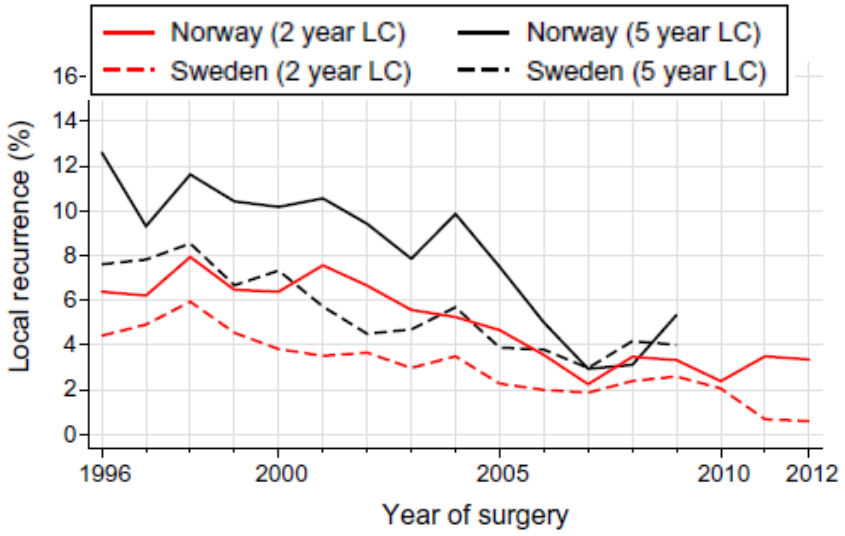
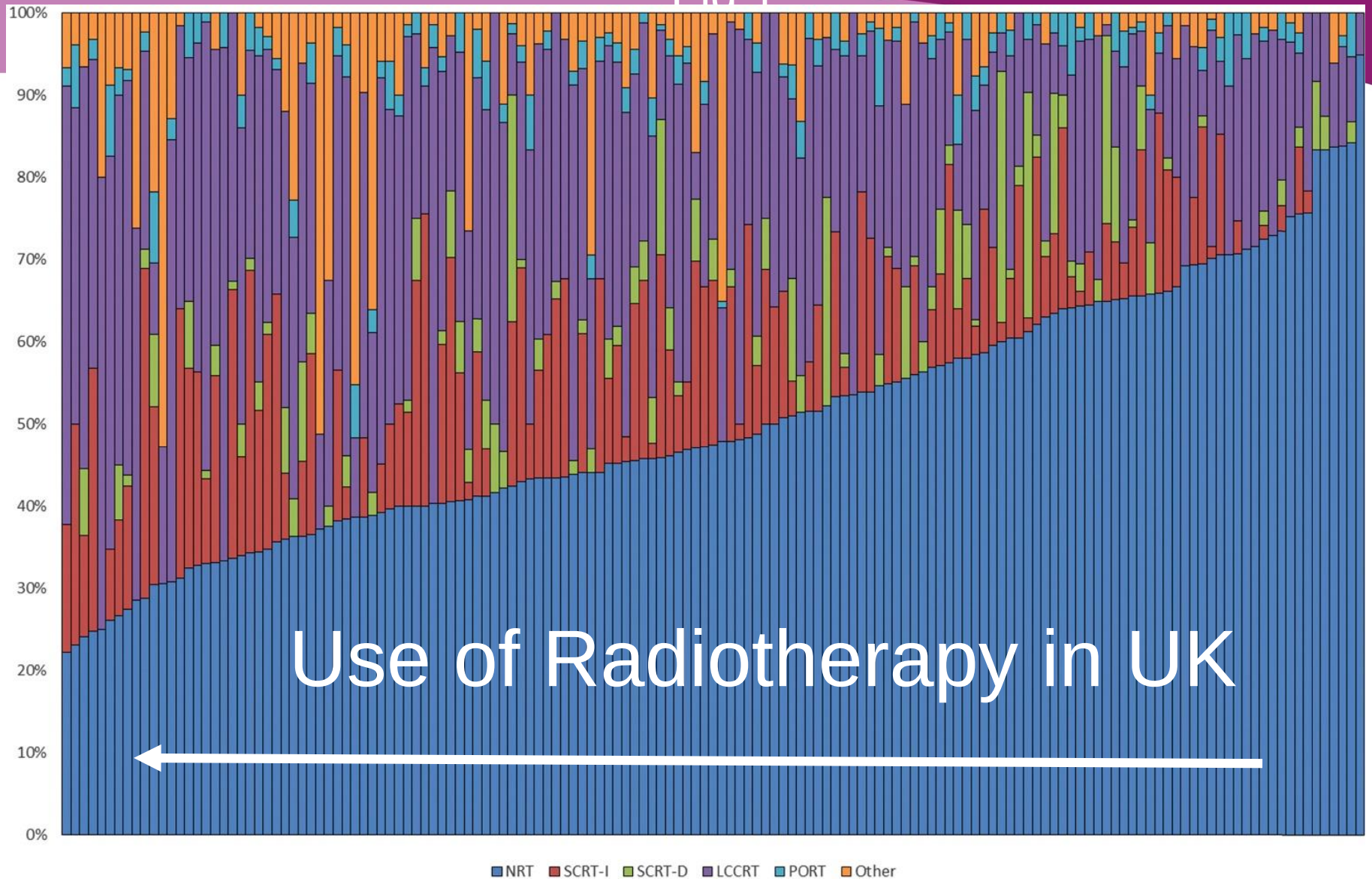


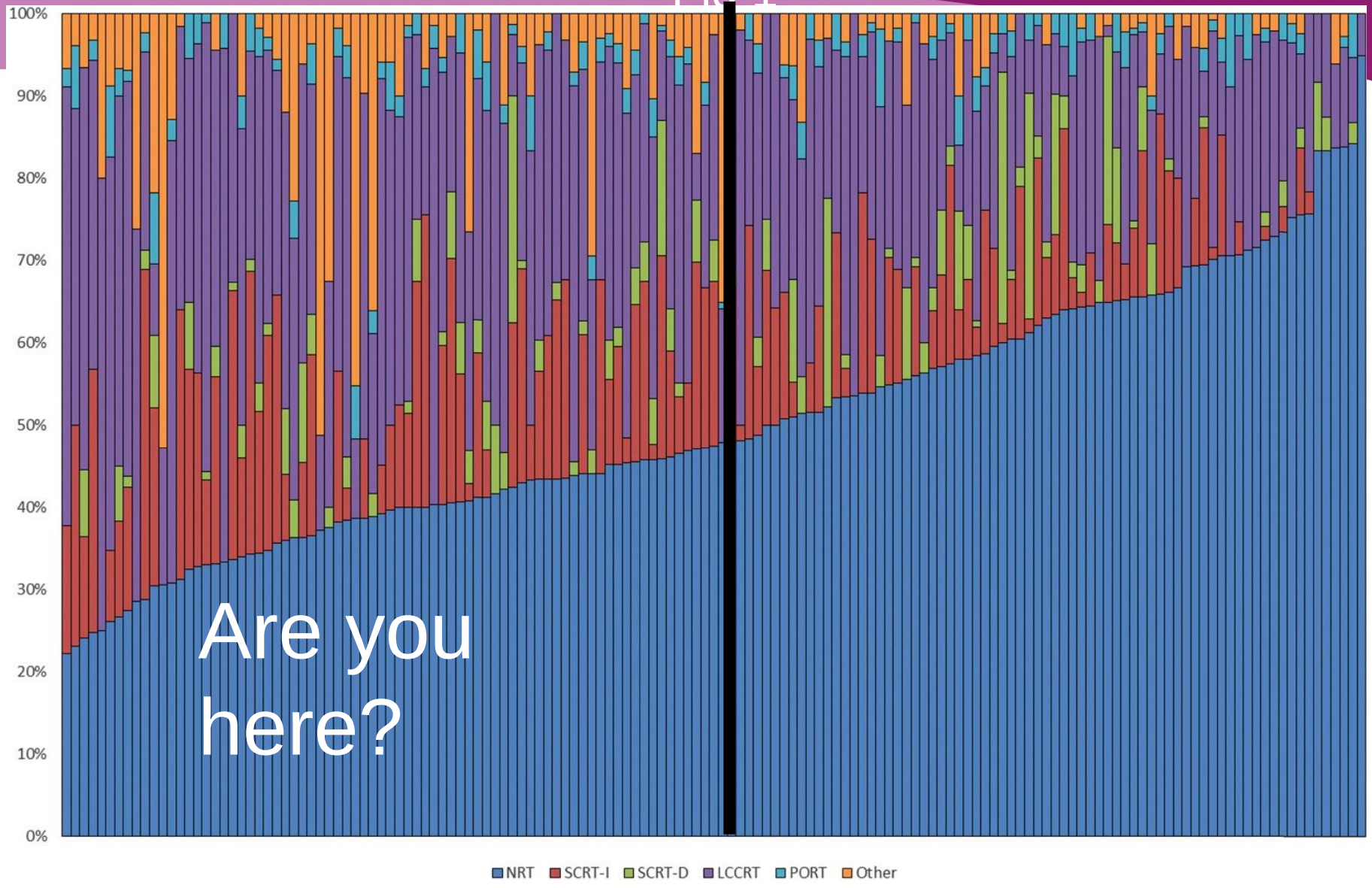
Fig 1



Use of Radiotherapy in UK

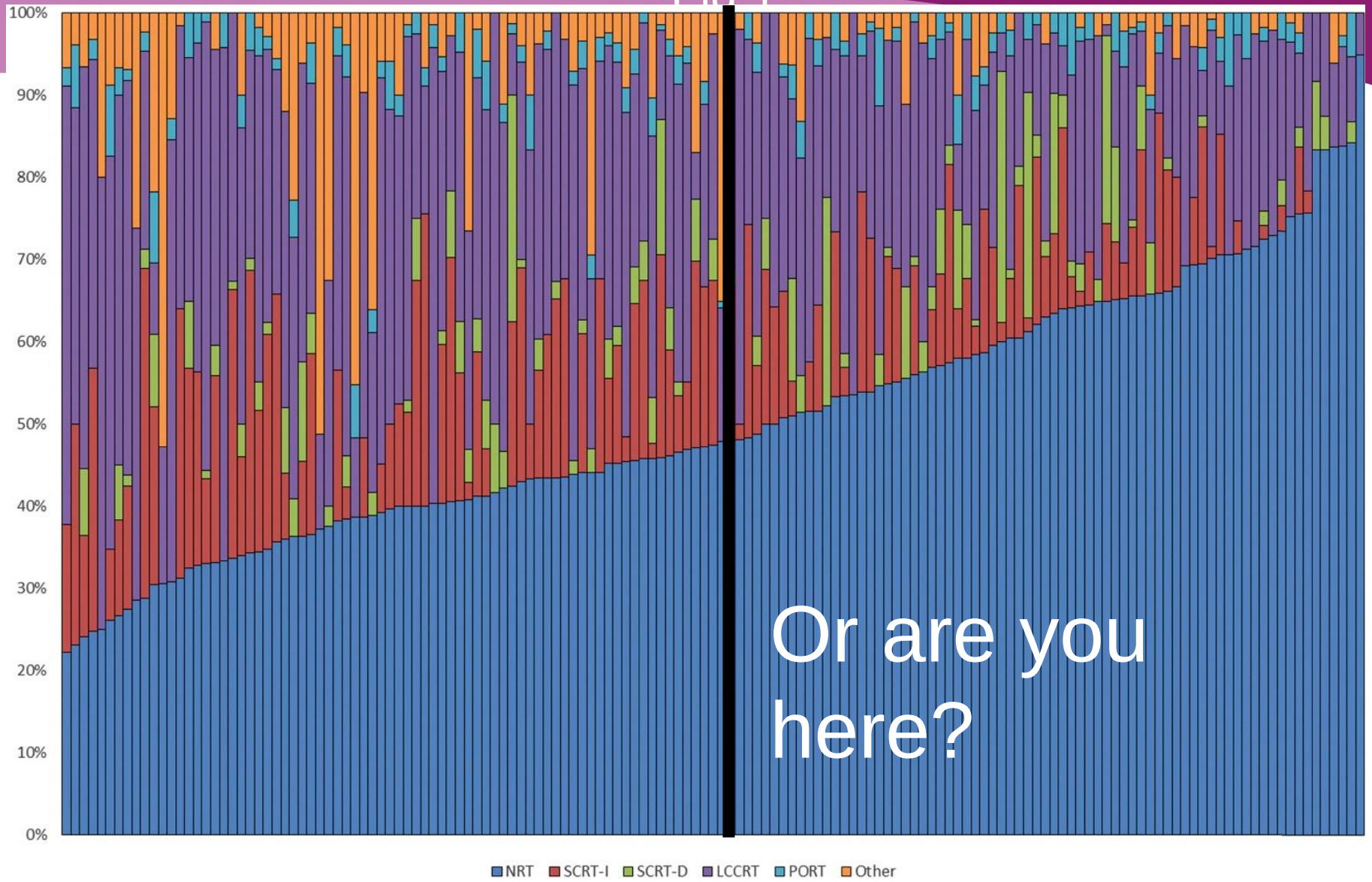
Morris EJ et al. 2016 _Clin Oncol (R Coll Radiol). 2016 Aug;28(8):522-31

Fig 1



Morris EJ et al. 2016 _Clin Oncol (R Coll Radiol). 2016 Aug;28(8):522-31

Fig 1



Morris EJ et al. 2016 _Clin Oncol (R Coll Radiol). 2016 Aug;28(8):522-31

Male Maintenance manager for Network Rail

40 years old - recently married for second time

Fit/No co-morbidity

Rectal bleeding

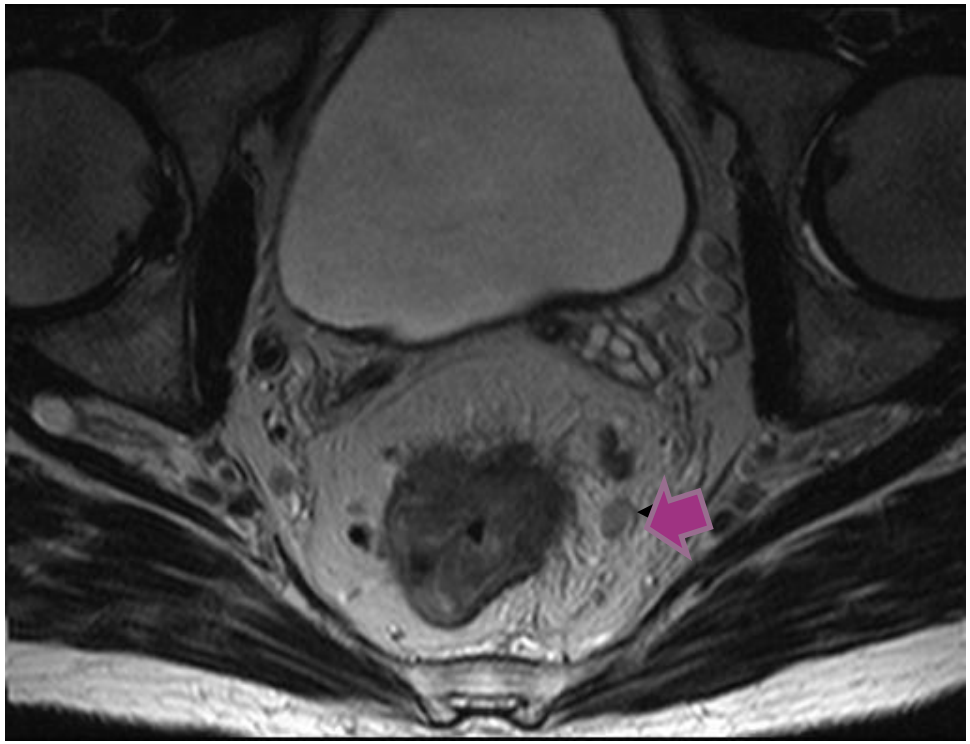
CT no metastases

CEA 8

MRI cT3 N1b EMVI+

Nodal Assessment: TNM

- **Nodal staging based on number of involved nodes**
  - N0: No nodes
  - N1: 1-3 regional nodes
    - N1a 1 node
    - N1b 2-3 nodes
    - N1c tumour deposit
  - N2: 4 or more nodes
    - N2a 4-6 nodes
    - N2b ≥7 nodes



Mesorectal node

MRI and CT

cT3b (3mm extent) mid/upper rectum

N1B (2 nodes)

No threat to CRM (at least 6mm)

EMVI +

M0

Any other investigations?

MRI and CT

cT3b mid/upper rectum

N1B (2 nodes)

No threat to CRM (at least 6mm)

EMVI +

M0

What are the features important for decision making?

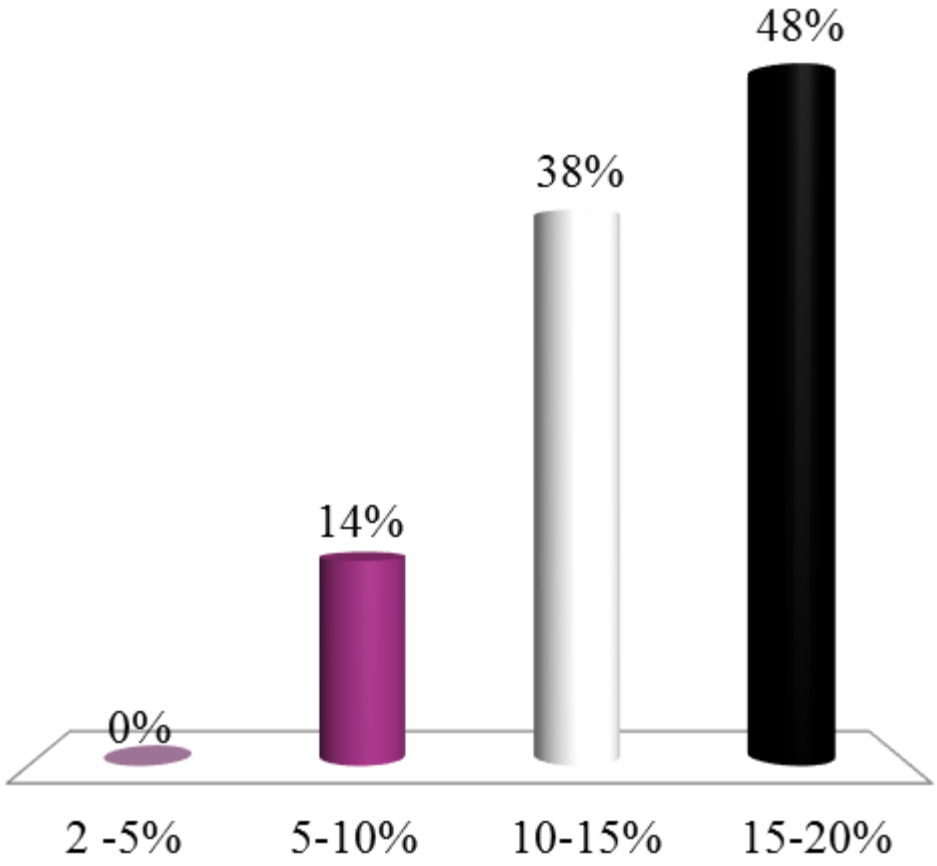
What is his risk of

Local recurrence?

Distant disease?

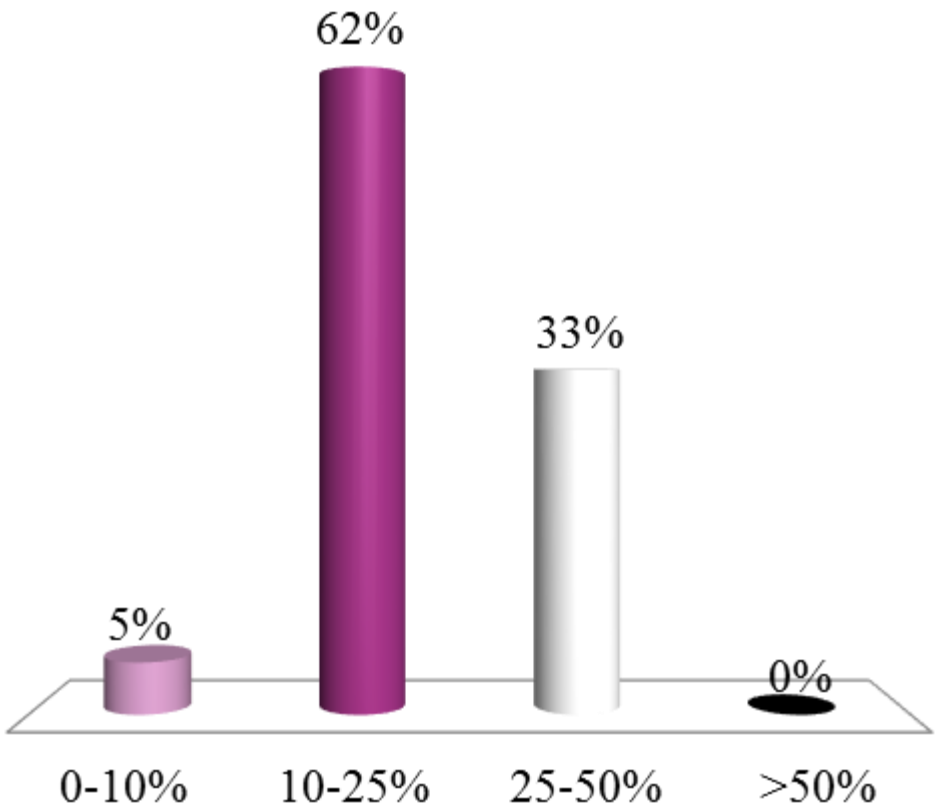
Risk of Local recurrence

A. 2 -5%
B. 5-10%
C. 10-15%
D. 15-20%



Risk of distant recurrence

A. 0-10%
B. 10-25%
C. 25-50%
D. >50%



Conventional high risk features for local recurrence

Rectal tumour extends within 1mm or beyond mesorectal fascia (CRM)

cT3 tumours at level of levators / involving levators especially anterior tumours

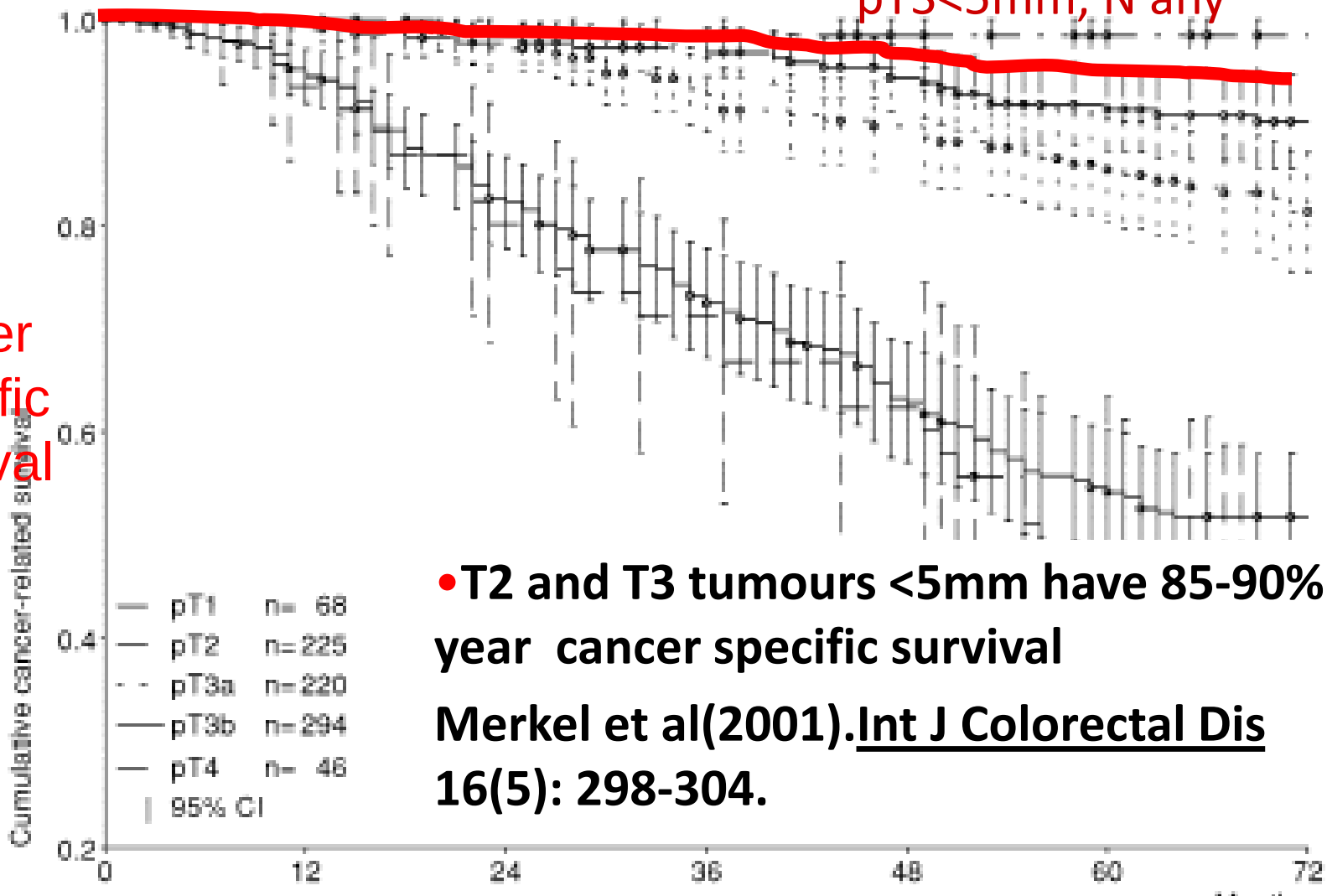
Tumour >5mm beyond muscul propria (T3c)

T4b tumours

Extramural vascular invasion (EMVI)

cN2 cancers ?? Unless extracapsular

Erlangen Data



- **T2 and T3 tumours <5mm have 85-90% 5 year cancer specific survival**

Merkel et al(2001).Int J Colorectal Dis 16(5): 298-304.

if cT3 >5mm have 54% 5 year cancer specific survival

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Fokas 2014 Updated Results of the CAO/ARO/AIO-94 Trial for CRT

Preop N category	No at risk	10-Year Cumulative Incidence of Local Recurrence (%)	No at risk	10-Year Cumulative Incidence of Distant Mets (%)	No at risk	10-Year DFS (%)
Overall	391	6.9	406	30.2	361	73
cN0	161	**7.7**	169	**31.2**	152	**71.6**
cN+	213	**6.9**	220	**28.9**	193	**74.7**

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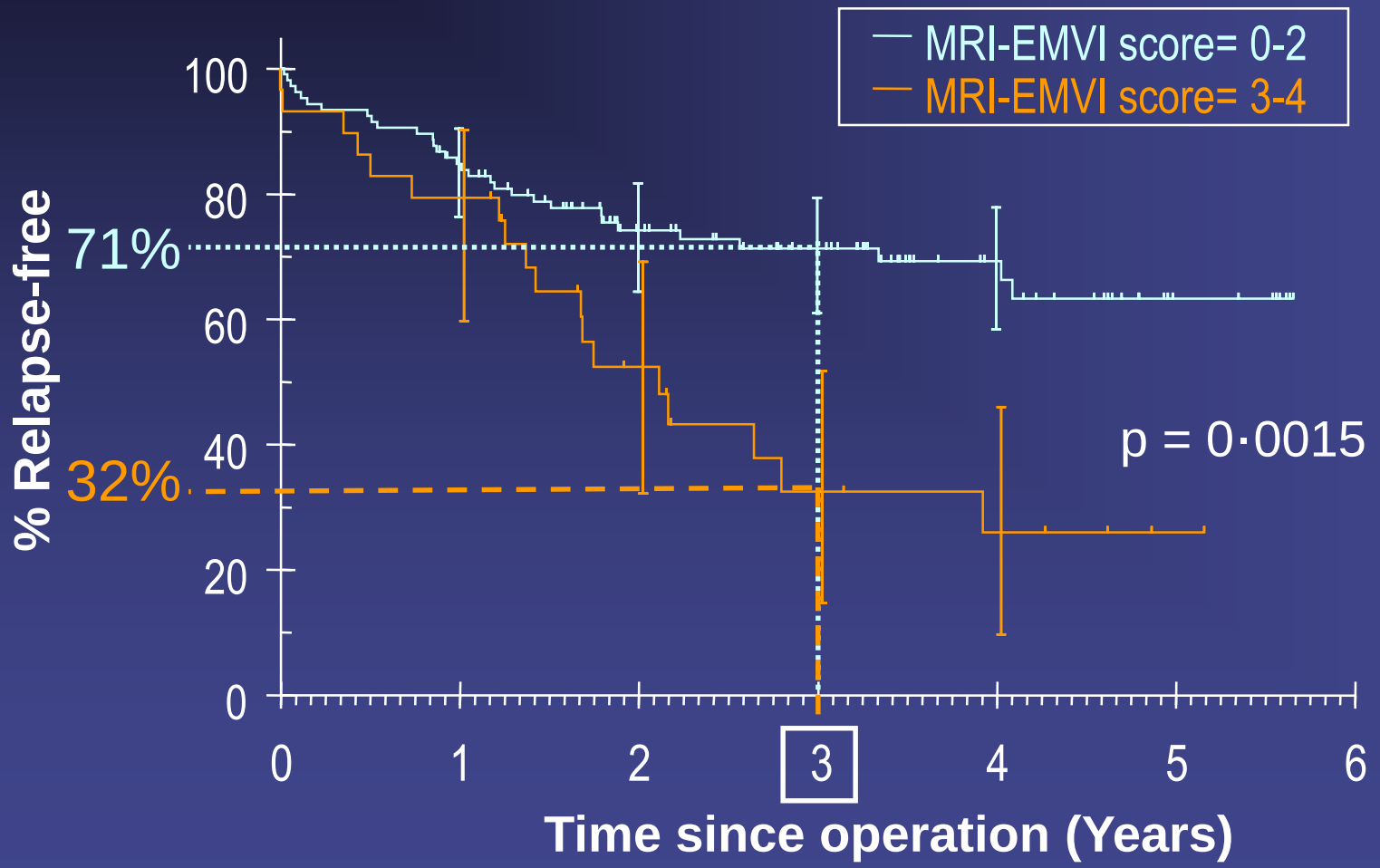
Table 1.

Patient Demographics and Survival Outcomes in 111 Patients Undergoing Preoperative Therapy in the MERCURY Study

Variable	No.	OS			DFS			LR		
		Rate	95% CI	*P*	Rate	95% CI	*P*	Rate	95% CI	*P*
MRI node stage										
N0	68	52	36 to 69		56	38 to 73		22	7 to 38	
N1-2	41	54	42 to 66		54	42 to 66		17	7 to 27	

MRI-EMVI score & Outcome

n=135. Median follow-up=3·12 (0·9-5·7) years.



With thanks to Gina Brown

4 Options for radiotherapy in locally advanced rectal cancer

1. Preoperative short course radiotherapy SCPRT (5 X 5 Gy) immediate surgery
2. Preoperative short course radiotherapy SCPRT (5 X 5 Gy) delayed surgery
3. Preoperative long course chemoradiotherapy CRT (25-28 X 1.8Gy Gy)

4. (Post-op CRT as adjuvant)

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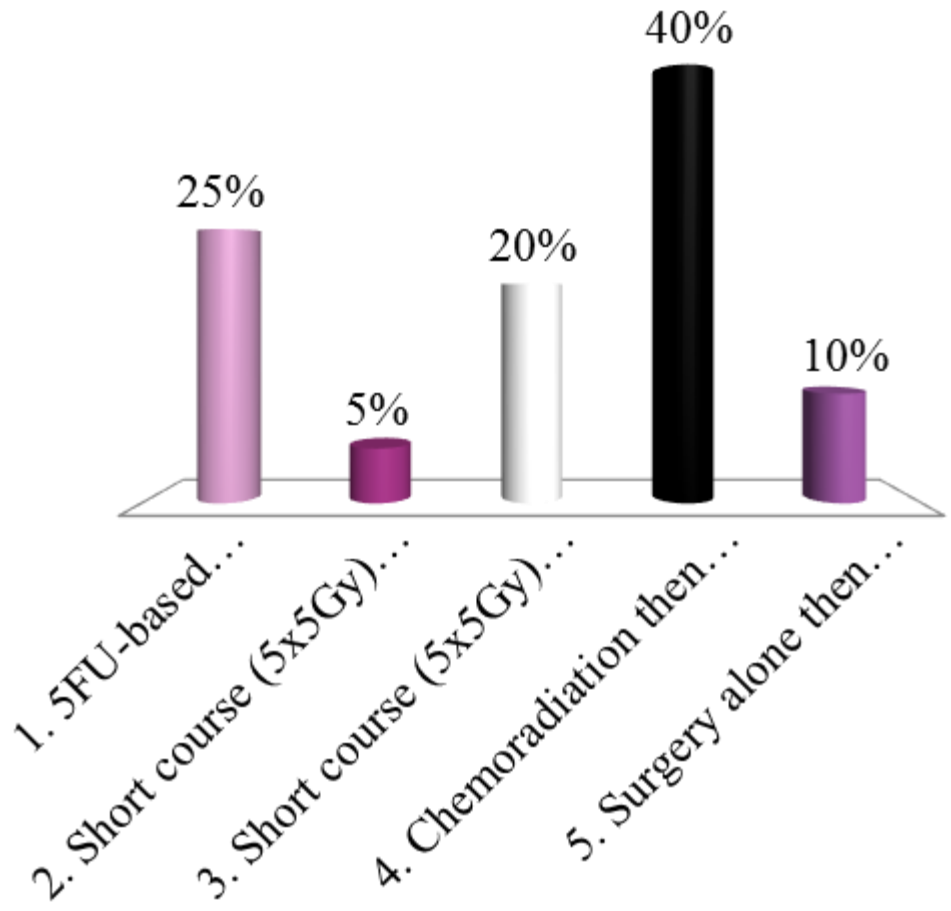
What are you going to recommend?

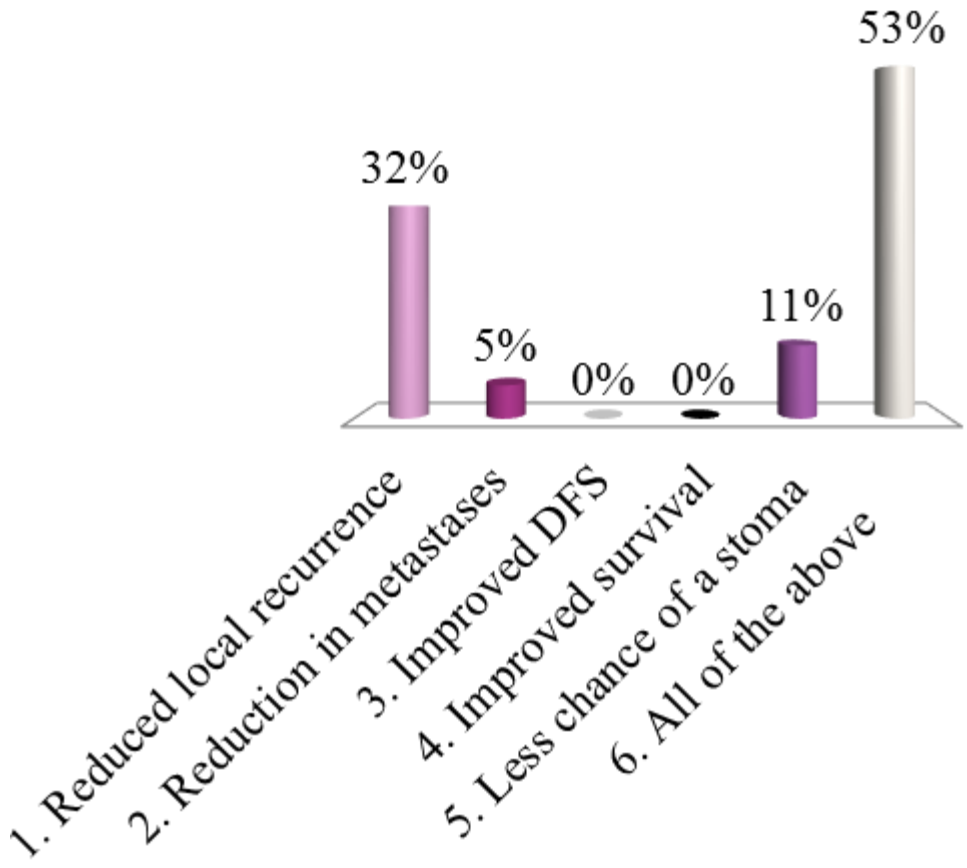
Turning point- How do you manage this patient?

1. 5FU-based Chemoradiation then surgery
2. Short course (5x5Gy) then surgery then chemo
3. Short course (5x5Gy) then chemo then surgery
4. Chemoradiation then surgery then chemo
5. Surgery alone then chemotherapy if node positive (stage III)



What are the advantages for this patient of RT/CRT?

1. Reduced local recurrence
2. Reduction in metastases
3. Improved DFS
4. Improved survival
5. Less chance of a stoma
6. All of the above



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3 Questions re use of chemotherapy

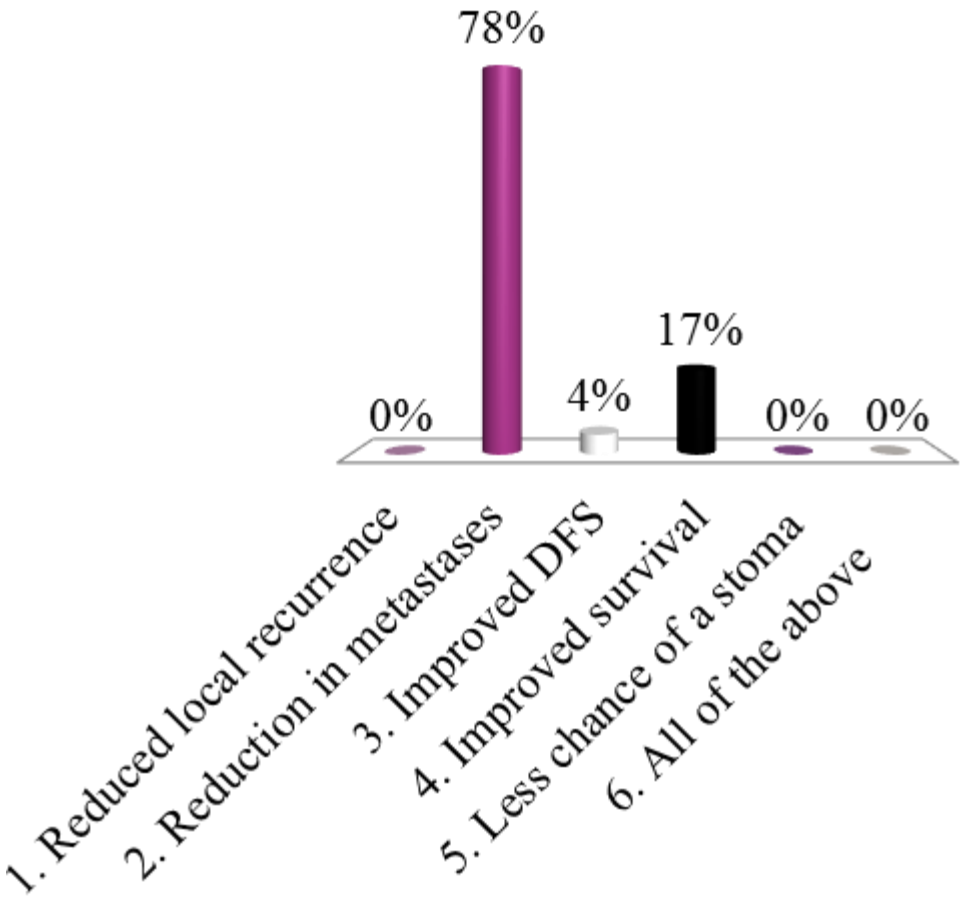
1. Do you simply want to reduce the risk of local recurrence (SCPRT or CRT needed)
2. Do you need to shrink the cancer to ensure an Ro resection?

(you can ignore data re irinotecan and biologicals on postop adjuvant)

3. Or do you want to reduce micro-metastases?*(you cant ignore data on postop adjuvant)*

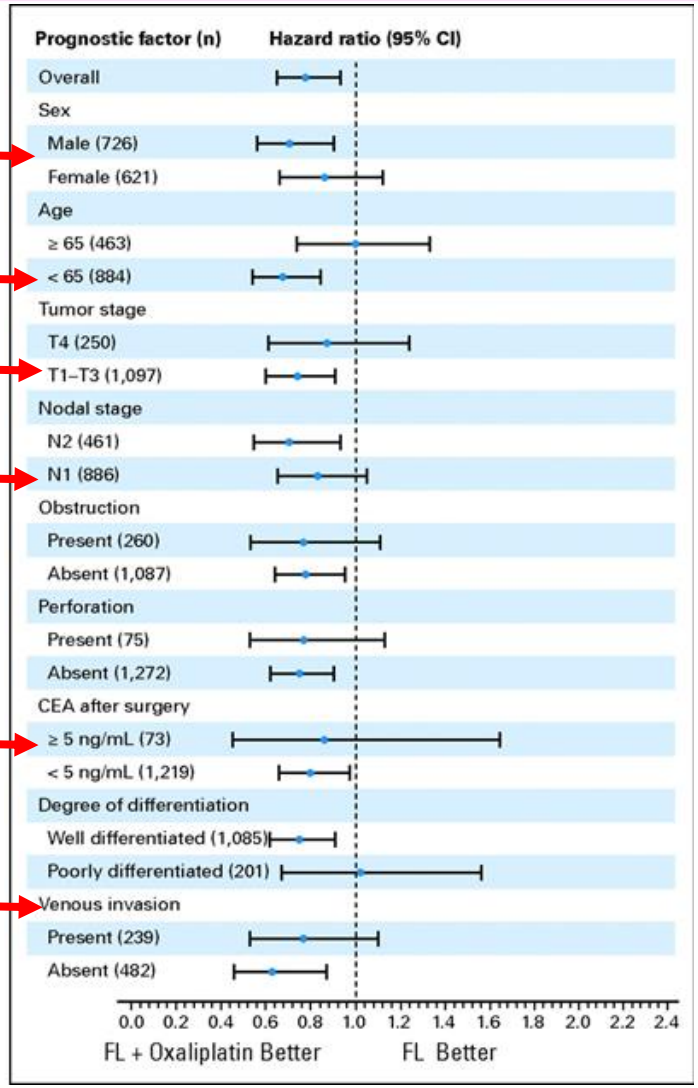
What are the advantages for this patient of oxaliplatin based chemo?

1. Reduced local recurrence
2. Reduction in metastases
3. Improved DFS
4. Improved survival
5. Less chance of a stoma
6. All of the above



Forrest Plot of factors for node positive patients

MOSAIC Trial Benefit of Oxaliplatin



Male
Age < 65
T3
N1
CEA
EMVI+

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Locally advanced Rectal Cancer (LARC) 1:

- Low doses of RT are administered
- Chemoradiation and SCPRT are potentially curative treatments for locally advanced rectal adenocarcinoma.
- Not usually intended to be curative ‘per se’ (unless brachytherapy/Papillon boost)

What is the mechanism of the effect of preoperative CRT in preventing local recurrence?

1. by treating microscopic areas not seen (discontinuous deposits) and so not routinely removed by surgeon ?
2. by treating areas not routinely removed by surgeon (external iliac nodes/obturator nodes etc..) ?
3. by countering spillage ie rendering cells non-viable with RT?
4. by countering spillage growing ie tumour bed effect?
5. by compensating for poor surgical technique?
6. by damaging tumour /vasculature and causing immune effects/loss of tolerance etc..?

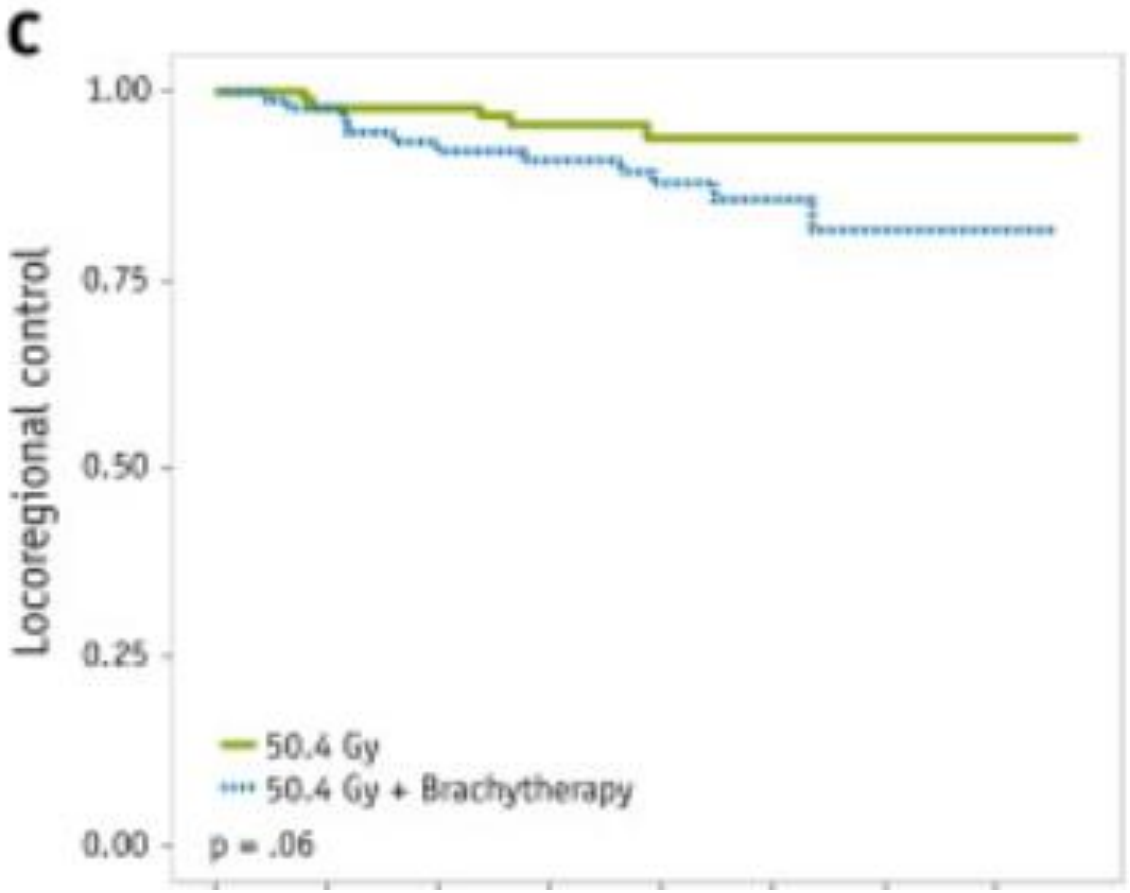
Chemoradiation

What about increasing the dose of RT with brachytherapy?

