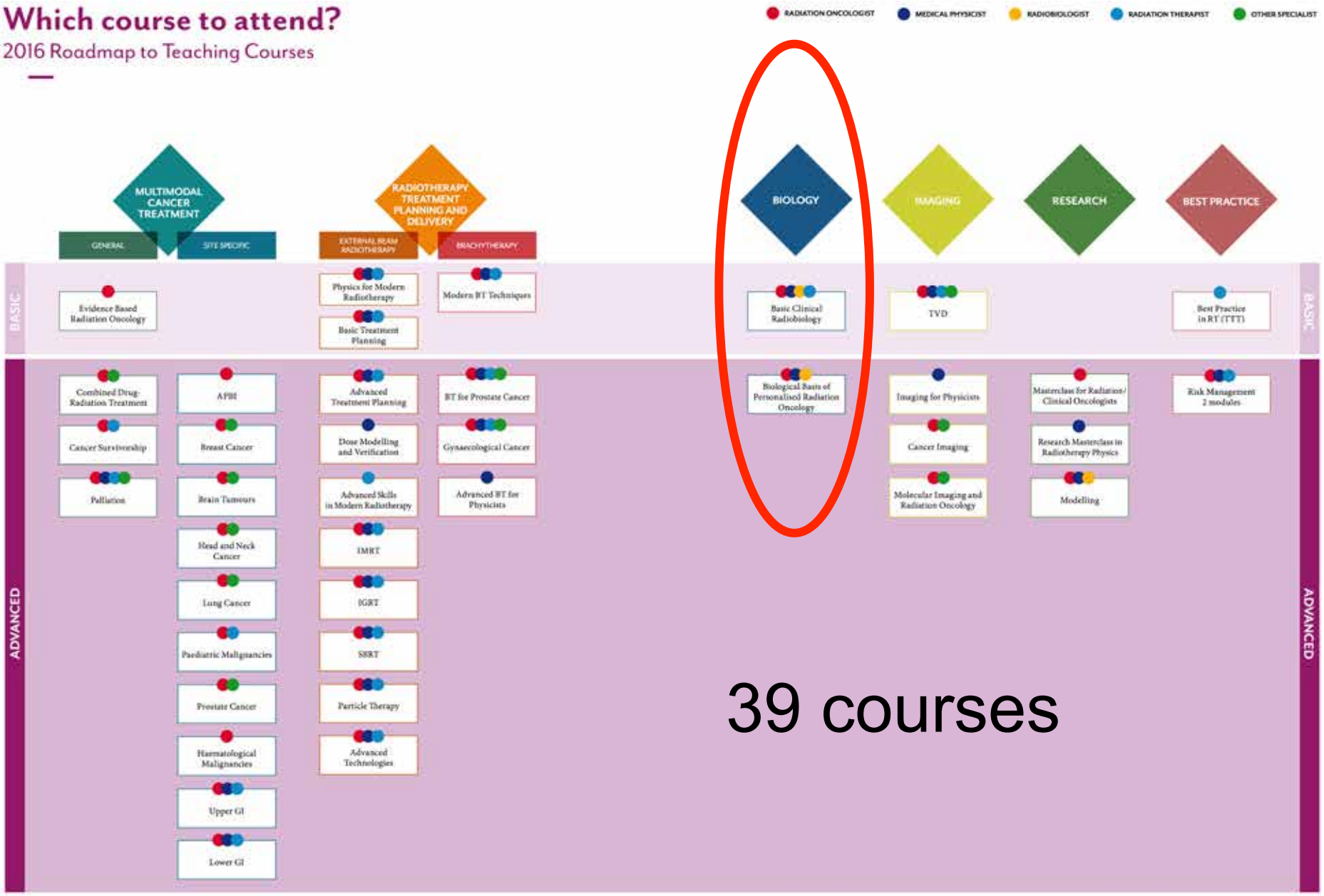

37th ESTRO teaching course on
Basic Clinical Radiobiology
Budapest, Hungary
February 2016

Which course to attend?

2016 Roadmap to Teaching Courses

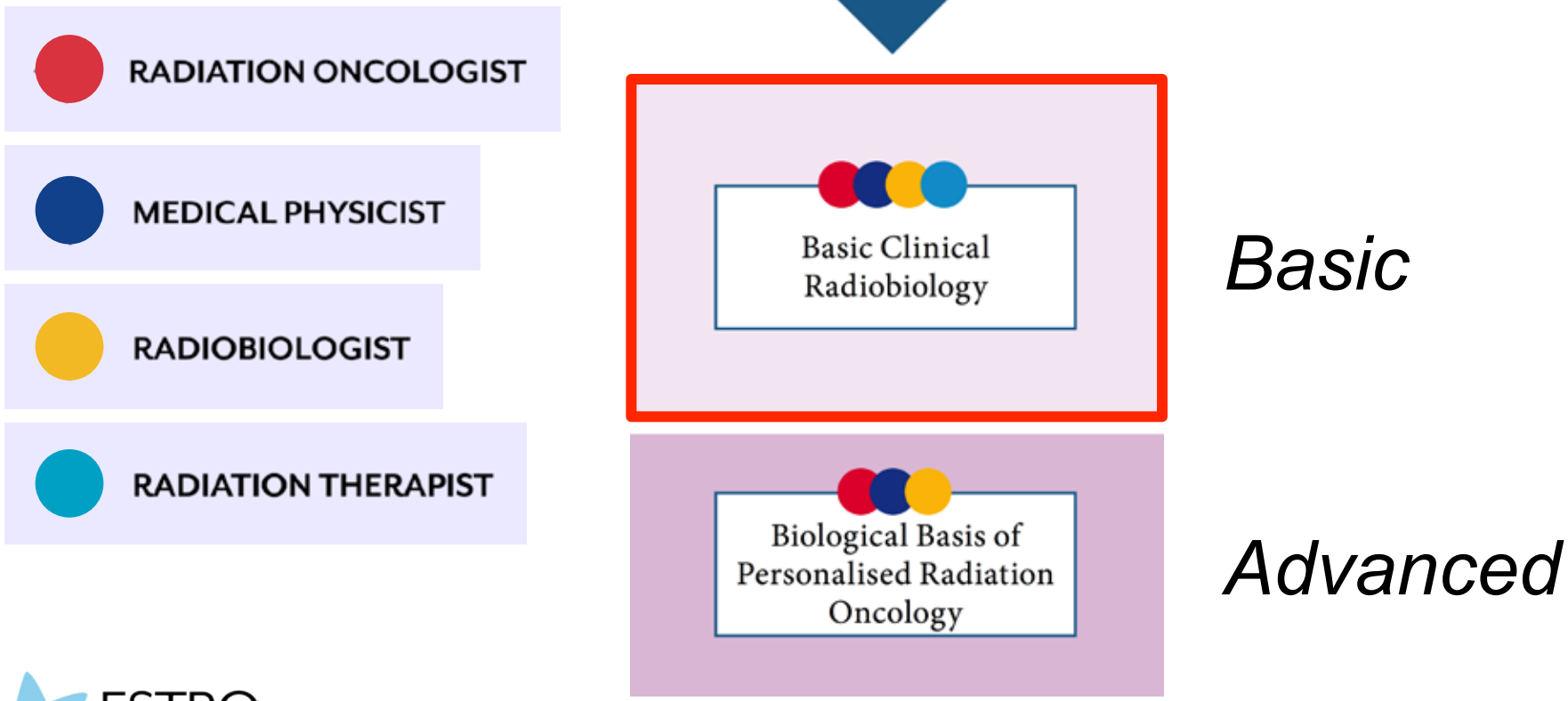


39 courses

ESTRO
European SocieTy for
RADIOTHERAPY
& ONCOLOGY

ESTRO School

Biology Courses



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Basic Clinical Radiobiology Locations

1.	Granada, Spain	16 – 20 November	1990
2.	Athens, Greece	5 – 9 October	1991
3.	Aarhus, Denmark	18 – 22 October	1992
4.	Tours, France	26 – 30 September	1993
5.	Prague, Czech Republic	16 – 20 October	1994
6.	Tübingen, Germany	24 – 28 September	1995
7.	Izmir, Turkey	24 – 28 November	1996
8.	Como, Italy	12 – 16 October	1997
9.	Lisboa, Portugal	25 – 29 October	1998
10.	Gdansk, Poland	17 – 21 October	1999
11.	Bratislava, Slovakia	8 – 12 October	2000
12.	Tenerife, Spain	7 – 11 October	2001
13.	St. Petersburg, Russia	25 – 29 August	2002
14.	Uppsala, Sweden	5 – 9 May	2002
15.	Santorini, Greece	12 – 16 October	2003
16.	Lausanne, Switzerland	19 – 23 September	2004
17.	Izmir, Turkey	2 – 6 October	2005
18.	Ljubljana, Slovenia	21 – 25 May	2006
19.	Lisboa, Portugal	17 – 21 September	2006

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Basic Clinical Radiobiology Locations

20. Beijing, China	3 – 7 June	2007
21. Sicily, Italy	14 – 18 October	2007
22. St. Petersburg, Russia	29 June – 3 July	2008
23. Dubrovnik, Croatia	5 – 10 October	2008
24. Sydney, Australia	22 – 27 March	2009
25. Shanghai, China	31 May – 5 June	2009
26. Toledo, Spain	18 – 23 October	2009
27. Prague, Czech Republic	16 – 20 May	2010
28. Kuala Lumpur, Malaysia	5 – 9 December	2010
29. Nijmegen, The Netherlands	1 – 5 June	2011
30. Rotorua, New Zealand	30 October – 3 November	2011
31. Athens, Greece	22 – 27 September	2012
32. Poznan, Poland	5 – 9 May	2013
33. Sydney, Australia	23 – 26 November	2013
34. Istanbul, Turkey	25 – 29 May	2014
35. Brussels, Belgium	7 – 11 March	2015
36. Brisbane, Australia	21 – 24 November	2015
37. Budapest, Hungary	**27 February – 3 March**	**2016**
38. Chengdu, China	6 – 10 July	2016

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Where, *When* do we teach BCR most?

Where

Three: Spain, Greece, Turkey, Australia, China

Two: Portugal, Italy, Czech Republic, Poland, Russia

When

Three: 2009 (Spain, China, Australia)

Two: 2002, 2006, 2007, 2008, 2010, 2011, 2013, 2015, 2016

Never before!

One: Hungary

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& ONCOLOGY

#18, 2006 in Ljubljana, Slovenia

Meet the Team

Budapest 2016

Bert van der Kogel, PhD

Netherlands & USA

Radiobiologist

Dept of Human Oncology
University of Wisconsin
Madison, WI

Rob Coppes, PhD

Netherlands

Radiobiologist

Dept of Radiation Oncology
University Medical Center
Groningen

Karin Haustermans, MD, PhD

Belgium

Radiation Oncologist

Dept of Radiation Oncology
University Hospital Gasthuisberg
Leuven

Vincent Grégoire, MD, PhD

Belgium

Radiation Oncologist

Dept of Radiation Oncology
Université Catholique de Louvain
St-Luc University Hospital
Brussels

Wolfgang Dörr, DVM, PhD

Austria & Germany

Radiobiologist

Dept of Radiation Oncology
Medical University of Vienna
Wien

Marianne Koritzinsky, PhD

Canada & Norway

Radiobiologist

Dept of Radiation Oncology
University of Toronto
Ontario Cancer Institute
Toronto

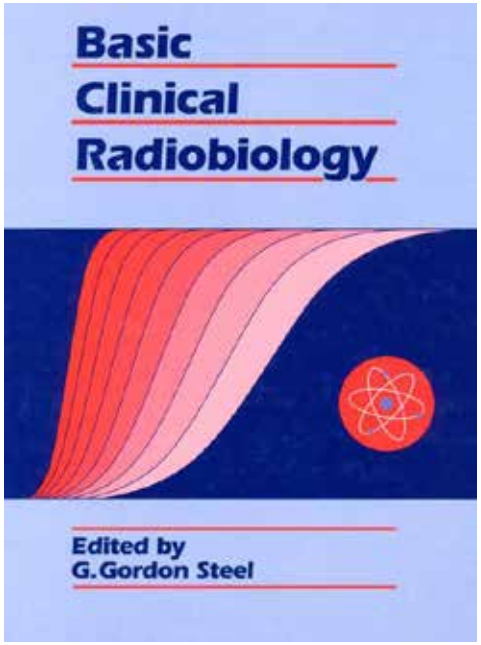
Mike Joiner, MA, PhD

USA & UK

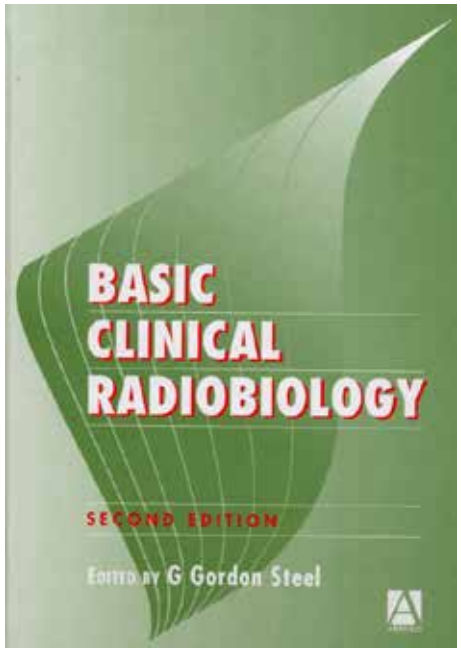
Radiobiologist

Dept of Oncology
School of Medicine
Wayne State University
Detroit, MI

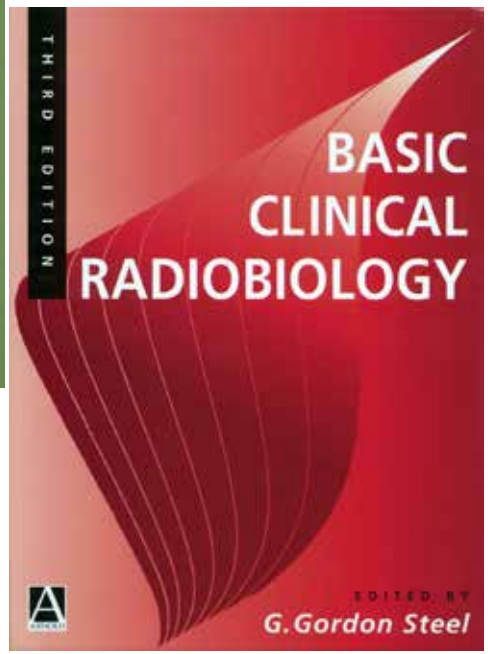
Meet the Book



1st Ed: 1993

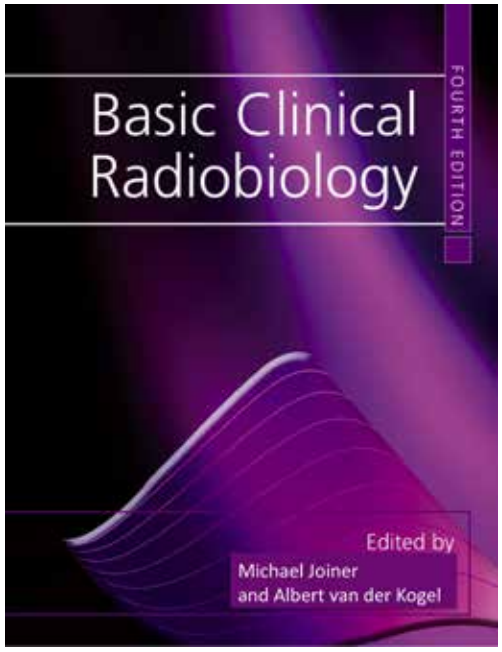


2nd Ed: 1997



3rd Ed: 2002

4th Ed: 2009

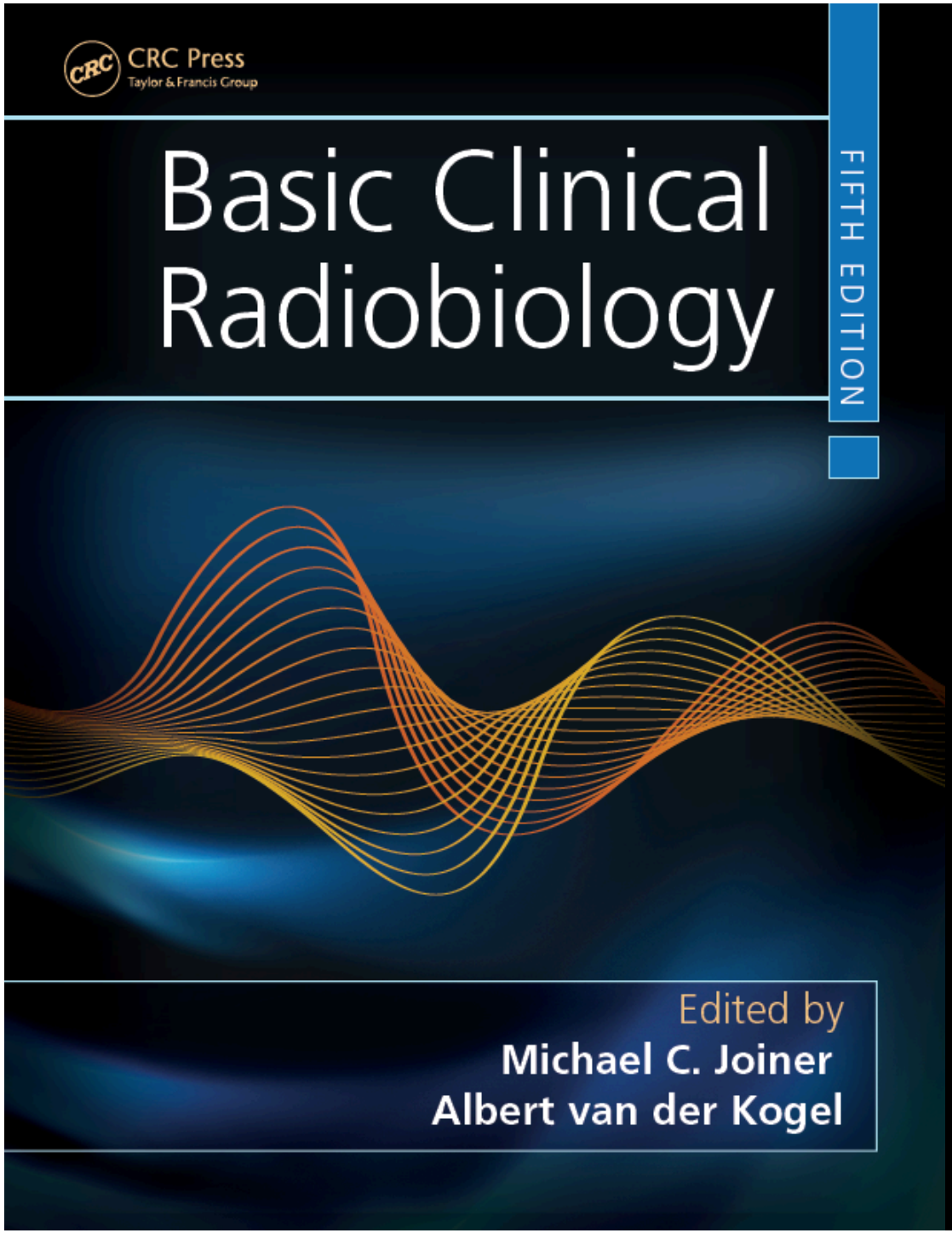


Translations of 4th edition

Chinese

Japanese

Russian



Appearing in 2016….

Radiation Oncology education and training in Europe is the best in the world

ESTRO

European Society for RADIOTHERAPY & ONCOLOGY

Countries attending BCR here in 2016

1	Albania	2	Greece	1	Russian Fed
1	Armenia	18	Hungary	1	Saudi Arabia
2	Austria	1	Jordan	1	Serbia
7	Belgium	1	Latvia	1	Slovakia
2	Bosnia/Herzegov.	1	Macedonia	8	Slovenia
1	Bulgaria	1	Malta	2	Spain
1	Croatia	1	Moldova Rep	7	Sweden
1	Czech Rep	1	Montenegro	10	Switzerland
5	Denmark	1	Morocco	15	The Netherlands
2	Estonia	9	Norway	1	Turkey
1	Finland	5	Poland	1	Ukraine
1	France	2	Portugal	1	United Kingdom
2	Germany	1	Romania		

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Specialities attending BCR here in 2016

Clinical Oncologist	**4**
Dosimetrist	**2**
Medical Physicist	**48**
Other Med Speciality	**4**
Other non-Med speciality	**1**
Radiation Oncologist	**45**
Radiobiologist	**10**
Therapist	**6**
	120

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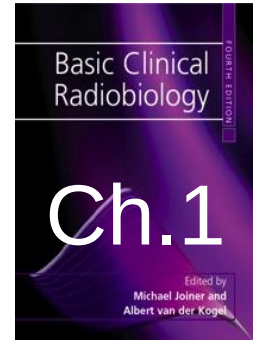
ESTRO School

Saturday 27 February

09:00-09:20	Introduction	M. Joiner
09.20-10.00	1.1 Importance of radiobiology in the clinic	V. Grégoire
10.00-10.30	1.2 Hallmarks of cancer	M. Koritzinsky
10.30-11.00	*Coffee break*	
11.00-11.45	1.3 Molecular basis of cell death	M. Koritzinsky
11.45-12.30	1.4 Cell survival – in vitro and in vivo	A. van der Kogel
12.30-13.00	General discussion	
13.00-14.00	*Lunch*	
14.00-14.45	1.5 Models of radiation cell killing	M. Joiner
14.45-15.30	1.6 Clinical side effects and its quantification	K. Haustermans
15.30-16.00	*Coffee break*	
16.00-17.00	1.7 Pathogenesis of normal tissue side effects	W. Dörr



Introduction to Clinical Radiobiology

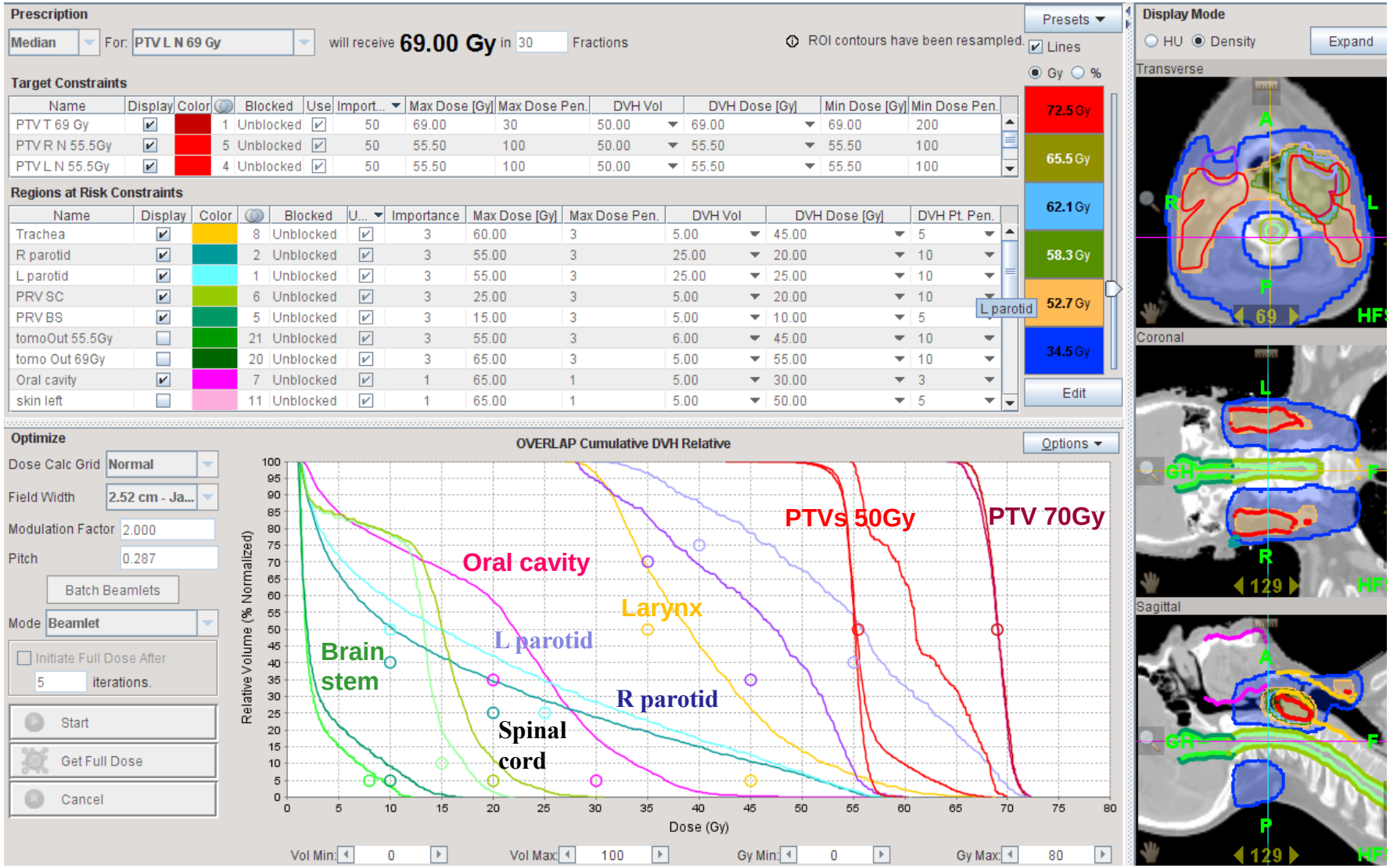
Prof. Vincent GREGOIRE
Université Catholique de Louvain,
Cliniques Universitaires St-Luc
Brussels, BELGIUM

ESTRO teaching course on basic clinical radiobiology

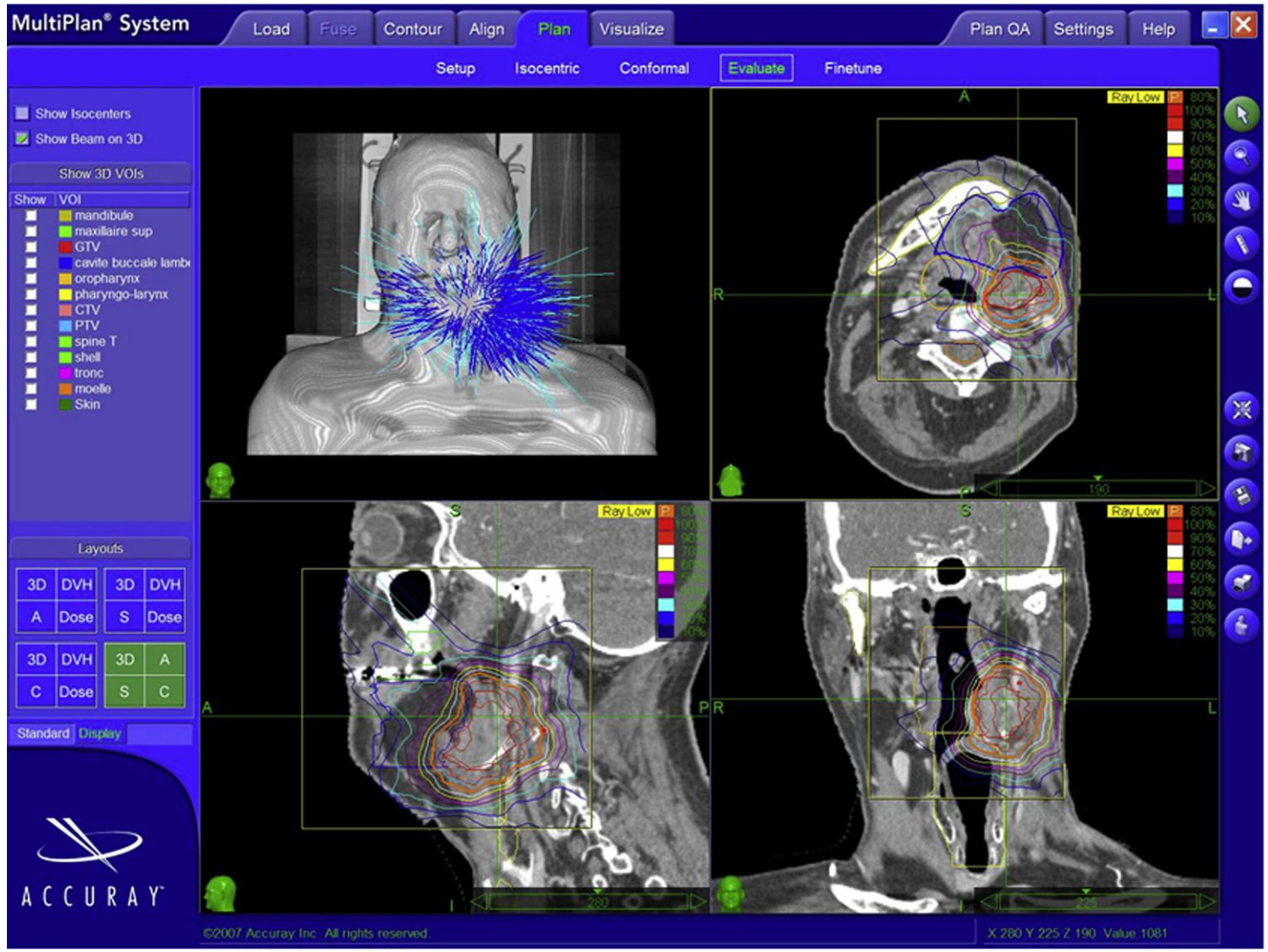
As pharmacology is to the internist so is radiation biology to the radiotherapist

H.Rodney Withers & Lester J. Peters
Textbook of Radiotherapy by G.H. Fletcher

“Supreme” conformality: IMRT, SBRT?



“Supreme” conformality: IMRT, SBRT?

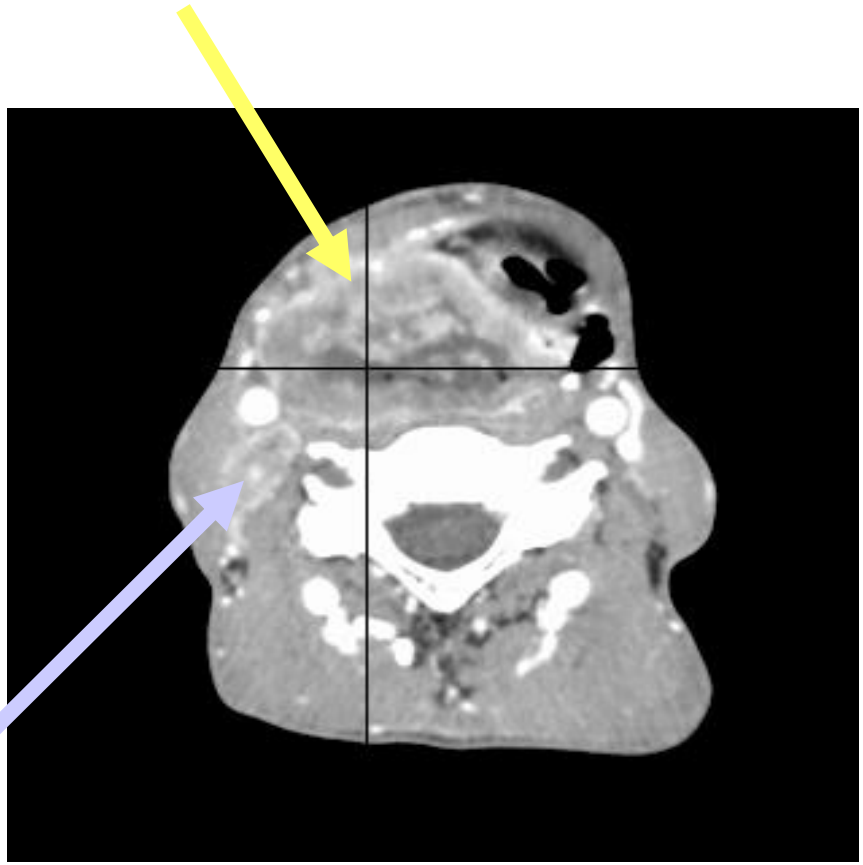


ESTRO 2015

Comet et al, 2012

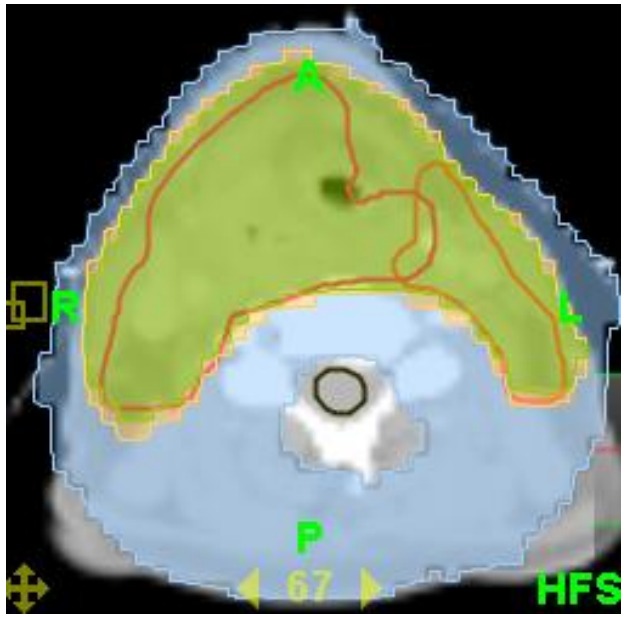
Clinical case

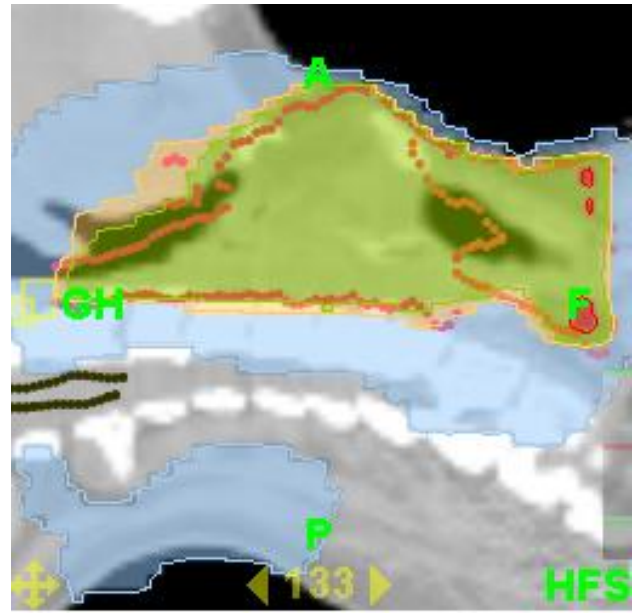
T4 N1 M0 hypopharyngeal SCC



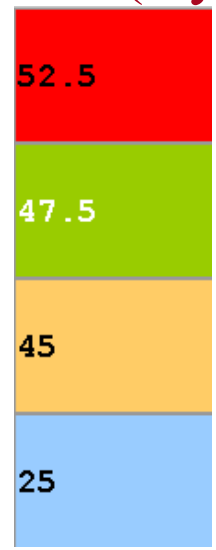
Pre-treatment

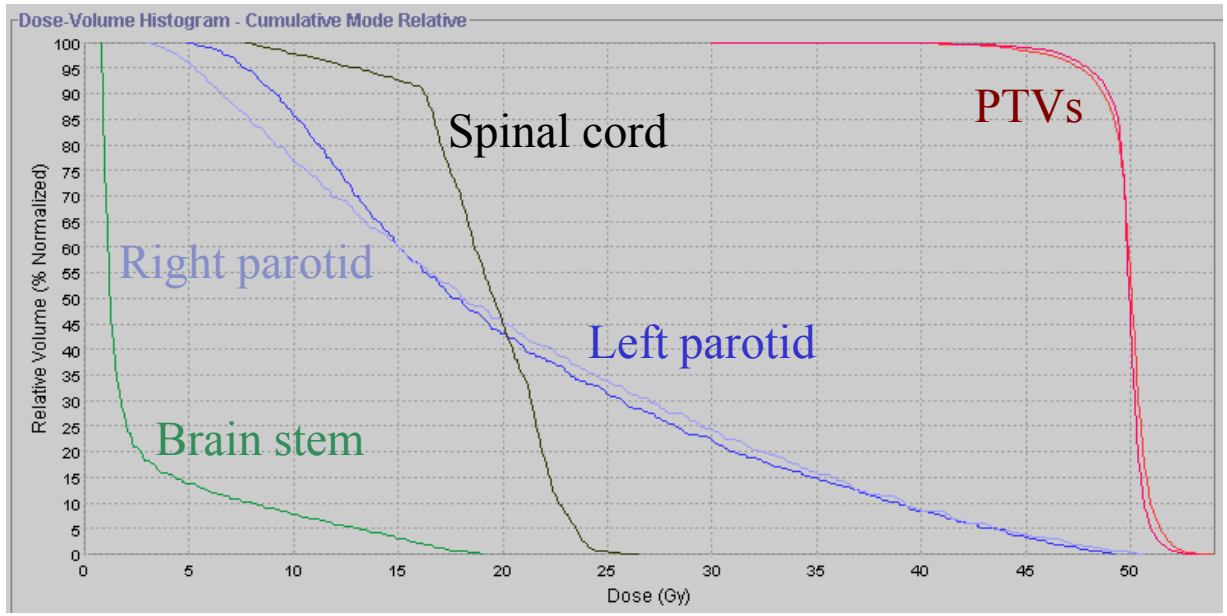
Tomotherapy and Head and Neck Tumors





Dose (Gy)





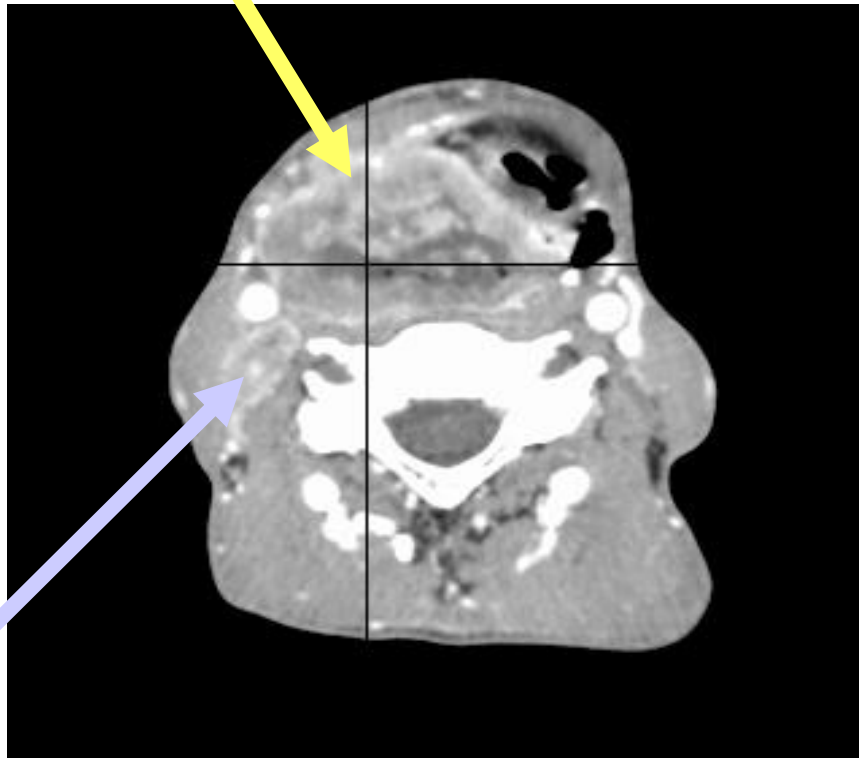
Hypopharyngeal SCC

T4-N1-M0

Dose: 25 x 2 Gy

Clinical case

T4 N1 M0 hypopharyngeal SCC



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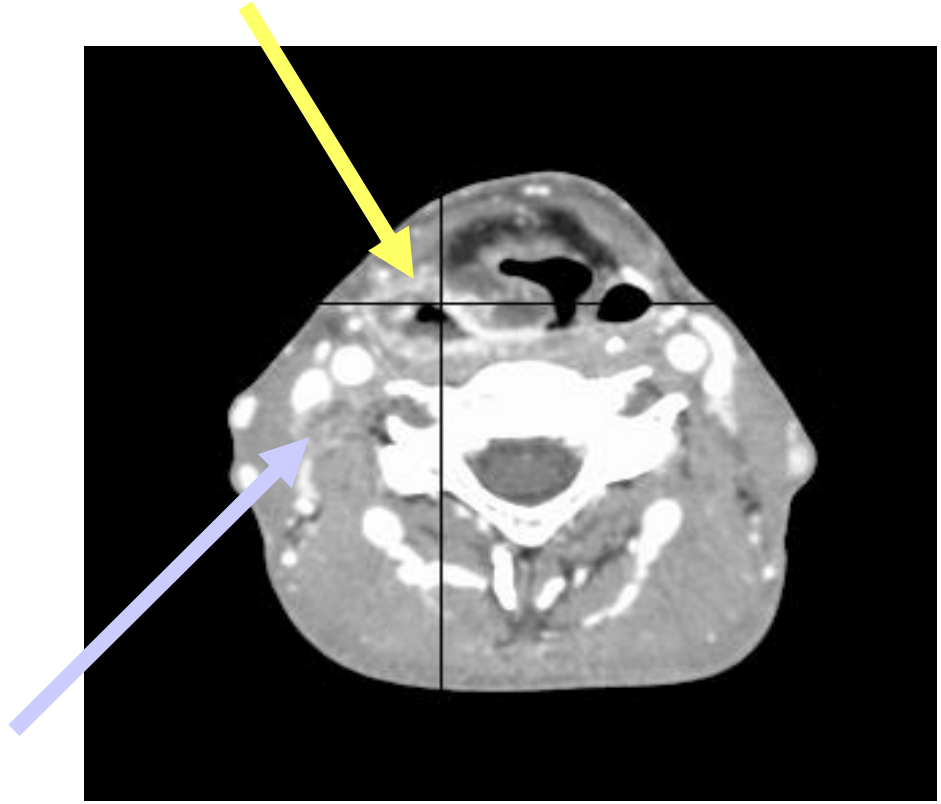

After 50 Gy

The “x” Rs of Radiotherapy

- Radiosensitivity
- Repair
- Repopulation
- Redistribution
- Reoxygenation
- iRradiated volume
- Restoration (long term recovery)
- Re-iRRadiation
- another “R” still to be invented…

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Conventional fractionation

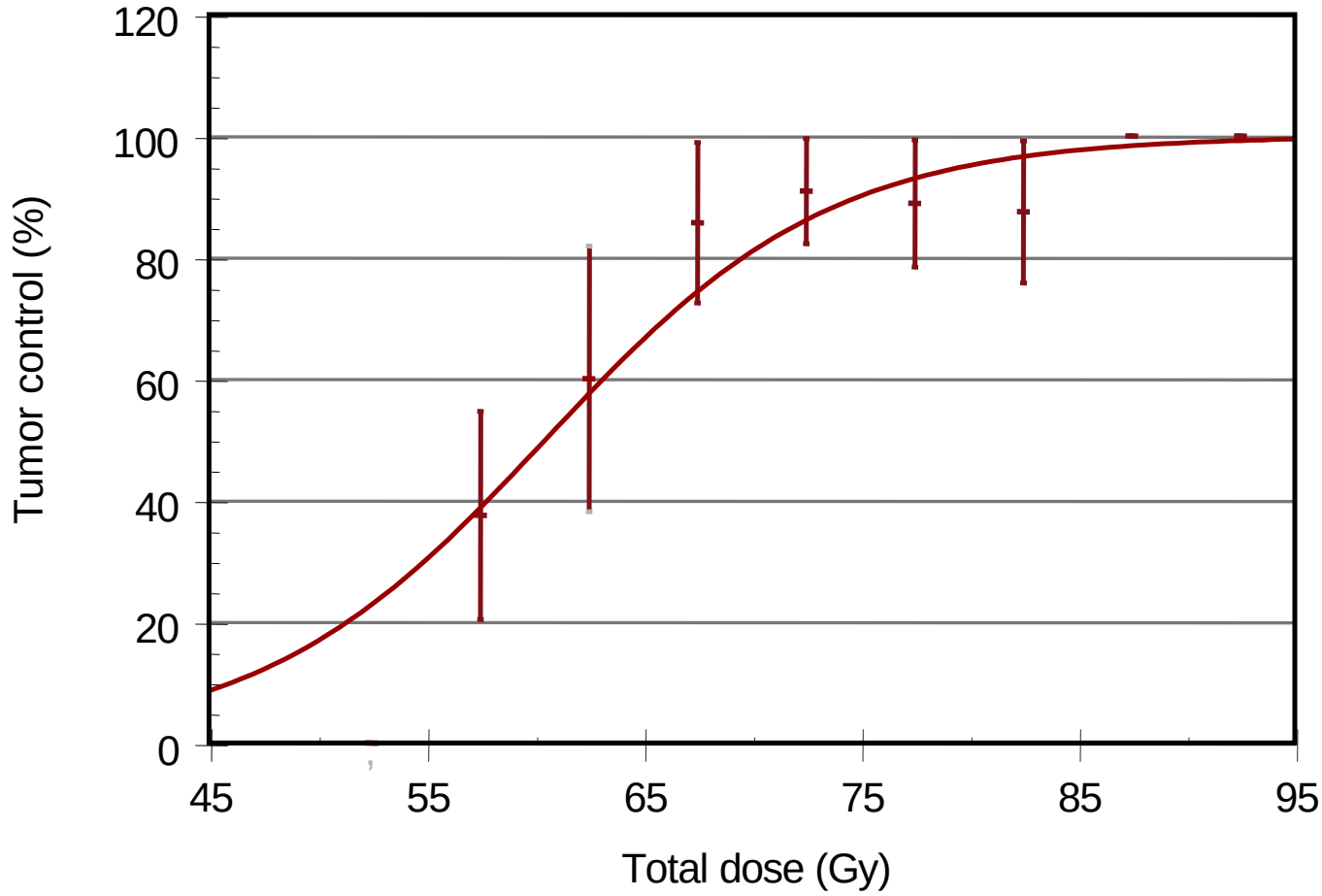
1.8 – 2.0 Gy per fraction, 5 fractions per week

IIIII IIIII IIIII IIIII IIIII IIIII IIIII

	Example	Dose (Gy)	Tumor control (%)
Sensitive	Seminoma, Lymphoma	≤ 45	≥ 90
Intermediate	SCC, Adeno-Ca	50	≥ 90 (subclinical)
		60	~ 85 (Ø 1 cm)
		70	~ 70 (Ø 3 cm)
			~ 30 (Ø 5 cm)
Resistant	Glioblastoma	≥ 60	none?
	Melanoma	≥ 60	none?

Tumor Control Probability (TCP)

Dose-response curve for neck nodes ≤ 3 cm



Bataini et al, 1982

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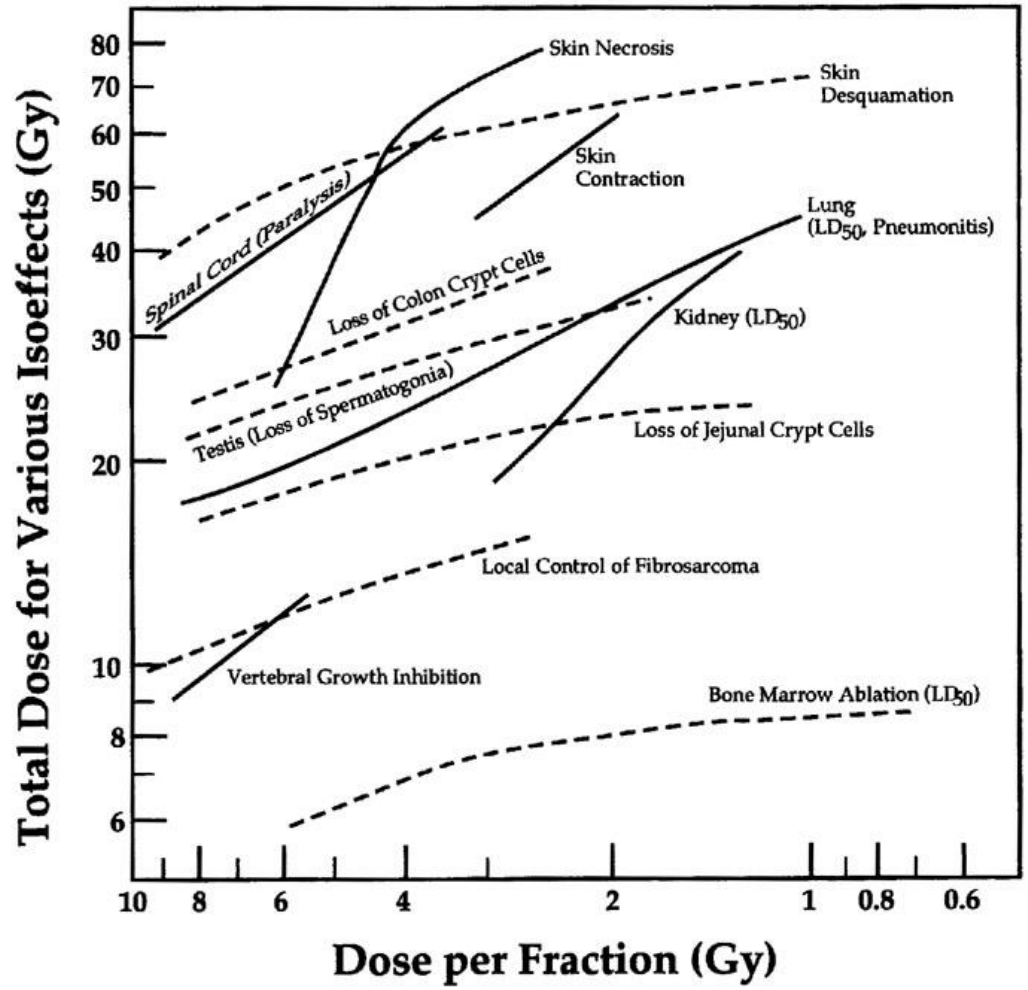
Fractionation sensitivity

"Typical" dose per fraction

- 1.8-2 Gy for standard fractionation
- 1.1-1.3 Gy for hyper-fractionation



Withers et al, 1983

RTOG 90-03: A Phase III Trial Assessing Relative Efficacy of Altered Fractionations

Stage III & IV
SCC of :
- Oral cavity
- Oropharynx
- Larynx
- Hypopharynx

Stratify :
- No vs N+
- KPS
  60-80 VS 90-100

RANDOMIZE

1. Conventional Fractionation:
   70 Gy / 35 F / 7 W
2. Hyperfractionation:
   81.6 Gy / 68 F / 7 W (1.2 Gy/F)
3. Accelerated Fractionation (Split):
   67.2 Gy / 42 F / 6 W (2 W Rest)
4. Accelerated Fractionation (CB):
   72 Gy / 42 F / 6 W (1.8-1.5 Gy/F)

The “x” Rs of Radiotherapy

- Radiosensitivity
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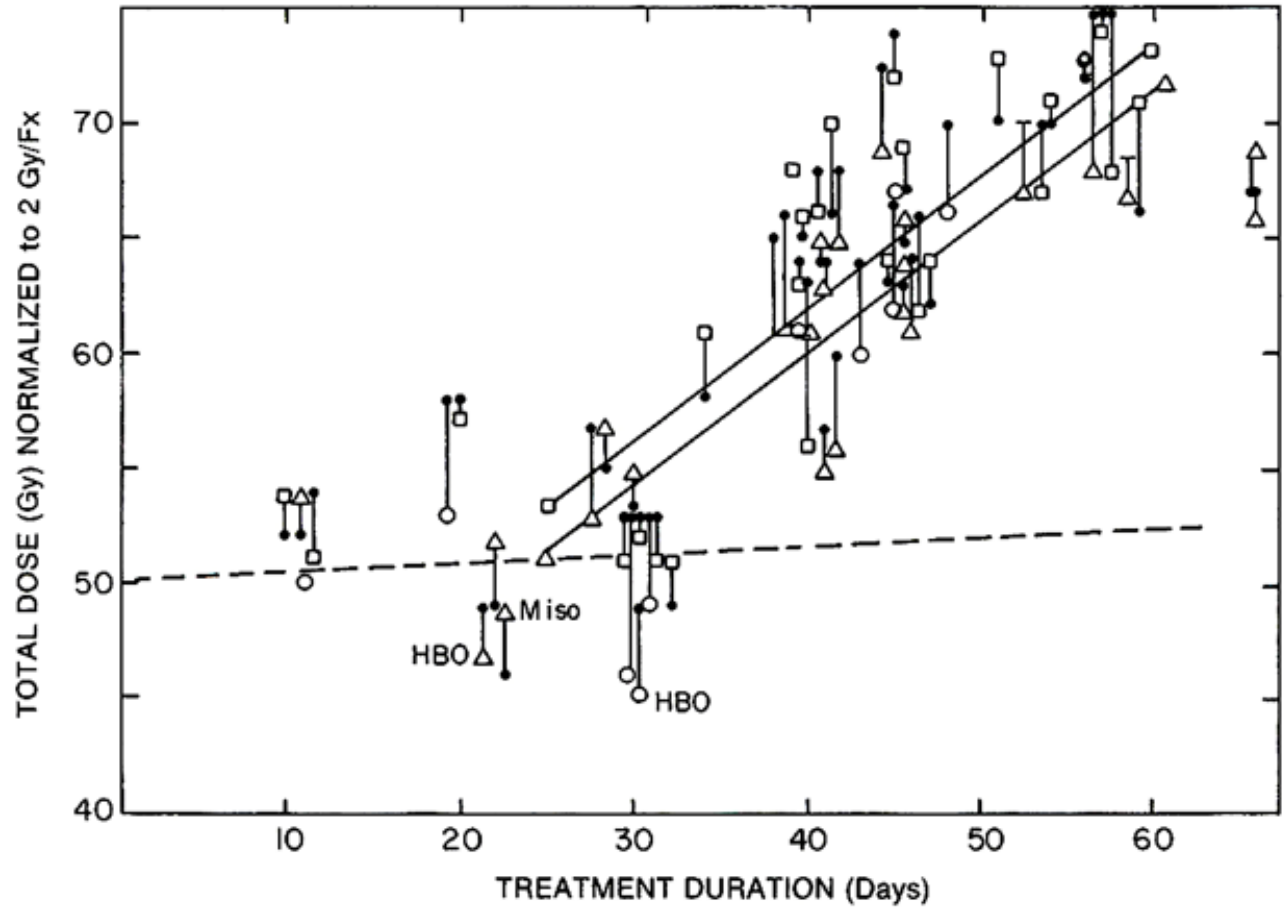
Influence of overall treatment time on HNSCC local control



Withers et al, 1988

Tissue proliferation and recovered dose D_{prolif}

Tissue	D_{prolif} (Gy.d^{-1})	T_k* (days)	
Early normal tissue reactions			
Skin (erythema)		0.12 (-0.12-0.22)	< 12
Mucosa (mucositis)		0.8 (0.7-1.1)	< 12
Lung (pneumonitis)		0.54 (0.13-0.95)	n.a.
Tumors			
Head and neck			
• larynx		0.74 (0.3-1.2)	n.a.
• tonsils		0.73	30
• various		0.8 (0.5-1.1)	21
• various		0.64 (0.42-0.86)	n.a.
NSCLC		0.45	n.a.
Medulloblastoma		0.52 (0.29-0.71	0 – 21

* onset of accelerated proliferation

Bentzen et al, 2002

RTOG 90-03: A Phase III Trial Assessing Relative Efficacy of Altered Fractionations

Stage III & IV
SCC of :

- Oral cavity
- Oropharynx
- Larynx
- Hypopharynx

Stratify :

- No vs N+
- KPS
  60-80 VS 90-100

R A N D O M I Z E

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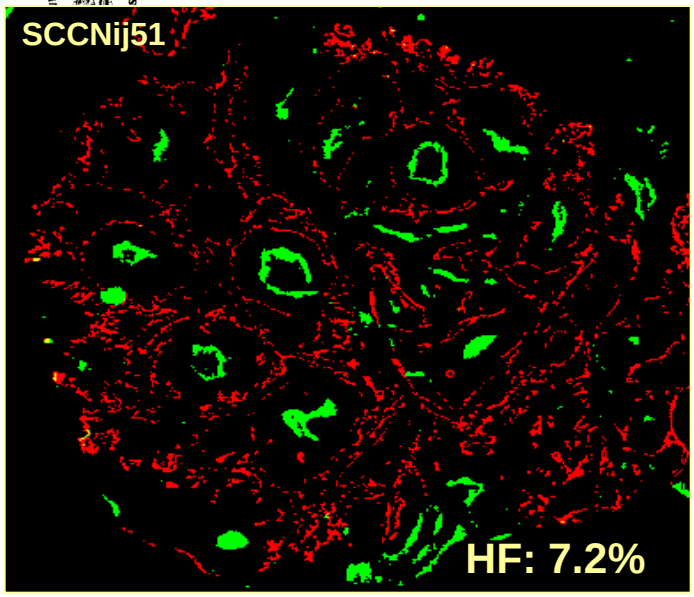
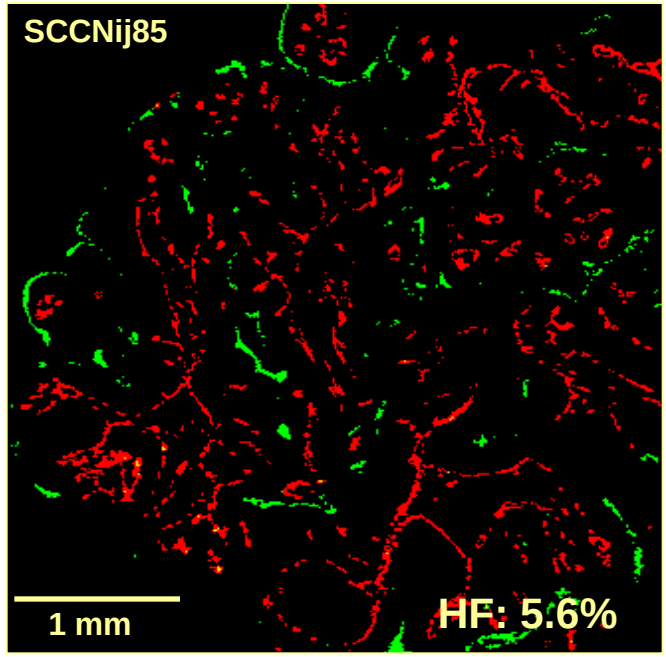
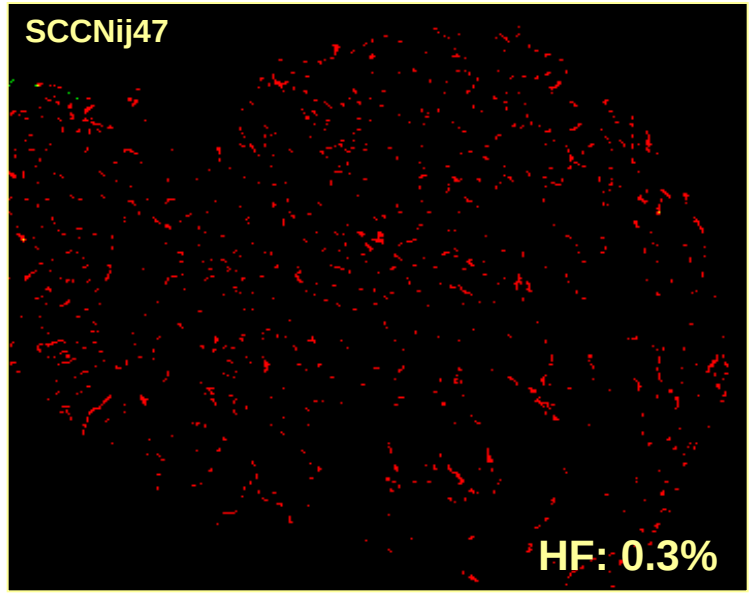
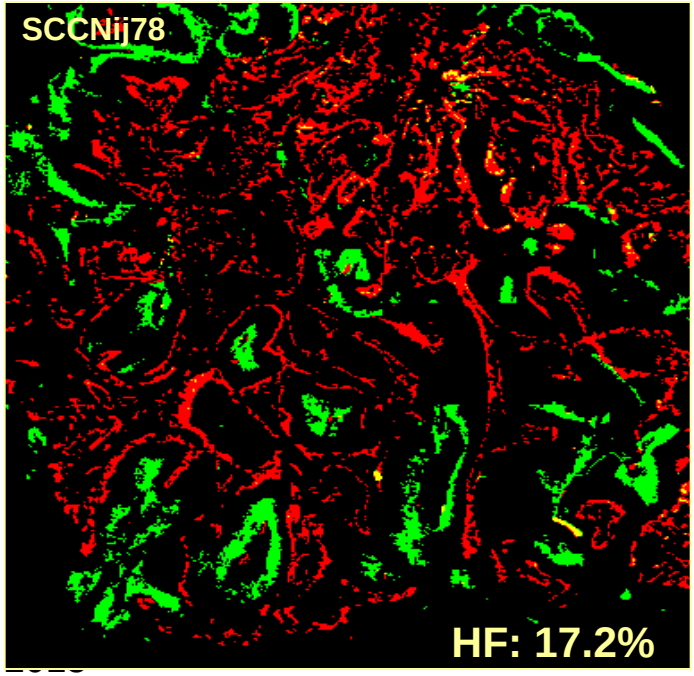
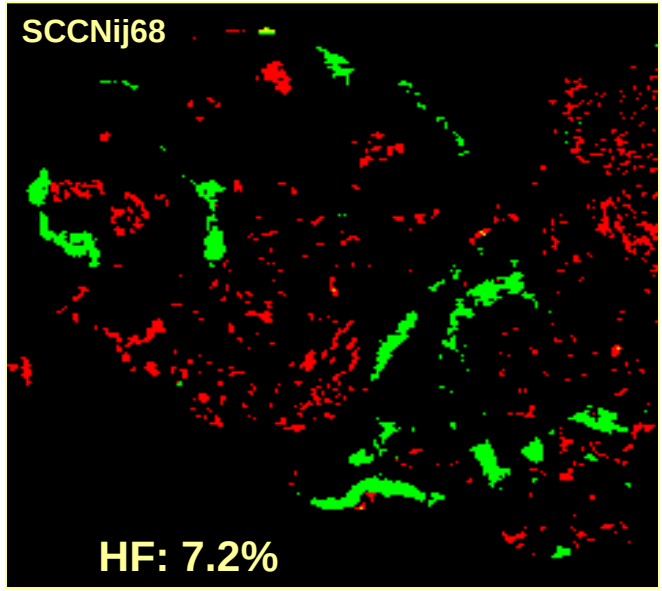
Hypoxia and vessels in H&N cancer biopsies

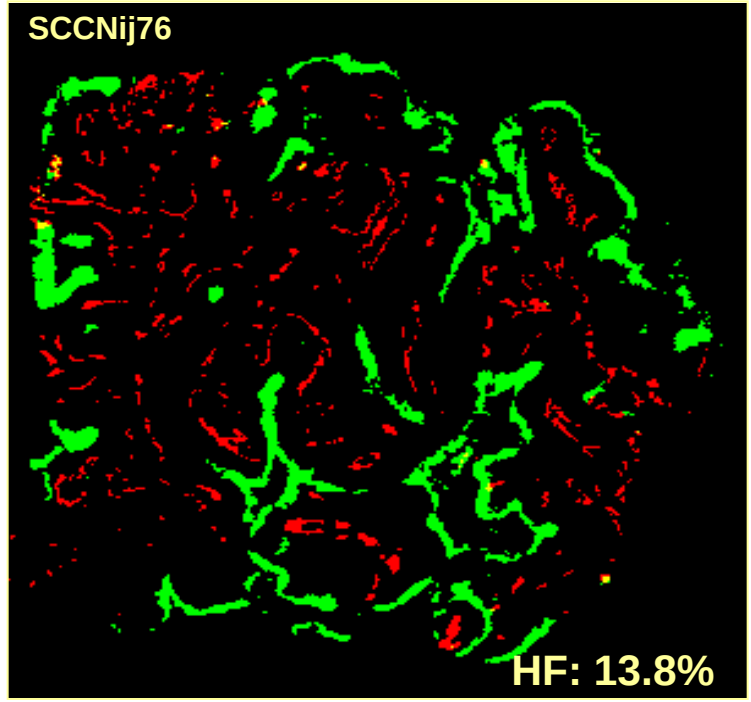




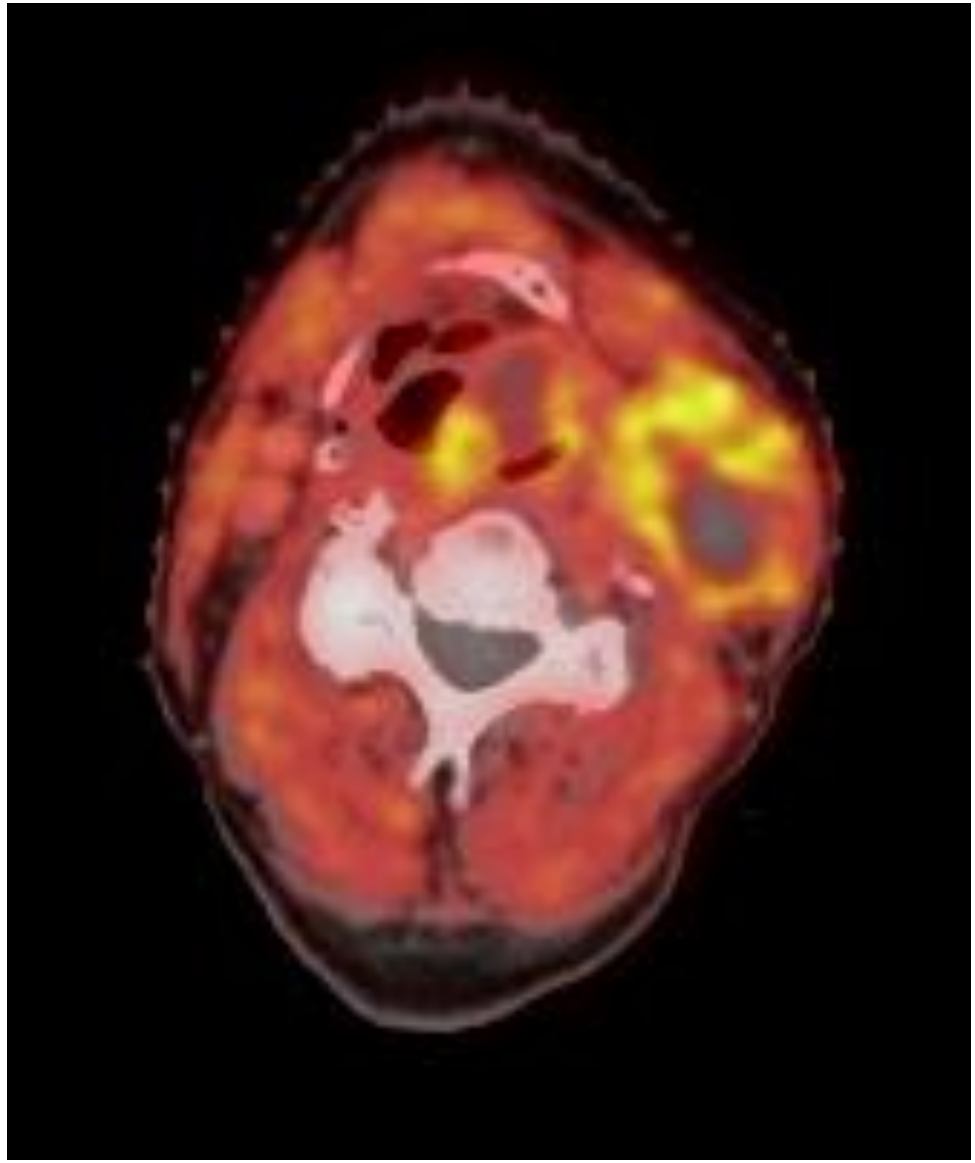






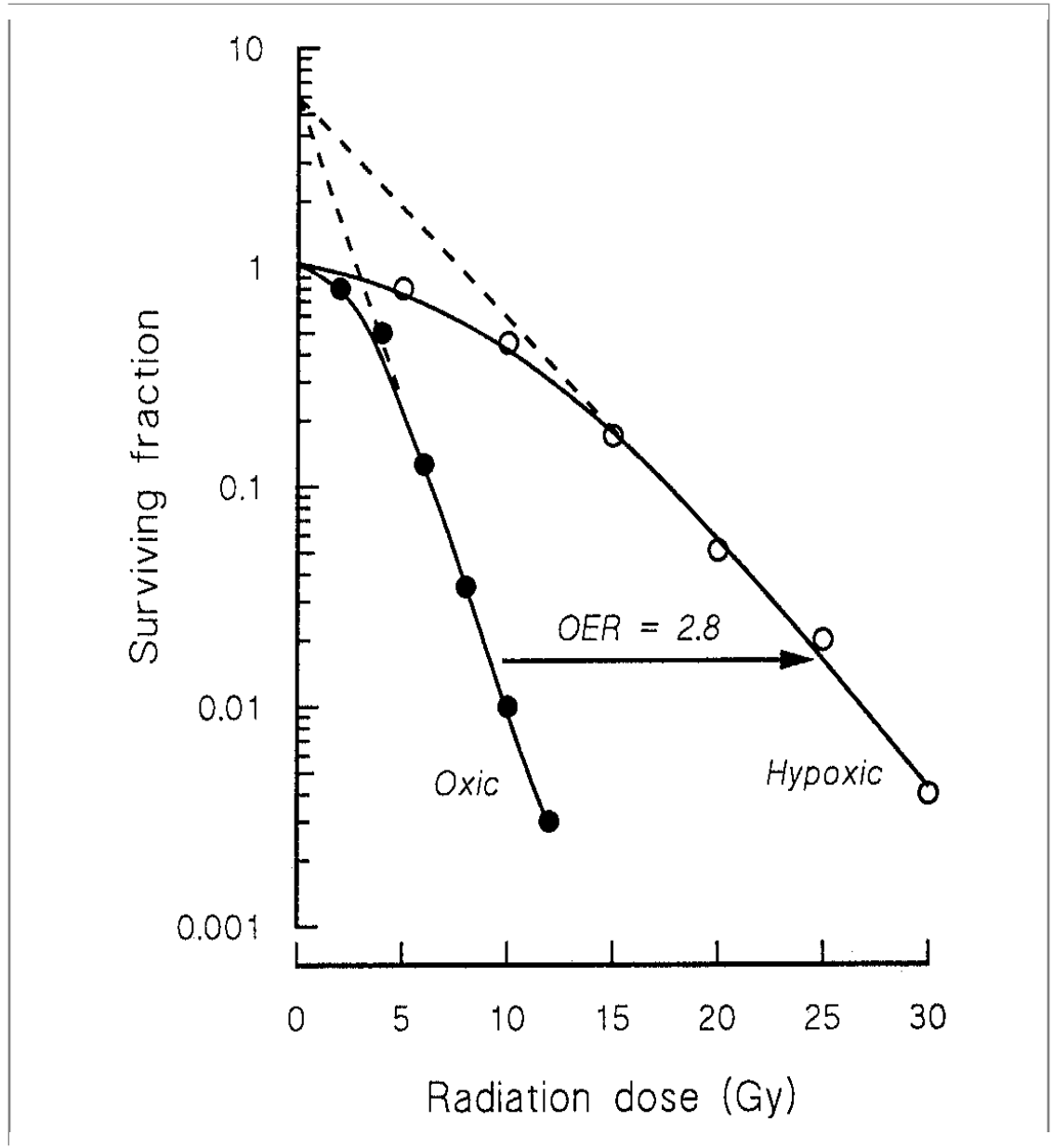


Hypoxic tracer ^{18}FAZA



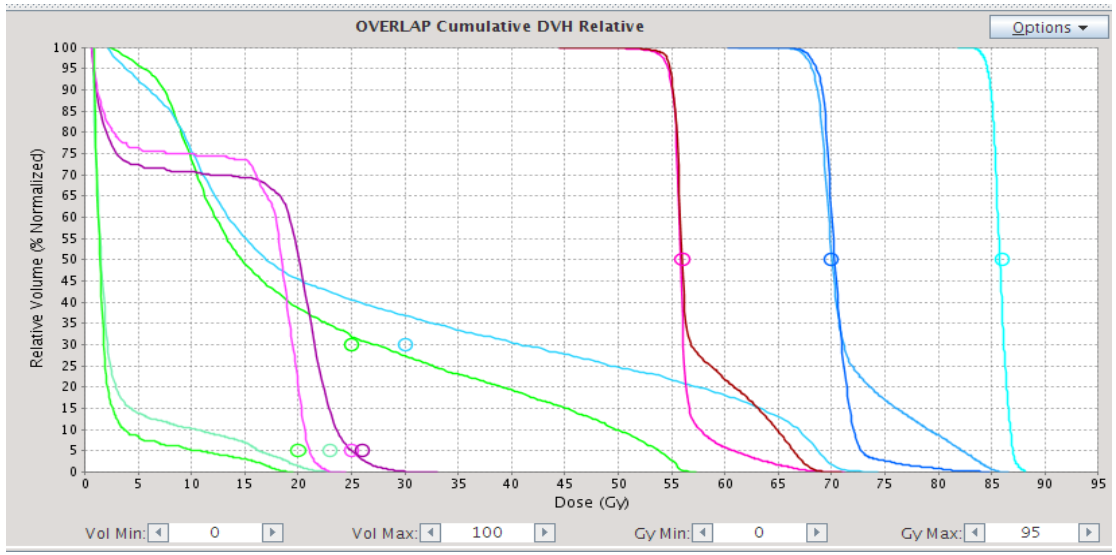
Servagi, 2013

Tumor hypoxia : a foe !

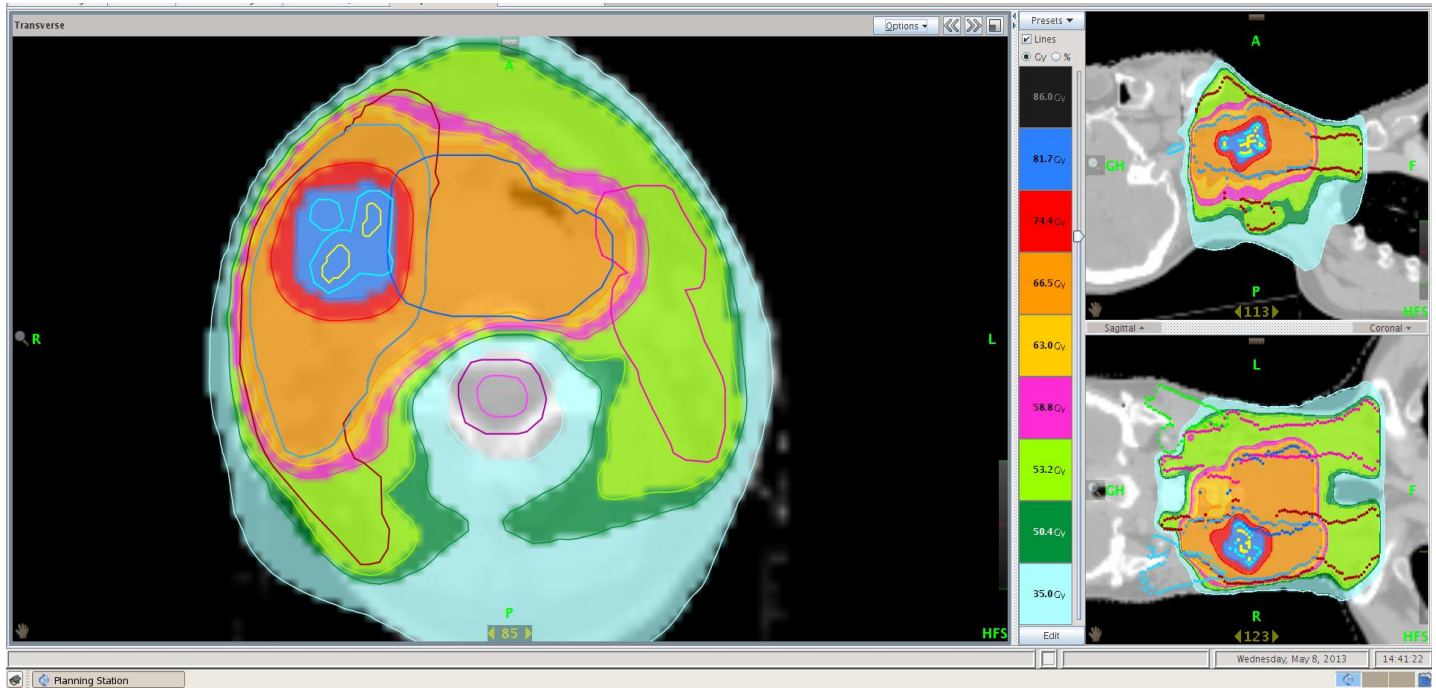


Steel, 1993

Hypoxia (^{18}F-AZA) dose painting



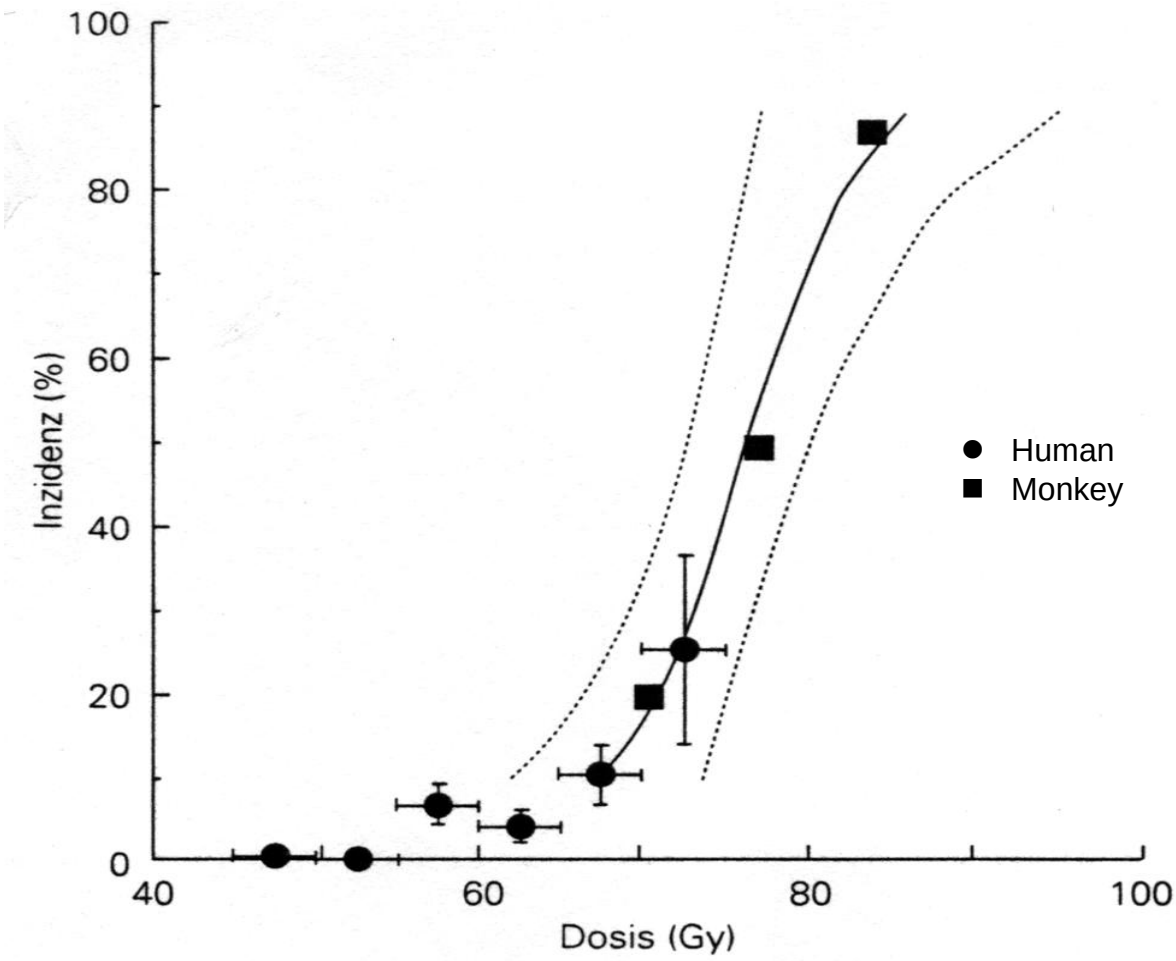
"Binary" dose escalation, e.g. from 70 to 86 Gy



Servagi, 2013

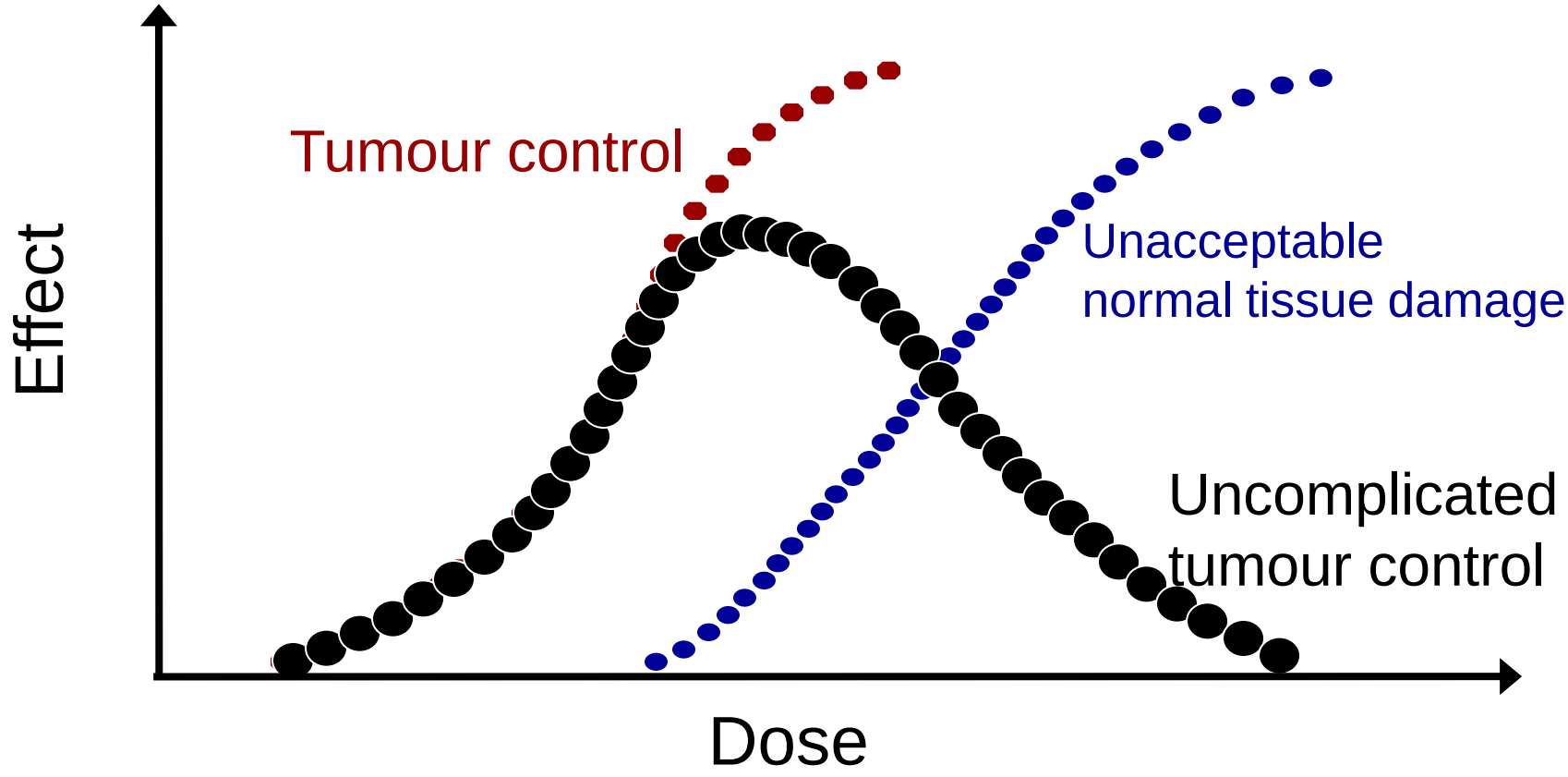
But …
The other face of the coin…

Normal Tissue Control Probability (NTCP)

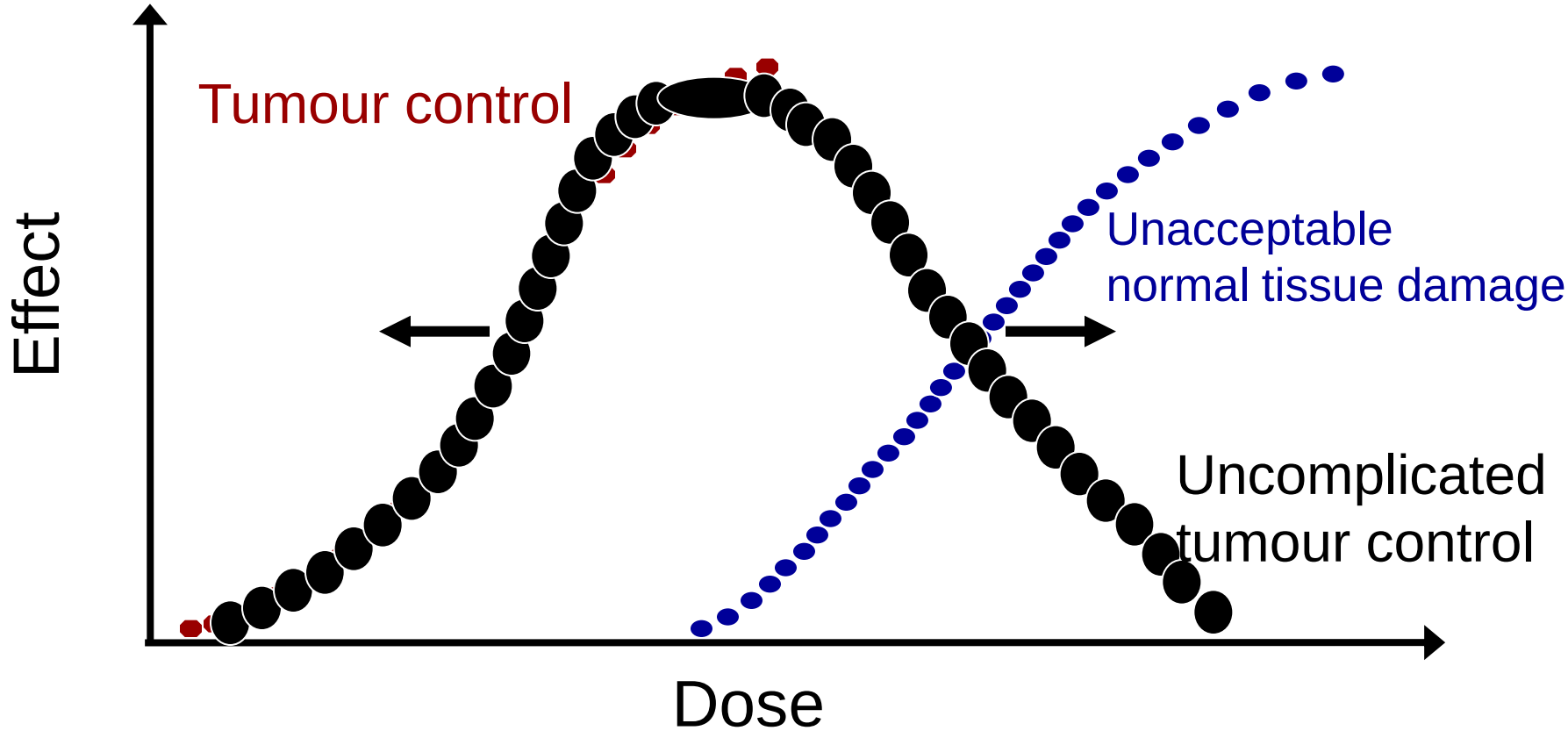


Baumann et al., *Strahlenther Onkol* 170: 131-139, 1994

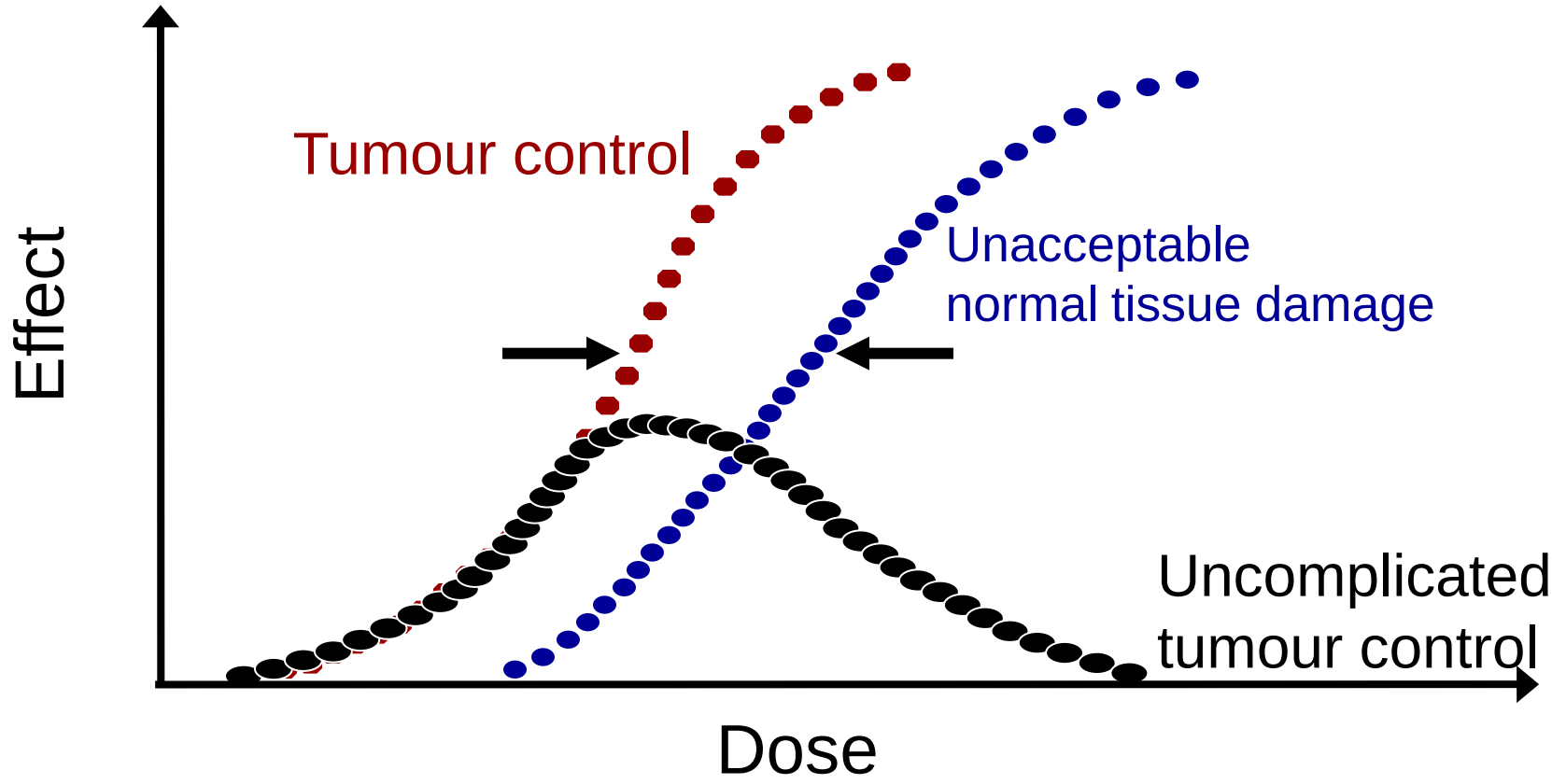
Uncomplicated tumor control: Therapeutic Ratio



Uncomplicated tumor control: Therapeutic Ratio



Uncomplicated tumor control: Therapeutic Ratio

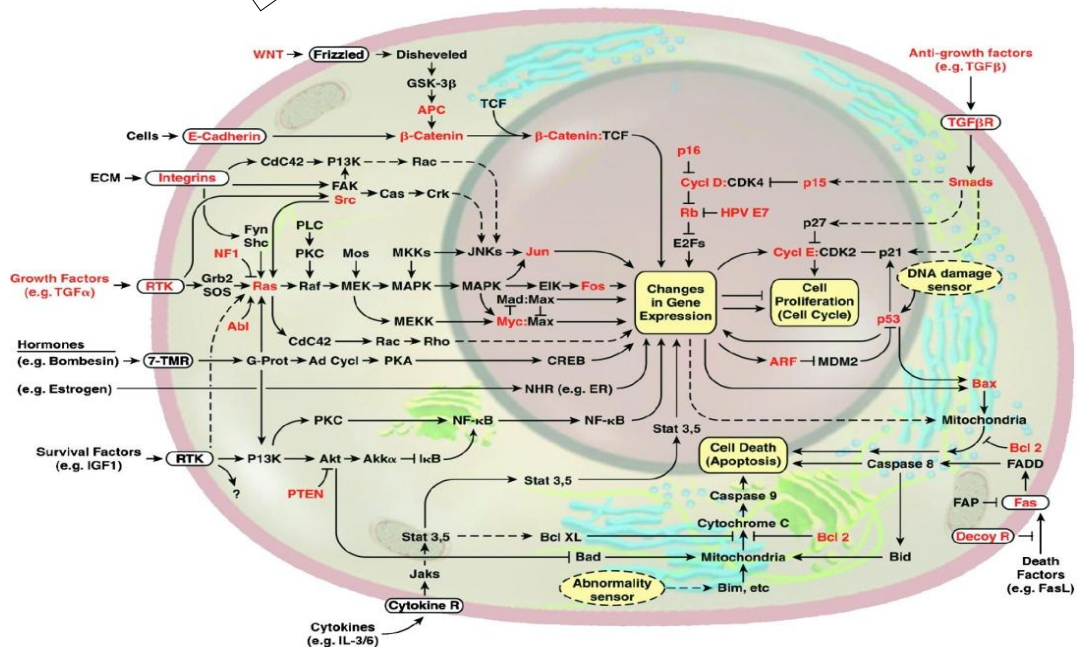


Target pathways that influence radiotherapy

HYPOXIA

REPOPULATION

INTRINSIC RADIOSENSITIVITY



Therapeutic interventions

- Modification of dose fractionation
- Modification of overall treatment time
- Combined modalities (chemo, biological modifiers)
- Non-conventional radiation beams
- Functional Image-guided IMRT
- …

Yes… but in my daily practice…

Mr John Drinker (56 years old) from Hopeless city:

- History of hypopharyngeal SCC 1 year ago
- RxTh (70 Gy) with concomitant cddp (100 mg/m^2)
- Diagnosed with upper esophageal SCC

Treatment with RT? If so, how and which dose?

Yes… but in my daily practice…

Mrs Julia BadGene (35 years old):

- Her son died with AT at the age of 15
- Diagnosed with left breast cancer (pT2-pN0-M0)
- Treatment should include breast radiotherapy

Risk of RT-induced late normal tissue toxicity? Dose reduction? Special RT technique?

Yes… but in my daily practice…

Julia Fisher (11 years old girl) from Heidelberg:

- Diagnosed with pelvic rhabdomyosarcoma
- 3 courses of chemotherapy
- Pelvic radiotherapy is planned

Risk of RT-induced secondary cancer? Benefit of hadrons therapy (protons or carbon ions)?

Yes… but in my daily practice…

Mr David PSA (82 years old) from Istambul:

- Diagnosed with prostate adenocarcinoma (Gleason 8) T2-N0-M0
- Prostate radiotherapy is proposed (78 Gy, 2.5 Gy/f)
- After 2 weeks, he has to travel to South Africa for unforeseen reason, thus a week break!

Probability of lower efficacy? RT dose adaptation? How?

Take home message

Stay with us in Brussels …

Enjoy the course …

The Hallmarks of Cancer

Marianne Koritzinsky

Princess Margaret Cancer Centre
Toronto, Canada
mazinsky@gmail.com

Radiobiology

- The response to radiation is different in normal tissues and cancer:
  - at the cellular level
  - at the tissue level

- These differences are due to the underlying biological properties of different tissues and cancers

Tumor Radiobiology

Fact: We deliver a known physical dose with a high degree of accuracy to similar tumors

Observation: The radiocurability of tumors varies widely

Aim: Understand the biological factors that influence the sensitivity of tumors and normal tissues to radiation

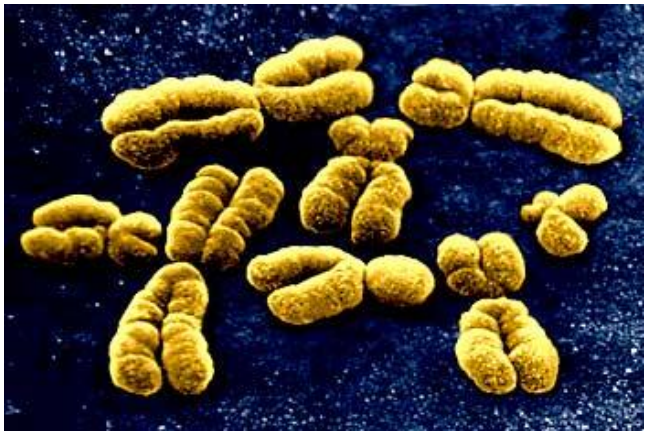
What is Cancer?

Cancer – Important Concepts

- Cancer cells are derived from normal cells in the body.
- Cancer cells have acquired a series of changes which distinguishes them from normal cells.
  - These changes are the basis for much of the difference in the ways tumors respond to radiation compared to normal tissues
- There are multiple ways of creating cancer
  - This can explain why even tumors of the same type can differ dramatically in how they response to radiation

Cancer is a genetic disease

- Disease involving dynamic changes in the genome
  - point mutations
  - gene amplification
  - chromosome instability
  - deletions, silencing
- 2 classes of cancer genes:
  - Oncogenes
  - Tumor suppressors
- "Driving" mutation:
  - Confers growth advantage
  - Causative of cancer
- "Passenger" mutation:
  - No growth advantage
  - No causative role in cancer



Cancer genome sequencing

- >25,000 whole cancer genomes have been sequenced per Feb 27th 2016
- Total # somatic mutations per individual tumor:

10^2	10^3	10^4	10^5
Medulloblastoma	Breast	Lung	
Testicular germline	Ovary	Melanoma	
Acute leukemia	Colorectal		
Carcinoids	Pancreas		
	Glioma		

From Stratton, Science 2011
And COSMIC

Cancer genes

110-400 (depends on definitions)

(~4000 mutations)

30-320

Oncogenes

~80

Tumor Suppressors

From Stratton, Science 2011

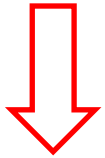
Somatic mutations in cancer

Majority of coding sequence of 11 colorectal tumors:

Total # mutated genes in 11 tumors: 769

Average # somatic protein coding mutations in 1 tumor: 77

Estimated # driving mutations in 1 tumor: 10

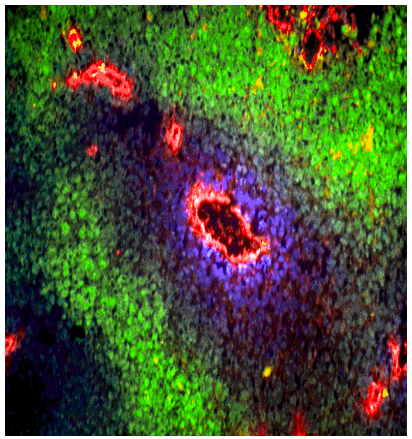


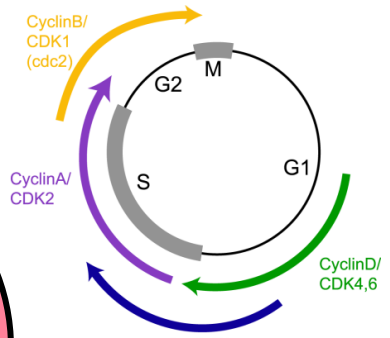
Minimal overlap in mutation spectrum between tumors.

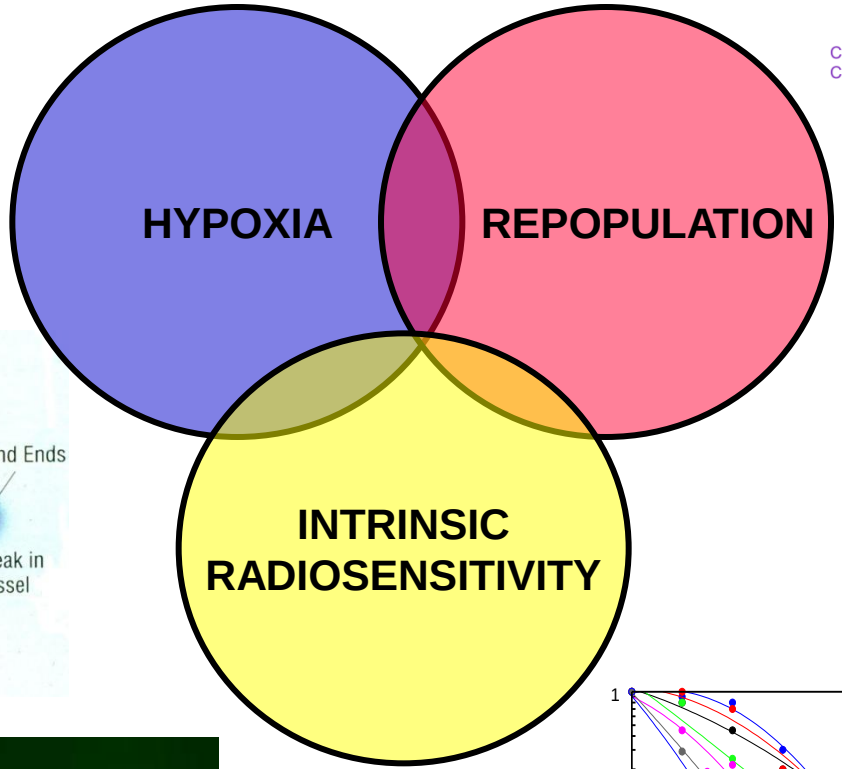
Large number of "passenger" mutations. These do not contribute to tumorgenesis, co-selection of random events with the "driving" mutations.

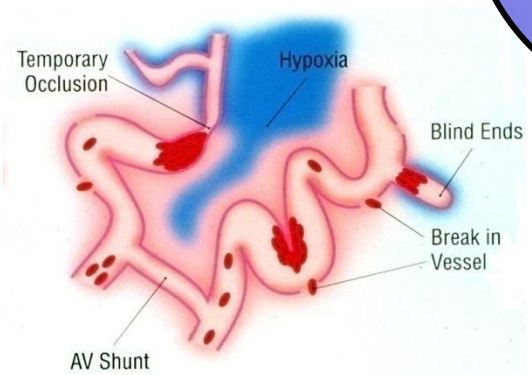
From Wood et al., Science 2007

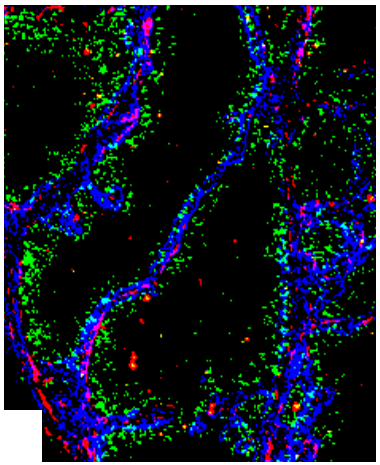
Biological contributors to outcome

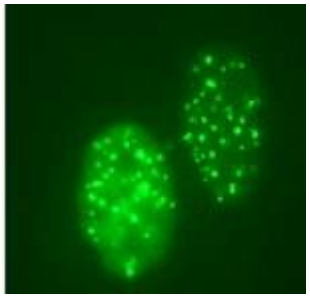


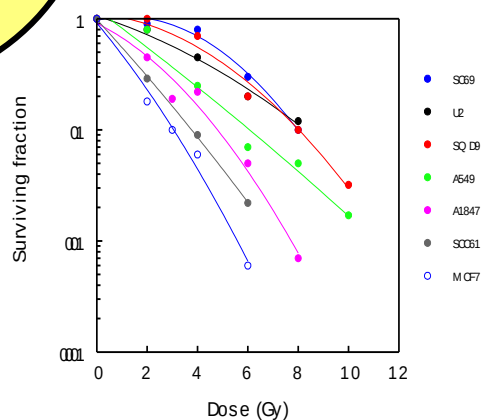










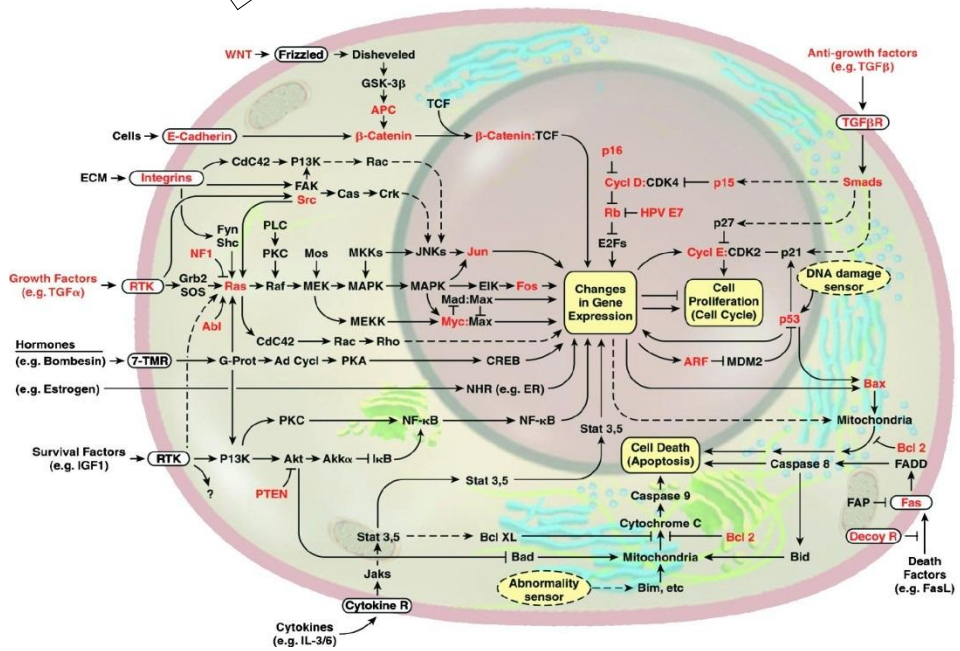


Biological contributors to outcome

HYPOXIA

REPOPULATION

INTRINSIC RADIOSENSITIVITY



Simplification!

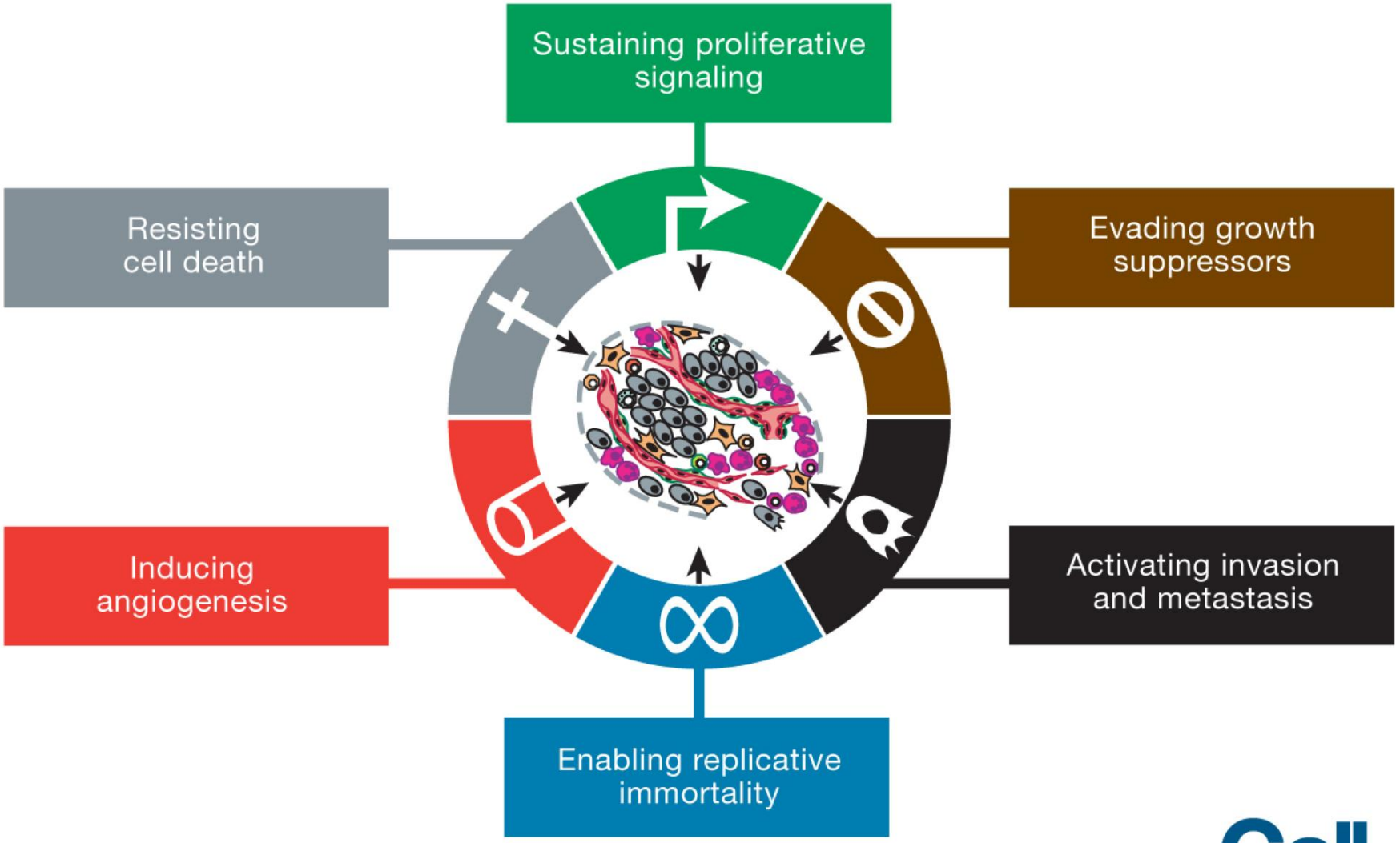
The Hallmarks of Cancer

Douglas Hanahan* and Robert A. Weinberg†

Cell, Vol. 100, 57–70, January 7, 2000, Copyright ©2000 by Cell Press

"The vast catalog of cancer cell genotypes is a manifestation of six essential alterations in cell physiology that collectively dictate malignant growth"

The 6 Hallmarks of Cancer



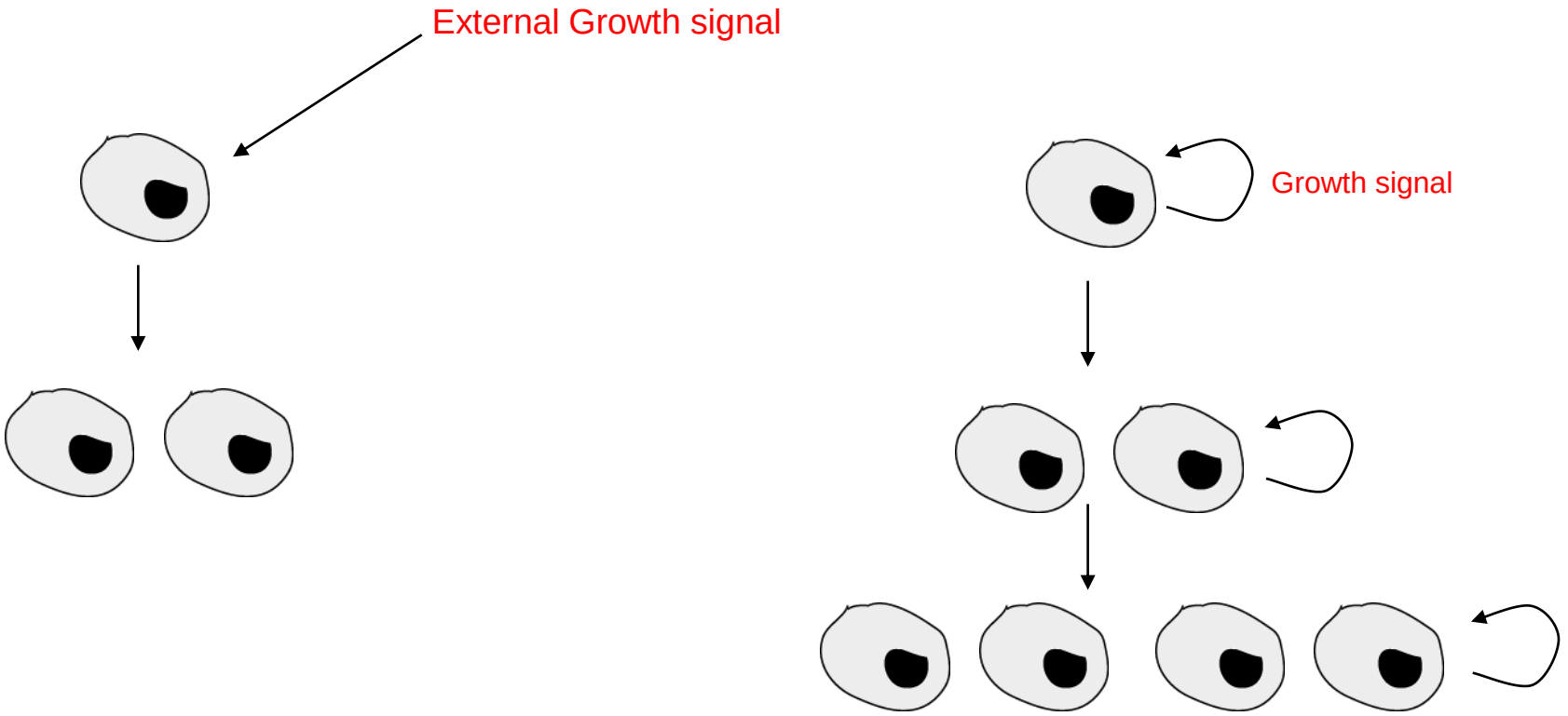
Hanahan and Weinberg, 2011

Cell PRESS

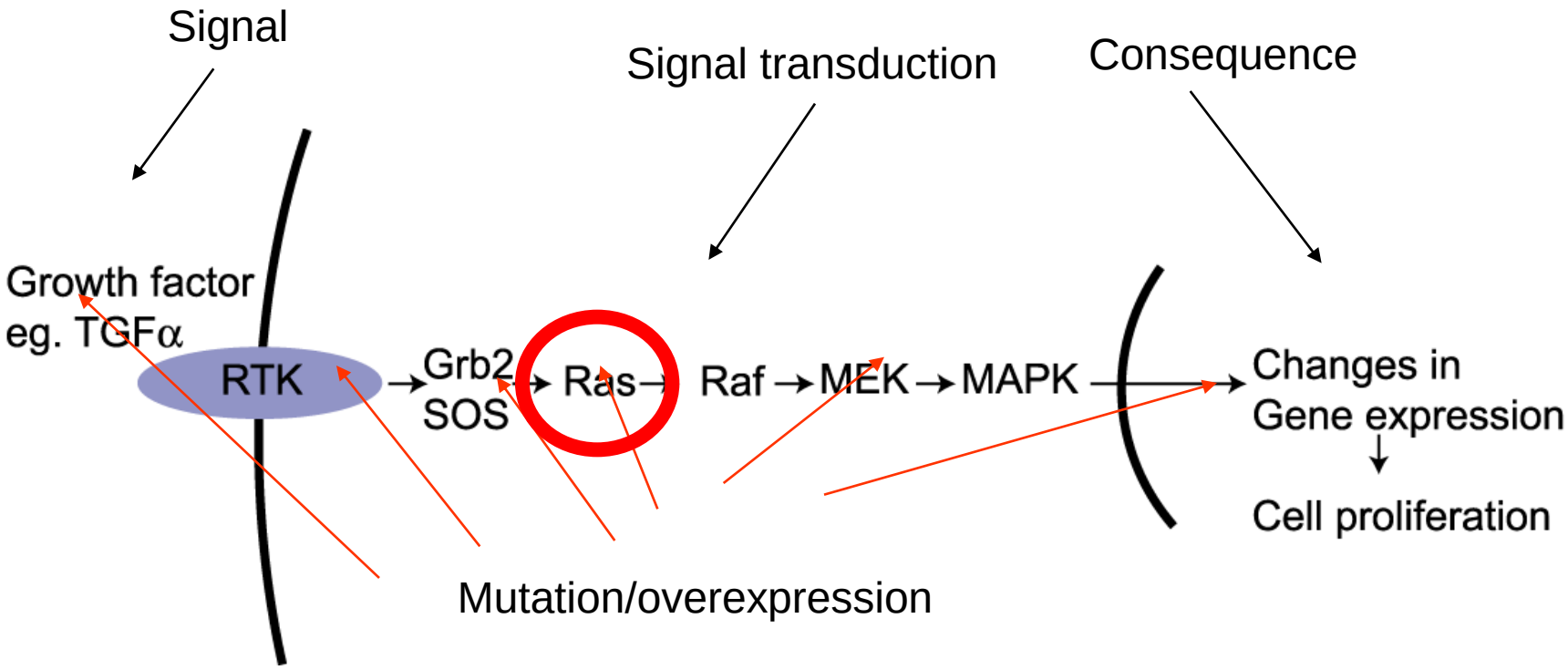
1) Sustaining proliferative signaling

Normal

Cancer



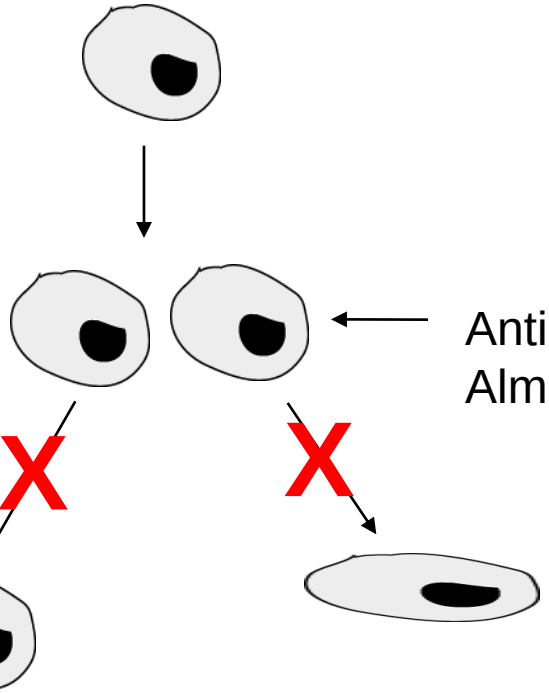
1) Sustaining proliferative signaling



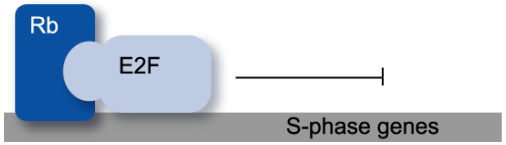
2) Evading growth suppressors

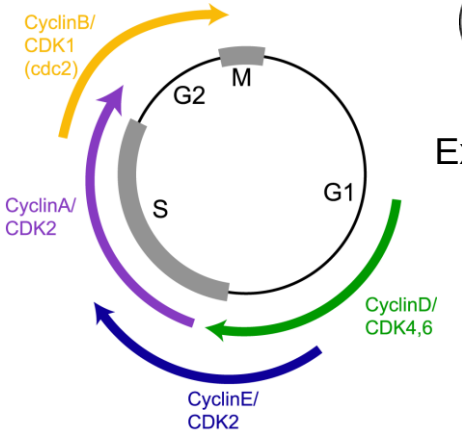
Normal cells

Cancer cells



Antiproliferative signal
Almost always through Rb

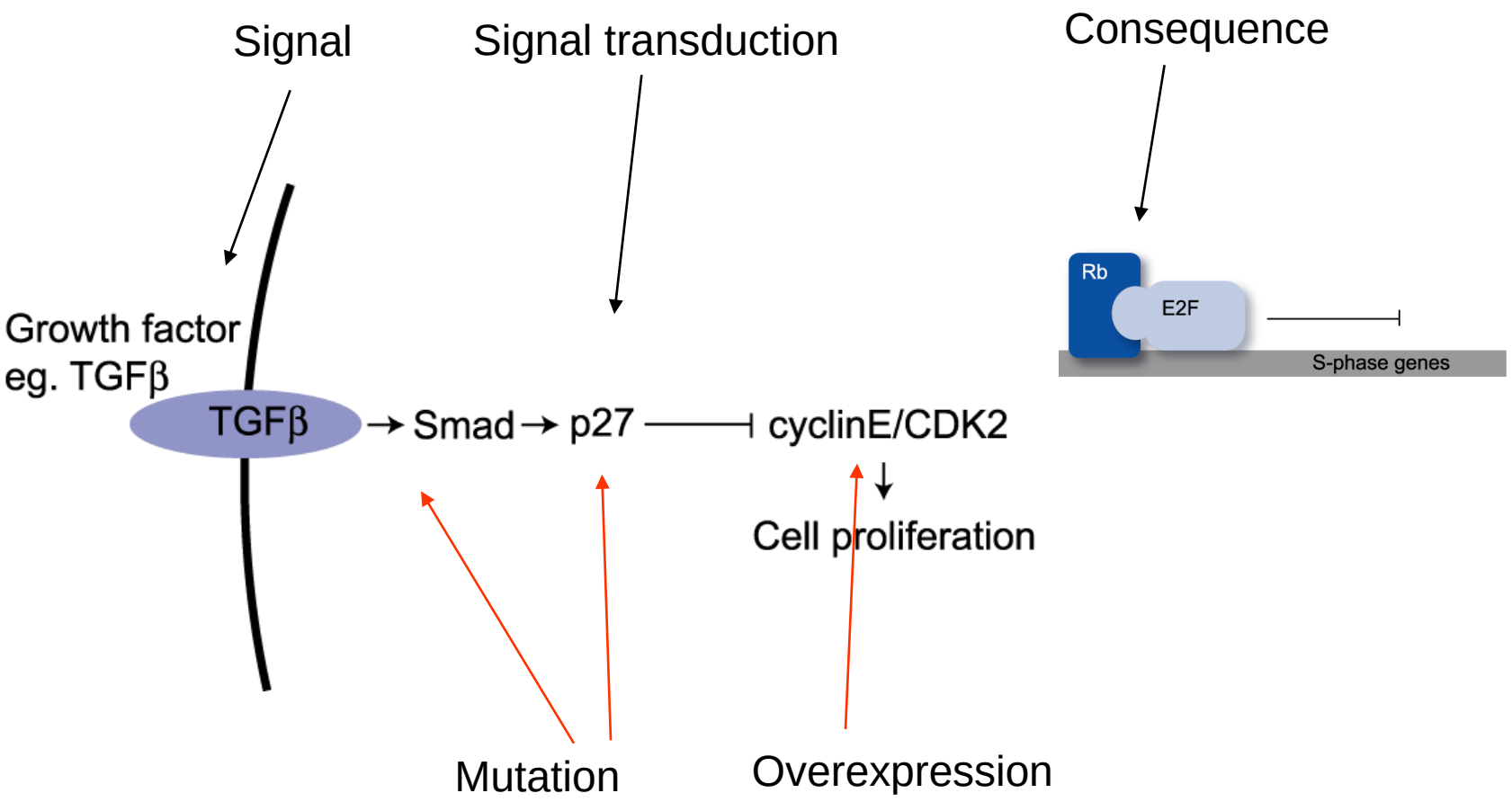




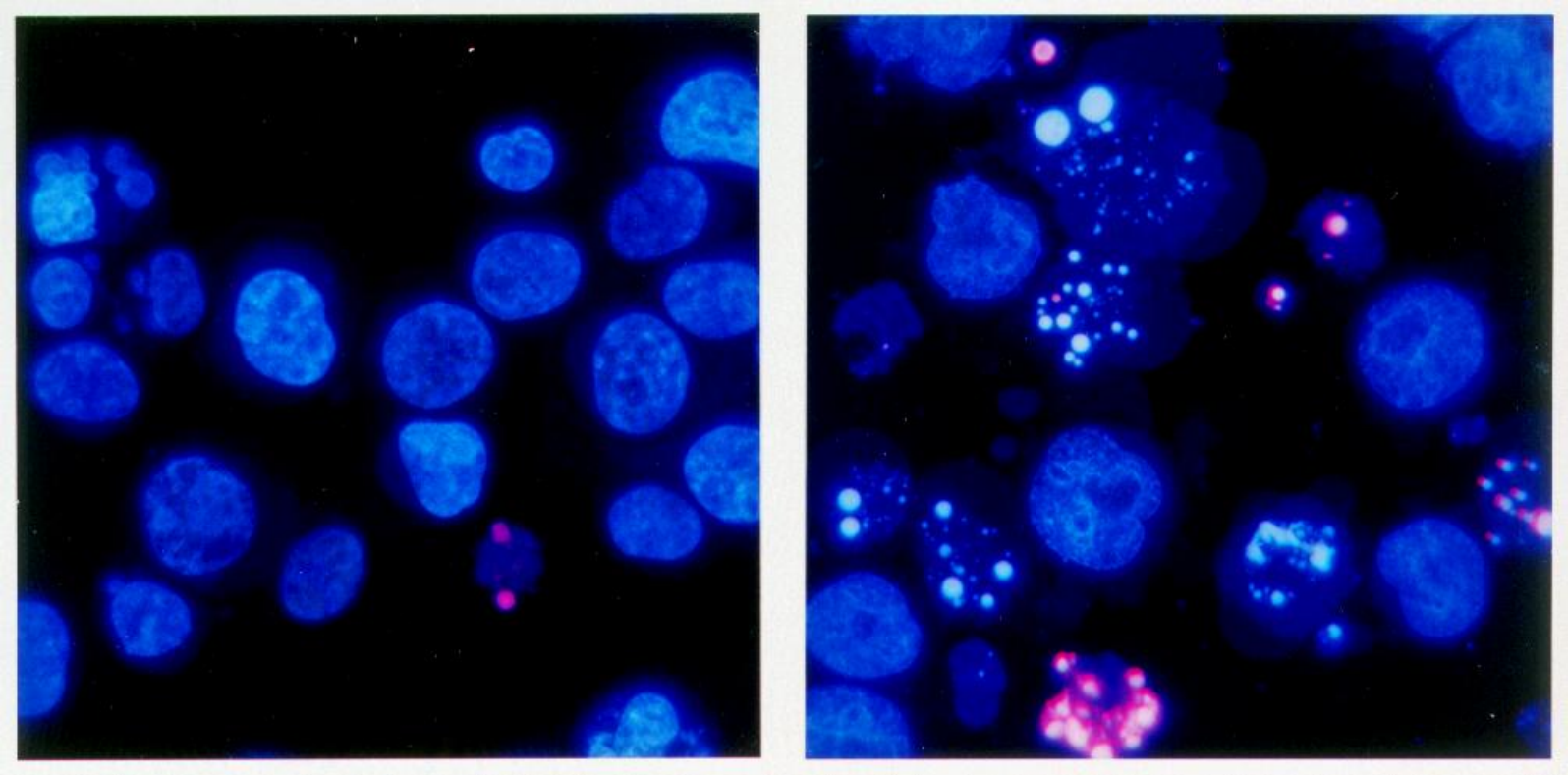
Exit the cell cycle - Go

Differentiation,
senescence

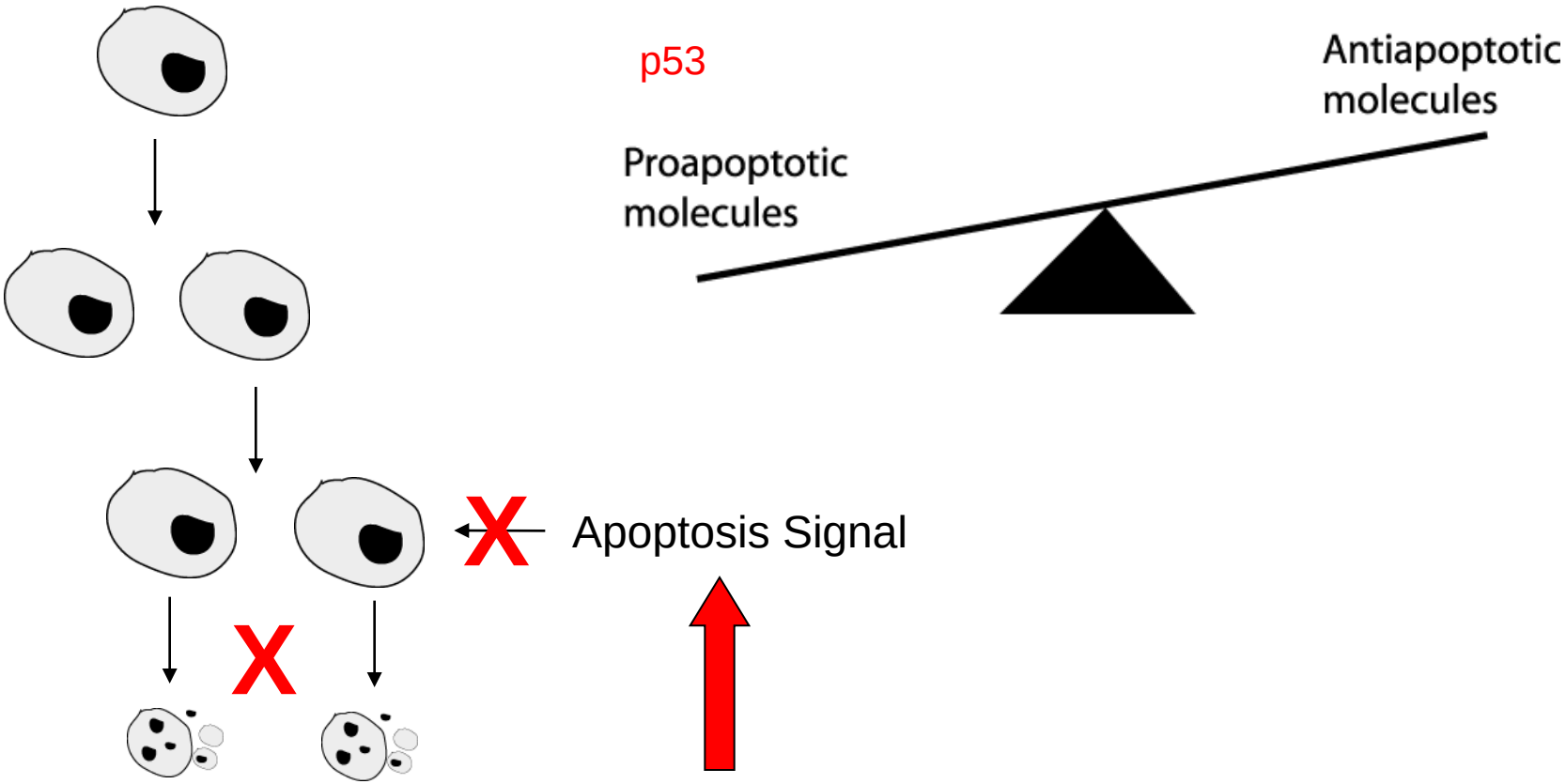
2) Evading growth suppressors



3) Resisting death

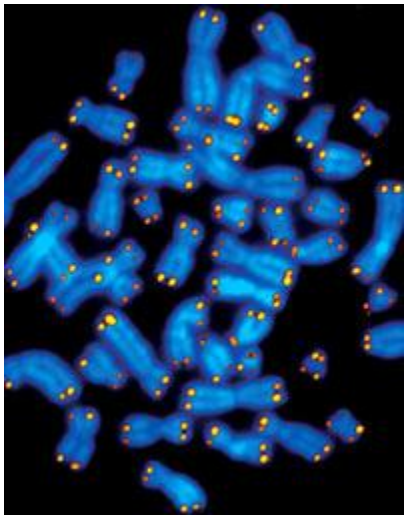


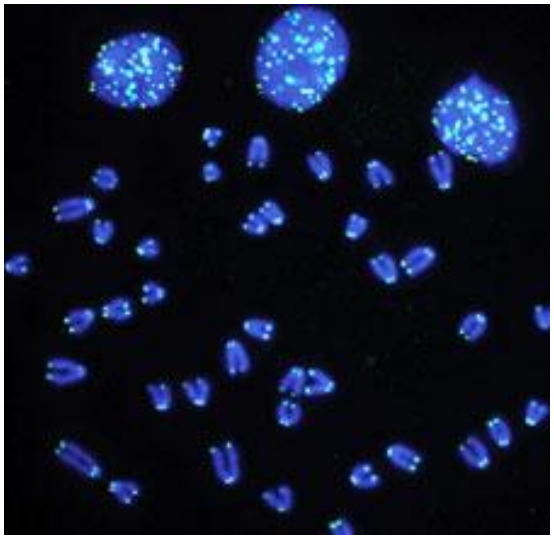
3) Resisting Apoptosis

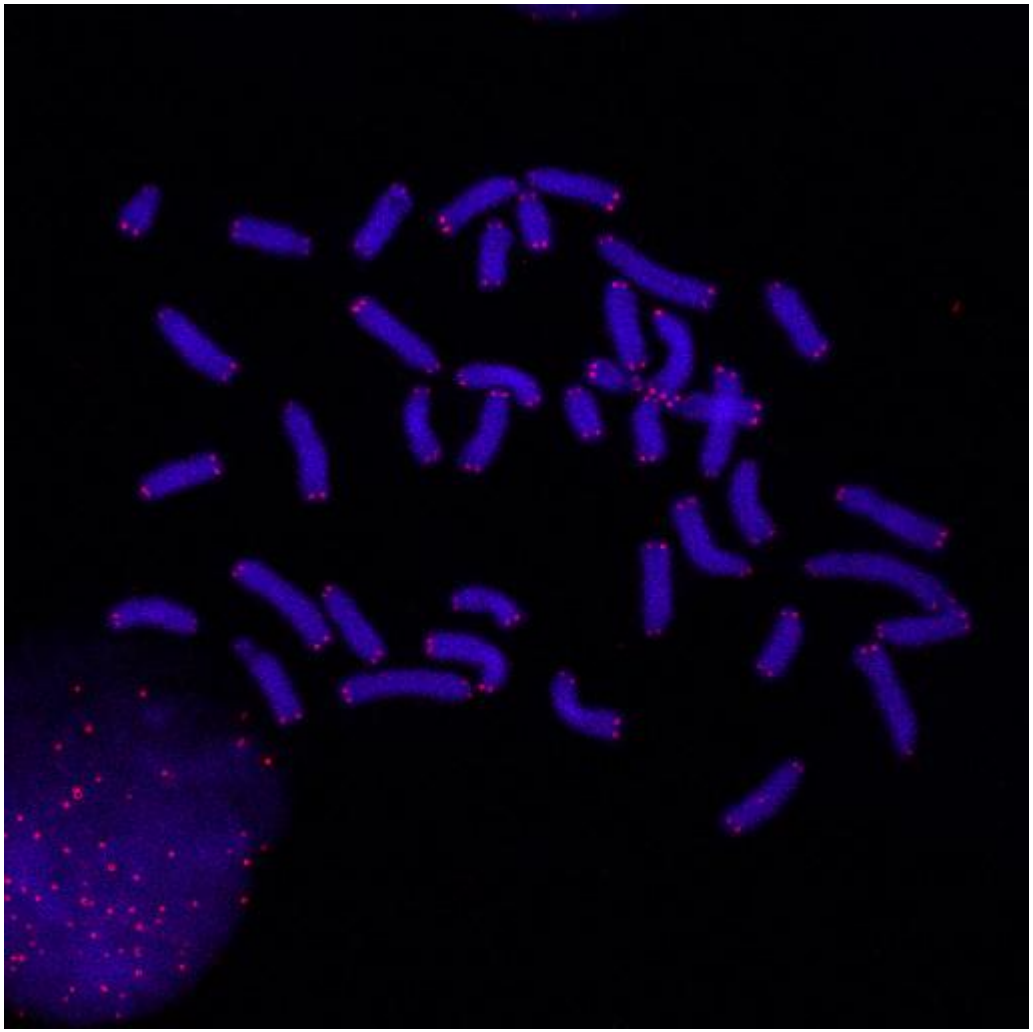


Tumor suppressor

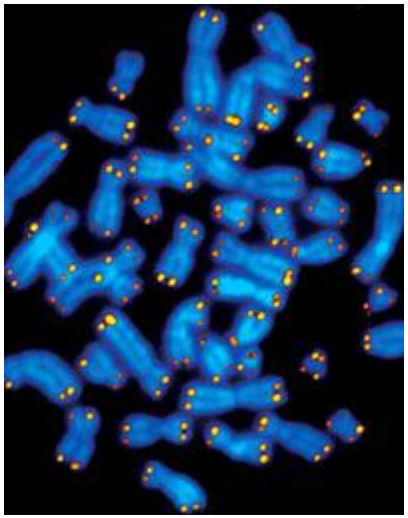
4) Enabling replicative immortality

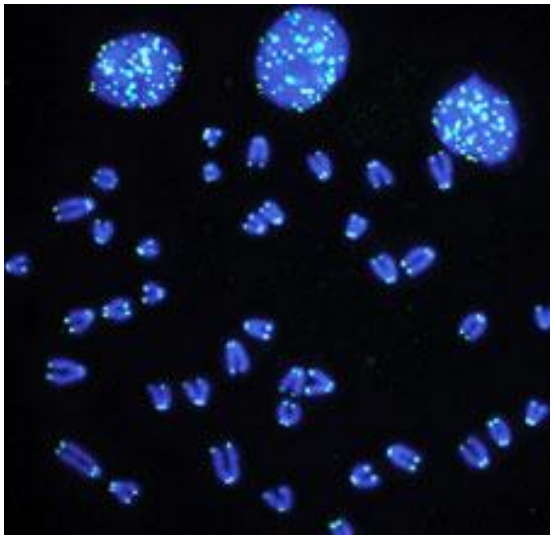


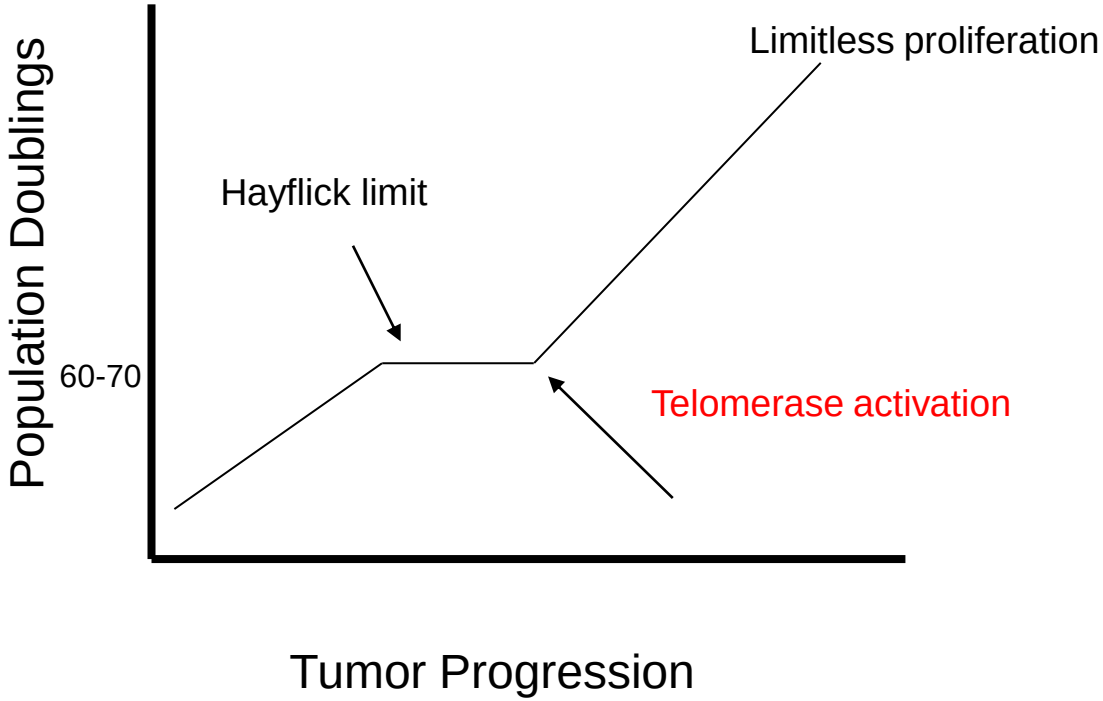




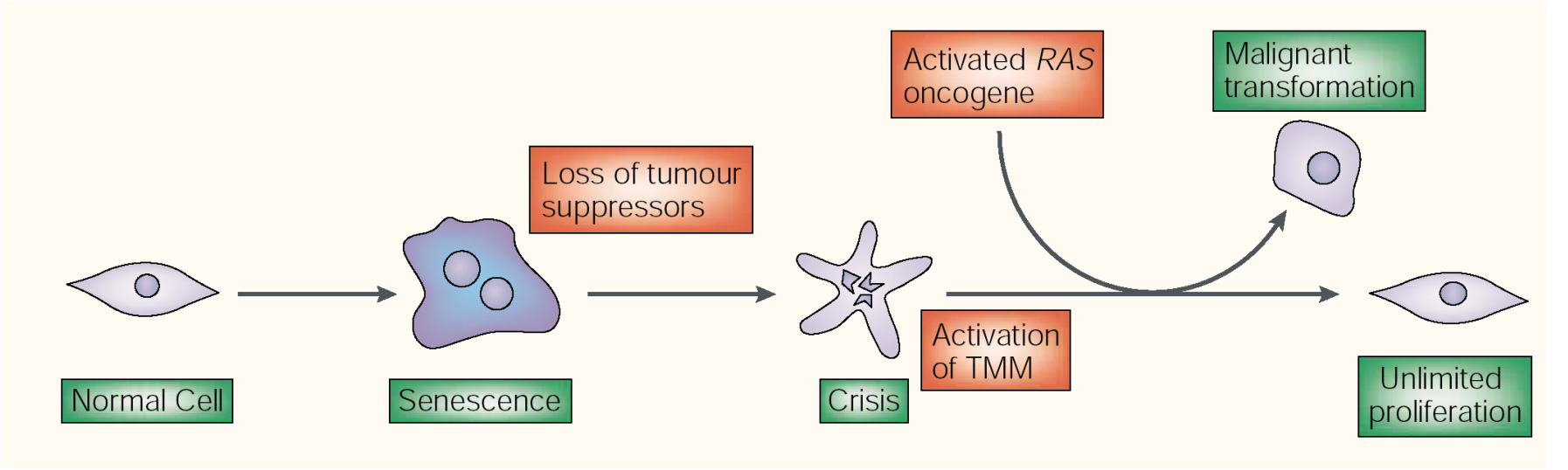
4) Enabling Replicative Immortality





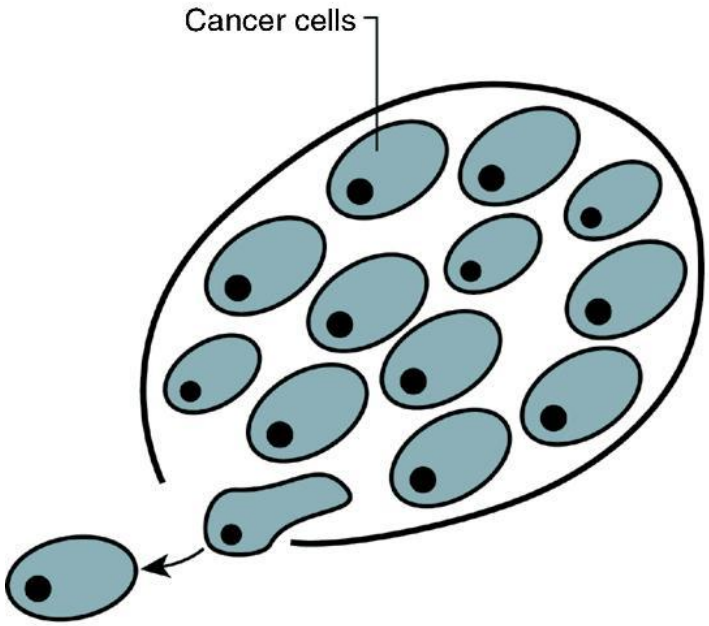


4) Avoiding Senescence and Crisis

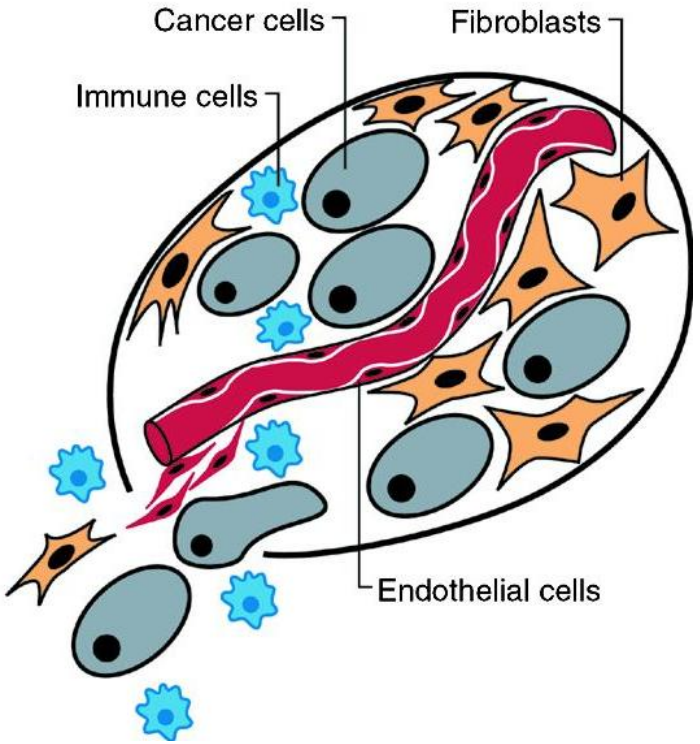


5) Inducing Angiogenesis

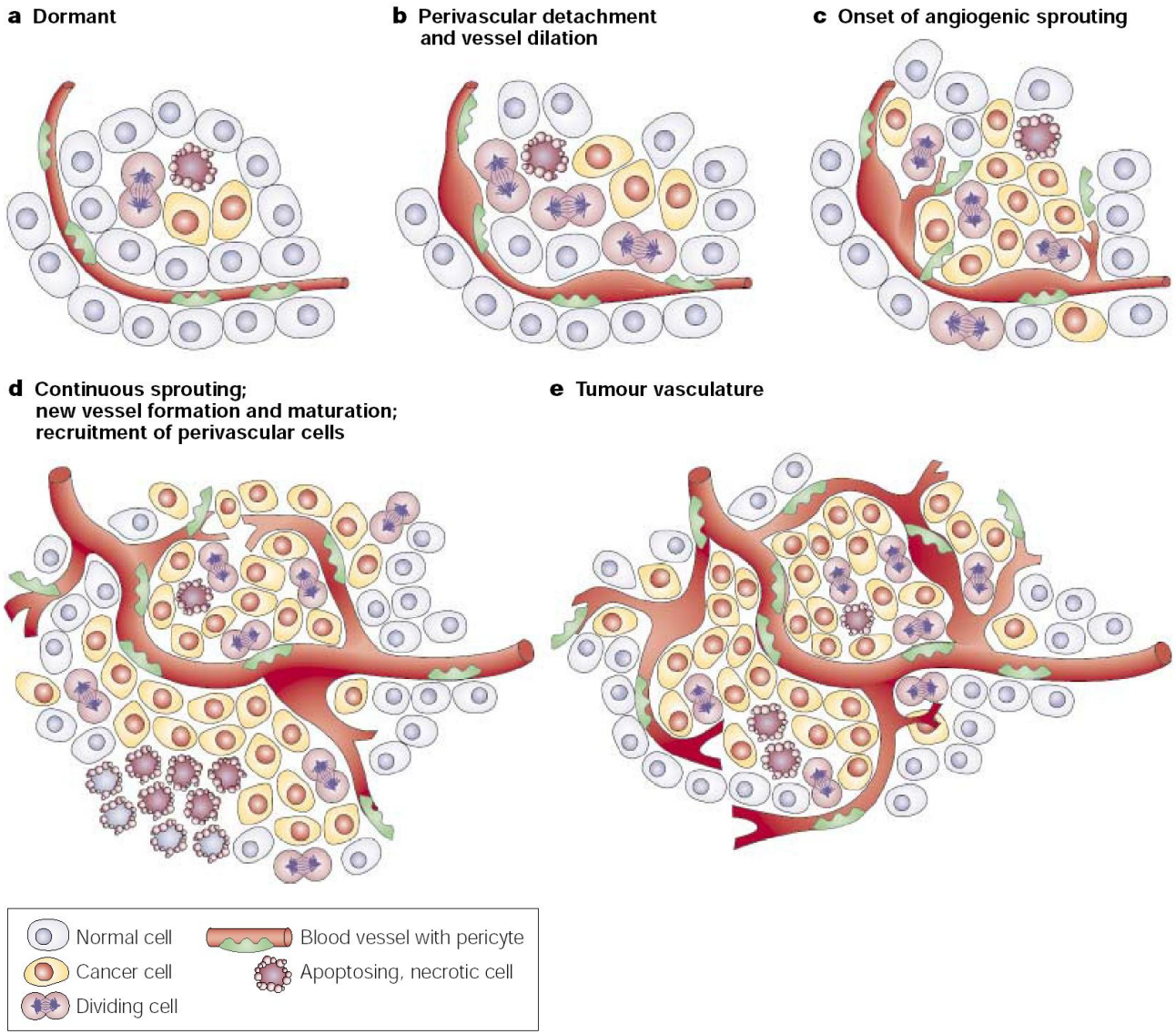
The Reductionist View



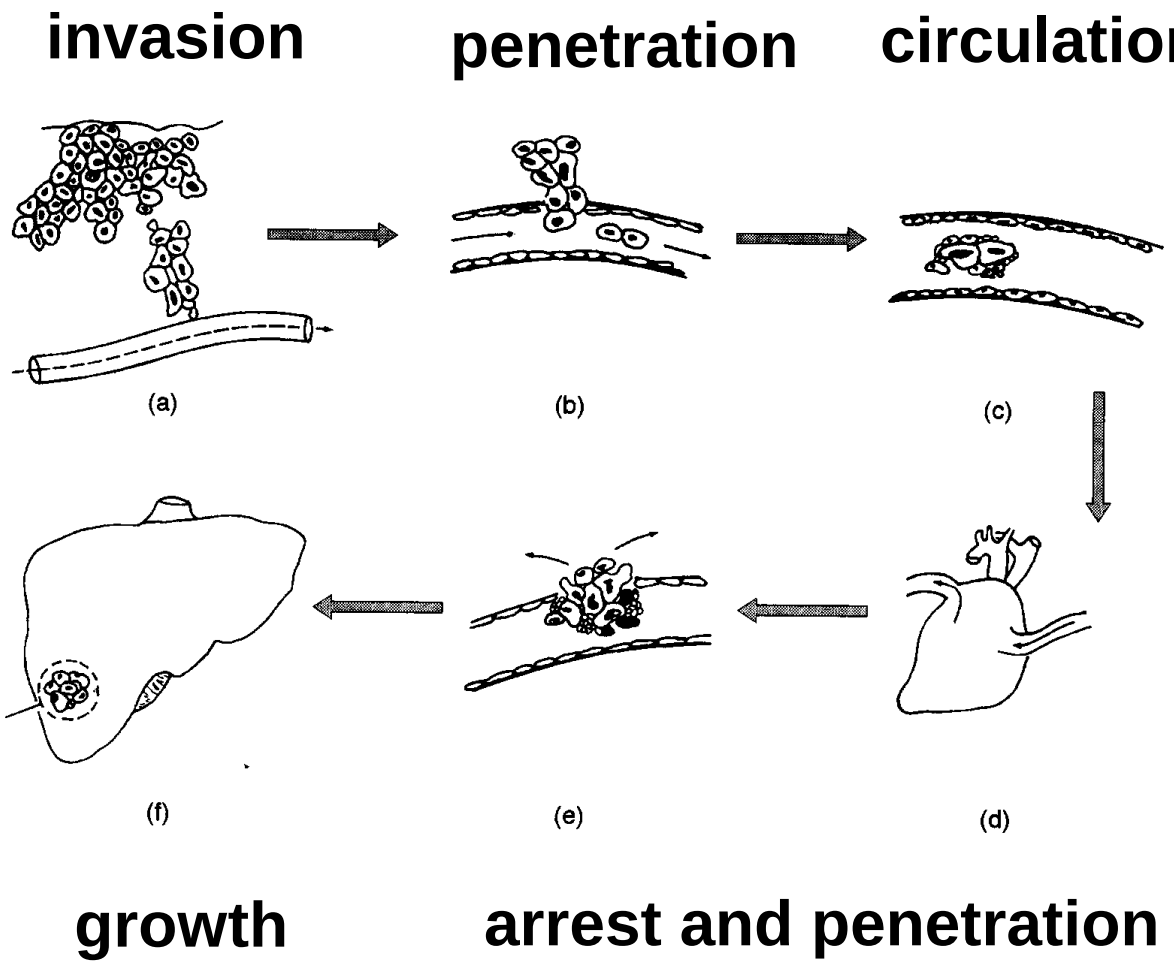
A Heterotypic Cell Biology



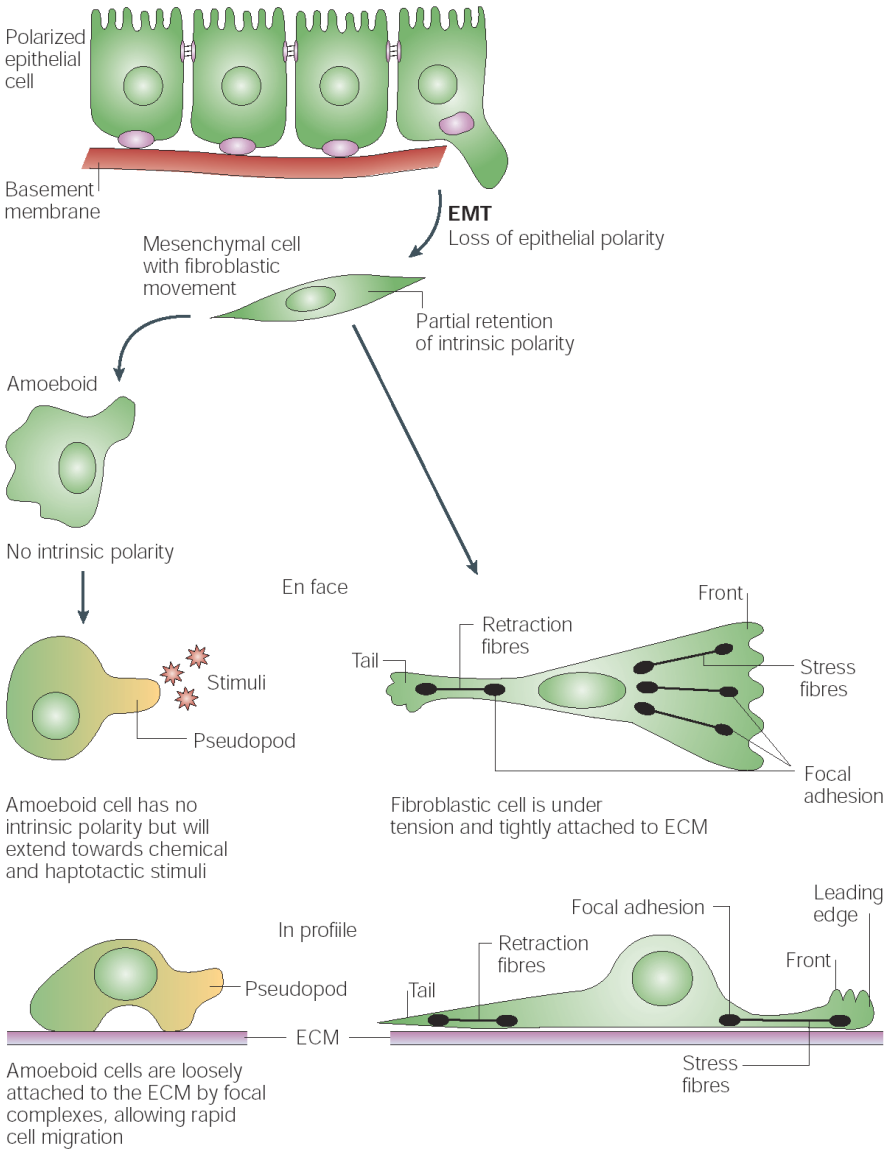
The Angiogenic Switch



6) Activating Invasion and Metastasis



Epithelial-Mesenchymal Transition (EMT)



Simplification!

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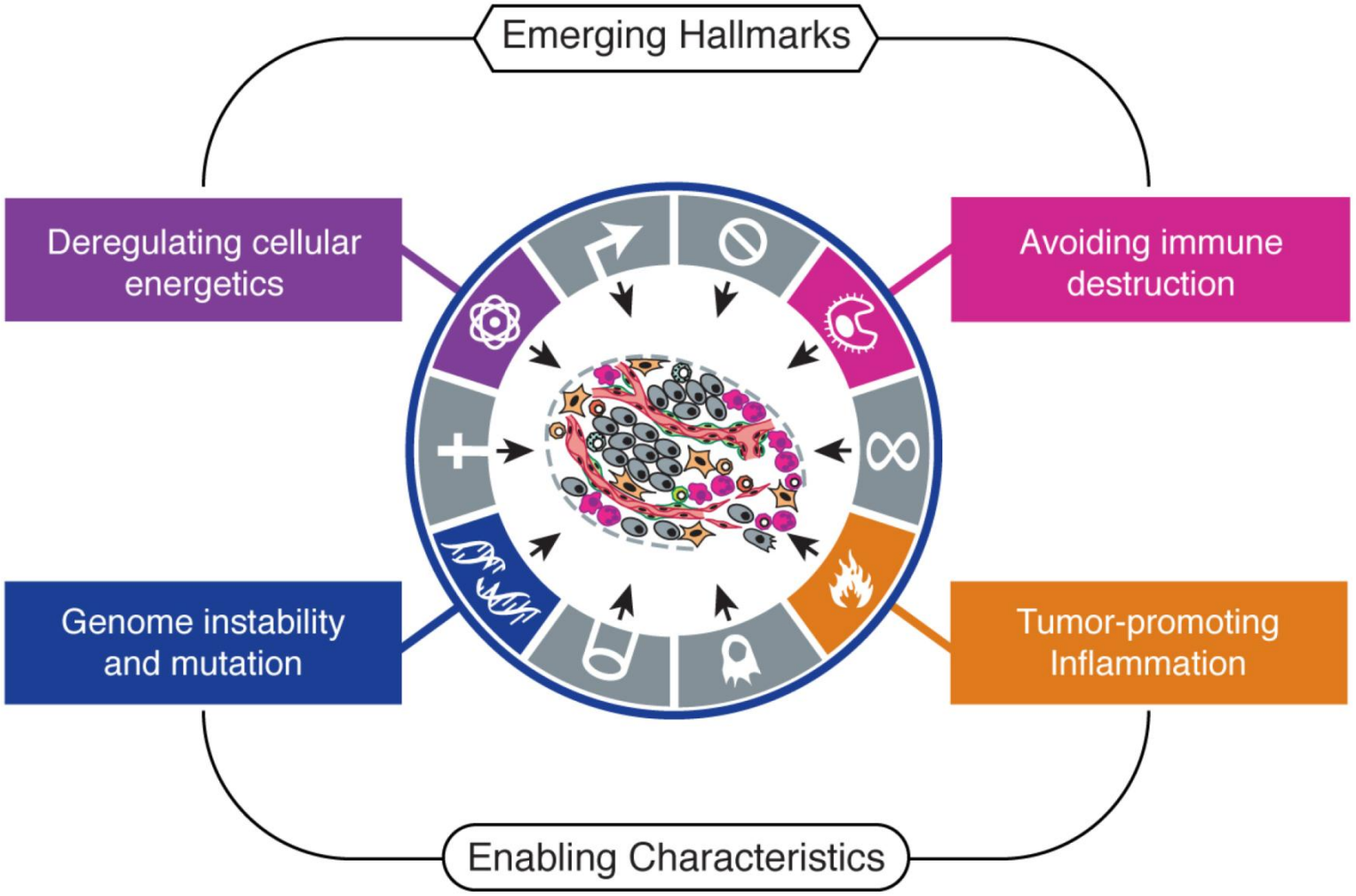
Douglas Hanahan* and Robert A. Weinberg†

Cell, Vol. 100, 57–70, January 7, 2000, Copyright ©2000 by Cell Press

"The vast catalog of cancer cell genotypes is a manifestation of six essential alterations in cell physiology that collectively dictate malignant growth"

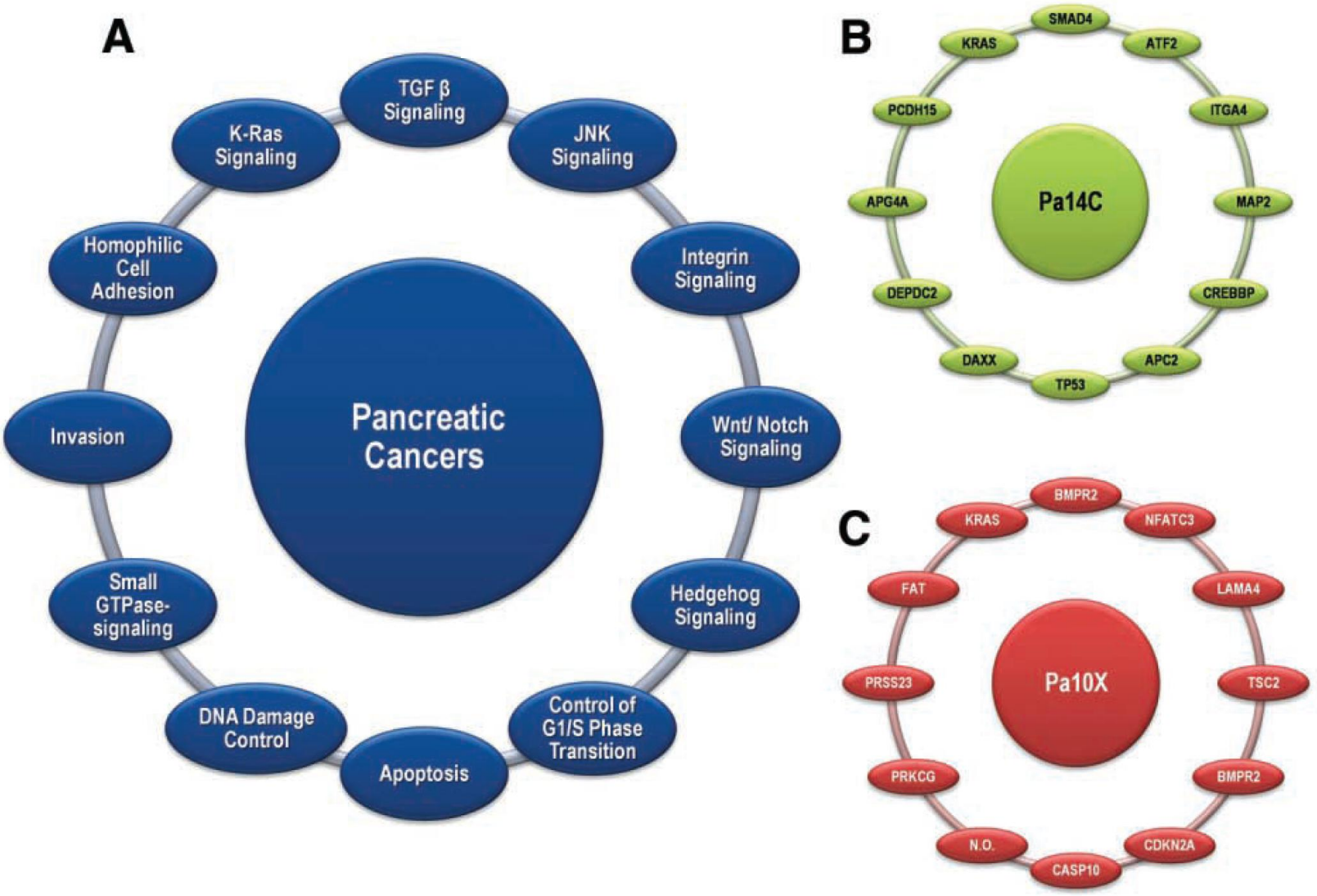
New Hallmarks and Enablers



Hanahan and Weinberg, 2011

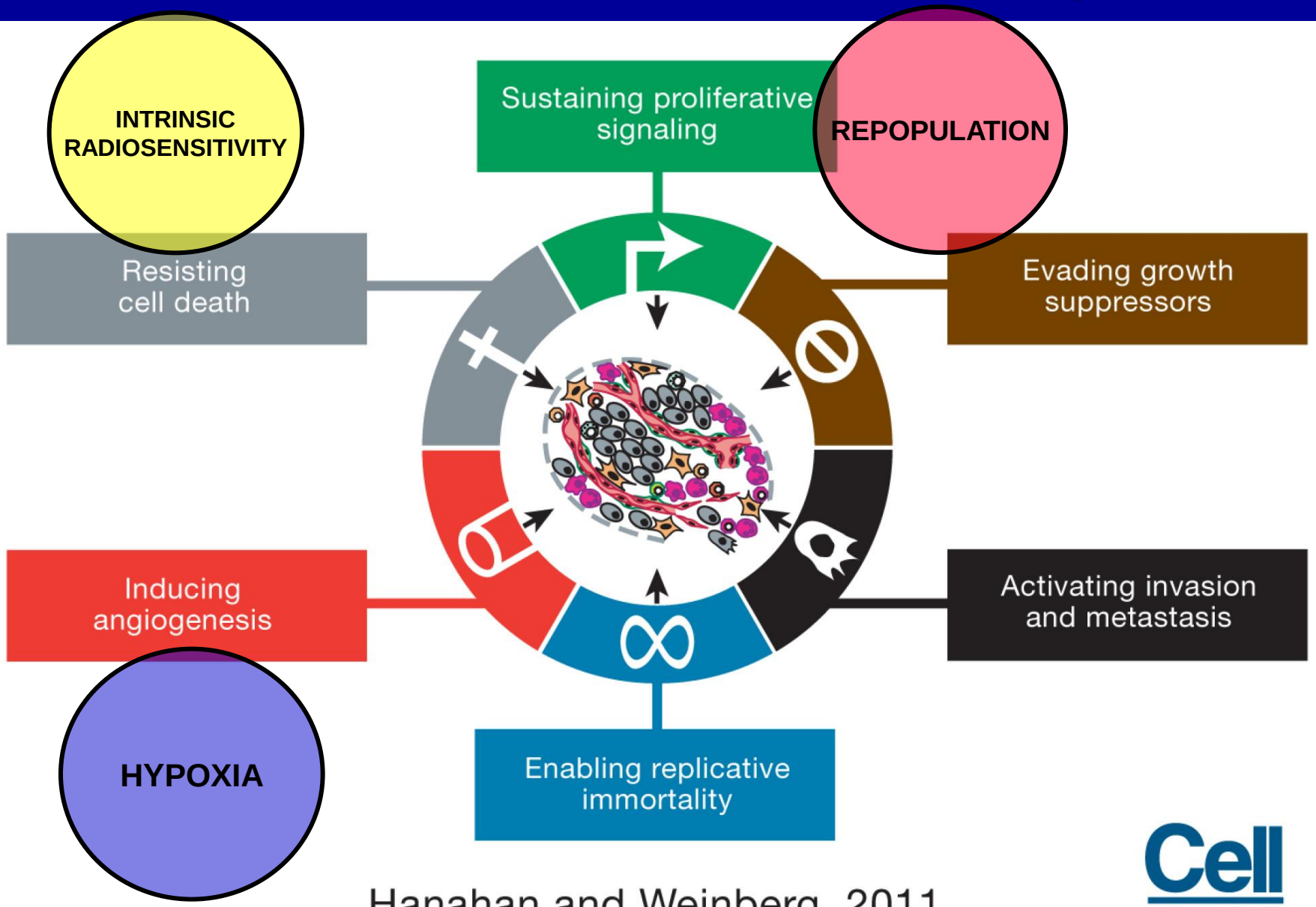
Cell PRESS

Genetic alterations in pancreatic cancer



Jones et al., Science 2008

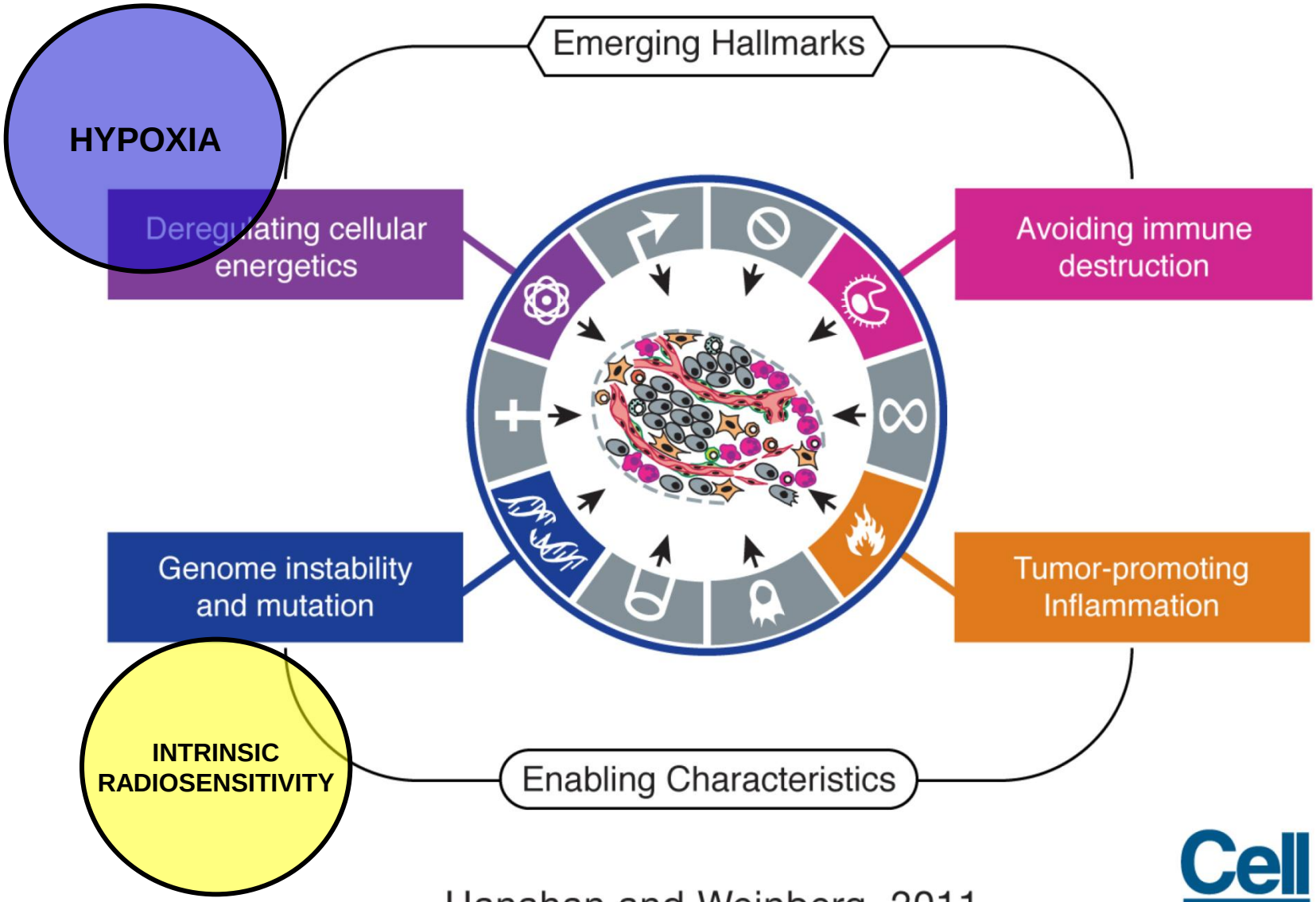
Hallmarks of Cancer & Radiation response



Hanahan and Weinberg, 2011

Cell PRESS

New Hallmarks and Enablers



Hanahan and Weinberg, 2011

Cell PRESS

Conclusions

- Cancer is caused by a series (~5-10) of changes in the genome
  - Additional ~10^3 passenger genetic alterations
- The changes which occur can be classified, giving rise to 6 essential acquired properties, 2 emerging properties and 2 enabling properties
- The hallmarks of cancer can be arrived at by many different genetic routes
  - As a result tumors are very heterogeneous. For each ‘type’ of cancer there are several genetic routes
- These hallmarks (and accompanying genetic alterations) affect treatment and radiation sensitivity in complex ways.
  - Understanding the molecular basis of cancer is important to understand radiation responses

Resources

- The International Cancer Genome Consortium (ICGC)
  - Coordinates large-scale cancer genome studies (genome, epigenome, transcriptome) in 50 tumor types
  - https://icgc.org/
  - https://dcc.icgc.org/
- The Cancer Genome Atlas (TCGA)
  - Creating a comprehensive atlas of the genomic changes involved in >20 tumor types
  - http://cancergenome.nih.gov/
- Catalogue of Somatic Mutations in Cancer (COSMIC)
  - Store and display somatic mutation information and related details in human cancers (benign/invasive tumours, recurrences, metastases and cancer cell lines)
  - http://www.sanger.ac.uk/genetics/CGP/cosmic
- cBioPortal
  - Mutations, gene expression per site
  - http://www.cbioportal.org/

Molecular Basis of Cell Death

Marianne Koritzinsky

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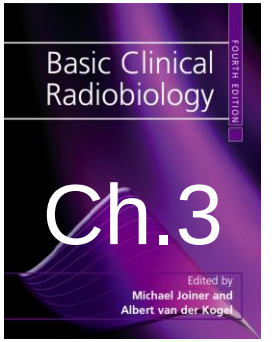
Toronto, Canada
mazinsky@gmail.com



What do we mean by cell death?

- Cell death
  - Loss of reproductive (clonogenic) capacity
  - Cell may or may not appear dead
  - Cells are unable to contribute to tumor growth or metastasis – goal of treatment

- For normal cells, this definition may not be relevant
  - Has no meaning for non-dividing cells
  - Different definitions may be better

How do cells die?

Type of death	Morphology			Biochemistry	Detection
	Nucleus	Membrane	Cytoplasm		
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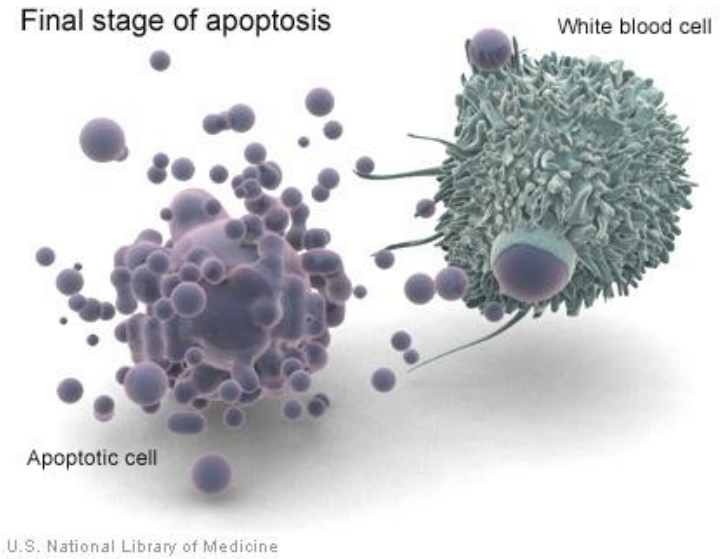
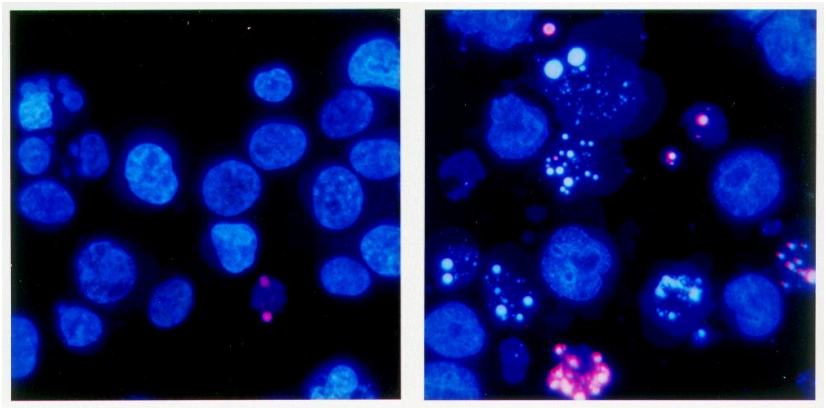
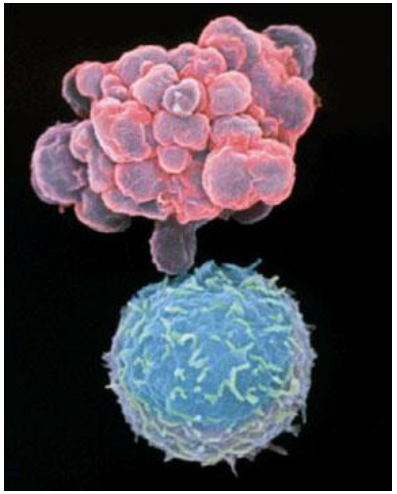
Apoptosis

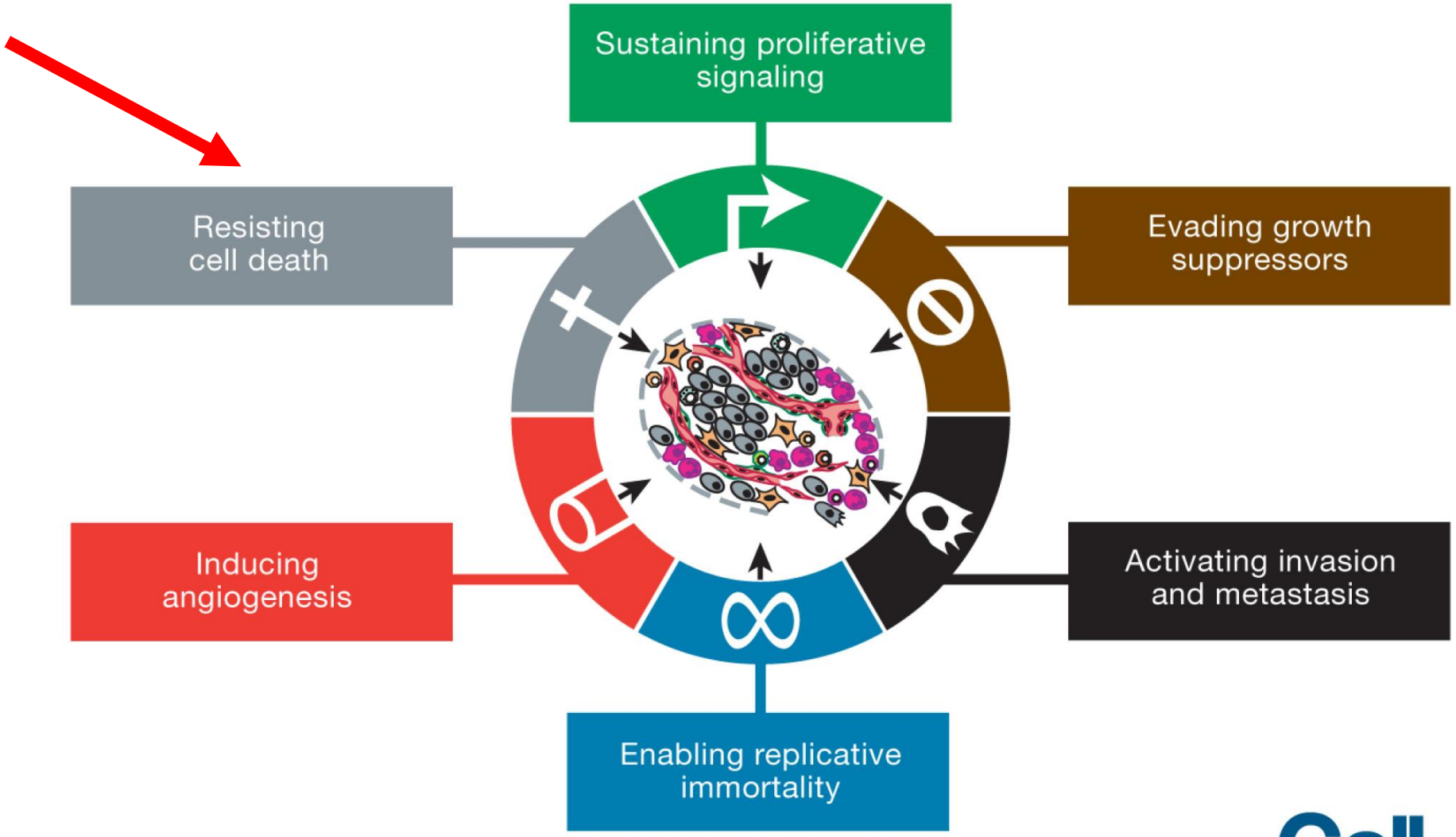


- Active (programmed) form of cell death
- A decision to die is made





The 6 Hallmarks of Cancer



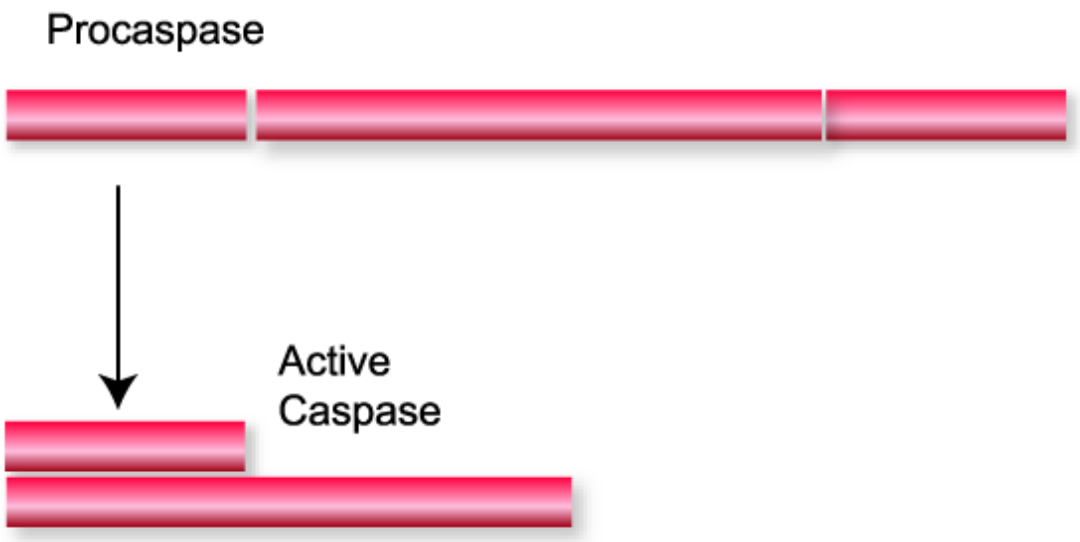
Hanahan and Weinberg, 2011

Cell PRESS

Apoptotic Machinery

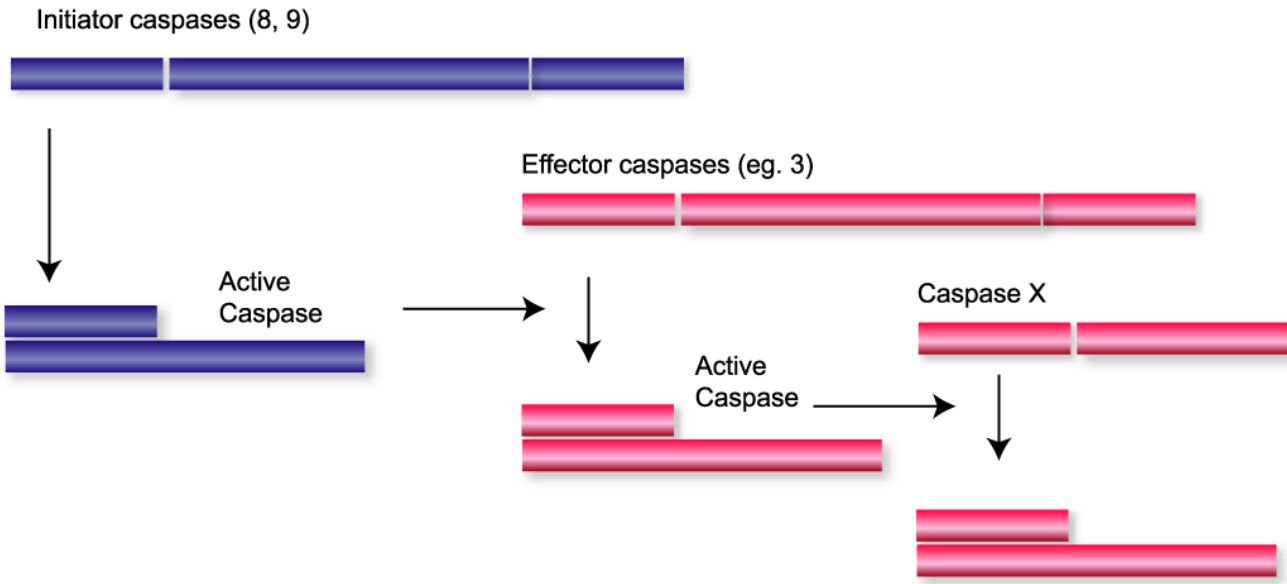
- Sensors
  - Monitor extracellular (extrinsic pathway) and intracellular (intrinsic pathway) environment for conditions of normality and abnormality e.g. hypoxia, growth factors, damage
- Effectors
  - Intracellular proteases called caspases

Effectors: Caspases



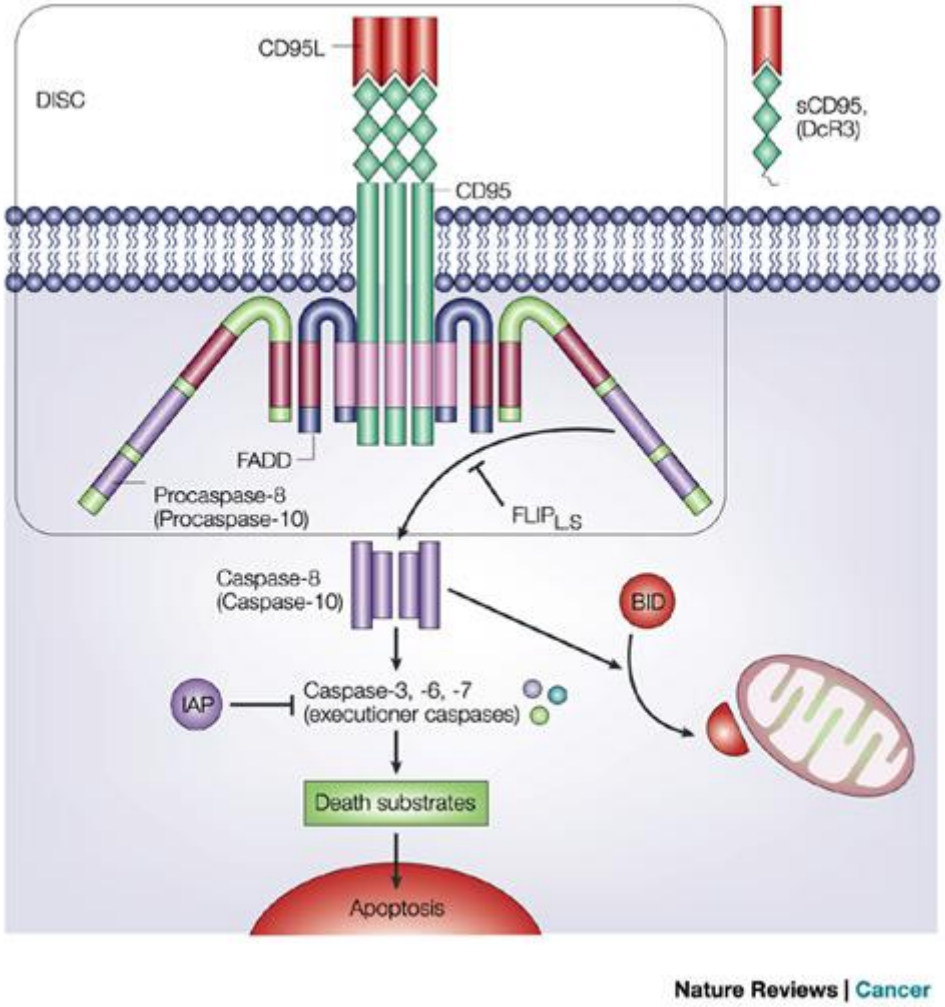
- Executioners of apoptosis
- Cleave proteins at certain sites
- Disassemble the cell
- Present in a pro-form (inactive)

Caspase cascade



Irreversible “switch” for cell death

Extrinsic Pathway – Death Receptors

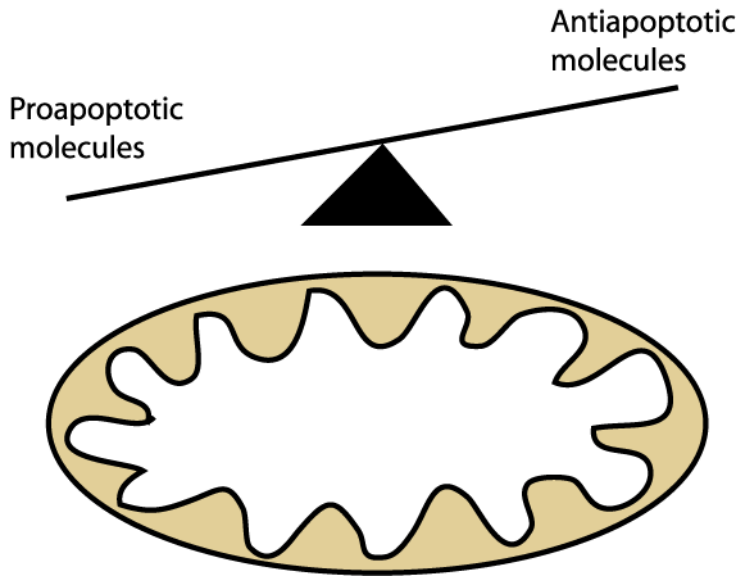


Extrinsic – caspase 8
– signal given to the cell

Receptors	Ligands
TRAILR1, TRAILR2	TRAIL
TNFR1	TNF
FAS	FASL

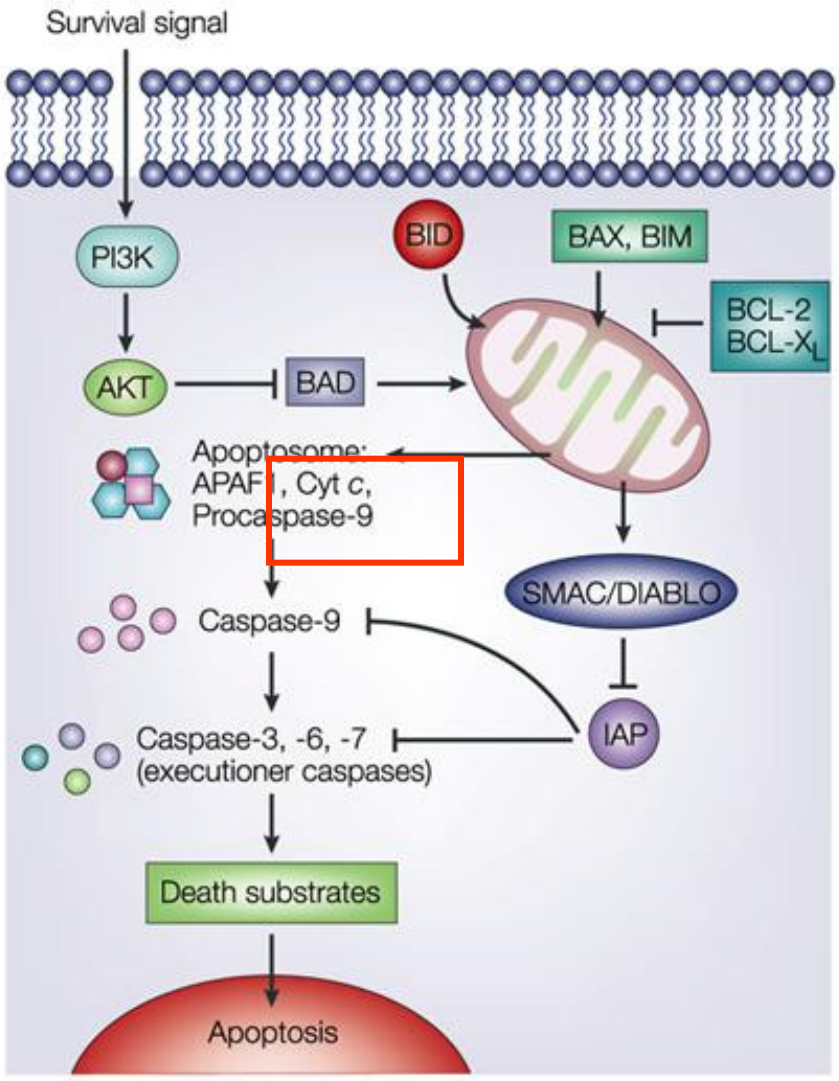
Intrinsic Pathway – Mitochondria dependent

- Mitochondria induce apoptosis when pro-apoptotic factors outnumber anti-apoptotic factors



Step 1)
Increase in the balance of proapoptotic to antiapoptotic factors (Bax/Bcl2)

Intrinsic Pathway



Mitochondria :

Storage site for apoptosis regulating molecules

Step 2) Release of cytochrome C, formation of apoptosome

Step 3) Activation of caspase 9

How do cells die?

Type of death	Morphology			Biochemistry	Detection
	Nucleus	Membrane	Cytoplasm		
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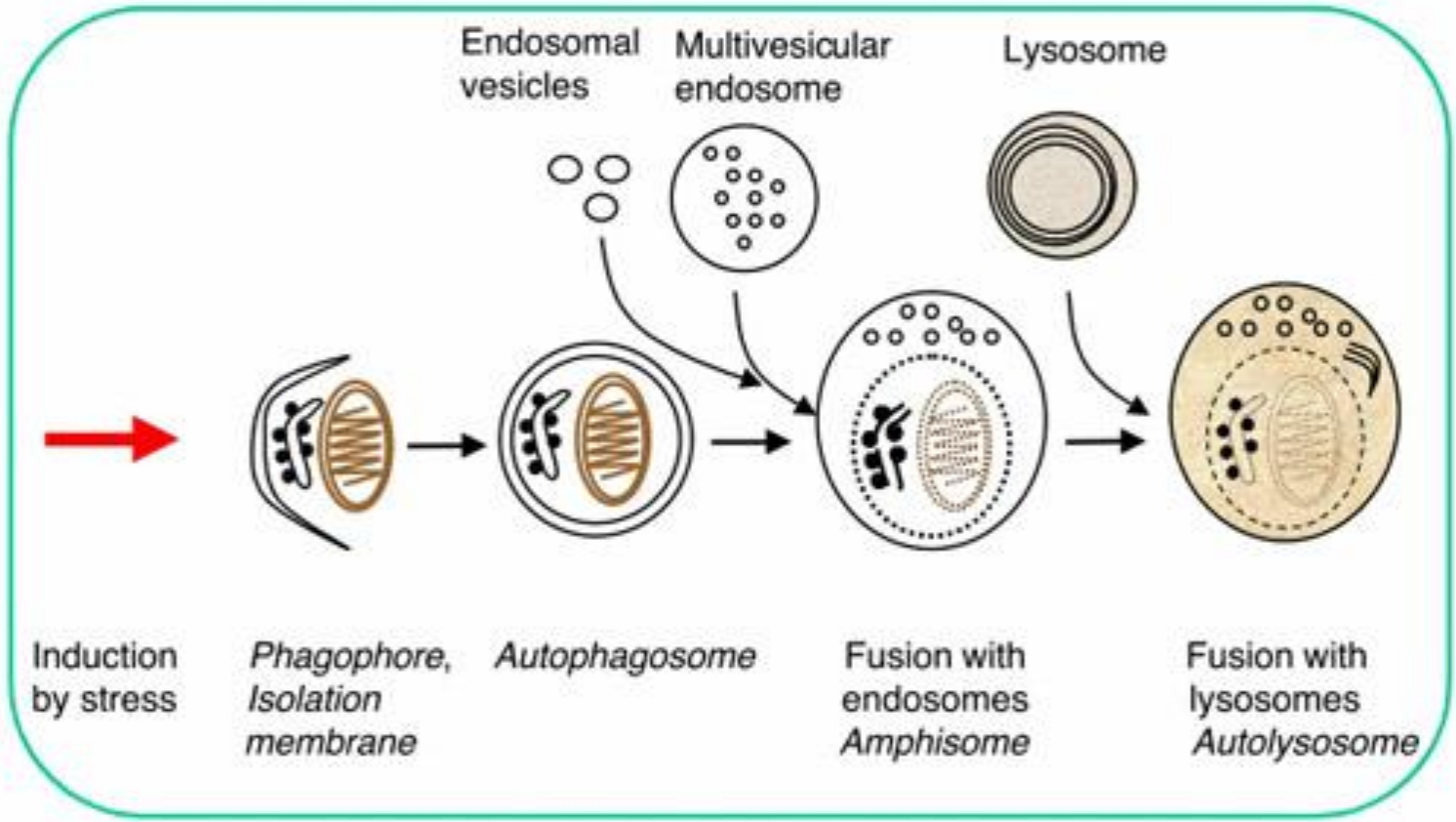
Autophagy

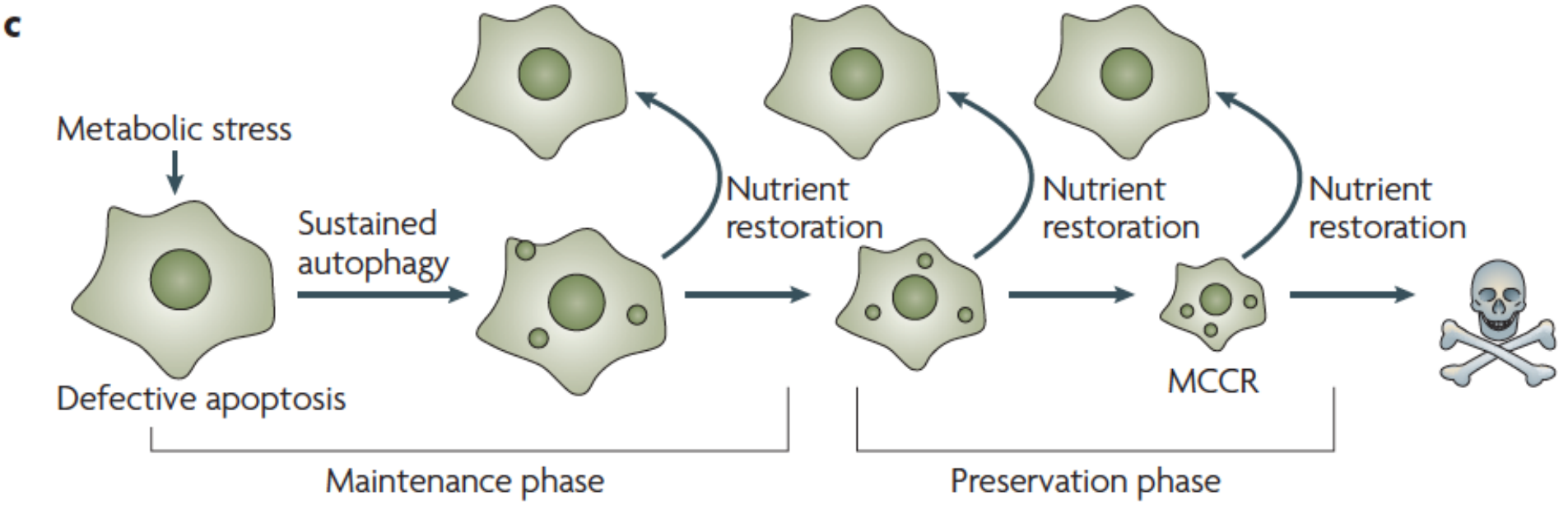
- Important survival mechanism during short-term starvation
  - Degradation of non-essential cell components by lysosomal hydrolases
  - Degradation products are transported back to cytoplasm for reuse in metabolism

- Important mechanism for quality control
  - Removal of defective organelles, proteins

Autophagy –to eat oneself



Autophagy – Survival or Death?



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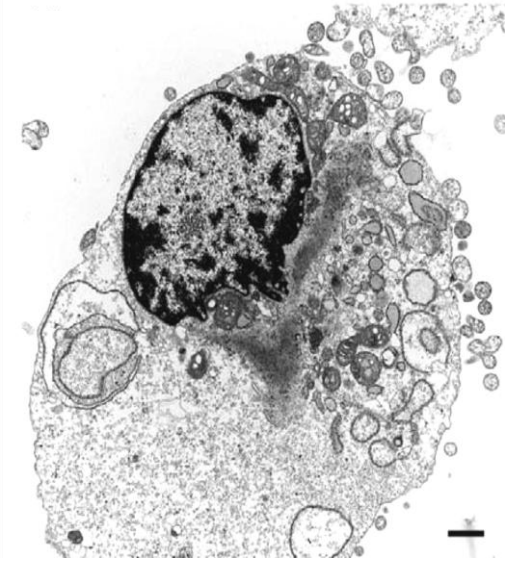
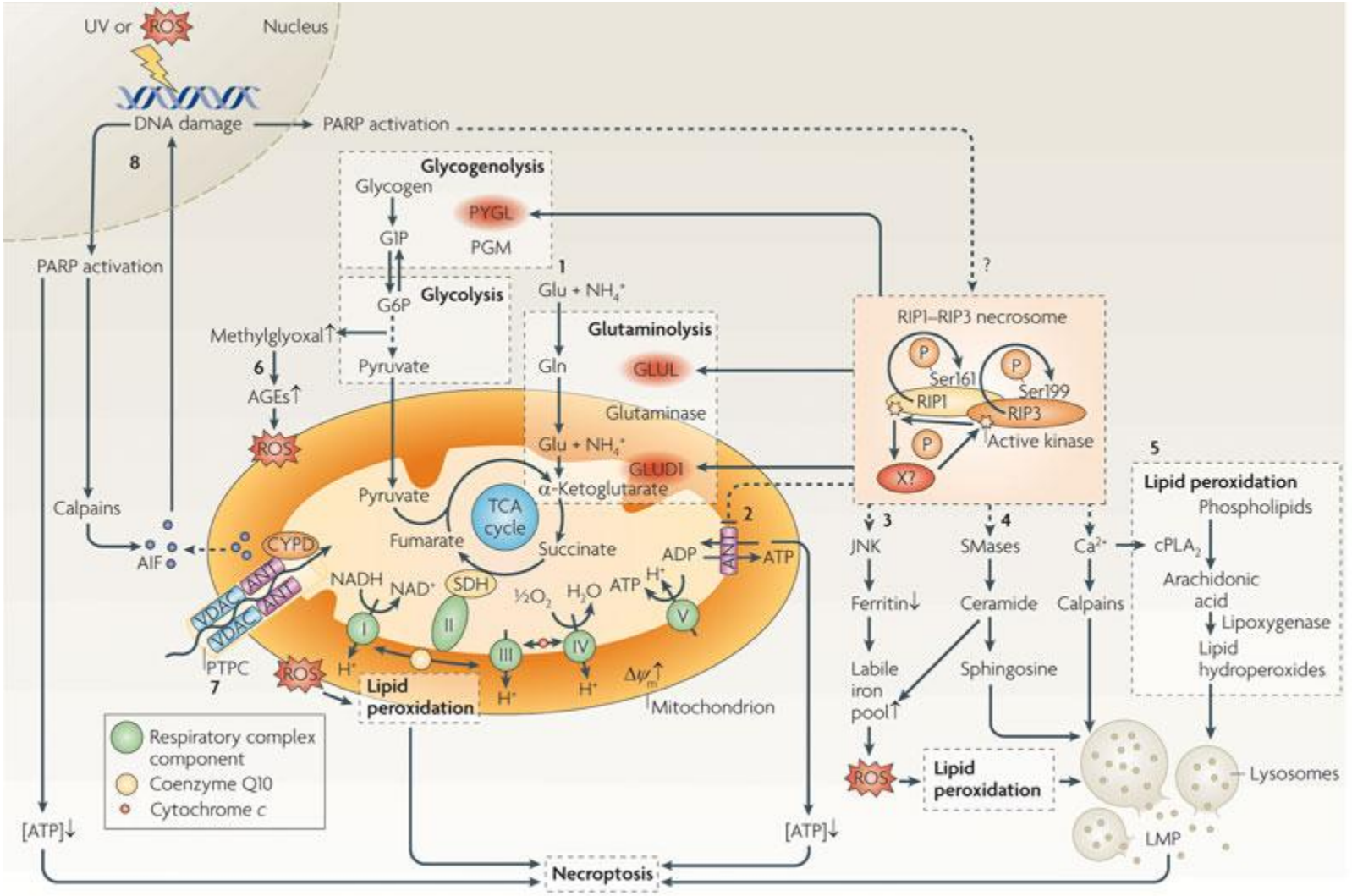
Necrosis

- Insults inducing necrosis
  - Defective membrane potential
  - Cellular energy depletion
  - Nutrient starvation
  - Damage to membrane lipids
  - Loss of function of ion channels/pumps



Execution of necroptosis



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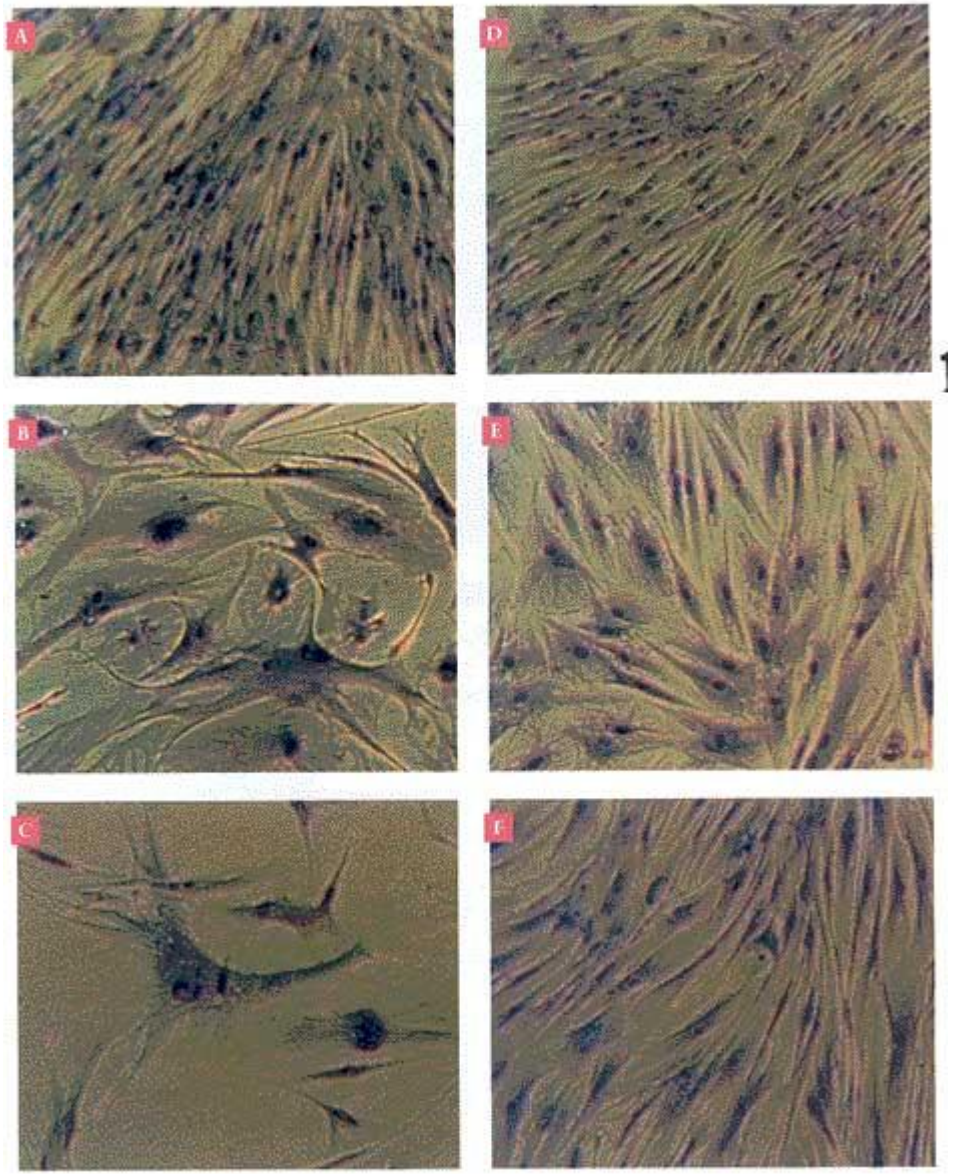
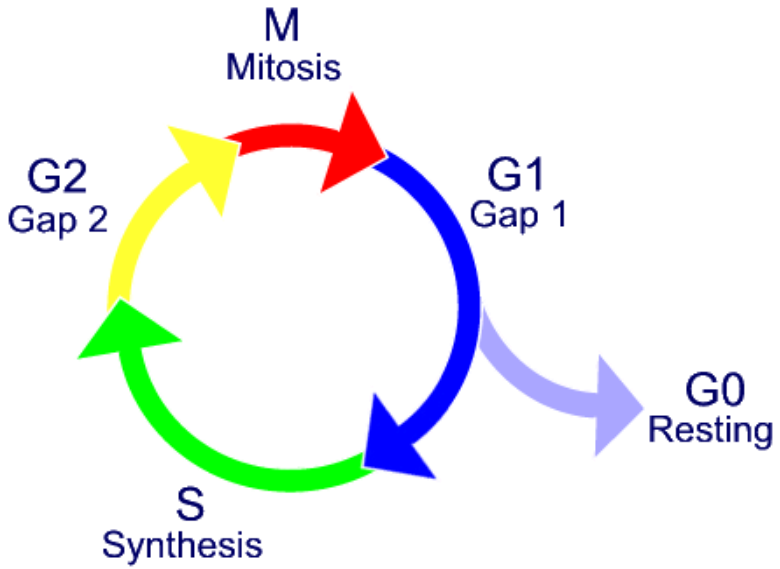
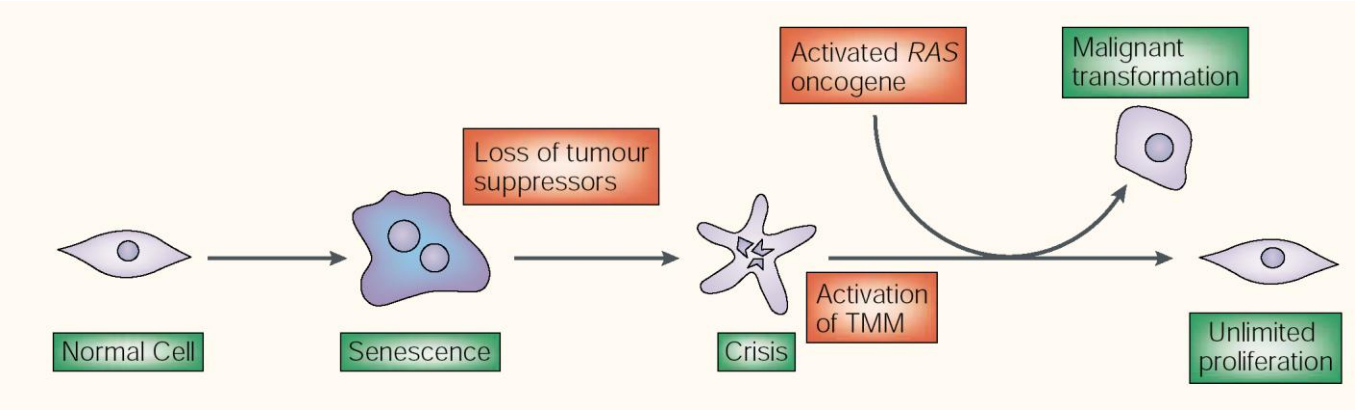
Senescence - Permanent loss of proliferative capacity





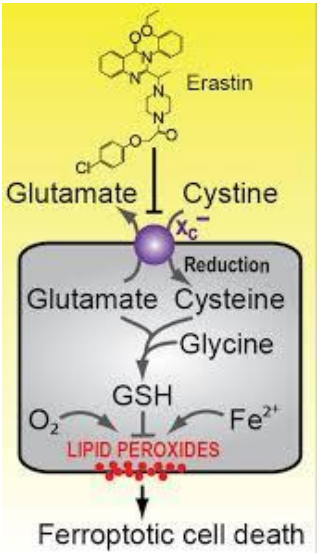
Senescence

- Associated with aging
  - Telomere shortening can induce senescence
  - Limits proliferation in normal cells
- Accelerated senescence
  - Induced by oncogenes, DNA damage
- Genes involved in the G1 checkpoint are important
  -

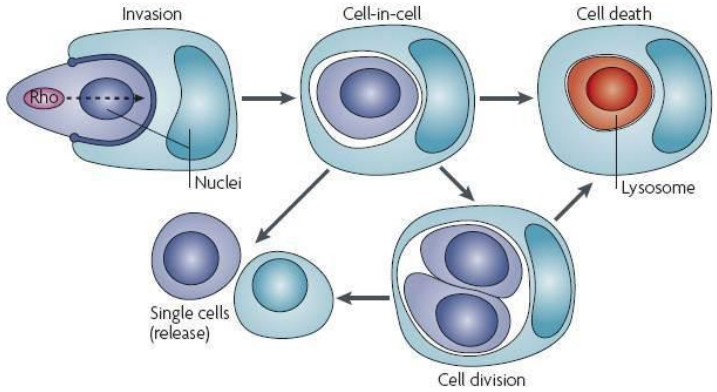


Other forms of cell death (emerging)

- Ferroptosis
  - Iron linked death caused by ROS



- Entosis
  - Cell engulfment



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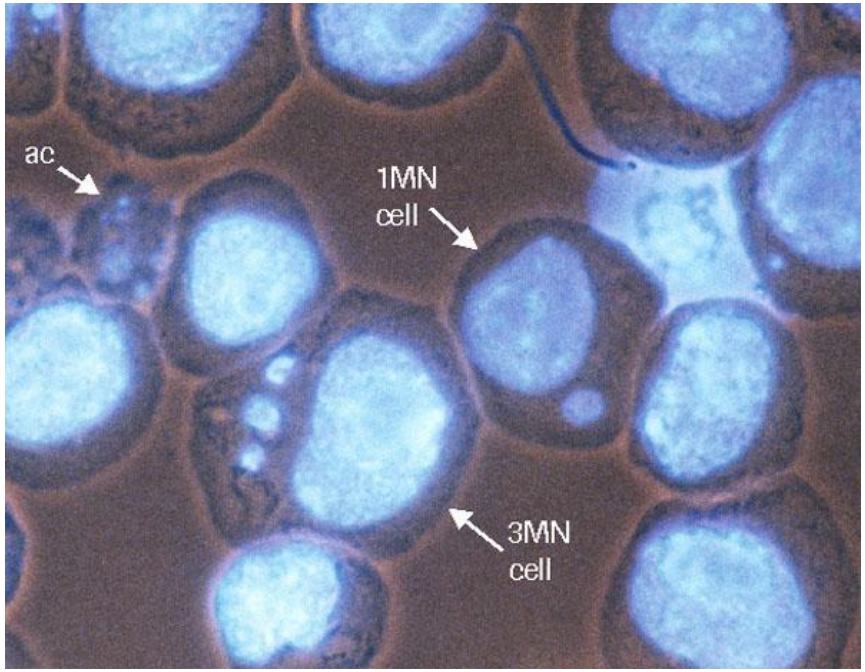
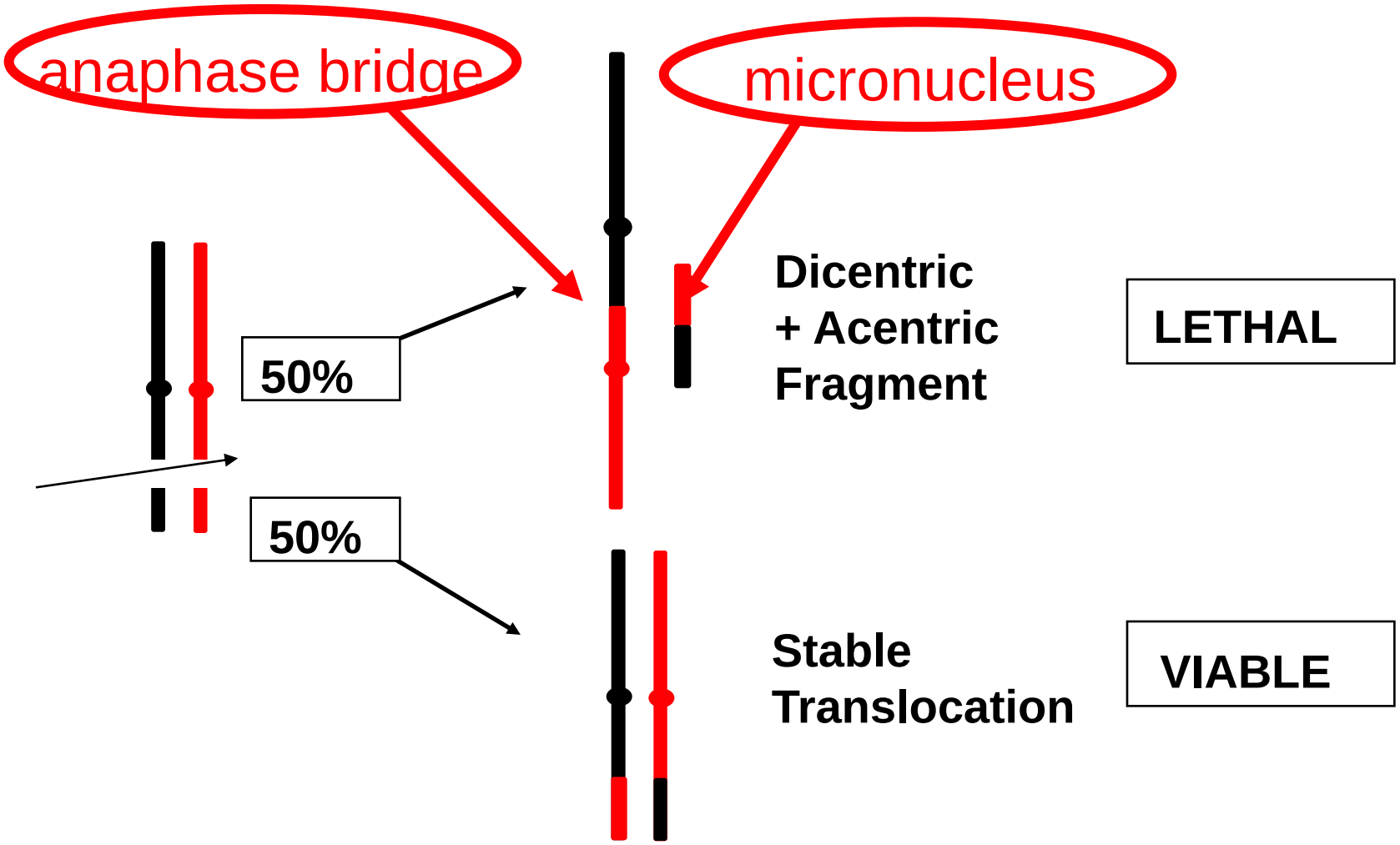
Mitotic Catastrophe

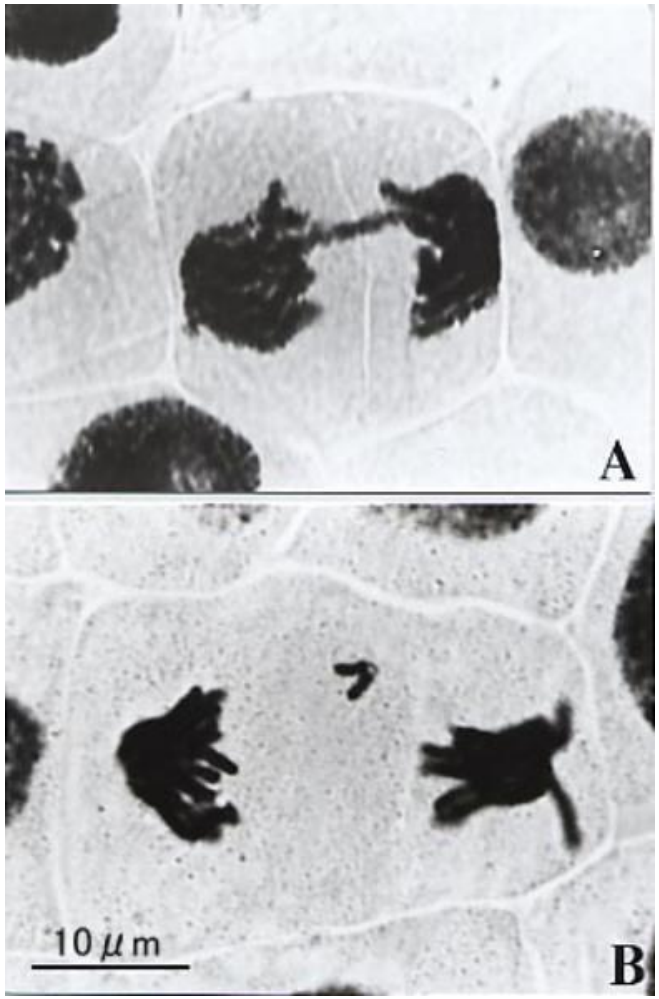


- Mitotic catastrophe
  - Cells attempt to divide without proper repair of DNA damage
- May lead to secondary death by apoptosis, necrosis, autophagy, or senescence

Mitotic catastrophe is caused by chromosome aberrations



Mitotic Catastrophe



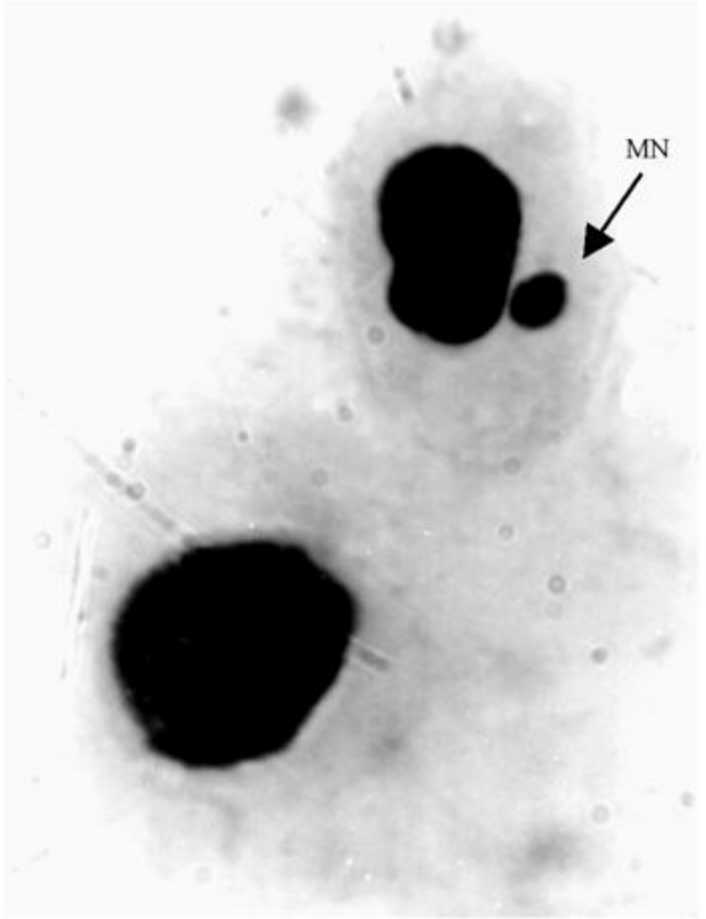


Figure 3 - Micronucleated erythrocyte (arrow) in *R. Catesbeiana* tadpole exposed to lambda-cyhalothrin. Giemsa-stained blood smear 1,000 x.

Mitotic Catastrophe

- Mitotic catastrophe takes place at long times after irradiation
  - Depends on proliferation rate
  - Influenced by DNA repair capacity
- Cell death may occur at different times following mitotic catastrophe
  - Nuclear fragmentation
  - Apoptosis, necrosis, senescence, autophagy
- Cells may attempt several divisions
  - Multiple failed divisions
  - Cell fusions
  - Giant cell formation, multiple micronuclei
- Genome becomes so unstable as to no longer support normal cell function

What about radiation?

- What is the contribution of these death pathways to radiation sensitivity ?
  - The genes controlling these pathways are frequently mutated in cancer
  - The propensity to initiate programmed cell death varies widely

How do cells die?

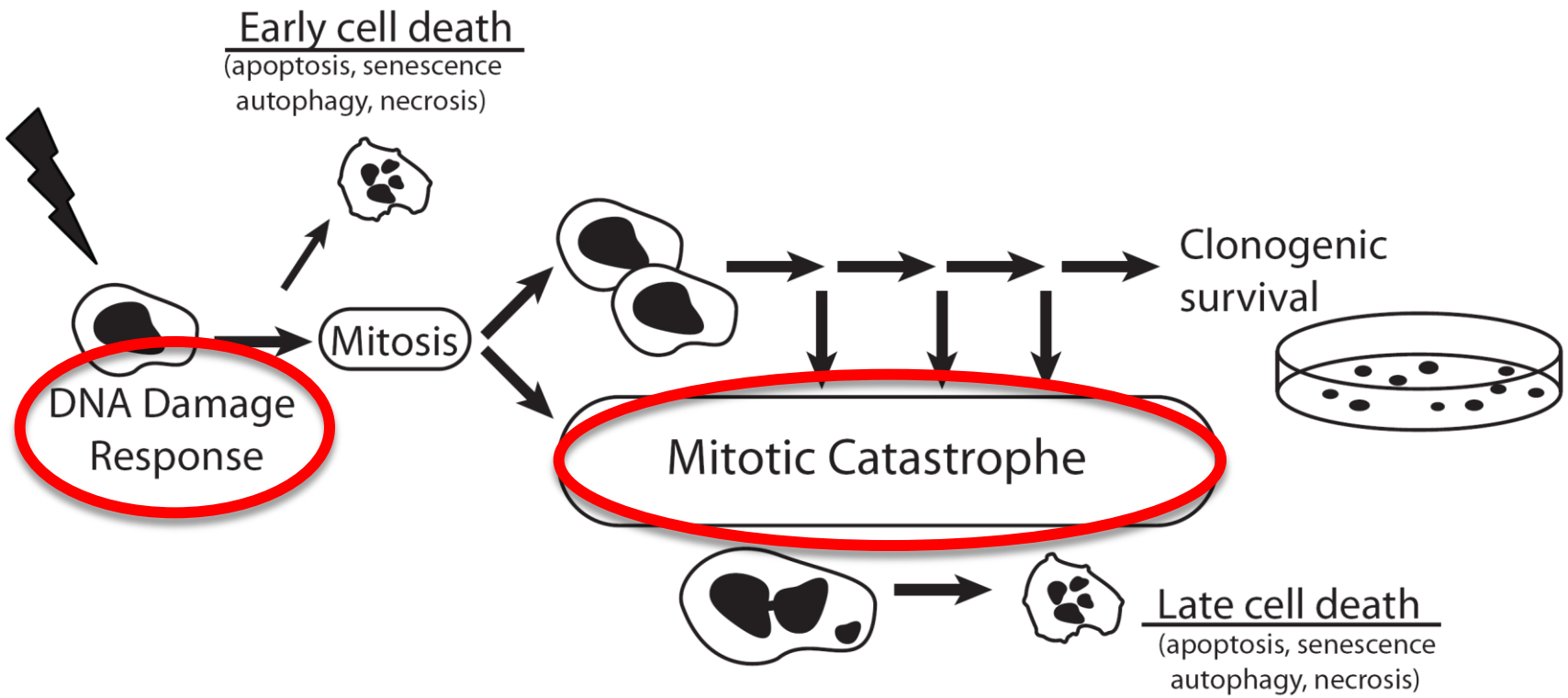
- Necrosis
- Senescence
- Apoptosis
- Autophagy
- …

Why do cells die?

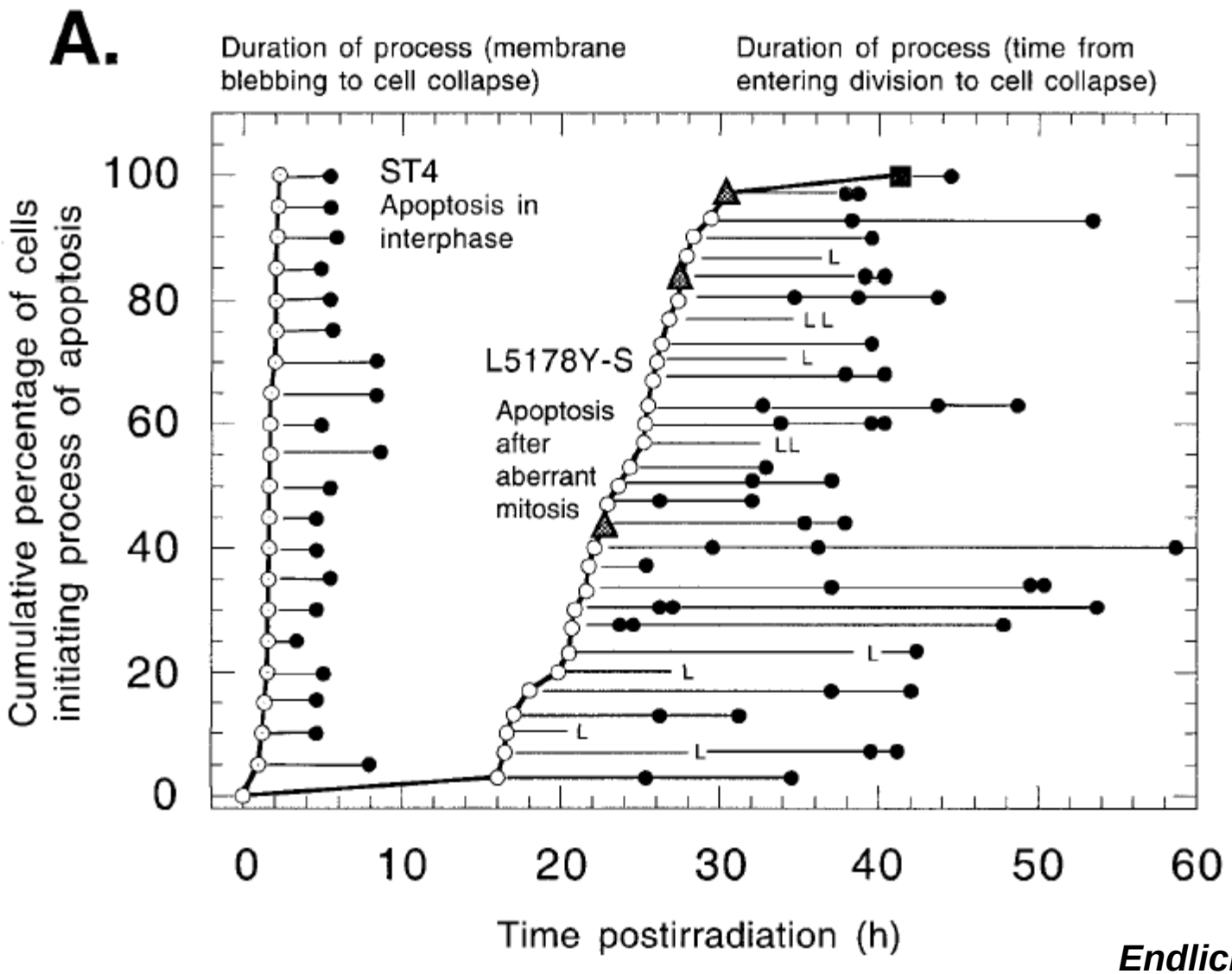
1) Initial damage to DNA (sometimes other molecules)

2) Mitotic catastrophy

What is the *cause* of cell death?



Two Types of Apoptosis - Pre and post mitotic



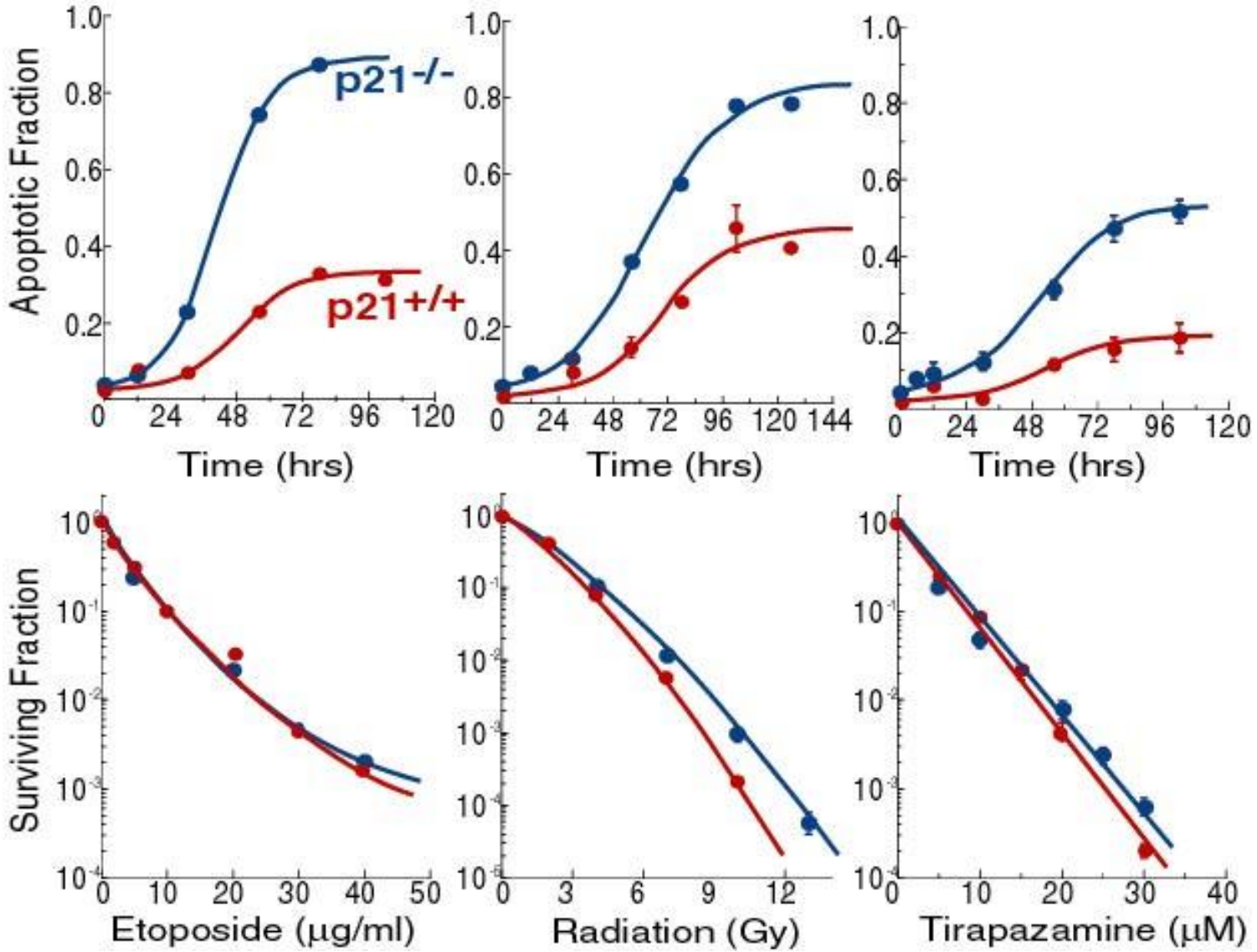
Endlich et al (2000)

Apoptosis is Both a Reason for Cell Death and a Type of Funeral

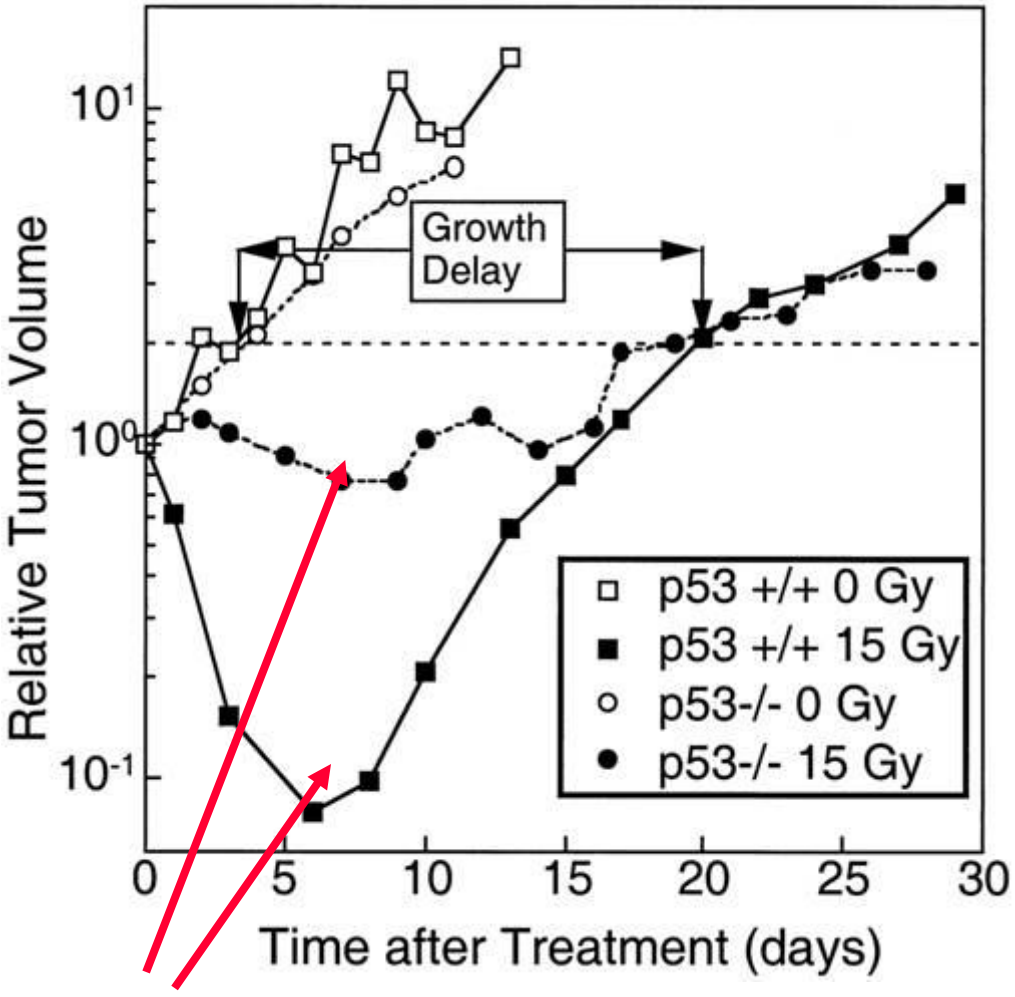
- Early apoptosis: Apoptosis is the reason the cell dies - it is the most sensitive mode of cell death and genes that affect apoptosis also affect cell death - e.g. some lymphomas and leukemias.

- Delayed apoptosis: The reason the cell dies is usually by mitotic catastrophe. However, the cell may, or may not, have an apoptotic “funeral”. Changing apoptotic sensitivity does not change overall cell killing - e.g. most epithelial cancers.

Apoptosis can change without affecting clonogenic survival of HCT116 tumor cells



Affecting how cells die can dramatically influence the rate at which cells die



apoptosis difference

Early Apoptosis explains:

- The sensitivity of lymphocytes at low radiation dose.

- The efficacy of low dose radiation dose in non-hodgkin lymphomas: 2x2 Gy results in a high proportion of responses in Low grade non-Hodgkin Lymphoma

Apoptotic index and prognosis in cancer

All studies using morphology or TUNEL since 2000 *(Wilson, 2003)*

	author	n, treatment	result		comment
Cervix	Jain	76, Rx	n.s.	😐	no correlation with either p53 or bcl-2
	Gasinska	130, Rx	n.s	😐	AI/MI index significant
	Lee	86, ?	n.s.	😐	correlation with progression, MVD, Ki-67 but not OS
	Kim	42, Rx	sig	🙂	high AI poor LTC, OS
	Liu	77, Rx	sig	🙂	high AI (or Ki-67) poor OS, no corr with IATs
	Zaghlo				
	Paxton				
NSCLC	Hanad				
	Wang				h bcl-2 and TA
	Hwang				OS
	Maclus				
	Lange				ith bcl-2
Breast	Srinivа				
	Kato				
	Ikpatt				
	Villar				bcl-2
	Lee				
	Wu				
	de Jong	172, ?	sig	🙂	high AI worse OS positive correlation with MI
	Lipponen	288. ?	sig	🙂	high AI worse OS
Rectum	Sogawa	75, pre Rx	n.s.	😐	AI increased after Rx but not correlated with OS
	Schwander	160, surg	n.s.	😐	inverse correlation with p53 and bcl-2
Bladder	Giannopolou	53, ?	n.s	😐	no correlation with pro-apoptotic proteins bax, FAS-R casp-3
	Moonen	83, Rx	n.s.	😐	high AI better LTC not OS, low AI shorter time to reccurrence
	Lara	55, Rx	sig	🙂	low AI better LTC and OS
Esoph	Rees	58, Rx, CTX, surg	n.s	😐	only TOPO II and not AI or Ki-67 showed clinical utility
	Shibata	72, surg	sig	☹	high AI better OS

Results

6 better outcome with high AI

8 worse outcome with high AI

13 not significant

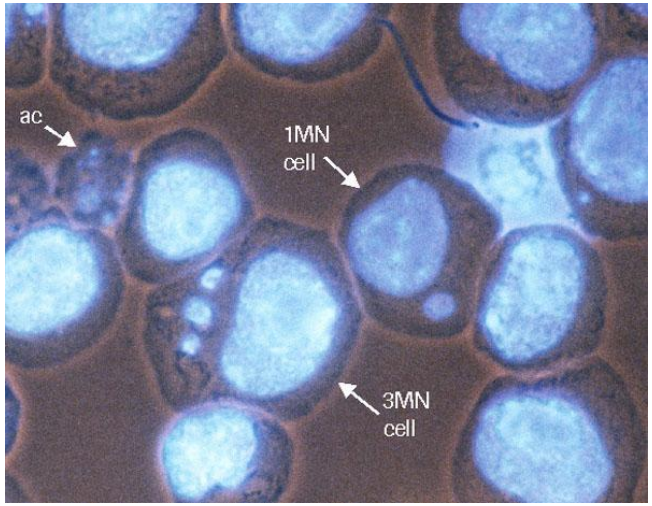
Summary of many clinical-preclinical studies

- The mechanism of killing of the cells of solid tumors is not by early apoptosis.
- Solid tumor cells may die of apoptosis, but it is by post-mitotic (delayed) apoptosis.
- Modification of post-mitotic apoptosis does not usually change overall cell kill.

(Brown and Attardi, Nat Rev Cancer, 5: 232, 2005)

Mitotic Catastrophe

- The major form of cell killing after ionizing radiation and other DNA damaging agents.
- Almost all death occurs after cells attempt division one or more times

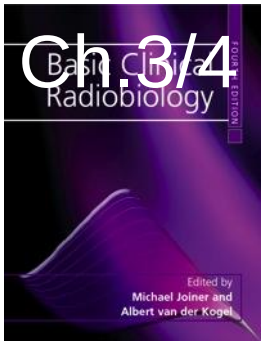


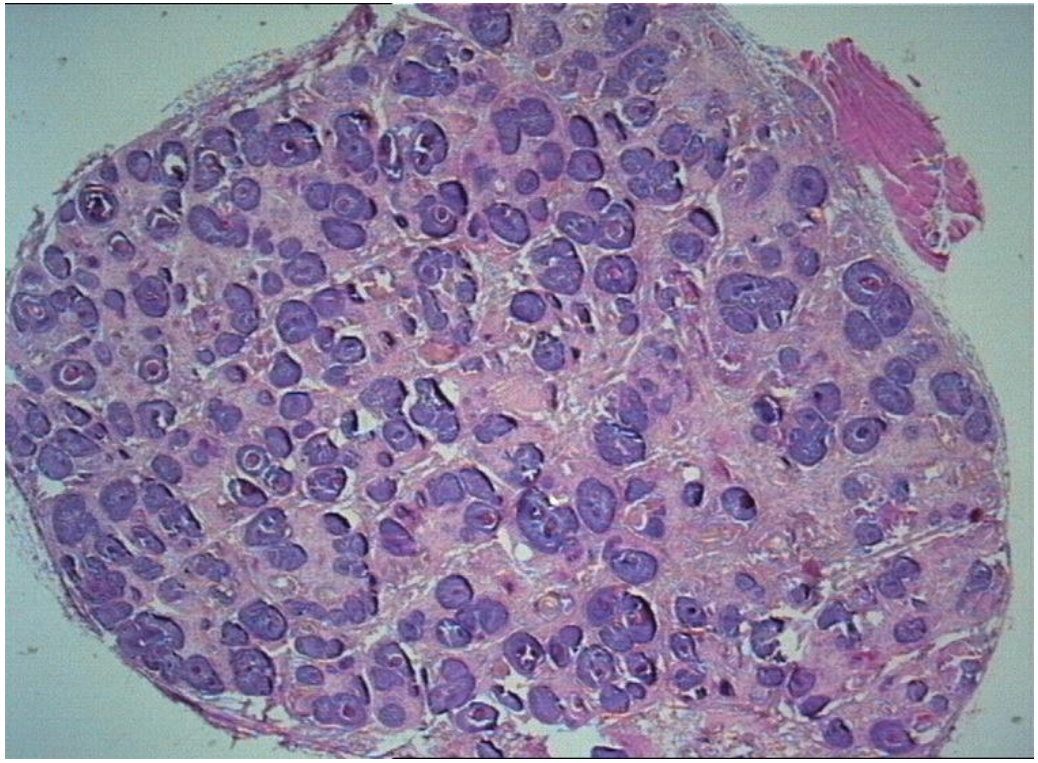
Movie

Conclusions

- Most cell death is controlled or programmed in some way.
  - Major pathways include apoptosis, senescence, autophagy and necrosis
- Measuring one form of cell death (eg Apoptosis) will not necessarily correlate with how many cells die
  - Cell may die by other mechanisms
- The form of cell death may influence the rate at which cells die
  - Affect tumor regression
- Genetic changes may dramatically alter how cells die without changing if they will die

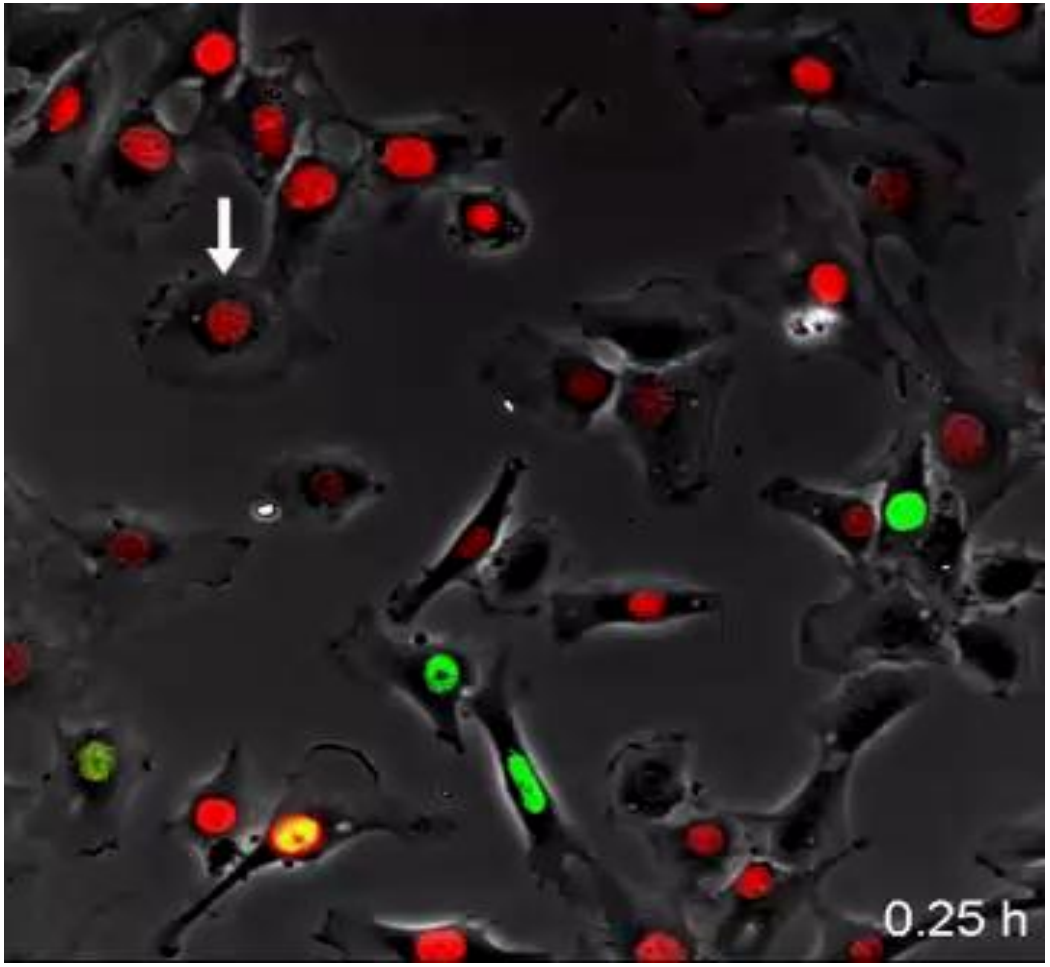
Basic Clinical Radiobiology
Clonogenic cell survival





Albert van der Kogel
Budapest, 2016

Dynamics of the cell cycle in a growing population



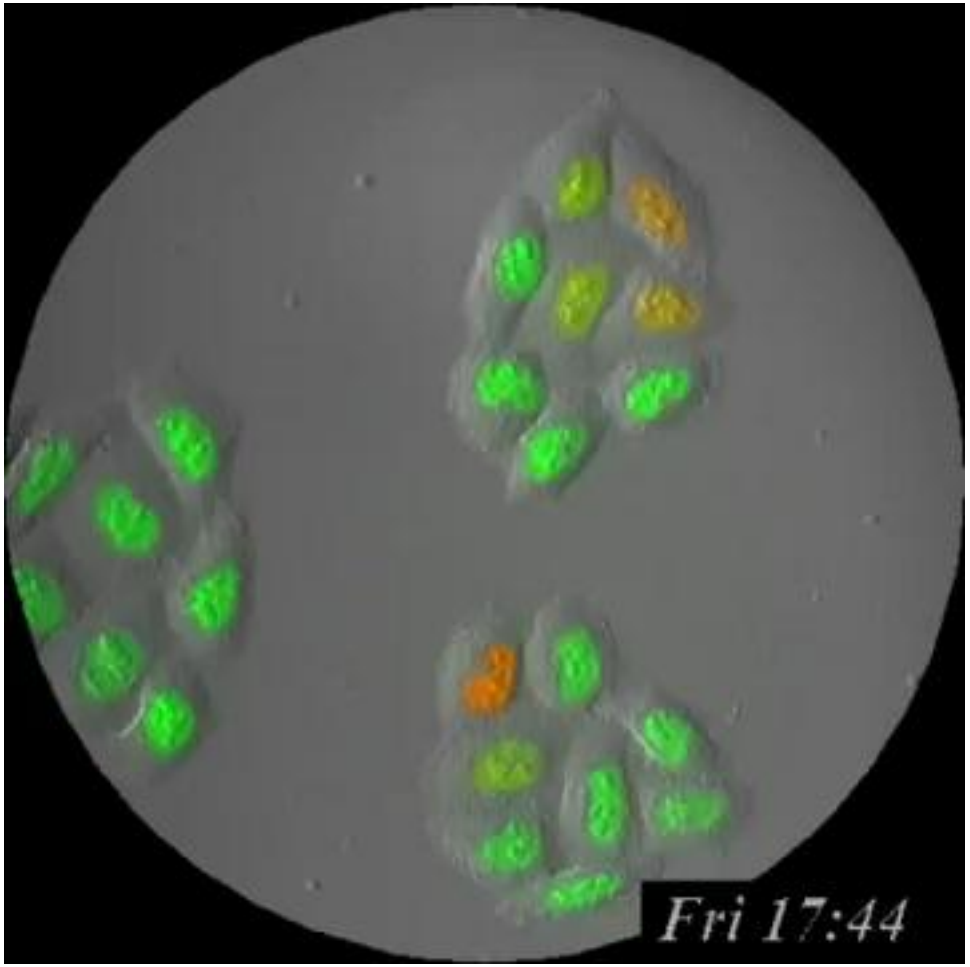
G1 - early S - late S & G2

FUCCI imaging of the cell cycle: two interphase regulators, Cdt1 & Geminin.

Cdt1 (red) only expressed during G1 and early S
Geminin (green) only expressed during S/G2.

human fibroblasts visualized by time-lapse live-cell imaging over period of 3 days

Dynamics of the cell cycle in a growing population

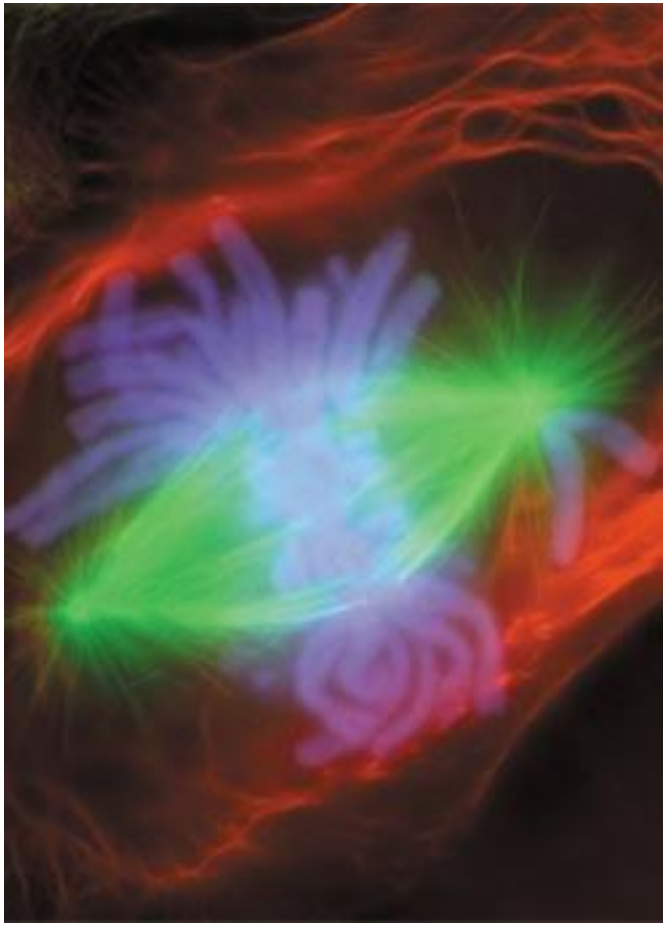


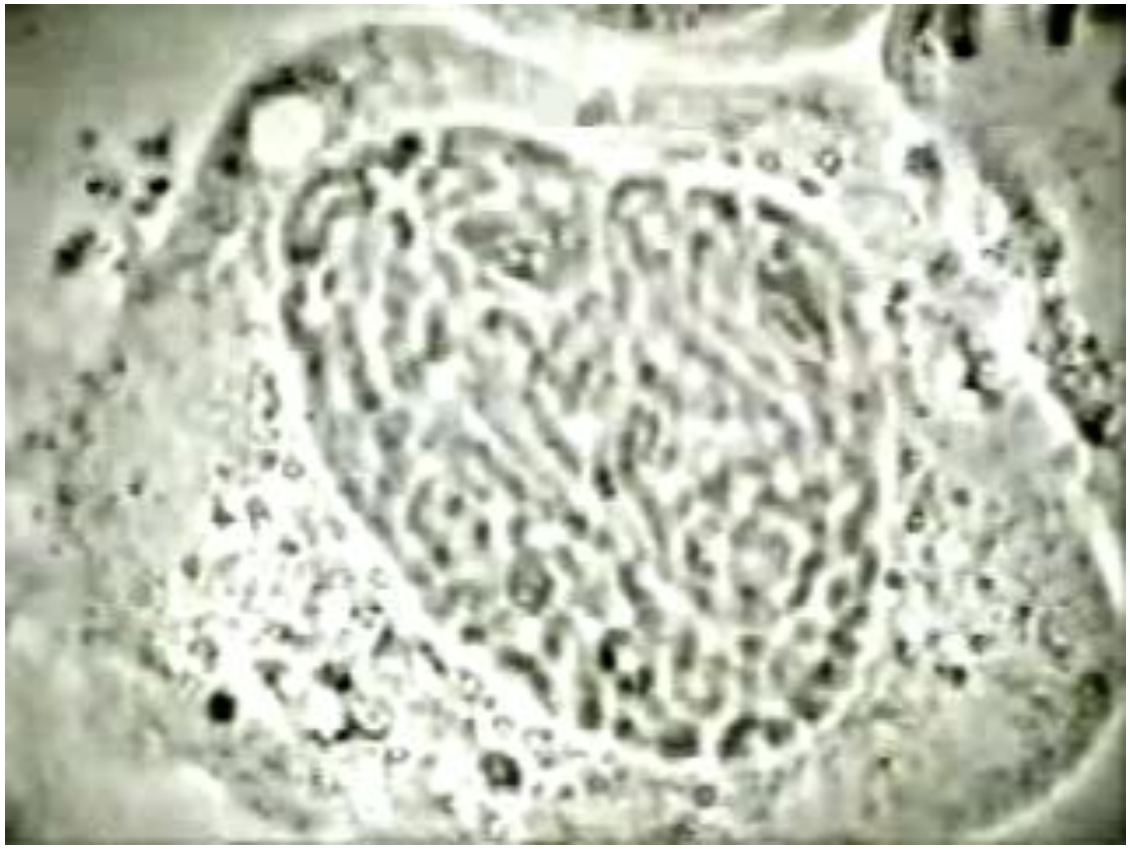
FUCCI imaging of HeLa cells over 3.5 day period

Red: G1/early S
Green: S/G2

G1 - early S - late S & G2

Effects of irradiation on mitosis





Effects on mitosis in plant cells:
endosperm of Haemanthus - time-lapse movie A. Bajer (1962)

Effects of irradiation on clonogenic survival in vitro

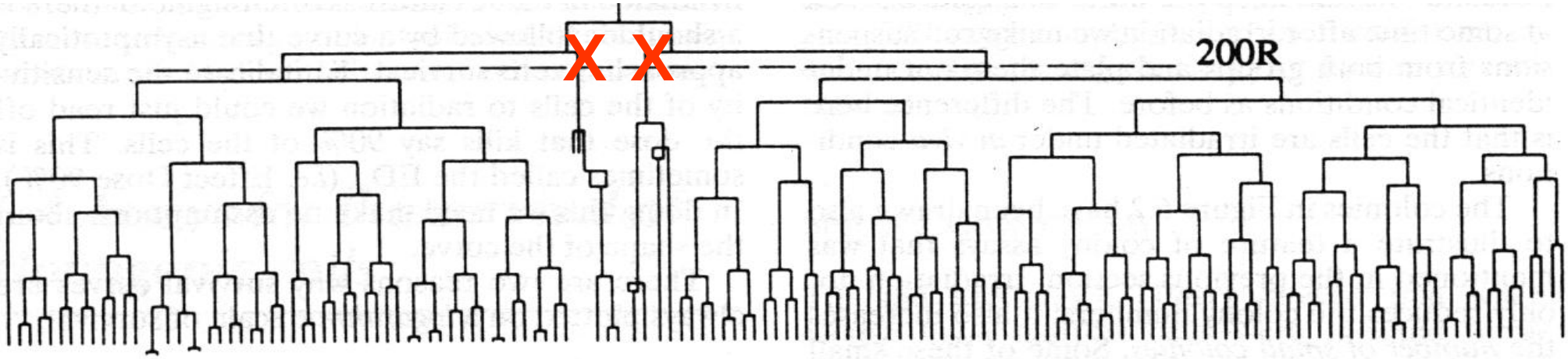
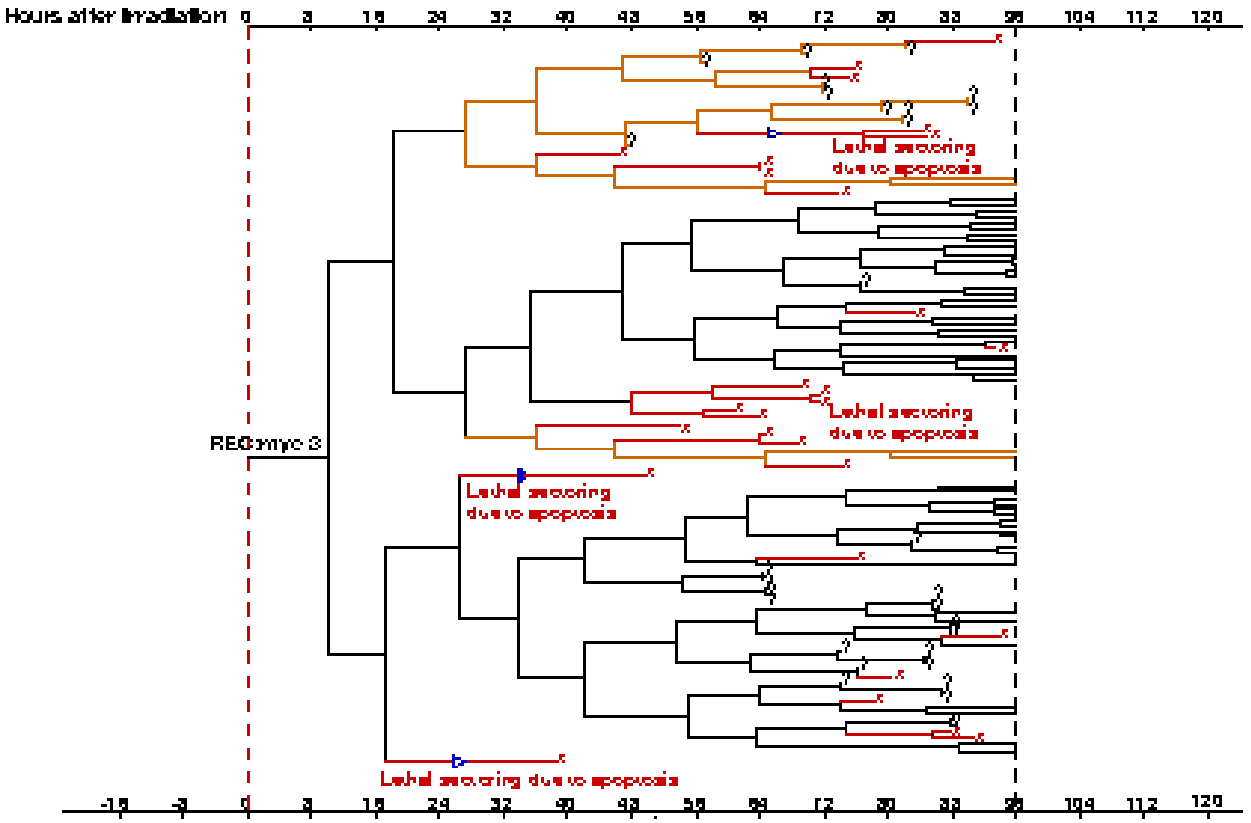


Figure 6.1 Pedigree of a clone of mouse L-cells irradiated with a dose of 200R (*i.e.* röntgens) at the 4-cell stage, illustrating the concept of surviving and non-surviving clonogenic cells. From Trott (1972), with permission.

