PROGRAMME

Basic Clinical Radiobiology

Paris, France

16 - 20 September 2017

Saturday 16 September			
	08:00-09:00	**Registrations**	
	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	R. Coppes
	12.30-13.00	General discussion	
	13.00-14.00	**Lunch**	
	14.00-14.45	1.5 Models of radiation cell killing	M. Joiner
	14.45-15.45	1.6 Pathogenesis of normal tissue side effects	W. Dörr
	15.45-16.15	**Coffee break**	
	16.15-17.00	1.7 Clinical side effects and their quantification	K. Haustermans

Sunday 17 September			
	09.00-09.45	2.1 The linear-quadratic approach to fractionation	M. Joiner
	09.45-10.30	2.2 Molecular basis of radiation response: DNA repair/checkpoints	M. Koritzinsky
	10.30-11.00	**Coffee break**	
	11.00-11.30	2.3 Normal tissues: radiosensitivity & fractionation	W. Dörr
	11.30-12.30	2.4 Normal tissues: overall treatment time	W. Dörr
	12.30-13.00	General discussion	
	13.00-14.00	**Lunch**	
	14.00-15.00	2.5 Modified fractionation in radiotherapy	V. Grégoire
	15.00-15.45	2.6a The LQ-model in practice – introduction to calculations	M. Joiner
	15:45-16:15	**Coffee break**	
	16.15-17.00	2.6b The LQ-model in practice – examples of calculations	M. Joiner / K. Haustermans
		Social Dinner	

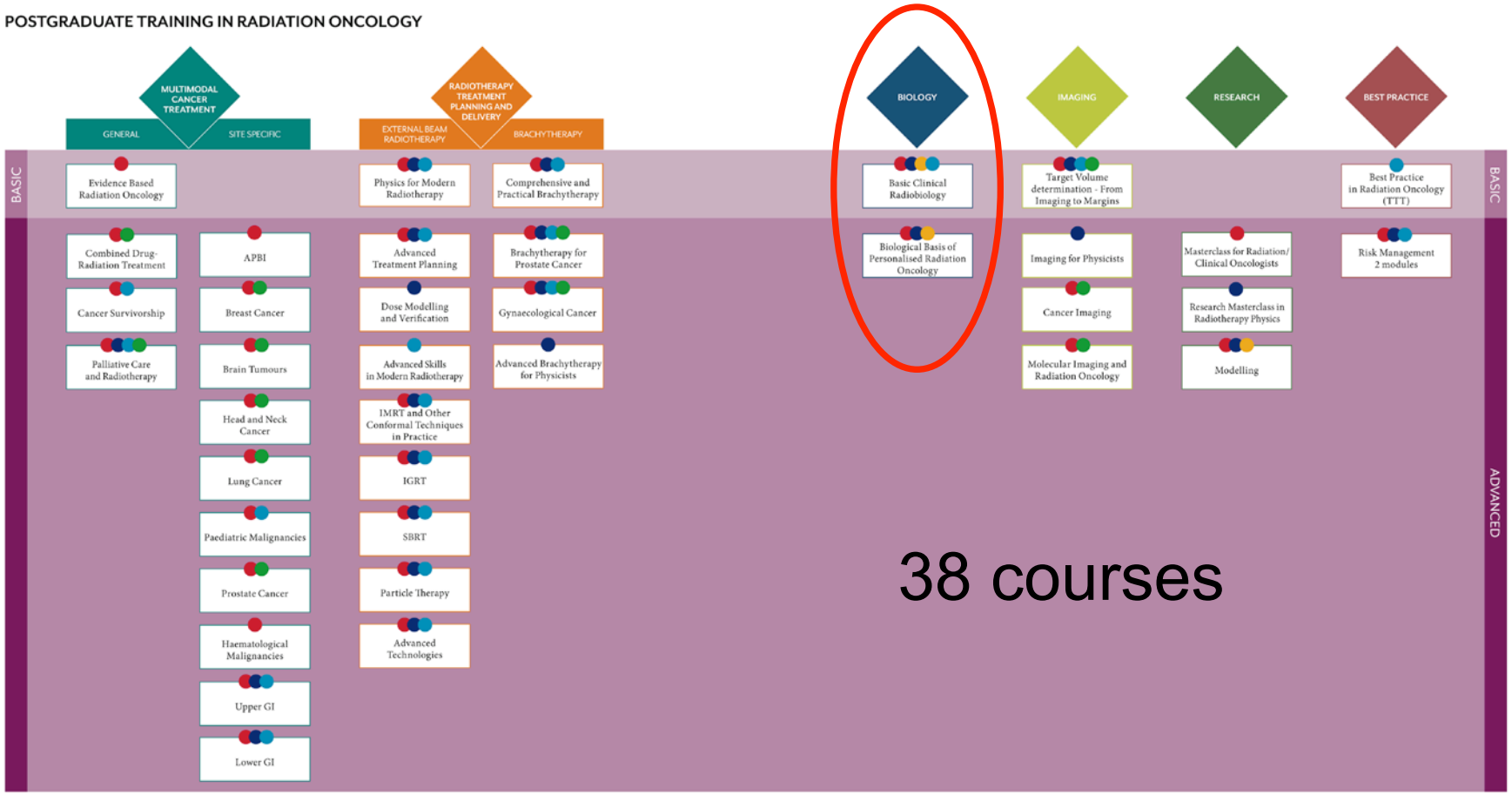
Monday 18 September			
	09.00-09.45	3.1 The volume effect in radiotherapy	W. Dörr
	09.45-10.45	3.2 The oxygen effect, hypoxia and the tumor microenvironment	M. Koritzinsky
	10.45-11.15	**Coffee break**	
	11.15-12.30	3.3 Clinical efforts to modify tumor hypoxia	K. Haustermans
	12.30-13.00	General discussion	
	13.00-14.00	**Lunch**	
	14.00-14.45	3.4 Dose-response relationships in radiotherapy	M. Joiner
	14.45-15.30	3.5 LET and RBE	M. Joiner
	15.30-16.00	**Coffee break**	
	16.00-17.30	3.6 Clinical examples – Lower GU	K. Haustermans / V. Grégoire

Tuesday 19 September			
	09.00-09.45	4.1 Biological response modifiers in tumours – preclinical	M. Koritzinsky
	09.45-10.30	4.2 Biological response modifiers in tumours – clinical	K. Haustermans
	10.30-11.00	**Coffee break**	
	11.00-11.45	4.3 Biological modifiers of normal tissue effects	R. Coppes
	11.45-12.30	4.4 Combined radiotherapy and chemotherapy	V. Grégoire
	12.30-13.00	General discussion	
	13.00-14.00	**Lunch**	
	14.00-14.45	4.5 Retreatment tolerance of normal tissues	R. Coppes
	14.45-15.30	4.6 Biological image guided radiotherapy	V. Grégoire
	15.30-16.00	**Coffee break**	
	16.00-17.30	4.7 Clinical examples – Head & Neck and Lung	V. Grégoire / K. Haustermans

Wednesday 20 September			
	09.00-09.45	5.1 Tumor growth and response to irradiation	K. Haustermans
	09.45-10.30	5.2 The dose-rate effect	R. Coppes
	10.30-11.00	**Coffee break**	
	11.00-11.45	5.3 Particles in radiotherapy	V. Grégoire
	11.45-12.30	5.4 Radiation-induced malignancies	M. Joiner
	12:30-13:00	Course evaluation and certificates	


39th ESTRO teaching course on
Basic Clinical Radiobiology
Paris, France
September 2017

2017 Roadmap to Teaching Courses



38 courses

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Biology Courses

- RADIATION ONCOLOGIST
- MEDICAL PHYSICIST
- RADIOBIOLOGIST
- RADIATION THERAPIST

Basic

Advanced

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
20.	Beijing, China	3 – 7 June	2007
21.	Sicily, Italy	14 – 18 October	2007

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Basic Clinical Radiobiology Locations

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
39.	**Paris, France**	**16 – 20 September**	**2017**
40.	Melbourne, Australia	10 – 13 May	2018
41.	Dublin, Ireland	15 – 19 September	2018
42.	……		

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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, France

When

Three: 2009 (Spain, China, Australia)

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

Here we are again! (after 24 years…)

Two: France

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Meet the Team

Paris 2017

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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

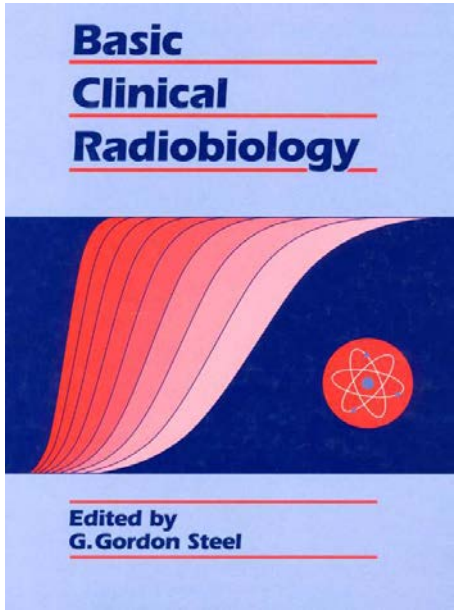
Mike Joiner, MA, PhD

USA & UK

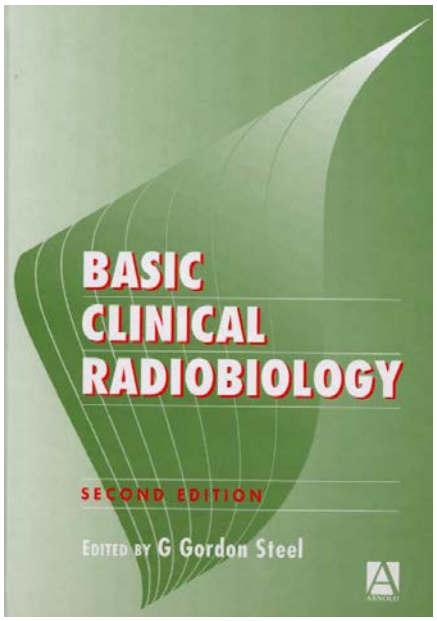
Radiobiologist

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

Meet the Book

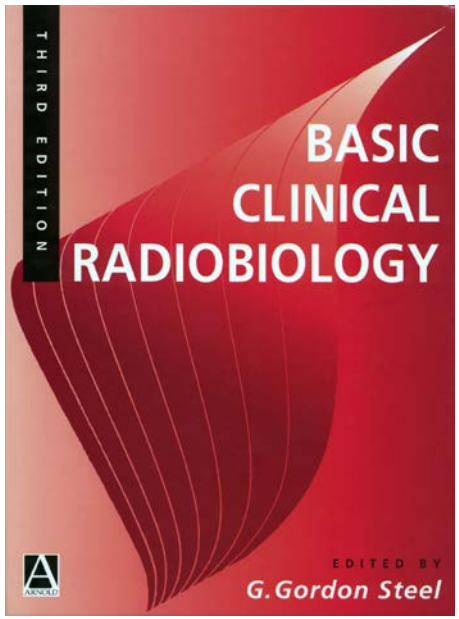


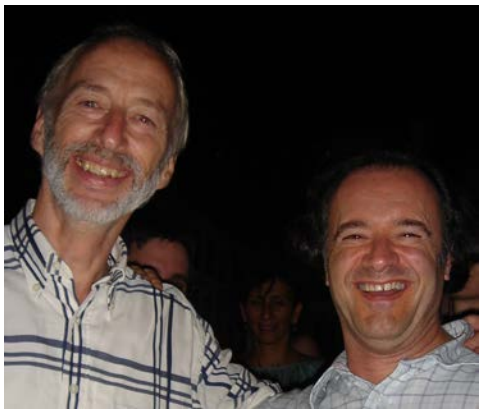
1st Ed: 1993



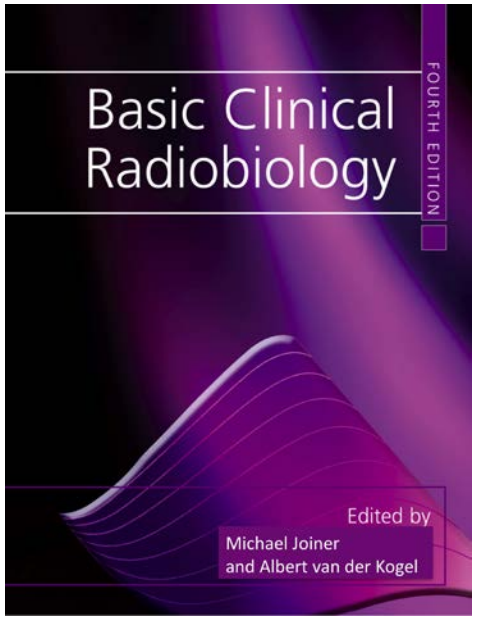
2nd Ed: 1997

3rd Ed: 2002



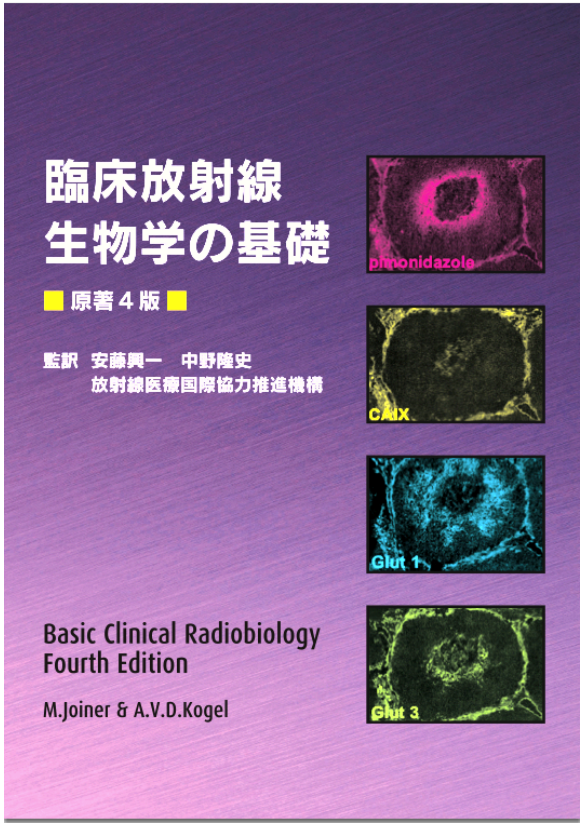


4th Ed: 2009

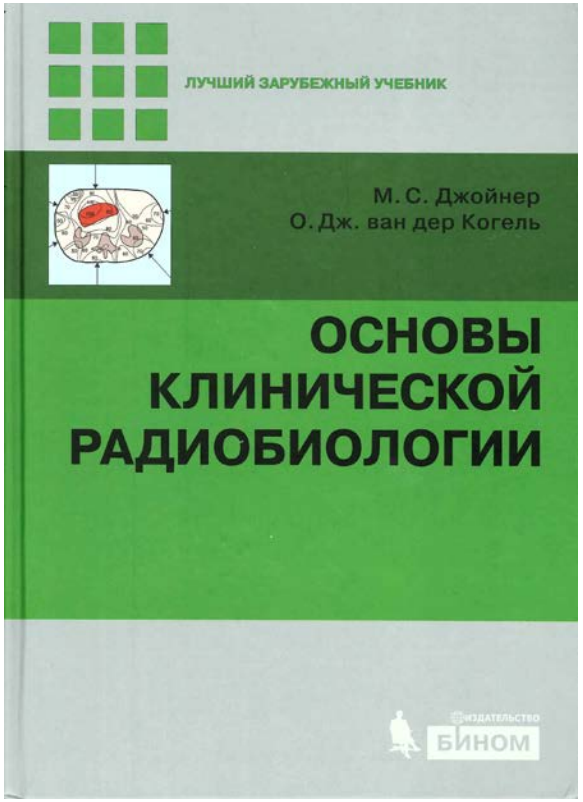


Translations of 4th edition

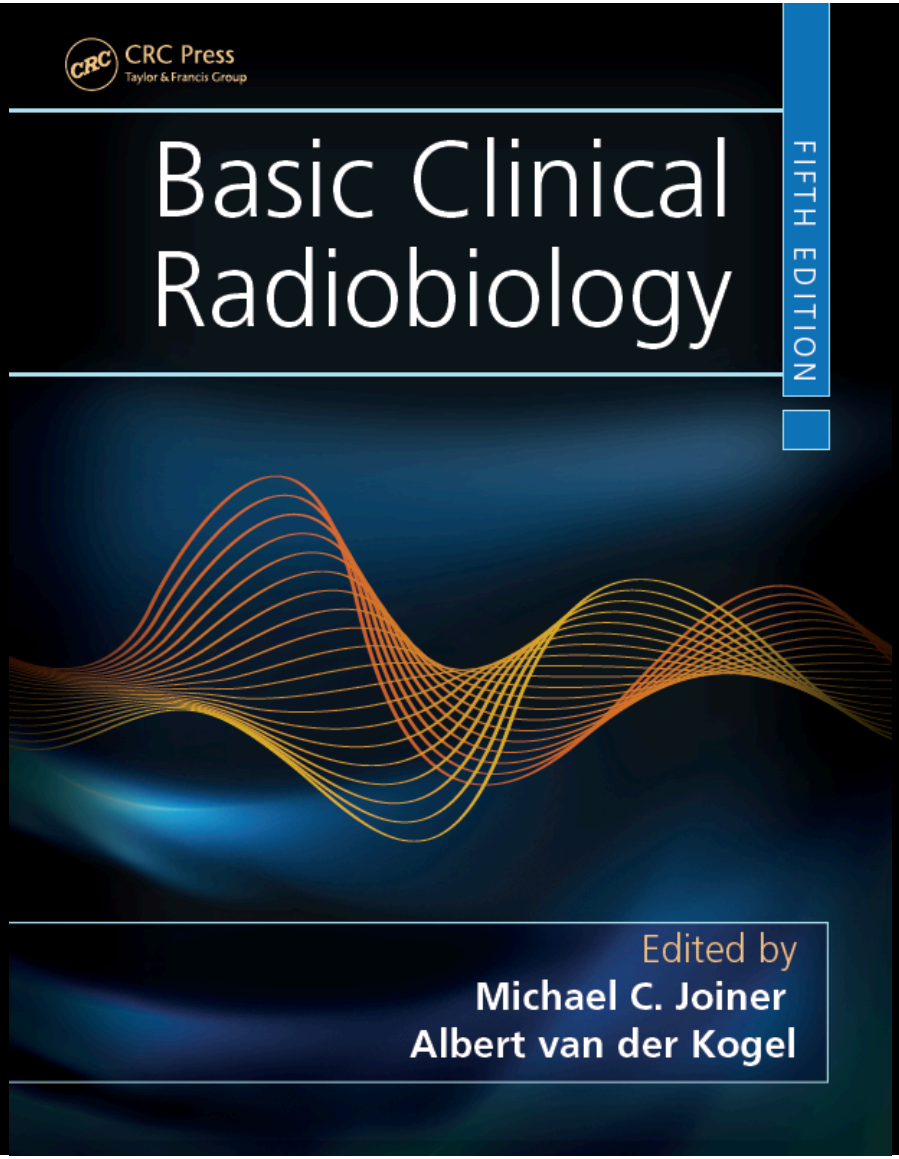
Chinese



Japanese



Russian



Appearing in 2018….

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

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Countries attending BCR here in 2017

2	Australia	1	Iran	1	Russian Fed
1	Austria	2	Ireland	1	Serbia
2	Belgium	3	Italy	1	Singapore
1	Bosnia/Herzegov.	1	Kazakhstan	2	Slovenia
1	Brazil	1	Lebanon	4	Spain
1	Canada	1	Lithuania	9	Sweden
6	Denmark	1	New Zealand	6	Switzerland
2	Estonia	11	Norway	2	Thailand
5	Finland	1	Philippines	25	The Netherlands
8	France	2	Poland	6	Turkey
6	Germany	6	Portugal	5	United Kingdom
1	Greece	1	Republic Korea		

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Specialities attending BCR here in 2017

Clinical Oncologist	9
Computer scientist	1
Dosimetrist	1
Medical Oncologist	1
Medical Physicist	**43**
Nuclear Medicine	1
Other Med Speciality	5
Other non-Med speciality	2
Radiation Oncologist	**53**
Radiobiologist	4
RO industry – corporate	2
Therapist	7
	129

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Saturday 16 September

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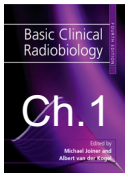

Introduction to Clinical Radiobiology

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

ESTRO teaching course on basic clinical radiobiology

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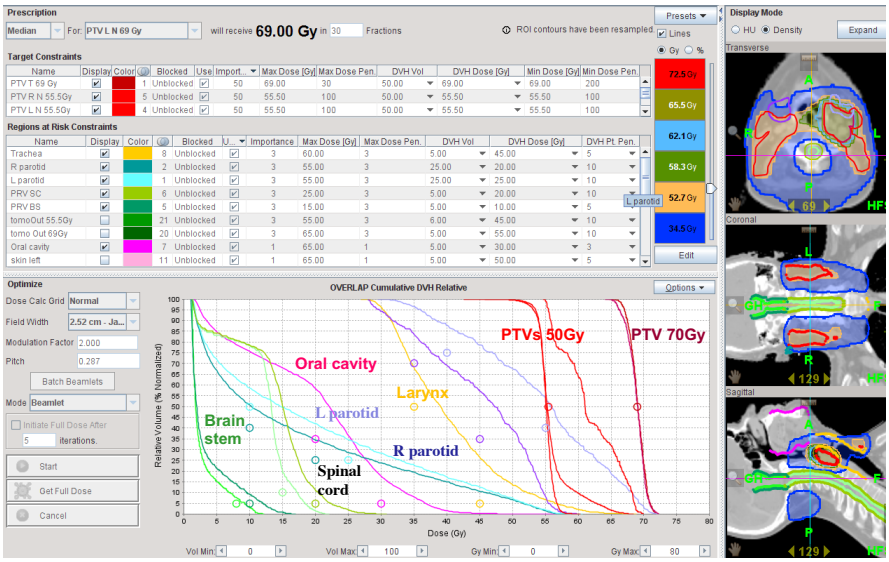
As pharmacology is to the internist so is radiation biology to the radiotherapist …

H.Rodney Withers & Lester J. Peters
Textbook of Radiotherapy by G.H. Fletcher, 3rd ed. 1980

“Exquisite” conformity: IMRT



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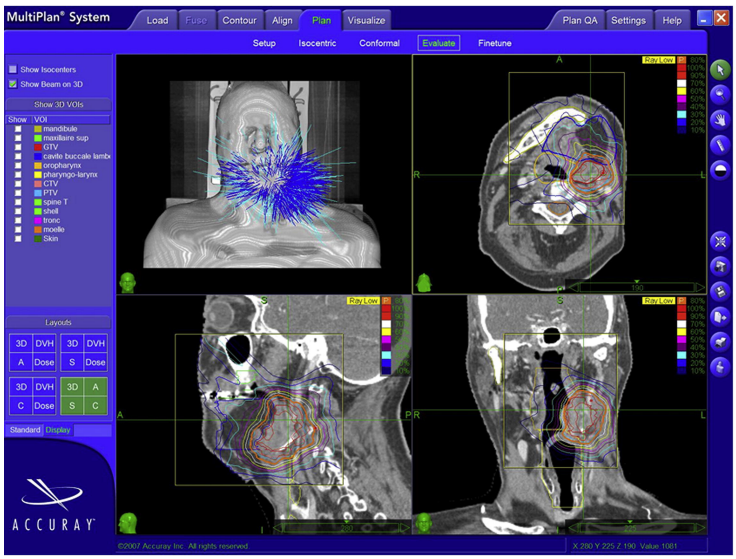
“Exquisite” conformity: SBRT



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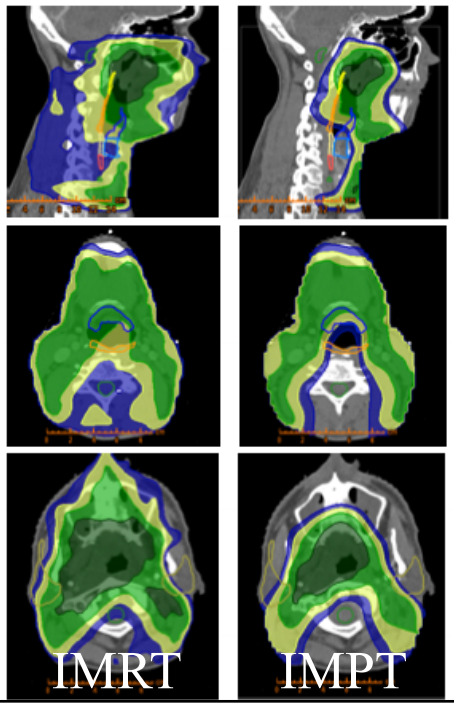
Comet et al, 2012



"Exquisite" conformity: IMPT

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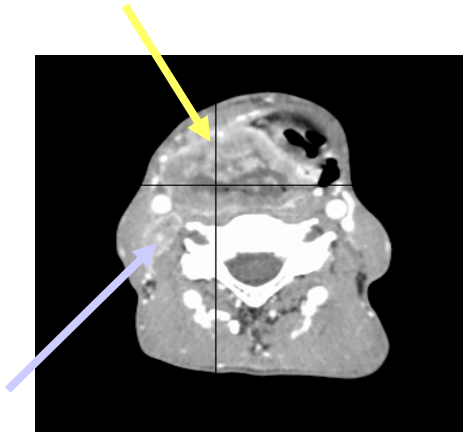
Langendijk, 2015

Clinical case

T4 N1 M0 hypopharyngeal SCC



Pre-treatment

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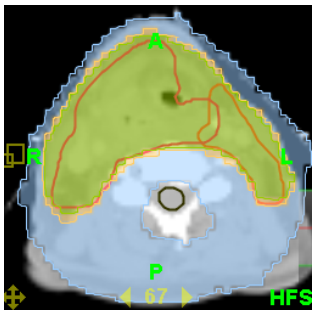
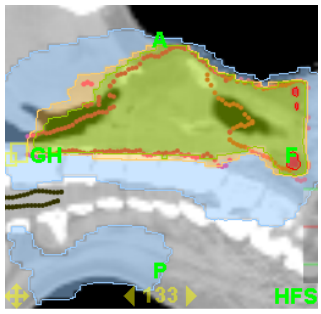
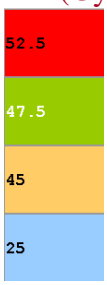
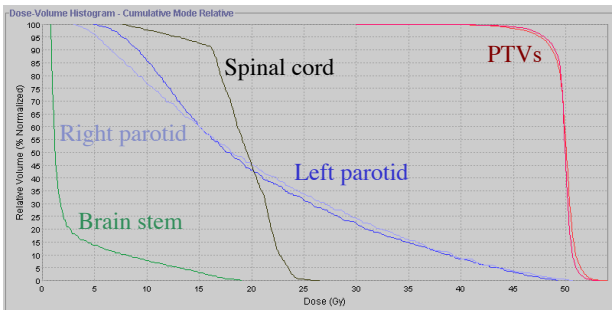
Tomotherapy and Head and Neck Tumors





Dose (Gy)





Hypopharyngeal SCC
T4-N1-M0
Dose: 25 x 2 Gy

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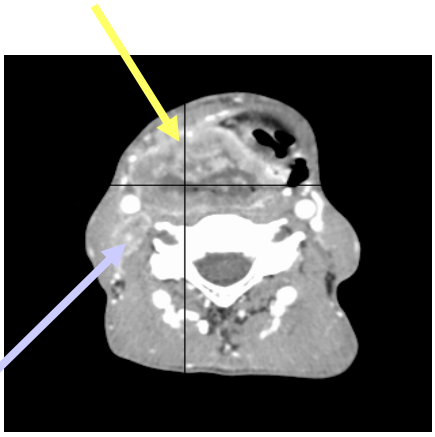
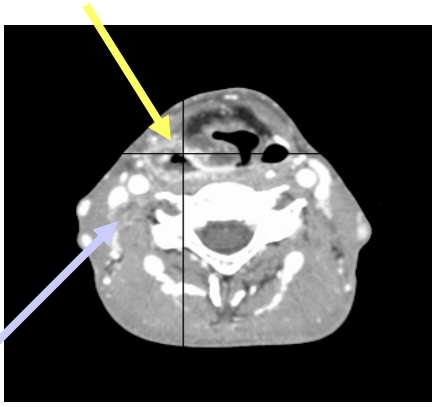
Clinical case

T4 N1 M0 hypopharyngeal SCC





Pre-treatment

After 50 Gy

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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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The "x" Rs of Radiotherapy

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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?

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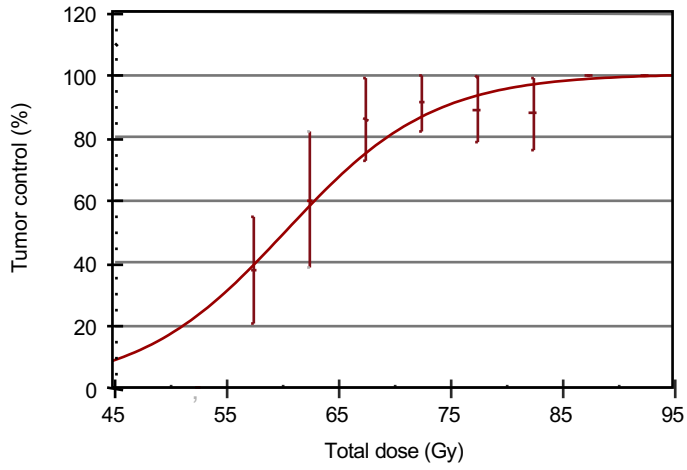
Tumor Control Probability (TCP)

Dose-response curve for neck nodes ≤ 3 cm



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Bataini et al, 1982

The "x" Rs of Radiotherapy

- Radiosensitivity
- **Repair**
- Repopulation
- Redistribution
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- iRradiated volume
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- Re-iRRadiation
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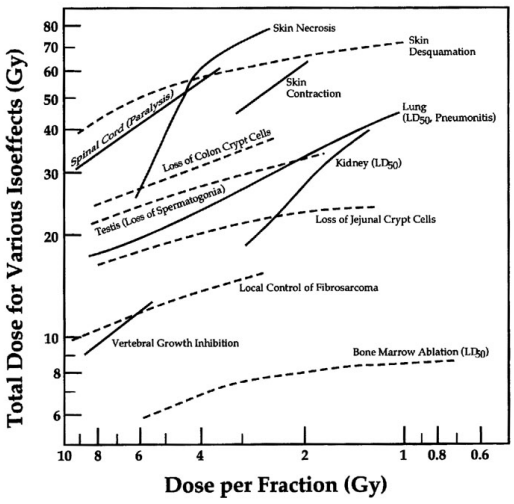
Fractionation sensitivity

"Typical" dose per fraction

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



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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)

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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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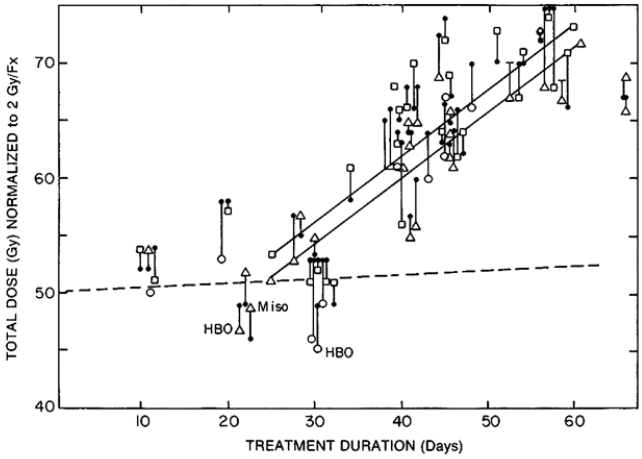
Radiobiological and clinical issues in IMRT for HNSCC

Influence of overall treatment time on HNSCC local control



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Withers et al, 1988

Radiobiological and clinical issues in IMRT for HNSCC

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

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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

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)

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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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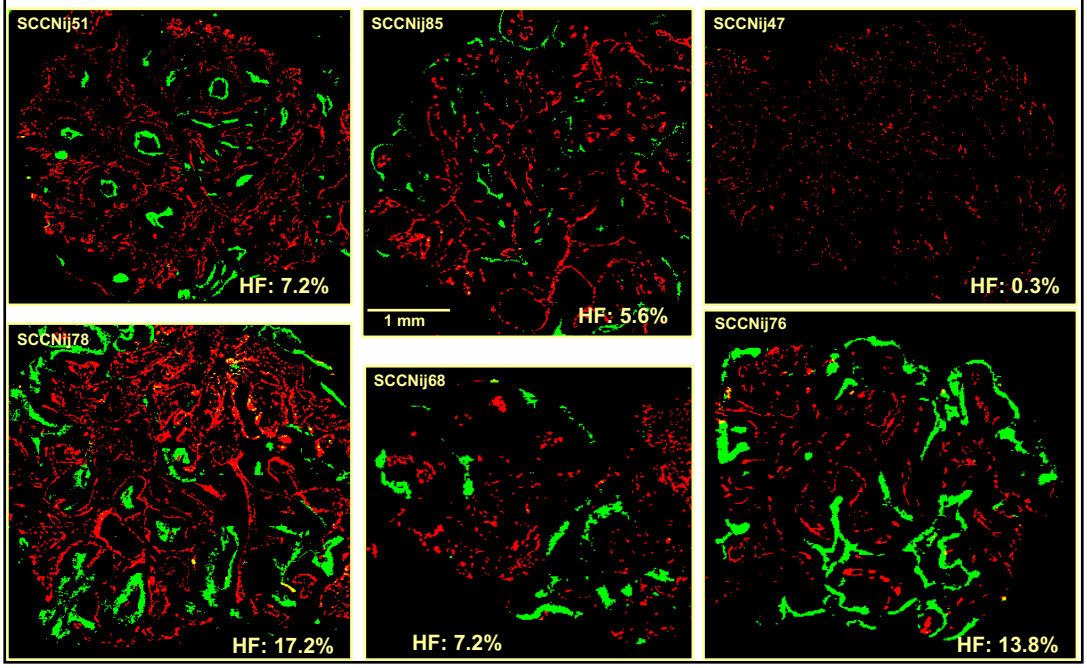
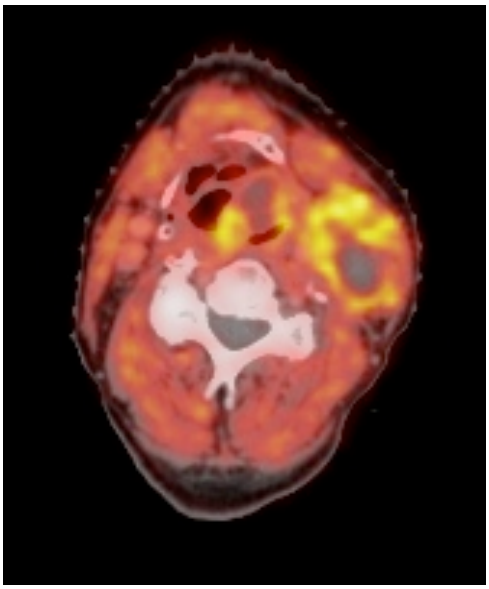
Hypoxia and vessels in H&N cancer biopsies



Hypoxic tracer ^{18}FAZA



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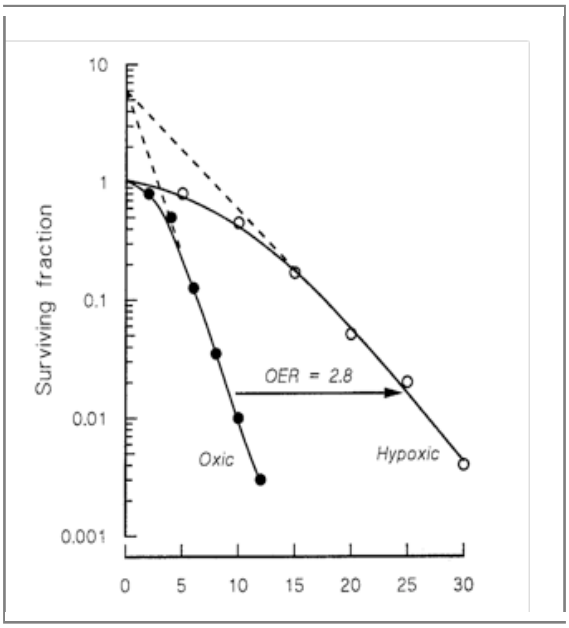
Servagi, 2013

Tumor hypoxia : a foe !



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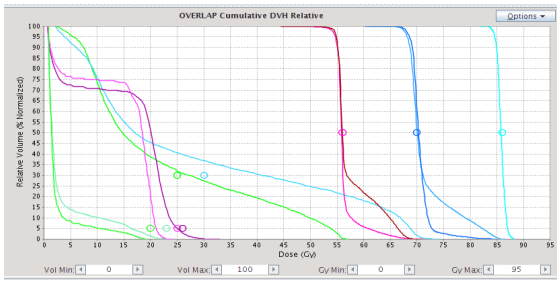
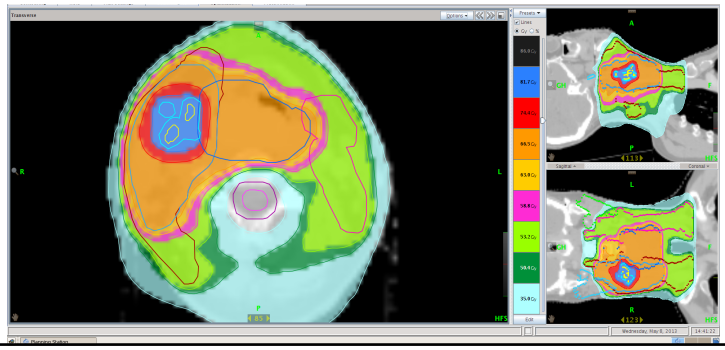
Steel, 1993

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



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



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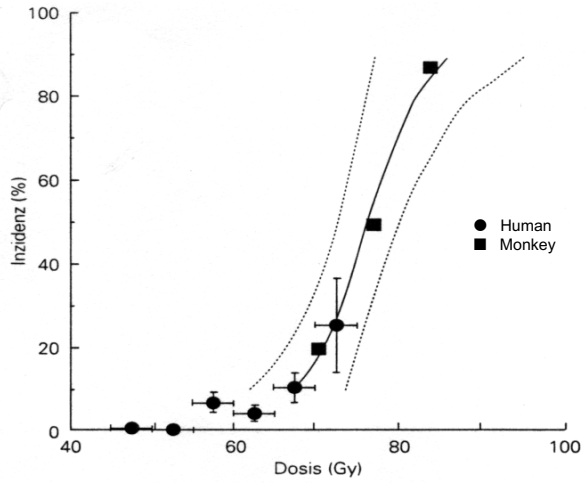
Servagi, 2013

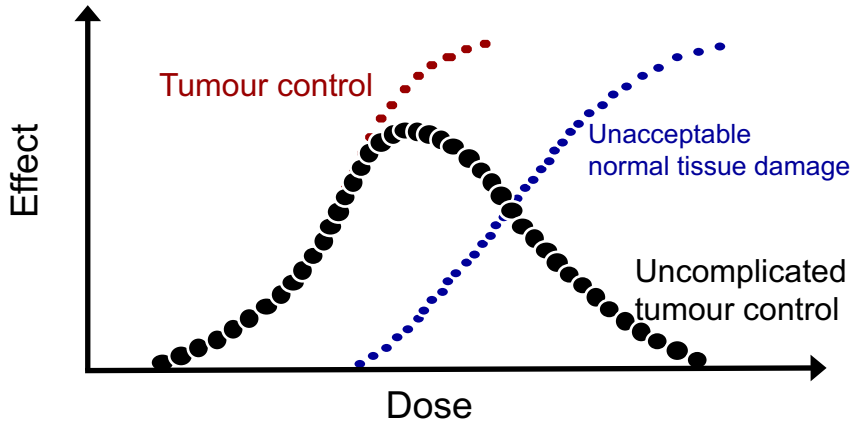
But …
The other face of the coin…

Normal Tissue Control Probability (NTCP)

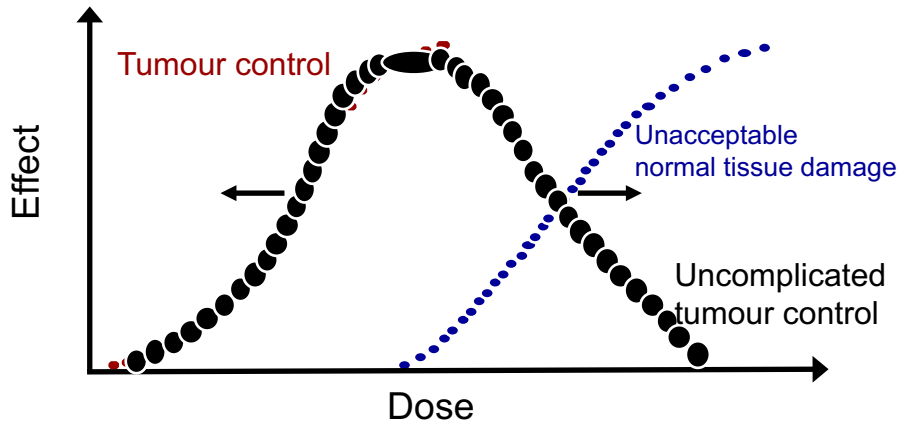


Baumann et al., *Strahlenther Onkol* 170: 131-139, 1994

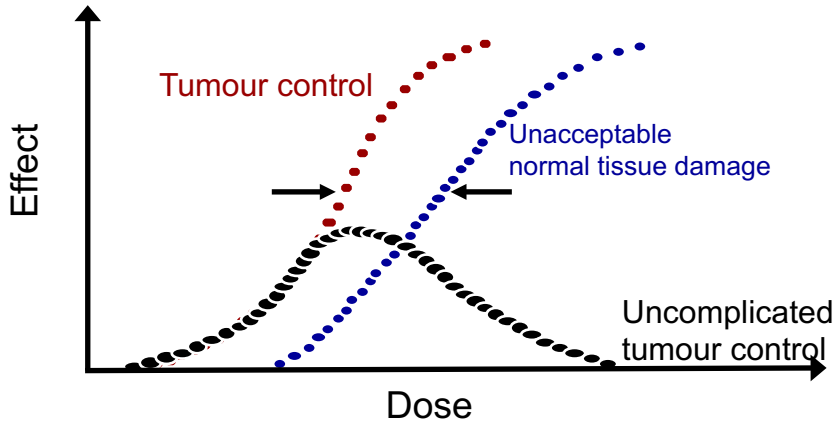
Uncomplicated tumor control: Therapeutic Ratio



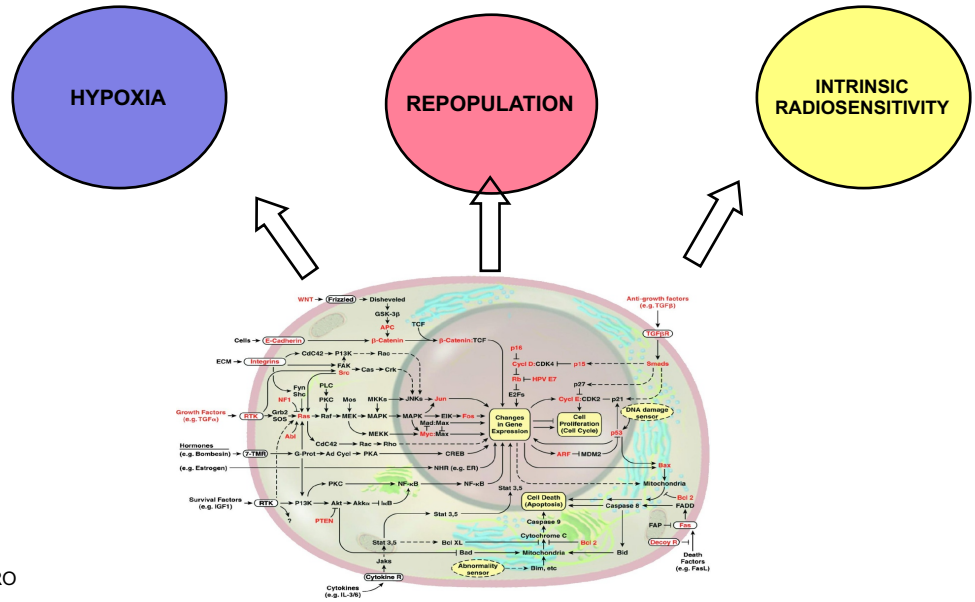
Uncomplicated tumor control: Therapeutic Ratio



Uncomplicated tumor control: Therapeutic Ratio



Target pathways that influence radiotherapy



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Therapeutic interventions

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

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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?

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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?

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Yes… but in my daily practice…

Julia Freud (11 years old girl) from Vienna:

- 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)?

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Yes… but in my daily practice…

Mr David PSA (82 years old) from Paris:

- 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?

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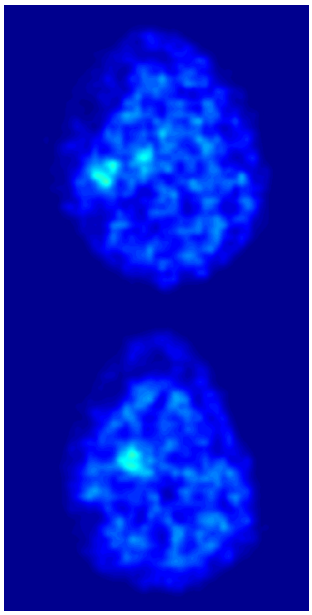
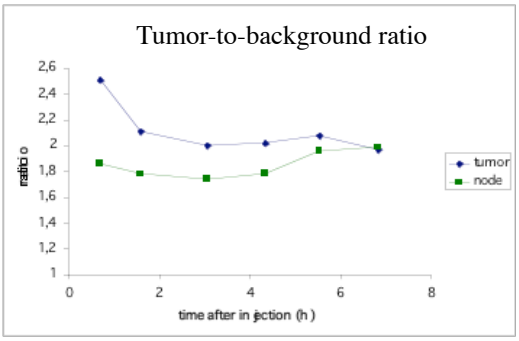
Take home message

Tumor Hypoxia [^{18}F] EF3



[^{18}F]-EF3 tracer
Hypopharyngeal SCC



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P Mahy, 2005

The Hallmarks of Cancer

Marianne Koritzinsky

Princess Margaret Cancer Centre
Toronto, Canada
Marianne.Koritzinsky@uhnresearch.ca

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

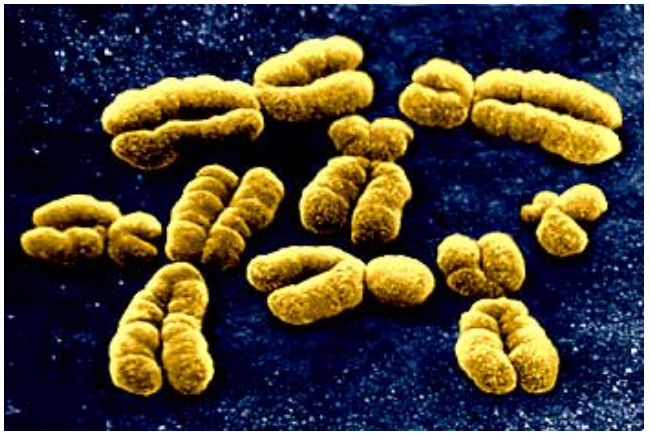
What is Cancer?

Cancer – Important Concepts

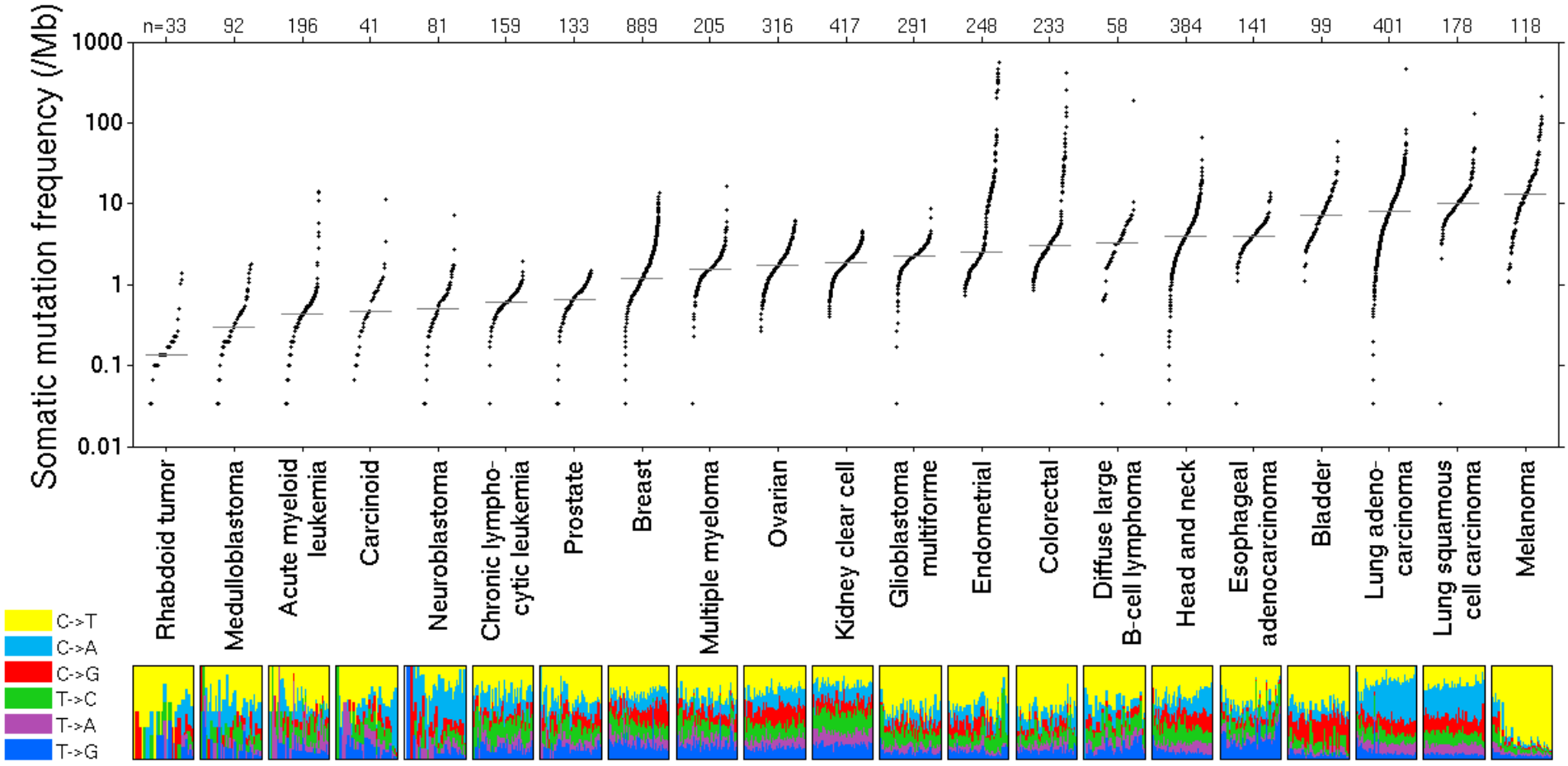
- Cancer cells are derived from normal cells in the body
- Cancer cells have acquired a series of changes which distinguishes them from normal cells.
  - These changes are the basis for much of the difference in the ways tumors respond to radiation compared to normal tissues
- There are multiple ways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

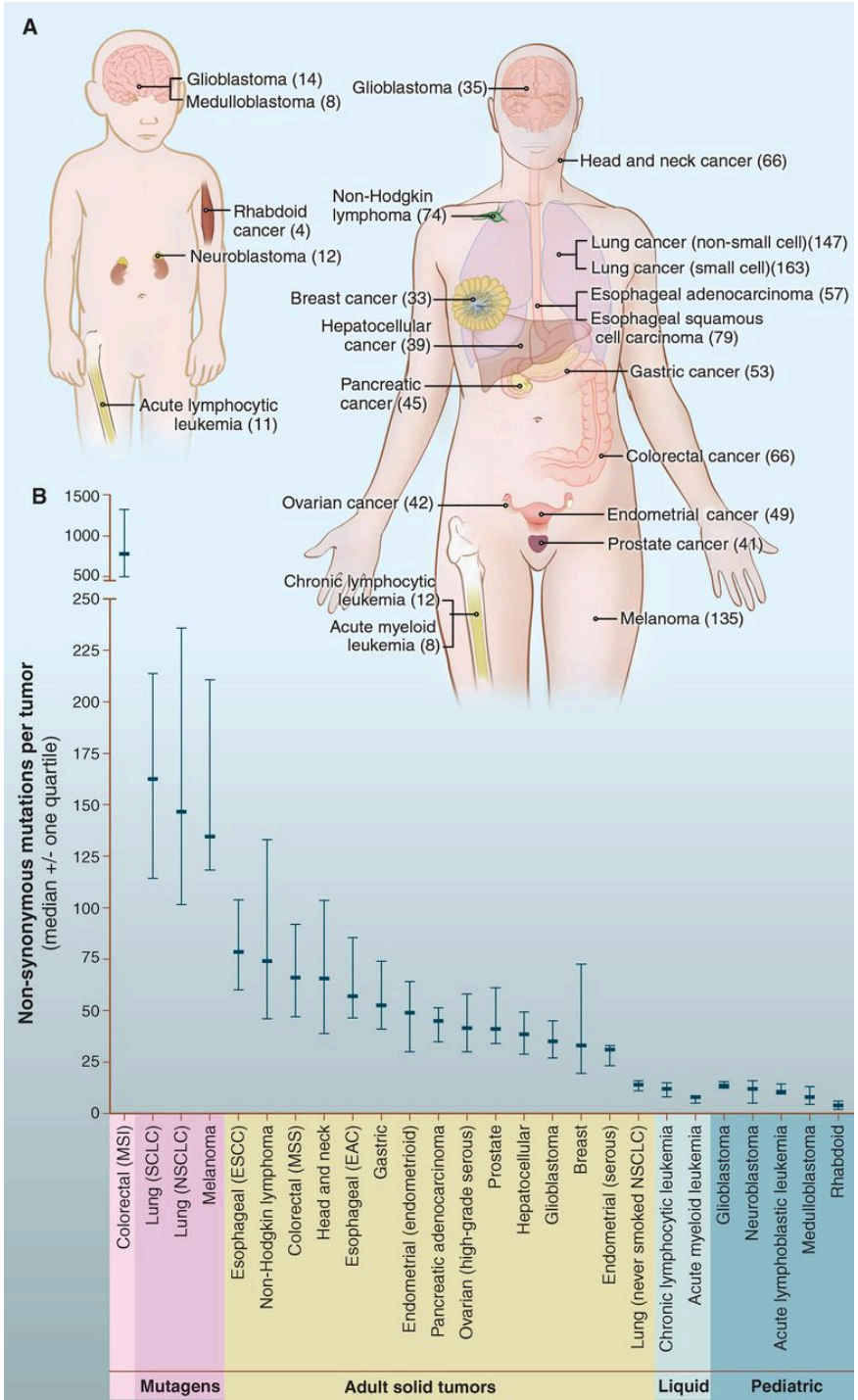
Cancer is a genetic disease

- Disease involving 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 Analysis - TCGA

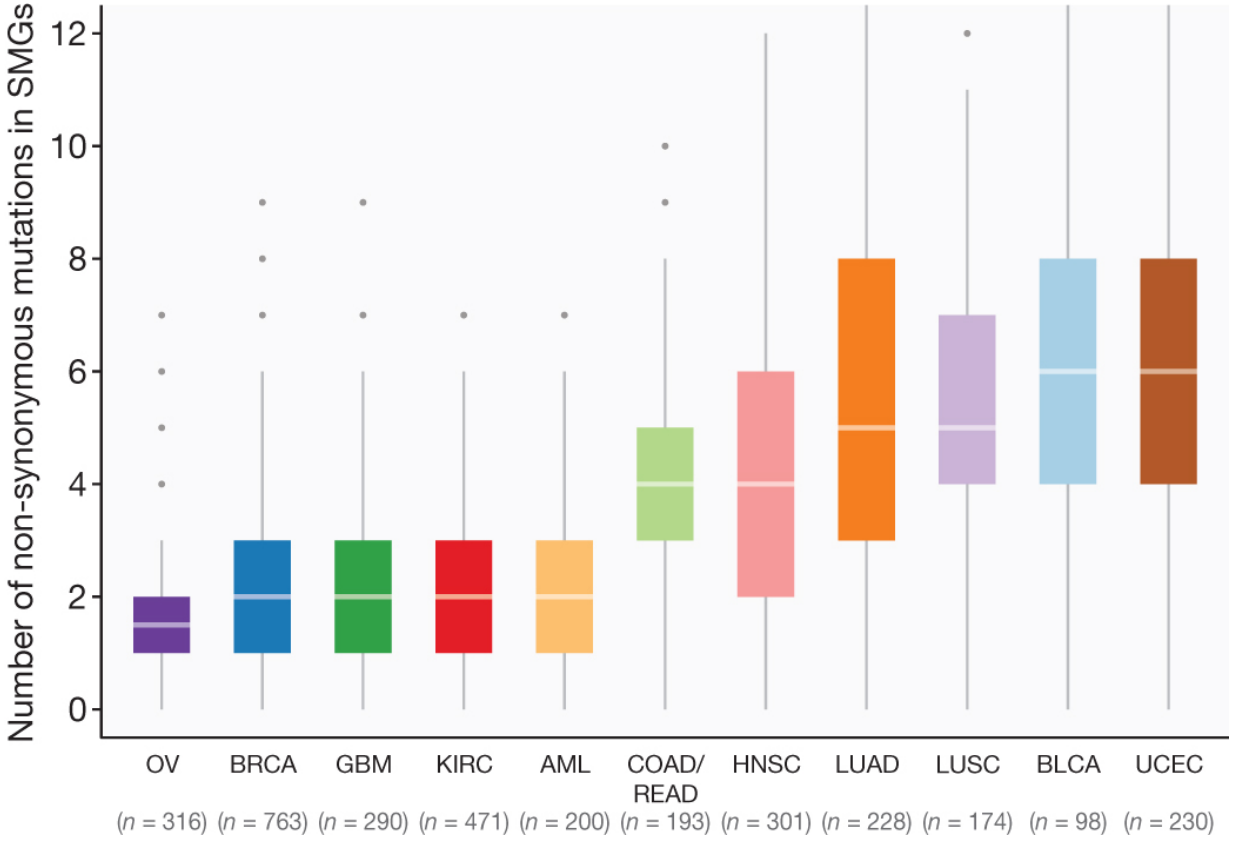




B Vogelstein et al. Science 2013;339:1546-1558

Identifying Drivers

Distribution of mutations in 127 SMGs across Pan-Cancer cohort.



•C Kandoth *et al. Nature* **502**, 333-339 (2013) doi:10.1038/nature12634

nature

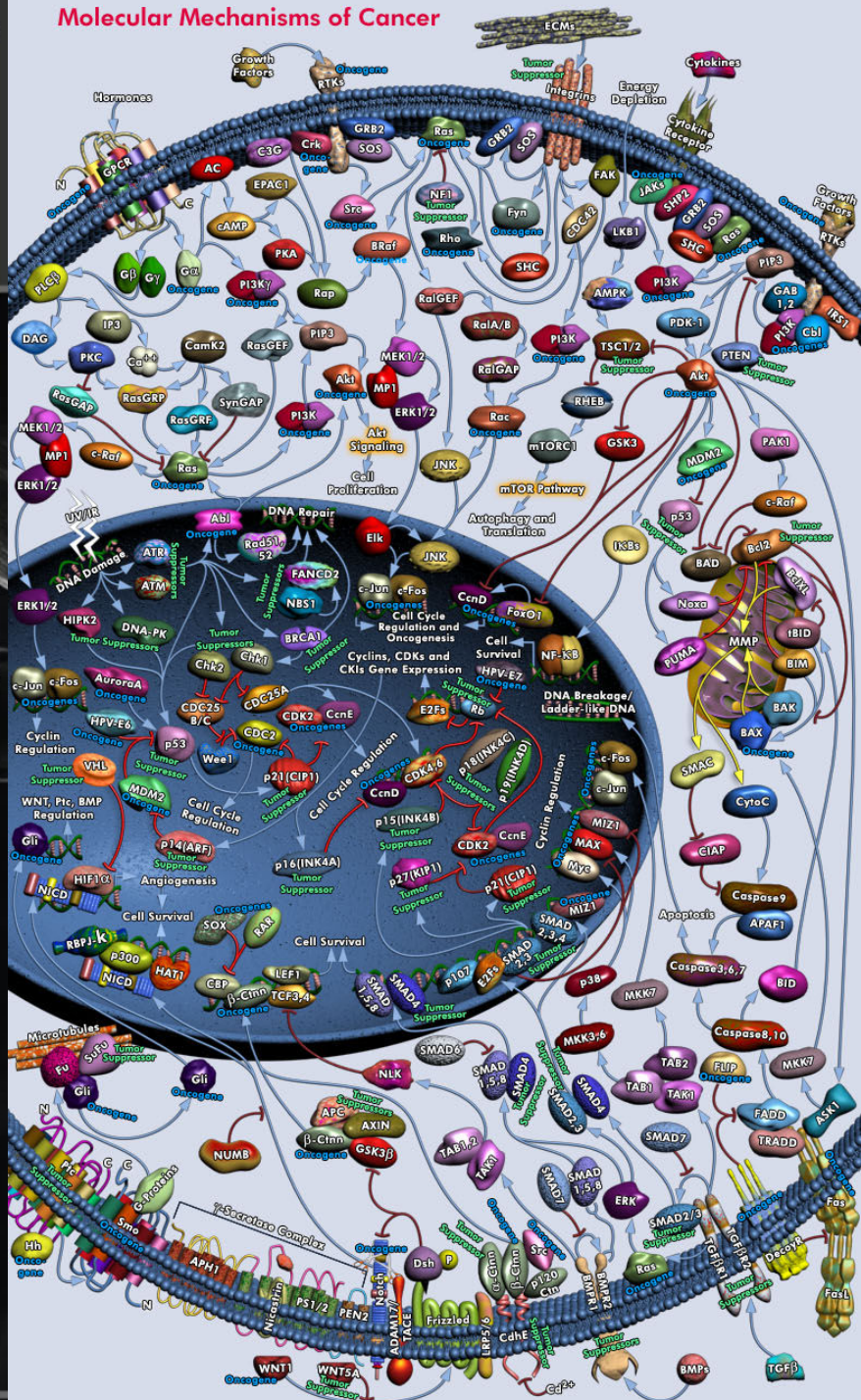
Summary

- Most cancers contain mutations in 2-8 commonly mutated cancer genes
- Many cancers have additional but rare cancer genes
- Much larger background of passenger mutations
- Passenger mutations increase with age

Pathways in Human Cancer

This poster summarizes some of the key signaling pathways implicated in tumorigenesis and tumor progression in humans. Within each pathway, gene products known to be mutated in human tumors - oncogenes and tumor suppressor genes - have been color-coded. The most common types of genetic alterations and conferred capabilities to the tumor are also appended for these gene products. Proteins are shown using a structural representative (see structural legend). Since not all known pathways or proteins could be included, we regret not being able to show the work of many, and refer the viewer to the textbook *The Biology of Cancer* by Robert A. Weinberg for an in-depth treatment of this material and references.

Molecular Mechanisms of Cancer



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"

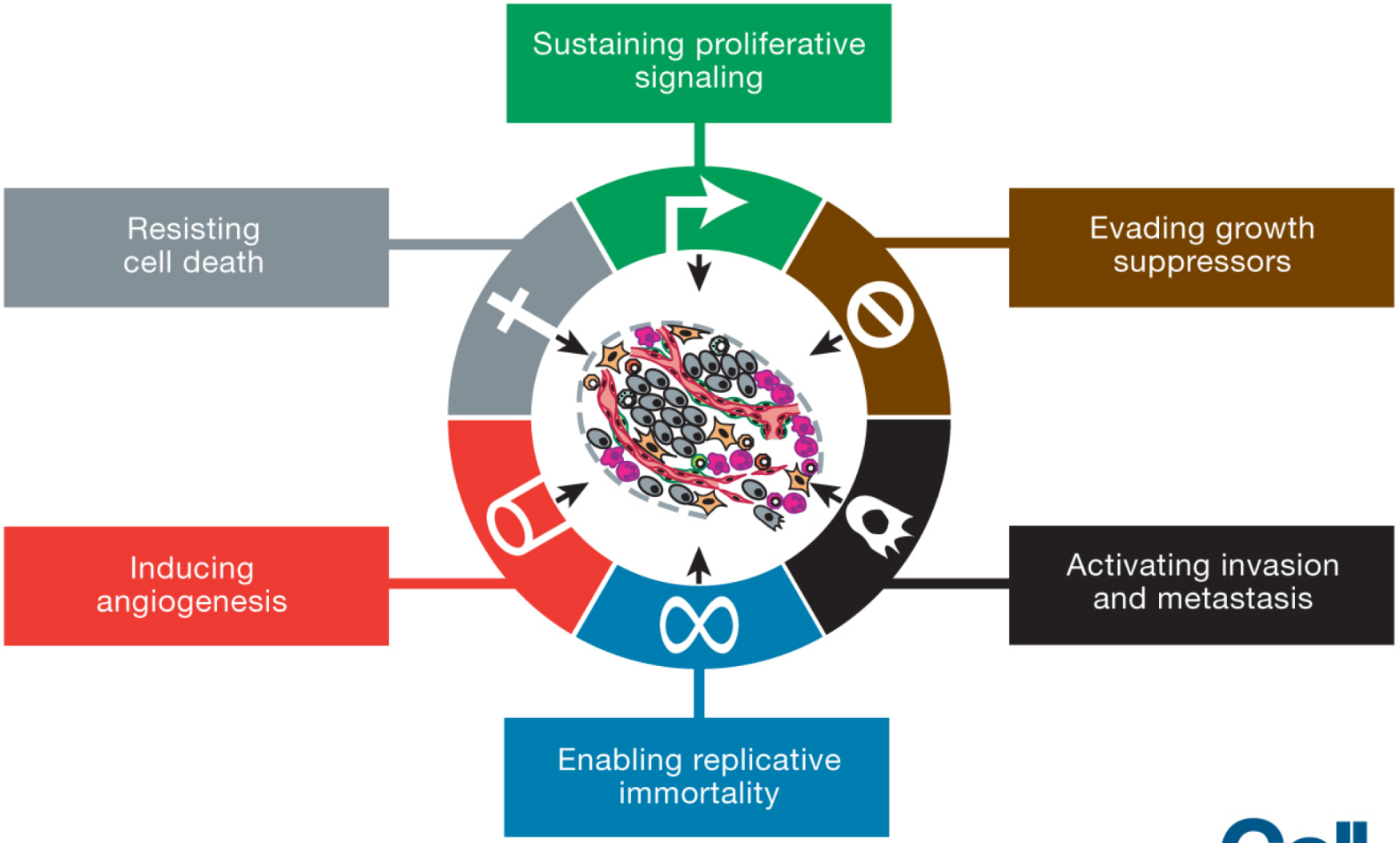
Hallmarks of Cancer: The Next Generation

Douglas Hanahan[1,2,*] and Robert A. Weinberg[3,*]

646 Cell *144*, March 4, 2011 ©2011 Elsevier Inc.

"Conceptual progress in the last decade has added two emerging hallmarks and two enabling characteristics."

The 6 Hallmarks of Cancer



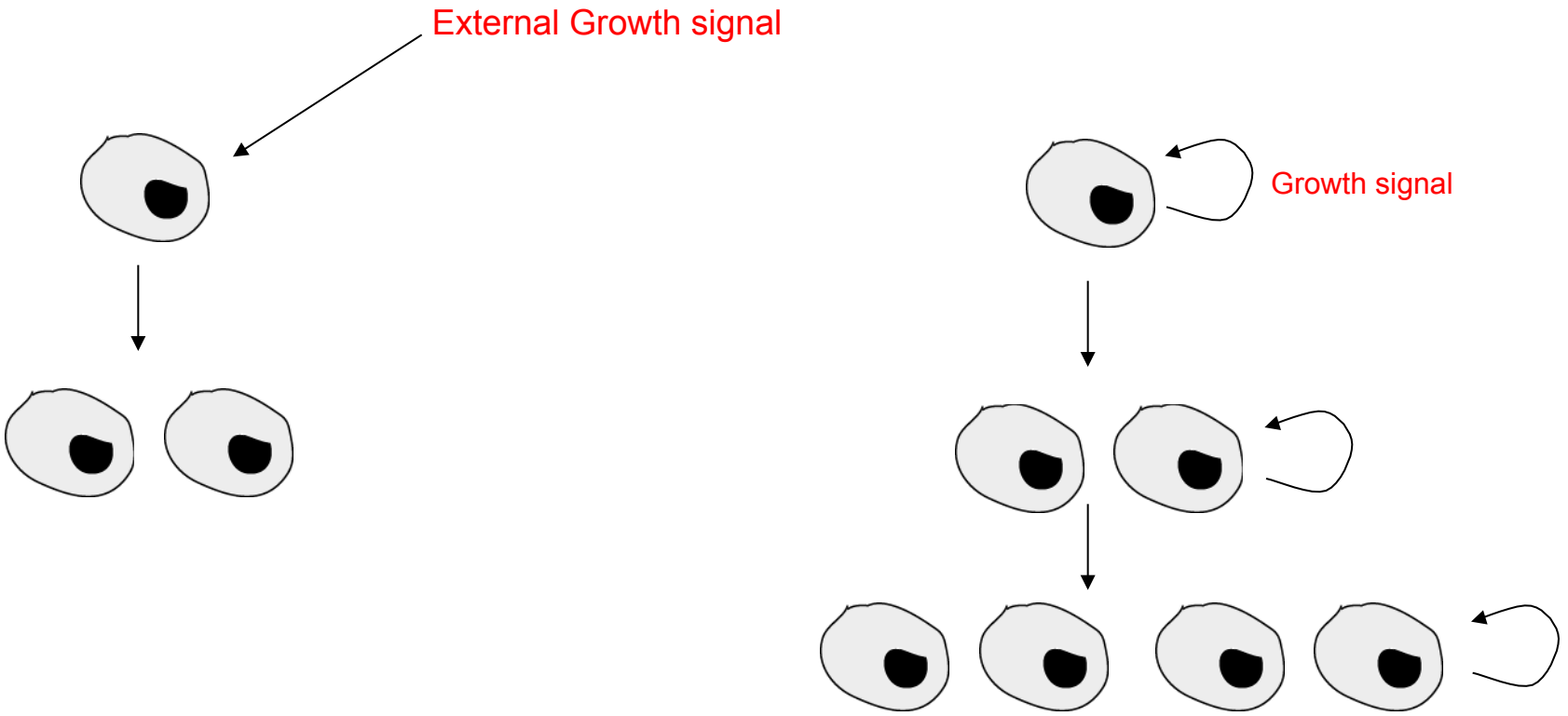
Hanahan and Weinberg, 2011

Cell PRESS

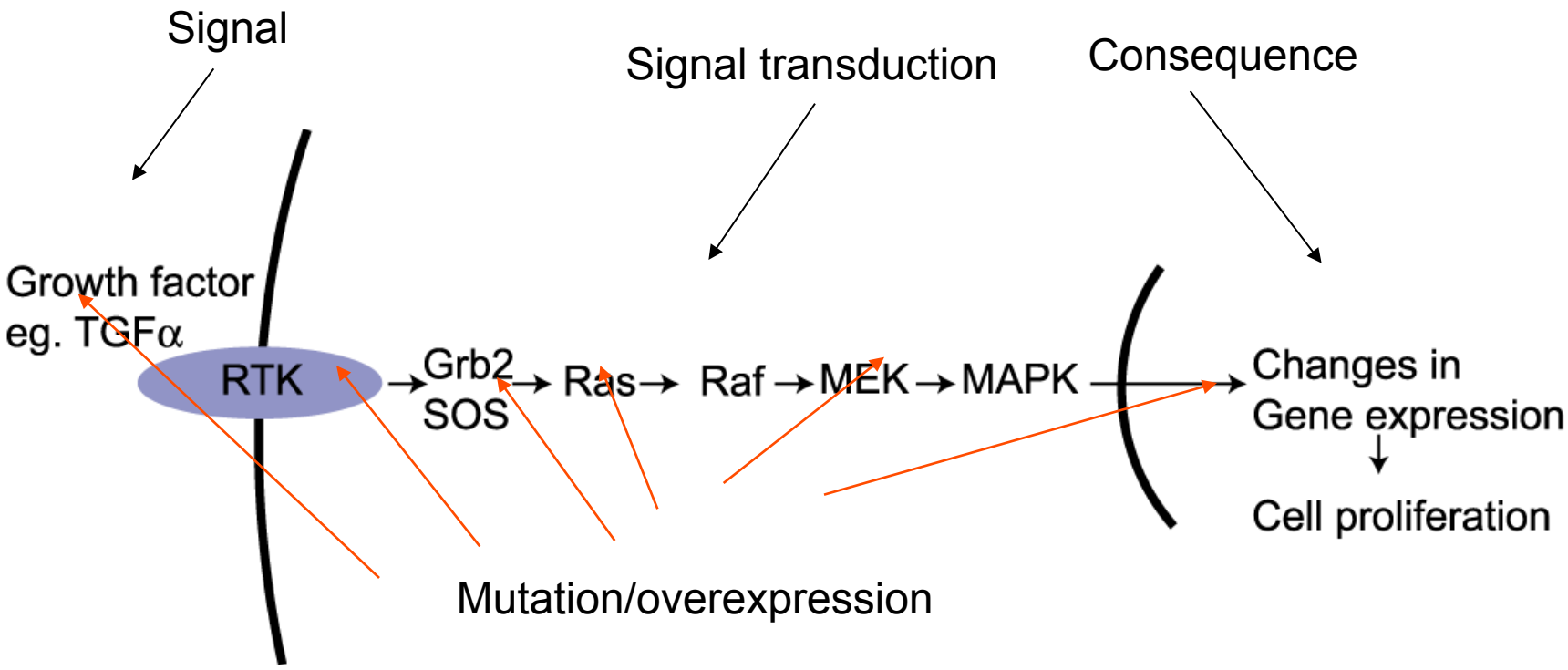
1) Sustaining proliferative signaling

Normal

Cancer



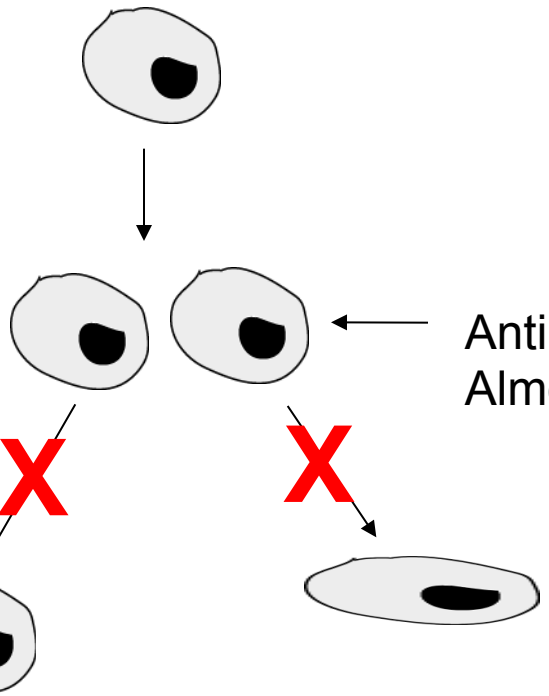
1) Sustaining proliferative signaling



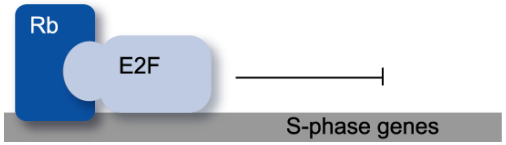
2) Evading growth suppressors

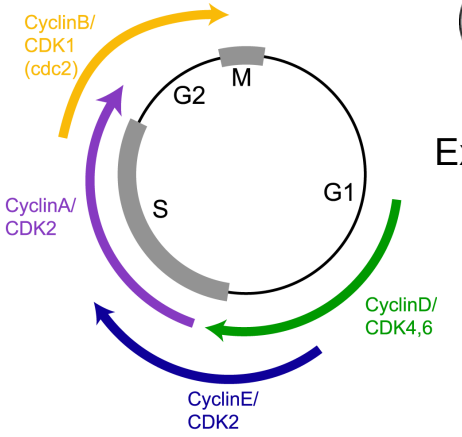
Normal cells

Cancer cells



Antiproliferative signal
Almost always through Rb

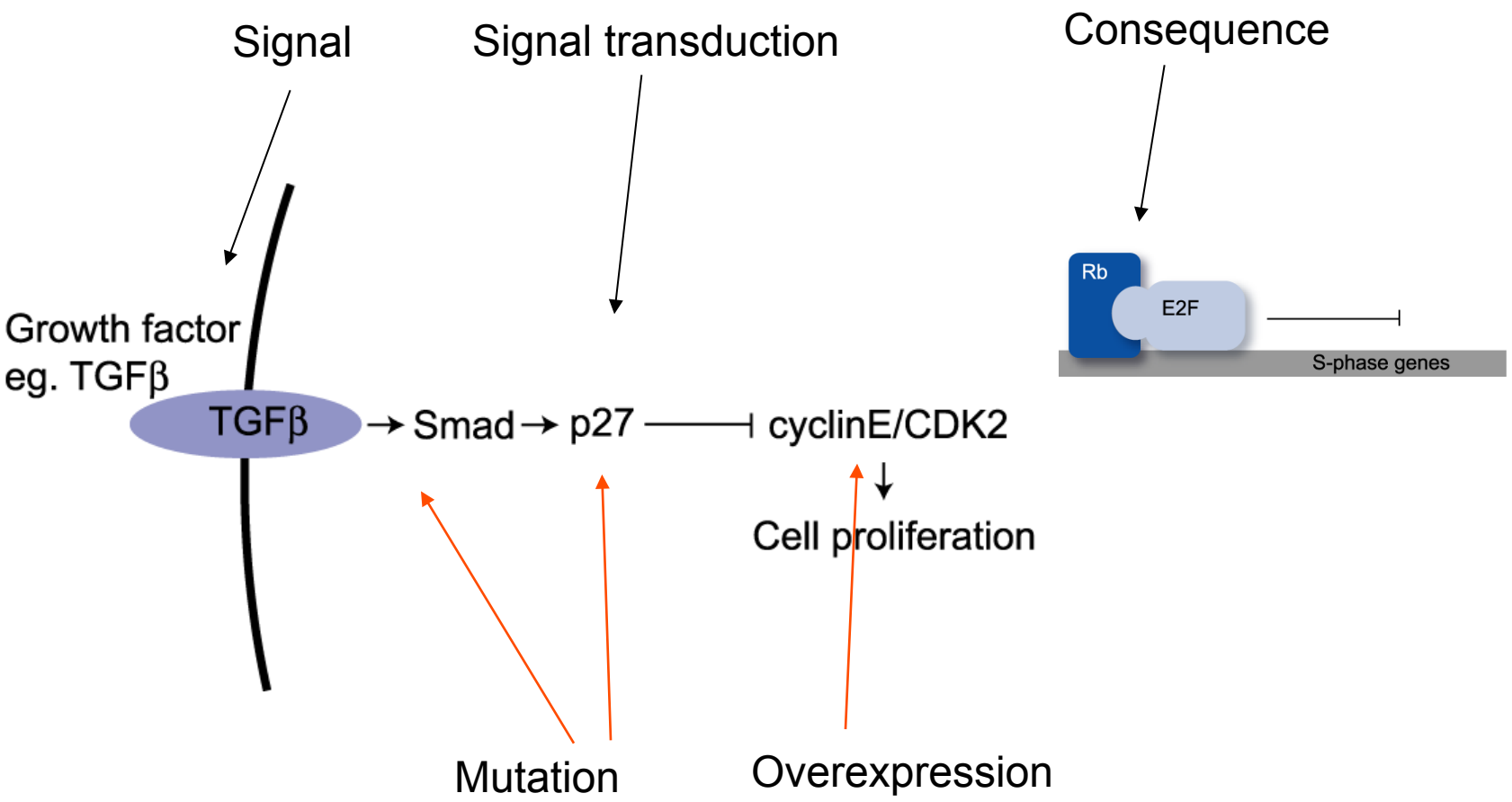




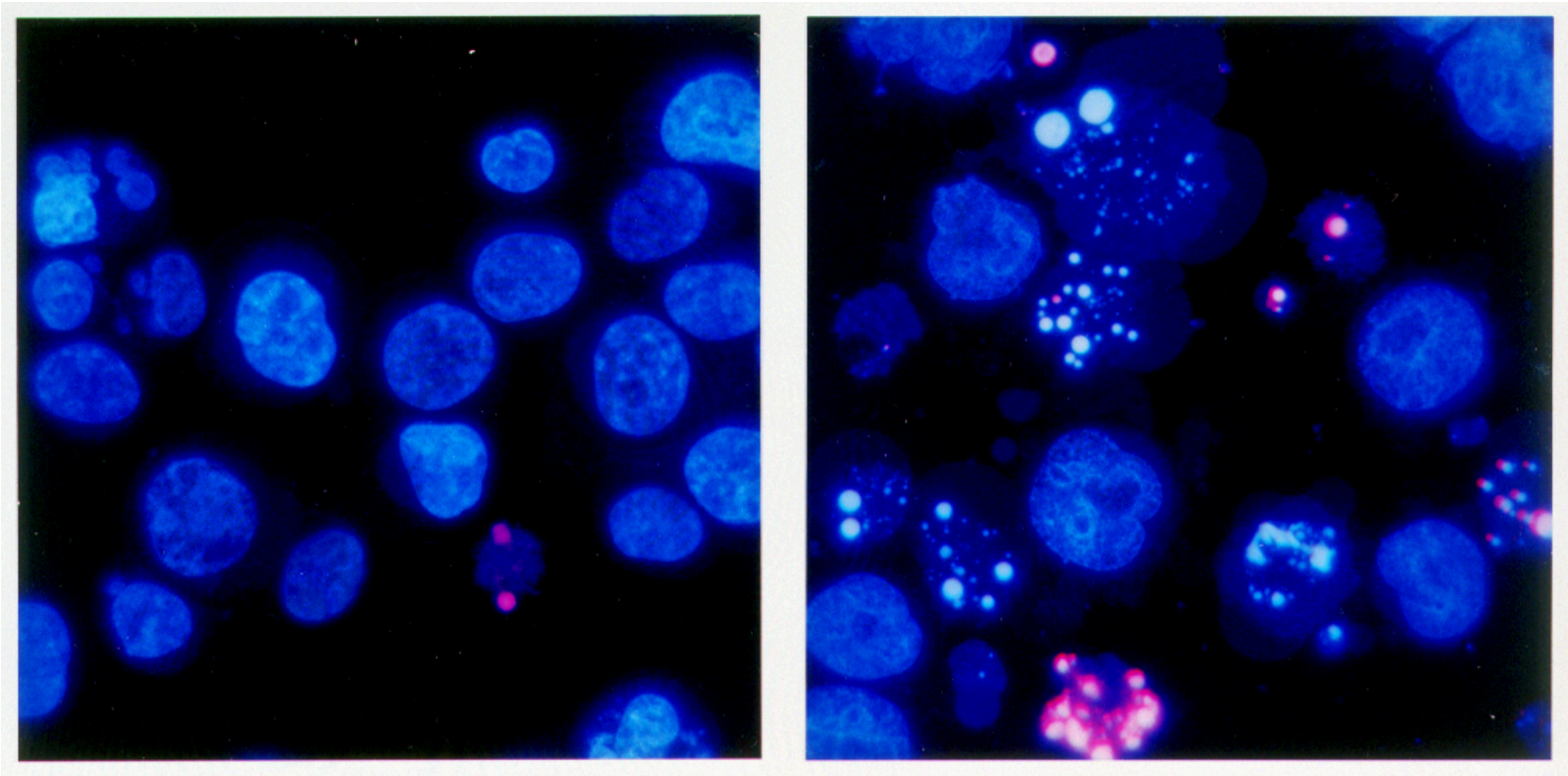
Exit the cell cycle - Go

Differentiation,
senescence

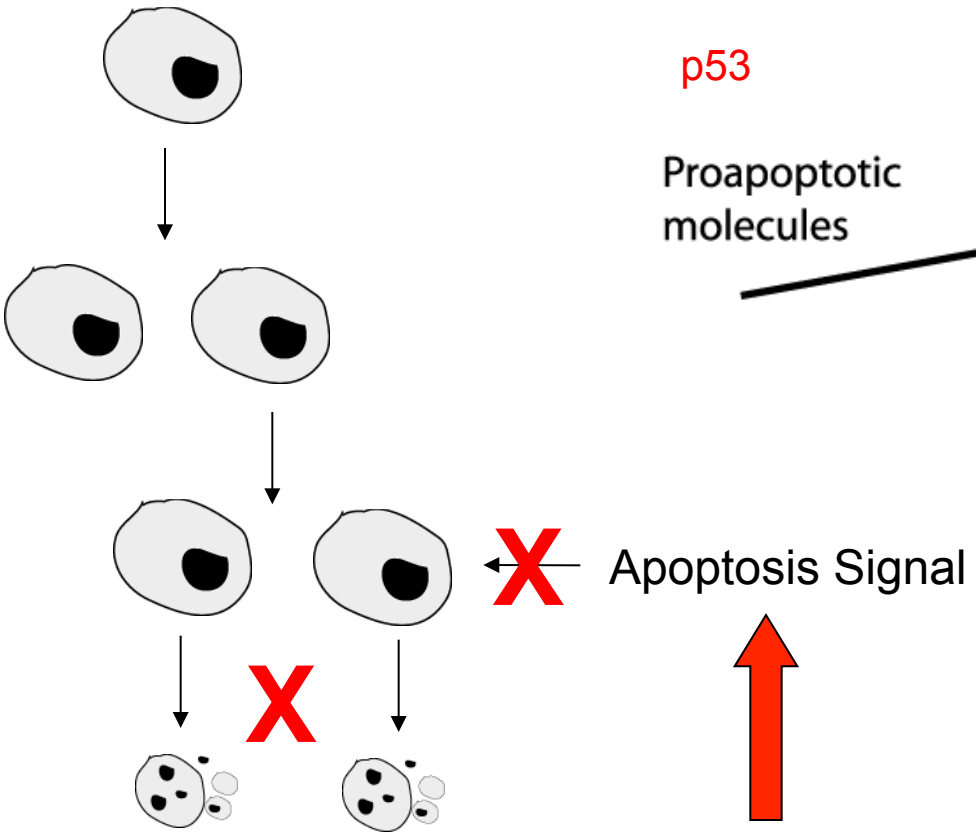
2) Evading growth suppressors



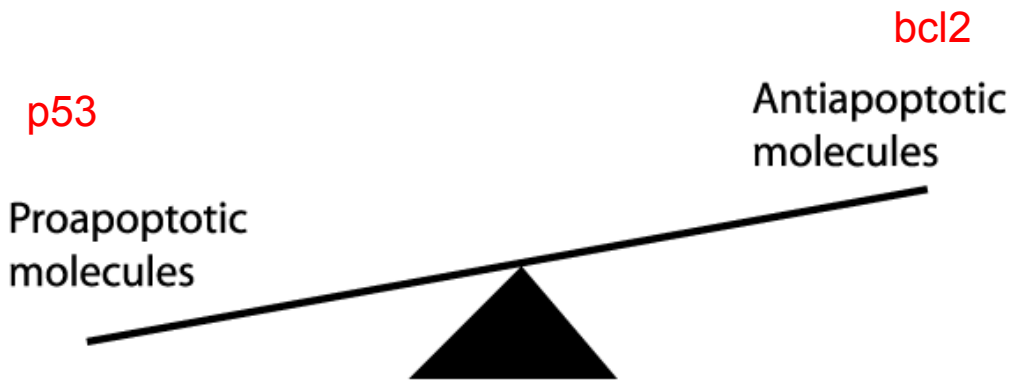
3) Resisting death



3) Resisting Apoptosis

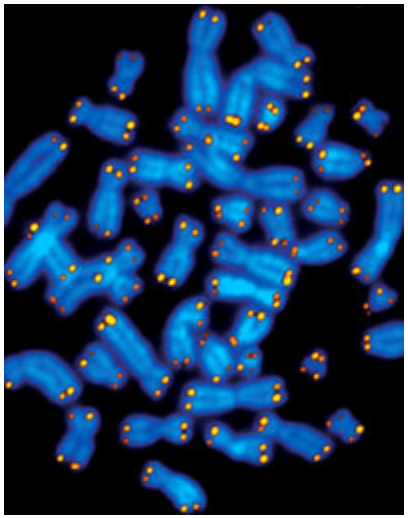


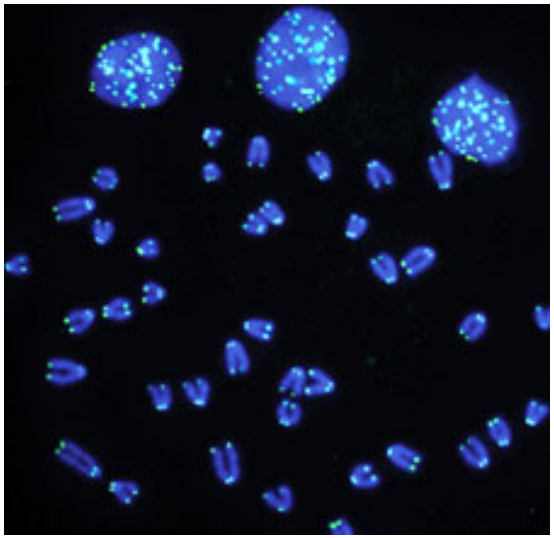
Apoptosis Signal

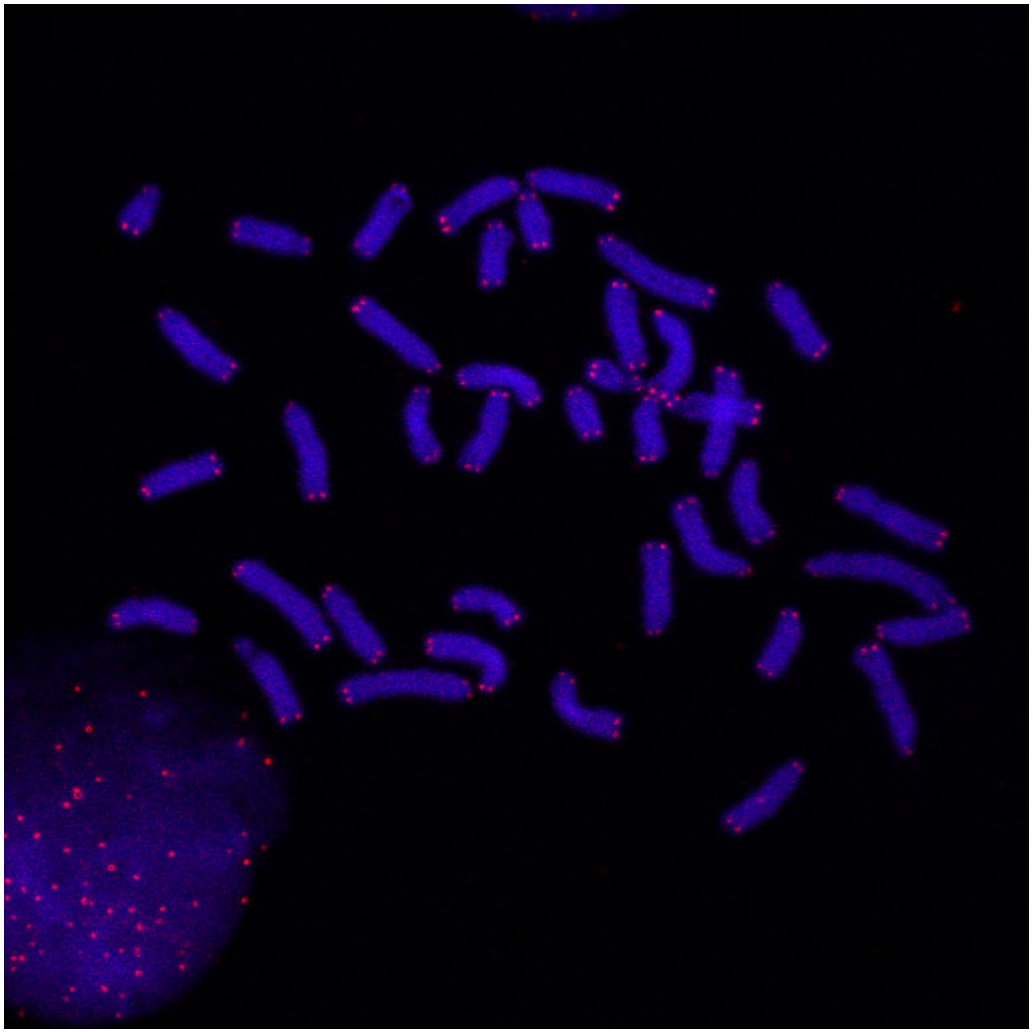


Tumor suppressor

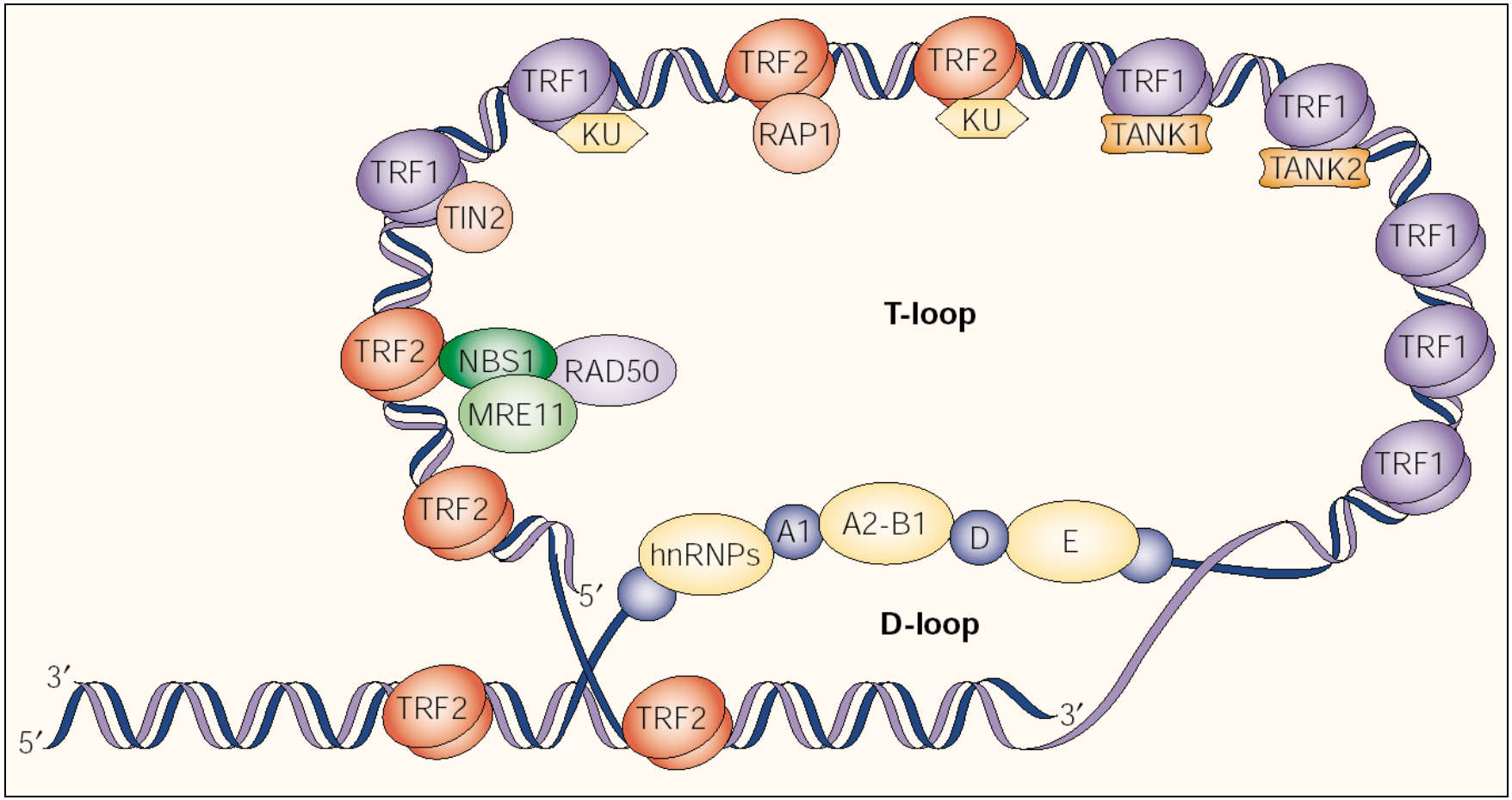
4) Enabling Replicative Immortality



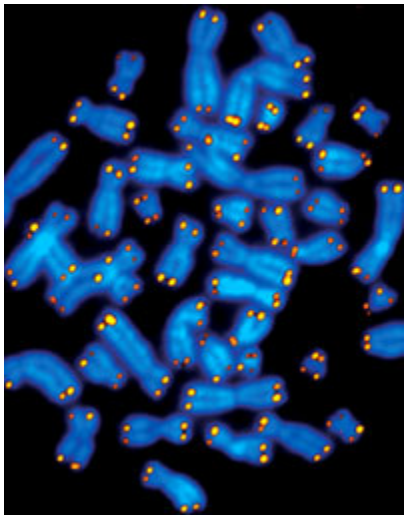


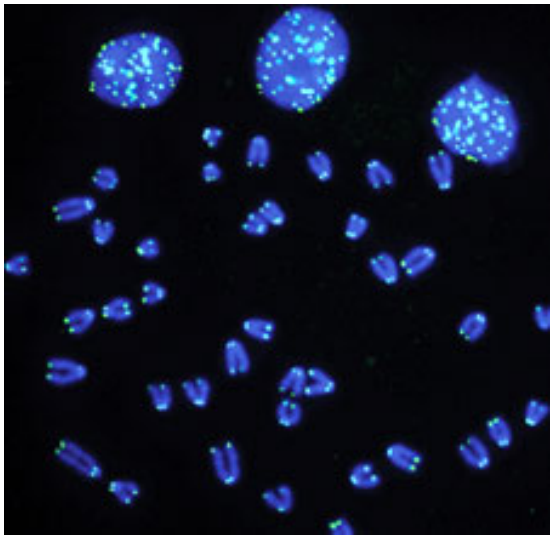


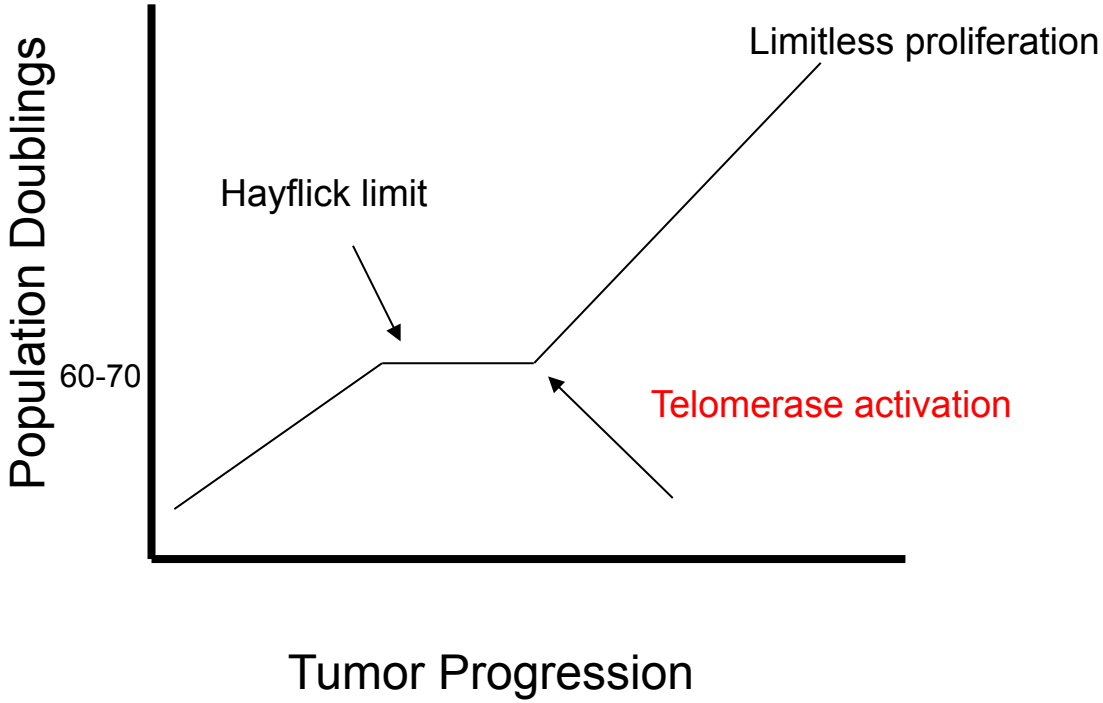
Telomeres


TRF1
KU
TRF2
RAP1
TRF2
KU
TRF1
TANK1
TRF1
TANK2
TRF1
TIN2
TRF1
T-loop
TRF2
NBS1
RAD50
MRE11
TRF1
TRF1
TRF2
hnRNPs
A1
A2-B1
D
E
5′
D-loop
3′
5′
TRF2
TRF2
3′

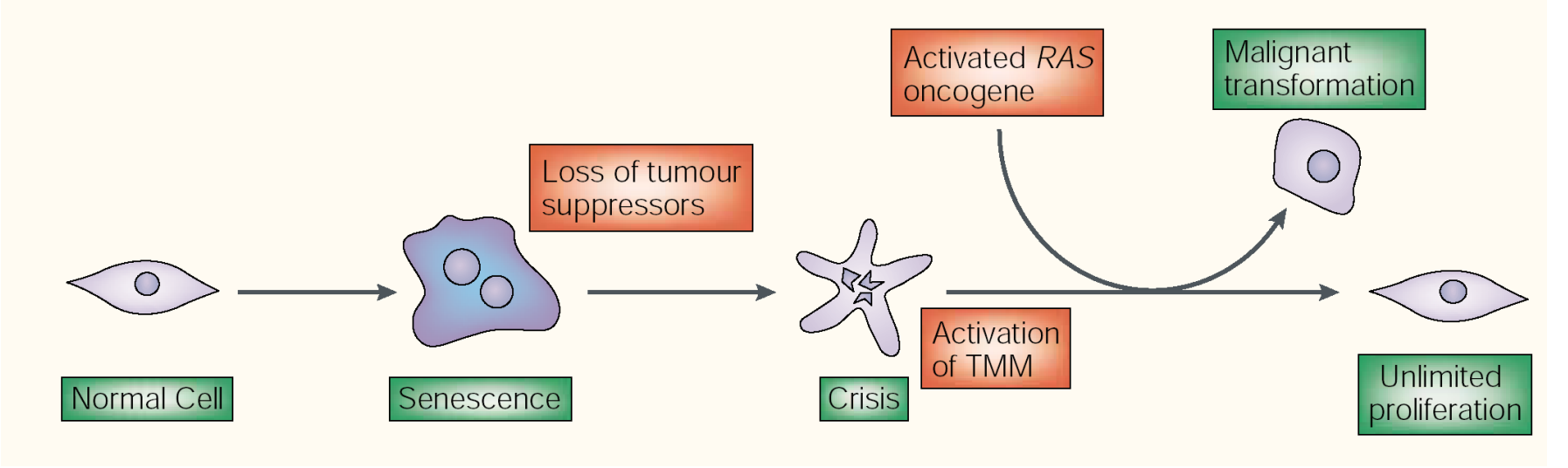
4) Enabling Replicative Immortality





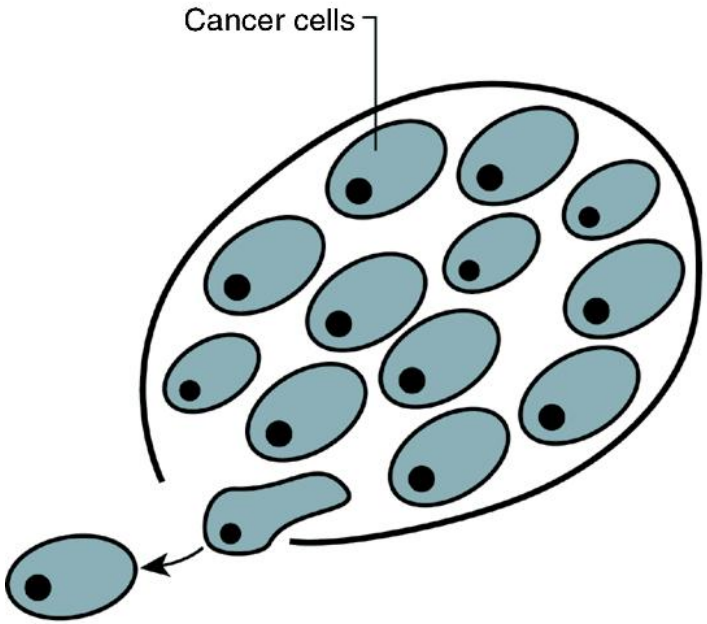


4) Avoiding Senescence and Crisis

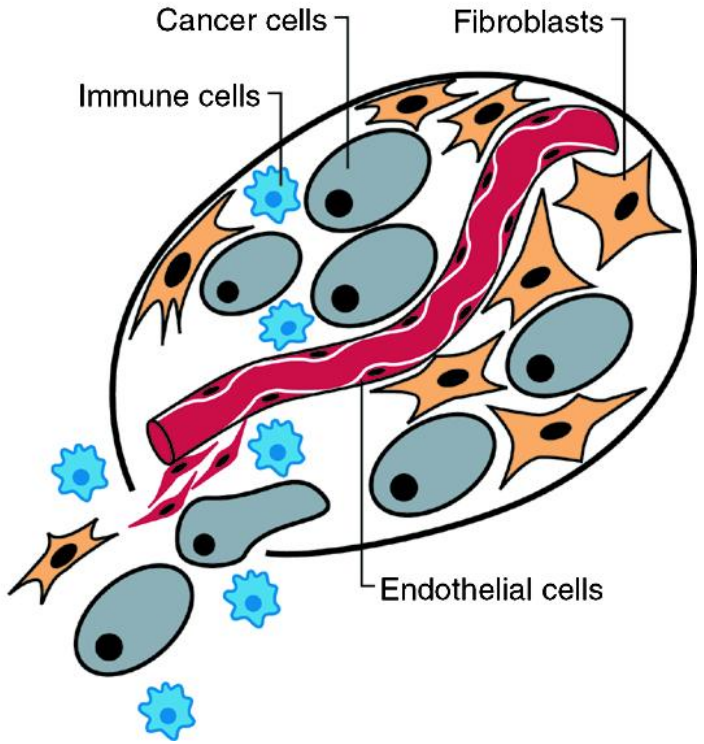


5) Inducing Angiogenesis

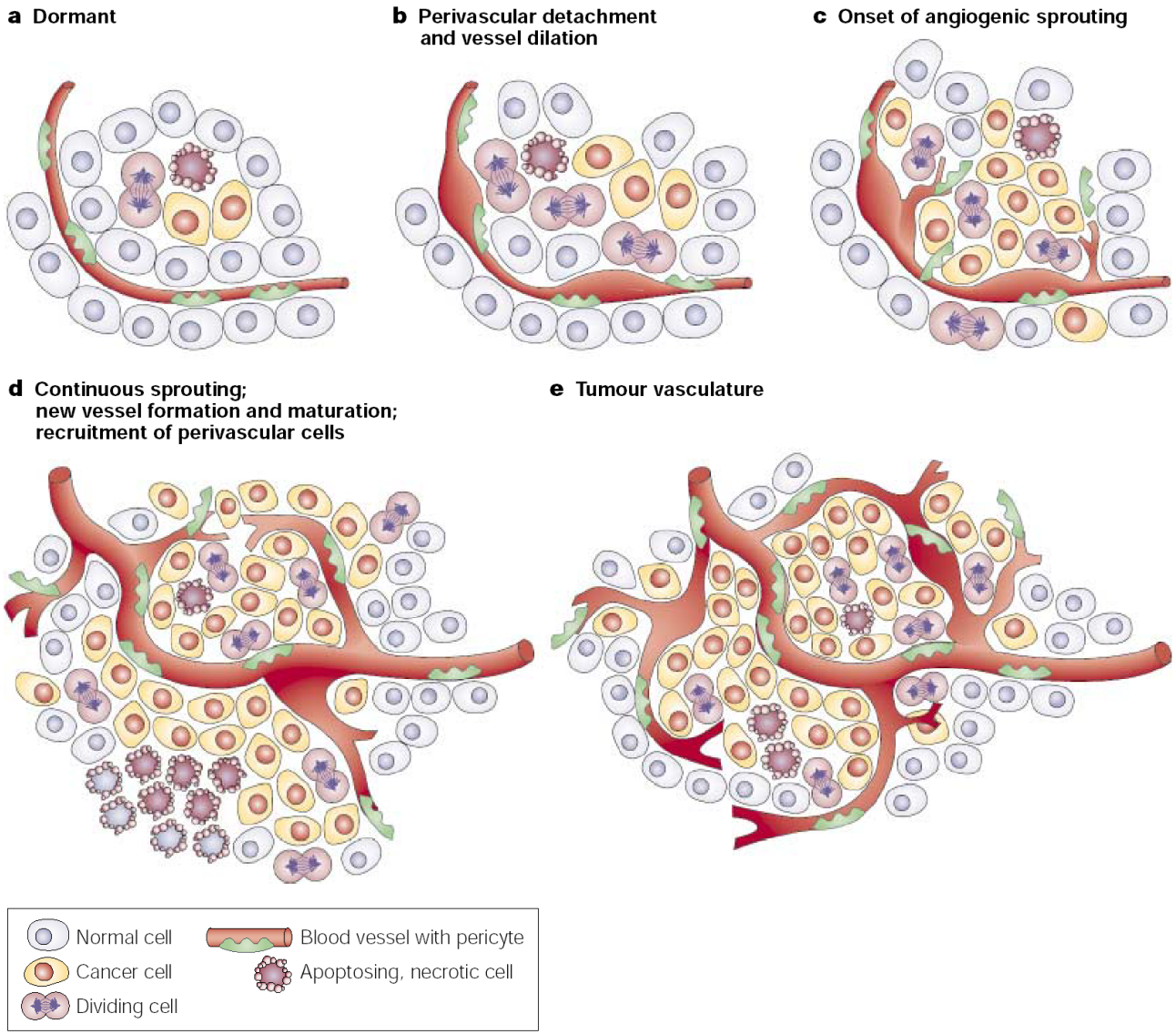
The Reductionist View



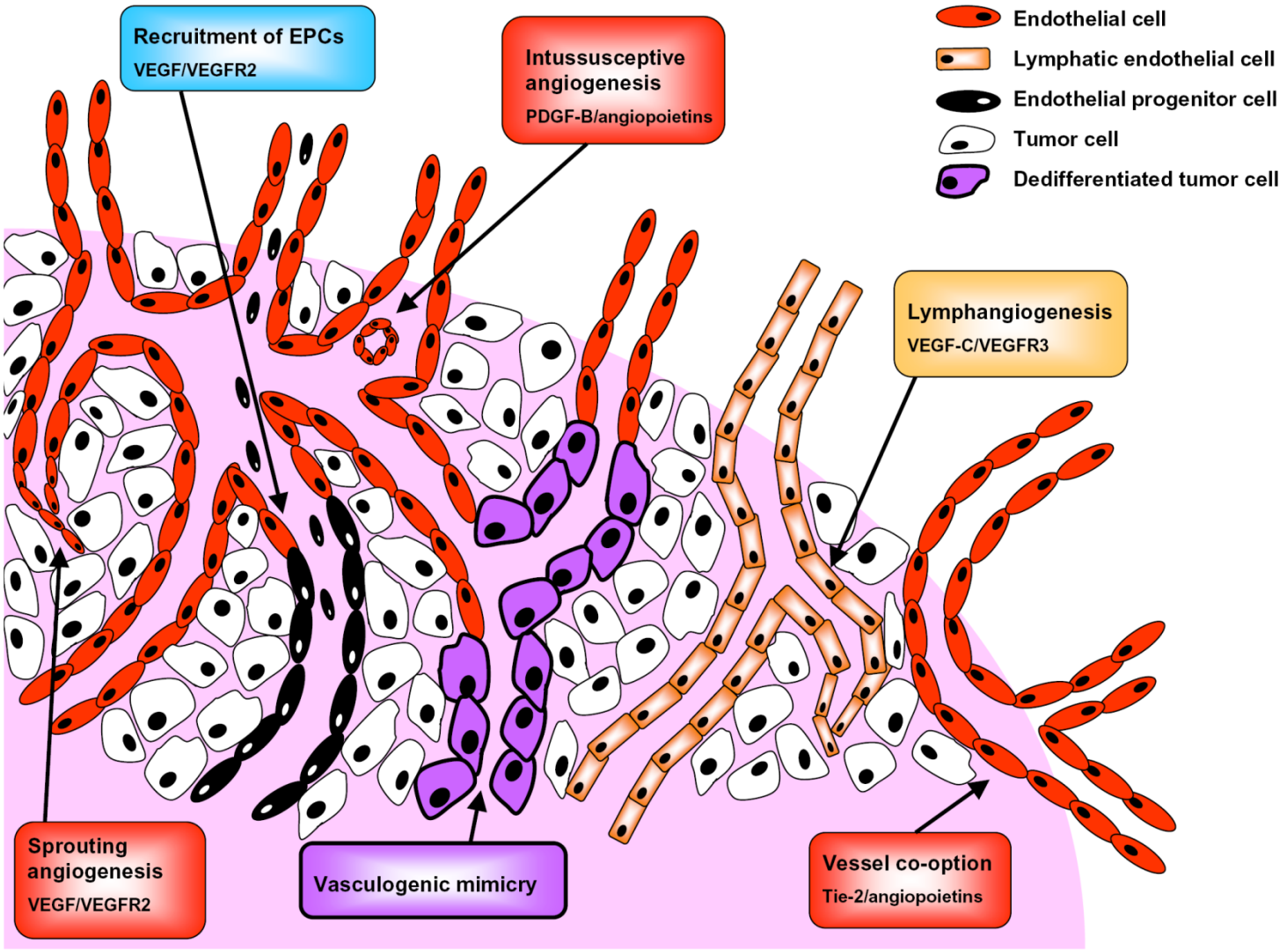
A Heterotypic Cell Biology



The Angiogenic Switch

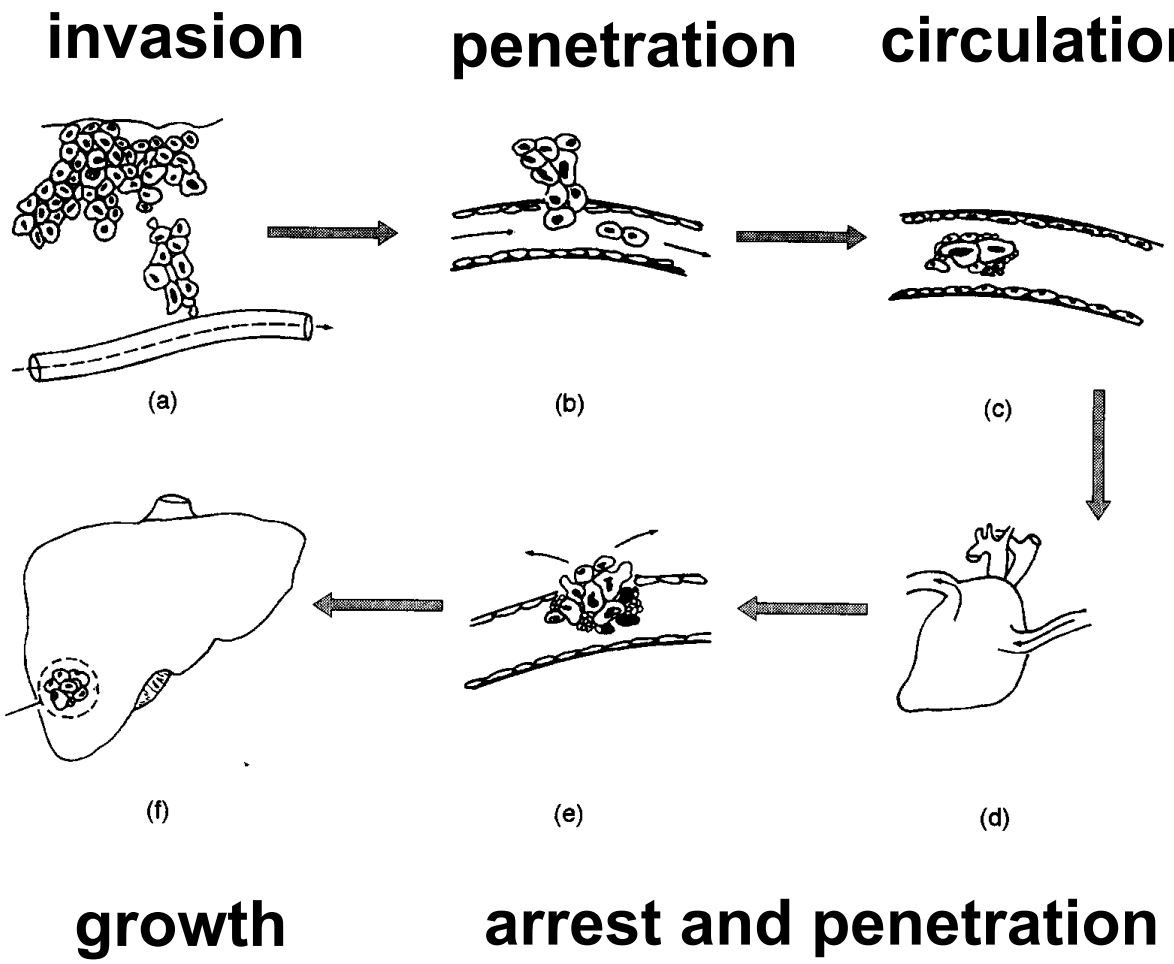


Mechanisms of tumor vascularization

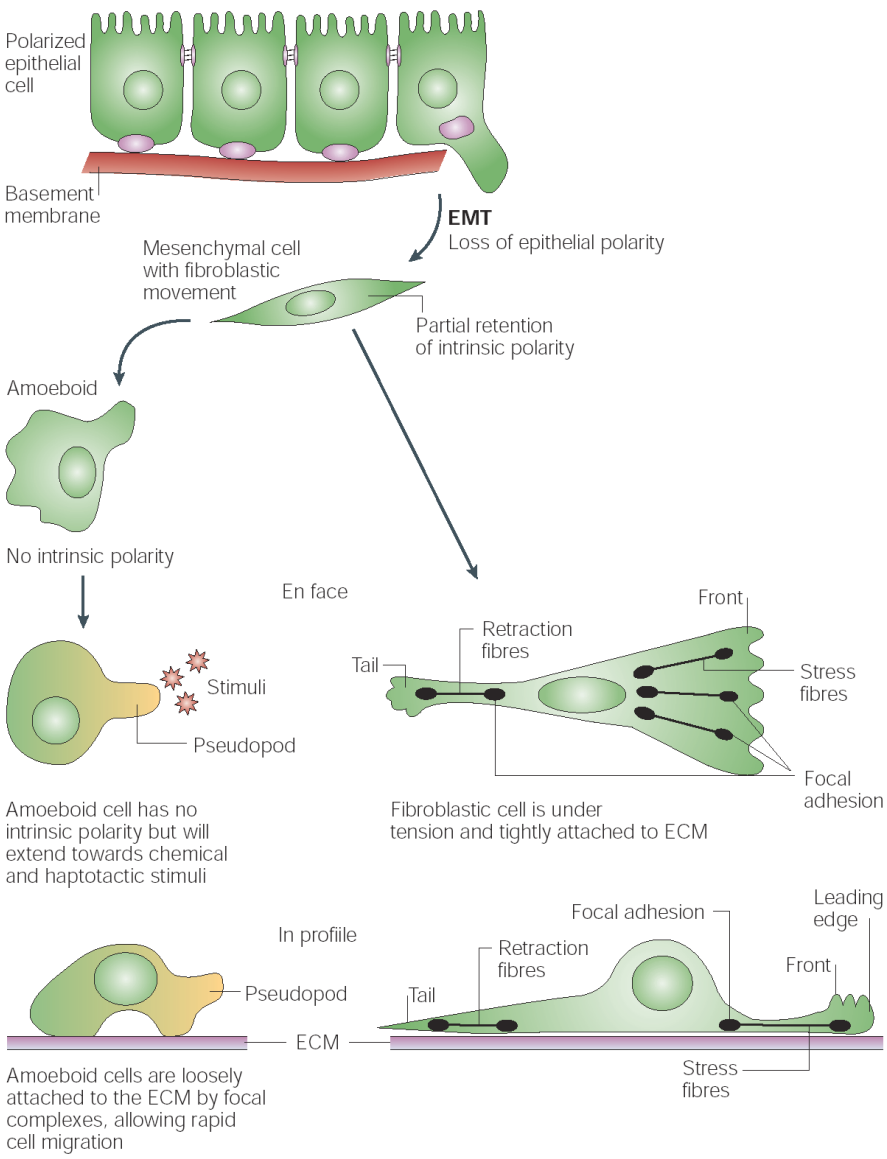


From Hillen, Cancer Metastasis Reviews 2007

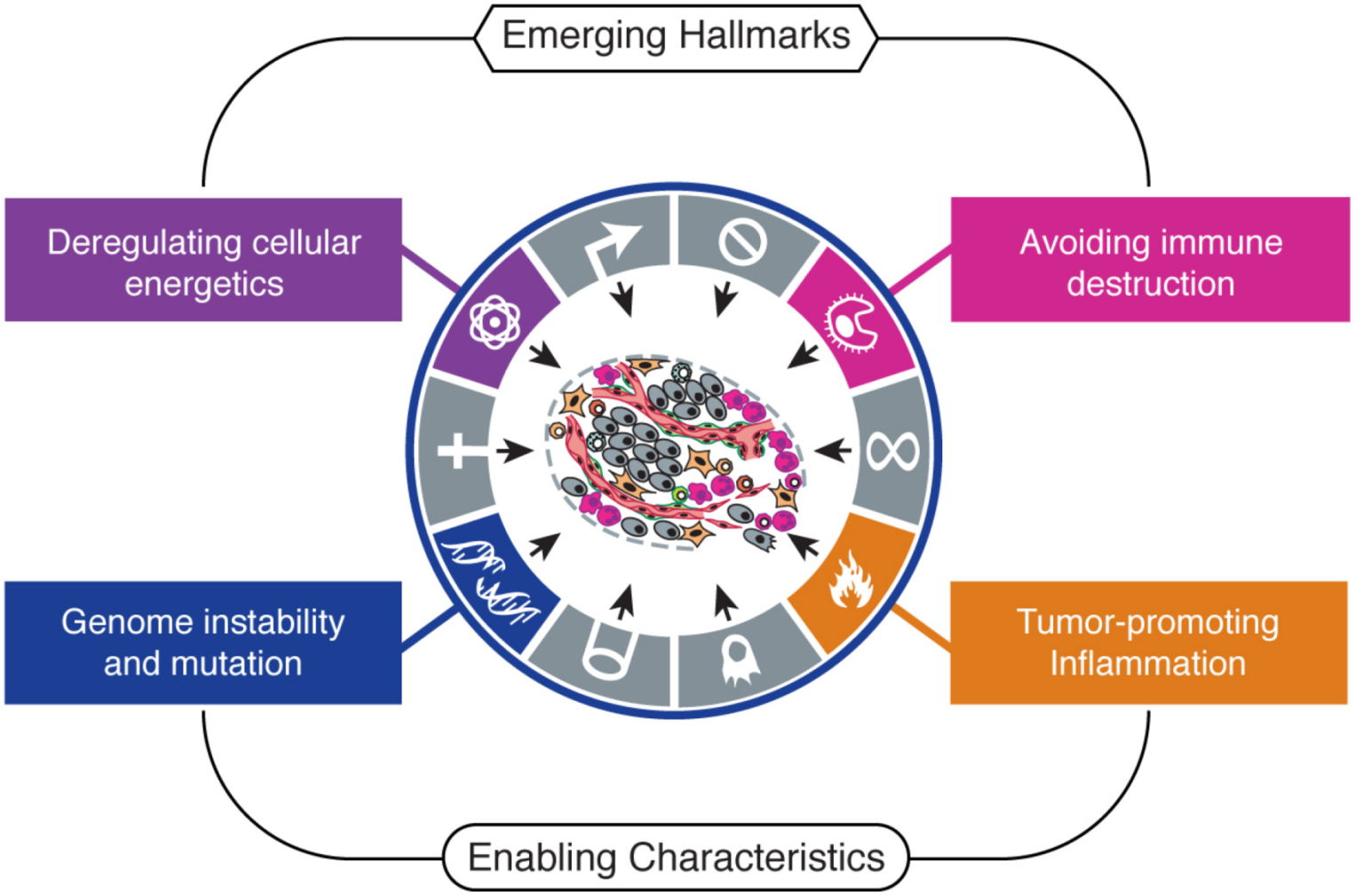
6) Activating Invasion and Metastasis



Epithelial-Mesenchymal Transition



New Hallmarks and Enablers



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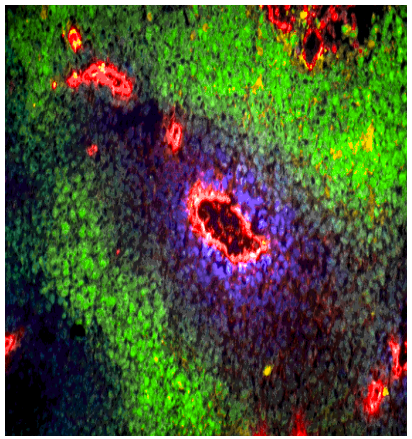
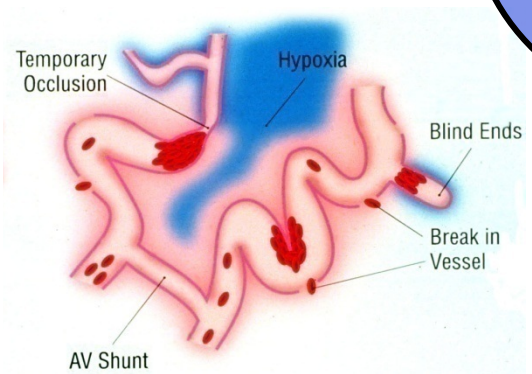
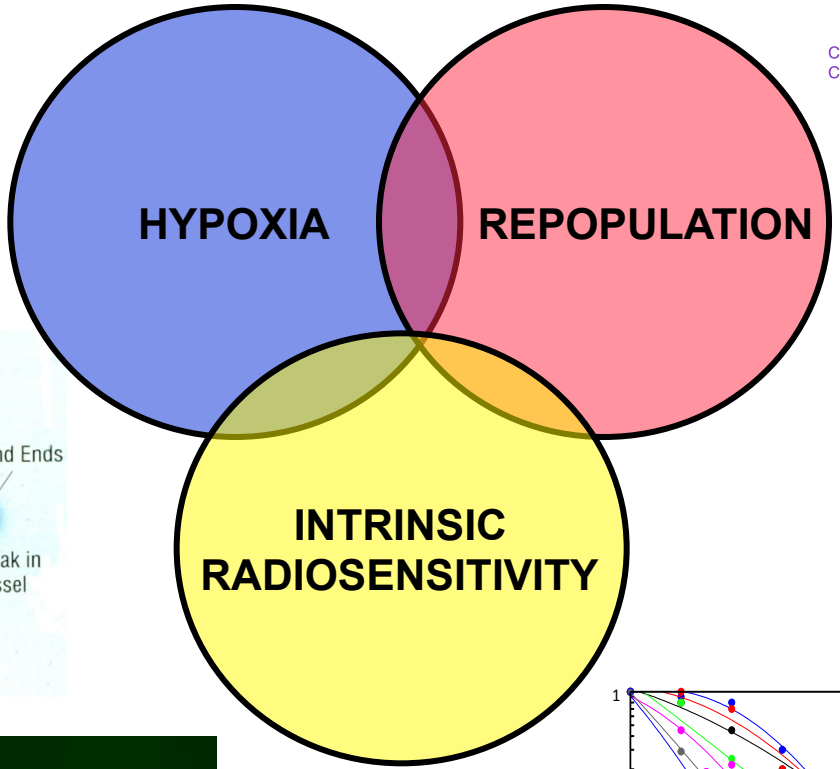
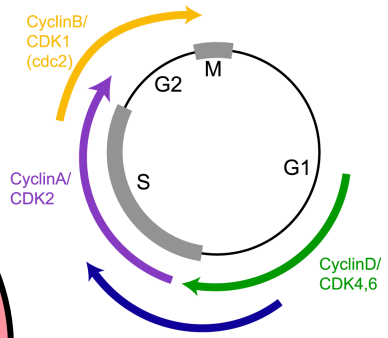
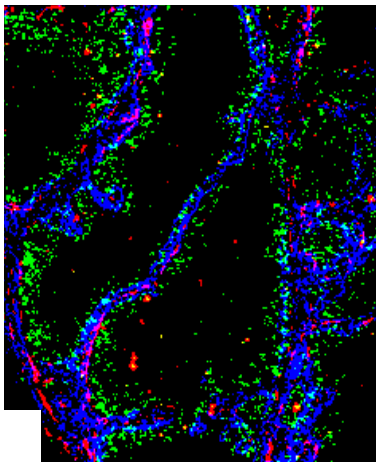
Biological contributors to outcome

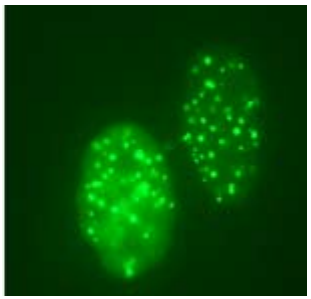


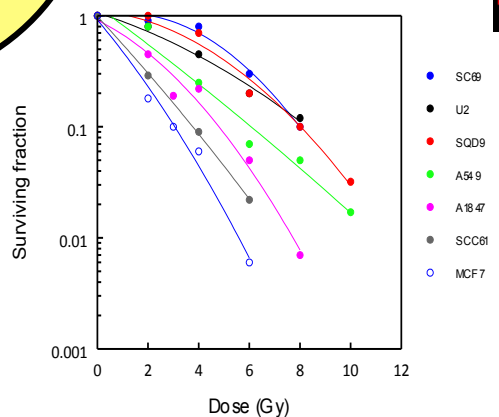




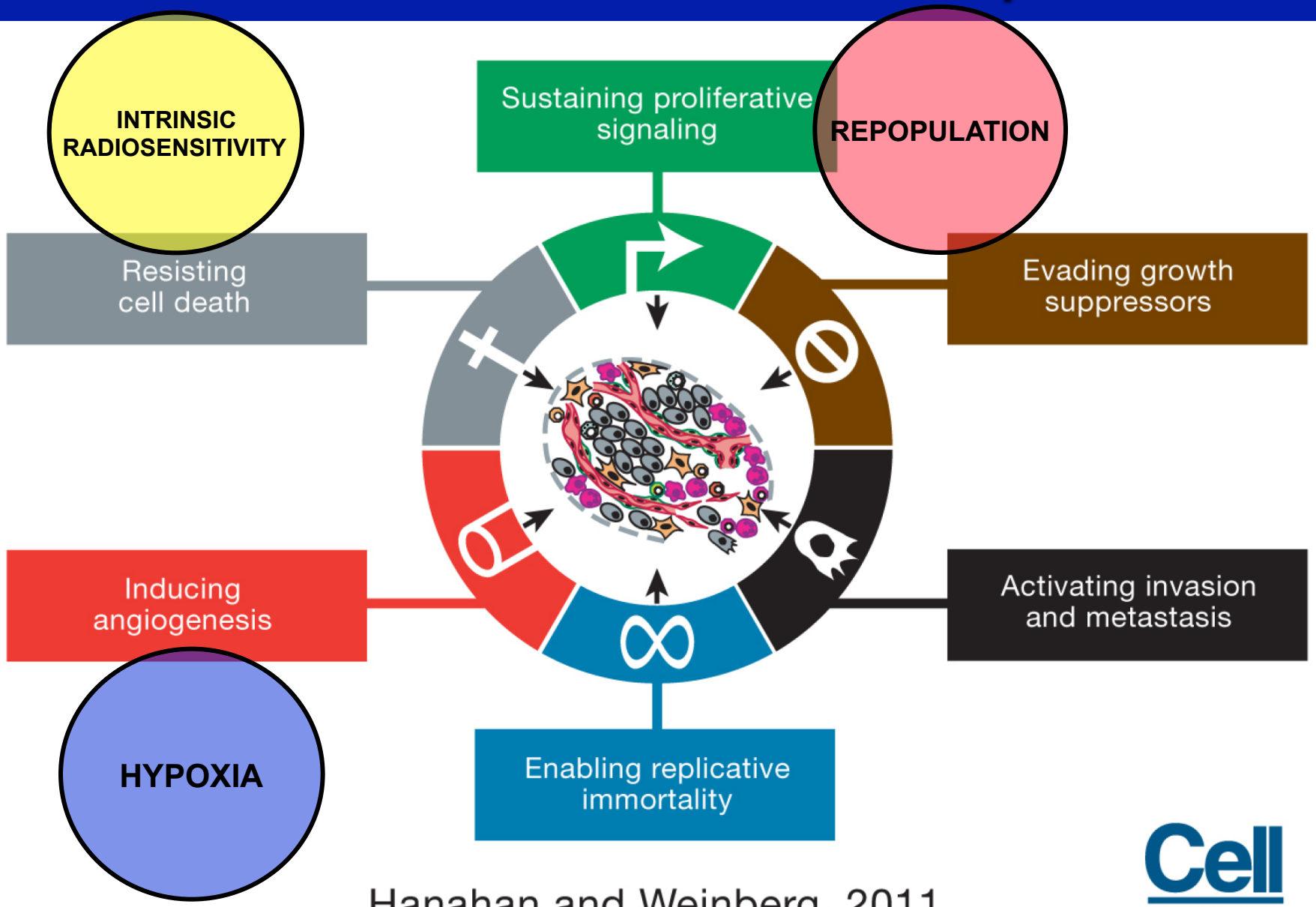








Hallmarks & Radiation Response



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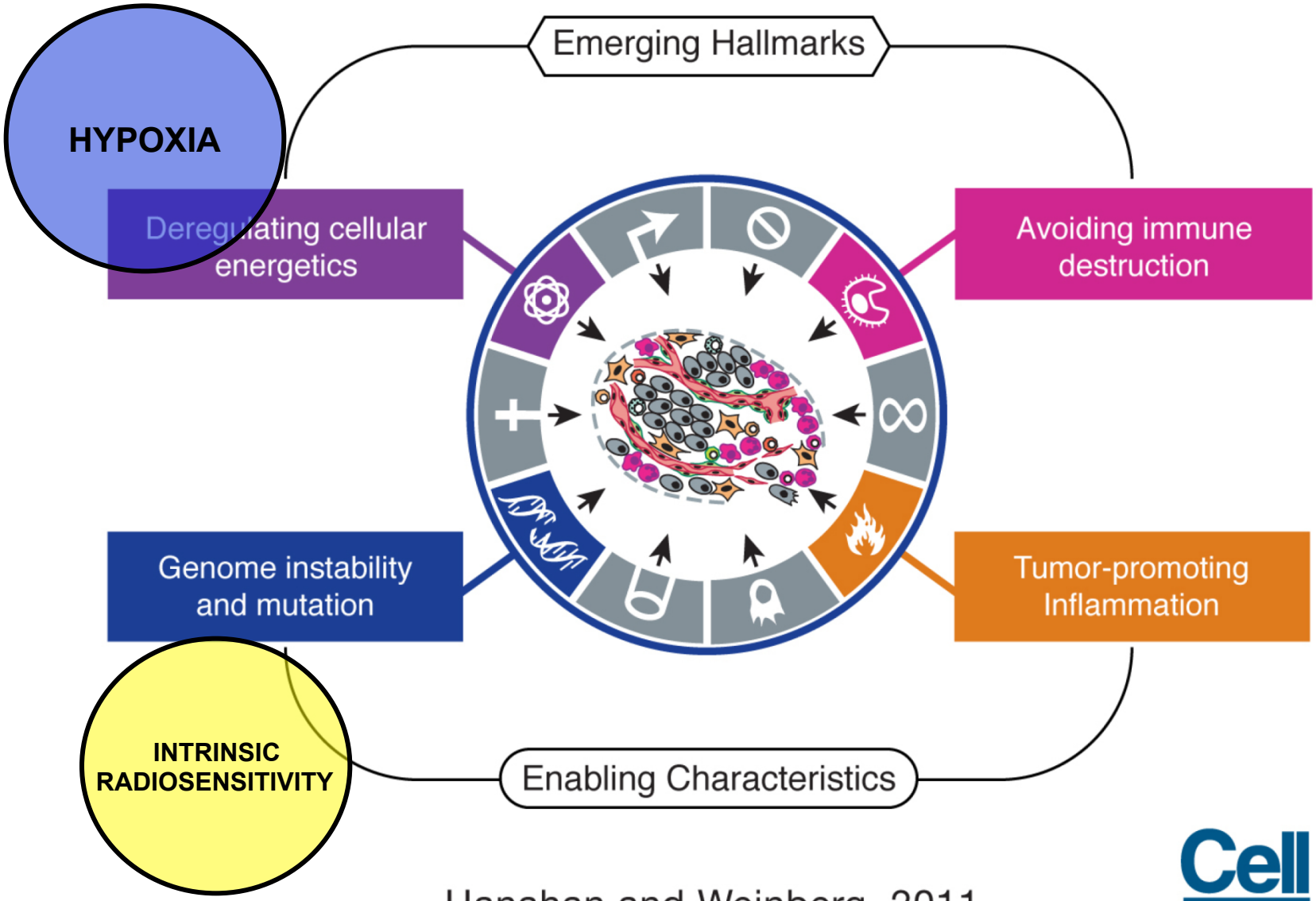

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Conclusions

- Cancer is caused by a series (~2-8) 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)
- The Cancer Genome Atlas (TCGA)
- Catalogue of Somatic Mutations in Cancer (COSMIC)
- cBioPortal
  - The cBioPortal for Cancer Genomics provides **visualization**, **analysis** and **download** of large-scale **cancer genomics** data sets.
  - http://www.cbioportal.org/

Molecular Basis of Cell Death

Marianne Koritzinsky

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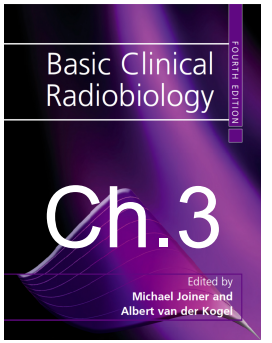

What do we mean by cell death?