Jakobsen A 2012: endpoints

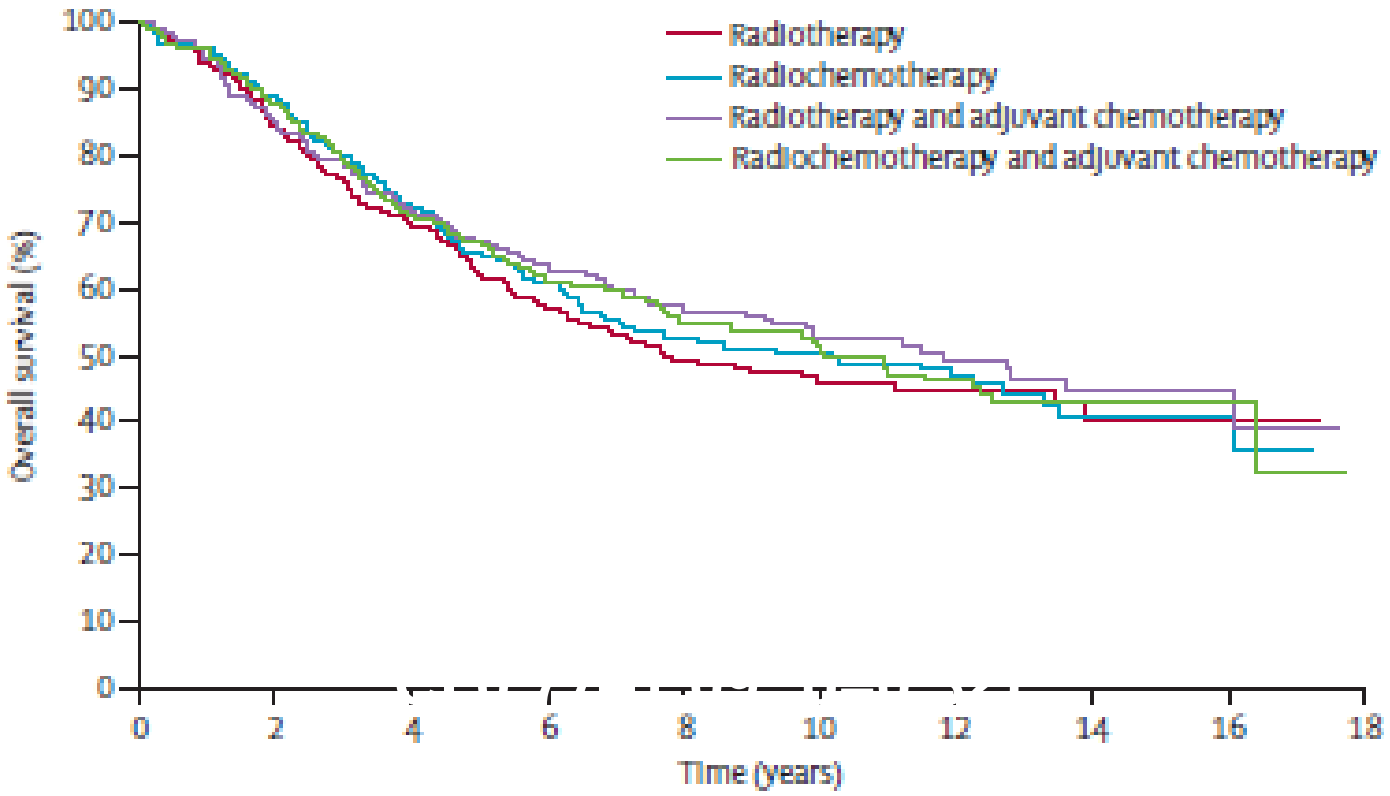
Endpoint	CRT +brachytherapy boost n=90	Standard CRT n= 92	P value
pCR	18%	18%	NS
R0 Resection	99%	90%	P= 0.03
Major response TRG 1 and 2	44% (35/80)	28% (23/82)	P= 0.04

Loco-regional control Appelt 2014



- Which begs the question regarding the mechanism of action for preventing local recurrence?

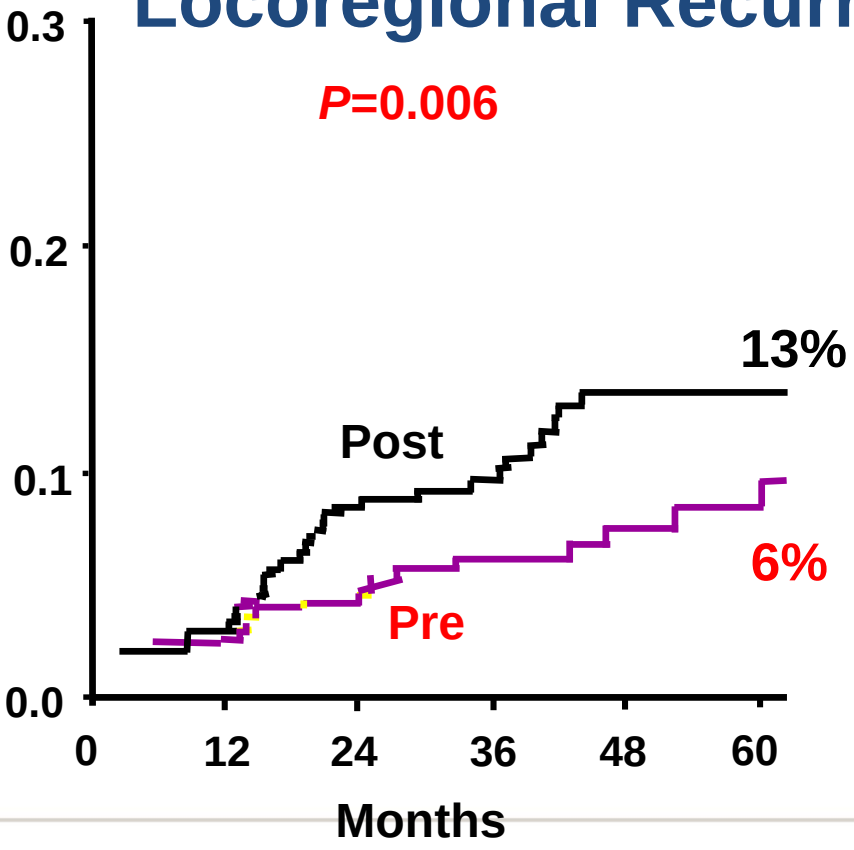
EORTC 22921 – Overall Survival



Number at risk									
Radiotherapy	252	208	165	129	98	62	32	15	5
Radiochemotherapy	253	223	173	135	96	66	41	19	9
Radiotherapy and adjuvant chemotherapy	253	212	171	140	102	69	42	18	8
Radiochemotherapy and adjuvant chemotherapy	253	221	174	143	108	77	44	18	4

Pre- vs post-operative chemoradiation CAO/ARO/AIO-94

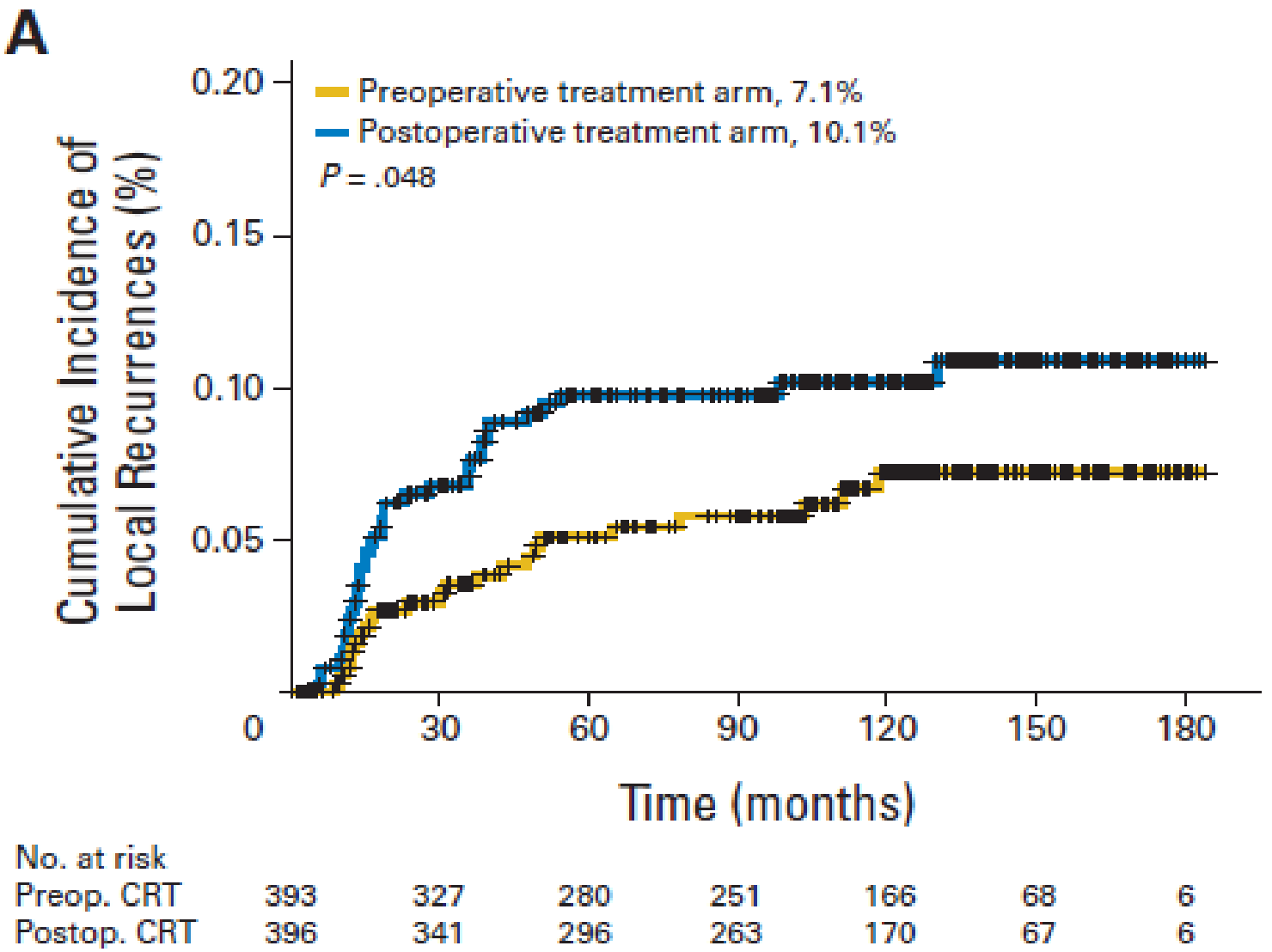
Locoregional Recurrences



Acute G3/4 adverse events
27% vs 40% (p=0.001)

Long-term G3/4 adverse events
14% vs 24% (p=0.01)

Sauer R. et al., N Engl J Med 2004;351: 1731-39



Long-term data on LOC REC from German study – 5/22 local recurrences ie 23% after 5 years (not like CR07)

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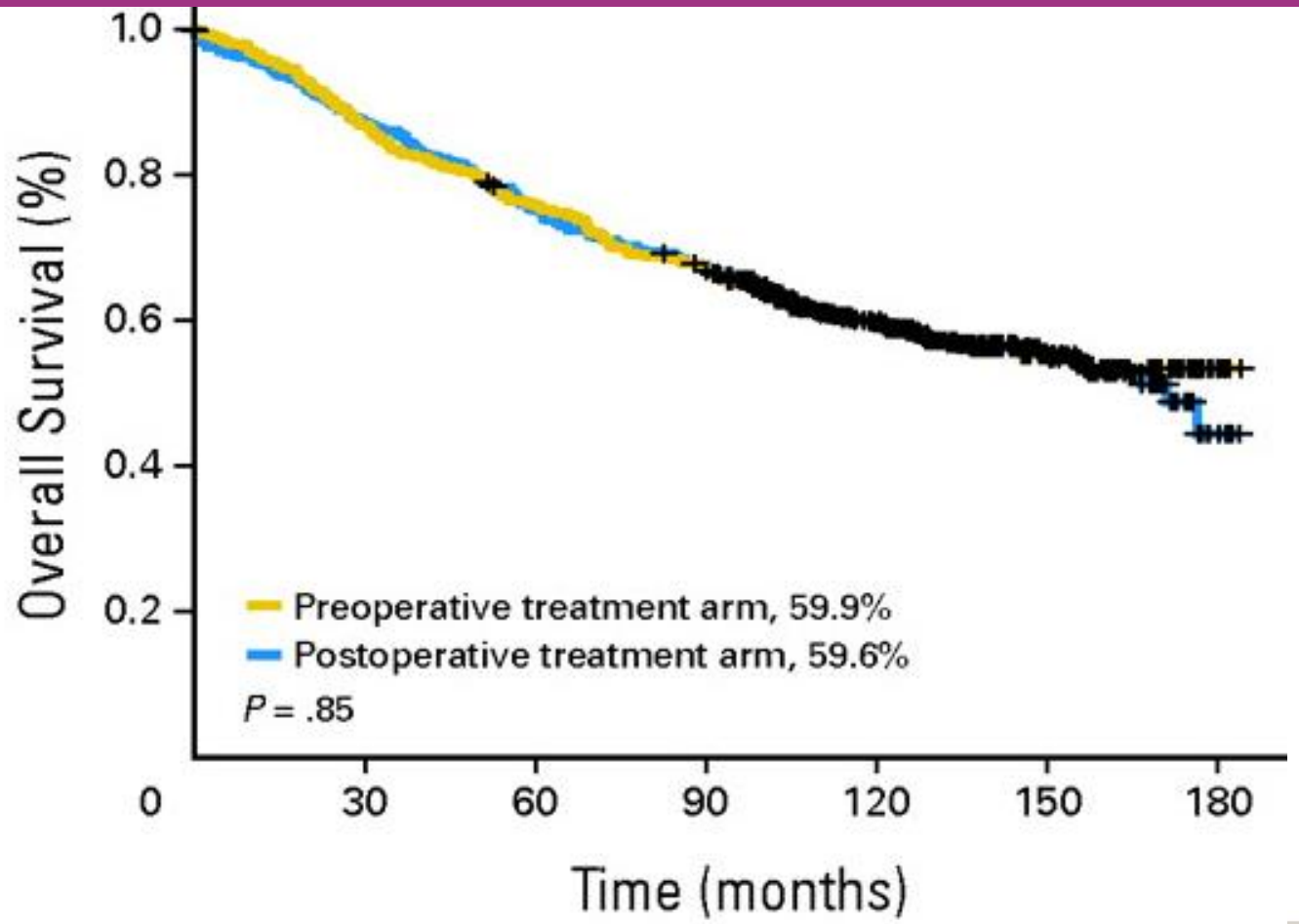
Pre- vs post-operative chemoradiation CAO/ARO/AIO-94



No. at risk							
Preop. CRT	404	351	305	268	174	67	6
Postop. CRT	395	342	295	262	172	70	6

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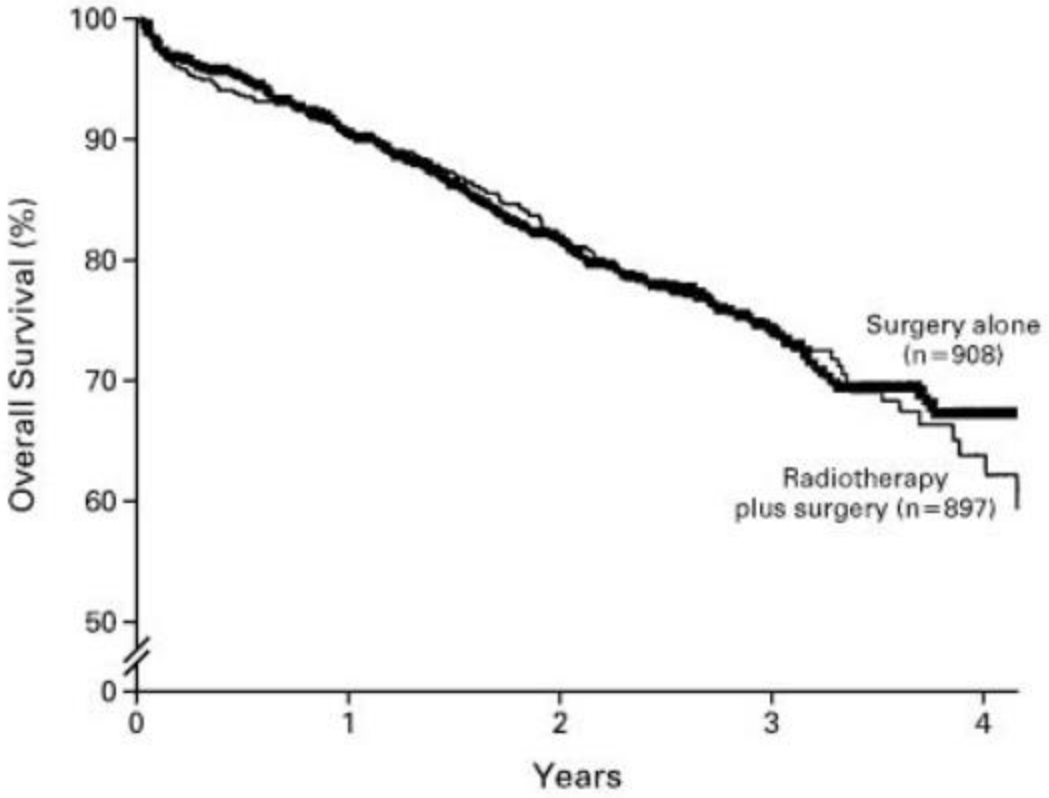
Dutch TME trial Kapiteijn NEJM 2001



No. at Risk					
Radiotherapy plus surgery	897	741	435	192	41
Surgery alone	908	744	454	207	42

At two years, overall survival was 82.0 percent in the group assigned to radiotherapy and surgery and 81.8 percent in the group assigned to surgery alone (P=0.84).

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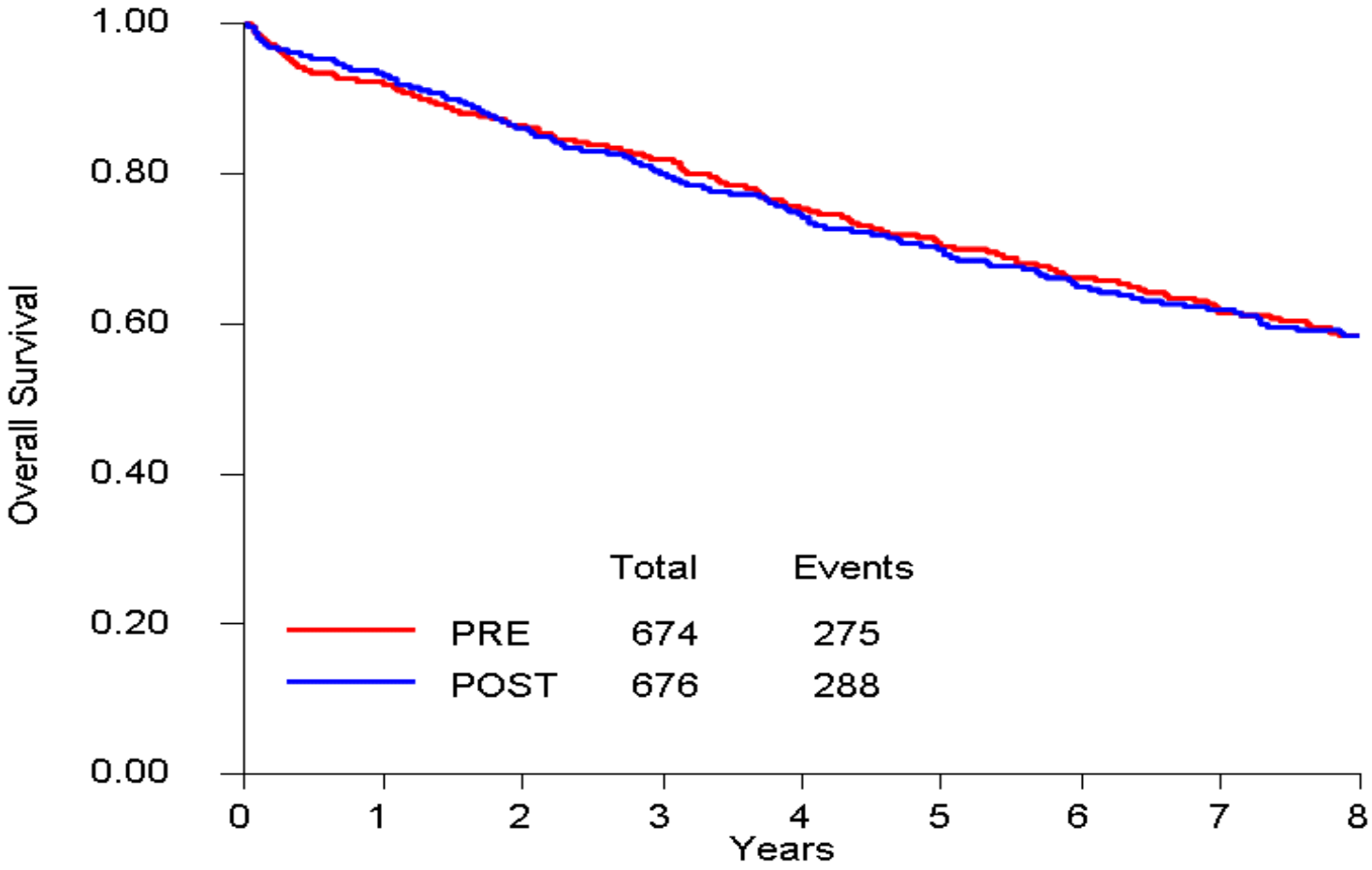
CR07 Overall Survival



Number at risk

PRE	674	611	571	539	490	445	359	271	204
POST	676	624	577	530	487	434	356	274	208

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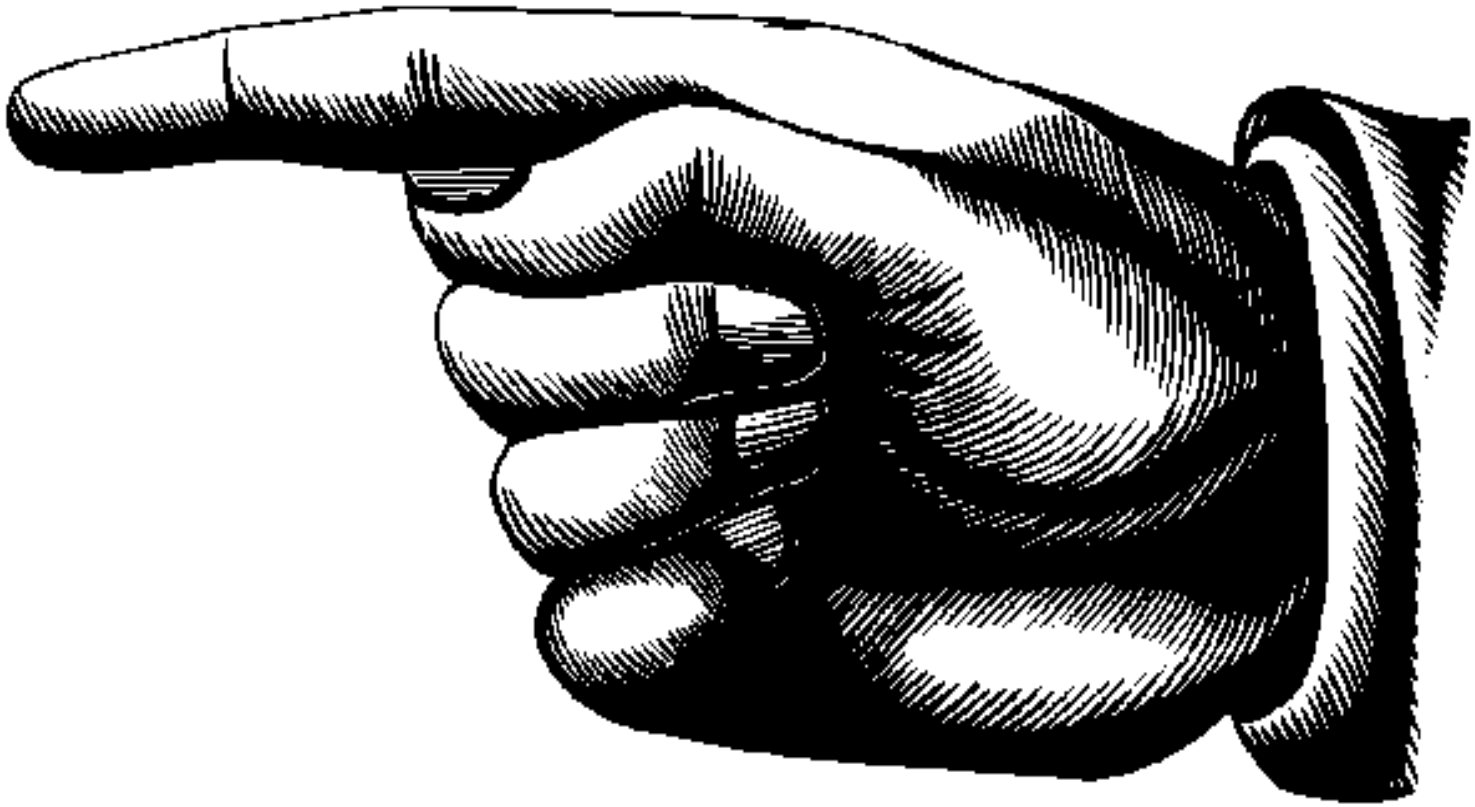
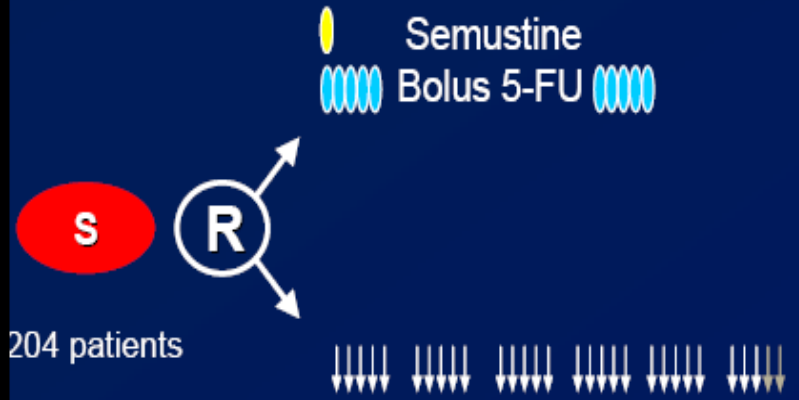
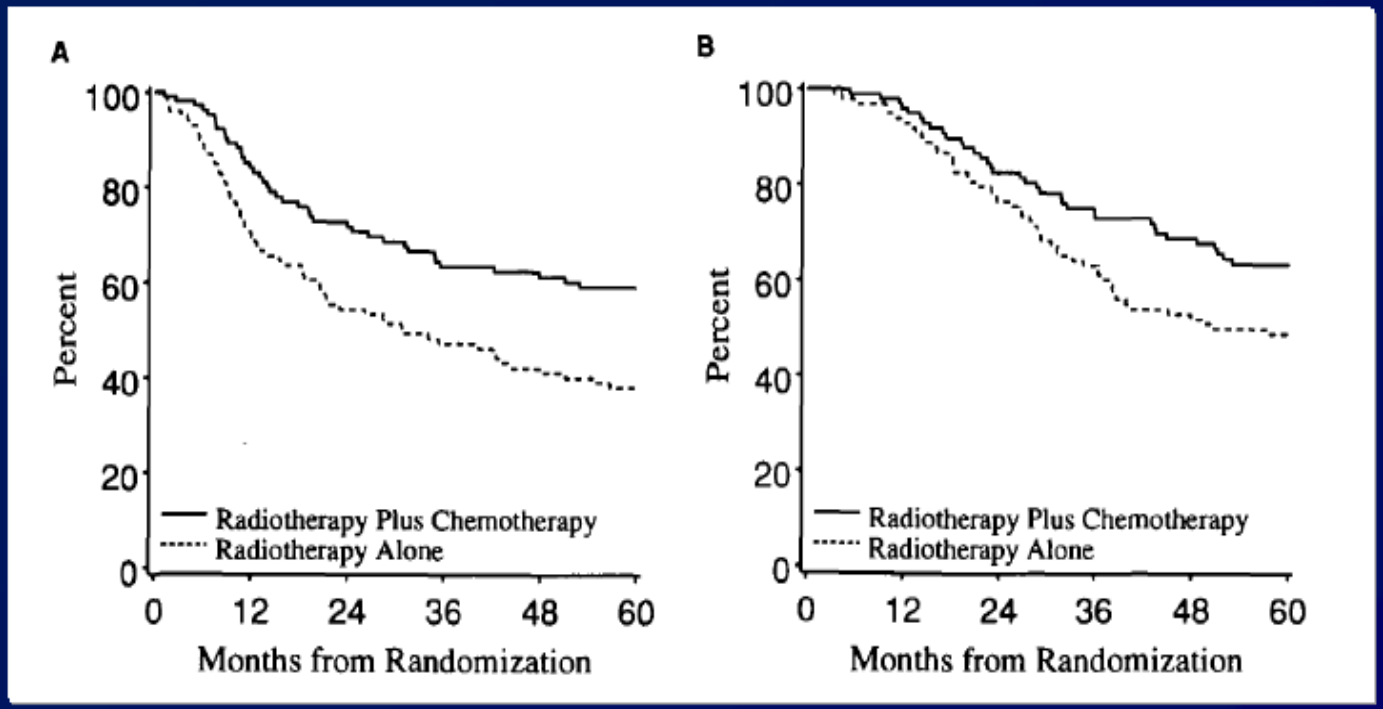
Historical staging



NCCTG/Mayo 794751



68% N+

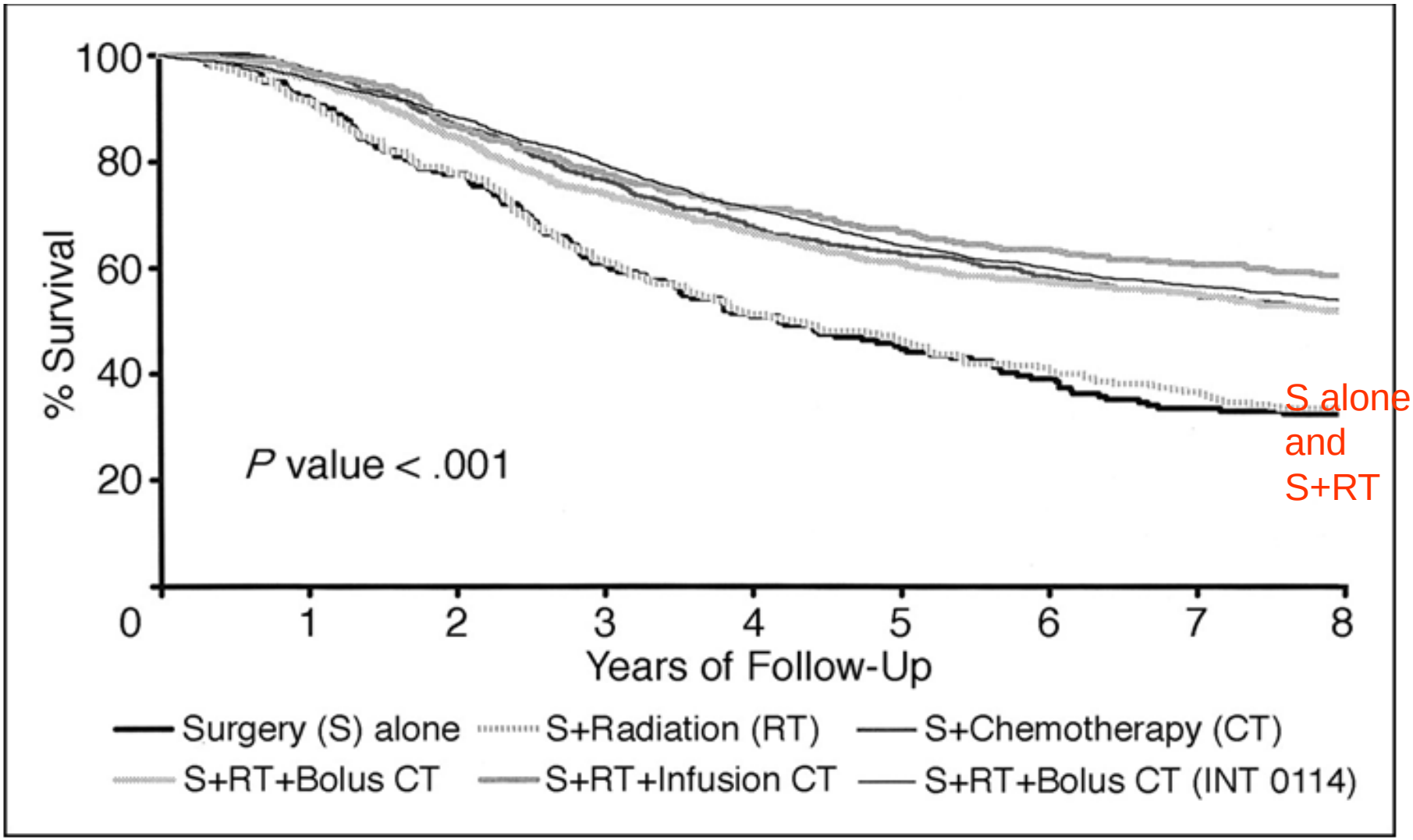


Disease-free survival

Overall survival

Krook et al. N Eng J Me 1991

Impact on overall survival of 6 methods of treatment in rectal cancer pooled analysis



S alone and S+RT

Gunderson, L. L. et al. J Clin Oncol; 22:1785-1796 2004

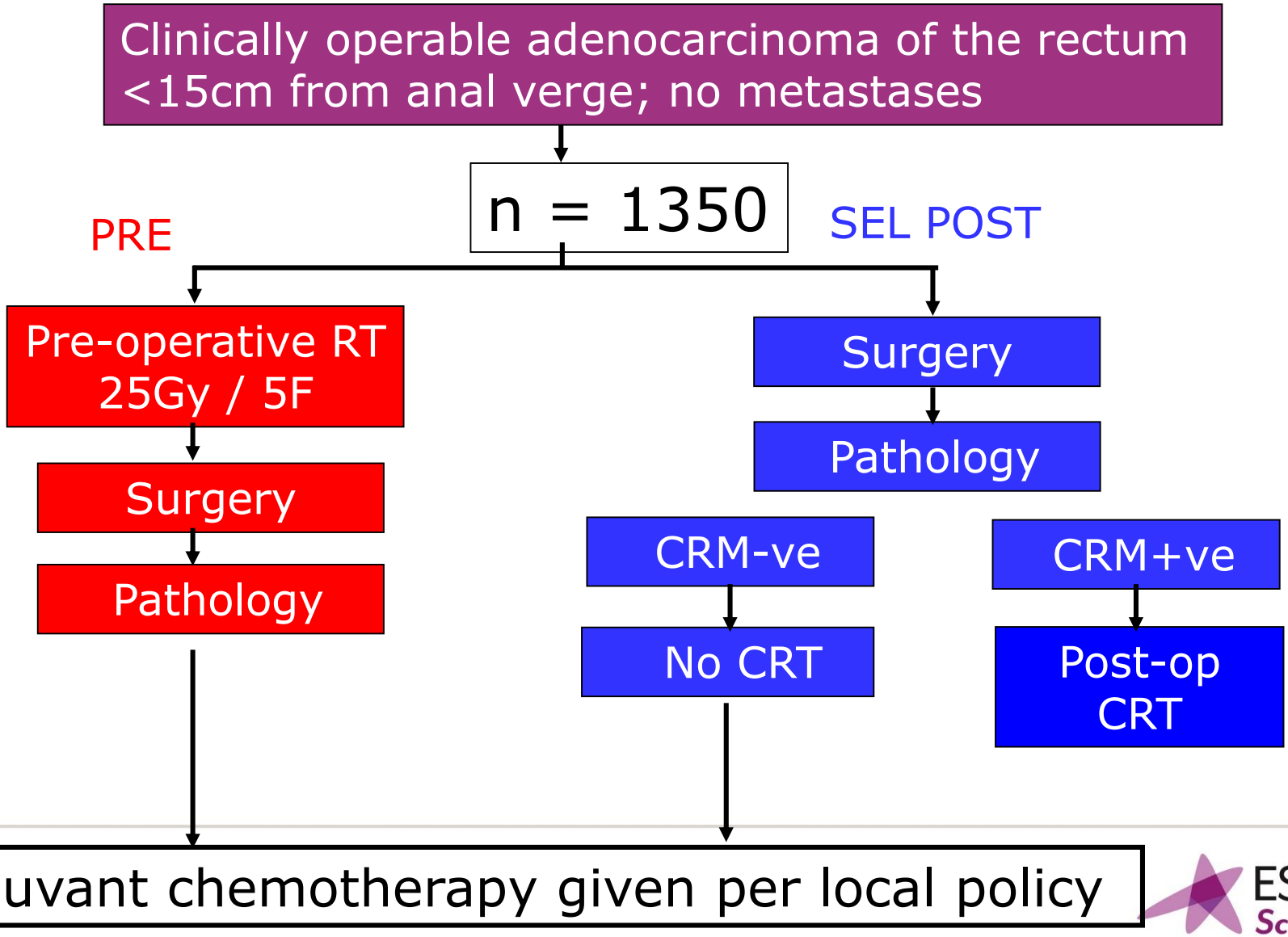
Current Wisdom

- Preoperative CRT better than postop
- Improves Local recurrence but not DFS or OS
- If CRM threatened on MRI needs response so CRT
- Low rectal cancers (below the levators) almost always have threat to CRM
- T1/T2N0 mid/upper rectum don't usually need RT or CRT unless to avoid radical surgery
- CRT helps preserve sphincters

Quality of surgery is the biggest factor in Local recurrence –not whether or not you have radiotherapy

Quality of surgery can be viewed and scored

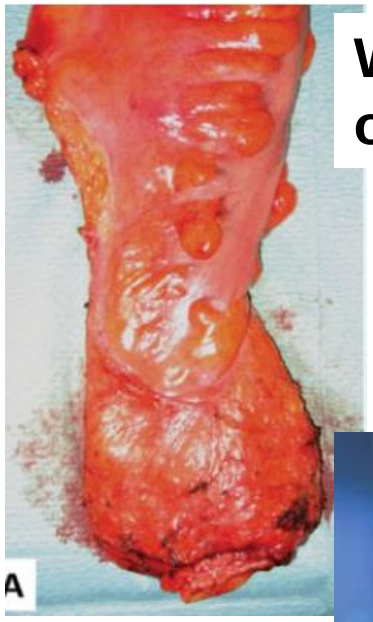
MRC CR07 NCIC C016 trial

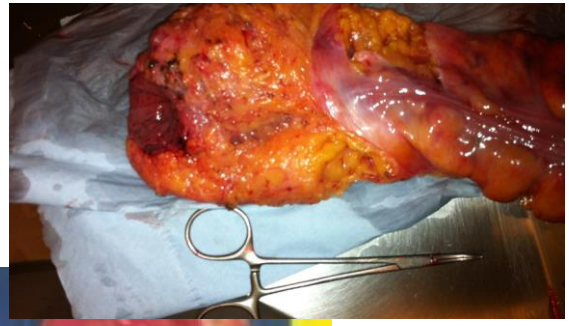


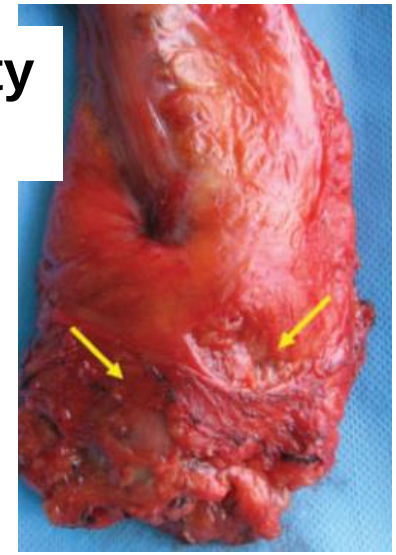
Scoring the Quality of the

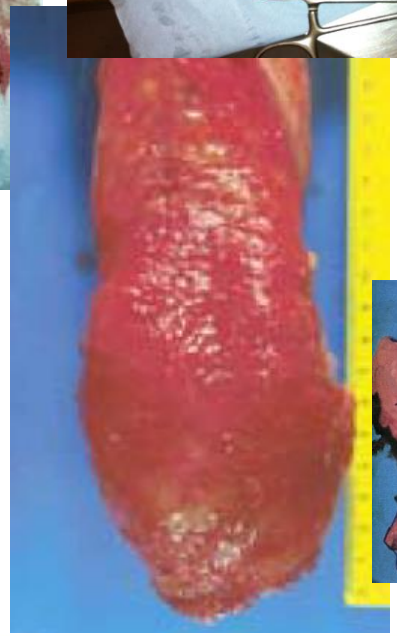
	Mesorectum	Defects	Coning	MRF
Complete	Intact, smooth	Not deeper than 5 mm	None	Smooth, regular
Nearly complete	Moderate bulk, irregular	No visible muscularis propria	Moderate	Irregular
Incomplete	Little bulk	Down to muscularis propria	Moderate–marked	Irregular

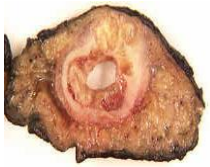
We can judge the quality of the Surgery

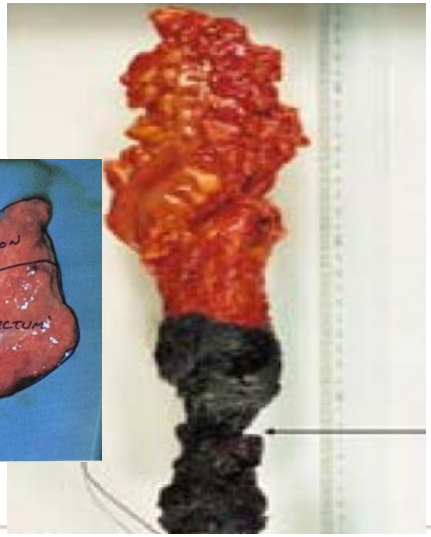


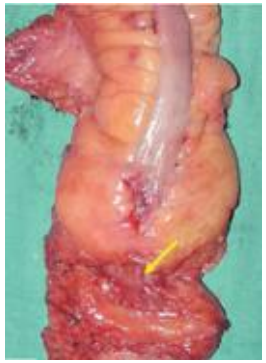


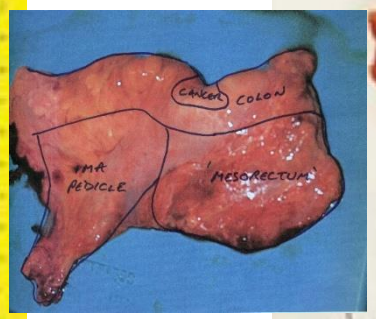






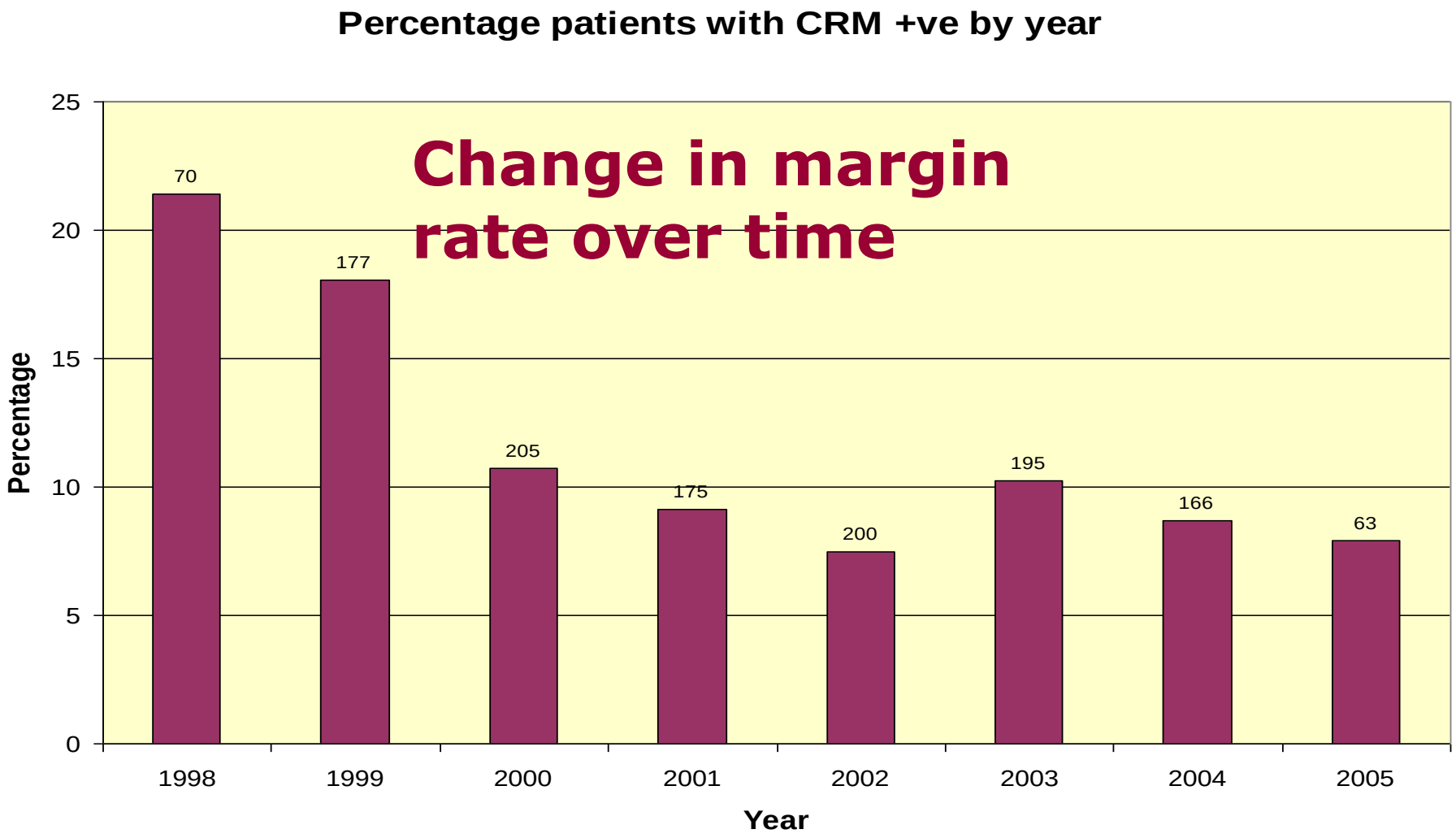






CR07

Percentage of patients with + CRM over time



CRM associations with plane of surgery

	Plane of surgery		
	Mesorectal	Intra-mesorectal	Muscularis propria
CRM +ve rate	9%	12%	19%
Stage I	29%	24%	27%
Stage II	27%	32%	30%
Stage III	44%	43%	41%

With thanks to Phil Quirke

CR07 rates of local recurrence

	Preop RT 674	Selective Post-op RT	HR
CRM +ve	13.8%	20.7%	0·64
CRM -ve	3.3%	8.9%	0·36

Sebag-Montefiore D et al., Lancet 2009

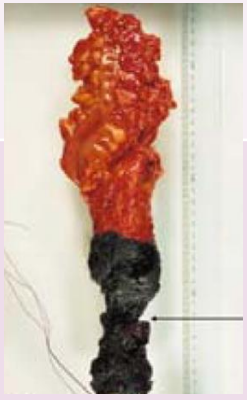
TME Northern Europe: Good quality mesorectal plane: no RT

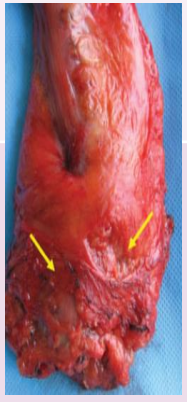
Study	Eligible	Good Quality Mesorectal	Local Recurrence	Actuarial
Swedish Rectal Cancer Trial 1997 (**574**)	T any N any	<10%	150/557 **27%**	>30%
CR07 overall (**592**) Quirke 2009	T any N any	51%	59/592 **10%**	11%
Dutch TME (**180**) Nagtegaal 2005	T any N any	56%	Not stated	8.7% at 2 years

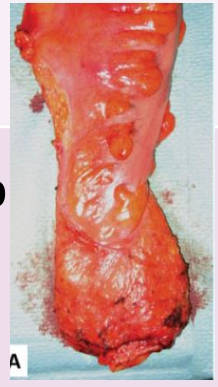
Local Recurrence rates in CRO7 according the plane of surgery

Quirke P et al Lancet. 2009 Mar 7; 373(9666): 821–828

	Plane of Surgery		
TNM stage	**Muscularis propria**	**Intra-mesorectal**	**Mesorectal**
I	**8%**	**2%**	**0%**
II	**6%**	**2%**	**5%**
III	**20%**	**14%**	**6%**







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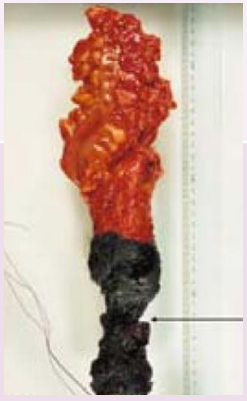

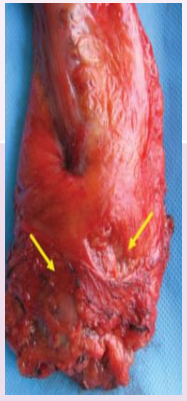

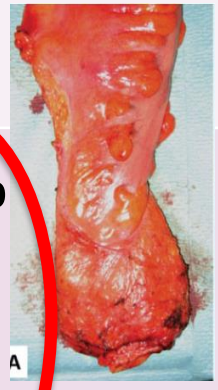

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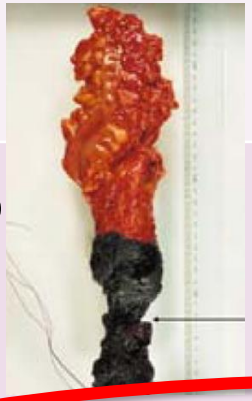

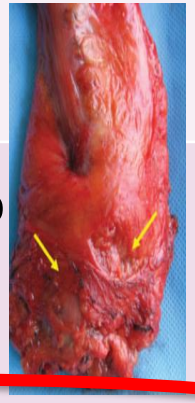

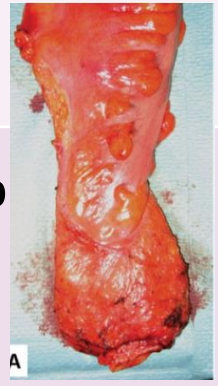

Pathologically defined Lymph nodes only affect your local recurrence rate if you leave them inside the patient!