Modes of cell death as analyzed in pedigree of irradiated cells



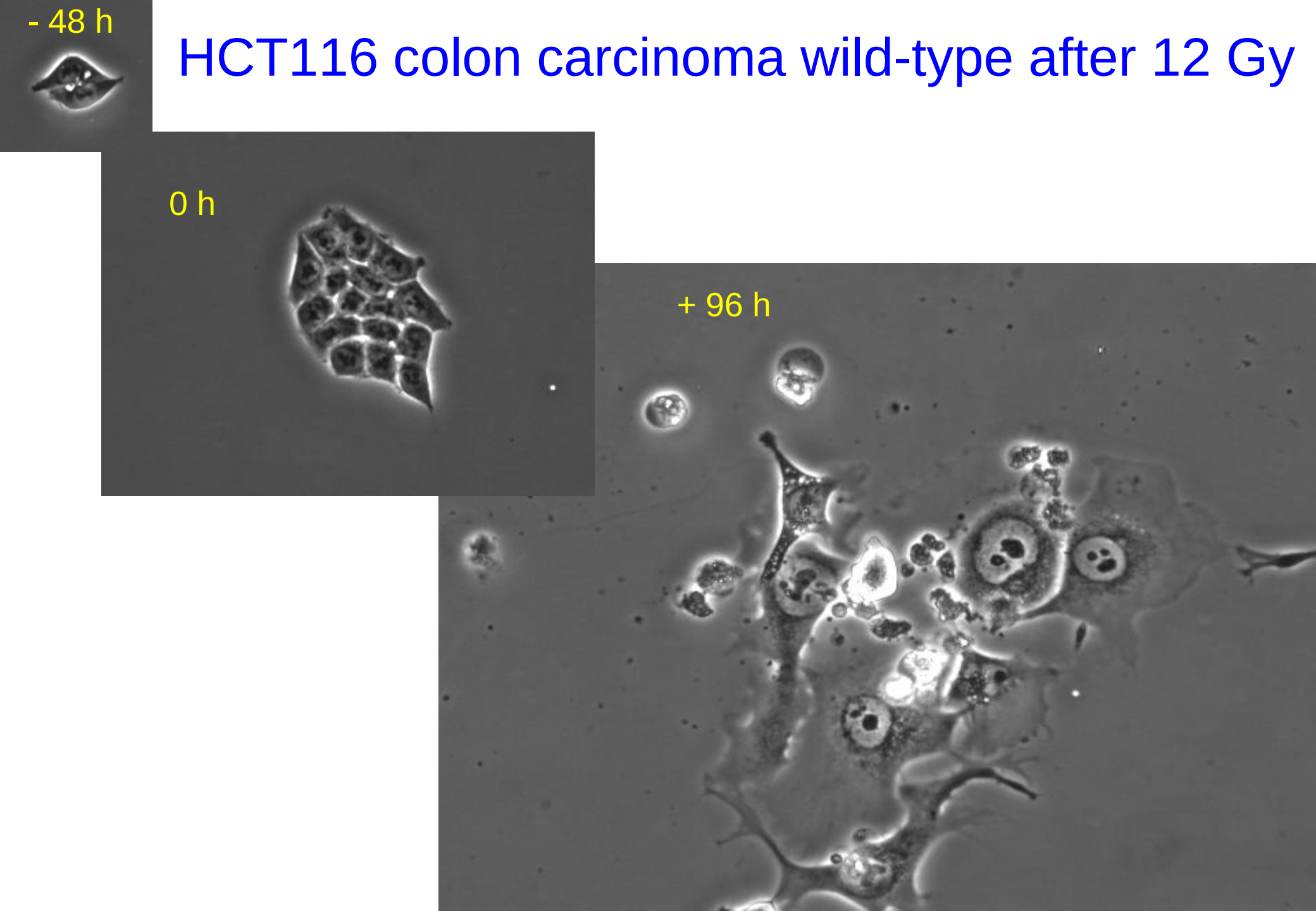
Pedigree of a colony formed from a cell irradiated with 2.5 Gy.

Each horizontal line represents the life of a cell, relative to the time of irradiation.

Black: cells which continue to divide (clonogenic survivors)

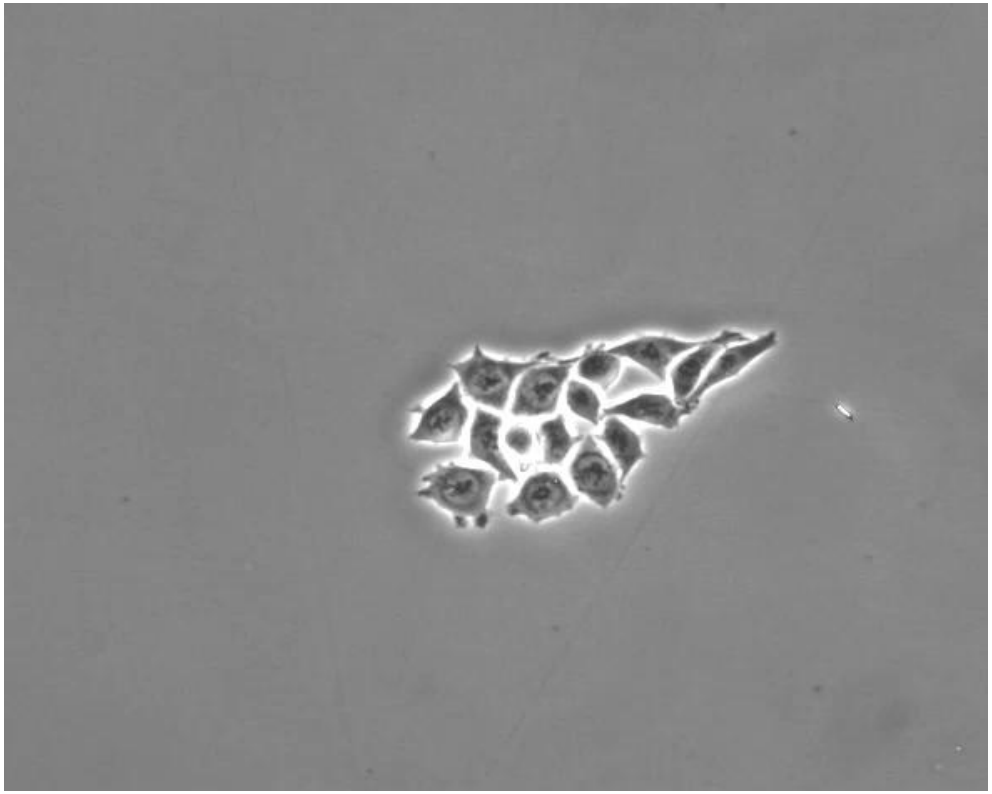
Red /orange : cells that die (apoptose) - but often after several divisions!

HCT116 colon carcinoma wild-type after 12 Gy

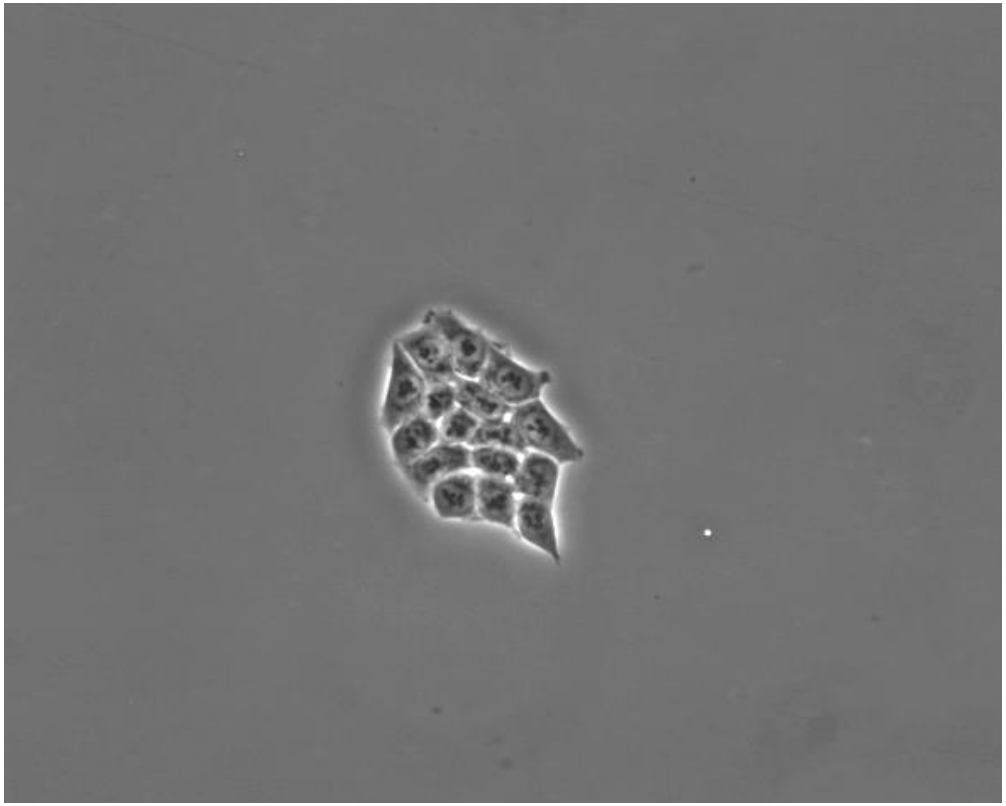


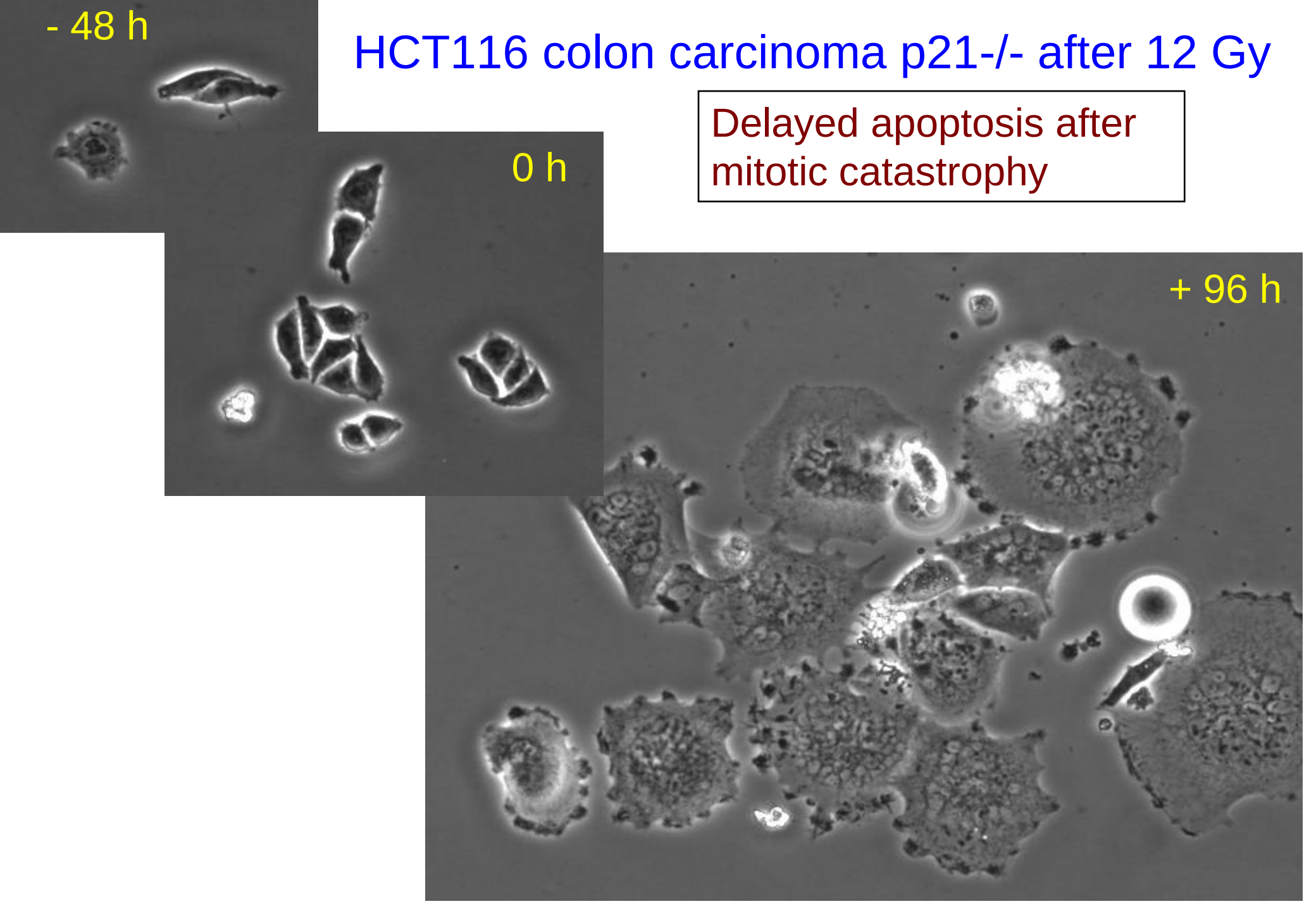
Cell death in HCT116 colon carcinoma cell colony (12 Gy)

14-3-3σ -/-



wild-type

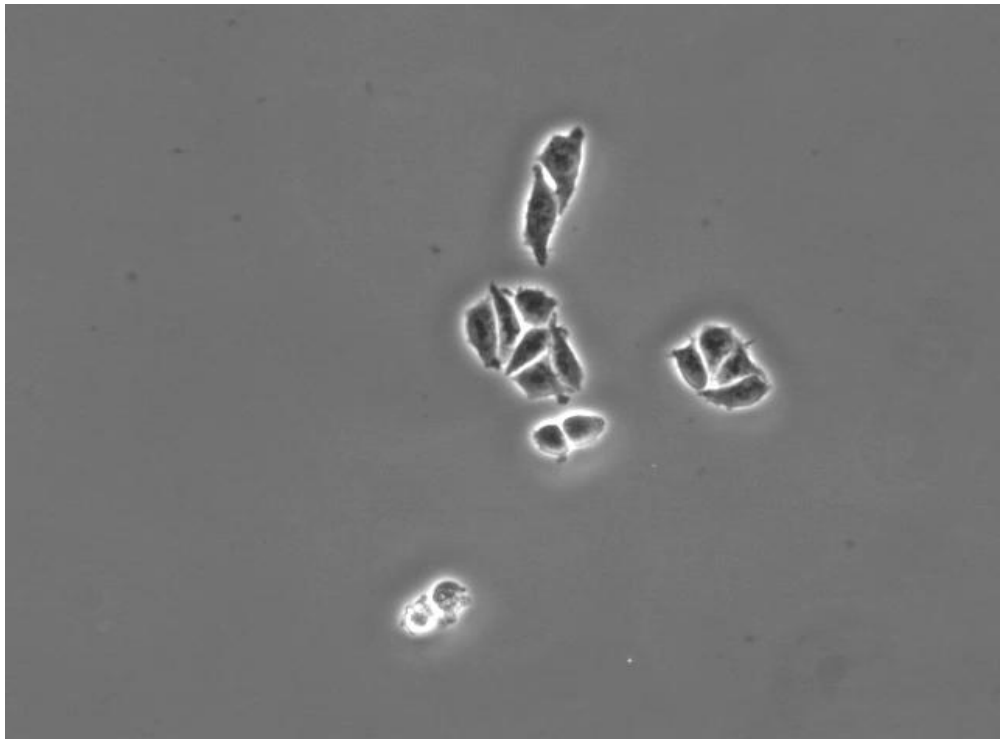


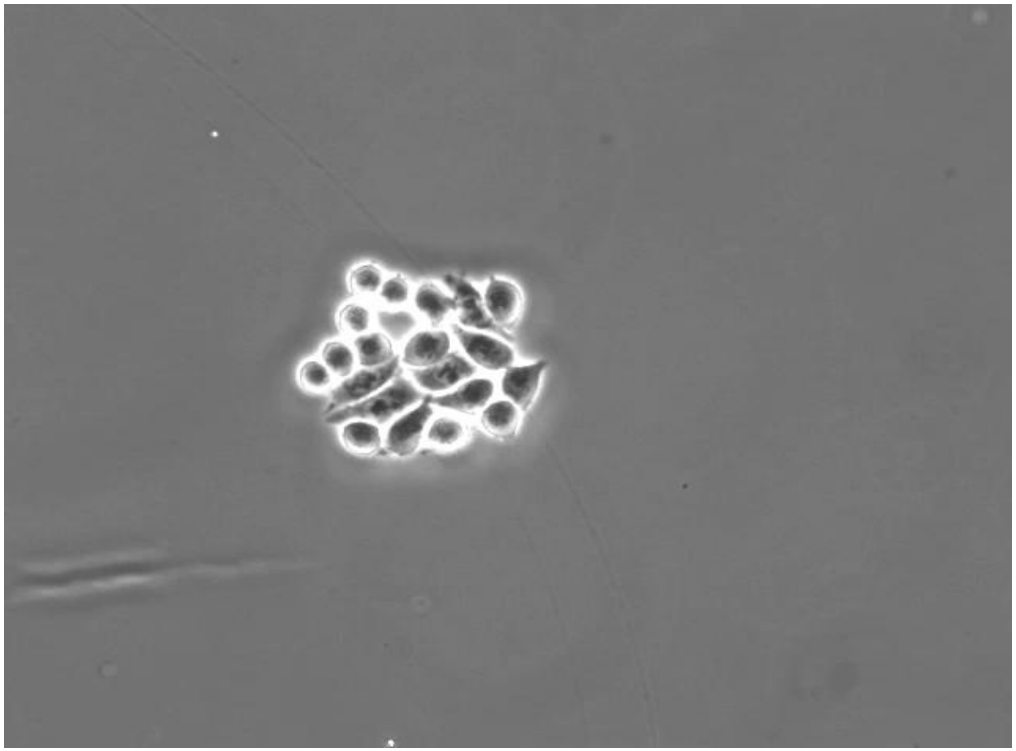


HCT116 colon carcinoma p21-/- after 12 Gy

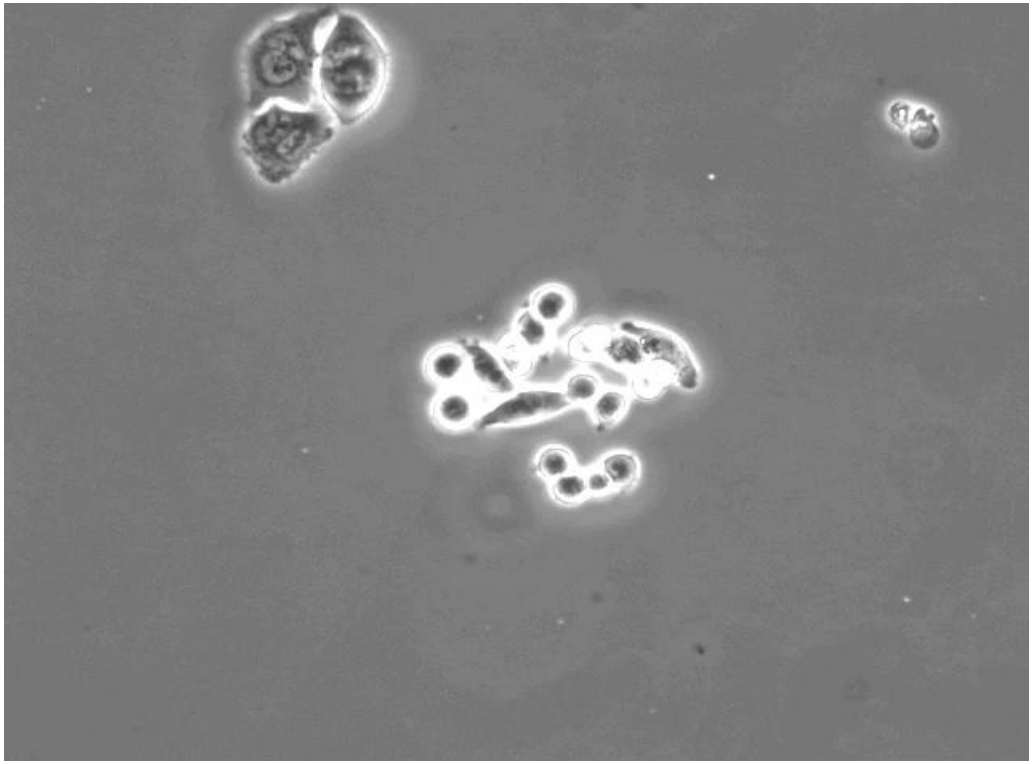
Delayed apoptosis after mitotic catastrophy

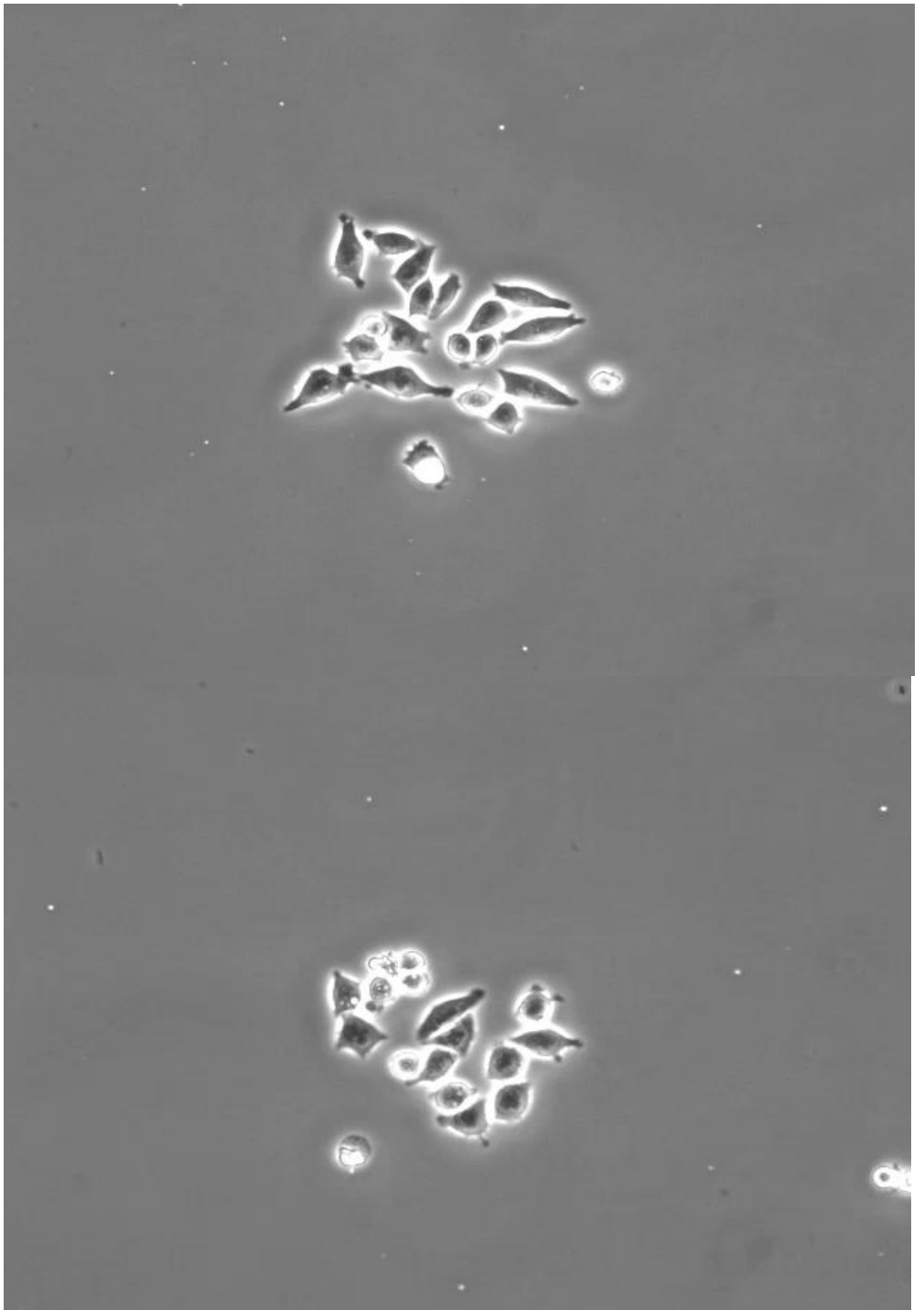
heterogeneity in reponse of individual clones: HCT116 - p21-/-



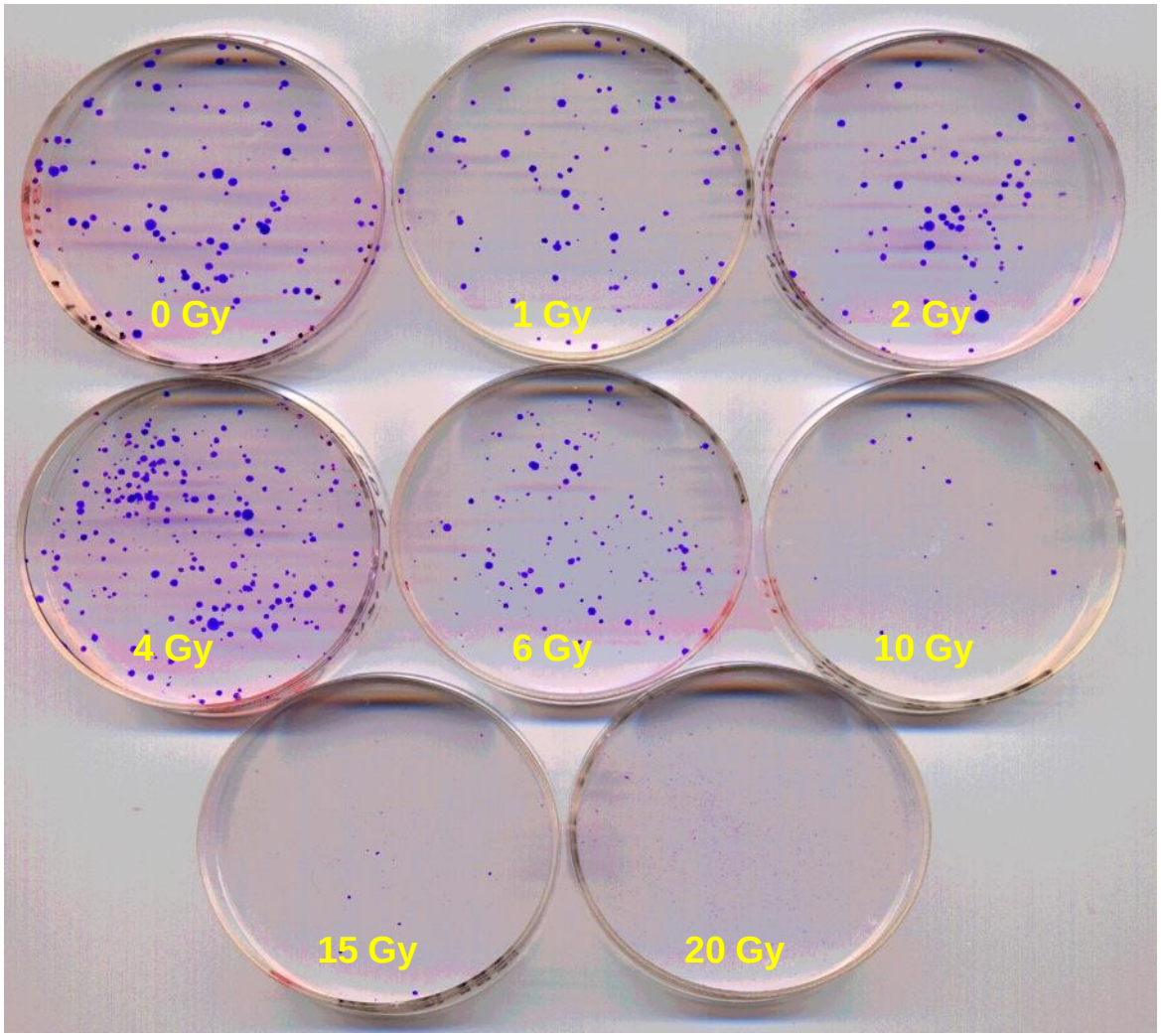


heterogeneity in reponse of individual clones: p21/14-3-3σ double KO

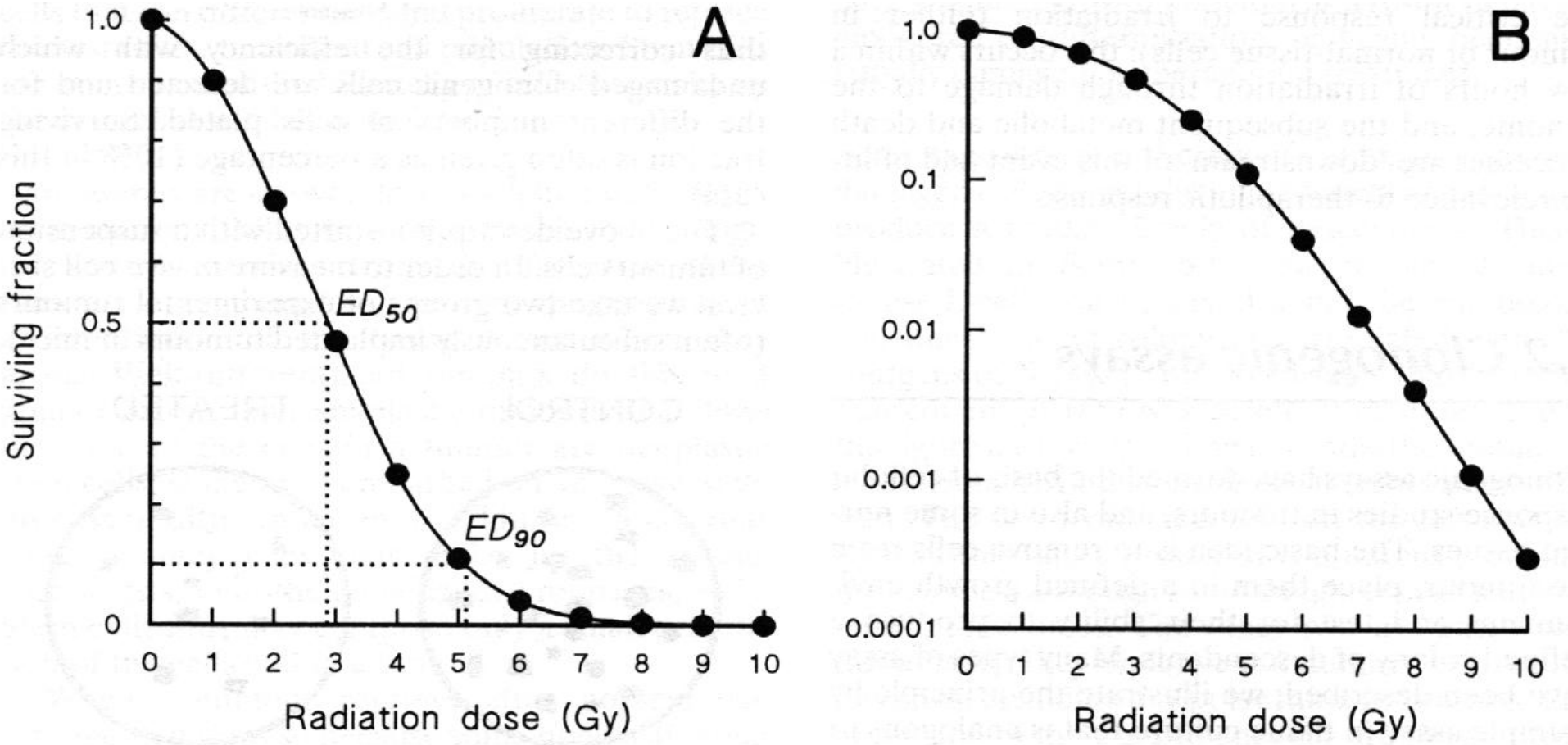




Colony assay: in vitro survival

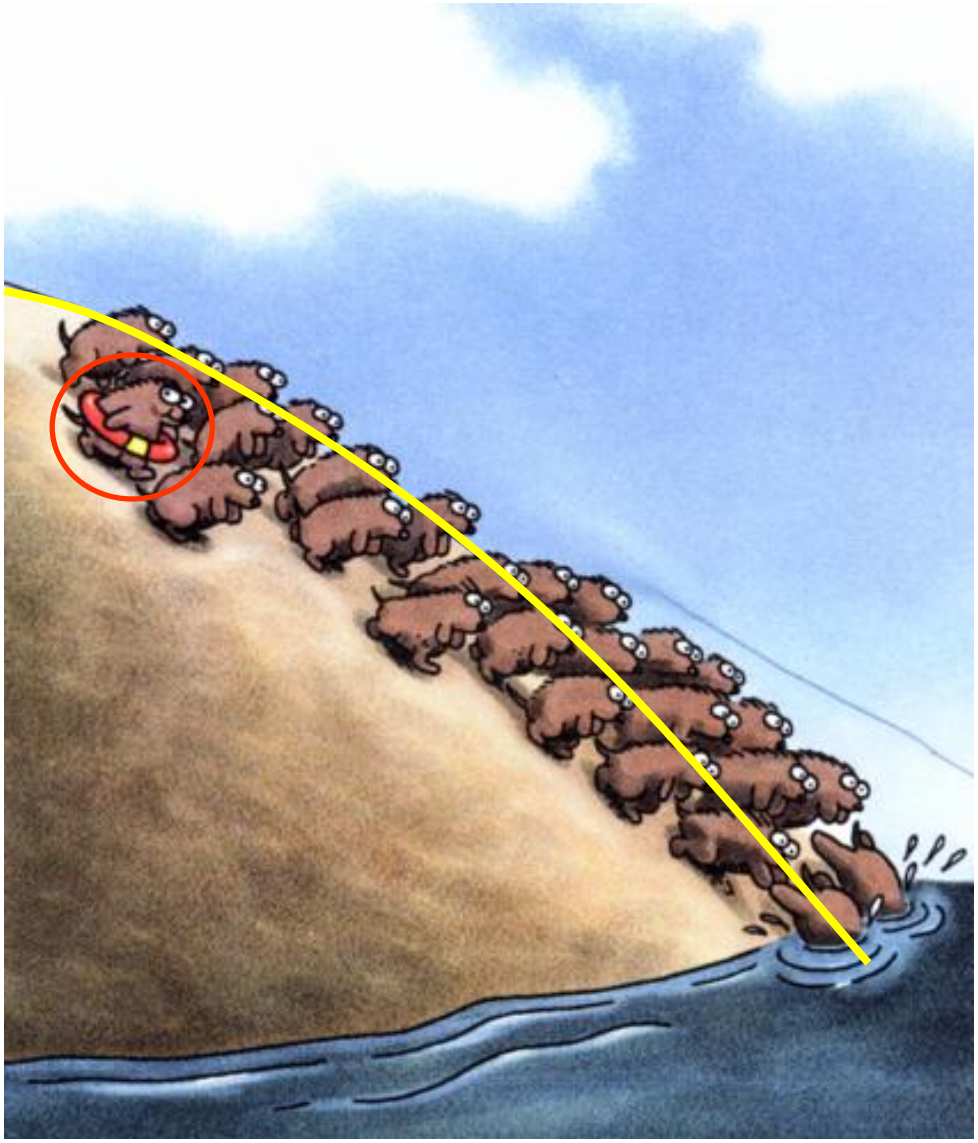


Cell survival curves



More in lecture Michael Joiner

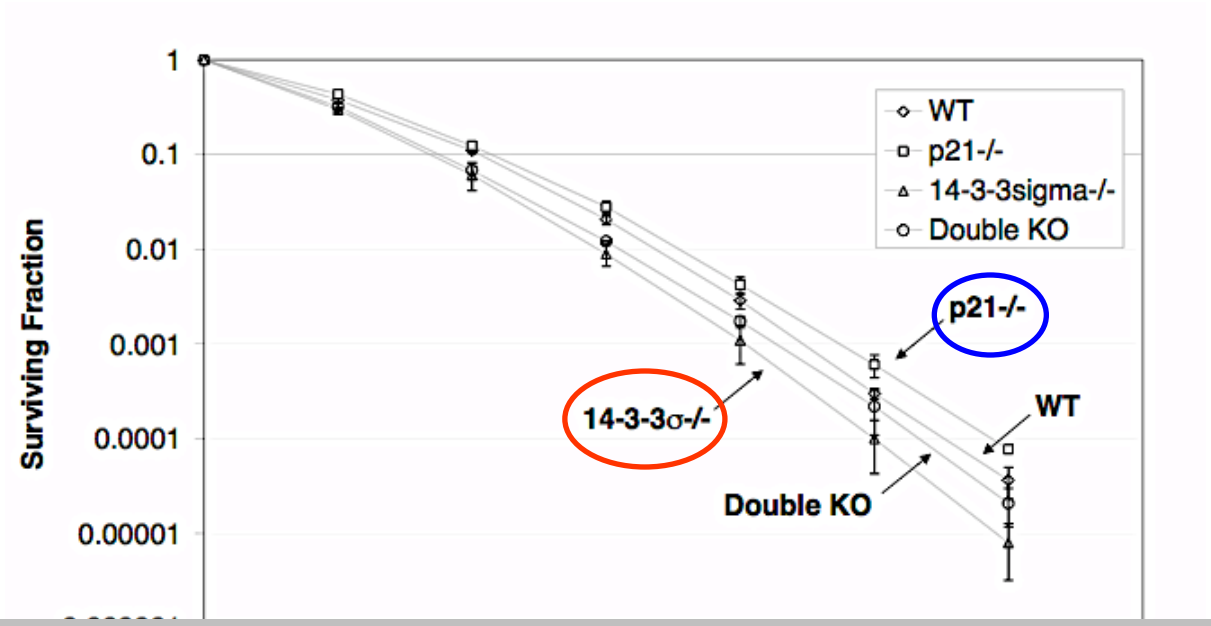
Cell death in a tumor: think exponential!

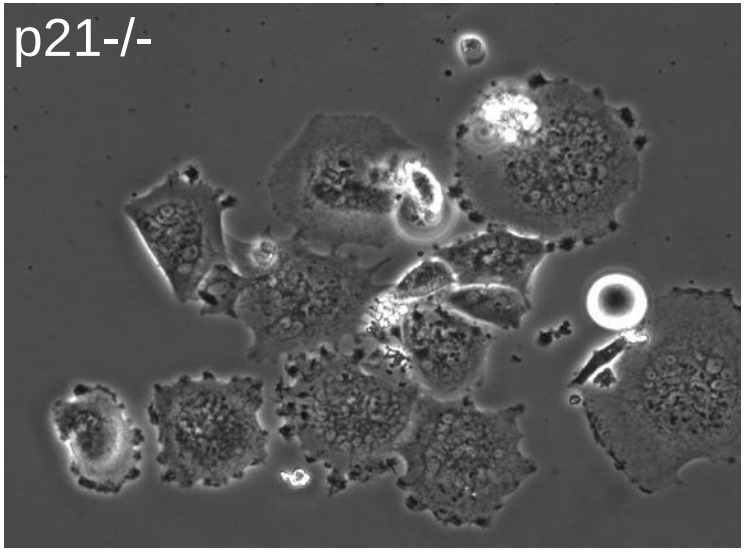


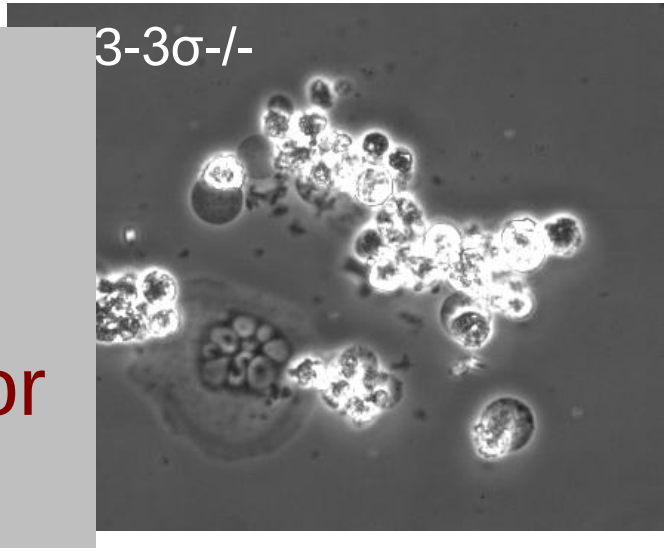
free after
Gary Larson

survival of HCT116 colorectal carcinoma cells

(Chu, Dewey et al, 2004)



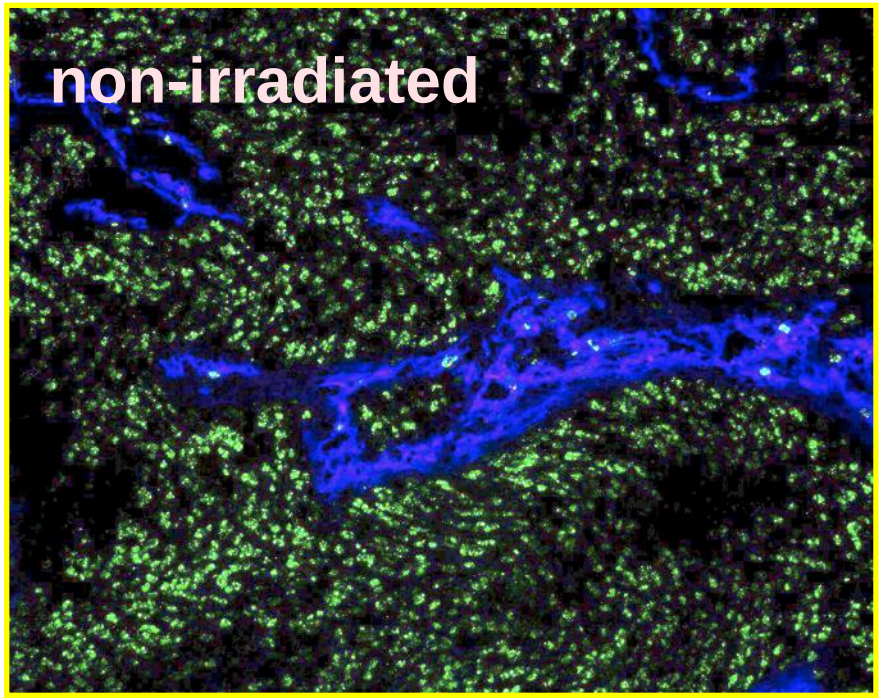


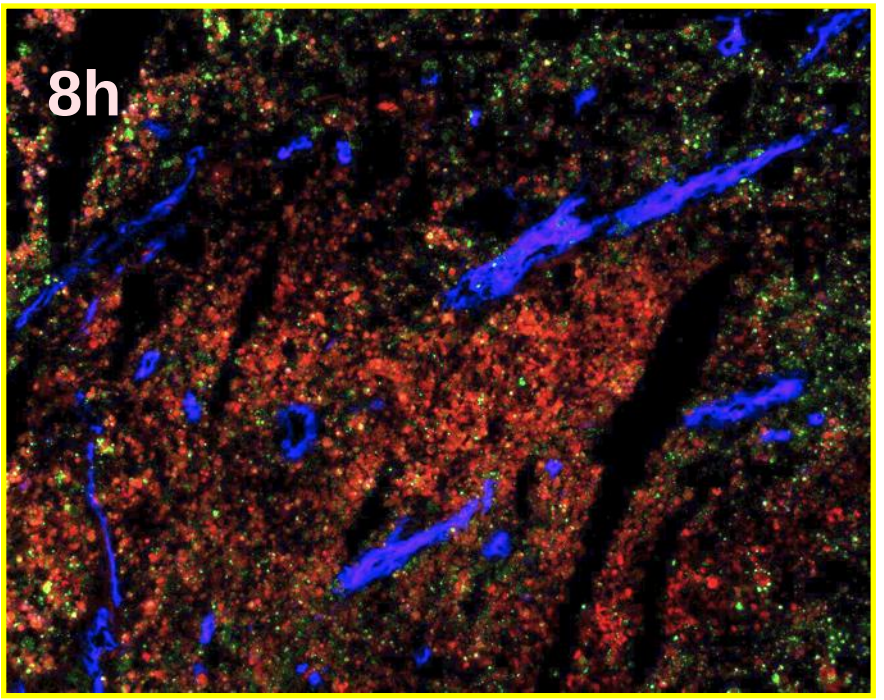


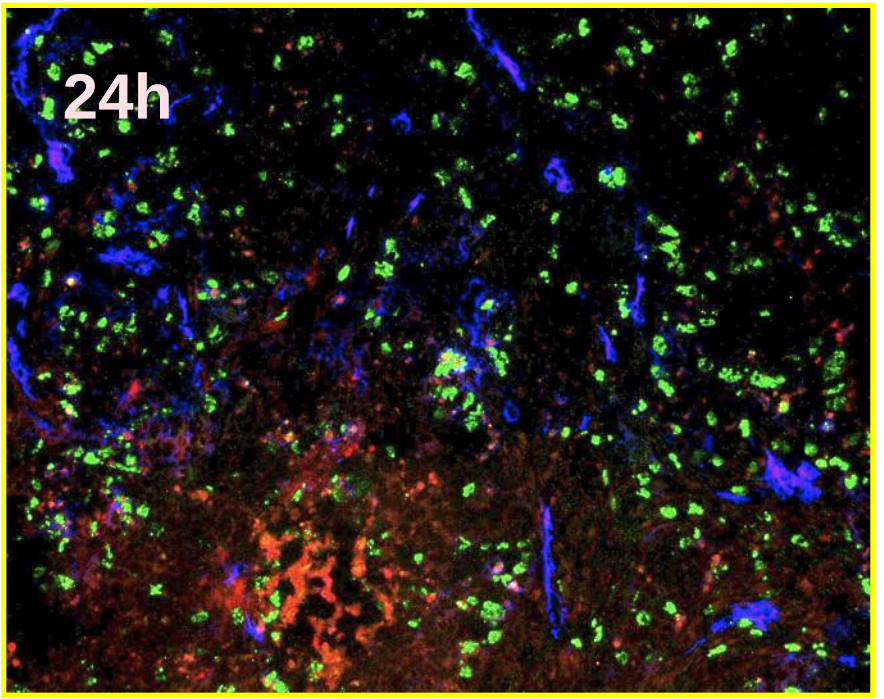
- The type of cell death has no relation with sensitivity
- Death and removal of cells after irradiation may take many days or even weeks

Cell death and clonogenic survival in tumors

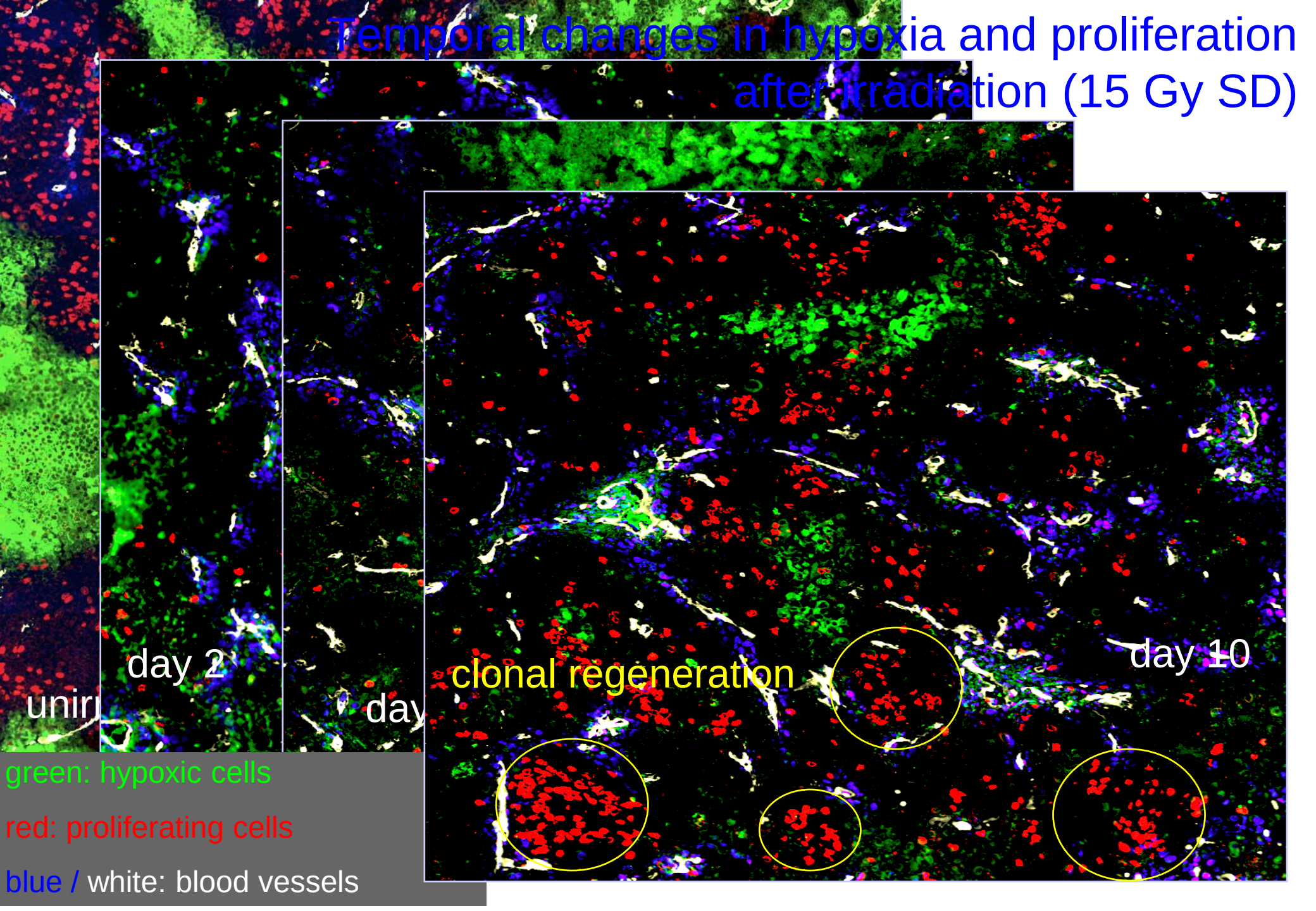
Effect of irradiation on tumors: cell death and proliferation



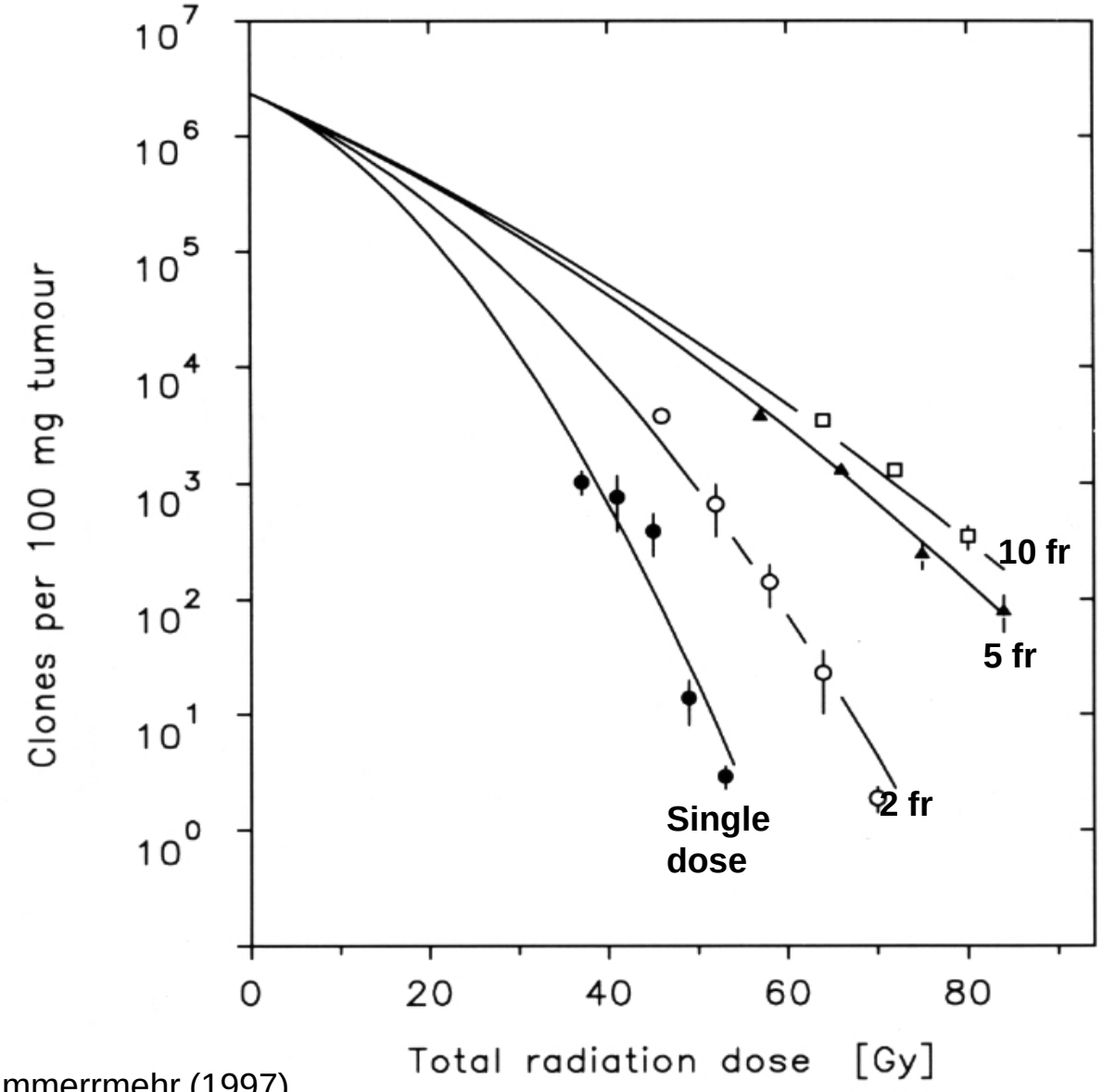




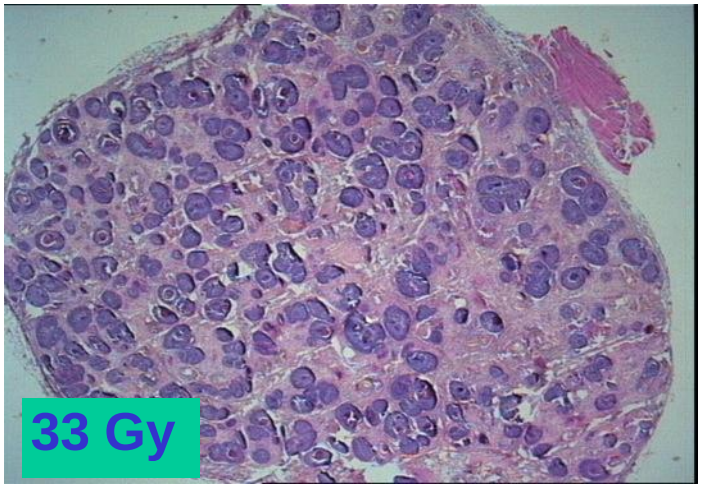
Proliferating cells
Apoptotic cells
blood vessels

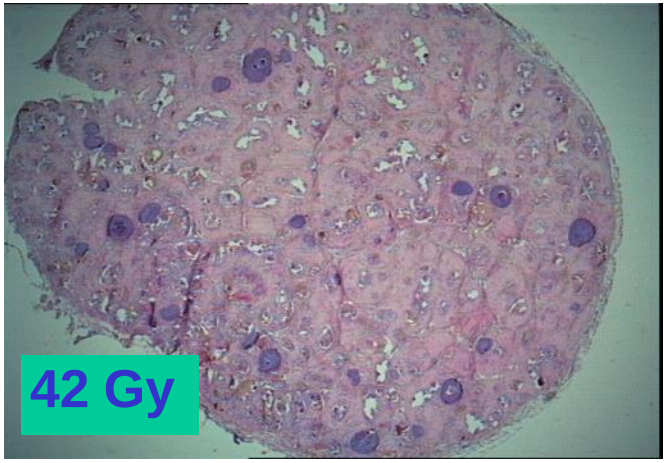

Temporal changes in hypoxia and proliferation
after irradiation (15 Gy SD)
unirr
day 2
day
clonal regeneration
day 10
green: hypoxic cells
red: proliferating cells
blue / white: blood vessels

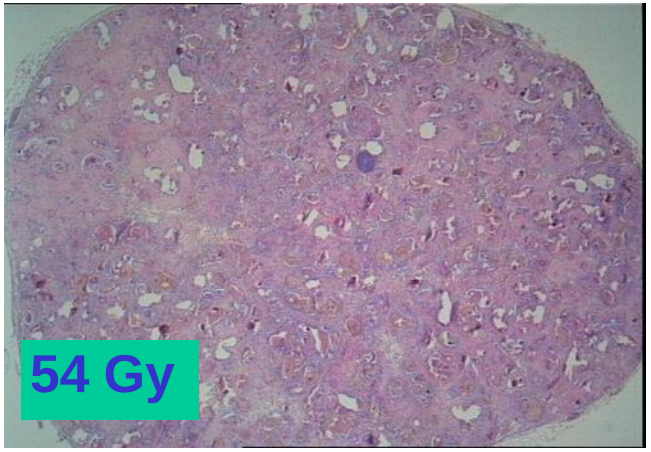
In situ survival curves of AT17 carcinoma (at 17 d)



Kummerrmehr (1997)



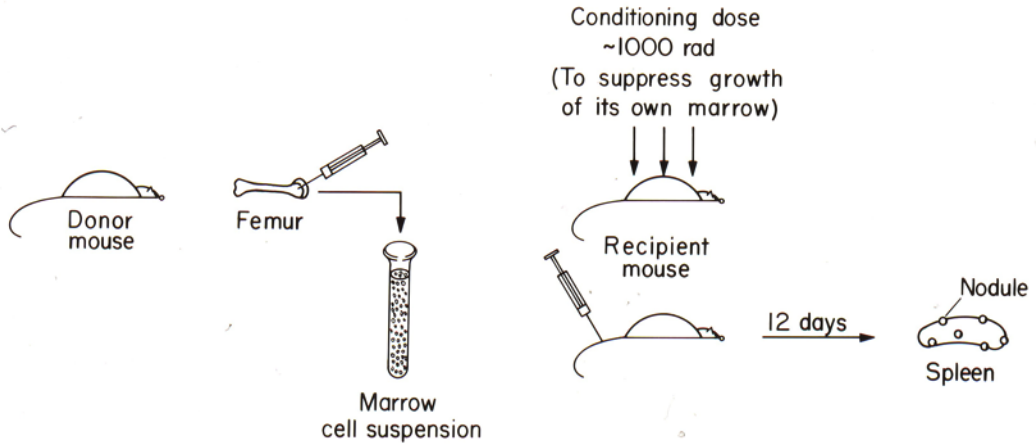


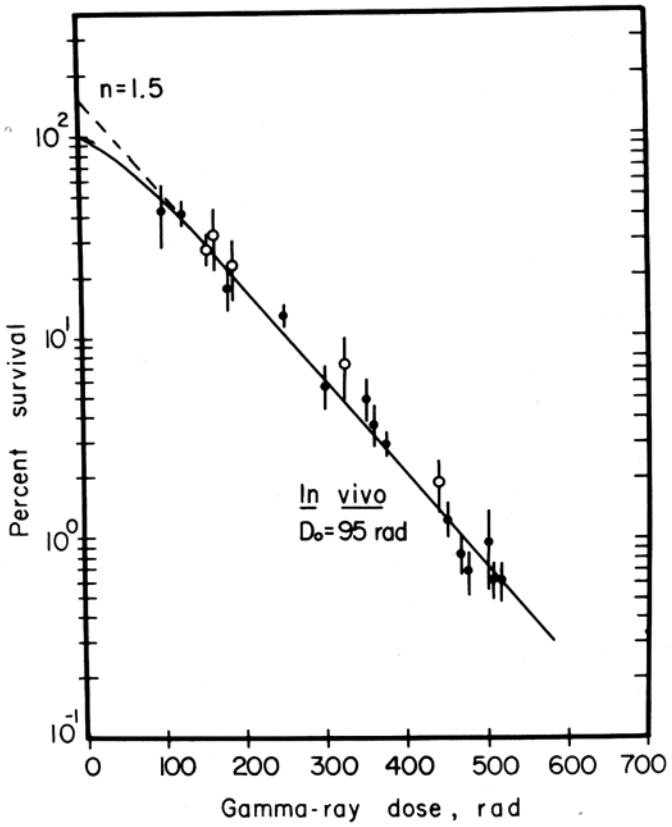


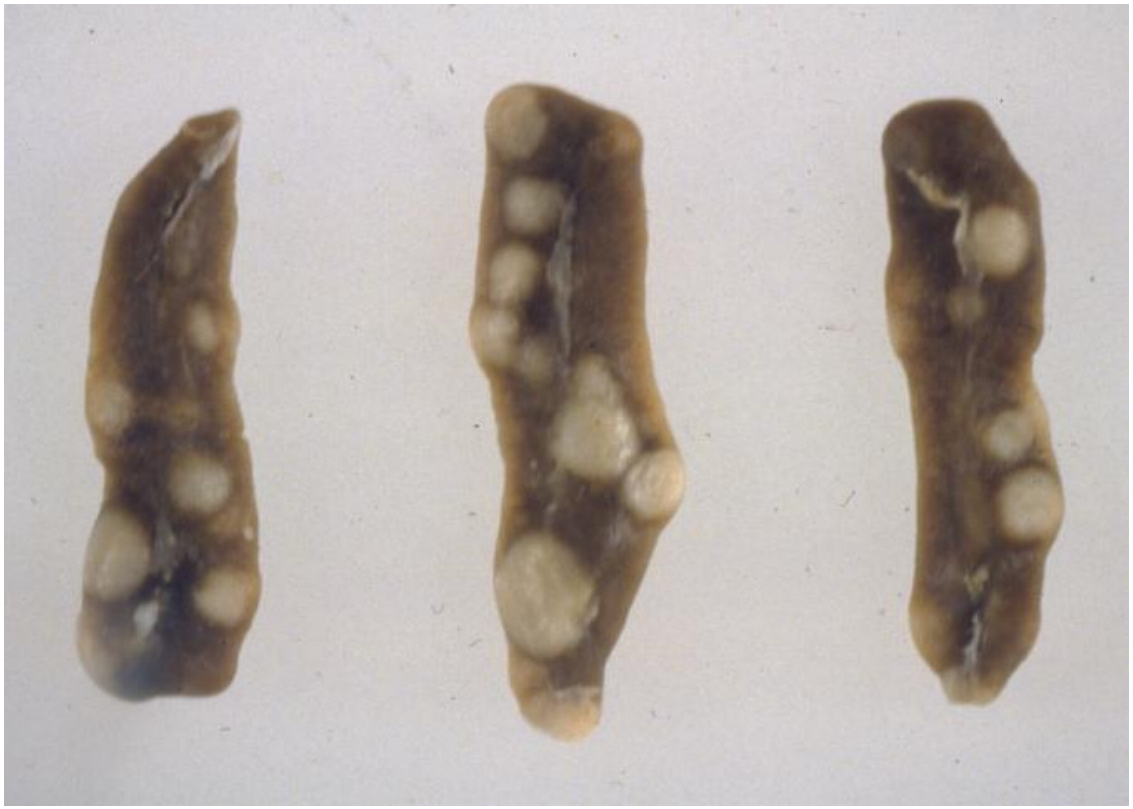
Cell death and clonogenic survival in normal tissues

clonogenic survival in normal tissues: spleen colony assay

(McCulloch&Till, 1962)



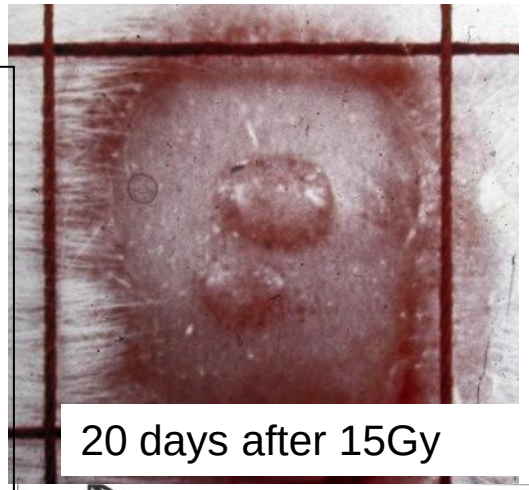




Dose-response for skin epithelium

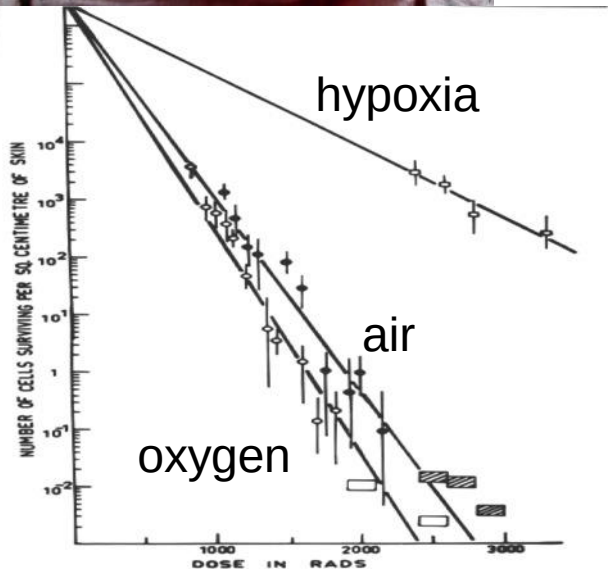
Withers 1966: Skin remains intact if clonogen survival is higher than about 5 per 10^{-6} per cm^2. Higher doses will cause moist desquamation.

Two clonally-derived islands of epithelium in a 1 cm diameter radiation-induced ulcer of the skin on the back of a mouse. Rapid regrowth on epithelial surfaces such as skin and mucosa provide a reason for protracting radiation therapy over several weeks.



20 days after 15Gy

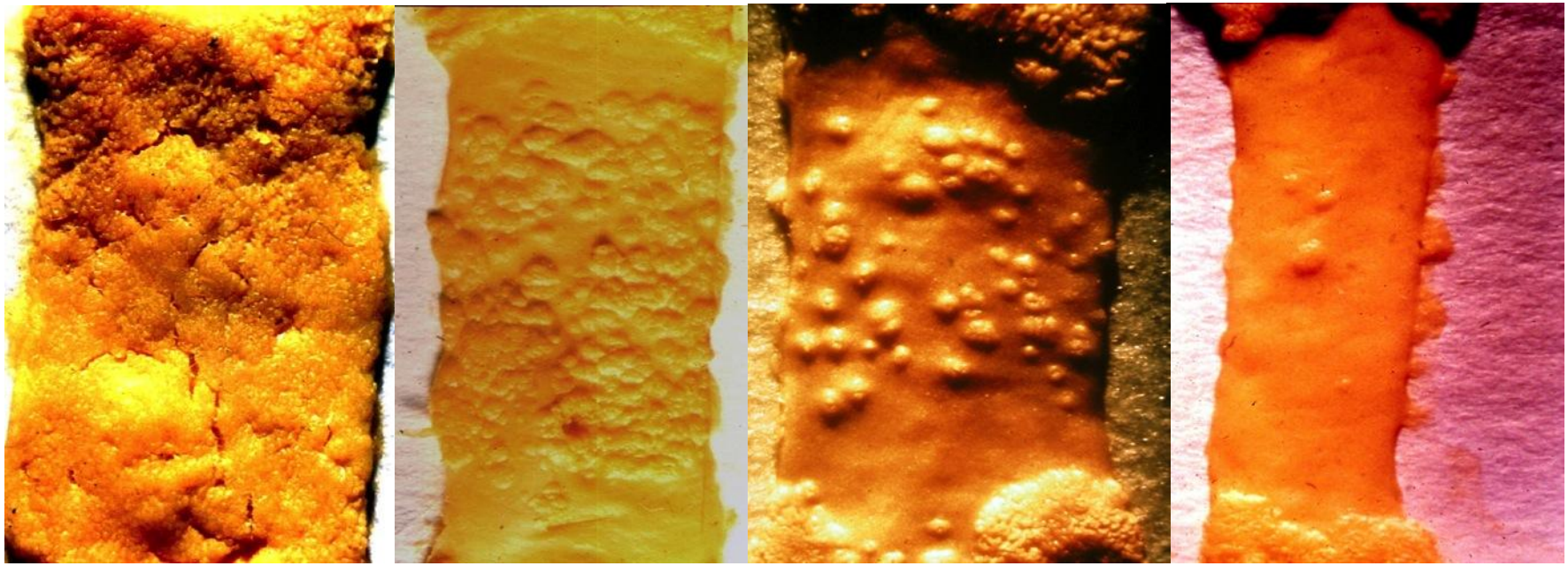
Dose-survival curves for mouse skin epithelial clonogenic (stem) cells in conditions of hyperbaric oxygen, air breathing or ischemic hypoxia induced by compression.



clonogenic survival in normal tissues: acute effects

Source: J. Hendry, Manchester, UK

Segment of mouse intestine irradiated with varying doses

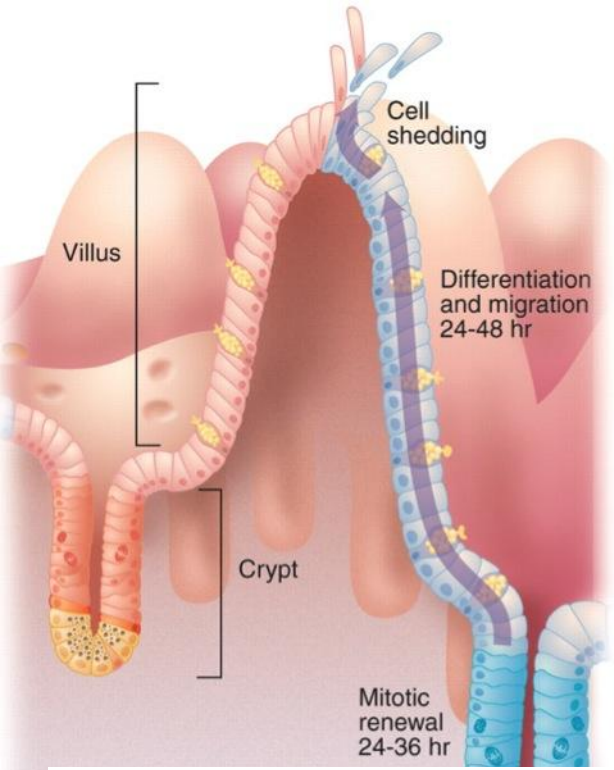


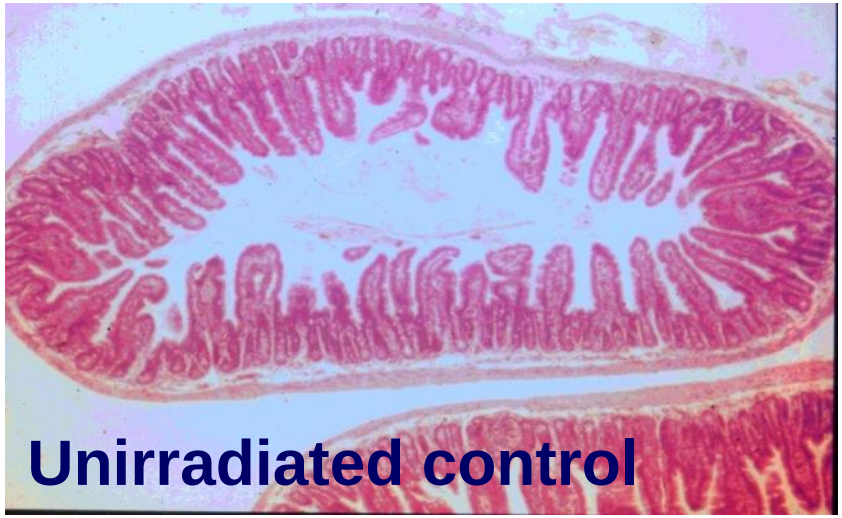
Day 13

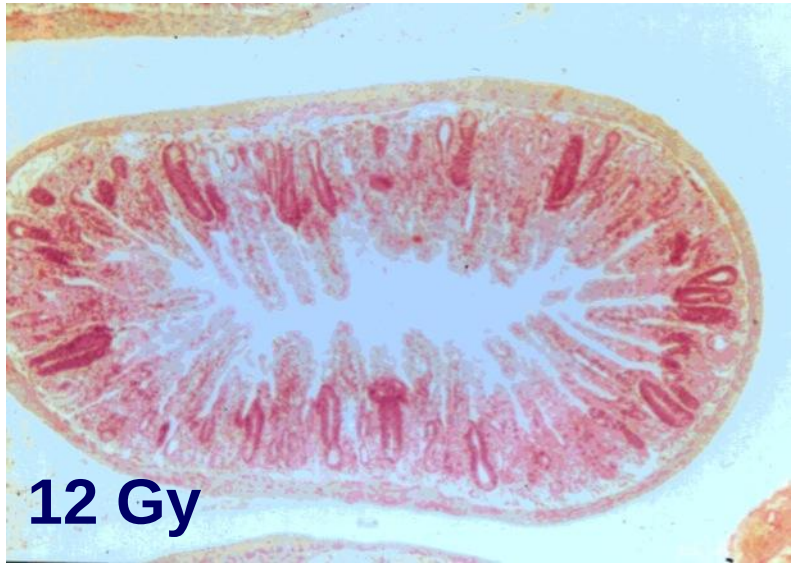
Overt tissue response (e.g. ulceration) is dose-dependent with a threshold followed by a rapid increase in severity.

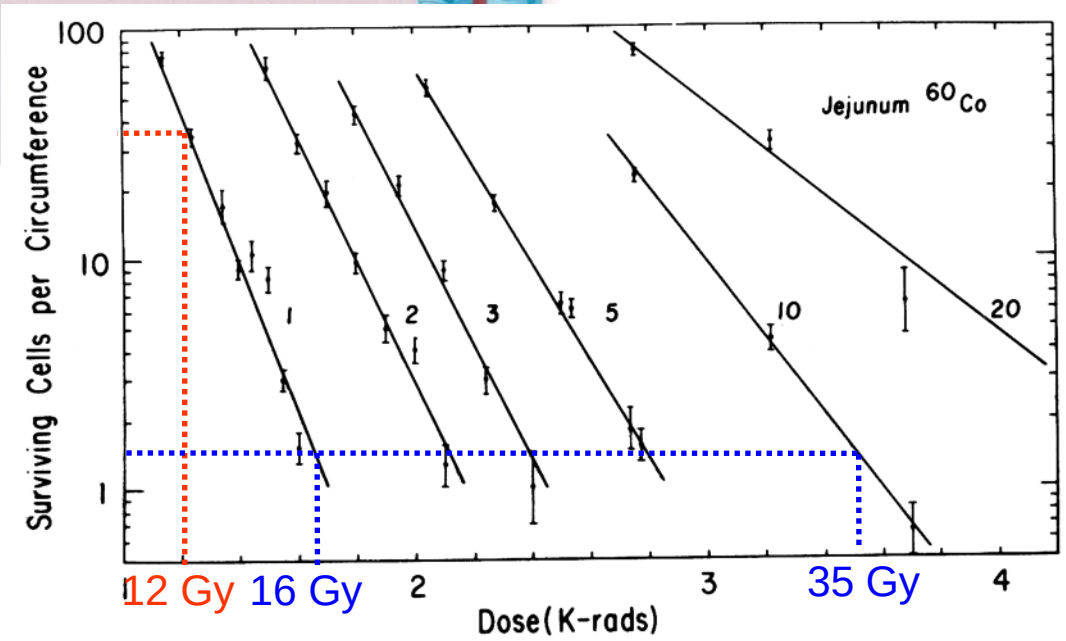
a. Patchy breakdown of mucosa except in shielded mucosa at top of specimen.
b. Ulcerated mucosa being resurfaced by near-confluent nodules regenerated from a large number of independently surviving jejunal clonogens.
c. Severe ulceration but with about 60 discrete clonogen-derived mucosal nodules.
d. As for c. but only 4 regenerated nodules.

Jejunal crypt assay (Withers, 1974)

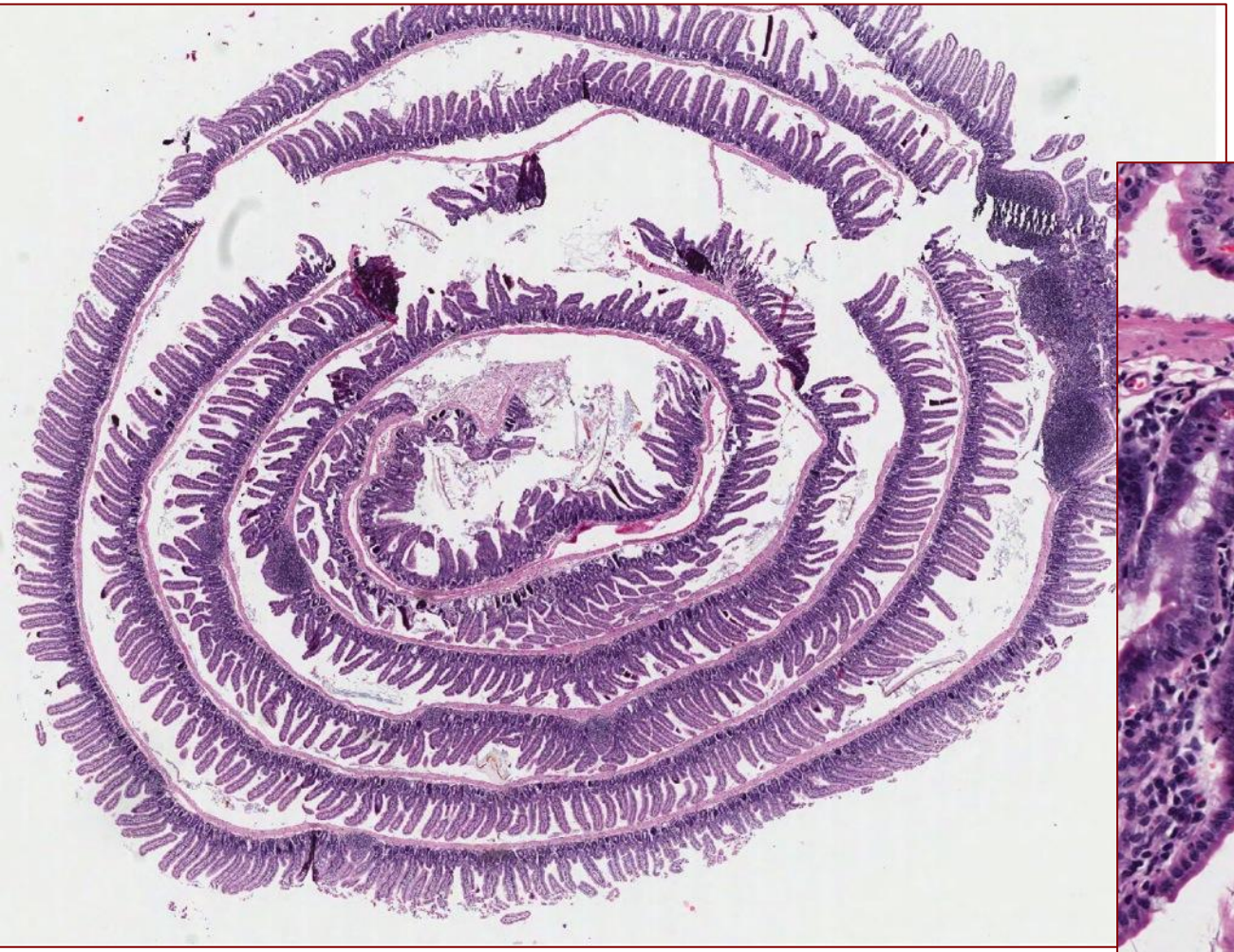


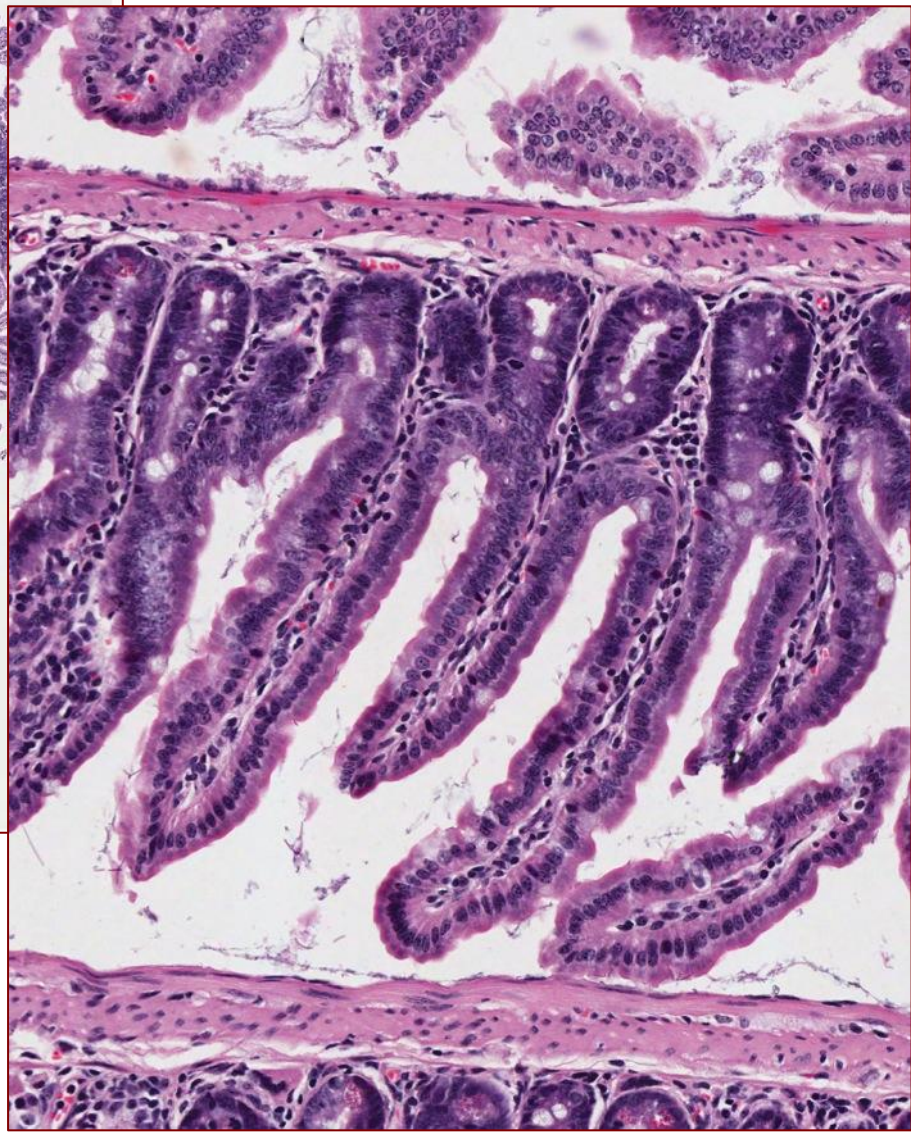






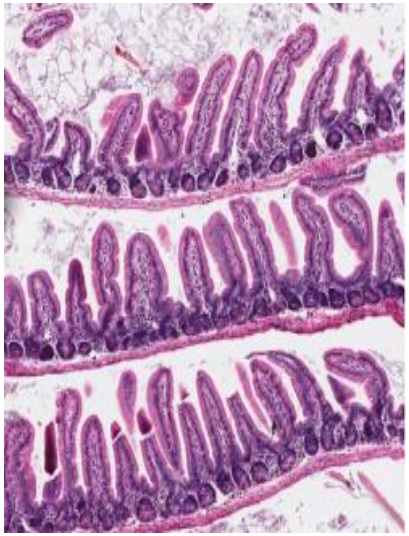
Intestinal crypt assay: the “Swiss roll”



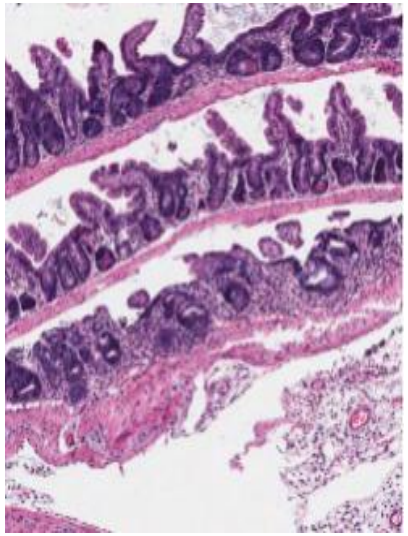


Courtesy of Kiltie & Groselj, 2014

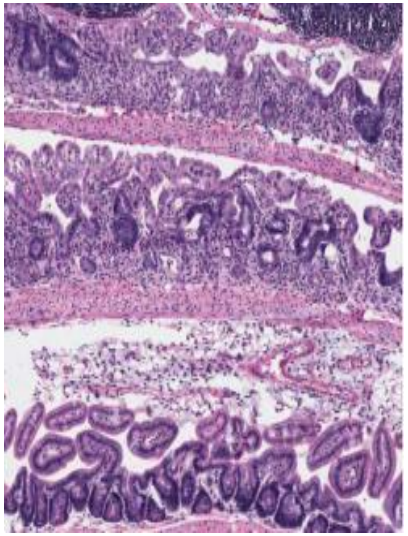
Intestinal crypt assay: the “Swiss roll”



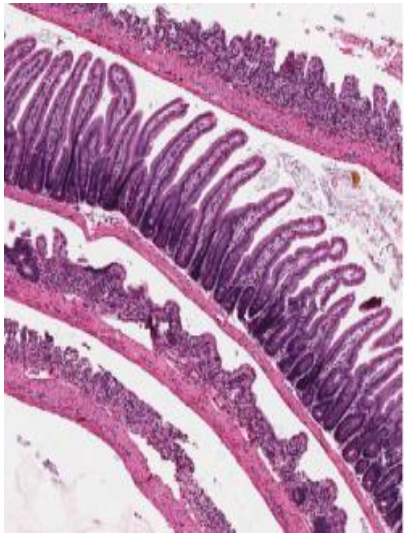
0 Gy



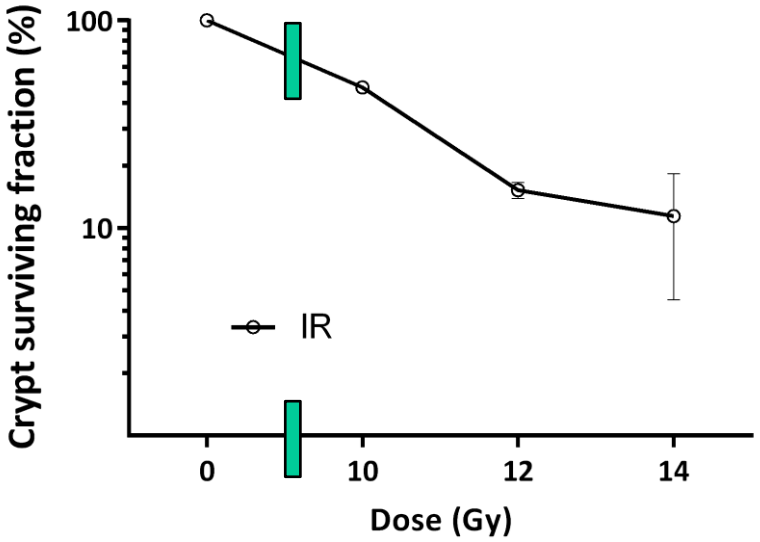
10 Gy

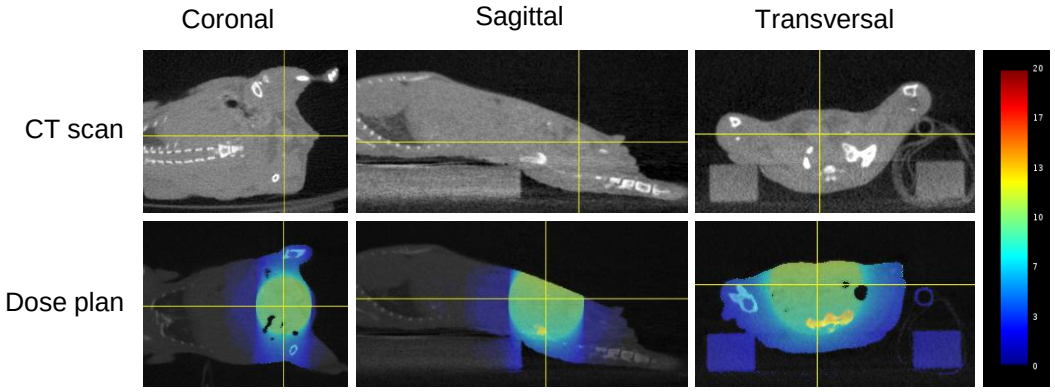


12 Gy



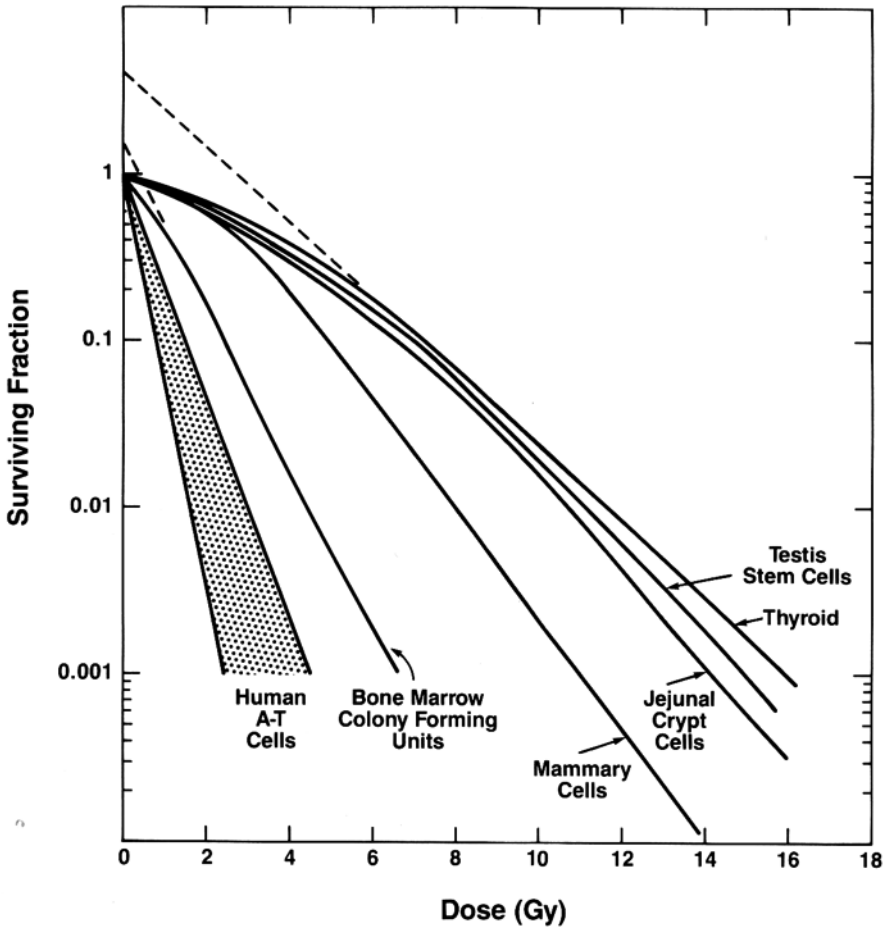
14 Gy





Courtesy of Kiltie & Groselj, 2015

Clonogenic survival in normal tissues summary



Stem cells from different tissues show large differences in radiosensitivity, as determined in assays of clonogenic survival

This only partly reflects the different sensitivities of different organs, as many other factors determine the radiation response and tolerance of different organs, especially late responding organs like CNS, lung, kidney, etc

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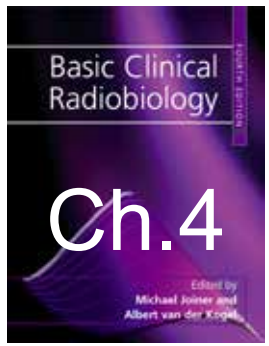
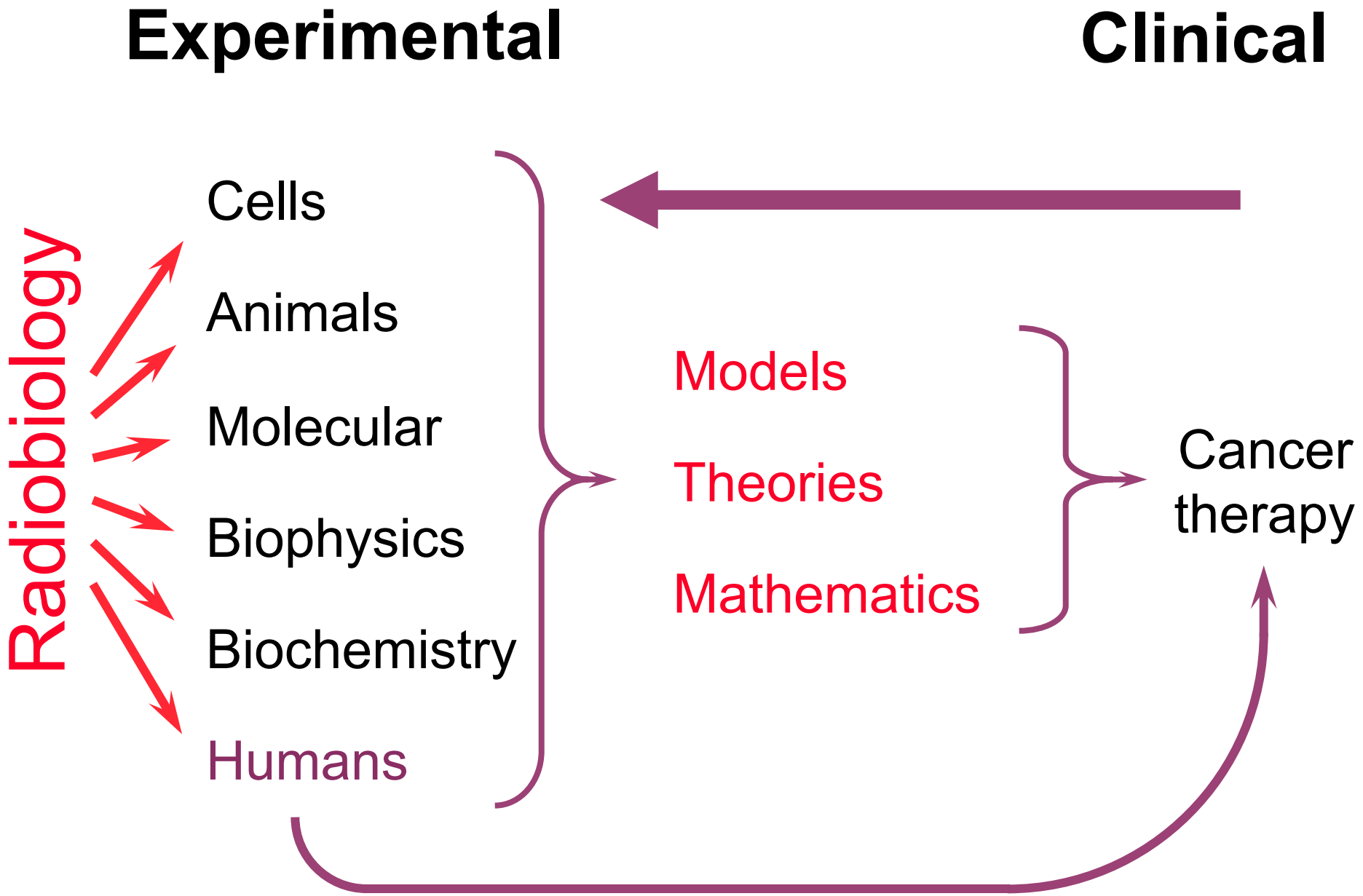
Basic Clinical Radiobiology

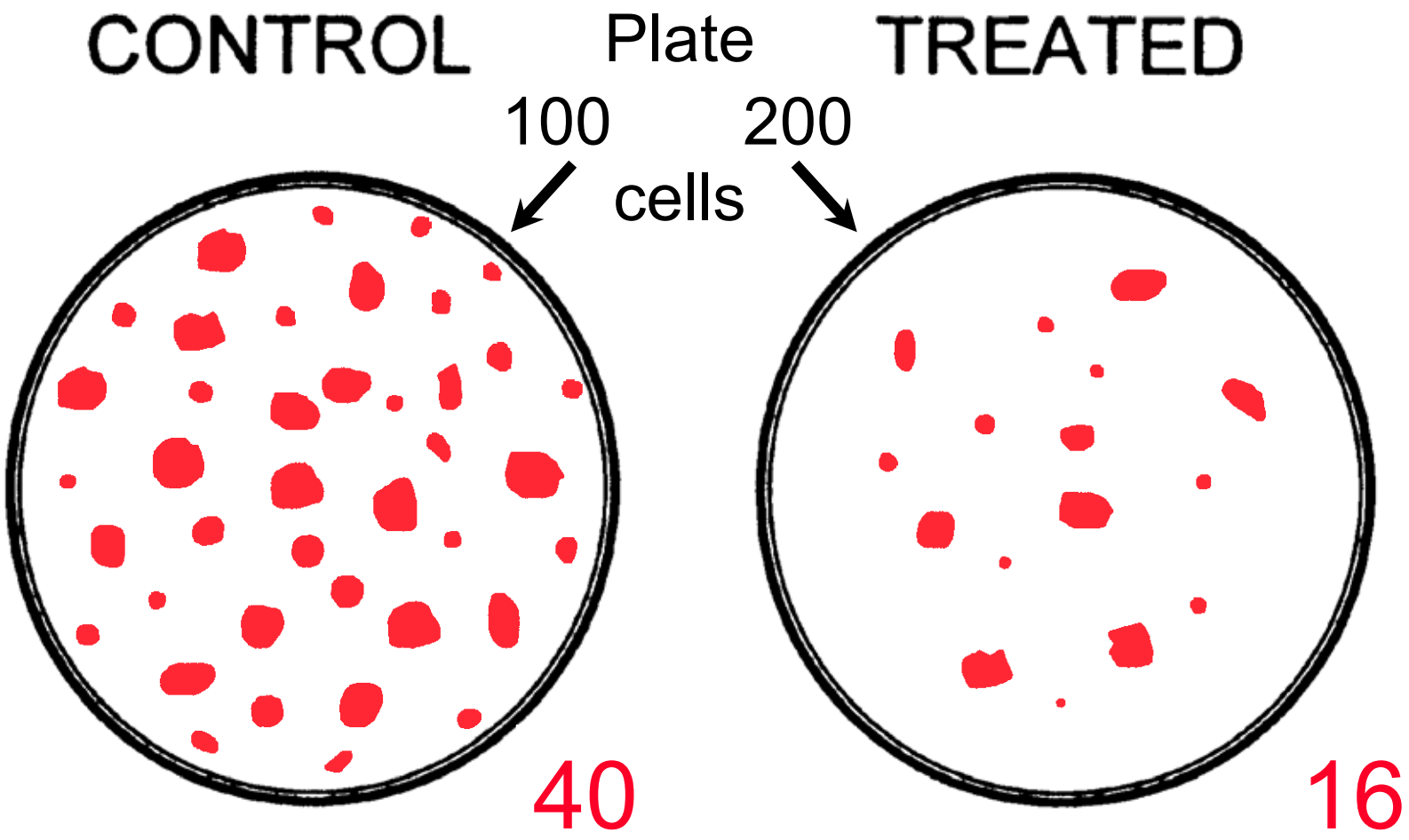
Quantifying cell kill and cell survival

Michael Joiner



Budapest 2016

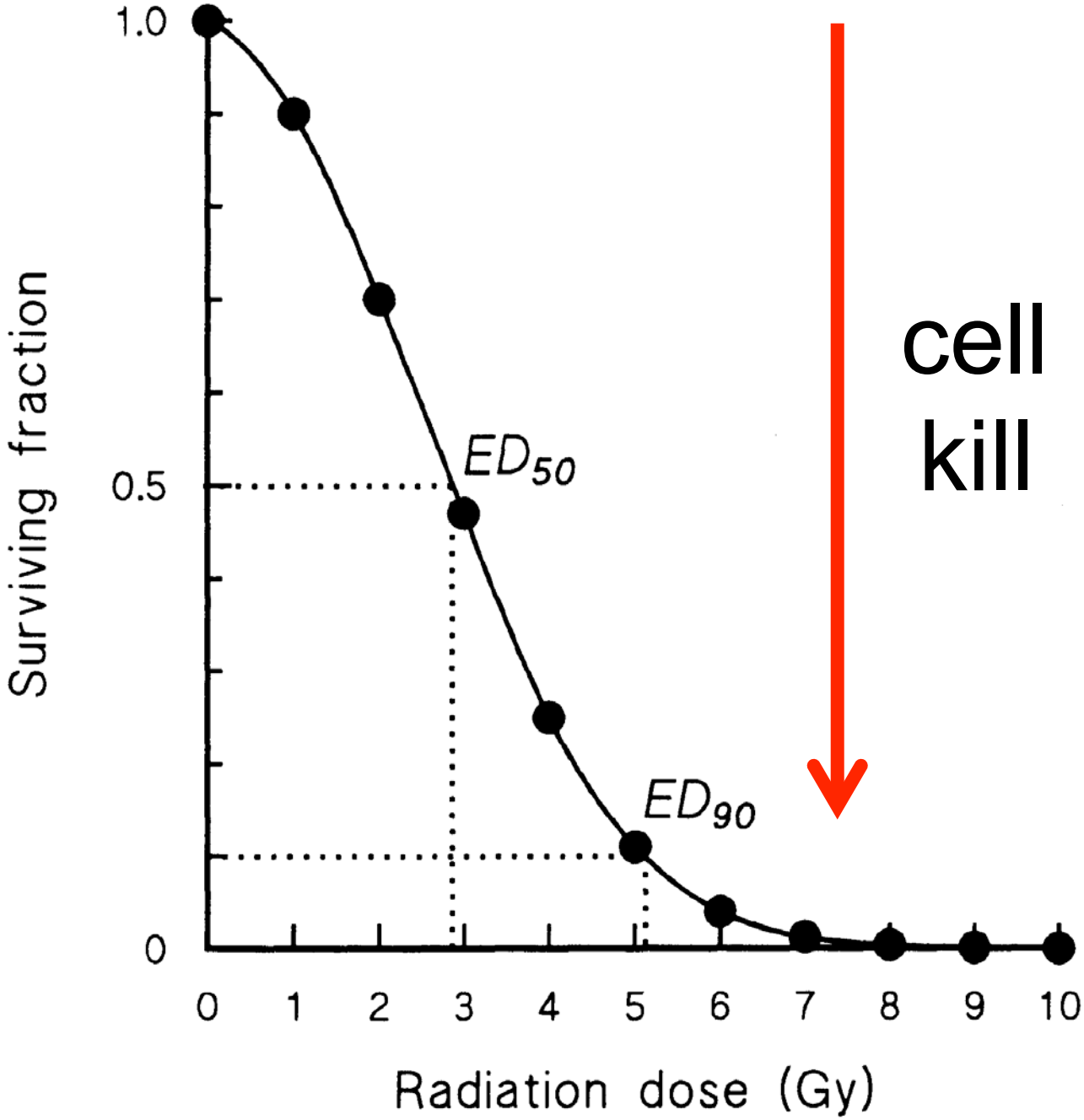

Experimental
Clinical
Radiobiology
Cells
Animals
Molecular
Biophysics
Biochemistry
Humans
Models
Theories
Mathematics
Cancer therapy



Plating efficiency (PE)

40/100 = 0.4 16/200 = 0.08

Surviving fraction (SF) = 0.08/0.4 = 0.2


1.0
0.5
0
Surviving fraction
ED_{50}
ED_{90}
cell
kill
0 1 2 3 4 5 6 7 8 9 10
Radiation dose (Gy)

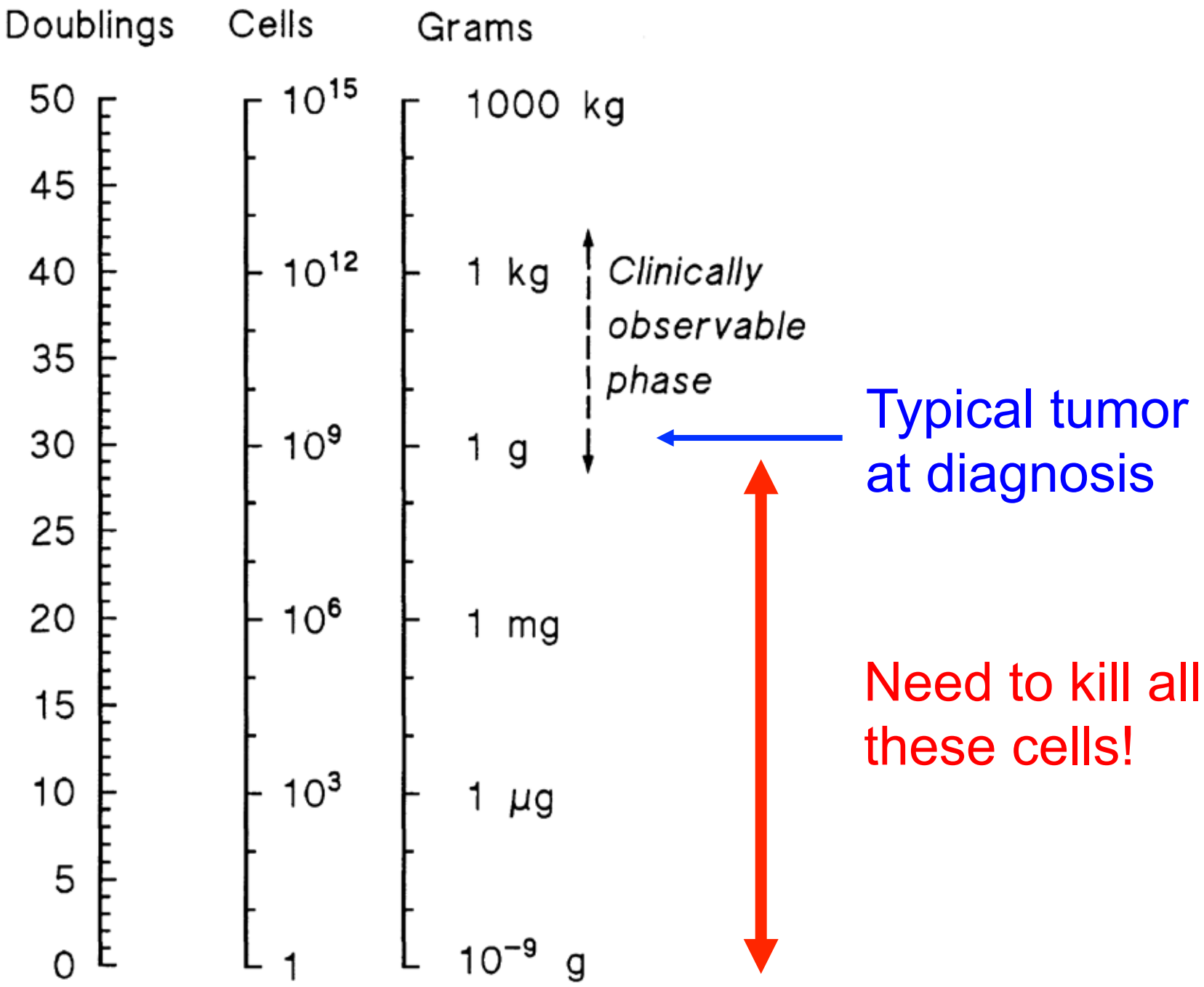
Simple Model for cell kill versus dose

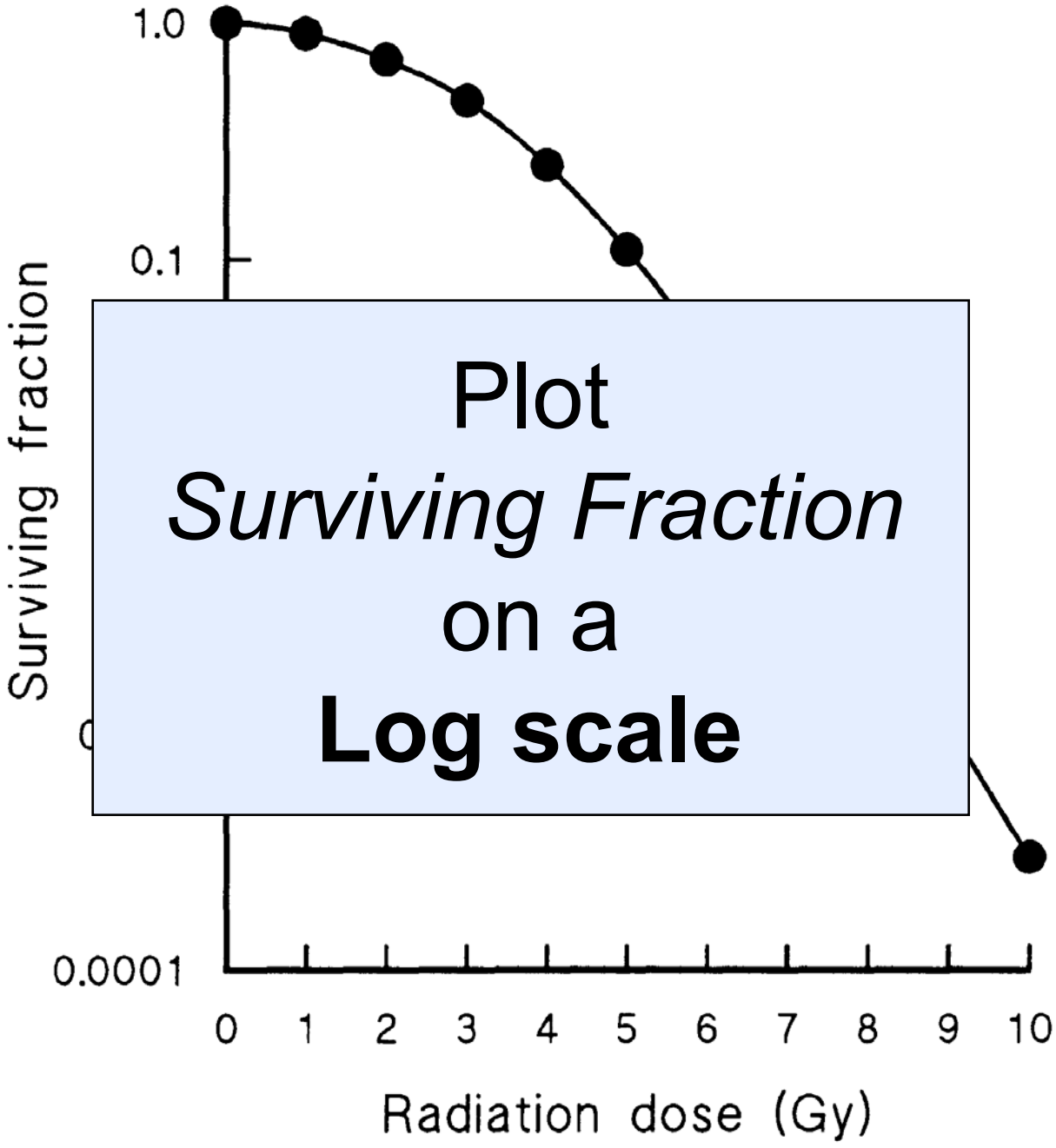
$2 + 2 = 4$ No !

$2 + 2 = 22$ Better…

$2 + 2 = 10{,}000$ Yes !

$$10^2 \times 10^2 = 10^4$$


Doublings
Cells
Grams
50
45
40
35
30
25
20
15
10
5
0
10^{15}
10^{12}
10^{9}
10^{6}
10^{3}
1
1000 kg
1 kg
1 g
1 mg
1 μg
10^{-9} g
Clinically observable phase
Typical tumor at diagnosis
Need to kill all these cells!



Plot
Surviving Fraction
on a
Log scale

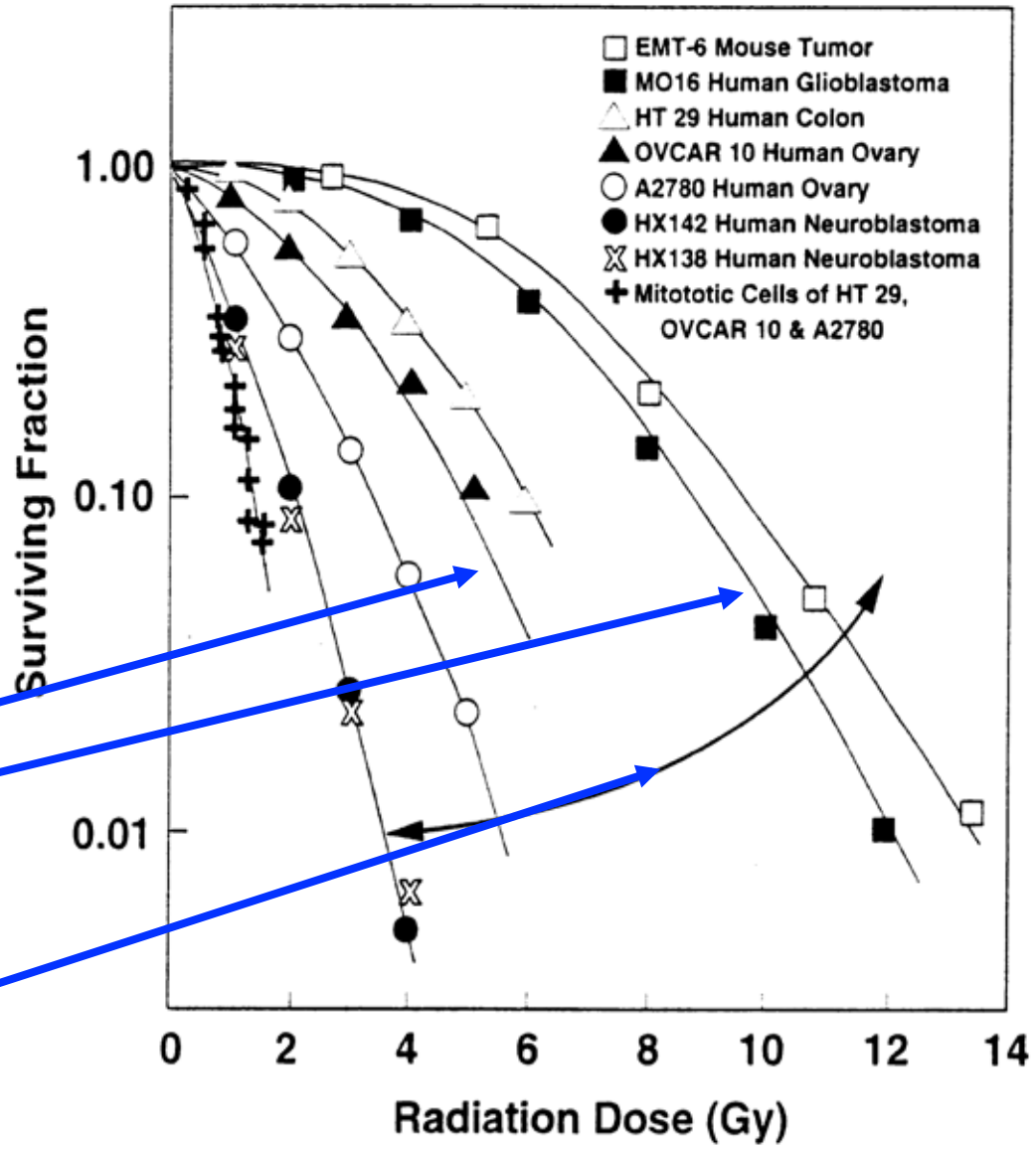
Cell sensitivity to radiation

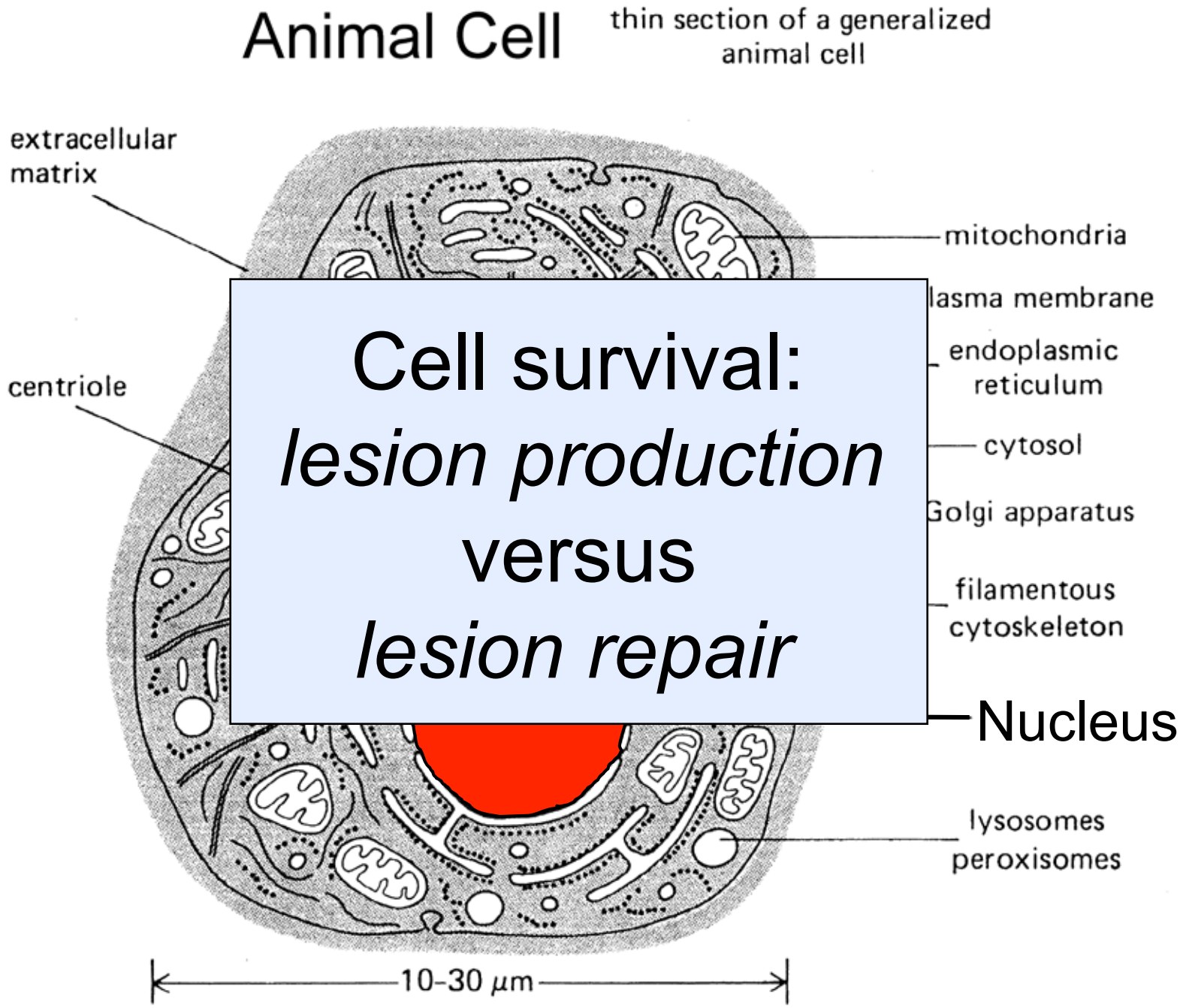
Cells show a wide range of sensitivity

After exposure to radiation, tumor cells die through mitotic catastrophe

How to draw these lines?

How to describe different sensitivity?




Animal Cell
thin section of a generalized animal cell
extracellular matrix
mitochondria
lasma membrane
endoplasmic reticulum
centriole
cytosol
Golgi apparatus
filamentous cytoskeleton
Nucleus
lysosomes
peroxisomes
10-30 μm
Cell survival:
lesion production
versus
lesion repair

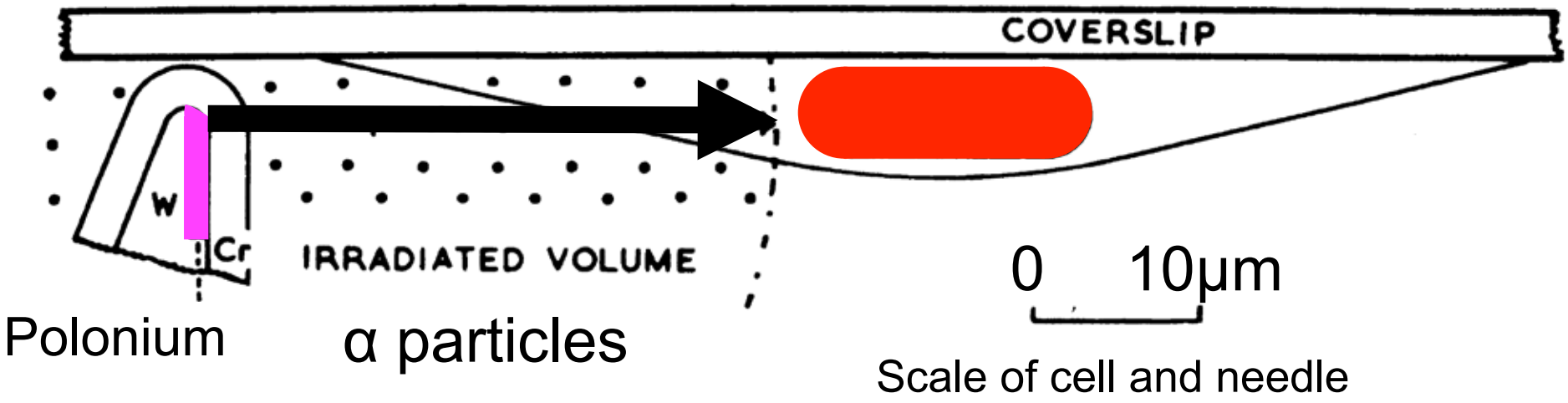
DNA is the principal target

Radiation Source	*Subcellular dose (Gy)*		
	Nucleus	*Cytoplasm*	*Membrane*
X-ray	3.3	3.3	3.3
^{3}H-Tdr	3.8	0.27	0.01
^{125}I-concanavalin	4.1	24.7	516.7

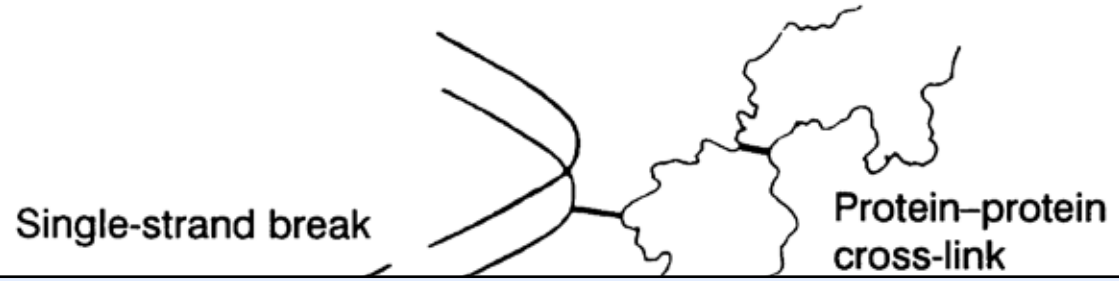
Warters et al. *Curr Top Radiat Res Q* 1977;12:389

DNA is the principal target

Microbeam experiments with α particles from polonium show that the cell nucleus is the sensitive site

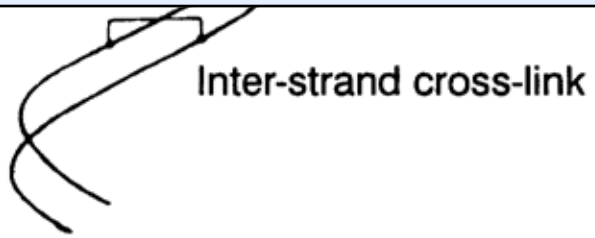


Munro TR. *Radiat Res* 1970;42:451



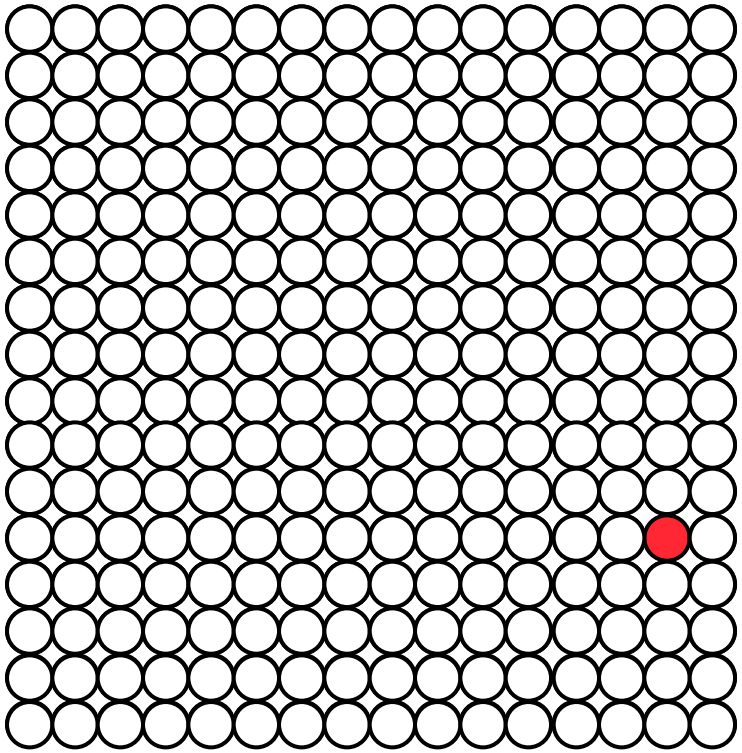
Each 1 Gy produces:

Base damage	>1000
single-strand breaks	~1000
double-strand breaks	~20
equivalent UV dose	10^6 dimers



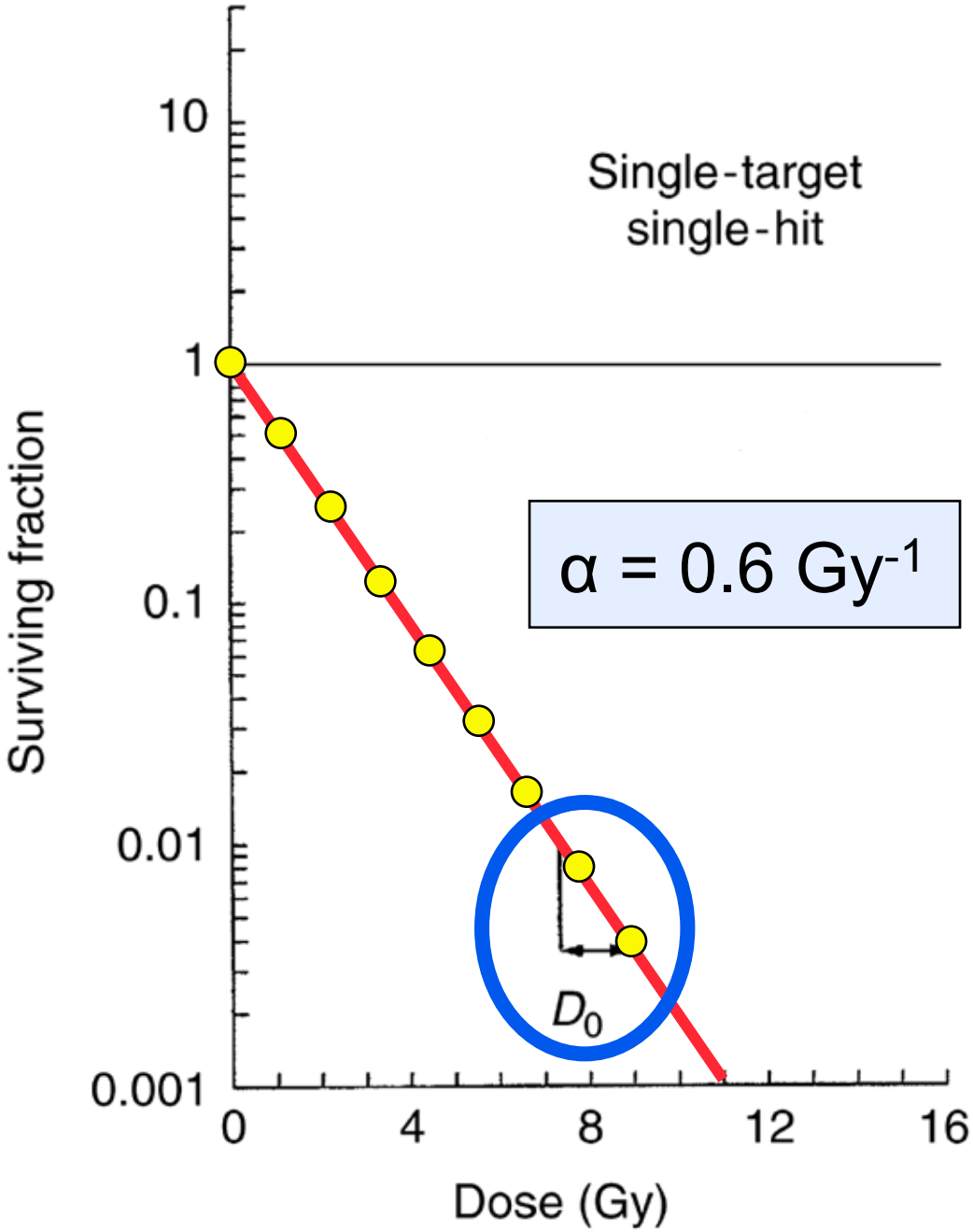
Modifier	Cell kill	**DSB**	SSB	Base damage	DPC
↑ LET	↑	↑	↓	↓	–
↑ hypoxia	↓	↓	↓	0	↑
↑ thiols	↓	↓	↓	0	↓
↑ heat	↑	↑	0	0	0

From Frankenberg-Schwager (1989)



$$\frac{N}{N_0} = S = e^{-\alpha D}$$

$$D_0 = 1/\alpha$$



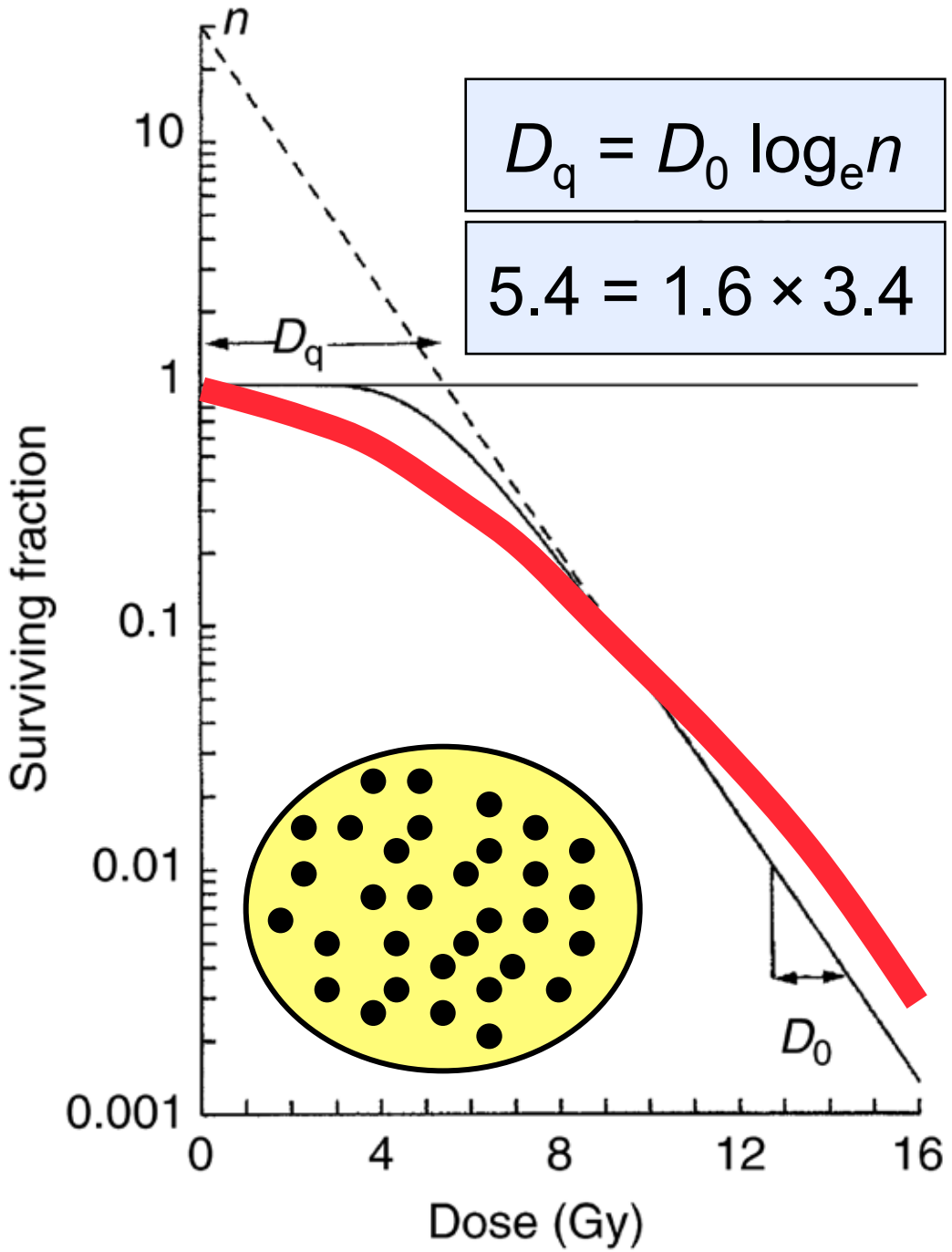
P(0 hits on a target)
$= e^{-D/D_0}$

P(≥1 hit on a target)
$= 1 - e^{-D/D_0}$

P(≥1 hit on n targets)
$= (1 - e^{-D/D_0})^n$

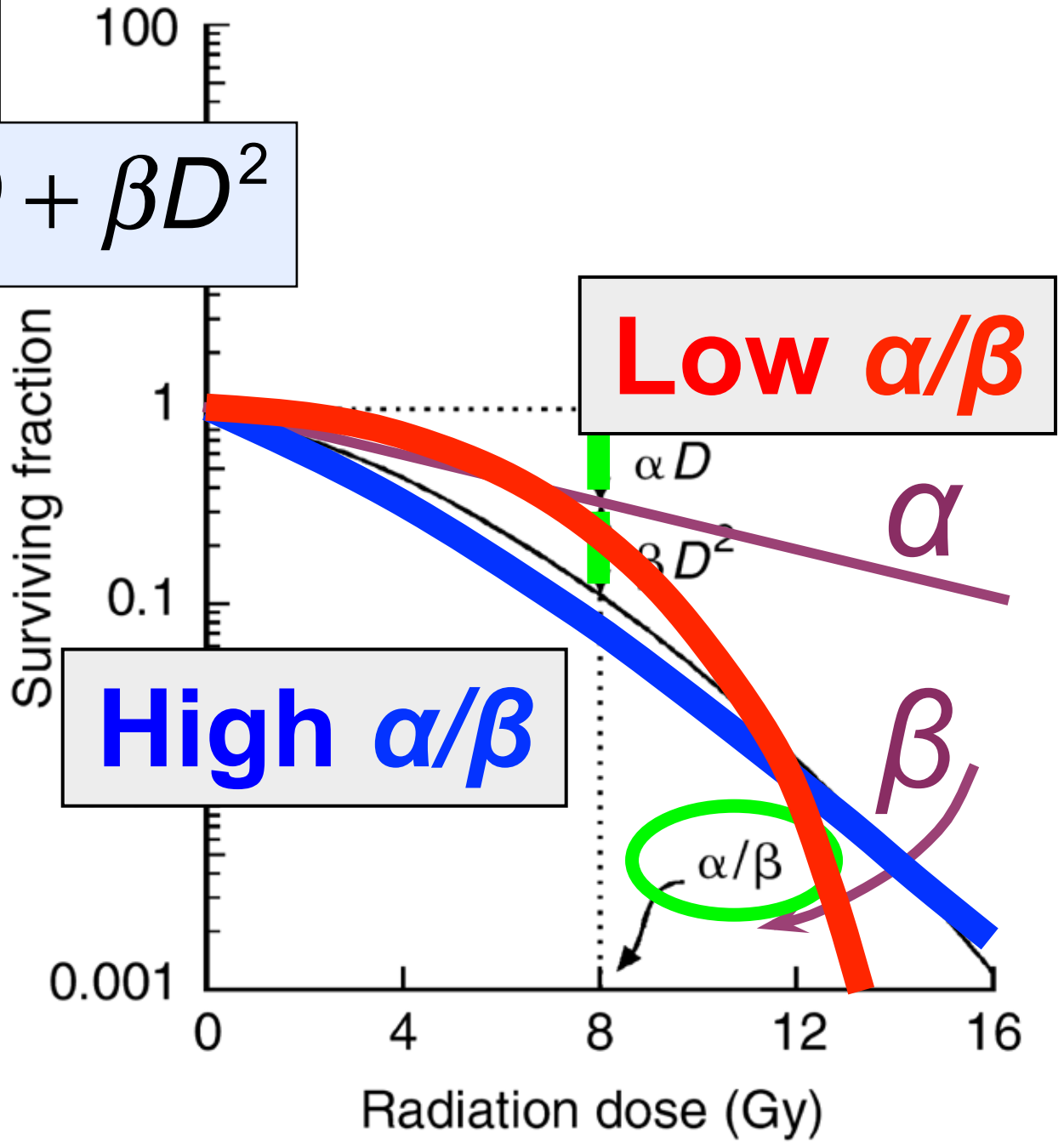
P(not **all** targets hit)
$= 1 - (1 - e^{-D/D_0})^n$

$$S = 1 - \left(1 - e^{-D/D_0}\right)^n$$

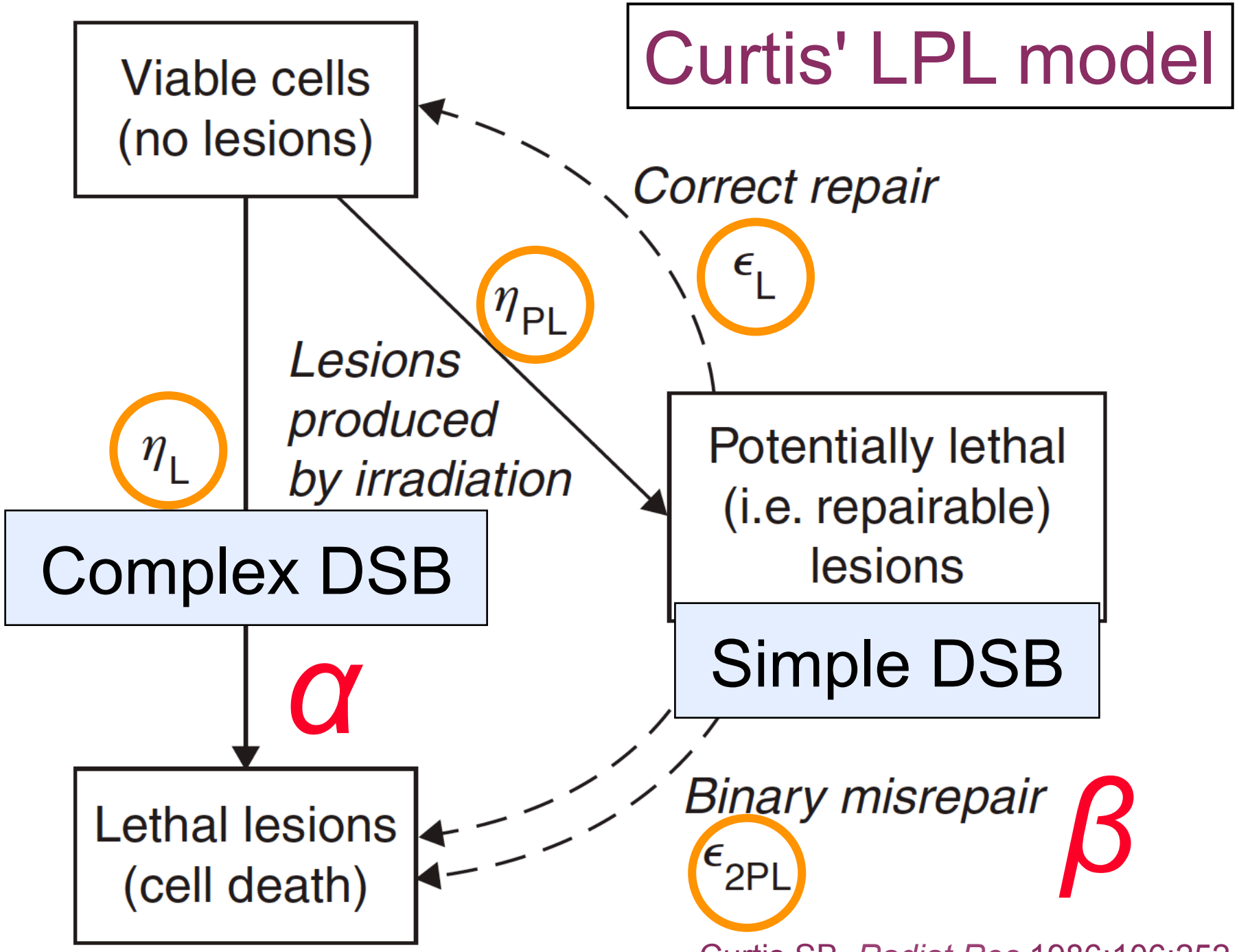


$$S = e^{-\alpha D - \beta D^2}$$

$$-\log_e S = \alpha D + \beta D^2$$

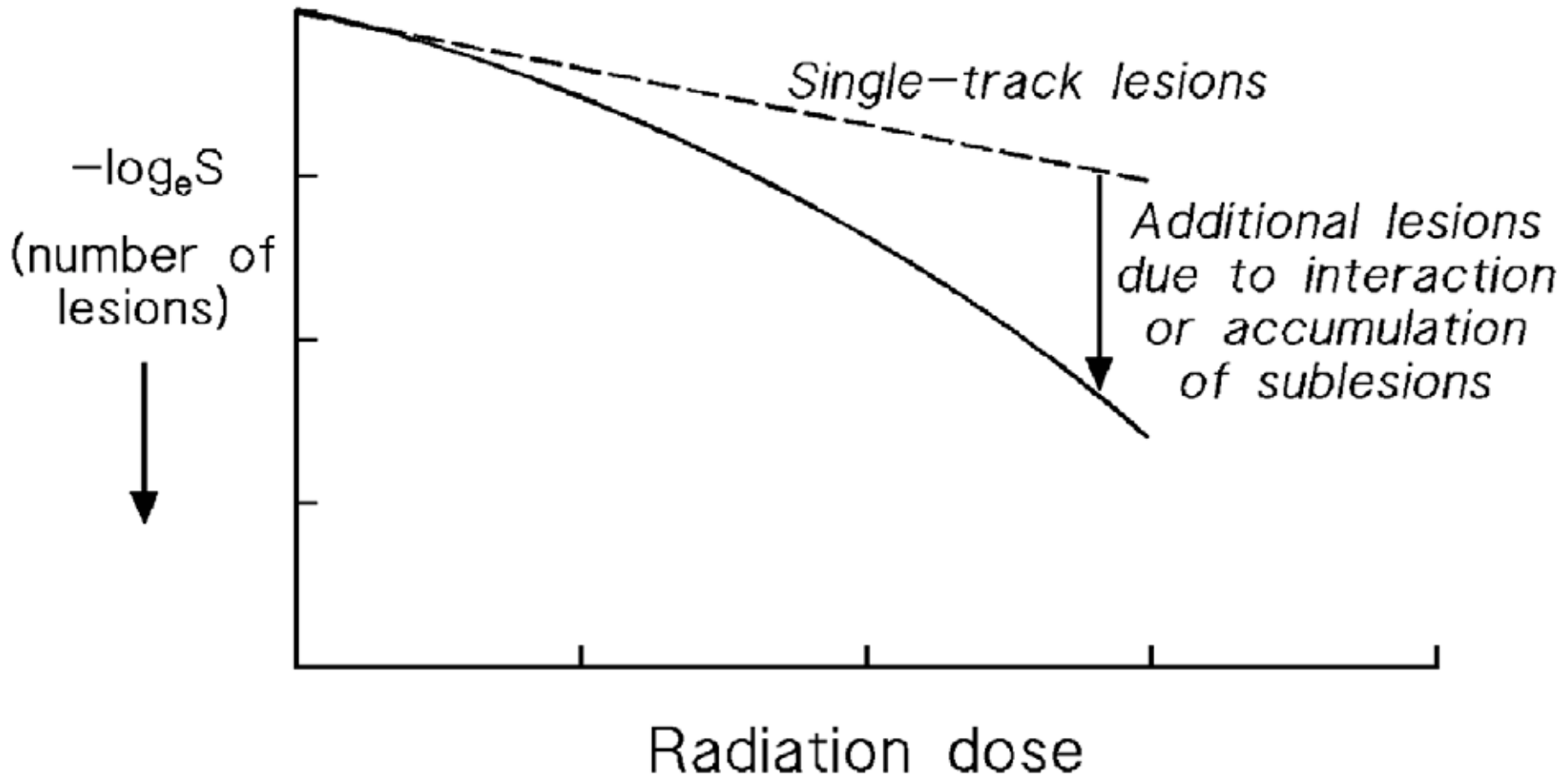


Curtis' LPL model

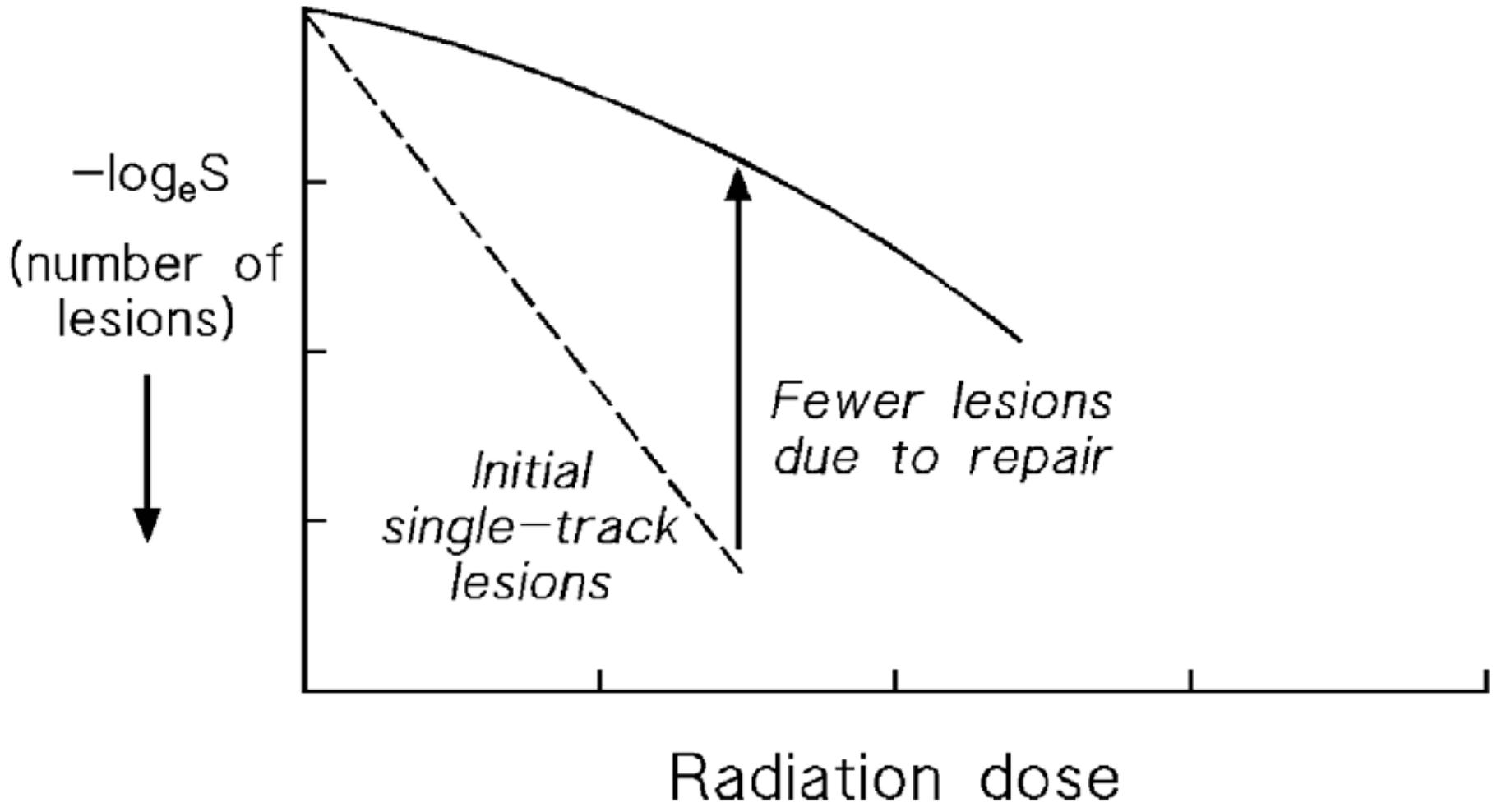


Curtis SB. *Radiat Res* 1986;106:252

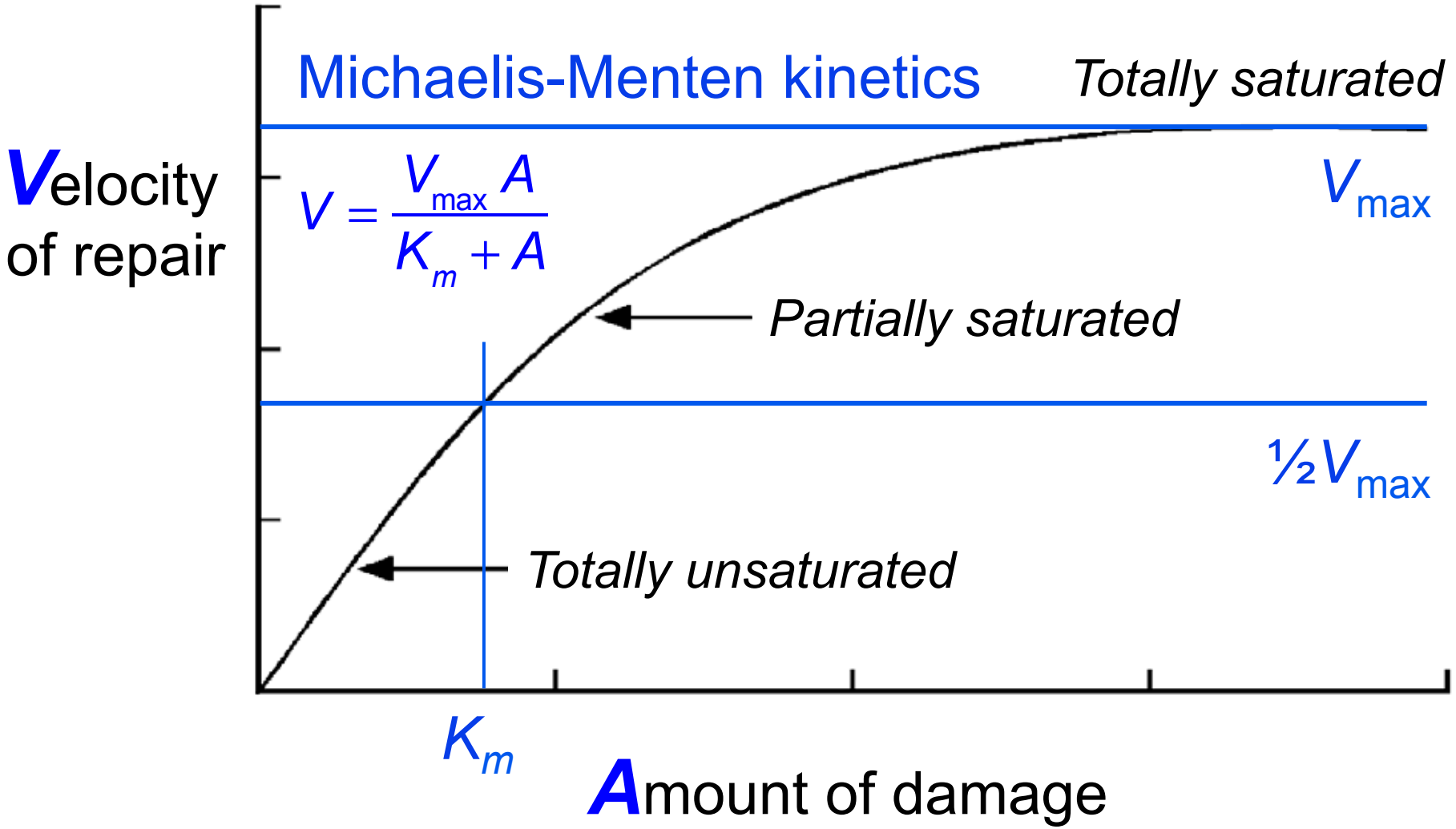
Curtis' LPL model



The concept of repair saturation



The concept of repair saturation



Lesion interaction vs repair saturation

Table 4.1 Different interpretations of radiobiological phenomena by lesion-interaction and saturable-repair models

Observation	Explanation Lesion interaction	Repair saturation
Curved dose–effect relationship	Interaction of sublesions	Saturation of capacity to repair sublesions
Split-dose recovery	Repair of sublesions (sublethal damage repair)	Recovery of capacity to repair sublesions
RBE increase with LET	More non-repairable lesions at high LET	High-LET lesions are less repairable
Low dose rate is less effective	Repair of sublesions during irradiation	Repair system not saturating

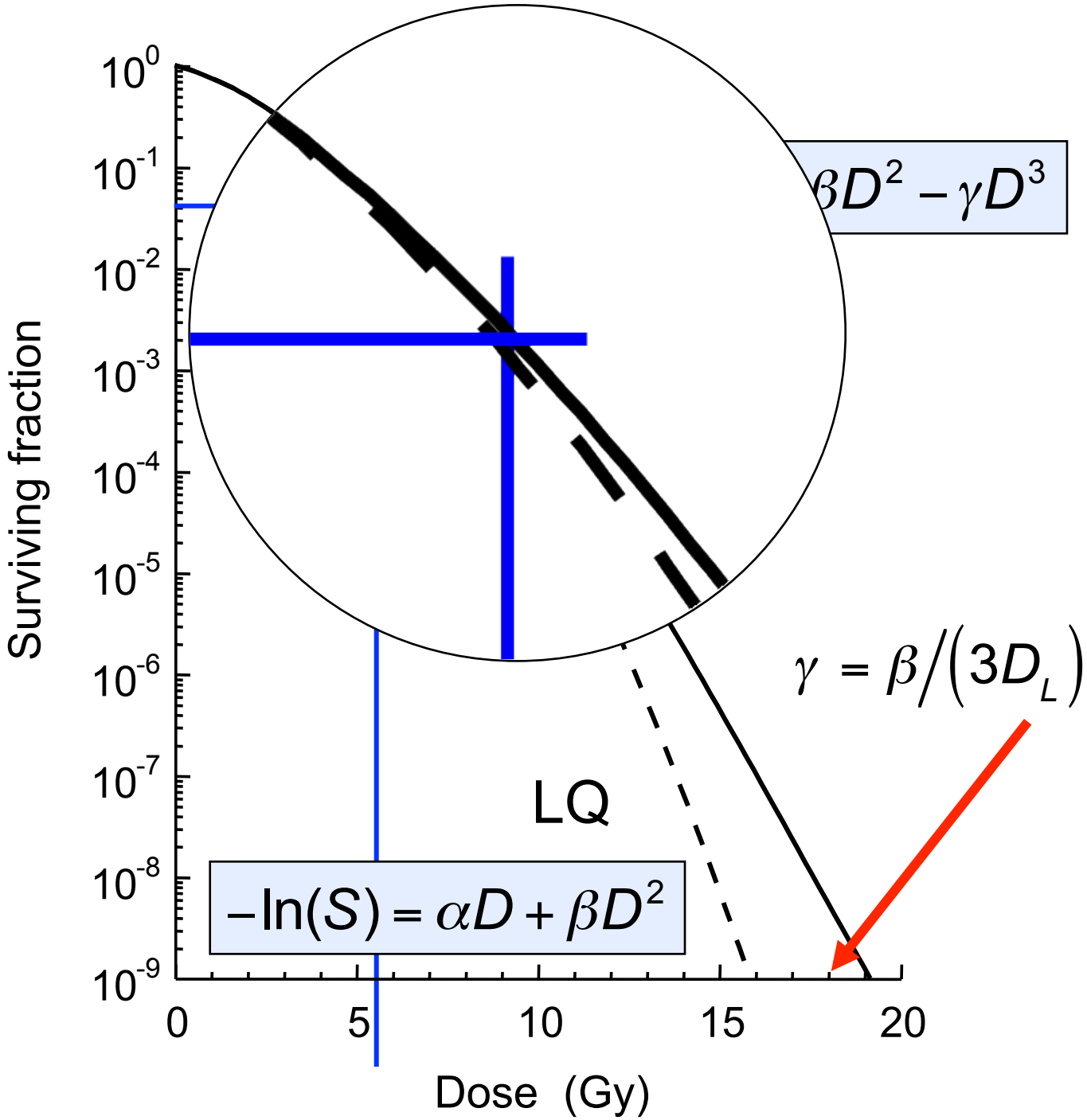
LET, linear energy transfer; RBE, relative biological effectiveness.

Adapted from Goodhead (1985).

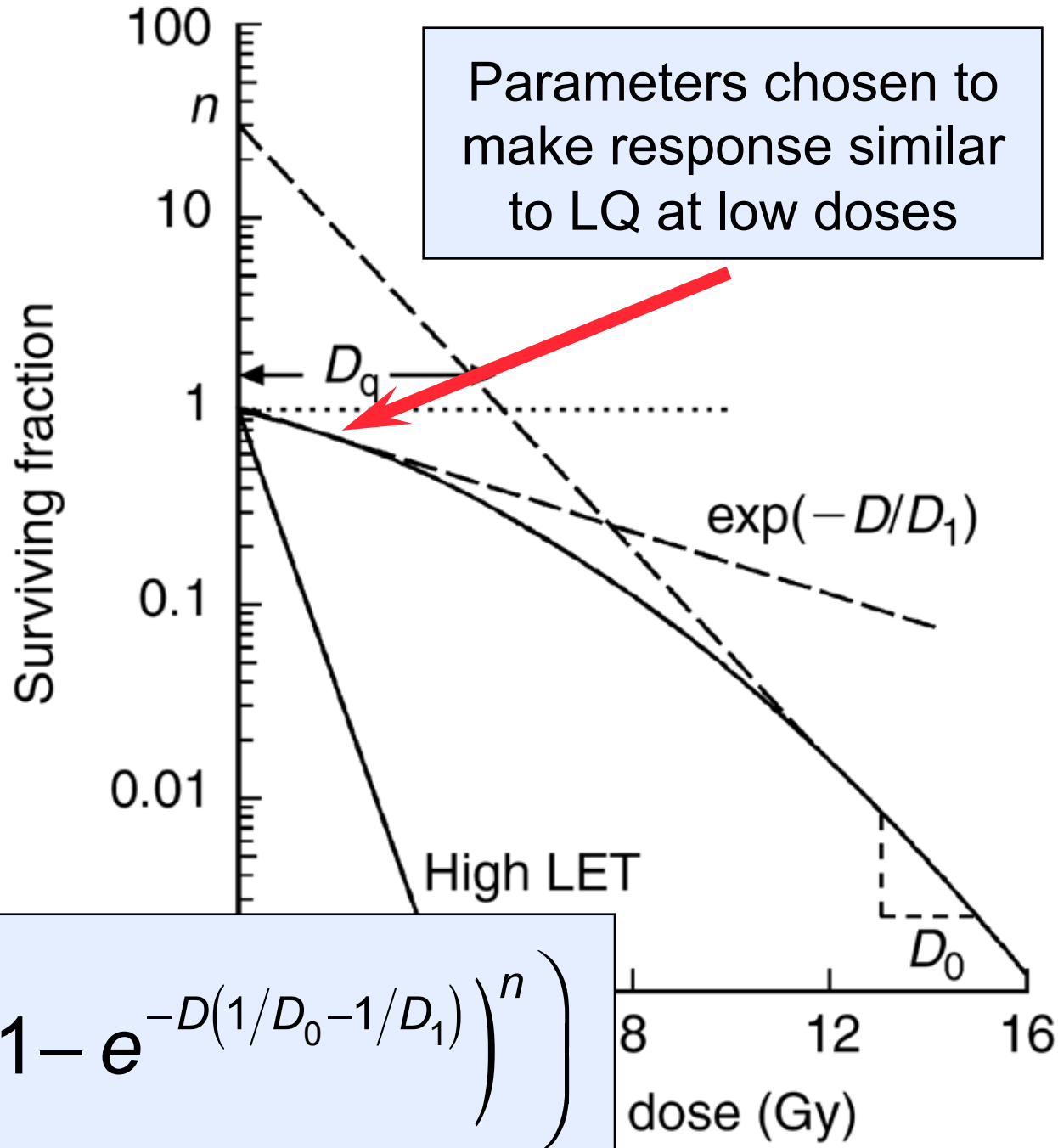
The **L**inear **Q**uadratic **C**ubic model

α/β = 3 Gy

SF2 = 0.5



Two-component model may also better describe response to **high-dose** fractions



$$S = e^{-D/D_1}\left(1-\left(1-e^{-D\left(1/D_0-1/D_1\right)}\right)^n\right)$$

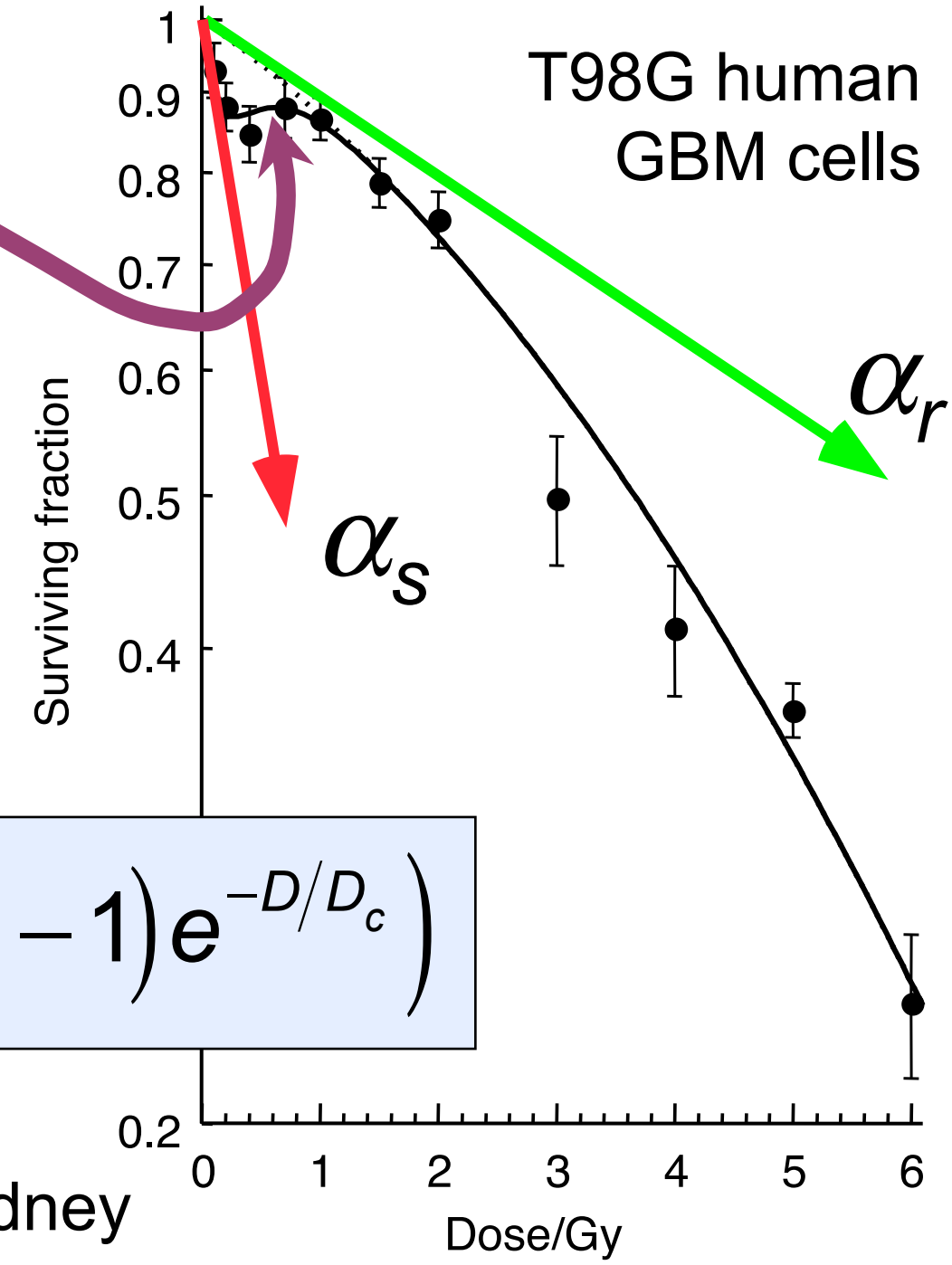
Low-dose hyper-radiosensitivity

Short S, Mayes C, Woodcock M, Johns H, Joiner MC (1999). Int J Radiat Biol 75: 847–55.

$$S = e^{-\alpha D - \beta D^2}$$

$$\alpha = \alpha_r \left(1 + \left(\alpha_s / \alpha_r - 1\right) e^{-D/D_c}\right)$$

First reported in 1986 in mouse epidermis and kidney



Int J Radiation Oncol Biol Phys, Vol. 91, No. 1, pp. 82–90, 2015

Biology Contribution

Cytogenetic Low-Dose Hyperradiosensitivity Is Observed in Human Peripheral Blood Lymphocytes

Isheeta Seth, PhD,* Michael C. Joiner, PhD,† and James D. Tucker, PhD*

*Departments of *Biological Sciences and †Radiation Oncology, Wayne State University, Detroit, Michigan*

Received Jun 18, 2014, and in revised form Sep 11, 2014. Accepted for publication Sep 13, 2014.

…Here we provide the first cytogenetic evidence of low-dose hyperradiosensitivity in human cells subjected to γ radiation in the G2 phase of the cell cycle…

International Journal of Radiation Oncology biology • physics

www.redjournal.org

- We use models to:
  - help make clinical predictions from experimental data
  - predict the change in outcome when we alter treatment
- This is possible because radiation biology is a quantitative discipline

Clinical side effects and their quantification

Karin Haustermans

Department of Radiation Oncology, University Hospitals Leuven, Belgium

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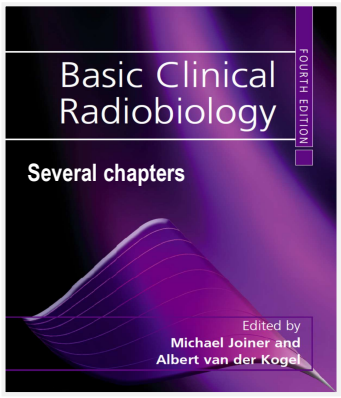
Overview

- Why?
- What?
  - Early adverse events
  - Late adverse events
  - Relevant factors
- How?
- Take home messages



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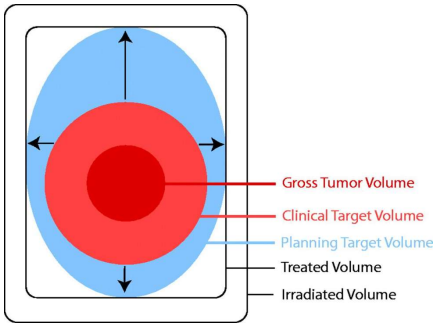
Target volume includes normal tissue

- Microscopic tumor infiltration in surrounding normal tissue
- Normal tissues within tumor (soft tissue, blood vessels)
- Normal structures in entrance and exit dose of the radiation beam



Side-effects cannot, a priori, be considered a consequence of incorrect treatment

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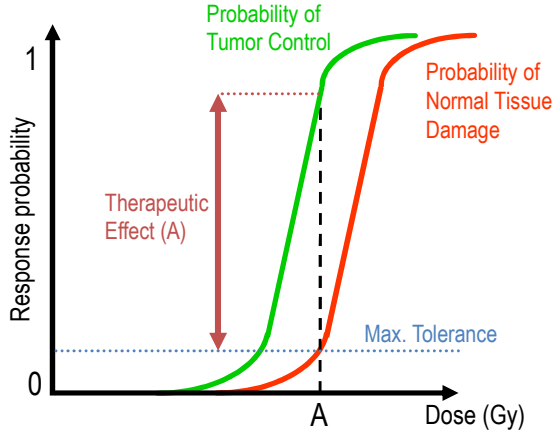
Why assess adverse effects?

- To assess the therapeutic ratio
  - eg change in treatment strategy



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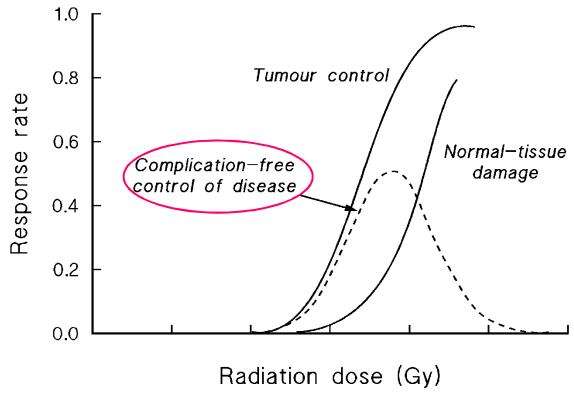
Why assess adverse effects?

- Manifestation of side-effects = indicator for optimum treatment and maximum TCP



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Why assess adverse effects?

- To facilitate the evaluation
  - Of new cancer therapies, treatment modalities and supportive measures
- To monitor safety data
  - To aid in the recognition of severe toxicity & to ensure regulatory reporting
- Essential to standardize reporting
  - Within and across treatment modalities
  - Between investigators, institutions and studies

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What?

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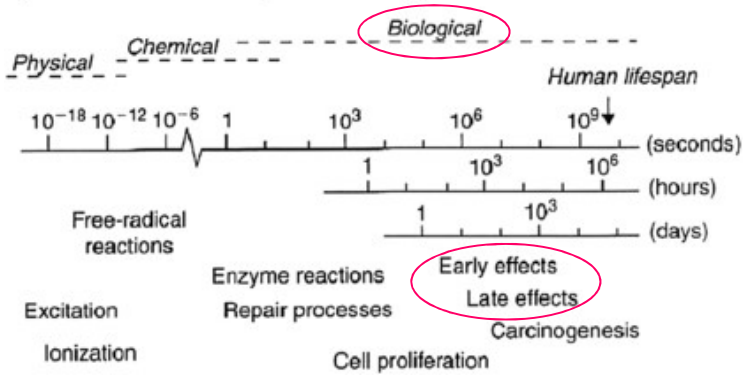
Time-scale of radiation effects

Figure 2 from Issam El Naqa et al 2012 Phys. Med. Biol. 57 R75



Radiation-induced effects may already appear during IR, but may also extend up to many years after exposure to IR and are due to killing of stem cells

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Typical clinical manifestation of EARLY normal tissue reactions

- Alopecia
- Bone marrow suppression
- Diarrhea
- Mucositis
- Pneumonitis
- Xerostomia
- Skin desquamation

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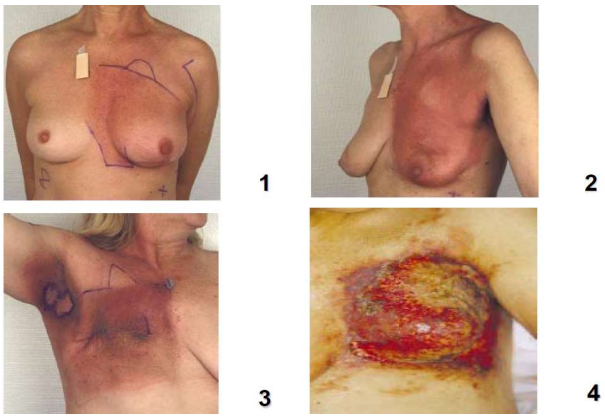
Early skin reactions grade 1-4



From Marianne Nordsmark

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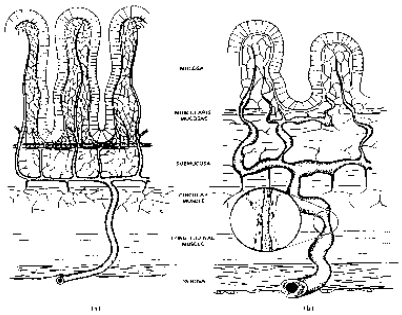
Small bowel toxicity

- Acute toxicity
  - Results of cell death in proliferative compartment
  - Failure to replace the villus epithelium
  - Shortening of the villus
  - Endothelial cell swelling and loss with increased vascular permeability
  - Breakdown of the mucosal barrier
  - Mucositis



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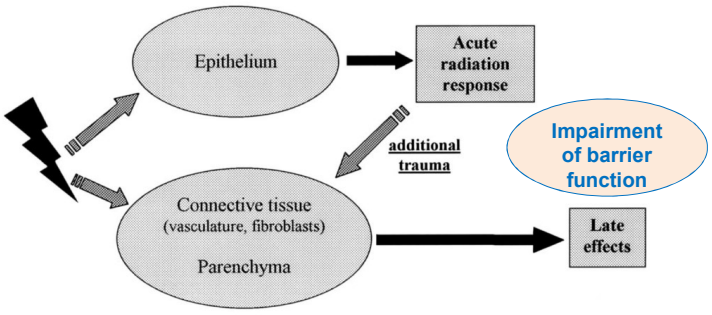
Consequential late effects



Dörr, Radiother Oncol 2001

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Typical clinical manifestation of LATE normal tissue reactions

- Fibrosis
- Lymphoedema
- Myelitis
- Nephritis
- Ostoradionecrosis
- Telangiectasia
  - Cosmetic problem vs bleeding

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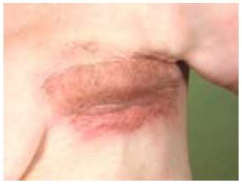
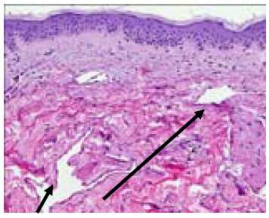
Late skin reactions: telangiectasia

Skin - cosmetic

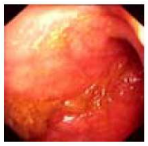


Histopathology

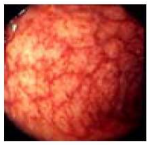


Vessel dilatation

Endoscopic case



Minus RT



Plus RT

From Marianne Nordsmark

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Small bowel toxicity

- Late toxicity
  - Mucosal atrophy
  - Vascular sclerosis
  - Focal ischemia, fibrosis, edema, serosal thickening
  - Malabsorption, dysmotility
  - Intestinal obstruction, fistula
  - Presents clinically 6 months to 3 years after radiation
  - May lead to:
    - Complications requiring surgery
    - Parenteral nutrition
  - Prognosis is poor

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Small bowel toxicity

- Radiation enteritis: oedema, hyperemia, stiffness

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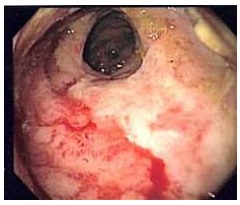
Chronic radiation proctitis

- Due to damage to blood vessels
  - Rectum deprived from oxygen and nutrients
- Several months to years after the end of RT
- Symptoms: diarrhea, rectal bleeding, painful defecation, intestinal blockage, fistulae



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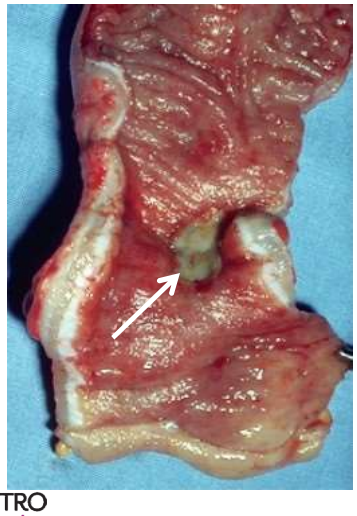
Radiation rectitis



Radiation ulcer
Fibrosis
Bleeding

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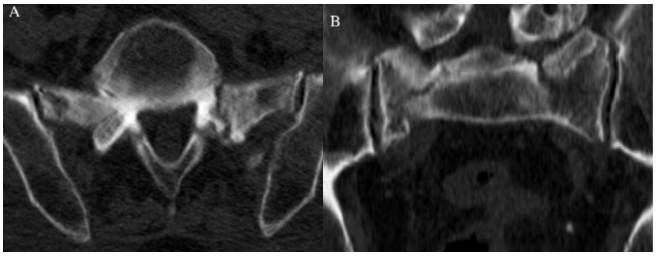
Sacral fractures

- 492 RC patients
- Median follow-up = 3,5 years
- Incidence: 7,1% (35/492)
- 4-year sacral-free rate: 0,91

Underdiagnosed!

Kim et al., IJROBP 2012



Lapina et al. Medicina 2014

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Sacral fractures

- Risk factors

Characteristic	Univariate analysis		Multivariate analysis	
	Unadjusted HR (95% CI)	Unadjusted *P* value	Adjusted HR (95% CI)	Adjusted *P* value
Age at radiotherapy, y				
≤60 (reference)	1	.01	1	
>60	2.48 (1.22-5.07)		2.50 (1.22-5.13)	.01
Sex				
Male (reference)	1		1	
Female	2.81 (1.40-5.65)	.004	2.64 (1.29-5.38)	.008
AJCC stage		.57 (global)		
I/II (reference)	1			
III/IV	0.60 (0.28-1.27)			
Recurrence	0.86 (0.20-3.73)			
NA	0.96 (0.36-2.61)			
Radiotherapy dose, cGy		.87 (global)		
5040 (reference)	1			
<5040	0.61 (0.08-4.46)			
≥5040	1.07 (0.15-7.83)			
Chemotherapy regimen*		.90 (global)		
5-FU based (reference)	1			
FOLFOX based	1.21 (0.52-2.79)			
Irinotecan based/other	0.90 (0.21-3.81)			
History of osteoporosis				
No (reference)	1		1	.02
Yes	4.84 (1.88-12.49)	.001	3.23 (1.23-8.50)	

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Kim et al., IJROBP 2012

Early versus late reactions

	Early reactions	Late reactions
Latency (Time to onset of clinical manifestion)	<90 days after onset RT; typically 3-9 weeks Not influenced by dose, but severity and duration of damage are dose-dependent	>90 days after onset RT; typically 0,5-5 years Inversely dependent on dose: higher dose leads to shorter latent period
Fractionation sensitivity	Low (high α/β ~ 6-10 Gy)	High (low α/β ~ 1-5 Gy)
Influence of overall treatment time (OTT)	Shorter OTT leads to greater injury	No significant influence
Clinical course	Typically transient, but consequential late reactions may occur	Progressive and irreversible Compensation may occur Rehabilitation or treatment for complications may relieve

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Relevant factors

- Organs in the irradiated volume
  - Normal tissue constraints
- Pathogenesis of functional tissue (L1.7)
  - Vascular component
  - Connective tissue
  - Specific functional tissue compartments
- Previous irradations
  - Retreatment tolerance (L4.5)

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Relevant factors

- Patient-related factors influencing normal tissue reactions
  - Age
  - Co-morbidity (e.g. cardiovascular diseases, diabetes)
  - Genetic syndromes (e.g. Ataxia Telangiectasia)
  - Infection (e.g. IBD, Crohn's disease)
  - Interaction with other treatments (e.g. chemotherapy)
  - Patient's general condition
  - Smoking

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Tumor-related factors

- Stage of disease
- Volume of the tumor
- Lymphatic spread

- Radiation dose
- Volume of normal tissue irradiated
- Fractionation schedule
- Use of concomitant chemotherapy

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Relevant factors

- Radiobiological-related factors influencing normal tissue reactions
  - Intrinsic radiosensitivity (L2.3)
  - Total radiation dose (L3.5)
  - Technique and irradiated volume (L3.6)
  - Fractionation schedule (late reactions) (L2.3)
  - Overall treatment time (early reactions) (L2.4)
  - Concomitant treatment (L4.4, L5.2)

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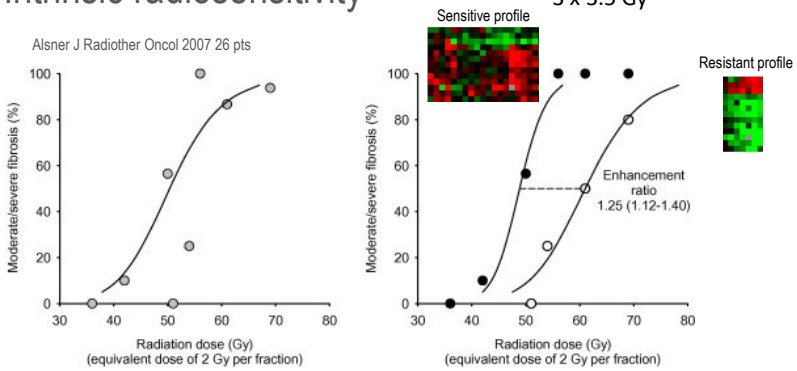
Relevant radiobiological factors

- Intrinsic radiosensitivity

26 patients derived fibroblasts
Hierarchical clustering
3 x 3.5 Gy



Differential gene expression in irradiated fibroblasts between pts with variable risk of radiation-induced fibrosis

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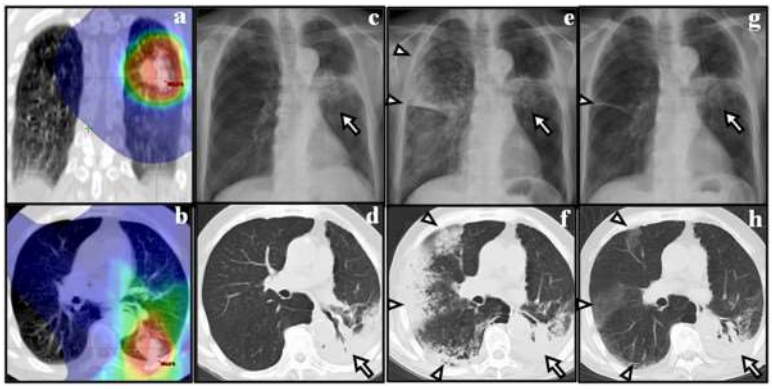
Relevant radiobiological factors

- Technique: stereotactic ablative radiotherapy



Radiation pneumonitis - 3 months after resolution: organizing pneumonitis – 5 mg prednison

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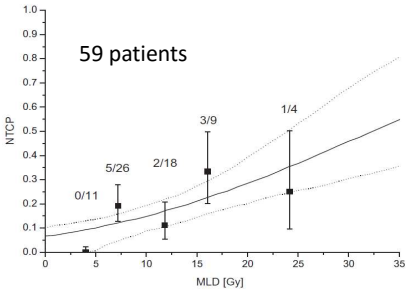
Murai Radiat Oncol 2012 189 pts

27

Relevant radiobiological factors

- Total radiation dose

Average MLD 10.3±5.6Gy
MLD Pts with RP12.5±4.3Gy > MLD pts without RP MLD 9.9±5.8Gy



Dose-response relationship for radiation-induced pneumonitis (RP) after pulmonary stereotactic body radiotherapy

Fig. 1. Patients were grouped in bins of 5 Gy MLD, observed incidences of radiation-induced pneumonitis (RP) for the median dose within each bin are shown and the error bars represent the 68% confidence interval (CI) of the observed incidences. The thick solid line shows the best fit of the NTCP model based on the MLD and the dashed lines represent the 68% CI of the fitted curve.

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Guckenberger Radiother Oncol 2010 59 pts

28

Relevant radiobiological factors

- Irradiated volume with SBRT

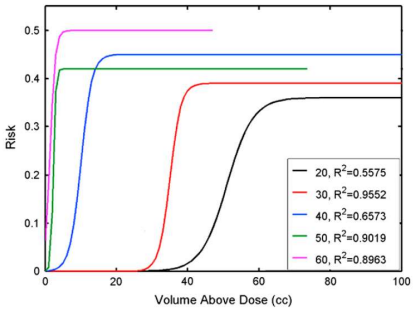

Fig. 1. Volume–risk analysis based on median effective concentration dose–response model for designated dose levels (20, 30, 40, 50, and 60 Gy) for development of severe chest wall toxicity.

Dunlap Int J Radiat Oncol 2010 60 pts

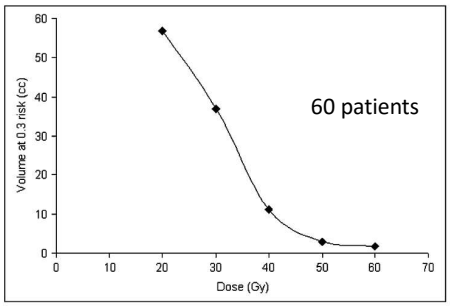

Fig. 2. Dose–volume relationship for 30% risk of severe chest wall toxicity.

Chest wall volume receiving >30Gy predicts risk of severe pain and/or rib fracture after lung SBRT

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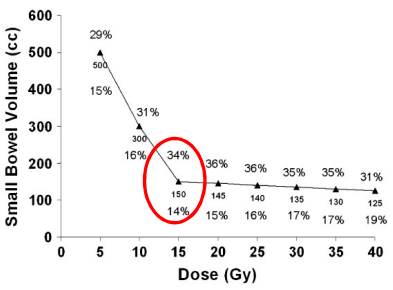
Small bowel toxicity

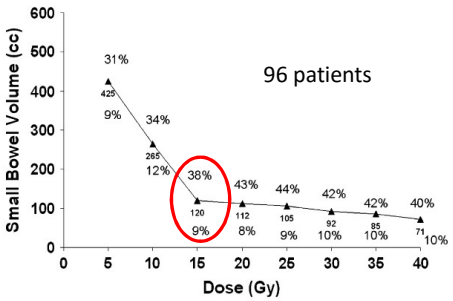
- Acute small bowel toxicity depends on irradiated volume

Better modeling of preoperative patients

Previous parameters



Revised parameters



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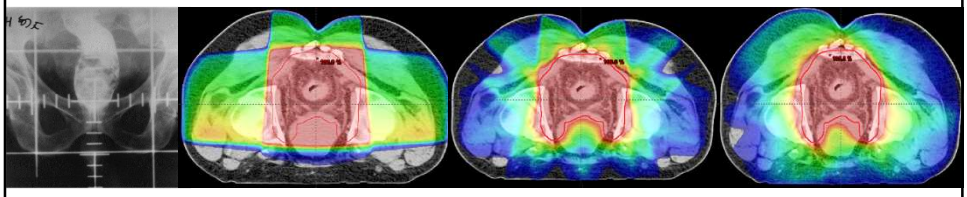
Robertson et al., Int J Rad Onc Biol Phys 2008

Tools to reduce toxicity

ADVANCES IN RT



Therapeutic ratio

Better dose distribution
Conforming radiation beams to the tumor
Avoiding high-dose irradiation of normal tissue

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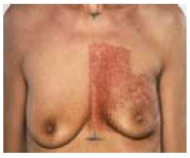
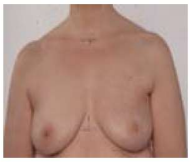
Relevant radiobiological factors

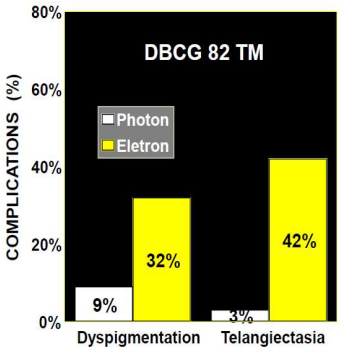
- Technique: electrons vs photons



Electron irraditation



Photon irraditation



Johansen et al. 1998

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Relevant radiobiological factors

- Fractionation schedule

Radiotherapy and Oncology 75 (2005) 9-17
www.elsevier.com/locate/radonline

Phase III randomised trial **Pre-START trial**

Fractionation sensitivity and dose response of late adverse effects in the breast after radiotherapy for early breast cancer: long-term results of a randomised trial

John Yarnold[a,*], Anita Ashton[b], Judith Bliss[c], Janis Homewood[c], Caroline Harper[c], Jane Hanson[a], Jo Haviland[c], Søren Bentzen[d], Roger Owen[b]

[a]Academic Radiotherapy Department, The Royal Marsden Hospital, Surrey, UK, [b]Department of Oncology, Gloucestershire Oncology Centre, Cheltenham, UK, [c]Clinical Trials and Statistics Unit, Institute of Cancer Research, Surrey, UK, [d]Human Cancer Biology and Informatics, Gray Cancer Institute, Northwood, UK

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Relevant radiobiological factors

- Fractionation schedule

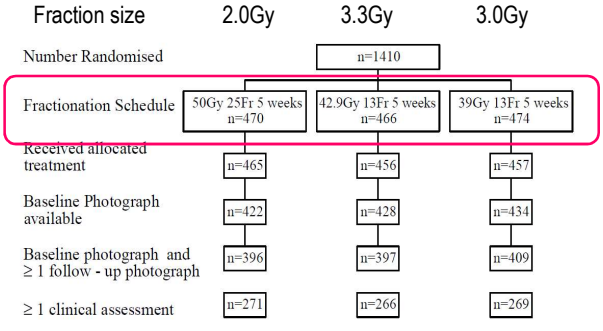

Fig. 1. Number of patients randomised into each fractionation schedule and with available follow-up data.

Yarnold Radiother Oncol 2005

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Relevant radiobiological factors

Yarnold Radiother Oncol 2005

- Fractionation schedule: relation to EQD_{2Gy}

α/β = 3	EQD_{2Gy}
39Gy/13fx	46.8Gy
50Gy/25fx	50Gy
42.9Gy/13fx	54Gy

Alpha/beta value of 3.6 Gy (95% CI 1.8-5.4 Gy)

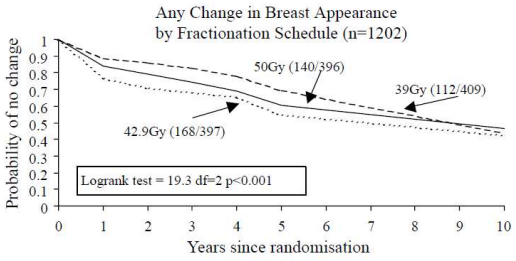

Fig. 2. Probability of any change in breast appearance late radiation effect ten years after radiotherapy by fractionation schedule.

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Relevant radiobiological factors

- Fractionation schedule

Hypofractionated radiotherapy is safe and effective for patients with early breast cancer

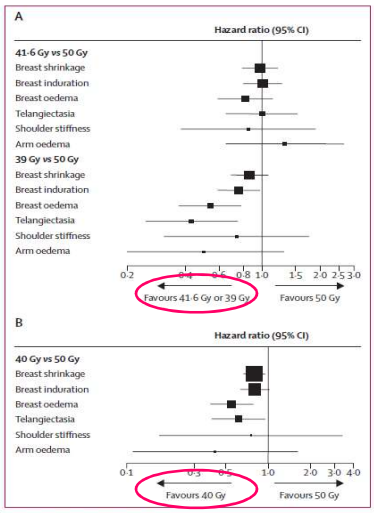

Figure 3: **Late normal tissue effects**
In START-A (A) and START-B (B). Assessed as moderate or marked by physicians.

Haviland Lancet Oncol 2013

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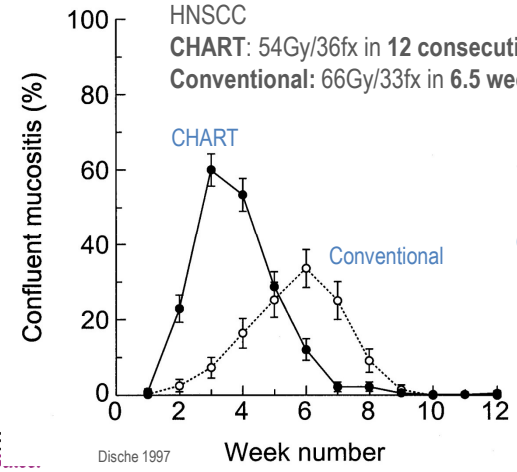
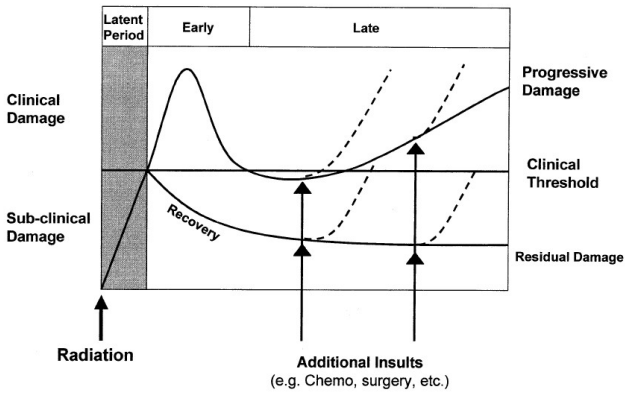
Relevant radiobiological factors

- Overall treatment time



Shorter OTT resulted in aggravation of early side effects

Combined modality treatment



How?

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Treatment-related toxicity

- Underreported, vague symptoms …
- Different scoring systems used
- Prospective vs retrospective data
- Patient vs physician
- Affects QoL
- Requires appropriate treatment
- Many patients have become long-term survivors

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How to measure normal tissue response?

- Scoring of gross tissue effects
  - Scoring systems: grade the severity of tissue damage using an arbitrary scale
- Assays of tissue function
  - Functional assays to measure radiation effects
    - E.g. blood counts as an indicator of bone marrow function
- Clonogenic assays (L1.4)
  - Methods by which colony of cells that derive from a single irradiated cell can be observed

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Scoring of side-effects: frequency

- Two aspects must be considered for documentation
  - Frequency
    - Early reactions can undergo considerable changes in clinical manifestation in short periods
      - Scoring at weekly basis: during and for some weeks after RT
    - Late reactions develop slowly and are usually irreversible
      - Scoring at intervals of several months after the end of RT (dynamics)
      - At later time points at annual intervals

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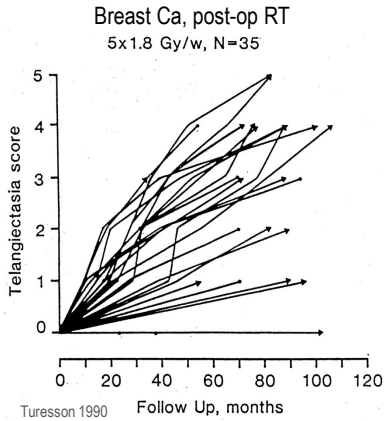
Scoring of side-effects: frequency

- Progressive nature of late reactions



Turesson 1990

Long latent times
Large inter-patient variation

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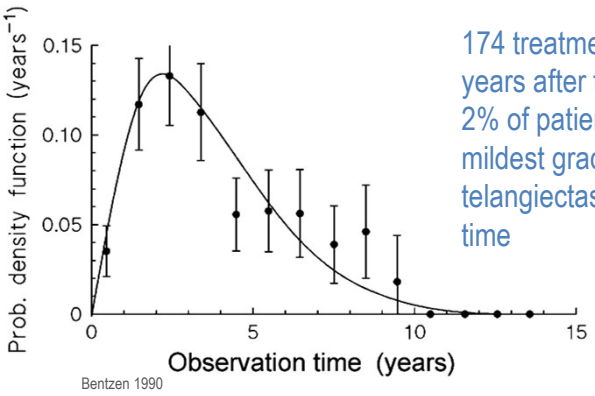
Scoring of side-effects: frequency

- Long latent time of late reactions



Bentzen 1990

174 treatment fields: even 9 years after treatment, about 2% of patients show the mildest grade of telangiectasia for the first time

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Scoring of side-effects: scoring sytems

- Two aspects must be considered for documentation
  - Scoring system used
    - WHO (World Health Organisation)
    - RTOG/EORTC (Radiation and Oncology Therapy Group/European Organisation for Research and Treatment of Cancer
    - CTCAE (Common Terminology Criteria for Adverse Events; latest version CTCAE v4.03)
    - LENT-SOMA (Late Effects of Normal Tissues – Subjective, Objective, Managment & Analytical)
    - IPSS (International Prostate System Score)

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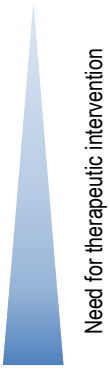
Scoring of side-effects: scoring sytems

Table 13.1 Systems for documentation of side effects, with examples for oral mucositis.

Grade	General	RTOG/EORTC	CTCAE v3	WHO
0	No change	No change	No change	No change
1	Mild	Erythema, mild soreness, painless erosions	Erythema; normal diet	Soreness, erythema
2	Moderate/ clear	Painful erythema, edema or ulcers; can eat	Patchy ulceration; can eat and swallow modified diet	Erythema, ulcers; can eat solids
3	Severe/ significant	Painful erythema, edema or ulcers; cannot eat	Confluent ulcerations, bleeding with minor trauma; unable to adequately aliment or hydrate orally	Ulcers; requires liquid diet only
4	Life-threatening	Requires parental or enteral support	Tissue necrosis; significant spontaneous bleeding	Alimentation not possible
5	Death due to side effects	Death due to side effects	Death due to side effects	Death due to side effects



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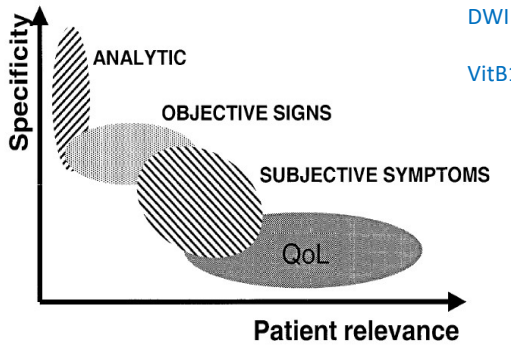
Scoring of side-effects: scoring systems

- Trade-off between specificity and patient relevance

QoL: some are health related, others not

DWI MRI: biological significance

VitB12: malabsorption



Bentzen Sem Rad Oncol 2003

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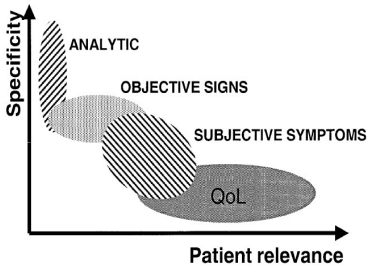
Scoring of side-effects: scoring systems

- Patient's role in toxicity reporting: how well do different scoring systems compare?



Patient-reported late toxicities have a negative impact on QoL

Patient-based questionnaires are an important contributor to capturing late RT effects

Bentzen Sem Rad Oncol 2003

Ho Radiother Oncol 2010

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Scoring of side-effects: key points

- Use a published system
- Minimize the number of variables
- Use forms easy to read
- Define endpoints
- Test inter-observer variability
- Document observations (e.g. pictures)
- Record
  - Baseline morbidity
  - Invasive procedures
  - Comorbidity
  - Other relevant treatments

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Take home messages

- Normal tissue side effects are mandatory to score
  - Therapeutic ratio
  - Quality assurance (QA)
- Both early and late reactions may develop in the same organ
- Use validated scoring systems to record normal tissue effects
- Score before, during and after RT!
  - Extend follow-up to several years after RT to get knowledge on late morbidity

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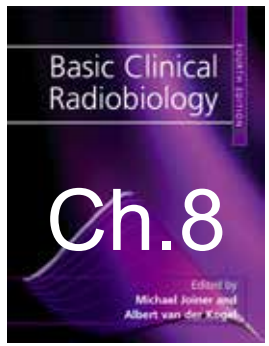
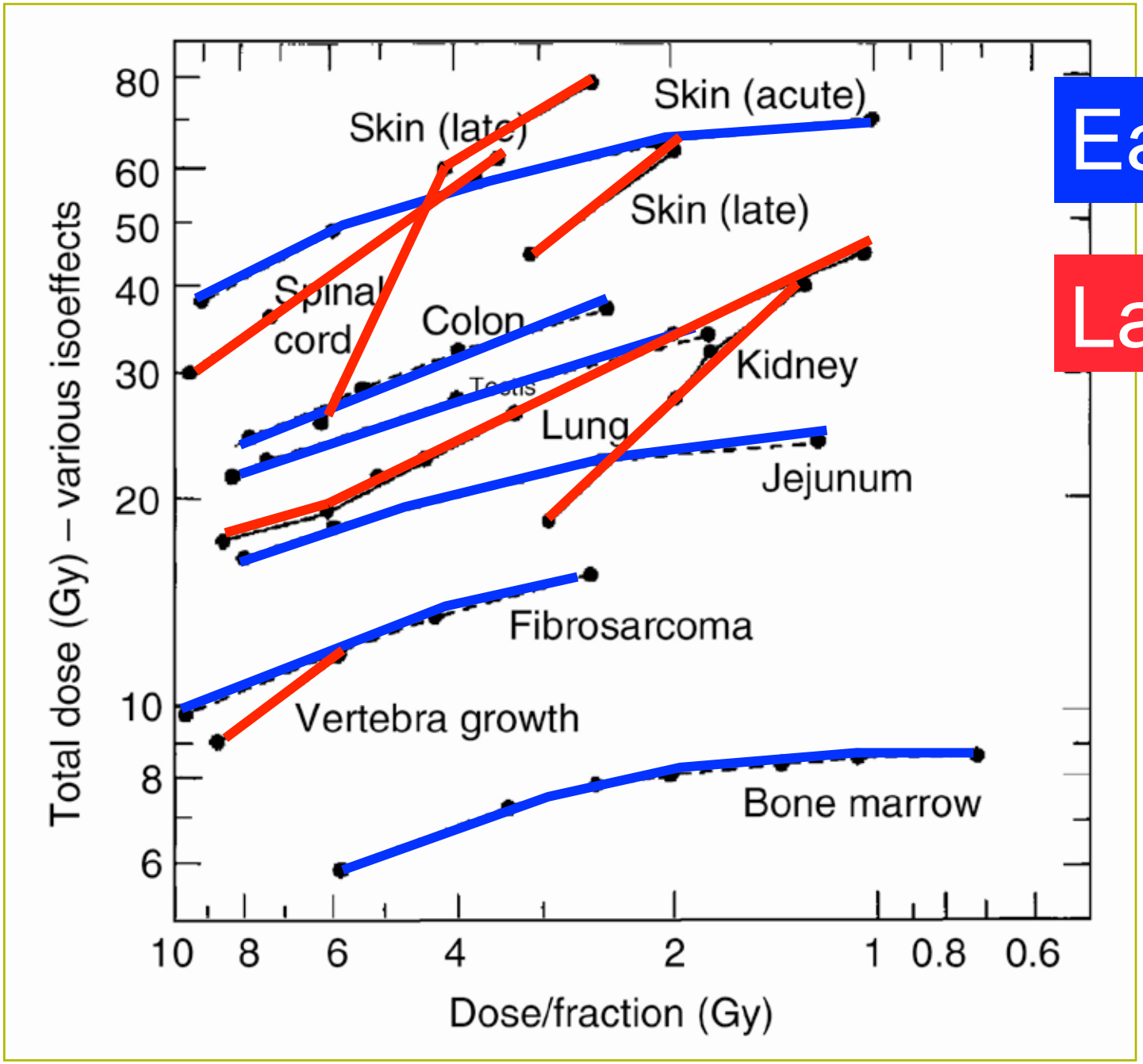
Basic Clinical Radiobiology

The Linear-Quadratic approach to fractionation

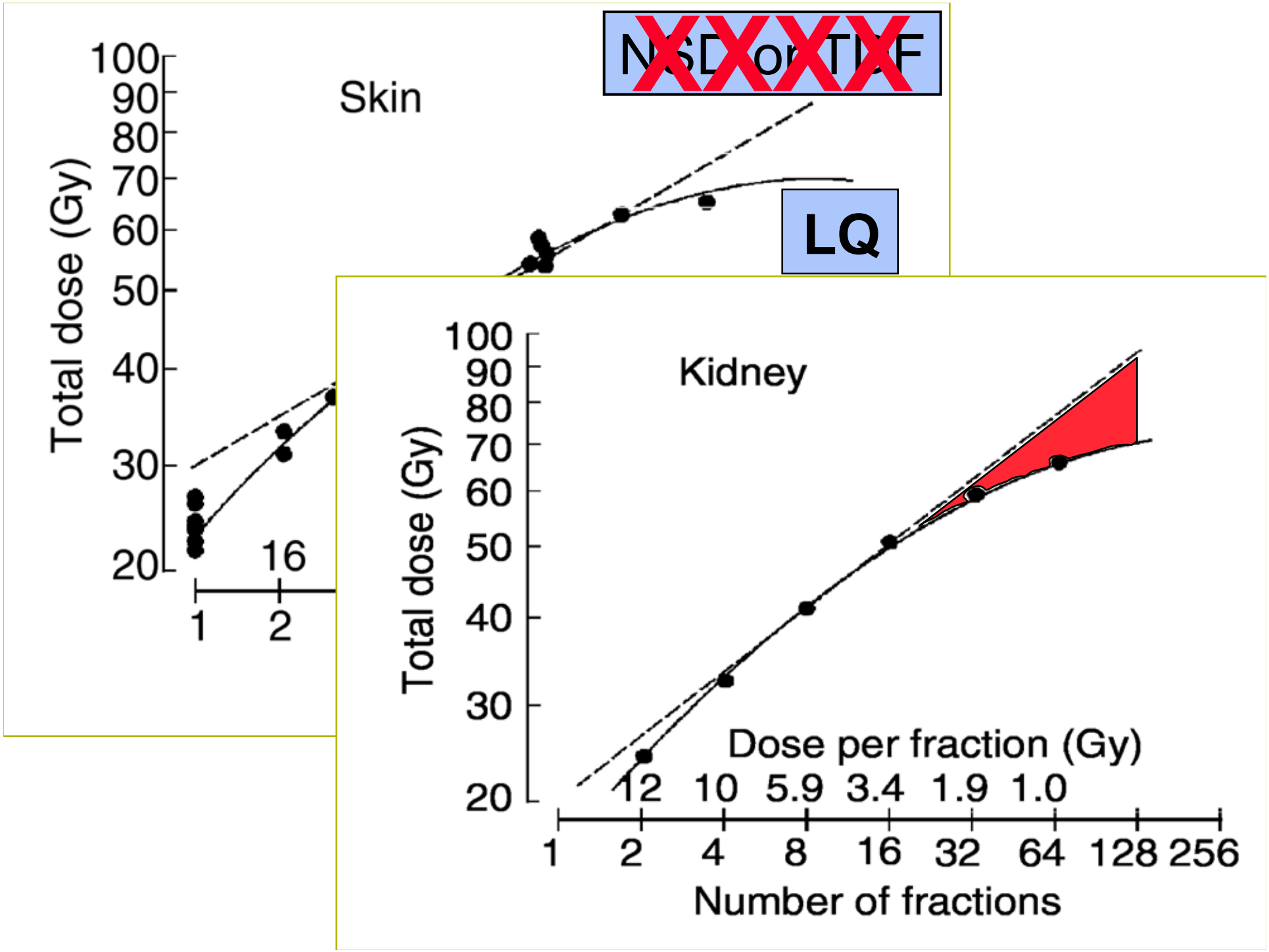
Michael Joiner

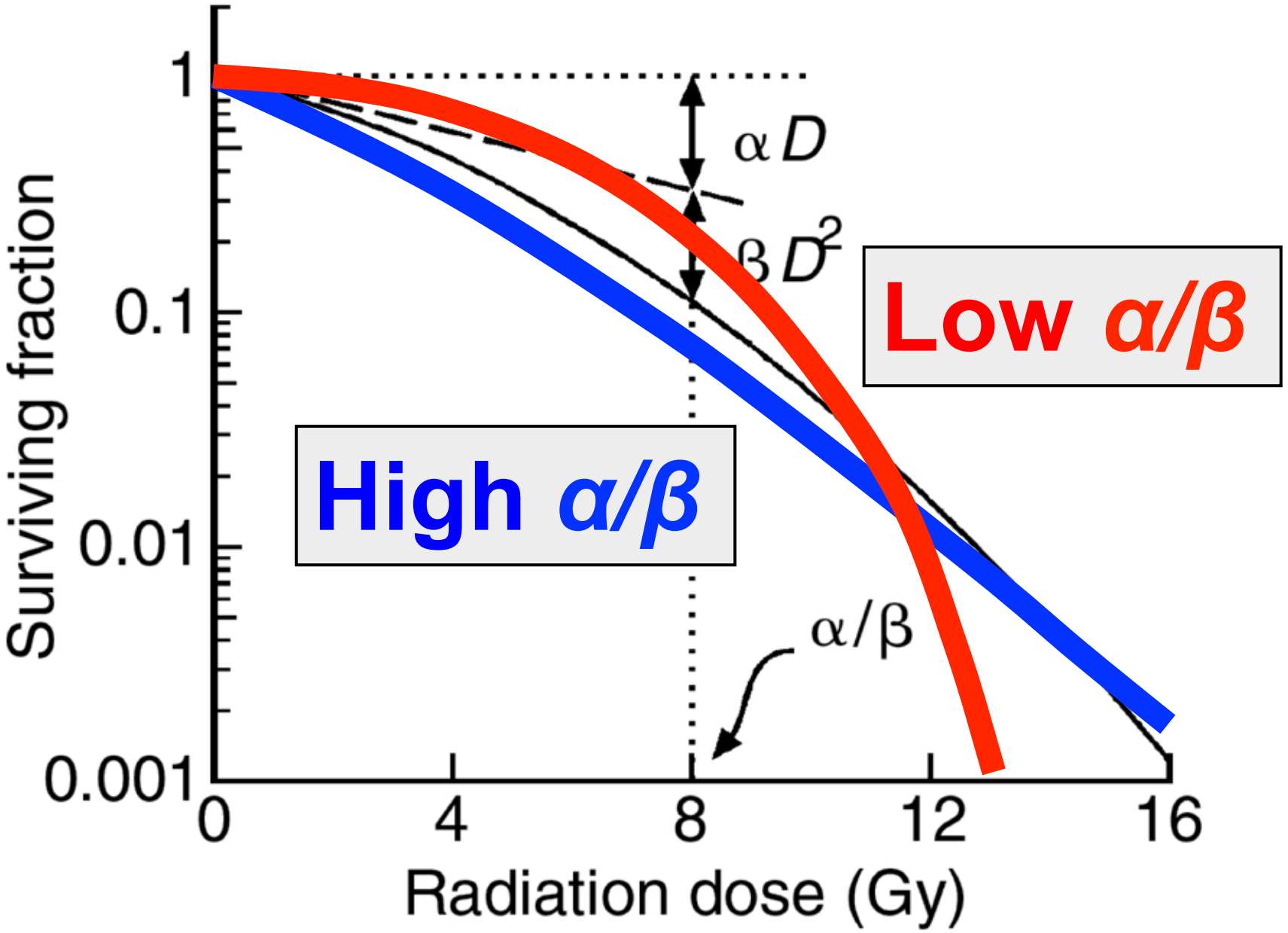


Budapest 2016

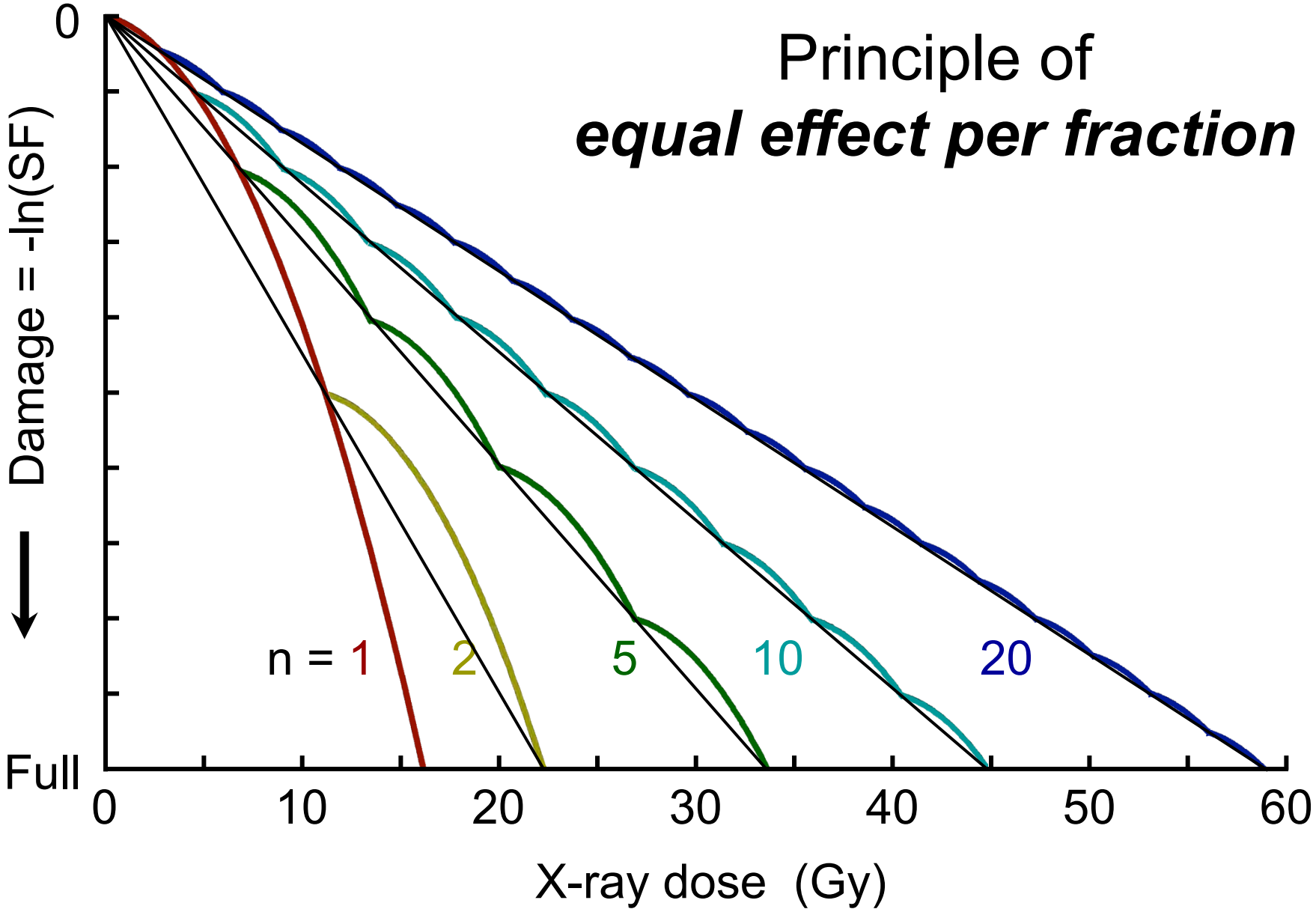


Thames et al. *Int J Radiat Oncol Biol Phys* 1982;8:219

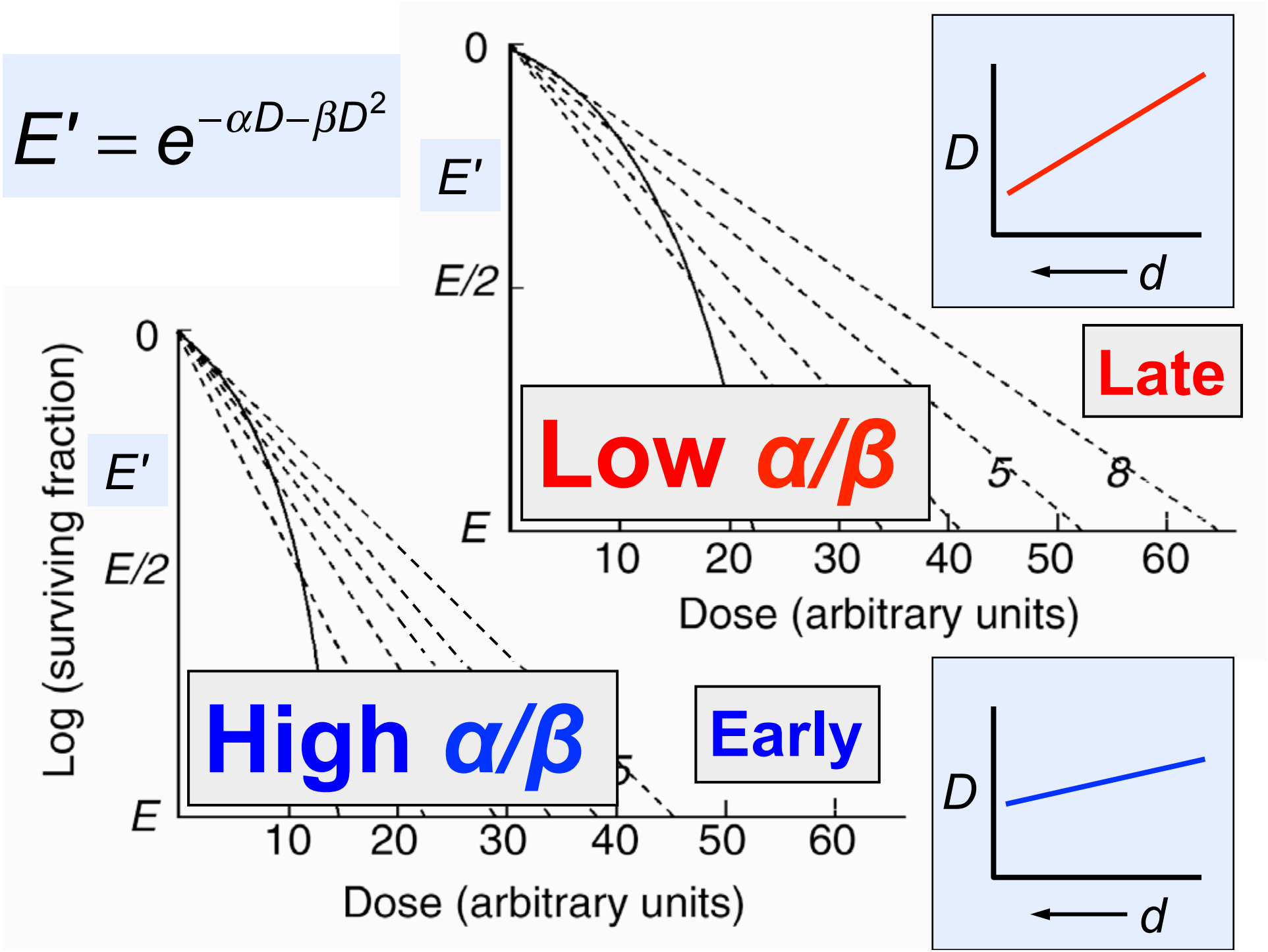

Skin
NSD or TDF
LQ
Total dose (Gy)
100
90
80
70
60
50
40
30
20
16
1
2
Kidney
Total dose (Gy)
100
90
80
70
60
50
40
30
20
Dose per fraction (Gy)
12 10 5.9 3.4 1.9 1.0
1 2 4 8 16 32 64 128 256
Number of fractions

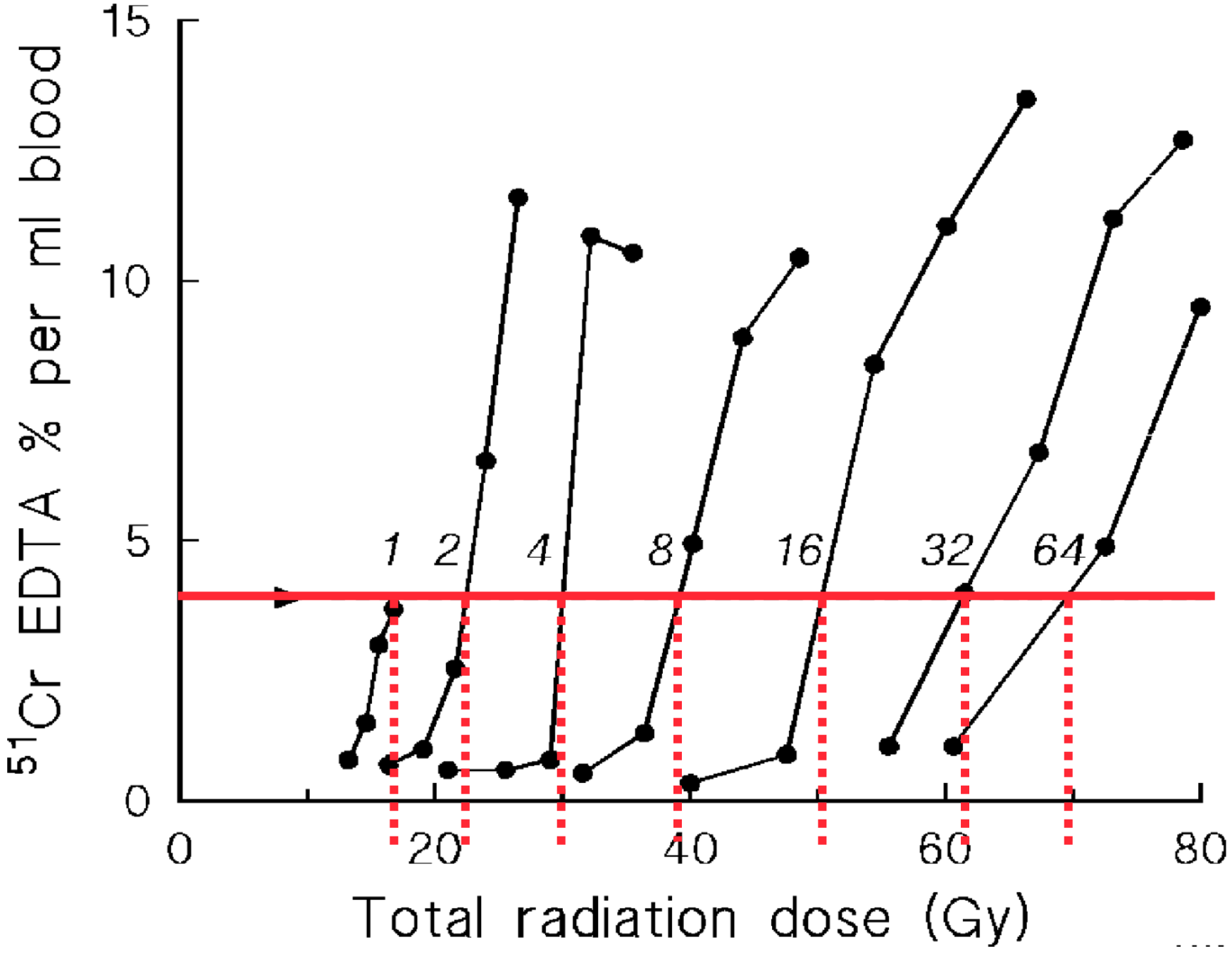

Surviving fraction
1
0.1
0.01
0.001
0
4
8
12
16
Radiation dose (Gy)
αD
βD2
α/β
Low α/β
High α/β

Less effect per gray at low doses/#



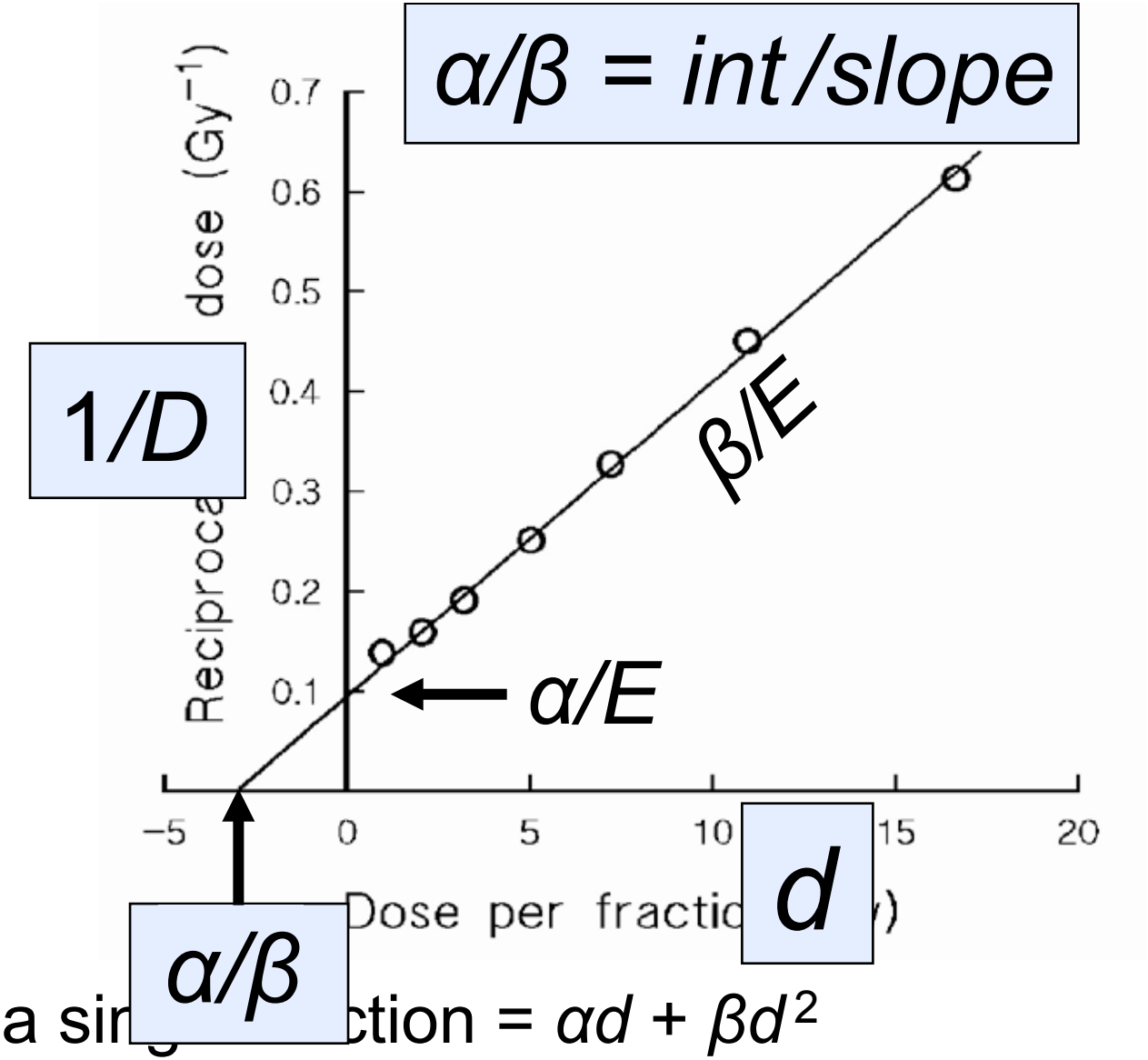
$$E' = e^{-\alpha D - \beta D^2}$$




15
10
5
0
^{51}Cr EDTA % per ml blood
1
2
4
8
16
32
64
0
20
40
60
80
Total radiation dose (Gy)

n	*D*	*d*	1/*D*	1/*n*
1	16.5	16.5	.0606	1.0
2	21.9	10.95	.0457	.5
4	29.4	7.35	.0340	.25
8	39.0	4.88	.0256	.125
16	50.3	3.14	.0199	.0625
32	60.9	1.90	.0164	.03125
64	69.3	1.08	.0144	.015625

d	1/*D*
16.5	.0606
10.95	.0457
7.35	.0340
4.88	.0256
3.14	.0199
1.90	.0164
1.08	.0144

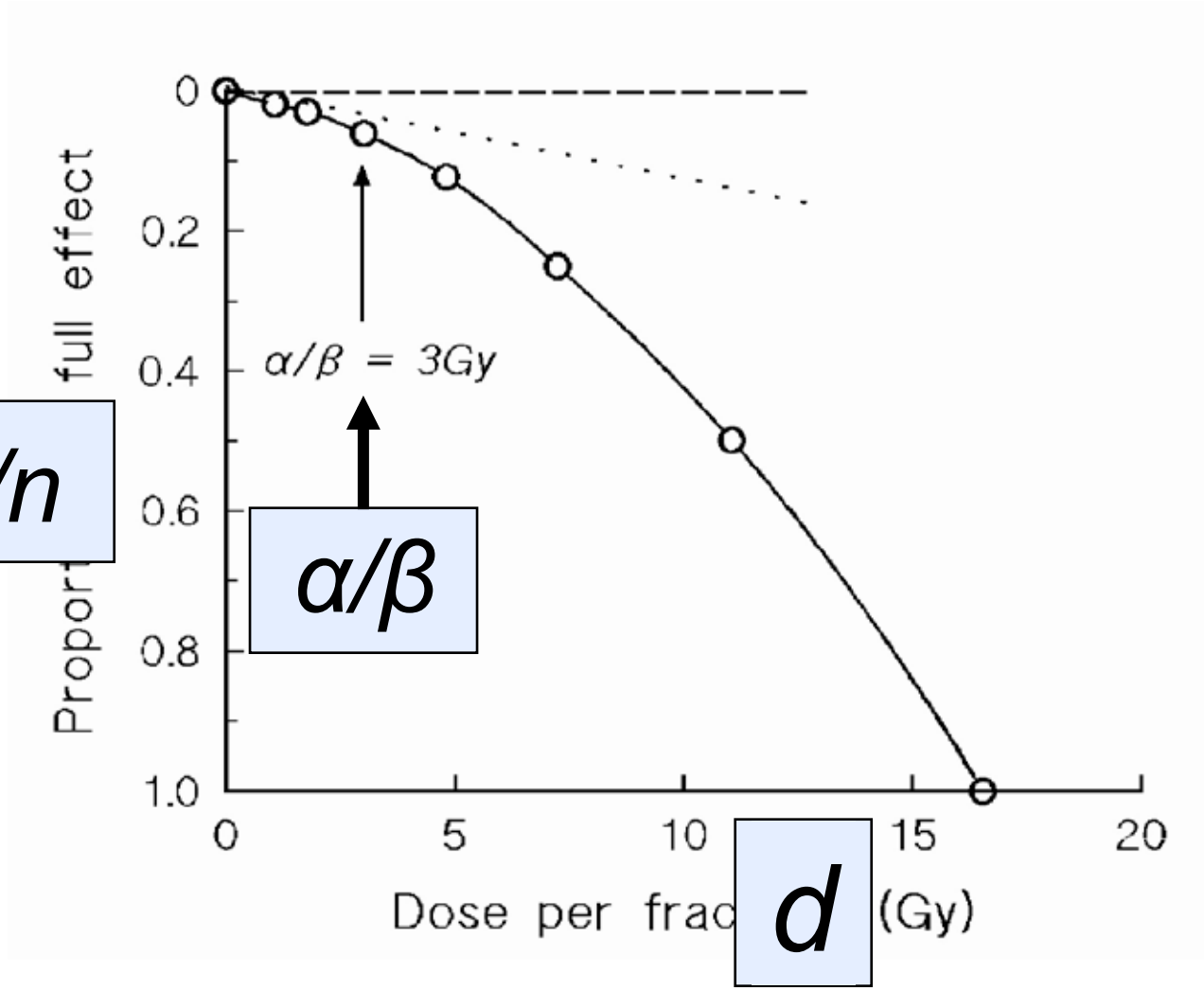


Damage from a single fraction = $\alpha d + \beta d^2$

Total damage from n fractions, $E = n(\alpha d + \beta d^2)$

$E = \alpha D + \beta d$D $\quad E/D = \alpha + \beta d \quad 1/D = (\alpha/E) + (\beta/E)d$

d	*1/n*
16.5	1.0
10.95	.5
7.35	.25
4.88	.125
3.14	.0625
1.90	.03125
1.08	.015625



Damage from a single fraction = $\alpha d + \beta d^2$

Total damage from n fractions, $E = n(\alpha d + \beta d^2)$

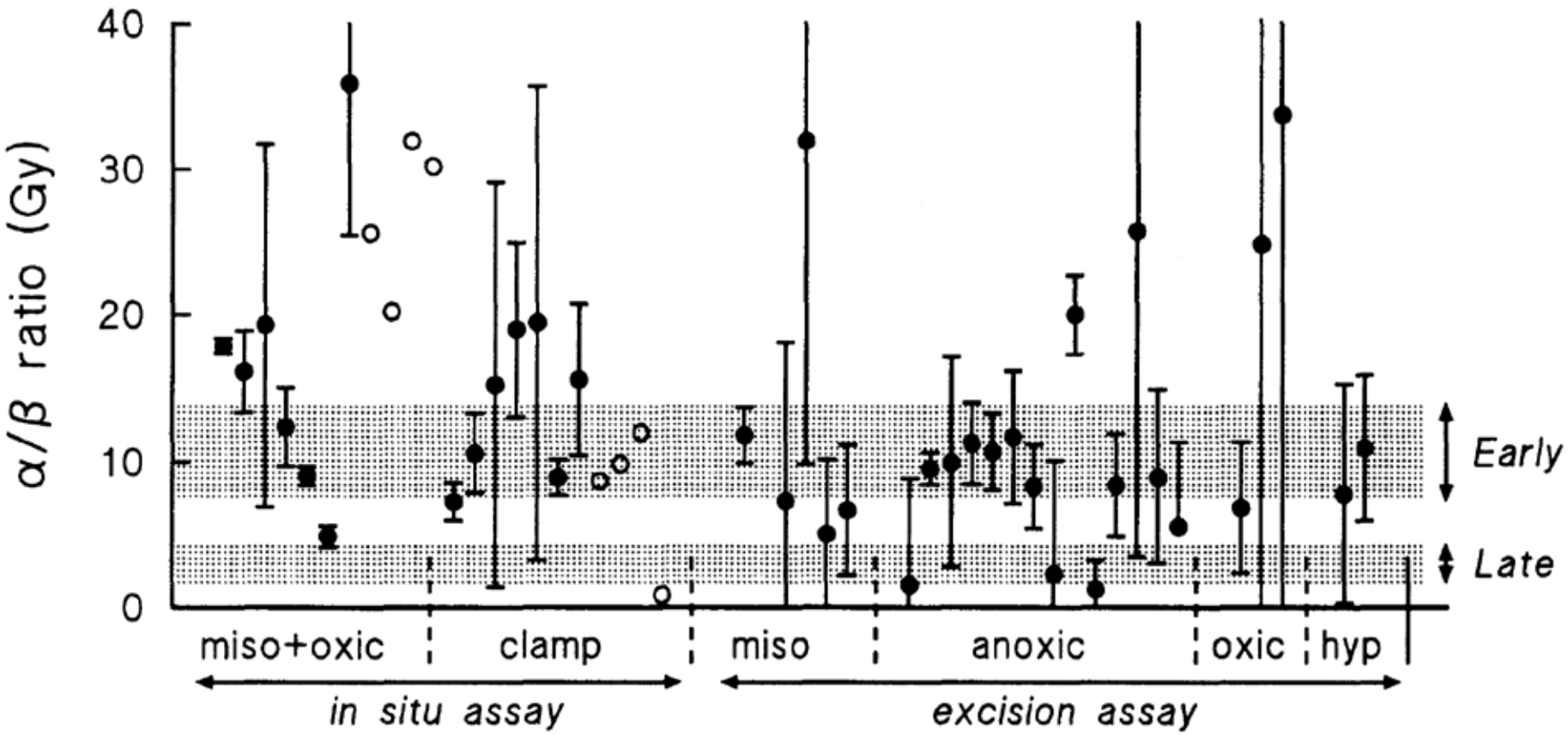
$E/n = \alpha d + \beta d^2$ $\qquad$ $1/n = (\alpha/E)d + (\beta/E)d^2$

Values of α/β for early and late responding normal tissues in animals

Early reactions	α/β	10.6 Gy	Late reactions	α/β	3.0 Gy
Skin			**Spinal cord**		
Desquamation	9.1 - 12.5	Douglas and Fowler (1976)	Cervical	1.8 - 2.7	van der Kogel (1979)
	8.6 - 10.6	Joiner *et al* (1983)	Cervical	1.6 - 1.9	White and Hornsey (1978)
	9 - 12	Moulder and Fischer (1976)	Cervical	1.5 - 2.0	Ang *et al* (1983)
Jejunum			Cervical	2.2 - 3.0	Thames *et al* (1988)
Clones	6.0 - 8.3	Withers *et al* (1976)	Lumbar	3.7 - 4.5	van der Kogel (1979)
	6.6 - 10.7	Thames *et al* (1981)	Lumbar	4.1 - 4.9	White and Hornsey (1978)
Colon				3.8 - 4.1	Leith *et al* (1981)
Clones	8 - 9	Tucker *et al* (1983)		2.3 - 2.9	Amols, Yuhas (quoted by Leith *et al*, 1981)
Weight loss	9 - 13	Terry and Denekamp (1984)			
Testis			**Colon**		
Clones	12 - 13	Thames and Withers (1980)	Weight loss	3.1 - 5.0	Terry and Denekamp (1984)
Mouse lethality			**Kidney**		
30d	7 - 10	Kaplan and Brown (1952)	Rabbit	1.7 - 2.0	Caldwell (1975)
30d	13 - 17	Mole (1957)	Pig	1.7 - 2.0	Hopewell and Wiernik (1977)
30d	11 - 26	Paterson *et al* (1952)	Rats	0.5 - 3.8	van Rongen *et al* (1988)
Tumour bed			Mouse	1.0 - 3.5	Williams and Denekamp
45d	5.6 - 6.8	Begg and Terry (1984)	Mouse	0.9 - 1.8	Stewart *et al* (1984 a)
			Mouse	1.4 - 4.3	Thames *et al* (1988)
			Lung		
			LD_{50}	4.4 - 6.3	Wara *et al* (1973)
			LD_{50}	2.8 - 4.8	Field *et al* (1976)
			LD_{50}	2.0 - 4.2	Travis *et al* (1983)
			Breathing rate	1.9 - 3.1	Parkins and Fowler (1985)
			Bladder		
			Frequency, capacity	5 - 10	Stewart *et al* (1984 b)

Table 8.1, Basic Clinical Radiobiology 4th Ed

α/β for many tumors is ~≥ α/β for early-reacting normal tissues



Fractionation in prostate cancer

Int J Radiation Oncology Biol Phys
2011;79:195-201

CLINICAL INVESTIGATION

CONFIRMATION OF A LOW α/β RATIO FOR PROSTATE CANCER TREATED BY EXTERNAL BEAM RADIATION THERAPY ALONE USING A POST-TREATMENT REPEATED-MEASURES MODEL FOR PSA DYNAMICS

Cécile Proust-Lima, Ph.D.,*† Jeremy M. G. Taylor, Ph.D.,‡§ Solène Sécher, Ph.D.,*†
Howard Sandler, M.D.,‖ Larry Kestin, M.D.,¶ Tom Pickles, M.D.,# Kyoungwha Bae, Ph.D.,**
Roger Allison, F.R.A.N.Z.C.R.,†† and Scott Williams, M.D., F.R.A.N.Z.C.R.‡‡

Mean = 1.55 [CL 0.46 – 4.52]

Results: Adjusted for other factors, total dose of EBRT and sum of squared doses per fraction were associated with long-term rate of change of PSA level ($p = 0.0017$ and $p = 0.0003$, respectively), an increase of each being associated with a lower rate of rise. The α/β ratio was estimated at 1.55 Gy (95% confidence band, 0.46–4.52 Gy). This estimate was robust to adjustment of the linear mixed model.

Fractionation in prostate cancer

1.55 (0.46–4.52) Gy 5093 patients Proust-Lima C
PSA evolution median follow up 4.7 years d/f < **2.8**
6 institutional datasets, no risk-group dependence
Int J Radiat Oncol Biol Phys 2011;79:195-201

1.4 (0.9–2.
Biochem r
7 institutio
Int J Radiat Oncol Biol Phys 2012;82:e17-e24

1.48 Gy

R
d/f < **6.7**
endence

1.86 (0.7–5.1) Gy 274 patients Leborgne F
Biochem disease free survival at 5 years d/f < **3.15**
Single institution, no risk-group dependence
Int J Radiat Oncol Biol Phys 2012;82:1200-7

Fractionation in breast cancer

Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: long-term results of a randomised trial

J Roger Owen, Anita Ashton, Judith M Bliss, Janis Homewood, Caroline Harper, Jane Hanson, Joanne Haviland, Soren M Bentzen, John R Yarnold

***Lancet Oncol* 2006: 7: 467–71**

Summary

Background Standard curative schedules of radiotherapy to the breast deliver 25 fractions of 2·0 Gy over 5 weeks. In a randomised trial, we tested whether fewer, larger fractions were at least as safe and as effective as standard regimens. In this analysis, we assessed the long-term results of tumour control in the same population.

Methods I
maximum
to receive
given over
elsewhere.
appearanc

Findings After a median follow-up of 9·7 years (IQR 7·8–11·8) for the 838 (95%) patients who survived, the risk of ipsilateral tumour relapse after 10 years was 12·1% (95% CI 8·8–15·5) in the 50 Gy group, 14·8% (11·2–18·3) in the 39 Gy group, and 9·6% (6·7–12·6) in the 42·9 Gy group (difference between 39 Gy and 42·9 Gy groups, χ^2 test, p=0·027). The sensitivity of breast cancer to dose per fraction was estimated to be 4·0 Gy (95% CI 1·0–7·8), similar to that estimated for the late adverse effects in healthy tissue from breast radiotherapy.

Interpretation Breast cancer tissue is probably just as sensitive to fraction size as dose-limiting healthy tissues. If this finding is confirmed, radiotherapy schedules can be greatly simplified by the delivery of fewer, larger fractions without compromising effectiveness or safety, and possibly improving both.

Mean = 4.0 [CL 1.0 – 7.8]

Published Online May 17, 2006
DOI:10.1016/S1470-2045(06)
70699-4

nd Reaction

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(Prof S M Bentzen PhD)

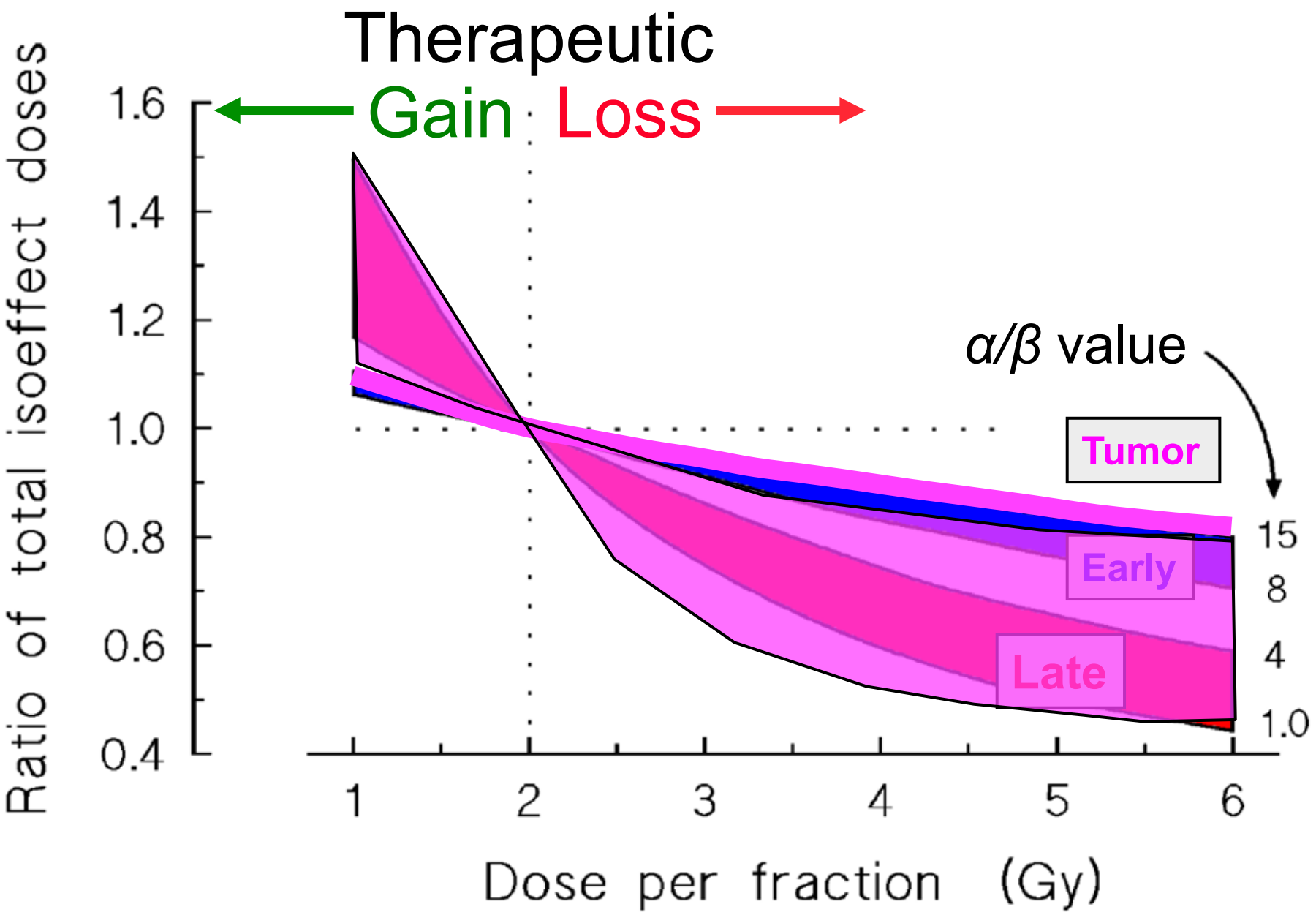
Table 9.1: *α/β* values for human normal tissues and tumors

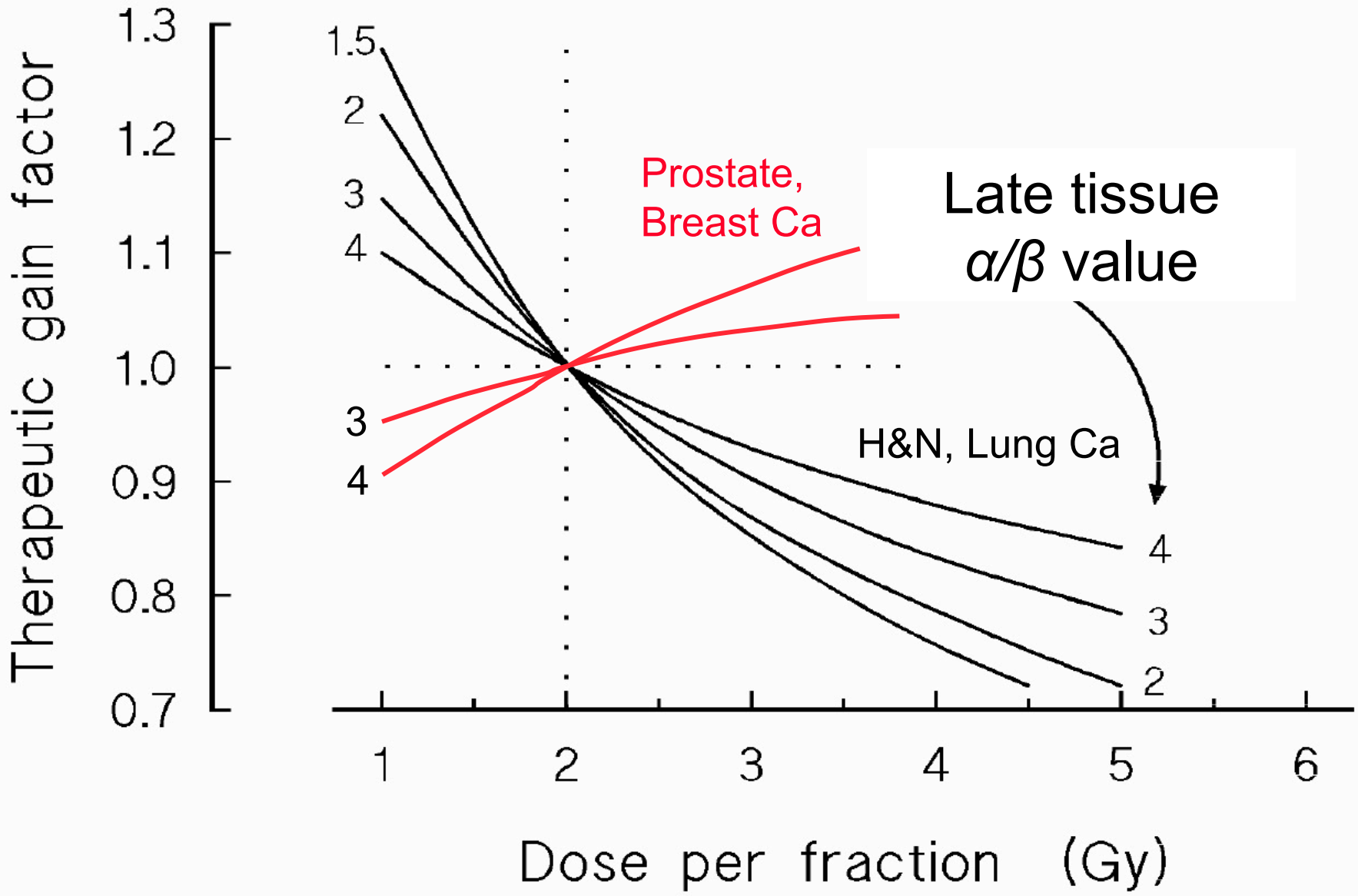
Tissue/organ	Endpoint	α/β(Gy)	95% CL (Gy)	Source
Early reactions				
Skin	Erythema	8.8	6.9; 11.6	Turesson and Thames (1989)
	Erythema	12.3	1.8; 22.8	Bentzen et al. (1988)
	Dry desquamation	≈ 8	N/A	Chogule and Supe (1993)
	Desquamation	11.2	8.5; 17.6	Turesson and Thames (1989)
C				
L				
S				
S				)
B				)
M				
N				
S				
E				
B				
B				
L				
H				
H				
S				
C				
Tumours				
Head and neck				
	Various	10.5	6.5; 29	Stuschke and Thames (1999)
	Larynx	14.5	4.9; 24	Rezvani et al. (1993)
	Vocal cord	≈ 13	'wide'	Robertson et al. (1993)
	Buccal mucosa	6.6	2.9; ∞	Maciejewski et al. (1989)
	Tonsil	7.2	3.6; ∞	Maciejewski et al. (1989)
	Nasopharynx	16	–11; 43	Lee et al. (1995)
Skin		8.5	4.5; 11.3	Trott et al. (1984)
Prostate		1.1	–3.3; 5.6	Bentzen and Ritter (2005)
Breast		4.6	1.1; 8.1	START Trialists Group (2008)
Oesophagus		4.9	1.5; 17	Geh et al. (2006)
Melanoma		0.6	–1.1; 2.5	Bentzen et al. (1989)
Liposarcoma		0.4	–1.4; 5.4	Thames and Suit (1986)

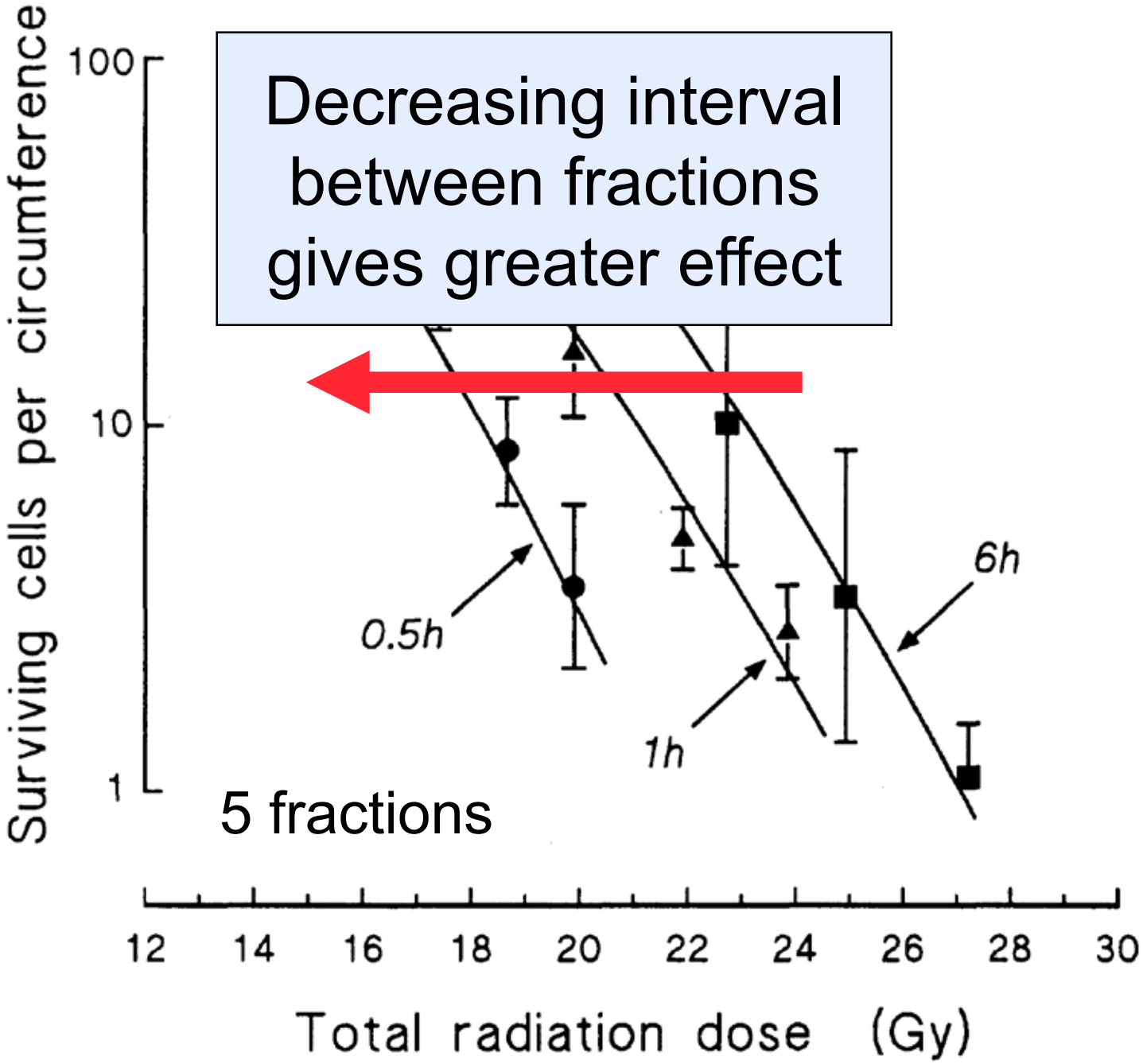
Mean Late 2.9

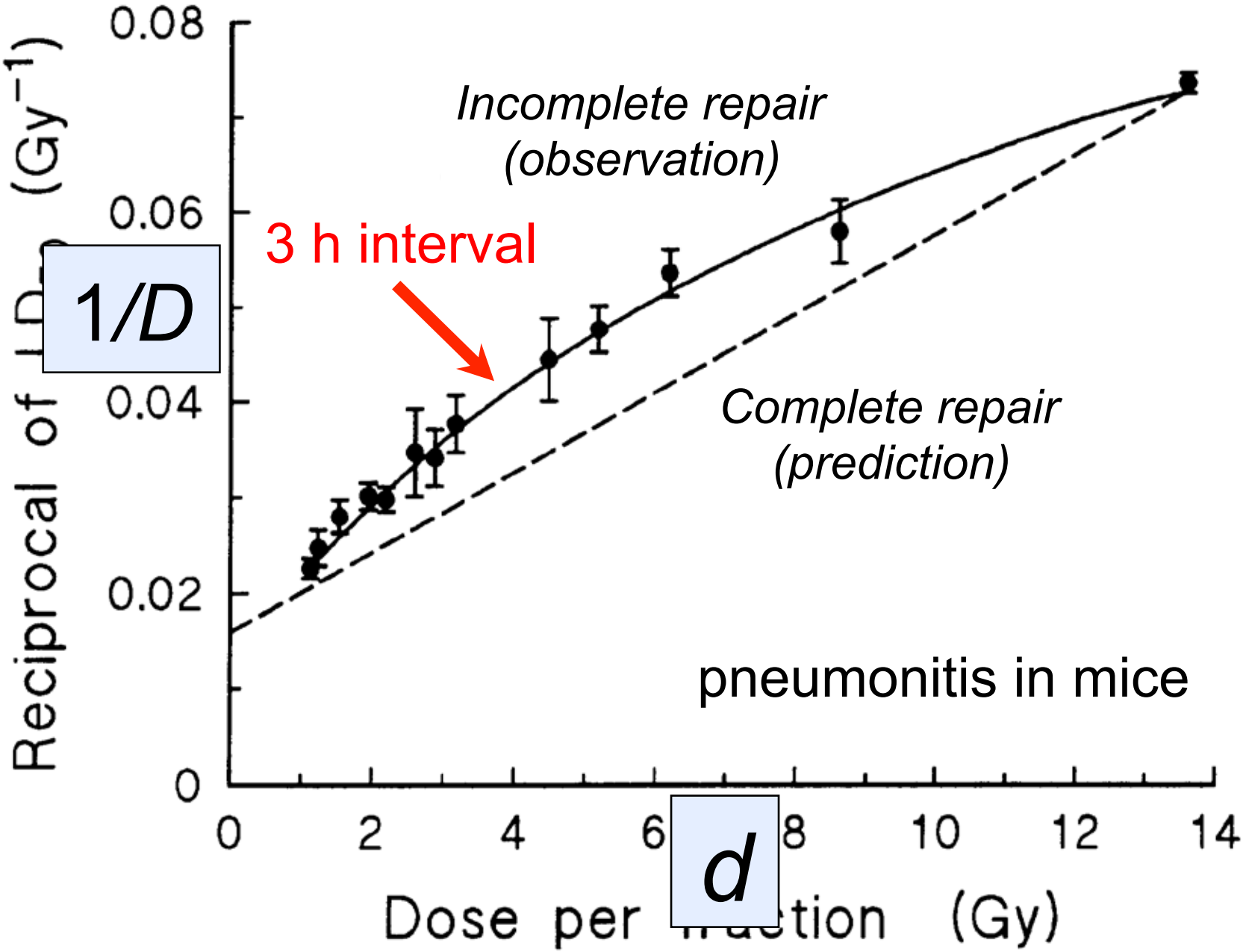
Mean Early 10.6

H&N, Lung tumors ***high***,
Breast, Prostate tumors ***low***


Therapeutic
Gain
Loss
Ratio of total isoeffect doses
1.6
1.4
1.2
1.0
0.8
0.6
0.4
α/β value
Tumor
Early
Late
15
8
4
1.0
1
2
3
4
5
6
Dose per fraction (Gy)


Therapeutic gain factor
1.3
1.2
1.1
1.0
0.9
0.8
0.7
1.5
2
3
4
3
4
Prostate,
Breast Ca
Late tissue
α/β value
H&N, Lung Ca
4
3
2
1
2
3
4
5
6
Dose per fraction (Gy)


Decreasing interval between fractions gives greater effect
Surviving cells per circumference
100
10
1
0.5h
1h
6h
5 fractions
12
14
16
18
20
22
24
26
28
30
Total radiation dose (Gy)


0.08
0.06
0.04
0.02
0
Reciprocal of LD (Gy^{-1})
1/D
3 h interval
Incomplete repair
(observation)
Complete repair
(prediction)
pneumonitis in mice
0
2
4
6
8
10
12
14
d
Dose per fraction (Gy)

Basic LQ equation:

$$-\log_e SF_n = E = n\left(\alpha d + \beta d^2\right) = D\left(\alpha + \beta d\right)$$

LQ equation with incomplete repair:

$$E = D\left(\alpha + \beta d\left(1 + H_m\right)\right)$$

m is the number of fractions per day

H_m varies from:

0 (“full repair”) to m-1 (“no repair”)

Incomplete repair factors: fractionated irradiation (H_m factors)

Repair half-time (hours)	Interval for m = 2 fractions per day						Interval for m = 3 fractions per day				
	3	4	5	6	8	10	3	4	5	6	8
0.50	0.016	0.004	0.001	0.000	0.000	0.000	0.021	0.005	0.001	0.000	0.000
0.75	0.063	0.025	0.010	0.004	0.001	0.000	0.086	0.034	0.013	0.005	0.001
1.00	0.125	0.063	0.031	0.016	0.004	0.000	0.177	0.086	0.042	0.021	0.005
1.25	0.190	0.109	0.063	0.036	0.012	0.004	0.277	0.153	0.086	0.049	0.016
1.50	0.250	0.158	0.099	0.063	0.025	0.010	0.375	0.227	0.139	0.086	0.034
2.00	0.354	0.250	0.177	0.125	0.063	0.031	0.555	0.375	0.257	0.177	0.086
2.50	0.435	0.330	0.250	0.190	0.109	0.063	0.707	0.512	0.375	0.277	0.153
3.00	0.500	0.397	0.315	0.250	0.158	0.099	0.833	0.634	0.486	0.375	0.227
4.00	0.595	0.500	0.420	0.354	0.250	0.177	1.029	0.833	0.678	0.555	0.375
5.00	0.660	0.574	0.500	0.435	0.330	0.250	1.170	0.986	0.833	0.707	0.512

Table 8.2

Half times for recovery ($T_{1/2}$) in normal tissues

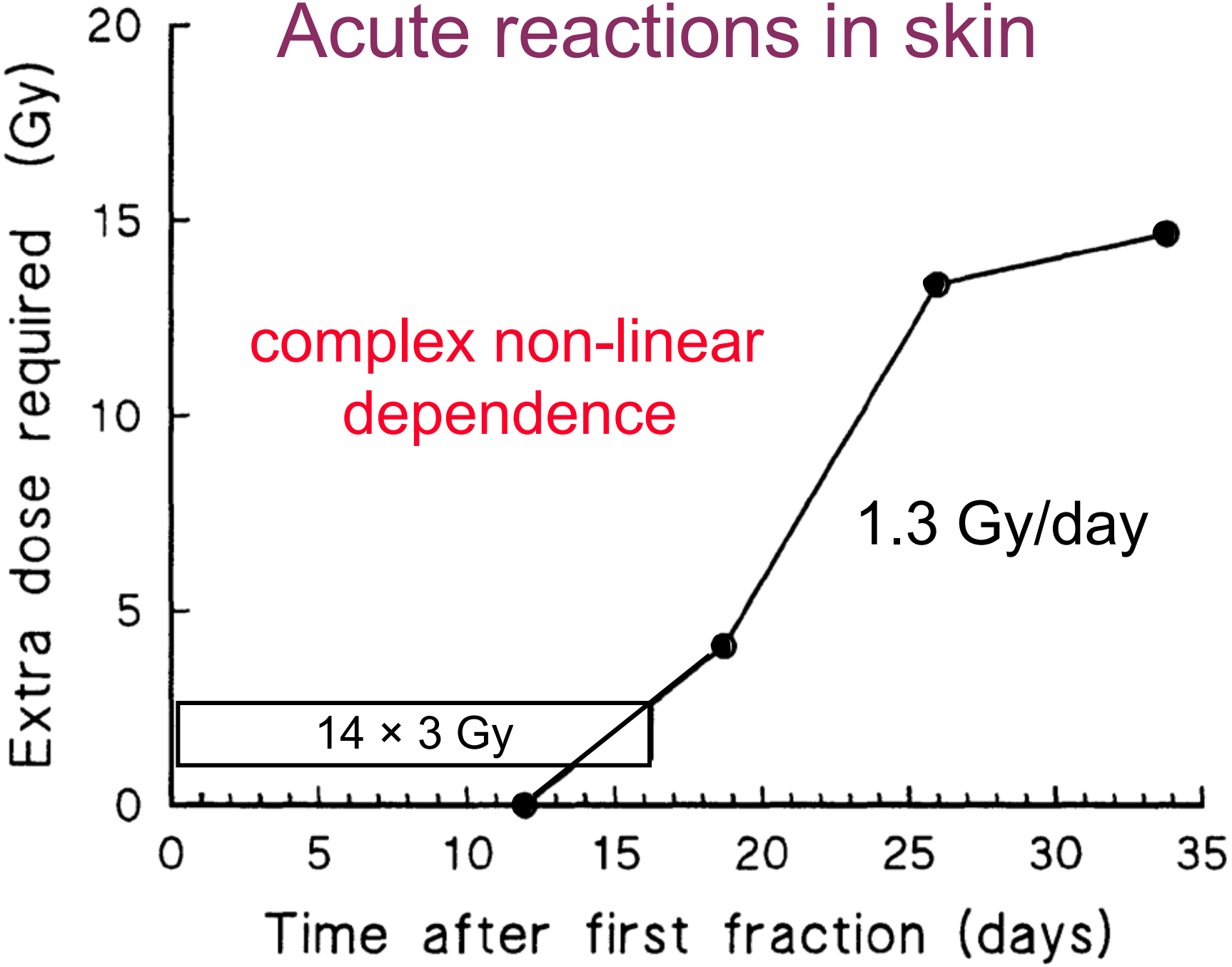
Tissue	Species	Dose delivery#	$T_{1/2}$ (hours)	Source
Haemopoietic	Mouse	CLDR	0.3	Thames *et al.* (1984)
Spermatogonia	Mouse	CLDR	0.3–0.4	Delic *et al.* (1987)
Jejunum	Mouse	F	0.45	Thames *et al.* (1984)
	Mouse	CLDR	0.2–0.7	Dale *et al.* (1988)
Colon (acute injury)	Mouse	F	0.8	Thames *et al.* (1984)
	Rat	F	1.5	Sassy *et al.* (1988)
Lip mucosa	Mouse	F	0.8	Ang *et al.* (1985)
	Mouse	CLDR	0.8	Scalliet *et al.* (1987)
	Mouse	FLDR	0.6	Stüben *et al.* (1991)
Tongue epithelium	Mouse	F	0.75	Dörr *et al.* (1993)
Skin (acute injury)	Mouse	F	1.5	Rojas *et al.* (1991)
	Mouse	CLDR	1.0	Joiner *et al.* (unpublished)
	Pig	F	0.4 + 1.2*	van den Aardweg and Hopewell (1992)
	Pig	F	0.2 + 6.6*	Millar *et al.* (1996)
Lung	Mouse	F	0.4 + 4.0*	van Rongen *et al.* (1993)
	Mouse	CLDR	0.85	Down *et al.* (1986)
	Rat	FLDR	1.0	van Rongen (1989)
Spinal cord	Rat	F	0.7 + 3.8*	Ang *et al.* (1992)
	Rat	CLDR	1.4	Scalliet *et al.* (1989)
	Rat	CLDR	1.43	Pop *et al.* (1996)
Kidney	Mouse	F	1.3	Joiner *et al.* (1993)
	Mouse	F	0.2 + 5.0	Millar *et al.* (1994)
	Rat	F	1.6–2.1	van Rongen *et al.* (1990)
Rectum (late injury)	Rat	CLDR	1.2	Kiszel *et al.* (1985)
Heart	Rat	F	>3	Schultz-Hector *et al.* (1992)

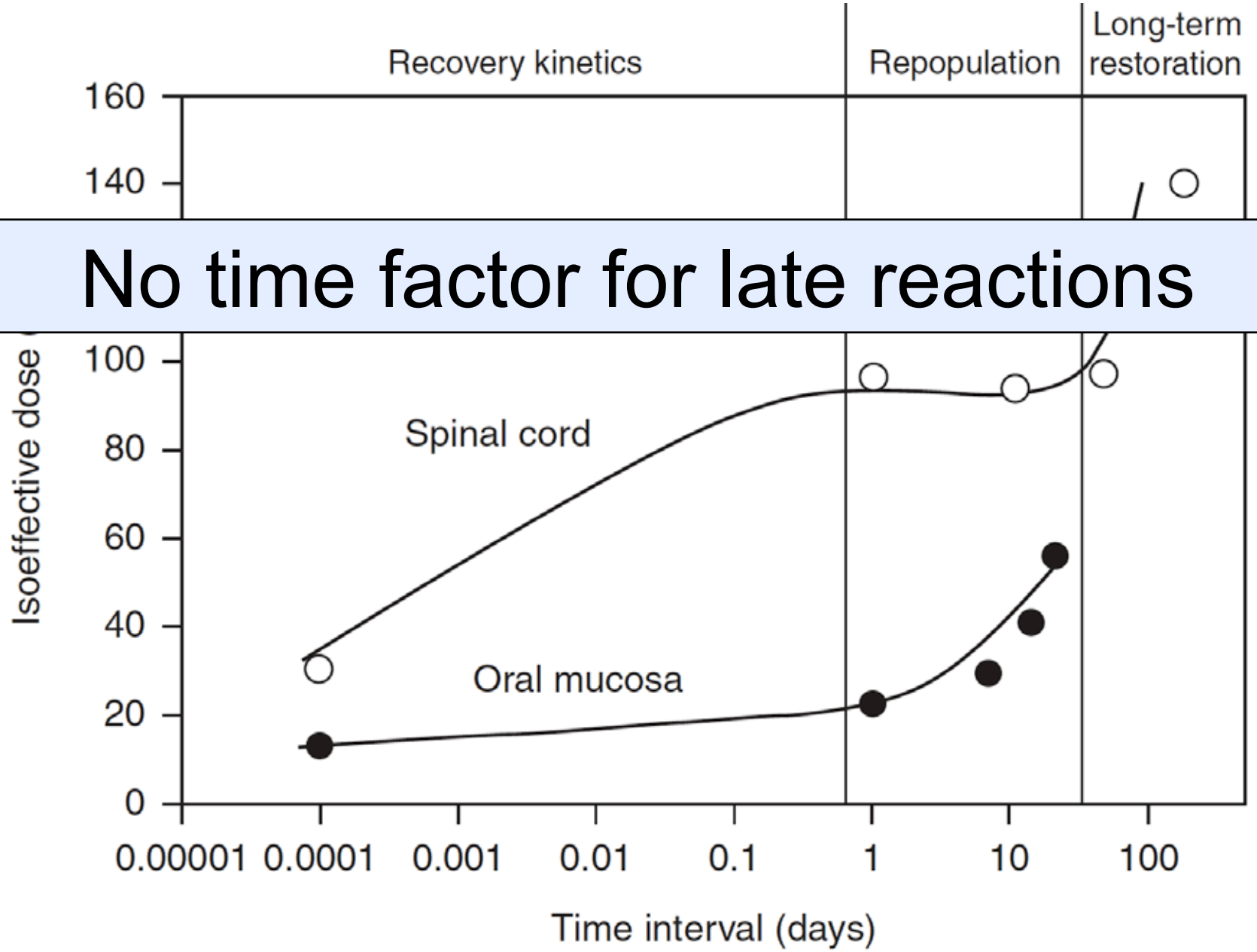
* Two components of repair with different half-times.

continuous low dose rate; F, acute dose fractions; FLDR, fractionated low dose rate.