- 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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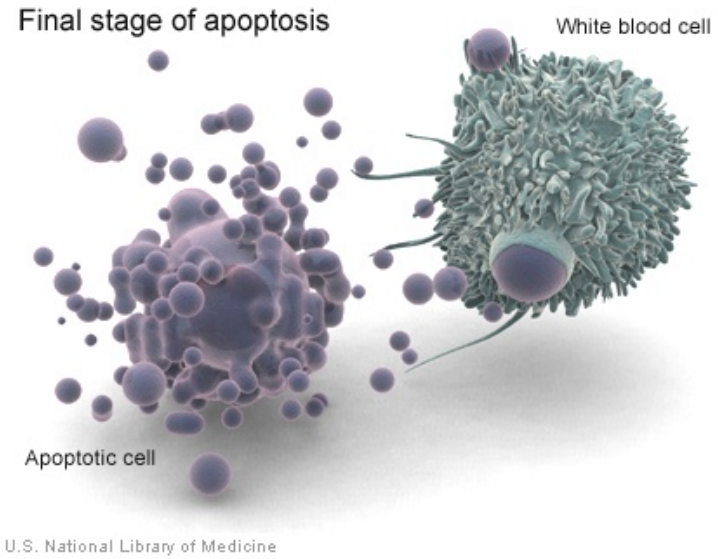
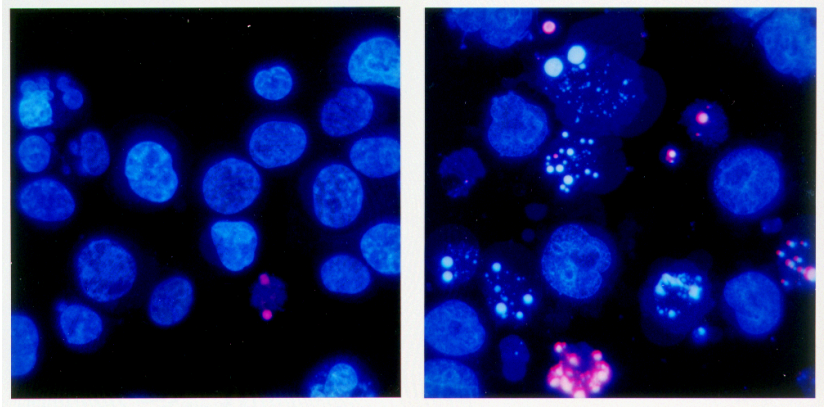
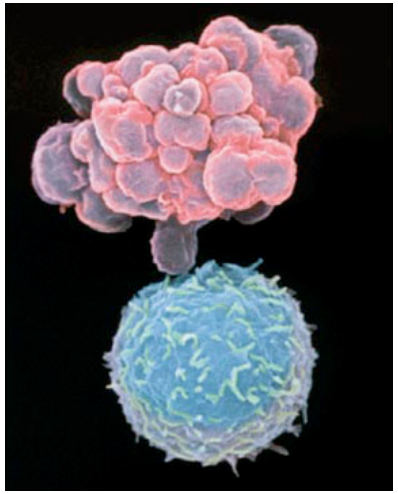
Apoptosis



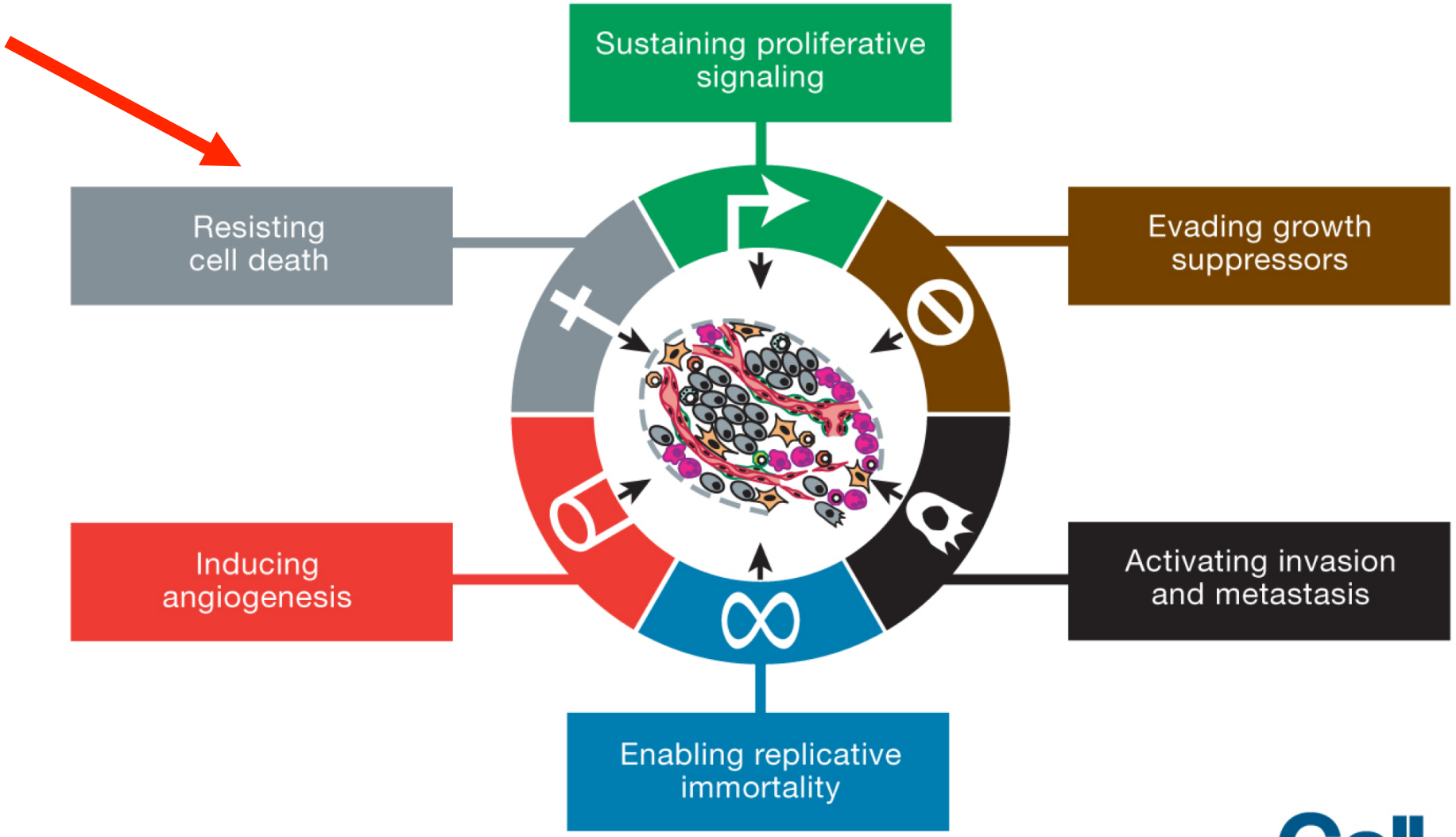
U.S. National Library of Medicine

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





The 6 Hallmarks of Cancer



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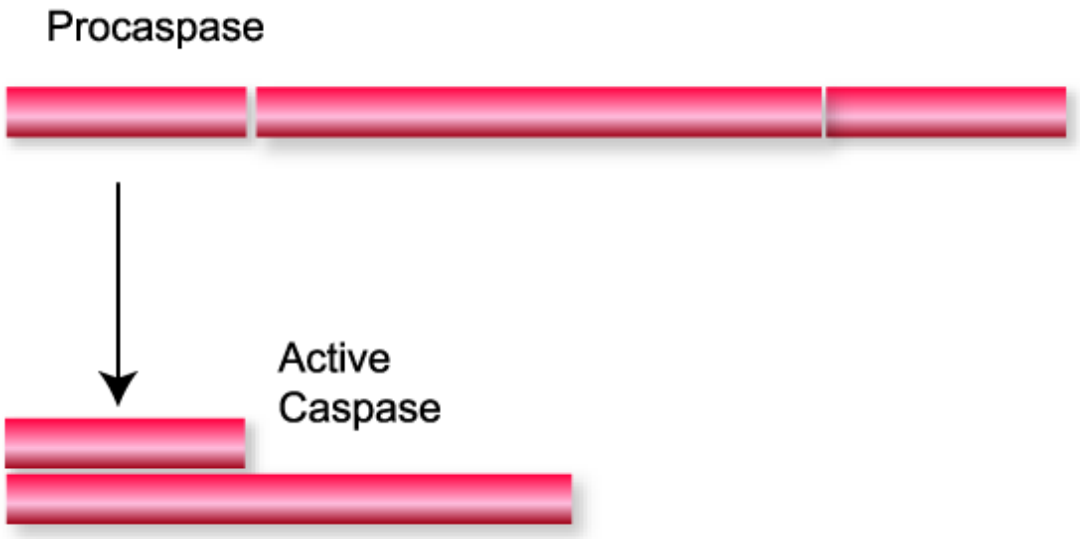
Apoptotic Machinery

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

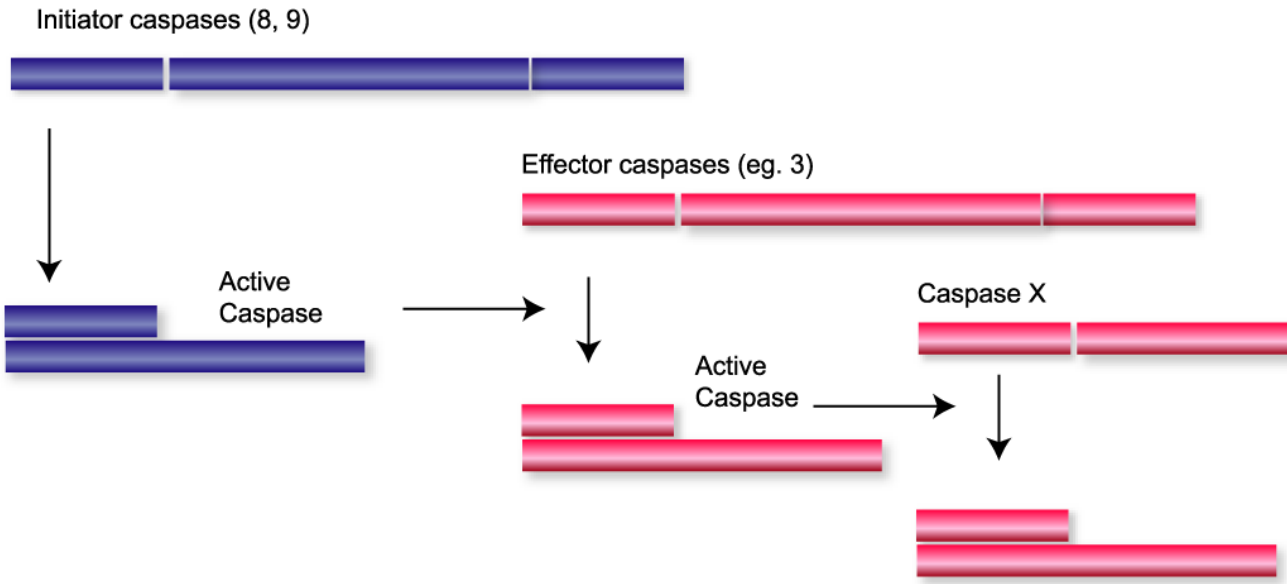
- Effectors
  - Intracellular proteases called caspases

Effectors: Caspases



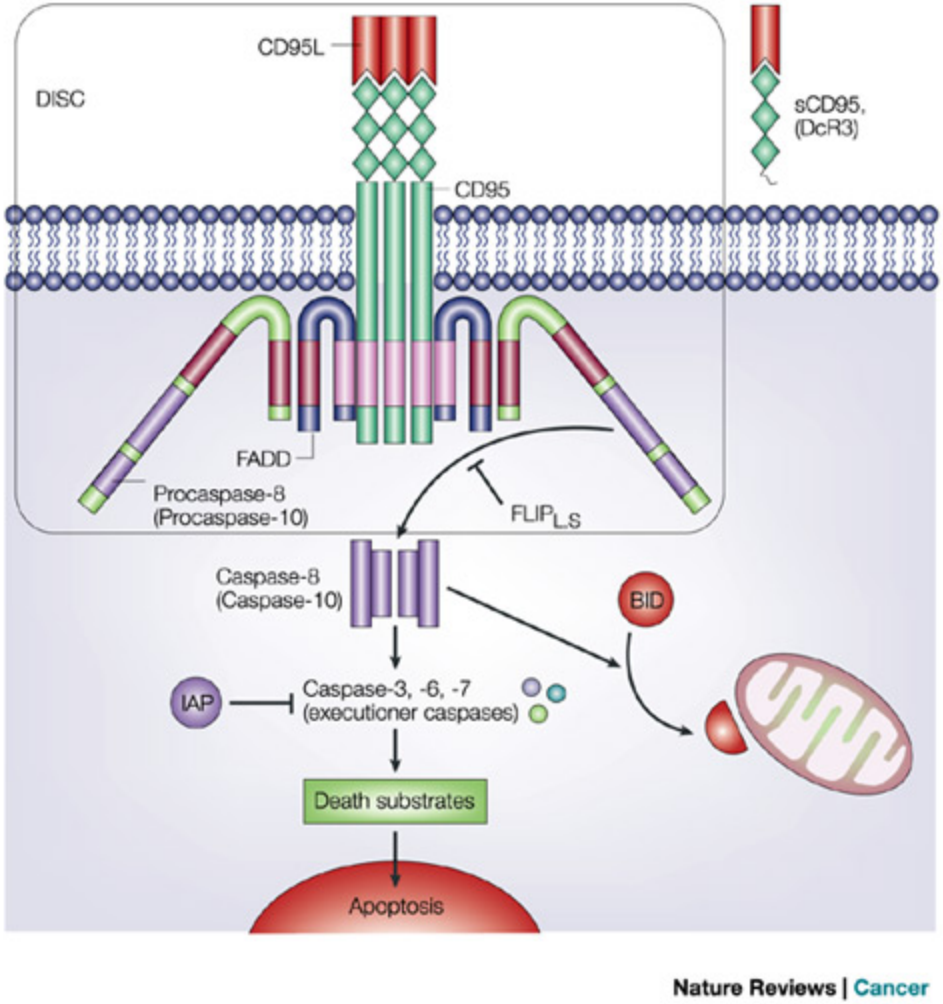
- Executioners of apoptosis
- Cleave proteins at certain sites
- Disassemble the cell
- Present in a pro-form (inactive)

Caspase cascade



Irreversible “switch” for cell death

Extrinsic Pathway – Death Receptors

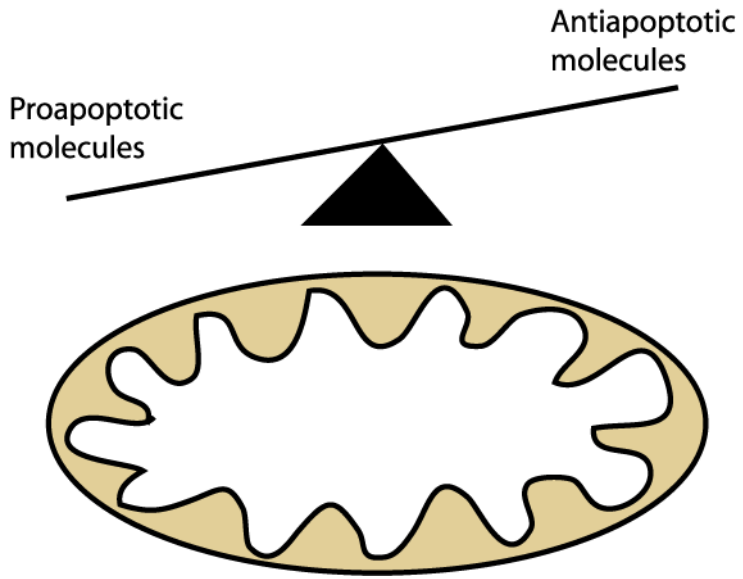


Extrinsic – caspase 8
– signal given to the cell

Receptors	Ligands
TRAILR1, TRAILR2	TRAIL
TNFR1	TNF
FAS	FASL

Intrinsic Pathway – Mitochondria dependent

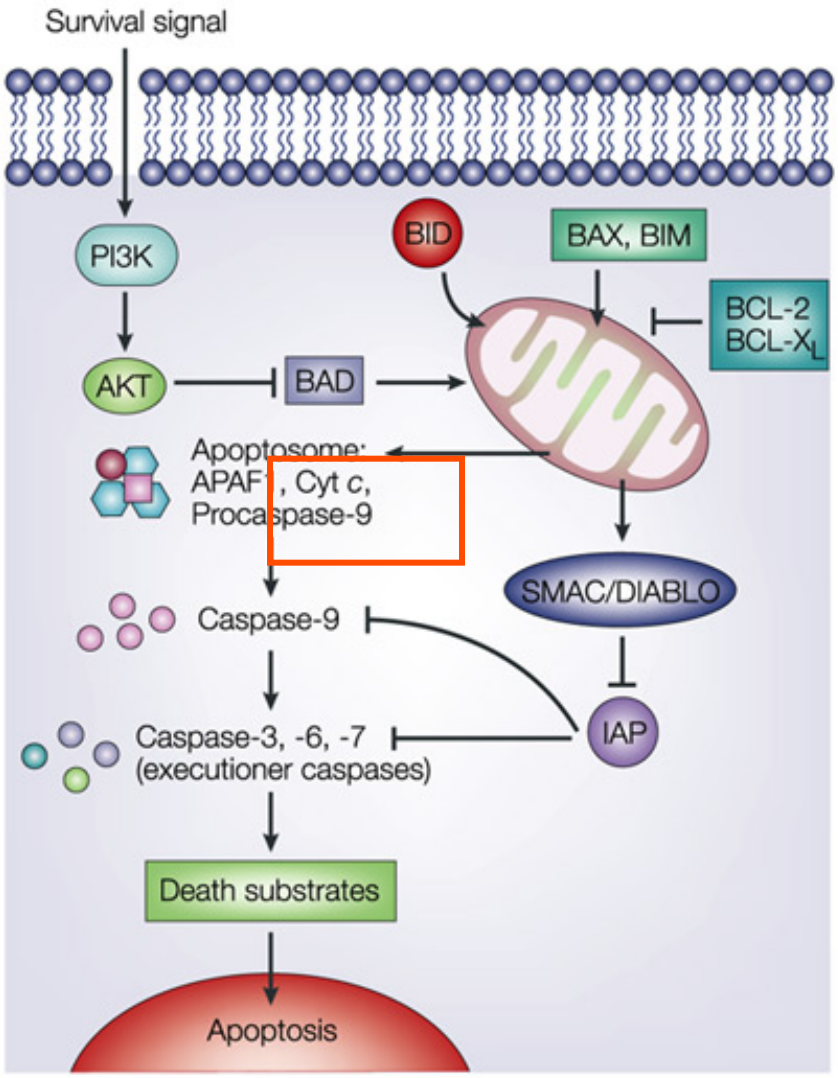
- Mitochondria induce apoptosis when pro-apoptotic factors outnumber anti-apoptotic factors



Step 1)

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

Intrinsic Pathway



Nature Reviews | Cancer

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?

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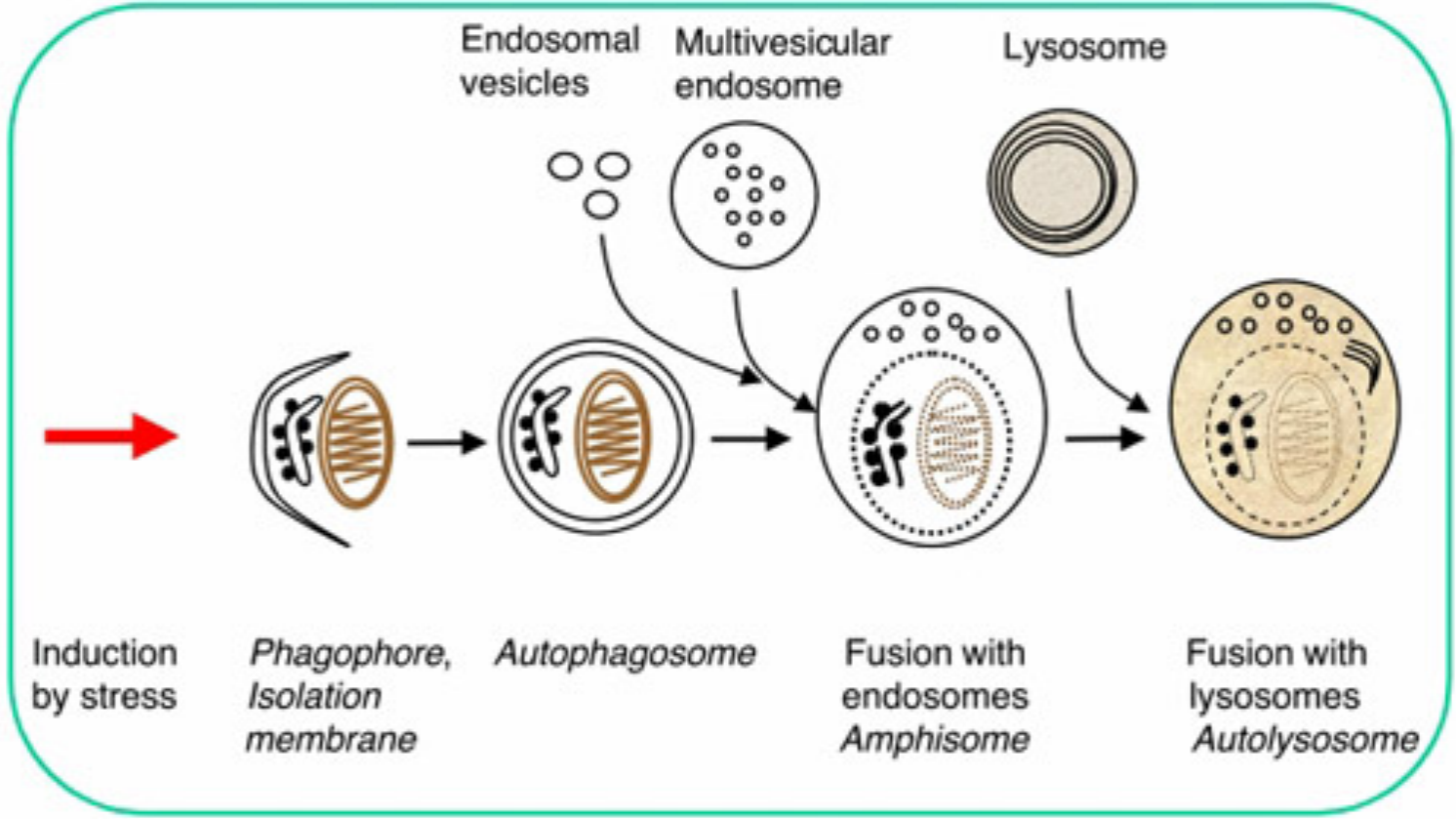
Autophagy

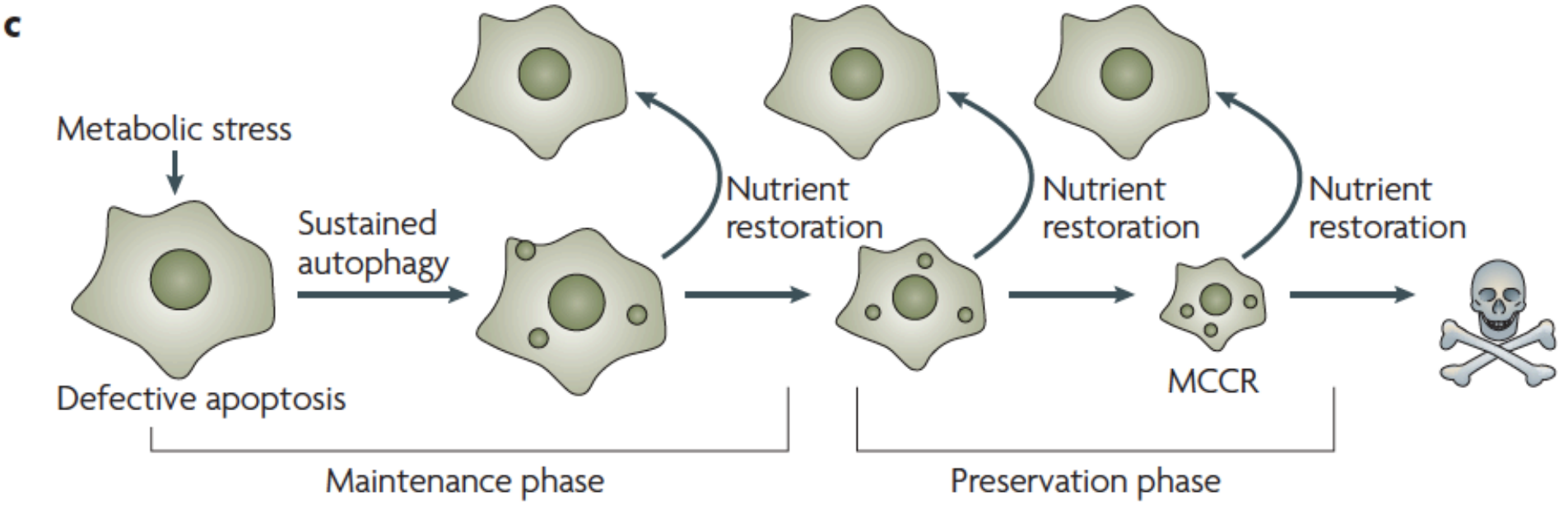
- Important survival mechanism during short-term starvation
  - Degradation of non-essential cell components by lysosomal hydrolases
  - Degradation products are transported back to cytoplasm for reuse in metabolism

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

Autophagy –to eat oneself



Autophagy – Survival or Death?



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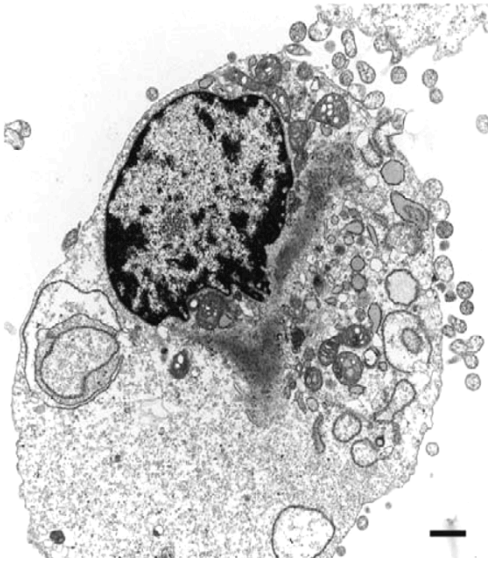
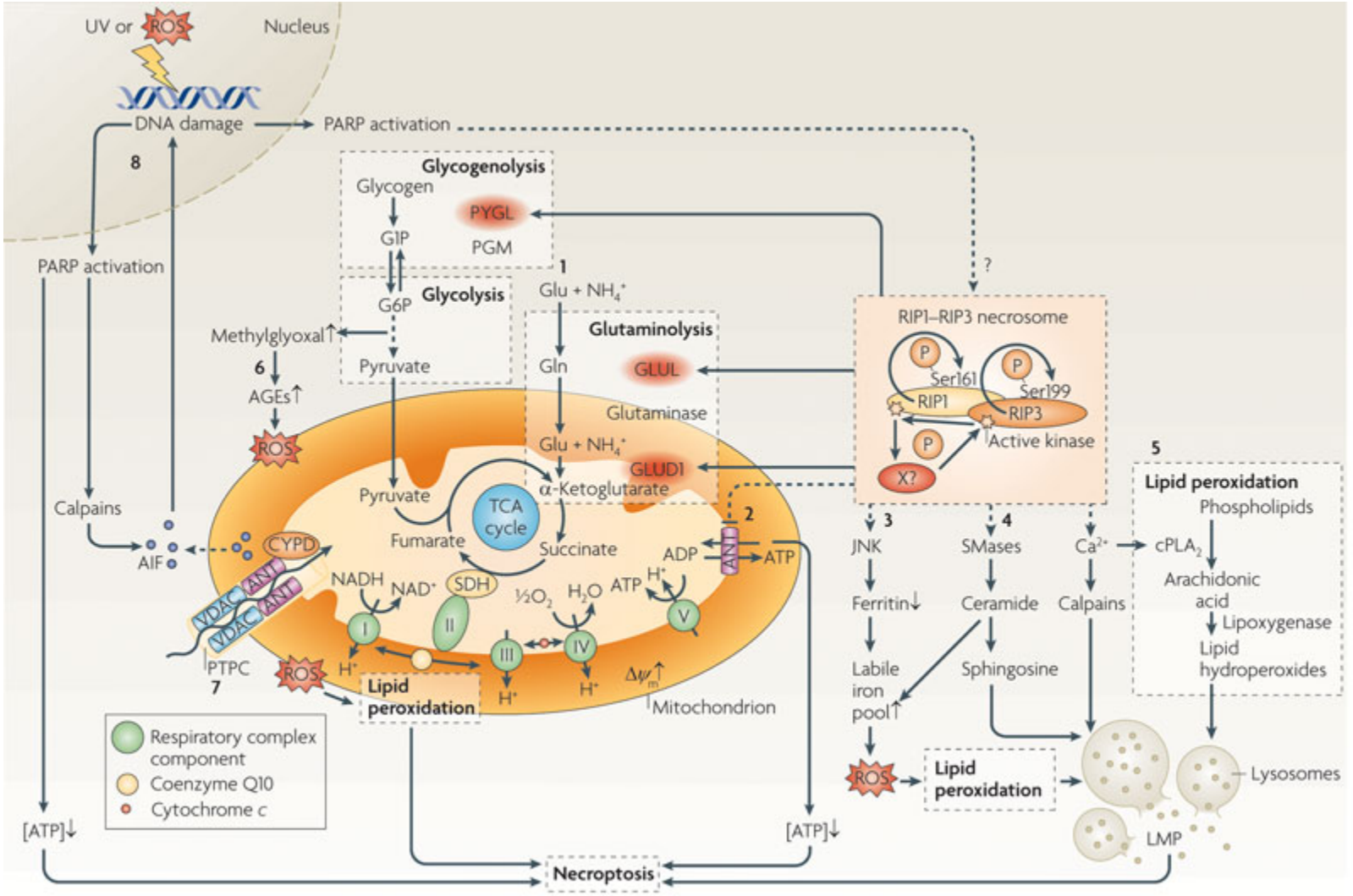
Necrosis

- 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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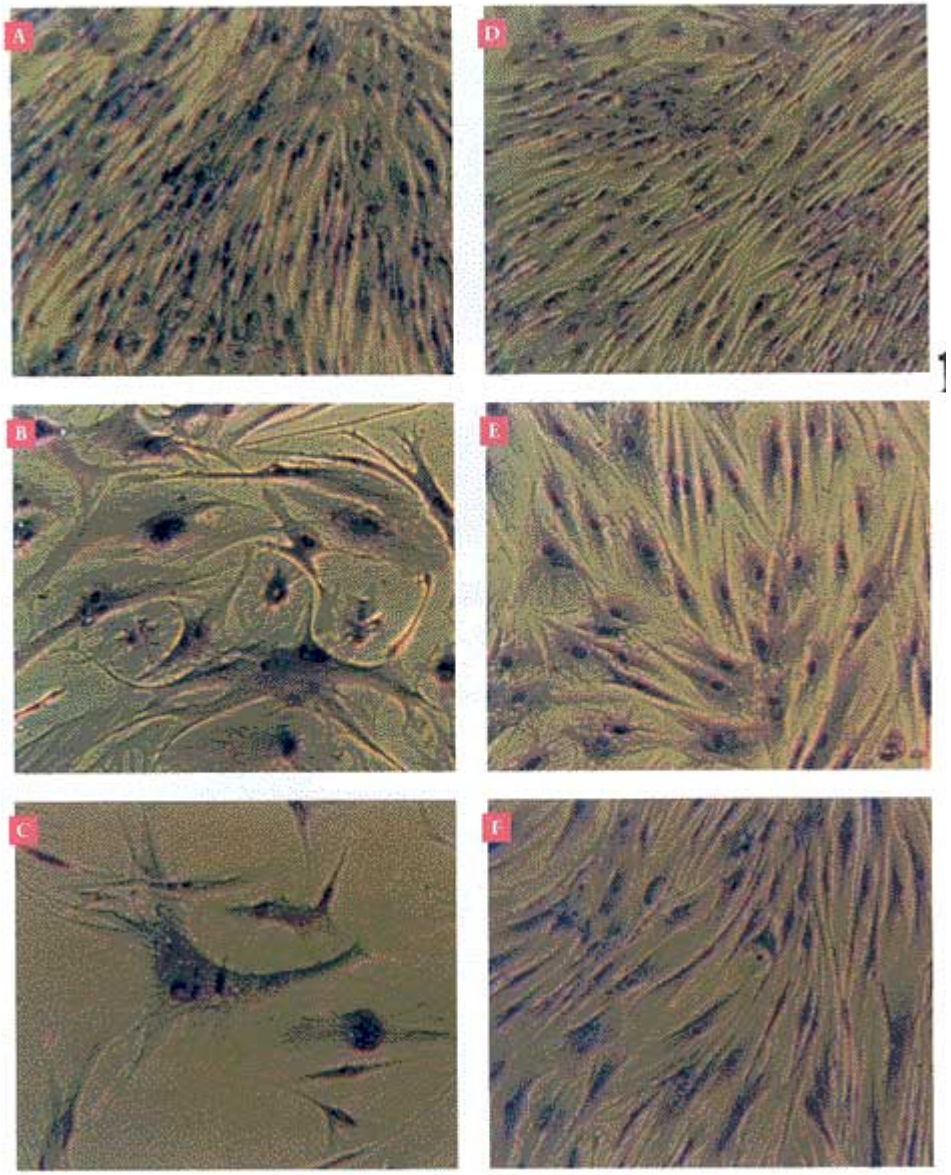
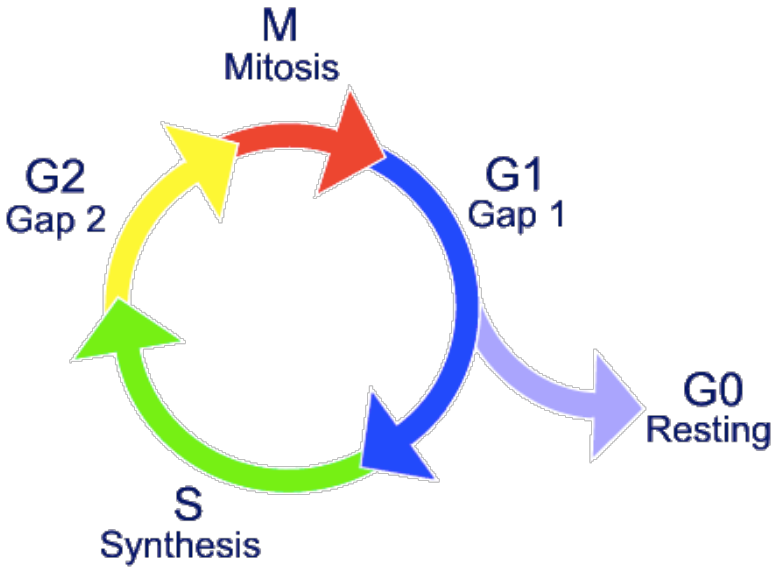
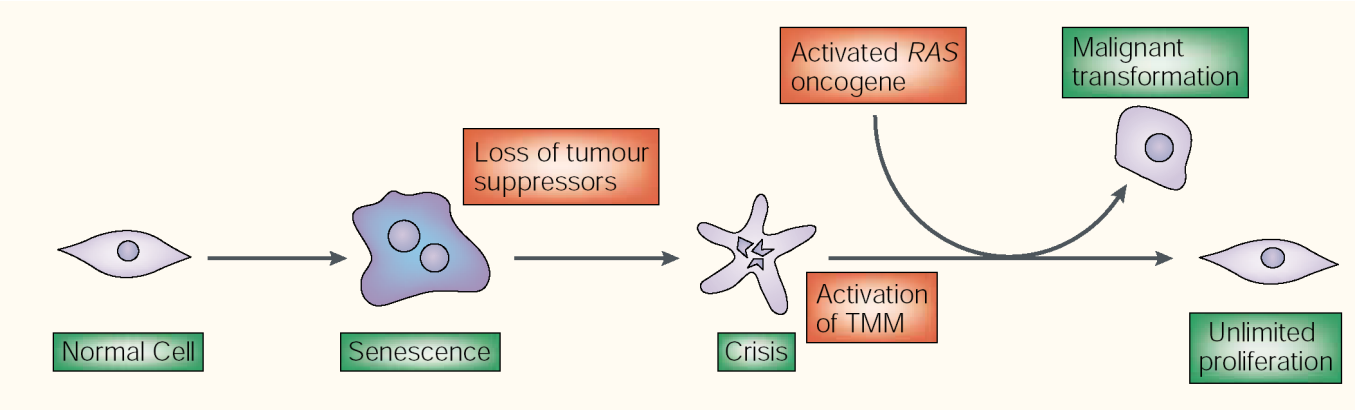
Senescence - Permanent loss of proliferative capacity





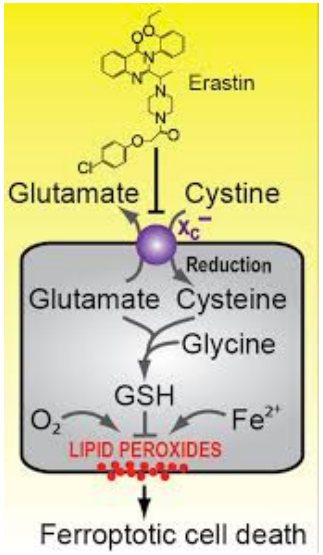
Senescence

- 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
  -

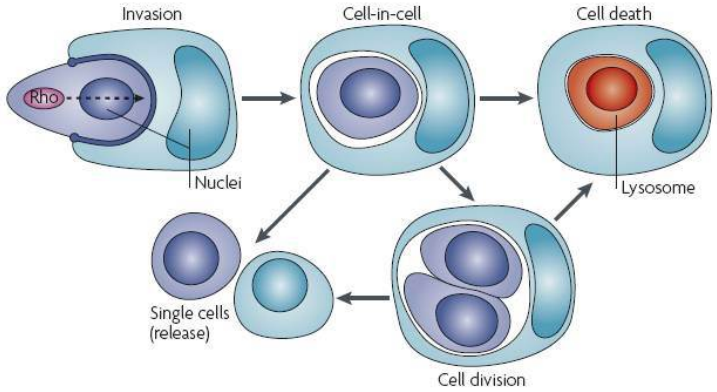


Other forms of cell death (emerging)

- Ferroptosis
  - Iron linked death caused by ROS



- Entosis
  - Cell engulfment



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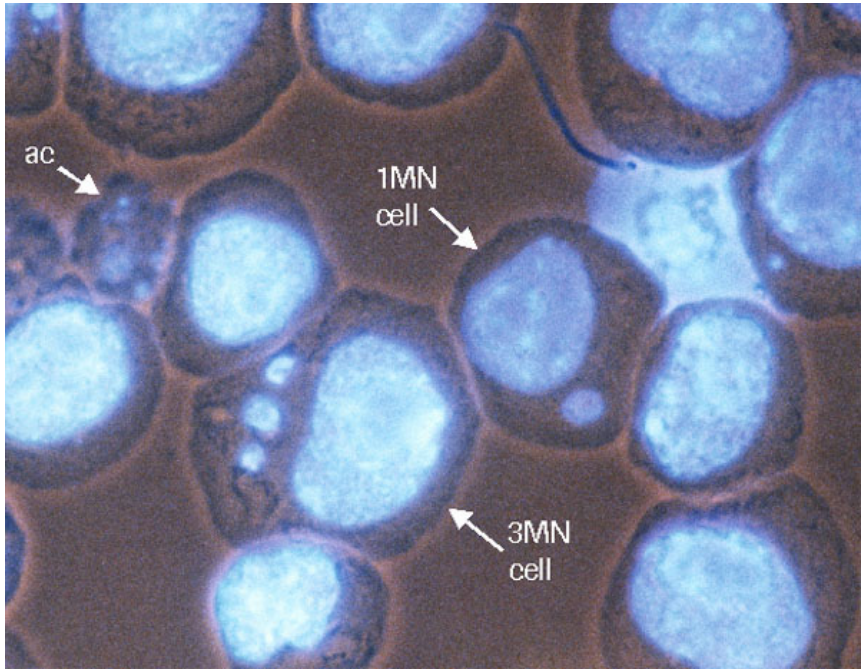
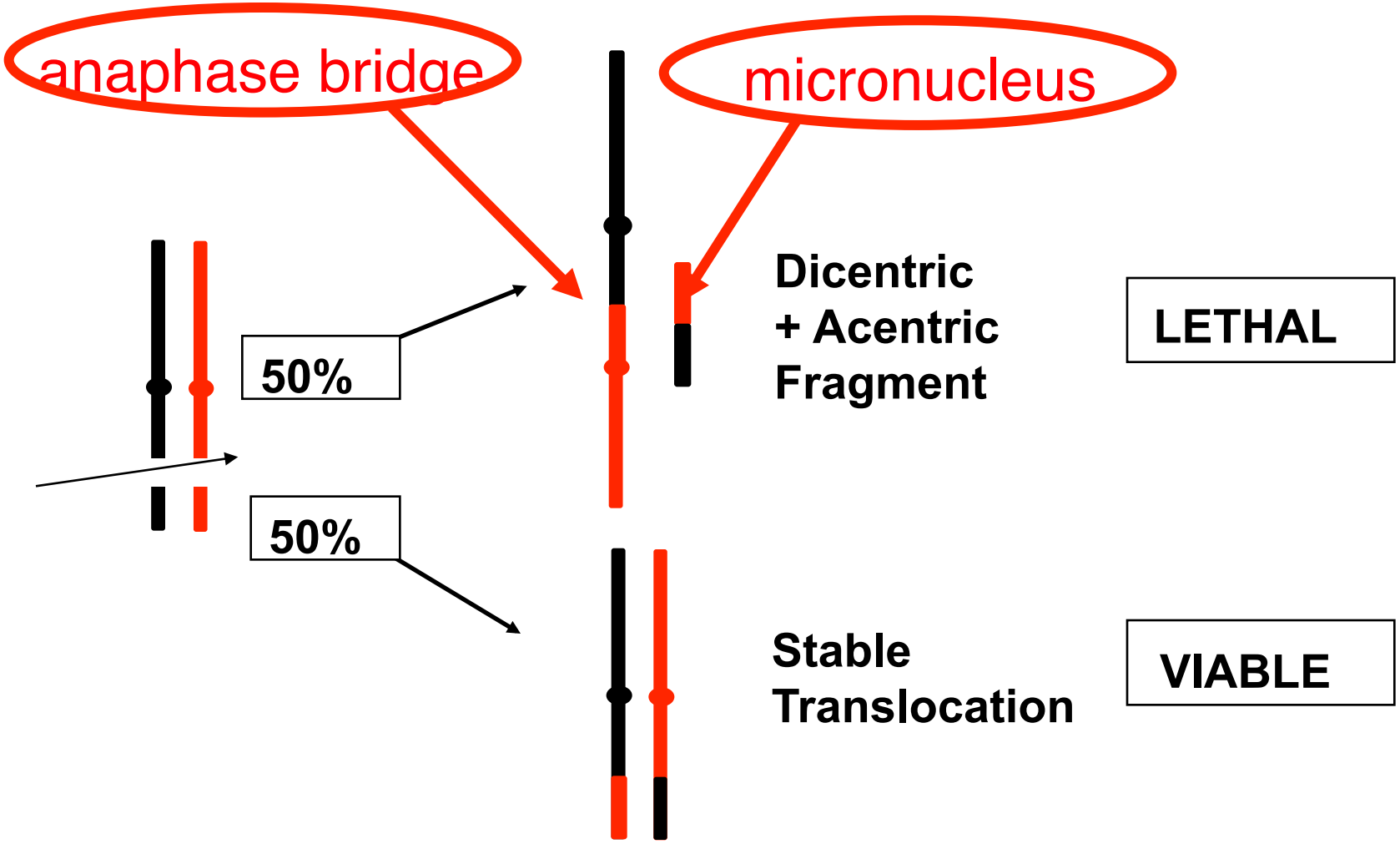
Mitotic Catastrophe

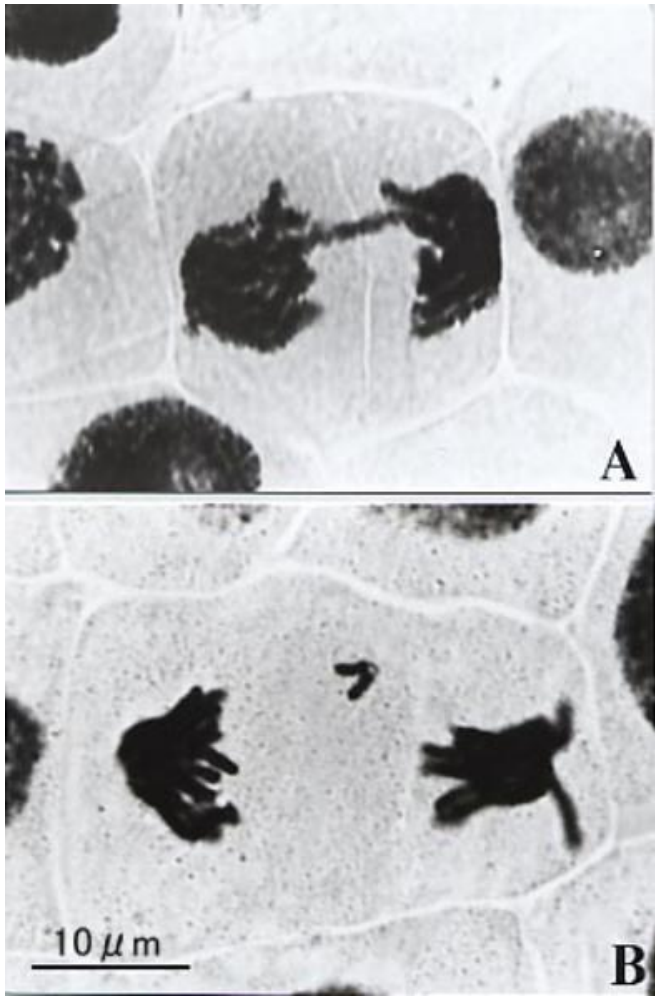


- Mitotic catastrophe
  - Cells attempt to divide without proper repair of DNA damage
- May lead to secondary death by apoptosis, necrosis, autophagy, or senescence

Mitotic catastrophe is caused by chromosome aberrations



Mitotic Catastrophe



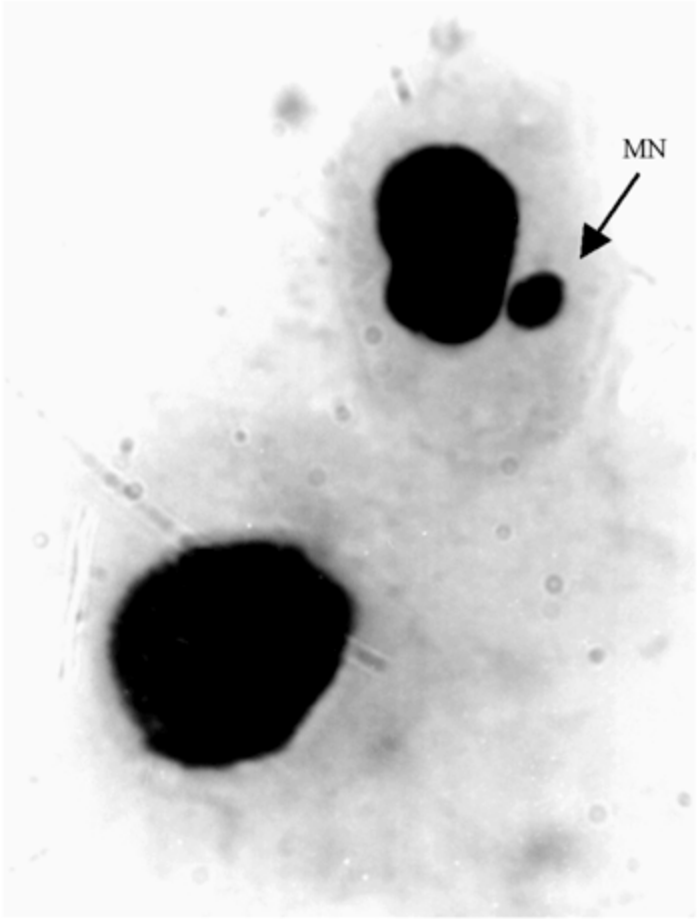


Figure 3 - Micronucleated erythrocyte (arrow) in *R. Catesbeiana* tadpole exposed to lambda-cyhalothrin. Giemsa-stained blood smear 1,000 x.

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 propensity to initiate programmed cell death varies widely
  - The genes controlling these pathways are frequently mutated in cancer

How do cells die?

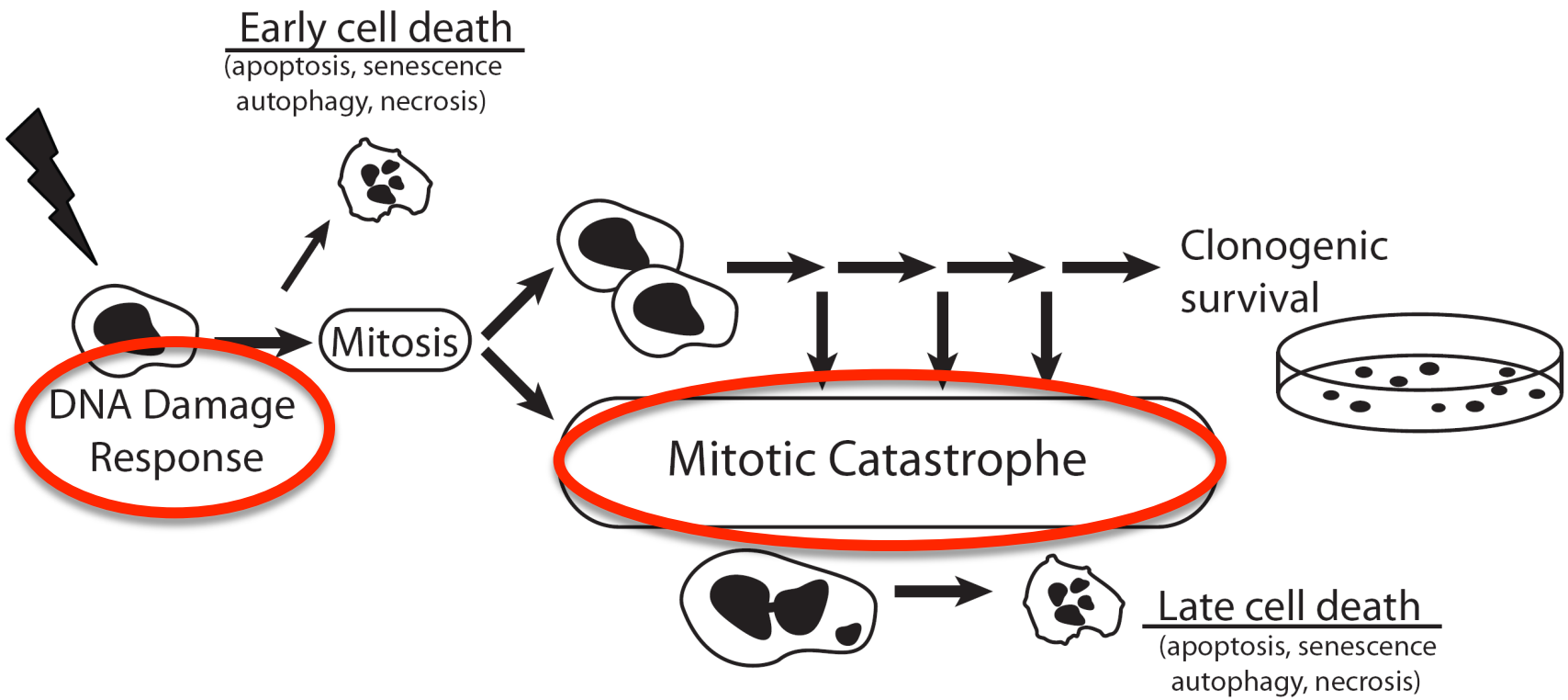
- Necrosis
- Senescence
- Apoptosis
- Autophagy
- …

Why do cells die?

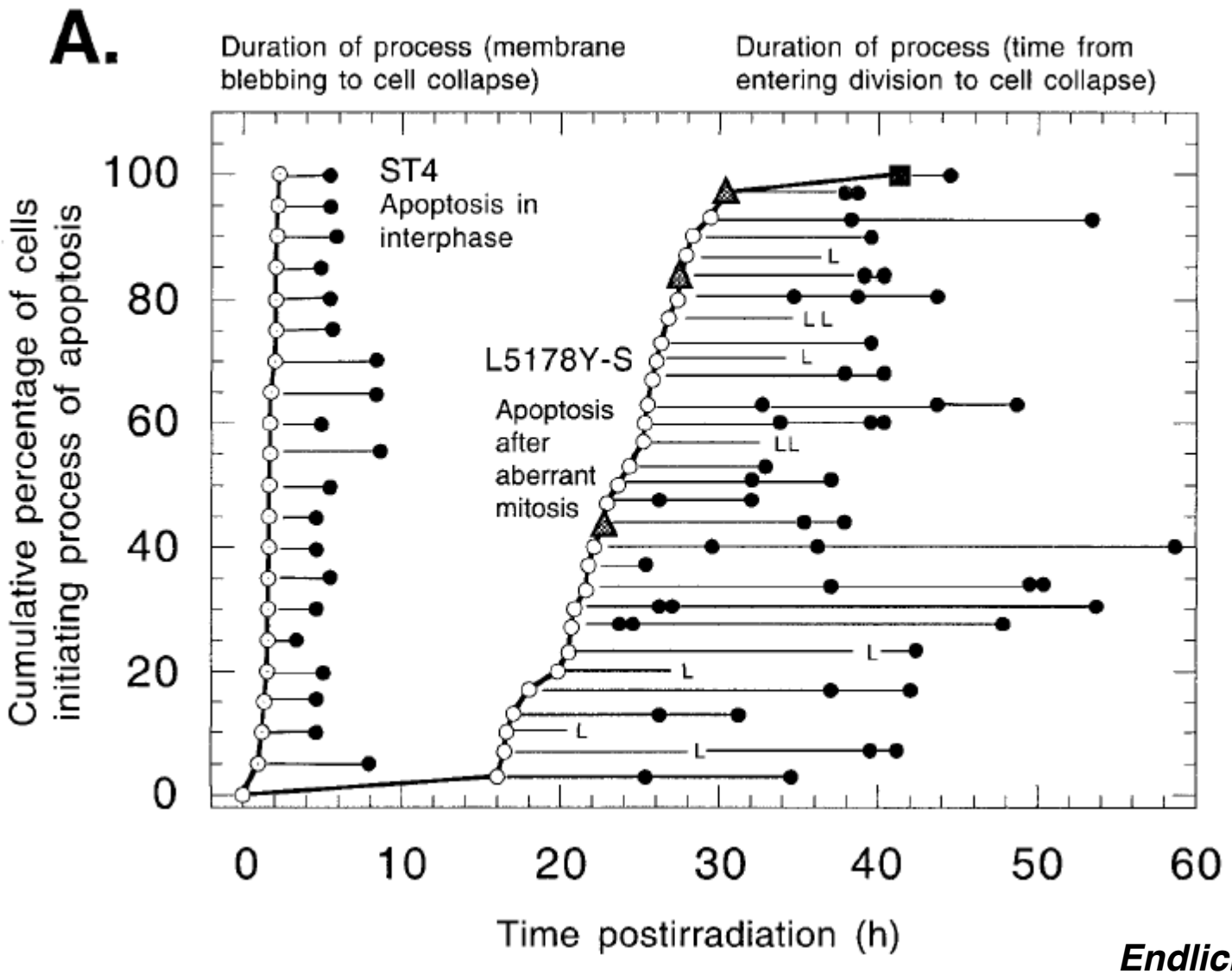
1) Initial damage to DNA (sometimes other molecules)

2) Mitotic catastrophy

What is the *cause* of cell death?



Two Types of Apoptosis - Pre and post mitotic



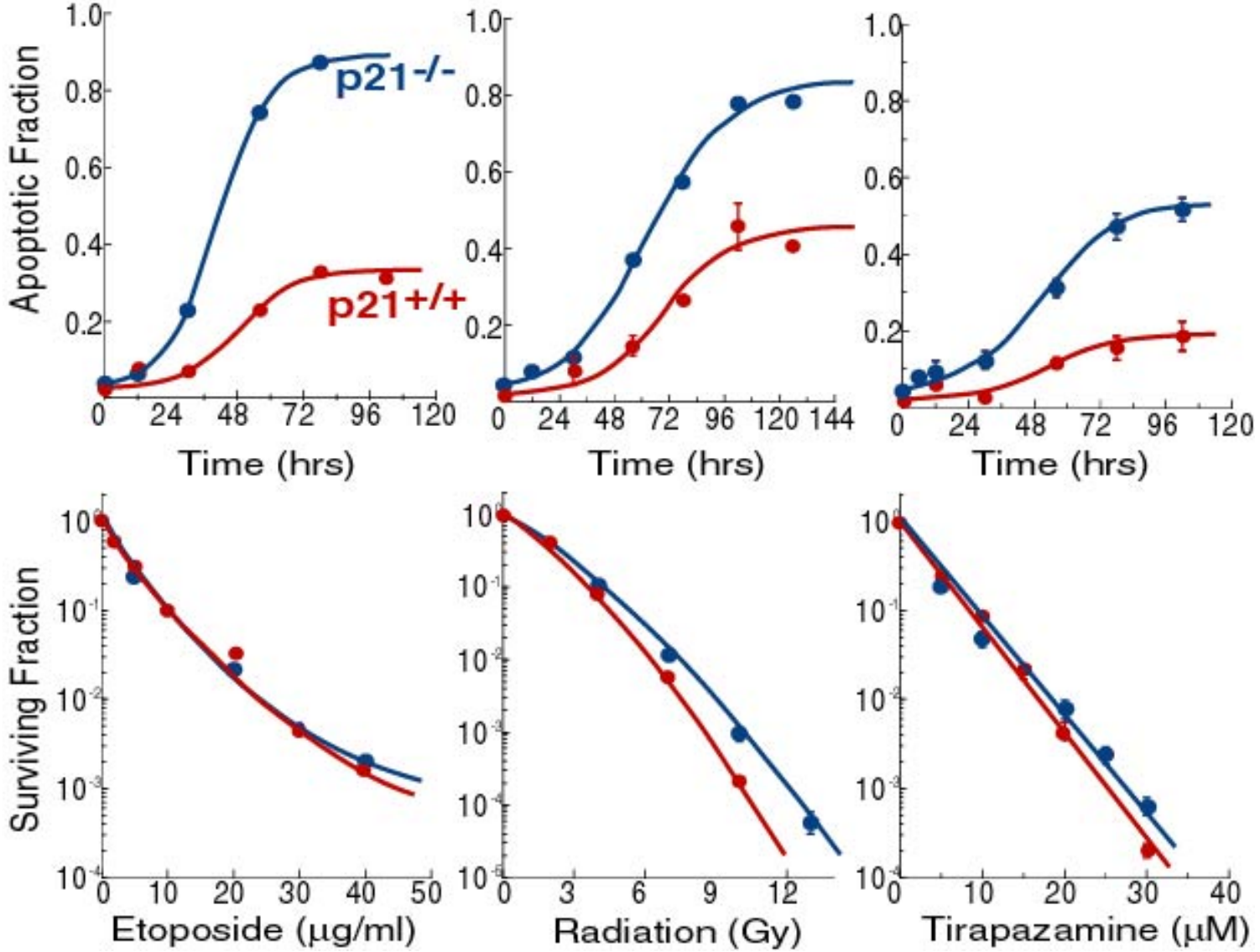
Endlich et al (2000)

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

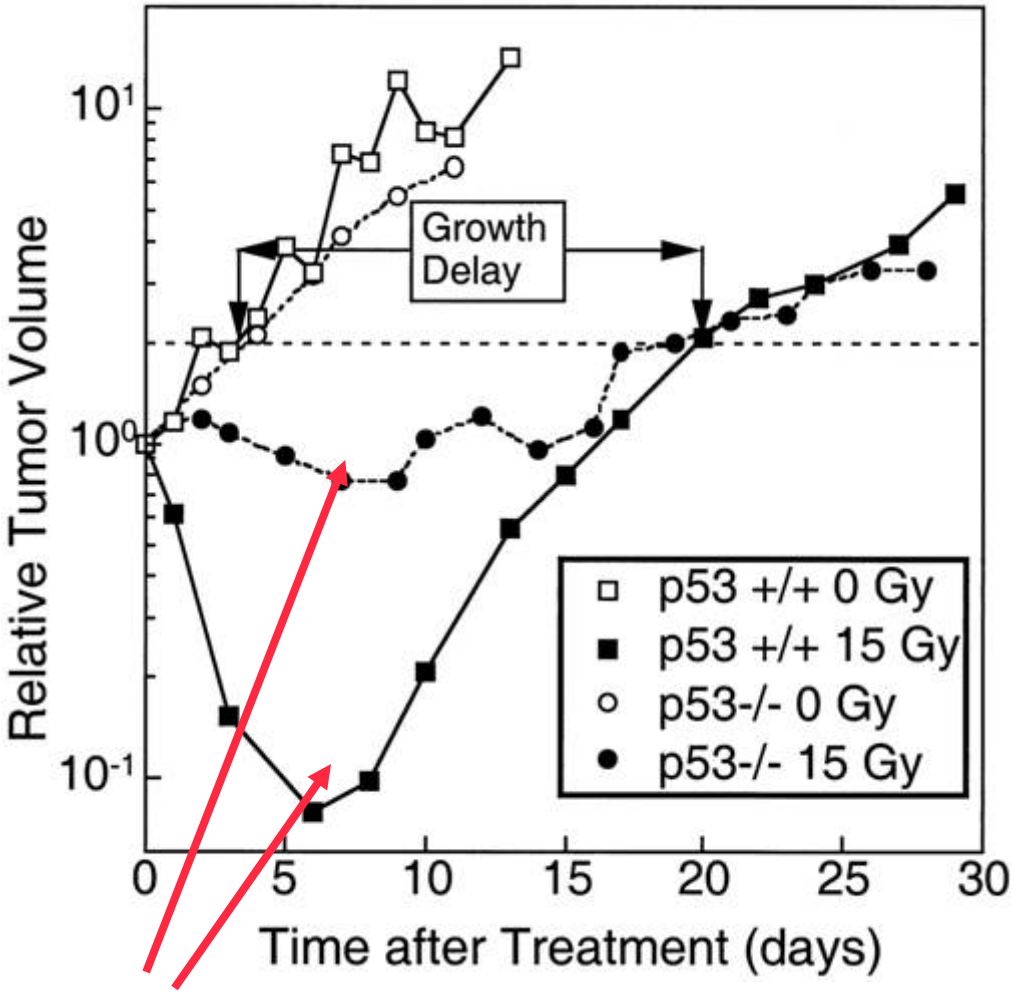
- Early apoptosis: Apoptosis is the reason the cell dies - it is the most sensitive mode of cell death and genes that affect apoptosis also affect cell death - e.g. some lymphomas and leukemias.

- 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			
	Paxtor			
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

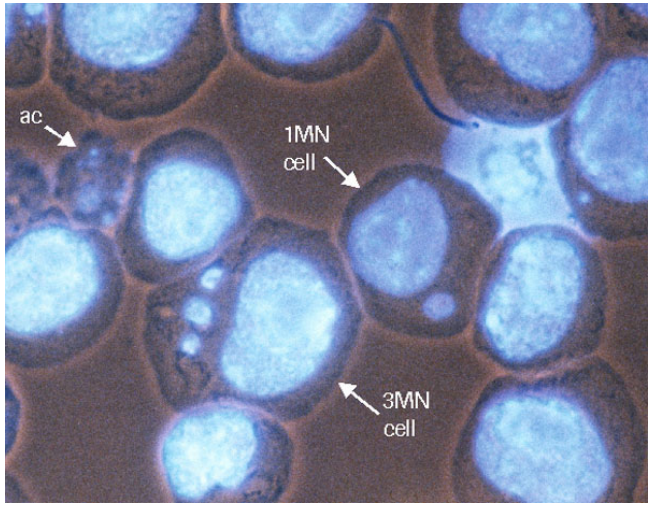
Summary of many clinical-preclinical studies

- 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

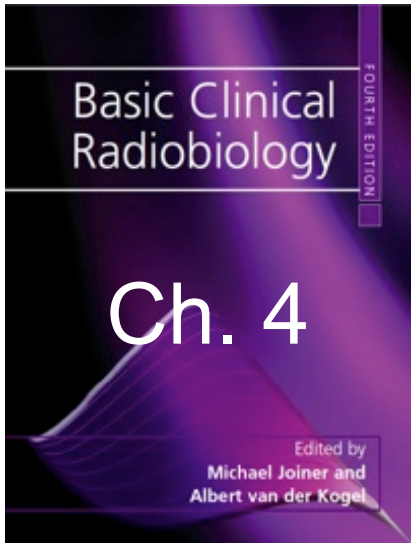
Conclusions

- 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

Clonogenic cell survival

Rob Coppes

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



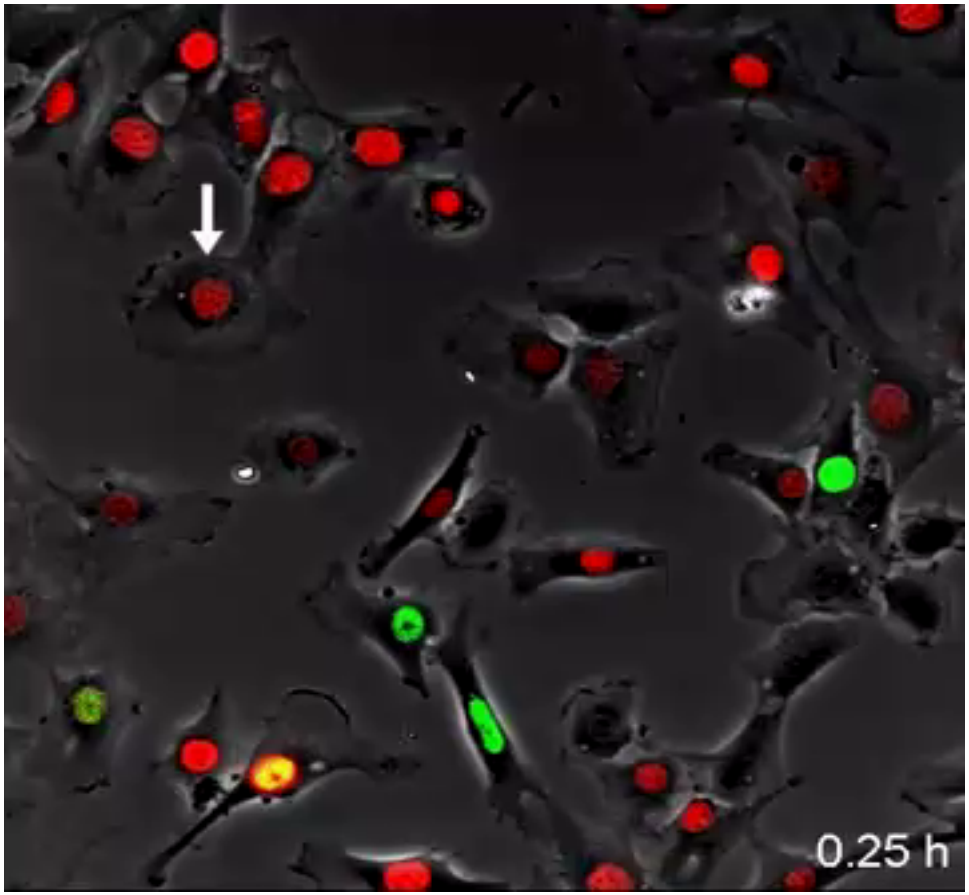
Many thanks to Bert van der Kogel for his slides

Cancer Research Center Groningen

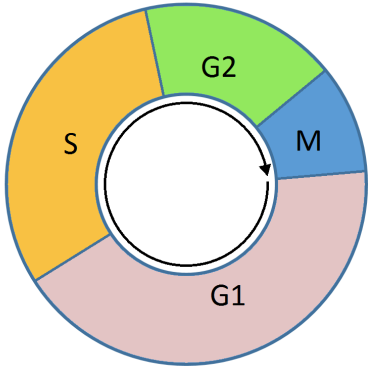
ESTRO School

UMCG

Dynamics of the cell cycle in a growing population



G1 - early S - late S & G2



G1 - Growth

S - DNA synthesis

G2 - Growth and preparation for mitosis

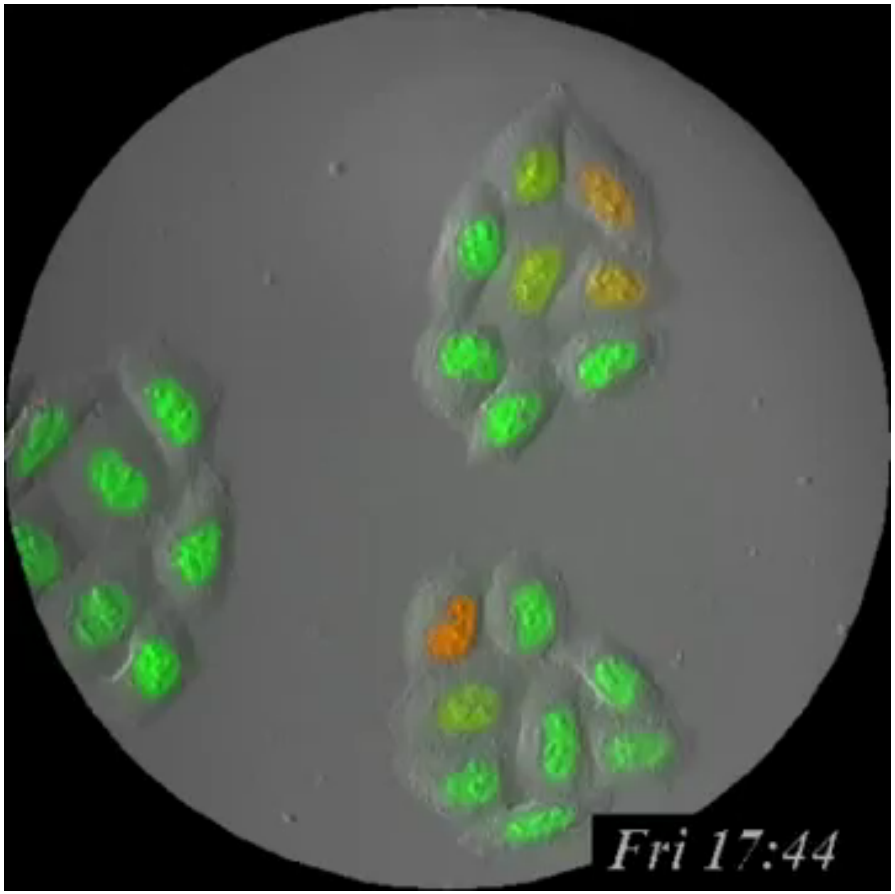
M - Mitosis (cell division)

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

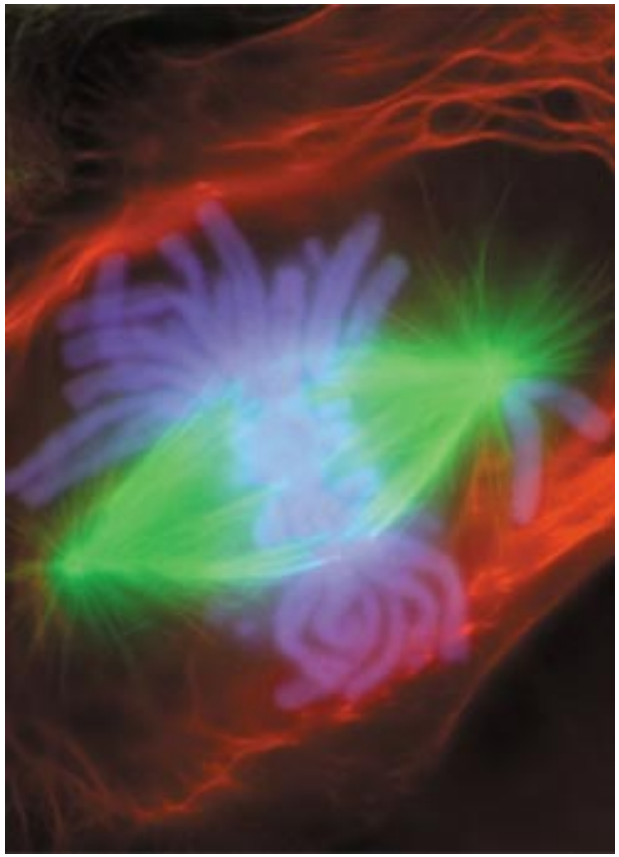


FUCCI imaging of HeLa cells over 3.5 day period

Red: G1/early S
Green: S/G2

G1 - early S - late S & G2

Effects of irradiation on mitosis

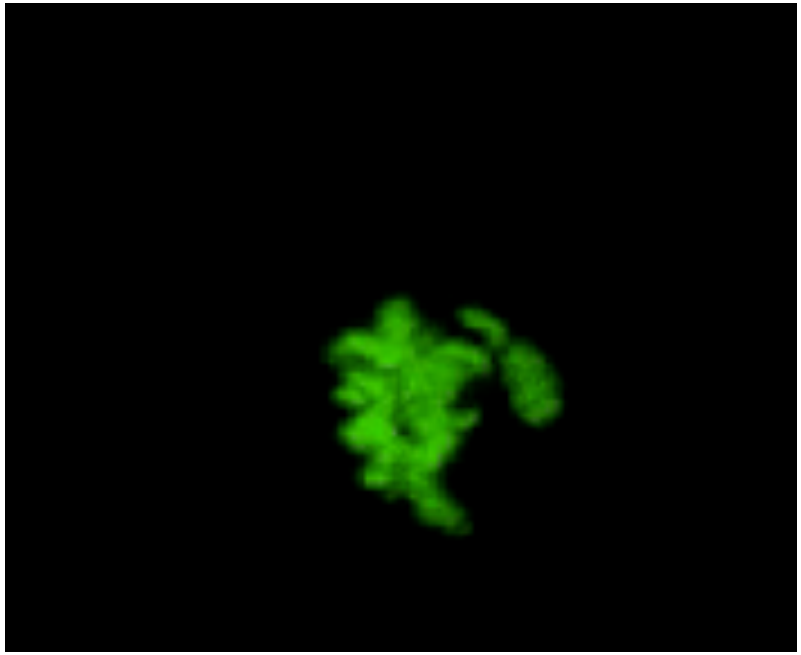


Mitosis and
cell plate formation in a
flattened endosperm cell
of the African blood lily,
Haemanthus katherinae,
observed with
phase contrast microscopy

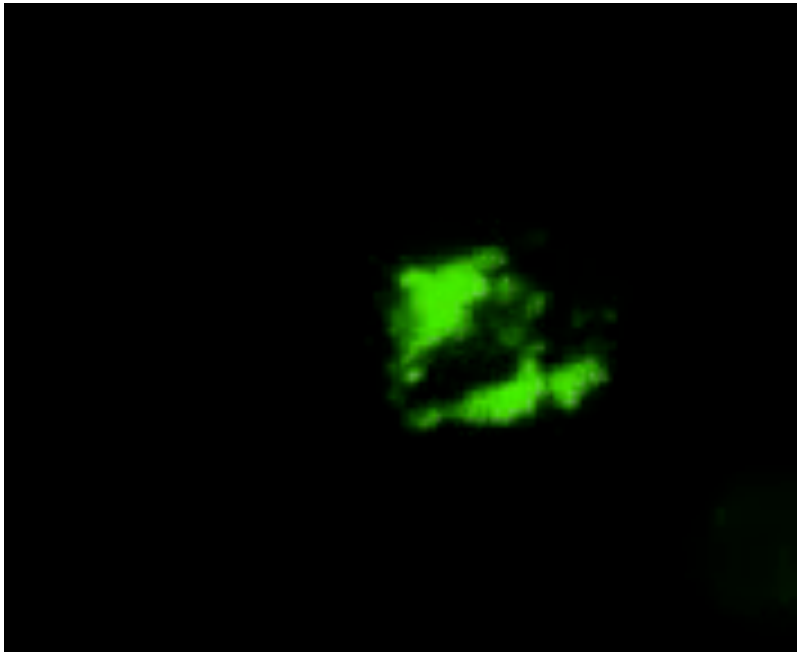
Effects on mitosis in plant cells:
endosperm of Haemanthus - time-lapse movie A. Bajer (1962)

Effects of irradiation on mitosis

Normal cell



Irradiated cell



Effects of irradiation on clonogenic survival in vitro

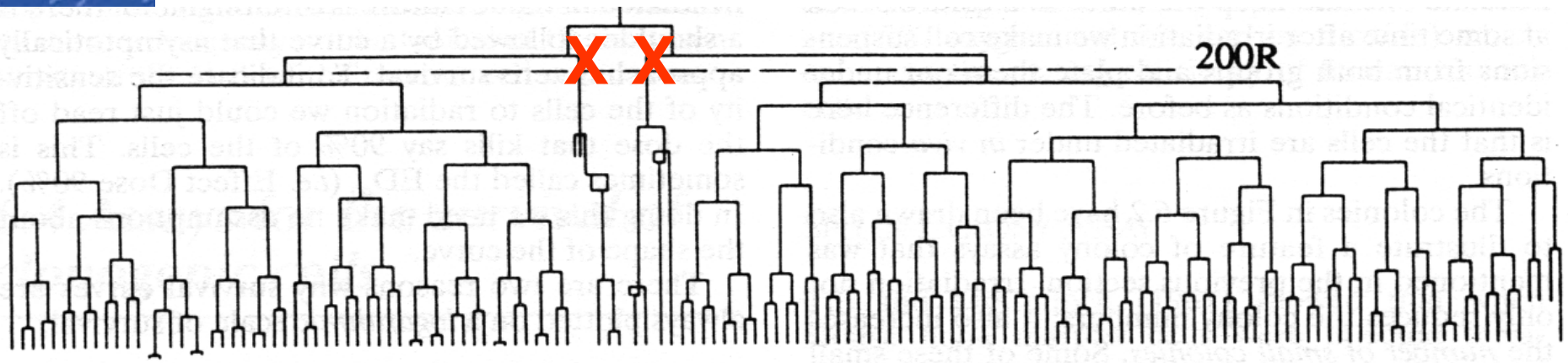
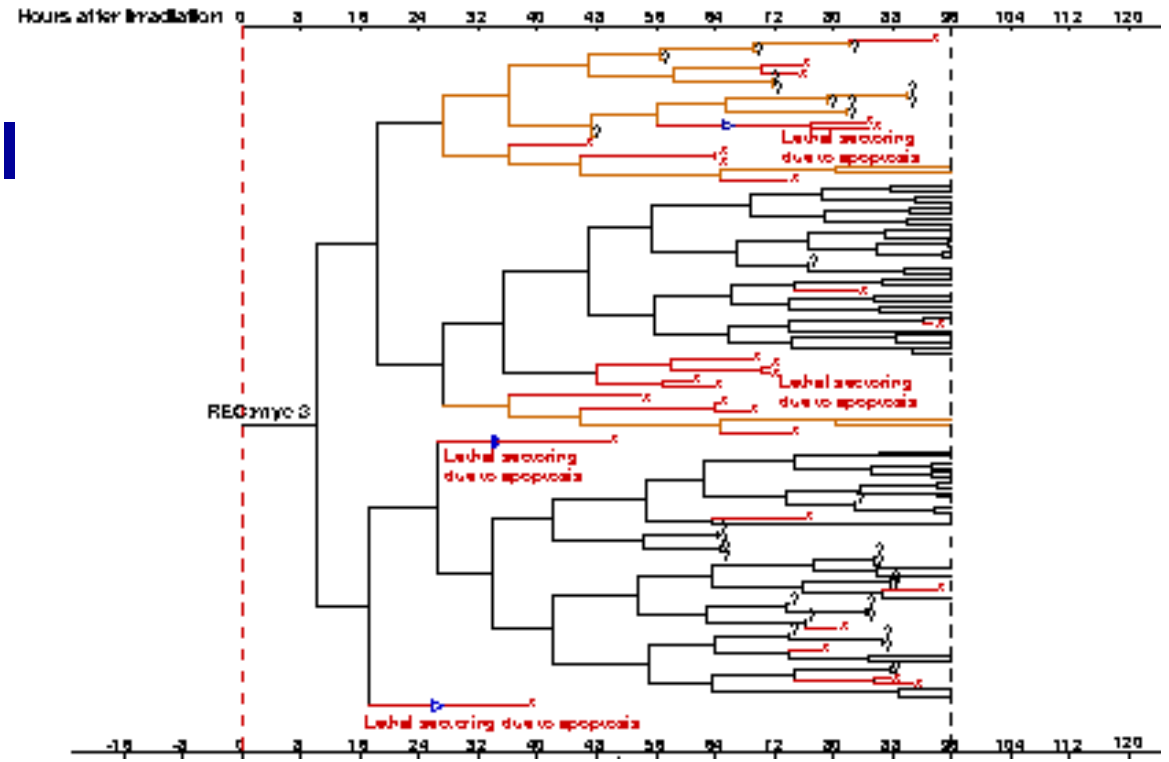


Figure 6.1 Pedigree of a clone of mouse L-cells irradiated with a dose of 200R (*i.e.* röntgens) at the 4-cell stage, illustrating the concept of surviving and non-surviving clonogenic cells. From Trott (1972), with permission.

Modes of cell death as analyzed in pedigree of irradiated cells



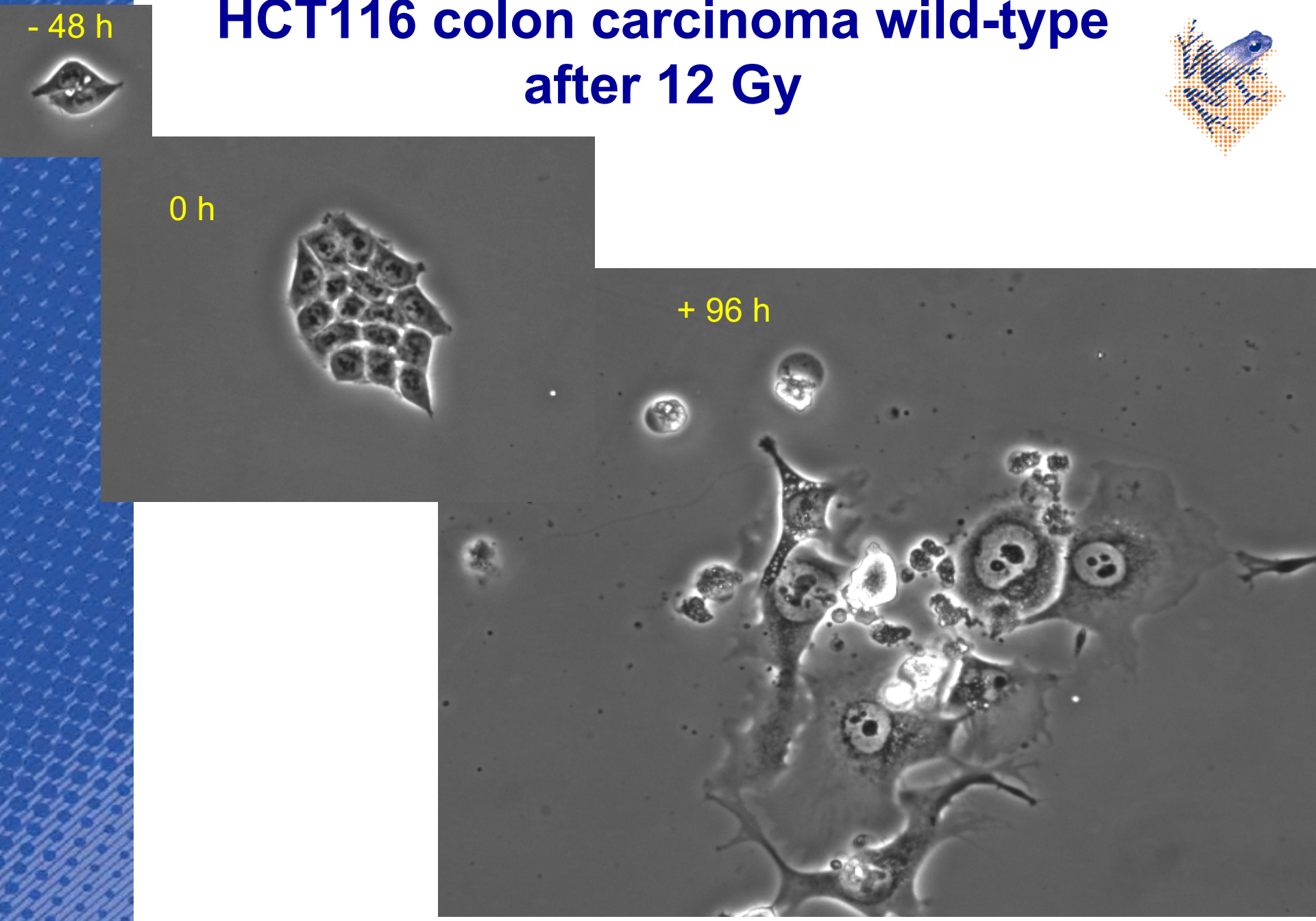
Pedigree of a colony formed from a cell irradiated with 2.5 Gy.

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

Black: cells which continue to divide (clonogenic survivors)

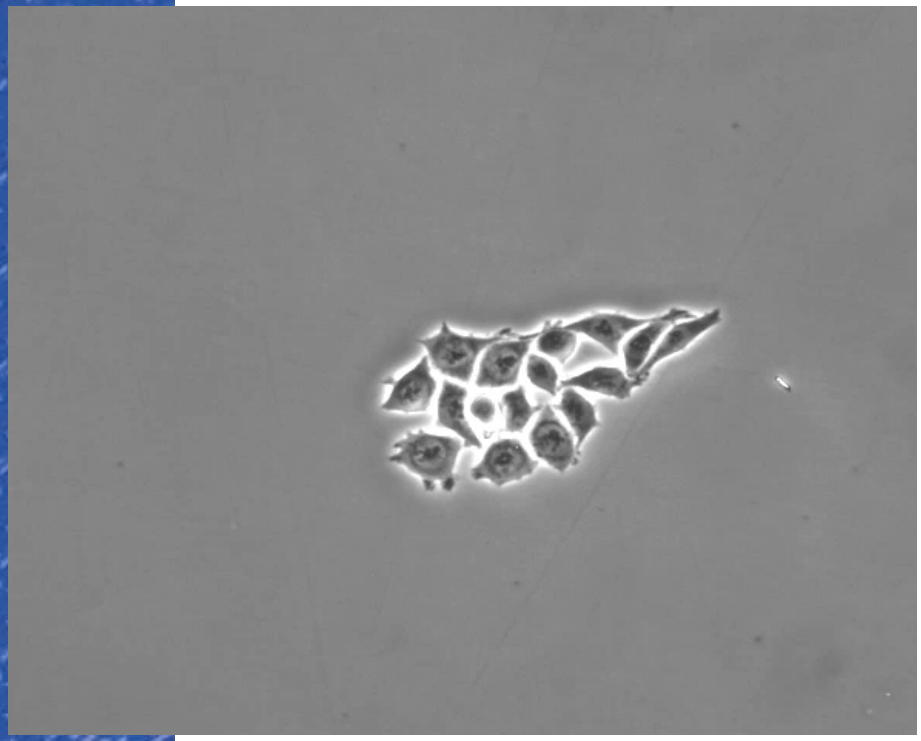
Red /orange : cells that die (apoptose) - but often after several divisions!

HCT116 colon carcinoma wild-type after 12 Gy

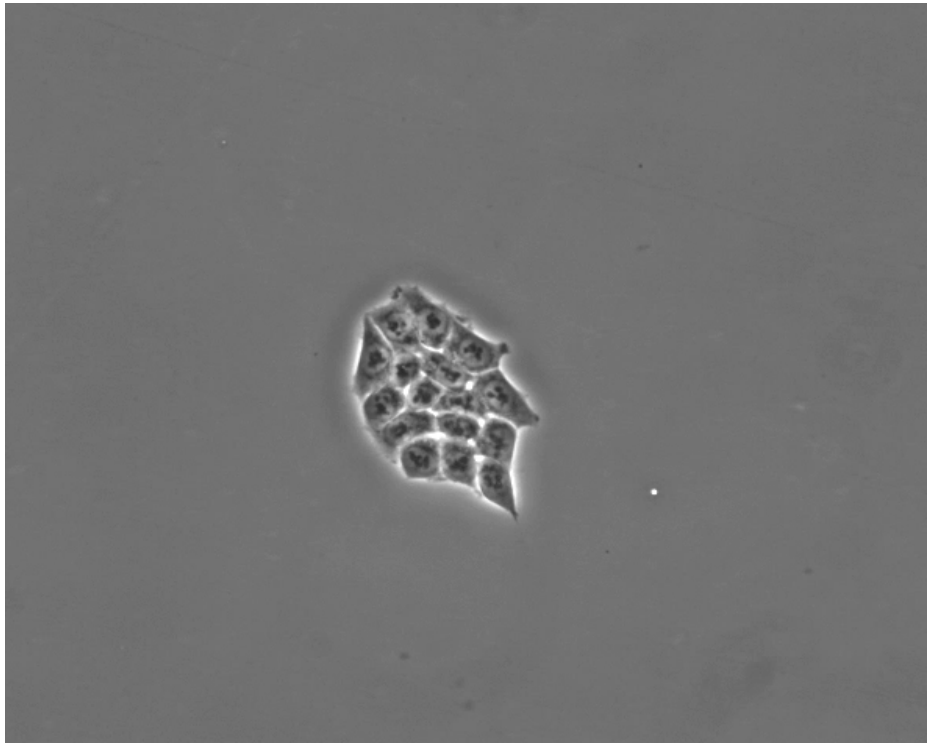


Cell death in HCT116 colon carcinoma cell colony (12 Gy, -G2/M)

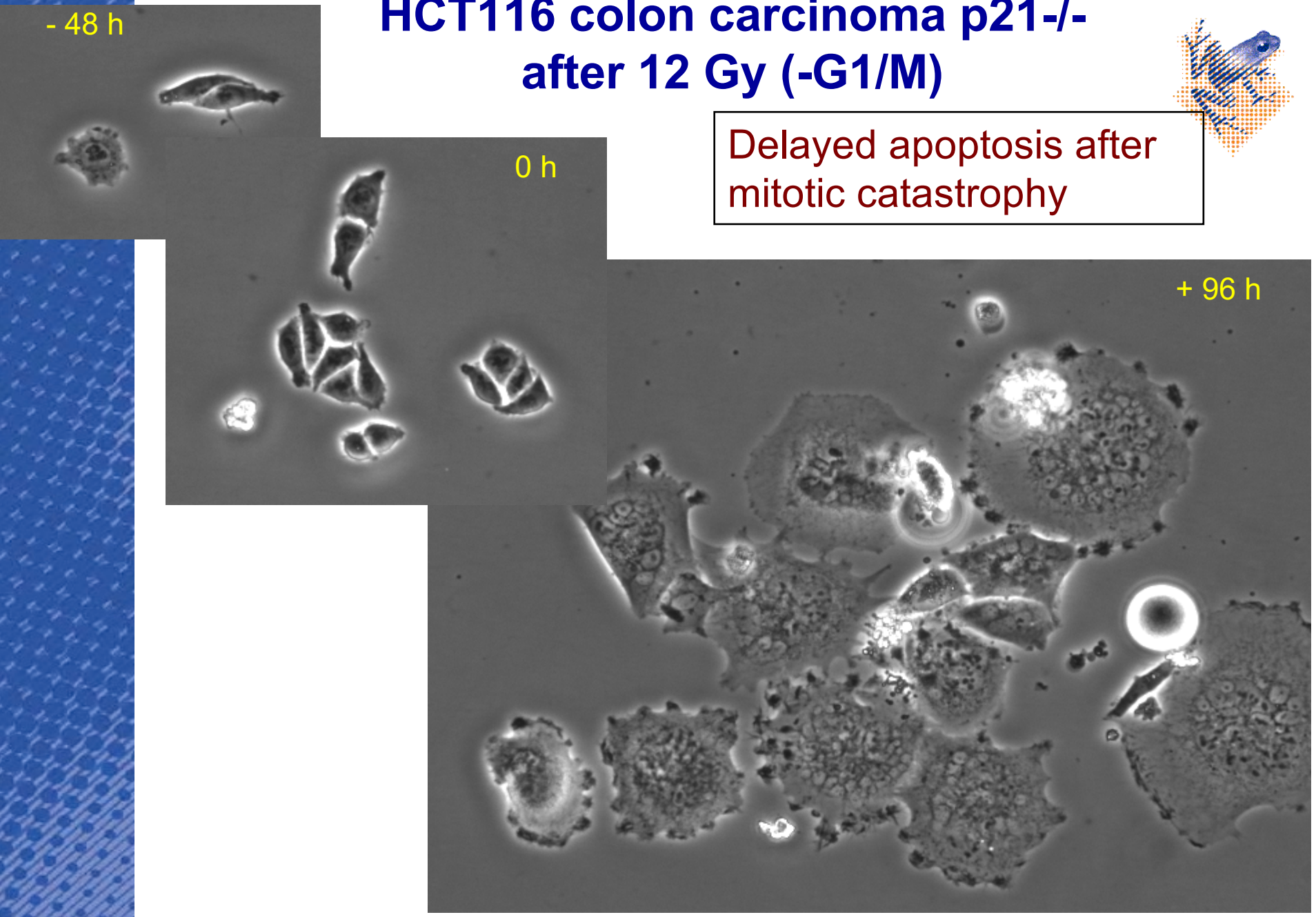
14-3-3σ -/-



wild-type

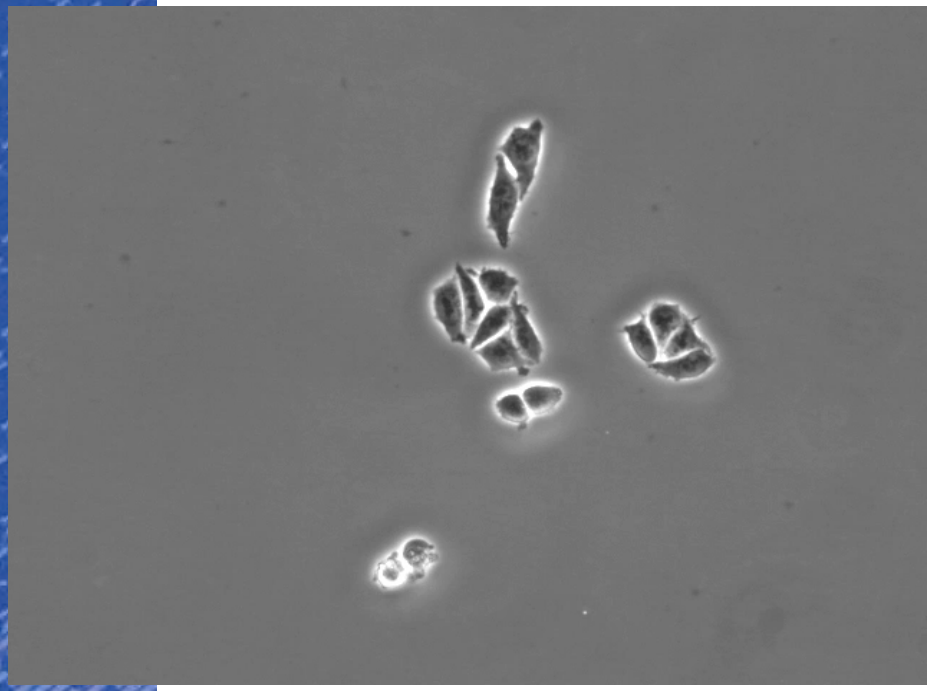


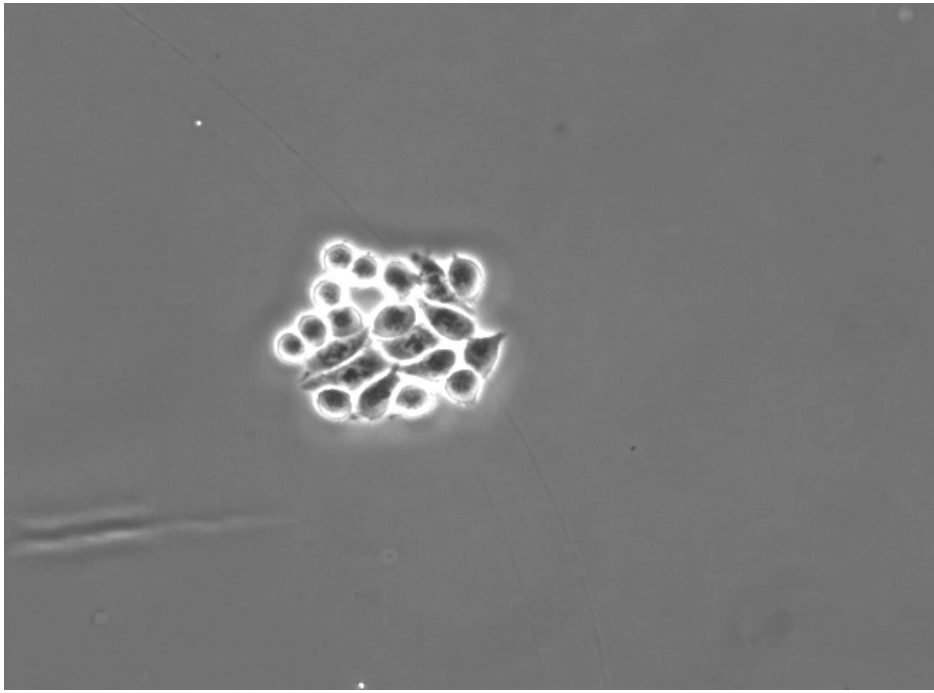
HCT116 colon carcinoma p21-/- after 12 Gy (-G1/M)



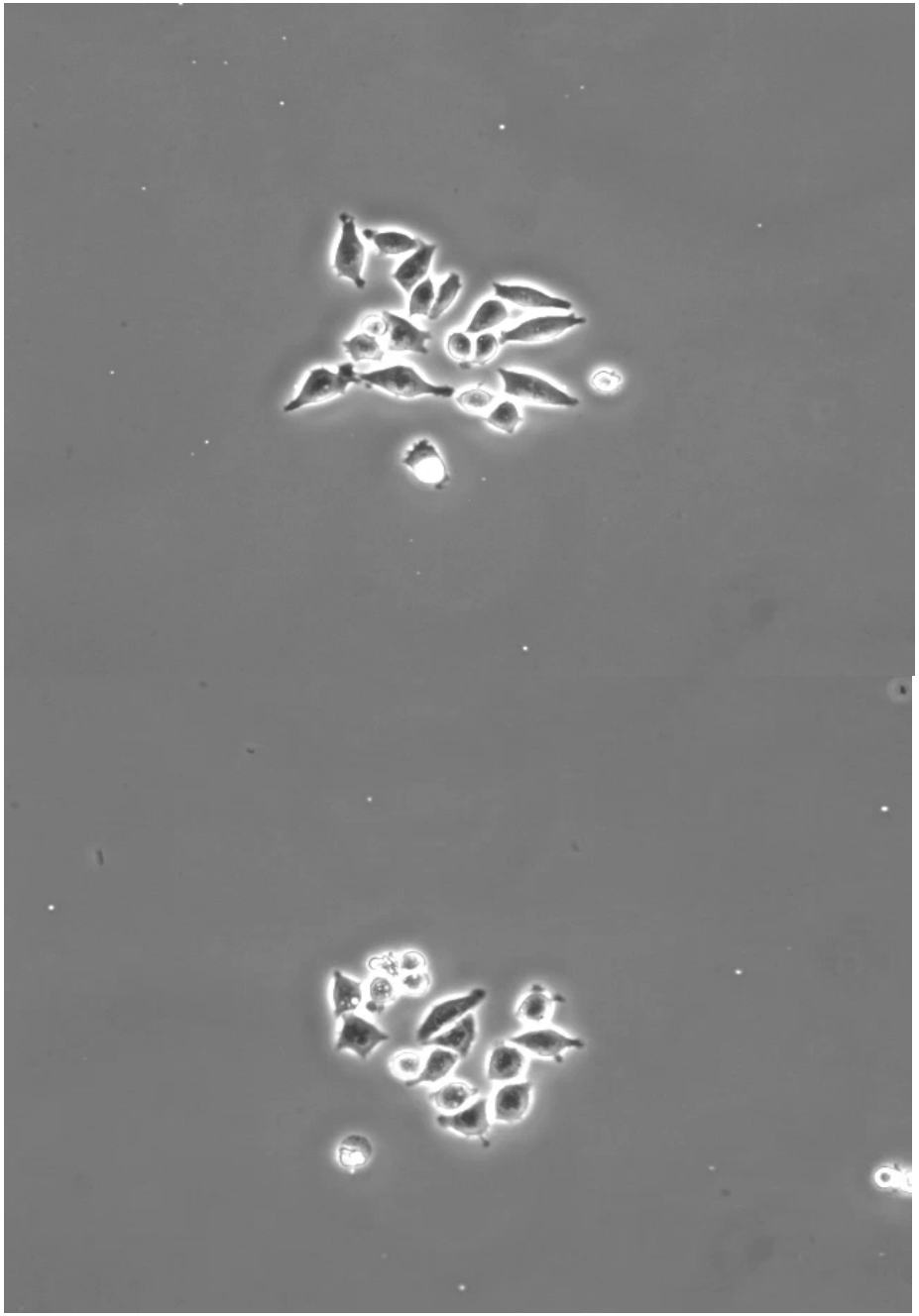
Delayed apoptosis after mitotic catastrophy

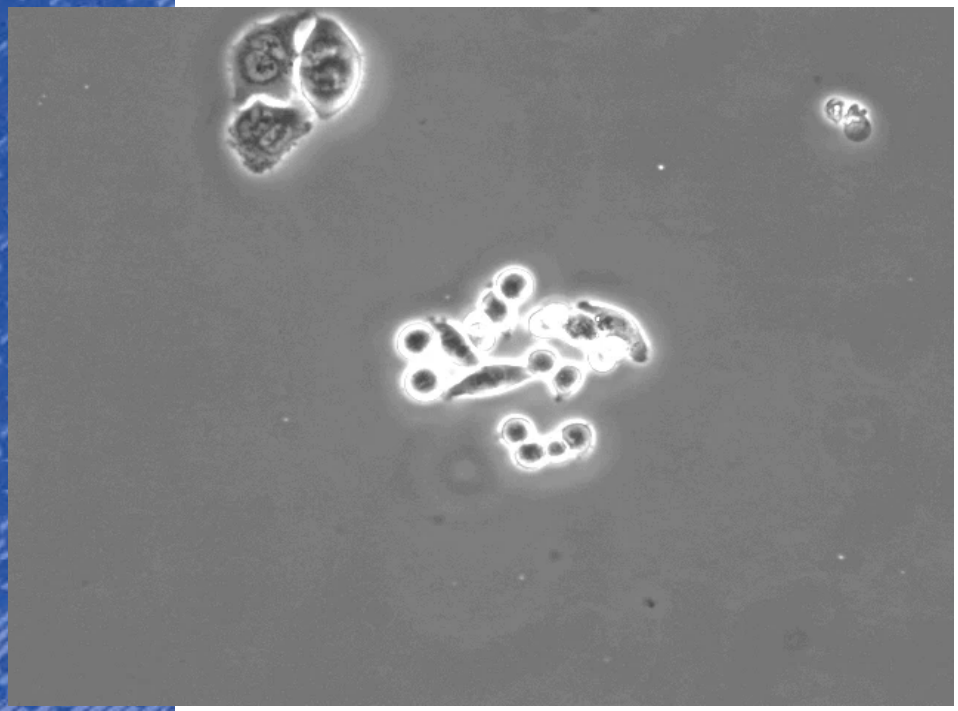
heterogeneity in response of individual clones:
HCT116 - p21-/-



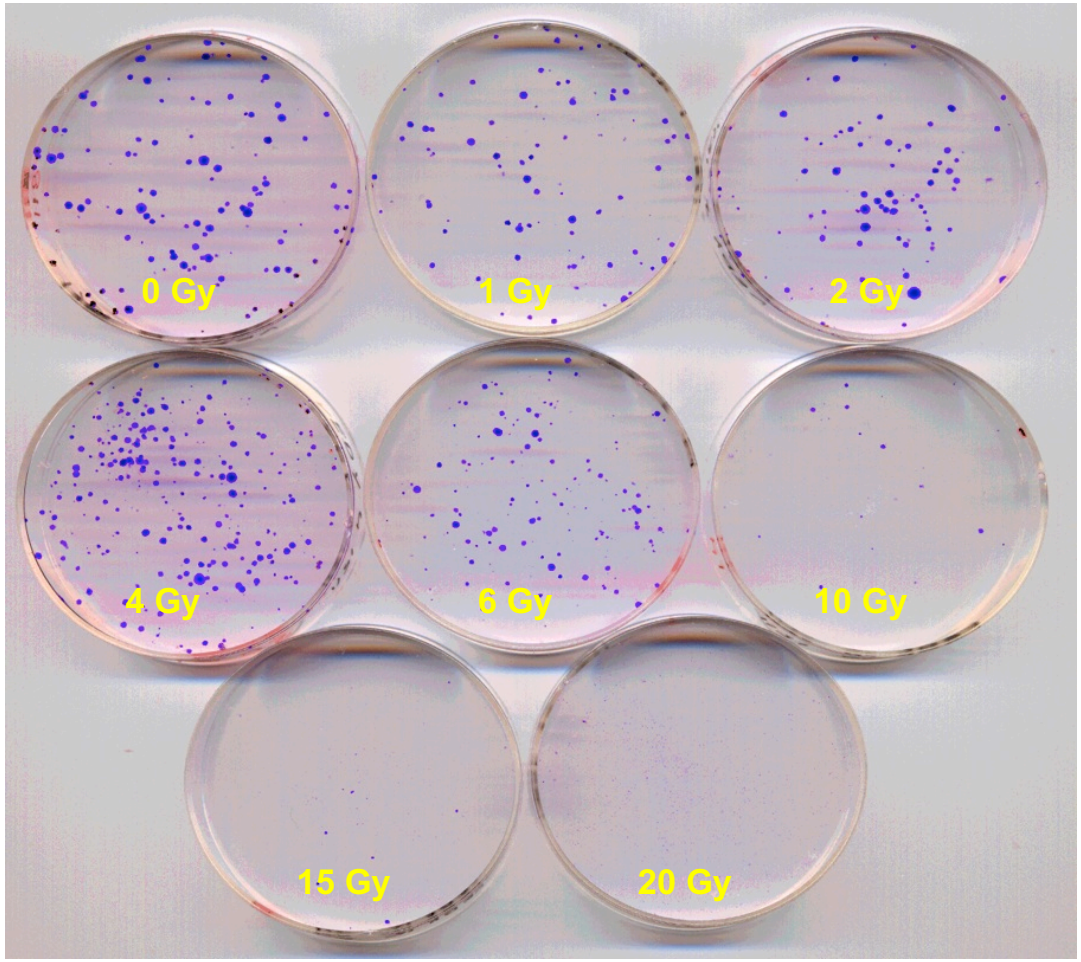


heterogeneity in response of individual clones:
p21/14-3-3σ double KO

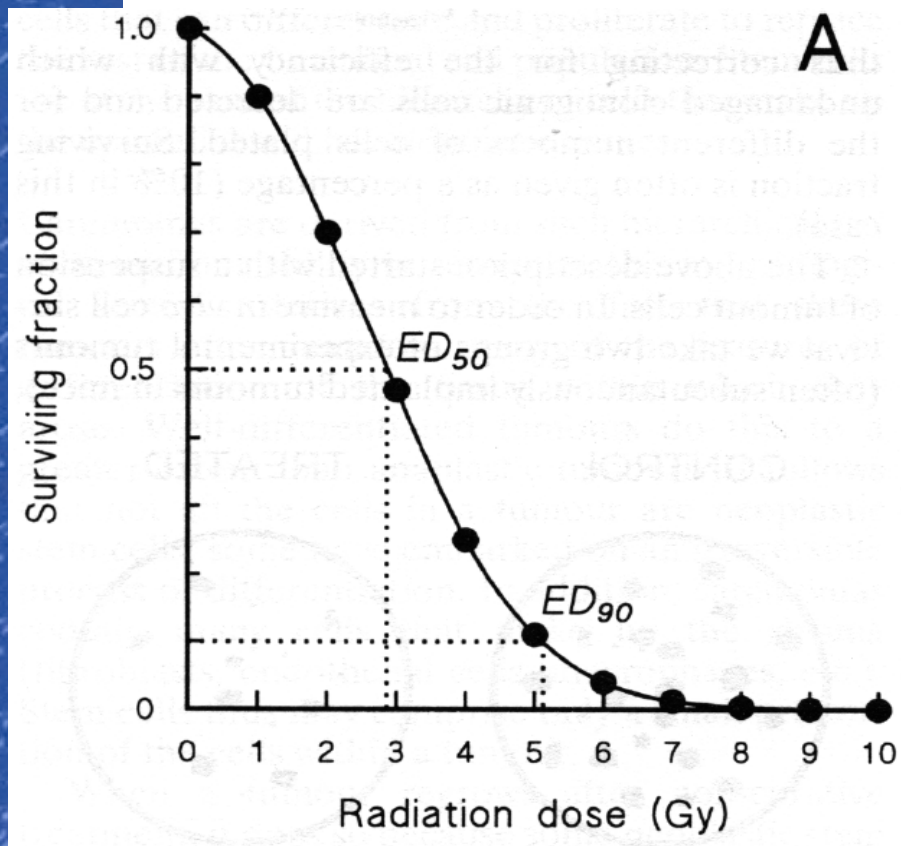


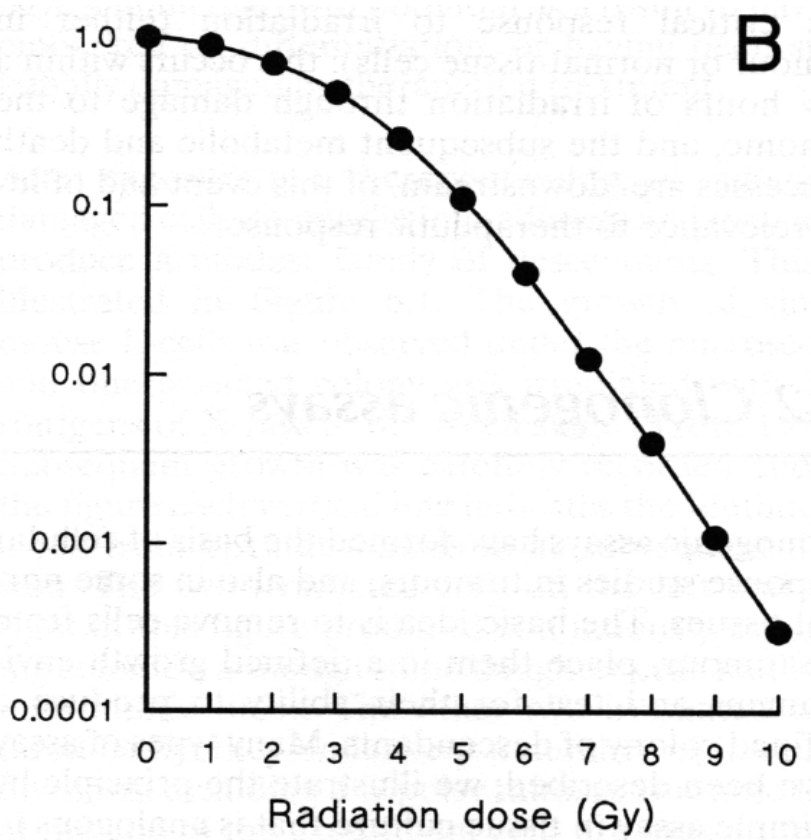


Colony assay: in vitro survival



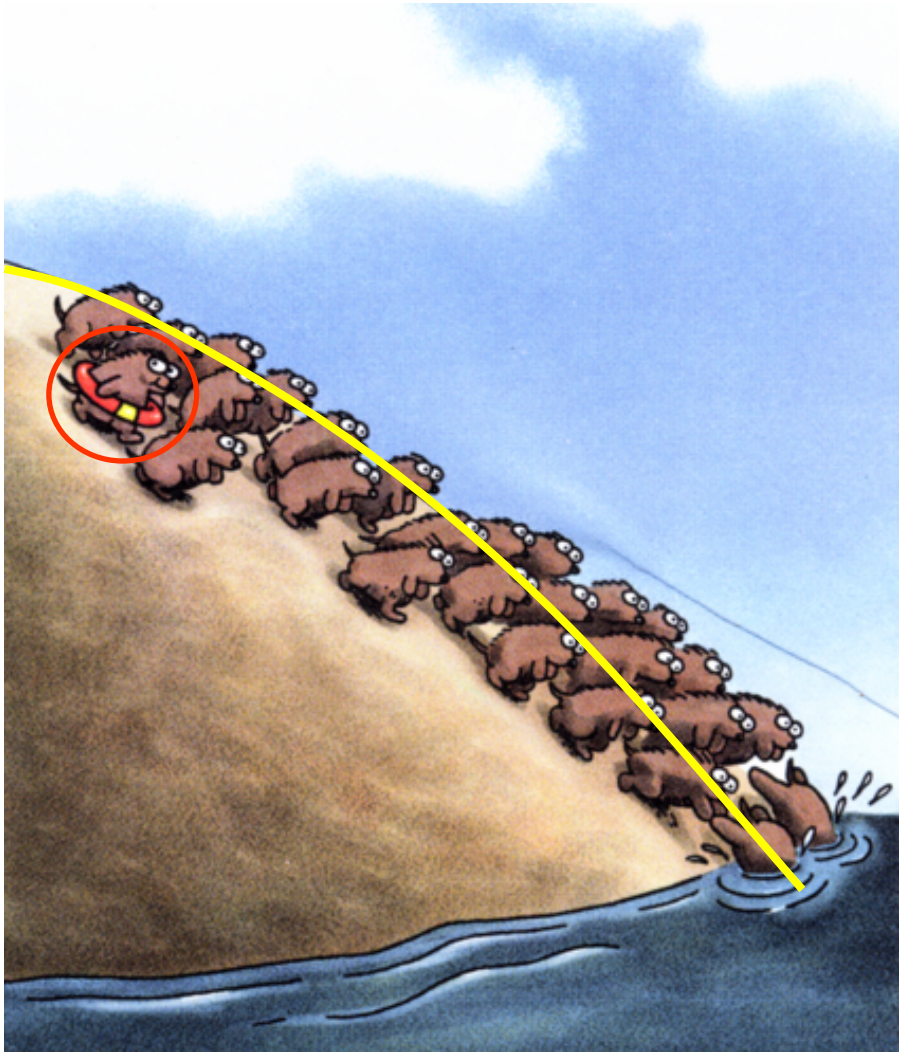
Cell survival curves





More in lecture by Michael Joiner

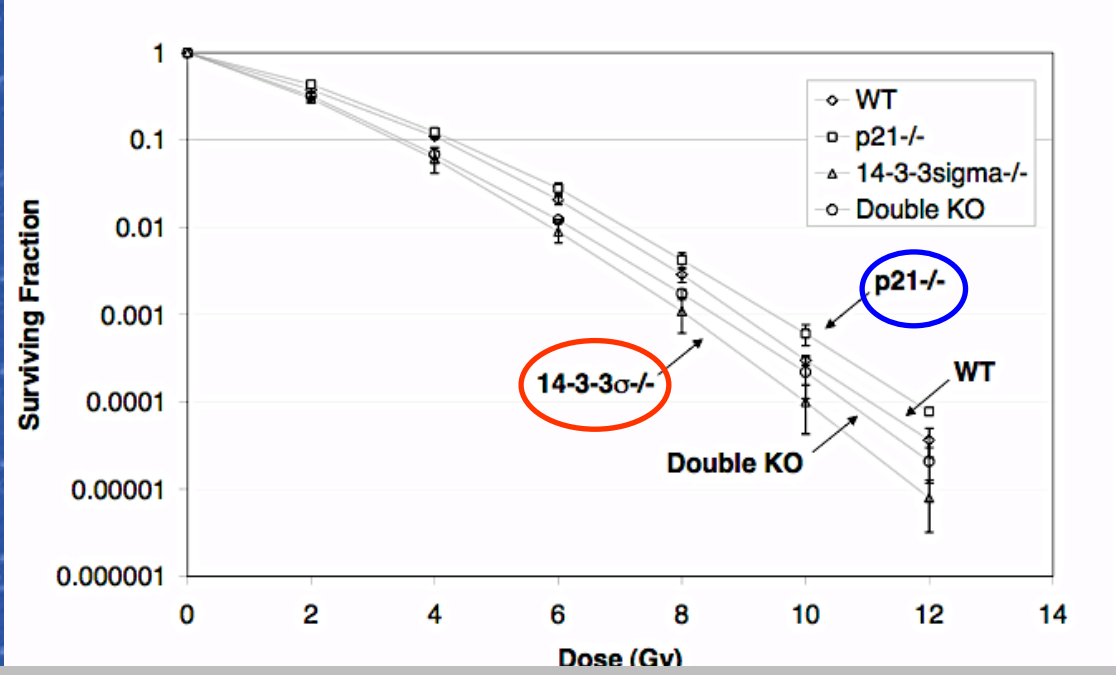
Cell death in a tumor: think exponential!