Lymph nodes on MRI (unless extracapsular spread – ie irregular borders) mean you are simply seeing LN enlarged

– it may actually say the host immune system is working

So - What about?

- Oxaliplatin
- Irinotecan
- Biologicals

So - What about?

- Oxaliplatin
- Irinotecan
- ~~Biologicals~~

Currently - Different Philosophies

Medical Oncology trials EXPERT, EXPERT C, SPANISH (Fernandez-Martos)/ RAPIDO use systemically active chemotherapy outside chemoradiation

Radiation Oncology trials ACCORD 12, STAR-01, CAO/ARO/AIO-04, NSABP R04 use oxaliplatin as radiosensitizer (non systemic doses)

Endpoint	STAR-01	ACCORD 12/0405	CAO/ARO/ AIO-04	NSABP R-04	PETACC-6
PCR	16% both arms	14% vs 19%	12.8% vs 16.5% (p=0.038)	19% vs 21%	11.5% vs 13%
CRM	4% vs 7%	8% vs 13%	5% vs 6%	No data	2% vs 2%
Node + (stage III)	29% vs 26%	30% vs 26%	27% vs 26%	Not stated	27% vs 26%

Control arm in red

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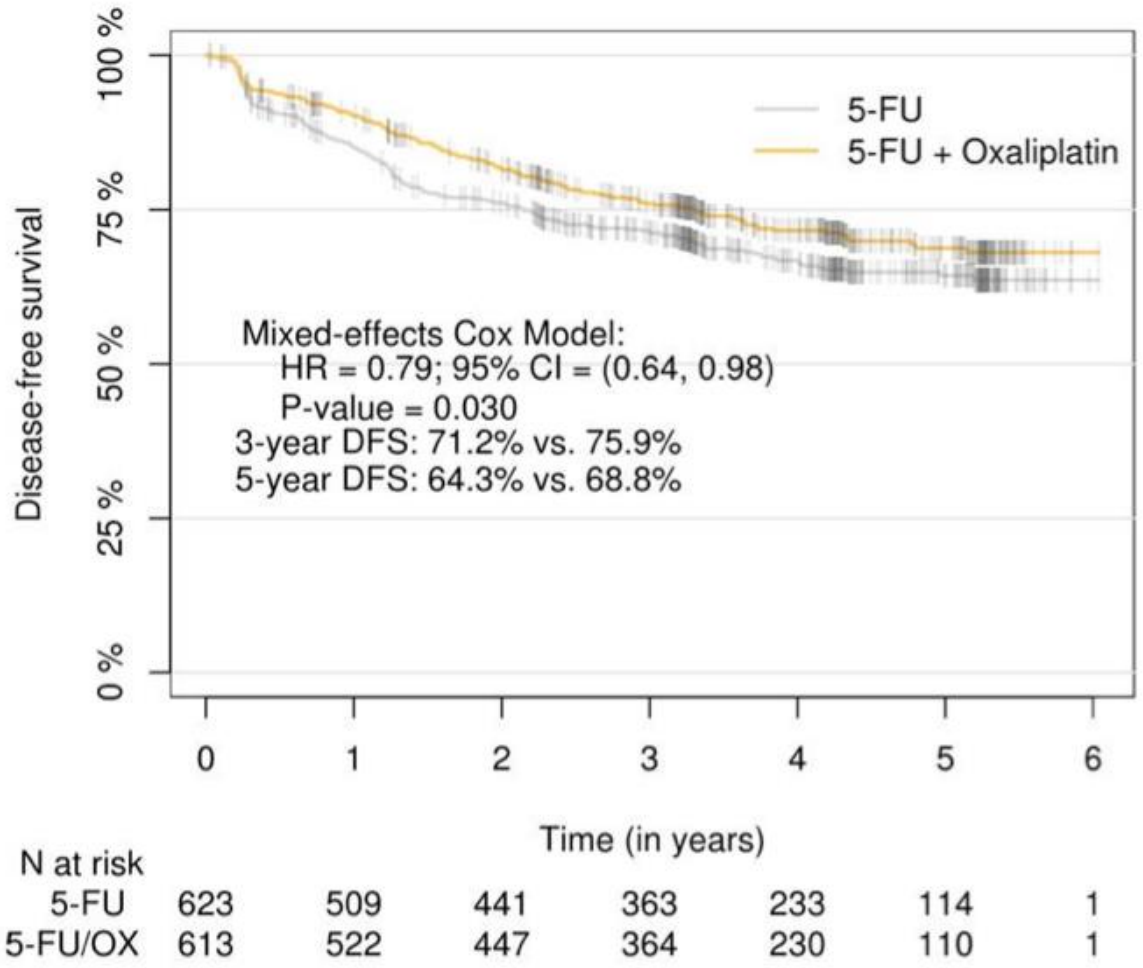
CAO/ARO/AIO-04 Trial



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Phase III: CAO/ARO/AIO-04

Best arm of CAO/ARO/AIO-94:

RT 50.4 Gy + 5-FU
1000 mg/m² days 1-5 + 29-33
623 patients

From Phase I/II Studies:

RT 50.4 Gy + 5-FU/OX
Ox: 50 mg/m² d 1, 8, 22, 29
5-FU: 250 mg/m² d 1-14 + 22-35

Note: Chemo gap 3rd week of RT !

613 patients

T M E

5-FU
500 mg/m² d 1-5, q29
4 cycles (4 months)

mFOLFOX6
Oxaliplatin: 100 mg/m² d1,q15
Folinic Acid: 400 mg/m² d1
5-FU: 2400 mg/m² d1-2
8 cycles (4 months)

Phase III Chemoradiotherapy trials with or without Oxaliplatin

Trial	No of patients	Regimens	DFS	Difference
CAO/ARO/AIO-04 Rodel Lancet Oncology 2015	1236	CRT + Ox 60mg Plus OX adjuvant	71.2% vs 75.9%	**+4.7%** (HR 0.79)
NSABP R-04 JNCI 2016	1606	CRT + Ox 60mg	64.2% vs 69.2%	**+5%** (HR = 0.91) **(p=0.34)**
ACCORD 12 updated 2016 GI ASCO	598	CRT + Ox 60mg + RT 50Gy	67.9% v 72.7%	**+4.3%**
STAR-01 WGICC 2016	747	CRT + Ox 60mg	5 year 66.3% vs 69.2 %	**+2.9%** (HR 0.89)
PETTAC-6	1090	CRT + Ox 60mg Plus OX adjuvant	75% vs 74% (lowest pCR)	**-0.6% outlier**
Chinese Trial Jiao 2015	208	CRT + Ox 60mg All received adjuvant FOLFOX 6−8 cycles	3-year DFS 69.9% vs 80.6% (P>0.05)	**+10.6%**

Adjuvant trials in colon cancer using oxaliplatin in the novel arm.

Trial	Patient No	Path Stage	Treatment arms	Median Age	Compliance to planned cycles	5 year DFS
MOSAIC (Andre 2004 updated 2015	2246	II, III	LV5FU2 FOLFOX4	60 61	86.5% 74.7%	67.5% vs 73.2% **+5.7%**
NSABP C07 (Kuebler 2007) updated 2011	2407	II, III	FULV FLOX	59 59	Not stated Not stated	64.2% vs 69.4% **+5.2%**
NO16968 (Haller 2011)	1886	III	FULV XELOX	61 62	83% 69%	3-year DFS 70.9% vs 66.5% **+4.4%**

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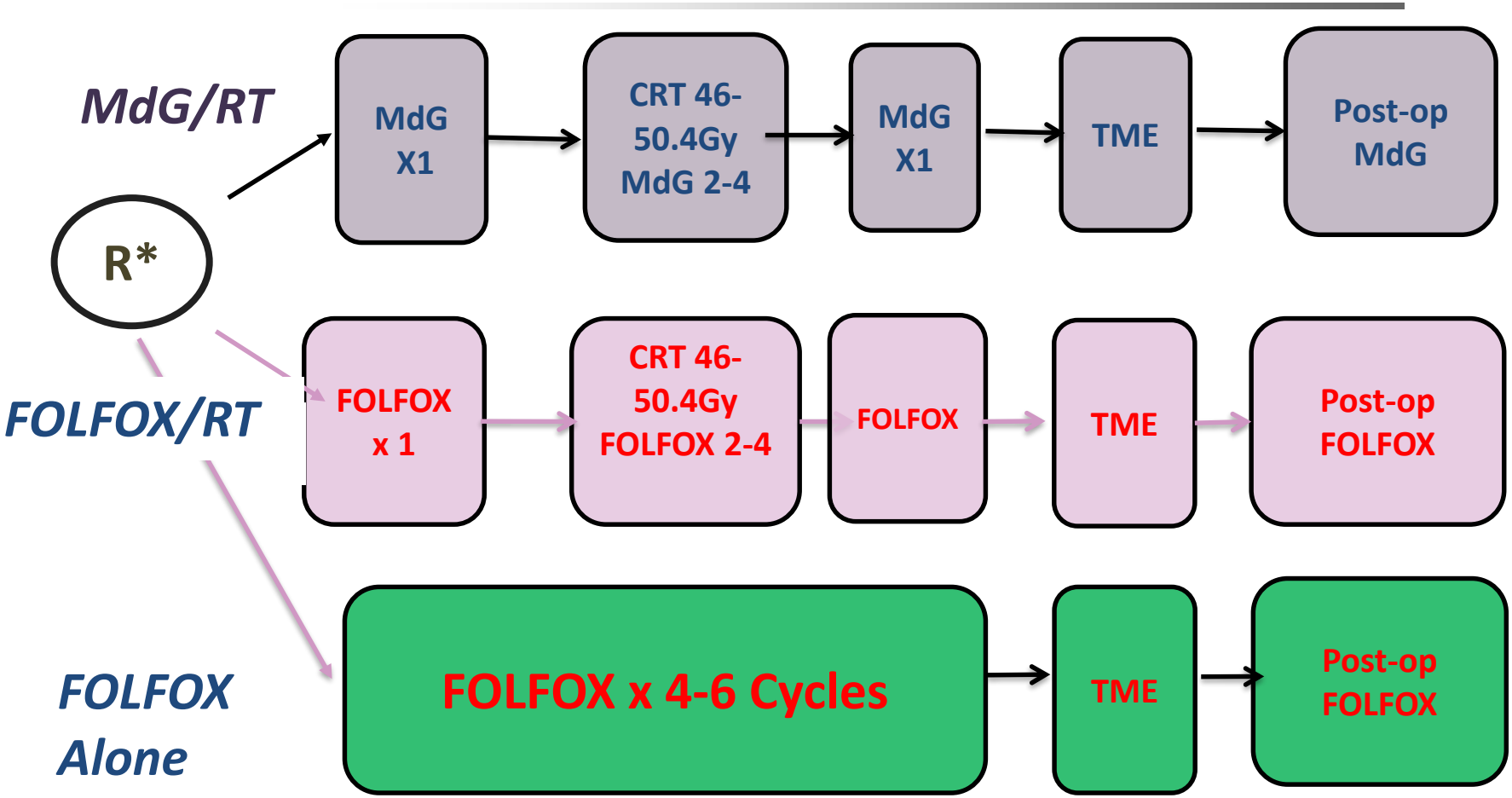
The FOWARC trial – Design



Endpoints

Primary endpoint: 3 yr DFS

Deng, J Clin Oncol 2016

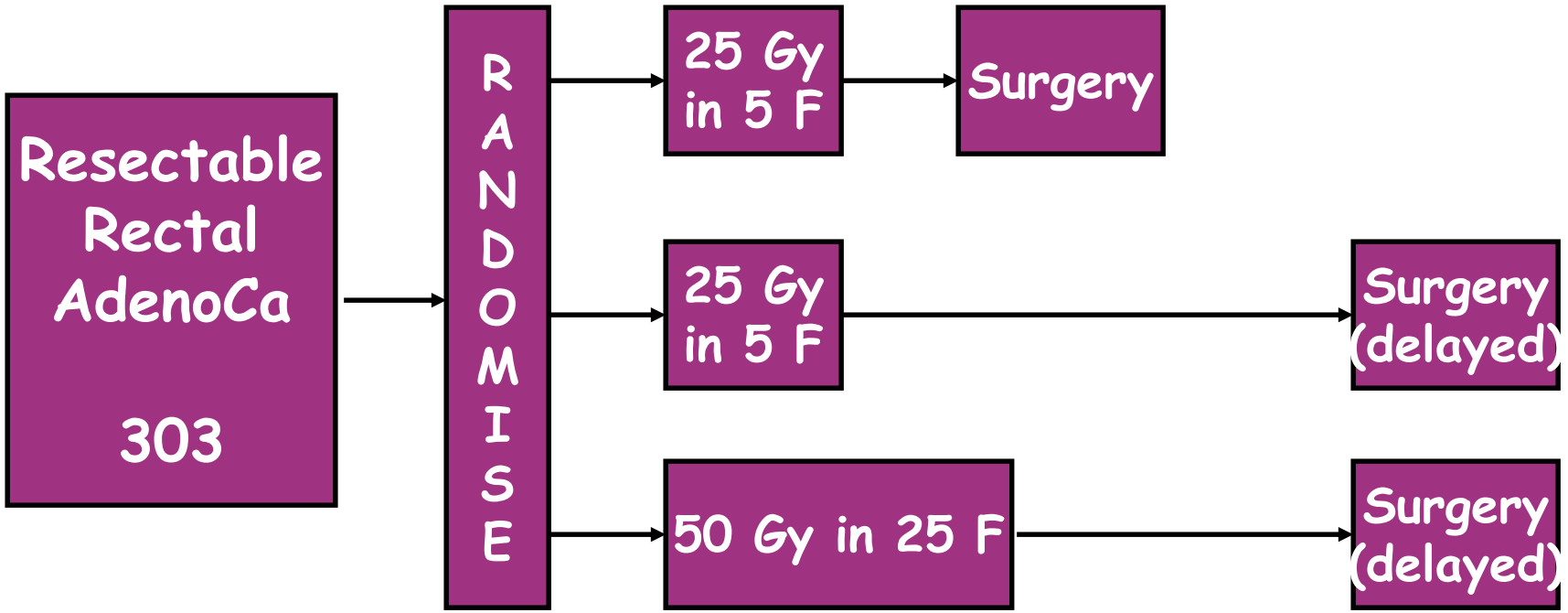
**Patients recruited from 15 Chinese Centres 2010-2015*

Regimens	Number of patients	G3/G4 toxicity Diarrhea	Interval to surgery (median in days)	ypN+	pCR	TRG0-1
De Gramont RT 46-50.4Gy	165	7.7%	53	19.9%	14%	49%
FOLFOX RT 46-50.4Gy	165	14.5%	52	12.6%	27.5%	68.5%
FOLFOX alone	165	7.3%	Not stated	26.5%	6.6%	32.9%

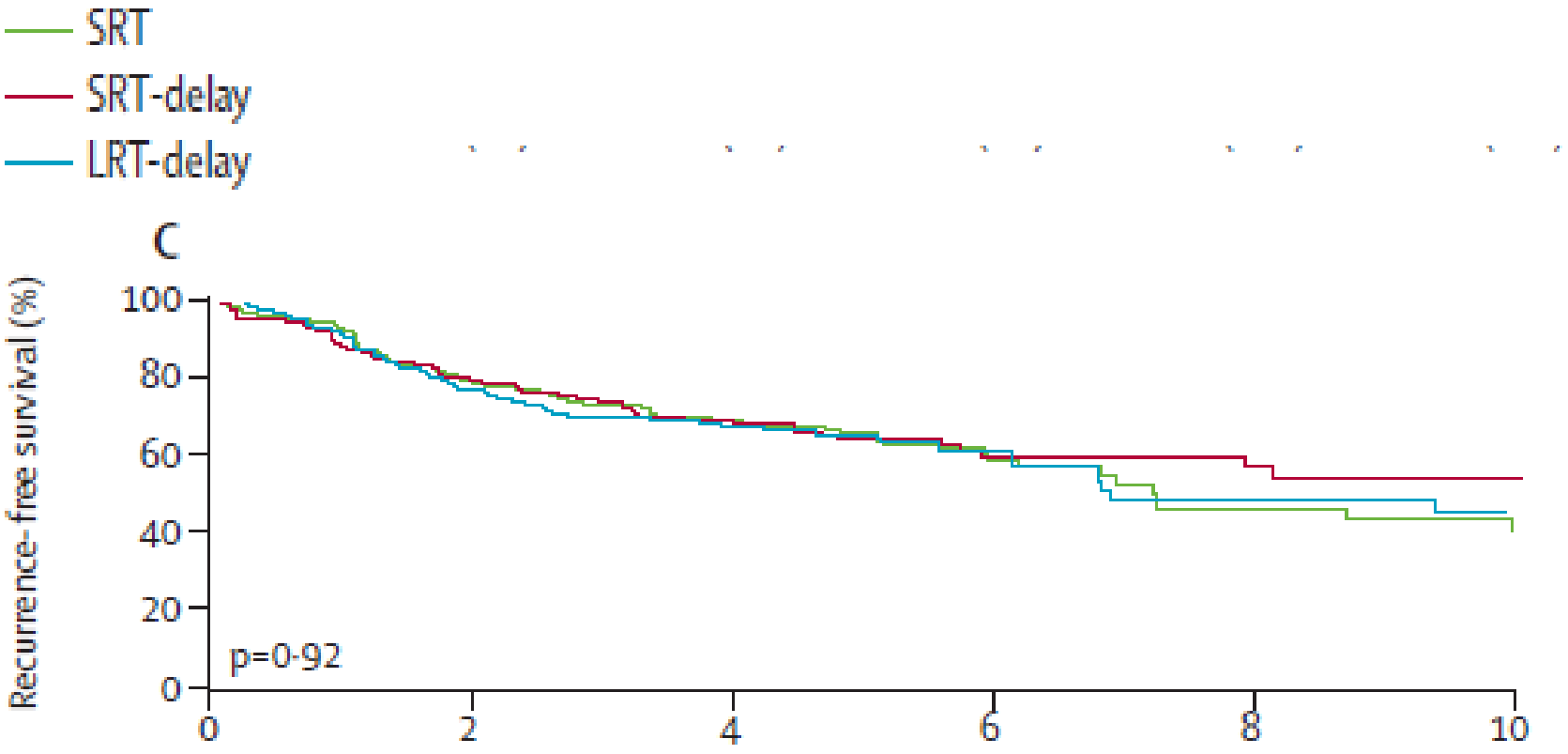
Endpoint	STAR-01	ACCORD 12/0405	CAO/ARO/ AIO-04	NSABP R-04	PETACC-6	FOWARC
PCR	16% both arms	14% vs 19%	12.8% vs 16.5% (p=0.038)	19% vs 21%	11.5% vs 13%	14% vs 27.5%
CRM	4% vs 7%	8% vs 13%	5% vs 6%	No data	2% vs 2%	9.2% vs 10% R1/R2
yp Node + (stage III)	29% vs 26%	30% vs 26%	27% vs 26%	Not stated	27% vs 26%	19.9% vs 12.6%

Control arm in red

STOCKHOLM III



Stockholm III trial :Recurrence Free



Number at risk (censored)						
SRT	129 (0)	101 (0)	82 (8)	36 (44)	18 (56)	12 (60)
SRT-delay	128 (0)	101 (0)	77 (11)	36 (45)	20 (59)	17 (62)
LRT-delay	128 (0)	97 (1)	74 (13)	34 (47)	20 (55)	9 (65)

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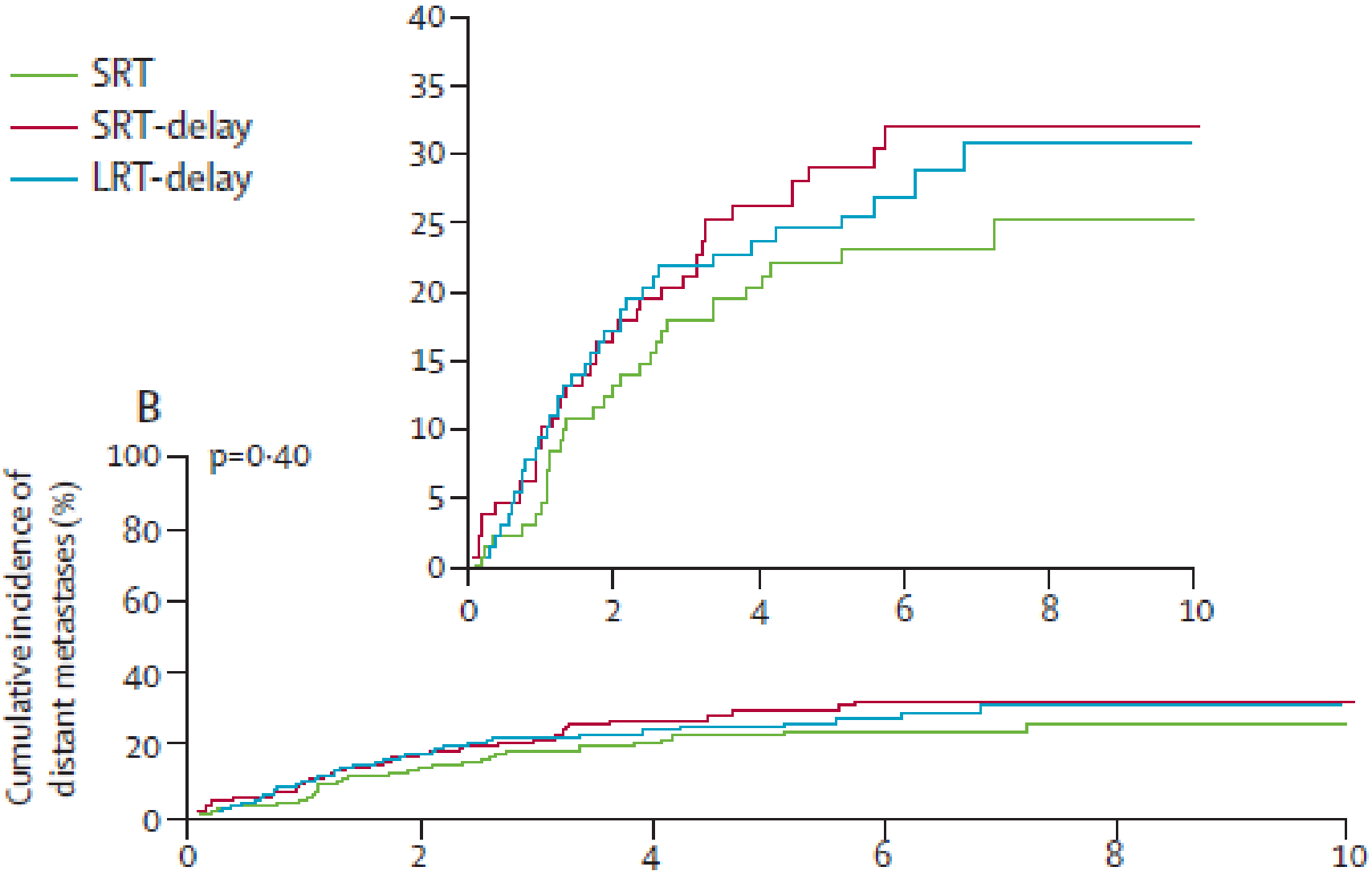
Stockholm III trial : incidence of metastases



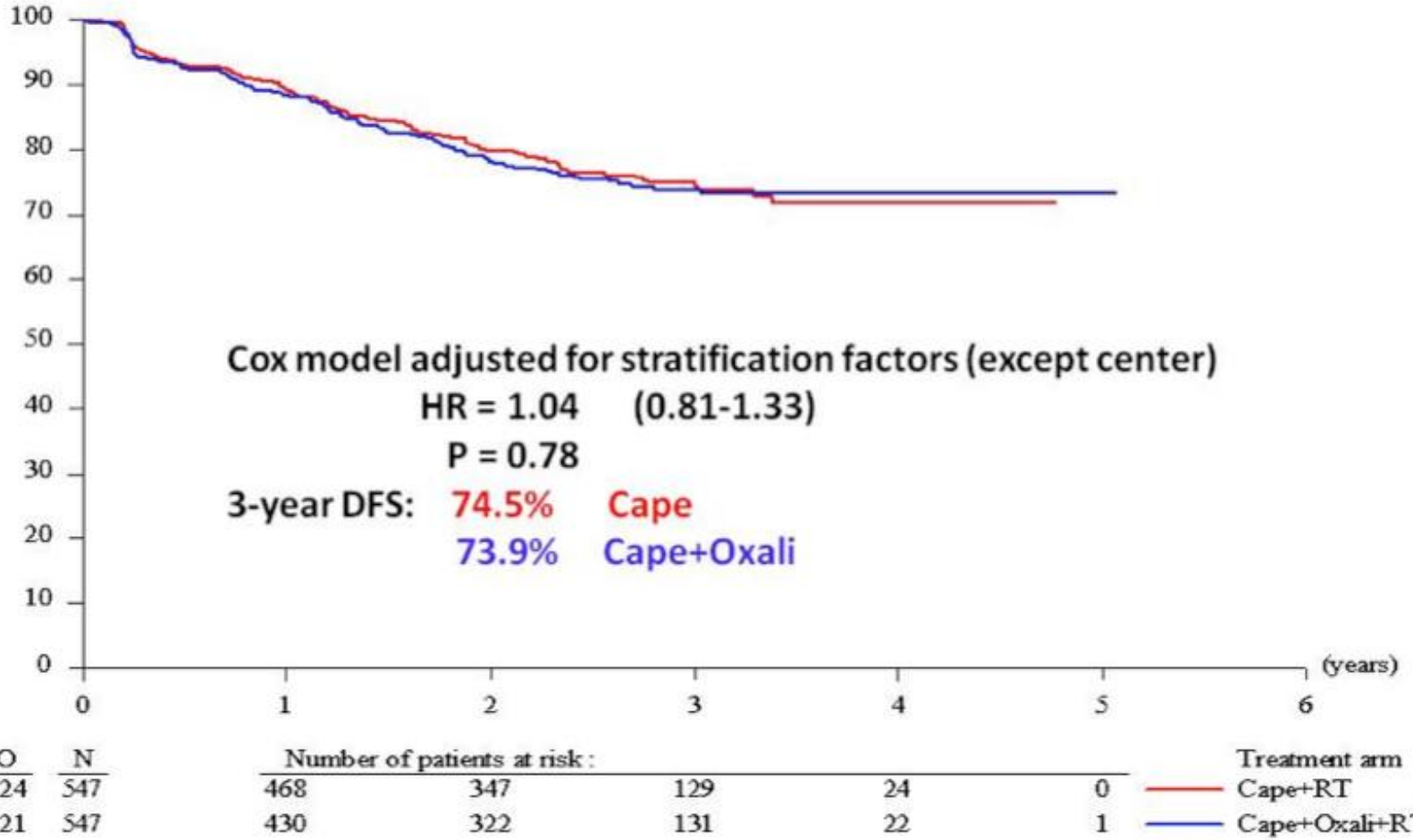
Phase III trials – Investigating

Trial	Eligibility	Fluoropyrimidine Platform
CAO/ARO/AIO-04	<12cm from anal verge T3/T4 cN0/N+ TRUS, CT and/or MRI	5FU 1000mg/2 X 5 days 1-5 + 29-33
NSABP R04 N=1606	<12cm; resectable stage II, III TRUS or MRI – CT if T4/ N1-2	PVI 5FU vs Capecitabine
FFCD N=598	Palpable; resectable; T3/4 N0-2; T2 distal anterior	Capecitabine in both arms
STAR – 01 N=747	Resectable stage II, III (c stage) <12cm from anal verge	PVI 5FU in both arms
PETTAC 6 N=1090	Stage II or III resectable or expected to become resectable <12cm from anal verge	Capecitabine in both arms

Endpoint	STAR-01	ACCORD 12/0405	CAO/ARO/ AIO-04	NSABP R-04	PETACC-6
PCR	16% both arms	14% vs 19%	12.8% vs 16.5% (p=0.038)	19% vs 21%	11.5% vs 13%
CRM	4% vs 7%	8% vs 13%	5% vs 6%	No data	2% vs 2%
Node + (stage III)	29% vs 26%	30% vs 26%	27% vs 26%	Not stated	27% vs 26%

Control arm in red

PETACC-6



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CAO/ARO/AIO-04 Trial

Primary Endpoint DFS **Median Follow-up: 50 months (range: 0.3-73)** **Time between randomisation and the first of the following events:**	**5-FU arm n=623**	**5FU/OX arm n=613**
Incomplete local resection (R2)	**10**	**5**
Locoregional recurrence after R0/R1 resection (+/- distant metastases)	**23 (3.7%)**	**12 (2%)**
Distant metastases / Progression	149	115
Death		
Overall	106	96
Cancer / treatment related/surgical mortality	69/4/6	54/7/4
Unrelated	26	31
Unknown	1	0
First events for DFS (total)	198	159

Prodige/ACCORD 12/0450 trial

Staging :- Evaluated by TRUS and/or MRI

N=598

Capecitabine 800mg/m2
45 Gy CRT

S

Centre policy

Oxaliaplatin 50mg/m2 x 5
Capecitabine 800mg/m2*
50.4Gy CRT

S

Centre policy

Primary end point- pCR 11% - 20% 85% power

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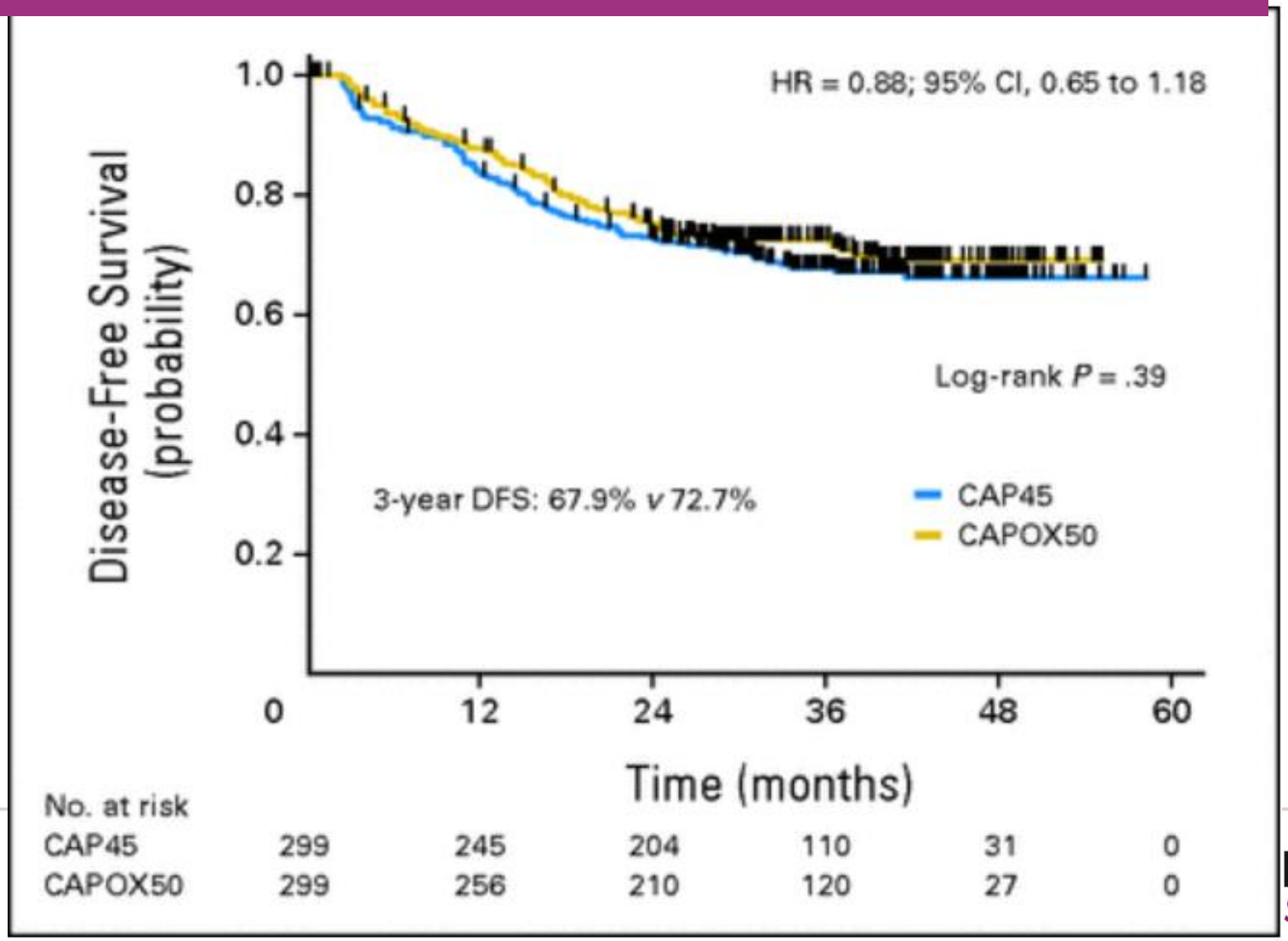
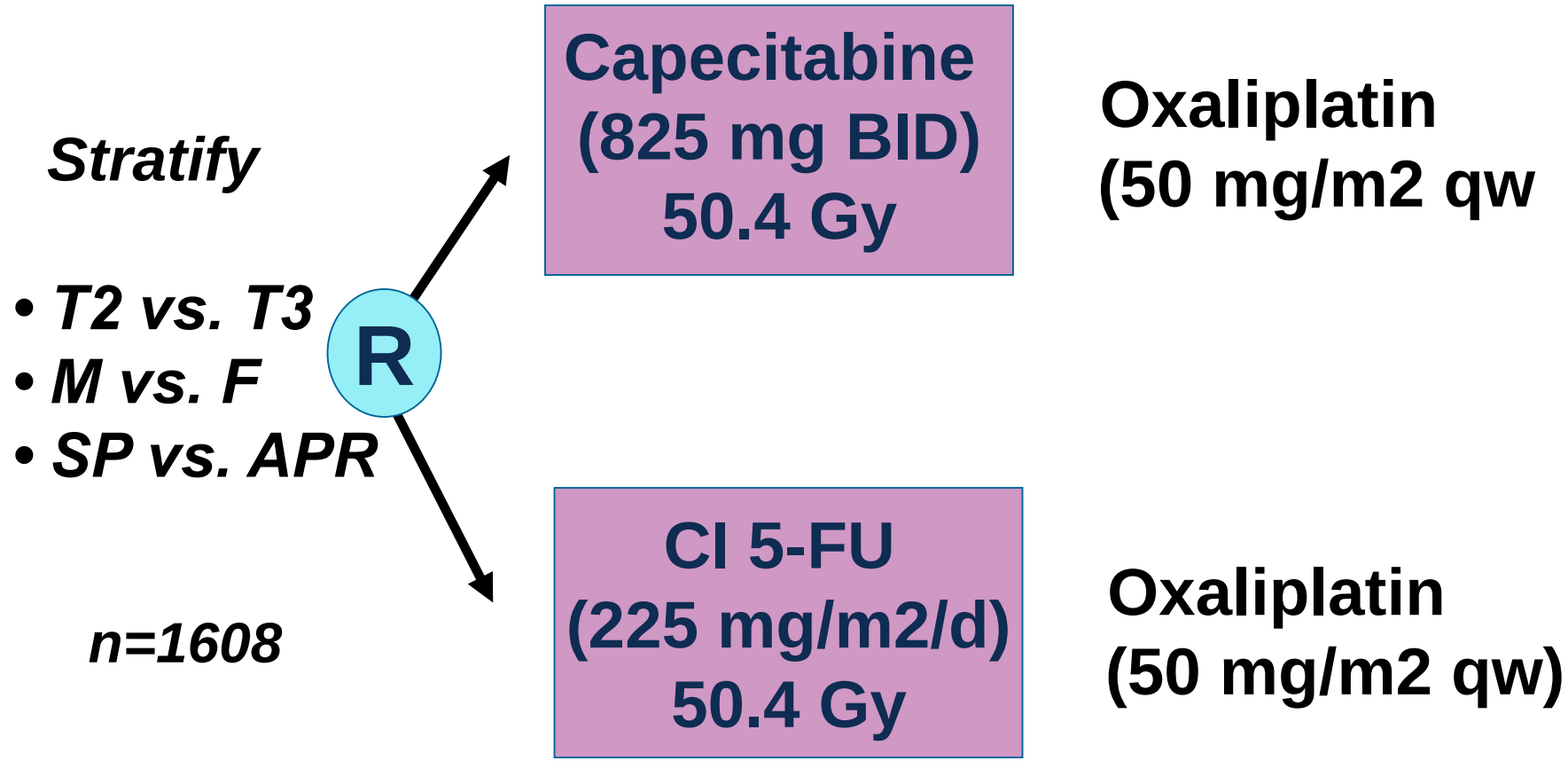
DFS: ACCORD 12/0405 PRODIGE 2

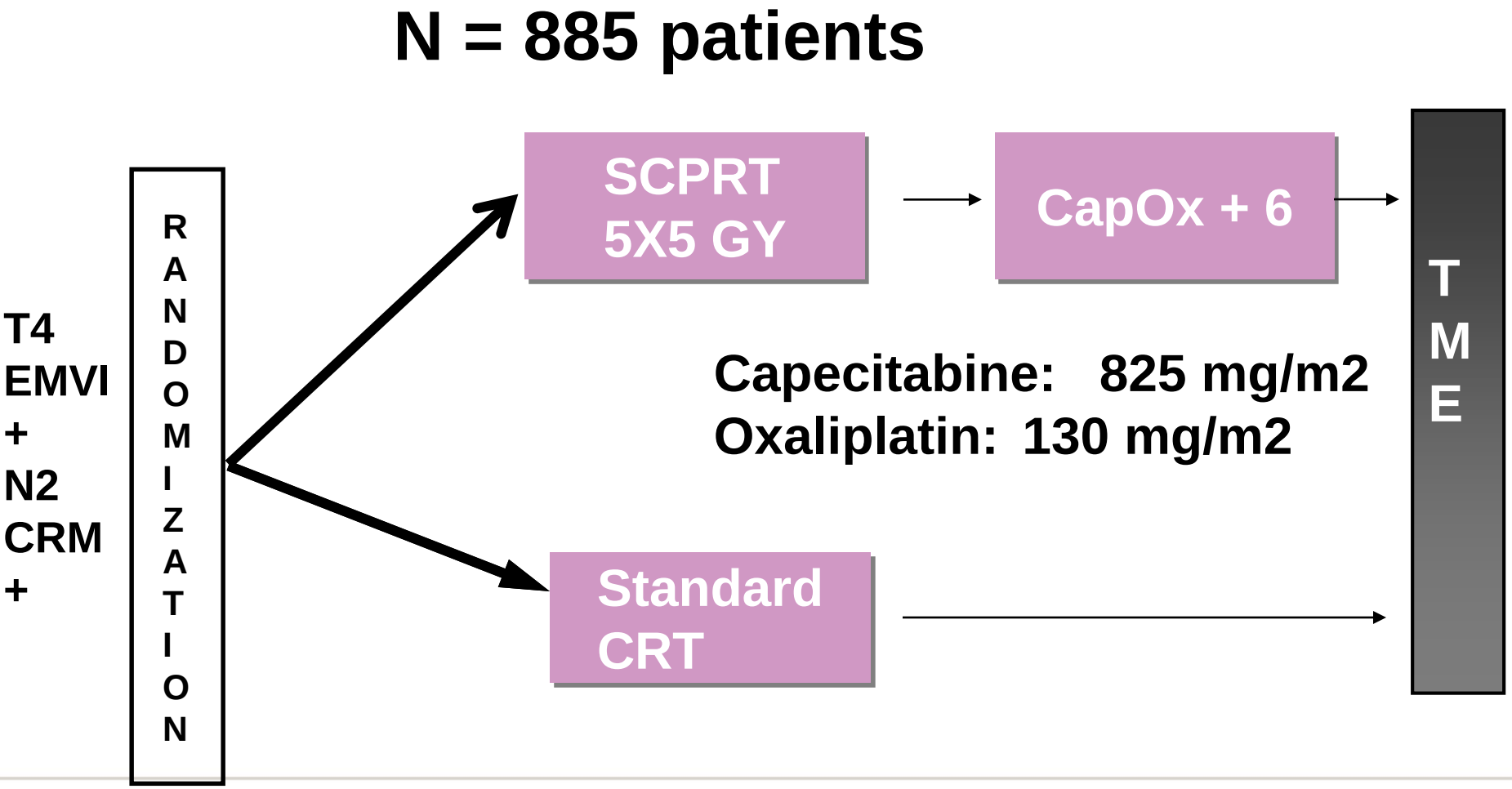


5-FU = Cape in Pre-op Rectal Cancer: NSABP R-04



NSABP R-04, Allegra et al; ASCO GI

RAPIDO Trial



Primary endpoint 3 year DFS

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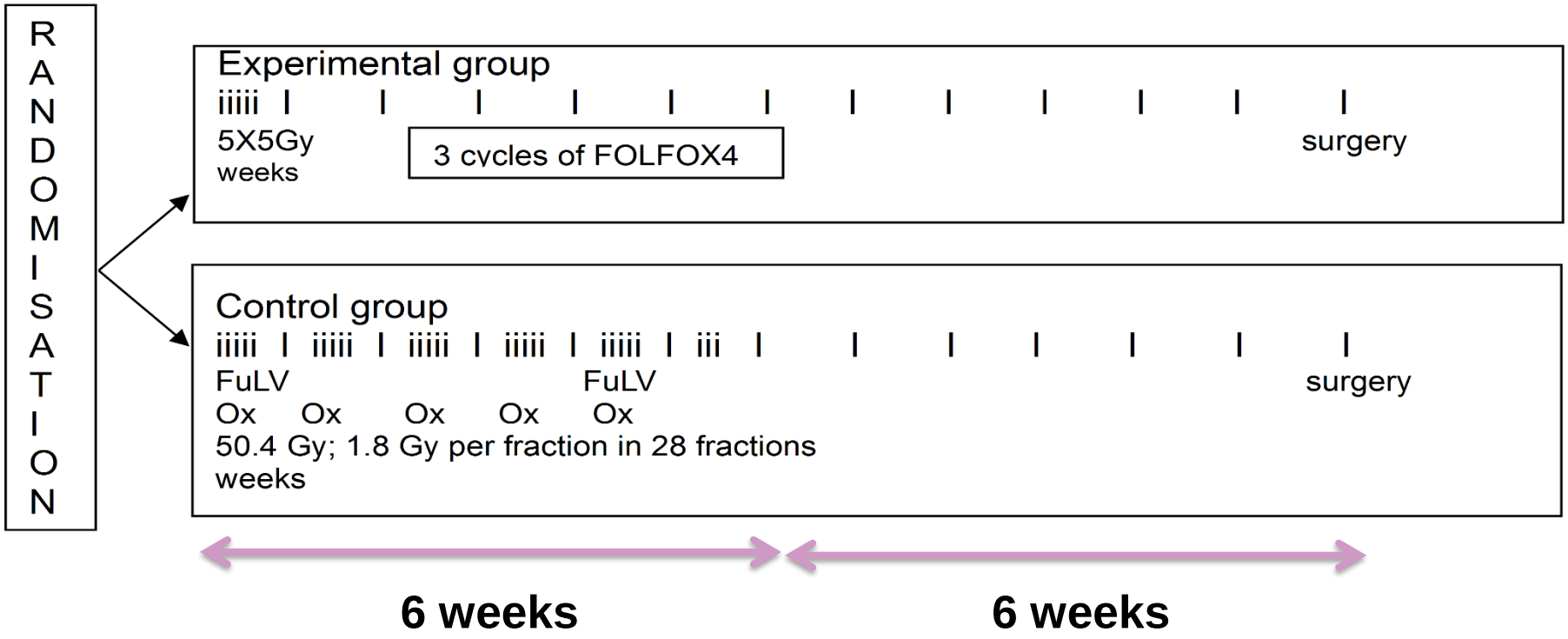
Polish-2: study design



N = 540, randomized 1:1

cT4 or fixed at DRE cT3

M0

ECOG 0-2

Treatment length and total oxaliplatin dose were balanced.