Tables 8.4, 9.2

Acute reactions in skin





No time factor for late reactions

Figure 11.1

Dörr & Kummermehr 1990, Dörr et al 1993, Ruifrok et al 1992, Landuyt et al 1997

Do not put proliferation factors in your LQ calculations.

Consider the effect of proliferation separately from changes in dose per fraction and interfraction interval.

This afternoon…
We do calculations!

Molecular basis of the DNA damage response

Marianne Koritzinsky

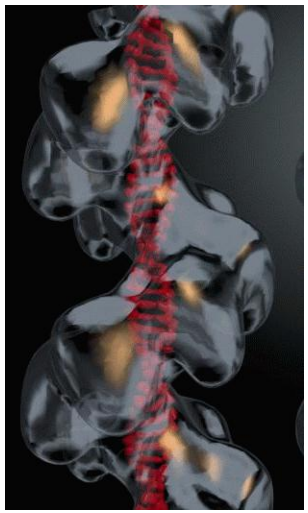
Princess Margaret Cancer Centre
Toronto, Canada
mazinsky@gmail.com

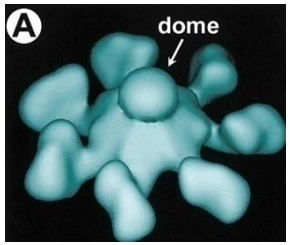
Initial cellular responses to radiation

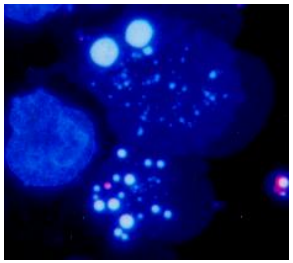
Sensors of damage

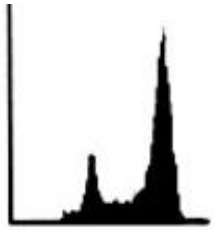
Biological Pathways

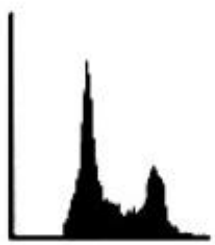
DNA Repair	Early Apoptosis	Cell cycle checkpoints	Gene expression

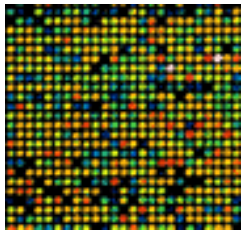


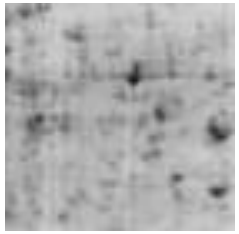


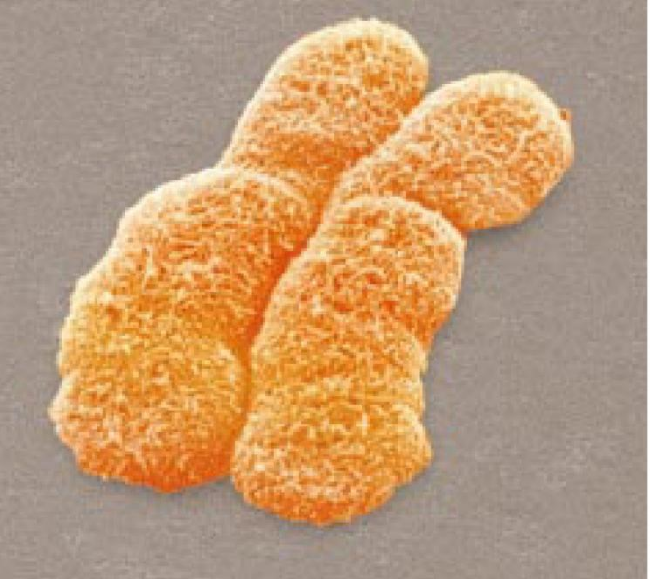












DNA

transcription translation

DNA → **RNA** → **Protein**

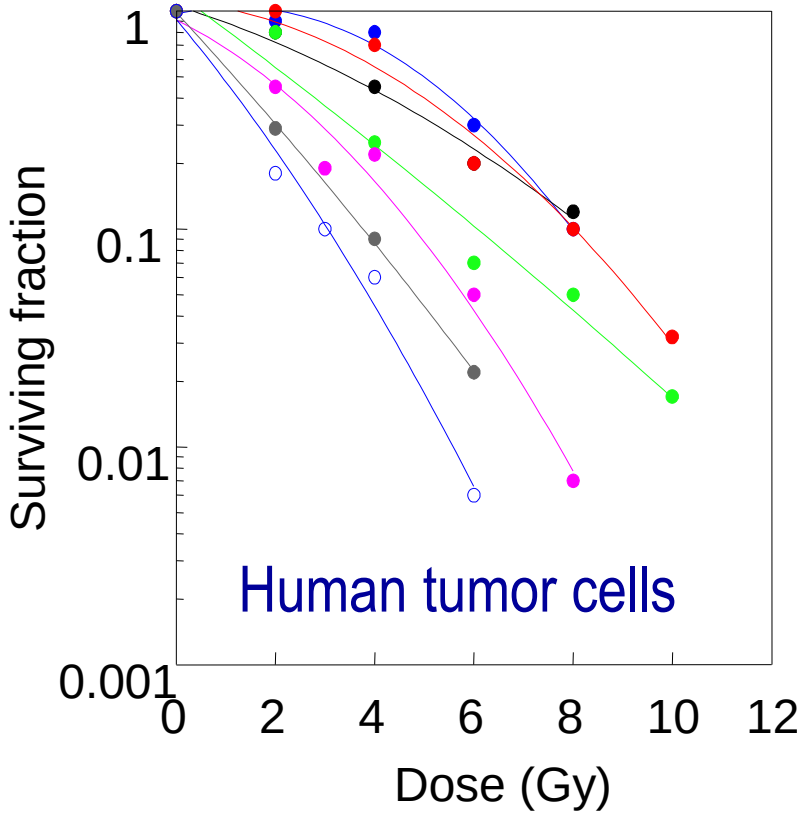
- Only molecule which is repaired

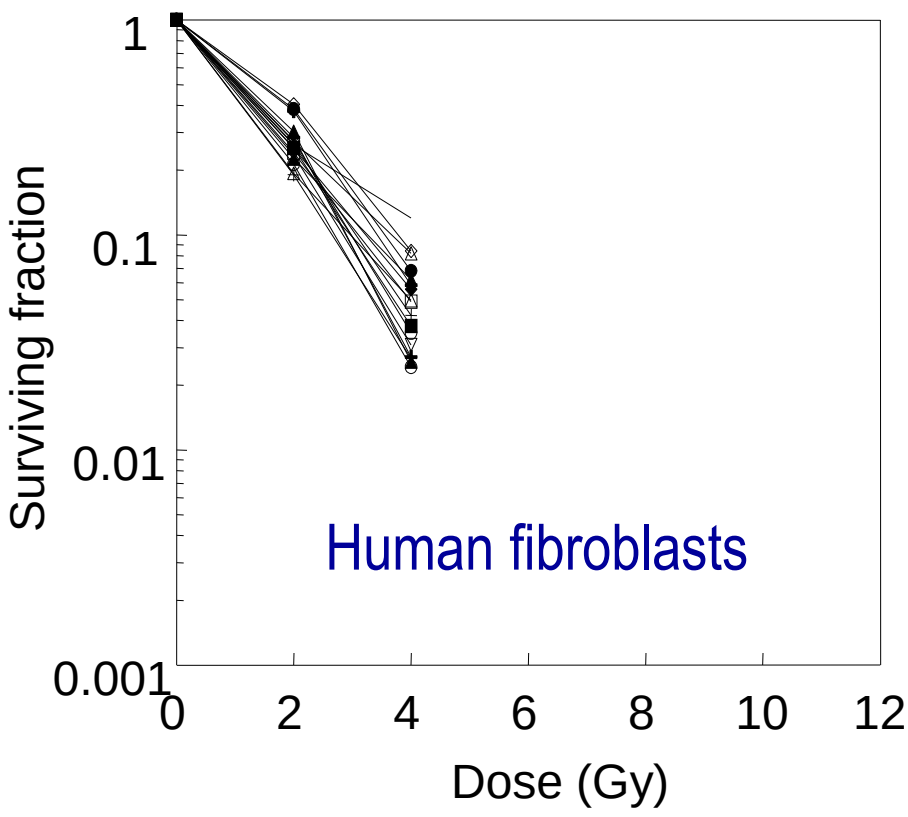
Endogenous DNA damage

- In every human cell per day:
  - 50,000 SSB
  - 10,000 depurinations
  - 600 deaminations
  - 2000 oxidative base damages
  - 5000 alkylation damage
  - 10 cross links
  - 10 DSB's

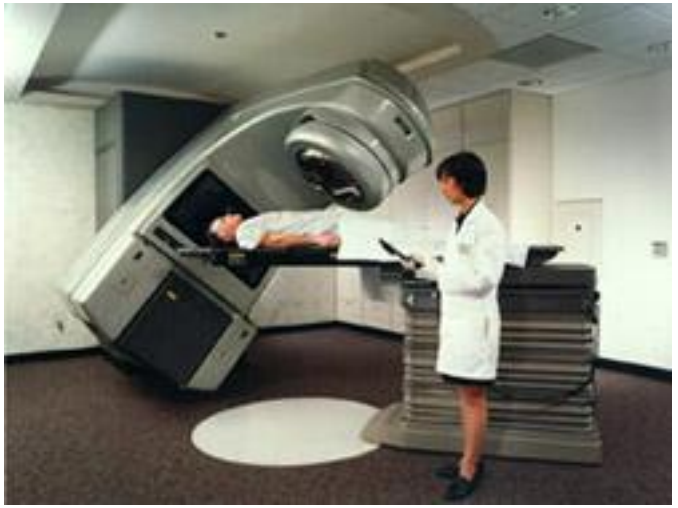
DNA Repair and Cancer

1. Most anticancer agents work by damaging DNA
2. Changes in DNA repair influence radiosensitivity





Ionizing Radiation Damage



Primary target is the DNA

1Gy of low LET Xrays produces:

1000	single strand breaks
40	double strand breaks
1000	altered bases

Comparison between IR and UV

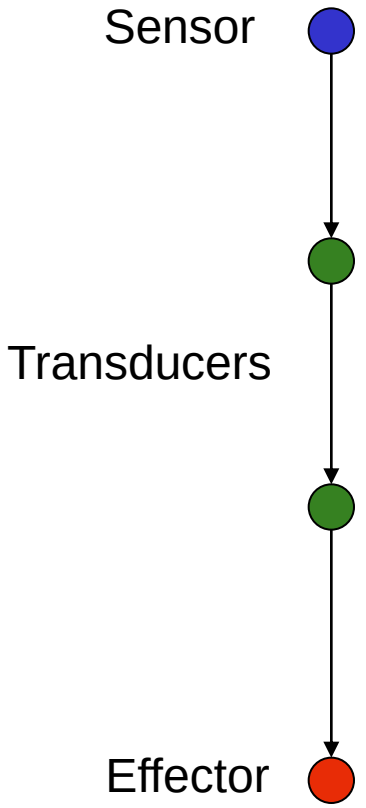
1000000 dimers = 40 DSBs

DNA Damage Response

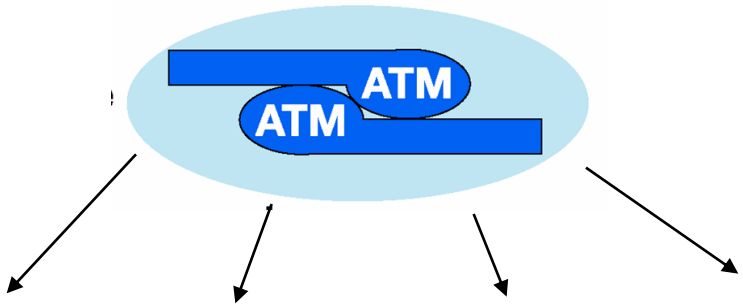
1) Damage Recognition

2) Recruitment of other proteins to the damage

3) Death, Checkpoints, and Repair

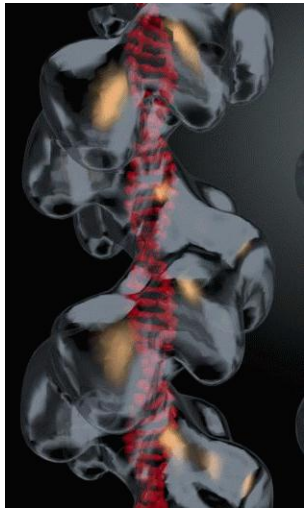


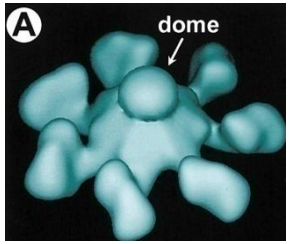
ATM – a key player in DNA damage response

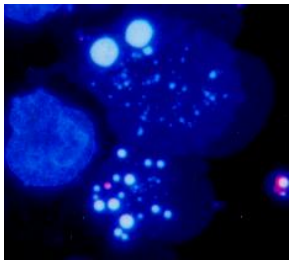


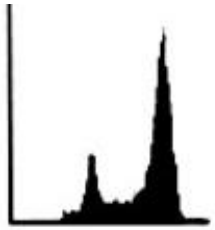
Biological Pathways

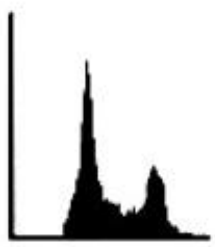
DNA Repair	Early Apoptosis	Cell cycle checkpoints	Gene expression

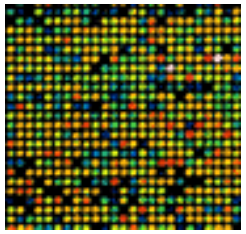


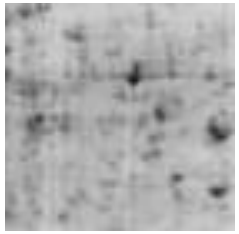






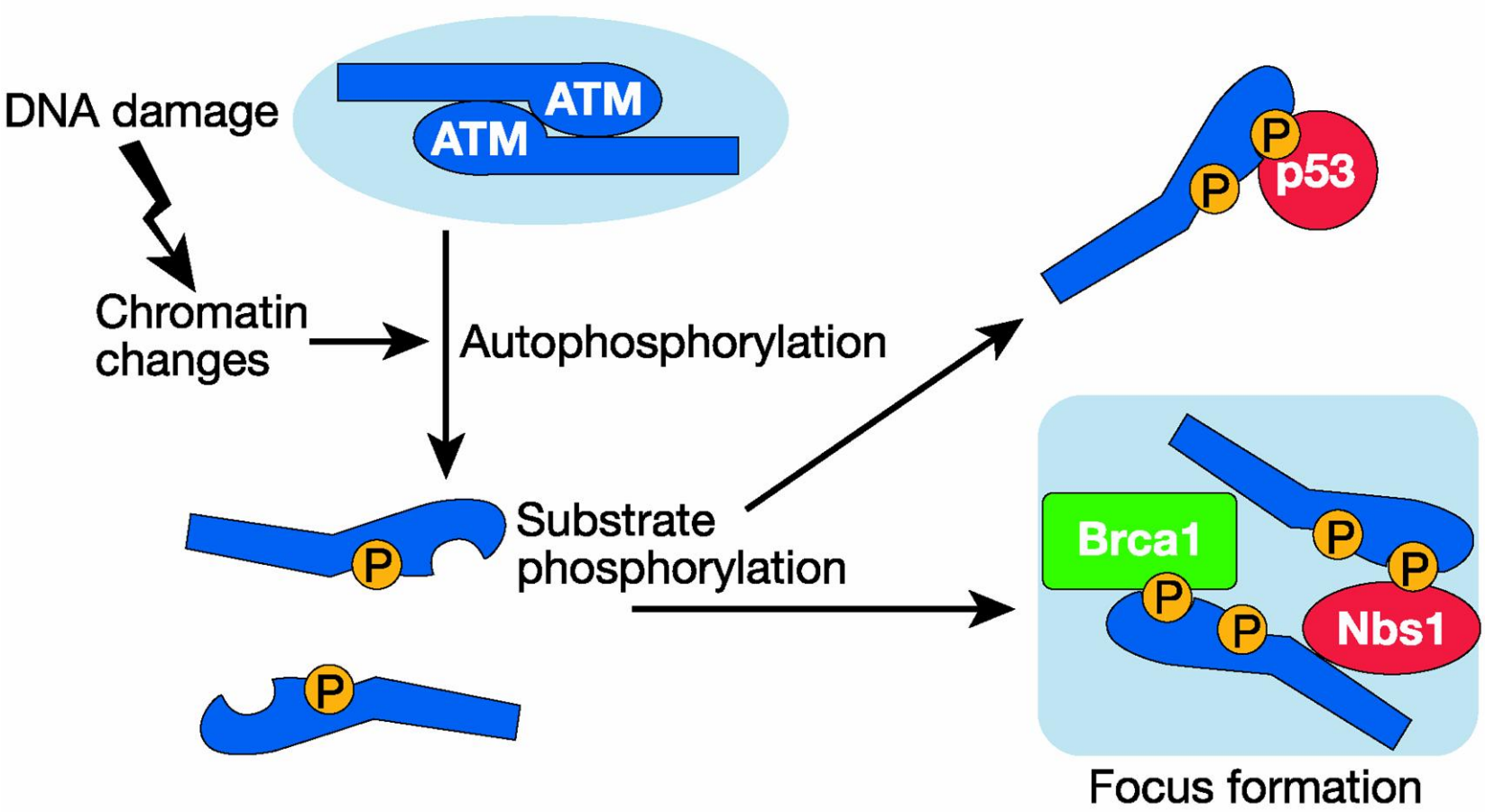




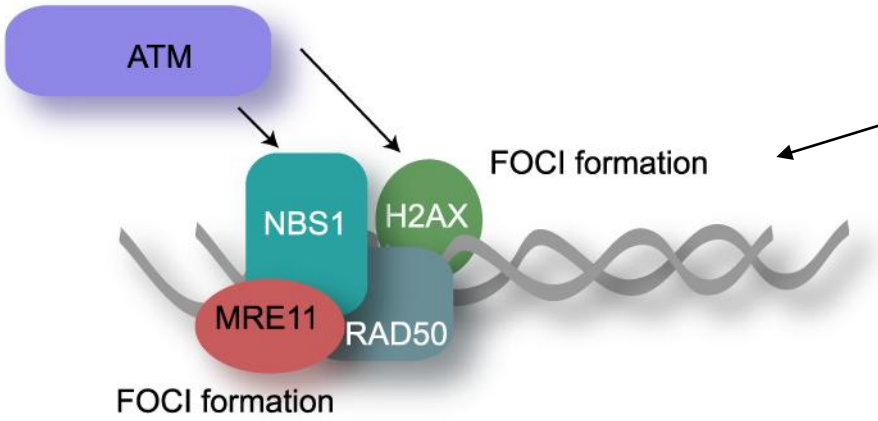


ATM activation

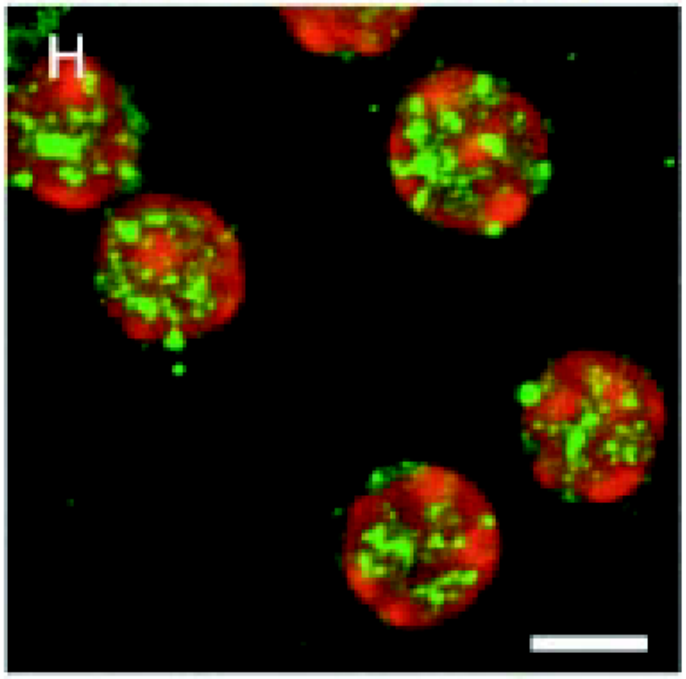
Activation of ATM – Kastan, Nature, 2003



ATM and MRN Sense DSBs



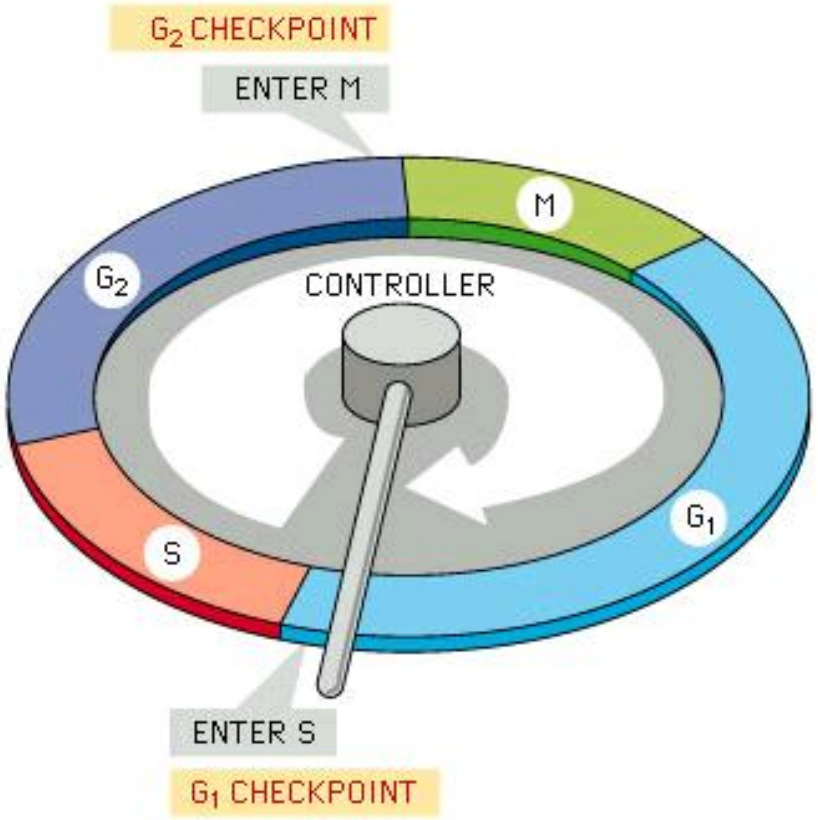
NBS/MRE11/RAD50 plays a role in sensing DSB



H2AX is phosphorylated at every DSB

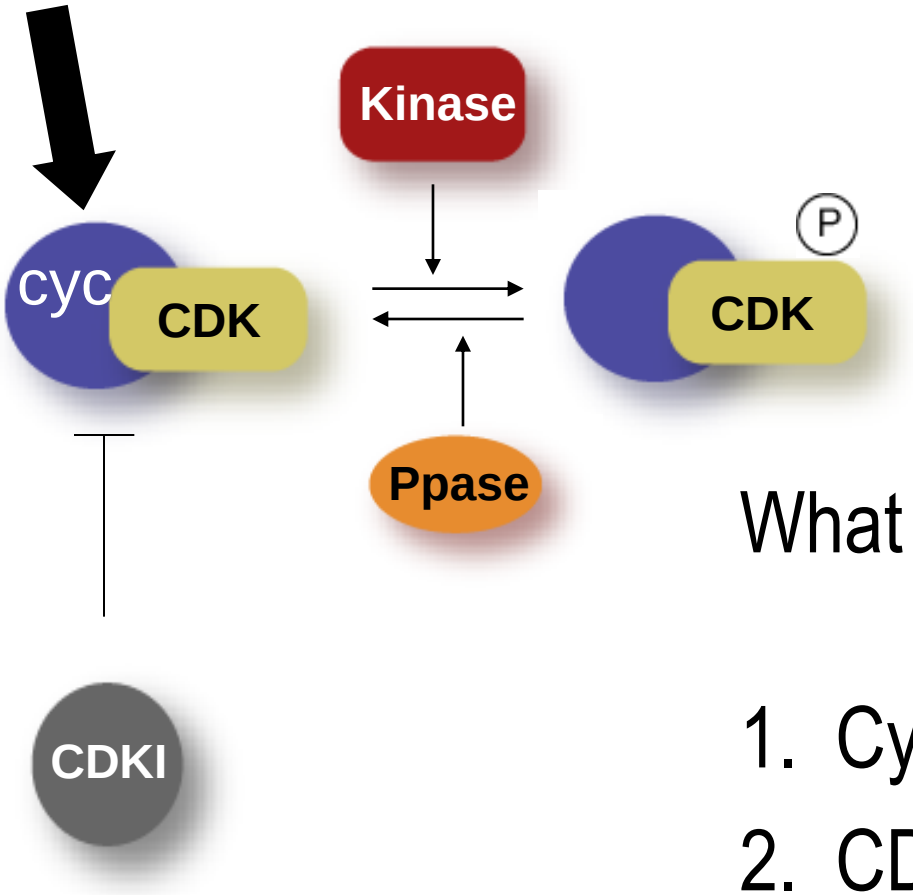
Checkpoints

Checkpoints occur at several points in the cell cycle



DNA damage?
Nutrients?
Growth factors?

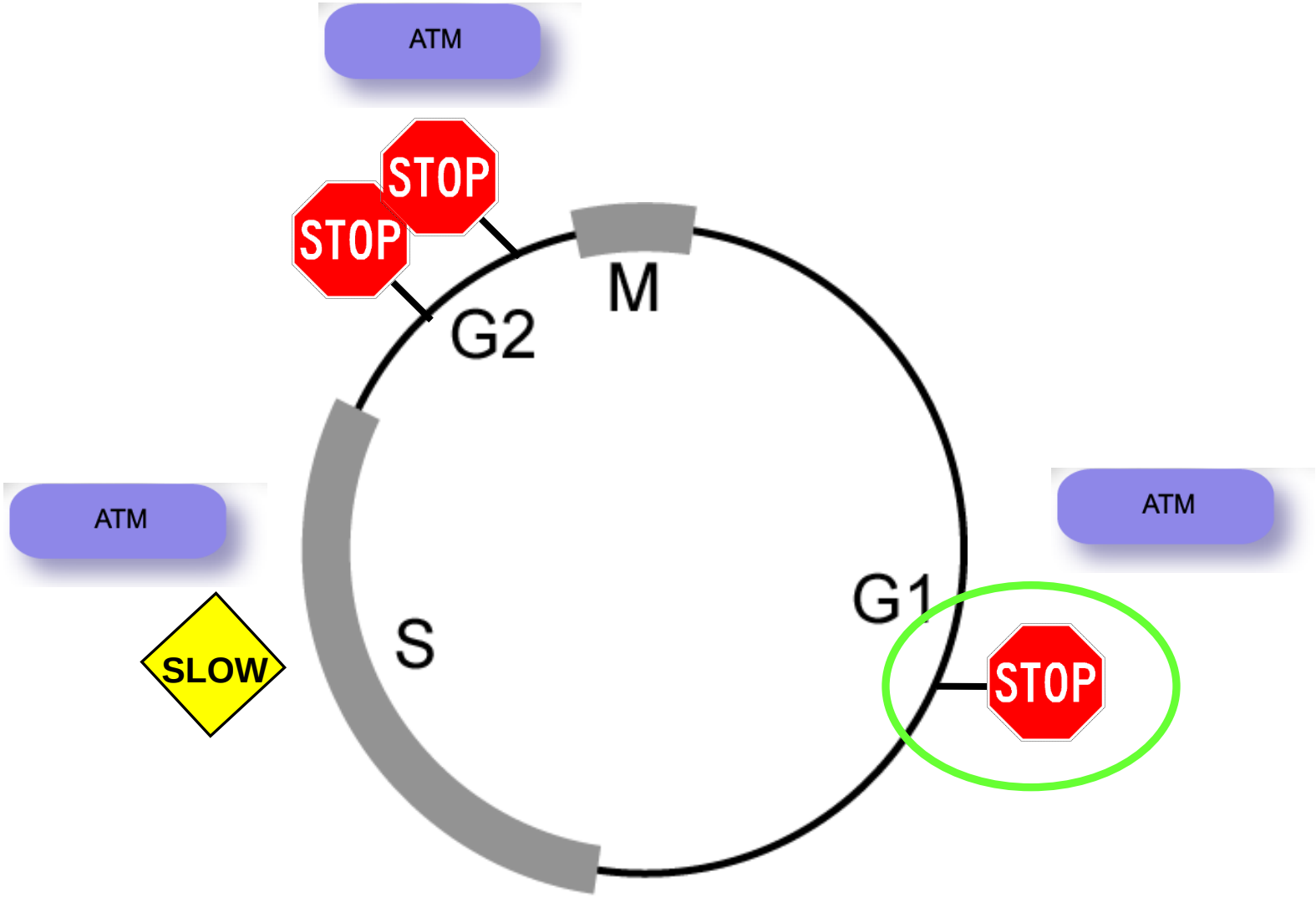
Regulation of the cell cycle - CDK



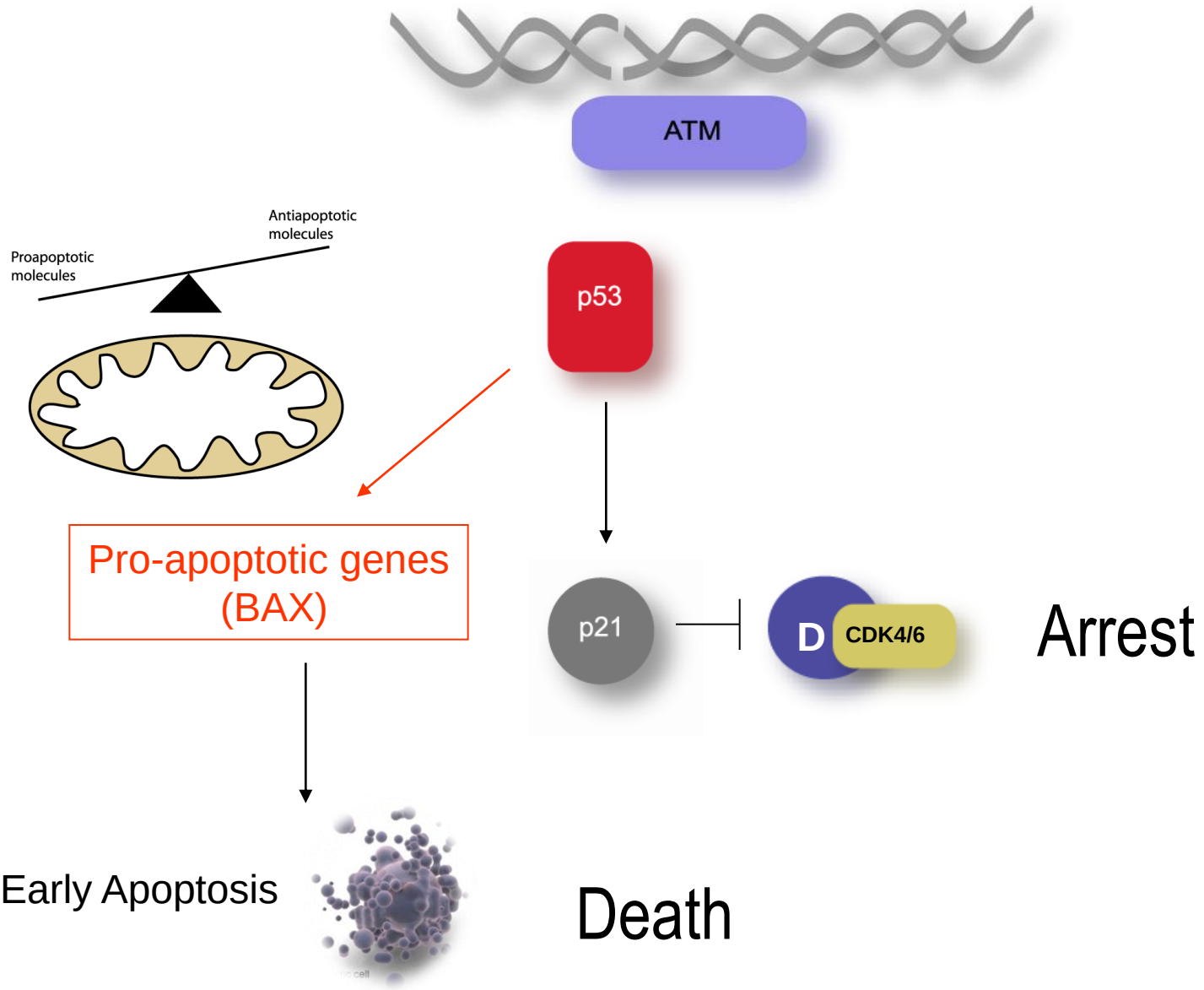
What regulates CDK activity?

1. Cyclin levels
2. CDK phosphorylation
3. CDK inhibitors

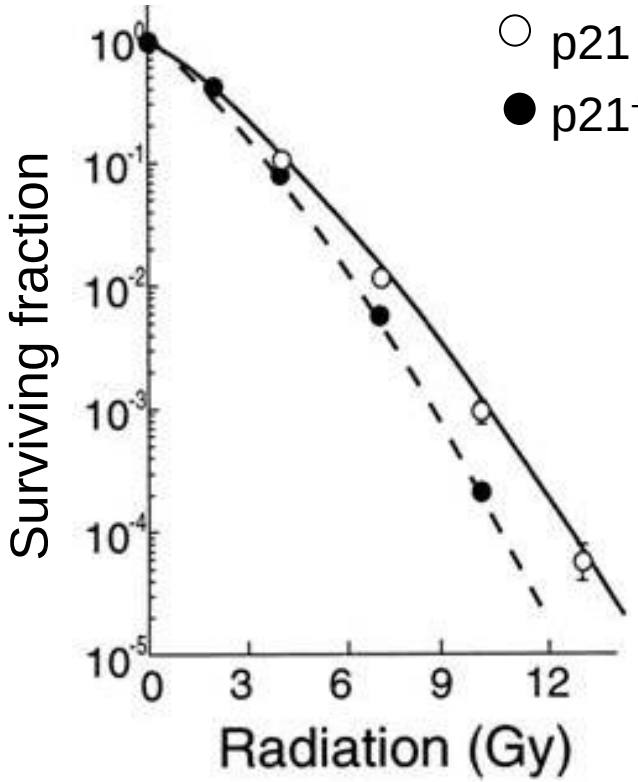
IR induces 4 distinct checkpoints

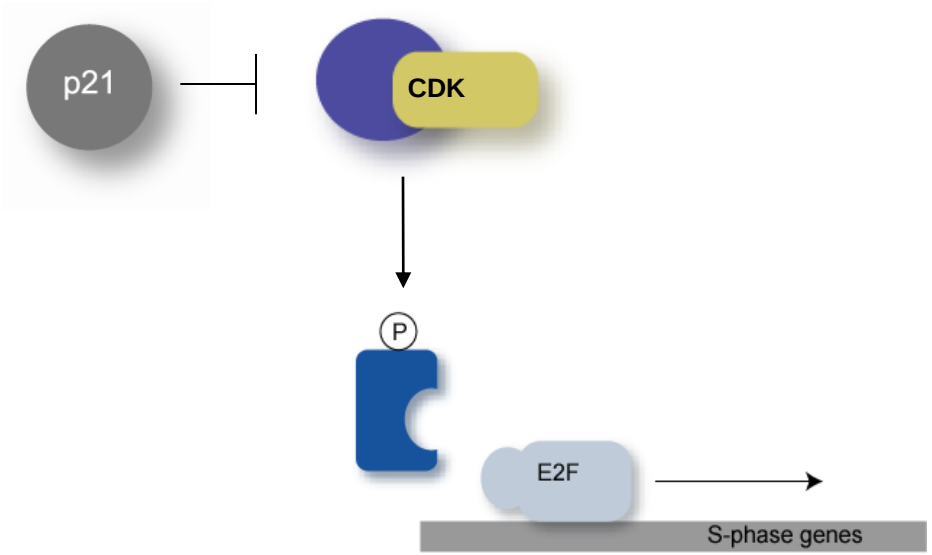


G1 checkpoint and early apoptosis



G1 checkpoint and radiosensitivity



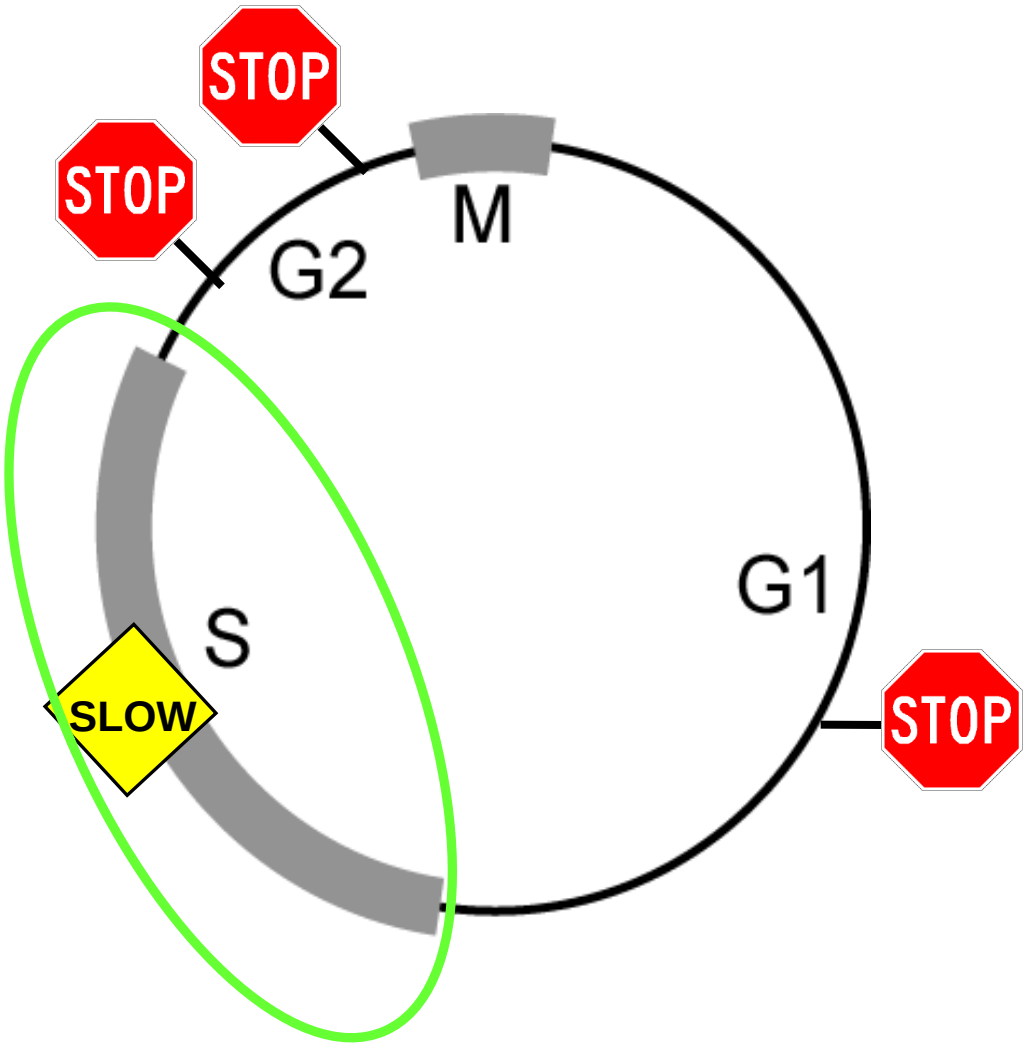


Wouters et al., Can.Res. 57, 1997

G1 checkpoint

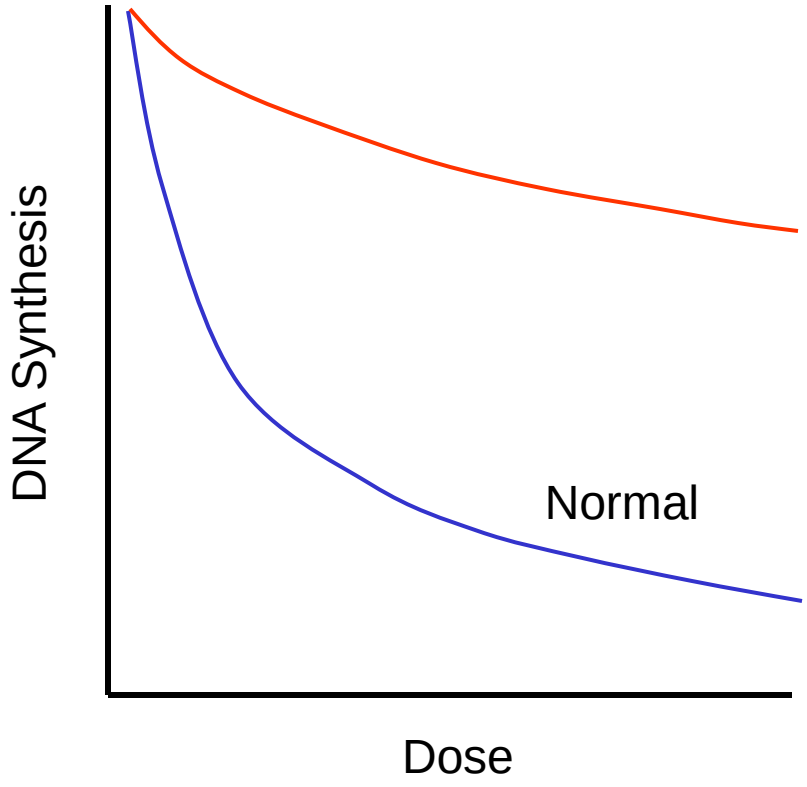
- Not important for intrinsic radiosensitivity
  - To single doses!
- Usually altered in cancer
  - Important for avoiding mutations
  - Tumor cells and normal cells proliferate differently after IR
- May lead to a permanent G1 arrest in normal cells (senescence/differentiation)
  - Normal tissue tolerance

IR induces 4 distinct checkpoints

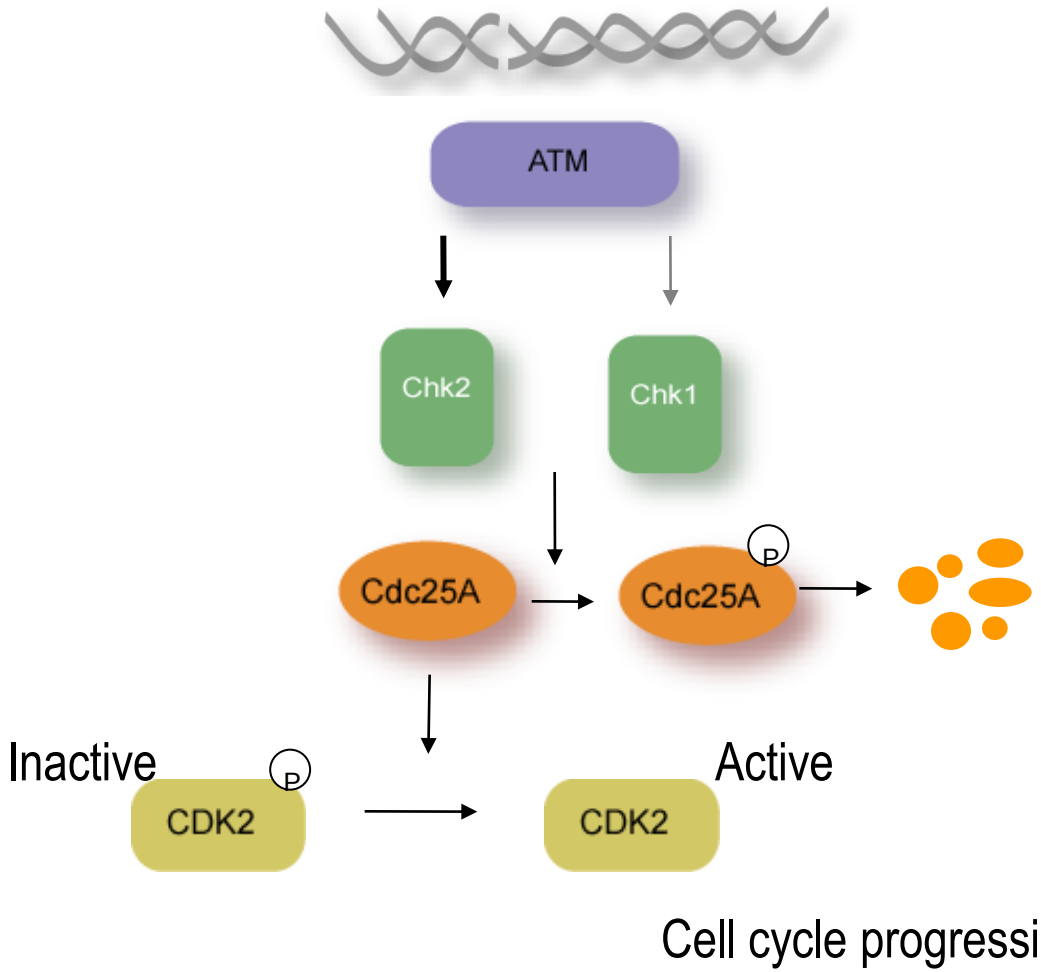


S-phase checkpoint

- Radioresistant DNA synthesis (RDS)



S-phase checkpoint



Sensor:
ATM

Transducers:
Chk2 (Chk1)

Effector:
Cdc25a

S-phase checkpoint

- Not important for intrinsic radiosensitivity
- Often altered in cancer
  - Important for avoiding mutations
  - Tumor cells and normal cells proliferate differently after IR
- May affect the next checkpoint in G2

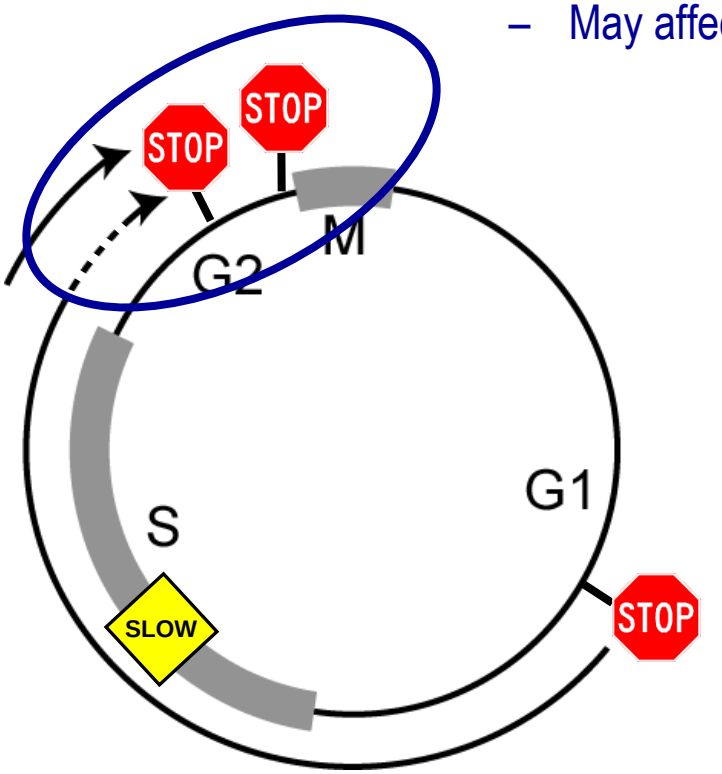
2 Distinct G2 checkpoints induced by IR

Early

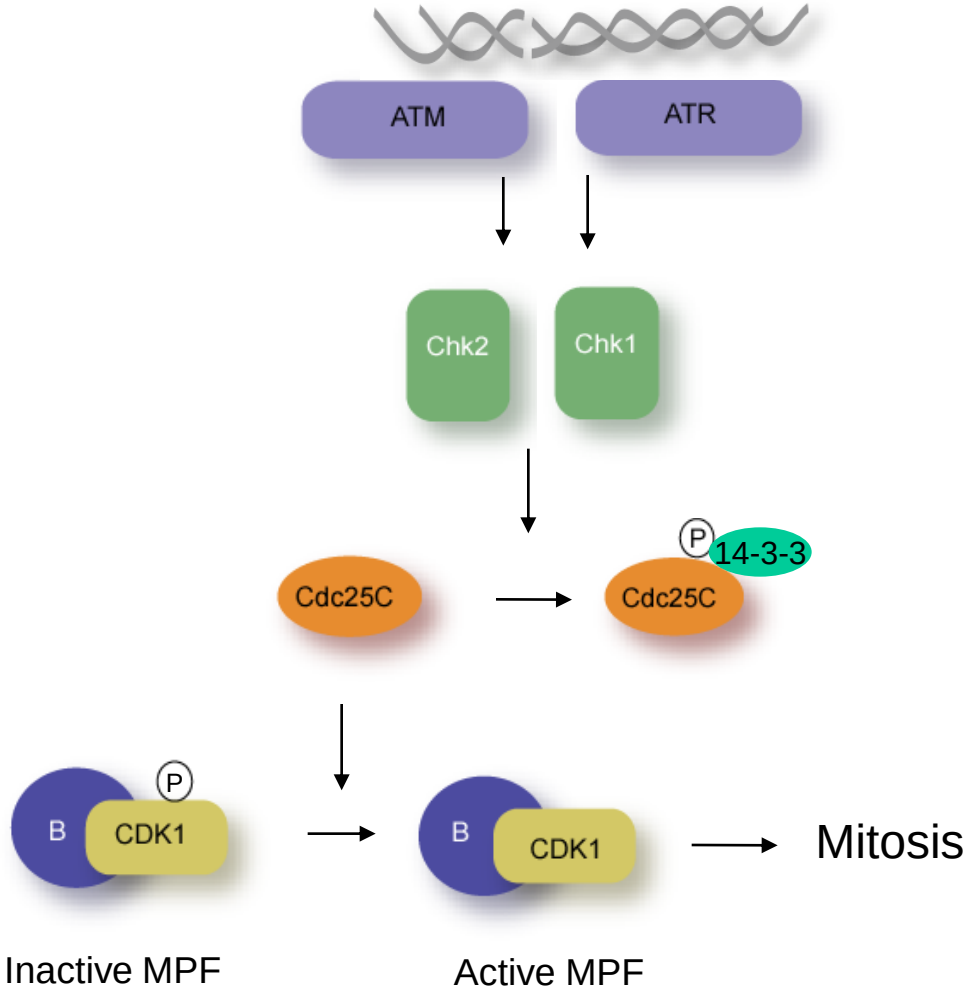
- Dose independent (1-10Gy)
- Applies to cells irradiated in G2
- ATM dependent
- Does not affect radiosensitivity

Late

- Dose dependent
- Applies to cells irradiated in G1 or S-phase
- “classical” G2 delay
- ATR dependent
- May affect radiosensitivity



Early G2 checkpoint



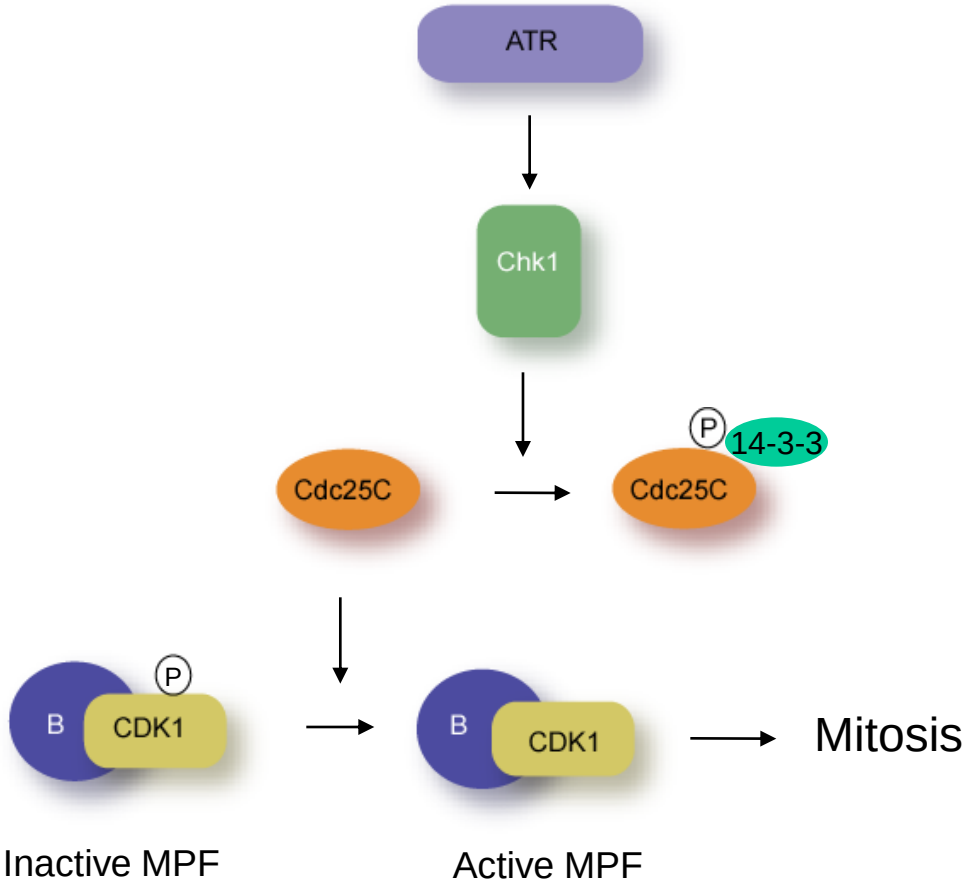
Sensors:
ATM
ATR

Transducers:
Chk2
Chk1

Effector:
Cdc25c

Applies to cells irradiated in G2 – blocks mitotic entry

Late G2 checkpoint



Sensors:
ATR

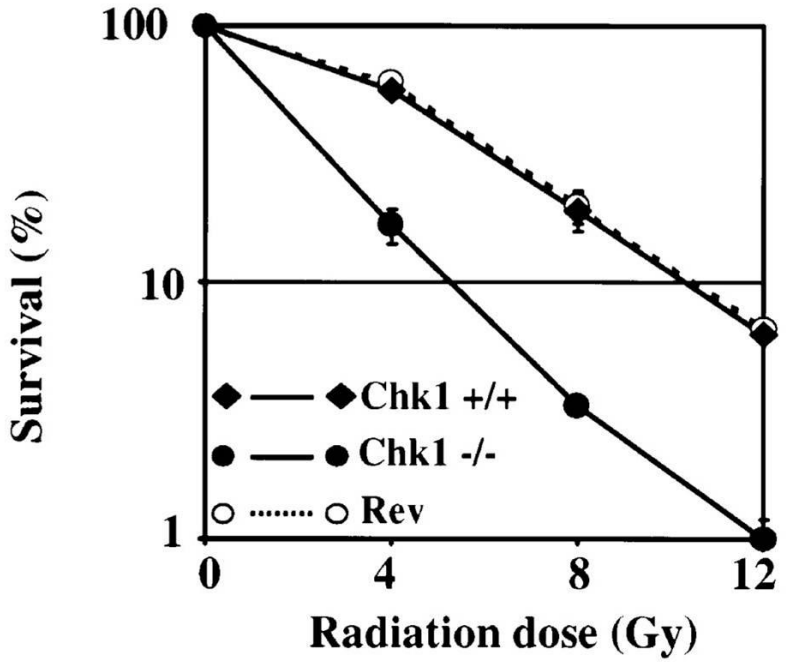
Transducers:
Chk1

Effector:
Cdc25c

Applies to cells irradiated in G1/S – accumulation in G2

G2 checkpoints and radiosensitivity

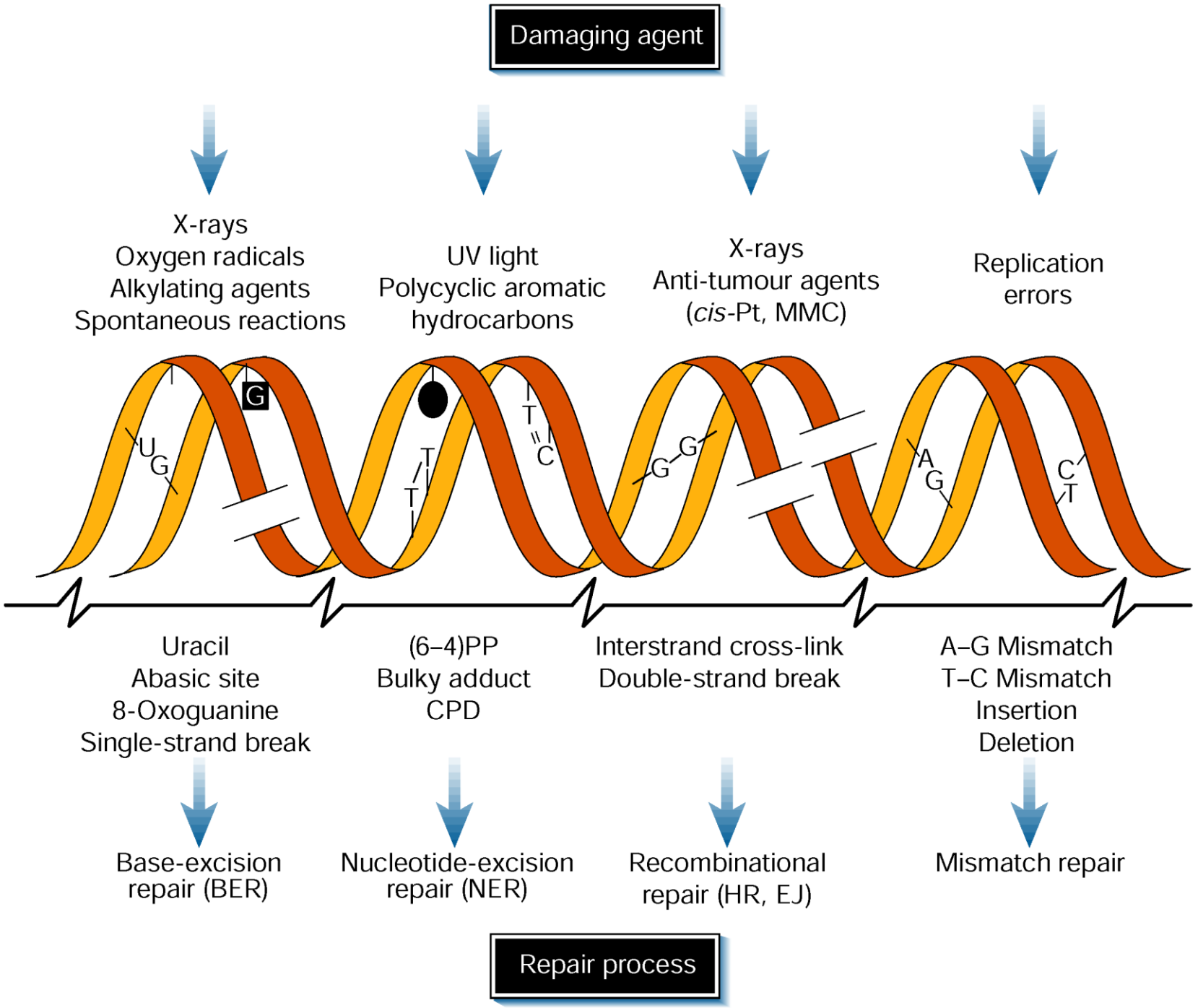
- Not all mutants with disrupted early G2 checkpoint are radiosensitive
- ATR or Chk1 deletion disrupts late G2 checkpoint and causes radiosensitivity



Zachos et al., EMBO 22(3), 2003

Summary of Checkpoints

- Checkpoints are activated by inhibiting CDK's
- Checkpoints are often disrupted in cancer
- 4 Checkpoints are activated by IR
  - G1 (ATM-p53), S (ATM), G2 early (ATM/ATR), G2 late (ATR)
- Loss of checkpoints affects tumor proliferation after IR
  - Can affect cell cycle Redistribution, response to multiple fractions

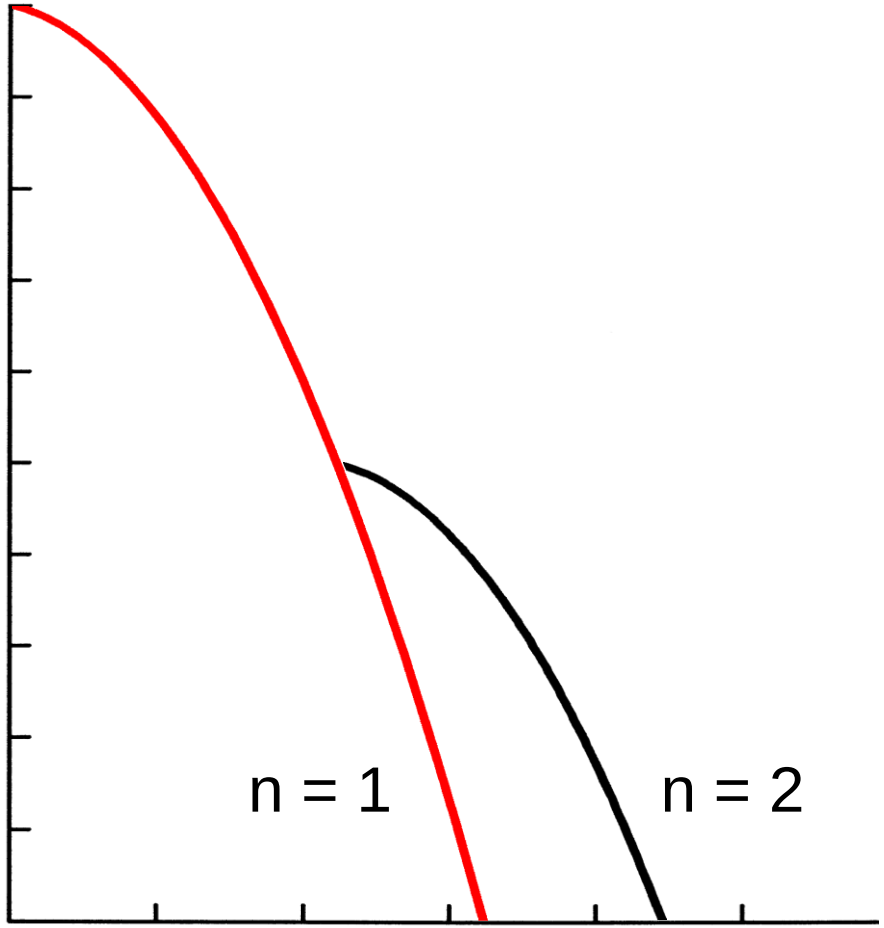

Damaging agent
X-rays
Oxygen radicals
Alkylating agents
Spontaneous reactions
UV light
Polycyclic aromatic
hydrocarbons
X-rays
Anti-tumour agents
(*cis*-Pt, MMC)
Replication
errors
U
G
G
T
T
T
C
G
G
A
G
C
T
Uracil
Abasic site
8-Oxoguanine
Single-strand break
(6–4)PP
Bulky adduct
CPD
Interstrand cross-link
Double-strand break
A–G Mismatch
T–C Mismatch
Insertion
Deletion
Base-excision
repair (BER)
Nucleotide-excision
repair (NER)
Recombinational
repair (HR, EJ)
Mismatch repair
Repair process

DNA Repair

- DNA repair is very important after irradiation
- Mutations in DNA repair genes cause (extreme) radiosensitivity
- Double-strand break repair is the most important

DNA Repair and Fractionation

- The fractionation effect is due mainly to DNA repair
- ½ time for recovery is similar to ½ time for repair



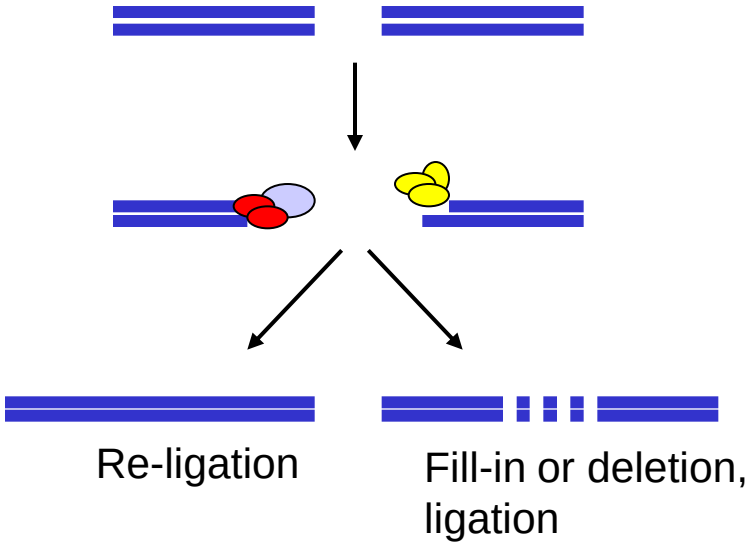
DSB Repair

Homologous Recombination (HR)

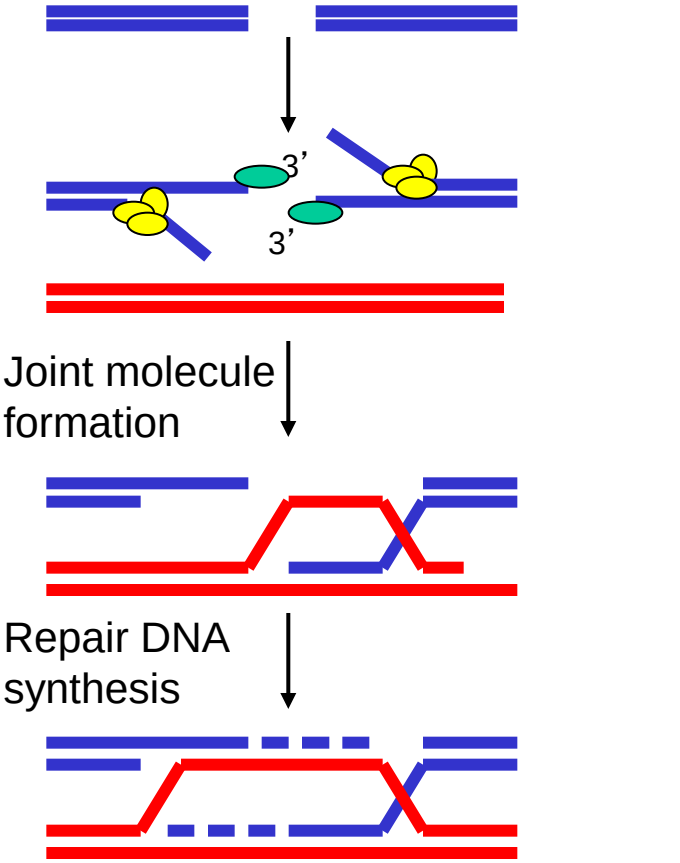
Non–homologous End-joining (NHEJ)

HR and NHEJ

Non-homologous end-joining

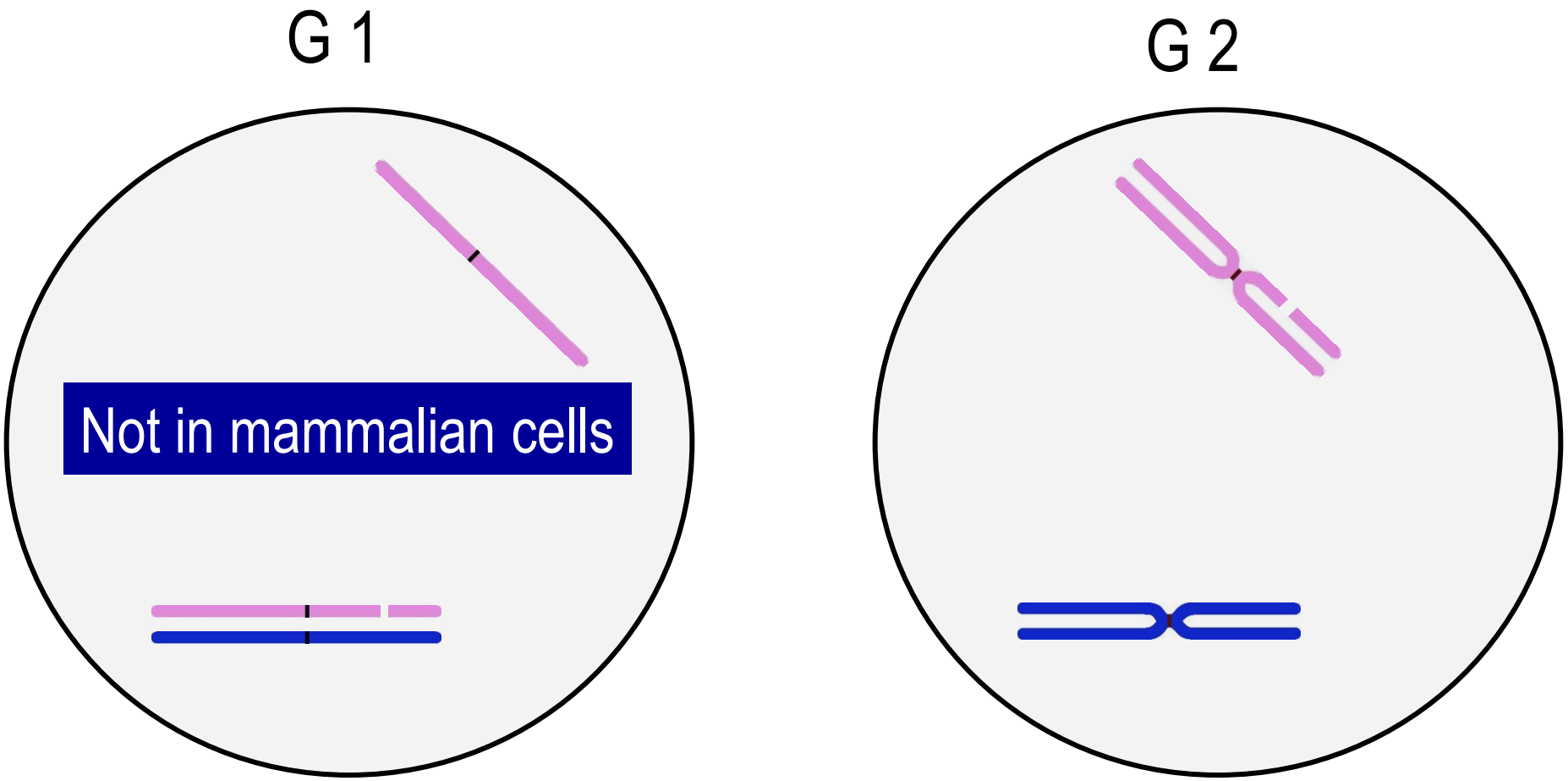


Homologous recombination



Cell-cycle dependence of HR repair

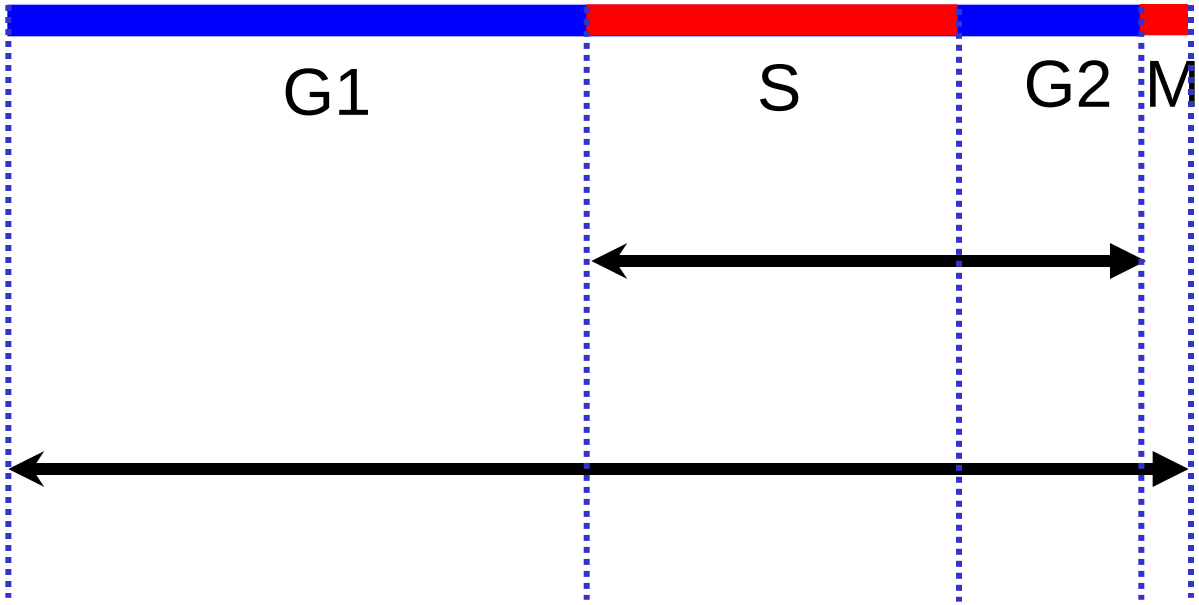
- HR requires a homologous template



DNA Repair Through the cell cycle

Homologous Recombination

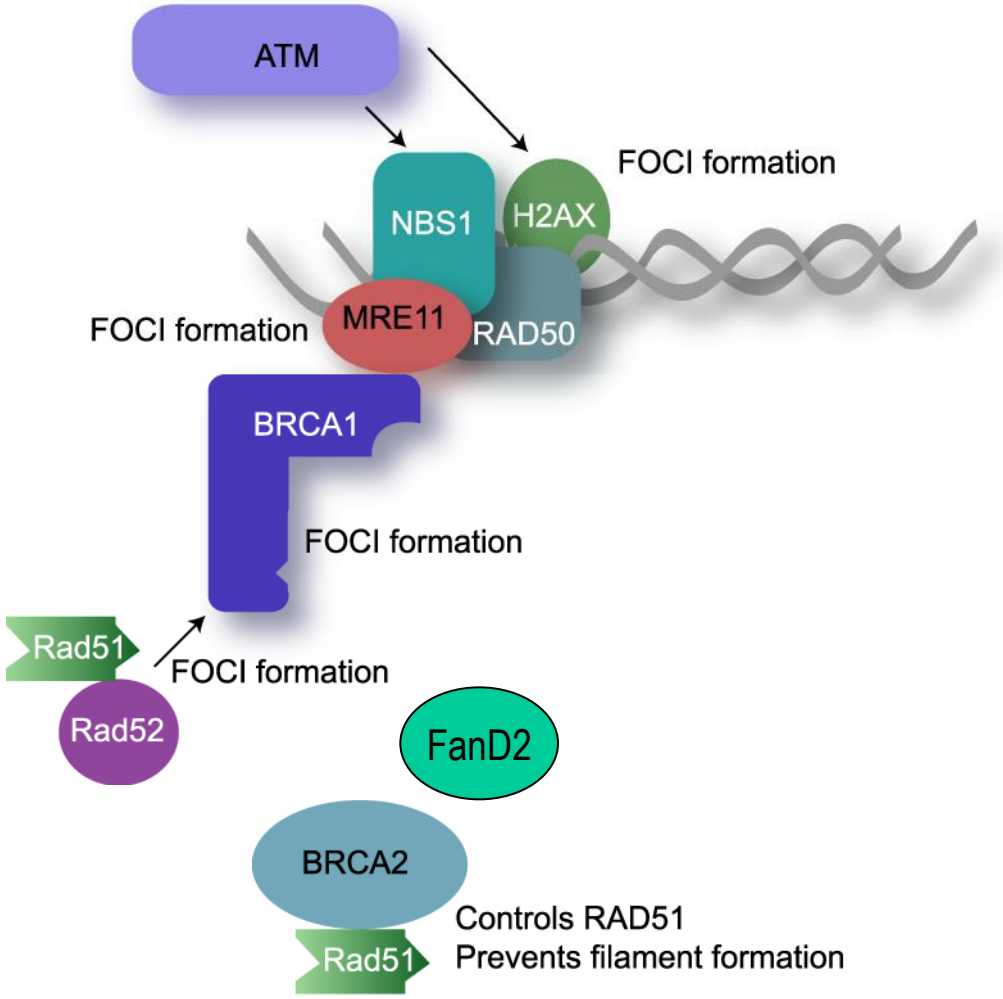
Non-Homologous End Joining



HR versus NHEJ

- NHEJ
  - Repairs most DSB - 80%
  - Very important for radiosensitivity
  - Error prone
  - All parts of the cell cycle
  - Similar in all cell types
- HR
  - Repairs fewer DSB – 20%
  - Important for radiosensitivity
  - Error free
  - S and G2 phase
  - responsible for change in sensitivity in the cell cycle
  - Varies more between cell lines (high in stem cells)
  - Defects common in cancer

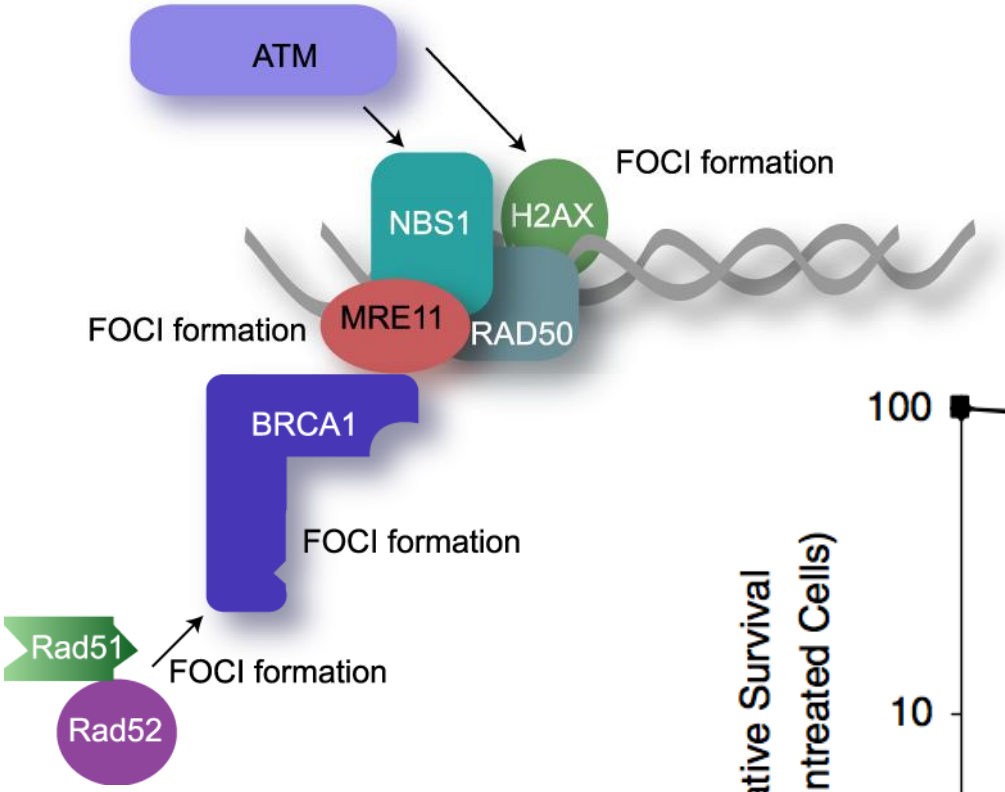
Recruitment of repair machinery - HR

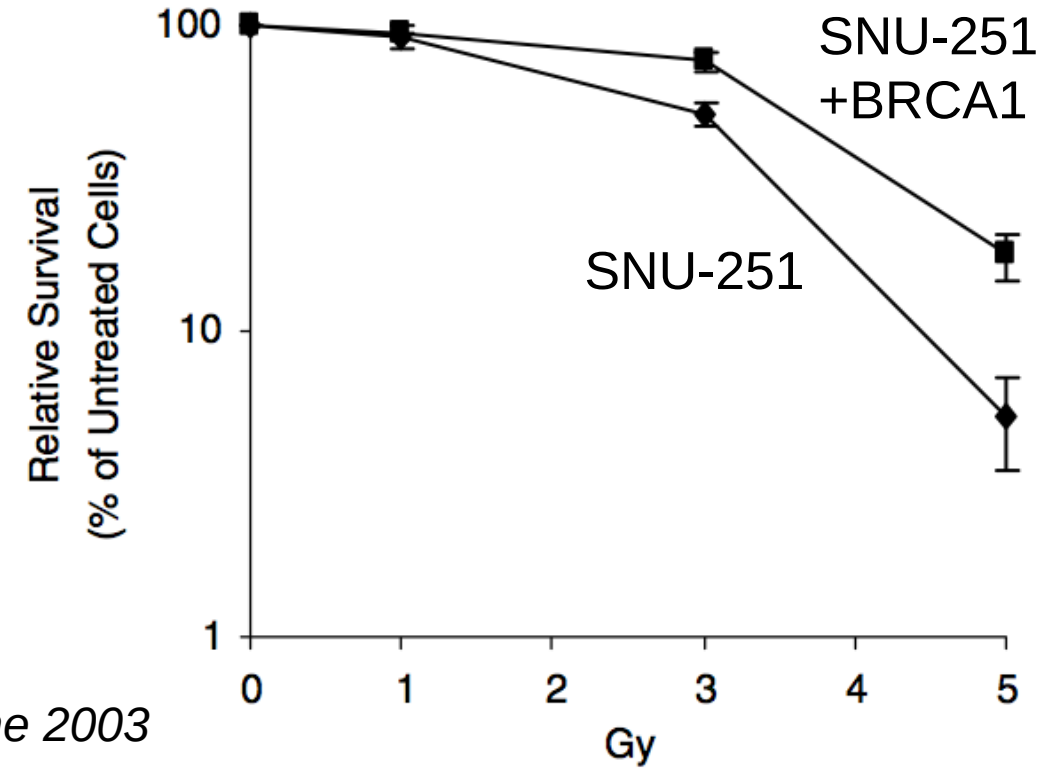


BRCA1 aids recruitment of HR machinery

HR machinery influenced by FANCD2 and BRCA2

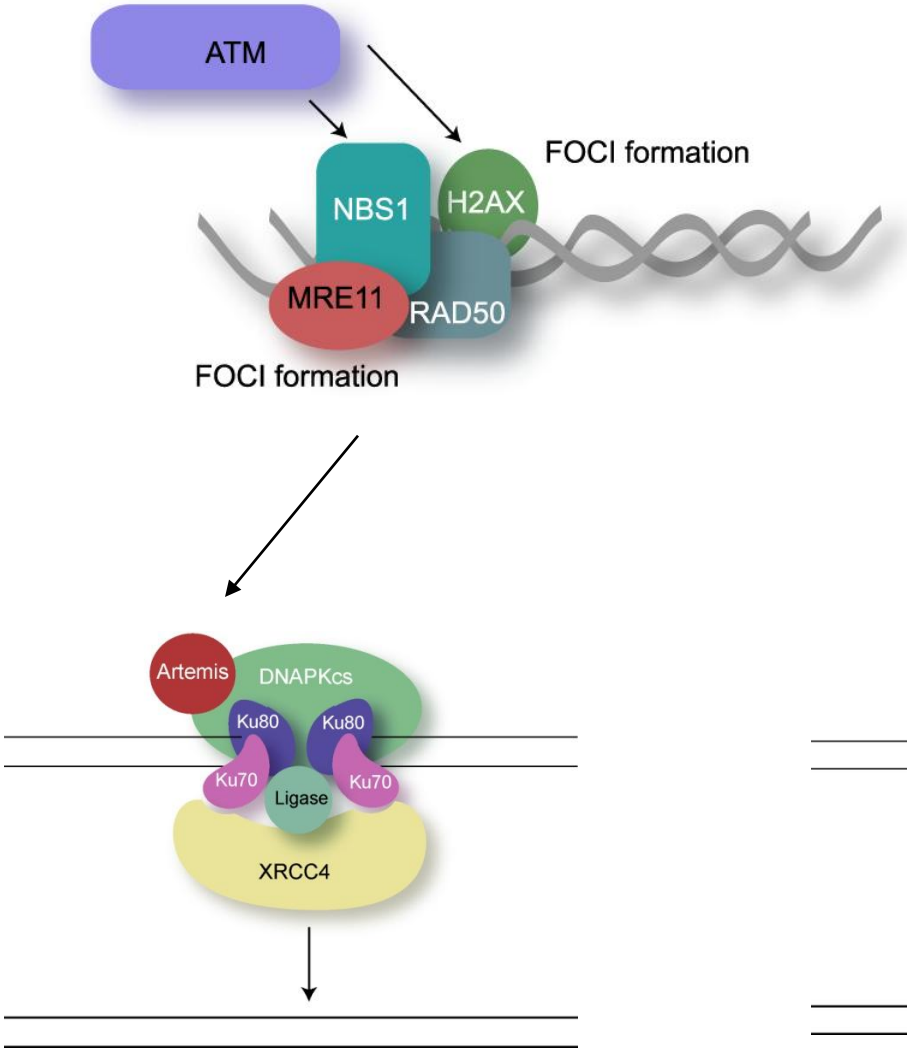
Recruitment of repair machinery - HR



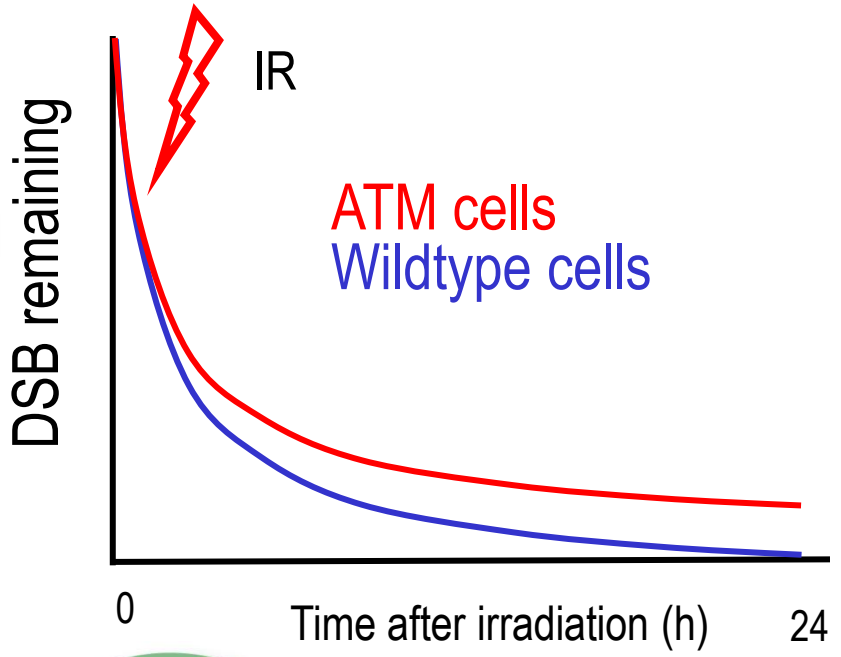


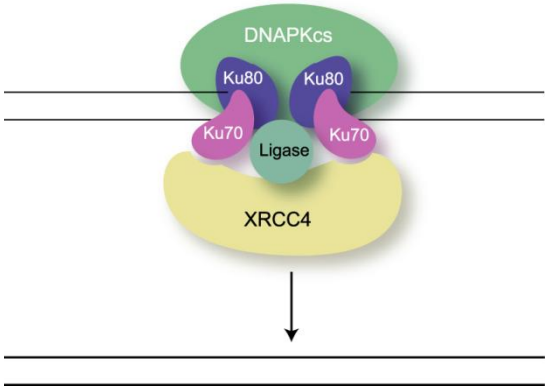
Zhou et al., Oncogene 2003

Recruitment of Repair Machinery - NHEJ



10% of NHEJ

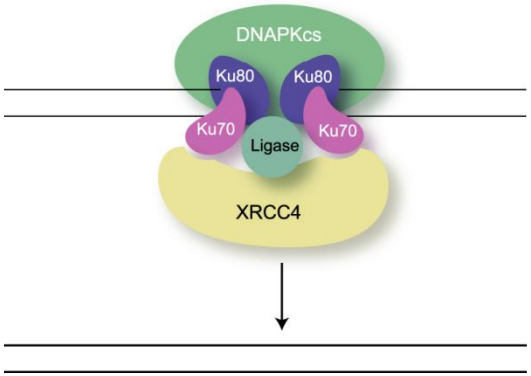


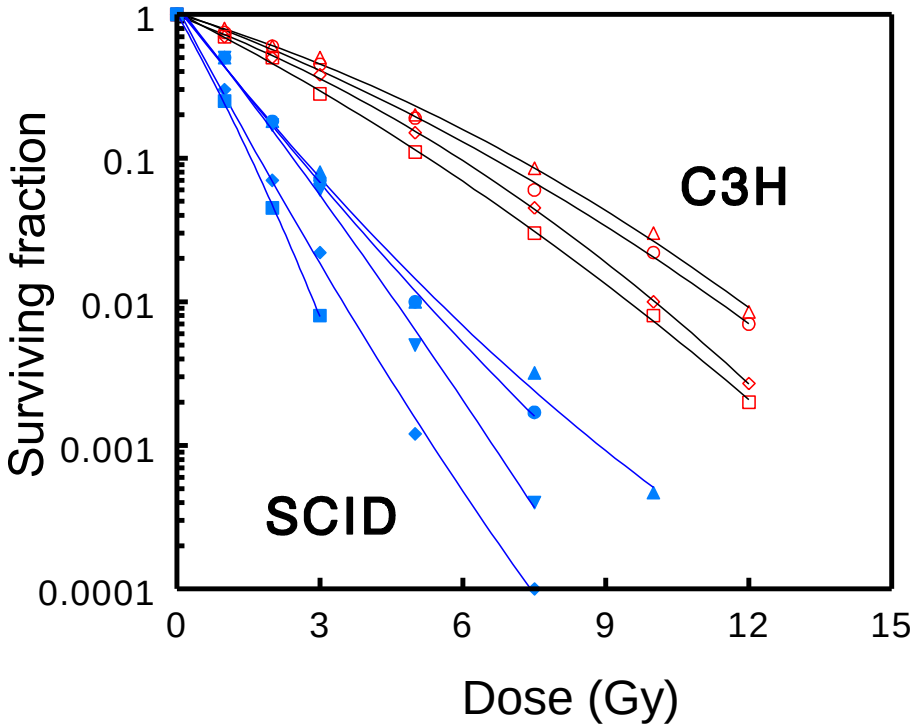


90% of NHEJ

NHEJ

Defects in EJ cause extreme radiosensitivity

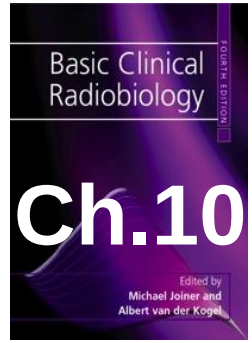




All tumors arising in DNA-PK deficient mice are radiosensitive

Summary of DNA damage repair

- DSBs are the most important damage produced by IR
- DSBs are sensed by ATM and MRN
  - Apoptosis (rarely)
  - Checkpoint activation
  - DNA repair
- Repair requires large repair factories containing many proteins
  - NHEJ (DNAPKcs, Ku70/80, Artemis, XRCC4, Ligase)
  - HR (BRCA1/2, Rad51/52, FANCD2)
- Impaired DNA repair machinery causes (extreme) radiosensitivity

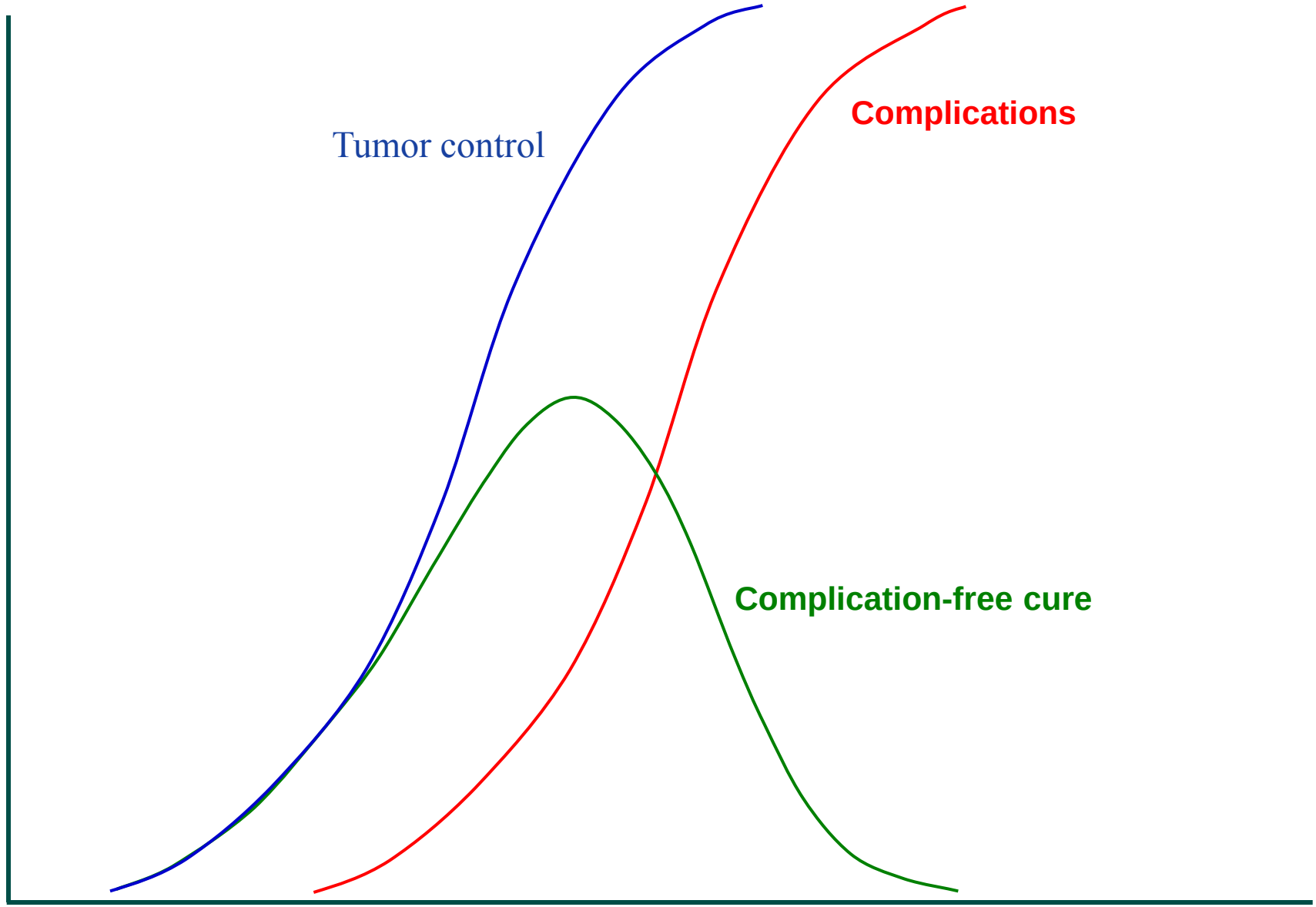


Hyper-, hypofractionation and accelerated radiotherapy

Prof. Vincent GREGOIRE
Université Catholique de Louvain,
Cliniques Universitaires St-Luc

ESTRO teaching course on basic clinical radiobiology

The paradigm of radiotherapy



Courtesy of K. Haustermans

Conventional fractionation

1.8 – 2.0 Gy per fraction, 5 fractions per week

IIIII IIIII IIIII IIIII IIIII IIIII IIIII

	Example	Dose (Gy)	Tumor control (%)
Sensitive	Seminoma, Lymphoma	≤ 45	≥ 90
Intermediate	SCC, Adeno-Ca	50	≥ 90 (subclinical)
		60	~ 85 (Ø 1 cm)
		70	~ 70 (Ø 3 cm)
			~ 30 (Ø 5 cm)
Resistant	Glioblastoma	≥ 60	none?
	Melanoma	≥ 60	none?

Prototypes of modified fractionation

- Hyperfractionation (HF)
- Accelerated fractionation (AF)
- (Hybrid schedules)
- Hypofractionation

Prototypes of modified fractionation

- Hyperfractionation (HF)
- Accelerated fractionation (AF)
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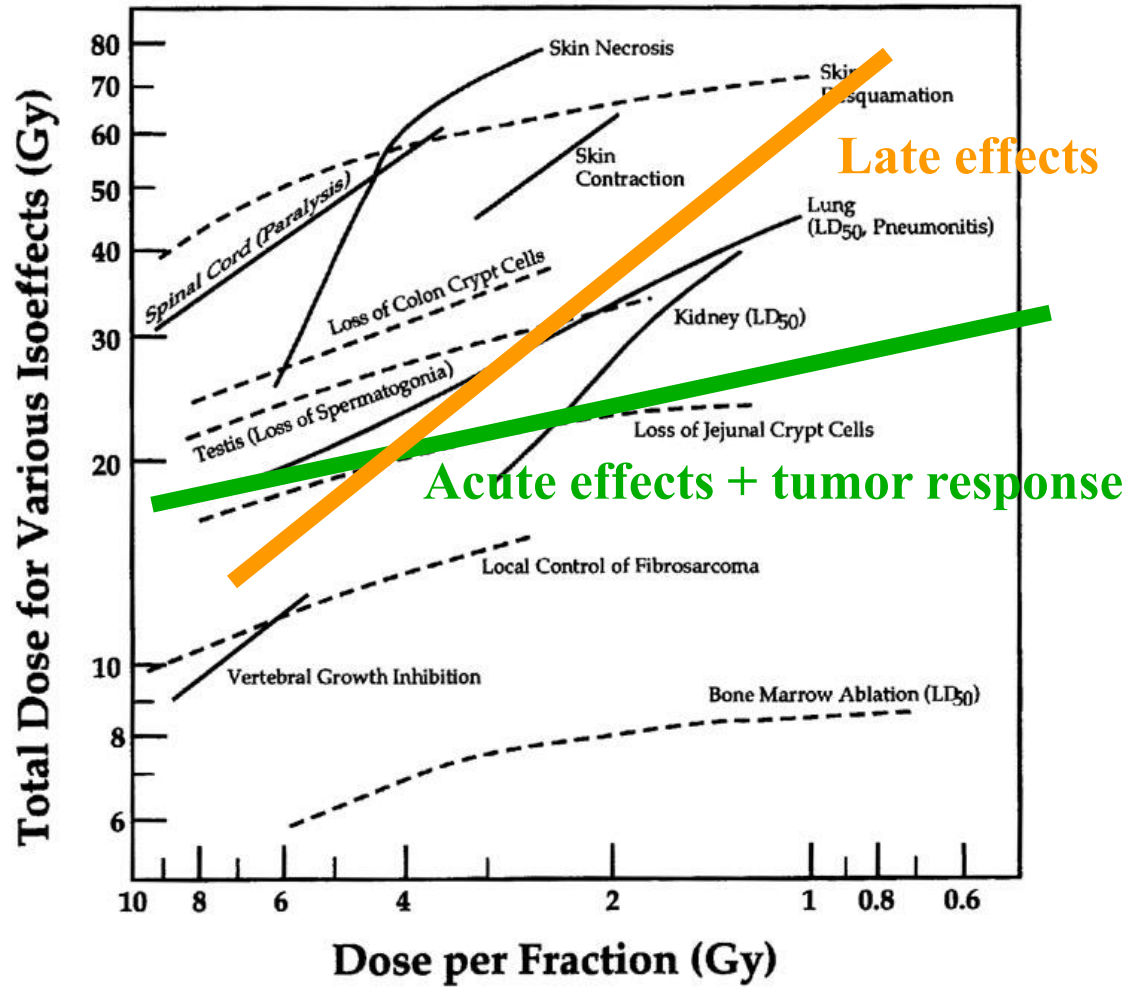
- Hypofractionation

Fractionation sensitivity

"Typical" dose per fraction

- 1.8-2 Gy for standard fractionation
- 1.1-1.3 Gy for hyper-fractionation



Withers et al, 1983

Hyperfractionation (HF)

reduced dose per fraction (< 1.8 Gy)

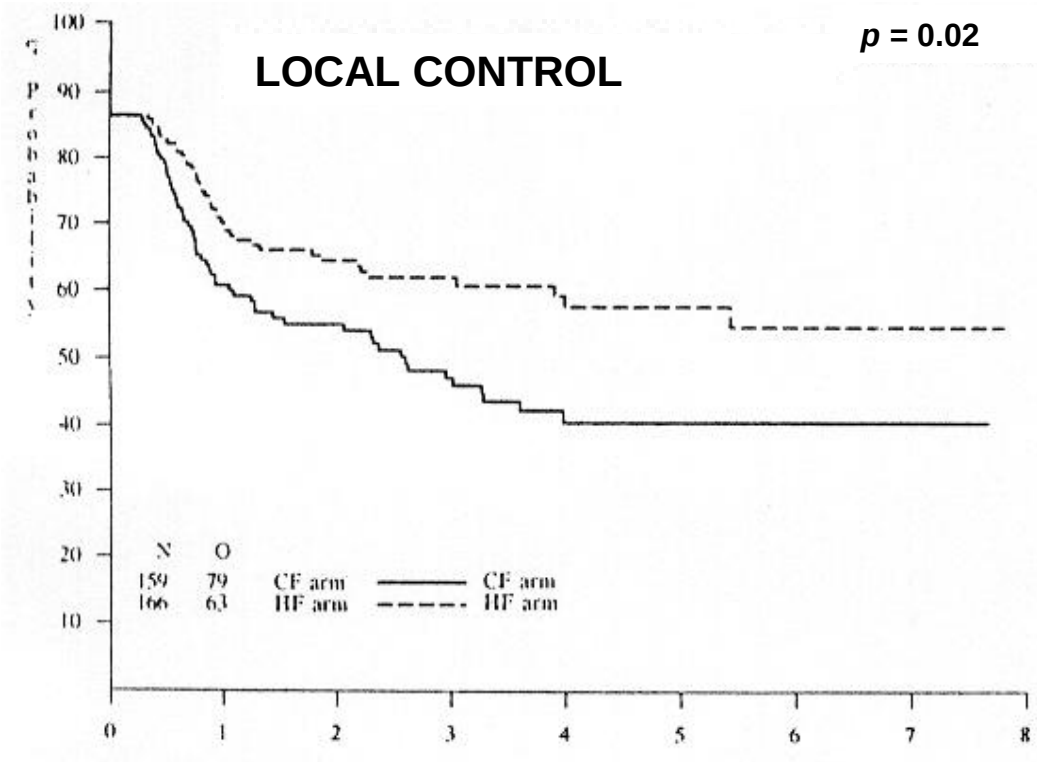
Expectations (dose-escalated HF):

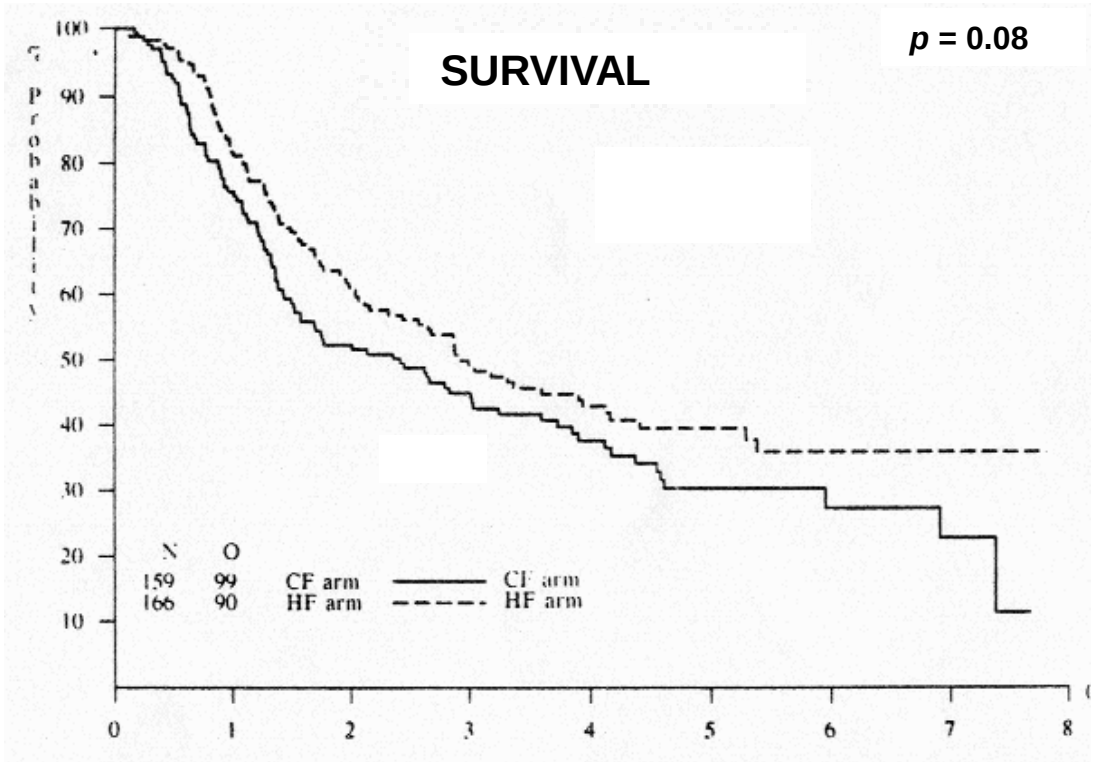
- Increased tumor control
- More severe early reactions
- Unchanged or less late reactions

EORTC Hyperfractionation trial in oropharynx cancer (N = 356)

Oropharyngeal Ca T2-3, N0-1

80.5 Gy - 70 fx - 7 wks vs 70 Gy - 35-40 fx - 7-8 wks





Horiot 1992

RTOG 90-03: A Phase III Trial Assessing Relative Efficacy of Altered Fractionations

Stage III & IV
SCC of :

- Oral cavity
- Oropharynx
- Larynx
- Hypopharynx

Stratify :

- No vs N+
- KPS
  60-80 VS 90-100

R A N D O M I Z E

1. Conventional Fractionation:
   70 Gy / 35 F / 7 W
2. Hyperfractionation:
   81.6 Gy / 68 F / 7 W (1.2 Gy/F)
3. Accelerated Fractionation (Split):
   67.2 Gy / 42 F / 6 W (2 W Rest)
4. Accelerated Fractionation (CB):
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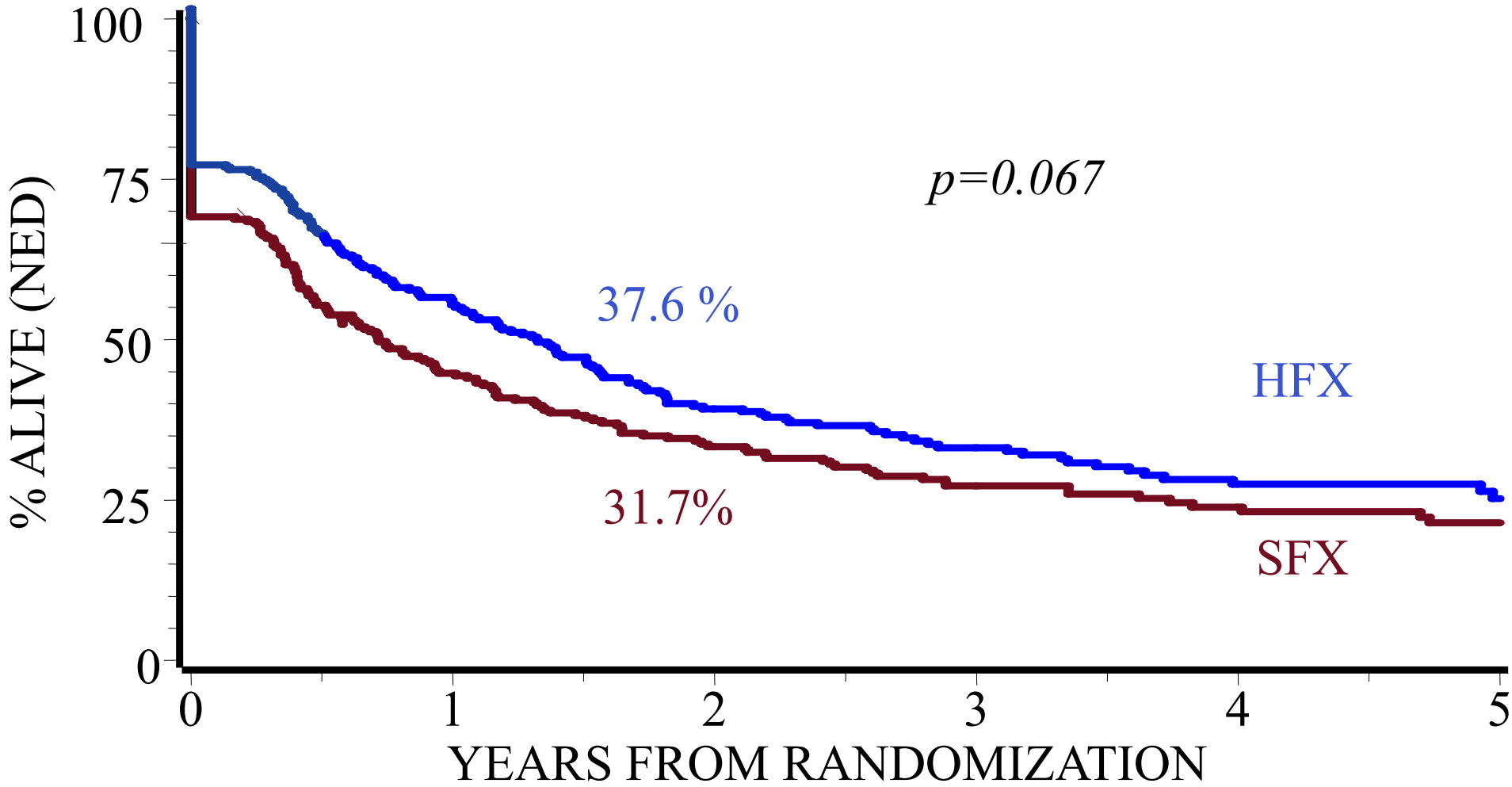
RTOG 9003

Disease-Free Survival



Toxicity of RT in HNSCC

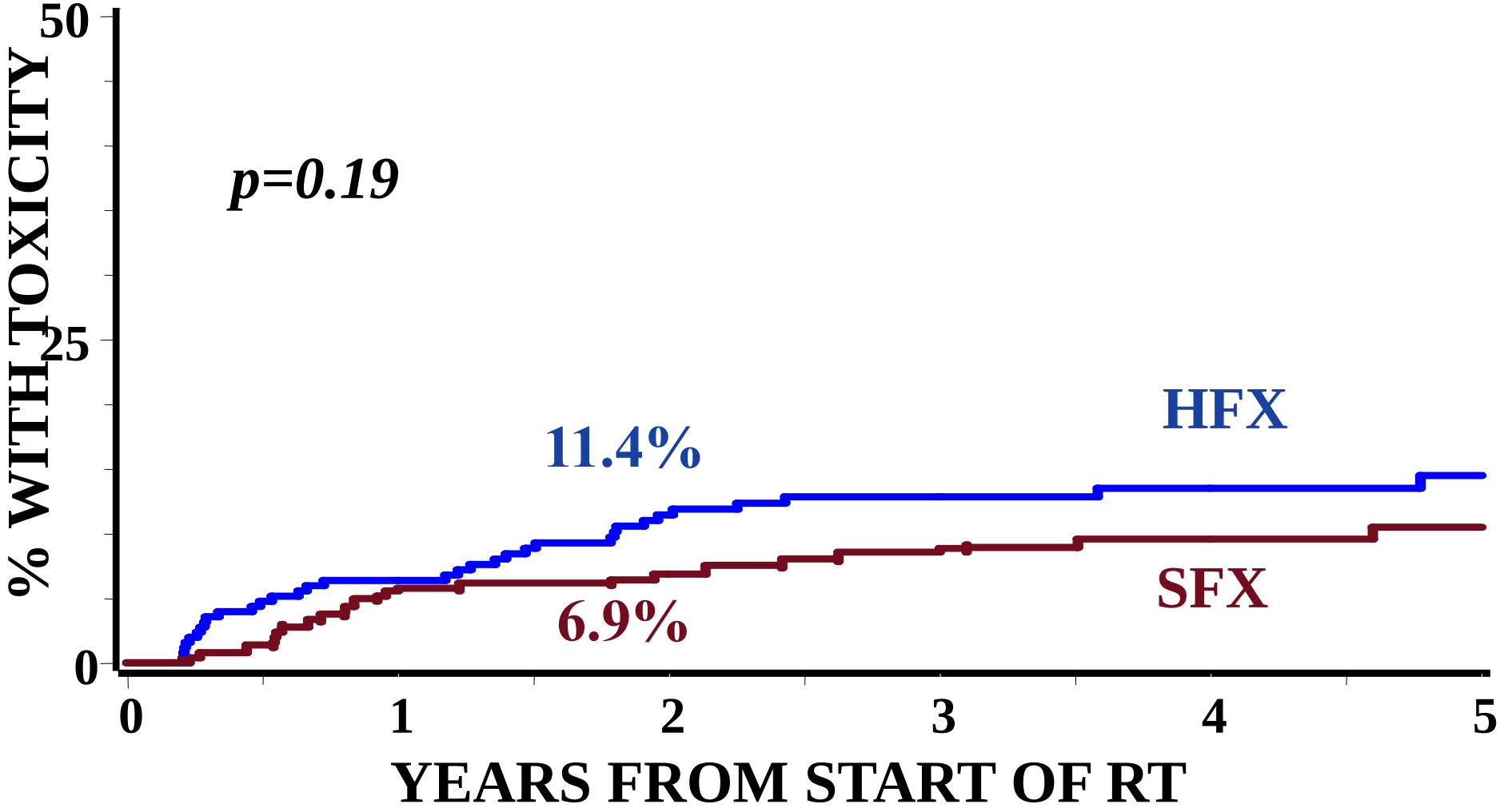
Early effect in accelerated or hyperfrationation RxTh

Author	Regimen	Grade 3-4 mucositis	
		Control	Experimental
Horiot (n=356)	HF	49%	67%
Horiot (n=512)	Acc. fract. + split	50%	67%
Dische (n=918)	CHART	43%	73%
Fu (n=536)	Acc. frac (CB)	25%	46%
Fu (n=542)	Acc. fract. + split	25%	41%
Fu (n=507)	HF	25%	42%
Skladowski (n=99)	Acc. Fract.	26%	56%

Dishes, 1997
Horiot, 1992
Fu, 2000
Skladowski, 2000

RTOG 9003

Time to Persistent Grade 3+ Late Toxicity



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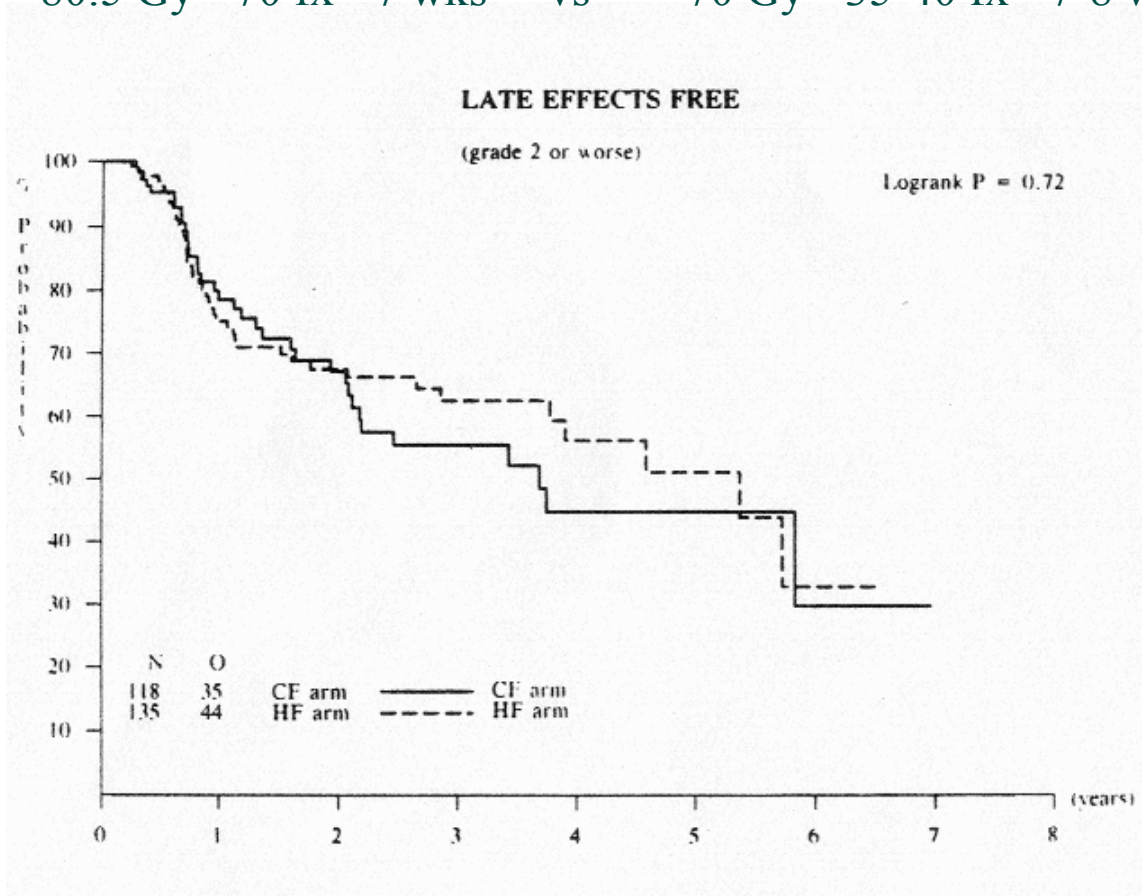
80.5 Gy - 70 fx - 7 wks vs 70 Gy - 35-40 fx - 7-8 wks



EORTC 22791; Horiot et al., *Radiother. Oncol.* 25: 231-241, 1992

Hyperfractionation in NSCLC

RTOG 83-11/ ECOG 4588, Phase III, NSCLC II-IIIB

			Survival		
Schedule	n	MST	1yr	2yrs	4yrs
60.0 Gy/ 2.0 Gy	152	11.4 m	46%	20%	4%
69.6 Gy/ 1.2 Gy b.i.d.	154	12.3 m	51%	24%	9%

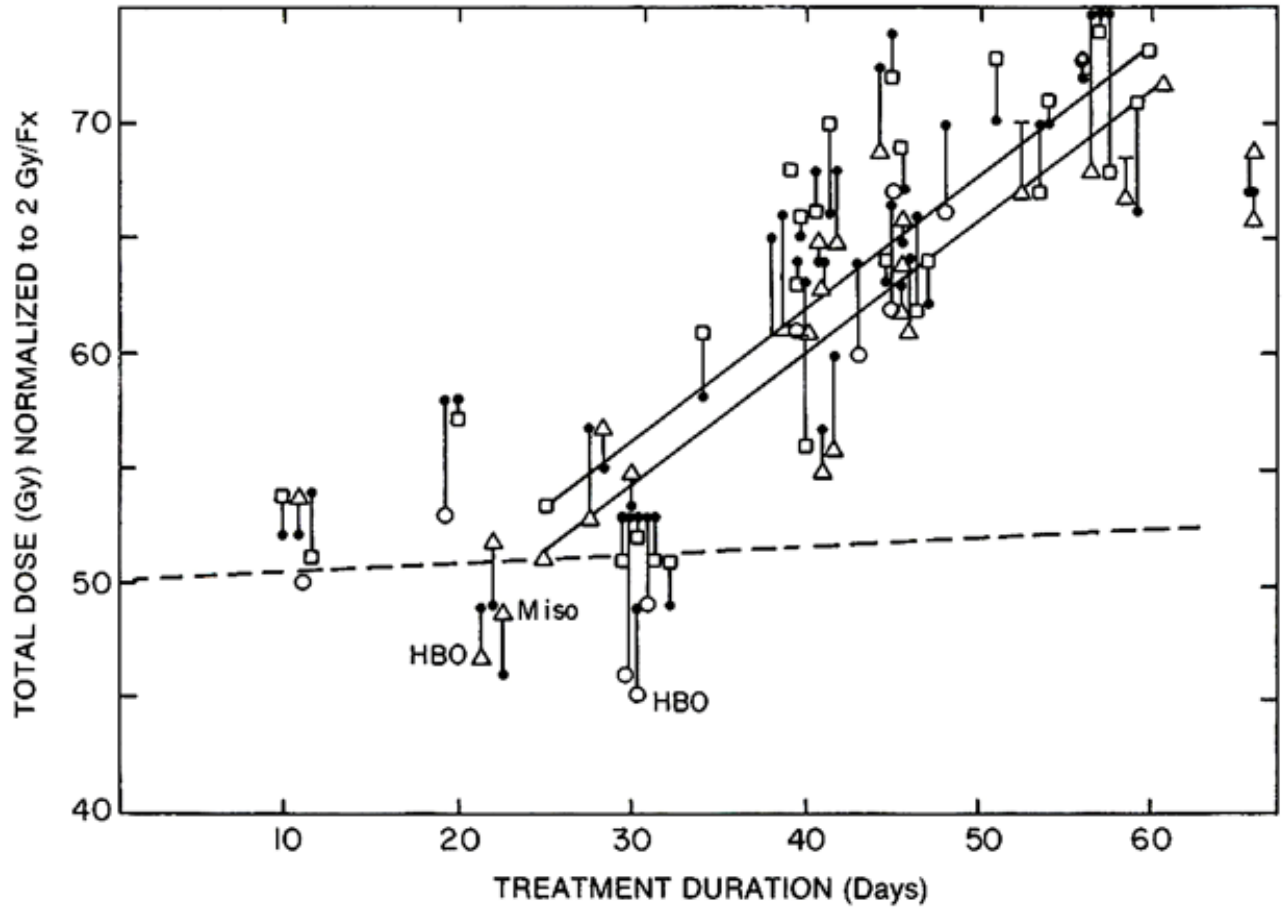
n.s.
Third arm neoadj. ChT

Sause et al., *J. Natl. Cancer Inst.* 87: 198-205, 1995
Komaki et al., *IJROBP* 39: 537-544, 1997

Prototypes of modified fractionation

- Hyperfractionation (HF)
- Accelerated fractionation (AF)
- (Hybrid schedules)
- Hypofractionation

Influence of overall treatment time on HNSCC local control



Withers et al, 1988

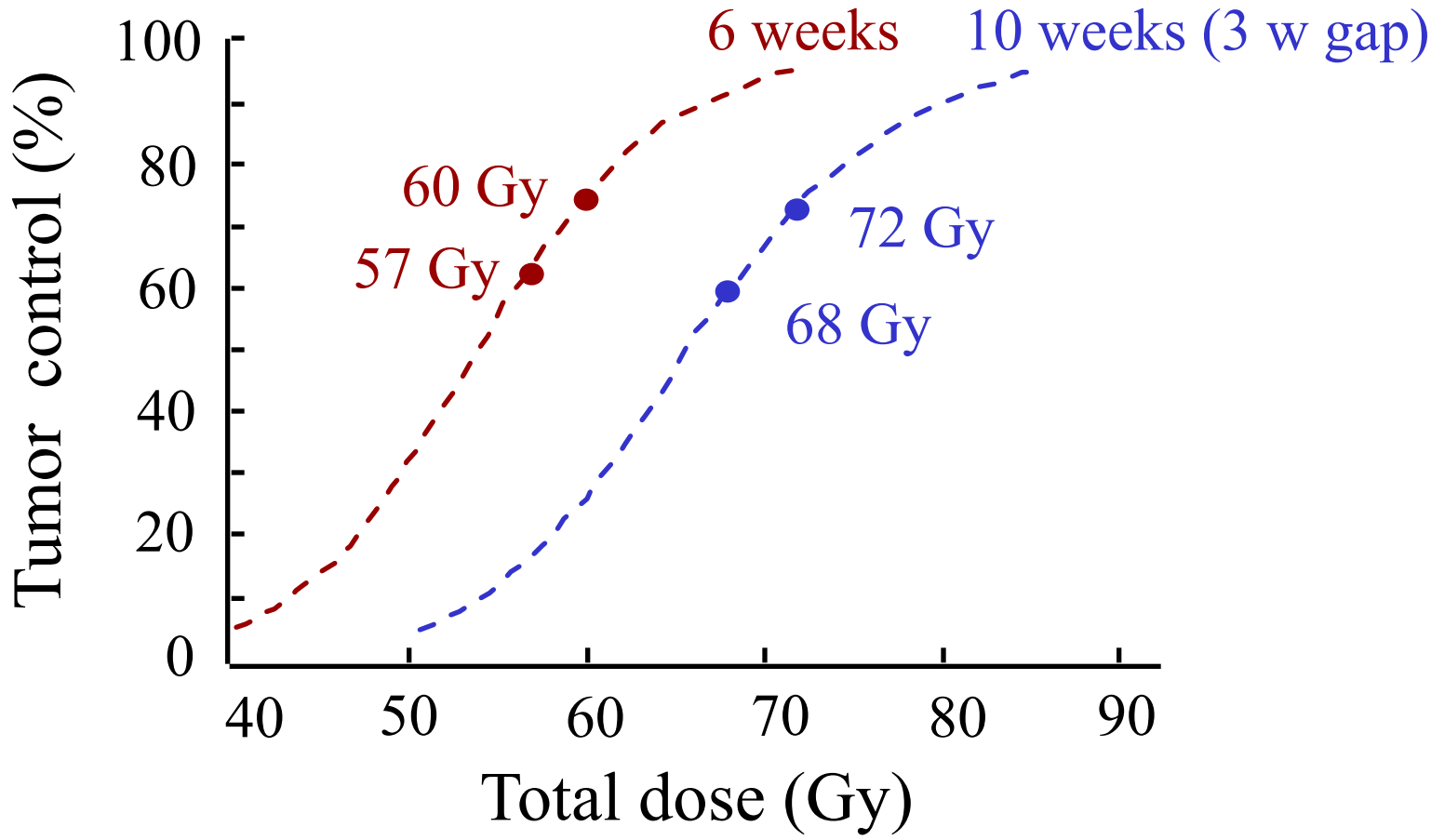
Tissue proliferation and recovered dose D_{prolif}

Tissue	D_{prolif} (Gy.d^{-1})	T_k* (days)
Early normal tissue reactions		
Skin (erythema)	0.12 (-0.12-0.22)	< 12
Mucosa (mucositis)	0.8 (0.7-1.1)	< 12
Lung (pneumonitis)	0.54 (0.13-0.95)	n.a.
Tumors		
Head and neck		
• larynx	0.74 (0.3-1.2)	n.a.
• tonsils	0.73	30
• various	0.8 (0.5-1.1)	21
• various	0.64 (0.42-0.86)	n.a.
NSCLC	0.45	n.a.
Medulloblastoma	0.52 (0.29-0.71	0 – 21

* onset of accelerated proliferation

Bentzen et al, 2002

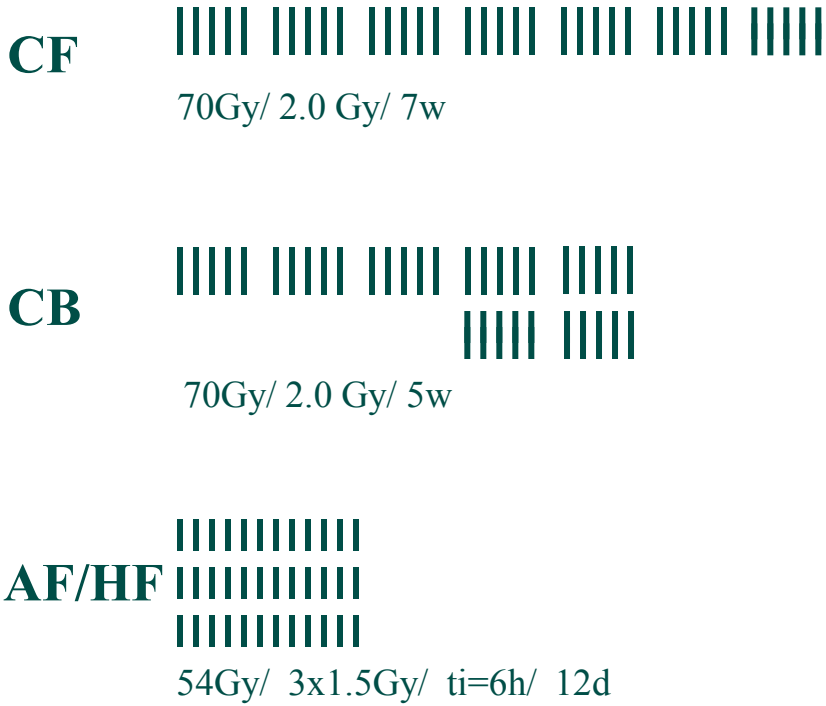
Influence of overall treatment time on HNSCC local control



Overgaard et al, 1988

Accelerated fractionation (AF)

Shortened overall treatment time, dose per week > 10 Gy



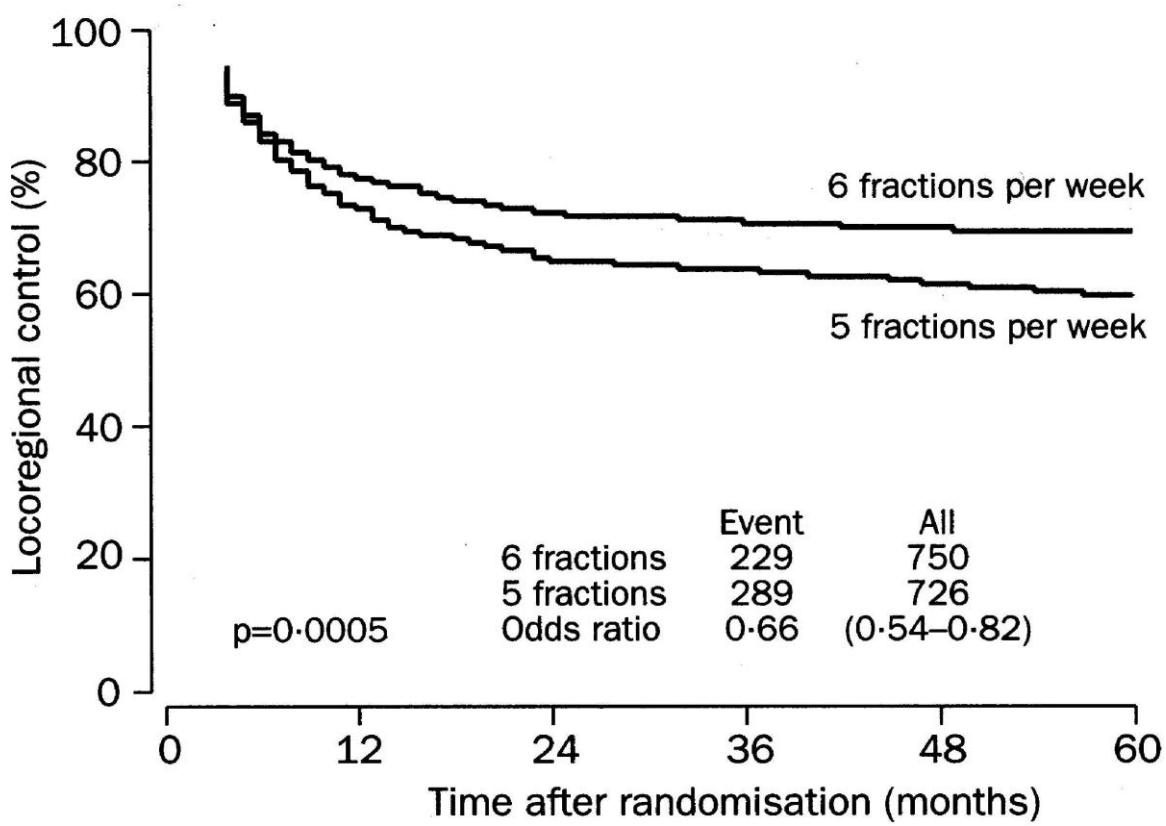
Expectations:

- Increased tumor control
- Increased early reactions
- Unchanged or decreased late damage (AF/HF and/or reduced total dose)

DAHANCA 6&7 - H&N

SCC - stage II-IV (n=1476)

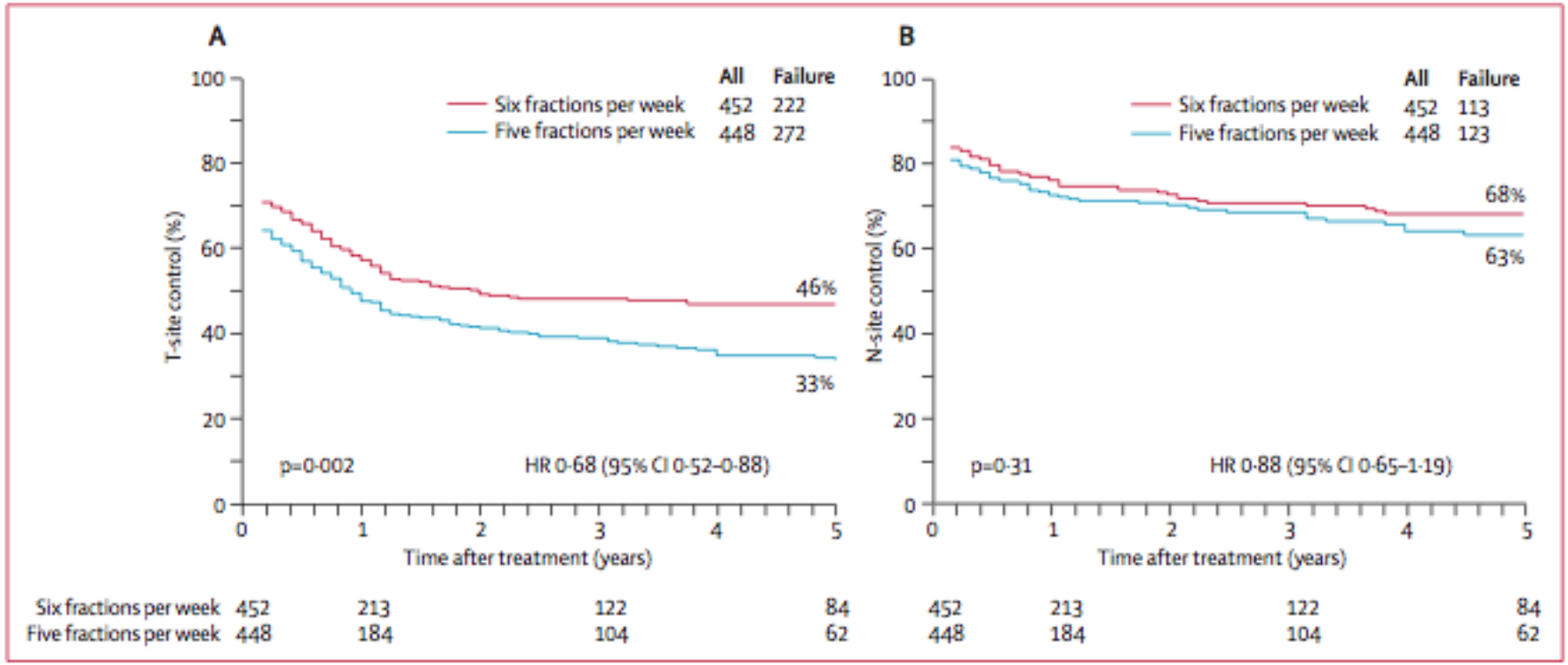
64-68 Gy/ 2.0 Gy/ 6.5w → 64-68 Gy/ 2.0 Gy/ 5.5w



Overgaard et al. Lancet, 2003

Five versus six fractions of radiotherapy per week for squamous-cell carcinoma of the head and neck (IAEA-ACC study): a randomized, multicentre trial

66-70 Gy/ 2.0 Gy/ 6.5-7.0 w → 66-70 Gy/ 2.0 Gy/ 5.5-6.0 w



ESTRO 2015

Overgaard et al. Lancet Oncol, 2010

RTOG 90-03: A Phase III Trial Assessing Relative Efficacy of Altered Fractionations

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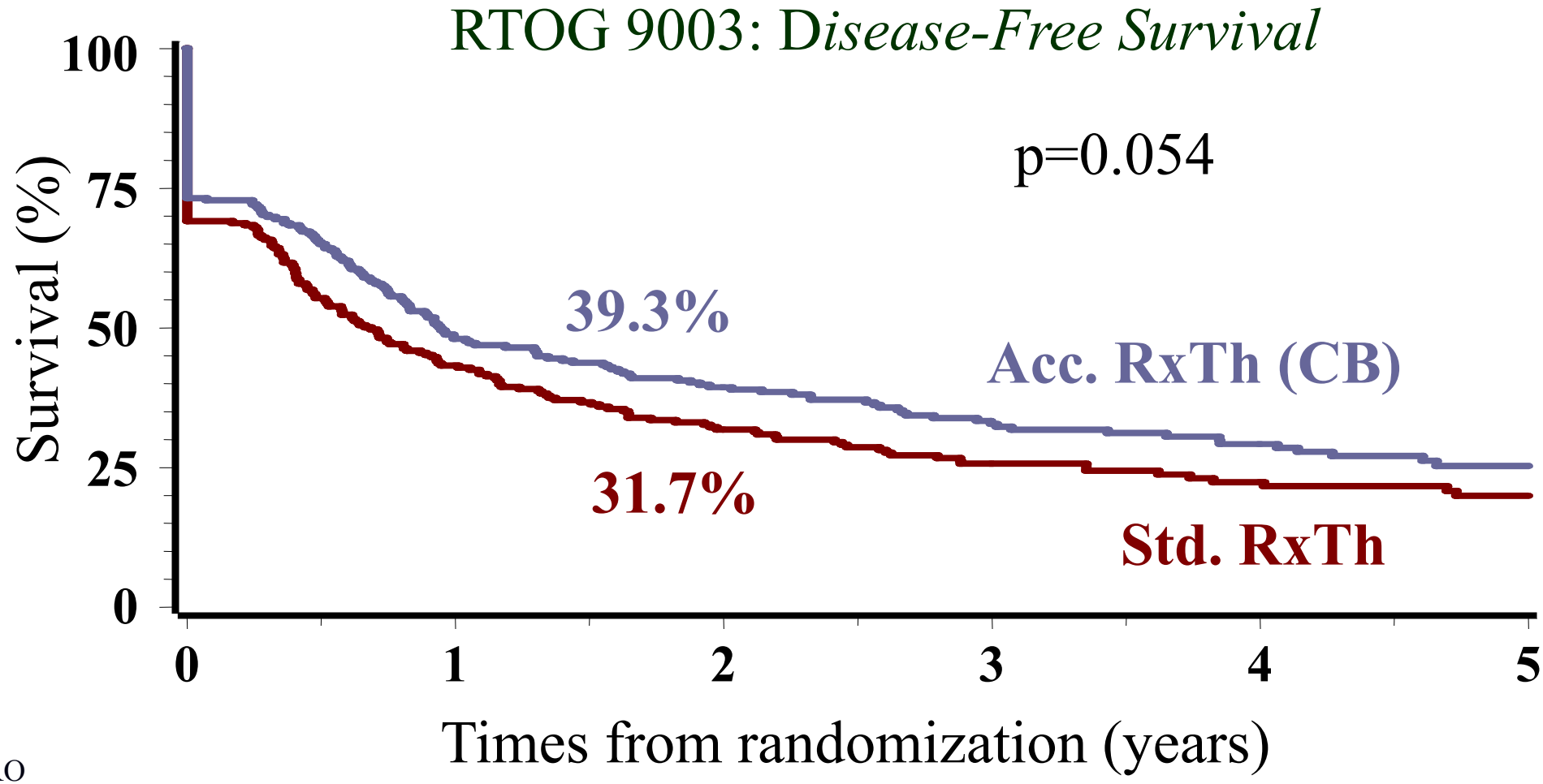
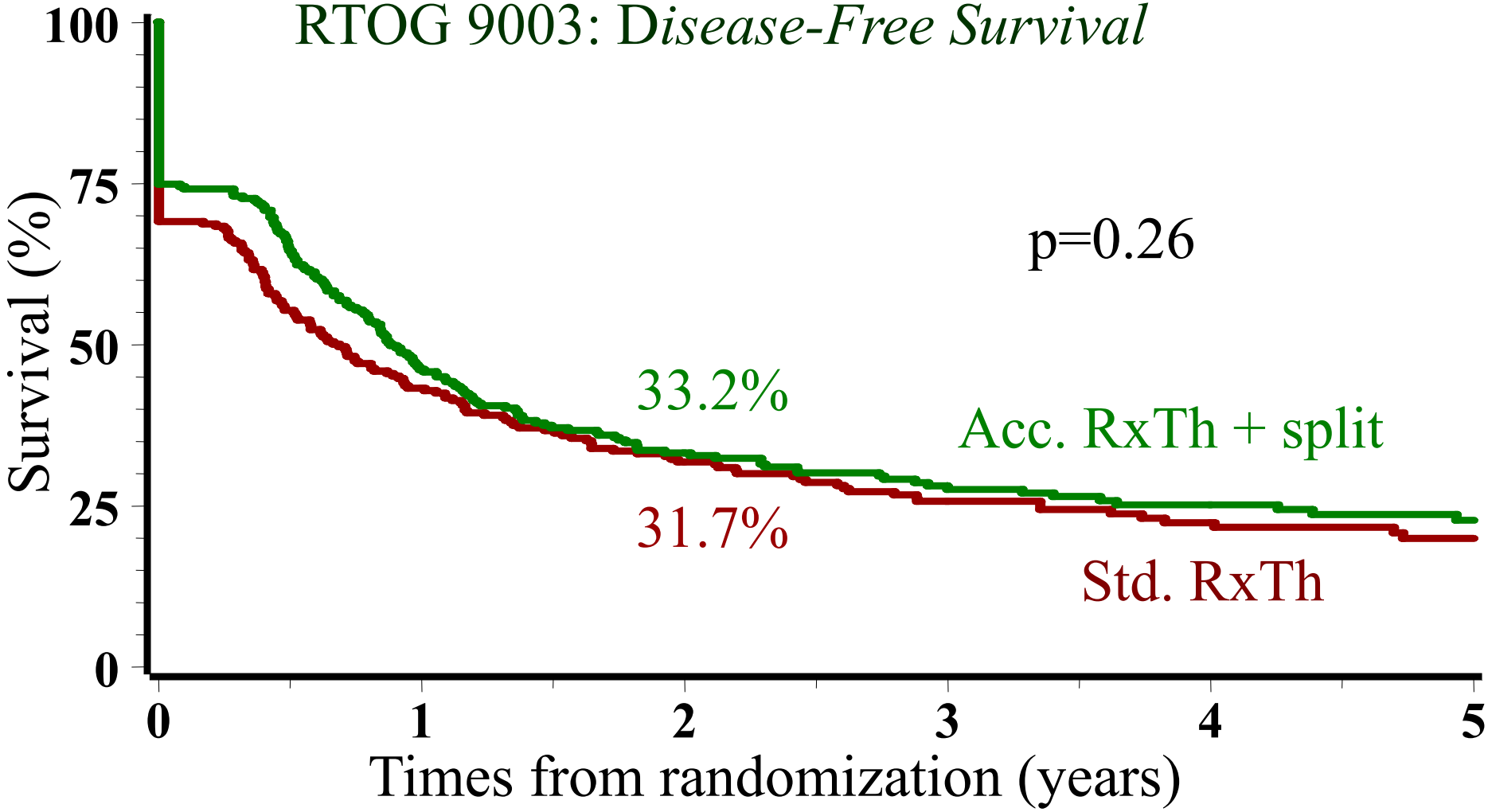
Influence of overall treatment time on HNSCC local control



Fu et al, 2000

Influence of overall treatment time on HNSCC local control



Fu et al, 2000

EORTC - Head & Neck (22851)

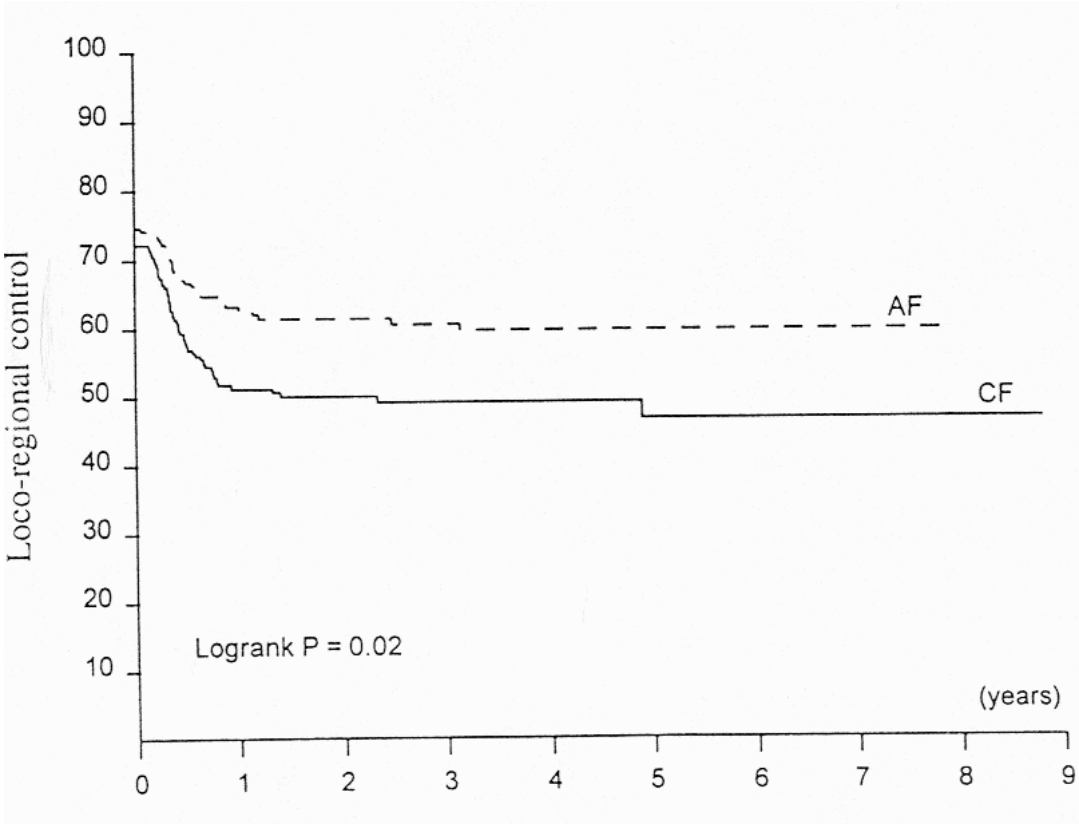
SCC, T2-4 N0-3 M0, WHO 0-2 (n=500)

IIIII IIIII IIIII IIIII IIIII IIIII IIIII

70 Gy/ 1.8-2.0 Gy/ 7 w (n=253)

IIIII I IIIII IIII
IIIII I IIIII IIII
IIIII I IIIII IIII

72 Gy/ 3 x 1.6 Gy/ ti 4 h/ Pause 12-14d/ 5w (n=247)



Accelerated RT:

- Tumor control increased
- Survival identical
- Very severe early NT reactions

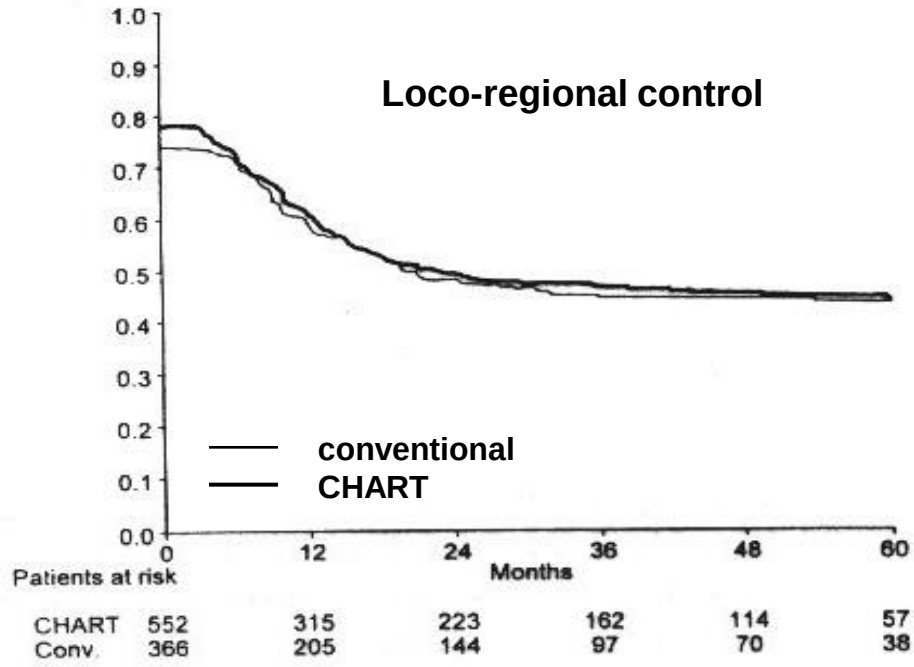
Horiot et al., *Radiother. Oncol.* 44: 111-121, 1997

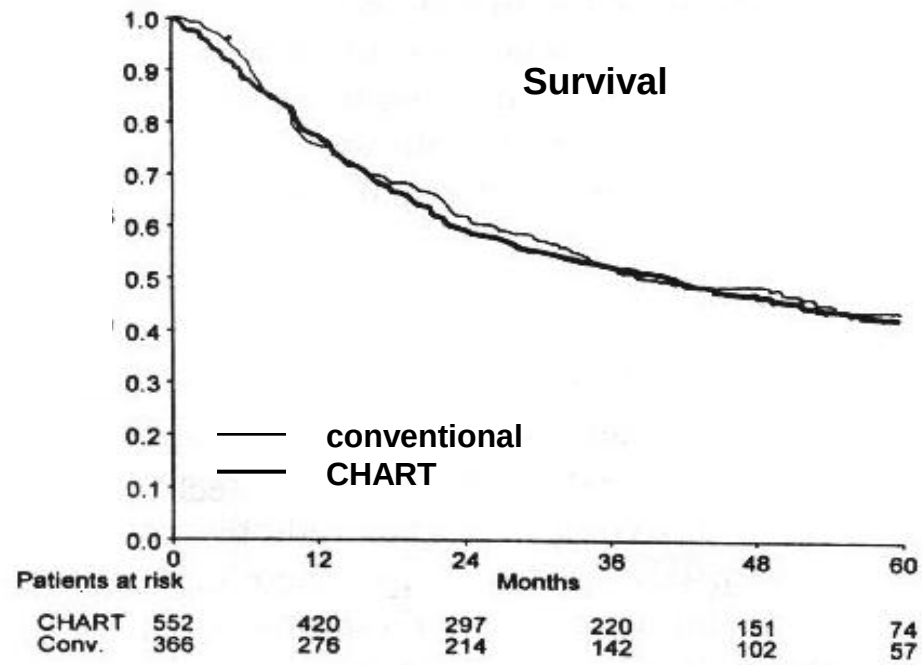
CHART - Head & Neck (MRC, UK)

SCC , >T1 N0 M0, WHO 0-1 (n=918)

66 Gy/ 2.0 Gy/ 6.5 w (n=366)

54 Gy/ 3 x 1.5 Gy/ ti 6 h/ 12 d (n=552)



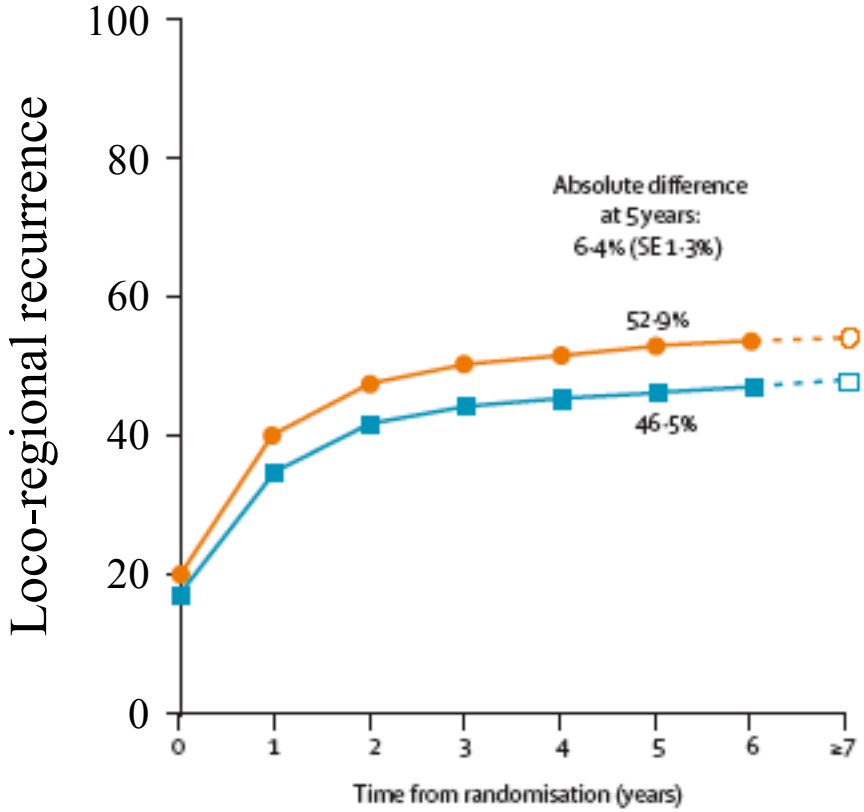


Dische et al., *Radiother. Oncol.* 44: 123-136, 1997

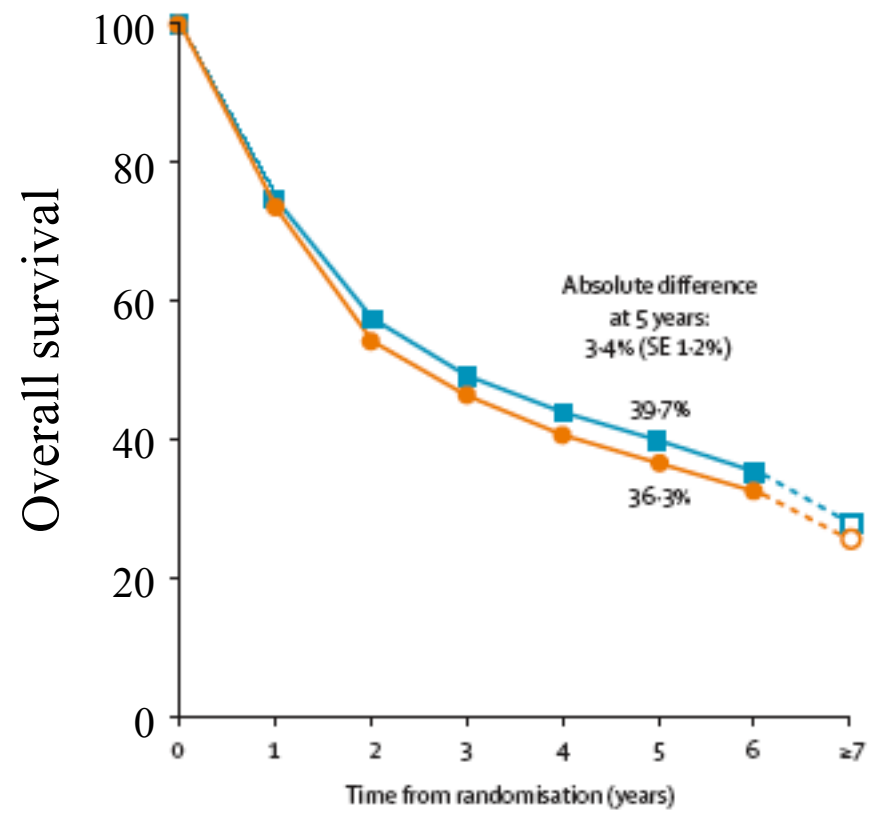
Meta-analysis on altered fractionation HNSCC

Randomized trials 1970-1998 (no postop RT)

15 trials included (6515 patients, individual data)



Death/person years by period	Years 0–2	Years 3–5	Years ≥6
Conventional RT	1612/7062	110/2995	19/1382
Altered fractionated RT	1479/7907	107/3652	24/1765



Death/ person years by period	Years 0–2	Years 3–5	Years ≥6
Conventional RT	1548/4988	506/3729	181/1643
Altered fractionated RT	1526/5447	563/4372	224/2042

Bourhis, Pignon 2006

Meta-analysis on altered fractionation HNSCC

	Hyperfractionation	Accelerated fractionation without total dose reduction	Accelerated fractionation with total dose reduction	p*	Overall	p†
Locoregional control	0·76 (0·66–0·89)	0·79 (0·72–0·87)	0·90 (0·80–1·02)	0·15	0·82 (0·77–0·88)	<0·0001
Local control‡	0·75 (0·63–0·89)	0·74 (0·67–0·83)	0·83 (0·71–0·96)	0·50	0·77 (0·71–0·83)	<0·0001
Regional control‡	0·83 (0·66–1·03)	0·90 (0·77–1·04)	0·87 (0·72–1·06)	0·83	0·87 (0·79–0·97)	0·01
Metastatic control	1·09 (0·76–1·58)	0·93 (0·74–1·19)	0·95 (0·68–1·32)	0·77	0·97 (0·82–1·15)	0·75

*Comparison of the three hazard ratios for each type of radiotherapy. †Test of overall treatment effect. ‡Data from 14 trials; for three trials, only locoregional failure without specification if the failurewas local, regional, or both, was available.

Table: **Hazard ratio (95% CI) of altered fractionated radiotherapy versus conventional radiotherapy on overall population and by type of radiotherapy for locoregional, local, regional, and metastatic control (n=7073)**

Bourhis, Pignon 2006

CHART Bronchus trial (MRC, UK)

Inoperable NSCLC, UICC I-IIIB, WHO 0-1

IIIII IIIII IIIII IIIII IIIII IIIII
60 Gy/ 2.0 Gy/ 6 w

→

IIIIIIIIIIII
IIIIIIIIIIII
IIIIIIIIIIII
54 Gy/ 3 x 1.5 Gy/ ti 6 h/ 12 d

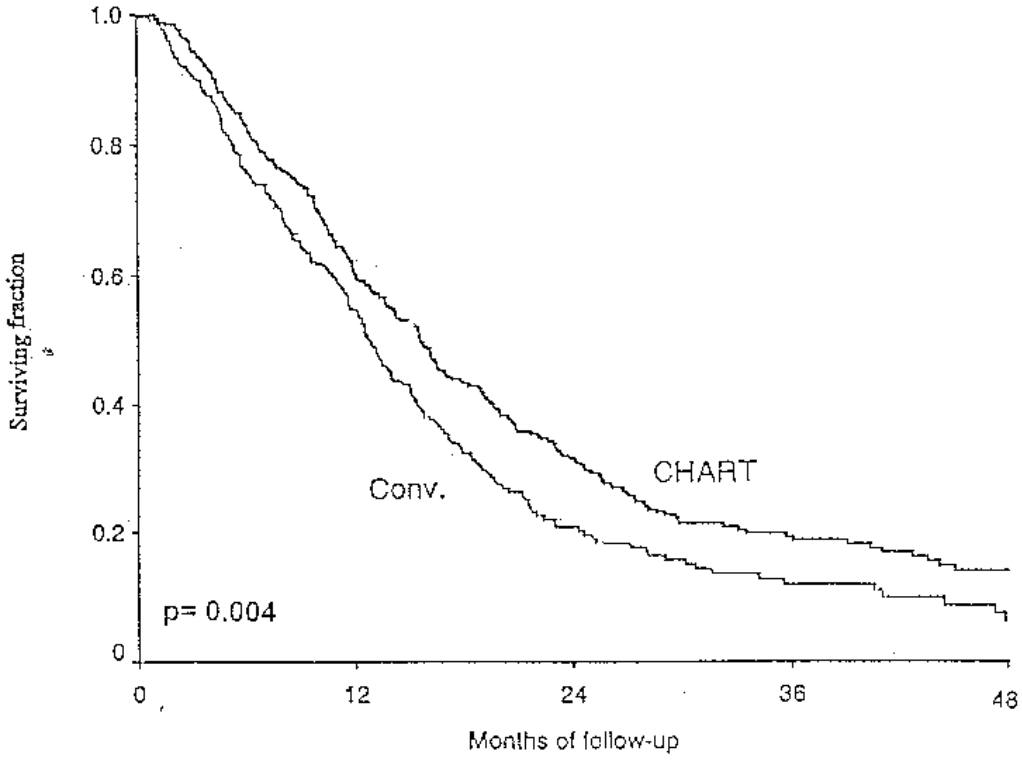


CHART:

- Oesophagitis increased
- Pneumonitis/ Fibrosis constant

Saunders et al., *Lancet* 350: 161-165, 1997

ECOG/RTOG/SWOG - SCLC

Limited disease (hemithorax), 4 cycles Cisplatin/ Etoposid, ti 3w

Start with cycle 1:

IIIII IIIII IIIII IIIII IIIII

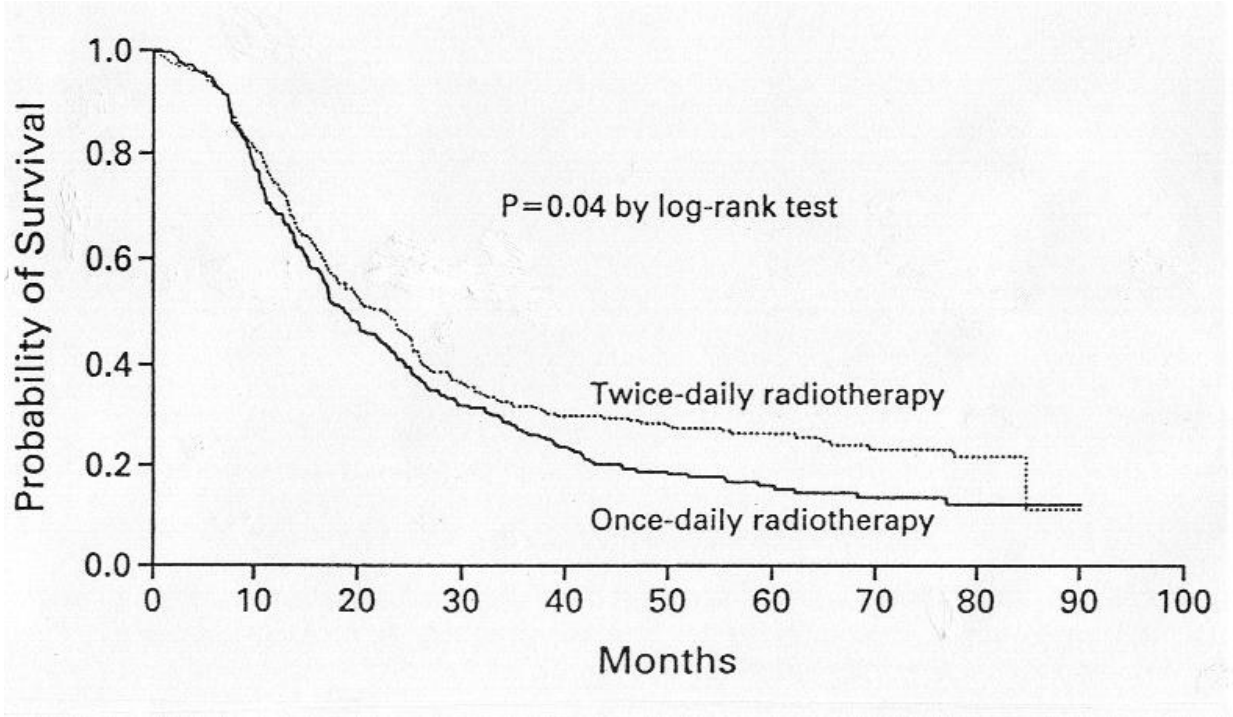
45 Gy/ 1.8 Gy/ 5w (n=206)

Start with cycle 1:

IIIII IIIII IIIII

IIIII IIIII IIIII

45 Gy/ 2 x 1.5 Gy/ 3 w (n=211)



Turrisi et al., *NEJM* 340: 265-271, 1999

Toxicity of RT in HNSCC

Early effect in accelerated or hyperfrationation RxTh

Author	Regimen	Grade 3-4 mucositis	
		Control	Experimental
Horiot (n=356)	HF	49%	67%
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Skladowski (n=99)	Acc. Fract.	26%	56%

Dishes, 1997
Horiot, 1992
Fu, 2000
Skladowski, 2000

RTOG 90-03, adverse effects

Early

Maximum toxicity per patient	Conventional boost	Hyperfract split	Concom	Acc +
Grade 1	5%	3%	4%	7%
Grade 2	57%	39%	36%	41%
Grade 3	35%	54%	58%	49%
Grade 4	0%	1%	1%	2%

Late (> 90 days)

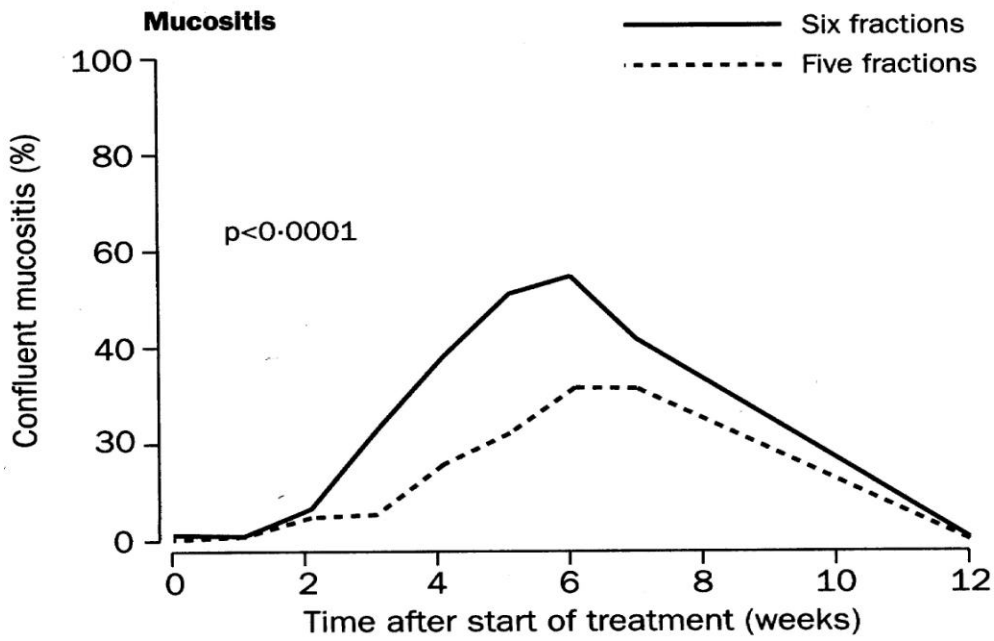
Maximum toxicity per patient	Conventional	Hyperfract boost	Concom split	Acc +
Grade 1	11%	8%	7%	16%
Grade 2	50%	56%	44%	50%
Grade 3	19%	19%	29%	20%
Grade 4	8%	9%	8%	7%
Grade 5	1%	0%	1%	1%

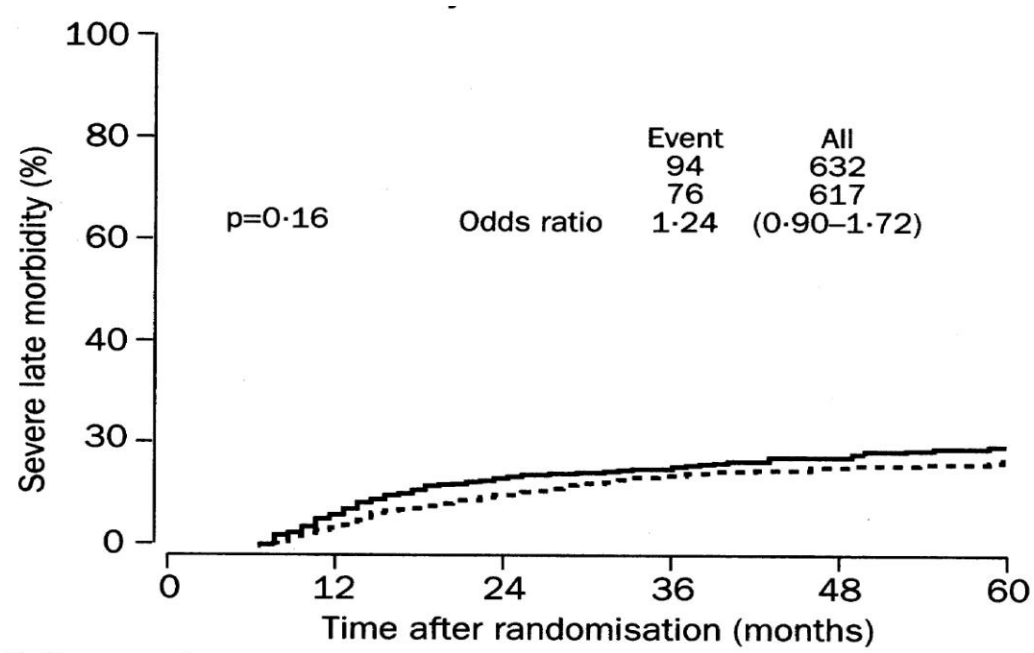
Fu et al, 2000

DAHANCA 6&7 - H&N

SCC - stage II-IV (n=1476)

64-68 Gy/ 2.0 Gy/ 6.5w → 64-68 Gy/ 2.0 Gy/ 5.5w





Overgaard et al. Lancet, 2003

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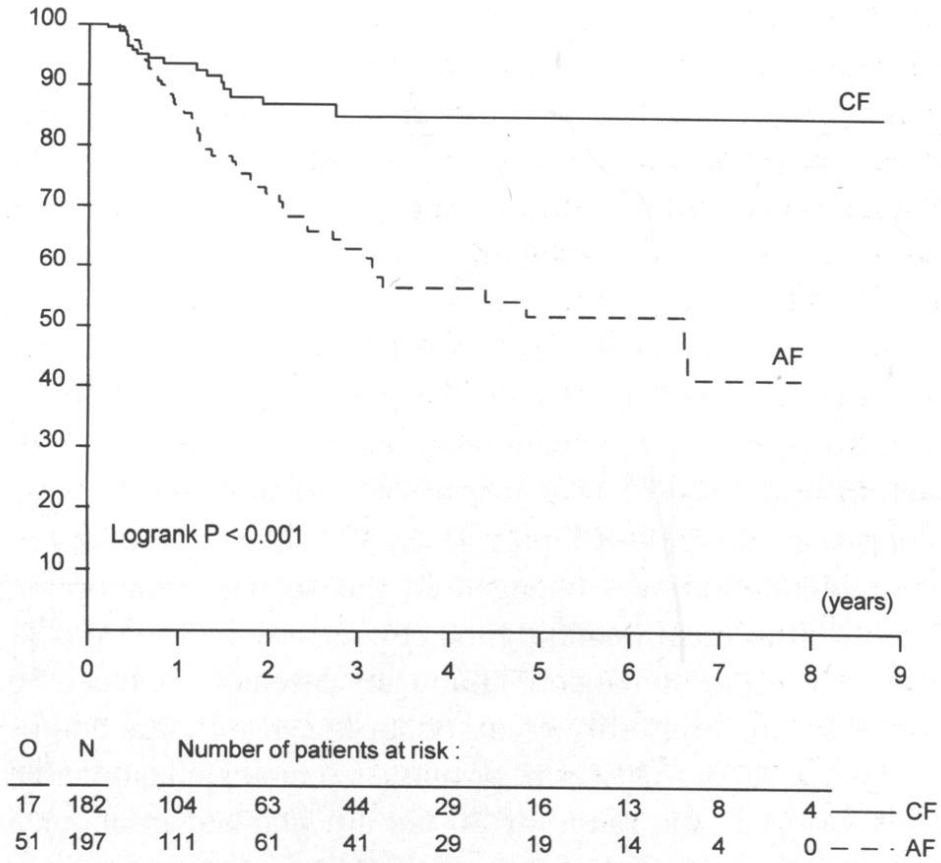
SCC, T2-4 N0-3 M0, WHO 0-2 (n=500)

70 Gy/ 1.8-2.0 Gy/ 7 w (n=253)

72 Gy/ 3 x 1.6 Gy/ ti 4 h/ Pause 12-14d/ 5w (n=247)



Late damage ≥ Grade 3

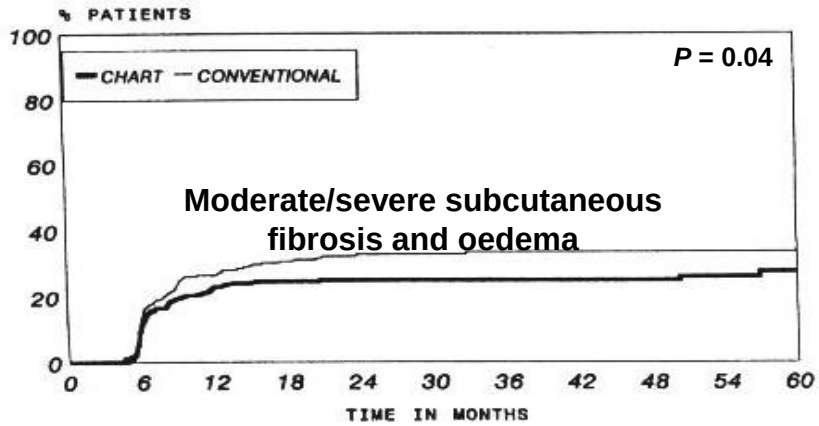
Horiot et al., *Radiother. Oncol.* 44: 111-121, 1997

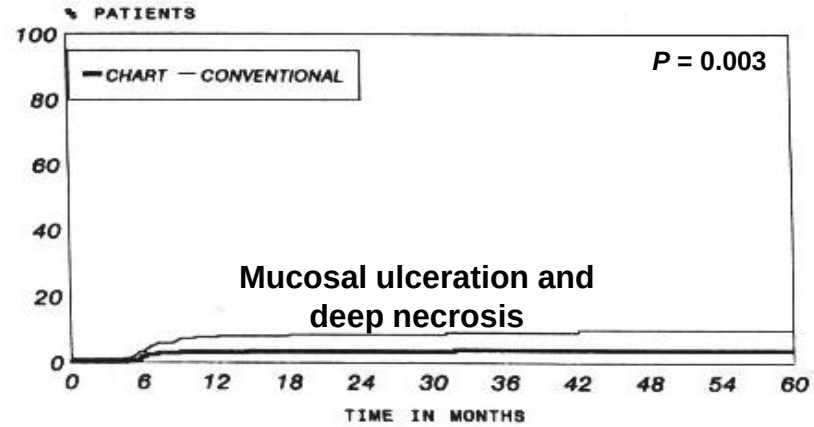
CHART - Head & Neck (MRC, UK)

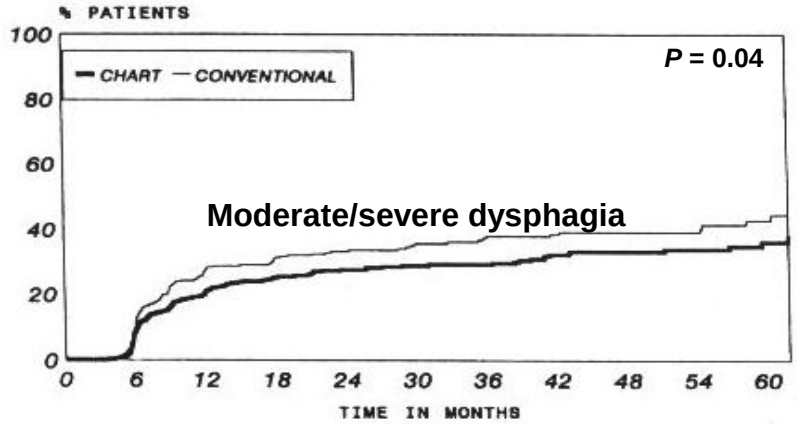
SCC , >T1 N0 M0, WHO 0-1 (n=918)

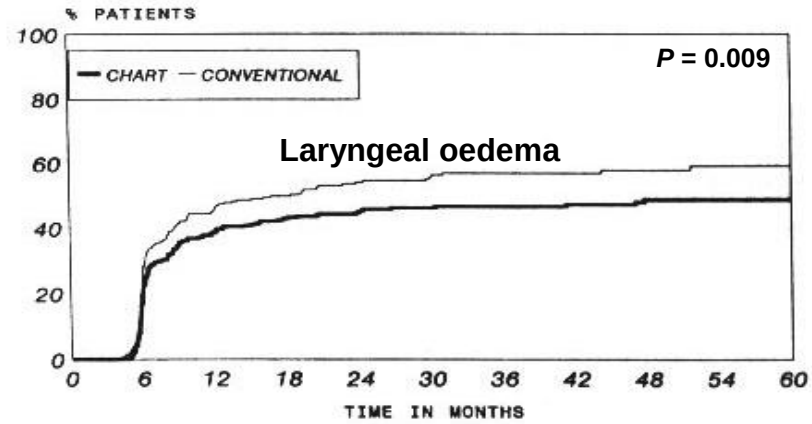
66 Gy/ 2.0 Gy/ 6.5 w (n=366)

54 Gy/ 3 x 1.5 Gy/ ti 6 h/ 12 d (n=552)









Dische et al., *Radiother. Oncol.* 44: 123-136, 1997

Prototypes of modified fractionation

- Hyperfractionation (HF)
- Accelerated fractionation (AF)
- (Hybrid schedules)
- Hypofractionation

Hypofractionation (HypoF)

Increased dose per fraction (> 2.0 Gy)

CF

60Gy/ 2.0 Gy/ 6w

Conventional

m HypoF

75Gy/ 2.5 Gy/ 5w

Moderate Hypo F (curative)

HypoF

67.5 Gy/13.5 Gy/ 2w

Curative RT

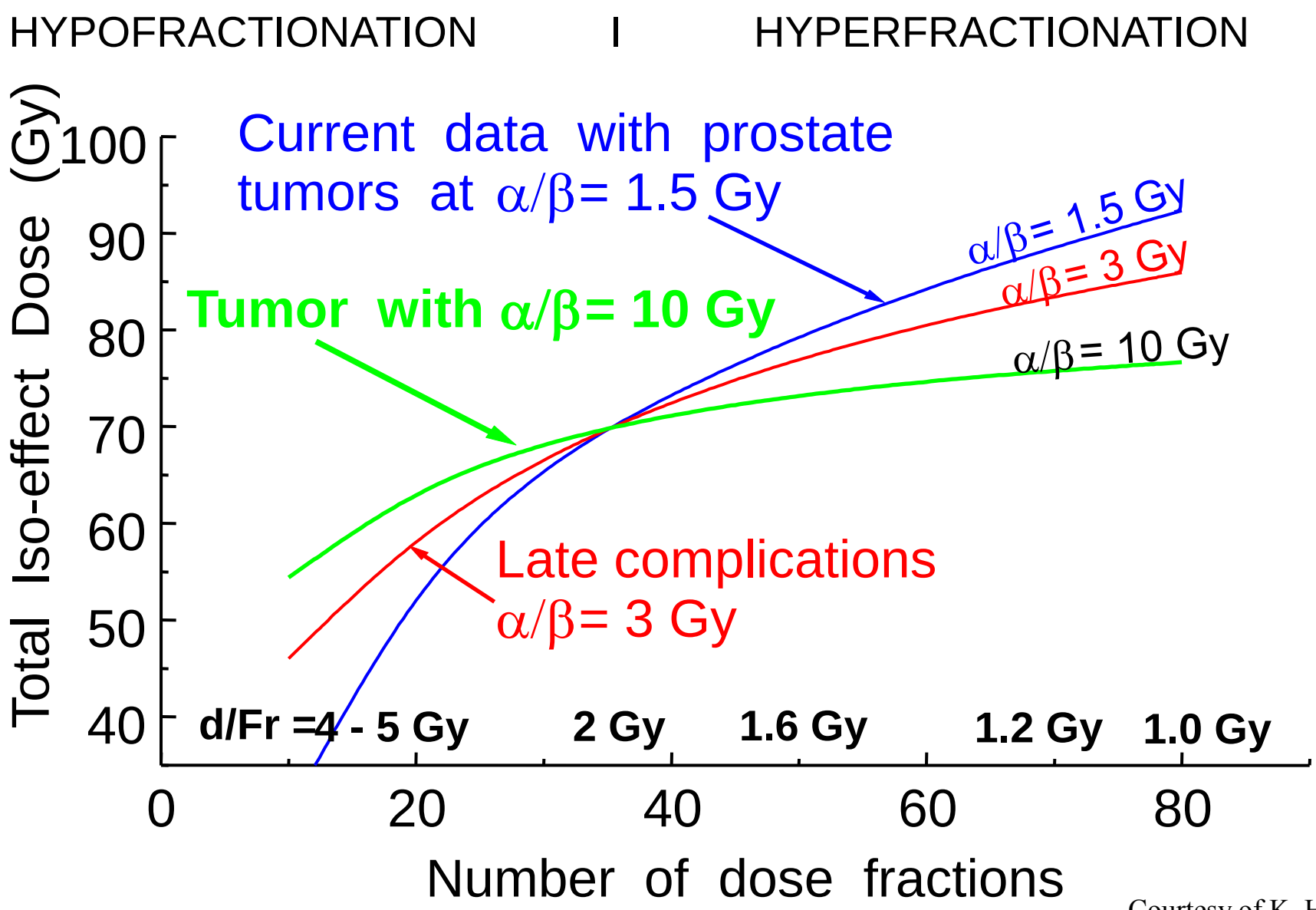
HypoF

SD 8 Gy

30 Gy/ 3.0 Gy/ 2w

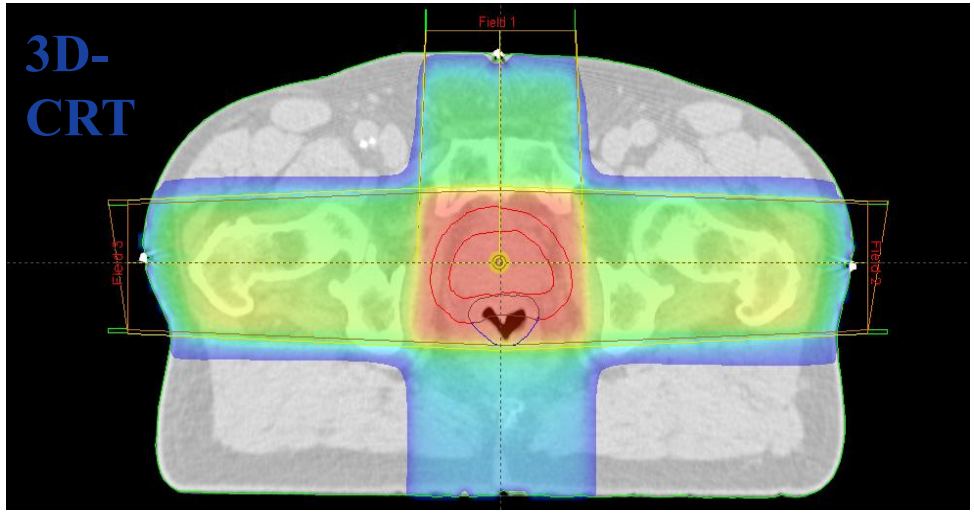
Palliative RT

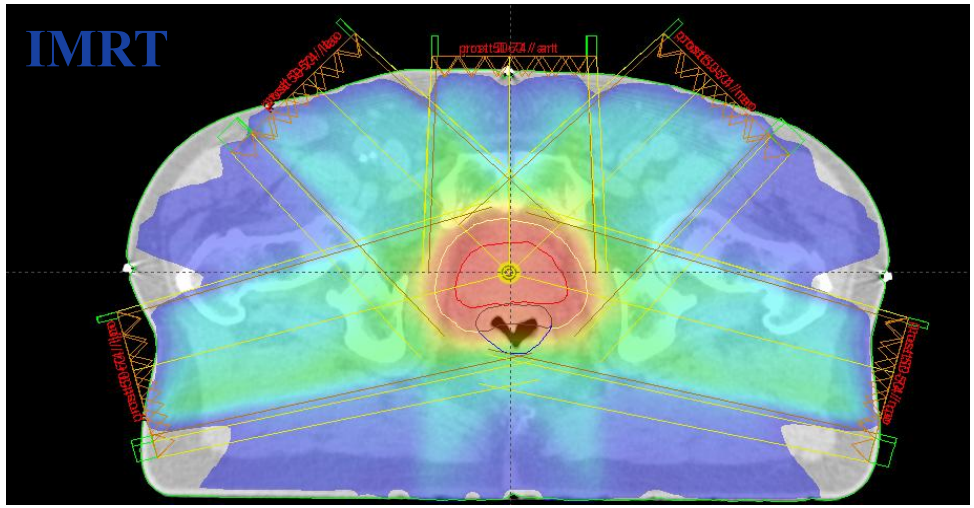
Radiobiological and clinical issues in IMRT for prostate C

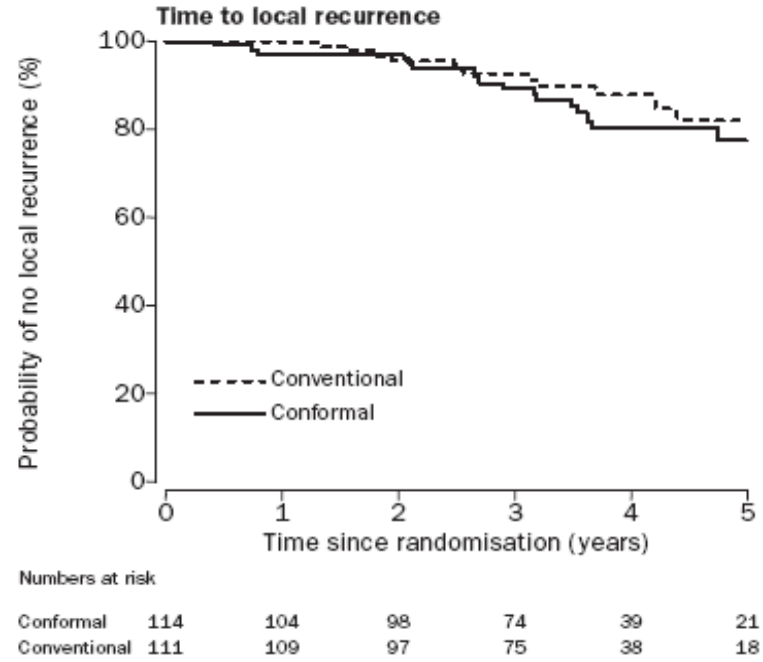


Courtesy of K. Haustermans

Conformal irradiation for prostate tumors



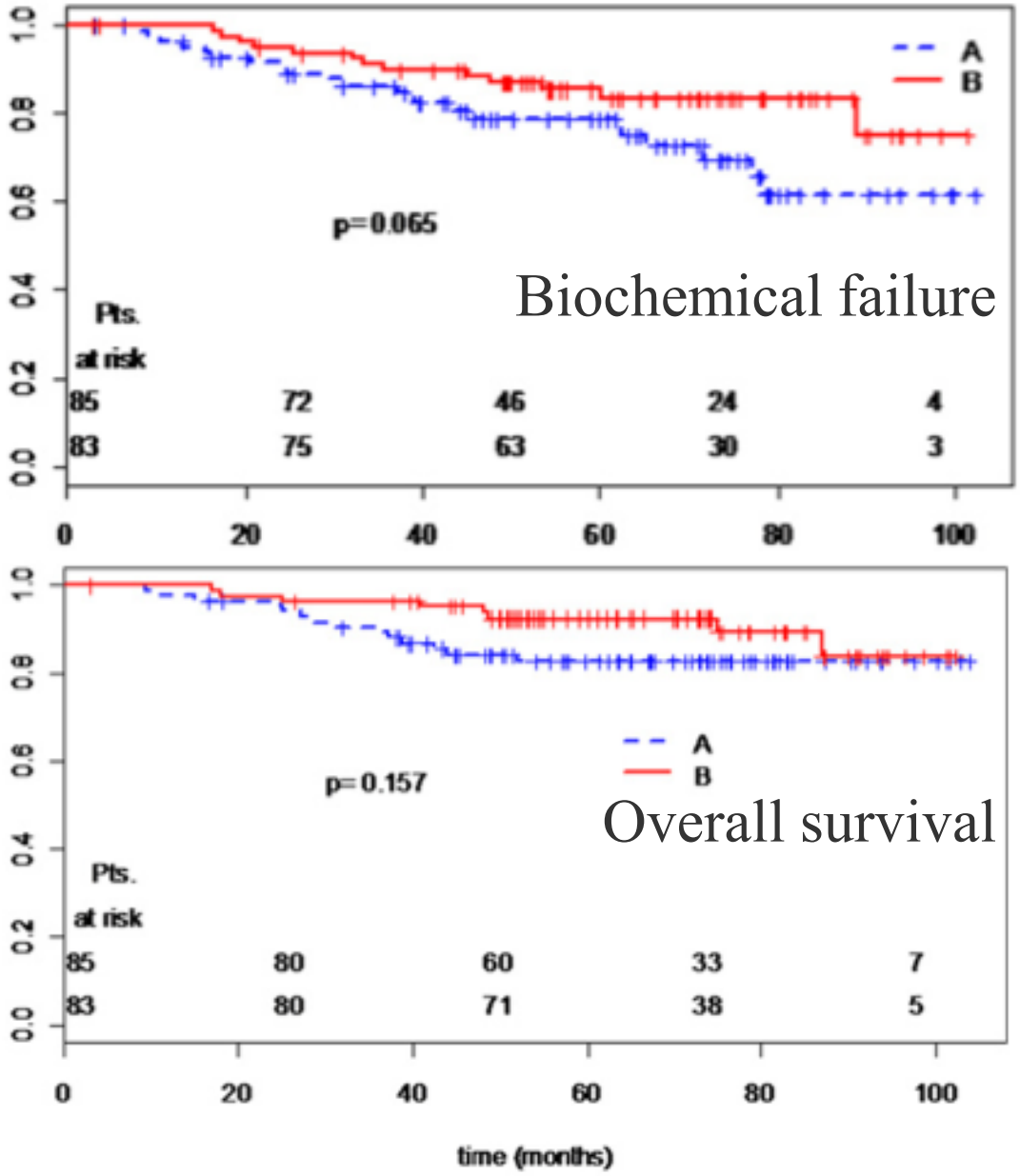




≥ grade 2 proctitis: 15% >< 5% (p= 0.01)

Dearlaney, 1999

Hypofractionation in prostate Ca



9 months of androgen deprivation

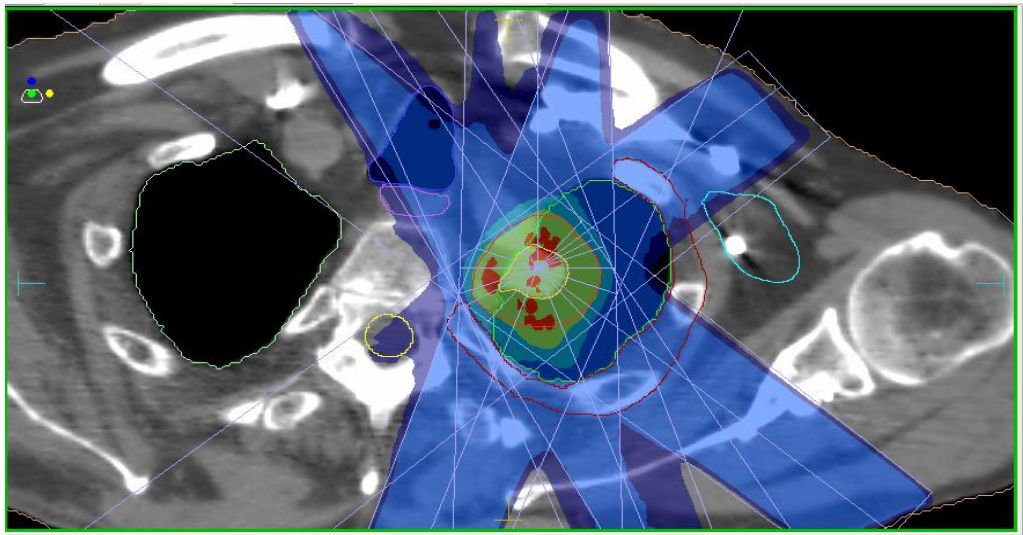
Arm A:
80 Gy, 2 Gy/f, 8 weeks

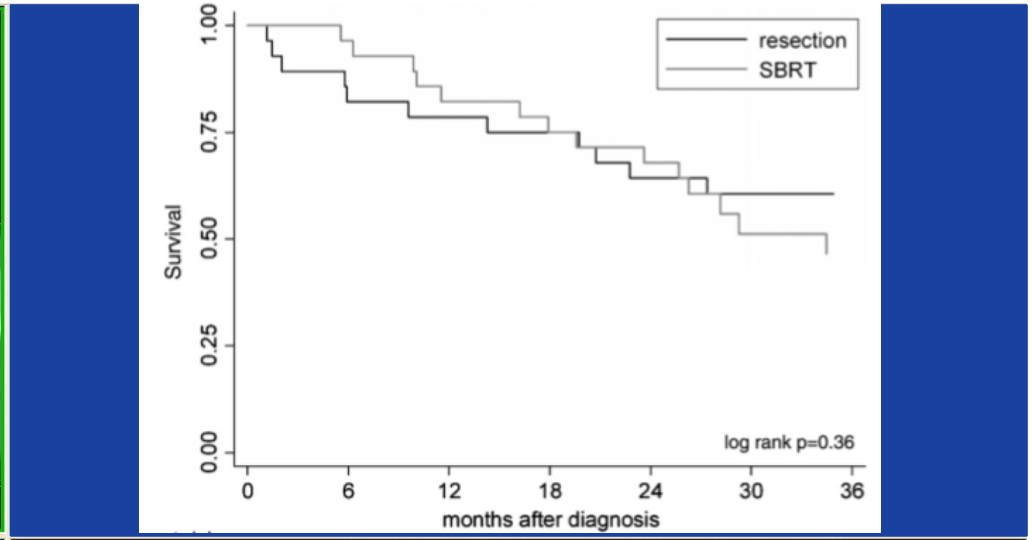
Arm B:
62 Gy, 3.1 Gy/f, 5 weeks

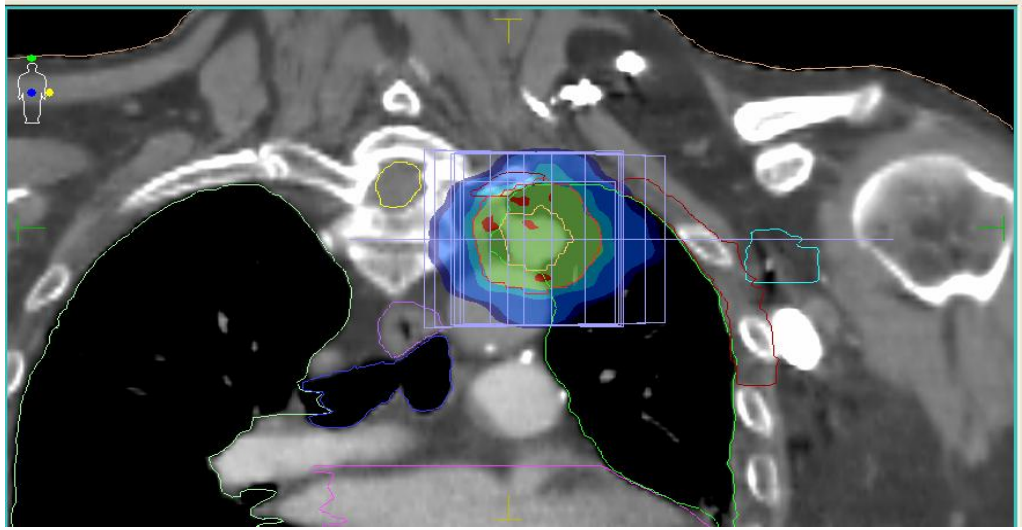
No statistical difference in acute and late radiation toxicity

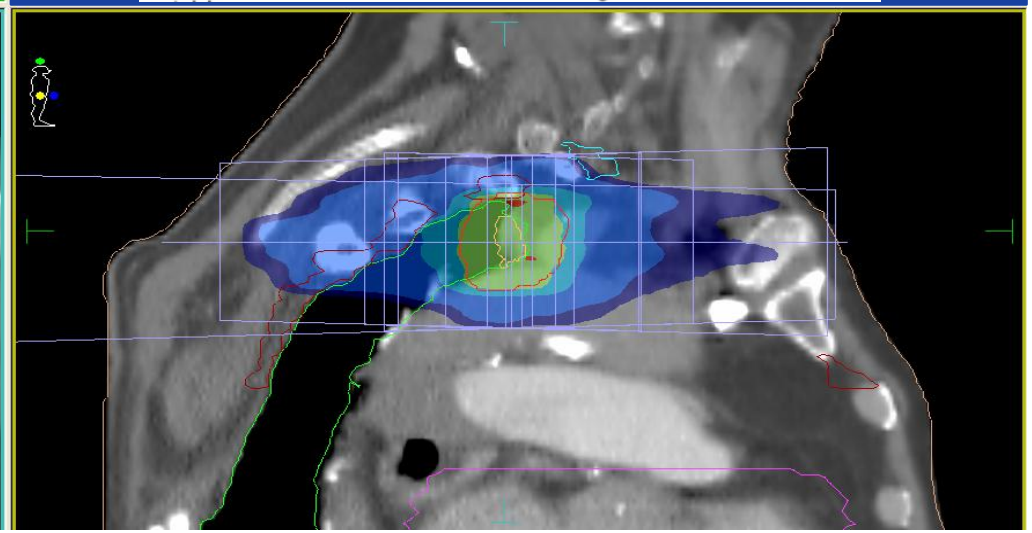
Arcangeli et al., IJROBP 2012

IMRT/SBRT for NSCLC









SBRT – early/late toxicity

- Severe toxicity rate < 5%
- Pneumonia ≥ G3 in 0-5%
- Chest wall toxicity in peripherally located tumors: wall pain, fibrosis, rib fracture in 10%
- Plexopathy in upper tumors
- Severe toxicities (fatale hemoptysis, fistulae…) in centrally-located with 3 fraction schemes

Hurkmans et al, Radiation Oncology 2009

Hypofractionation in NSCLC

Selected published series of stereotactic body radiotherapy for primary non-small cell lung cancer

Reference	Type of publication	Number of patients	Accounting for tumour movement	Location	Dose	Follow-up	Local control	Overall survival	Grade ≥3 radiation toxicity
[21]	Multi-centre retrospective series	257	Varied (breath hold; respiratory gating; slow computed tomography scan)	Peripheral or central	30–84 Gy/1–14 fractions	Median 38 months (2–128)	5 year 84% for BED ≥ 100 Gy	5 year 47% (71% for medically operable, and BED ≥ 100 Gy)	5.4% lung 1% oesophagitis 1.2% dermatitis
[23]	Multi-centre retrospective series	138	Abdominal pressure if needed	Peripheral (mainly) or central	30-48 Gy/2–4 fractions	Median 33 months	88% at median 33 months	3 year 55%	10%
[26]	Multi-centre phase II	57	Abdominal pressure if needed	Peripheral	45 Gy/3 fractions	Median 35 months	3 year 92%	3 year 60%	26% grade 3 2% grade 4
[24]	Single centre retrospective series	68	Planning target volume margins guided by computed tomography assessment	Peripheral or central	24–40 Gy/3–5 fractions	Mean 17 months	3 year 88%	3 year 53%	6% pneumonitis 3% rib fracture
[14]	Single centre phase I, dose escalation	47	Abdominal pressure	Peripheral or central	24 Gy/3 fractions escalating to 72 Gy/3 fractions	Median 15 months	79% at median 15 months	–	11% lung 2% pericardial 2% dermatitis
[27]	Single centre phase II	70	Abdominal pressure	Peripheral or central	60–66 Gy/3 fractions	Median 17.5 months	2 year 95%	2 year 54%	20% (includes 6 possible grade 5 cases)
[28]	Single centre retrospective series	27	Four-dimensional computed tomography planning	Central or superior	40–50 Gy/4 fractions	Median 17 months	100% at median 17 months (50 Gy) or 57% (4 Gy)	–	11% grade 2–3 pneumonitis/ chest wall pain
[30]*	Single centre retrospective series	59	Synchrony respiratory tracking system	Peripheral or central	15–67.5 Gy/1–5 fractions	1–33 months	90% free from persistent or recurrent disease	86%	0% grade 4/5 toxicity 7% grade 1–3 pneumonitis
[9]*	Single centre retrospective series	70	Synchrony respiratory tracking system	Peripheral	45 or 60 Gy/3 fractions	Median 15 months	2 year 96% (60 Gy) or 78% (45 Gy)	2 year 62%	10% late toxicity 4% acute toxicity

Martin et al., 2010

Hypofractionation

Economical consideration

- Significant reduction in machine time
- Less time consuming for the physicists
- Saving of patient time and travel

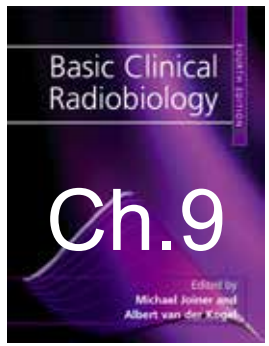
Courtesy of K. Haustermans

ESTRO School

Basic Clinical Radiobiology

Correcting dose errors in radiation treatment delivery

Michael Joiner



Budapest 2016

Example:

Standard treatment is 35 × 2 Gy to 70 Gy.

Initially the schedule is given in error as
4 Gy per fraction for the first 6 fractions

i.e. the first 24 Gy is given “hypofractionated”

How do you correct?

Considering late injury, using $\alpha/\beta = 3$ Gy,

$$EQD2_{late} = 24\left(\frac{4+3}{2+3}\right) = 33.6$$

Therefore, giving the rest of the treatment as

$70 - 33.6 = \mathbf{36.4}$ Gy in 2 Gy fractions

would give equal late injury as 35 × 2 Gy.

In practice, $36.4 \div 2 \approx 18$ (maybe 19) fractions.

Considering tumor effect, using $\alpha/\beta = 10$ Gy,

$$EQD2_{tumor} = 24\left(\frac{4+10}{2+10}\right) = 28$$

Therefore, giving the rest of the treatment as

$70 - 28 = \mathbf{42}$ Gy in 2 Gy fractions

would give equal tumor effect as 35 × 2 Gy.

Thus:

To maintain equal late injury,
total tumor *EQD2* is
28 + 36.4 = **64.4** Gy underdosing by 8%
(12–20% loss in LTCP?)

To maintain equal tumor effect,
total late injury *EQD2* is
33.6 + 42 = **75.6** Gy overdosing by 8%
(10–30% increase in complications?)

A better solution:

The initial error was *hypo*fractionated.

∴ It should be corrected by *hyper*fractionating to achieve identical tumor effect *and* late injury as expected with 35 × 2 Gy.

Solution numerical:

Propose to give the balance of the treatment as ***d*** Gy per fraction to total dose ***D***.

$$D\left(\frac{d+3}{2+3}\right)=36.4$$ for equal late injury

$$D\left(\frac{d+10}{2+10}\right)=42$$ for equal tumor effect

$$\therefore \frac{d+10}{d+3}=\frac{504}{182} \qquad 10D-3D=504-182$$

Thus $d=0.9565[217]$ Gy and $D=46$ Gy

Observation:

24 Gy (4 Gy/#) + 46 Gy (0.96 Gy/#)
= 70 Gy (2 Gy/#)

i.e. the total doses of "error" plus "correction" sum to the ***original total dose prescribed***

How general is this result?

Definitions:

Planned: p Gy per fraction to P Gy

Error: e Gy per fraction to E Gy

Correctdion: d Gy per fraction to D Gy

Int. J. Radiation Oncology Biol. Phys., Vol. 58, No. 3, pp. 871–875, 2004

A SIMPLE α/β-INDEPENDENT METHOD TO DERIVE FULLY ISOEFFECTIVE SCHEDULES FOLLOWING CHANGES IN DOSE PER FRACTION

MICHAEL C. JOINER, M.A., PH.D.

Department of Radiation Oncology, Karmanos Cancer Institute, Wayne State University, Detroit, MI

Purpose: Dosimetric errors in delivering the prescribed dose per fraction made early in a treatment can be corrected by modifying the dose per fraction and total dose given subsequently to discovery of the error, using the linear-quadratic model to calculate the correcting doses which should be completed within the same overall time as originally prescribed. This study shows how these calculations can be carried out independently of any α/β ratios to bring the treatment back exactly to planned tolerance simultaneously for all tissues and tumor involved.

Methods: Planned treatment is defined as p Gy per fraction to a total dose P Gy; the initial error is e Gy per fraction given to a total of E Gy. The linear-quadratic formula is assumed to describe all isoeffect relationships between total dose and dose per fraction.

Results and Conclusion: An exact solution is found that describes a compensating dose of d Gy per fraction to a total of D Gy. The formulae are:

$$D = P - E$$

$$d = \frac{Pp - Ee}{P - E}$$

Thus the total dose for the complete treatment (error plus compensation) remains as originally prescribed, with hyperfractionation being used to correct an initial hypofractionation error and hypofractionation being used to correct an initial hyperfractionation error. Incomplete repair is shown to perturb this exact solution. Thus compensating treatments calculated with these formulae should not be scheduled in such a manner that would introduce incomplete repair.

Result

$$D \equiv P - E$$

$$d = \frac{Pp - Ee}{P - E}$$

Example revisited:

Standard treatment is 35 × 2 Gy to 70 Gy.

Initially the schedule is given in error as 4 Gy per fraction for the first 6 fractions

i.e. the first 24 Gy is given "hypofractionated"

Compensation:

$$70 - 24 = 46$$

$$\frac{70 \times 2 - 24 \times 4}{70 - 24} = 0.9565...$$

46/0.9565… = **48** fractions; *d* = **0.958 Gy**

Another example:

Standard treatment is 35 × 2 Gy to 70 Gy.

Initially the schedule is given in error as 4 Gy per fraction for the first 3 fractions

i.e. the first 12 Gy is given "hypofractionated"

Compensation:

$$70 - 12 = 58$$

$$\frac{70 \times 2 - 12 \times 4}{70 - 12} = 1.5862...$$

58/1.5862… = **37** fractions; *d* = **1.568 Gy**

Common errors - summary

Planned 35 × 2 Gy to 70 Gy, Error = 4 Gy per fraction

Error	Correction		
	***D* Gy**	***d* Gy**	***n***
1 × 4 Gy to **4** Gy	66	1.886	35
2 × 4 Gy to **8** Gy	62	1.722	36
3 × 4 Gy to **12** Gy	58	1.568	37
4 × 4 Gy to **16** Gy	54	1.421	38
5 × 4 Gy to **20** Gy	50	1.190	42
6 × 4 Gy to **24** Gy	46	0.958	48

Further example:

Standard treatment is 35 × 2 Gy to 70 Gy.

Initially the schedule is given in error as 1 Gy per fraction for the first 4 fractions

i.e. the first 4 Gy is given "*hyper*fractionated"

Compensation:

$$70 - 4 = 66$$

$$\frac{70 \times 2 - 4 \times 1}{70 - 4} = 2.0606...$$

66/20.0606… = **32** fractions; *d* = **2.063 Gy**

Common errors - summary

Planned 35 × 2 Gy to 70 Gy, Error = 1 Gy per fraction

Error	Correction		
	***D* Gy**	***d* Gy**	***n***
1 × 1 Gy to **1** Gy	69	2.029	34
2 × 1 Gy to **2** Gy	68	2.000	34
3 × 1 Gy to **3** Gy	67	2.030	33
4 × 1 Gy to **4** Gy	66	2.063	32
5 × 1 Gy to **5** Gy	65	2.097	31
6 × 1 Gy to **6** Gy	64	2.065	31

Remember…

$$D = P - E$$

$$d = \frac{Pp - Ee}{P - E}$$

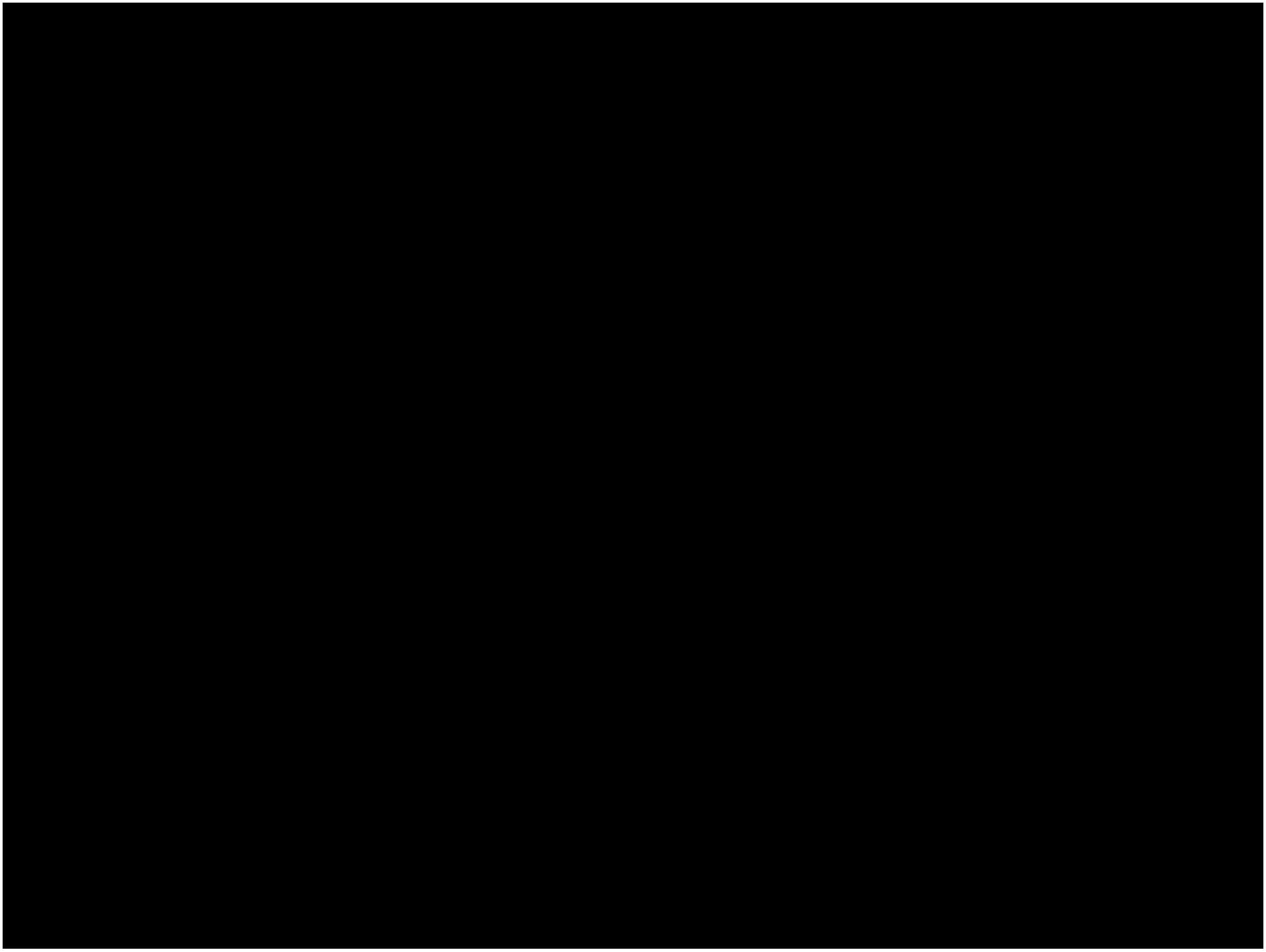
Joiner MC.
Int J Radiat Oncol Biol Phys
2004:58,871-5

Generalization

Any plan (P, p) of dose per fraction p to total dose P, may be given to identical effect in all tissues and tumors using components (Q, q), (R, r), (S, s), (T, t) etc., where:

$$P = Q + R + S + T + \ldots$$

$$Pp = Qq + Rr + Ss + Tt + \ldots$$



Correcting dose errors in radiation treatment delivery: *Derivation of formulae*

Michael Joiner

Int. J. Radiation Oncology Biol. Phys., Vol. 58, No. 3, pp. 871–875, 2004

BIOLOGY CONTRIBUTION

A SIMPLE α/β-INDEPENDENT METHOD TO DERIVE FULLY ISOEFFECTIVE SCHEDULES FOLLOWING CHANGES IN DOSE PER FRACTION

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Results and Conclusion: An exact solution is found that describes a compensating dose of d Gy per fraction to a total of D Gy. The formulae are:

$$D = P - E$$

$$d = \frac{Pp - Ee}{P - E}$$

Thus the total dose for the complete treatment (error plus compensation) remains as originally prescribed, with hyperfractionation being used to correct an initial hypofractionation error and hypofractionation being used to correct an initial hyperfractionation error. Incomplete repair is shown to perturb this exact solution. Thus compensating treatments calculated with these formulae should not be scheduled in such a manner that would introduce incomplete repair.

Definitions:

Planned: *p* Gy per fraction to *P* Gy
Error: *e* Gy per fraction to *E* Gy
Correctdion: *d* Gy per fraction to *D* Gy

α/β for Late injury *L*
α/β for Tumor effect *T*

Try to remember these!

late injury from error $$D_{pEQlate} = E\left(\frac{e+L}{p+L}\right)$$

balance to get planned late effect $$P - E\left(\frac{e+L}{p+L}\right)$$

but $$P - E\left(\frac{e+L}{p+L}\right) = D\left(\frac{d+L}{p+L}\right)$$

$$\therefore \boxed{P\left(p+L\right) - E\left(e+L\right) = D\left(d+L\right)}$$

tumor effect from error $D_{pEQtumor} = E\left(\frac{e+T}{p+T}\right)$

balance to get
planned tumor effect $P - E\left(\frac{e+T}{p+T}\right)$

but $P - E\left(\frac{e+T}{p+T}\right) = D\left(\frac{d+T}{p+T}\right)$

$$\therefore \boxed{P\left(p+T\right) - E\left(e+T\right) = D\left(d+T\right)}$$

$$P(p+L)-E(e+L)=D(d+L)$$

$$P(p+T)-E(e+T)=D(d+T)$$

Expanding:

$$\cancel{Pp}+PL-\cancel{Ee}-EL=\cancel{Dd}+DL$$

$$\cancel{Pp}+PT-\cancel{Ee}-ET=\cancel{Dd}+DT$$

Subtracting and grouping:

$$P\cancel{(L-T)}-E\cancel{(L-T)}=D\cancel{(L-T)}$$

$$\boxed{D=P-E}$$

QED

$$D = P - E$$

Notes:

1. This is independent of α/β for either late injury or tumor response.
   i.e. L and T can take **any** values and still $D = P - E$.
2. Because of α/β independence, it follows that *acute* injury will also be identical to the original plan. In fact, **all** biological effects will be the same as the original plan, so long as their radiation response is described by LQ.

Substitute back: $D = P - E$ into

either $Pp + PL - Ee - EL = Dd + DL$

or $Pp + PT - Ee - ET = Dd + DT$

Hence:

$$d = \frac{Pp - Ee}{P - E}$$

Notes:

3. Size of *d* is also independent of all *α*/*β* values.

Result

$$D = P - E$$

$$d = \frac{Pp - Ee}{P - E}$$

Generalization

Any plan (P, p) of dose per fraction p to total dose P, may be given to identical effect in all tissues and tumors using components (Q, q), (R, r), (S, s), (T, t) etc., where:

$$P = Q + R + S + T + \ldots$$

$$Pp = Qq + Rr + Ss + Tt + \ldots$$

After thoughts

1. What initial errors (*e*, *E*) would it **not** be possible to compensate exactly for?

After thoughts 1

Refer to: $d = \frac{Pp - Ee}{P - E}$

If $E < P$ **and** $e < p$ (**hyper**fractionation error), this can be compensated only if $D > d$,

i.e. $(P - E)^2 > Pp - Ee$

This is always true if $E/e \leq P/p$, *i.e.* the number of fractions given in error never exceeds the original number of fractions planned.

After thoughts 1

Refer to: $d = \frac{Pp - Ee}{P - E}$

If $E < P$ **and** $e > p$ (**hypo**fractionation error), this can be compensated only if

$$Ee < Pp$$

This could easily be violated, *e.g.* in the teaching example $Pp = 140$, $e = 4$, so if ≥ 9 fractions are given in error then compensation is not possible.

After thoughts

2. What about Incomplete Repair?

After thoughts 2

Recall: $$P\left(p+L\right)-E\left(e+L\right)=D\left(d+L\right)$$

$$P\left(p+T\right)-E\left(e+T\right)=D\left(d+T\right)$$

If *d* is small, multiple fractions per day might be used to compensate (*e*, *E*)

Hence:

$$P\left(p+L\right)-E\left(e+L\right)=D\left(d(1+H_{ML})+L\right)$$

$$P\left(p+T\right)-E\left(e+T\right)=D\left(d(1+H_{MT})+T\right)$$

After thoughts 2

Subtracting and grouping:

$$P\left(L-T\right)-E\left(L-T\right)=D\left(L-T\right)$$
$$+Dd\left(H_{ML}-H_{MT}\right)$$

If repair half-times for different tissues (*e.g.* late and tumor) are equal, then the *Dd* term disappears. However, generally this will not be the case.

After thoughts 2

Therefore to use these simple formulæ for calculating compensating schedules, plan a *maximum* of 2 fractions per day with *maximum* interval between to **avoid** incomplete repair.

Use weekend days to achieve correction, when possible.

After thoughts

3. What about Dose Inhomogeneity?

After thoughts 3

Suppose the formulæ are used to correct the 100% isodose. At any other point in the treatment plan, the dose delivered is a fraction *f* of the 100% isodose. Do the formulæ still hold?

At any other point, the doses now are:

Planned:	*fp* Gy per fraction to *fP* Gy
Error:	*fe* Gy per fraction to *fE* Gy
Correctdion:	*fd* Gy per fraction to *fD* Gy

After thoughts 3

Correcting the doses at point f:

$$D_f = fP - fE = f(P - E)$$

$$\therefore \quad \boxed{D_f = fD} \quad QED$$

$$d_f = \frac{fPfp - fEfe}{fP - fE} = \frac{f^2(Pp - Ee)}{f(P - E)}$$

$$\therefore \quad \boxed{d_f = fd} \quad QED$$

Hence the simple formulæ correct for all tissues and all points in the treatment plan simultaneously, producing a result that is **biologically identical**, in the patient, to the effects of the original treatment plan.

Conclusion

$$D = P - E$$

$$d = \frac{Pp - Ee}{P - E}$$

Joiner MC.
Int J Radiat Oncol Biol Phys
2004;58:871-5

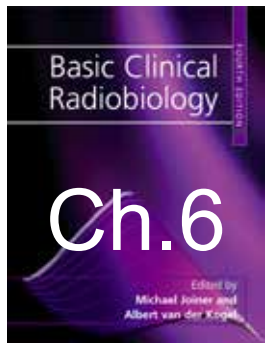
ESTRO School

Basic Clinical Radiobiology

LET and RBE

Michael Joiner

Budapest 2016



Wide spectrum of DNA damage

Class	Initial physical damage	Typical energy and target dimensions	Possible target	Frequency of occurrence (cell^{-1} Gy^{-1})†	Comment
1	Sparse	Few tens of eV within ~2 nm	DNA segment	~10^3	Little biological rele
2	Moderate cluster	~100 eV within ~2 nm	DNA segment	~20–100	Charact ~repair
3	Large cluster	~400 eV within 5–10 nm	Nucleosome	~4–100	Char ~un
4	Very large cluster	~800 eV within 5–10 nm	(Nucleosome)	~0–4	Unique to high-LET;

SSB

simple DSB

complex DSB

very complex DSB

†These frequencies assume that the targets are as in the previous column and that all the cell's DNA (~6 pg) is arranged in this way (Goodhead and Nikjoo 1989).

Linear Energy Transfer (LET)

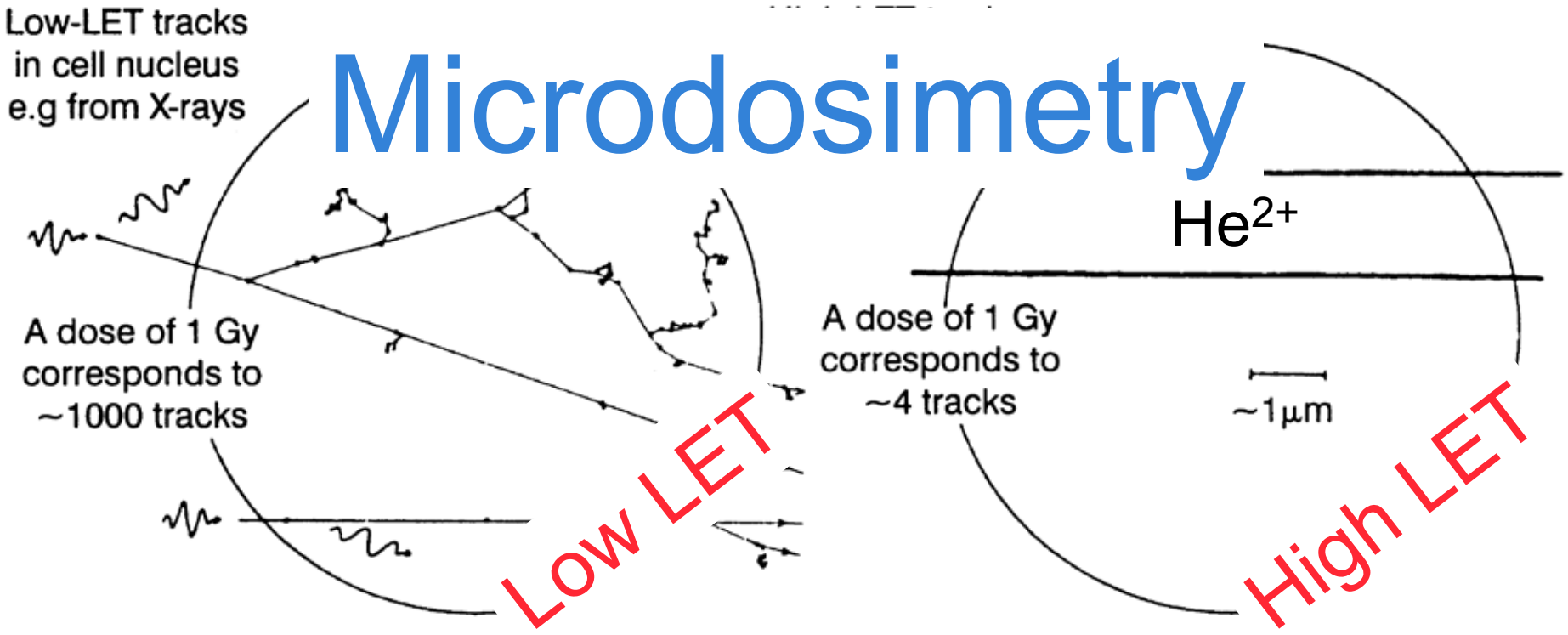
$$\mathrm{LET} = \mathrm{d}E/\mathrm{d}l$$

Where:

$\mathrm{d}E$ is the average energy locally imparted to the medium by a charged particle of a specified energy in traversing a distance of length $\mathrm{d}l$.

Units are typically $\mathrm{keV\ \mu m^{-1}}$ (keV/μm)

Microdosimetry



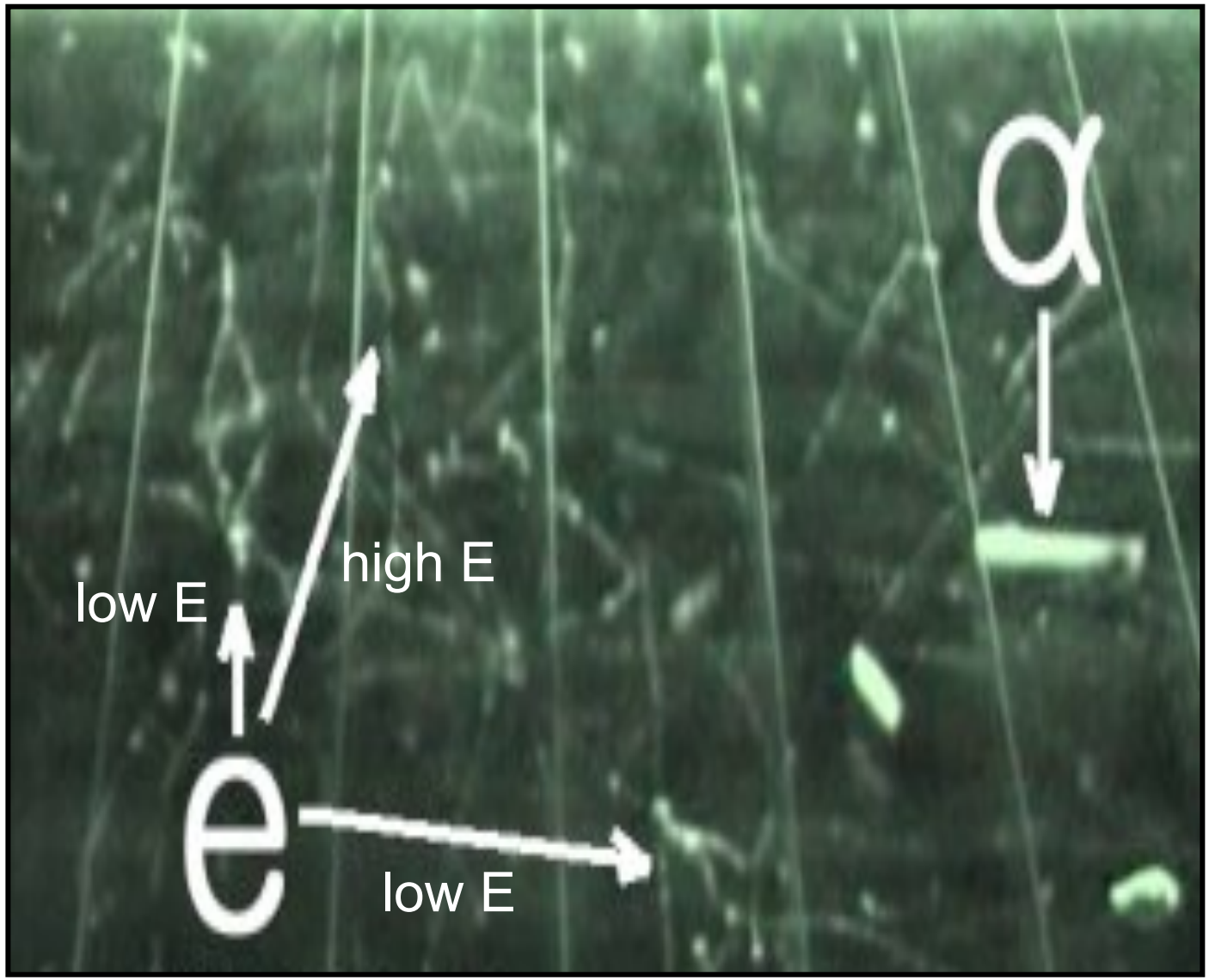
LET: Linear Energy Transfer.

A measure of average ionization density.

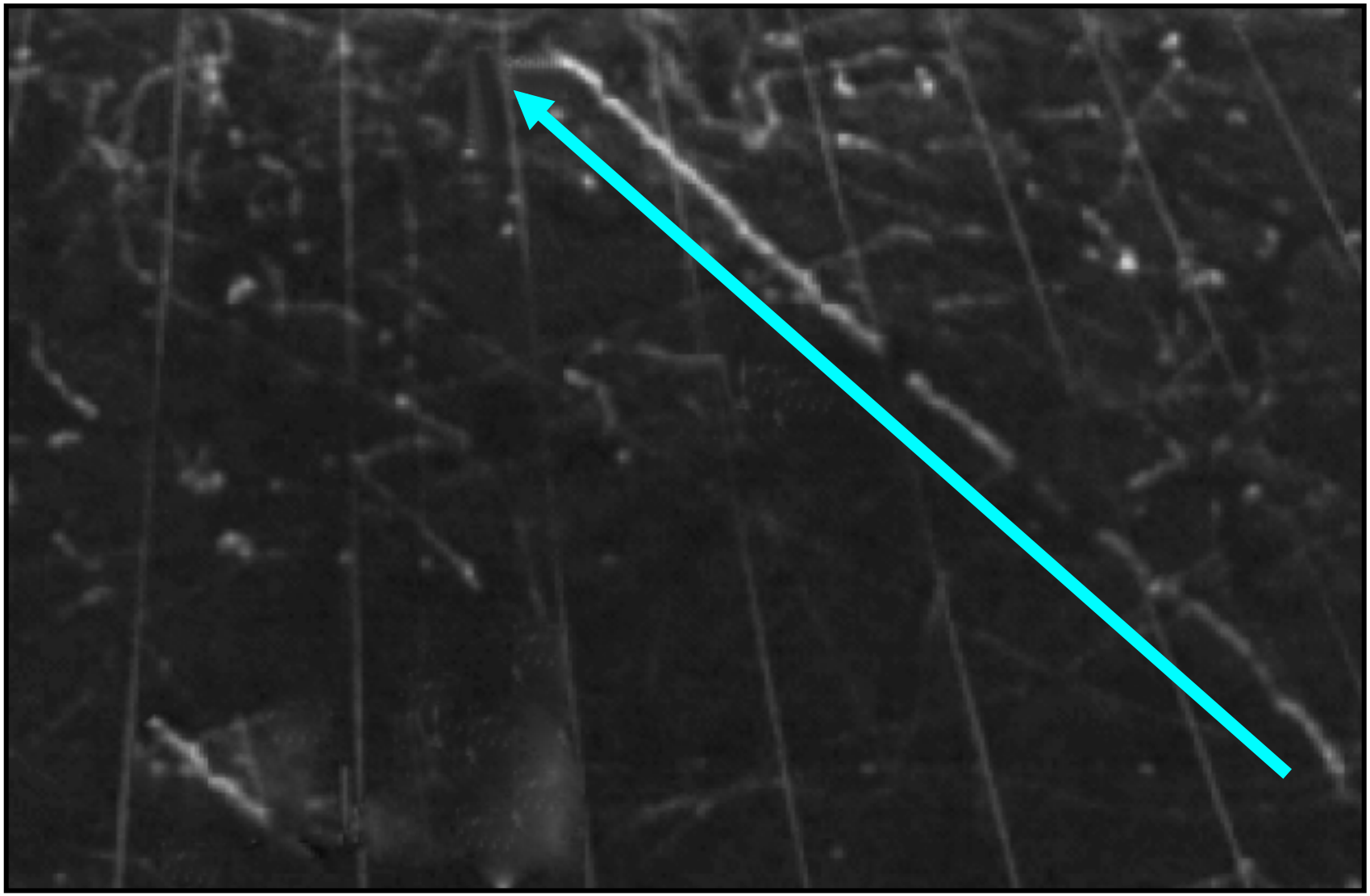
$$LET \propto \frac{charge^2}{velocity^2}$$

Charged particle tracks in a cloud chamber

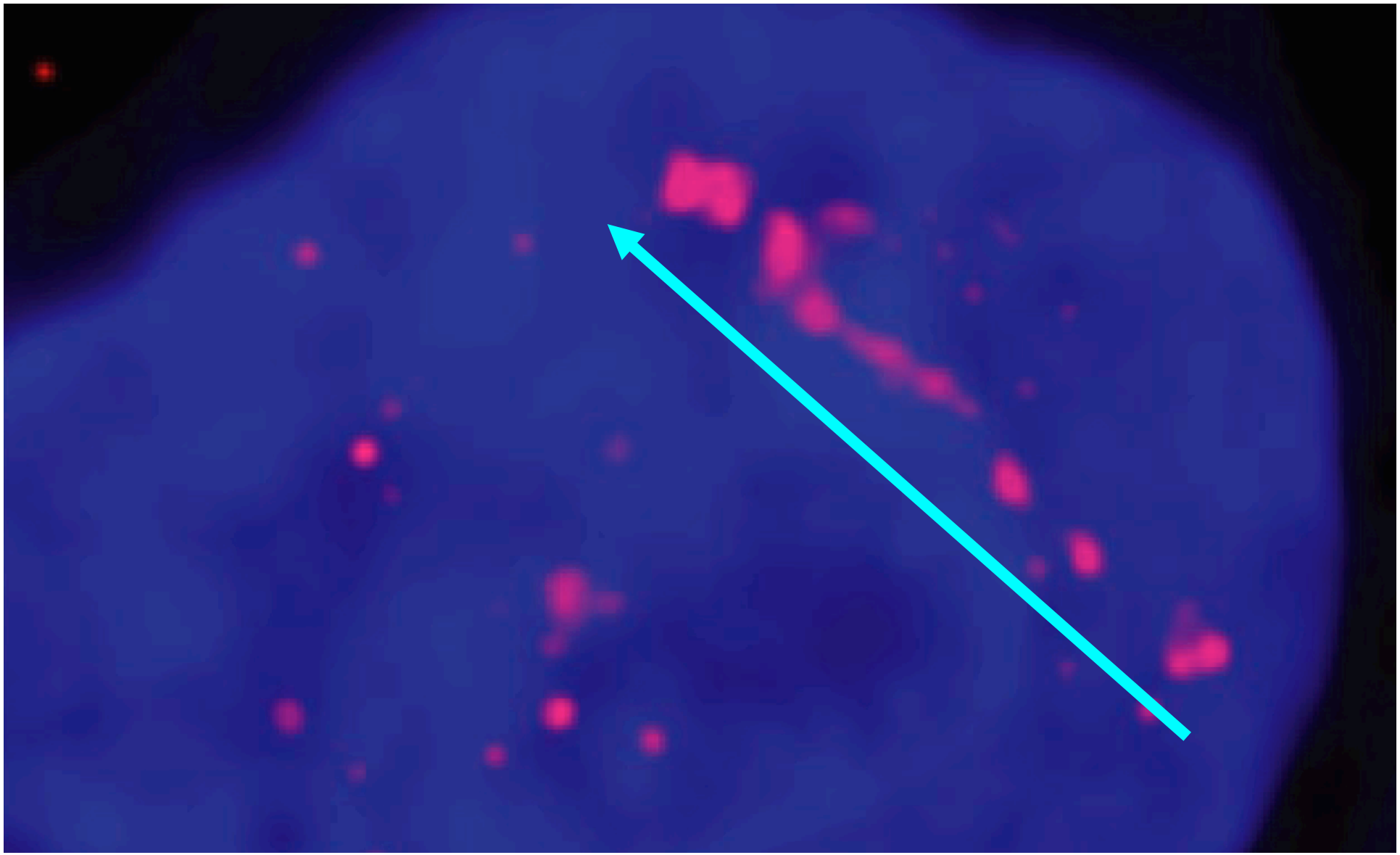
Cloud chamber photograph shows many high-energy electrons (thin tracks), low energy electrons (thicker tracks), and α particles (thickest tracks)



Cloud chamber photo of charged particle slowing down from lower right to upper left



Initial DNA damage from an α particle, measured by histone H2AX accumulation



Typical LET values

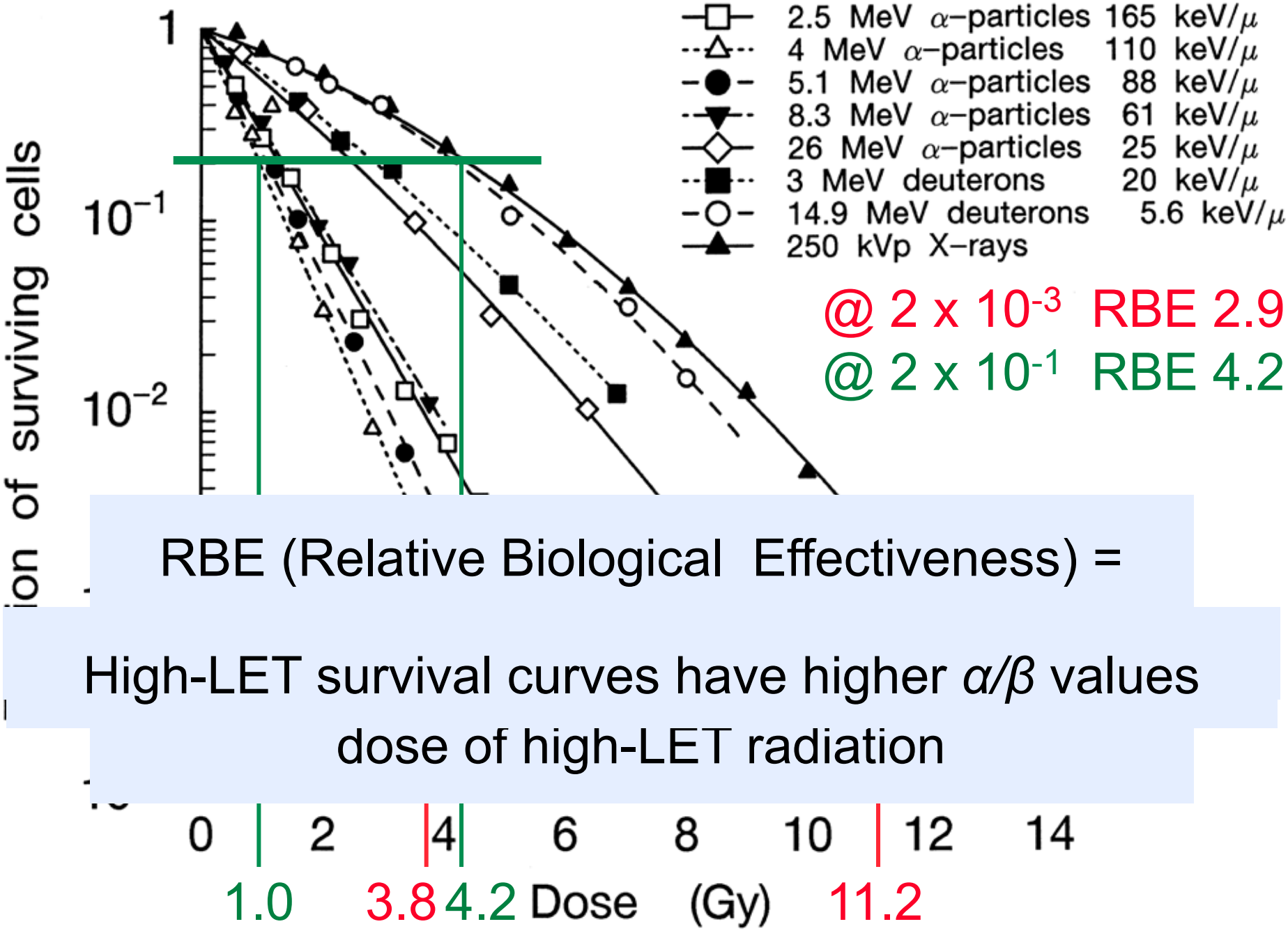
Radiation	Linear Energy Transfer, KeV/μm		
Cobalt-60 γ-rays		0.2	
250-kV x-rays		2.0	
10-MeV protons		4.7	
150-MeV protons		0.5	
	Track Avg.		Energy Avg.
14-MeV neutrons	12		100
2.5-MeV α-particles		166	
2-GeV Fe ions		1,000	

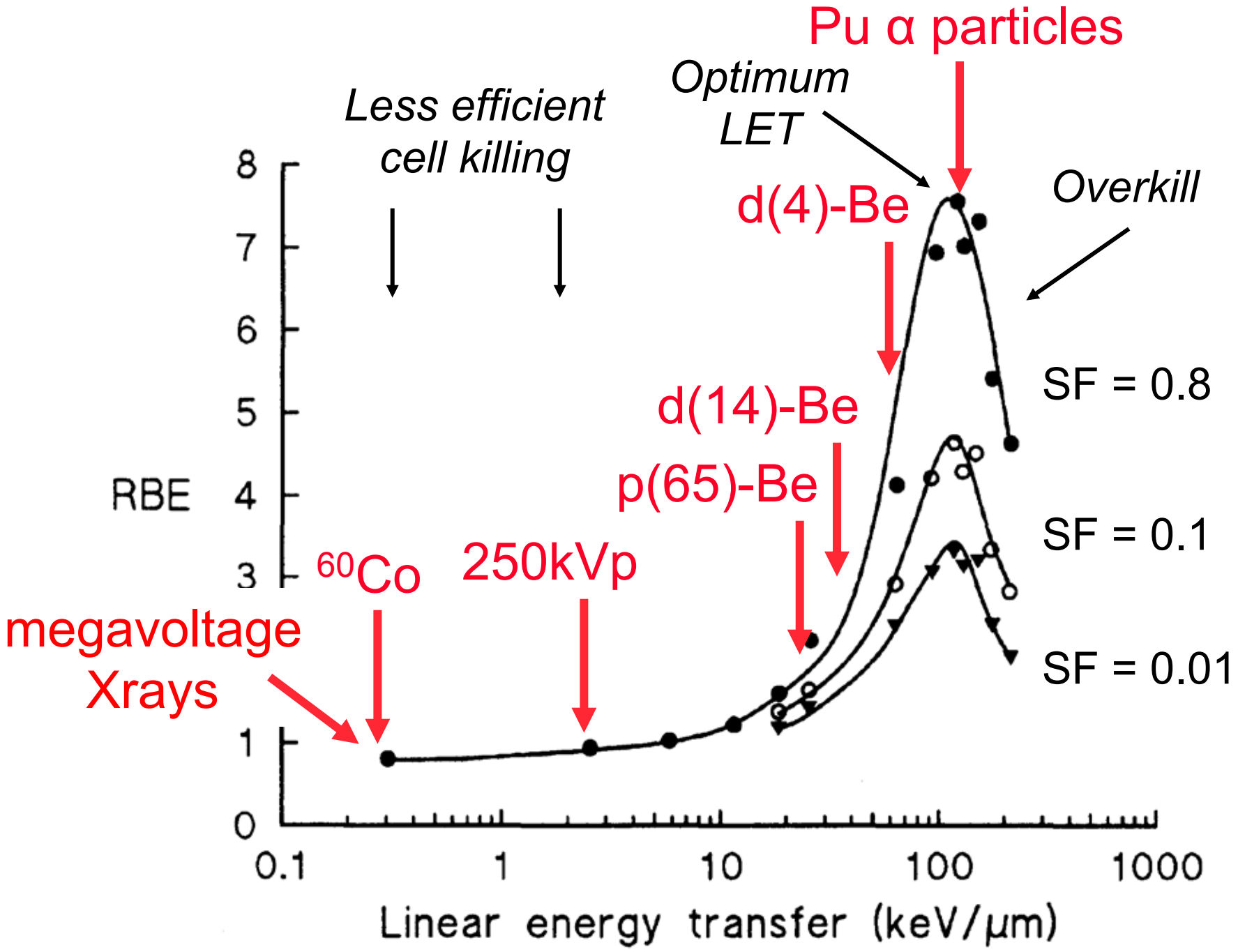
Relative Biological Effectiveness (RBE)

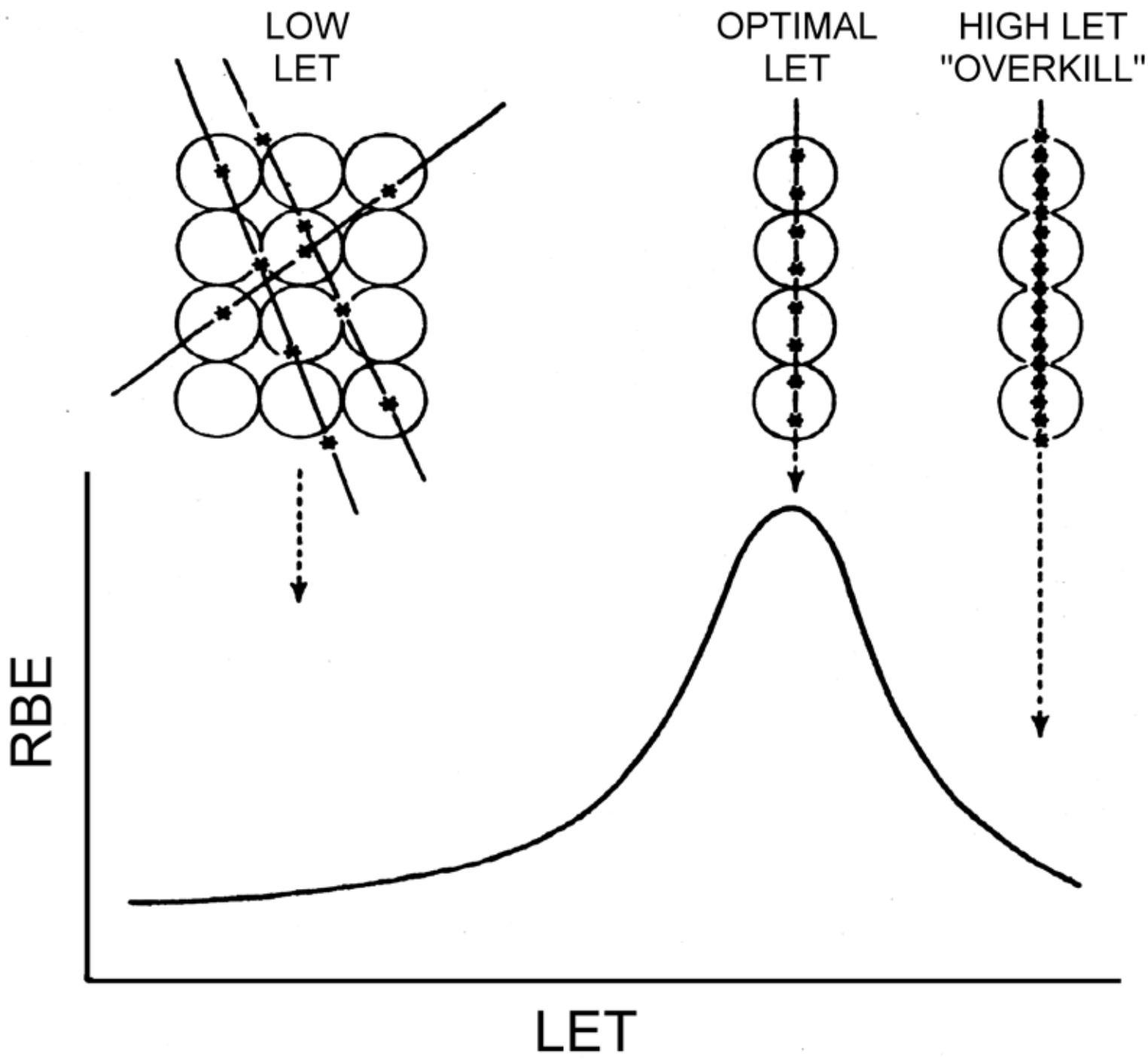
$$RBE = \frac{\textit{dose of a } \textbf{standard radiation}}{\textit{dose of the } \textbf{test radiation}}$$

to produce the same biological effect, where the "standard radiation" is usually either orthovoltage X rays (~250 kVp) or ^{60}Co γ rays

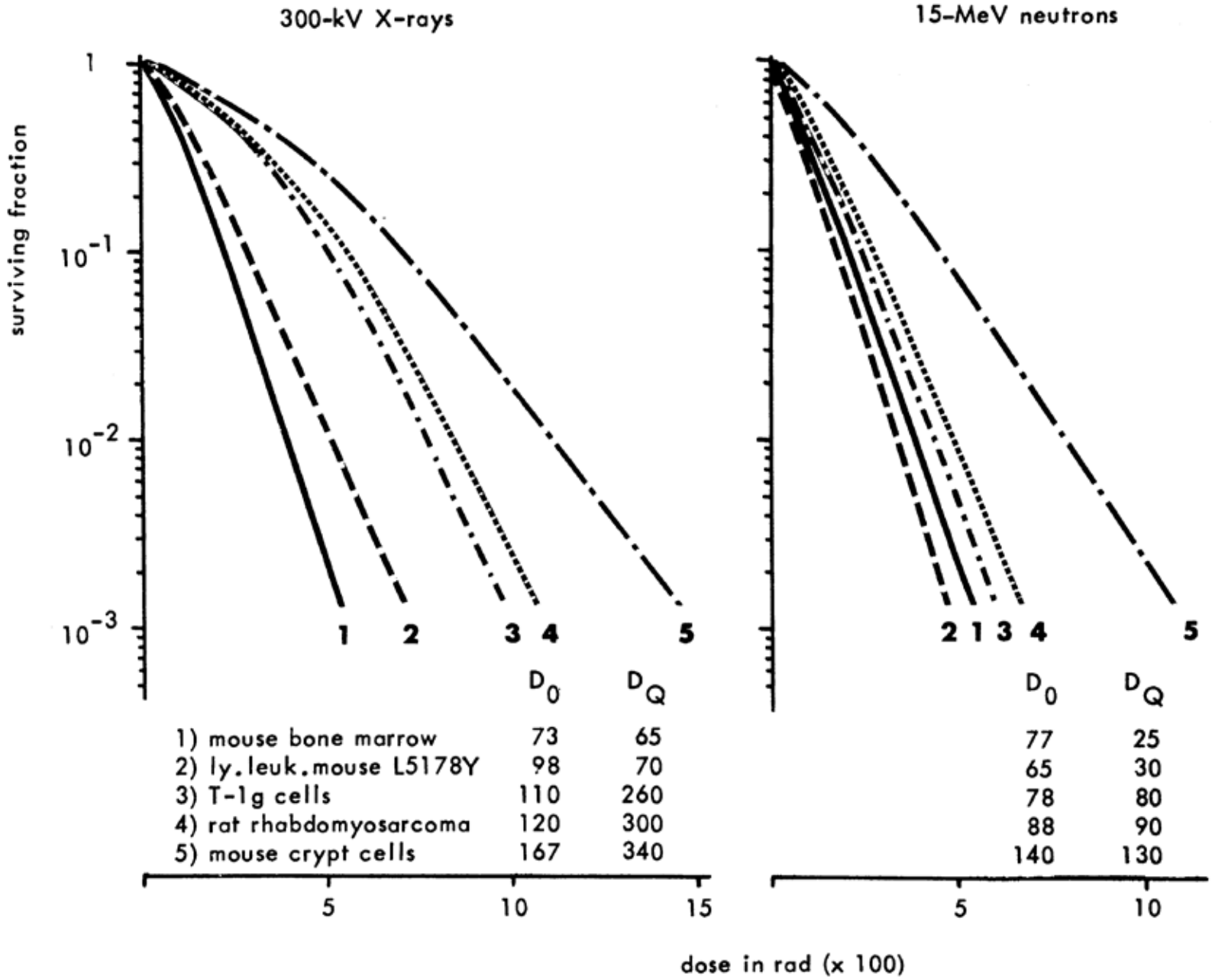
Note: The RBE between 250kVp X and ^{60}Co γ (and MV) is about 1.10–1.15 (depending on dose)


2.5 MeV α–particles 165 keV/μ
4 MeV α–particles 110 keV/μ
5.1 MeV α–particles 88 keV/μ
8.3 MeV α–particles 61 keV/μ
26 MeV α–particles 25 keV/μ
3 MeV deuterons 20 keV/μ
14.9 MeV deuterons 5.6 keV/μ
250 kVp X–rays
1
10^{-1}
10^{-2}
ion of surviving cells
@ 2 x 10^{-3} RBE 2.9
@ 2 x 10^{-1} RBE 4.2
RBE (Relative Biological Effectiveness) =
High-LET survival curves have higher α/β values
dose of high-LET radiation
0
2
4
6
8
10
12
14
1.0
3.8
4.2
Dose (Gy)
11.2


Pu α particles
Optimum LET
Less efficient cell killing
Overkill
d(4)-Be
d(14)-Be
p(65)-Be
SF = 0.8
SF = 0.1
SF = 0.01
RBE
8
7
6
5
4
3
1
0
60Co
250kVp
megavoltage Xrays
0.1
1
10
100
1000
Linear energy transfer (keV/μm)


LOW
LET
OPTIMAL
LET
HIGH LET
"OVERKILL"
RBE
LET

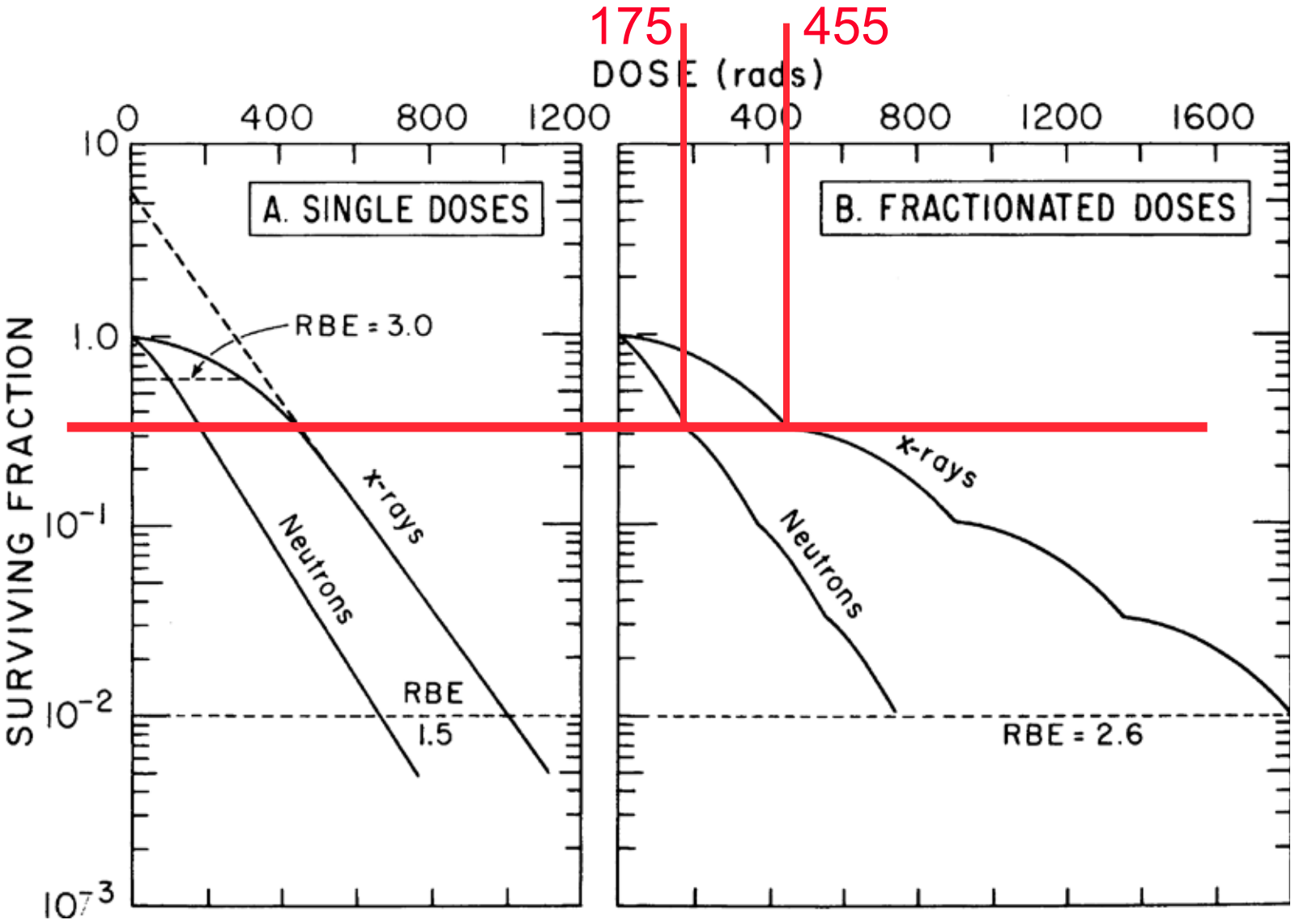
Dependence of RBE on type of cell irradiated



Dependence of RBE on the type of cell irradiated

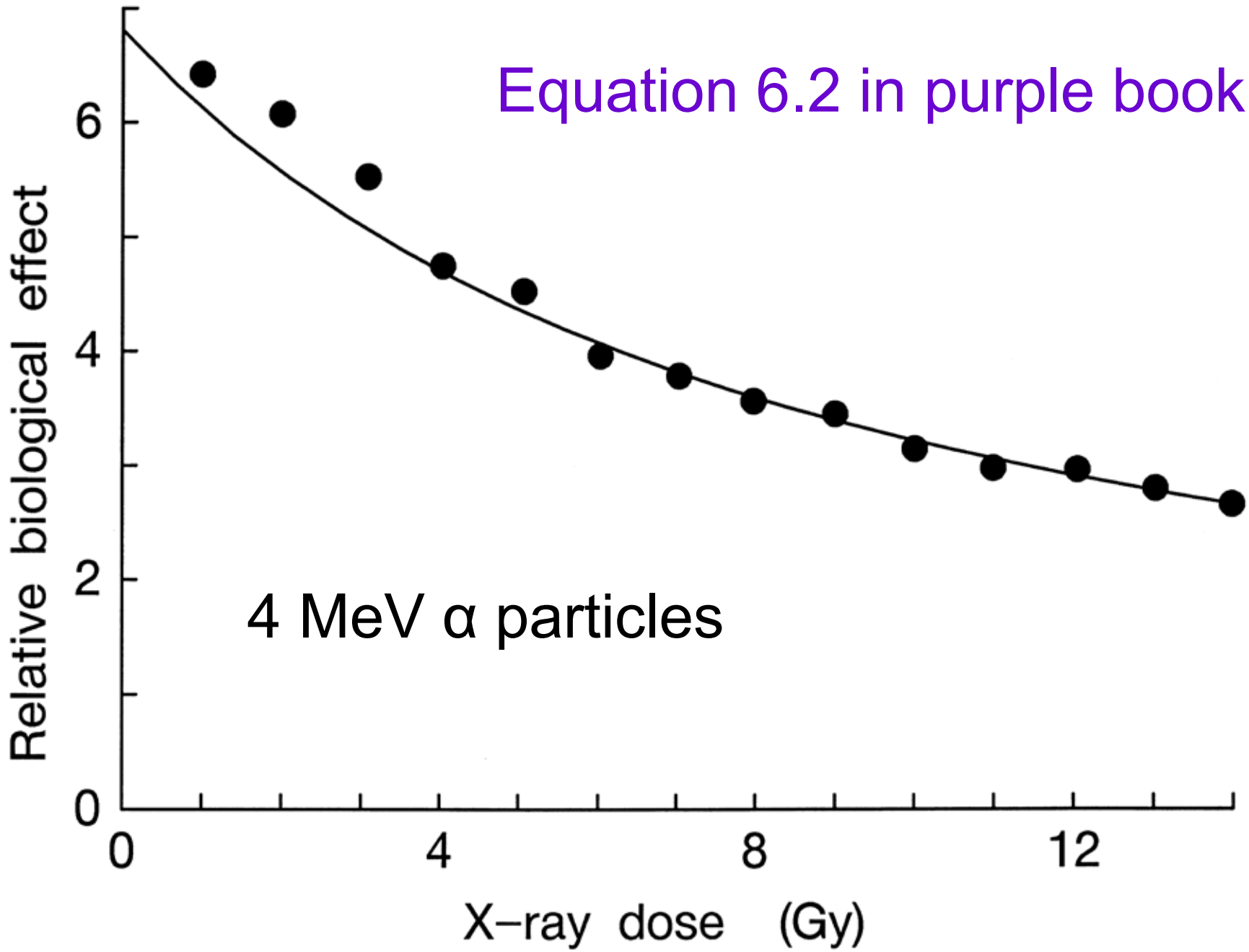
- In general, cells which exhibit large shoulders in their X-ray survival curves will have high RBEs
- Conversely, cells with *little, if any, shoulder* will have *low RBEs*
- But there are exceptions, due to the different interaction mechanisms between low- and high-LET radiations *e.g.* cell-cycle effect

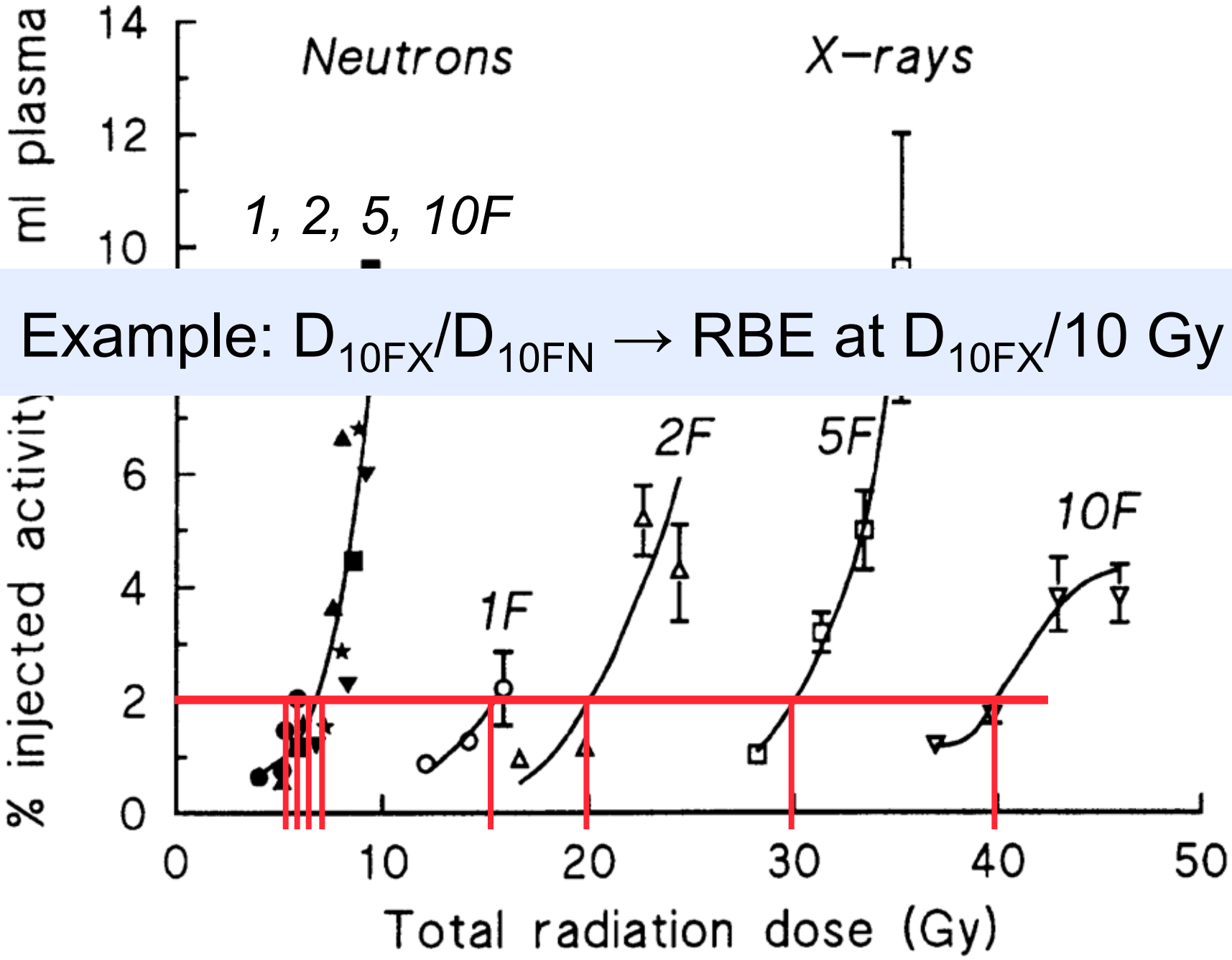
Effect of dose and dose per fraction on the RBE



Effect of dose and dose per fraction on the RBE

At low doses (and low doses per fraction), the RBE will be higher since the dose in the numerator of the RBE equation will be relatively higher at low doses than that in the denominator because of repair at low doses with the low-LET standard radiation

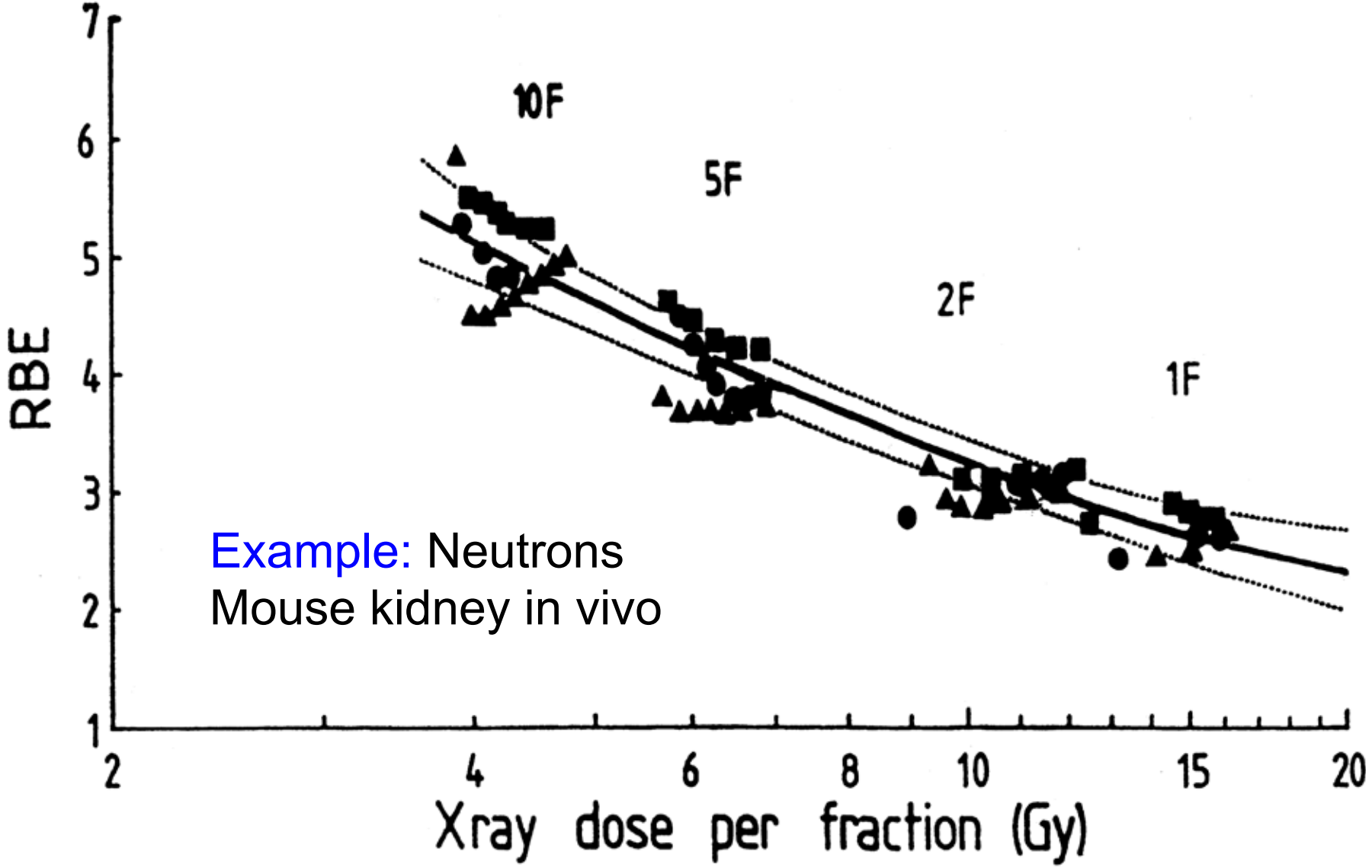

Equation 6.2 in purple book
4 MeV α particles
Relative biological effect
0
2
4
6
0
4
8
12
X–ray dose (Gy)



Example: $D_{10FX}/D_{10FN} \rightarrow$ RBE at D_{10FX}/10 Gy

RBE **increases**

with *decreasing dose per fraction*



Example: Neutrons
Mouse kidney in vivo

Factors which influence the RBE

RBE depends upon:

- radiation quality (LET)
- radiation dose (dose per fraction)
- dose rate
- biological system or endpoint
- conditions, *e.g.* oxygenation

Applications in Radiation Protection

Radiation Weighting Factor (W_R)

Equivalent Dose = dose × W_R

where W_R is a “rounded” value of the RBE.