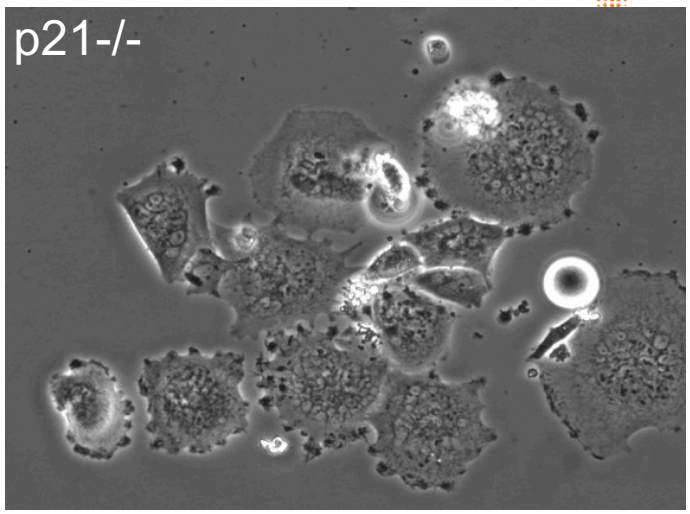


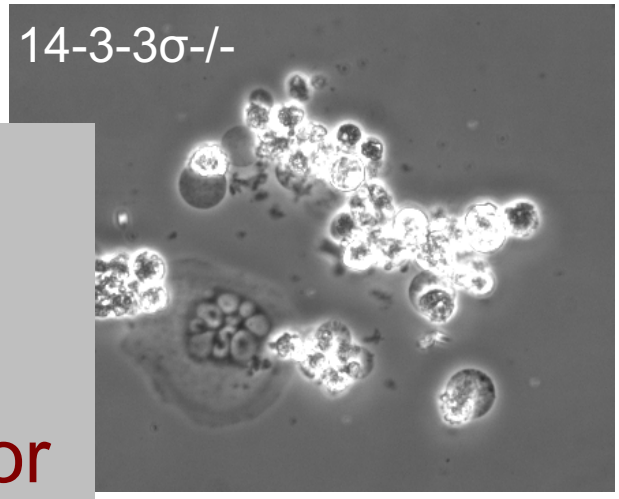
free after
Gary Larson

survival of HCT116 colorectal carcinoma cells

(Chu, Dewey et al, 2004)



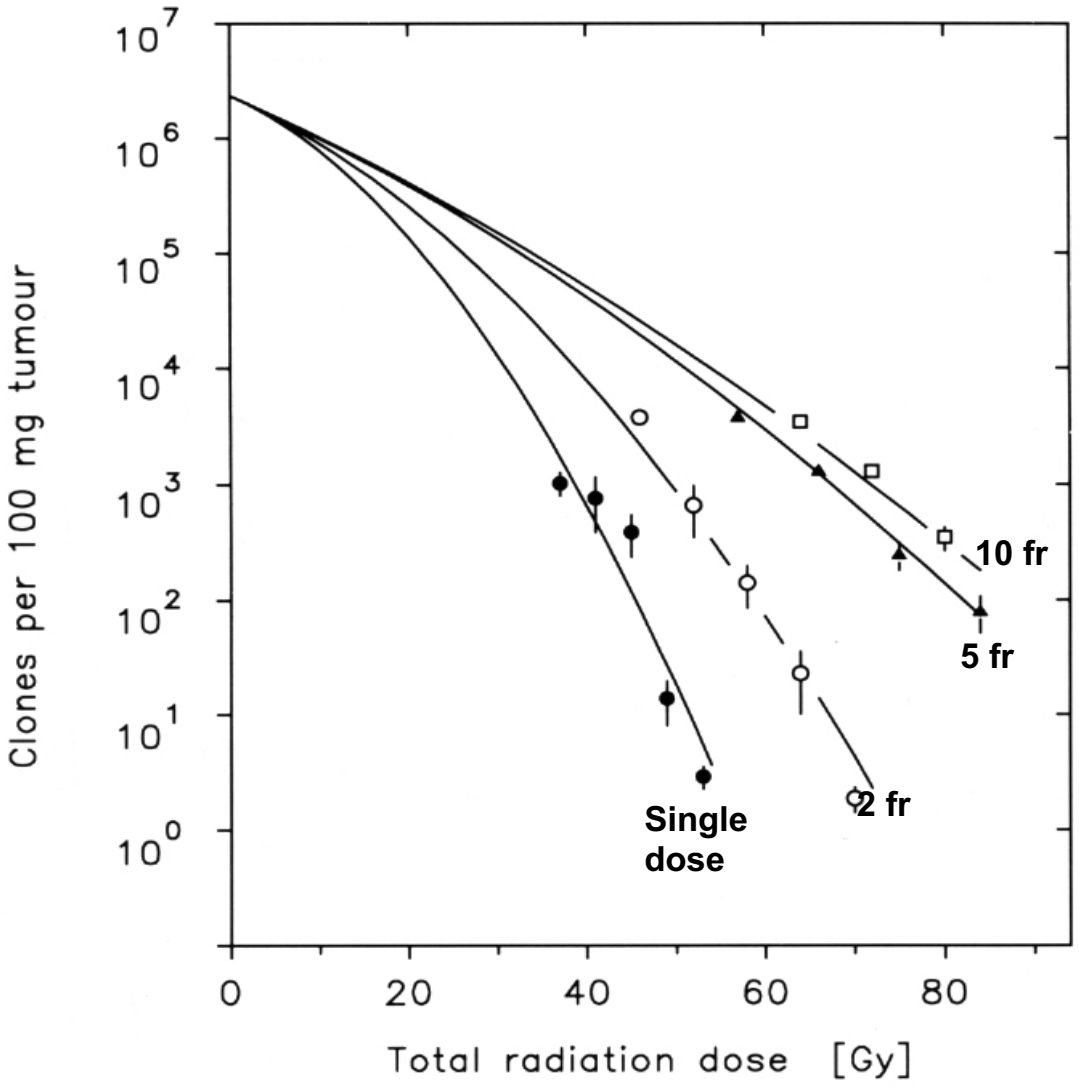


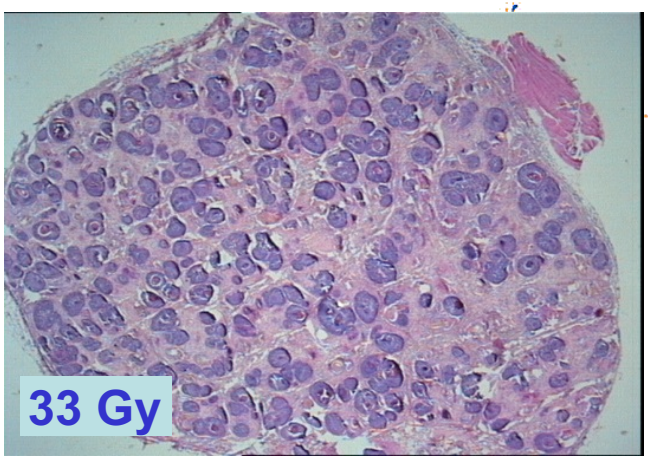


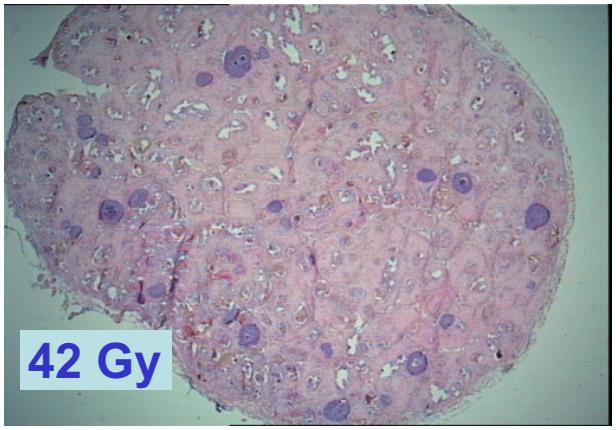
- The type of cell death has no relation with sensitivity
- Death and removal of cells after irradiation may take many days or even weeks

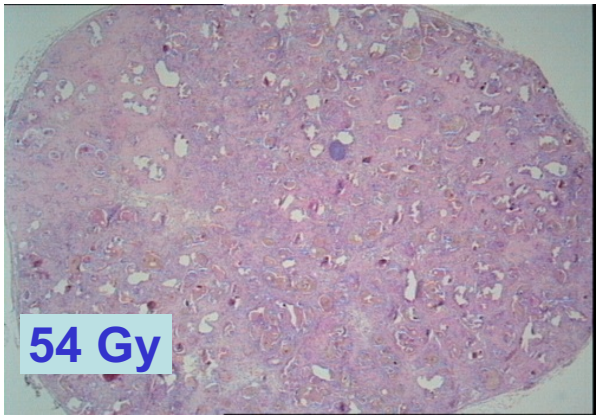
Cell death and clonogenic survival in tumors

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





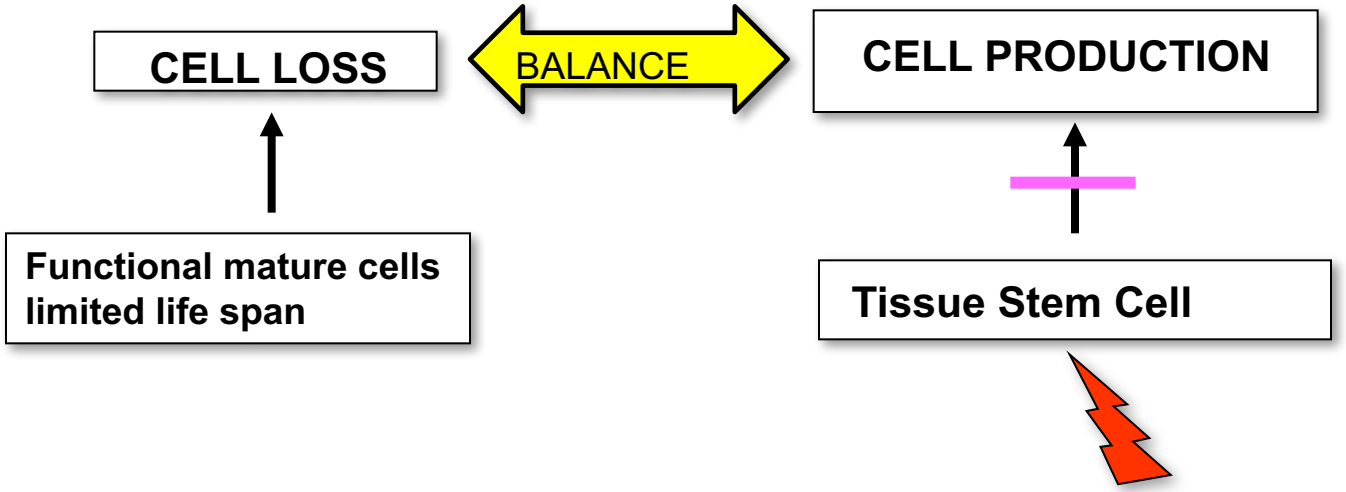




Kummerrmehr (1997)

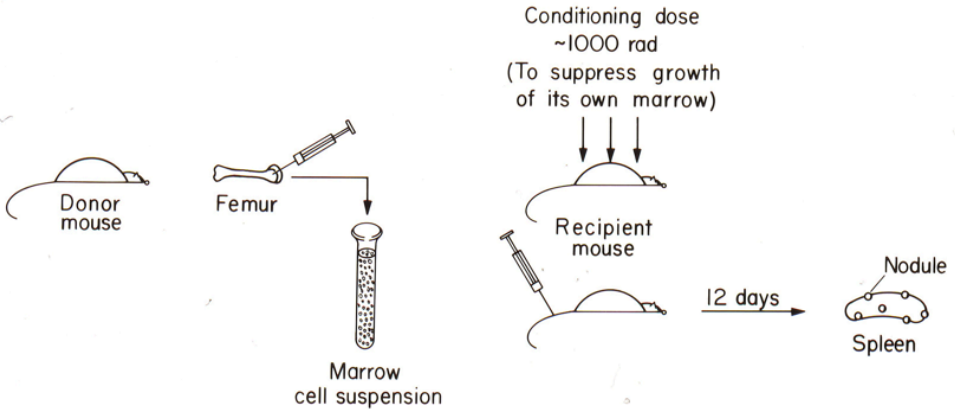
Cell death and clonogenic survival in normal tissues

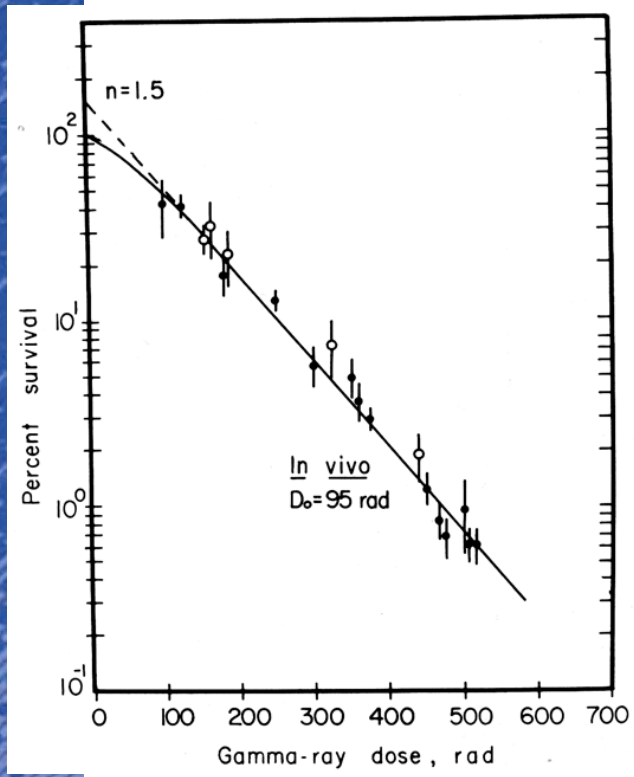
Normal tissue homeostasis

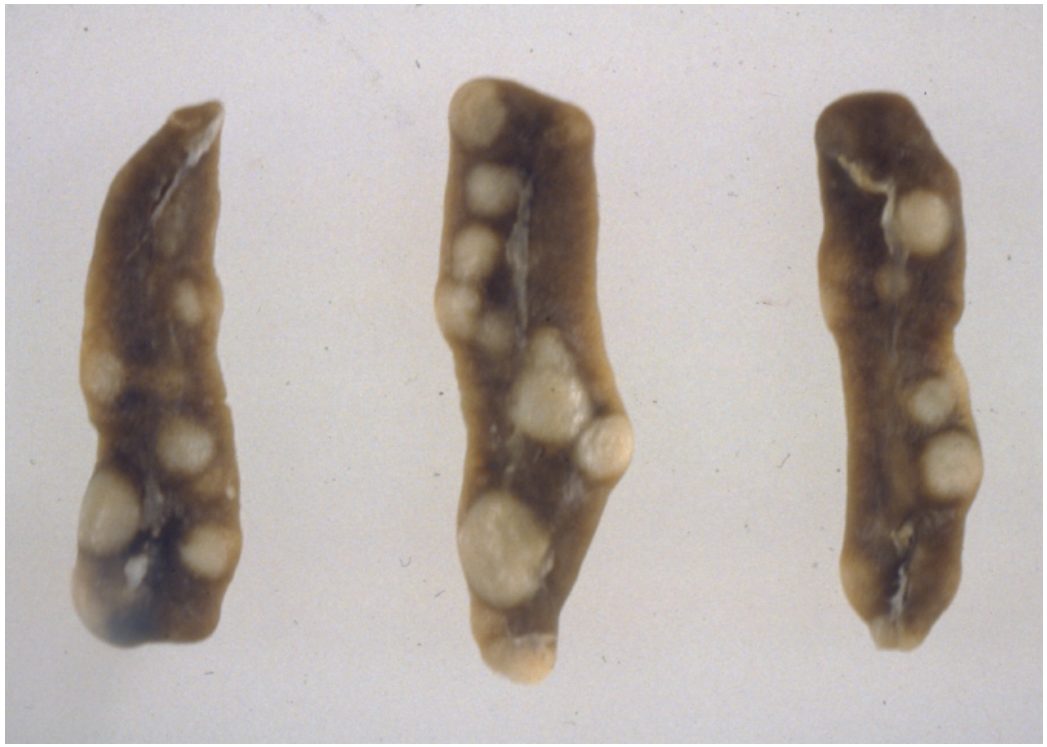


clonogenic survival in normal tissues: *spleen colony assay*

(McCulloch&Till, 1962)



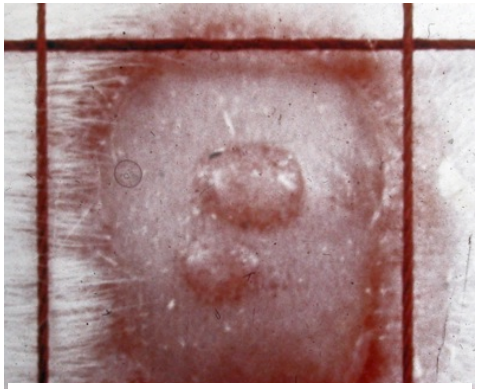




Dose-response for skin epithelium

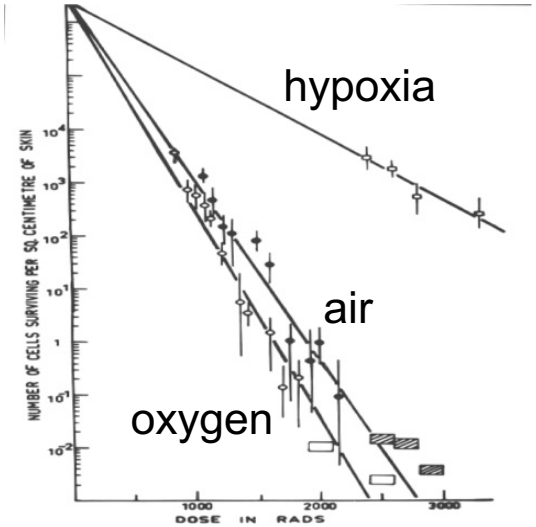
Withers 1966: Skin remains intact if clonogen survival is higher than about 5 per 10^{-6} per cm^2. Higher doses will cause moist desquamation.

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.

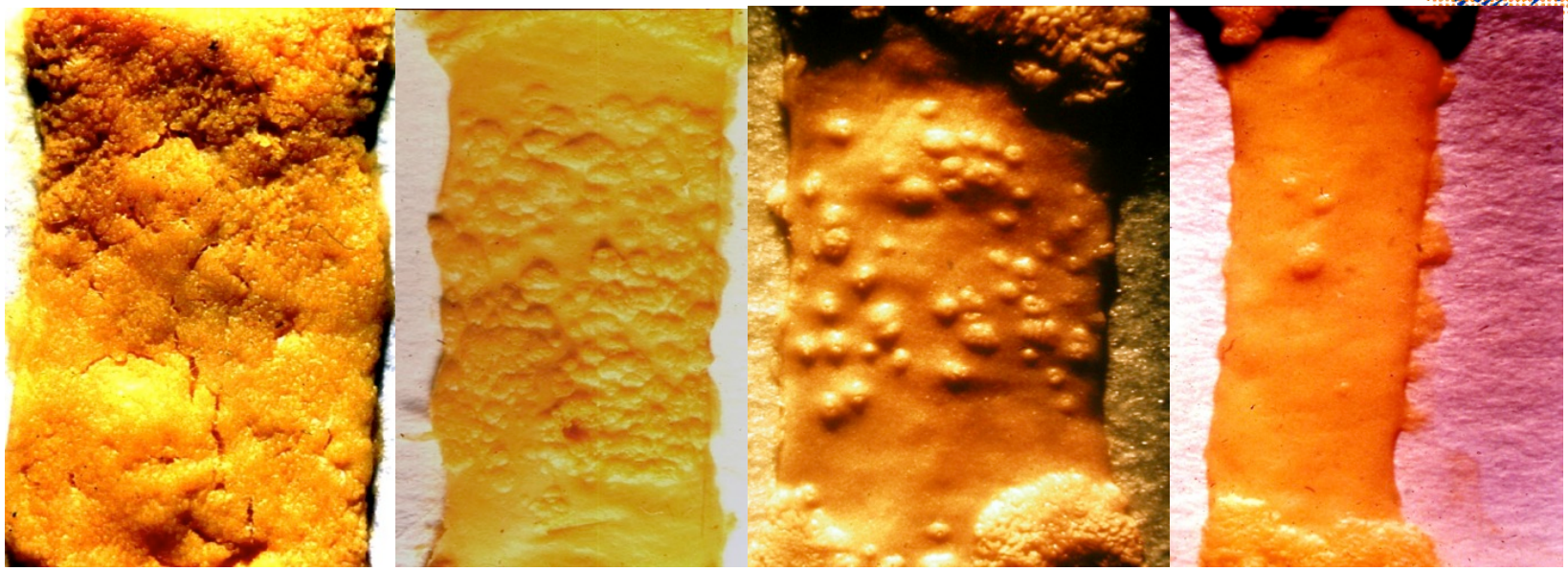


clonogenic survival in normal tissues: acute effects

Source: J. Hendry, Manchester, UK

XRT

Segment of mouse intestine irradiated with varying doses



a	b	c	d
12.5Gy	14.0Gy	15.5Gy	17.0Gy

Day 13

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

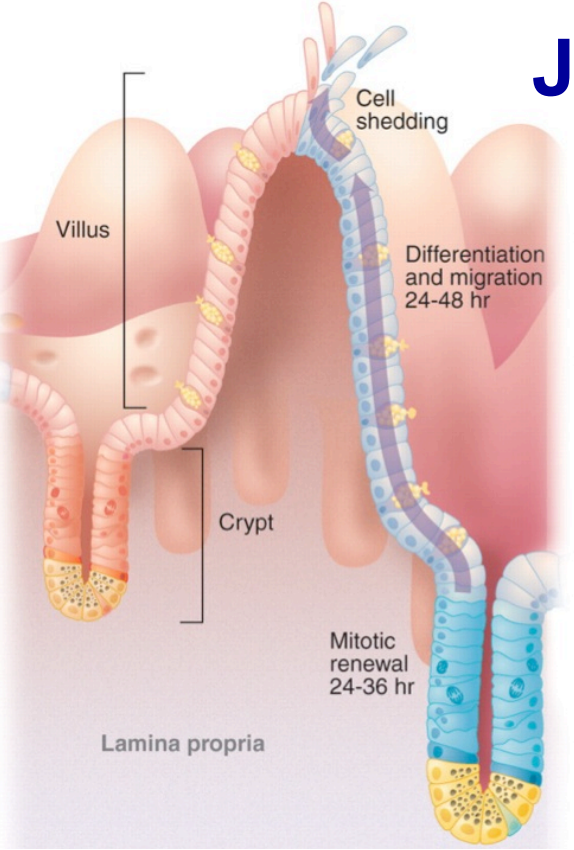
a. Patchy breakdown of mucosa except in shielded mucosa at top of specimen.

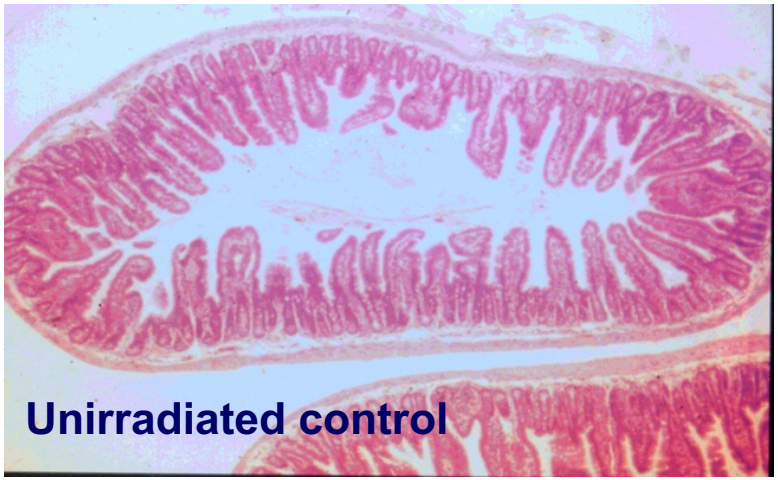
b. Ulcerated mucosa being resurfaced by near-confluent nodules regenerated from a large number of independently surviving jejunal clonogens.

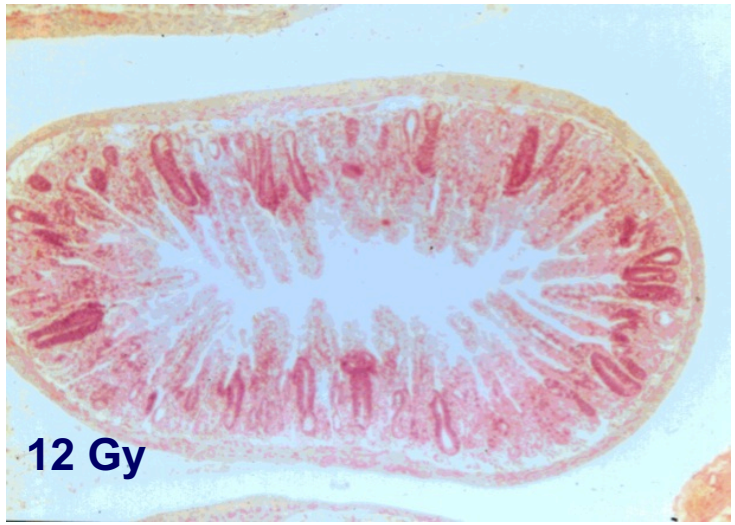
c. Severe ulceration but with about 60 discrete clonogen-derived mucosal nodules.

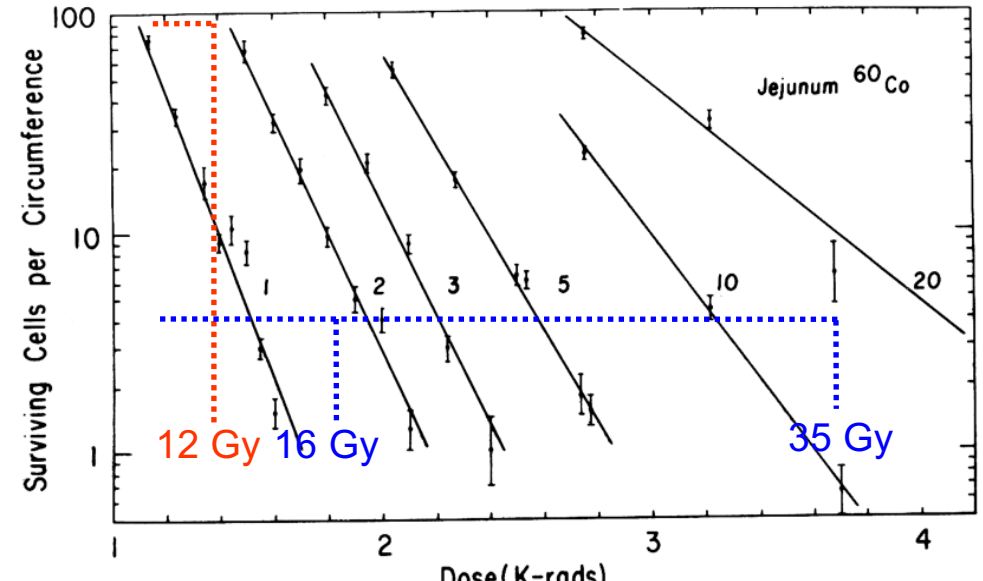
d. As for c. but only 4 regenerated nodules.

Jejunal crypt assay (Withers, 1974)

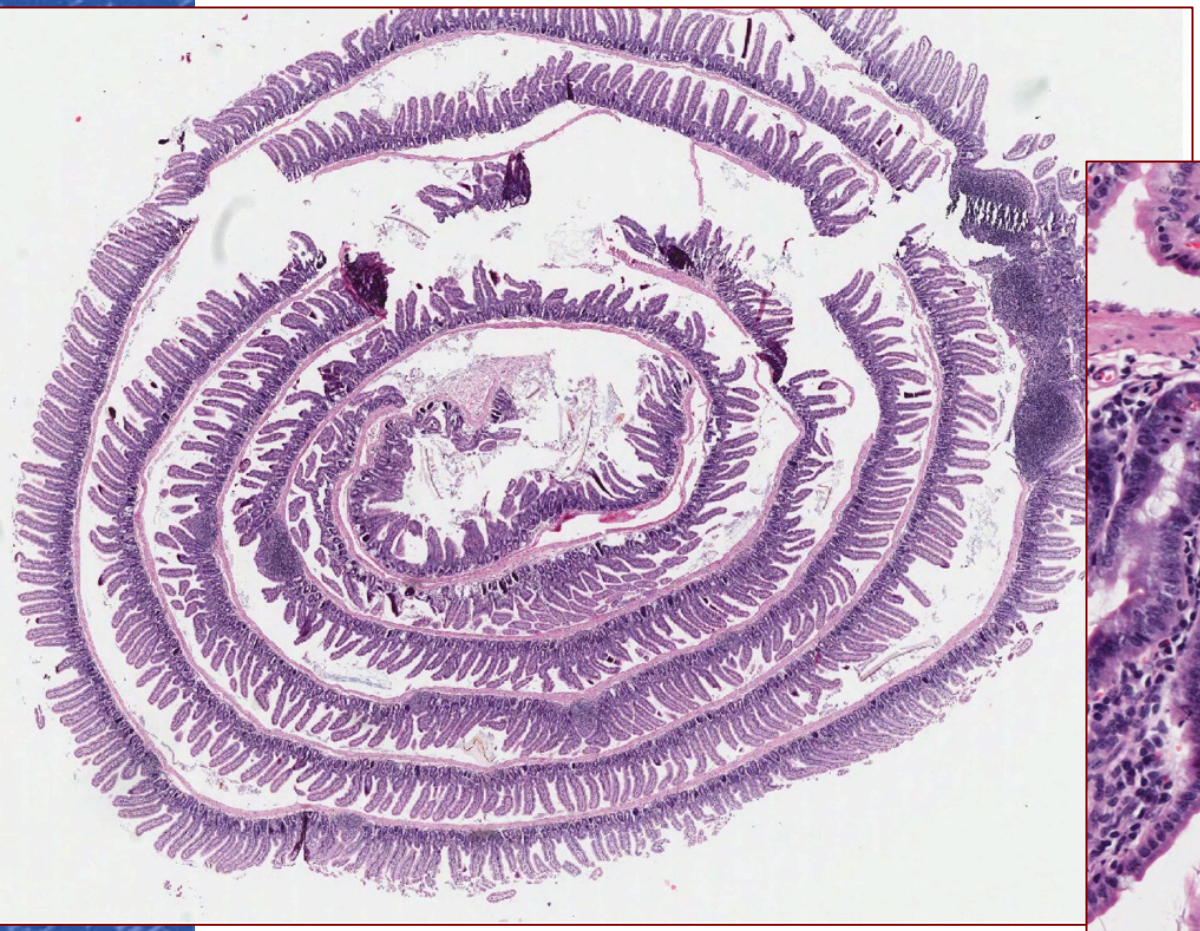


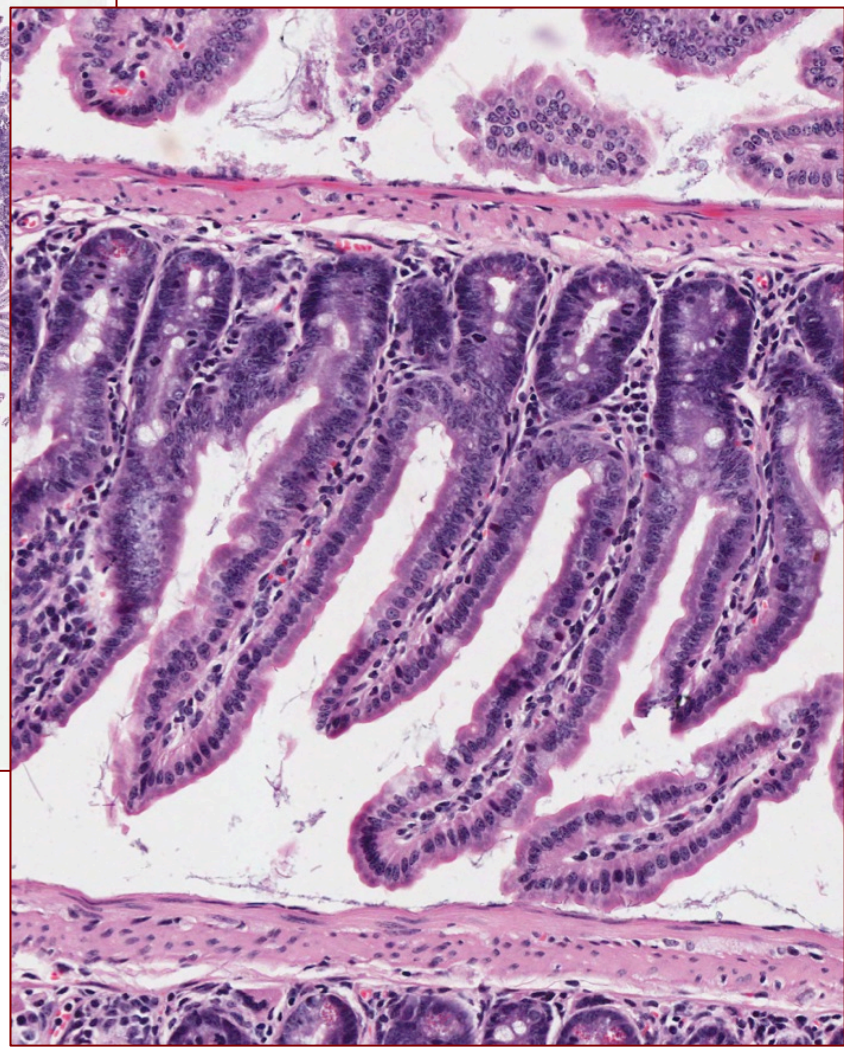






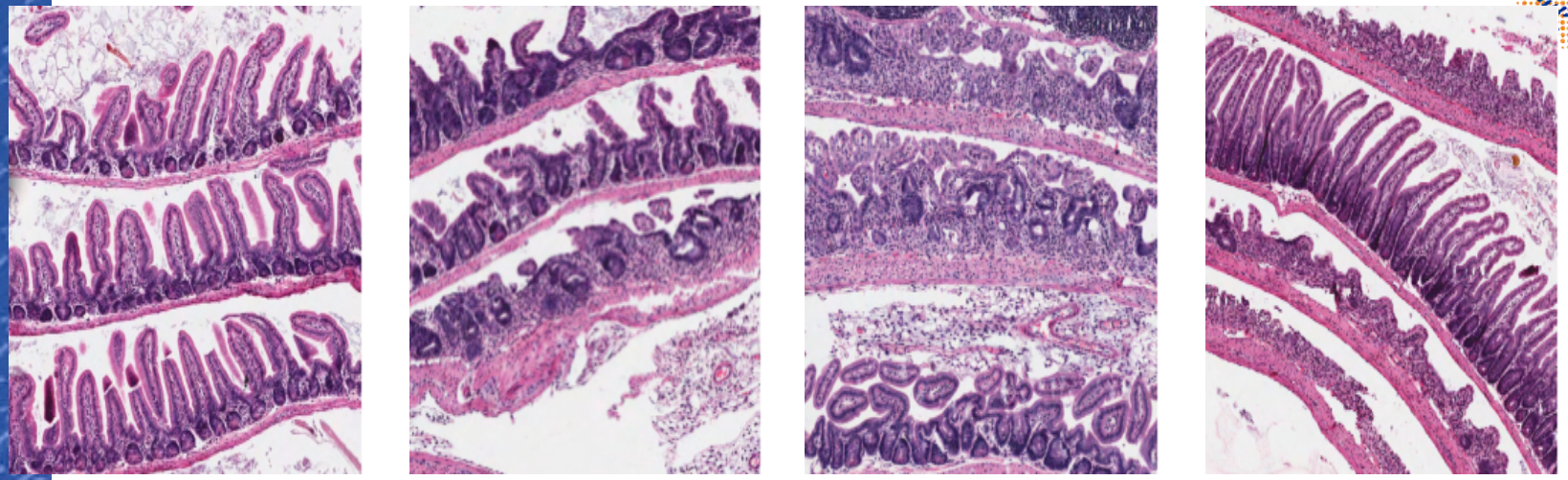
Intestinal crypt assay: the “Swiss roll”



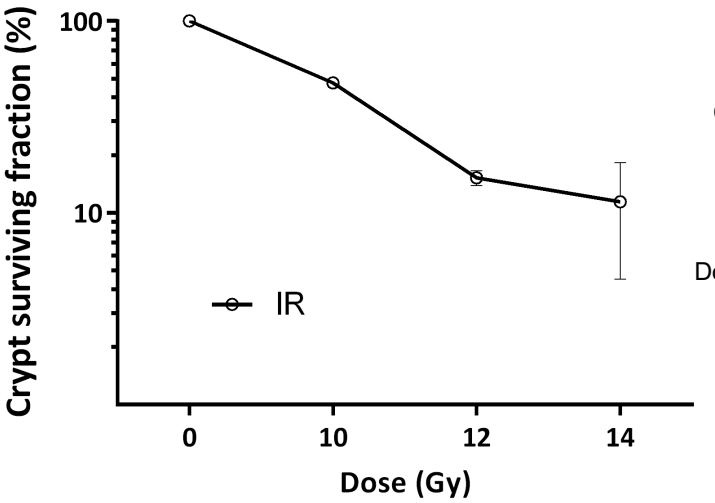


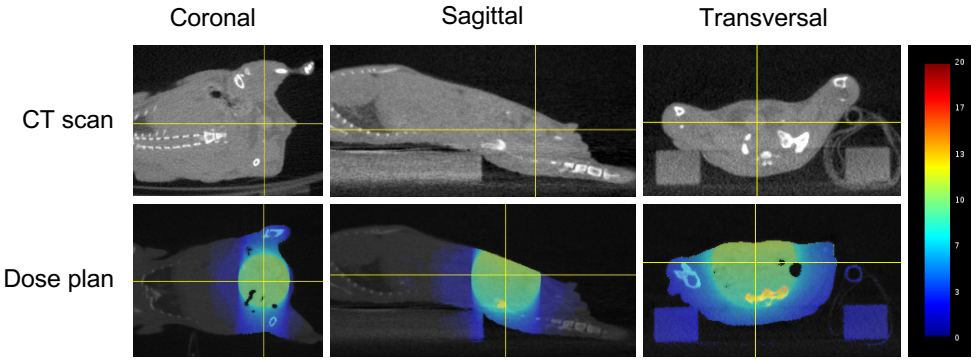
Courtesy of Kiltie & Groselj, 2014

Intestinal crypt assay: the “Swiss roll”



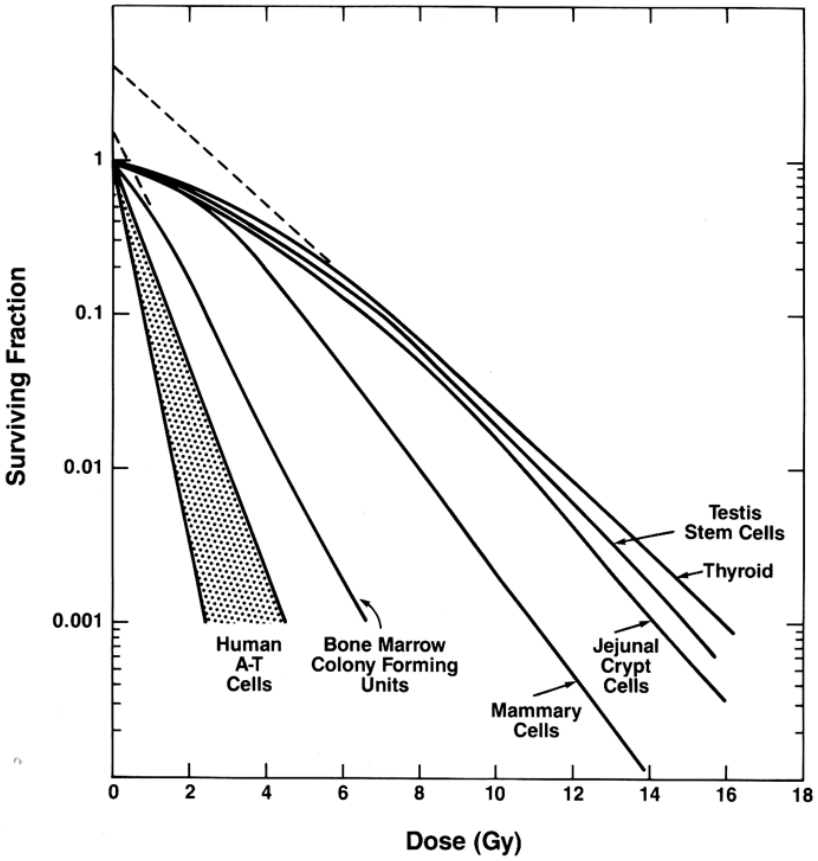
0 Gy 10 Gy 12 Gy 14 Gy





Courtesy of Kiltie & Groselj, 2015

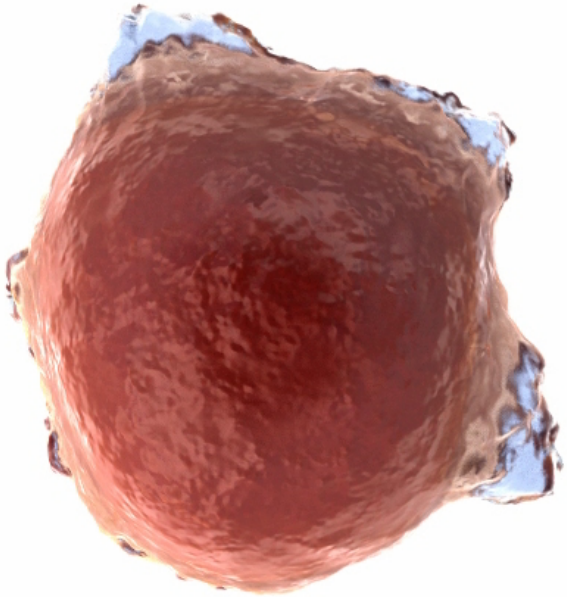
Clonogenic survival in normal tissues summary



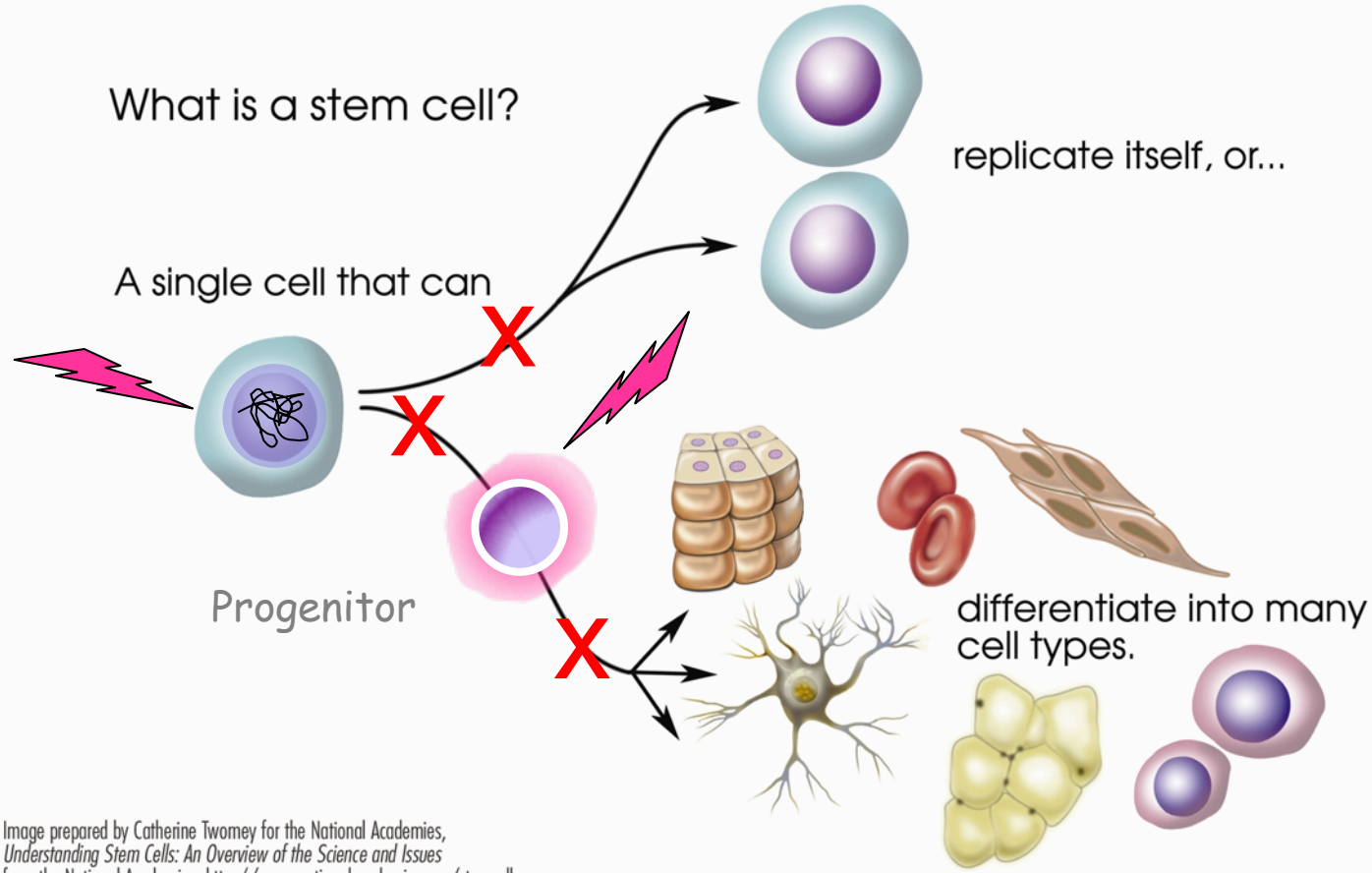
Stem cells from different tissues show large differences in radiosensitivity, as determined in assays of clonogenic survival

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

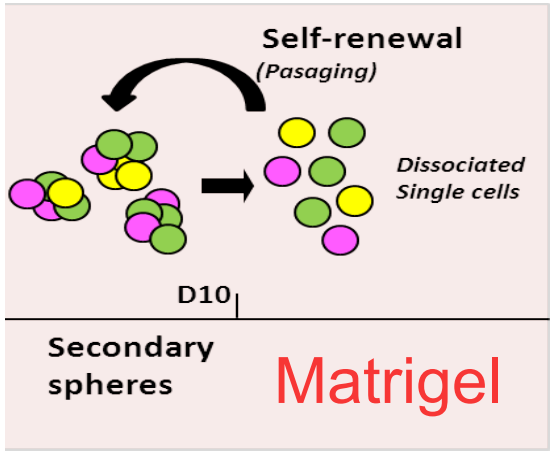
What are adult/tissue stem cells

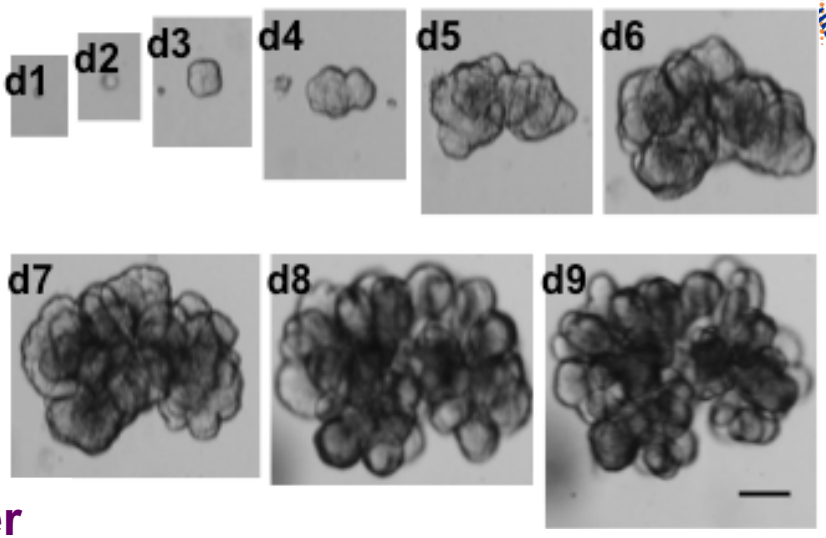


What is a stem cell

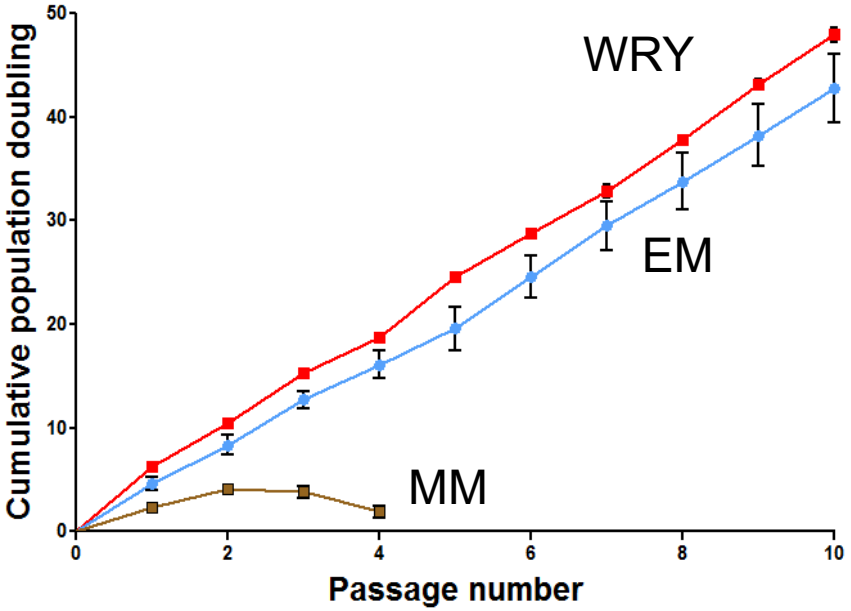


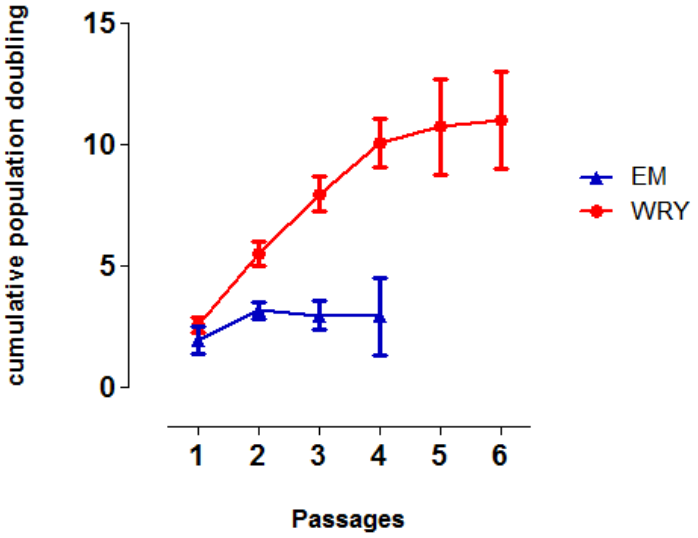
Expansion of adult stem cells





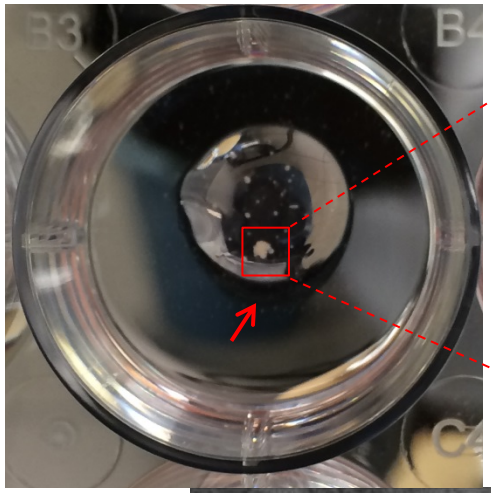
Expansion of stem cell number

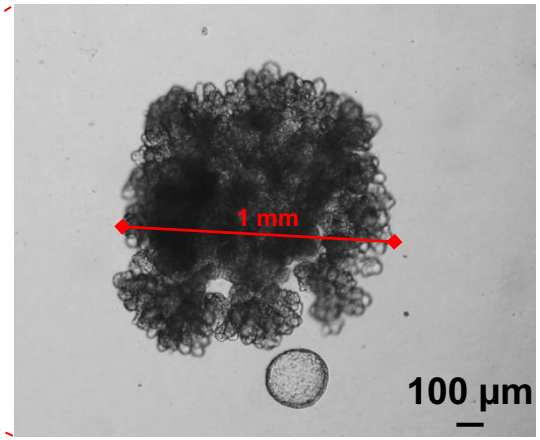


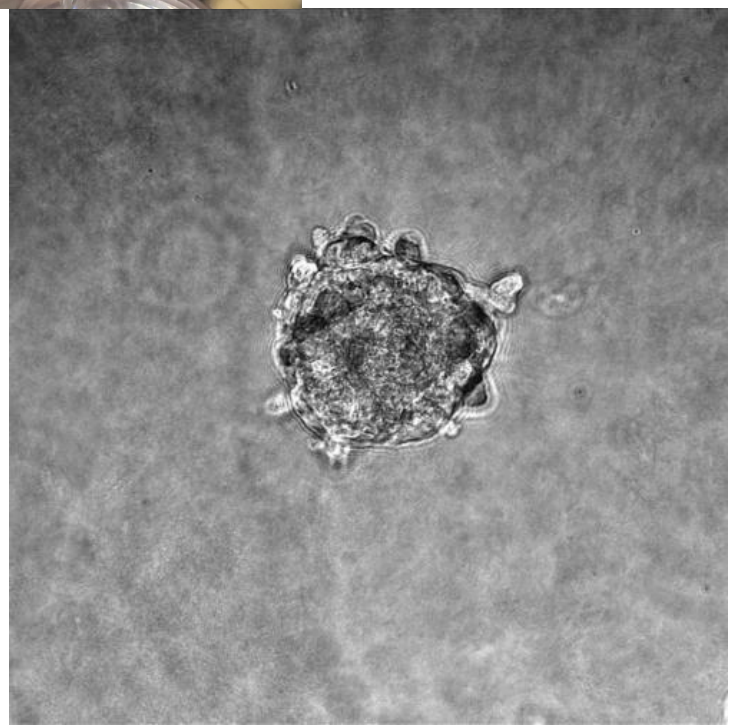


Nanduri et al Stem Cell Reports 2014
Maimets et al. Stem Cell Reports 2016

Differentiation of 1 cell to organoid

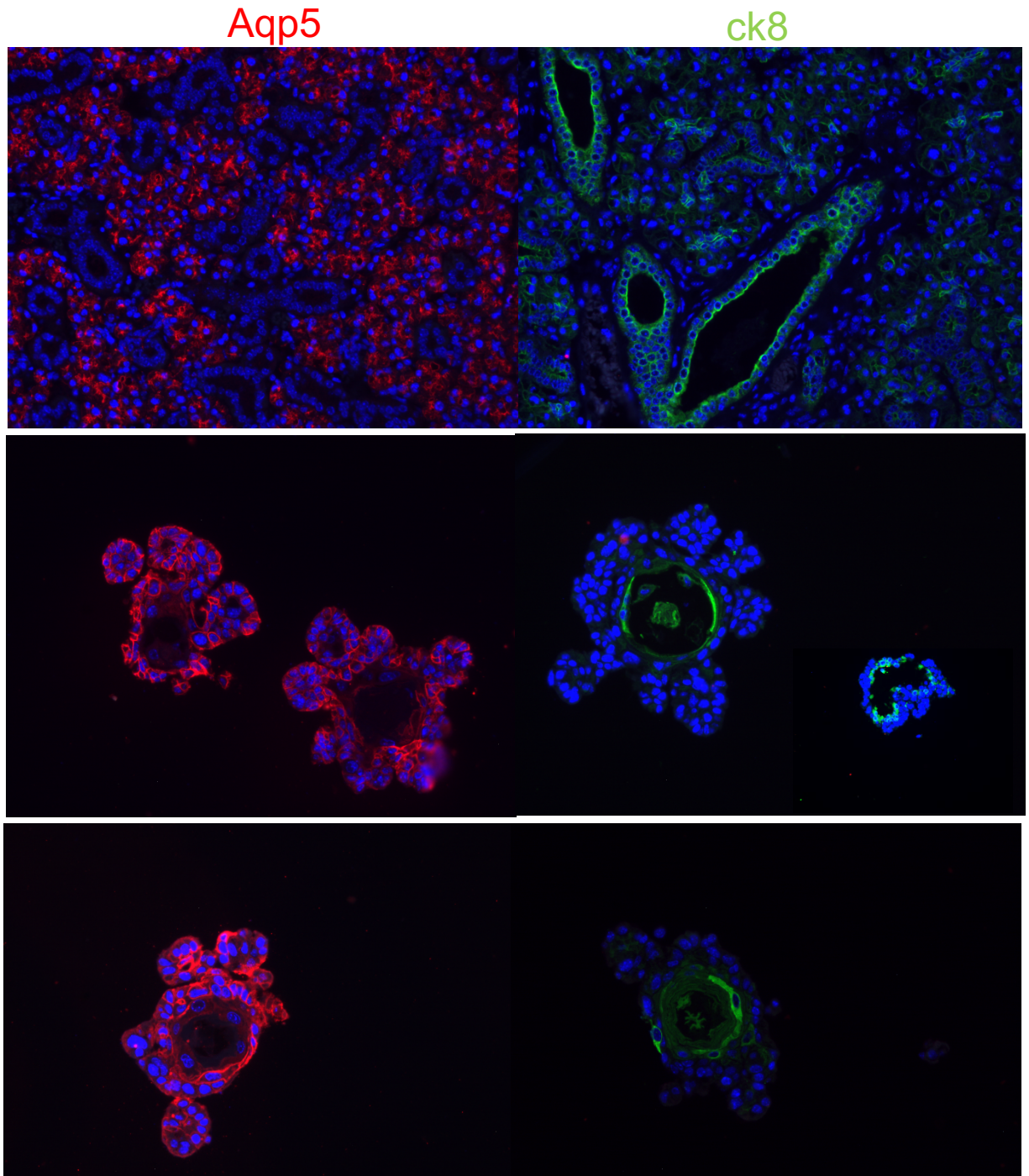




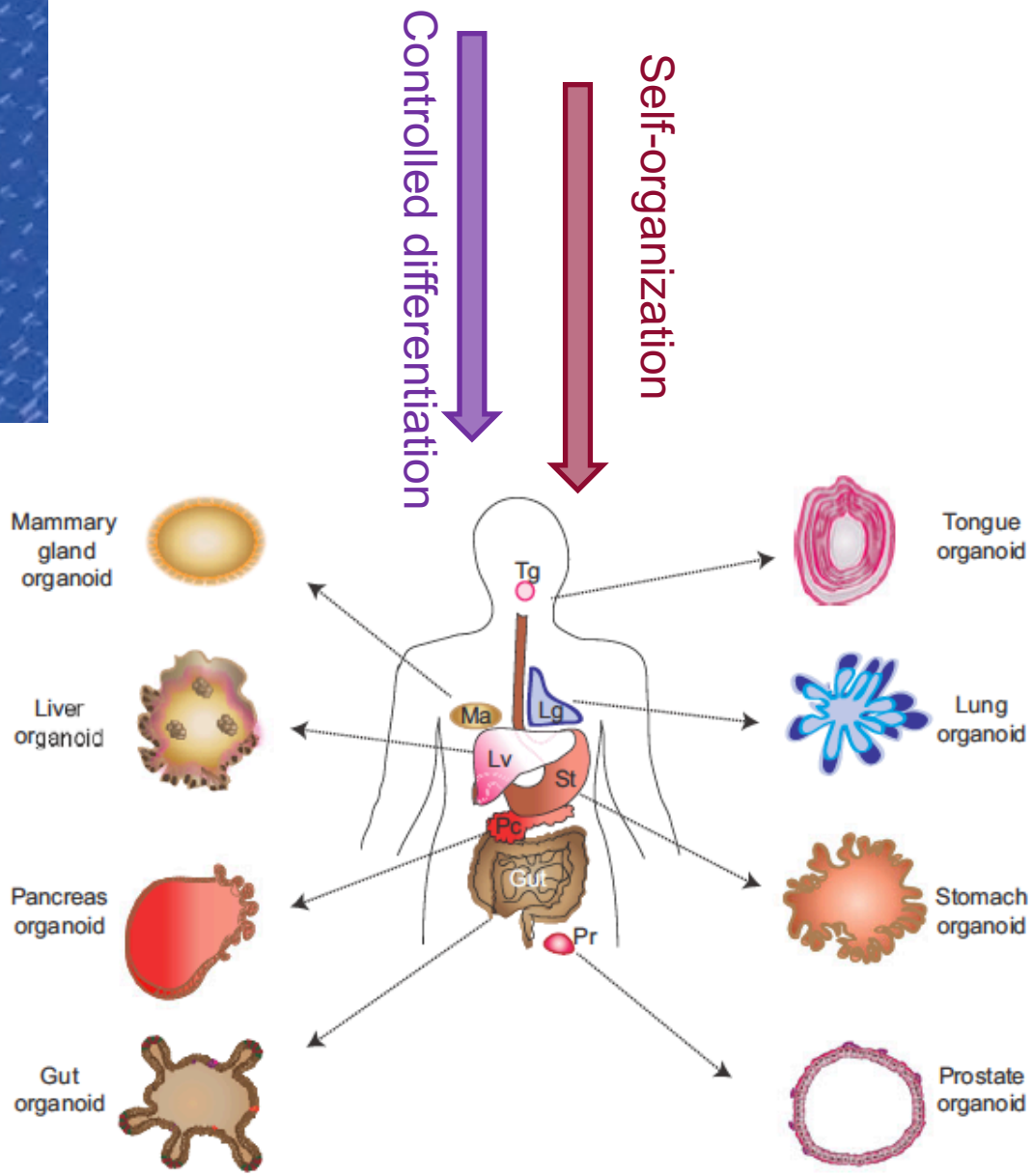


Johan de Rooij, UMCU

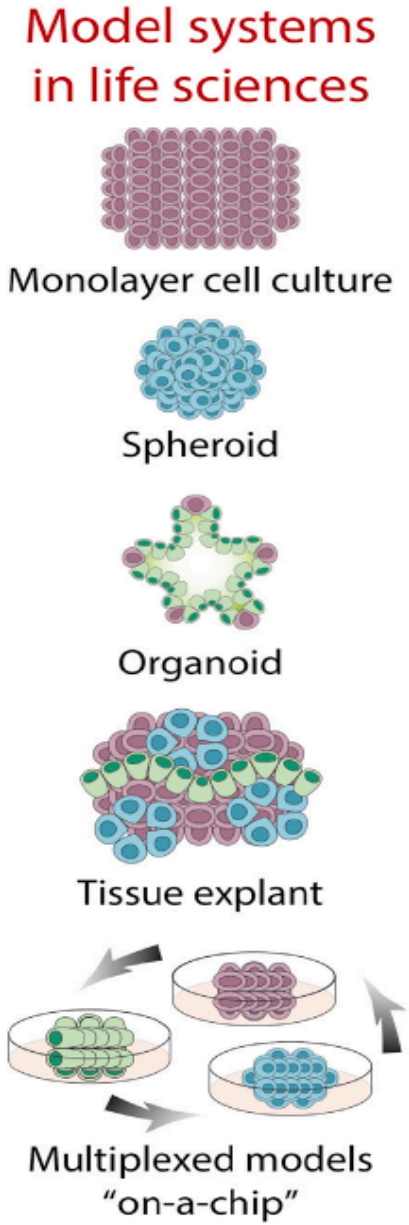
Martti Maimets Stem Cell Reports 2016


Aqp5
ck8
Tissue
Organoids

Adult stem cells

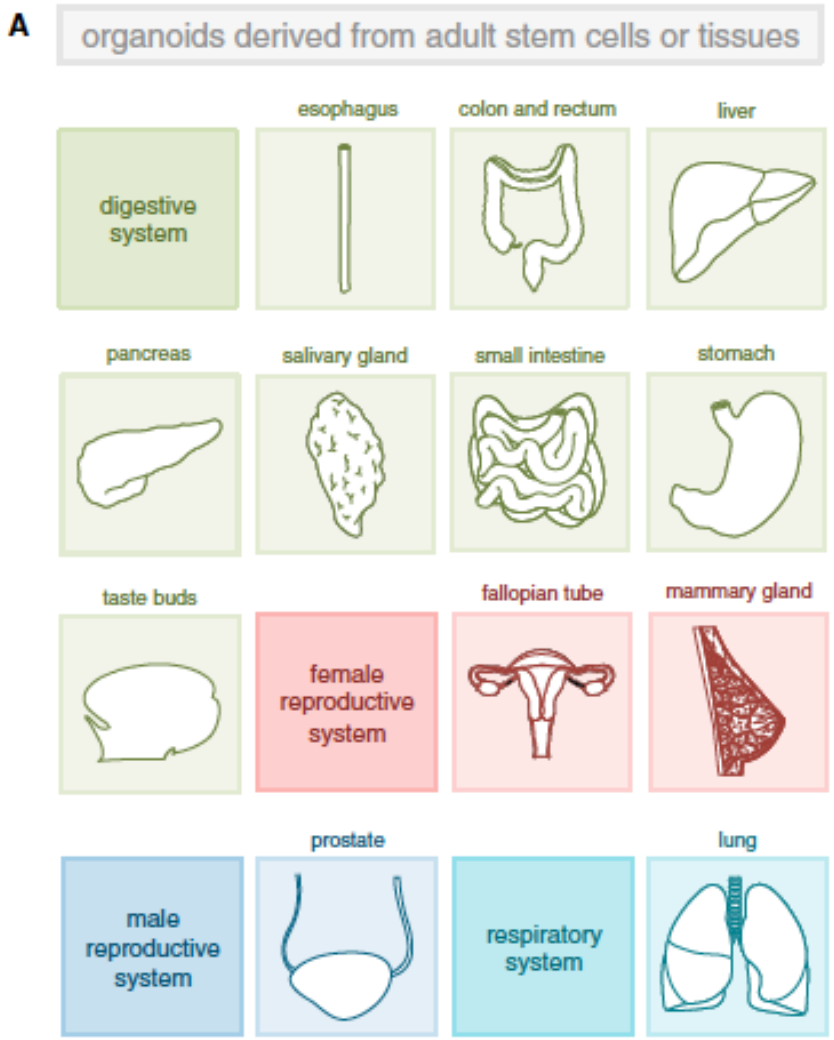


Huch and Koo Development 2015

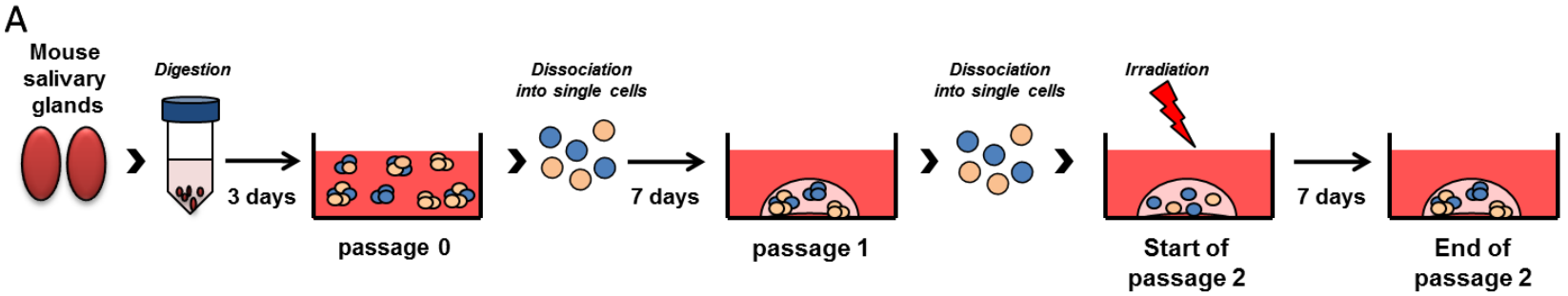


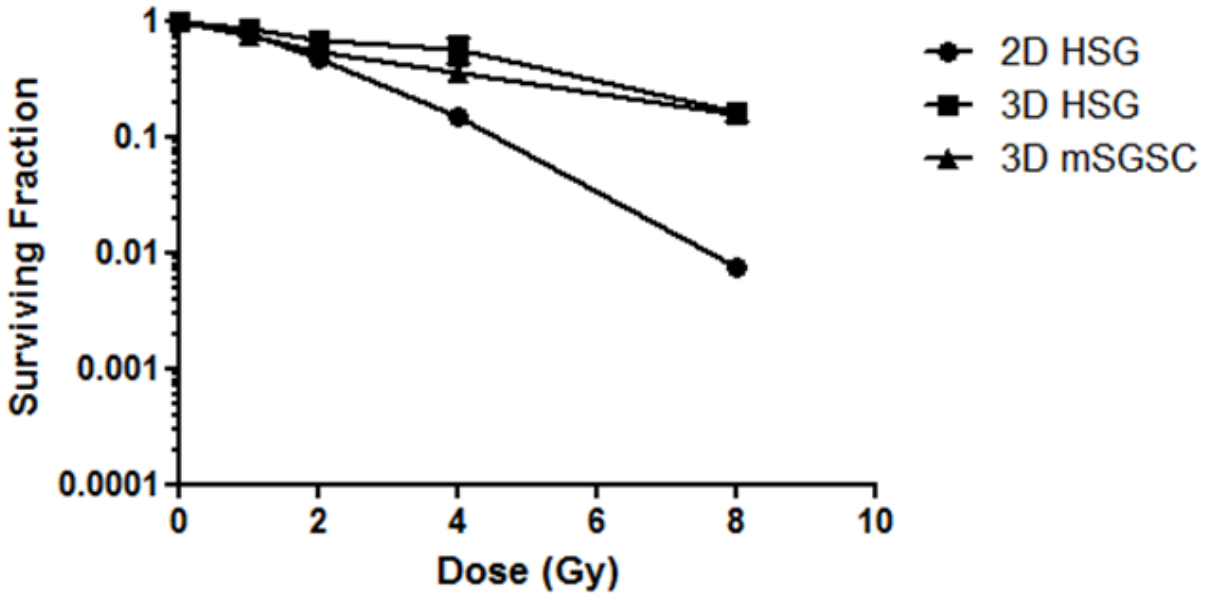
Yin et al Cell Stem Cell 2015

Established organoid cultures



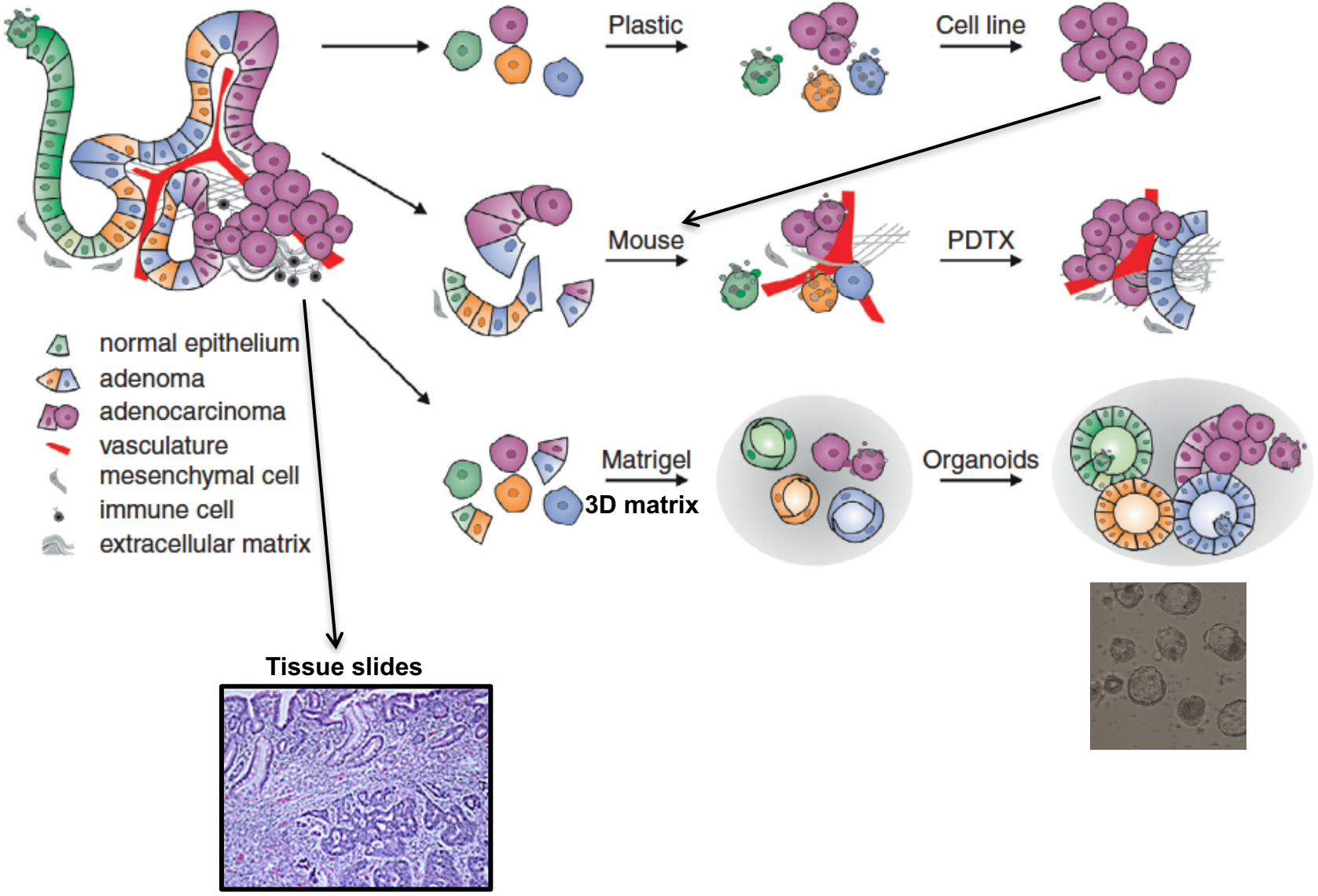
Kretzschmar and Clevers Developmental Cell 2016





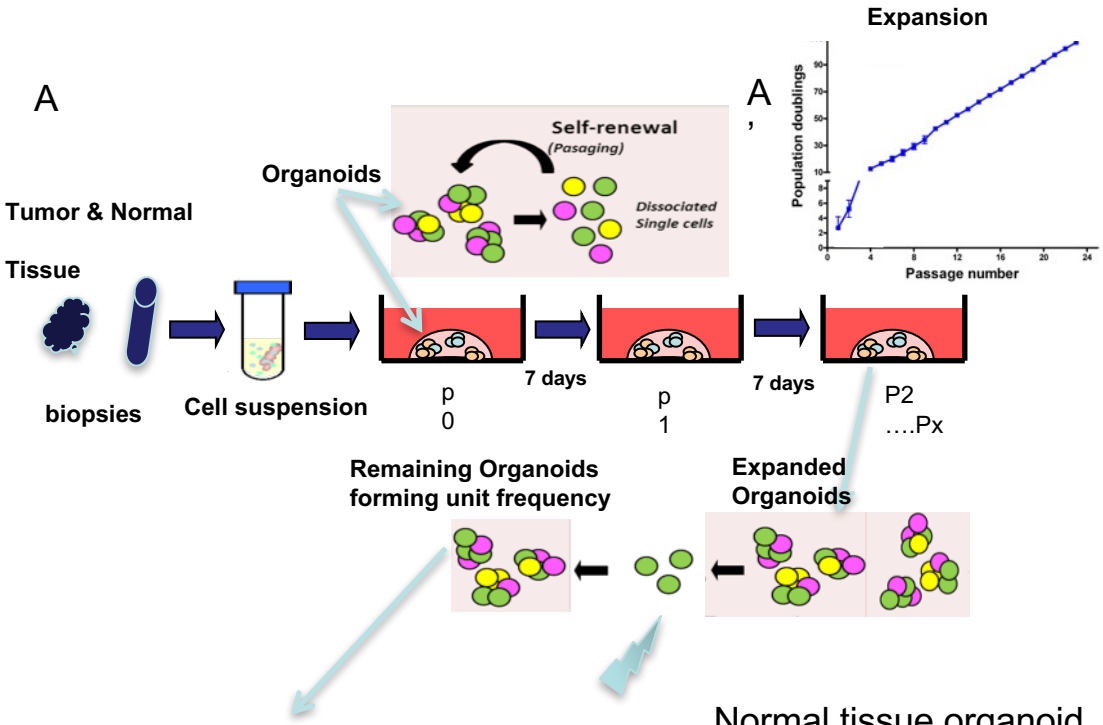
Nagle et al IJROBP2016

Models to study CRT response



Adapted from Sachs and Clevers, Current Opinion in Genetics & Development 2014, 24:68–73

Organoid radiation response assessment



Response to treatment?

Normal tissue organoid
vs
tumor organoid,
therapeutic ratio?

Summary

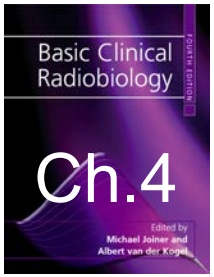
- Tumor recurrence depends on surviving clones.
- Evaluation of the survival of clonogenic cells following treatment is an important aspect of experimental cancer therapy.
- Hyper-radiosensitivity at very low radiation doses may be of clinical importance for normal tissue.
- Patient specific normal and tissue organoid cultures may provide future assays to personalized medicine.

ESTRO School

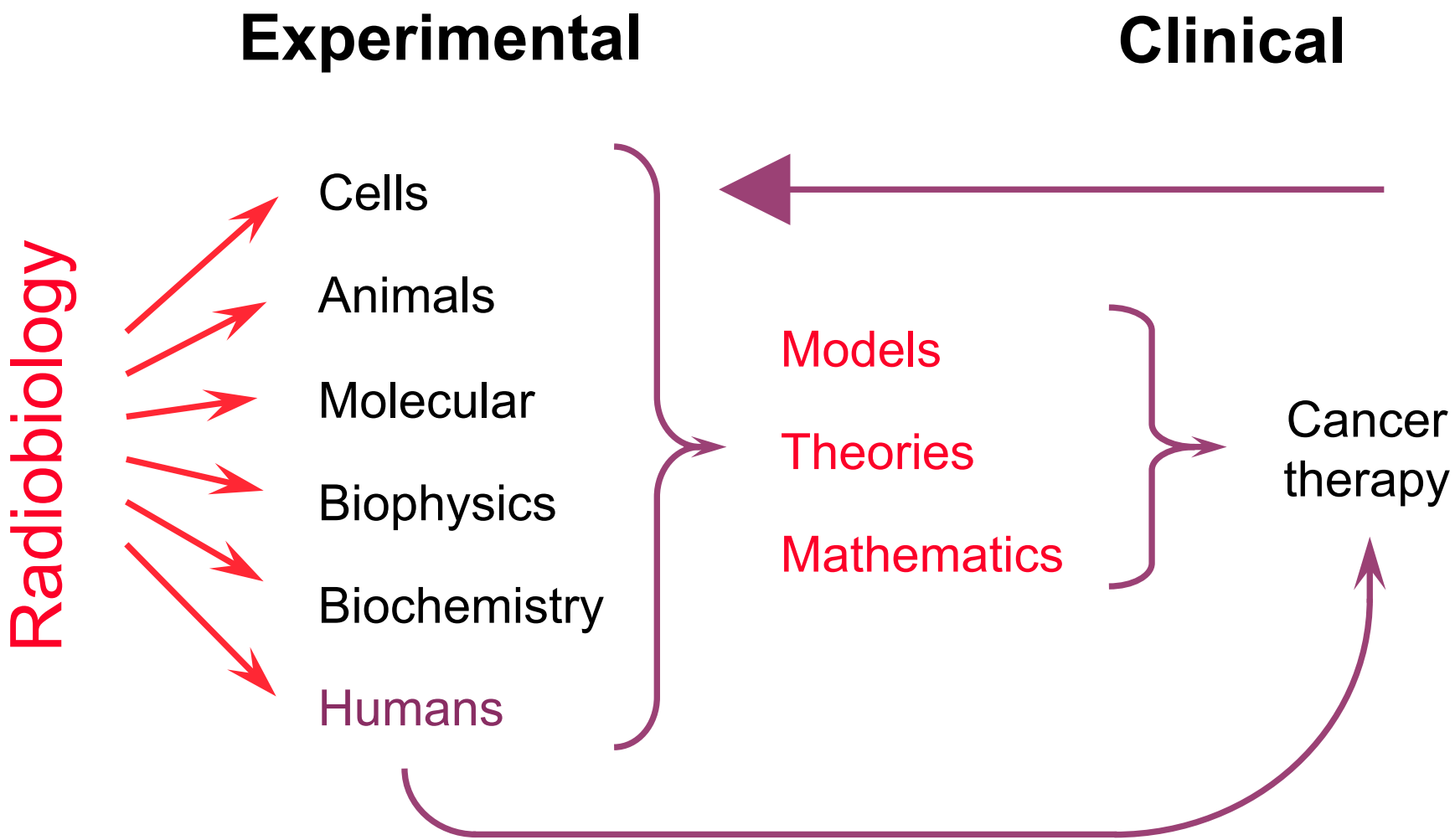
Basic Clinical Radiobiology

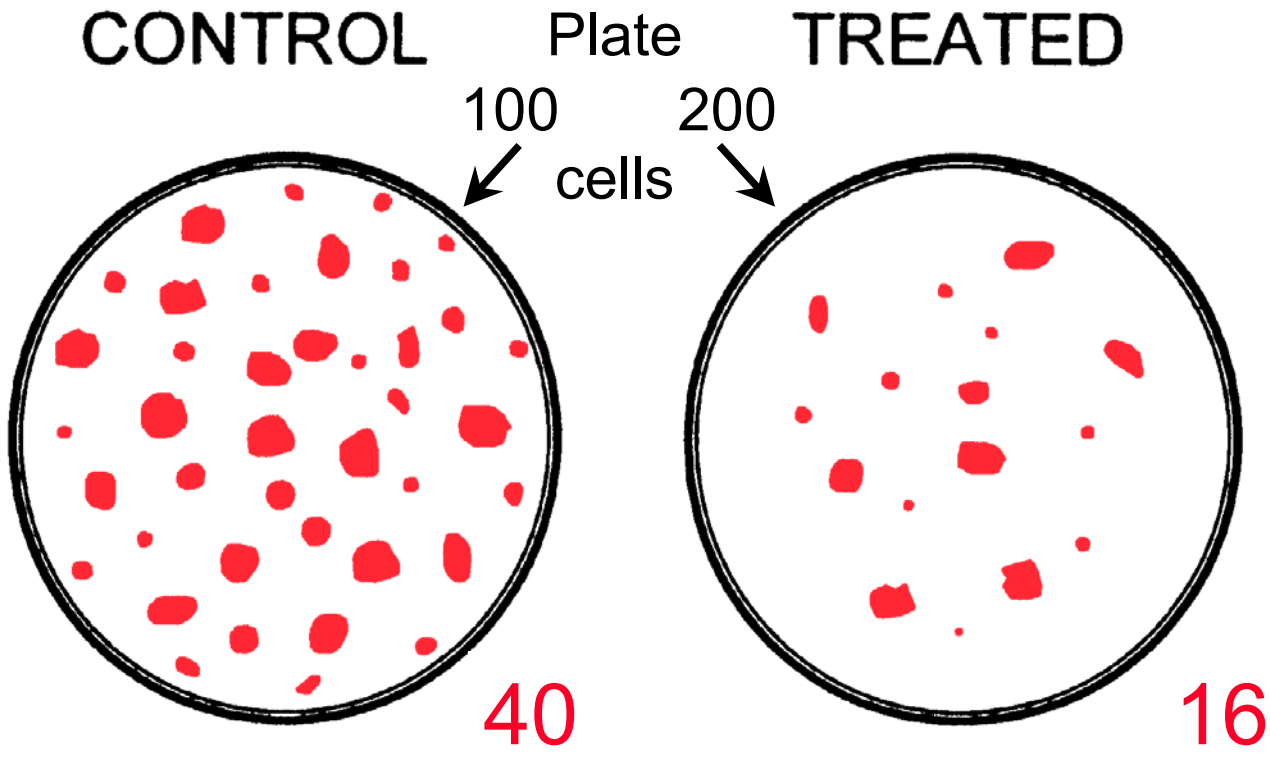
Quantifying cell kill and cell survival

Michael Joiner



Paris 2017


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

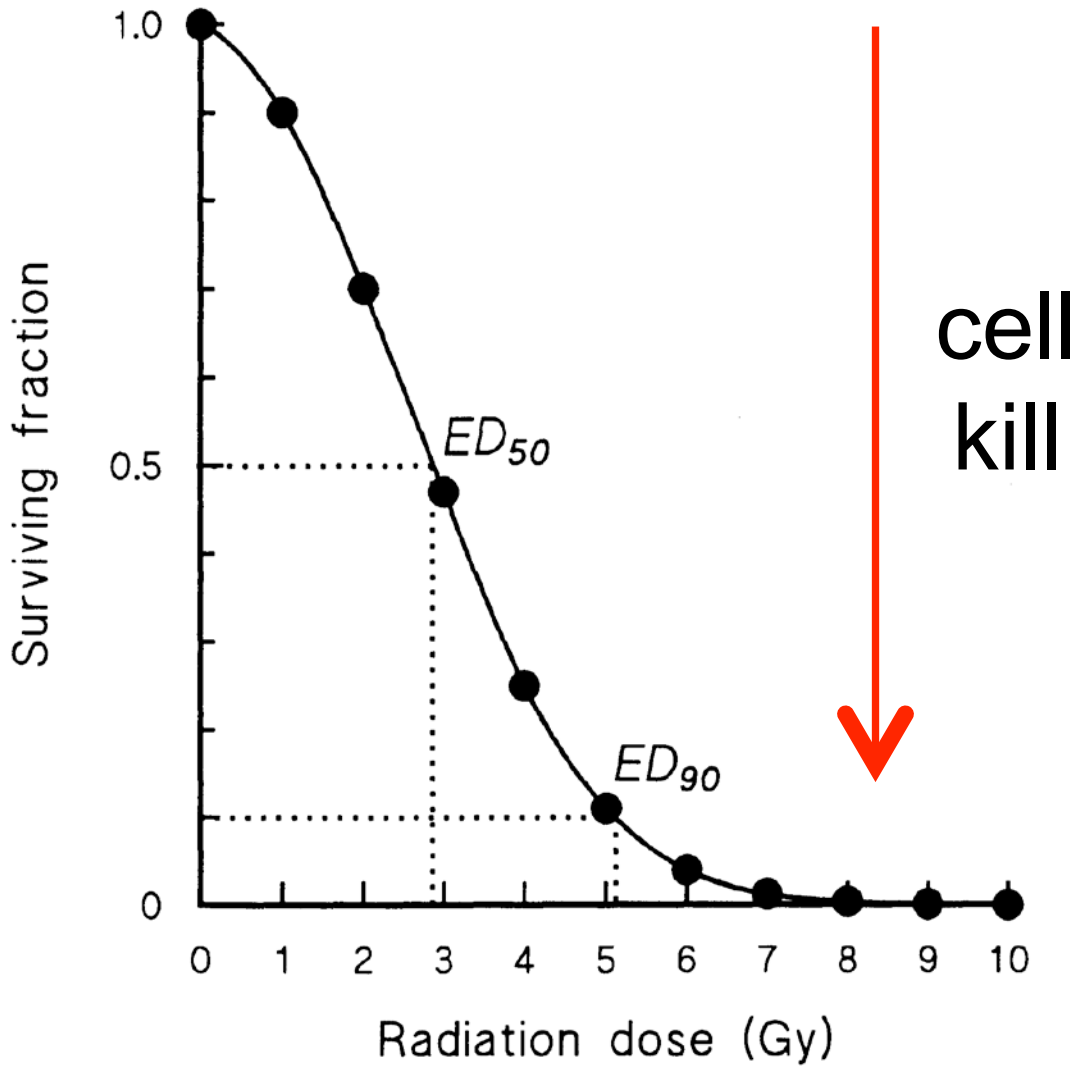


Plating efficiency (PE)

40/100 = 0.4 16/200 = 0.08

Surviving fraction (SF) = 0.08/0.4 = 0.2

Linear scale of
Surviving fraction



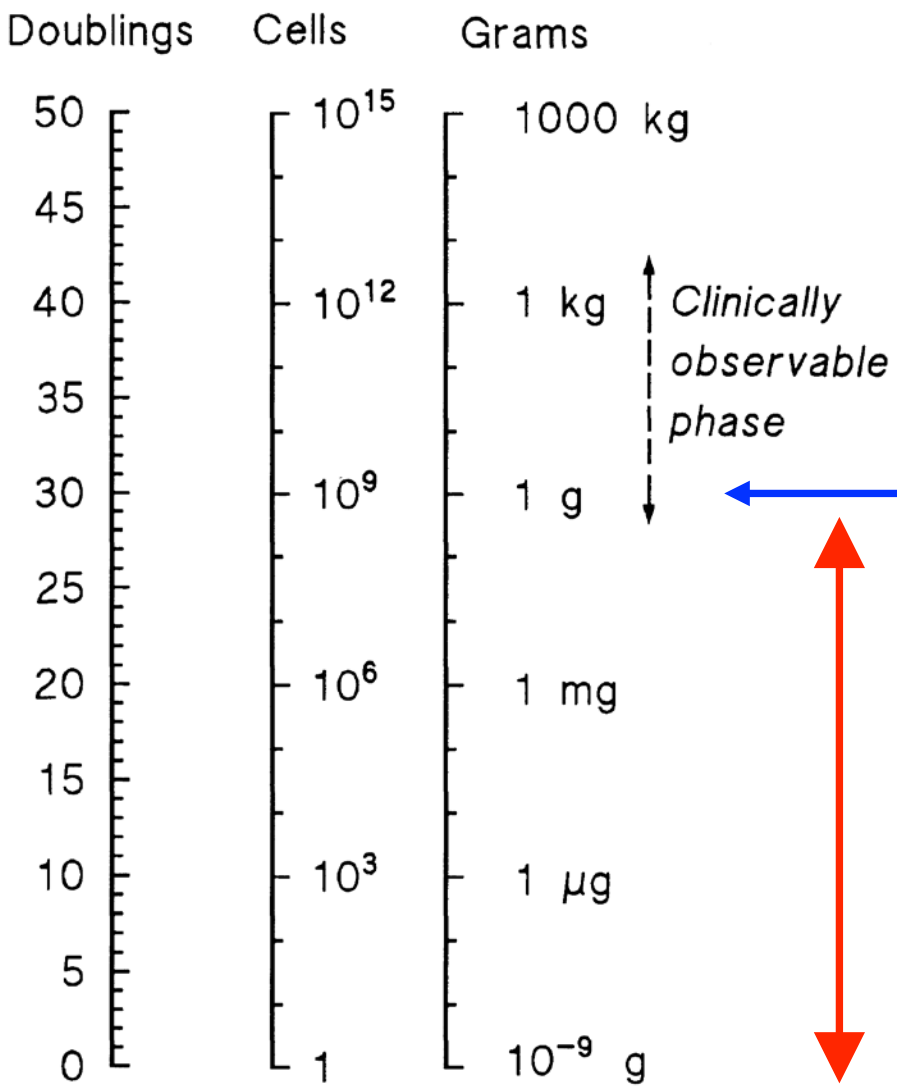
Simple Model for cell kill versus dose

$2 + 2 = 4$ No !

$2 + 2 = 22$ Better…

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

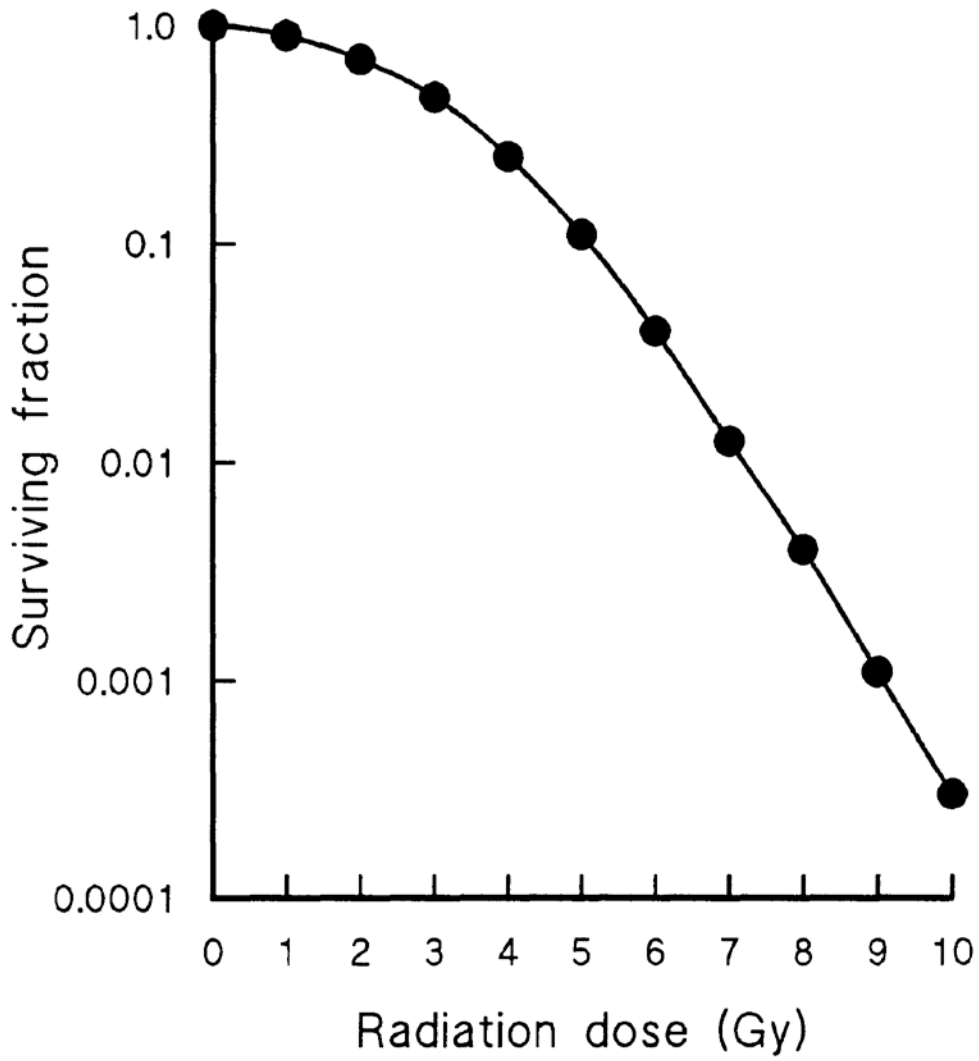
$$10^2 \times 10^2 = 10^4$$



Typical tumor at diagnosis

Need to kill all these cells!

Plot
Surviving Fraction
on a
Log scale



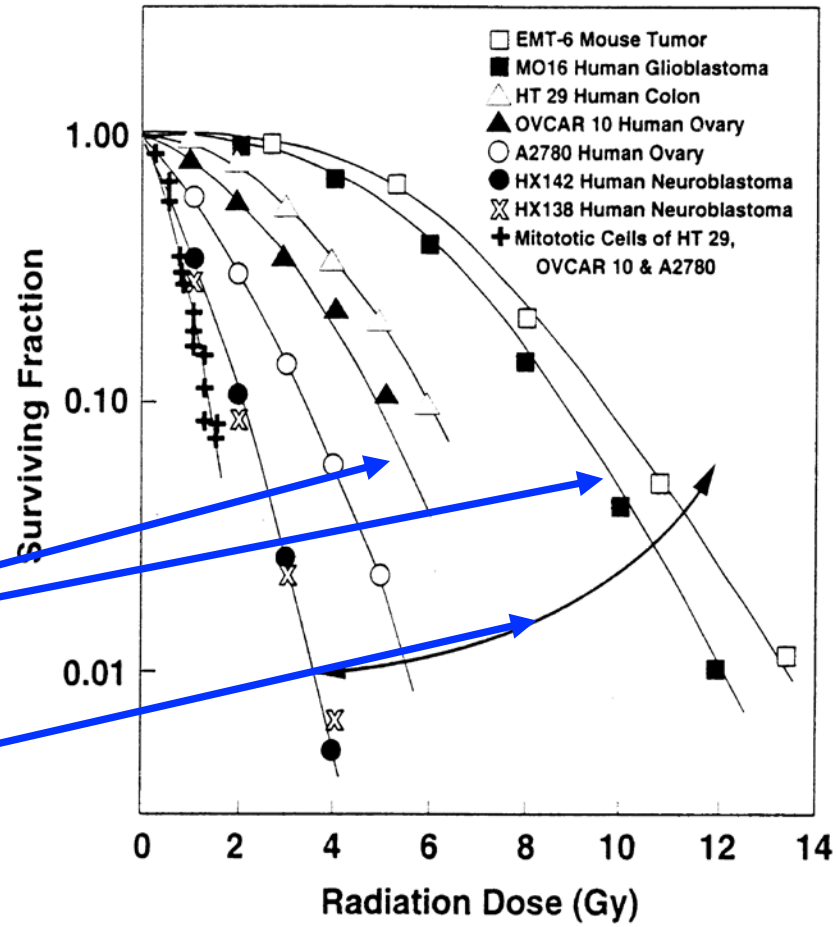
Cell sensitivity to radiation

Cells show a wide range of sensitivity

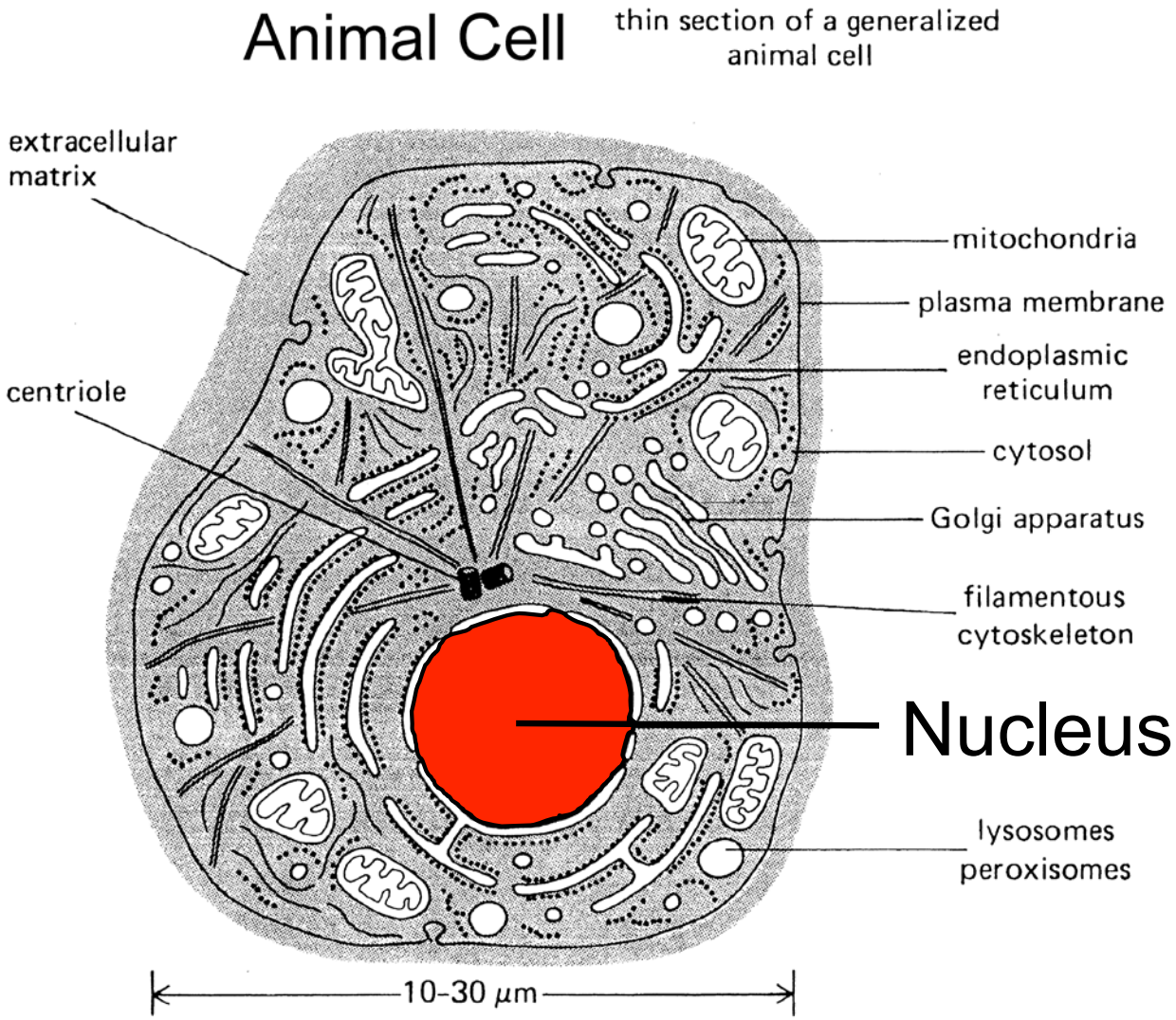
After exposure to radiation, tumor cells die through mitotic catastrophe

How to draw these lines?

How to describe different sensitivity?