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Primary end-point [n=515]

R0 resection rates (surgery performed & pathologic R0 status):

77% for SCPRT with 3 cycles of chemotherapy

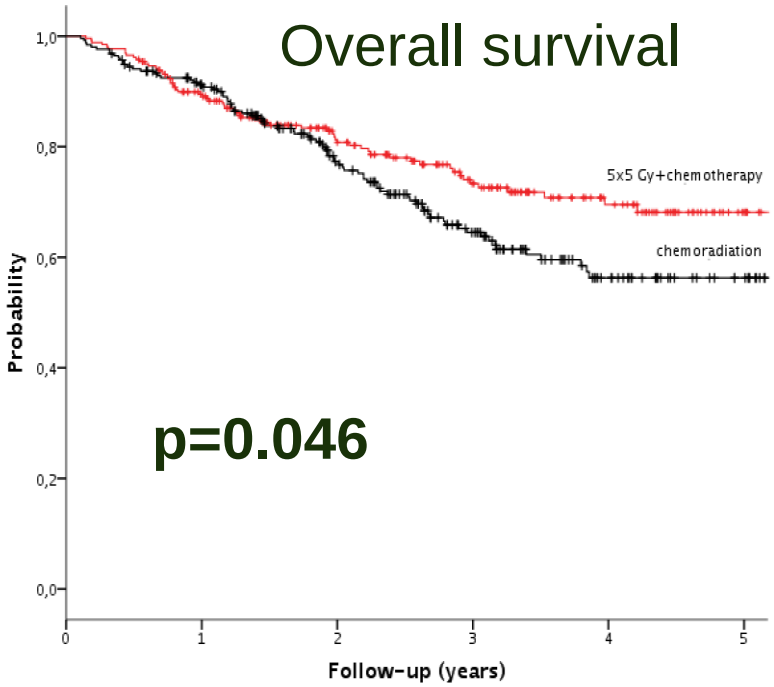
71% for CRT (control arm)

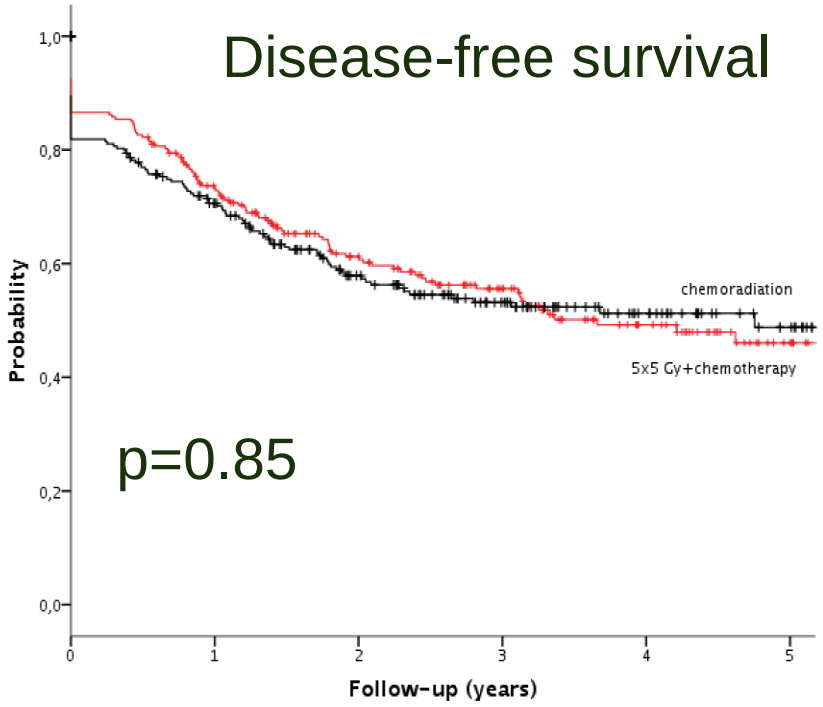
(p=0.081)

Secondary end-points

	SCRTx + FOLFOX4	CRTx	P value
Overall acute toxicity	**75%**	**83%**	**p= 0.006**
Grade III/IV toxicities	23%	21%	NS
pCR rate	16%	12%	p= 0.17

Polish-2: Secondary end-points





chemoradiation

short-course radiotherapy with consolidating chemotherapy

[median follow-up: 36 months]

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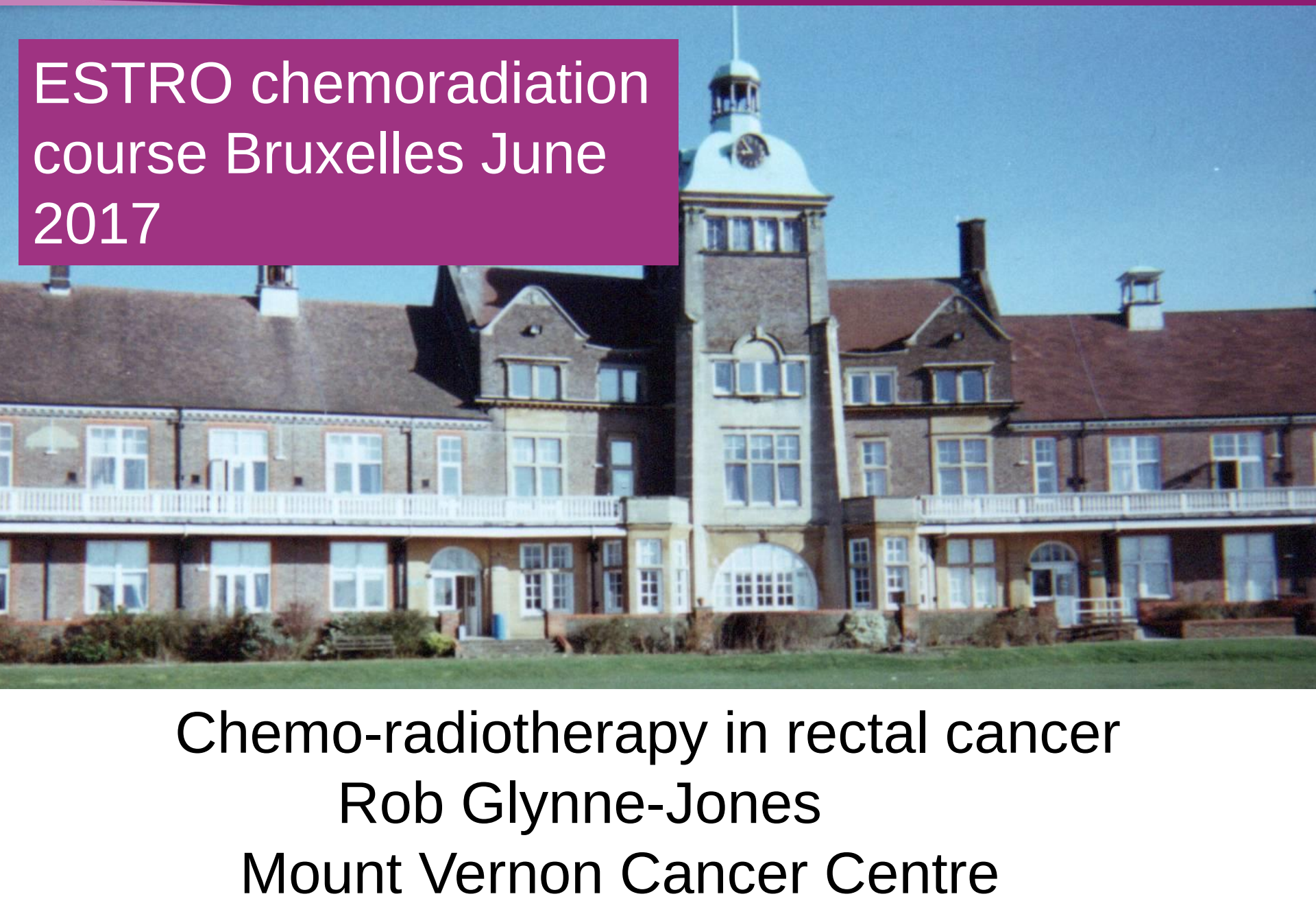
Conclusions

1. SCPRT = CRT in resectable cancer
2. cN+ probably inaccurate - most patients pN0
3. Radio-sensitizing 5FU-based CRT with sub therapeutic oxaliplatin ?
4. But minimal benefit for T3N0 on mets
5. Immunotherapy is coming


Thank you for listening



ESTRO chemoradiation course Bruxelles June 2017

Chemo-radiotherapy in rectal cancer

Rob Glynne-Jones
Mount Vernon Cancer Centre

My Disclosures: last 5 years

Speaker: Roche, Merck Serono, Sanofi Aventis, Pfizer, AIS

Advisory Boards: Roche, Merck Serono, Sanofi Aventis, Astra Zeneca, Servier, BMS

Funding to attend meetings: Roche, Merck Serono, Sanofi Aventis,

Research funding: Roche, Merck Serono, Sanofi Aventis

My Inherent Bias

De Ruysschers Principle of SER

(the interval between the start of treatment and the end of radiotherapy should be as short as possible)

De Ruysscher D, et al., Time between the first day of chemotherapy and the last day of chest radiation is the most important predictor of survival in limited-disease small-cell lung cancer. **J Clin Oncol 2006;24(7):1053-63**

Preoperative Options to influence outcomes in rectal cancer

Radiotherapy (5 x 5Gy)

Chemoradiation (with fluoropyrimidine)

Neoadjuvant chemotherapy +/- Biologicals (Immunotherapy)

Different combinations and sequences of the above (4 x 3 x 2 x 1= 24)

In different countries

Glimelius
Radiother
Oncol 2017

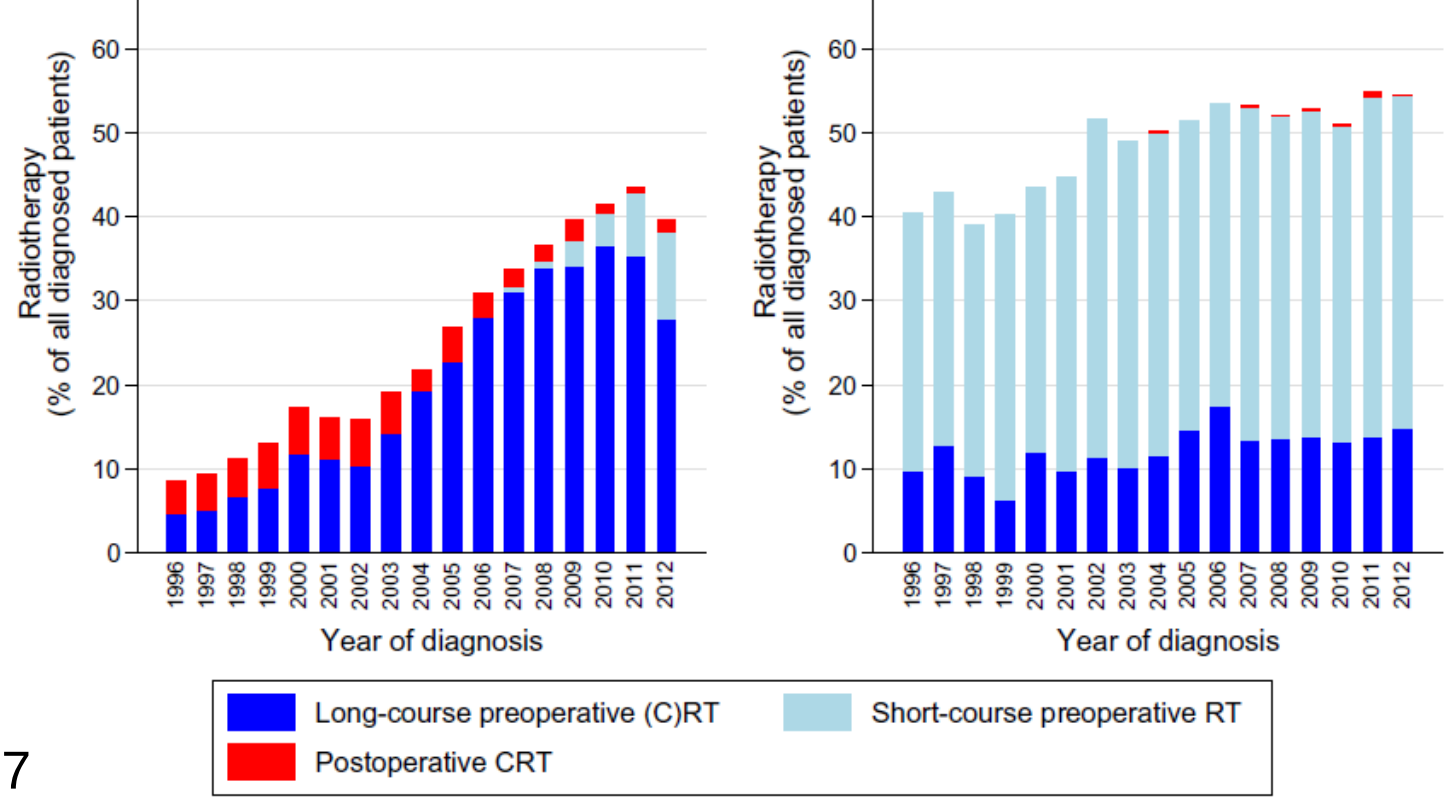
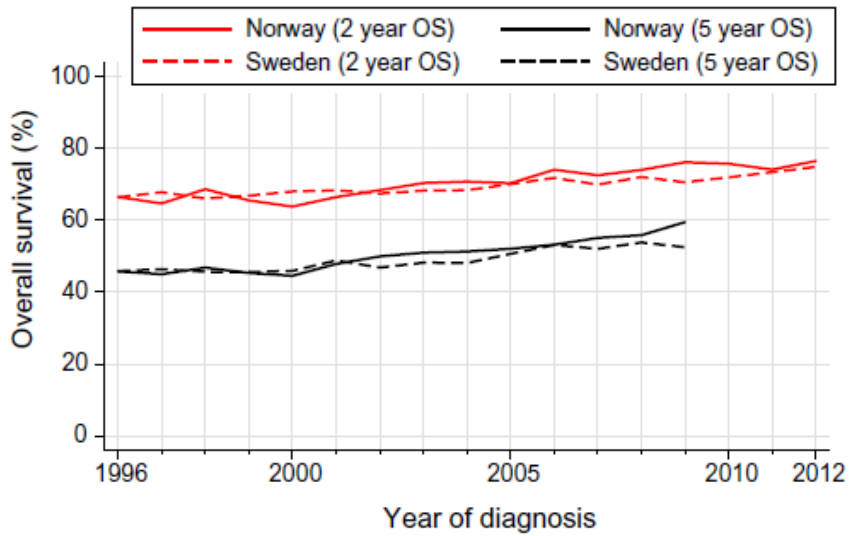
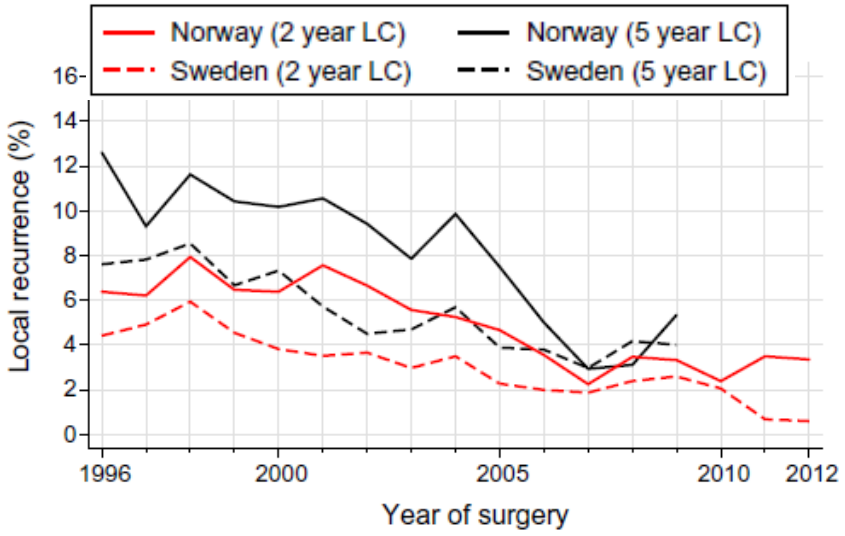


Fig. 2. Radiotherapy (RT) for all patients diagnosed with rectal cancer in Sweden and Norway from 1996 to 2012.





Relevant Endpoints in rectal cancer

Local recurrence

Disease-free survival

Overall survival

Sphincter sparing

Late effects

Which of the following are important to you?

Issue	Score
Overall survival?	
Avoidance of stoma?	
Avoidance of local recurrence?	
Complete Response to CRT ?	
Preservation of function?	
Toxicity/QOL?	

Please discuss with your neighbour for 2 minutes

Male Maintenance manager for Network Rail

40 years old - recently married for second time

Fit/No co-morbidity

Rectal bleeding

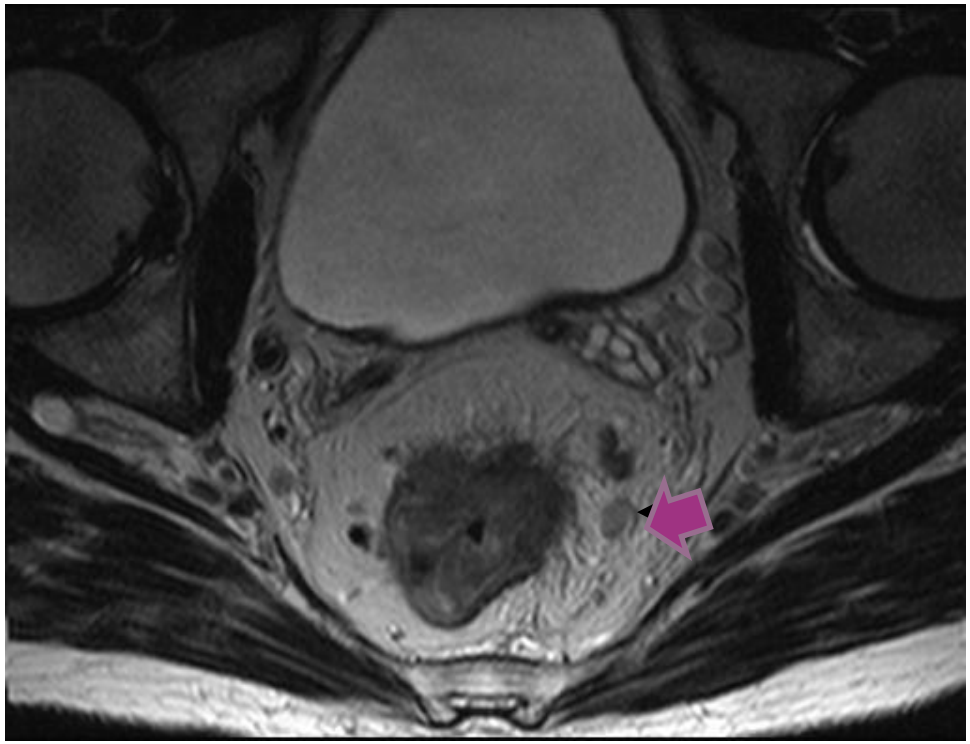
CT no metastases

CEA 8

MRI cT3 N1b EMVI+

Nodal Assessment: TNM

- **Nodal staging based on number of involved nodes**
  - N0: No nodes
  - N1: 1-3 regional nodes
    - N1a 1 node
    - N1b 2-3 nodes
    - N1c tumour deposit
  - N2: 4 or more nodes
    - N2a 4-6 nodes
    - N2b ≥7 nodes



Mesorectal node

MRI and CT

cT3/cT4a mid/upper rectum

N1B (2 nodes)

No threat to CRM (at least 6mm)

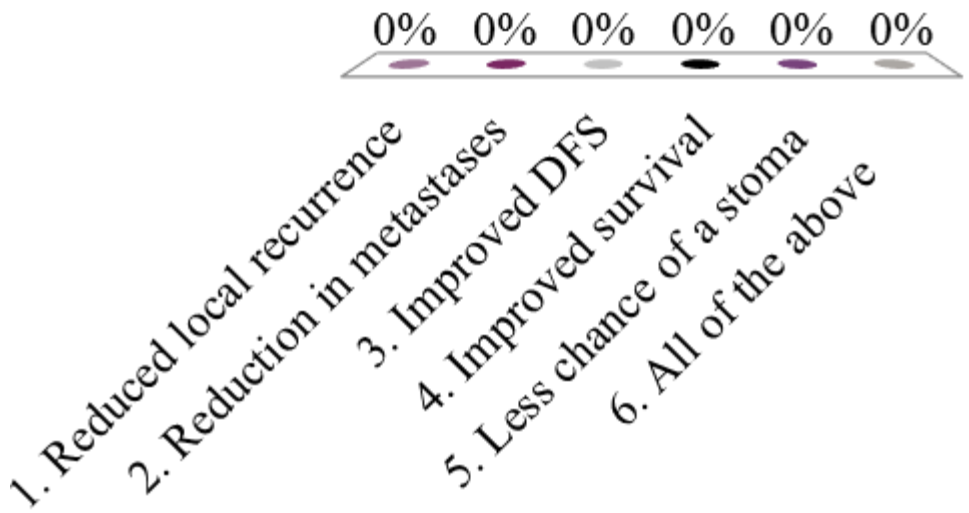
EMVI +

M0

Imagine you are in the MDT and dicsuss with your neighbour

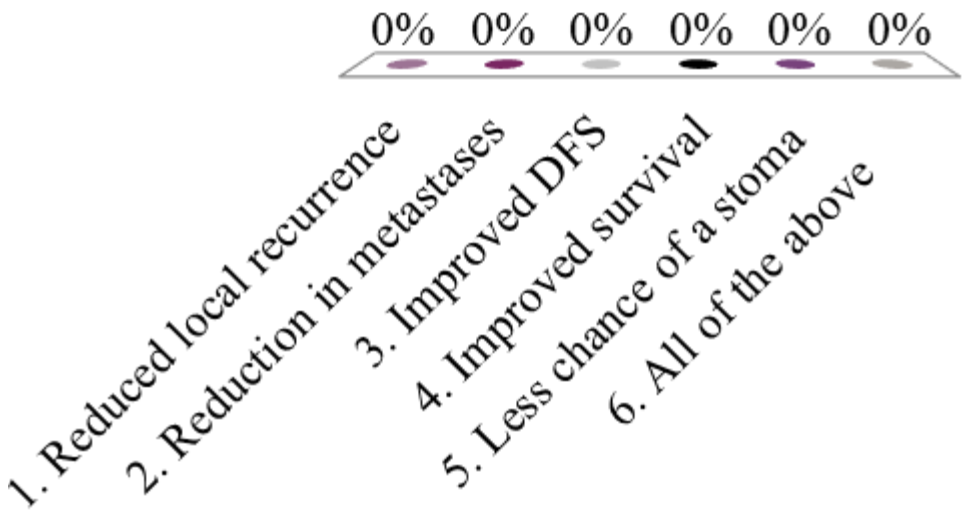
What are the advantages for this patient of RT/CRT?

1. Reduced local recurrence
2. Reduction in metastases
3. Improved DFS
4. Improved survival
5. Less chance of a stoma
6. All of the above



What are the advantages for this patient of oxaliplatin based chemo?

1. Reduced local recurrence
2. Reduction in metastases
3. Improved DFS
4. Improved survival
5. Less chance of a stoma
6. All of the above



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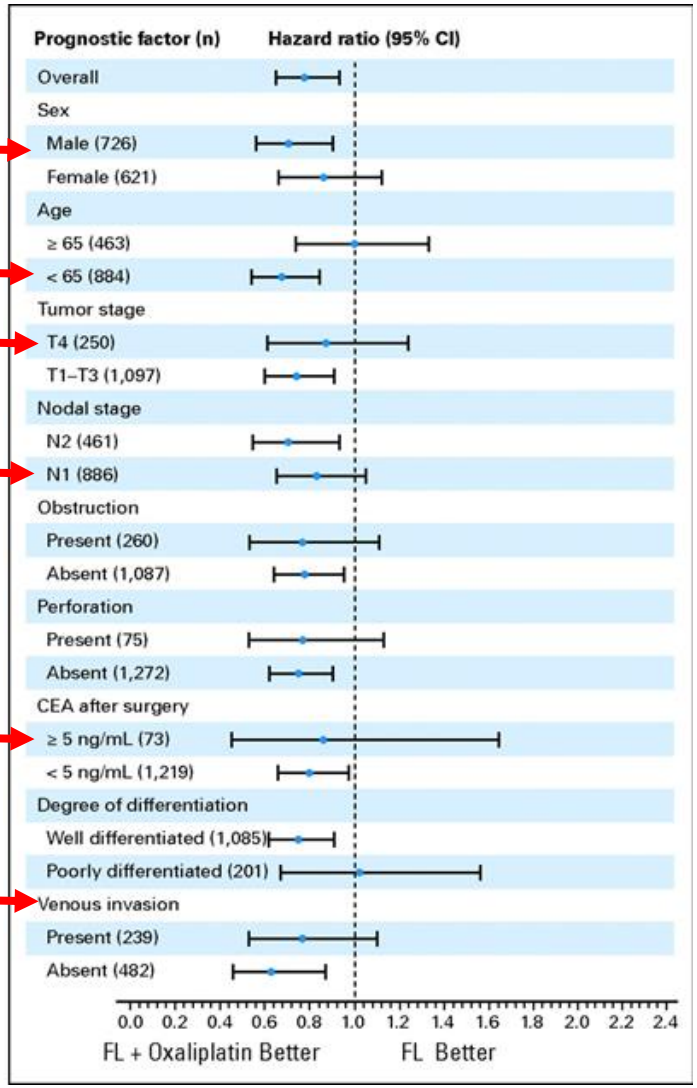
Forrest Plot of factors for node positive patients

MOSAIC Trial Benefit of Oxaliplatin

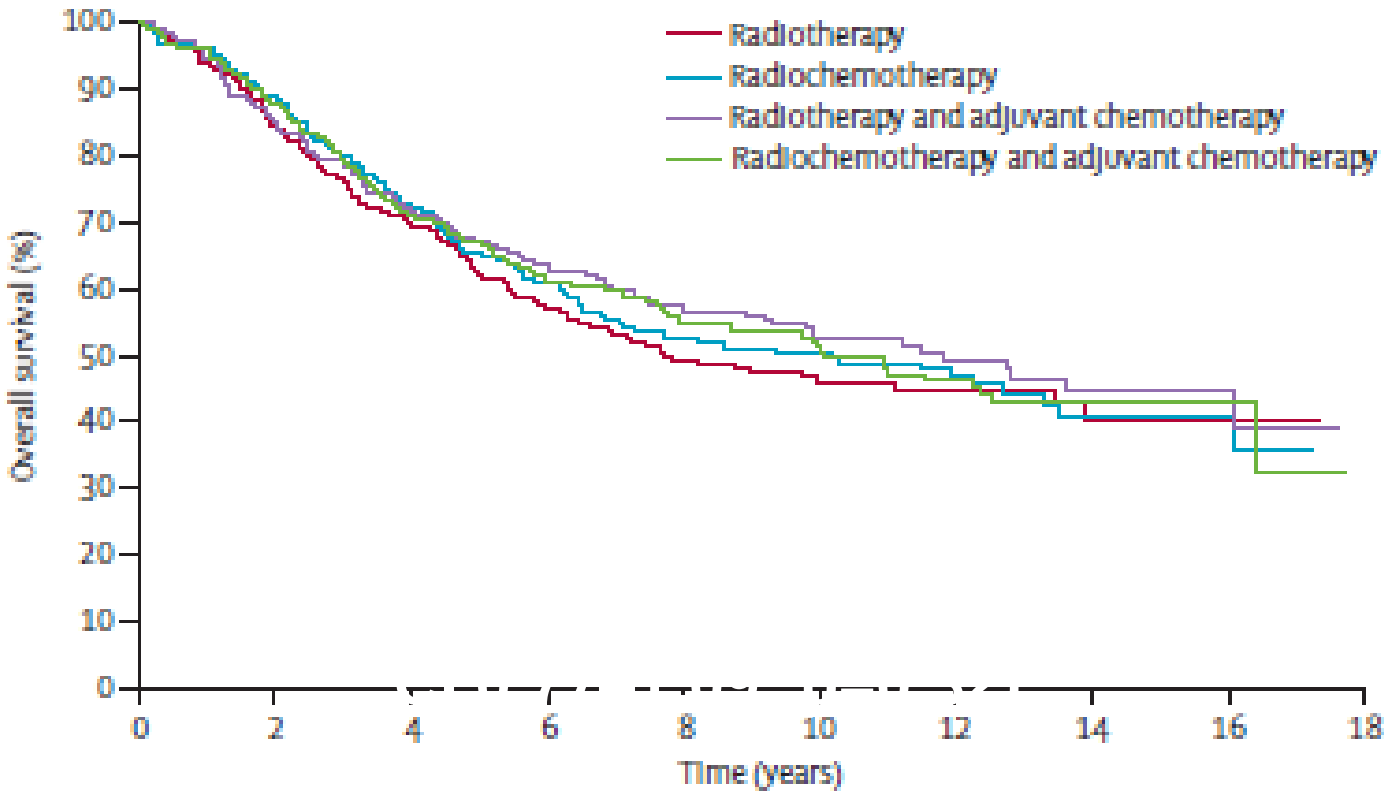


Male
Age < 65
T3/4a
N1
CEA
EMVI+

We have never performed a study of CRT versus control

so we don’t know the results of CRT ‘per se’ compared to surgery alone

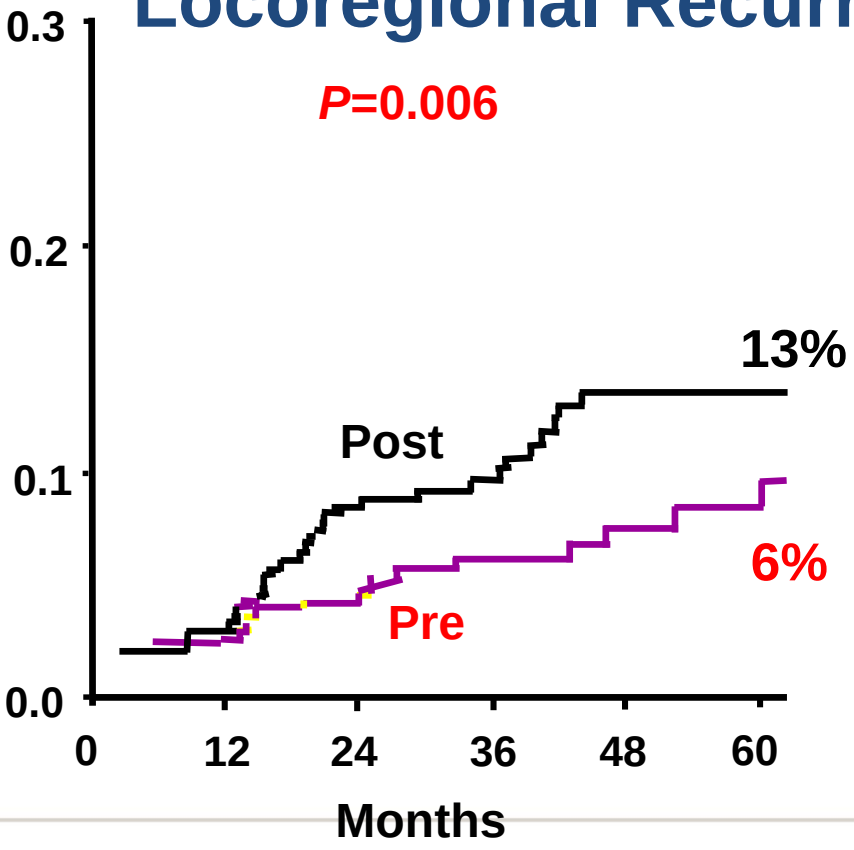
EORTC 22921 – Overall Survival



Number at risk									
Radiotherapy	252	208	165	129	98	62	32	15	5
Radiochemotherapy	253	223	173	135	96	66	41	19	9
Radiotherapy and adjuvant chemotherapy	253	212	171	140	102	69	42	18	8
Radiochemotherapy and adjuvant chemotherapy	253	221	174	143	108	77	44	18	4

Pre- vs post-operative chemoradiation CAO/ARO/AIO-94

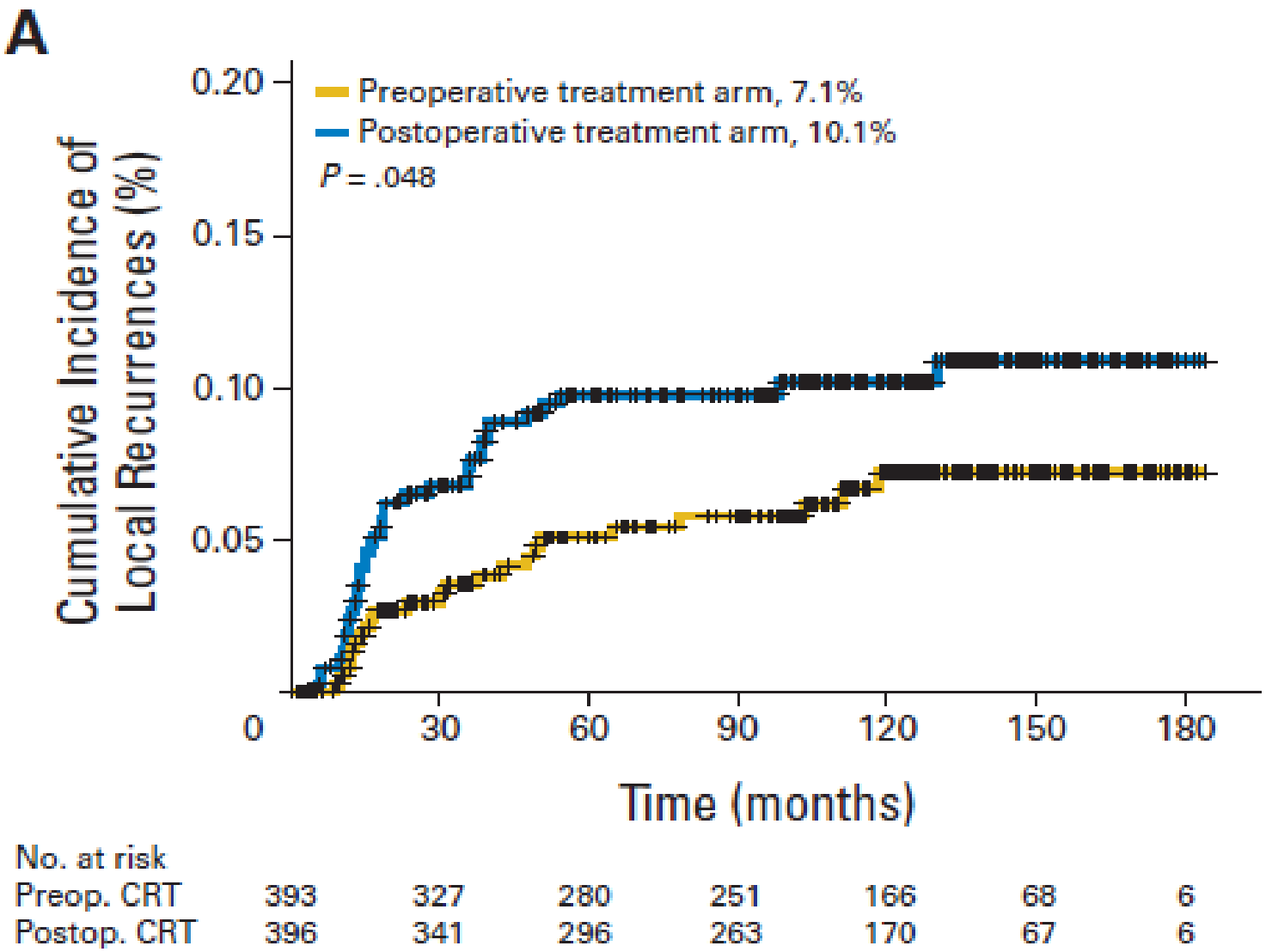
Locoregional Recurrences



Acute G3/4 adverse events
27% vs 40% (p=0.001)

Long-term G3/4 adverse events
14% vs 24% (p=0.01)

Sauer R. et al., N Engl J Med 2004;351: 1731-39



Long-term data on LOC REC from German study – 5/22 local recurrences ie 23% after 5 years (not like CR07)

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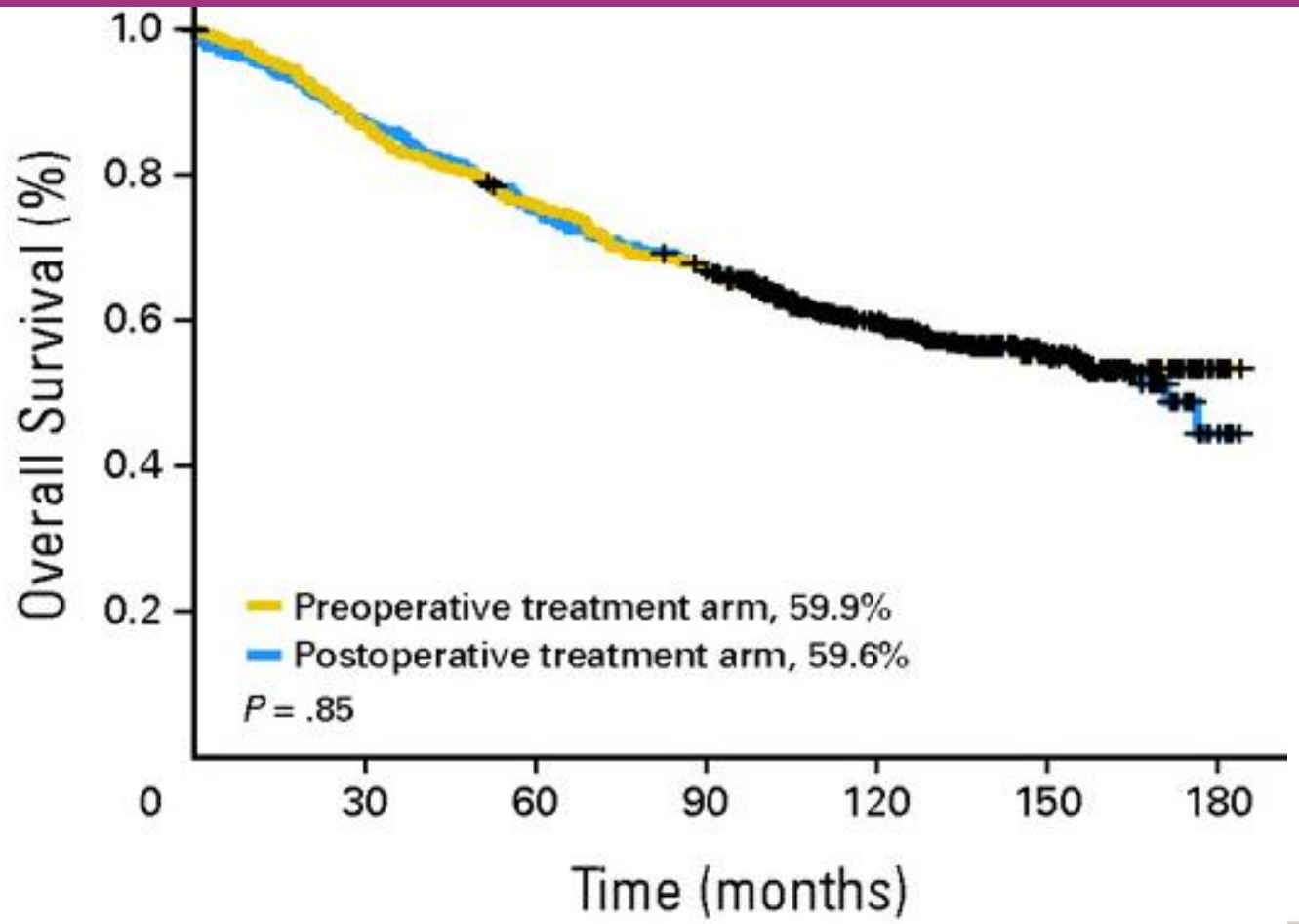
Pre- vs post-operative chemoradiation CAO/ARO/AIO-94



No. at risk							
Preop. CRT	404	351	305	268	174	67	6
Postop. CRT	395	342	295	262	172	70	6

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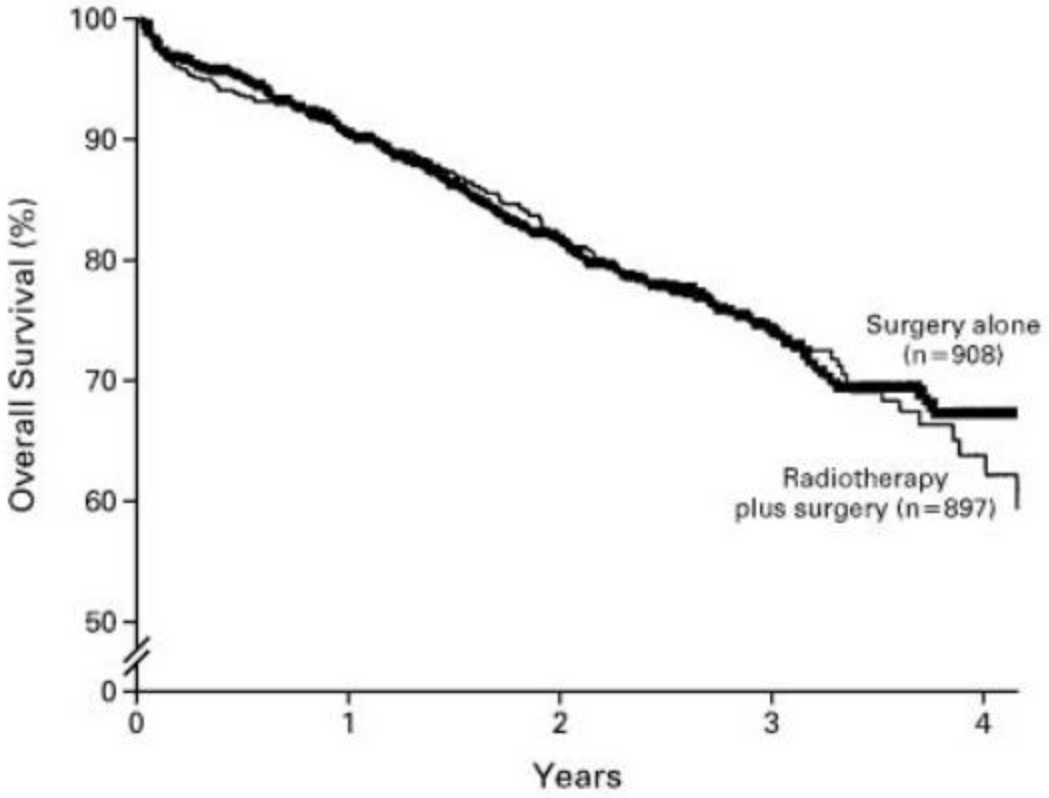
Dutch TME trial Kapiteijn NEJM 2001



No. at Risk					
Radiotherapy plus surgery	897	741	435	192	41
Surgery alone	908	744	454	207	42

At two years, overall survival was 82.0 percent in the group assigned to radiotherapy and surgery and 81.8 percent in the group assigned to surgery alone (P=0.84).