A “rounded” (approximate) RBE is needed to cover all biological systems, doses, and endpoints, in radiation protection.

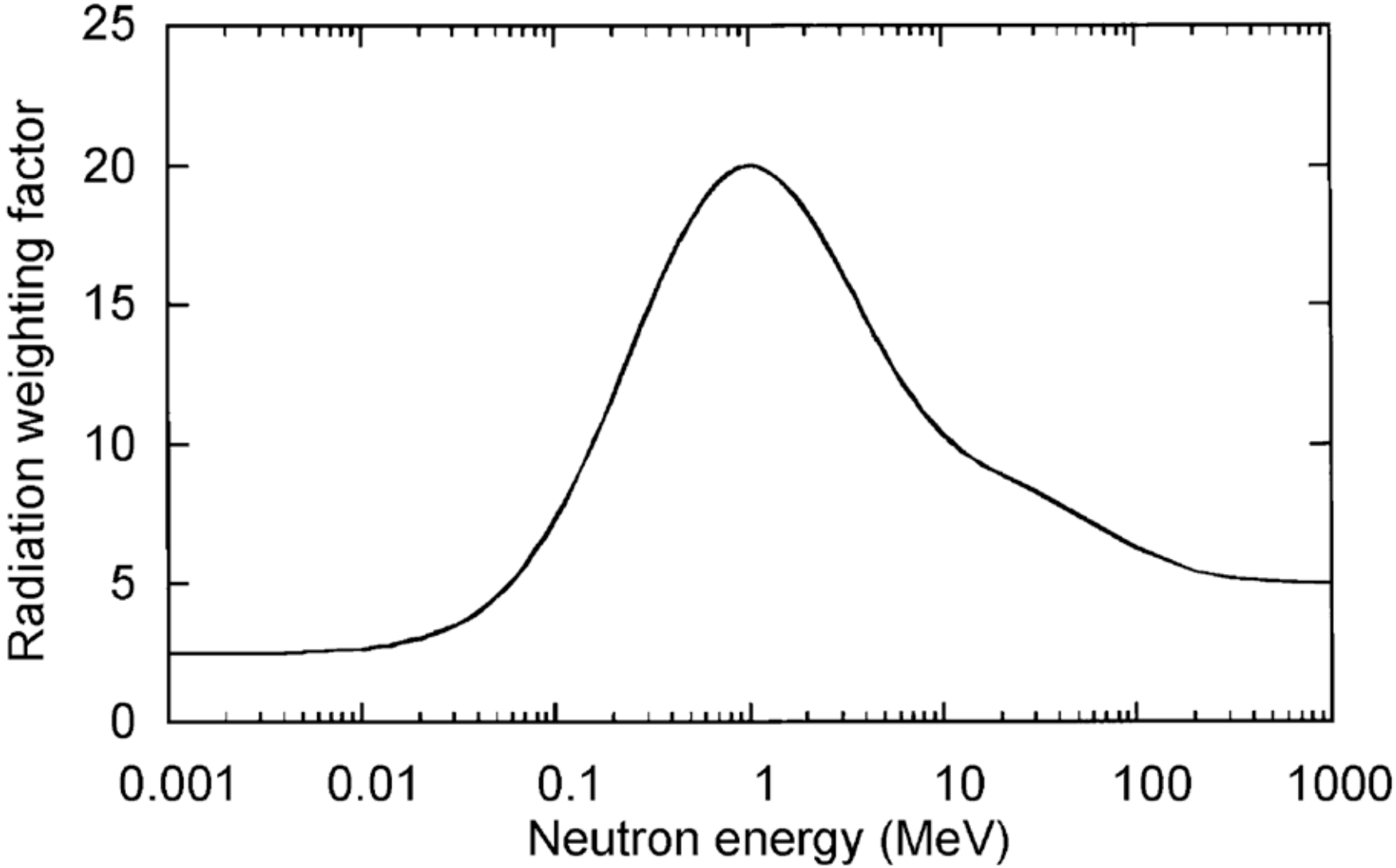
Radiation weighting factors (W_R)

ICRP 92 (2003), ICRP 103 (2007)

Radiation type	W_R
Photons (X-rays and gamma-rays):	1
Electrons and muons:	1
Neutrons:	function of neutron energy
Protons and charged pions:	2
Alpha-particles, fission fragments, heavy ions:	20

W_R for neutrons

ICRP 92 (2003), ICRP 103 (2007)



Conclusions 1

- LET is the average energy transferred per unit path length of the track of a charged particle
- X rays and gamma rays are usually referred to as low LET, although this is actually the LET of the charged particles released when they interact

Conclusions 2

Typical values of LET are:

~0.3 keV μm^{-1} for high-energy X and γ rays

~2 keV μm^{-1} for orthovoltage (~250 kVp) X rays

>100 keV μm^{-1} for heavy charged particles

Conclusions 3

- RBE is the ratio of the dose of some “standard” radiation to the dose of the radiation of interest to produce the same biological effect
- The “standard” radiation is either orthovoltage X rays (~250 kVp) or ^{60}Co gamma rays
- RBE increases with increase in LET up to a maximum at ~100 keV μm^{-1}, and thereafter decreases due to the “overkill” effect

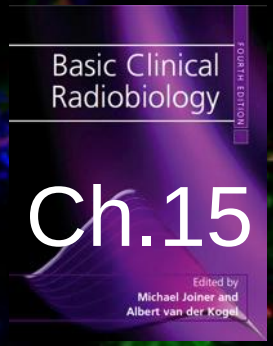
Conclusions 4

- RBE increases as the dose per fraction (or dose rate) decreases or the LET increases
- RBE depends on:
  - *radiation quality (LET)*
  - *radiation dose (dose/fraction)*
  - *dose rate*
  - *biological system or endpoint*
  - *conditions*

Conclusions 5

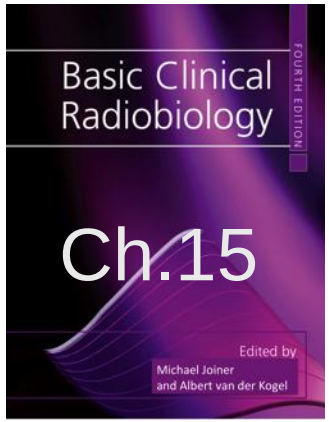
- The radiation weighting factor (W_R) is used in **radiation protection**
  (that is, **NOT** in radiation oncology!)
  as a surrogate for RBE because the RBE depends on so many variable factors
- Equivalent Dose is: Dose × W_R

The oxygen effect: Basic principles



Albert van der Kogel

ESTRO teaching course on basic clinical radiobiology
Budapest, 2016



Intermediate O_2

Surviving fraction

10
1
0.1
0.01
0.001

OER = 2.8

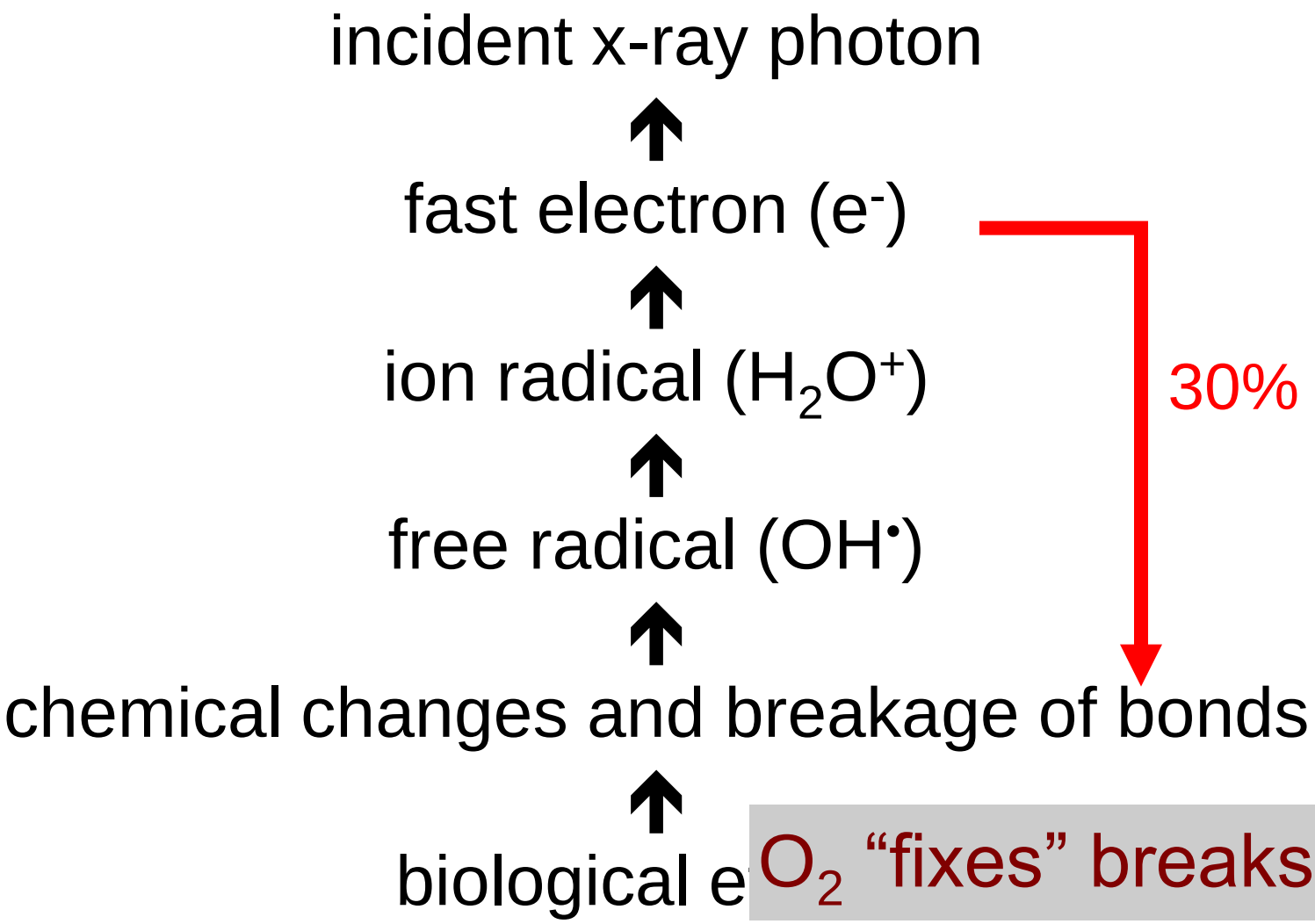
Oxic

Hypoxic

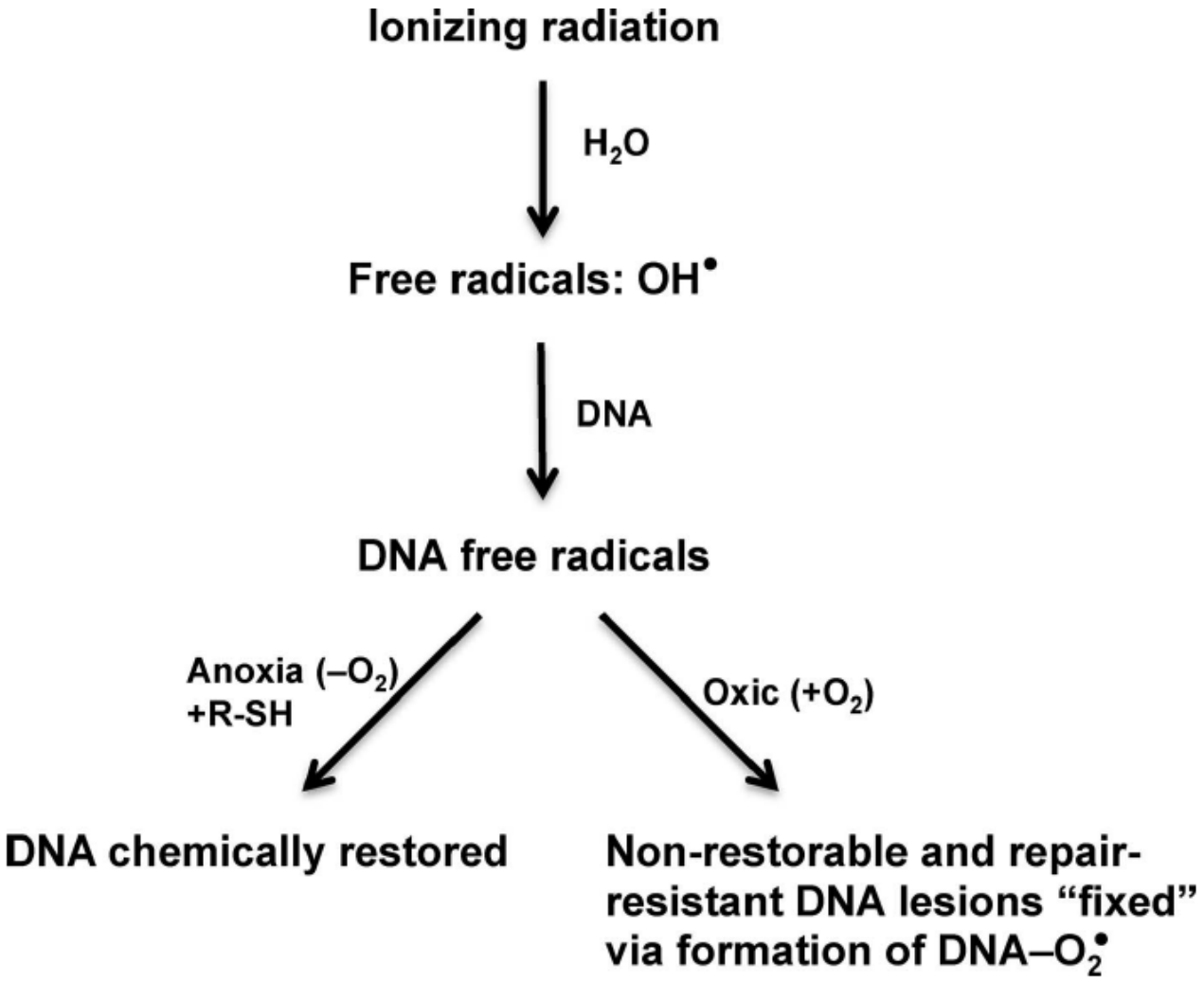
0 5 10 15 20 25 30

Radiation dose (Gy)

Chain of events leading to biological effects



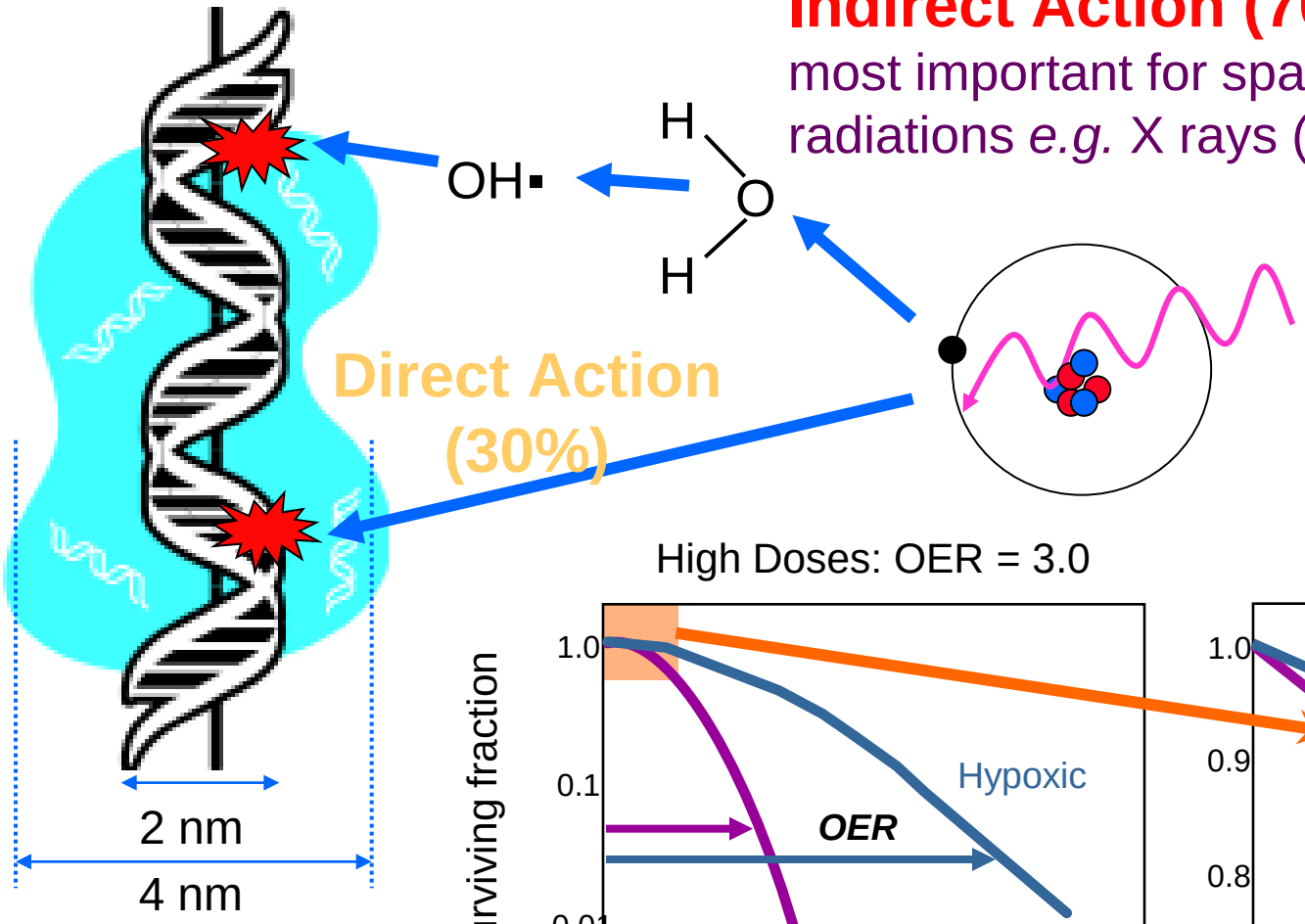
Chain of events leading to biological effects

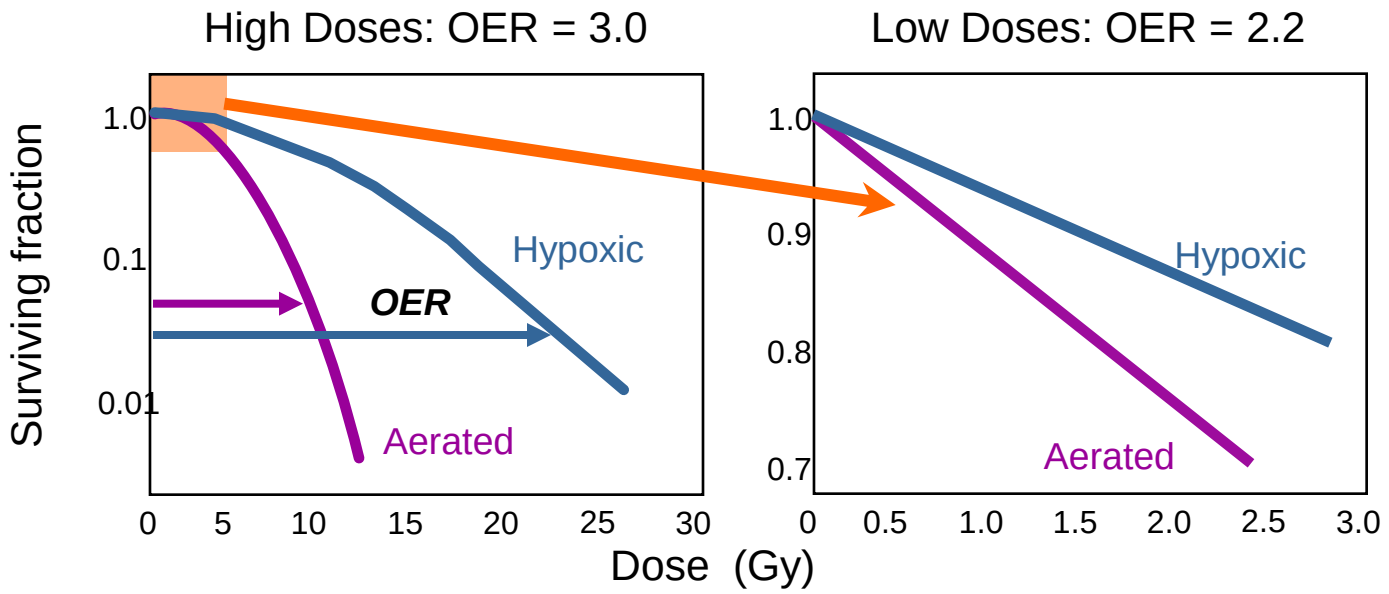


Direct and *Indirect* action of radiation in biological systems – X-rays & photons

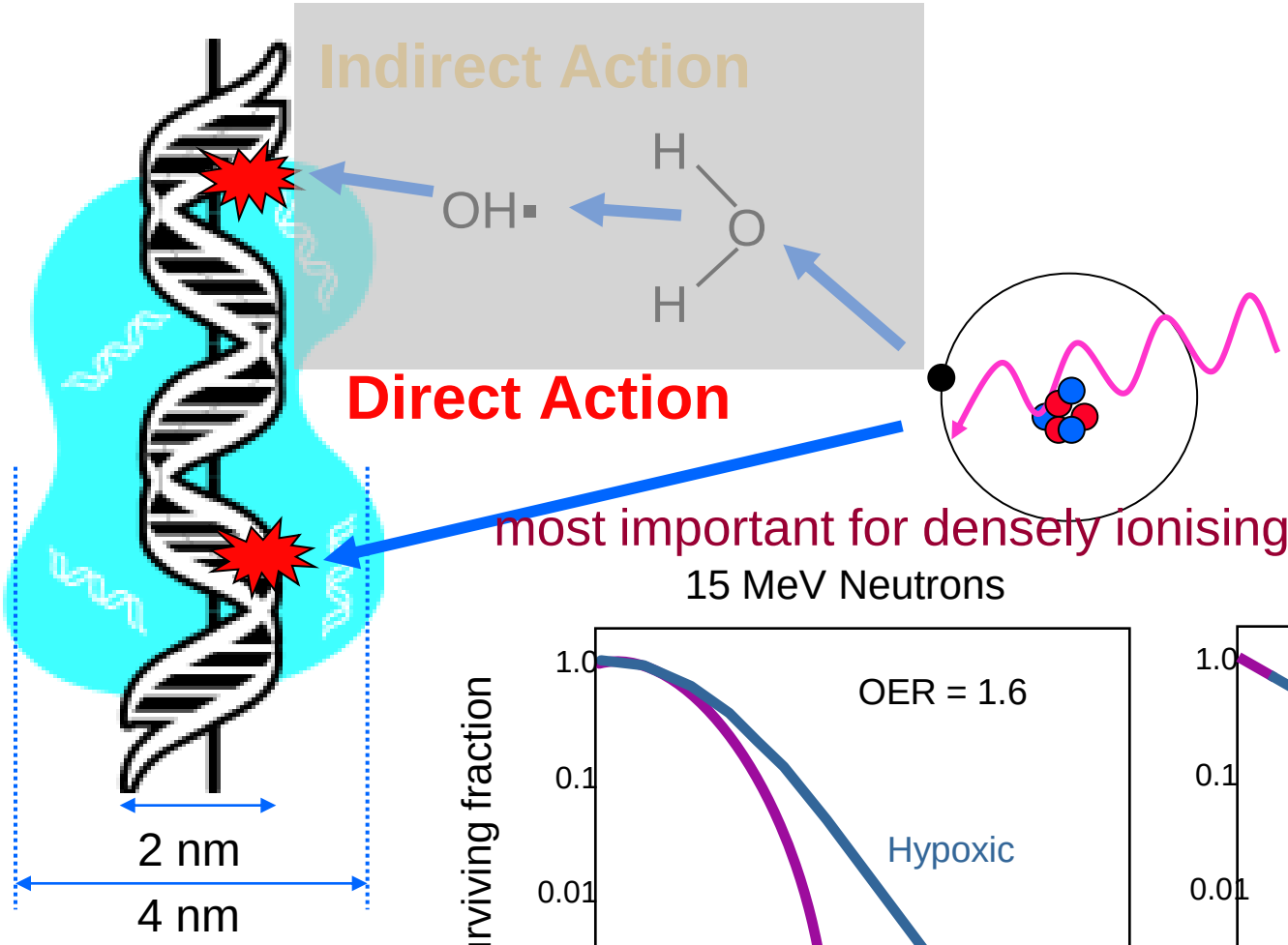
Indirect Action (70%)

most important for sparsely ionising radiations *e.g.* X rays (=low LET)

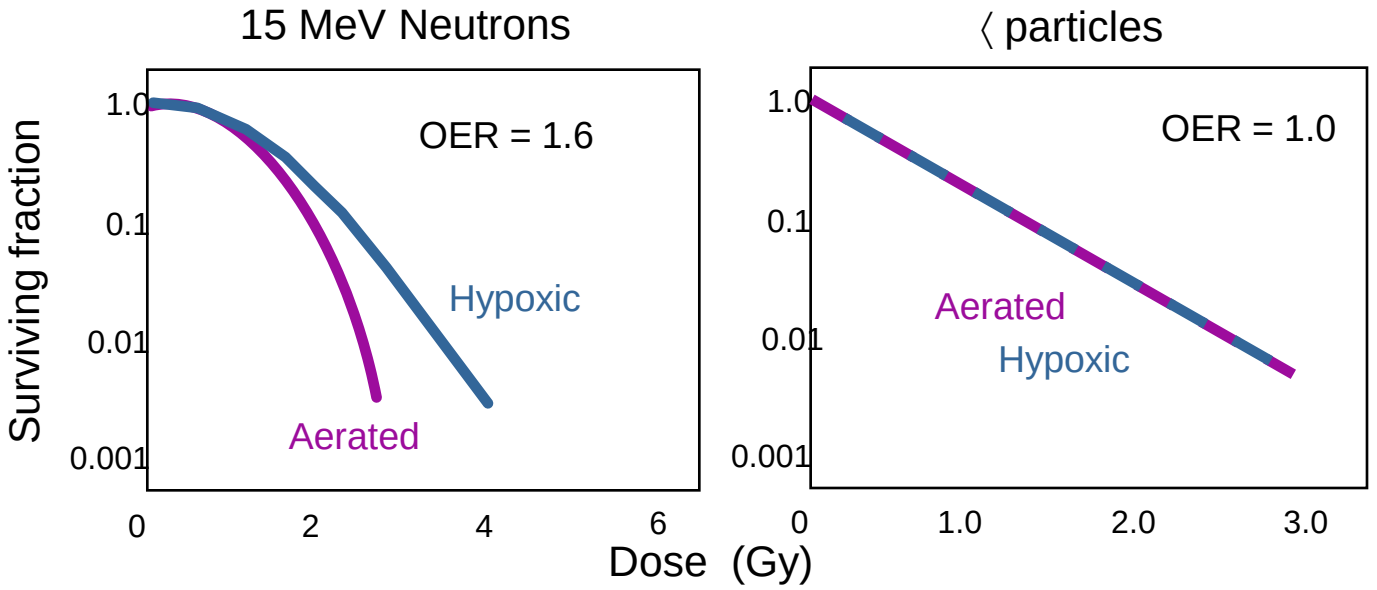




Direct and *Indirect* action of radiation in biological systems - particles

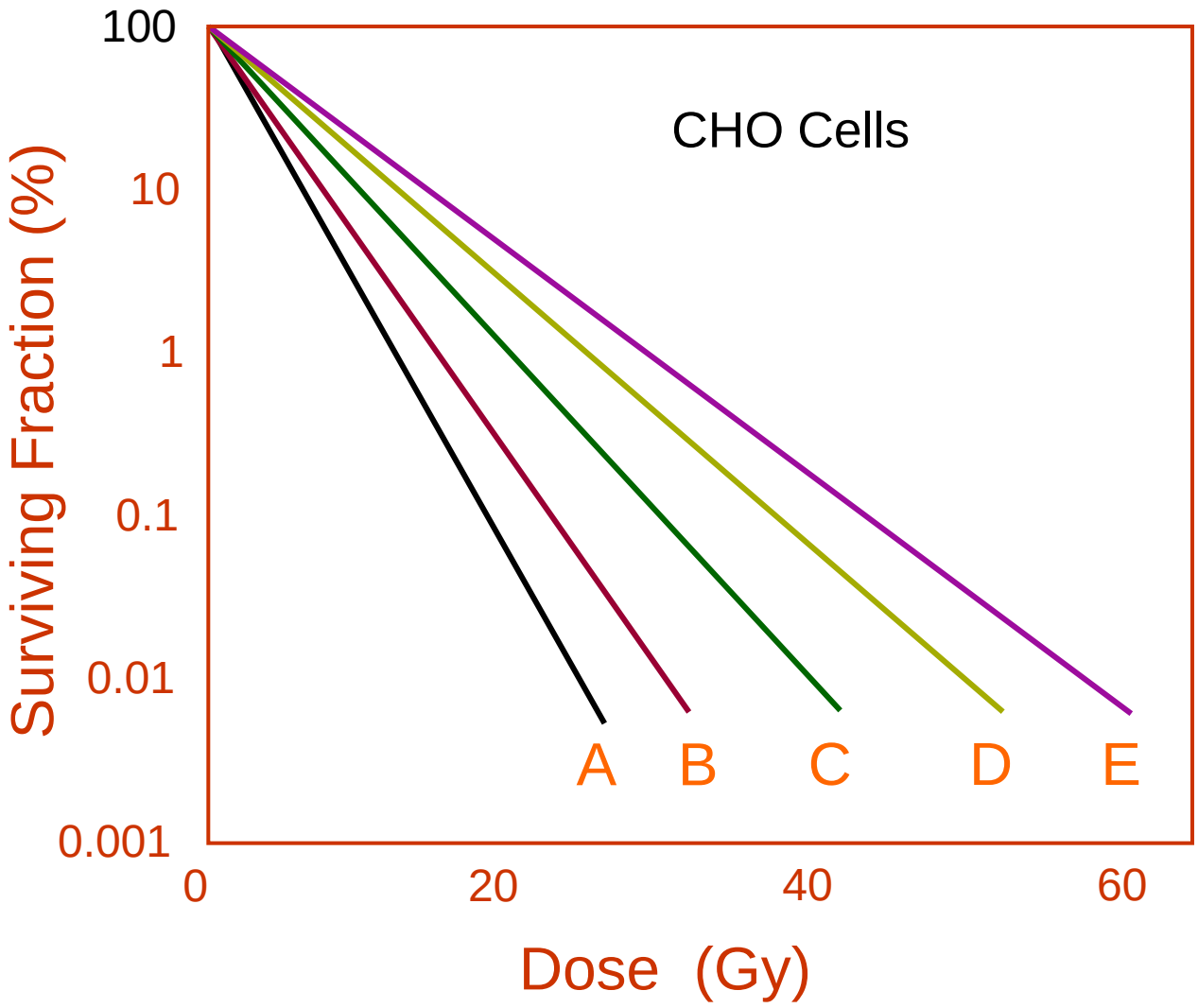


most important for densely ionising radiations (high LET)

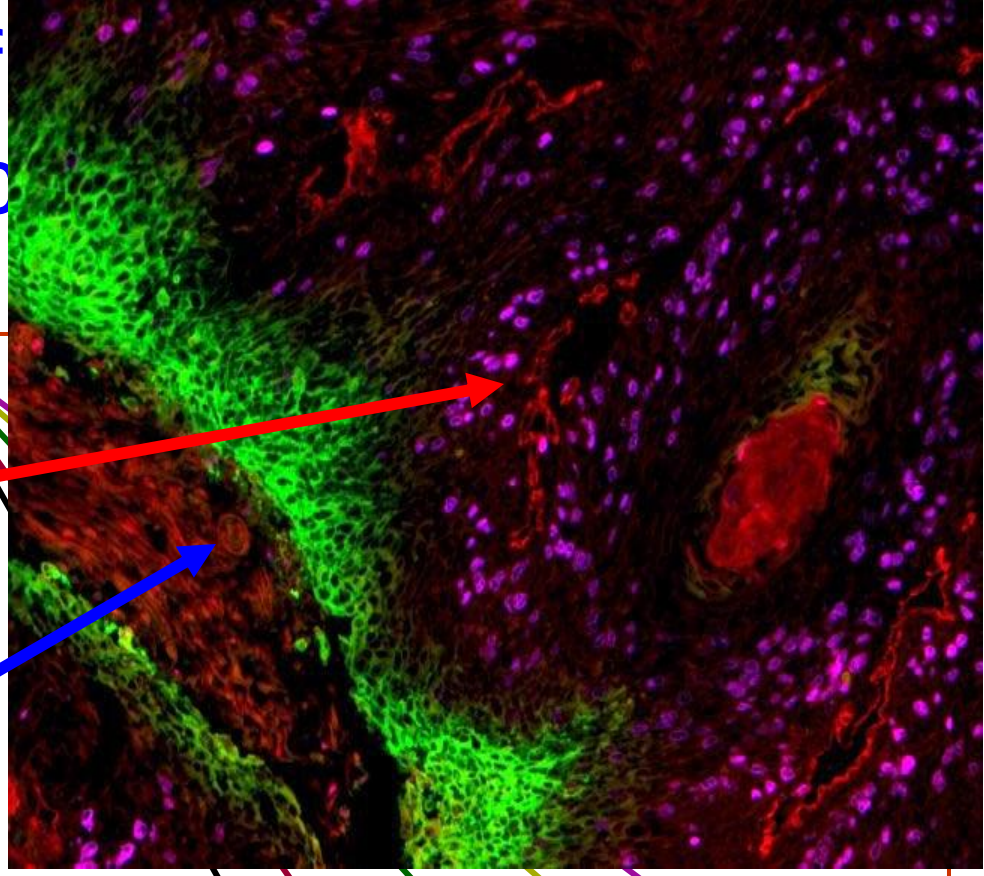


Dependence of X-ray cell killing on oxygen concentration

A 5% O_2
B 2% O_2
C 0.4% O_2
D 0.1% O_2
E 0.01% O_2



Dependence of
on oxygen c



A 5% O_2

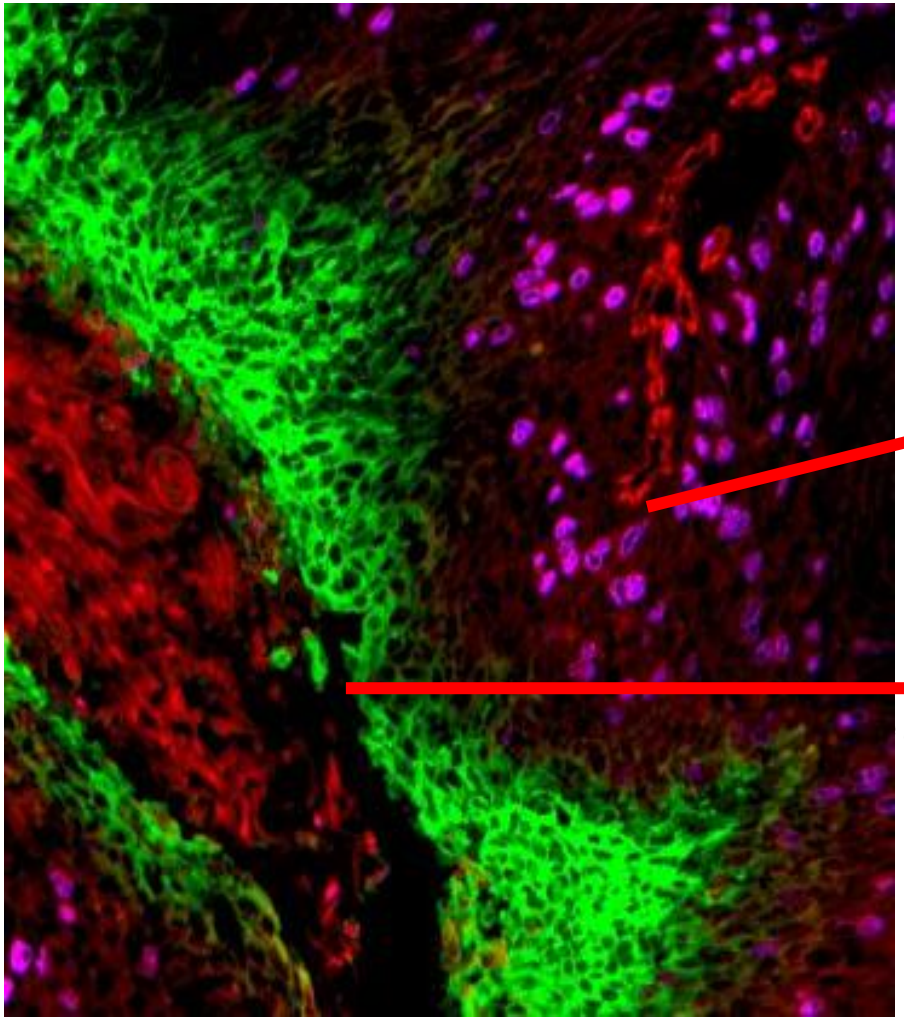
B 2% O_2

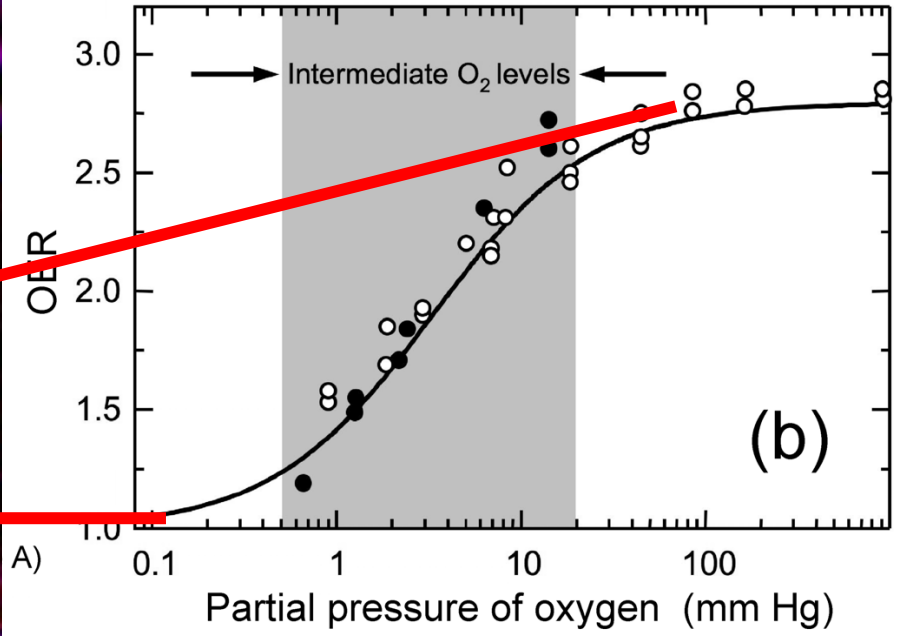
C 0.4% O_2

D 0.1% O_2

E 0.01% O_2

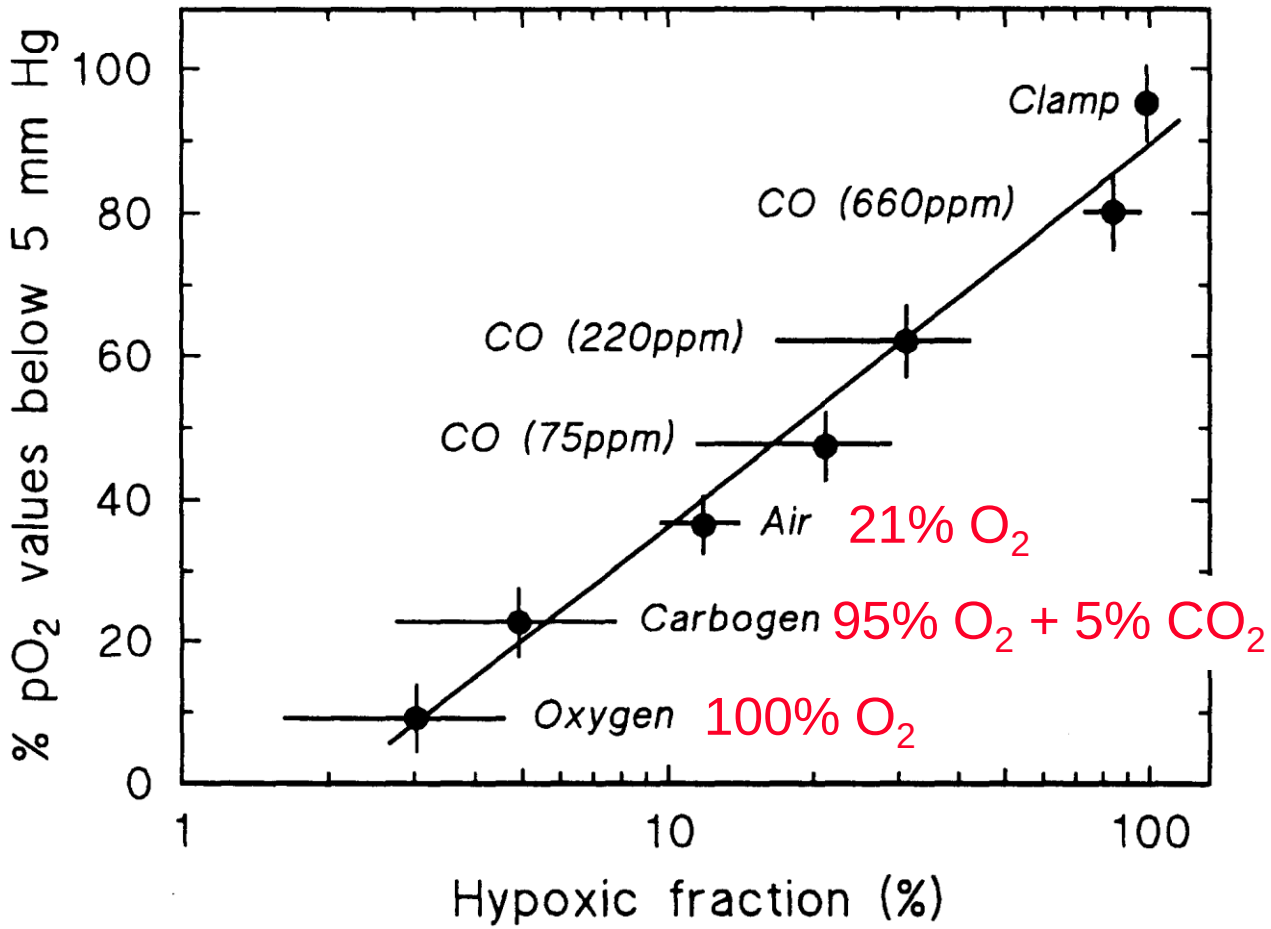
Variation of OER with O_2 partial pressure





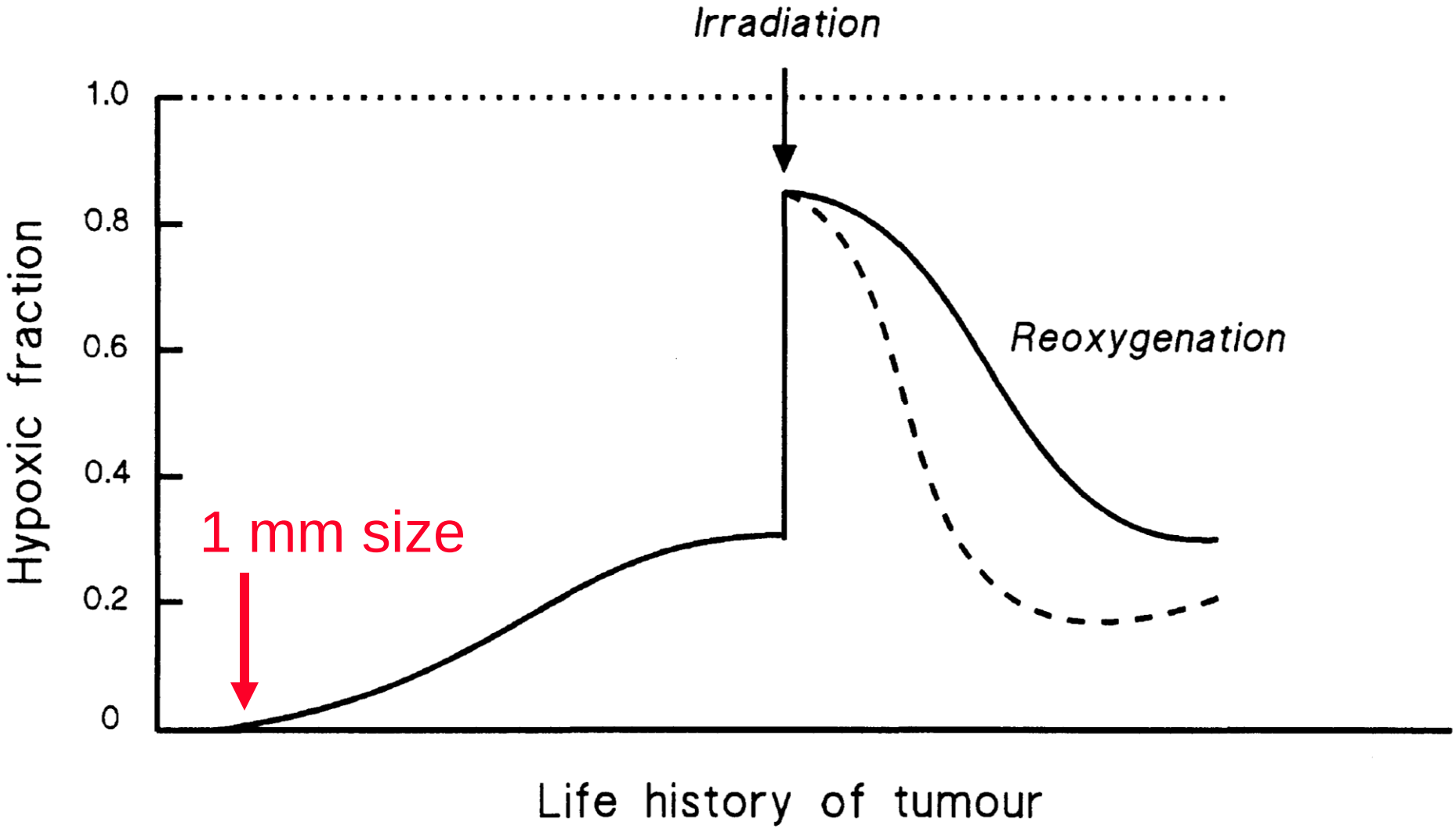
(Wouters & Brown, 1997)

pO_2 measured with electrodes correlates with radiobiological hypoxic fraction in C3H mammary carcinoma

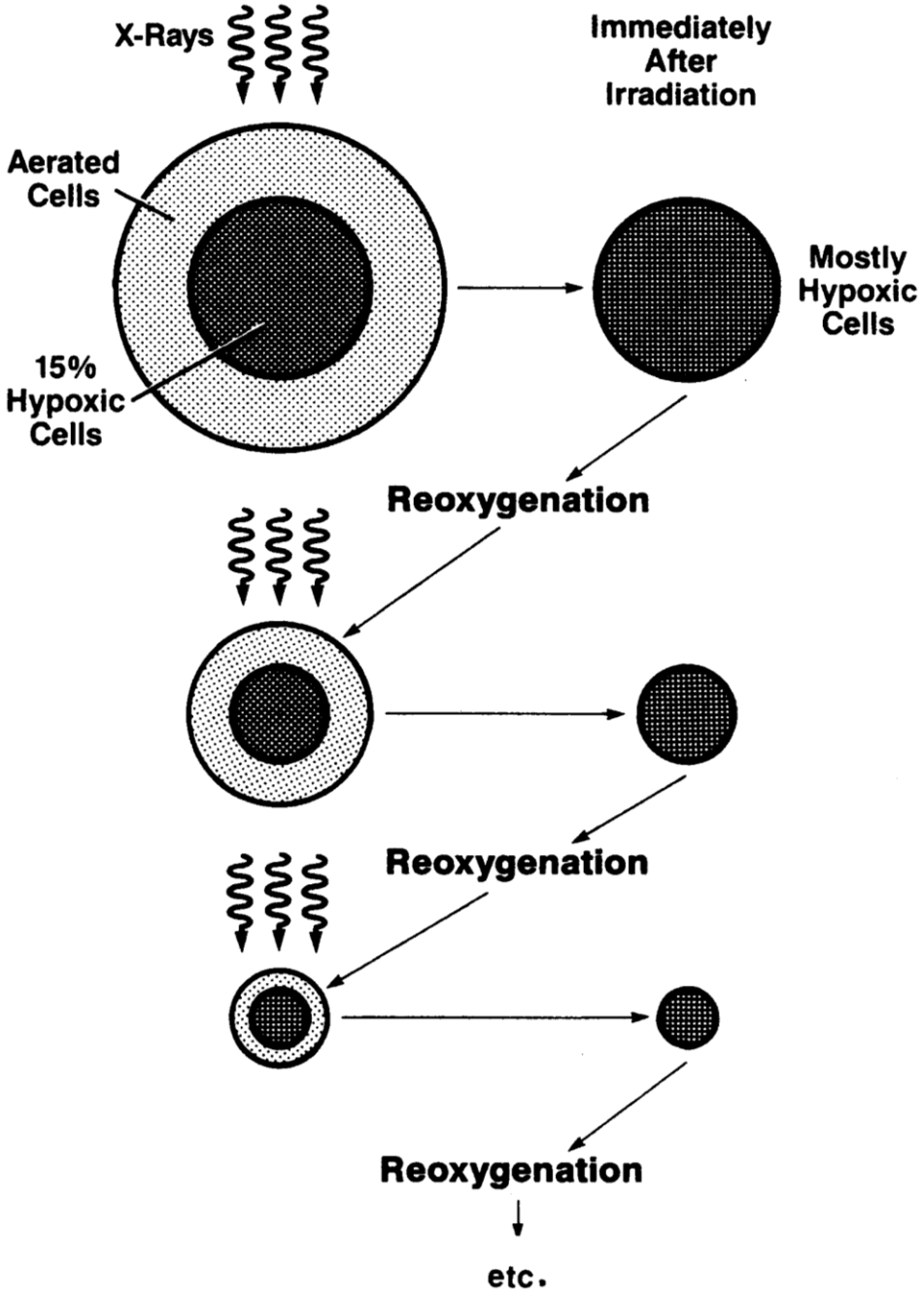


From: Horsman & Nordsmark

The “classic” explanation of reoxygenation



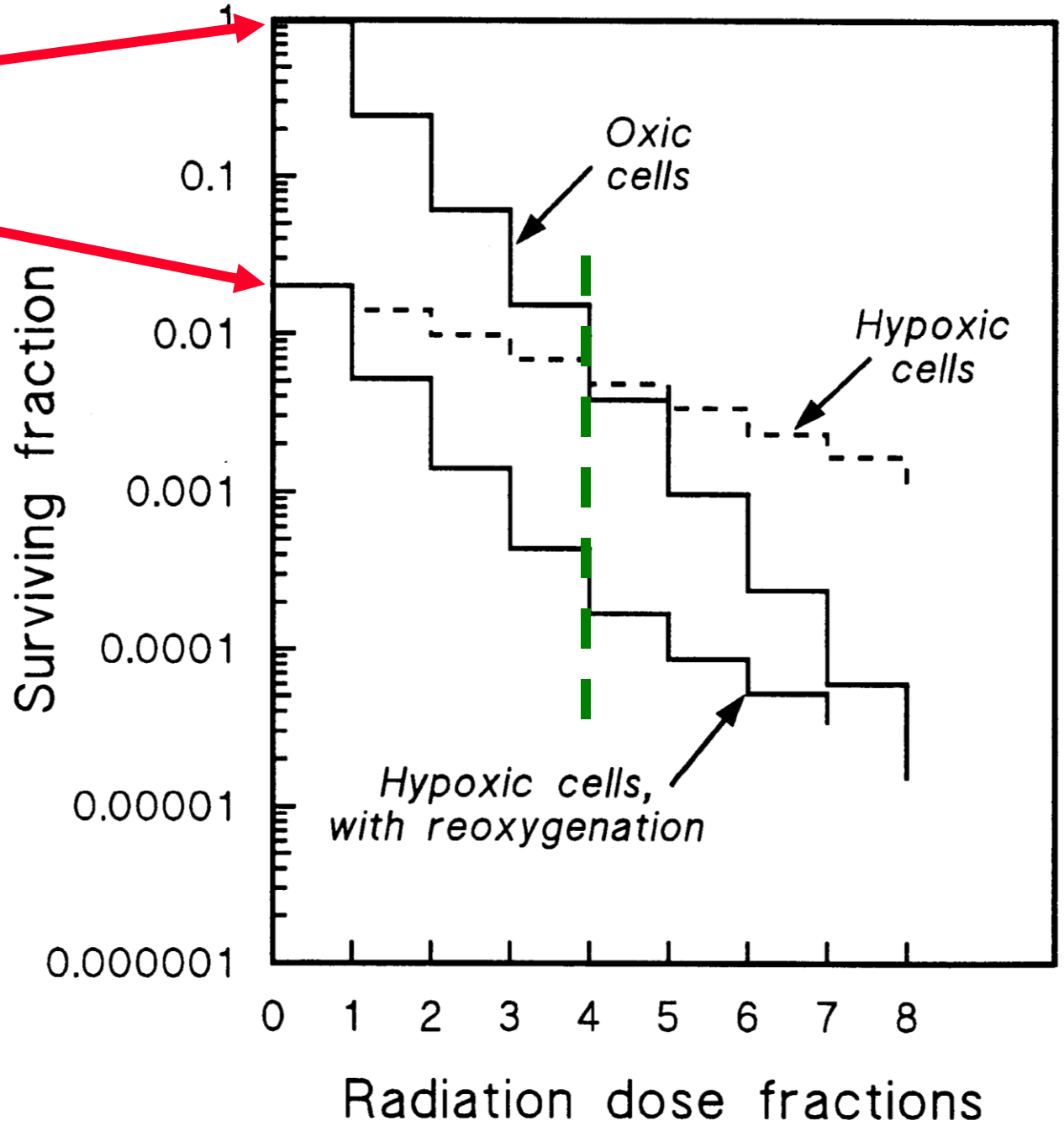
The classic concept of reoxygenation during fractionated radiotherapy



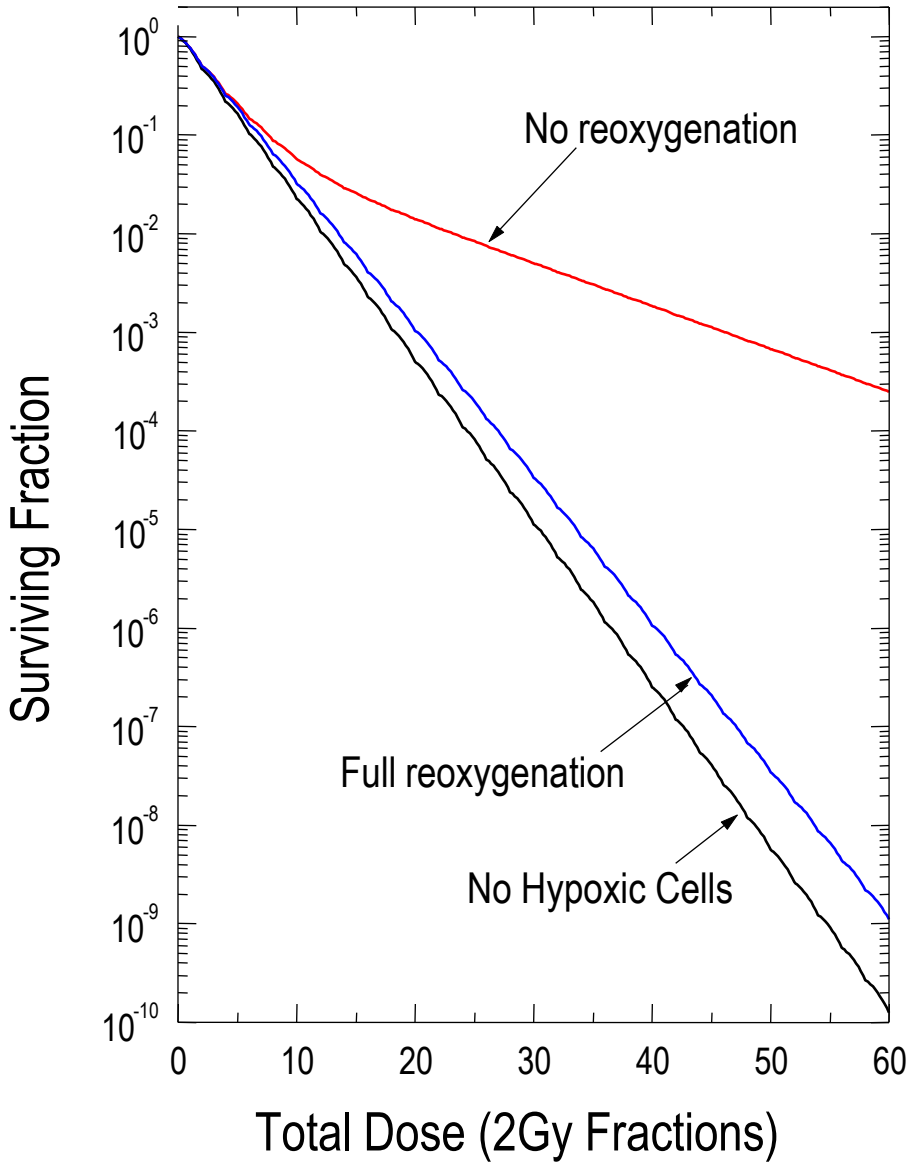
98% oxic

2% hypoxic

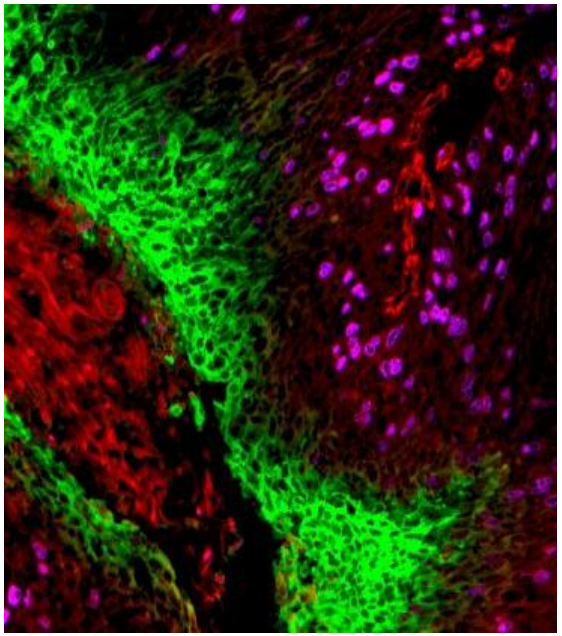
Without reoxygenation, survival of hypoxic cells exceeds survival of oxic cells after just four 2 Gy fractions

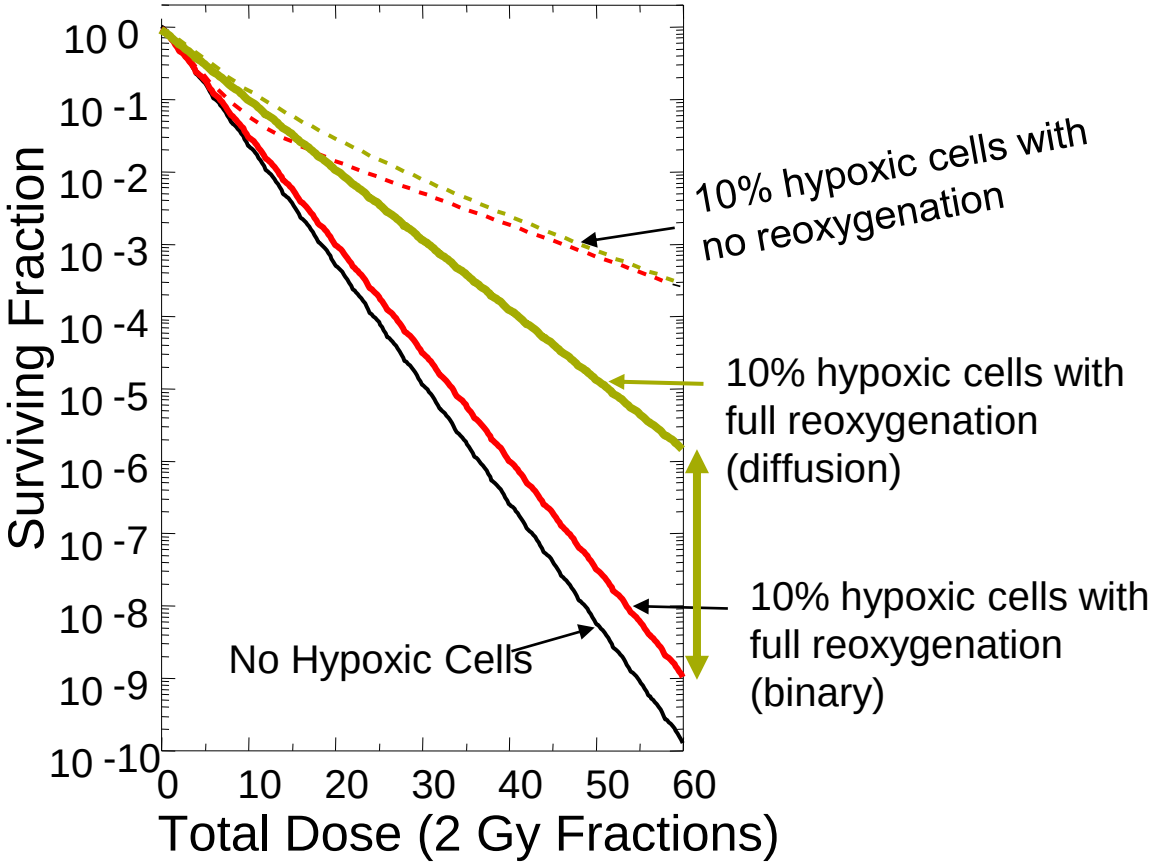


Reoxygenation during radiotherapy



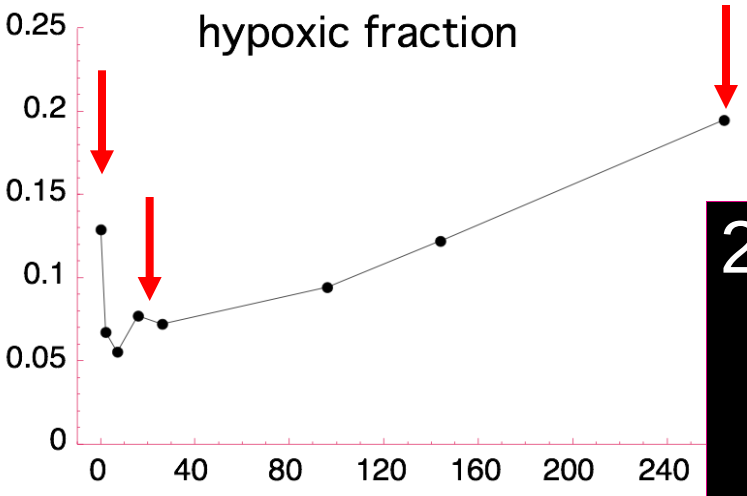
cells at intermediate hypoxia levels may determine the response of fractionated irradiation

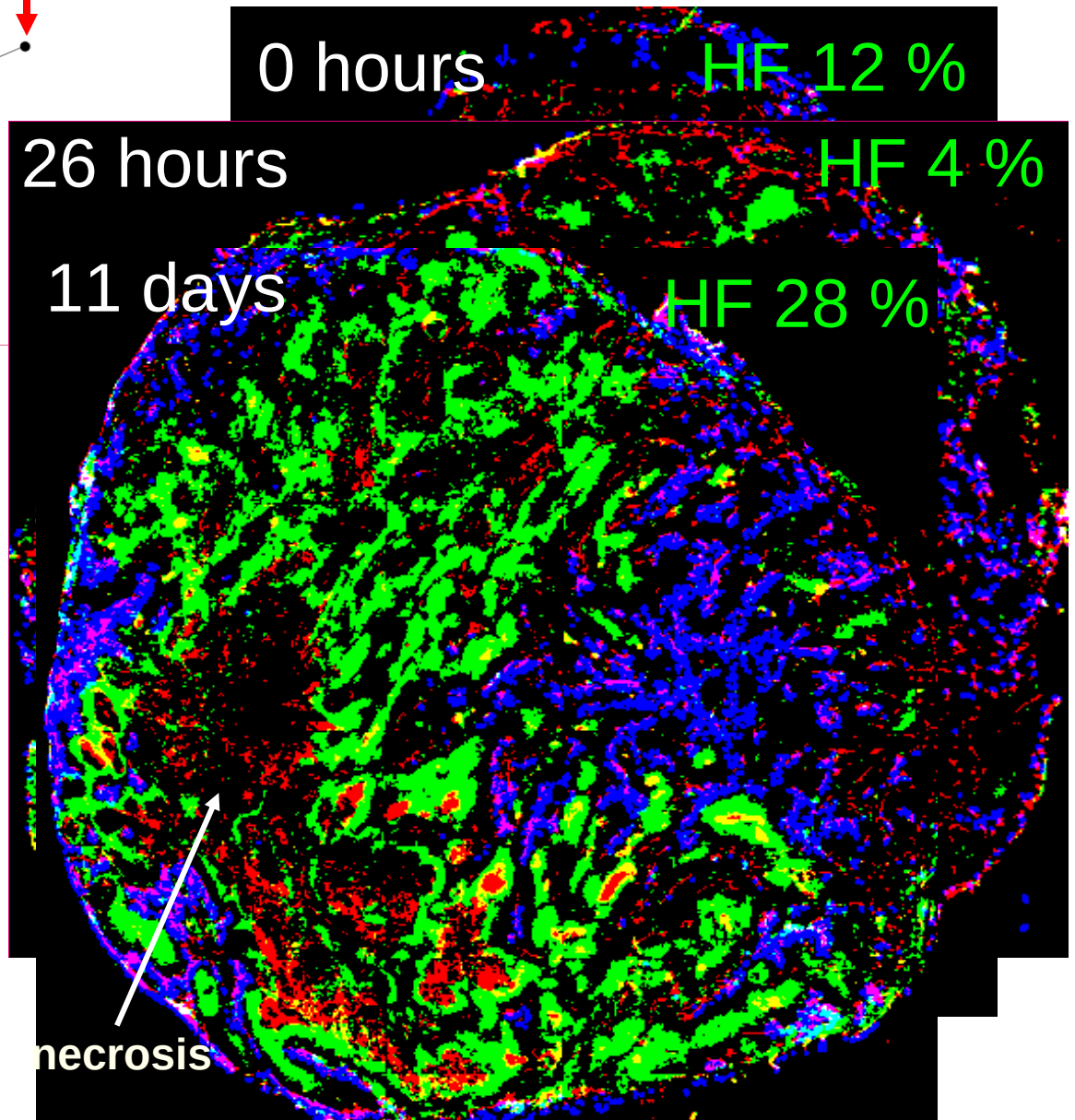




Wouters and Brown, 1997

Effect of irradiation on tumor oxygenation

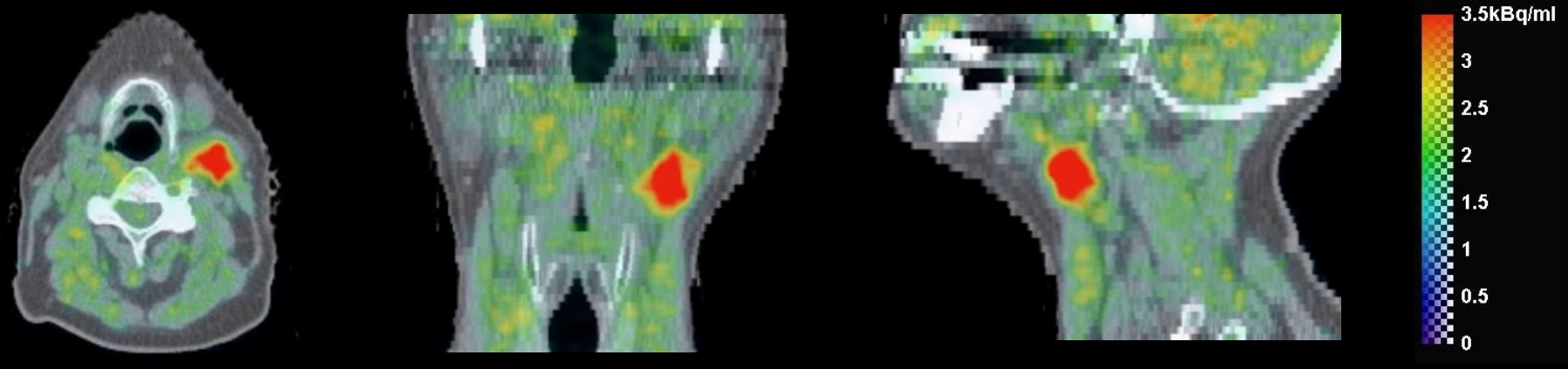




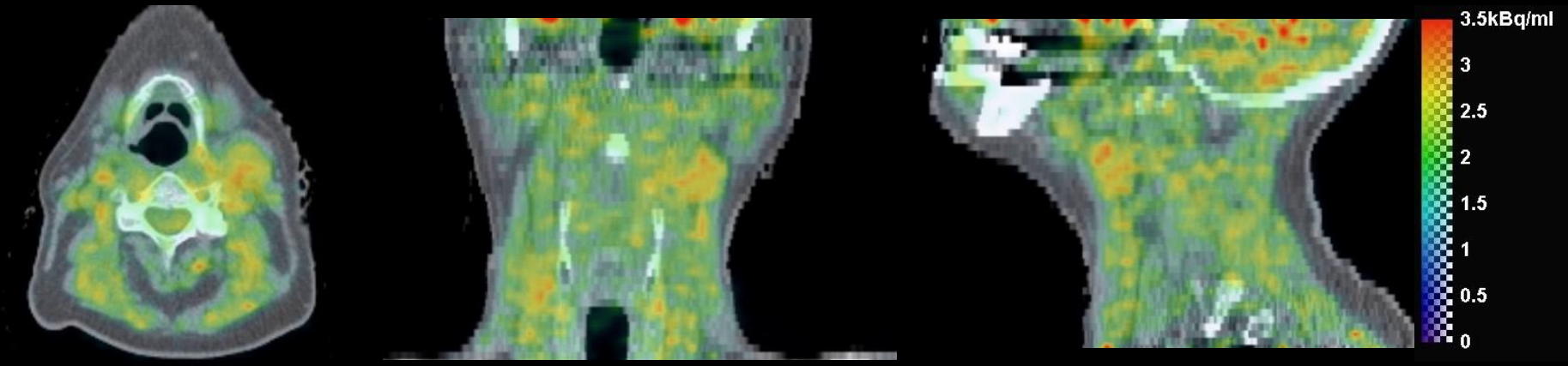
Bussink et al., Rad Res. 2000

Reduced hypoxia after 5 X 2 Gy in H&N cancer (^{18}F-FMISO)

PRE THERAPY (baseline)



POST THERAPY (after 5X 2Gy)



Nancy Lee, Rachel Bart let, Heiko Schoder and John Humm, MSKCC, New York

Different mechanisms of reoxygenation

1. Classic: preferential killing of well-oxygenated cells, and the surviving hypoxic cells getting access to O_2. Caveat: it takes time for cells to physiologically die, even after several divisions, and in human tumors this may take several days.
2. Reoxygenation due to acute/cycling hypoxia. Based on changes in perfusion (min-hours) and vascular function/remodelling (hours-days).
3. Reoxygenation due to reduced energy metabolism. Occurring rapidly and detectable by nitroimidazole PET or IHC markers. Caveat: reoxygenated cells after irradiation may be clonogenically dead (but they don't know it yet).

Mechanisms and time-scales of tumor reoxygenation

Fluctuating perfusion	minutes
Reduced respiration after RT	minutes to hours
Death of irradiated cells	hours - days
Cord shrinkage as dead cells are removed	days

Impact of tumor hypoxia:

- Hypoxic cells more radioresistant
- Hypoxic cells more chemoresistant
- Hypoxic cells can reoxygenate/repopulate
- Hypoxic cells drive neovascularization
- Hypoxic cells drive disease progression

Hypoxia - the basic message

- Hypoxia is important:
  - *Radiation resistance (the oxygen effect)*
  - *Promotes malignancy (bad for all forms of treatment)*
- Design radiation therapy to minimize the effects of hypoxia

Hypoxia and Tumor Microenvironment

Marianne Koritzinsky

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Tumor hypoxia

1. How and why hypoxia arises in tumors
2. Heterogeneity in tumor oxygenation
3. Cellular consequences of hypoxia

Tissue hypoxia – poor oxygenation

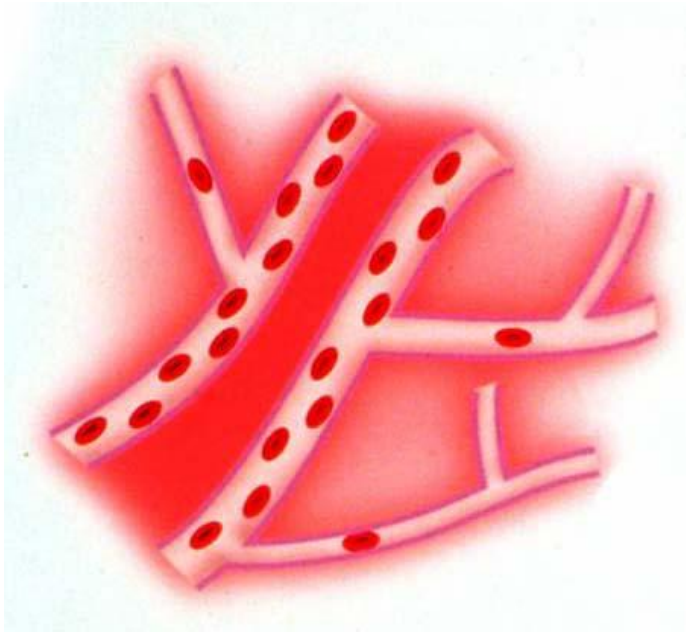
Air: 21% O2
Tissue normoxia: 5-7% O2
Tissue hypoxia: < 3% O2

Physiology

- **Development**
- **Exercise**
- **Altitude**

Pathology

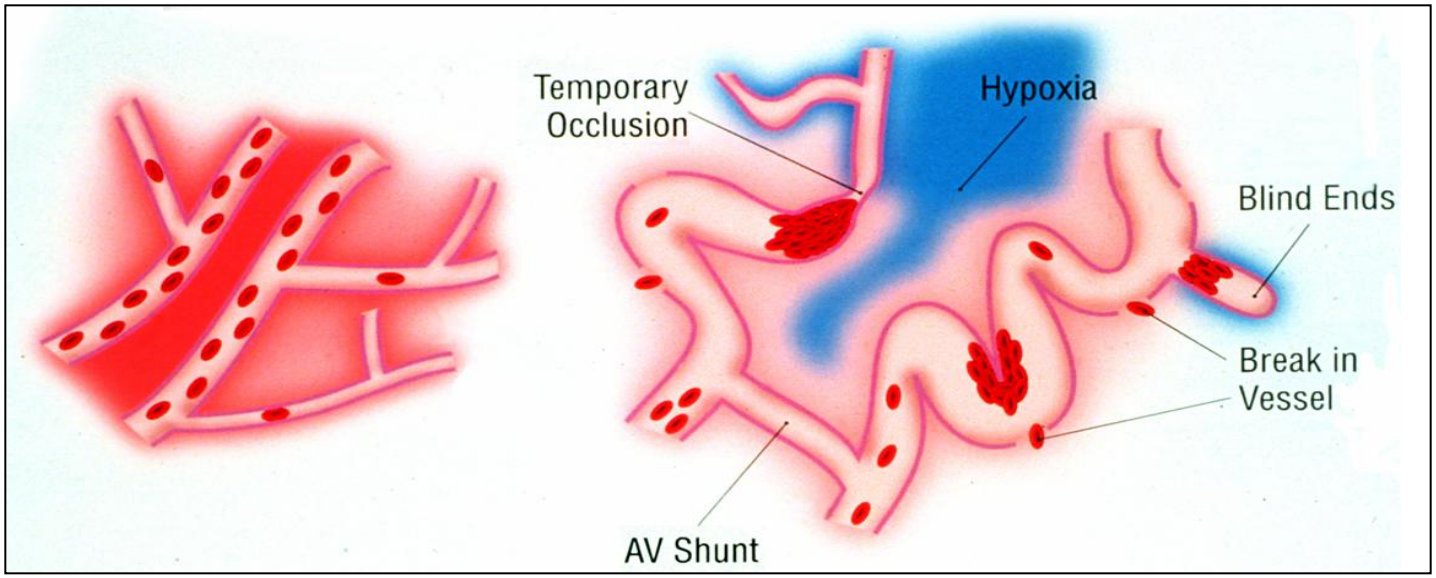
- **Wound**
- **Stroke**
- **Infarctation**
- **Solid tumors**



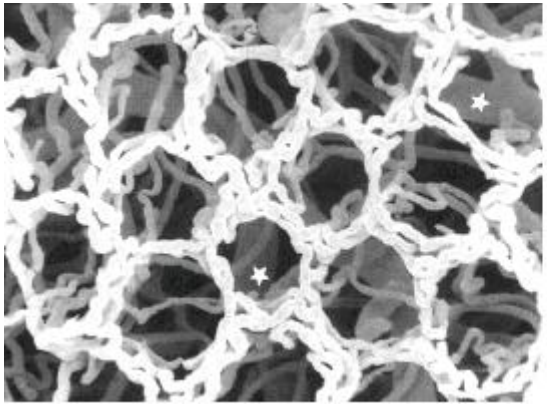
1) How and why hypoxia arises

Tumor hypoxia

Abnormal vasculature is a prime cause of hypoxia in cancer



Corrosion castings

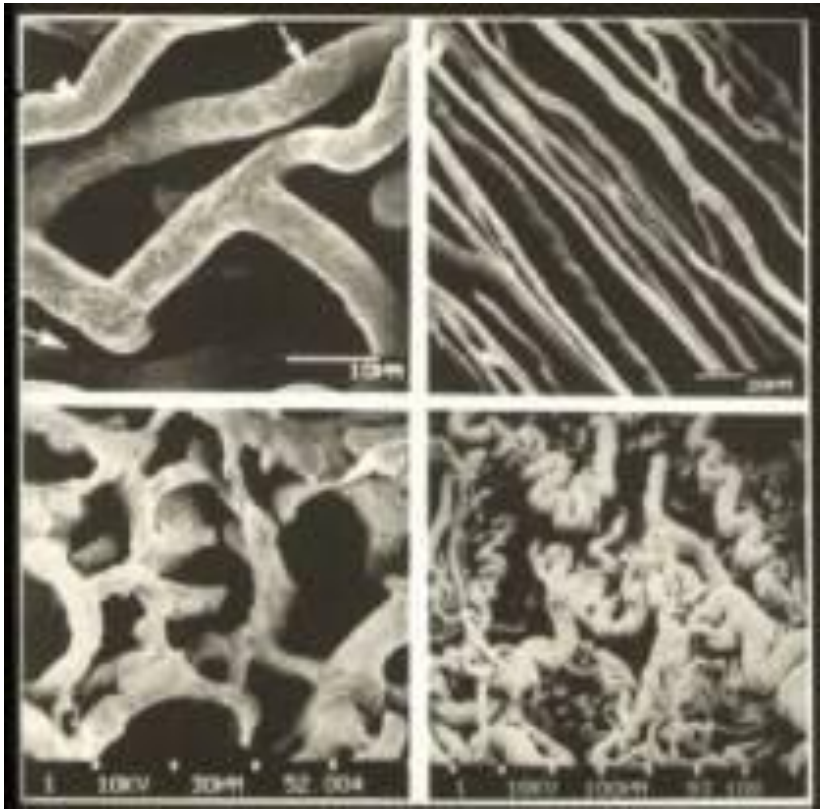


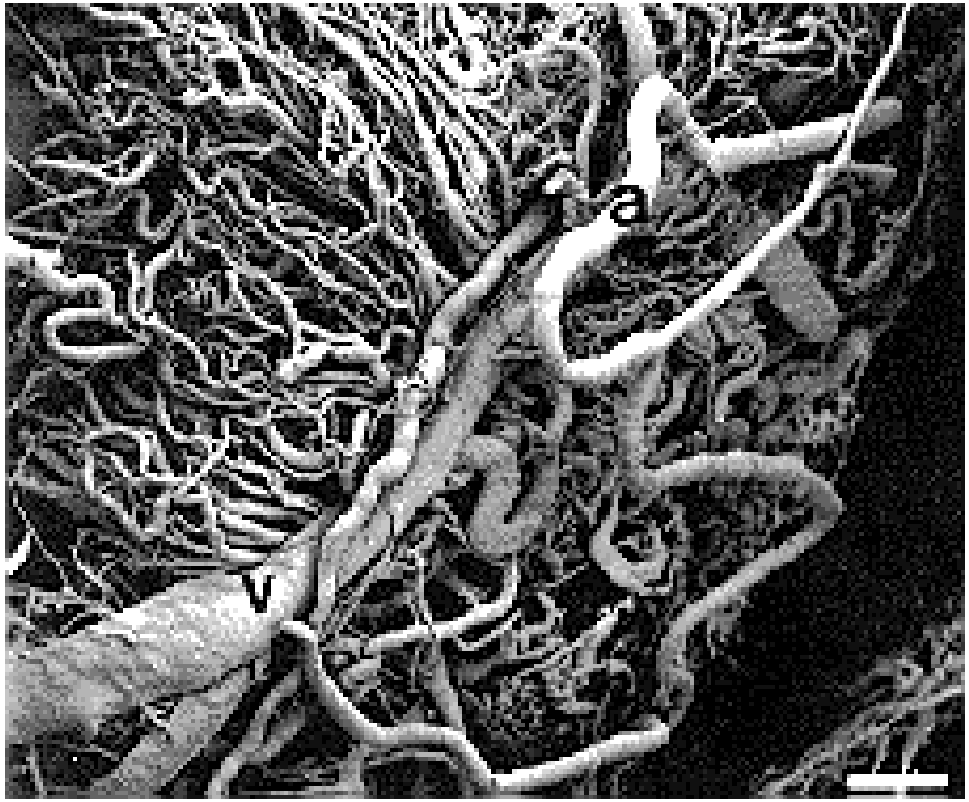
Normal colon

Colon xenograft

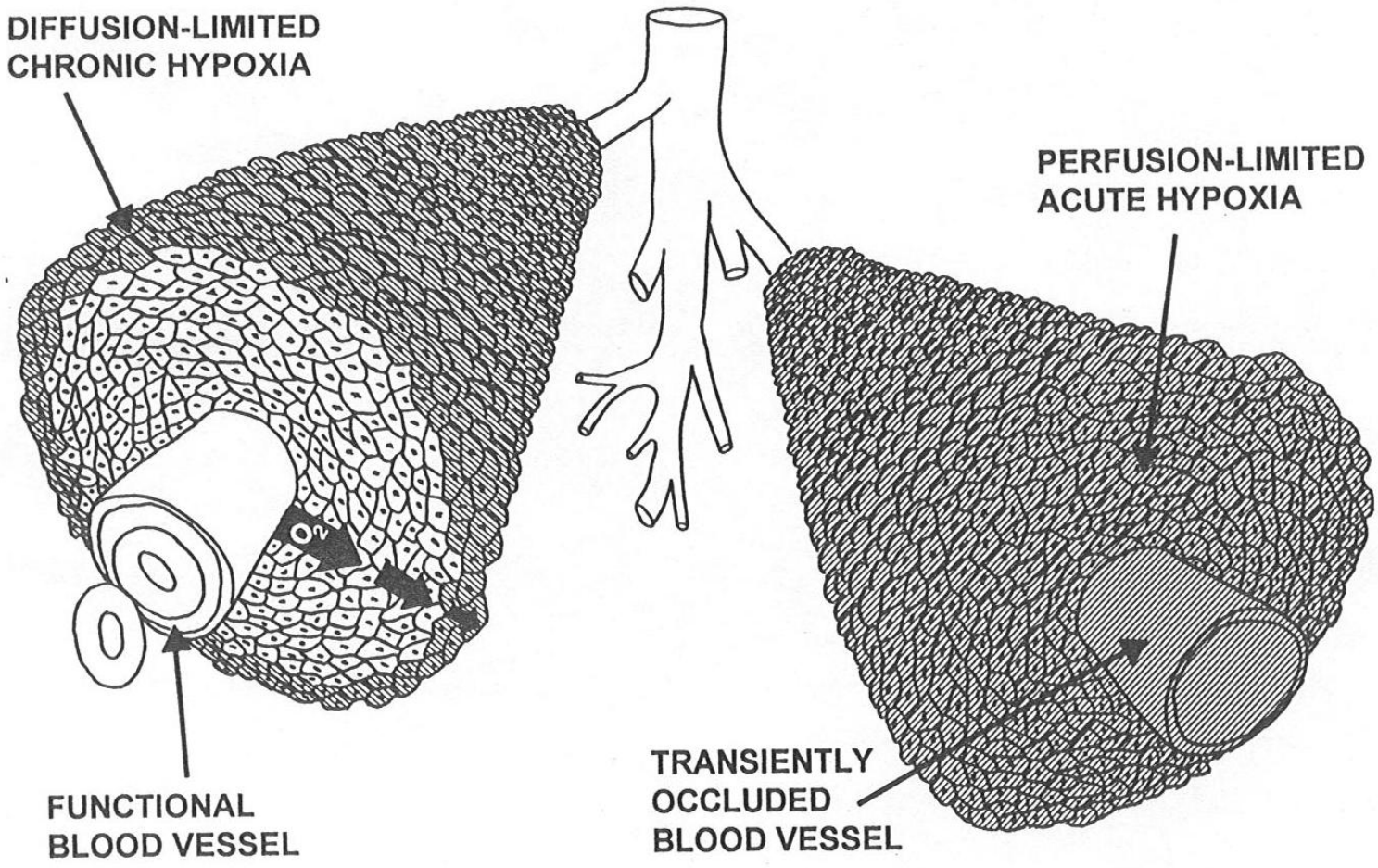
The vasculature in tumors is abnormal

Leads to low overall levels of oxygen in most tumors, with many areas being extremely hypoxic.

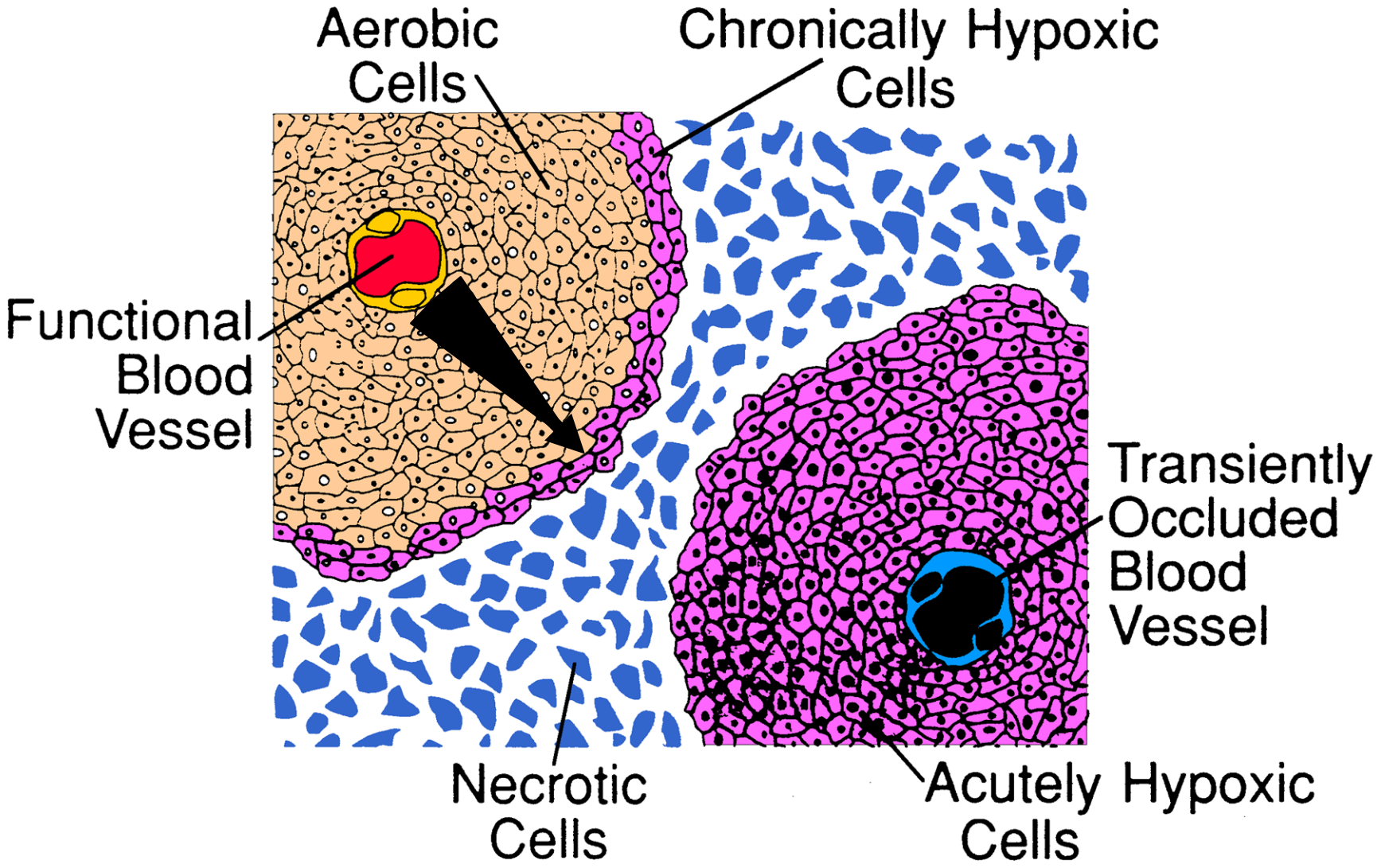




Chronic versus acute hypoxia



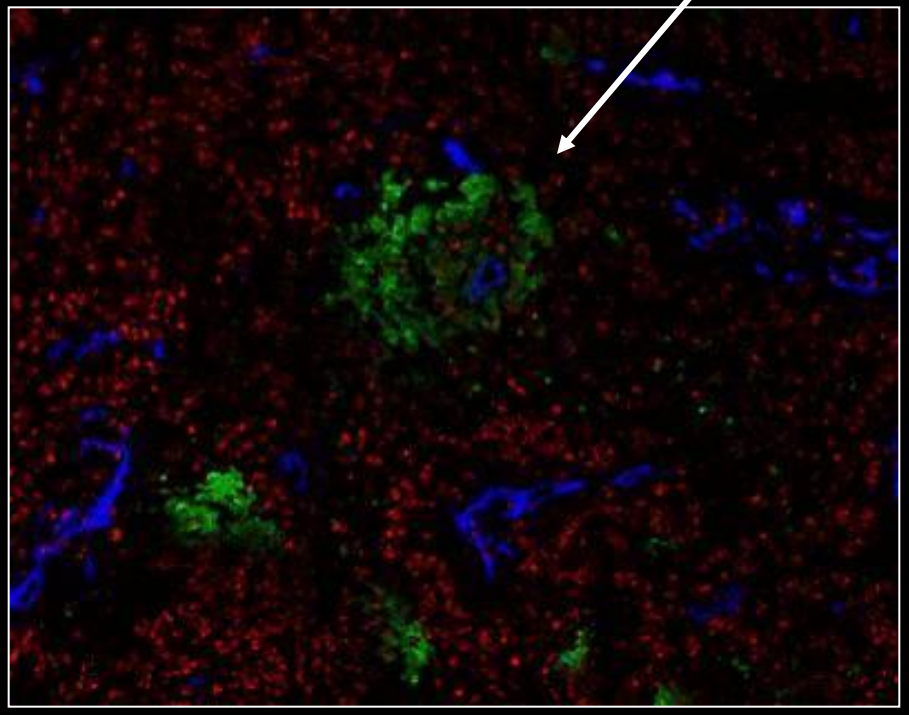
Chronic versus acute hypoxia



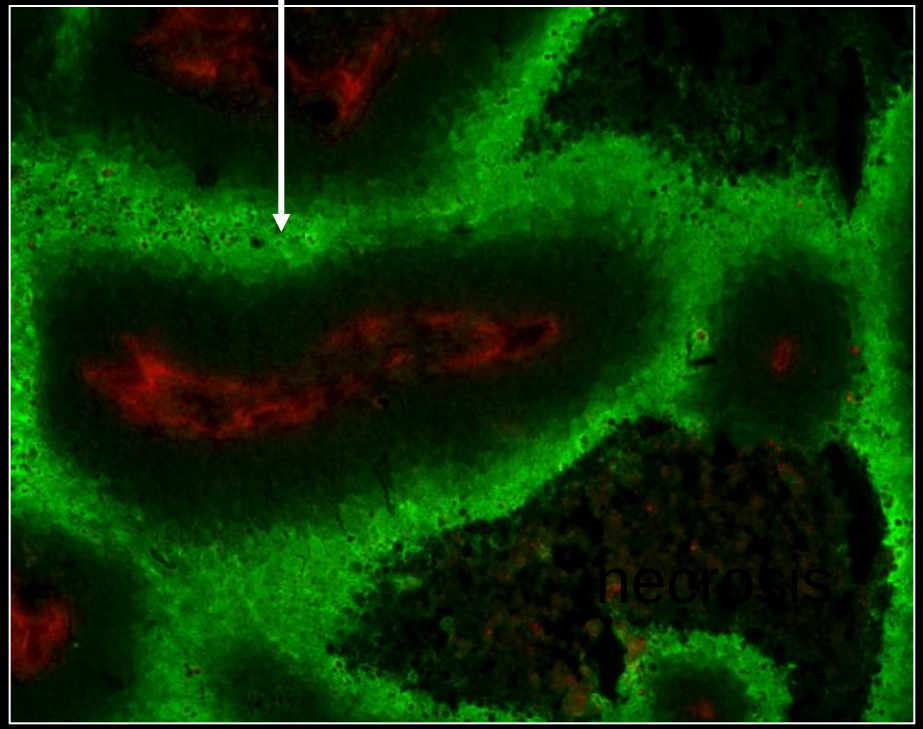
Different types of hypoxia

Perfusion-limited (“acute”)
Diffusion-limited (“chronic”)

Hypoxia: CCI-103F (-2.5h)
Proliferation: BrdU (-0.5h)
Vessels



Hypoxia
Vessels



Hypoxia is a result of:

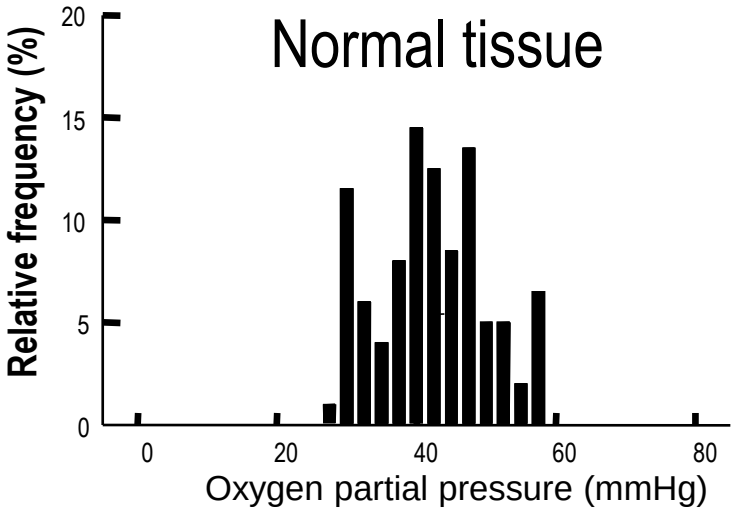
- Oxygen delivery
- Oxygen consumption
- Hypoxia tolerance

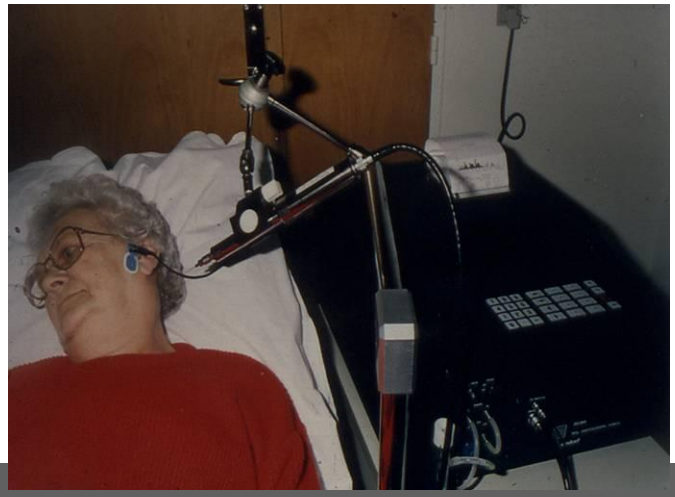
2) Heterogeneity of tumor oxygenation

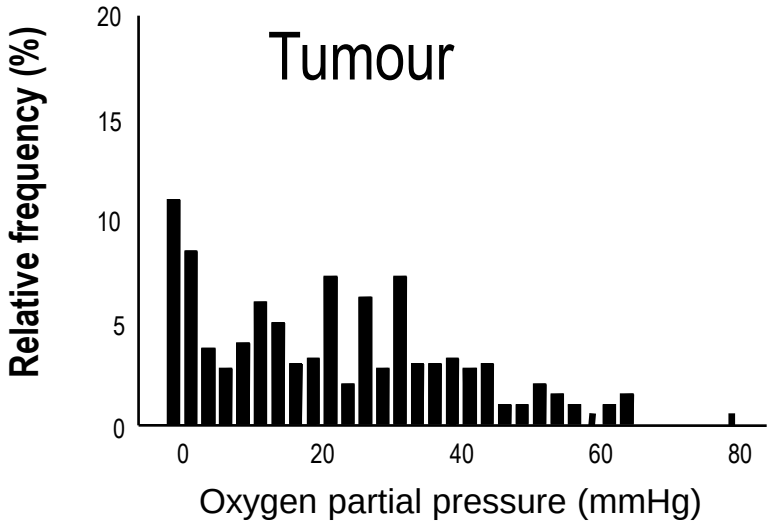
Heterogeneity in Oxygenation

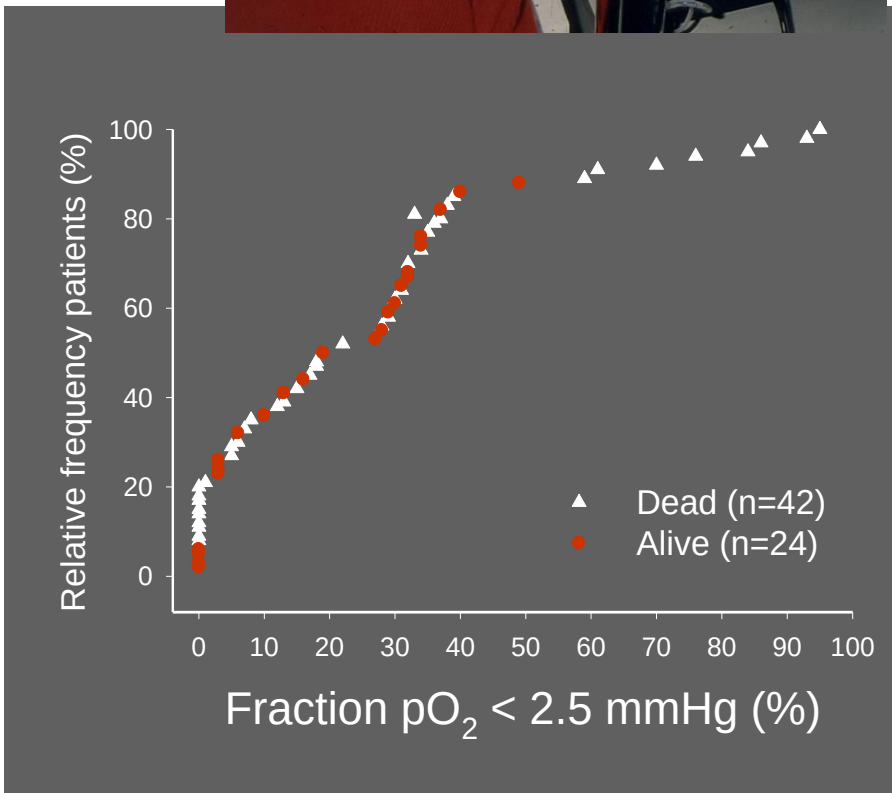
a) Amount (%) amongst patients
b) In severity
c) In space
d) In time

a) Heterogeneity in hypoxia (%) amongst patients

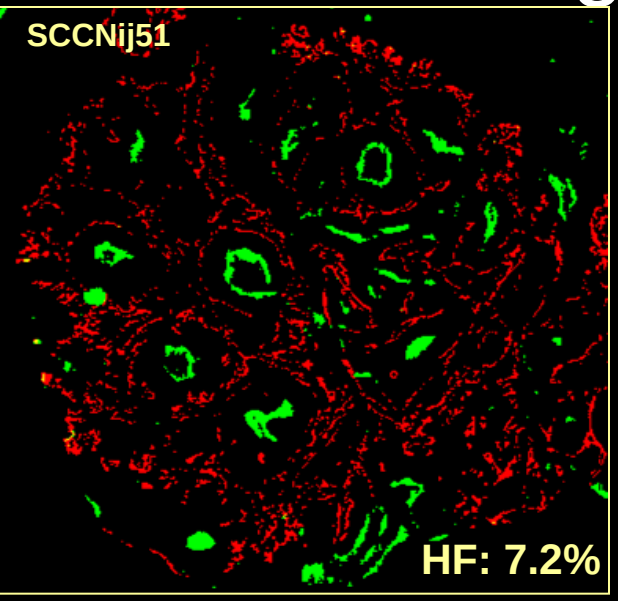


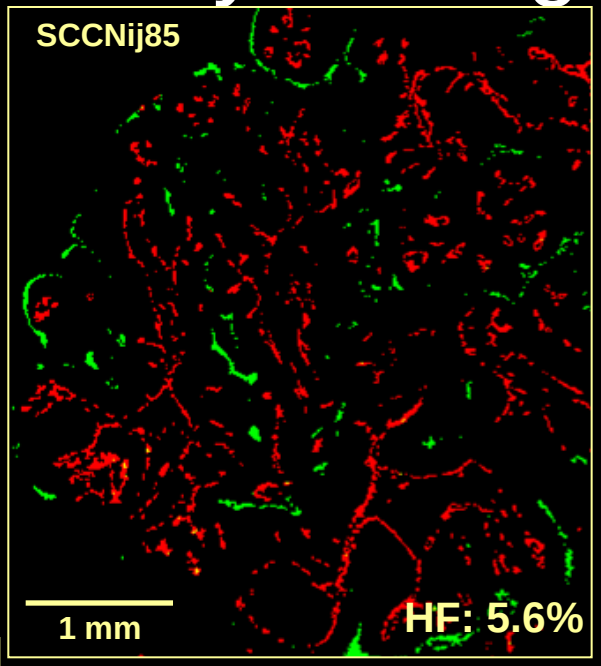


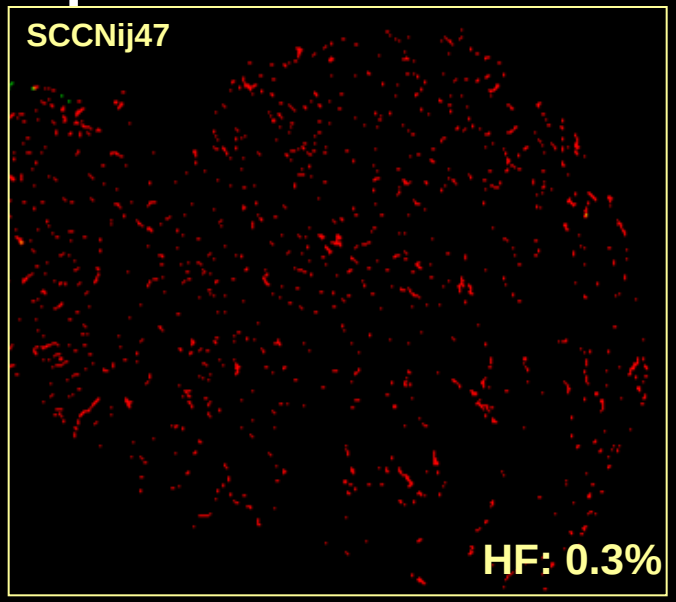


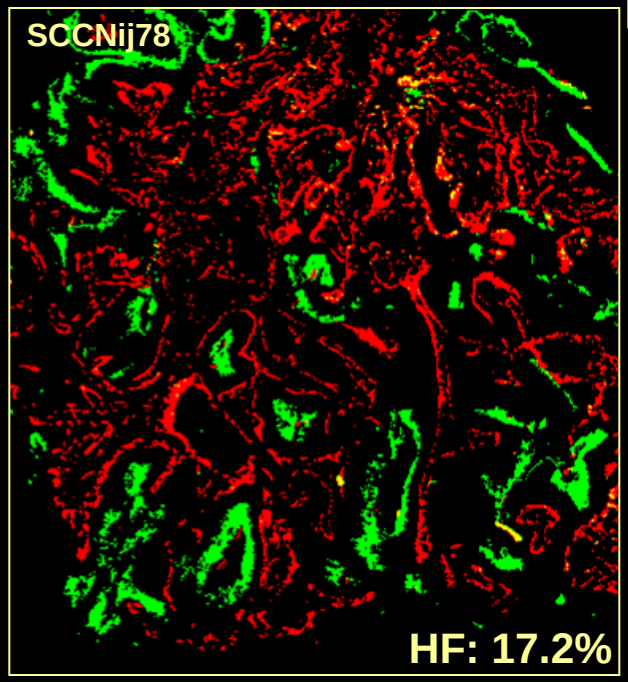


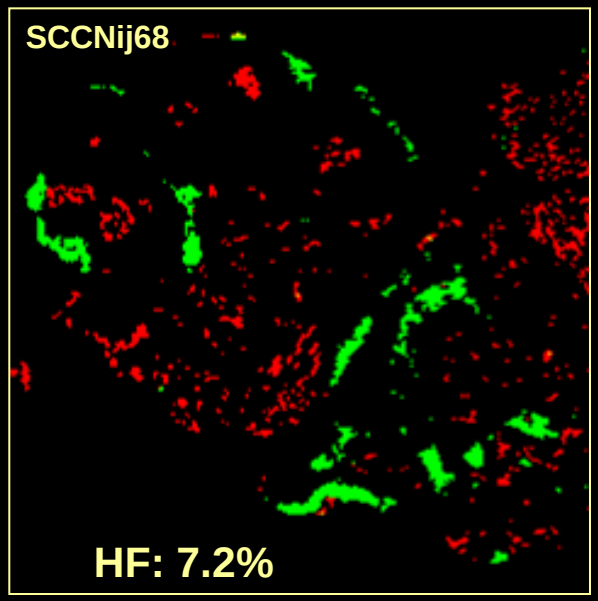
Heterogeneity amongst patients

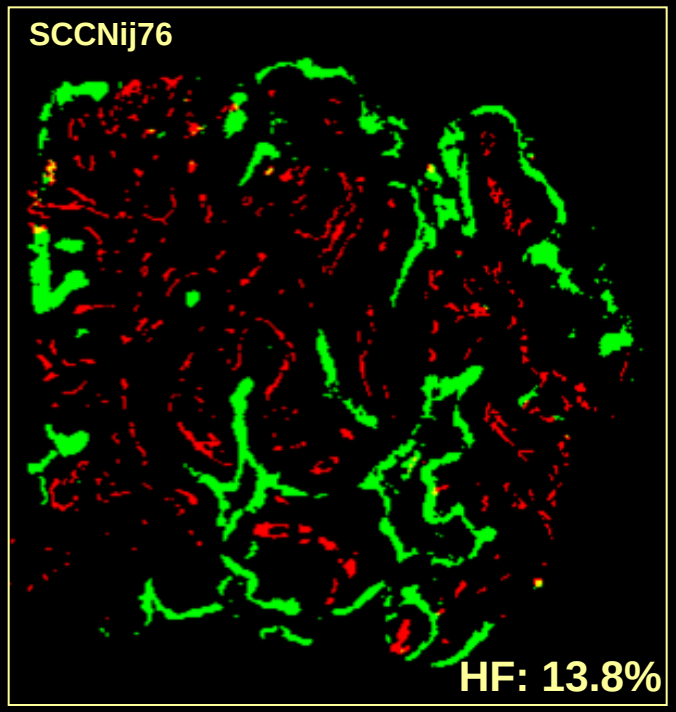












Hypoxia predicts for poor outcome

397 head and neck patients – 7 centers
Nordsmark M et al, Radiother Oncol. 2005

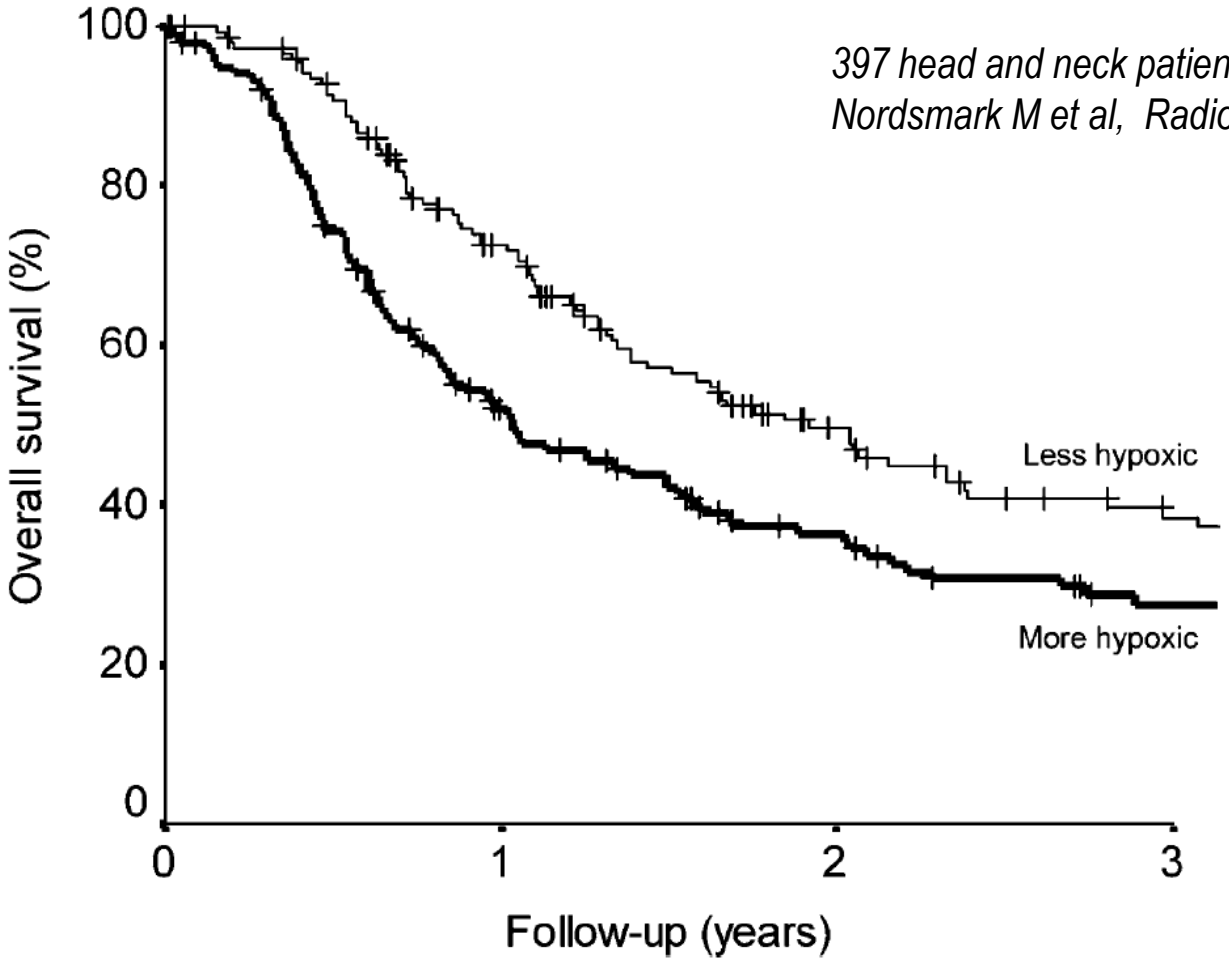
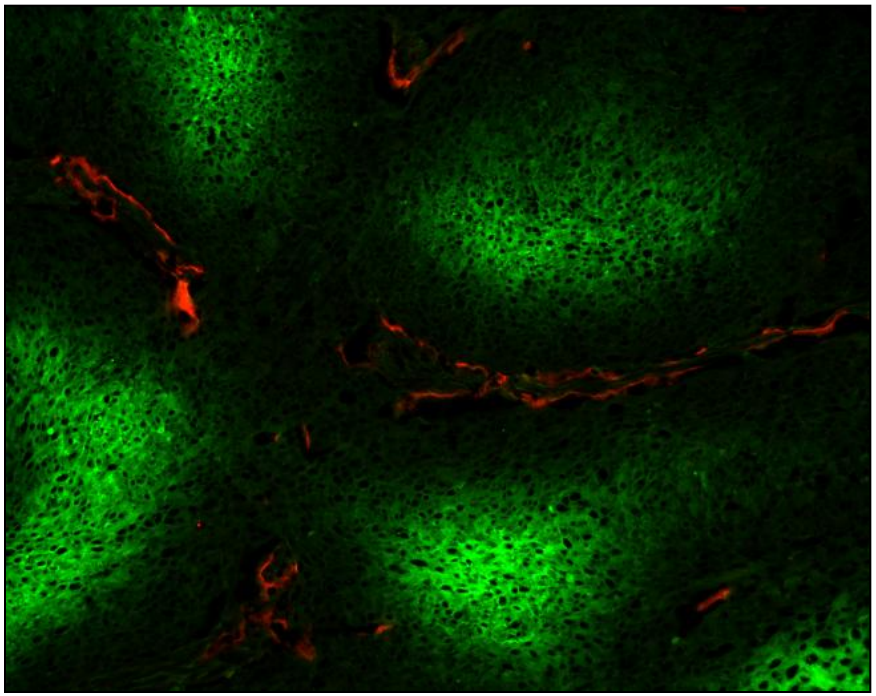
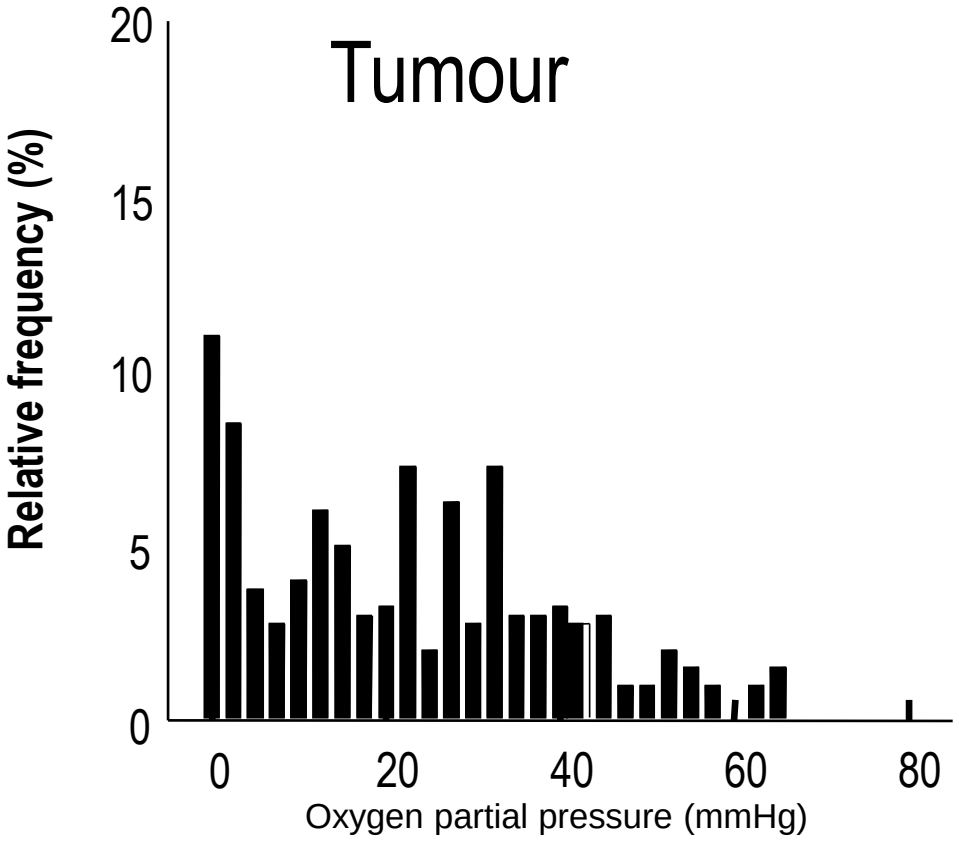


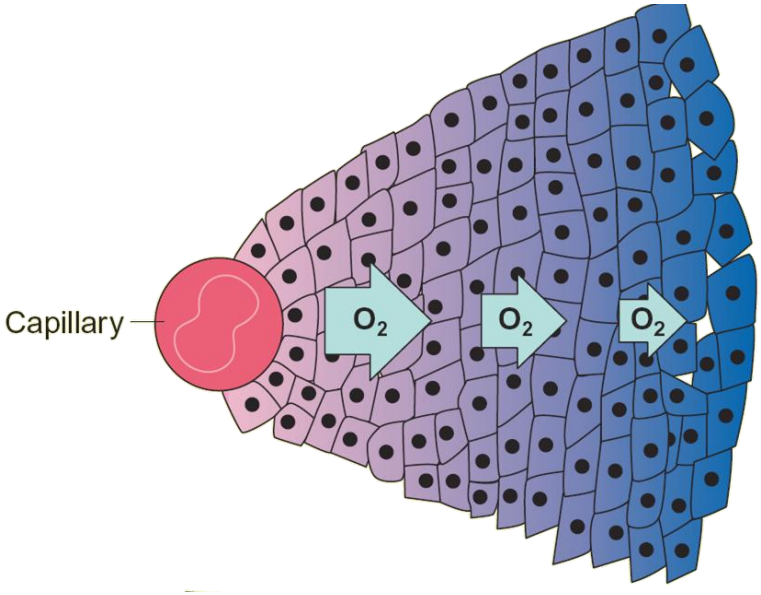
Fig. 2. Actuarial overall survival rate for patients with less hypoxic tumors ($HP_{2.5} \leq 19\%$, thin line) compared with more hypoxic tumors ($HP_{2.5} > 19\%$, bold line), $P = 0.006$.

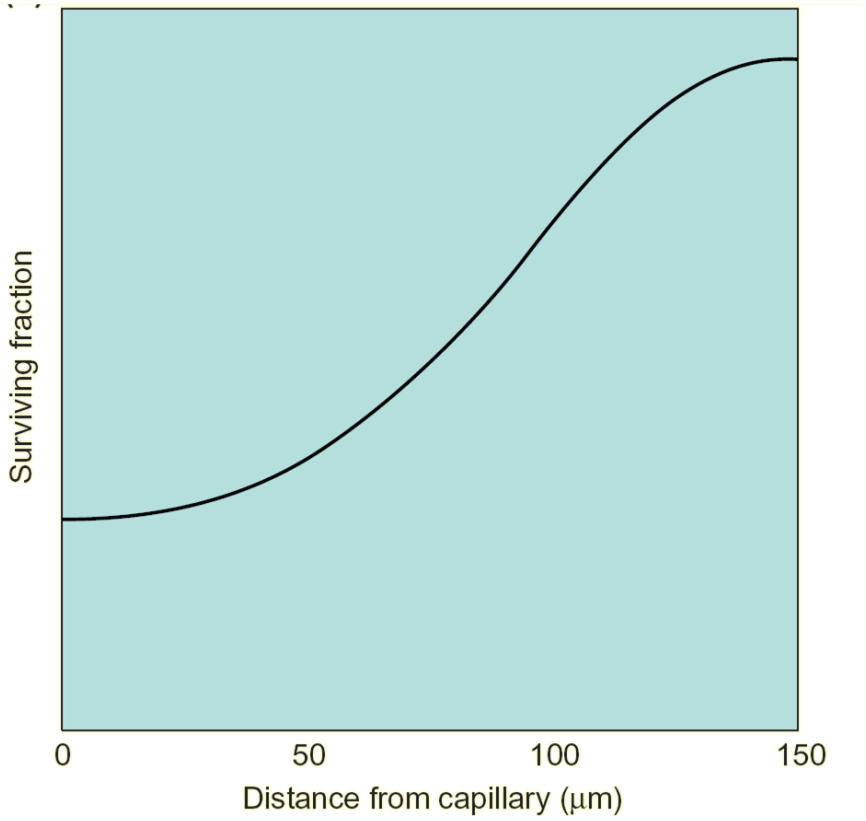
b) Heterogeneity in severity





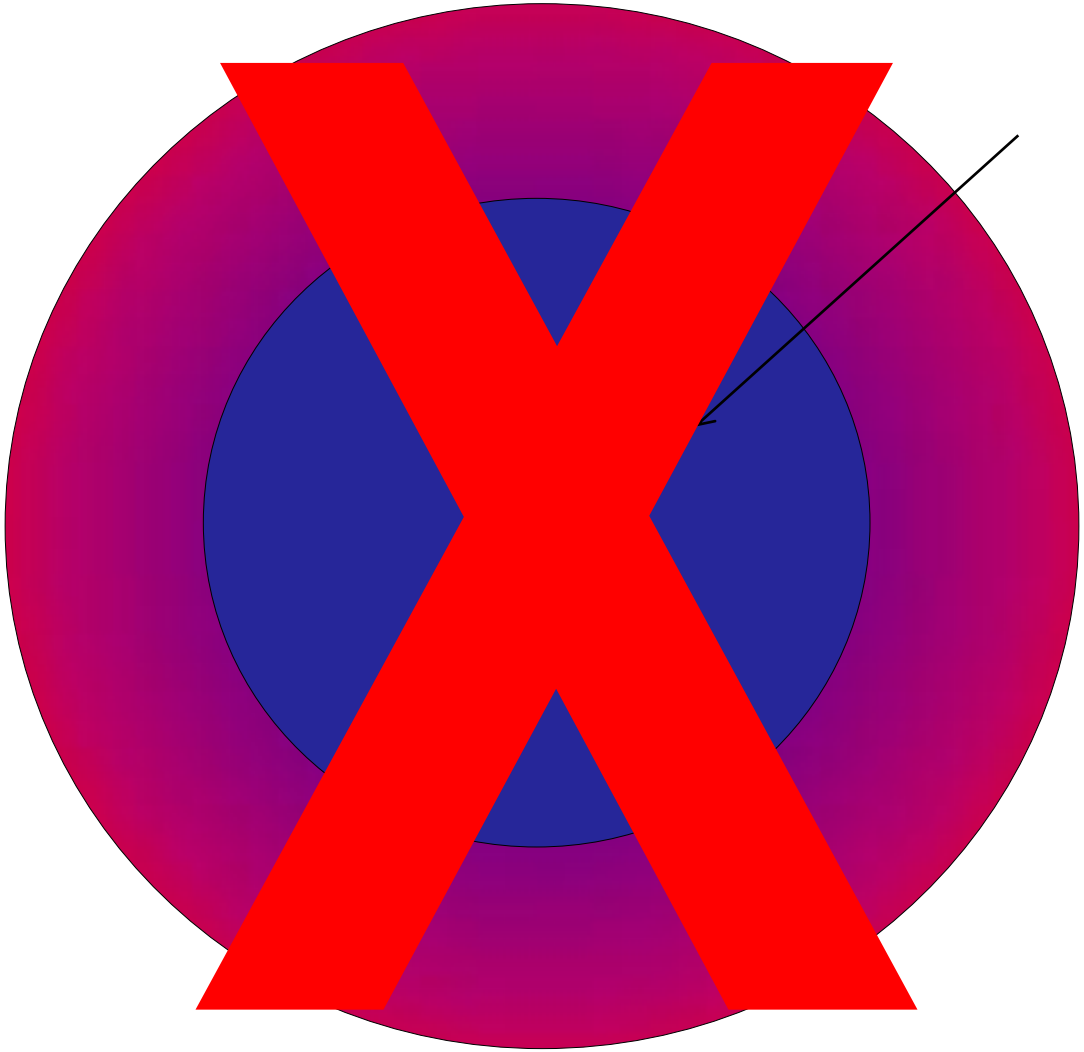
Severity and radiation response



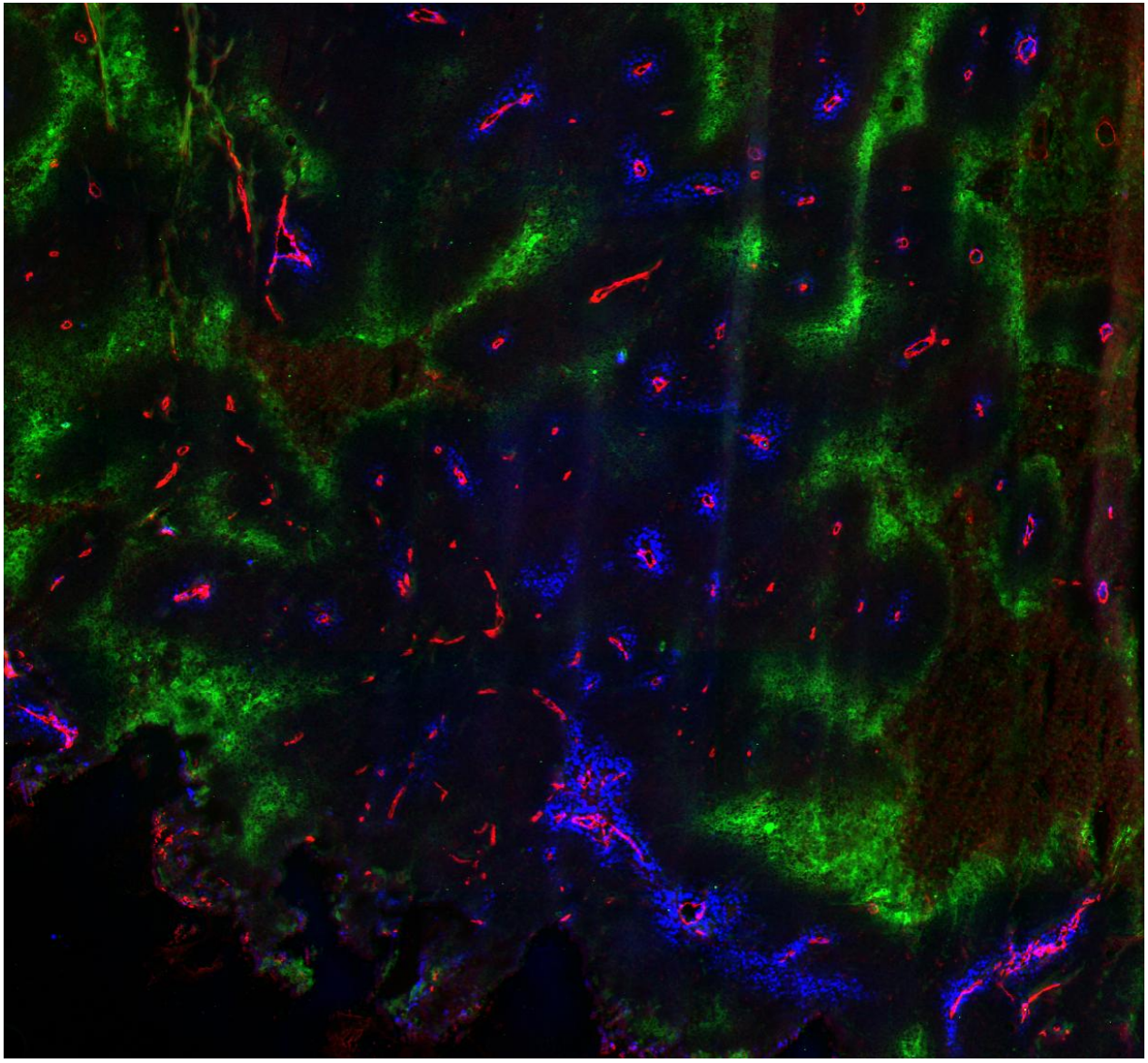


Cell killing by radiation will be reduced as a function of distance from the capillary.

c) Heterogeneity in space



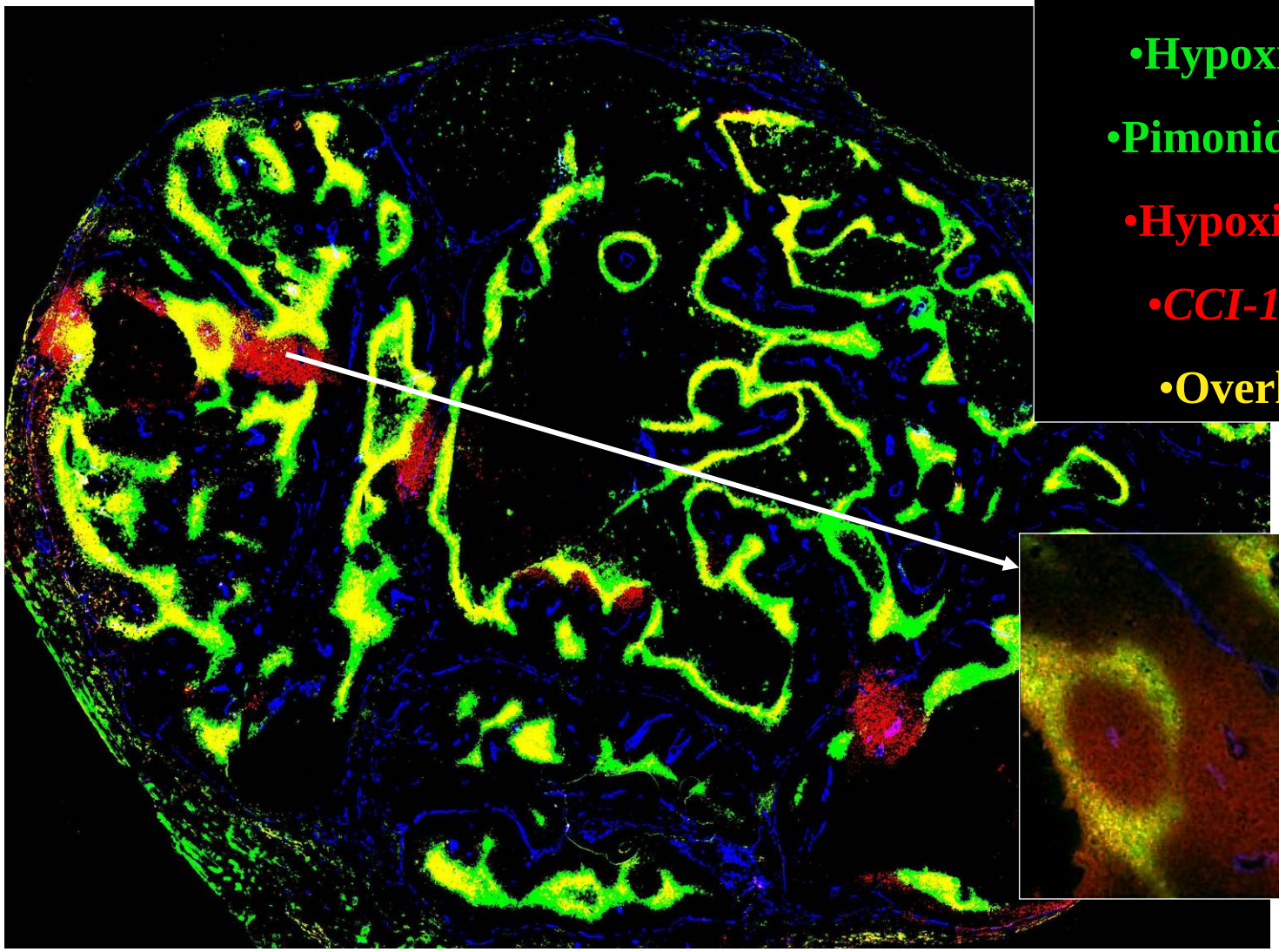
c) Heterogeneity in space



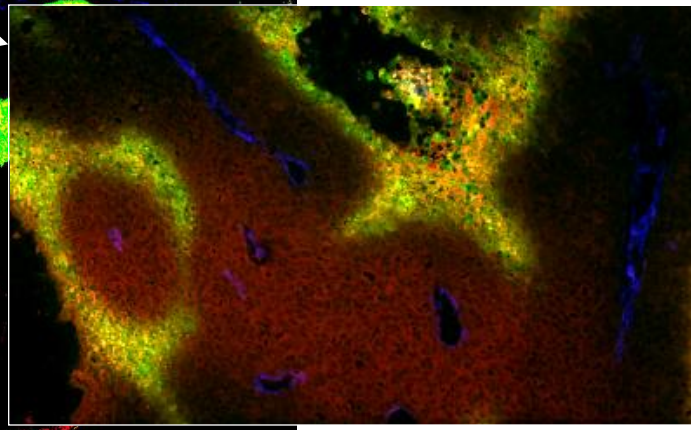
c) Consequences of spatial heterogeneity

- Hypoxia can exist around all vessels in a tumor
  - No relationship between hypoxia and tumor size!
- Oxygenation varies at the cellular (micron) level
- Imaging hypoxia always involves averaging over very large numbers of cells.
  - Hypoxic cells are likely to exist in all imaging voxels
  - It will never be possible to deliver dose specifically to hypoxic cells

d) Heterogeneity in time



- **Vessels (blue)**
- **Hypoxic marker 1:**
- **Pimonidazole (-4.5 h)**
- **Hypoxic marker 2 :**
- ***CCI-103F (-2.5h)***
- **Overlap: yellow**



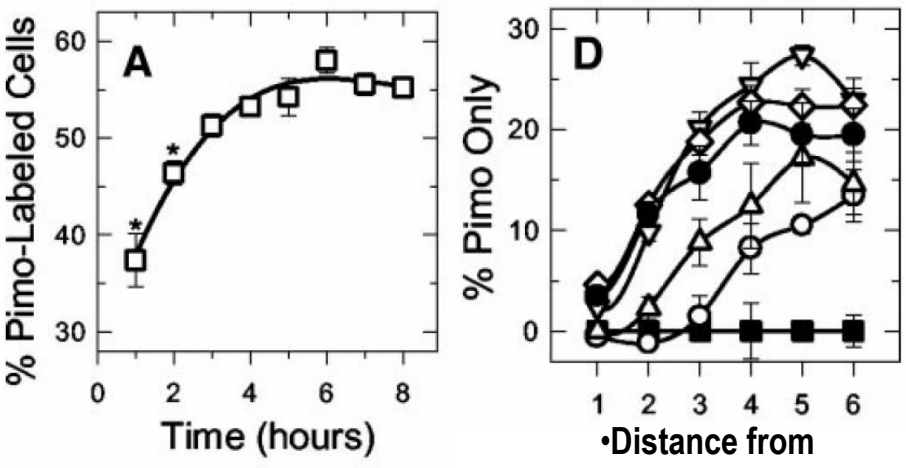
d) Heterogeneity in time

[CANCER RESEARCH 64, 6183–6189, September 1, 2004]

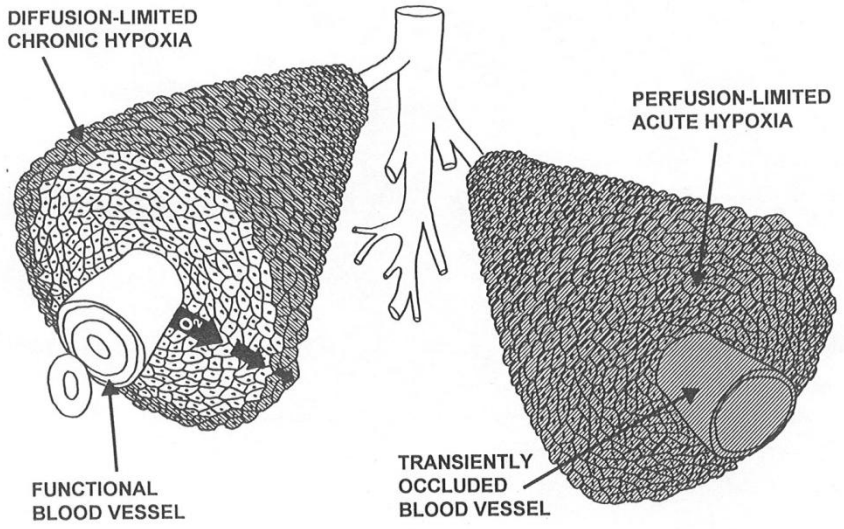
Quantifying Transient Hypoxia in Human Tumor Xenografts by Flow Cytometry

Kevin L. Bennewith and Ralph E. Durand

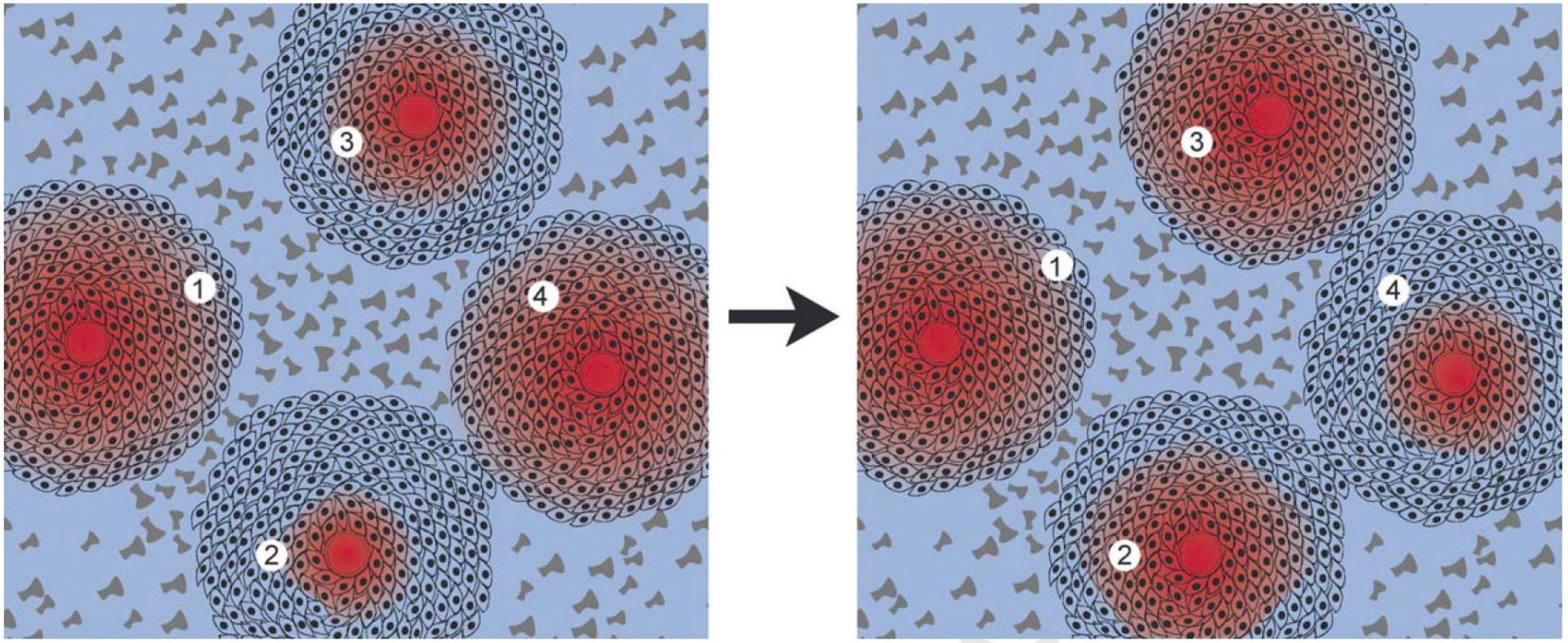
Medical Biophysics Department, British Columbia Cancer Research Centre, Vancouver, British Columbia, Canada



- Distance from
- blood vessel



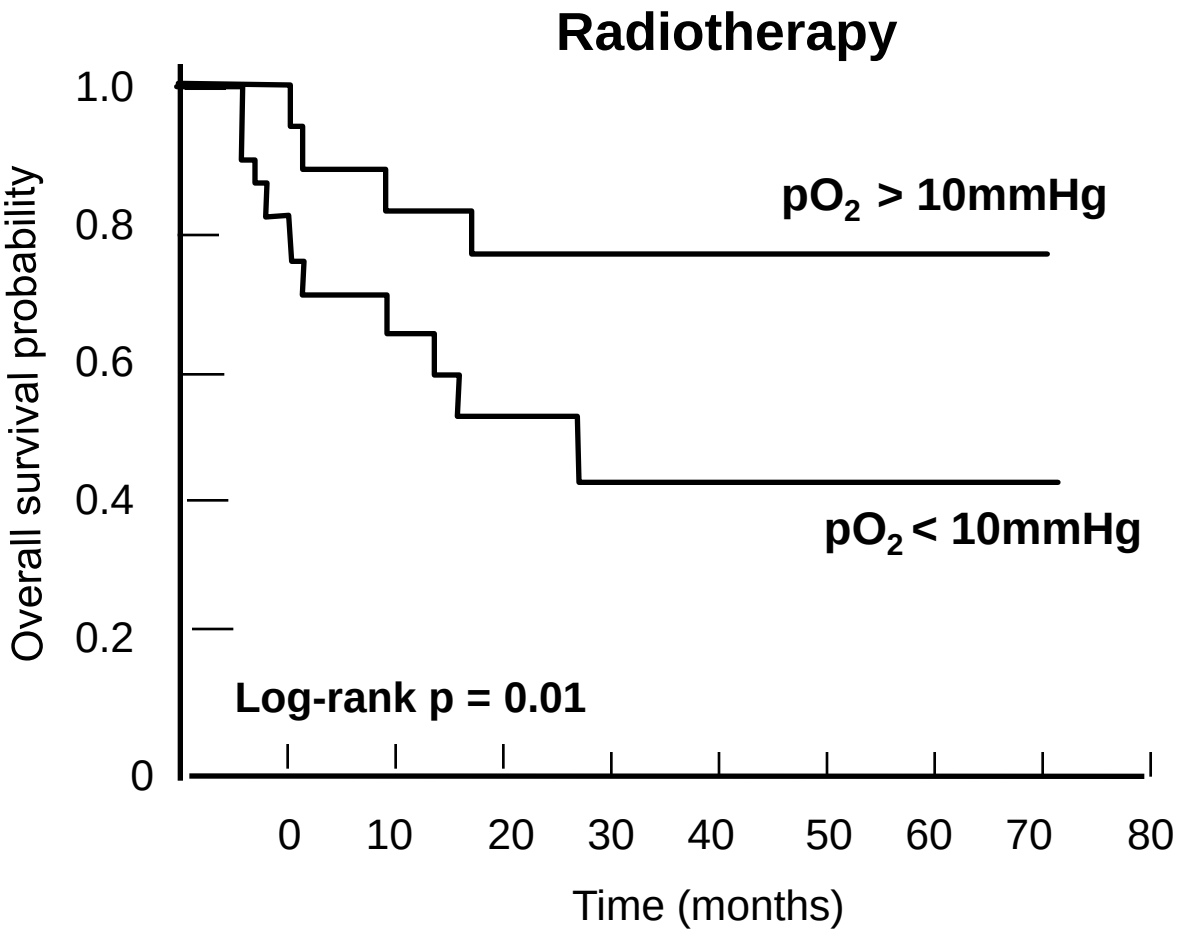
Oxygenation is dynamic



Hypoxic cells vary at every fraction

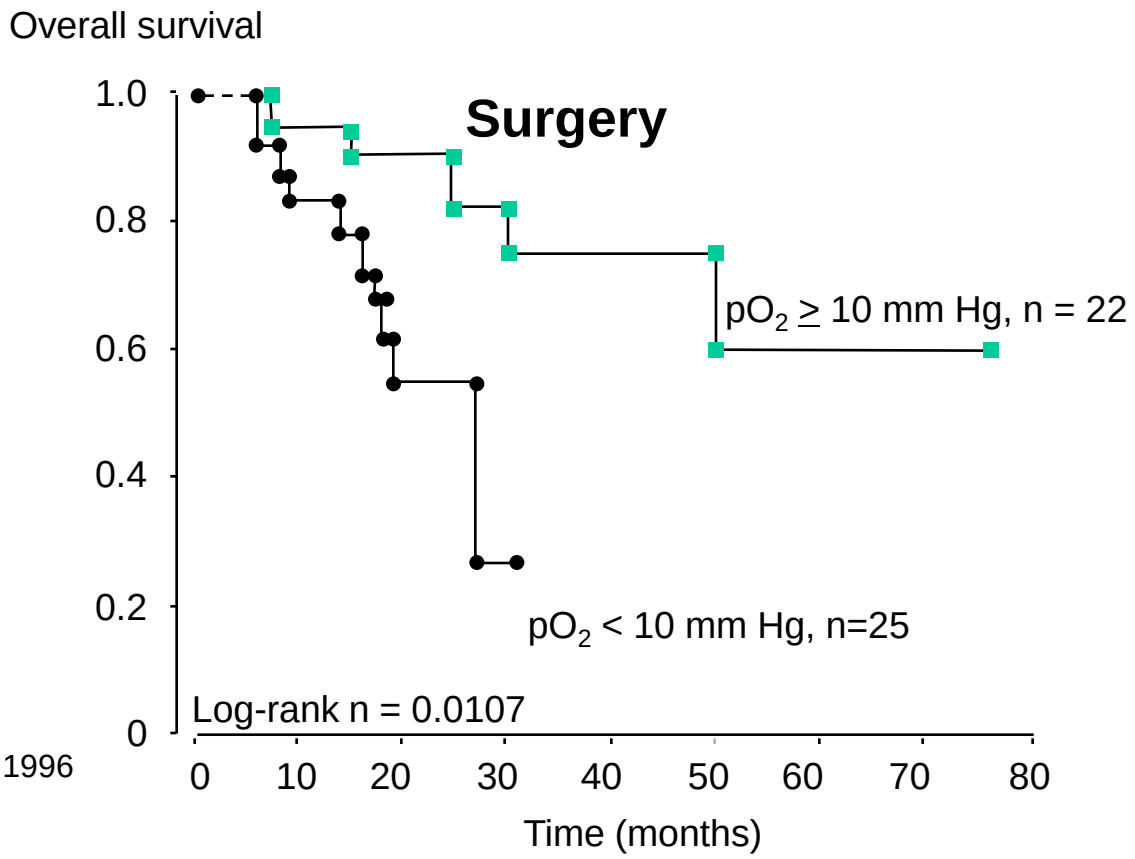
3) Cellular consequences of hypoxia

Treatment resistance - Radiotherapy



Höckel M. et al. Cancer Res 56, 4509-4515 (1996)

Hypoxia and Treatment Outcome - Surgery



Höckel M. et al, 1996

Hypoxia is a prognostic factor

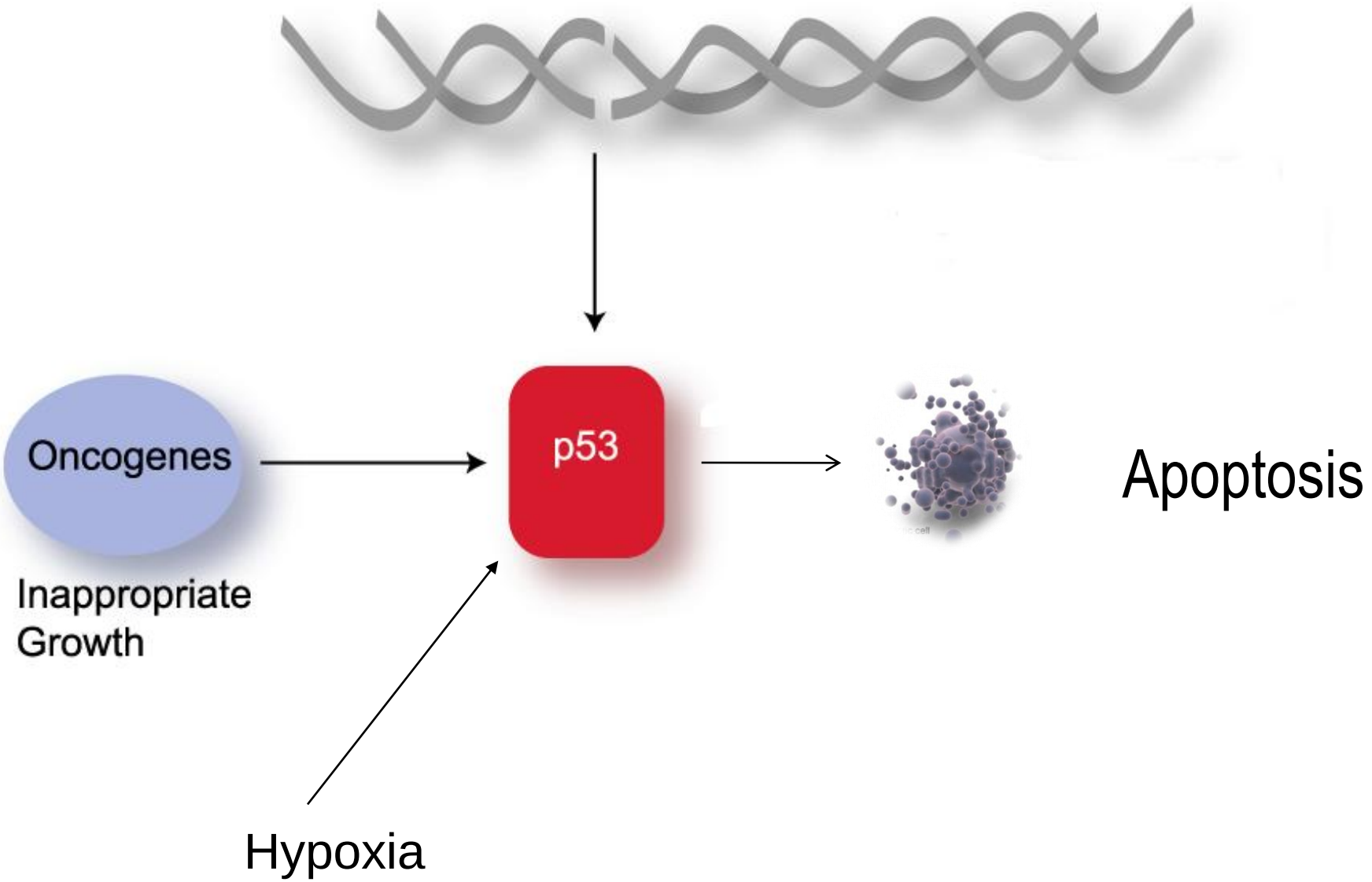
- **Hypoxic tumors are more malignant**
  - Cervix tumors have larger extensions, more frequent parametrial spread, more lymph-vascular space involvement
  - recurrent tumors are more hypoxic than primary tumors
  - predicts for the likelihood of distant metastases in soft tissue sarcomas
  - hypoxia is a strong prognostic factor (*Independent of primary mode of treatment)*

Hypoxia and malignancy – mechanisms

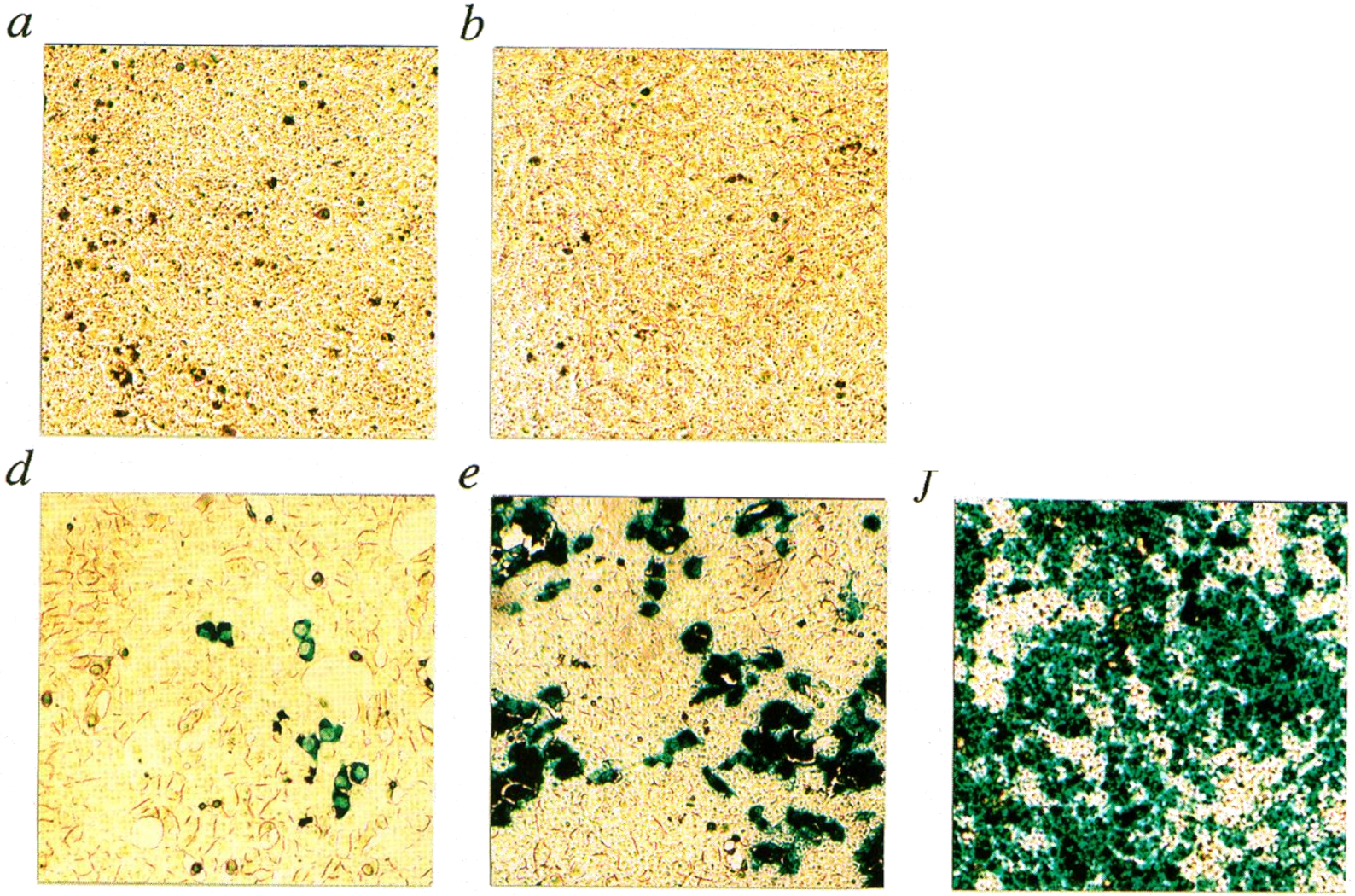
a) Tumor hypoxia can “select” for cells that are more malignant

b) Cellular response to hypoxia affect cell behavior in an adverse way

Hypoxia activates p53

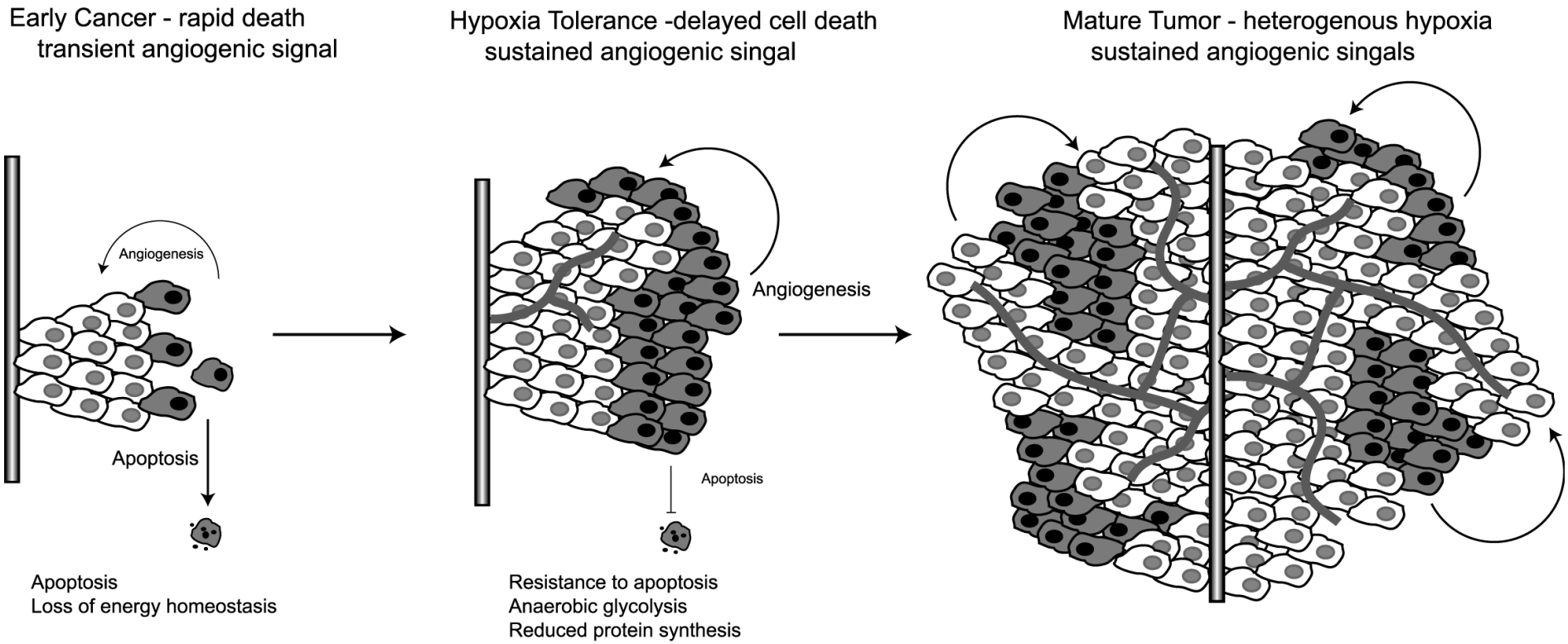


Hypoxia mediated selection of cells

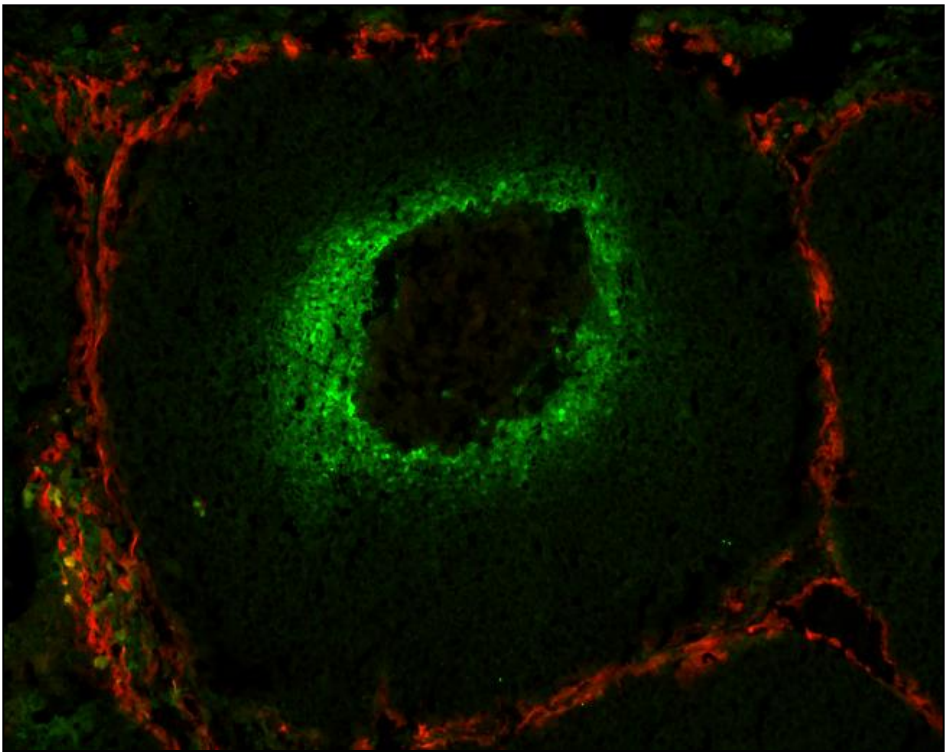


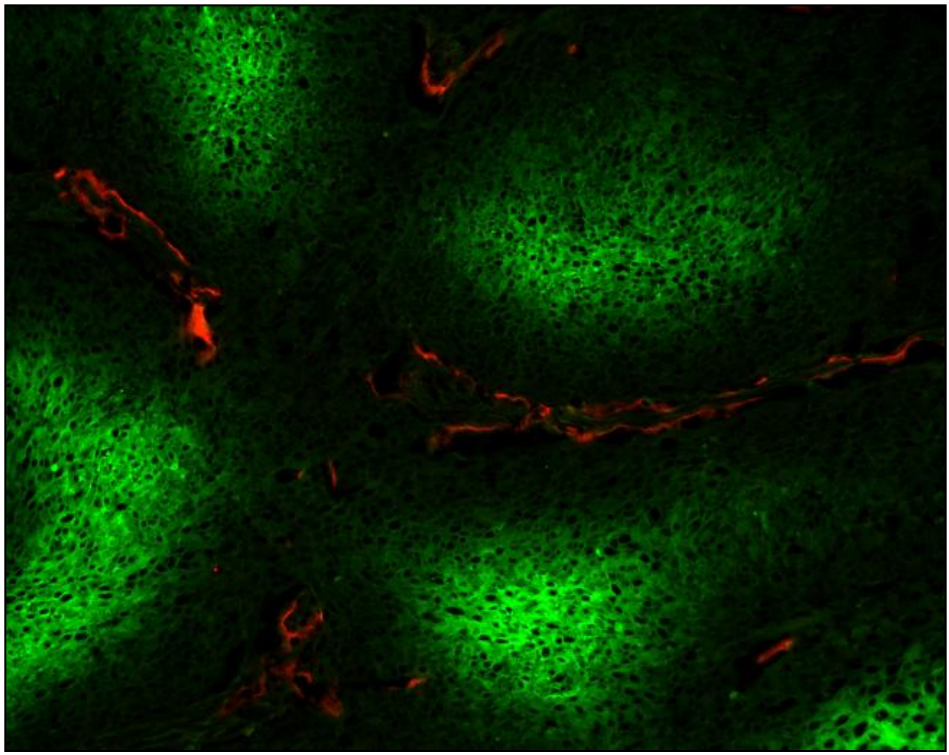
Graeber, Nature 1996

The concept of hypoxia tolerance



Hypoxia tolerance varies amongst tumors



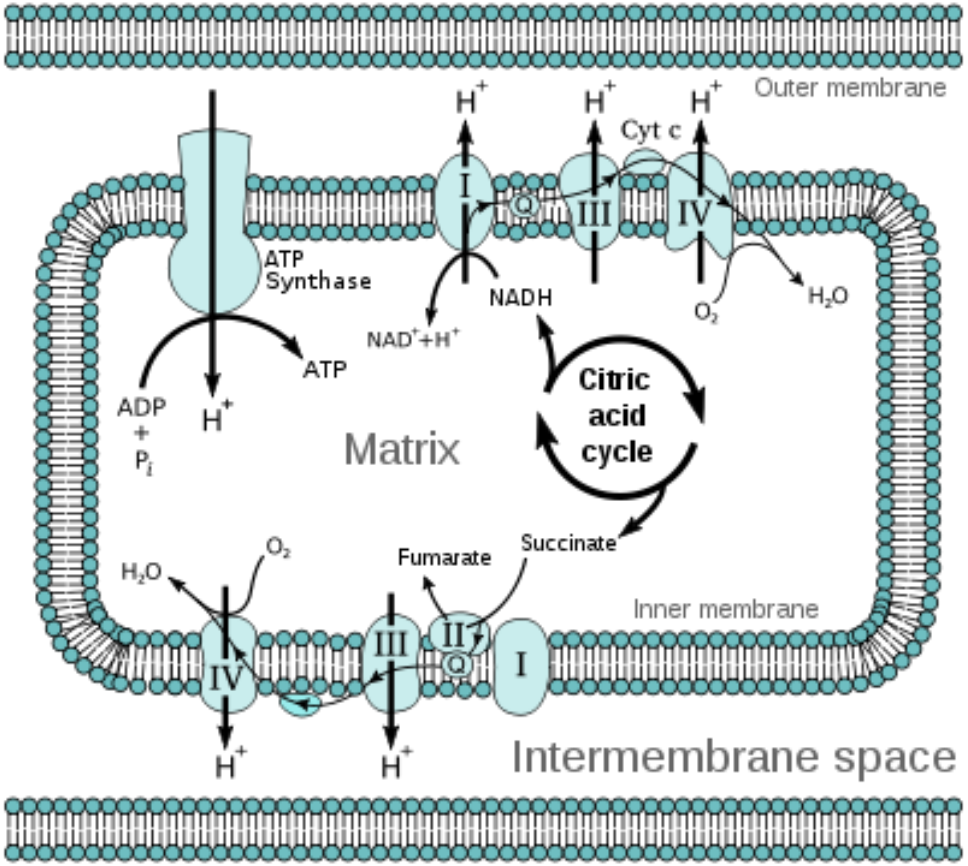


Cellular responses to hypoxia promote malignancy

- Hypoxia causes biological changes that promote
  - Metabolic adaptation
  - Angiogenesis / vasculogenesis
  - Migration, invasion and metastasis (EMT)
  - Genetic instability
  - Cell cycle checkpoints

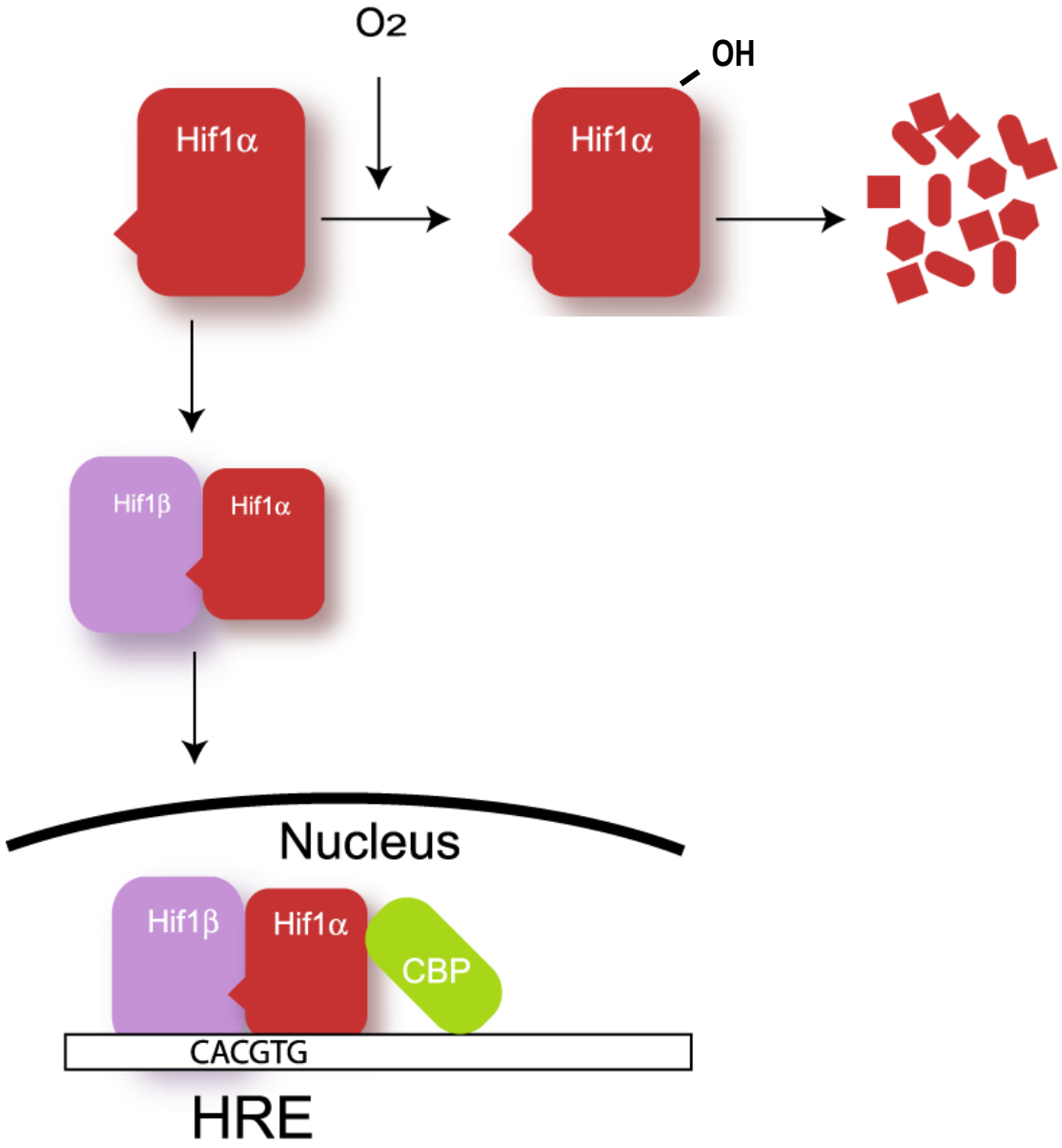
Biological changes are a consequence of altered protein activity and gene expression

Oxygen sensors: cytochrome c oxidase

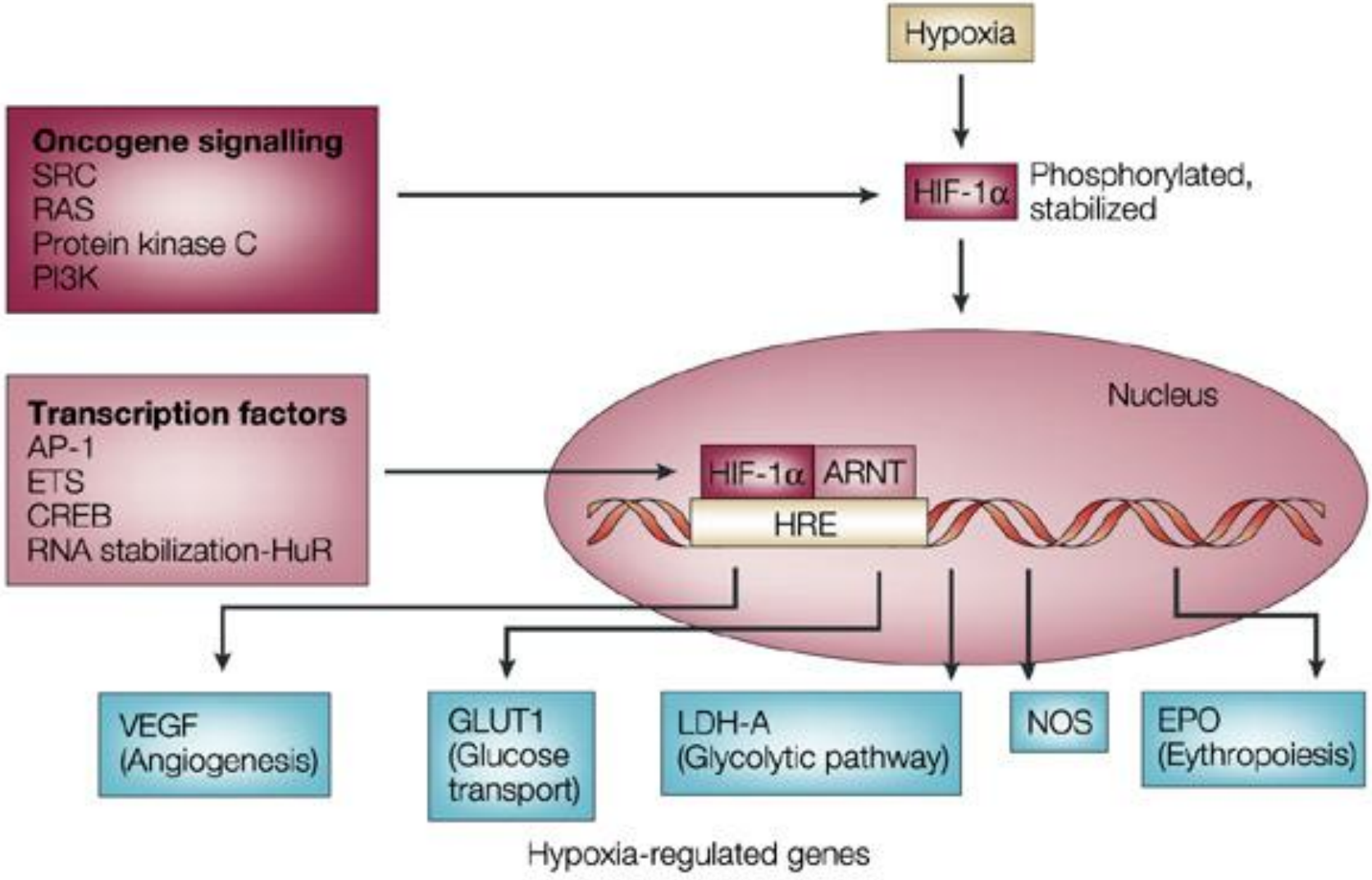


- ~80% oxygen consumption
- Reprogrammed metabolism
- ATP drop
  - Signaling pathways

Oxygen sensors: HIF hydroxylases



HIF mediated pathways

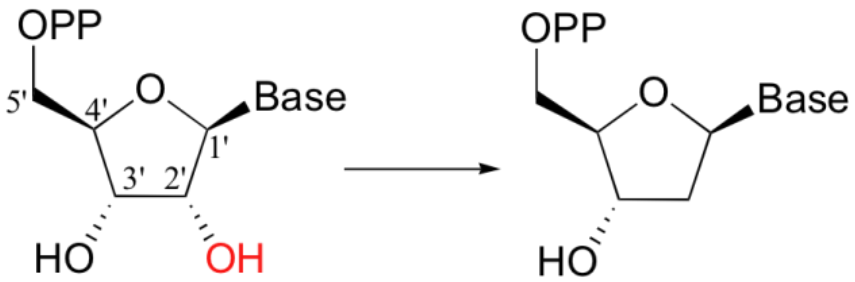


Nature Reviews | Cancer

HIF and cancer

- Loss of VHL causes overexpression of HIF and renal cell carcinoma
- HIF is overexpressed in many cancers
  - Mimics hypoxia biology in normoxia

Oxygen sensors: Ribonucleotide reductase

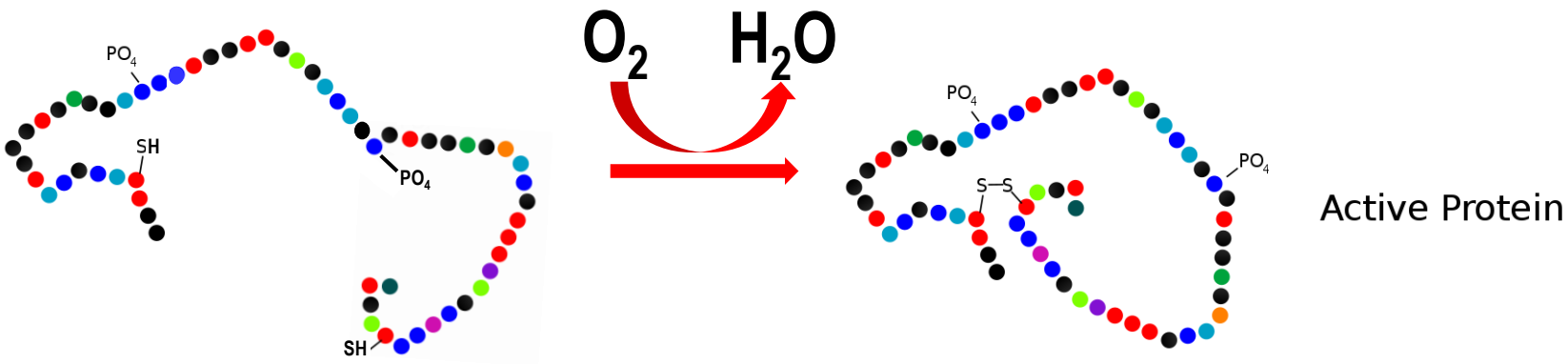


ribonucleotide diphosphate (RNA)

deoxyribonucleotide diphosphate (DNA)

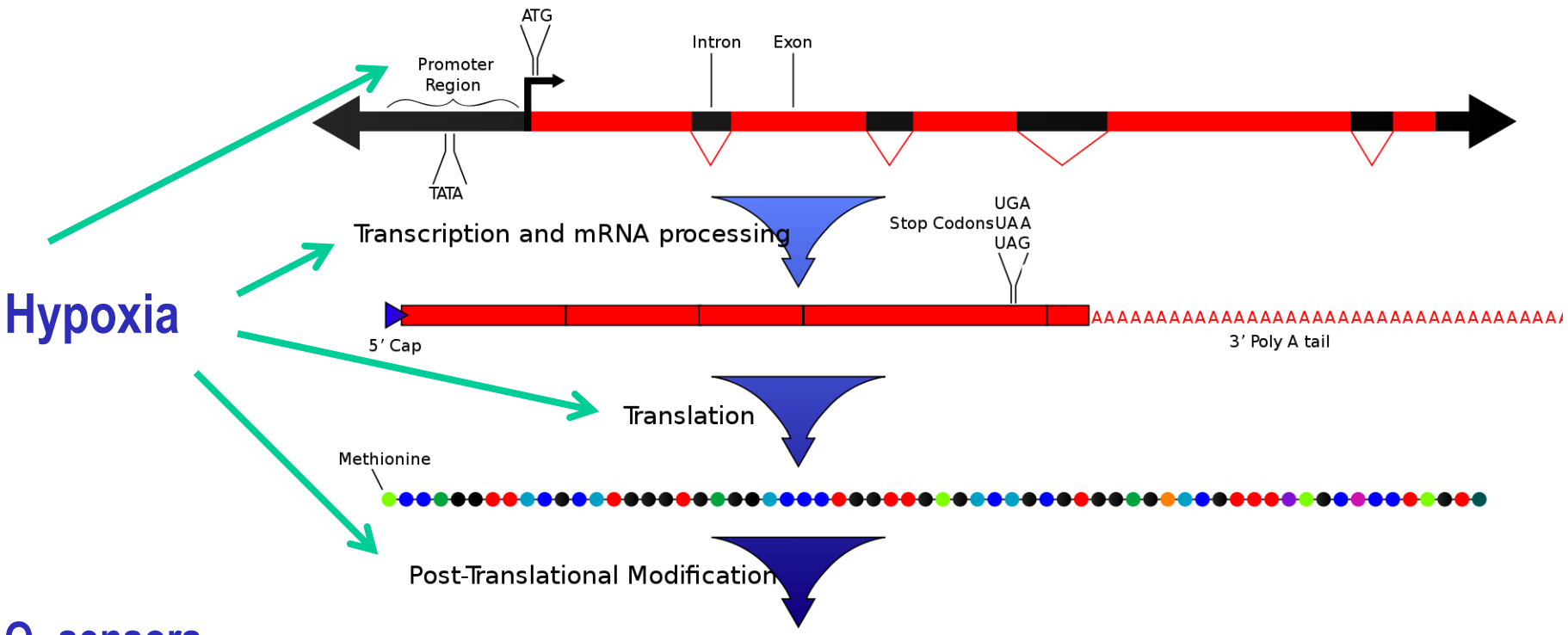
DNA synthesis

Oxygen sensors: disulfide oxidases



“Unfolded protein response”
Transcription
Translation

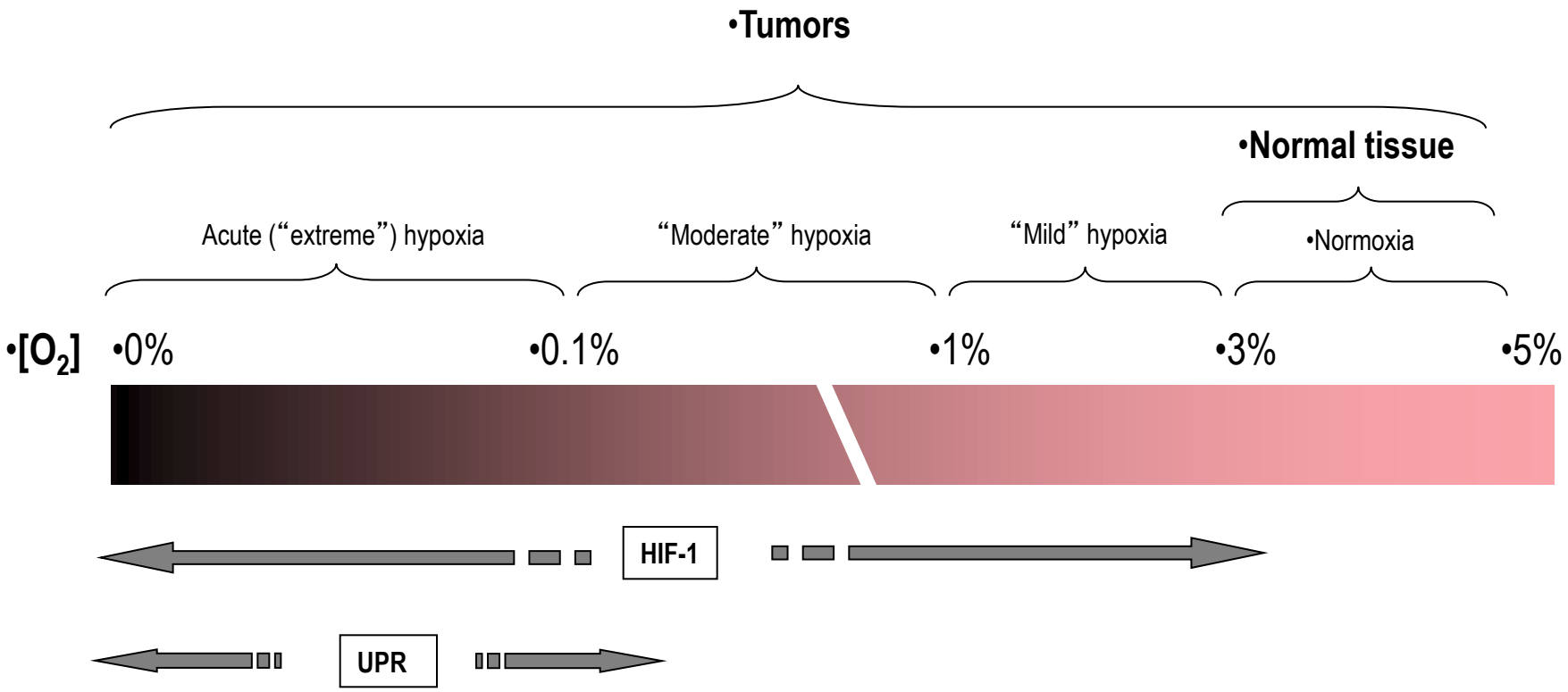
Molecular consequences of hypoxia



Hypoxia

O_2 sensors
Cytochrome c oxidase
Hydroxylases
Ribonucleotide reductase
Disulfide oxidases
Demethylases

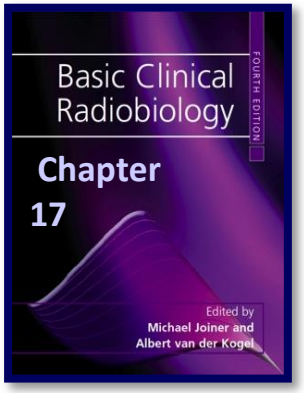
Hypoxic severity affects cellular response

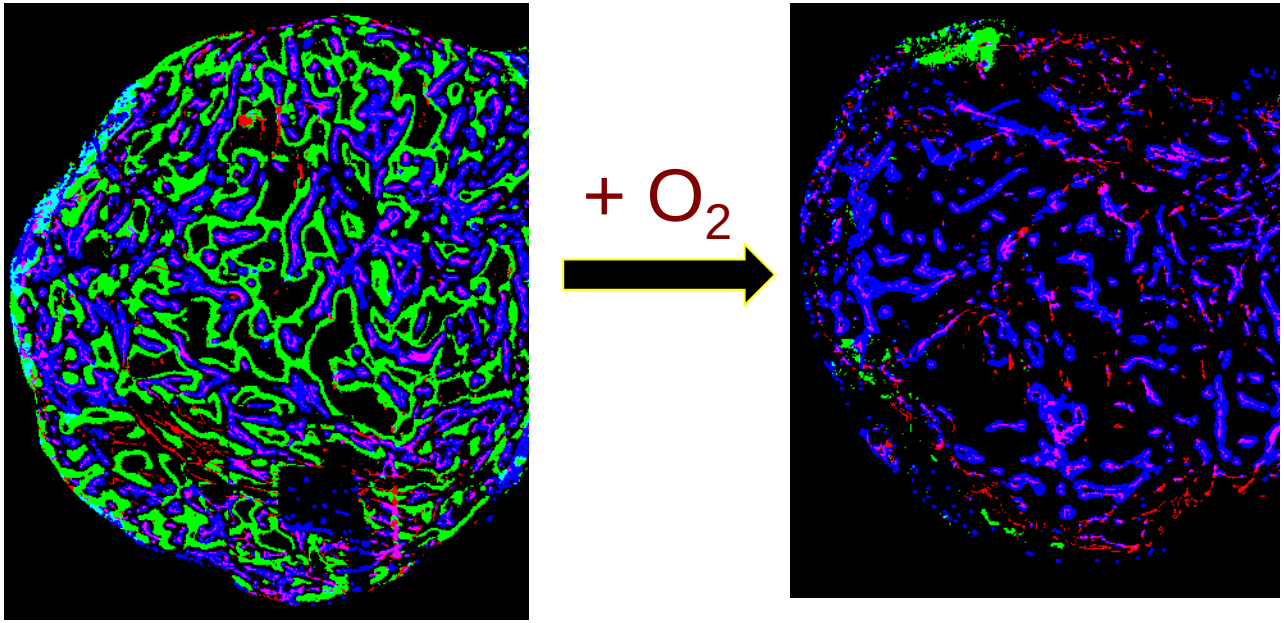


Summary of tumor hypoxia

- Mechanisms responsible for tumor hypoxia
  - chronic and acute
  - Supply, demand, tolerance
- Hypoxia is heterogeneous
  - amount, spatial, severity, time
- Hypoxia can promote malignancy
  - Tumors become hypoxia tolerant (selection for p53 mutations)
  - Hypoxia alters cellular function through transcription, translation and protein activity

Clinical Efforts to Modify Tumor Hypoxia



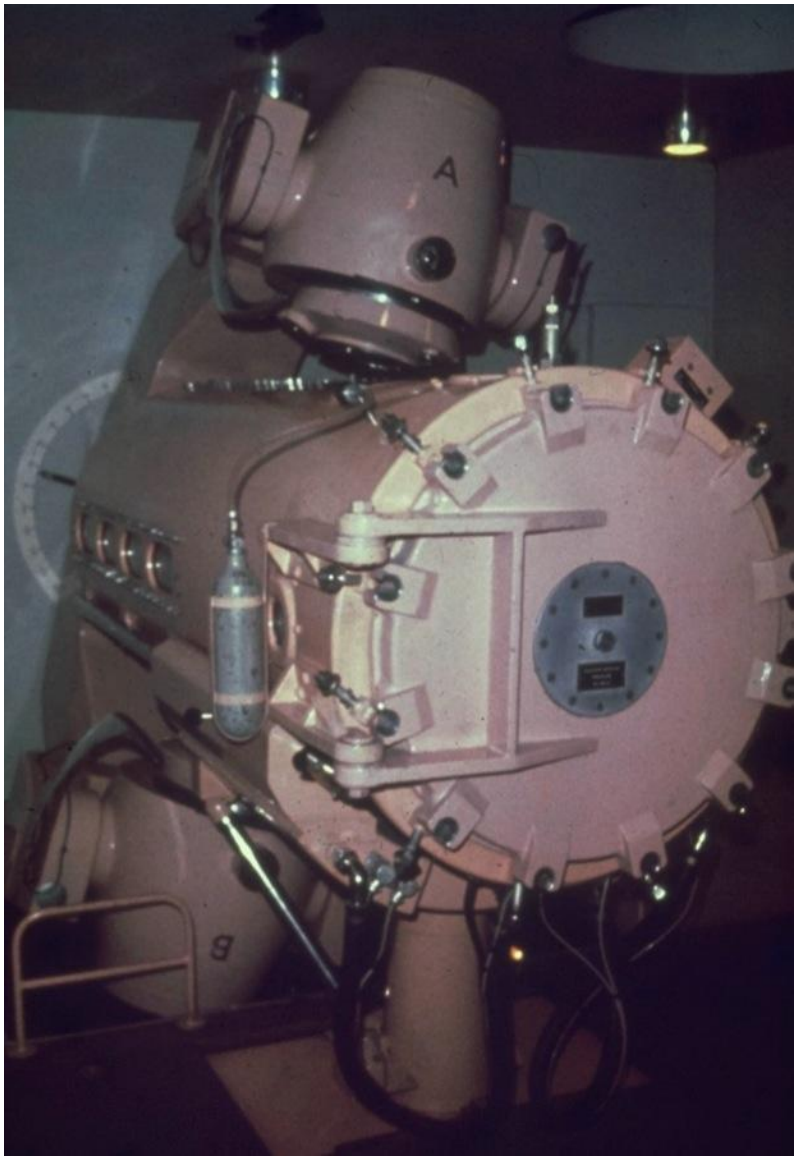


Albert van der Kogel
Budapest, 2016

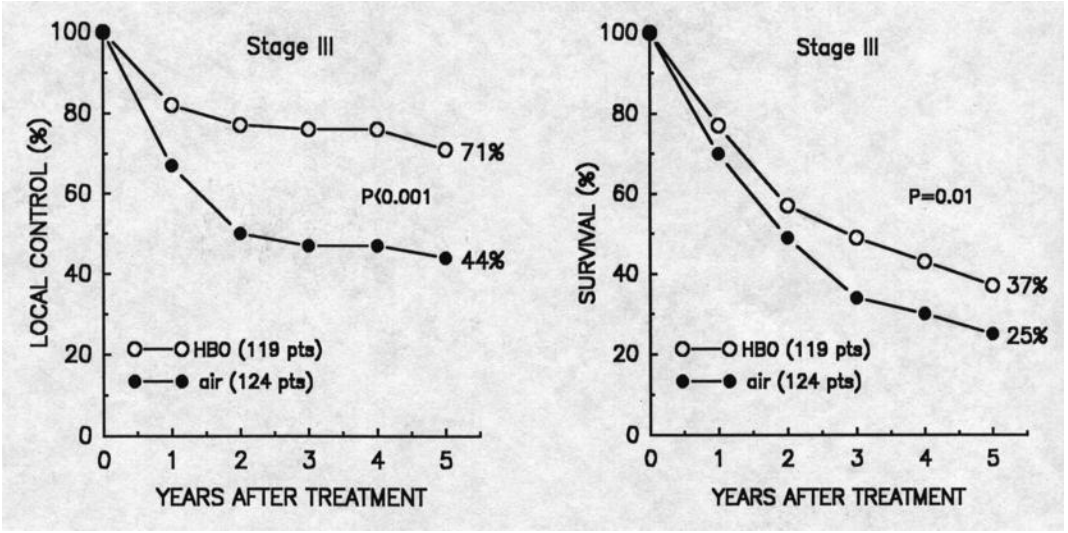
Therapeutic approaches to tumor hypoxia

- Raising the oxygen content of inspired gas
- Hypoxic cell radiosensitizers
- Increasing haemoglobin concentration
- Overcoming acute & chronic hypoxia in tumors

Hyperbaric oxygen



MRC Trial in Carcinoma of the Uterine Cervix
Watson et al. 1978



Hyperbaric Oxygen and Radiotherapy

Table 1
Randomized clinical trials with hypoxic modification of radiotherapy in HNSCC.

References	Trial acronym	Year	No. pts	fx[a]	RT schedule	Hypoxic modification
[21]	van den Brenk	1968	30	HH	7.75 Gy x4vs7.25 Gy x4 with HBO	HBO 4 atm
[22]	Evans 1	1970	40	LL	60 Gy/30 fx	Normobaric 02
[23]	Tobin	1971	17	LL	60 Gy/30 fx	HBO 3 atm
[24]	Chang	1973	51	HHL	6 Gy x6+ HBO vs 6 Gy x7 or 60 Gy/30 fx	HBO 3 atm
[25]	Shigamats u	1973	31	HH	60–79 Gy/10 fx vs. 40–50 Gy/8–10 fx + HBO	HBO
[26]	Evans 2	1975	44	LL	60 Gy/30 fx	Normobaric 02
[27]	MRC 1 trial	1977	276	HH	35–45 Gy x10	HBO 3 atm
[26]	MRC 3, trial	1979	24	HL	45–50/15 el 48.5–55/20 air vs. 40–45/10 HBO	HBO

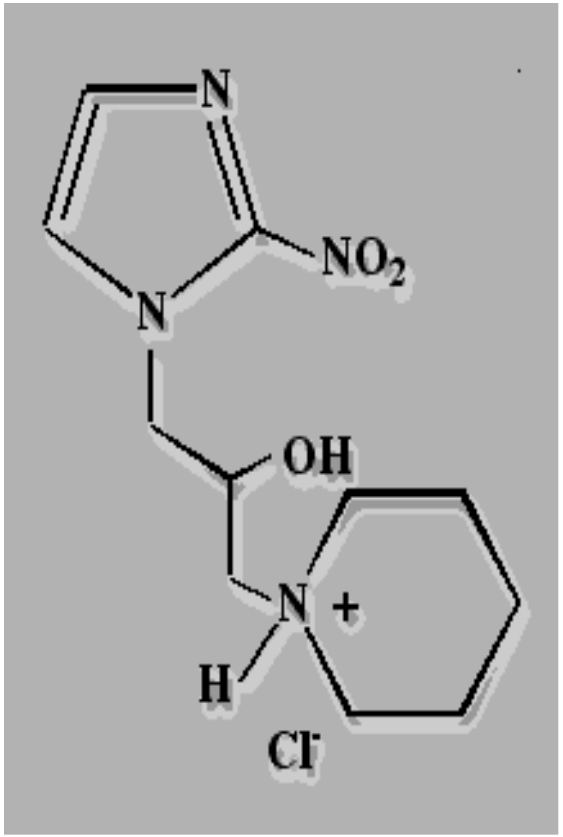
Overgaard et al Radiother Oncol 2011

Therapeutic approaches to tumor hypoxia

- Raising the oxygen content of inspired gas
- Hypoxic cell radiosensitizers
- Increasing haemoglobin concentration
- Overcoming acute & chronic hypoxia in tumors

Nitroimidazole-family

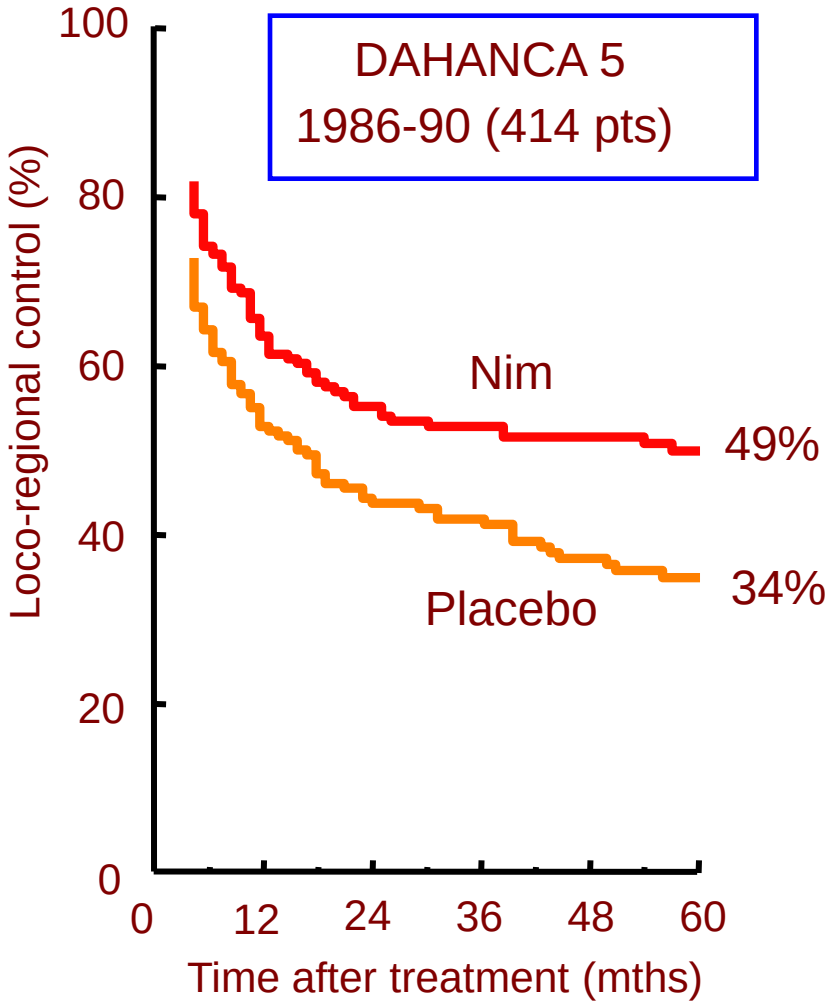
Radiation sensitizers



- Metronidazole (Flagyl)
- Misonidazole
- Nimorazole
- Etanidazole
- Pimonidazole

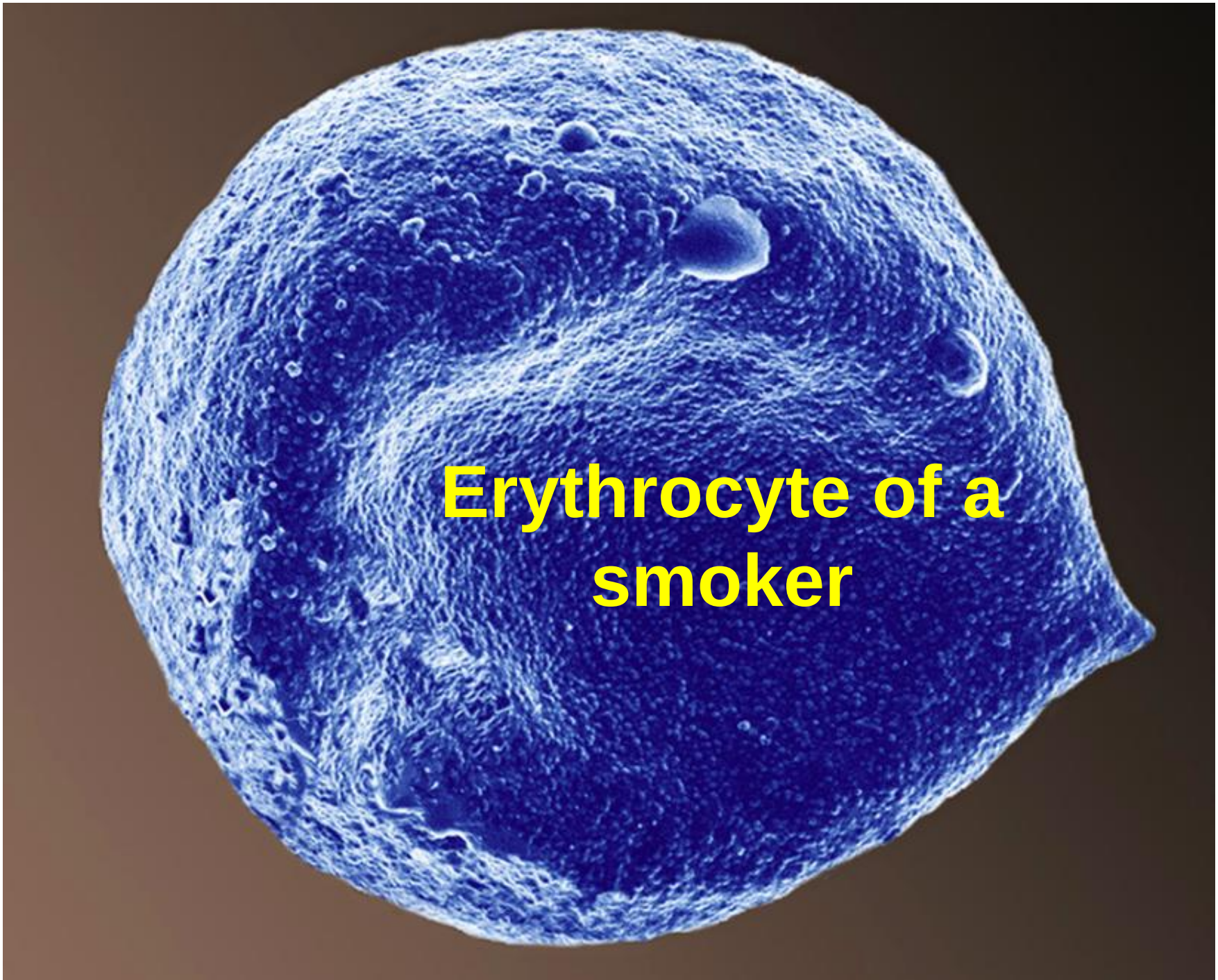
Compounds that mimic oxygen by their electron-affinity

Hypoxic sensitizers: Nimorazole in the Danish head&neck studies



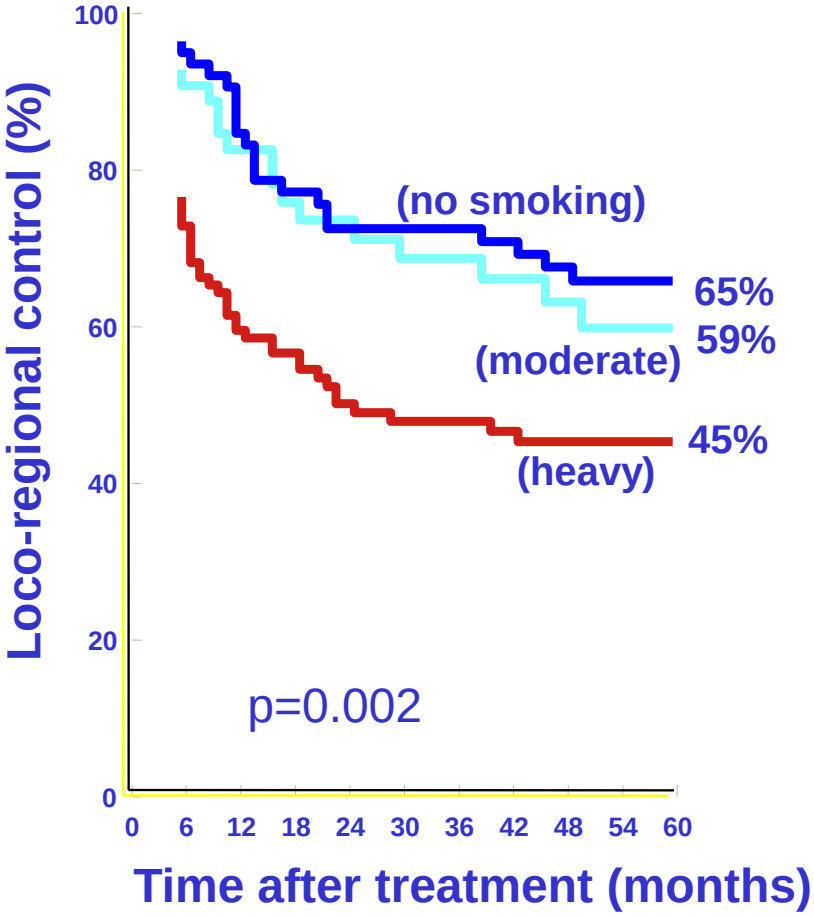
Therapeutic approaches to tumor hypoxia

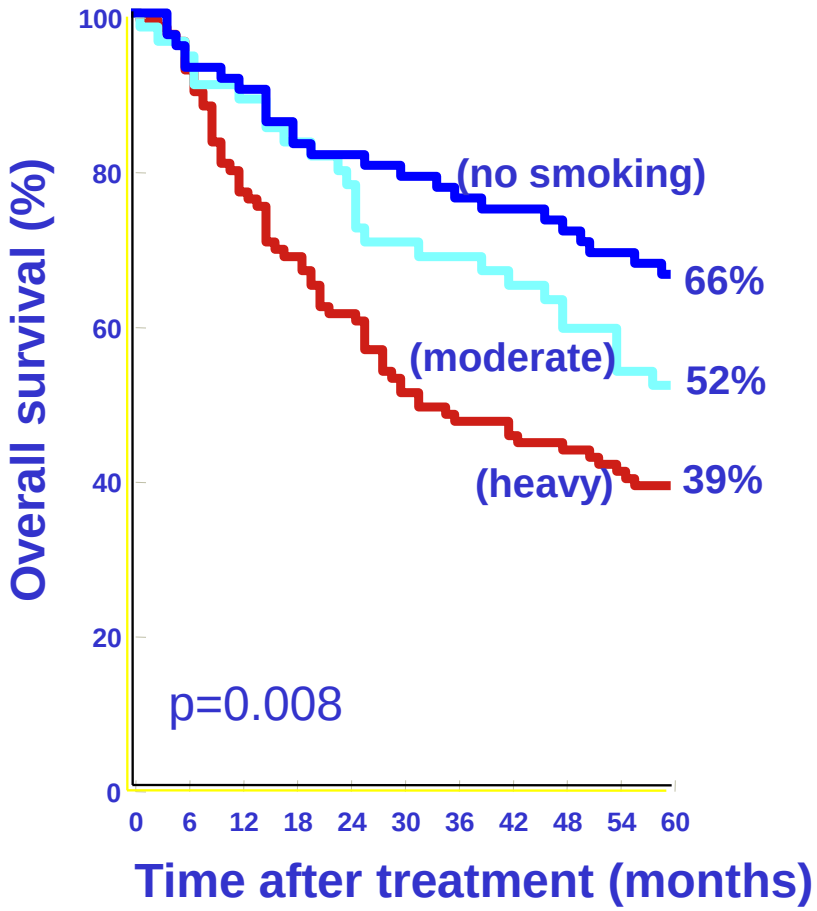
- Raising the oxygen content of inspired gas
- Hypoxic cell radiosensitizers
- Increasing haemoglobin concentration
- Overcoming acute & chronic hypoxia in tumors


Erythrocyte of a smoker

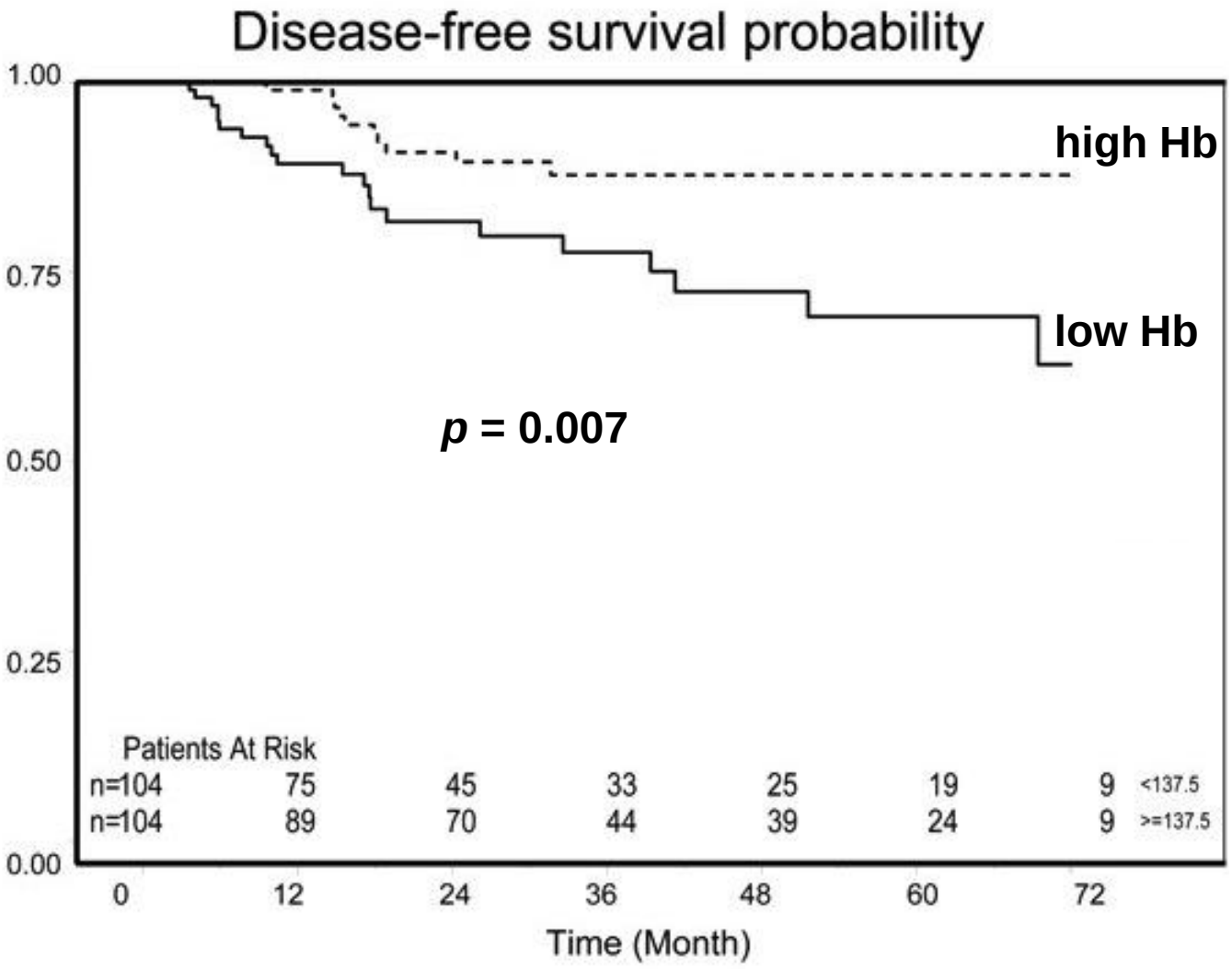
Smoking and treatment outcome

Radiotherapy treatment of Head and Neck Carcinoma (233 pts)
DAHANCA

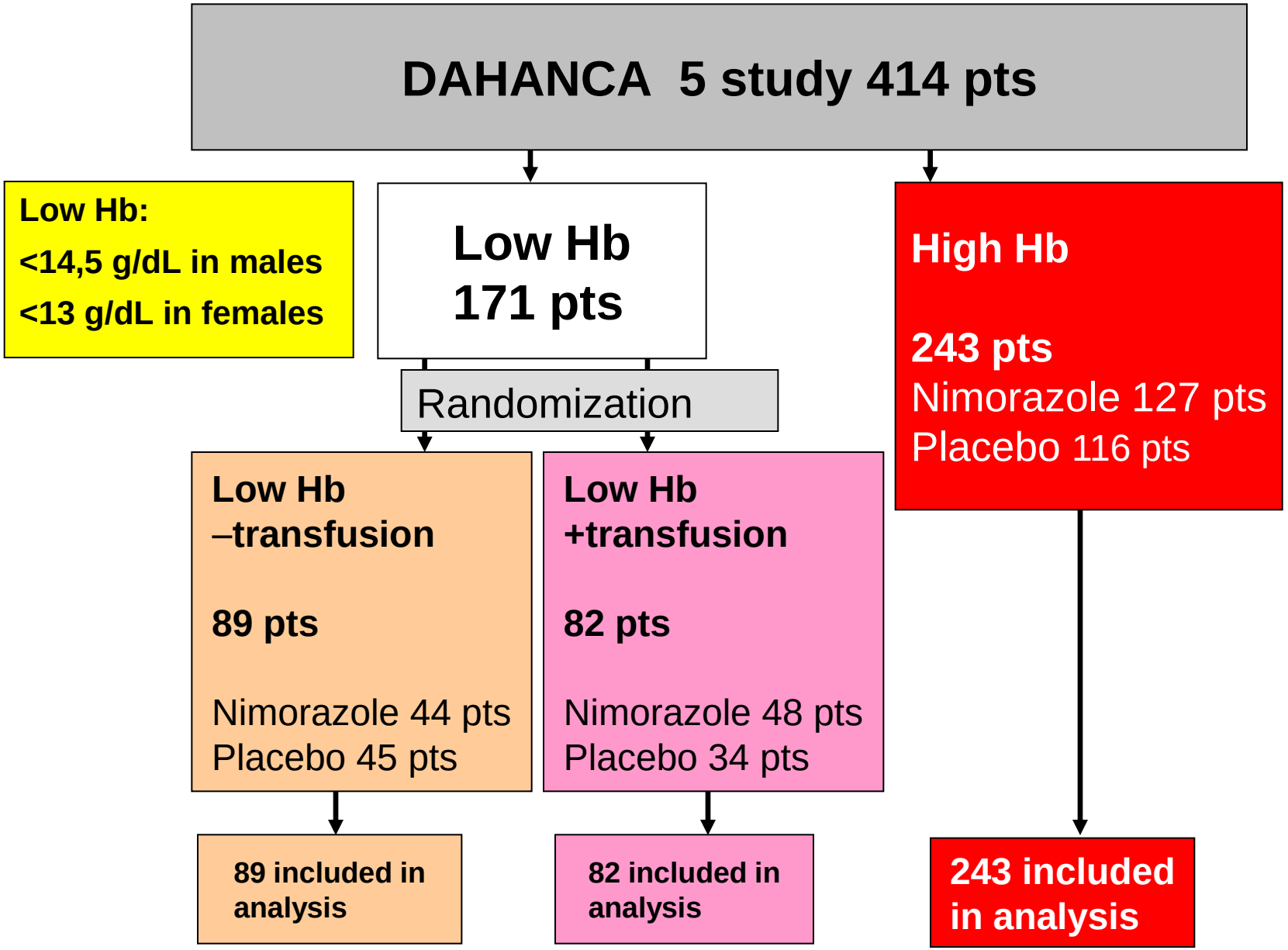




Pre-treatment Hb is associated with poor prognosis
(larynx carcinomas)

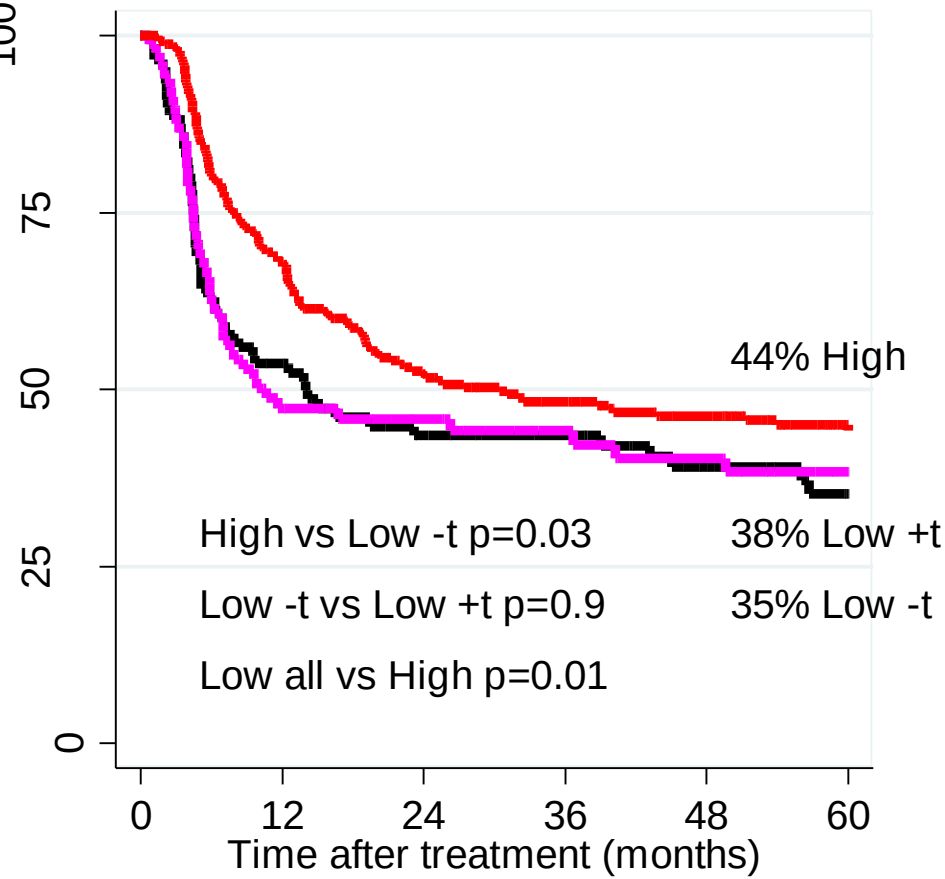


Haugen et al., Clin Cancer Res 2004

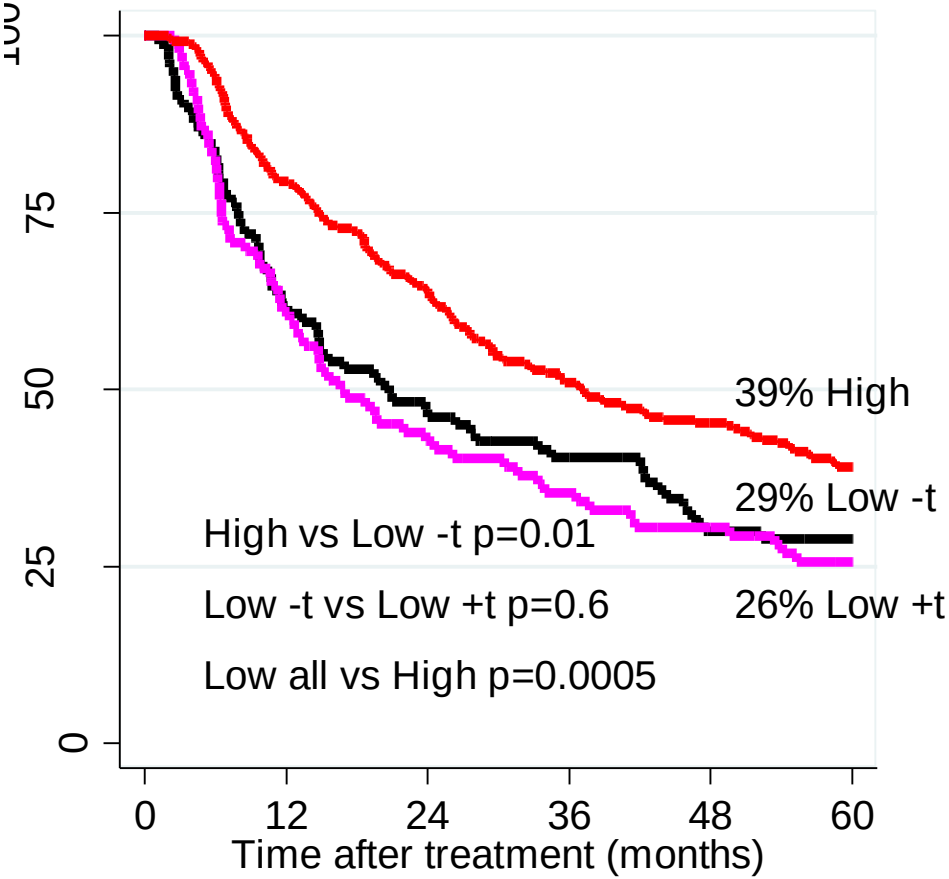


Hoff et al Radiother Oncol 2010

Locoregional control



Overall survival



Hoff et al Radiother Oncol 2010

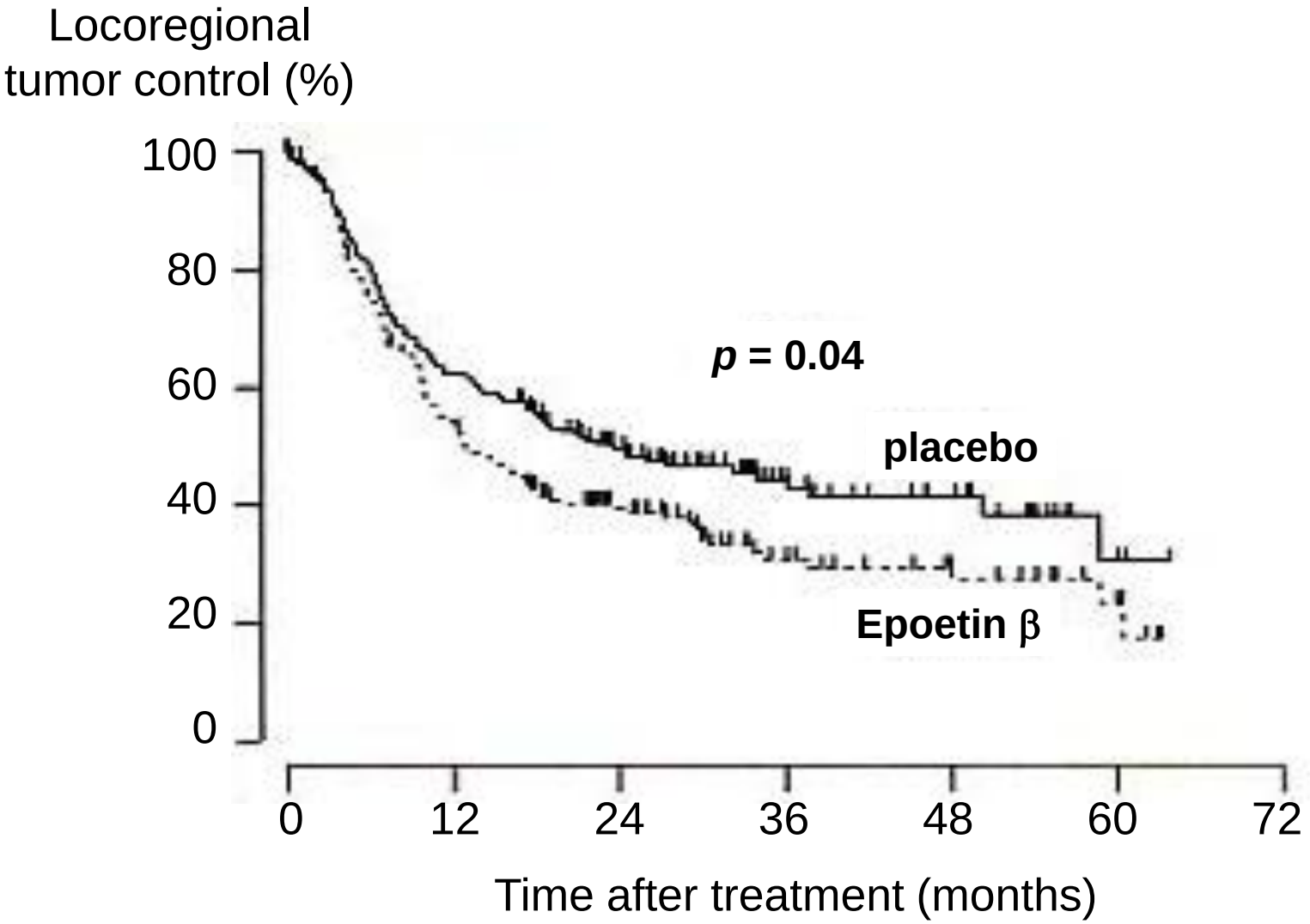
Conclusion from DAHANCA 5

Low hemoglobin level is
associated with poor prognosis

Hemoglobin level was raised with transfusion during radiotherapy

Transfusion was unable to improve the effect of radiotherapy in head and neck cancer patients

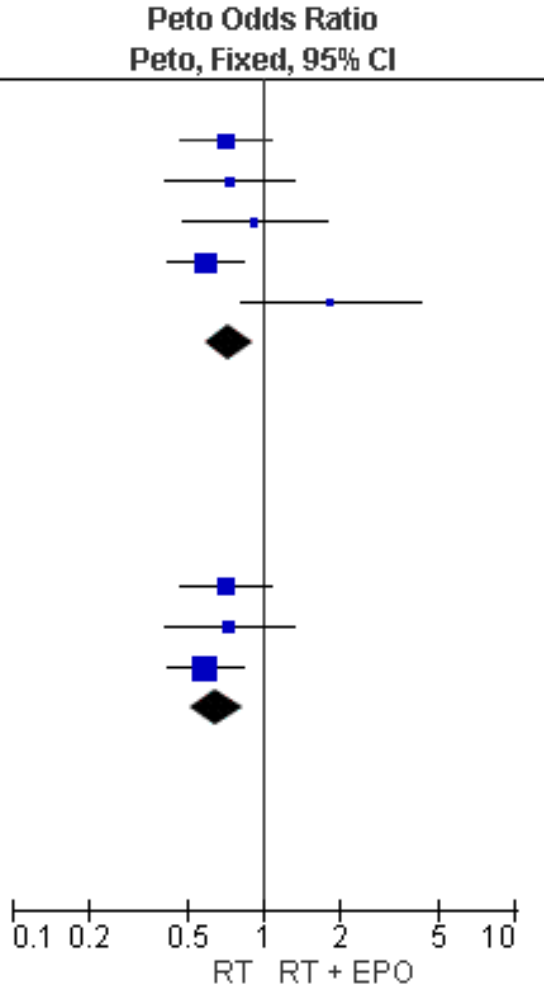
Randomized trial with EPO in H&N cancer patients with anemia



Henke et al, Lancet 2003

EPO plus RT versus RT alone, outcome: overall survival (proportion alive at end of study period)

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 P et al Cochrane review 2009

Conclusions from EPO Cochrane review in Head and Neck 2009

Erythropoietic proteins, as an adjuvant treatment with (chemo) radiotherapy, worsens survival for patients with head and neck cancer.

Lambin P et al Cochrane review 2009

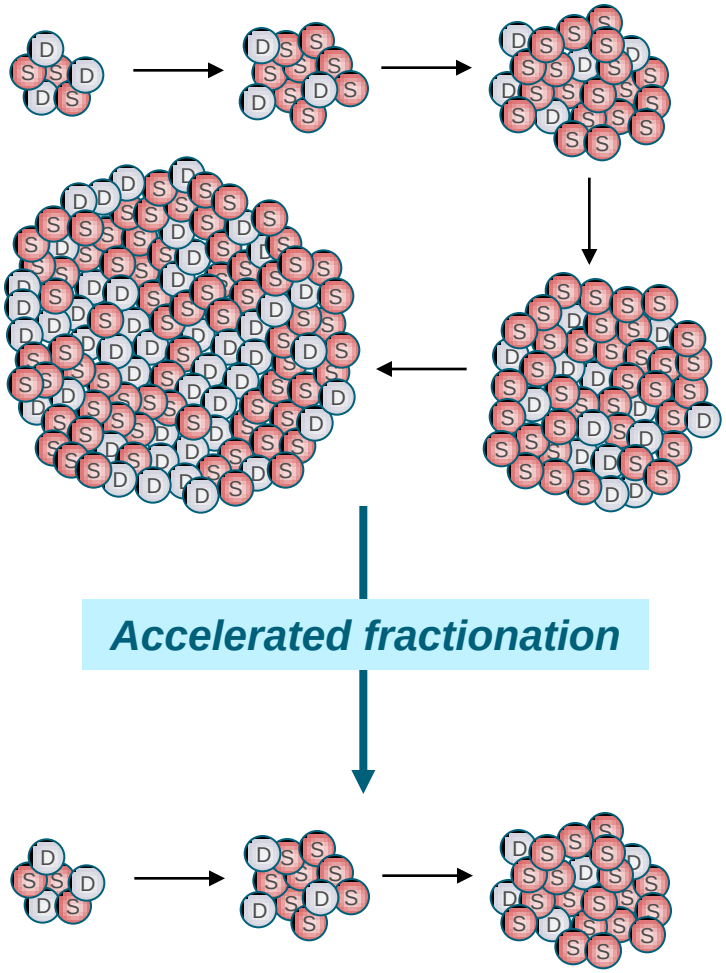
Therapeutic approaches to tumor hypoxia

- Raising the oxygen content of inspired gas
- Hypoxic cell radiosensitizers
- Increasing haemoglobin concentration
- Overcoming acute & chronic hypoxia in tumors

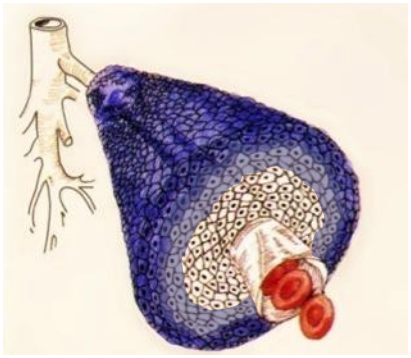
ARCON

Accelerated Radiotherapy + CarbOgen + Nicotinamide

Tumor cell proliferation

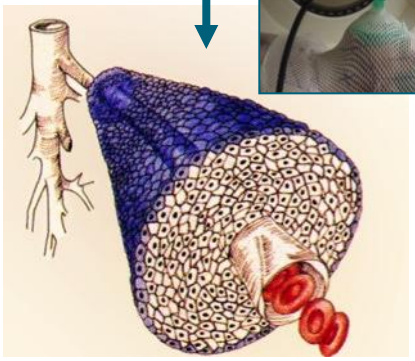


Chronic hypoxia



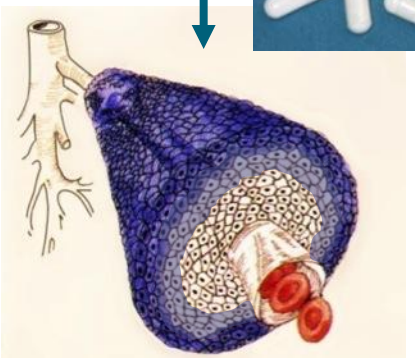
Carbogen

98% O_2 + 2% CO_2

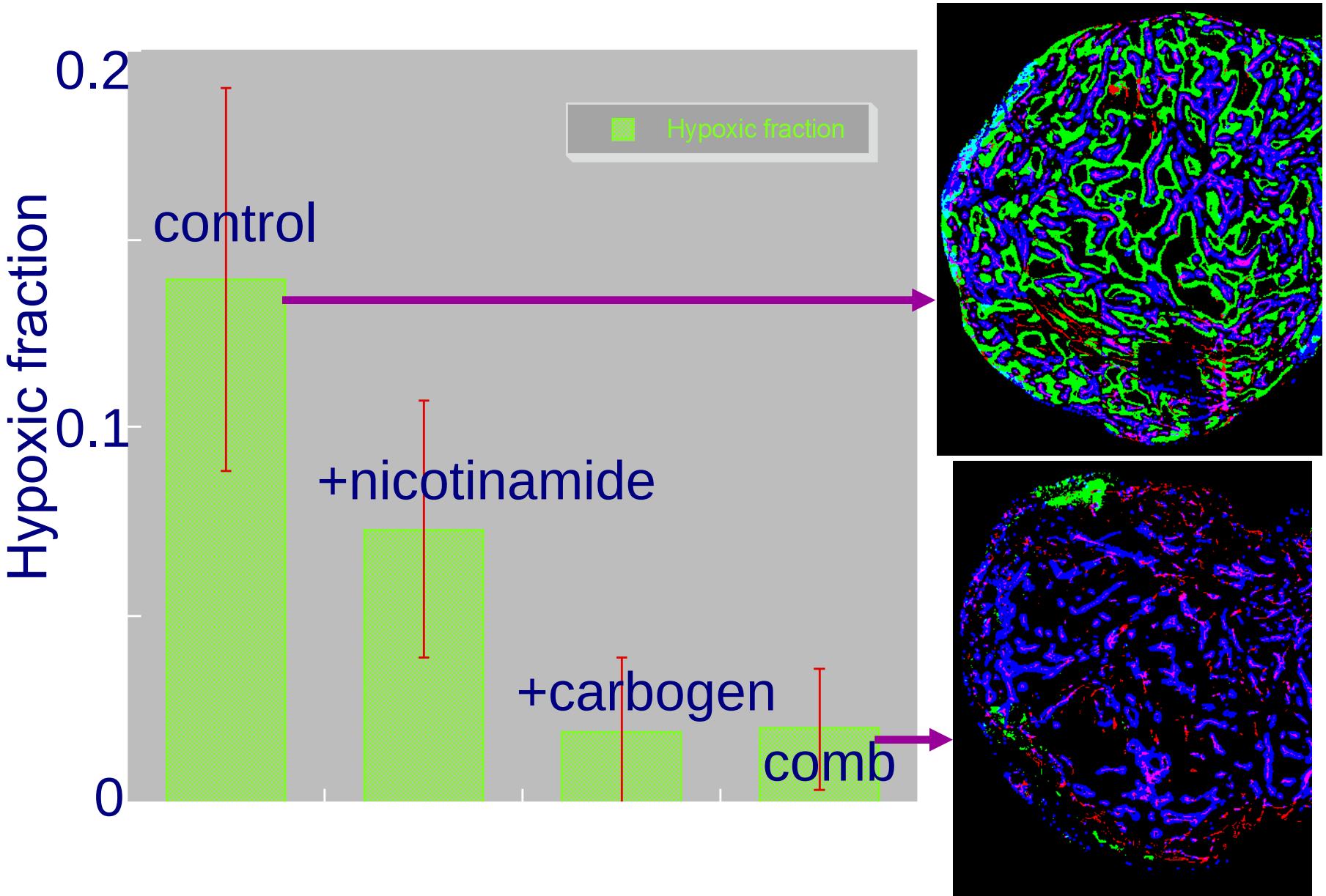


Acute hypoxia

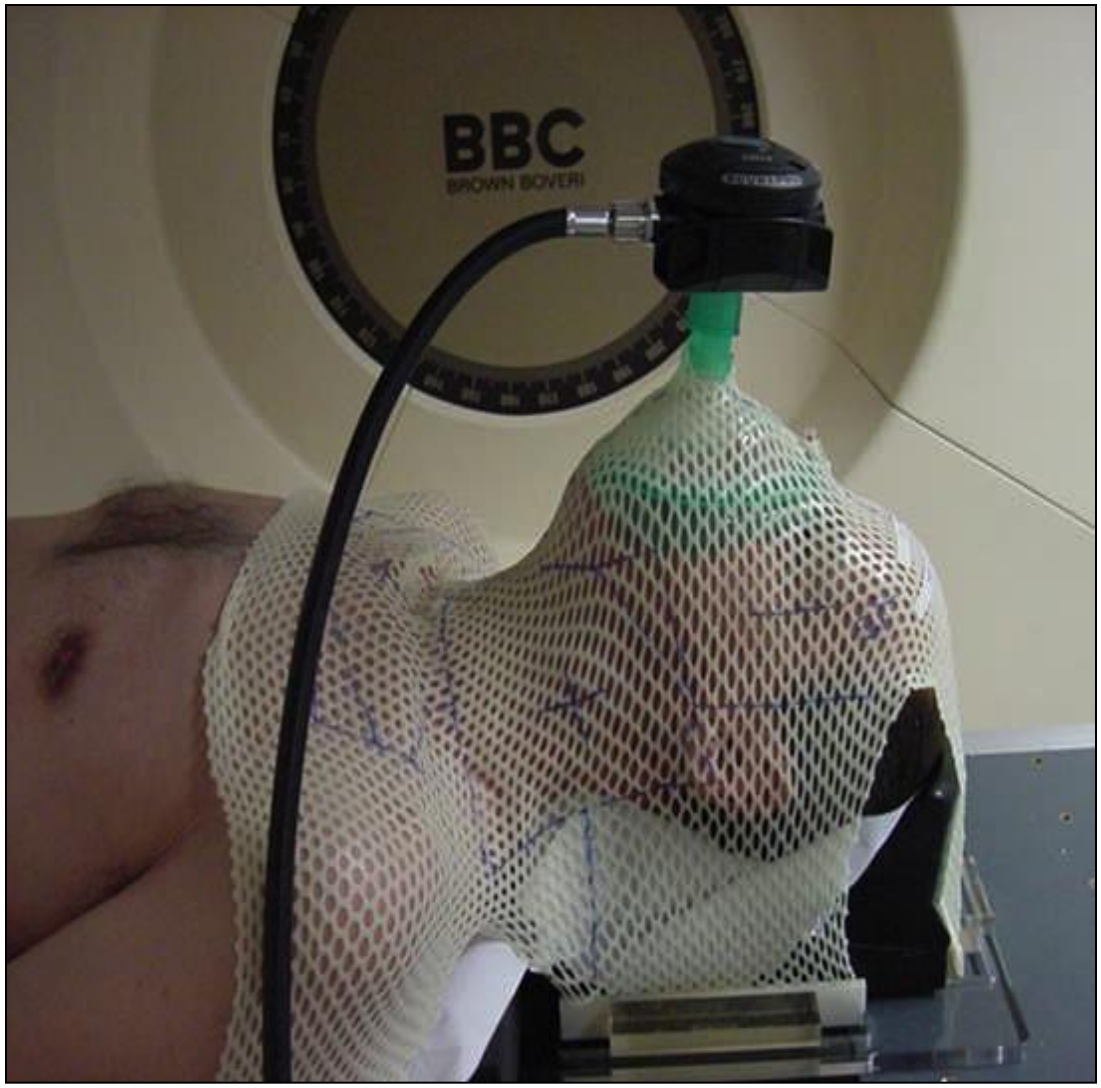
Nicotinamide



carbogen and nicotinamide reduce hypoxia in mouse colon carcinoma



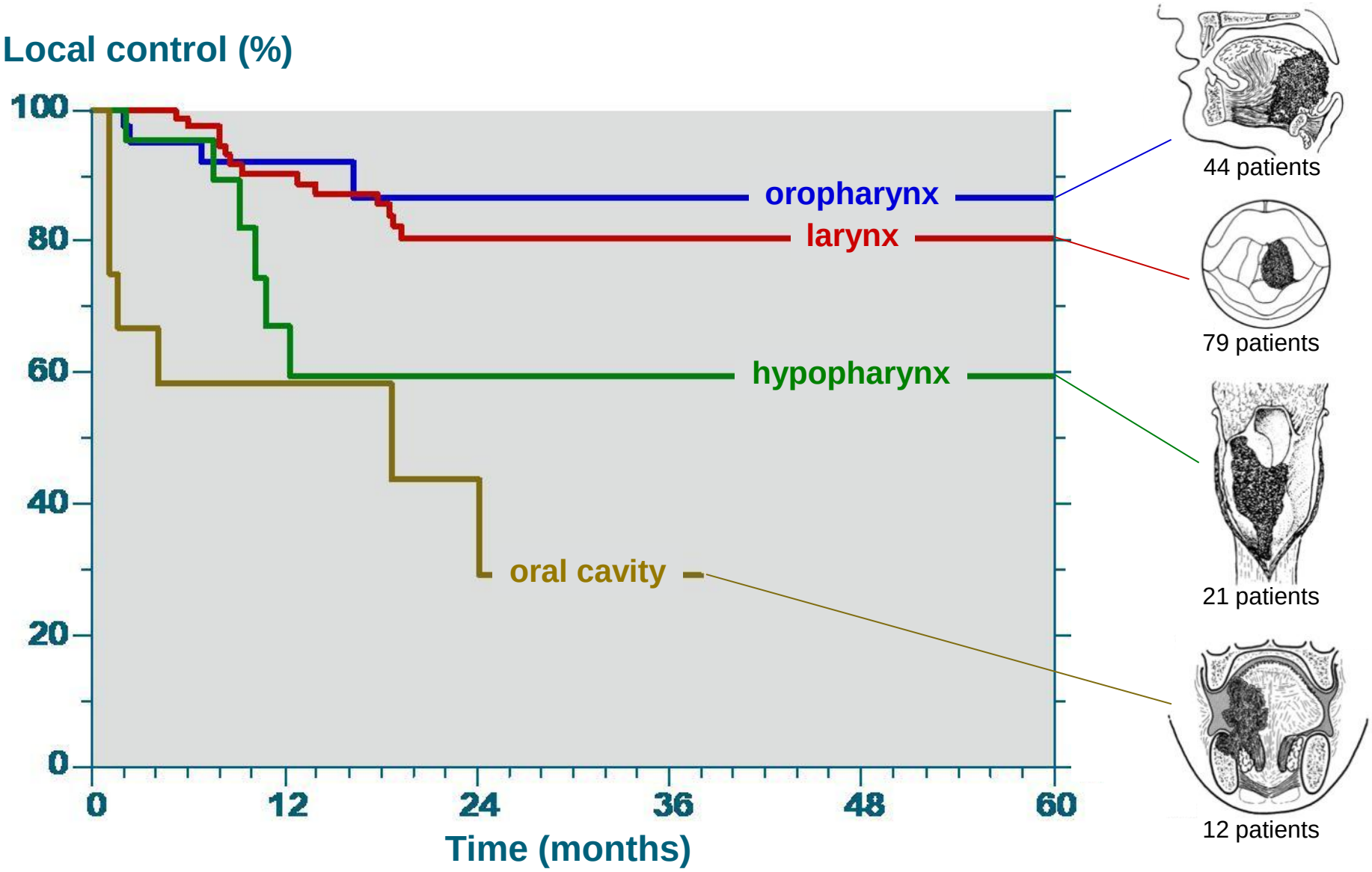
ARCON



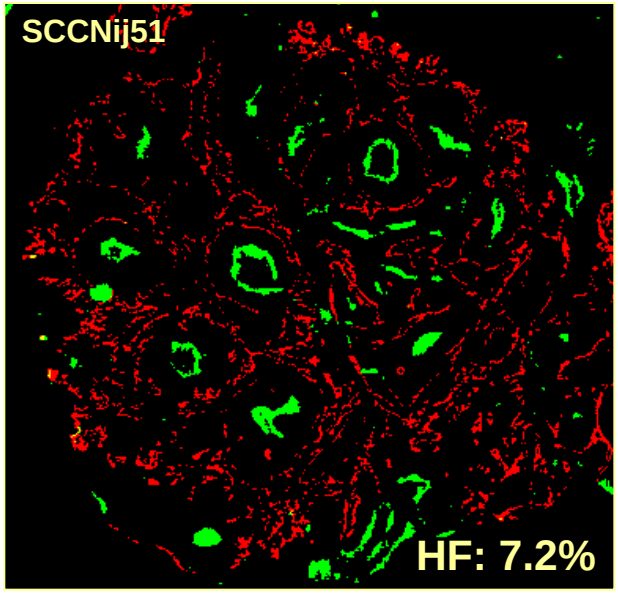
carbogen
(95% O_2 / 5% CO_2)

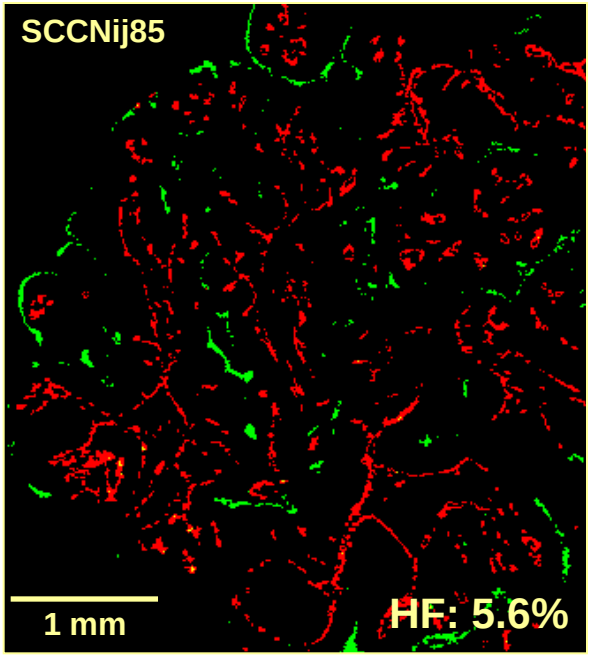
“carbogen-light”
(98% O_2 / 2% CO_2)

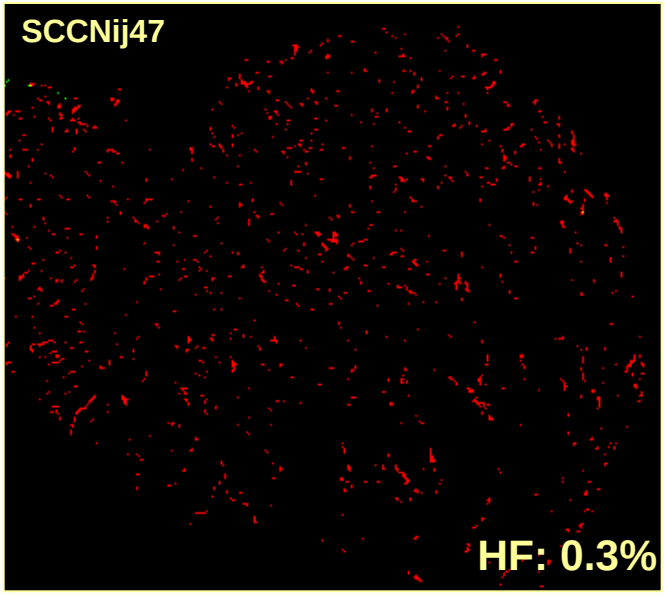
ARCON phase II trial: high local control rates in T3-4 tumors

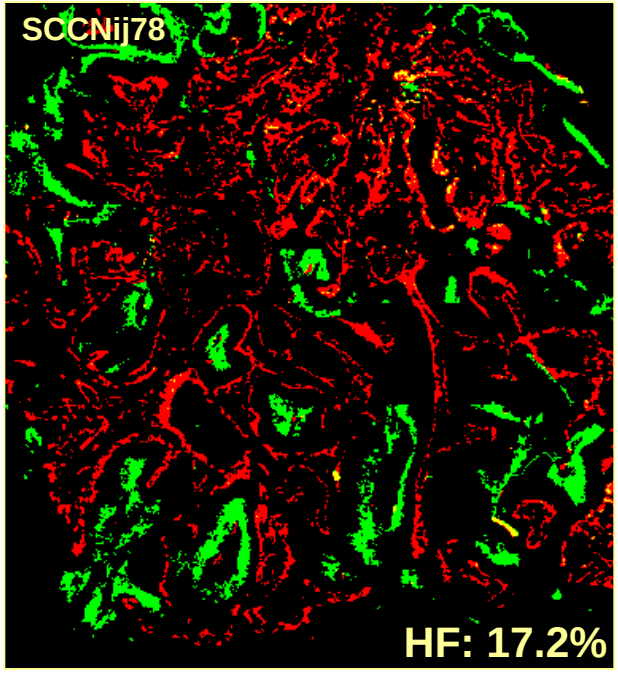


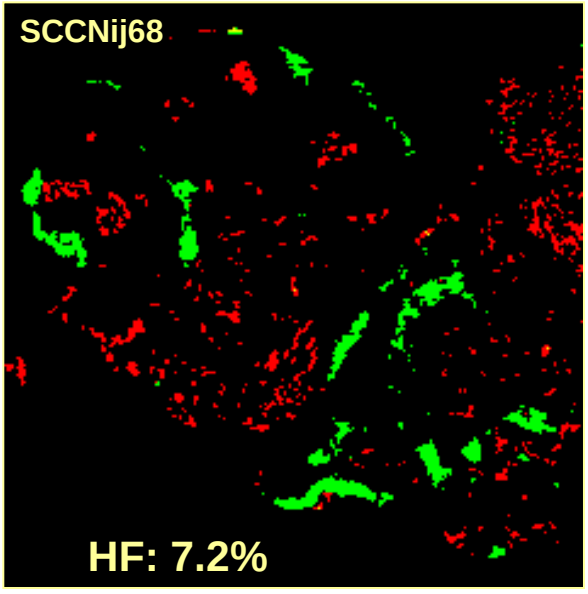
Hypoxia and vessels in H&N cancer biopsies

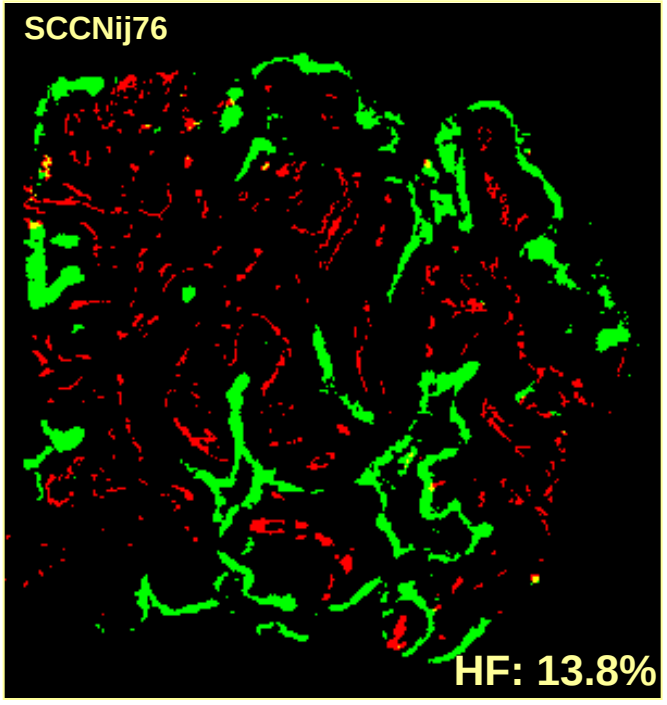






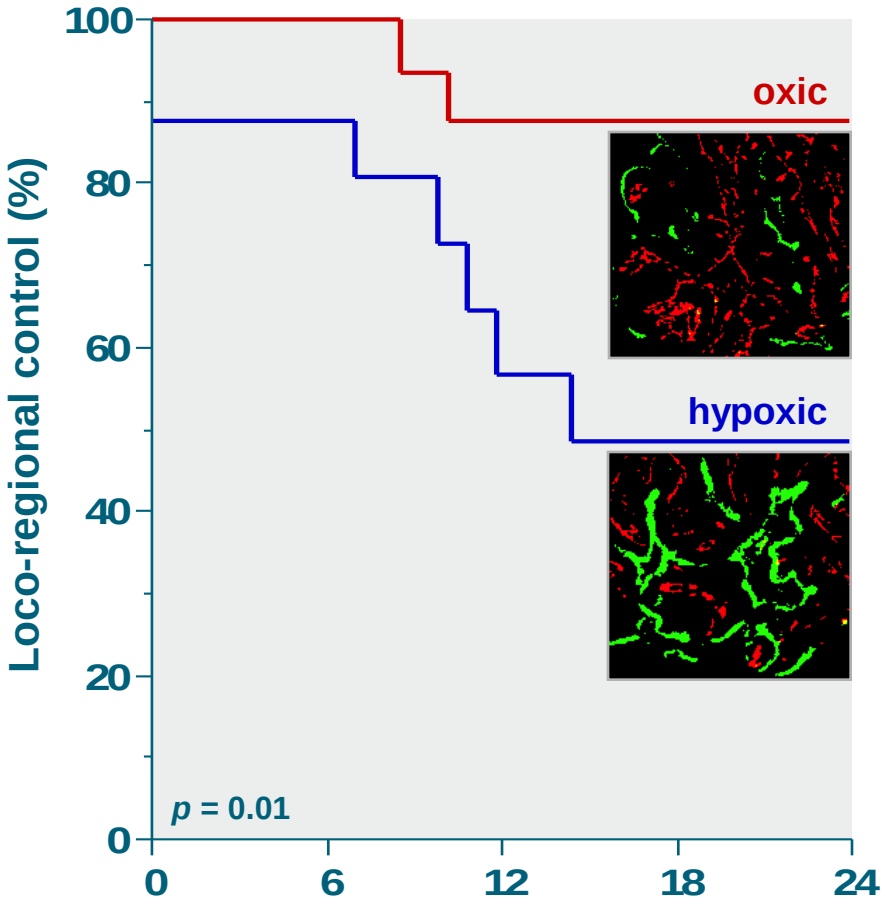




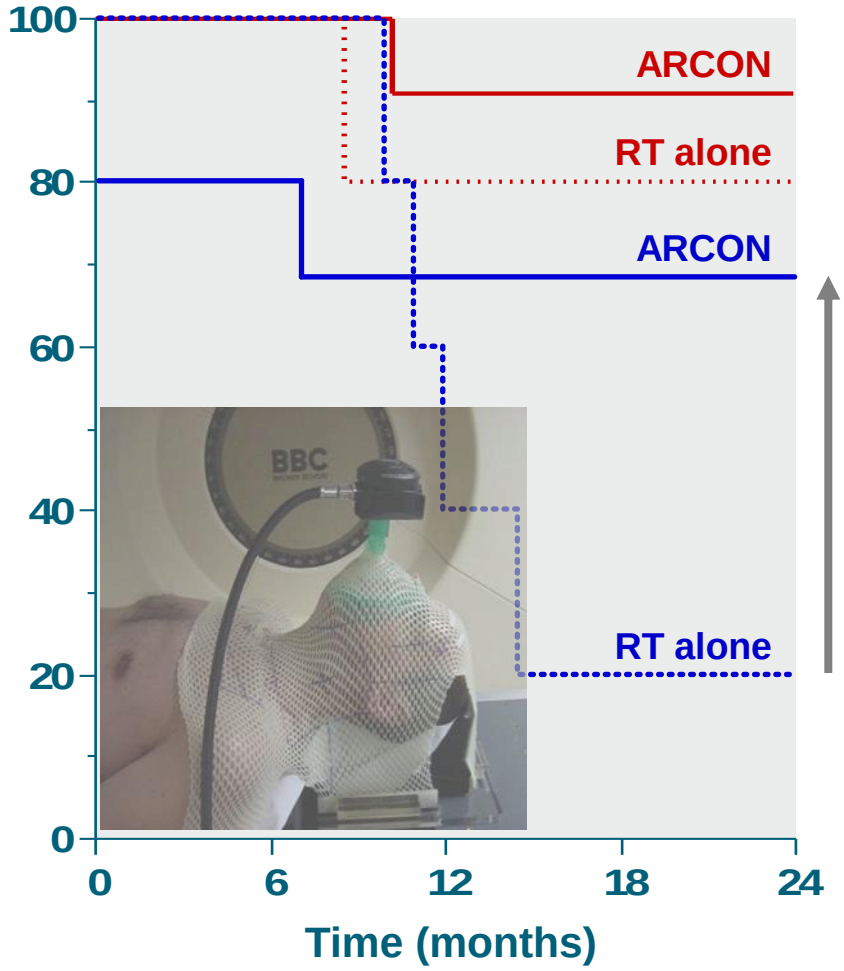


Loco-regional tumor control after radiotherapy: hypoxic versus non-hypoxic tumors

prognostic indicator



predictive assay



Kaanders et al. Cancer Res 2002

ARCON for T2-4 squamous cell carcinoma of the larynx

Randomization

Accelerated Radiotherapy

Accelerated Radiotherapy + carbogen and nicotinamide

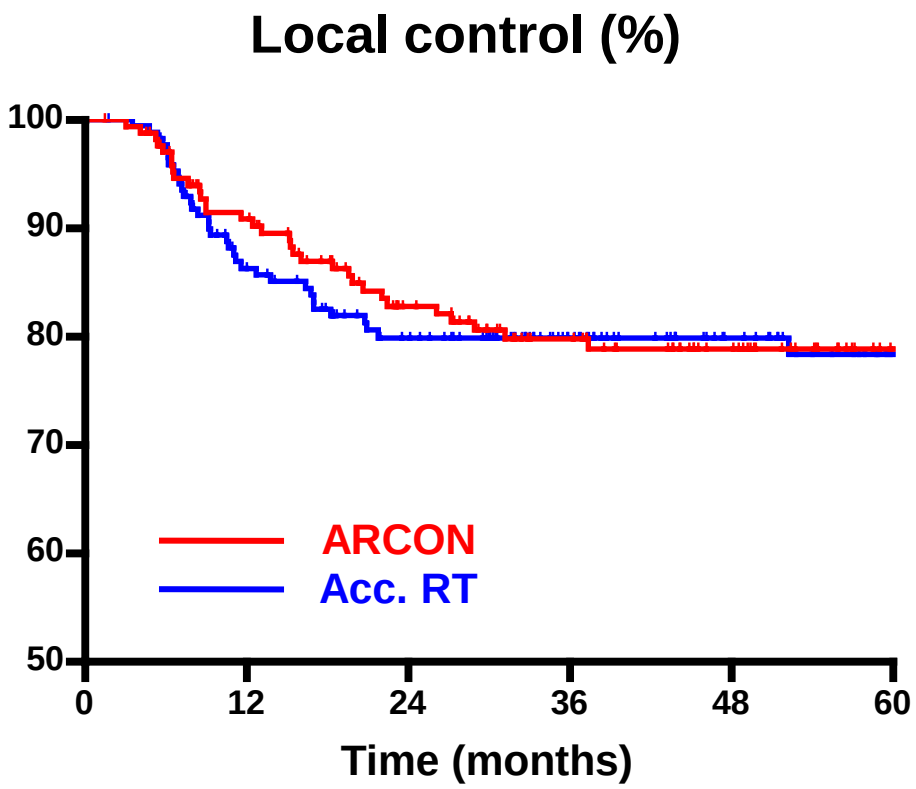
Fractionation schedule:

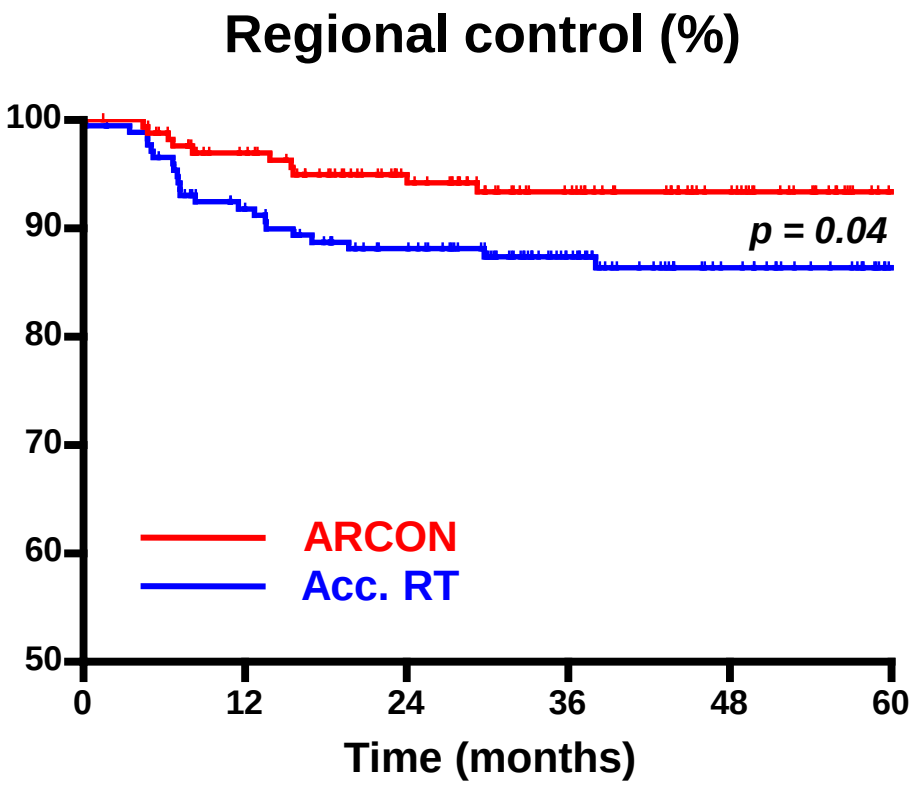
	primary	metastatic nodes
Acc. RT	68 Gy	68 Gy
ARCON	64 Gy*	68 Gy

*Aim: improve tumor control with equal toxicity between arms!