Cell survival:
lesion production
versus
lesion repair



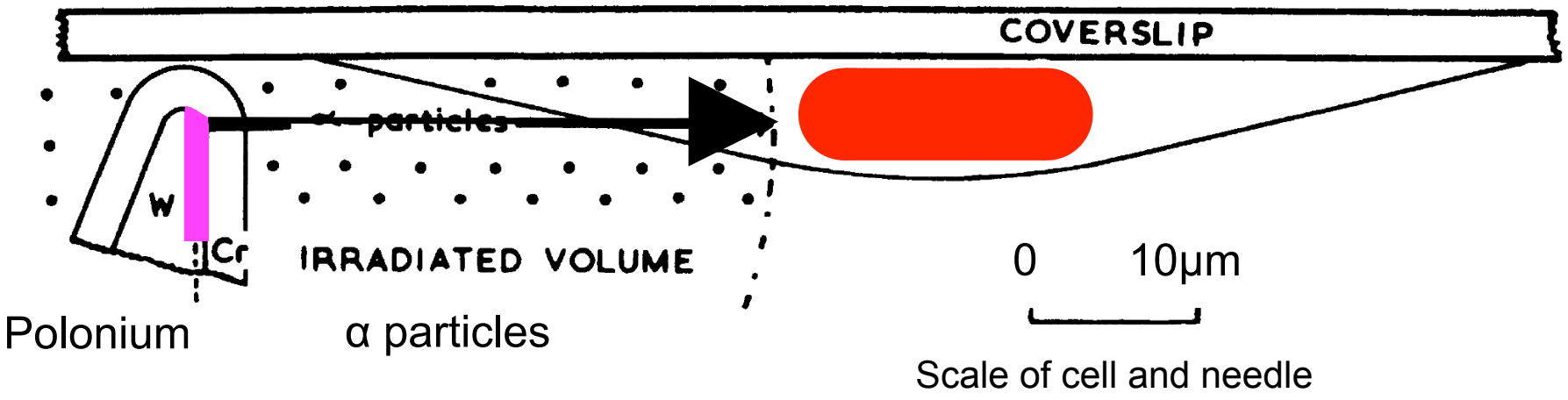
DNA is the principal target

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

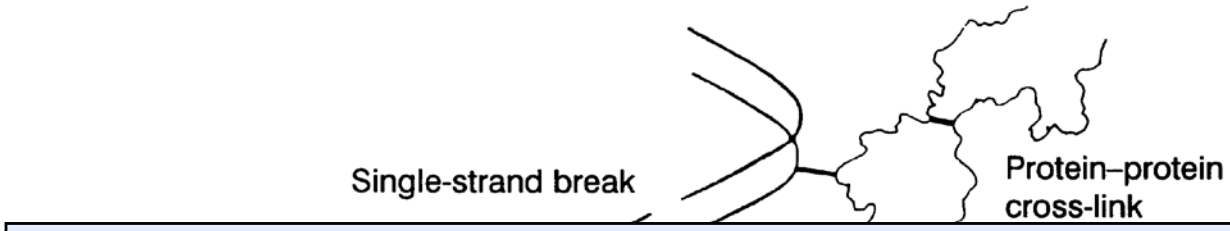
Warters et al. *Curr Top Radiat Res Q* 1977;12:389

DNA is the principal target

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

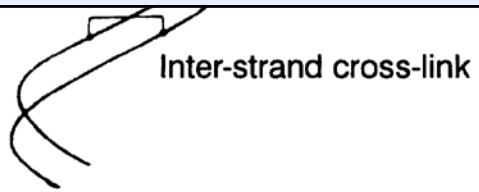


Munro TR. *Radiat Res* 1970;42:451



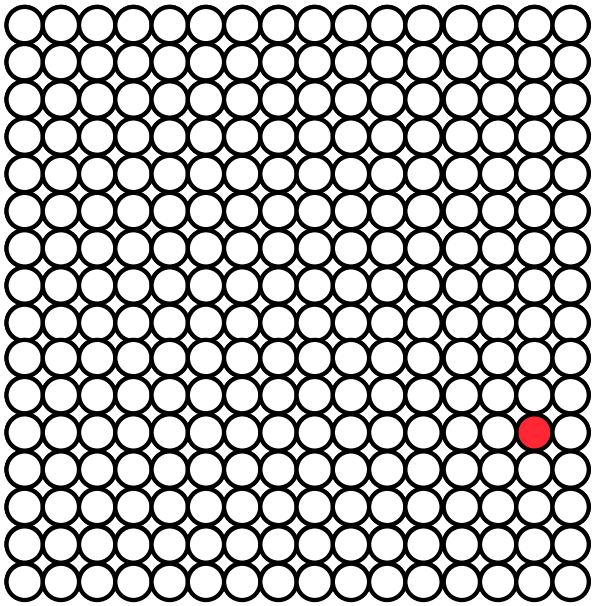
Each 1 Gy produces:

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



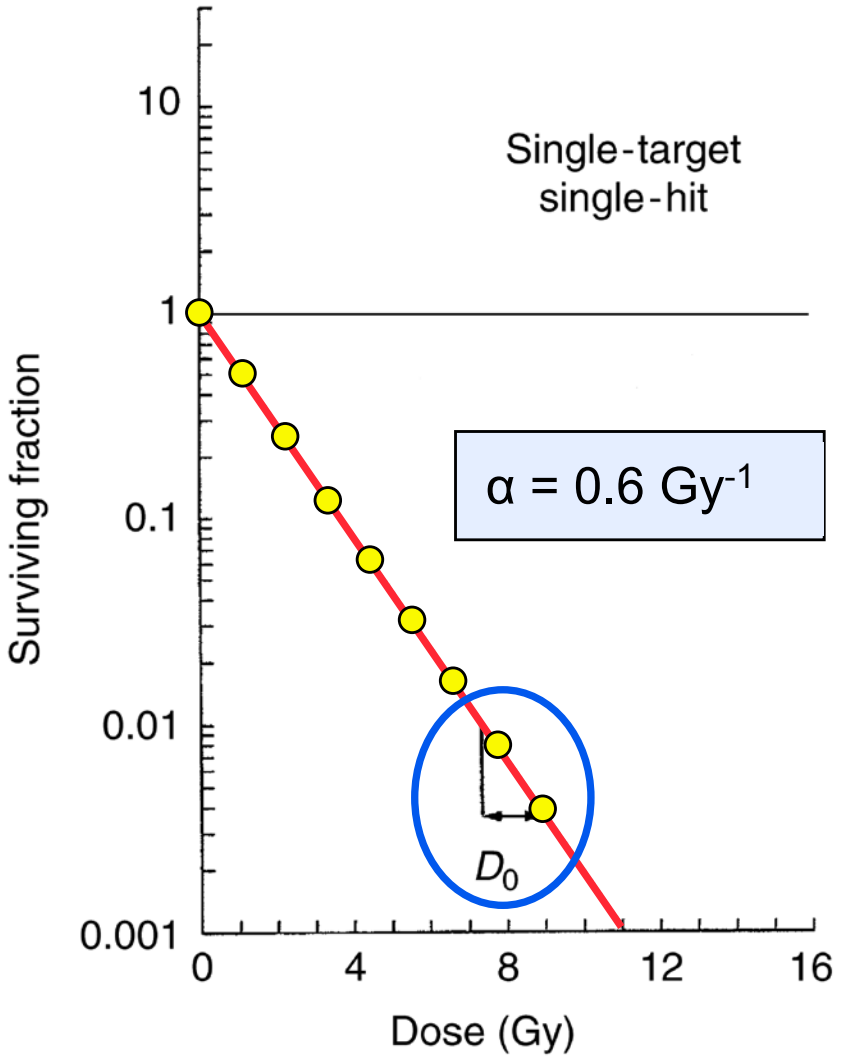
Modifier	Cell kill	**DSB**	SSB	Base damage	DPC
↑ LET	↑	↑	↓	↓	–
↑ hypoxia	↓	↓	↓	0	↑
↑ thiols	↓	↓	↓	0	↓
↑ heat	↑	↑	0	0	0

From Frankenberg-Schwager (1989)



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

$$D_0 = 1/\alpha$$



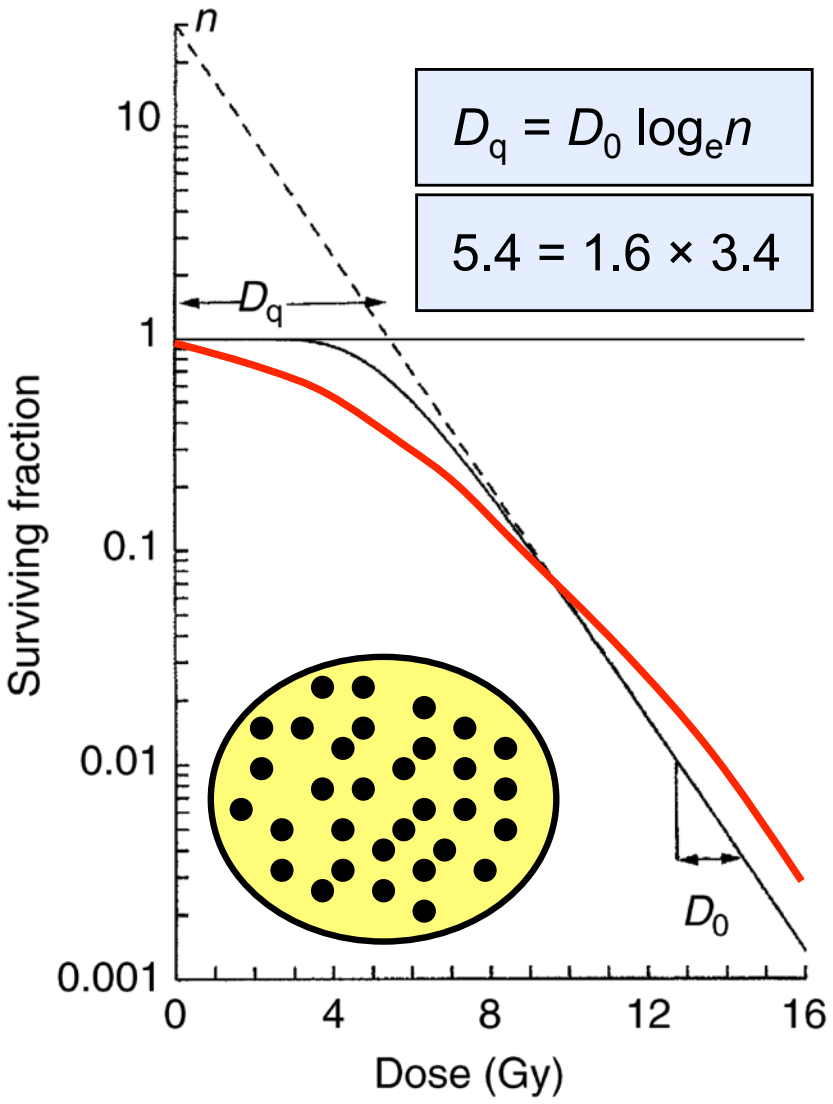
P(0 hits on a target) $= e^{-D/D0}$

P(≥1 hit on a target) $= 1 - e^{-D/D0}$

P(≥1 hit on n targets) $= (1 - e^{-D/D0})^n$

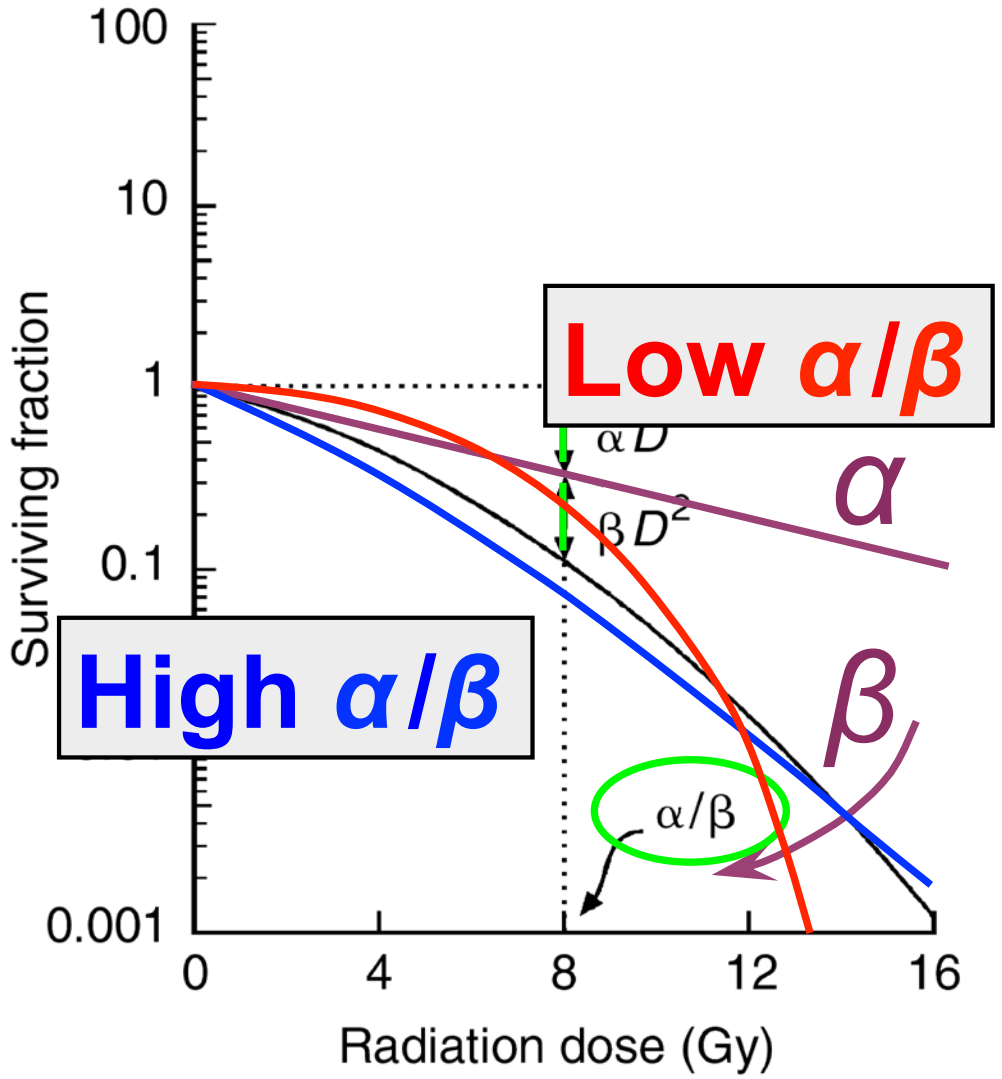
P(not **all** targets hit) $= 1 - (1 - e^{-D/D0})^n$

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

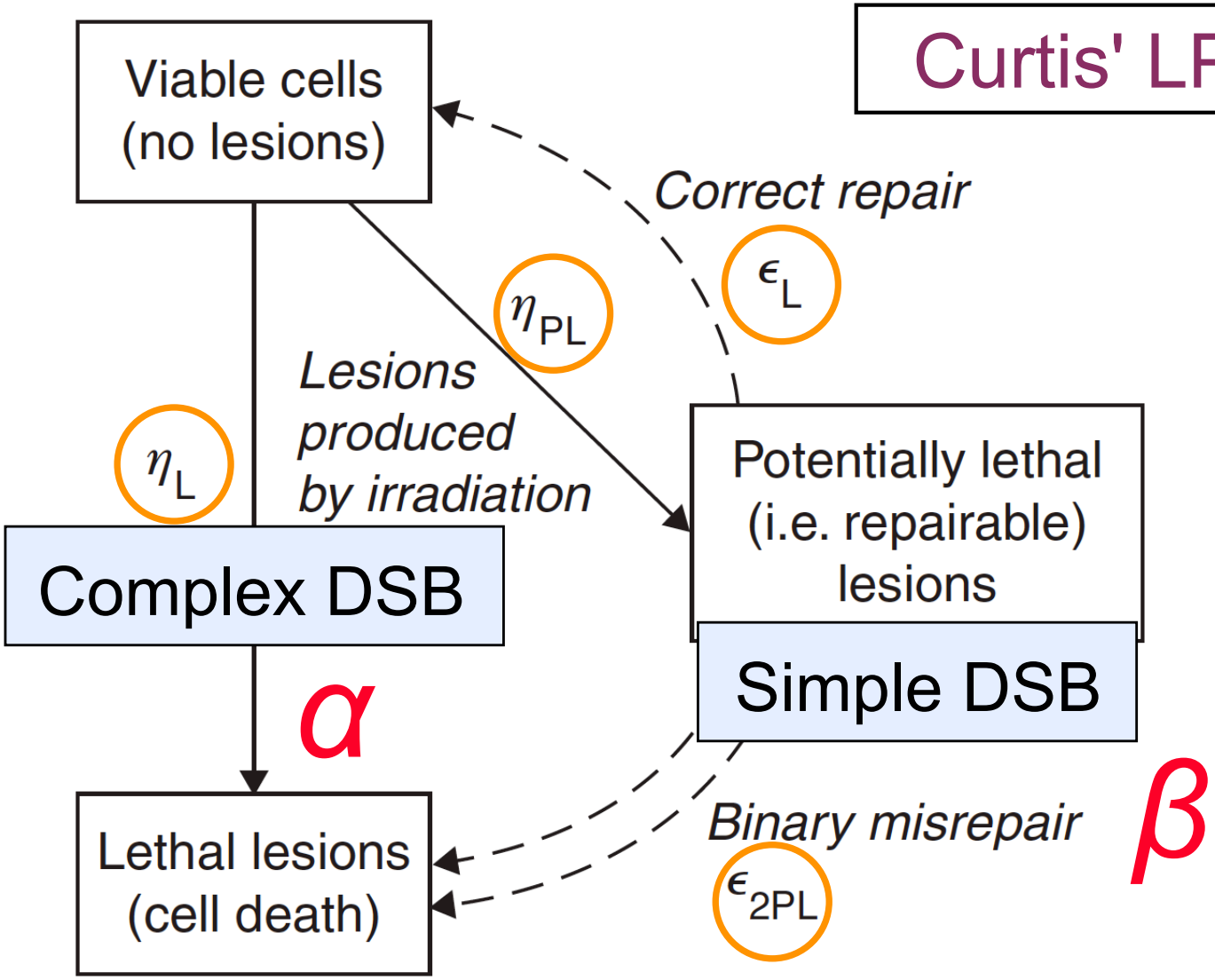


$$S = e^{-\alpha D - \beta D^2}$$

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

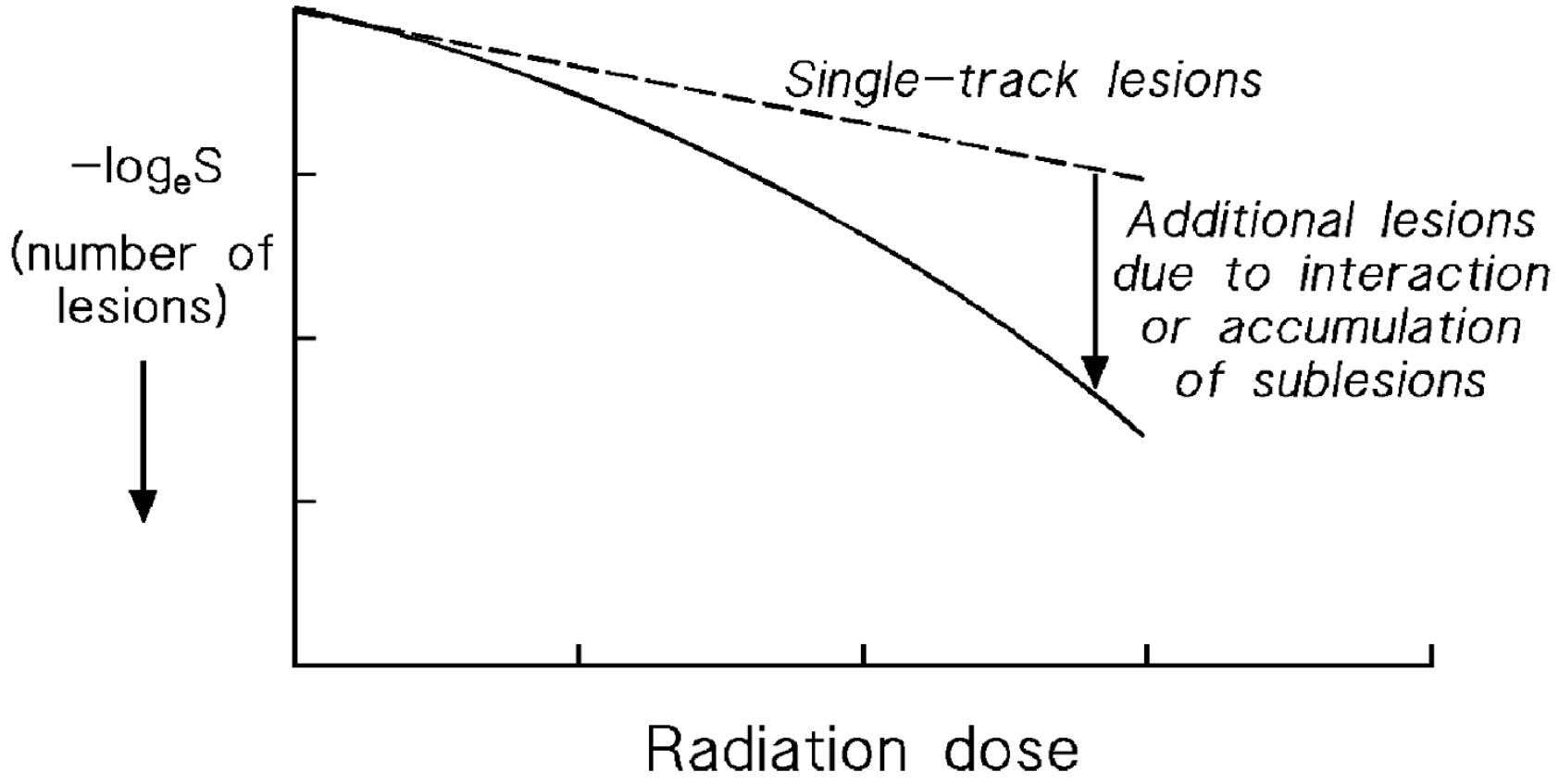


Curtis' LPL model

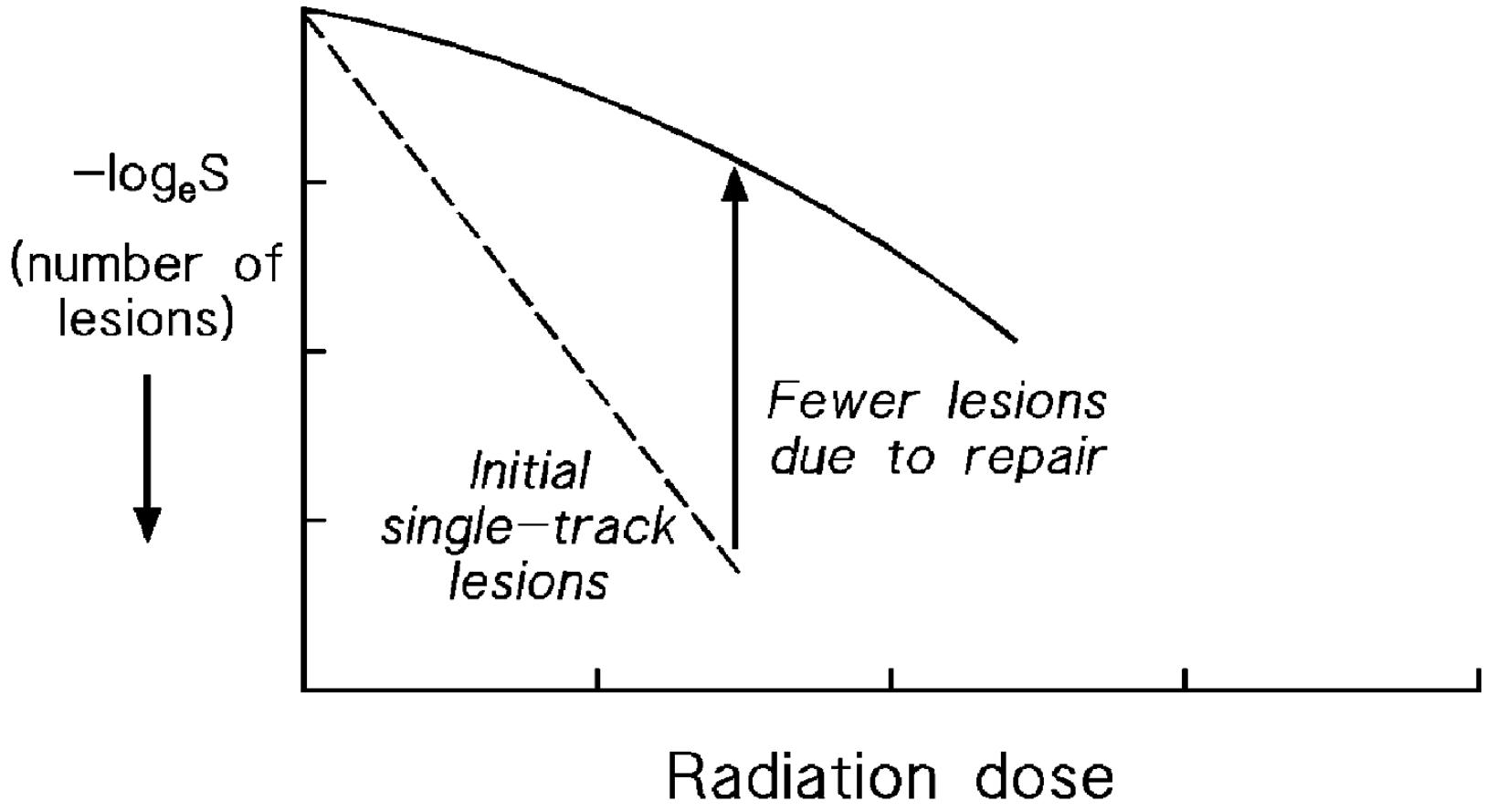


Curtis SB.
Radiat Res
1986;106:252

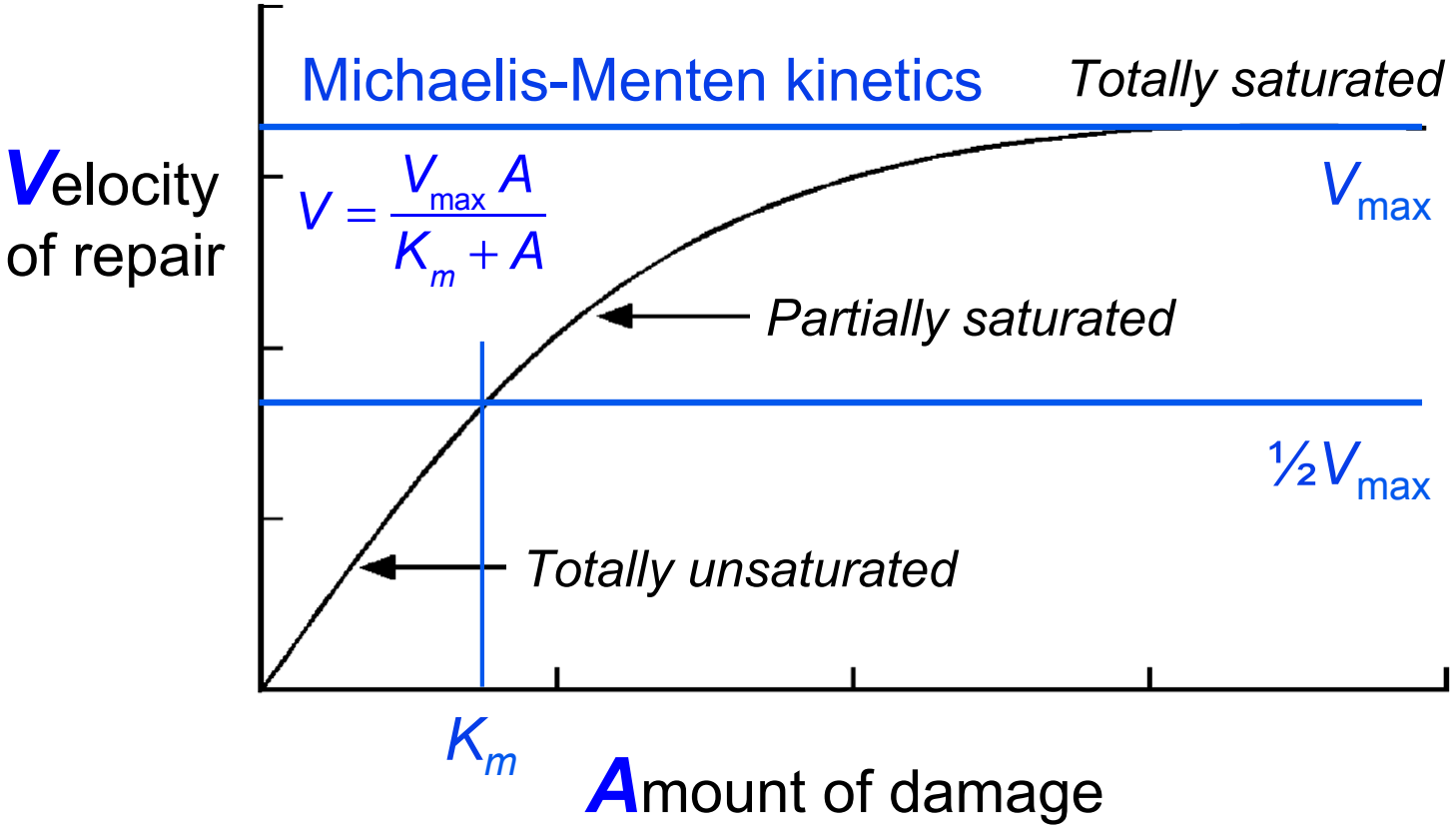
Curtis' LPL model



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

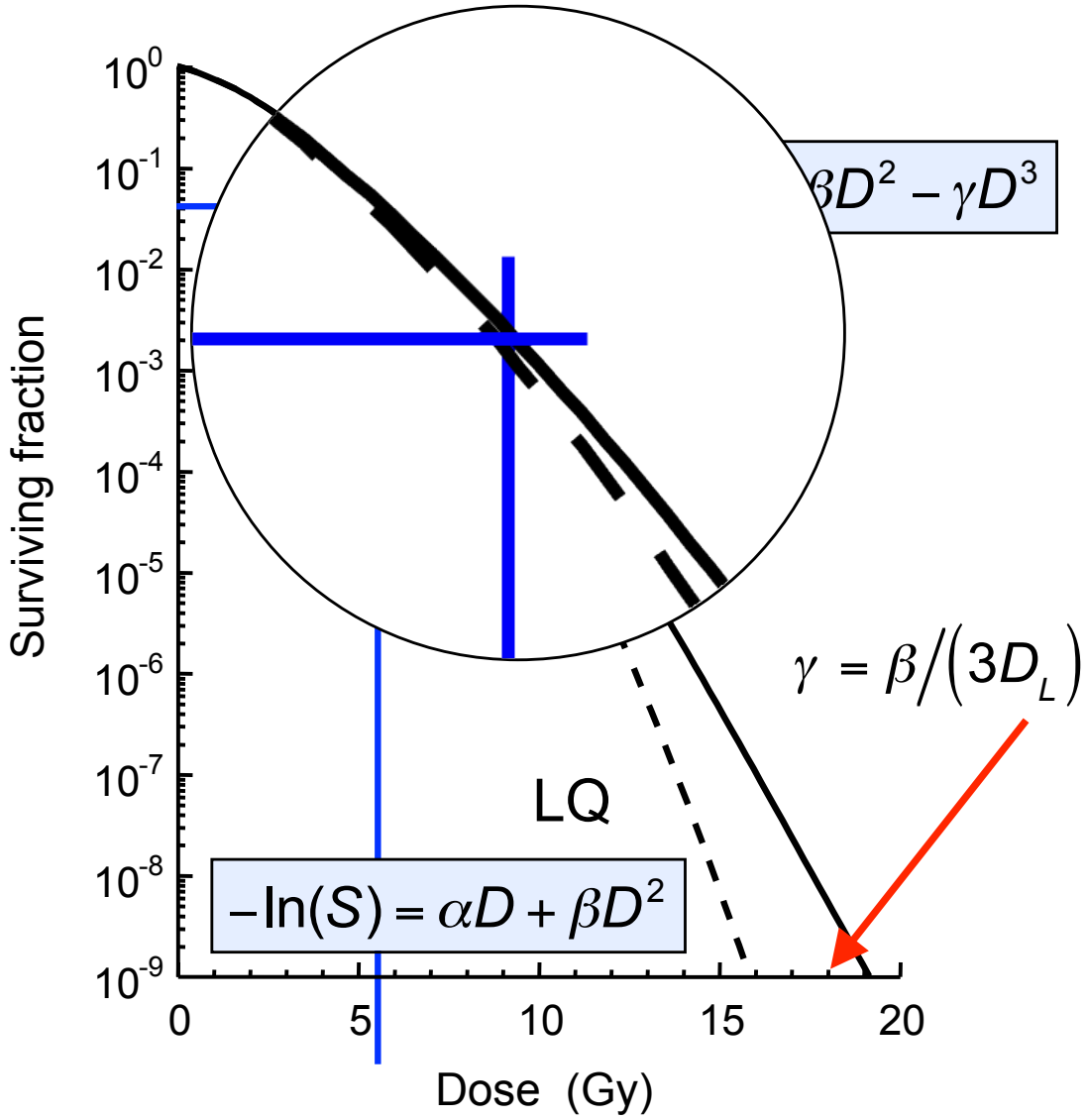
LET, linear energy transfer; RBE, relative biological effectiveneness.

Adapted from Goodhead (1985).

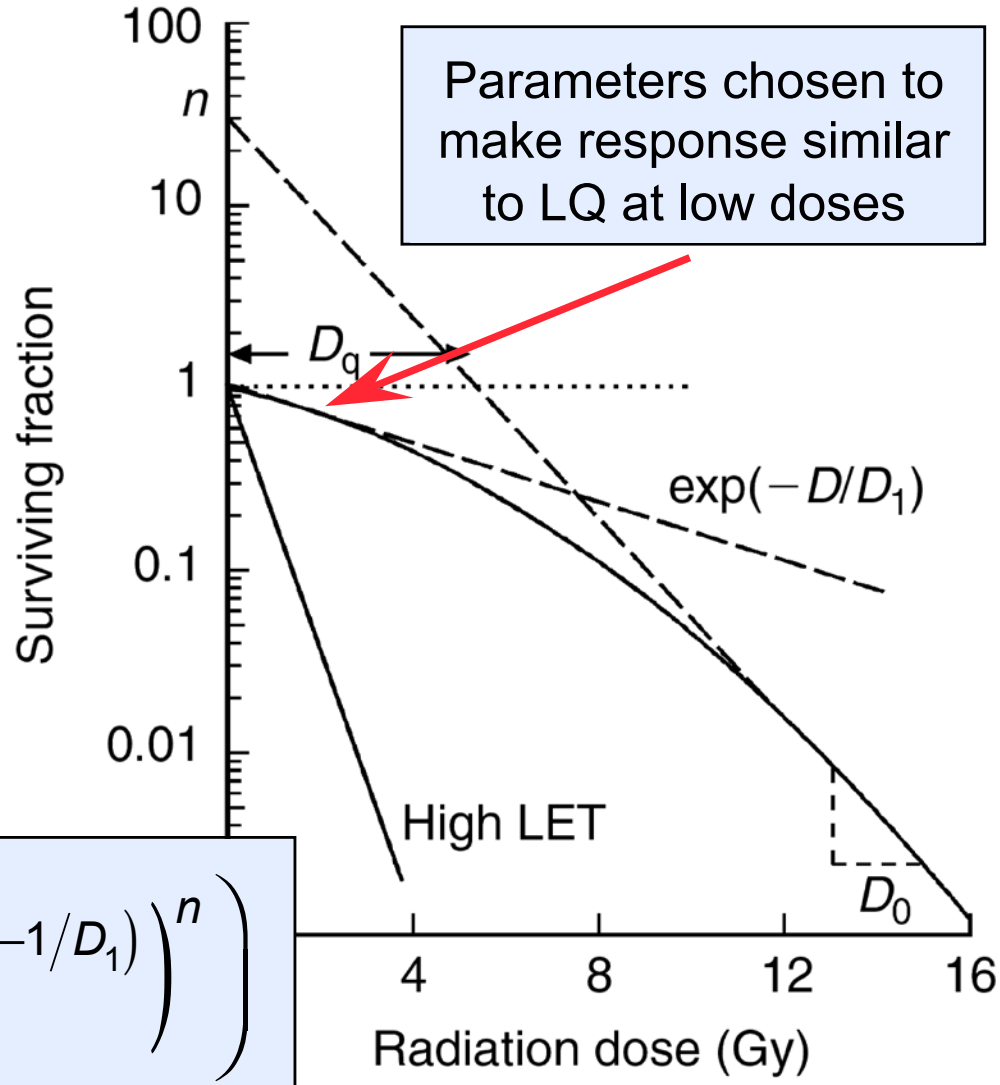
The **L**inear **Q**uadratic **C**ubic model

α/β = 3 Gy

SF2 = 0.5



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



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

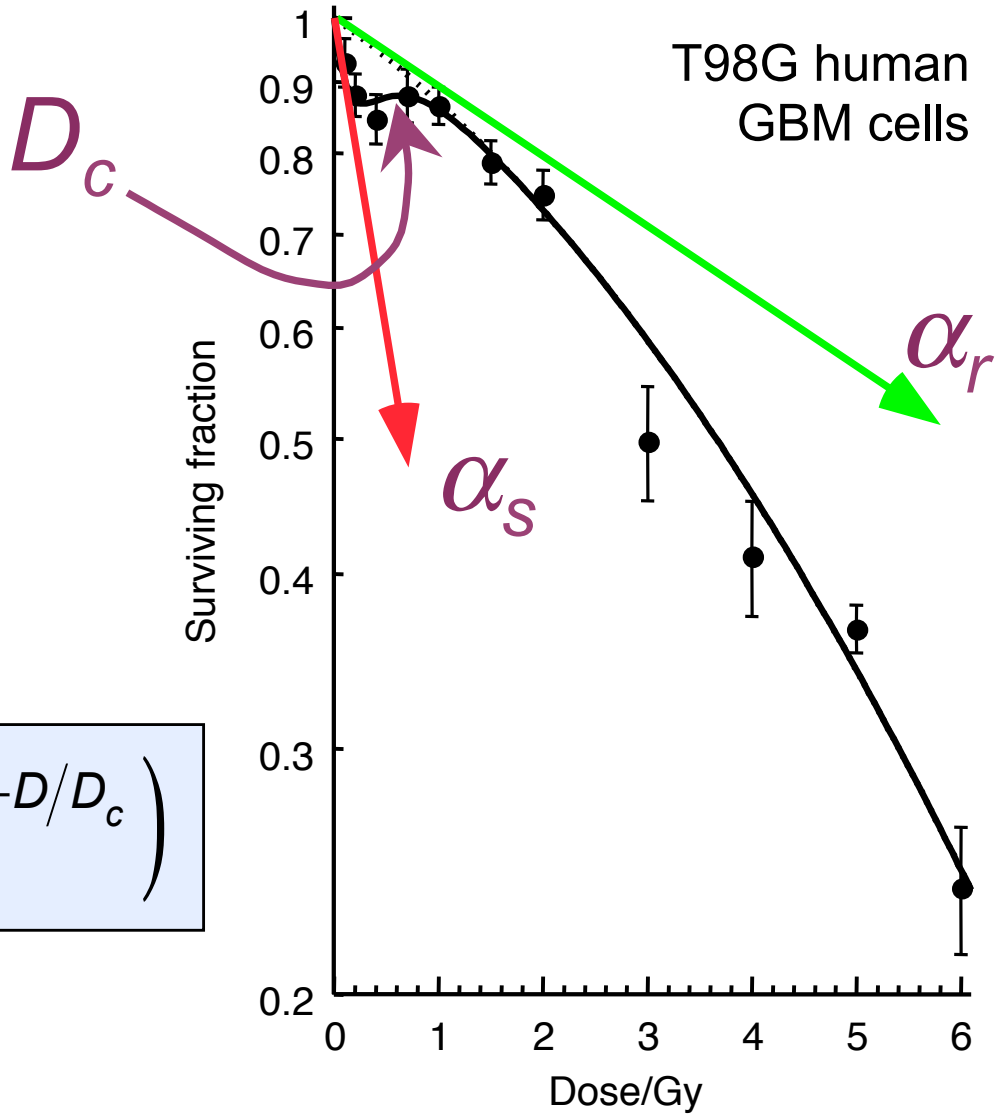
Low-dose hyper-radiosensitivity

Short S, Mayes C, Woodcock M, Johns H, Joiner MC.
Int J Radiat Biol 1999;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.

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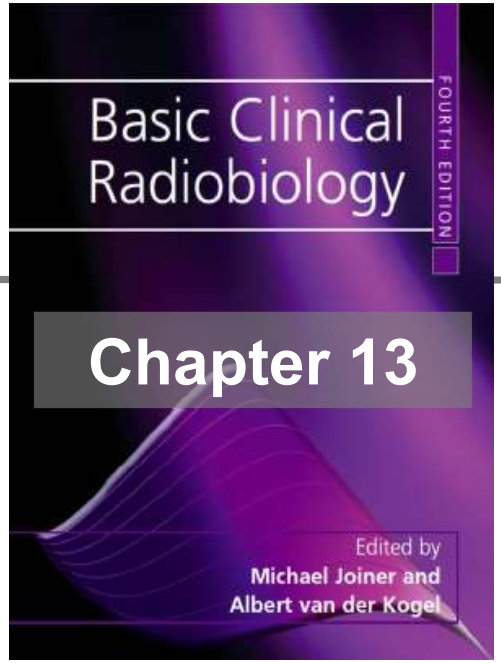
www.redjournal.org

…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…

- 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

Pathogenesis of normal tissue side effects



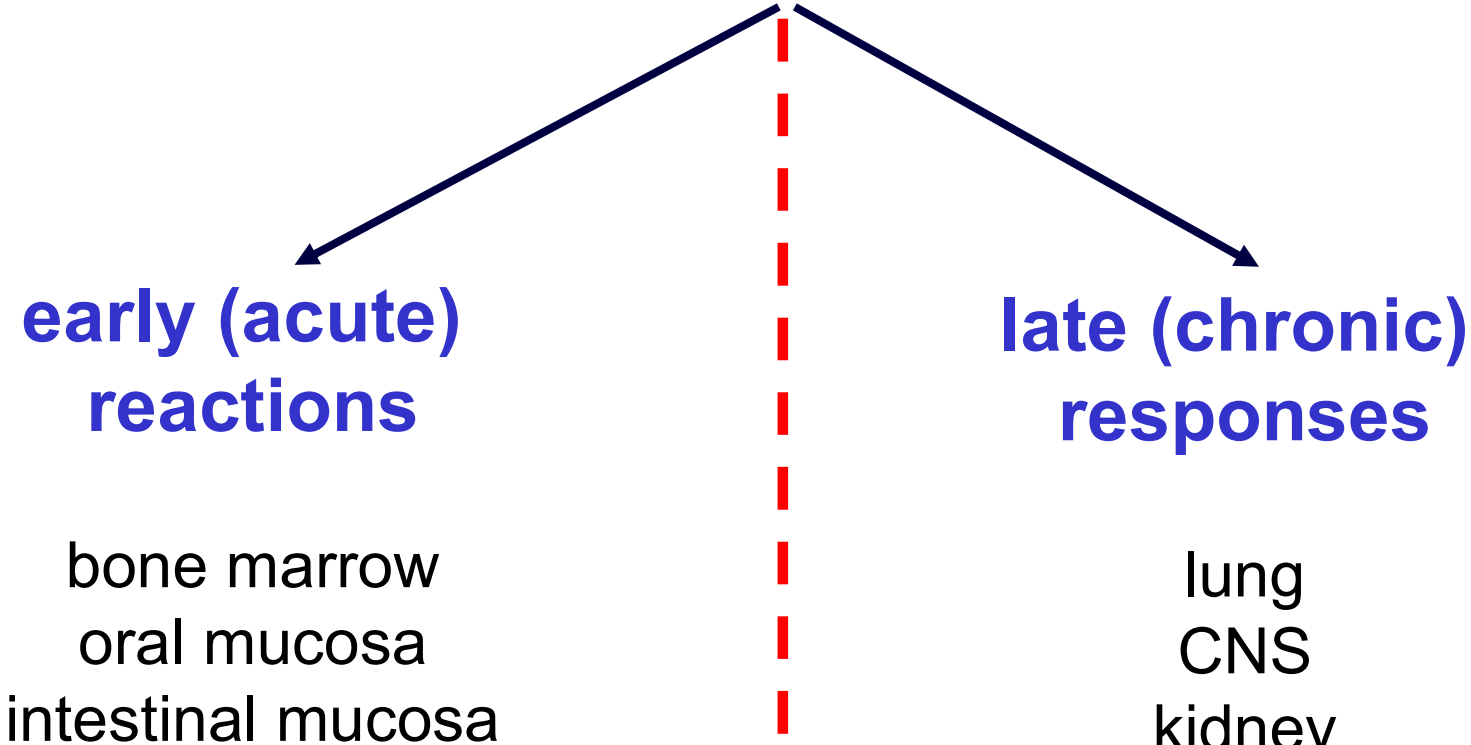
Wolfgang Dörr

ATRAB – Applied and Translational Radiobiology

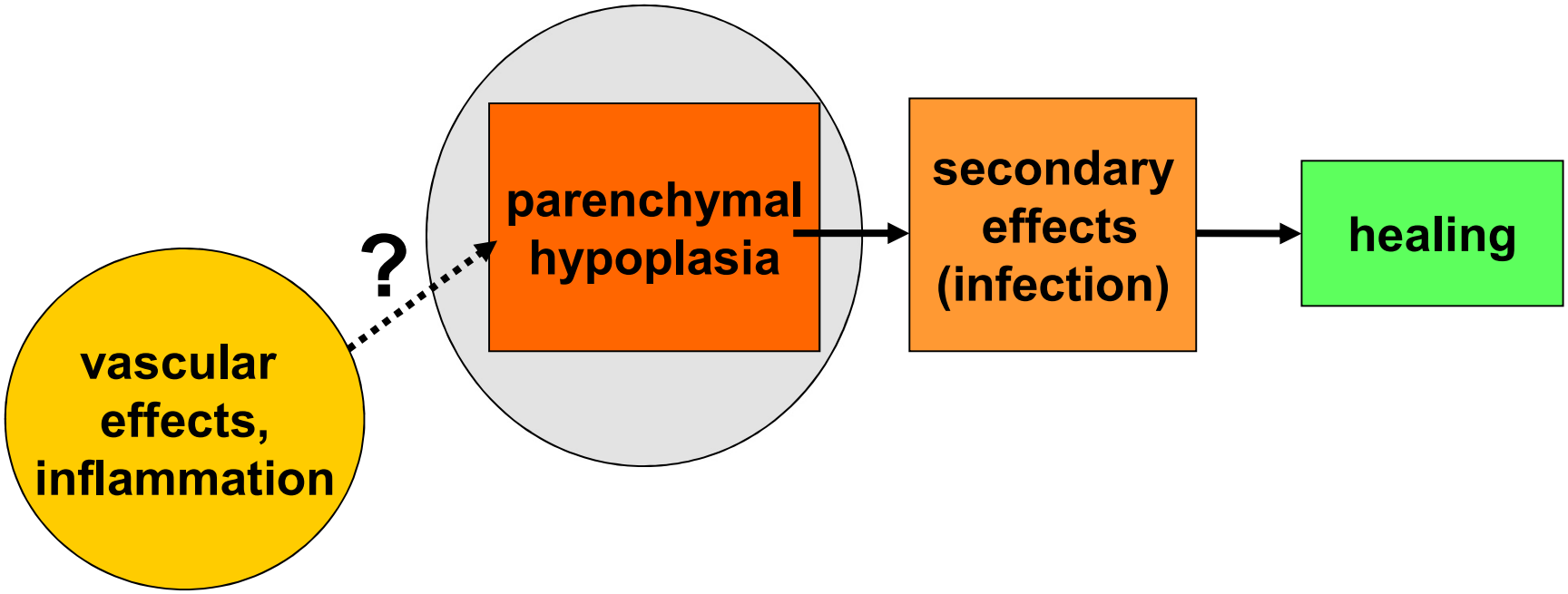
Dept. of Radiation Oncology &
RadOnc - CD Laboratory for Med.Rad.Res. for Rad.Oncol.

Medical University of Vienna, Austria

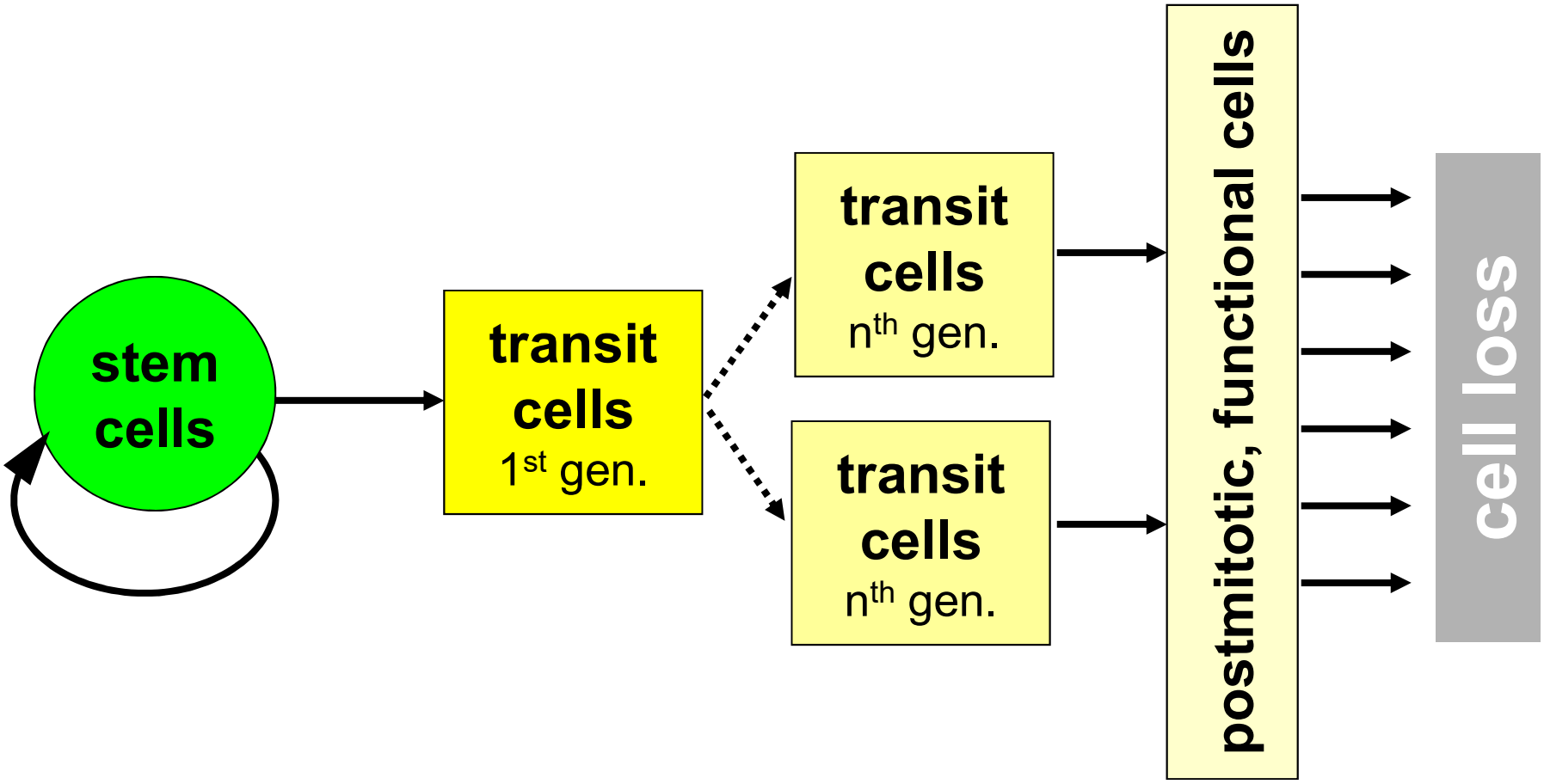
Radiotherapy side effects



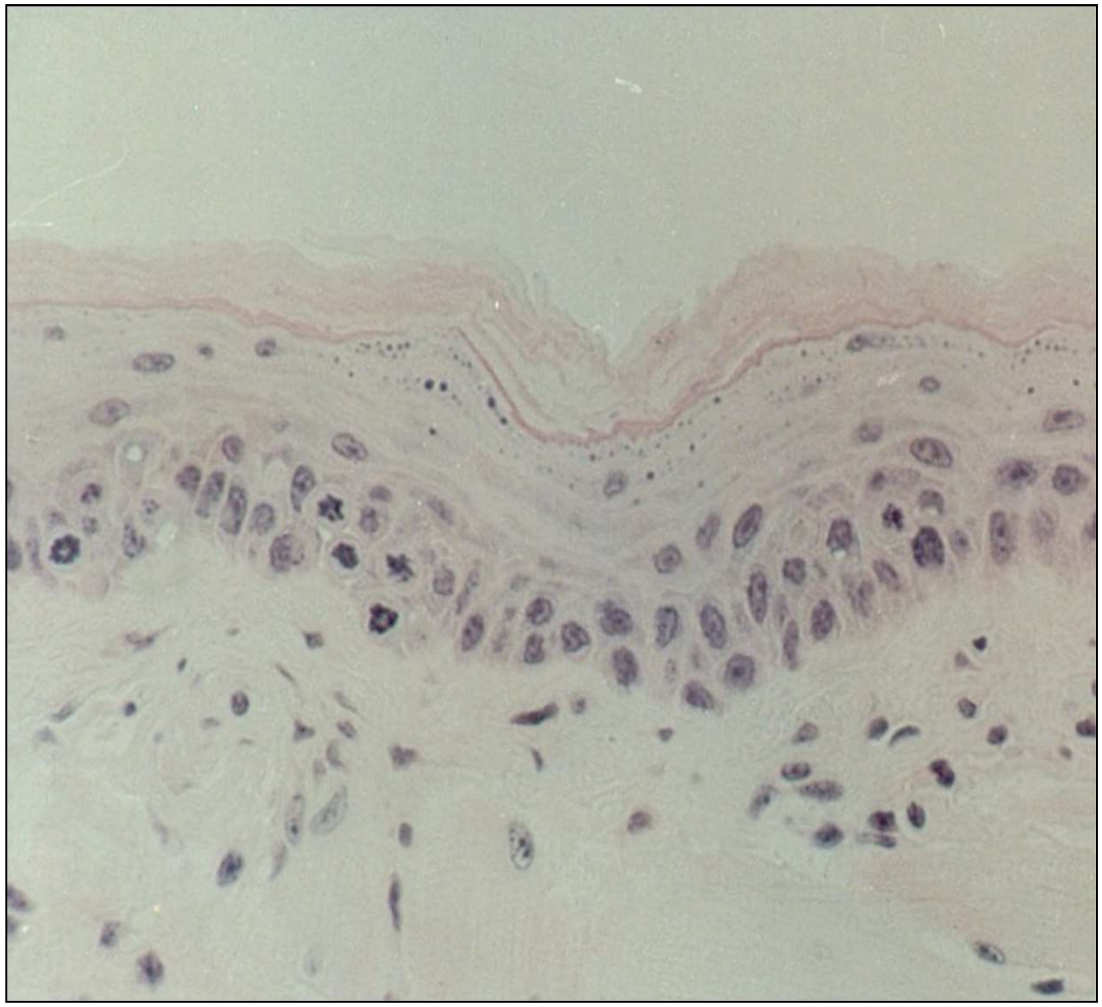
Early reactions: Sequence of events



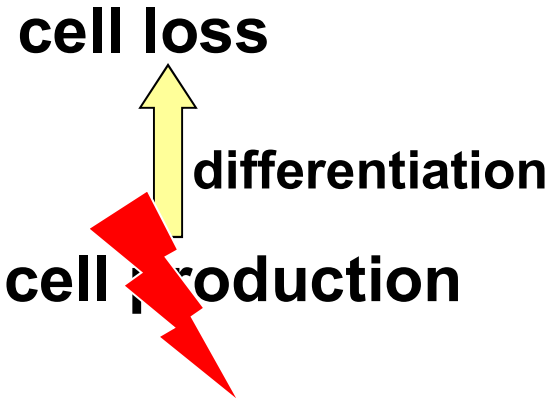
Turnover tissues: Hierarchical organisation



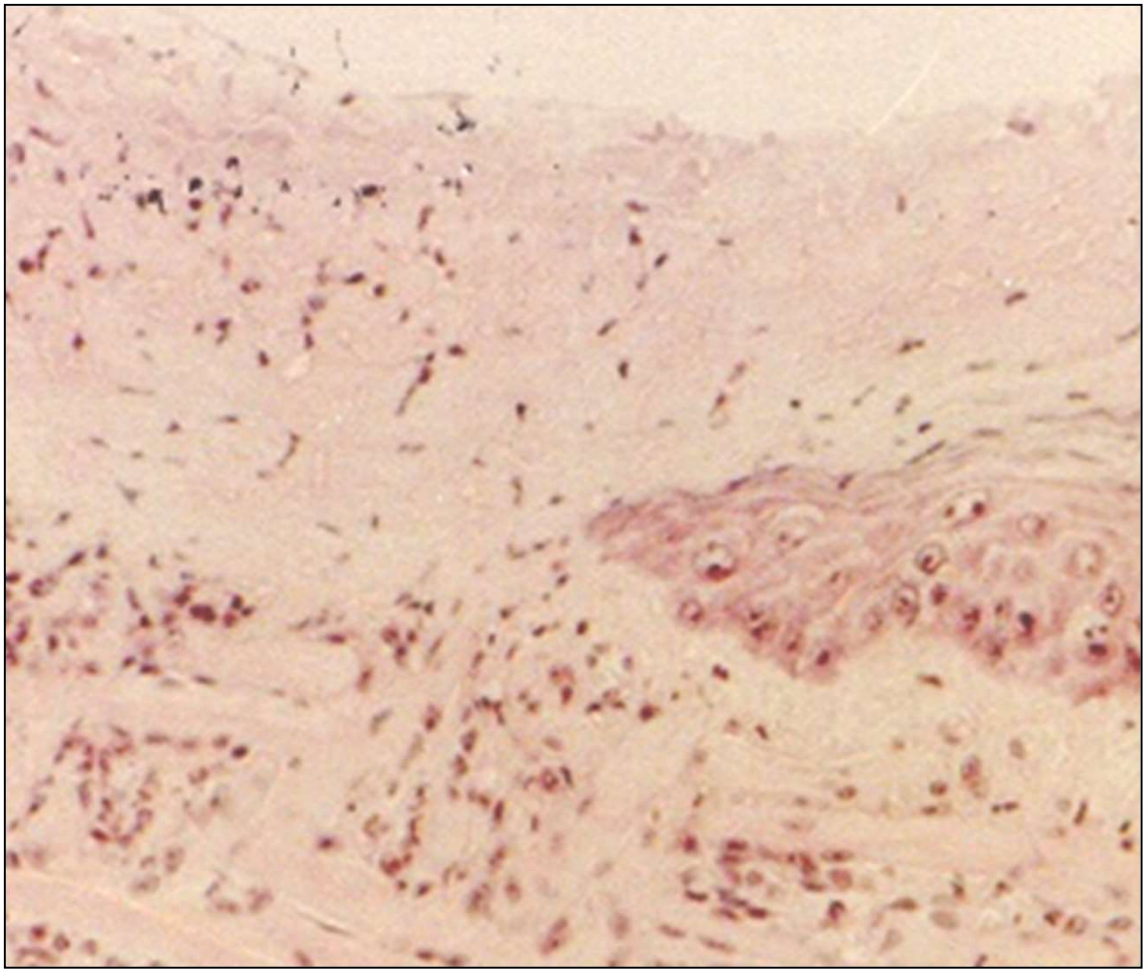
Turnover tissues: Oral mucosal epithelium



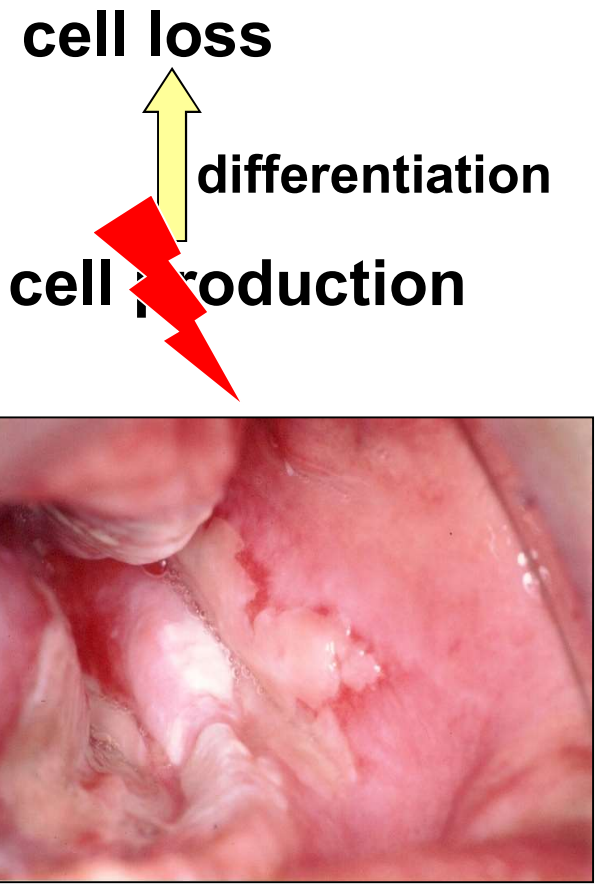
mouse tongue mucosa



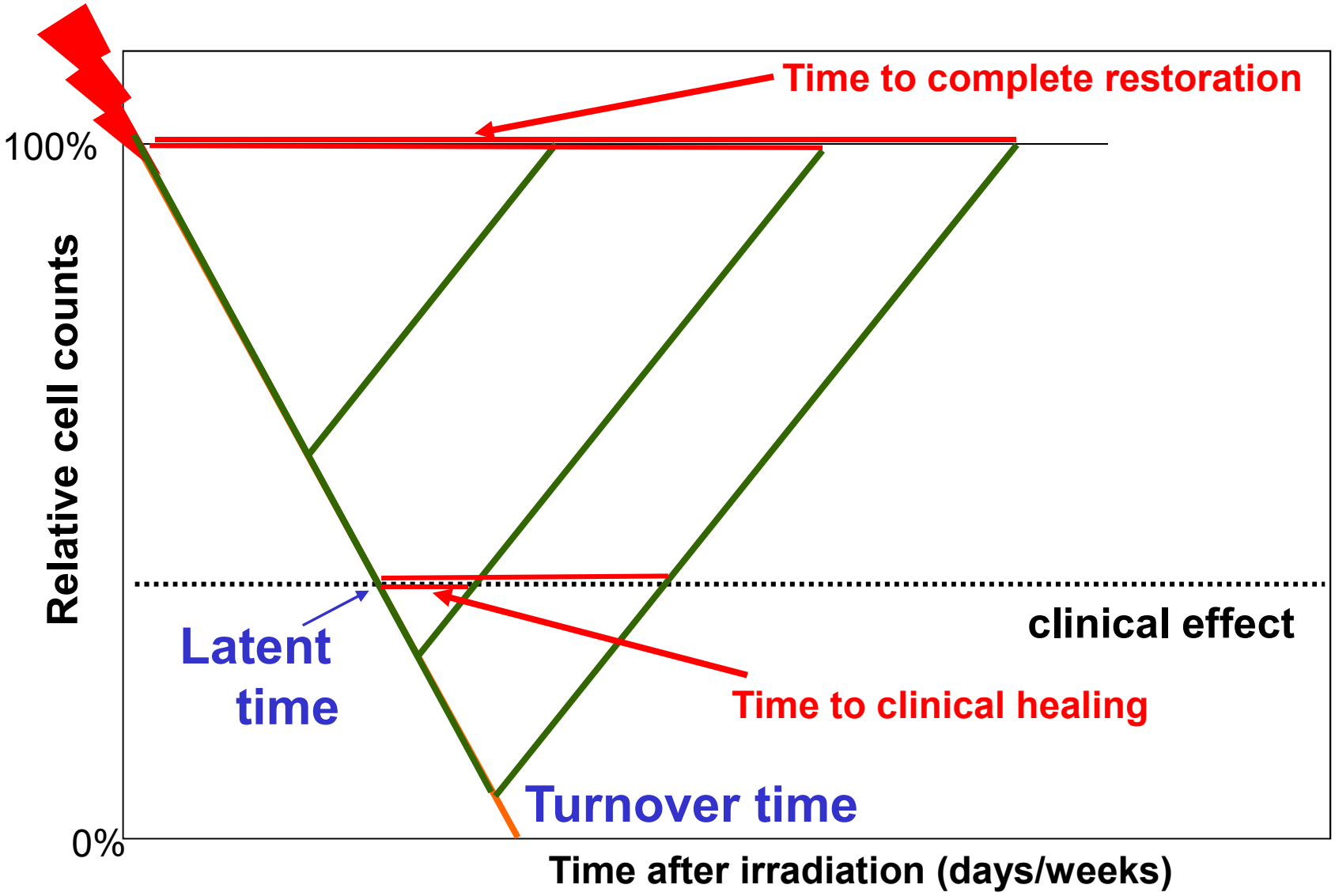
Oral mucosa: Desquamation



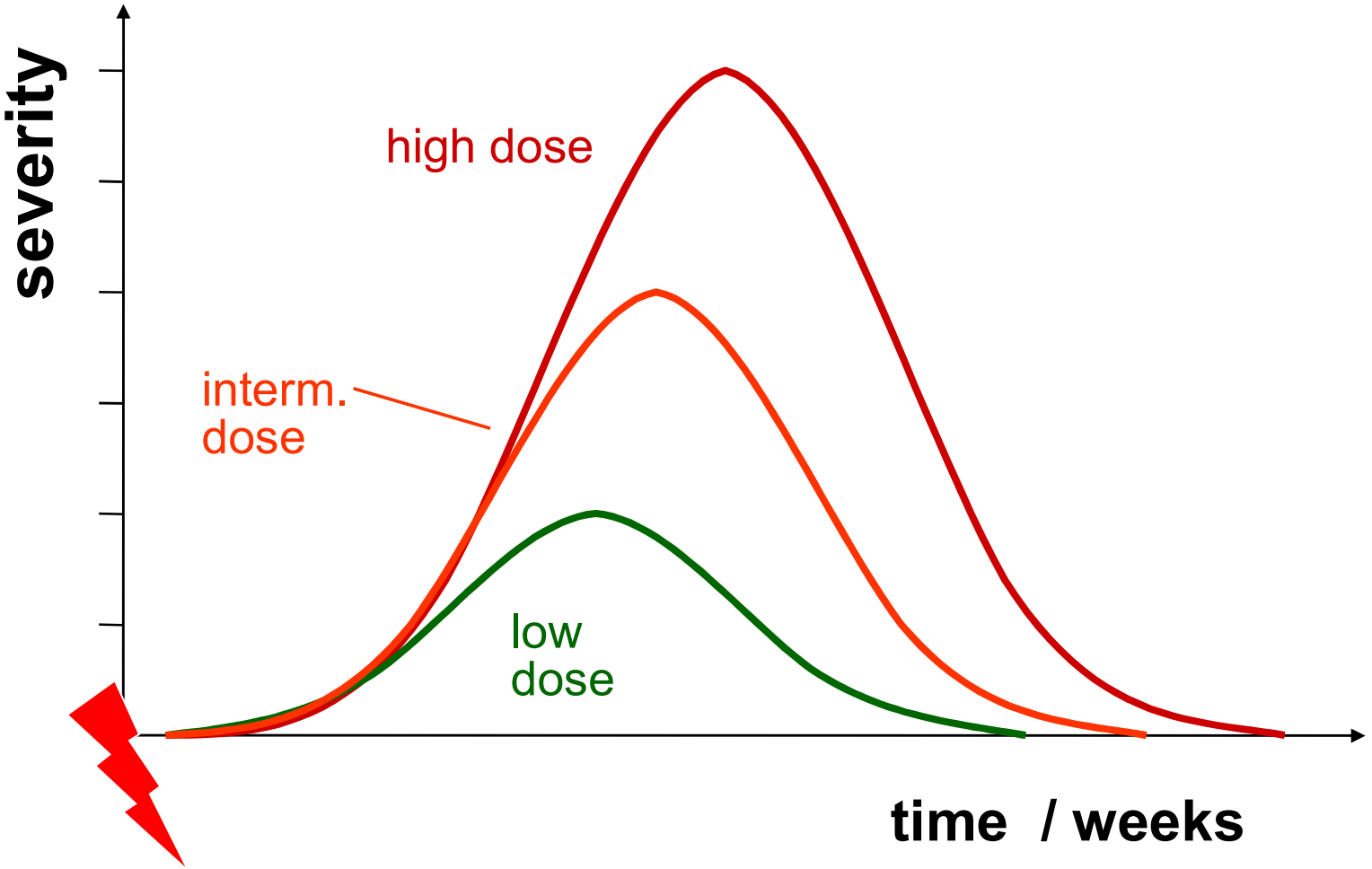
mouse tongue mucosa, 15 Gy, day 11



Turnover tissues: Changes in cell numbers

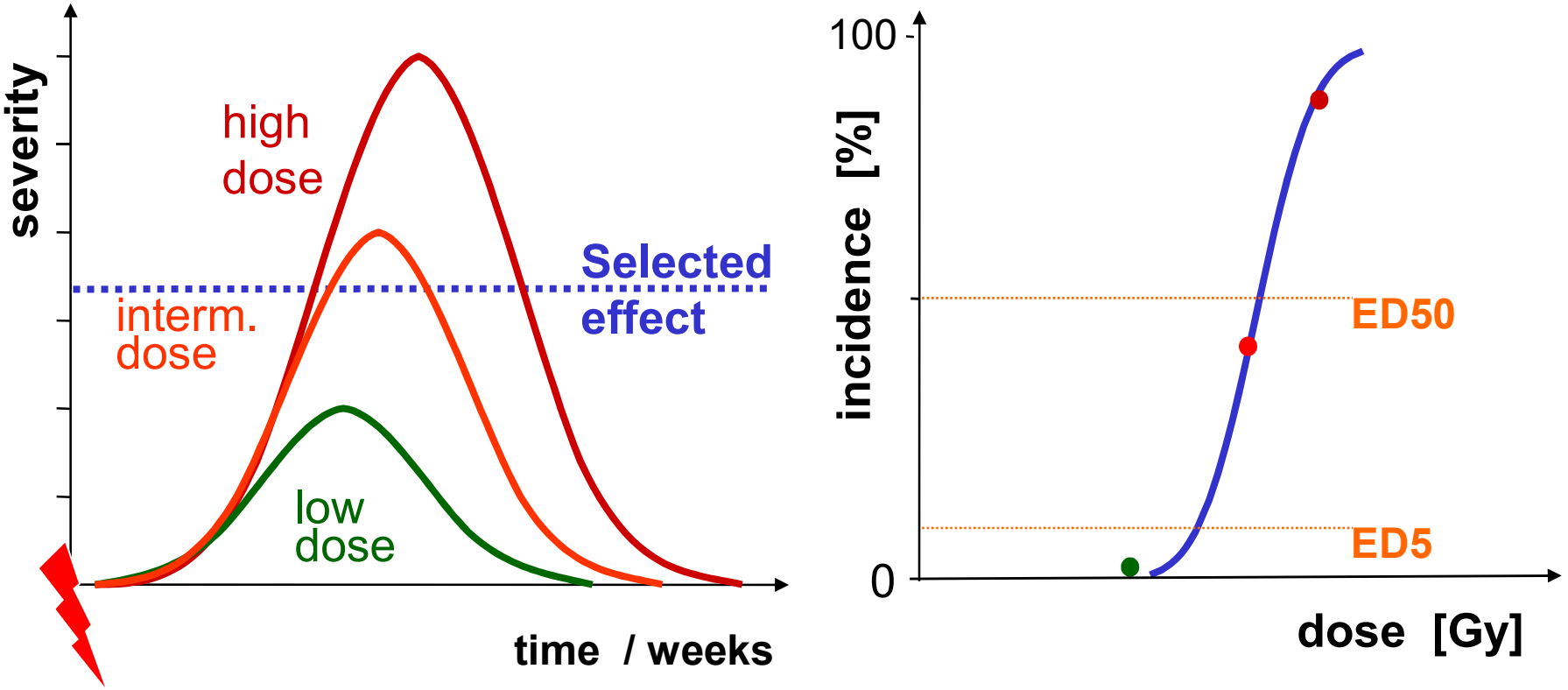


Turnover tissues: Clinical time course

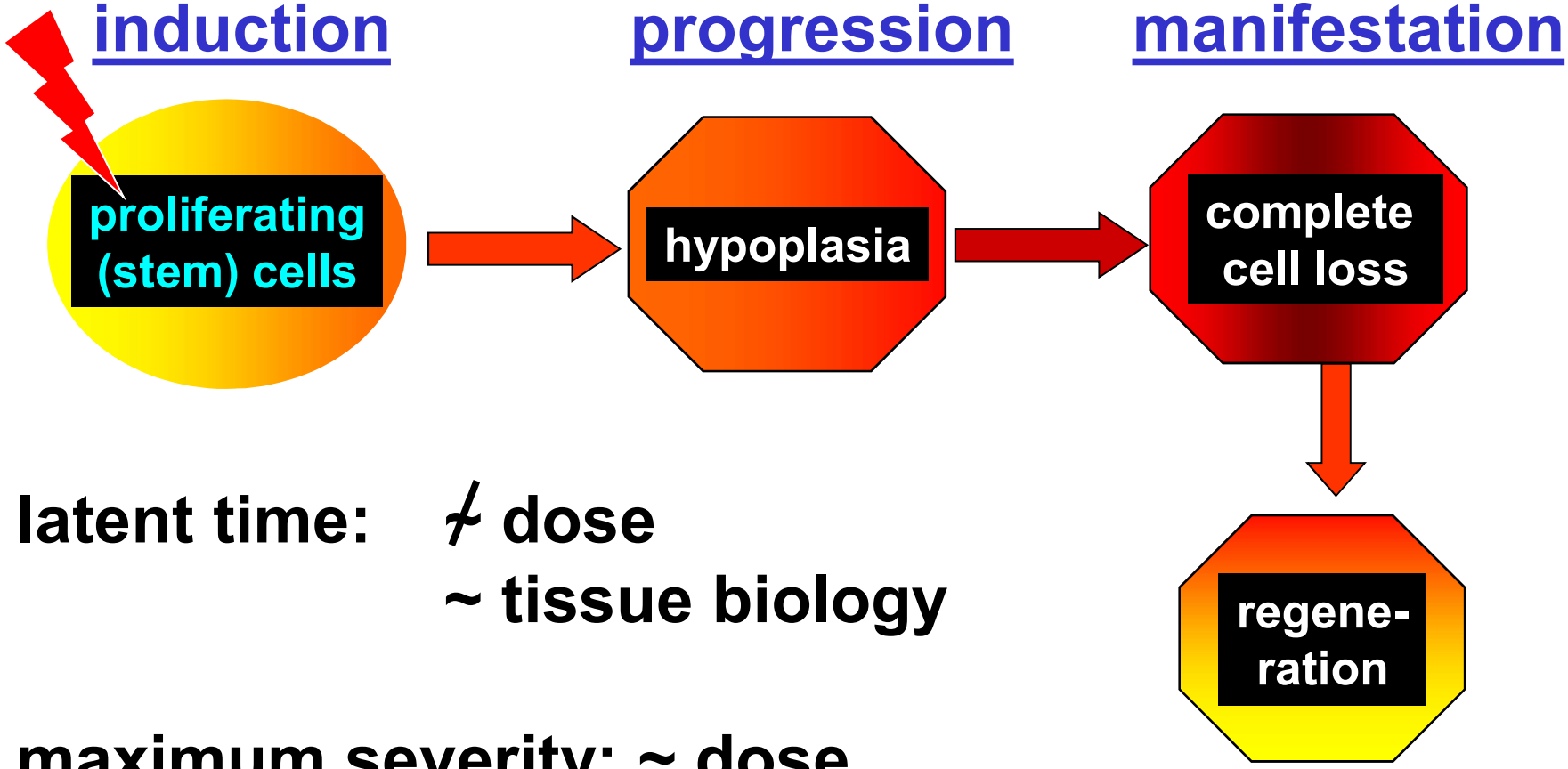


How to get a dose-effect relationship?

Quantalisation



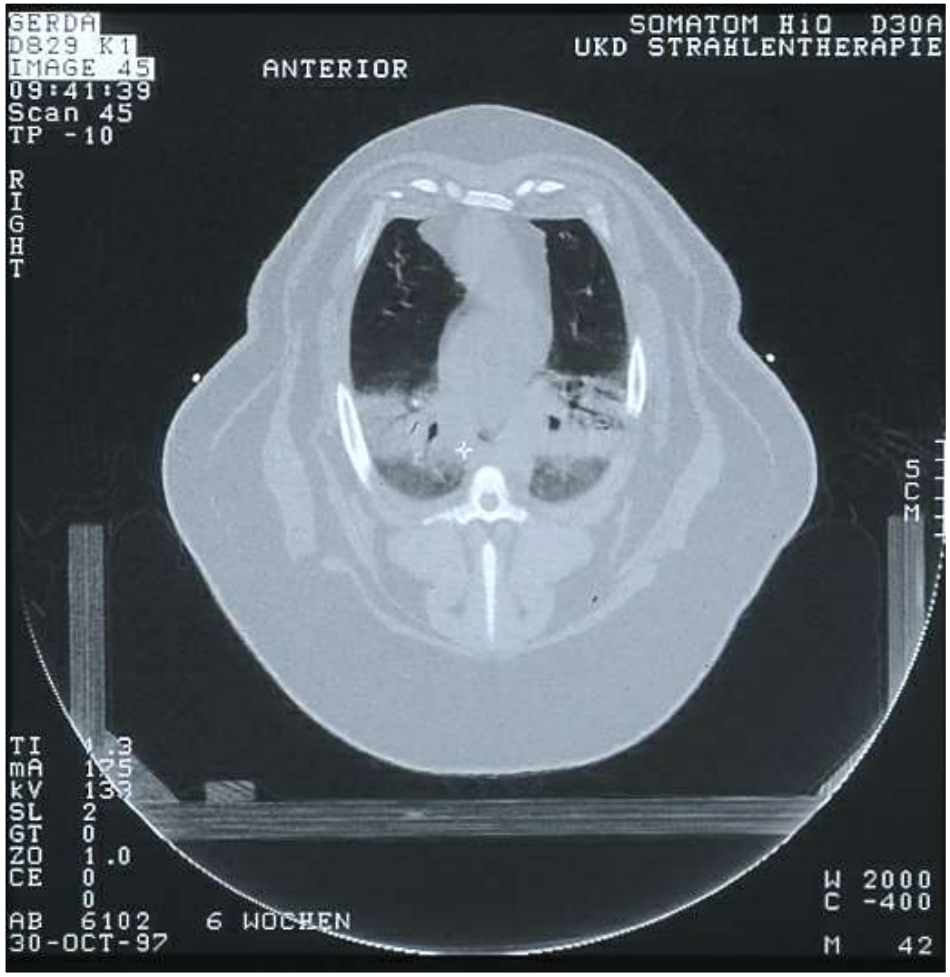
Early radiation effects: Summary

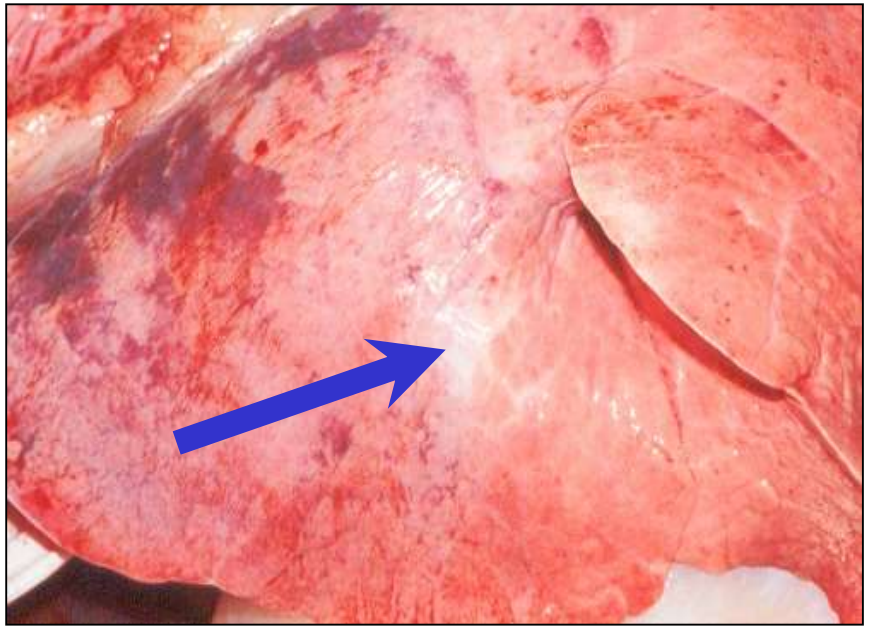


latent time: ≠ dose
~ tissue biology

maximum severity: ~ dose
time to restoration: ~ dose

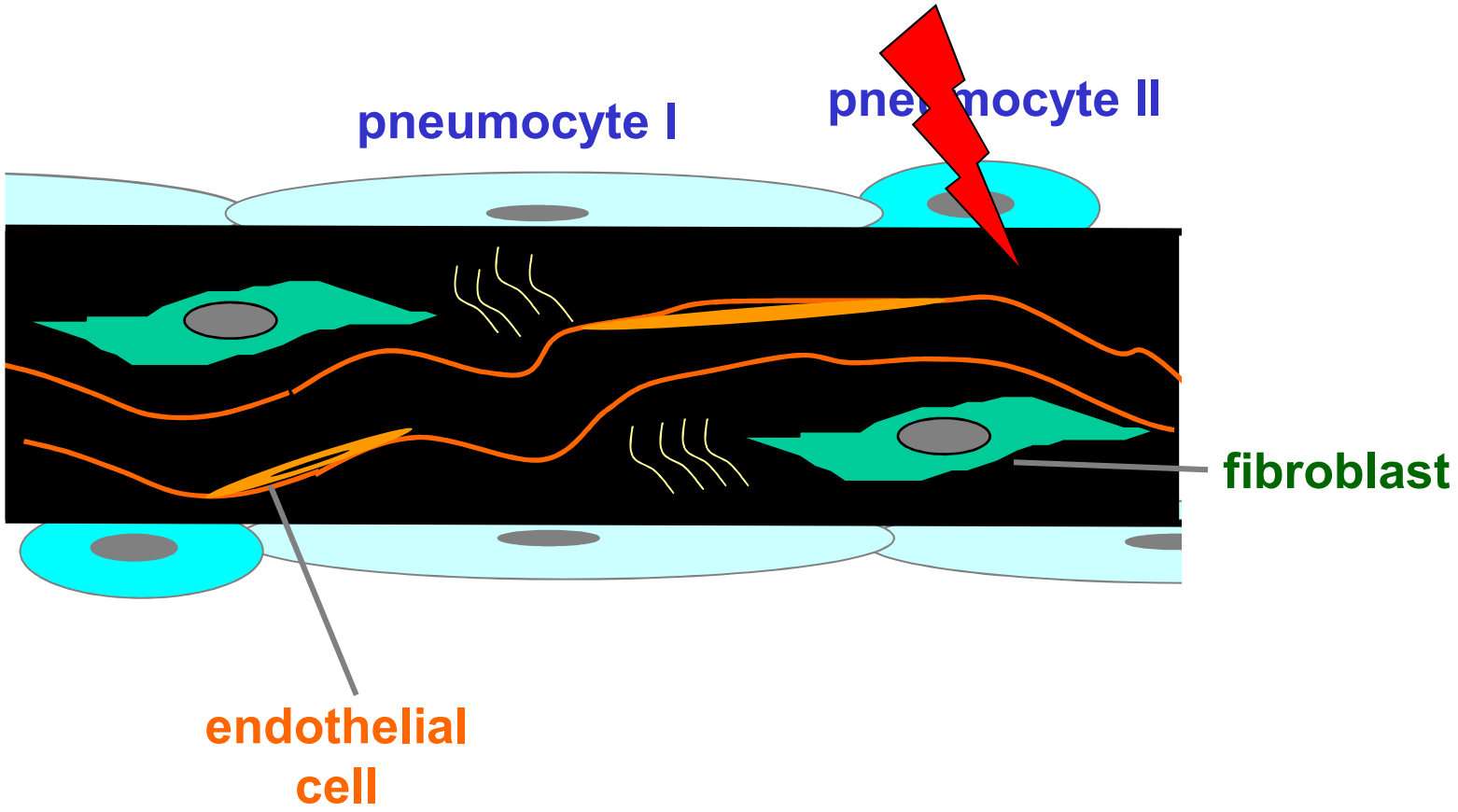
Late radiation effects



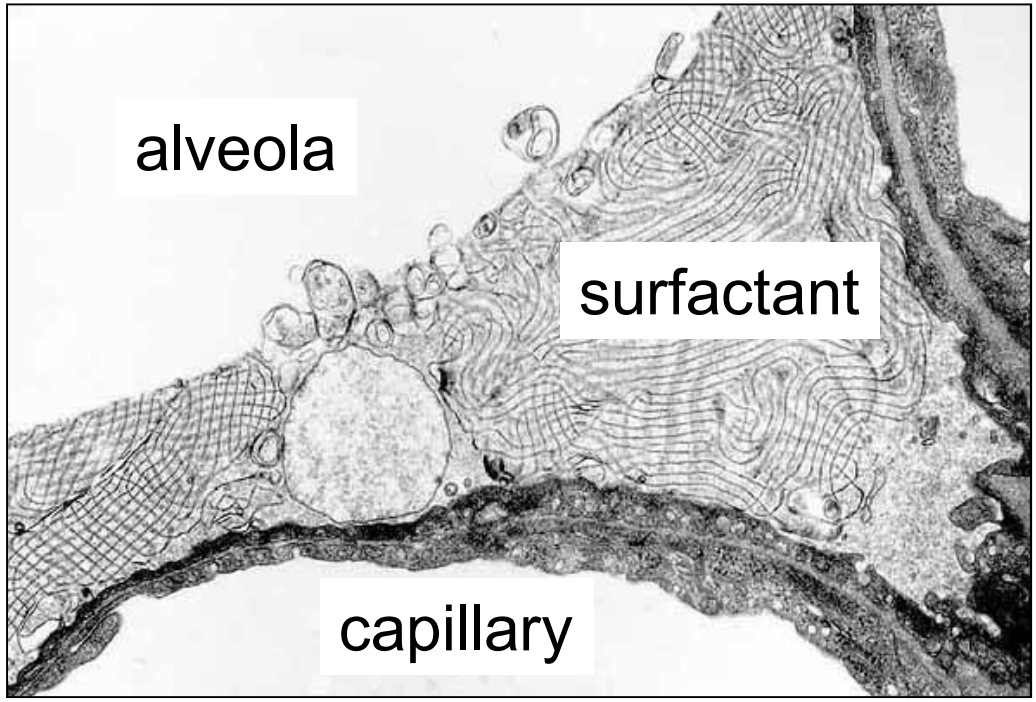


minipig,
9 months post
5x9 Gye ^{12}C-irradiation

Lung: Alveolar wall



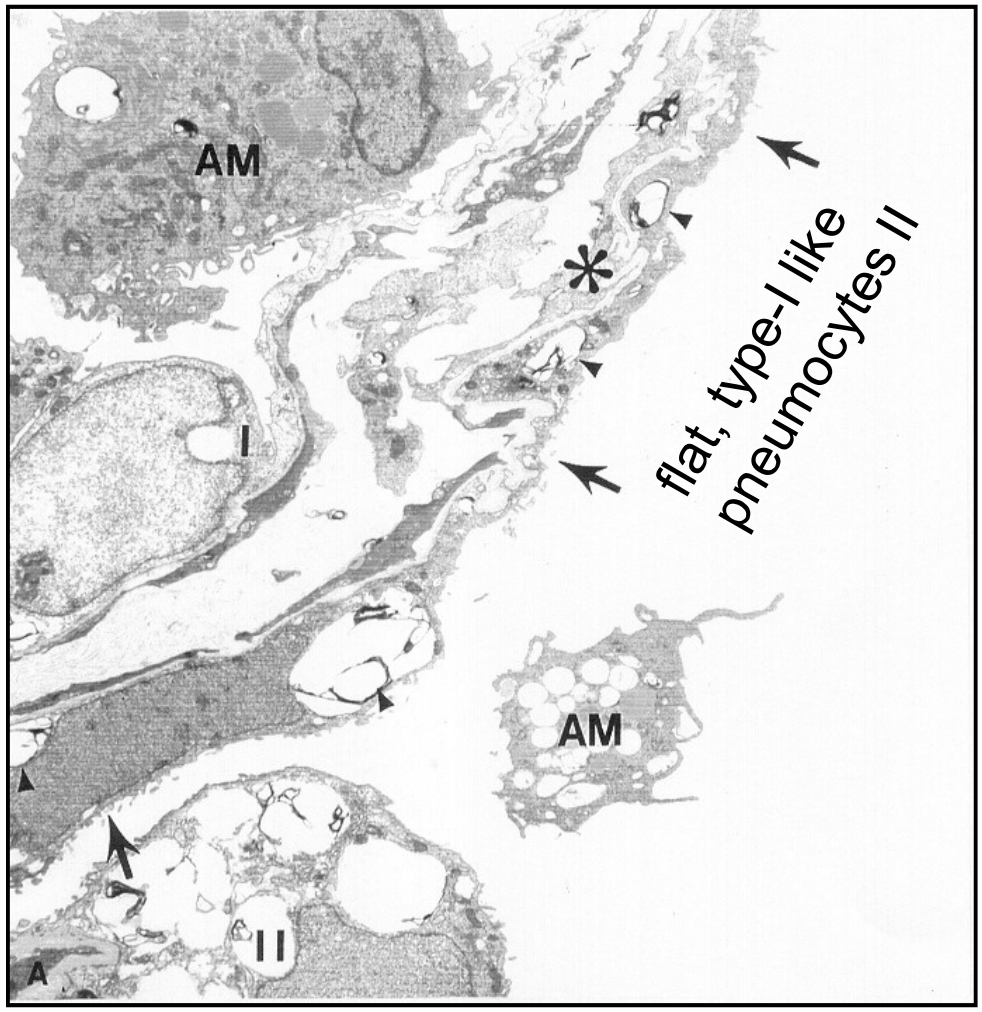
Lung: Parenchymal response



surfactant: intracellular ↓ => ↑

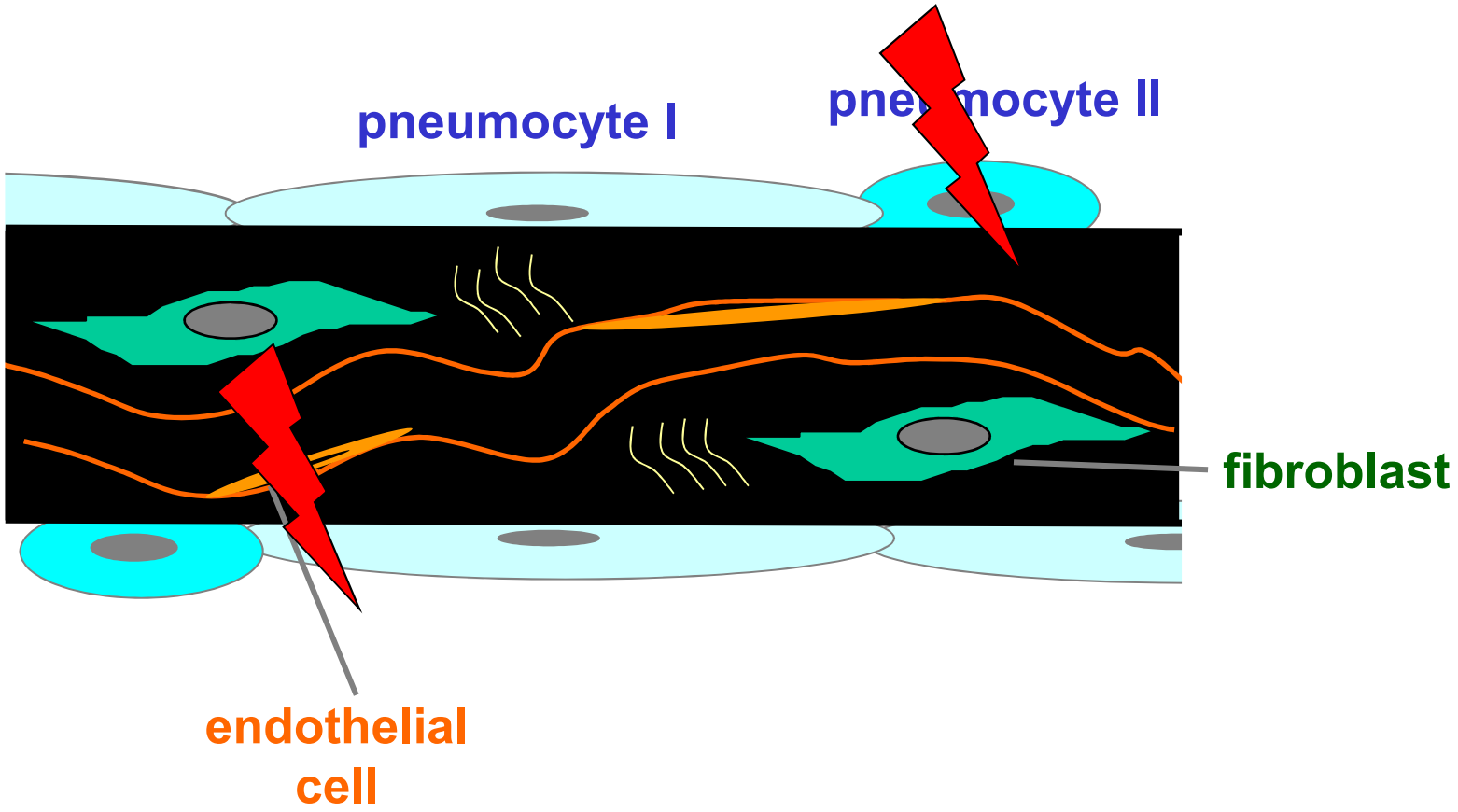
alveolar ↑ =>+/-

Lung: Parenchymal response

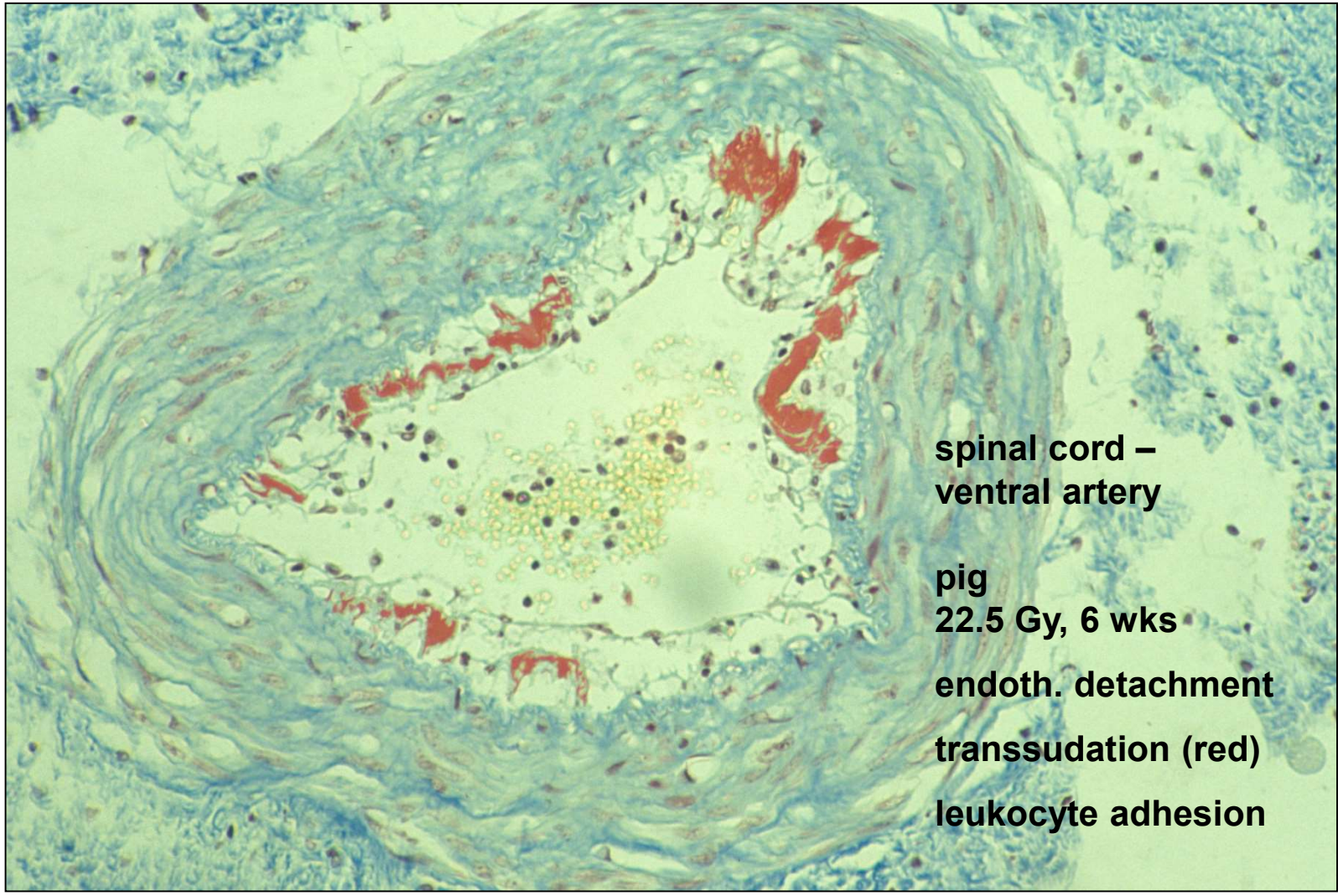


depletion of epithelial („parenchymal“) cells

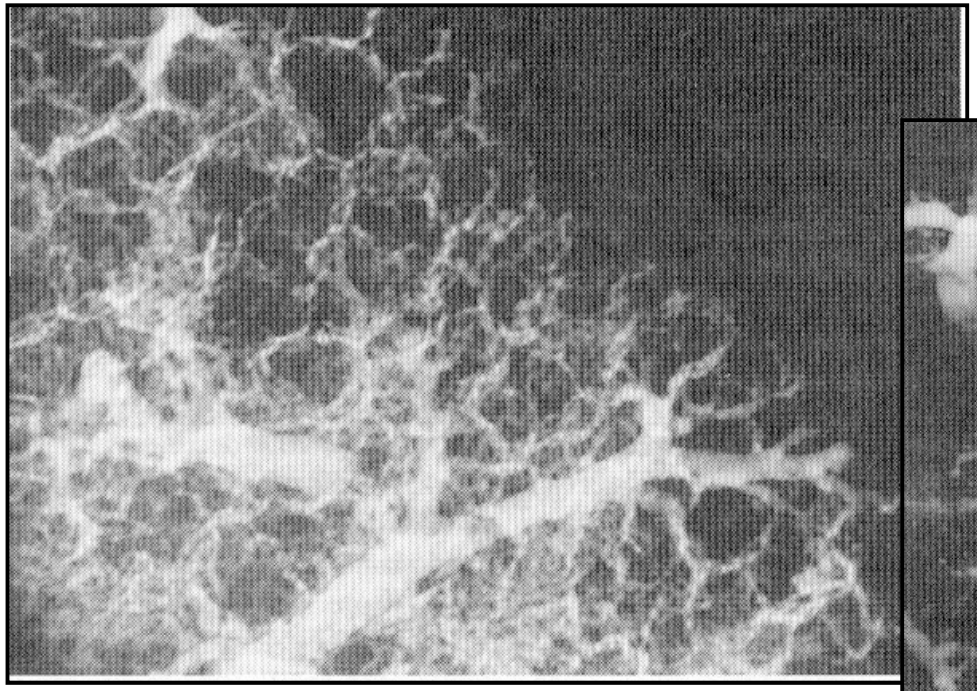
Lung: Alveolar wall



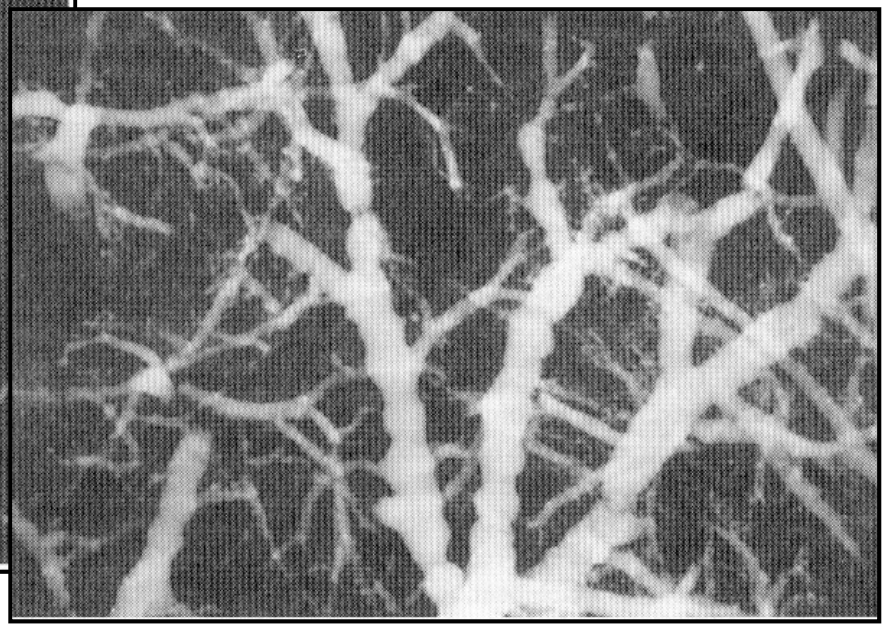
Lung: Vascular response



Lung: Vascular response



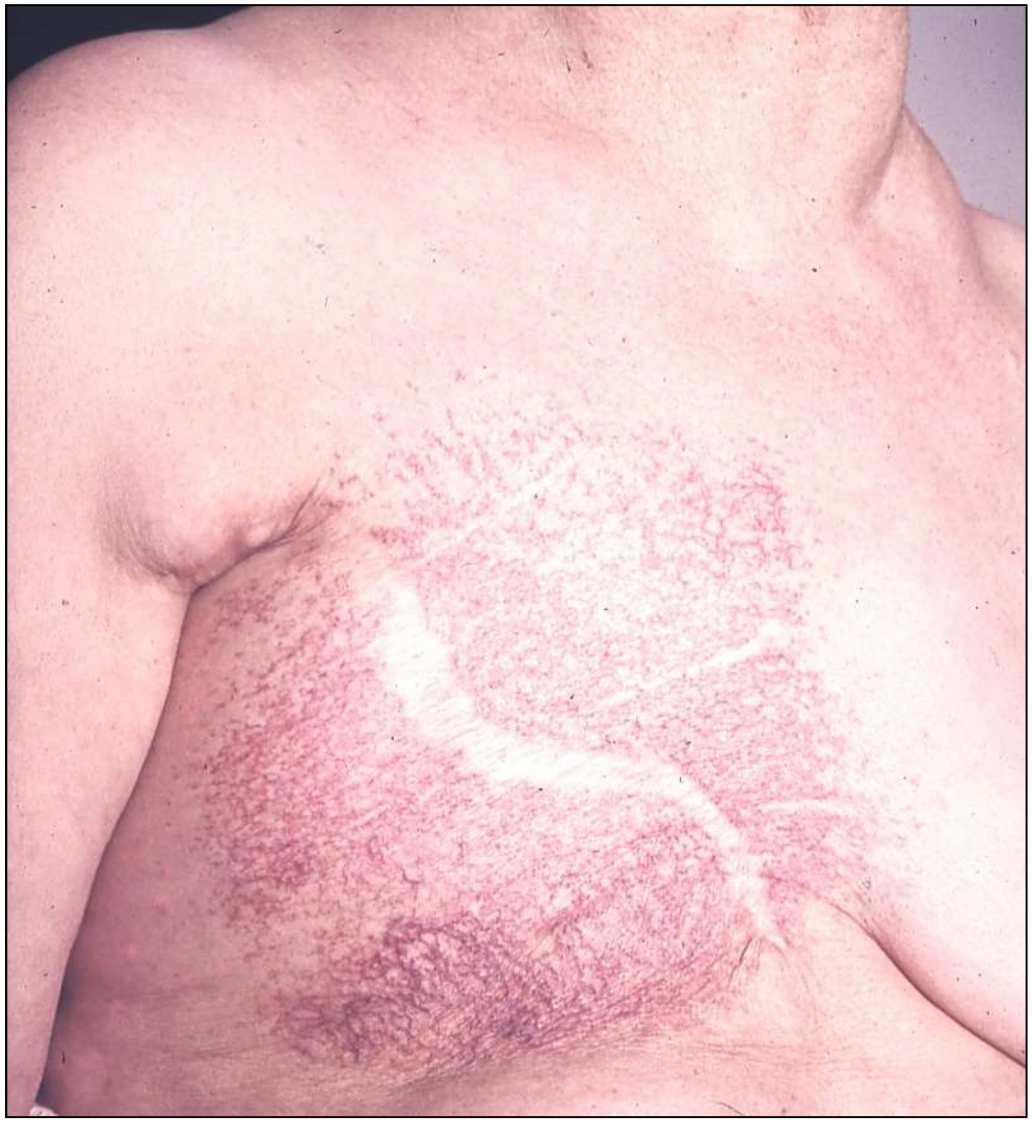
rat lung, control



rat lung, 5x6 Gy, 6 weeks
„sausage-like“ arterioles,
loss of capillaries

Kwock et al., Radiat. Res. 111, 1987, 276-291

Skin: Vascular response



dilation
telangiectasia

loss of function
bleeding

Vascular response: Summary

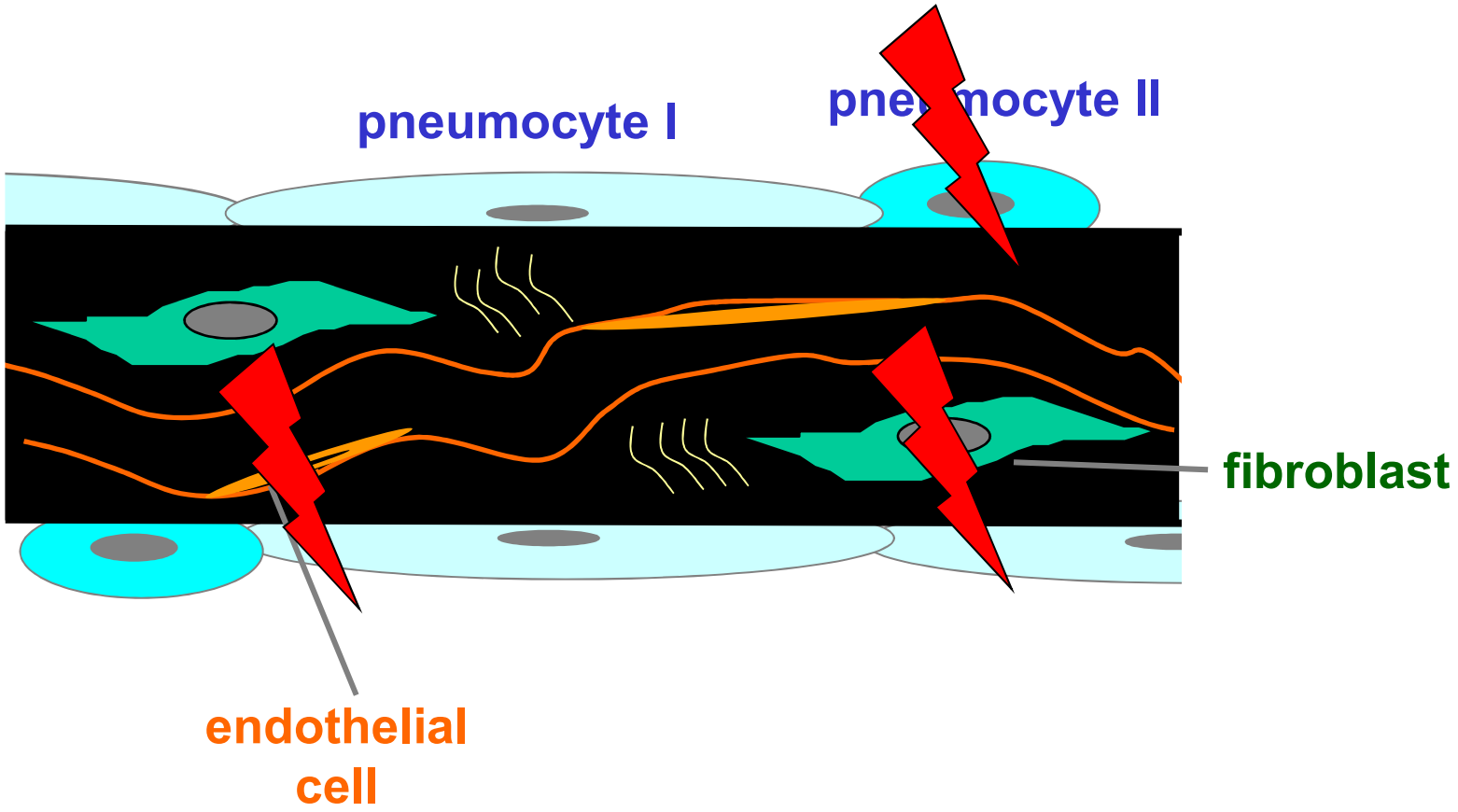
endothelial detachment
endothelial vacuolisation
subendothelial edema
endothelial cell loss

thrombus formation
vascular occlusion

loss of capillaries

telangiectasia: loss of function, bleeding

Lung: Alveolar wall

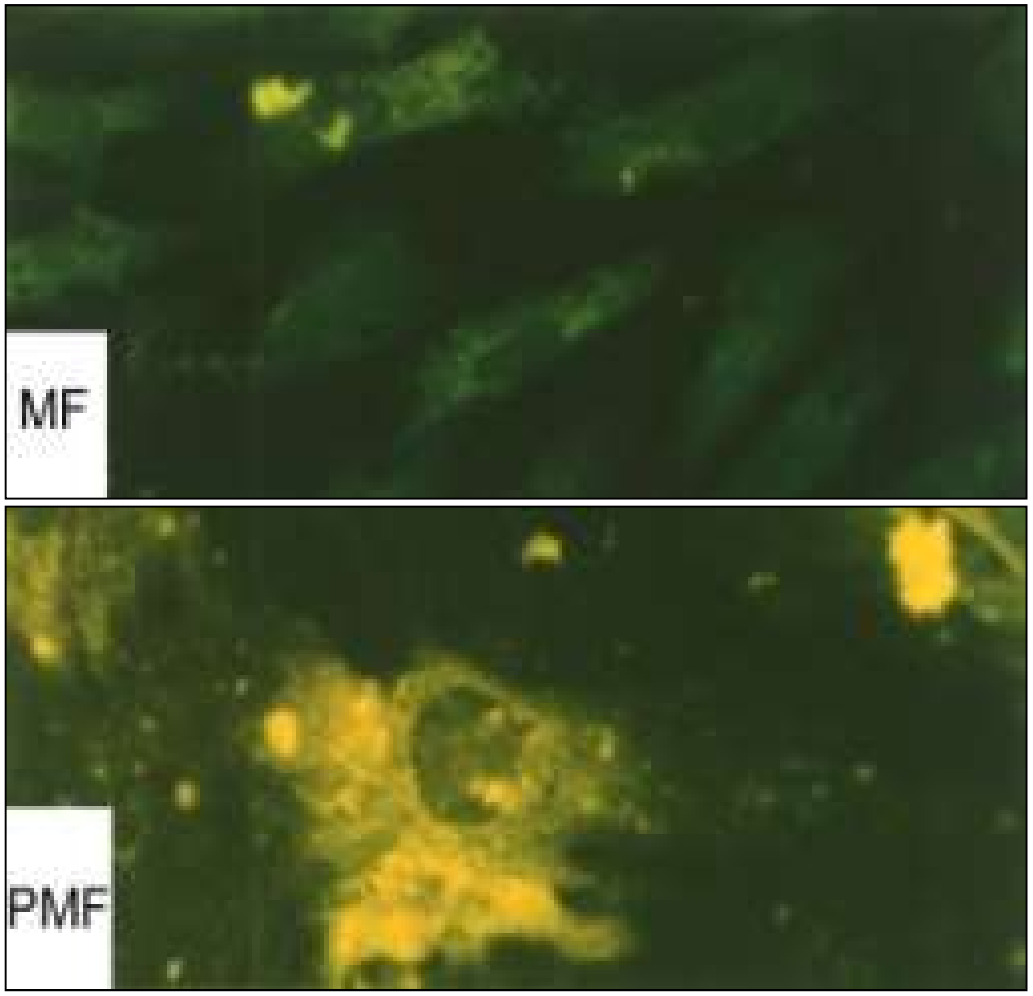


Fibroblast response

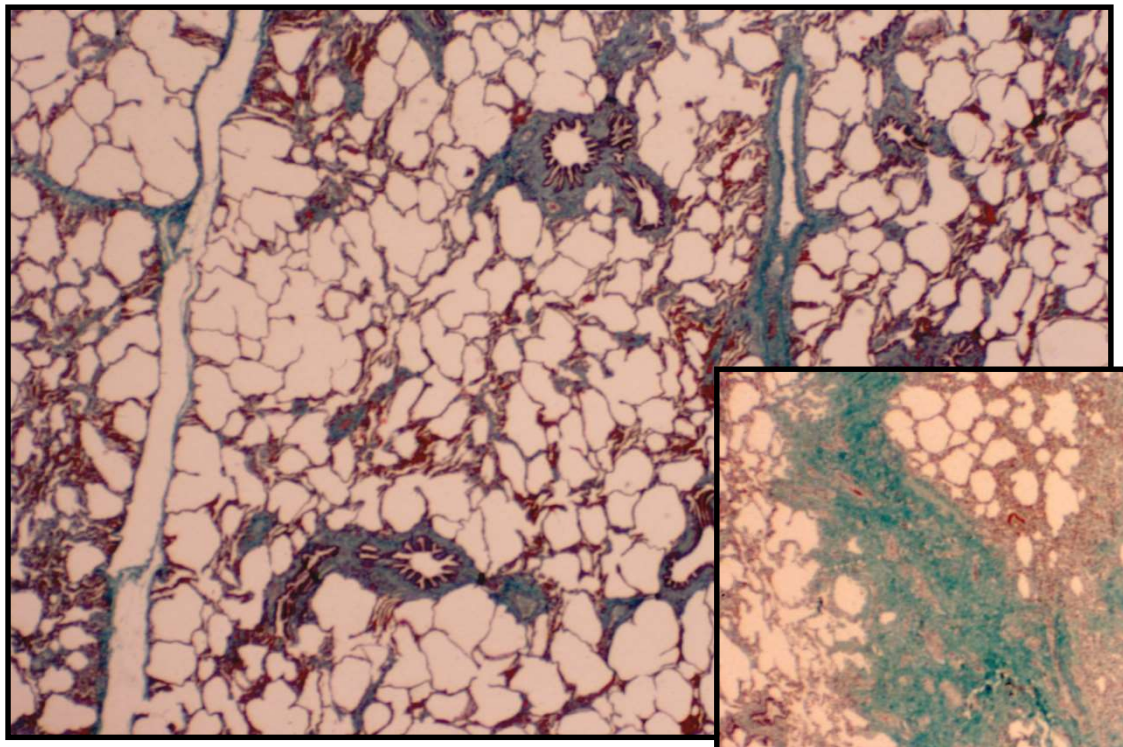
collagen I immunohistochemistry

mitotic fibroblasts

postmitotic fibrocytes



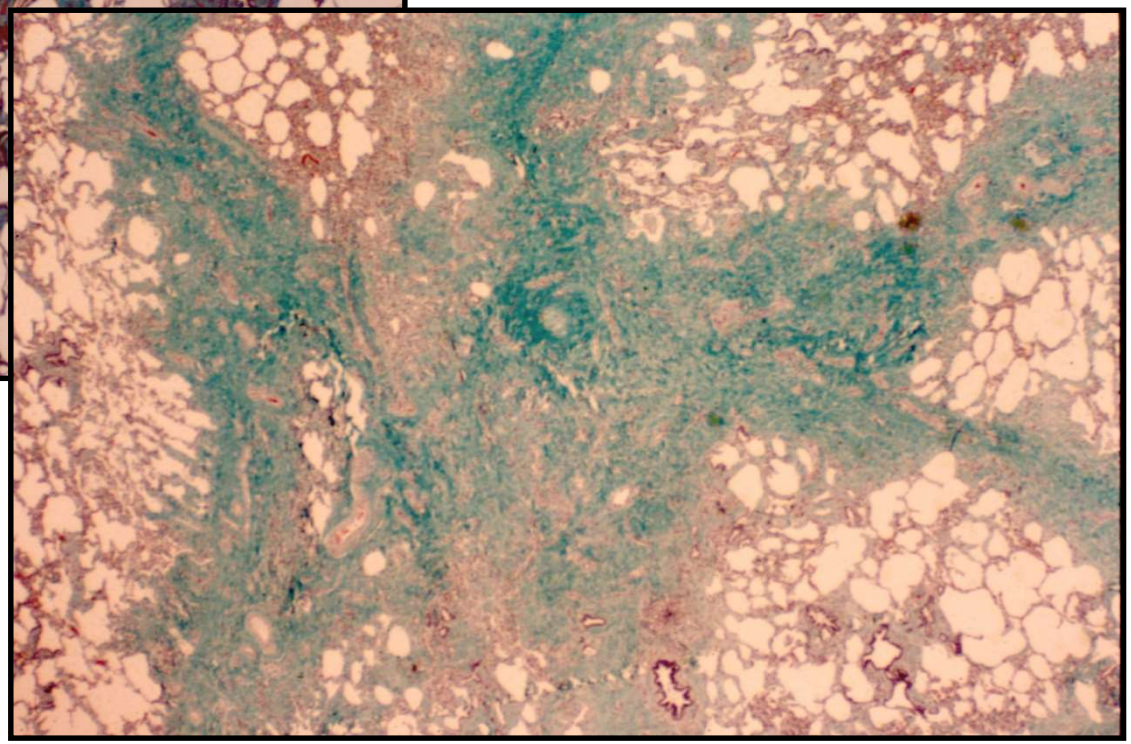
Fibroblast response



control

pig lung

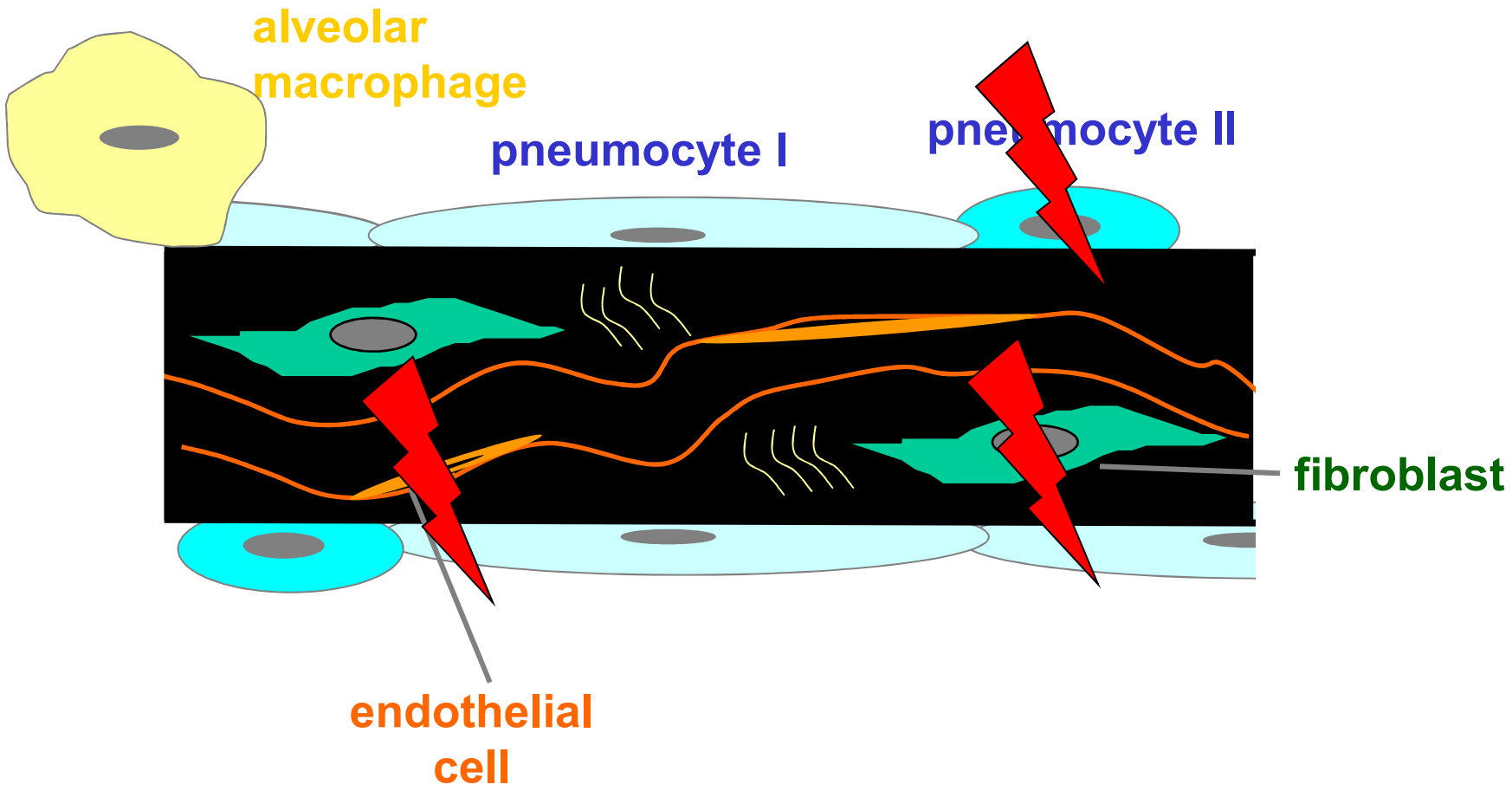
Goldner stain
(collagen)



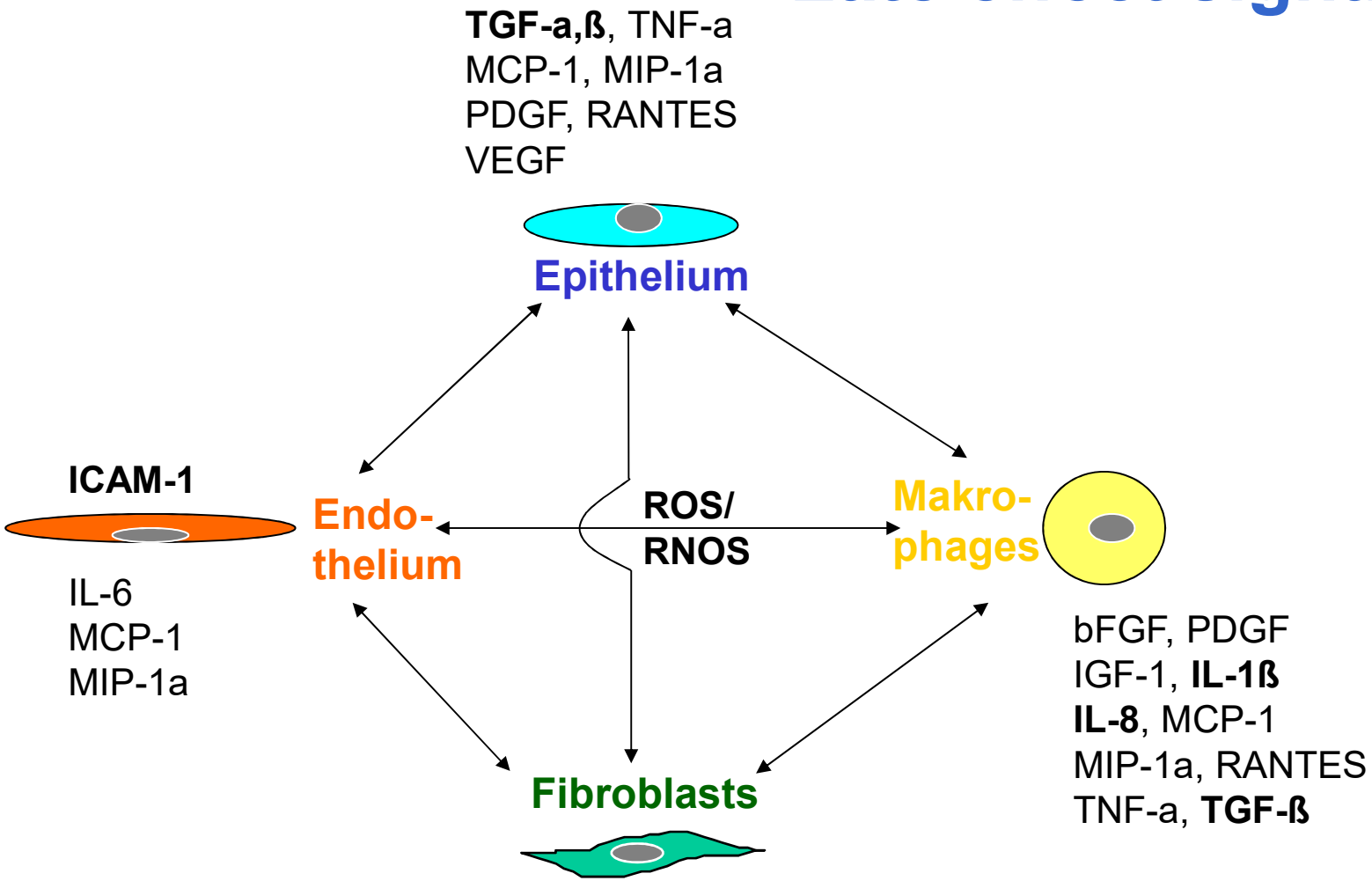
5x7 Gy,
9 months

© Photograph: Th. Herrmann, Dresden, Germany

Lung: Alveolar wall

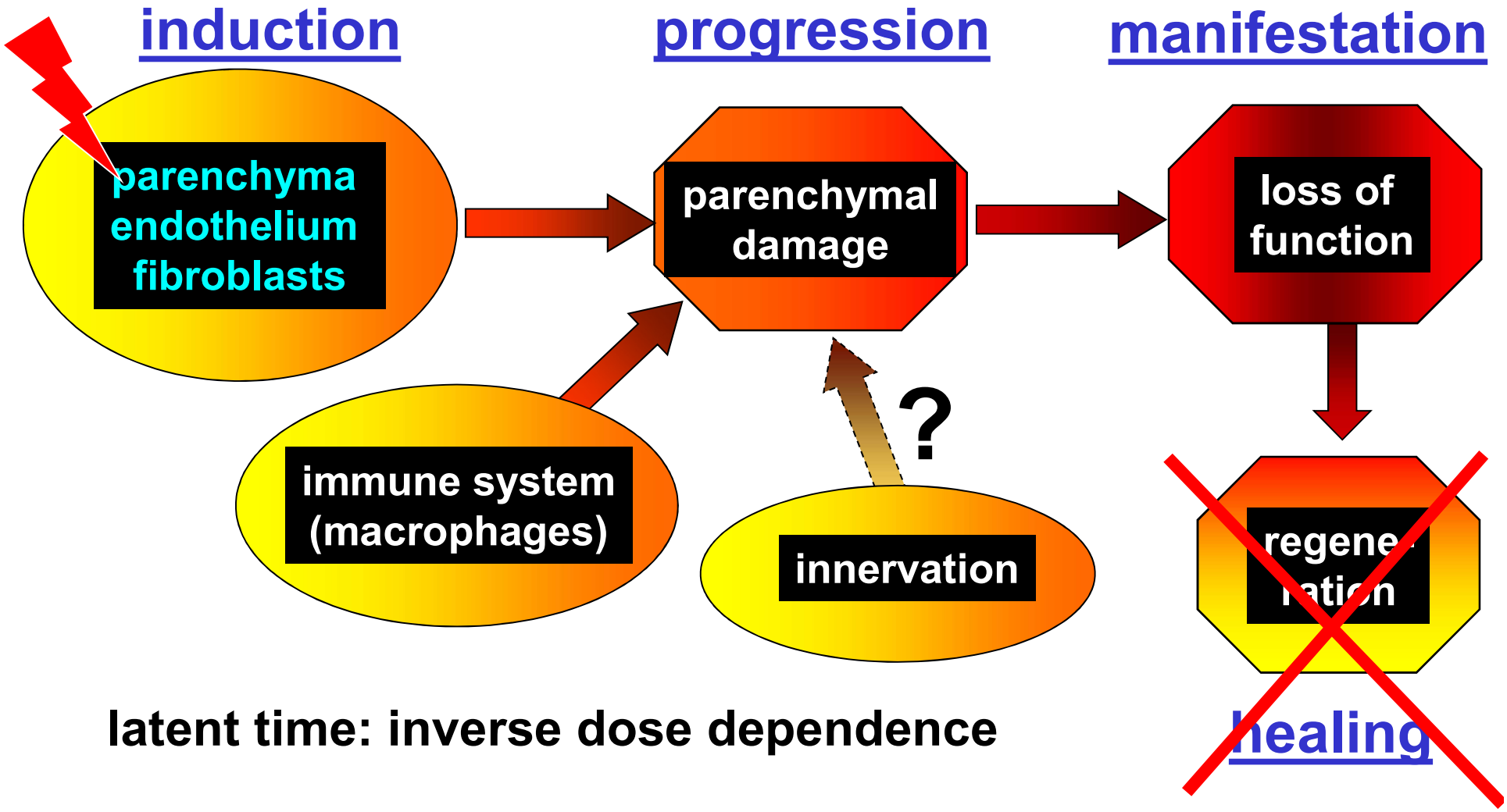


Late effect signaling



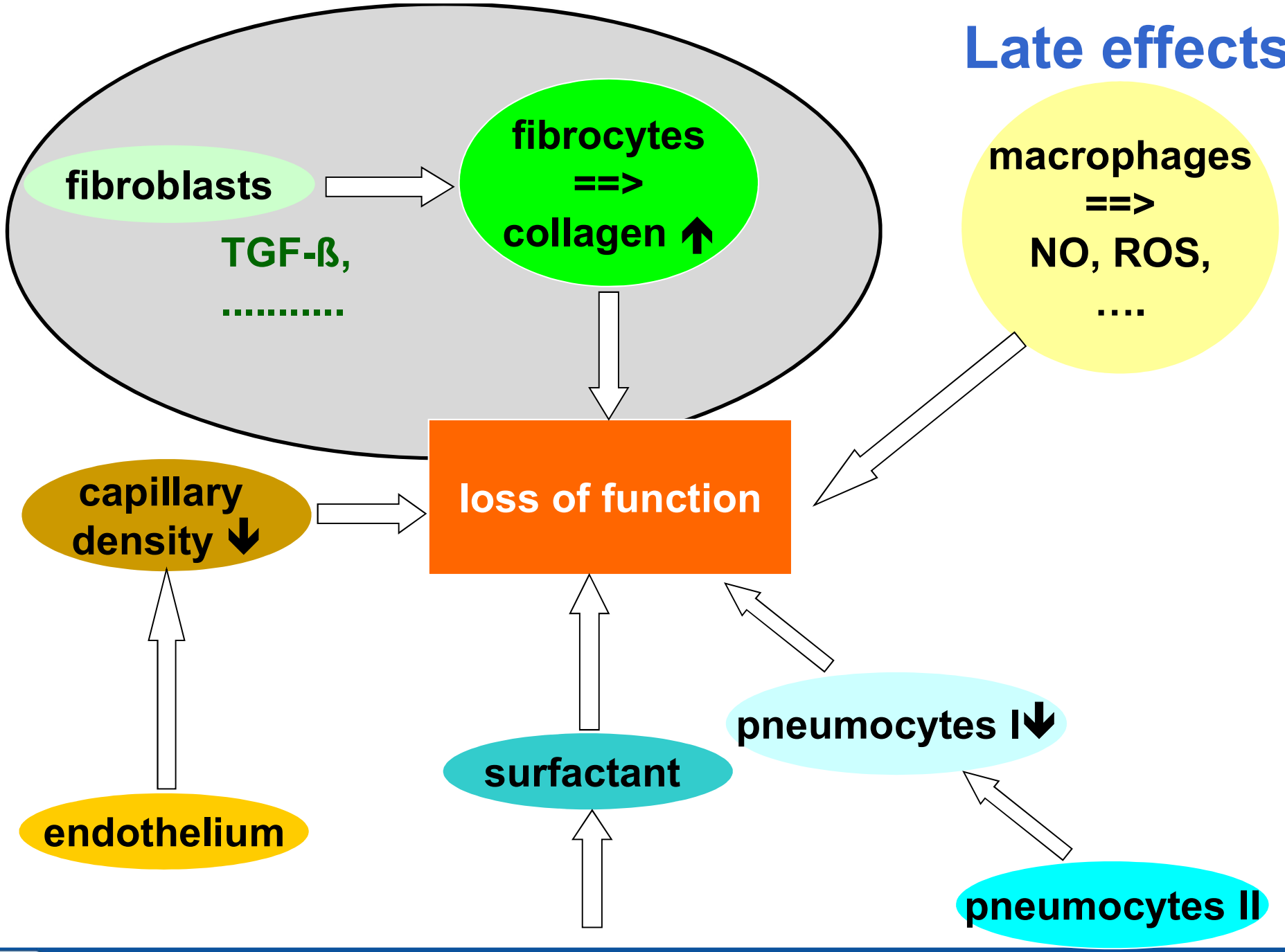
Dörr and Herrmann,
In: Nieder et al. (Eds.), Springer-Verlag 2003

Late radiation effects: Summary

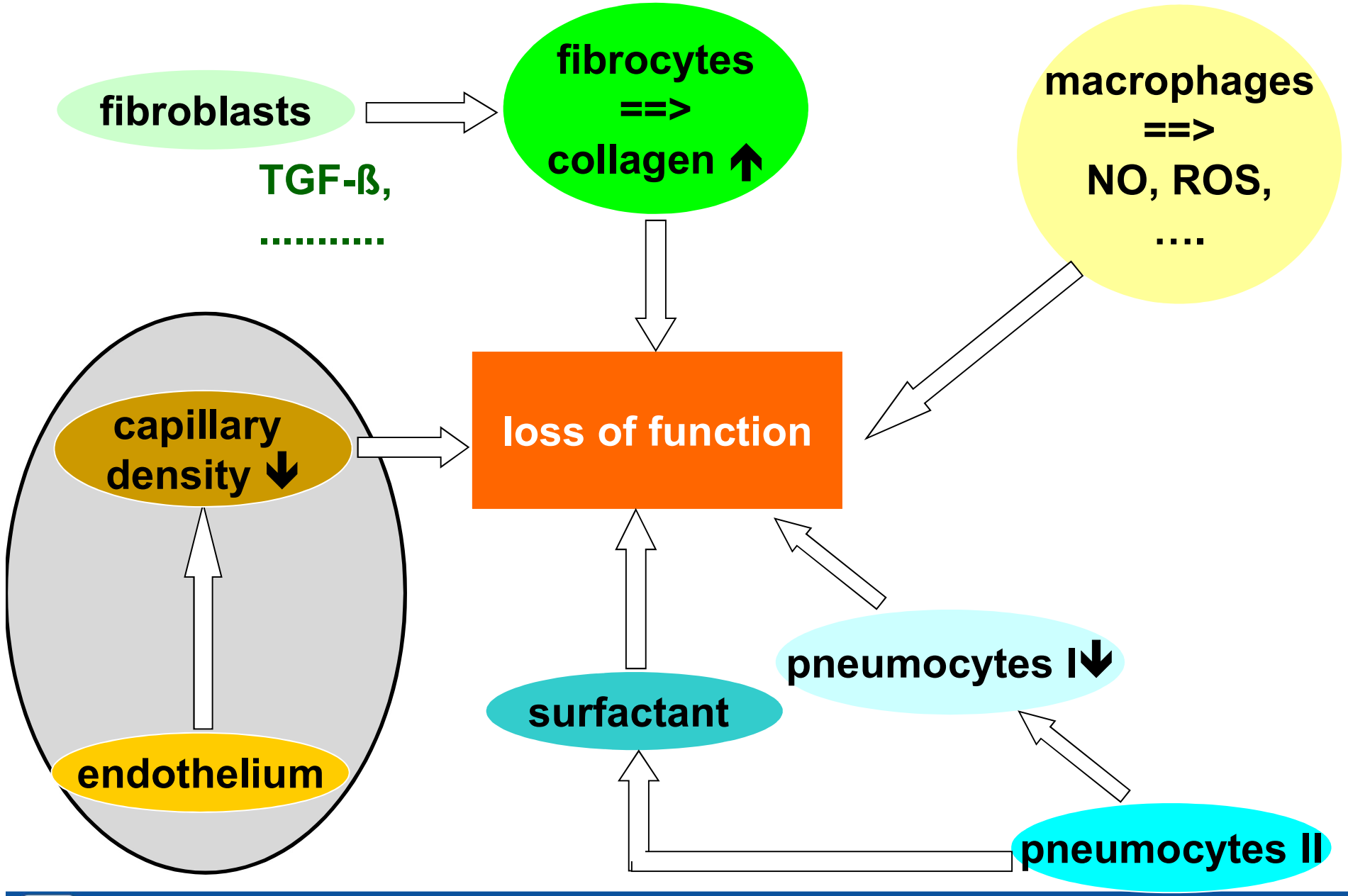


latent time: inverse dose dependence

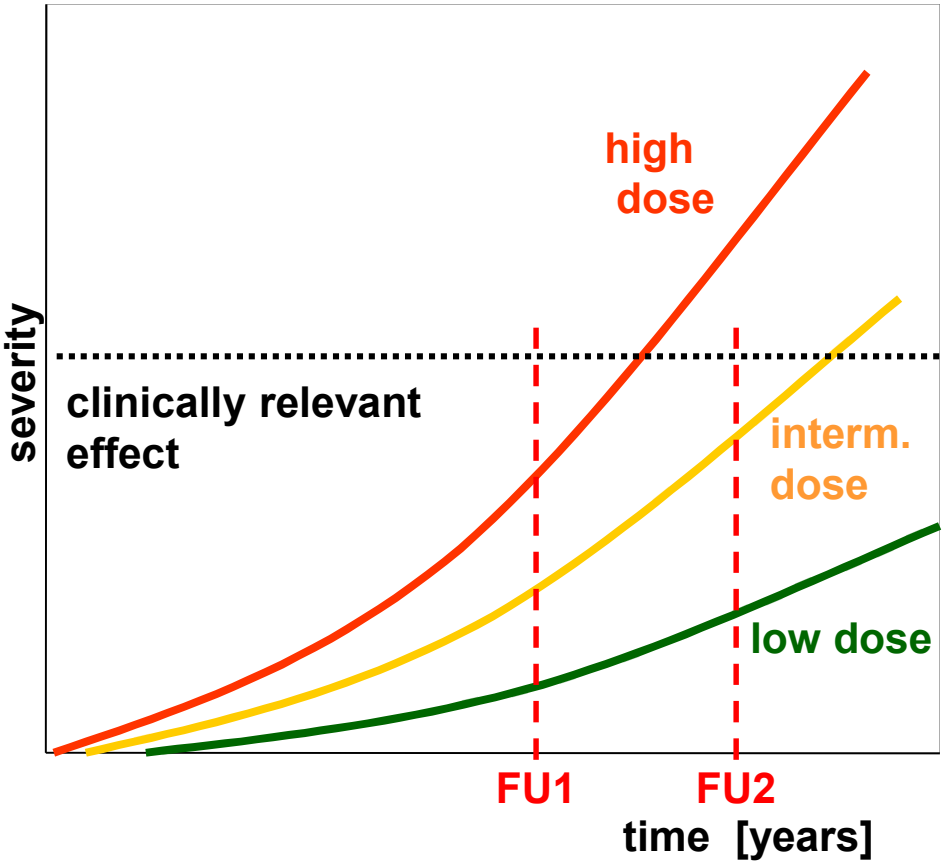
Late effects

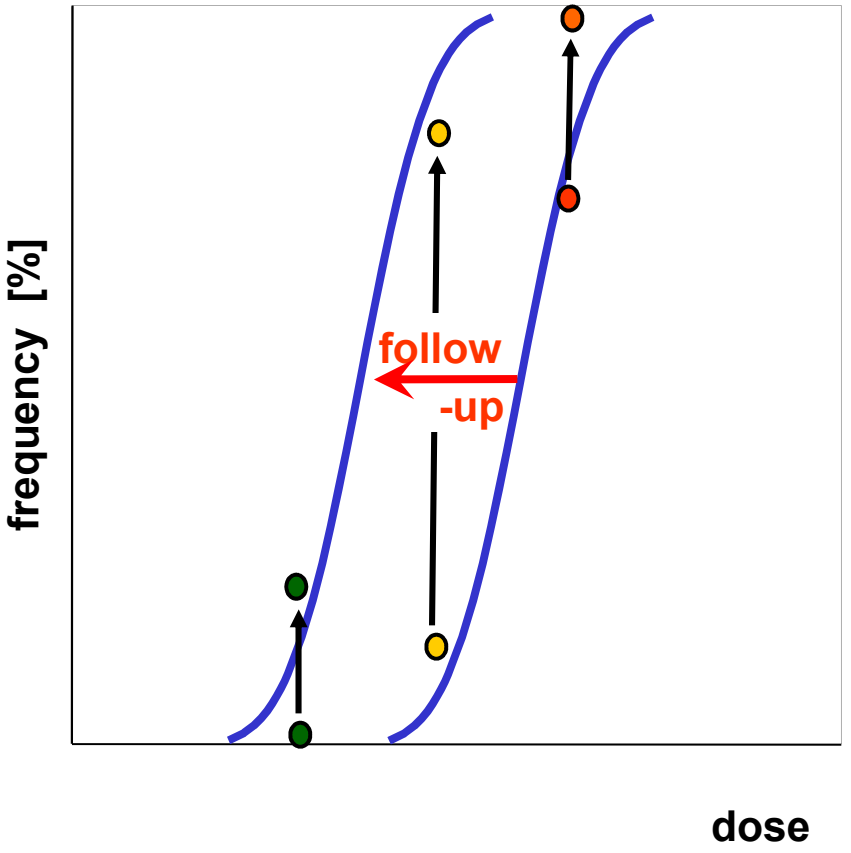


Late effects



Late effects – Dose-effect relationship



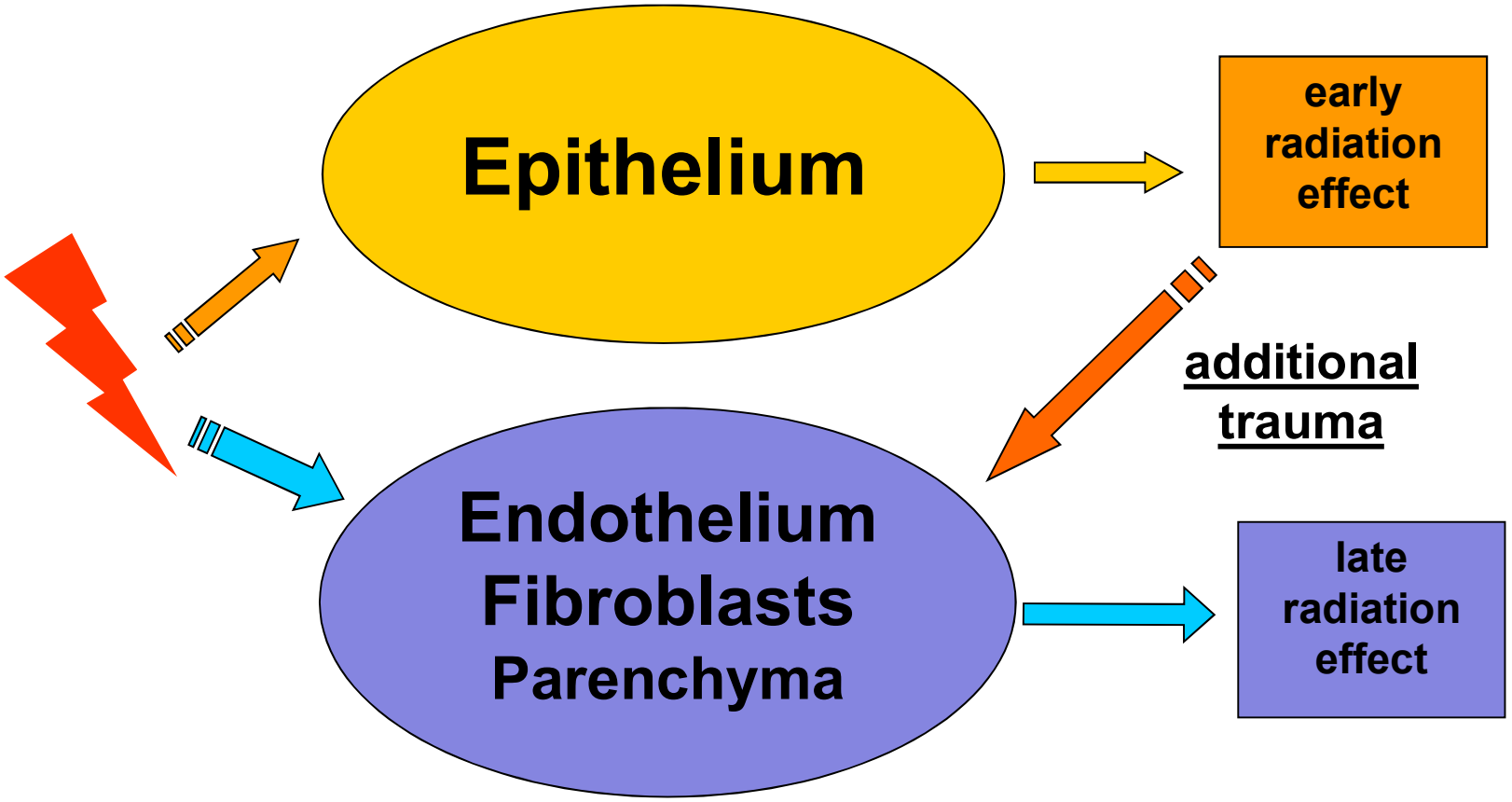


Tolerance doses for late responding tissues require information on the duration of follow up!