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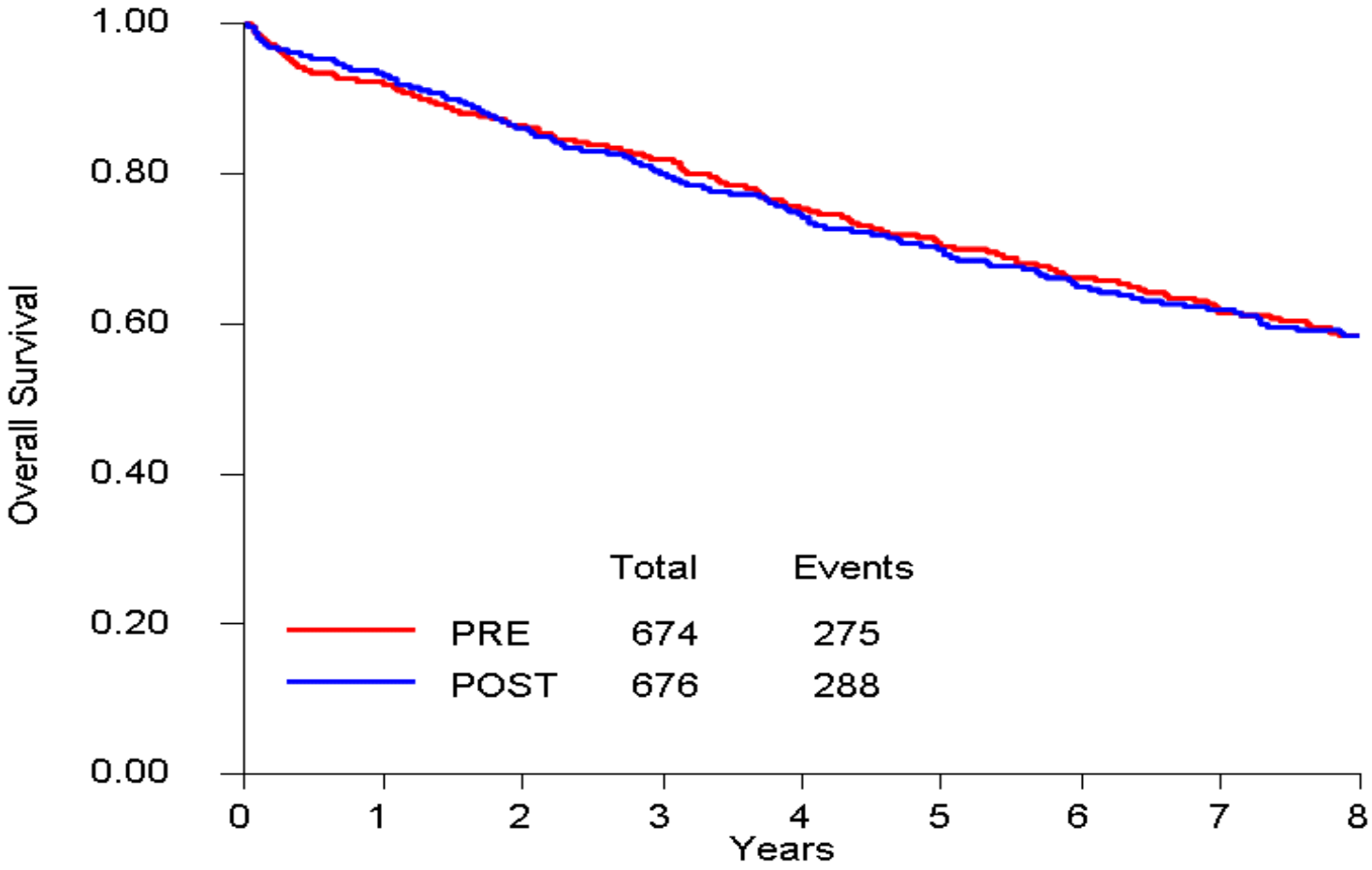
CR07 Overall Survival



Number at risk

PRE	674	611	571	539	490	445	359	271	204
POST	676	624	577	530	487	434	356	274	208

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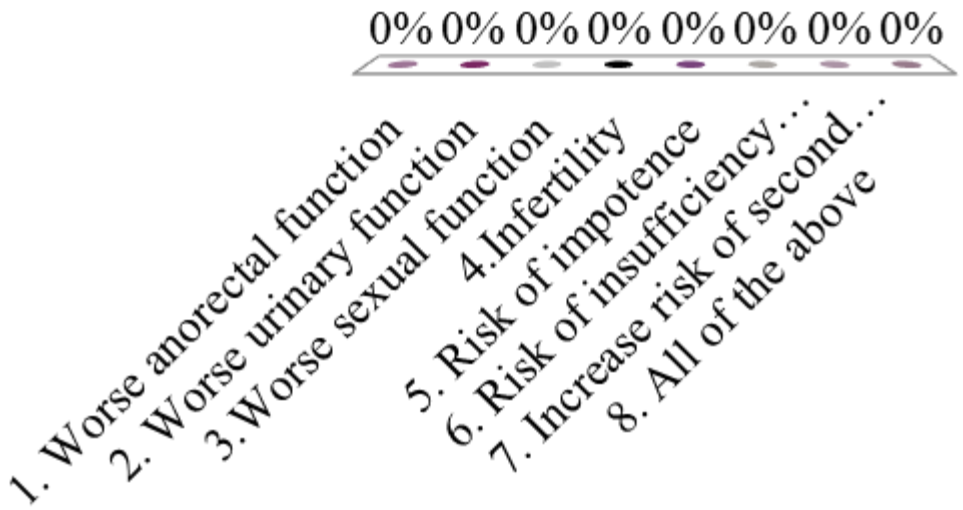
What are the dis-advantages for this patient?

1. Worse anorectal function
2. Worse urinary function
3. Worse sexual function
4. Infertility
5. Risk of impotence
6. Risk of insufficiency fractures
7. Increase risk of second malignancy
8. All of the above



Current Wisdom

- Preoperative CRT better than postop
- Improves Local recurrence but not DFS or OS
- If CRM threatened on MRI needs response so CRT
- Low rectal cancers (below the levators) almost always have threat to CRM
- T1/T2N0 mid/upper rectum don't usually need RT or CRT unless to avoid radical surgery
- CRT helps preserve sphincters

Do you treat?

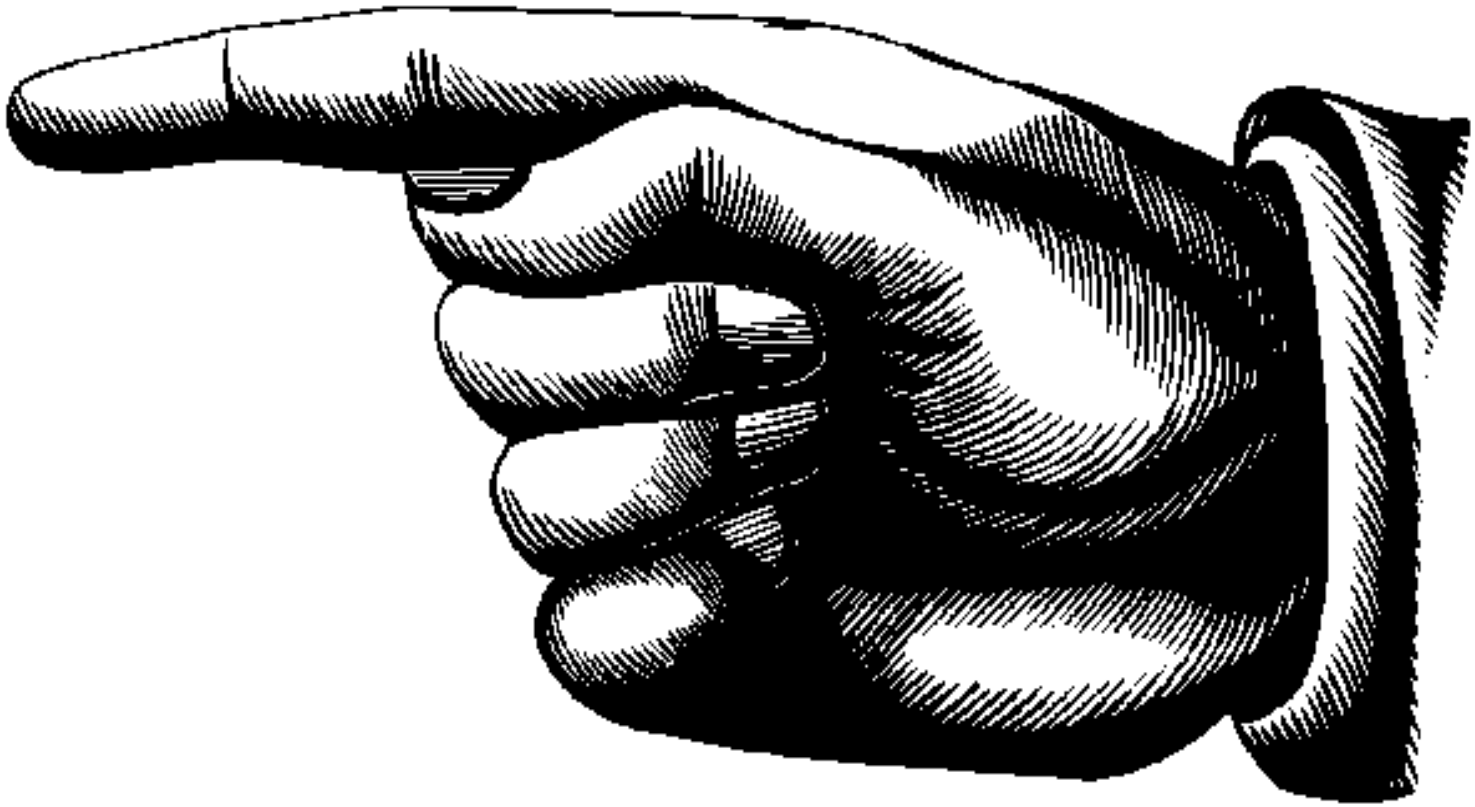
Low risk Dukes B colon cancer patients with adjuvant chemo?

High Risk Dukes C colon cancer with adjuvant chemo?

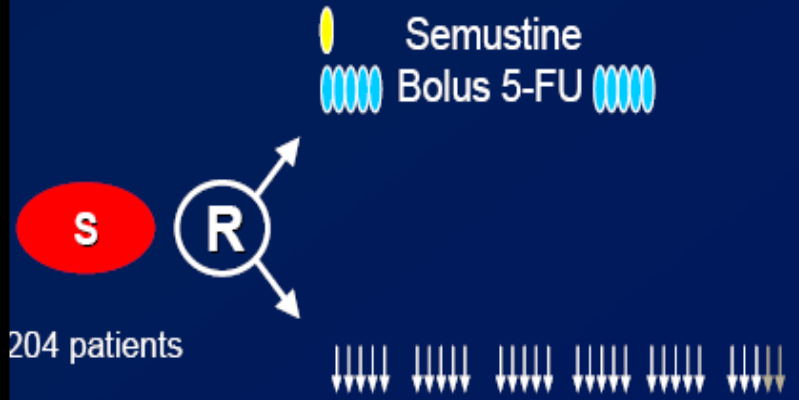
FOLFOX or XELOX?

When do you want to start?

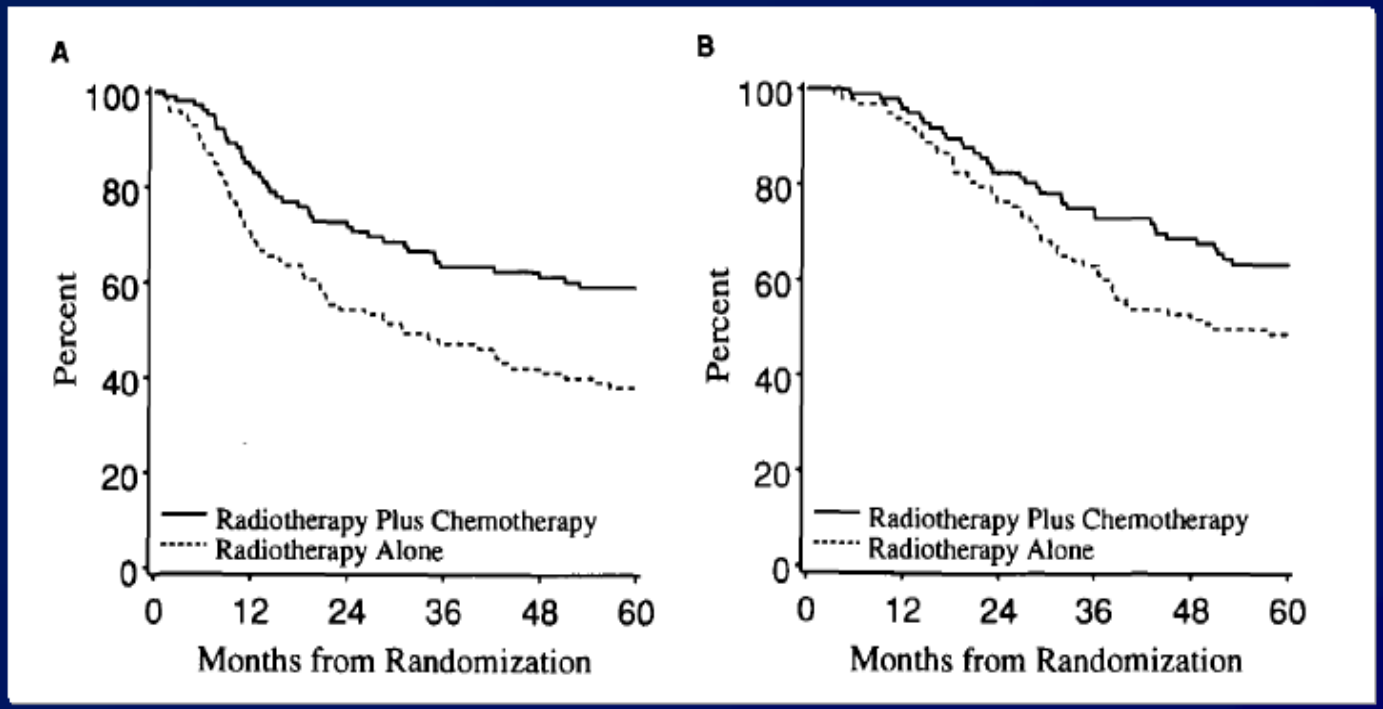
Historical staging



NCCTG/Mayo 794751



68% N+

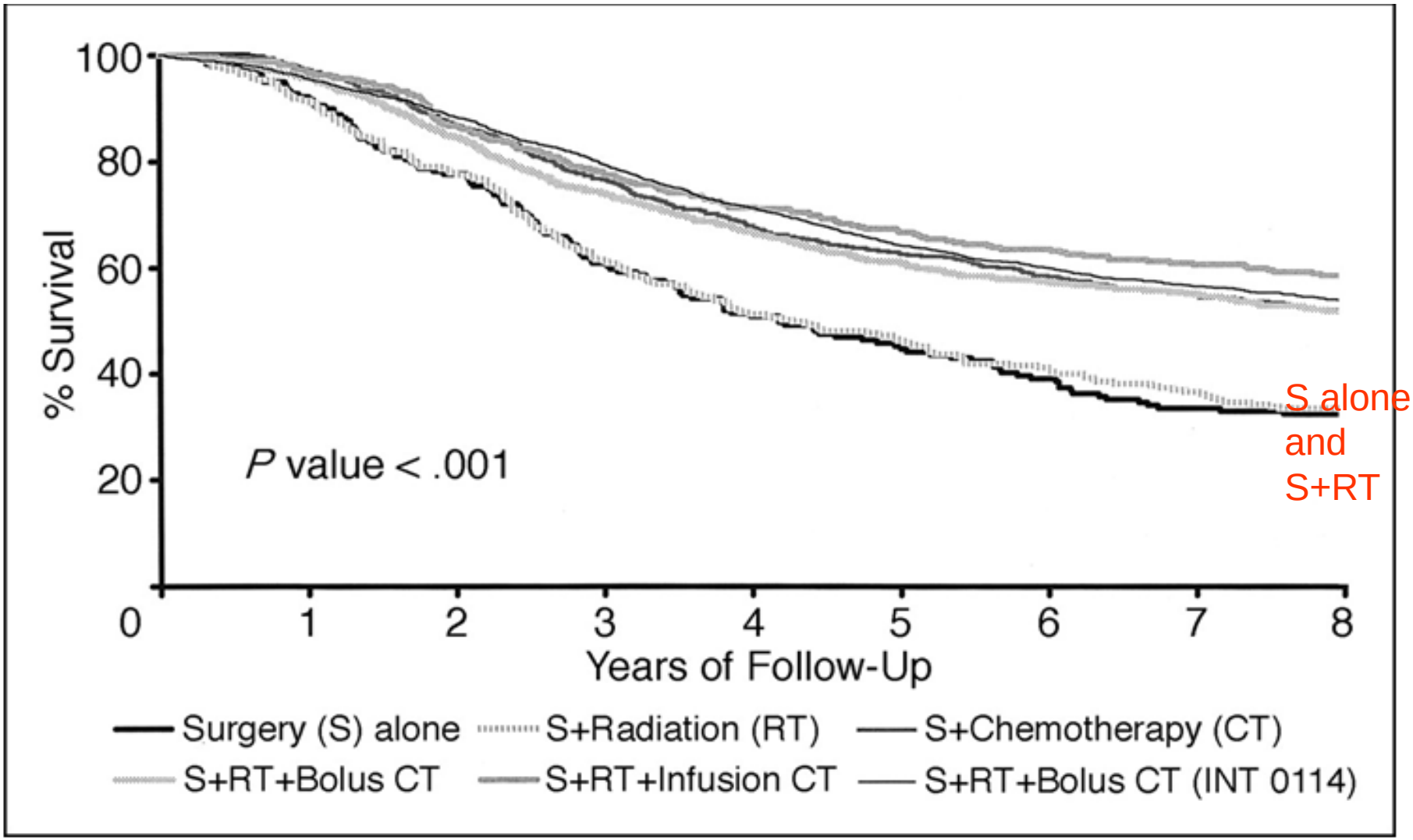


Disease-free survival

Overall survival

Krook et al. N Eng J Me 1991

Impact on overall survival of 6 methods of treatment in rectal cancer pooled analysis



S alone and S+RT

Gunderson, L. L. et al. J Clin Oncol; 22:1785-1796 2004

Evidence Base: Sphincter sparing

- Meta-analysis Bujko 2006

  No evidence preop RT/CTRT achieves sphincter sparing surgery
- Cochrane Review Wong 2007

  No evidence preop RT/CTRT achieves sphincter sparing surgery
- Polish and TROG 01.04 phase III trials

  No evidence preop CTRT achieves sphincter sparing surgery

Although……

Discounts

- Local excision after CRT
- Organ sparing procedures eg Habr Gama

Sphincter sparing CAO/ARO/AIO-94

Table 4. Rates of Sphincter-Sparing Surgery in 194 Patients Determined by the Surgeon before Randomization to Require Abdominoperineal Resection, According to Actual Treatment Given.

Variable	Preoperative Chemoradiotherapy (N=415)	Postoperative Chemoradiotherapy (N=384)	P Value
Abdominoperineal resection deemed necessary — no. (%)	116 (28)	78 (20)	
Sphincter-preserving surgery performed — no./total no. (%)	45/116 (39)	15/78 (19)	0.004

Sauer 2004 NEJM NB Zelen randomisation

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No difference in Survival

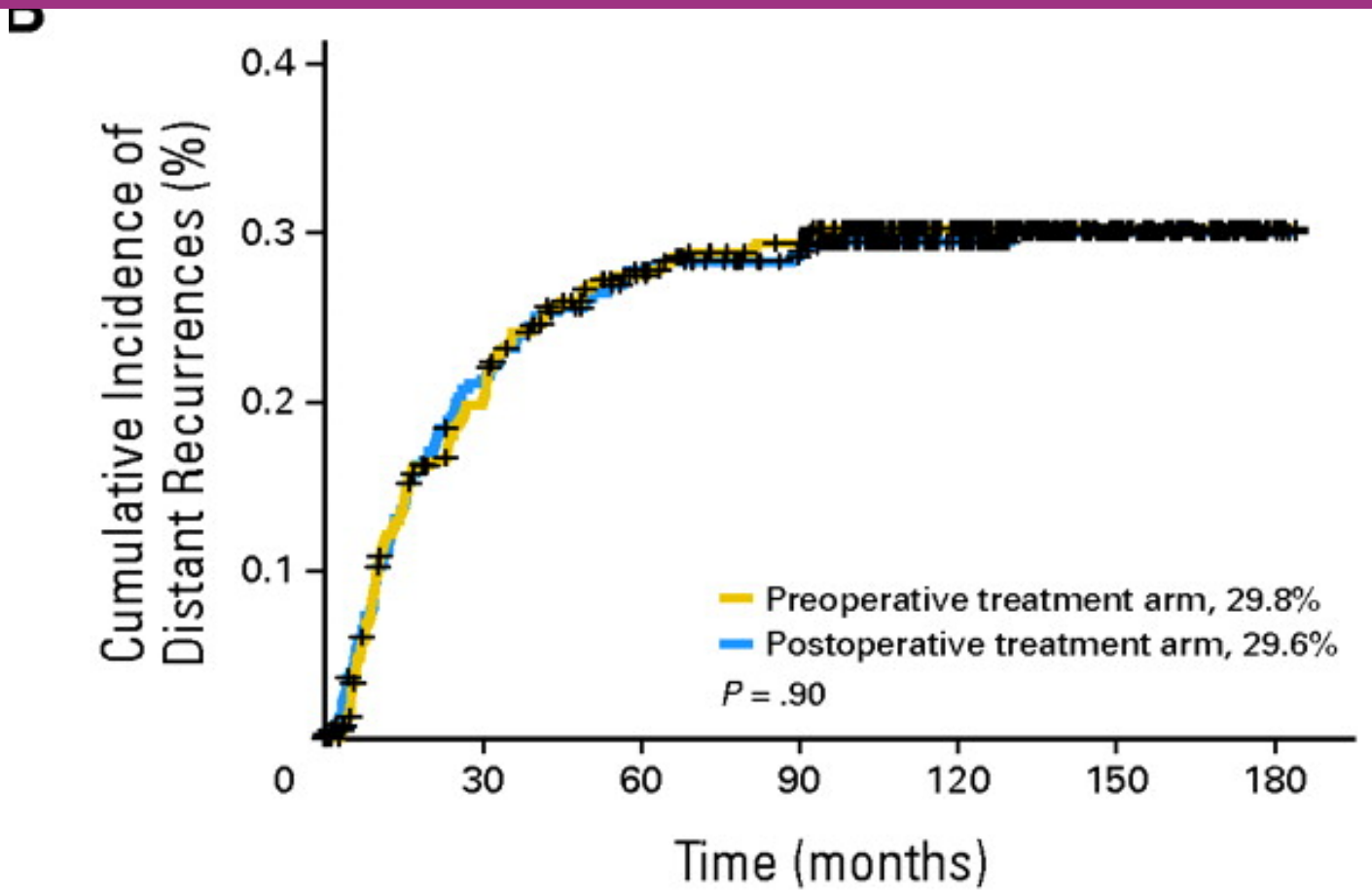
Pre versus post-op CRT

SCPRT versus CRT

RT versus CRT

SCPRT versus selective postop CRT

Pre- vs post-operative chemoradiation CAO/ARO/AIO-94



No. at risk							
Preop. CRT	393	295	262	241	158	60	5
Postop. CRT	396	310	267	246	162	63	6

So why have post-op CRT studies shown an improvement in survival

whereas preop CRT has not?

Possible reasons

Pathological stratification means we were comparing like with like

Selection of more advanced tumours (68% N+ in NCCTG) with more risk

Better surgery nowadays (TME)

Control arm is more active

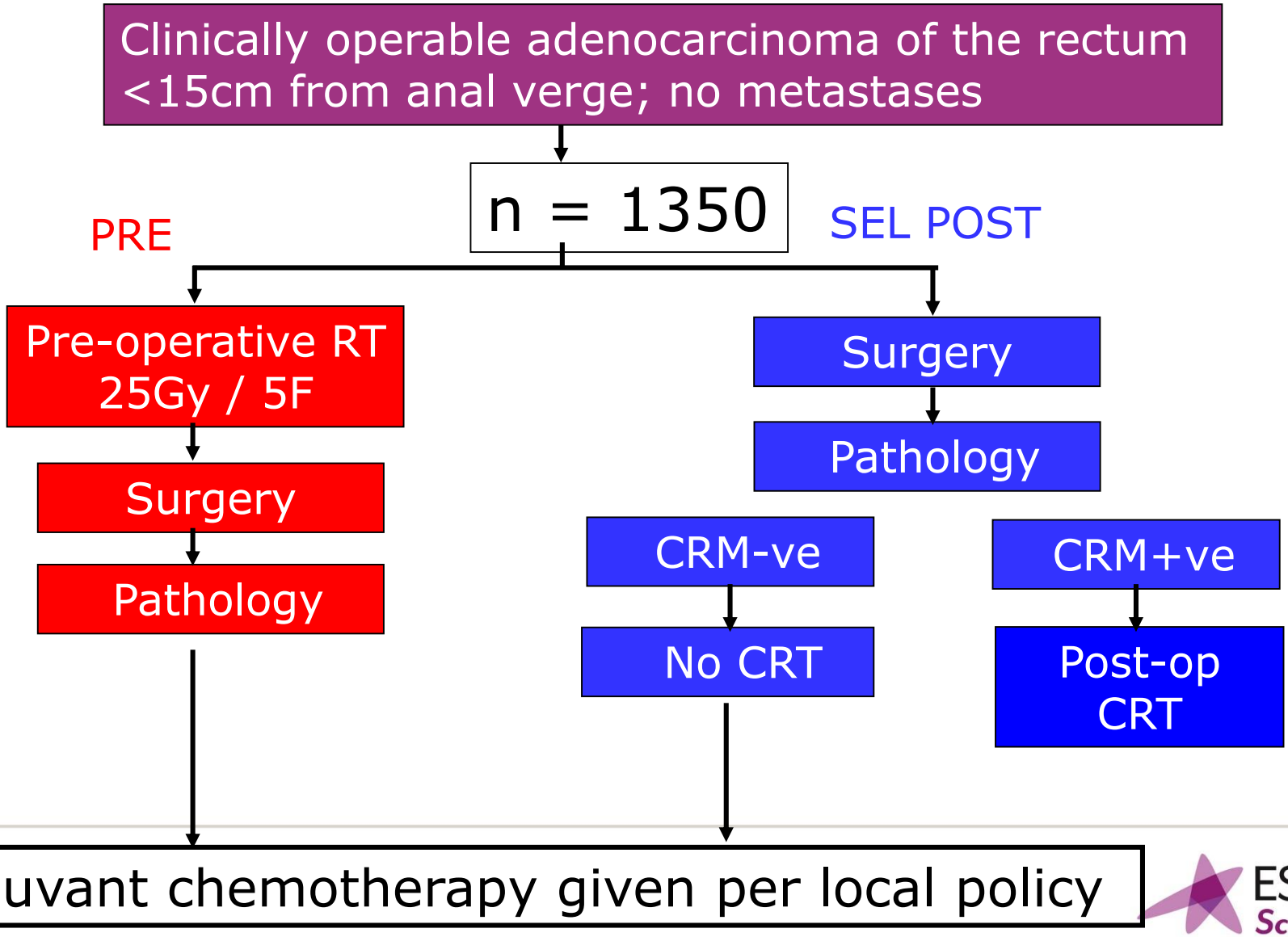
Rectal cancer is a heterogenous/ complex entity – outcomes may depend on

- Upper/middle/lower
- Anterior/ posterior
- Male/female
- Resectability/CRM
- T stage
- N stage
- EMVI/LVI/PNI
- Extranodal deposits

Quality of surgery is the biggest factor in Local recurrence –not whether or not you have radiotherapy

Quality of surgery can be viewed and scored

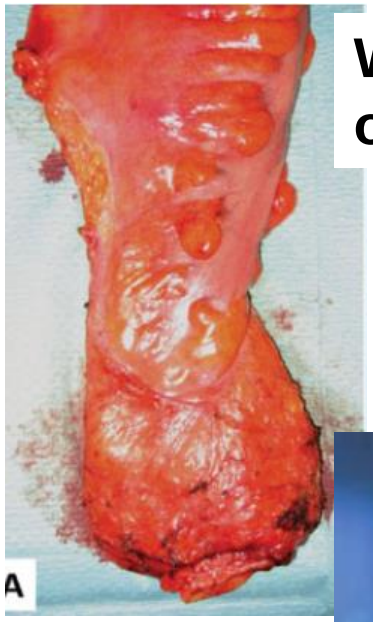
MRC CR07 NCIC C016 trial

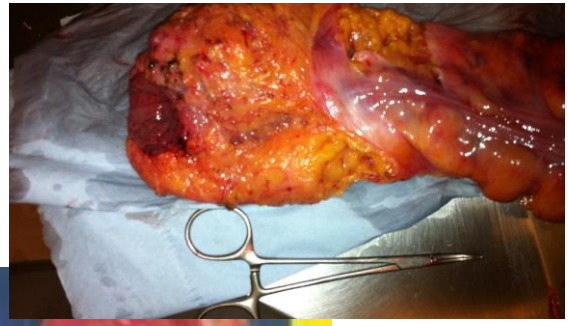


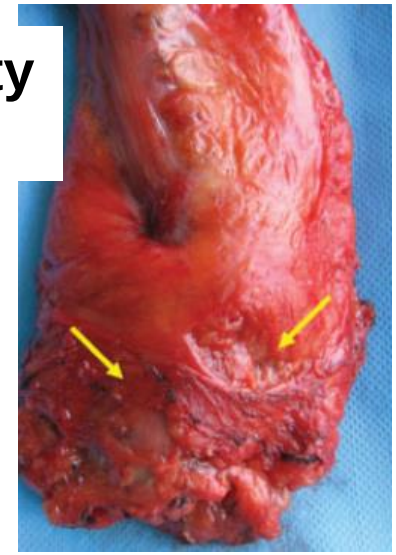
Scoring the Quality of the

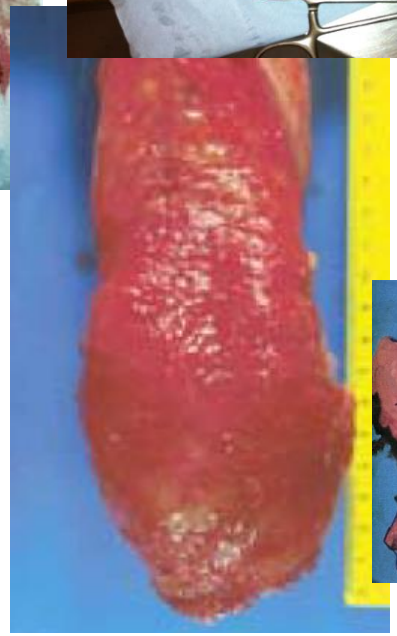
	Mesorectum	Defects	Coning	MRF
Complete	Intact, smooth	Not deeper than 5 mm	None	Smooth, regular
Nearly complete	Moderate bulk, irregular	No visible muscularis propria	Moderate	Irregular
Incomplete	Little bulk	Down to muscularis propria	Moderate–marked	Irregular

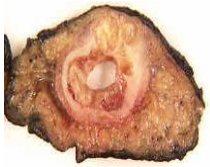
We can judge the quality of the Surgery

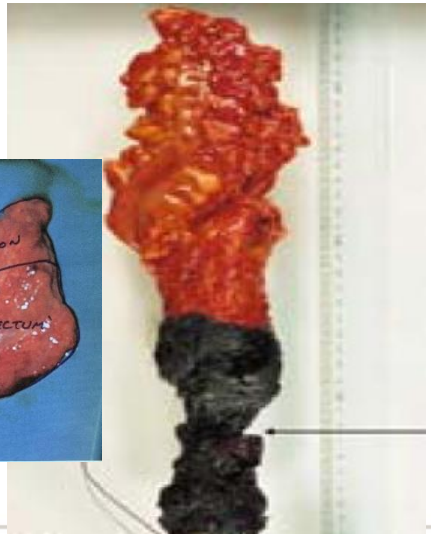


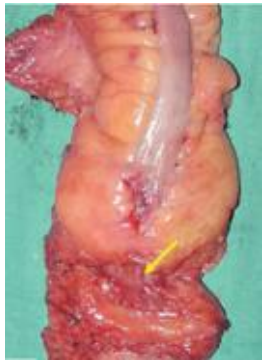


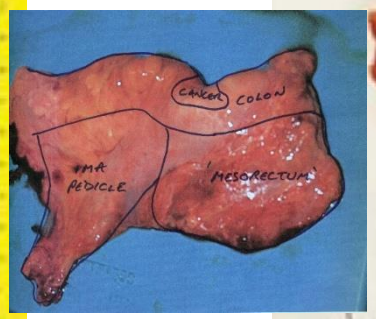




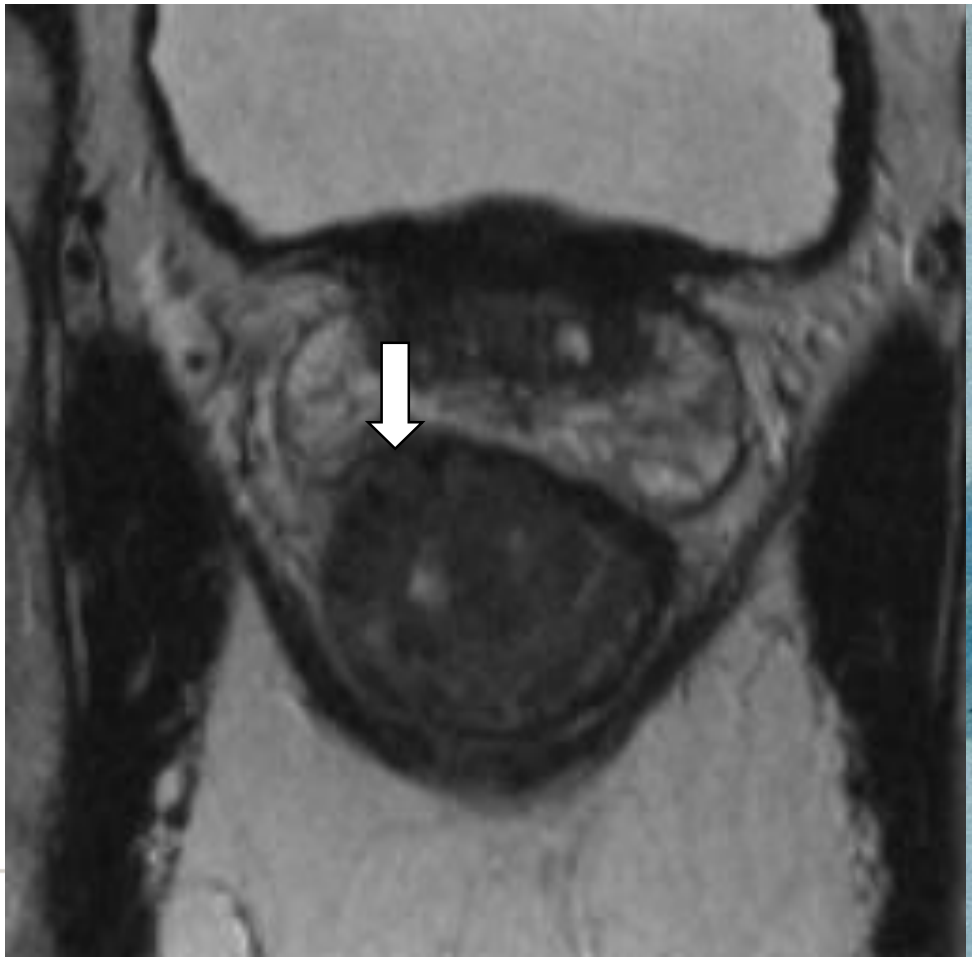


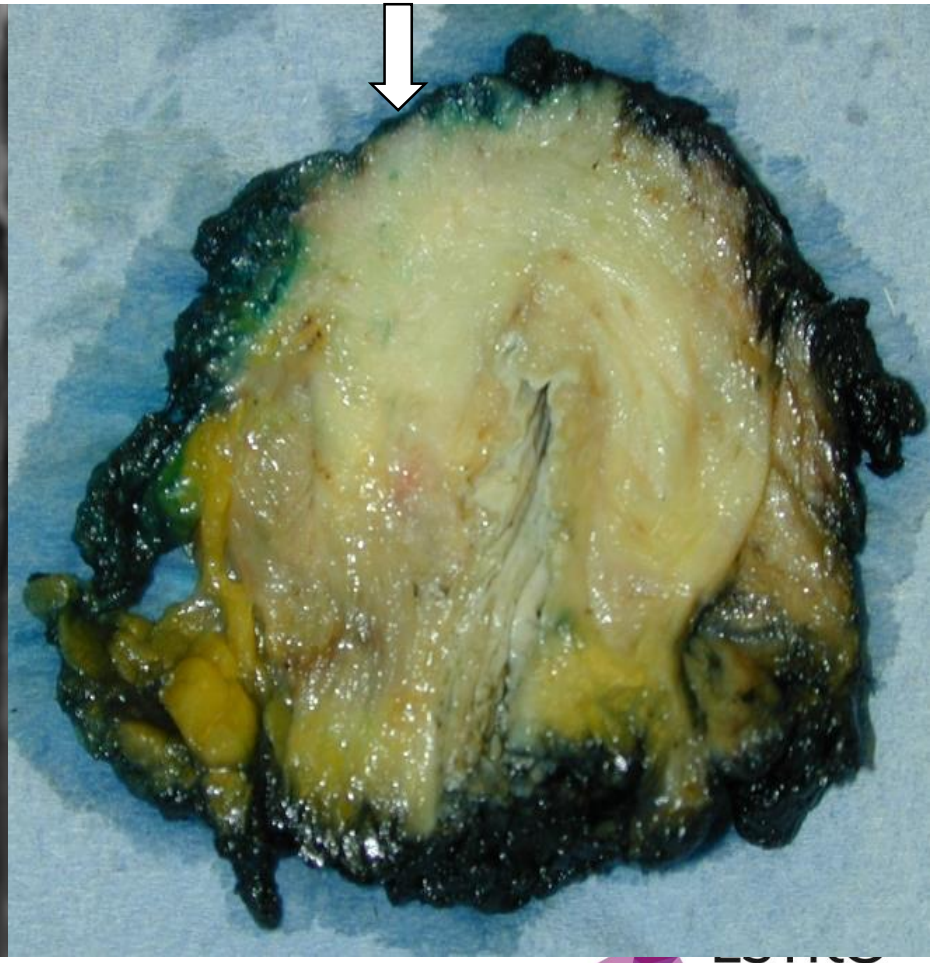






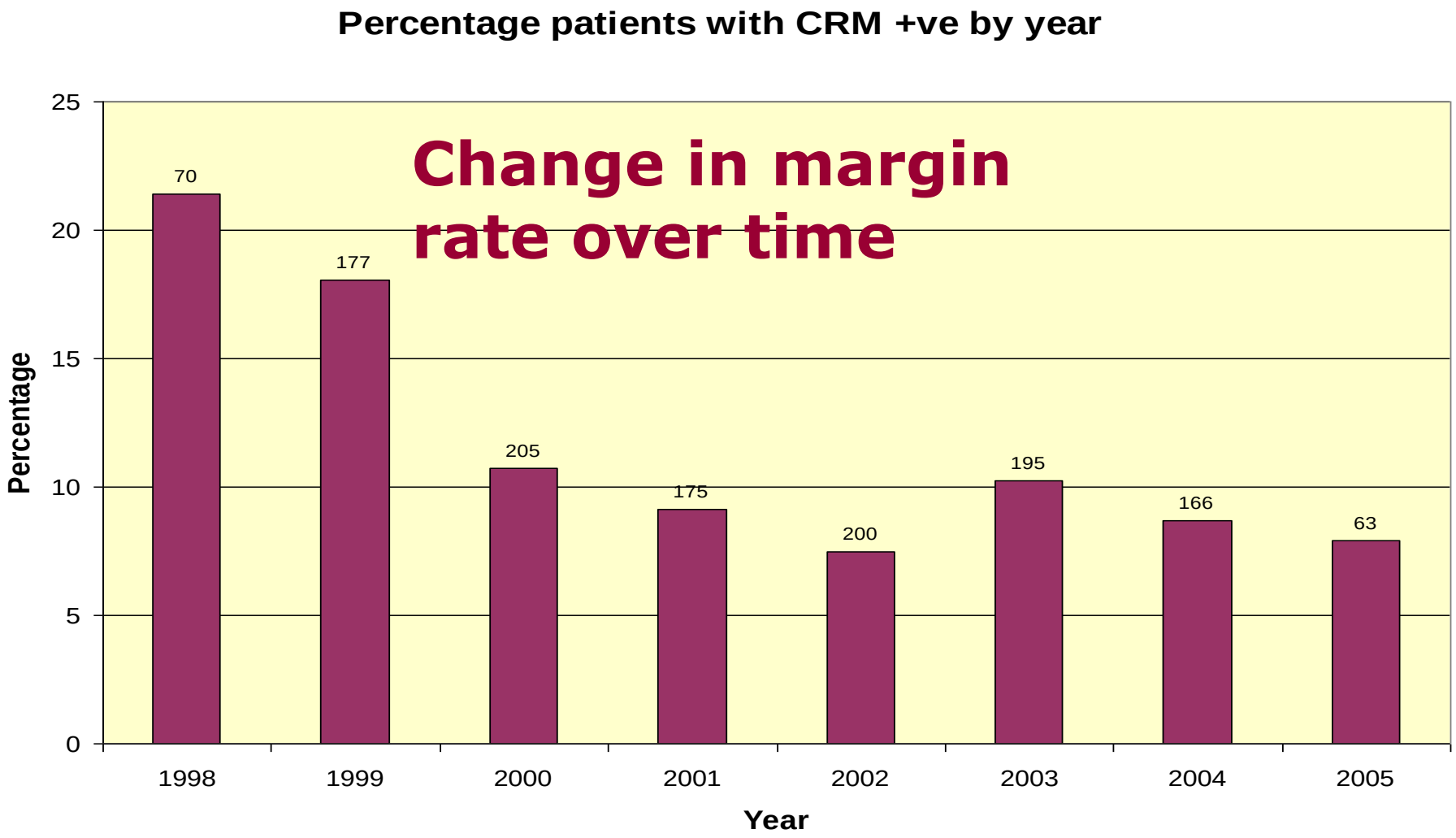
Margin at risk disease





CR07

Percentage of patients with + CRM over time



CRM associations with plane of surgery

	Plane of surgery		
	Mesorectal	Intra-mesorectal	Muscularis propria
CRM +ve rate	9%	12%	19%
Stage I	29%	24%	27%
Stage II	27%	32%	30%
Stage III	44%	43%	41%

With thanks to Phil Quirke

CR07 rates of local recurrence

	Preop RT 674	Selective Post-op RT	HR
CRM +ve	13.8%	20.7%	0·64
CRM -ve	3.3%	8.9%	0·36

Sebag-Montefiore D et al., Lancet 2009

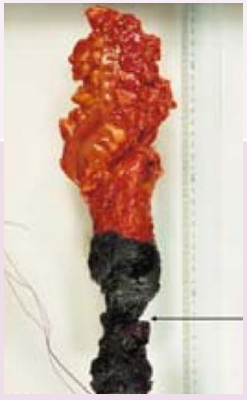
TME Northern Europe: Good quality mesorectal plane: no RT

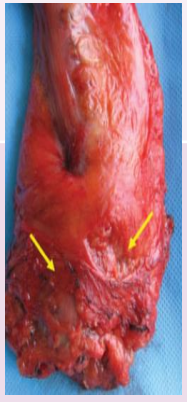
Study	Eligible	Good Quality Mesorectal	Local Recurrence	Actuarial
Swedish Rectal Cancer Trial 1997 (**574**)	T any N any	<10%	150/557 **27%**	>30%
CR07 overall (**592**) Quirke 2009	T any N any	51%	59/592 **10%**	11%
Dutch TME (**180**) Nagtegaal 2005	T any N any	56%	Not stated	8.7% at 2 years

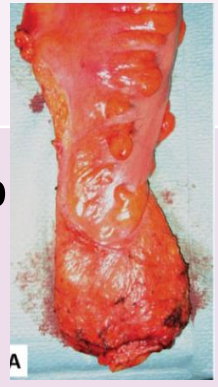
Local Recurrence rates in CRO7 according the plane of surgery

Quirke P et al Lancet. 2009 Mar 7; 373(9666): 821–828

	Plane of Surgery		
TNM stage	**Muscularis propria**	**Intra-mesorectal**	**Mesorectal**
I	**8%**	**2%**	**0%**
II	**6%**	**2%**	**5%**
III	**20%**	**14%**	**6%**