Kaanders et al 2012

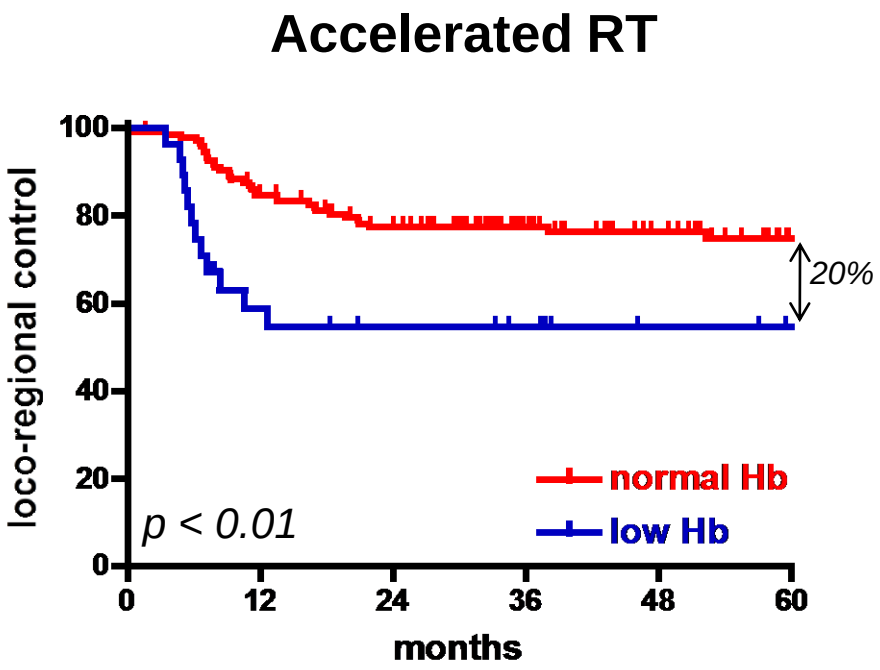
ARCON for larynx carcinoma, local and regional control

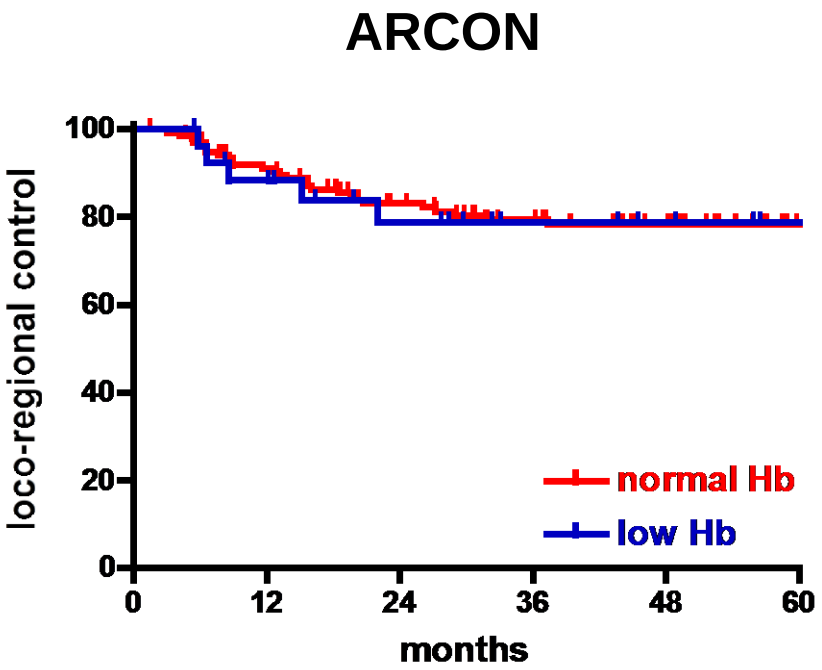




Janssens et al., J Clin Oncol 2012

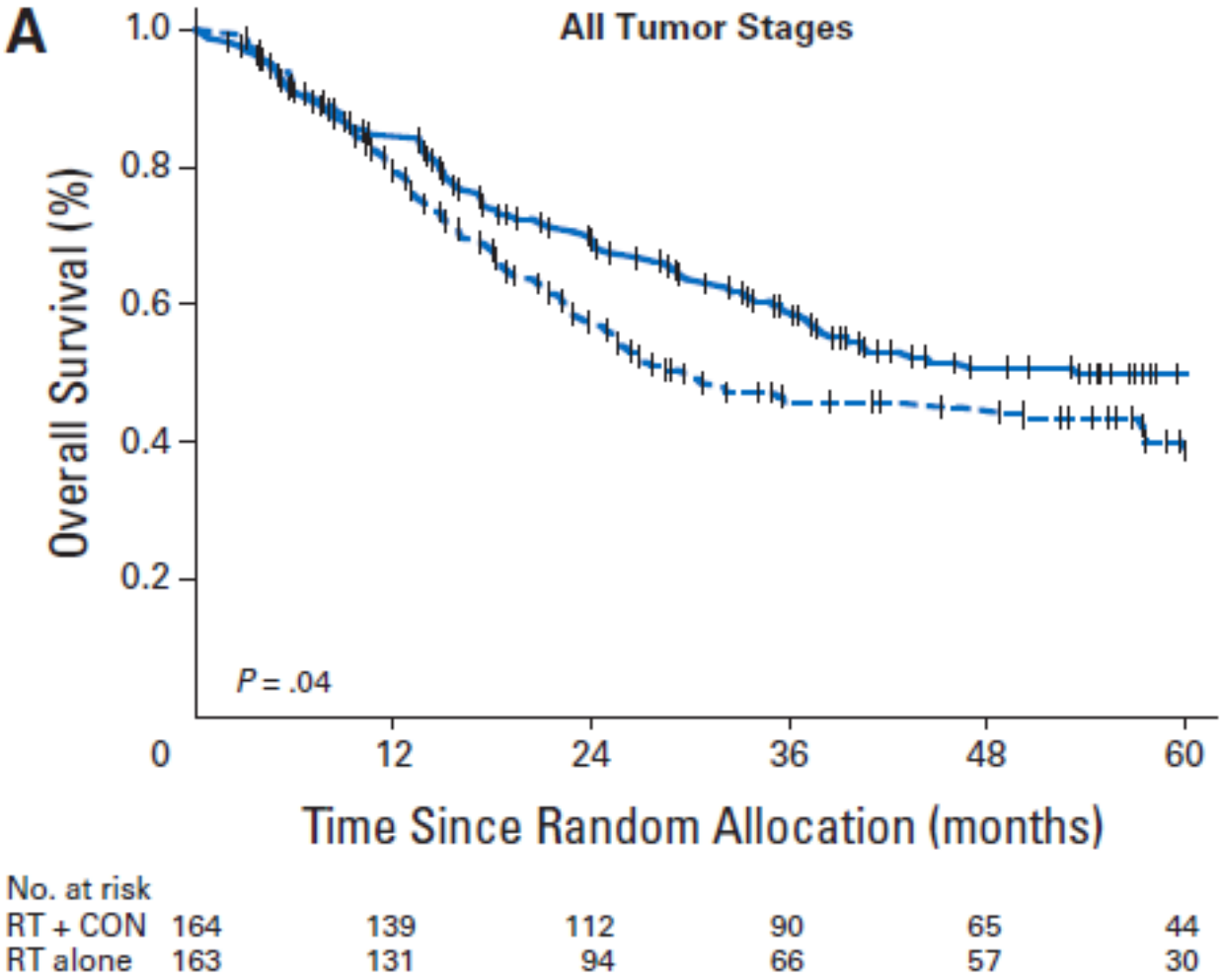
ARCON improves loco-regional control in anemic patients





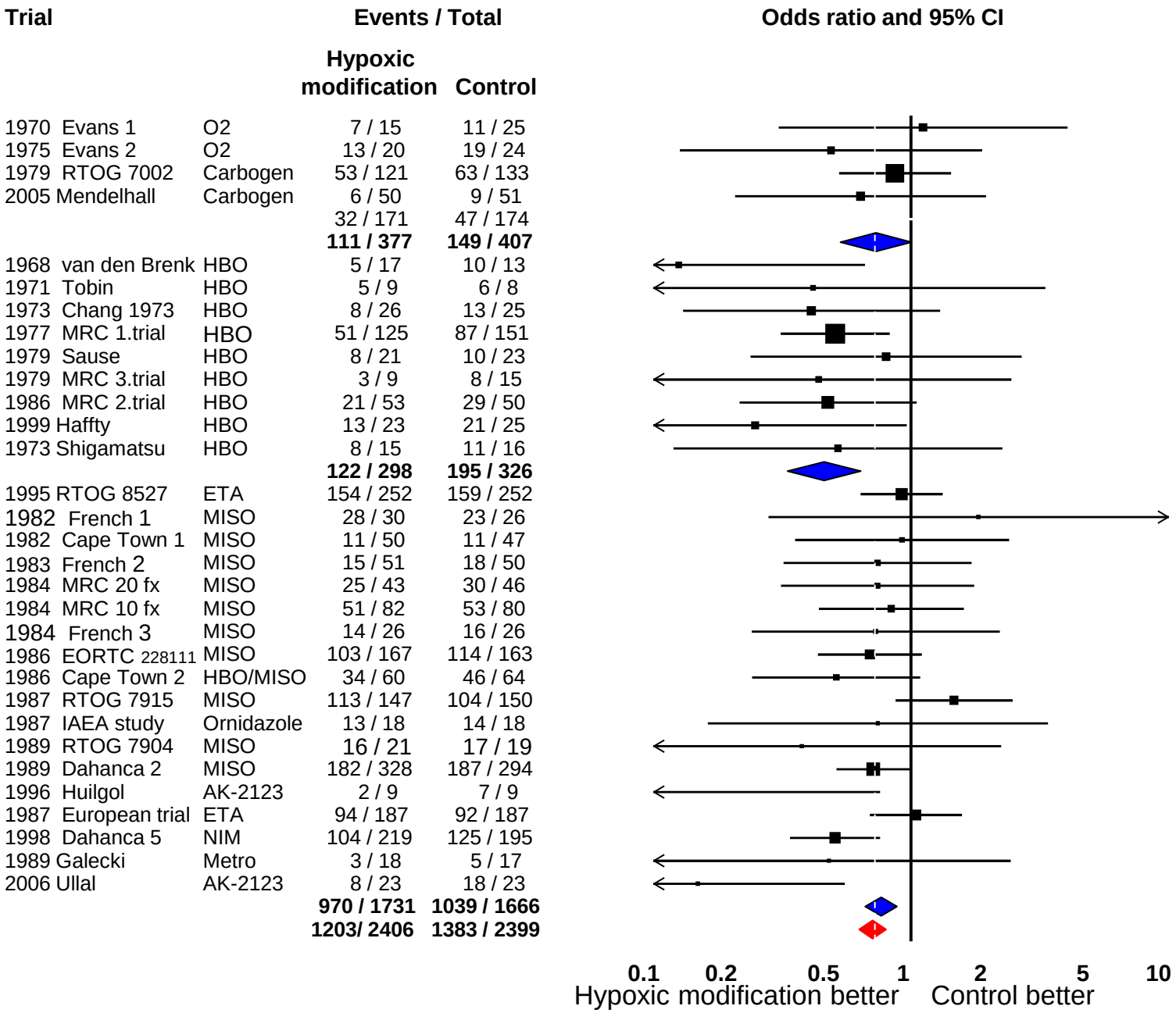
Kaanders, ESTRO 2012

Radiotherapy +/- CARBOGEN & Nicotinamide to bladder cancer



Hoskin P J et al. JCO 2010;28:4912-4918

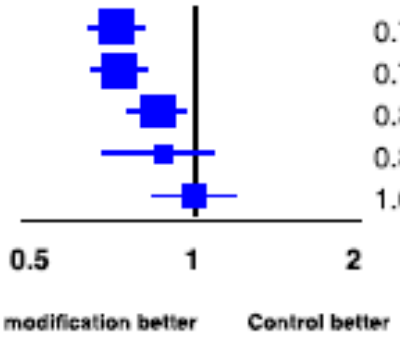
Meta Analysis - Hypoxic modification of radiotherapy in head and neck cancer



Meta Analysis - Hypoxic modification of radiotherapy in head and neck cancer

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 Radiother Oncol 2011

Back to the future: SBRT & tumor hypoxia

- With the developments in image-guided radiotherapy (IGRT), the use of high single doses or a few large fractions is rapidly gaining popularity in the clinic.
- Stereotactic Body RadioTherapy (SBRT) is now widely used for early stage lung cancer, but also metastases in various sites.
- One reason fractionated radiotherapy became standard was the absence of a therapeutic window with large single doses, predominantly because of hypoxia!

Targeting hypoxia – holy grail of radiotherapy?

- hypoxia targeting has come a long way, from increasing oxygen supply and enhancing perfusion, to inhibitors of specific signaling or metabolic pathways
- tumor hypoxia represents a highly dynamic condition, distributed heterogenously in tumors and changing over time.
- the concept of acute vs chronic hypoxia is clearly an oversimplification of a complex condition
- the comeback of large doses/fx or even single doses also needs consideration of adding relatively non-toxic hypoxic sensitizers like nimorazole: “back to the future”

Key points

- Hypoxic cell radioresistance is a significant cause of faillure in local tumor control in particular in SCC of head and neck and uterine cervix.
- Using high oxygen content gas breathing, chemical radiosensitizers or blood transfusion have shown mixed results.
- Meta-analysis of randomized trials does however demonstrate a significant benefit and level 1a evidence for head and neck tumors

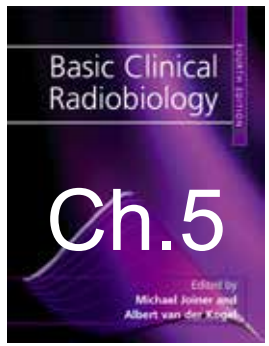
ESTRO School

Basic Clinical Radiobiology

Dose-response relationships in radiotherapy

Michael Joiner

Budapest 2016

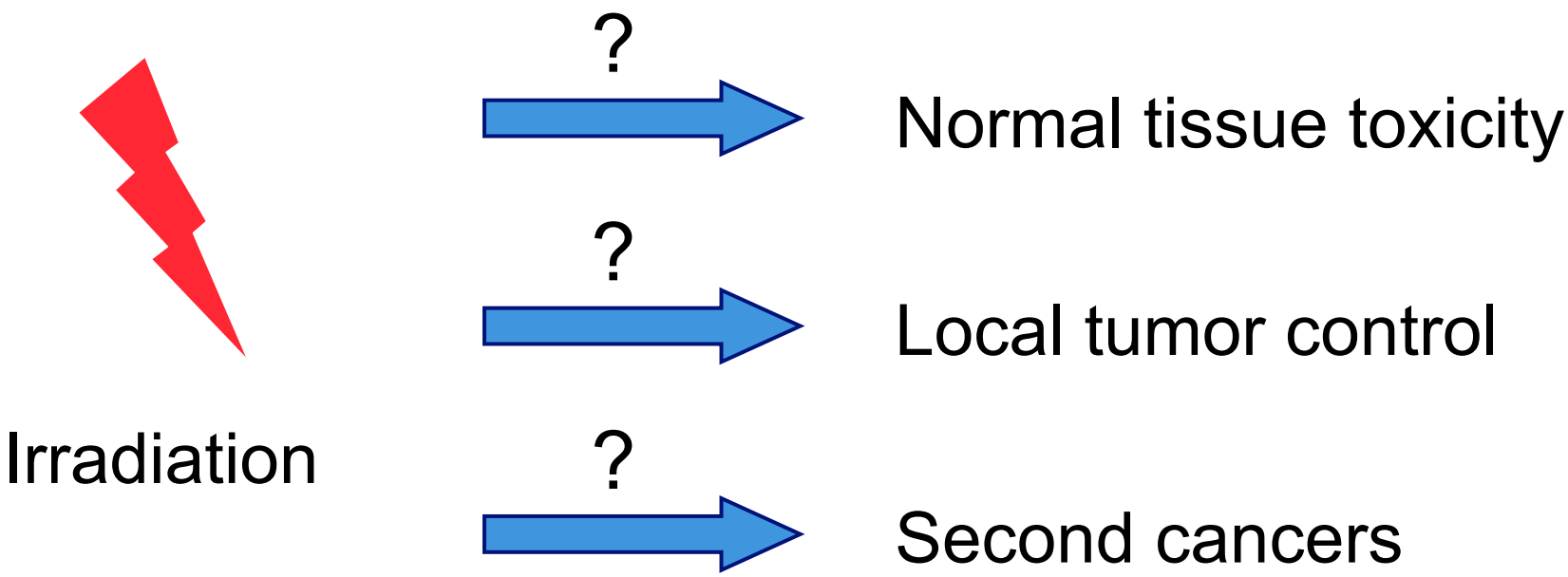


Definitions

Dose Response: Relationship between a given physical absorbed dose and the resulting biological response

Endpoint: A specific event that may or may not have occurred at a given time after irradiation

Dose response

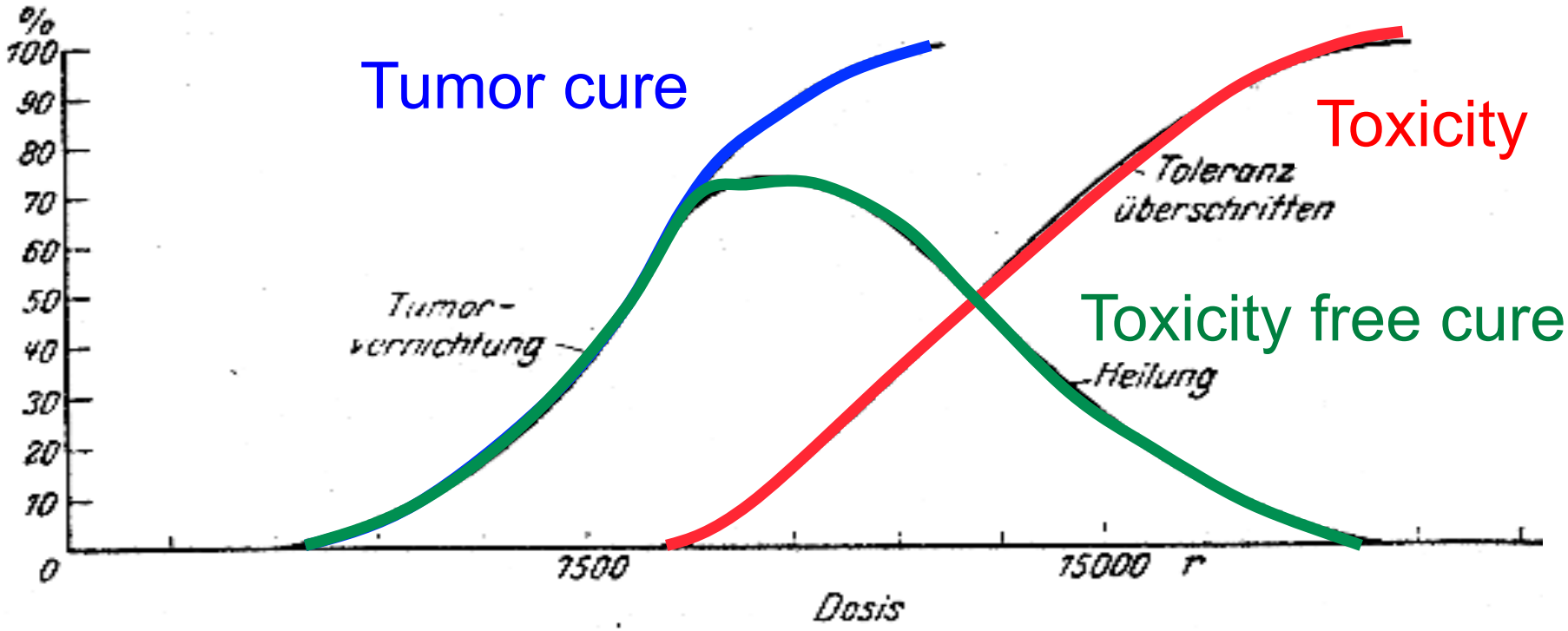


Relationship between given dose and each clinically relevant outcome needs to be defined

i.e. Define the incidence or probability of a certain outcome after a defined dose

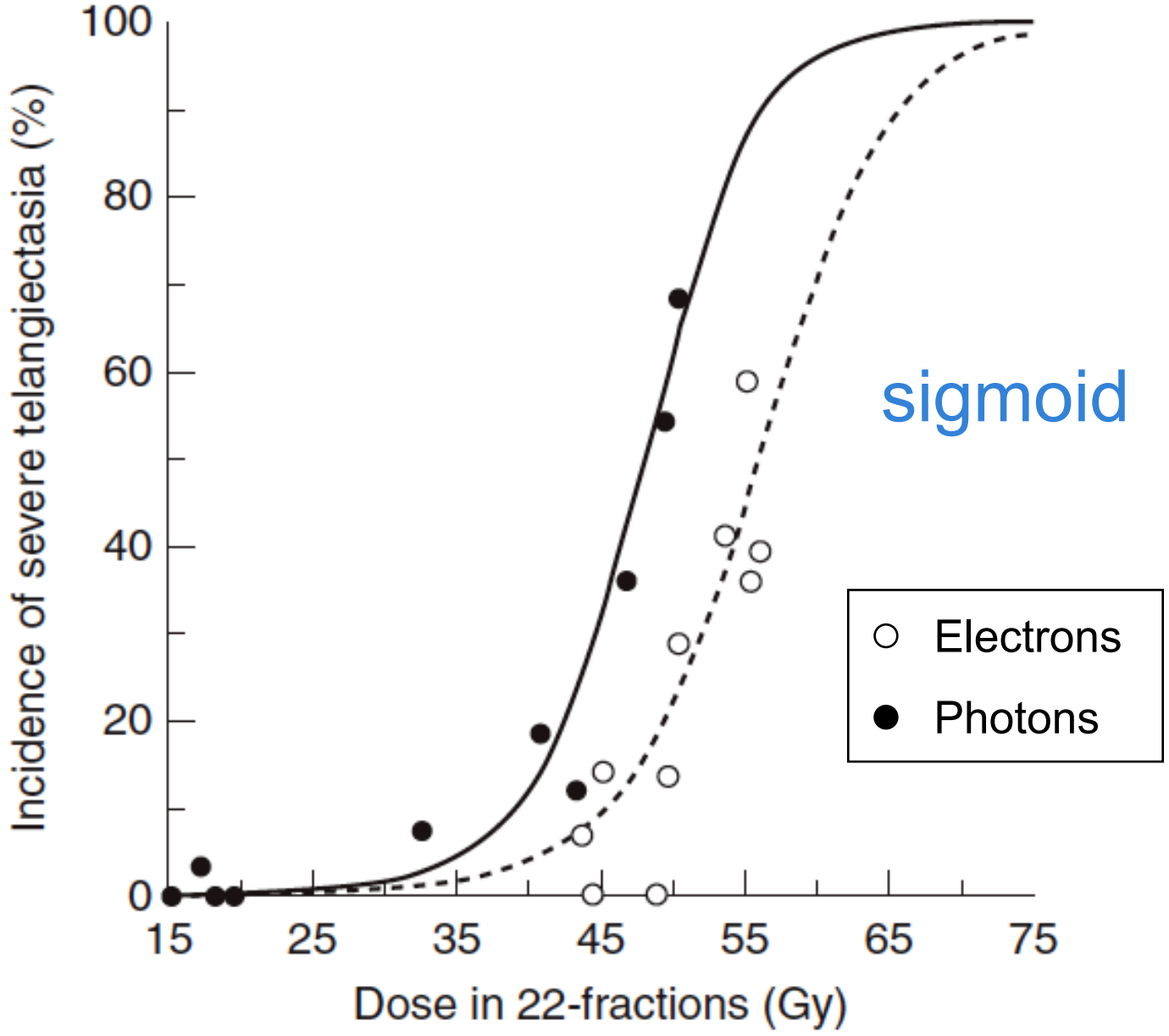
Dose response: Empirical data

Sigmoid curves indicate variability of clinical radioresponse



Holthusen. *Strahlentherapie* 1936;57:254-68

Examples of dose-response relationships



Dose response models

Most frequently used models to fit sigmoid dose-response curves:

- Poisson model …tumor
- Logistic model …normal

Dose response model: Tumor control

The target cell hypothesis: Munro & Gilbert 1961

- Relevant is the number of tumor stem cells (clonogenic cells) left at the end of treatment
- This is reduced with dose in a manner which accounts for randomness in radiation effects, described by Poisson statistics
- The probability of tumor cure depends on the average number of clonogens surviving per tumor

Simulation of Poisson distribution of surviving cells

0	0	0	2	1	1	1	0	0	0
0	0	0	0	0	0	0	0	1	0
0	0	0	2	1	2	1	2	0	1
1	0	0	0	0	2	1	0	1	2
1	2	0	0	0	0	0	0	0	3
0	0	0	0	0	0	0	1	1	0
1	0	2	0	0	0	0	0	0	1
0	0	0	0	0	3	0	0	1	0
0	3	1	1	1	1	0	0	0	1
0	1	2	1	1	0	0	1	1	0

100 tumors.
Average number of surviving clonogens per tumor = 0.5

Each box indicates the number of surviving clonogens in that tumor

Poisson Statistics

In the **Poisson** statistical distribution, the probability $P(x)$ of obtaining x surviving cells per tumor when the mean number of surviving cells per tumor is λ, is given by:

$$P(x) = \frac{e^{-\lambda}\lambda^{x}}{x!}$$

Condition: a very, very **large** number of cells in each tumor, but the probability that any given cell survives is very, very **small**

Poisson Statistics: Tumor control (cure)

Tumor Control Probability, *TCP*, is the probability of **no** surviving cells in the tumor (*i.e.* $x = 0$).

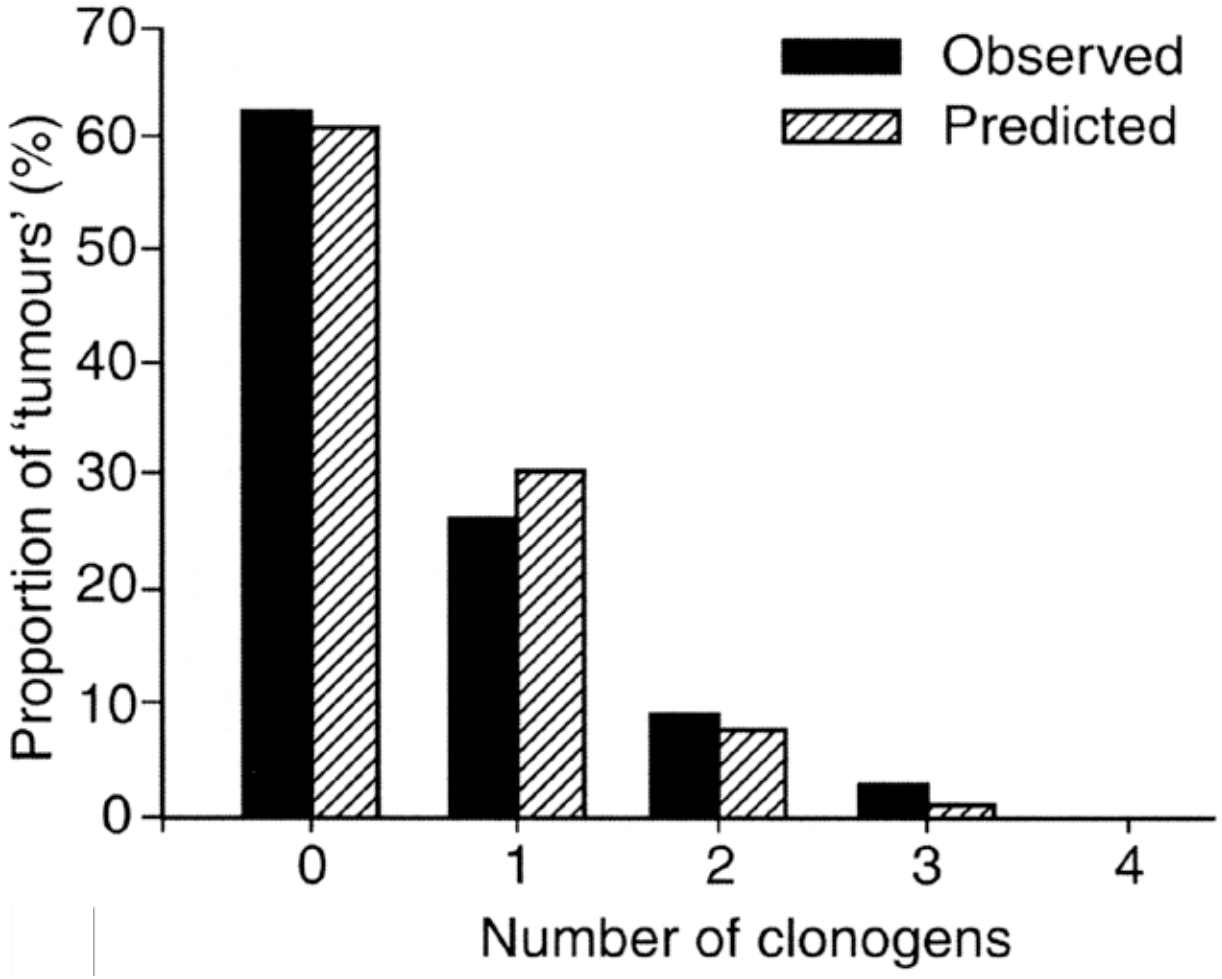
TCP is therefore given by:

$$TCP = P(0) = \frac{e^{-\lambda}\lambda^{0}}{0!} = e^{-\lambda} = \exp\left(-\lambda\right)$$

λ is mean number of surviving cells per tumor

Poisson “predicted” versus Monte Carlo “observed”

Average number of surviving clonogens = 0.5



Poisson distribution confirmed by “observation”

But λ is a function of:
dose per fraction, *d*, and number of fractions, *n*.

Remember that:

$$S = \lambda / N_0 = e^{-n\left(\alpha d + \beta d^2\right)}$$

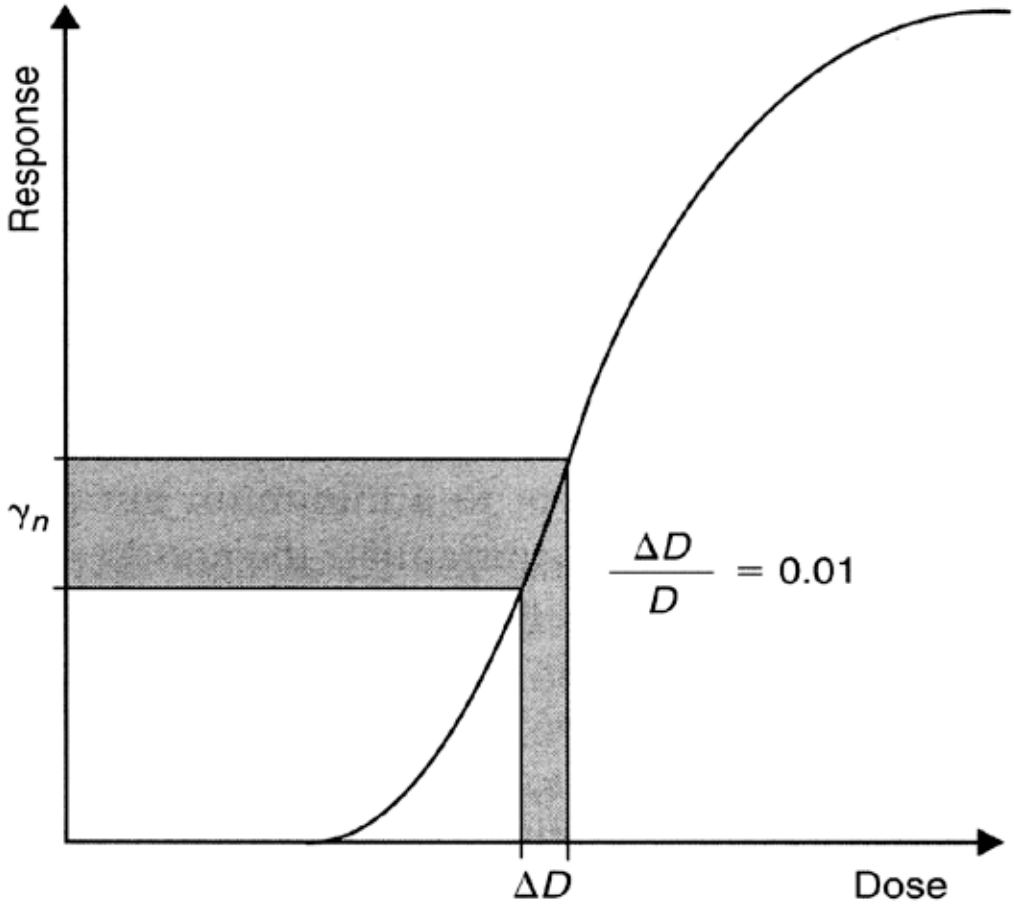
$$= \exp\left(-\alpha D - \beta d D\right)$$

Therefore:

$$TCP = \exp\left[-N_0 \exp\left(-\alpha D - \beta d D\right)\right]$$

Definition of dose-response curve slope

Normalized dose response gradient, γ: $\Delta P \approx \gamma \frac{\Delta D}{D}$



1% change in dose gives increase in response = γ %

Usually defined at steepest part of curve: With Poisson model, at Response = 37% (0.3679, e^{-1})

It can be shown that:

$$\gamma_{37} = \frac{\ln N_0}{e}$$

This may be useful for deducing the number of “tumor clonogens” but relevance to normal tissue response is doubtful

Logistic model of response

$$P = \frac{\exp(u)}{1+\exp(u)} \qquad u = \ln\left(\frac{P}{1-P}\right)$$

$$u = a_0 + a_1 D + a_2 D d + \ldots$$

P/(1-*P*) is called the ***odds*** of the response,
u is called the ***logit*** of *P*

With Logistic, the inflection (max slope) occurs at Response = 50%

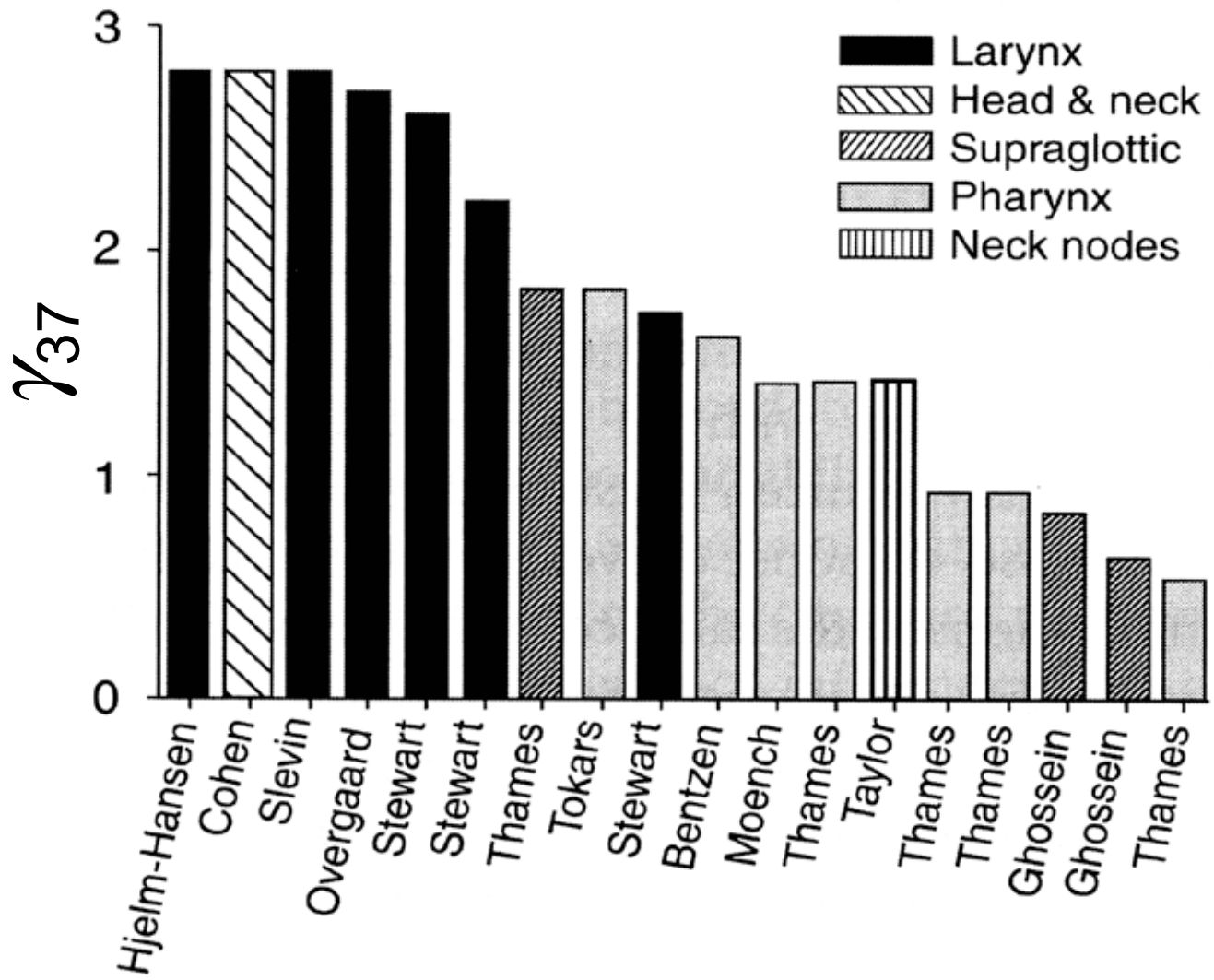
Beware: γ changes with response level

γ_{50}	Response level, %								
	10	20	30	40	50	60	70	80	90
1	0.2	0.4	0.7	0.9	1.0	1.1	1.0	0.9	0.6
2	0.5	1.1	1.5	1.8	2.0	2.0	1.9	1.5	0.9
3	0.9	1.7	2.3	2.8	3.0	3.0	2.7	2.1	1.3
4	1.2	2.3	3.2	3.7	4.0	3.9	3.5	2.8	1.6
5	1.6	3.0	4.0	4.7	5.0	4.9	4.4	3.4	2.0

Clinical estimates of γ

Average γ_{37} for H&N ≈ 2%

From studies in which dose per fraction was fixed

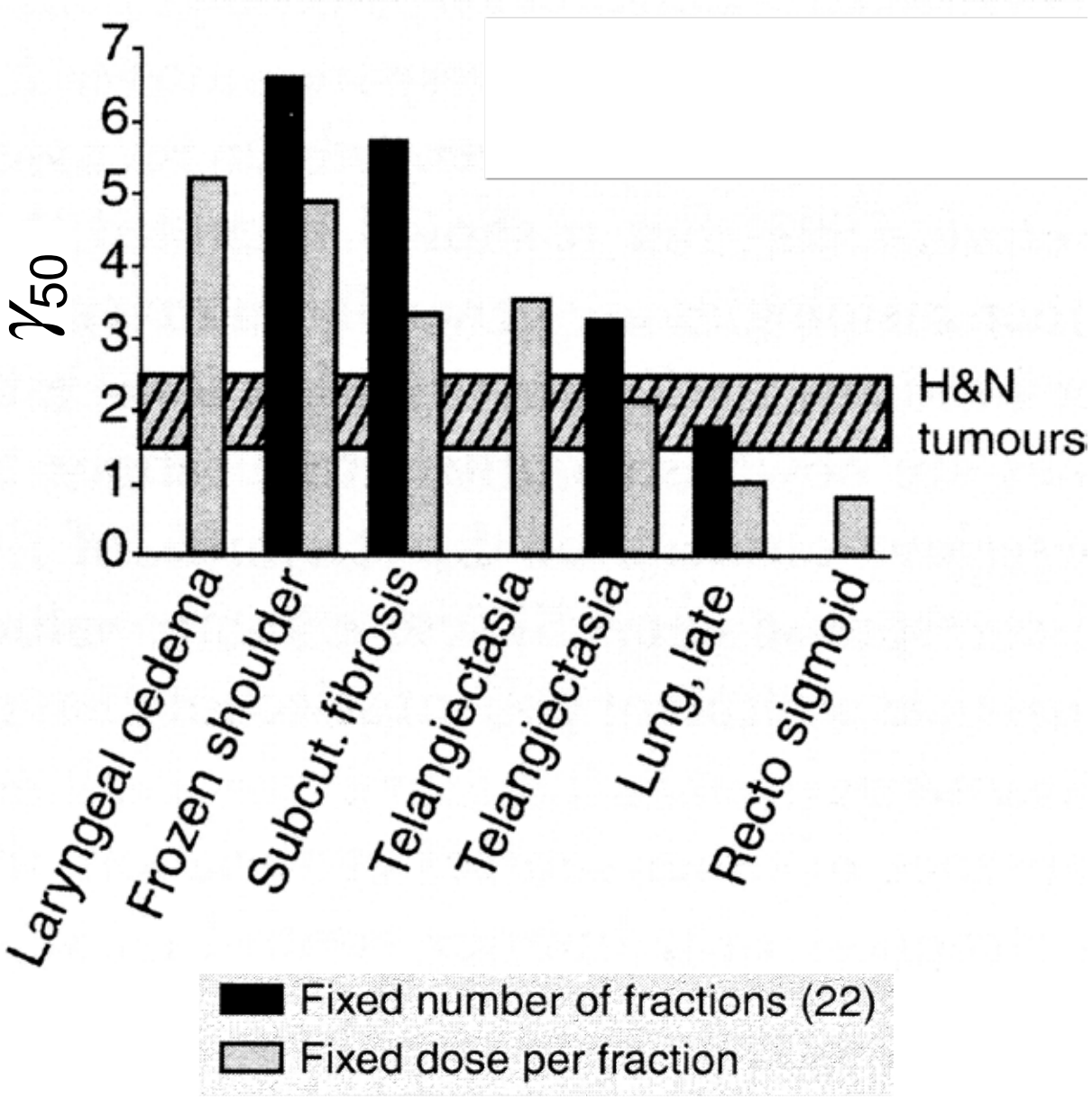


Value of γ in some late-reacting tissues

Compared with tumors,

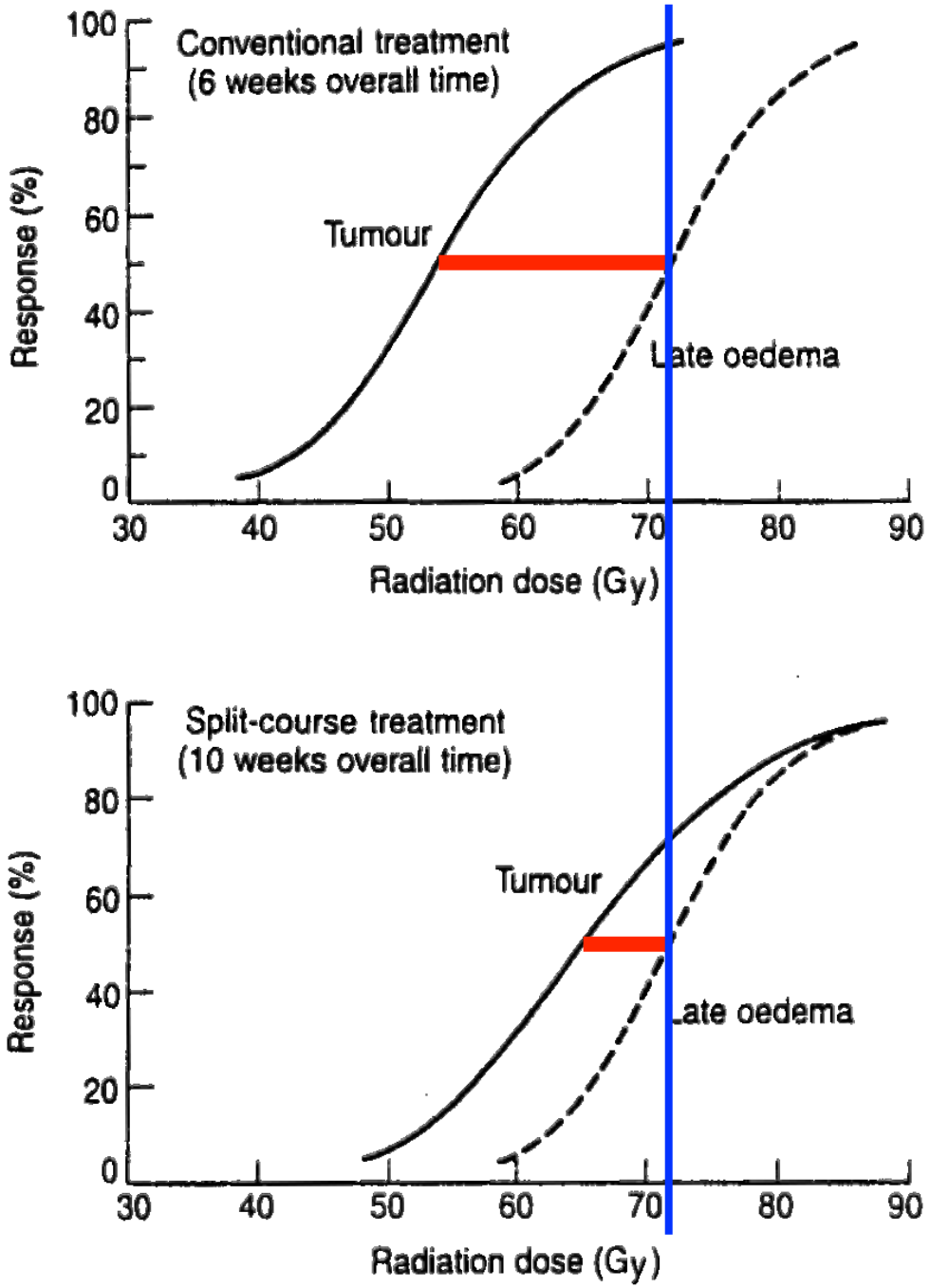
γ is usually larger

Dose response curves can be steeper, more so when fixed fraction number, *i.e.* higher dose per fraction



Balancing risks and benefits: The therapeutic window

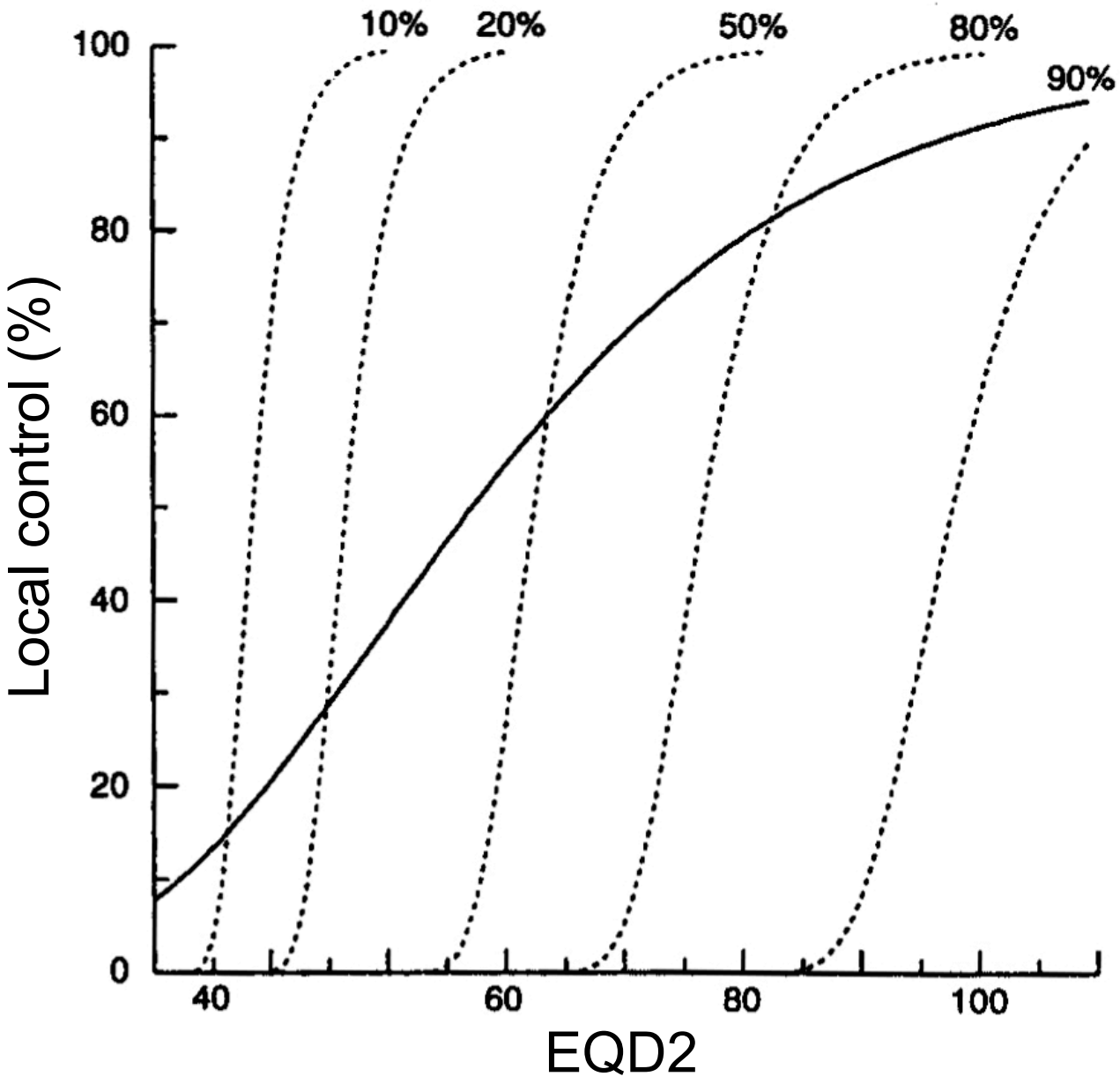
Example: protraction of overall treatment time is detrimental!



Modifying the steepness of the dose-response

Oropharyngeal cancer

Homogeneous patient populations with radiosensitivity equal to selected percentiles of radiosensitivity distribution in total population



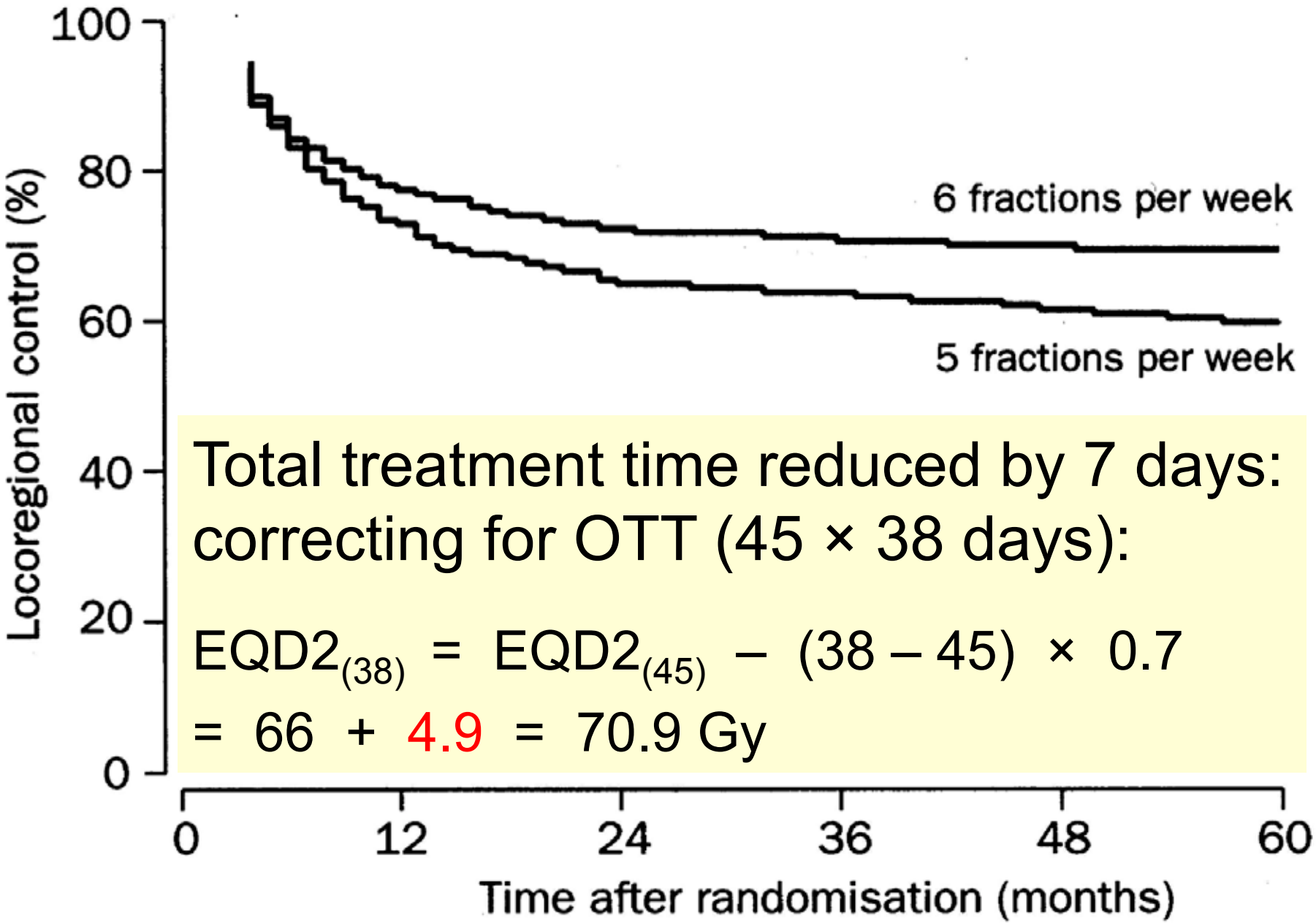
Clinical data to test modeling

Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6&7 randomised controlled trial

Jens Overgaard, Hanne Sand Hansen, Lena Specht, Marie Overgaard, Cai Grau, Elo Andersen, Jens Bentzen, Lars Bastholt, Olfred Hansen, Jørgen Johansen, Lisbeth Andersen, Jan F Evensen, on behalf of the Danish Head and Neck Cancer Study Group

Lancet 2003;362:933-40

Convert from a change in dose
to a change in response rate



Total treatment time reduced by 7 days: correcting for OTT (45 × 38 days):

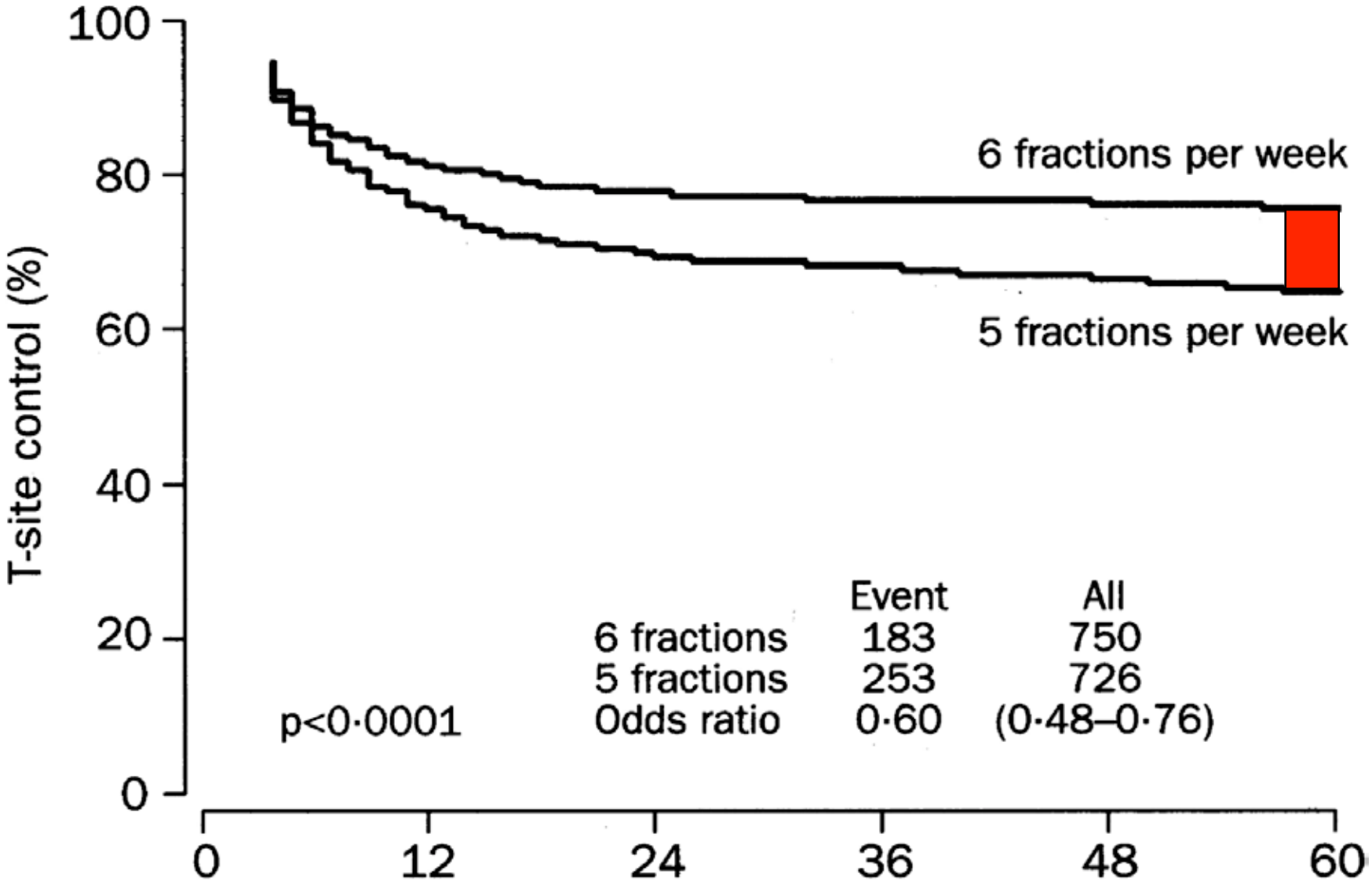
$EQD2_{(38)} = EQD2_{(45)} - (38 - 45) \times 0.7$

$= 66 + 4.9 = 70.9$ Gy

From change in dose to change in RR

$$\Delta R \approx \gamma \times \frac{\Delta D}{D} \times 100\%$$

$$= 1.6 \times \frac{4.9}{66} \times 100 = 12\%$$



Tumor control improved: 76% – 64% = 12%

Dose-volume models for normal tissues

- Predicting normal tissue toxicity has become more complicated by the use of IMRT, non-uniform dose distributions and partial organ irradiation
- Mathematical and biophysical models are developed to describe late normal tissue toxicity
- Toxicity is assessed from the complete dose distribution throughout an OAR in an integrative manner

NTCP models

Example: The Lyman model of dose-volume effects in normal tissue:

- Relates NTCP to dose and volume irradiated
- Assumes a normal distribution of complications as a function of dose for each uniformly irradiated fractional organ volume

Lyman model

$$NTCP(D,V) = \frac{1}{\sqrt{2\pi}} \cdot \int_{-\infty}^{u(D,V)} \exp(-\tfrac{1}{2} \cdot x^2)\, dx$$

$$u(D,V) = \frac{D - TD_{50}(V)}{m \cdot TD_{50}(V)}$$

$0 < n < 1$
Larger n,
more volume effect

$$TD_{50}(V) = \frac{TD_{50}(1)}{V^n}$$

(see BCR book, Ch 5.9)

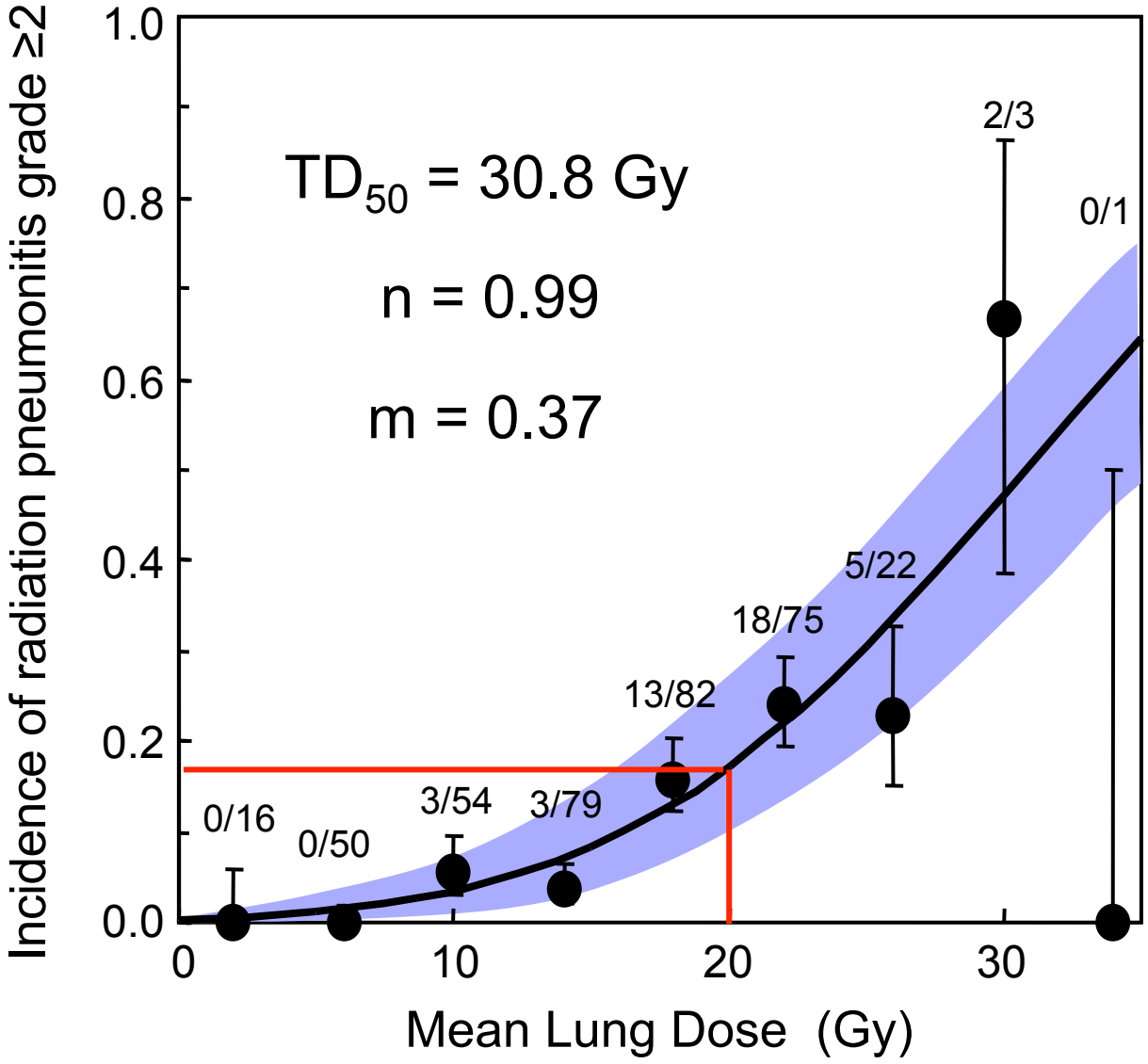
TD_{50} = uniform dose producing 50% incidence of specific effect
n = denotes influence of volume effect in organ of interest
m = inverse of dose response curve gradient

NTCP models

Organ	**Toxicity**	**TD_{50}**	**Volume effect** (n)	**Dosimetric descriptor**
Parotid gland	Xerostomia	28.4 Gy	large (1)	mean dose
Lung	gr≥2 pneumonitis	30.8 Gy	large (0.99)	V20, MLD
Heart	RIHD		intermediate (0.35–0.64)	Vd, MHD
Spinal cord	myelopathy		marginal (except very small volumes)	EQD2
Liver	RILD	40-45 Gy	large (0.69–0.97)	MLD, Vd
Rectum	proctitis, ulceration	80 Gy	small (serial)	V70, V50

Kong et al. *Semin Radiat Oncol* 2007;17:108-20

Complications versus mean lung dose



Seppenwoolde et al. *Int J Radiat Oncol Biol Phys* 2003;55:724-35

Summary

- Dose-response data are defined in terms of probability
- Steepness of dose response at defined level can be used to convert change in dose to response
- Dose-response curves for normal tissues are steeper than those for tumors
- Heterogeneity in population data tend to make dose-response curves less steep
- NTCP models are not well validated and require caution when applied to clinical data; simpler dosimetric descriptors may be more useful

Biological response modifiers Preclinical

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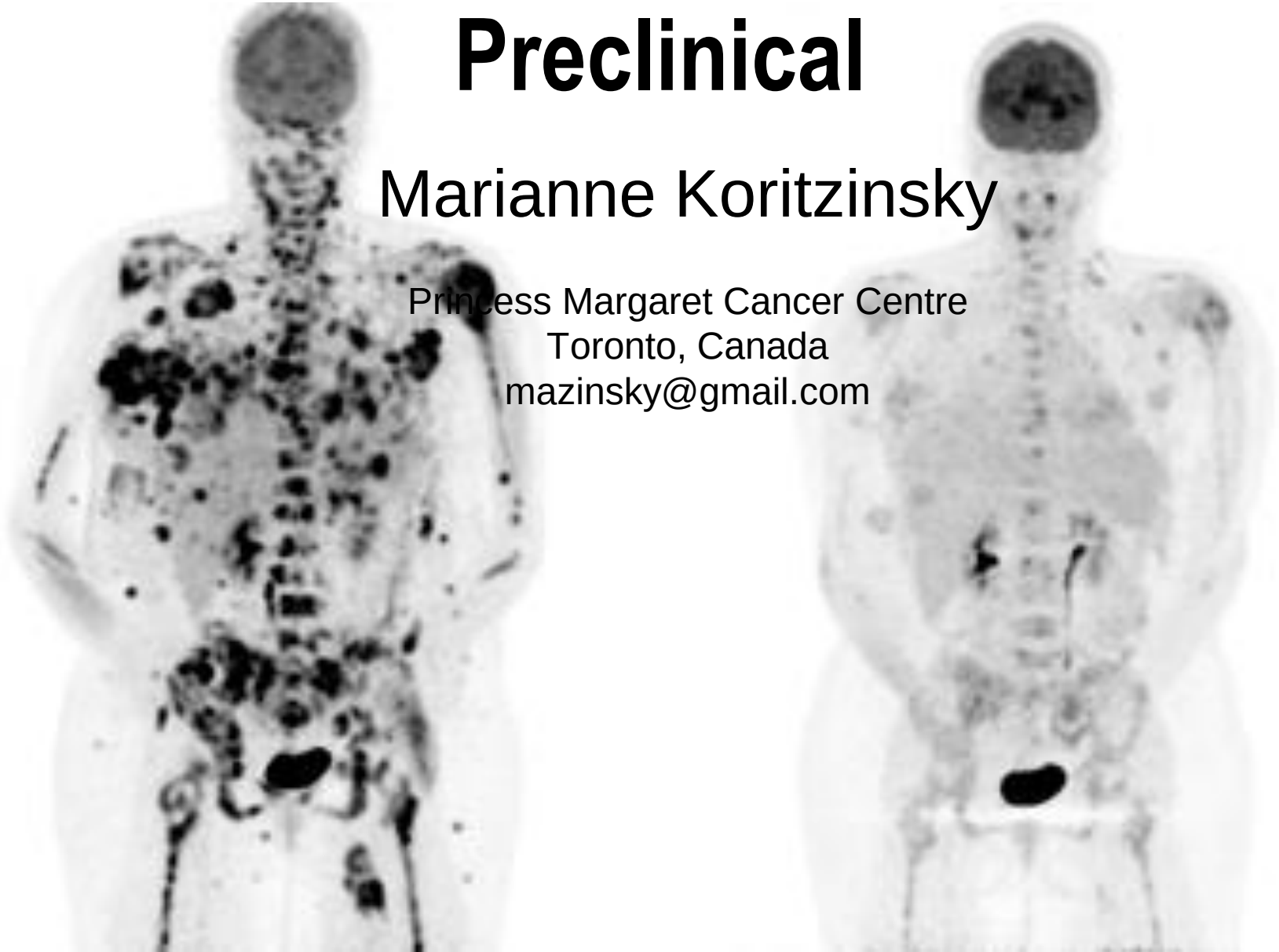
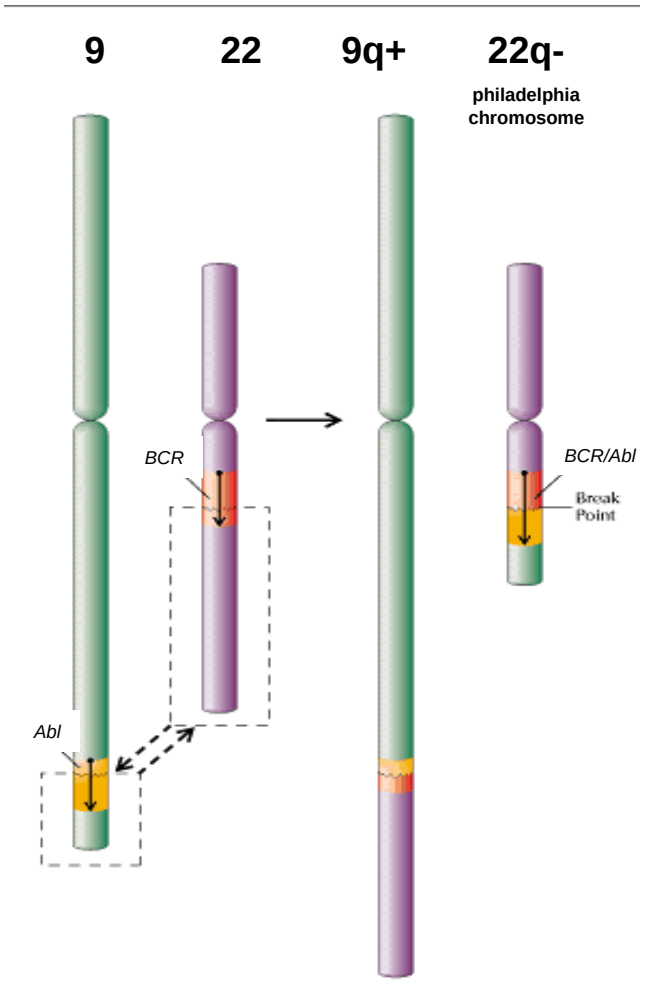
Toronto, Canada
mazinsky@gmail.com



Molecular Targeting of Cancer

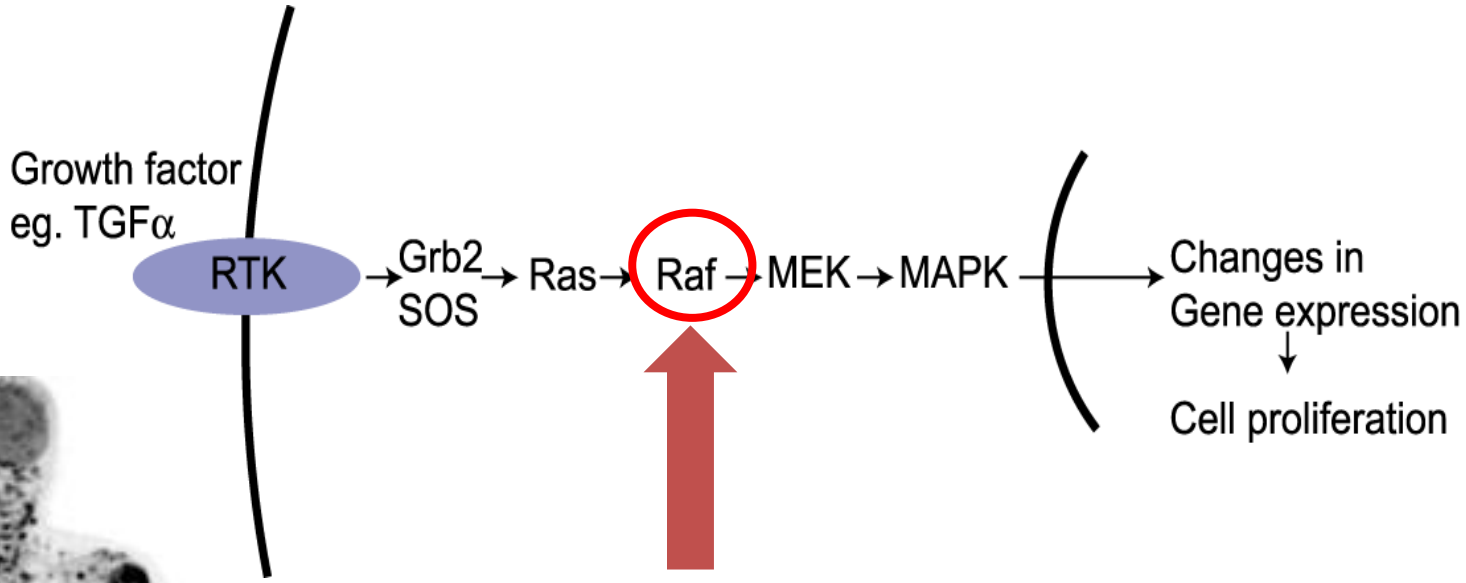


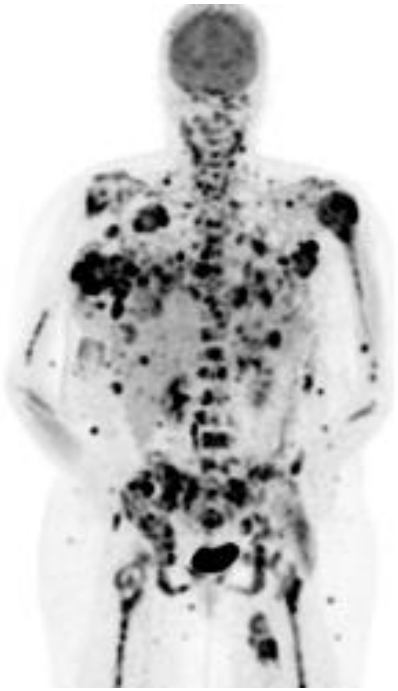
Individualization

"Here's my sequence..."

Nature, 2000

Molecular Targeting of Cancer





V600E

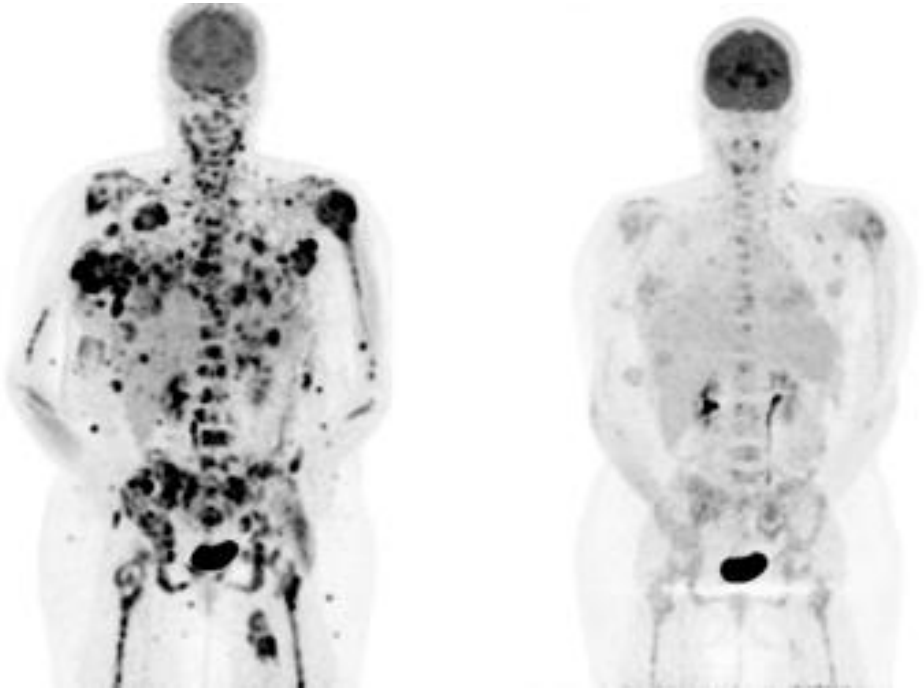
Valine – glutamic acid

non-polar–polar

Molecular Targeting of Cancer

The New York Times

February 2010



Biological response modifiers

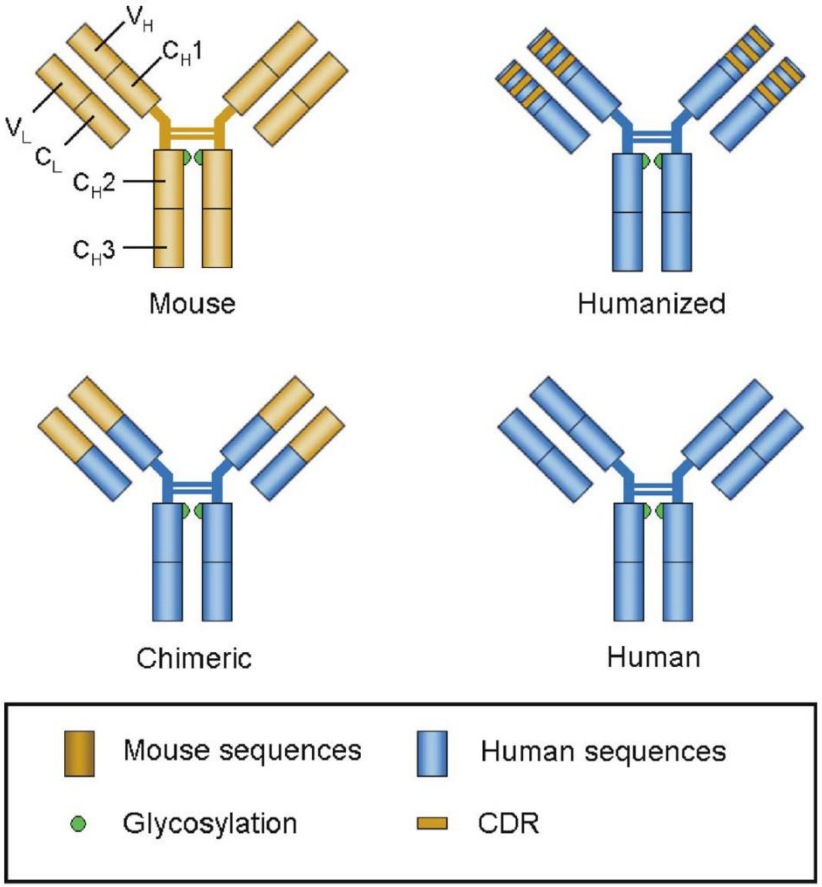
- New drugs designed to target the function of specific molecules
  - Small molecules
  - Antibodies
- Can have low toxicity
- Can have extremely high specificity

Name	Target	Company	Class
Bevacizumab	VEGF	Genentech	Monoclonal antibody
BIBW 2992 (Tovok)	EGFR and Erb2	Boehringer Ingelheim	Small molecule
Cetuximab	EGFR	Imclone/BMS	Monoclonal antibody
Imatinib	Bcr-Abl	Novartis	Small molecule
Trastuzumab	Erb2 (Her2)	Genentech/Roche	Monoclonal antibody
Gefitinib	EGFR	AstraZeneca	Small molecule
Ranibizumab	VEGF	Genentech	Monoclonal antibody
Pegaptanib	VEGF	OSI/Pfizer	Small molecule
Sorafenib	Multiple targets	Onyx/Bayer	Small molecule
Dasatinib	Multiple targets	BMS	Small molecule
Sunitinib	Multiple targets	Pfizer	Small molecule
Erlotinib	EGFR	Genentech/Roche	Small molecule
Nilotinib	Bcl-Abr	Novartis	Small molecule
Lapatinib	EGFR/Erb2	GSK	Small molecule
Panitumumab	EGFR	Amgen	Monoclonal antibody

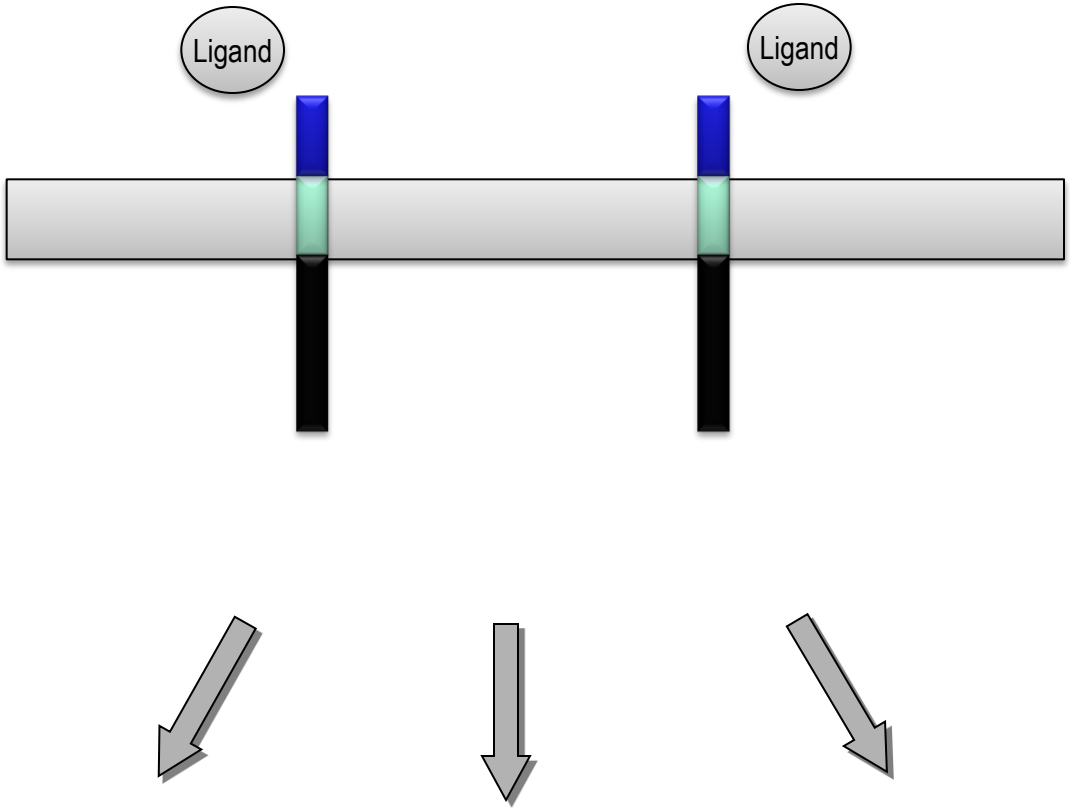
+ many more

Mechanisms of mAB Action

- Signal transduction changes
  - Ligand-receptor interaction
  - Clearance of ligand
- Delivery of cytotoxic payloads
  - Radioisotopes
  - Toxins
- Interaction with immune system
  - Antibody-dependent cellular cytotoxicity
  - Complement-dependent cytotoxicity

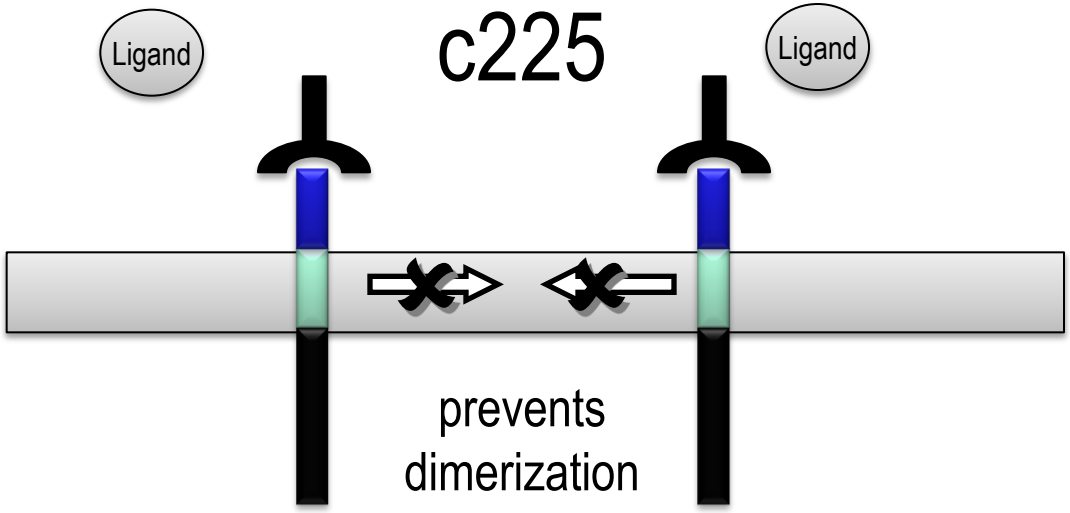


EGFR-signaling

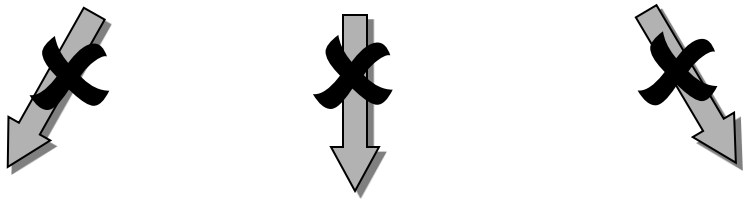


Proliferation, DNA repair, angiogenesis

Cetuximab prevents EGFR-signaling

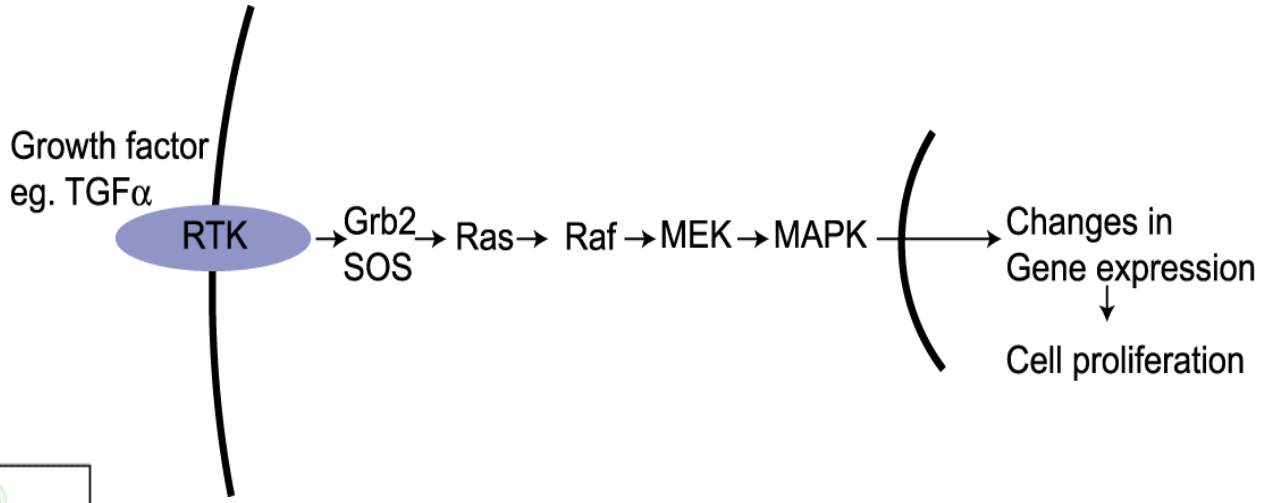


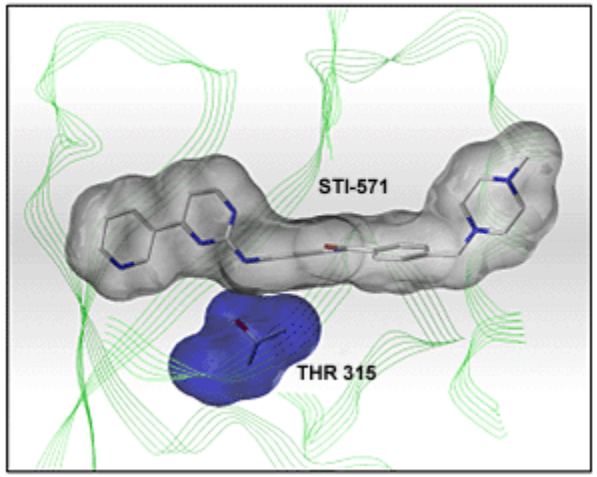
No downstream signalling



Proliferation, DNA repair, angiogenesis

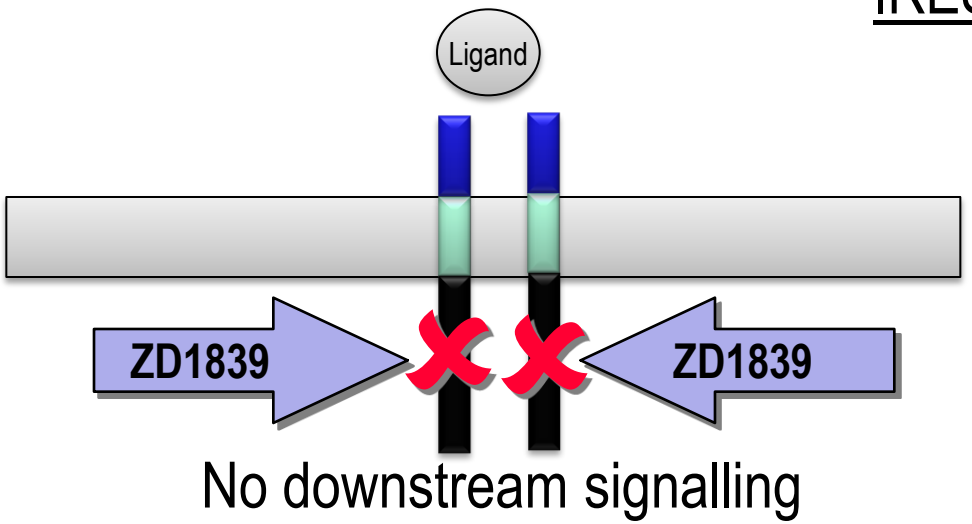
Small molecules

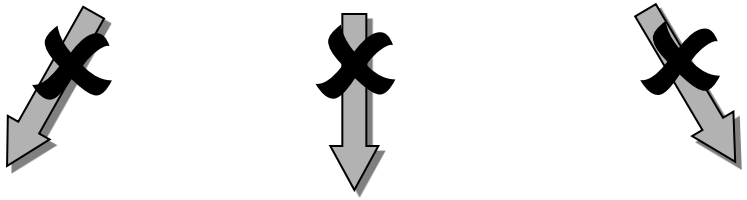




- Tyrosine Kinase Inhibitors
  - Imatinib – gleevec
  - EGFR - Iressa
  - VEGFR
- Farnesyl transferase inhibitors
  - Ras
- Prostaglandin (PGE2) pathway
  - COX-2

Small molecule EGFR inhibitors





Proliferation, DNA repair, angiogenesis

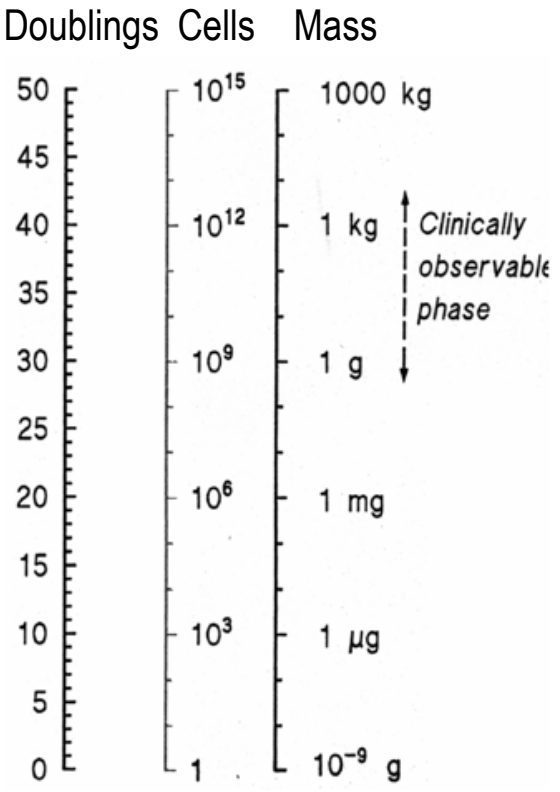
IRESSA / ZD1839

- orally bioavailable
- selective inhibitor of EGFR tyrosine kinase
- competitive inhibitor of ATP-binding

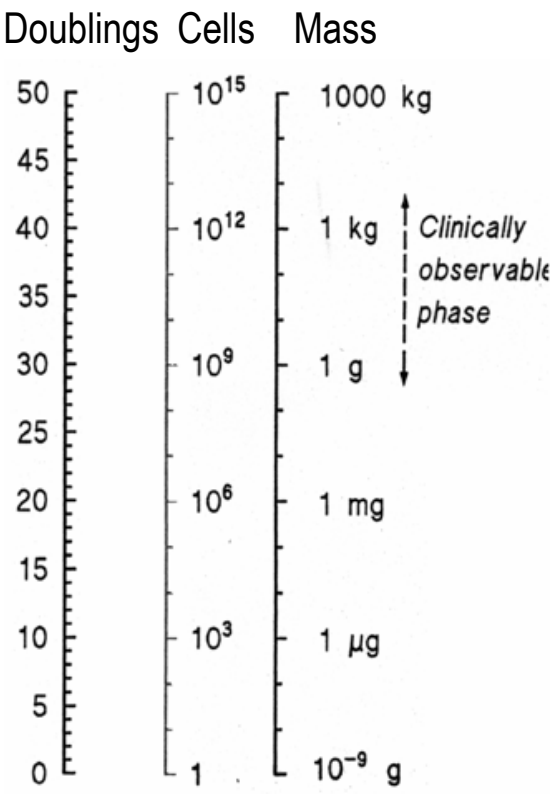
Targeting with RT: achieving cure

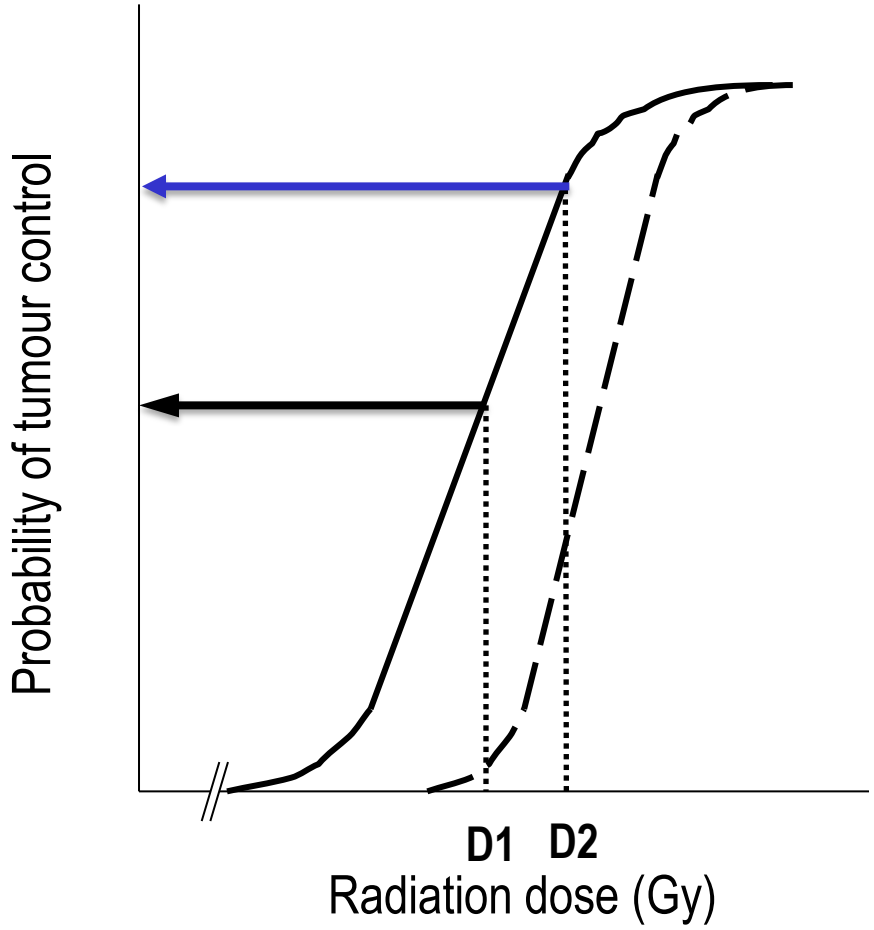
New targeted drugs unlikely to be effective stand-alone therapies

- Number of cells
- Heterogeneity in the target
- Adaptation to the agent

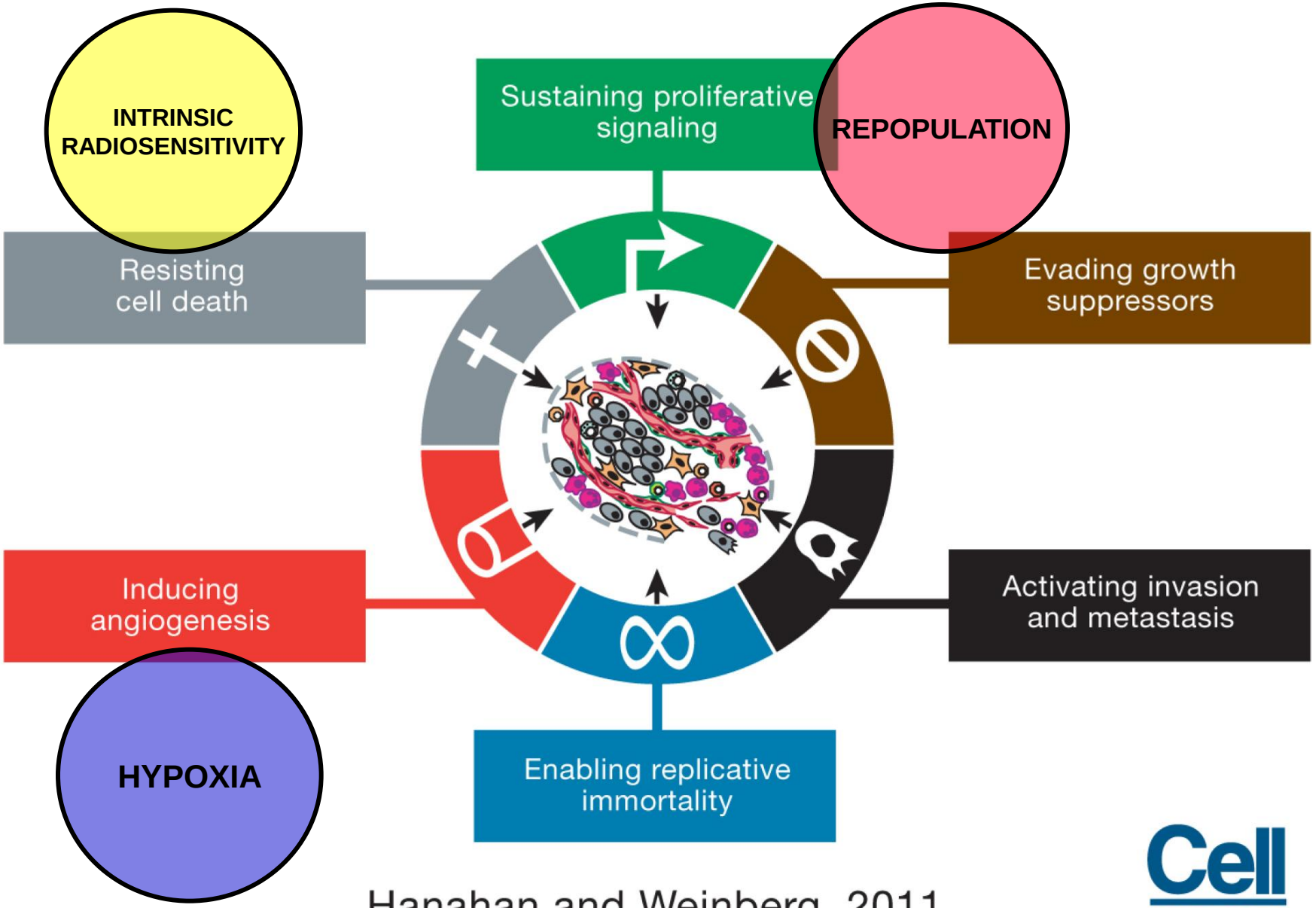


Targeting with RT: the last drop





Targeting with RT: favorable combinations

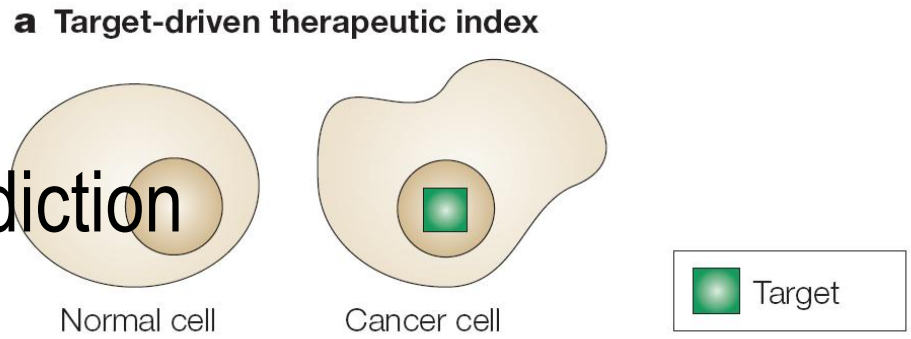


Hanahan and Weinberg, 2011

Cell PRESS

Making choices: Therapeutic index

Oncogene addiction



Bcr-abl (Gleevec)
B-raf (PLX4032)
EGFR (Iressa)

Synthetic lethality

PARP/BRCA2

Contextual synthetic lethality

VEGF (Avastin)
Hypoxia tolerance

Example 1: Target driven lethality - EGFR

Tumors showing high EGFR expression

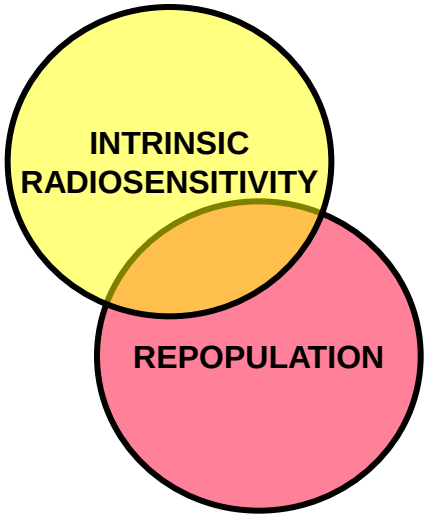
• NSCLC	40-80%
• Prostate	40-80%
• Gastric	33-74%
• Breast	14-91%
• Colorectal	25-77%
• Pancreatic	30-50%
• Ovarian	35-70%
• Bladder	31-48%
• Renal cell	50-90%
• H&N	80-100%
• Glioma	40-63%
• Esophageal	43-89%

High expression generally associated with

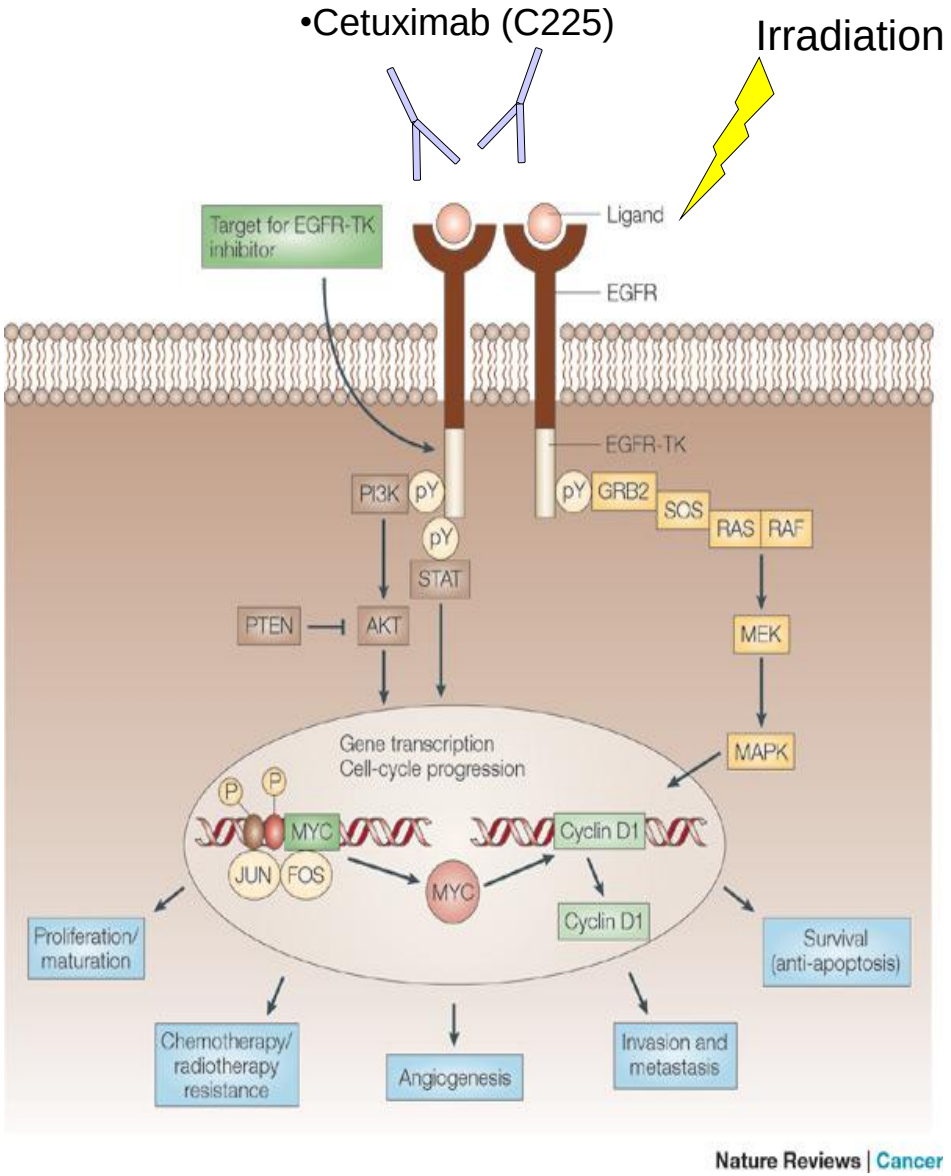
- **Invasion**
- **Metastasis**
- **Late-stage disease**
- **Chemo-/Radiotherapy resistance**
- **Poor outcome**

Example 1: Target driven lethality (EGFR)

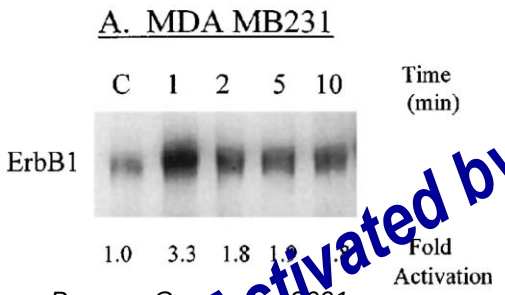
EGFR



- **Proliferation**
  - MAPK signaling
- **Radiosensitivity**
  - PI3K signaling
  - DNA repair

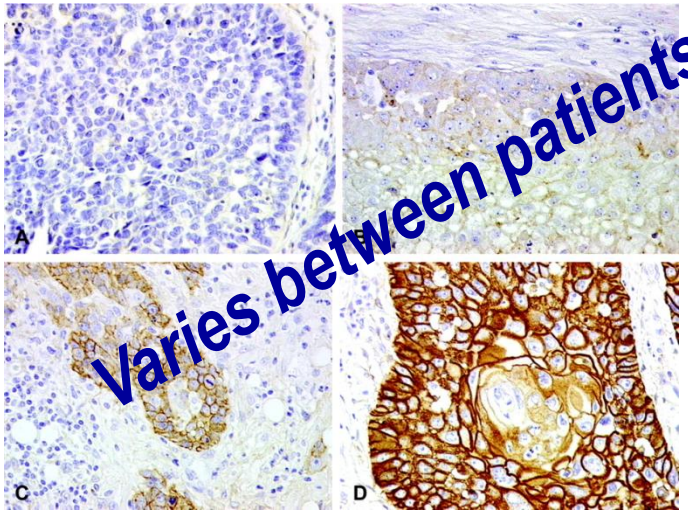


Example 1: Target driven lethality (EGFR)

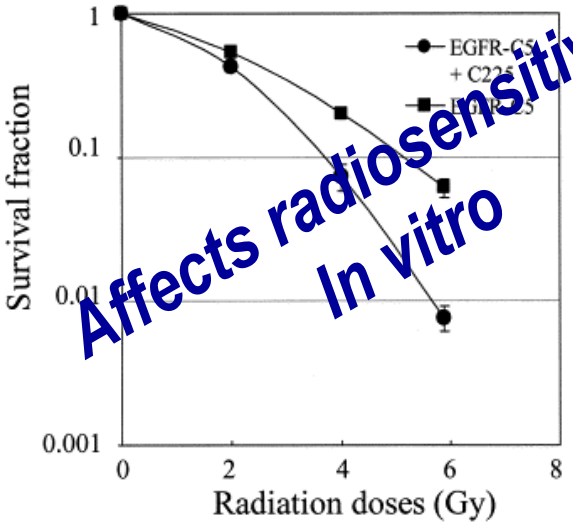


Bowers, Oncogene, 2001

Activated by radiation

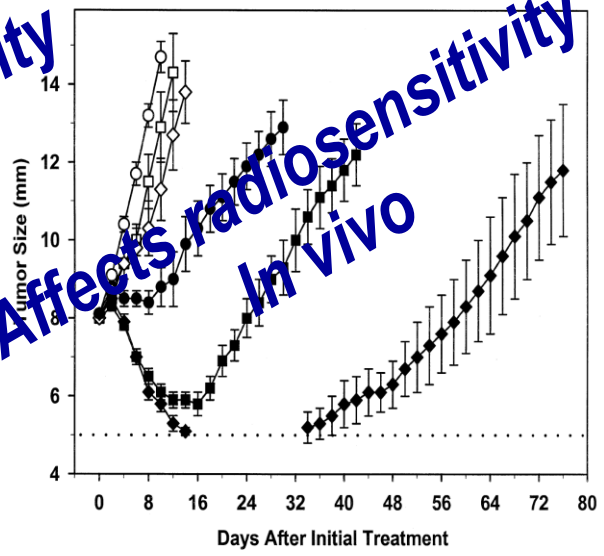


Varies between patients

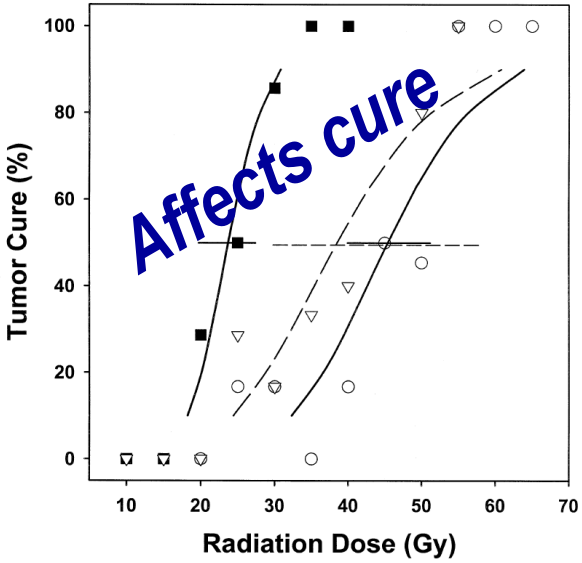


Affects radiosensitivity In vitro

Liang, IJROBP, 2003



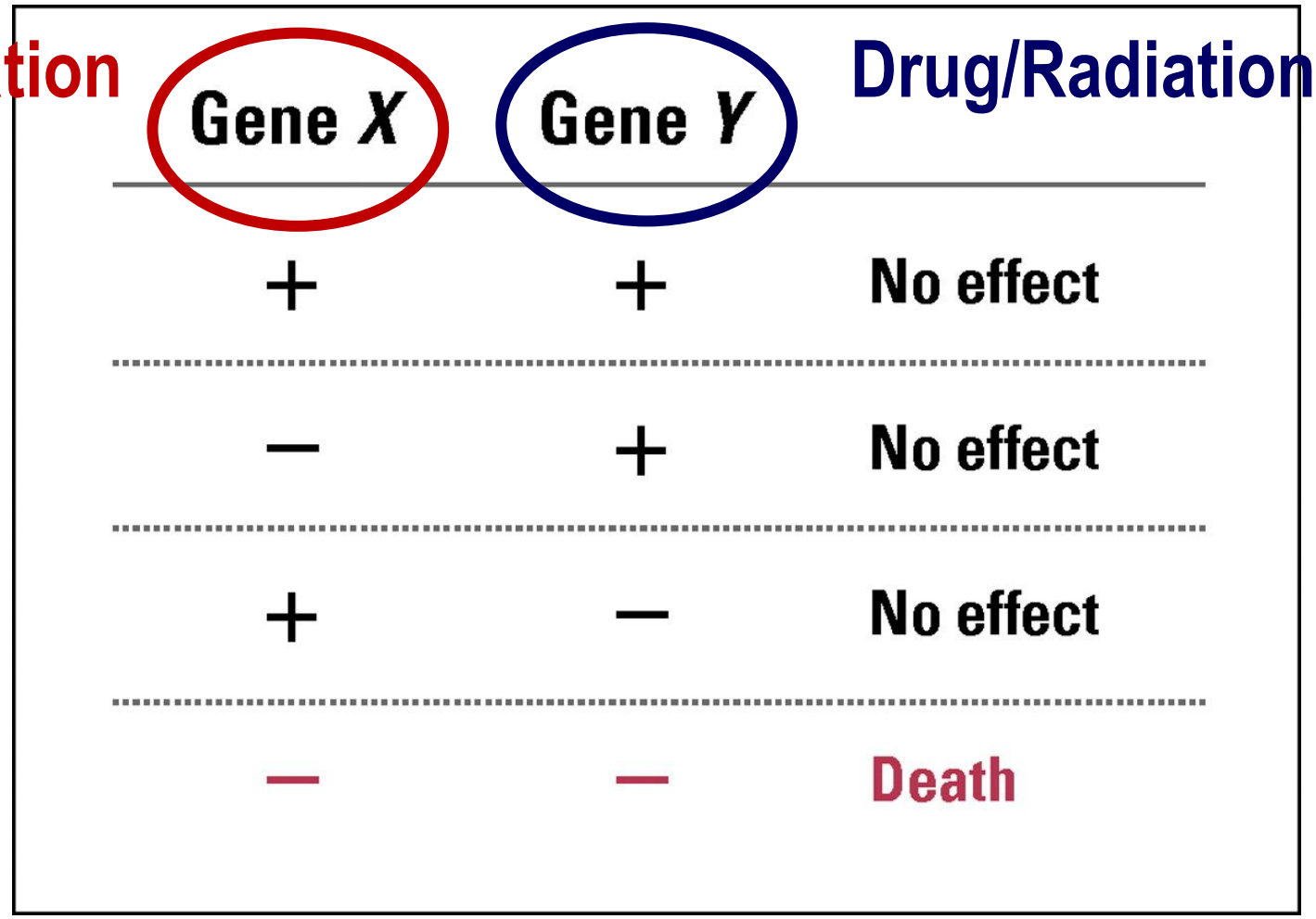
Affects radiosensitivity In vivo



Affects cure

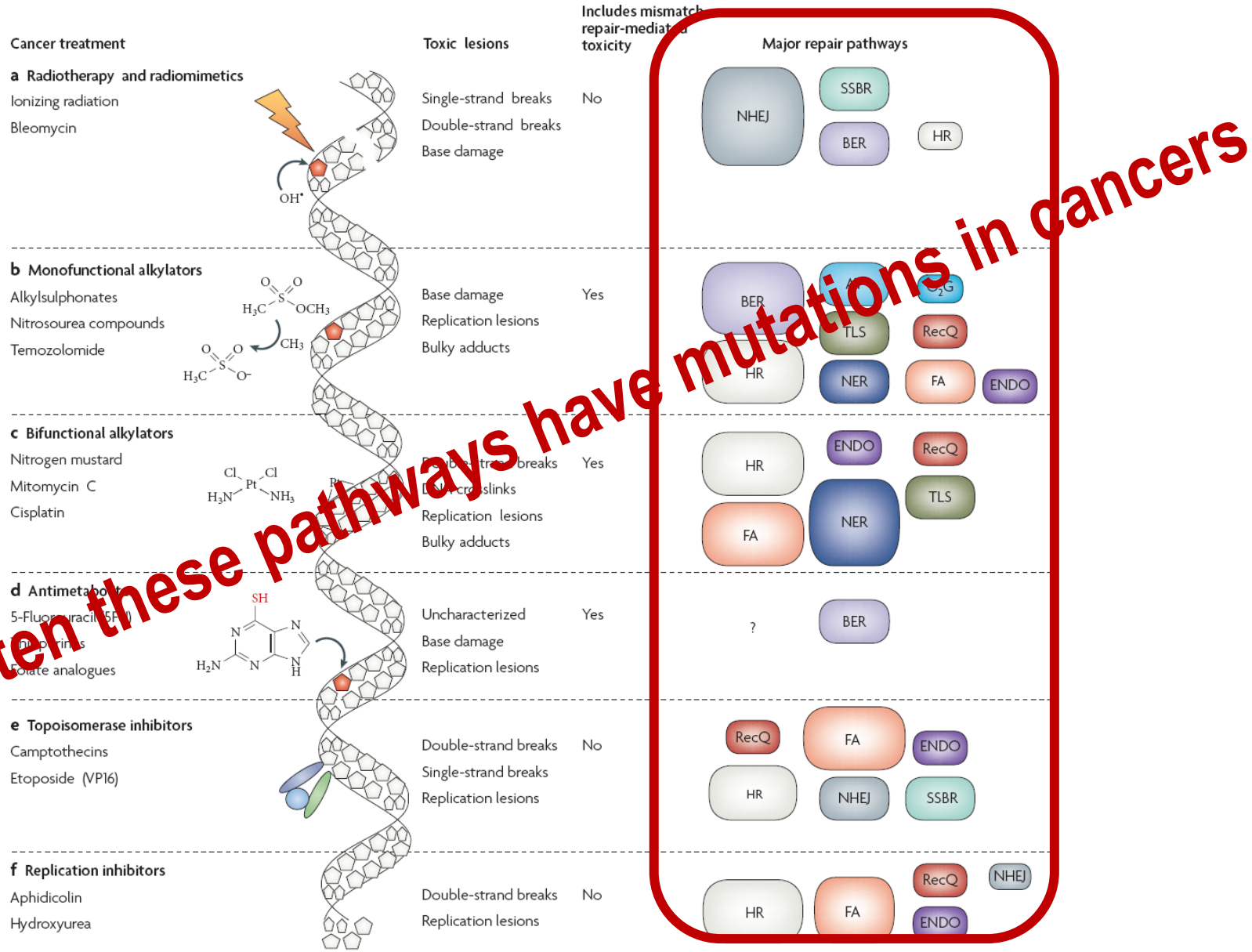
Milas, IJROBP, 2004

The Concept of Synthetic Lethality



Ashworth, A. J Clin Oncol; 26:3785-3790 2008

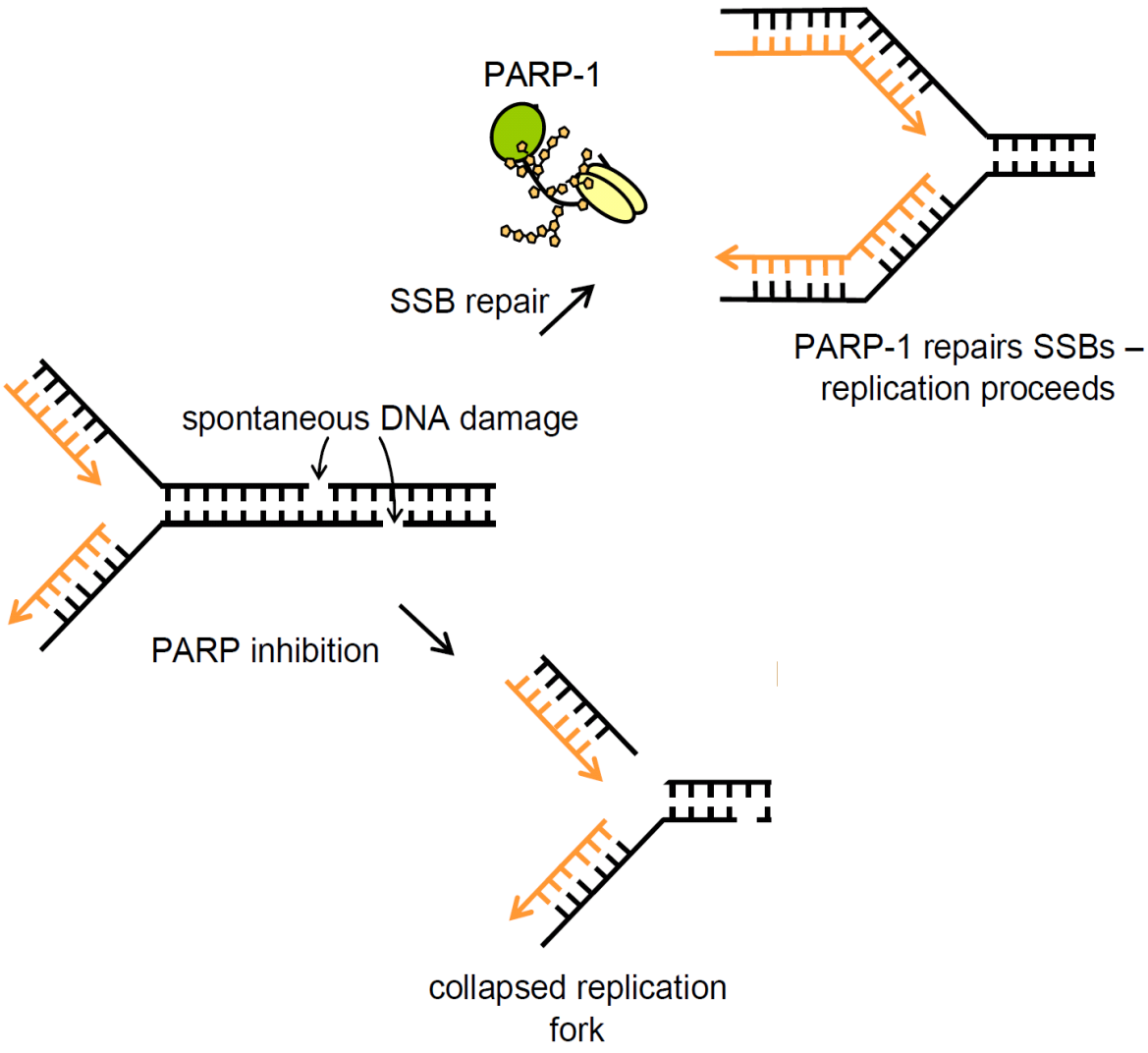
Example 2 – Synthetic lethality



INTRINSIC RADIOSENSITIVITY

Often these pathways have mutations in cancers

2. Synthetic lethality: PARP inhibitors for BRCA2$^{-/-}$



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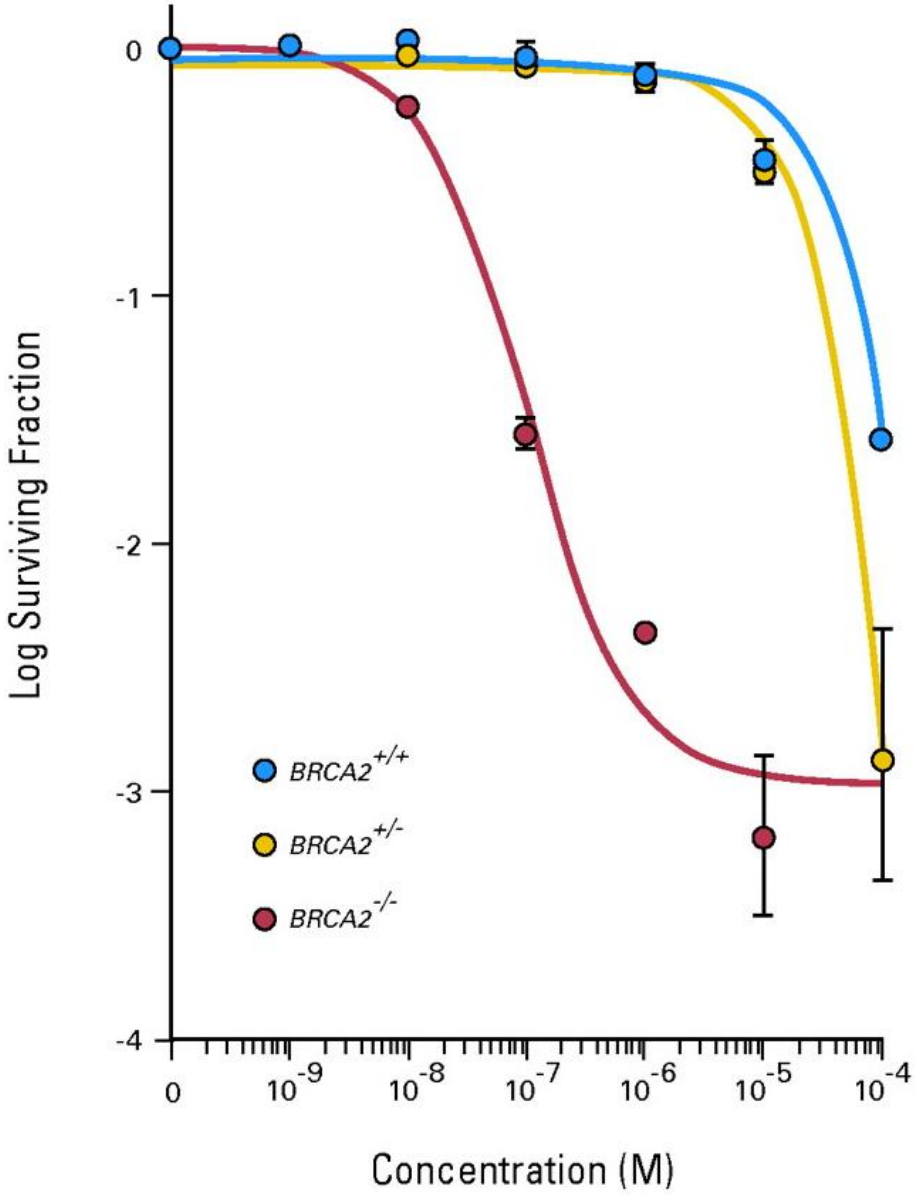


Ashworth, A. J Clin Oncol; 26:3785-3790 2008

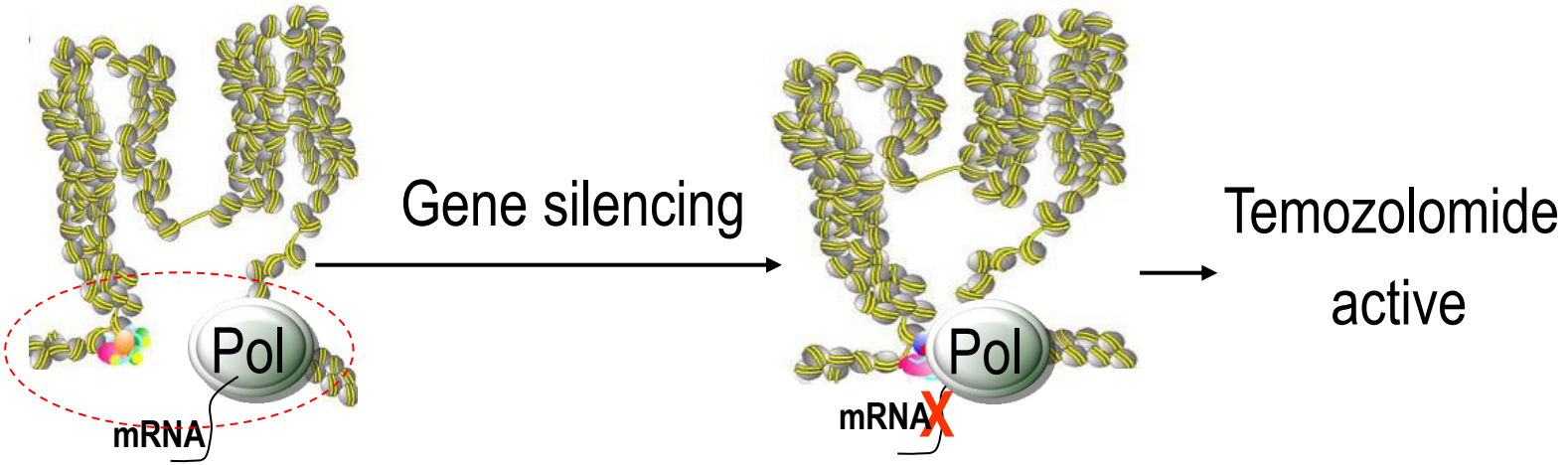
2. Synthetic lethality: Temozolomide for MGMT silencing

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

MGMT Gene Silencing and Benefit from Temozolomide in Glioblastoma

Monika E. Hegi, Ph.D., Annie-Claire Diserens, M.Sc., Thierry Gorlia, M.Sc., Marie-France Hamou, Nicolas de Tribolet, M.D., Michael Weller, M.D., Johan M. Kros, M.D., Johannes A. Hainfellner, M.D., Warren Mason, M.D., Luigi Mariani, M.D., Jacoline E.C. Bromberg, M.D., Peter Hau, M.D., René O. Mirimanoff, M.D., J. Gregory Cairncross, M.D., Robert C. Janzer, M.D., and Roger Stupp, M.D.



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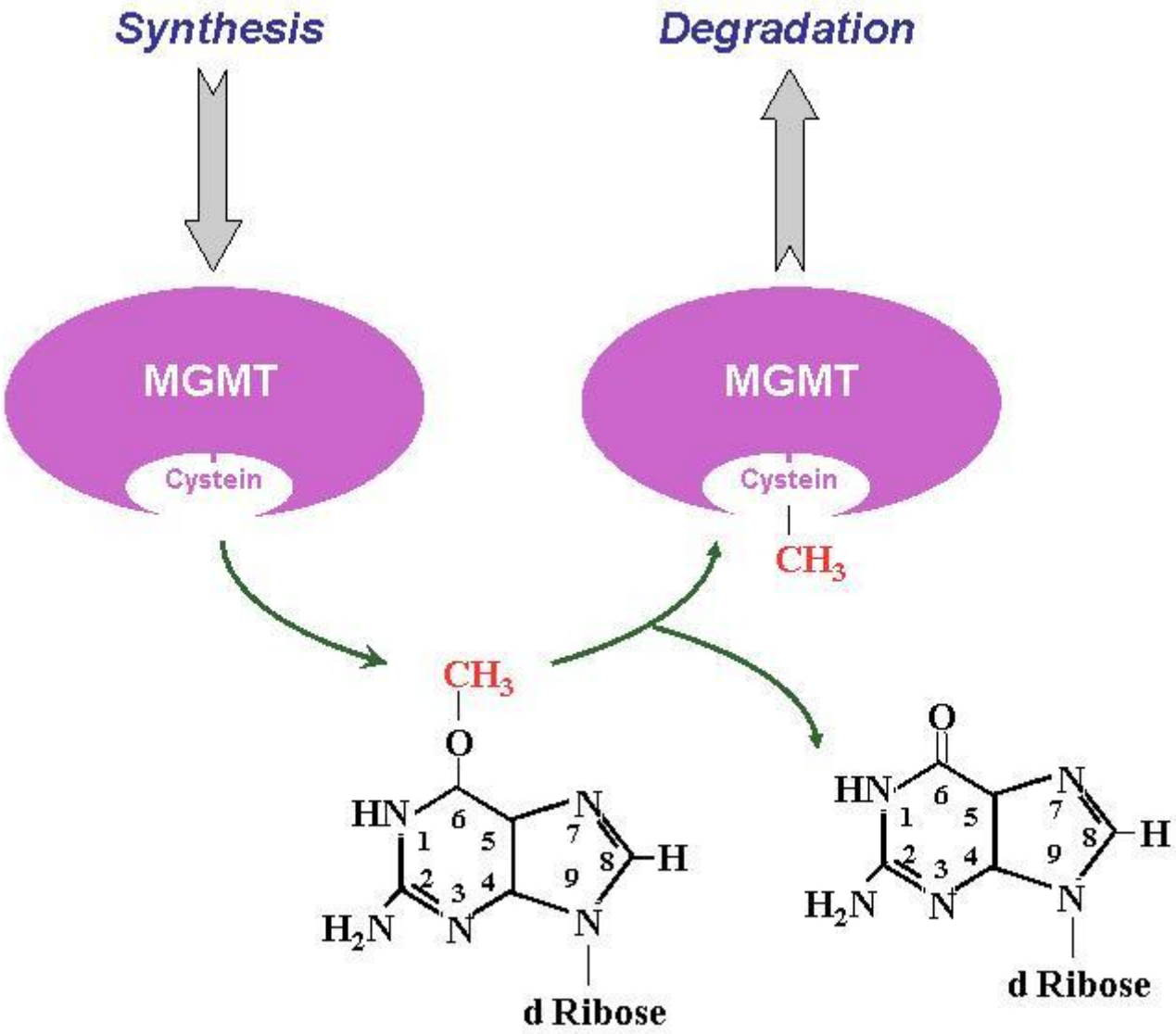
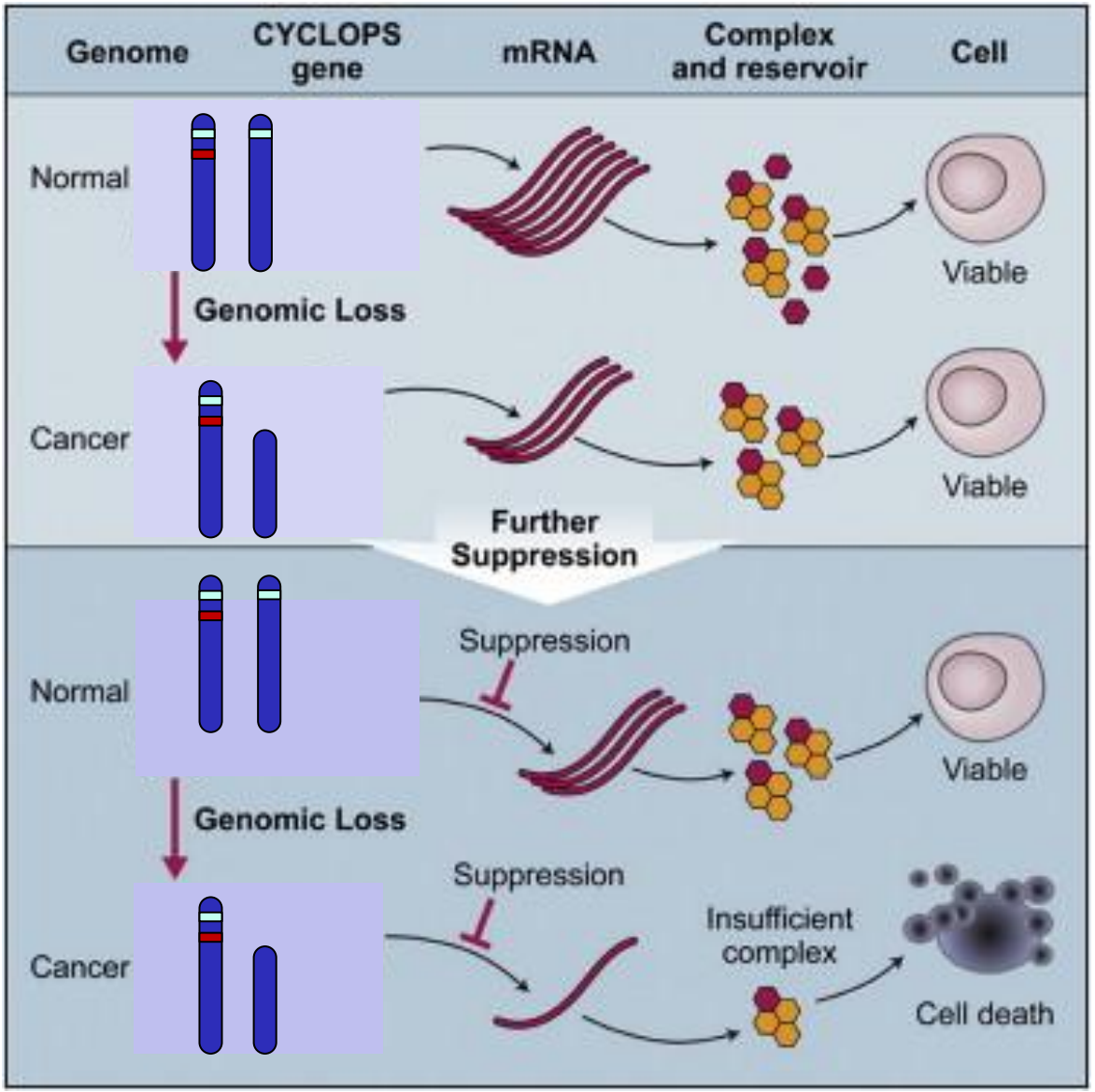


2. Synthetic lethality: CYCLOPS

Copy number alterations Yielding Cancer Liabilities Owing to Partial losS

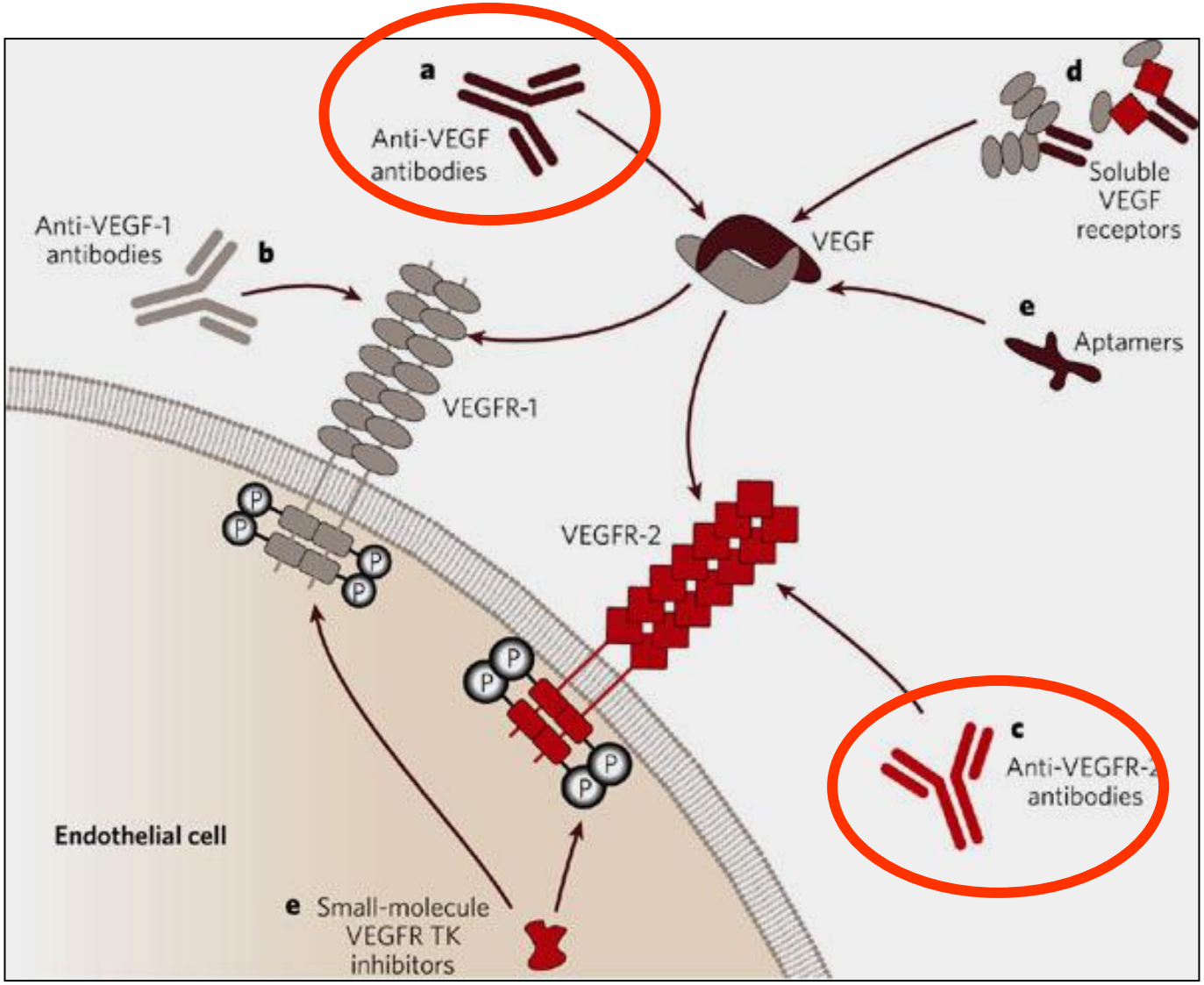
- Tumor suppressor
- CYCLOPS gene



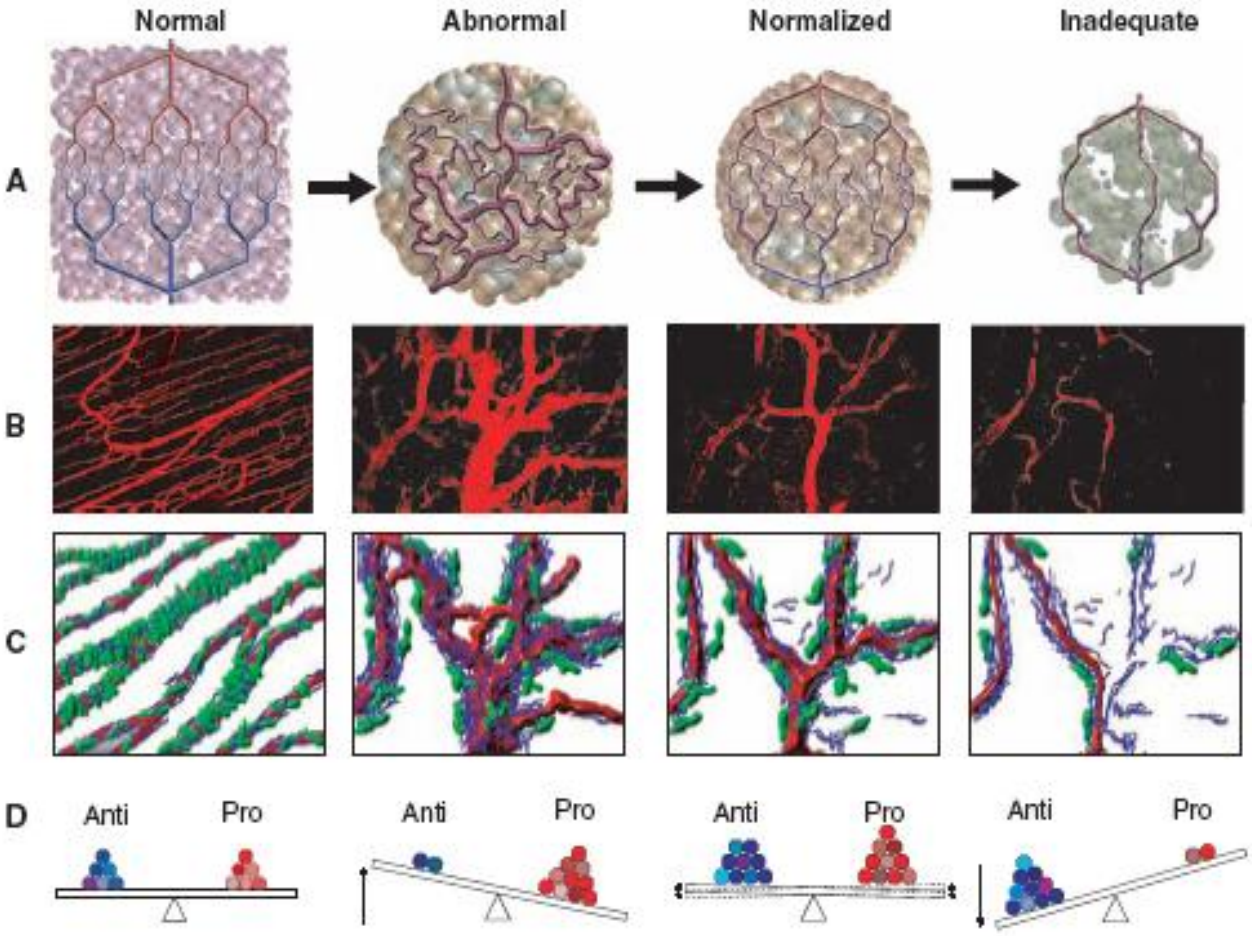
Nijhawan et al., Cell 2012

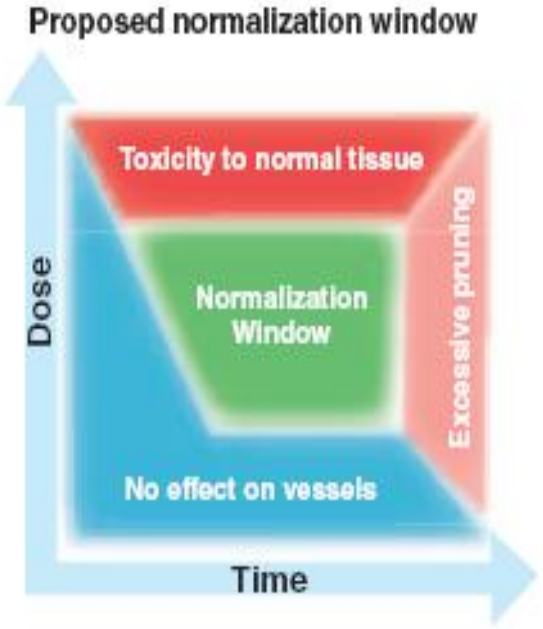
Example 3: Contextual lethality - VEGF

HYPOXIA

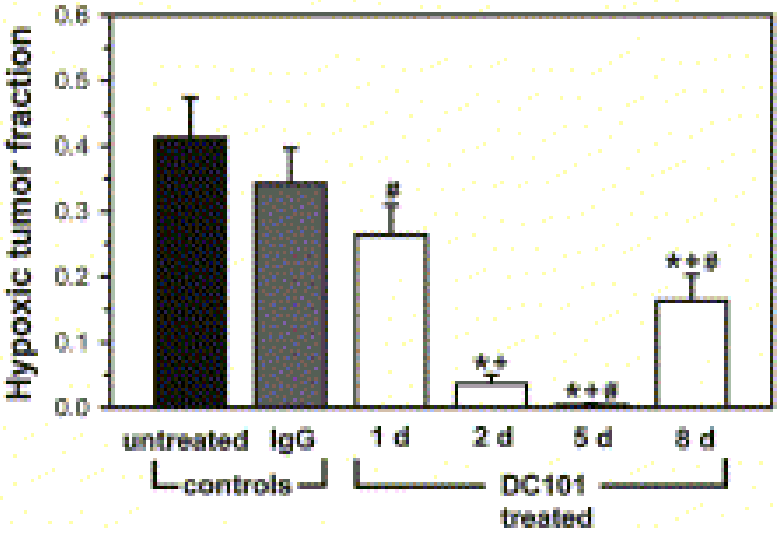


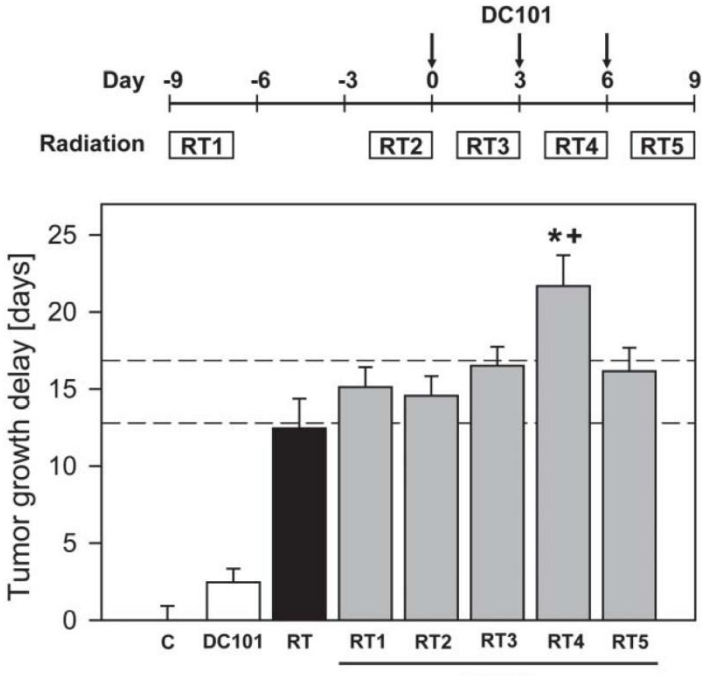
Normalisation of Tumour Vasculature

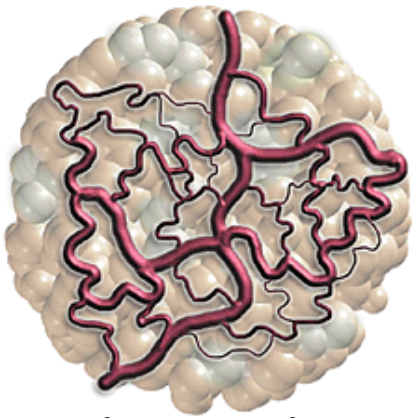




VEGF targeting can improve radiation response



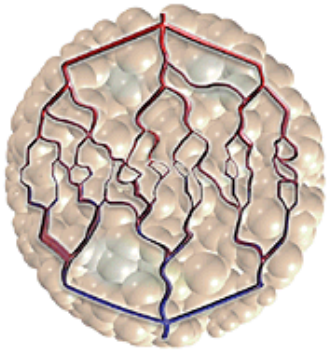




abnormal vasculature

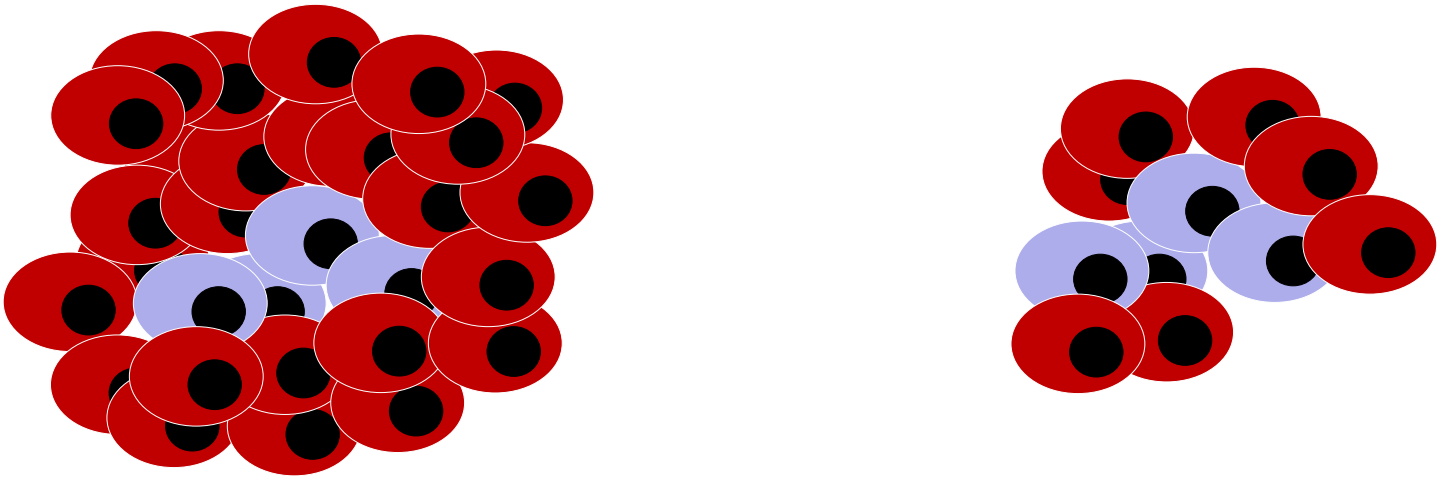
during treatment with DC101

Winkler et al., Cancer Cell,2004, 6, 553ff



normalized vasculature

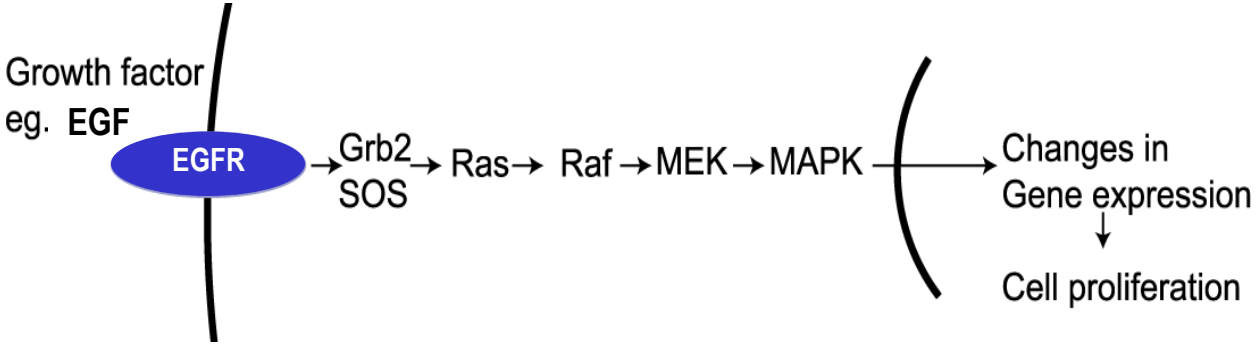
Molecular targeting: Challenges
Tumor subpopulations



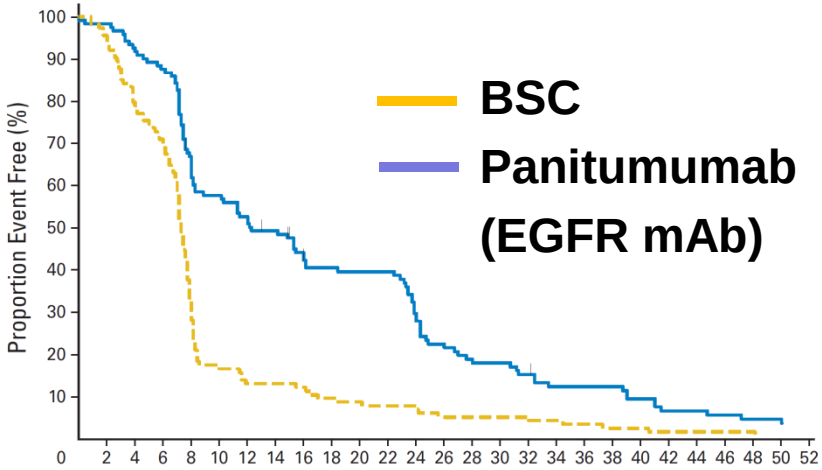
Tumor bulk, determines response

Rare cell, determines cure

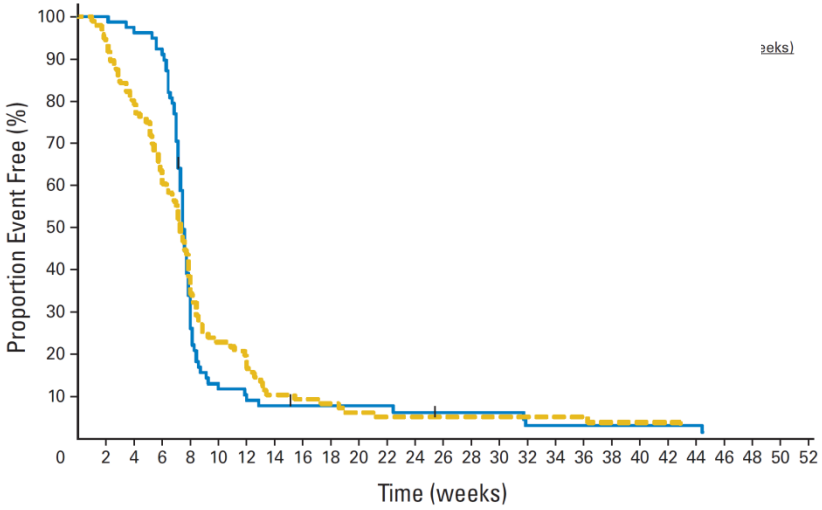
Molecular targeting: Challenges Biomarkers



Ras WT

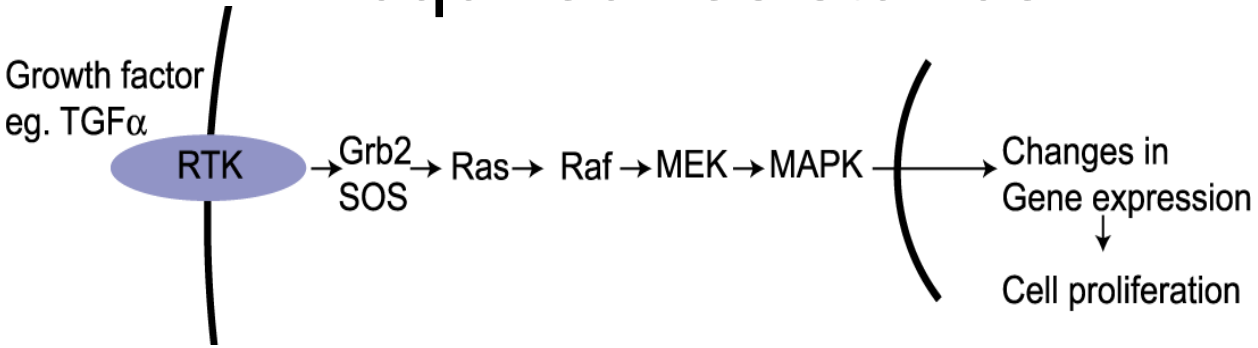


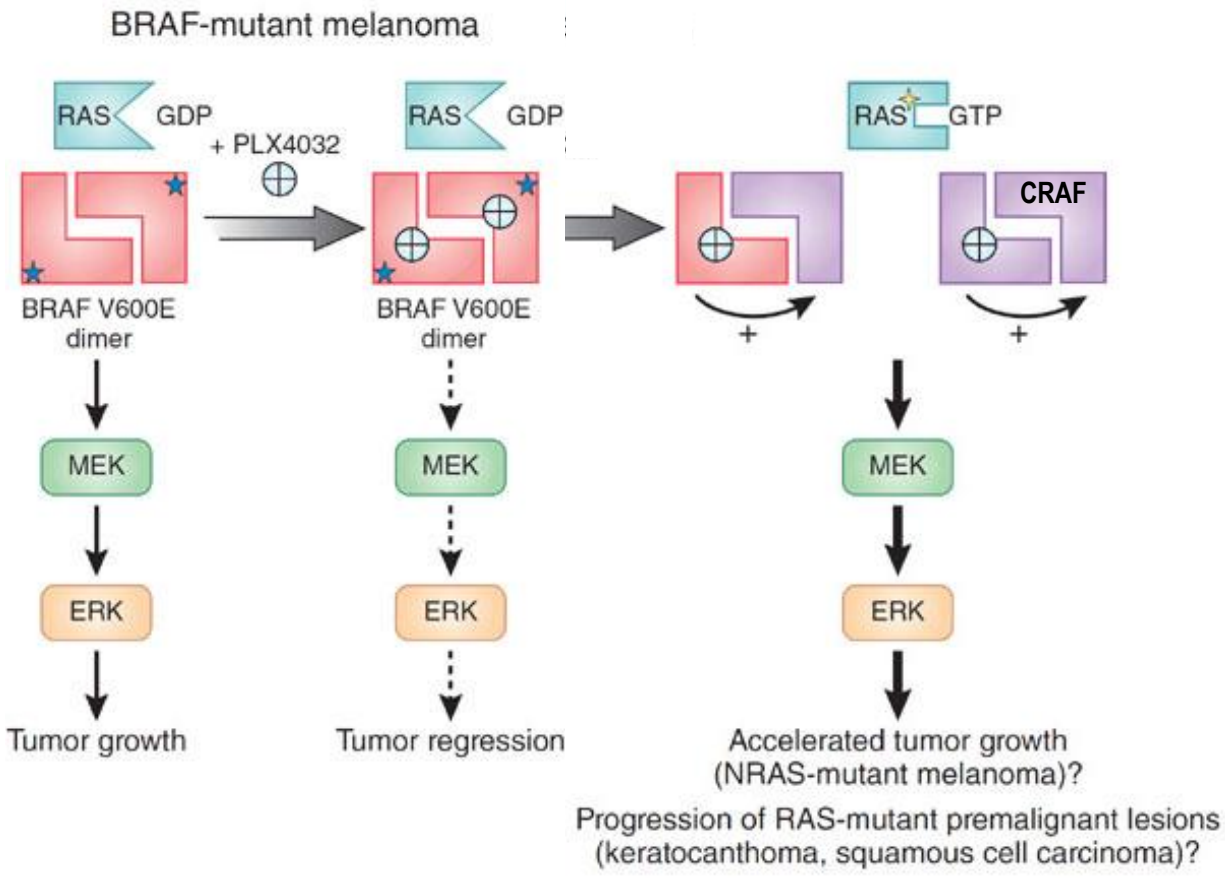
Ras MT



Amado, JCO 2008

Molecular targeting: challenges
Acquired resistance



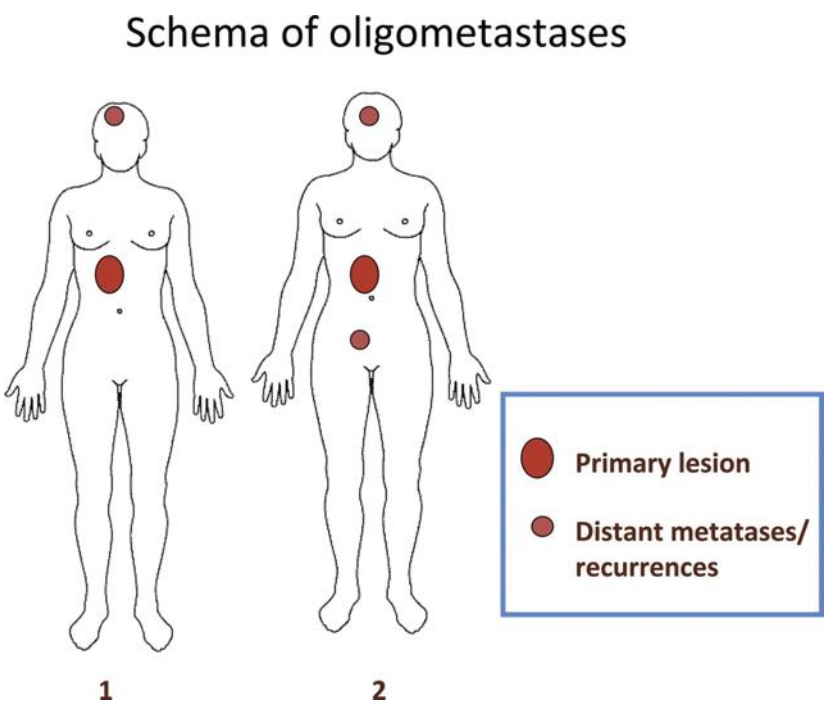


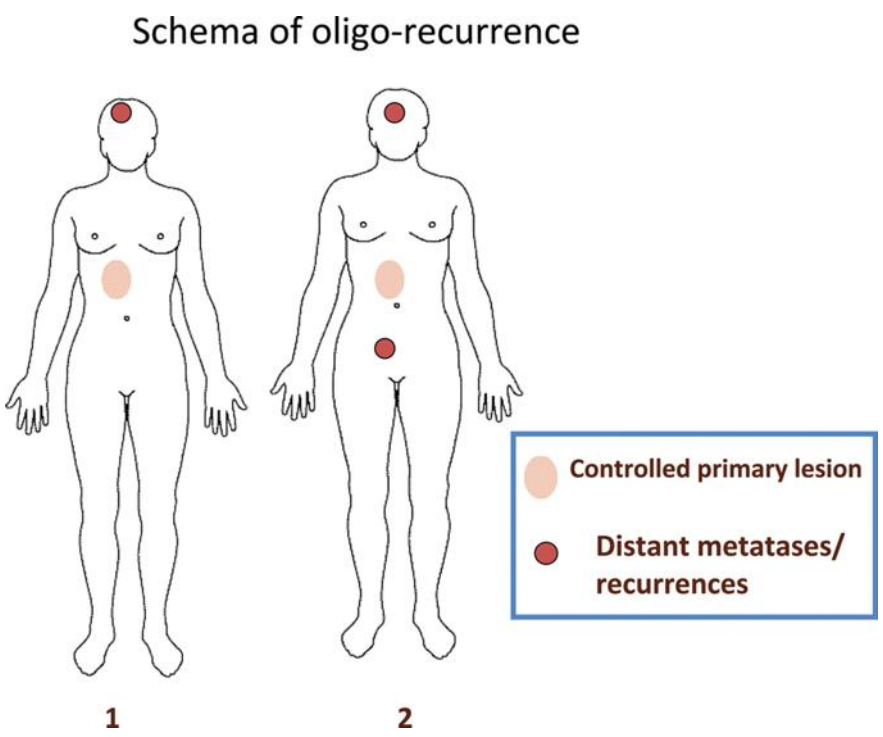
Challenge - High quality translational research

- New targeted therapies require different clinical trials
  - New therapies may be highly TUMOR or PATIENT specific – *need biomarkers*
  - Single attributes (eg hypoxia) or single molecules (EGFR) are targets
  - Benefit limited to specific, perhaps small patient populations

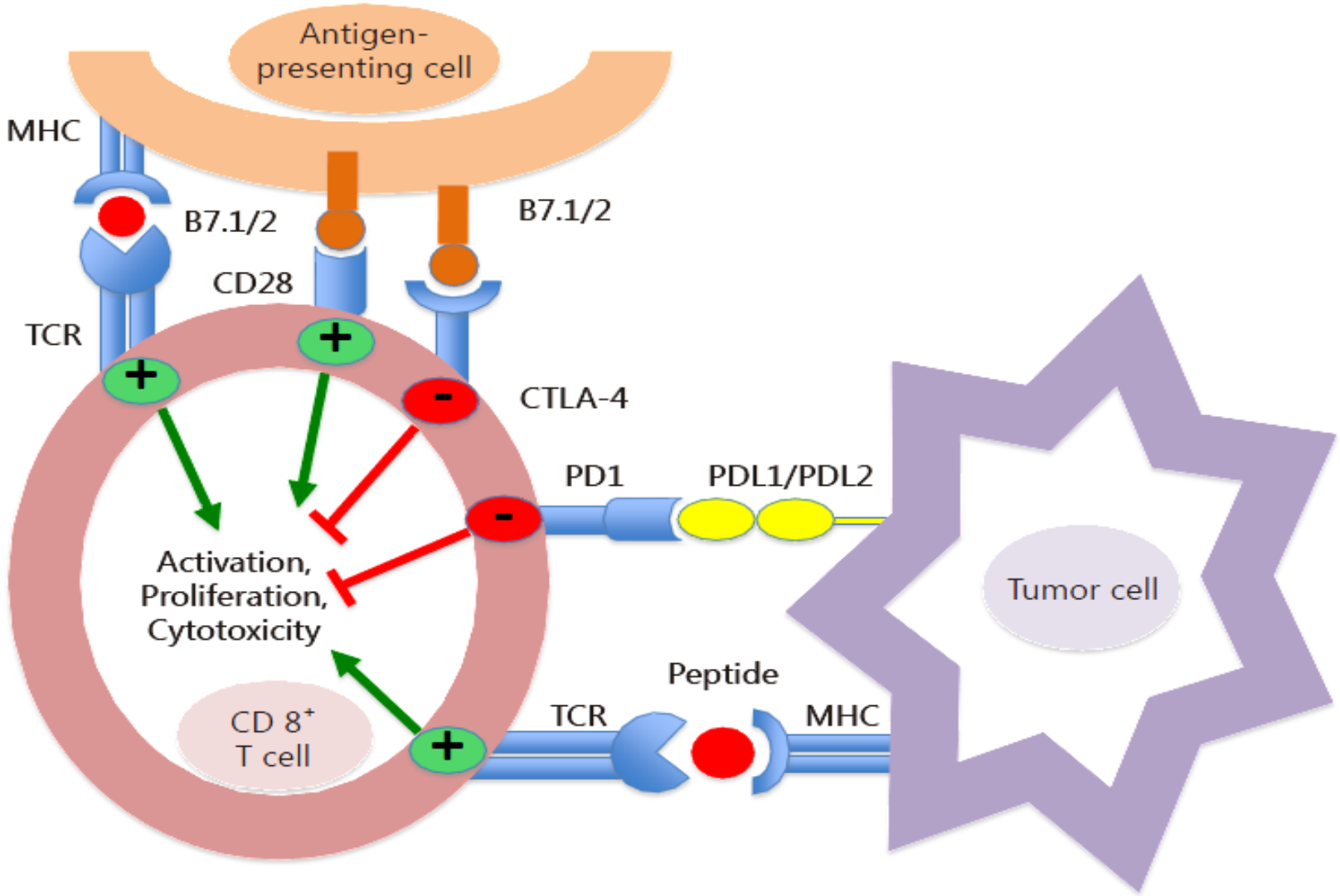
Radiation will become a part of curative systemic therapies

Oligometastases





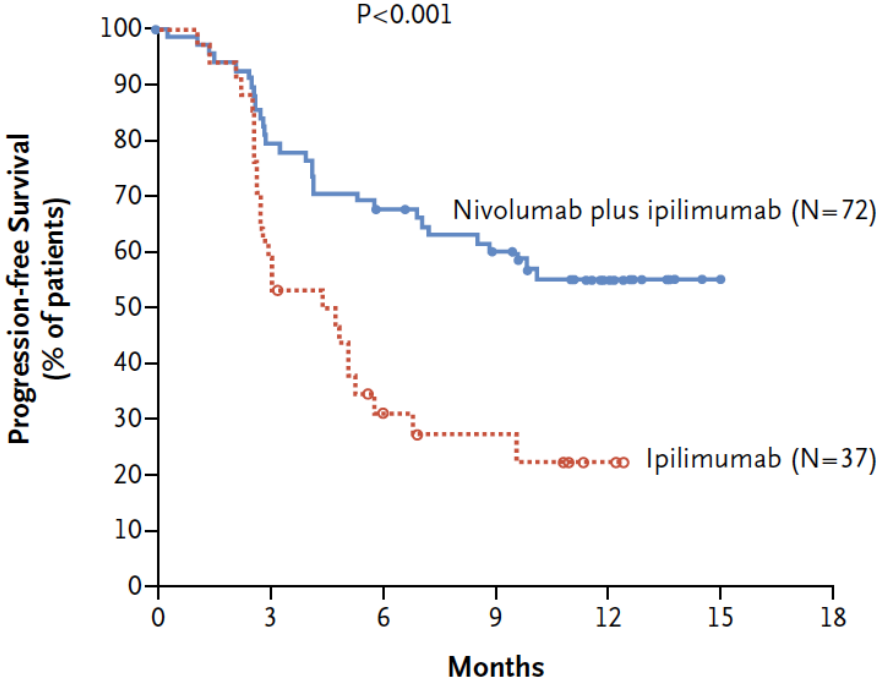
Immune therapies: Blocking CTLA4 and PD1 signaling



Immune therapy

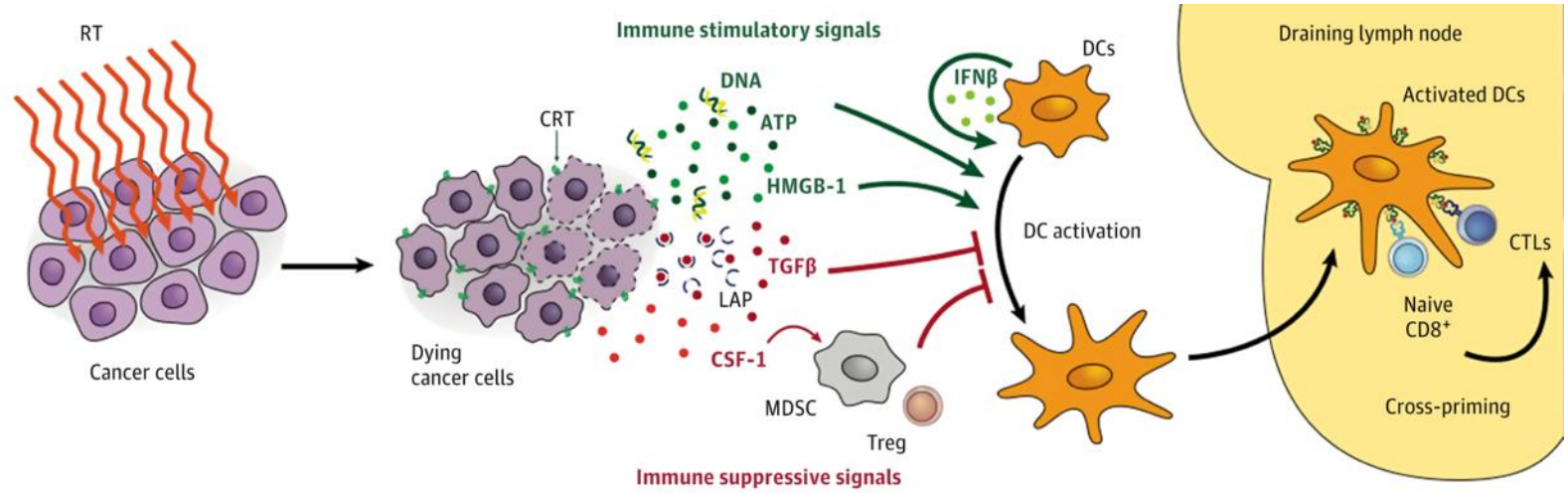
	Death or Disease Progression	Median Progression-free Survival
	no. of patients/total no.	*mo (95% CI)*
Nivolumab plus Ipilimumab	30/72	NR
Ipilimumab	25/37	4.4 (2.8–5.7)

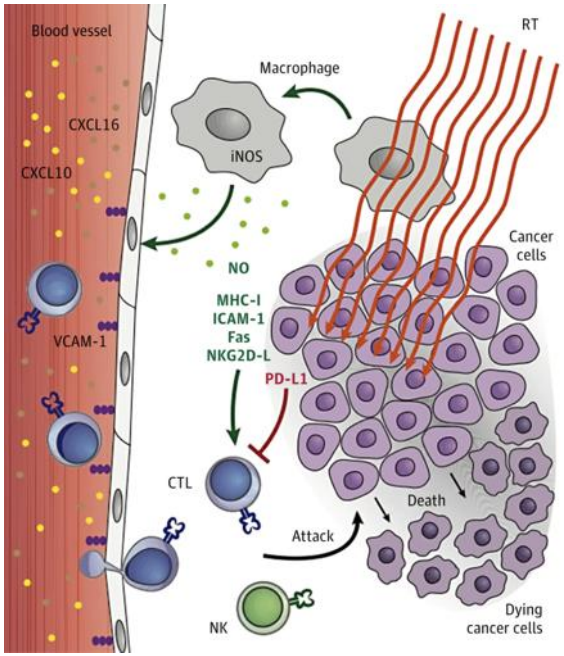
Hazard ratio, 0.40 (95% CI, 0.23–0.68)
P<0.001



No. at Risk							
Nivolumab plus ipilimumab	72	54	45	38	20	1	0
Ipilimumab	37	20	9	6	2	0	0

NEJM - 2015





The total dose and fractionation dose affect these processes in a way that may be distinct from effects on cell survival

•JAMA Oncol. Published online August 13, 2015. doi:10.1001/jamaoncol.2015.2756

Summary

- New biological agents are here and more are coming monthly
- Biological agents can be combined with radiation in a rational way
  - Target something important/different in cancer
  - Target something important for radiotherapy
- Patient selection/individualization will become more important as these agents enter the clinic

Biological response modifiers Clinical

Karin Haustermans

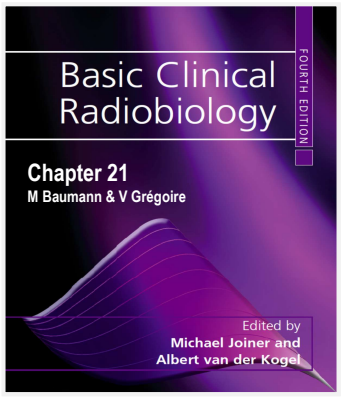
Department of Radiation Oncology, University Hospitals Leuven, Belgium

ESTRO School

1

Overview

- Introduction
- Target driven lethality
  - EGFR inhibitors
- Synthetic lethality
  - DNA-repair inhibitors
- Contextual lethality
  - VEGF inhibitors
  - Vascular disrupting agents
  - Immune activation
- Take home messages



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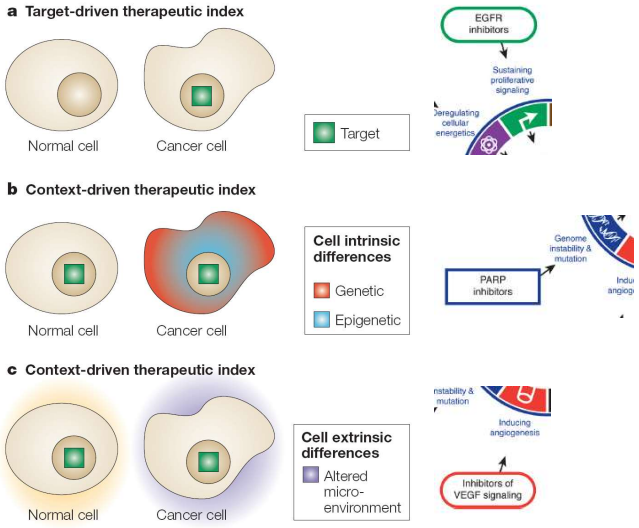
2

Framework

Target driven lethality
(Oncogene addiction)

Synthetic lethality

Contextual synthetic lethality



Kaelin Nat Rev 2005

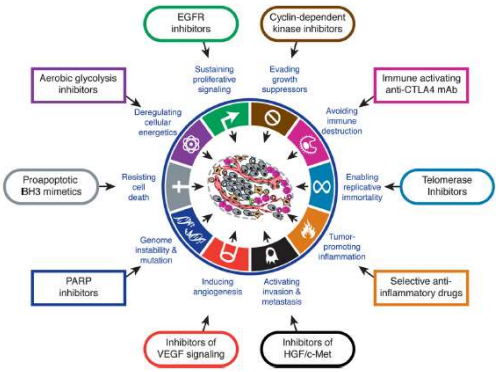
ESTRO School

3

Targeting the hallmarks of cancer

- High specificity
- Low toxicity (different from RT)
- Interaction with RT
  - Radiosensitivity
  - Hypoxia
  - Proliferation
  - Immune activation
- High therapeutic index

Hanahan & Weinberg Cell 2011



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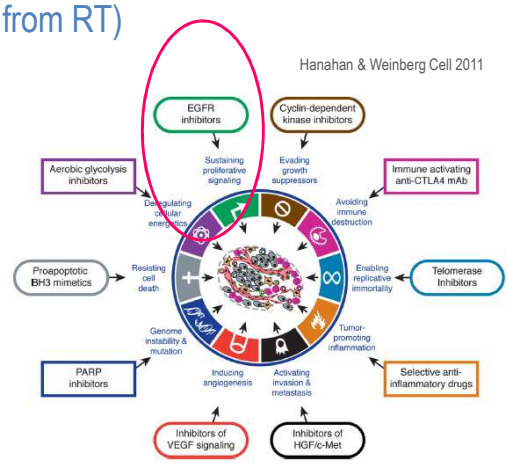
Target driven lethality

ESTRO School

5

Target driven lethality

- High specificity
- Low toxicity (different from RT)
- Interaction with RT
  - Radiosensitivity
  - Hypoxia
  - Proliferation
  - *Immune activation*
- Therapeutic index
  - Target driven
  - Synthetic lethality
  - Contextual lethality



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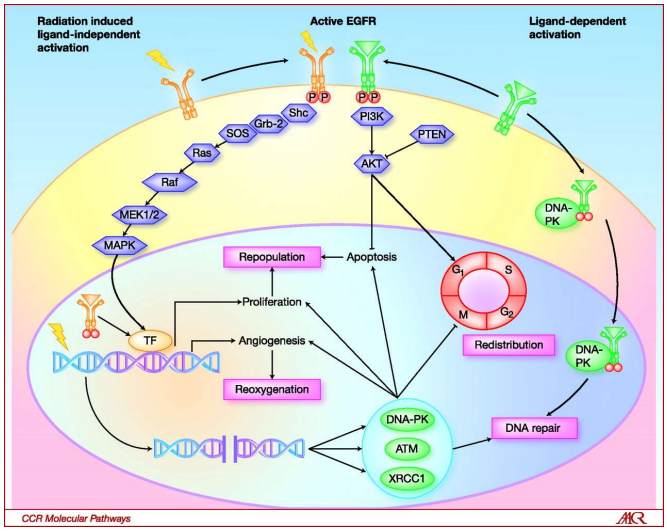
6

EGFR signaling

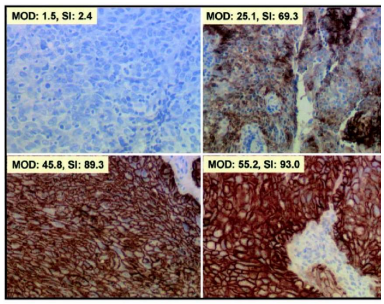


ESTRO School

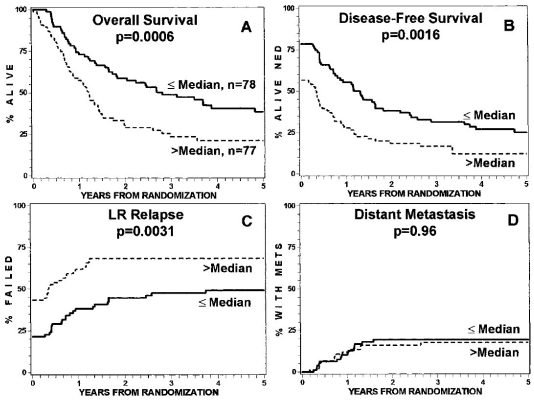
Debucquoy Clin Cancer Res 2010

EGFR expression & prognosis

- Independent prognostic indicator for OS and DFS
  - Conventional radiotherapy, mean absorbance



Large variation in EGFR expression in HNCSCC



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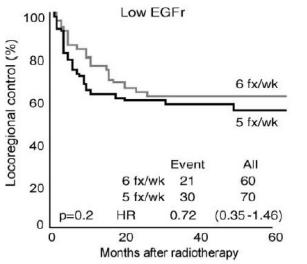
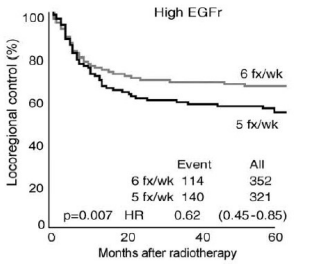
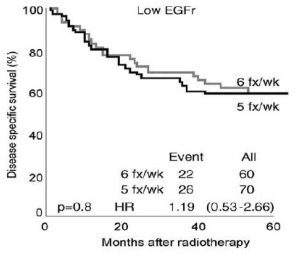
Ang Cancer Res 2002

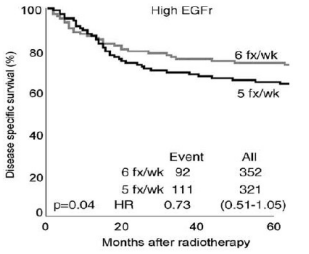
EGFR expression & prognosis





HR 0.62





HR 0.70

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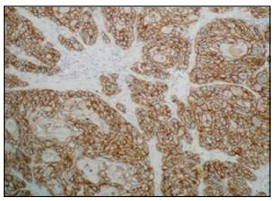
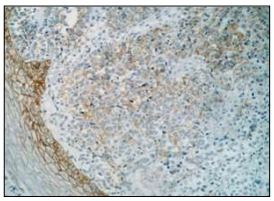
Eriksen Radiother Oncol 2005

EGFR expression & prognosis

- Tumors with high EGFr and well/moderate differentiation did benefit from moderate acceleration of treatment regarding locoregional control, HR 0.54 (0.37-0.78)
- Such an effect was not seen in tumors with low EGFr and/or poor differentiation, HR 0.8 (0.51-1.25).





Eriksen, DAHANCA 6,7

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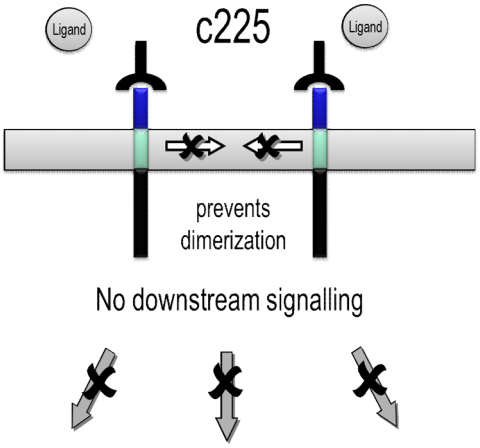
Cetuximab (c225)



Proliferation, DNA repair, angiogenesis

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The landmark trial

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

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Bonner et al NEJM 2006
Bonner Lancet Oncol 2010

Phase III RCT RT ± Cetuximab

Primary tumor site: oropharynx, hypopharynx, larynx

Stratify by

- Karnofsky score: 90-100 vs. 60-80
- Regional Nodes: Negative vs. Positive
- Tumor stage: AJCC T1-3 vs. T4
- RT fractionation: Concomitant boost vs. Once daily vs. Twice daily

RANDOMIZE

Arm 1 (RT)
Radiation therapy

Arm 2 (RT+Cetuximab)
Radiation therapy + Cetuximab, weekly

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Bonner et al NEJM 2006

Study treatment

- Arm 1 – Radiation therapy

Table 1. Radiotherapy Regimens.

Regimen	Total Radiation Dose	Once-Daily Fractions	Twice-Daily Fractions
Once daily	70.0 Gy in 35 fractions	2.0 Gy/fraction; 5 fractions/wk for 7 wk	Not applicable
Twice daily	72.0–76.8 Gy in 60–64 fractions	Not applicable	1.2 Gy/fraction; 10 fractions/wk for 6.0–6.5 wk
Concomitant boost	72.0 Gy in 42 fractions	32.4 Gy; 1.8 Gy/fraction; 5 fractions/wk for 3.6 wk	Morning dose: 21.6 Gy; 1.8 Gy/fraction; 5 fractions/wk for 2.4 wk Afternoon dose: 18.0 Gy; 1.5 Gy/fraction; 5 fractions/wk for 2.4 wk

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Bonner et al NEJM 2006

Study treatment

- Arm 2 – Radiation therapy + Cetuximab
  - Cetuximab
    - Week 1 (no radiation): 400mg/m² IV
    - Week 2-8: 250mg/m² IV followed by radiation *

    *Radiation therapy – cfr. previous slide
- Post-radiation neck dissection
  - Recommended for >N1 neck disease

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Bonner et al NEJM 2006

Randomization

	RT	RT+c225
Patients randomized	N=213	N=211
Stratification factors	(%)	(%)
KPS: 90-100 / 60-80	67 / 33	67 / 33
N-stage: N0 / N+	19 / 81	20 / 80
T-stage: T1-3 / T4	72 / 28	72 / 28
RT fractionation		
Concomitant boost	56	56
Once-a-day	27	26
Twice-a-day	17	18

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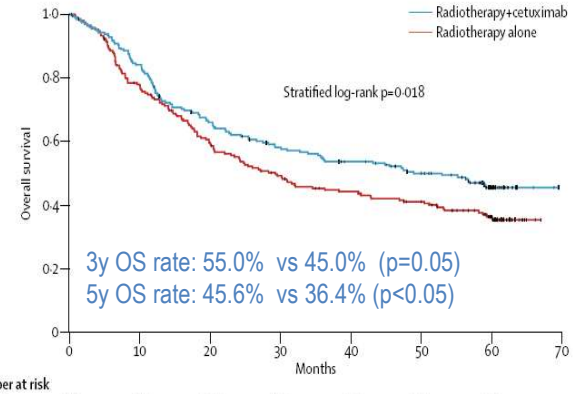
Bonner et al NEJM 2006

Efficacy

- Cetuximab+RT improves OS compared with RT



3y OS rate: 55.0% vs 45.0% (p=0.05)
5y OS rate: 45.6% vs 36.4% (p<0.05)

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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Bonner Lancet Oncol 2010

Adverse events

Adverse Event	Radiotherapy Alone (N = 212)		Radiotherapy plus Cetuximab (N = 208)		P Value†	
	All Grades	Grades 3–5	All Grades	Grades 3–5	All Grades	Grades 3–5
	percent of patients					
Mucositis	94	52	93	56	0.84	0.44
Acneiform rash	10	1	87	17	<0.001	<0.001
Radiation dermatitis	90	18	86	23	0.24	0.27
Weight loss	72	7	84	11	0.005	0.12
Xerostomia	71	3	72	5	0.83	0.32
Dysphagia	63	30	65	26	0.68	0.45
Asthenia	49	5	56	4	0.17	0.64
Nausea	37	2	49	2	0.02	1.00
Constipation	30	5	35	5	0.35	1.00
Taste perversion	28	0	29	0	0.83	—
Vomiting	23	4	29	2	0.18	0.42
Pain	28	7	28	6	1.00	0.84
Anorexia	23	2	27	2	0.26	1.00
Fever	13	1	26	1	0.001	1.00
Pharyngitis	19	4	26	3	0.10	0.80
Dehydration	19	8	25	6	0.16	0.57
Oral candidiasis	22	0	20	0	0.63	—
Coughing	19	0	20	<1	1.00	0.50
Voice alteration	22	0	19	2	0.47	0.06
Diarrhea	13	1	19	2	0.11	0.50
Headache	8	<1	19	<1	0.001	1.00
Pruritus	4	0	16	0	<0.001	
Infusion reaction	2	0	15	3	<0.001	0.01
Insomnia	14	0	15	0	0.89	—
Dyspepsia	9	1	14	0	0.13	0.50
Increased sputum	15	1	13	<1	0.78	0.62
Infection	9	1	13	1	0.28	1.00
Anxiety	9	1	11	<1	0.75	1.00
Chills	5	0	11	0	0.03	—
Anemia	13	6	3	1	<0.001	0.006

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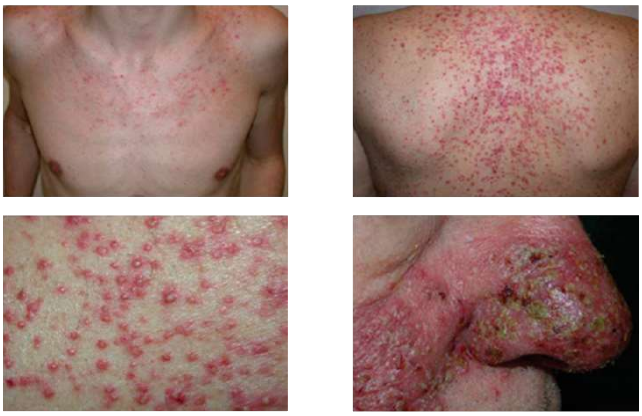
Bonner NEJM 2006

Acneiform rash

- Predictive of response to therapy?



Segaert S Ann Oncol, 2005

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Acneiform rash

- Prominent cetuximab-induced rash ~ better survival

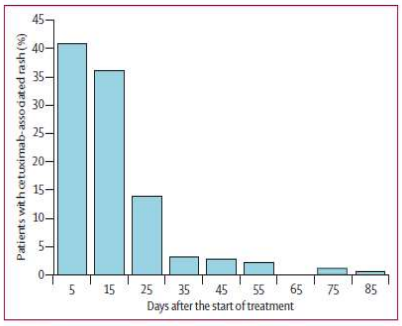

Figure 4: The onset of cetuximab-induced rash following the initiation of first treatment

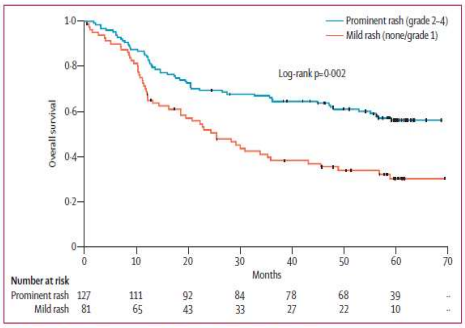

Figure 5: Overall survival by severity of rash in cetuximab-treated patients

Bonner JA, Lancet Oncol 2010

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EGFR inhibition + RCT in HNSCC

- Benefit with chemotherapy?
  - RTOG0522
    - Randomized Phase III
    - Concurrent accelerated radiation and cisplatin vs concurrent accelerated radiation, cisplatin and cetuximab
    - Stage III and IV HNSCC
    - Initial results: Cetuximab did not improve PFS or OS and was associated with higher rates of mucositis and skin reactions.

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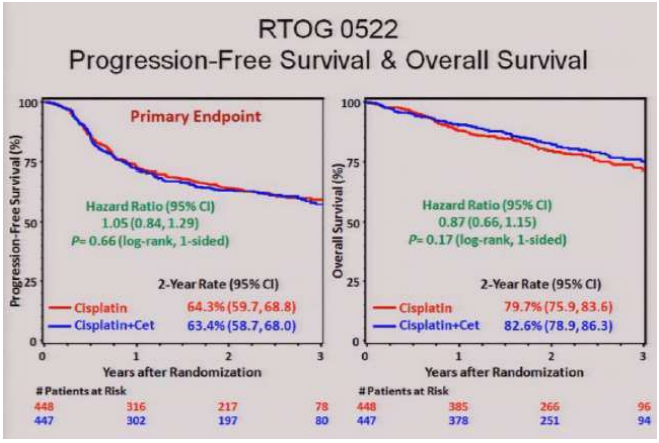
EGFR inhibition + RCT in HNSCC

- Benefit with chemotherapy?



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Ang KK, J Clin Oncol. 2011;29, ASTRO

EGFR inhibition + RCT in HNSCC

- Benefit with chemotherapy?

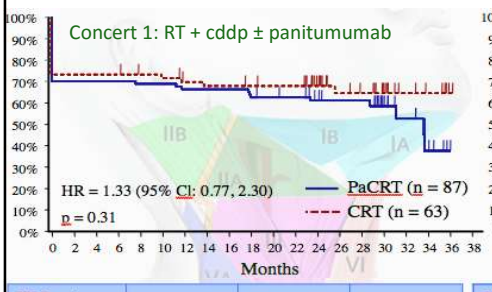
RTOG 0522: Acute Toxicity

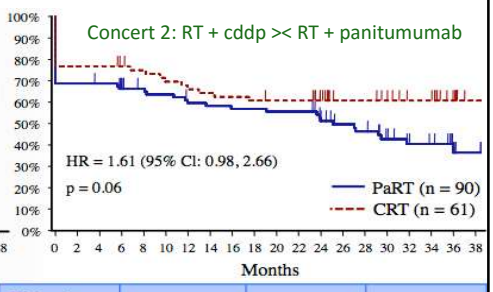
RT + Cisplatin	Cetuximab No (448)	Cetuximab Yes (447)
Mucositis ($P = 0.004$)		
None	126 (28%)	85 (19%)
Grade 1-2	174 (39%)	172 (38%)
Grade 3-4	148 (33%)	190 (43%)
Skin Reactions Outside Portal ($P < 0.001$)		
None	385 (86%)	87 (19%)
Grade 1-2	60 (13%)	273 (61%)
Grade 3-4	3 (1%)	87 (19%)
Skin Reactions Inside Portal ($P < 0.001$)		
None	98 (22%)	104 (23%)
Grade 1-2	285 (64%)	231 (52%)
Grade 3-4	65 (15%)	112 (25%)

Ang KK, J Clin Oncol. 2011;29, ASTRO

Radiotherapy ± cddp ± Panitumumab

Local-Regional Control





KM estimate (95% CI)	CRT	PaCRT	Difference
LRC at 24 months	68% (54%, 78%)	61% (50%, 71%)	-7% (-23%, 9%)

KM estimate (95% CI)	CRT	PaRT	Difference
LRC at 24 months	61% (47% , 72%)	51% (40% , 62%)	-9% (-23% , 9%)

- Oral cavity, oropharynx, hypopharynx and larynx
- Stade III and IV SCC
- IMRT and 3D-CRT

Giralt et al., 2013

EGFR inhibition + RCT in HNSCC

- Benefit with chemotherapy?
  - Initial results
    - Triplet did not improve PFS or OS
    - EGFr inhibition cannot replace CDDP
    - Cetuximab was associated with higher rates of mucositis and skin reactions

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EGFR inhibition + RCT in rectal cancer

- Relatively low pCR in pts receiving cetuximab along with CRT as preop R\ in rectal cancer in phase I/II

Cetuximab, capecitabine, and RT

Machiels Ann Oncol 2007

Table 3. Preoperative T stage compared with pathologic T stage (n = 19)

Preoperative staging[a]	pT (no. of patients)				
	pT0	pT1	pT2	pT3	pT4
T2 (n = 2)	1	0	1	0	0
T3 (n = 29)	1	0	6	21	1
T4 (n = 6)	0	1	2	3	0
Total (n = 37)	2	1	9	24	1

[a]By endorectal ultrasound.

pCR = 5% (2/37)

Cetuximab, capecitabine, oxaliplating and RT

Rödel C Int J Radiat Oncol Biol Phys 2008

Table 4. Pathologic stage for 45 operated patients treated at recommended capecitabine dose level of 1,650 mg/m^2

	Pathologic stage							
Baseline stage	ypT0	ypT1	ypT2	ypT3	ypT4	ypN0	ypN1	ypN2
T3 (n = 39)	4		12	21	2			
T4 (n = 6)			2	3	1			
N– (n = 9)						7	1	1
N+ (n = 36)						21	5	10
Total	4		14	24	3	28	6	11

pCR = 9% (4/45)

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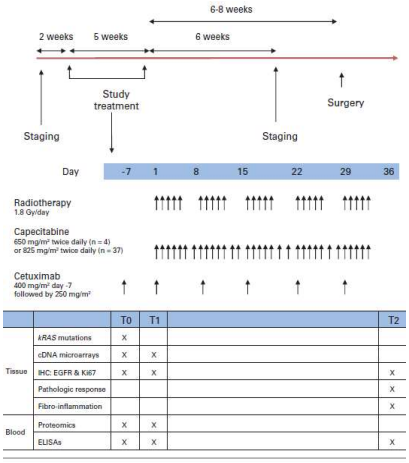
EGFR inhibition + RCT in rectal cancer

- Importance of translational research



		T0	T1		T2
Tissue	*kRAS* mutations	x			
	cDNA microarrays	x	x		
	IHC: EGFR & Ki67	x	x		x
	Pathologic response				x
	Fibro-inflammation				x
Blood	Proteomics	x	x		
	ELISAs	x	x		x

Debucquoy JCO 2009

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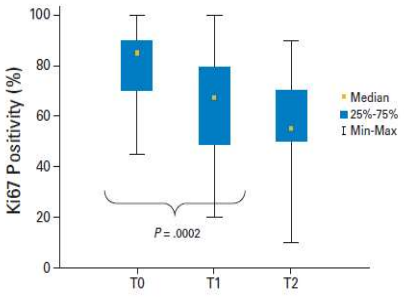
EGFR inhibition + RCT in rectal cancer

- CRT might have been compromised by cetuximab pretreatment
  - Pre-CRT initial dose of cetuximab decreased tumor cell proliferation
  - Capecitabine needs to be taken up by proliferating cells to exert its effects



Debucquoy JCO 2009

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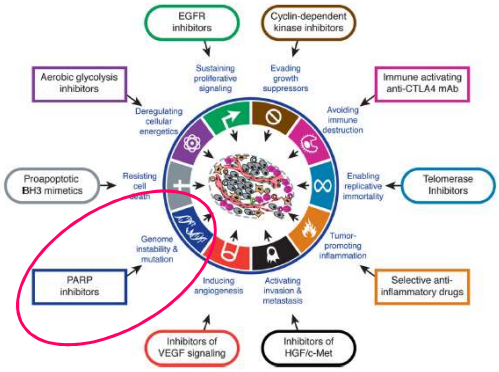
Synthetic lethality

- High specificity
- Low toxicity (different from RT)
- Interaction with RT
  - Radiosensitivity
  - Hypoxia
  - Proliferation
  - Immune activation
- Therapeutic index
  - Target driven
  - Synthetic lethality
  - Contextual lethality

Hanahan & Weinberg Cell 2011



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Gene *X*	Gene *Y*	
+	+	No effect
−	+	No effect
+	−	No effect
−	−	Death

Synthetic lethality

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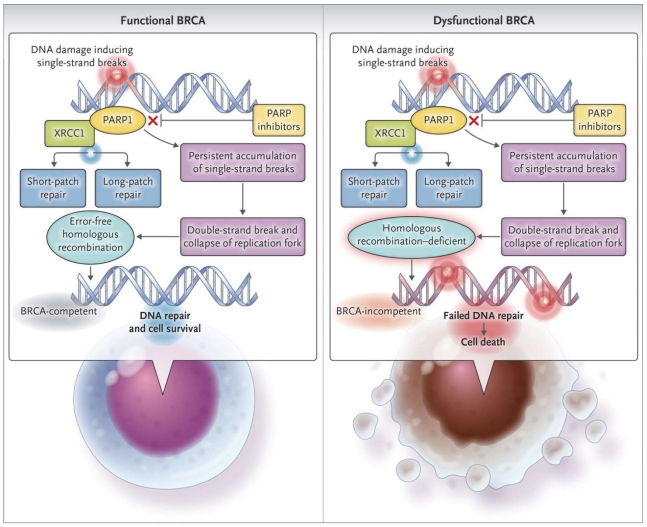
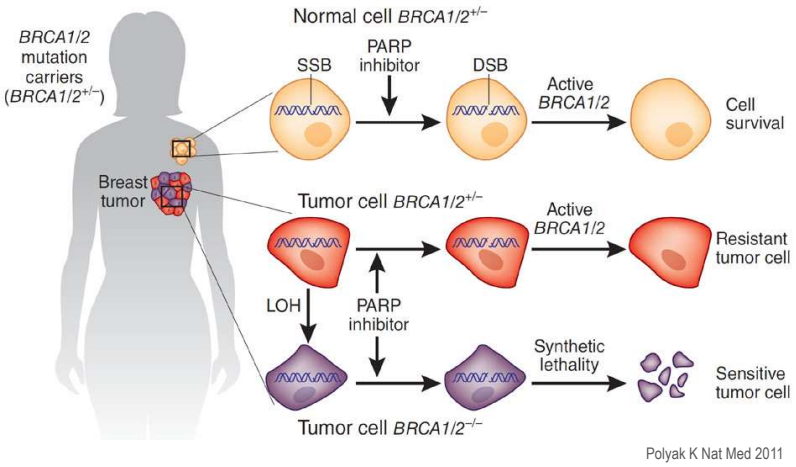
PARP inhibition and BRCA status



McLornan NEJM 2014

PARP inhibition and BRCA status



Polyak K Nat Med 2011

Clinical trials: PARP inhibitors + radiotherapy

- Several ongoing trials (clinical trials.gov)
  - Veliparib With Radiation Therapy in Patients With Inflammatory or Loco-regionally Recurrent Breast Cancer
  - Olaparib and Radiotherapy in Inoperable Breast Cancer
  - Olaparib and Radiotherapy in Inoperable Breast Cancer
  - A Trial Evaluating Concurrent Whole Brain Radiotherapy and Iniparib in Multiple Non Operable Brain Metastases
  - …

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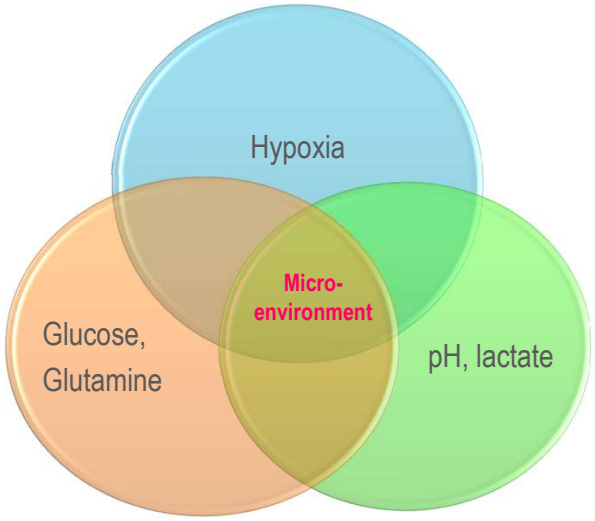

Contextual lethality

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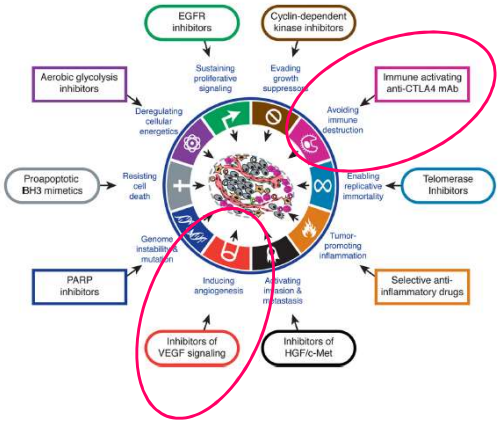
Contextual lethality

- High specificity
- Low toxicity (different from RT)
- Interaction with RT
  - Radiosensitivity
  - Hypoxia
  - Proliferation
- Therapeutic index
  - Target driven
  - Synthetic lethality
  - Contextual lethality
  - Immune modulation

Hanahan & Weinberg Cell 2011



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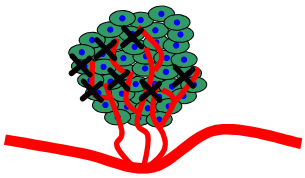
Tumor vasculature as a target

- Angiogenesis inhibiting agents
  - Target angiogenesis process
  - E.g. bevacizumab



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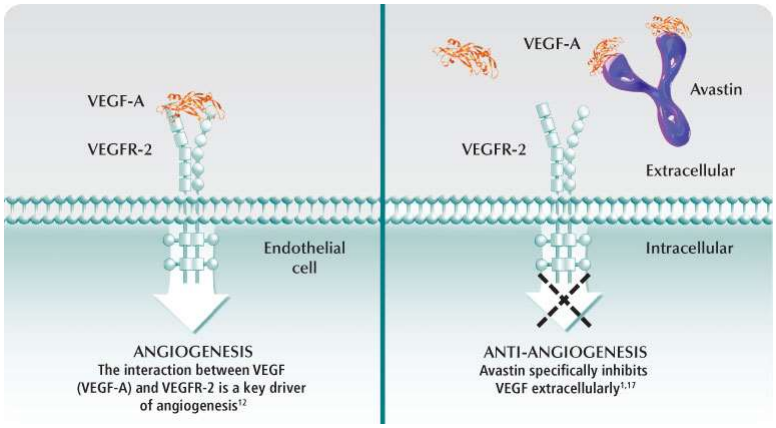
Bevacizumab

- Chimeric monoclonal antibody that targets VEGF



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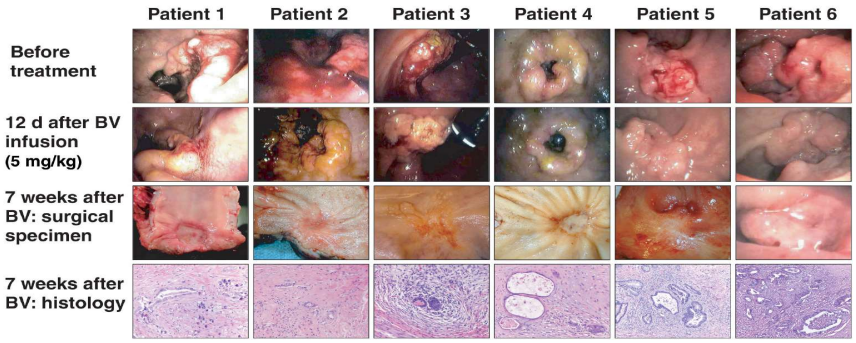
Neo-adjuvant BV in rectal cancer

- Landmark trial: Phase I study results in 6 LARC pts



Bevacizumab 5 mg/kg

Willett Nat Med 2004
Willett CG,J Clin Oncol 2005

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BV in (neo-)adjuvant setting: overview

- A review of trials of bevacizumab in CRT schedules showed a pooled pCR rate of 19.6% with up to 36% post-op wound complications
- No definitive signal of improved efficacy (lack of phase III)
- Long-term outcomes (DFS, OS) might be better influenced by intensification of adjuvant thx

Glynne-Jones J Gastrointest Oncol 2013

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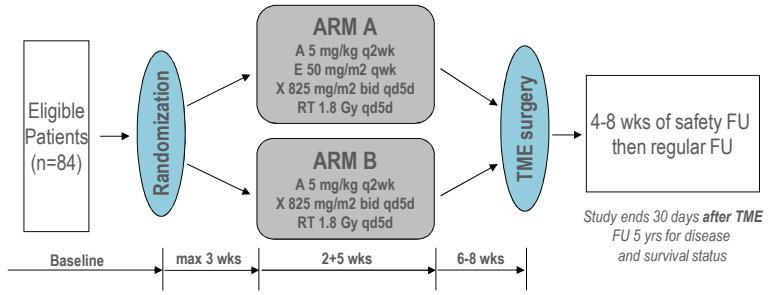
AXEBeam study

- Study design



PRIMARY ENDPOINT

- Pathological complete response rate (pCR) > 20% (8/40) in Arm A

SECONDARY ENDPOINTS

- R0 and negative CRM resection rate
- Surgical complication rate at 1 mth
- Toxicity (CTCAE version 3.0)
- Recurrence rates at 3 and 5 yrs
- DFS and OS at 3 and 5 yrs

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AXEBeam study

- Primary endpoint

Dworak TRG	Arm A AXE+RT	Arm B AX+RT	Total
	N=43 *(%)*	N=41 *(%)*	N=84 *(%)*
0	1 *(2)*	4 *(10)*	5 *(6)*
1	4 *(9)*	6 *(15)*	10 *(12)*
2	7 *(16)*	14 *(34)*	21 *(25)*
3	15 *(35)*	12 *(29)*	27 *(32)*
4 (pCR)	14 *(33)*	4 *(10)*	18 *(21)*
N/A	2 *(5)*	1 *(2)*	3 *(4)*
Total	43	41	84

Main endpoint reached:
ypCR rate in Arm A 33%

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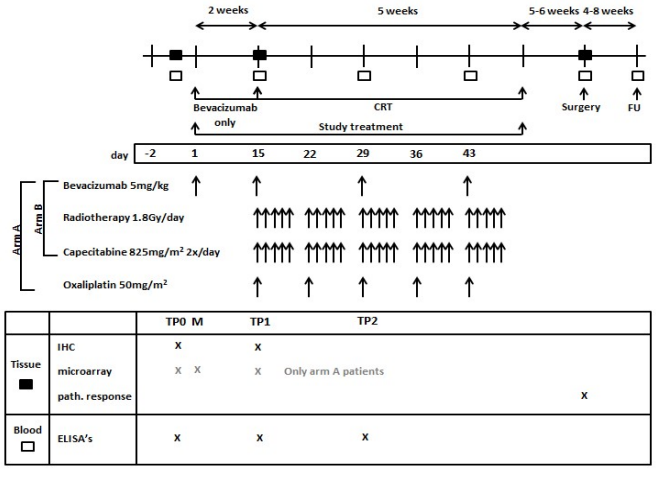
AXEBeam study

- Translational research



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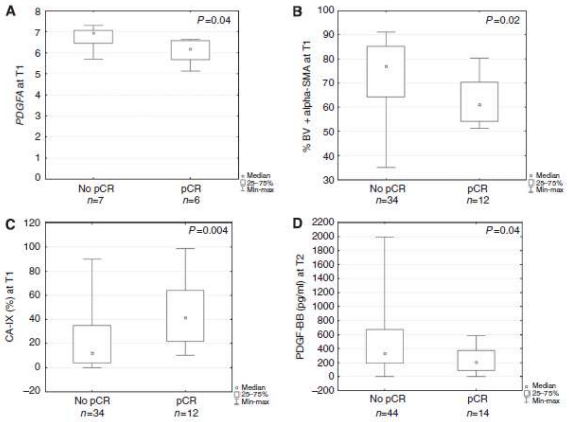
AxeBeam study: biomarkers



Verstraete et al, Br J Cancer. 2015

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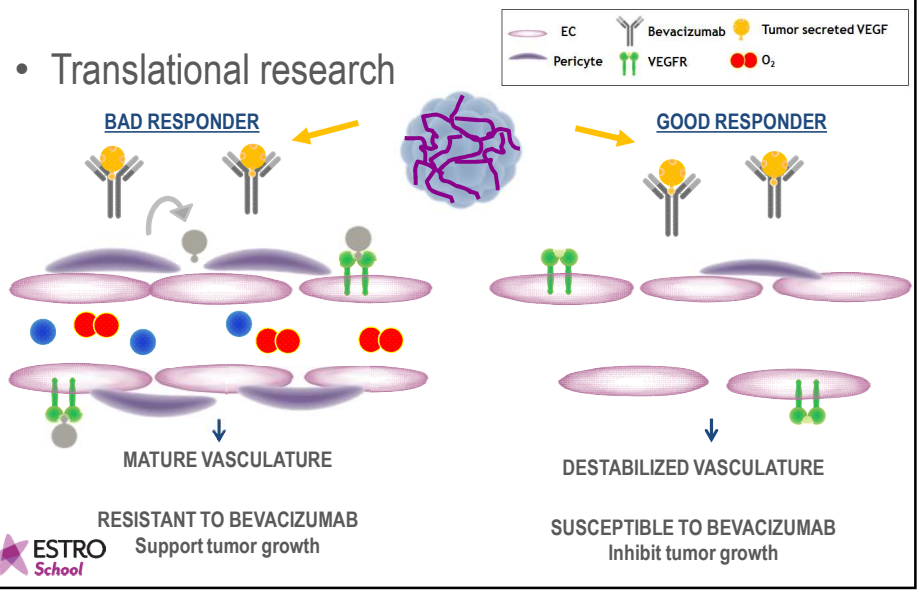
AXEBeam study

- Translational research



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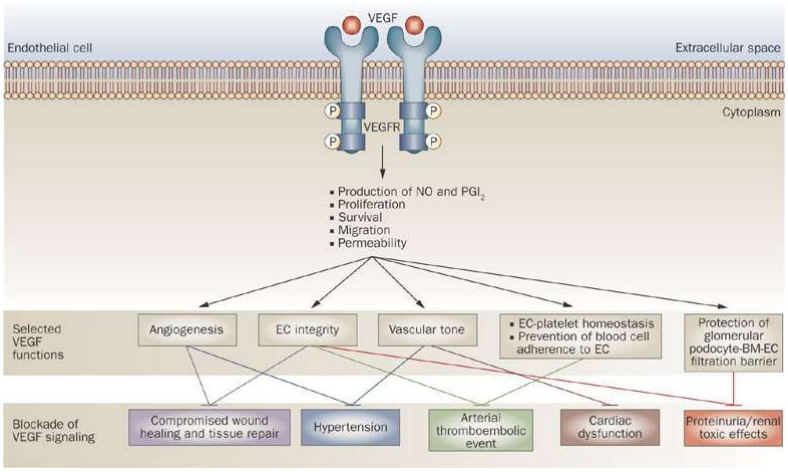
Toxicity



Chen & Cleck Nat Rev Clin Oncol 2009

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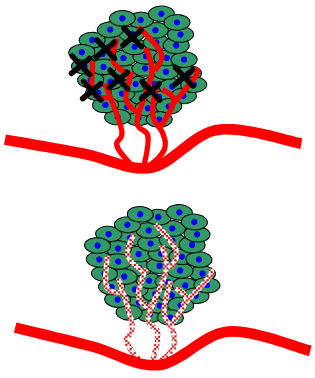
Tumor vasculature as a target

- Angiogenesis inhibiting agents
  - Target angiogenesis process
- Vascular disrupting agents
  - Damage tumor blood vessels
  - Affect blood flow



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Vascular disrupting agents

- Working mechanisms
  - Selective shut-down of established tumor blood supply
  - Selectivity for tumor over normal vessels
  - Interrupt blood flow to tumor
  - Induction of hemorrhage
  - Necrosis (due to oxygen and nutrient starvation)
- Examples
  - Flavone acetic acid family, combrestatins, arsenic trioxide, colchicine derivates,...

Tozer GM Nat Rev Cancer 2005

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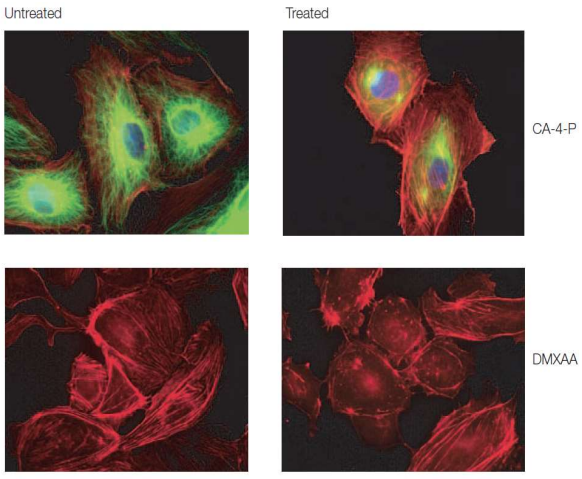
Vascular disrupting agents



Tozer GM Nat Rev Cancer 2005

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Combretastatin-A4-phosphate + RT

- Phase Ib trial in pts with NSCLC, PCa and HNSCC
  - Materials & Methods
    - Radiotherapy

	NSCLC	PCa	HNSCC
RT	27Gy in 6fx, twice daily over 3 weeks	55Gy in 20fx over 4 weeks	66Gy in 33fx over 6 weeks

    - CA4P:
      - dose-escalation from 50mg/m² to 63mg/m²
      - CA4P exposure increased from one to three to six doses
    - Patients with HNSCC received cetuximab in addition
  - Results: RT with CA4P appears well tolerated in most patients. The combination of CA4P, cetuximab and RT needs further study before it can be recommended for clinical studies.

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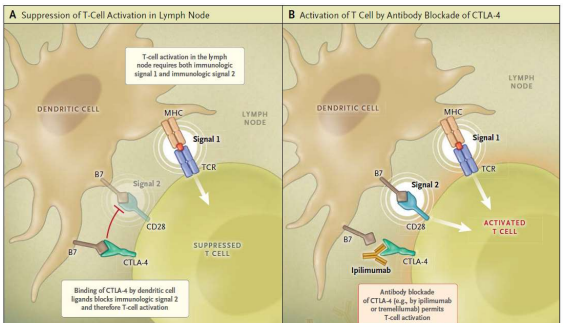
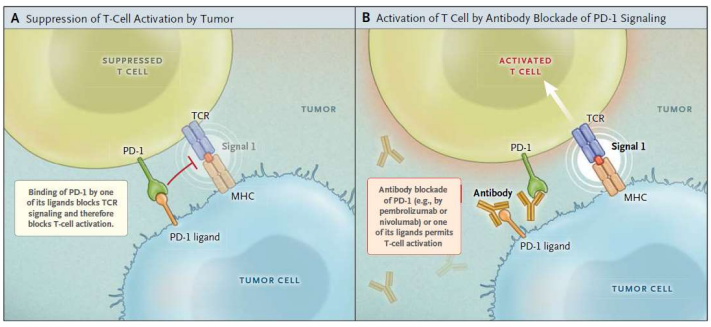
Ng Ann Oncol 2012





Ribas, NEJM 2015

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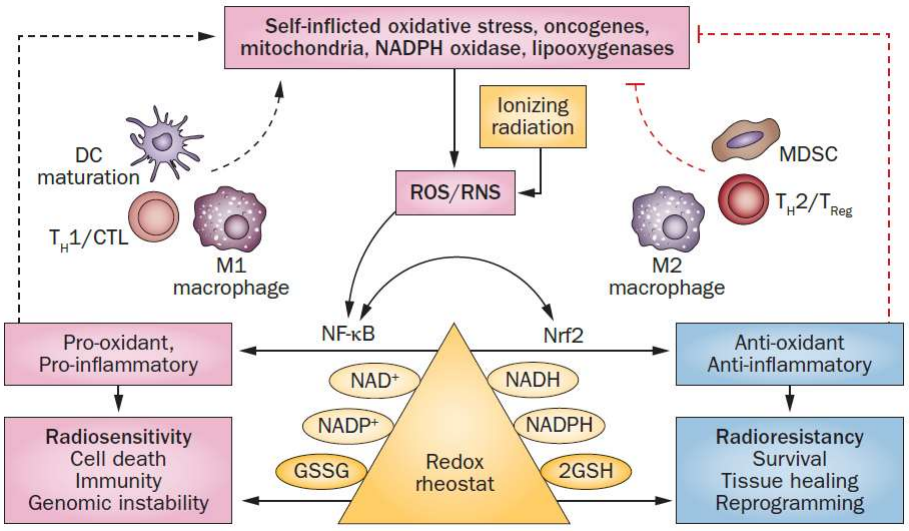

Dörthe Schaue and William H. McBride, Nature 2015

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Rationale for combination with anti-PD-L1 Ab

- Radio(chemo)-immunotherapy: the focused beam expands: **works with various solid tumors**

Local radiotherapy and granulocyte-macrophage colony-stimulating factor to generate abscopal responses in patients with metastatic solid tumours: a proof-of-principle trial

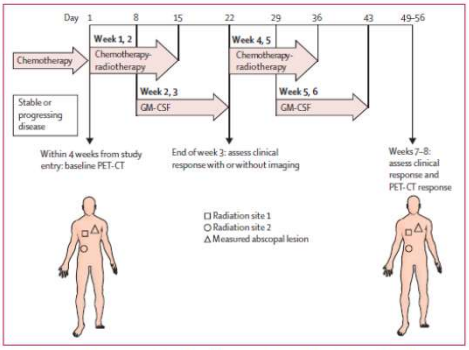
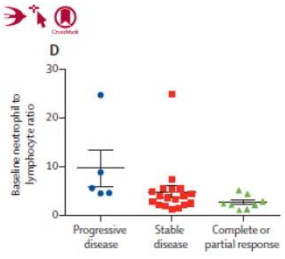


Figure 1: Treatment and assessment schema for induction and determination of abscopal responses



In Golden and colleagues' study,[5] the combination of granulocyte-macrophage colony-stimulating factor (GM-CSF) with radiochemotherapy resulted in abscopal responses in four (22%) of 18 patients with non-small-cell lung cancer and five (36%) of 14 patients with breast cancer. These findings emphasise that systemic anti-tumour immunity can be induced by rendering the tumour cells immunogenic. Radiotherapy alone

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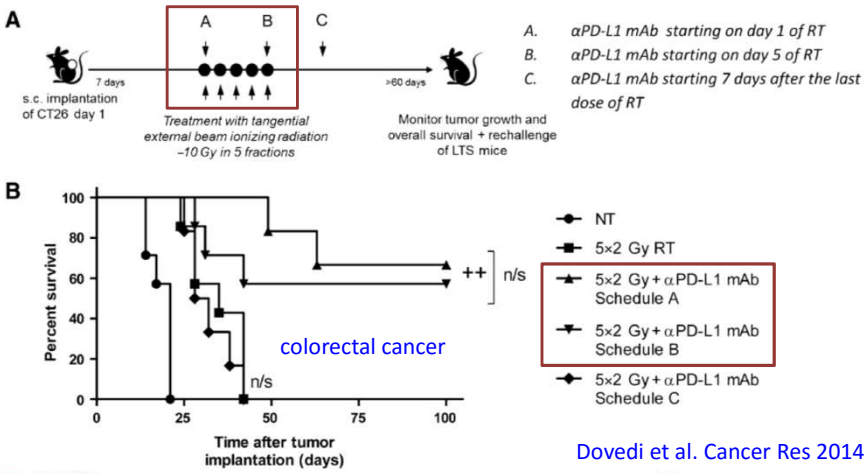
Golden et al., Lancet Oncology, 2015 and Frey, Gaipl, Lancet Oncology

Rationale for combination with anti-PD-L1 Ab

- Dosing schedule is critical for outcome of combined radio-immunotherapy – **concurrently is beneficial**



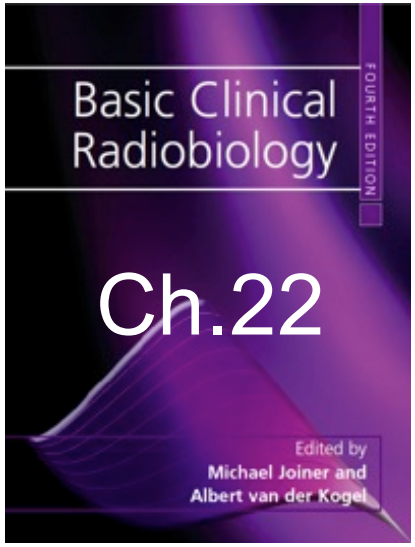
Dovedi et al. Cancer Res 2014

Take home messages

- Numerous trials in progress combining RT + targeted agents
- Challenges
  - Bridge between preclinical and clinical models (tumor growth delay vs tumor control (TCD_{50}))
  - Translational research
    - Biomarkers
  - Trial design – patient stratification
  - New toxicities – late effects

Biological modifiers of normal tissue effects

Rob Coppes
Departments of Radiation Oncology & Cell Biology
University Medical Center Groningen,
University of Groningen,
The Netherlands



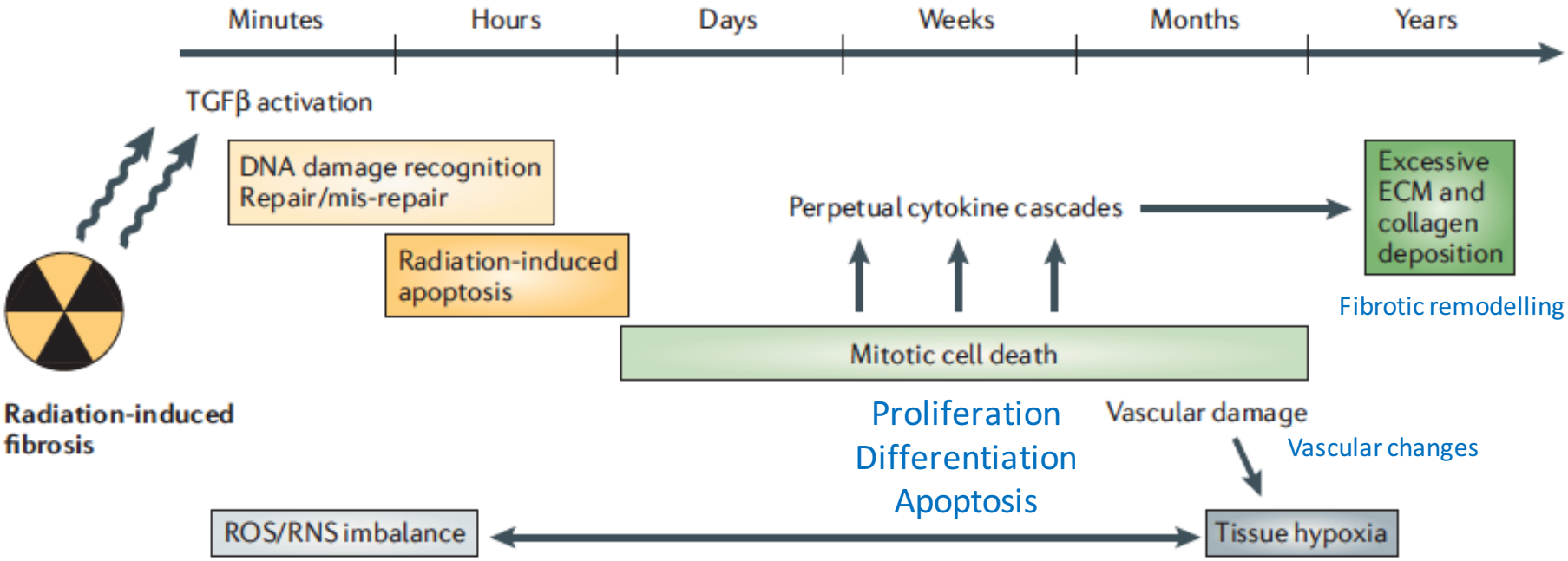
many thanks to Wolfgang Dörr for his slides

Cancer Research Center Groningen

ESTRO School

umcg

Mechanism of normal tissue damage

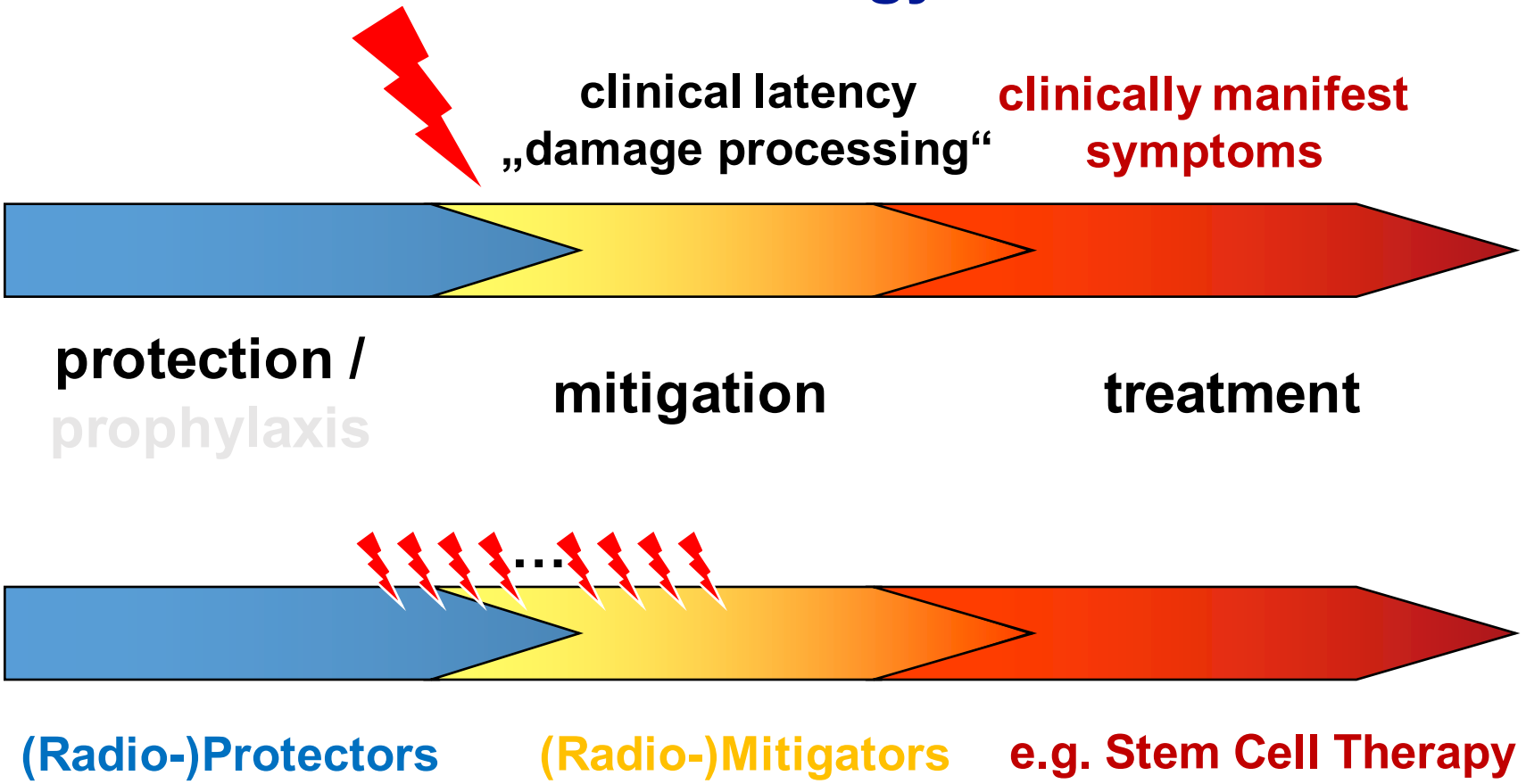


Bentzen Nature Review Cancer 2006

Parenchymal changes

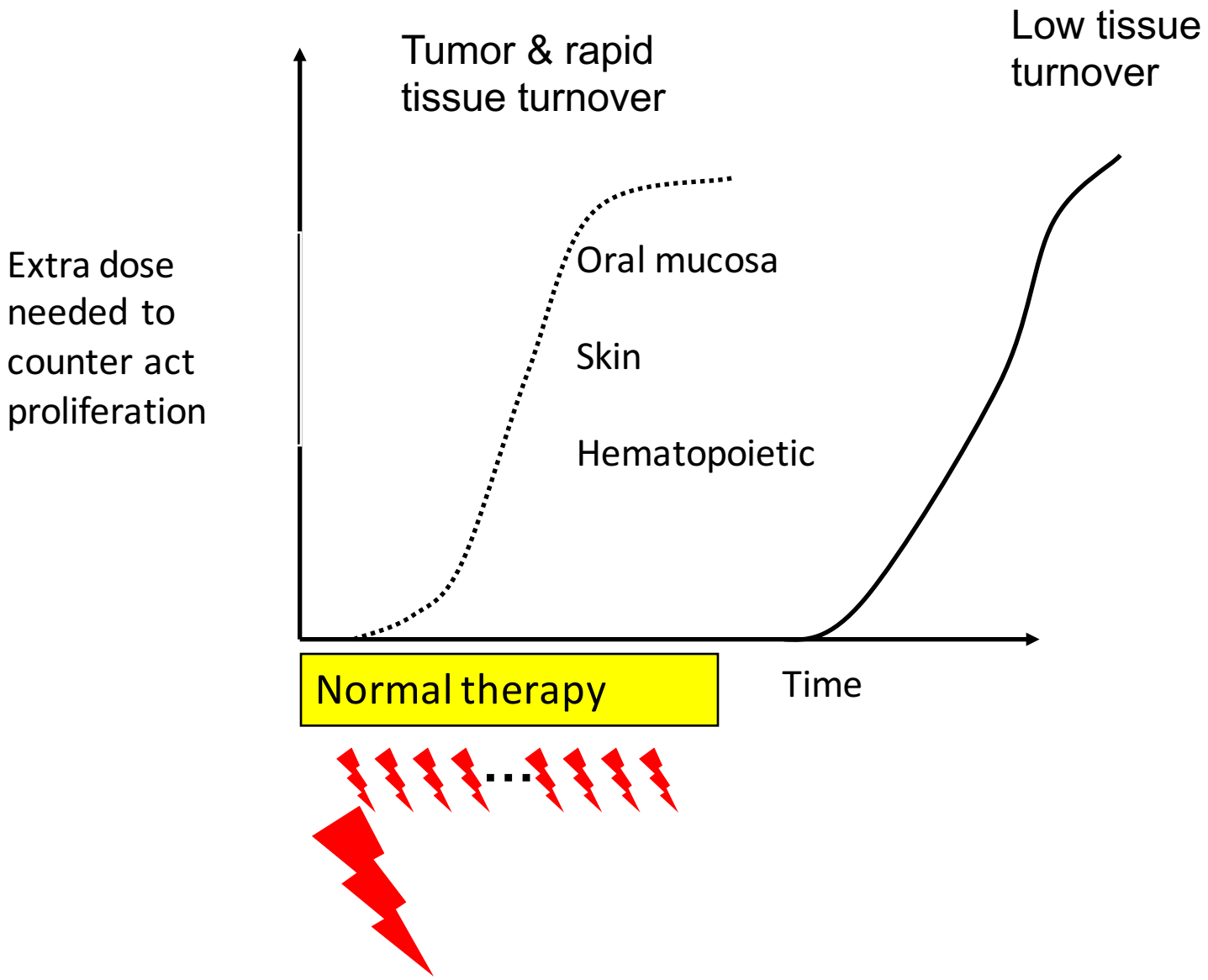
Transcription factors
Signaling chains
Inflammatory response

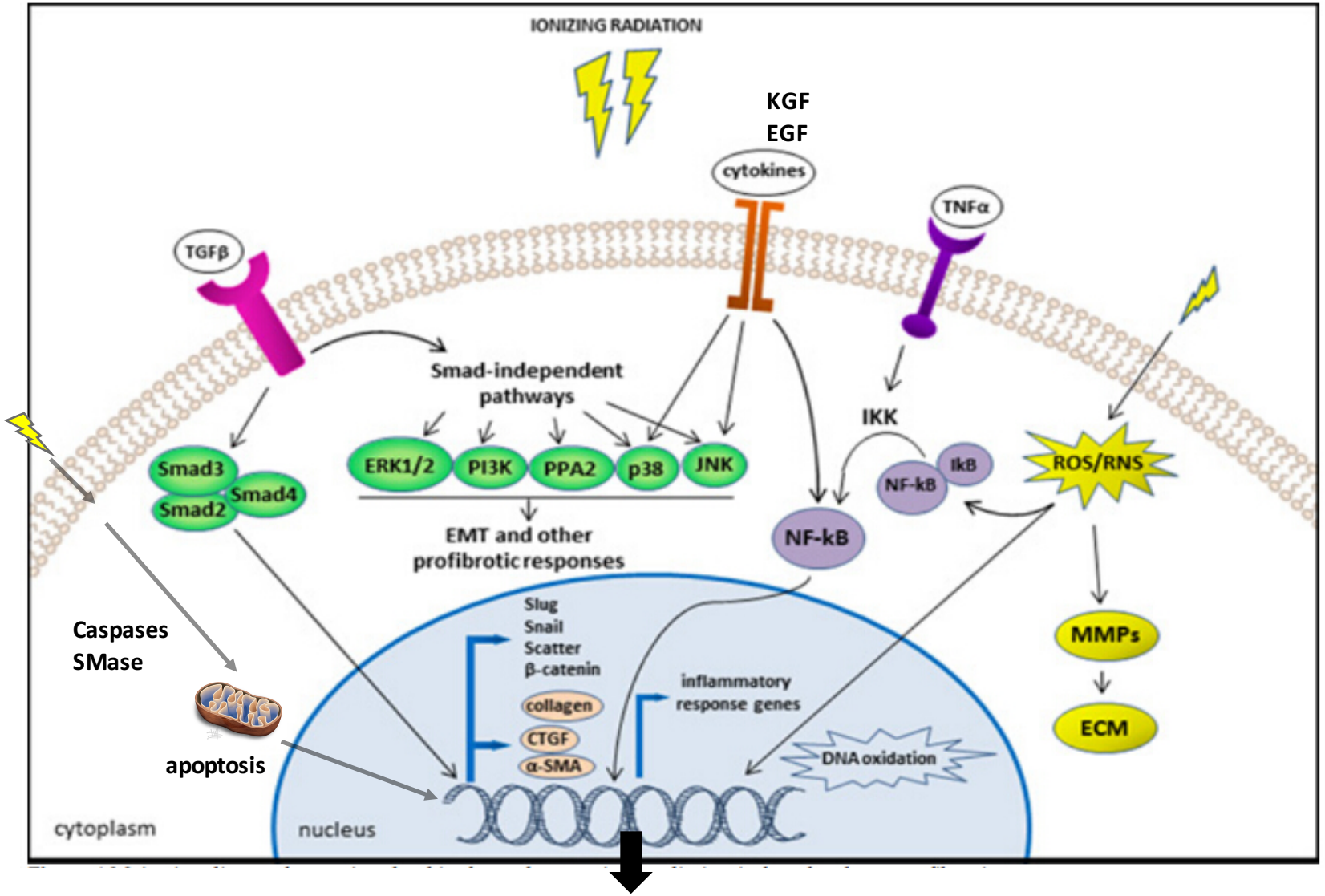
Terminology



Stone et al., Radiat. Res. 2001 (NCI Workshop Report)
Coleman et al., Radiat. Res. (2003)

Mechanism of normal tissue damage

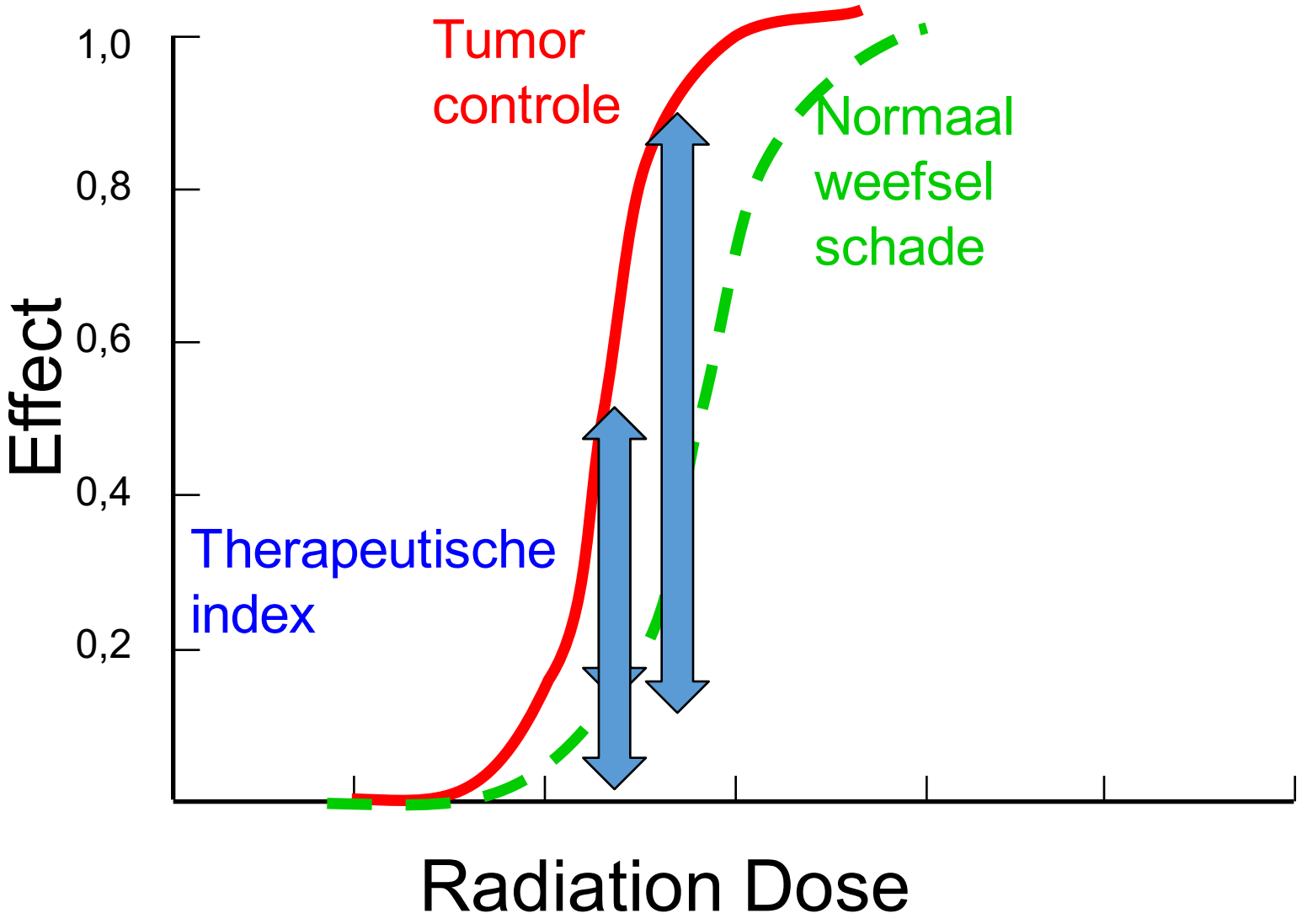




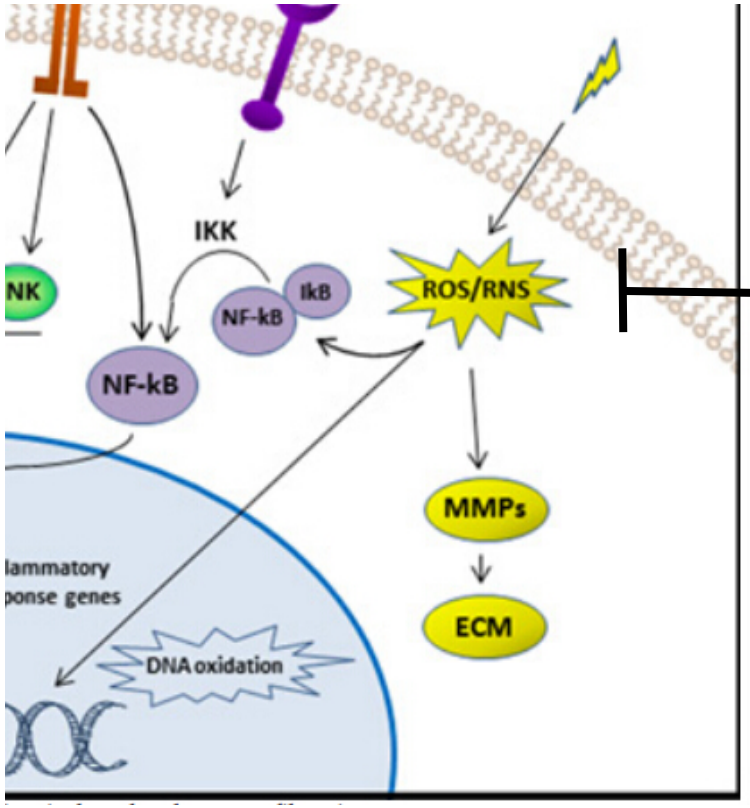
Proliferation
Differentiation
Senescence
Apoptosis
Inflammation

Adapted from Mariangela et al., 2015

Optimizing radiation oncology



Radical scavenging/detoxification



- **Superoxide dismutase**
- **Amifostine**
- **Selenium**

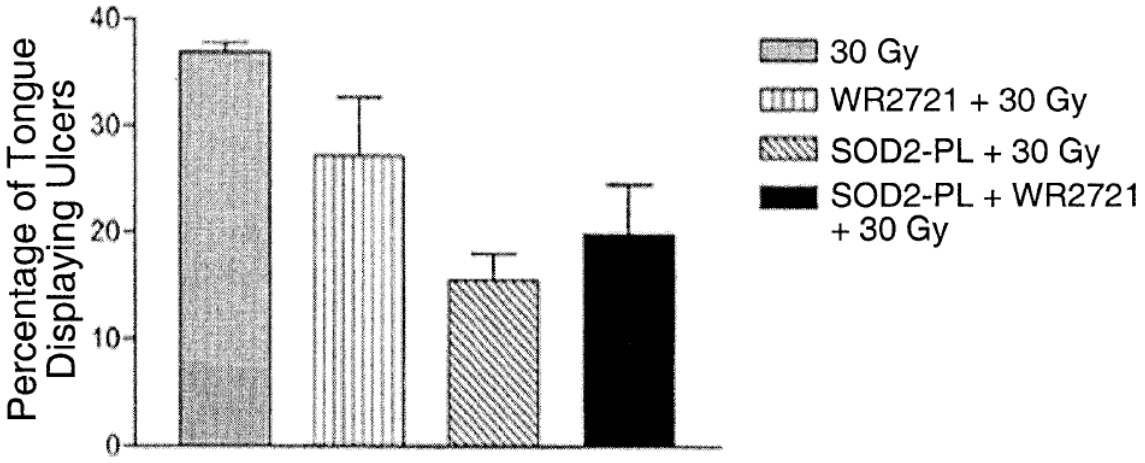
Endogenous: increase MnSOD production in cells

Exogenous: Add radical scavengers

Radical scavenging/detoxification

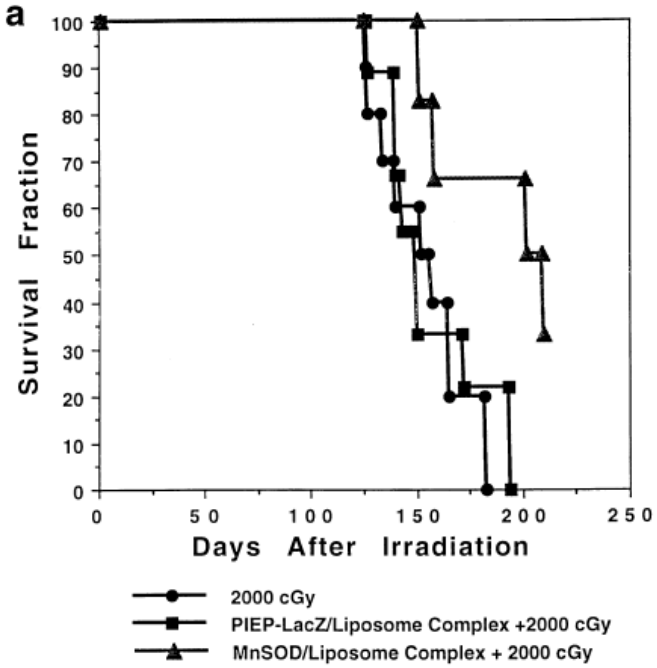
Mn-SOD gene therapy

Mouse mucosa, day 5 post irr.



Guo et al., Radiat. Res. (2003)

Lung

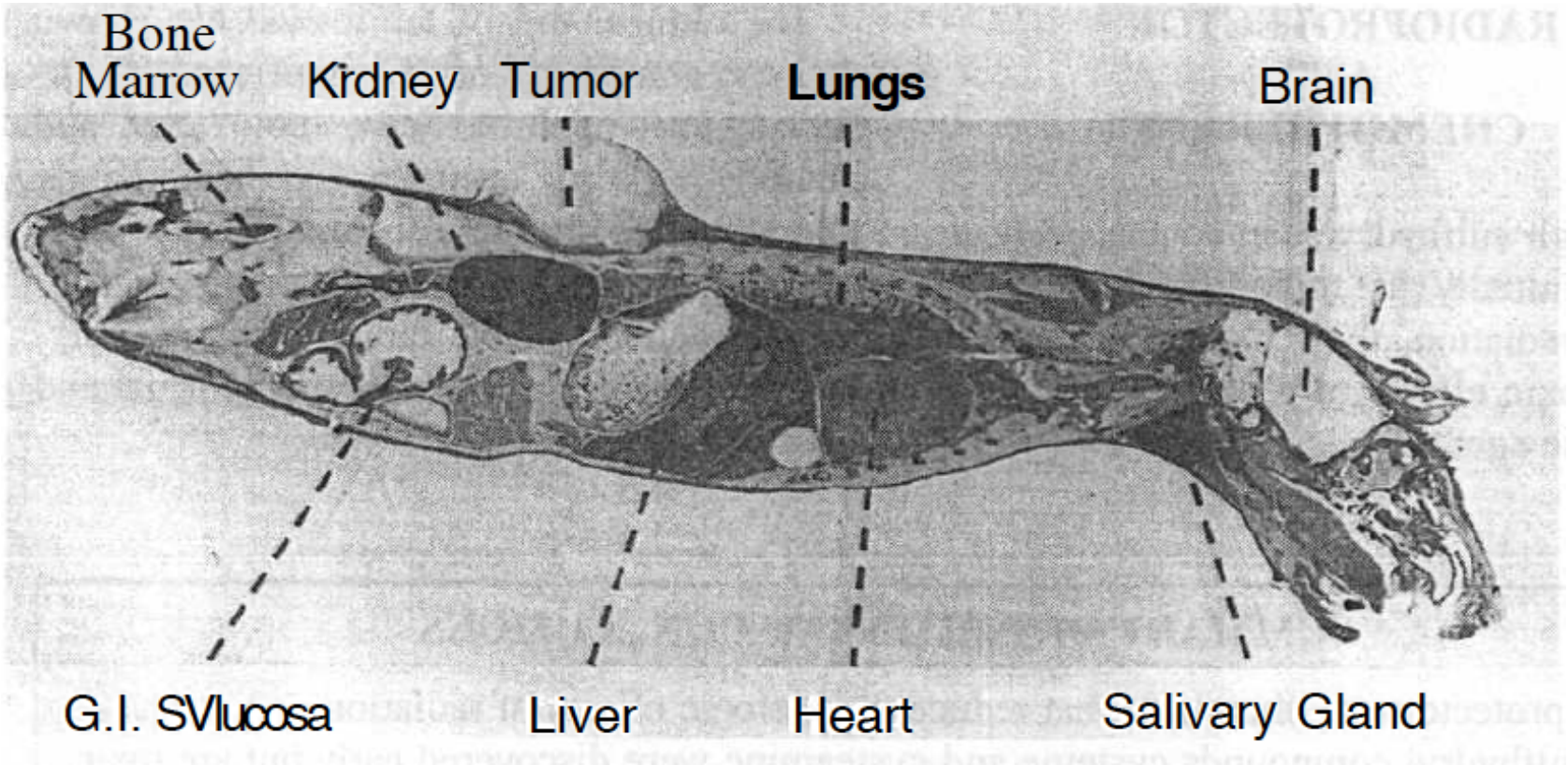


Epperly et al 1998

Radical scavenging/detoxification

Distribution

Amifostine

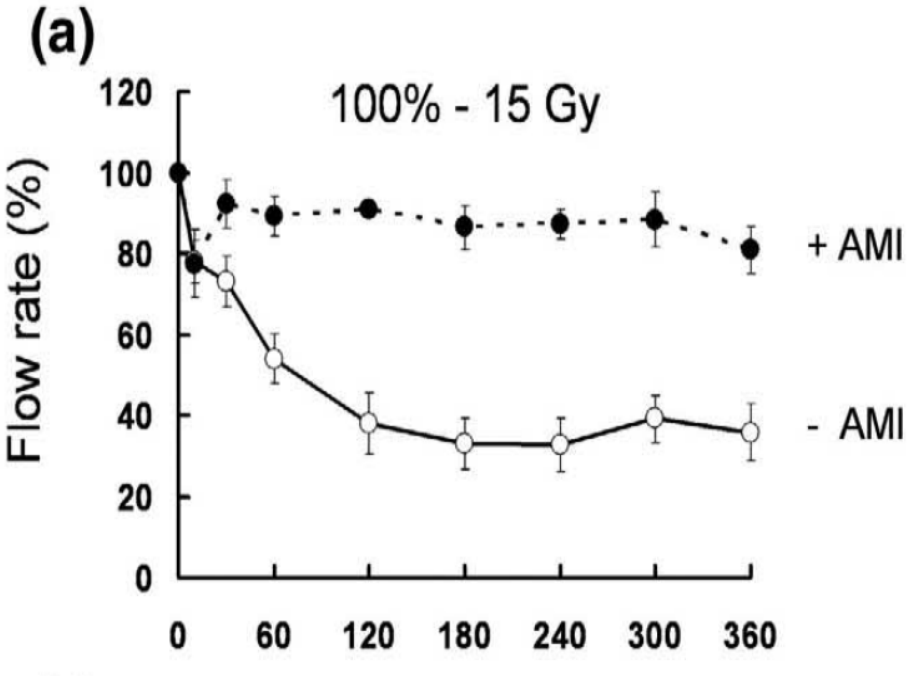


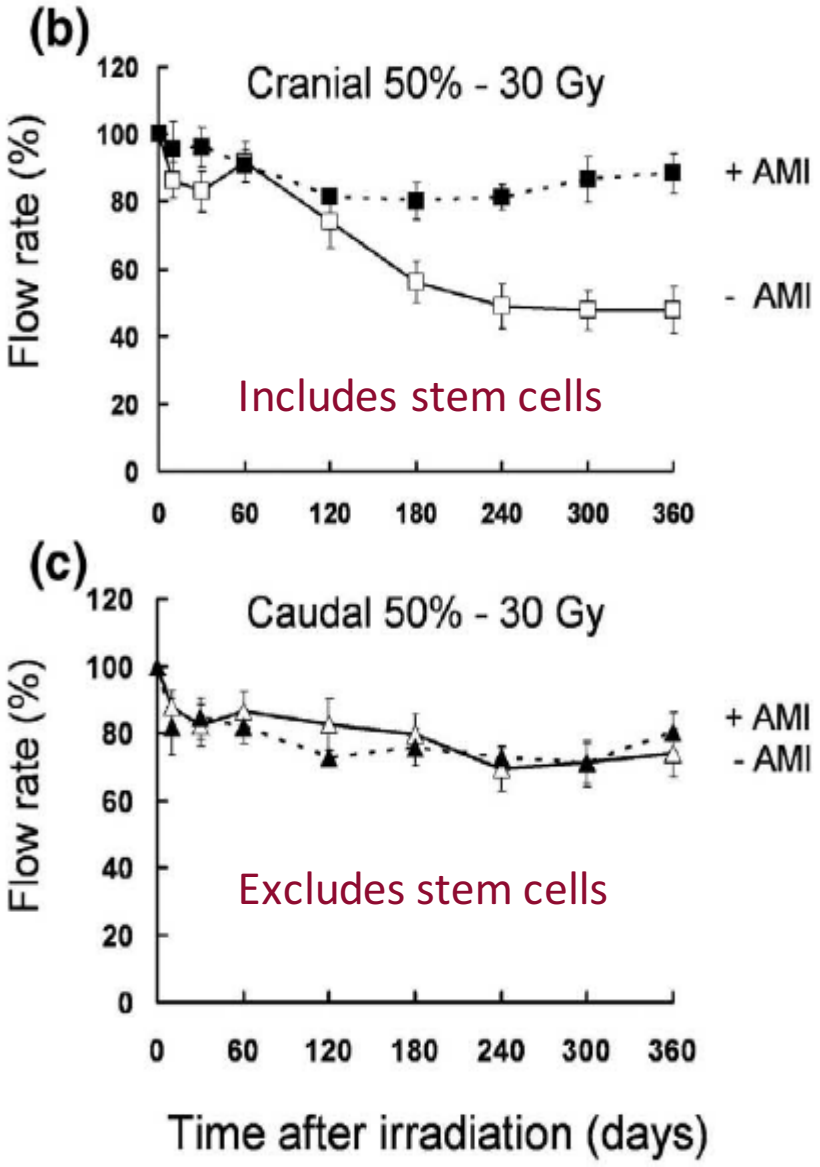
Utley et al. Rad Res 1976

Radical scavenging/detoxification

Salivary glands

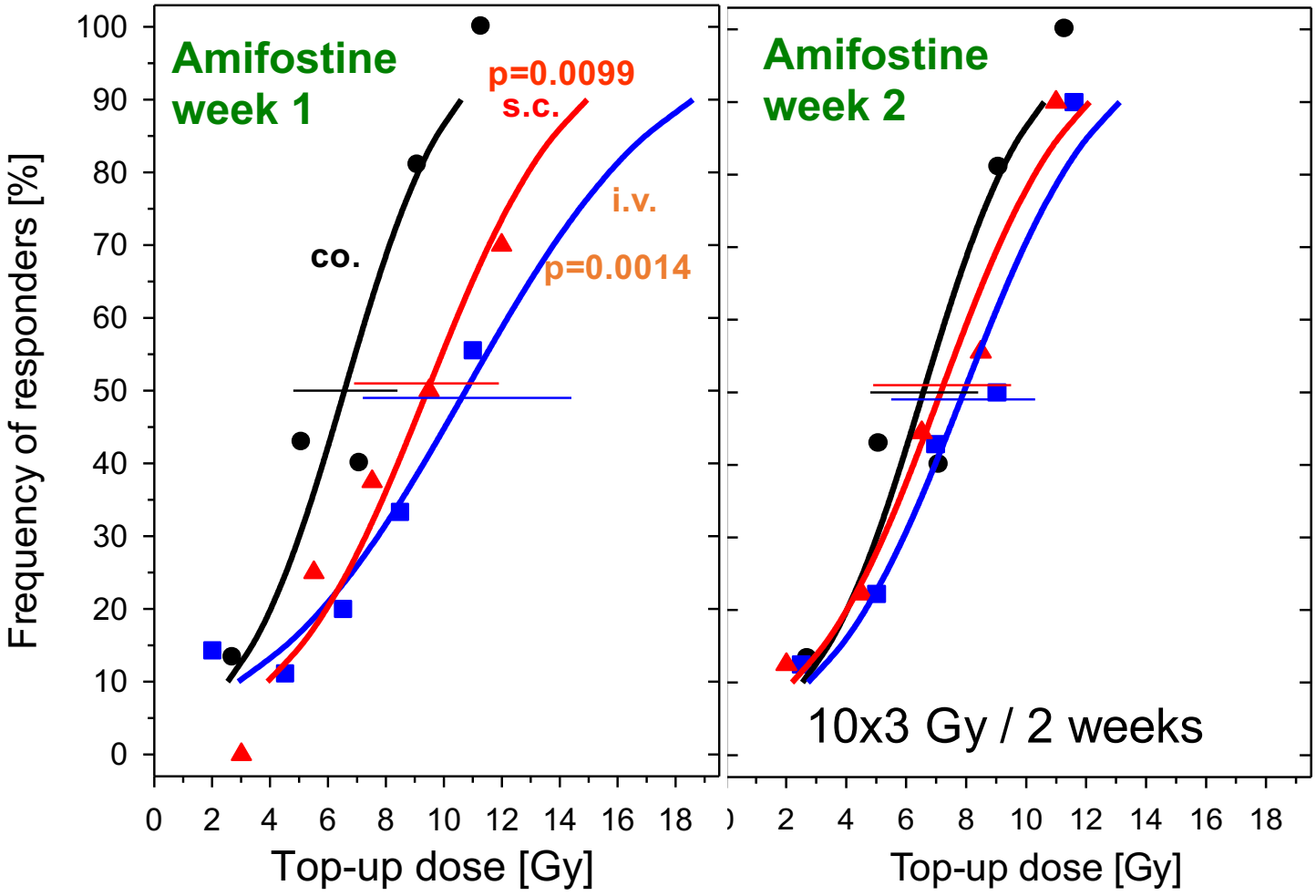
Amifostine





Konings et al 2005

Radical scavenging/detoxification

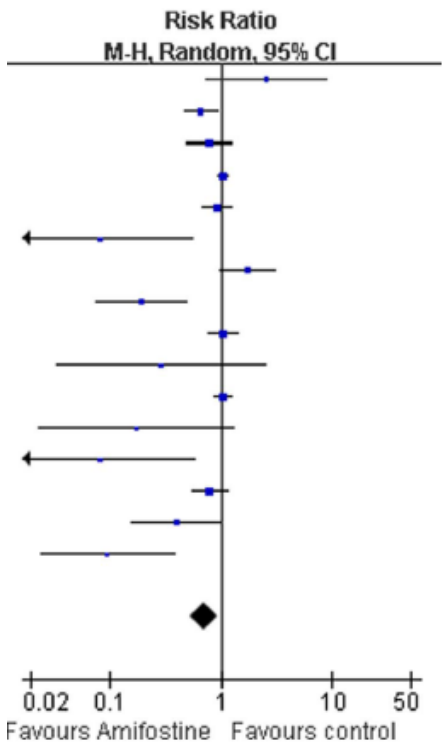


oral mucosa, mouse ulcer induction

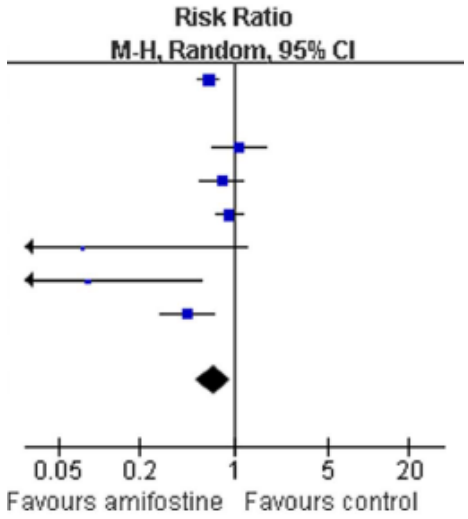
Fleischer and Dörr, Strahlenther. Onkol. 182, 2006, 567-575

Amifostine
Systematic review

Mucositis



Xerostomia

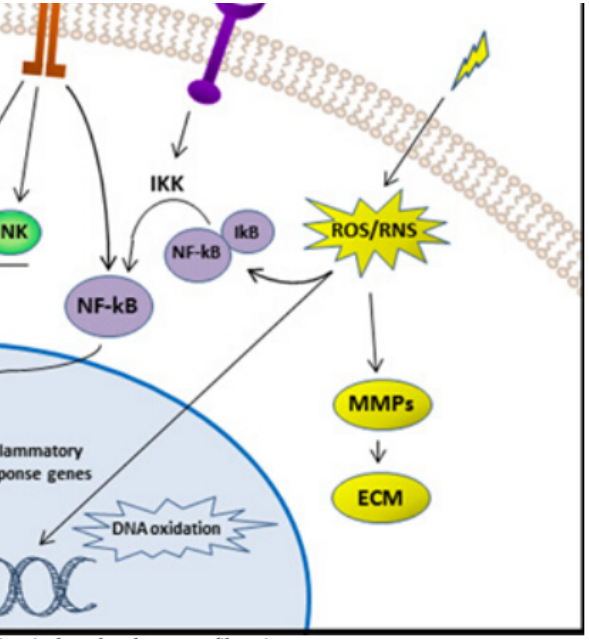


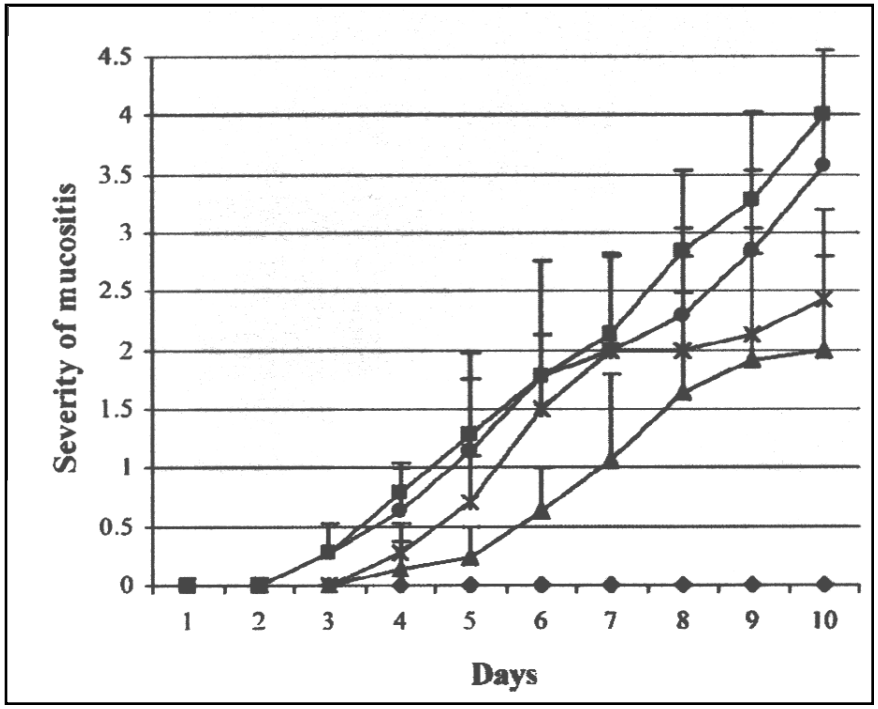
Gu et al Plos One 2014

Radical scavenging/detoxification

Vitamin E

oral mucosa, rat





15 Gy
15 Gy + Vit. E
+ L-carnitine

15 Gy + L-carnitine

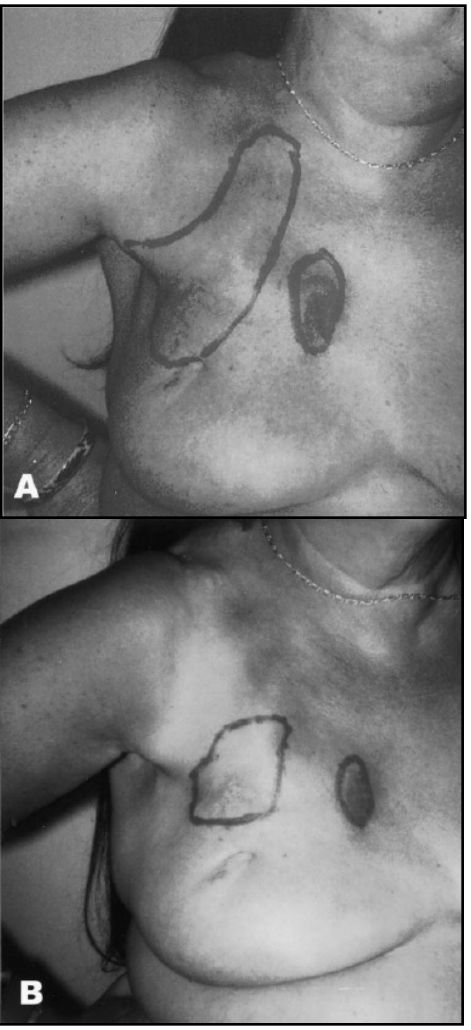
15 Gy + Vit. E

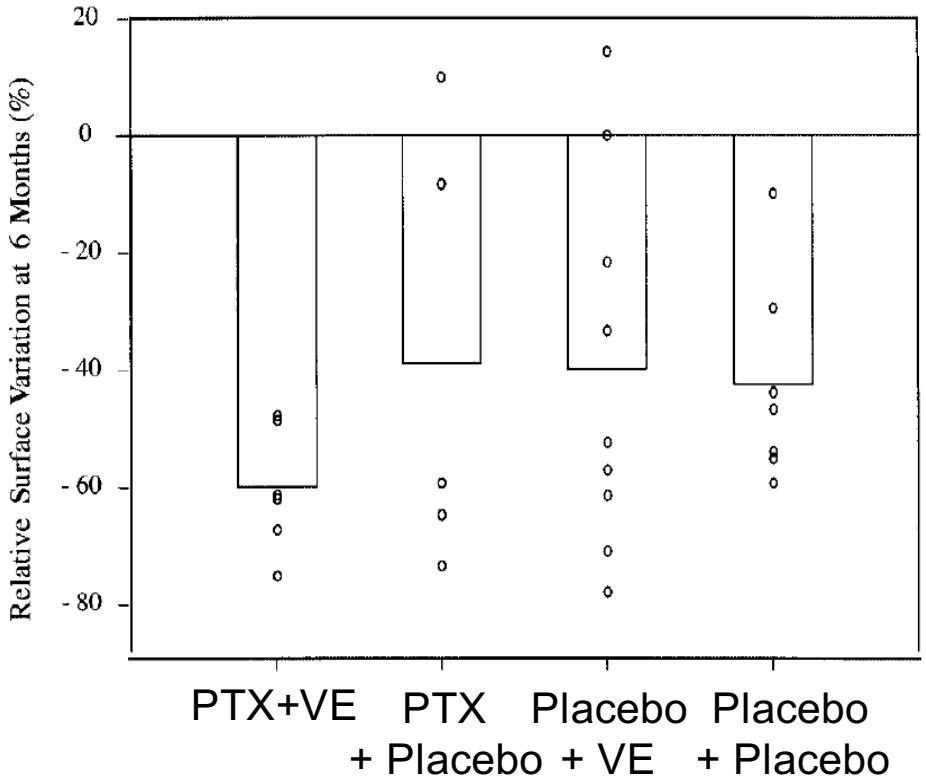
Ücüncü et al., J. Radiat. Res. 47, 2006, 91-102

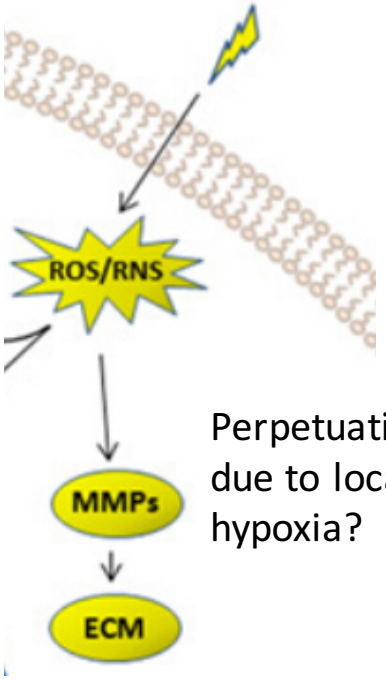
Radical scavenging/detoxification

Pentoxifylline, Vitamin E

Skin fibrosis:







Perpetuating due to local hypoxia?