Consequential late effects (CLE)

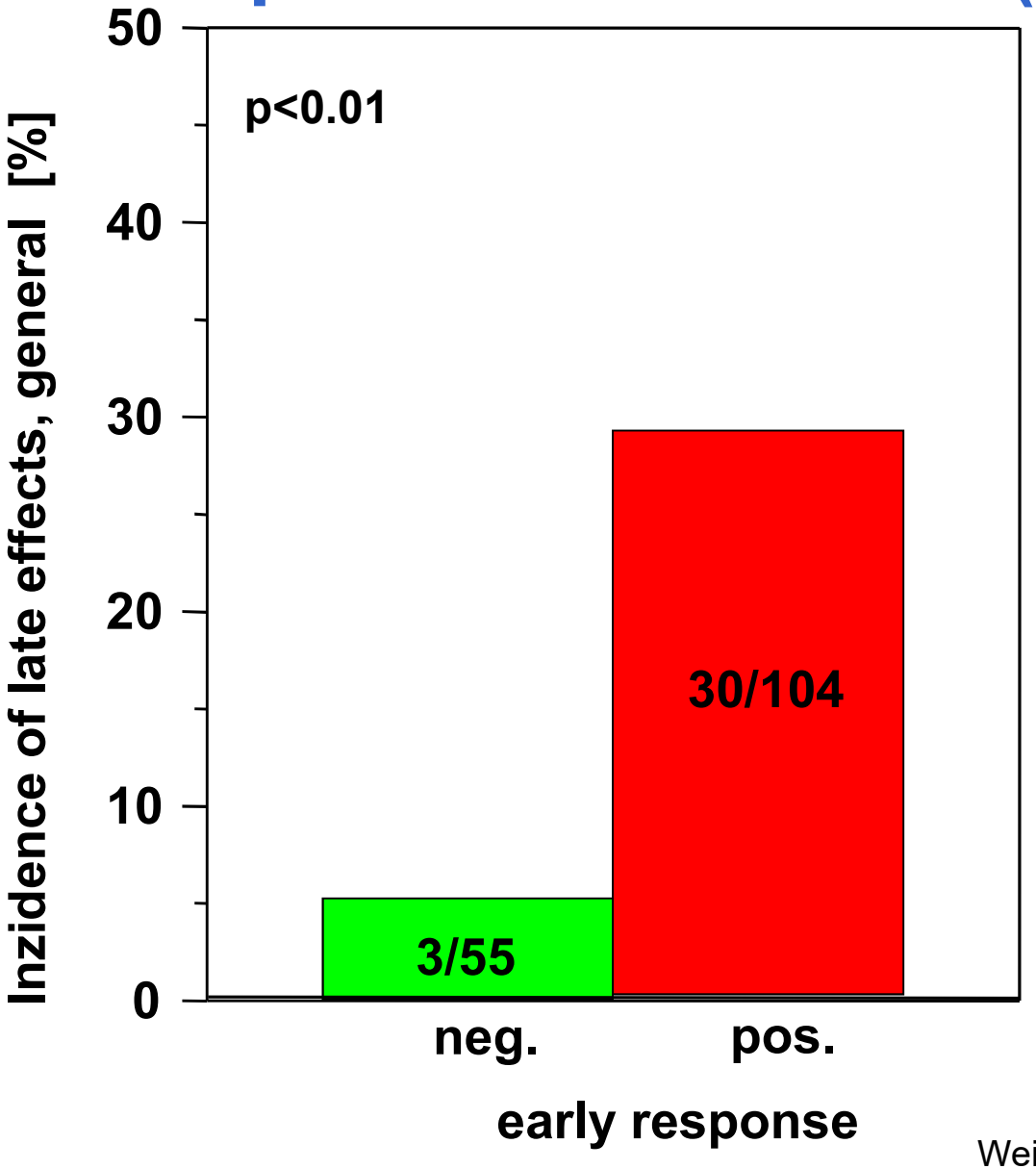
Late radiation effects, which are influenced by the extent (severity, duration) of the corresponding early effect *in the same organ/tissue*.

Consequential late effects (CLE): Mechanisms



modified from: Dörr and Hendry, Radiother. Oncol. 61, 2001, 223-231

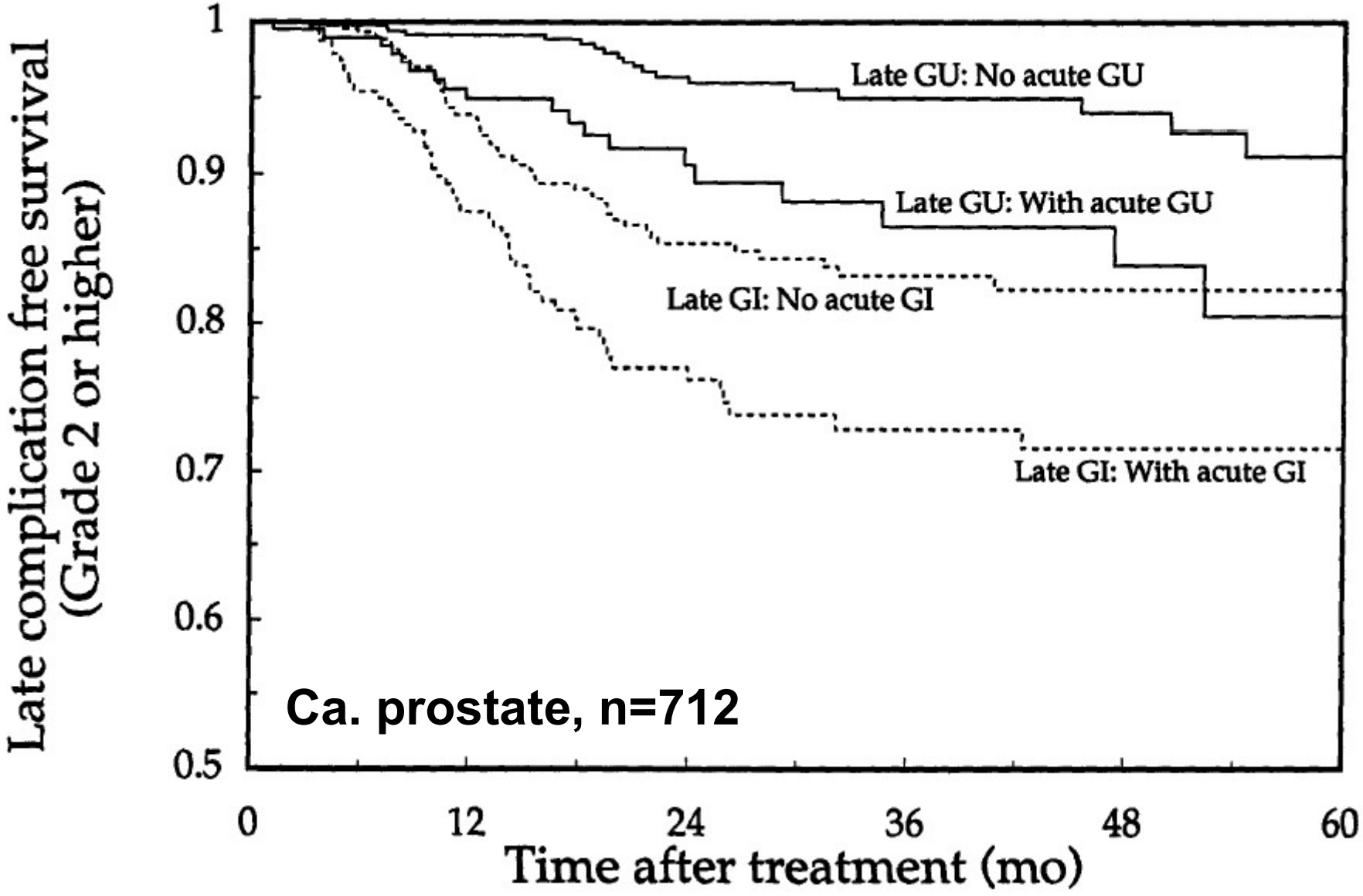
Consequential late effects (CLE): Examples



Endometrium-Ca I+II, adjuvant radiotherapy n=159

Weiss et al., Radiother. Oncol. 53, 1999, 37-44

Consequential late effects (CLE): Examples



Schultheiss et al., IJROBP 7, 1997, 3-11

Radiotherapy and Oncology 122 (2017) 212–216

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

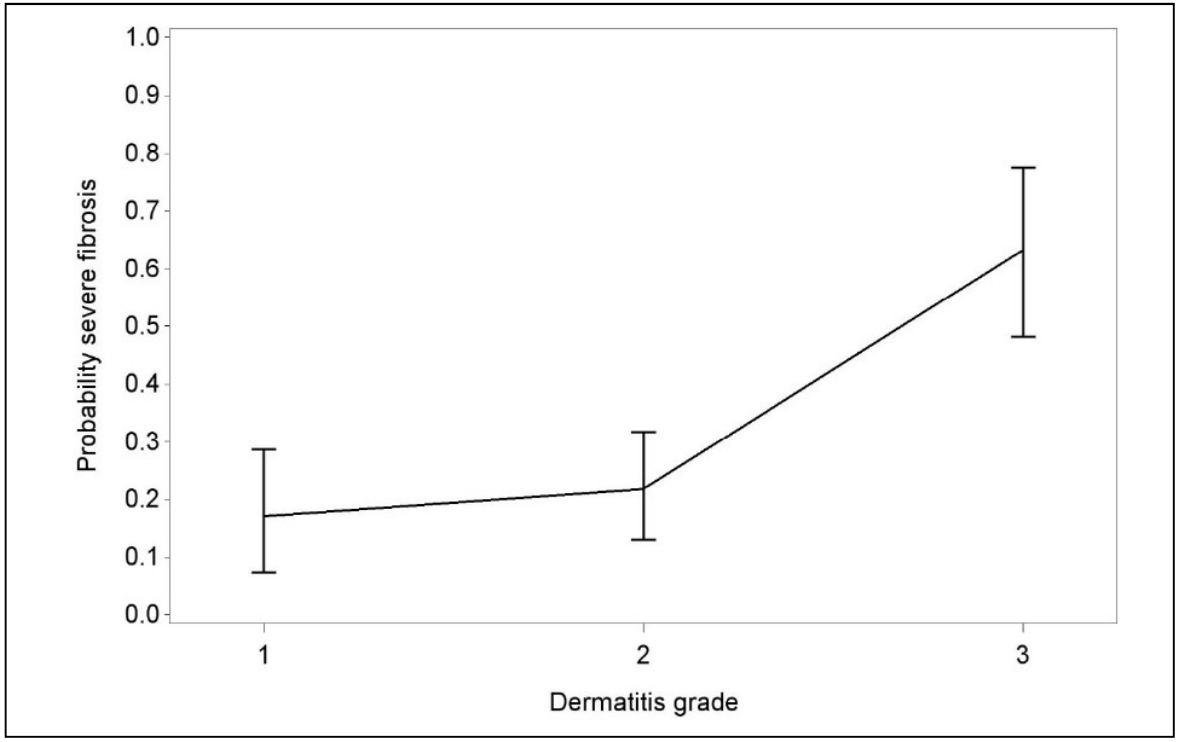
Morbidity of head and neck radiotherapy

Radiotherapy induced dermatitis is a strong predictor for late fibrosis in head and neck cancer. The development of a predictive model for late fibrosis

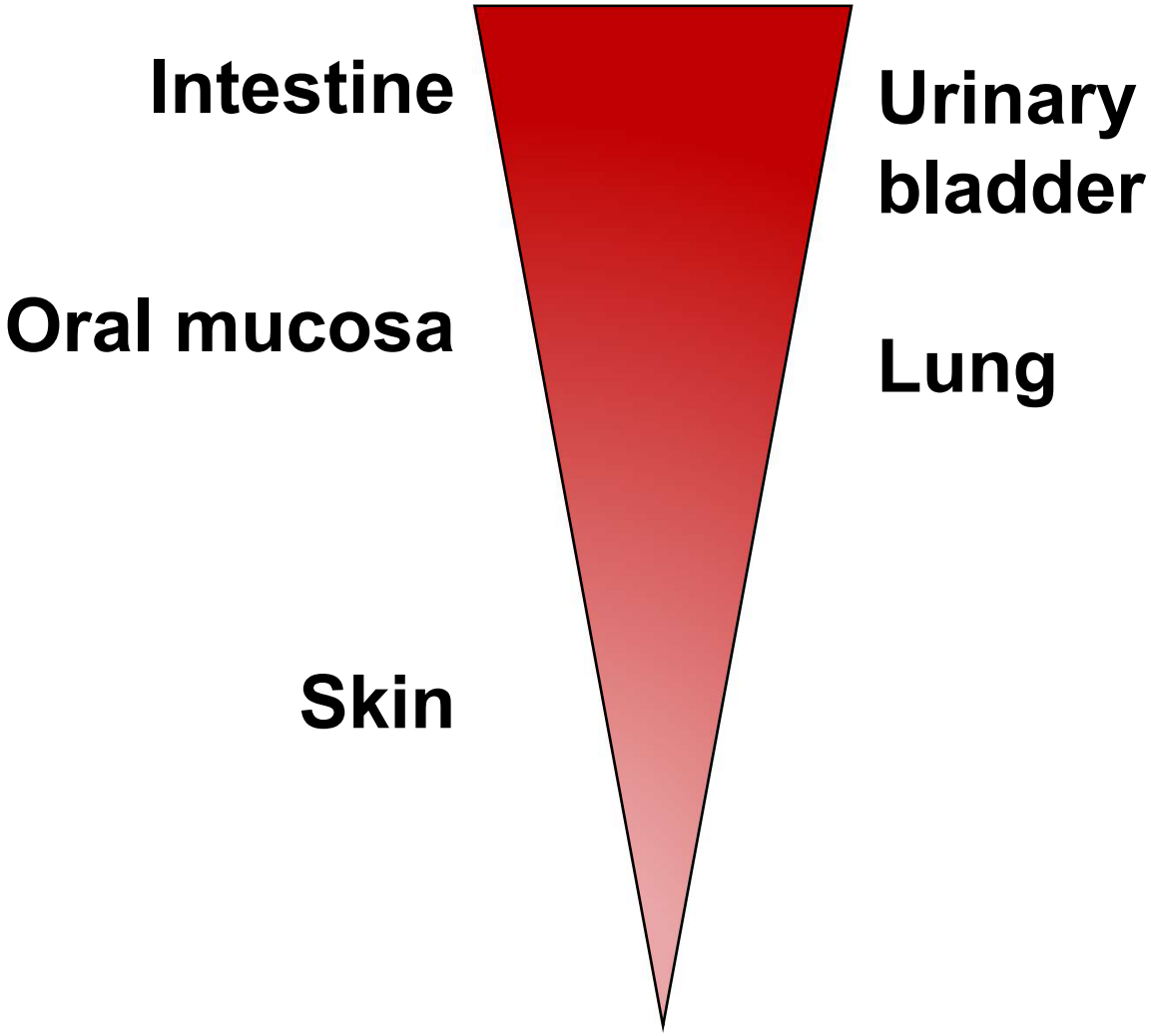
Daan Nevens *, Fréderic Duprez, Jean Francois Daisne, Annouschka Laenen, Wilfried De Neve, Sandra Nuyts

University Hospitals Leuven, Belgium

Conclusion: A model for the prediction of fibrosis $RTOG_{2-4}$ following R(C)T for head and neck cancer is presented with an AUC of 0.92. Interestingly, radiodermatitis grade $\geqslant 3$ at the end of R(C)T is associated with $RTOG_{2-4}$ fibrosis at 6 months.

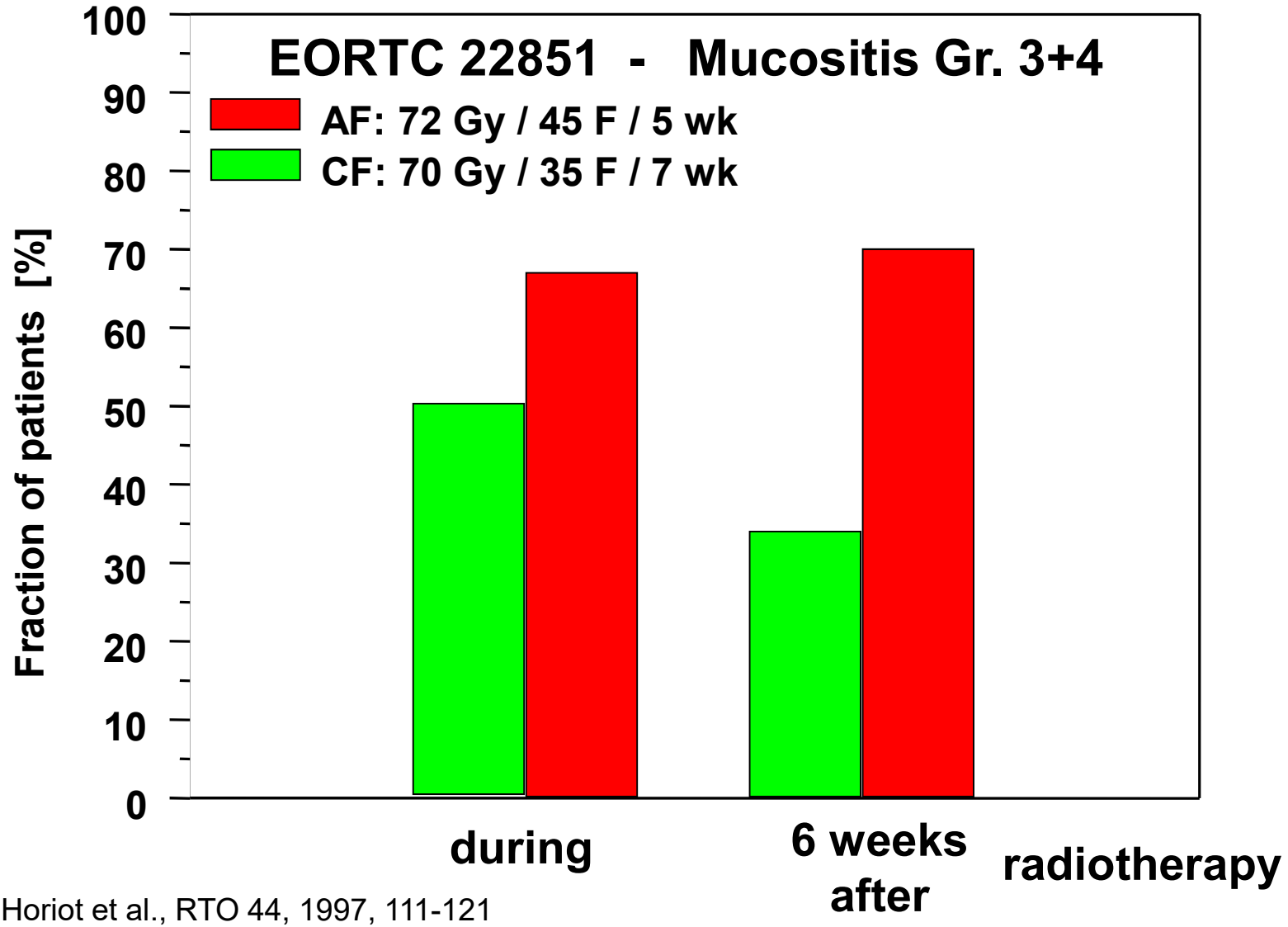


Consequential late effects



CLE: Consequences

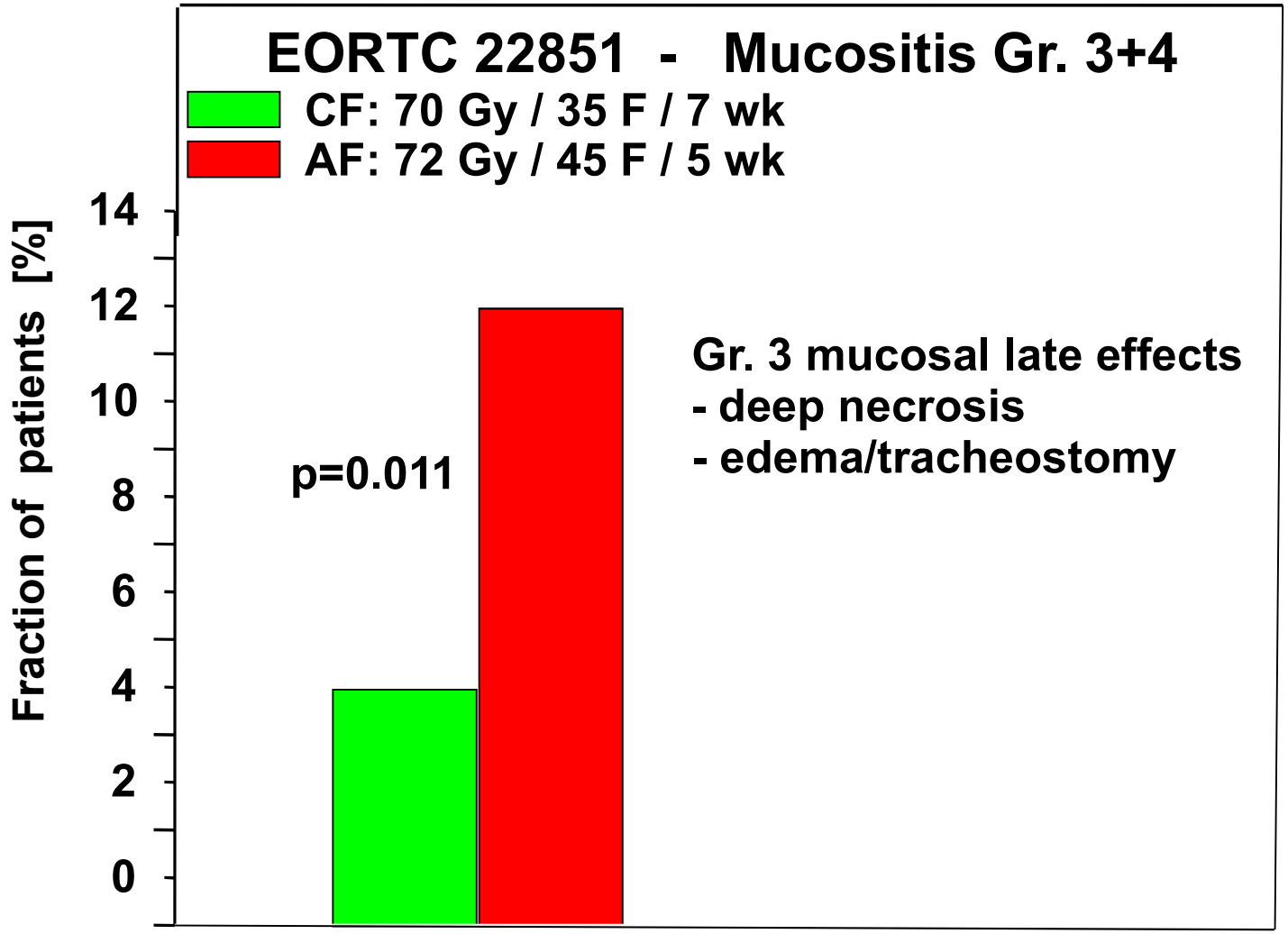
Effect of overall treatment time



data from: Horiot et al., RTO 44, 1997, 111-121

CLE: Consequences

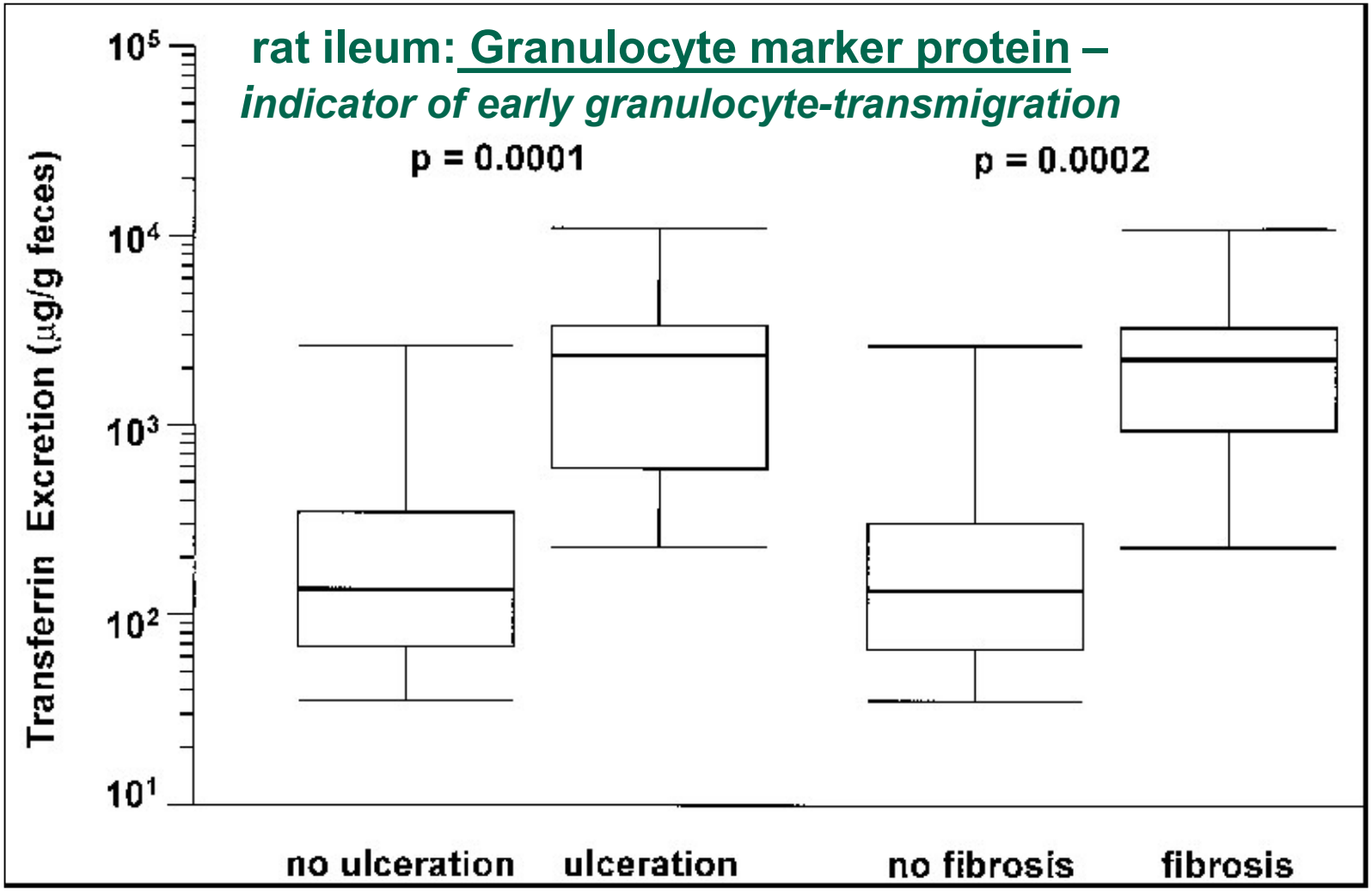
Effect of overall treatment time



data from: Horiot et al., RTO 44, 1997, 111-121

CLE: Consequences

Early biomarkers

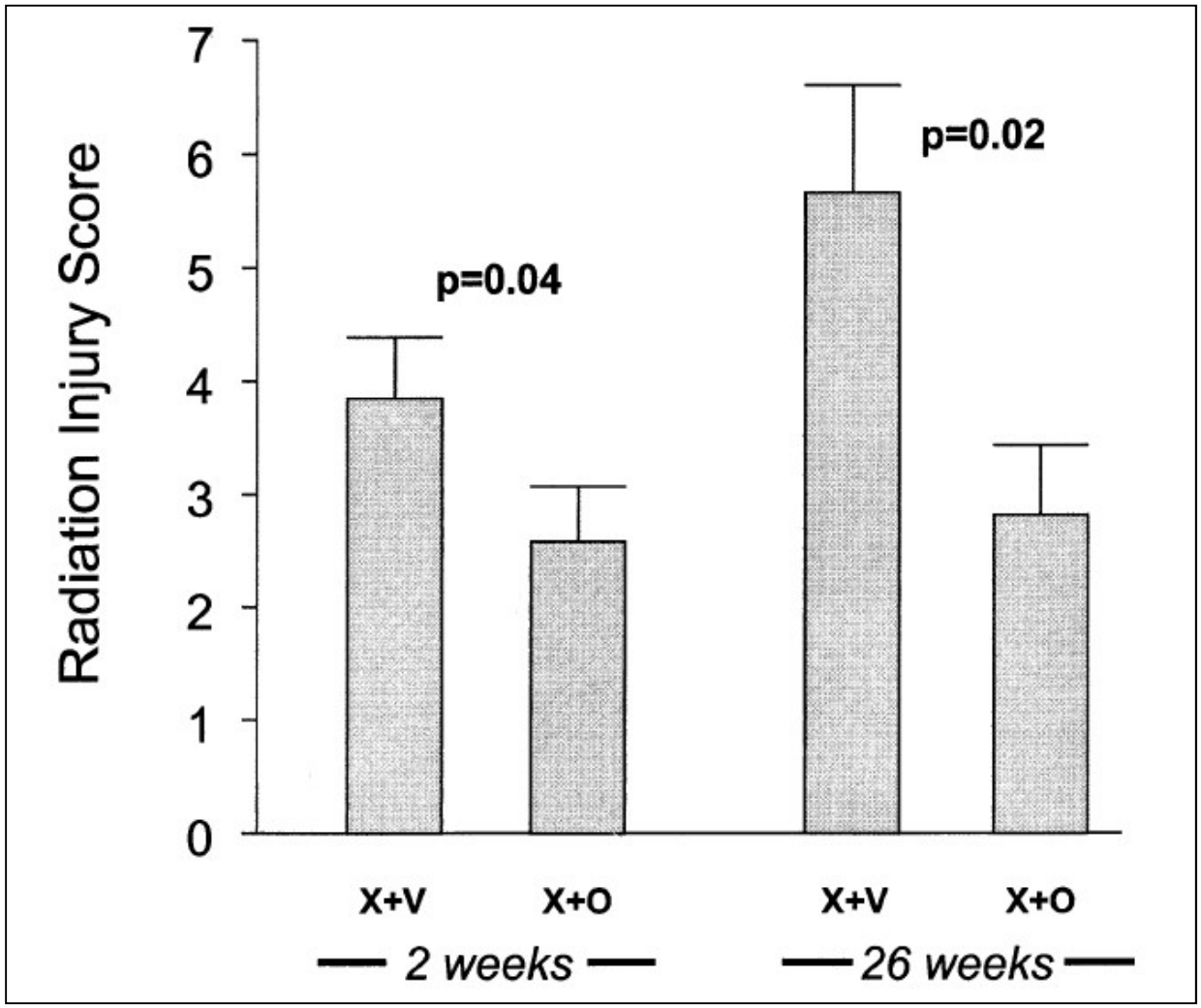


Richter et al., Radiat. Oncol. Invest. 5, 1997, 275-282

CLE: Consequences

Modulation of early effects

rat ileum: octeotride – *reduction of proteolytic pancreatic activity*



administration
day -2 to +10

Wang et al.,
IJROBP 45, 1999, 1289-1296

Take home message I

Early effects:

- turnover tissues - proliferating cells
- latent time: ≠ dose; ~ tissue biology
- maximum severity: ~ dose
- time to restoration: ~ dose

Take home message II

Late effects:

- **all tissues**
- **complex pathogenesis**
  (parenchyma, fibroblasts, endothelium, macrophages)
- **irreversible (?)**
- **dose-dependent latency**
- **dose-dependent progression rate**
- **incidence (tolerance) ~ follow up**

Take home message III

Consequential late effects (CLE):

- **radiobiological characteristics of early effects (fractionation, overall treatment time)**
- **correlate with markers for early effects**
- **modulated by treatment of early effects**

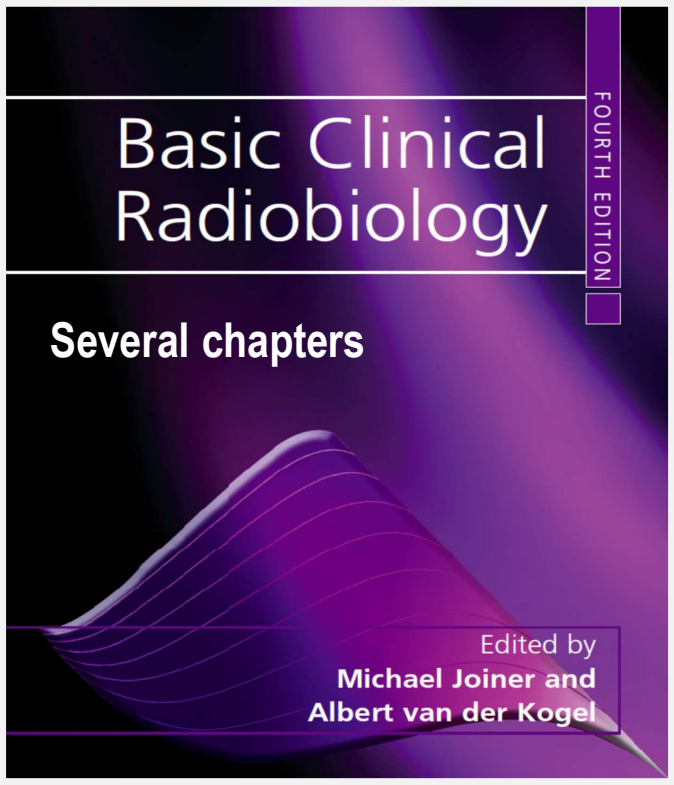
Clinical side effects and their quantification

Karin Haustermans

Department of Radiation Oncology, University Hospitals Leuven, Belgium

Overview

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

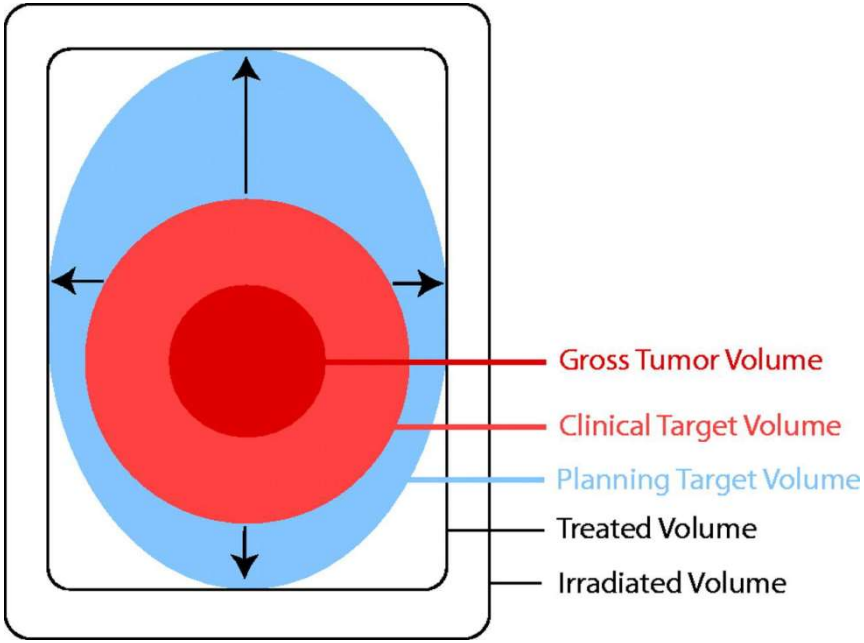


"As soon as we solve one problem, another one appears.
So let's keep this problem going for as long as we can!"

Why?

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



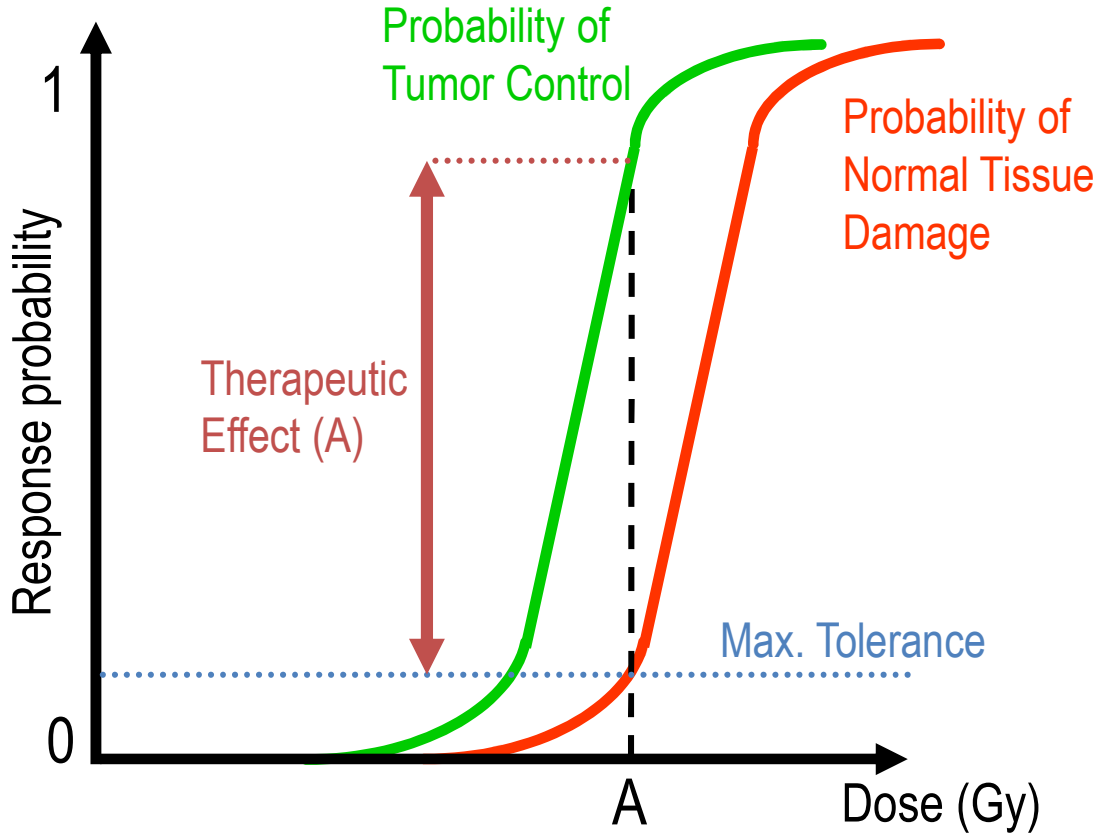
Side-effects cannot, a priori, be considered a consequence of incorrect treatment

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

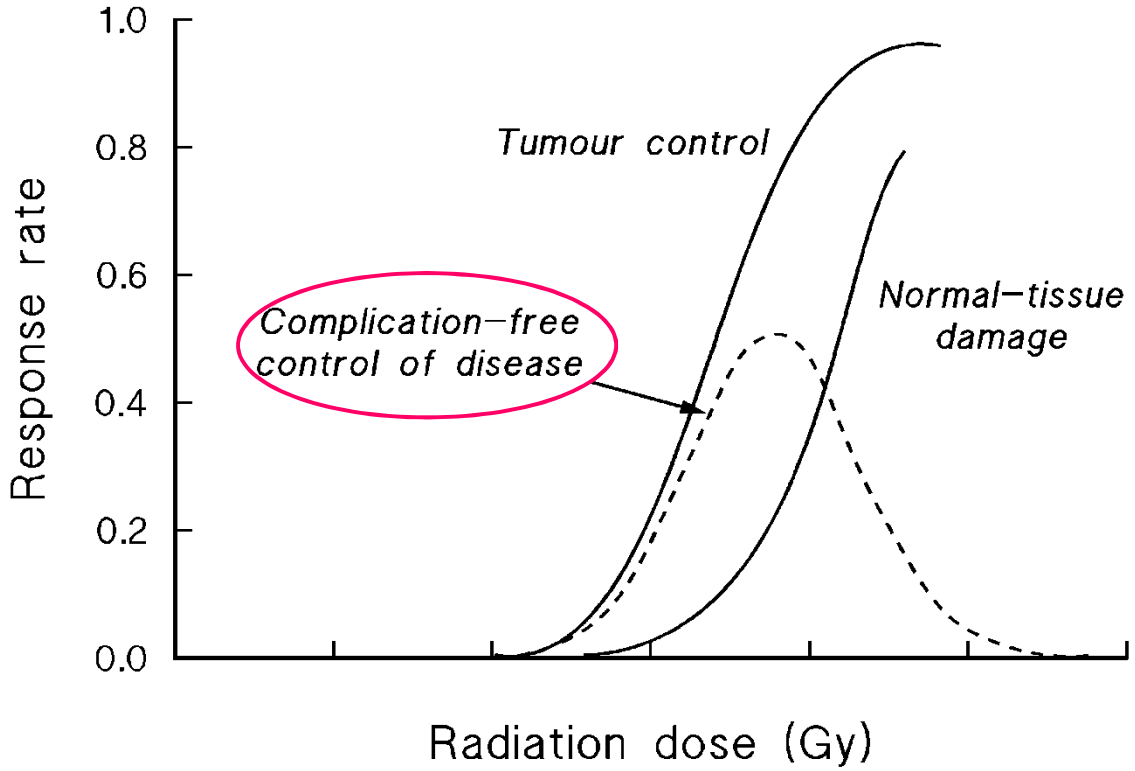
Why assess adverse effects?

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



Why assess adverse effects?

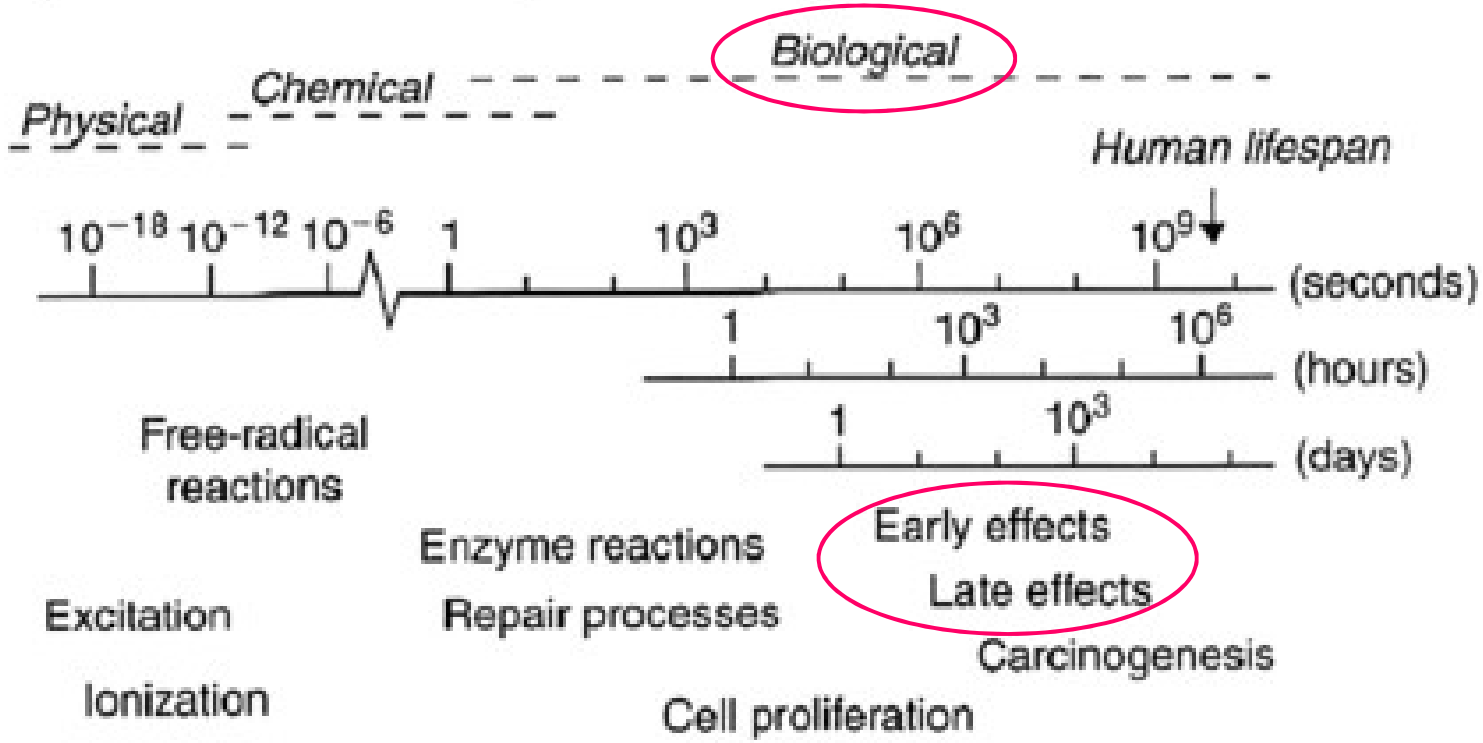
- Manifestation of side-effects = indicator for optimum treatment and maximum TCP



What?

Time-scale of radiation effects

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

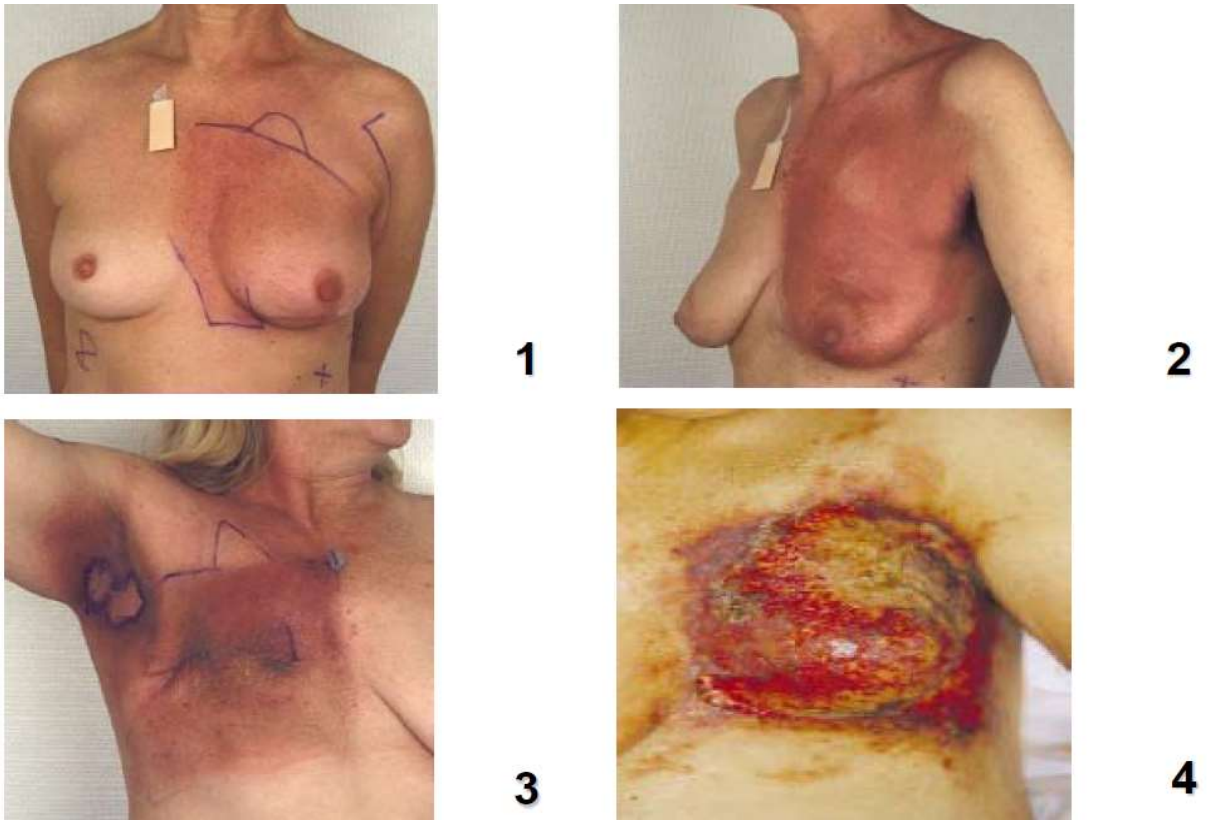


Radiation-induced effects may already appear during IR but may also extend up to many years after exposure to IR and are due to killing of stem cells

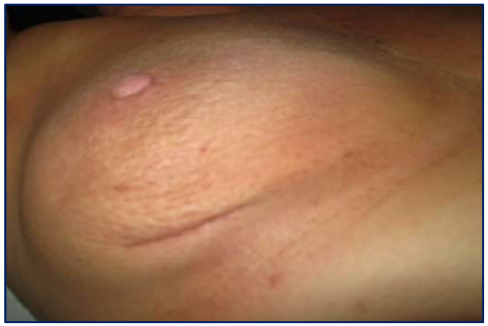
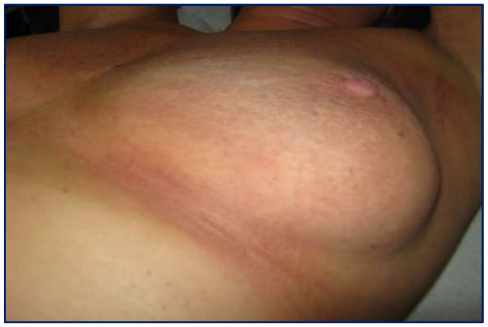
Typical clinical manifestation of EARLY normal tissue reactions

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

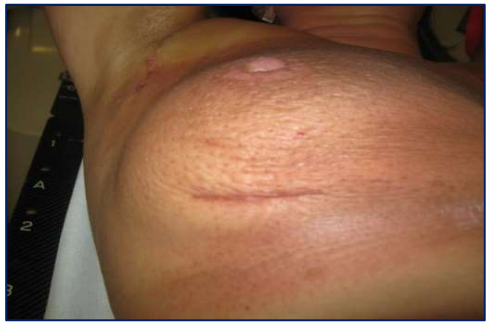
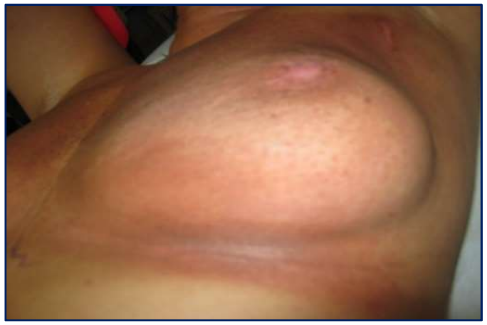
Early skin reactions grade 1-4



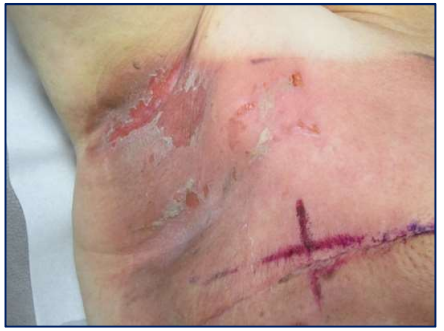
From Marianne Nordsmark

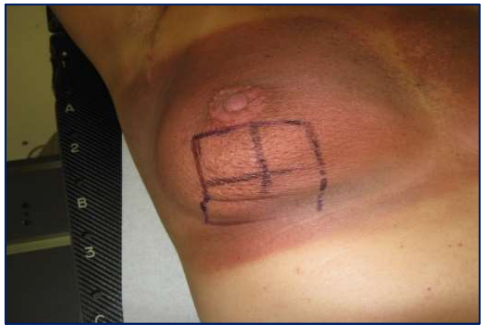
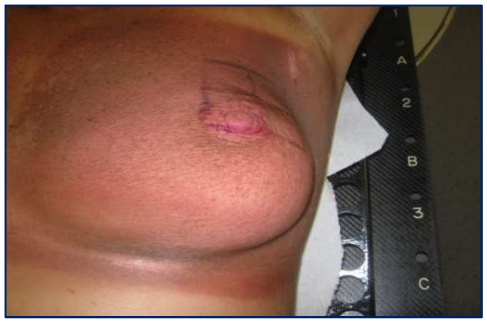



36Gy

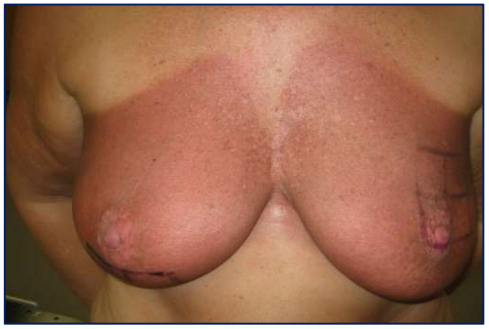



46Gy



52Gy



66Gy

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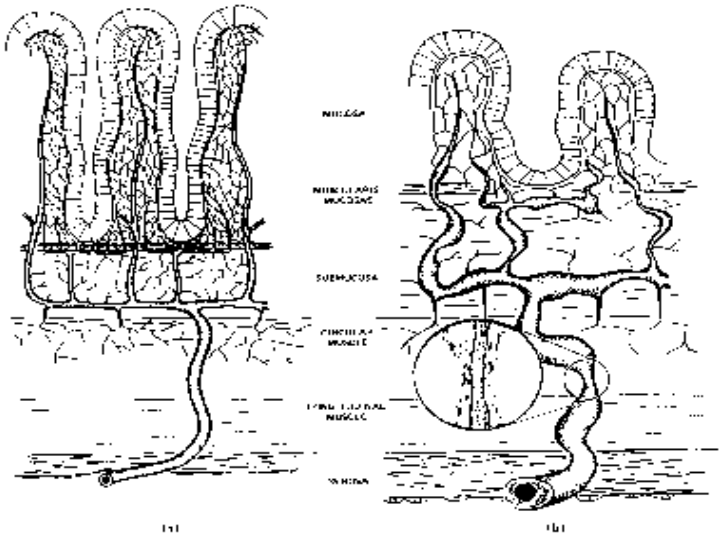
Small bowel toxicity

- 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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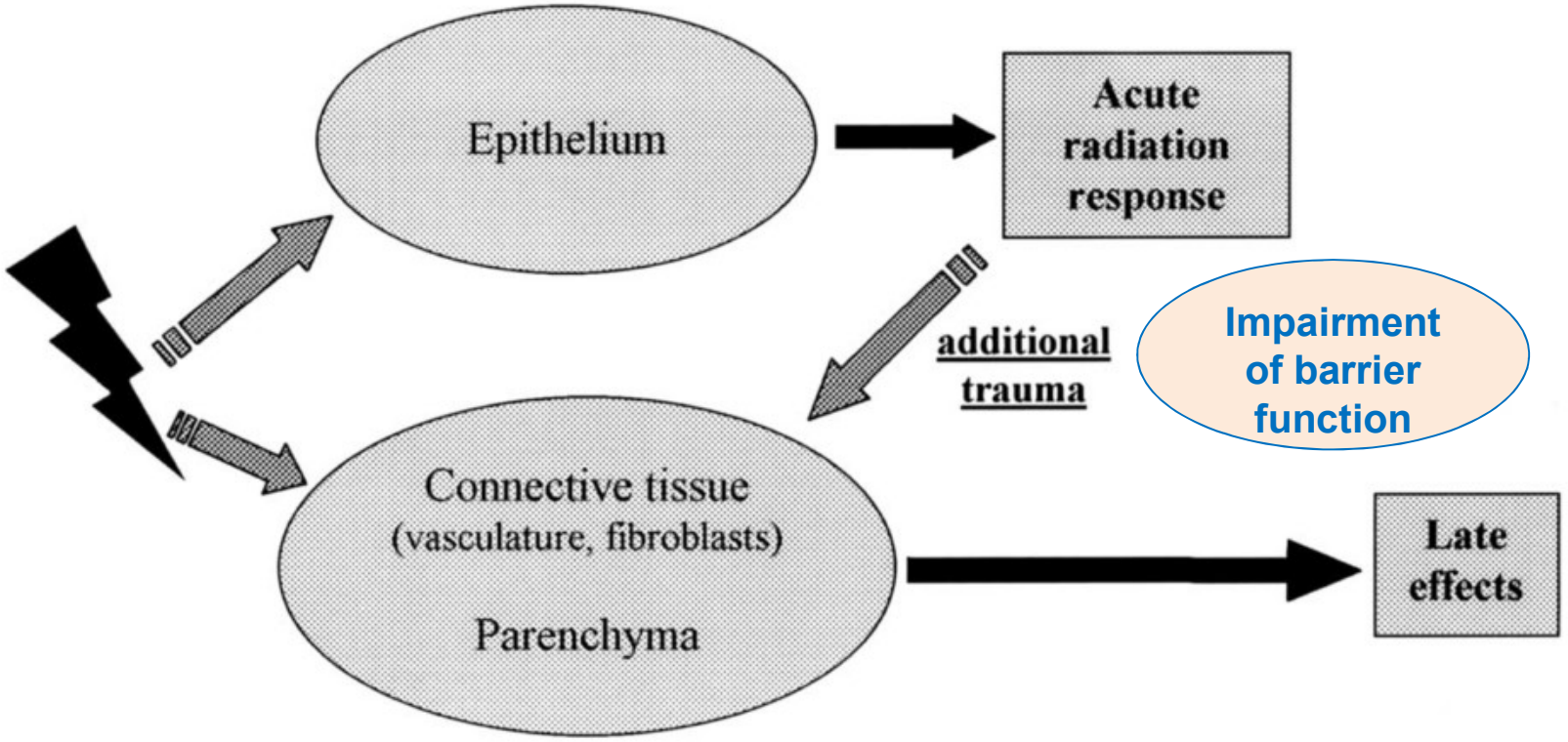
Consequential late effects

Dörr, Radiother Oncol 2001

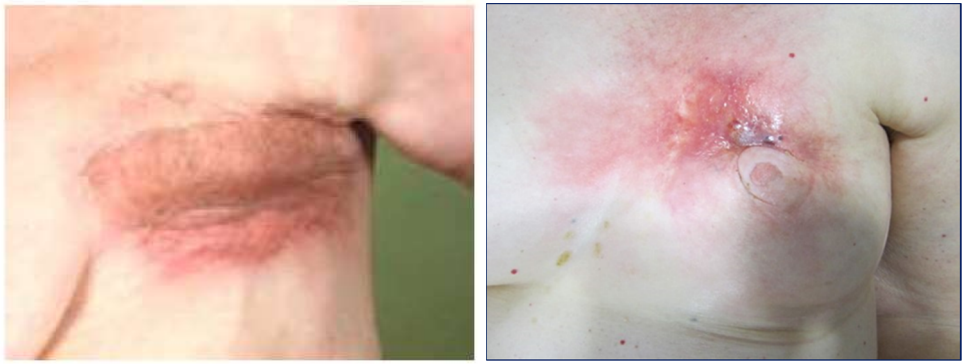


Typical clinical manifestation of LATE normal tissue reactions

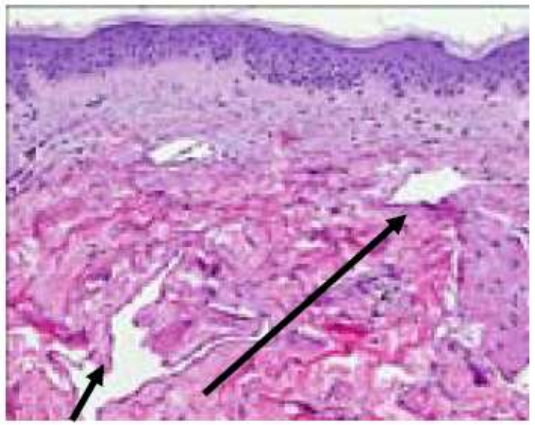
- Fibrosis
- Lymphoedema
- Myelitis
- Nephritis
- Osteoradionecrosis
- Telangiectasia
  - Cosmetic problem vs bleeding

Late skin reactions: telangiectasia

Skin - cosmetic



Histopathology



Vessel dilatation

Small bowel toxicity

- Radiation enteritis: oedema, hyperemia, stiffness

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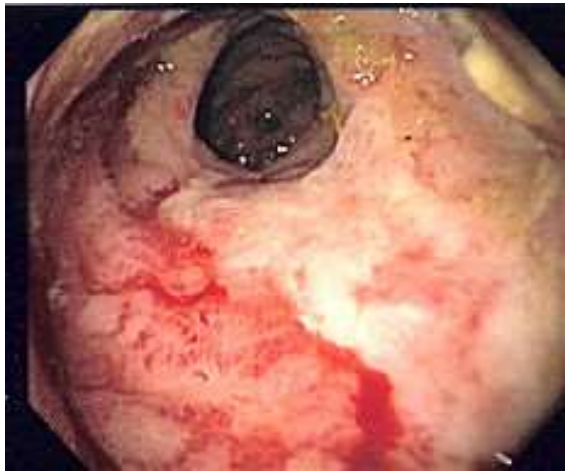
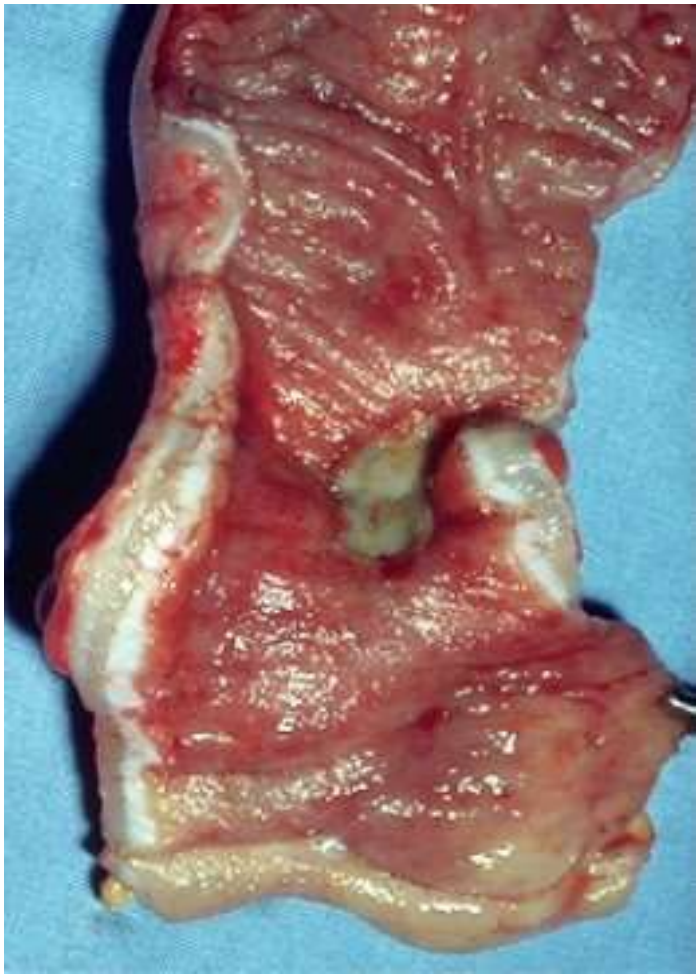
Chronic radiation proctitis

- 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



Radiation proctitis

- Radiation ulcer
- Fibrosis
- Bleeding



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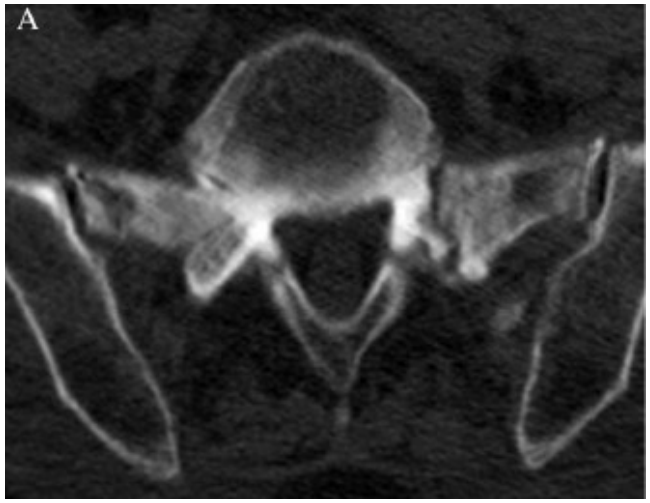
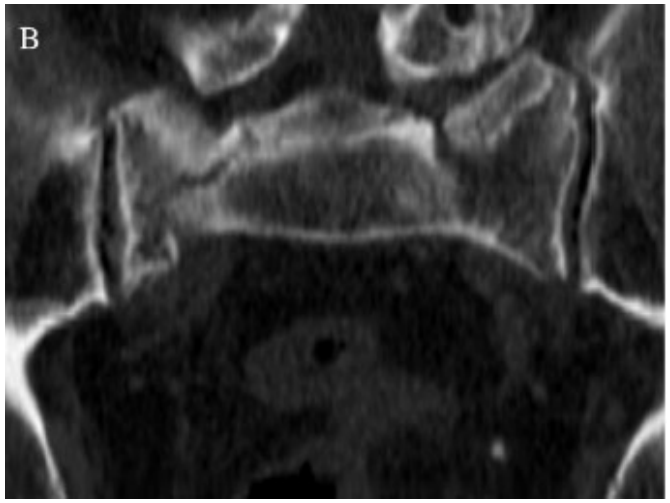
Sacral fractures

Kim et al., IJROBP 2012

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

Underdiagnosed!





Lapina et al. Medicina 2014

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Sacral fractures

- Risk factors

Kim et al., IJROBP 2012

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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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

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)

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

Relevant factors

- Tumor-related factors influencing normal tissue reactions
  - Stage of disease
  - Volume of the tumor
  - Lymphatic spread

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

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)

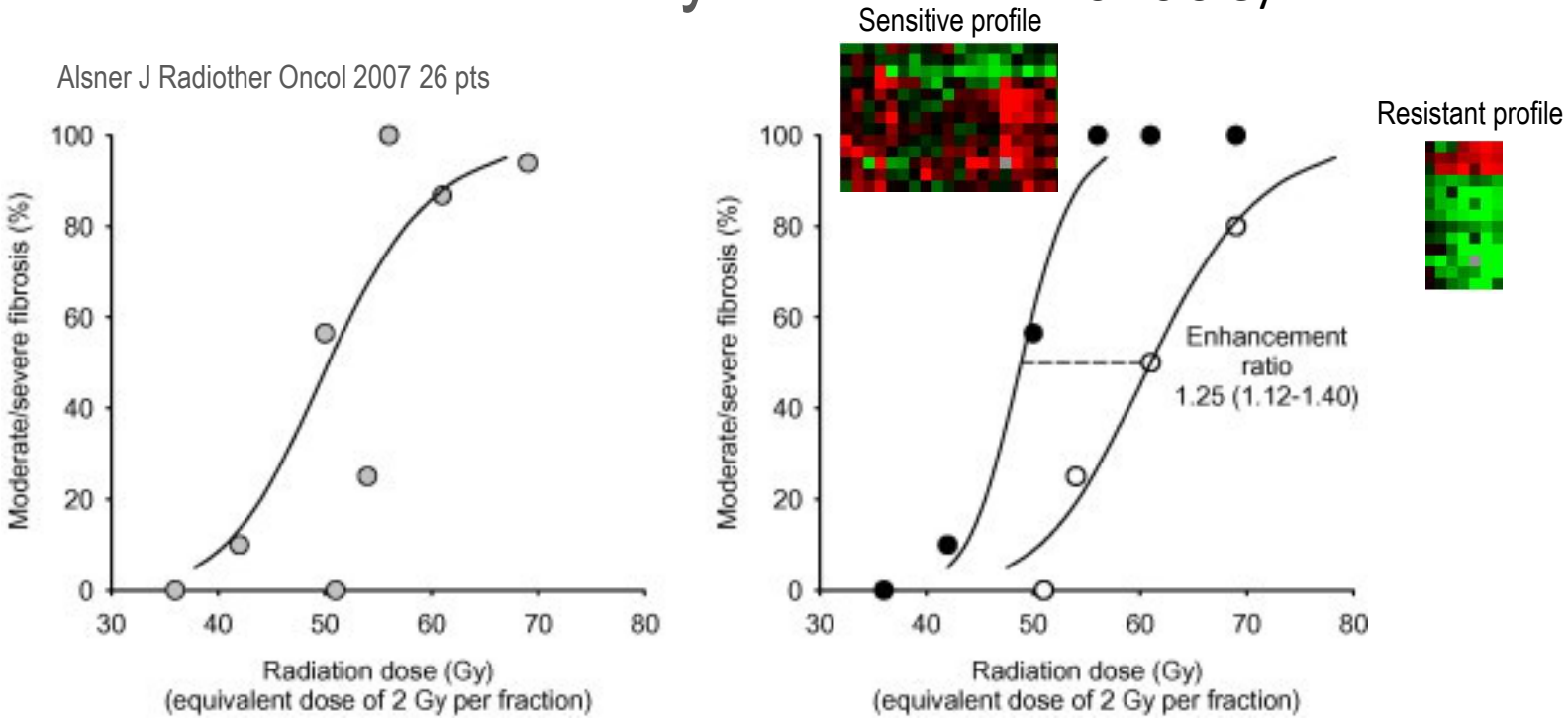
Relevant factors

- 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)

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

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)

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

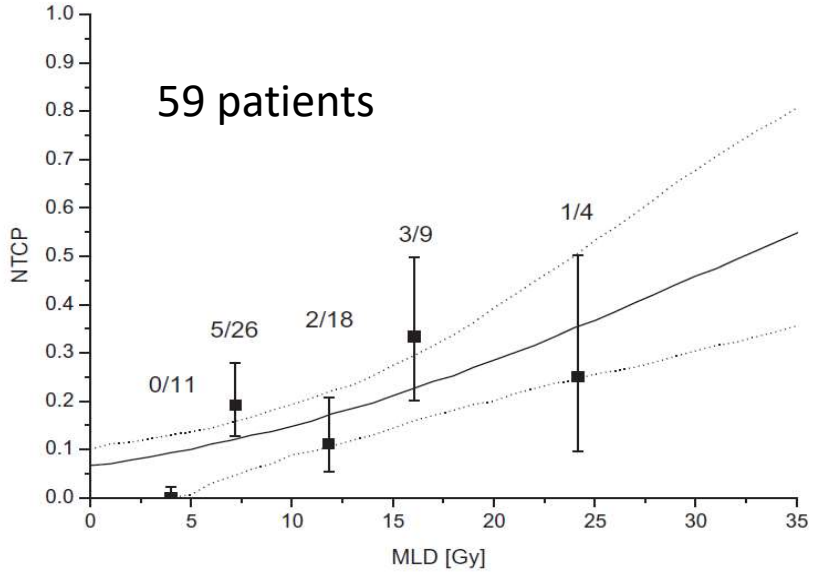


Fig. 1. Patients were grouped in bins of 5 Gy MLD, observed incidences of radiation-induced pneumonitis (RP) for the median dose within each bin are shown and the error bars represent the 68% confidence interval (CI) of the observed incidences. The thick solid line shows the best fit of the NTCP model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

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

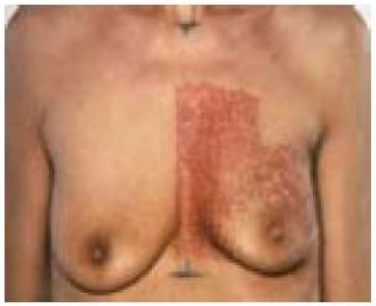
Guckenberger Radiother Oncol 2010 59 pts

Relevant factors

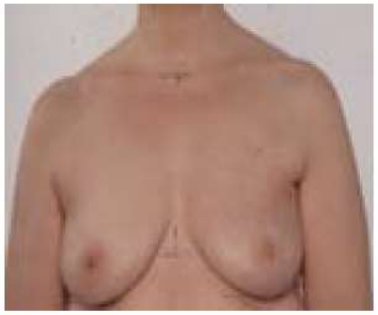
- Radiobiological-related factors influencing normal tissue reactions
  - Intrinsic radiosensitivity (L2.3)
  - Total radiation dose (L3.5)
  - Technique and irradiated volume (L3.6)
  - Fractionation schedule (late reactions) (L2.3)
  - Overall treatment time (early reactions) (L2.4)
  - Concomitant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

Relevant radiobiological factors

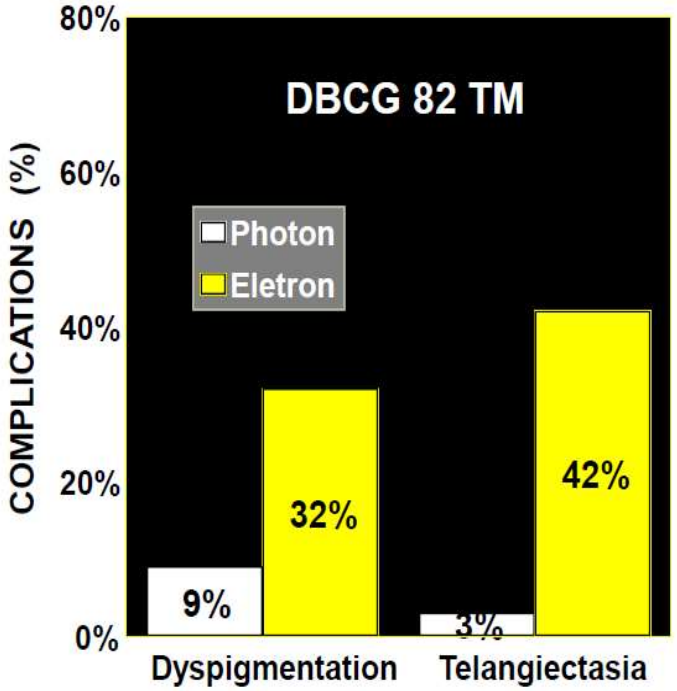
- Technique: electrons vs photons



Electron irraditation



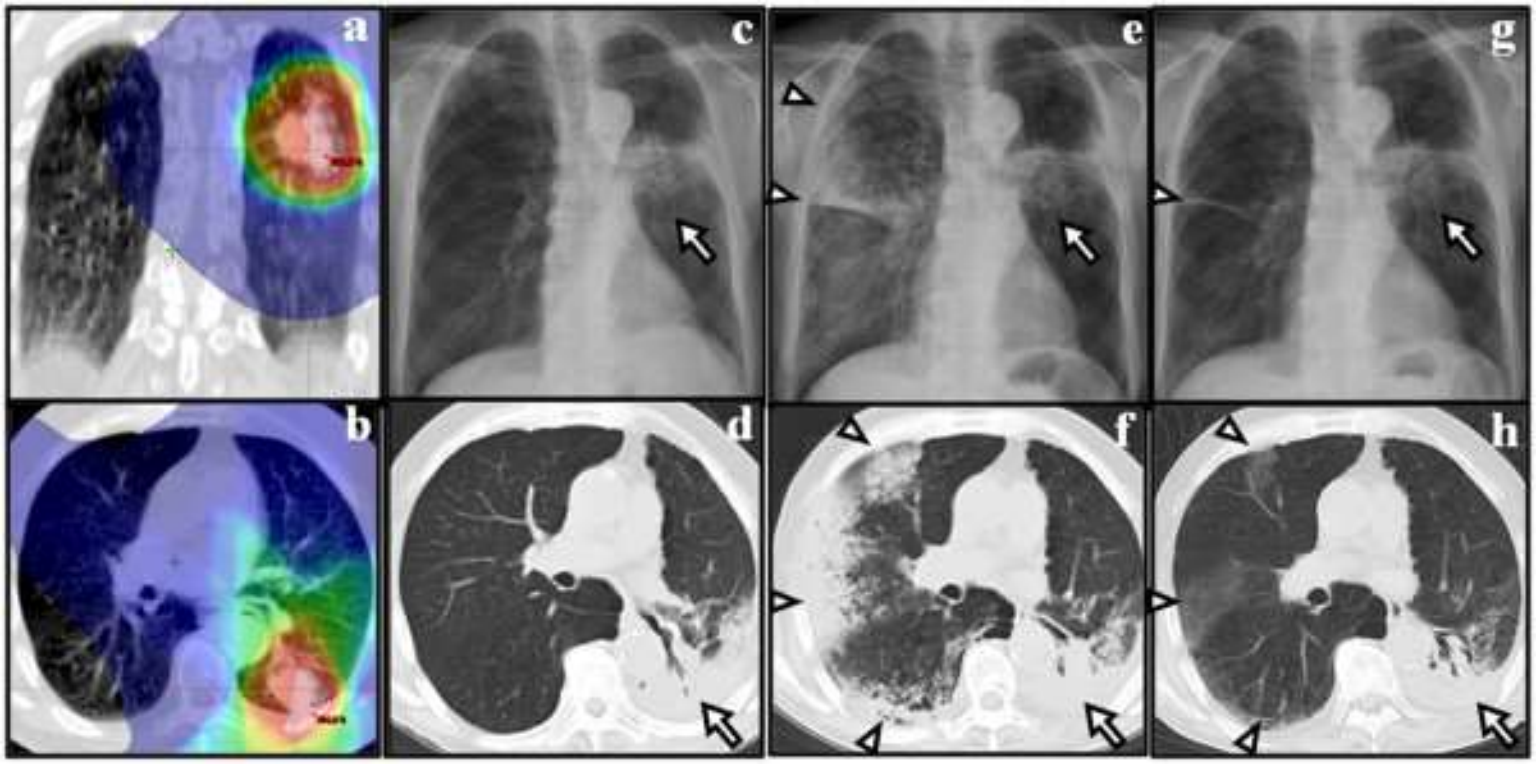
Photon irraditation



Johansen et al. 1998

Relevant radiobiological factors

- Technique: stereotactic ablative radiotherapy



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

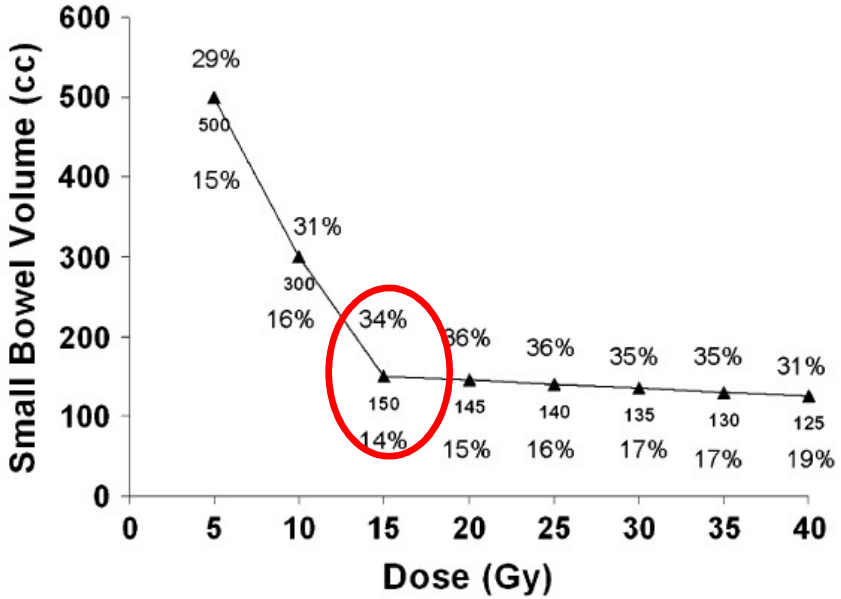
Murai Radiat Oncol 2012 189 pts

Small bowel toxicity

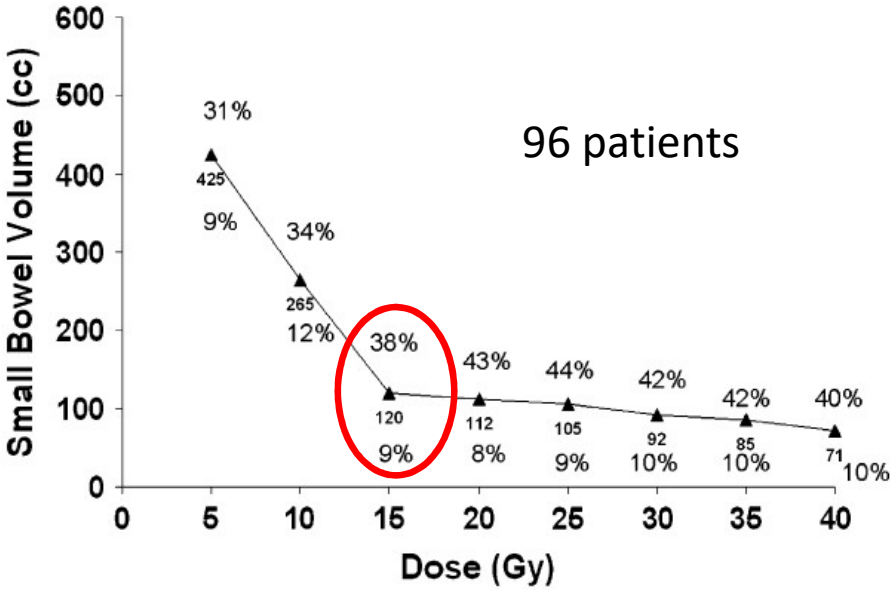
- Acute small bowel toxicity depends on irradiated volume

Better modeling of preoperative patients

Previous parameters



Revised parameters



ESTRO School

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

Relevant radiobiological factors

- Irradiated volume with SBRT

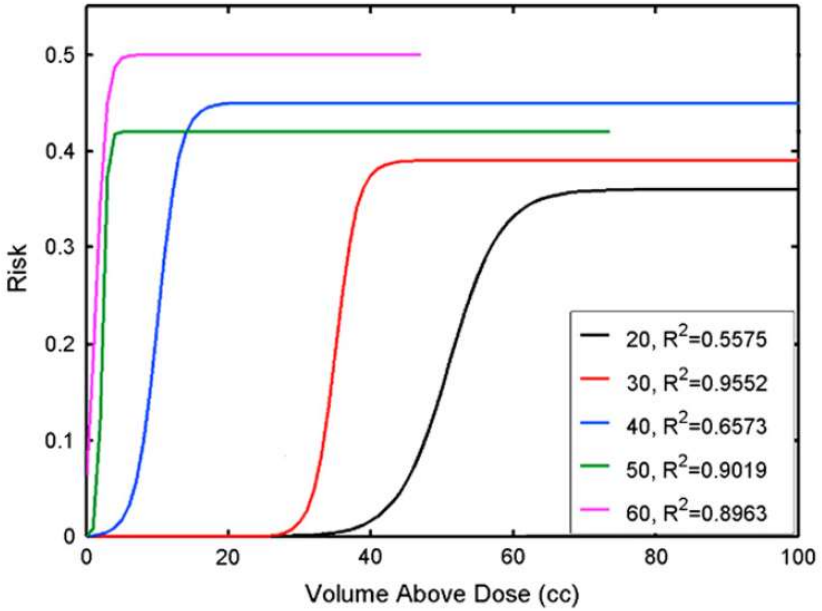


Fig. 1. Volume–risk analysis based on median effective concentration dose–response model for designated dose levels (20, 30, 40, 50, and 60 Gy) for development of severe chest wall toxicity.

Dunlap Int J Radiat Oncol 2010 60 pts

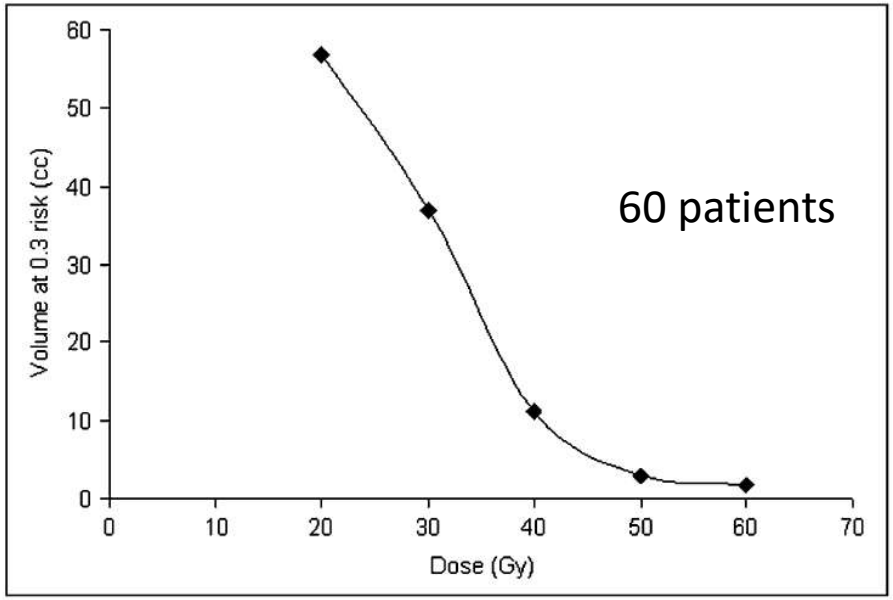


Fig. 2. Dose–volume relationship for 30% risk of severe chest wall toxicity.

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

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)

Relevant radiobiological factors

- Fractionation schedule START-A

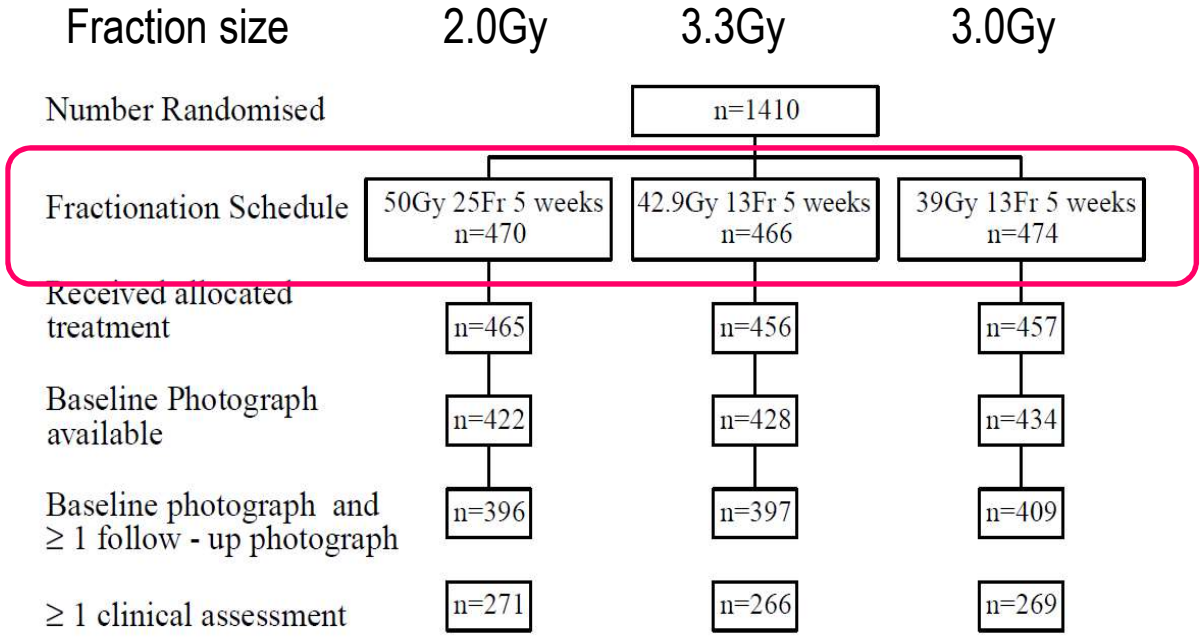


Fig. 1. Number of patients randomised into each fractionation schedule and with available follow-up data.

Yarnold Radiother Oncol 2005

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

α/β of 3.6 Gy
(95% CI 1.8-5.4 Gy)

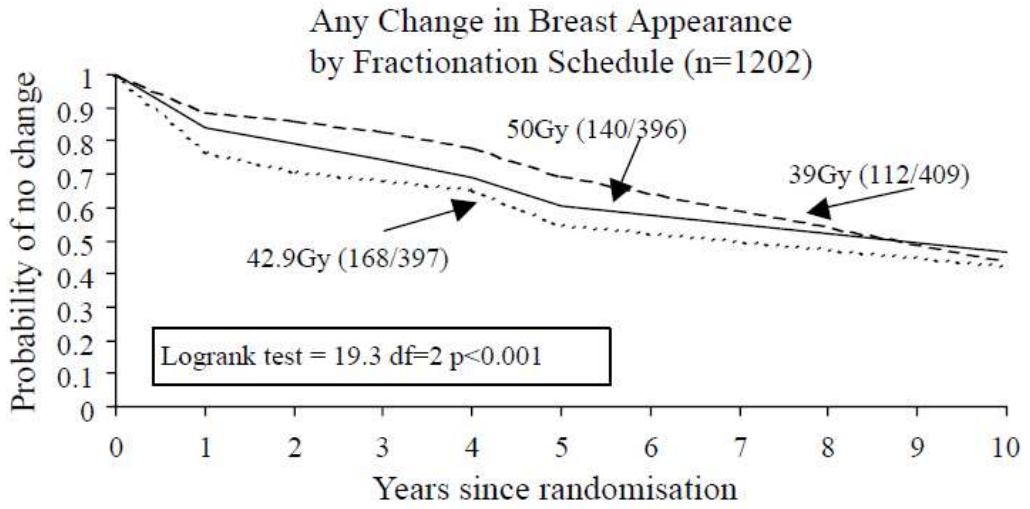


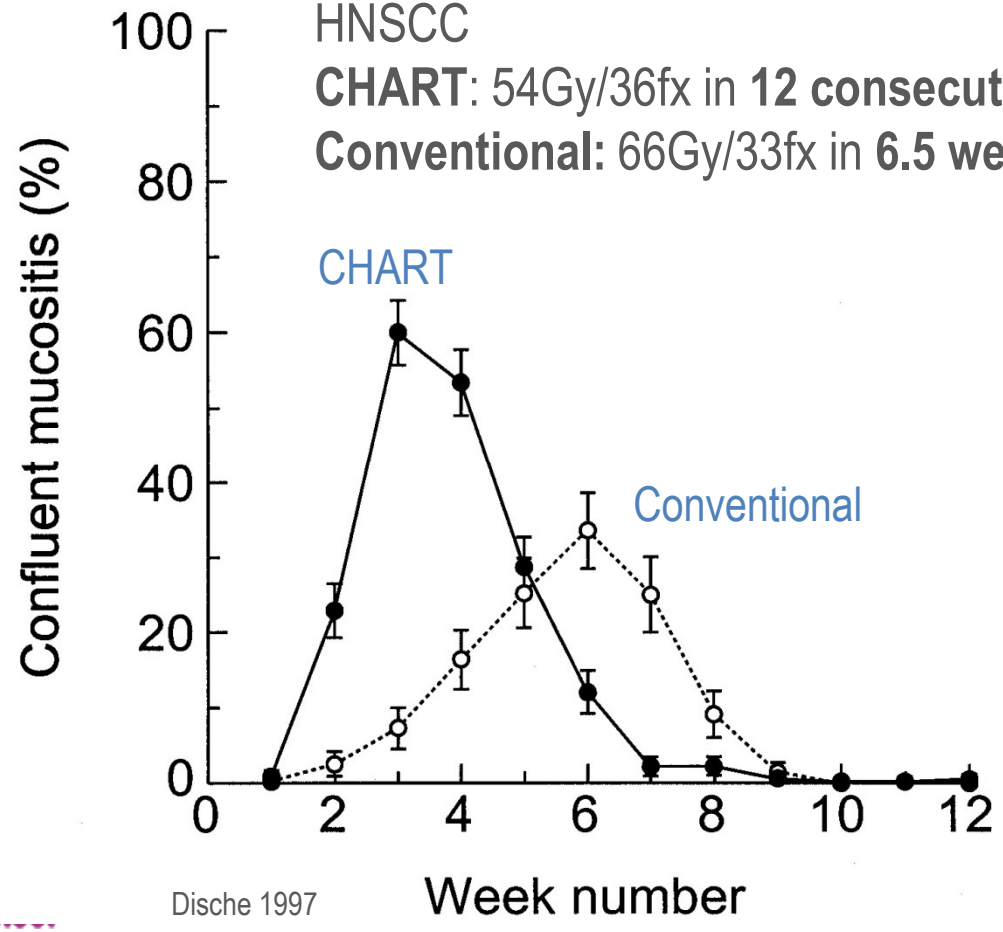
Fig. 2. Probability of any change in breast appearance late radiation effect ten years after radiotherapy by fractionation schedule.

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)

Relevant radiobiological factors

- Overall treatment time



Shorter OTT resulted in aggravation of early side effects

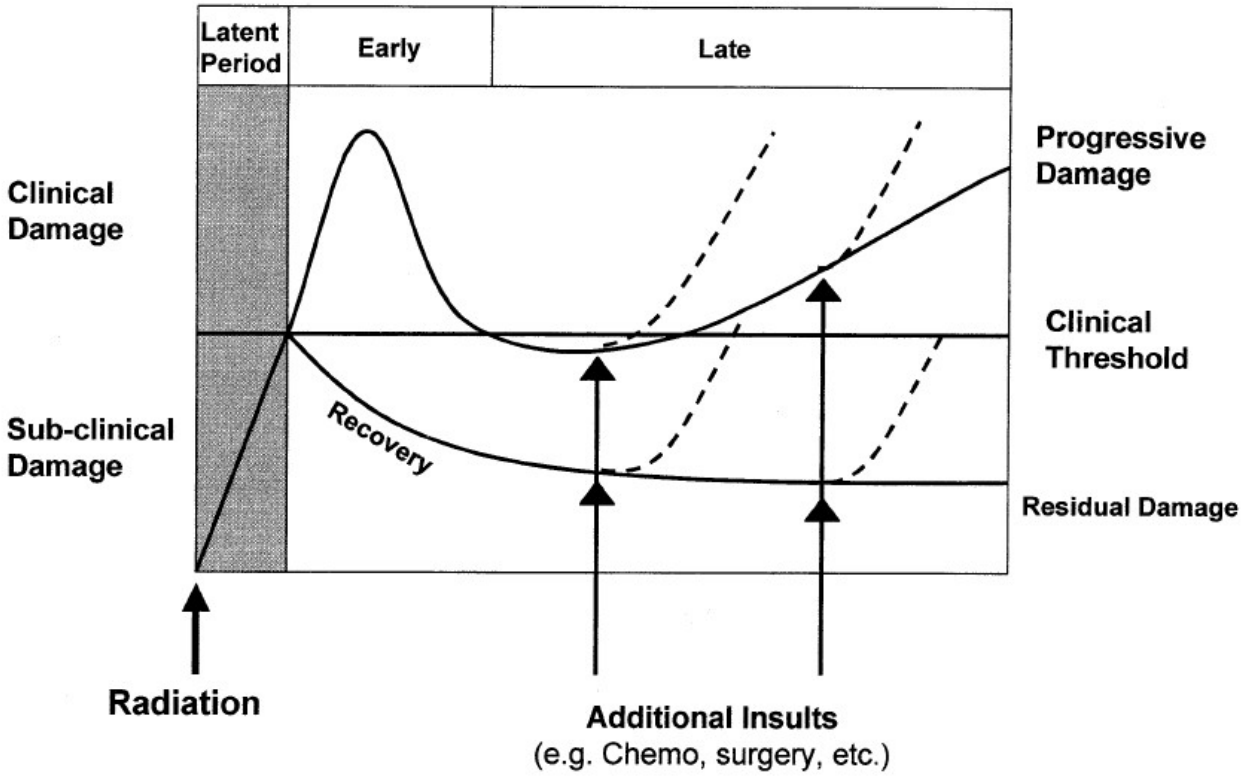
Dische 1997

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)

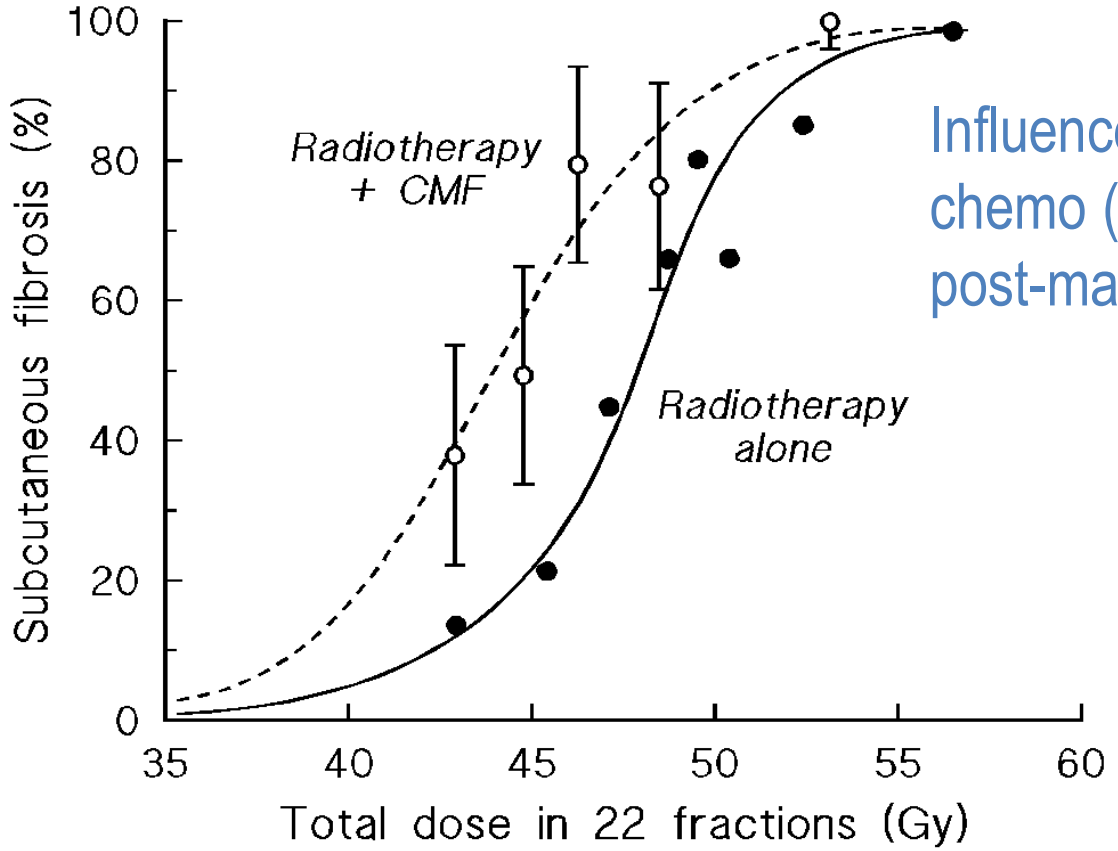
Relevant radiobiological factors

- Combined modality treatment



Relevant radiobiological factors

- Concomitant treatment



Influence of adjuvant chemo (CMF) on post-mastectomy RT

Bentzen 1989

How?

Treatment-related toxicity

- Underreported, vague symptoms … → result in greater morbidity that is costly to patients and the health system
- Different scoring systems used
- Prospective vs retrospective data
- Patient vs physician
- Affects QoL
- Requires appropriate treatment
- Many patients have become long-term survivors

How to measure normal tissue response?

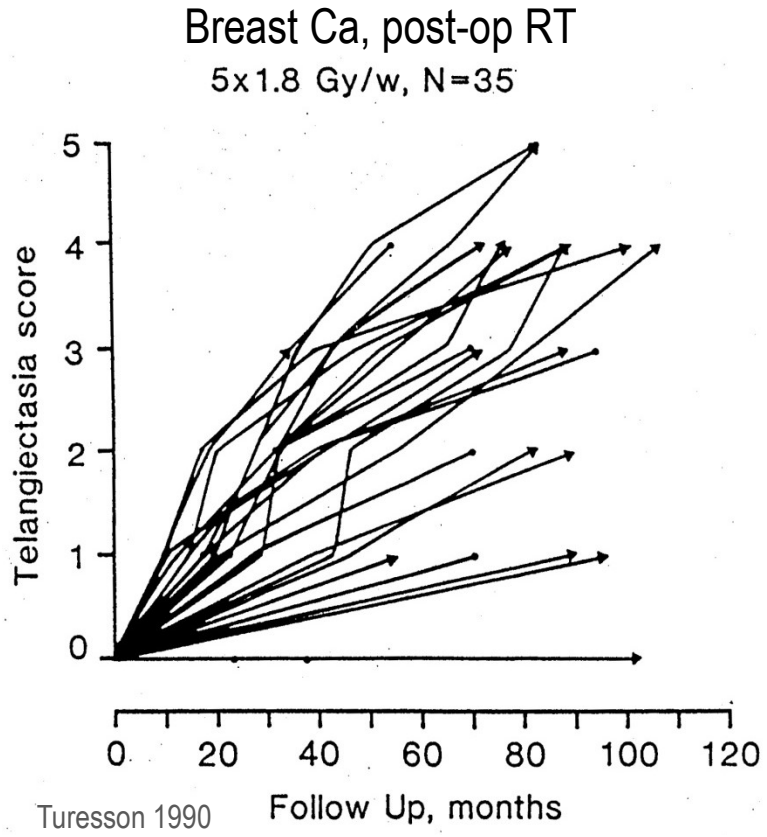
- Scoring of gross tissue effects
  - Scoring systems: grade the severity of tissue damage using an arbitrary scale
- Assays of tissue function
  - Functional assays to measure radiation effects
    - E.g. blood counts as an indicator of bone marrow function
- Clonogenic assays (L1.4)
  - Methods by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

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

Scoring of side-effects: frequency

- Progressive nature of late reactions

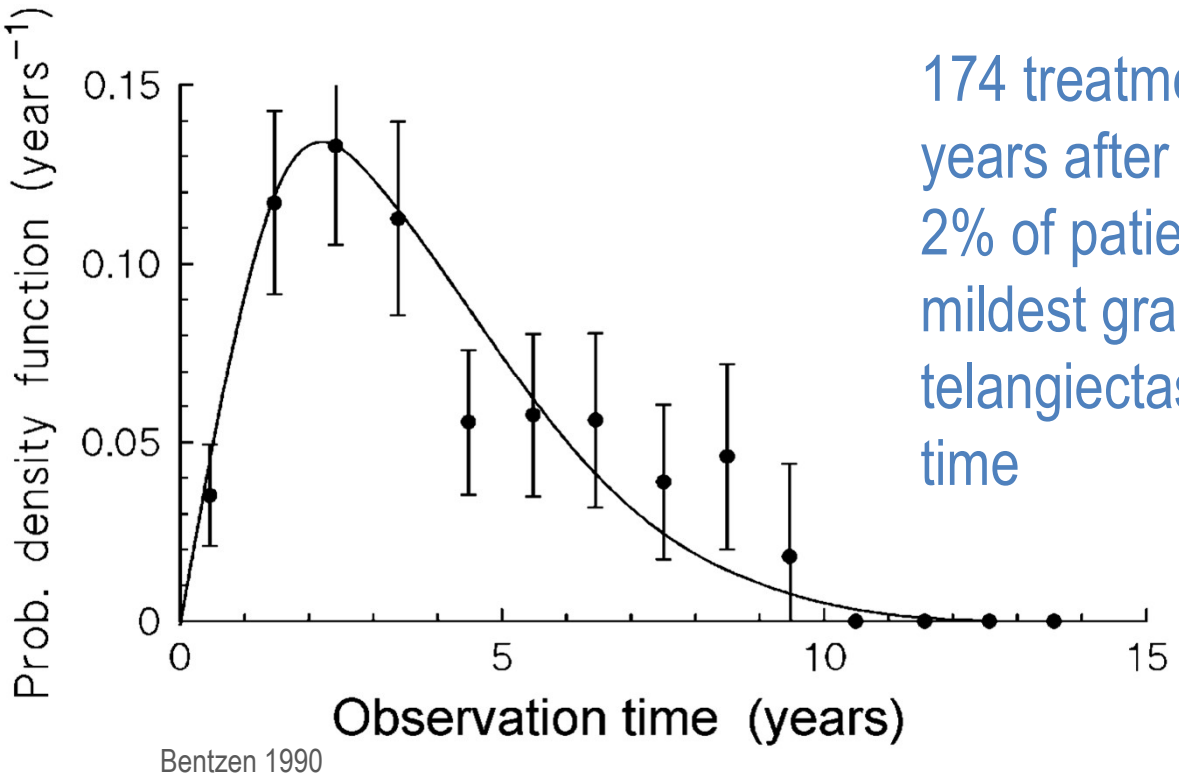


Turesson 1990

Long latent times
Large inter-patient variation

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

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)

Scoring of side-effects: scoring sytems

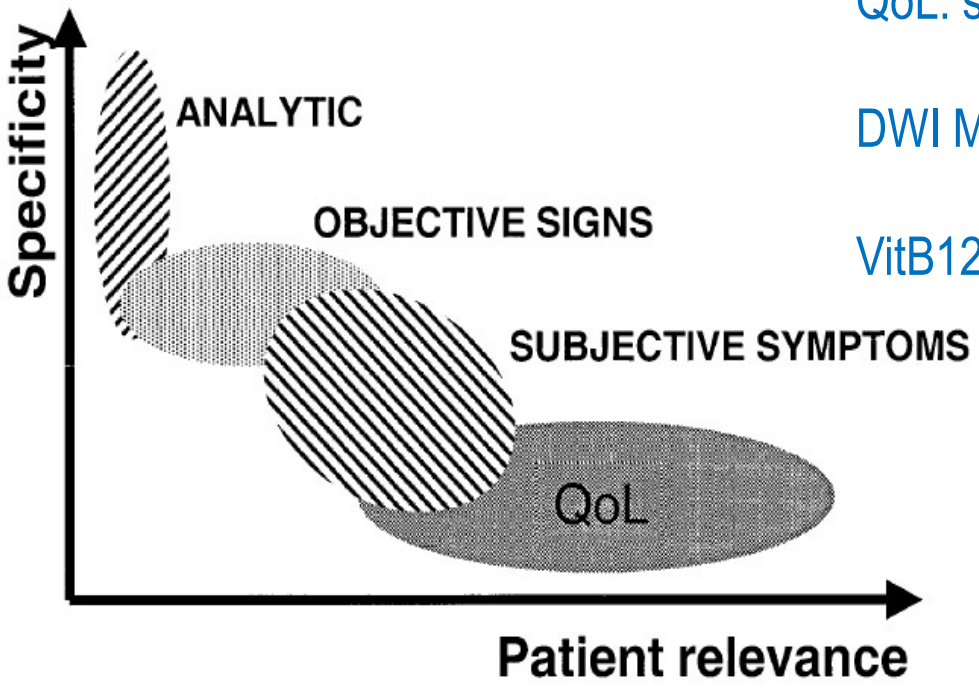
Table 13.1 Systems for documentation of side effects, with examples for oral mucositis.

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

Need for therapeutic intervention

Scoring of side-effects: scoring systems

- Trade-off between specificity and patient relevance



QoL: some are health related, others not

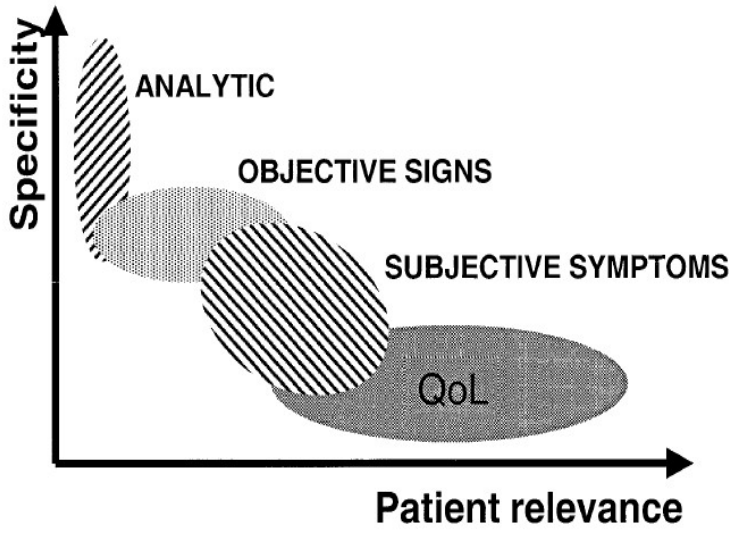
DWI MRI: biological significance

VitB12: malabsorption

Bentzen Sem Rad Oncol 2003

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

Patient-reported outcome measures

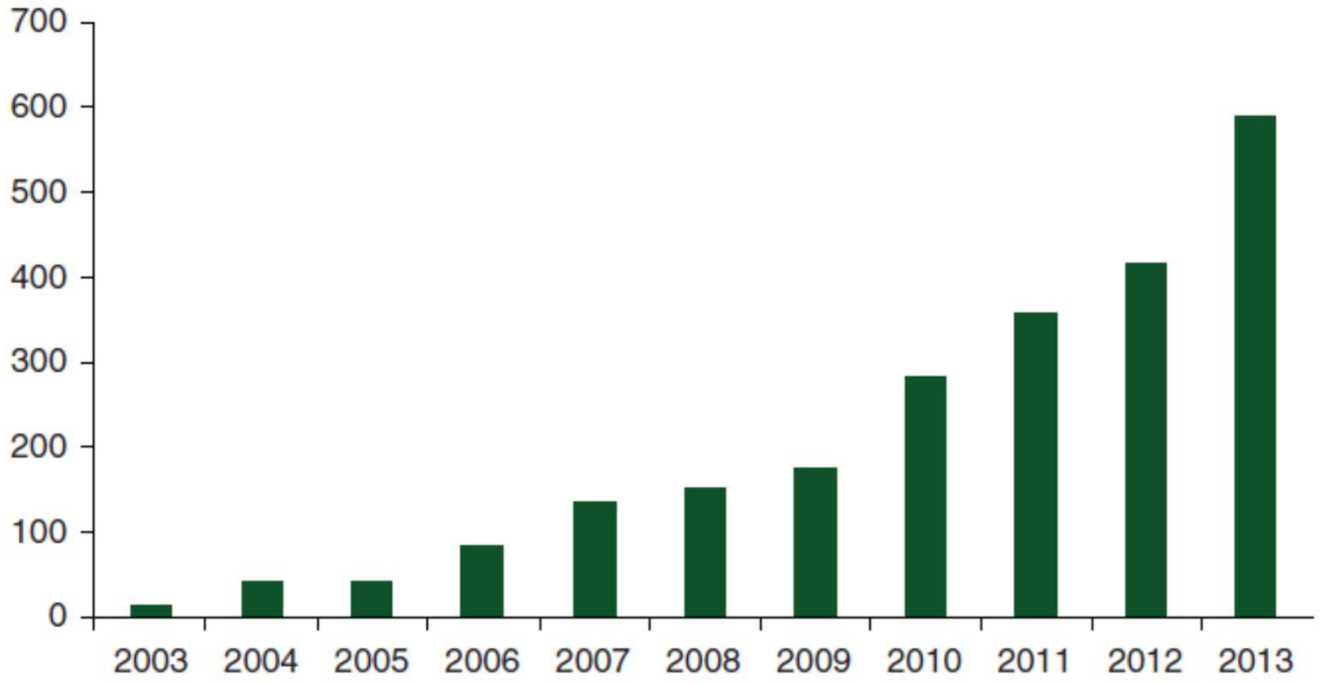
Howell D et al Ann Oncol 2015

- PROM
  - = ‘any report coming directly from the patient about a health condition and its treatment’ using a self-reported measure’
  - focus on physical symptoms, treatment toxicities, psychosocial problems or global health-related QoL impacts of a health condition
  - valued for ensuring that the patients’ experience of cancer and treatment is represented in the measurement of health and for capturing the effectiveness of clinical interventions

Patient-reported outcome measures

Howell D et al Ann Oncol 2015

- Trend of published articles citing PROMs



Implementation of PROMs

Howell D et al Ann Oncol 2015

- Implementation of PROMs in routine cancer care
  - Increased patient satisfaction with clinical consultations
  - Better perceived quality of care
  - Improved overall patient well-being
  - Early detection and monitoring of symptoms / improved symptom management
  - Improved patient-physician communication (emotional, psychosocial, sensitive issues)
  - Support clinical decision making / psychosocial referrals
  - No significant impact on length of clinical encounter (if results available before consultation)

Implementation of PROMs

Howell D et al Ann Oncol 2015

Barriers

- Clinicians
  - Time constraints
  - Lack of training on the use and interpretation of PROMs
  - Value add
  - Liability issues

Enablers

- Clinicians
  - Integration with clinical practice guidelines
  - Automatic ‘flagging’ of clinically important scores
  - Provide longitudinal interpretation of what signifies a clinically important difference in PROMs data

Implementation of PROMs

Howell D et al Ann Oncol 2015

Barriers

- Patients
  - Length and complexity of the scale
  - Availability of translated and culturally meaningful versions
  - Patient comfort level with technology
  - Degree of disability

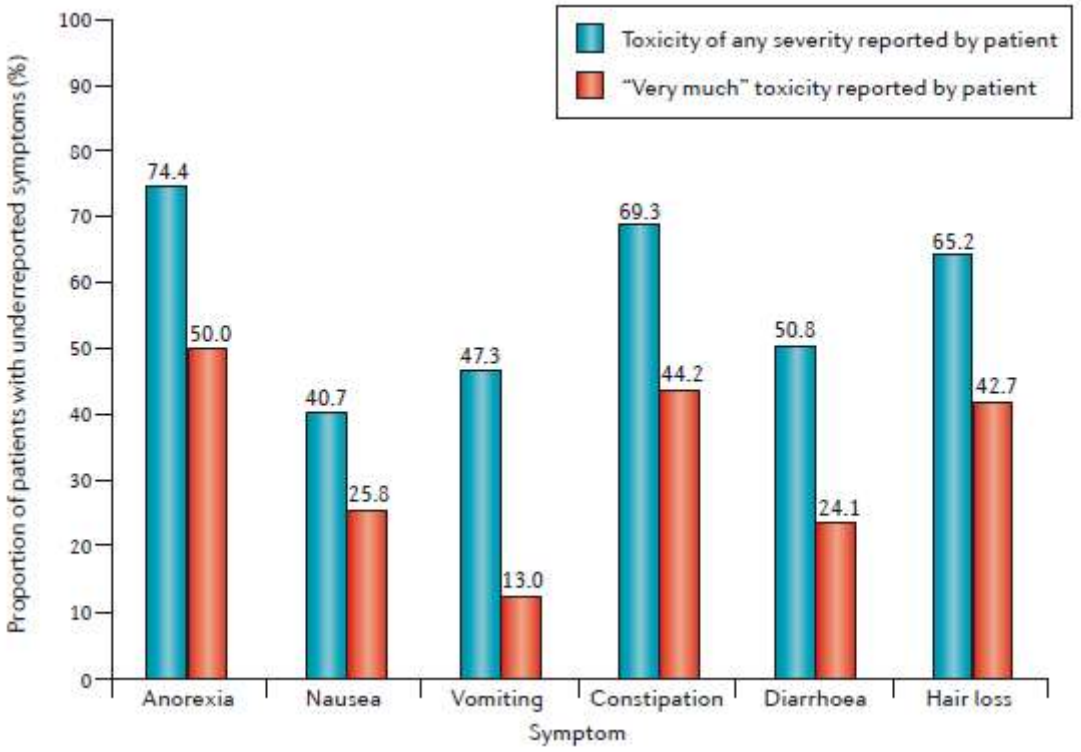
Enablers

- Patients
  - More disease-specific questions
  - Simplifying scales

PROMs in the evaluation of toxicity

Di Maio M, Nature 2016

- Underreporting of anticancer treatment-related toxicity by physicians



Effect of PROMs on QoL and survival

Basch E et al JAMA 2017;318(2):197

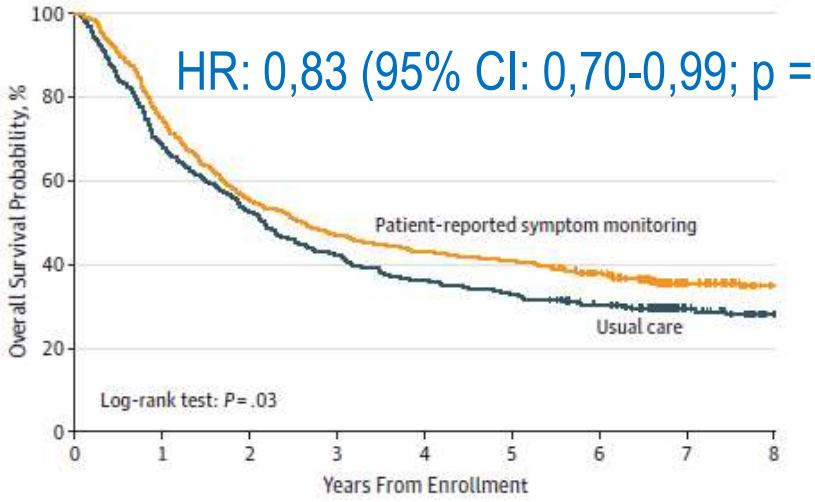
- On-line self-reporting of symptoms improves QoL and extends survival

766 consecutive patients initiating routine chemotherapy for metastatic solid tumor

Randomization: usual care vs electronic PROMs

Median OS was 5 months longer in PROMs group (p = ,03)

Figure. Overall Survival Among Patients With Metastatic Cancer Assigned to Electronic Patient-Reported Symptom Monitoring During Routine Chemotherapy vs Usual Care

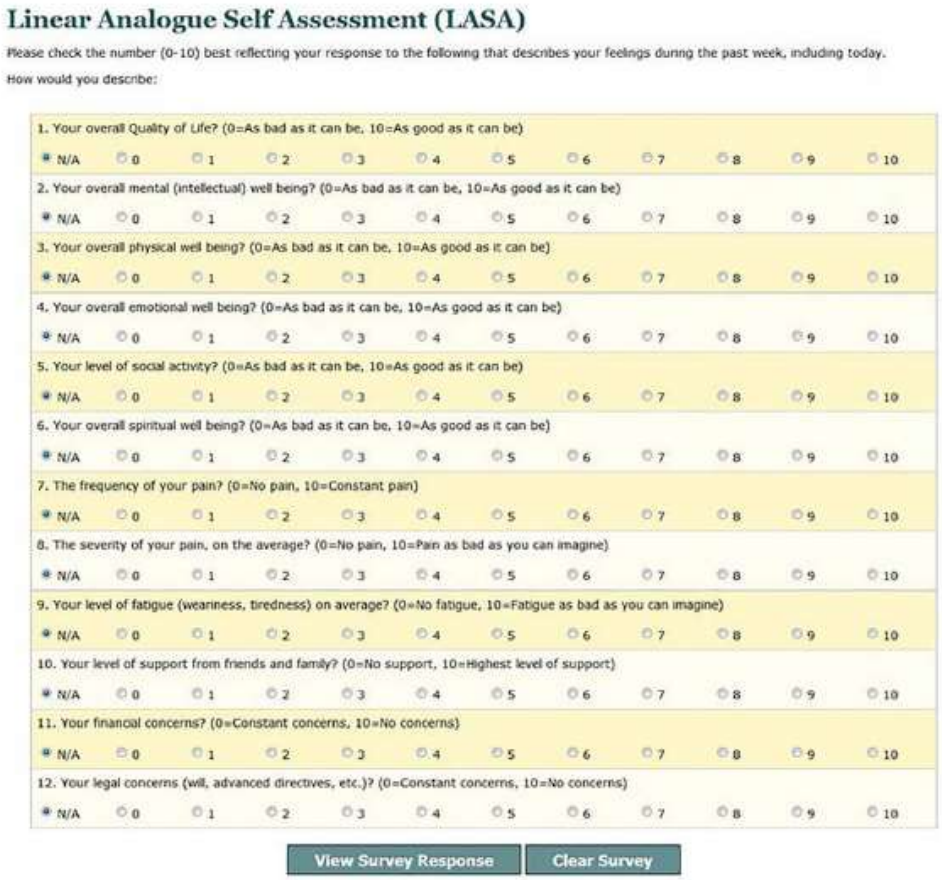


No. at risk									
Patient-reported symptom monitoring	441	331	244	207	190	181	148	65	33
Usual care	325	223	171	137	118	107	89	50	27

PROMs and radiotherapy

Niska JR et al Qual Life Res 2017

- Electronic patient-reported outcomes and toxicities during RT for HNSCC
  - 65 pts
  - Electronic, real-time, 12-item LASA
  - Timepoints: baseline, before biweekly appointments and at last week of RT
  - Changes in QoL domains over time



Linear Analogue Self Assessment (LASA)

Please check the number (0-10) best reflecting your response to the following that describes your feelings during the past week, including today.