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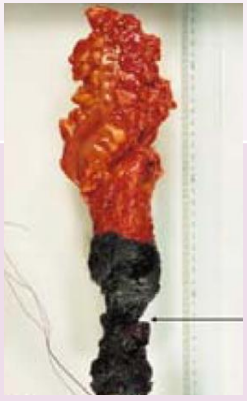
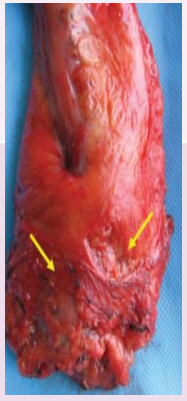
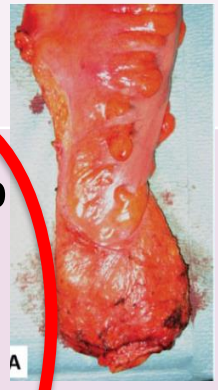
III	**20%**	**14%**	**6%**



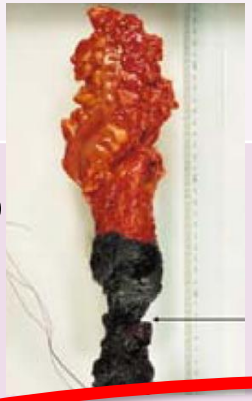


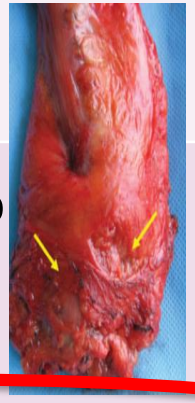


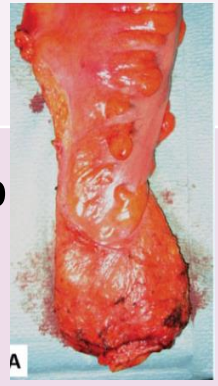
Local Recurrence rates in CRO7 according the plane of surgery

Quirke P et al Lancet. 2009 Mar 7; 373(9666): 821–828

	Plane of Surgery		
TNM stage	**Muscularis propria**	**Intra-mesorectal**	**Mesorectal**
I	**8%**	**2%**	**0%**
II	**6%**	**2%**	**5%**
III	**20%**	**14%**	**6%**





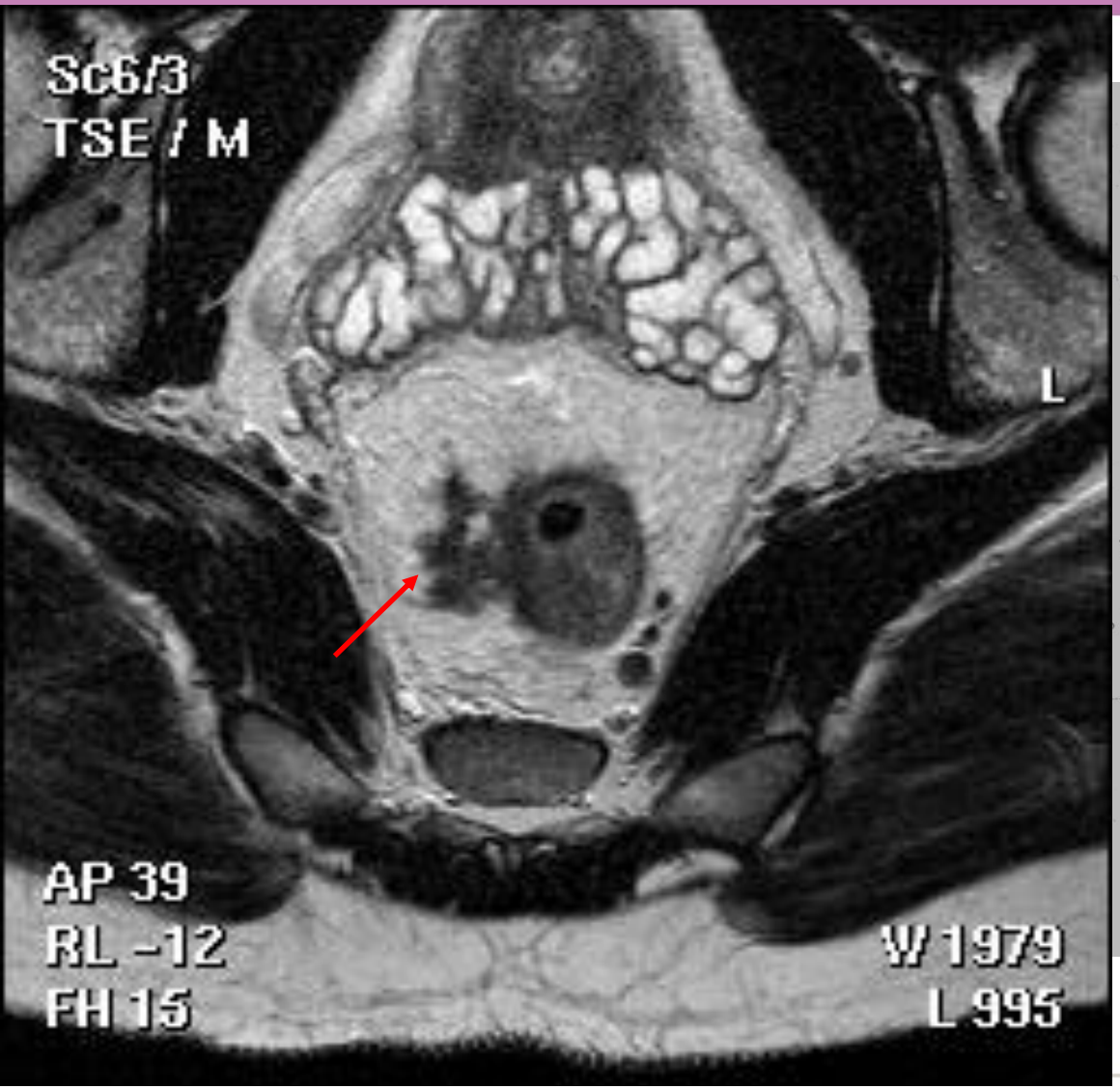


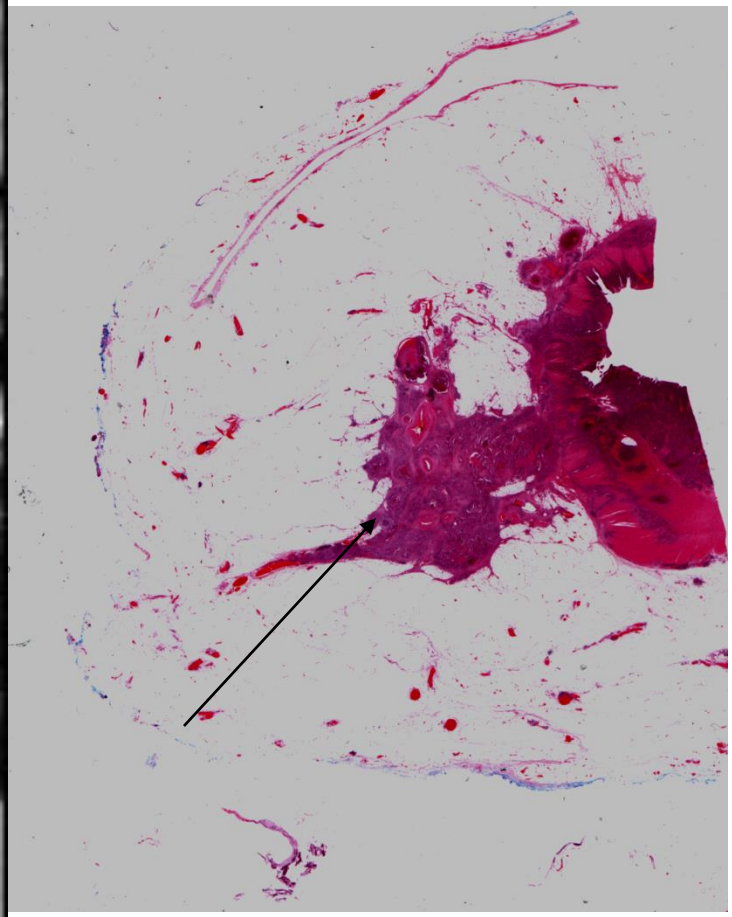
Pathologically defined Lymph nodes only affect your local recurrence rate if you leave them inside the patient!

High Quality MRI

- Gives the surgeon a road map for surgery
- Determines need for neoadjuvant chemoradiotherapy

Extramural venous invasion





With thanks to Gina Brown

Node + rate in randomised Trials of 5FU-based Chemoradiation

	n	stage	RT (Gy)	CT	Control %	preop, %
AIO/ARO	312	T3/circ/teth	50.4	FU CI	**40**	**25**
TROG-01.04	163	T3	50.4	FU PVI	**40**	**35**
Polish Study	157	T3-4	50	FU+LV	**48**	**32**
NSABP R03	123	T3-4	50.4	FU+LV	**48**	**33**

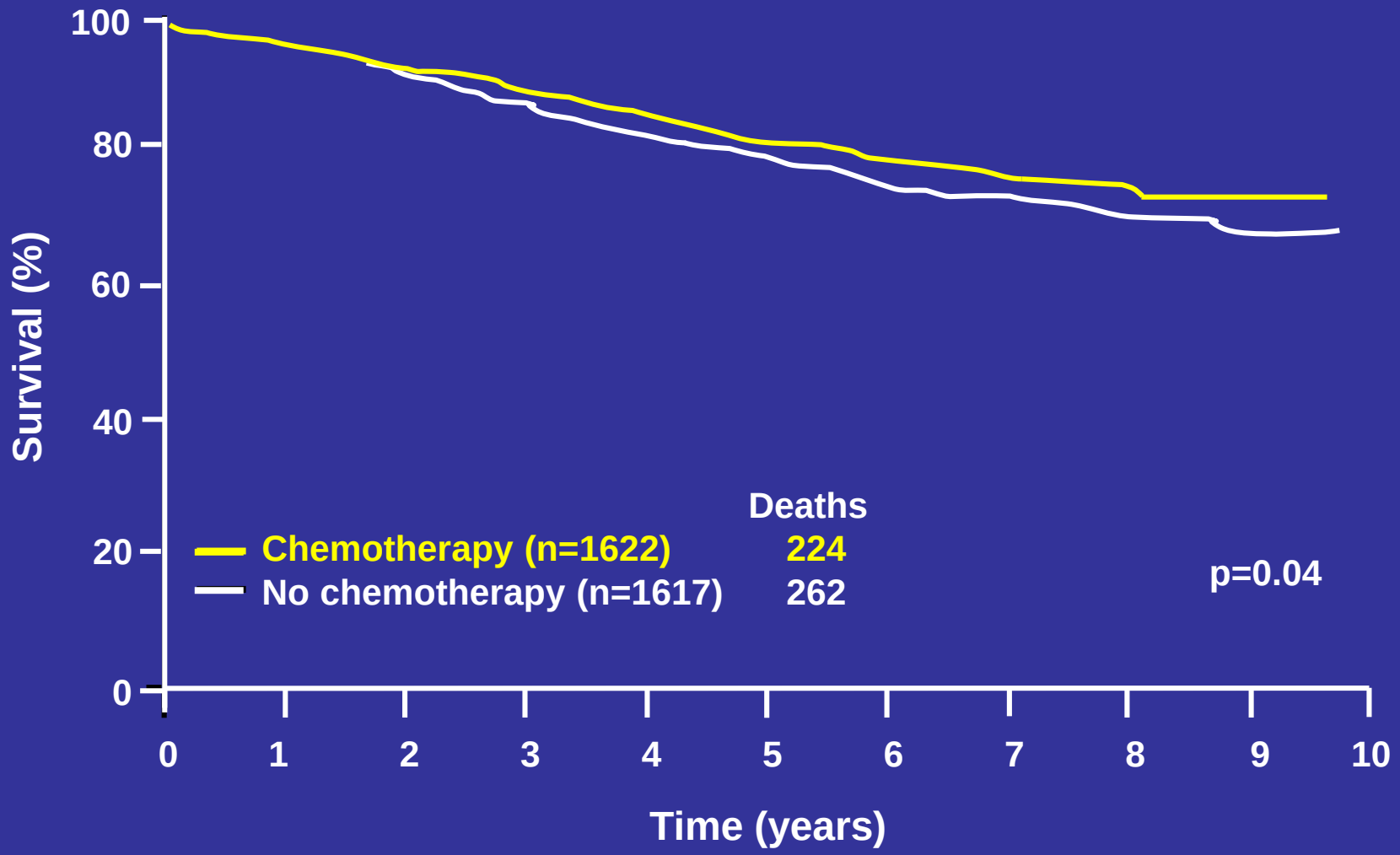
Suggests that in the trials

50-60% cN0

Approx 30% of nodes are sterilized

Compliance to postoperative adjuvant chemotherapy approx 50%

QUASAR: survival in stage II patients



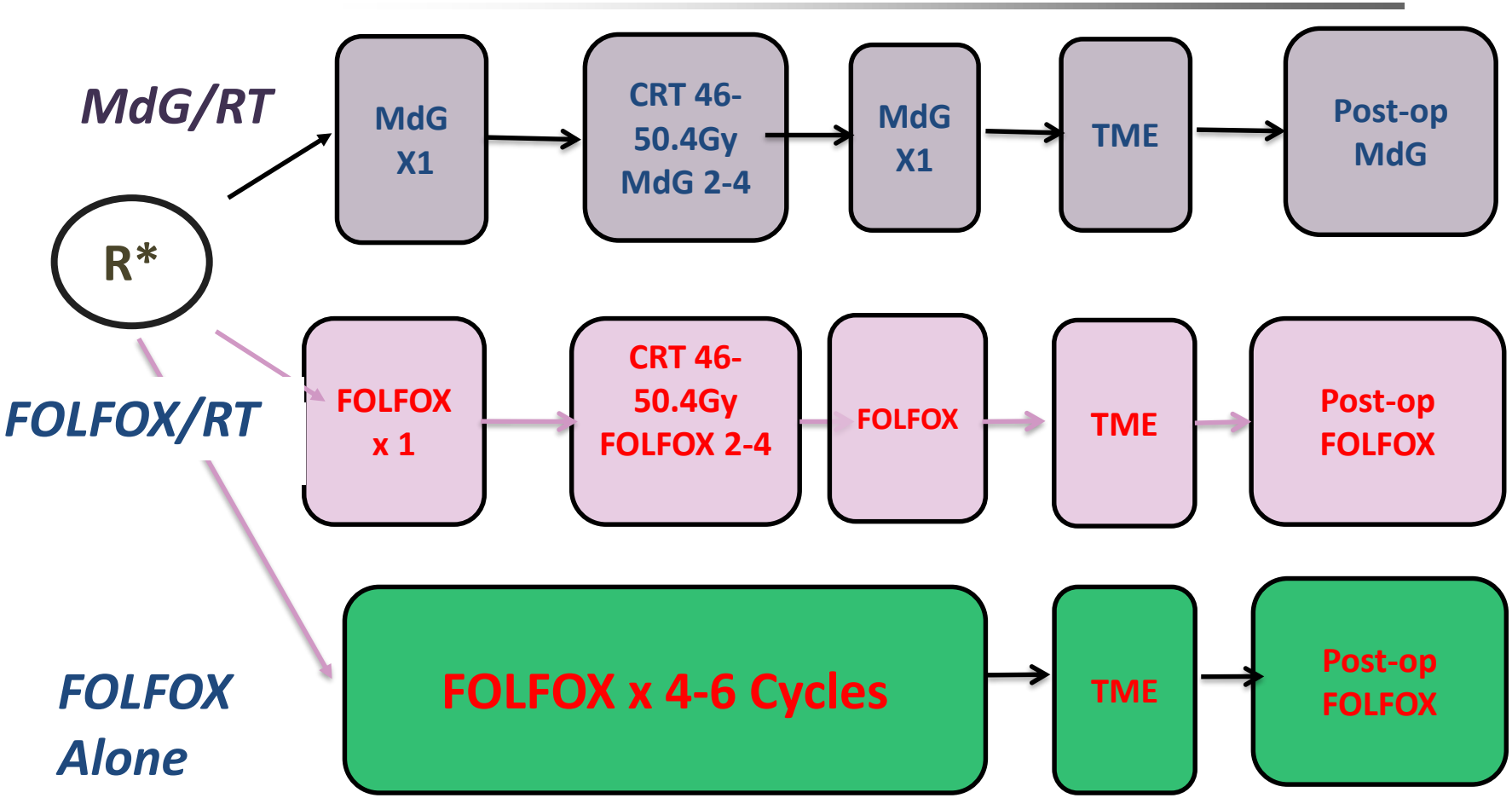
Endpoint	STAR-01	ACCORD 12/0405	CAO/ARO/ AIO-04	NSABP R-04	PETACC-6
PCR	16% both arms	14% vs 19%	12.8% vs 16.5% (p=0.038)	19% vs 21%	11.5% vs 13%
CRM	4% vs 7%	8% vs 13%	5% vs 6%	No data	2% vs 2%
Node + (stage III)	29% vs 26%	30% vs 26%	27% vs 26%	Not stated	27% vs 26%

Control arm in red

Clinical Stage in the Trials

Trial	Number of patients	Clinical nodal status	5FU/ Cape	5FU/Cape + OX
PETACC-6	1081	cN+ (%)	72%	71%
German CAO/ARO/AIO-04	1236	cN+ (%)	72%	74%

The FOWARC trial – Design



Endpoints

Primary endpoint: 3 yr DFS

Deng, J Clin Oncol 2016

**Patients recruited from 15 Chinese Centres 2010-2015*

Regimens	Number of patients	G3/G4 toxicity Diarrhea	Interval to surgery (median in days)	ypN+	pCR	TRG0-1
De Gramont RT 46-50.4Gy	165	7.7%	53	19.9%	14%	49%
FOLFOX RT 46-50.4Gy	165	14.5%	52	12.6%	27.5%	68.5%
FOLFOX alone	165	7.3%	Not stated	26.5%	6.6%	32.9%

Endpoint	STAR-01	ACCORD 12/0405	CAO/ARO/ AIO-04	NSABP R-04	PETACC-6	FOWARC
PCR	16% both arms	14% vs 19%	12.8% vs 16.5% (p=0.038)	19% vs 21%	11.5% vs 13%	14% vs 27.5%
CRM	4% vs 7%	8% vs 13%	5% vs 6%	No data	2% vs 2%	9.2% vs 10% R1/R2
yp Node + (stage III)	29% vs 26%	30% vs 26%	27% vs 26%	Not stated	27% vs 26%	19.9% vs 12.6%

Control arm in red

Polish trial Bujko et al Radiotherapy and Oncology 2004

T3/T4, resectable n=316
palpable on DRE,<75yrs .

Planned operation recorded

Short course pre-op RT

Immediate surgery

Pre-op CRT 50.4 + 5FU/LV

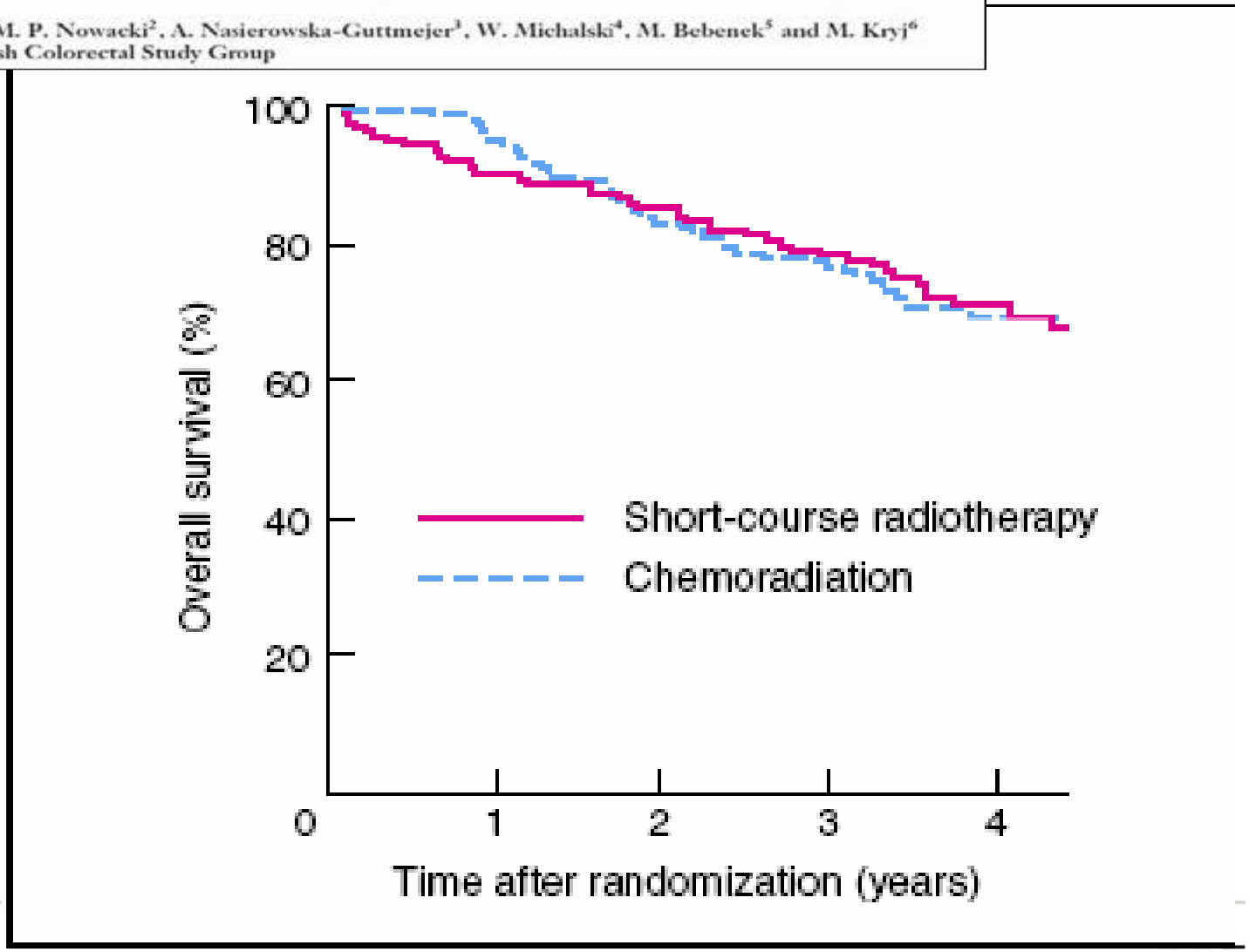
6-8 week interval

Surgery

Randomized clinical trial

Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer

K. Bujko[1], M. P. Nowacki[2], A. Nasierowska-Guttmejer[3], W. Michalski[4], M. Bebenek[5] and M. Kryj[6] for the Polish Colorectal Study Group



TROG AGIT LSSANZ RACS trial Ngan JCO 2012

T3/T4, resectable n=316
palpable on DRE,<75yrs .

Planned operation recorded

Short course pre-op RT

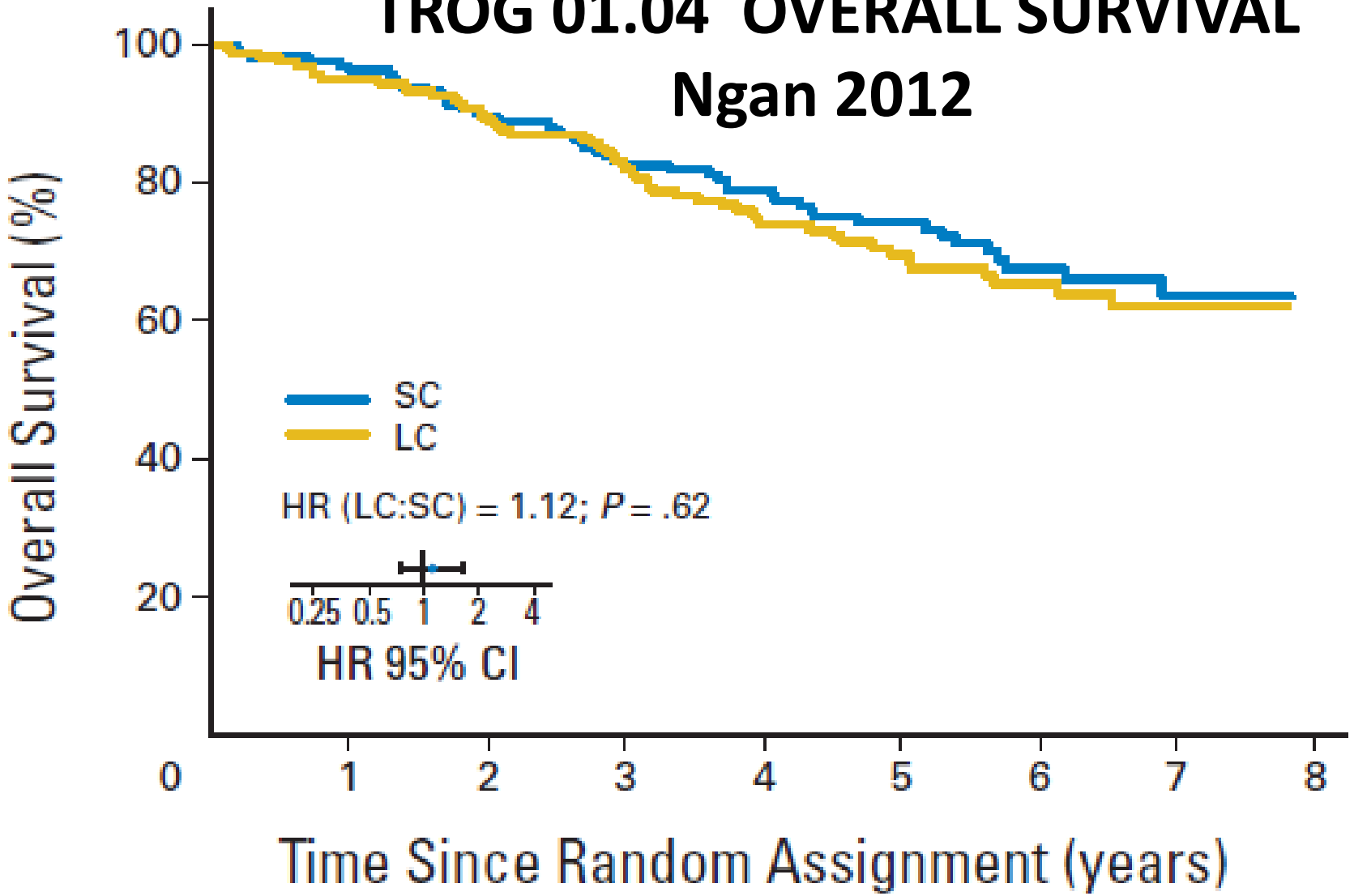
Pre-op CRT 50.4 + 5FU/LV

Immediate surgery

6-8 week interval

Surgery

TROG 01.04 OVERALL SURVIVAL
Ngan 2012



No. at risk

SC	162	155	143	129	104	76	46	22	0
LC	161	152	143	130	100	71	50	21	0

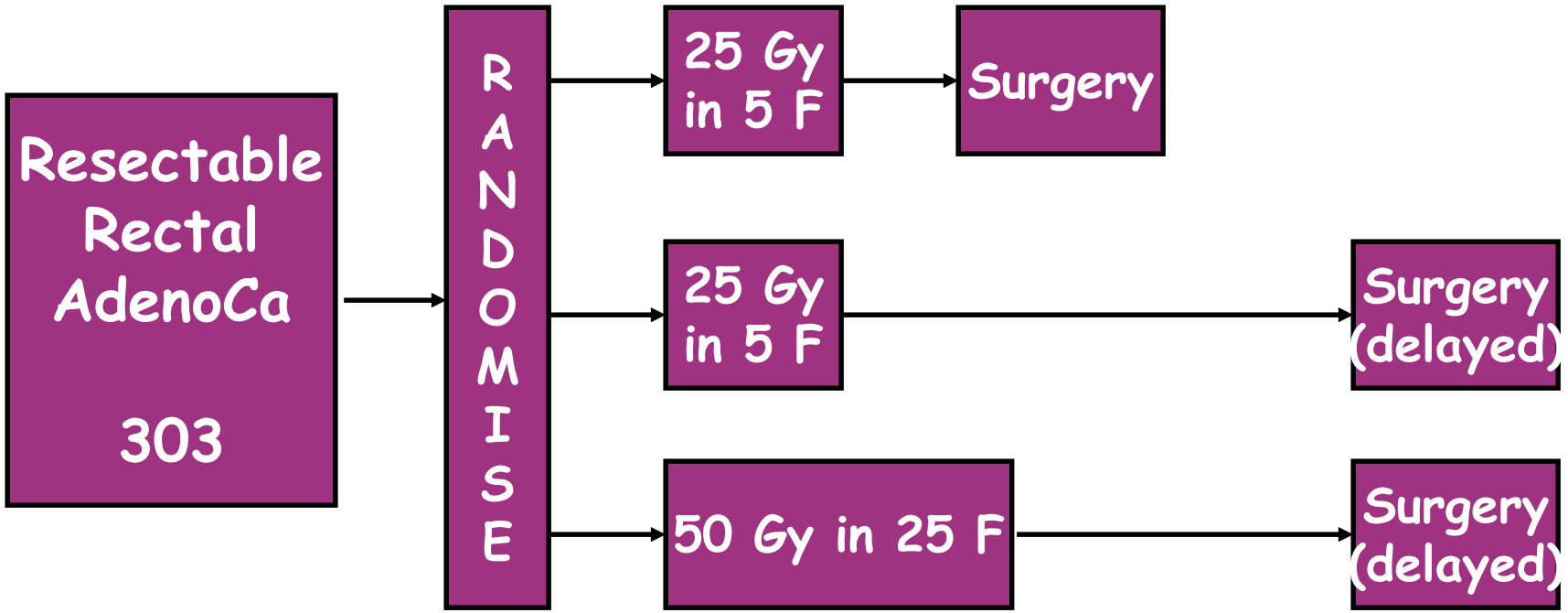
In locally advanced rectal cancer (CRM/MRF not threatened

SCPRT = CRT??

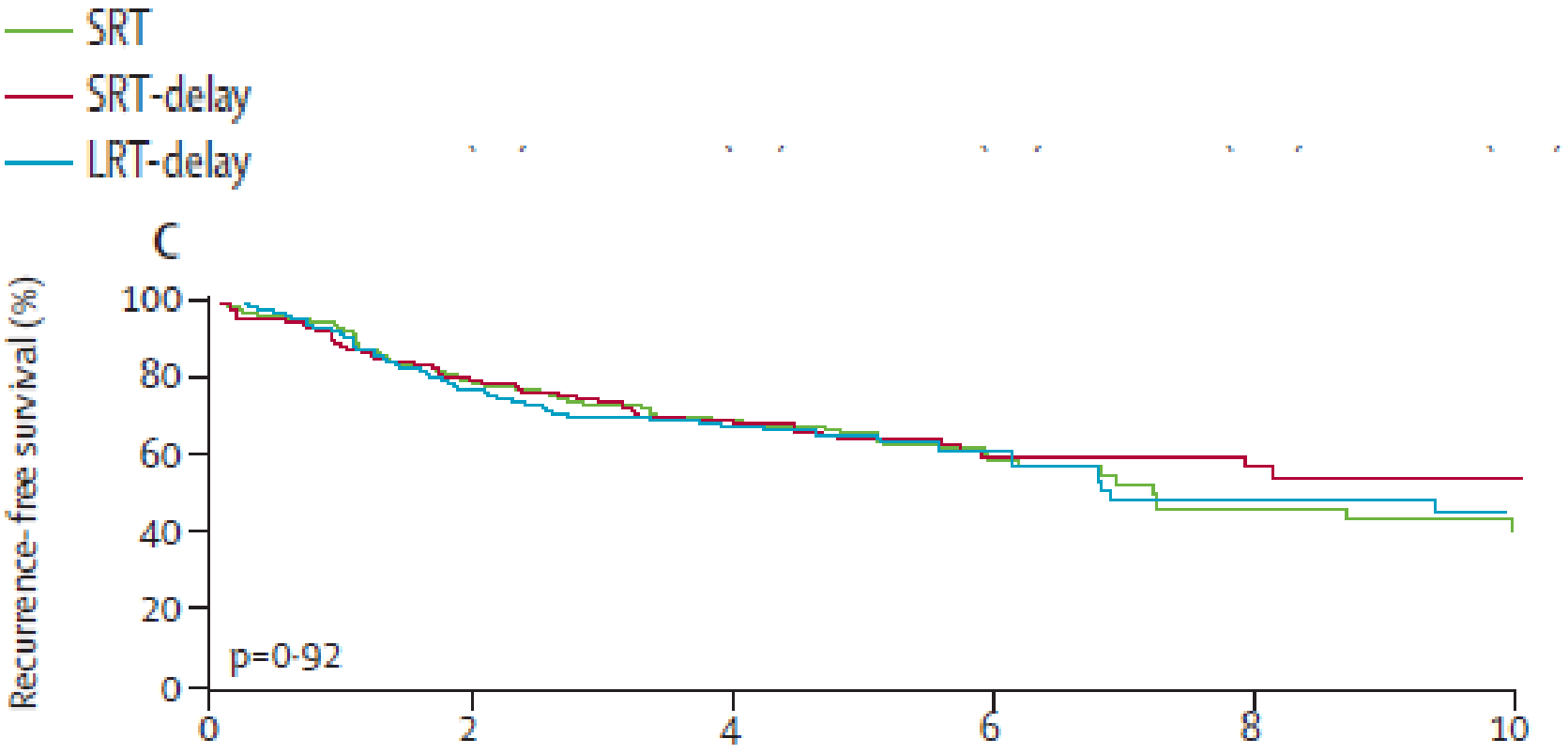
Short course (5x5 Gy) and immediate Surgery

Short course (5x5 Gy) and wait 6-8 weeks

STOCKHOLM III



Stockholm III trial :Recurrence Free



Number at risk (censored)						
SRT	129 (0)	101 (0)	82 (8)	36 (44)	18 (56)	12 (60)
SRT-delay	128 (0)	101 (0)	77 (11)	36 (45)	20 (59)	17 (62)
LRT-delay	128 (0)	97 (1)	74 (13)	34 (47)	20 (55)	9 (65)

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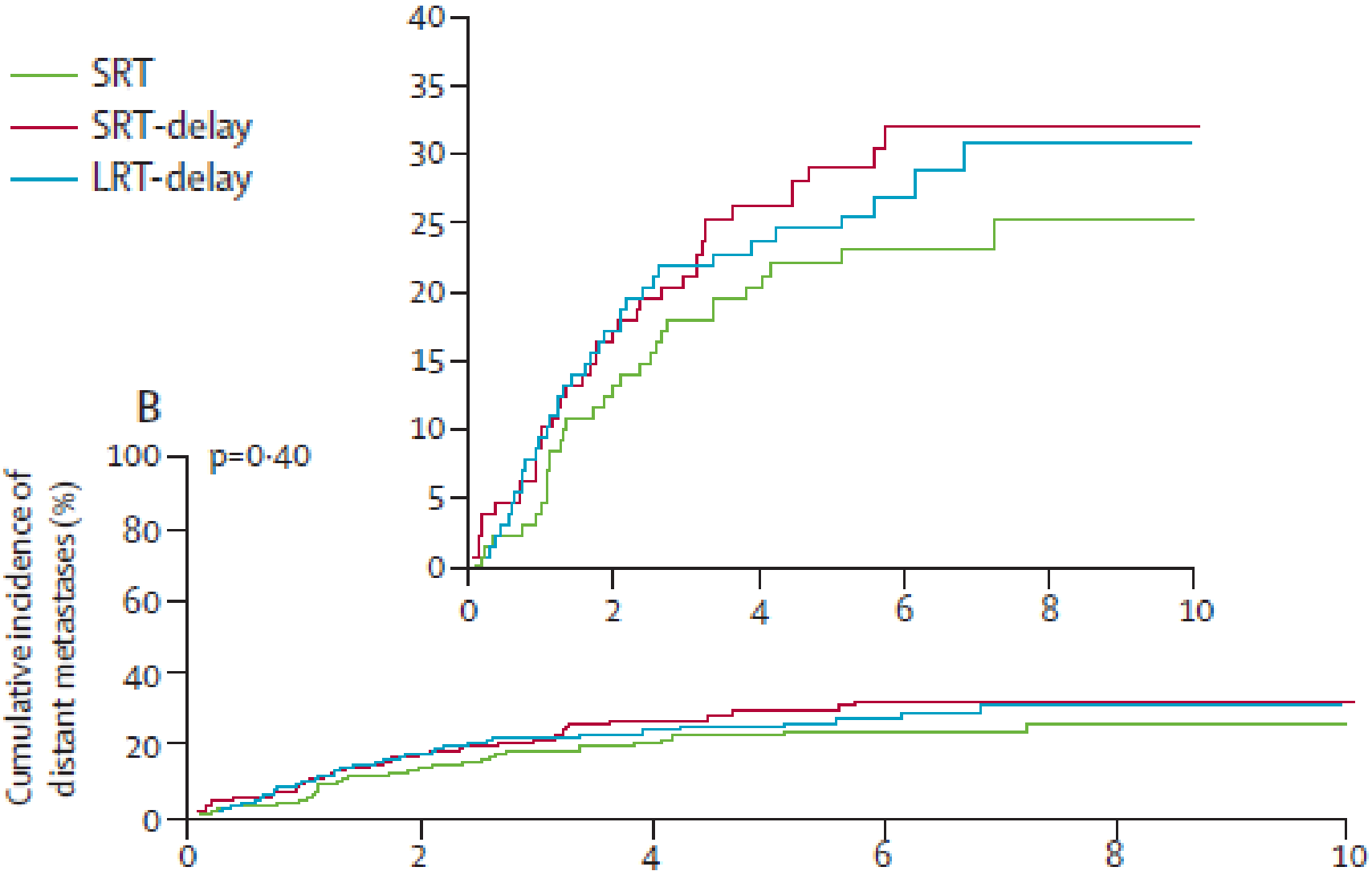
Stockholm III trial : incidence of metastases



So - What about?

- Oxaliplatin
- Irinotecan
- Biologicals

Currently - Different Philosophies

Medical Oncology trials EXPERT, EXPERT C, SPANISH (Fernandez-Martos)/ RAPIDO use systemically active chemotherapy outside chemoradiation

Radiation Oncology trials ACCORD 12, STAR-01, CAO/ARO/AIO-04, NSABP R04 use oxaliplatin as radiosensitizer (non systemic doses)

Questions

Does oxaliplatin add anything as a radiosensitizer to preop CRT?

Does postoperative adjuvant oxaliplatin add anything to preop CRT as adjuvant chemotherapy to reduce metastases?

So what have the trials shown us?

All 5 Oxaliplatain trials used low dose oxaliplatin as a radiosensitizer with CRT

2 trials mandated oxaliplatin also as postoperative adjuvant (so if benefit which component?)

Some of the 5 trials did not mandate TME

Phase III: CAO/ARO/AIO-04

Best arm of CAO/ARO/AIO-94:

RT 50.4 Gy + 5-FU
1000 mg/m² days 1-5 + 29-33
623 patients

From Phase I/II Studies:

RT 50.4 Gy + 5-FU/OX
Ox: 50 mg/m² d 1, 8, 22, 29
5-FU: 250 mg/m² d 1-14 + 22-35

Note: Chemo gap 3rd week of RT !

613 patients

T M E

5-FU
500 mg/m² d 1-5, q29
4 cycles (4 months)

mFOLFOX6
Oxaliplatin: 100 mg/m² d1,q15
Folinic Acid: 400 mg/m² d1
5-FU: 2400 mg/m² d1-2
8 cycles (4 months)

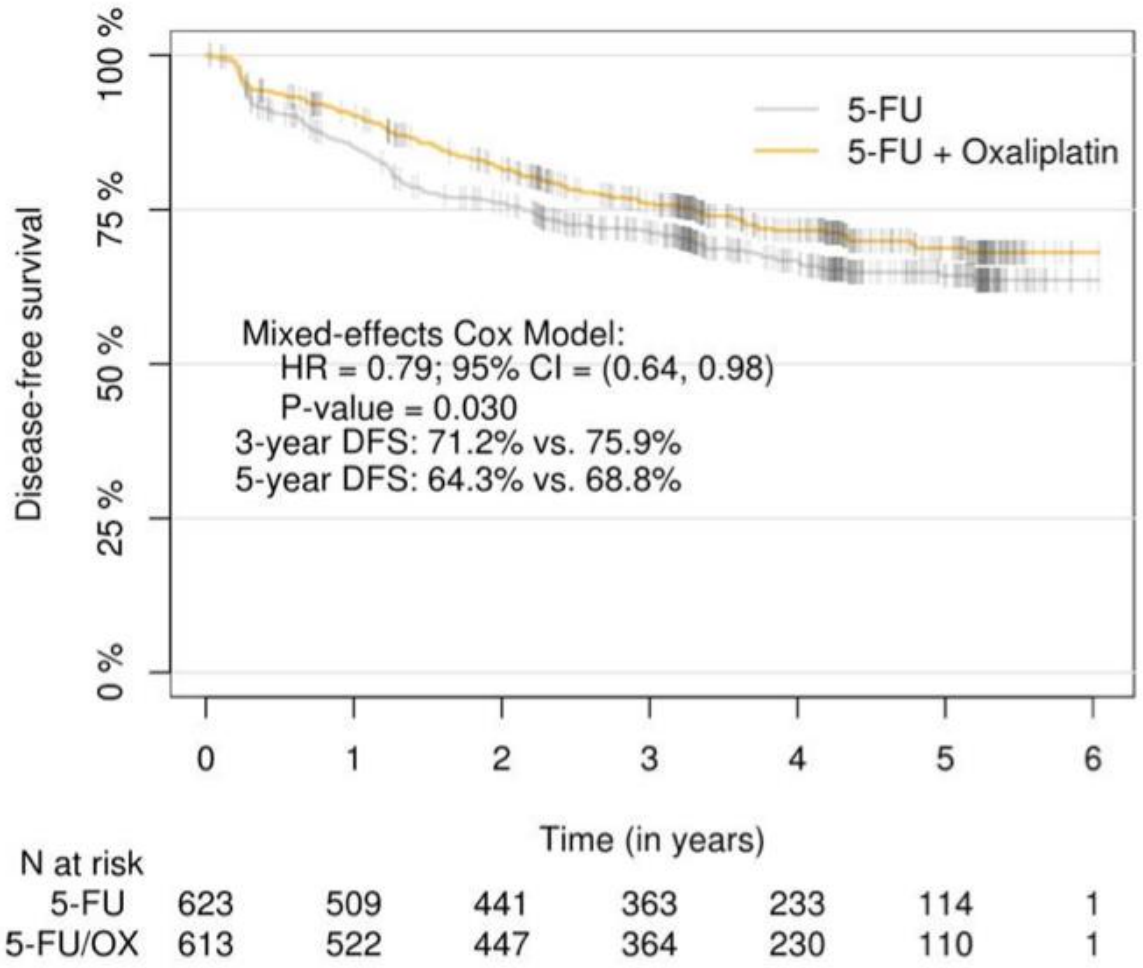
Phase III trials – Investigating

Trial	Eligibility	Fluoropyrimidine Platform
CAO/ARO/AIO-04	<12cm from anal verge T3/T4 cN0/N+ TRUS, CT and/or MRI	5FU 1000mg/2 X 5 days 1-5 + 29-33
NSABP R04 N=1606	<12cm; resectable stage II, III TRUS or MRI – CT if T4/ N1-2	PVI 5FU vs Capecitabine
FFCD N=598	Palpable; resectable; T3/4 N0-2; T2 distal anterior	Capecitabine in both arms
STAR – 01 N=747	Resectable stage II, III (c stage) <12cm from anal verge	PVI 5FU in both arms
PETTAC 6 N=1090	Stage II or III resectable or expected to become resectable <12cm from anal verge	Capecitabine in both arms

Endpoint	STAR-01	ACCORD 12/0405	CAO/ARO/ AIO-04	NSABP R-04	PETACC-6
PCR	16% both arms	14% vs 19%	12.8% vs 16.5% (p=0.038)	19% vs 21%	11.5% vs 13%
CRM	4% vs 7%	8% vs 13%	5% vs 6%	No data	2% vs 2%
Node + (stage III)	29% vs 26%	30% vs 26%	27% vs 26%	Not stated	27% vs 26%

Control arm in red

CAO/ARO/AIO-04 Trial



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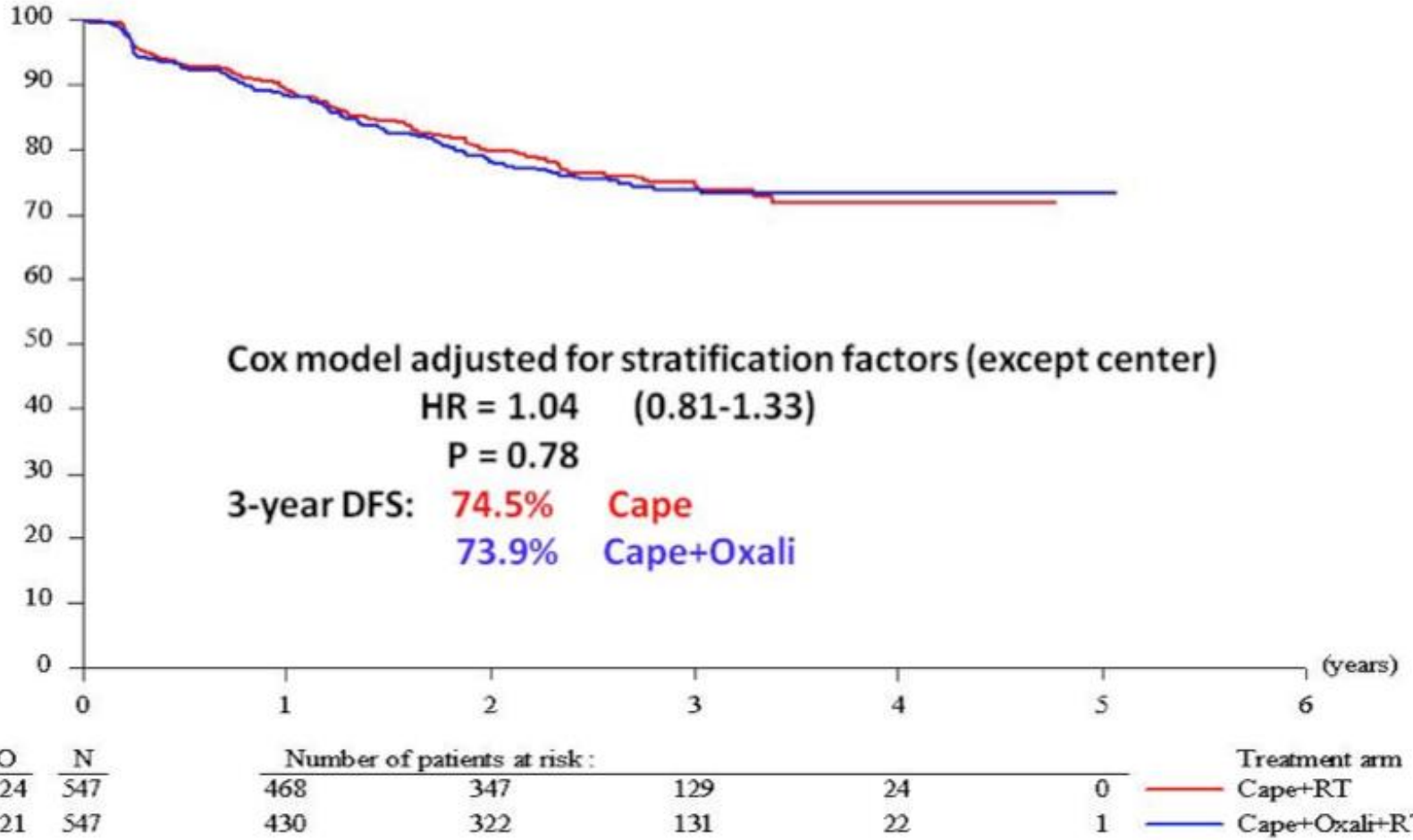
PETACC-6