Delanian et al., JCO 21, 2003, 2545-2550

Radical scavenging/detoxification

Pentoxifylline, Vitamin E

Skin fibrosis:

ELSEVIER

Radiotherapy and Oncology 73 (2004) 133–139

RADIOTHERAPY & ONCOLOGY
JOURNAL OF THE EUROPEAN SOCIETY FOR THERAPEUTIC RADIOLOGY AND ONCOLOGY

www.elsevier.com/locate/radonline

Double-blind placebo-controlled randomised trial of vitamin E and pentoxifylline in patients with chronic arm lymphoedema and fibrosis after surgery and radiotherapy for breast cancer

Lone Gothard[a], Paul Cornes[a], Judith Earl[b], Emma Hall[c], Julie MacLaren[d], Peter Mortimer[e], John Peacock[a], Clare Peckitt[c], Mary Woods[d], John Yarnold[a,*]

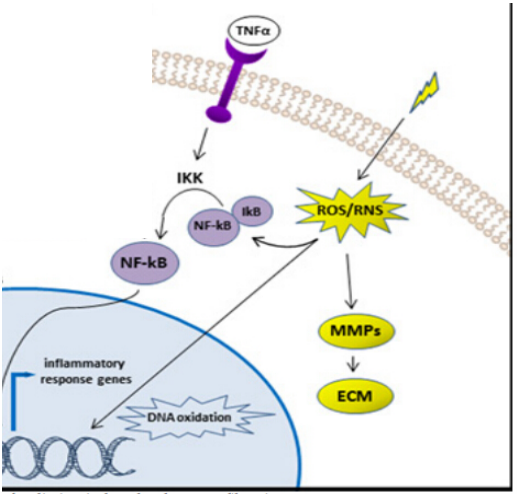
Change in induration score of fibrosis of 2 grades or more by randomisation at 12 months from baseline ($n=64$)

Induration	All patients	Placebo	Treatment	*P*-value
Site 1	6/37 = 16.2	4/20 = 20.0	2/17 = 11.8	0.45
Site 2	8/28 = 28.6	4/14 = 28.6	4/14 = 28.6	1.00

Anti-inflammation/Immunomodulation

Misoprostol (PGE_2-Analogon)

Rectum



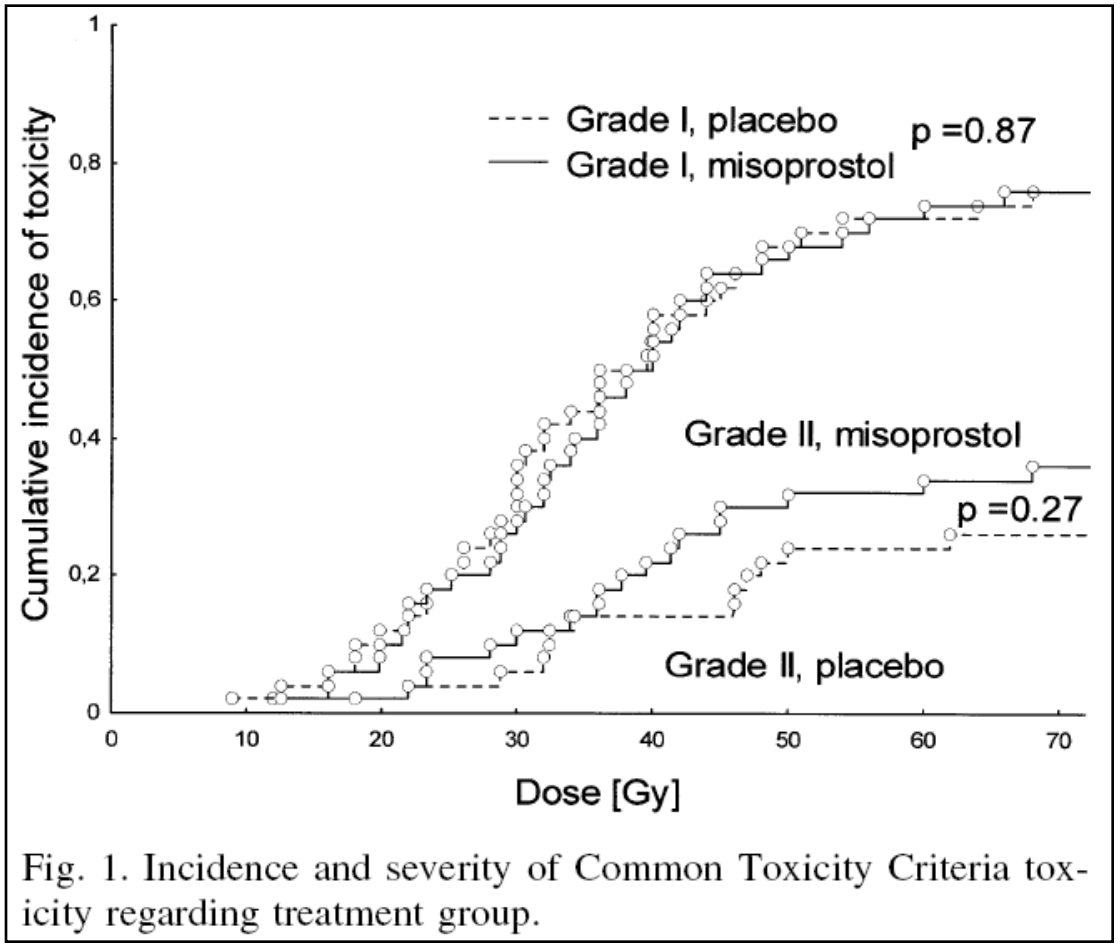


Fig. 1. Incidence and severity of Common Toxicity Criteria toxicity regarding treatment group.

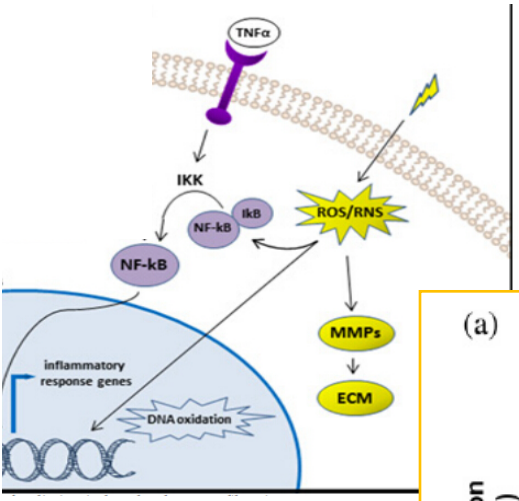
Hille et al., IJROBP 63, 2005, 1488-1493

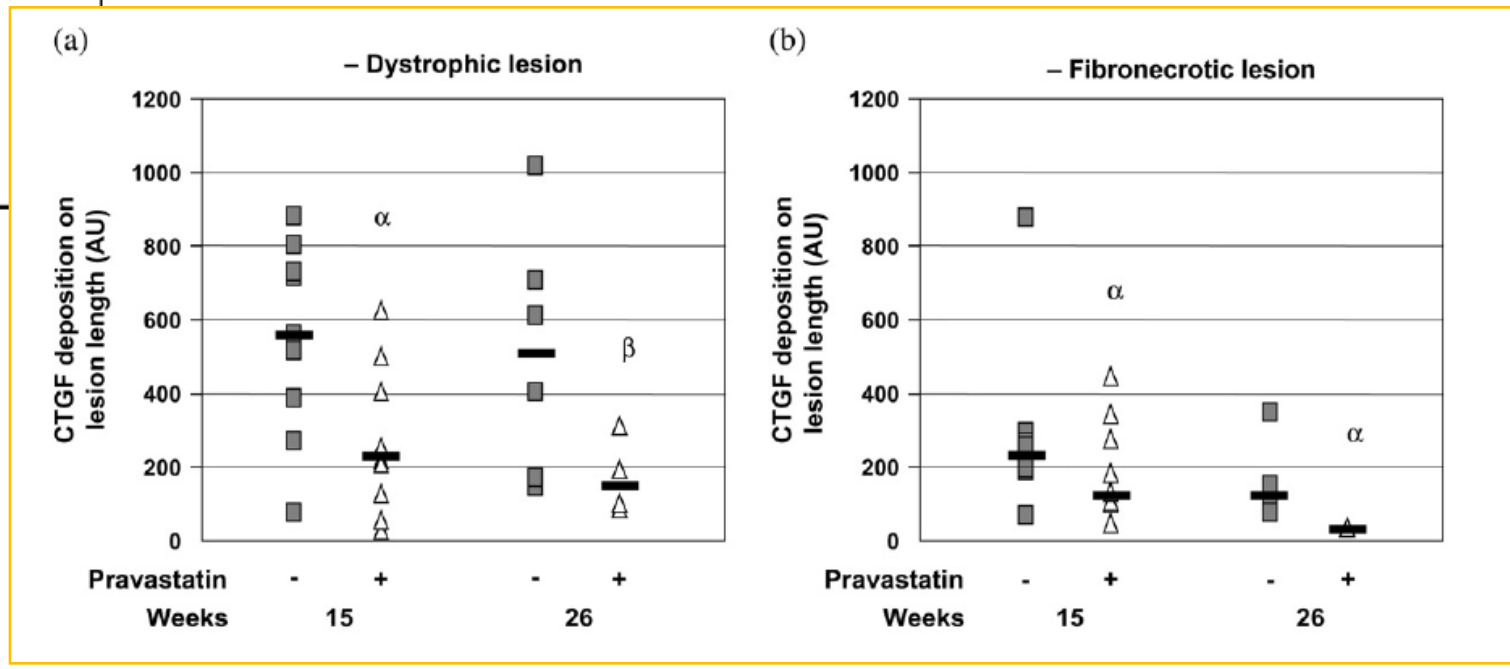
Intervention with signaling

Statins (or HMG-CoA reductase inhibitors)

Pravastatin

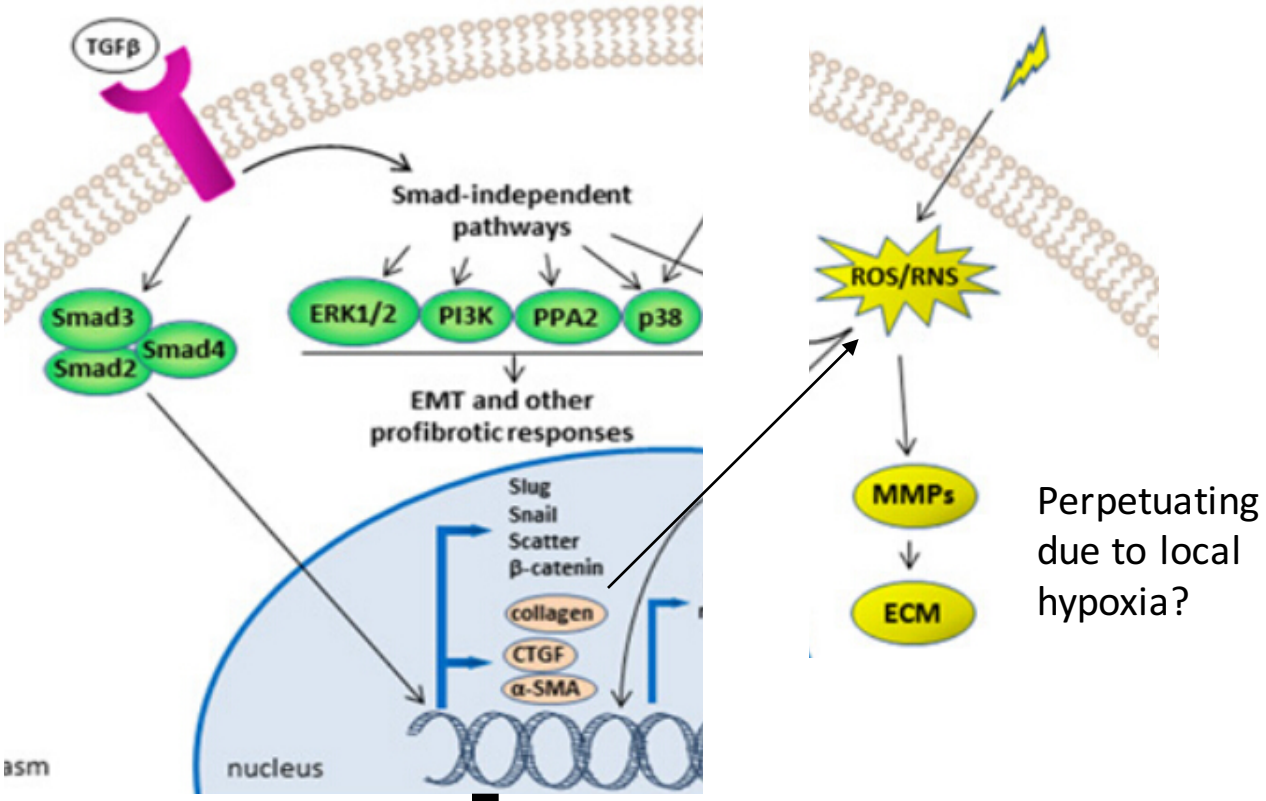
Rat, intestinal fibrosis 19 Gy





Haydont et al., IJROBP 68, 2007, 1471-1482

Intervention with signaling



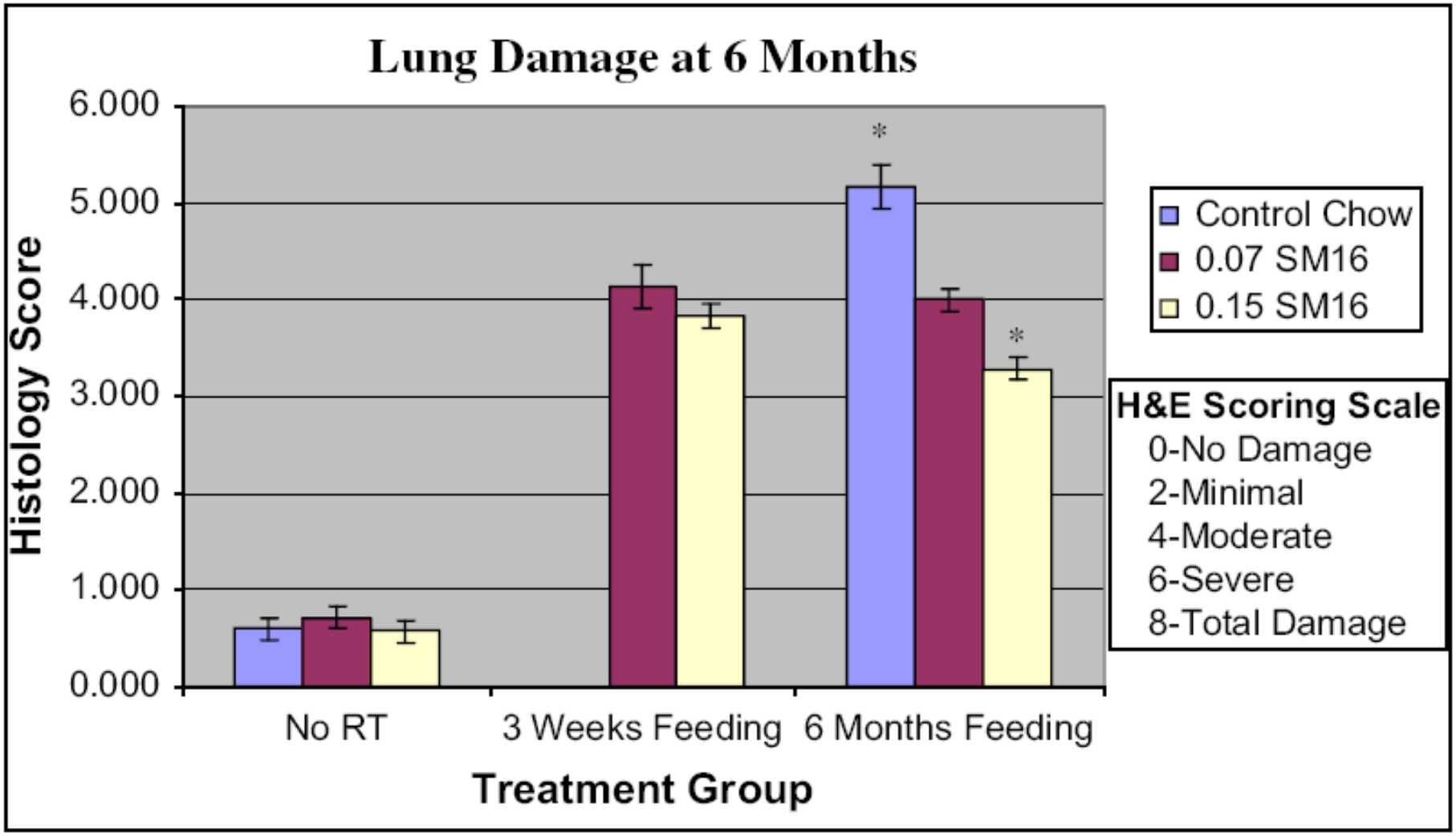
Perpetuating due to local hypoxia?

Proliferation
Differentiation
Senescence
Apoptosis
Inflammation

Adapted from Mariangela et al., 2015

Intervention with signaling

Anti-TGFß

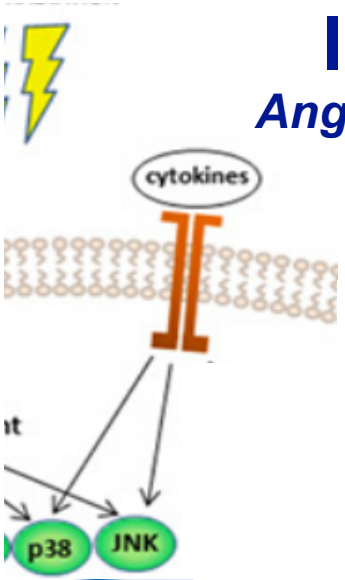


Anscher et al., IJROBP 71, 2008, 829-837

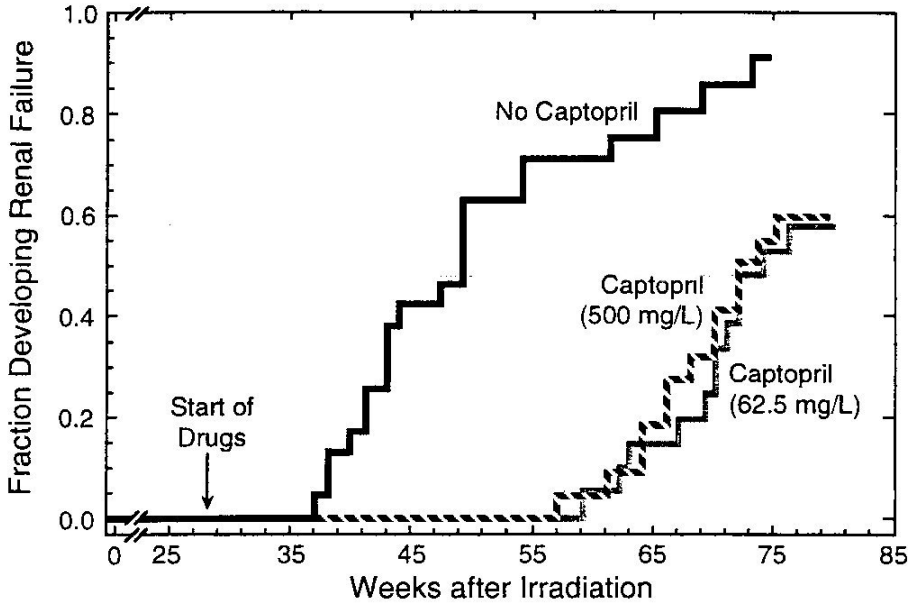
Intervention with signaling

Angiotensin-1-Converting-Enzyme (ACE)-Inhibition: Captopril

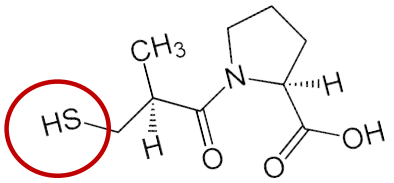
Rat kidney TBI + BMT

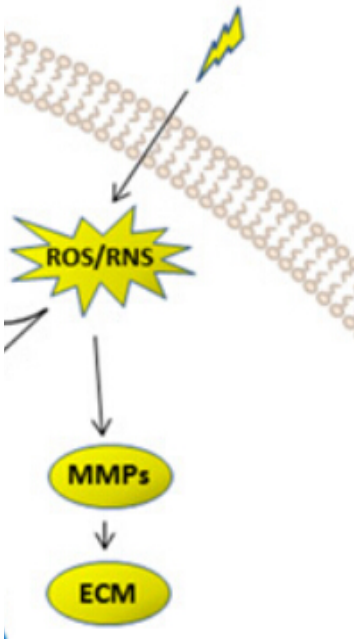


Proliferation
Differentiation
Senescence
Apoptosis
Inflammation



Actuarial risk of renal failure during treatment of established radiation nephropathy with captopril.

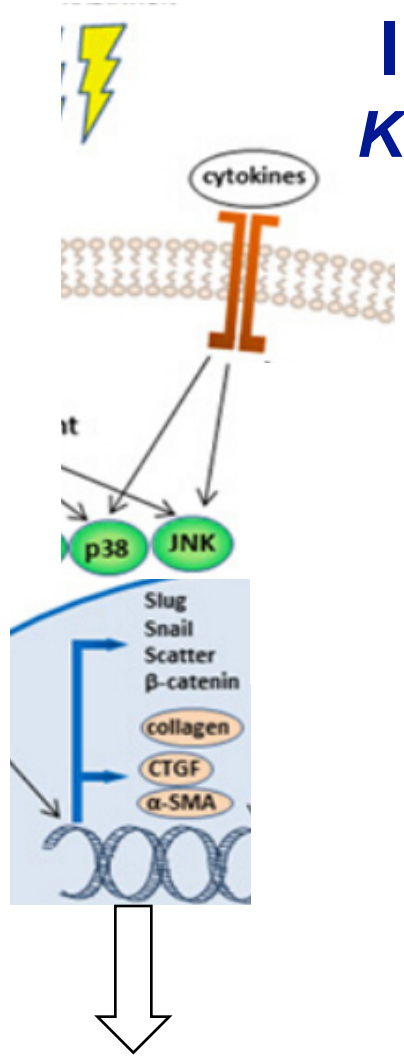




Moulder et al., Int. J. Radiat. Biol. 73, 1998, 415-421

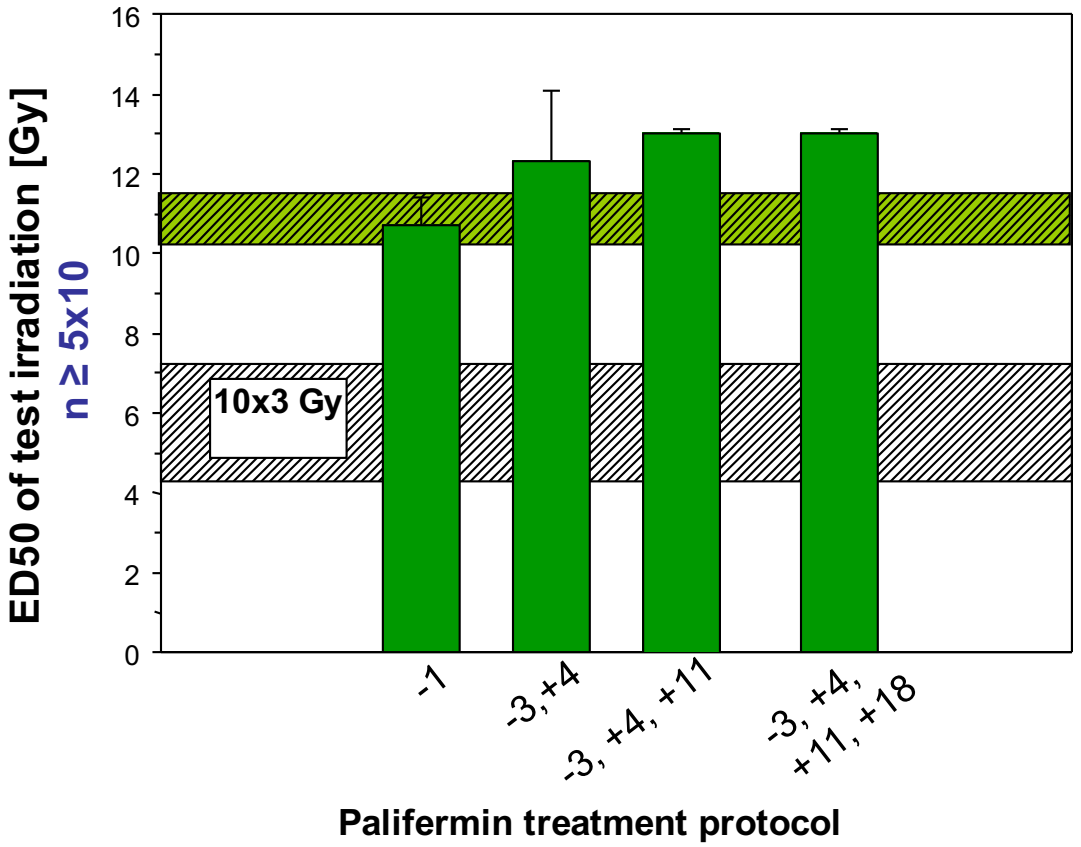
Intervention with signaling

Keratinocyte Growth Factor (Palifermin)



Proliferation
Differentiation
Senescence
Apoptosis
Inflammation

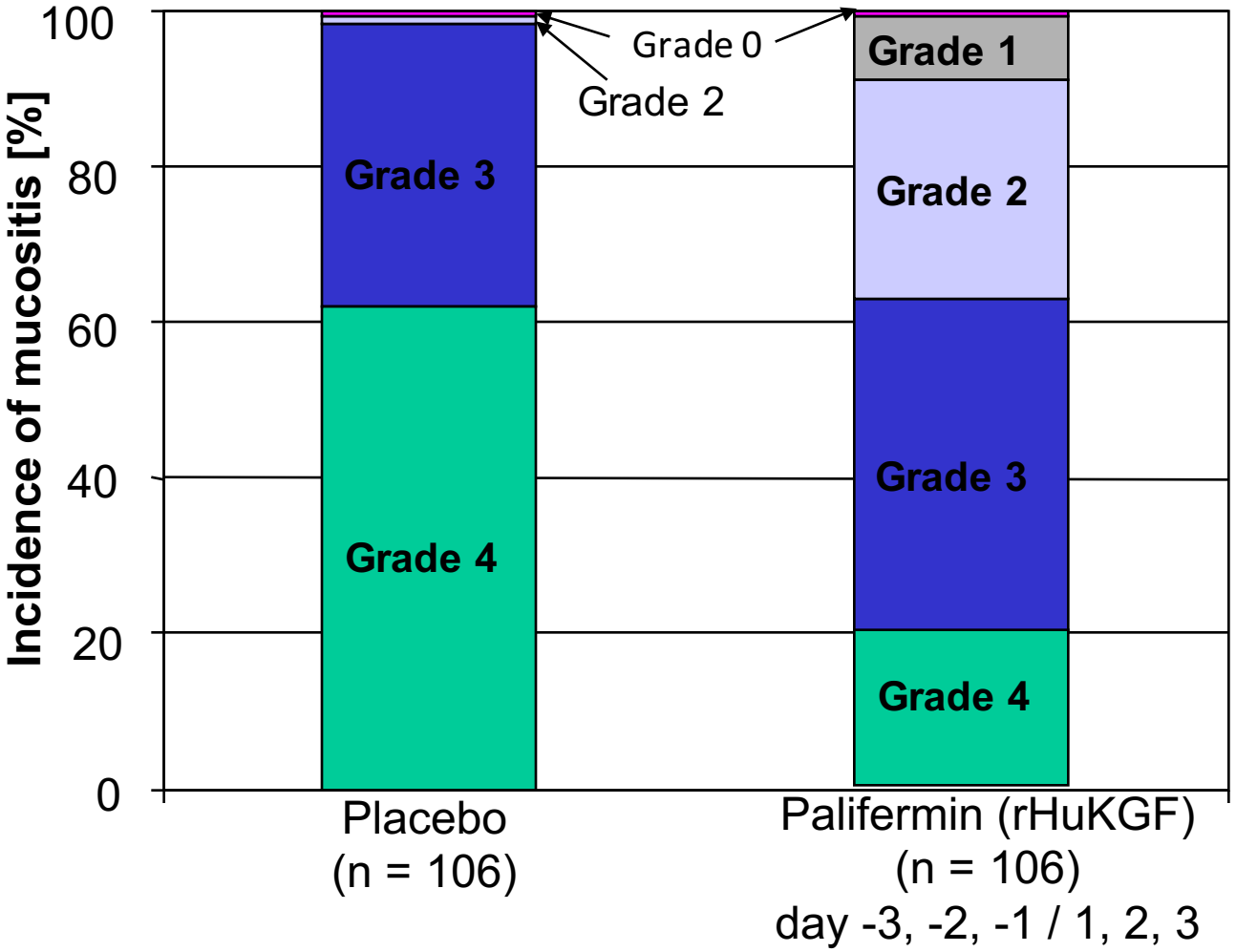
oral mucosa, mouse ulcer induction



Dörr et al., RTO (2005)

Intervention with signaling

Keratinocyte Growth Factor (Palifermin)



TBI + ChT
Phase III
randomised,
placebo
controlled

Spielberger et al., NEJM 35, 2004, 2590-2598

Intervention with signaling

Keratinocyte Growth Factor (Palifermin)

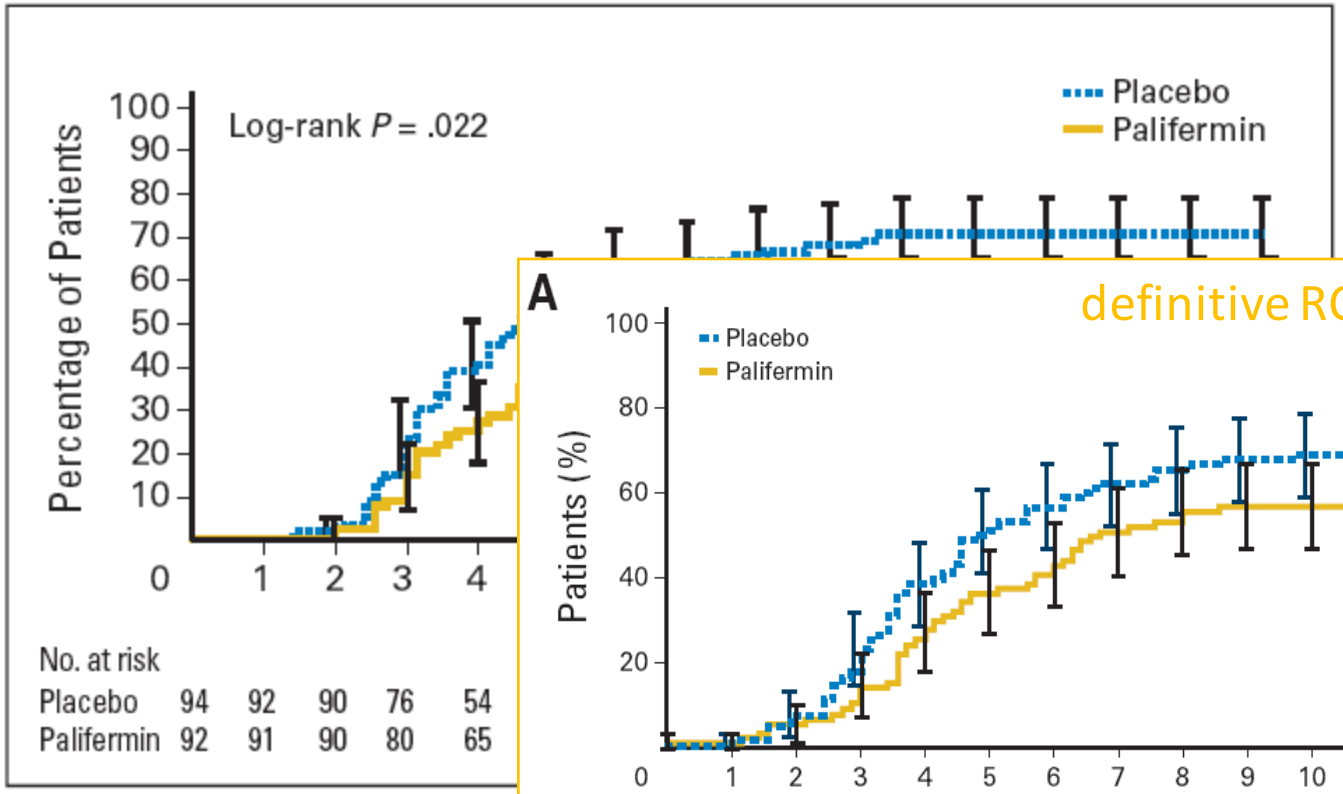
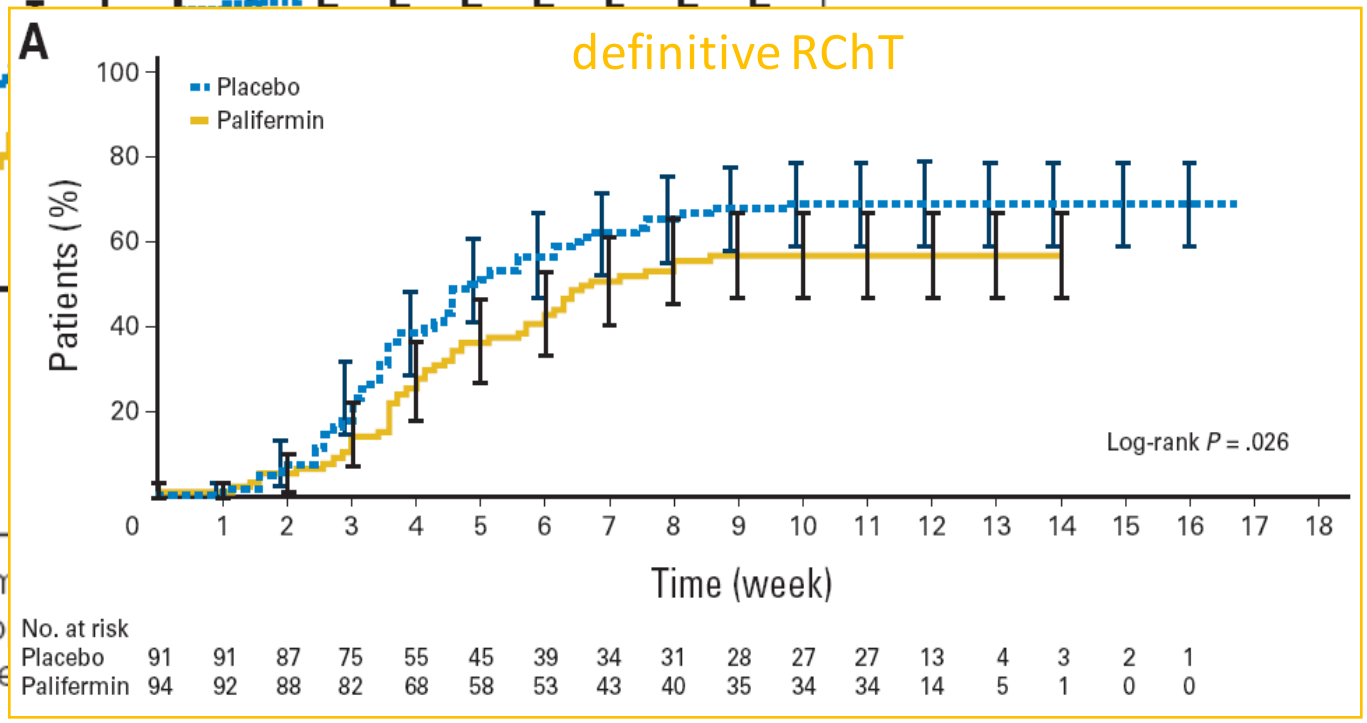


Fig 3. Kaplan-Meier plot of tim
3 to 4) during combined posto
therapy for locally advanced he



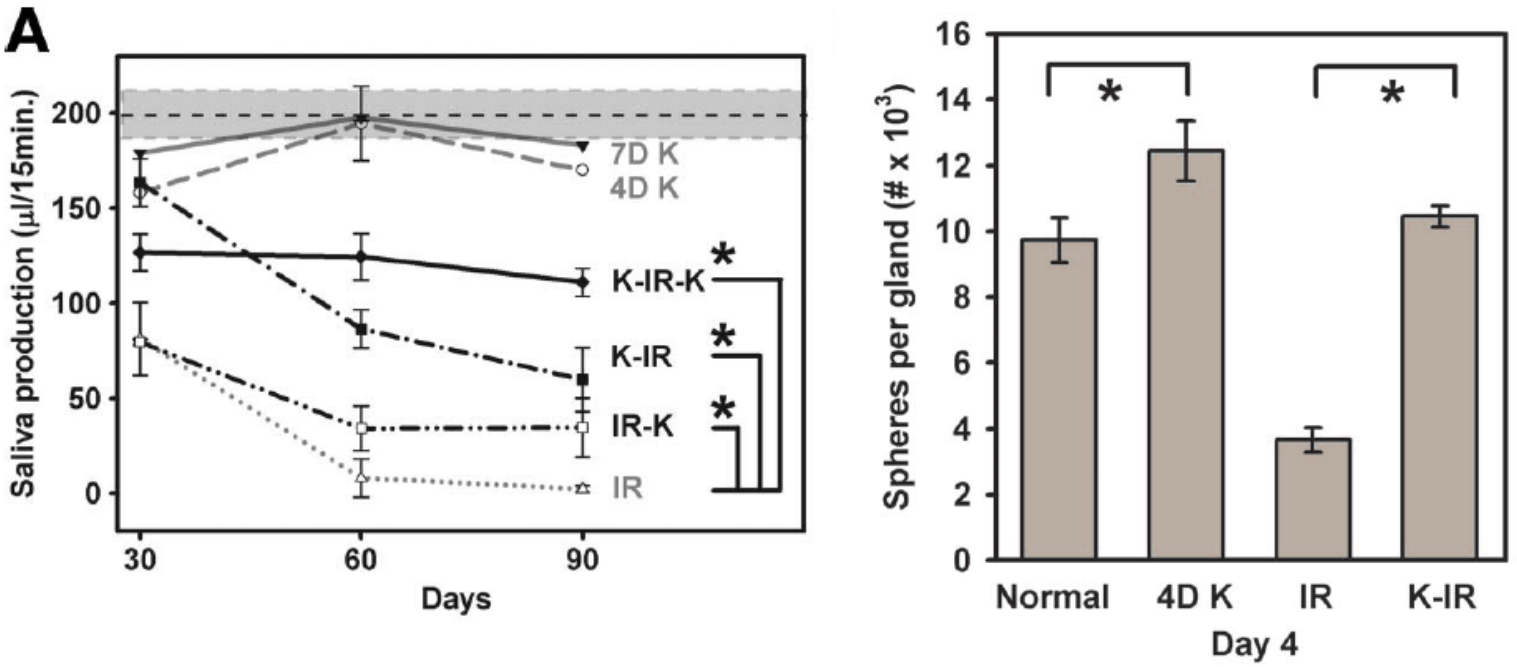
Henke et al., J Clin Oncol 2011,29:2815-2820.

Le et al., J Clin Oncol 2011,29:2808-2814.

Intervention with signaling

Keratinocyte Growth Factor (Palifermin)

Salivary gland

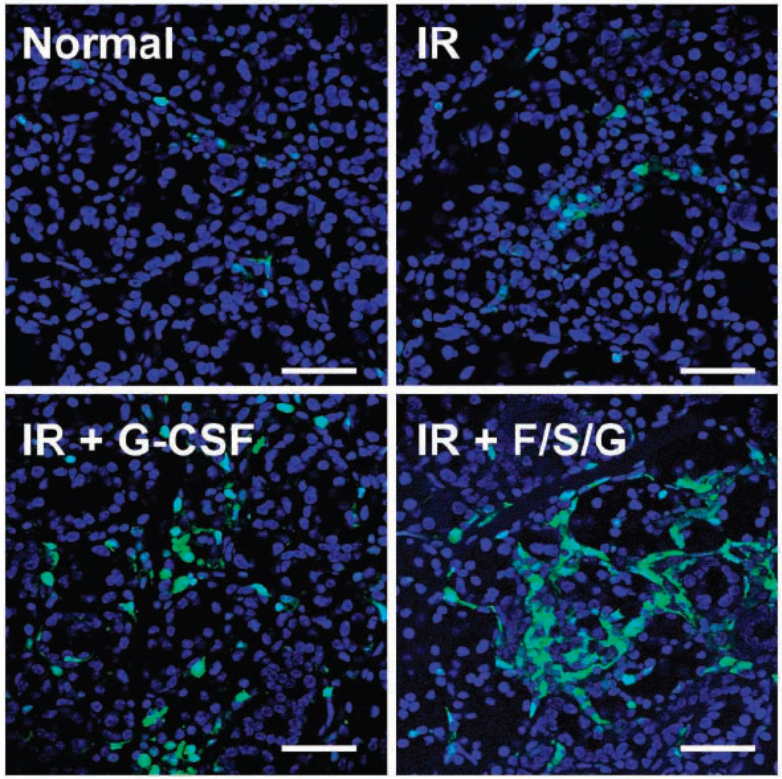


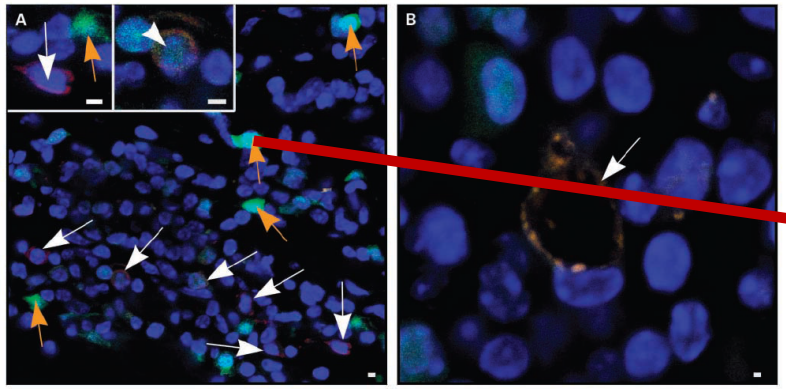
Lombaert et al Stem Cells (2008)

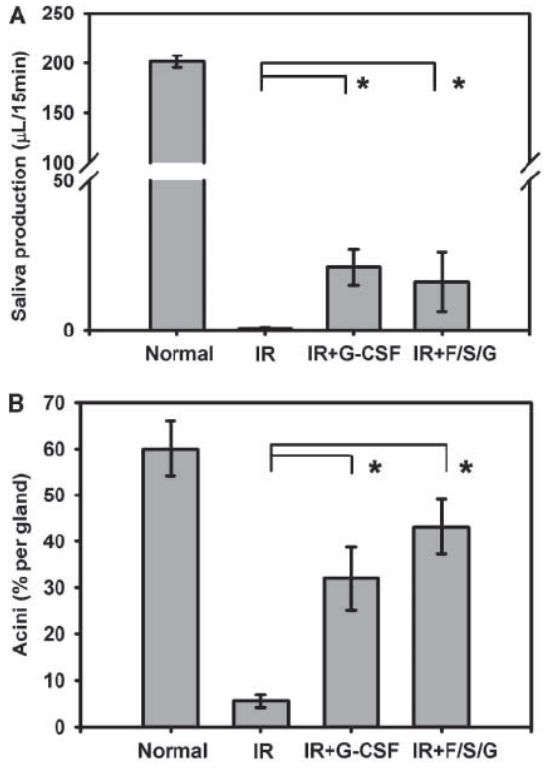
Stem Cell Expansion!!!!

Intervention with signaling / stem cell therapy

Bone marrow stem cell mobilisation (G-CSF)





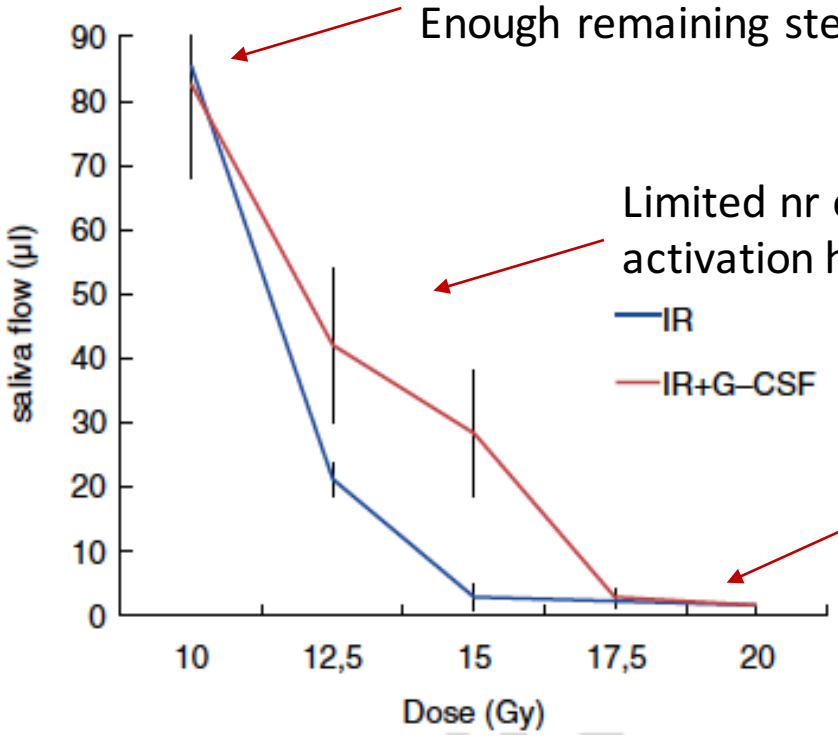


Lombaert et al Clin. Can. Res. 2008

Mesenchymal cells
Secrete KFG, FGFs, etc.
Stimulate resident surviving stem cells

Intervention with signaling / stem cell therapy

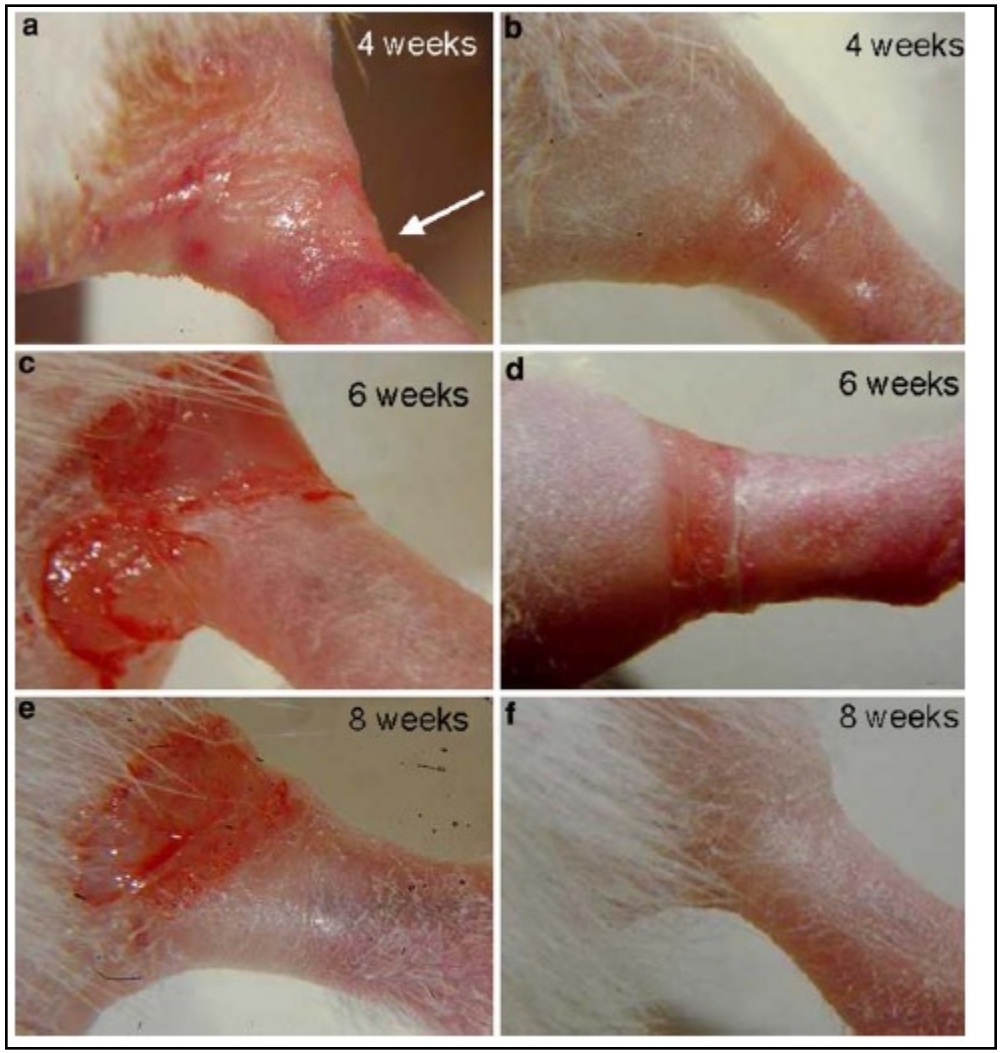
Bone marrow stem cell mobilisation (G-CSF)



Works only when enough surviving stem cells are presence

Intervention with signaling / stem cell therapy

30 Gy 30 Gy + MSC



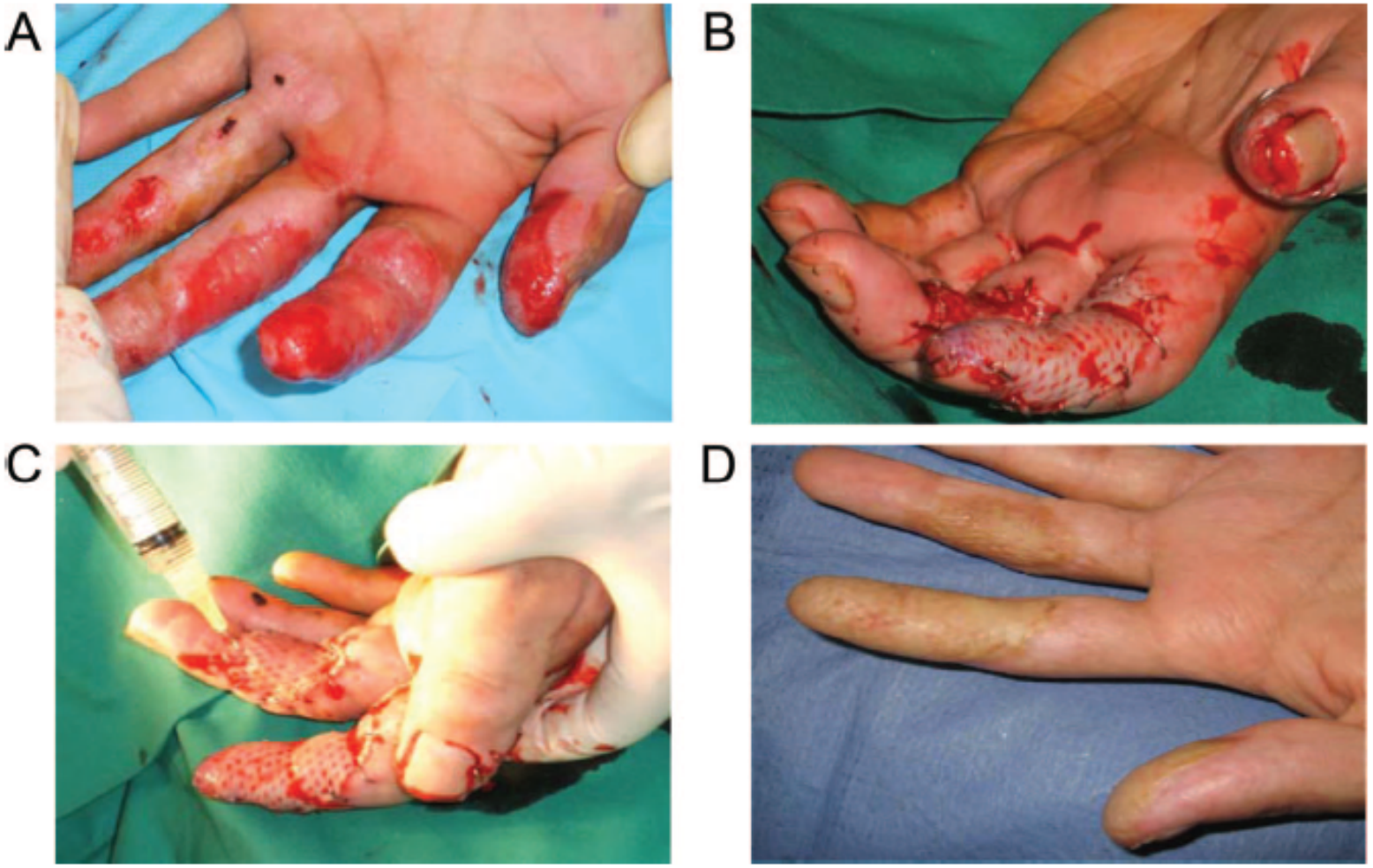
Stem cell therapy: MSC transplantation

Do not participate in the tissue do no differentiate into tissue cells

Inhibit apoptosis
Reduce inflammation
Inhibit fibrosis
Induce proliferation of stem cells

Francois et al., Ann Hematol. 86, 2007, 1-8

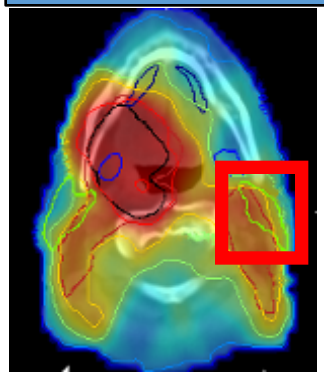
Intervention with signaling / stem cell therapy



Benderitter et al 2010

Stem cell therapy

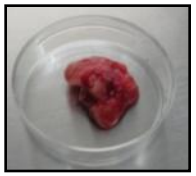
Treatment plan



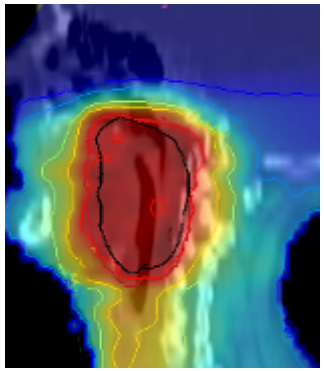
Patient with tumor

Probability of xerostomia

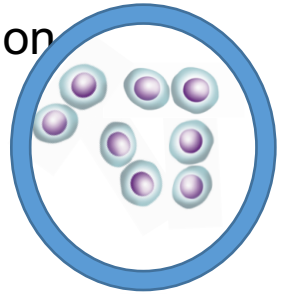
Salivary gland biopsy



Treatment

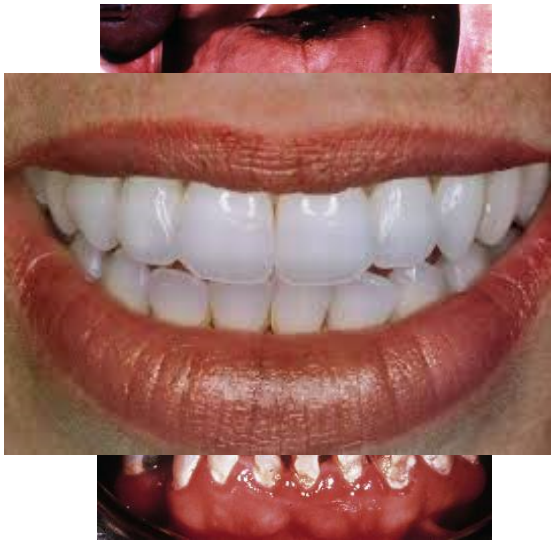


Stem cell culture and selection

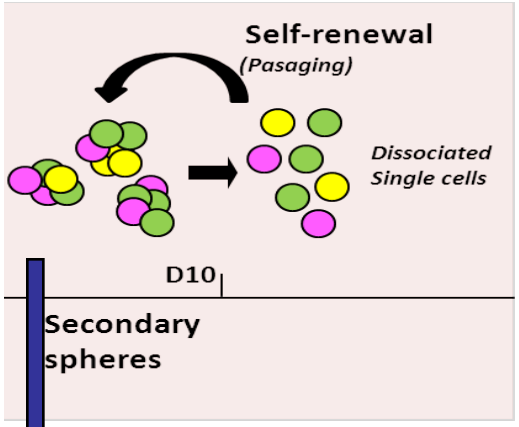


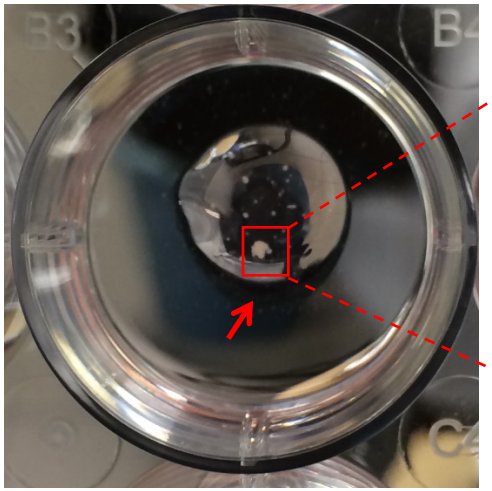
transplantation

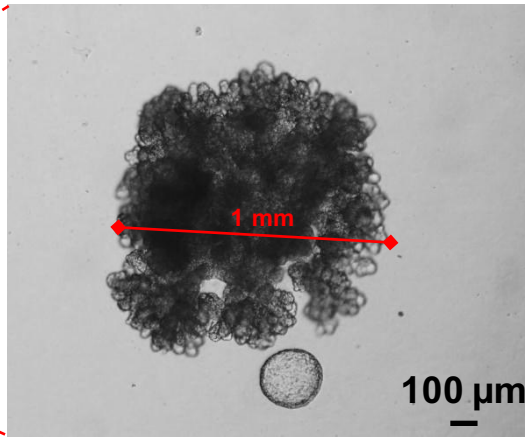
How?

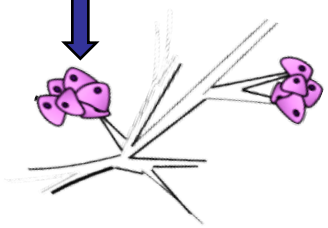


Differentiation of 1 cell to organoid

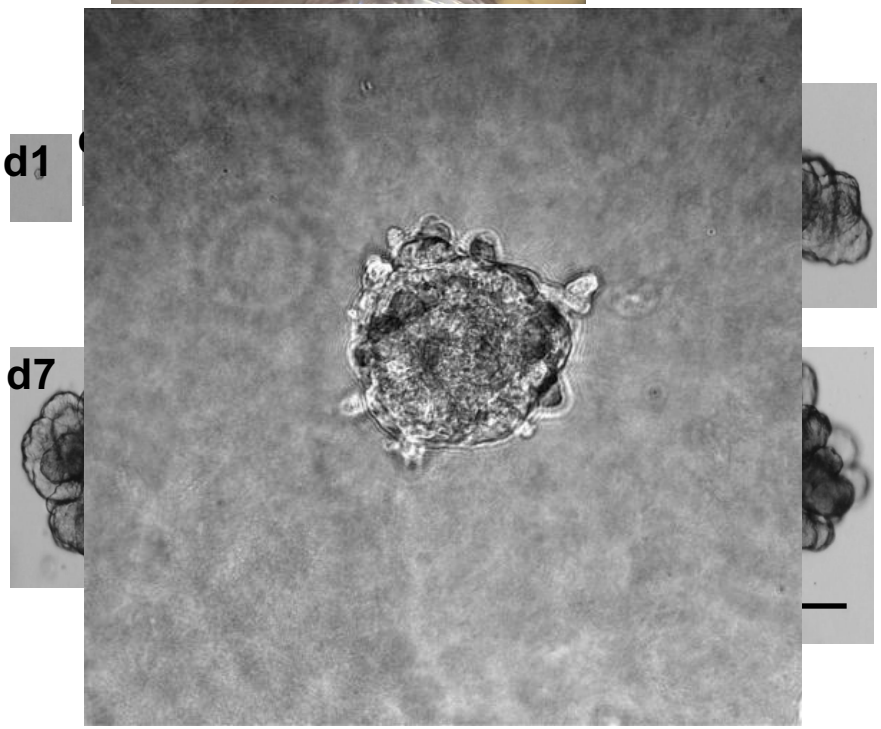








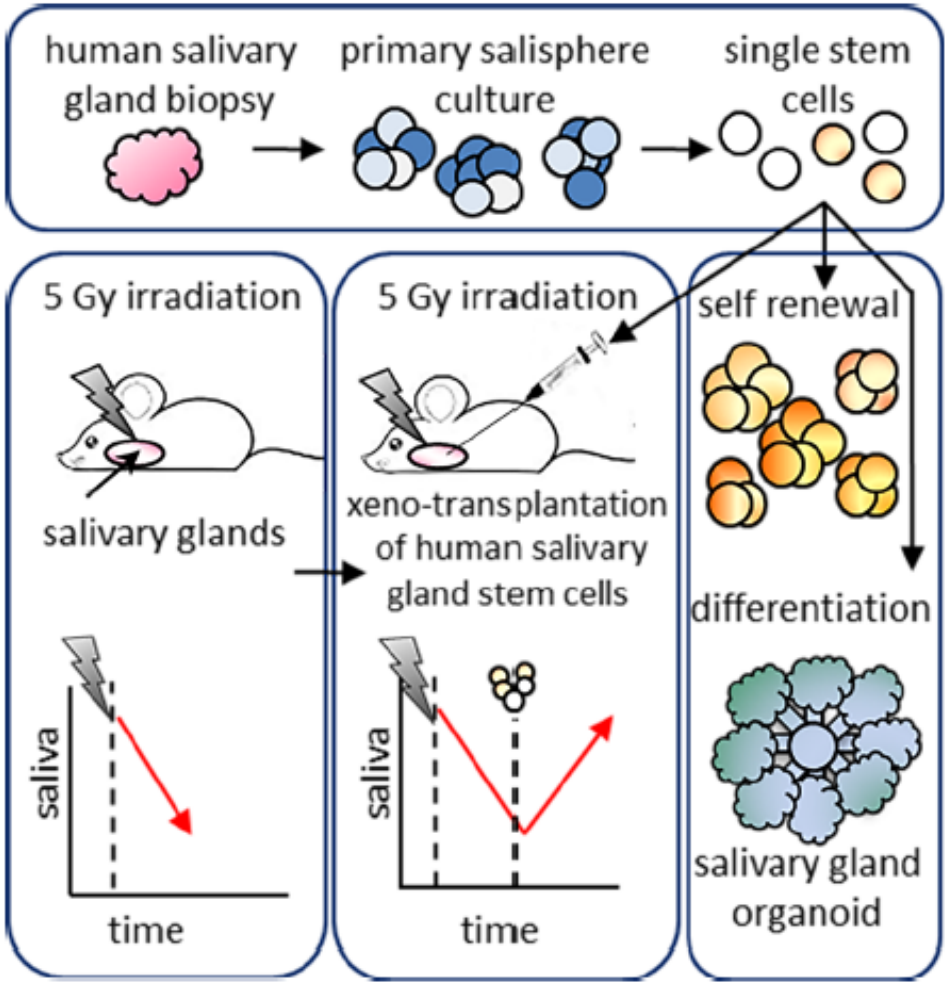
Differentiation

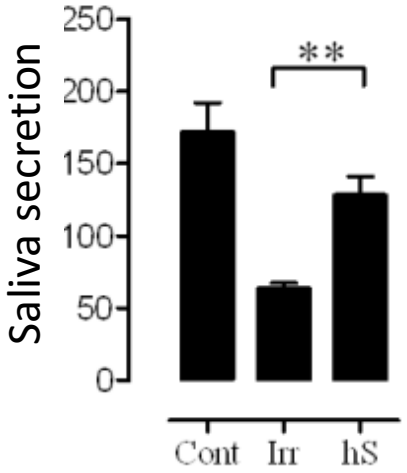


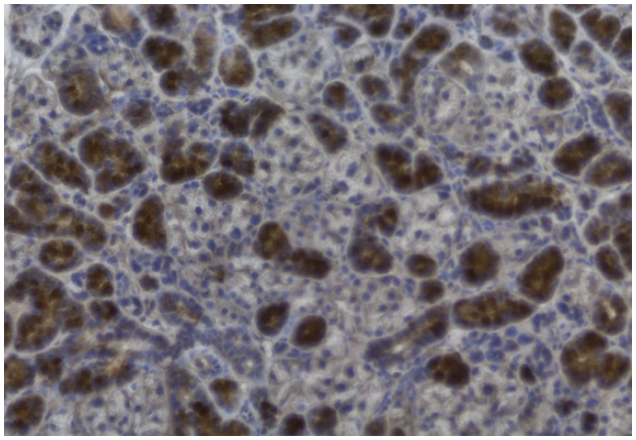
Martti Maimets et al Stem Cell Reports 2016

Johan de Rooij, UMCU

Stem cell therapy

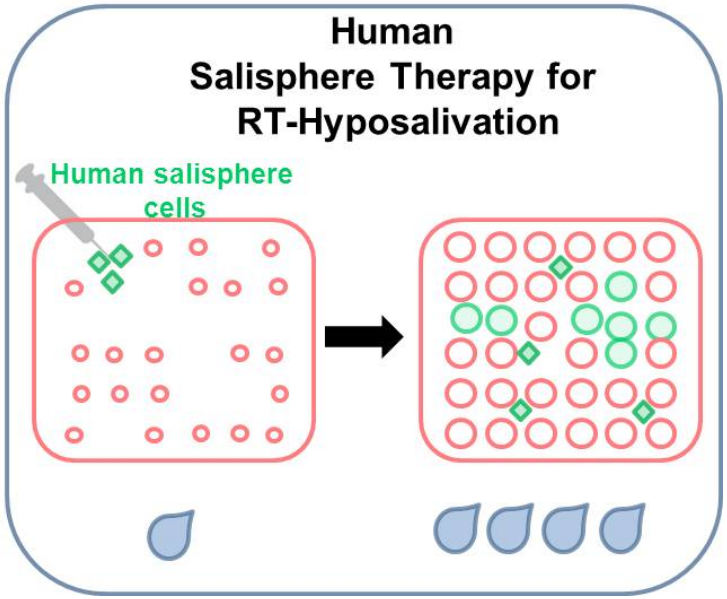






Pringle et al Stem Cells 2016

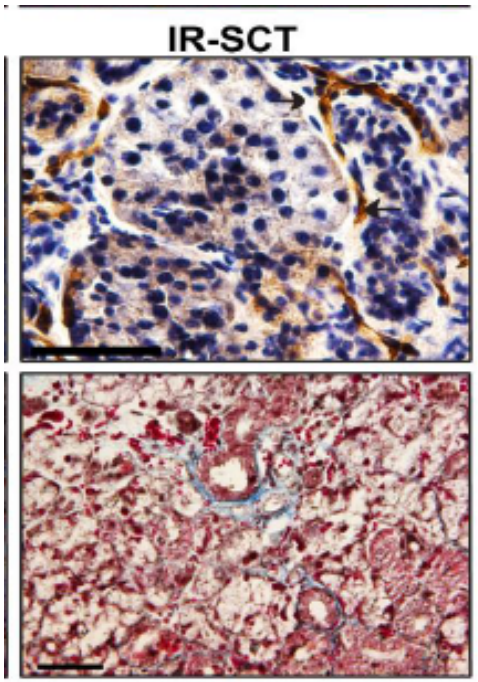
Stem cell therapy



Pringle et al Stem Cells 2016

Restoration of tissue + endocrine stimulation

- Re-entrance in cell cycle
- ECM remodelling
- Reduction of fibrosis
- Re-vascularisation

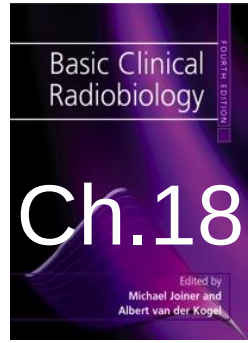


Nanduri et alRadiother & Oncol 2013

Optimum intervention strategies required

- precise knowledge of the signaling chains
  - cell type/ tissue specific/*tumor*?
- clarification of mechanisms
- validation in suitable animal models
  - with clinically relevant endpoints
  - with relevant treatment protocols
- proof of selectivity
  (tumour studies, same premises)
- Modification cocktails!?
  Localize effect?
  Long-term effects?

ESTRO School



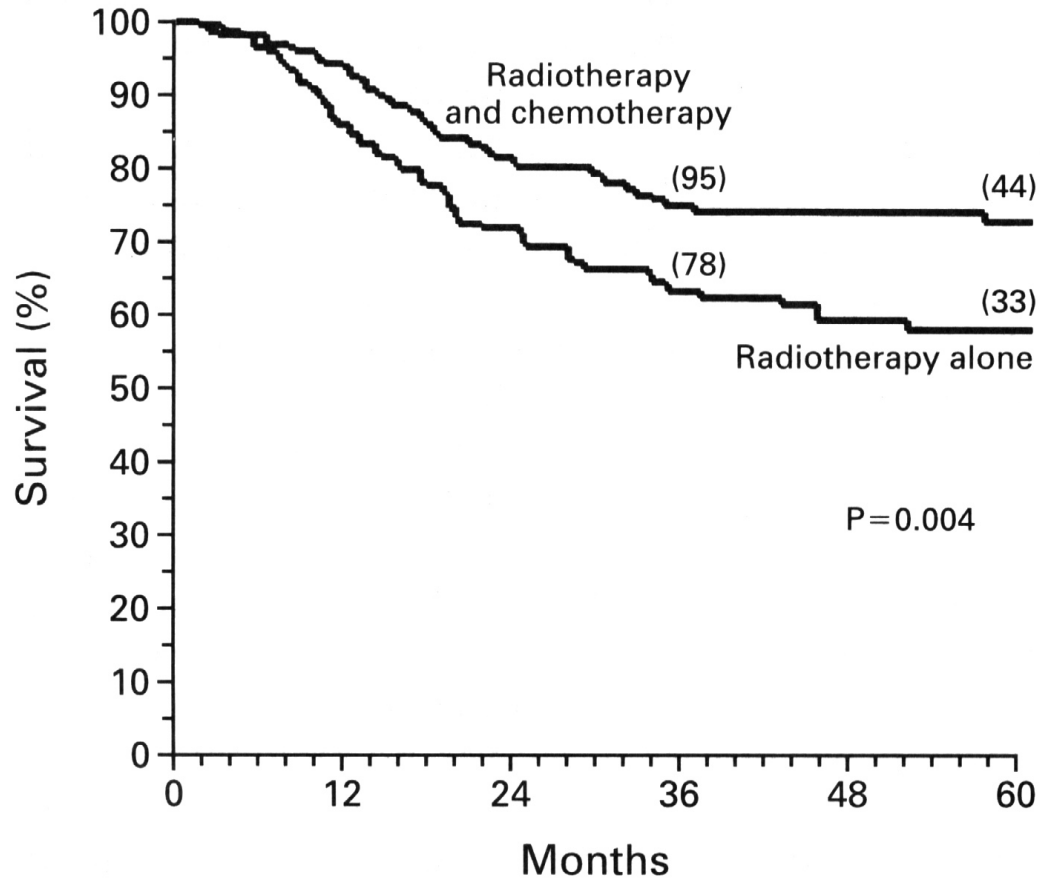
Chemo-radiation: biological basis

Prof. Vincent GREGOIRE
Université Catholique de Louvain,
Cliniques Universitaires St-Luc

ESTRO teaching course on basic clinical radiobiology

Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer.

M. Morris et al, NEJM, 340:1137-1143, 1999.



Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer.

M. Morris et al, NEJM, 340:1137-1143, 1999.

	RT (n=193)	RT+Chemo (n=195)
5y overall survival	58%	73 (p=0.004)
LR recurrence	35%	19% (p<0.001)
Distant relapse	33%	14% (p<0.001)

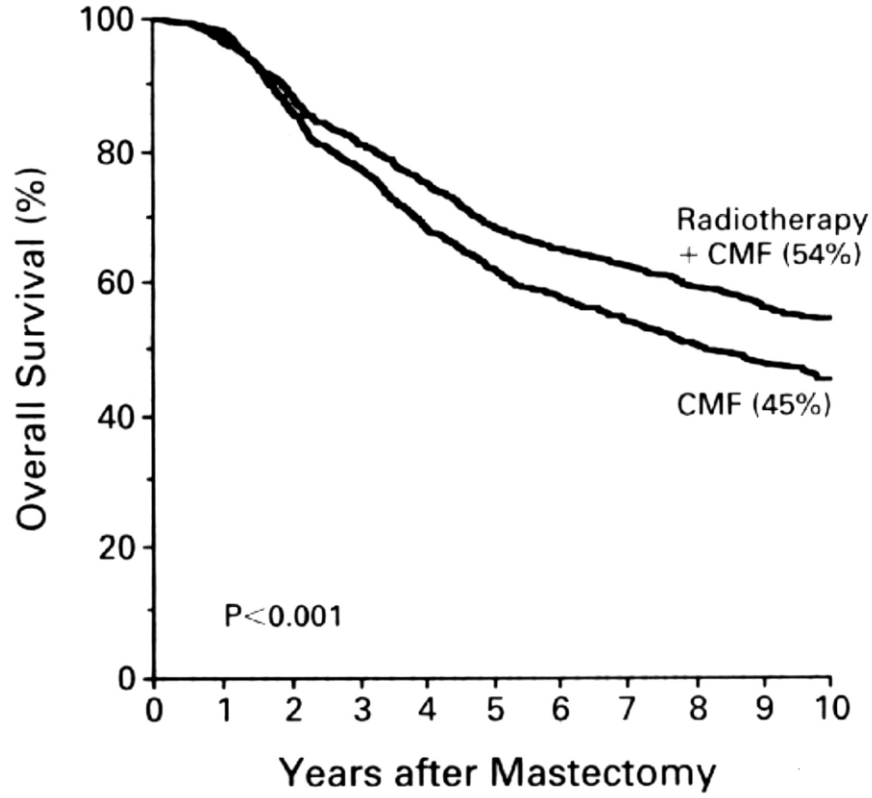
RT: 45 Gy + brachytherapy (total dose ≥ 85 Gy)
Chemo: cddp (75mg/m^2, d1), 5Fu (1g/m^2/d, d1-4), x3

Combined chemo- and radiotherapy treatment

- Spatial co-operation (e.g. breast carcinoma)
- Independent cell kill (e.g. Hodgkin lymphoma)
- Interaction (e.g. H&N, cervix, NSCLC)
- “diluted” toxicity (e.g. Hodgkin lymphoma)

Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial

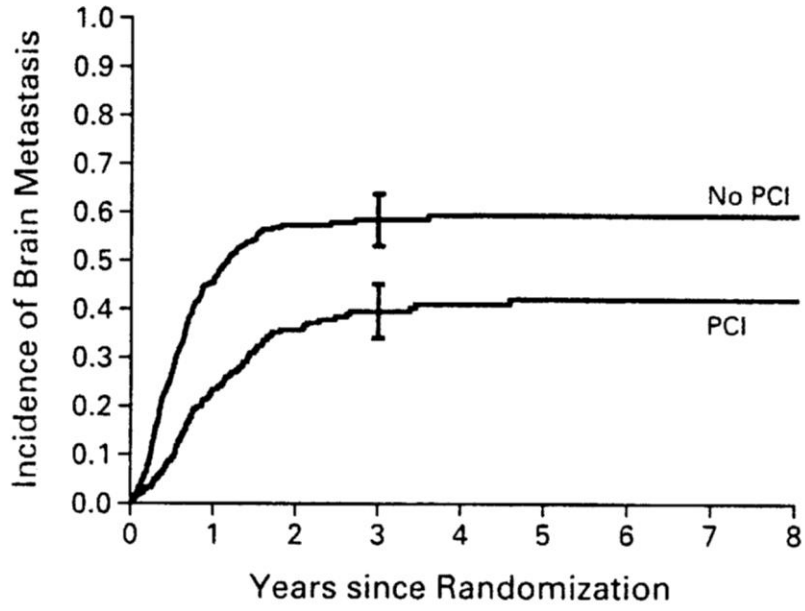
M. Overgaard et al., N. Engl. J. Med., 337: 949-955, 1997



Radiotherapy + CMF	852	755	641	555	392	188
CMF	856	738	587	494	329	163

Prophylactic cranial RT in SCLC (meta-analysis, n=981)

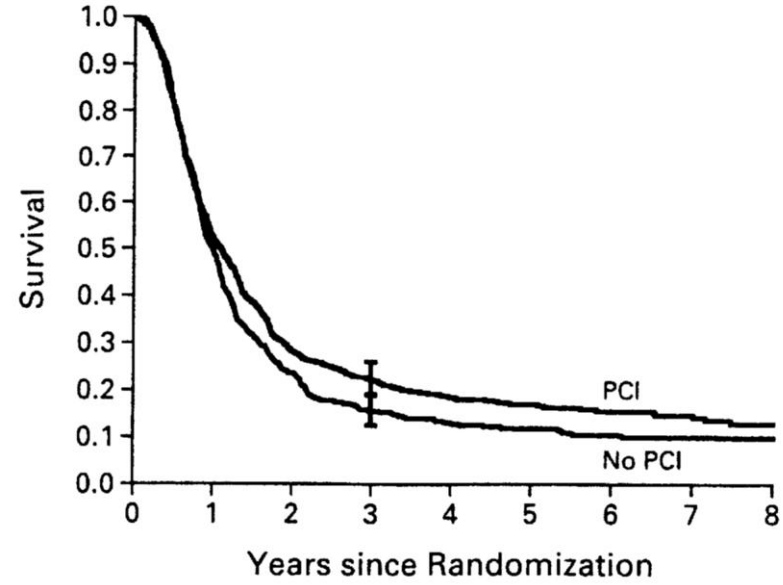
B



No. at Risk

No PCI	457	171	88	57	41	32	21	18	14
PCI	524	248	133	96	66	52	40	29	17

A



No. at Risk

No PCI	461	224	103	61	44	34	23	19	15
PCI	526	276	139	101	66	52	40	29	17

Aupérin et al., *NEJM* 341: 476, 1999

Combined chemo- and radiotherapy treatment

- Spatial co-operation (e.g. breast carcinoma)
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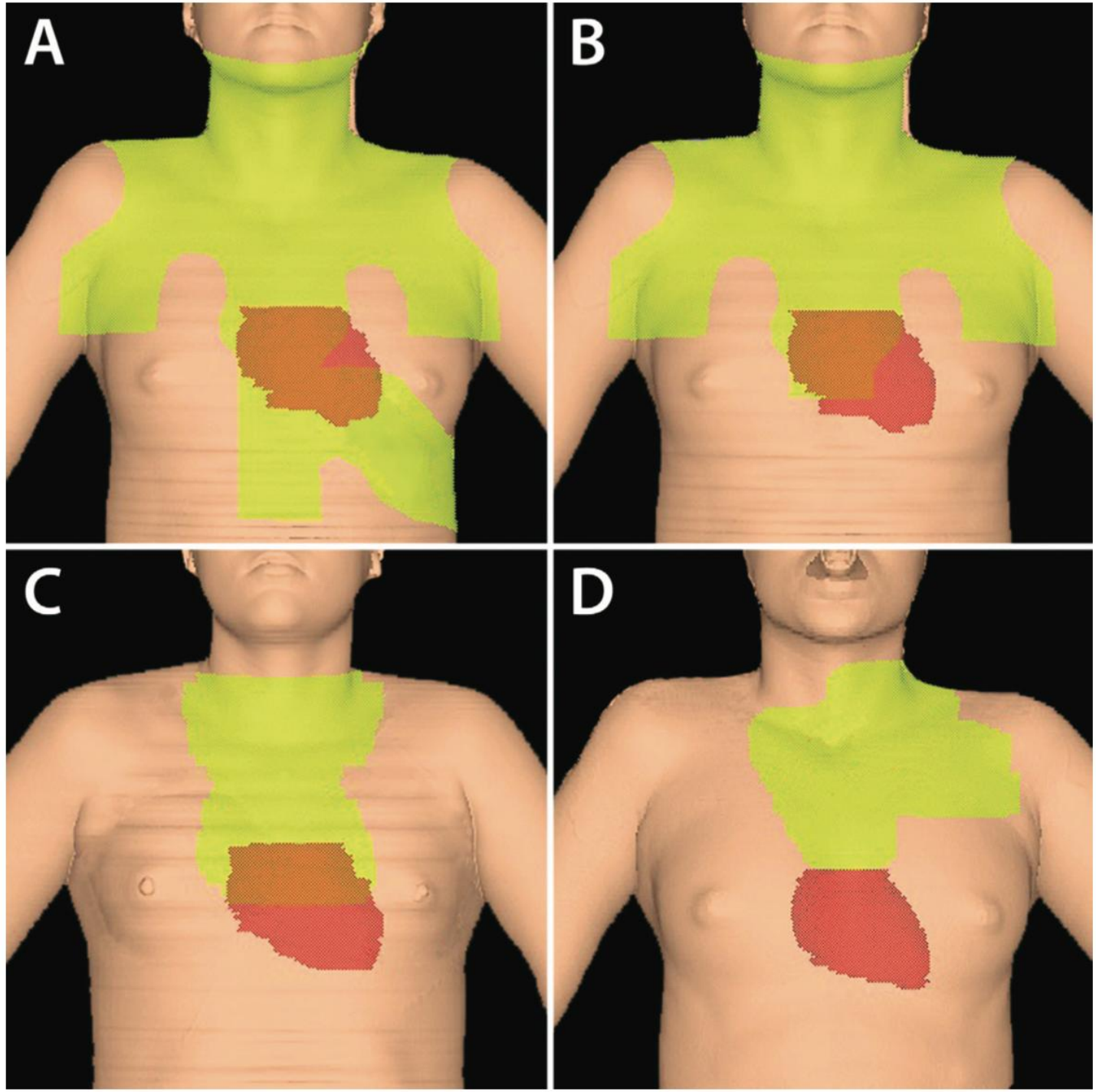
- Interaction (e.g. H&N, cervix, NSCLC)
- “diluted” toxicity (e.g. Hodgkin lymphoma)

Stage I and II Hodgkin disease (very favorable and favorable categories)

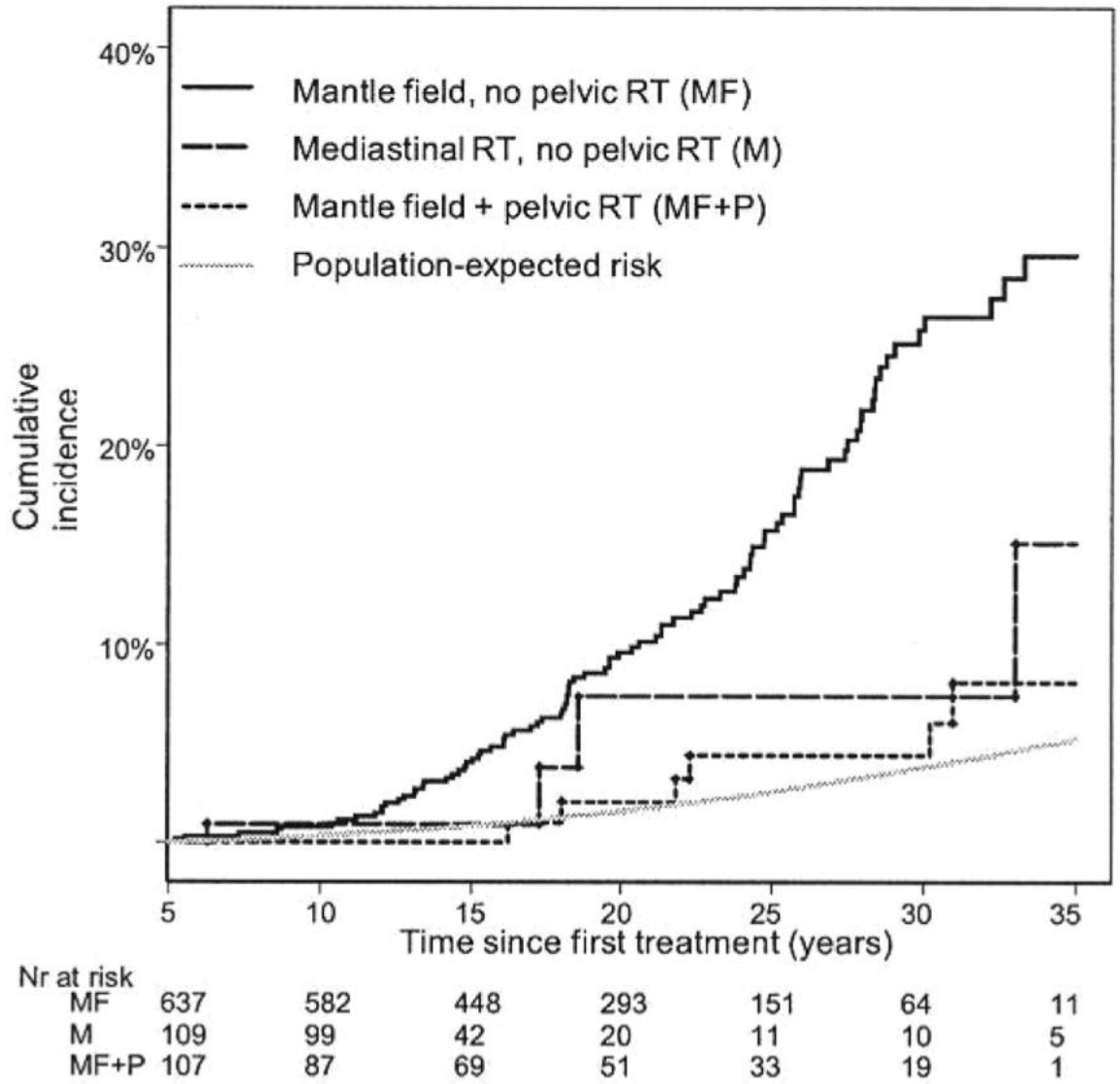
	RT (EF, 40 Gy)	CH (MOPP/ABVD)	CH+RT (IF, ≤ 40 Gy)
10 y over. survival	80-90%	80-90%	≈90%
Complications (RR)			
-leukemia	11.0	70.0	significantly reduced
-lymphoma	21.0	22.0	significantly reduced
-solid tumor	2.8	1.1	significantly reduced
-cardiac	2.2-3.1	≈1.0	significantly reduced



ESTRO 2015

Hodgson, Hematology 2011

Cumulative incidence of invasive breast cancer after RT for Hodgkin disease



Hodgson, Hematology 2011

Combined chemo- and radiotherapy treatment

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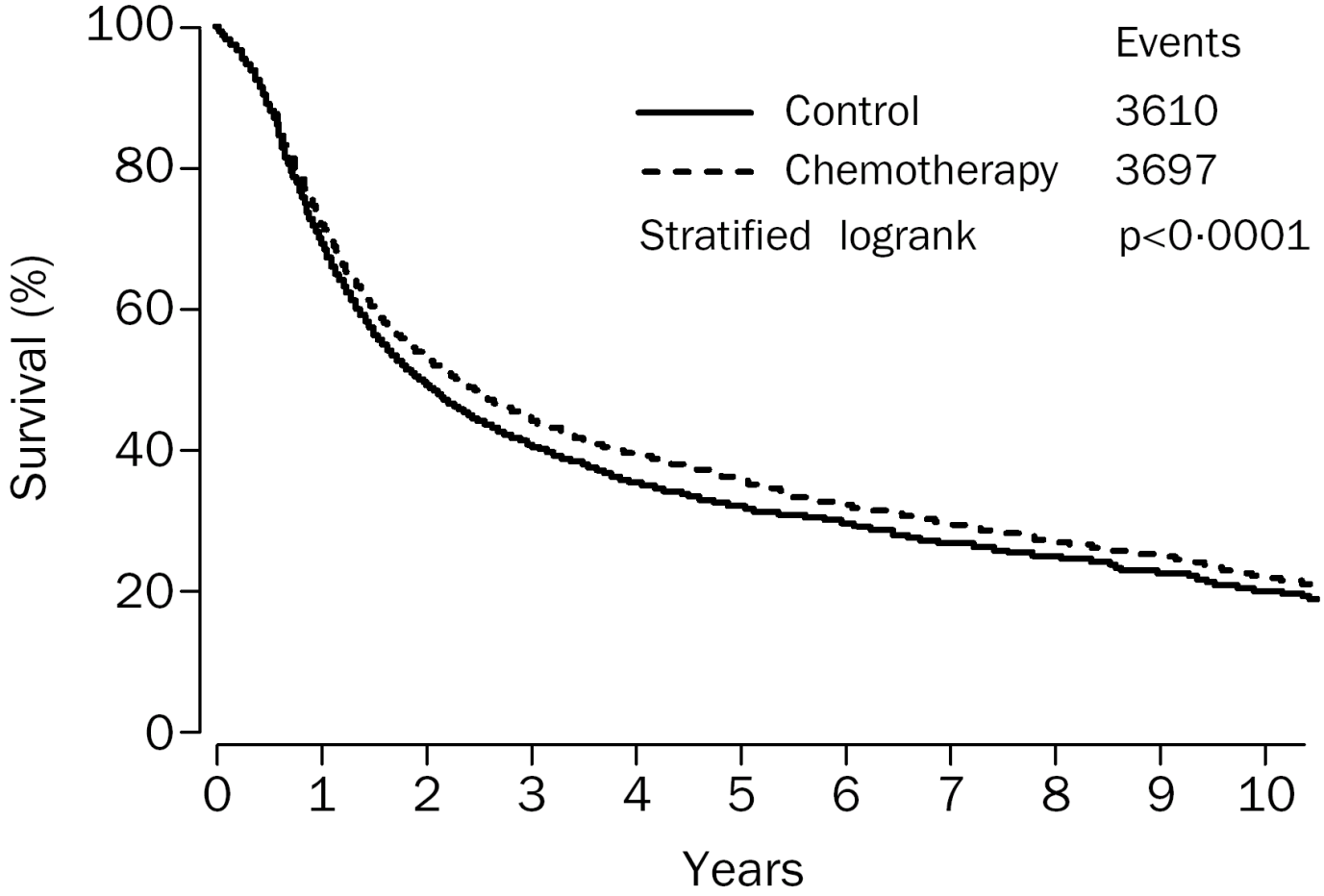
- Interaction (e.g. H&N, cervix, NSCLC)
- “diluted” toxicity (e.g. Hodgkin lymphoma)

H&N SCC: MACH-NC



ESTRO 2015

Pignon et al., *Lancet* 355: 949-955, 2000

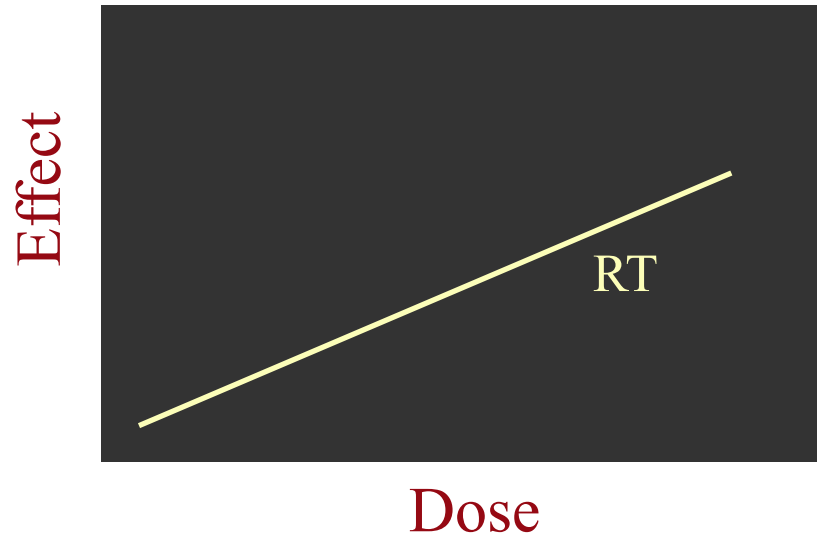
H&N SCC: MACH-NC

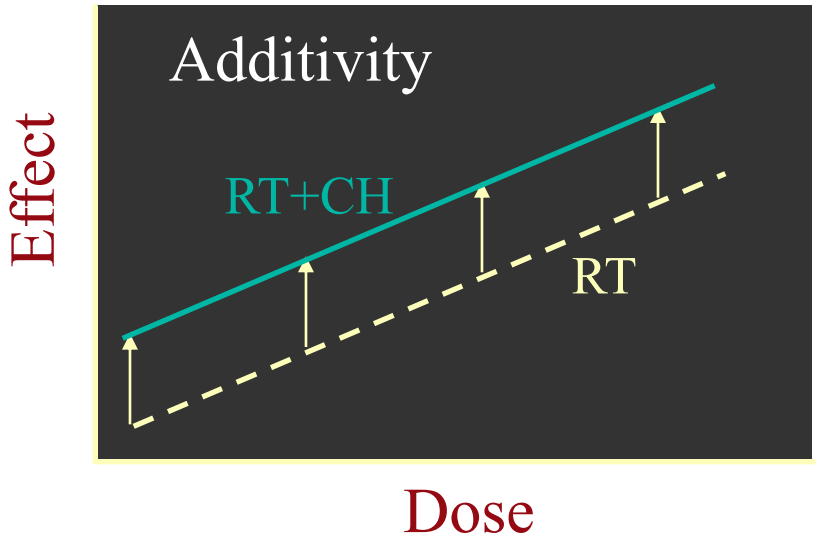
Trial category	Hazard ratio (95% CI)	Chemo-therapy effect (p)	Heterogeneity (p)	Absolute benefit	
				At 2 years*	At 5 years*
Adjuvant	0·98 (0·85–1·19)	0·74	0·35	1%	1%
Neoadjuvant	0·95 (0·88–1·01)	0·10	0·38	2%	2%
Concomitant	0·81 (0·76–0·88)	<0·0001	<0·0001	7%	8%
Total	0·90 (0·85–0·94)	<0·0001	<0·0001	4%	4%

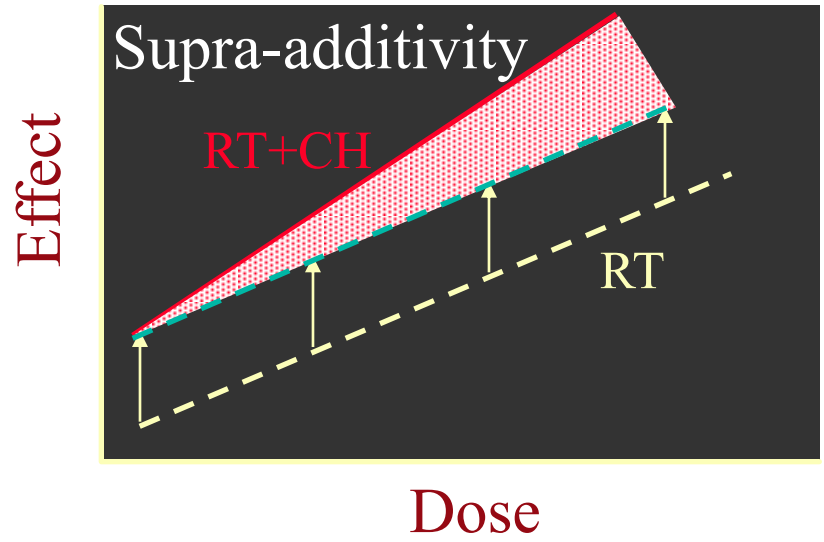
*Assuming survival rates of 50% at 2 years and 32% at 5 years in control groups.

Pignon et al., *Lancet* 355: 949-955, 2000

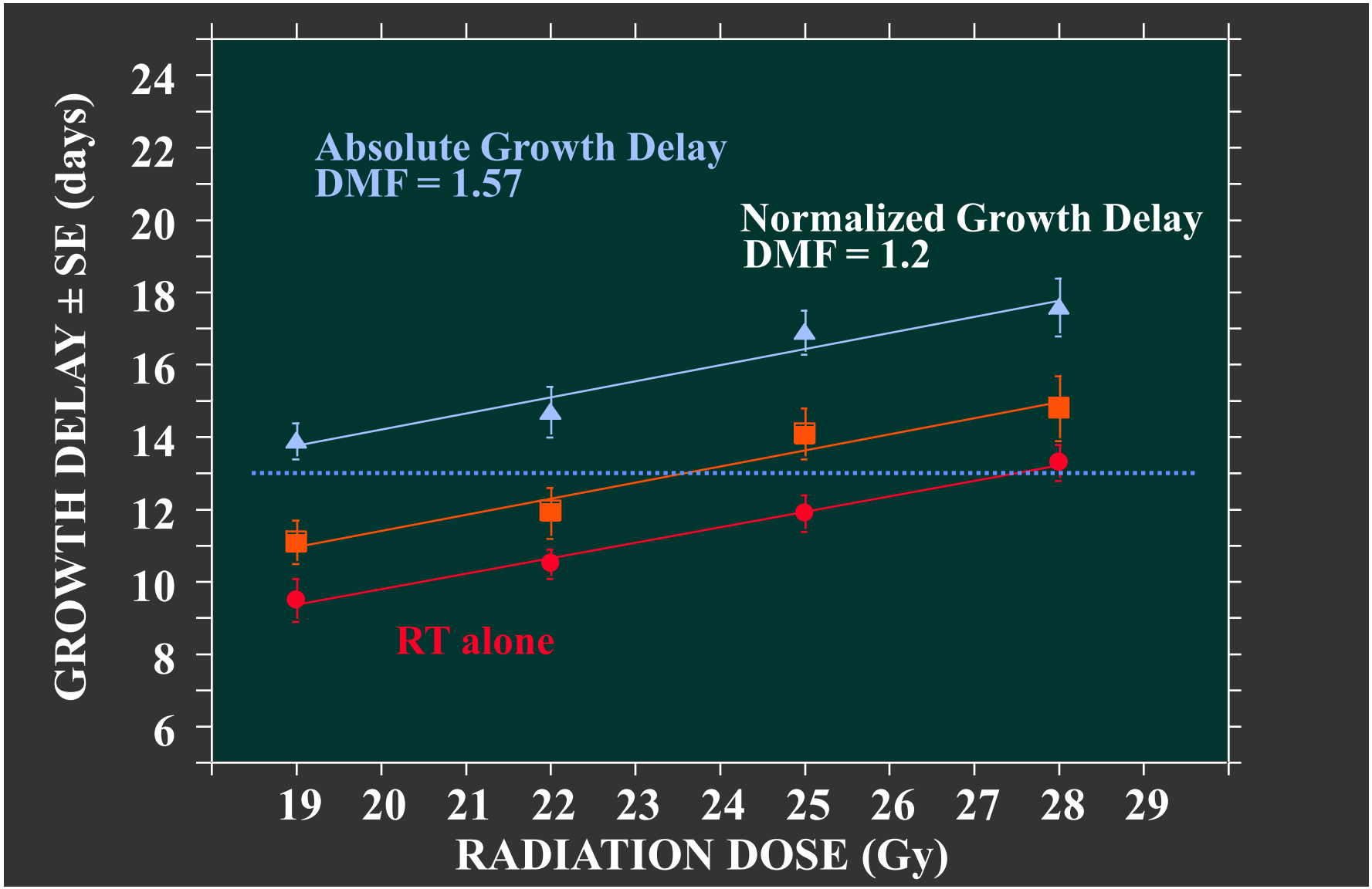
Combined chemo- and radiotherapy treatment



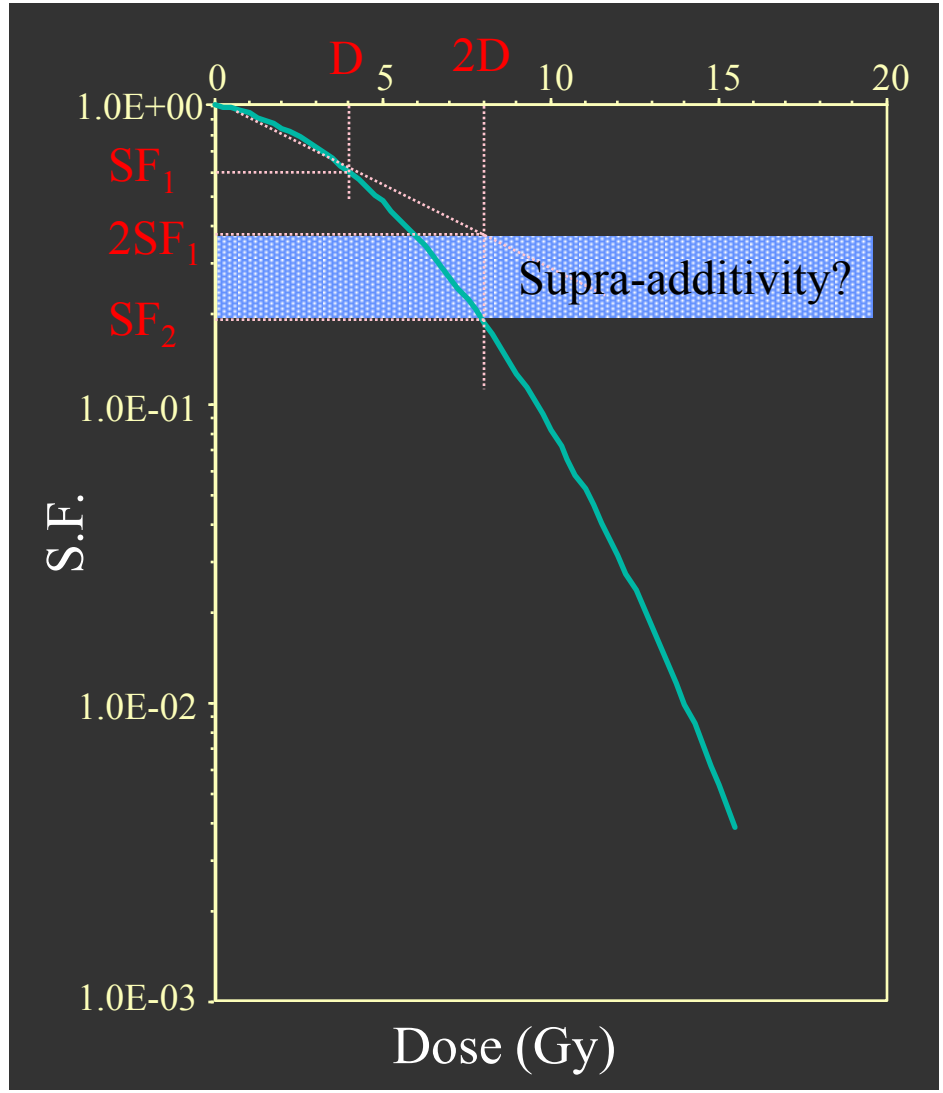




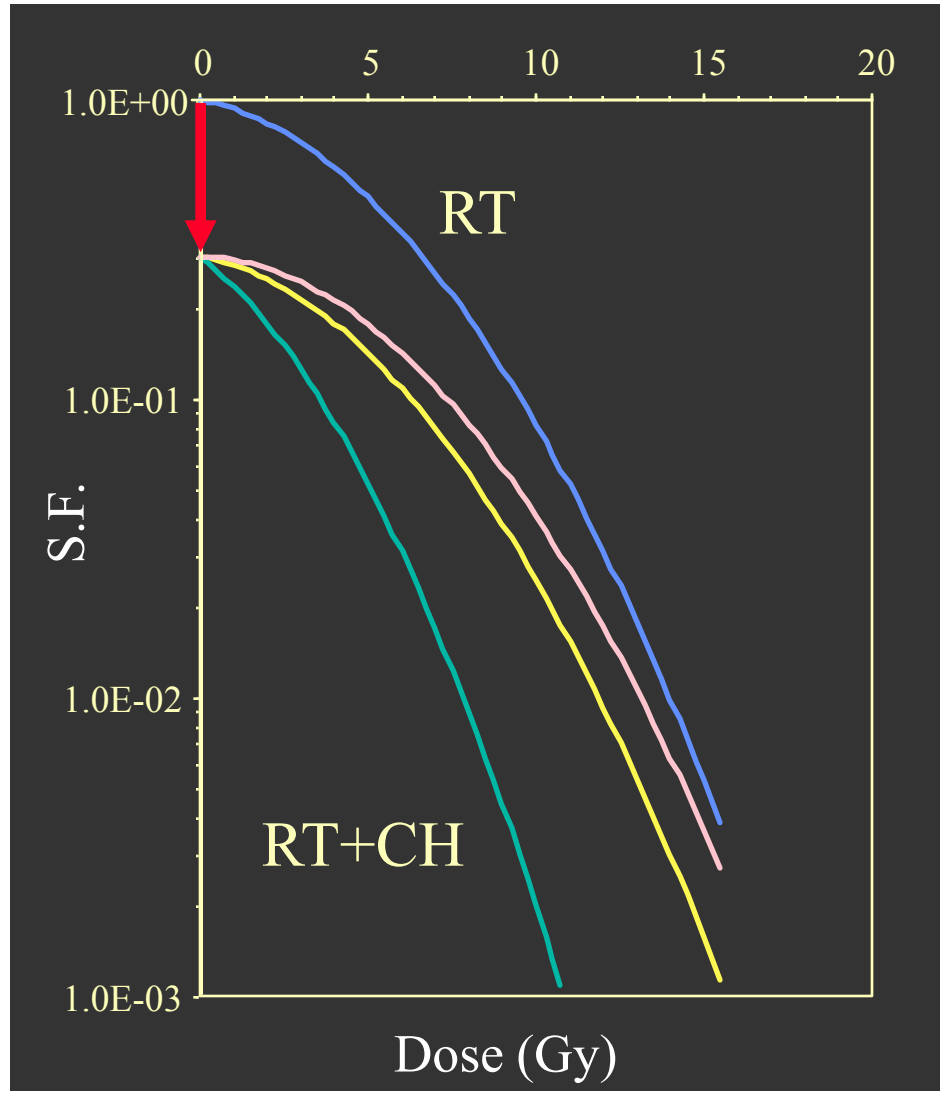
DOSE MODIFICATION FACTOR IN SA-NH TUMOR AFTER SINGLE IRRADIATION COMBINED WITH FLUDARABINE (800 mg/kg)



Combined chemo- and radiotherapy treatment

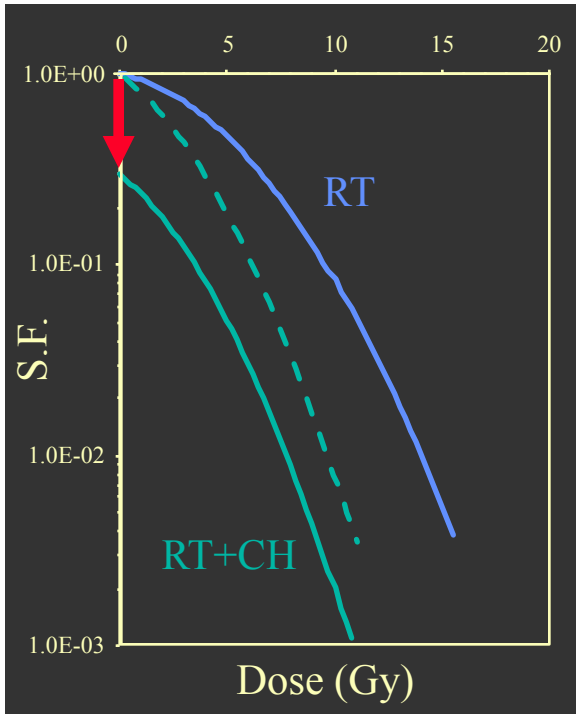


Combined chemo- and radiotherapy treatment

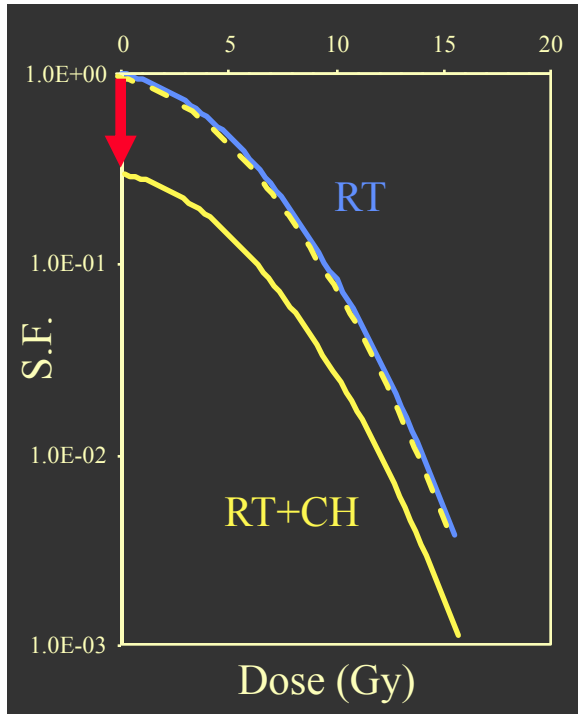


Combined chemo- and radiotherapy treatment

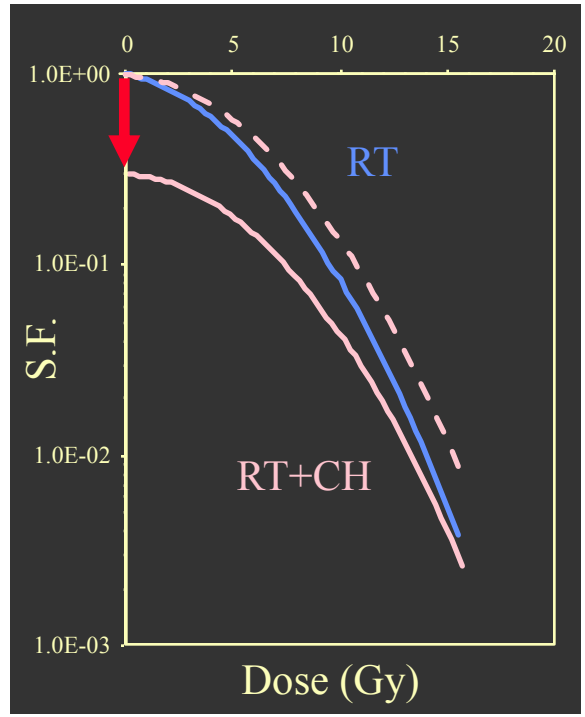
Enhancement



Non-interaction

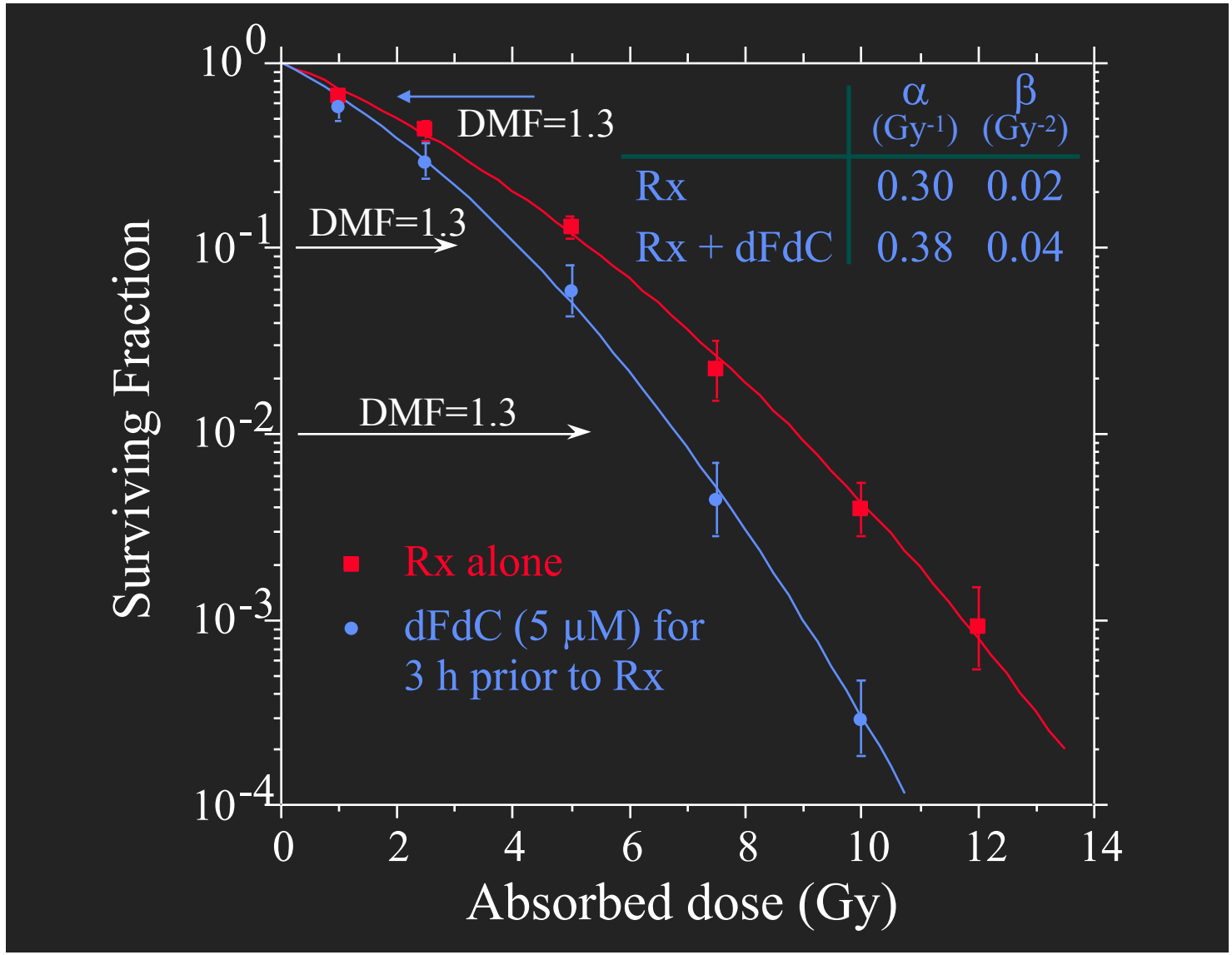


Inhibition



Redrawn from Steel

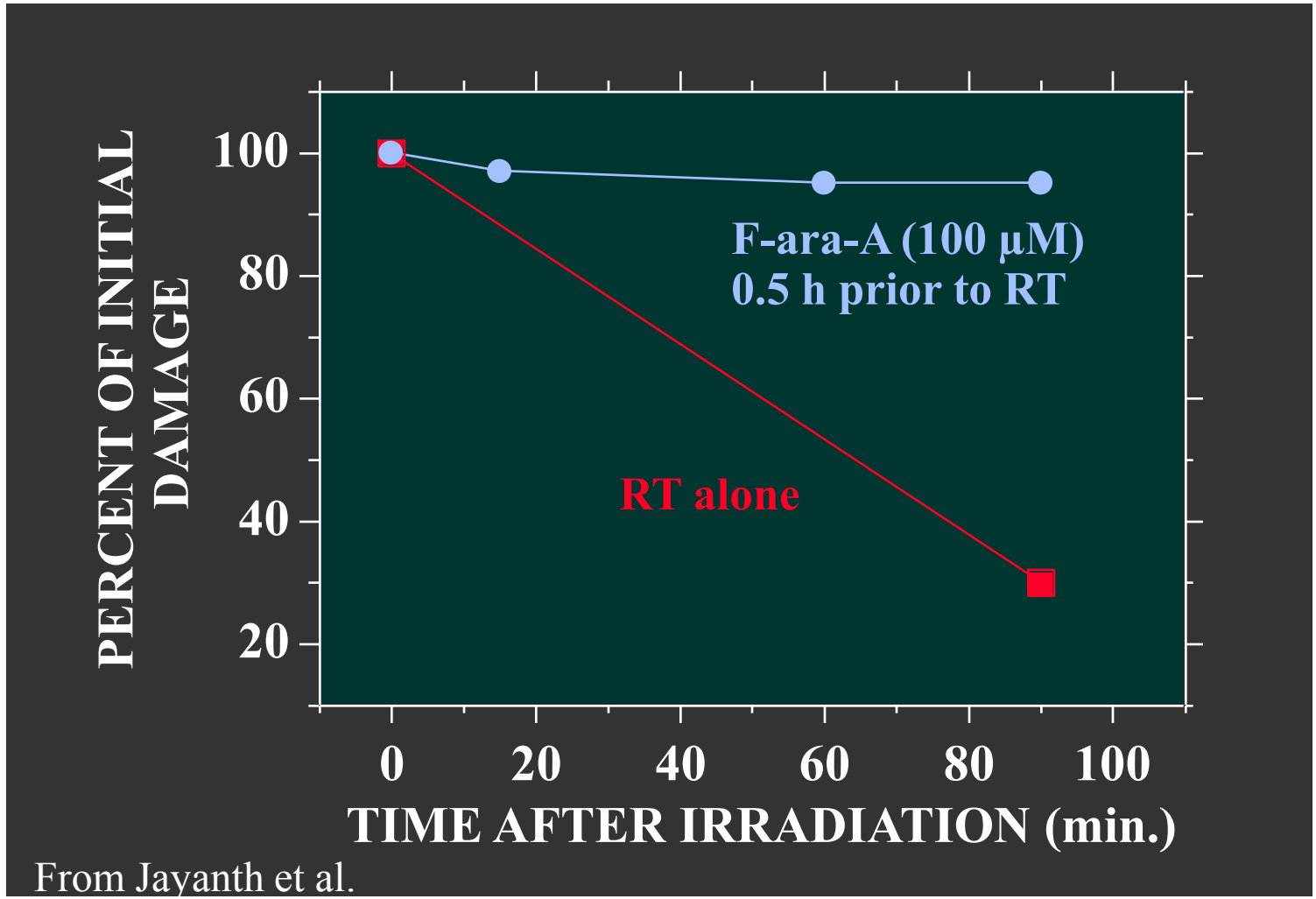
Radio-enhancement by dFdC of a human squamous cell carcinoma cell line (SQD9)



Rationales for combining chemotherapeutic agents and ionizing radiation

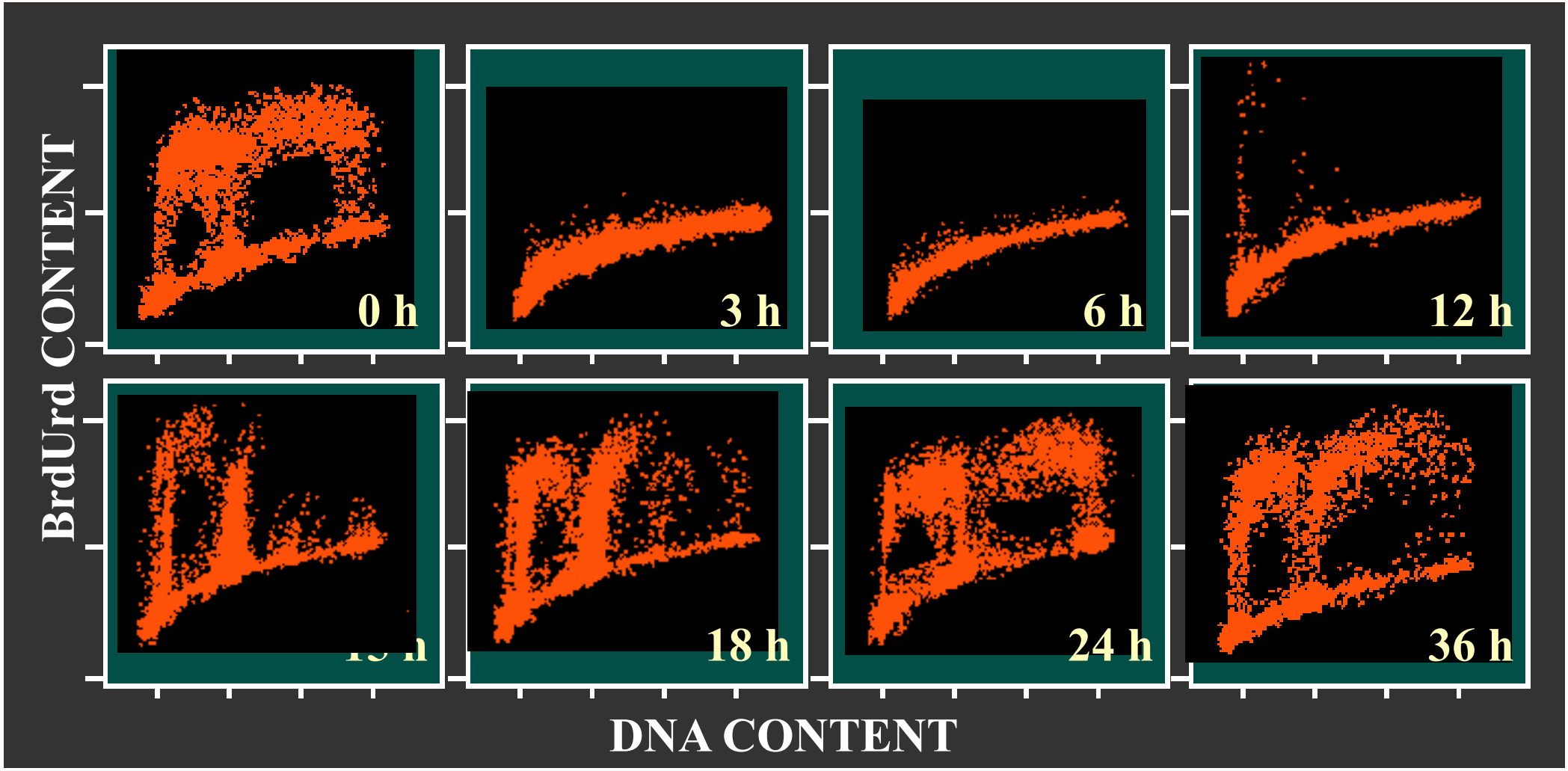
- modulation of DNA/chromosome repair
- regulation of tumor cell proliferation
- increased tumor cell loss
- enhancement of nucleoside analogue-induced apoptosis by IR
- increased tumor cell re-oxygenation

EFFECT F-ara-A ON CHROMOSOME BREAK REPAIR AFTER SINGLE DOSE IRRADIATION (4 Gy) IN HUMAN LYMPHOCYTES



From Jayanth et al.

CELL CYCLE REDISTRIBUTION INDUCED BY FLUDARABINE (800 mg/kg) IN SA-NH TUMOR



Combined chemo- and radiotherapy treatment: Cellular / molecular interaction

Antimetabolites

	DNA damage induction	DNA damage repair	Chromosome aberration	Cell Cycle	Apoptosis
5-Fu	-	-/+	-	+	?
MTX	?	?	?	?	?
HU	?	-/+	+	+	?
dFdC	-	-	+	+	-
F-ara-A	-	-	+	+	-?

Combined chemo- and radiotherapy treatment: Cellular / molecular interaction

Alkylating agents

	DNA damage induction	DNA damage repair	Chromosome aberration	Cell Cycle	Apoptosis
Cis-platinum	+?	+	?	-	?
BCNU	?	+	-	?	?
Cyclophosphamide	?	?	-	?	?

Combined chemo- and radiotherapy treatment: Cellular / molecular interaction

Topo-isomerase inhibitor

	DNA damage induction	DNA damage repair	Chromosome aberration	Cell Cycle	Apoptosis
Adriamycine	-	±	±	+	?
Etoposide	?	+?	-	+	+
Camptothecine	?	?	-	-/+	-/+

Combined chemo- and radiotherapy treatment: Cellular / molecular interaction

Anti-microtubule agents

	DNA damage induction	DNA damage repair	Chromosome aberration	Cell Cycle	Apoptosis
Vinca-alcaloides	?	-	?	+	?
Taxanes	?	-	+	+	+

Combined chemo- and radiotherapy treatment: Cellular / molecular interaction

Antibiotics

	DNA damage induction	DNA damage repair	Chromosome aberration	Cell Cycle	Apoptosis
Mitomycin-C	?	?	-	?	?
Bleomycin	?	-	-/+	+	?
Actinomycin-D	?	+?	?	?	-

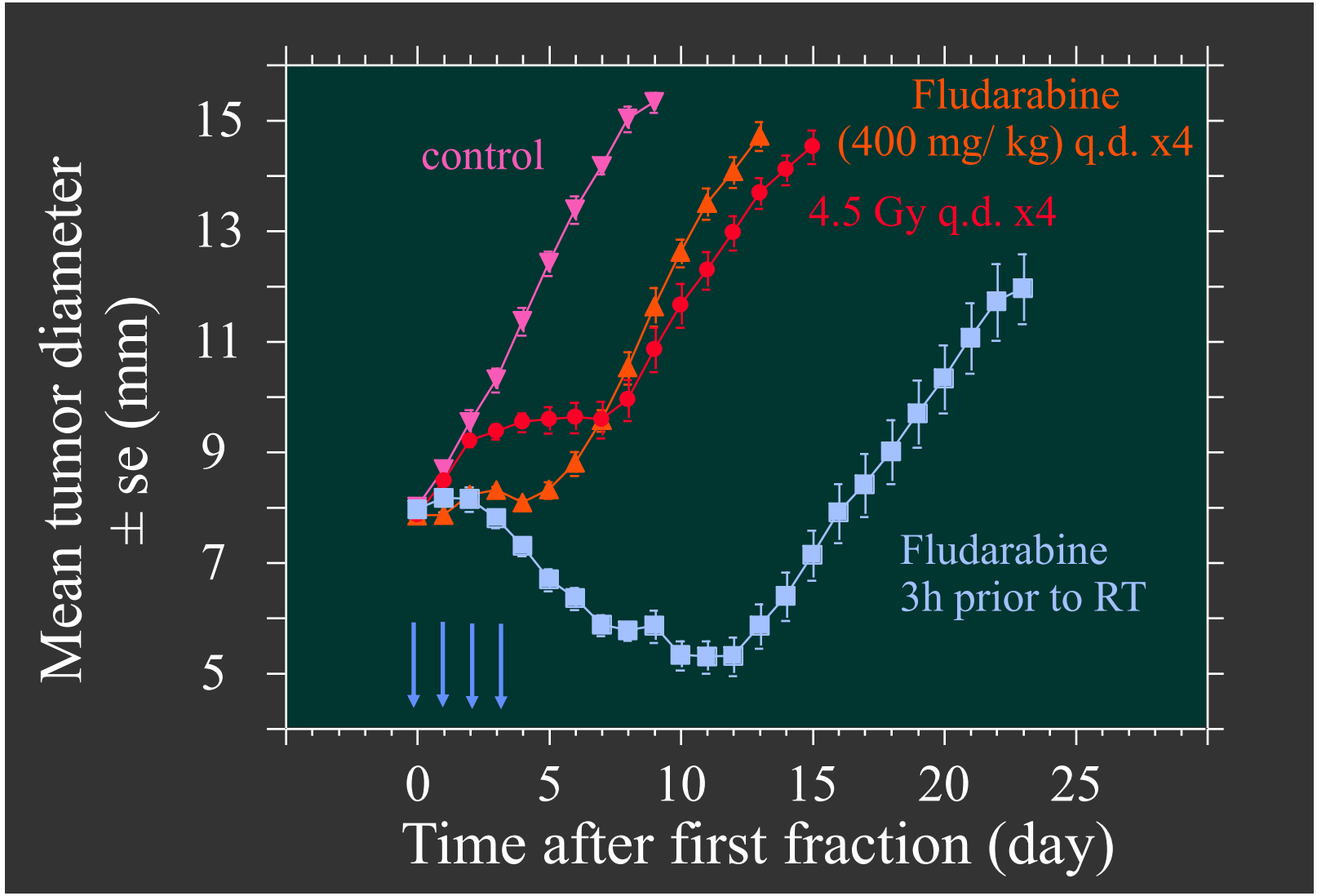
Combined chemo- and radiotherapy treatment

Cellular / molecular interaction

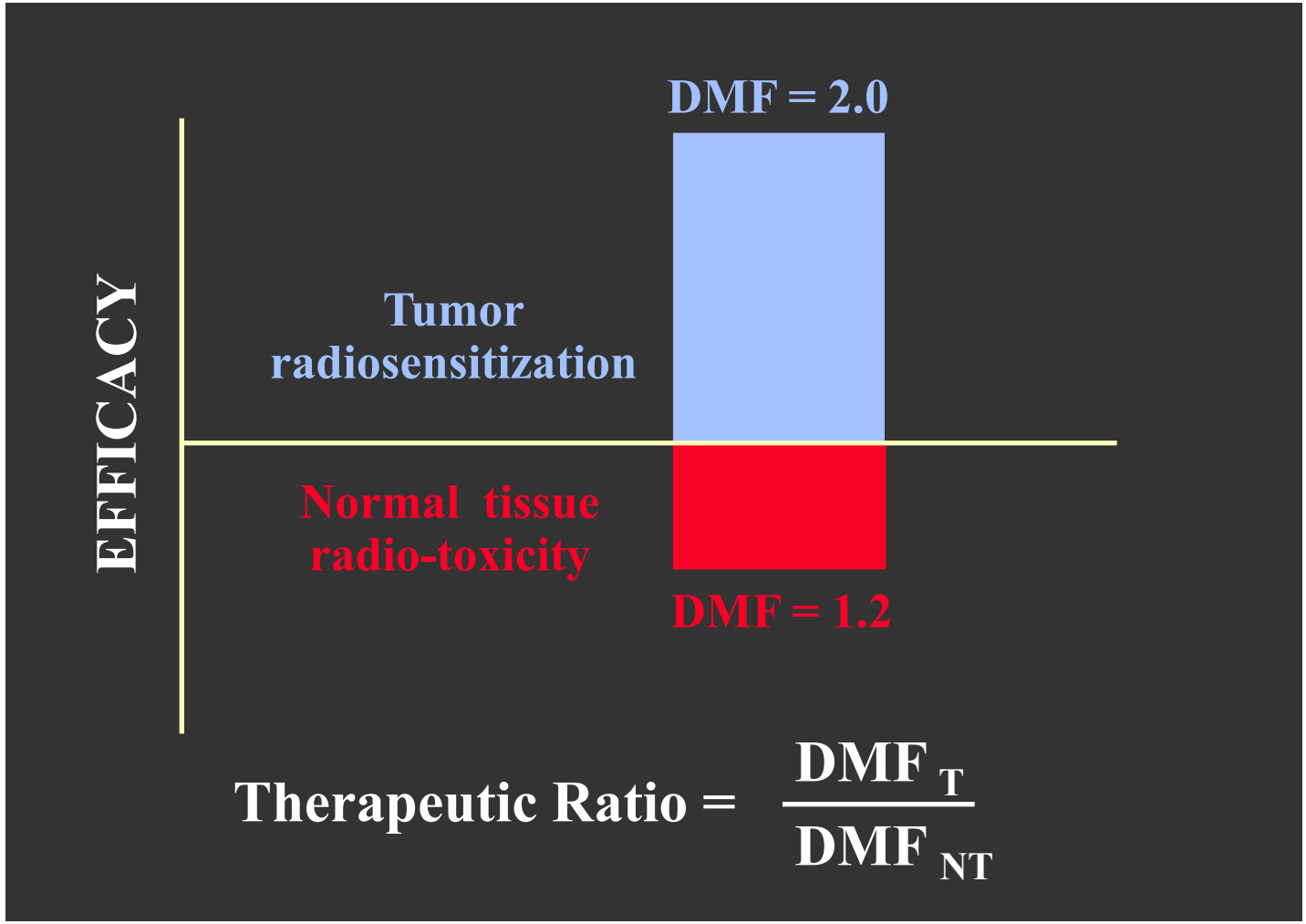
or

Tissular interaction ?

Modulation of regrowth delay in SA-NH tumor by fractionated irradiation and fludarabine administration



THE CONCEPT OF THERAPEUTIC RATIO



Combined chemo- and radiotherapy treatment:normal tissue toxicity

	Acute effect	Late effect
Antimetabolites		
5-Fu	++ (GI, skin)	
MTX	++ (GI)	
HU	++ (GI)	
dFdC	++ (GI)	± (lung)
F-ara-A	++ (GI)	± (SNC)
Alkylating agents		
cis-platinum	++ (GI)	+ (kidney)
BCNU	++ (GI)	+ (lung)
cyclophosphamide	++ (GI, skin)	+ (lung, bladder, SNC)
Antimetabolites		
adriamycine	++ (GI, skin)	+ (heart, lung)
mitomycin-C	++ (GI, BM)	+ (lung)
bleomycin	++ (skin, GI)	+ (skin, lung)
actinomycine-D	++ (GI, BM, skin)	+ (lung)
Plant derivatives		
Vinca-alcaloides	- (GI, BM)	?
Etoposide	?	?
Taxanes	+ (GI)	?

Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer.

M. Morris et al, NEJM, 340:1137-1143, 1999.

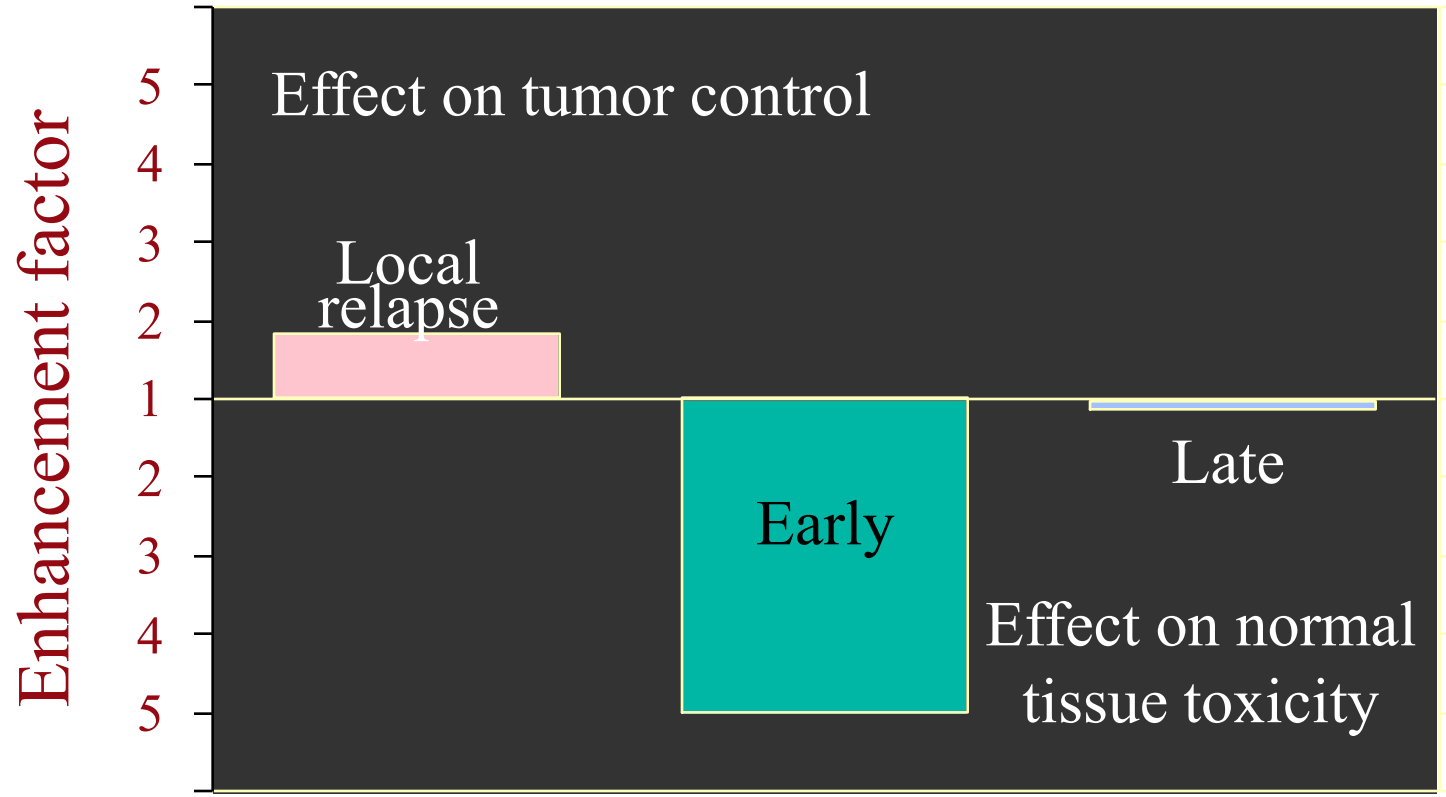
	RT (n=193)	RT+Chemo (n=195)
Early toxicity (G3-5)	10 (5%)	88 (45%)
Early toxicity* (G3-5)	4 (2%)	20 (10%)
Late toxicity (G3-5)	22 (11%)	24 (12%)

* non hematologic only

RT: 45 Gy + brachytherapy (total dose ≥ 85 Gy)
Chemo: cddp (75mg/m^2, d1), 5Fu (1g/m^2/d, d1-4), x3

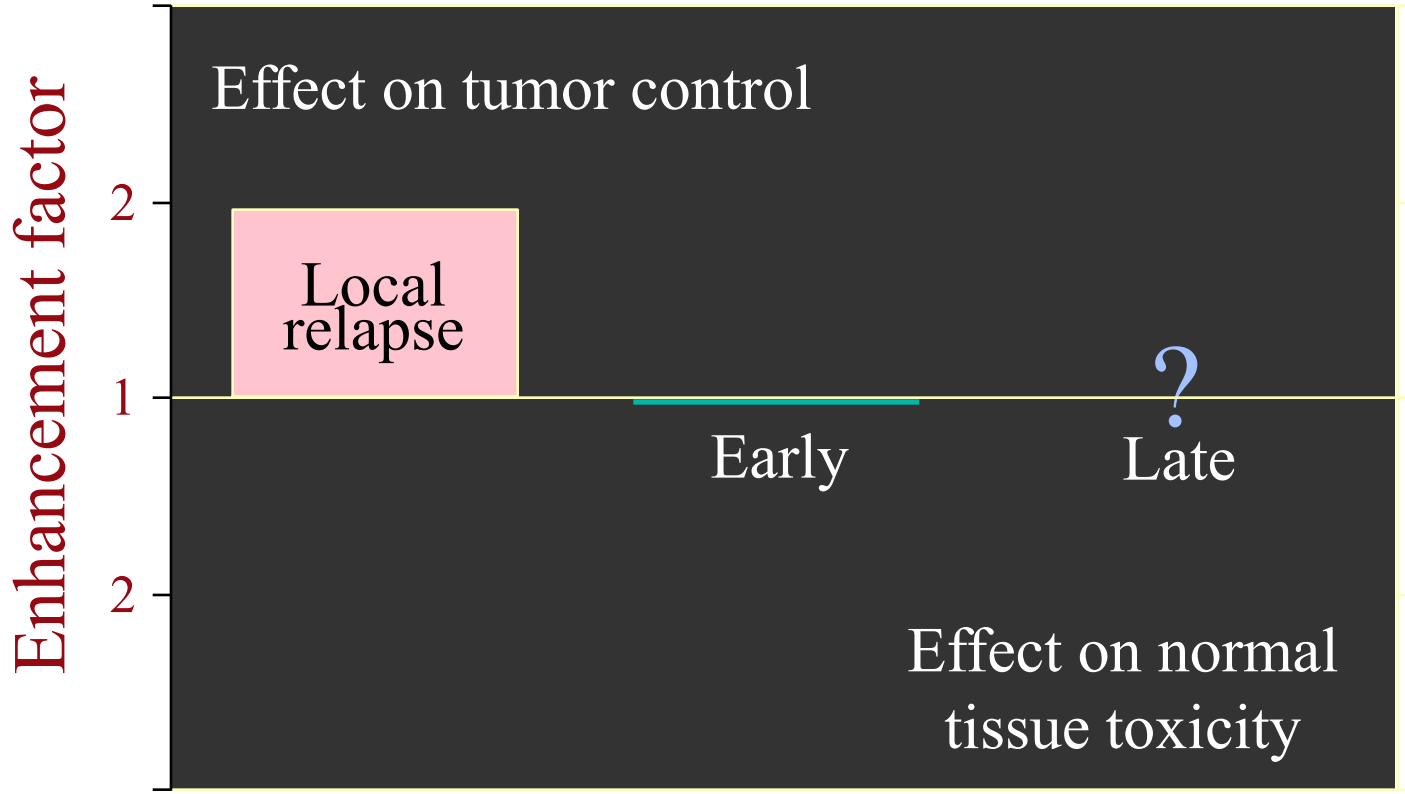
Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer.

M. Morris et al, NEJM, 340:1137-1143, 1999.



Treatment of advanced squamous-cell carcinoma of the head and neck with alternating chemotherapy and radiotherapy.

M. Merlano et al, NEJM, 327:1115-1121, 1992.



RT: 70 Gy, 7 weeks

RT+CH: 3 x 20 Gy, 9 weeks;
cddp (20mg/m^2/d, d1-5)-5Fu (200 mg/m^2/d, d1-5) x4

Combined chemo- and radiotherapy treatment

- “Objective-oriented” design of clinical trials
- Benefit of RT+Chemo is due to tissular interaction
- Anti-proliferation-based efficacy and toxicity
- More data needed to design combined RT+Chemo trial based on cellular/molecular interaction
- Equal dose trial <> equal toxicity trial

Retreatment tolerance of normal tissues

Karin Haustermans

Department of Radiation Oncology, University Hospitals Leuven, Belgium

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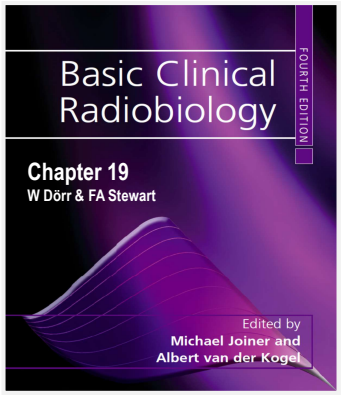
1

Overview

- Introduction
- Retreatment tolerance
  - Experimental studies
    - Early effects
    - Late effects
  - Clinical studies
- Take home messages



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Introduction

- Another R...

Radiation sensitivity
Recovery
Redistribution
Repopulation
Reoxygenation
iRradiated volume
RESTORATION (long term recovery)

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Introduction

- Reirradiation of previously treated areas: why?
  - New primary tumor
    - Cancer survivors are at an increased risk of developing secondary malignancies
      - Pts still retain more risk (e.g. molecular predisposition)
      - Aetiological factors can continue (e.g. Smoking)
      - Therapy itself
    - Within or close to initial high-dose treatment volume
  - Recurrence
    - Within or close to original gross tumor volume
  - Nodes and metastases

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Introduction

- Factors influencing decision on how to retreat
  - Previous dose/fractionation and volume irradiated
  - Organs at risk eg. spinal cord
  - Time from the first treatment
  - Local disease or metastases
  - Curative or palliative intent
  - Alternatives to reirradiation

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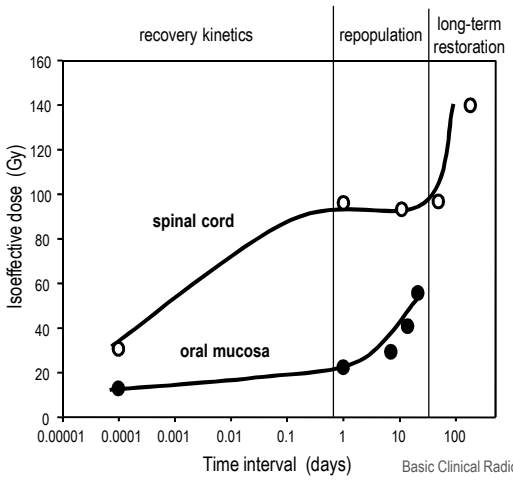
Introduction

- Changes in normal tissue tolerance with time



Long-term recovery from radiation injury in some tissues (not all!)

Basic Clinical Radiobiology, 4th Ed, page 150

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Introduction

No further treatment

- If the radiation tolerance within a given volume or organ has already been exceeded during the first treatment
- And function is lost (or loss is to be expected)

Retreatment possible

- If initial radiation treatment was in subtolerance dose range
- With the induction of only subclinical or minimal damage
- And with possible long-term recovery or potential residual damage after longer periods

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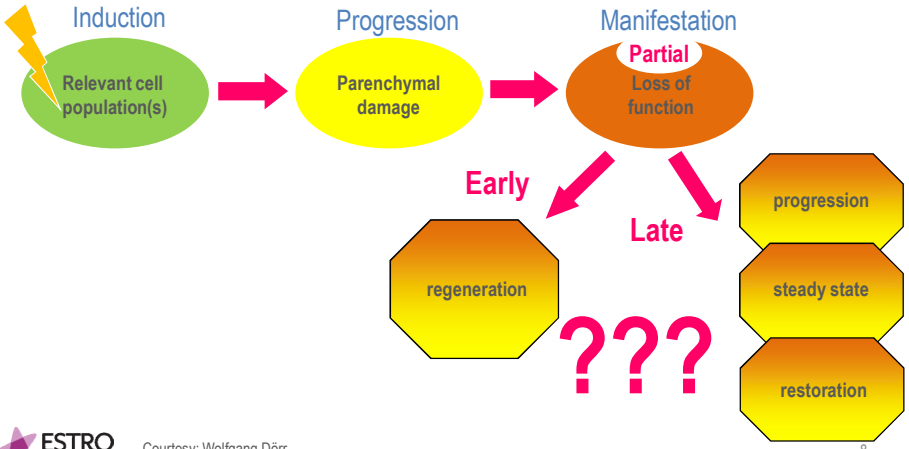
Introduction

- Pathogenesis of normal tissue radiation effects



ESTRO School Courtesy: Wolfgang Dörr

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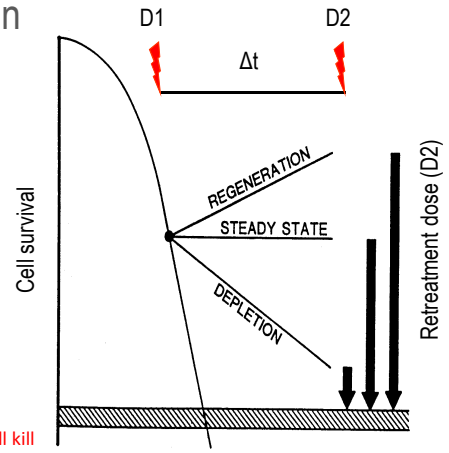
Introduction

- Retreatment tolerance depends on the level of cell kill and regeneration



"E"
Level of cell kill for tissue damage

Courtesy: Gordon Steel

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Introduction

- Some concepts
  - EQD_2: equivalent dose in 2-Gy fractions
    - Calculated using LQ-model with α/β values
      - 10 Gy for early reactions
      - 3 Gy for late reactions
  - EQD_{2tol}: tolerance doses
    - Threshold doses above which defined grades of toxicity are observed
  - % EQD_{2tol}: intensity of the initial treatment or the retreatment

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Experimental studies
Early effects

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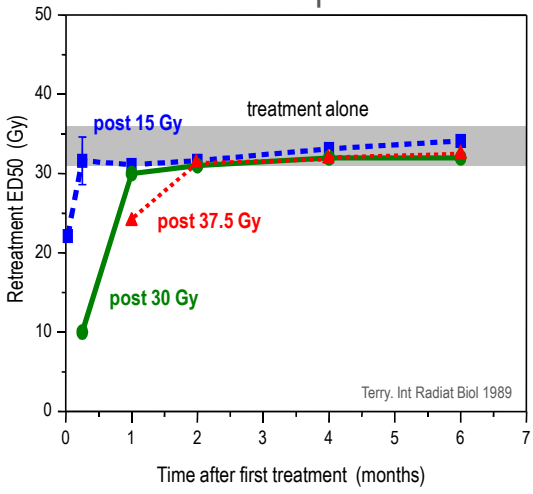
Epidermis

- Retreatment tolerance of mouse epidermis

Recovery to full tolerance within 1-2 months



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Retreatment skin and oral mucosa

- Rapid proliferative recovery begins within 2 weeks
- Full re-irradiation tolerance for early injury is reached within 2-3 months
- Re-irradiation tolerance for late damage will be less (cfr. slides mouse limb)

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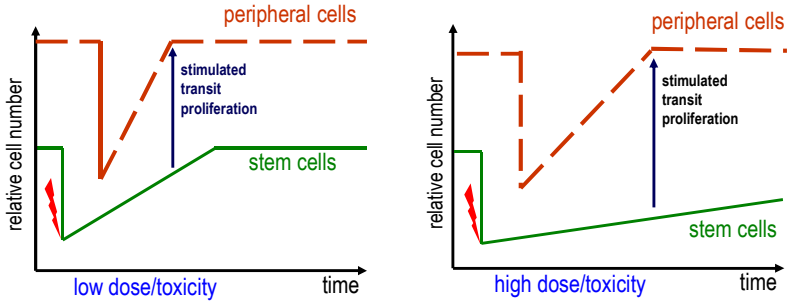
Bone marrow

- Toxicity of initial treatment must be considered, independently of blood cell counts that may be misleading!

Earlier recovery of peripheral cell number does not reflect recovery of stem cell population (*i.e.* restoration of radiation tolerance)



Courtesy W Dörr; Basic Clinical Radiobiology, 4th Ed, page 262

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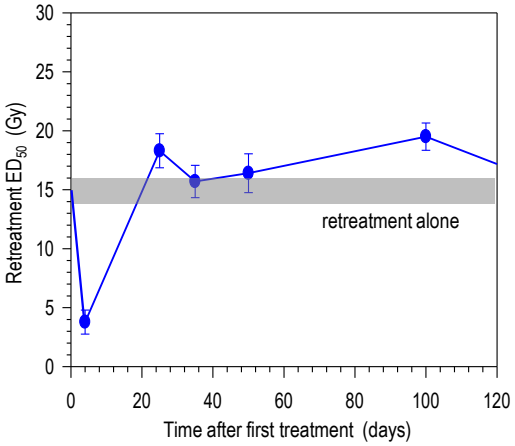
Urinary bladder (mouse)

- Original tolerance restored between 25-50 days

First treatment:
5 × 5.3 Gy over 1 week
Endpoint:
50% reduction in bladder storage capacity at 1–3 weeks
post retreatment



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Basic Clinical Radiobiology, 4th Ed, page 262; Satthoff & Dörr unpublished

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Retreatment principles: early effects

- Can achieve complete restoration of the initial tolerance
  - Epidermis: 2-3 months (rodents)
  - Oral mucosa: 12 days (but long term effects possible)
- Restoration of the stem cell compartment may take longer than “morphological” recovery

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Experimental studies
Late effects

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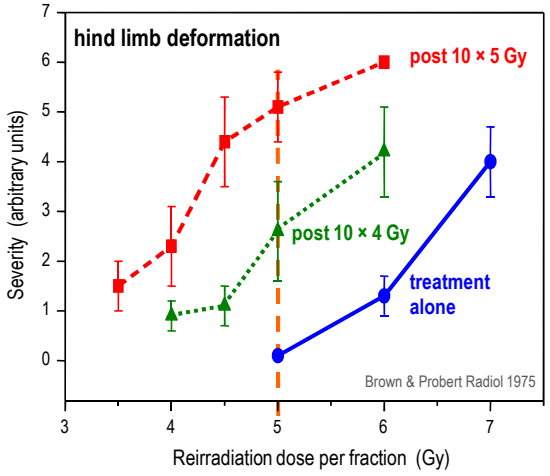
Skin

- Late radiation effects – mouse hind-limb

Two 10-fraction courses separated by 6 months

Effect of re-irradiation more pronounced after more aggressive initial treatment

Poorer retreatment tolerance than for early skin reactions



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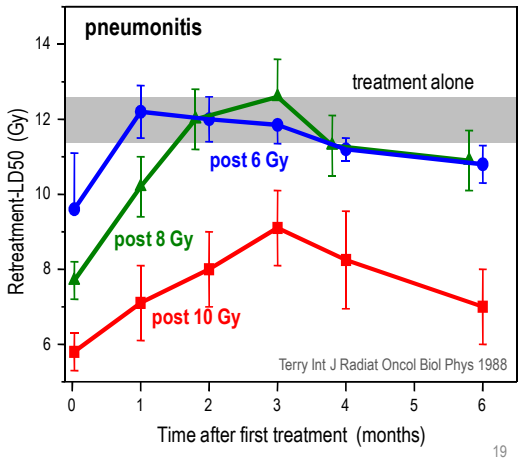
Lung

- Retreatment tolerance of the mouse lung

Initial dose <50% tolerance: *full recovery*, 2 months

Higher initial doses: *partial recovery*, 3 months

Only applies for pneumonitis phase: retreatment tolerance fibrosis might be poorer



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Kidney

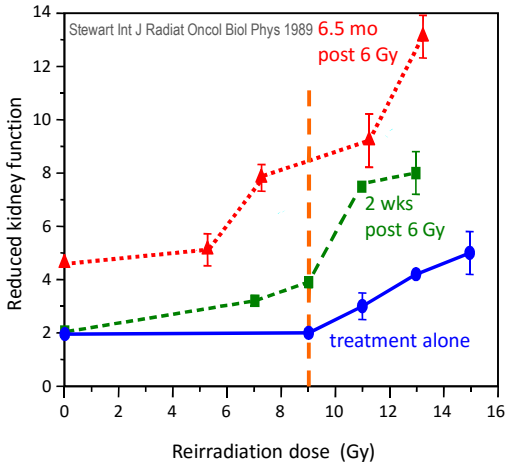
- Retreatment tolerance mouse kidney

No recovery between 1 day and 6 months after initial treatment

Progression of (subclinical) damage

Retreatment tolerance decreases with time

Extreme caution when re-irradiating kidneys!



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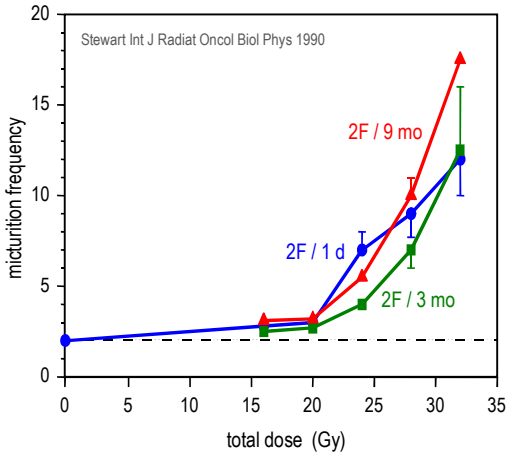
Urinary bladder

- Retreatment tolerance mouse bladder

No recovery between 1 day and 9 months after initial treatment

Progression of (subclinical) damage results in shortening of latent times after retreatment

Extreme caution when re-irradiating urinary bladder!



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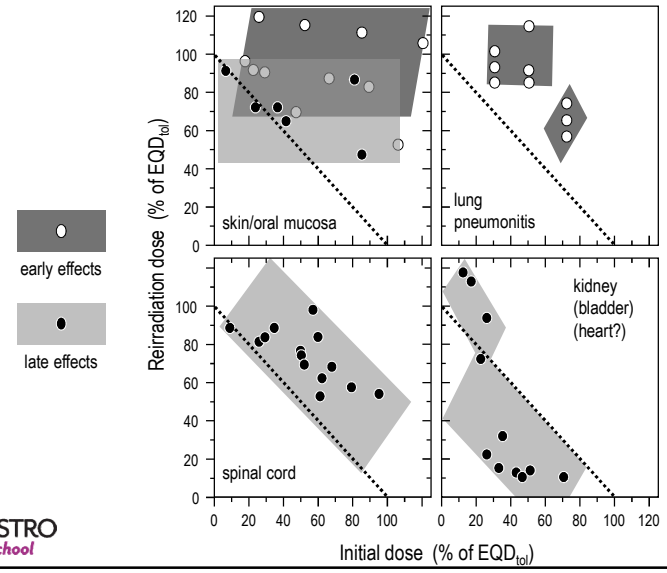
Summary experimental data

Modified from Stewart FA & van der Kogel AJ *Semin Radiat Oncol* 1994



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Summary experimental data

Several, but not all, normal tissues are able to tolerate considerable retreatment with radiation

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Clinical studies

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Pitfalls

- Problems with clinical data!
  - Extremely heterogeneous populations
  - Curative and palliative intent in the same series
  - Changes in staging and radiotherapy techniques
  - Changes in normal tissue scoring

Experimental animal systems *have been* essential to understand the radiobiology of retreatment tolerance

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Head & neck

- Review post-op RT for recurrent HNSCC
  - Major late complications are fibrosis, mucosal ulceration/necrosis and osteoradionecrosis
  - Nevertheless, high-dose re-irradiation recommended

Kasperts Oral Oncol 2005

Table 8 Results of studies of postoperative radiotherapy for recurrent head and neck cancer

Author	Clinical response rate	Survival	Acute complications	Late complications	Treatment-related deaths
Emami[31] (1967–1985)	CR at 3 months: 81% PR at 3 months: 4%	2 years OS: 45% 5 years OS: 20%	Not reported	Marked fibrosis: 16/99 (16%)† Trismus: 3/99 (3%) Fistula: 3/99 (3%) Esophagal stenosis: 2/99 (2%) Osteoradionecrosis: 1/99 (1%)	None
Benchalal[32] (1988–1996)	Local recurrence (in field): 9/14 (64%) Local recurrence (out field): 2/14 (14%)	1 years OS: 64% 2 years OS: 36% Mean survival: 21 months	Mucositis grade III: 9/19 (47%) Trismus: 1/19 (5%)	There were 15 late complications: Grade III 2/17 (12%) Osteoradionecrosis: 1 pt Dry eye syndrome: 1 pt	None
De Crevoisier[33] (1991–1996)	6-months LC: 64%	2 years OS: 48% 2 years DFS: 36% 5 years OS: not reported 5 years DFS: 26%	Mucositis grade III–IV: 13/25 (52%) Grade III dermatitis: 3/25 (12%) Hand and foot syndrome: 4/25 (16%) Grade III hematotoxicity: 1/25 (4%)	Fibrosis grade II–III: 11/25 (44%) Trismus: 6/25 (24%) Osteoradionecrosis: 4/25 (16%) (2 required hemimandibulectomy)	None
Errington[34] (1971–1983)	CR at 6 months: 82% PR at 6 months: 18%	2 years OS: 42% 5 years OS: 30%	Not reported	Grade I–III necrosis 7/28 (25%) Grade IV necrosis 6/28 (21%) (skin/subcutis, bone, facial nerve, and temporal bone)	Carotid rupture: 4% (1/28)
Nag[35] (1992–1997)	6-months LC: 33% 2 years LC: 4% Median time to LR-failure: 4 months	2 years OS: 21% 3 years OS: 8% Median survival: 7 months	Wound dehiscence: 1/38 (3%)	Orocutaneous fistula: 2/38 (5%) Tracheal dehiscence: 1/38 (3%) Carotid occlusion: 1/38 (3%) Tracheovascular fistula (FX): 1/38 (3%)	Tracheovascular fistula: 3% (1/38)

Complications not specified for patients who underwent salvage surgery and postoperative reirradiation Abbreviations: CR = complete response, PR = partial response, NR = no response, C = local control, LRC = local-regional control, LRRFS = local-regional recurrence free survival, OS = overall survival, DFS = disease free survival.

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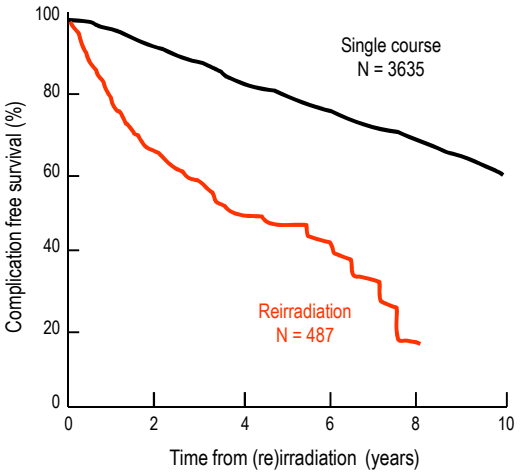
Head & neck

- Risk of late damage is higher in retreated patients…
- But cumulative total dose for 20% complication rate at 5 y is higher than predicted from single course treatment ($EQD2_3$ = 86 vs 67 Gy) indicating partial recovery!



Lee AWM et al. Int J Radiat Oncol Biol Phys 20000

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Head & neck

- Summary studies by Lee AWM et al
  - Local control: T1>T2>T3
  - Local control: EB+IRT >IRT or EBRT only
  - Initial dose (calculated as EQD2) correlated significantly with late complications (α/β = 2–3 Gy)
    No correlation with retreatment LC (α/β = 10 Gy)
  - Retreatment dose (calculated as EQD2) correlated significantly with LC (α/β = 10 Gy)
    Borderline correlation with late complications
    (p = 0.54 to 0.86 for α/β = 2–3 Gy)

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Head & neck

115 patients
reirradiation + various CT

Initial treatment median 68 Gy
Retreatment median 65 Gy

Table 7. Grade 4–5 complications*

Complication	*n*
Carotid hemorrhage	6
Osteoradionecrosis	13
Brain necrosis	0
Myelopathy	1
Peripheral neuropathy	1

* Using common terminology criteria for adverse events.

Salama Int J Radiat Oncol Biol Phys 2006

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Head & neck

- Head & neck reirradiation: selection criteria
  - Patient related considerations
    - No severe sequelae of previous radiation treatment
    - No significant comorbidities
    - PET-CT is suggested for staging
    - Interval between RT courses: at least 6 months, preferably longer (1y)
    - Better prognosis:
      - Previous surgery
      - Small (<30cm³) tumor size; caution with bulky tumors (>60cm³)
      - True second primary tumors (as compared to recurrences)
      - Tumors in nasopharynx and larynx
      - EGFR expression/HPV status: uncertain (needs to be evaluated in the context of re-irradiation)

Cacicedo Cancer Treatment Reviews 2014

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Head & neck

- Head & neck reirradiation: selection criteria
  - Treatment related considerations
    - Previous treatment plan: previous dose in area of recurrence ≤50Gy preferred (≥60-70Gy higher risk)
    - CTV = GTV + margin
    - Re-irradiation dose:
      - ≥ 60Gy to achieve more local control
    - Critical structures:
      - Spinal cord: do not exceed 50Gy (total cumulative dose)
      - No cases of myelopathy if cumulative doses ≤60Gy in 2Gy equivalent doses
    - Brachytherapy for small recurrences in oral cavity and oropharynx
    - IMRT or SBRT to reduce treatment-related toxicity

Cacicedo Cancer Treatment Reviews 2014

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Head & neck

- Head & neck reirradiation: selection criteria
  - General considerations
    - Treatment decision in multidisciplinary team
    - Consider including patient in clincial trial if possible

Cacicedo Cancer Treatment Reviews 2014

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Rectum

- Palliative reirradiation for recurrent rectal cancer (n=52)
  - Median reirradiation dose 30.6 Gy,
  - 2 × 1.2 Gy/f per day or 2 Gy/f per day
- Significantly lower risk of late complications with hyperfractionated treatment delivery (2 × 1.2 Gy/day)

Table 2. Late toxicity

RTOG Grade 3 toxicity	12/52 (23%)
Small bowel obstruction	9/52 (17%)
Cystitis	3/52 (6%)
RTOG Grade 4 toxicity	5/52 (10%)
Fistula	4/52 (8%)
Skin ulceration	1/52 (2%)

Table 4. Logistic regression analysis of factors influencing late toxicity

Factor	*p*-Value	Odds ratio	95% Confidence interval	
			Upper	Lower
RT technique	<0.04	3.937	1.074	14.438
Disease-free interval	NS			
Reirradiation dose	NS			
Total cumulative dose	NS			

Lingareddy V et al. Int J Radiat Oncol Biol Phys 1997;38:785–90

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Rectum

- Pre-op retreatment (hyperfractionation + chemotherapy) for rectal cancer
- Initial dose ≤55Gy; Re-irradiation dose 30Gy + boost of 10.8Gy with 2x1.2Gy per day
- Low acute toxicity and acceptable incidence of late complications

Valentini Int J Radiat Oncol Biol Phys 2006

Table 8. Acute toxicity (chemoradiation)

Grade	0	1	2	3	4
Hematologic	53 (89.8%)	5 (8.5%)	1 (1.7%)	0 (0.0%)	0 (0.0%)
Skin	57 (96.6%)	2 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gastrointestinal	29 (49.2%)	14 (23.7)	13 (22.0%)	3 (5.1%)	0 (0.0%)
Urologic	49 (83.0%)	7 (11.9%)	3 (5.1%)	0 (0.0%)	0 (0.0%)

Table 9. Late toxicity

Toxicity	*n* %
Skin fibrosis	2
Male impotence	2
Urinary incontinence	1
Small bowel obstruction*	1
Dysuria	1

* Requiring surgery.

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Prostate

- Brachytherapy is a feasible salvage option for pts with local recurrences after initial RT for prostate cancer

Table 1 Studies of re-irradiation for salvage of prostate cancer failures after primary radiotherapy

Study	No. of patients	Treatment (No. of pts)	Median follow-up (months)	Biochemical/ DFS (%) [years]	Definition of failure	Survival % (years)	Percent receiving ADT (%)
Goffinet et al. 1980; Cumes et al. [21]	14	I^{125}	6–36 (range)	79*	Palpable DRE abnormality	NR	29
Wallner et al. [33]	13	I^{125}	36	51 [5]	Progressive DRE Abnormality	OS 59 [5]	0
Loening and Turner [28]	31	Au^{198}	23(mean)	40 [1]	Cancer present at biopsy	OS 67 [5]	3
Dattoli et al. [22]	17	Pd^{103}	38	65*	PSA>1 ng/mL	NR	100
Butler et al. [35]; Teh et al. [31]	30	Au^{198}	54	17*	3 consecutive rises, PSA >1, metastases	NR	0
Grado et al. [23]	49	I^{125} (37) Pd^{103} (12)	64	34 [5]	2 consecutive rises above nadir	OS 56 [5] DSS 79 [5]	14
Beyer [							47
Koutrouvelis et al. [23]	31	I^{125} (24)	30	87*	ASTRO* or nadir >4 ng/mL	OS 100*	97
Wong et al. [34]	17					OS 71 [4] DSS 100*	100
Nguyen et al. [30]	25	I^{125}	47	70 [4]	Phoenix	NR	0
Lee et al. [26]	21	HDR	19	89 [2]	ASTRO	OS 100*	52
Allen et al. [18]	12	I^{125} (4)c Pd^{103} (8)	45	63 [4]	ASTRO	OS 54 [4] DSS 100*	100
Lee et al. [27]	21	Pd^{103}	36	38 [5]	ASTRO	OS 81 [5] DSS 100*	57
Tharp et al. [32]	7	HDR ± EBRT	58	71*	ASTRO	OS 71*	100
Aaronson et al. [17]	24	I^{125} (19) Pd^{103} (5)	30	88*	Phoenix	DSS 96*	17
Burri et al. [20]	37	Pd^{103} (36) I^{125} (1)	86	65 [5] 54 [10]	Phoenix	OS 94 [5] DSS 96 [5]	84
Moman et al. [29]	31	I^{125}	108 (mean)	20 [5]	Phoenix	OS 72 [5] DSS 74 [5]	16
Jo et al. [24]	11	HDR	29 (mean)	64*	ASTRO	NR	45

Prospective studies needed to better define efficacy and toxicity

Ramey World J Urol 2013

Prostate

- Toxicity fairly high

Ramey World J Urol 2013

Study	Number of patients	Treatment Modality, dose[a]	GU Grade 1–2 (%)	GU Grade 3–4 (%)	GI Grade 1–2 (%)	GI Grade 3–4 (%)	Incontinence (%)	ED (%)	Fistula formation (%)
Butler et al. [35]; Teh et al. [31]	30	Au_{198}, 20 Gy	A-37 L-7	0	A-13 L-3	0	NR	NR	NR
Wong et al. [34]	17	I_{125}, 127-139 Gy Pd_{103}, 119 Gy	53	47	65	6	18[b]	NR	0
Nguyen et al. [30]	25	I_{125}, 137 Gy	NR	20	NR	20	12	NR	13
Lee et al. [26]	21	HDR, 36 Gy/6 fractions	86	14	14	0	0	92	0
Allen et al. [18]	12	I_{125}/Pd_{103}, 90–112.5 Gy	42	0	0	0	25	NR	0
Lee et al. 27	21	Pd_{103}, 90 Gy	29	0	5	0	NR	NR	0
Tharp et al. [32]	7	HDR, 6-9 Gy/2-6 fractions ?	71	29[c]	14	0	29	100	0
Aaronson et al. [17]	24	I_{125}/Pd_{103}, 72 Gy	33	0	8	4	4	NR	0
Burri et al. [20]	37	Pd_{103}, 110 Gy I_{125}, 135 Gy	32	8	5	3	5	75	3
Moman et al. [29]	31	I_{125}, 145 Gy	A-87 L-55	A-3 L-19	A-55 L-51	A-0 L-6	NR	NR	6
Jo et al. [24]	11	HDR, 22 Gy/2 fractions	"Low"	0	0	0	0	NR	0

Lung

- High-dose re-irradiation for locoregional recurrent NSCLC might be beneficial in selected patients

	Number of patients	Median follow-up (months)	Median interval first RT and re-RT (months)	Median overall survival (months)	Median time to progression (months)
Wu et al[28]	23	15	13	14	Not stated
Okamoto et al[29]	18 (radical)	Not stated	23	15	Not stated
Peulen et al[30]	29	12	14	19	Not stated
Coon et al[31]	12	12	Not stated	Not stated	7·7
Kelly et al[32]	36	15	22	24	12
Evans et al[33]	35	42	Not stated	Not stated	Not stated
Liu et al[34]	72	16	21	Not stated	Not stated
Meijneke et al[35]	20	12	Not stated	15	7
McAvoy et al[36]	33	11	36	11·1	4·5
Reyngold et al[37]	39	12·6	37	22	13·8
Kilburn et al[38]	33	17	18	21	16
Yoshitake et al[39]	17	12·6	Not stated	18	8

RT=radiotherapy. Re-RT=re-irradiation. OS=overall survival.

Table 4: Efficacy of high-dose re-irradiation

De Ruysscher Lancet Oncol 2014

Scarcity of high-quality data!

	Re-RT technique	Grade 1–2 toxicity	≥Grade 3 toxicity
Wu et al[28]	3DCRT	G1+G2 lung (22%); G1+G2 oesophagus (9%)	None
Okamoto et al[29]	3DCRT	G2 oesophagus (24%)	G3 lung (21%); G3 oesophagus (6%)
Peulen et al[30]	SABR	..	G4 fistula and stenosis* (one case); G5 bleeding (10%)
Coon et al[31]	SABR	..	None
Kelly et al[32]	SABR	G2 lung (31%)	G3 lung (19%); G3 oesophagus (8%); G3 skin (6%); G3 cough (3%)
Evans et al[33]	SABR	..	G5 bleeding (6%)
Liu et al[34]	SABR	..	G3 lung (19%); G5 lung (1%)
Meijneke et al[35]	SABR	..	None
McAvoy et al[36]	Protons	..	G3 lung (21%); G3 oesophagus (9%); G4 lung (6%); G4 oesophagus (3%)
Reyngold et al[37]	SABR	G2 lung (18%); G2 fatigue (15%); G2 chest wall pain (13%); G2 skin (3%)	G3 lung (5%)
Kilburn et al[38]	SABR	G2 (all) (30%)	G3 lung (3%); G5 bleeding (3%)
Yoshitake et al[39]	3DCRT	..	None
Trovo et al[40]	SABR	..	G3 lung (23%); G5 lung (0·5%); G5 bleeding (0·5%)
Griffioen et al[41]	3DCRT	G1+G2 oesophagus (46%); G1+G2 cough (42%); G1+G2 skin (33%); G1+G2 fatigue (25%)	G5 bleeding (12%)

Re-RT=re-irradiation. 3DCRT=three-dimensional radiotherapy. SABR=stereotactic ablative radiotherapy. G=grade. Lung=pneumonitis. *Fistula between the trachea and a gastric tube reconstruction/superior vena cava stenosis.

Table 3: Normal tissue toxicity after high-dose re-irradiation

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Breast

- Partial breast irradiation after second BCS is viable alternative to mastectomy

Sedlmayer The Breast 2013

Primary treatment and time to IBTR.

Study	*N* (pts.)	Primary treatment		Time to IBTR (months)	
		EQD_2 (max. to the tumour bed)	Technique	Minimum	Median
Chadha 2008	15	Not reported	Not reported	28	94
Hannoun-Levi 2004	69	50 Gy + boost (not specified)	EBRT	Not reported	70
Trombetta 2009	26	60.4 Gy physical dose	EBRT	4.8	96
Guix 2010	16	50 Gy + boost (not specified)	EBRT + boost (HDR)	12	38
Hannoun-Levi 2011	63	50 Gy + boost	EBRT	12	132
Polgar 2012	15	Not reported	Not reported	Not reported	79.7
Kauer-Dorner 2012	39	62.5 Gy – 75.9 Gy	EBRT + boost (LDR or HDR)	12	131
Resch 2002	17	50 Gy + boost (not specified)	HDR	12	70
Deutsch 2002	31	50 Gy + boost (not specified)	EBRT	12	72
Kraus-Tiefenbacher 2007	17	62 Gy	EBRT	36	120
Total	**315**				

Evidence for brachytherapy more solid

Little info about effectiveness PBI via EBRT or IORT

Secondary treatment.

Study	Secondary treatment			
	Physical dose (max)	Fractionation	Technique	Treated volumes
Chadha 2008	45 Gy	0.5 Gy/h	LDR	Not stated
Hannoun-Levi 2004	50 Gy	Not reported	HDR	Not stated in ccm information on implant sizes: one vs. two planes, <vs. ≥5 wires
Trombetta 2009	34 Gy or 50 Gy	3.4 Gy bid or 0.5 Gy/h	HDR or LDR	V100: 105 ccm (36–260)
Guix 2010	30 Gy	12 fx/5 d	HDR	Not stated
Hannoun-Levi 2011	34 Gy	10 fx/5 d	HDR	PTV: mean 68 ccm (31.2–146); V100: 90 ccm (60–97)
Polgar 2012	22 Gy	5 fx/5 d	HDR	Not stated
Kauer-Dorner 2012	50.1 Gy	0.8 Gy/h	PDR	PTV 58 ccm (18 SD)
Resch 2002	30 Gy + 12.8 Gy	2 Gy/d + 0.8 Gy/h	EBRT + PDR or PDR alone	PTV 58.3 ccm (25–152)
Deutsch 2002	50 Gy	2 Gy/d	EBRT	Not stated
Kraus-Tiefenbacher 2007	14.7 Gy – 20 Gy	Single dose	50-kV-IORT	Not applicable

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Summary clinical data

- Re-irradiation is an option for patients with recurrent or second tumors
- Risk of normal tissue damage and impact on quality of life must be taken into account

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Take home messages

- If tolerance has already been exceeded: no re-irradiation possible without loss of function
- Early effects
  - Low to moderate doses:
    - Restitution of original tolerance may be complete after tissue-specific and dose-dependent time intervals
  - High doses:
    - Residual damage may remain for longer intervals, particular at the stem cell level, which is not necessarily reflected in functional tissue compartments

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Take home messages

- Late-responding tissues
  - Partial (CNS, lung) or complete (skin) restoration of tolerance after low to moderate doses (<60% initial tolerance)
  - Progression of damage at subclinical level (kidney, urinary bladder) must be expected thus precluding re-irradiation without exceeding tolerance

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Take home messages

- Strategies for retreatment
  - Alternative treatment options must be considered before re-irradiation
  - If (curative) re-irradiation is to be considered
    - Use best available treatment planning
    - Consider hyperfractionation for treatment with curative intent
    - Consider combined EBRT and brachytherapy

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Spinal cord data

THANK YOU BERT!

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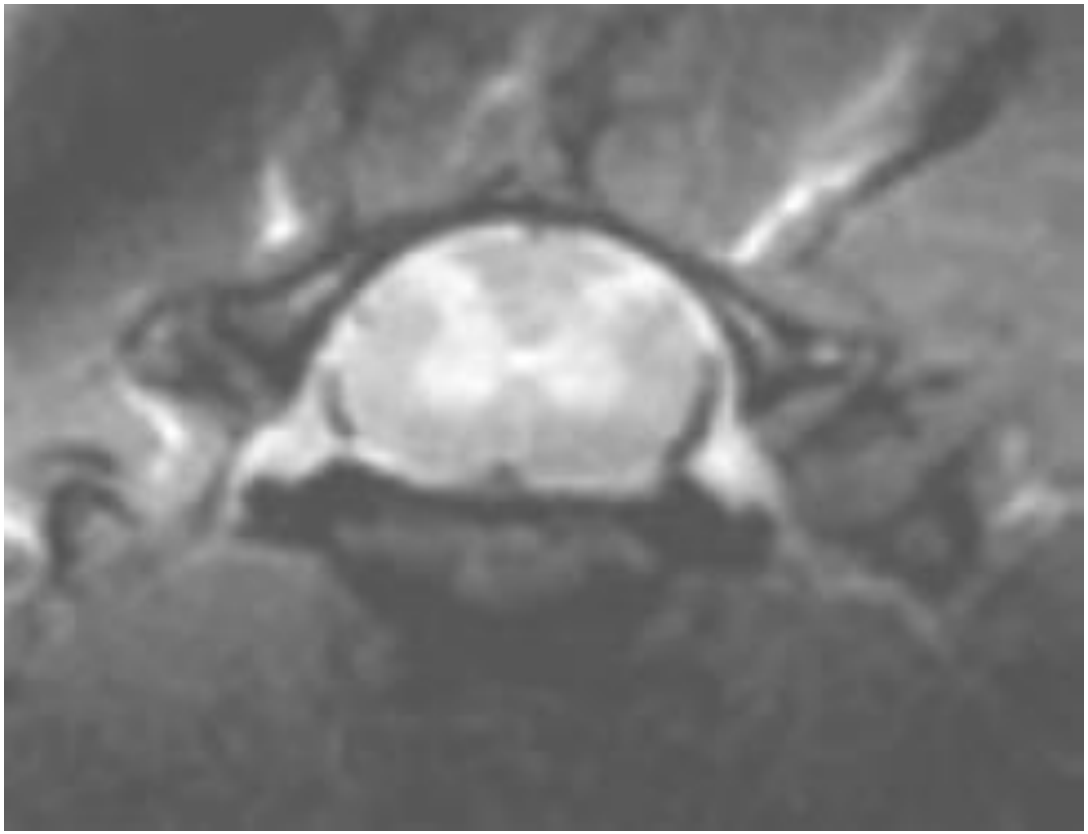
retreatment tolerance of spinal cord



Albert van der Kogel

Dept of Human Oncology, Univ of Wisconsin School of Medicine, Madison, USA

Clinical radiation doses for spinal cord: the 1998 international questionnaire

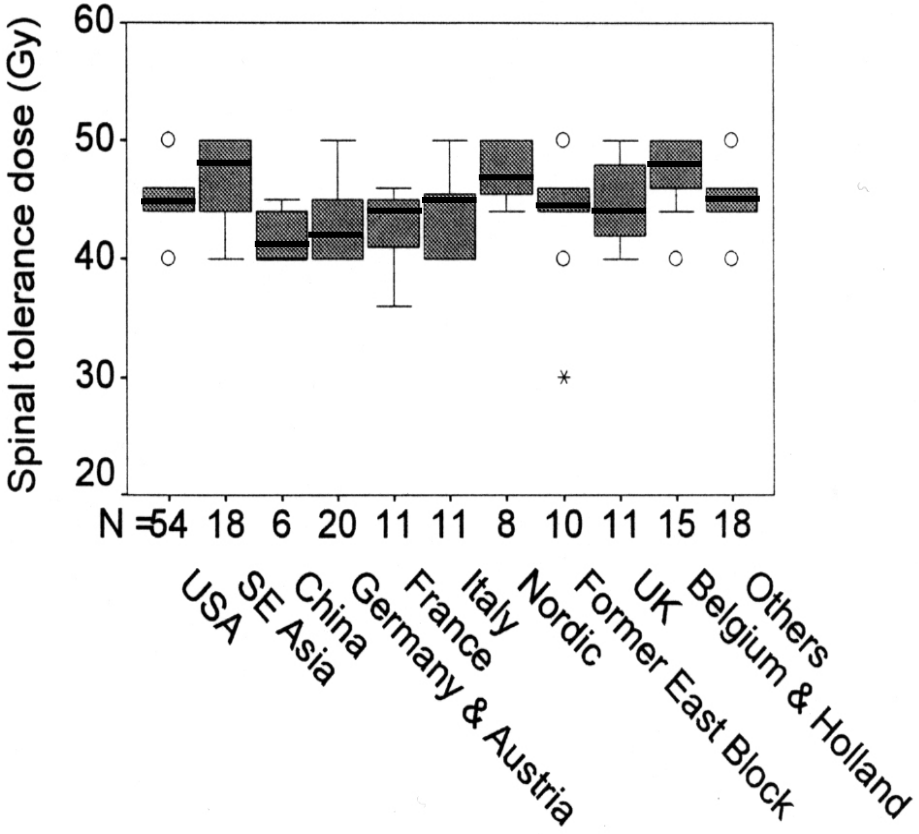
J.F. Fowler, S.M. Bentzen, S.J. Bond, K.K. Ang, A.J. van der Kogel, W. van den Bogaert, E. van der Schueren

Radiotherapy & Oncology, 55: 295-300, 2000

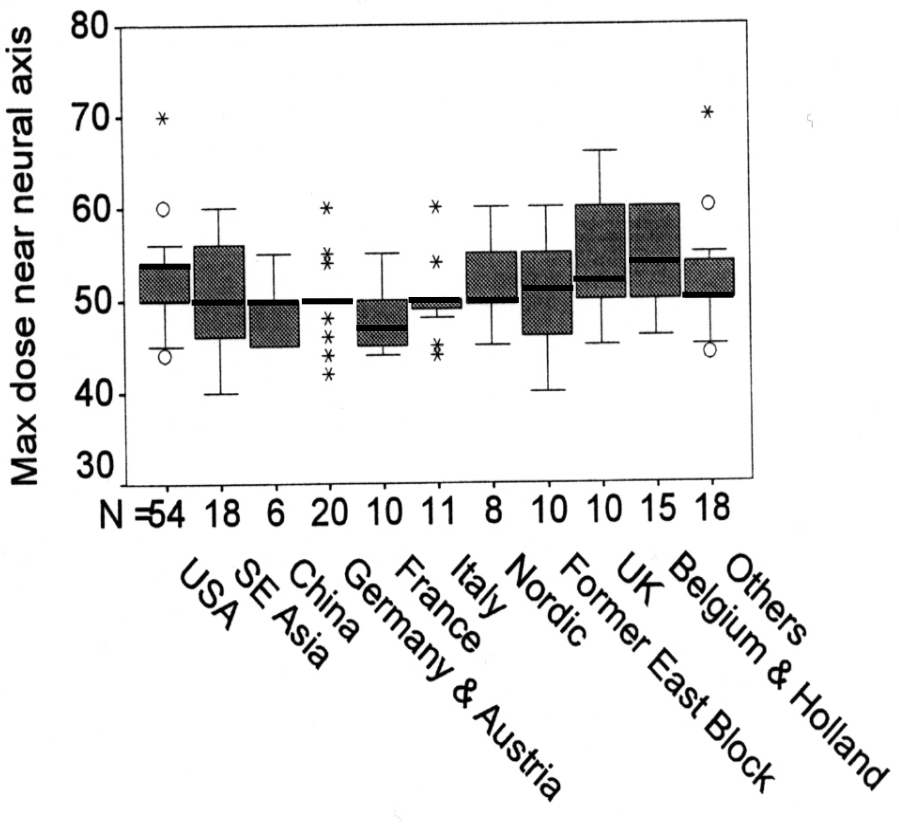
Geographical variation in accepted doses to spinal cord (1998)

Response to questionaires sent to RT departments around the world

A) normally accepted

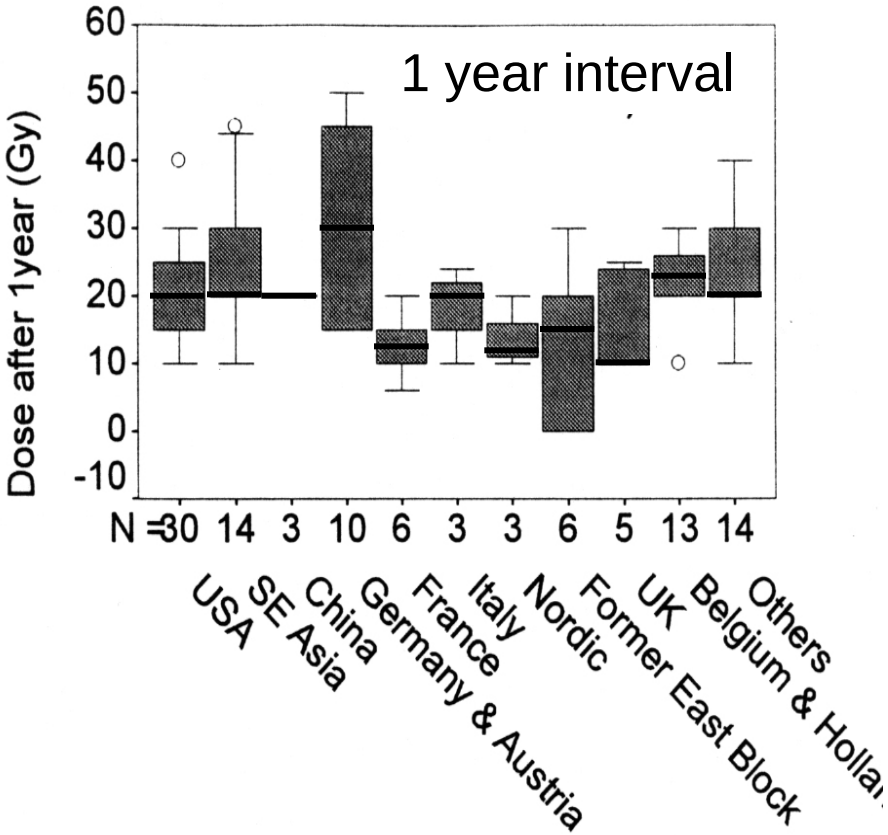


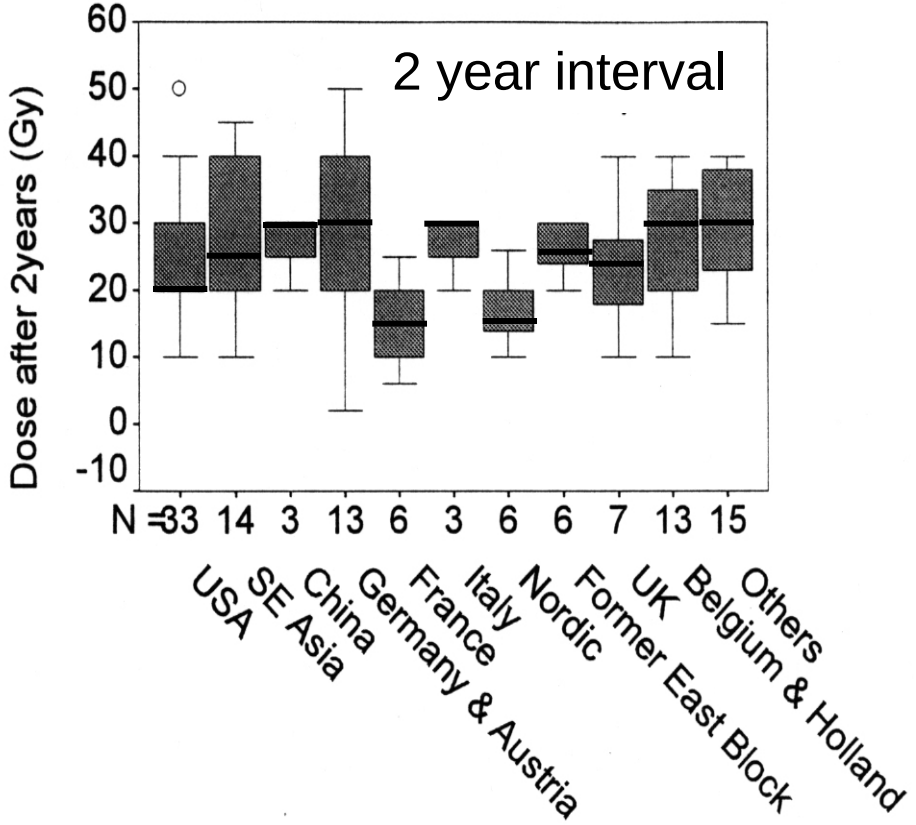
B) tumors close to cord



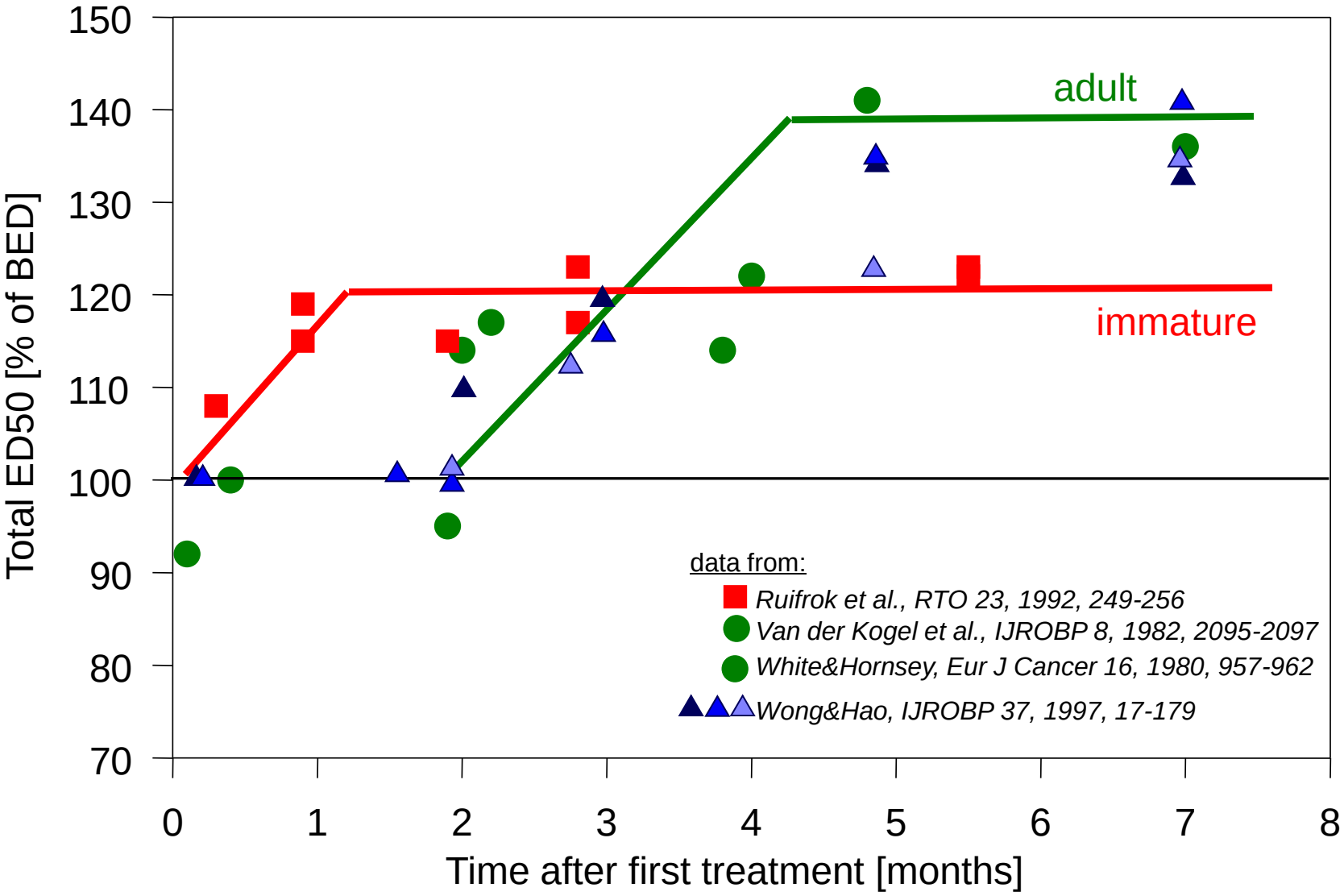
Opinions of retreatment after 40 Gy (2 Gy/fr) on 10 cm of thoracic cord

Response to questionaires sent to RT departments around the world

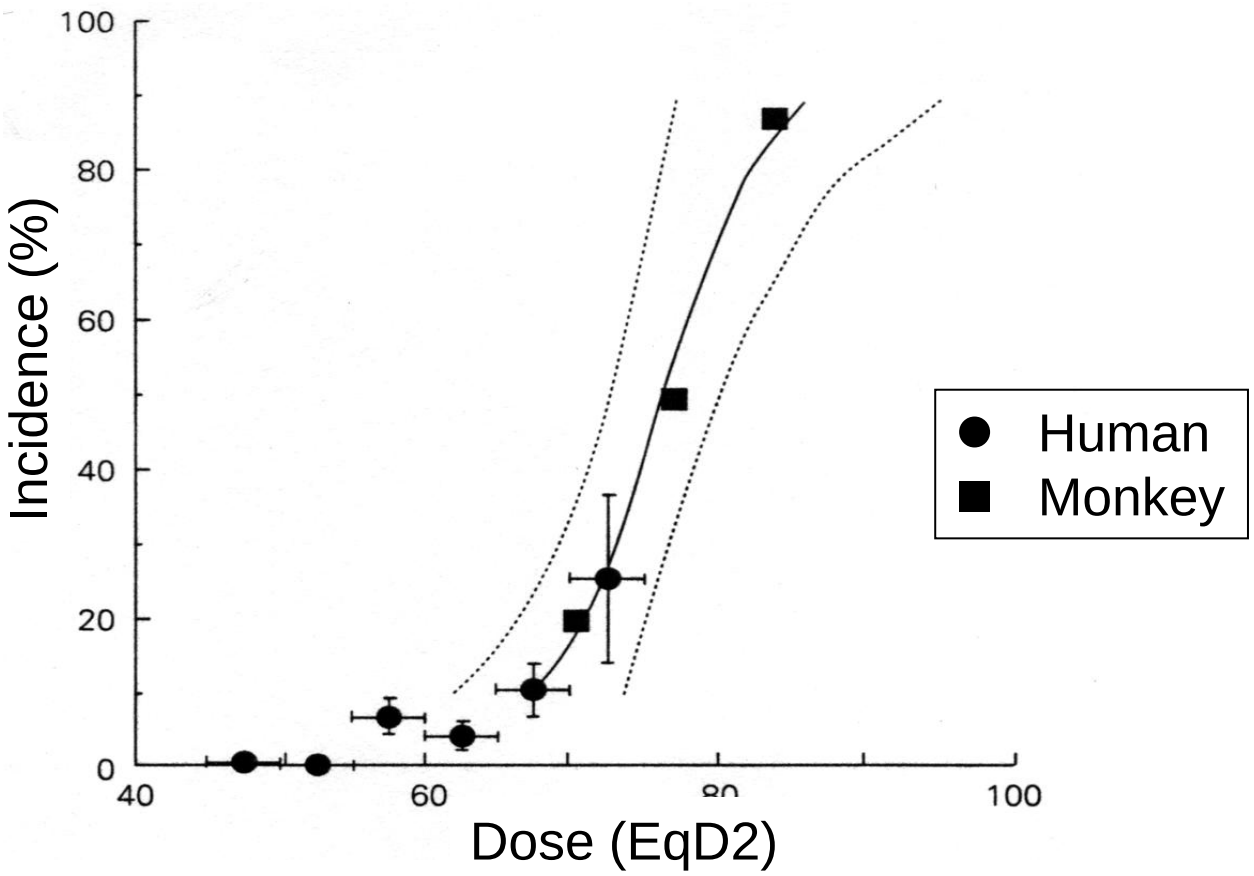




Re-irradiation of rat spinal cord

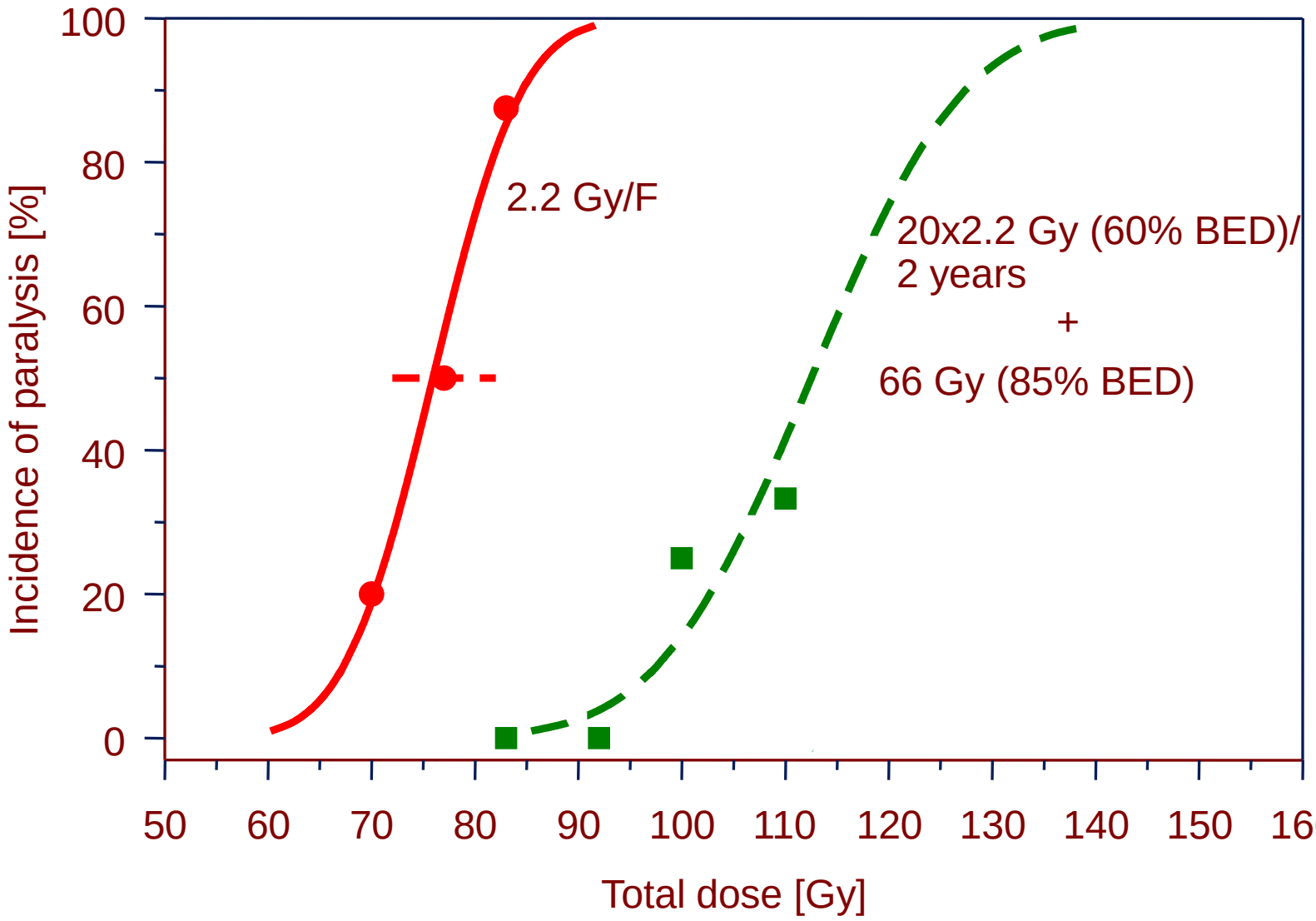


Myelopathy incidence in humans & monkeys



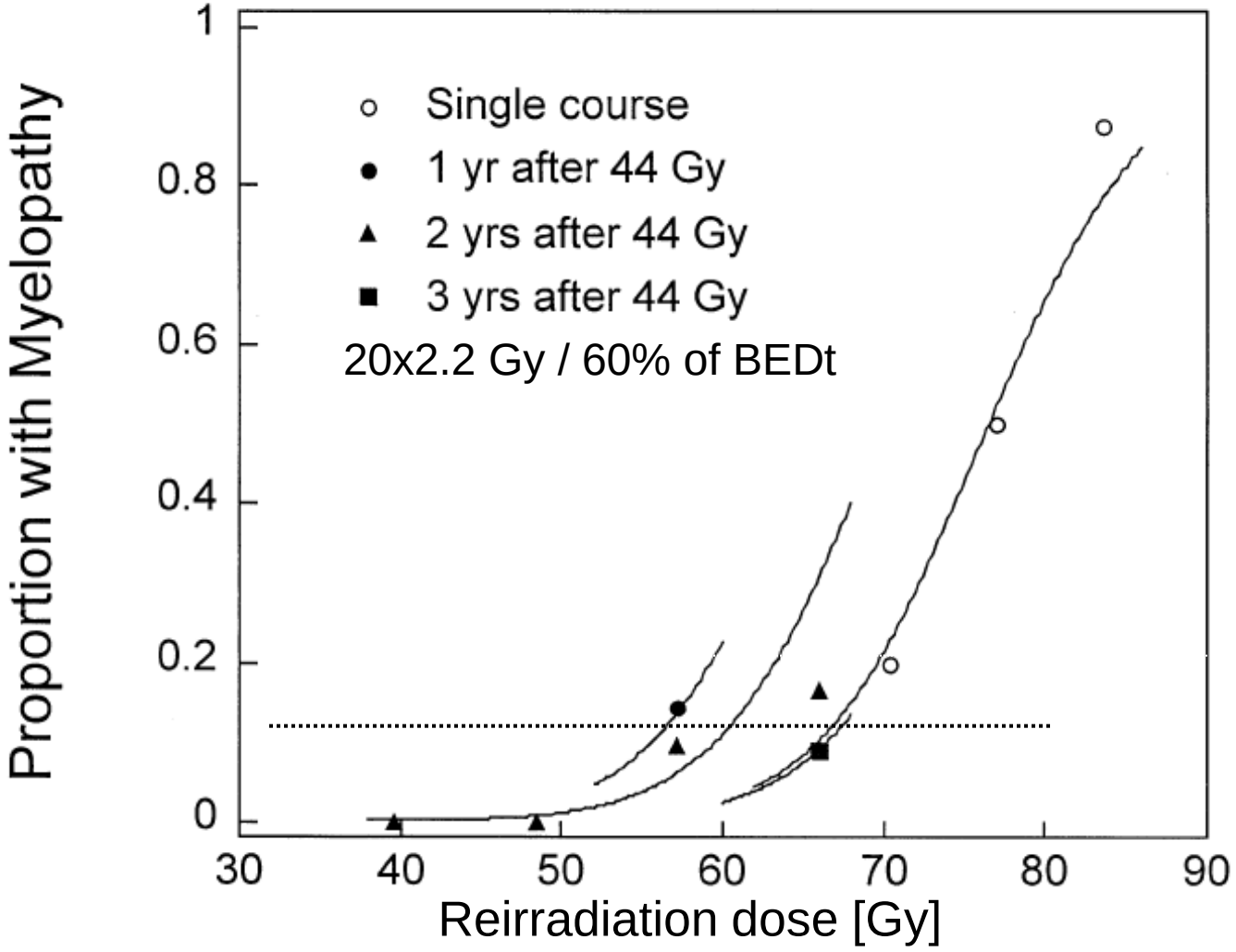
Baumann et al., *Strahlenther Onkol* 170: 131-139, 1994

Radiation tolerance of spinal cord: primates



data from Ang et al., IJROBP 1993

Retreatment tolerance of spinal cord: primates



D_{10} SC = 66 Gy

<u>20x2.2 Gy +</u>

D_{10} 0 y = 22 Gy

D_{10} 1 y = 55 Gy

D_{10} 2 y = 59 Gy

D_{10} 3 y = 66 Gy

Ang et al. 2001

Spinal Cord Tolerance to Radiosurgical Dose Distributions

UT Southwestern Medical Center

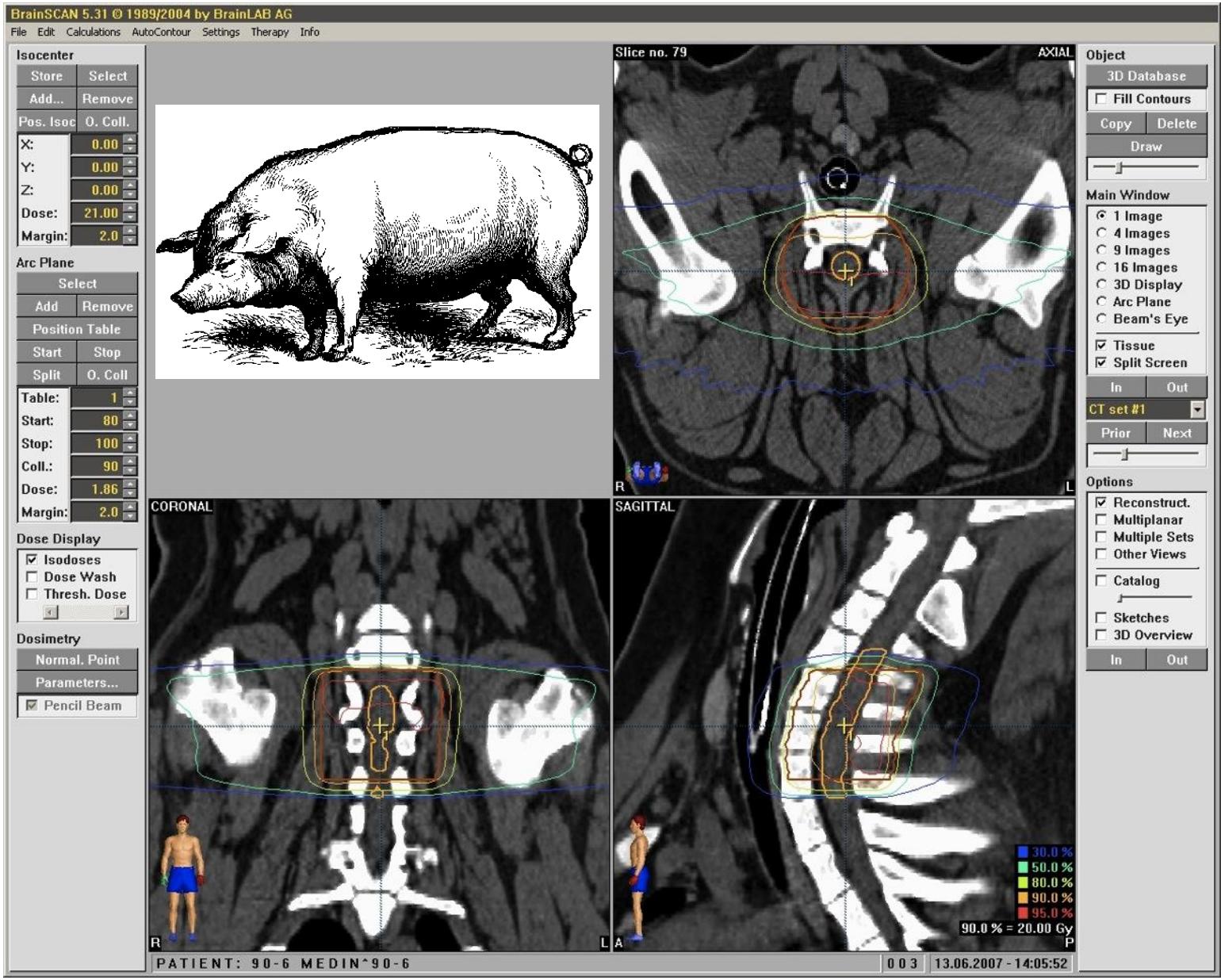
Dallas, Texas

Paul Medin
Ryan Foster
Tim Solberg

This project is funded entirely by an R01 grant (NINDS).

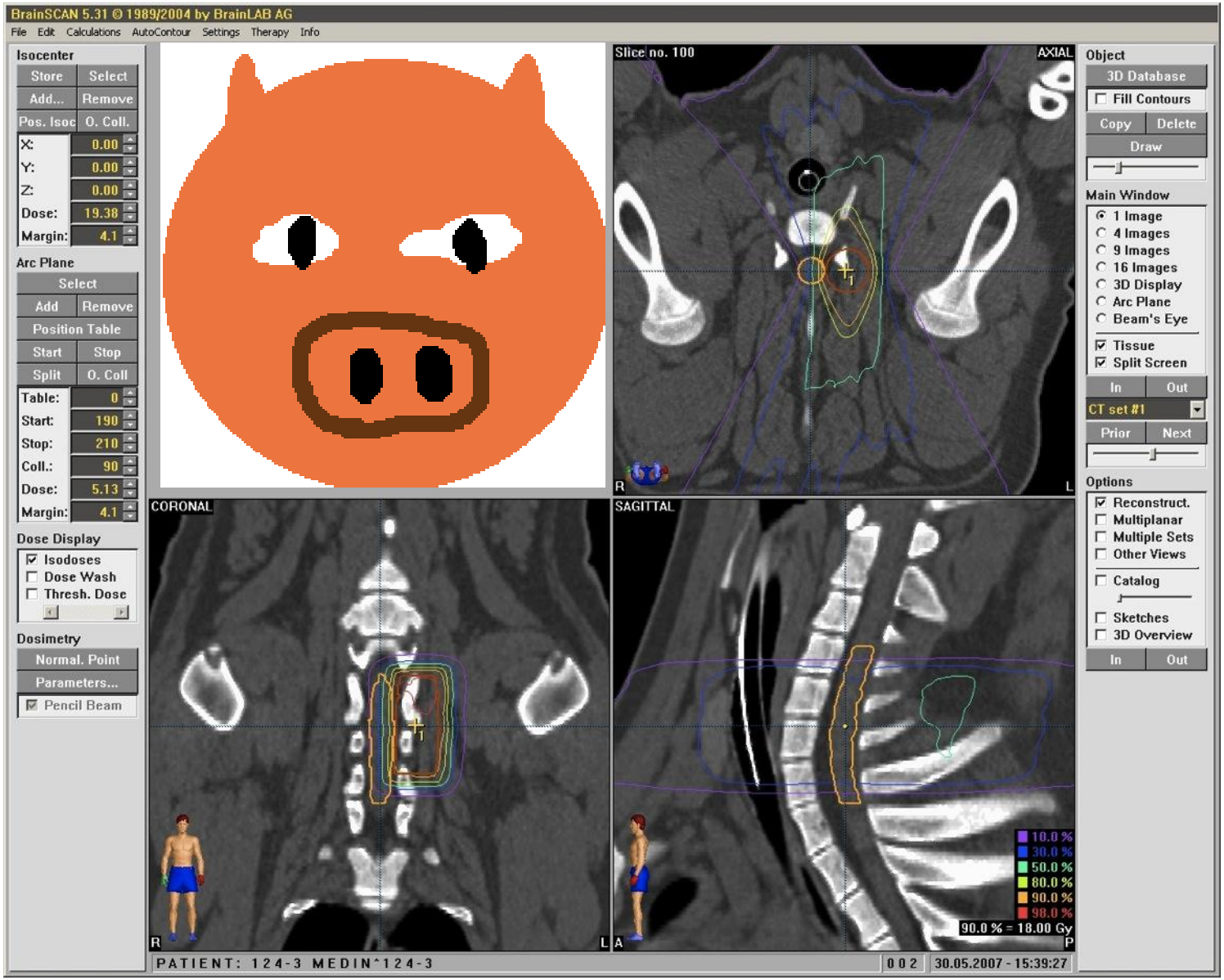
Dose Distribution Whole-cord

Rx Dose is always to the 90% Isodose Line (Orange)



Dose Distribution Hemi-cord

Rx Dose is always to the 90% Isodose Line (Orange)



SRS – whole cord vs hemi-cord irradiation

whole cord

Dose (Gy)	response
16	0/2
18	1/3
20	4/4
22	3/3

hemi cord

Dose (Gy)	response
16	0/5
18	1/5
20	4/5
22	4/4
24	4/4

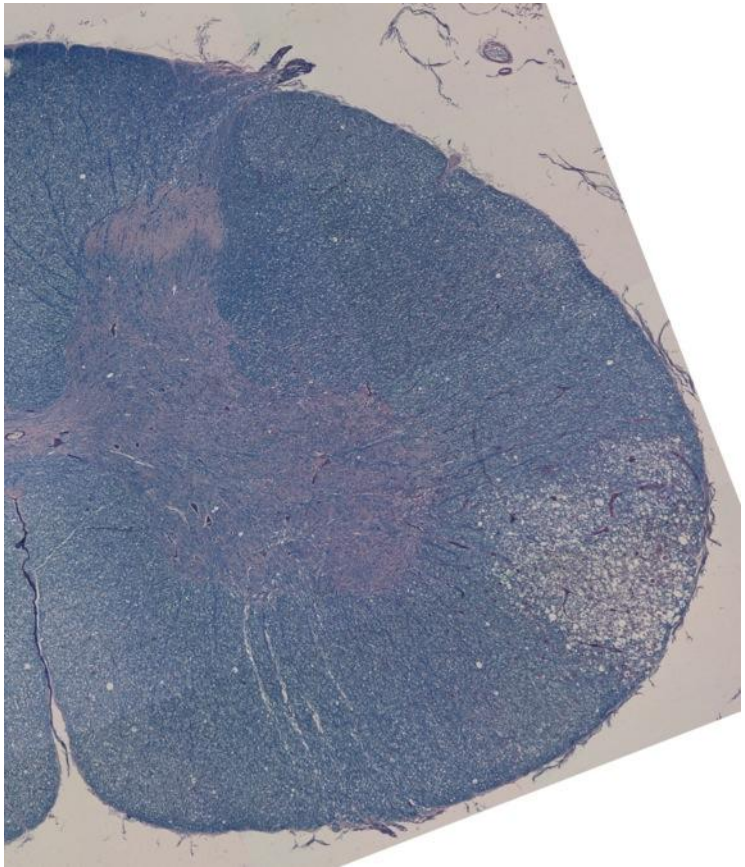
$ED_{50} \approx 19$ Gy

- Similar dose response for whole cord compared to hemi-cord irradiation.
- Morbidity is less for hemi-cord as lesions are limited to lateral high dose region

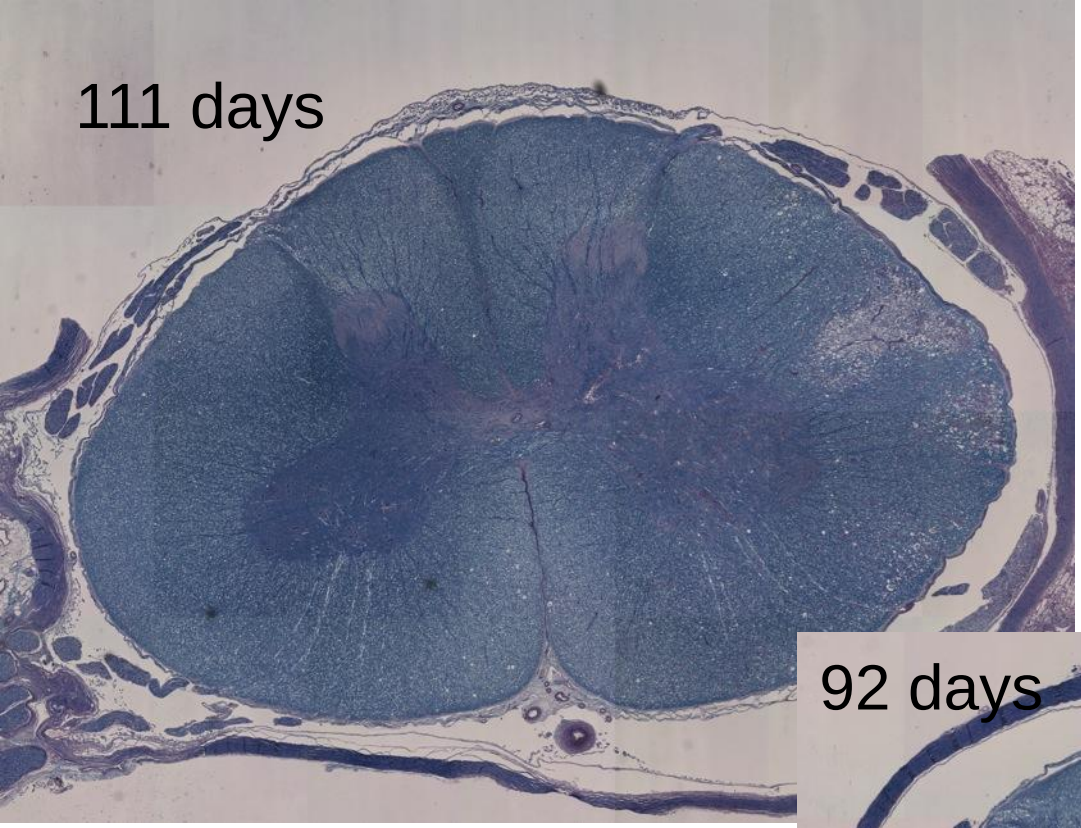
Stereotactic radiosurgery of pig spinal cord

Initial treatment: 10 X 3 Gy whole cord: EqD_2 = 37.5 Gy

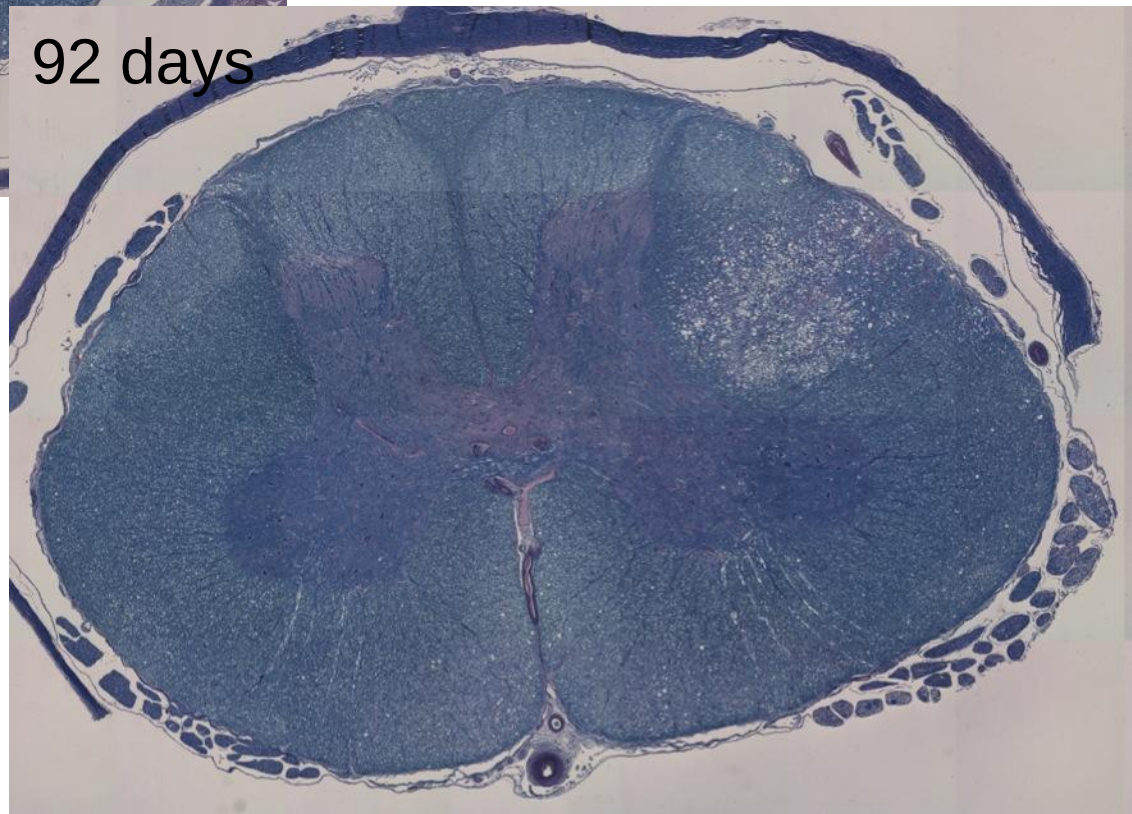
After 1 year SRS hemicord re-irradiation
Endpoint: paresis with histological confirmation



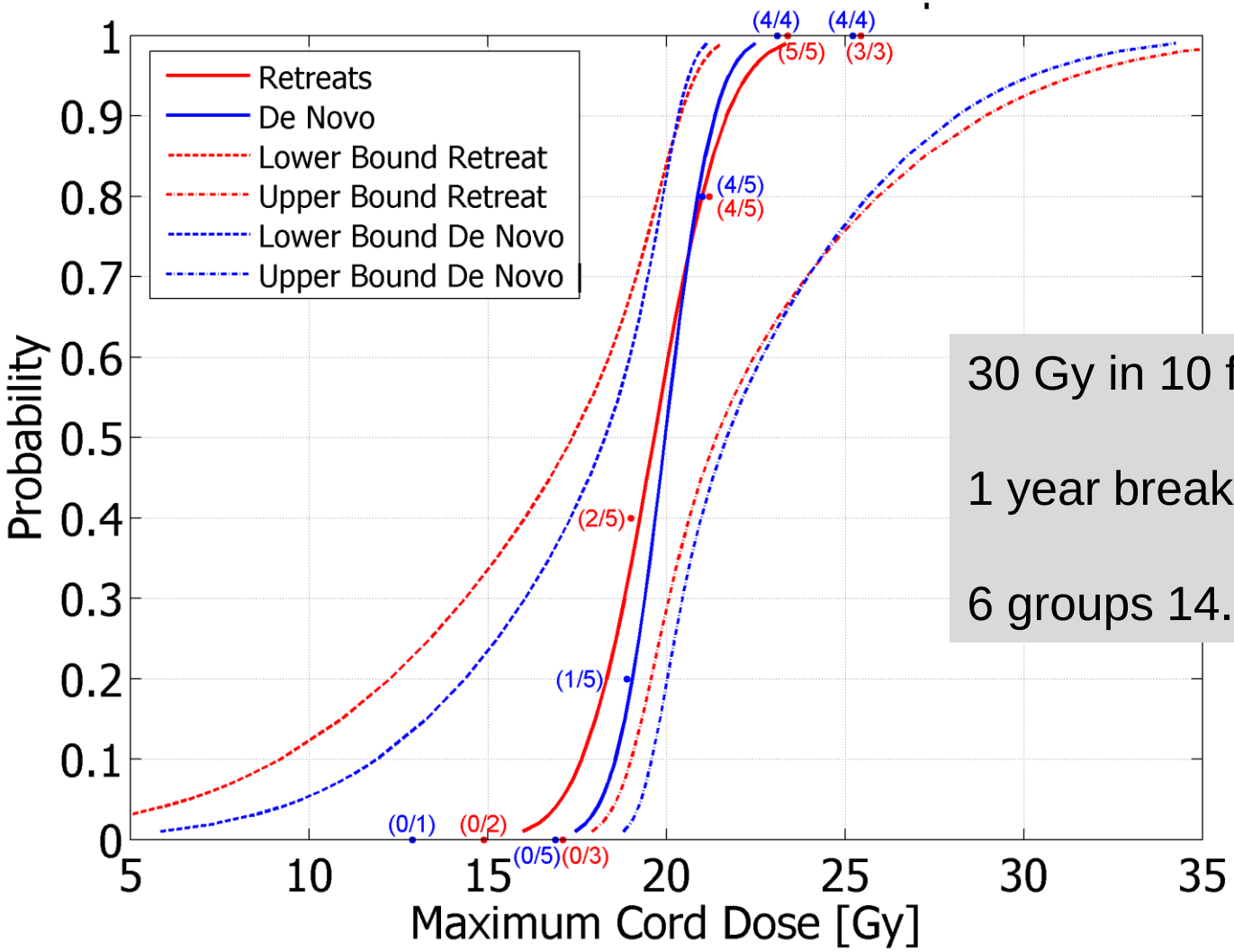
Stereotactic radiosurgery of pig spinal cord: re-irradiation



10 * 3 Gy whole cord
– 1 yr –
20 Gy lateral SRS



De novo vs retreated dose response



30 Gy in 10 fx

1 year break

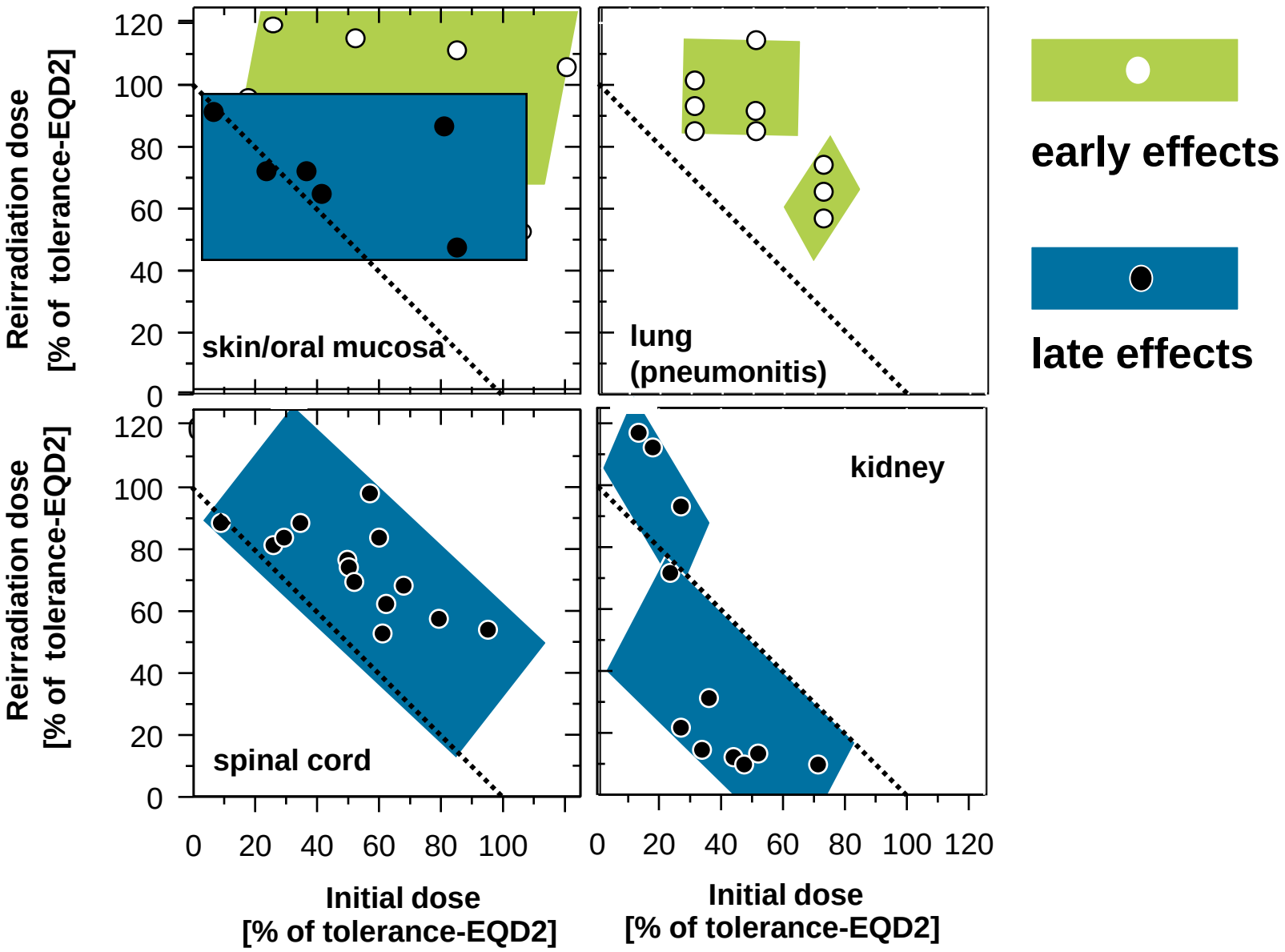
6 groups 14.9 – 25.4 Gy

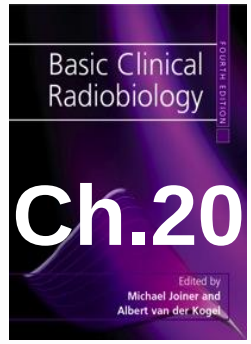
Medin et al IJRBP 2012

Stereotactic radiosurgery of pig spinal cord: re-irradiation after one year

These results confirm the large capacity of the spinal cord to recover from subclinical damage (shown in rats and primates), and offers excellent opportunities for radiation retreatment of tumors close to or compressing the cord.

Retreatment: Summary





Molecular image guided radiotherapy

Vincent GREGOIRE, M.D., Ph.D., Hon. FRCR

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ESTRO teaching course on basic clinical radiobiology

ESTRO 2015

Volume 96 Issue 3 September 2010 ISSN 0167-8140

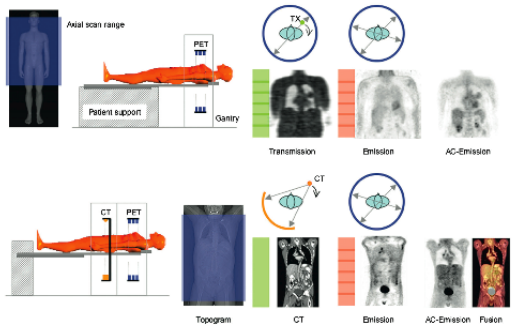
ELSEVIER

Radiotherapy &Oncology

Journal of the European Society for Therapeutic Radiology and Oncology

Special Issue:

PET in Radiotherapy Planning



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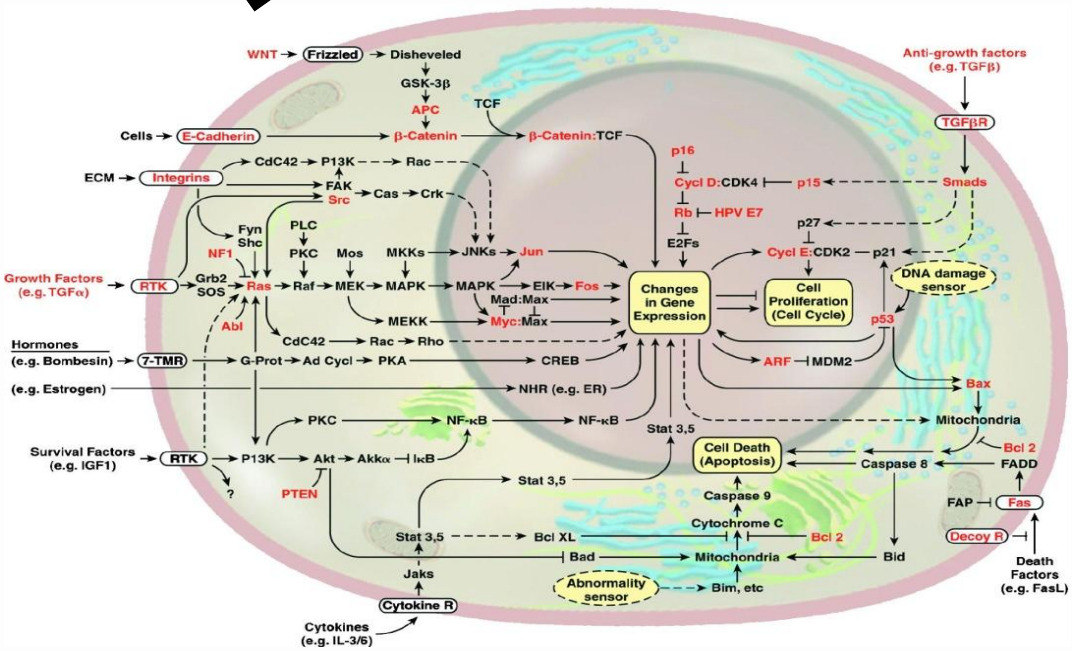
Target pathways that influence radiotherapy

HYPOXIA

REPOPULATION

INTRINSIC RADIOSENSITIVITY

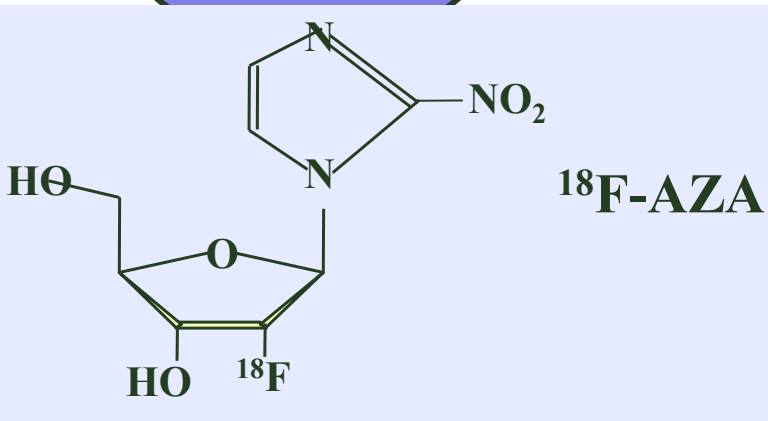


Target pathways that influence radiotherapy

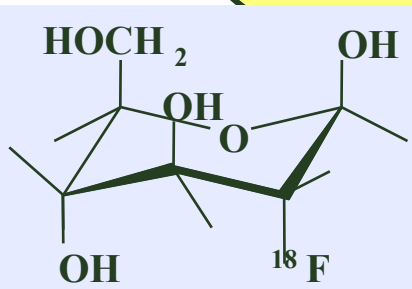
HYPOXIA

REPOPULATION

INTRINSIC RADIOSENSITIVITY

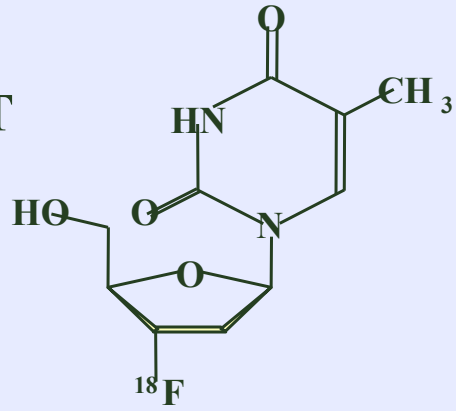


^{18}F-AZA

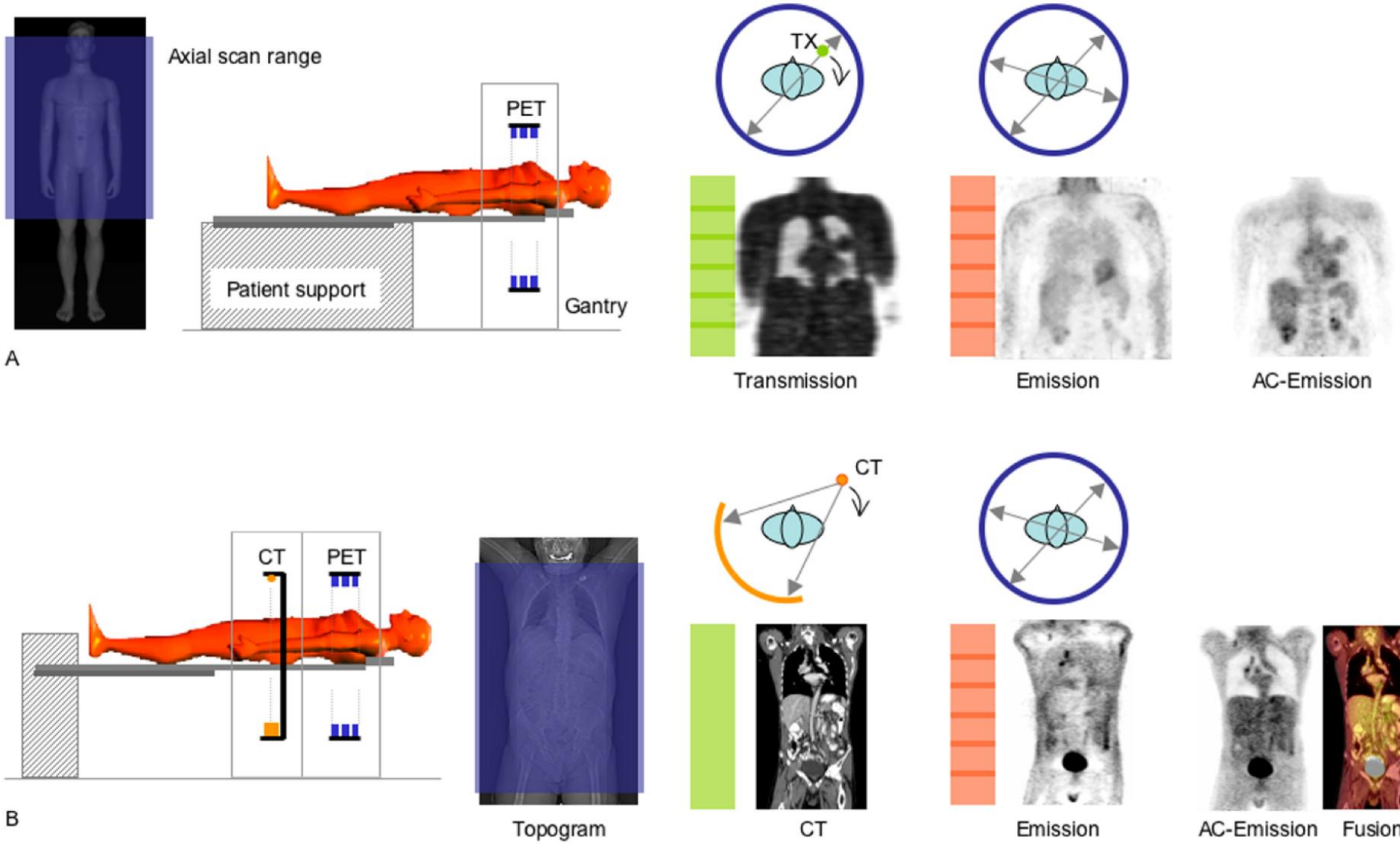


[^{18}F]FDG

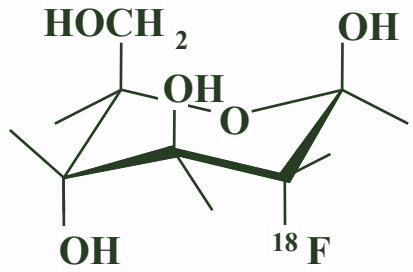
[^{18}F]FLT



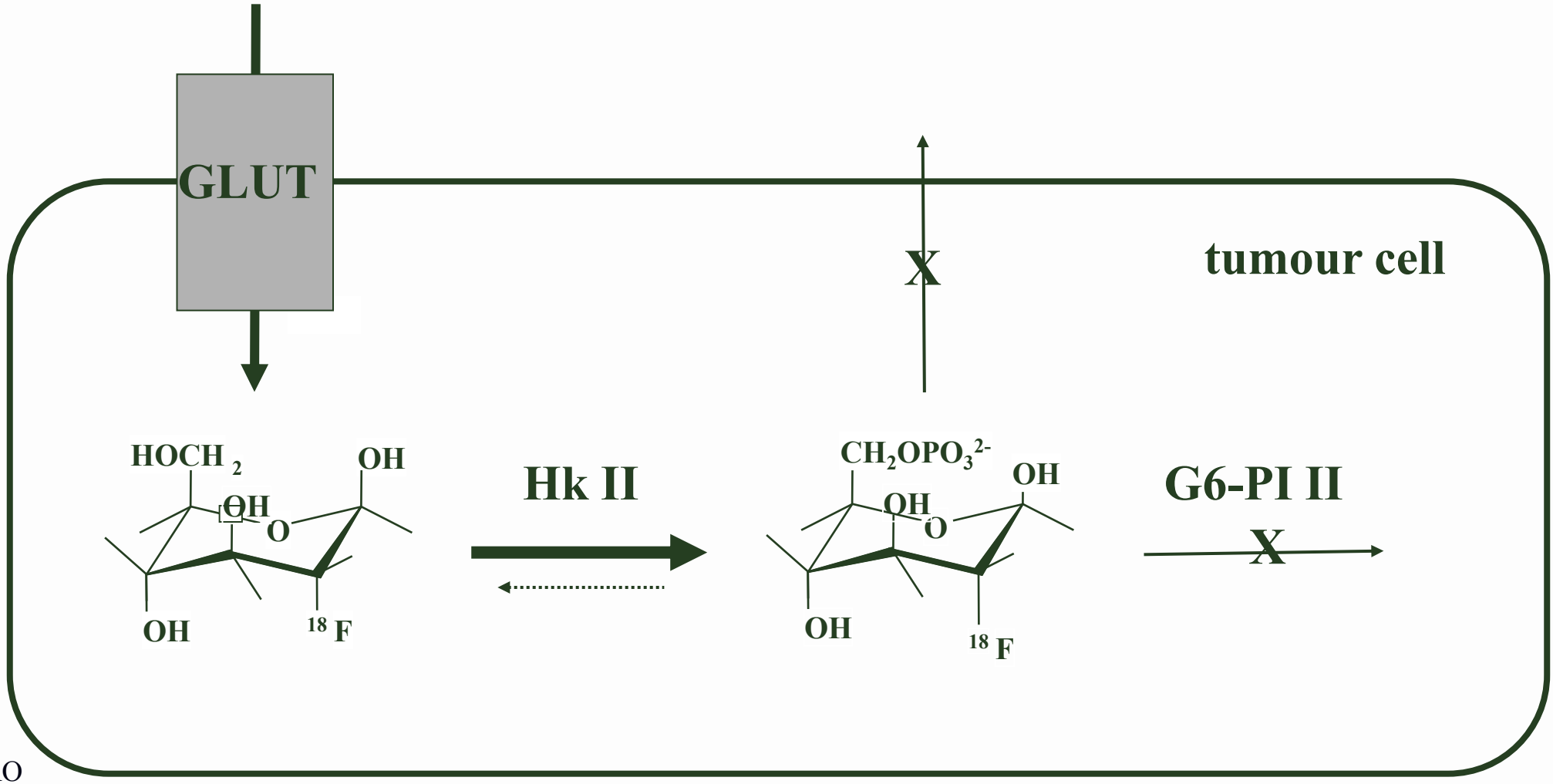
Molecular Imaging: PET / PET-CT



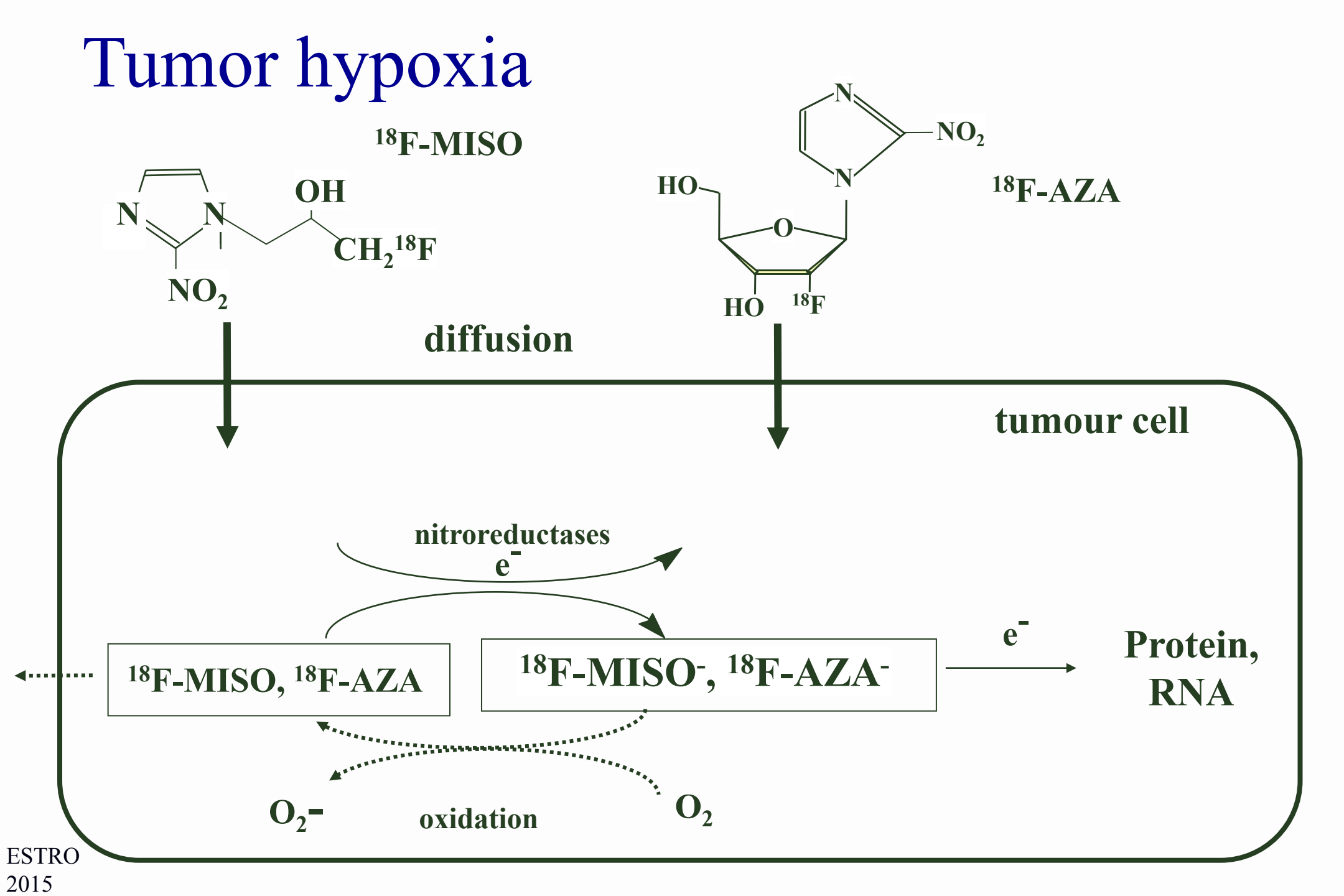
Tumor metabolism



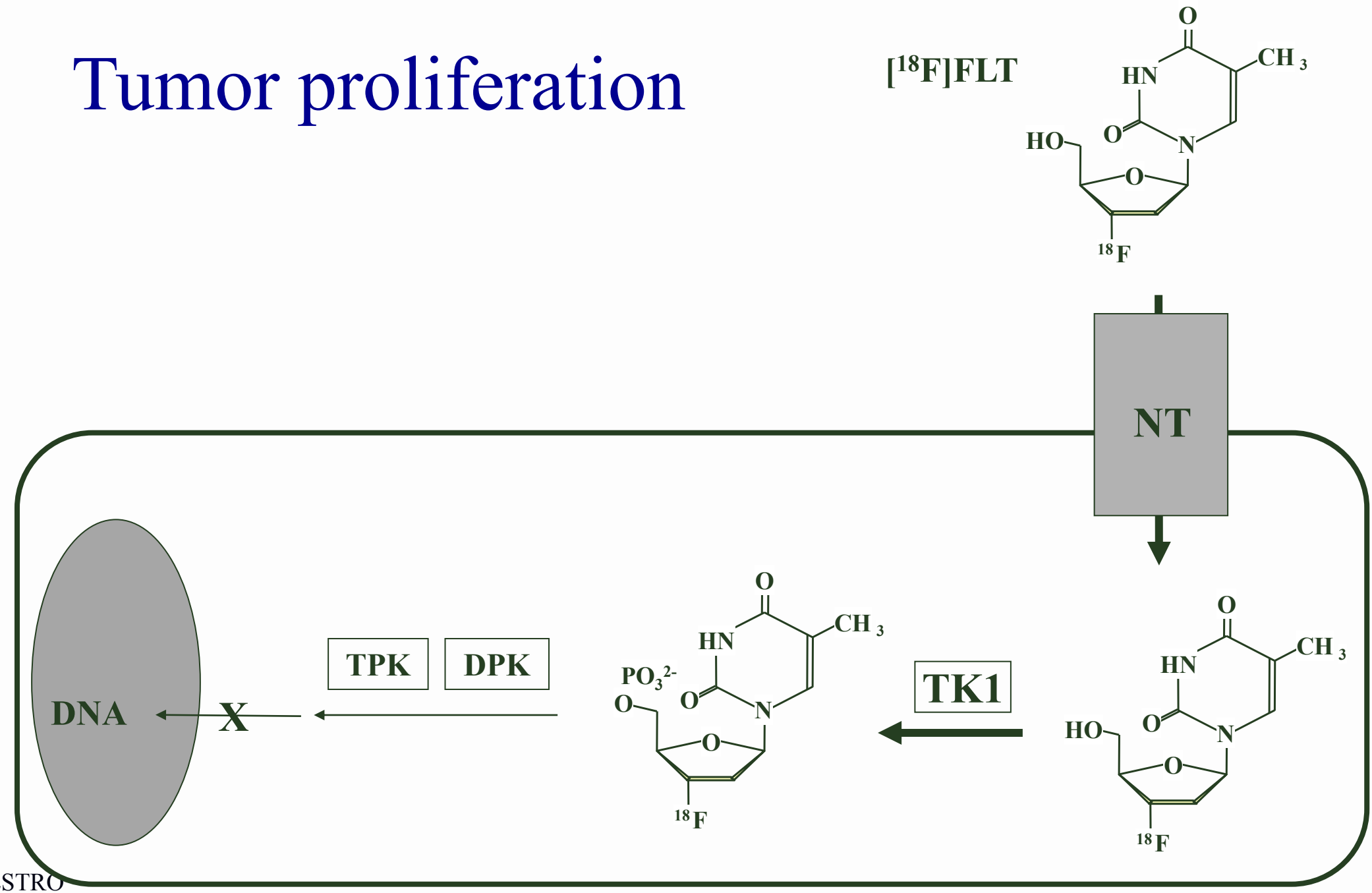
[18F]FDG



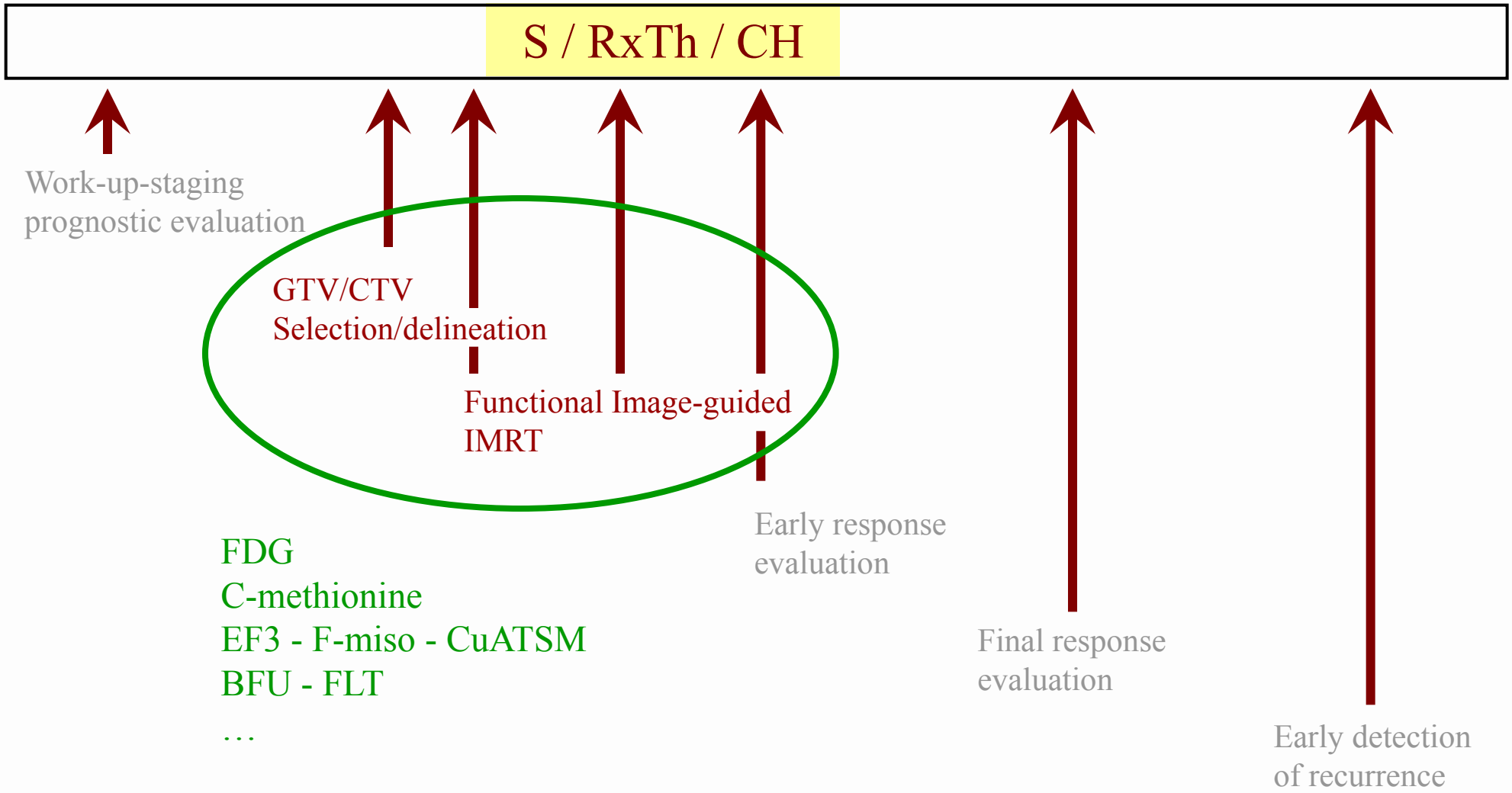
Tumor hypoxia



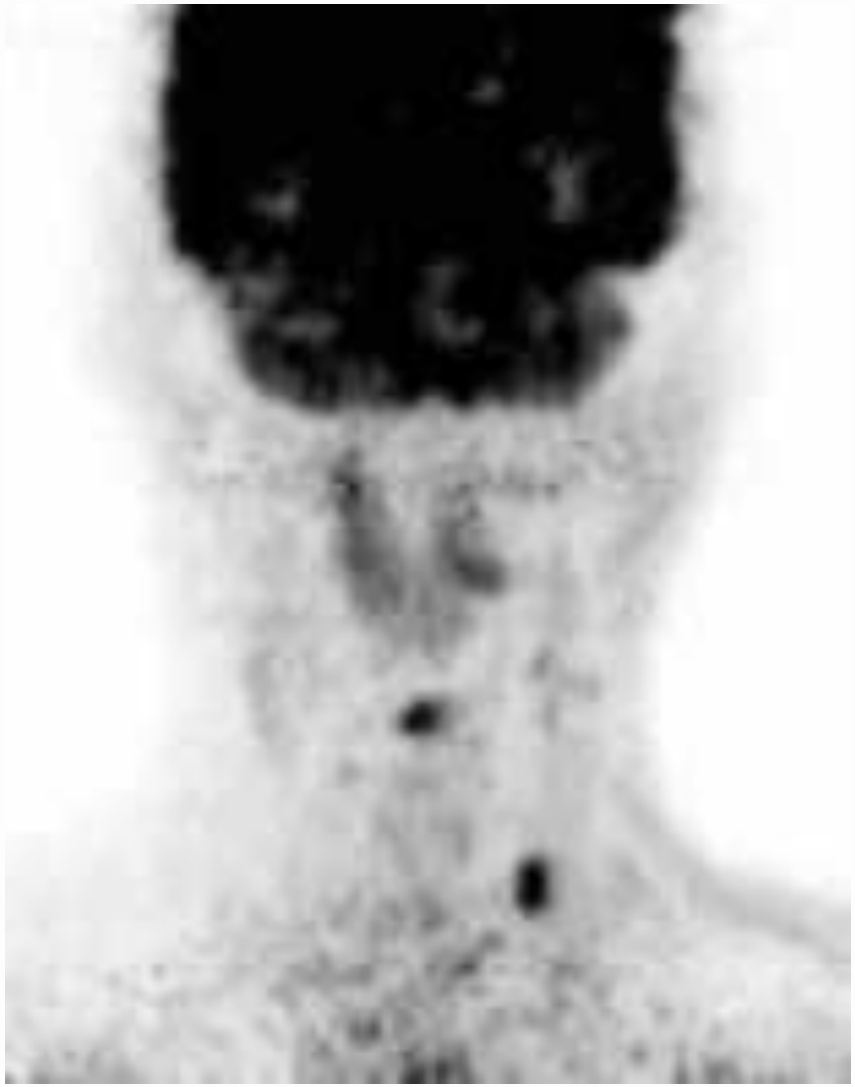
Tumor proliferation



Potential added-value of PET in oncology



The use of FDG-PET for the selection of Target Volume: setting the scene



Laryngeal SCC: T2-N1-M0

Q: unilateral vs bilateral neck irradiation?

A: highly **sensitive** examination

Detection of metastatic disease in the neck

- Meta-analysis: n= 1236 patients (32 studies)
- HNSCC (all sites)
- Neck dissection for all patients

Diagnostic methods compared	No. of studies (references)	Independent estimates (95% CI)		Likelihood ratio (95% CI)	
		Sensitivity	Specificity	LR+	LR−
CT	16 (20,21,23,24,26,28,31, 32,36,40,43–47,49,50)	0.74 (0.61 to 0.83)	0.76 (0.68 to 0.83)	3.12 (2.32 to 4.21)	0.35 (0.23 to 0.51)
^{18}F-FDG PET		0.82 (0.72 to 0.89)	0.86 (0.78 to 0.91)	5.64 (3.61 to 8.83)	0.22 (0.14 to 0.34)
MRI	9 (20,21,24,31,40,43, 44,47,48,51)	0.78 (0.54 to 0.92)	0.80 (0.67 to 0.88)	3.86 (2.01 to 7.38)	0.27 (0.10 to 0.70)
^{18}F-FDG PET		0.78 (0.64 to 0.87)	0.85 (0.79 to 0.90)	5.07 (3.47 to 7.41)	0.27 (0.16 to 0.44)
CT + MRI	4 (19,27,34,47)	0.66 (0.44 to 0.82)	0.76 (0.53 to 0.90)	2.73 (1.43 to 5.19)	0.45 (0.28 to 0.72)
^{18}F-FDG PET		0.73 (0.58 to 0.84)	0.89 (0.84 to 0.93)	6.85 (4.50 to 10.42)	0.30 (0.18 to 0.49)
USFNA	4 (20,21,25,39)	0.42 (0.01 to 0.97)	0.96 (0.76 to 0.99)	10.87 (0.51 to 230.6)	0.61 (0.12 to 3.19)
^{18}F-FDG PET		0.45 (0.27 to 0.64)	0.88 (0.76 to 0.95)	3.79 (1.49 to 9.60)	0.63 (0.42 to 0.92)

* CI = confidence interval; LR+ = positive likelihood ratio; LR− = negative likelihood ratio; CT = computed tomography; ^{18}F-FDG PET = positron emission tomography using ^{18}F-fluorodeoxyglucose; MRI = magnetic resonance imaging; USFNA = ultrasound-guided fine-needle aspiration.

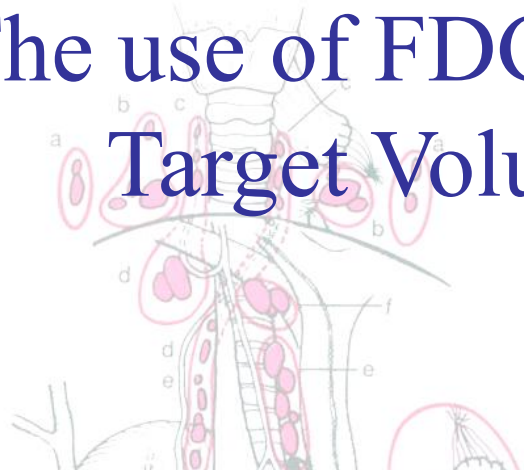
Kyzas et al., JNCI 2008

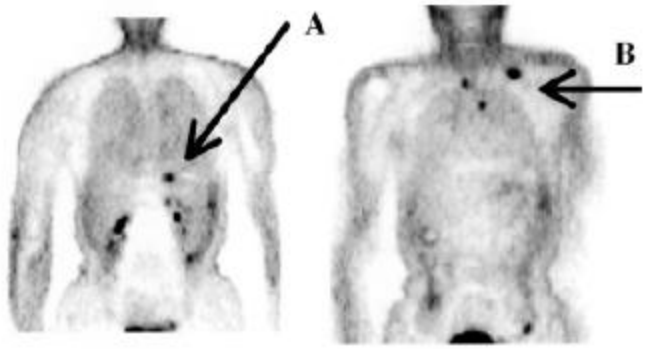
Detection of N2-N3 in NSCLC

	Poncelet		Pieterman		Kernstine
n	64		188		237
	CT	PET	CT	PET	PET
sens	55	67	75	91	82
spec	68	85	66	86	82
PPV	23	43	-	74	51
NPV	90	93.6	-	95	95
Acc	66	82	69	87	82

Poncelet et al. Eur J Cardiothorac Surg 2001;20:468-475
Pieterman et al. N Engl J Med 2000;343:254-261
Kernstine et al. Ann Thorac Surg 2002;73:394-402

The use of FDG-PET for the selection of Target Volume: setting the scene





Oesophageal SCC

Q: should one increase the CTV based on a FDG-PET^{+}?