How would you describe:

1. Your overall Quality of Life? (0=As bad as it can be, 10=As good as it can be)
2. Your overall mental (intellectual) well being? (0=As bad as it can be, 10=As good as it can be)
3. Your overall physical well being? (0=As bad as it can be, 10=As good as it can be)
4. Your overall emotional well being? (0=As bad as it can be, 10=As good as it can be)
5. Your level of social activity? (0=As bad as it can be, 10=As good as it can be)
6. Your overall spiritual well being? (0=As bad as it can be, 10=As good as it can be)
7. The frequency of your pain? (0=No pain, 10=Constant pain)
8. The severity of your pain, on the average? (0=No pain, 10=Pain as bad as you can imagine)
9. Your level of fatigue (weariness, tiredness) on average? (0=No fatigue, 10=Fatigue as bad as you can imagine)
10. Your level of support from friends and family? (0=No support, 10=Highest level of support)
11. Your financial concerns? (0=Constant concerns, 10=No concerns)
12. Your legal concerns (will, advanced directives, etc.)? (0=Constant concerns, 10=No concerns)

N/A 0 1 2 3 4 5 6 7 8 9 10

View Survey Response | Clear Survey

PROMs and radiotherapy

- Most pts had meaningful decreases in all QoL domains except level of support, financial and legal concerns

Niska JR et al Qual Life Res 2017

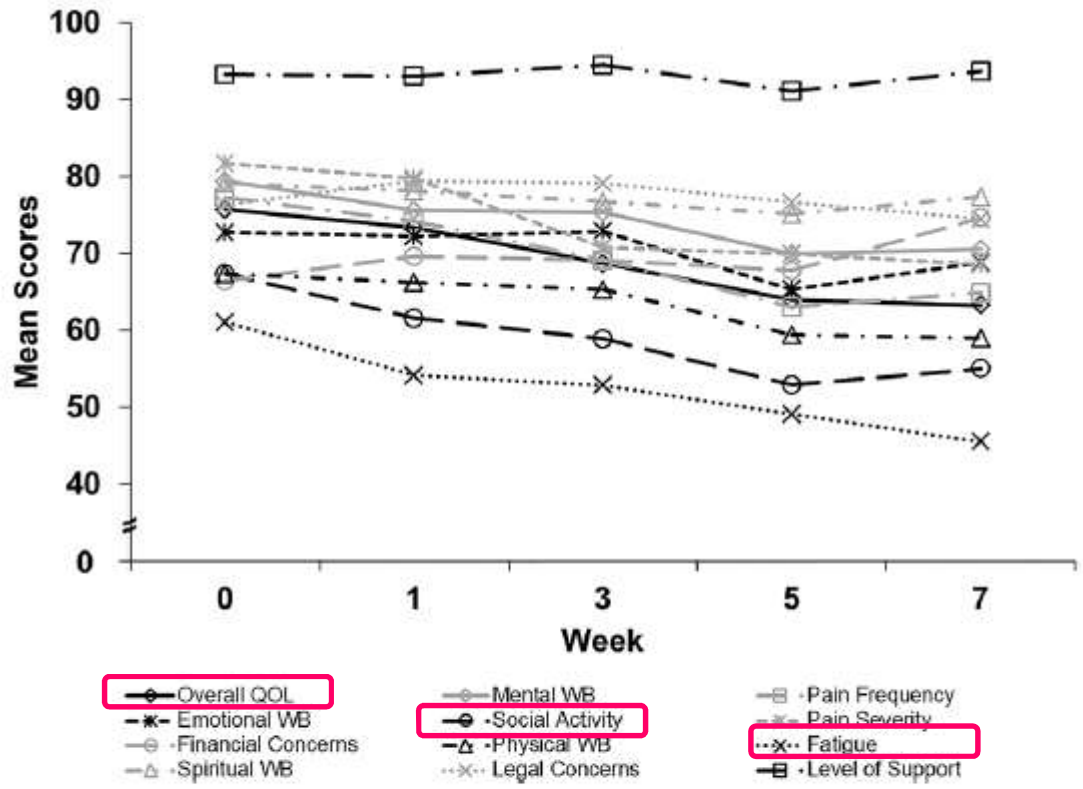


Fig. 3 Overall LASA scores (0 = Low QOL; 100 = High QOL). *LASA* indicates linear analog self-assessment; *QOL* quality of life; *WB* well-being

PROMs and radiotherapy

Niska JR et al Qual Life Res 2017

- Real-time ePROs allow providers to monitor QoL at multiple time points during RT, potentially allowing early intervention to improve QOL and mitigate AEs.

Patient XYZ01 : LASA Scores by Week Since Treatment Started

Return to Main Menu | Click here to log out

Please click on the QOL domain links for Disease Management Pathways.

Items in **BLUE** represent complaints that are worse than average (5 points or below for QOL OR 5 points or above for Pain/Fatigue) and may warrant attention.
Items in **RED** represent a drop of 2 points or more
Items in **GREEN** represent a 2 points or more improvement on the measure since the last visit.

Factor Measured (0=Worst QOL and 10=Best QOL) or **(0=No Pain/Fatigue and 10=Constant Pain/Tiredness)	Baseline	Week 1	Week 3	Week 5	Last Week of Tx	Last Week of Tx Minus Week 5
Quality of Life	9	4	6	7	6	-1
Mental (intellectual) WB	9	4	6	8	7	-1
Physical WB	8	4	7	5	6	1
Emotional WB	7	4	7	7	7	0
Social Activity Level	9	6	8	7	6	-1
Spiritual WB	8	8	9	9	8	-1
Pain Frequency**	1	6	5	4	3	1
Pain Severity**	1	3	3	2	2	0
Fatigue Level**	2	5	7	5	7	-2
Level of Support	10	8	10	9	9	0
Financial Concerns	8	3	3	3	8	5
Legal Concerns	1	2	10	0	10	10

Fig. 2 Data display provided to clinicians. *LASA* indicates linear analog self-assessment; *QOL* quality of life; *WB* well-being

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

Take home messages

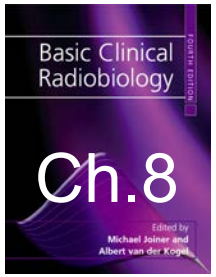
- Normal tissue side effects are mandatory to score
  - Therapeutic ratio
  - Quality assurance (QA)
- Both early and late reactions may develop in the same organ
- Use validated scoring systems to record normal tissue effects
- Score before, during and after RT
  - Extend follow-up to several years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

ESTRO School

Basic Clinical Radiobiology

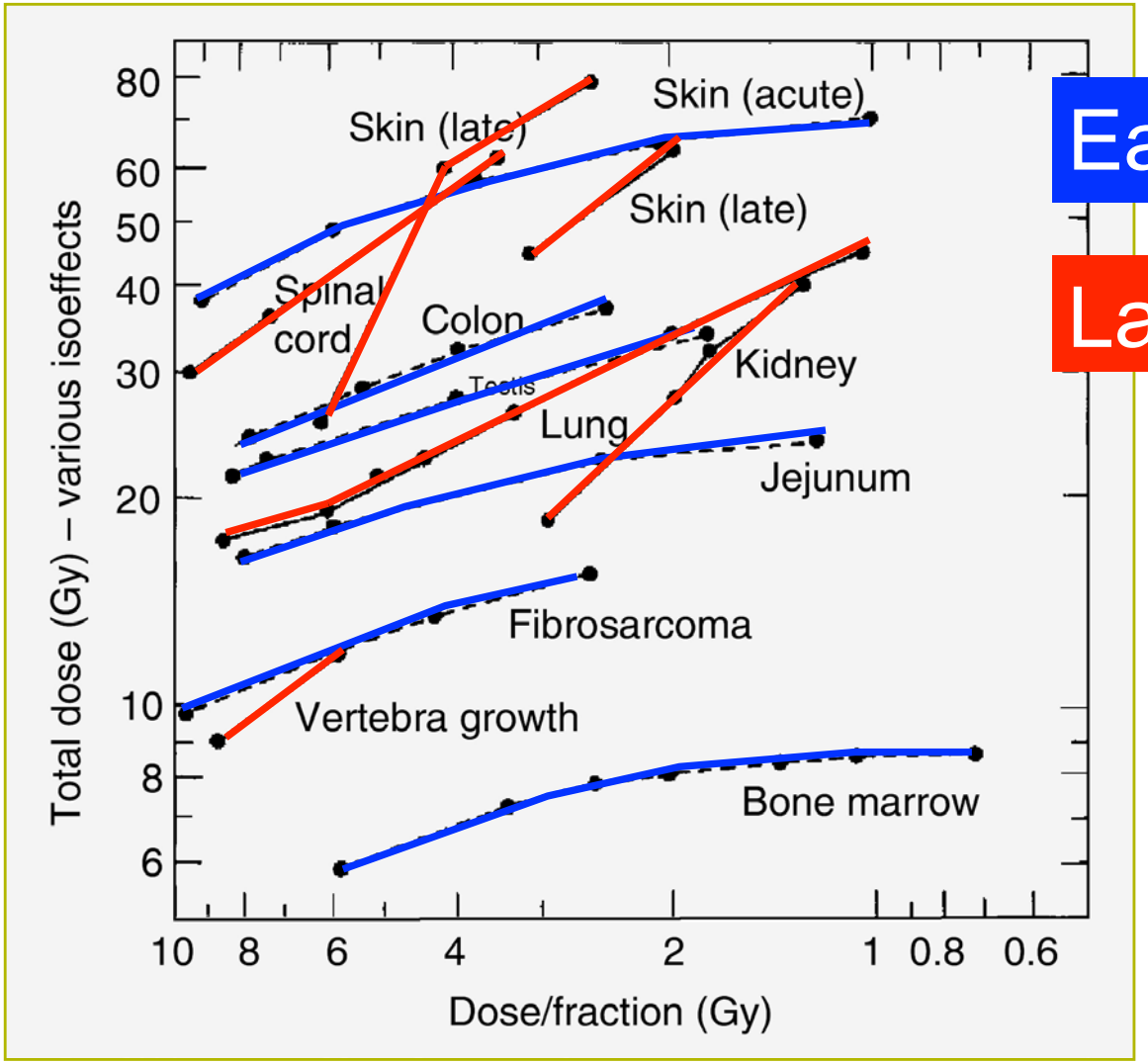
The Linear-Quadratic approach to fractionation

Michael Joiner



Paris 2017

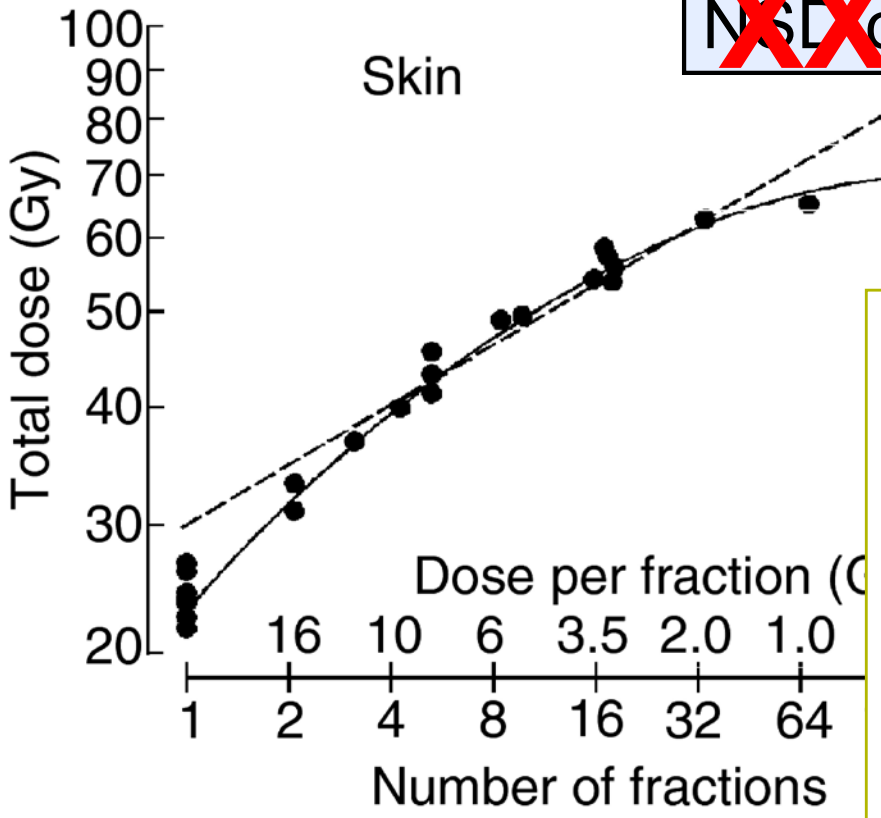
Thames HD, Withers HR, Peters LJ, Fletcher GH.
Int J Radiat Oncol Biol Phys
1982;8:219

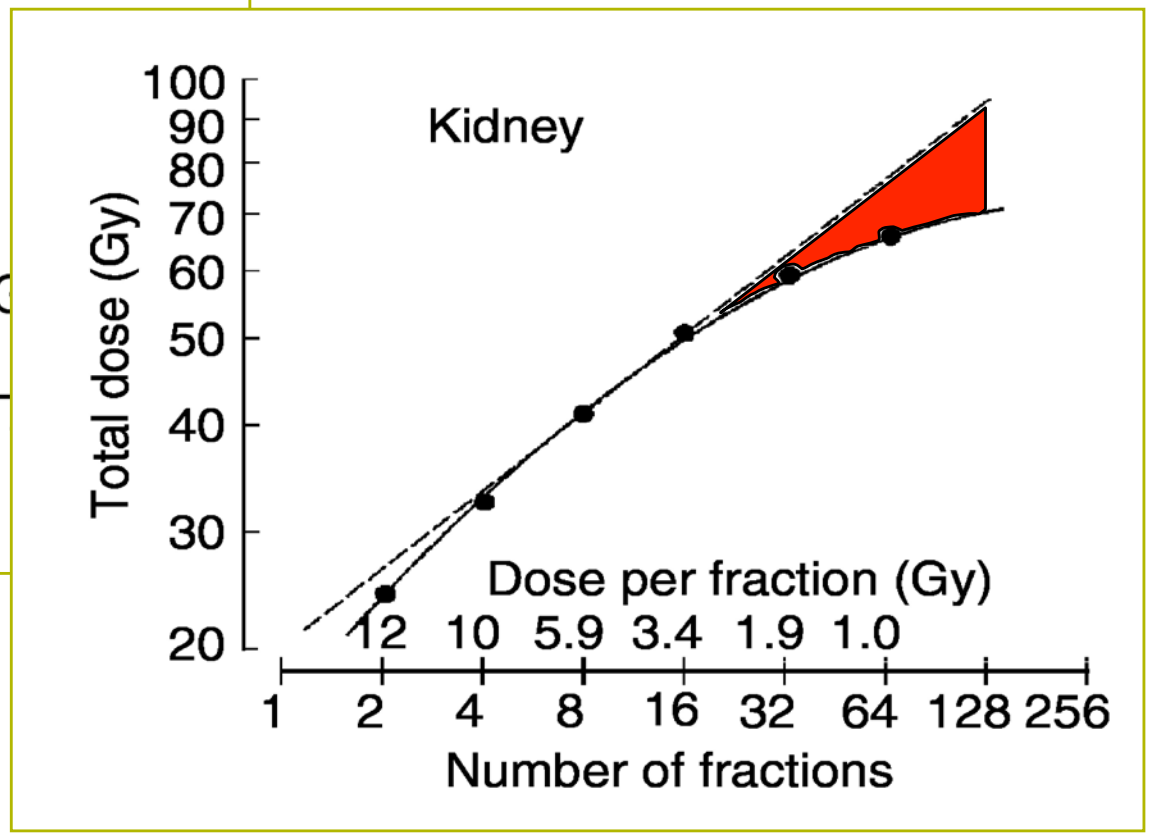


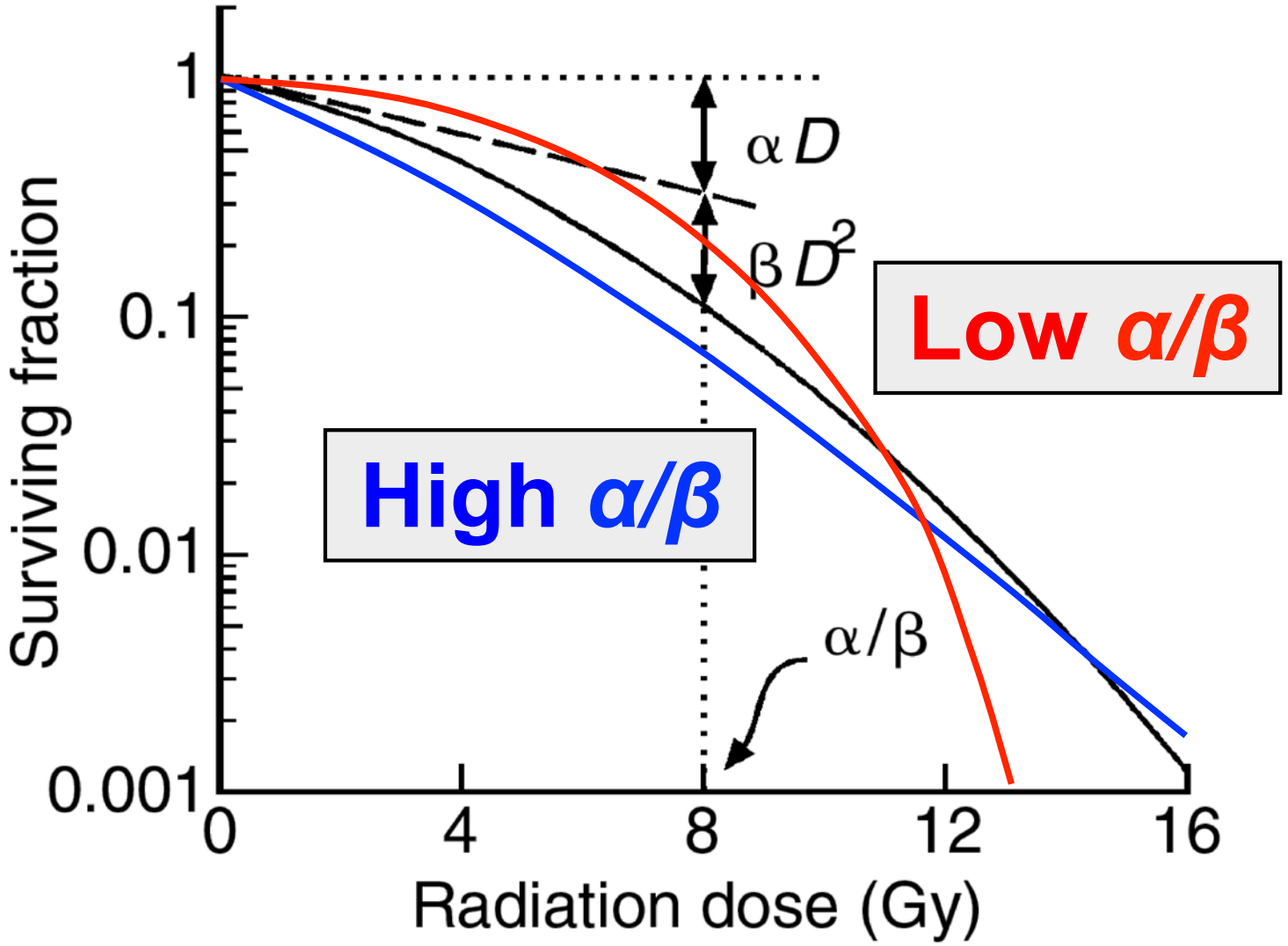
NSD or TDF

XXXX

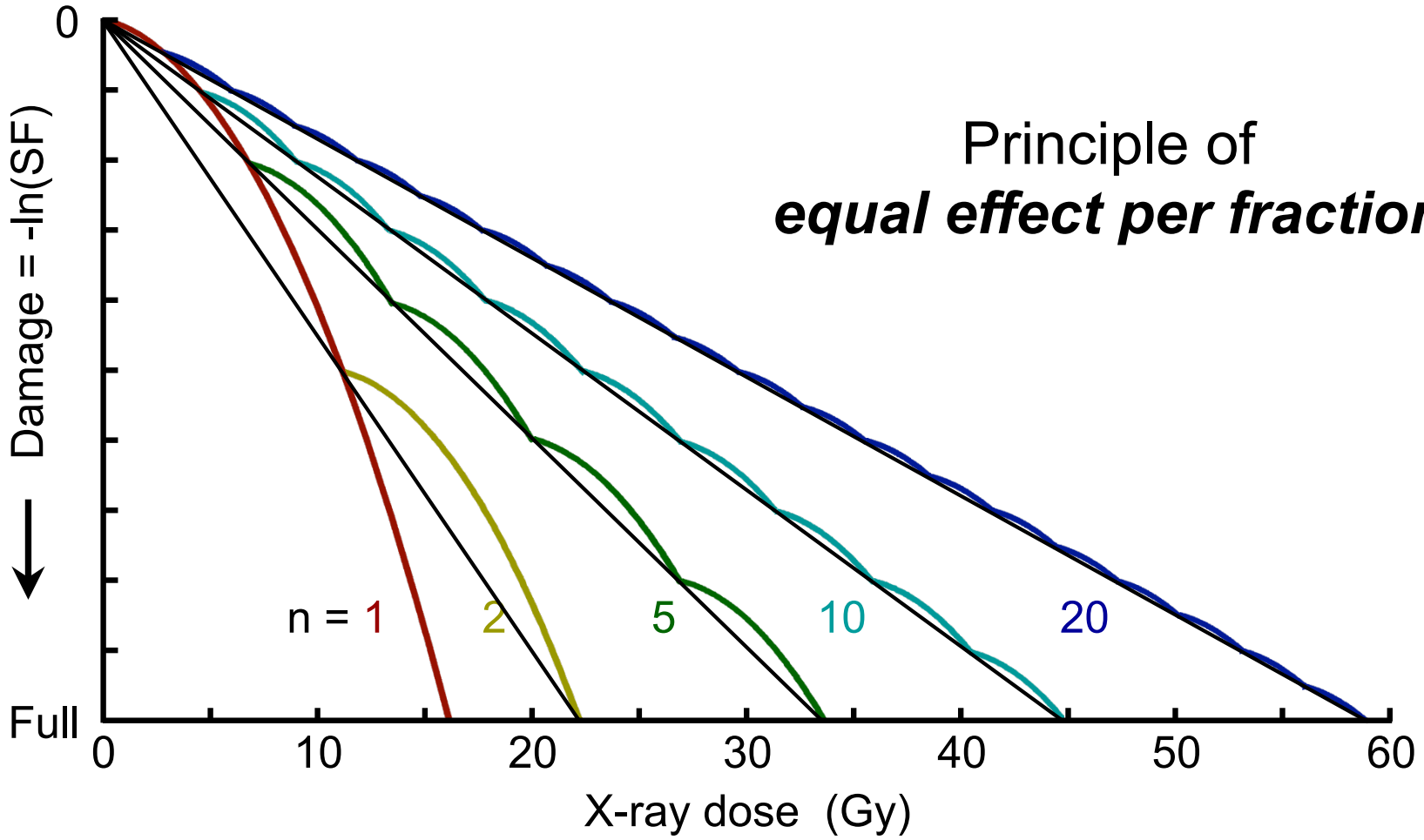
LQ



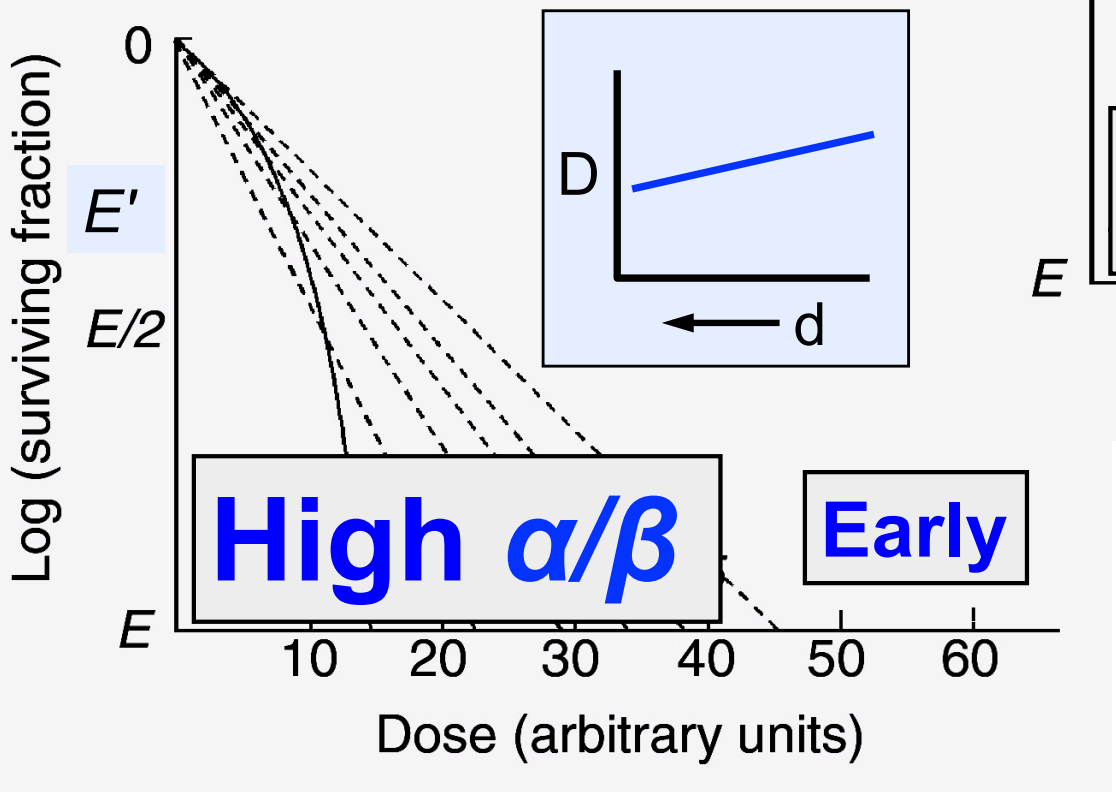


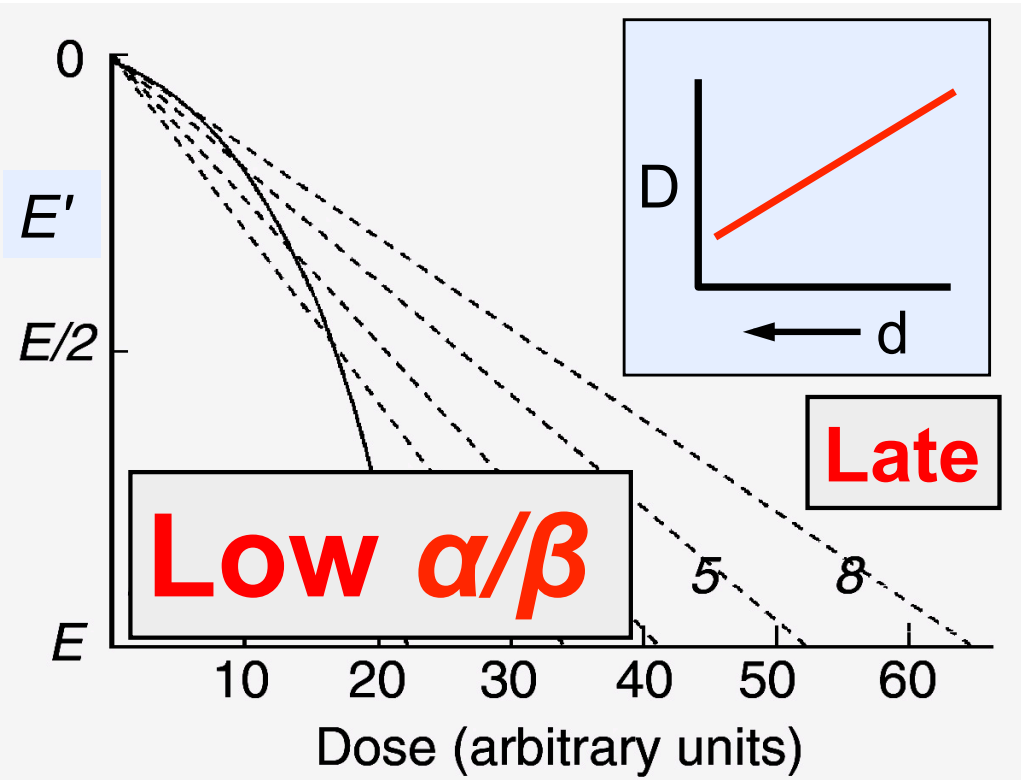

Surviving fraction
1
0.1
0.01
0.001
0
4
8
12
16
Radiation dose (Gy)
αD
βD2
α/β
Low α/β
High α/β

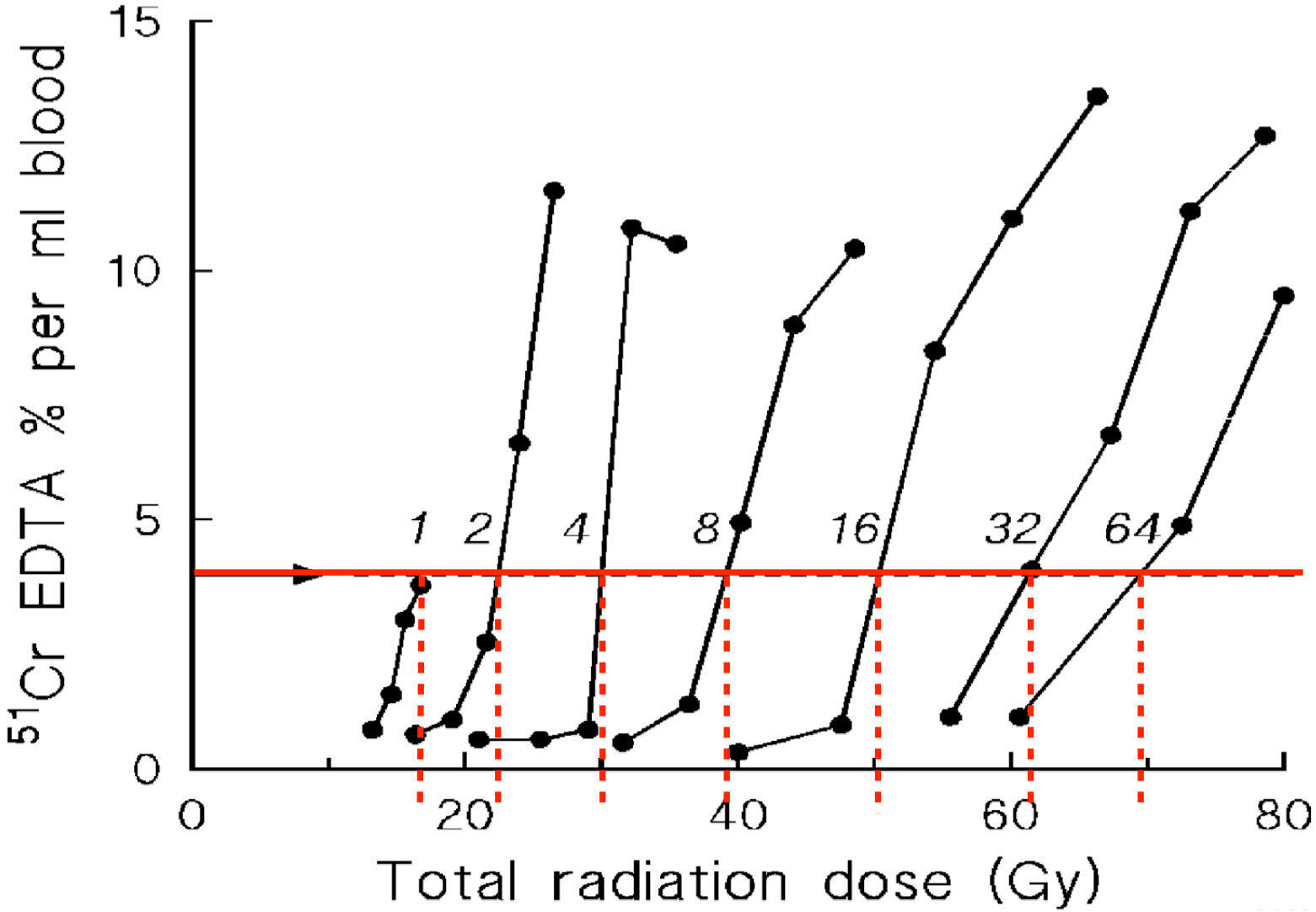
Less effect per gray at low doses per fraction



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

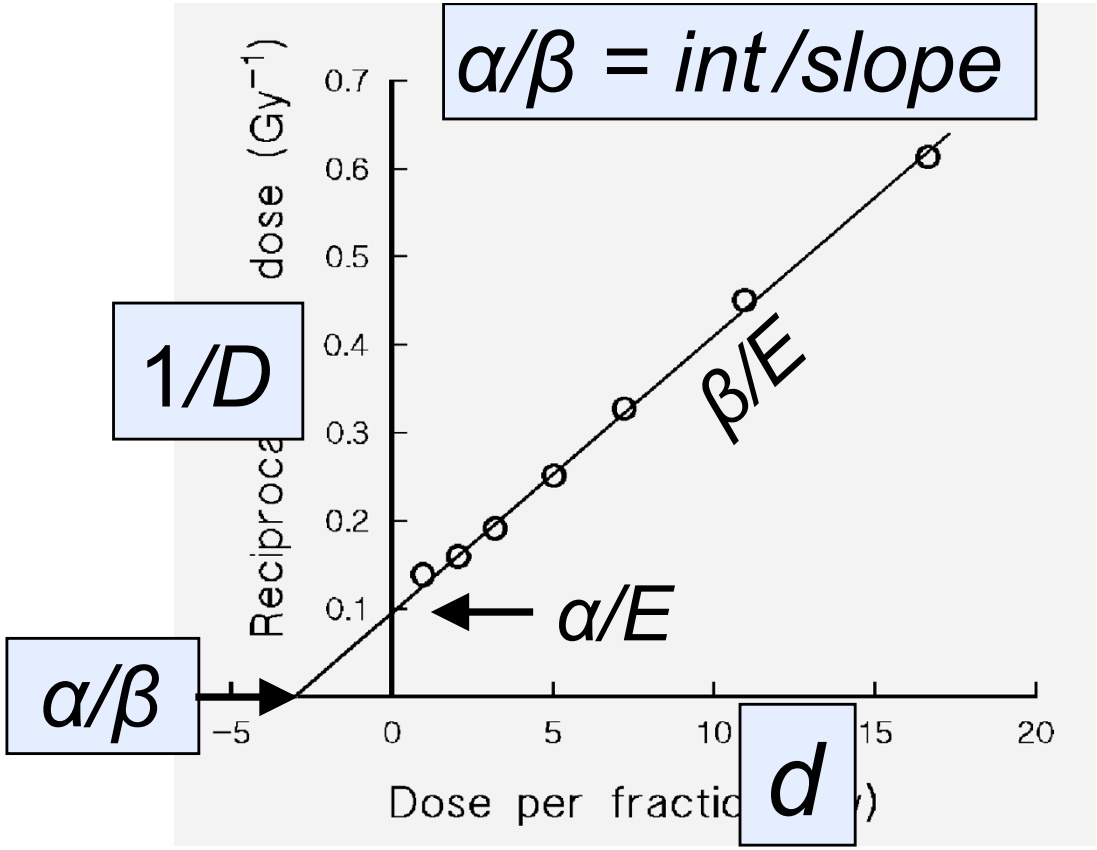





15
10
5
0
^{51}Cr EDTA % per ml blood
1
2
4
8
16
32
64
0
20
40
60
80
Total radiation dose (Gy)

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

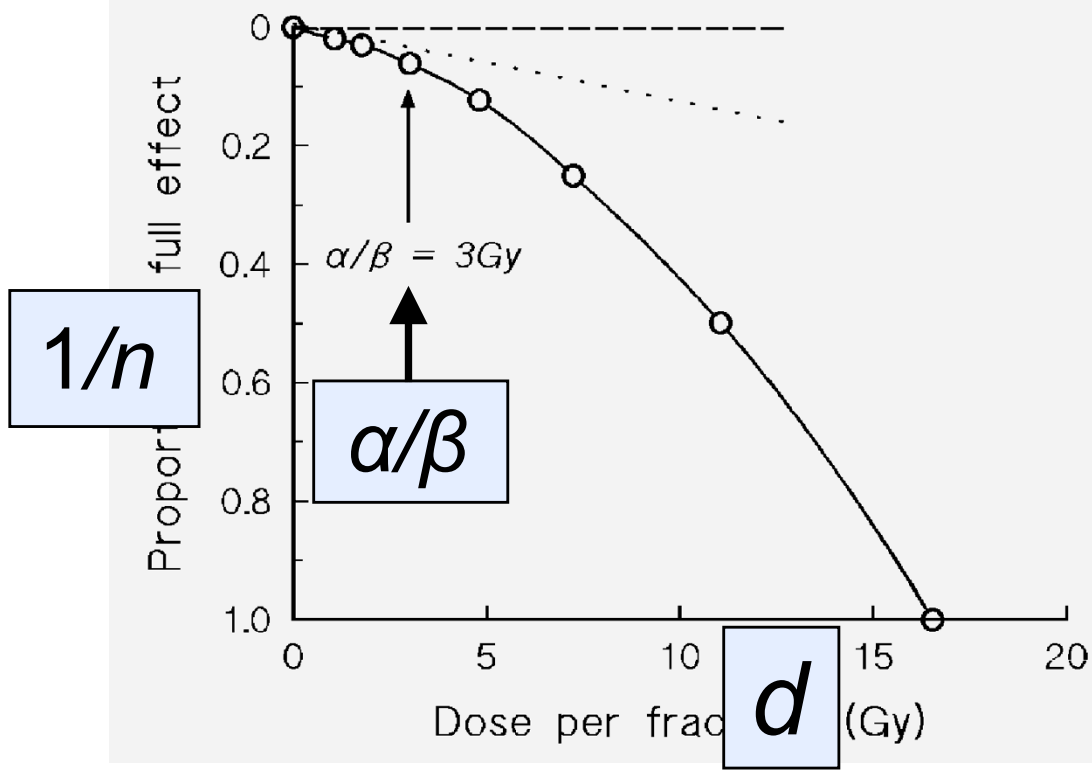


Damage from a single fraction = $\alpha d + \beta d^2$

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

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

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, $E = n(\alpha d + \beta d^2)$

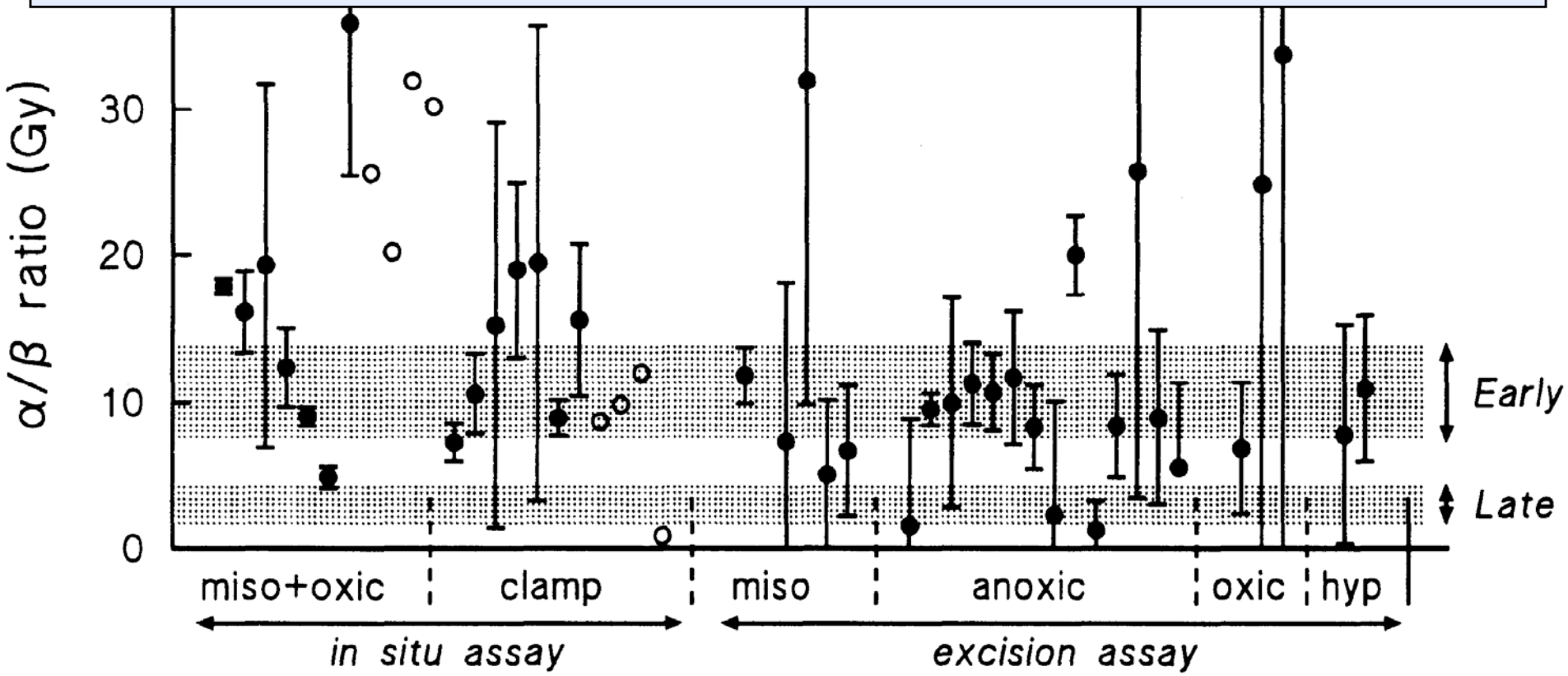
$E/n = \alpha d + \beta d^2$ $\qquad$ $1/n = (\alpha/E)d + (\beta/E)d^2$

α/β for early and late responding animal normal tissues

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 **experimental** 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.‡‡

*INSER... France;
Departm... cology,
Cedars-... k, MI;
#British... ia, PA;
††D... gy,

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 Gy**
6 institutional datasets, no risk-group dependence
Int J Radiat [illegible] 01

1.4 (0.9–2.2 [illegible] R
Biochem rel [illegible] /f < **6.7 Gy**
7 institutiona [illegible] dence
Int J Radiat Oncol Biol Phys 2012;82:e17-e24

1.48 Gy

1.86 (0.7–5.1) Gy 274 patients Leborgne F
Biochem disease free survival at 5 years d/f < **3.15 Gy**
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 In 1986–98, we randomly assigned 1410 women with invasive breast cancer (tumour stage 1–3 with a maximum of one positive node and no metastasis) who had had local tumour excision of early stage breast cancer to receive 50 C
given over 5
elsewhere. He
appearance of

Findings After
ipsilateral tumour relapse after 10 years was 12·1% (95% CI 8·8–15·3) 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

See Reflection and Reaction page 445

Department of Radiotherapy, den Hospital, (J Hanson BSc, nold FRCR); nt of Oncology, shire Oncology eltenham, UK RCR, A Ashton RCN); Clinical Trials and Statistics Unit (ICR-CTSU), Section of Clinical Trials, Institute of Cancer Research, Sutton, UK (Prof J M Bliss MSc, J Homewood BSc, C Harper MSc, J Haviland MSc); and Department of Human Oncology, University of Wisconsin Medical School, Madison, WI, USA

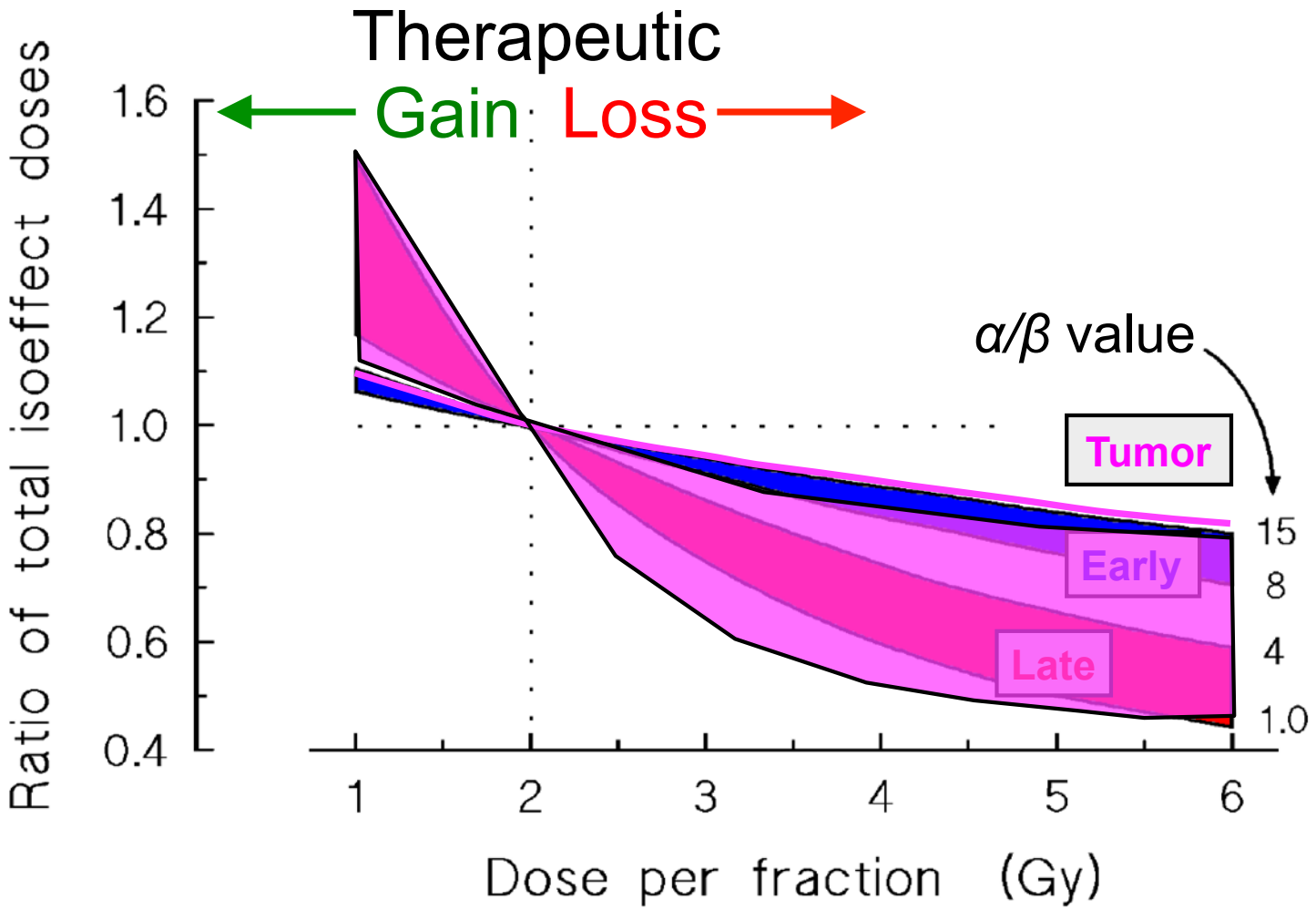
Table 9.1: α/β ratios for **human** normal tissues and tumors

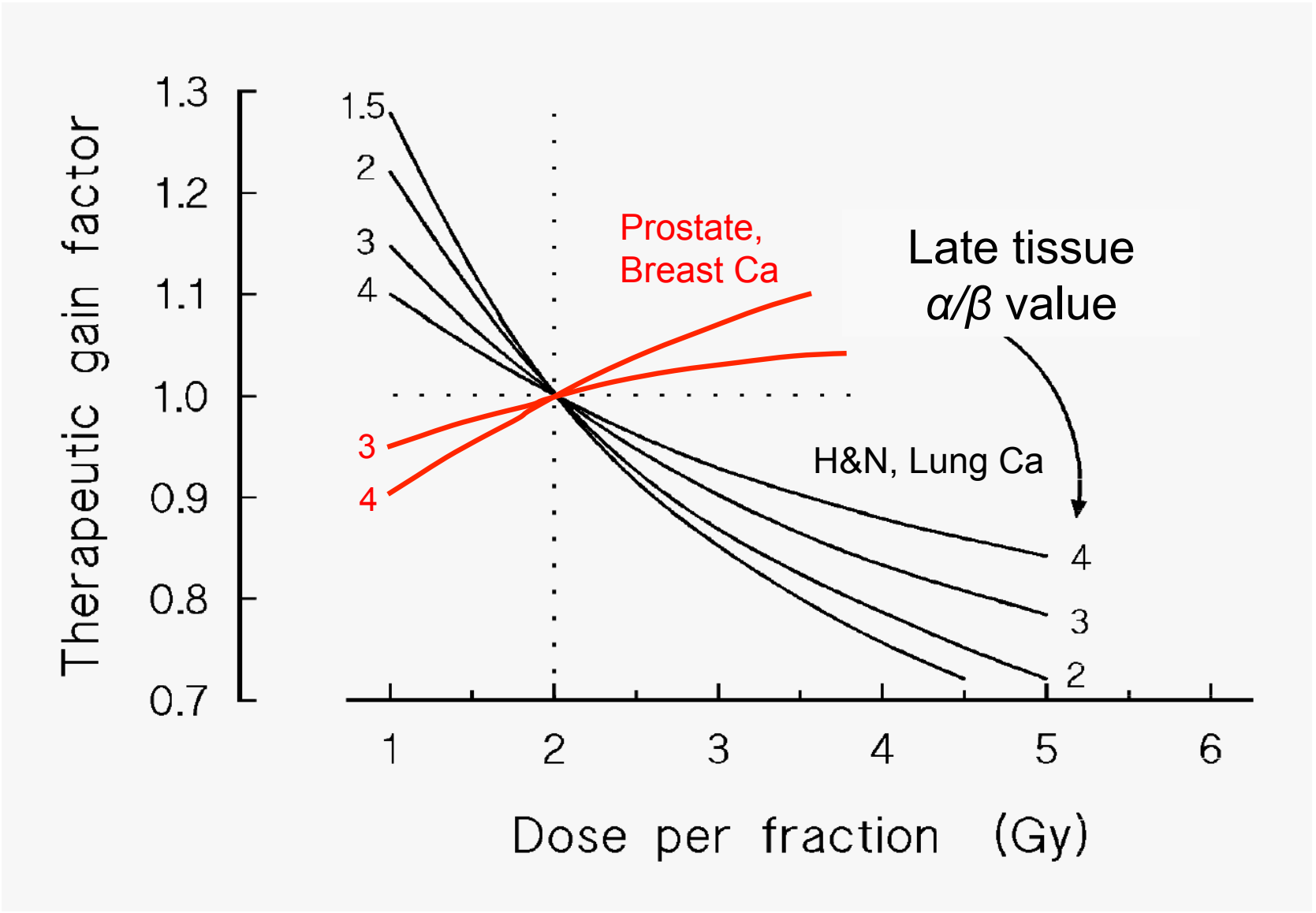
Tissue/organ	Endpoint	α/β (Gy)	95% CL (Gy)	Source
Early reactions				
Skin	Erythema	8.8	6.9; 11.6	Turesson and Thames (1989)
	Erythema	12.3	1.8; 22.8	Bentzen et al. (1988)
	Dry desquamation	≈ 8	N/A	Chogule and Supe (1993)
	Desquamation	11.2	8.5; 17.6	Turesson and Thames (1989)
Oral mucosa	Mucositis	9.3	5.8; 17.9	Denham et al. (1995)
Late reactions				
Skin/vasculature				989)
Subcutis				1991)
Breast				1991)
				008)
Muscle/vasculatu				
Nerve				
Spinal cord				
Eye				
Bowel				
Bowel				
Lung				
Head and neck				
Head and neck				999)
Supraglottic lary				
Oral cavity + oro				
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)

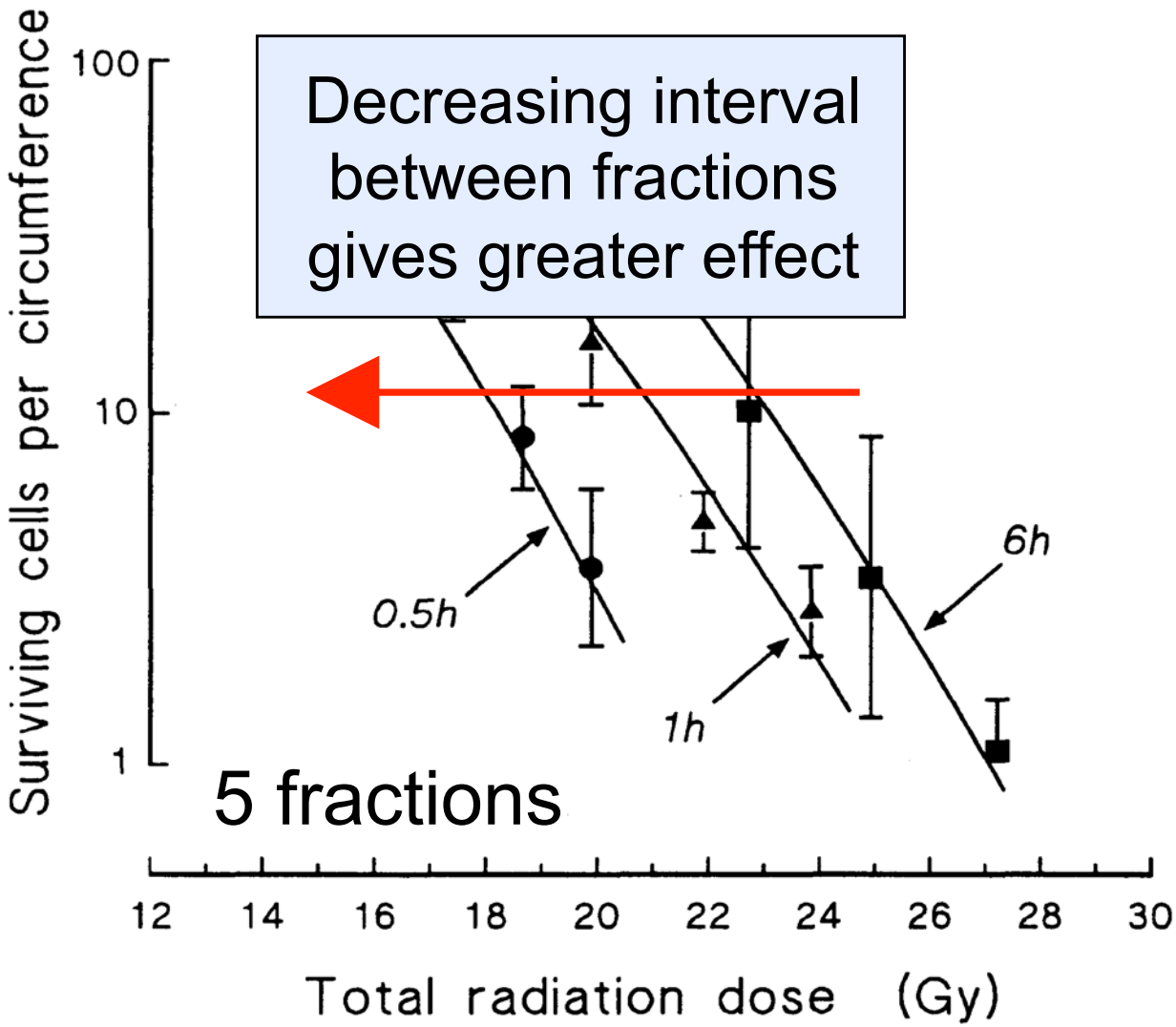
Mean Late 2.9

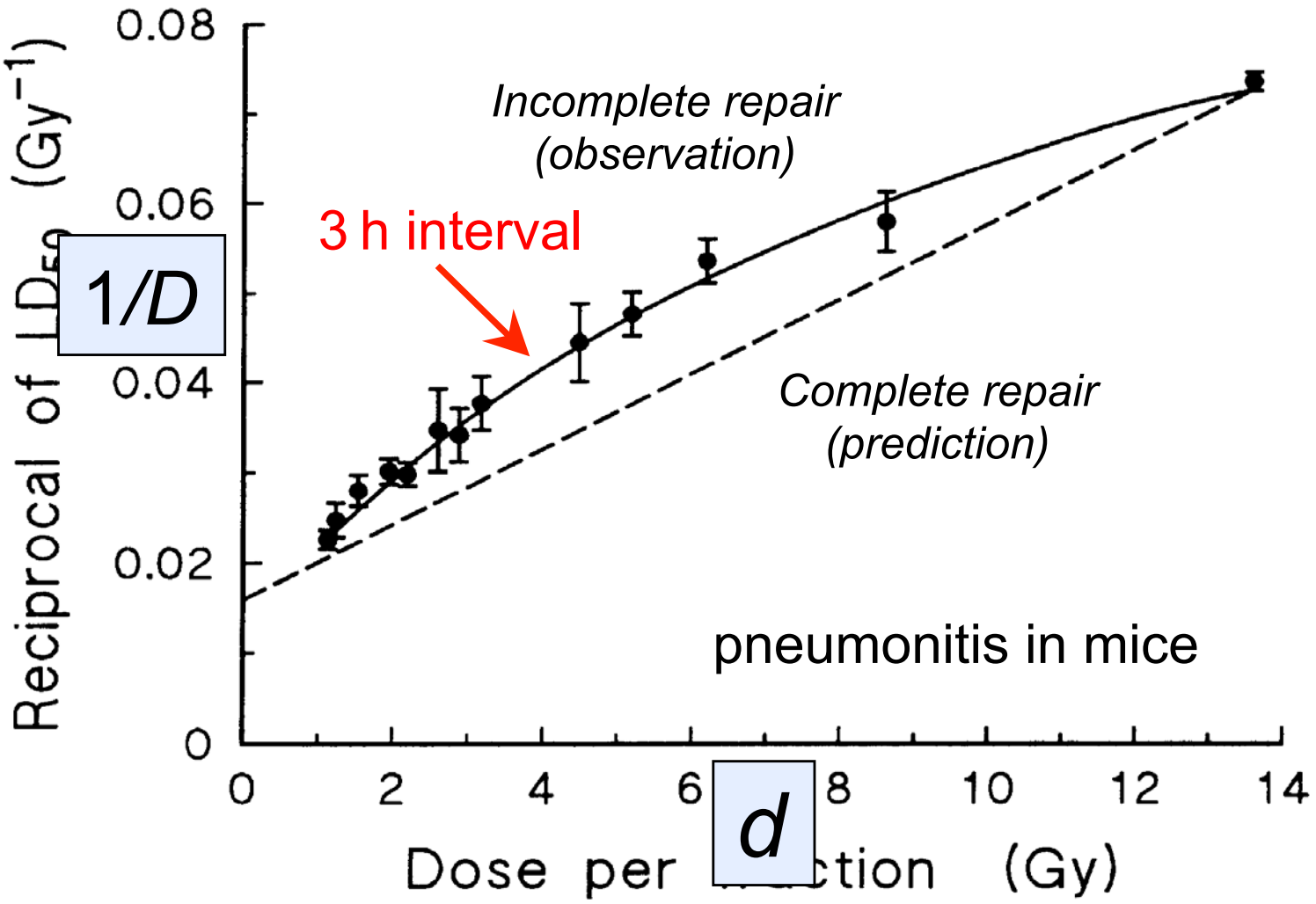
Mean Early 10.6

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
1/D
Reciprocal of LD50 (Gy−1)
Incomplete repair
(observation)
3 h interval
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

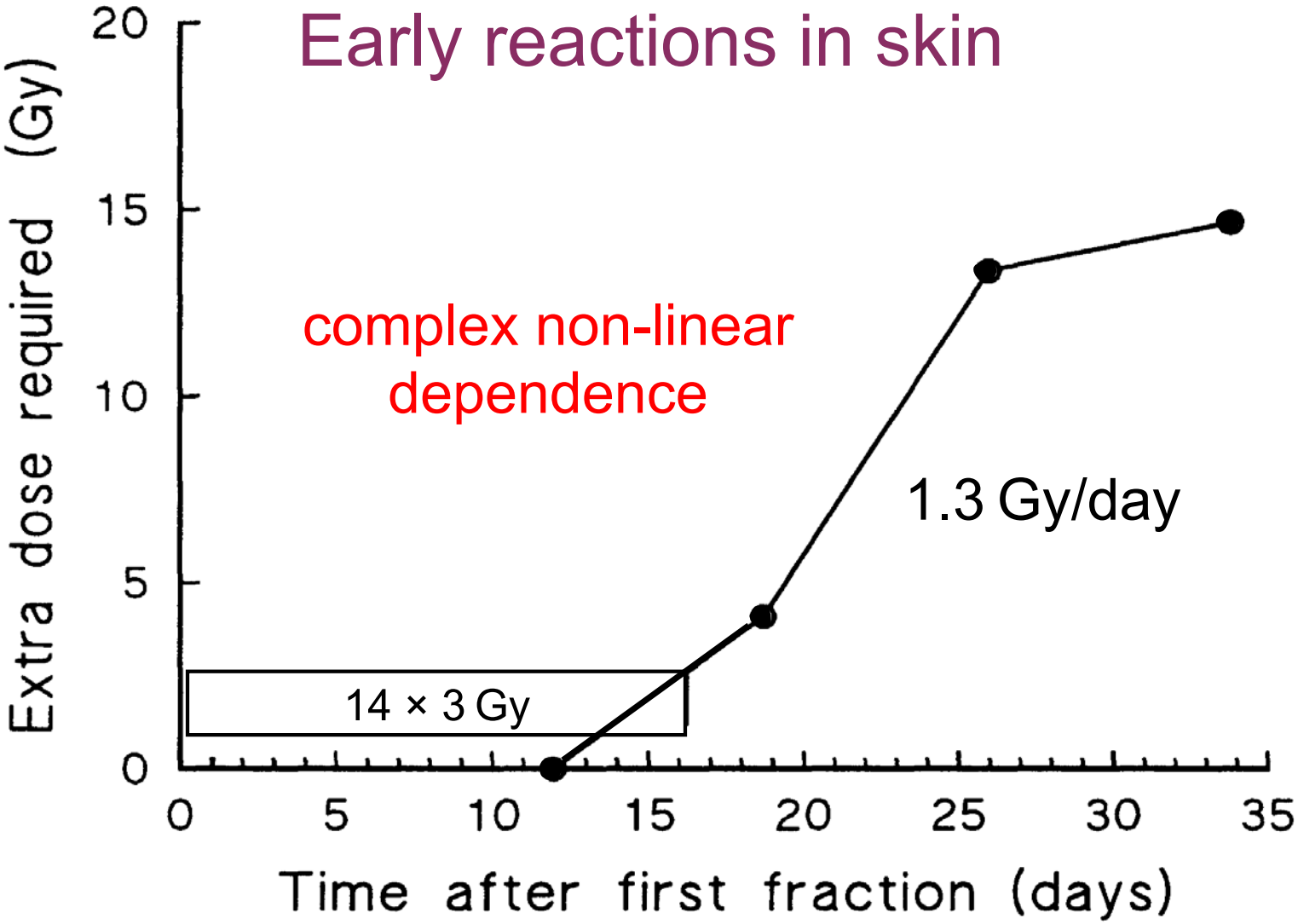
Half times for recovery ($T_{1/2}$) in normal tissues

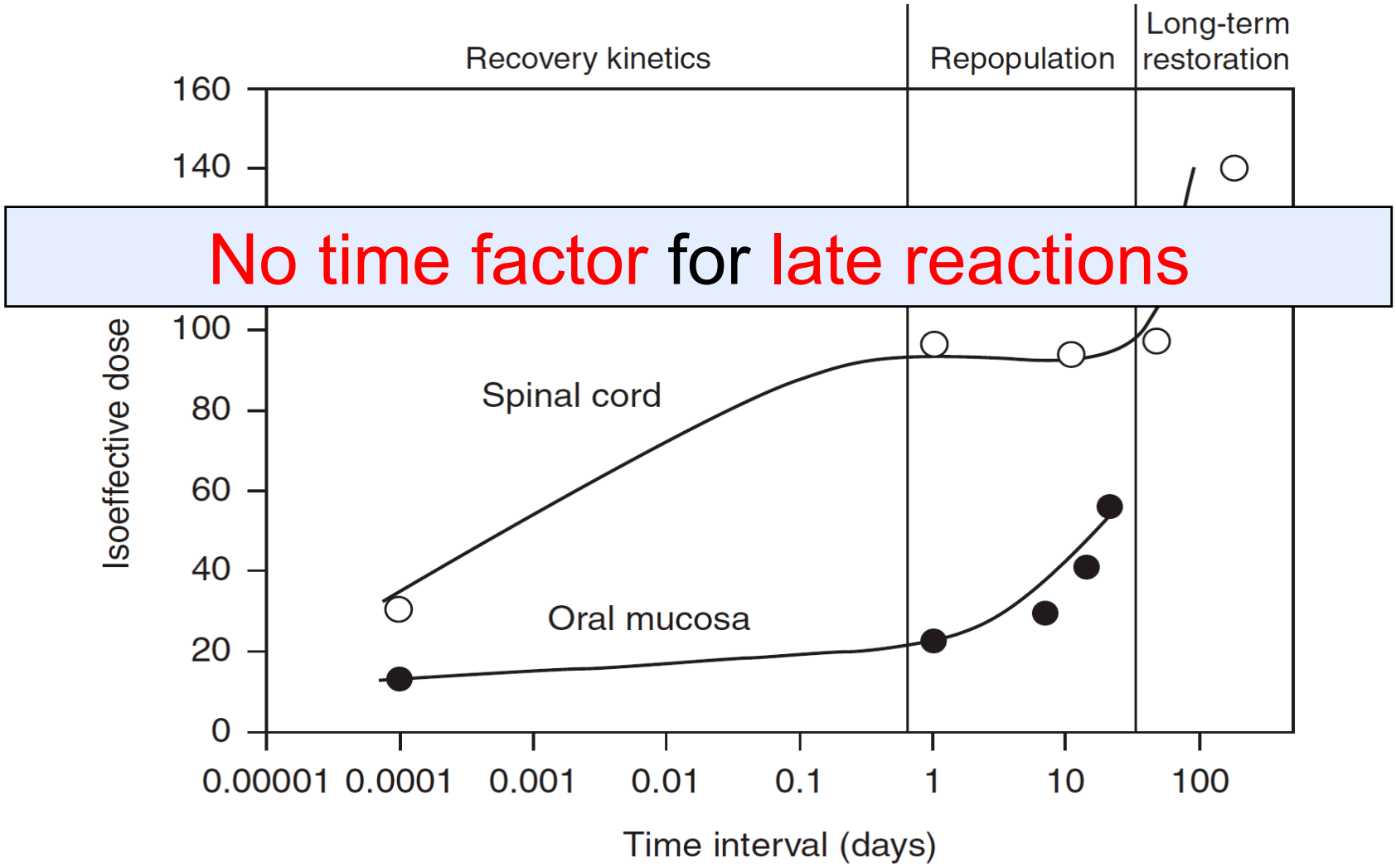
Tissue	Species	Dose delivery#	$T_{1/2}$ (hours)	Source
Haemopoietic	Mouse	CLDR	0.3	Thames *et al.* (1984)
Spermatogonia	Mouse	CLDR	0.3–0.4	Delic *et al.* (1987)
Jejunum	Mouse	F	0.45	Thames *et al.* (1984)
	Mouse	CLDR	0.2–0.7	Dale *et al.* (1988)
Colon (acute injury)	Mouse	F	0.8	Thames *et al.* (1984)
	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

Early reactions in skin





No time factor for late reactions

Figure 11.1: Dorr & Kummermehr 1990, Dorr 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.

EQD2…

Coming up…
Calculations!

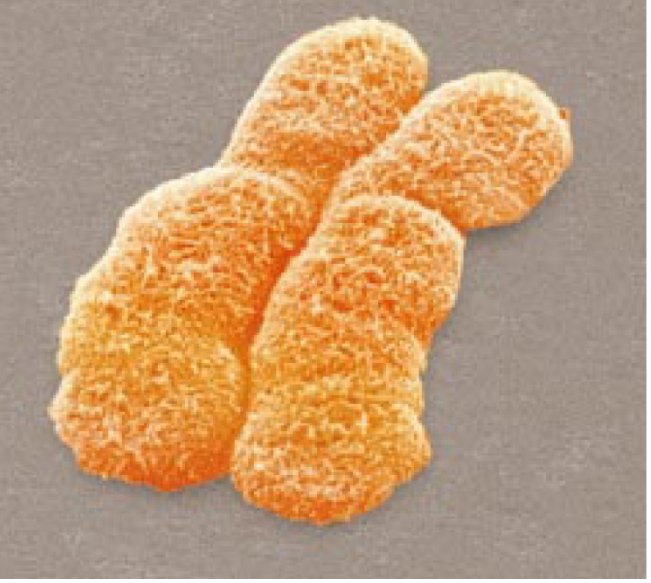
Molecular basis of the DNA damage response

Marianne Koritzinsky

Princess Margaret Cancer Centre
Toronto, Canada
Marianne.Koritzinsky@uhnresearch.ca

DNA - The Main Target of Radiation

DNA **D**amage **R**esponse



DNA

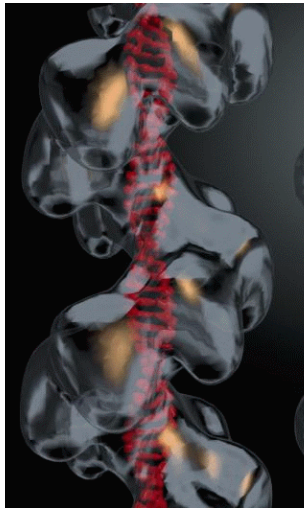
- Only molecule which is repaired

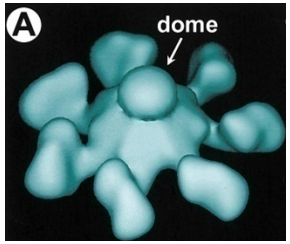
Initial cellular responses to radiation

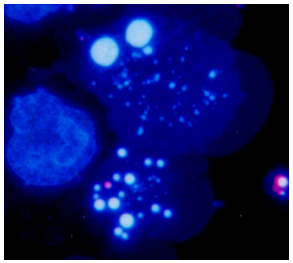
Sensors of damage

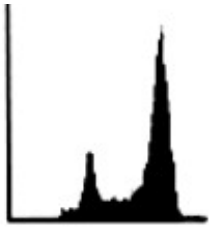
Biological Pathways

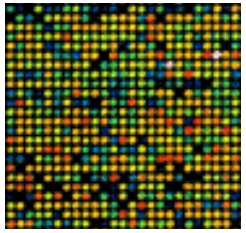
DNA Repair	Early Apoptosis	Cell cycle checkpoints	Gene expression

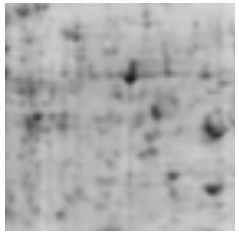












Endogenous DNA damage

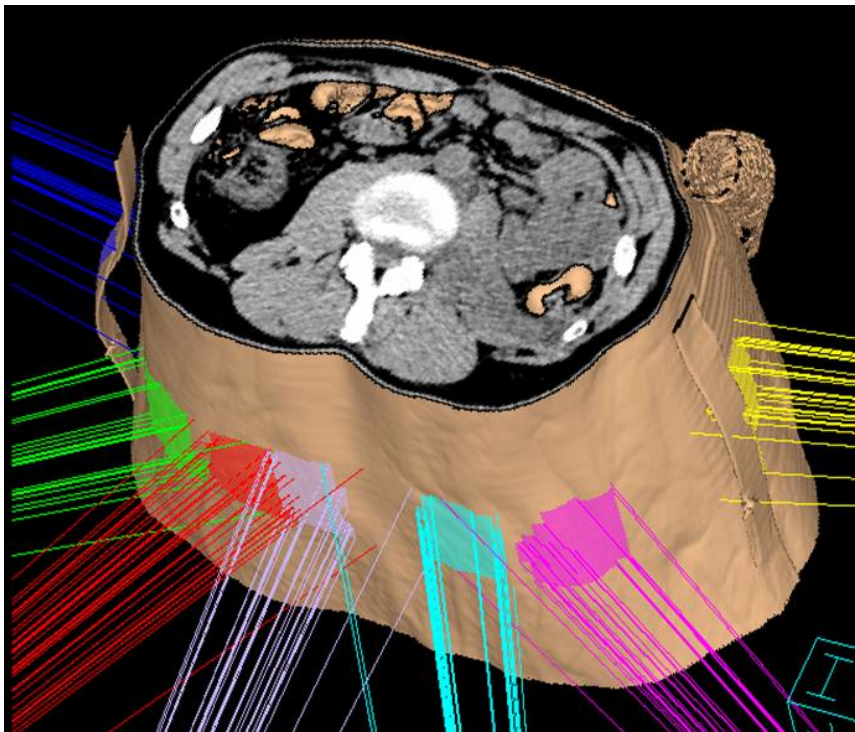
- In every human cell per day:
  - 50,000 SSB
  - 10,000 depurinations
  - 600 deaminations
  - 2000 oxidative base damages
  - 5000 alkylation damage
  - 10 cross links
  - 10 DSB's

Ionizing radiation damage

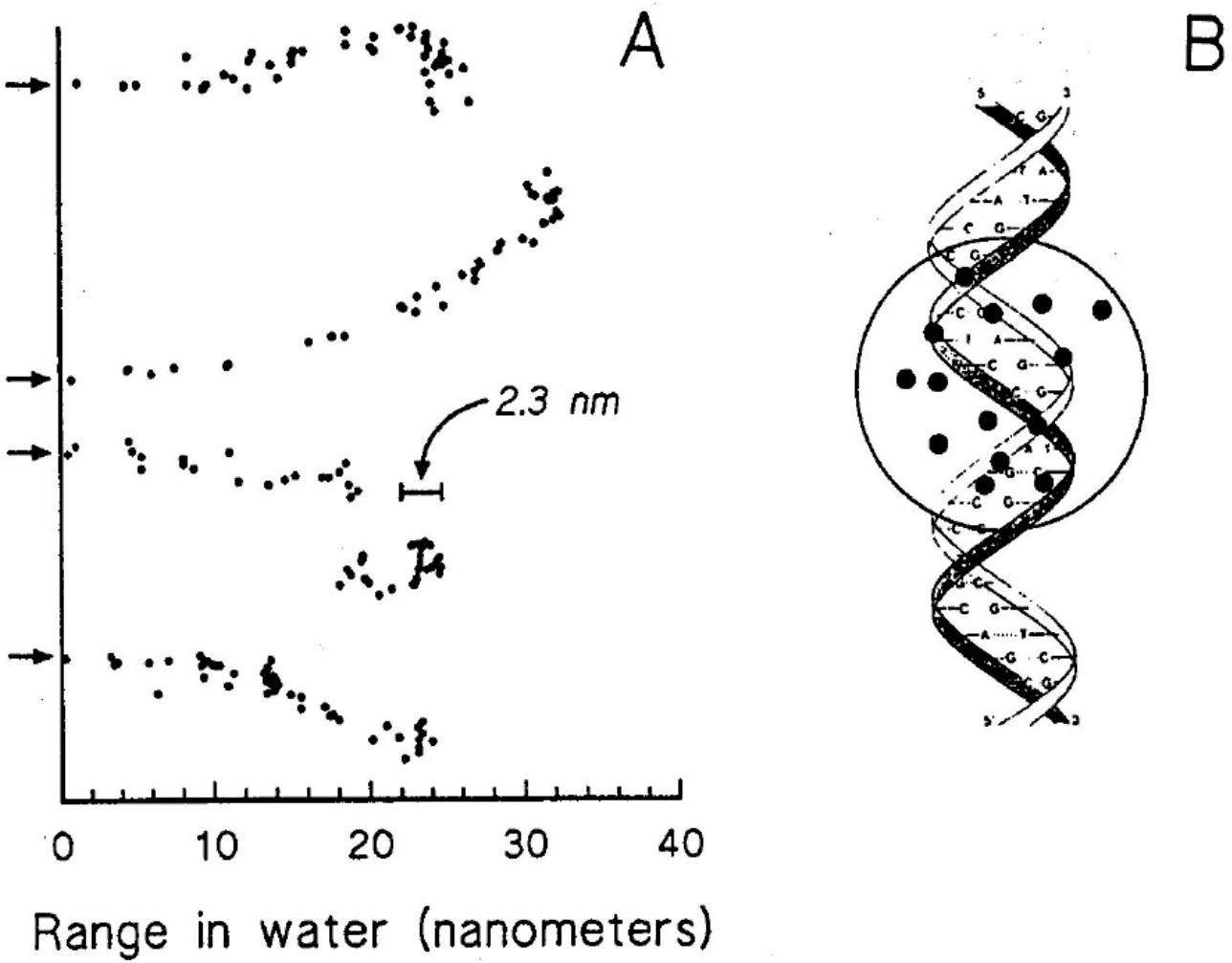
Primary target is the DNA

1Gy of low LET Xrays produces:

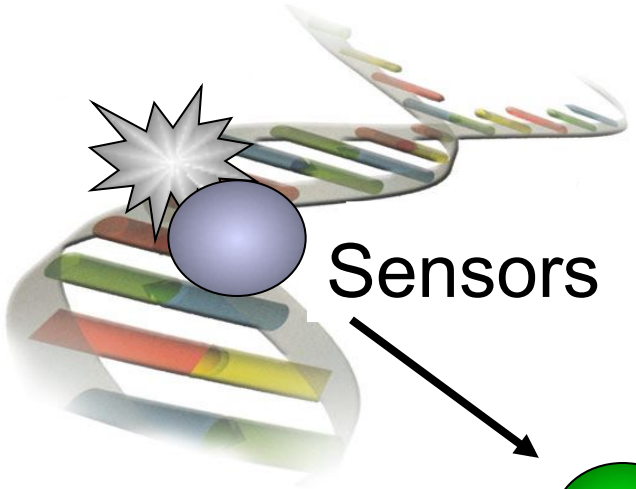
1000	single strand breaks
40	double strand breaks
1000	altered bases



Multiple damaged sites



DNA Damage Response



Sensors

Transducers/Mediators

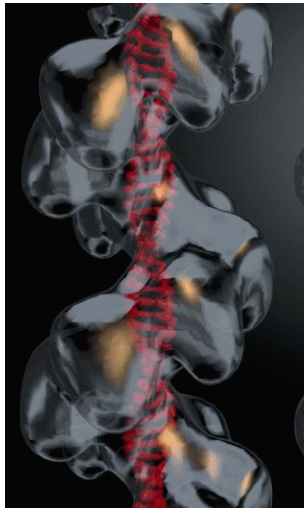
Effectors

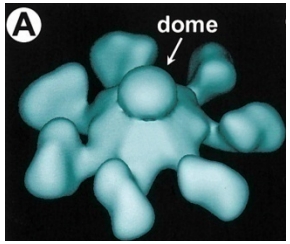
Initial cellular responses to radiation

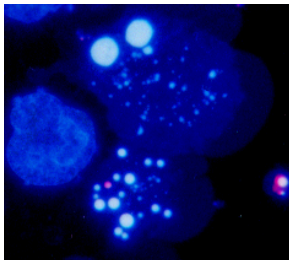
Sensors of damage

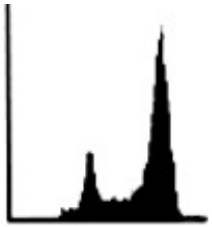
Biological Pathways

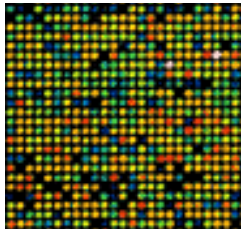
DNA Repair	Early Apoptosis	Cell cycle checkpoints	Gene expression

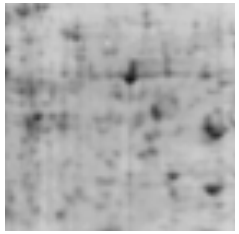




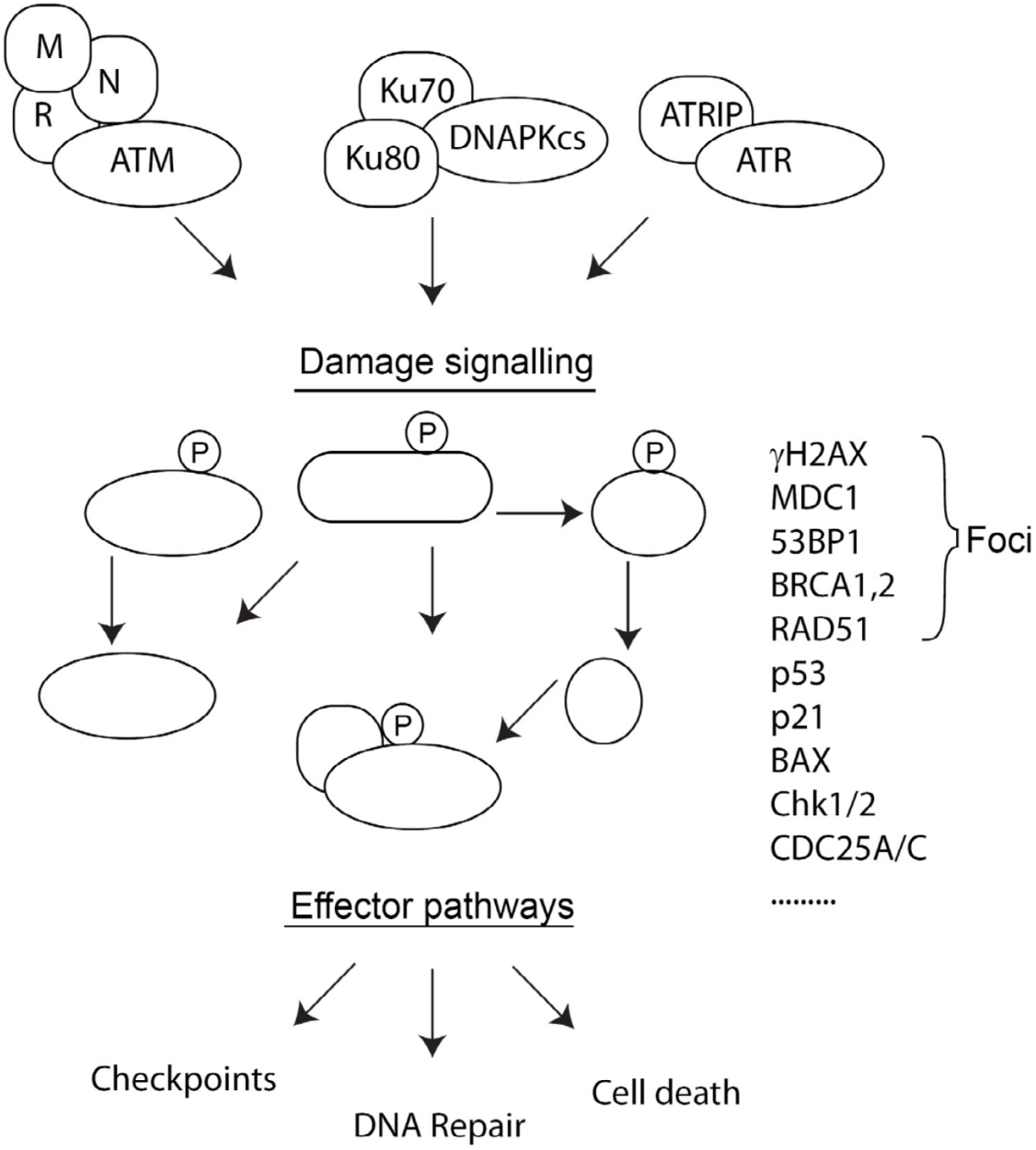




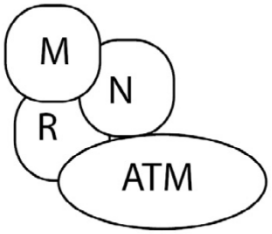




DNA damage signaling

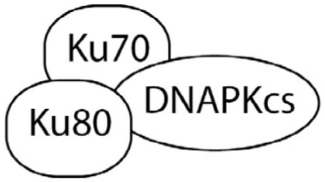


The Sensors



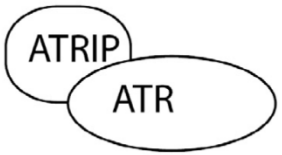
ATM
- PIKK kinase
- mutated in Ataxia Telangiectasia
- patients are radiosensitive
- activated by DNA damage (DSB), phosphorylates many proteins

MRN
- important for ATM activation, recruitment
- involved in processing damage
- nuclease activity



DNAPKcs
- PIKK kinase
- activated by DNA damage (DSB)
- involved directly in repair

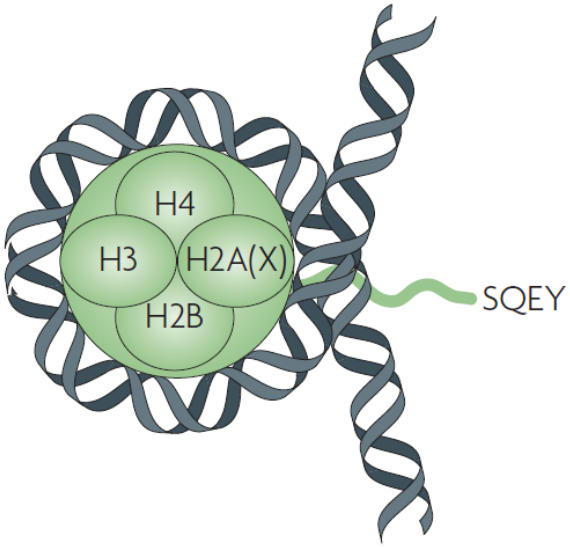
Ku
- DNA end binding proteins
- recognize damage, recruit DNAPKcs

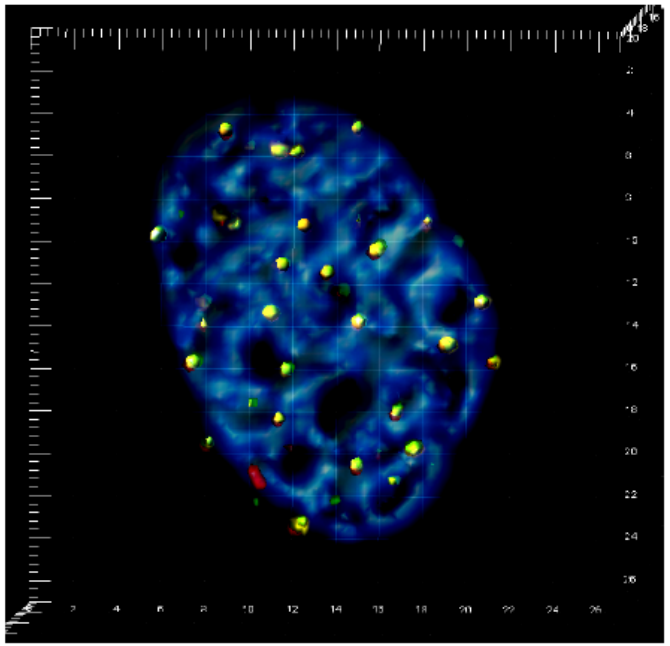


ATR
- PIKK kinase
- ATM and rad3 related kinase
- not involved in recognizing DSB
- important for replication stress, stalled forks
- is often activated during DSB repair

IRIF

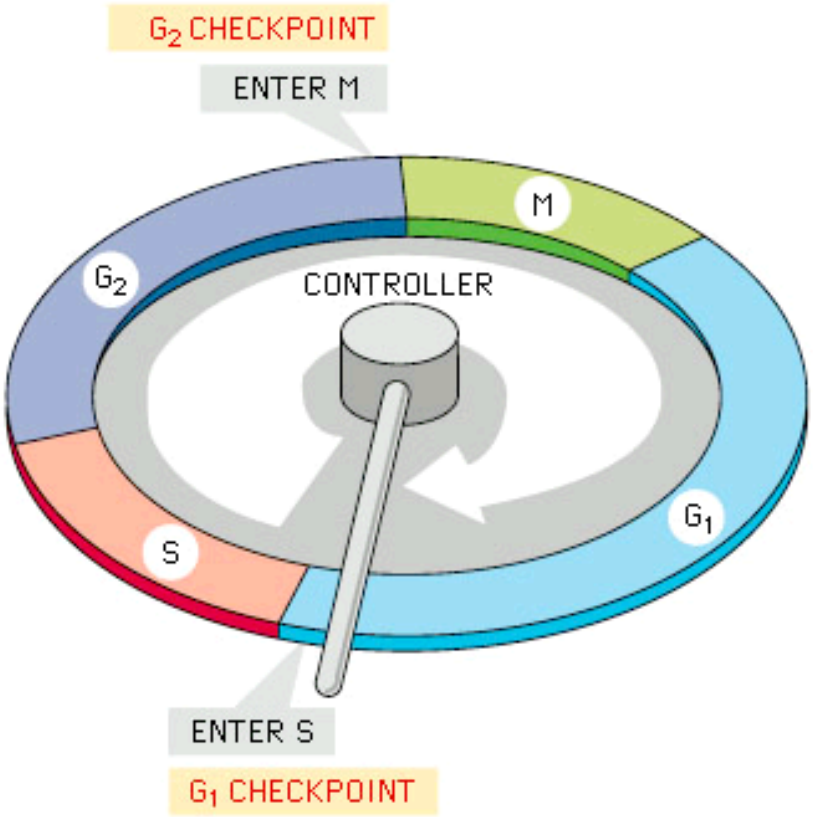
- Form rapidly after irradiation – minutes
- Occur at sites of damage
- Foci extend over larges region around the break





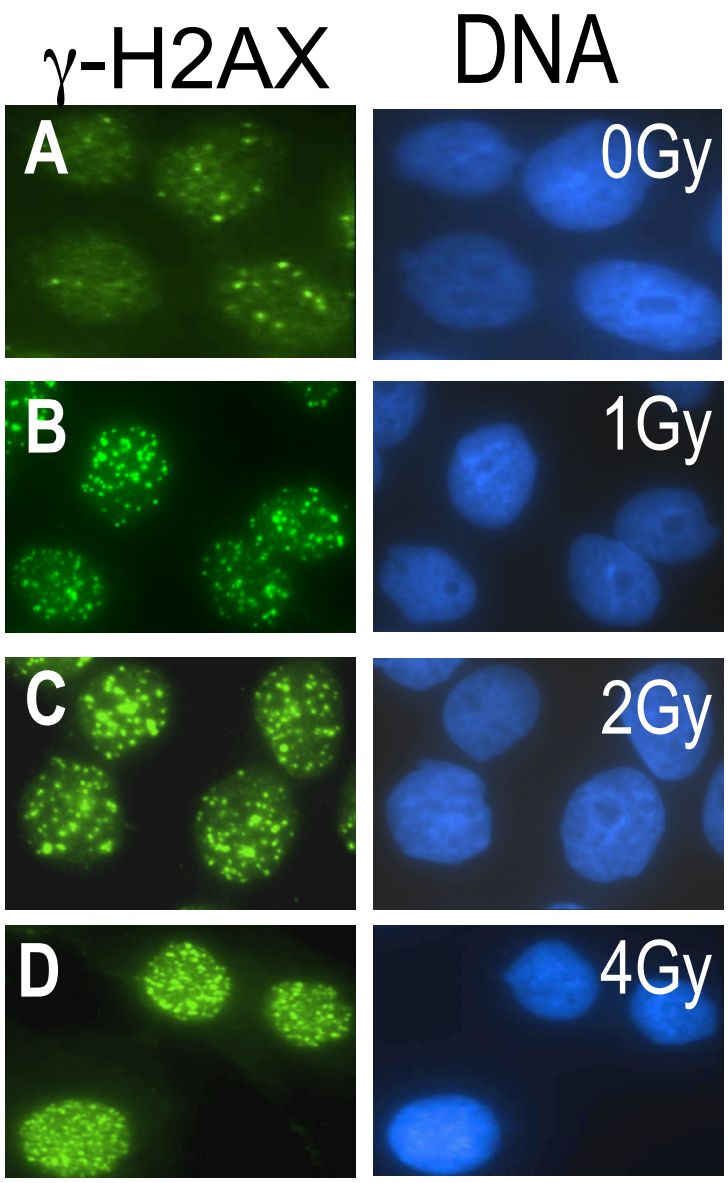
Checkpoints

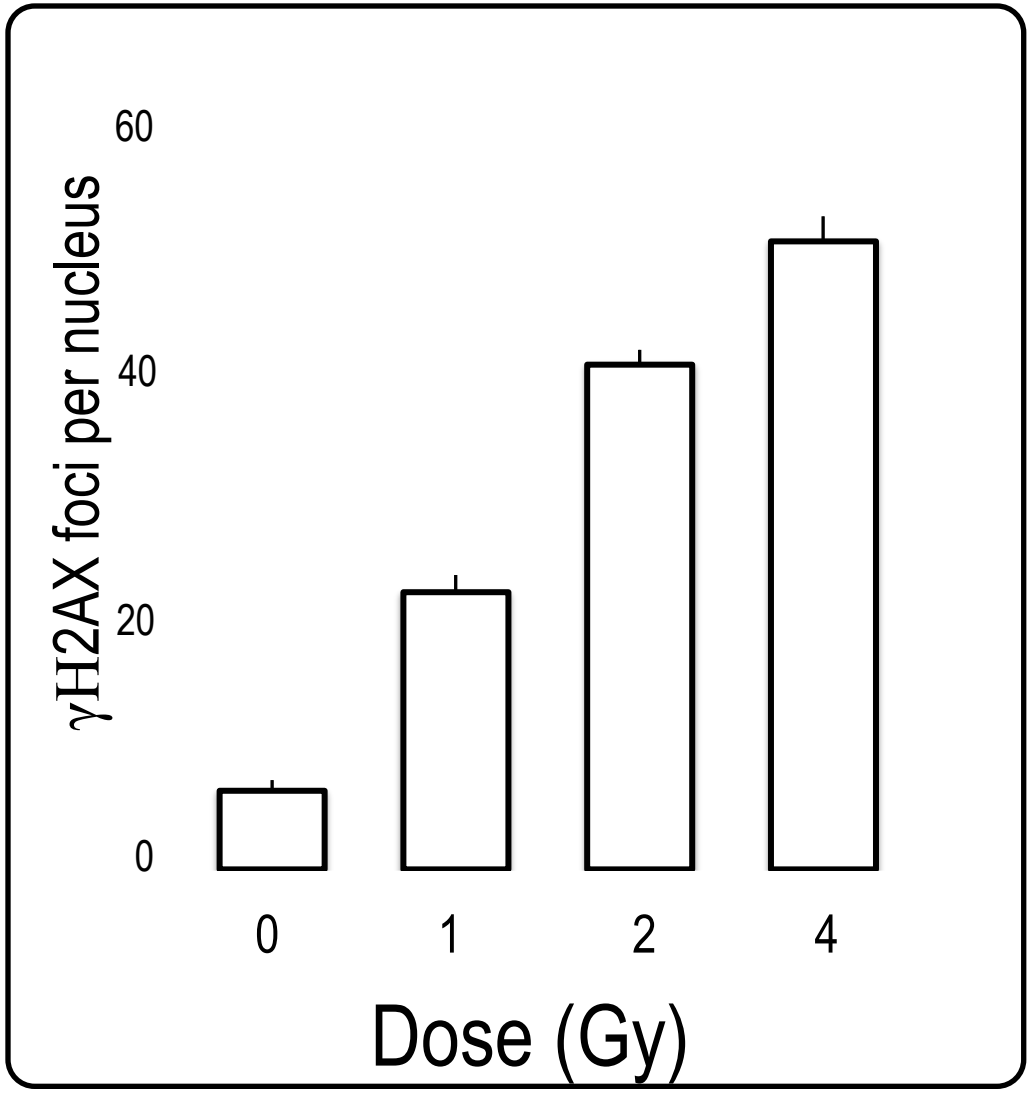
Checkpoints occur at several points in the cell cycle



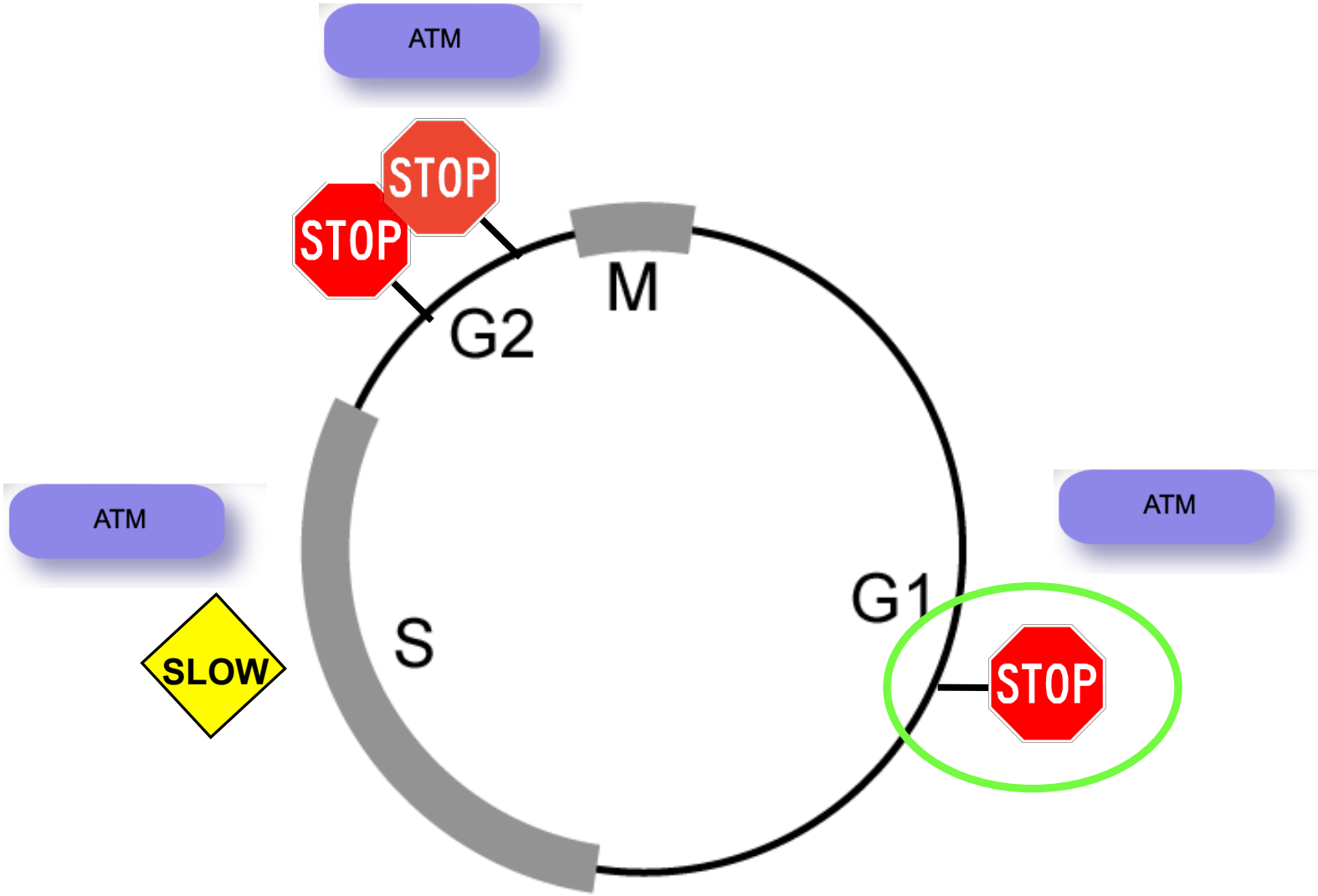
DNA damage?
Nutrients?
Growth factors?

IRIF mark DSBs





IR induces 4 distinct checkpoints



G1, S and Early G2 checkpoints

- Rapidly activated after IR
- Blocks entry into the next cell cycle phase
- Not important for intrinsic radiosensitivity
  - To single doses!
- Often altered in cancer
  - Important for avoiding mutations
  - Tumor cells and normal cells proliferate differently after IR
- Involved in activation of premature senescence

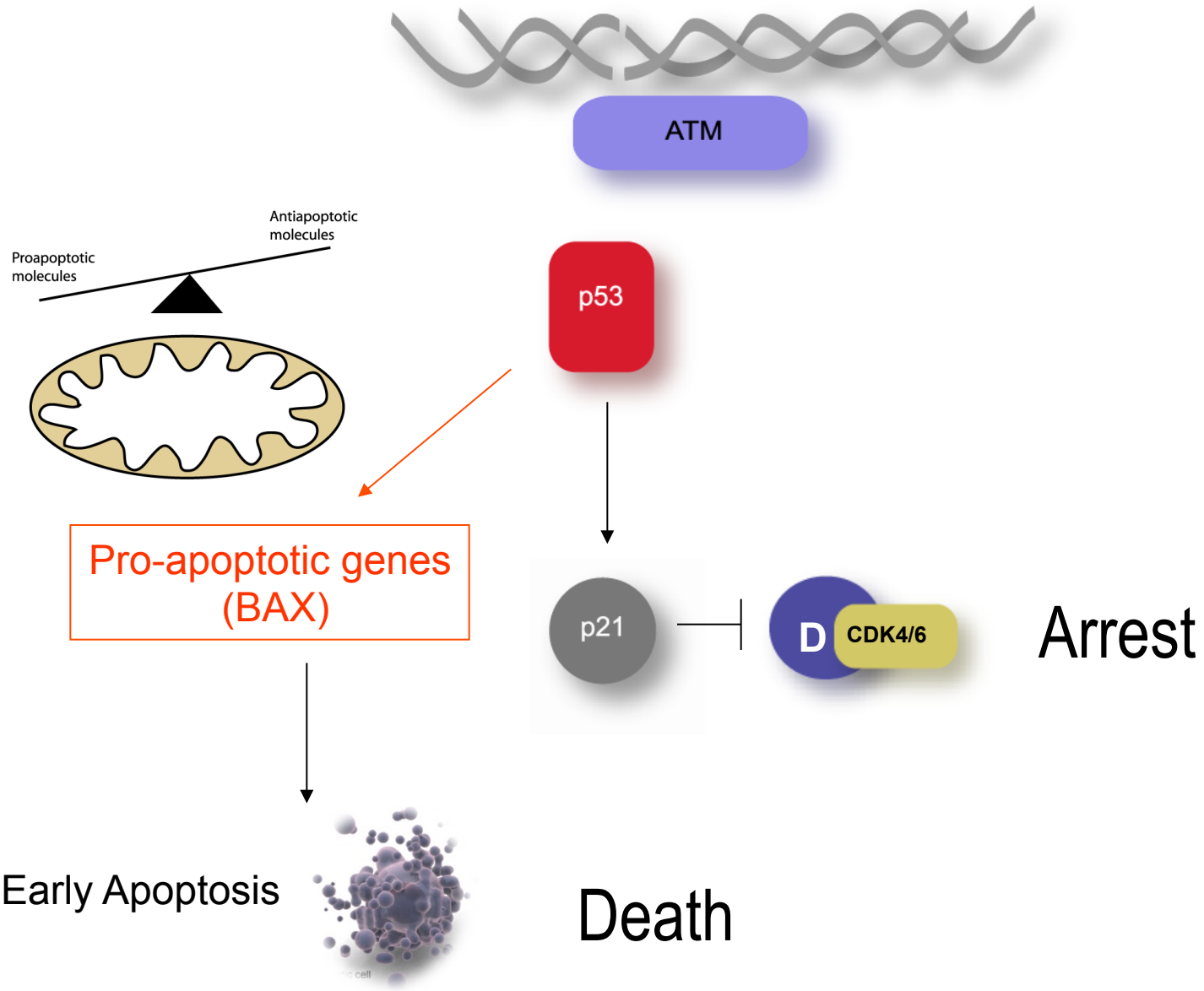
Late G2 checkpoint

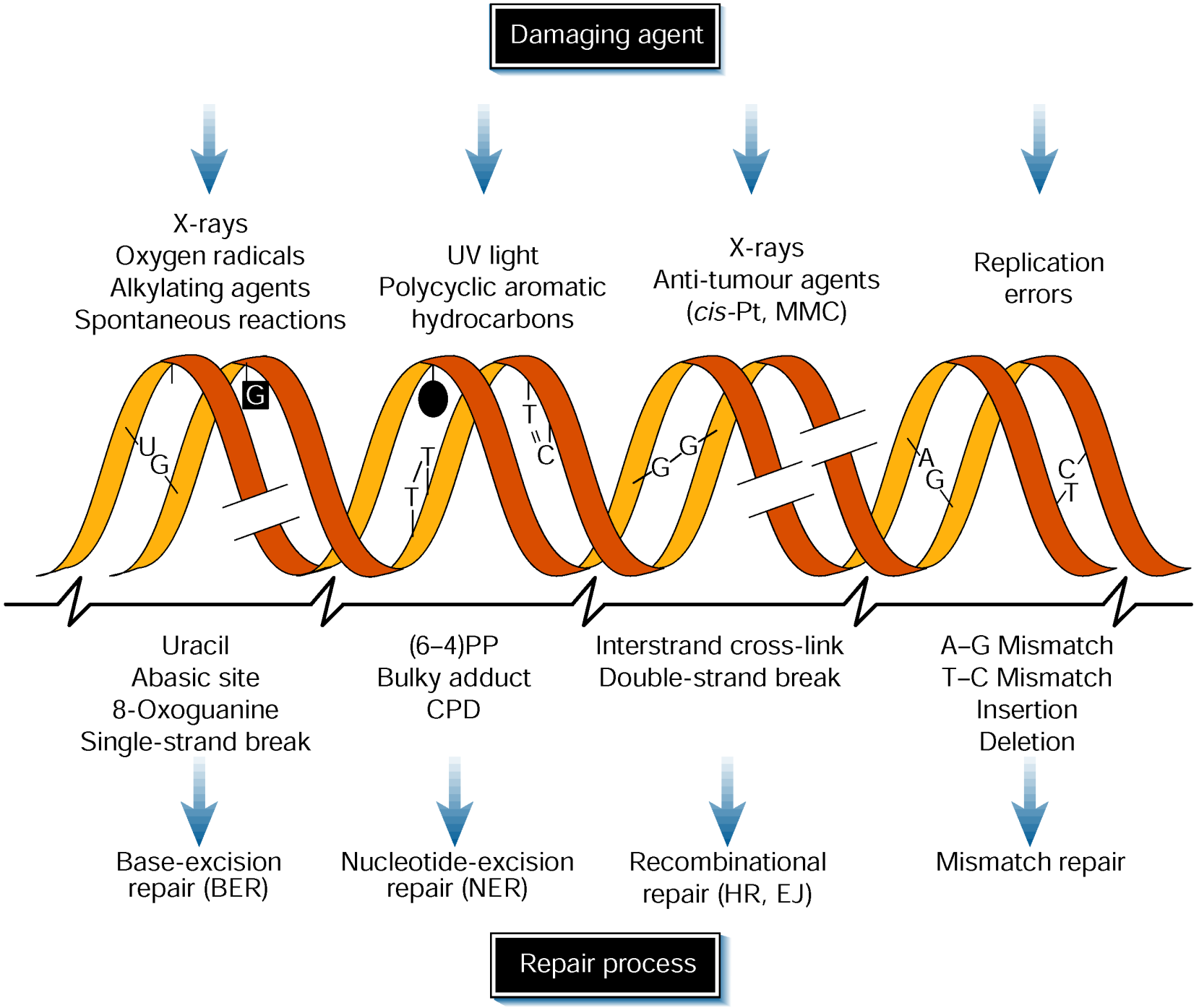
- Not part of the initial DDR
  - Becomes evident many hours after irradiation
- Checkpoint is activated in cells irradiated in G1, S and G2 that arrive at mitosis with damage

- *Protects against mitotic catastrophe*

- Important for radiation sensitivity

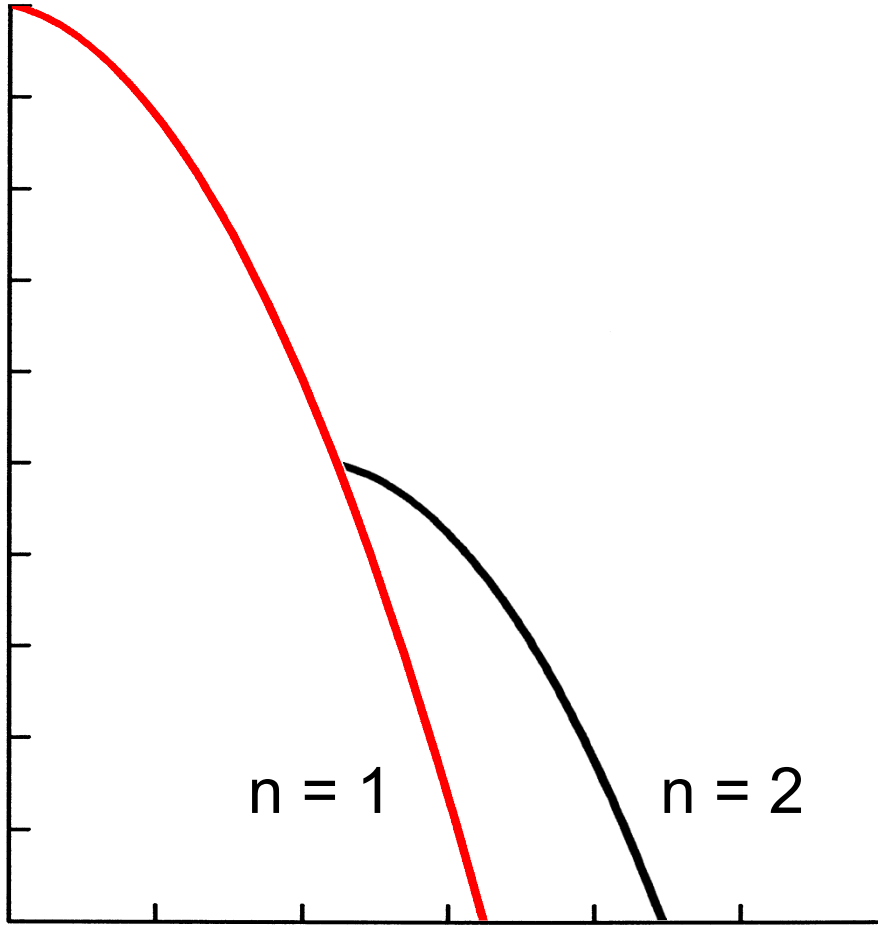
G1 checkpoint and early apoptosis

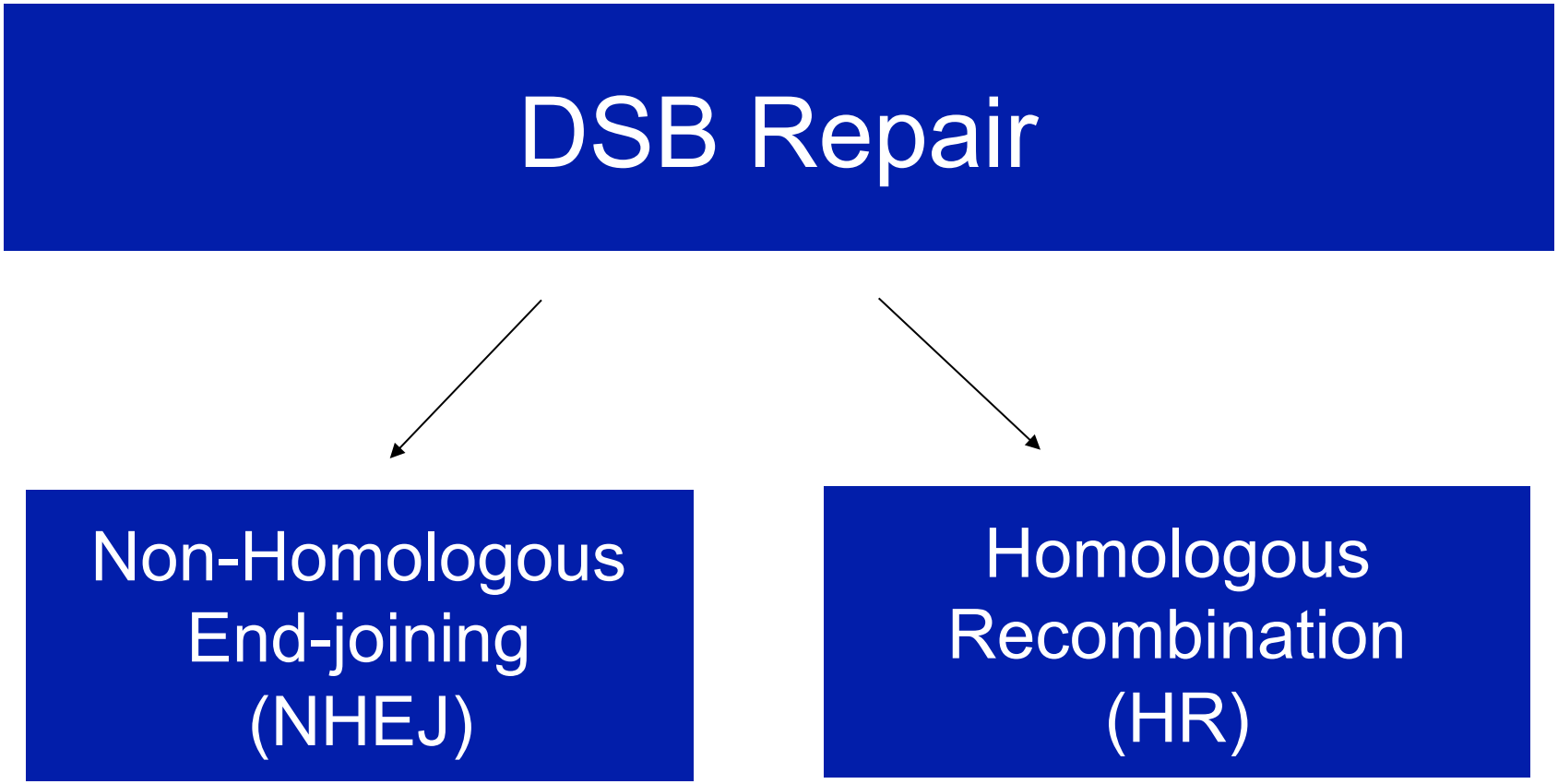



Damaging agent
X-rays
Oxygen radicals
Alkylating agents
Spontaneous reactions
UV light
Polycyclic aromatic
hydrocarbons
X-rays
Anti-tumour agents
(cis-Pt, MMC)
Replication
errors
U
G
G
T
T
T
C
G
G
A
G
C
T
Uracil
Abasic site
8-Oxoguanine
Single-strand break
(6–4)PP
Bulky adduct
CPD
Interstrand cross-link
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 and Fractionation

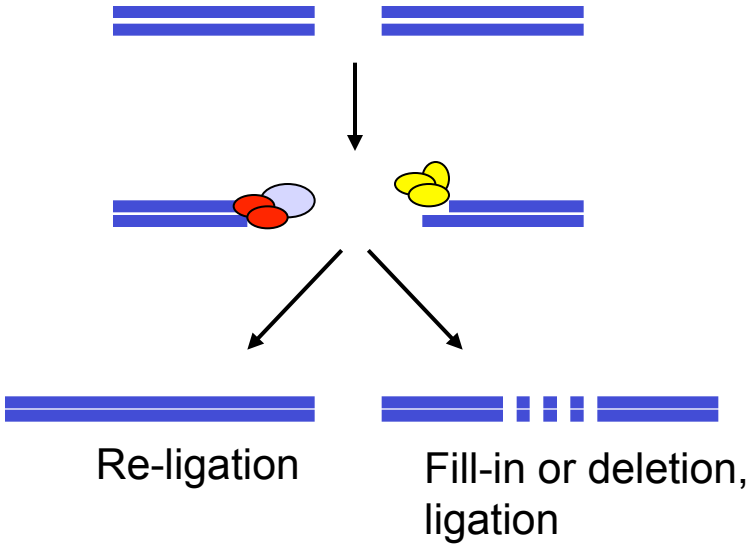
- The fractionation effect is due mainly to DNA repair
- ½ time for recovery is similar to ½ time for repair



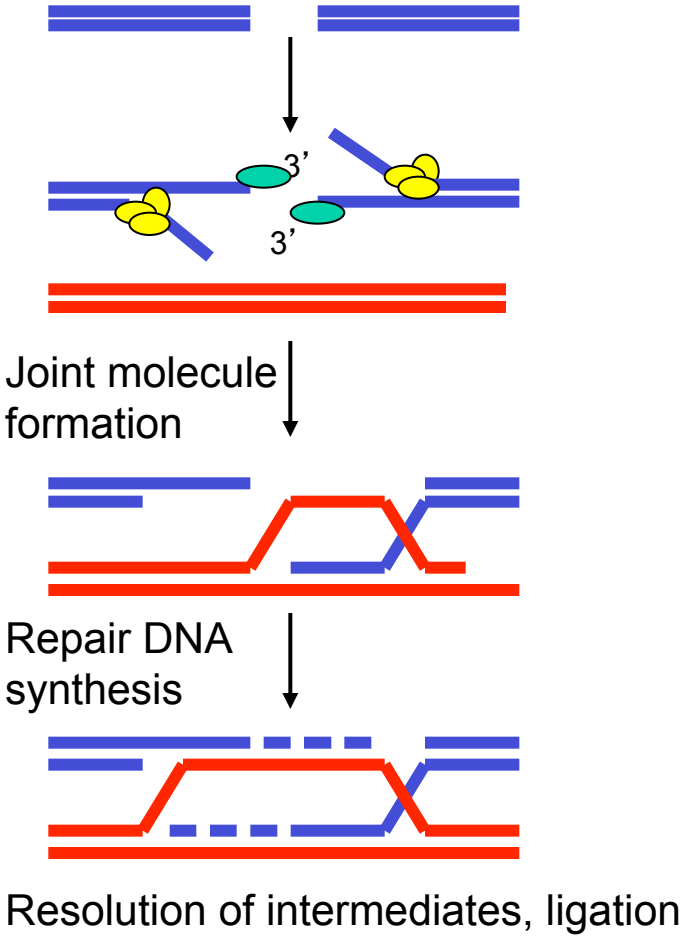

DSB Repair
Non-Homologous End-joining (NHEJ)
Homologous Recombination (HR)