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CAO/ARO/AIO-04 Trial

Primary Endpoint DFS **Median Follow-up: 50 months (range: 0.3-73)** **Time between randomisation and the first of the following events:**	**5-FU arm n=623**	**5FU/OX arm n=613**
Incomplete local resection (R2)	**10**	**5**
Locoregional recurrence after R0/R1 resection (+/- distant metastases)	**23 (3.7%)**	**12 (2%)**
Distant metastases / Progression	149	115
Death		
Overall	106	96
Cancer / treatment related/surgical mortality	69/4/6	54/7/4
Unrelated	26	31
Unknown	1	0
First events for DFS (total)	198	159

Prodige/ACCORD 12/0450 trial

Staging :- Evaluated by TRUS and/or MRI

N=598

Capecitabine 800mg/m2
45 Gy CRT

S

Centre policy

Oxaliaplatin 50mg/m2 x 5
Capecitabine 800mg/m2*
50.4Gy CRT

S

Centre policy

Primary end point- pCR 11% - 20% 85% power

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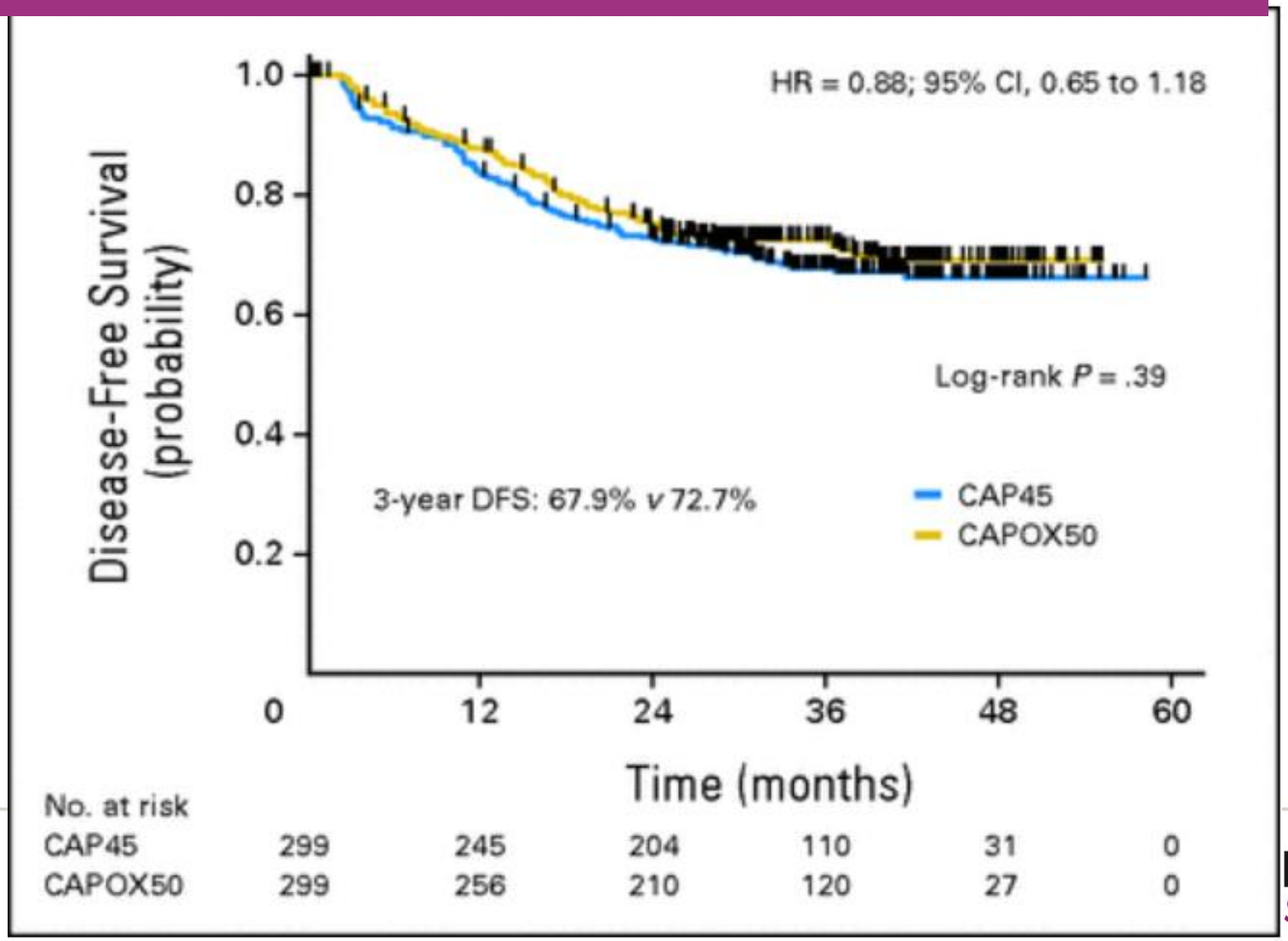
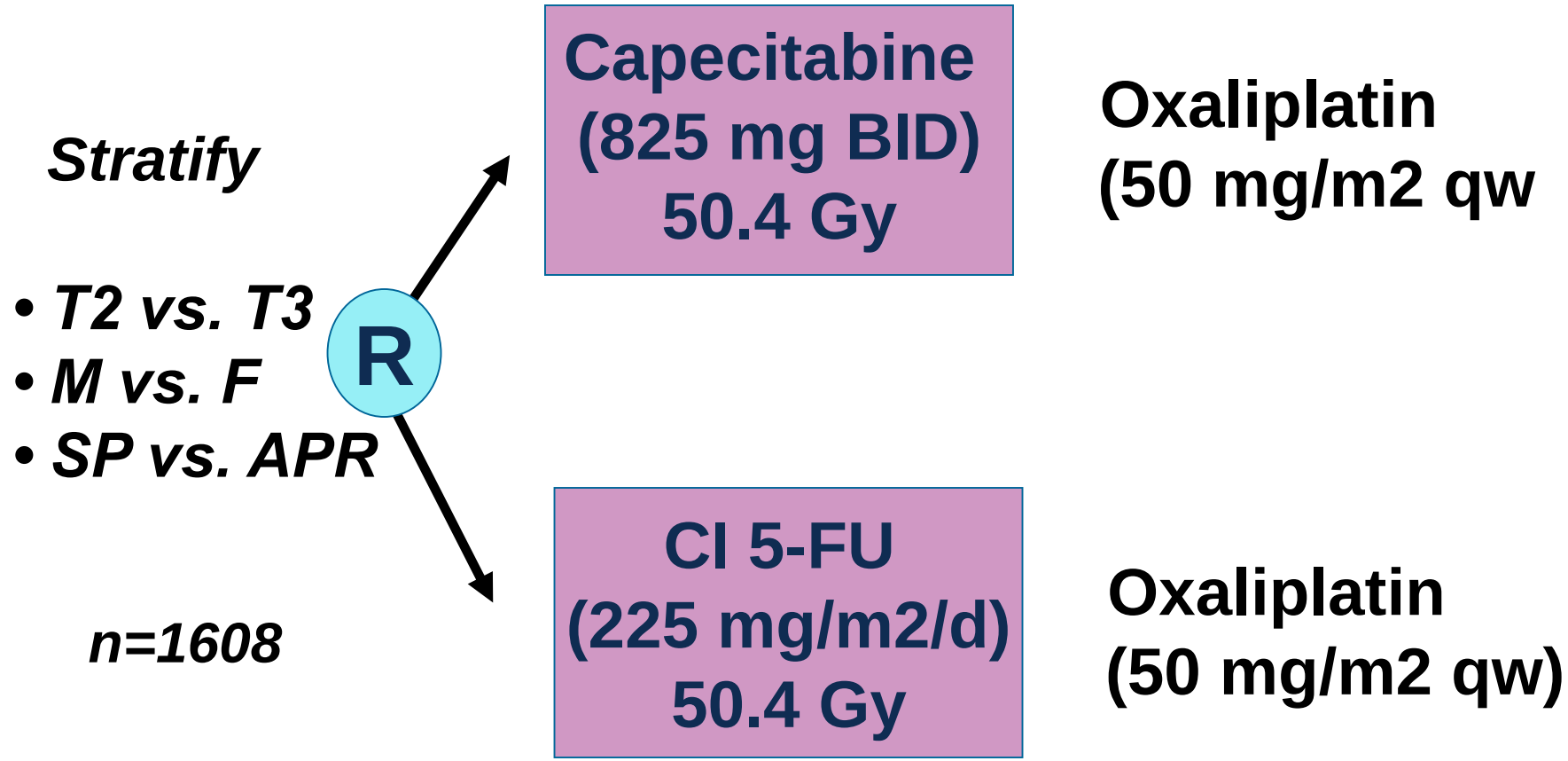
DFS: ACCORD 12/0405 PRODIGE 2

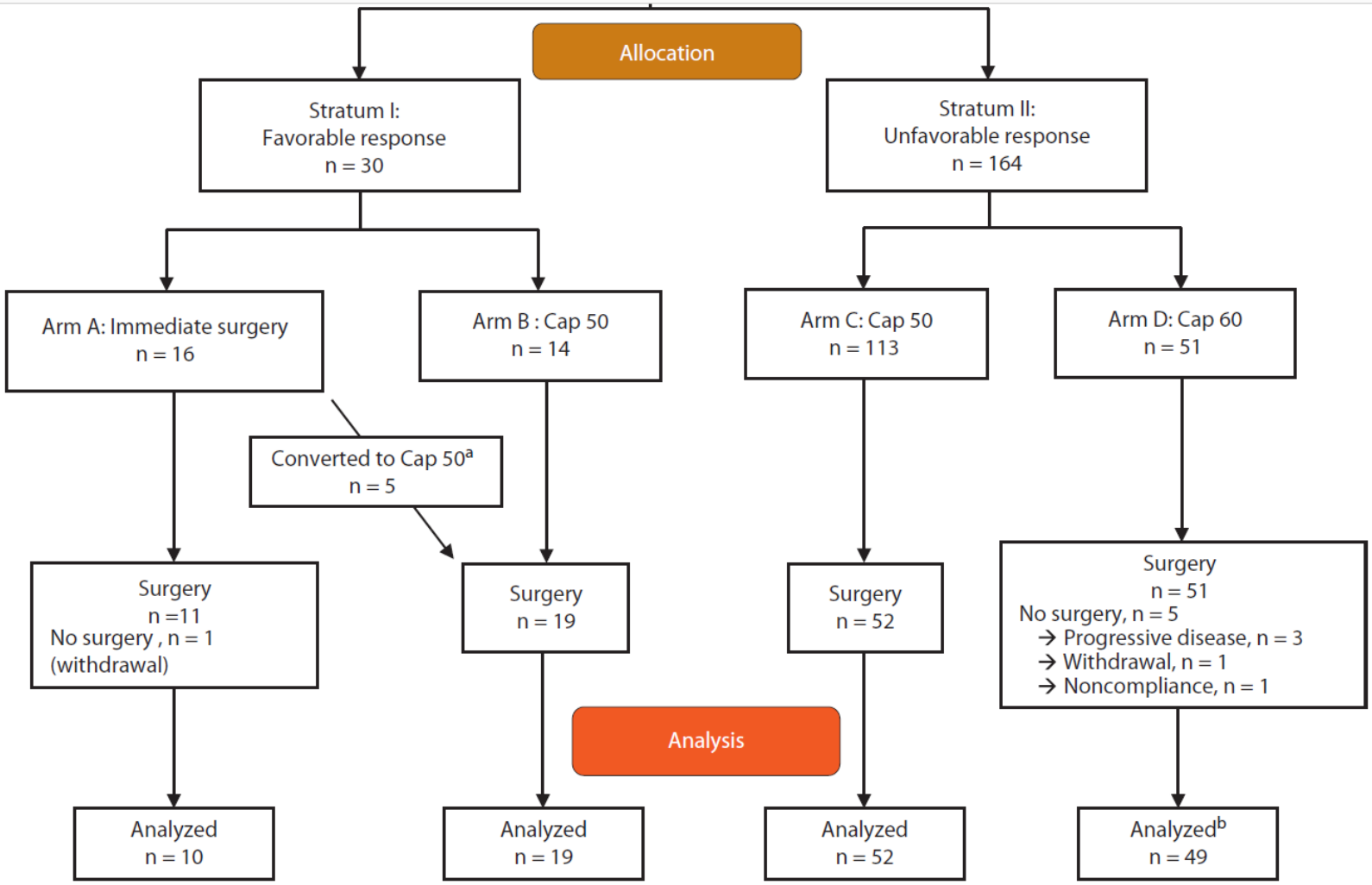


5-FU = Cape in Pre-op Rectal Cancer: NSABP R-04



NSABP R-04, Allegra et al; ASCO GI

GRECCAR 4 phase II trial



Rouanet P et al Dis Colon Rectum 2017

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	Good Respose		Poor Respose	
	Group A 11	Group B 19	Group C 52	Group D 51
Analysed	FOLFIRINOX **alone no CRT** **11**	FOLFIRINOX + standard CRT **19**	**52**	FOLFIRINOX + **high dose RT** **51**
Ro Resection	100%	100%	83%	88%
CRM ≤1mm	0%	0%	14%	7%
No residual tumour	1/10 (10%)	11/19 (58%)	7/52 (13.5%)	9/46 (20%)

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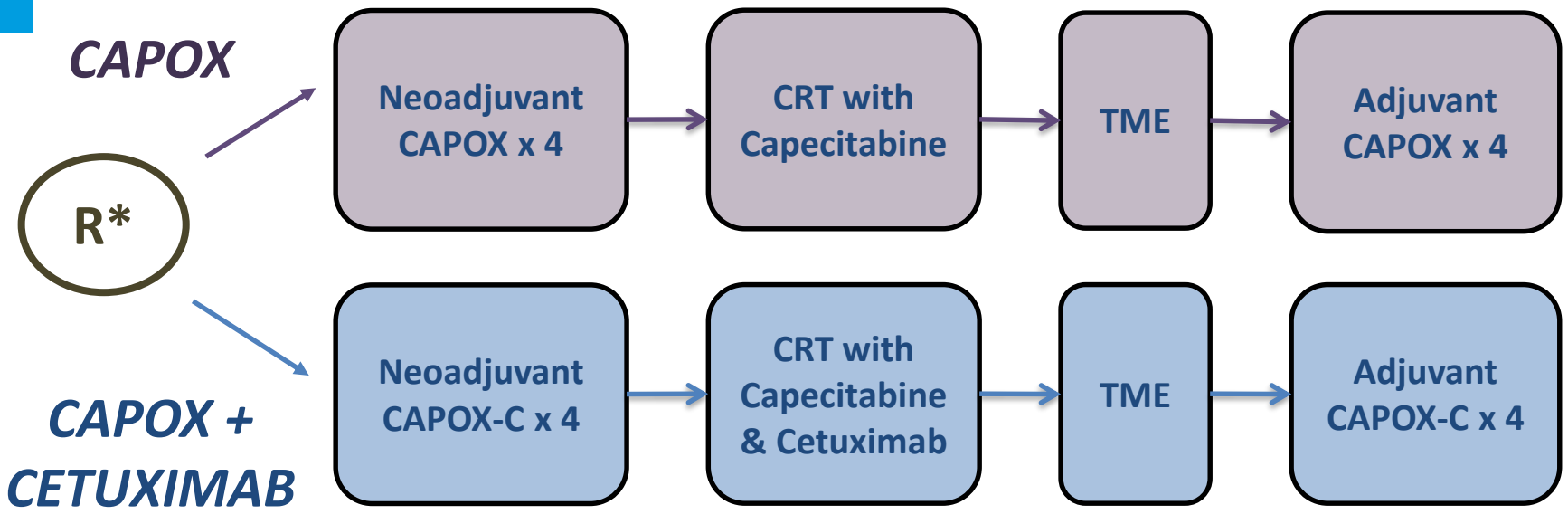
The EXPERT-C trial – Design



**Patients recruited from 15 European Centres 2005-2008*

Key inclusion criteria:

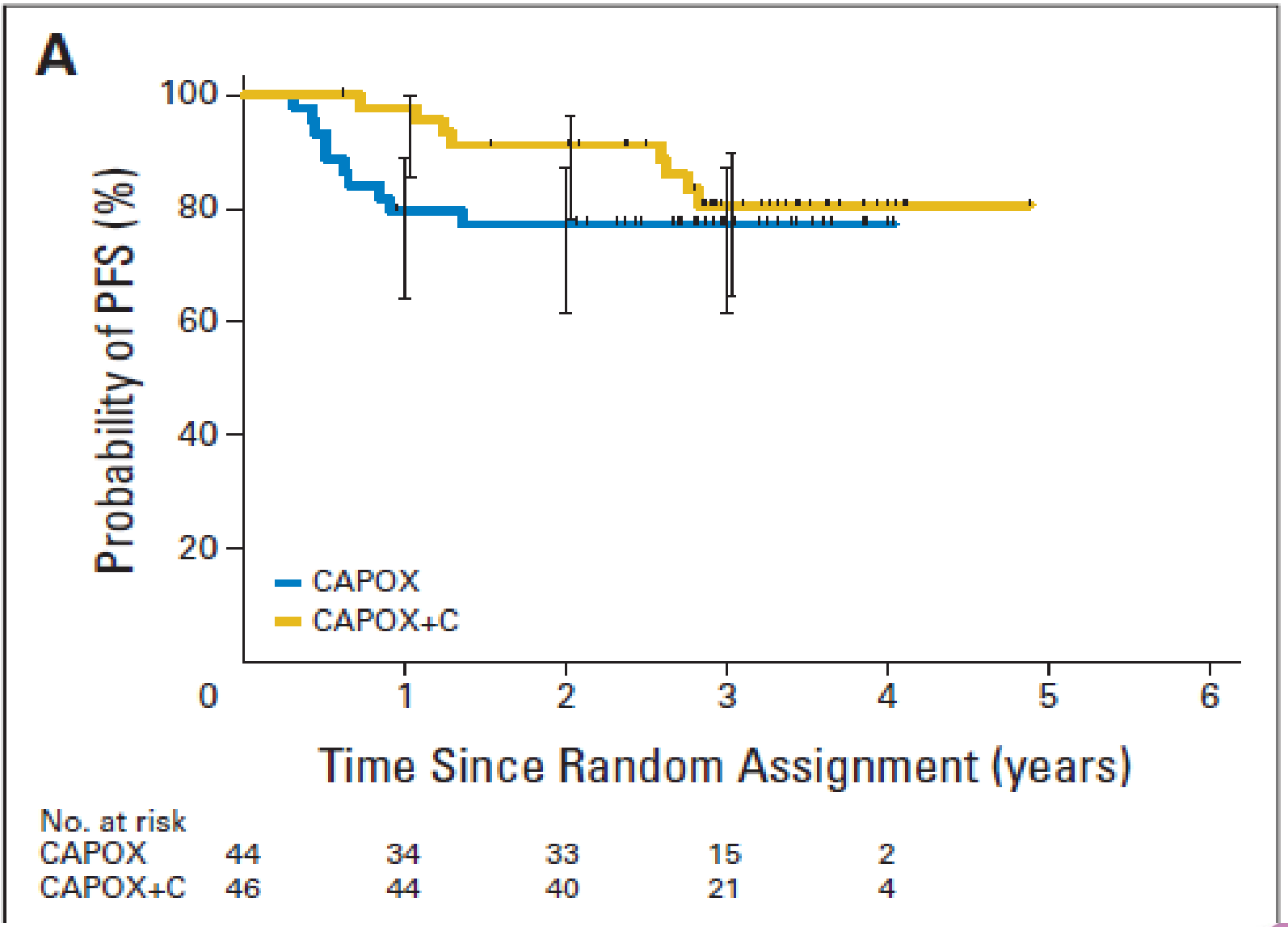
- Tumours within 1mm of mesorectal fascia
- Tumours extending ≥5mm into peri-rectal fat
- T4 tumours
- Presence of extramural vascular invasion
- T3 tumours at/below levators

Endpoints

- Primary endpoint:
  CR in *KRAS/BRAF* WT patients
- Secondary endpoints:
  RR, PFS, OS, safety and QoL

Dewdney, J Clin Oncol 2012

EXPERT-C KRAS WT PFS (Dewdney 2012)



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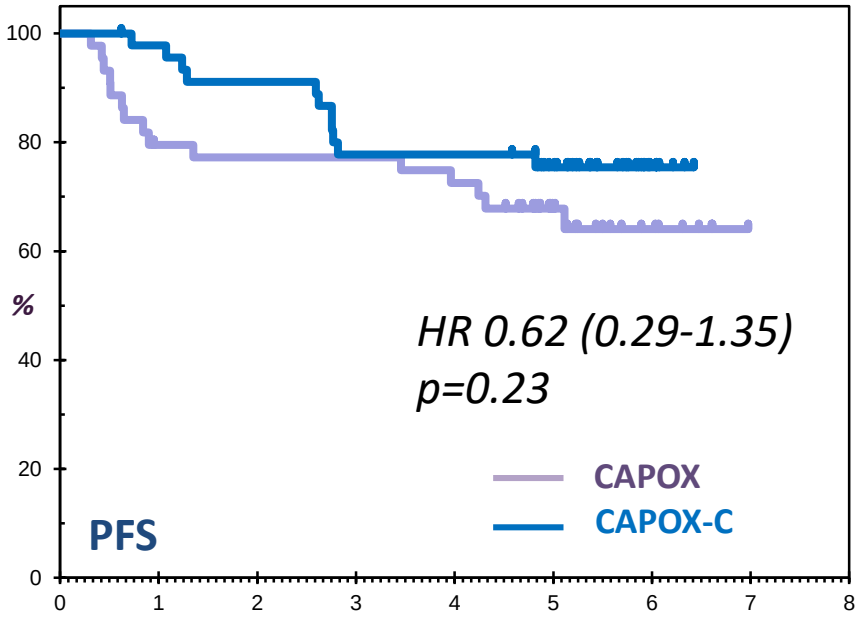
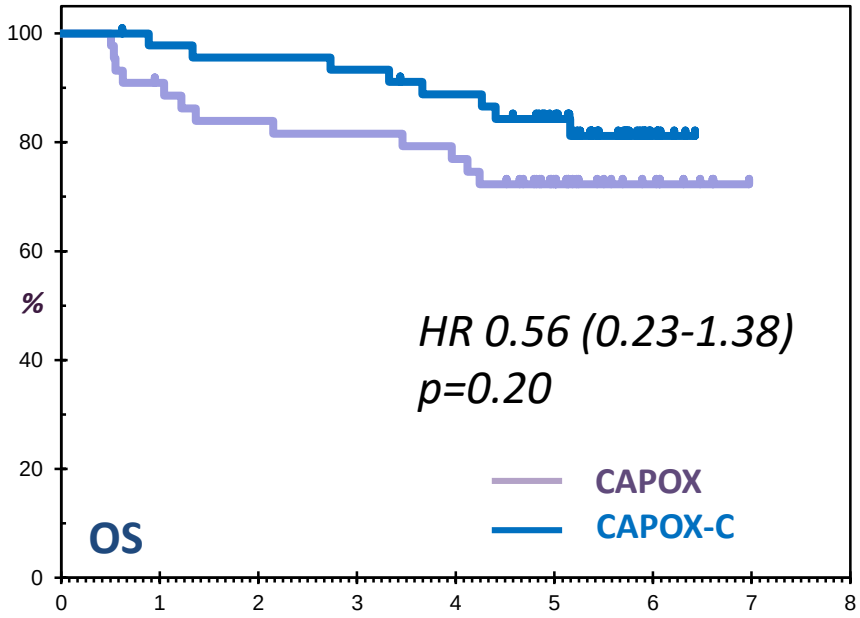
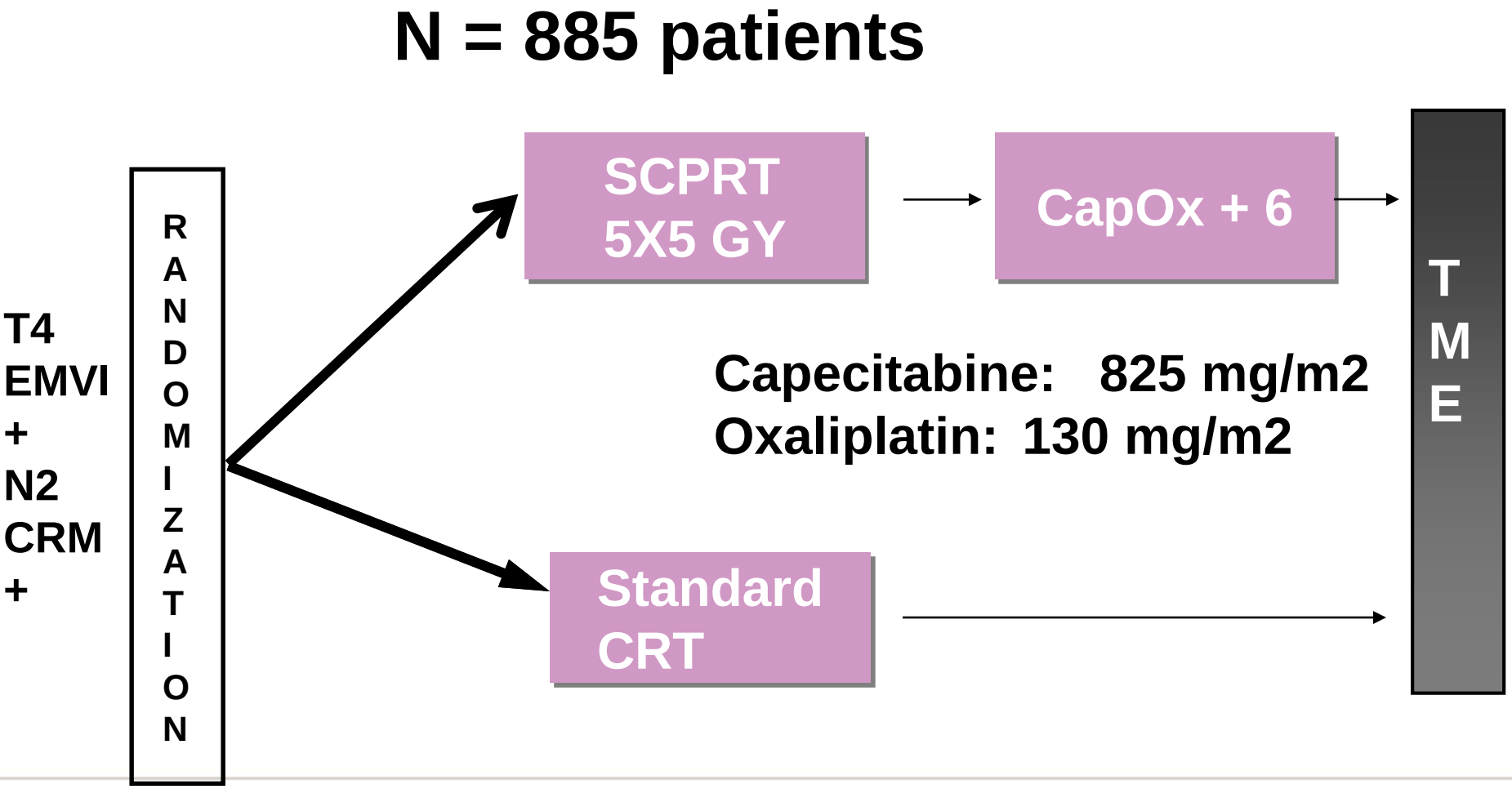
The EXPERT-C trial – Results

- No significant improvement in PFS and OS in the *KRAS/BRAF* WT group (median follow-up 63.8 months)





RAPIDO Trial



Primary endpoint 3 year DFS

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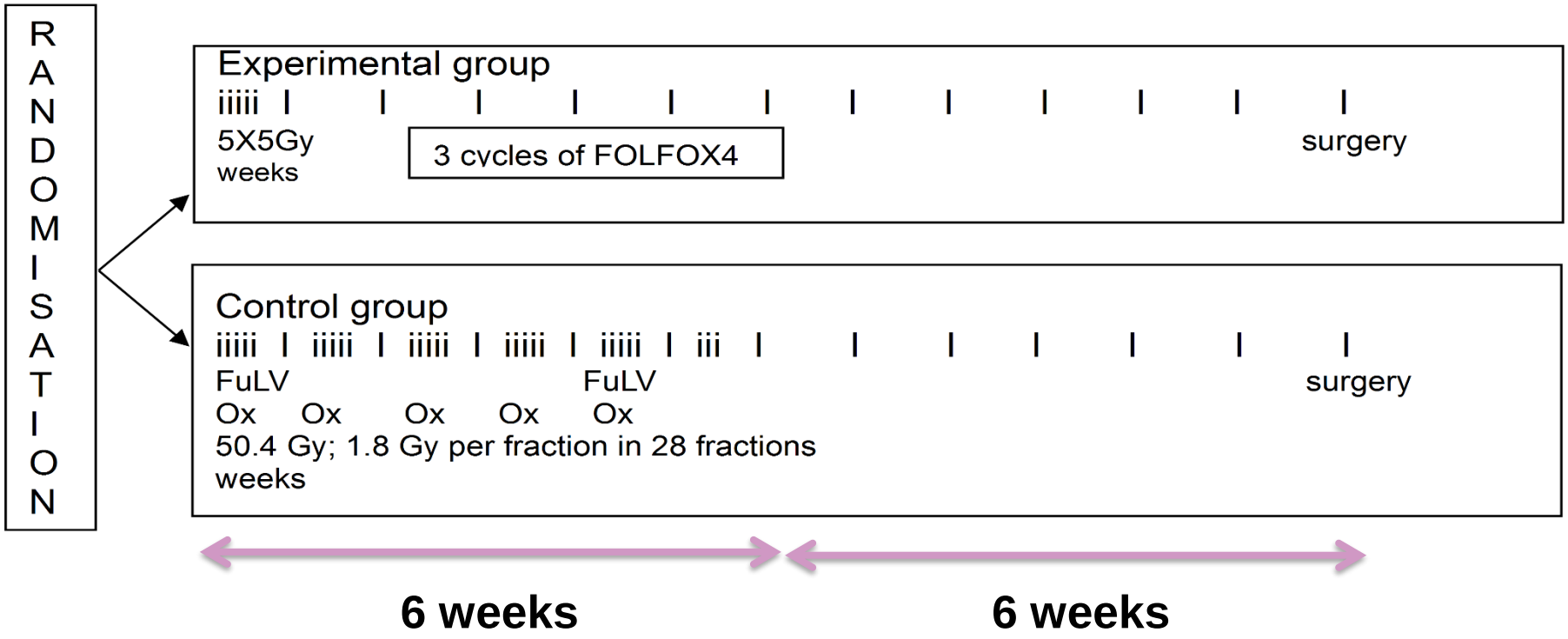
Polish-2: study design



N = 540, randomized 1:1

cT4 or fixed at DRE cT3

M0

ECOG 0-2

Treatment length and total oxaliplatin dose were balanced.

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Primary end-point [n=515]

R0 resection rates (surgery performed & pathologic R0 status):

77% for SCPRT with 3 cycles of chemotherapy

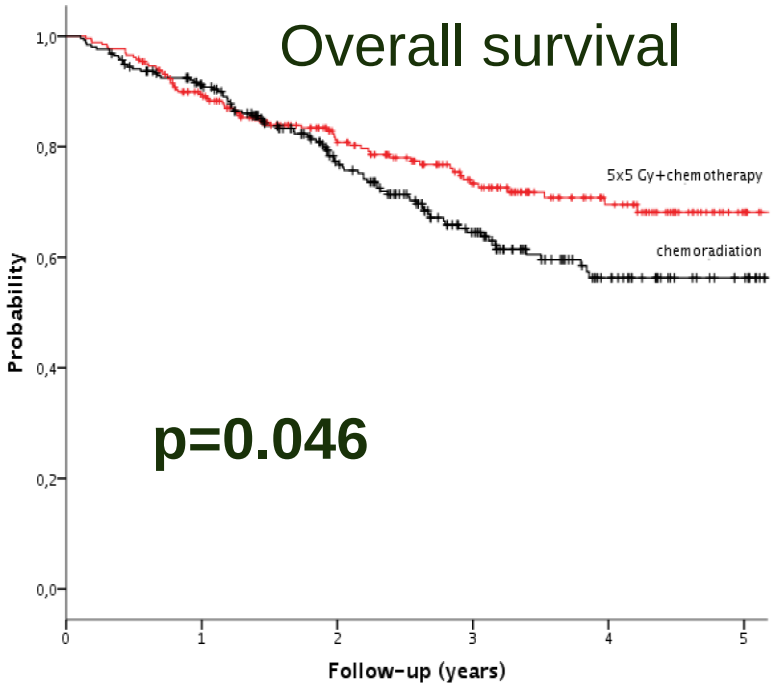
71% for CRT (control arm)

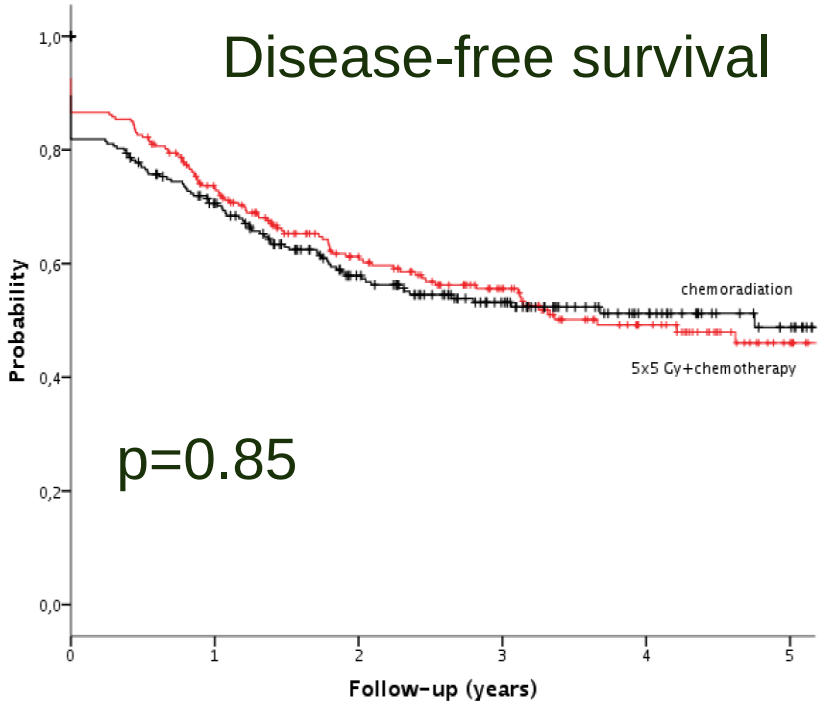
(p=0.081)

Secondary end-points

	SCRTx + FOLFOX4	CRTx	P value
Overall acute toxicity	**75%**	**83%**	**p= 0.006**
Grade III/IV toxicities	23%	21%	NS
pCR rate	16%	12%	p= 0.17

Polish-2: Secondary end-points





chemoradiation

short-course radiotherapy with consolidating chemotherapy

[median follow-up: 36 months]

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Conclusions

1. 5FU-based CRT more effective (downsizing) than RT but no improvement in SpS, DFS or OS
2. SCPRT = CRT in resectable cancer
3. Radio-sensitizing 5FU-based CRT with sub therapeutic oxaliplatin ?
4. But minimal benefit for T3N0 on mets
5. Biologicals have not yet delivered
6. Immunotherapy is coming


Thank you for listening

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NEW DRUGS AND RT: WHAT IS KNOWN AND WHAT IS NOT?

Barbara Alicja Jereczek-Fossa, MD PhD

European Institute of Oncology & University of Milan, Milan, Italy

AIRC

Fondazione Umberto Veronesi – per il progresso delle scienze

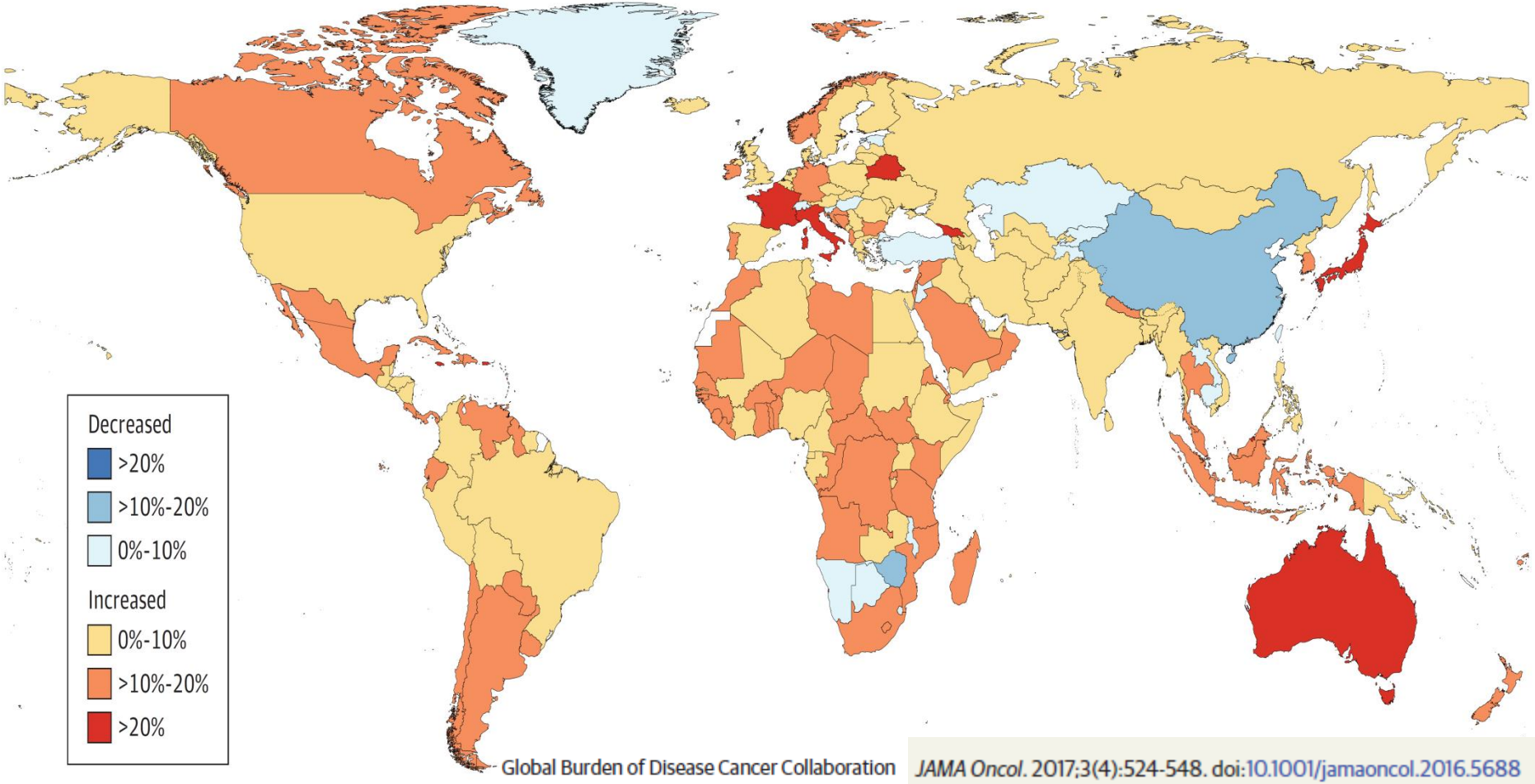
UNIVERSITÀ DEGLI STUDI DI MILANO

Fondazione IEO·CCM RICERCA ONCOLOGICA E CARDIOVASCOLARE

IEO Istituto Europeo di Oncologia

Cancer incidence is increasing

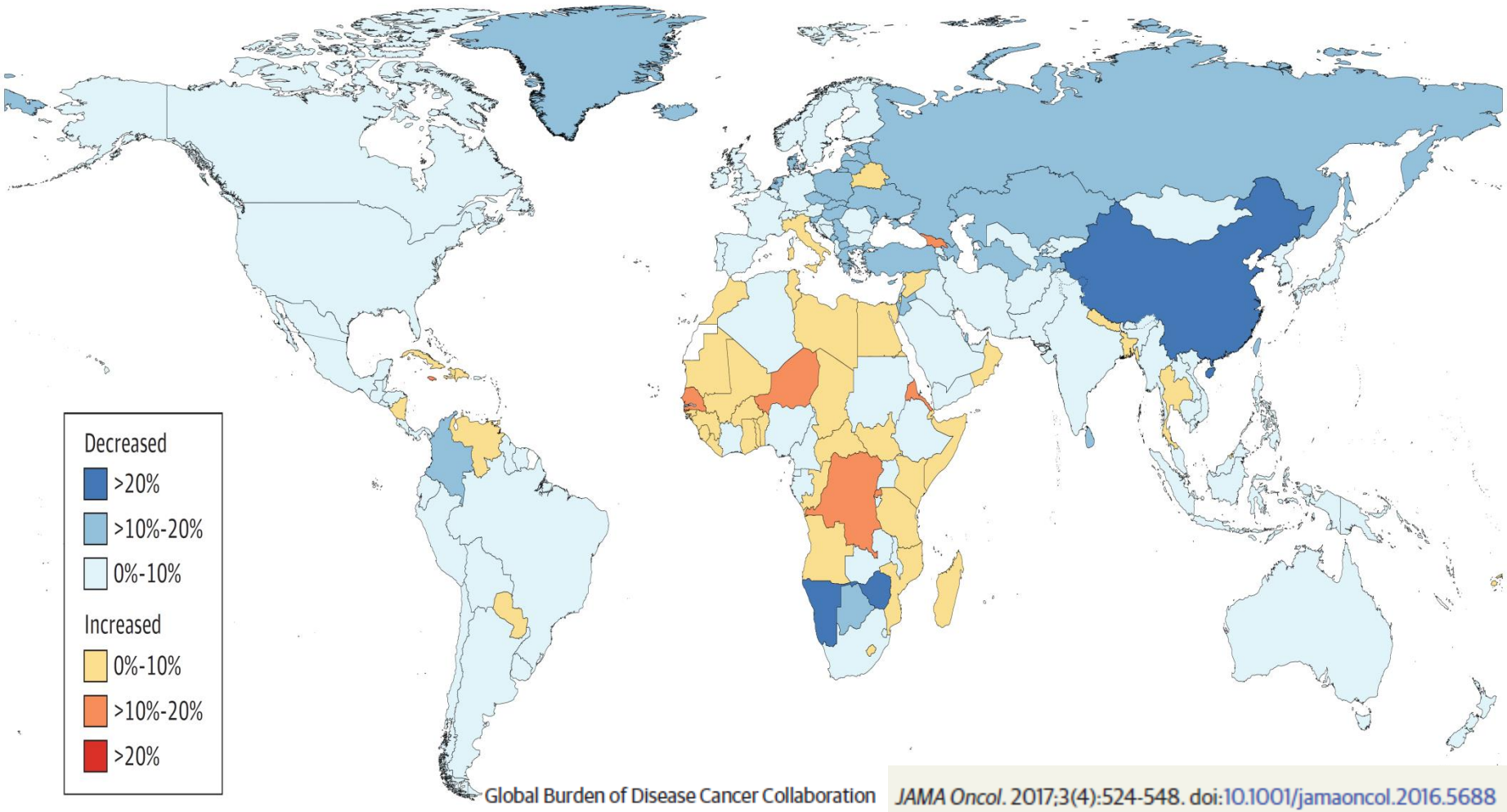
Figure 2. Relative Changes in Age-Standardized Cancer Incidence Rates in Both Sexes for All Cancers in 195 Countries or Territories From 2005 to 2015



JAMA Oncol. 2017;3(4):524-548. doi:10.1001/jamaoncol.2016.5688

Cancer mortality is decreasing

Figure 3. Relative Changes in Age-Standardized Cancer Mortality Rates in Both Sexes for All Cancers in 195 Countries or Territories From 2005 to 2015



JAMA Oncol. 2017;3(4):524-548. doi:10.1001/jamaoncol.2016.5688

COMBINED DRUG + RT

1. RT + CHT
2. RT+ HT
3. RT+ target therapy
4. RT+ immunotherapy

RT + CHT

Advanced and large tumors

RT+CHT: one of the strongest impacts on current cancer radiation therapy practice