A: highly **specific** examination

Vrieze, Haustermans et al., 2004

Pre-treatment staging of esophageal carcinoma: distant lymph nodes

Table 5. Parameters of Diagnostic Accuracy of ^{18}F-Fluorodeoxyglucose Positron Emission Tomography for the Detection of Distant Lymph Node and Organ Metastases (M stage)

Study	Year	Sensitivity		Specificity		Positive Predictive Value		Negative Predictive Value		Prevalence
		Value	95% CI	Value	95% CI	Value	95% CI	Value	95% CI	
Block et al[33]	1997	0.65	0.42 to 0.87	0.97	0.90 to 1.03	0.92	0.76 to 1.07	0.83	0.62 to 1.04	0.36
Kole et al[34]	1998	1.00	—	0.95	0.85 to 1.05	0.75	0.33 to 1.17	1.00	—	0.13
Rankin et al[35]	1998	—	—	—	—	—	—	—	—	—
Kobori et al[36]	1999	0.87	0.70 to 1.04	0.94	0.84 to 1.05	0.93	0.79 to 1.06	0.90	0.73 to 1.05	0.45
Choi et al[38]	2000	0.56	0.32 to 0.81	1.00	—	1.00	—	0.82	0.73 to 1.05	0.33
Flamen et al[42]	2000	0.74	0.59 to 0.88	0.90	0.81 to 0.99	0.86	0.74 to 0.99	0.80	0.65 to 0.95	0.46
Meltzer et al[41]	2000	0.70	0.42 to 0.98	0.92	0.83 to 1.01	0.70	0.42 to 0.98	0.92	0.75 to 1.09	0.22
Jager et al[43]	2001	0.80	0.45 to 1.51	1.00	—	1.00	—	0.93	0.68 to 1.18	0.28
Junginger et al[39]	2002	0.33	0.07 to 0.60	1.00	—	1.00	—	0.64	0.17 to 1.11	0.46
Kato et al[37]	2002	0.71	0.48 to 0.95	1.00	—	1.00	—	0.82	0.58 to 1.06	0.44
Wren et al[40]	2002	0.67	0.40 to 0.93	0.92	0.76 to 1.07	0.89	0.68 to 1.09	0.73	0.44 to 1.02	0.50
Yoon et al[44]	2003	0.43	0.06 to 0.80	0.99	0.96 to 1.01	0.75	0.33 to 1.17	0.95	0.73 to 1.17	0.09
Pooled estimate		0.67	0.58 to 0.76	0.97	0.90 to 1.0	—	—	—	—	—

Van Westreenen, JCO, 2004

Potential added-value of PET for TV selection

Comparison between CT and FDG-PET for nodal staging.

Site	Sensitivity		Specificity		
	CT	FDG-PET	CT	FDG-PET	
Head and neck cancer	36-86%	50-96%	56-100%	88-100%	?
NSC lung cancer	45%	80-90%	85%	85-100%	
Cervix carcinoma	57-73%[1]	75-91%	83-100%[1]	92-100%	
Esophageal cancer	11-87%	30-78%	28-99%	86-98%	

[1]CT or MRI

Grégoire, 2004

Potential added-value of PET in oncology

Table 3. Accuracy of Different Imaging Procedures When Assessing N Stage

	Sensitivity		Specificity				
Imaging	%	95% CI	%	95% CI	PPVs (%)	NPVs (%)	Accuracy (%)
PET/CT	92	85 to 96	93	87 to 96	88	94	92
PET + CT	88	80 to 94	89	83 to 93	83	92	88
PET	85	76 to 91	88	82 to 93	82	90	87
CT	64	53 to 73	83	77 to 89	70	79	76

NOTE. Sensitivities, specificities, PPVs, NPVs, and accuracies of the different imaging procedures when assessing N stage. The standard of reference defined 161 patients as N-negative and 99 patients as N-positive. Patients with Nx status (lymph node metastases without known primary) were called positive for lymph node metastases.

Abbreviations: N, node; PET/CT, fused positron emission tomography and computed tomography; PET + CT, side-by-side PET and CT; PPV, positive predictive value; NPV, negative predictive value.

Antoch et al., 2004

Molecular Imaging across the board

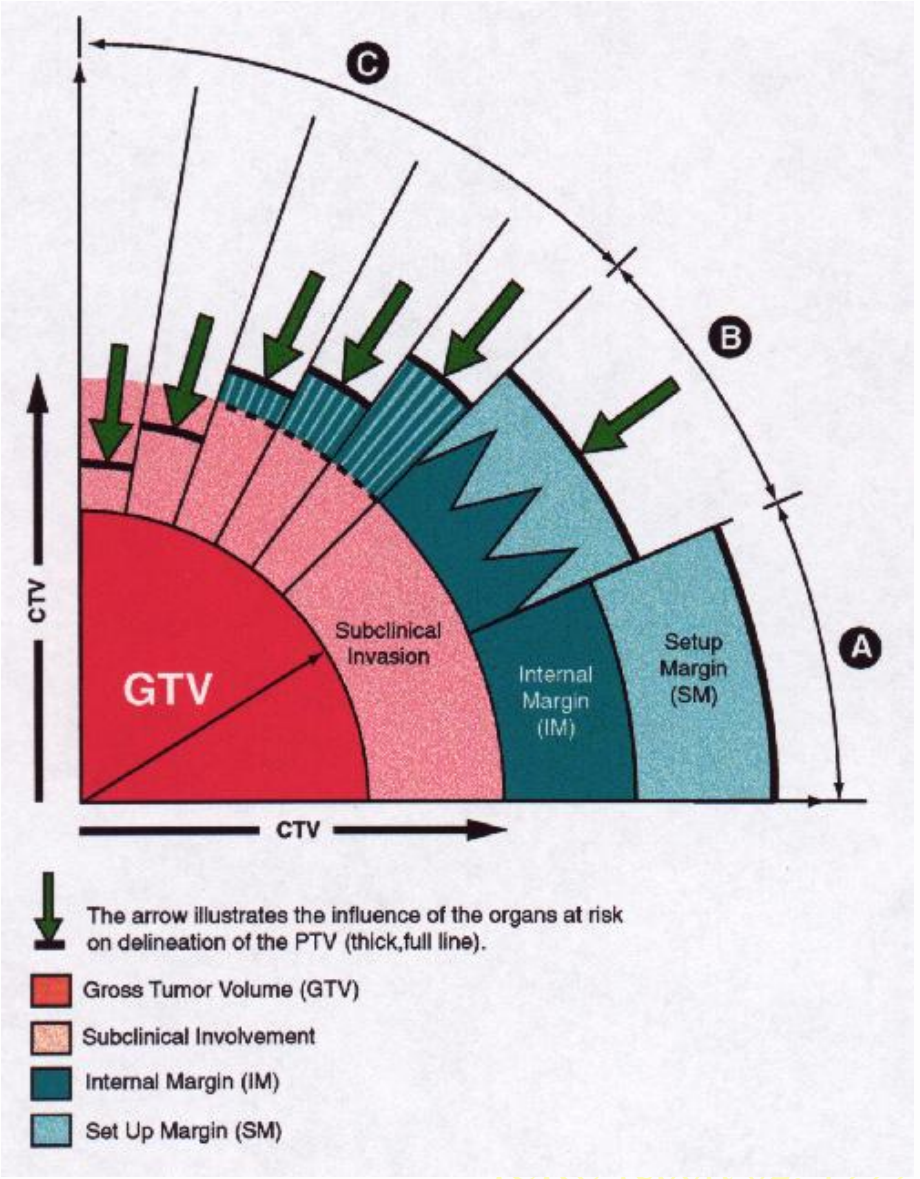
- Lung carcinoma: more accurate delineation of the NSCLC GTV
- Esophageal tumor: in progress…
- Brain tumor: ^{11}C-Met in low grade glioma and meningioma
- Rectal tumor: promising data to be confirm…
- Cervix carcinoma: proof on concept only…

Target

J. John, 1974

Target volumes in Radiation Oncology: ICRU 50 and 62:

- Gross Tumor Volume: GTV
- Clinical Target Volume: CTV
- Internal Target Volume: ITV
- Planning Target Volume: PTV
- Organ at Risk: OAR
- Planning Organ at Risk Volume: PRV



Target selection and delineation

Betrayal of images

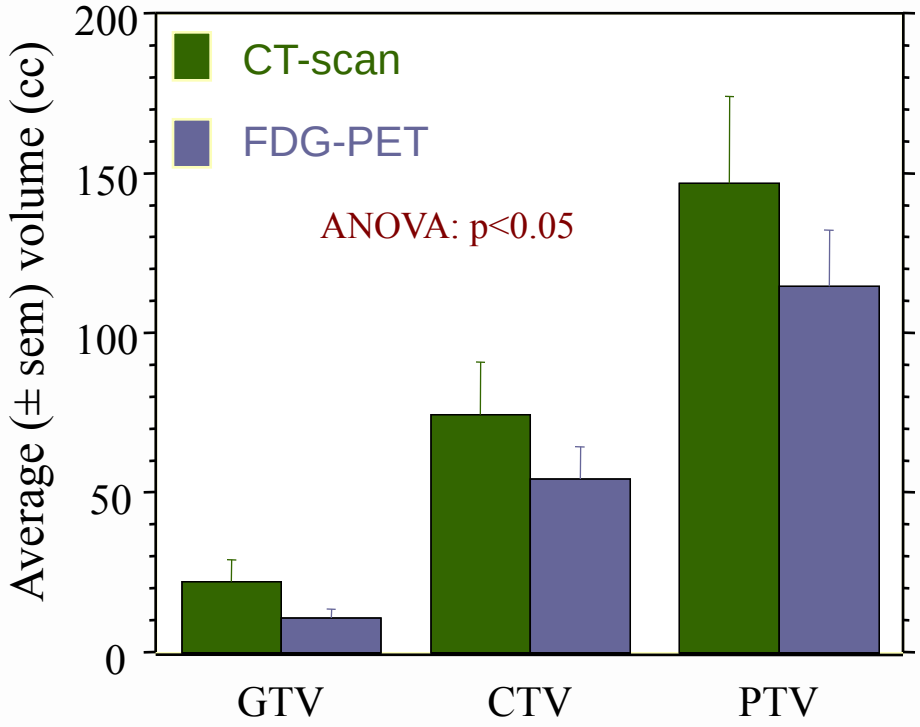
This is not an apple…

R. Magritte

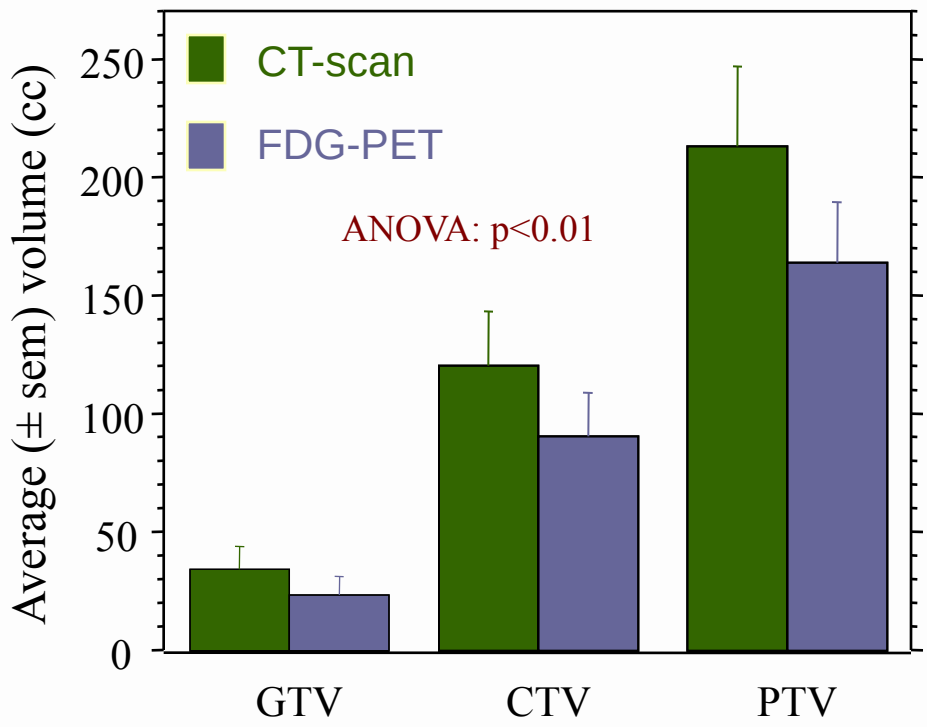
Image-Guided Radiation Therapy in HNSCC

Impact of imaging modality on CTV/PTV delineation

Larynx/hypopharynx (n=9)



Oropharynx (n=10)

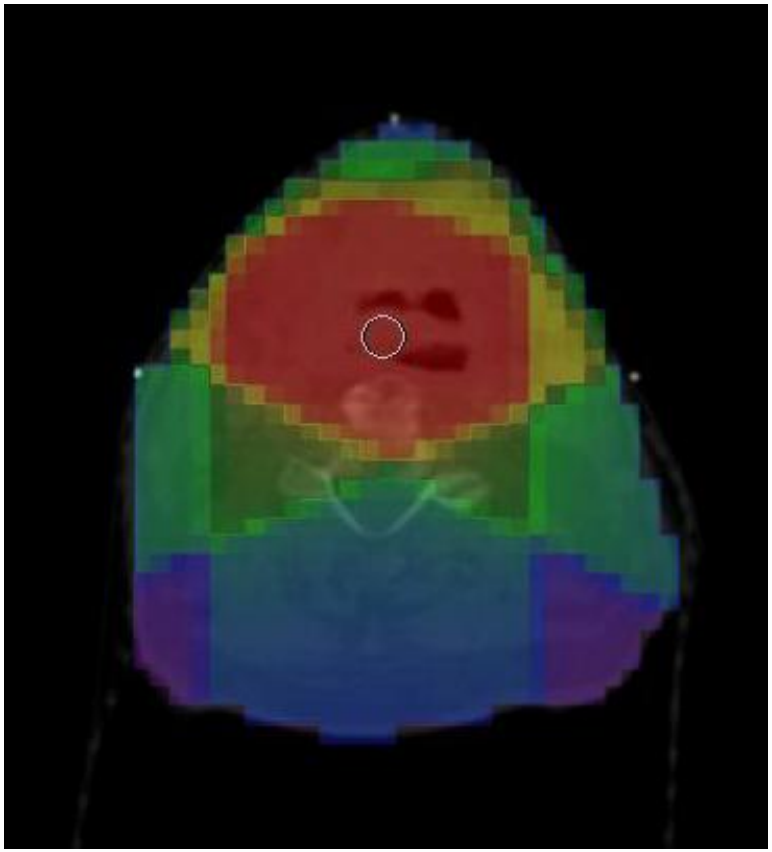


Geets *et al*, 2003

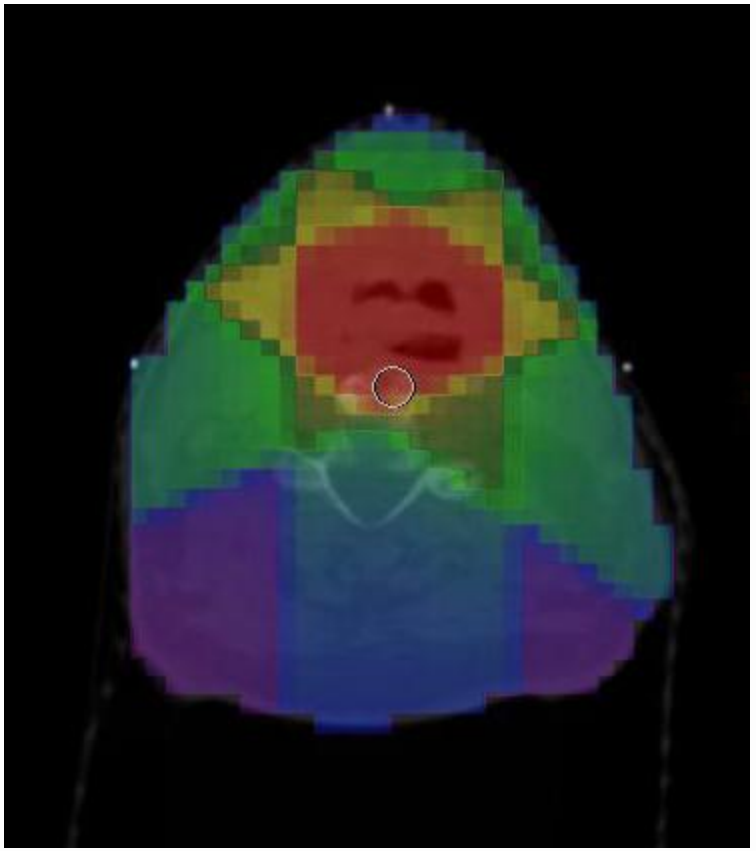
Image-Guided Radiation Therapy in HNSCC

Impact of imaging modality on dose distribution

CT-based target volume



FDG PET-based target volume



Use of FDG-PET for target volume delineation in 3D-CRT/IMRT for head and neck tumors

Primary objective of the study

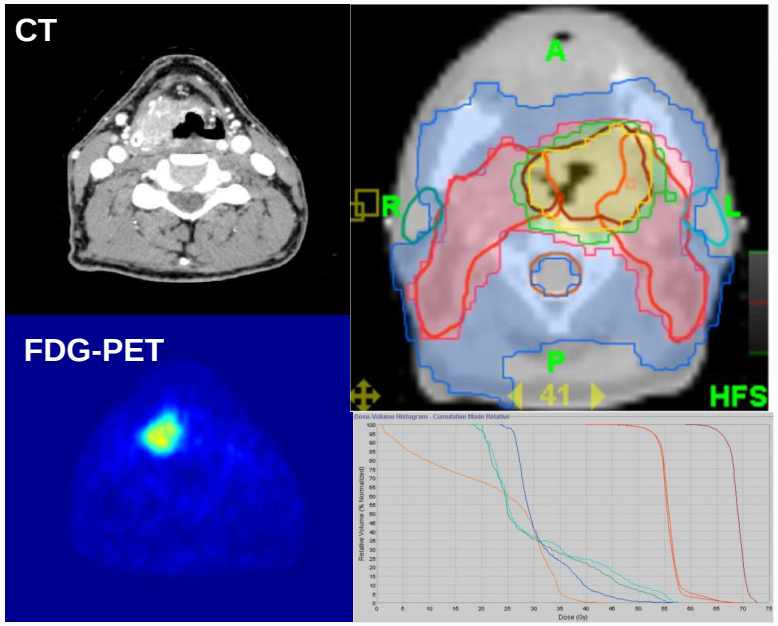
To evaluate the feasibility and safety of the use of FDG-PET for primary tumor GTV delineation in locally advanced H&N SCC patients treated by 3D-CRT and IMRT in a multicentric setting

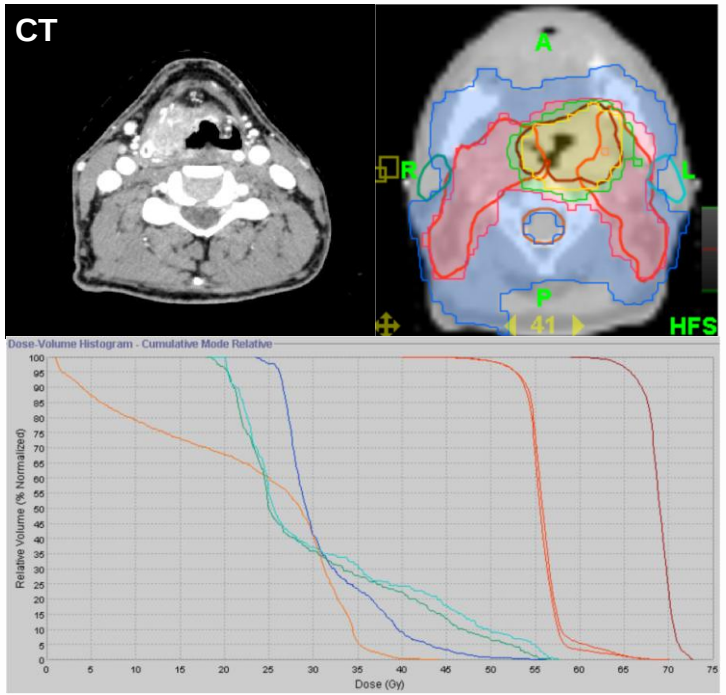
Cliniques universitaires St-Luc, Brussels, Belgium
Centre OscartLambret, Lille, France
Cliniques St-Elisabeth, Namur, Belgium

Validation study in locally advanced HNSCC

R/ PET-based IMRT treatment

CT-based IMRT planning





No difference in conformity: p = ns

Grégoire & Leclerc, 2013

Validation study in locally advanced HNSCC

- Local relapse: 9/41
  - No marginal recurrence (i.e. in the CTV_{CT} and not CTV_{PET})
- Regional relapse: 2/41
- Metastasis: 6/41
- Second primary: 2/41

Grégoire & Leclerc, 2013

Validation study in locally advanced HNSCC

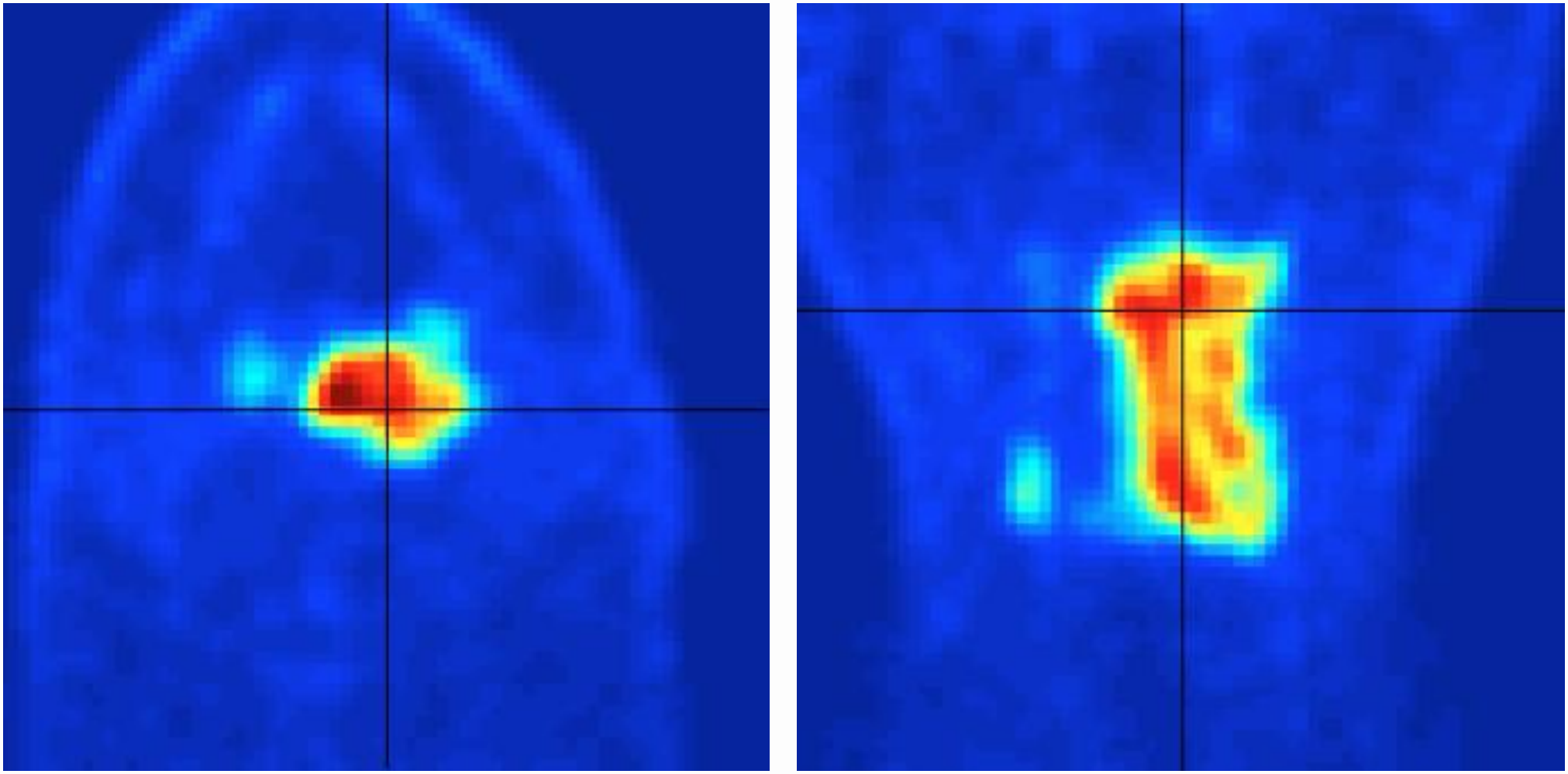
Use of FDG-PET for target volume delineation in 3D-CRT/IMRT for head and neck tumors

- $GTV\text{-}T_{FDG\text{-}PET} < GTV\text{-}T_{CT}$
- $CTV\text{-}T_{FDG\text{-}PET} < CTV\text{-}T_{CT}$
- $PTV\text{-}T_{FDG\text{-}PET} < PTV\text{-}T_{CT}$ (oropharyngeal SCC)
- More parotid sparing with the use of FDG-PET (oropharyngeal SCC)
- Loco-regional control probability within the expected range

Grégoire & Leclerc, 2013

Dose-painting by number (DPBN)

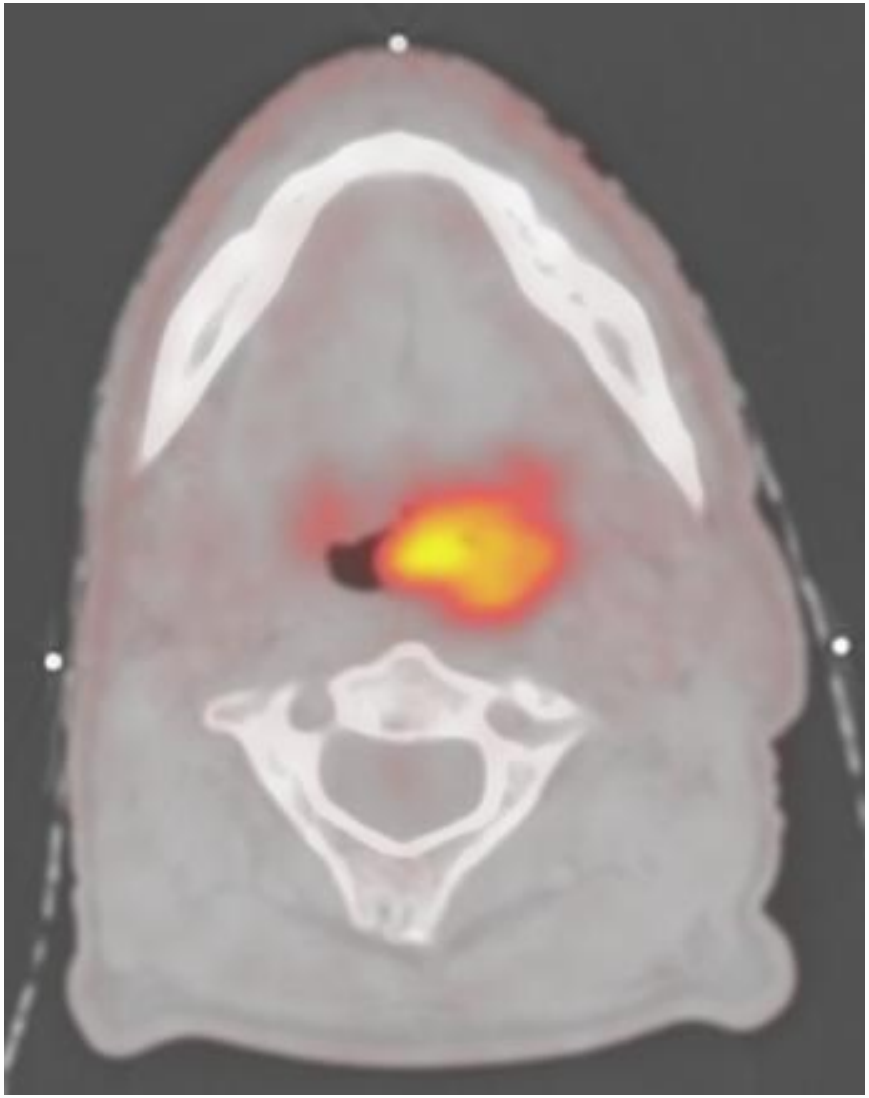
SCC oropharynx: T4b-N0-M0

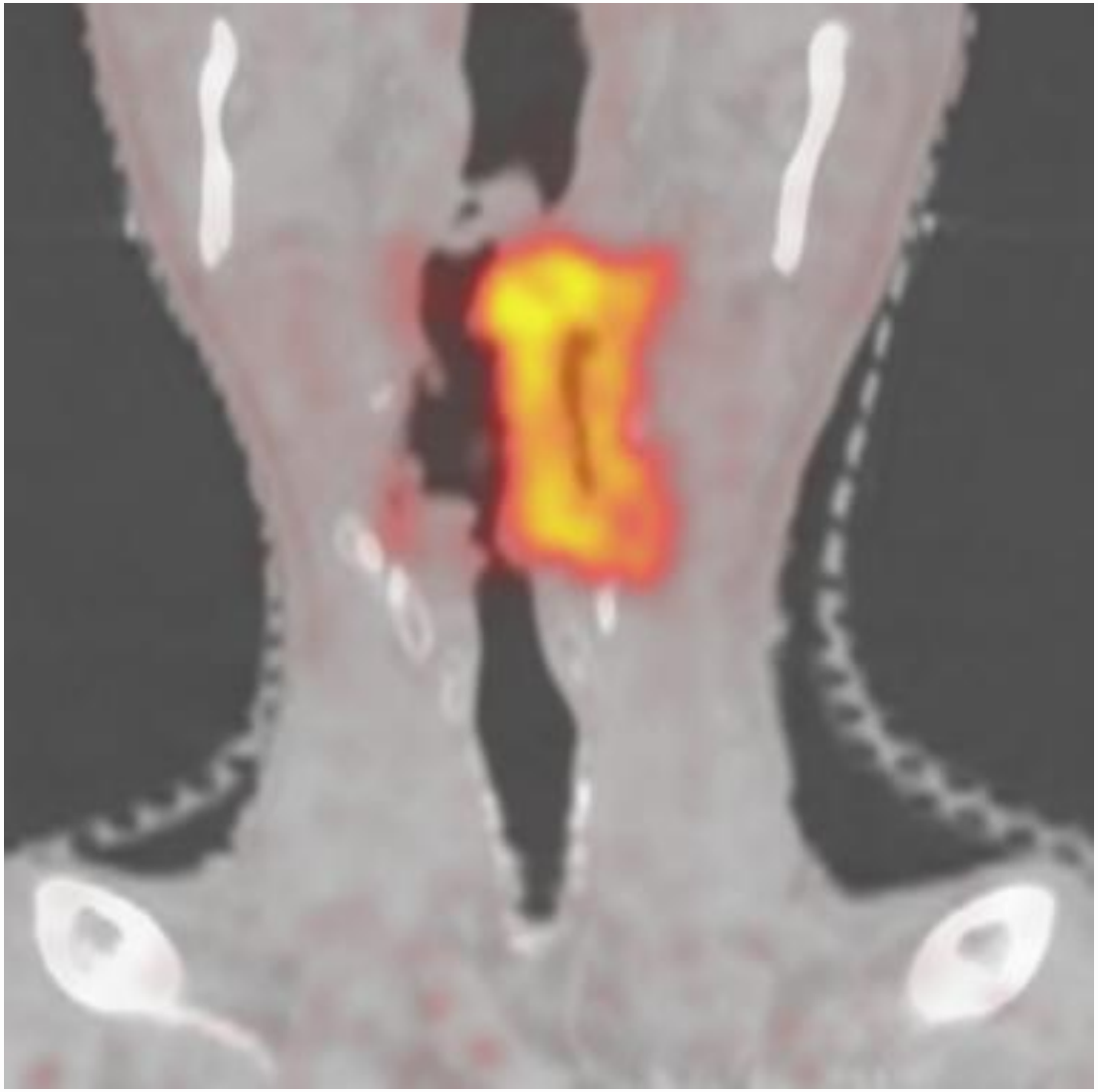


Courtesy of S. Differding, 2012

Dose-painting by number (DPBN)

SCC oropharynx: T4b-N0-M0

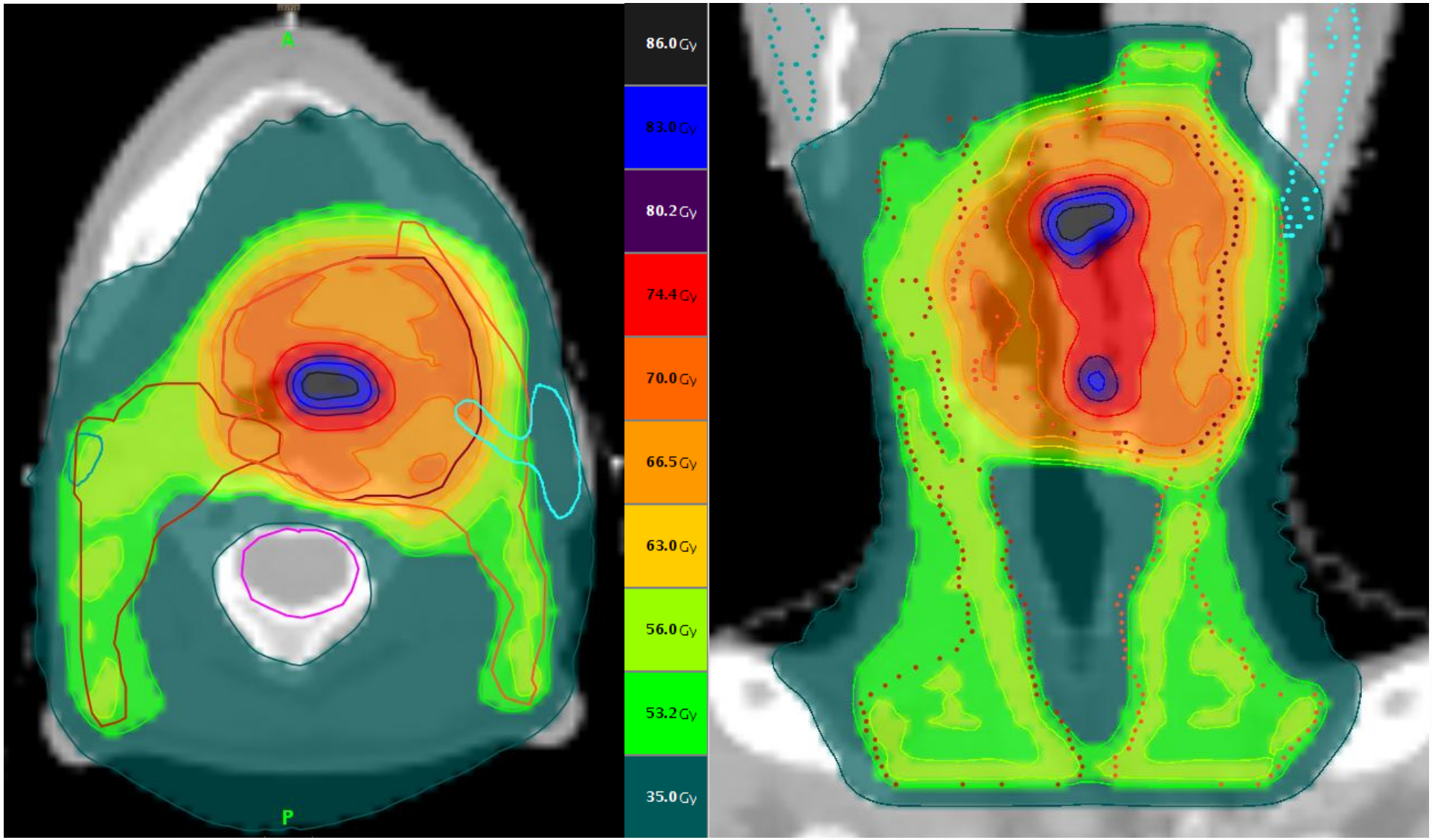




Courtesy of S. Differding, 2012

Dose-painting by number (DPBN)

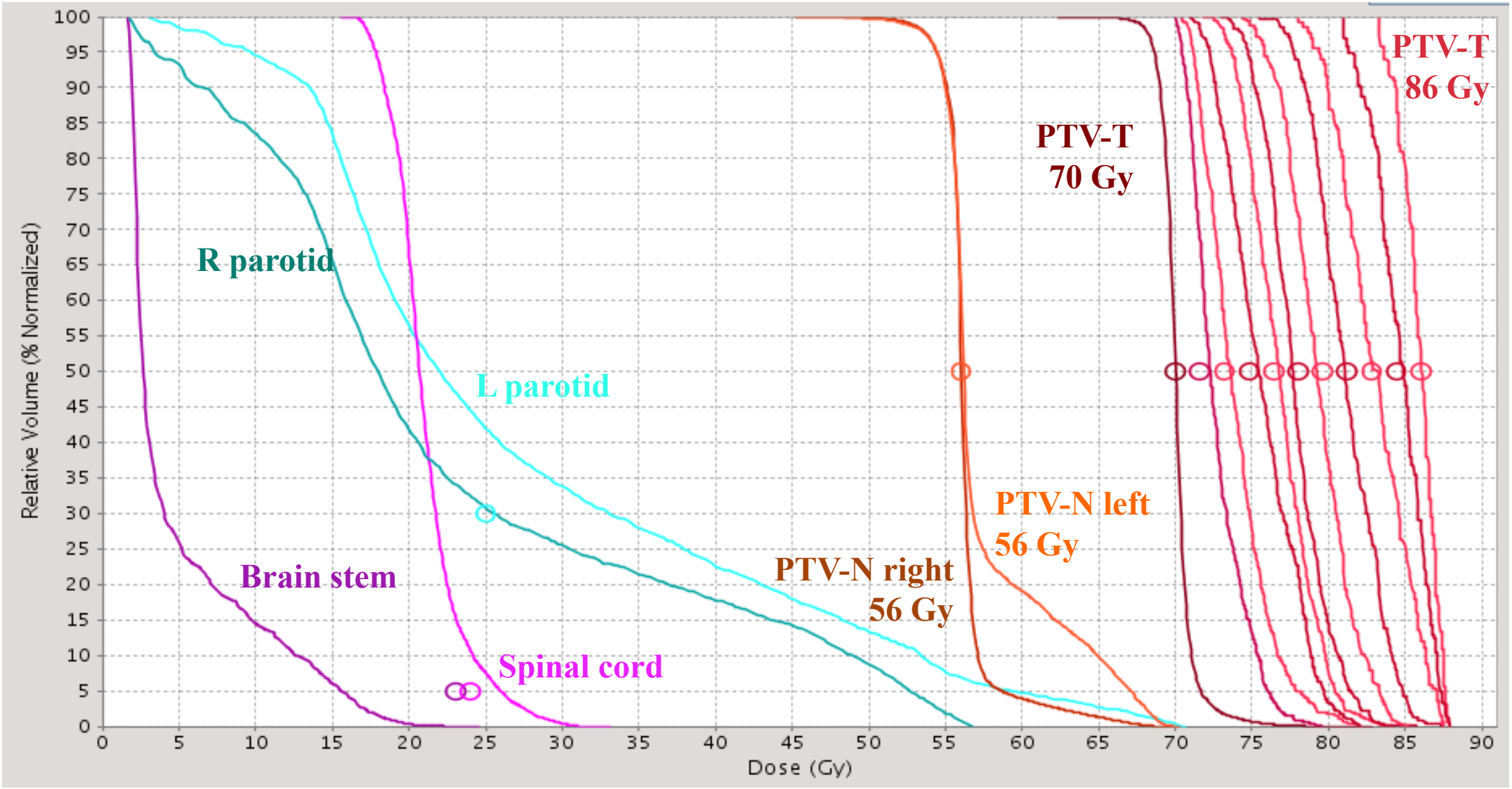
SCC oropharynx: T4b-N0-M0



Courtesy of S. Differding, 2012

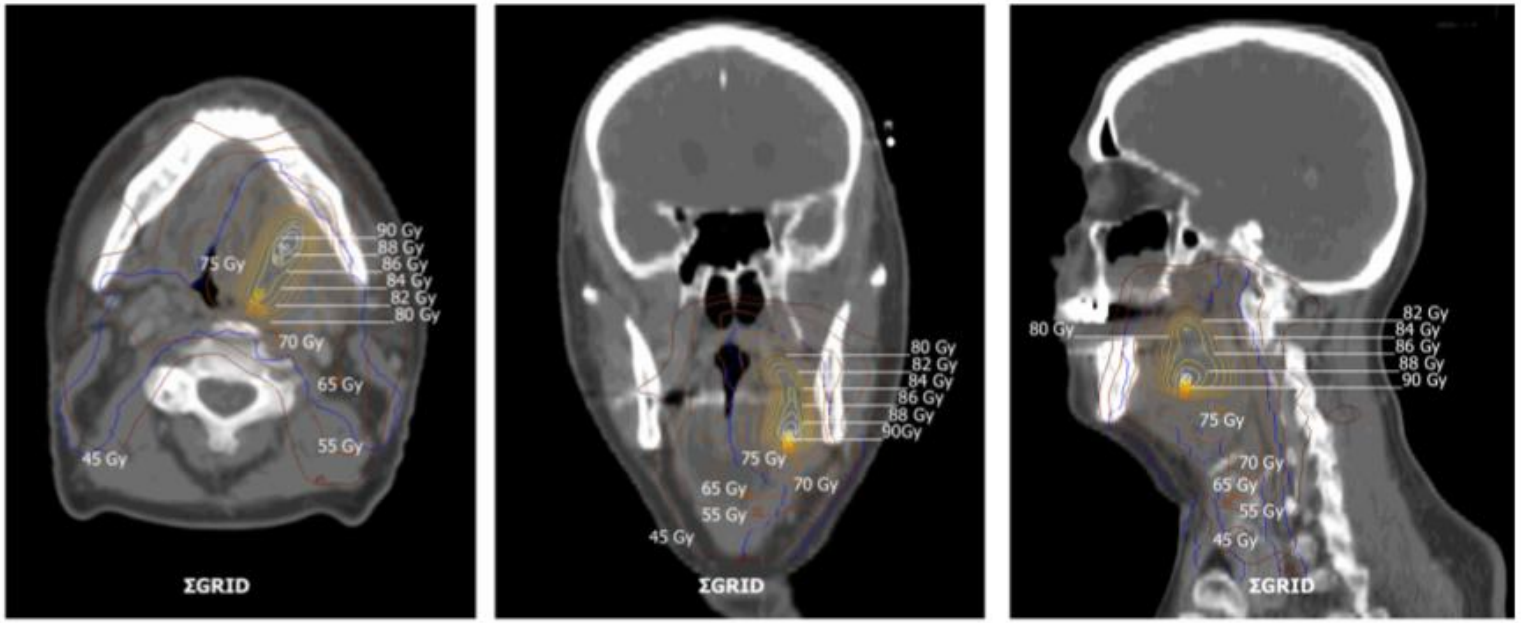
Dose-painting by number (DPBN)

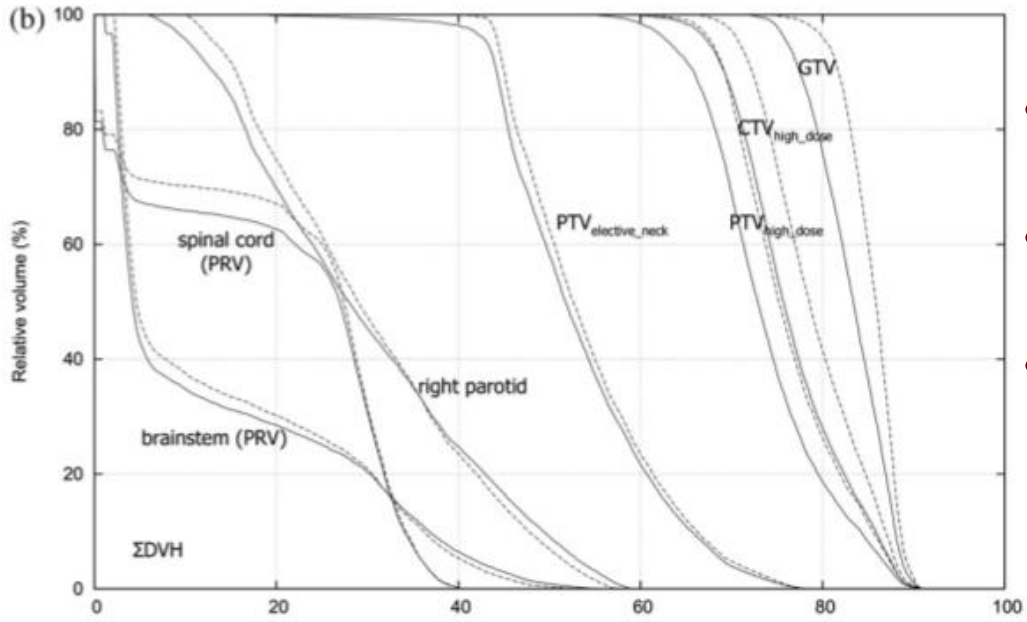
SCC oropharynx: T4b-N0-M0



Courtesy of S. Differding, 2012

Molecular imaging dose painting by number

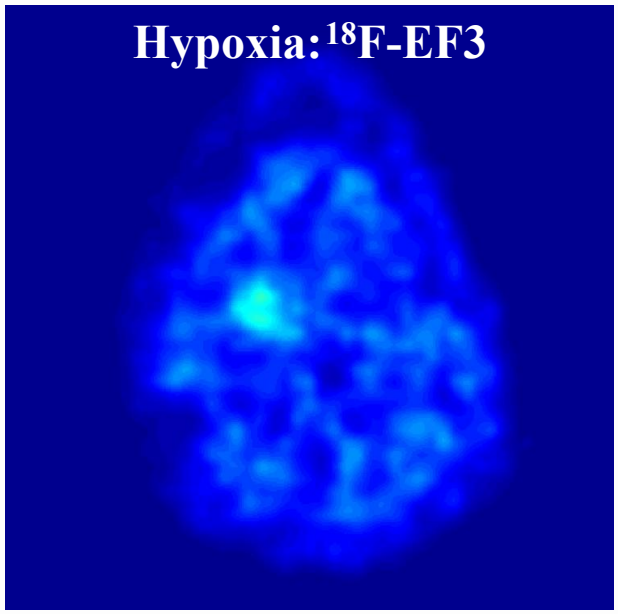


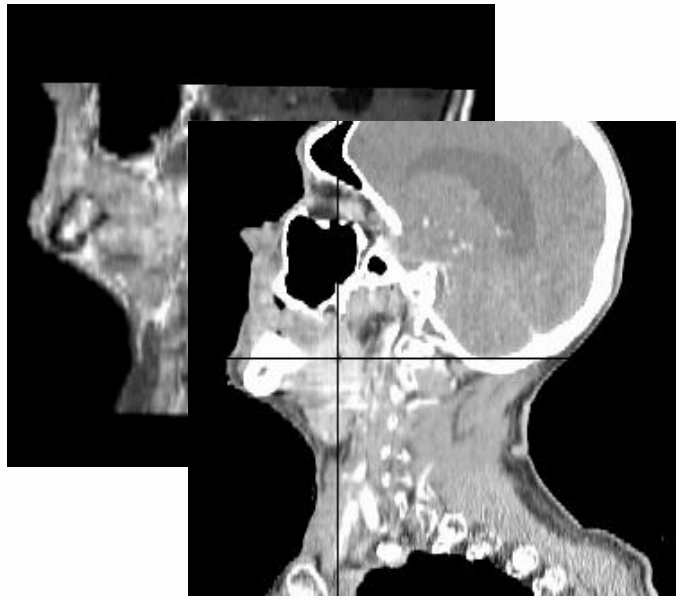


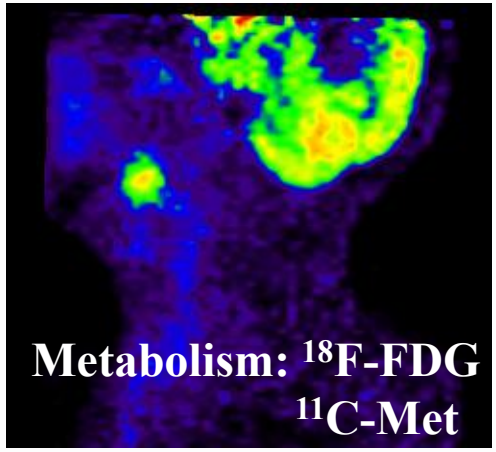
- DPBN based on FDG-PET
- Median dose of 80.9 Gy (n=7) et 85.9 Gy (n=14)
- No grade 4 acute toxicity

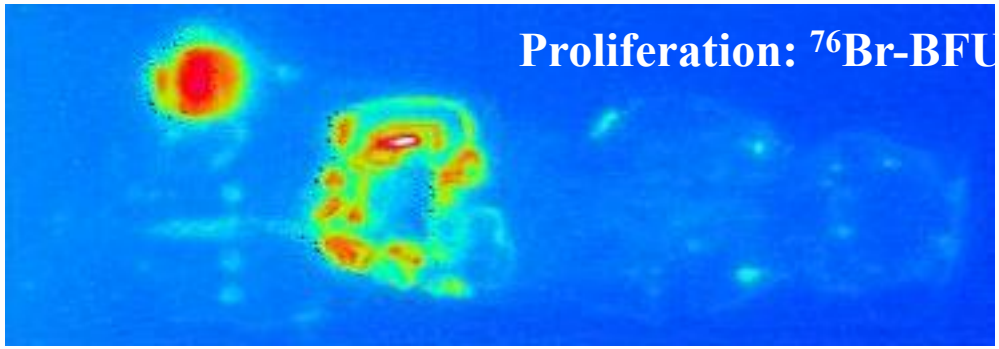
Duprez et al., 2010

Which biological pathways? …

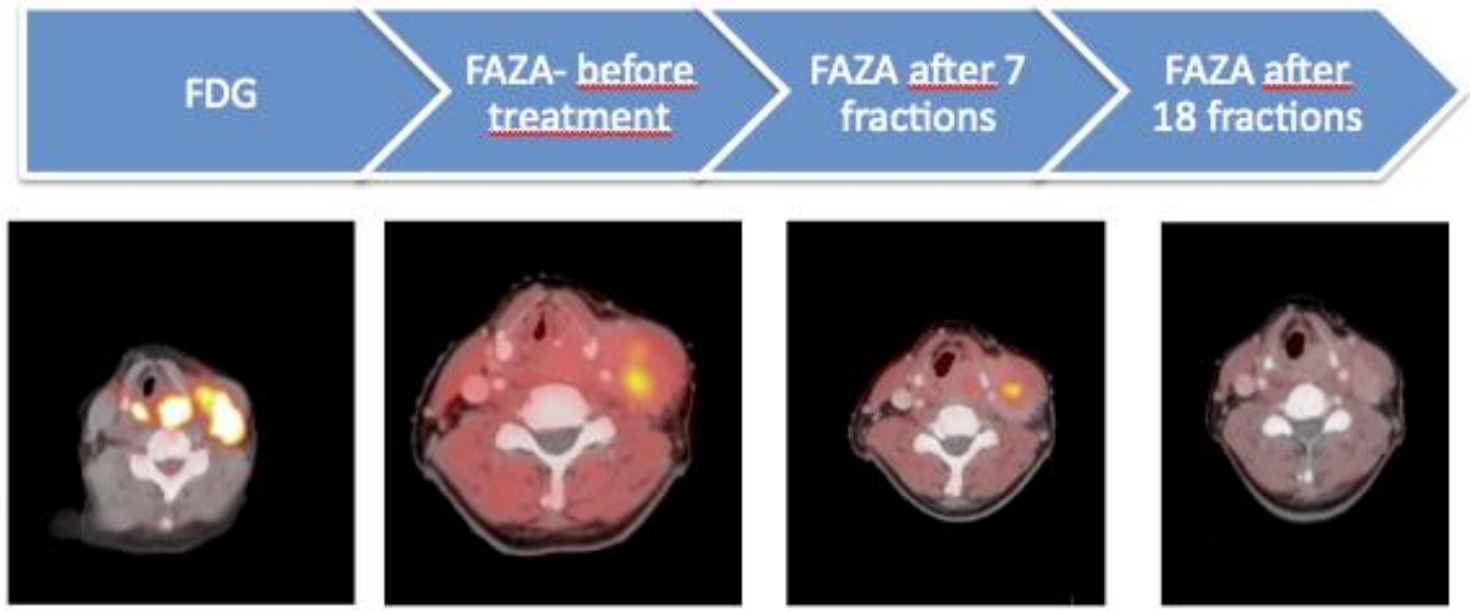




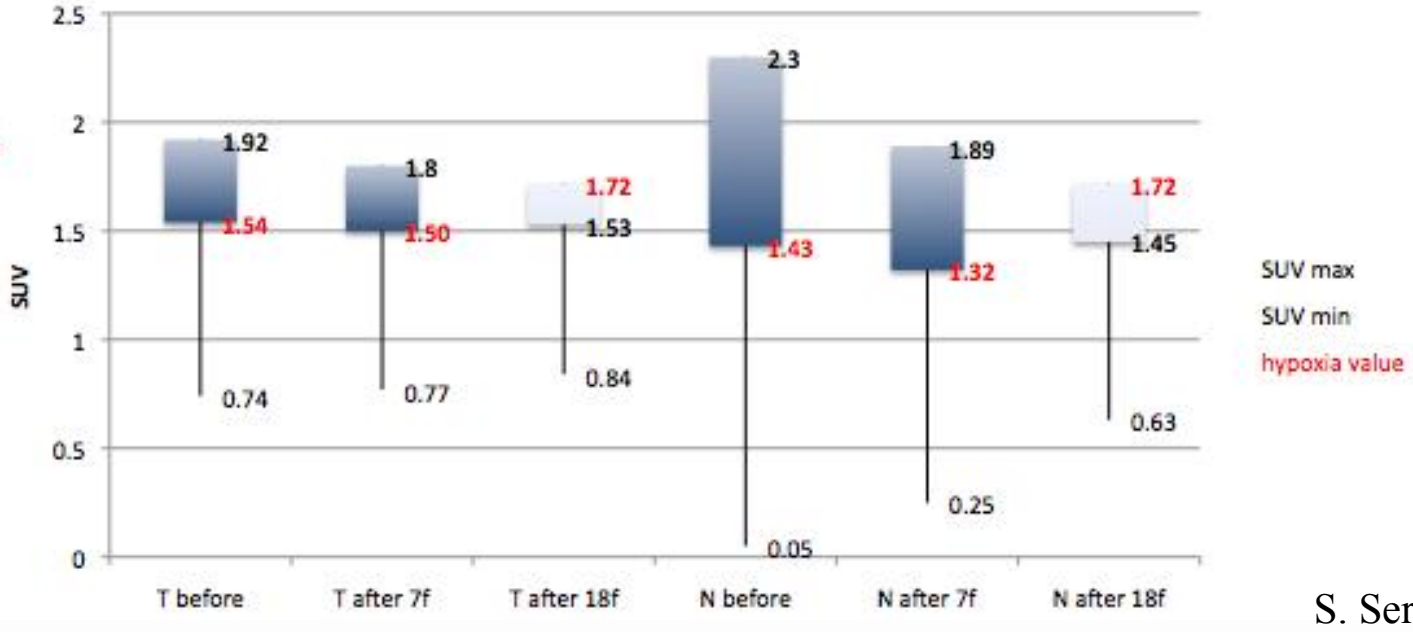




Variation of hypoxia during RT-CH



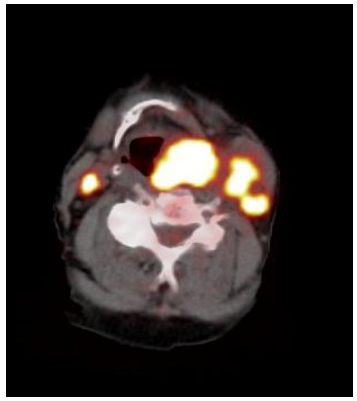
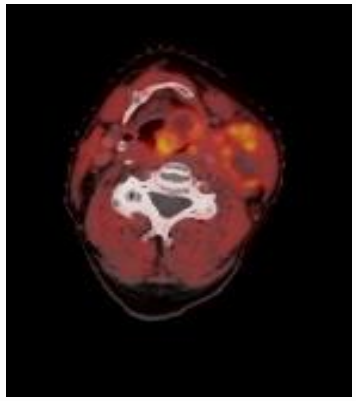
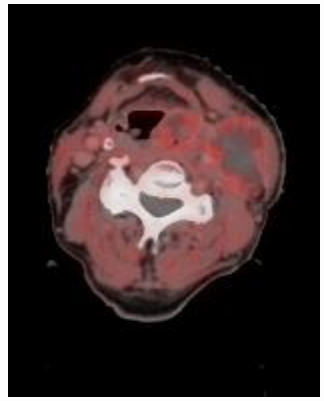
Hypopharynx
T3N2b



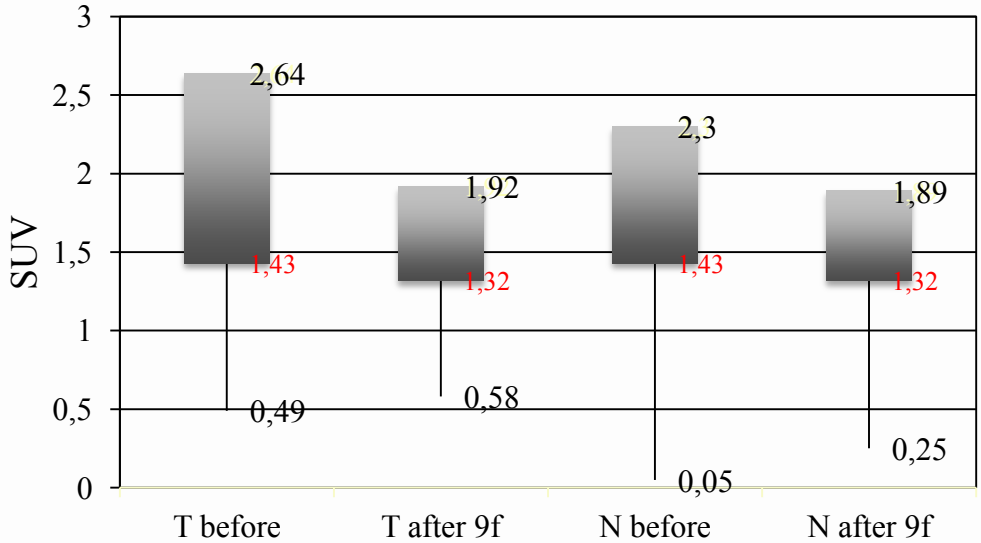
S. Servagi, 2013

Variation of hypoxia during RT-CH

FDG → FAZA-before treatment → FAZA after 9 fractions

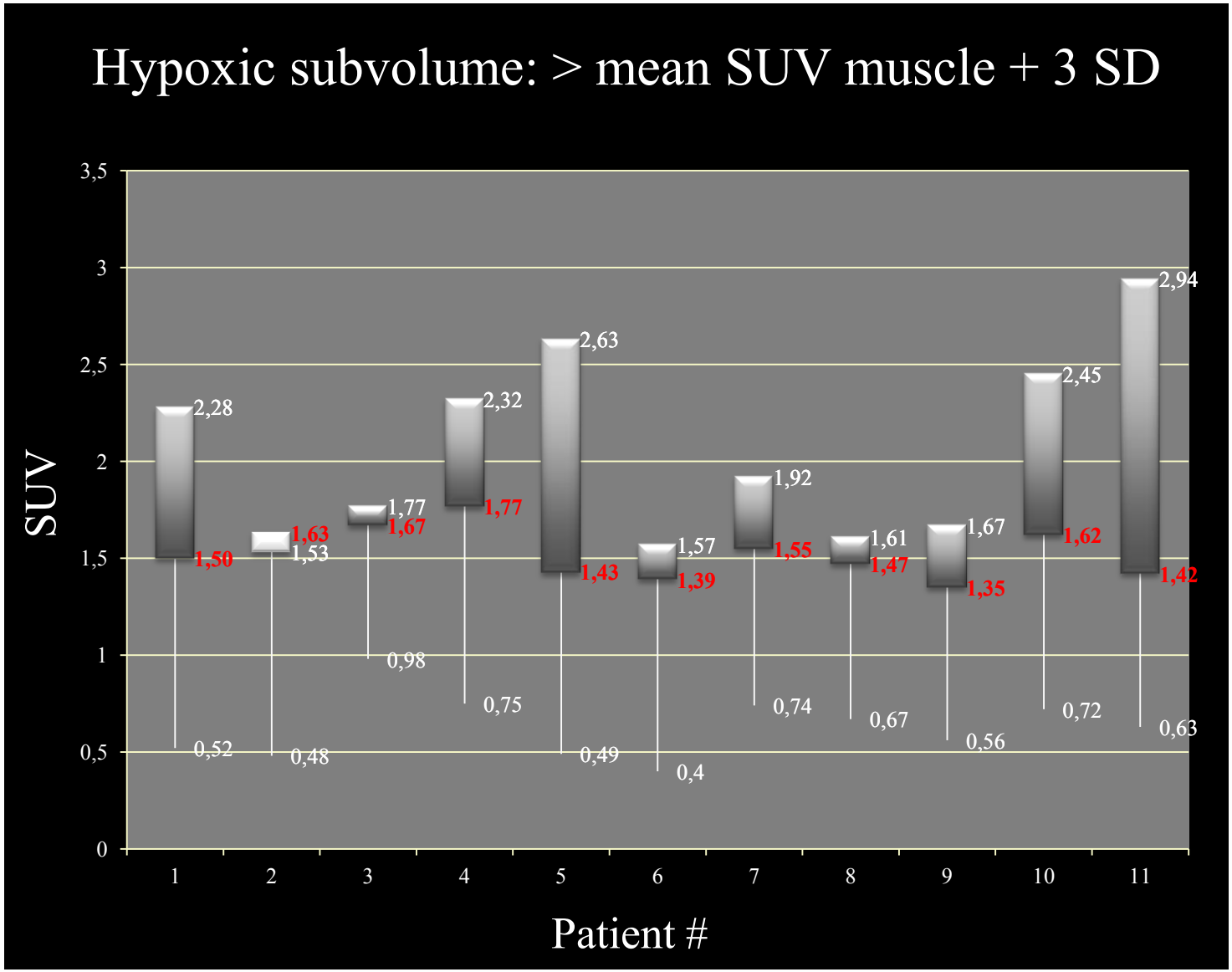
Piriform sinus
T4b N2b



ouverture
SUV max
SUV min
hypoxia value

S. Servagi, 2013

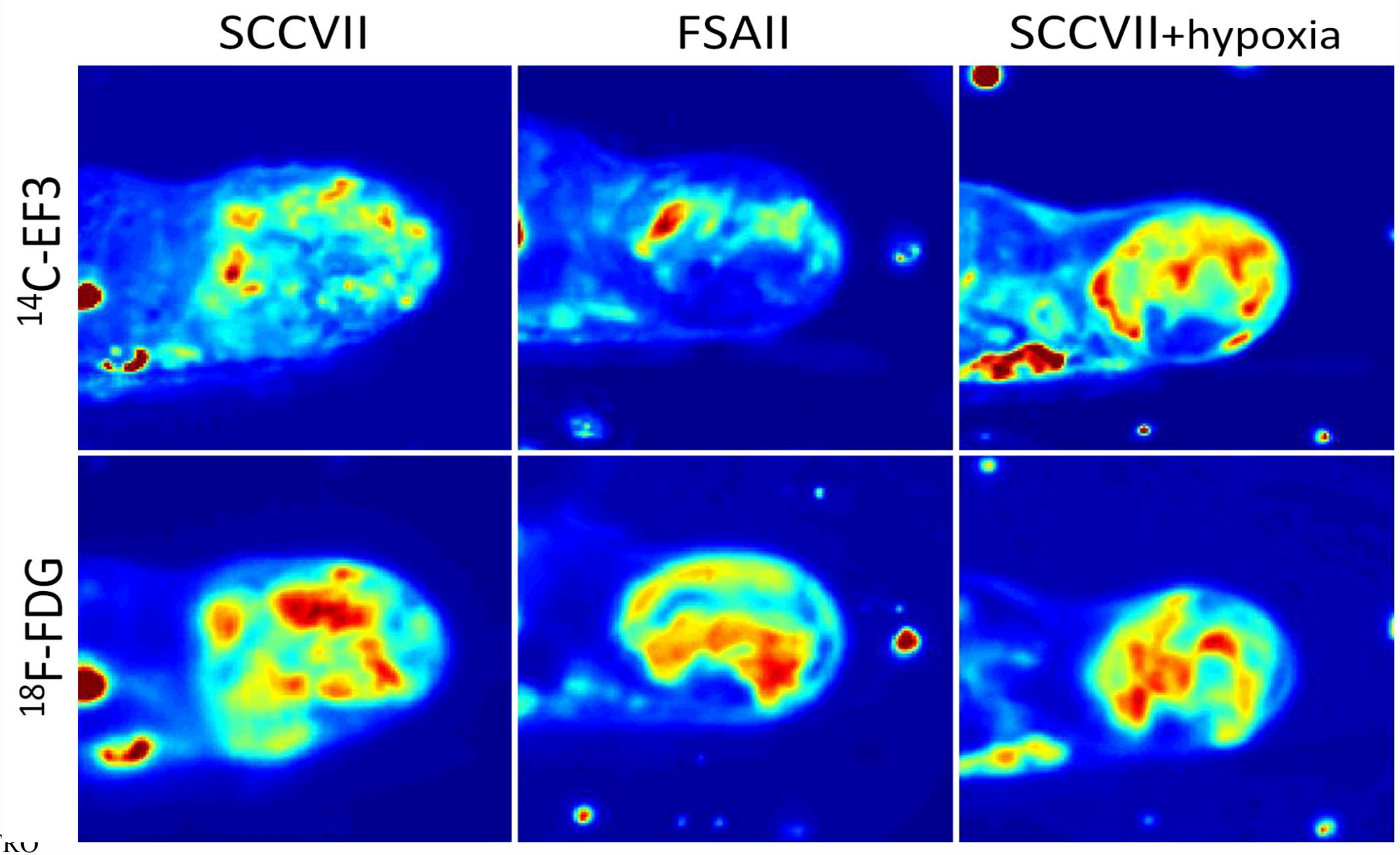
^{18}F-AZA image segmentation



S. Servagi, 2013

Pending issues …

Comparison ^{18}F-FDG / ^{14}C-EF3



N. Christian, 2010

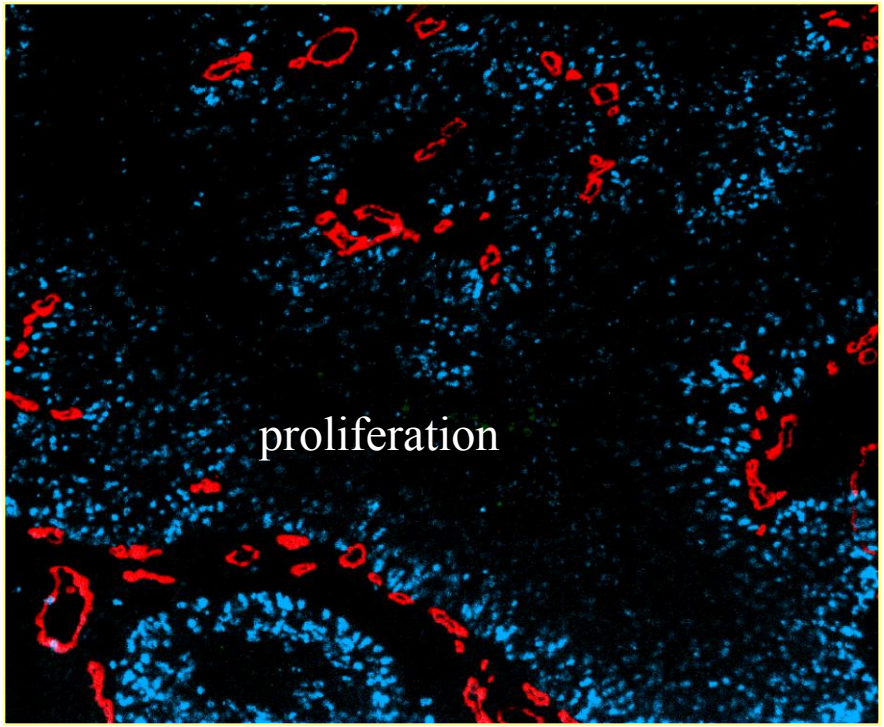
Dose painting and dose painting …

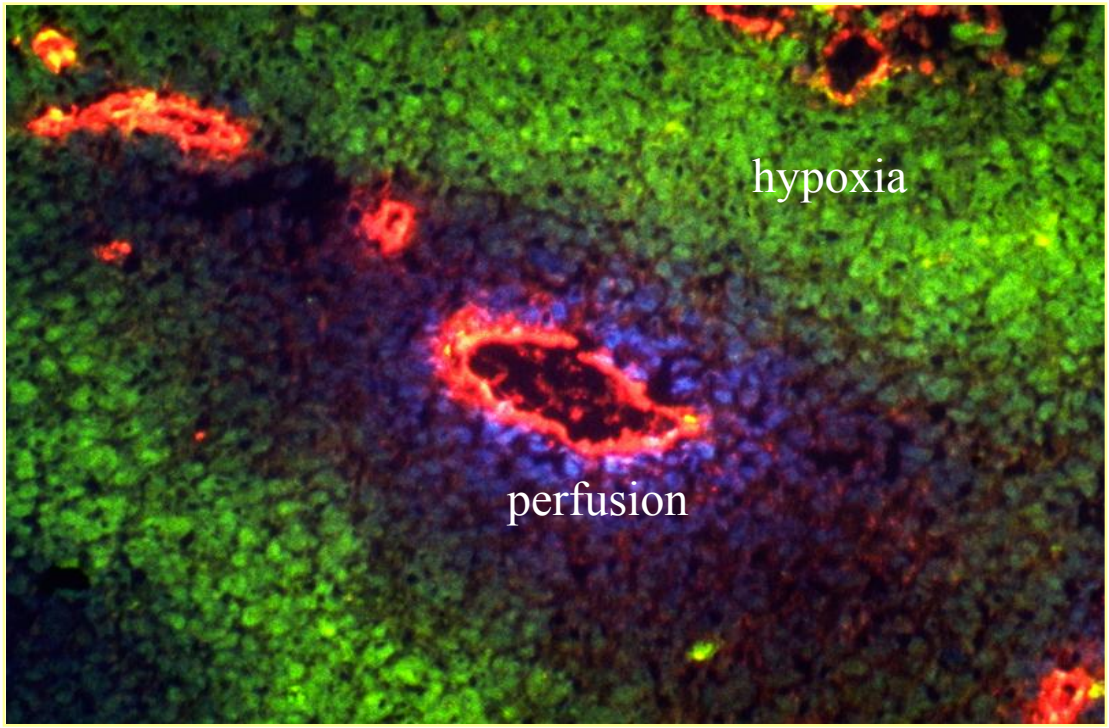
?

Dose Painting By Number ⟷ Dose Painting By Volume

Courtesy of John Schreiner, Kingston Regional Cancer Centre, Ontario

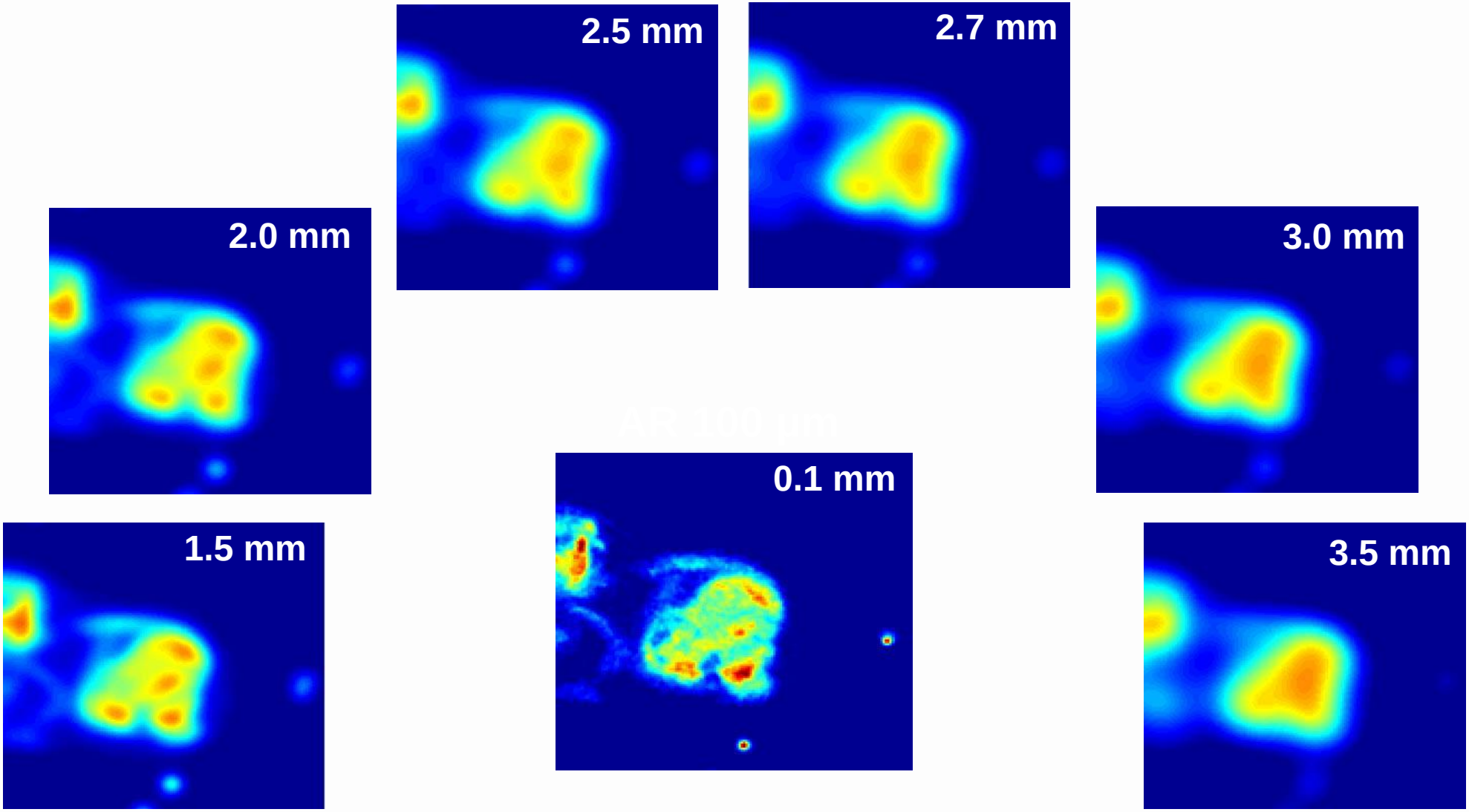
The Graal …





From Kaanders., 2001

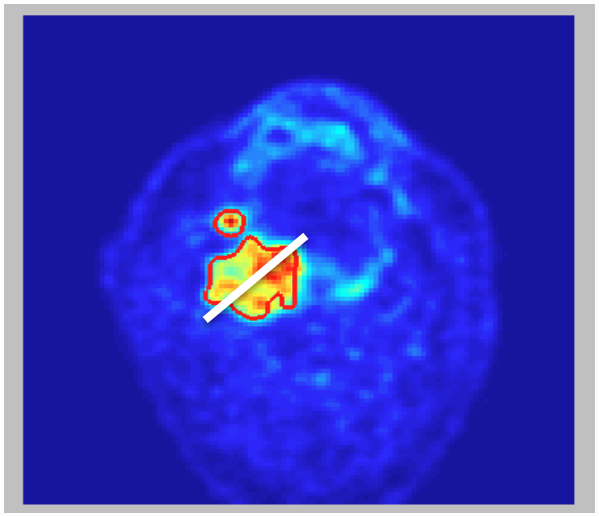
Effect of PET resolution (^{18}F-)

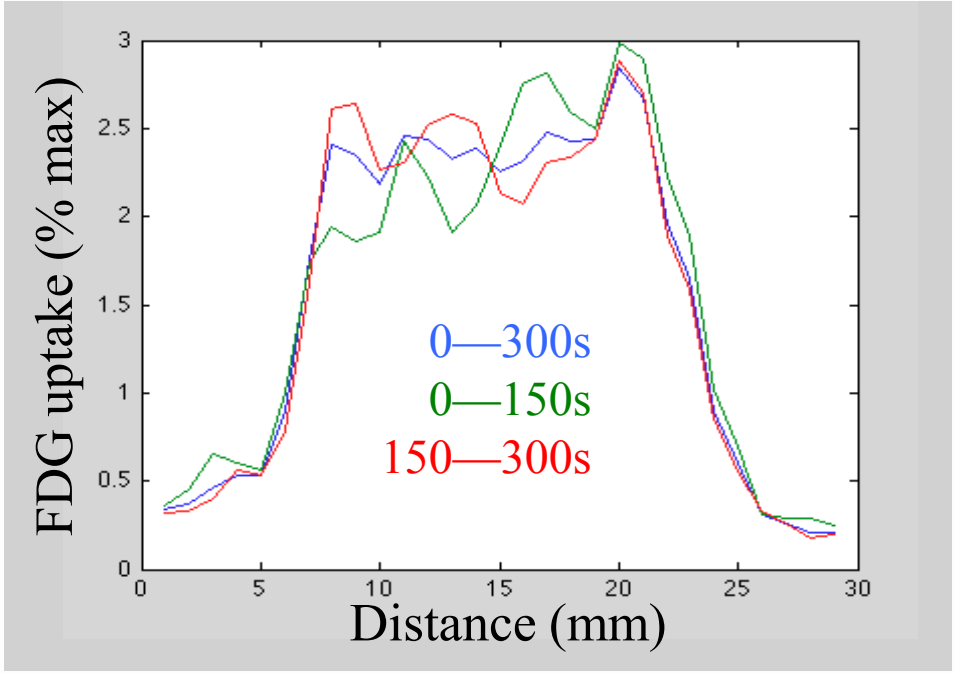


N. Christian, 2010

Statistical noise in image reconstruction

- H&N patient with locally advanced pharyngeal tumor
- 10 mCi FDG injection / 5 min acquisition after 2h resting time
- reconstruction of 2 images by splitting data into 2*2.5 minutes

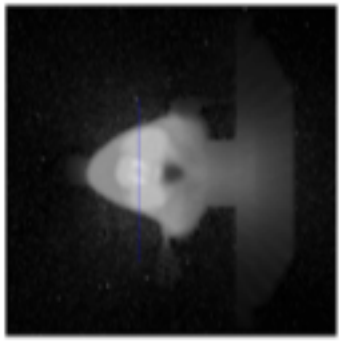


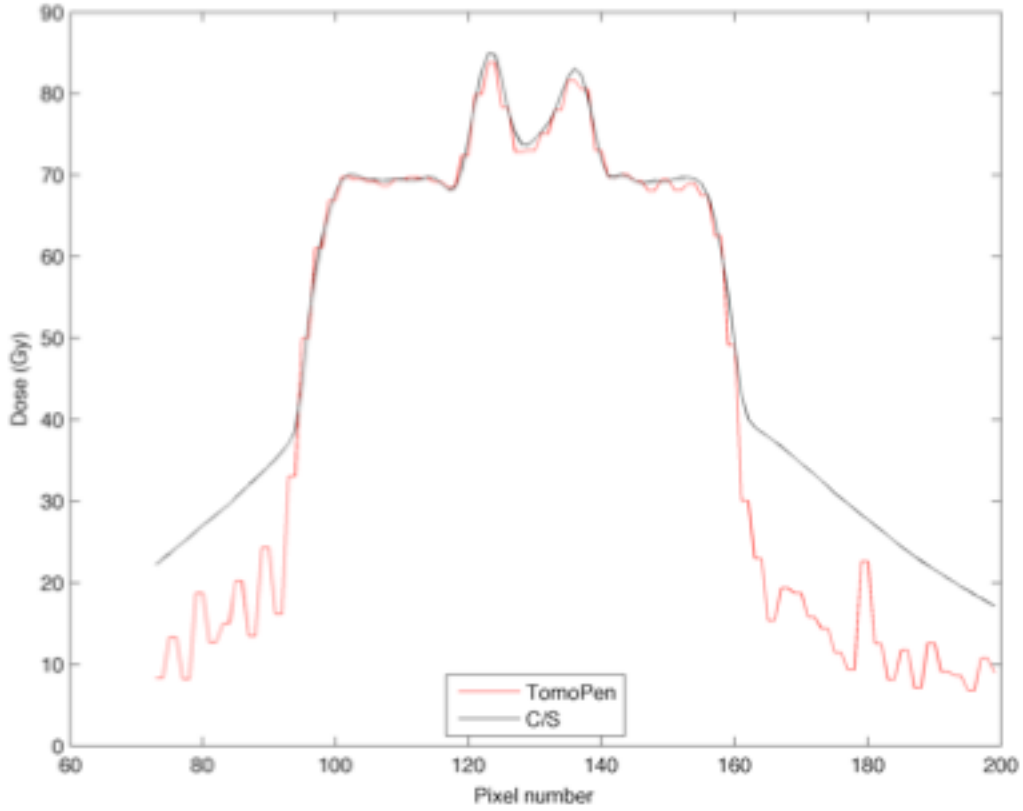


Courtesy of J. Lee, 2013

Dose painting : the dose planning issue

Comparison between MonteCarlo and TomoTherapy convolution-superposition algorithm





Courtesy of E. Sterpin

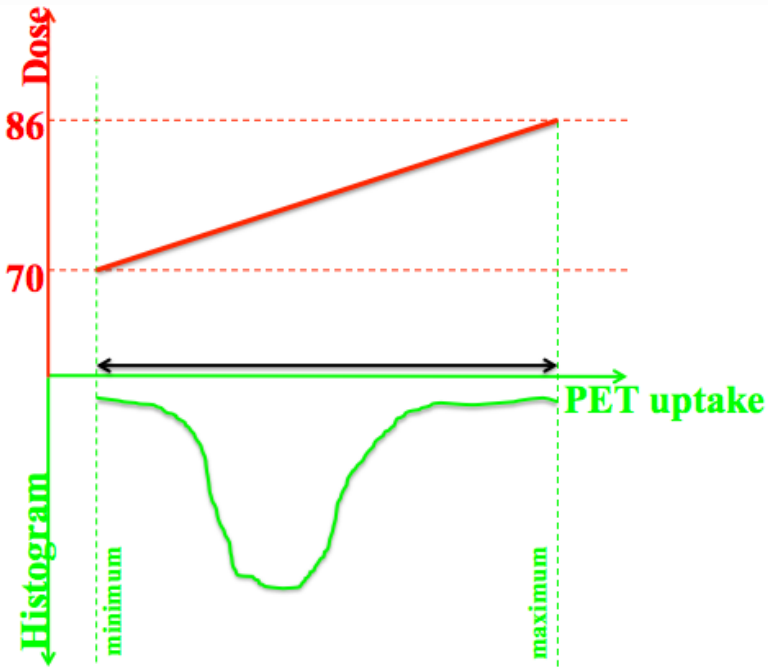
Dose painting: dose prescription function

"Radiosensitivity"

Dose Prescription for Dose Painting by Numbers

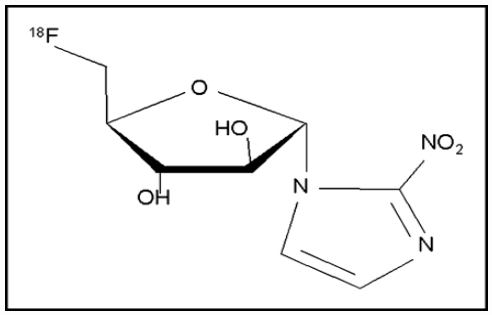
The simplest, reasonable, voxel-based prescription function is a linear interpolation between a minimum dose, D_{min}, and a maximum dose D_{max} when the voxel image intensity, I, varies between its lower and upper bound, I_{min} and I_{max} within the target volume[9,89]:

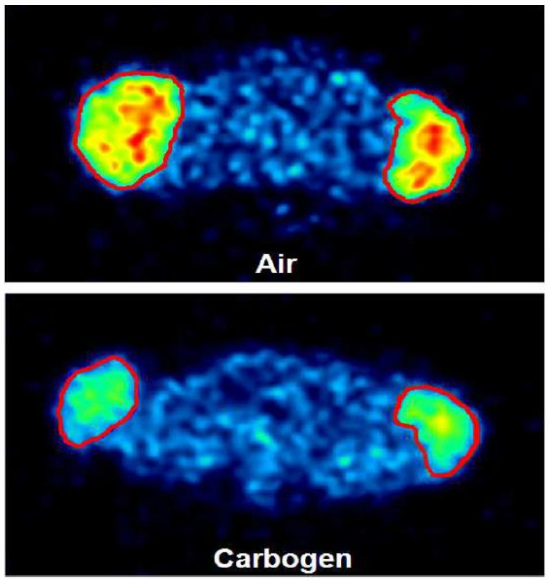
$$D(I) = D_{min} + \frac{I - I_{min}}{I_{max} - I_{min}} \cdot (D_{max} - D_{min})$$

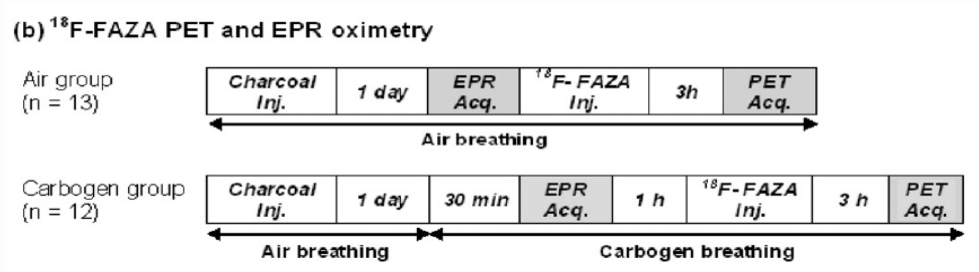


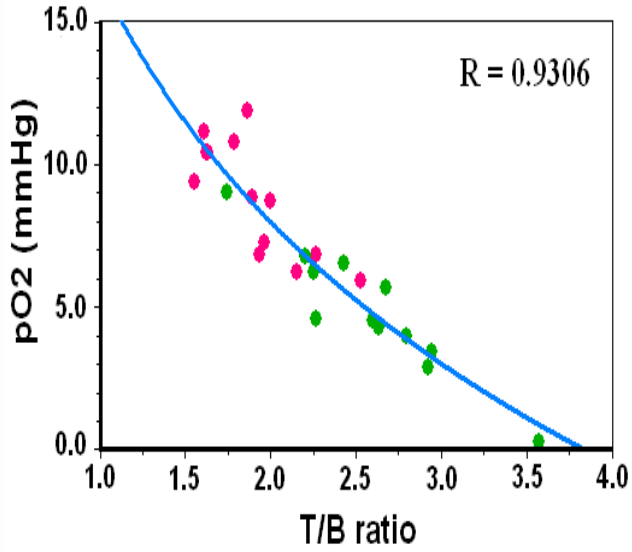
Vanderstareten, 2006

^{18}F-FAZA accumulation in tumors as a function of pO2
Qualification by EPR oximetry







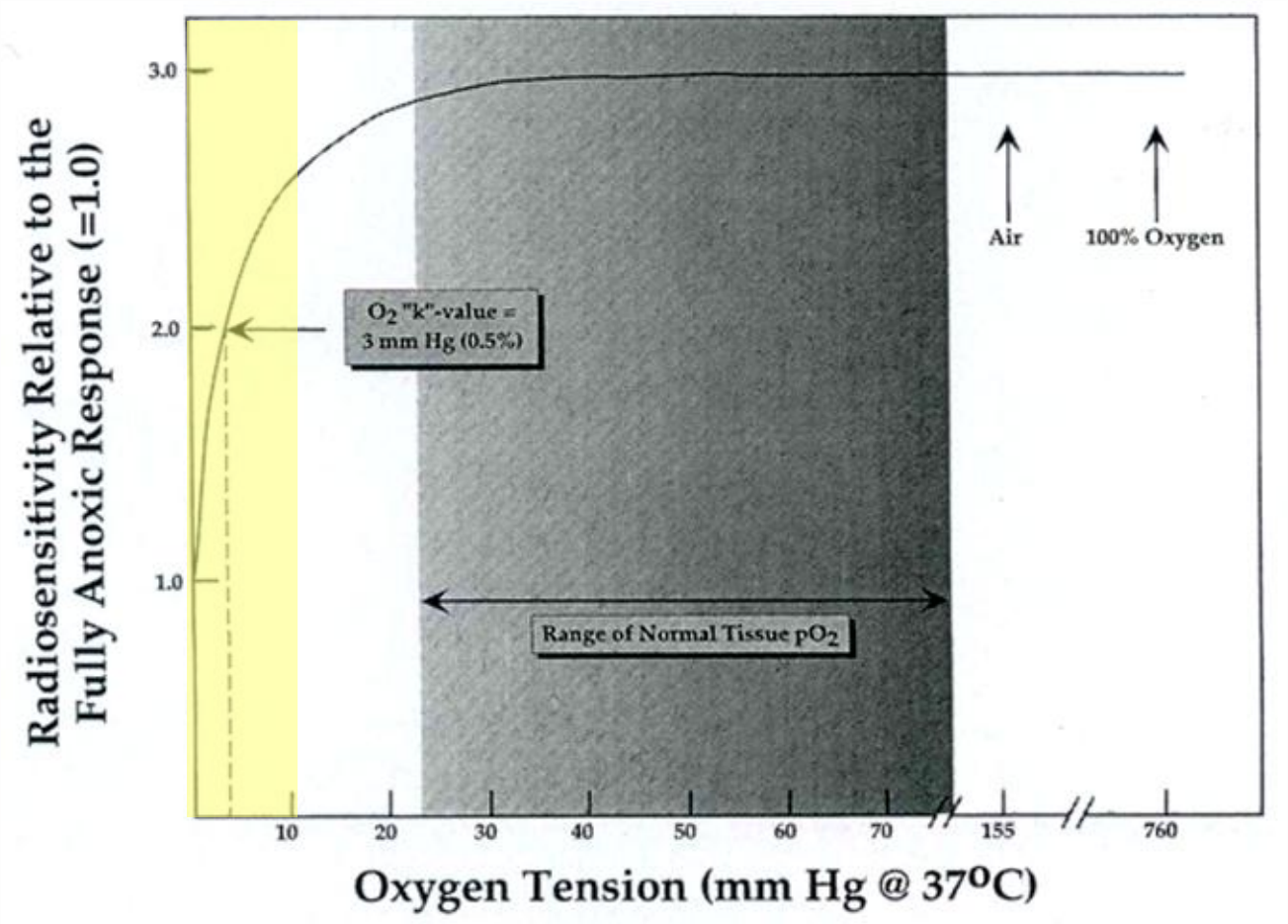


Accumulation increases under 10 mm Hg
(radiobiologically relevant hypoxia)

Tran et al, Radiother. Oncol. 2012, 67, 53

Dose painting: dose prescription function

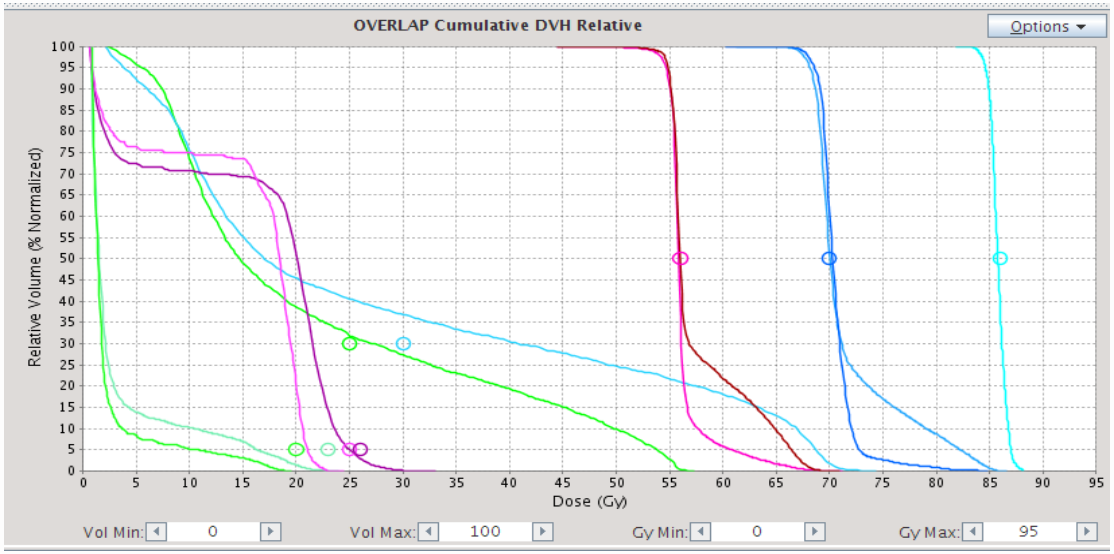
Hypoxia



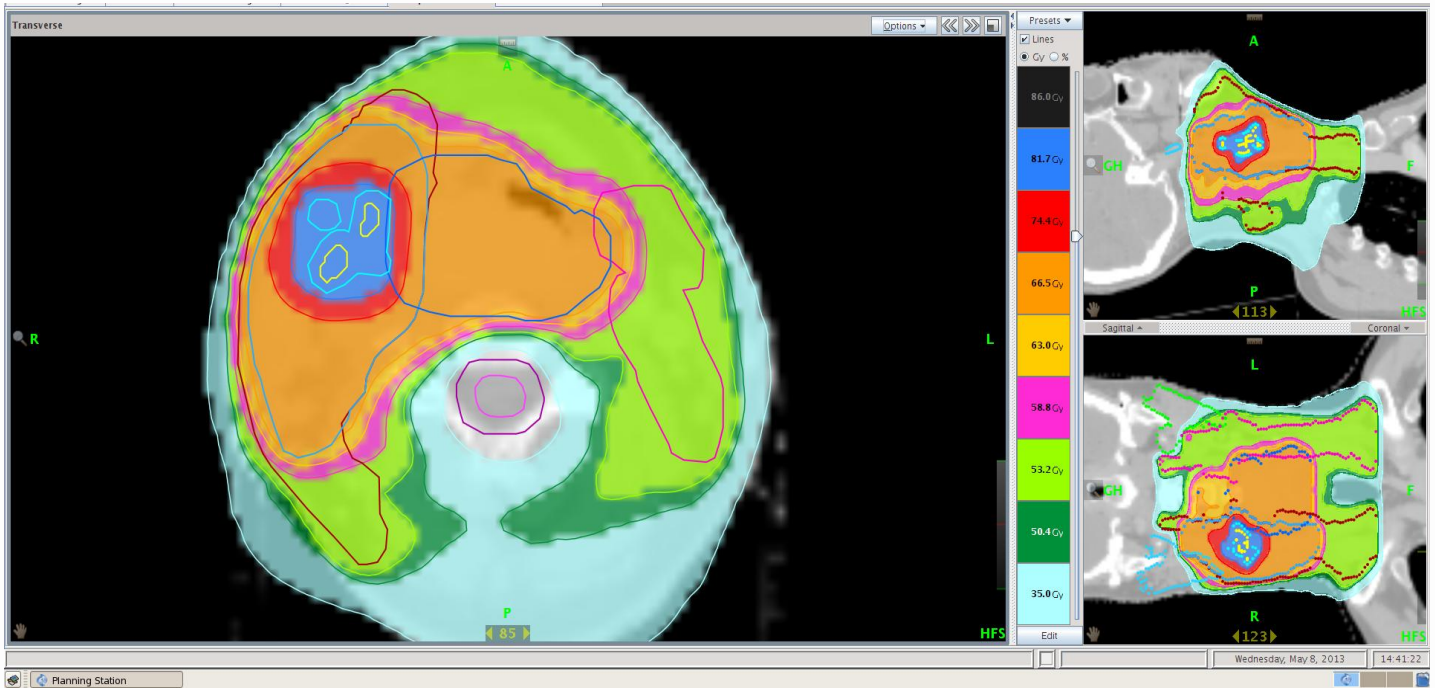
PET tracer range

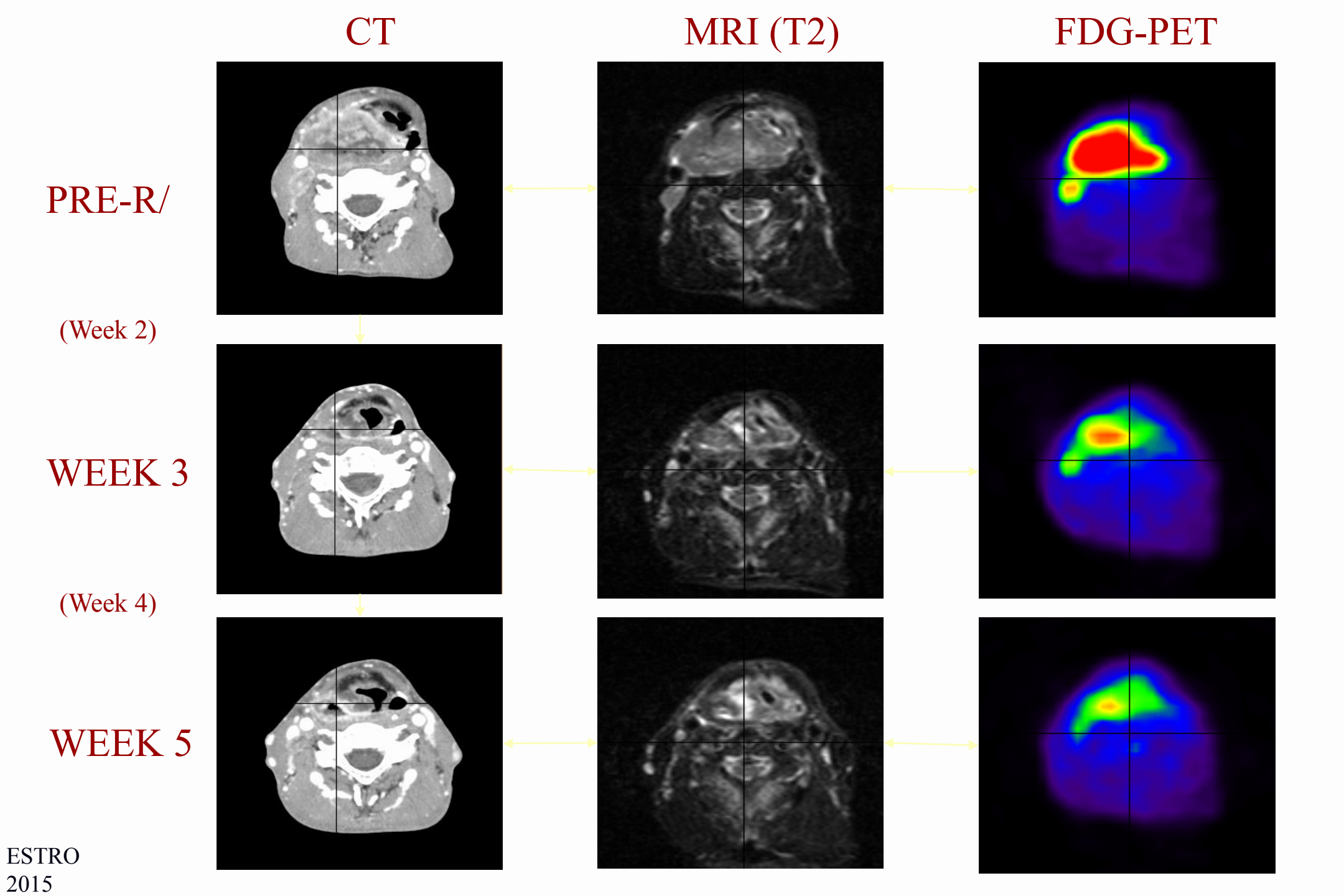
From Zeman, 2000

Hypoxia (^{18}F-AZA) dose painting

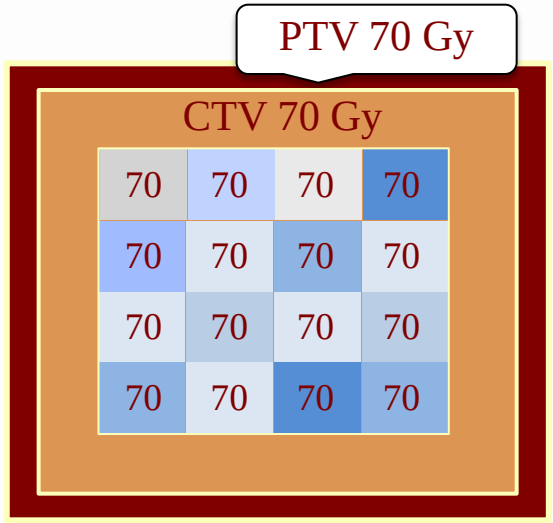


"Binary" dose escalation, e.g. from 70 to 86 Gy

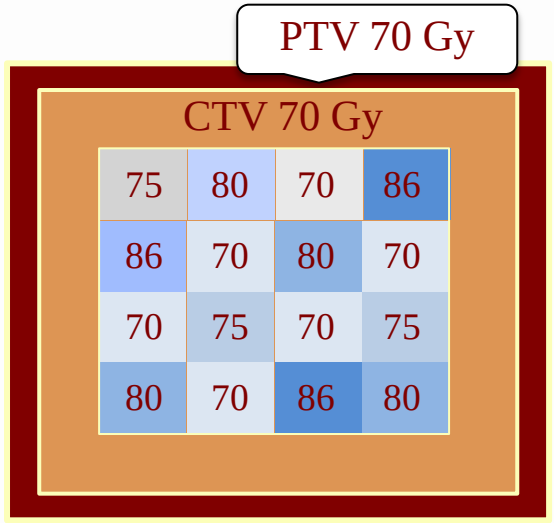



CT
MRI (T2)
FDG-PET
PRE-R/
(Week 2)
WEEK 3
(Week 4)
WEEK 5
ESTRO
2015

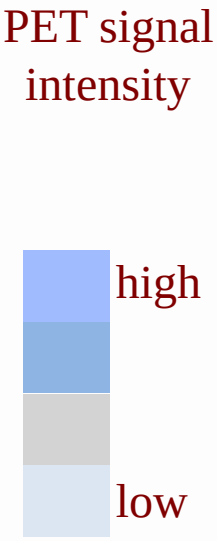
Dose-painting: randomized phase-II study design



Standard arm
Median GTV dose:
70 Gy

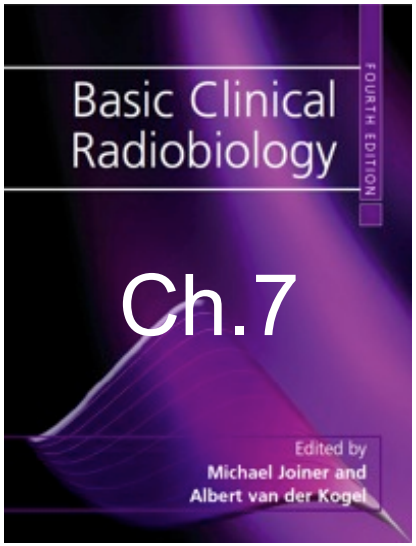


Experimental arm A:
PET-based dose increase
Median GTV dose: 75 Gy



Tumor growth & response to irradiation

Rob Coppes
Departments of Radiation Oncology & Cell Biology
University Medical Center Groningen,
University of Groningen,
The Netherlands



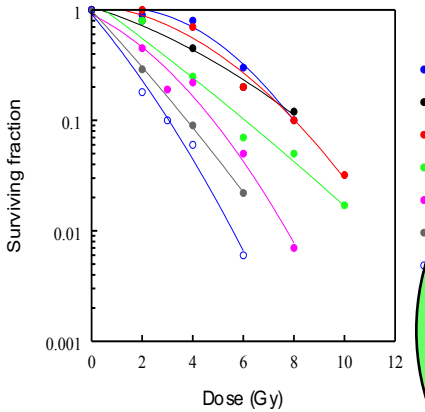
Many thanks to Bert van der Kogel for his slides

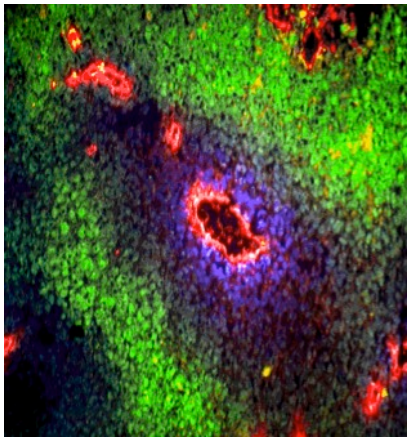
ESTRO School

Cancer Research Center Groningen

umcg

Biological contributors to outcome of tumor treatment with radiation





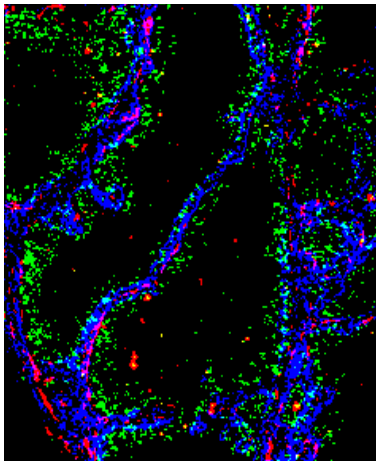
Tumor cell radiosensitivity

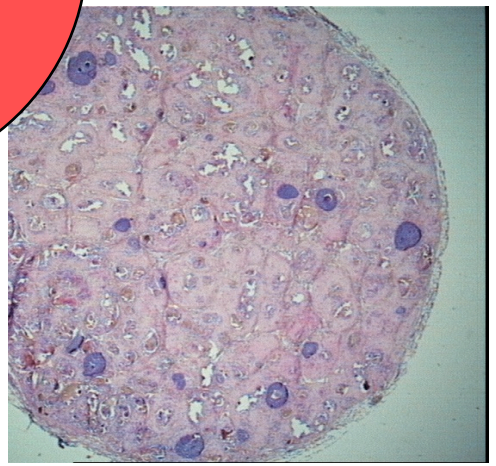
Hypoxia

Proliferation

Vascular Radiosensitivity?

Volume (Stem cell proportion)



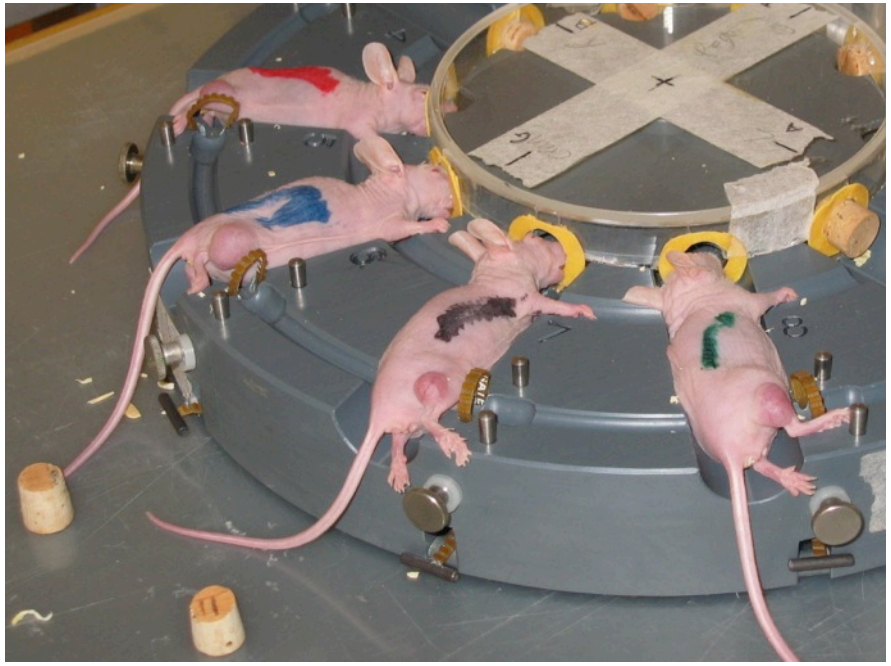


Tumor Models

- **Syngeneic mouse models**
- Tumor models derived from spontaneous tumors in mice
- Usually non-immunogenic
- Can be transplanted to other syngeneic mice

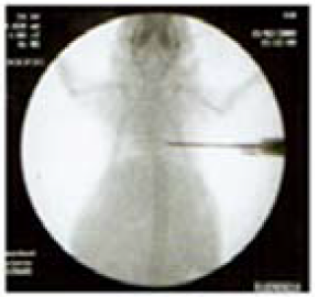
- **Xenografts**
- Human tumors grown in immunodeficient mice: Nu/Nu (nude mice), SCID

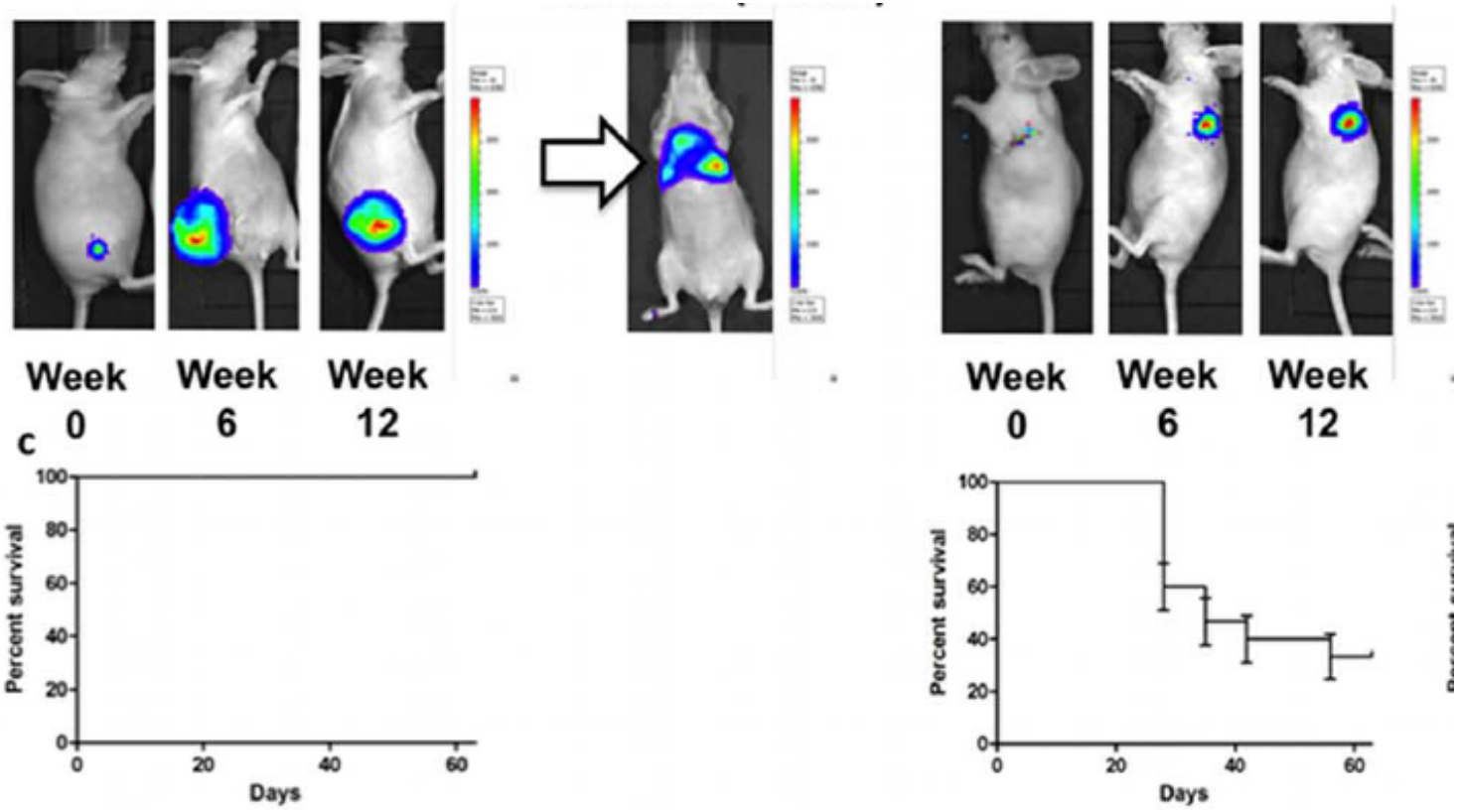
  Orthotopic models
  Subcutaneously
  - *patient-derived cell lines*
  - *patient-derived organoids*
  - *patient-derived xenografts*



- **Tumors arising in genetically modified mice**
- Transgene, knockout, knock-in, etc.

Orthotopic tumors: lung
bioluminescence imaging

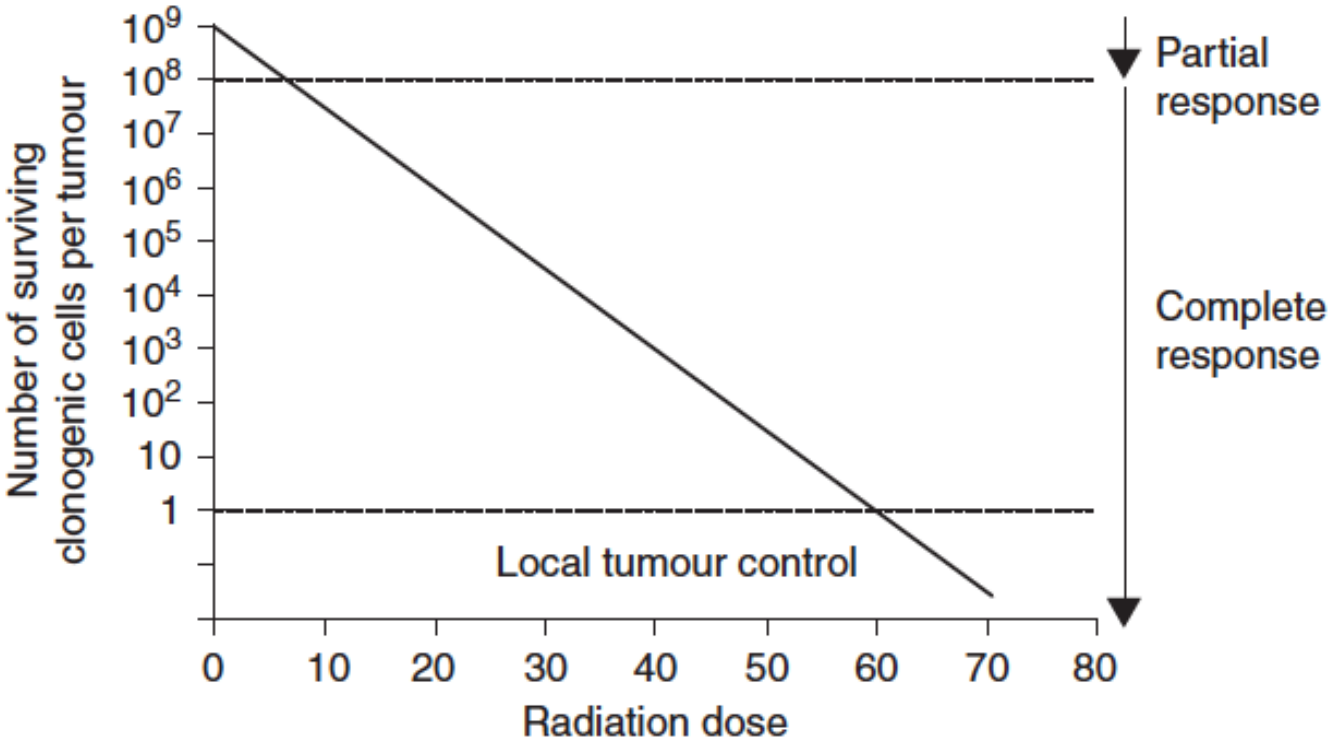




Mordant et al, Plos One 2011

Tumor Models

- Tumor derived cell lines
- tumor tissue slices



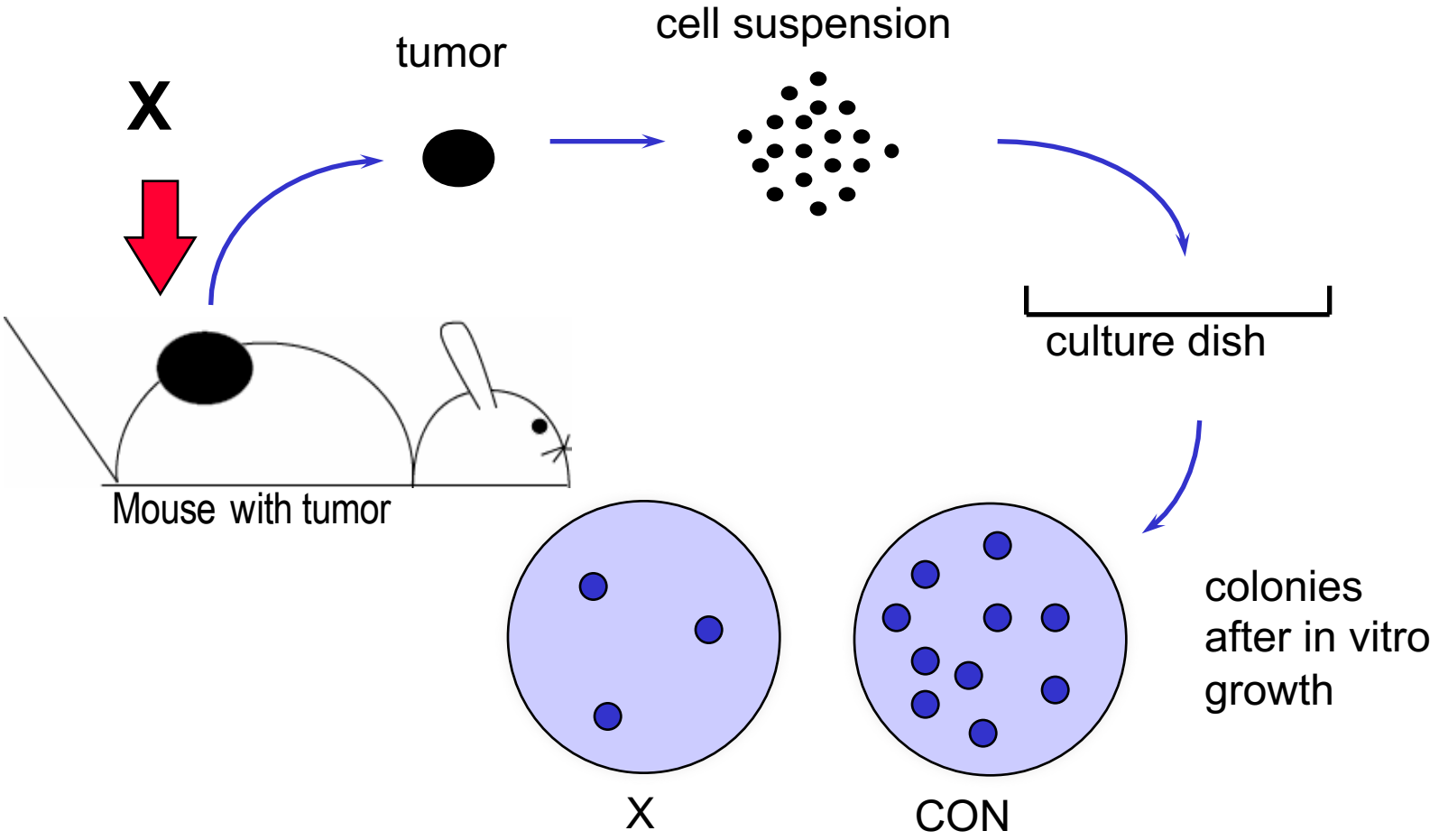
Assays for Tumor Response to Radiation

- Clonogenic assays (plating assays): tumors are excised, reduced to single cells, and grown in a test environment
  - provide a direct measure of the surviving fraction of clonogenic cells.
  - limitation: relationship between clonogens (in test environment) and stem cells (in situ) is uncertain.

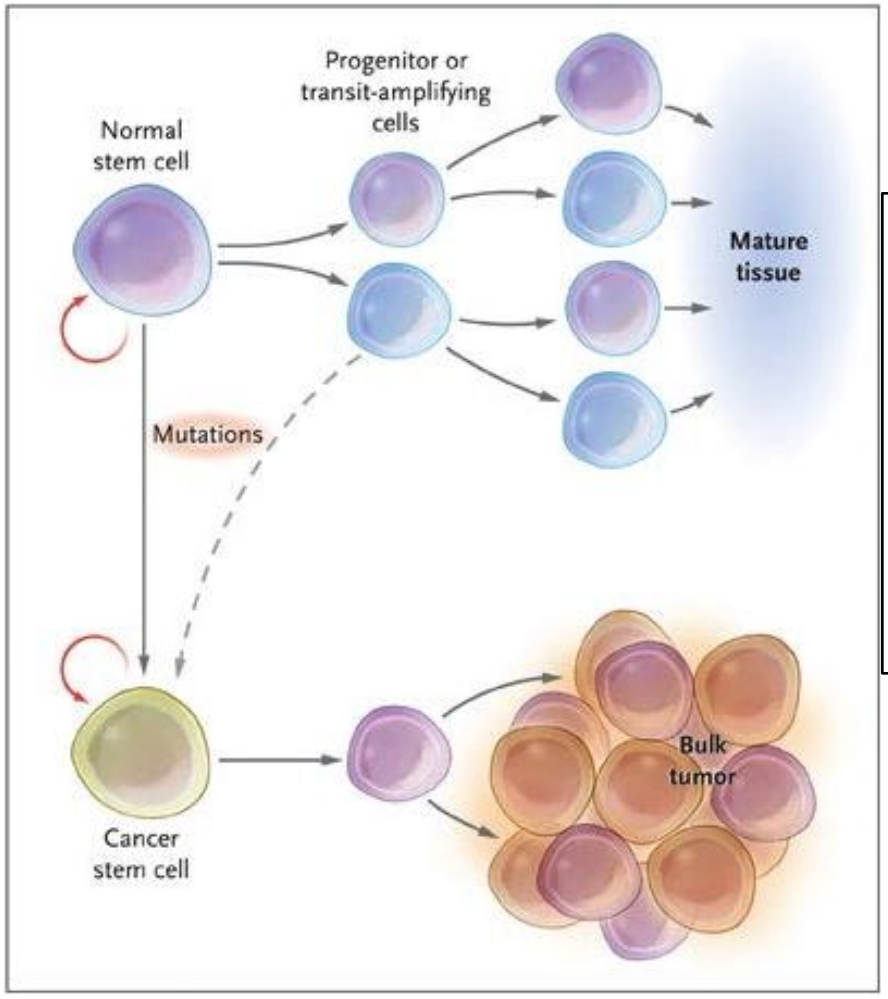
- Culturing as organoids: tumors are excised, reduced to single cells, and grown in 3D matrix
  - Measurement of tumor stem cells
  - Show potential to differentiate in all tumor subtype cells
  - lack of environmental factors,… vascularisation

- In Situ assays (growth delay, tumor control): tumors left in place.
  - measure response of effective and potential stem cells.
  - limitation: no quantitation of stem cells; surviving fraction is difficult to assess.

Cell survival: ex vivo



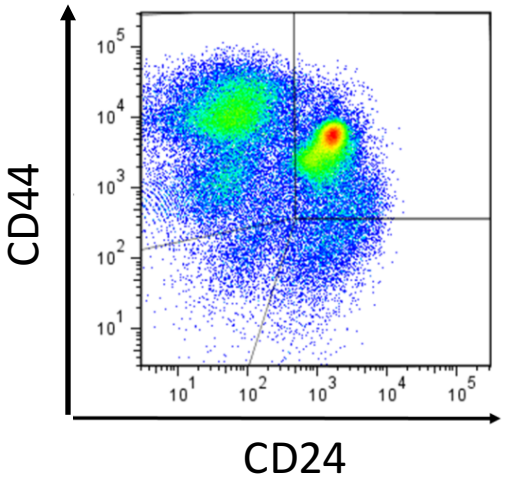
Cancer Stem Cells (CSCs)



- Self-renewal
- Capability to develop into multiple lineages
- Chemo- and radiation resistant
- Formation of spheres in suspension culture
- Generation of tumors when transplanted in immunodeficient mice with limited number of cells

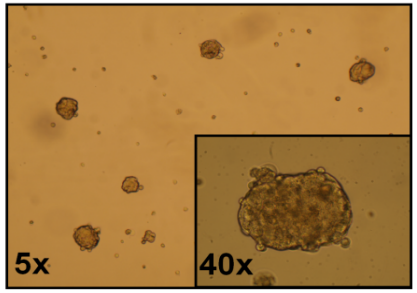
Jordan et. al. Cancer Stem Cells 2006

Cell survival: ex vivo

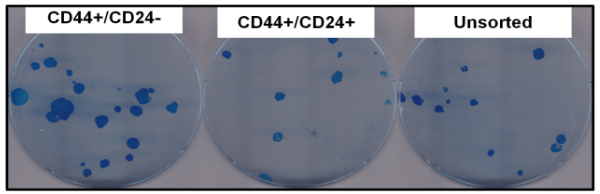


Stem Cells

B

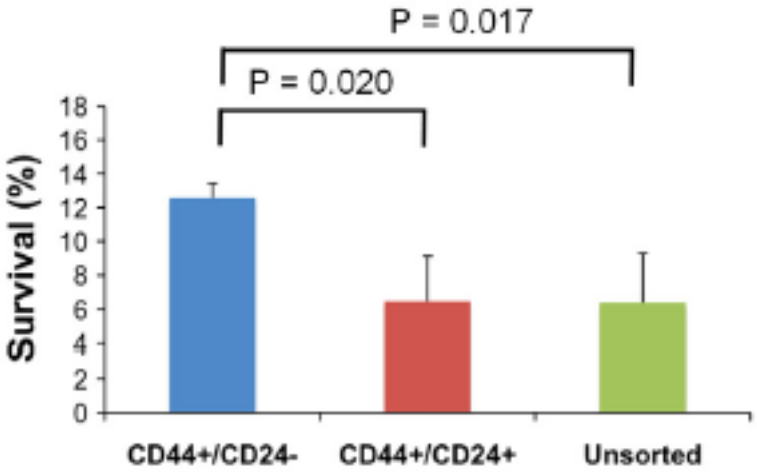


C



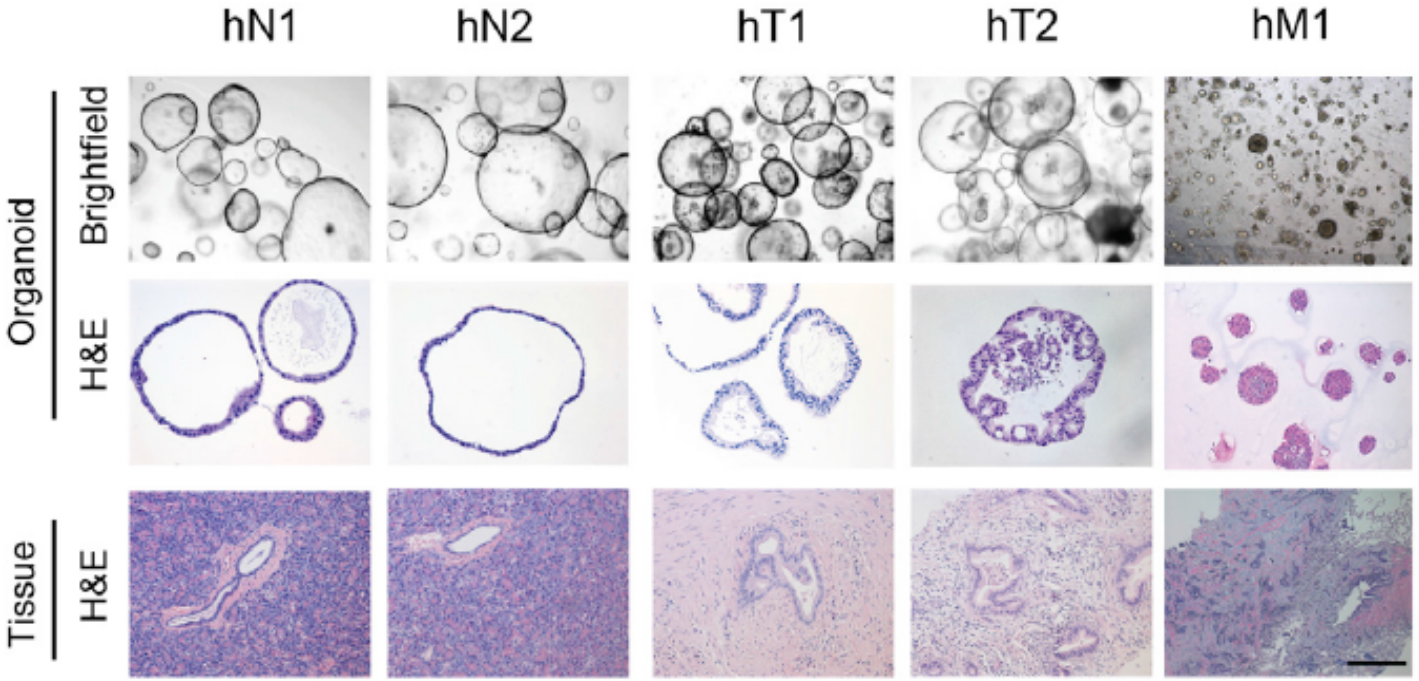
Clonogenics

D



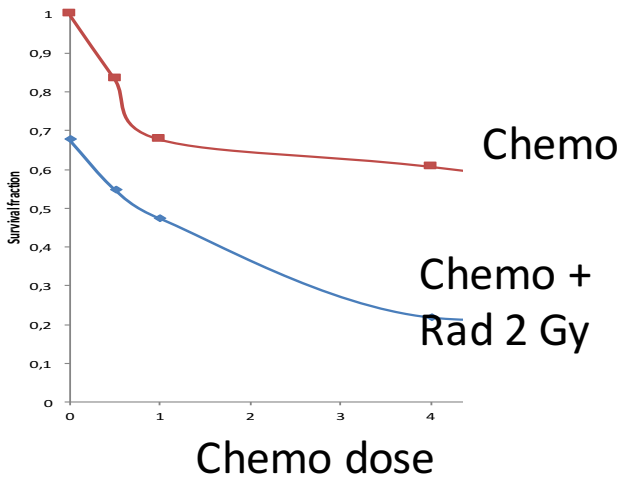
SMIT ET AL 2013

Cancer stem cells derived organoids?

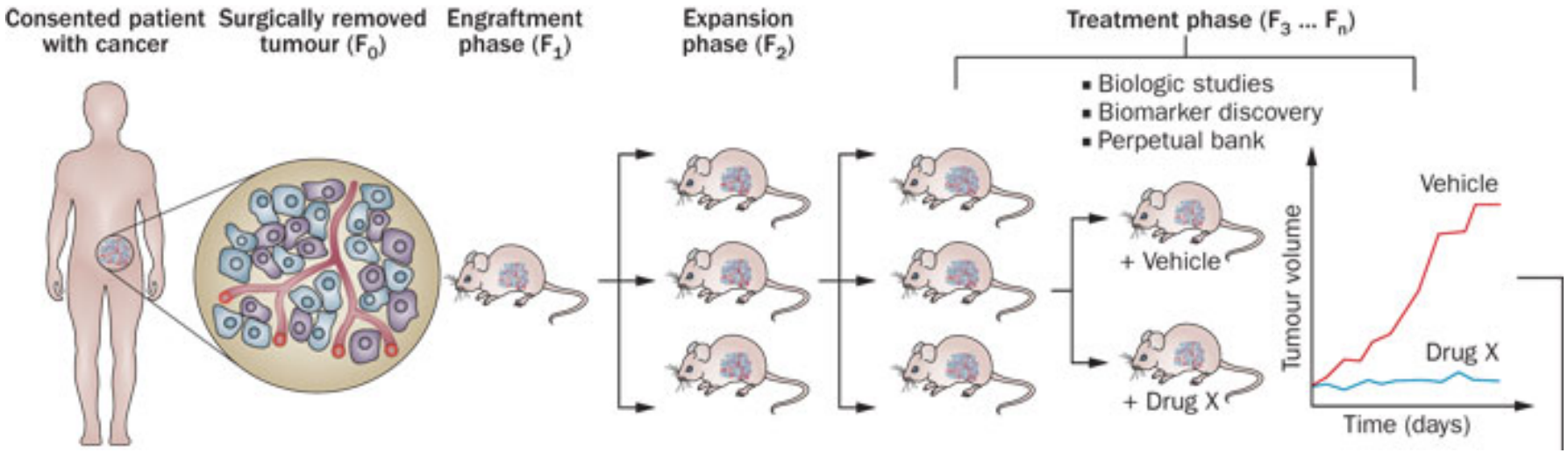


Boj et al Cell 2015

Organoid surviving fraction



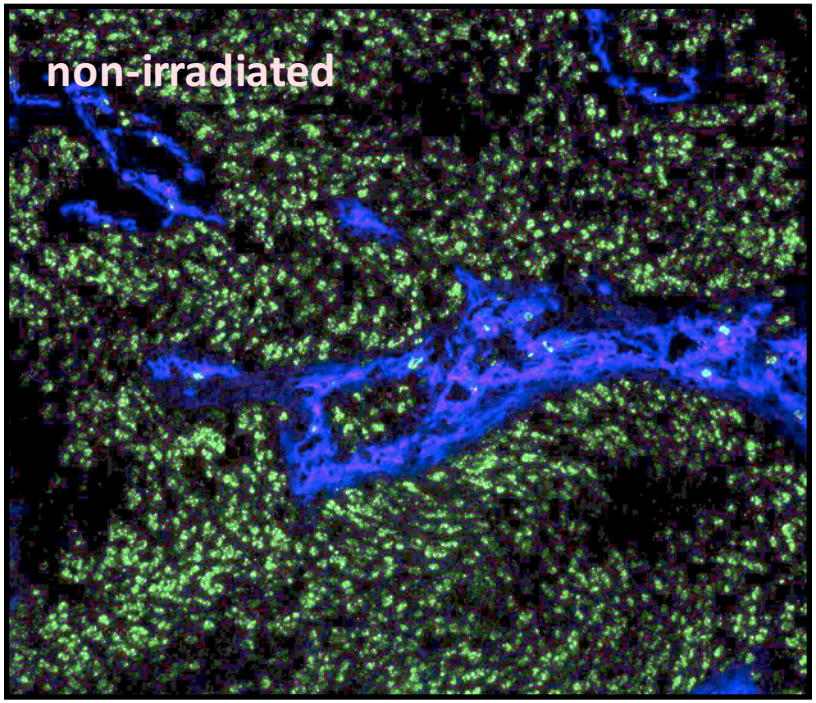
Patient Derived Xenografts

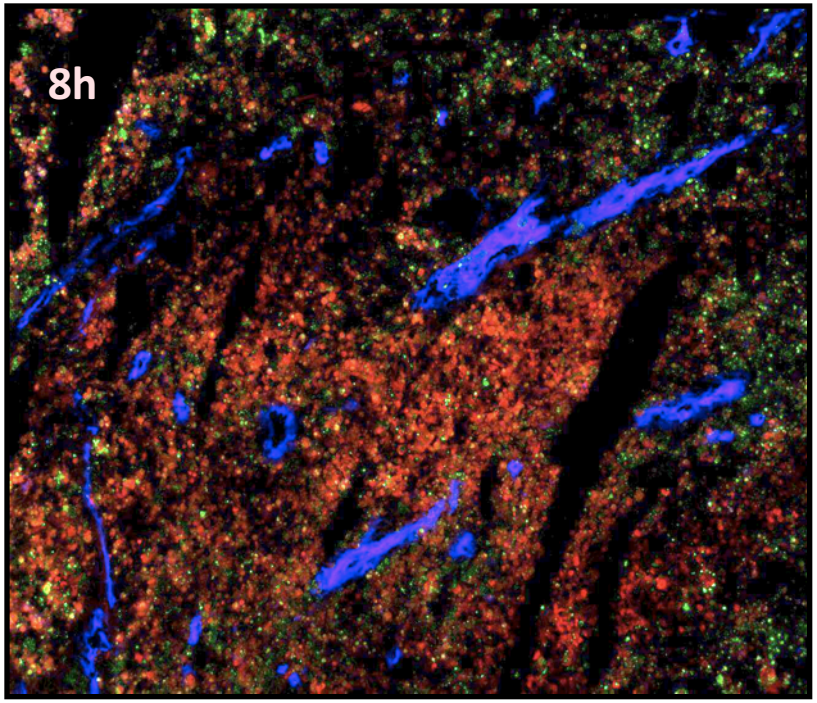


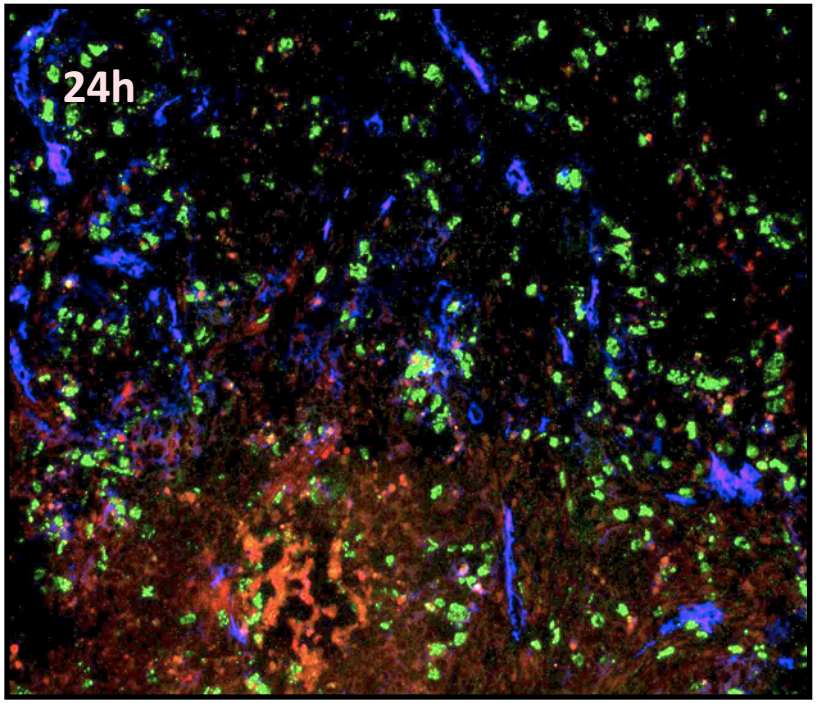
Tentler et al Nature review in clinical oncology 2012

Includes:
blood vessels
Patient derived stroma

Effect of irradiation on tumors: cell death and proliferation

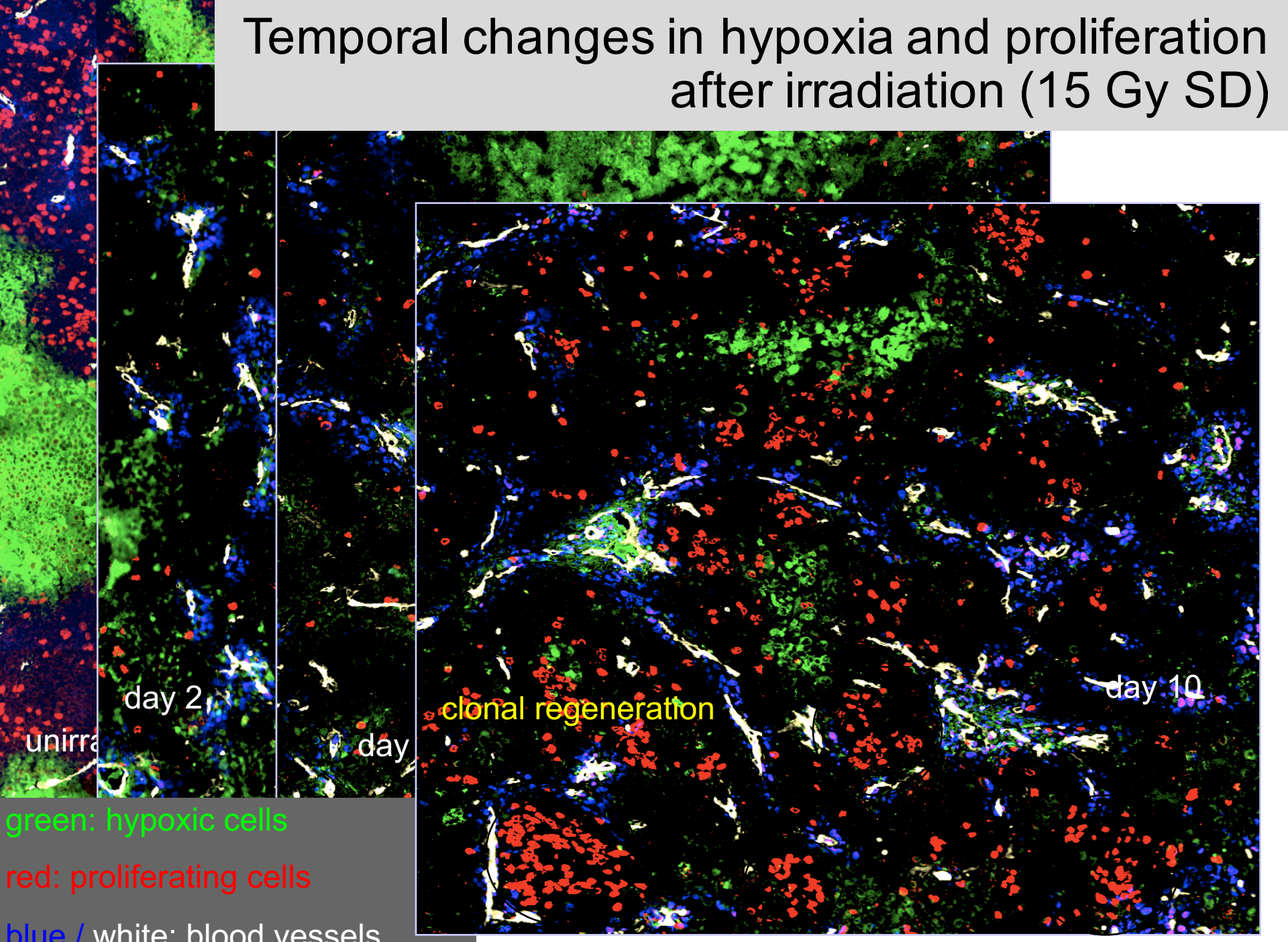




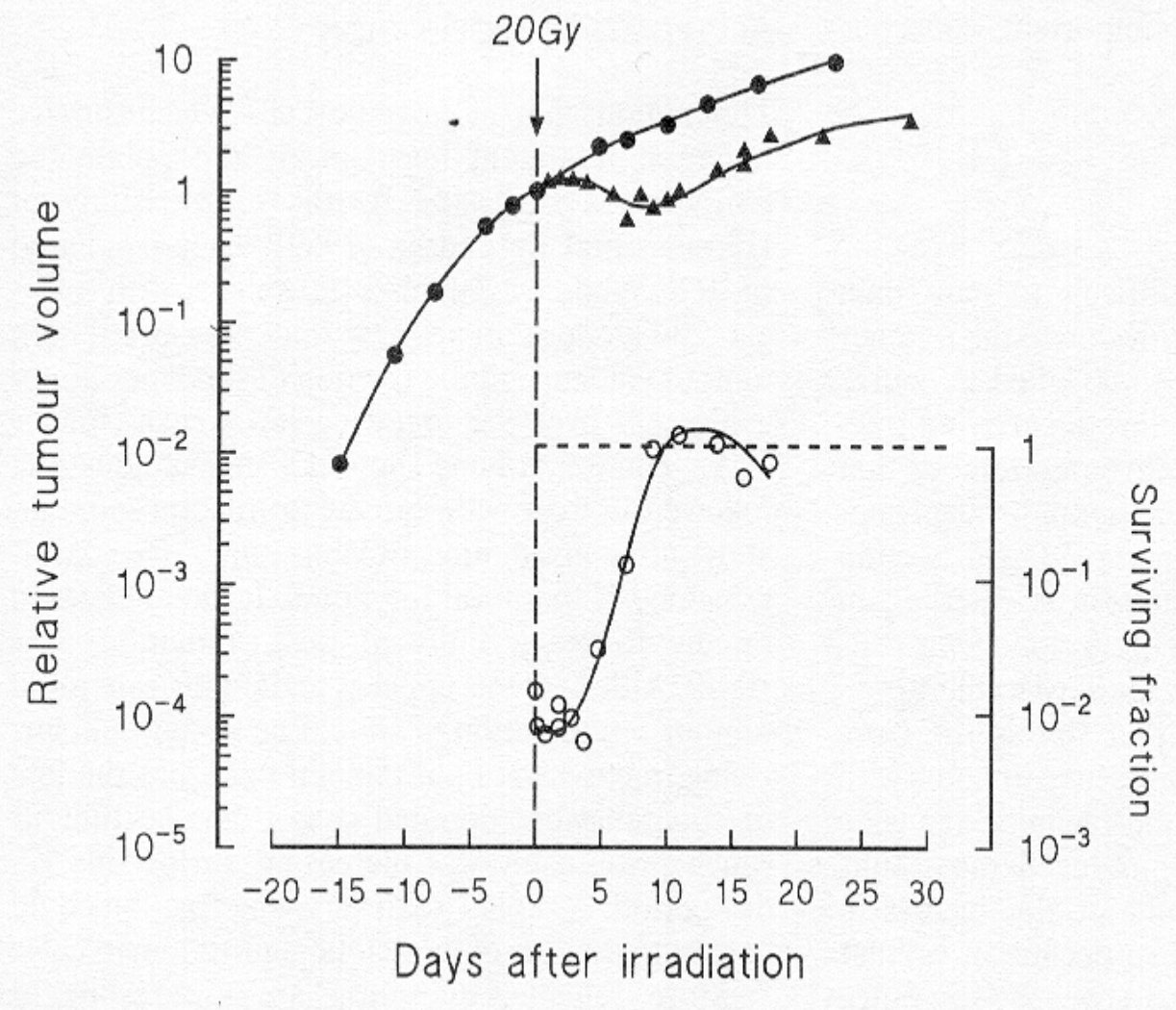


Proliferating cells
Apoptotic cells
blood vessels

Temporal changes in hypoxia and proliferation after irradiation (15 Gy SD)

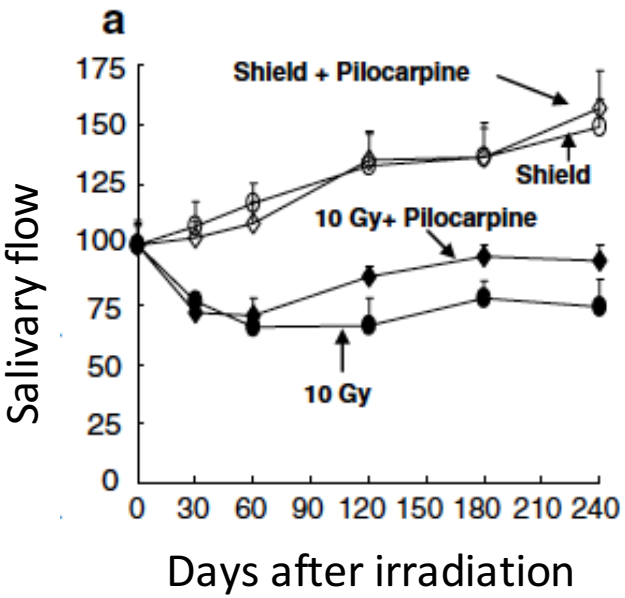


tumour regression ≠ cell survival

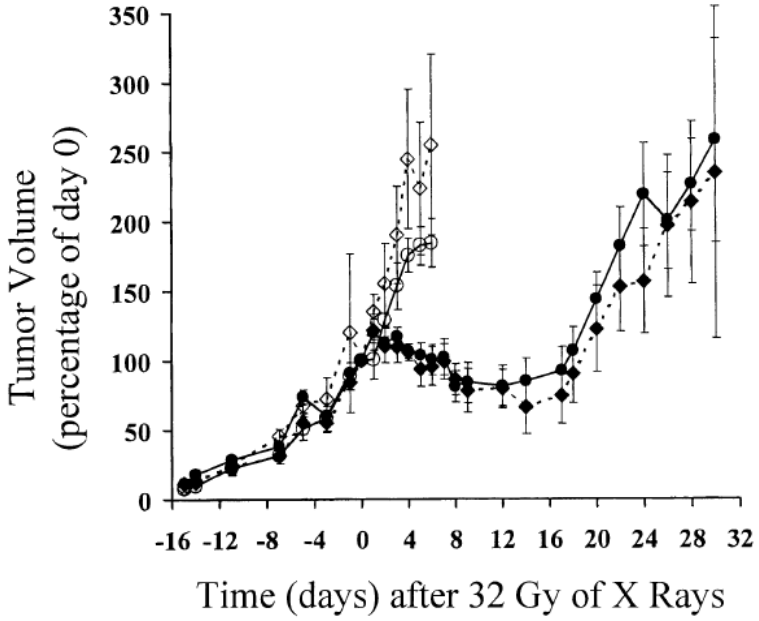


Hermens and Barendsen, *Eur. J. Cancer* 1969

Effect of normal tissue modulators



Burlage et al 2008

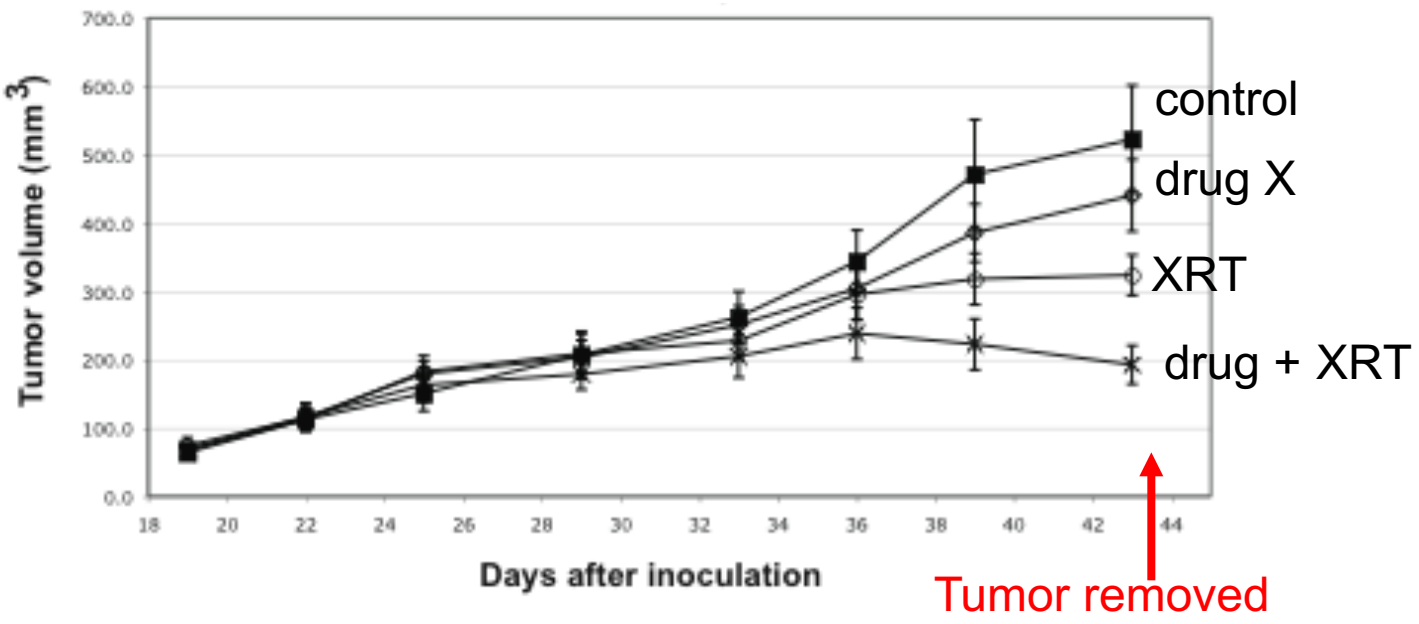


Licht et al 2002

- ◇ Saline-treated, sham-irradiated
- ○ pilocarpine-treated, sham-irradiated
- ◆ 35 Gy
- ● pilocarpine-treated + 35 Gy.

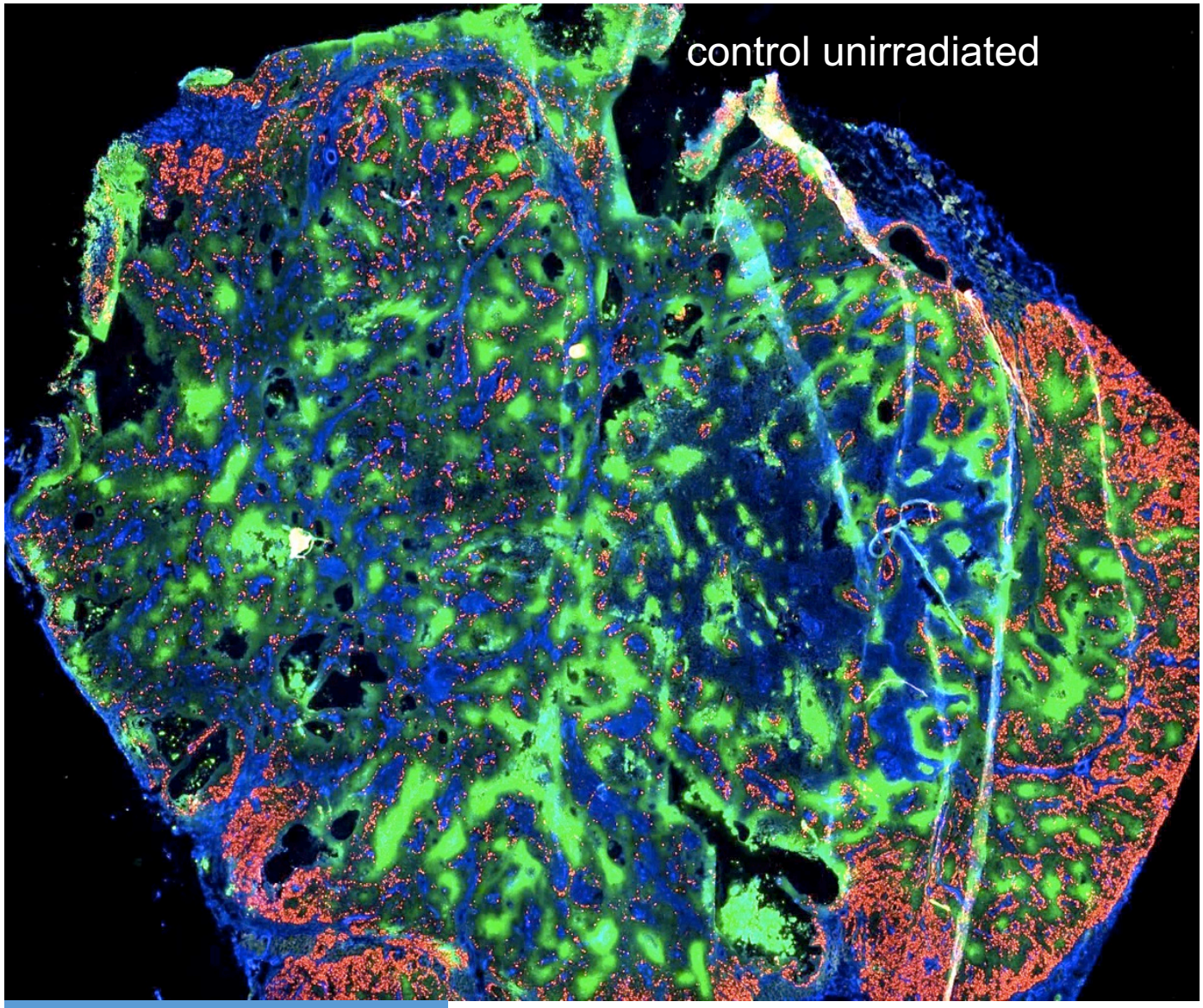
tumour regression ≠ cell survival

Human s.c.c. xenograft treated with 8 X 3 Gy / 4 wks

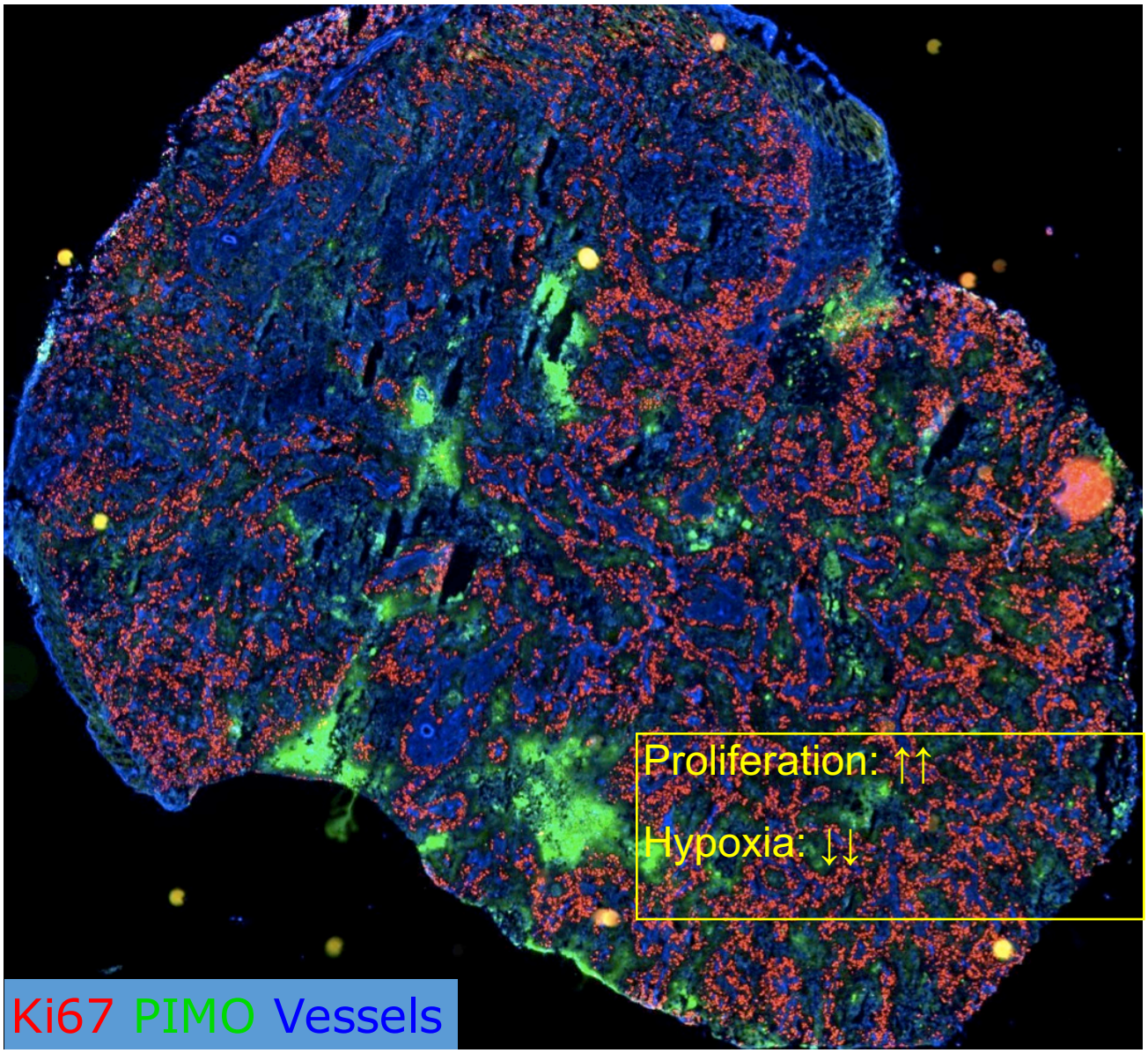


drug X = VEGFR2 inhibitor

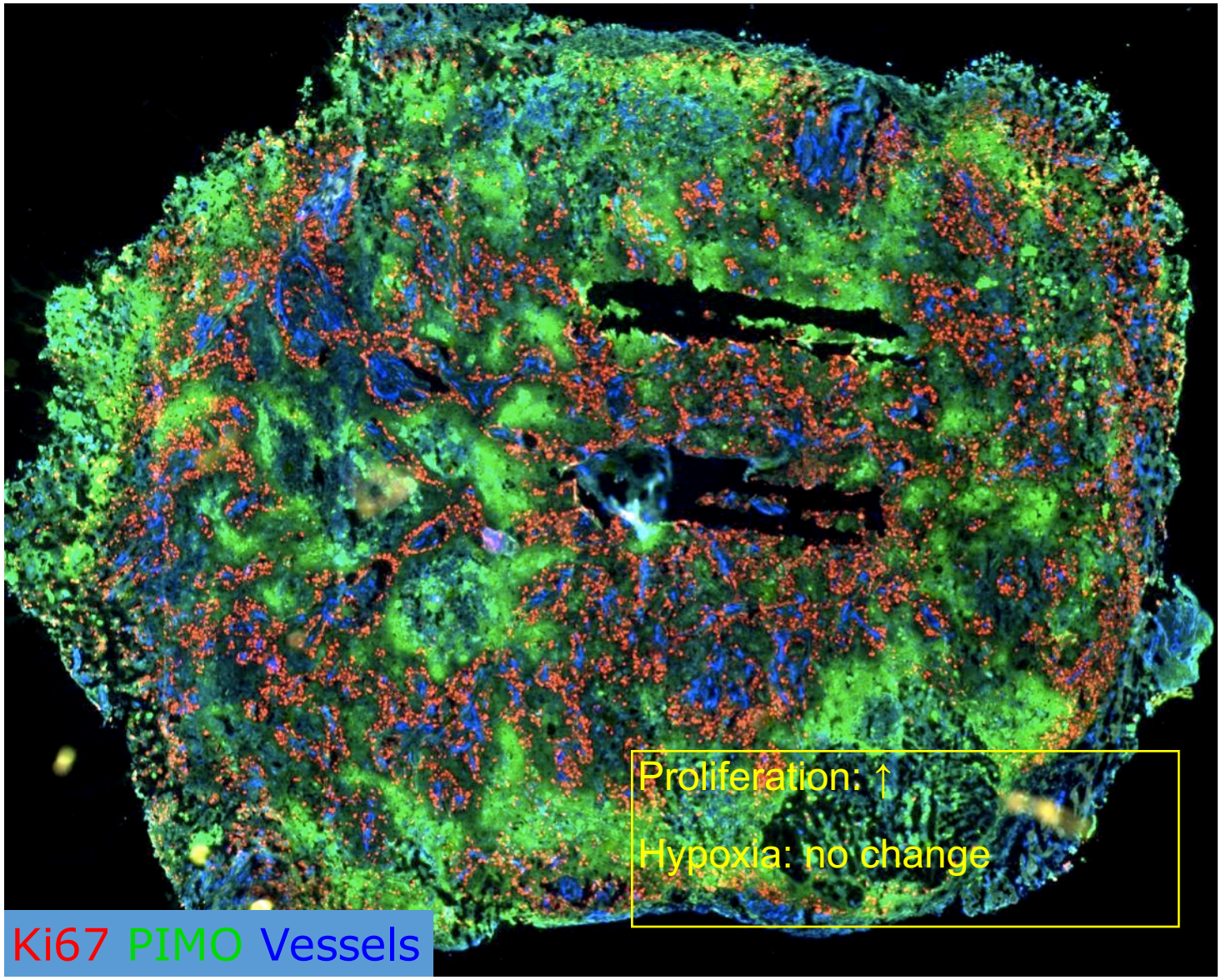
Proliferation & hypoxia in s.c.c. xenograft



Proliferation & hypoxia in s.c.c. xenograft after 8 X 3 Gy/4 weeks

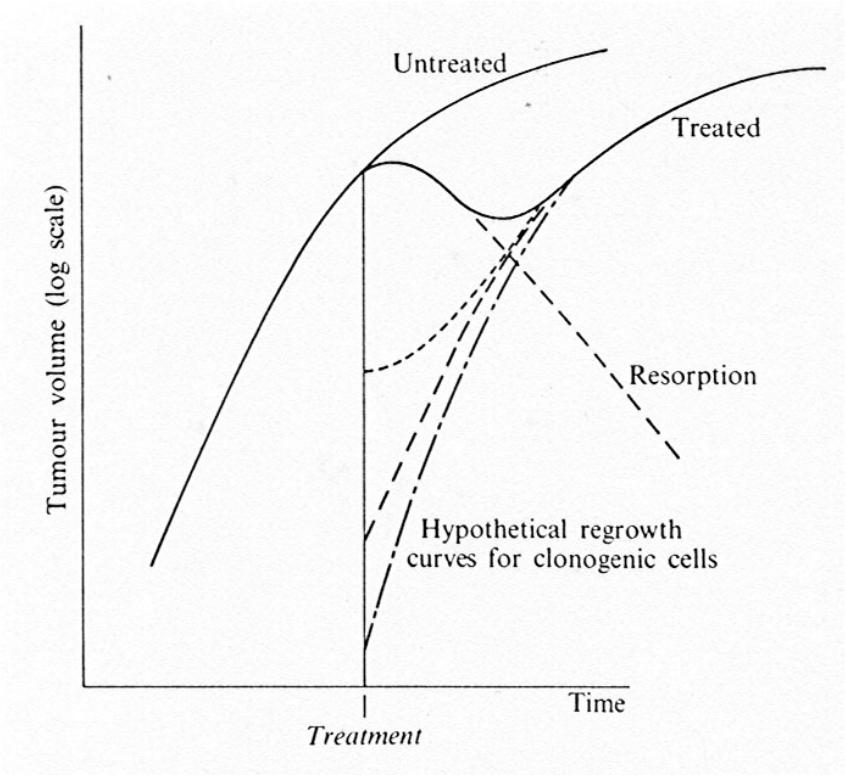


Proliferation & hypoxia in s.c.c. xenograft after 8 X 3 Gy/4 weeks + VEGFR-inhibitor



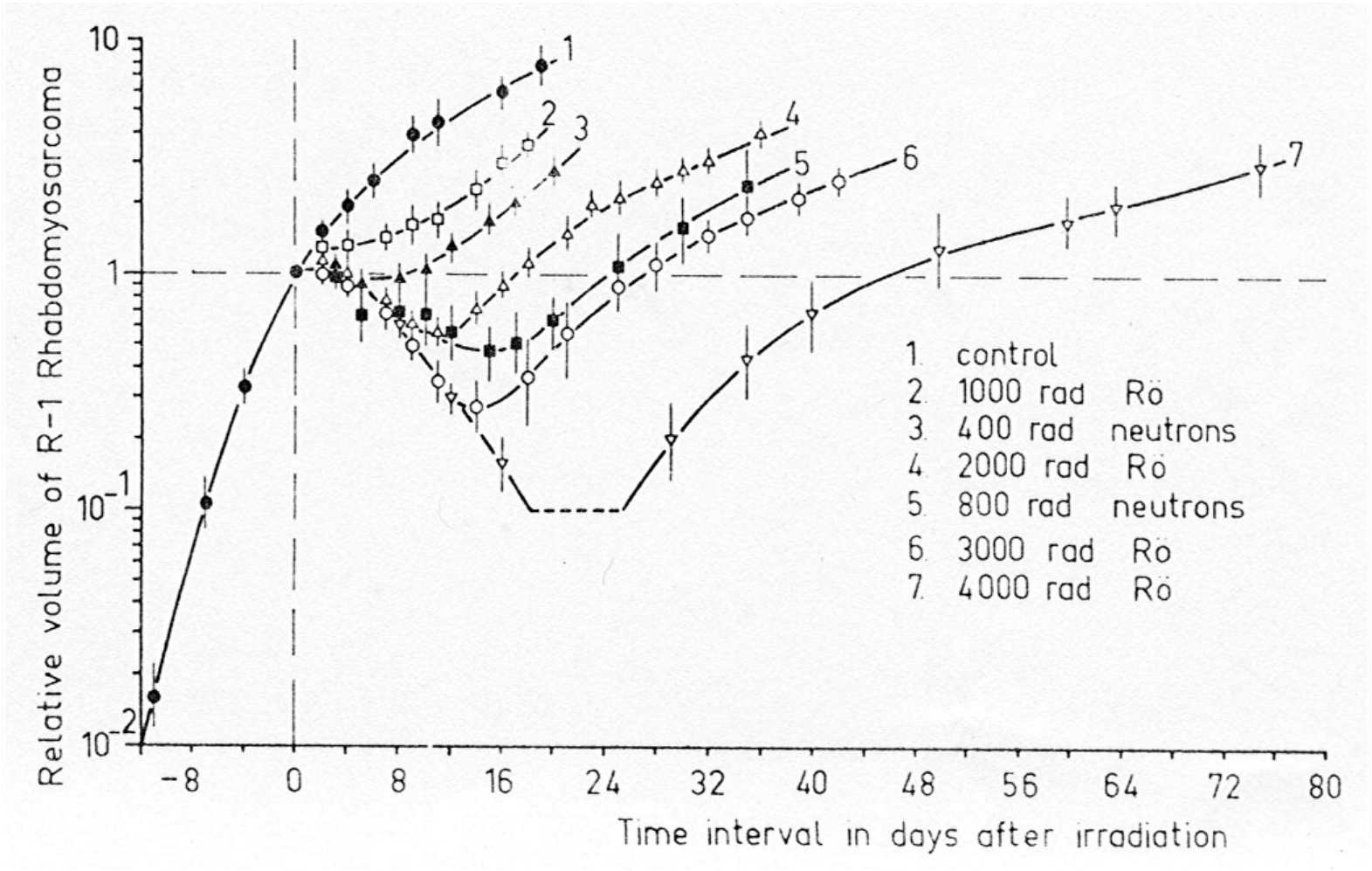
Regrowth Delay Assay

- Comparison of growth curves of treated and untreated tumors gives the delay caused by treatment.
- Relationship between growth delay and surviving fraction of stem cells is complex.
- Regrowing cells have different environment: surrounded by dead and dying cells; vascular network is already in place.
- Tumor bed effect



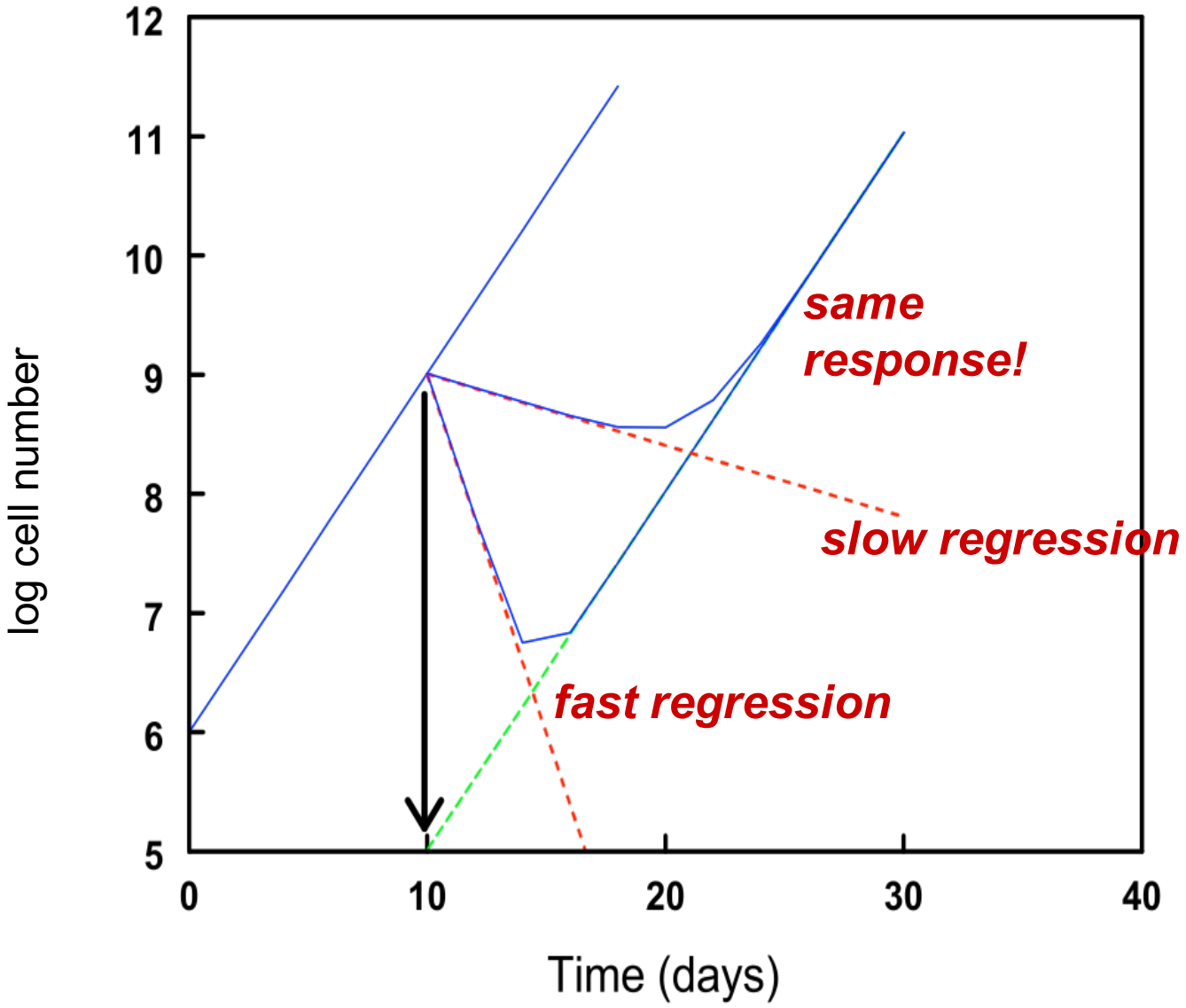
Growth Kinetics of Tumors, G.G. Steel, 1977

Application of Regrowth Delay Assay: Comparison of different treatments

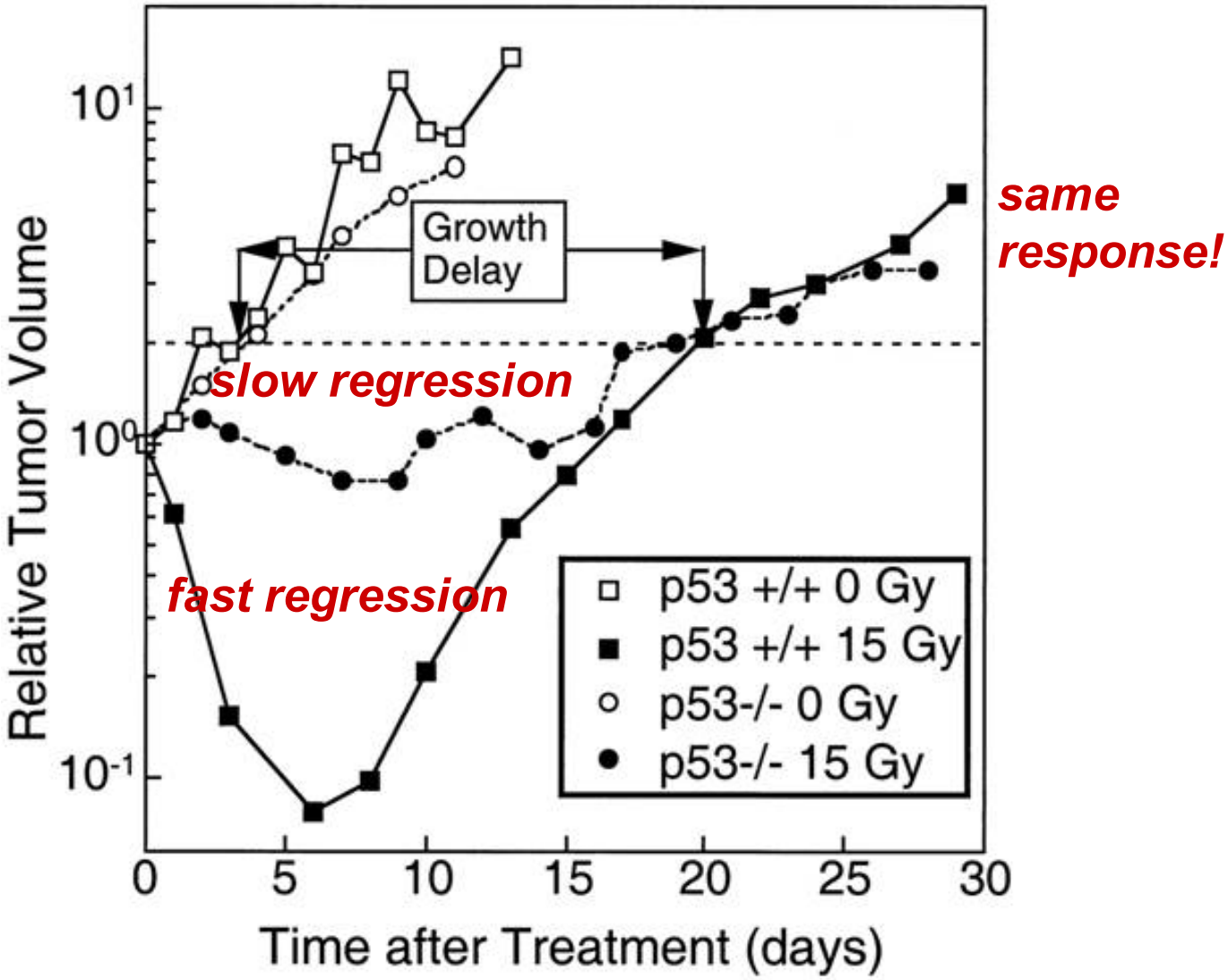


(Barendsen and Broerse, Eur. J. Cancer 1969).

Delay independent of regression rate



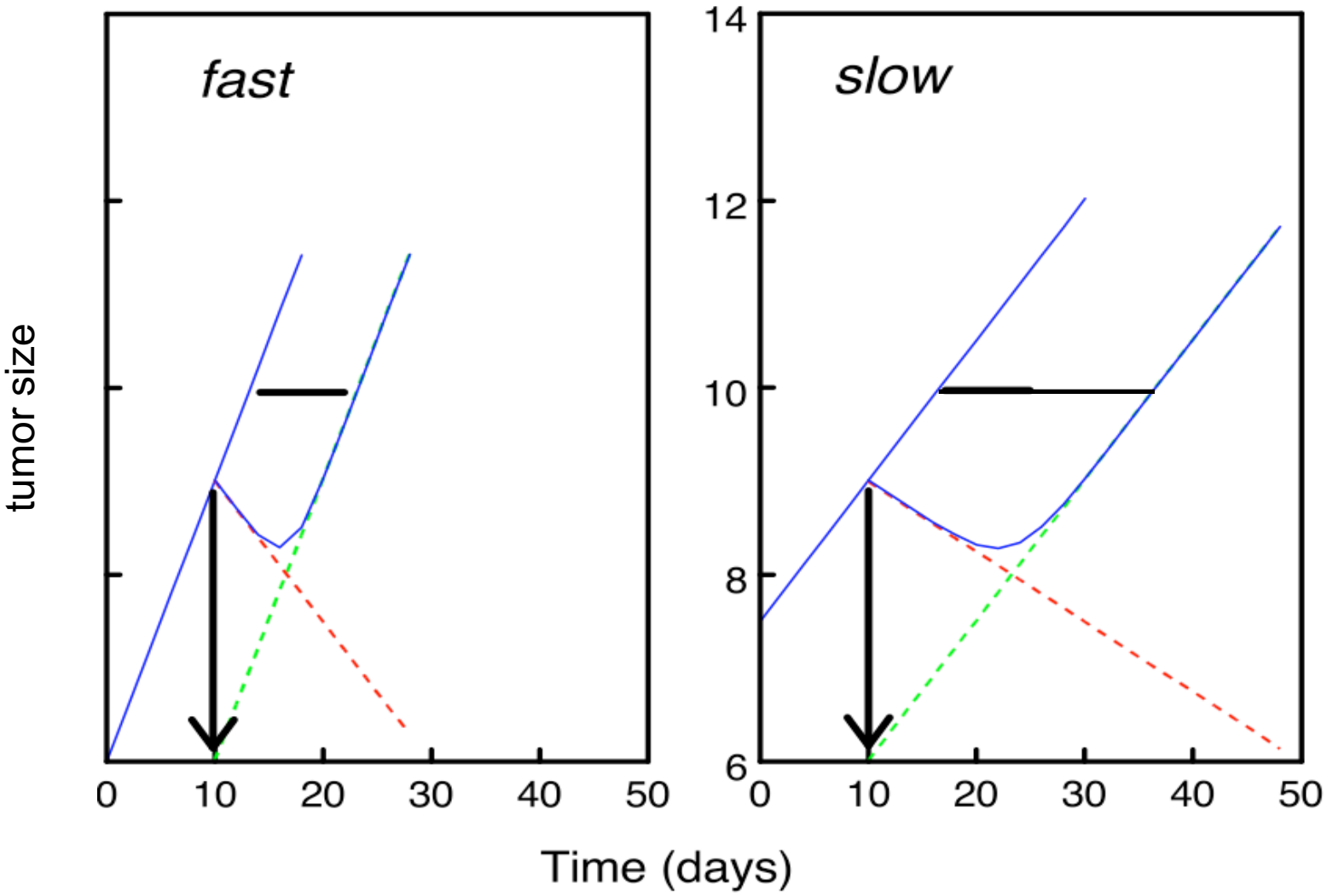
Delay independent of regression rate



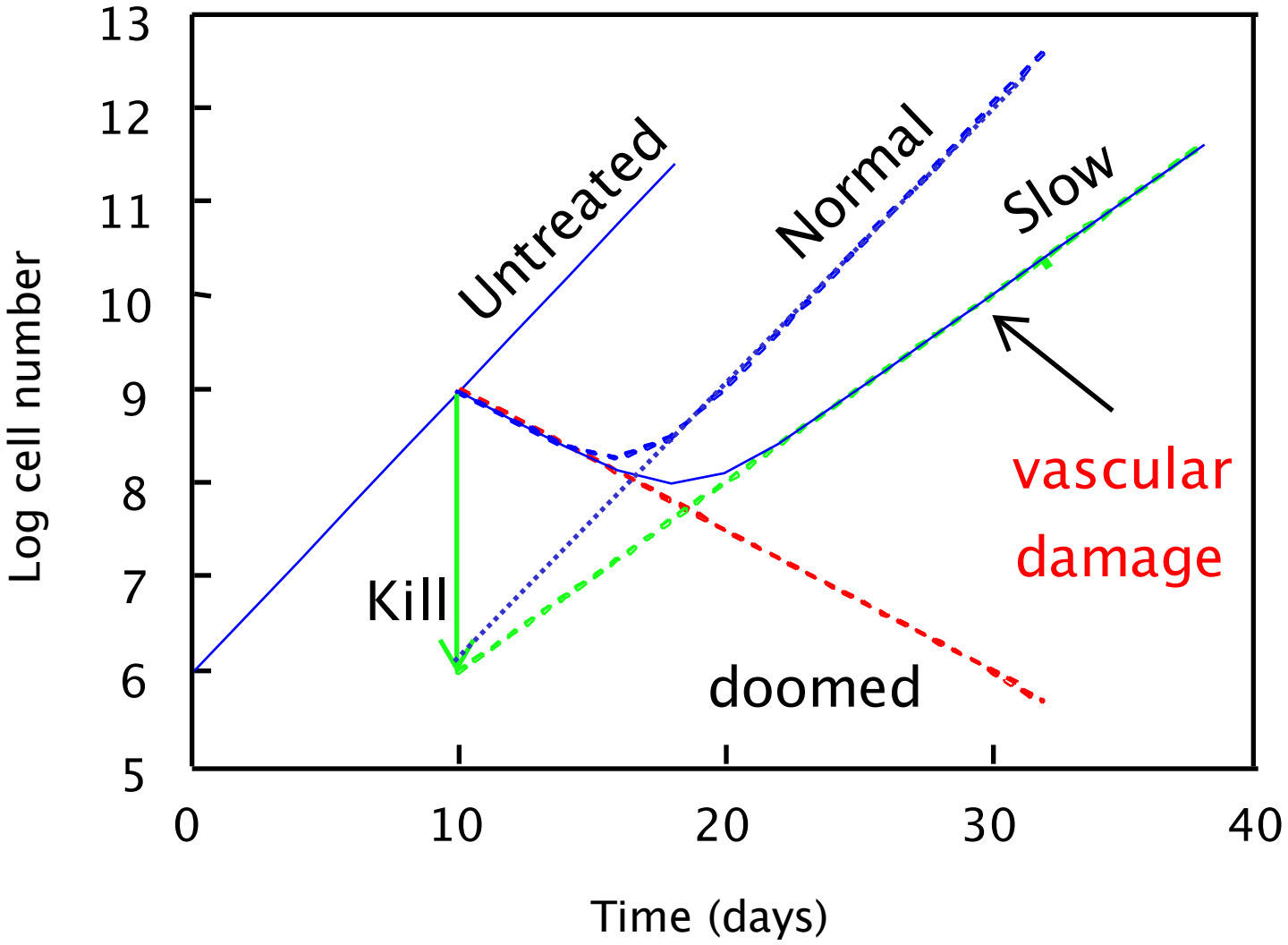
same response!

Wouters & Brown, 1999

Growth delay depends on doubling time



Vascular damage: tumor bed effect



summary: tumor growth delay

- dependent on reliable volume measurement (difficult!)
  with ultrasound imaging or bioluminescence more reliable than manual caliper

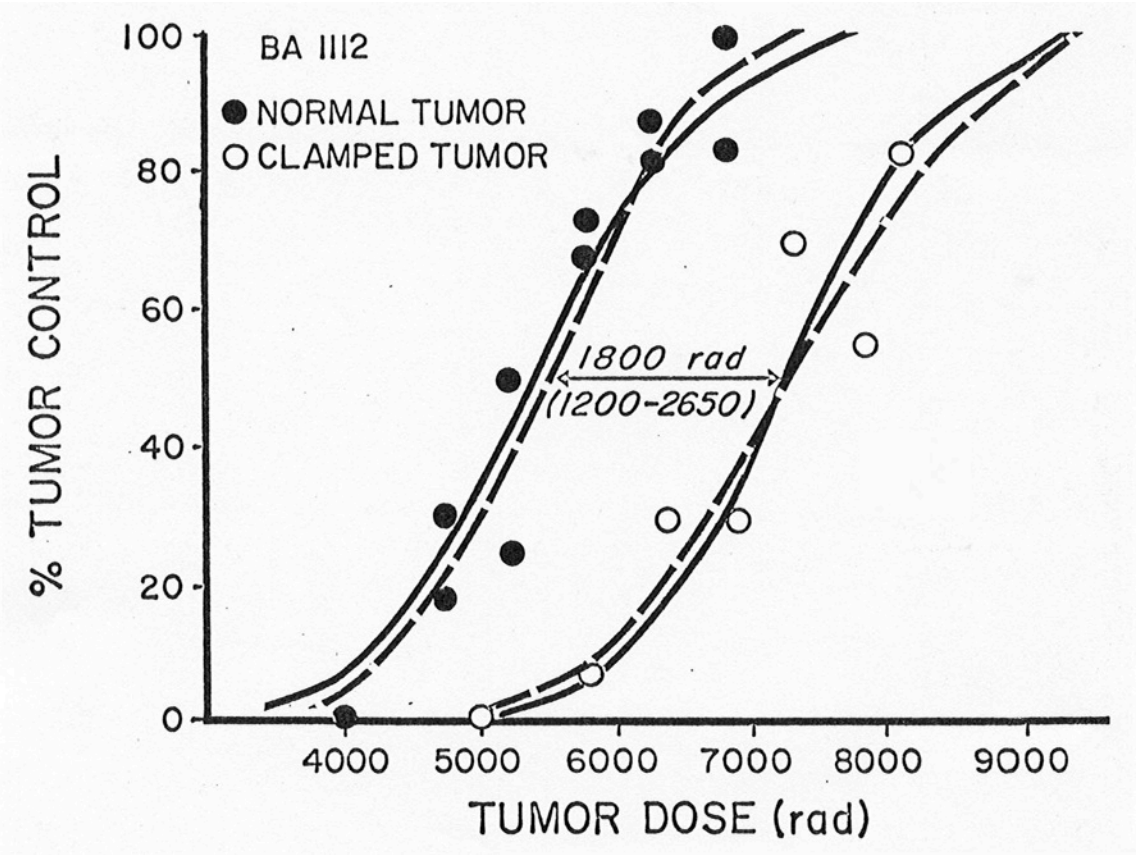
- only suitable for few logs of tumor cells (selection)
- reflects growth rate of clonogenic and non-clonogenic cells
- dependent on growth rate of tumor
  - comparison of different tumors difficult
  - drugs may change growth rate (overestimation of efficacy)
  - radiation damage of vessels changes growth rate (tumor bed effect; overestimation of efficacy)

Endpoints: local tumor control
TCD_{50} assay

- Irradiation of tumors in vivo
- Groups of tumors, different dose levels (graded doses)
- Follow up: Local control or recurrence
- Evaluation of local control rates for each dose level
- Construction of dose response curves

Tumor Control (Cure) – TCD_{50}

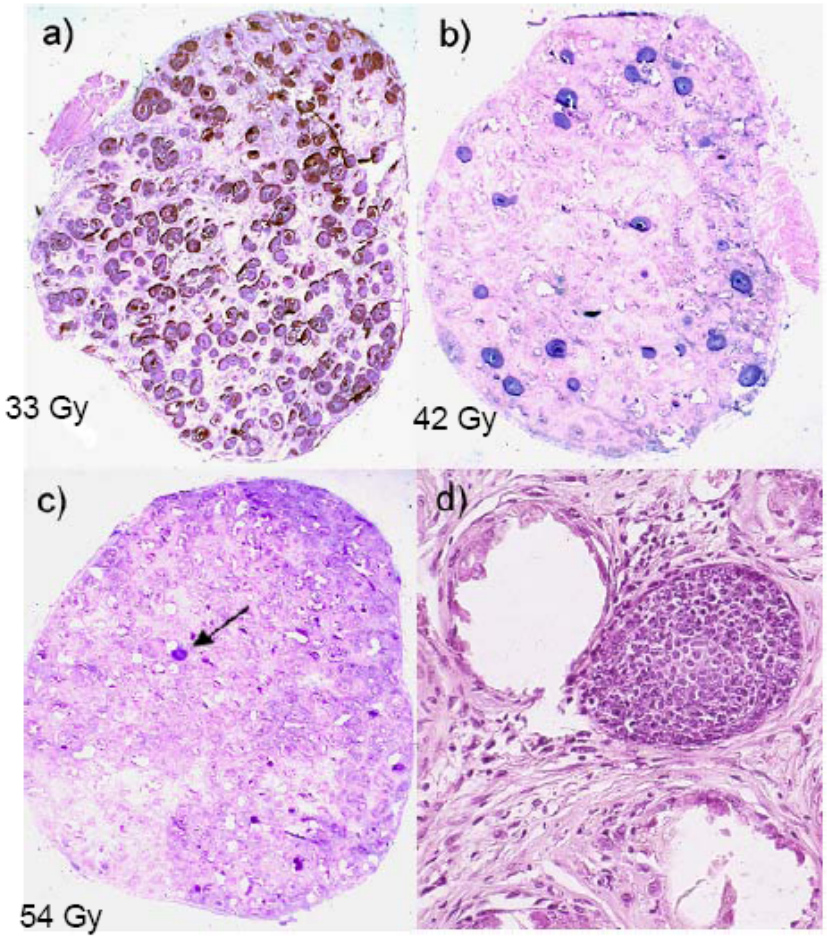
(Moulder & Rockwell, Int. J. Radiat. Oncol. Biol. Phys. 1984).

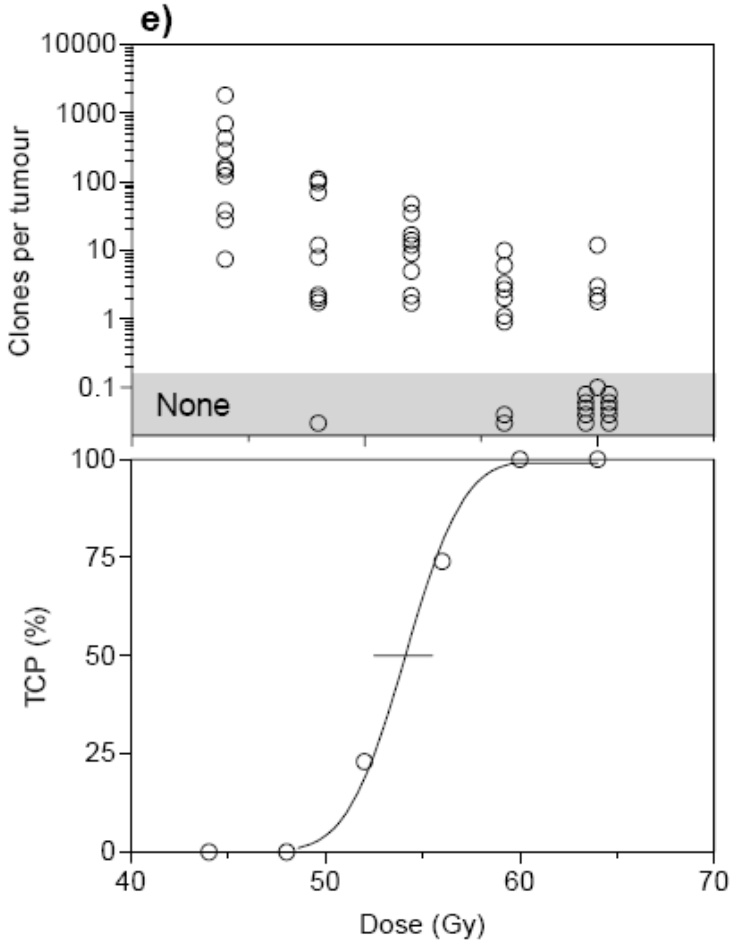


The radiation dose which cures 50% of a homogeneous population of tumors (TCD_{50}) is estimated.

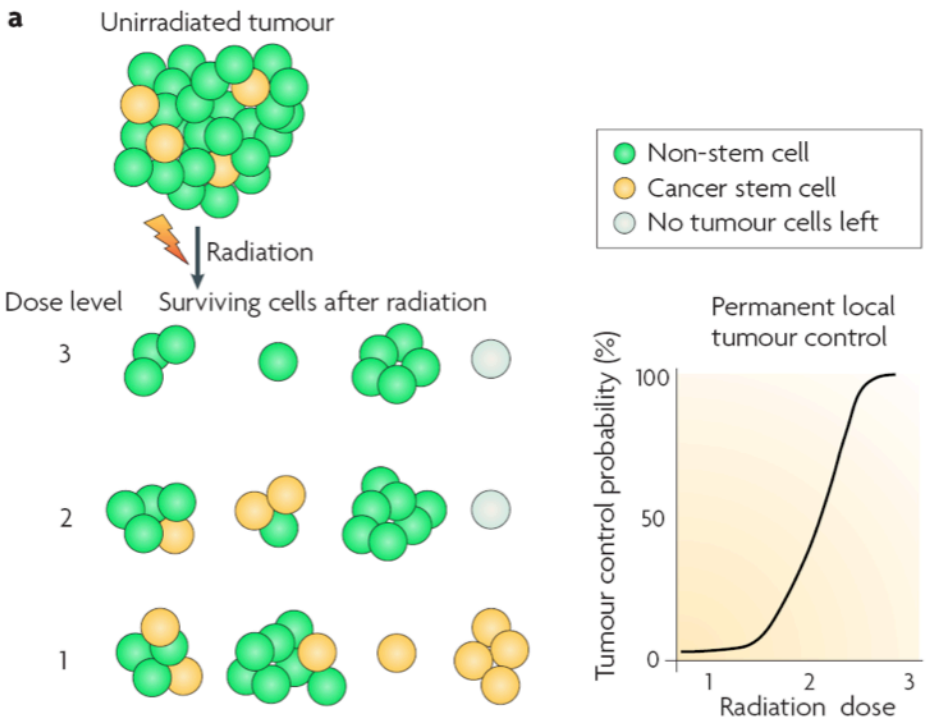
This assay most directly assesses the sensitivity of the stem cell population in the tumour.

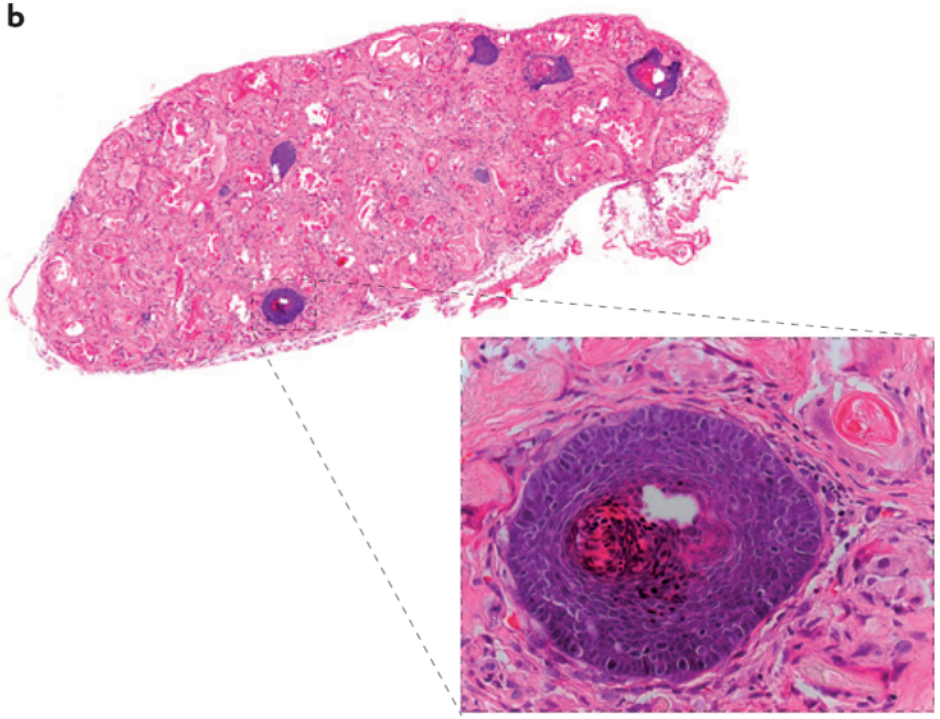
Endpoints: local tumour control





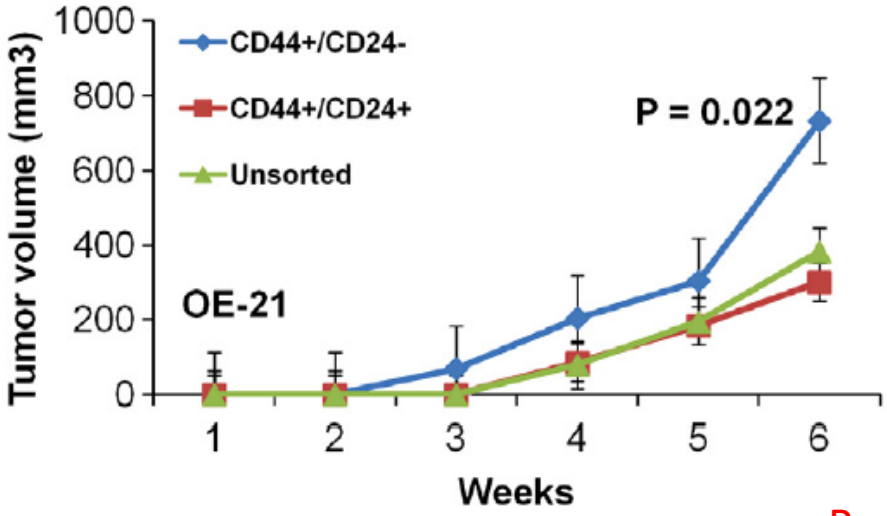
Killing all cancer stem cells is necessary for local tumour control

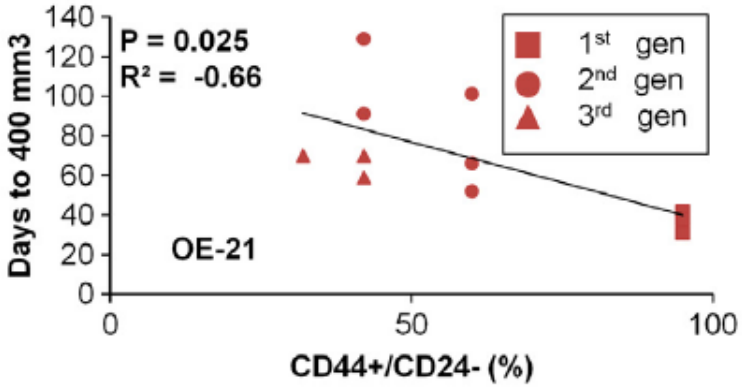


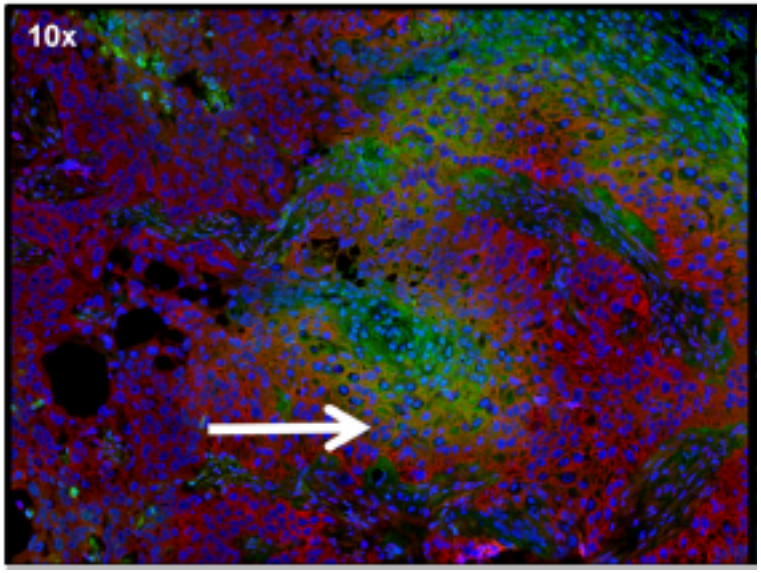


Baumann, Krause, Hill, *Nature Rev Cancer* 545-554, 2008

Cancer stem cells

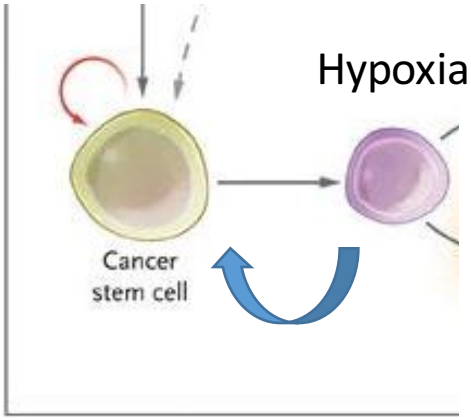






Red is CD44

Green is pimonidazole

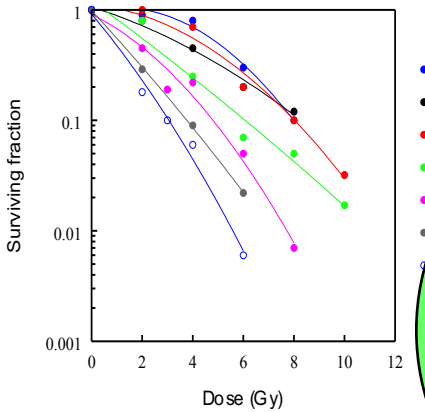


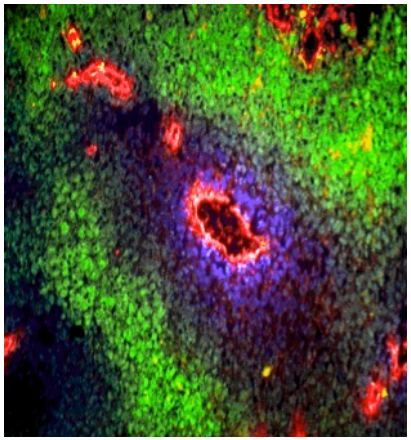
Smit et. al. Radiotherapy & Oncology 2013

Endpoints: local tumour control
TCD_{50} assay

- best assay available for experimental radiotherapy
- most relevant for clinical practice
- tumour cells remain in situ
- dependent only on clonogenic cells
- All clonogenic cells are assayed, not only some logs.
  Thus also survival of small resistant subgroups of clonogens can be assayed.
- good for radiobiological modelling

Biological contributors to outcome of tumor treatment with radiation





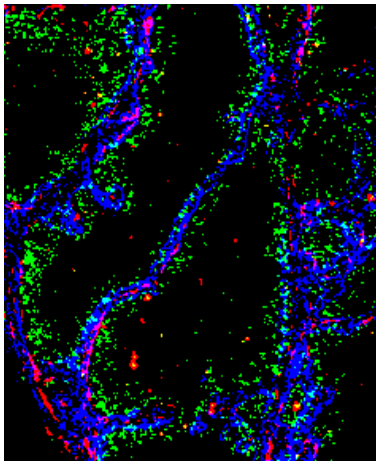
Tumor cell radiosensitivity

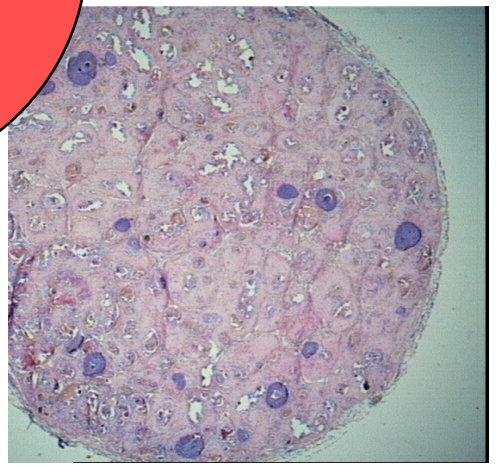
Hypoxia

Proliferation

Vascular Radiosensitivity?

Volume
(Stem cell proportion)

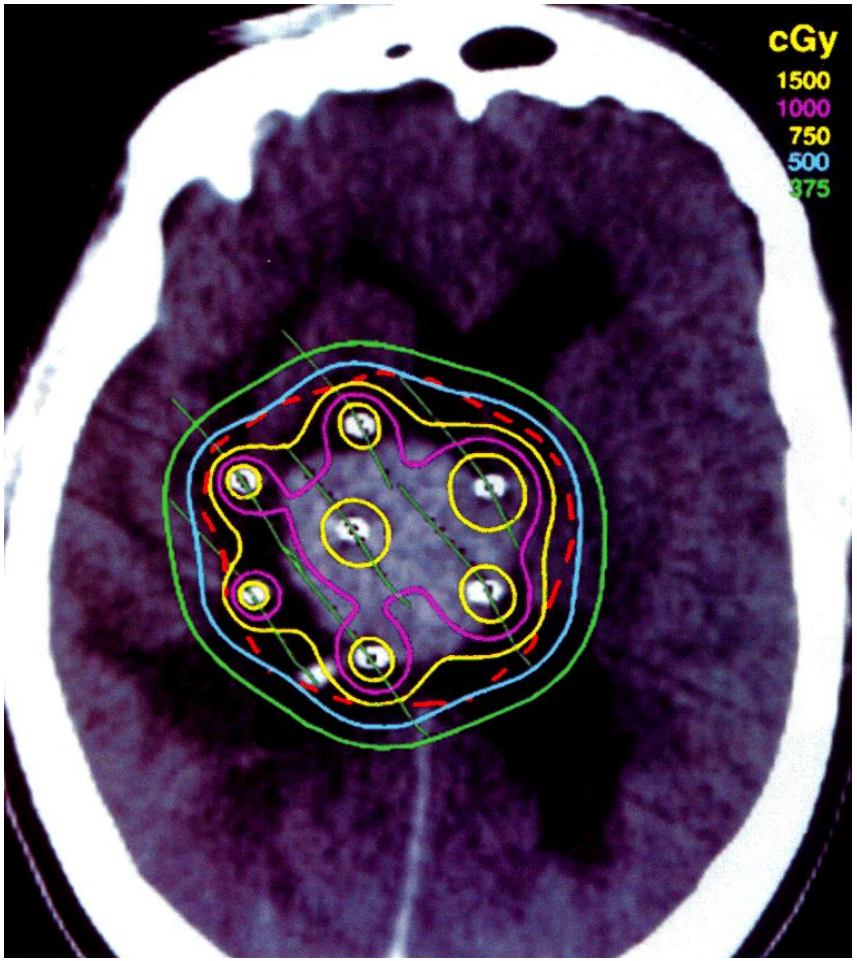




Summary

- Response of tumors depends on
  - intrinsic cellular radiosensitivity
  - stromal interactions (vasculature)
  - microenvironment (hypoxia)
  - tumour volume (stem cell number)
  - cellular proliferation (repopulation).
- Tumor models can be used to explore
  - different treatment regimes
  - importance of biological pathways
- Volume response:
  - measure time to regrowth, not regression.
  - correct for doubling time when comparing tumors
- Tumor cure: gold standard
  - not possible with drugs alone (insufficient kill)
  - many animals and long time, so only use as confirmation

Brachytherapy & radiobiology of low dose rate



Albert van der Kogel

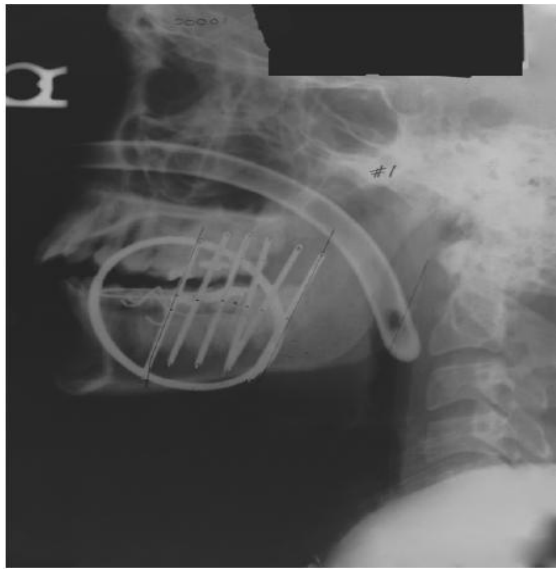
Department of Human Oncology

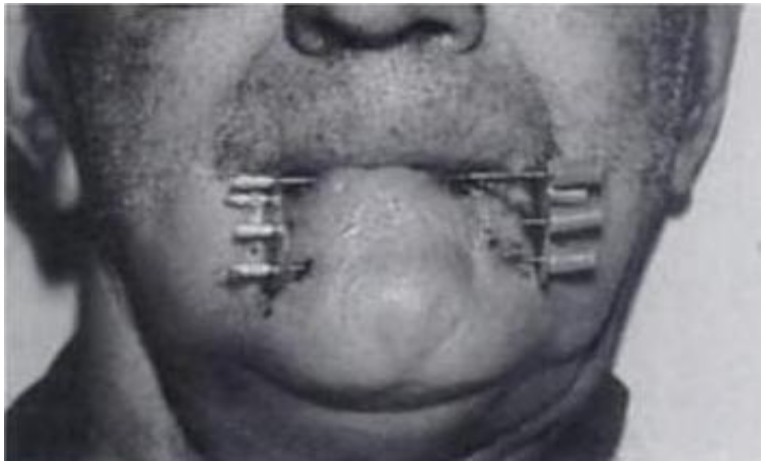
University of Wisconsin School of Medicine & Public Health

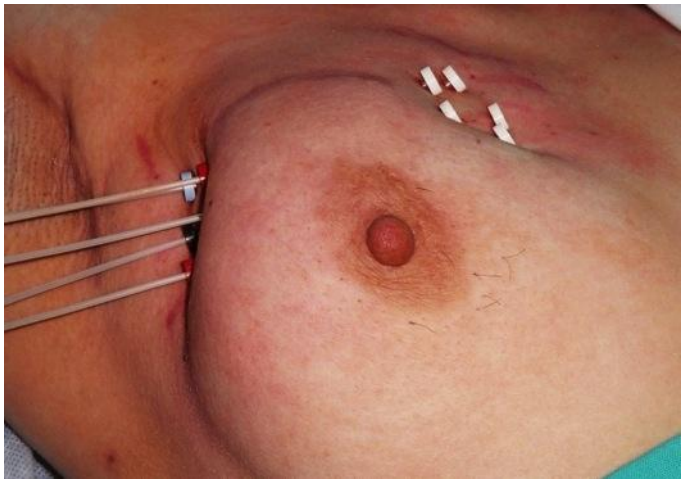
Madison, Wisconsin, USA

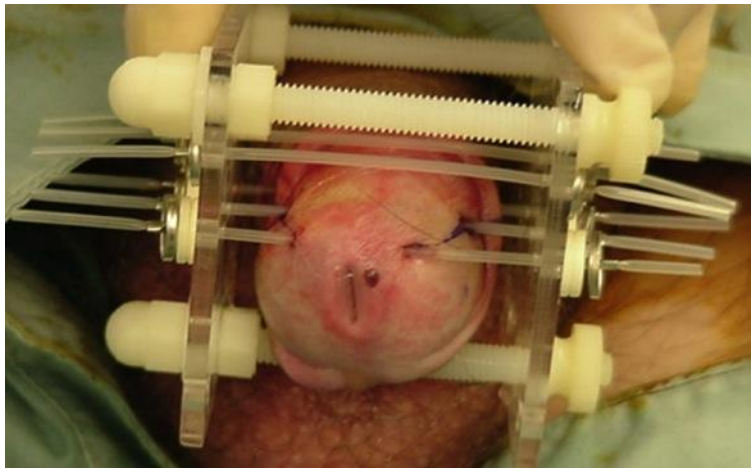
Claudius Regaud 1870-1940
Father of Fractionation
Low Dose Rate Radium Treatment of Tongue and Cervical Cancer 1918

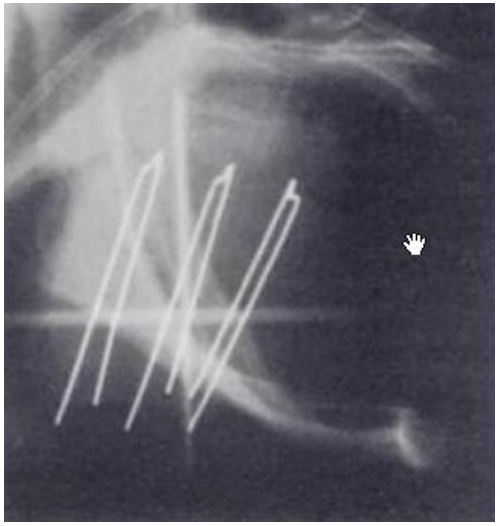
LDR Brachytherapy

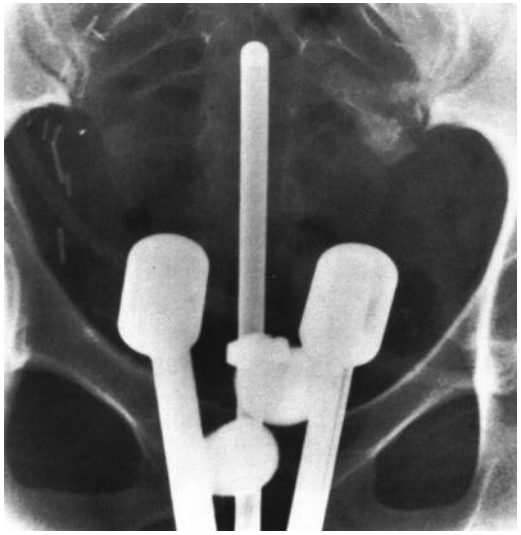




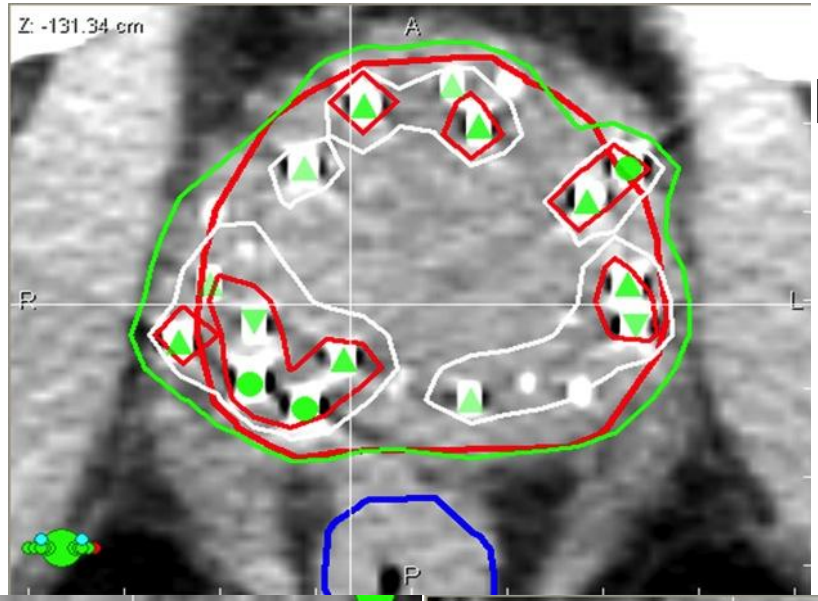


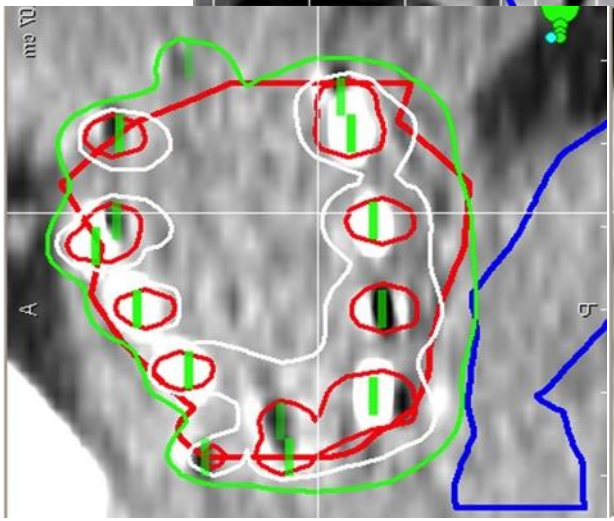


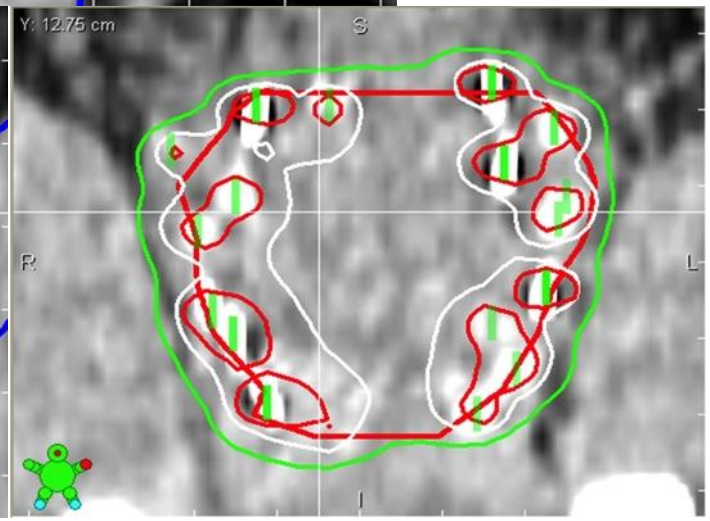




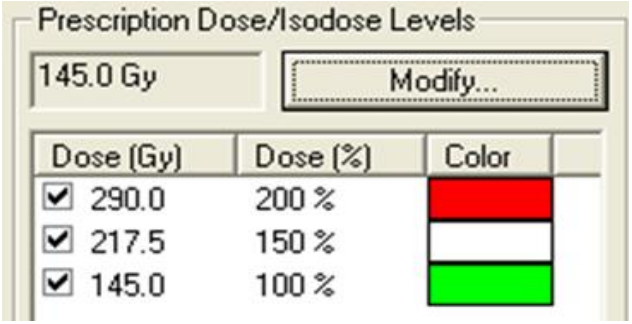
Prostate Brachytherapy





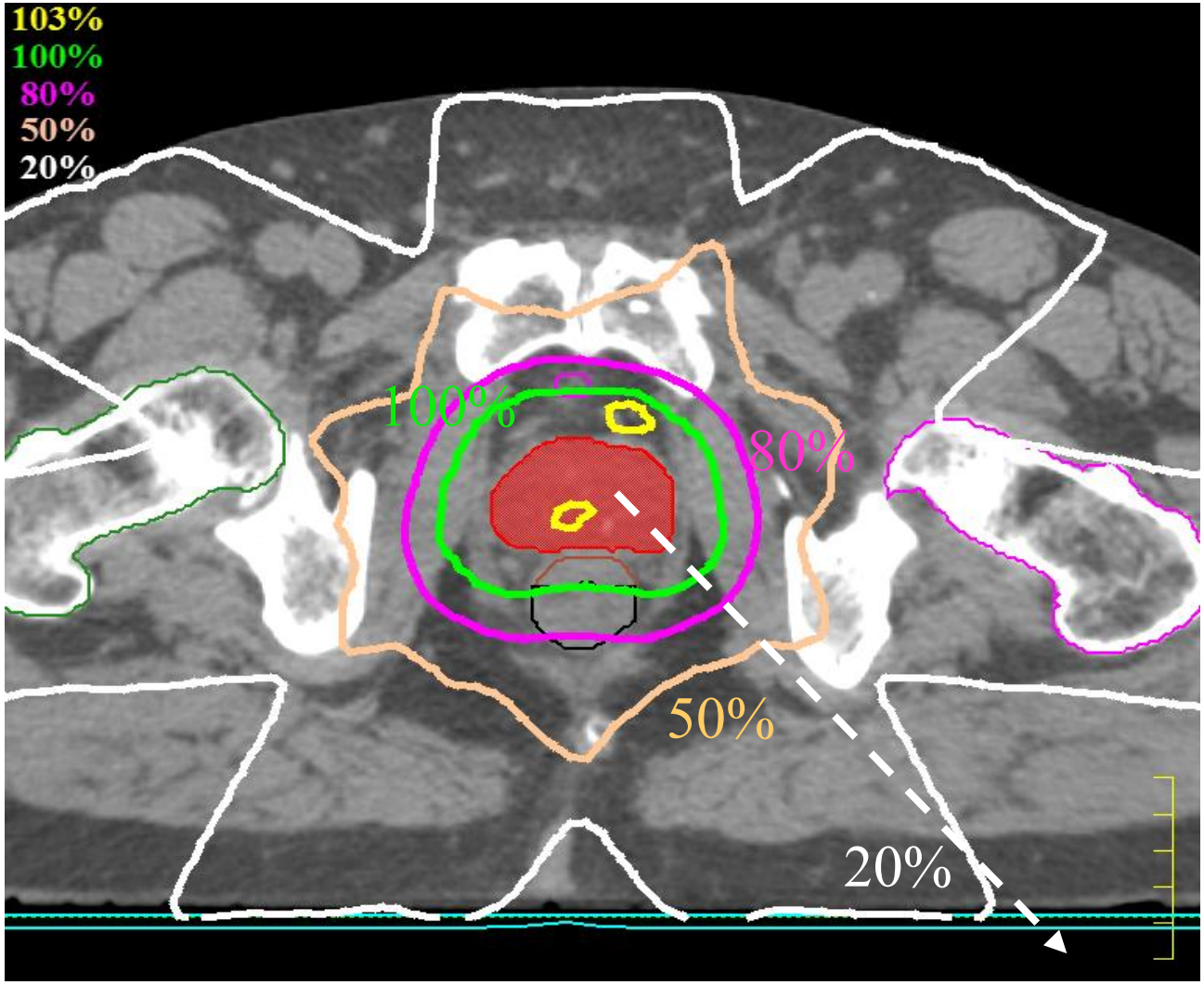


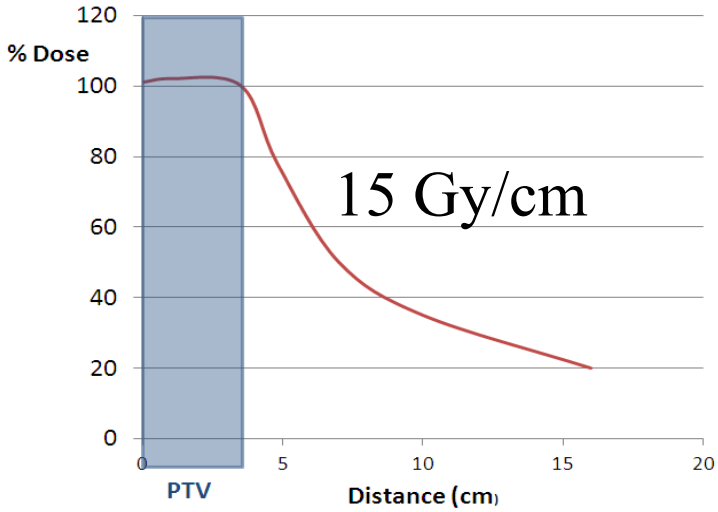
Prescribed Dose = 145 Gy (100%)
Mean Dose = 245 Gy (170%)



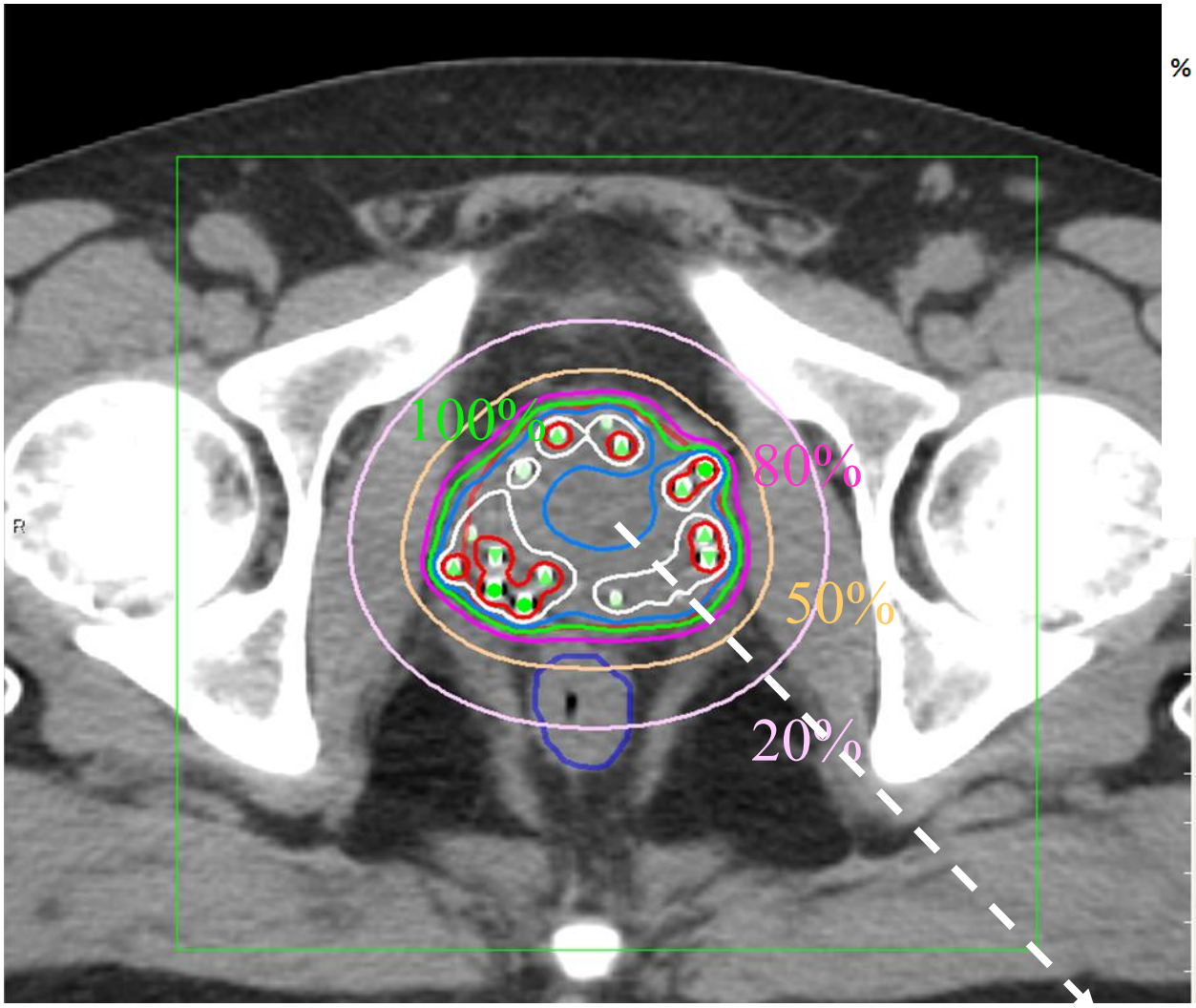
Much greater dose inhomogeneity within the target. What dose is actually given?

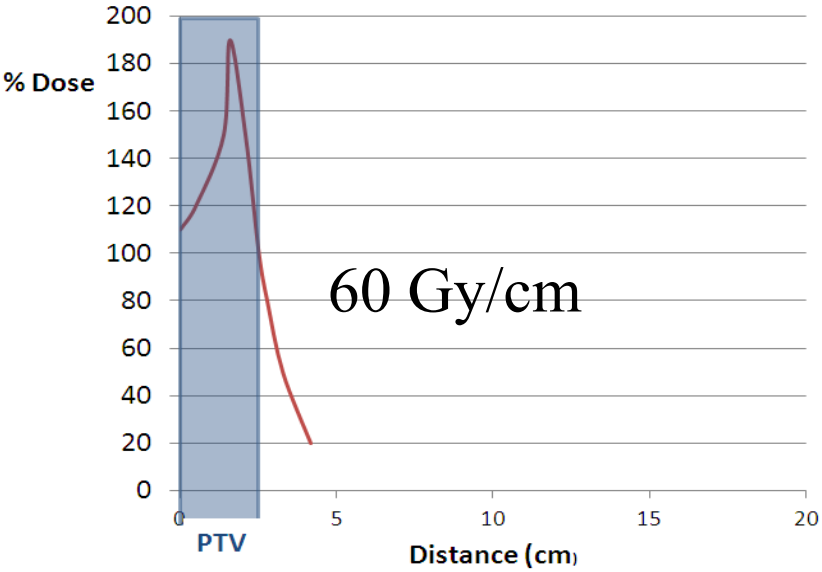
Prostate External Beam RT





Prostate Brachytherapy

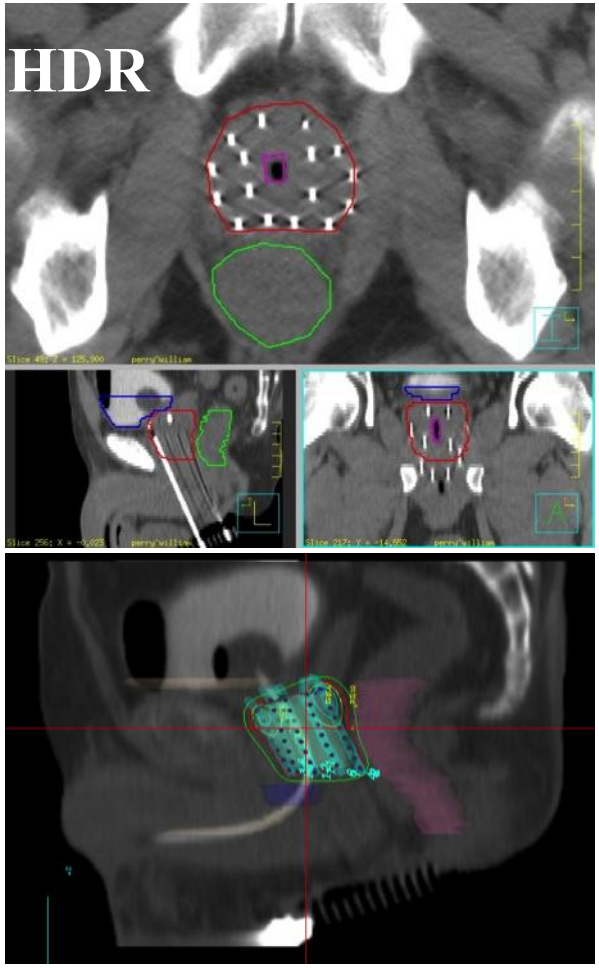




Dose (Gy)	Dose (%)	Color
☑ 290.0	200 %	
☑ 217.5	150 %	
☑ 174.0	120 %	
☑ 145.0	100 %	
☐ 137.7	95 %	
☑ 116.0	80 %	
☑ 72.5	50 %	
☑ 29.0	20 %	

Prostate Brachytherapy

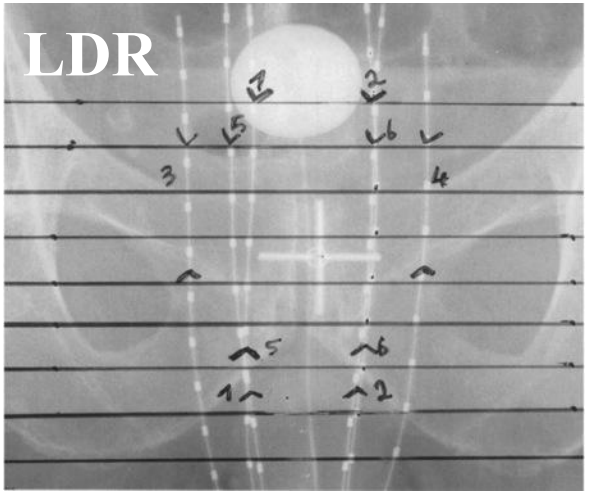
HDR (^{192}Ir)

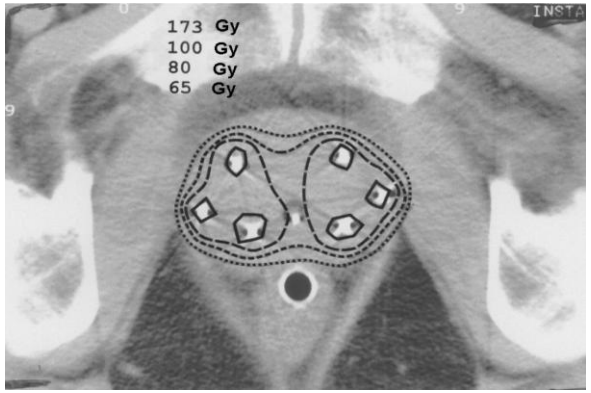


38 Gy/4 f in 2 days

> 60 Gy/hr

LDR (^{192}Ir, ^{137}Cs)

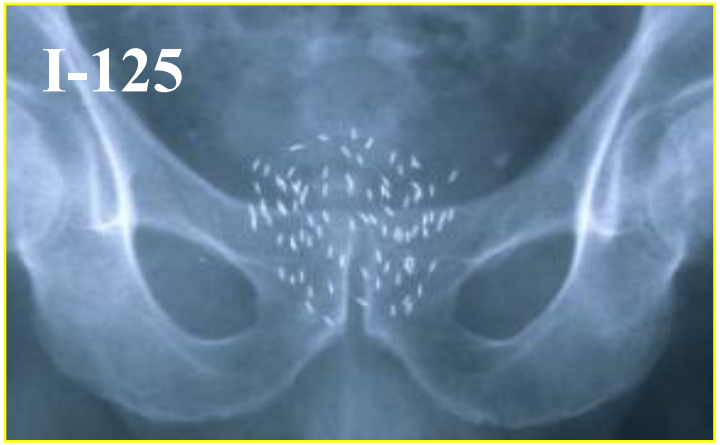


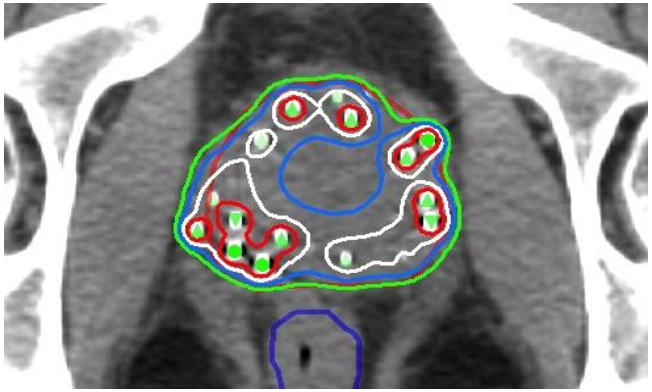


80 Gy ~ 6 days

0.6 Gy/hr

I-125 seeds

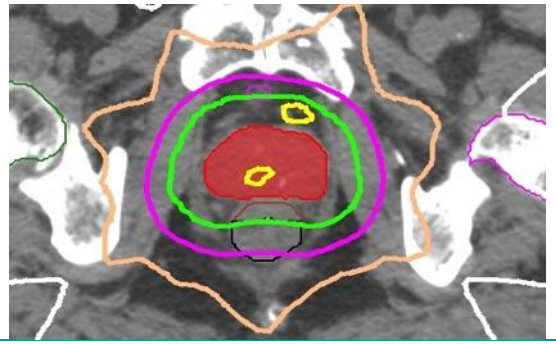


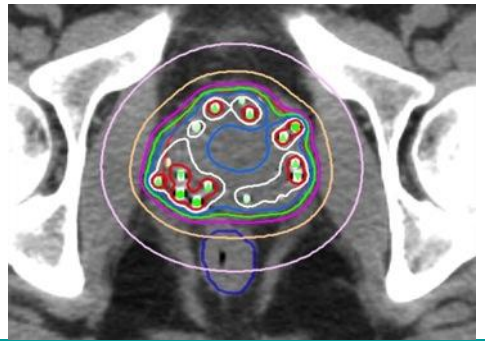


145 Gy Permanent

< 0.1 Gy/hr

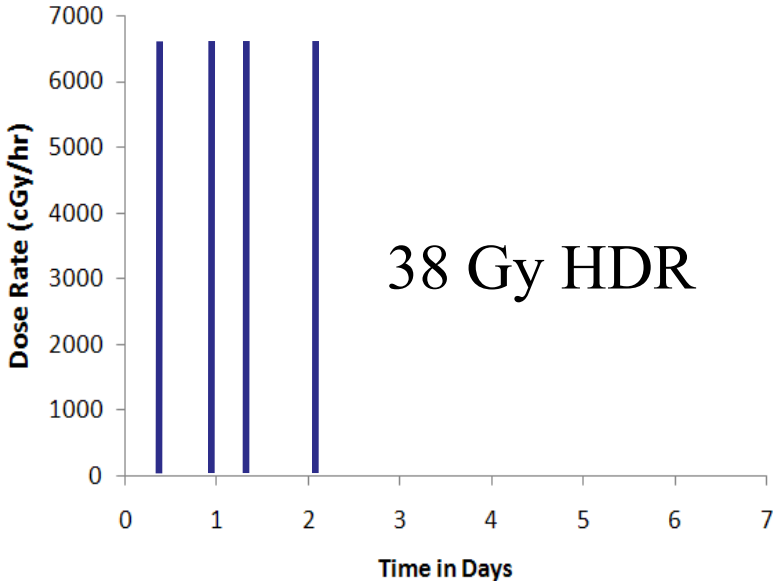
External Beam vs Brachytherapy

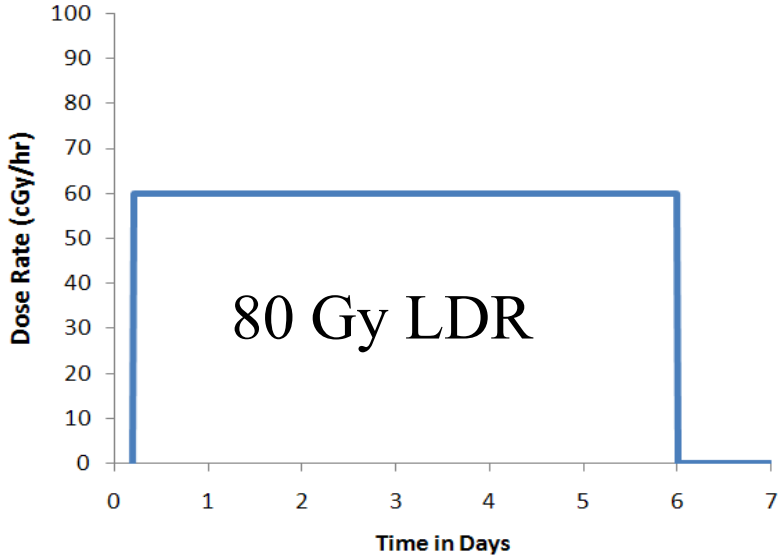


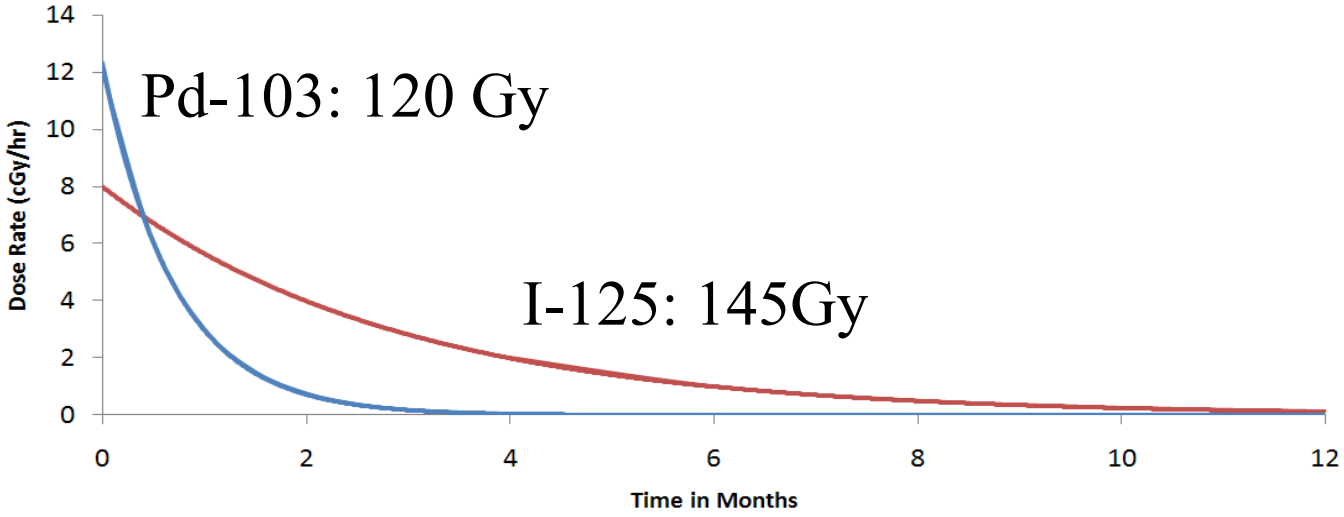


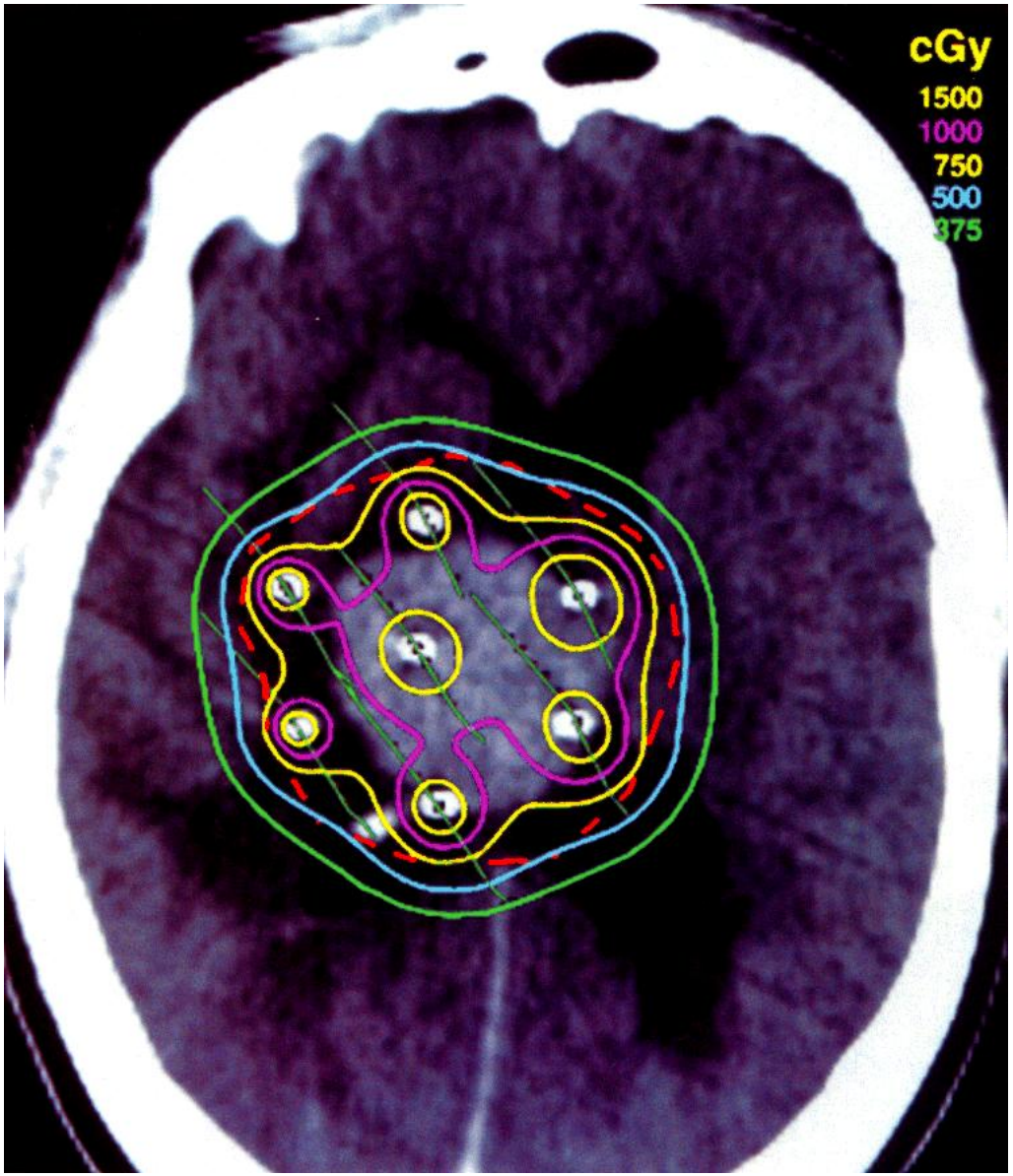
	EBRT	Brachytherapy
Homogeneity	Tight	Huge hot areas
Dose	High	Very High
Volume	Variable	Small
Dose Fall-Off	Moderate	Very Rapid
Dose Rate	High	Variable
Duration	5-8 weeks	days - months

Schedules &dose rates for (prostate) brachytherapy









Treatment plan for brain implant

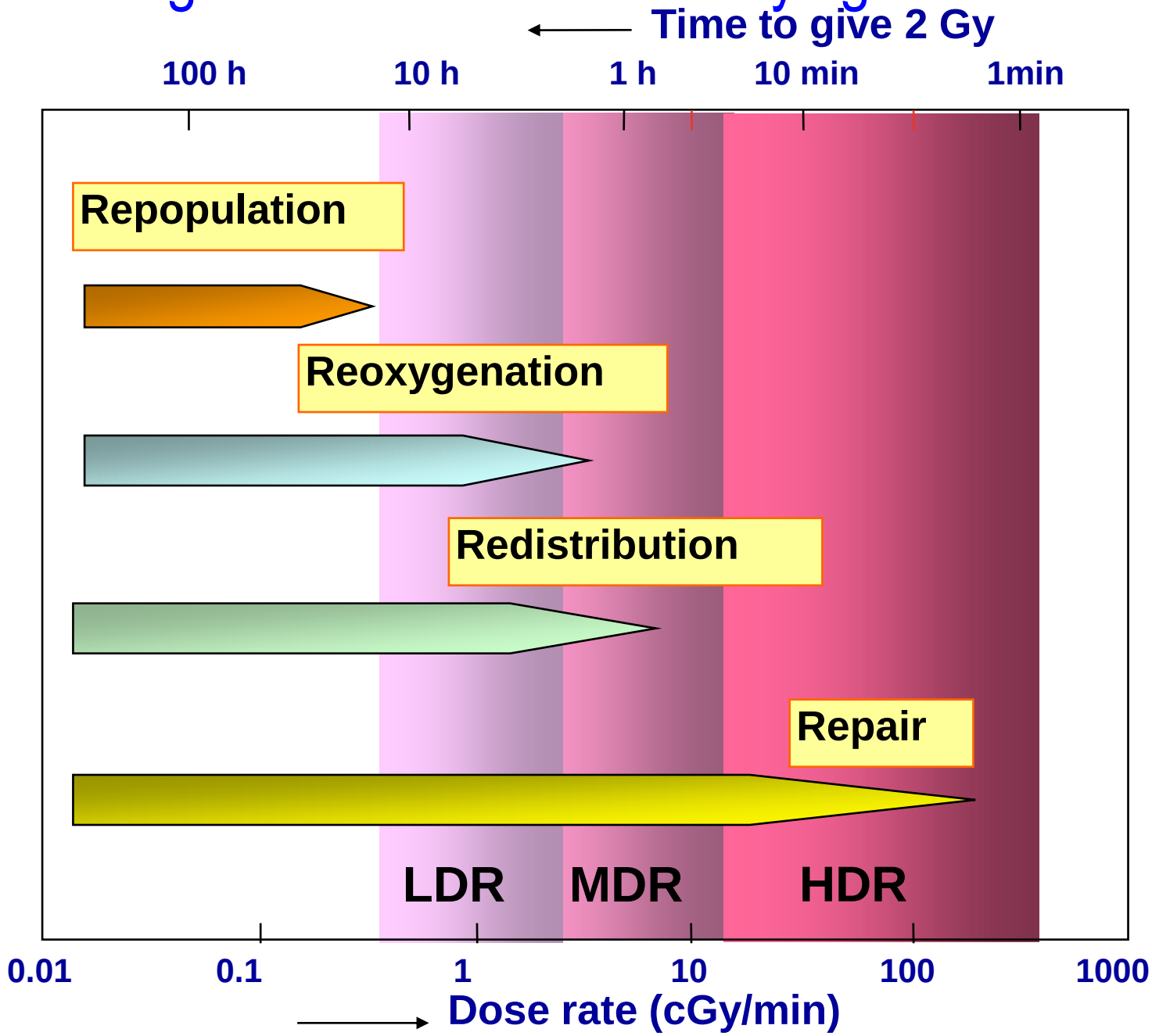
Inverse of “double trouble” at a distance from implants:

- decreasing dose rates
- decreasing total dose

In addition:

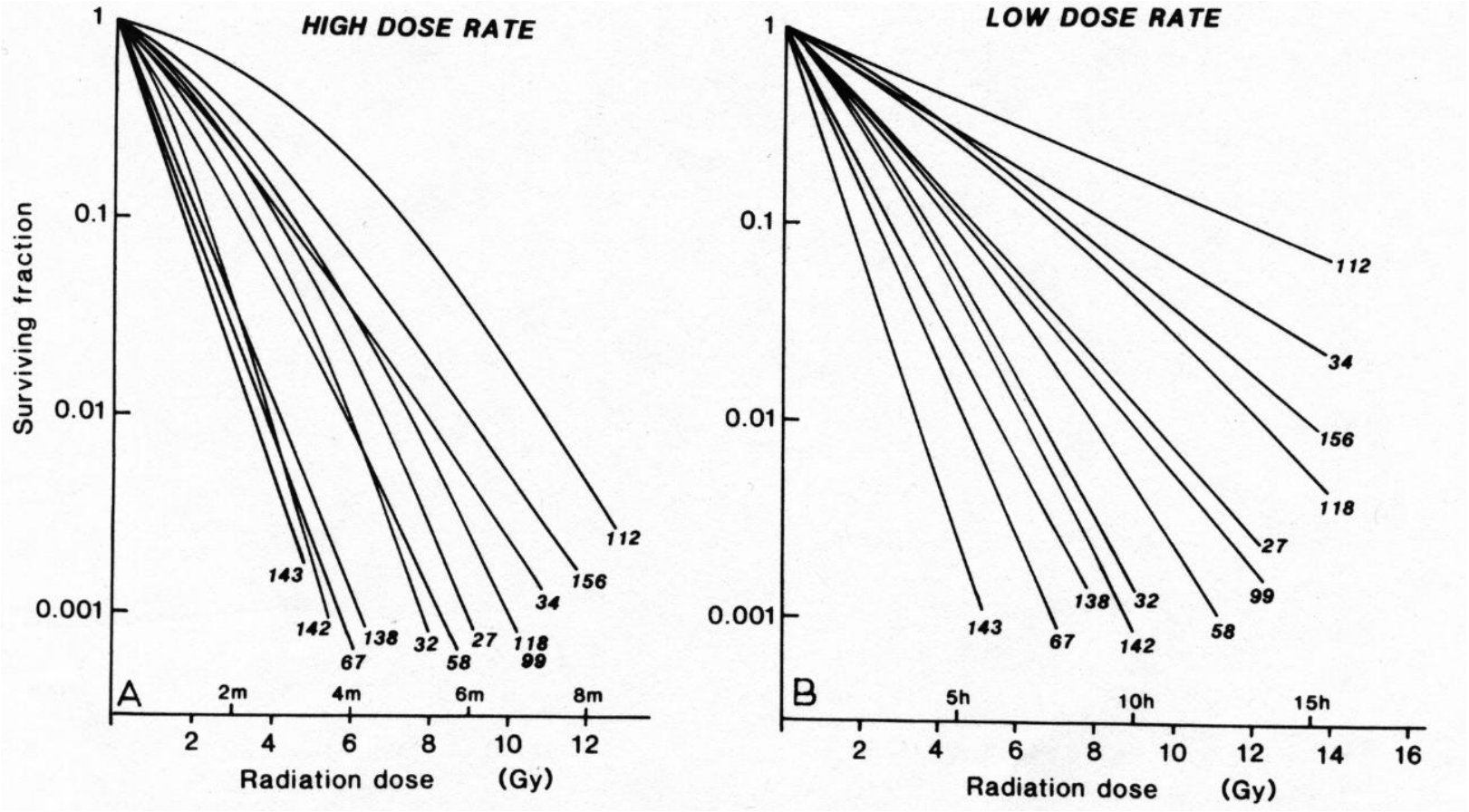
Small volumes

Radiobiological mechanisms underlying the dose rate effect



Modified from *Steel et al* (1986)

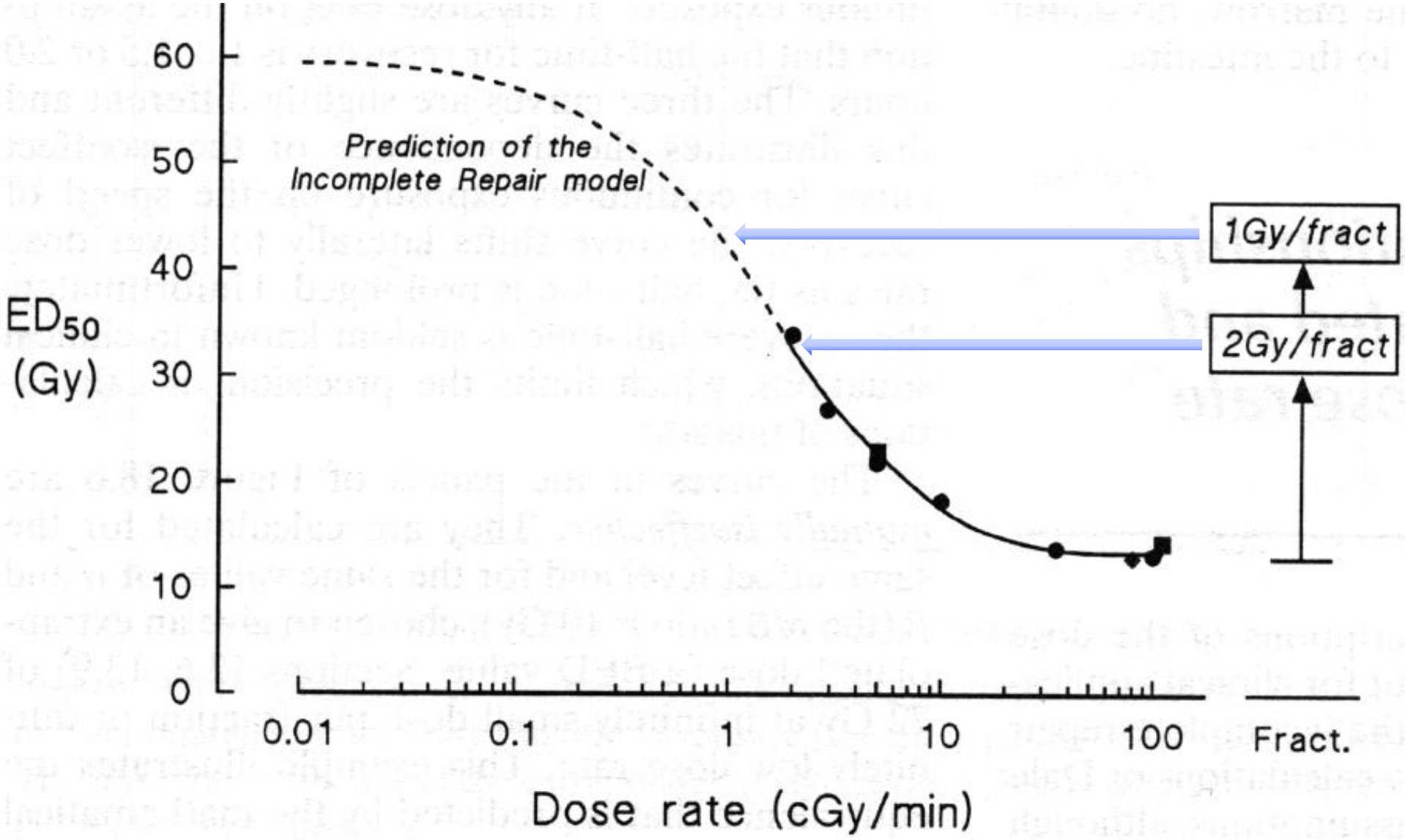
Cell survival curves for human cell lines



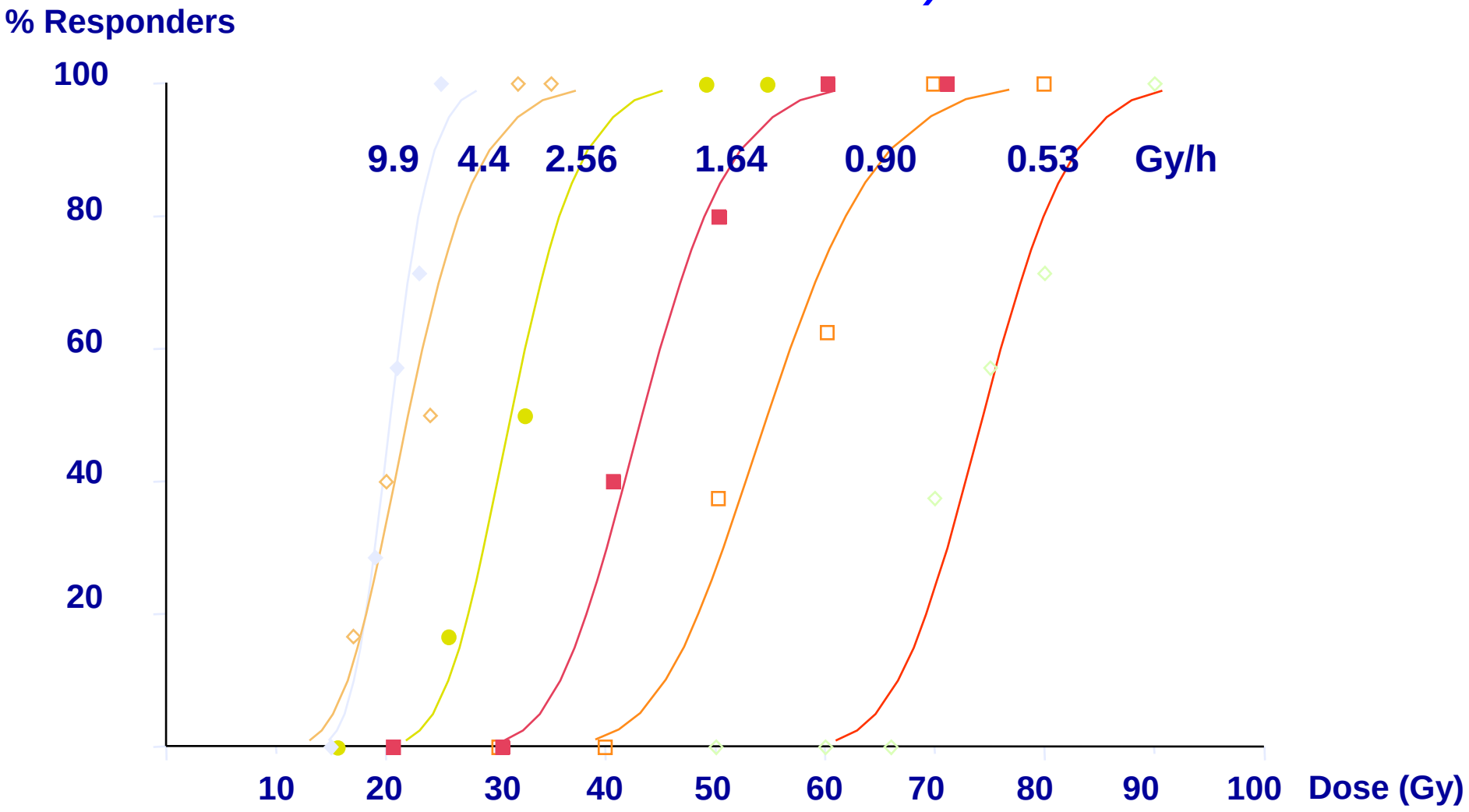
low dose rate: better discrimination between cells with different radiosensitivity

Dose rate effects in normal tissues

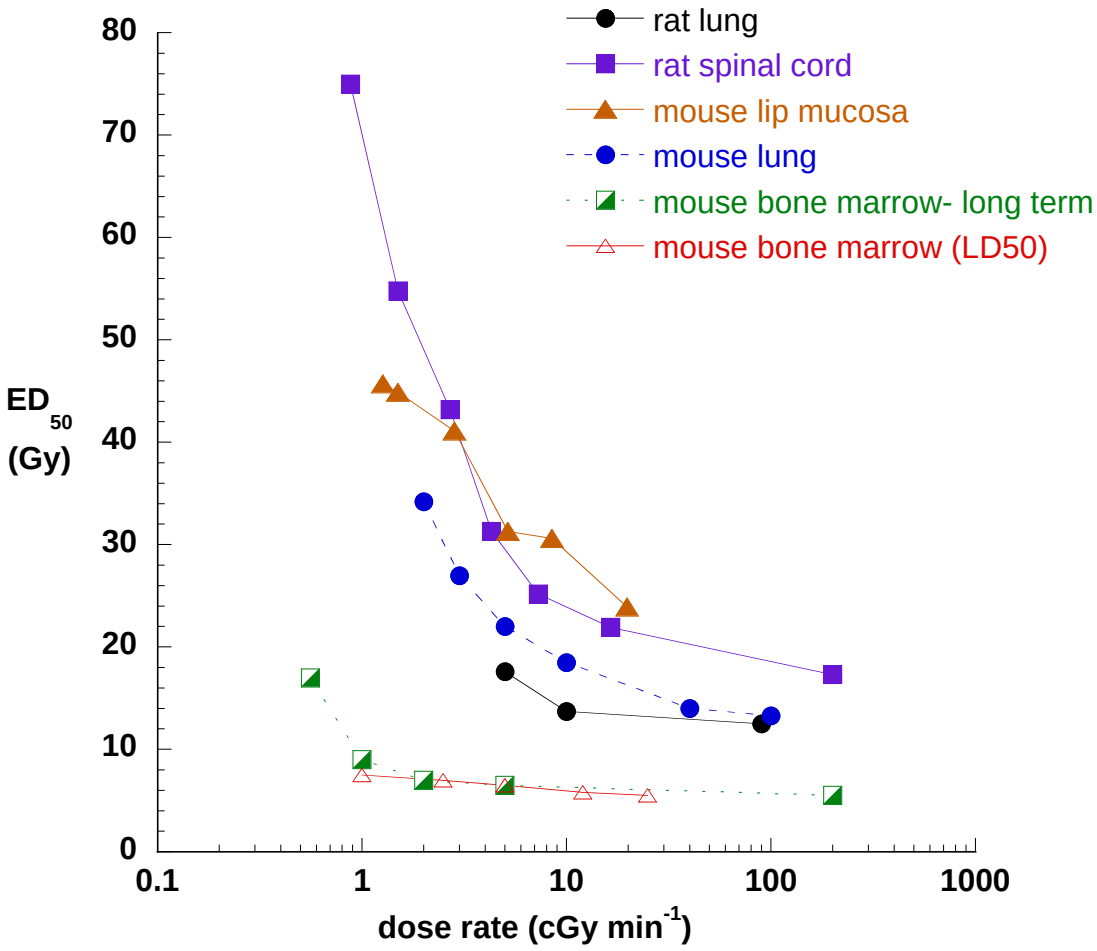
Dose-rate effect for pneumonitis in mice



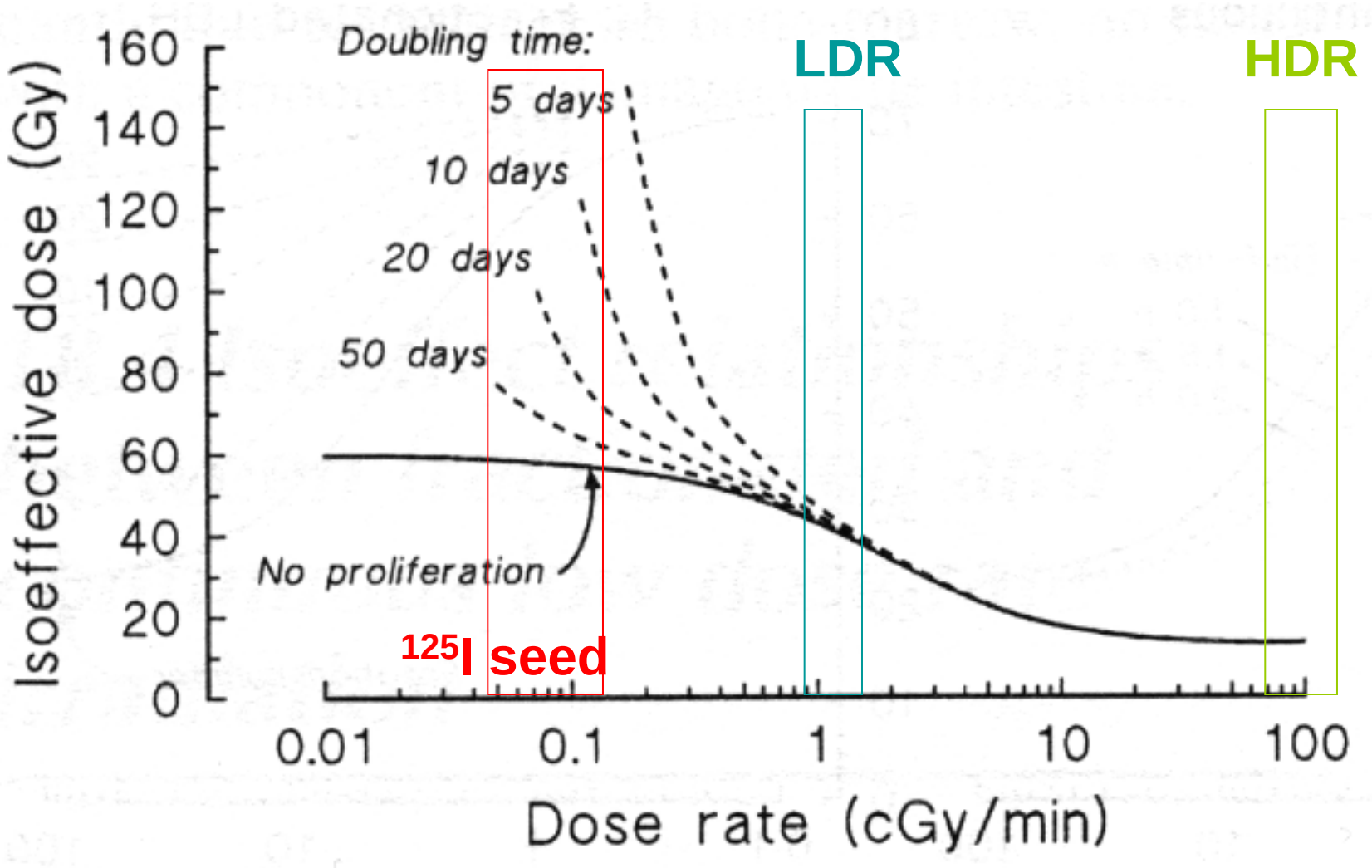
Dose-rate effects in rat spinal cord: continuous irradiation using ^{192}Ir- wires (= 6 different constant dose rates)



Dose-rate effect in murine normal tissues



Effect of cell proliferation during brachytherapy



In HDR & LDR brachytherapy, both the α/β ratio and repair half-times are mutually involved in the radiobiological effectiveness of a treatment

Half times for recovery from radiation damage ($T_{1/2}$) in various normal tissues

Tissue	Species	Dose delivery#	$T_{1/2}$ (hours)	Source
Haemopoietic	Mouse	CLDR	0.3	Thames *et al.* (1984)
Spermatogonia	Mouse	CLDR	0.3–0.4	Delic *et al.* (1987)
Jejunum	Mouse	F	0.45	Thames *et al.* (1984)
	Mouse	CLDR	0.2–0.7	Dale *et al.* (1988)
Colon (acute injury)	Mouse	F	0.8	Thames *et al.* (1984)
	Rat	F	1.5	Sassy *et al.* (1988)
Lip mucosa	Mouse	F	0.8	Ang *et al.* (1985)
	Mouse	CLDR	0.8	Scalliet *et al.* (1987)
	Mouse	FLDR	0.6	Stüben *et al.* (1991)
Tongue epithelium	Mouse	F	0.75	Dörr *et al.* (1993)
Skin (acute injury)	Mouse	F	1.5	Rojas *et al.* (1991)
	Mouse	CLDR	1.0	Joiner *et al.* (unpublished)
	Pig	F	0.4 + 1.2*	van den Aardweg and Hopewell (1992)
	Pig	F	0.2 + 6.6*	Millar *et al.* (1996)
Lung	Mouse	F	0.4 + 4.0*	van Rongen *et al.* (1993)
	Mouse	CLDR	0.85	Down *et al.* (1986)
	Rat	FLDR	1.0	van Rongen (1989)
Spinal cord	Rat	F	0.7 + 3.8*	Ang *et al.* (1992)
	Rat	CLDR	1.4	Scalliet *et al.* (1989)
	Rat	CLDR	1.43	Pop *et al.* (1996)
Kidney	Mouse	F	1.3	Joiner *et al.* (1993)
	Mouse	F	0.2 + 5.0	Millar *et al.* (1994)
	Rat	F	1.6–2.1	van Rongen *et al.* (1990)
Rectum (late injury)	Rat	CLDR	1.2	Kiszel *et al.* (1985)
Heart	Rat	F	>3	Schultz-Hector *et al.* (1992)

* Two components of repair with different half-times.