HR and NHEJ

Non-homologous end-joining

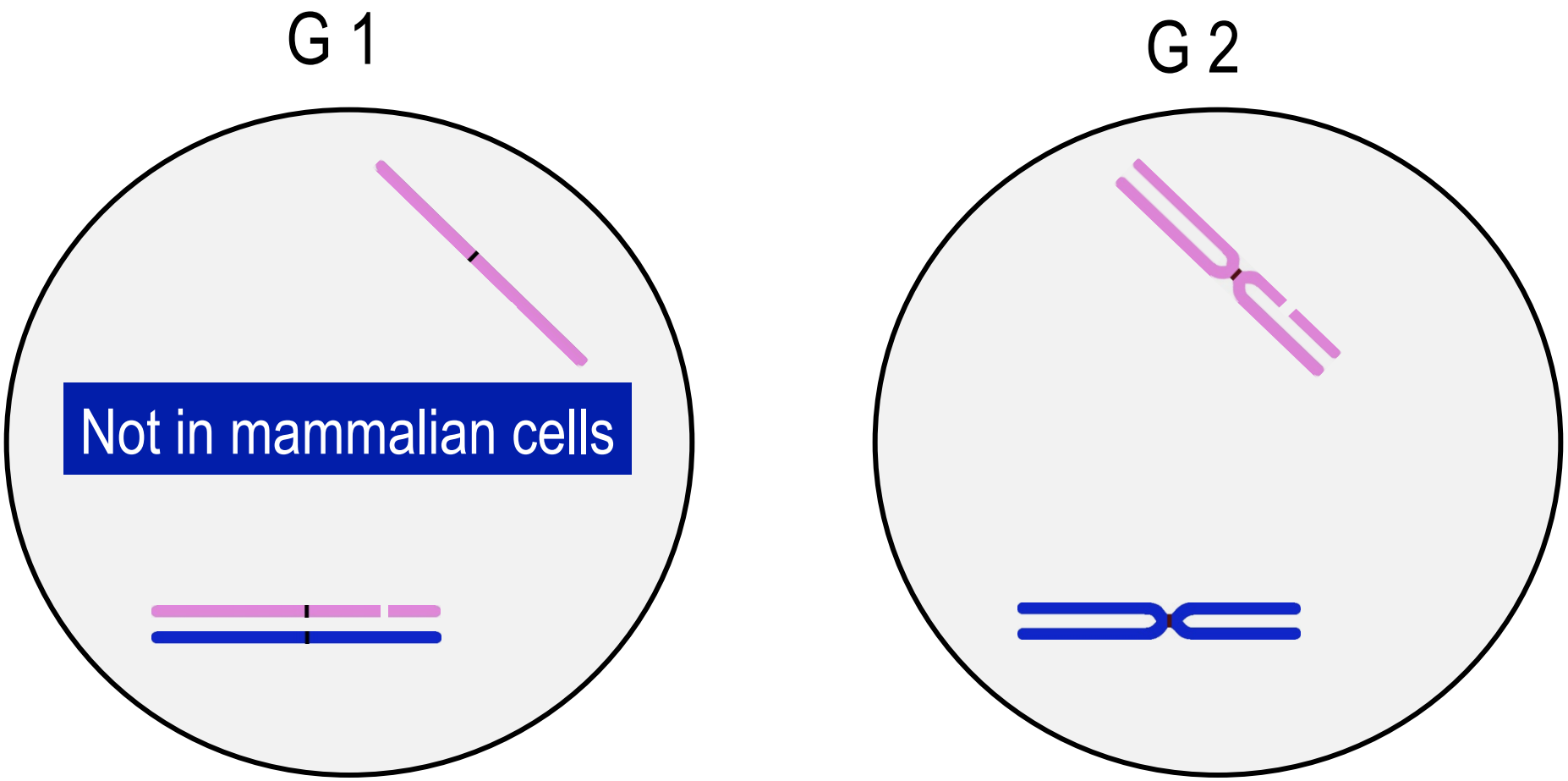


Homologous recombination

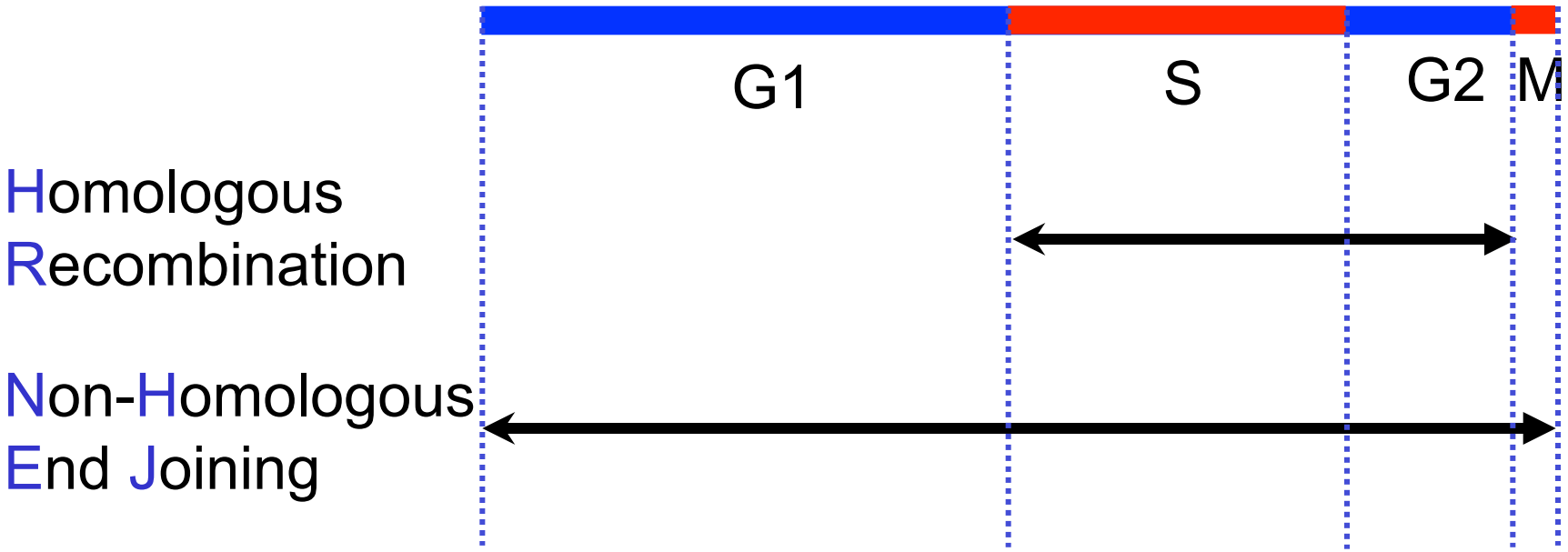


Cell-cycle dependence of HR repair

- HR requires a homologous template



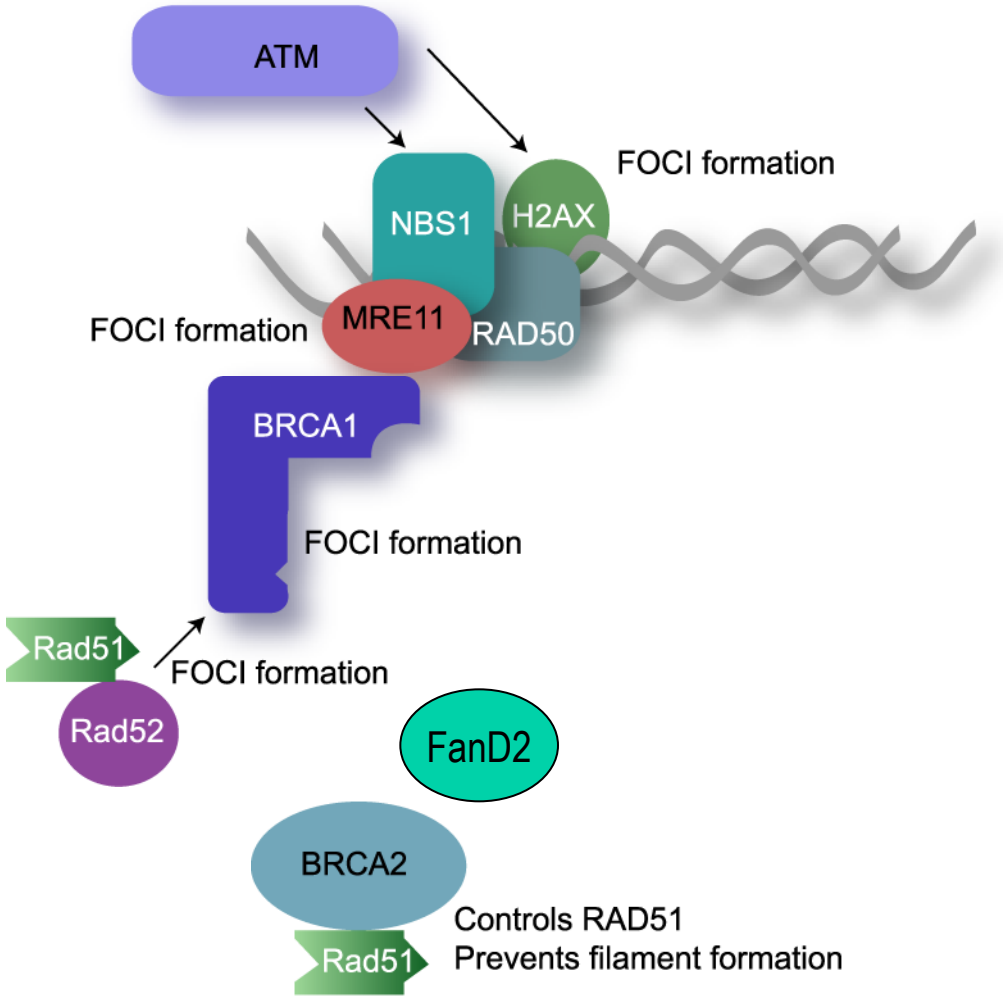
DNA Repair Through the cell cycle



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

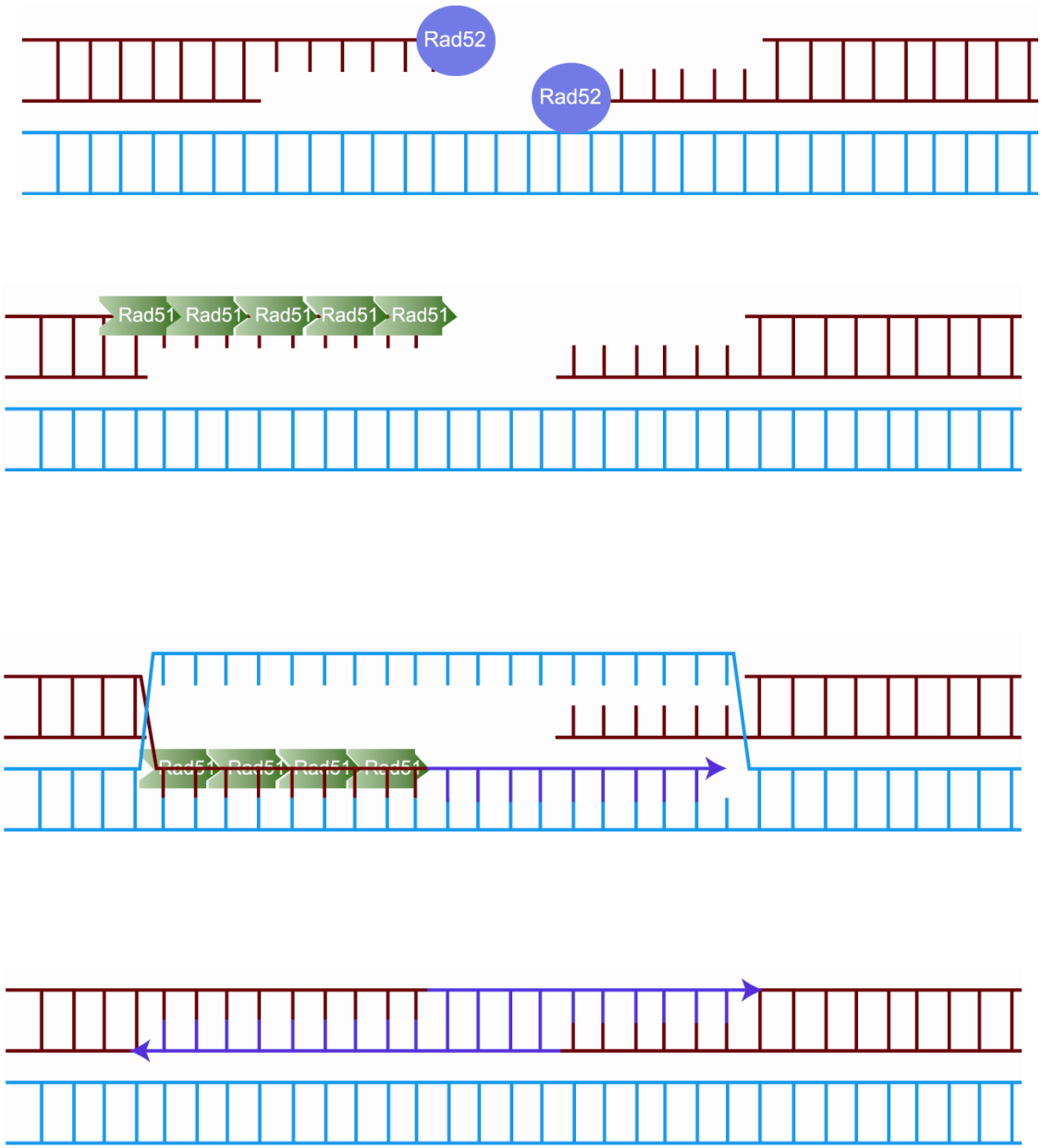
Recruitment of repair machinery - HR



BRCA1 aids recruitment of HR machinery

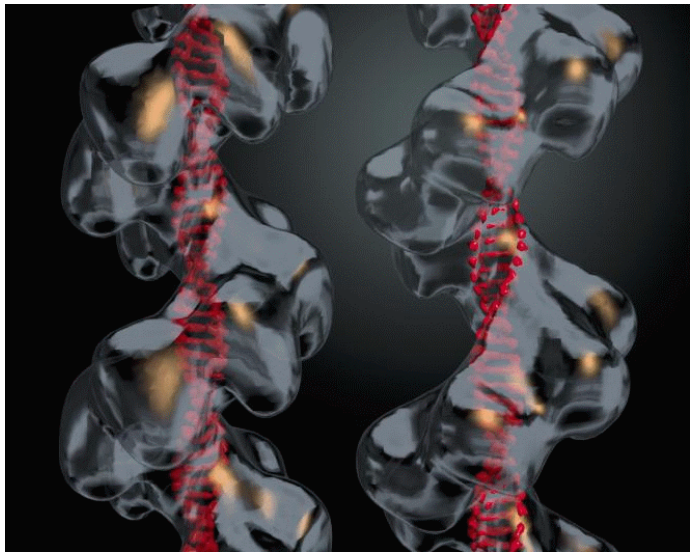
HR machinery influenced by FANCD2 and BRCA2

Homologous Recombination - HR

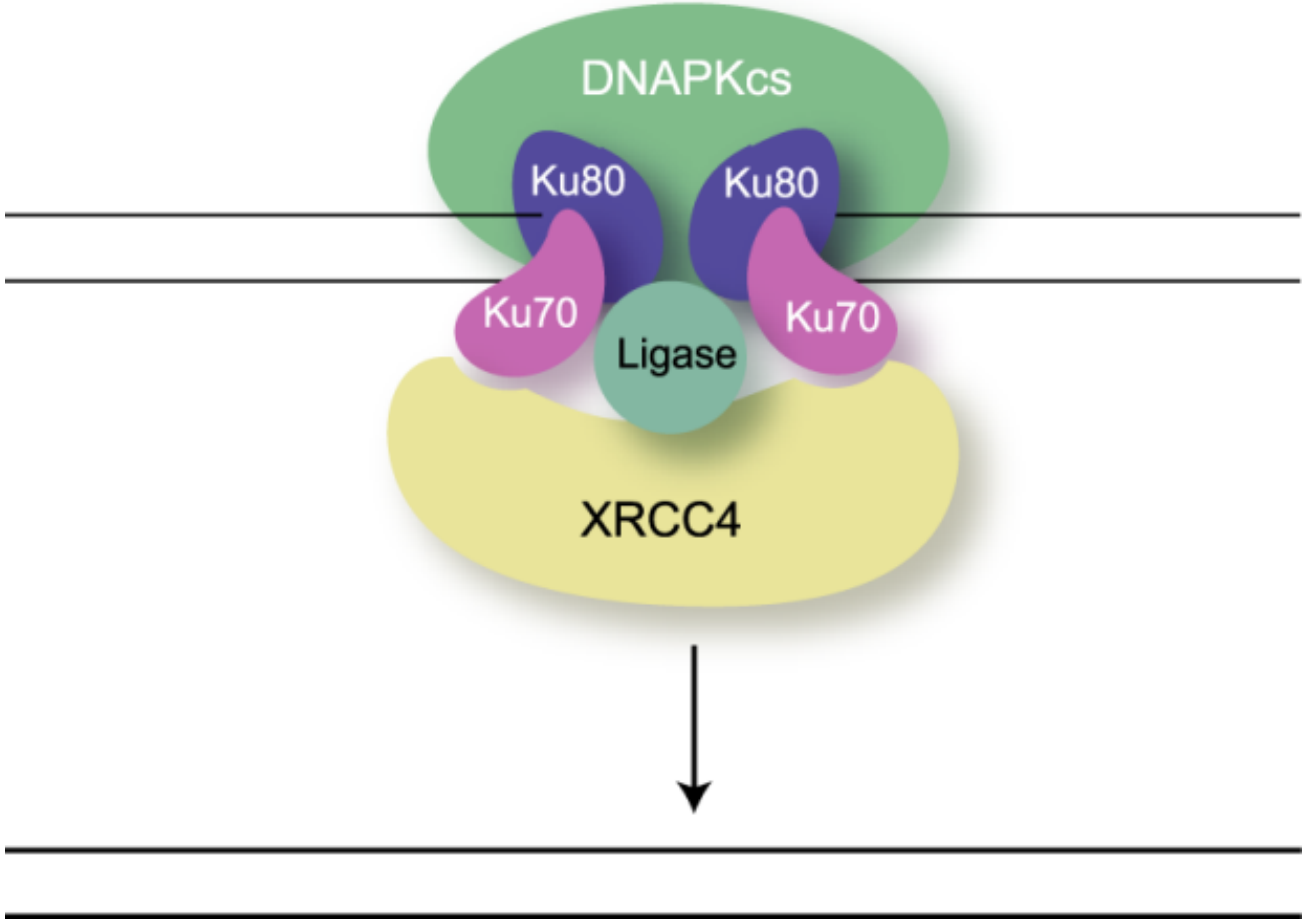


Accurate repair of a double stand break

Requires a sister chromatid as undamaged template

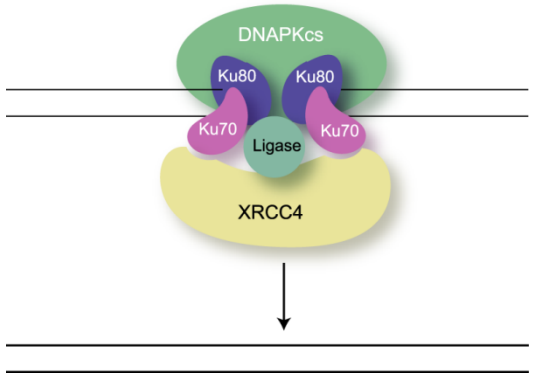


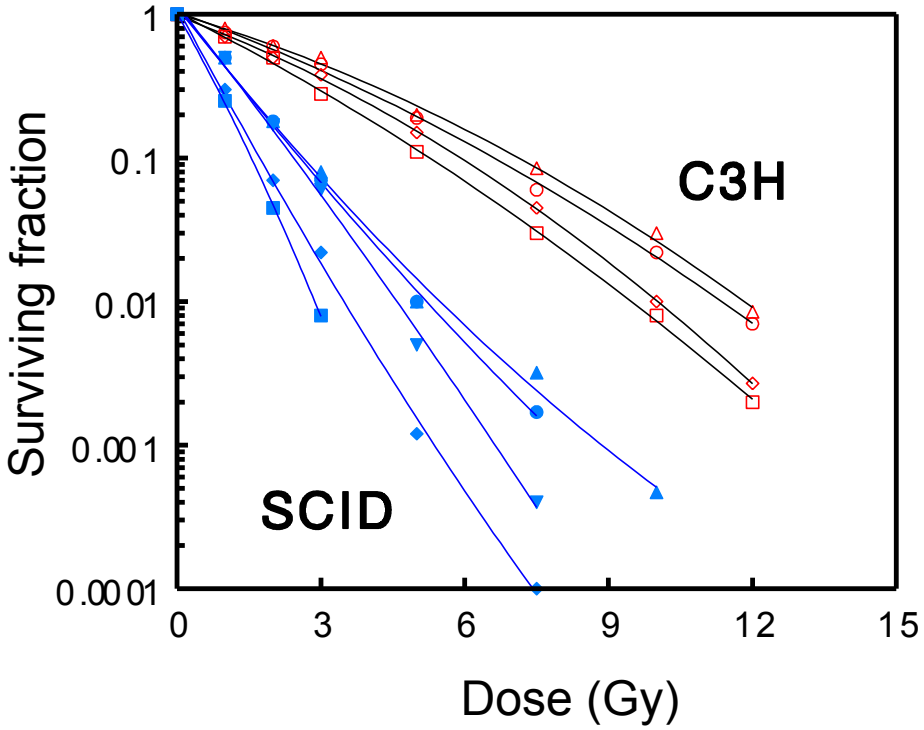
NHEJ



NHEJ

Defects in EJ cause extreme radiosensitivity





All tumors arising in DNA-PK deficient mice are radiosensitive

Clinical: DNA repair inhibitors

- BRCA tumours
  - BRCA proteins are haplosufficient tumor suppressors
  - BRCA biallelic loss causes mild radiosensitivity
- Synergy with PARP inhibition (Base excision repair, Single strand break repair)

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 (NHEJ) causes (extreme) radiosensitivity

Normal tissues: Radiosensitivity and fractionation

ESTRO School

Wolfgang Dörr

ATRAB – Applied and Translational Radiobiology

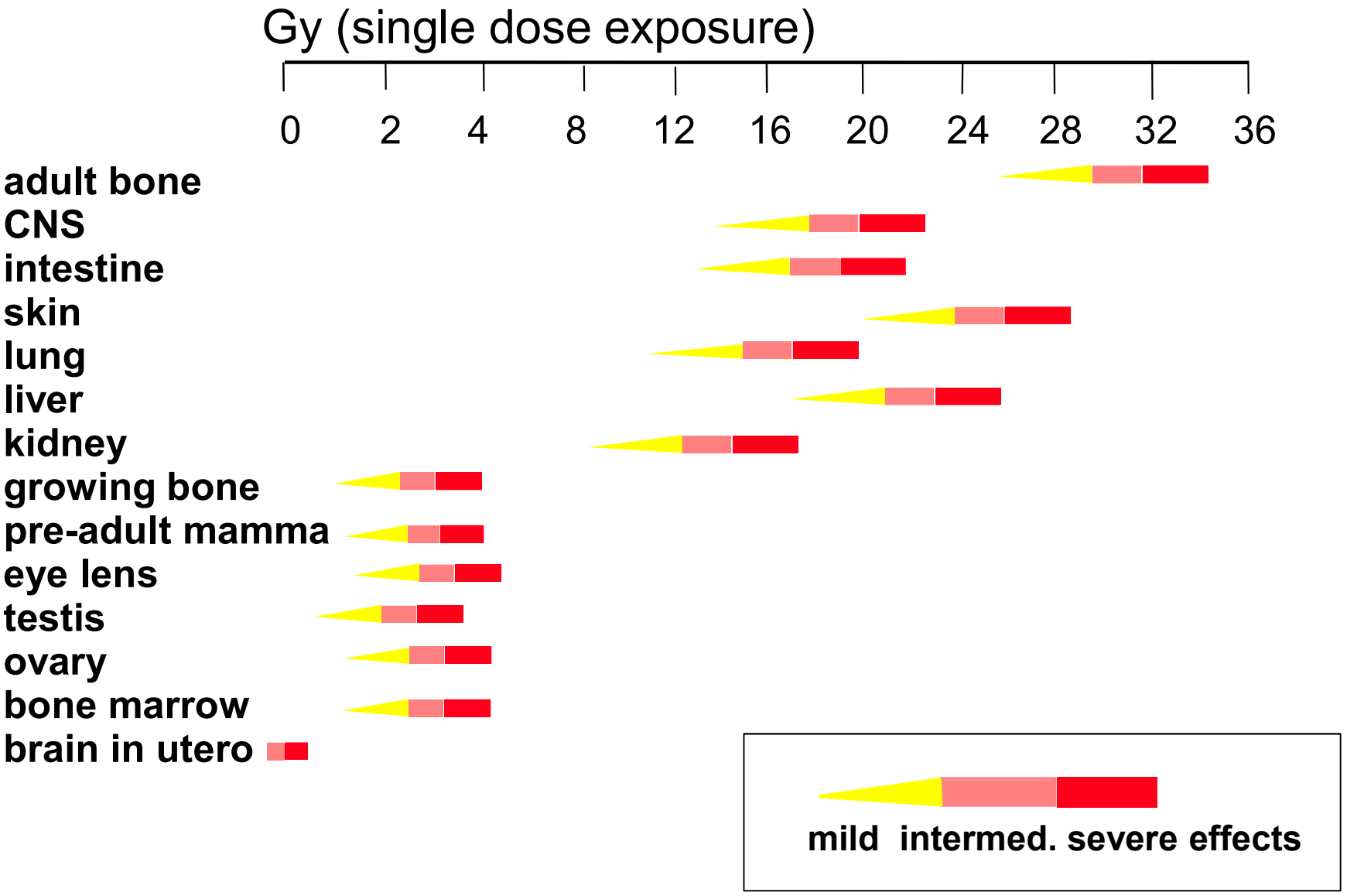
Dept. of Radiation Oncology &
RadOnc - CD Laboratory for Med.Rad.Res. for Rad.Oncol.

Medical University of Vienna, Austria

Radiation effects - 5 Rs of radiotherapy

Radiation sensitivity
Recovery
Redistribution
Repopulation
Reoxygenation

Intrinsic (tissue) radiosensitivity



Radiation effects - 5 Rs of radiotherapy

Radiation sensitivity

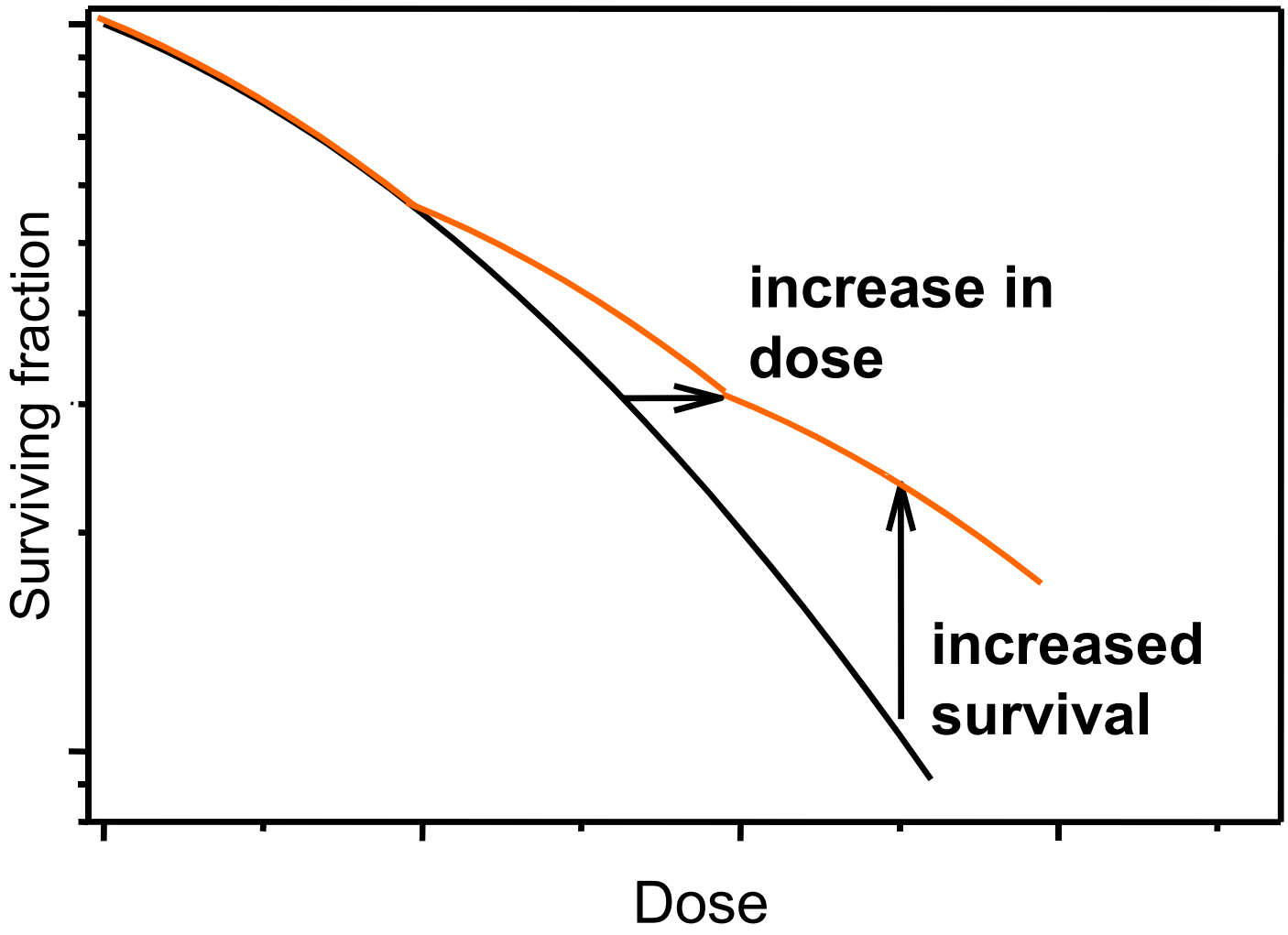
Recovery

Redistribution

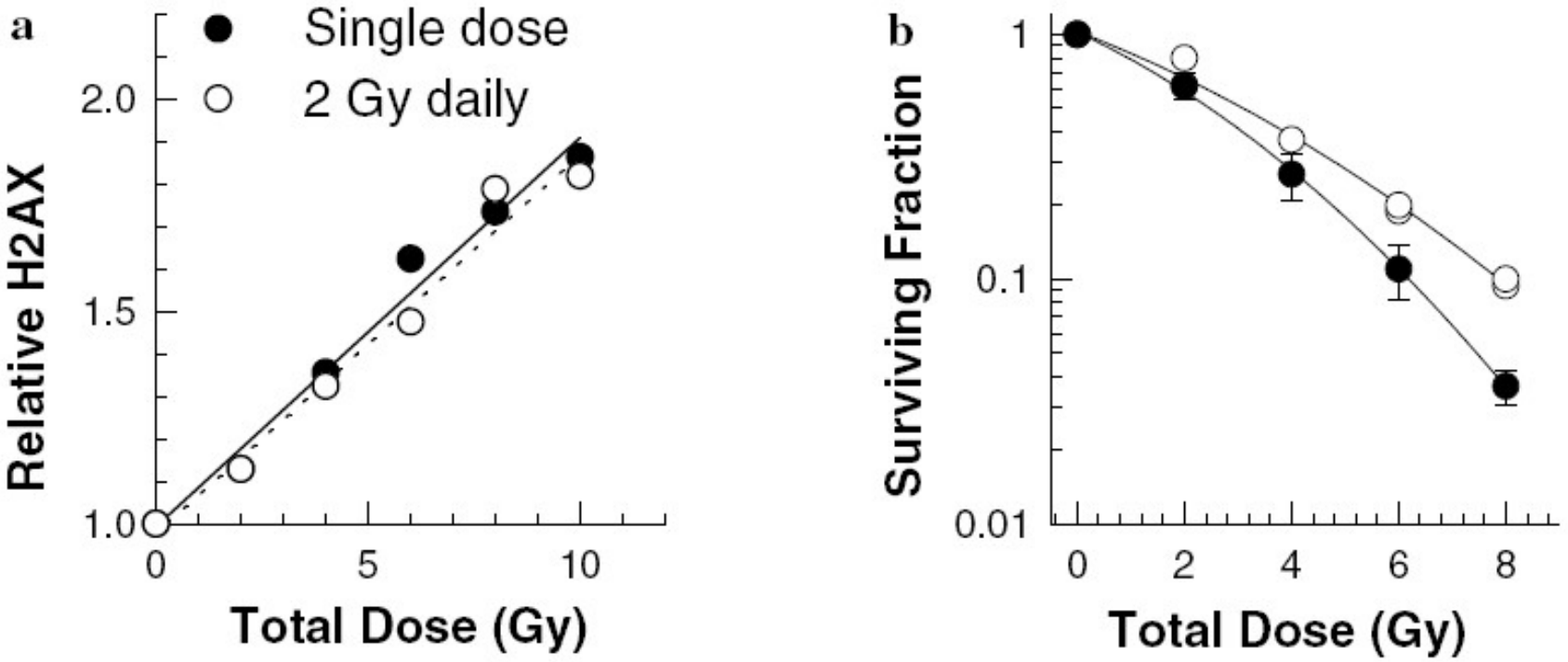
Repopulation

Reoxygenation

Recovery – in vitro



Recovery and DNA-Repair – in vitro

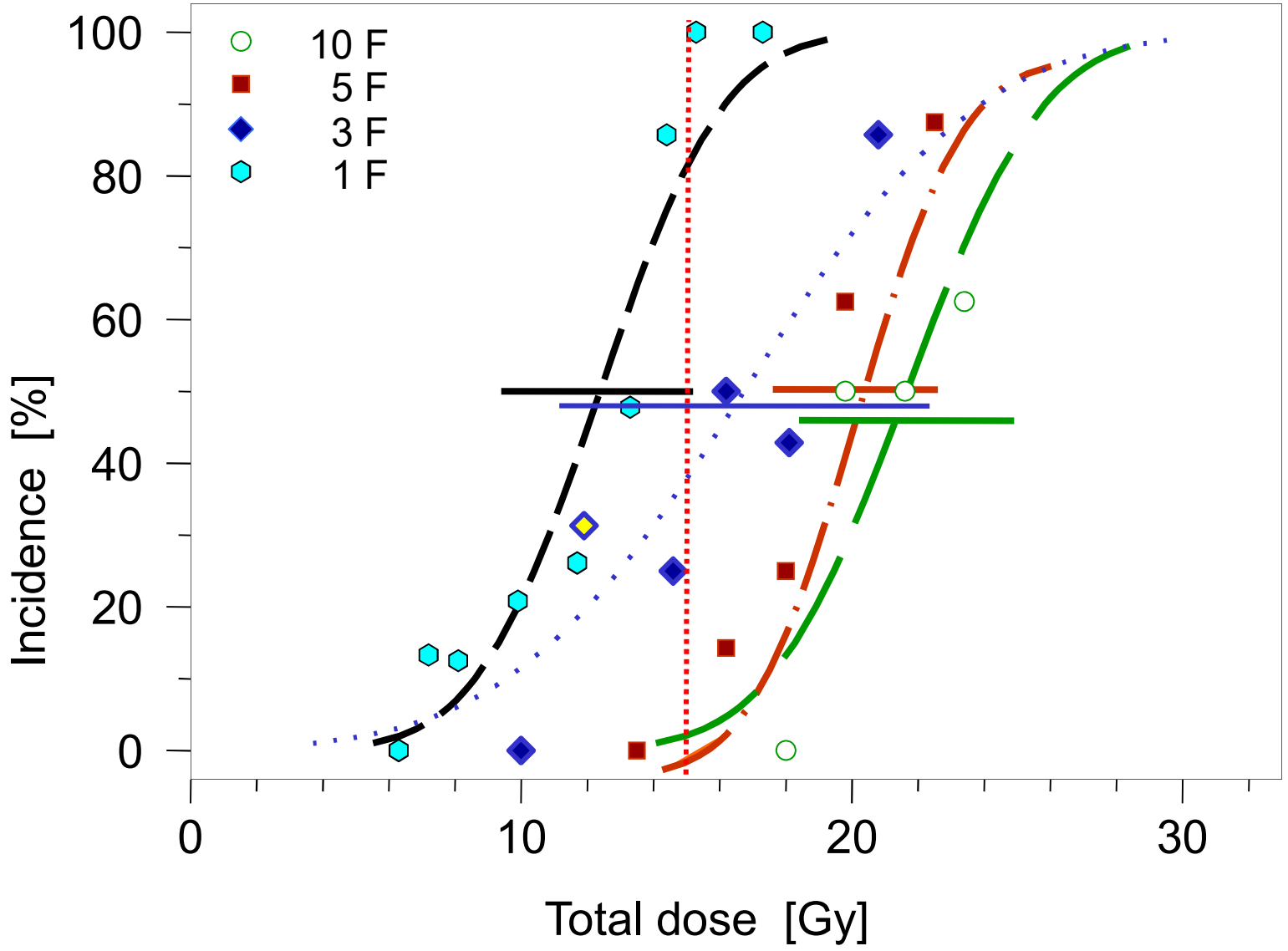


in vitro: DNA-Repair ?

in vivo ??? – more complex, DNA-Repair +++

modified from: Klokov et al., RTO 80, 2006, 223-229

Dose fractionation: Split course studies

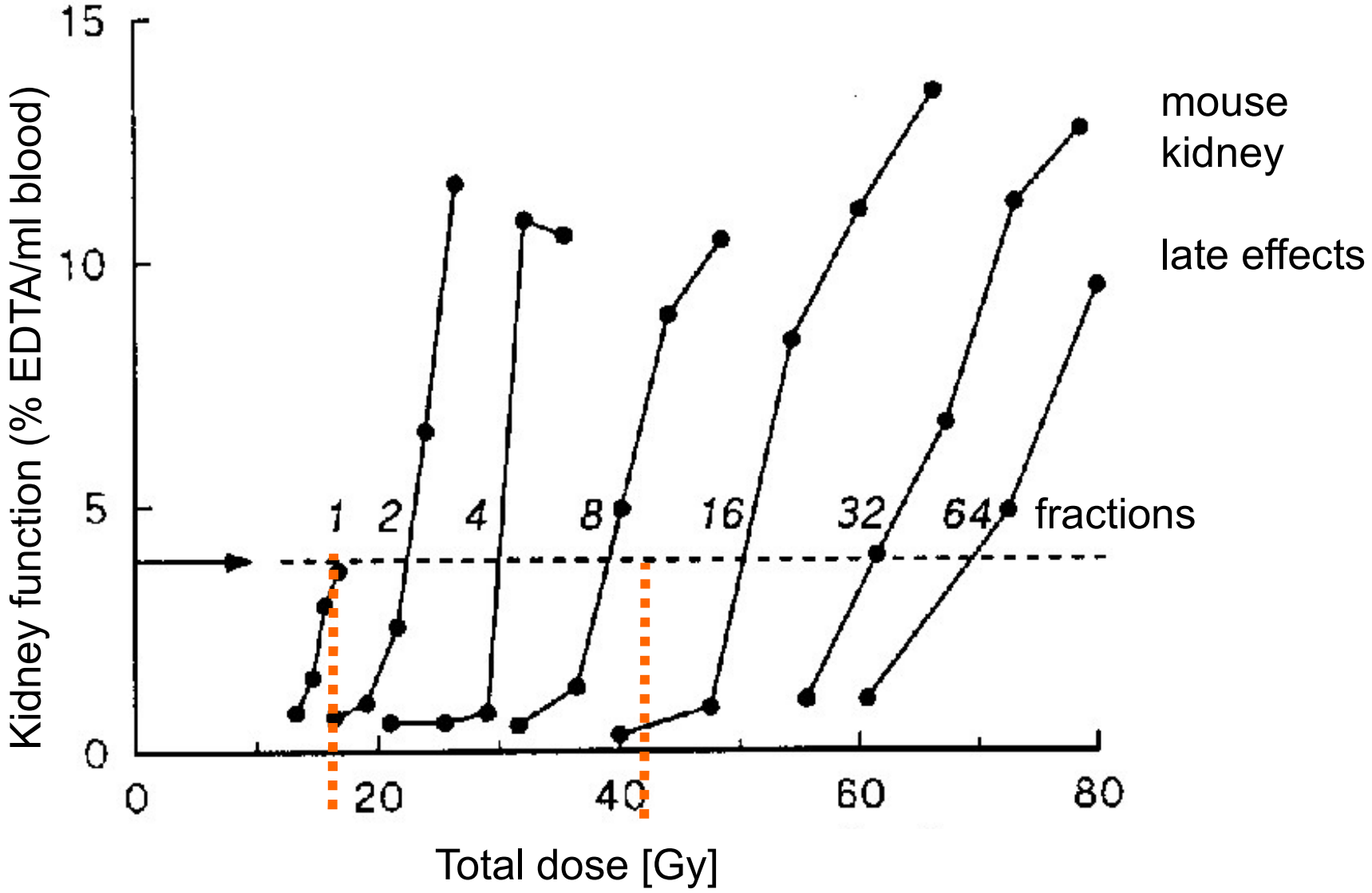


mouse tongue mucosa

early response

modified from: Dörr et al., RTO 27, 1993, 36-45

Dose fractionation: Split course studies



modified from: Stewart et al., Radiat. Res. 98, 1984, 407-420

Dose fractionation: LQ formalism

α/β-value - early effects / experimental data

	Tissue/reaction	α/β-value [Gy]	Ref.
Epidermis	Desquamation	**9.1-12.5** **8.6-10.6** 9-12 **49.6 [42.2;58.6]**	Douglas and Fowler 1976 Joiner et al. 1983 Moulder and Fischer 1976 Ruifrok et al. 1994
Oral mucosa	Ulceration	7.9 [1.5;…] 16.4 [14.6;18.2] 11.6 [6.8;18.9] 11 [7.4;20.2]	Ang et al. 1985 Mose… and Kummermehr 1986 (Reanalysis) …alliet et al. 1987 Stü…n et al. 1991 Dör… et al. 1993 Nickstadt and Dörr, unpublished
Intestine	Crypt survival Weight loss	6.0-8… 6.6-10.7 … 13.3 …13	Withers et a. 1976 Thames et al. 1981 Tucker et al. 1983 Huczkowski and Trott 1984 Tucker and Denekamp 1984
Urinary bladder	Impaired function	**13.9 [8.4;24.6]** **11.0 [7.5;16.1]**	Dörr and Schultz-Hector 1992 Dörr 1995
Testis	clon. survival	**12-13**	Thames and Withers 1980

λ6 Gy (10 Gy)

Dose fractionation: LQ formalism

α/β-value - late effects / experimental data

Tissue / reaction		α/β-value [Gy]	Ref.
Spinal cord	**cervical**	**1.8-2.7**	van der Kogel 1979
		1.6-1.9	White and Hornsey 1978
		1.5-2.0	Ang et al. 1983
		2.2-3.0	Thames et al. 1981
	lumbar	**3.7-4.5**	van der Kogel 1979
		4.1-4.9	White and Hornsey 1978
		3.9-4.1	Leith et al 1981
		2.3-	Amals and Yuhas
Intestine	Weight loss	**1-5**	Terry and Denekamp
	Rectal stenosis		Trott and Kummermehr 1994
Kidney		**1.7-2.0**	Caldwell 1975
		1.7-2.0	Hopewell and Wiernik 1977
		3.5-3.8	van Rongen et al. 1988
		1.0	liams and Denekamp 1984
		0.9-	Stewart et al. 1984
		1.4-	Thames et al. 1988
Urinary bladder	Impaired function	**6.6 [2.2;14]**	Stewart et al. 1984
		5.8 [3.-8]	Bentzen et al. 1992
		4.4 [2.0;8.4]	Dörr and Bentzen 1999
Lung	LD50	**4.4-6.3**	Wara et al. 1973
		2.8-4.8	Field et al 1976
		2.0-2.4	Travis et al. 1983
	Breathing frequency	**1.9-3.1**	Parkins and Fowler 1985

v 6 Gy (3 Gy)

Dose fractionation: LQ formalism - Tumours

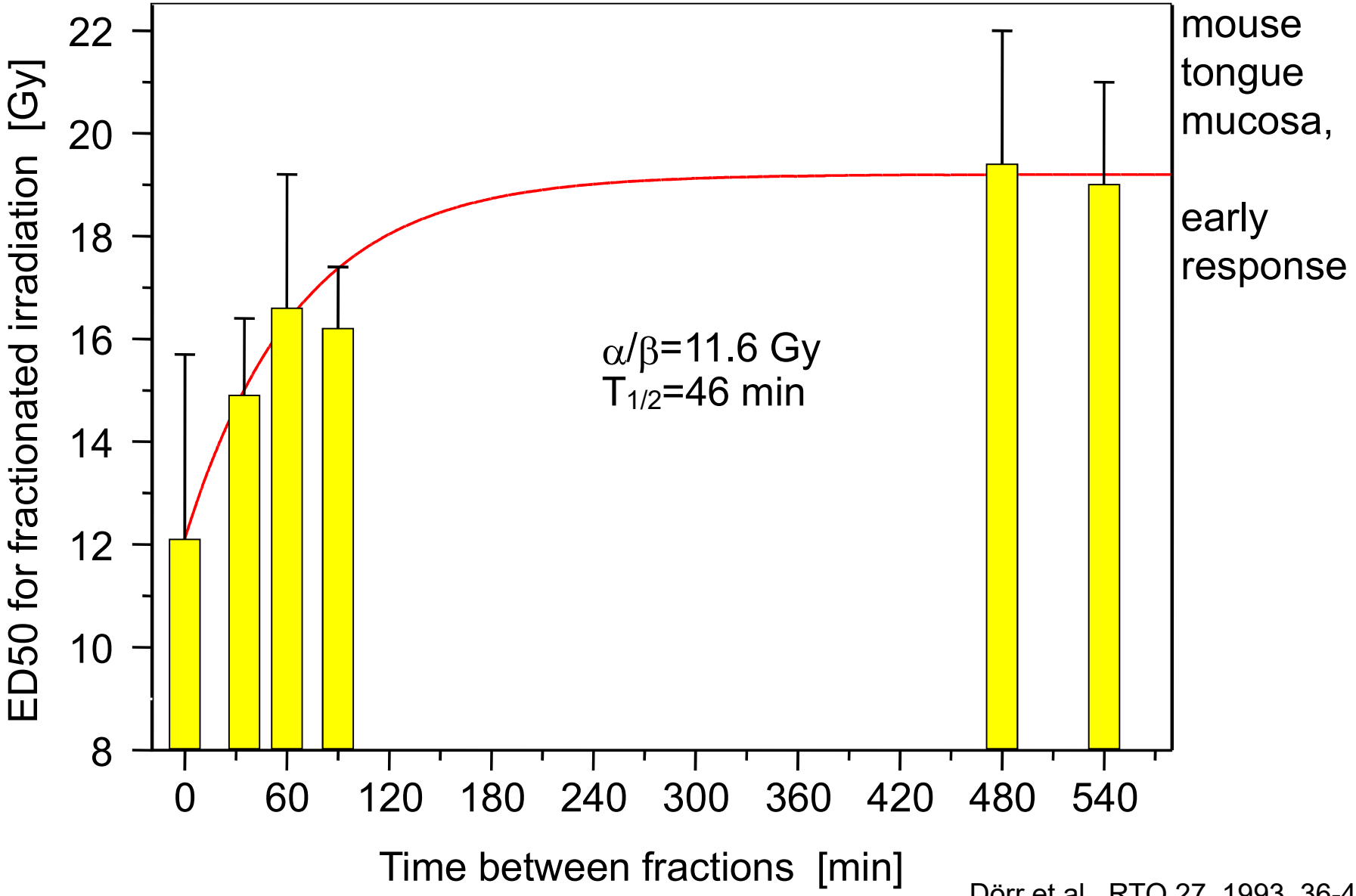
Table 9.1 Fractionation sensitivity of human normal tissues and tumours.

Tissue/organ	Endpoint	α/β (Gy)	95% CL (Gy)	Source
Tumours				
Head and neck				
Various		10.5	[6.5; 29]	Stuschke and Thames (1999)
Larynx		14.5*	[4; 24]	Rezvani *et al.* (1993)
Vocal cord		~13	"wide"	Robertson *et al.* (1993)
Buccal mucosa		6.0	[3.9; infinity]	Maciejewski *et al.* (1989)
Tonsil		12	[3.6; infinity]	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)
Esophagus		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)

(>) 10 Gy

Basic Clinical Radiobiology, 4th Ed.

Dose fractionation: Time interval



Dörr et al., RTO 27, 1993, 36-45

Dose fractionation: Time interval

Table 9.2 Repair halftime for human normal-tissue endpoints.

Endpoint	Dose delivery*	$T_{1/2}$ (hours)	95% CL (hours)	Source
Erythema, skin	MFD	0.35 and 1.2**	?	Turesson [illegible]89)
Mucositis, head and neck	MFD	2–4	?	P [illegible]996)
	FLDR	0.3–0.7	[illegible]	[illegible] *et al.* (1995)
Laryngeal oedema	MFD	4.9	[illegible]	Bentzen *et al.* (1999)
Radiation myelopathy	MFD	[illegible]	?	Dische and Saunders (1989)
Skin telangiectasia	MFD	[illegible]	?	Turesson and Thames (1989)
	[illegible]	3.8	[2.5; 4.6]	Bentzen *et al.* (1999)
Subcutaneous fibrosis	[illegible]	4.4	[3.8; 4.9]	Bentzen *et al.* (1999)
Temporal lobe ne[illegible]	MFD	> 4	?	Lee *et al.* (1999)
Various p[illegible] [illegible]ons	HDR/LDR	1.5–2.5	?	Fowler (1997)

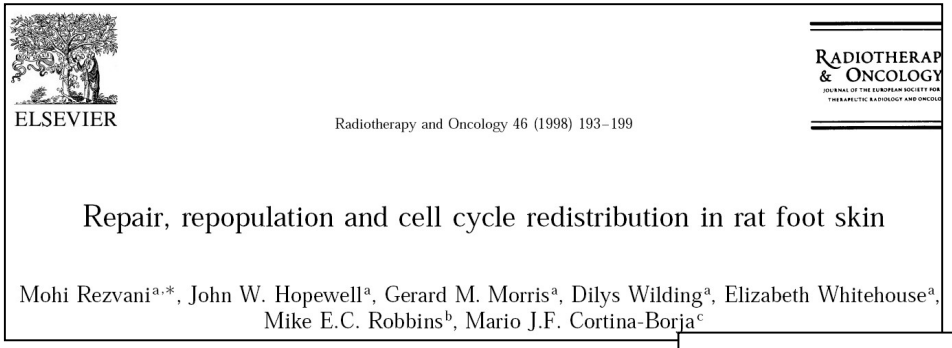
caution: $T_{1/2}$ in rodents << humans

*MF[illegible]ple fractions per day; FLDR: fractionated low-dose rate irradiation; HDR/LDR: high d[illegible]e-rate/low dose-rate comparison

**Evidence of two components of repair with different halftimes.

Basic Clinical Radiobiology, 4th Ed.

Dose fractionation:
Equal effect of dose per fraction (???)



ELSEVIER

Radiotherapy and Oncology 46 (1998) 193–199

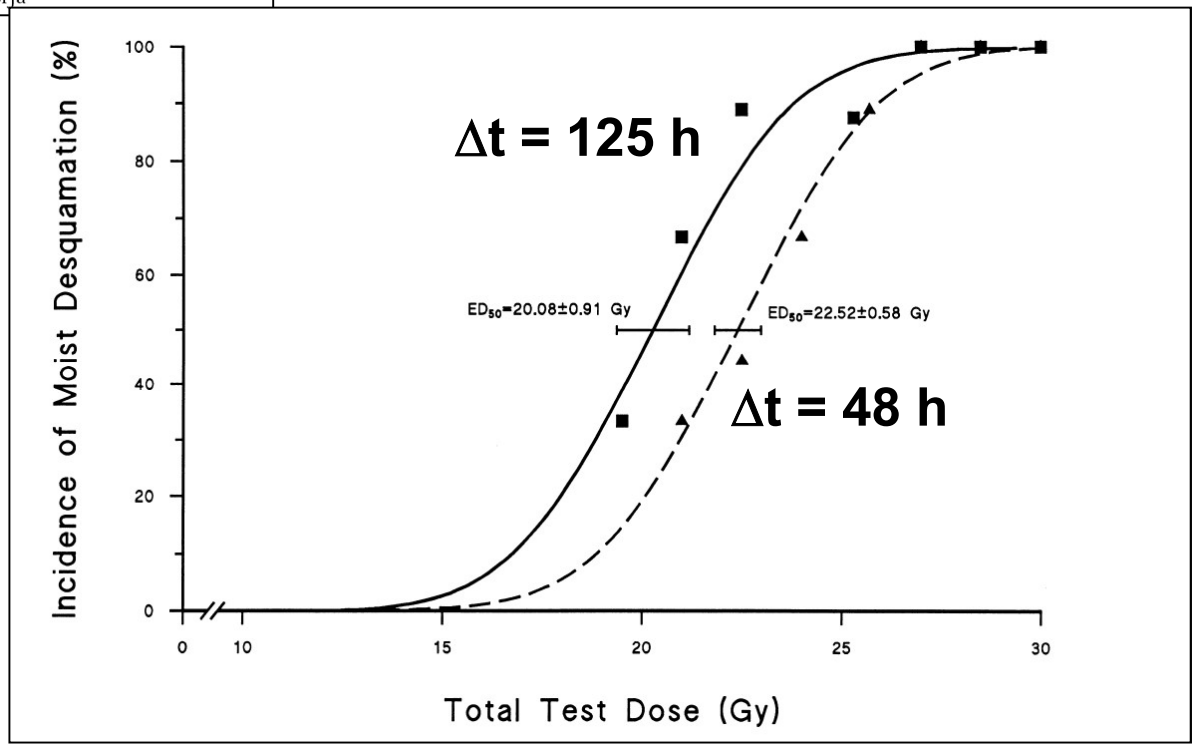
RADIOTHERAP & ONCOLOGY

Repair, repopulation and cell cycle redistribution in rat foot skin

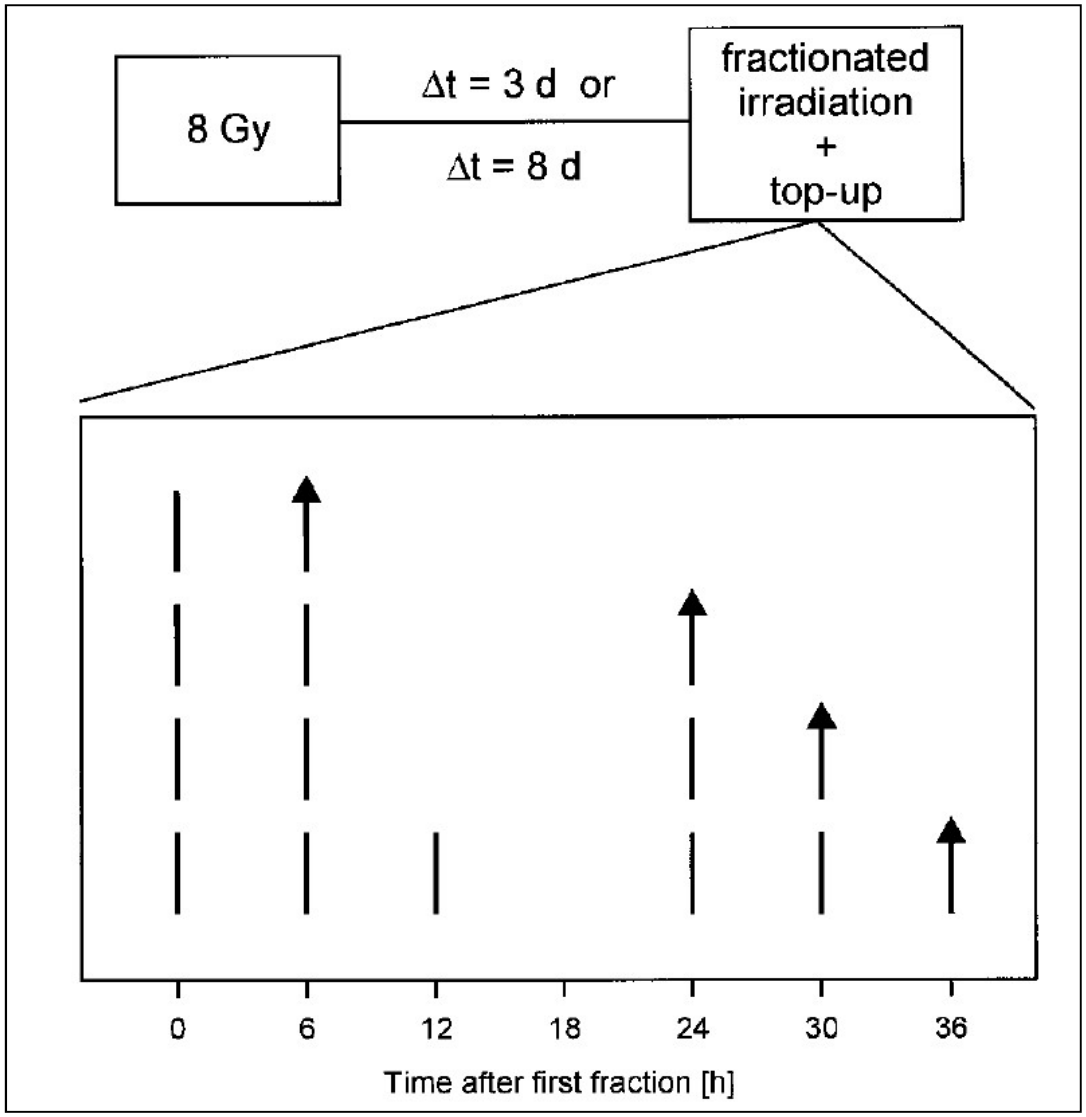
Mohi Rezvani[a,*], John W. Hopewell[a], Gerard M. Morris[a], Dilys Wilding[a], Elizabeth Whitehouse[a], Mike E.C. Robbins[b], Mario J.F. Cortina-Borja[c]

16.8 Gy + 3 F

p<0.01



Dose fractionation: Equal effect of dose per fraction (???)



Dörr et al., Int. J. Radiat. Biol 76, 2000, 383-390

Dose fractionation: Equal effect of dose per fraction (???)

Treatment protocol	Fractionation: $ED_{50} \pm \sigma$ (Gy)	p^a
Fractions: repair capacity study		
1	4.0 ± 1.8	–
2	5.9 ± 2.6	0.829
3	4.3 ± 2.2	0.808
5	5.3 ± 1.8	0.048
Interval (min): repair kinetics study		
5	2.8 ± 1.3	0.020/–
10	3.3 ± 0.7	0.101/0.179
15	2.5 ± 1.0	0.009/0.544
30	3.4 ± 1.3	0.234/0.281
45	3.3 ± 1.1	0.183/0.281
60	2.8 ± 1.4	0.030/0.808
90	2.8 ± 0.8	0.017/0.999
120	2.6 ± 1.0	0.009/0.643
240	3.4 ± 1.2	0.147/0.228

Day 3

Dörr et al., Int. J. Radiat. Biol 76, 2000, 383-390

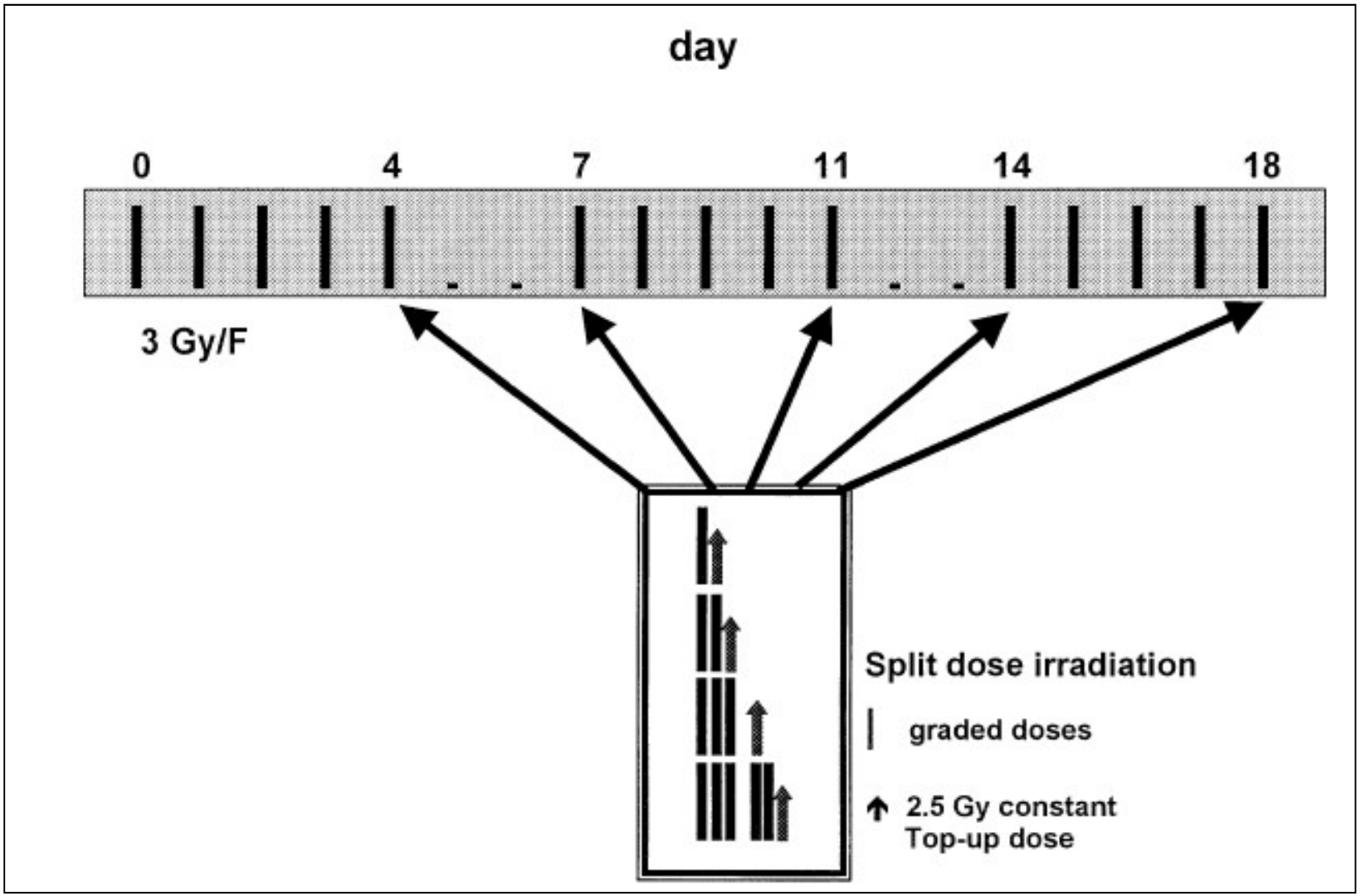
Dose fractionation: Equal effect of dose per fraction (???)

Treatment protocol	Fractionation: $ED_{50} \pm \sigma$ (Gy)	p^a
Fractions: repair capacity study		
1	5.8 ± 2.1	–
2	5.6 ± 0.9	0.828
3	5.3 ± 1.3	0.142
5	6.4 ± 0.8	0.576
Interval (min): repair kinetics study		
5	4.5 ± 1.8	0.260/–
10	5.3 ± 2.1	0.139/0.268
15	5.5 ± 2.4	0.595/0.126
30	6.1 ± 2.5	0.903/0.032
45	5.8 ± 2.2	0.809/0.067
60	6.3 ± 2.3	0.681/0.011
90	5.5 ± 2.1	0.498/0.175
120	6.6 ± 3.0	0.543/0.008
240	6.0 ± 2.4	0.981/0.044

Day 8

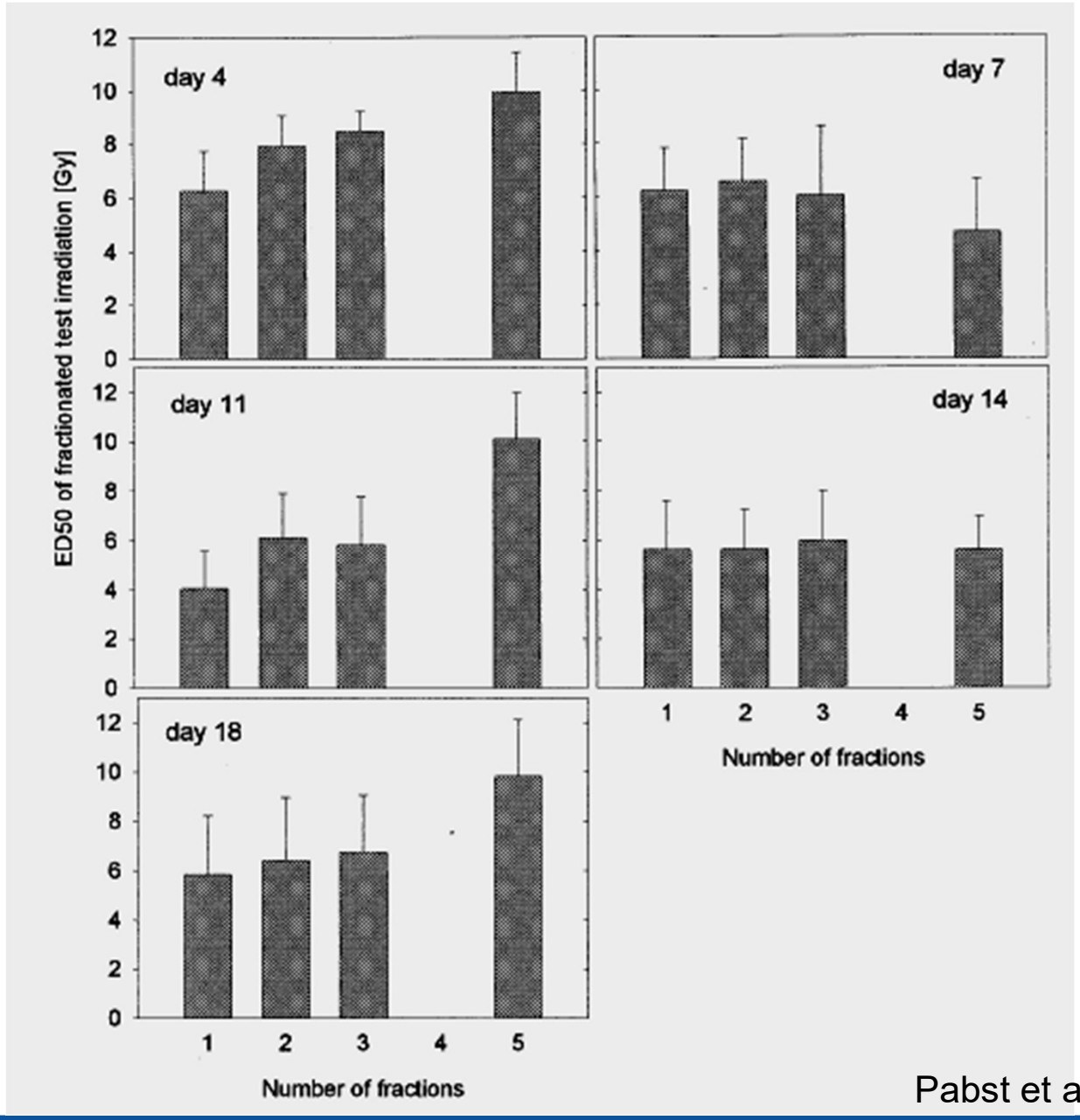
Dörr et al., Int. J. Radiat. Biol 76, 2000, 383-390

Dose fractionation: Equal effect of dose per fraction (???)



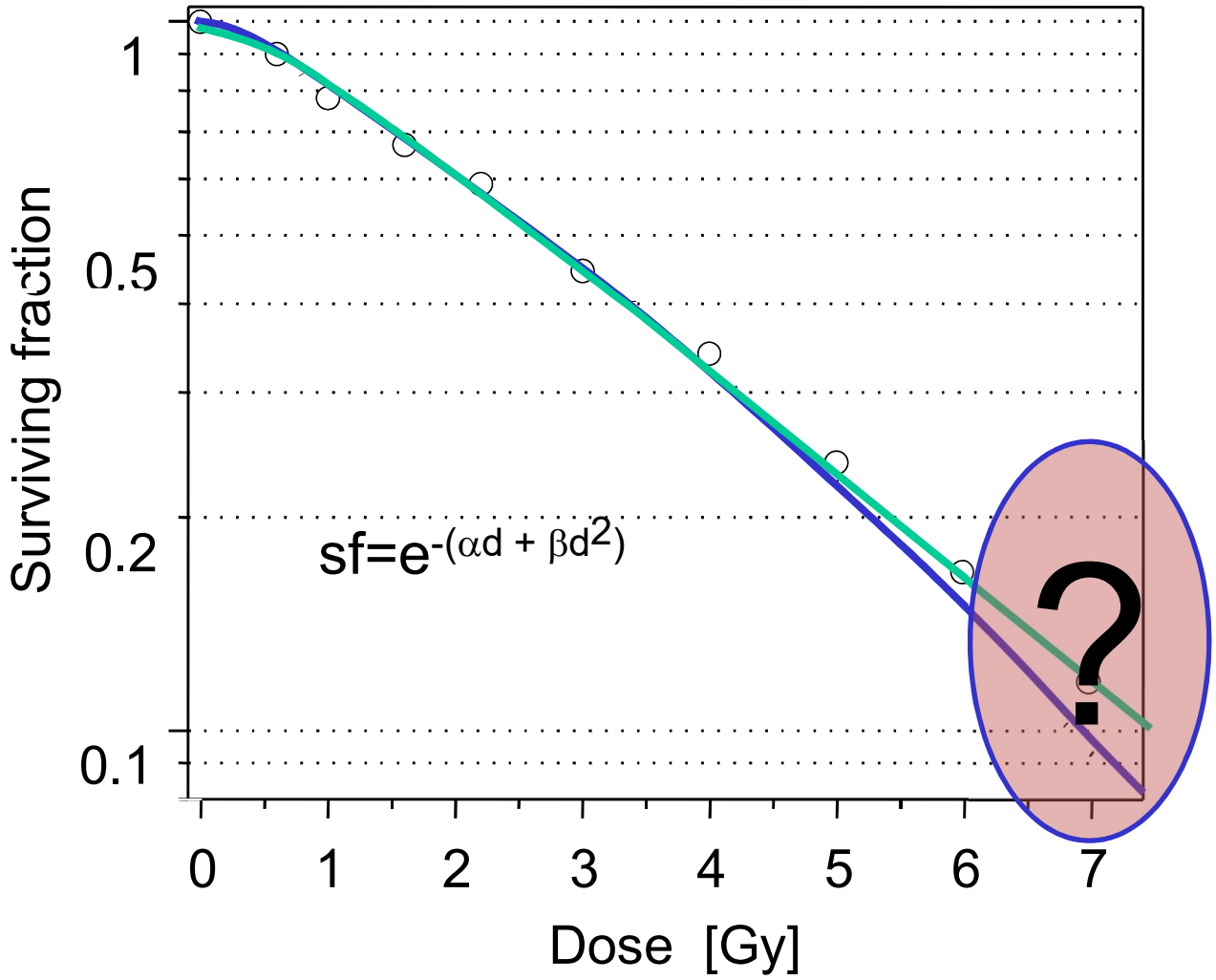
Pabst et al. IJROBP 58, 2004, 485-492

Dose fractionation: Equal effect of dose per fraction (???)

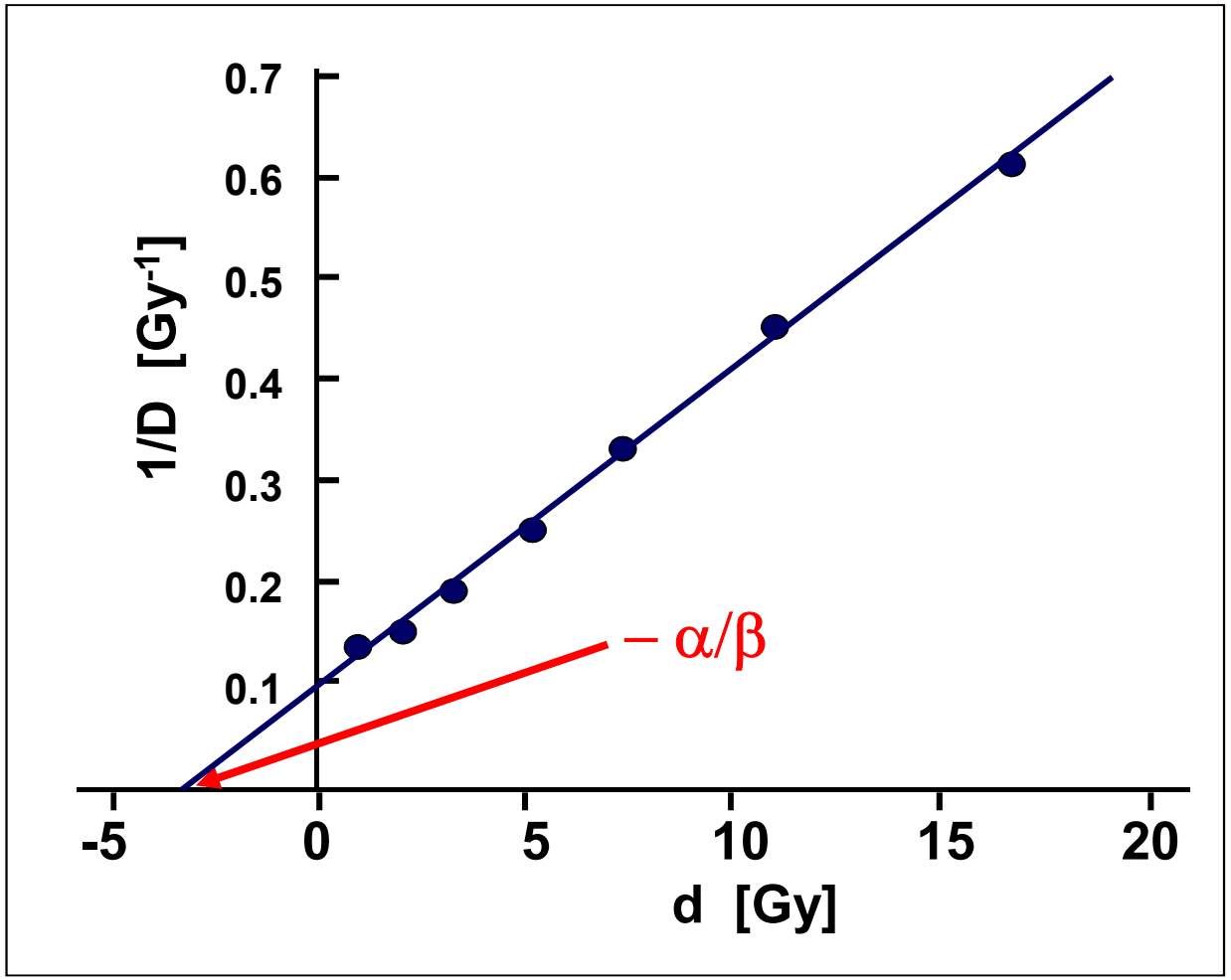


Pabst et al. IJROBP 2004

Dose fractionation:
LQ at high doses per fraction (???)



Dose fractionation: LQ at high doses per fraction (???)



Mouse kidney, late response

data from:
Stewart et al.
Radiat. Res. 98,
1984, 407-420

F_e-Plot

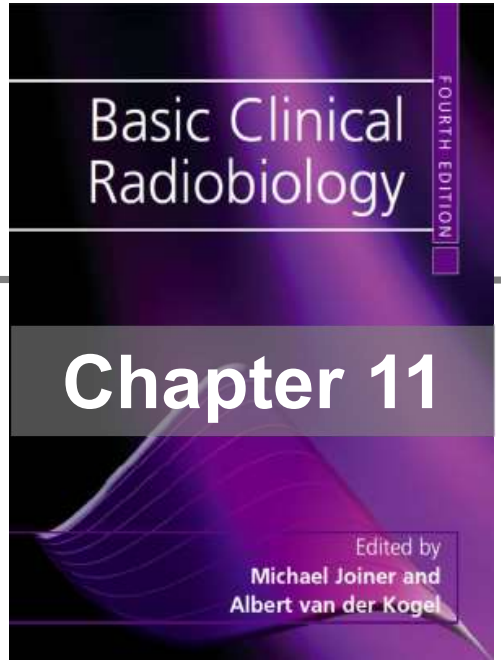
Douglas und Fowler 66, 1976, 401-426

Take home message

Recovery:

- **marked for late effects (low α/β-value)**
- **significant but less pronounced for early effects**
  - and tumours (exceptions!)
  - and consequential late effects
- **time interval between fractions important**

Normal tissues:
Overall treatment time



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Radiation effects - 5 Rs of radiotherapy

Radiation sensitivity
Recovery
Redistribution
Repopulation
Reoxygenation

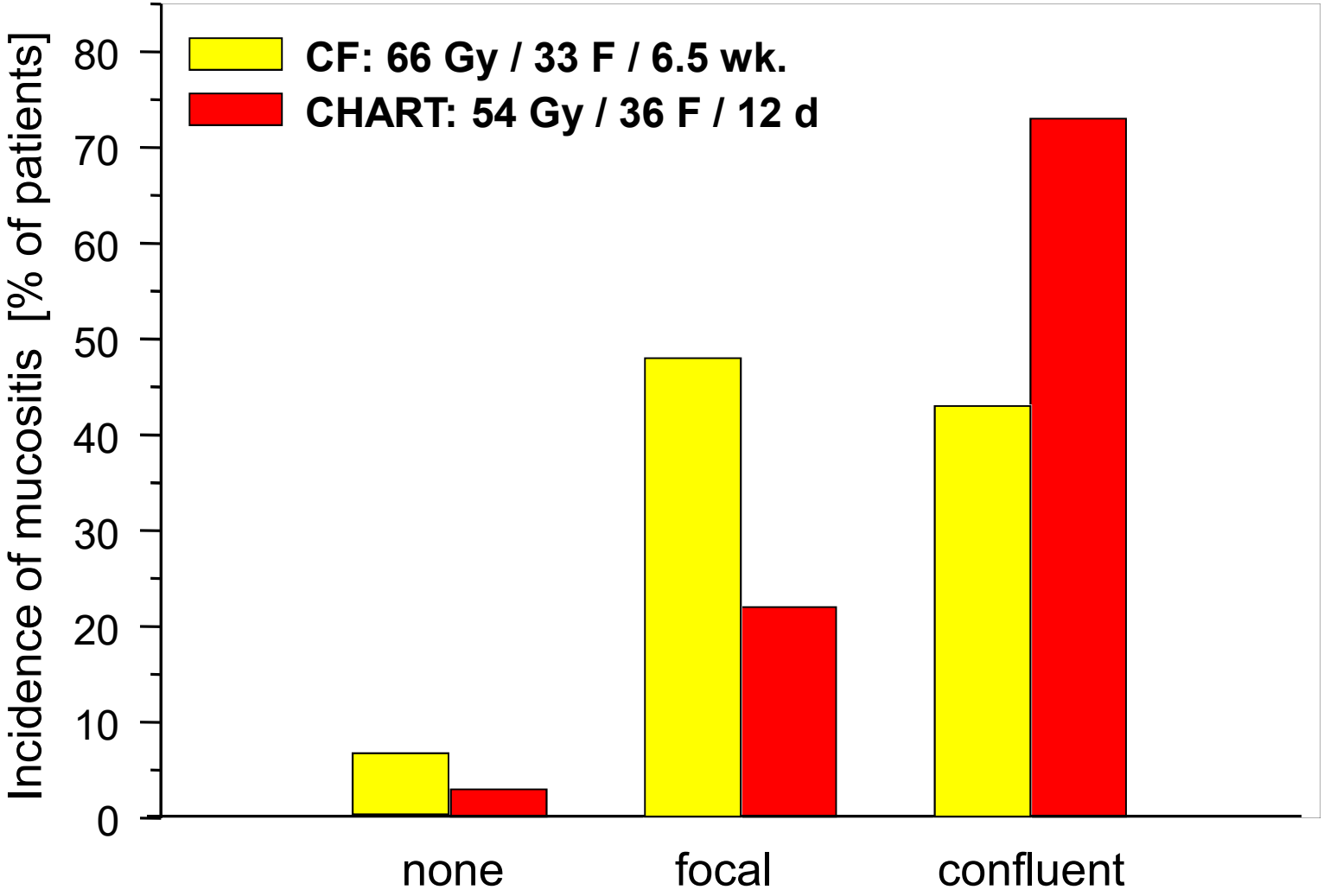
Repopulation

Regeneration response of turnover tissues and tumours to radio-therapy, resulting in increased radiation tolerance with increasing overall treatment time.

==> overall treatment time
==> accelerated radiotherapy

Repopulation – clinical observations

CHART head-and neck-trial

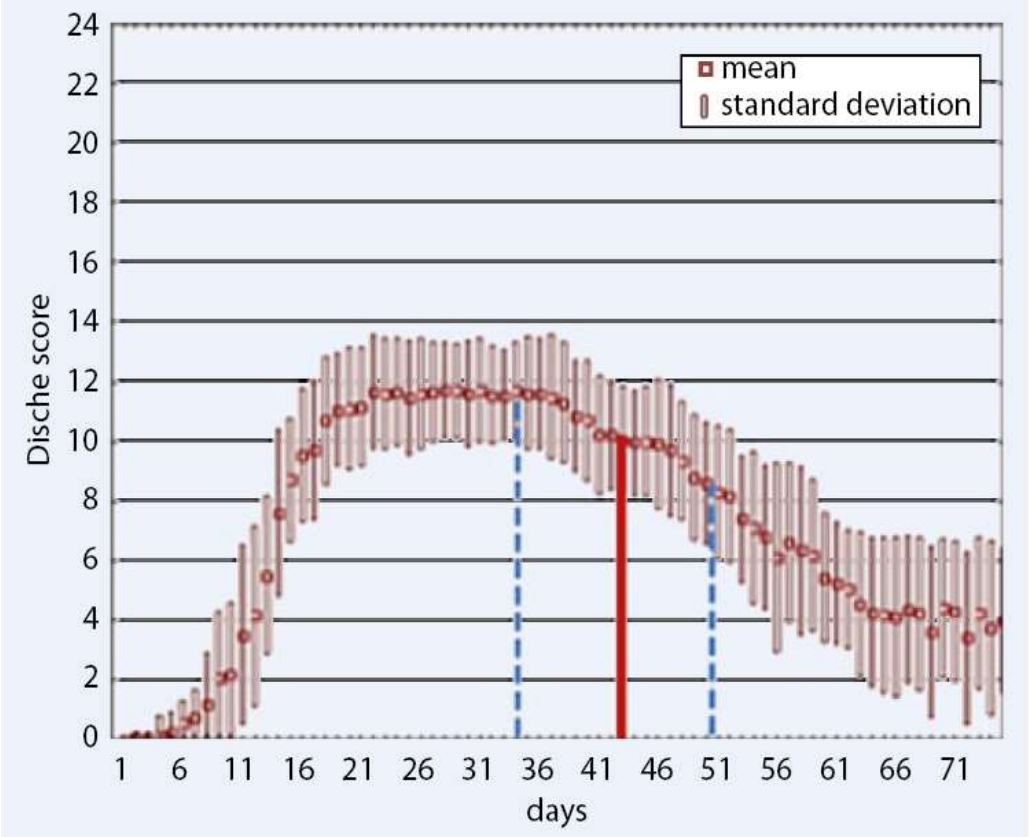


Dische et al., RTO 44, 1997, 123-136

Repopulation – clinical observations

Healing of mucositis during last treatment weeks

	Type 1 continual increase	Type 2 increase–plateau	Type 3 decreasing
CF	9/33 (27%)	13/33 (40%)	11/33 (33%)
AF	8/33 (24%)	16/33 (49%)	9/33 (27%)



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A. Wygoda · T. Rutkowski · M. Hutnik · K. Składowski · M. Goleń · B. Pilecki
Ist Department of Radiation Oncology, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland, Gliwice

Acute mucosal reactions in patients with head and neck cancer

Three patterns of mucositis observed during radiotherapy

Wygoda et al.,
Strahlenther. Onkol. 189, 2013, 547-551

Repopulation – clinical observations

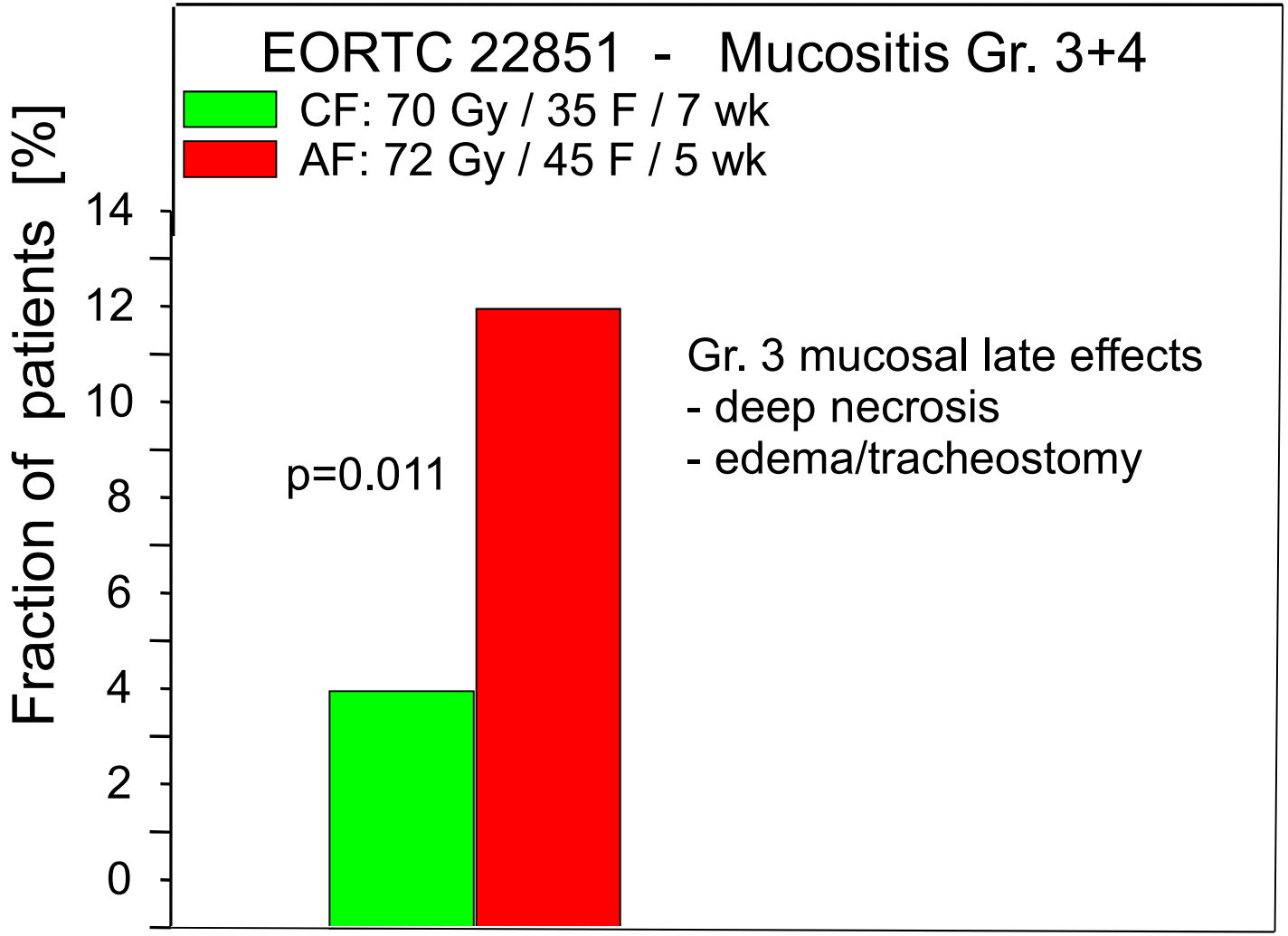
Mucositis after treatment breaks

2x1.6 Gy/d (32 Gy/12 d)	9-13 d →	2x1.5→2.0 Gy/d (34-38 Gy/12-14 d)
14/16 pat. (90%) confl. mucositis		0/15 pat. (0%) confl. mucositis

Maciejewski et al., RTO 22, 1991, 7-11

Repopulation – clinical observations

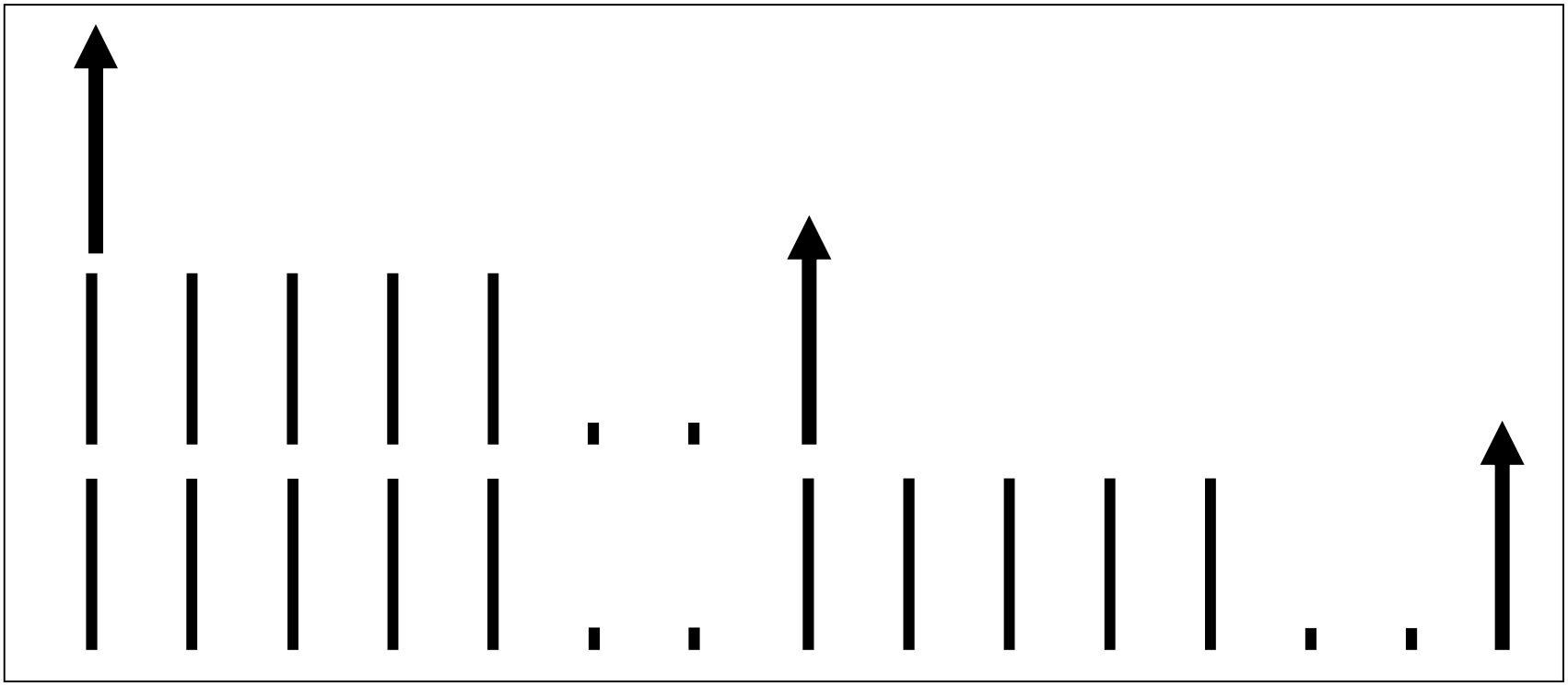
Changes in consequential late effects



data from: Horiot et al., RTO 44, 1997, 111-121

Repopulation – experimental observations

Top-up design - fractionated irradiation

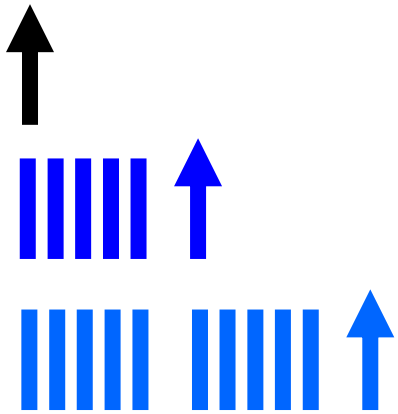


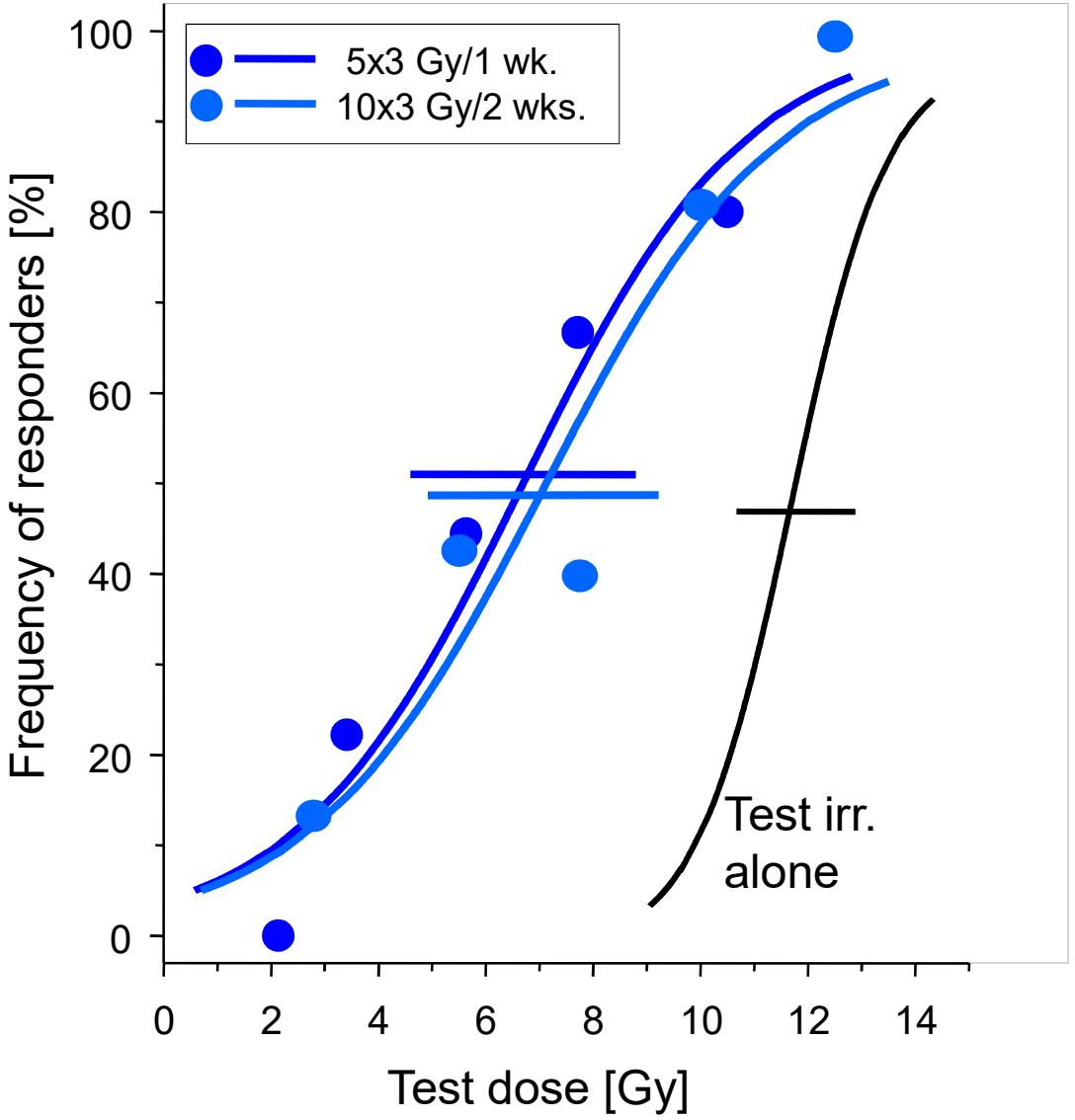
3 Gy

No irradiation

Top-up irradiation (test irradiation)
Graded doses, 5 dose groups x 10-12 animals each

Repopulation – experimental observations

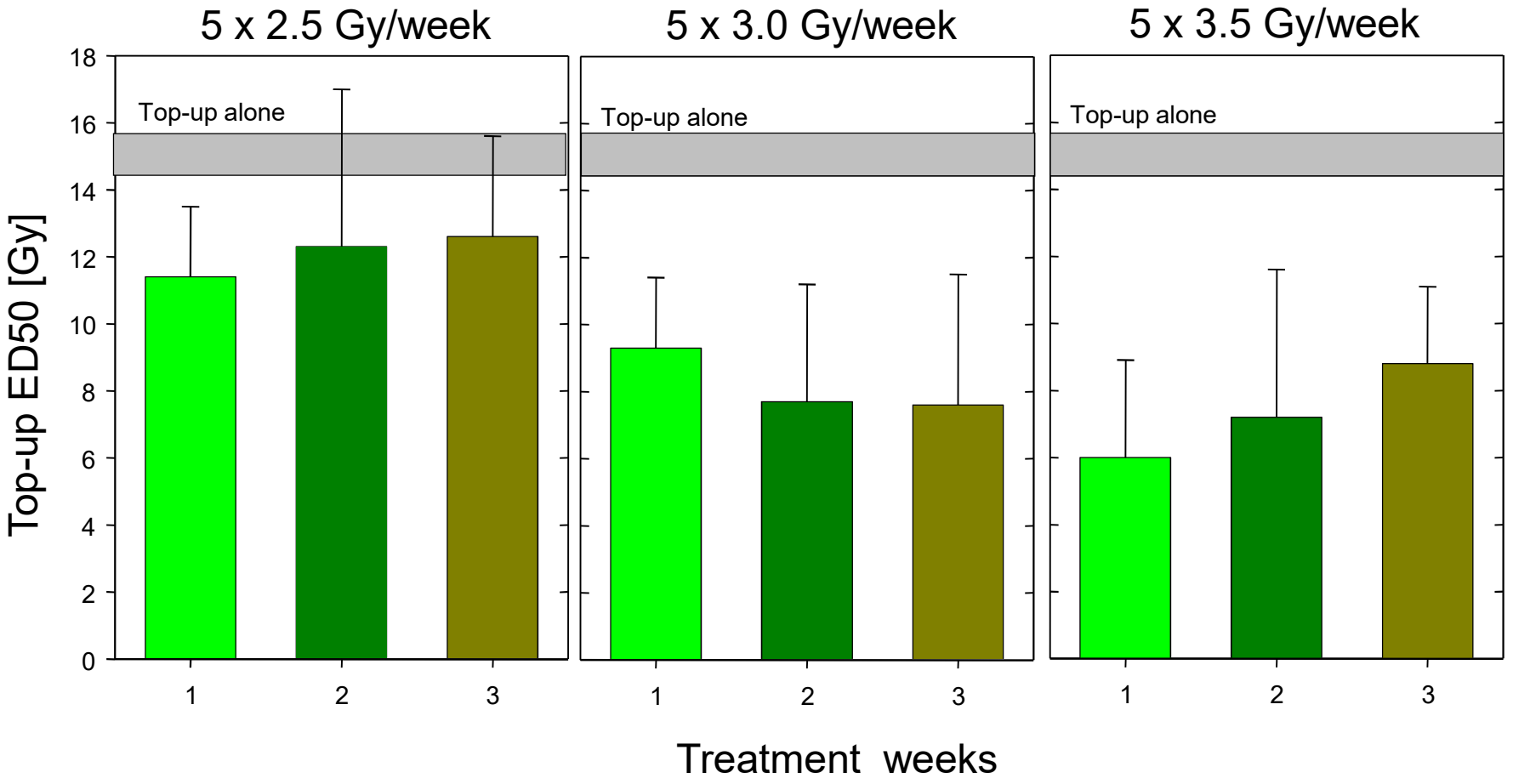




mouse tongue mucosa

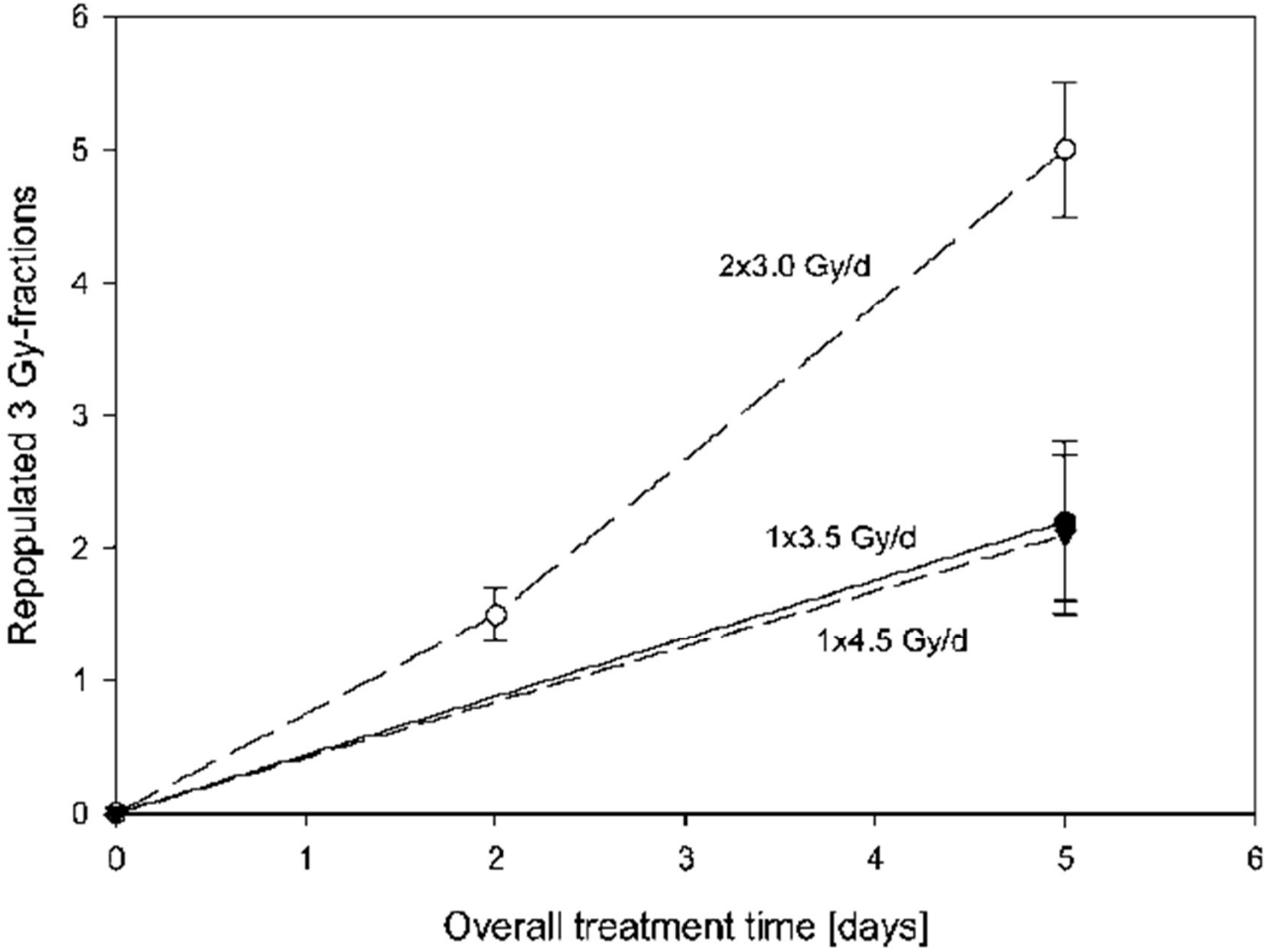
Dörr and Kummermehr, RTO 17, 1990, 249-259

Repopulation – experimental observations



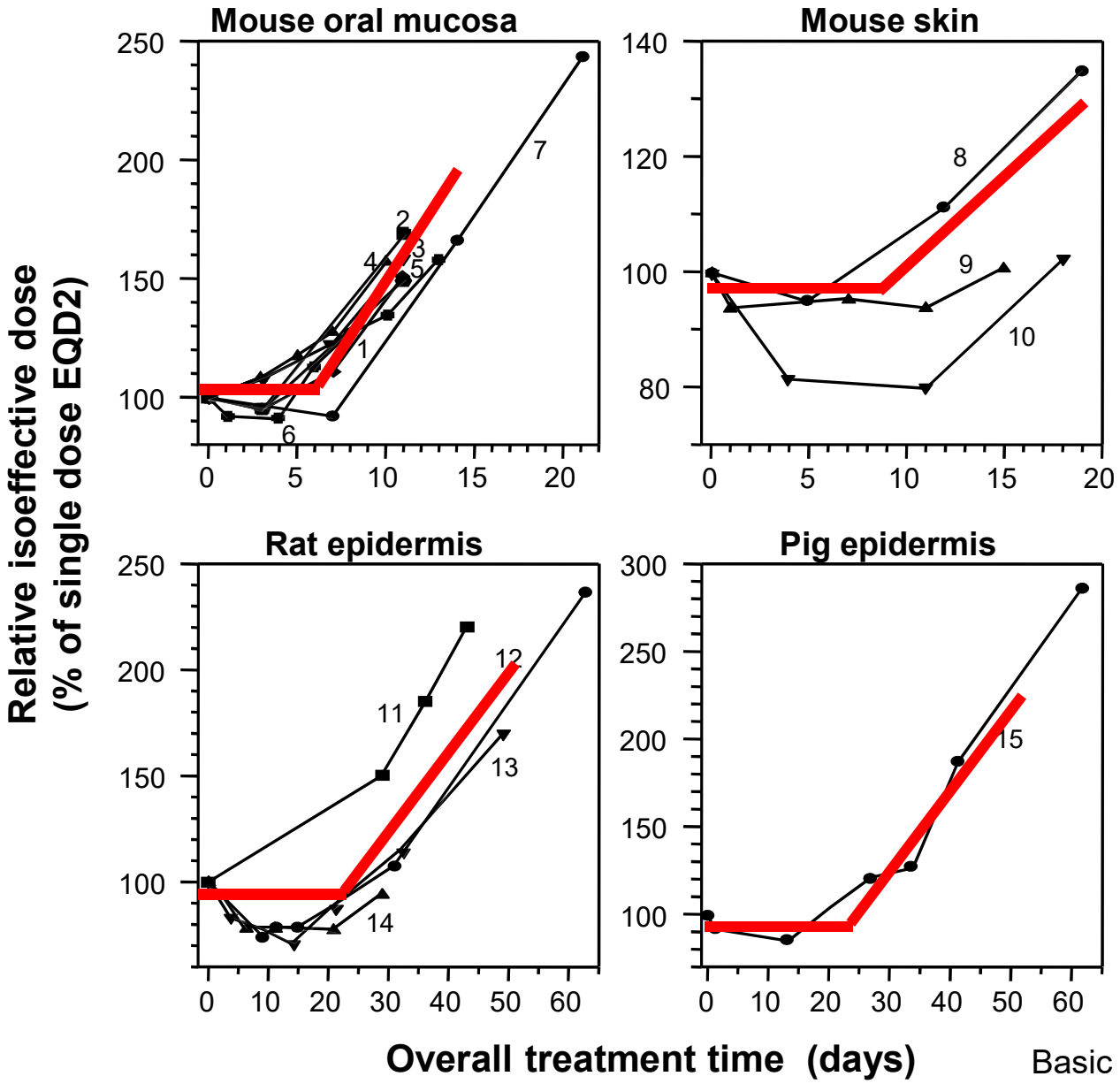
modified from: Dörr and Kummermehr, RTO 17, 1990, 249-259

Repopulation – dose dependence



Dörr, Int. J. Radiat. Biol. 79, 2003, 531-537

Repopulation – experimental observations



Dörr, Habil. Thesis 1997/
Basic Clinical Radiobiology, 4th Ed.

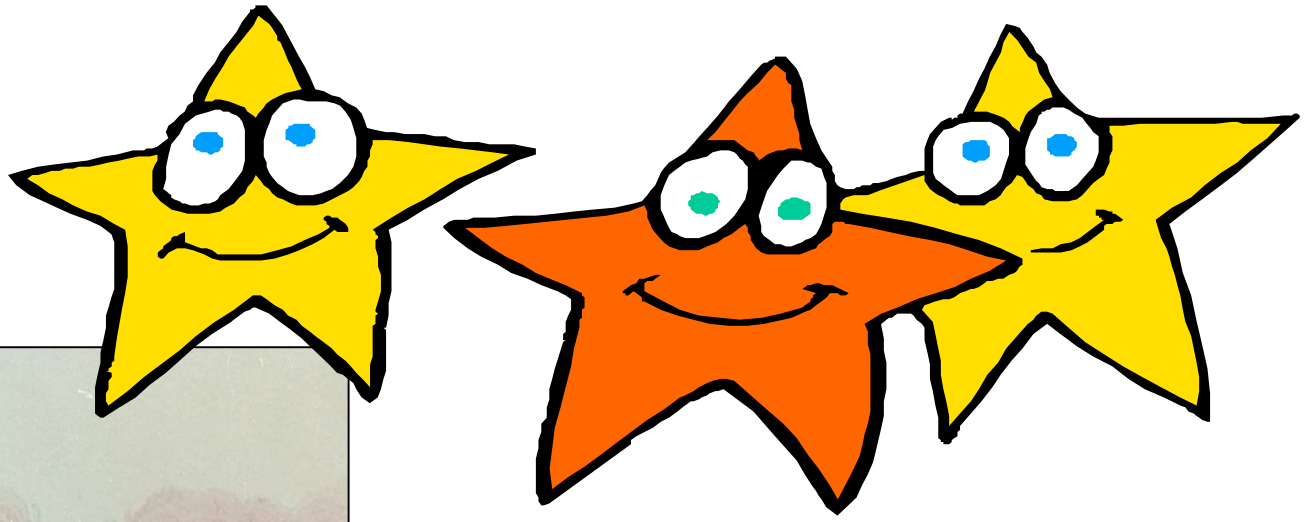
Repopulation

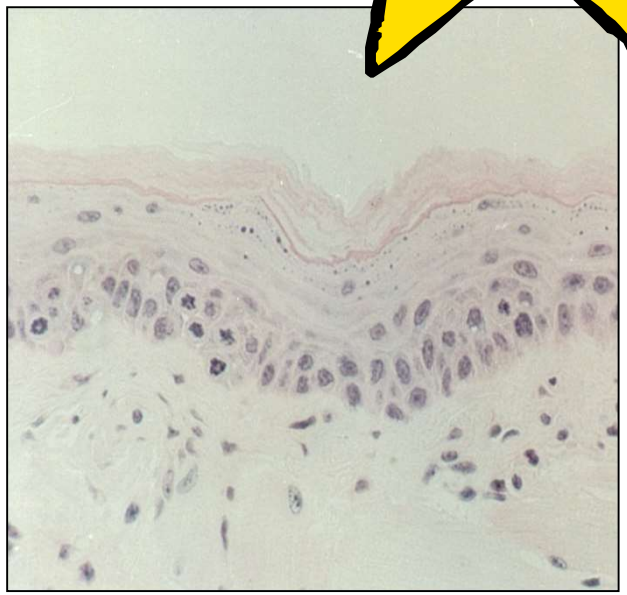
Tissue	EQD2 / day (number of 2 Gy-fractions/day)	Reference
human oral mucosa	**0.6**	Fletcher 1962
	1.0	Maciejewski et al. 1991
	<1	ham et al. 1996
	<0.5	ızen et al. 2001
mouse oral mucosa		
lip	**0.5**	Ang et al. 1985
tongue	**0.9**	Dörr et al. 1990, 1995
rat epidermis		Moulder&Fischer 1976
	1.2	Van Rongen&Kal 1984
mouse epiderm	**0.2**	Denekamp et al. 1973]
	1.4-2.0	Abe&Urano 1990
pig epidermis	**0.3**	Van den Aardweg et al. 1988

~1 2 Gy-fraction / day

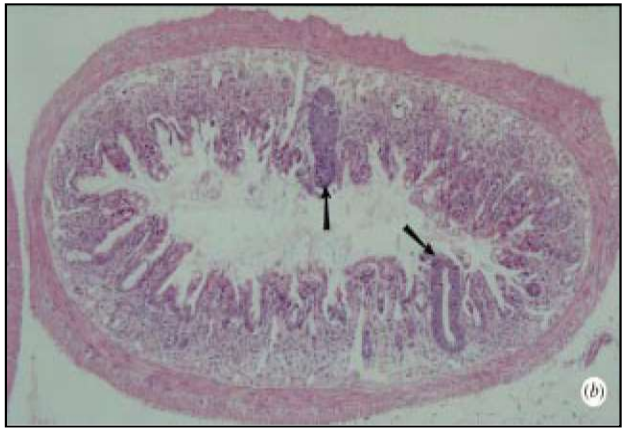
Extended from: Dörr, Habil. Thesis 1997

Mechanisms of repopulation



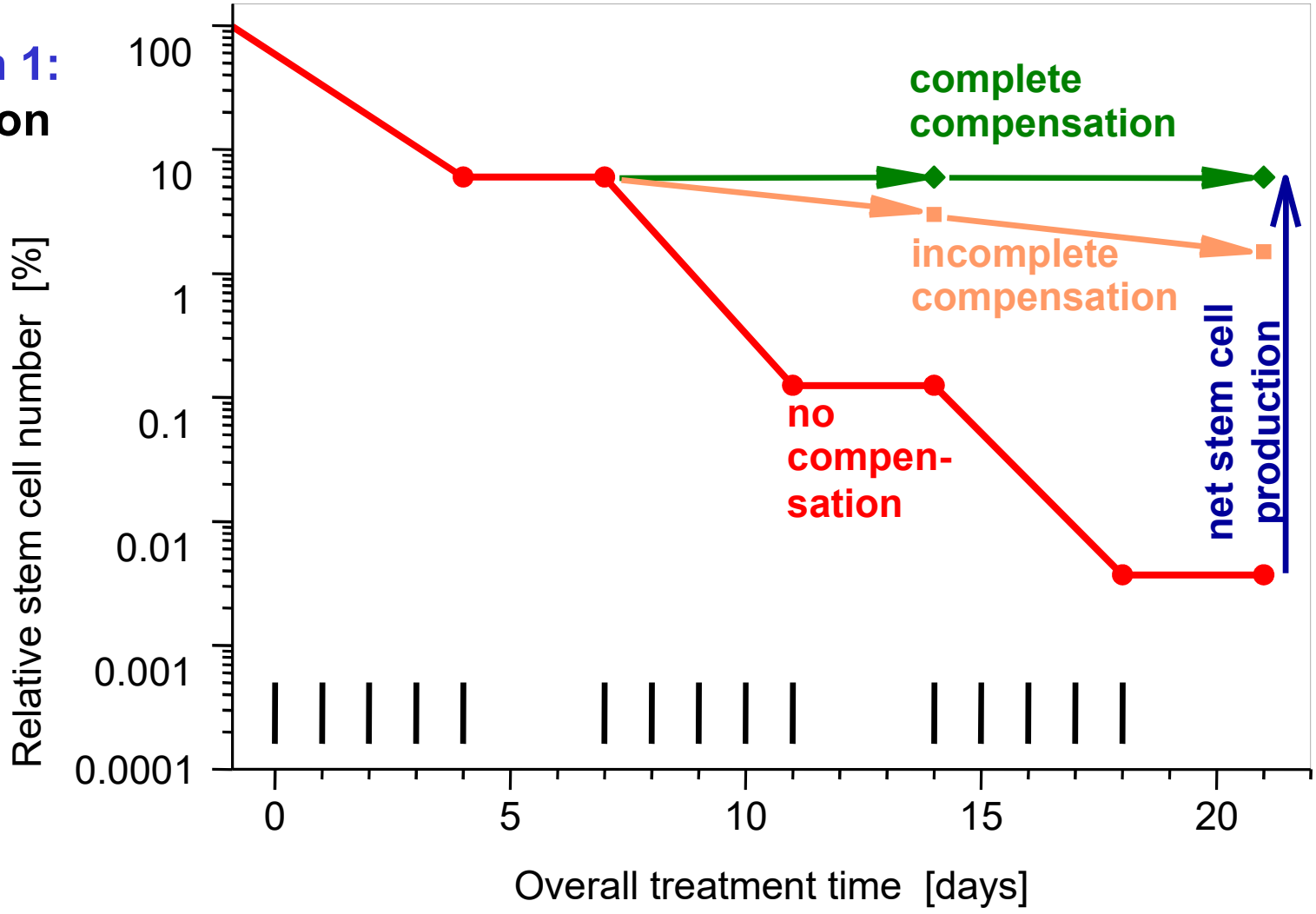


Target cell hypothesis / Stem cell concept

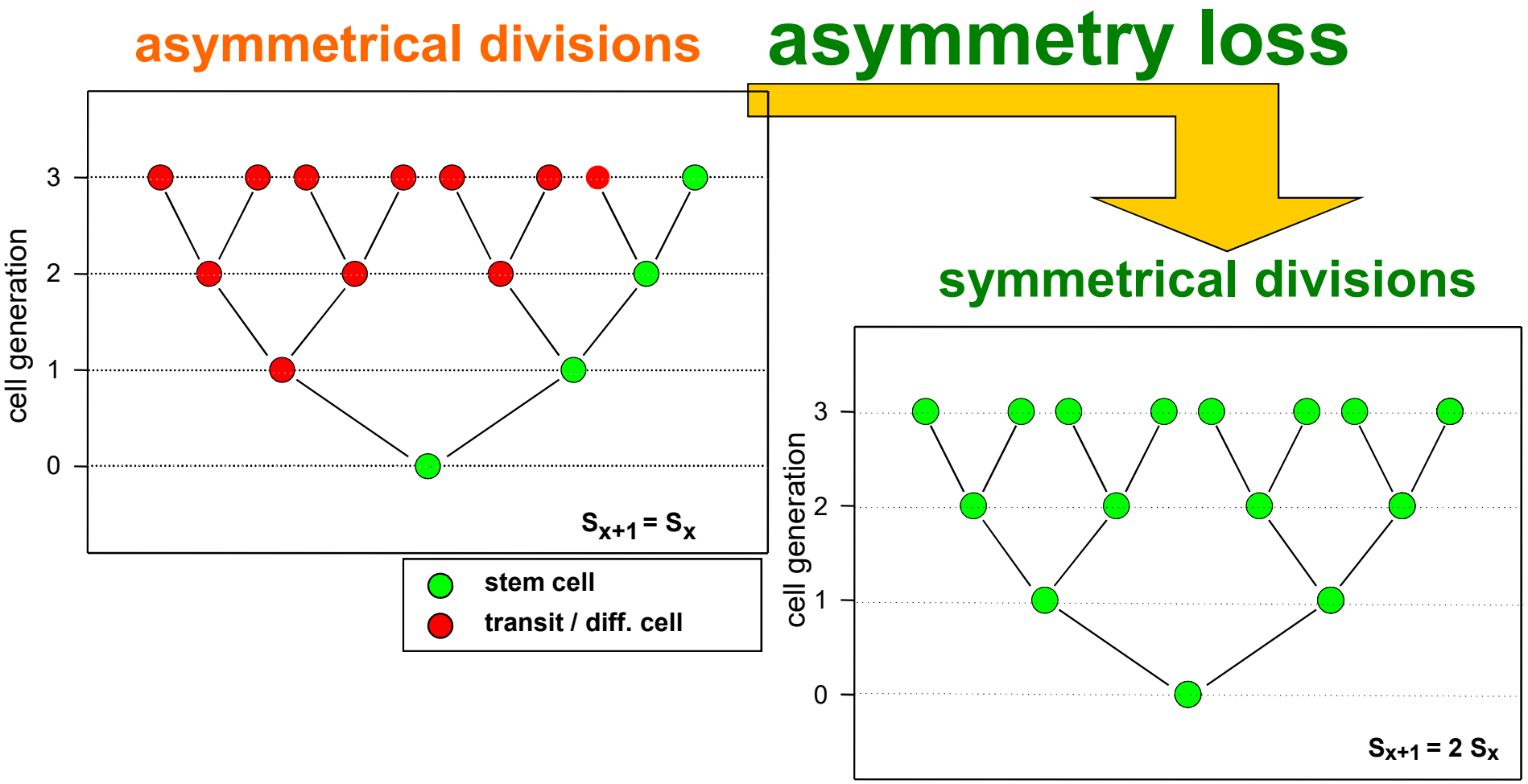


Repopulation: Mechanisms

Observation 1:
compensation of dose

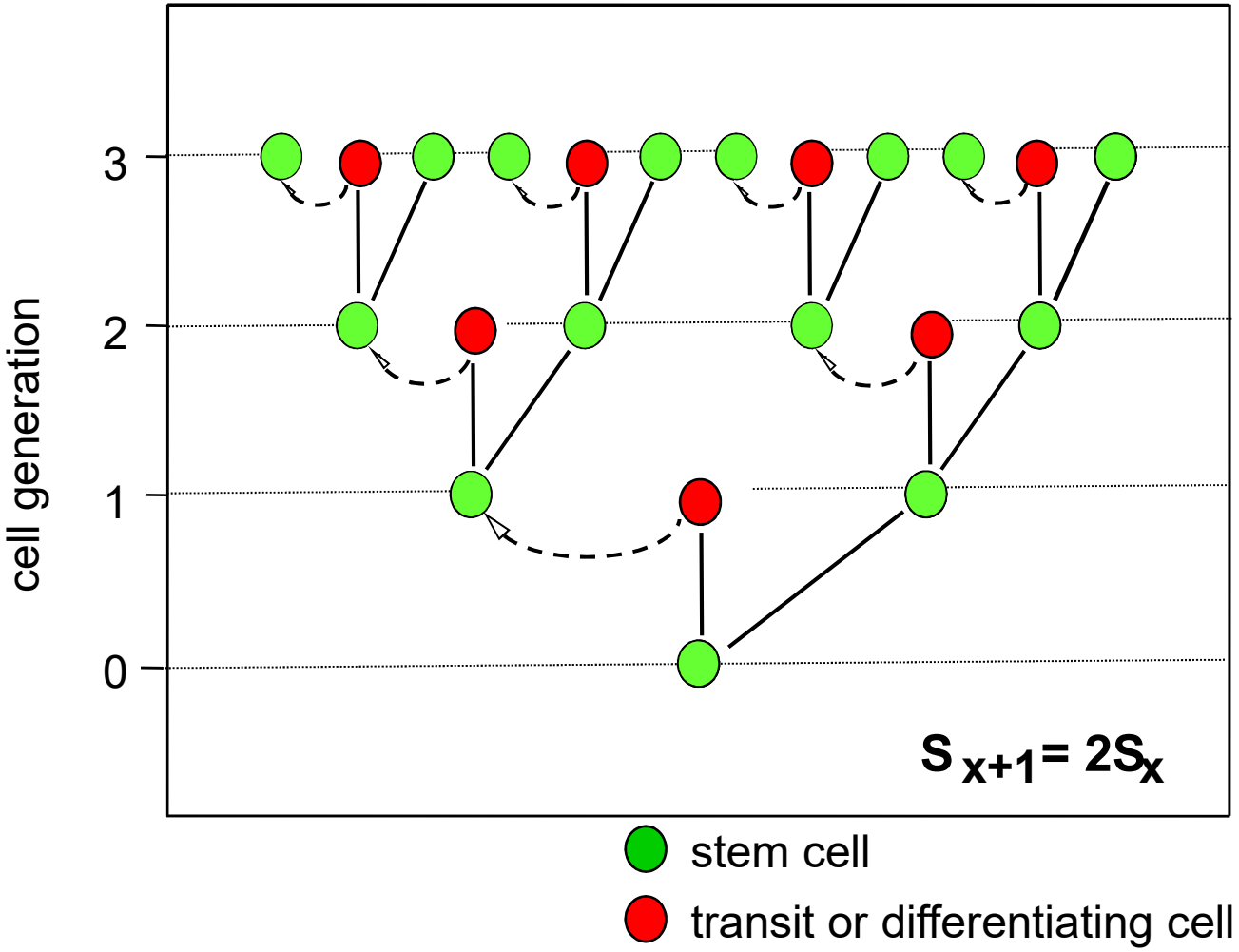


Repopulation: Mechanisms



Repopulation: Mechanisms

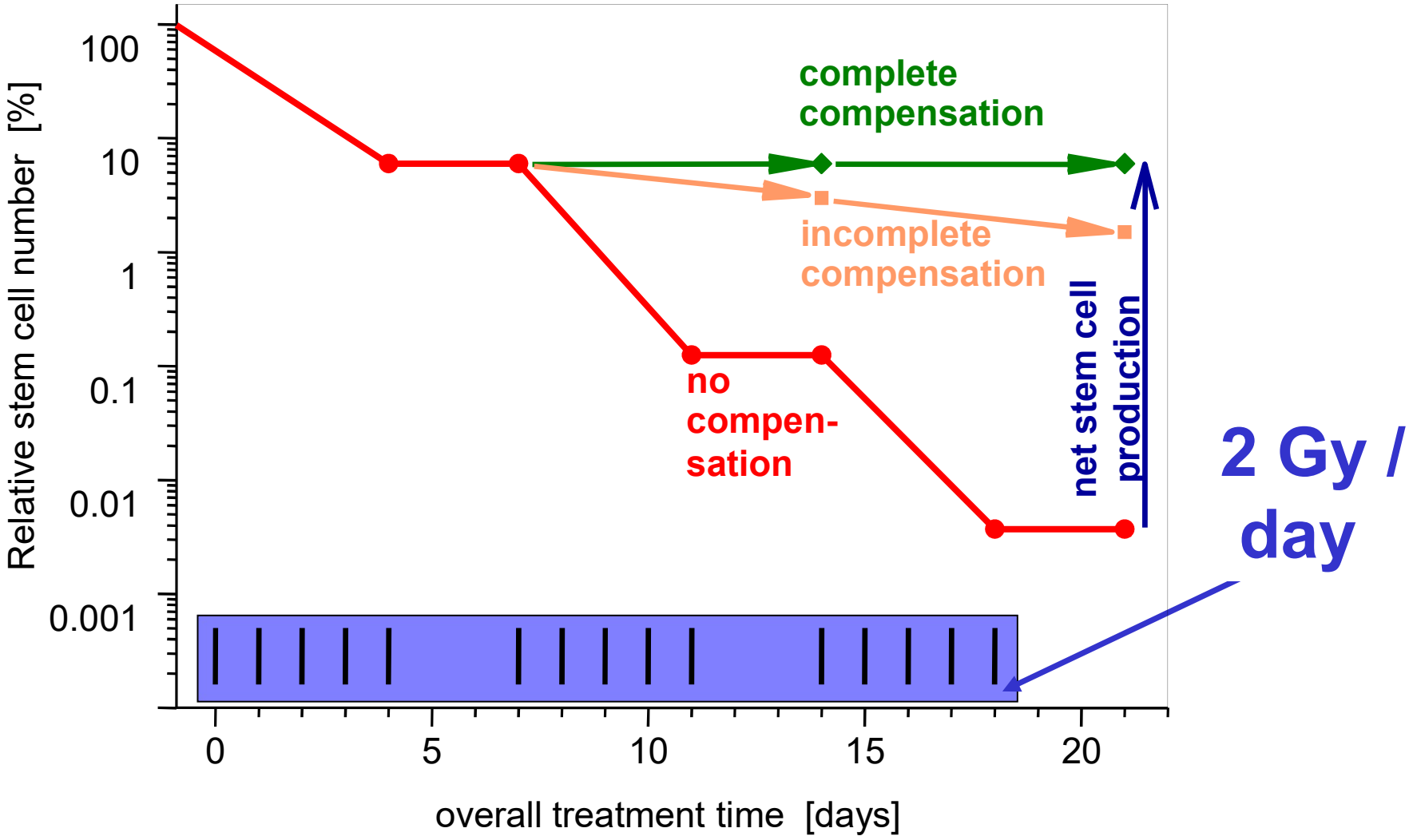
complete symmetry, differentiation block