In particular concurrent approach

Superior to radiation therapy alone in

controlling locoregional disease and in improving patient survival

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RATIONALE RT+CHT: increase therapeutic ratio

- Spatial cooperation
- Independent toxicity
- Enhancement of tumor response
- Protection of normal tissue

Steel and Peckham 1979

MECHANISMS (1)

- Increasing initial radiation damage
- Inhibition of cellular repair
- Cell cycle distribution
- Counteracting hypoxia-associated tumor resistance

MECHANISMS (2)

- Inhibition of tumor cell repopulation
- Molecular signaling pathways responsible for radioresistance
- Targeting tumor microenviroment
- Targeting tumor stem cells (radioresistance)

Mechanisms of radiosenstitization

Platinum-based compounds	Inhibition of DNA synthesis Inhibition of transcription elongation by DNA interstrand cross-links Inhibition of repair of radiation-induced DNA damage
Taxanes	Cellular arrest in the G_2M phase of the cell cycle Induction of apoptosis Reoxygenation of tumor cells
Topoisomerase I inhibitors	Inhibition of repair of radiation-induced DNA strand breaks Redistribution into G_2 phase of the cell cycle Conversion of radiation-induced single-strand breaks into double-strand breaks
Hypoxic cell cytotoxins	Complementary cytotoxicity with radiation on euoxic and hypoxic tumor cells
Antimetabolites	Nucleotide pool perturbation Lowering apoptotic threshold Cell cycle redistribution Tumor cell reoxygenation
Temozolomide	DNA repair inhibition (radiosensitization effect may be subject to MGMT status)

Perez Brady's 2013

We know how to combine

Strategy	Advantages	Disadvantages
Sequential chemoradiation	• Least toxic • Maximizes systemic therapy • Smaller radiation fields if induction shrinks tumor	• Increased treatment time • Lack of local synergy
Concurrent chemoradiation	• Shorter treatment time • Radiation enhancement	• Compromised systemic therapy • Increased toxicity • No cytoreduction of tumor
Concurrent chemoradiation and adjuvant chemotherapy	• Maximizes systemic therapy • Radiation enhancement • Both local and distant therapy delivered up front	• Increased toxicity • Increased treatment time • Difficult to complete chemotherapy after chemoradiation
Induction chemotherapy and concurrent chemoradiation	• Maximizes systemic therapy • Radiation enhancement	• Increased toxicity • Increased treatment time • Difficult to complete chemoradiation after induction therapy

Perez Brady's 2013

Perez Brady's 2013

We know who benefits

Disease Site	Commonly Used Chemotherapeutic Agents	Sequencing and Intent of Therapy	Benefit of Combined-Modality Approach
Locally advanced head and neck cancer	Cisplatin, 5-FU, hydroxyurea, carboplatin, cetuximab	• Definitive concurrent • Postoperative concurrent	Definitive: Organ preservation/survival benefit Postoperative: DFS/LRC benefit; overall survival benefit in subset of patients
Glioblastoma multiforme	Temozolomide	• Postoperative concurrent • Definitive concurrent in unresectable cases	Overall survival
Locally advanced/unresectable non–small cell lung cancer	Cisplatin, carboplatin, paclitaxel, cisplatin, etoposide, vinblastine	• Definitive concurrent • Sequential	Overall survival
Limited-stage small cell lung cancer	Cisplatin/etoposide	• Definitive concurrent	Overall survival
Esophageal cancer	Cisplatin/5-FU	• Preoperative concurrent • Definitive concurrent	Local control, overall survival
Gastric cancer	5-FU, leucovorin	• Postoperative concurrent	Overall survival
Pancreatic cancer	5-FU, gemcitabine	• Postoperative concurrent • Definitive concurrent in unresectable patients	Locoregional control, possibly survival
Locally advanced rectal cancer	5-FU, Xeloda	• Preoperative concurrent	Improved sphincter preservation, improved DFS
Anal cancer	5-FU, mitomycin-C	• Definitive concurrent	Improved colostomy-free survival
Cervical cancer	Cisplatin, 5-FU, hydroxyurea	• Definitive concurrent	Overall survival benefit
Bladder cancer	Cisplatin, 5-FU, mitomycin-C	• Definitive concurrent	Bladder preservation

Level 1 evidence

Primary	Systemic agent	Advantage of combined treatment compared with radiation alone
Glioblastoma (brain)	Temozolomide	Improved OS
Head and neck	Cisplatin, cetuximab	Improved OS
Lung	Cisplatin	Improved OS
Esophagus	5FU + cisplatin	Improved OS
Stomach	5FU + leucovorin	Improved OS compared with no treatment
Rectum	5FU	Improved OS
Anus	5FU + mitomycin	Improved local control
Cervix	Cisplatin	Improved OS
Prostate	Androgen deprivation therapy	Improved OS
Bladder	5FU + mitomycin	Improved local control

CHEMORADIATION HAS STILL VERY NARROW THERAPEUTIC INDEX

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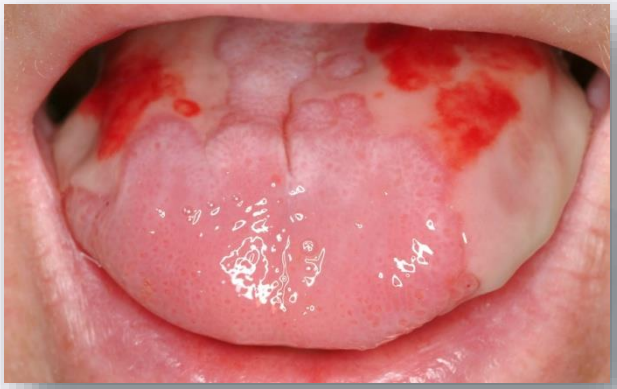
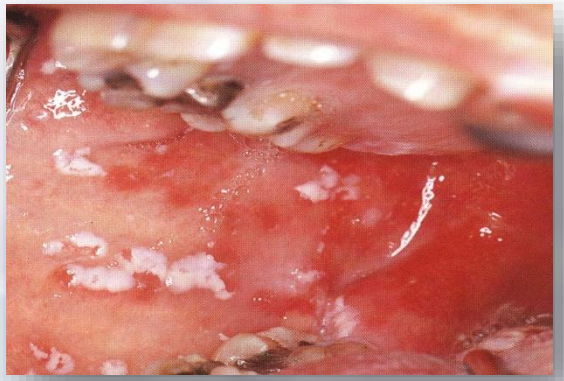
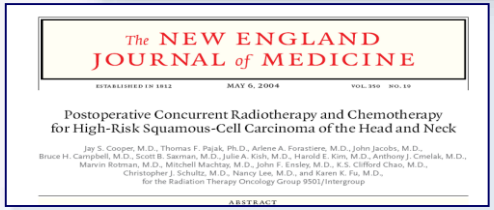
ACUTE TOXICITY: G3-G4







The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 6, 2004 VOL. 350 NO. 19

Postoperative Concurrent Radiotherapy and Chemotherapy for High-Risk Squamous-Cell Carcinoma of the Head and Neck

Jay S. Cooper, M.D., Thomas F. Pajak, Ph.D., Arlene A. Forastiere, M.D., John Jacobs, M.D., Bruce H. Campbell, M.D., Scott B. Saxman, M.D., Julie A. Kish, M.D., Harold E. Kim, M.D., Anthony J. Cmelak, M.D., Marvin Rotman, M.D., Mitchell Machtay, M.D., John F. Ensley, M.D., K.S. Clifford Chao, M.D., Christopher J. Schultz, M.D., Nancy Lee, M.D., and Karen K. Fu, M.D., for the Radiation Therapy Oncology Group 9501/Intergroup

ABSTRACT

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Postoperative Irradiation with or without Concomitant Chemotherapy for Locally Advanced Head and Neck Cancer

Jacques Bernier, M.D., Ph.D., Christian Domenge, M.D., Mahmut Ozsahin, M.D., Ph.D., Katarzyna Matuszewska, M.D., Jean-Louis Lefèbvre, M.D., Richard H. Greiner, M.D., Jordi Giralt, M.D., Philippe Maingon, M.D., Frédéric Rolland, M.D., Michel Bolla, M.D., Francesco Cognetti, M.D., Jean Bourhis, M.D., Anne Kirkpatrick, M.Sc., and Martine van Glabbeke, Jr., M.Sc., for the European Organization for Research and Treatment of Cancer Trial 22931

ABSTRACT

Study	RT	CHT-RT
RTOG	34%	77%
EORTC	21%	41%

- **Toxic deaths: 2%**

Combined toxicity

Agent	Toxicity	Mechanism
Bleomycin	Pneumonitis/pulmonary fibrosis	Undefined but related to total drug dose and effects on pulmonary macrophages, type I and II alveolar cells; effects/lethality exacerbated by the administration of radiation.
Actinomycin D	Hepatopathy	Altered liver function postradiation leads to decreased metabolism of agents, including actinomycin, which in turn worsens the hepatopathy.
Doxorubicin	Cardiomyopathy	There is an additive interaction between doxorubicin and radiation with recall of radiation effects occurring. Primary radiation effect is on the endothelial cell, whereas doxorubicin affects the connective tissue stroma of the myocardium.
Methotrexate	Leukoencephalopathy	Methotrexate may cause this syndrome on its own. Radiation effects on the blood–brain barrier and the choroid plexus can alter methotrexate clearance, leading to higher levels in the brain. Effects are increased when both modalities are used.
Cisplatin	Sensorineural hearing loss	While cisplatinum alone can cause this, reports suggests radiation therapy concurrently with cisplatin may contribute to sensorineural hearing loss.

Perez Brady's 2013

COMBINED DRUG + RT

1. RT + CHT
2. RT+ HT
3. RT+ target therapy
4. RT+ immunotherapy

TARGET THERAPY
AND
HIGH PRECISION RADIOTHERAPY

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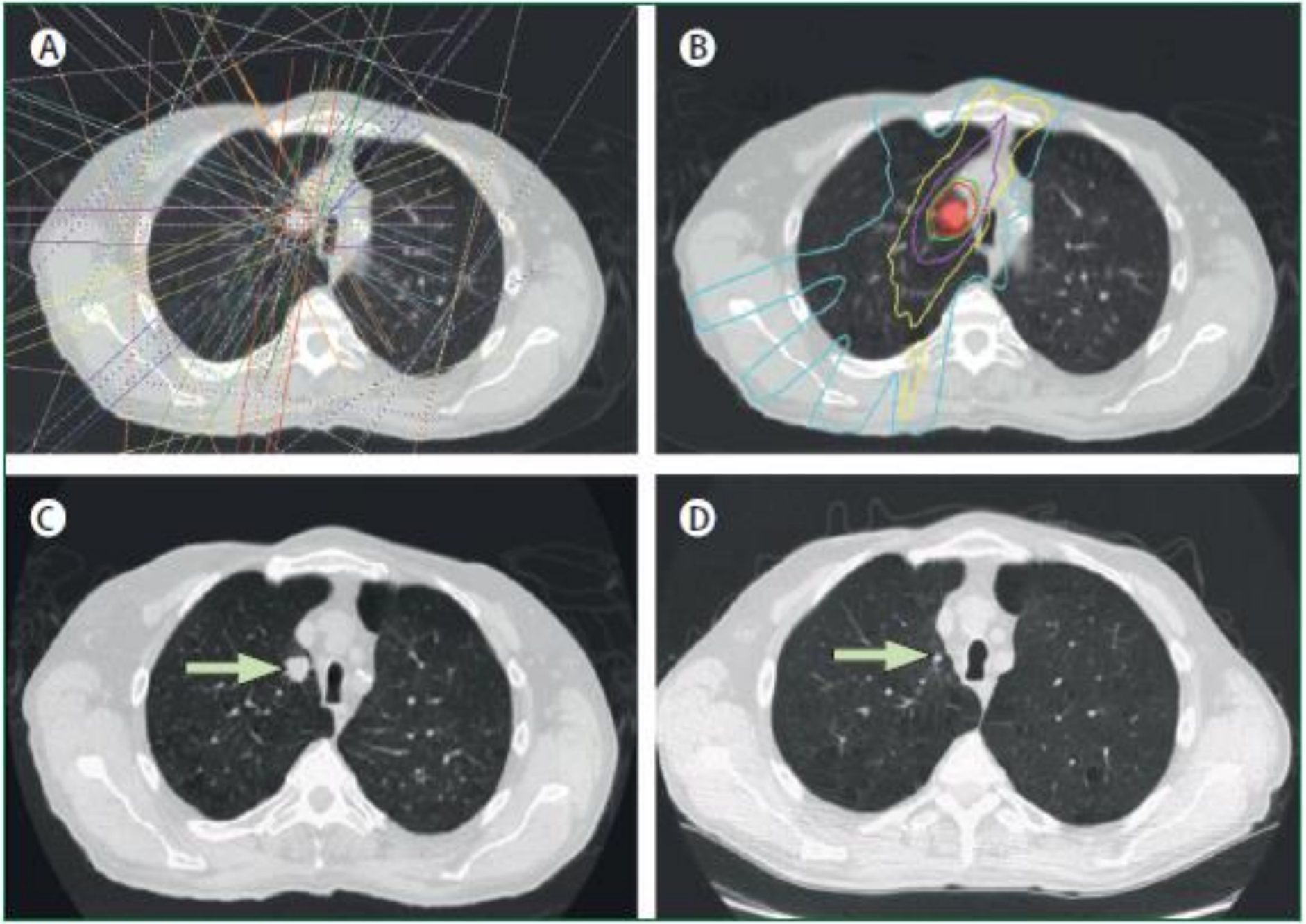
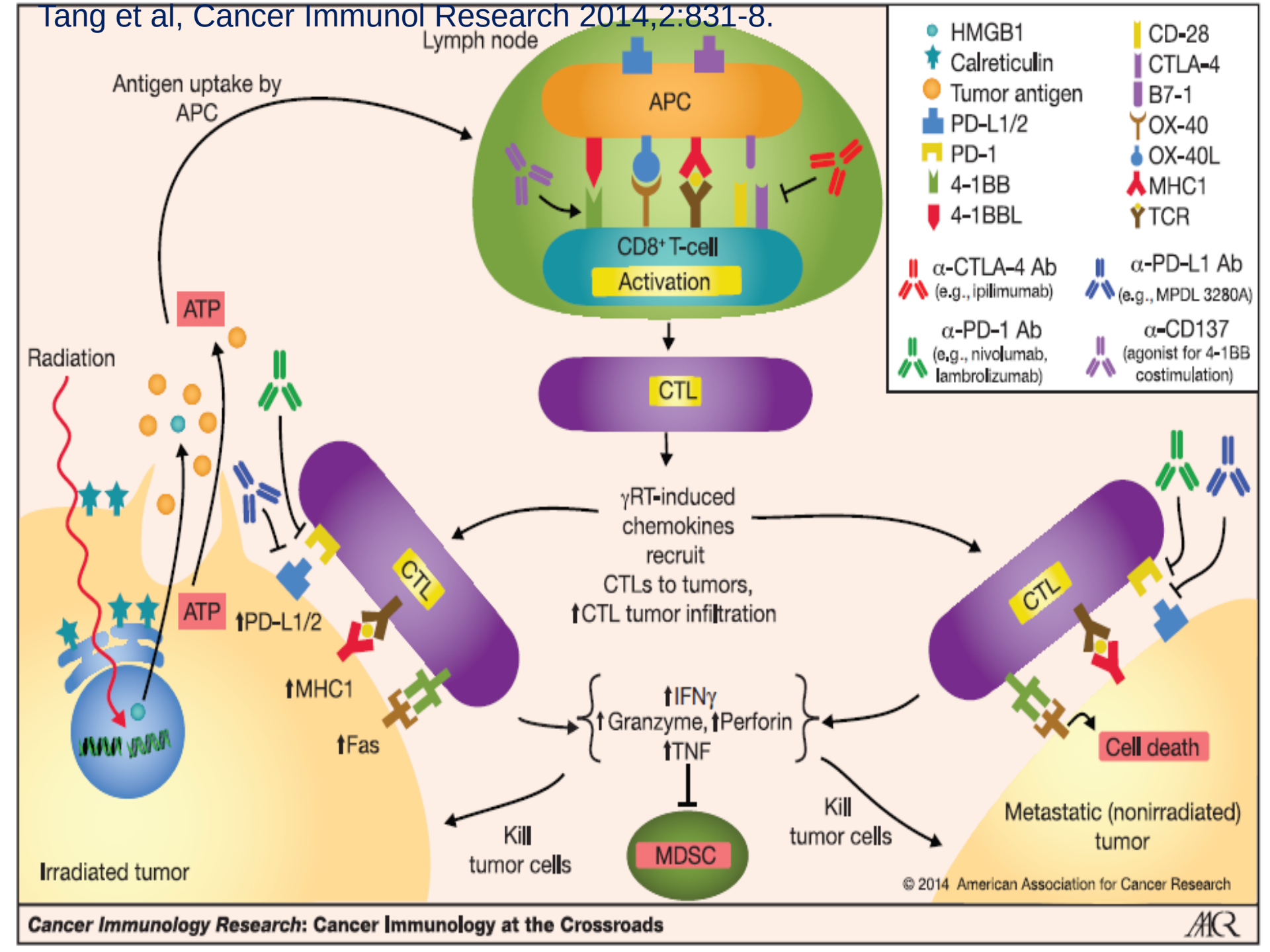


Figure 1: SABR in the lung

Tang et al, Cancer Immunol Research 2014,2:831-8.



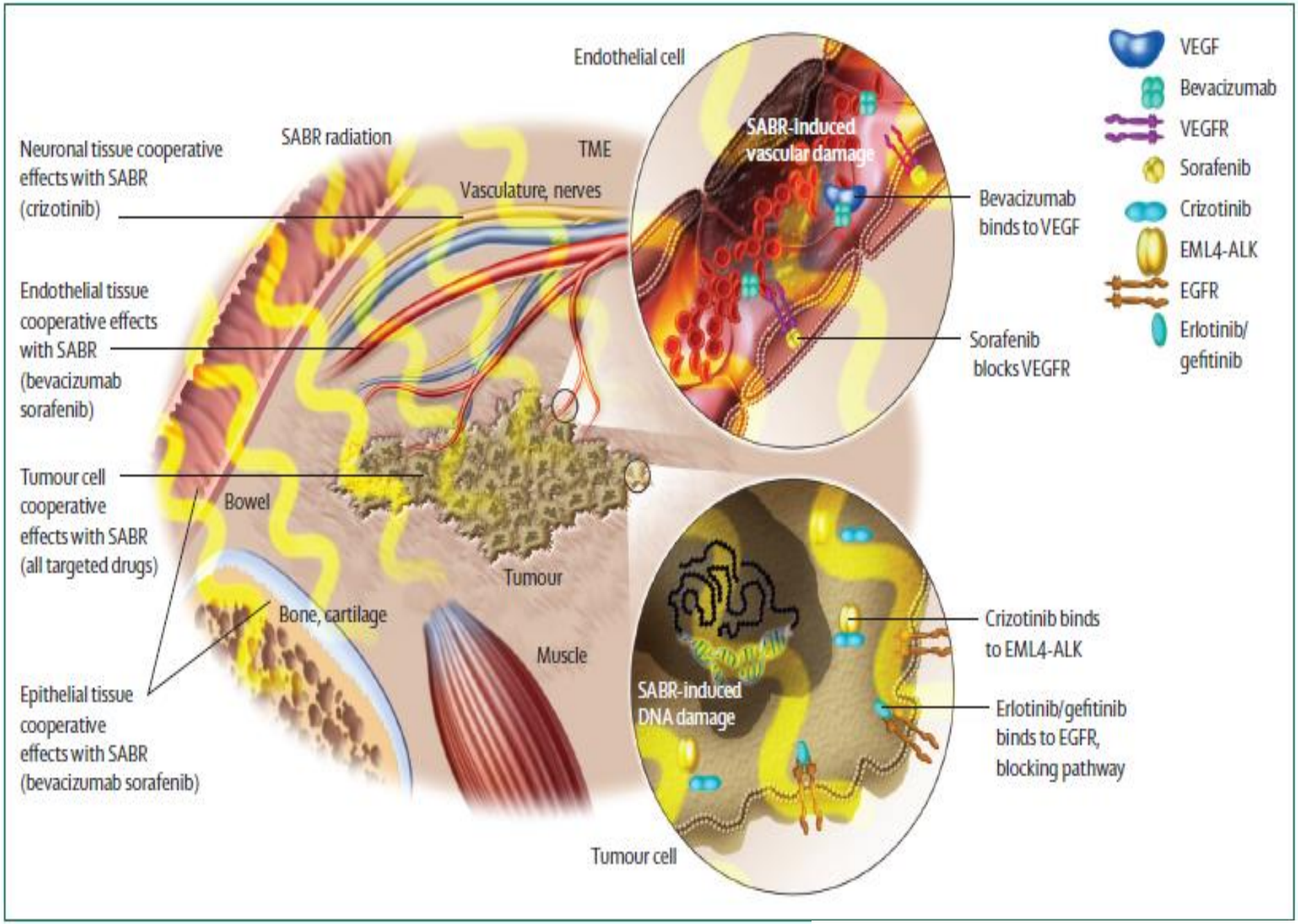


Figure 2: Potential interactions between SABR and targeted drugs

Zeng et al. *Lancet Oncol* 2014; 15: e426–34

SBRT and drugs

Mechanisms

1. Reversal of hypoxia (normalisation of tumor flow)
2. Reduction of tumor size (direct and indirect)
3. Facilitation of apoptosis
4. Prevention of SBRT re-vascularisation
5. Improvement of immune response (microenvironment)

Tree et al. Lancet Oncol 2013, De Meerleer et al. Lancet Oncol 2014
Grimaldi et al. Oncoimmunol 2014, Scheithauer et al. Radiat Oncol 2014

EVIDENCE?

Very few new drug–radiotherapy combinations are registered

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EVIDENCE?

There are no guidelines on the

RT+new agents evaluation.

Almost all data are retrospective

NEW DRUGS AND RT: WHAT IS KNOWN?

SBRT and drugs

- Combined modality mainly studied in:

•brain metastases
•or recurrent glioblastoma

- Less data is available for extra-cranial SRT.

TOXICITY OF TARGET THERAPY AND RADIOTHERAPY

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Toxicity of concurrent SRT and antibody therapy

Anti-VEGF (bevacizumab)

- additional risk of concurrent cranial SRT and bevacizumab is small (neurological toxicity)
- possibly protective to the development of radionecrosis.
- combination of bevacizumab and extra-cranial SBRT: scarce data
- concurrent abdominal SRT and bevacizumab should be practised with caution.

Kroeze S et al. Cancer Treatment Reviews 53 (2017) 25–37

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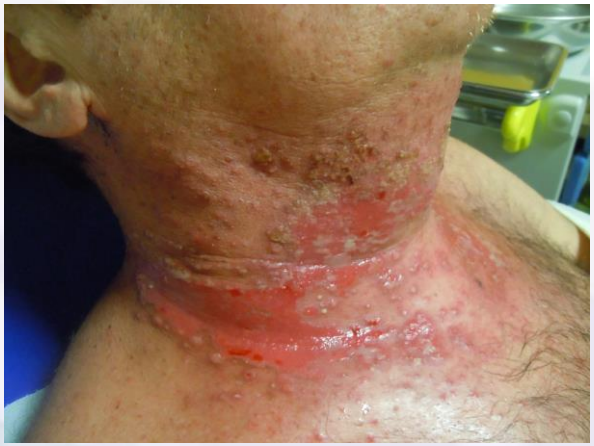
Toxicity of concurrent SRT and antibody therapy

Anti-EGF-R (cetuximab)



- Cetuximab + SRT studied only in recurrent HNC (re-RT)
- Considerable risk of severe toxicity (re-RT)
- Not clear to which extent concurrent cetuximab adds to the toxicity.

Kroeze S et al. Cancer Treatment Reviews 53 (2017) 25–37

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Toxicity of concurrent SRT and antibody therapy

Anti-Her2 (trastuzumab)

- Very limited available data **does not indicate increased toxicity** of cranial SRT combined with trastuzumab.

- Data on trastuzumab and extra-cranial SRT is lacking.

Kroeze S et al. Cancer Treatment Reviews 53 (2017) 25–37

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Toxicity of concurrent SRT and immune checkpoint inhibition

Anti-CTLA-4 (ipilimumab)

- **Concurrent cranial SRT with ipilimumab is safe.**

- **Limited data on the use ipilimumab concurrent with extra-cranial SRT.**

Toxicity of concurrent SRT and immune checkpoint inhibition

Anti-PD-1/PD-L1 (nivolumab, pembrolizumab)

- Data on combined SRT and nivolumab is **insufficient** for conclusions, both for cranial and extra-cranial SRT.

- Data about the combination of pembrolizumab with SRT is **not available.**

Kroeze S et al. Cancer Treatment Reviews 53 (2017) 25–37

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Toxicity of concurrent SRT and tyrosine kinase inhibitors (TKIs)

Multi receptor TKIs (sorafenib, sunitinib)

- Cranial SRT **+ sorafenib or sunitinib: safe** but one grade 5 toxicity has been observed for sunitinib.
- For extra-cranial SRT, liver SRT combined with **sorafenib is associated with severe toxicity**
- No radiation induced toxicity sunitinib and extra-cranial SRT.

Kroeze S et al. Cancer Treatment Reviews 53 (2017) 25–37

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Toxicity of concurrent SRT and tyrosine kinase inhibitors (TKIs)

EGF-R-inhibitors (gefitinib, erlotinib, lapatinib)

- Concurrent EGF-R-targeting TKIs and extra-cranial SRT: **increased toxicity within the irradiated volume** in the treatment of abdominal and thoracic metastases

- No increased toxicity in cranial SRT

- Data on lapatinib+SRT is not available.

Kroeze S et al. Cancer Treatment Reviews 53 (2017) 25–37

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Toxicity of concurrent SRT and ALK-inhibitors

crizotinib, ceritinib, alectinib

available data **does not allow for a robust conclusion** on safety of combined crizotinib, ceritinib, alectinib and SRT.

Kroeze S et al. Cancer Treatment Reviews 53 (2017) 25–37

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Toxicity of concurrent SRT and BRAF-inhibitors

vemurafenib, dabrafenib

- Conflicting data on CNS toxicity after cranial SRT and BRAF-inhibitors
- **High rates of toxicity warrant caution.**
- No data on BRAF inhibitors and extra-cranial SRT.

Kroeze S et al. Cancer Treatment Reviews 53 (2017) 25–37

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Toxicity of concurrent SRT and MEK-inhibitors

MEK-inhibitors (trametinib)

Very small number of patients

No data

Kroeze S et al. Cancer Treatment Reviews 53 (2017) 25–37

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Safety: SBRT and drugs

- Safety data is available for SRT combined with

- Bevacizumab
- Ipilimumab
- EGFR-targeting TKIs.

❑ Bevacizumab may possible even prevent SRT-induced radionecrosis

Kroeze S et al. Cancer Treatment Reviews 53 (2017) 25–37

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RT + new drugs

1. Combination strategies not universally associated with increased risks

2. All combinations need to be evaluated individually

3. Different half-life of targeted therapy (range 24 h – 50d)

Sharma RA et al. Nature Reviews Clin Oncol 2016;13:627-

CONSENSUS STATEMENT

OPEN

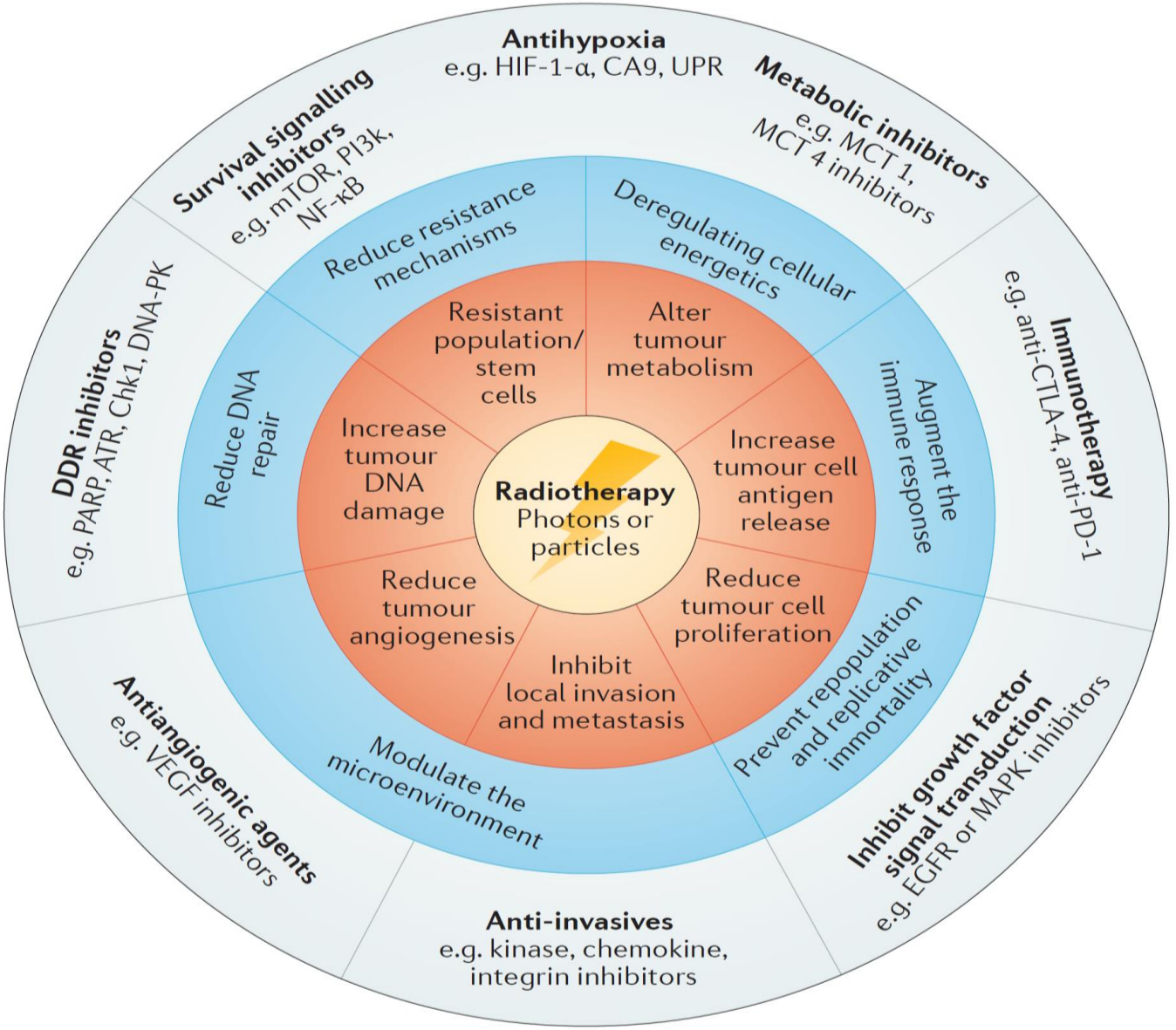
Clinical development of new drug–radiotherapy combinations

Ricky A. Sharma[1], Ruth Plummer[2], Julie K. Stock[3], Tessa A. Greenhalgh[4], Ozlem Ataman[5], Stephen Kelly[6], Robert Clay[7], Richard A. Adams[8], Richard D. Baird[9], Lucinda Billingham[10], Sarah R. Brown[11], Sean Buckland[6], Helen Bulbeck[12], Anthony J. Chalmers[13], Glen Clack[14], Aaron N. Cranston[15], Lars Damstrup[16], Roberta Ferraldeschi[17], Martin D. Forster[1], Julian Golec[18], Russell M. Hagan[19], Emma Hall[20], Axel-R. Hanauske[21], Kevin J. Harrington[20], Tom Haswell[12], Maria A. Hawkins[4], Tim Illidge[22], Hazel Jones[3], Andrew S. Kennedy[23], Fiona McDonald[20], Thorsten Melcher[24], James P. B. O'Connor[22], John R. Pollard[18], Mark P. Saunders[22], David Sebag-Montefiore[11], Melanie Smitt[25], John Staffurth[8], Ian J. Stratford[22] and Stephen R. Wedge[2] on behalf of the NCRI CTRad Academia-Pharma Joint Working Group

J Natl Cancer Inst 2013;105:11–24

NCI–RTOG Translational Program Strategic Guidelines for the Early-Stage Development of Radiosensitizers

Yaacov Richard Lawrence, Bhadrasain Vikram, James J. Dignam, Arnab Chakravarti, Mitchell Machtay, Boris Freidlin, Naoko Takebe, Walter J. Curran Jr, Soren M. Bentzen, Paul Okunieff, C. Norman Coleman, Adam P. Dicker



Combination strategies to augment biological effects of RT

Sharma RA et al. Nature Reviews Clin Oncol 2016;13:627-

IEO Istituto Europeo di Oncologia

Sharma RA et al. Nature Reviews Clin Oncol 2016;13:627-

CONSENSUS STATEMENT

OPEN

Clinical development of new drug–radiotherapy combinations

- 4 out of 10 patients with cancer who are cured by treatment receive radiotherapy.
- Combining novel drugs with RT has clear potential to significantly improve patient outcomes.
- When companies are considering testing a novel combination for an agent, they should consider drug–RT combinations as important as drug–drug combinations.

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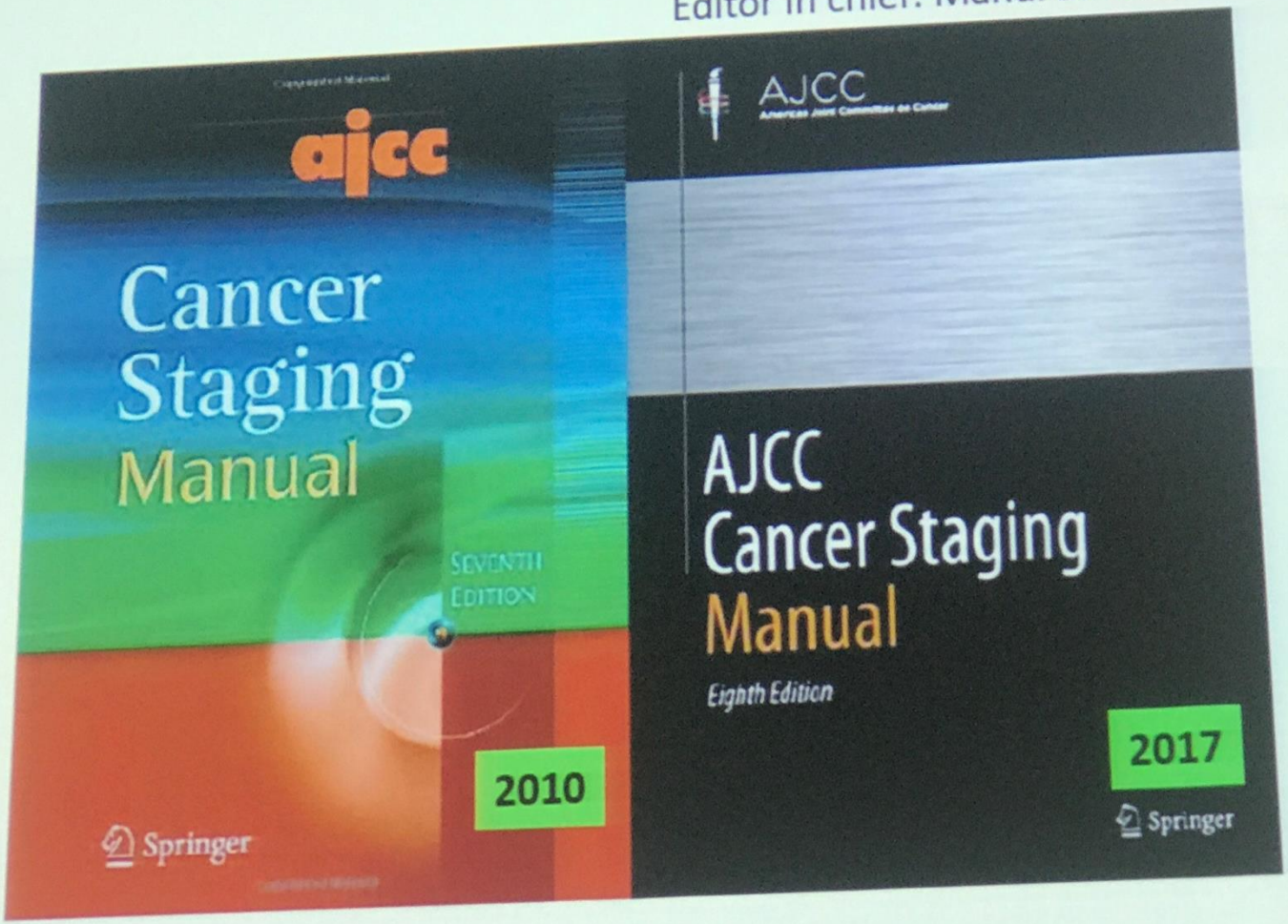
CHALLENGES

- 3% of all patients in the USA are included in the trials
- Linking genetic-clinical data re missing
- Even conventional prognostic factors are changing (TNM)
- Who should pay?

Editor in chief: Mahul B. Amin

1



"In order to ensure that the cancer care community has the necessary infrastructure in place for documenting 8th Edition stage, the **AJCC** Executive Committee, in dialogue with the National Cancer Institute **(NCI-SEER)**, Centers for Disease Control and Prevention **(CDC)**, the College of American Pathologists **(CAP)**, the National Comprehensive Cancer Network **(NCCN)**, the National Cancer Data Base **(NCDB)**, and the Commission on Cancer **(CoC)**, made the **decision to delay the implementation of the 8th Edition Cancer Staging System to January 1, 2018.**
All newly diagnosed cases through December 31, 2017 should be staged with the 7th edition." (From the AJCC website)

CHALLENGES

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CHALLENGES

3% of all patients in the USA are included in the trials

Linking genetic-clinical data re missing

Even conventional prognostic factors are changing (TNM)

Inequality in access to cancer cure

Global access to RT

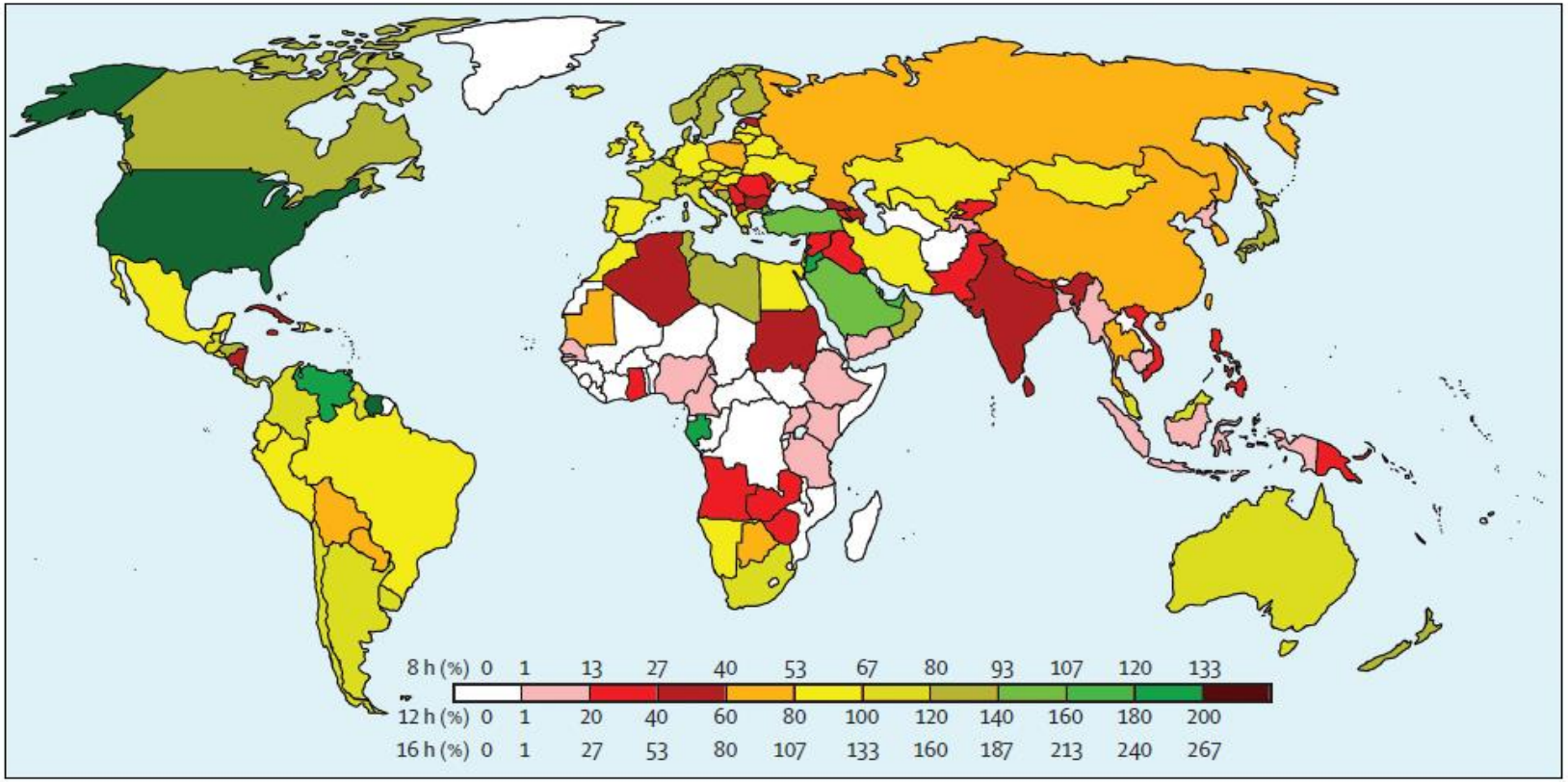

Figure 9: **Coverage of radiotherapy services according to country as determined by global equipment databases, an activity-based operations model, cancer incidence, and evidence-based estimates of radiotherapy need**

Estimates depend on the nature of equipment use. The colour bar shows the operational model: 12 h operation was used as the feasible case, but 8 h and 16 h were also modelled to capture typical and potential capacity, respectively.

Atun R et al. Lancet Oncol 2015;16:1153-86

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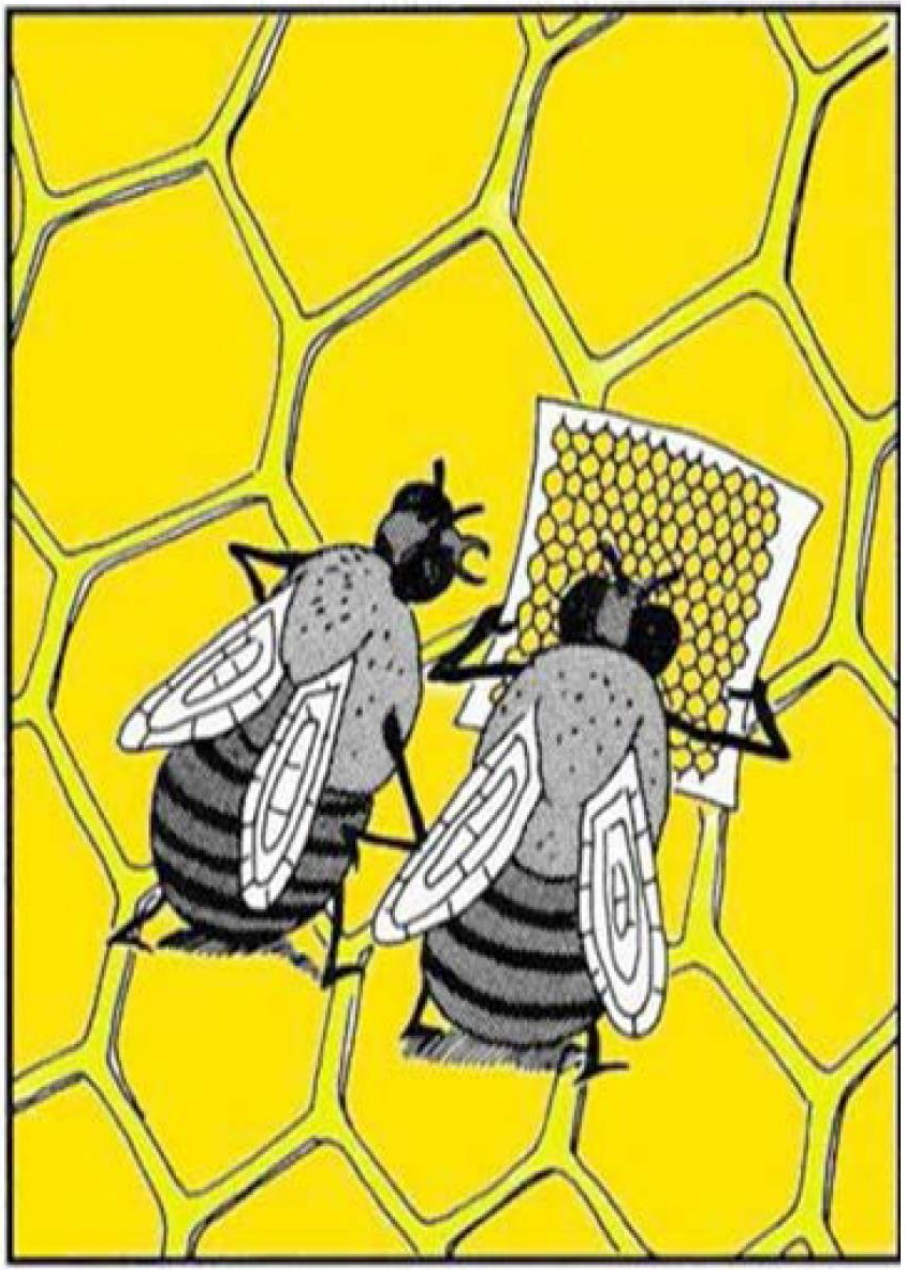
ESTRO Vision 2020

“

Every cancer patient in Europe will have access to state-of-the-art radiation therapy as part of a multidisciplinary approach where treatment is individualised for the specific patient’s cancer, taking account of the patient’s personal circumstances.

”

- ESTRO vision 2020 -



A lot to be done

Goodbye Bruxelles!