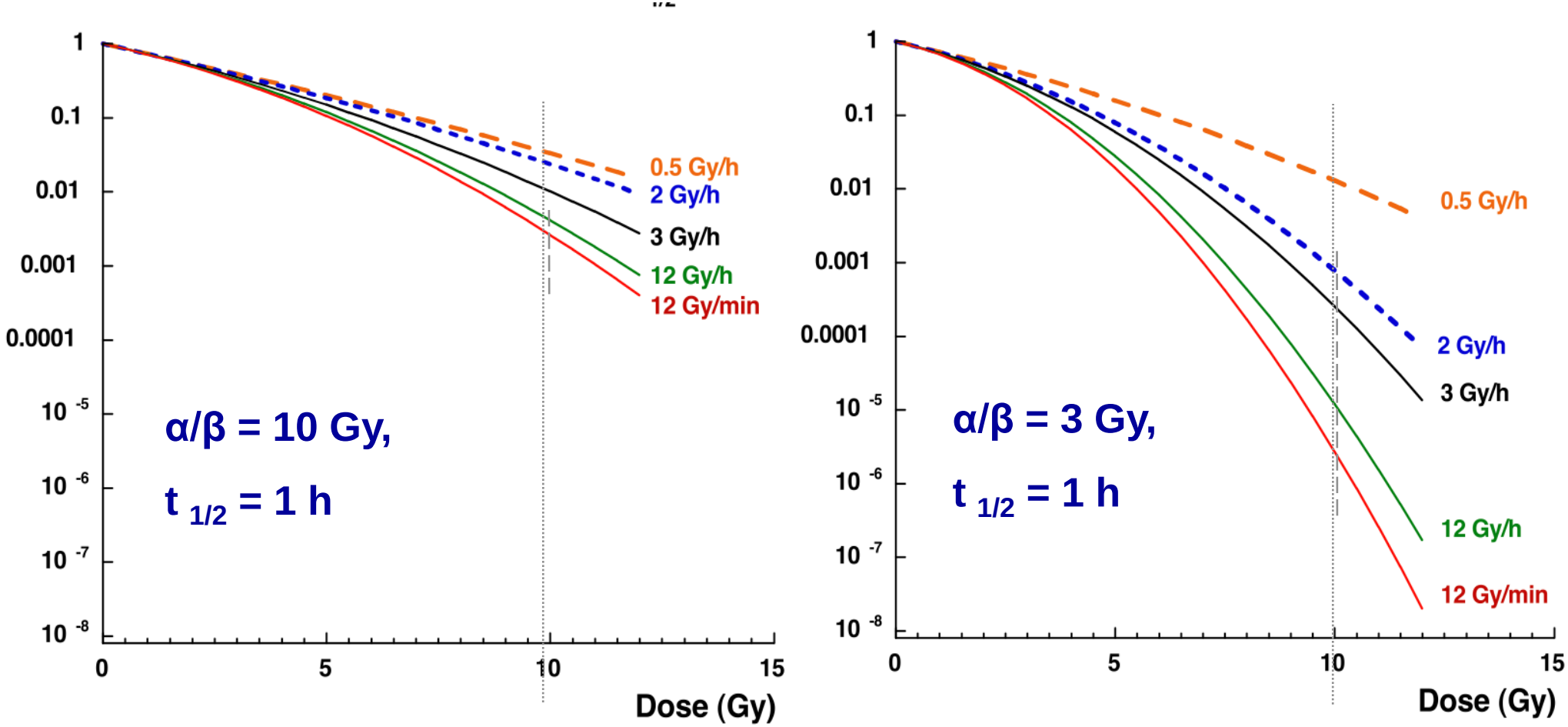
continuous low dose rate; F, acute dose fractions; FLDR, fractionated low dose rate.

$T_{1/2}$ for late-responding human tissues

Endpoint	$T_{1/2}$ (h)	2.5%-tile (h)	97.5%-tile (h)
Laryngeal oedema	4.9	3.7	6.1
Skin telangiectasia	3.8	2.9	4.5
Subcutaneous changes	4.4	4.0	4.8

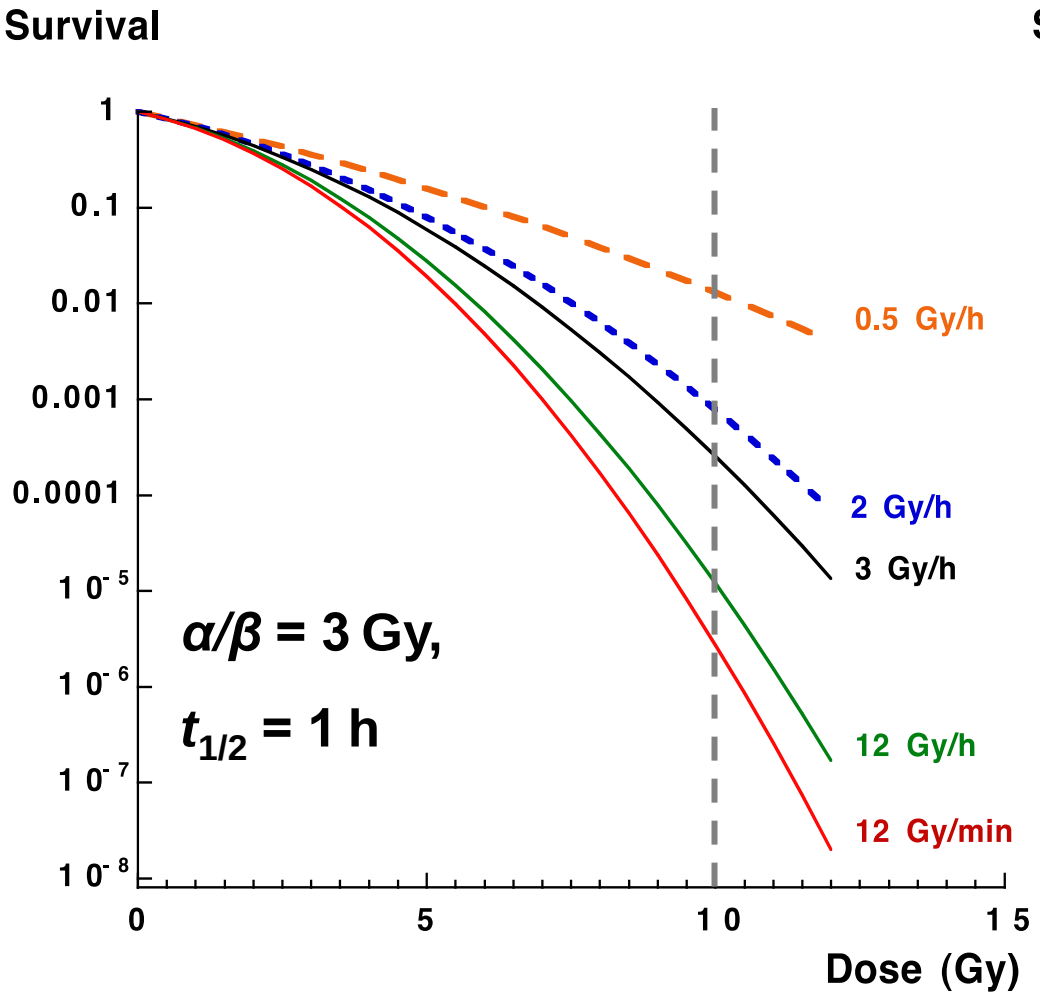
Bentzen et al. *Radiother & Oncol* 53: 219 (1999)

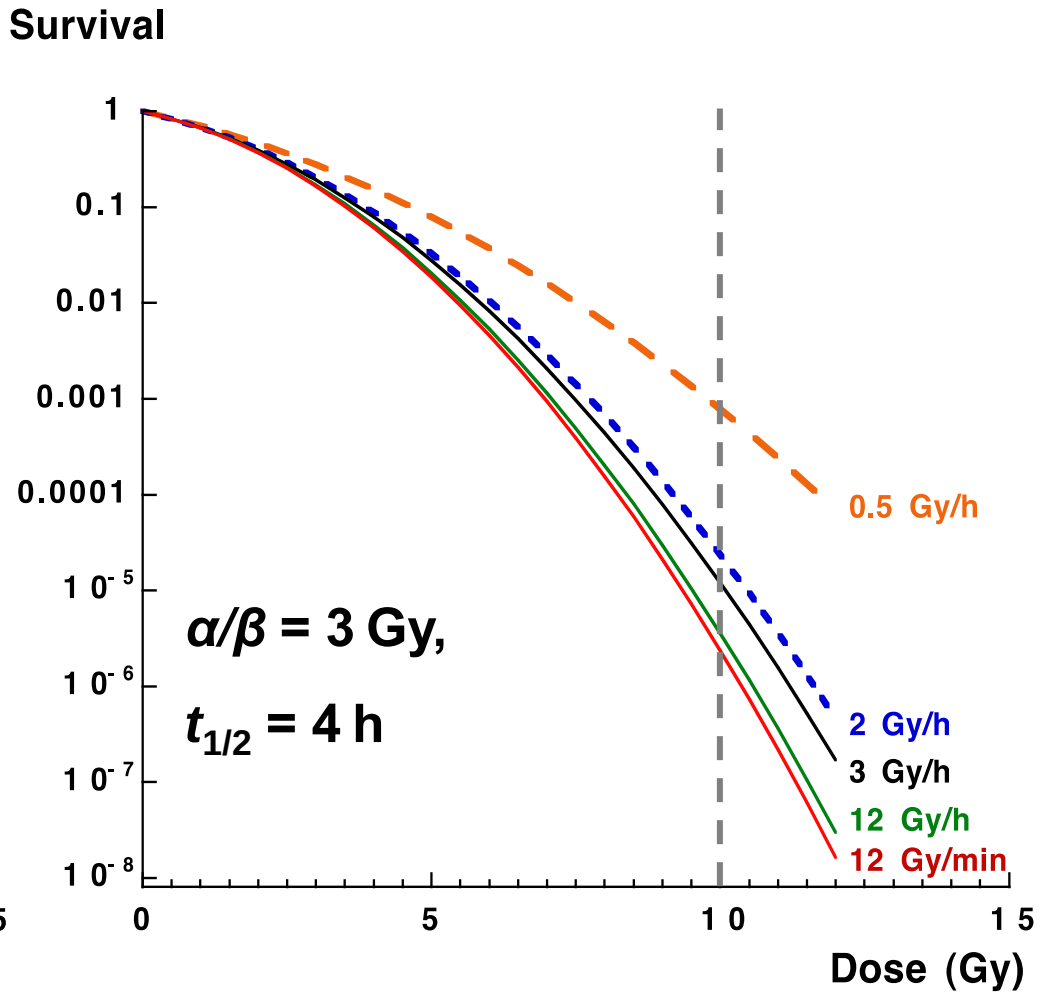
Effects at different dose rates: variation in α/β ratio



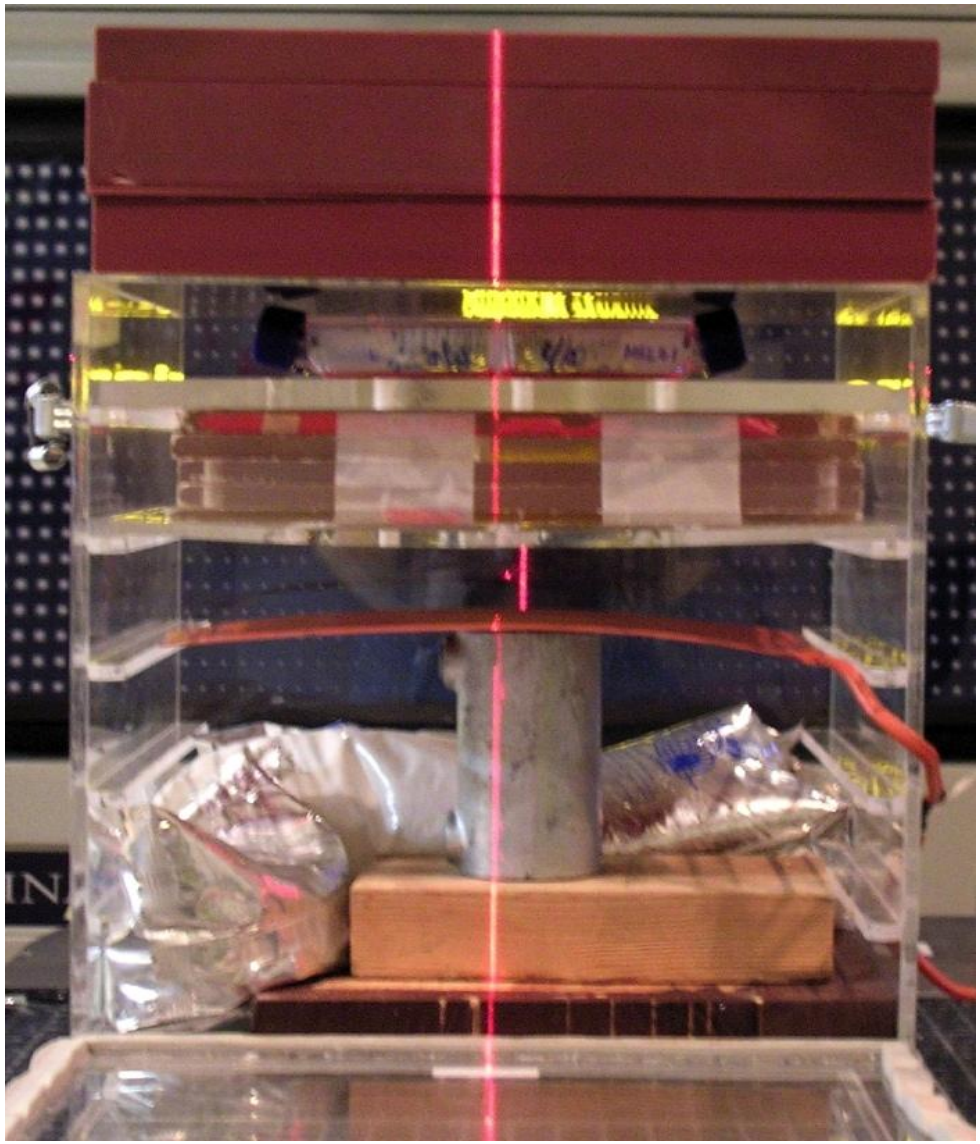
Tissue with low α/β more sensitive to change in dose rate

Low α/β values: variation in repair half-times ($t_{1/2}$)



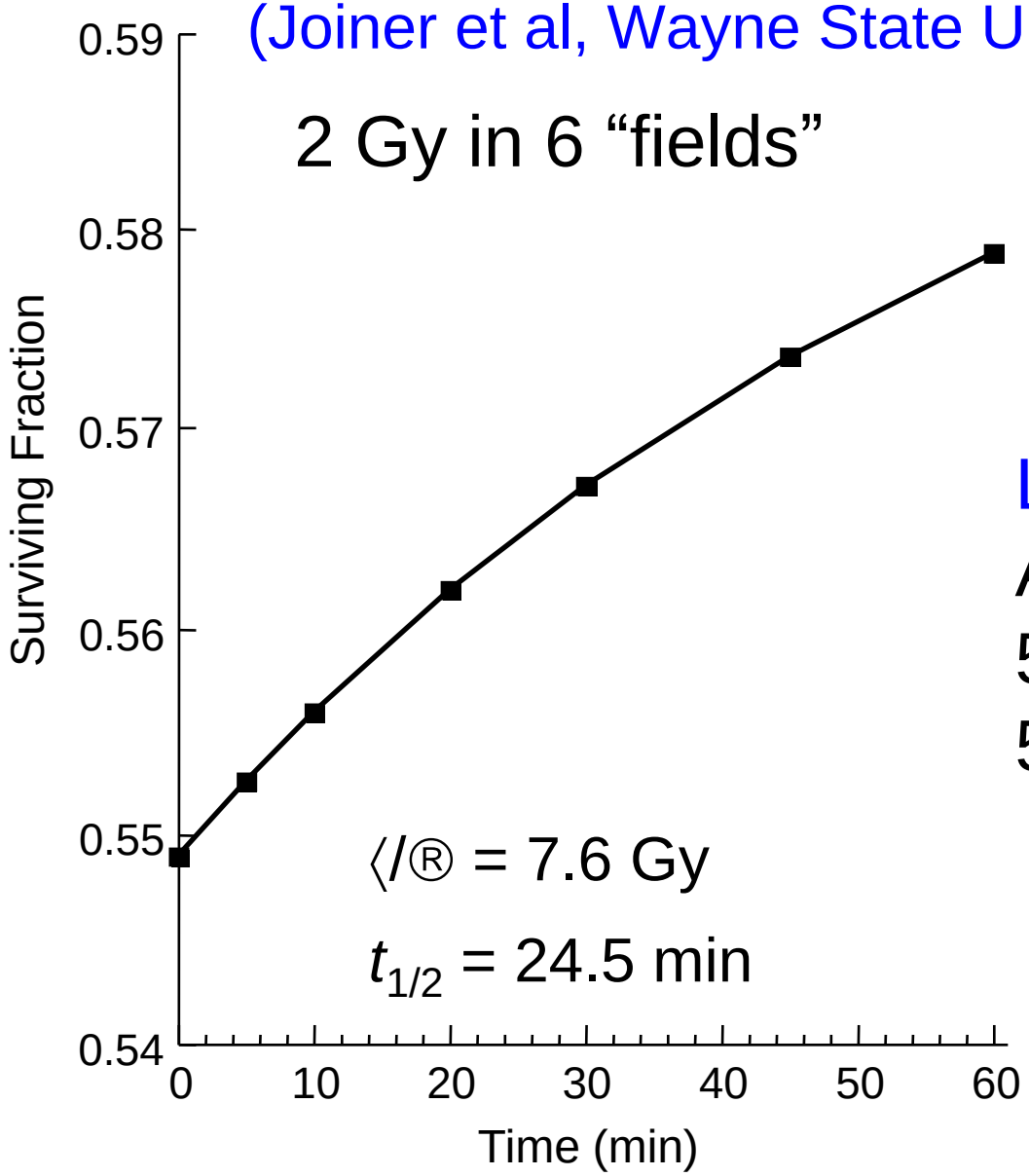


Loss of effect with increased treatment time in IMRT?



Joiner et al, Med. Phys. June 2010

Potential loss of effect in IMRT:
Prostate PC-3 cell survival in vitro
(Joiner et al, Wayne State University, Detroit)



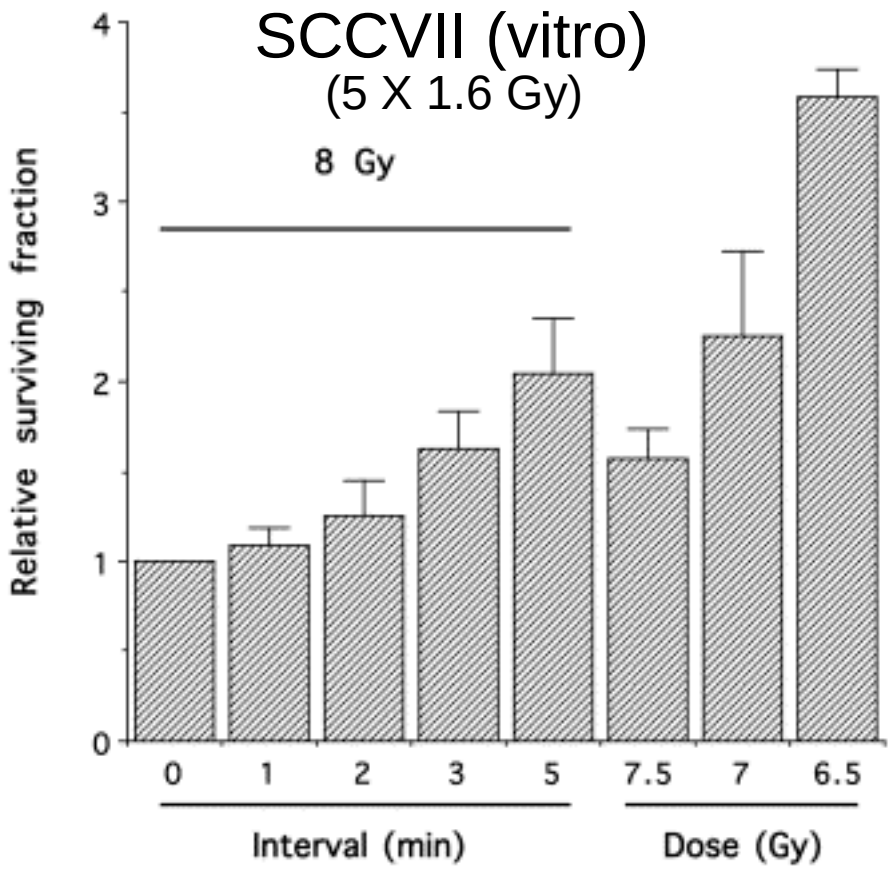
Loss in effective dose:

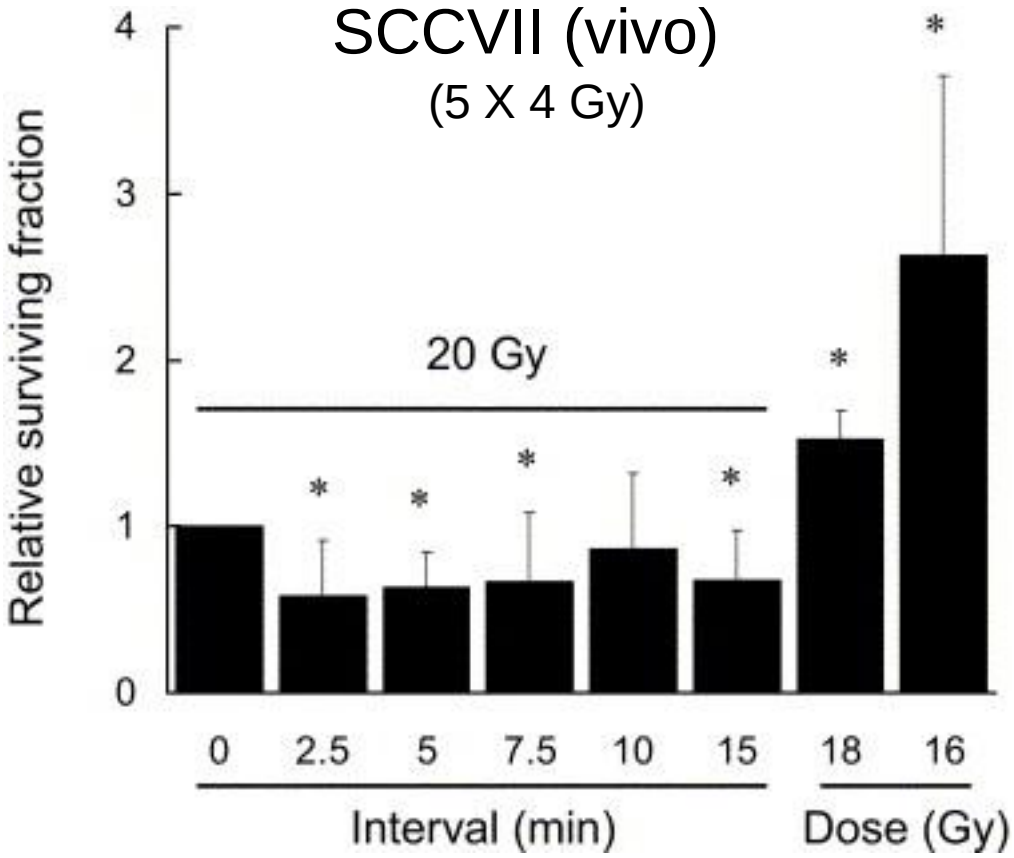
Acute to 60 min: 9%

5 min to 45 min: 6%

5 min to 30 min: 4%

intermittent irradiation: loss of effect?

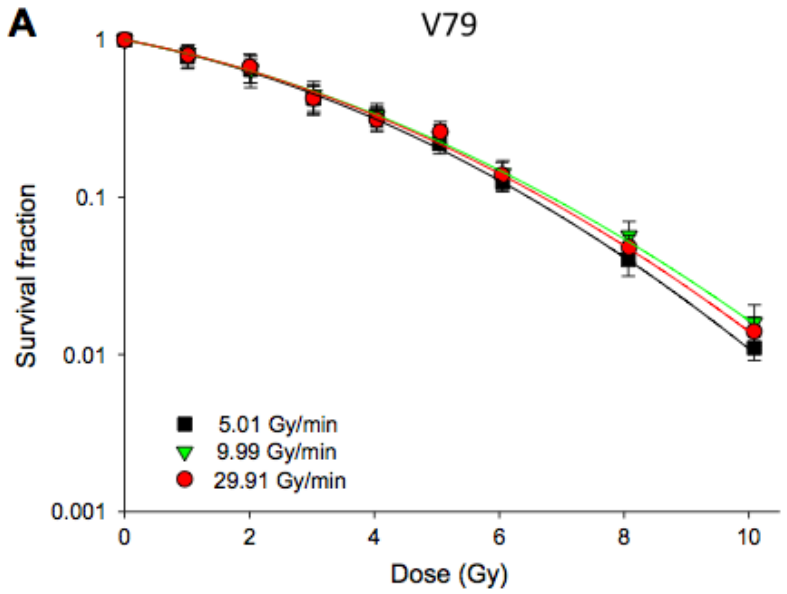


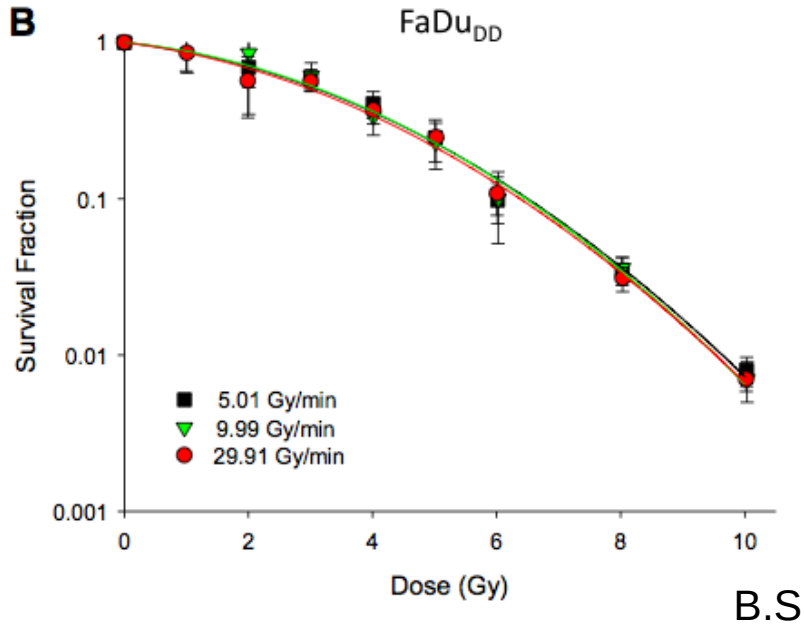


in vitro: loss of effect with short intervals

in vivo: recovery of sublethal damage compensated by reoxygenation

(Tomita et al, 2008)





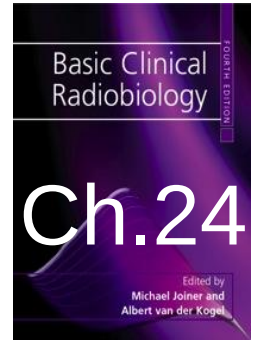
Effectiveness of very high dose rate

With the development of flattening filter-free linear accelerators for radiotherapy, the instantaneous dose rate has increased by approximately a factor 4.
The present study investigates the radiobiological effect of this high instantaneous dose rate on two cell lines

B.S. Sørensen et al. Radiother & Oncol 101 (2011) 223–225

Summary

- Continuous low dose rate irradiation
  - Irradiation times (hours - days) are long as compared to the half time of repair (0.5 - 1.5 hour). Effect dominated by repair capacity (α/β ratio)
- High dose rate irradiation
  - Irradiation time is too short for repair during the irradiation, unless repair is very fast (in the order of minutes).
- IMRT
  - For complex treatments lasting ≥20-30 min, loss of effective dose may be 5-10%, but depends on α/β and $T_{1/2.}$
  - Possibly compensated by reoxygenation in vivo
  - High instantaneous dose rate (flattening filter-free): no change in effect



Particles in radiotherapy

Prof. Vincent GREGOIRE
Université Catholique de Louvain,
Cliniques Universitaires St-Luc

ESTRO teaching course on basic clinical radiobiology

Radiotherapy and Oncology 95 (2010) 3–22

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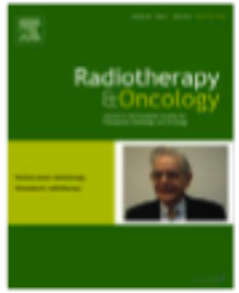
journal homepage: www.thegreenjournal.com



Review

Proton *vs* carbon ion beams in the definitive radiation treatment of cancer patients

Herman Suit [a,*], Thomas DeLaney [a], Saveli Goldberg [a], Harald Paganetti [a], Ben Clasie [a], Leo Gerweck [a], Andrzej Niemierko [a], Eric Hall [b], Jacob Flanz [a], Josh Hallman [a], Alexei Trofimov [a]

[a] *Department of Radiation Oncology, Boston, MA, USA;* [b] *Center for Radiological Research, Columbia University, New York, NY, USA*

ESTRO
2015

Uncharged	Charged	
X rays γ rays	e^- p^+ He^{2+}	Low LET
Neutrons	C^{6+} Ne^{10+} Si^{14+} Ar^{18+}	High LET

HadronTherapy: the clinical aspects

Prof. Vincent GREGOIRE
Université Catholique de Louvain,
Cliniques Universitaires St-Luc

Improvement of radiotherapy

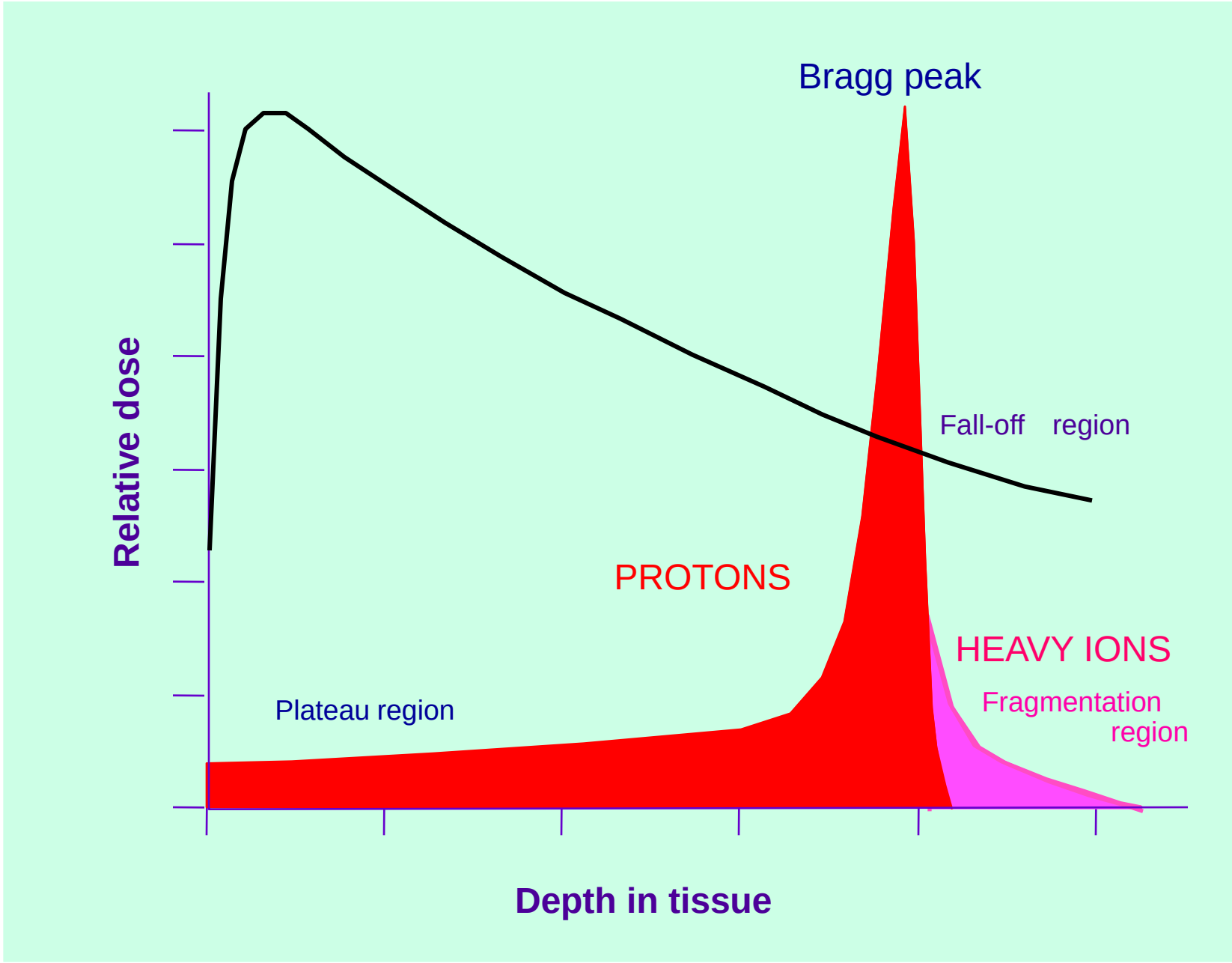
Ballistic selectivity

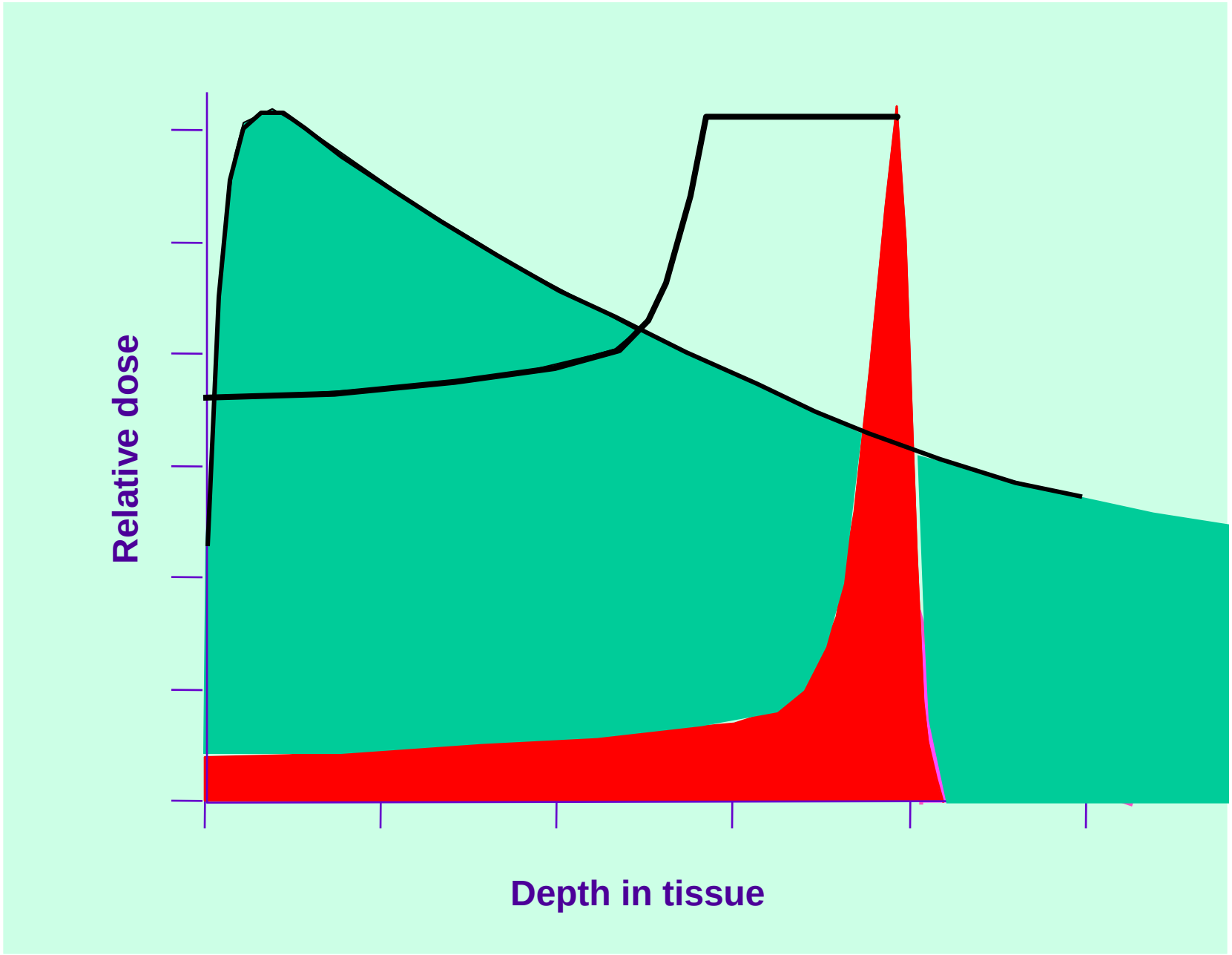
Increasing the dose to the tumo
while reducing the dose to th
surrounding normal tissues

Differential effect

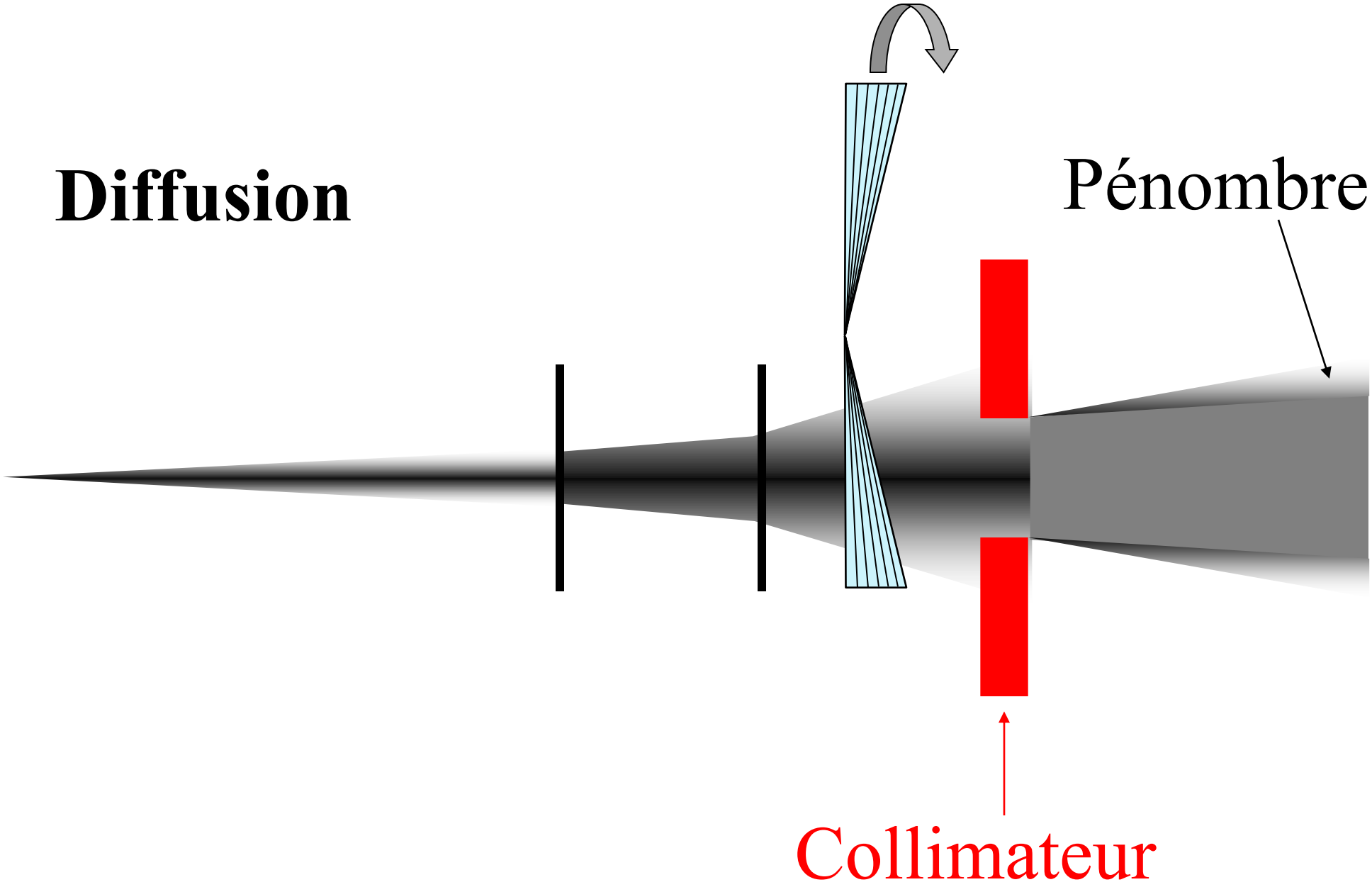
Compared to conventional radiation
the effect is relatively more marke
on the tumour than on the norm
tissues (RBE)

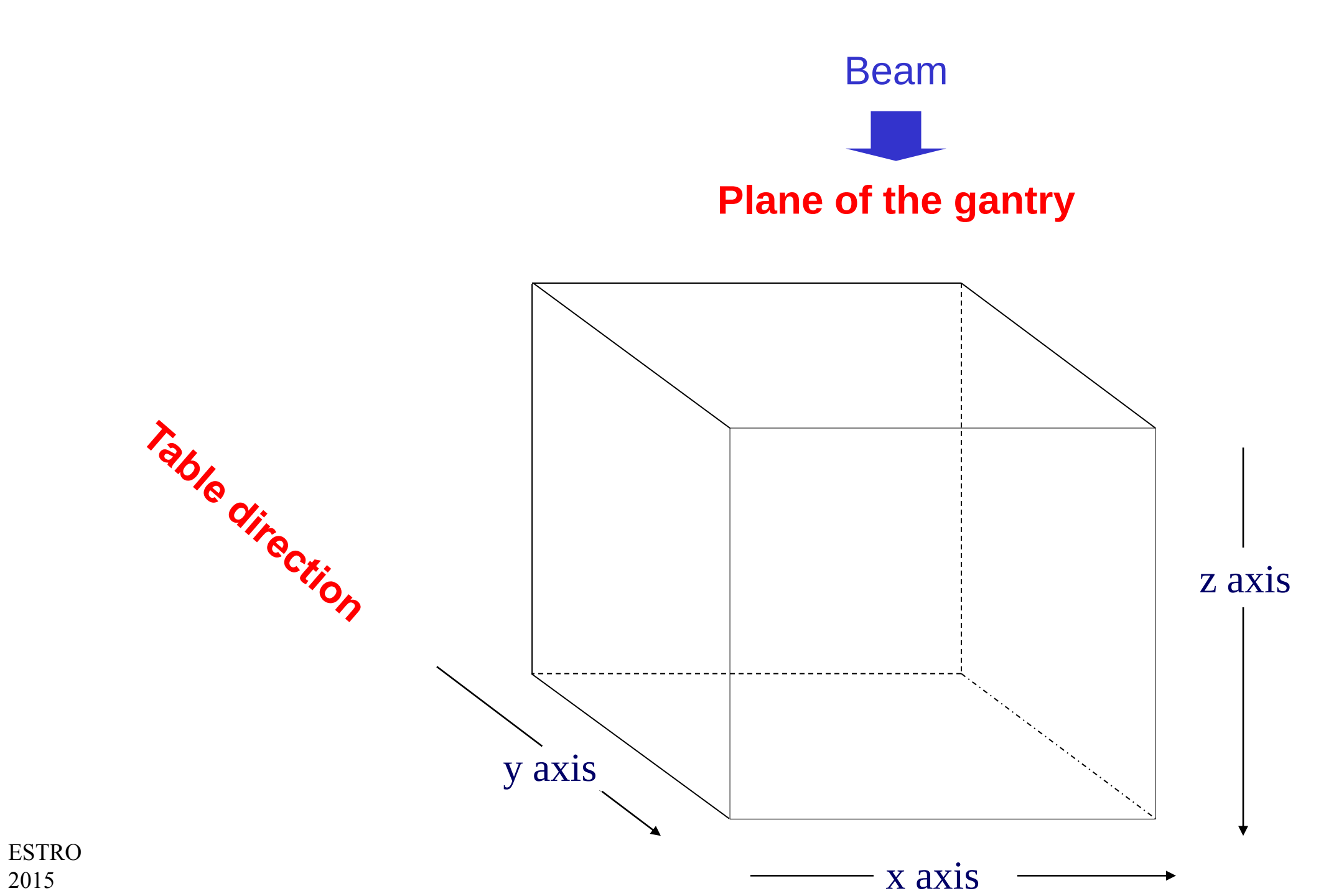
Improvement of **ballistic selectivity**

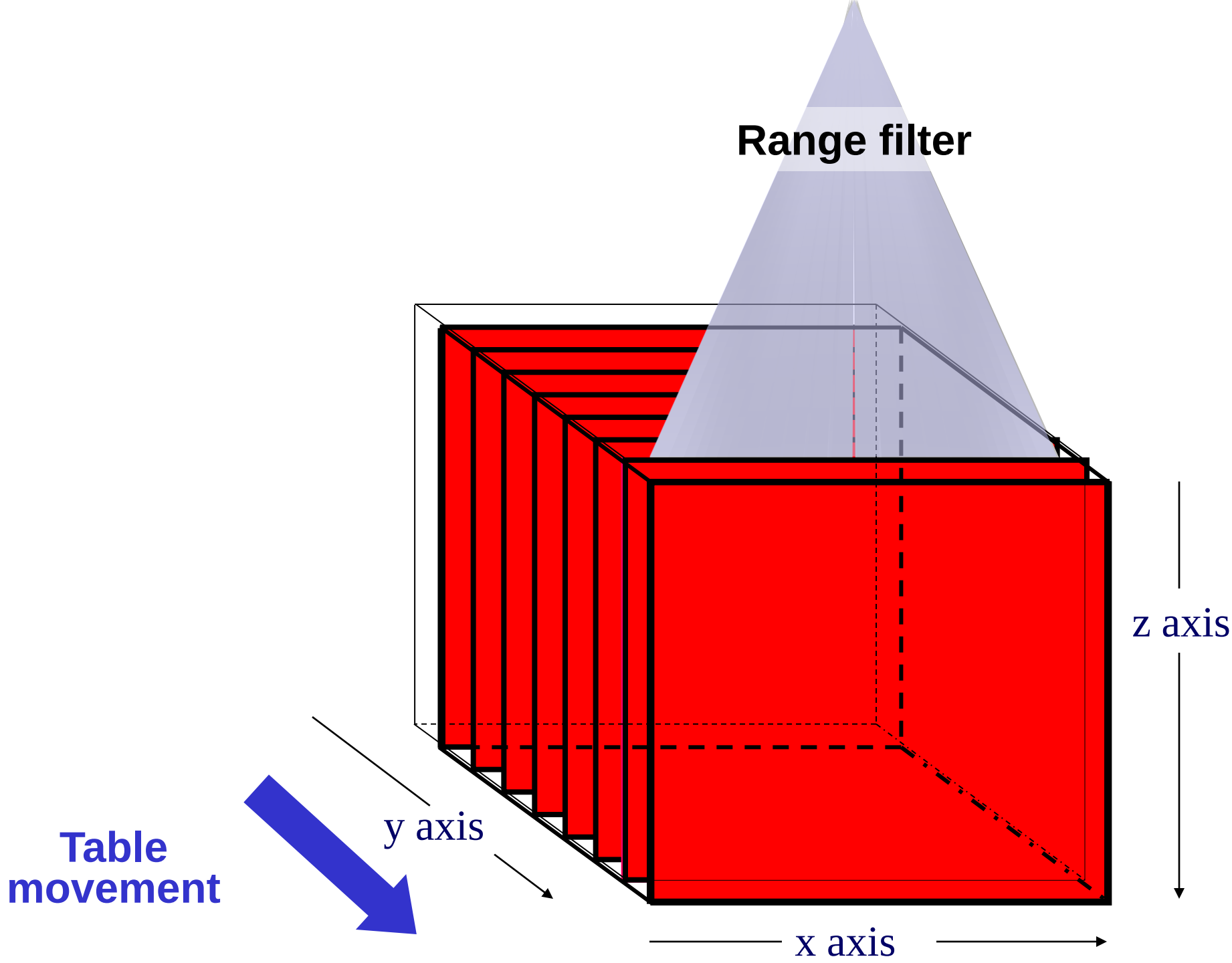

Bragg peak
Relative dose
Fall-off region
PROTONS
HEAVY IONS
Fragmentation region
Plateau region
Depth in tissue


Relative dose
Depth in tissue

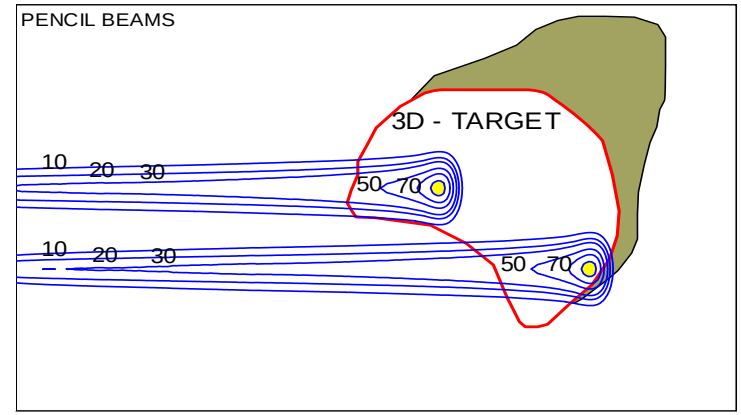
Diffusion

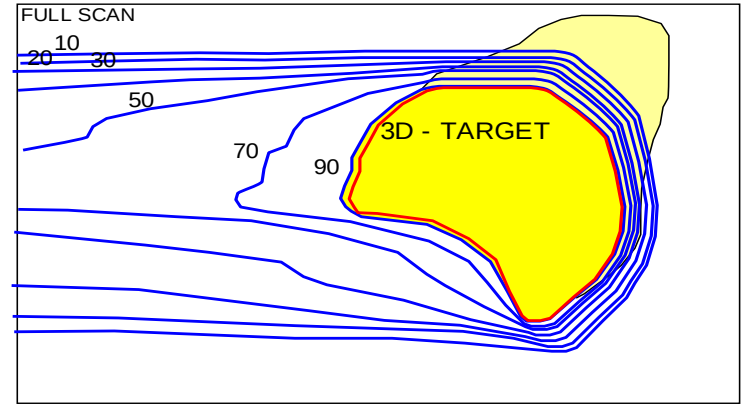



Beam
Plane of the gantry
Table direction
y axis
z axis
x axis

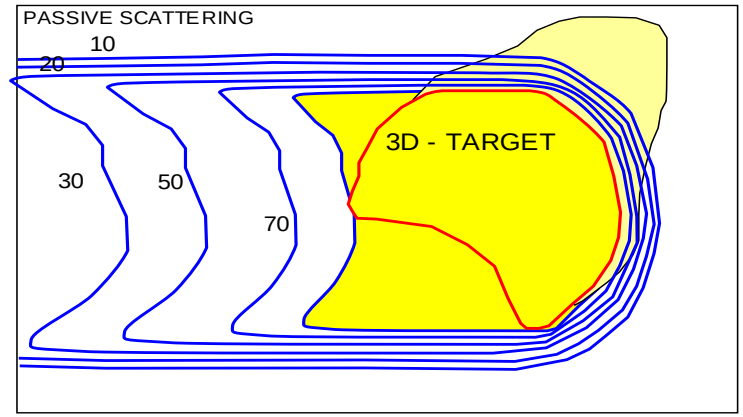

Range filter
z axis
y axis
x axis
Table movement

BEAM SCANNING





PASSIVE SCATTERING



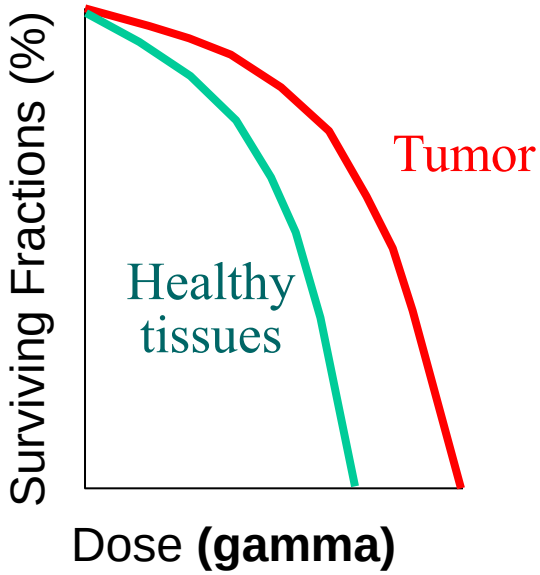
Improvement of **differential effect**

Reduction of radiosensitivity differences :

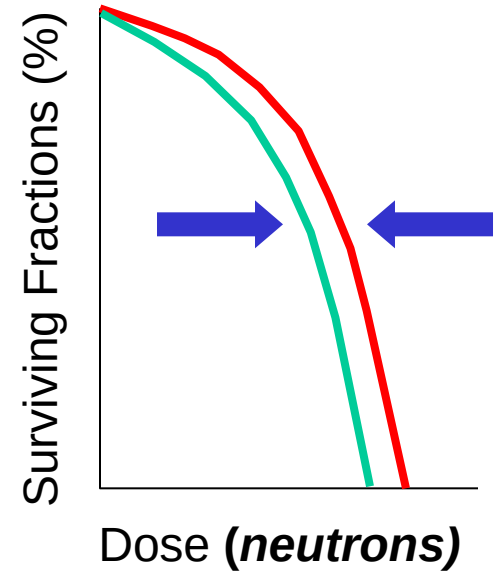
Potential therapeutic advantage

when the tumor is radioresistant
in comparison with healthy tissues

unfavourable !



less unfavourable !



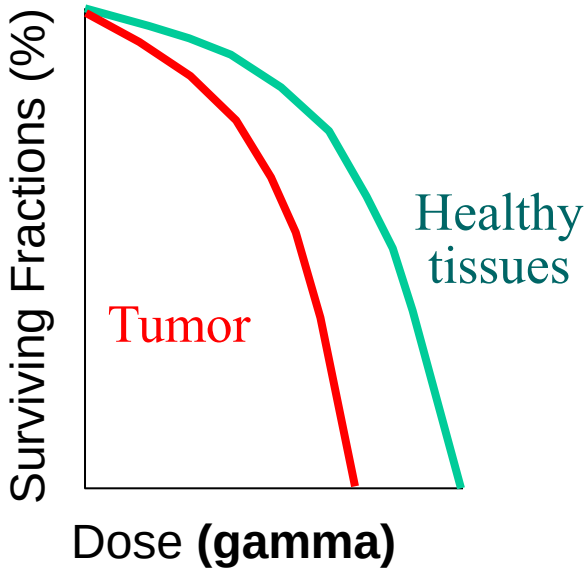
Potential therapeutic benefit due to the ***reduction***
of an ***unfavourable*** *differential effect*

Reduction of radiosensitivity differences :

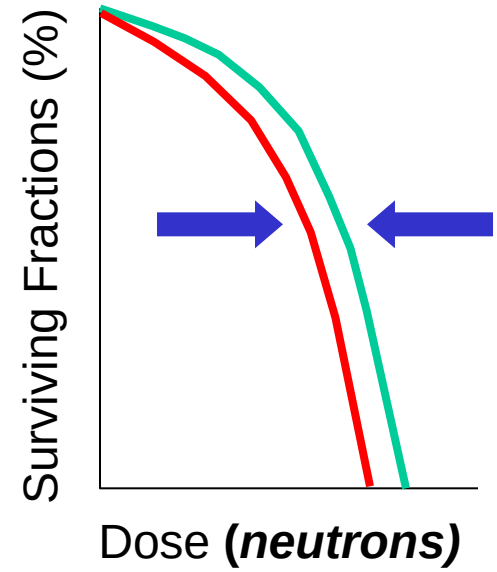
contra-indication

when the healthy tissues are radioresistant
In comparison with the tumor

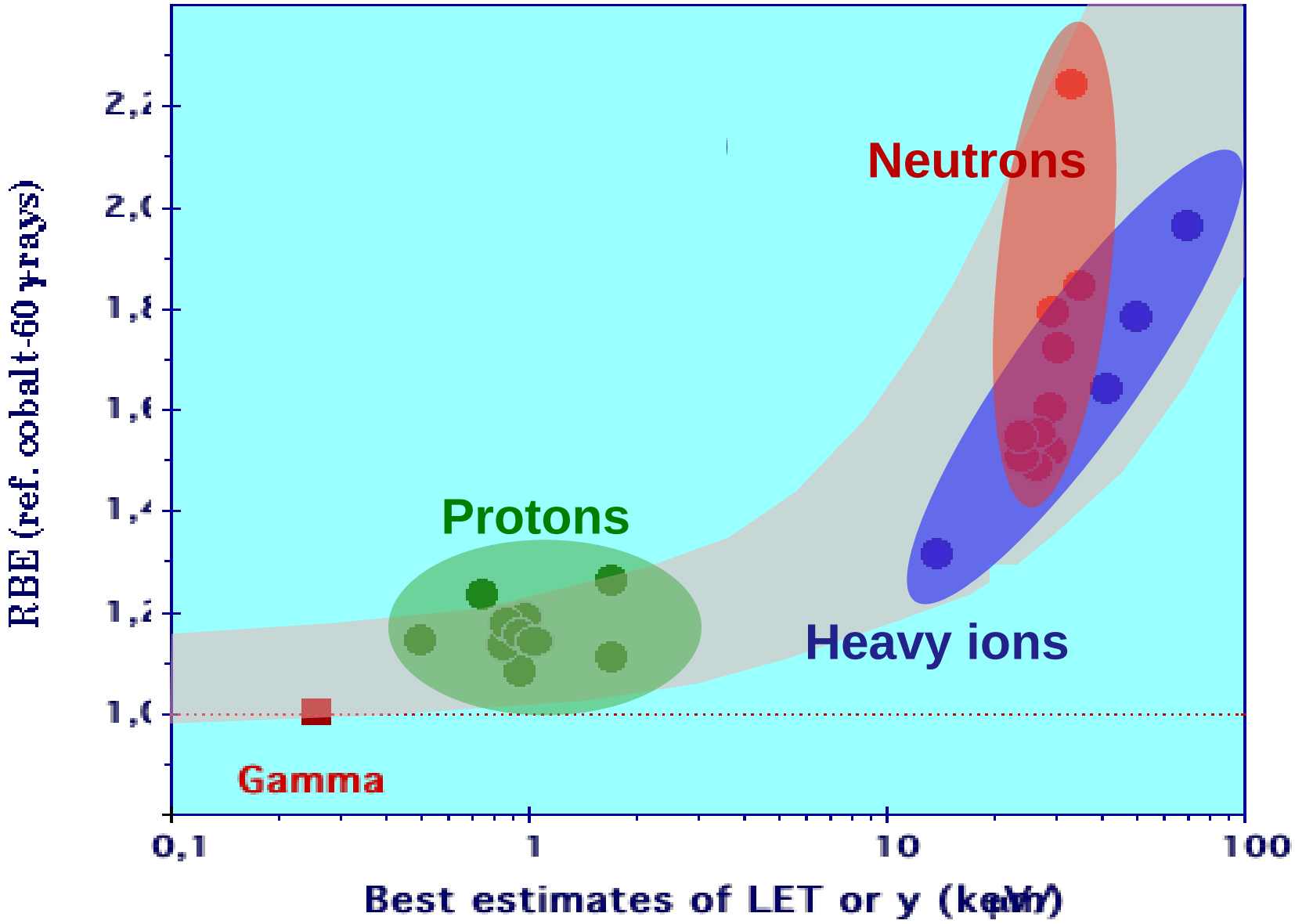
favourable !

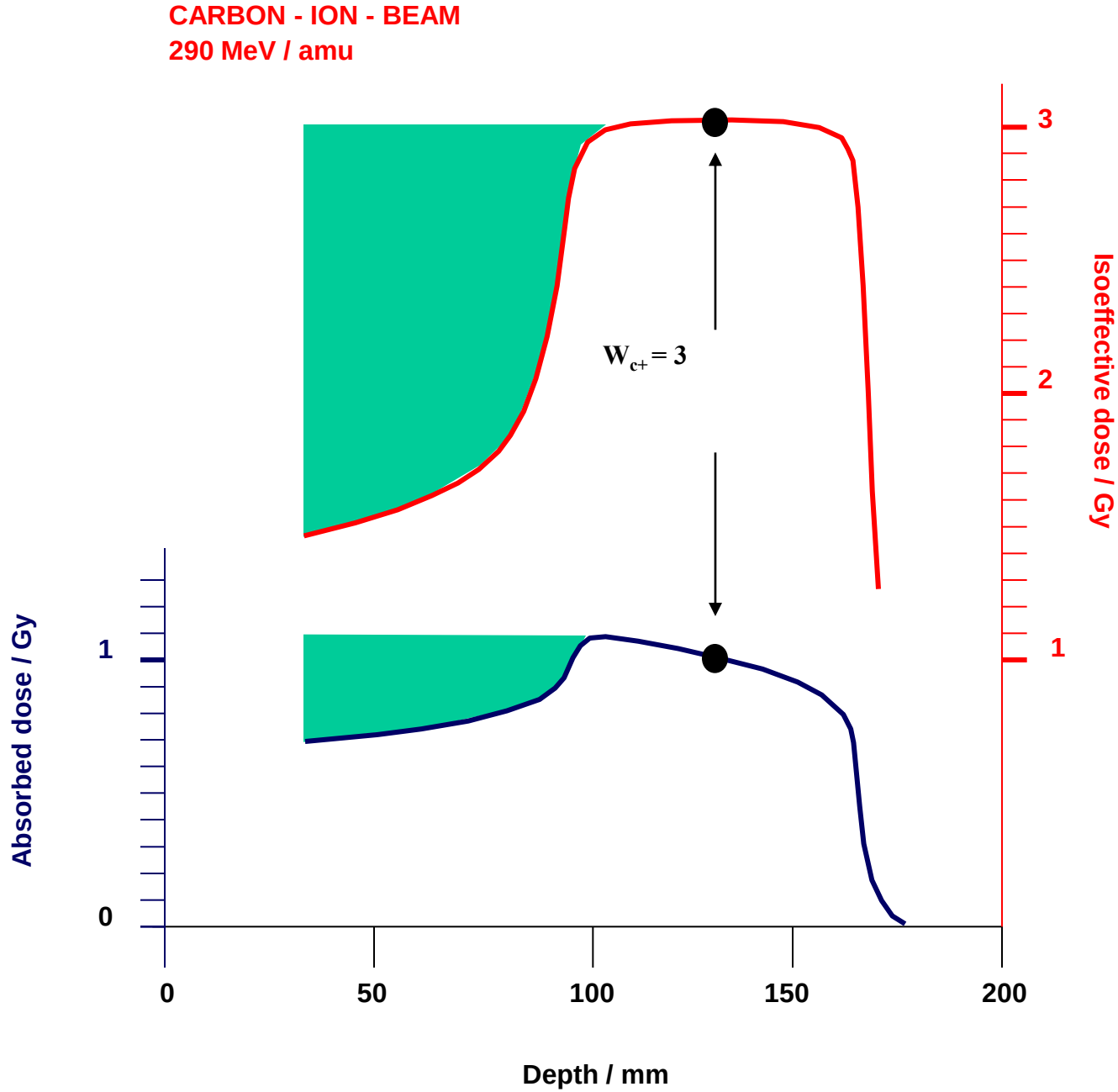


less favourable !

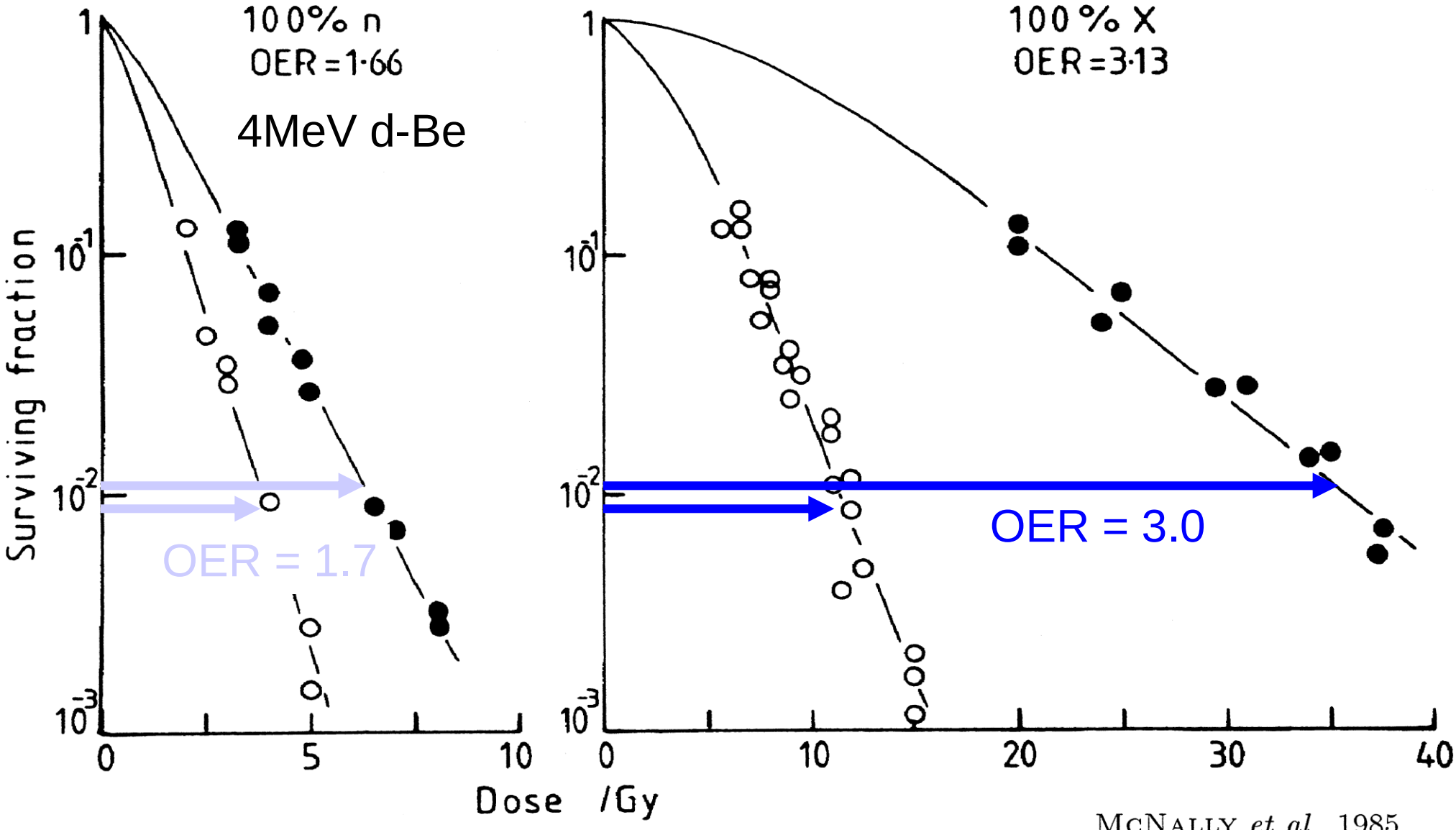


Contra-indication due to the ***reduction*** *of a* ***favorable*** *differentiel effect*

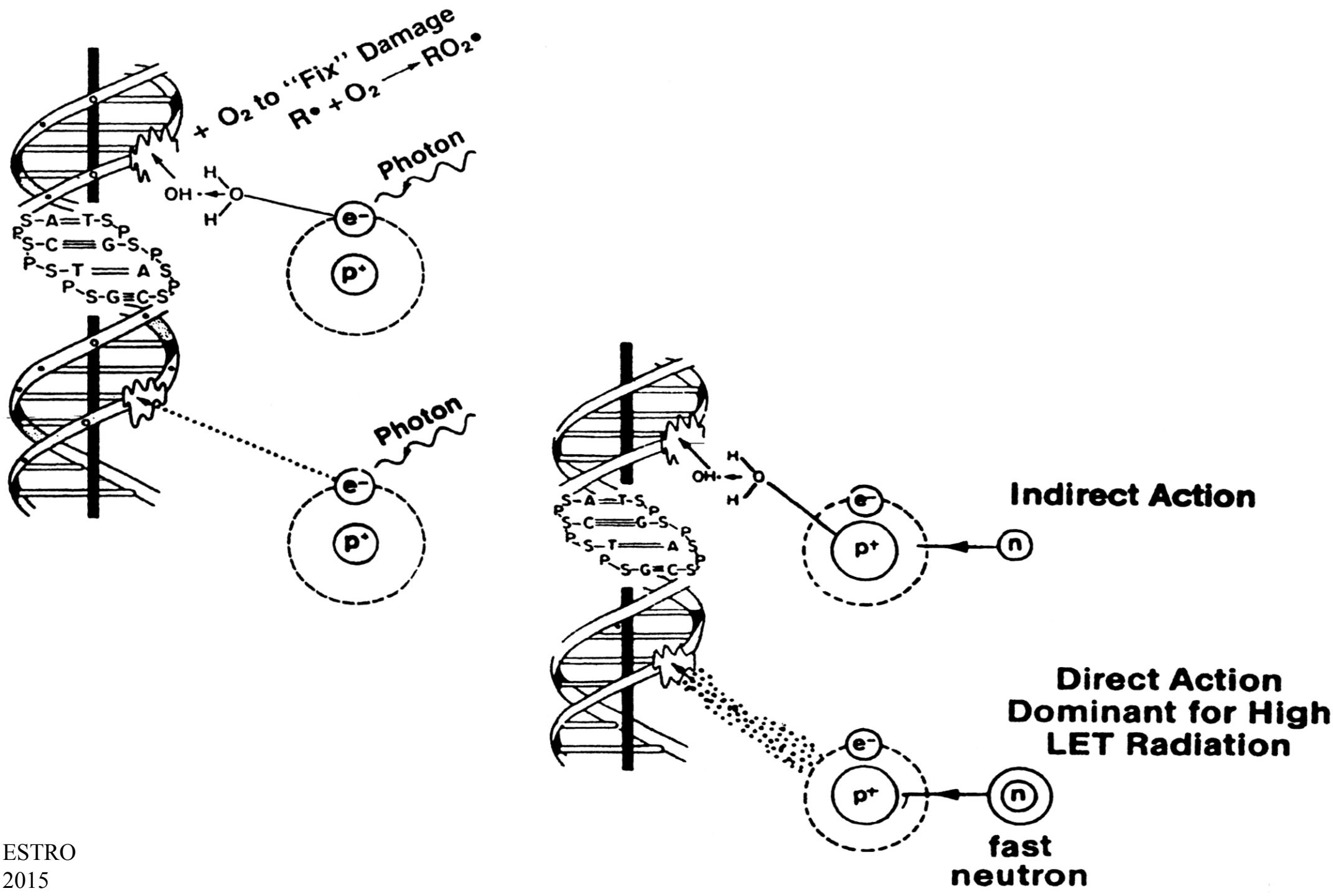

RBE (ref. cobalt-60 γ-rays)
Neutrons
Protons
Heavy ions
Gamma
0,1
1
10
100
Best estimates of LET or y (keV/µm)


CARBON - ION - BEAM
290 MeV / amu
$W_{c+} = 3$
Absorbed dose / Gy
Isoeffective dose / Gy
0
1
1
2
3
0
50
100
150
200
Depth / mm

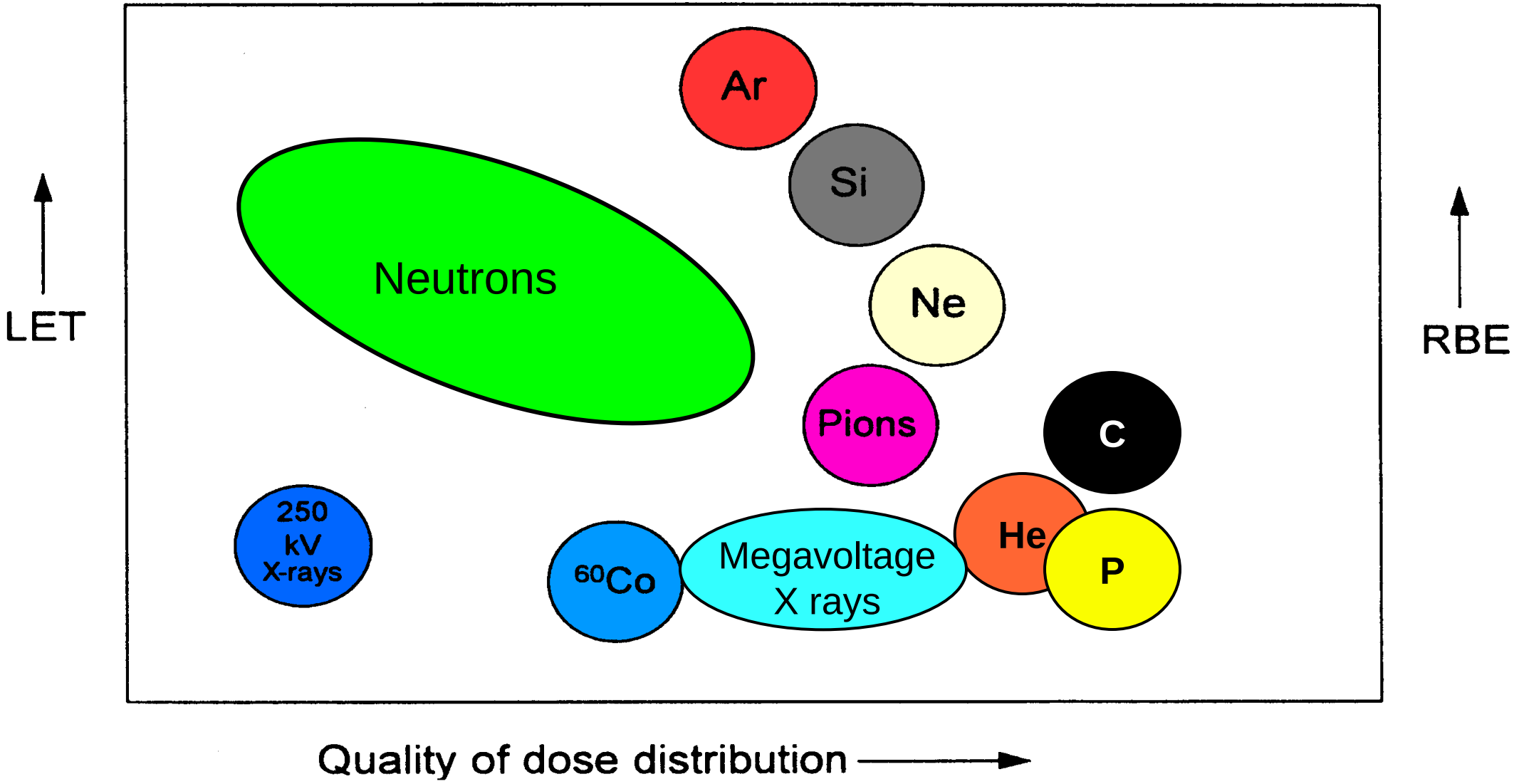
Reduced effect of oxygen



McNally *et al.*, 1985,
Int. J. Radiat. Biol., **48**, 847


+ O2 to "Fix" Damage
R• + O2 → RO2•
Photon
OH
H
O
H
e⁻
p+
S-A=T-S-P
S-C≡G-S-P
P-S-T=A-S-P
P-S-G≡C-S-P
Photon
e⁻
p+
Indirect Action
OH
H
O
H
e⁻
p+
n
Direct Action
Dominant for High
LET Radiation
e⁻
p+
n
fast
neutron

Potential **clinical benefit** of Protons


LET
RBE
Ar
Si
Neutrons
Ne
Pions
C
He
P
250 kV X-rays
60Co
Megavoltage X rays
Quality of dose distribution

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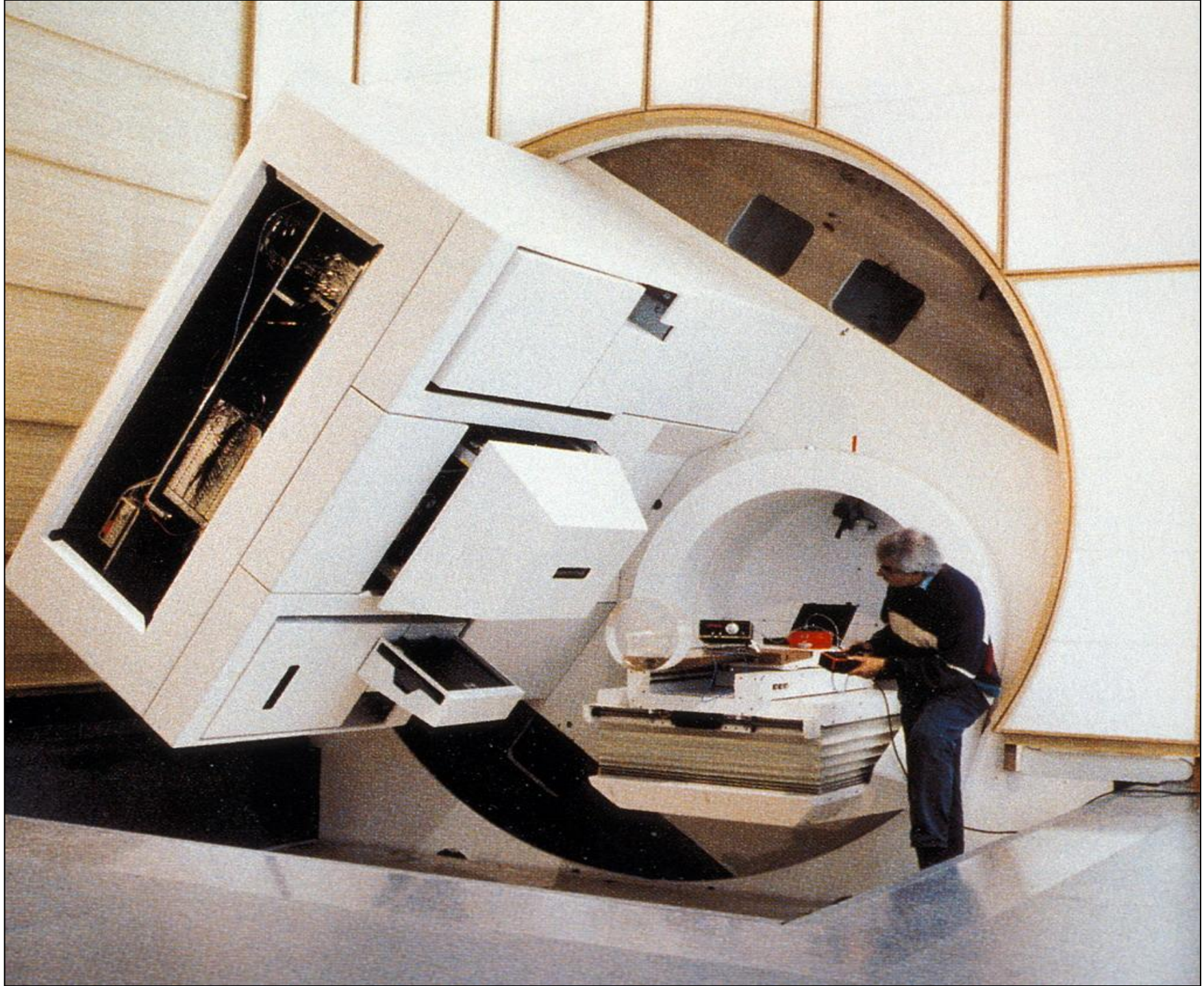

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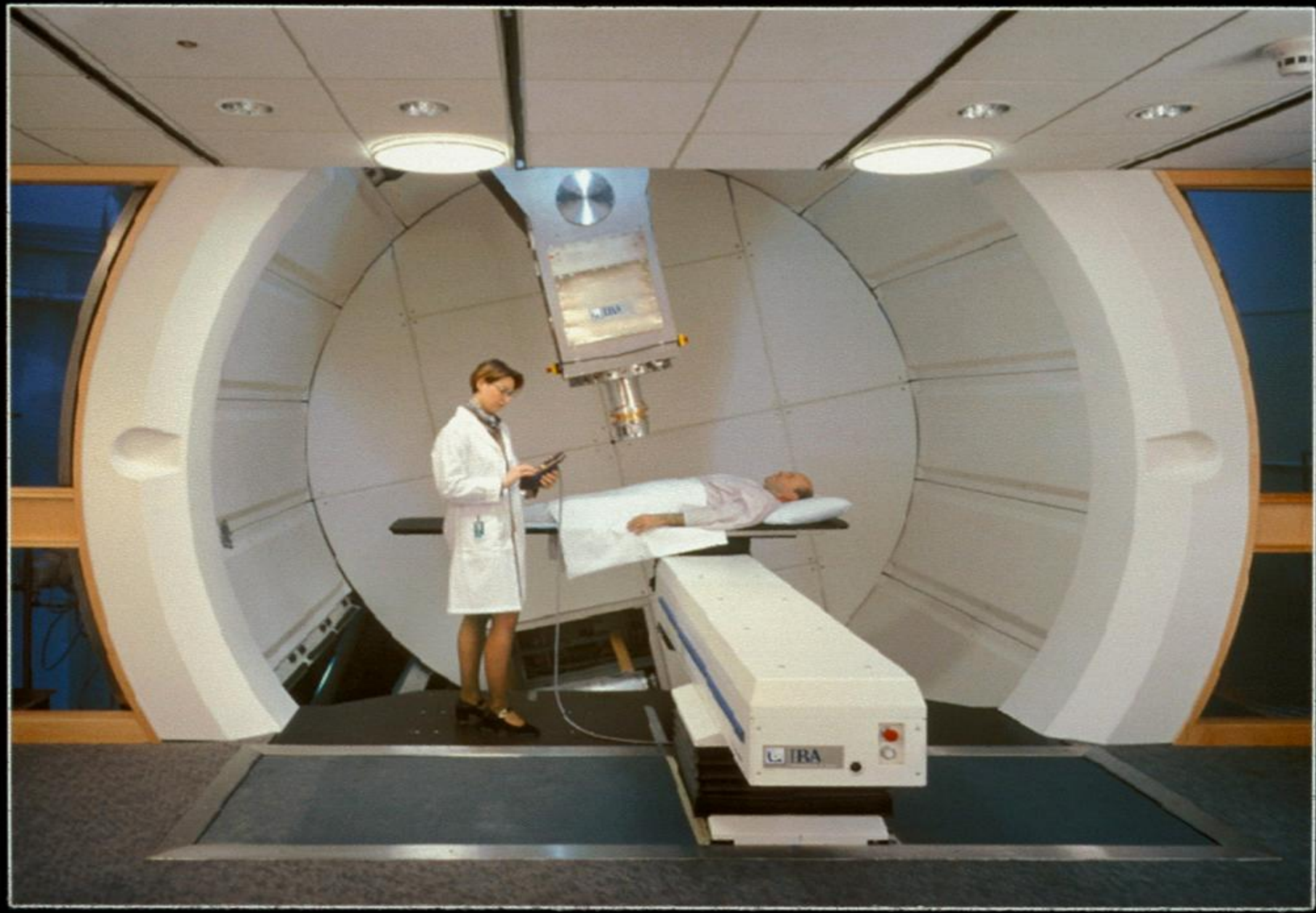
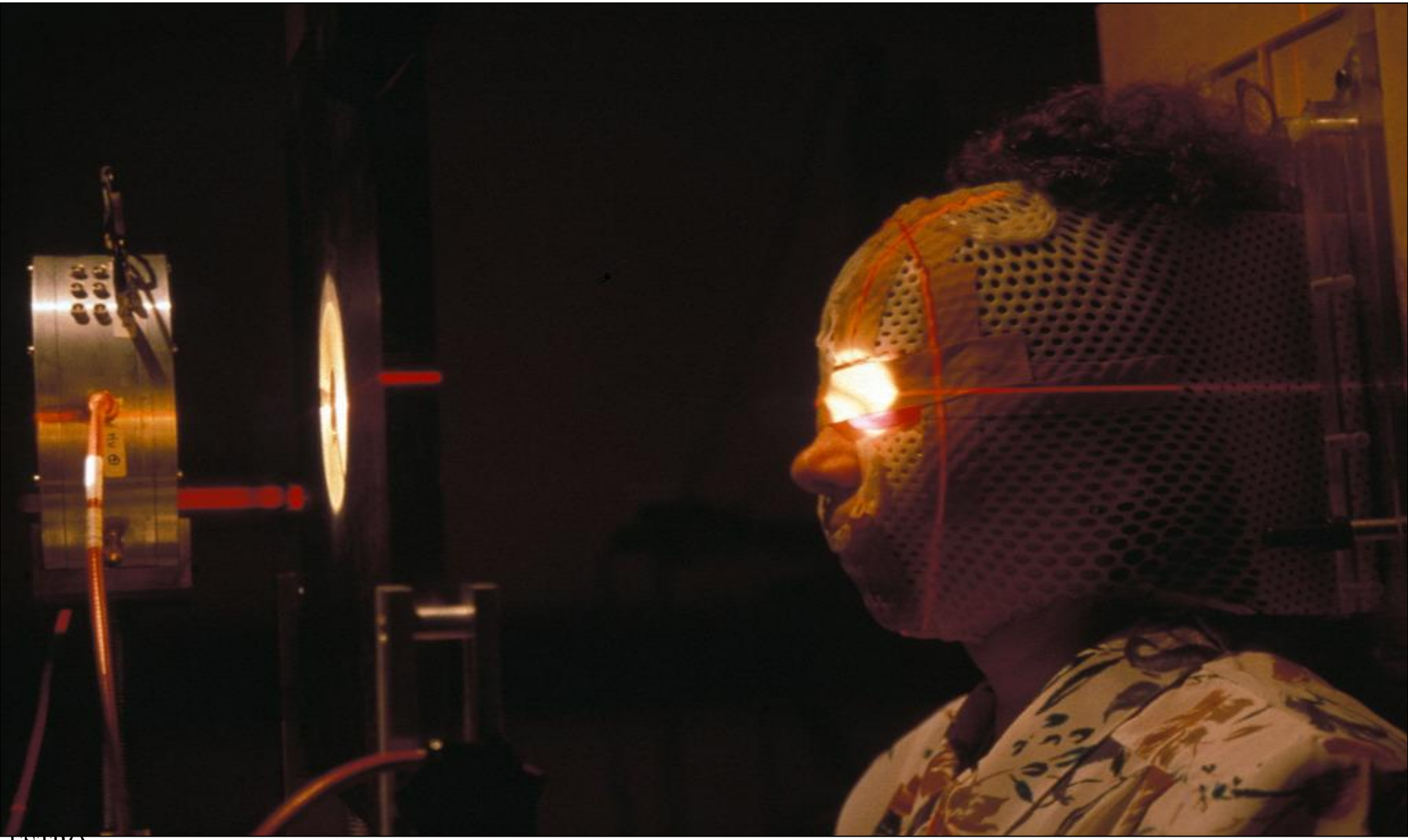
Isocentric Gantry at the NPTC





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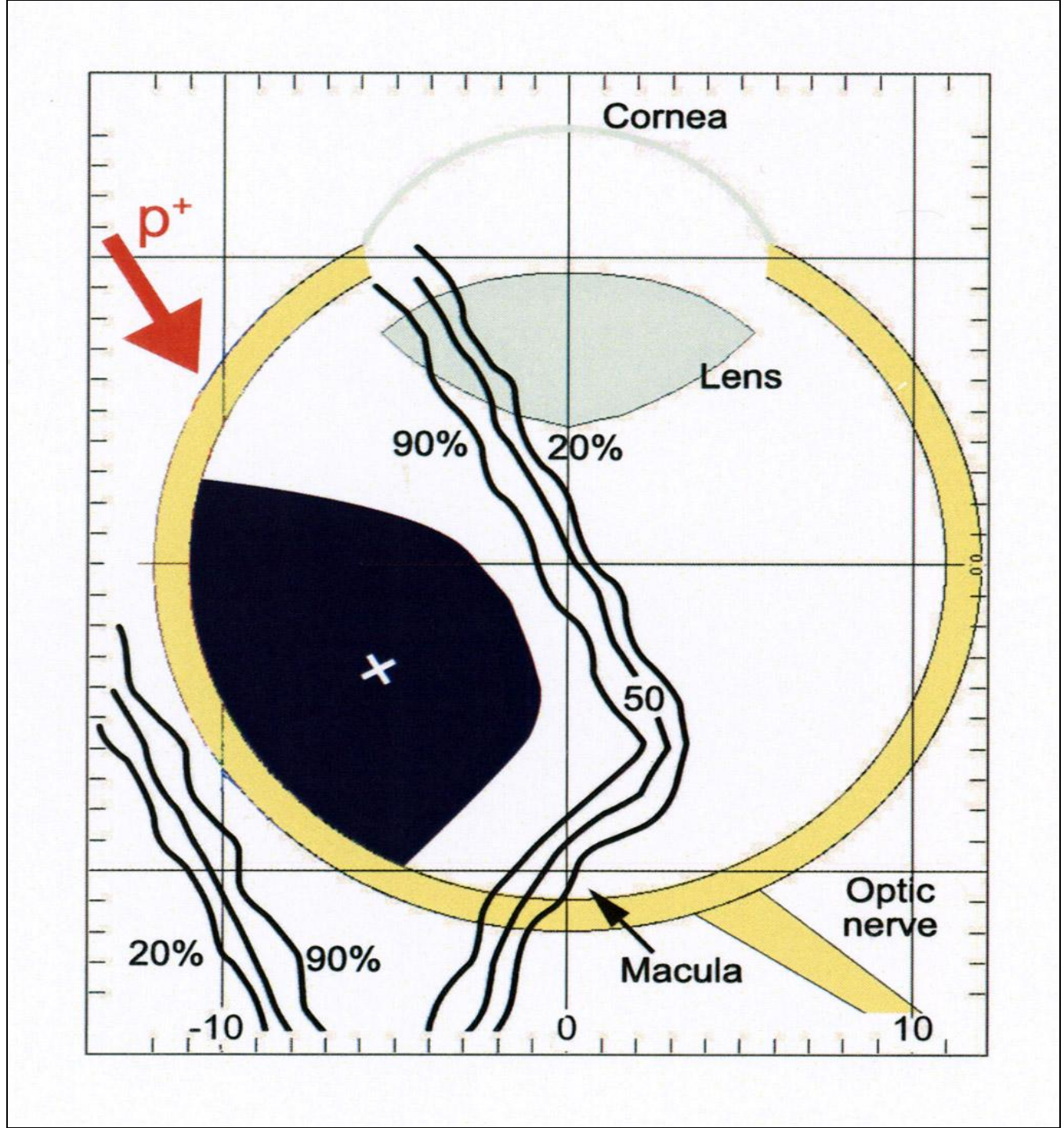
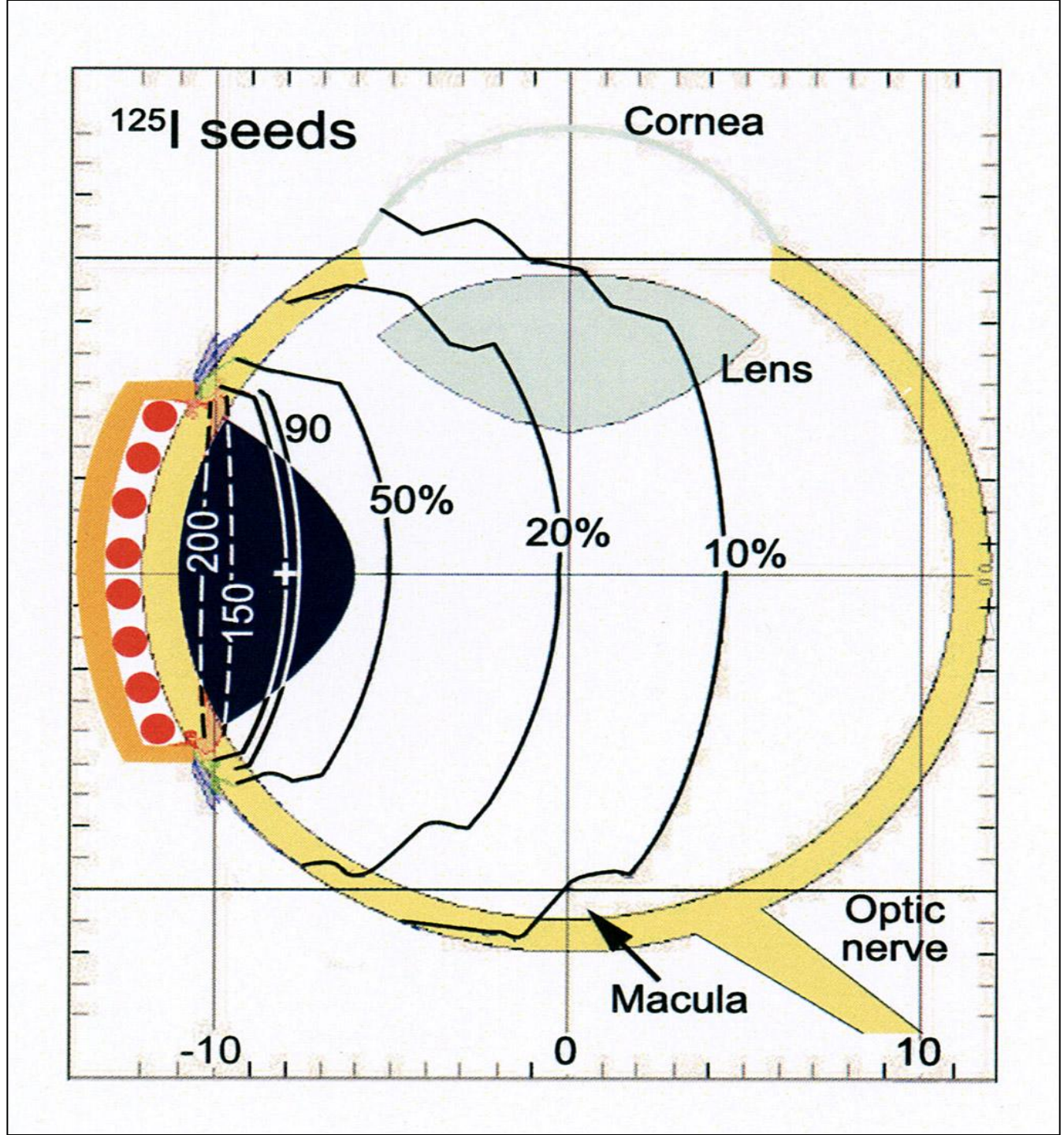

Cornea
p+
Lens
90%
20%
50
20%
90%
Optic
nerve
Macula
-10
0
10


^{125}I seeds
Cornea
Lens
90
50%
20%
10%
200
150
Optic nerve
Macula
-10
0
10

Proton beam, IMPT, … for a bone sarcoma

scattered

scanned (uniform)

scanned IMPT

single beam

three beams

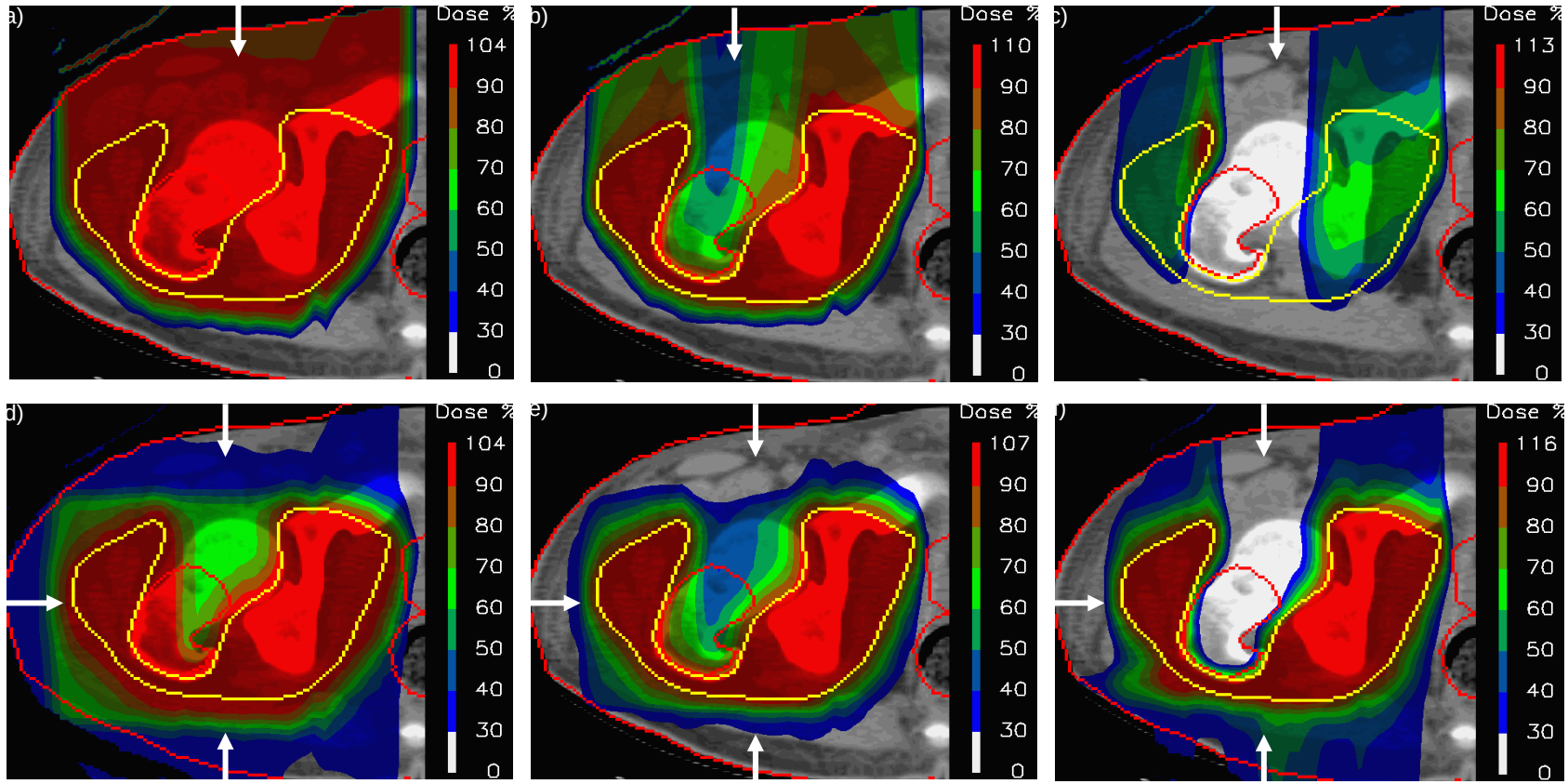


Image from M. Goitein, Radiation Oncology: A physicist's-eye-view Springer, 2007.

IMRT and IMPT for Ewing sarcoma

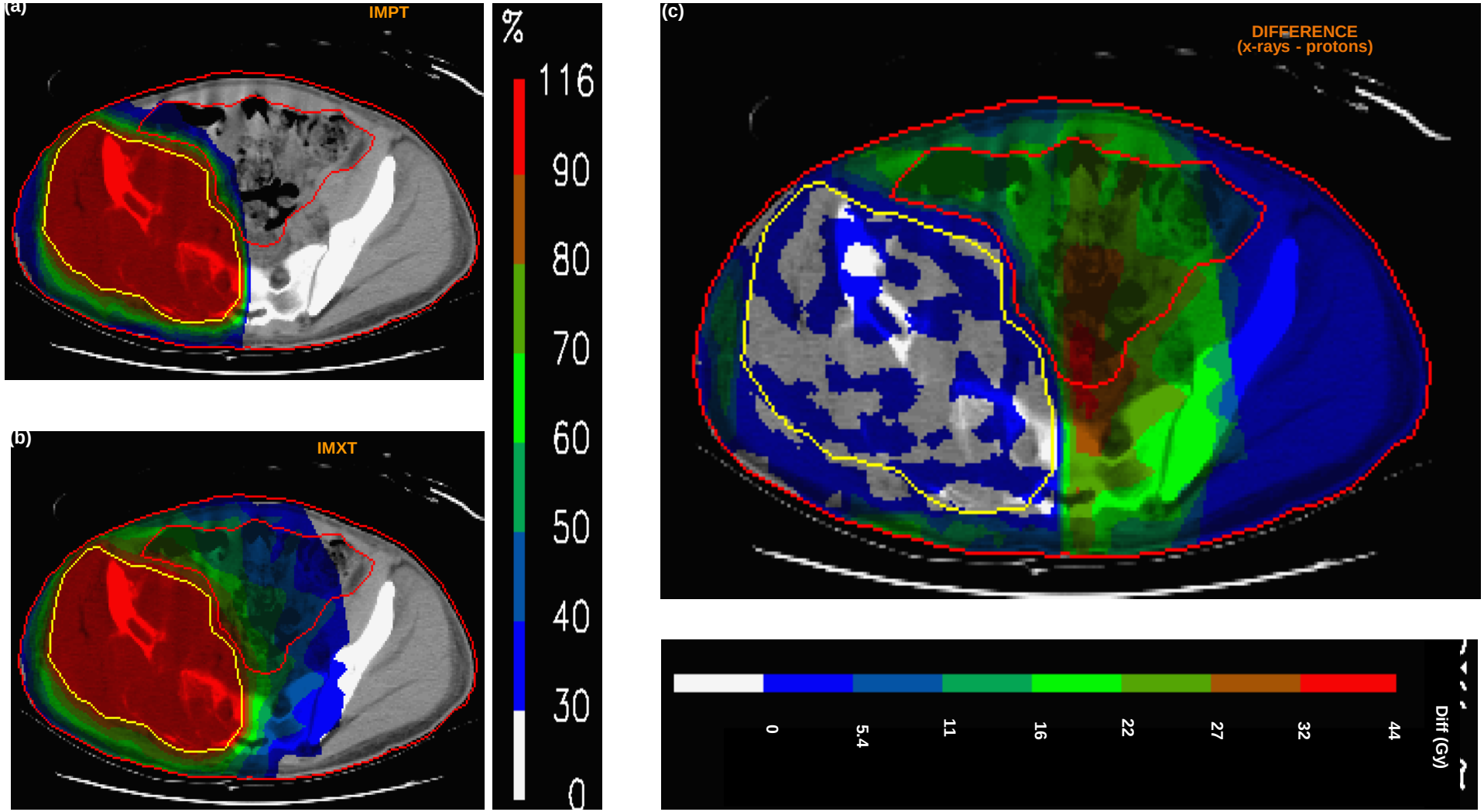


Image from M. Goitein, Radiation Oncology: A physicist's-eye-view Springer, 2007.

IMPT for a nasopharyngeal carcinoma

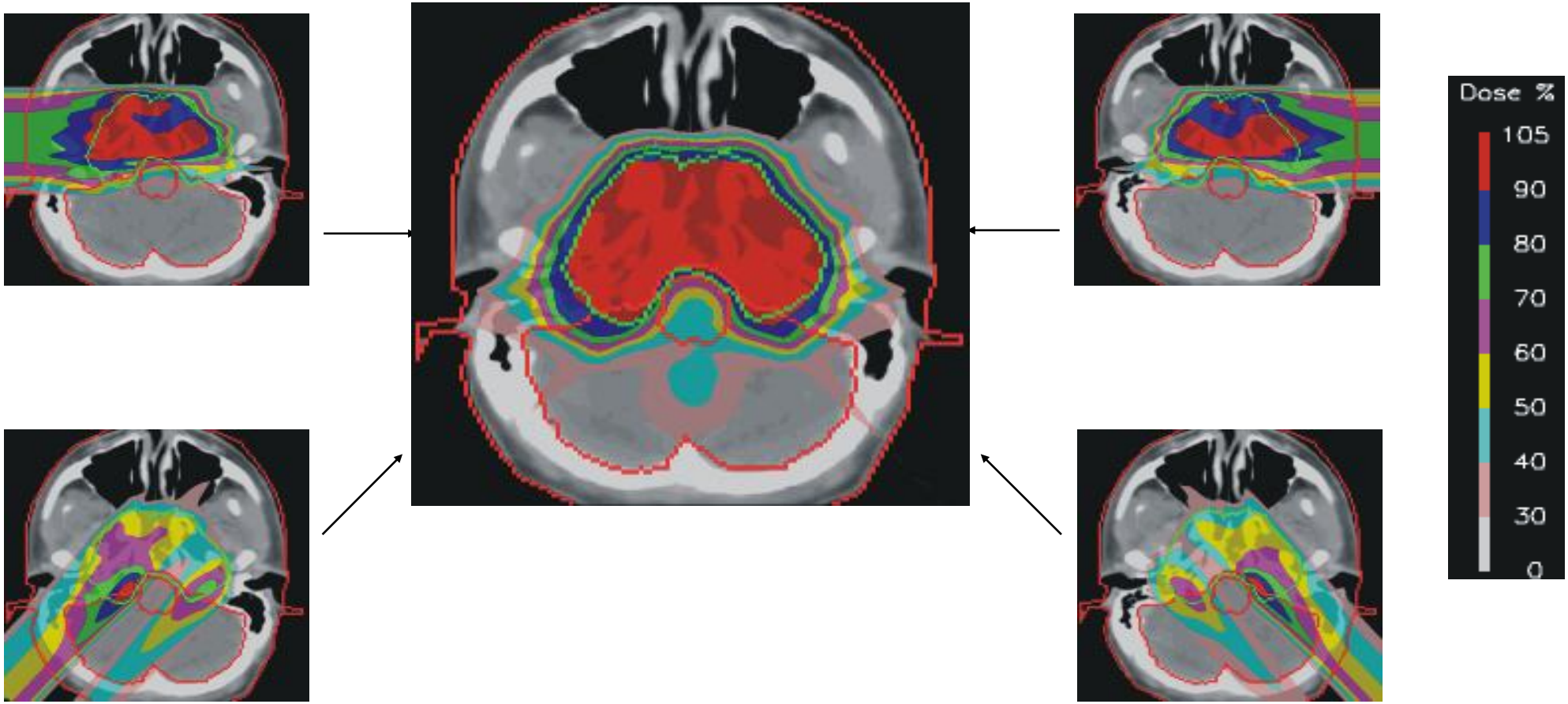


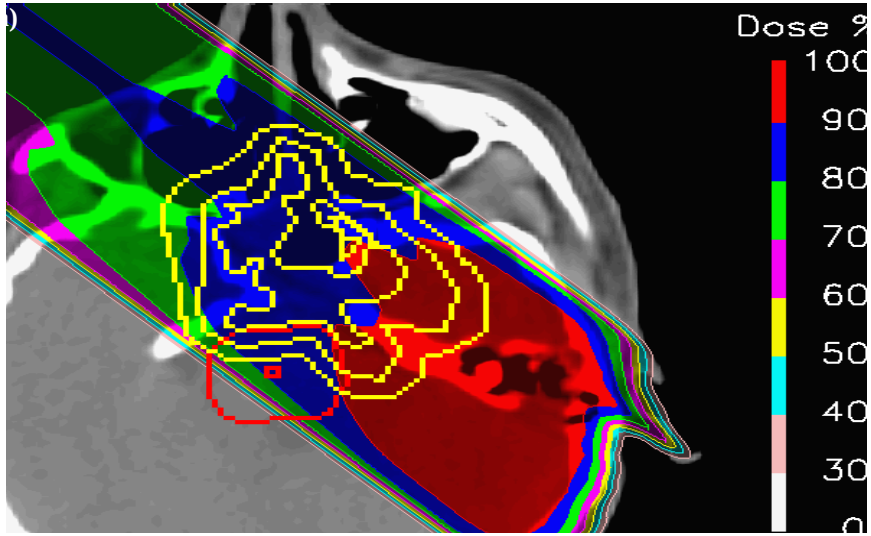
Image from M. Goitein, Radiation Oncology: A physicist's-eye-view Springer, 2007.

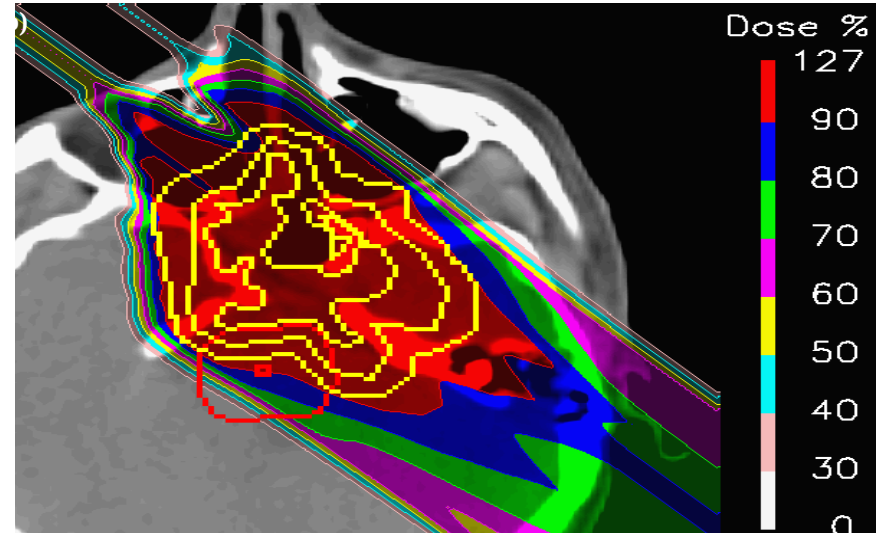
Single beam, IMRT and IMPT for meningioma

photons

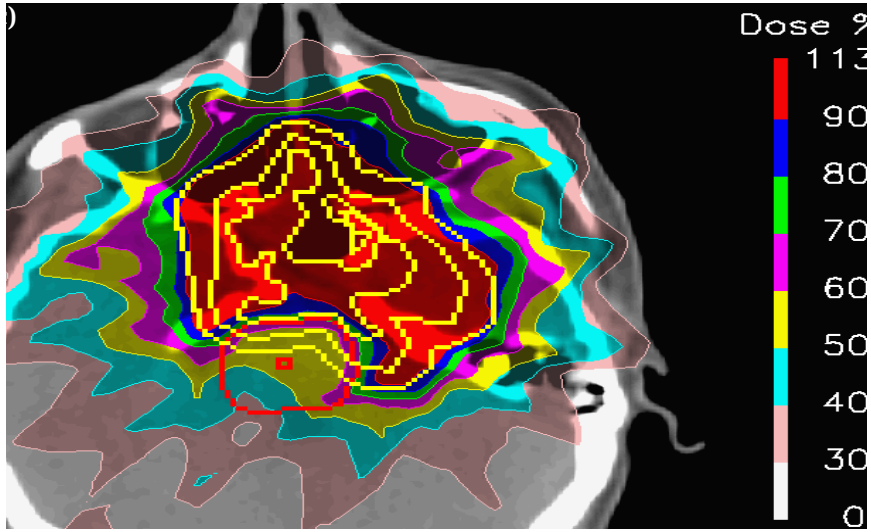
protons

single beam





IMRT



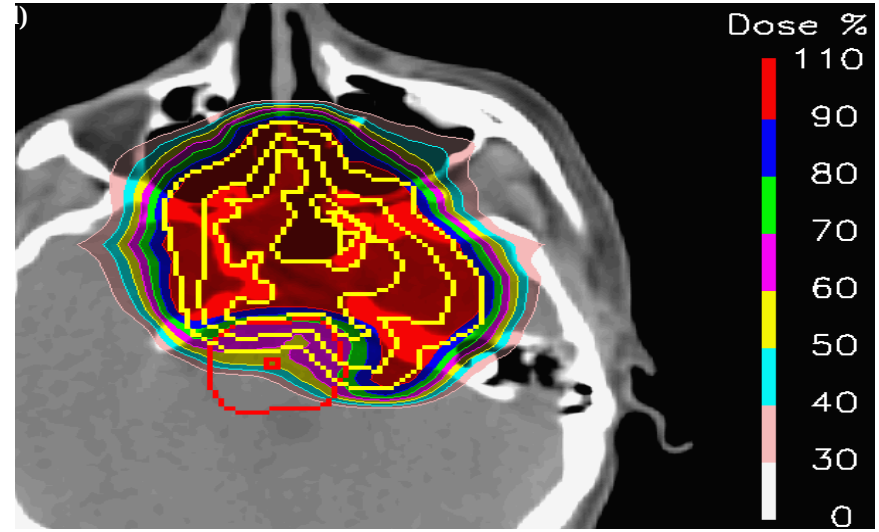


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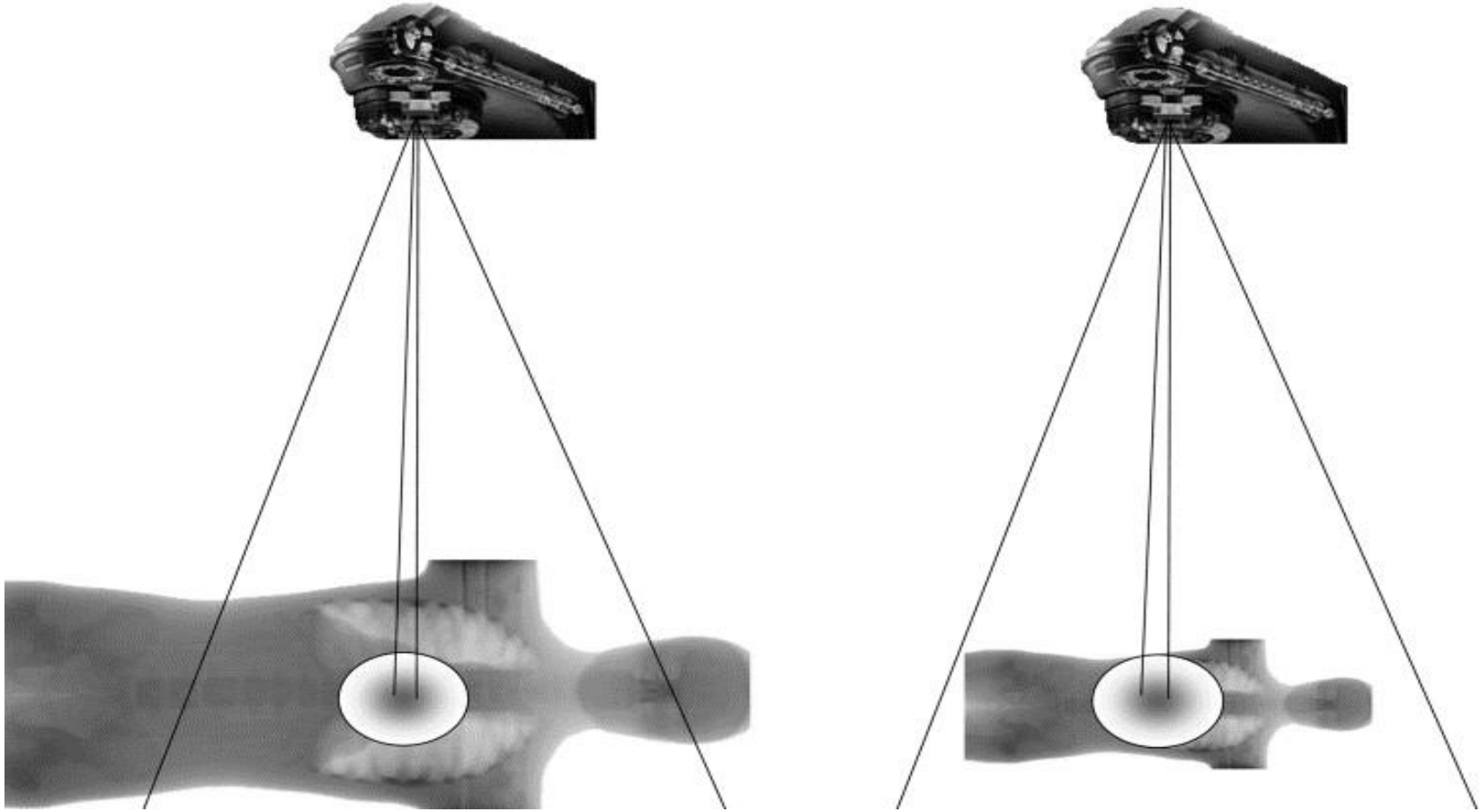
Image from M. Goitein, Radiation Oncology:
A physicist's-eye-view Springer, 2007.

IRRADIATION OF CHILD

Same Leakage for Adult RT vs. Pediatric RT — But in Pediatric RT Scatter from the Treatment Volume Is More Significant



Hall, 2006

PROTON THERAPY: CLINICAL RESULTS

PRIMARY TUMOR	D_{RBE} Gy (RBE)	NUMBER OF PATIENTS	LOCAL CONTROL	REFERENCE
Uveal melanoma	70 in 5 Fx	990 1922	99 % at 5 yr 96 % at 10 yr	Egger *et al*. (2001) Gragoudas *et al*. (2002)
Skull base chondrosarcoma	~ 69	202	95 % at 10 years	Liebsch, N., Personal communication (2005)
Chordoma	~ 69	132	59 % / 44 % at 5 / 10 yr	Terahara *et al*. (1999)
Prostate TIII - TIV (photons ± proton boost)	67.2 vs. 75.6 (Phase III trial)	202	80 % vs. 92 % at 5 yr 60 % vs. 77 % at 8 yr	Shipley *et al*. (1995)
Prostate TIa - TII	74	1255	75 % / 73 % biochemical disease-free survival at 5 / 8 yr	Slater *et al*. (2004)
Prostate TI - TII (photons ± proton boost)	70.2 vs. 79.2	393	61.4% vs. 80.4% at 5 yr	Zietman *et al*. (2005)
Non-small cell lung cancer. Stage I	73.8	27	86% at 2 yr	Bush *et al*. (2004a)
Hepatic cancer	72 (16 Fx in 29 days) 63 (15 Fx in 3	162 34	87 % at 5 yr 75% at 2 yr	Chiba *et al*. (2005) Bush *et al*. (2004b)
Glioblastoma multiforme	90 BID in 5 weeks	23	34 % / 18 % survival at 2 / 3 yr	Fitzek *et al*. (1999)
Adenocystic carcinoma of the paranasal sinus	76 ± surgery	23	93% at 5 years	Pommier *et al*. (2005)
Axial skeleton: Chondrosarcoma Chordoma	 72.2 74.6	 6 14	 100% at 5 yr 53% at 5 yr	Hug *et al*. (1995)

PROTON THERAPY INDICATIONS

REGION	LESION
Brain and spinal cord	Isolated brain metastases Selected brain tumor recurrences Pituitary adenomas Arteriovenous malformations (AVMs)
Base of skull	Meningiomas Acoustic neuromas Chordomas and chondrosarcomas
Eye	Uveal melanomas Macular degeneration
Head and neck	Nasopharynx (primary and recurrent) tumors Oropharynx (locally advanced) tumors Paranasal sinus tumors
Chest and abdomen	Medically inoperable non-small-cell lung cancer Chordomas and chondrosarcomas Hepatic tumors Retroperitoneal tumors Paraspinal tumors
Pelvis	Prostate tumors Chordomas and chondrosarcomas
Pediatric lesions	Brain and spinal cord tumors Orbital and ocular tumors Sarcomas of the base of skull and spine Abdominal and pelvic tumors

PROTON THERAPY INDICATIONS

International Journal of
Radiation Oncology
biology • physics

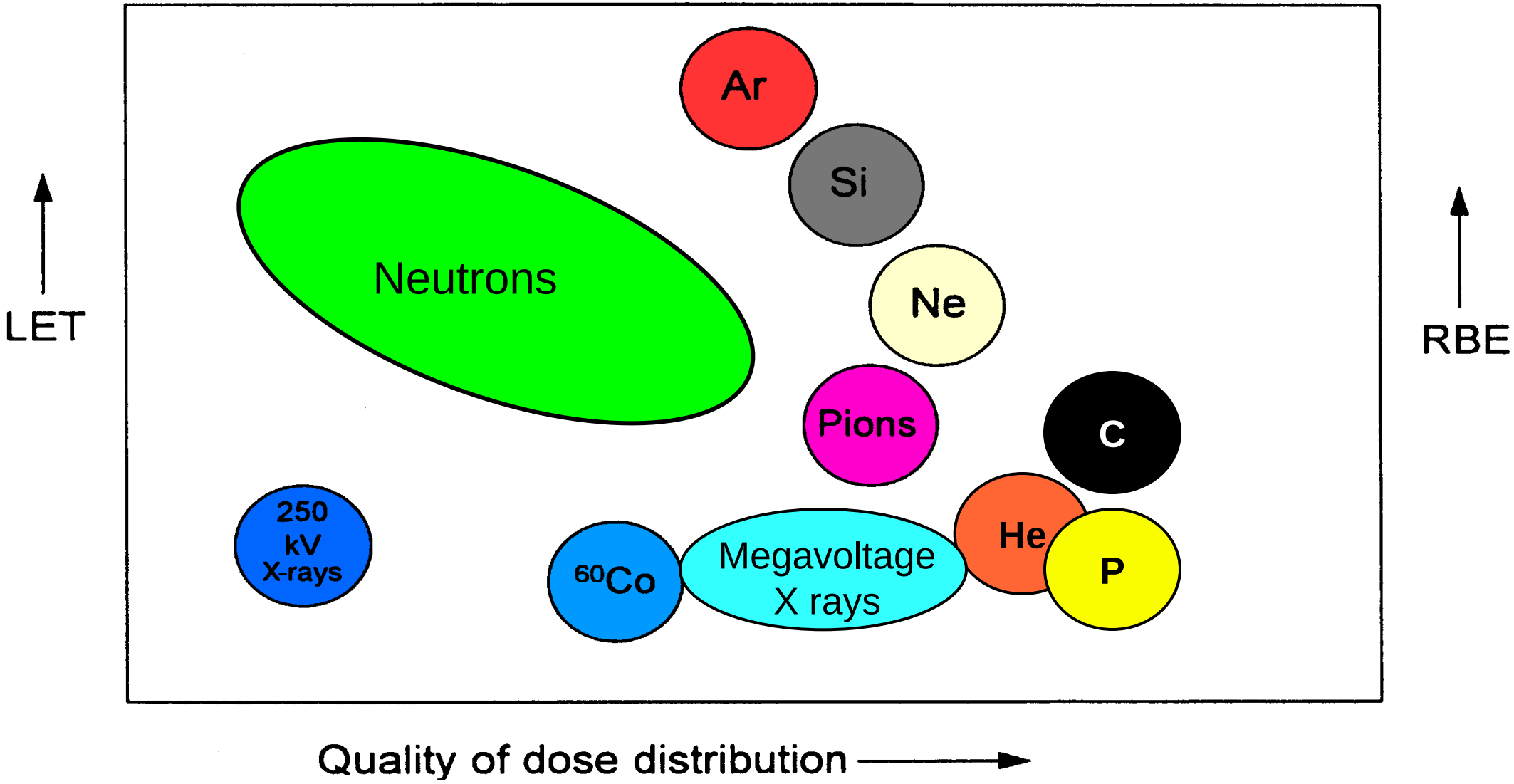
www.redjournal.org

POINT/COUNTERPOINT

Pediatric medulloblastoma: Is proton beam the only ethically appropriate radiation treatment?

Anthony Zietman, MD, FASTRO, *Editor-in Chief IJROBP*

Potential **clinical benefit** of ions


LET
RBE
Ar
Si
Neutrons
Ne
Pions
C
He
P
250 kV X-rays
60Co
Megavoltage X rays
Quality of dose distribution

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Salivary gland tumors

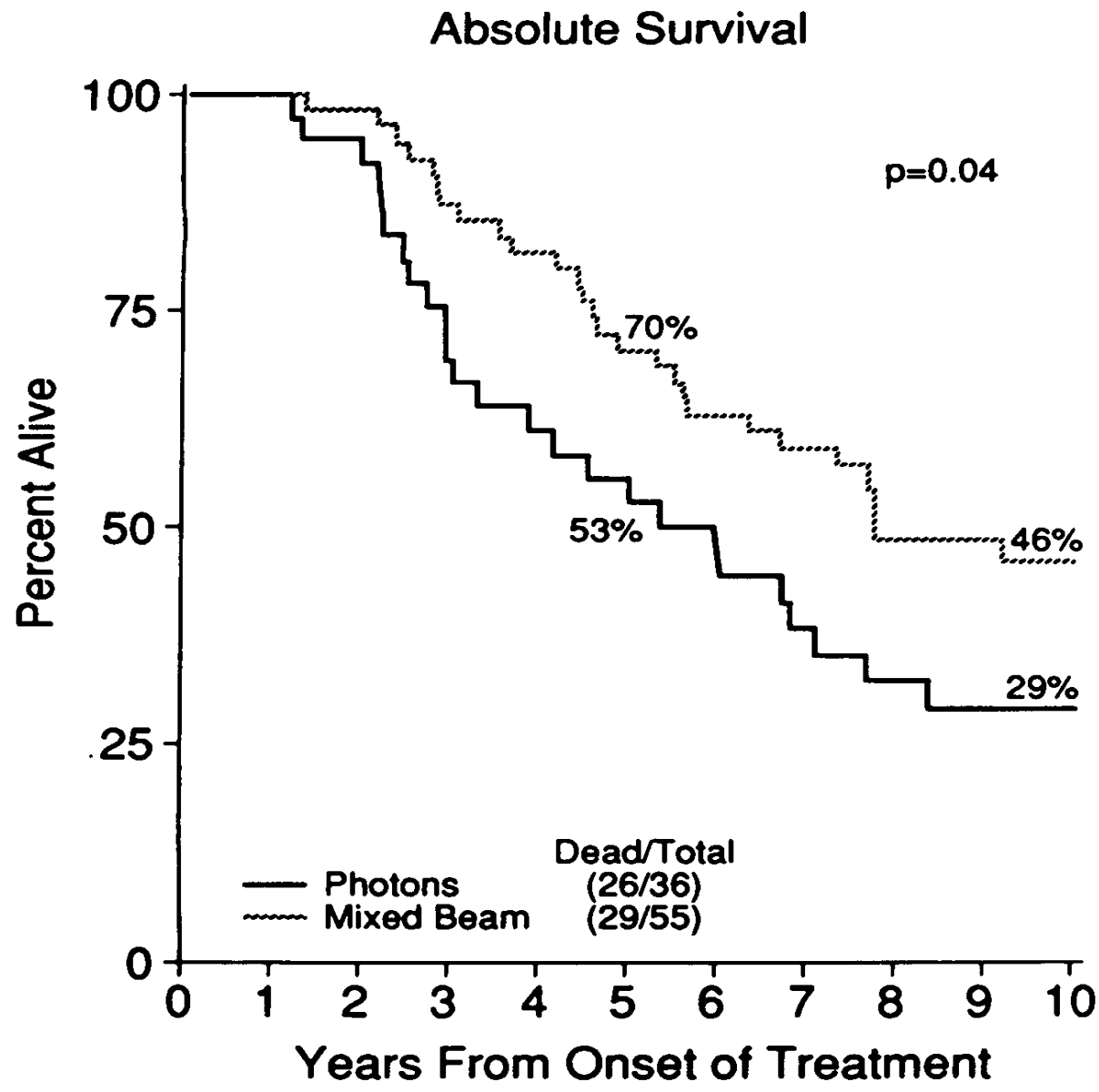
STUDY RESULTS

	TWO YEARS
LOCAL CONTROL	
* Photons	17% ± 11%
* Neutrons	67% ± 14%
SURVIVAL	
* Photons	25% ± 14%
* Neutrons	62% ± 14%

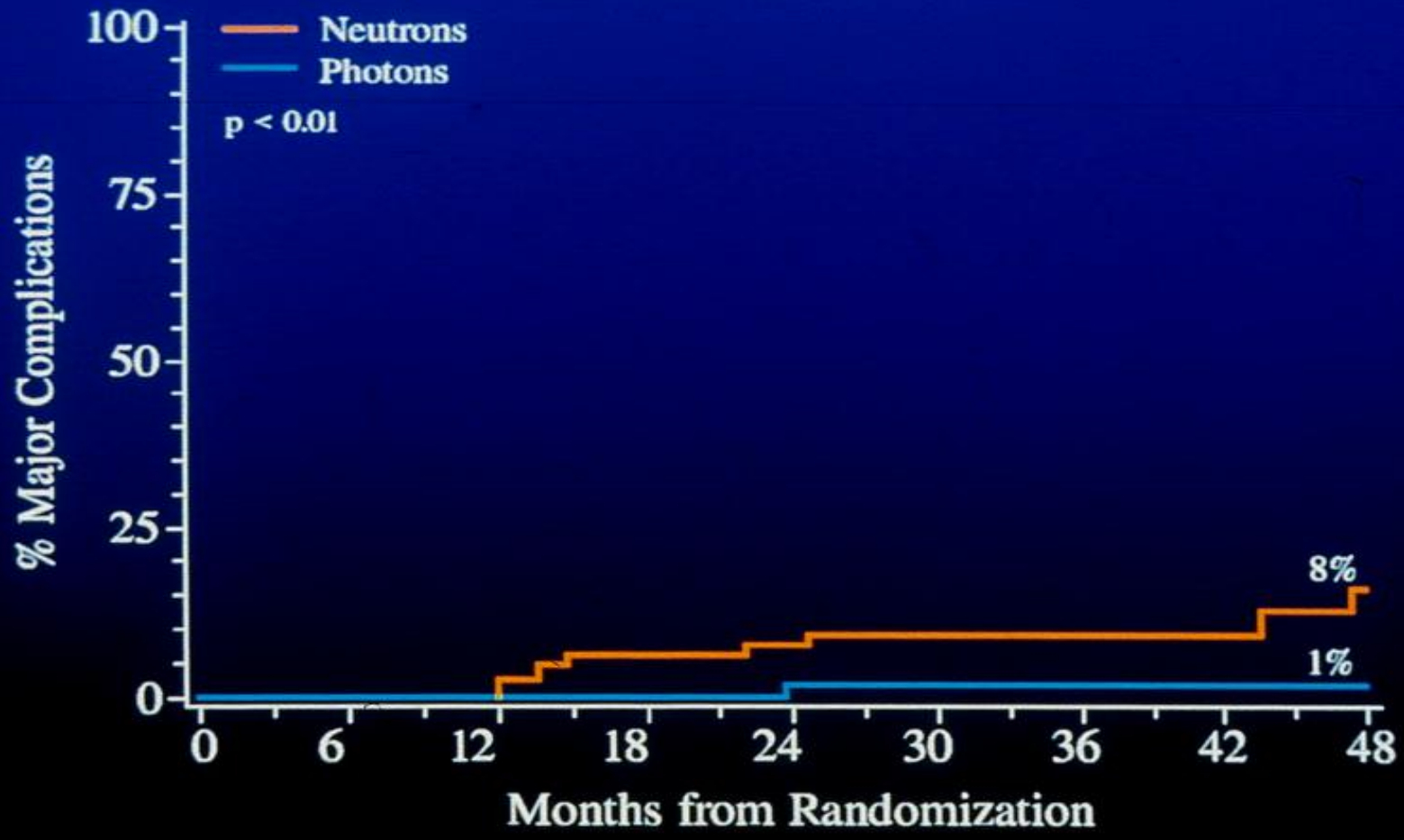
± 1985

Randomized clinical trial of photons vs mixed beam neutrons plus photons for prostate Ca

RTOG 77-04
Laramore *et al,* 1993.
Prostate carcinomas are slow growing and hence should be well suited for neutron therapy. The neutrons are usually used for the small “boost” volume in order to minimize late normal tissue damage.



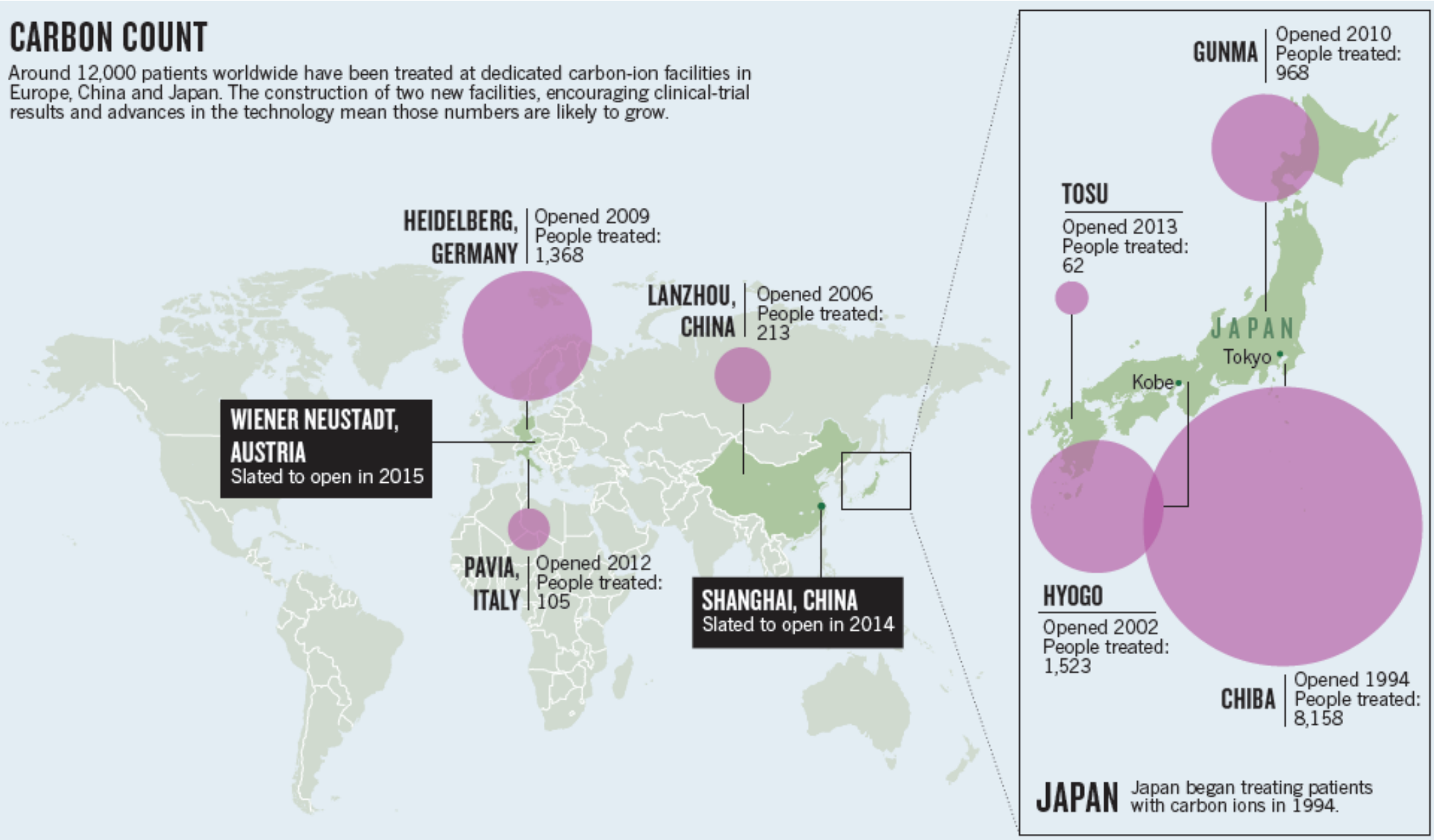
Neutron Prostate Study
Major Complications



Laramore, 1993

CARBON COUNT

Around 12,000 patients worldwide have been treated at dedicated carbon-ion facilities in Europe, China and Japan. The construction of two new facilities, encouraging clinical-trial results and advances in the technology mean those numbers are likely to grow.



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Nature April, 2014

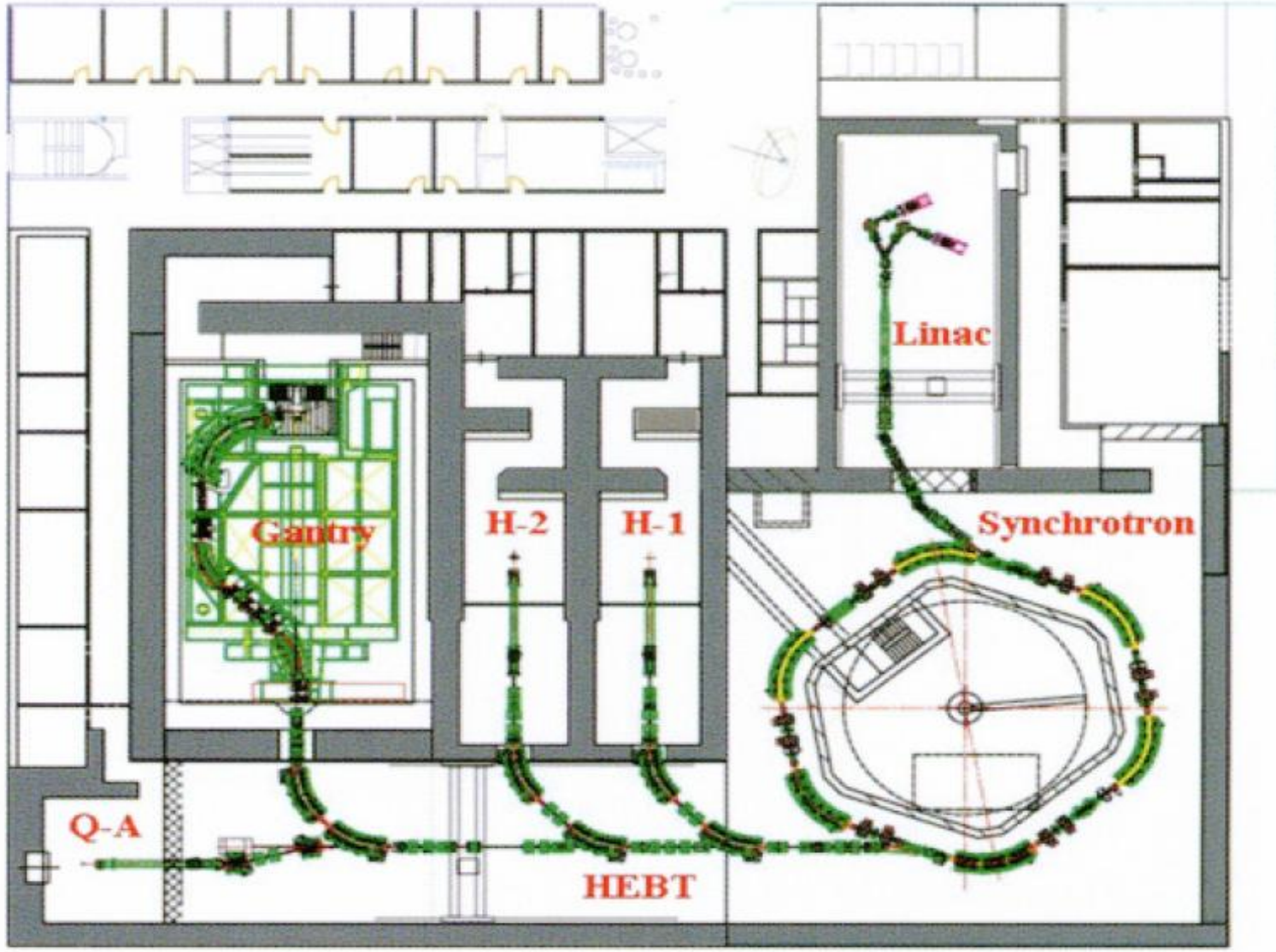
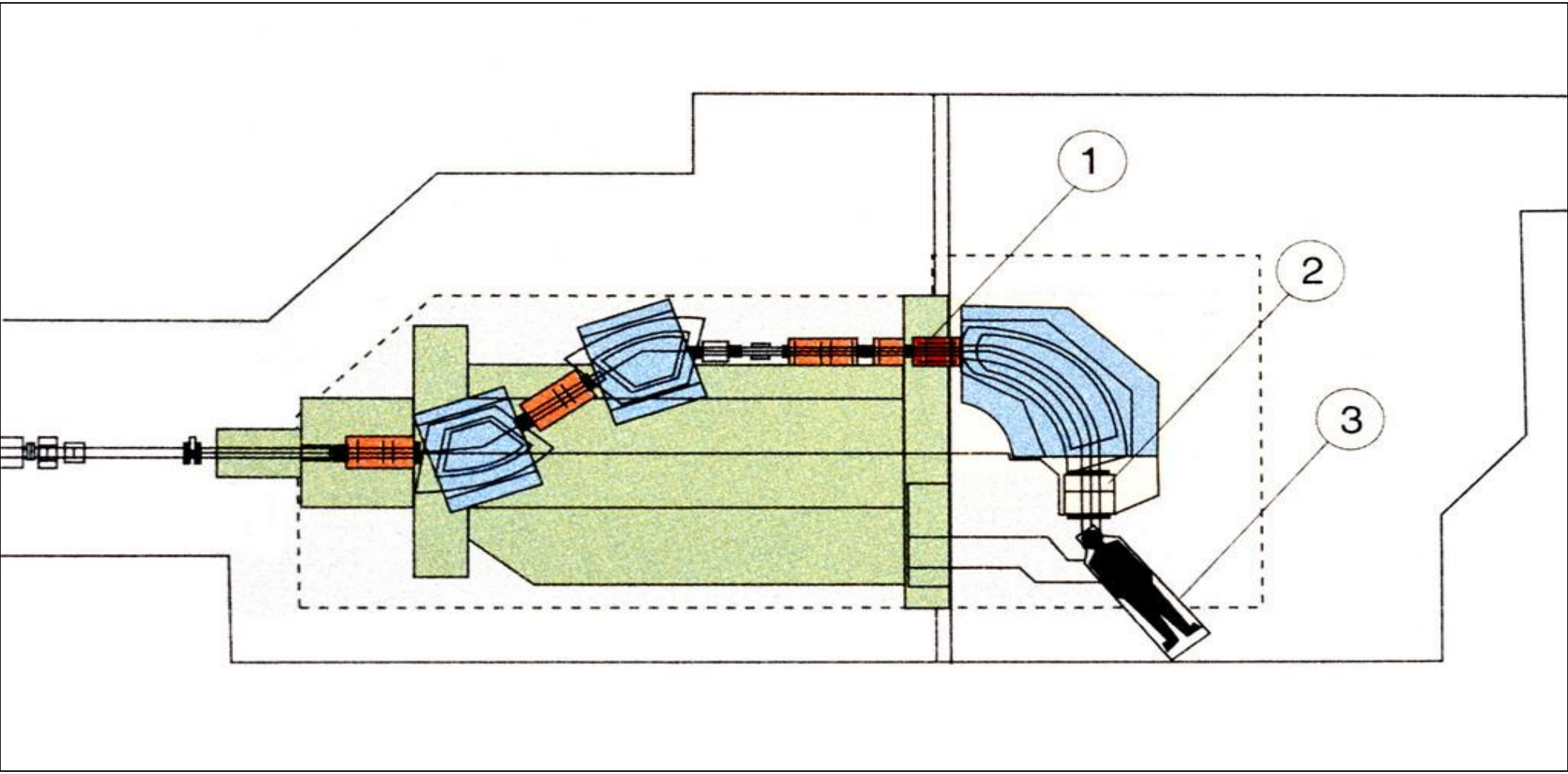
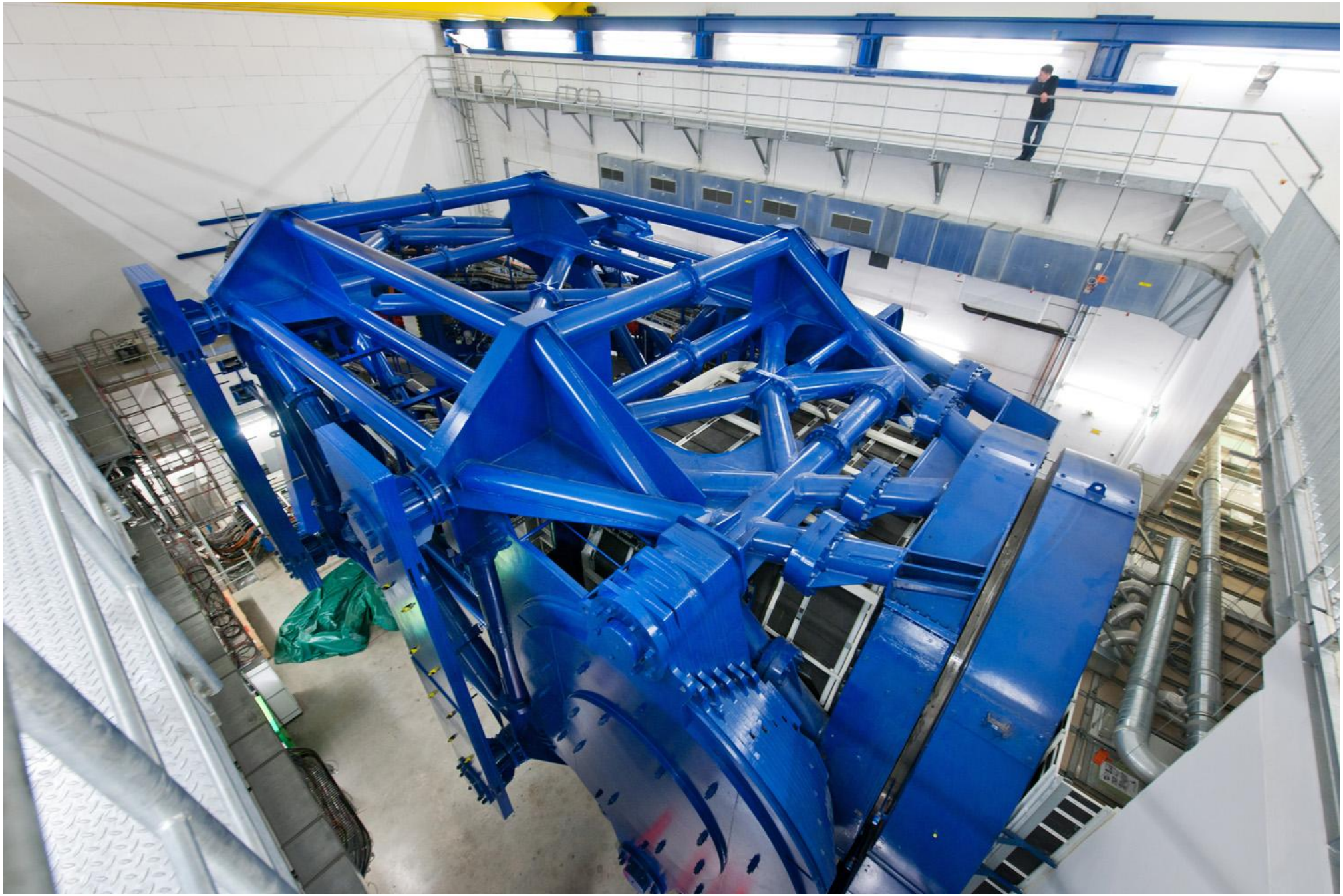


Fig.38: Ground plan of the layout of the HIT facility showing the ion source and the synchrotron from where the beam is guided to the two medical areas with fixed horizontal beam and to the gantry room.

View of the accelerating synchrotron. Dipole magnets (in red) at the left and right held the beam on its duty cycle while the quadrupoles (yellow) focus the beam.

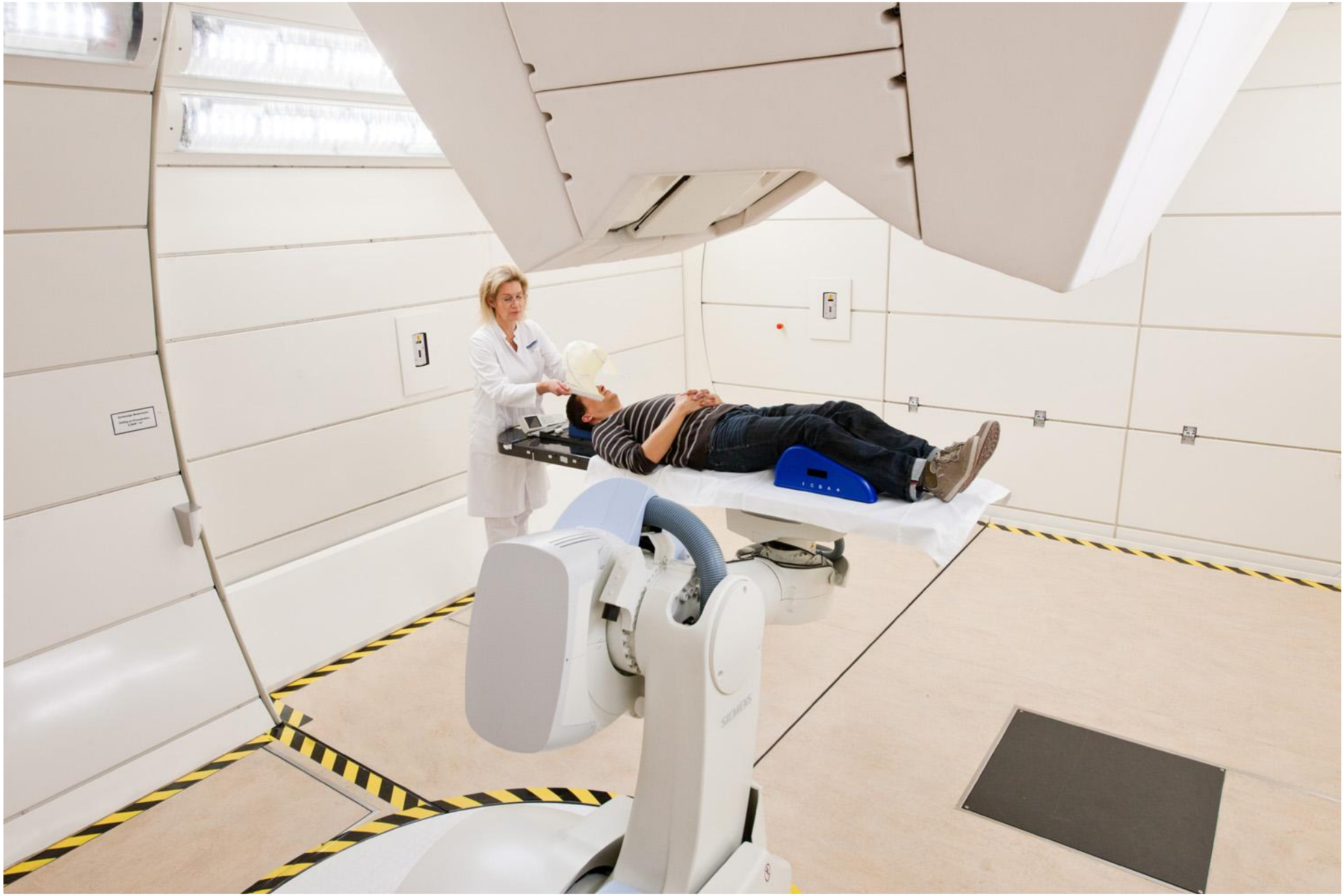

1
2
3



ESTRO 2015

ESTRO
2015

ESTRO
2015



ESTRO 2015

ESTRO
2015

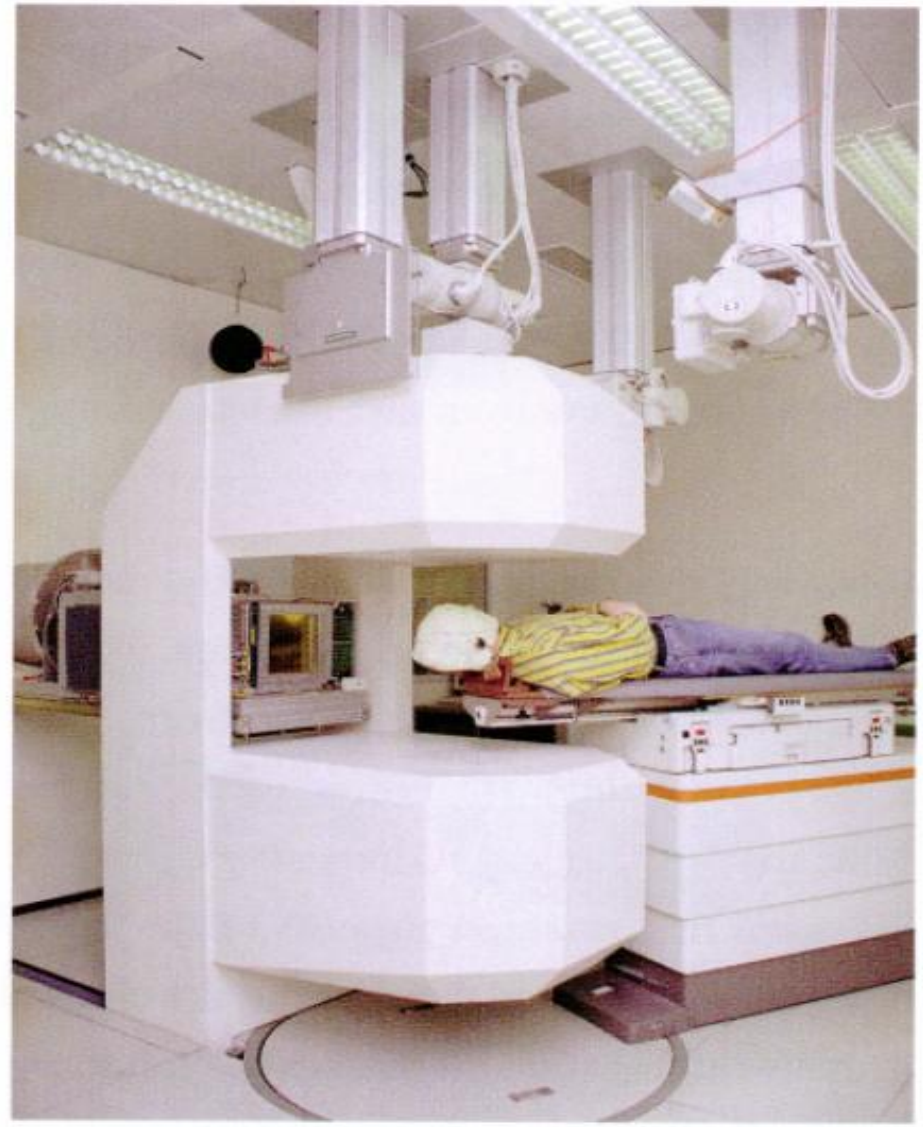
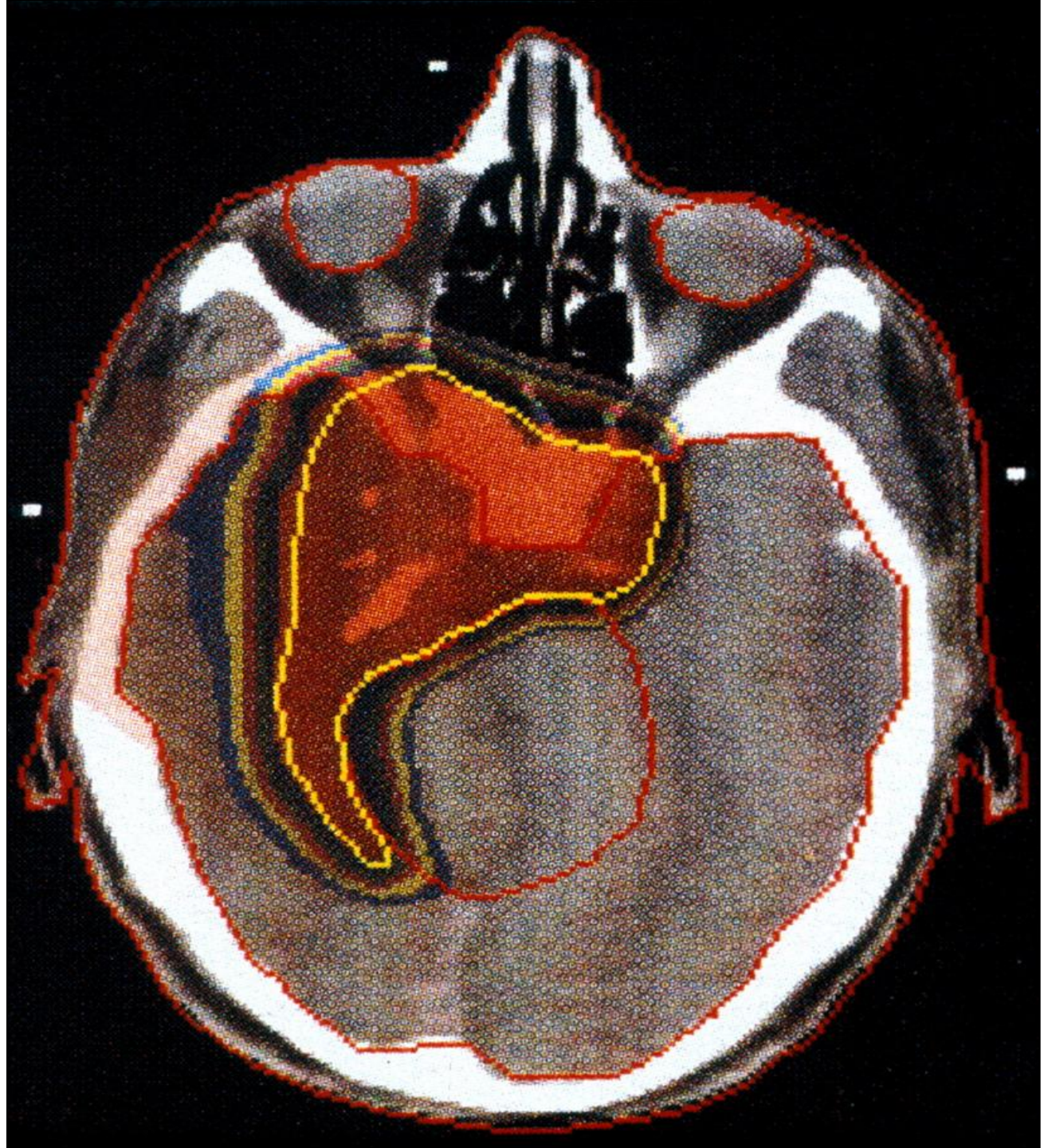


Fig.12: Patient positioned in front of the exit-window before irradiation. The X-ray equipment is removed and positioned at the ceiling. The two heads of the PET-camera are above and below the patient's head.



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Carbon Ion Therapy for Chordoma

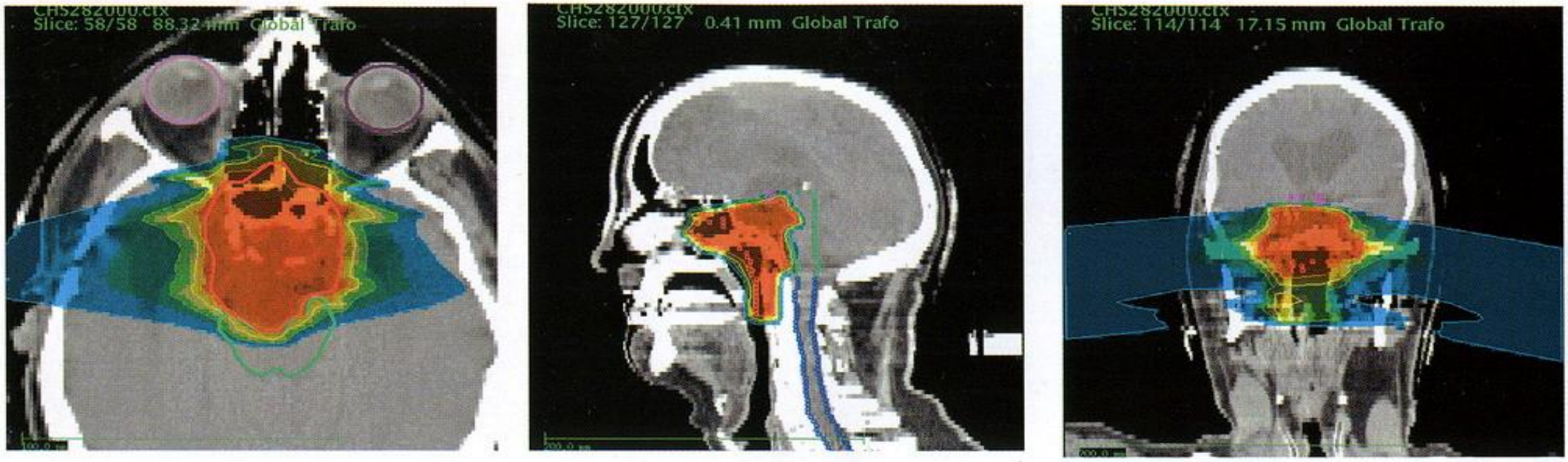


Figure 5 Three-dimensional biologically optimized dose distribution in a patient with skull-base chordoma treated with carbon ion RT, total dose 60 CGE in 20 fractions within 3 weeks. Red line = target volume, orange line = 90% isodose, yellow line = 70% isodose, green line = 50% isodose, blue line = 20% isodose line. Two opposed lateral fields were used.

Carbon Ions versus IMRT

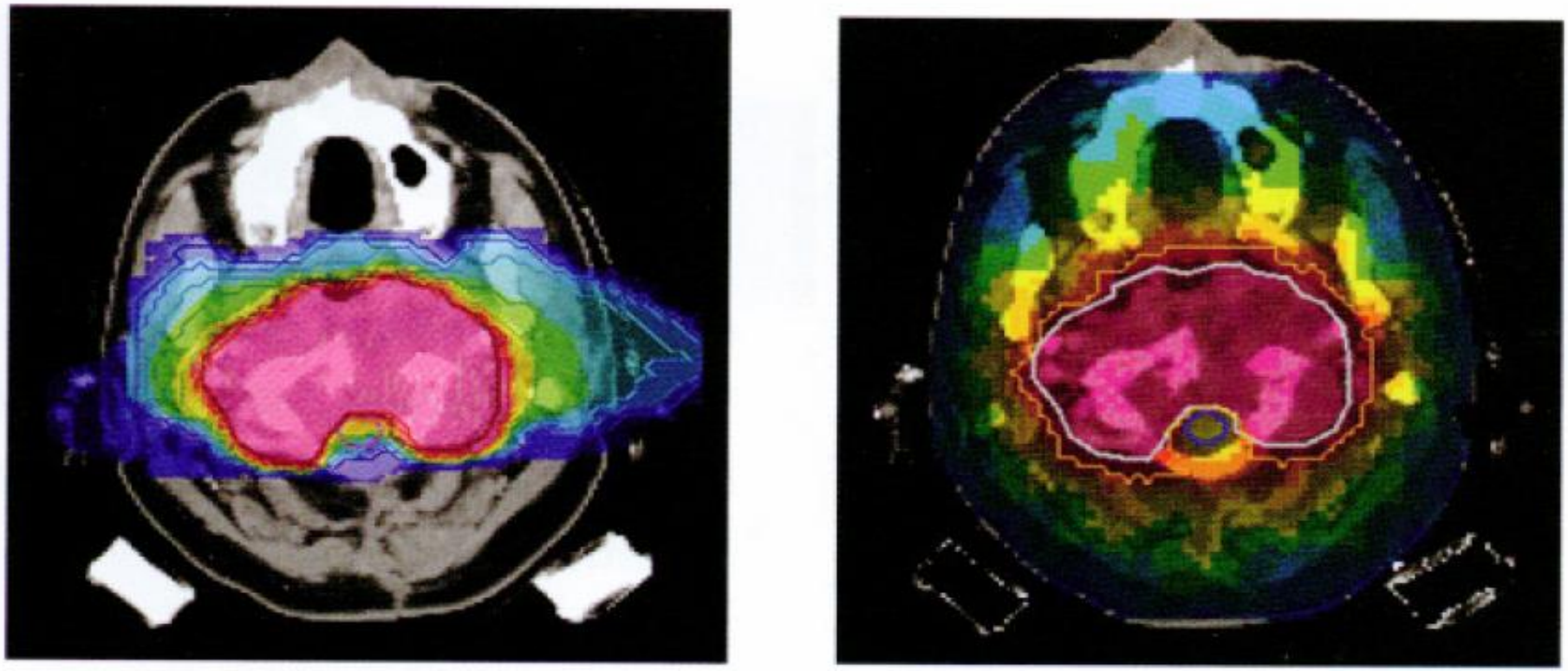


Fig. 4: Comparison of carbon irradiation (left) and photon irradiation (right). For photon IMRT, nine channels are used which distribute the dose to the normal tissue. For carbon therapy with a scanned beam, the dose in the only two entrance channels is much smaller than for IMRT.

IMRT, protons, IMPT and Carbon Ions

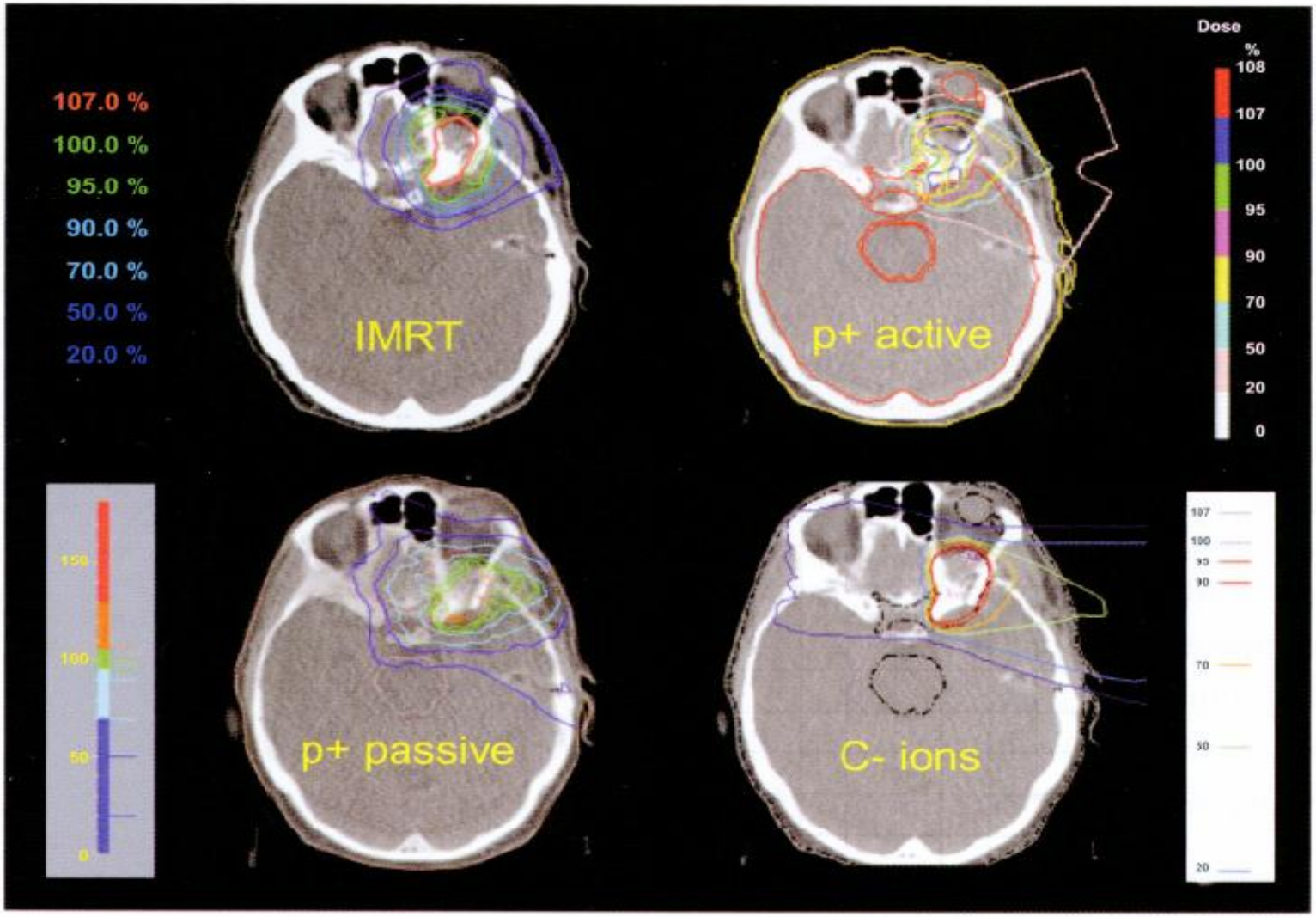
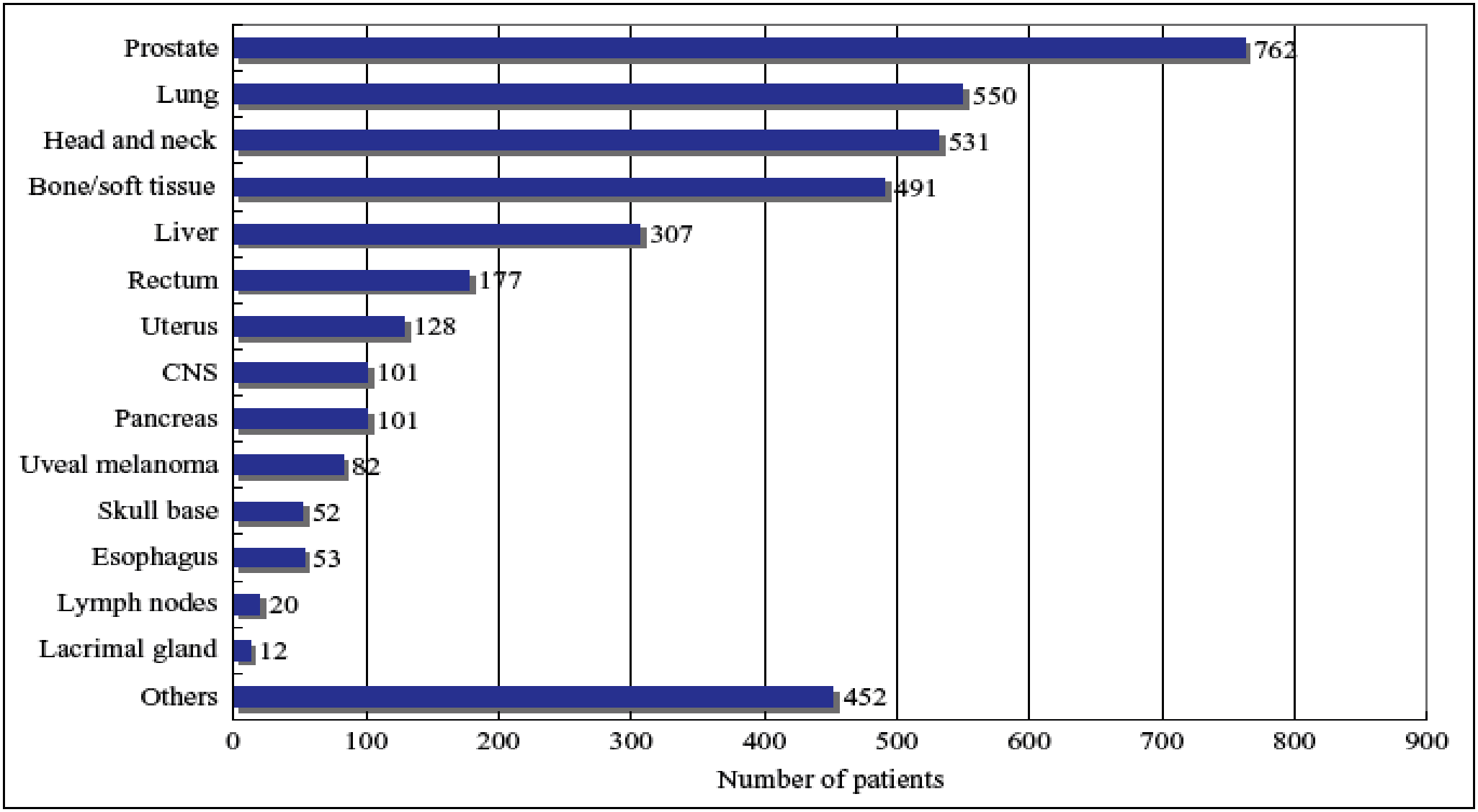


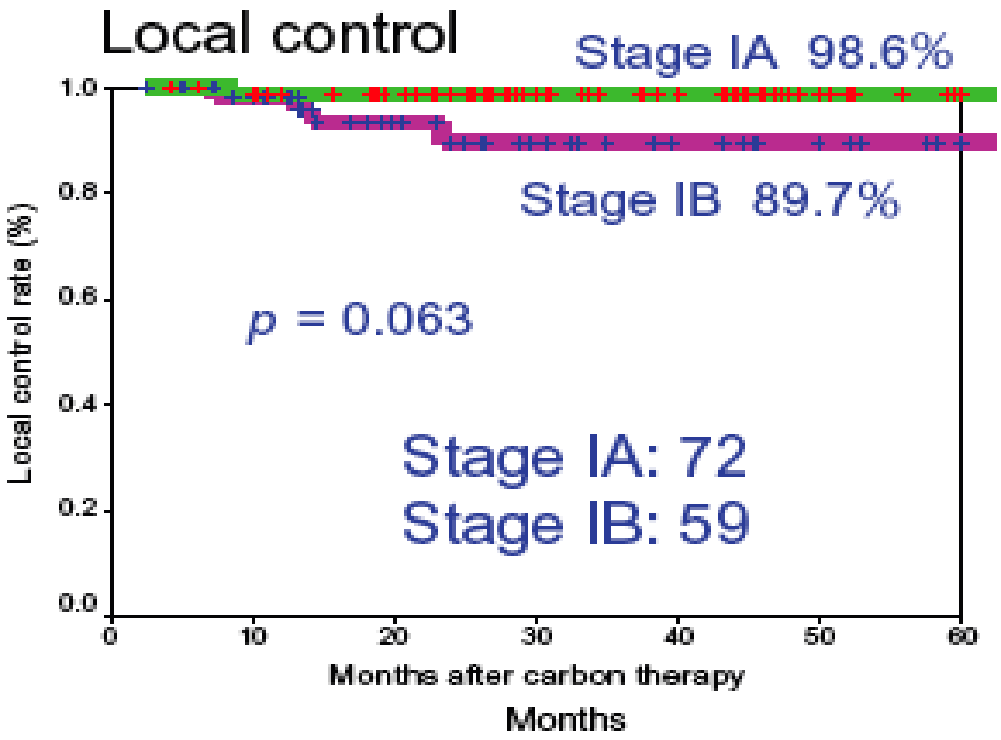
Fig.29: Comparison of the planned dose distributions of a carcinoma in the front part of the head. Upper left: IMRT planning with high energy photons. Lower left: passive proton application. Upper right: active application of protons. Lower right active application of carbon ions which yields the best dose distribution. (These figures are supplied by Dr. M. Krengli, CNAO, Italy.)

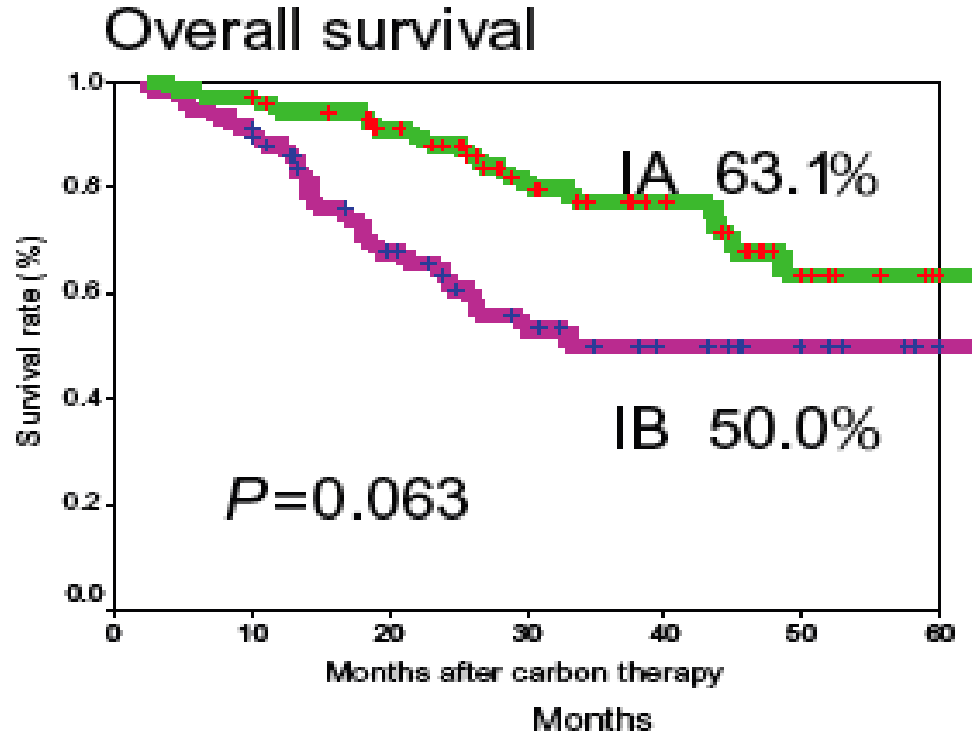
Carbon Ion Therapy at NIRS



Tsujii, 2008

Carbon Ion Therapy for stage I NSCLC at NIRS (4 or 9 fractions)





Tsujii, 2008

Ion Therapy versus photons at NIRS

indication	end point	results, photons	results, ions -NIRS-	results, ions -GSI-
Nasopharynx carcinoma (advanced state)	5y-S	40 - 50 %	63 %	
Chordoma	LCR	30 - 50 %	65 %	70 %
Chondrosarcoma	LCR	33 %	88 %	89 %
Glioblastoma	AST	12 month	16 month	
Choroid melanoma	5y-S	95 %	96 % preservation of eyesight	
Paranasal sinuses tumors	LCR	21 %	63 %	
Pancreatic carcinoma	AST	6.5 month	7.8 month	
Liver tumors	5y-S	23 %	100 %	
Salivary gland tumors	LCR	24 - 28 %	61 %	77.5 %
Soft-tissue carcinoma	5y-S	31 - 75 %	52 - 83 %	

LCR: local control rate
5y-S: 5 year survival

PFSR: survival without tumor growth
AST: average survival time

Carbon Ion Therapy for chordomas and chondrosarcomas

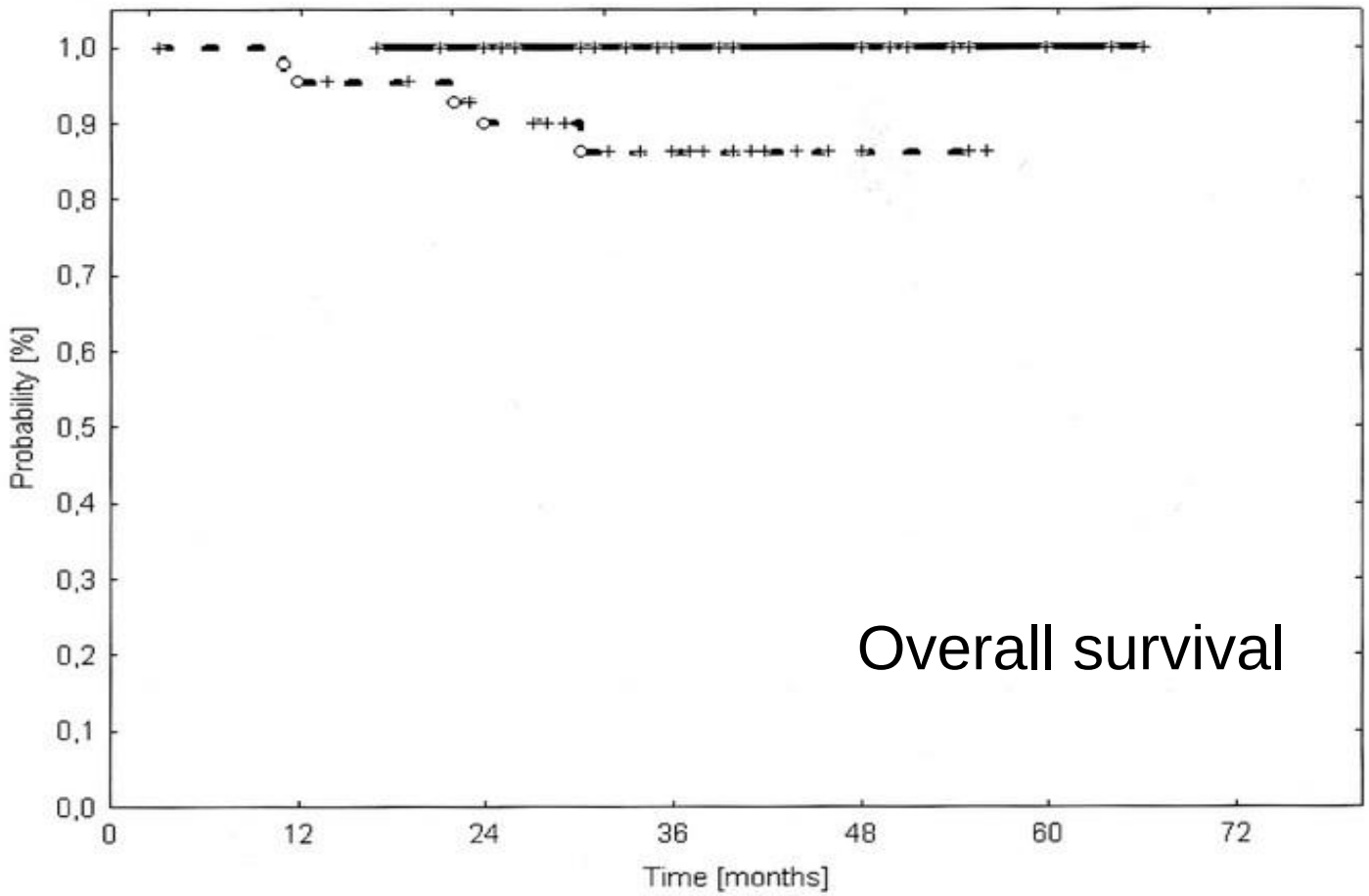


Figure 2. Actuarial overall survival (Kaplan Meier curve) for 67 patients treated with carbon ion RT for chordomas (dotted line, n=44) and low grade chondrosarcomas (solid line, n=23) of the skull base.

Schultz-Ertner, 2004

Carbon Ion Therapy versus protontherapy

Table 1 Treatment Results After Charged Particle RT for Skull-Base Chordomas

Author, Year	Patients (n)	RT Modality	Tumour-Dose (GGE)	Local Control
Munzenrider, 1999	375	Protons + Photons	66–83	73%/5 y
Hug, 1999	58	Protons	64.8–79.2	59%/5 y
Noel, 2003	67	Protons + Photons	67 (median)	71%/3 y
Schulz-Ertner, 2004	67	Carbon ions	60 (median)	74%/4 y

Potential indications of ions…?

Pending questions…
Are hadrons really needed?

- For which patients?
- With which setting?
- For which money?

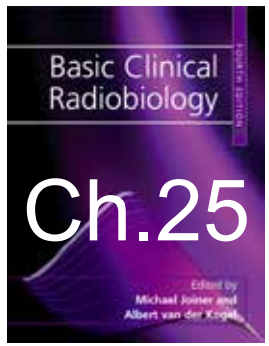
ESTRO School

Basic Clinical Radiobiology

Radiation-induced malignancies

Michael Joiner

Budapest 2016



Radiation
induced cancers

Radiotherapy
induced cancers

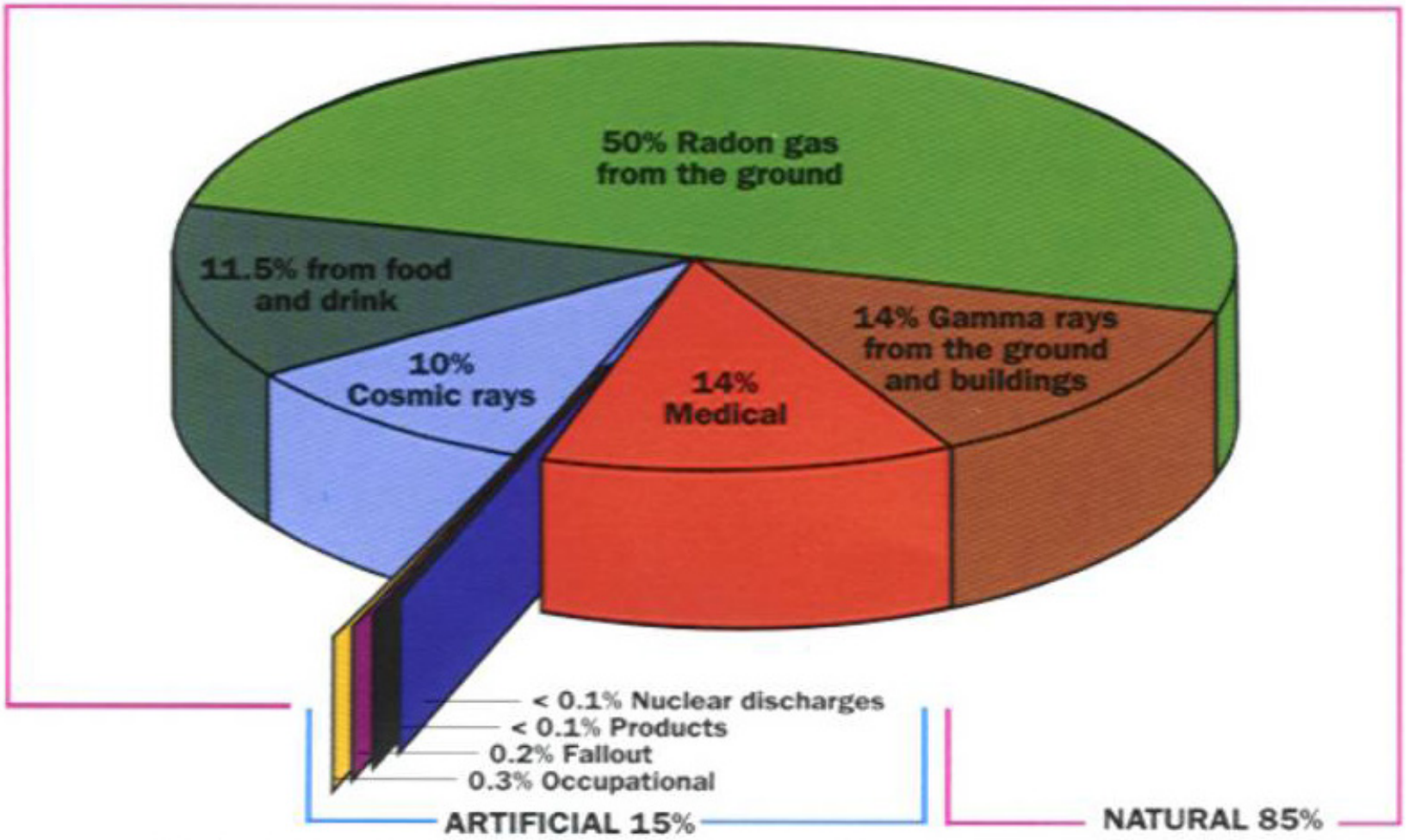
BED = Banana Equivalent Dose

0.5 g potassium per banana, 15 Bq radioactivity

37 MBq = 1 mCi

http://en.wikipedia.org/wiki/Banana_equivalent_dose

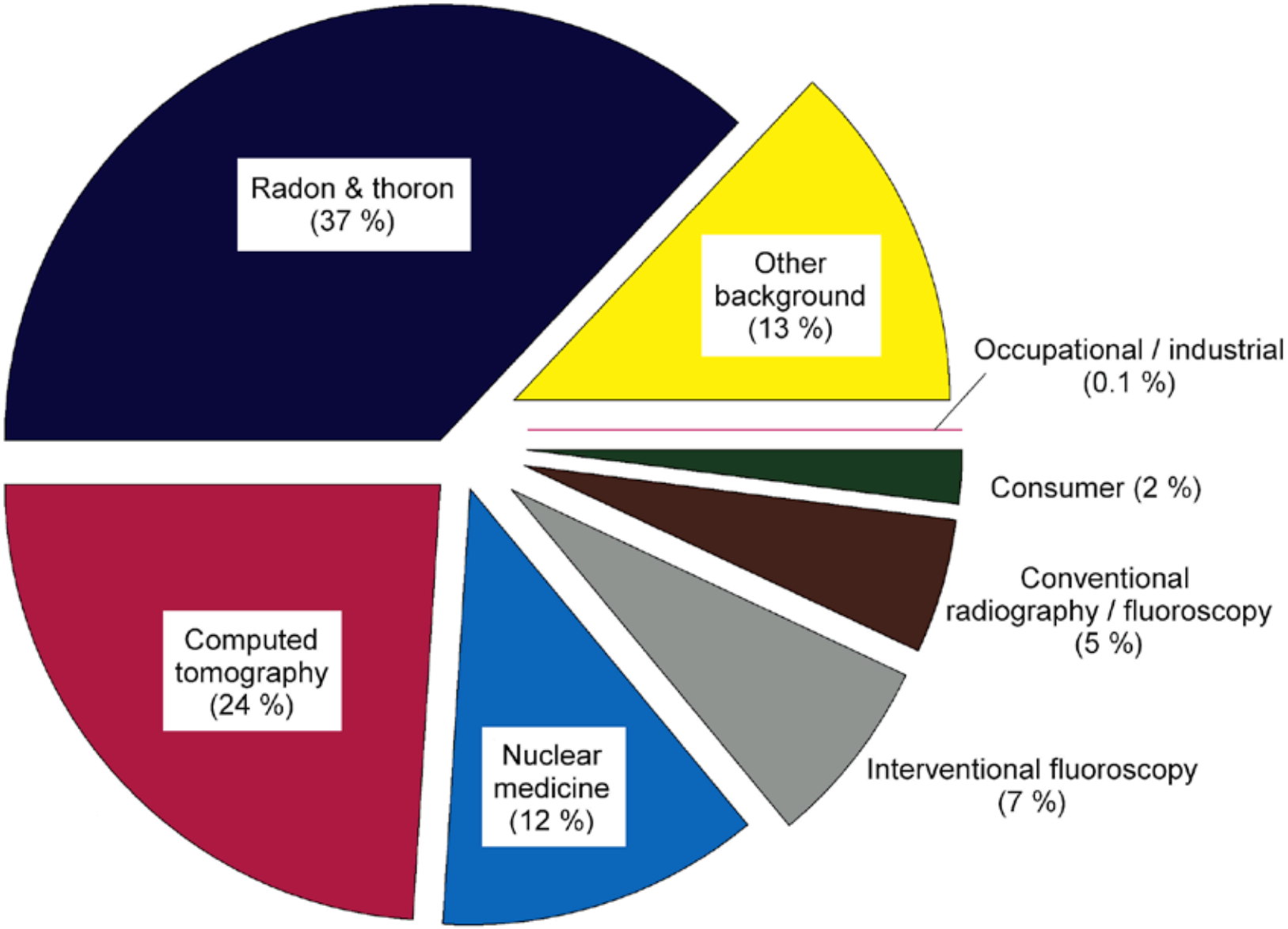
Sources of radiation dose to the general population in 1980



http://www.new.ans.org/pi/resources/dosechart/

NCRP Report 160, 2006

Ionizing Radiation Exposure of the US Population



First reports on harmful effects of radiation

1902: *radiation-induced skin cancer* reported

1911: *radiation-induced leukemia* described

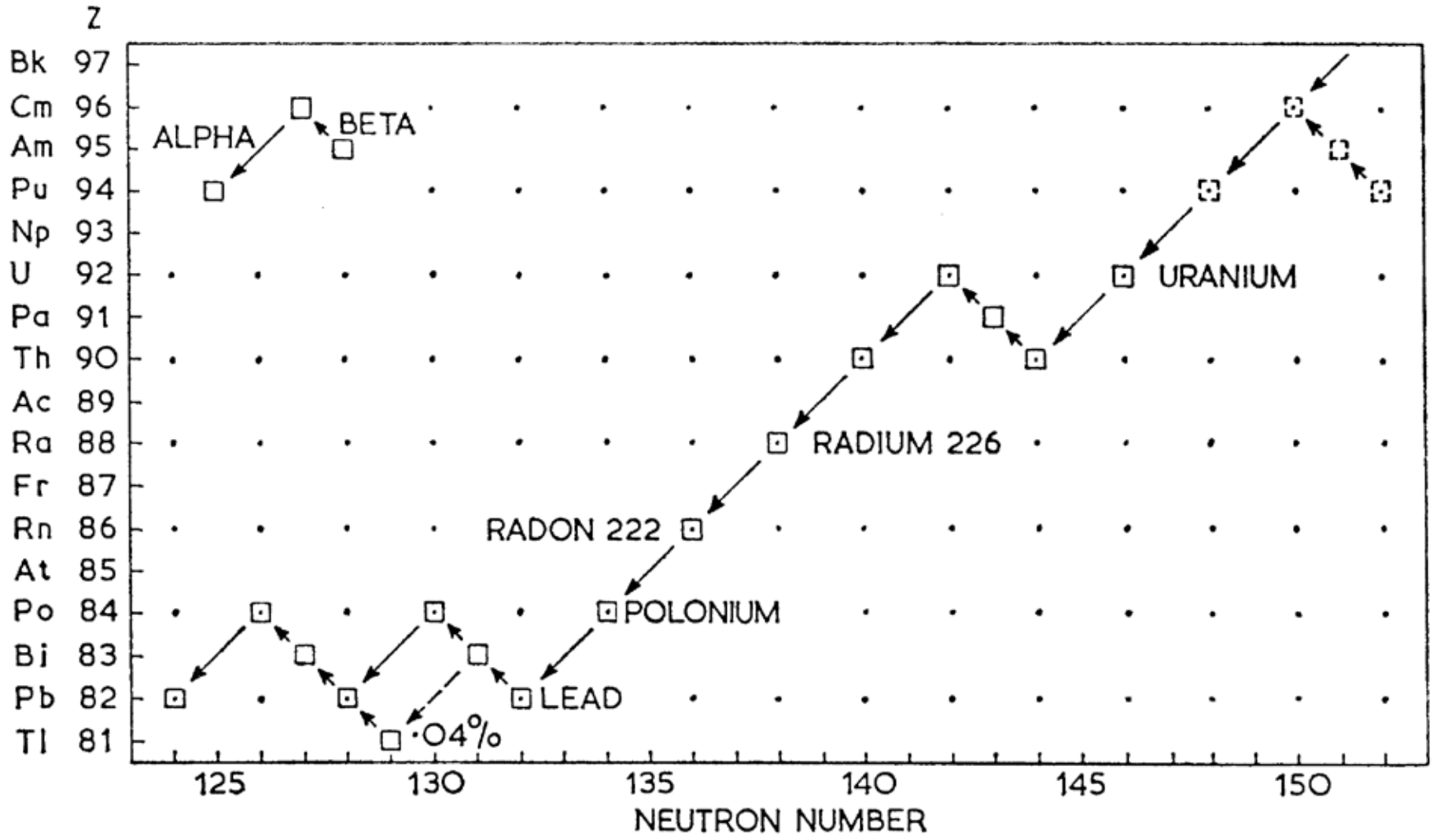
1920s: *bone cancer* in radium dial painters

1930s: *liver cancer and leukemia* due to Thorotrast administration

1940s: excess *leukemia* in the first radiologists

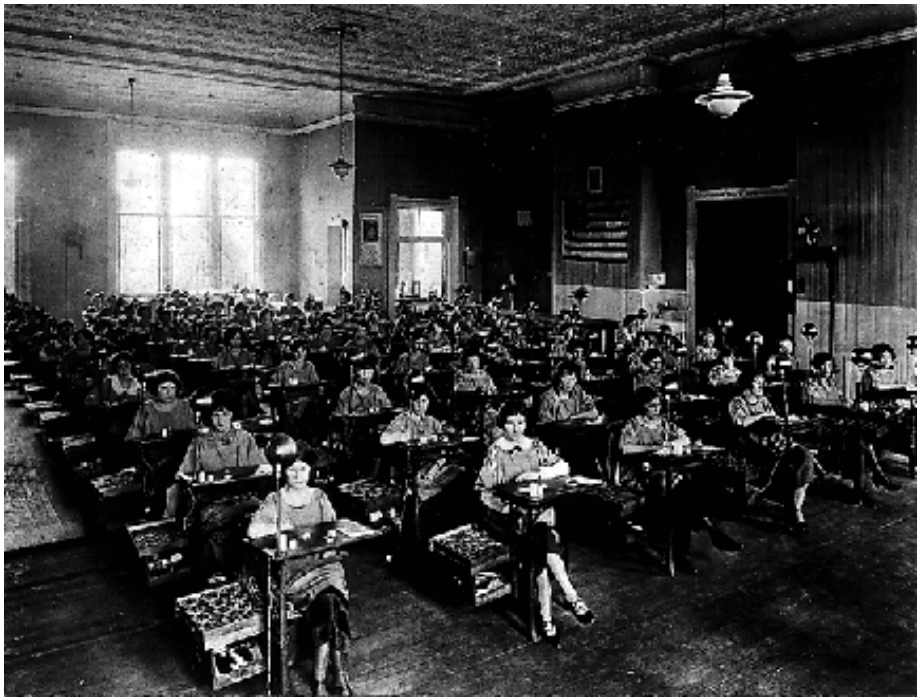
www.curie.fr

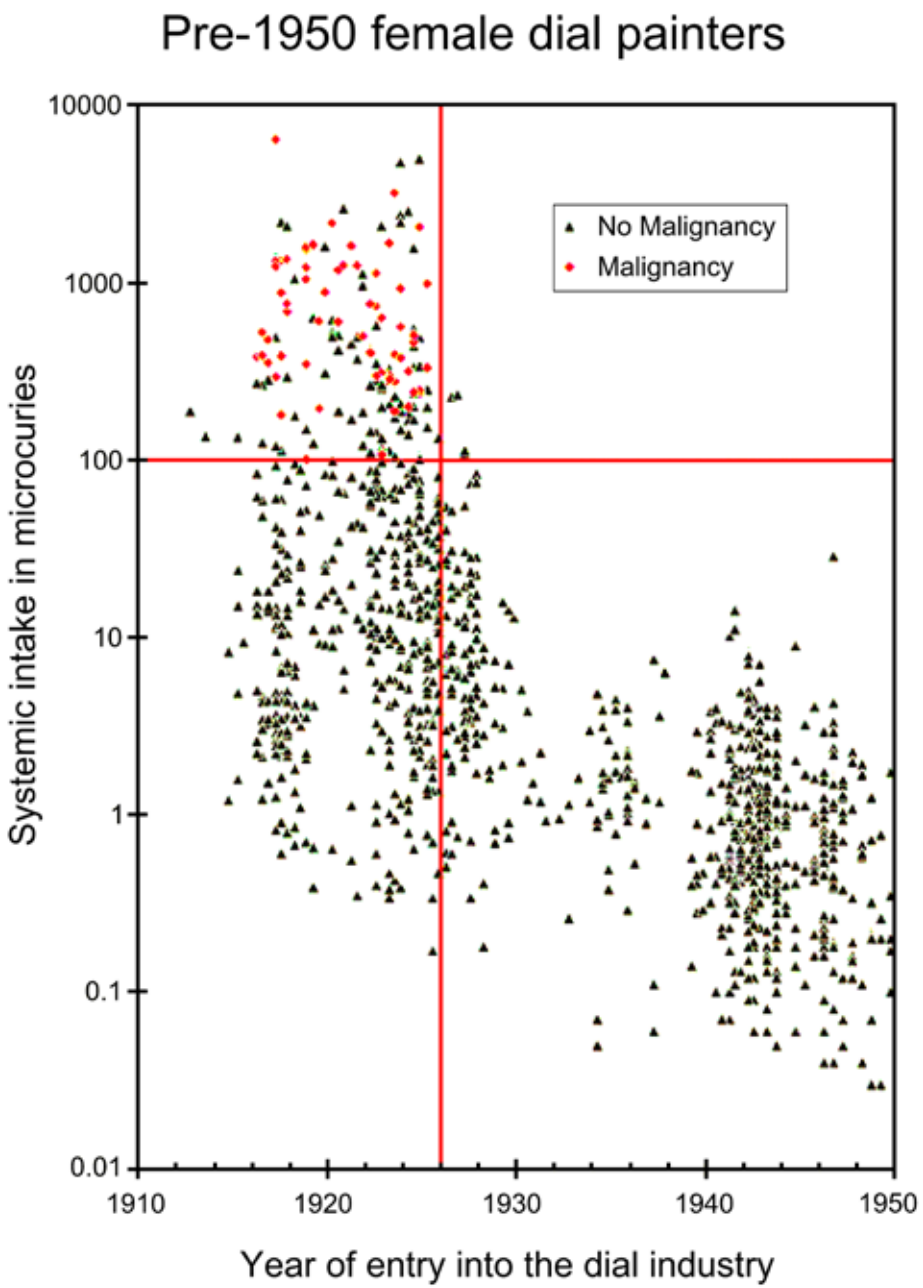
Lewicki AM, *Radiology* 2002;223:299-303



PART OF THE CHART OF THE NUCLIDES.

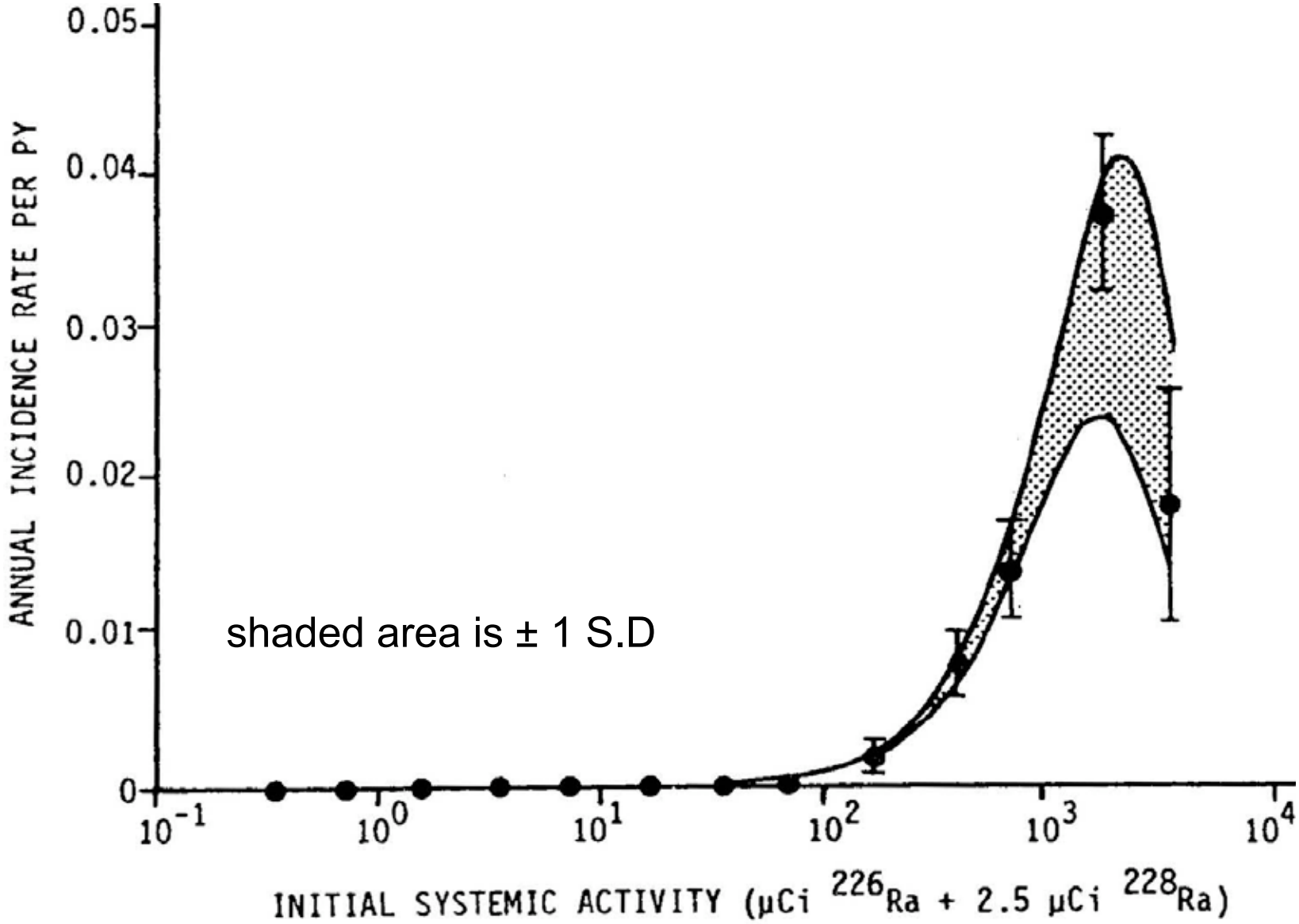
This shows successive radioactive disintegrations in the **uranium 238 series.** Shorter-lived nuclides, for example those shown as dotted squares, decay into the chain but do not occur naturally on earth.



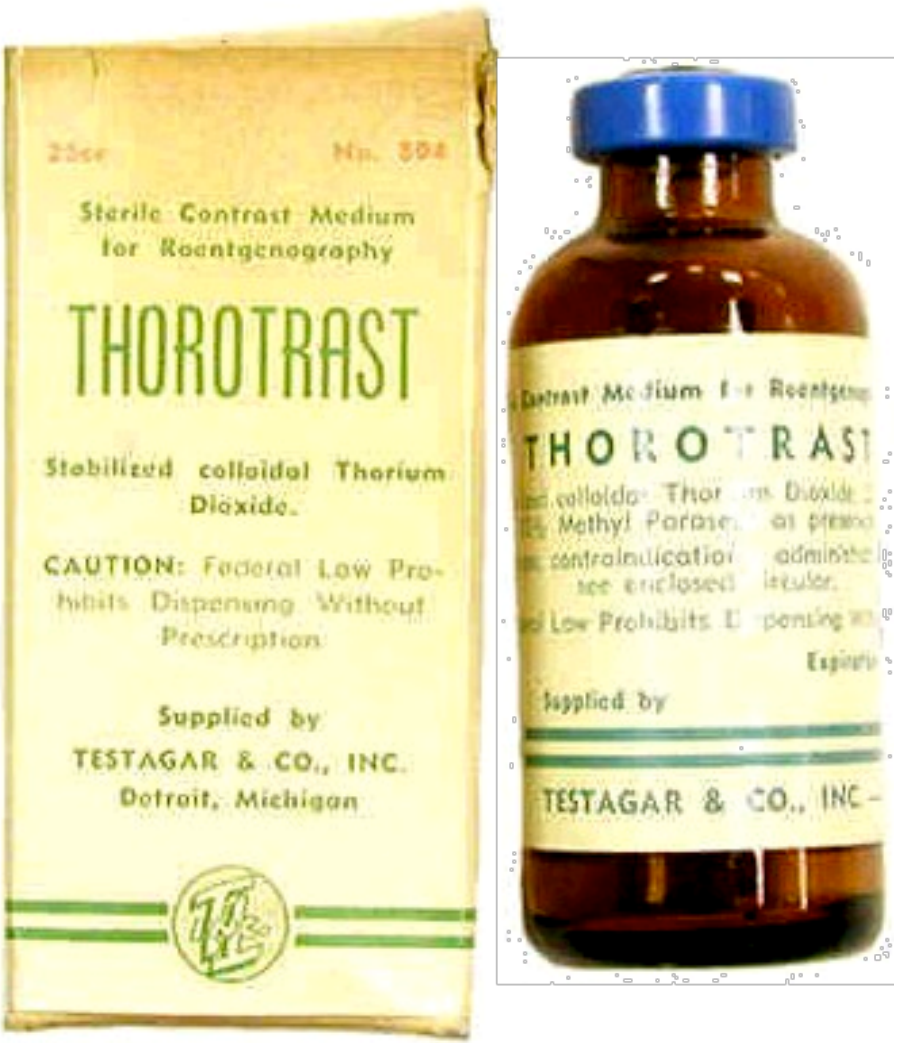


Rowland RE. Radium in Humans: A Review of U.S. Studies. Argonne National Laboratory, Argonne Ill, 1994

Radium-induced bone sarcomas



Rowland R et al. *Health Phys* 1983;44:15-31



- Suspension containing particles of thorium dioxide
- Contrast medium in X-ray diagnostics in 1930s and 40s
- Excellent images: thorium has high absorption cross section
- The naturally abundant nuclide ^{232}Th is slightly unstable, decays through emission of an alpha particle
- Drug is distributed to liver, spleen, lymph nodes, bone
- Biological half-life is 22 years, physical half life $>10^{10}$ years

Thorotrast cancers

Site	Relative risk	95% CL
All cancer	3.4	2.9 – 4.1
Stomach	2.7	1.1 – 7.9
Liver	∞	44 – ∞
Bile ducts	26	4.3 – 1133
Gall bladder	11	1.3 – 391
Pancreas	3.8	1.3 – 12.3
Peritoneum, other digestive	∞	1.7 – ∞
Ovary, tube, broad ligament	4.3	1.1 – 24.3
Prostate	4.5	1.6 – 16.3
Kidney	5.7	1.9 – 21.0
Leukemia, all non-CLL	15	4.4 – 149
Thorotrast related cancers†	76	32 – 248

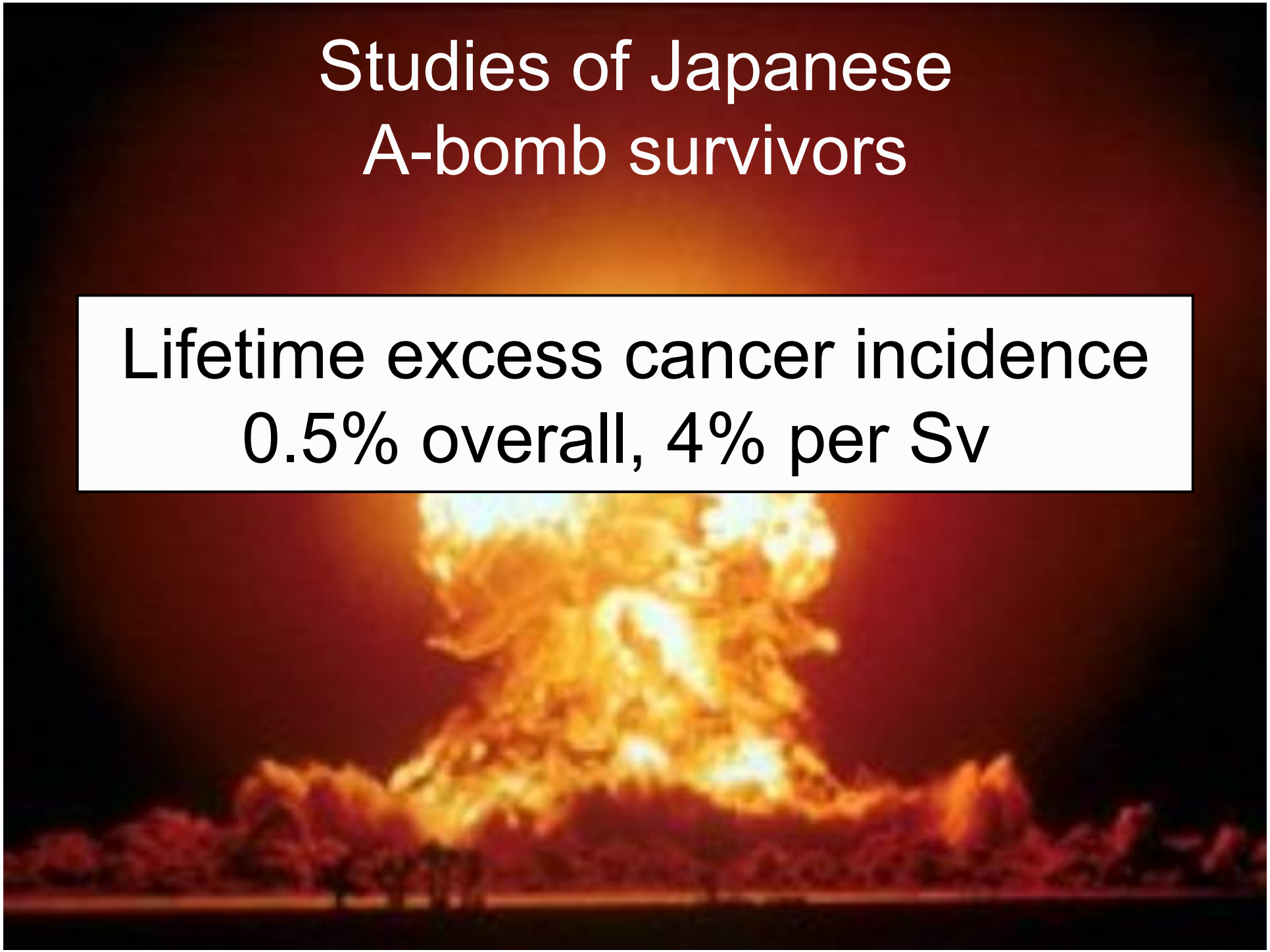
†non-CLL and primary cancers of liver, gall bladder and bile ducts

Travis LB et al. *Radiat Res* 2003;160:691-706

Relative risk is preferred to ***Absolute risk***

- ***Relative risk (RR):*** an expression of excess risk relative to the underlying (baseline) risk. If excess risk is zero, RR is 1 (100%). If excess risk equals the baseline risk, RR is 2 (200%)
- ***Absolute risk:*** an expression of excess risk based on the assumption that the excess risk from radiation exposure *adds to* the underlying risk by an increment dependent on dose but independent of the underlying natural risk

Studies of Japanese A-bomb survivors



Lifetime excess cancer incidence
0.5% overall, 4% per Sv

Summary of the 1958–1994 cancer incidence data in A bomb survivors

Colon dose, Sv	Subjects	Solid cancers	Estimated excess
beyond >3,000 m	23,493	3,230	0
<0.005 Sv within <3,000 m	10,159	1,301	1
0.005–0.1	30,524	4,119	77
0.1–0.2	4,775	739	60
0.2–0.5	5,862	982	164
0.5–1	3,048	582	177
1–2	1,570	376	165
>2	470	126	80

724

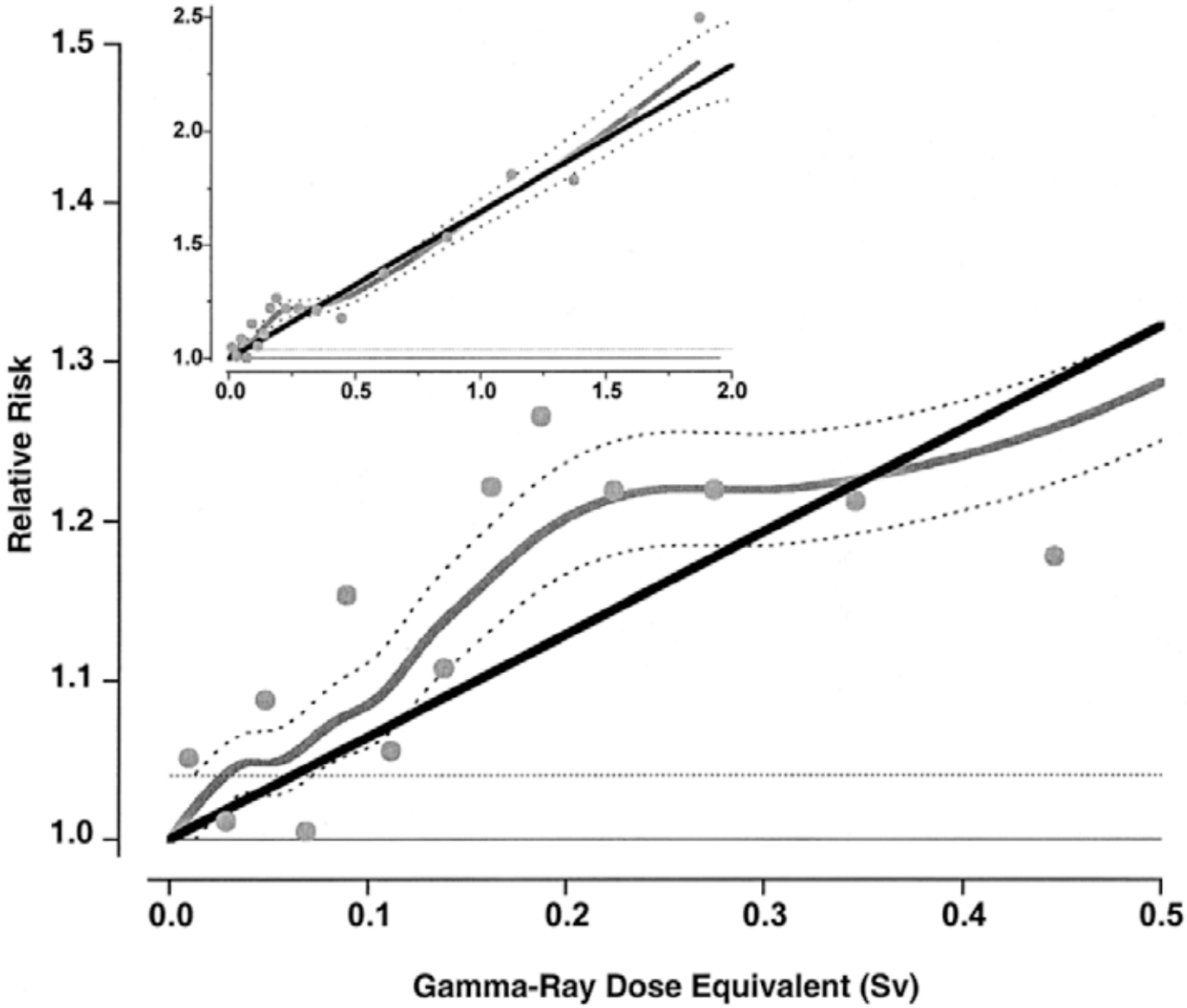
Pierce DA, Preston DL. *Radiat Res* 2000;154:178-86

Excess cancer mortality:

Lifetime risk per 100,000 at 0.1 Sv

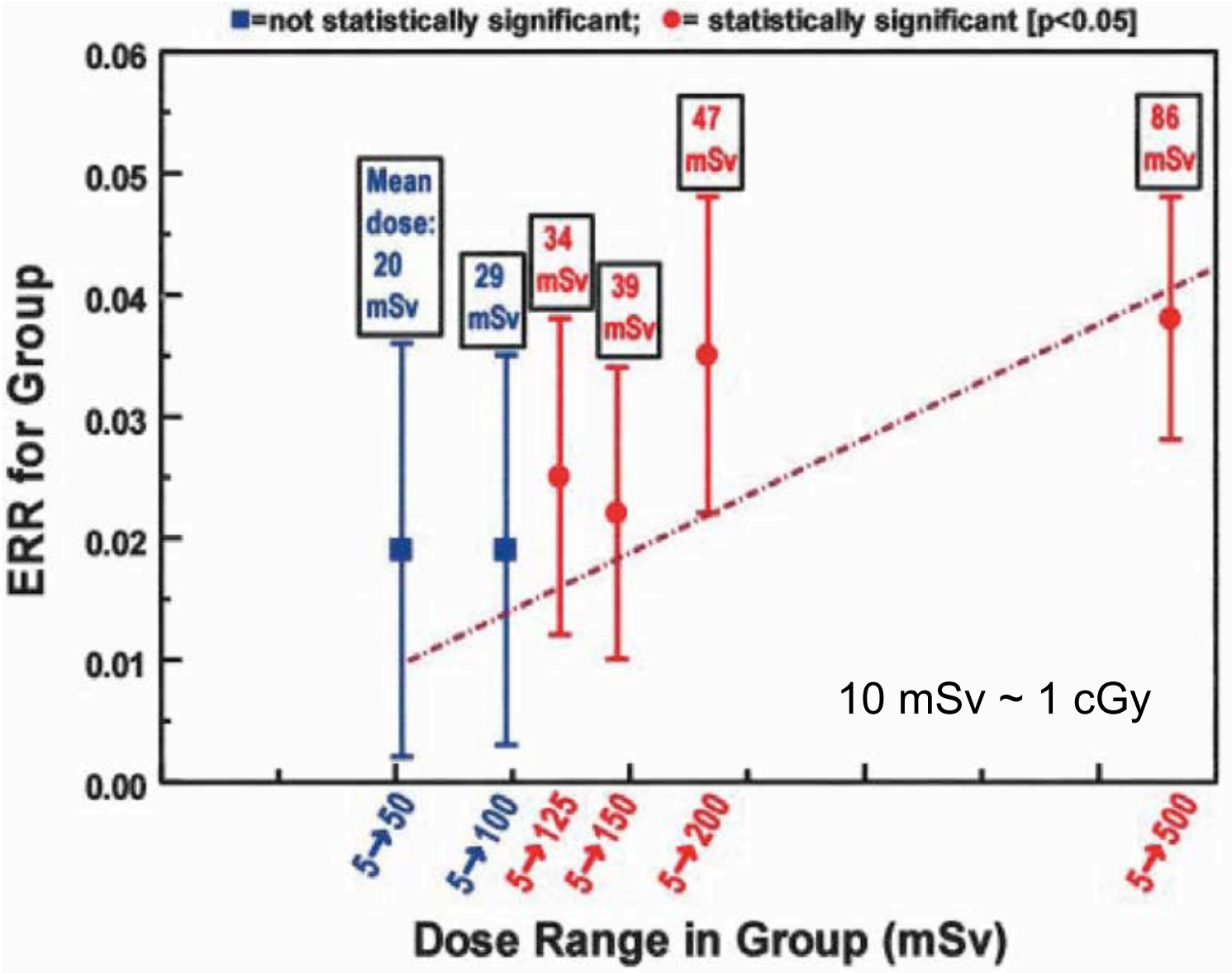
	BEIR V (U.S. Population)			
	Males	Females	UNSCEAR 88 (Japanese Population)	
Breast	—	70	Breast	60
Respiratory	190	150	Lung	151
Digestive system	170	290	Stomach	126
			Colon	79
Other solid	300	220	Other solid	194
Leukemia	110	80	Leukemia	100
Total	770	810	Total	710

Radiation related cancer risk: A bomb survivors



Pierce DA, Preston DL. *Radiat Res* 2000;154:178-86

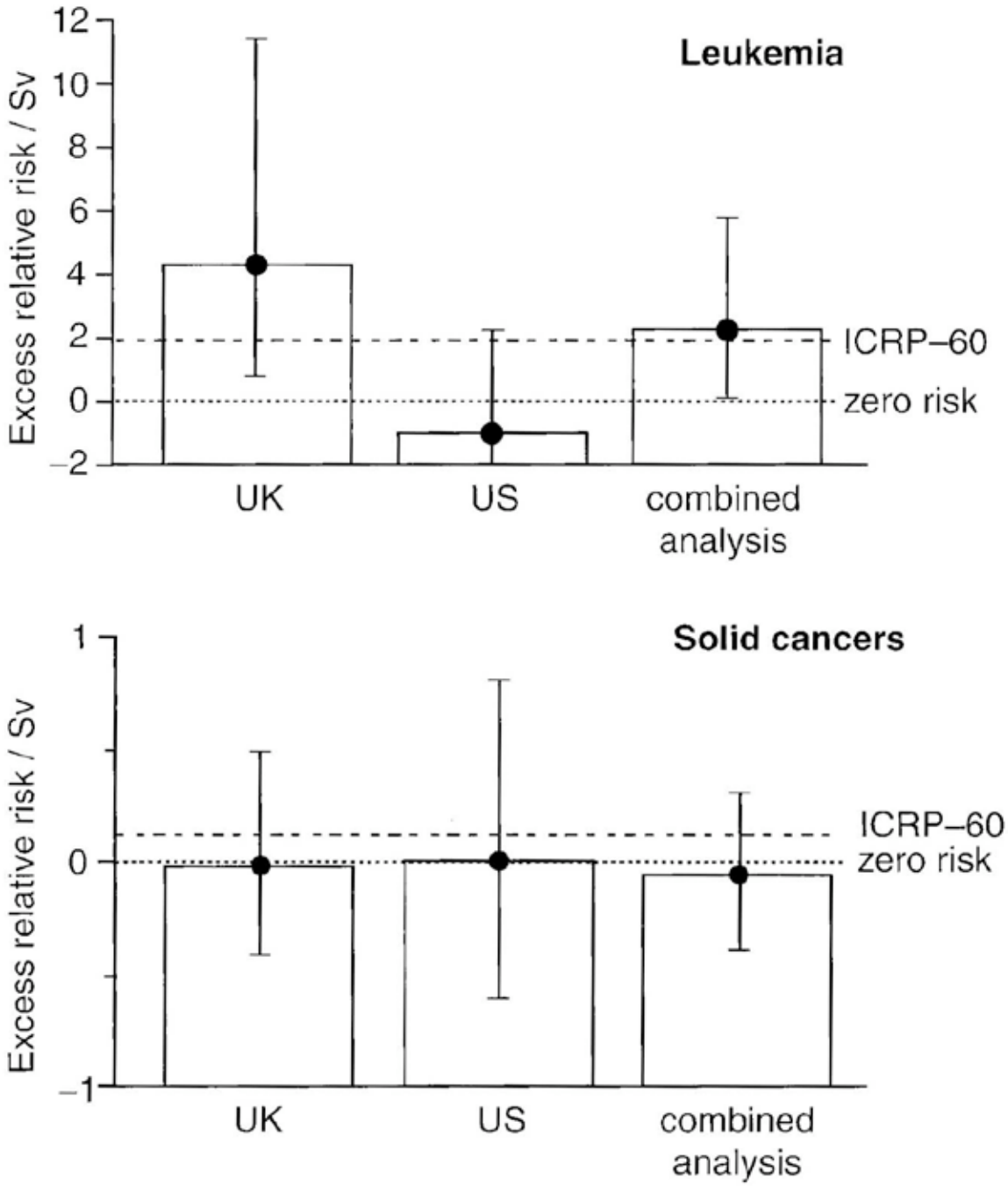
Solid cancer mortality from A bomb



Brenner DJ et al. *PNAS* 2003;100:13761-6

Cancer risk in 95,000 nuclear industry workers

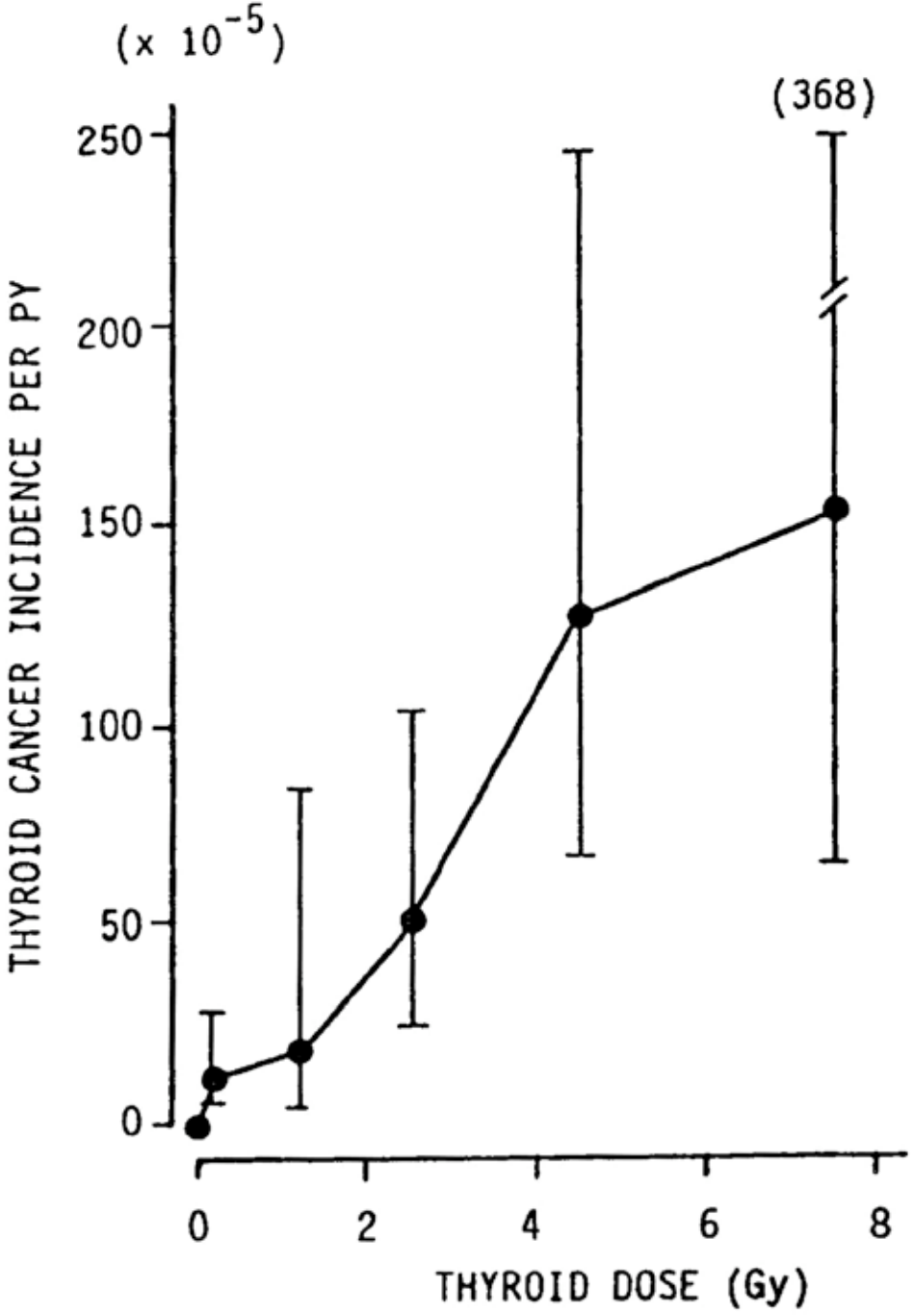
From Dr. David Brenner



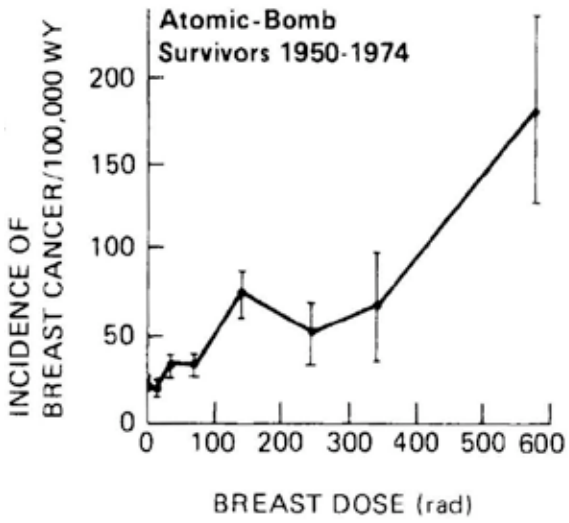
Thyroid tumors following thymus irradiation

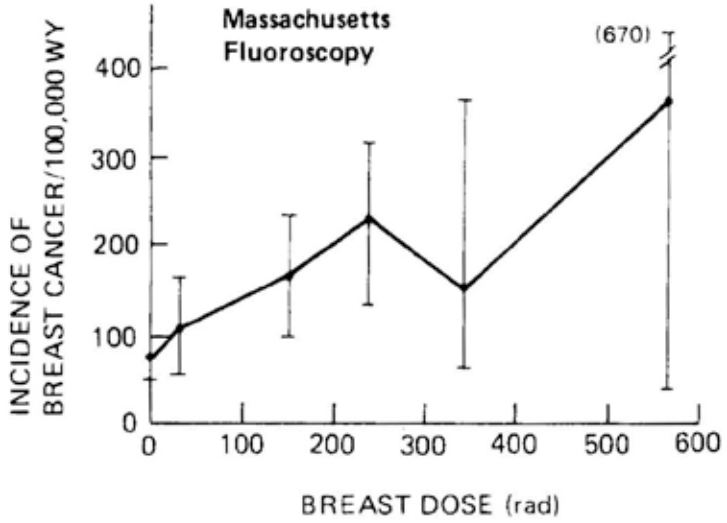
0.1%

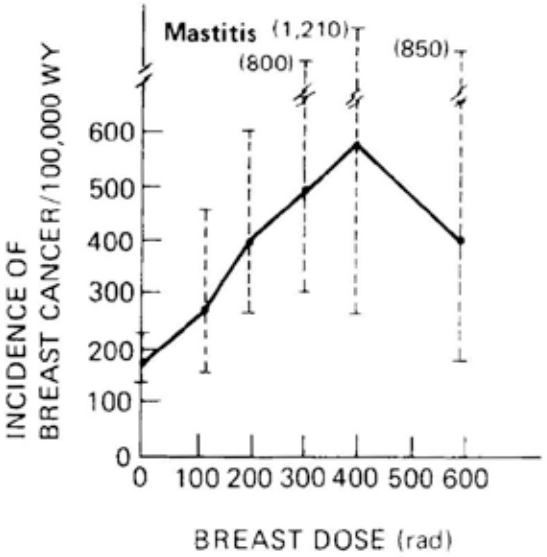
Shore RE et al.
JNCI 1985;74:1177-84

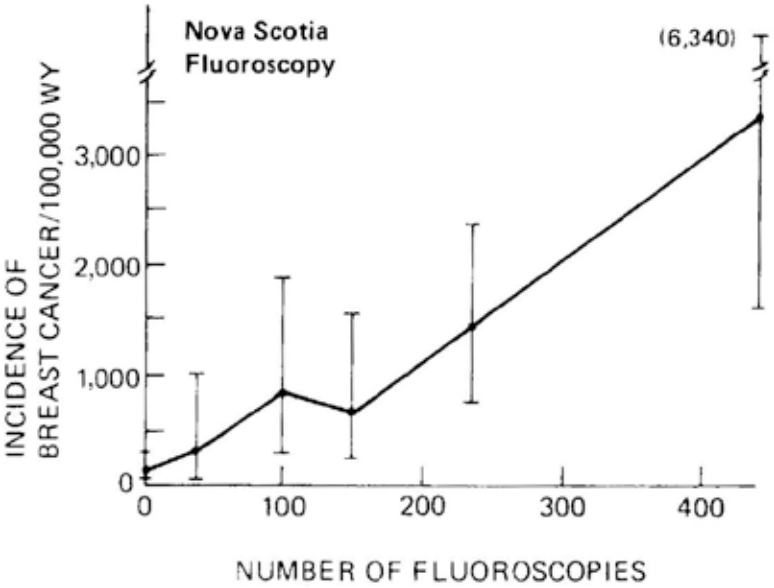


Breast cancer following fluoroscopy



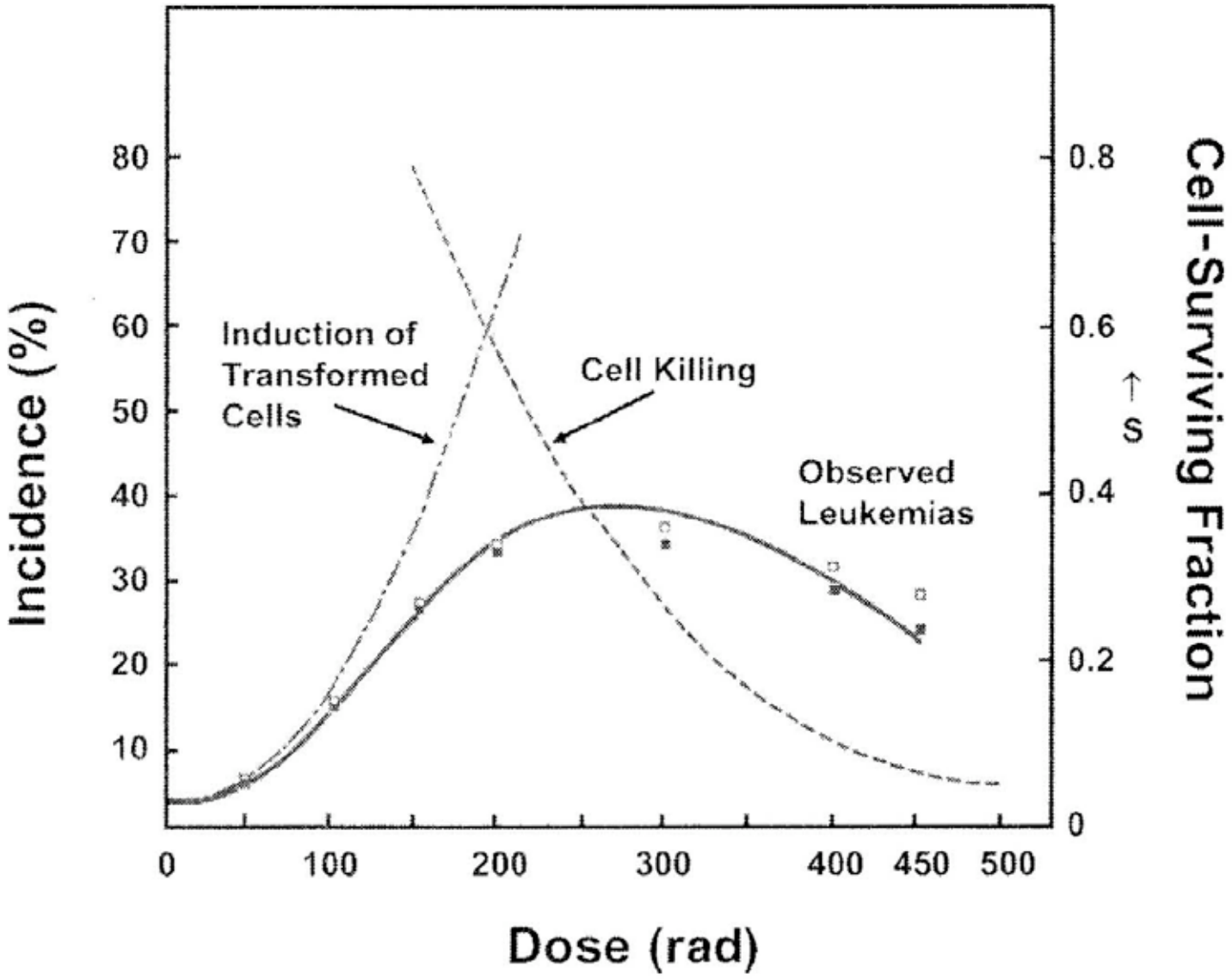






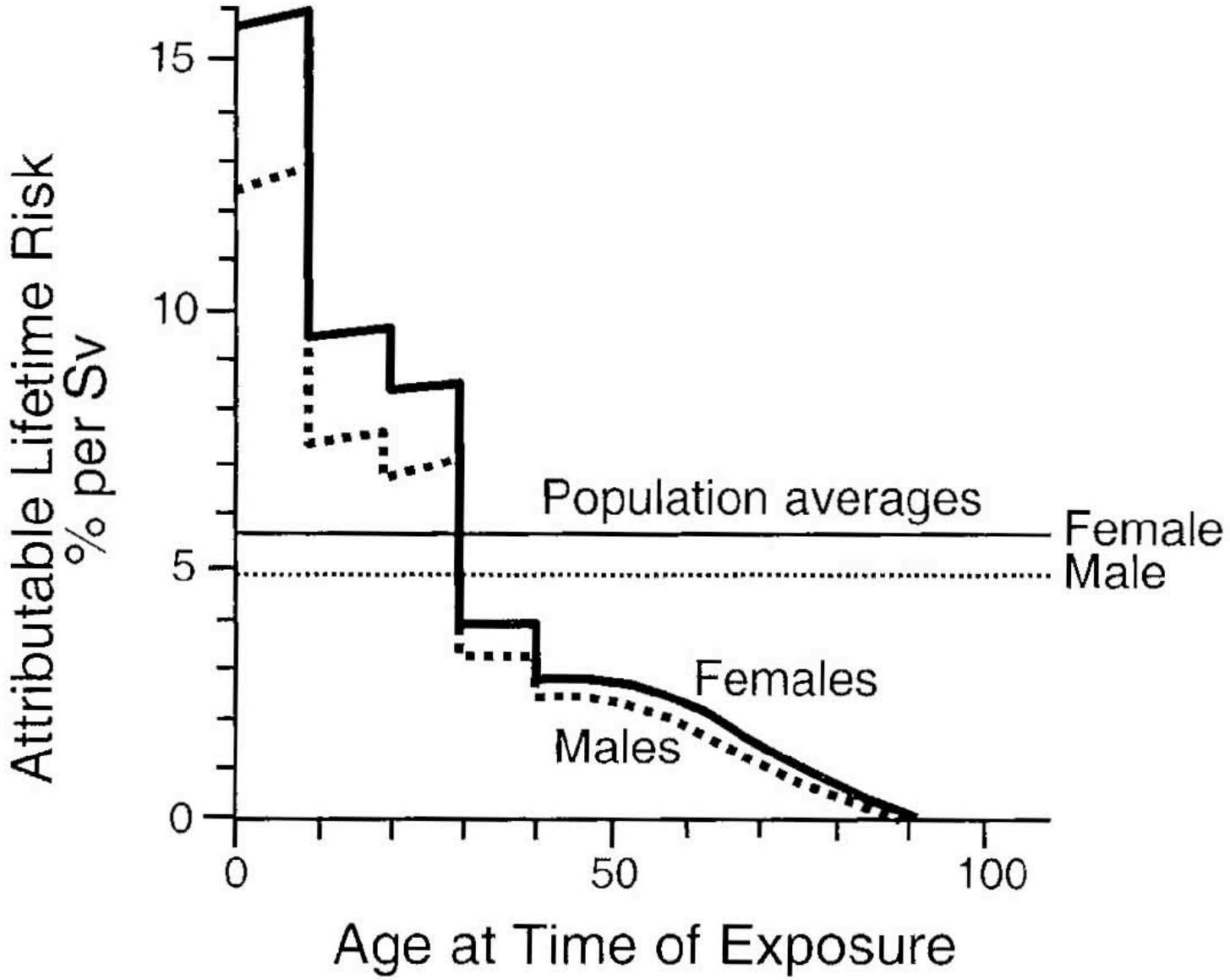
Boice JD et al. *Radiology* 1979;131:589-97

Bell-shaped cancer incidence curve



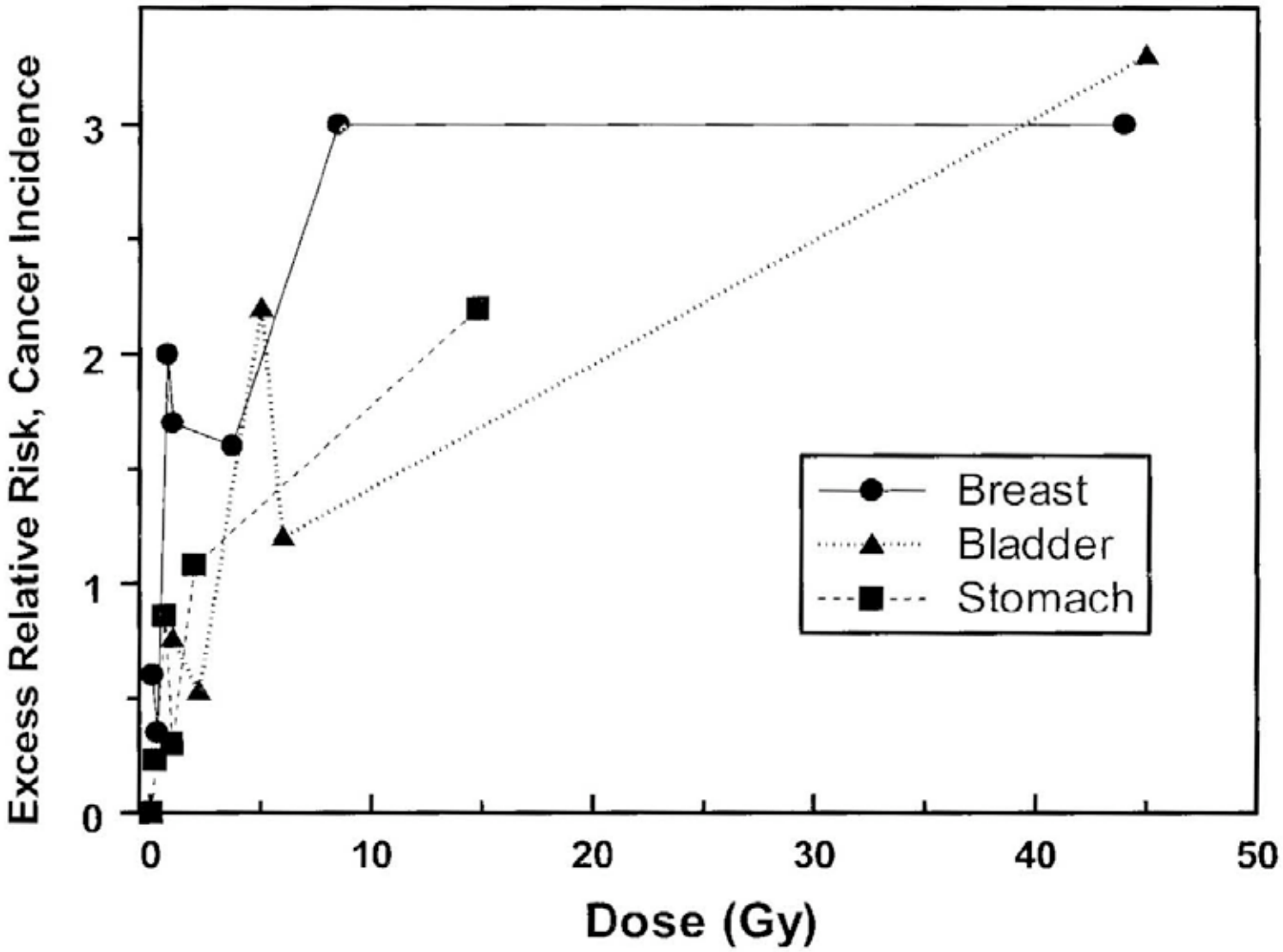
Gray LH, Radiation biology and cancer. In: *Cellular Radiation Biology.* William & Wilkins, Baltimore, pp 8-25, 1965

Age dependence of cancer risk



ICRP. *Ann ICRP Pub* **60**, Pergamon Press, Oxford, England, 1990

Dose response for carcinogensis



Compiled by Dr. Elaine Ron. Data <2 Gy from A-bomb survivors, high-dose data from radiotherapy patients

Risk of cancer lethality by radiation

*ICRP 103 (2007)

	High dose High dose rate	Low dose Low dose rate
Working population	8.2×10^{-2} per Sv	4.1×10^{-2} per Sv
Whole population	11.0×10^{-2} per Sv	5.5×10^{-2} per Sv

*International Commission on Radiological Protection

http://www.icrp.org

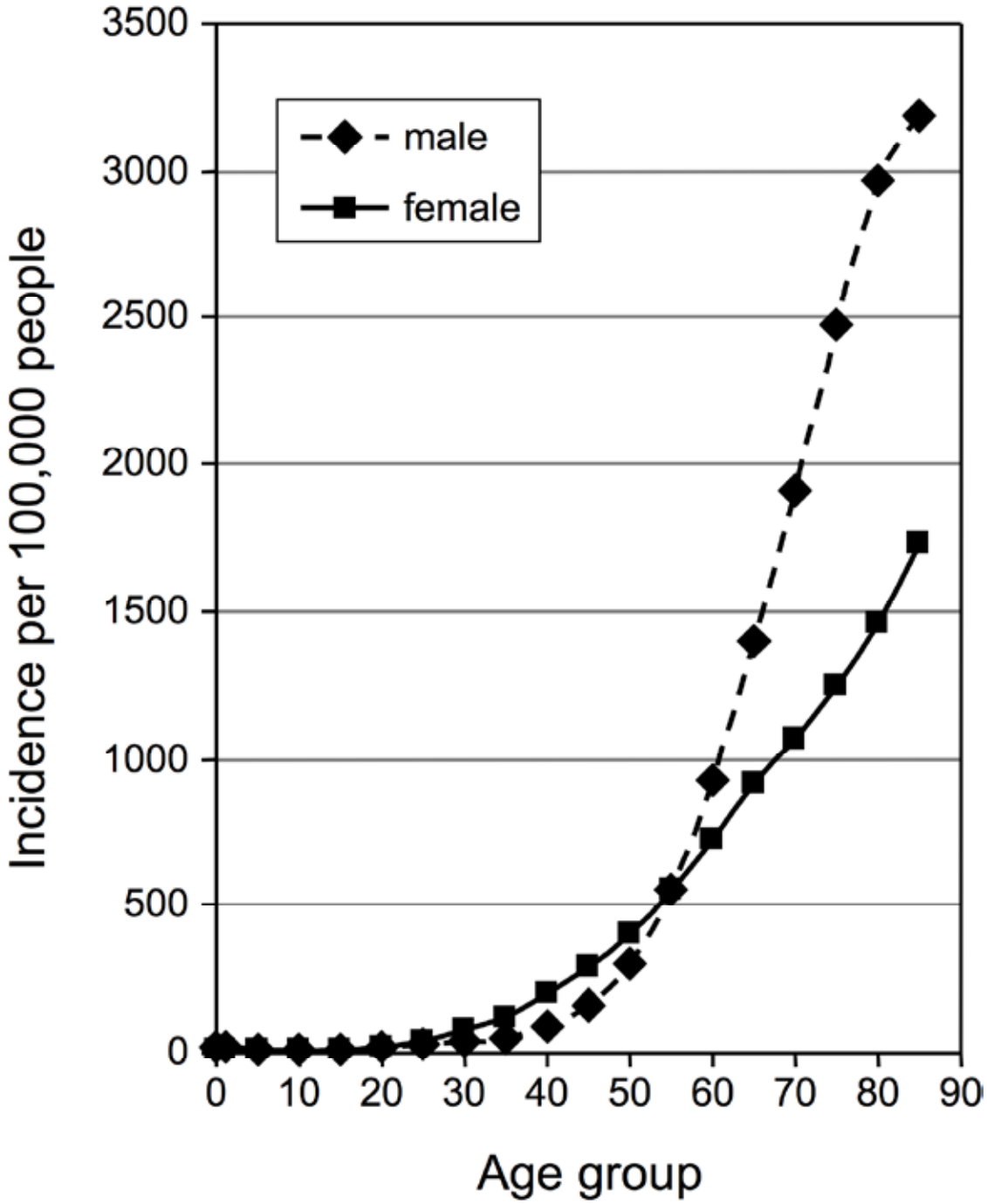
Radiation weighting factors (W_R)

ICRP 92 (2003), ICRP 103 (2007)

Radiation type	W_R
Photons (X-rays and gamma-rays):	1
Electrons and muons:	1
Neutrons:	function of neutron energy
Protons and charged pions:	2
Alpha-particles, fission fragments, heavy ions:	20

Radiotherapy induced cancers

Average annual cancer incidence in the United Kingdom by sex and attained age



Spontaneous cancer incidence risk

Age at treatment (years)	Cancer risk within the next 5 years (%)	
	Males	Females
50	1.5	2.0
55	2.5	2.7
60	5.0	3.6
65	7.0	4.6
70	10.0	5.4
75	12.5	6.3

Follow-up period 5 years, in patients treated with radiotherapy at different ages. Data from UK, England and Wales 1983-1987

2nd cancers after RT of cervix Ca

Site of second cancer	Radiation dose (Gy)	Number of 2nd cancers after radiotherapy/surgery	Relative risk after >10 years
Rectum	30–60	274 / 33	2 after 10 y 4 after 30 y
Colon	24	296 / 56	no increase
Bladder	30–60	265 / 23	>2 after 10 y 6 after 30 y
Stomach	2	143 / 19	1.2
Lung	0.3	276 / 91	no increase
Breast	0.3	366 / 114	decrease 20–40% after 10 y and 30 y
Leukaemia	4.5	82 / 15	2

Kleinerman RA et al. *Cancer* 1995;76:442-52

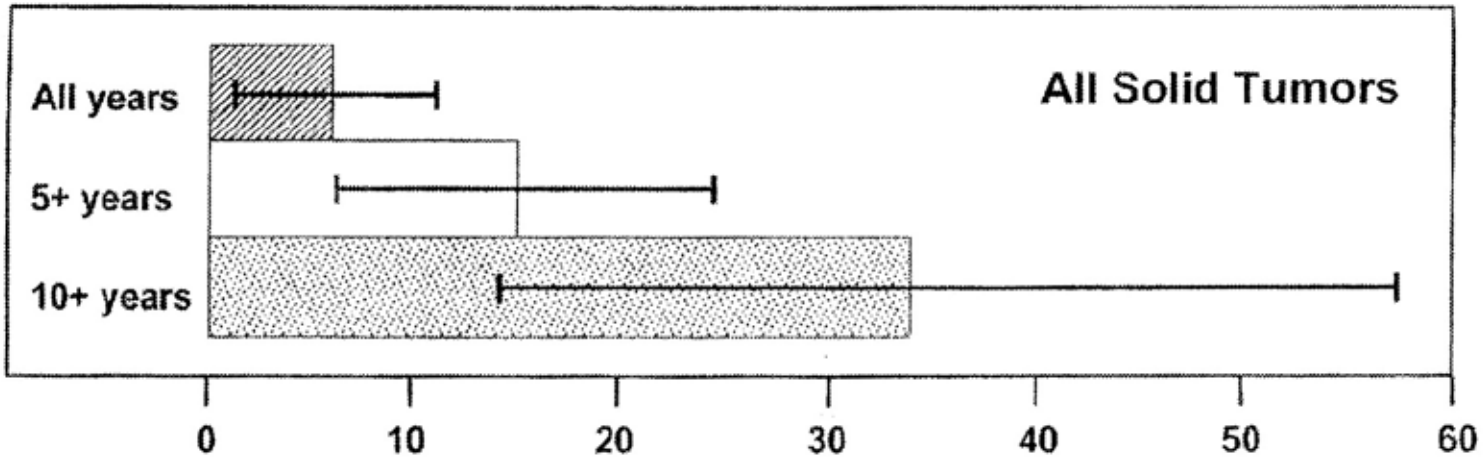
2nd cancers after RT of prostate Ca

	Relative Risk	
	After >5 years	**After >10 years**
All second cancers	1.11 (p<0.007)	1.27 (p<0.002)
Bladder	1.55 (p<0.0001)	1.77 (p<0.01)
Rectum	1.35 (p<0.06)	2.05 (p<0.03)
Lung	1.22 (p<0.01)	1.42 (p<0.02)
Leukaemia in first 10 years:		
Surgery patients	**Irradiated patients**	**Relative risk in 10 y**
39 in 343,690 person-years	25 in 112,422 person-years	2 (p<0.05)

Brenner DJ et al. *Cancer* 2000;88:398-406

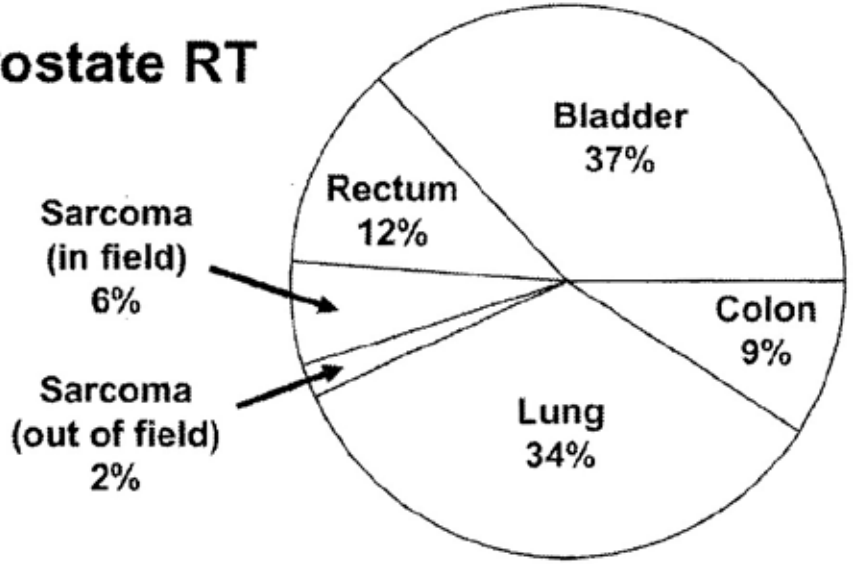
2nd cancers after RT of prostate Ca

Percentage Increase in Relative Risk for RT vs. Surgery %



Second Cancers after Prostate RT

% contribution to total number of radiation-induced second cancers

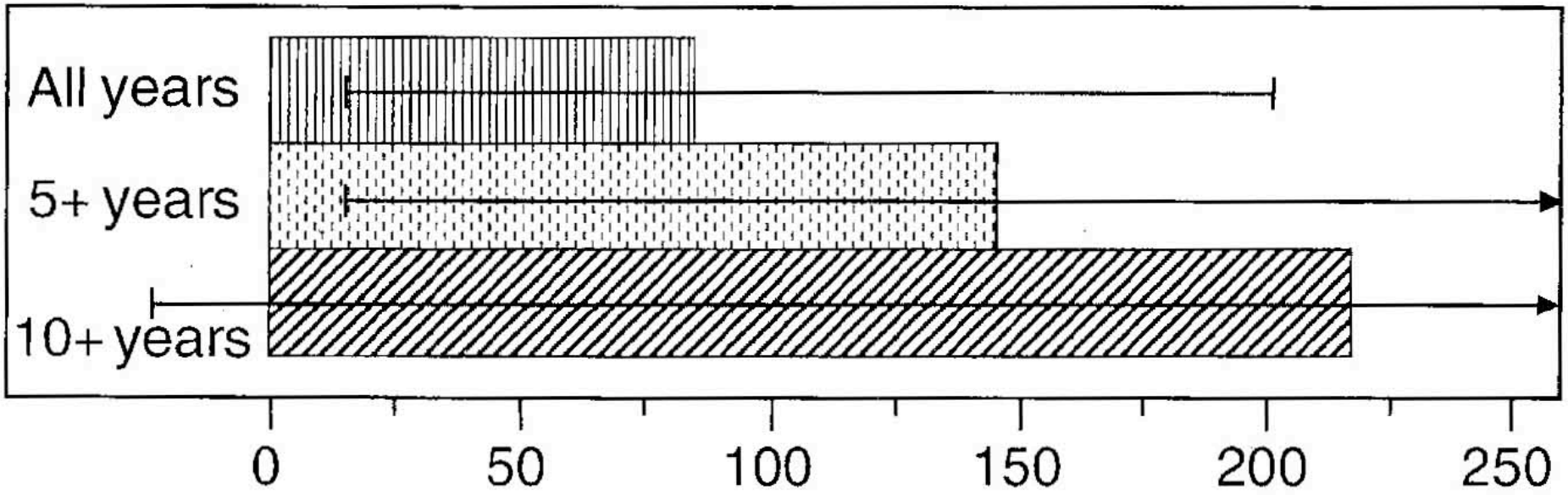


Brenner DJ et al. *Cancer* 2000;88:398-406

2nd cancers after RT of prostate Ca

Percentage Increase in Relative risk for RT vs. Surgery %

Sarcomas in or near the treatment field



Brenner DJ et al. *Cancer* 2000;88:398-406

2nd lung cancers after RT of breast Ca

Duration of follow-up (years)	Number of second cancers		Lung cancer mortality ratio
	Ipsilateral	Contralateral	
<10	161	134	1.2
10–15	65	44	1.5
>15	57	21	2.7

Ipsilateral and contralateral second lung cancers in patients treated with post-operative radiotherapy of breast cancer, 1973-2001

Darby SC et al. *Lancet Oncol* 2005;6:557-65

Summary: Radiation 1

- Radiation carcinogenesis is a stochastic effect
- Human experience of radiation-induced carcinogenesis includes early workers exposed occupationally, patients exposed to medical irradiation, survivors of A-bomb attacks on Hiroshima and Nagasaki, and Chernobyl
- Shortest latency is for leukemia, with a peak at 5 to 7 years. For solid tumours, latency may extend to > 60 years
- Radiation-induced cancer risks are usually based on a time-related Relative Risk (RR) model
- A dose and dose-rate effectiveness factor (DDREF) converts risk estimates from acute exposures (*e.g.* A-bomb data) to the low dose and low dose rates encountered in radiation protection. ICRP conservatively assumes DDREF = 2

Summary: Radiation 2

- For working populations, ICRP suggests risk estimates of excess cancer mortality:
  8.2×10^{-2} per sievert for high doses and high dose rates
  4.1×10^{-2} per sievert for low doses and low dose rates
- For the general population, ICRP risk estimates are:
  11.0×10^{-2} per sievert for high doses and high dose rates
  5.5×10^{-2} per sievert for low doses and low dose rates
- Workers in the nuclear industry are not more likely to develop cancer than non-nuclear workers
- Irradiation *in utero* by diagnostic X rays gives RR = 1.4 for leukemia and childhood cancers. This is high because malignancies in children are rare, but absolute risk is about 6% per gray, similar to risk in adult A-bomb survivors

Summary: Radiotherapy 1

- In radical radiotherapy, radiation exposure to non-involved organs and tissues may cause 2nd cancers to occur several decades later
- In adult cancer patients, the risk of radiation-induced 2nd cancers is much smaller than the risk of recurrent primary cancer
- In adults, >90% of 2nd cancers after radiotherapy are due simply to increased life expectancy after cure of primary
- Risk of radiation-induced 2nd cancers is much greater in younger cancer patients; these increased cancer rates may persist lifelong
- Most radiation-induced 2nd cancers occur in the high-dose volume but can also appear in the low dose (<2 Gy) volume

Summary: Radiotherapy 2

- Pronounced differences in types of radiation-induced 2nd cancers exist between children, young adults and elderly patients treated with radiotherapy
- Types of 2nd cancers after radiotherapy are different from those induced by low-dose total body irradiation, *e.g.* in the Japanese A-bomb survivors
- Different biological mechanisms can lead to 2nd cancers after radiotherapy, depending on dose distribution and age of the irradiated patient.
  Dose risk relationships, therefore, can be complex
- Risk of radiotherapy-induced 2nd cancers should *not* be estimated using the effective dose method proposed by ICRP for radiation protection purposes