Repopulation: Mechanisms

Observation	Mechanism
dose compensation	asymmetry loss

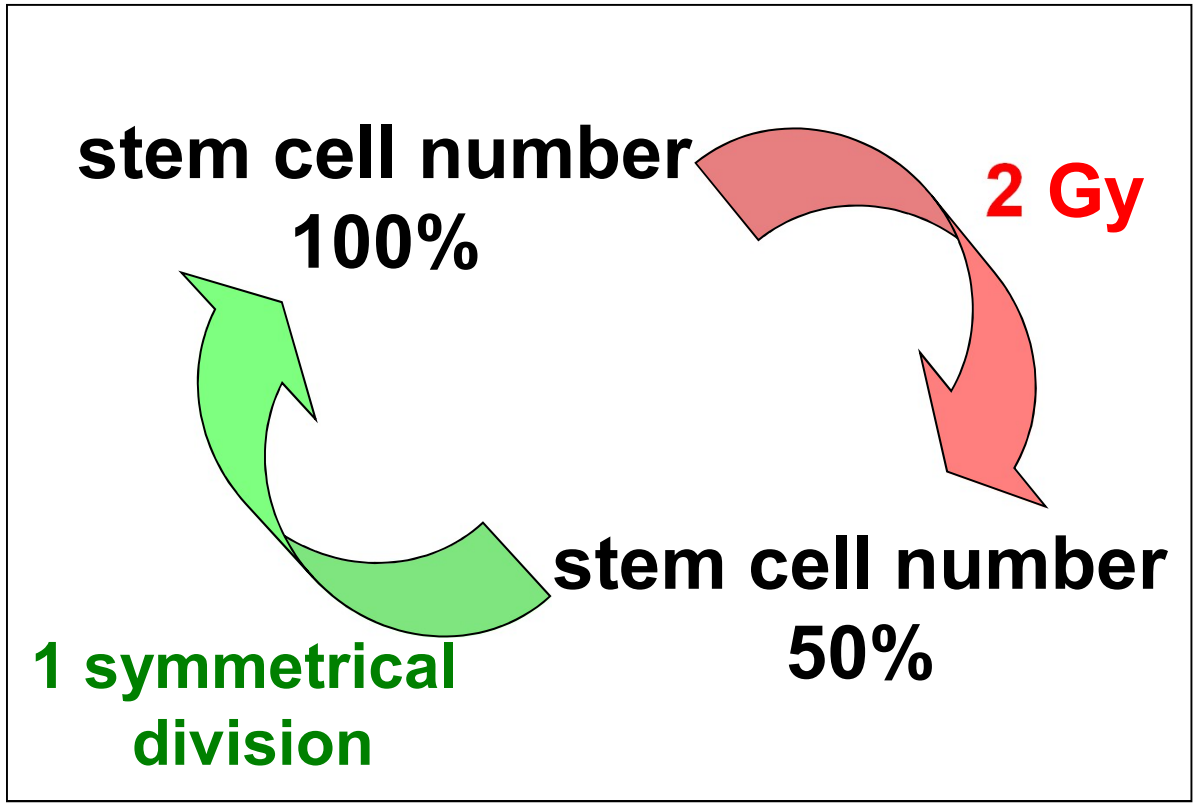
Repopulation: Mechanisms



Repopulation: Mechanisms

Observation 2:
compensation of
2 Gy/day

oral mucosal cells: SF_2 =0.5-0.6

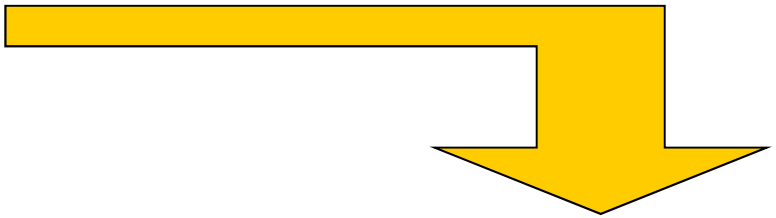


Repopulation: Mechanisms

control mucosa

cell cycle time ~3.5 d

Acceleration



repopulation

compensation of 5x2Gy / 7 d
==>
5 (sym.) divisions / 7 d

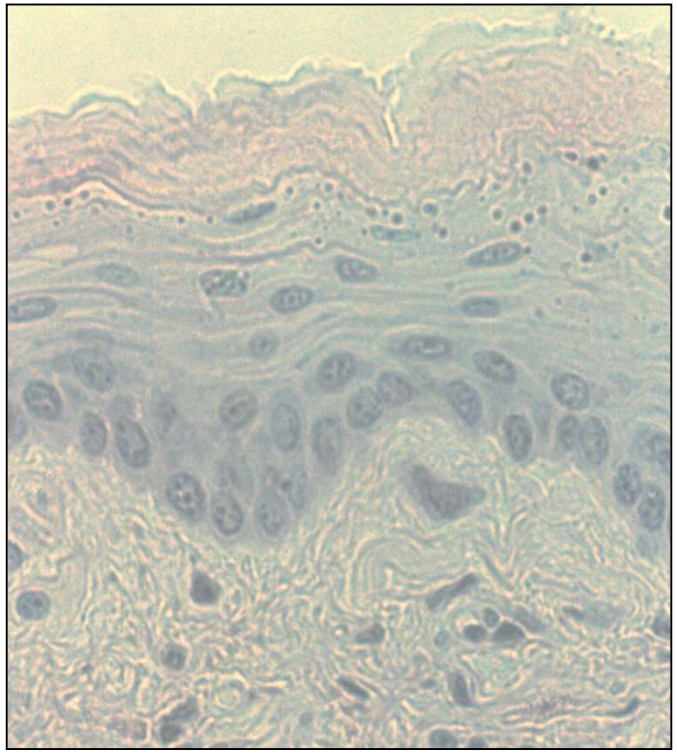
cell cycle time ~1.4 d

Repopulation: Mechanisms

Observation	Mechanism
dose compensation	asymmetry loss
rate of dose compensation	acceleration

Repopulation: Mechanisms

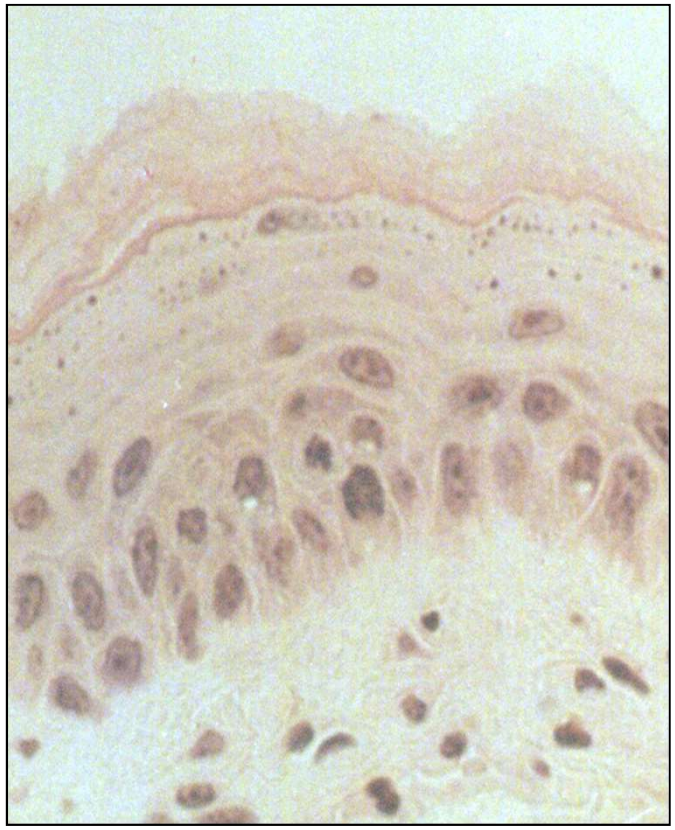
Observation 3:
Compensation of normal cell loss



control

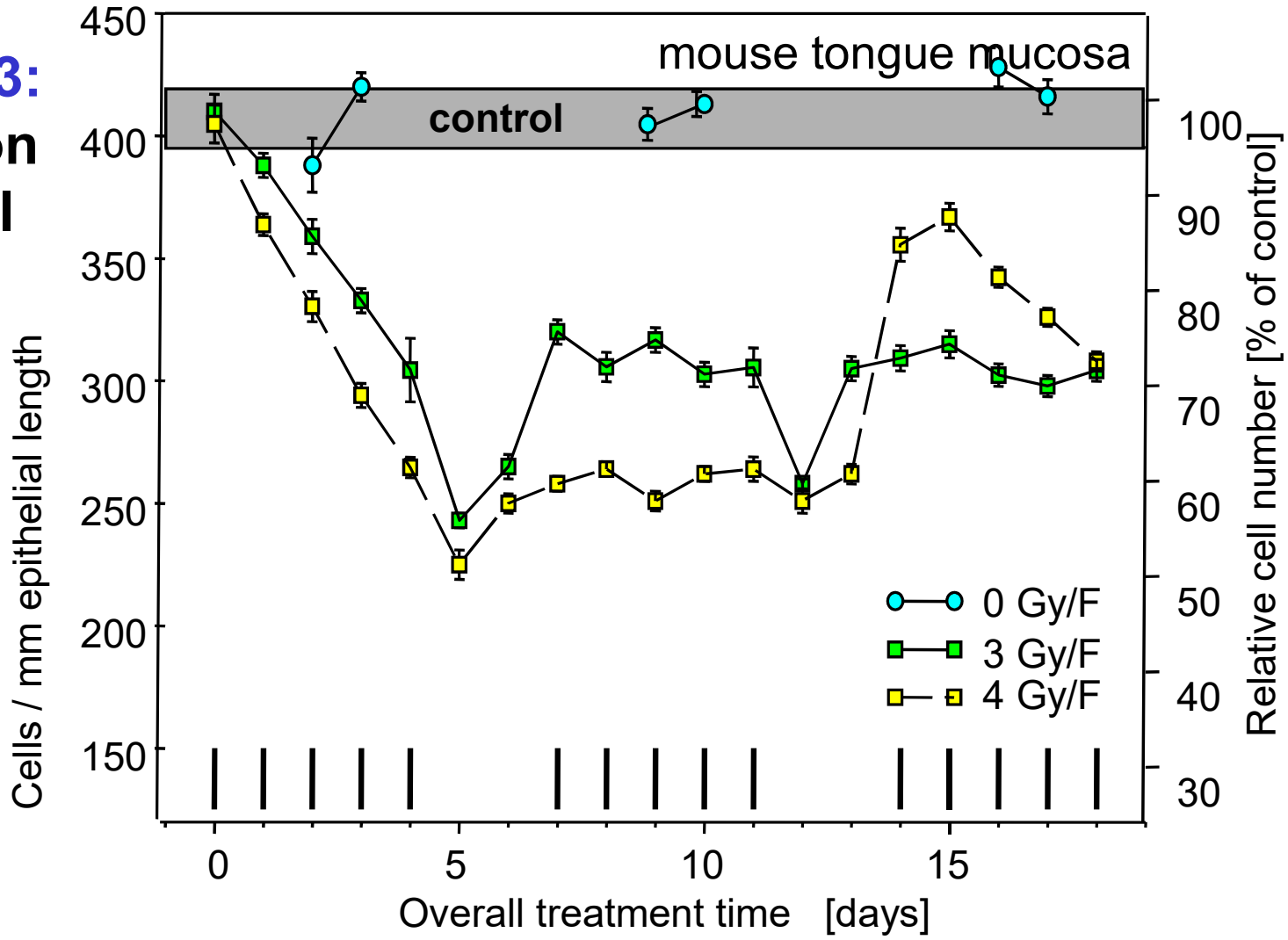
mouse tongue mucosa

10 x 2 Gy/2 weeks



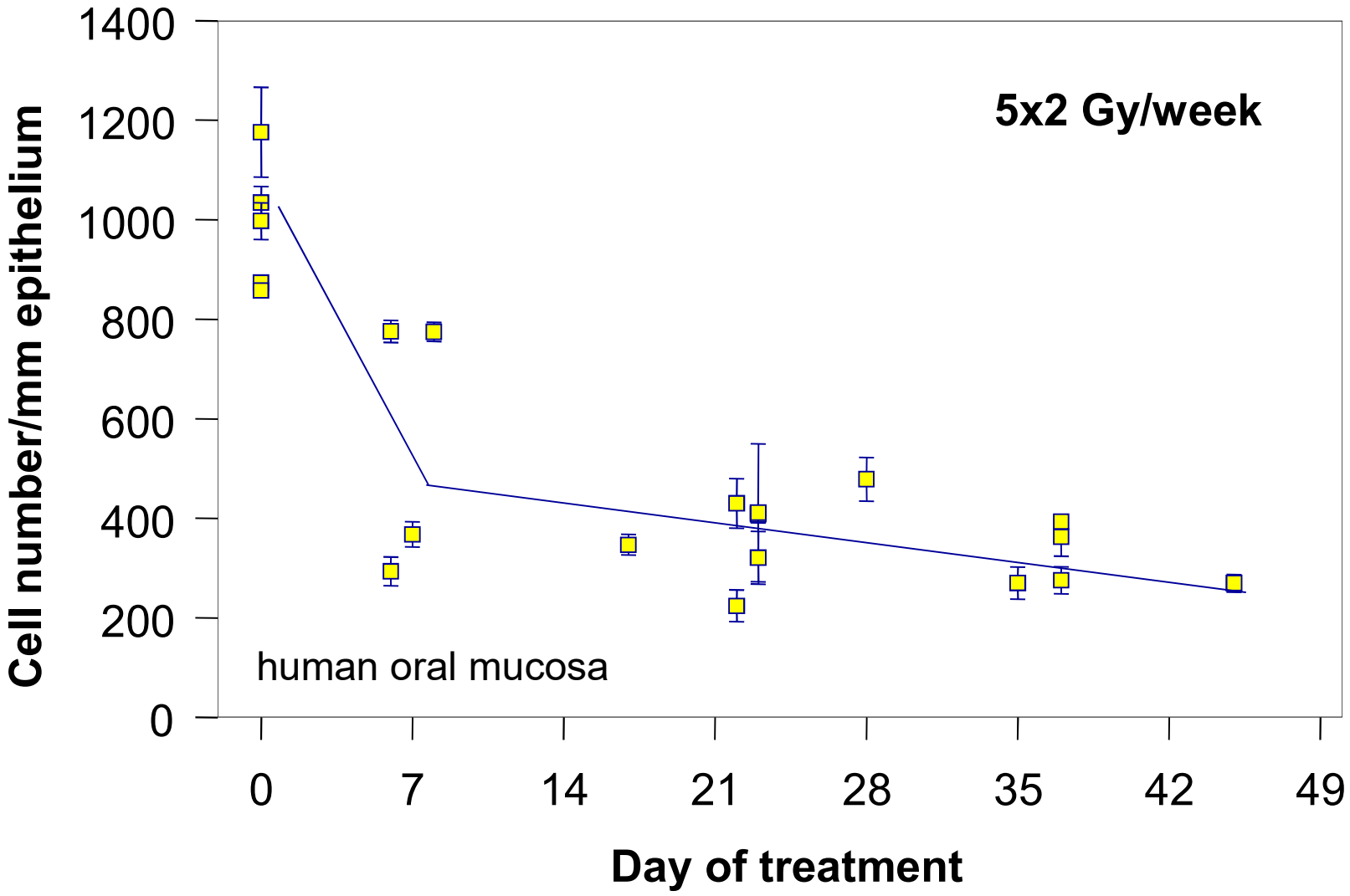
Repopulation: Mechanisms

Observation 3:
Compensation of normal cell loss



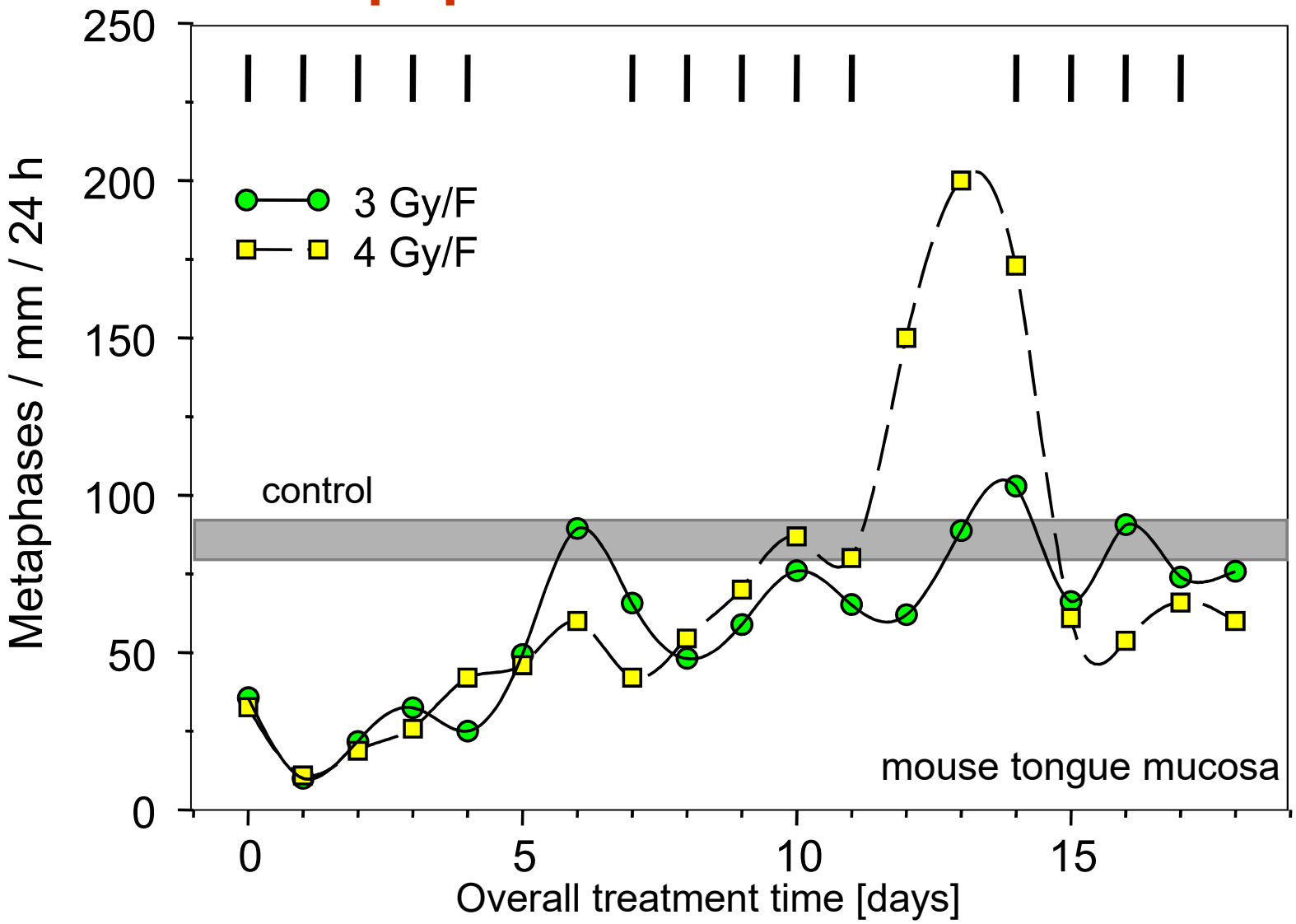
Dörr et al., Int. J. Radiat. Biol. 66, 1994, 157-167

Repopulation: Mechanisms



Dörr et al., IJROBP 52, 2002, 911–917

Repopulation: Mechanisms



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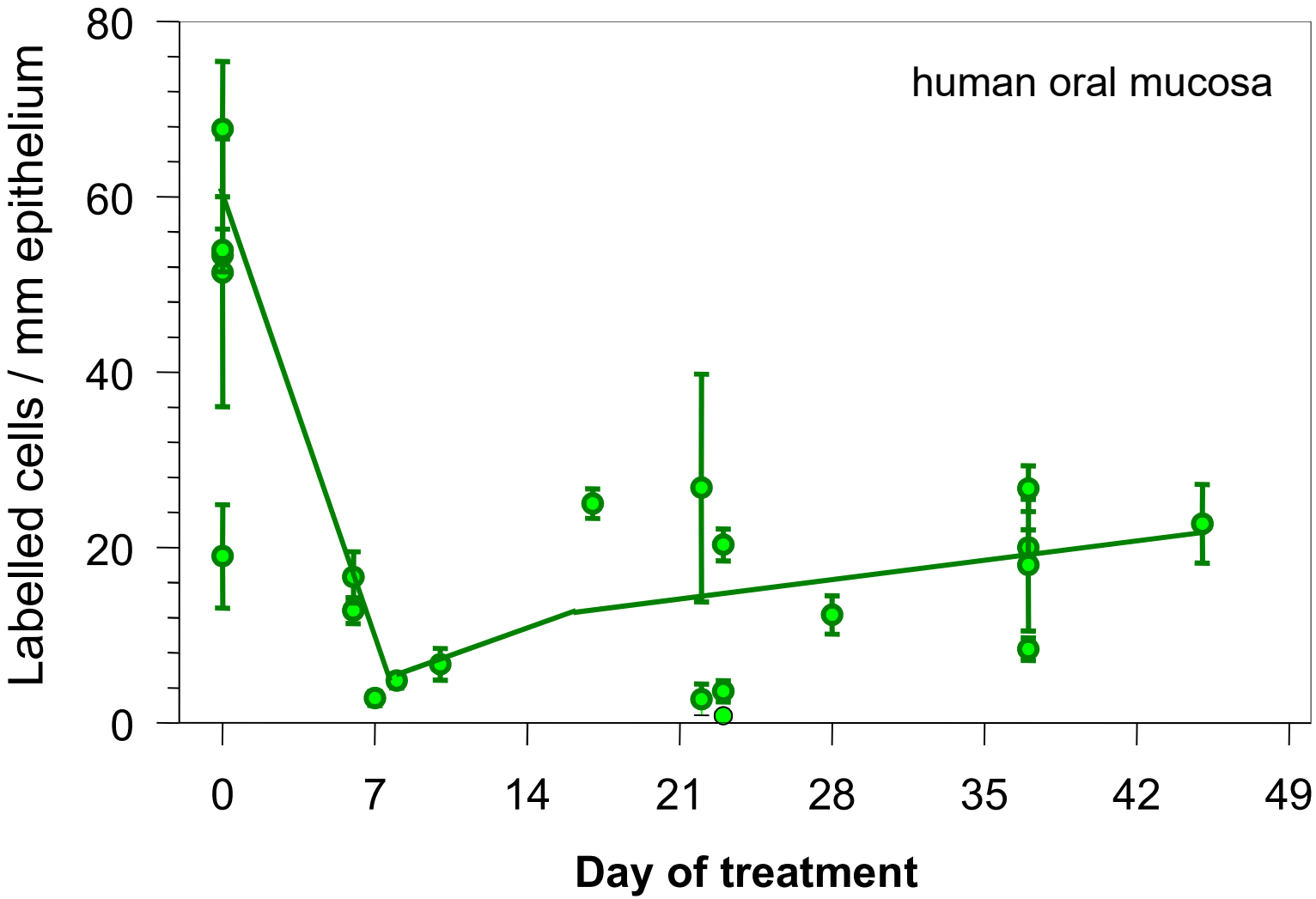
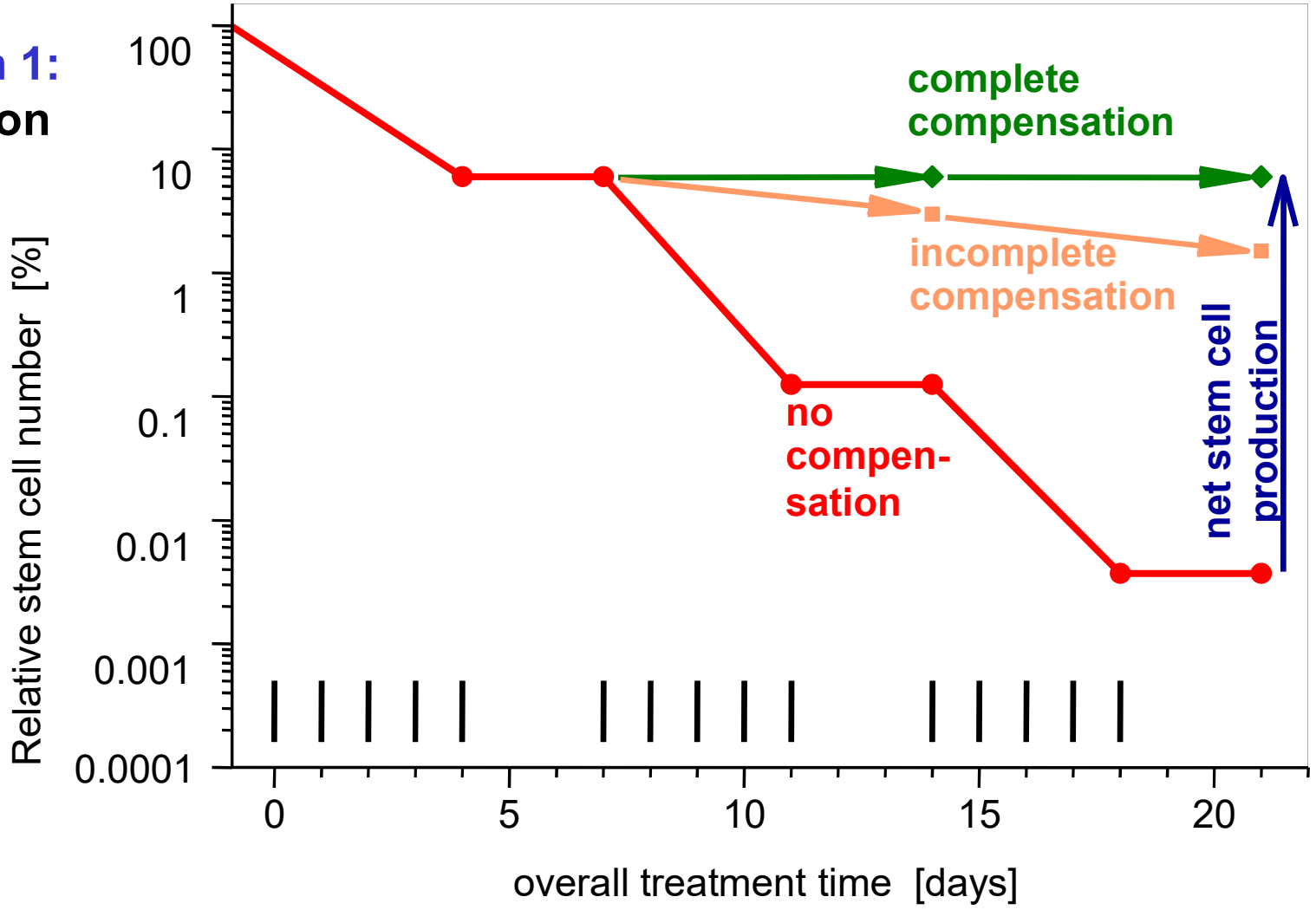
Repopulation: Mechanisms



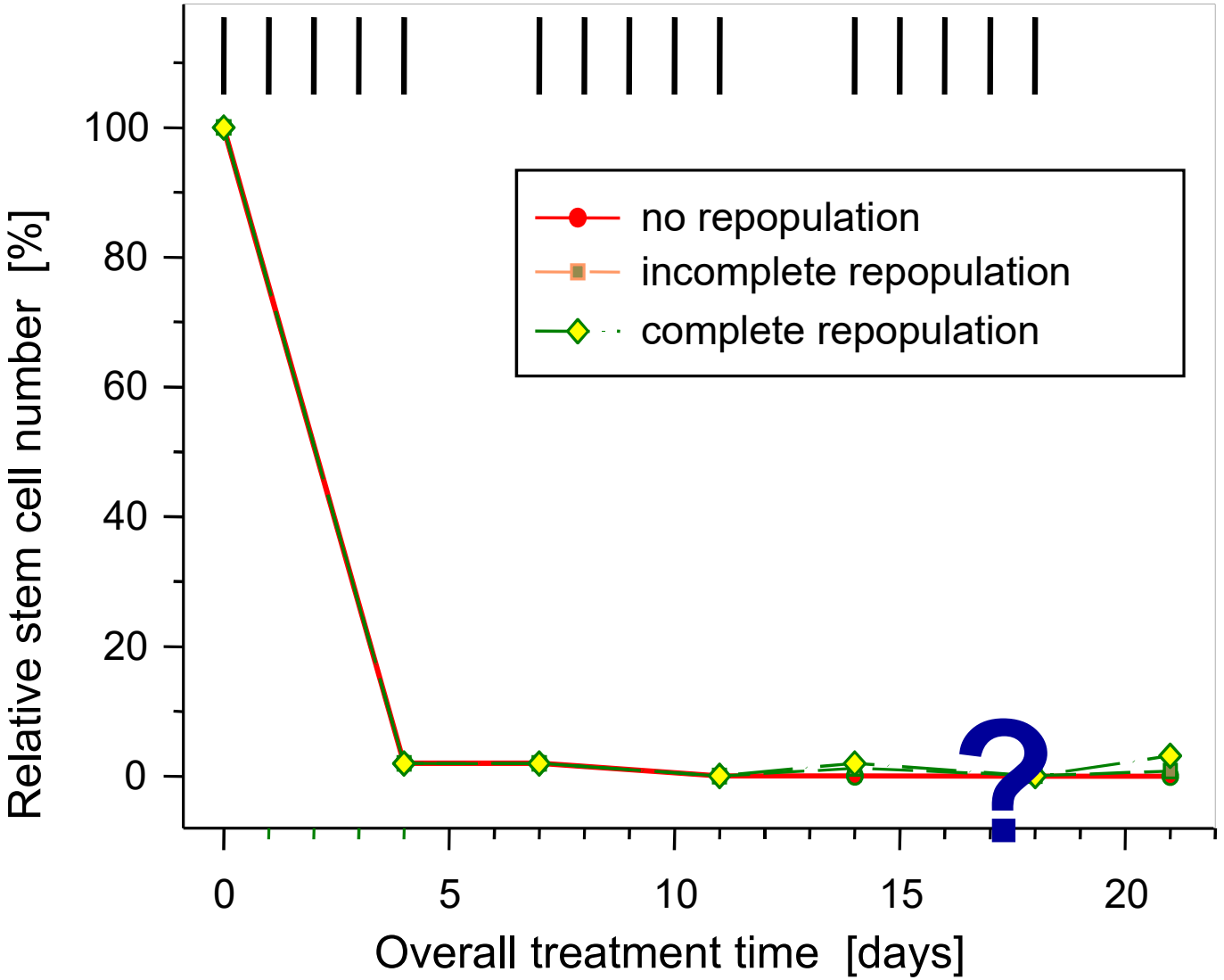
Dörr et al., IJROBP 52, 2002, 911–917

Repopulation: Mechanisms

Observation 1:
compensation of dose

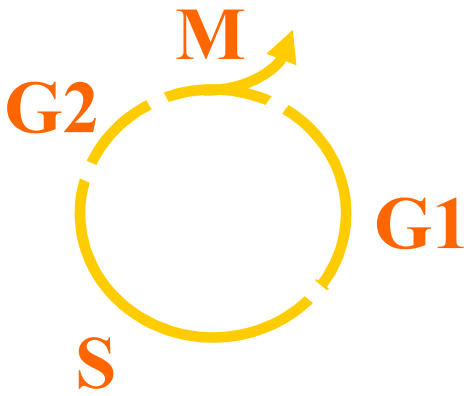


Repopulation: Mechanisms

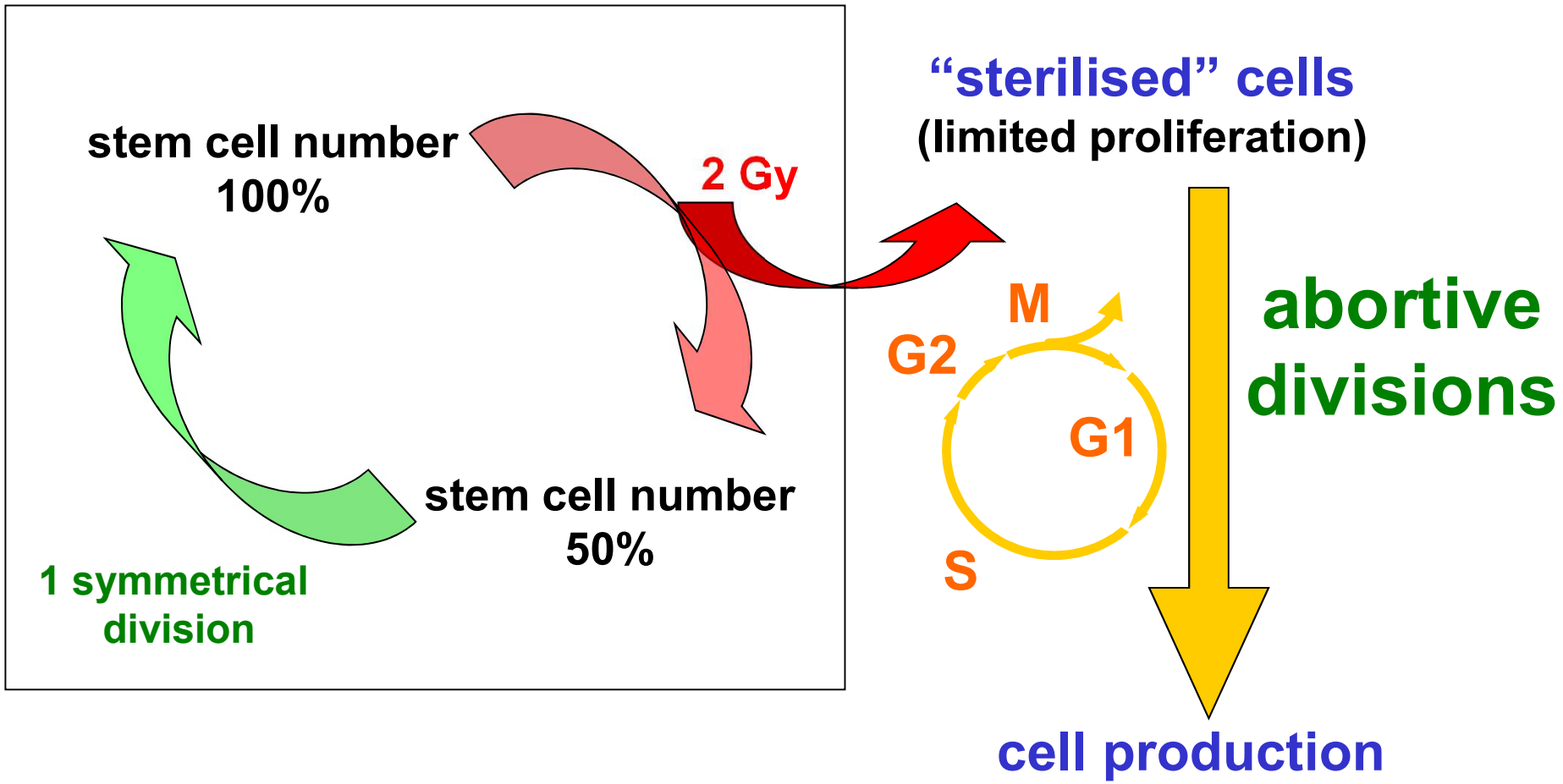


Repopulation: Mechanisms

Dose	relative stem cell number	cell cycle time
control	100 %	3.5 d
5x2 Gy	9 %	8 h
5x3 Gy	2 %	2 h



Repopulation: Mechanisms



Repopulation: Mechanisms

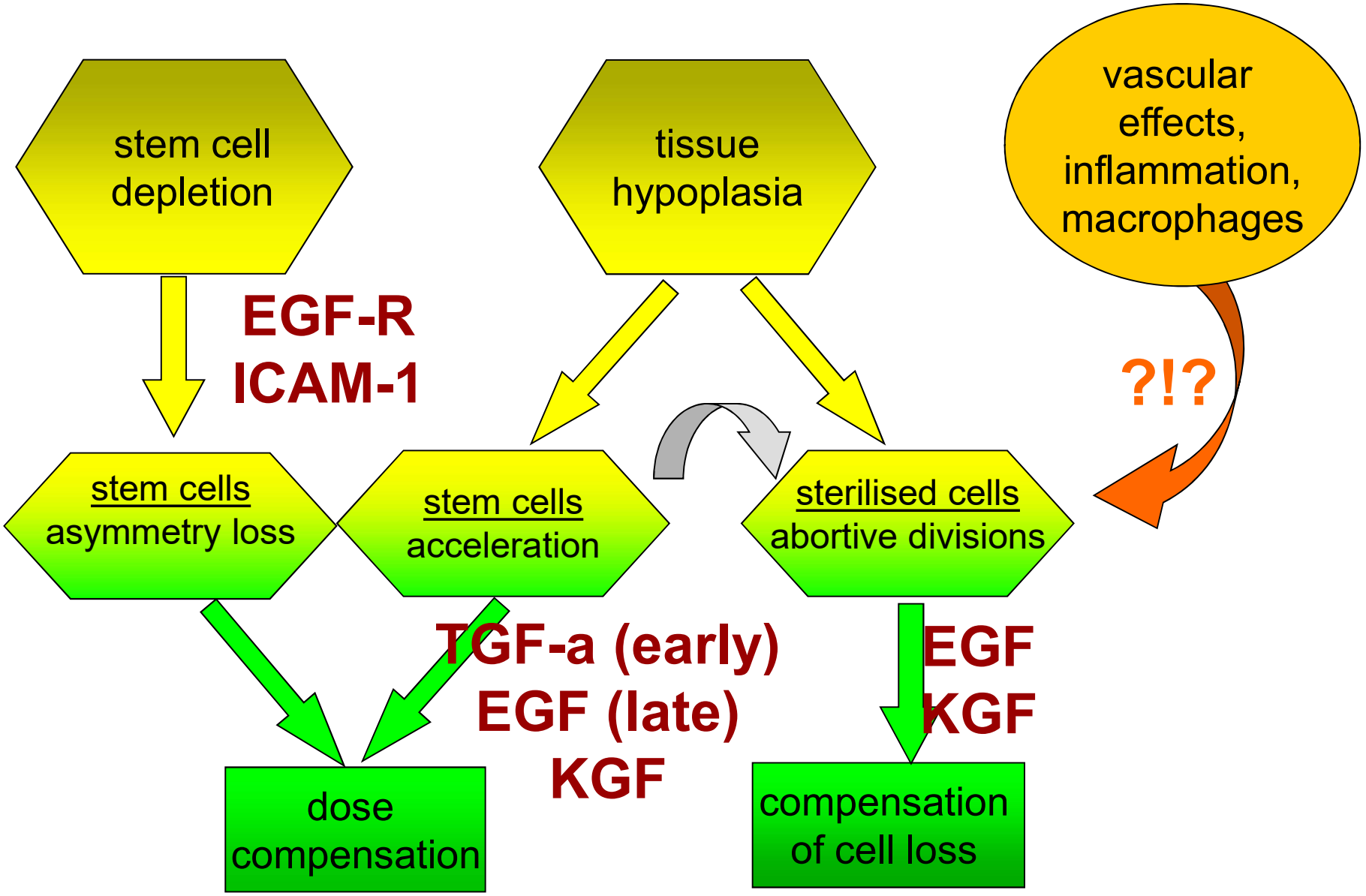
3 A

Observation	Mec
dose compensation	
rate of dose	ration
com	abortive divisions

???? NTCP time factor ????

NO!!!!!!

Repopulation: Mechanisms



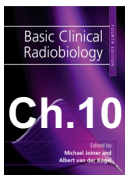
Take home message

Overall treatment time / repopulation:

- early effects (turnover tissues) and tumours
- not in late effects (exception: CLE)
- biology/mechanisms complex

NTCP models:

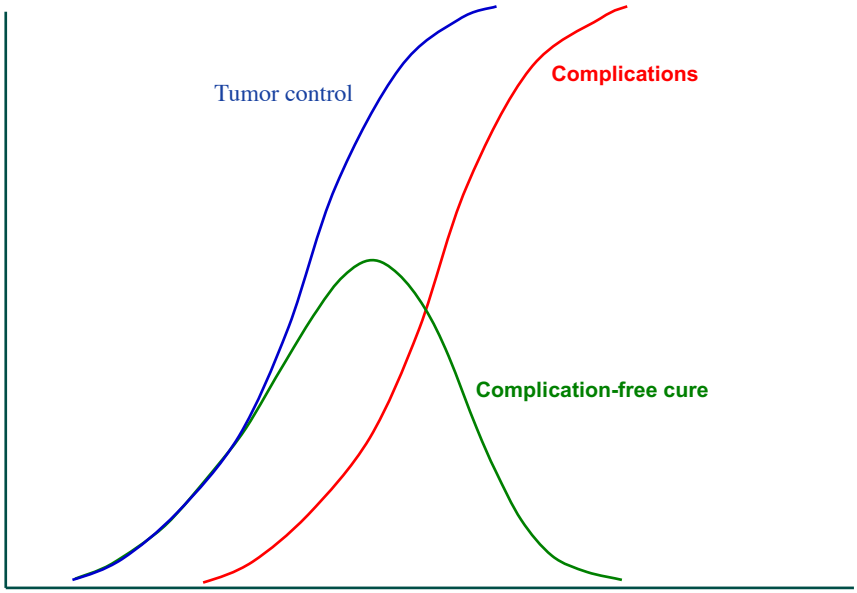
- no time factor !!!



Hyper-, hypofractionation and accelerated radiotherapy

Vincent GREGOIRE, MD, PhD, Hon. FRCR

The paradigm of radiotherapy



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

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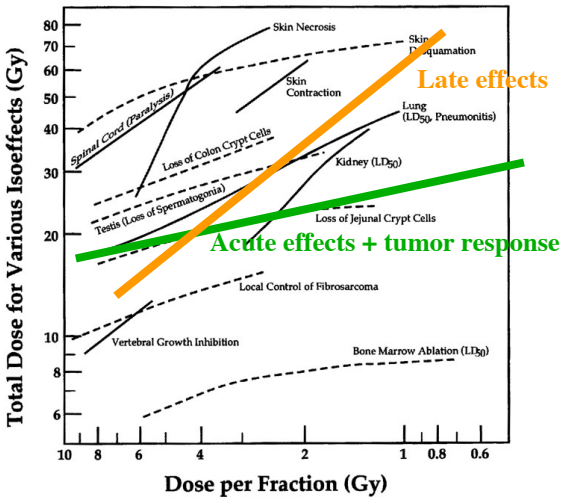
Fractionation sensitivity

"Typical" dose per fraction

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



Withers et al, 1983

Hyperfractionation (HF)

reduced dose per fraction (< 1.8 Gy)

CF 70Gy/ 2.0 Gy/ 7w

HF 80.5Gy/ 2x1.15 Gy/ ti=6h/ 7w

Expectations (dose-escalated HF):

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

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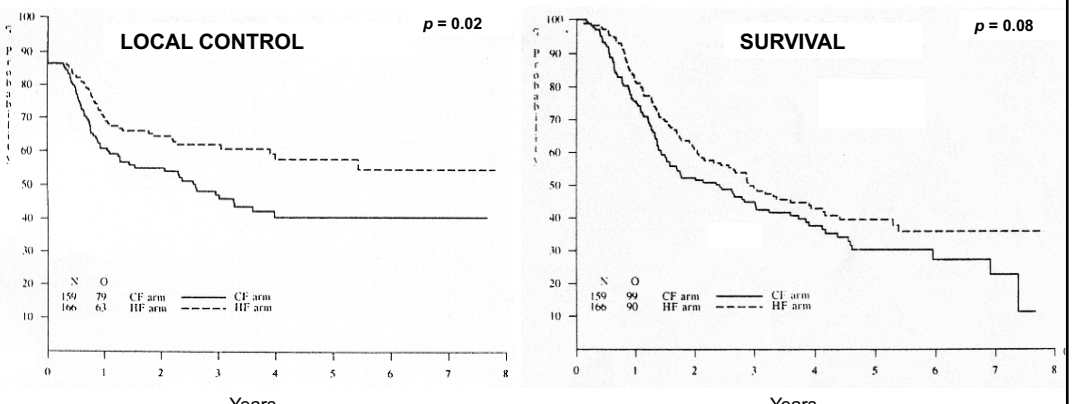
EORTC Hyperfractionation trial in oropharynx cancer (N = 356)

Oropharyngeal Ca T2-3, N0-1

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



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Horiot 1992

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%

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Dishes, 1997 Fu, 2000
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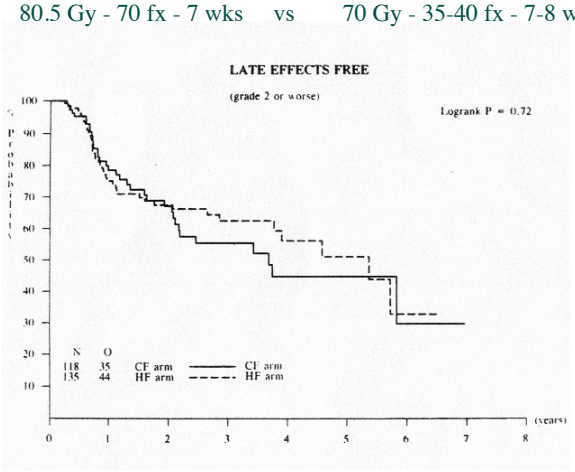

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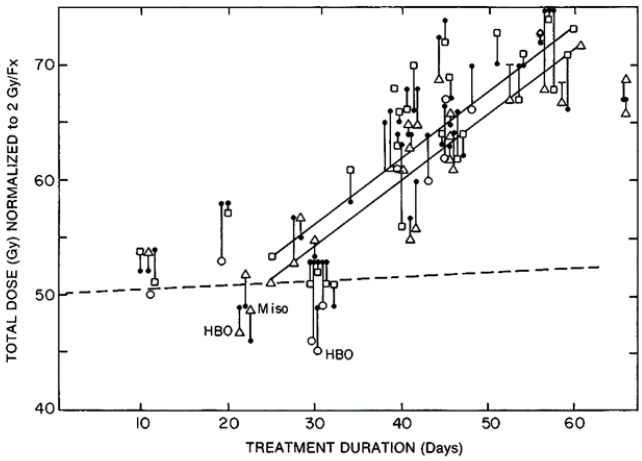
EORTC 22791; Horiot et al., *Radiother. Oncol*. 25: 231-241, 1992

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

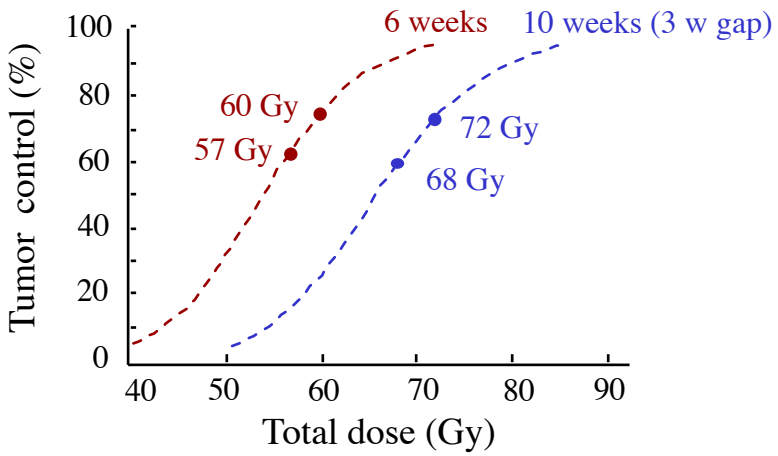
Tissue proliferation and recovered dose D_{prolif}

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

CF

70Gy/ 2.0 Gy/ 7w

CB

70Gy/ 2.0 Gy/ 5w

AF/HF

54Gy/ 3x1.5Gy/ ti=6h/ 12d

Expectations:

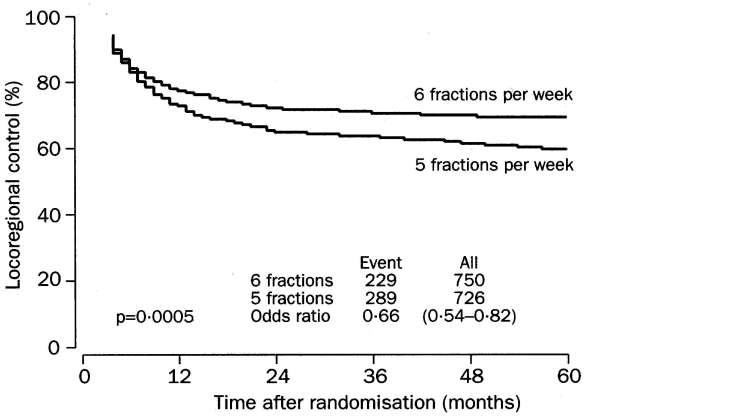
- Increased tumor control
- Increased early reactions
- Unchanged or decreased late damage (AF/HF and/or reduced total dose)

ESTRO 2017

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



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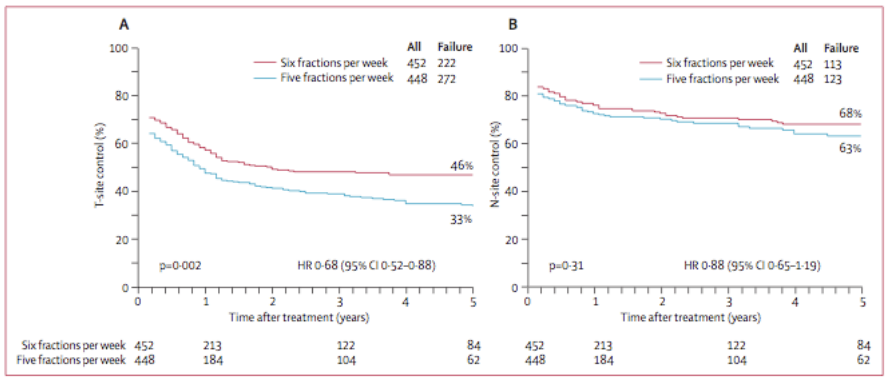
Overgaard et al. Lancet, 2003

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 2017

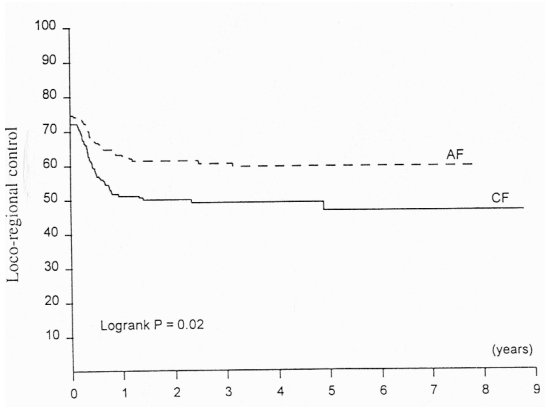
Overgaard et al. Lancet Oncol, 2010

EORTC - Head & Neck (22851)

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)



Accelerated RT:

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

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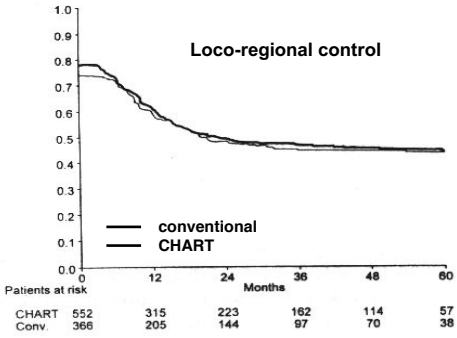
Horiot et al., *Radiother. Oncol*. 44: 111-121, 1997

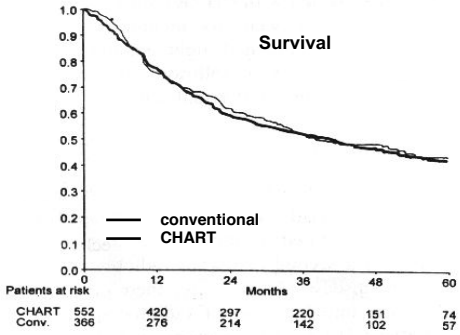
CHART - Head & Neck (MRC, UK)

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)





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

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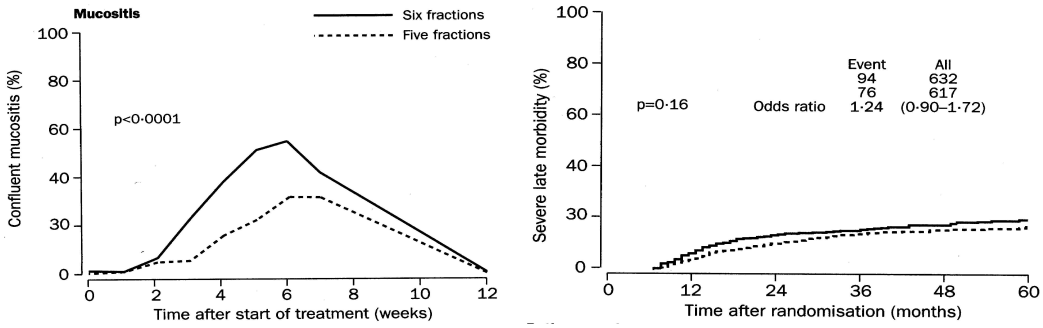

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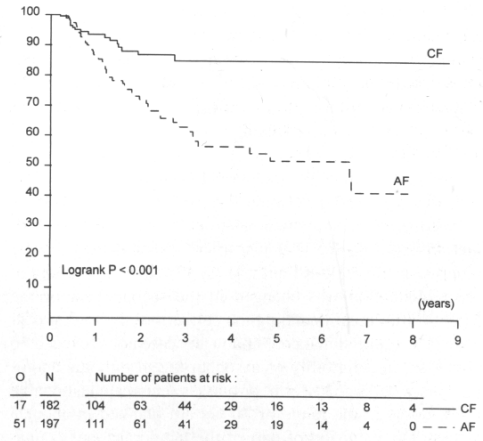

Late damage ≥ Grade 3

ESTRO 2017

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

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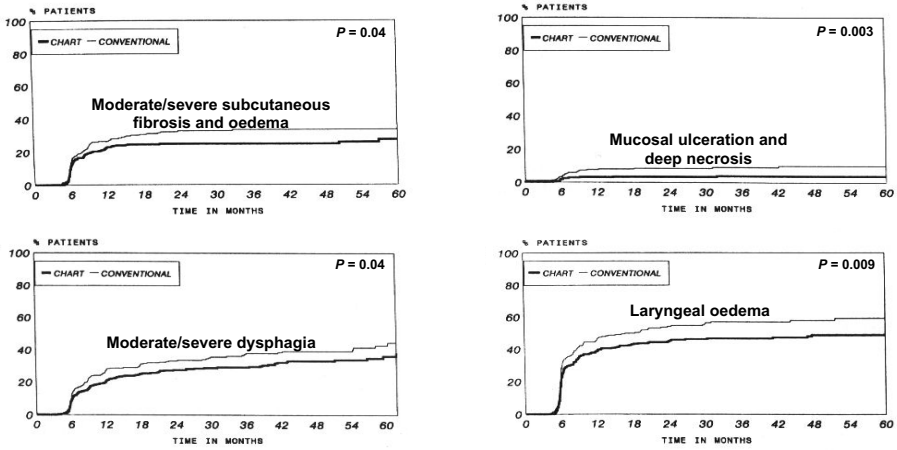

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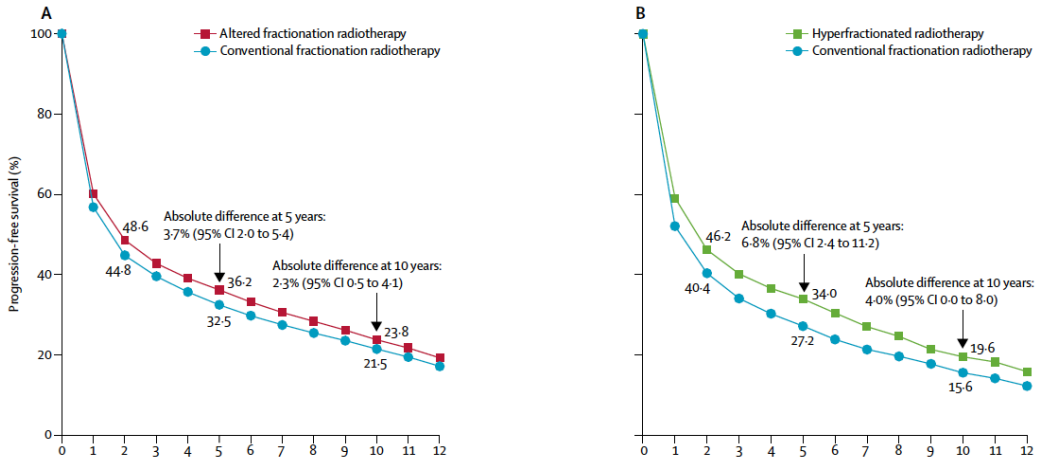
Meta-analysis on altered fractionation HNSCC

Randomized trials 1970-2010 (no postop RT)

33 trials included (11423 patients, individual data)



ESTRO 2017

Lacas et al., 2017

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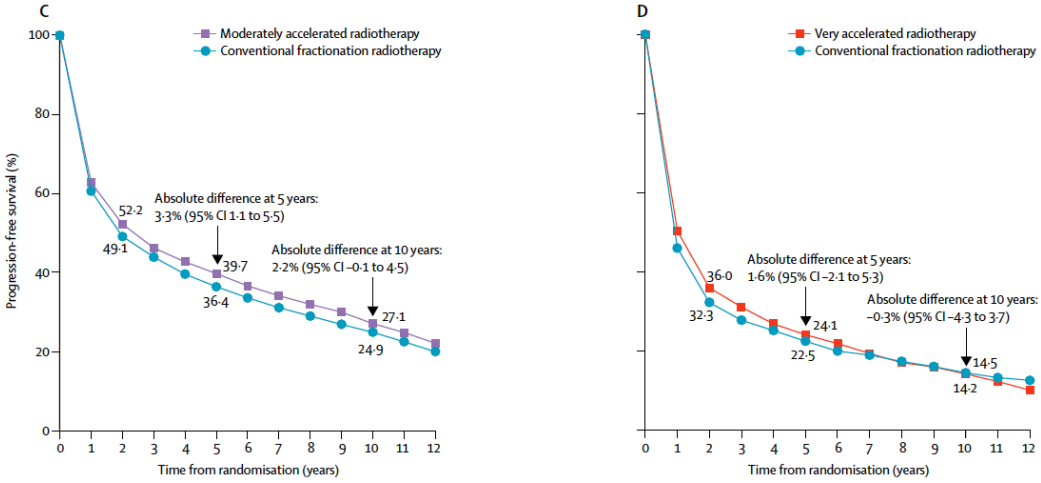
Randomized trials 1970-2010 (no postop RT)

33 trials included (11423 patients, individual data)



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Lacas et al., 2017

Meta-analysis on altered fractionation HNSCC

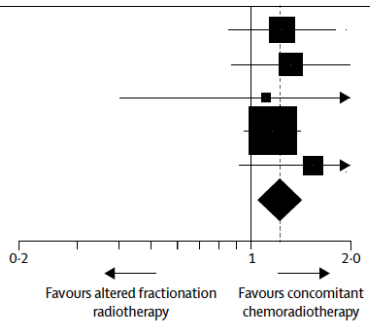
Randomized trials 1970-2010 (no postop RT)

33 trials included (11423 patients, individual data)

	Events (n)/patients (N)		Observed minus expected	Variance	HR (95% CI)
	Altered fractionation radiotherapy	Concomitant chemoradiotherapy			
INRC-HN-9[43]	58/66	55/70	5·9	27·9	1·24 (0·85–1·79)
ORO 9301[55]	50/65	42/64	6·2	22·7	1·32 (0·87–1·98)
EORTC 22962[45]	7/13	9/15	0·4	3·8	1·11 (0·40–3·03)
GORTEC 9902[36]	207/281	196/279	14·7	100·2	1·16 (0·95–1·41)
TMH 1114[37]	34/68	26/65	6·3	14·7	1·54 (0·92–2·56)
Total	**356/493**	**328/493**	**33·6**	**169·4**	**1·22 (1·05–1·42)**

χ^2 test for hetergeneity: p=0·87, I^2=0%

Treatment effect: p=0·0098



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Lacas et al., 2017

Meta-analysis on altered fractionation HNSCC

Randomized trials 1970-2010 (no postop RT)

33 trials included (11423 patients, individual data)

	Comparisons (n)	Patients (n)	Proportion of patients with toxicity receiving altered fractionation radiotherapy*	Proportion of patients with toxicity receiving conventional radiotherapy, n/N (%)	Odds ratio (95% CI)	p value for safety	I^2	p value for heterogeneity
Acute toxicities								
Mucositis (all trials)	20	8541	38·9%	1155/4233 (27·3%)	2·02 (1·81–2·26)	<0·0001	78%	<0·0001
Mucositis (no heterogeneity)	16	7051	35·2%	845/3499 (24·1%)	2·10 (1·84–2·41)	<0·0001	0%	0·66
Dermatitis (all trials)	15	4997	17·7%	410/2483 (16·5%)	1·09 (0·93–1·29)	0·29	36%	0·083
Dermatitis (no heterogeneity)	13	4314	20·1%	376/2143 (17·5%)	1·20 (1·01–1·42)	0·041	0%	0·83
Weight loss (all trials)	5	2053	3·6%	43/1023 (4·2%)	0·87 (0·56–1·36)	0·54	7%	0·37
Need for feeding tube (all trials)	6	2859	52·1%	563/1420 (39·6%)	1·75 (1·49–2·05)	<0·0001	89%	<0·0001
Need for feeding tube (no heterogeneity)	4	1871	35·6%	252/929 (27·1%)	1·63 (1·34–1·99)	<0·0001	3%	0·38
Late toxicities								
Xerostomia (all trials)	12	4726	51·3%	1193/2337 (51·0%)	1·01 (0·88–1·14)	0·94	20%	0·25
Xerostomia (no heterogeneity)	11	4414	54·6%	1181/2182 (54·1%)	1·02 (0·90–1·17)	0·73	0%	0·50
Bone toxicity (all trials)	11	3219	4·4%	64/1585 (4·0%)	1·12 (0·80–1·57)	0·52	0%	0·77
Mucosal toxicity (all trials)	8	2298	14·5%	149/1114 (13·4%)	1·10 (0·87–1·40)	0·41	49%	0·058
Mucosal toxicity (no heterogeneity)	7	1921	14·4%	140/937 (14·9%)	0·96 (0·74–1·24)	0·74	0%	0·64
Neck fibrosis (all trials)	15	5557	7·6%	188/2744 (6·9%)	1·13 (0·92–1·39)	0·23	70%	<0·0001
Neck fibrosis (no heterogeneity)	12	4250	7·0%	138/2109 (6·5%)	1·09 (0·85–1·38)	0·50	0%	0·45

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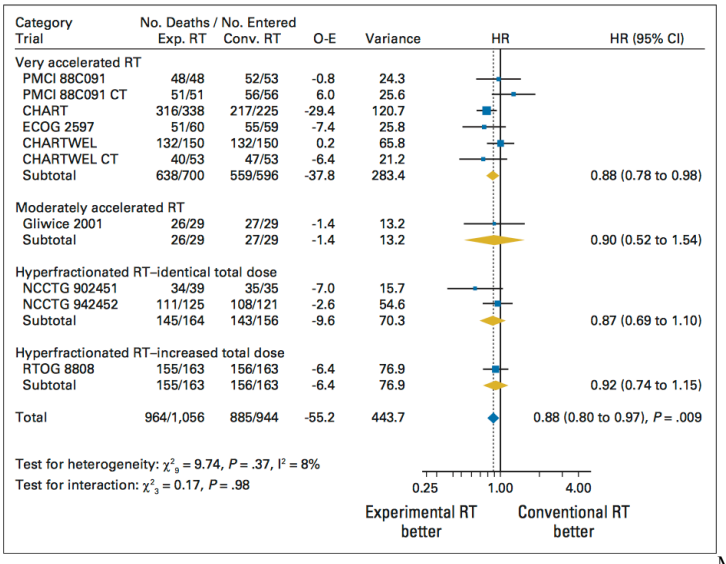
Lacas et al., 2017

Meta-analysis on altered fractionation in loc. adv. NSCLC

Randomized trials 1970-2005 (no postop RT)

10 trials included (2000 patients, individual data)



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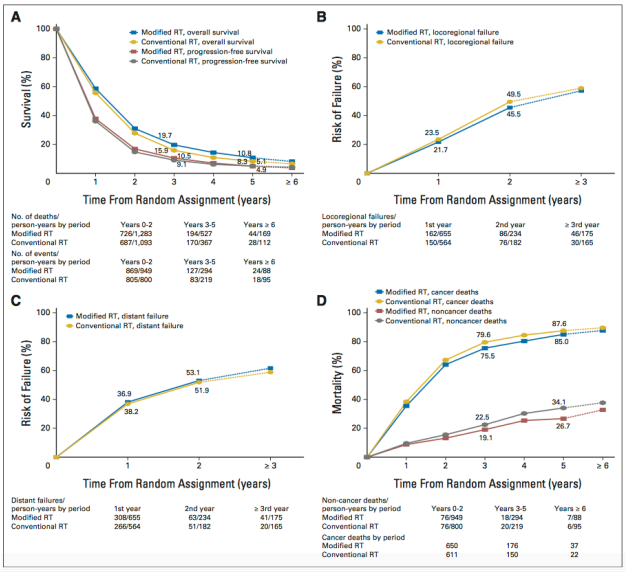
Mauguen et al., 2012

Meta-analysis on altered fractionation in loc. adv. NSCLC

Randomized trials 1970-2005 (no postop RT)

10 trials included (2000 patients, individual data)



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Mauguen et al., 2012

Meta-analysis on altered fractionation in loc. adv. NSCLC

Randomized trials 1970-2005 (no postop RT)

10 trials included (2000 patients, individual data)

Table 2. Effect of Modified Radiotherapy Compared With Conventional Radiotherapy on Toxicity Events

Severe Toxicity	Availability: No. of Trials	Availability: No. of Patients	Toxicity Rate in Control Arm (%)	Toxicity Rate in Experimental Arm (%)*	Result: OR	Result: 95% CI	*P* Efficacy	I^2 (%)	*P* Heterogeneity
Non–small-cell lung cancer									
Acute toxicity									
Esophageal	10	1,968	9	19	2.44	1.90 to 3.14	< .001	57	.01†
Pulmonary	9	1,390	7	5	0.67	0.42 to 1.05	.08	0	.65
Cardiac	6	940	1	1	1.33	0.46 to 3.83	.59	0	.92
Hematologic‡	5	607	34	29	0.79	0.48 to 1.32	.38	0	.54
Neutrophils	5	600	33	28	0.80	0.46 to 1.40	.44	3	.39
Platelets	5	595	13	8	0.55	0.32 to 0.96	.03	0	.98
Hemoglobin	6	677	1	1	1.36	0.46 to 4.08	.58	0	.86
Late toxicity									
Pulmonary	7	866	15	16	1.07	0.73 to 1.56	.73	0	.56
Esophageal	7	861	3	4	1.24	0.61 to 2.56	.55	0	.89
Cardiac	4	515	1	1	1.49	0.40 to 5.60	.55	0	.96
Any of above	4	533	13	16	1.27	0.79 to 2.06	.33	0	.97

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Mauguen et al., 2012

Prototypes of modified fractionation

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

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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 to 30 Gy/ 3.0 Gy/ 2w	Palliative RT

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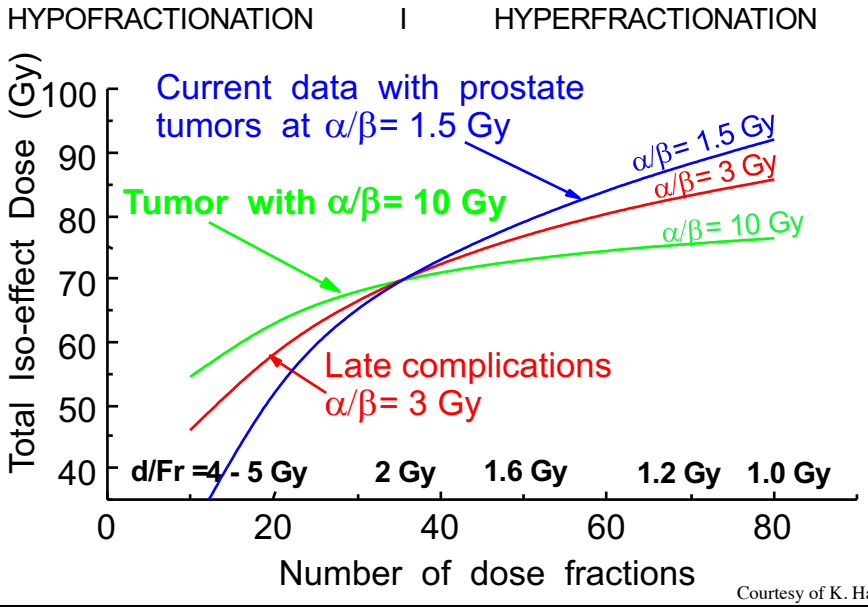
Radiobiological and clinical issues in IMRT for prostate C



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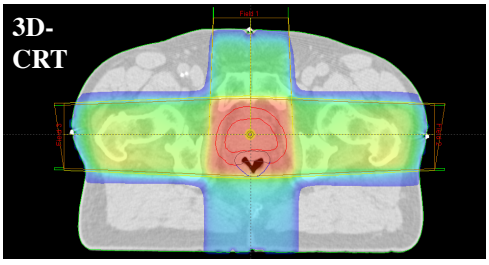
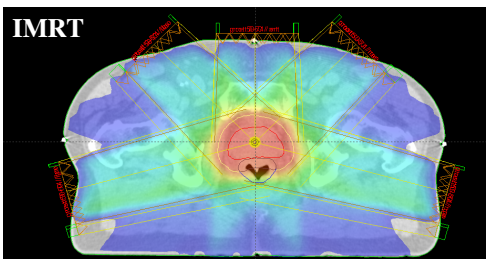
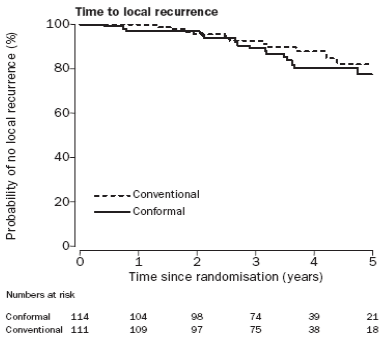
Courtesy of K. Haustermans

Conformal irradiation for prostate tumors







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

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Dearlaney, 1999

Hypofractionation in prostate Ca

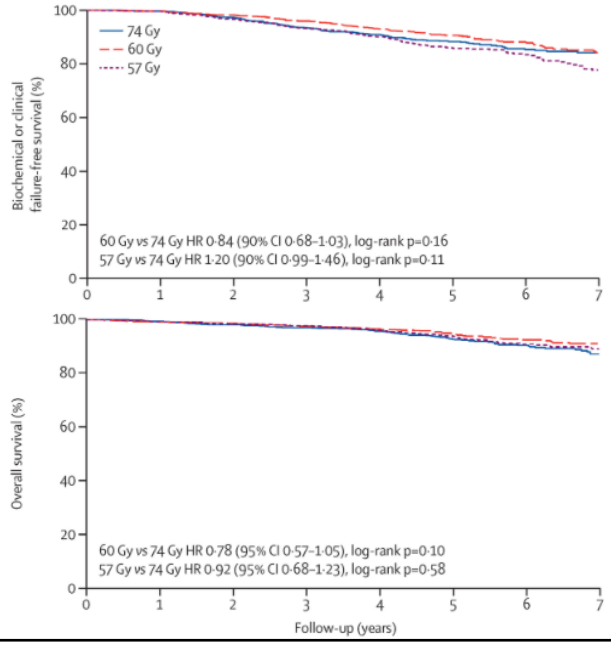
Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial

David Dearnaley, Isabel Syndikus, Helen Mossop, Vincent Khoo, Alison Birtle, David Bloomfield, John Graham, Peter Kirkbride, John Logue, Zafar Malik, Julian Money-Kyrle, Joe M O'Sullivan, Miguel Panades, Chris Parker, Helen Patterson, Christopher Scrase, John Staffurth, Andrew Stockdale, Jean Tremlett, Margaret Bidmead, Helen Mayles, Olivia Naismith, Chris South, Annie Gao, Clare Cruickshank, Shama Hassan, Julia Pugh, Clare Griffin, Emma Hall, on behalf of the CHHiP Investigators*

74 Gy (37 x 2 Gy) in 7.4 w >< 60 Gy (20 x 3.0 Gy) in 4w >< 57 Gy (19 x 3 Gy) in 3.8w

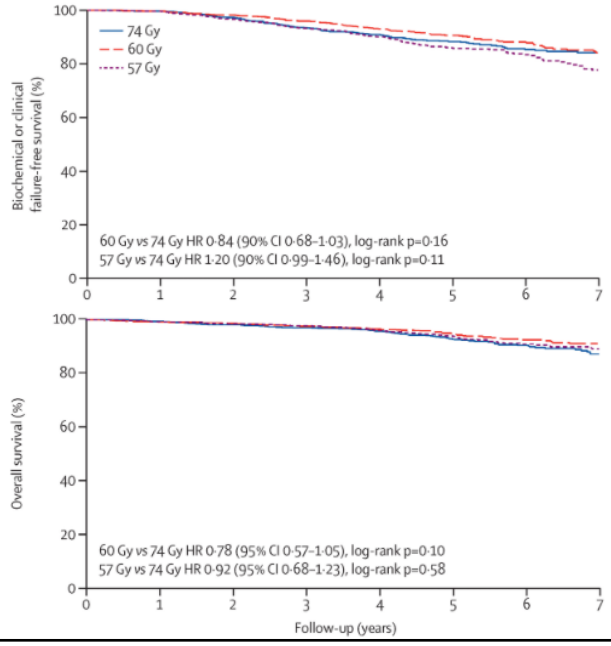
Dearnaley et al., Lancet Oncology, 2016

Hypofractionation in prostate Ca



y et al., Lancet Oncology, 2016

Hypofractionation in prostate Ca



α/β: 1.8 Gy

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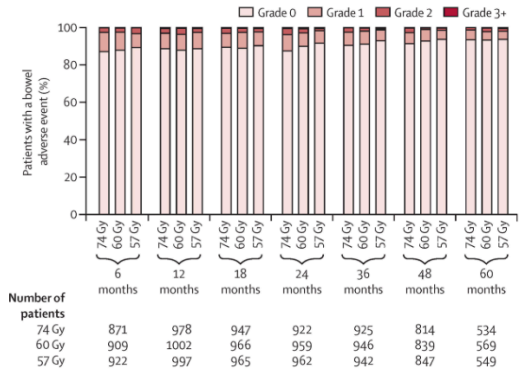
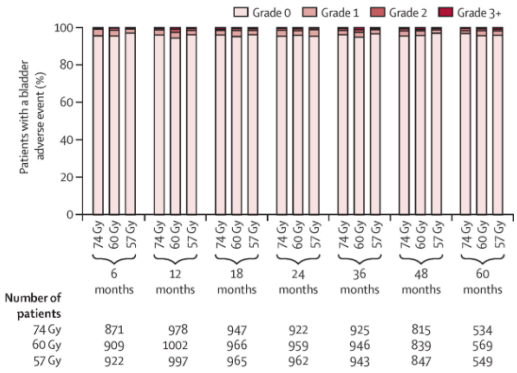
y et al., Lancet Oncology, 2016

Hypofractionation in prostate Ca

Late bowel toxicity



Late bladder toxicity



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Dearnaley et al., Lancet Oncology, 2016

Hypofractionation in breast cancer

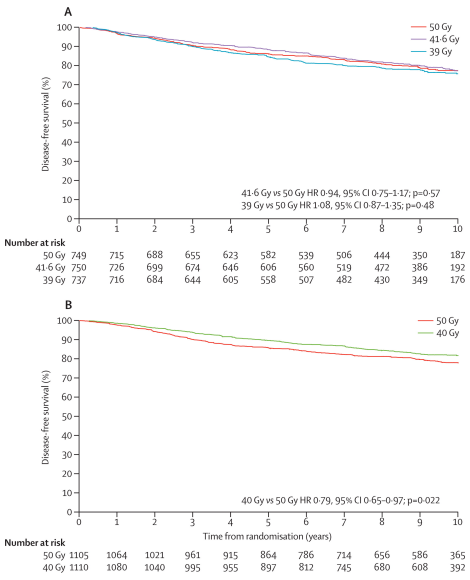
The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials

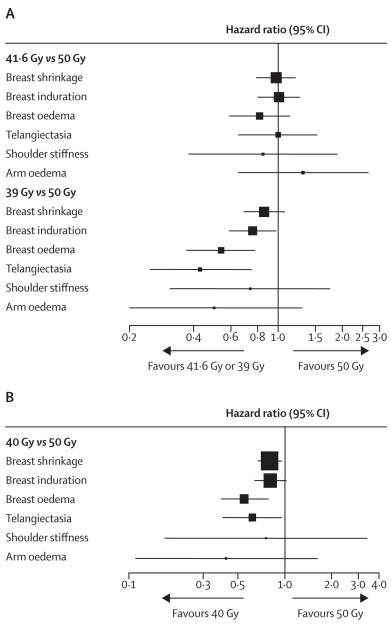
Joanne S Haviland, J Roger Owen, John A Dewar, Rajiv K Agrawal, Jane Barrett, Peter J Barrett-Lee, H Jane Dobbs, Penelope Hopwood, Pat A Lawton, Brian J Magee, Judith Mills, Sandra Simmons, Mark A Sydenham, Karen Venables, Judith M Bliss, John R Yarnold*, on behalf of the START Trialists' Group†*

50 Gy (25 x 2 Gy) in 5 w ≈ 40 Gy (15 x 3.3 Gy) in 3w

Lancet Oncology, 2013

Hypofractionation in breast cancer

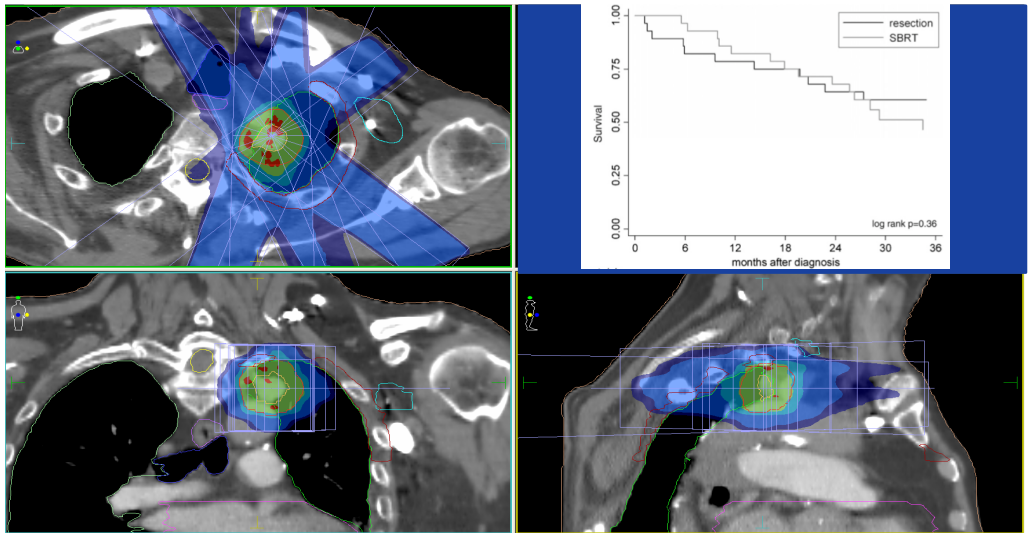




α/β: 3.5 Gy (95% CI: 1.2-5.7)

Lancet Oncology, 2013

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

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Martin et al., 2010

Conclusions

- Benefit of hyper- and accelerated fractionation for loco-regional control probability
- Slight increase in acute toxicity but no change in late toxicity
- Moderately hypofractionation for tumors with low α/β
- Extreme hypofractionation for well selected indications, e.g. small peripheral lung tumors (dose distribution effect only!)

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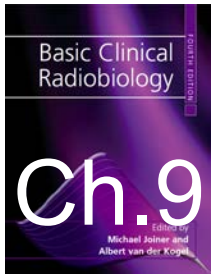
Basic Clinical Radiobiology

Correcting dose errors in radiation treatment delivery

Michael Joiner

Paris 2017



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 = **36.4** Gy in 2 Gy fractions

would give equal late injury as 35 × 2 Gy.

In practice, 36.4 ÷ 2 ≈ 18 (maybe 19) fractions.

Considering tumor effect, using α/β = 10 Gy,

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

Therefore, giving the rest of the treatment as

70 – 28 = **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

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

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:

$$D = P - E$$

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

Result

$$D = P - E$$

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

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:

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

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

Radiobiology in practice

Mike Joiner

Karin Haustermans

ESTRO School

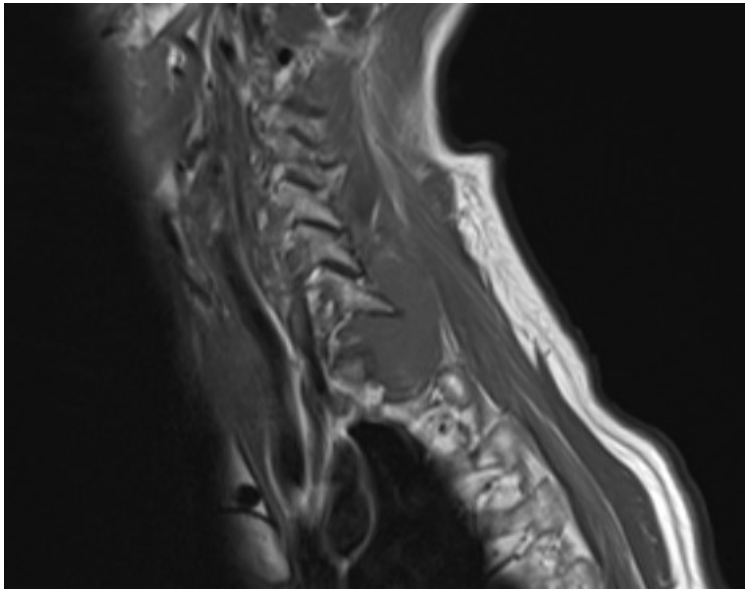
ESTRO School

Clinical case

- Woman, 75 y
- 11-2016: D/ adenocarcinoma of the colon -> surgery: pT4bN2b with peritoneal metastasis
- 01-2017: liver and lung metastasis -> mFOLFOX
- 07-2017: progressive disease (liver) -> mFOLFIRI
- 08-2017: osteolytic bone metastasis: C6 + Th1

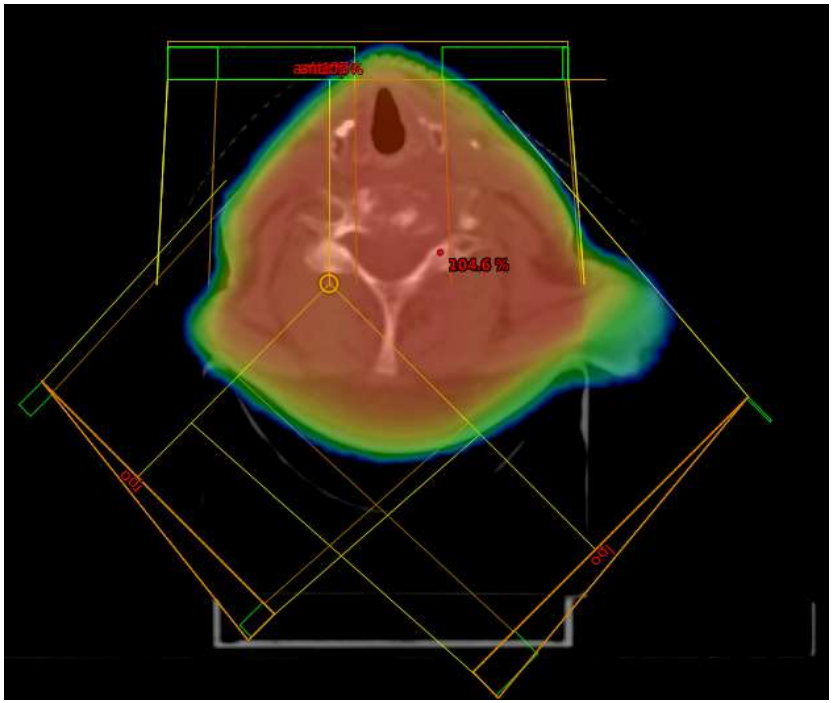
Clinical case

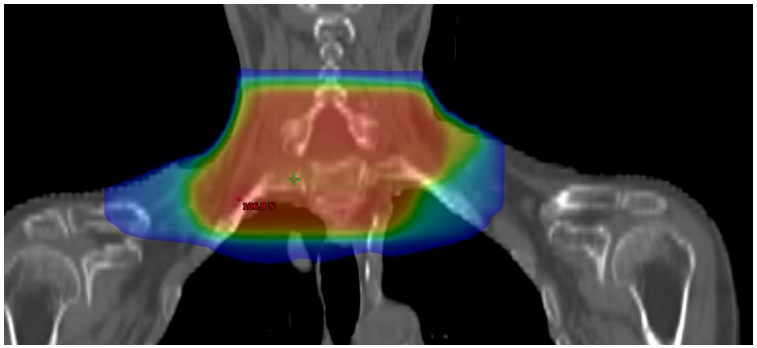
- MRI

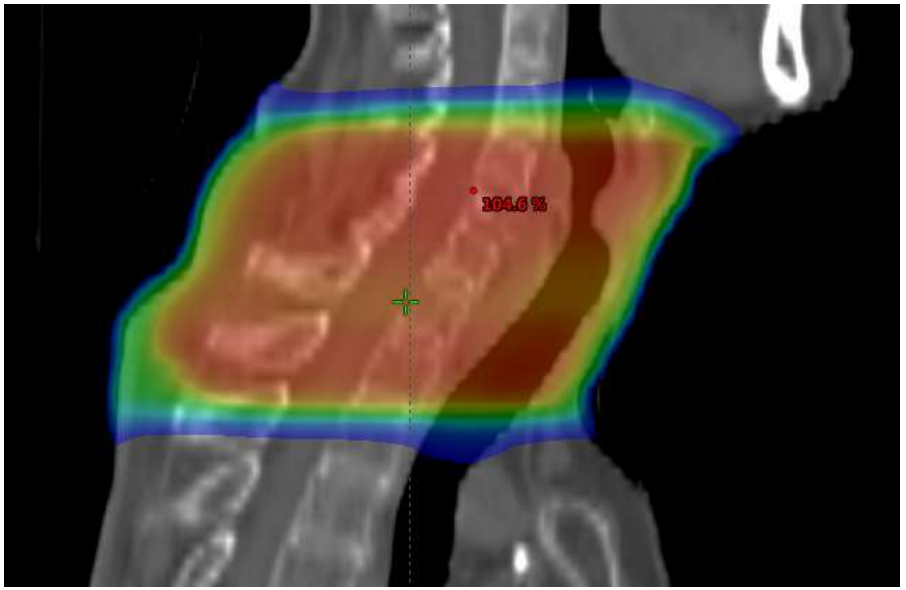


- Planned treatment: 13 x 3 Gy = 39 Gy

Clinical case







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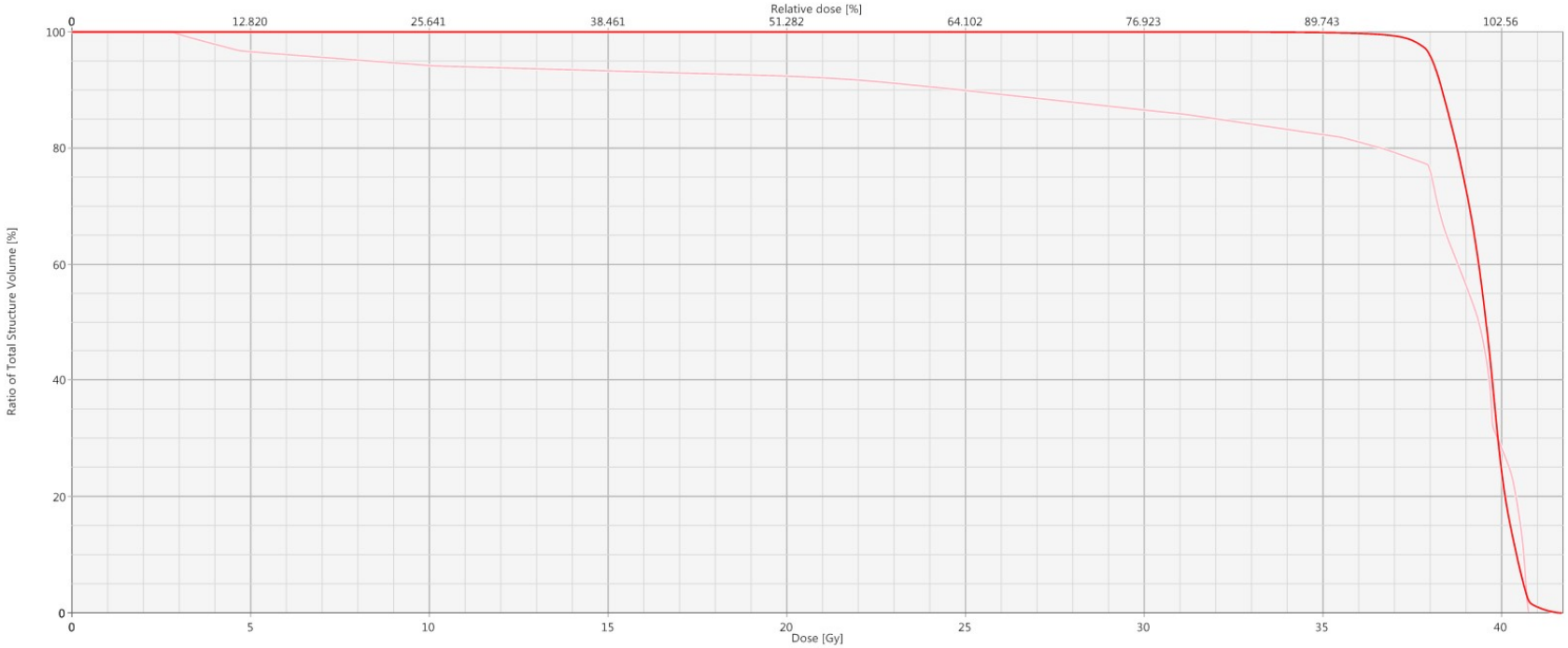
DVH & Double Trouble

- Planned treatment: 13 x 3 Gy = 39 Gy



- PTV: red
- Spinal cord: pink

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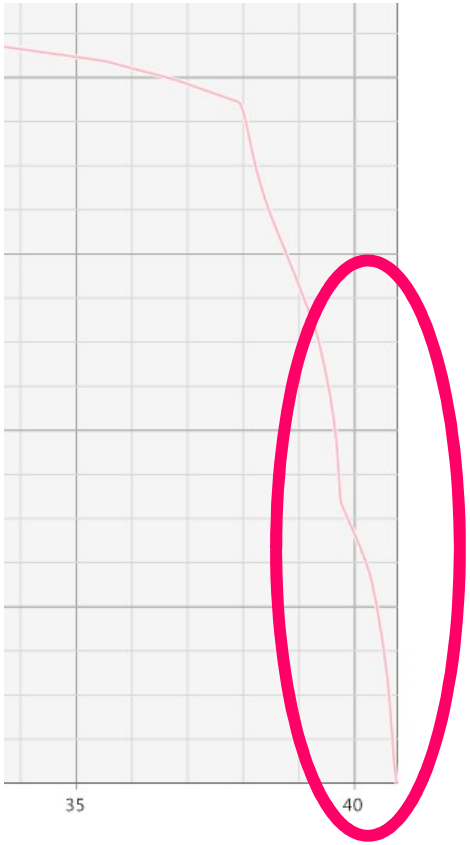
DVH & Double Trouble

- Spinal cord Dmax 105% or 40,76 Gy (physical dose)



Clinical case

- Do we exceed the myelum tolerance dose, regarding the biological dose in the overlap zone?
  (α/β is assumed to be 2 Gy for spinal cord late toxicity)

- $EQD_2 = D \frac{d + (\alpha/\beta)}{2 + (\alpha/\beta)}$

- $EQD_2 = 40{,}76 \times \frac{3{,}135 + 2}{2 + 2}$

- $EQD_2 = 40{,}76 \times 1{,}284$

- $EQD_2 = 52{,}34$

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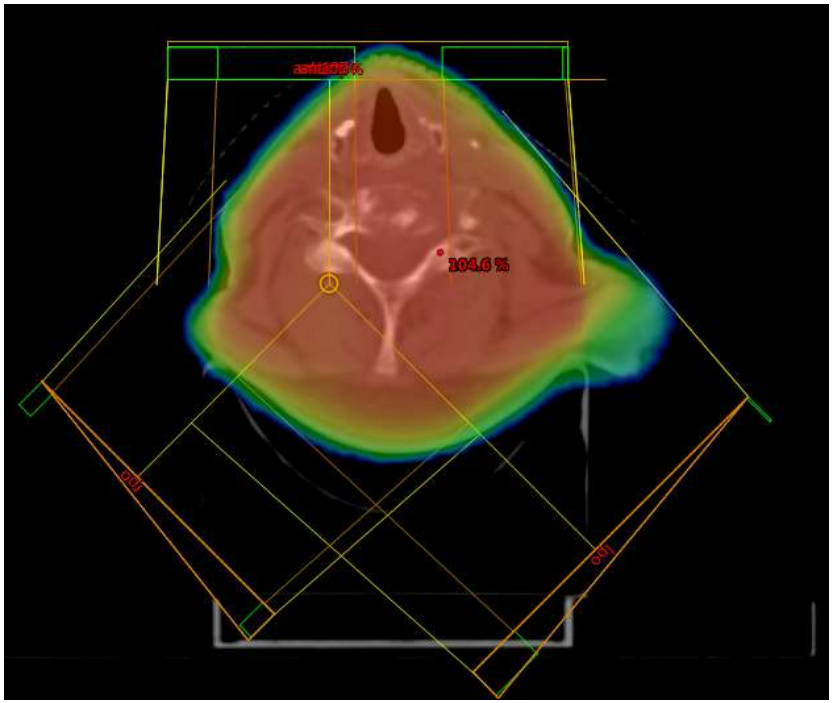
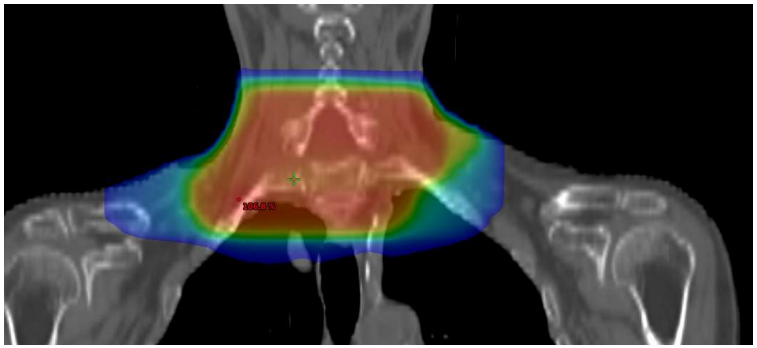
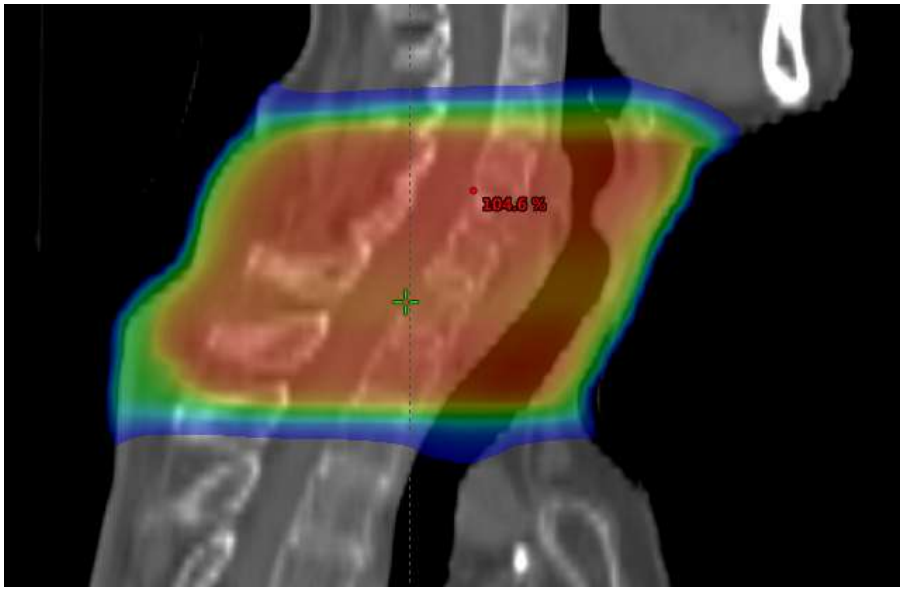
Clinical case







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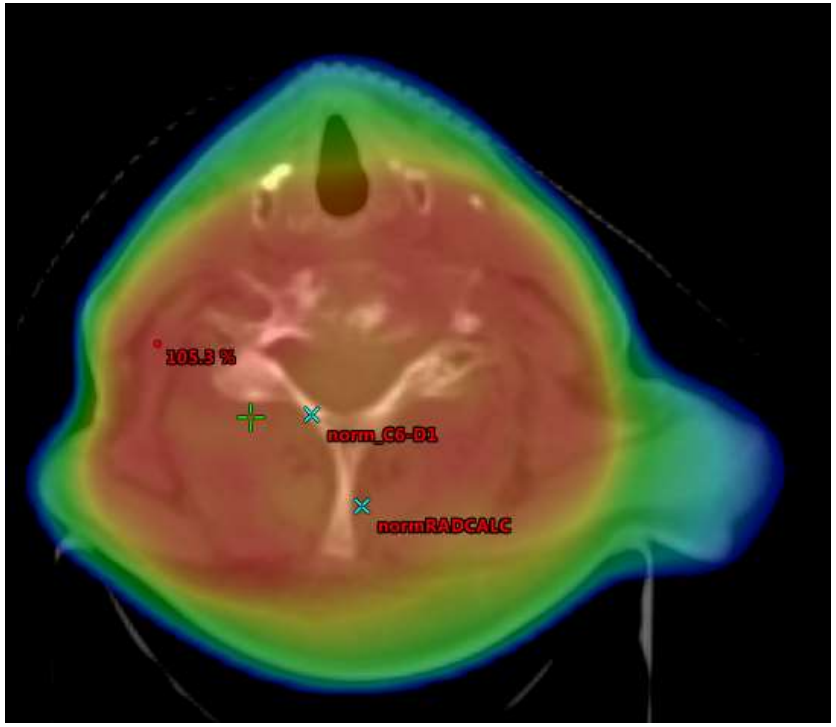
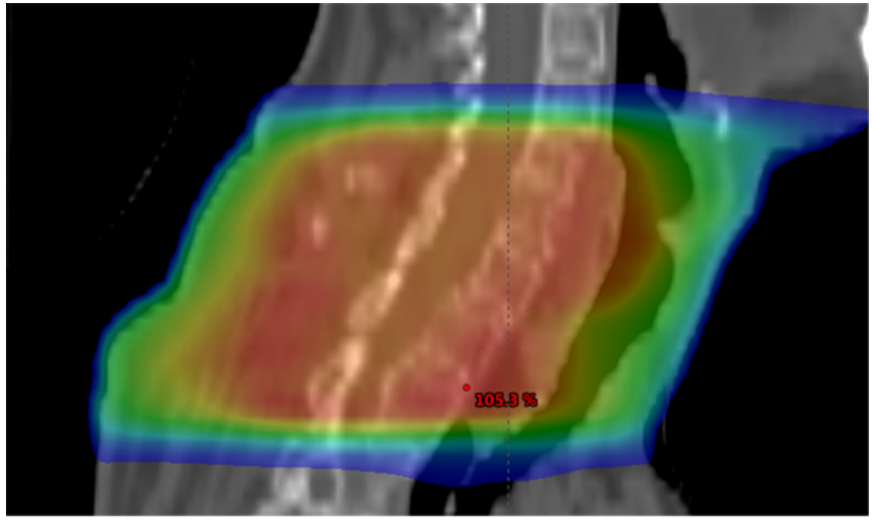
Clinical case

- Volumetric modulated arc therapy (VMAT)





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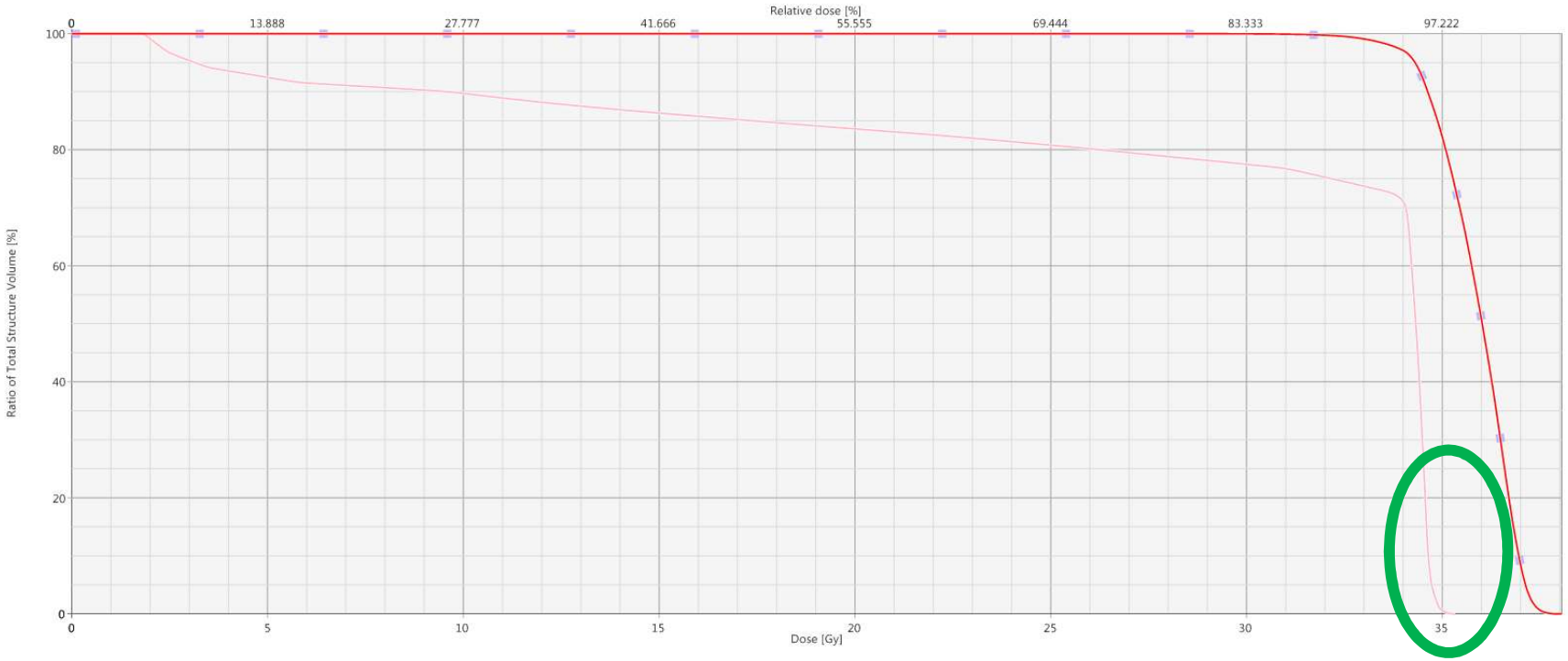
Clinical case

- Volumetric modulated arc therapy (VMAT); DVH



- PTV: red
- Spinal cord: pink

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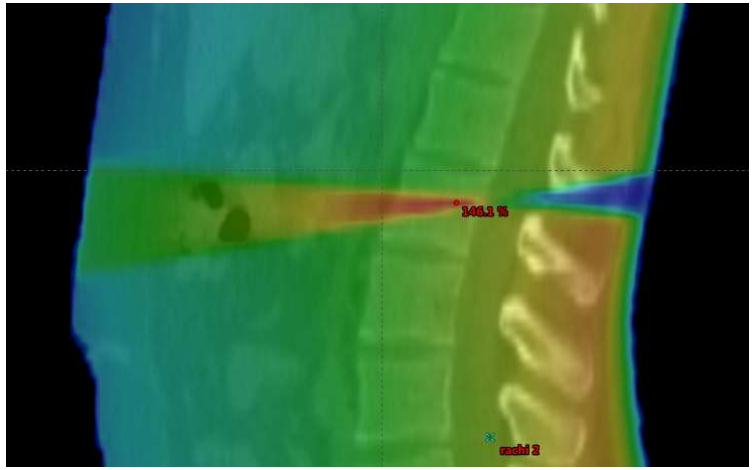
Craniospinal irradiation case

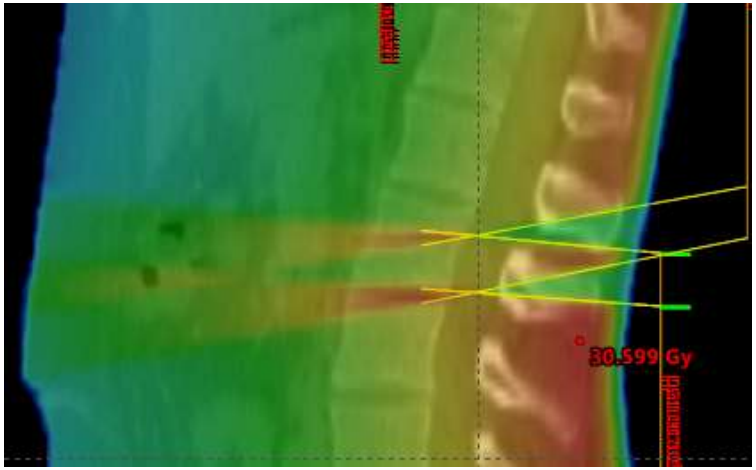
- A patient was treated with 39 Gy in 13 fractions to the craniospinal axis.
- A shift was foreseen after 7 fractions.
- As result of a mistake an overlap of 1 cm was created instead of a gap of 1 cm after 7 fractions. This mistake was applied for 2 fractions.
- In the overlap region of 1 cm, the spinal cord received 7x 3.1 Gy Dmax and 2 x 6.2 Gy.

Planning technique of craniospinal irradiation

Gap-junction method
No Field Edge Matching



Junction shift
Dose feathering



- Not robust for setup errors, i.e. 100% dose difference expected for setup errors larger than 5-7 mm

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Craniospinal irradiation case

- What is the physical dose in the overlap zone?

- Do we exceed the spinal cord tolerance in the overlap zone?

Craniospinal irradiation case

- What is the physical dose in the overlap zone?

- D = 7 x 3,1 Gy + 2 x 6,2 = 33,9 Gy

- Do we exceed the spinal cord tolerance, regarding the biological dose in the overlap zone?
  (α/β is assumed to be 2 Gy for spinal cord late toxicity)

- $EQD_2 = D \frac{d + (\alpha/\beta)}{2 + (\alpha/\beta)}$
- $EQD_2 = 21{,}7 \times \frac{3{,}1 + 2}{2 + 2} = 27{,}67$ Gy (7 fractions)
- $EQD_2 = 12{,}4 \times \frac{6{,}2 + 2}{2 + 2} = 25{,}42$ Gy (2 overlap fractions)

Craniospinal irradiation case

- Do we exceed the spinal cord tolerance dose?
  (α/β is assumed to be 2 Gy for spinal cord late toxicity)

- EQD_2 = 27,67 Gy + 25,42 Gy = 53,09 Gy (Total)

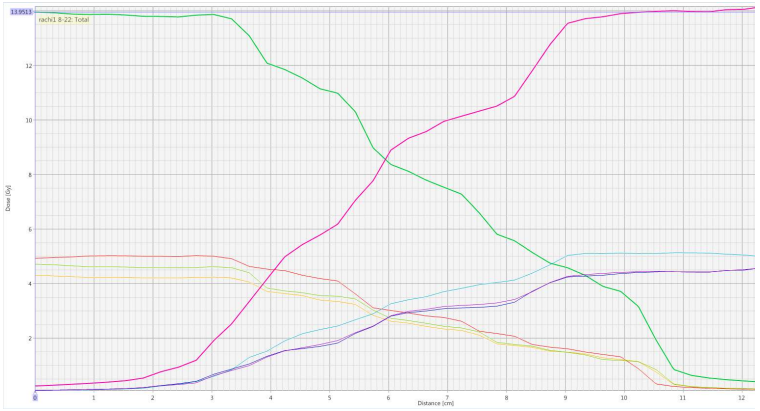
DVH & Double Trouble

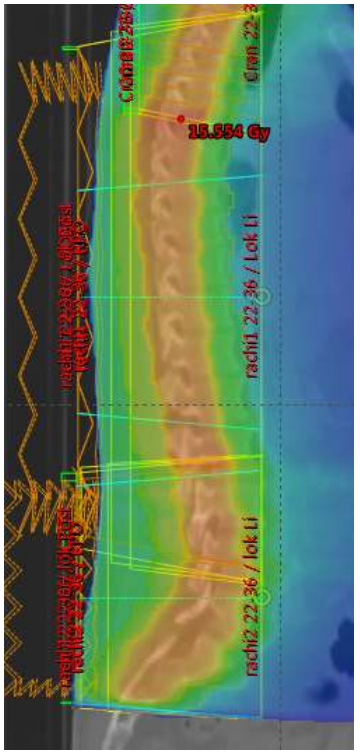
		EQD_2	
% Pres dose	Phys dose (cGy)	α/β = 1,0 Gy	α/β = 10,0 Gy
130	260	310	275
120	240	270	250
110	220	235	225
100	200	200	200
90	180	170	175
80	160	140	155
70	140	110	135

Planning technique of craniospinal irradiation

- IMRT: The inferior edges of the lateral brain fields and the superior edge of the lower posterior spine field are manually designed with long, smooth dose gradients by IMRT field-in-field (FIF) techniques.

- More robust for setup errors
- 1%/mm dose gradient in junction
- 1 cm shift will result in 5-10% dose difference





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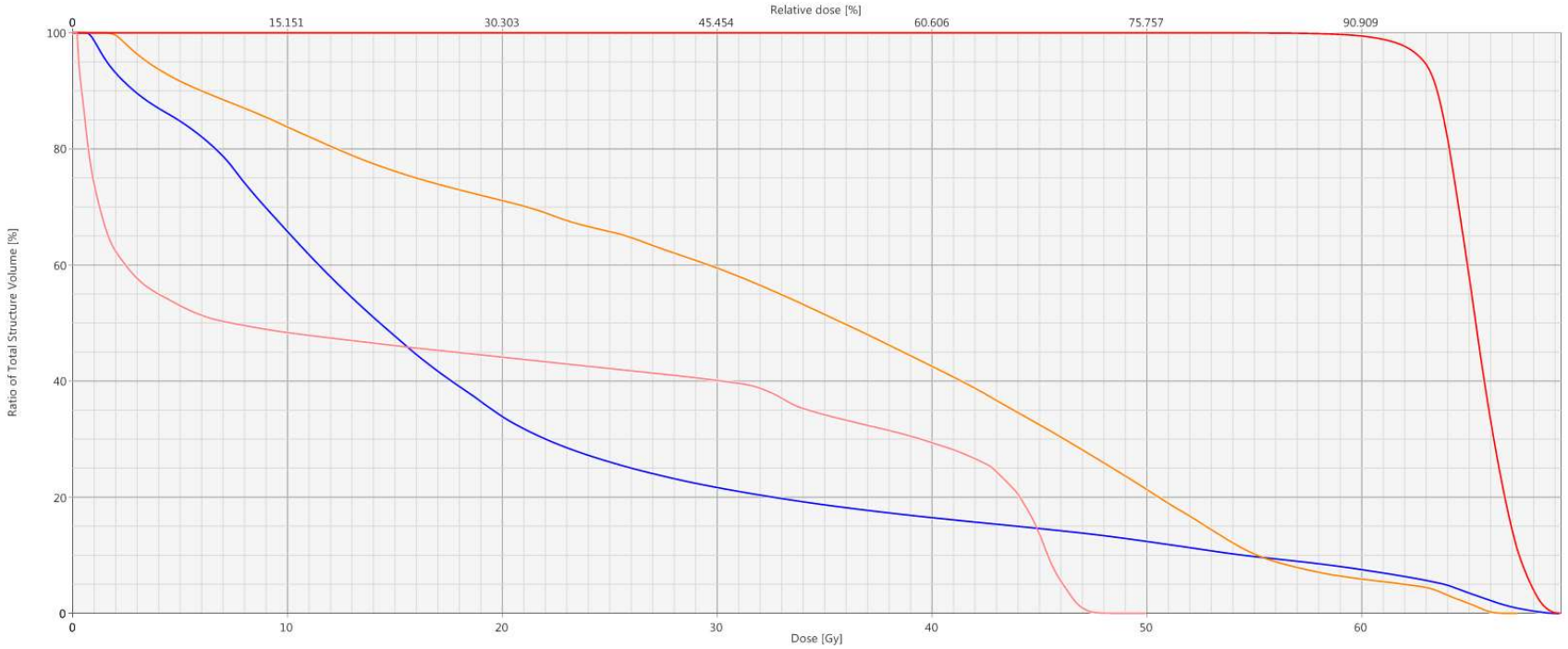
DVH & Double Trouble

- Lung cancer patient; planned treatment: 24 x 2,75 Gy = 66Gy



- PTV: red
- Spinal cord: pink
- Heart: orange
- Lung-GTV: blue

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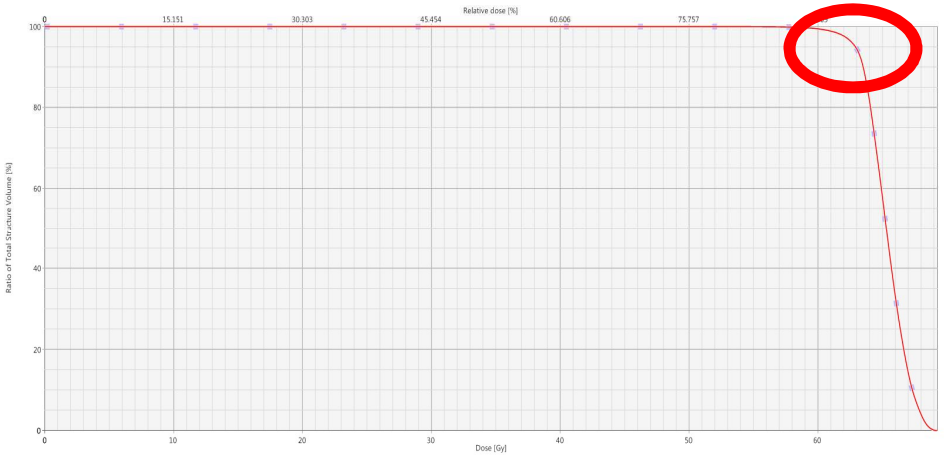
DVH & Double Trouble

- Lung cancer patient; planned treatment: 24 x 2,75 Gy = 66Gy

- PTV

Volume	Constraint	Case
99 %	90 % PD	92,14 %
95 %	95 % PD	95,28 %
D_{max}	< 115 %	105 %



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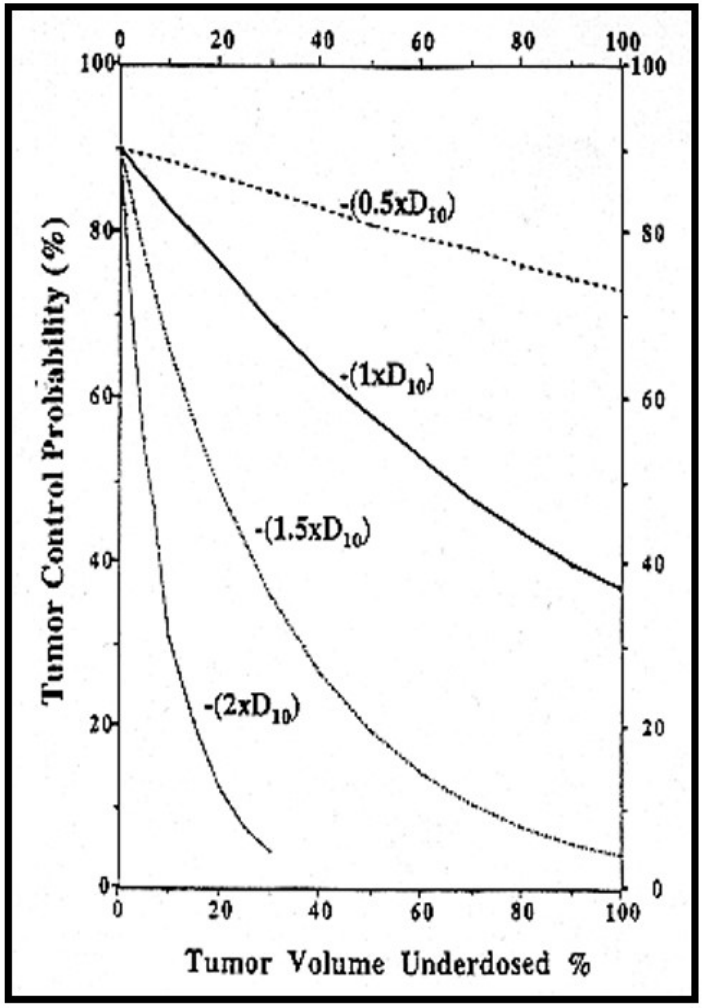
Tumor DVH



TCP & Geographic Underdosage

- **Magnitude of underdosage is the major factor in decreasing TCP**
- **Fastest rate of decline in TCP is when volume underdosed is small**
- **Significant inhomogeneity, esp. to small volumes, are likely to occur in CRT/IMRT applied to mobile tumors**

ESTRO School

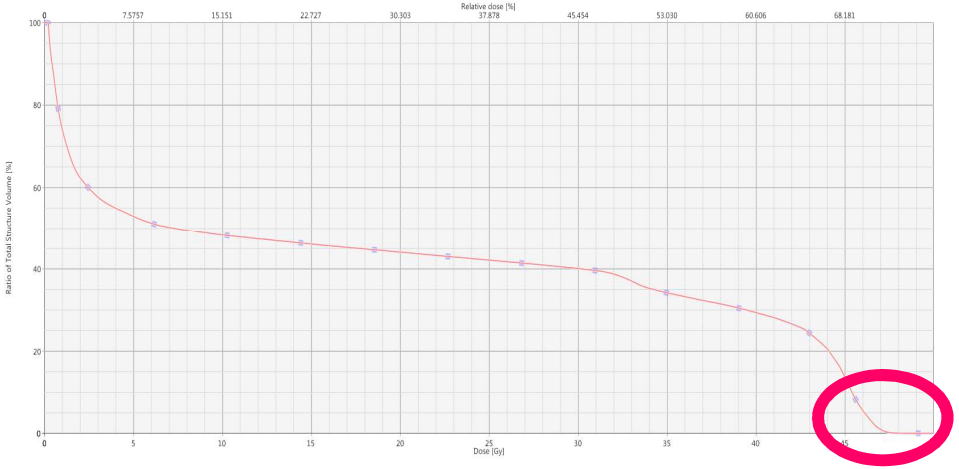
Withers, H. R., Acta Oncologica 39(5): 569-577, 2000

DVH & Double Trouble

- Lung cancer patient; planned treatment: 24 x 2,75 Gy = 66Gy

- Spinal cord = Serial

Constraint	EQD_2	Case
D_{max}	50 Gy	48 Gy



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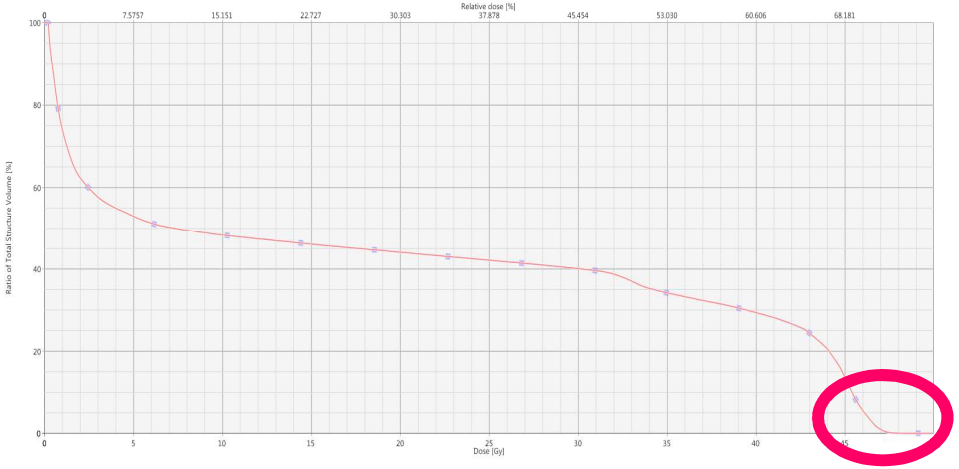
DVH & Double Trouble

- Lung cancer patient; planned treatment: 24 x 2,75 Gy = 66Gy

- Spinal cord = Serial

Constraint	24x 2,75 Gy	EQD_2	Case
D_{max}	49 Gy	50 Gy	48 Gy



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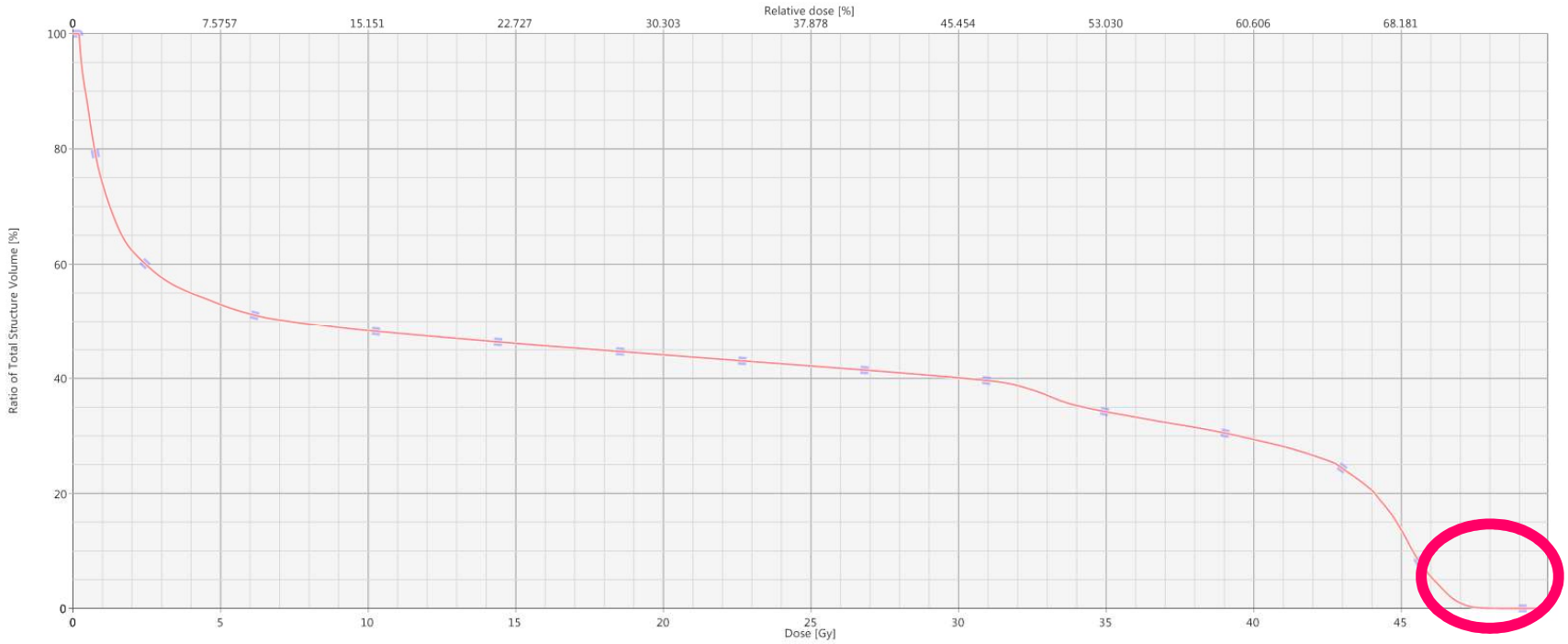
DVH & Double Trouble

- Spinal cord = serial

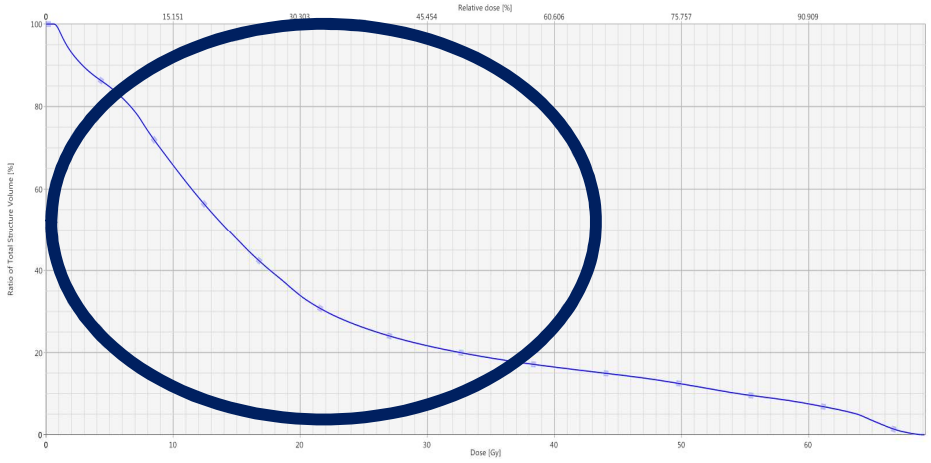


DVH & Double Trouble

- Lung cancer patient; planned treatment: 24 x 2,75 Gy = 66Gy

- Lung (– GTV) = Parallel

Constraint	EQD_2	Case
D_{mean}	< 20 Gy	20 Gy



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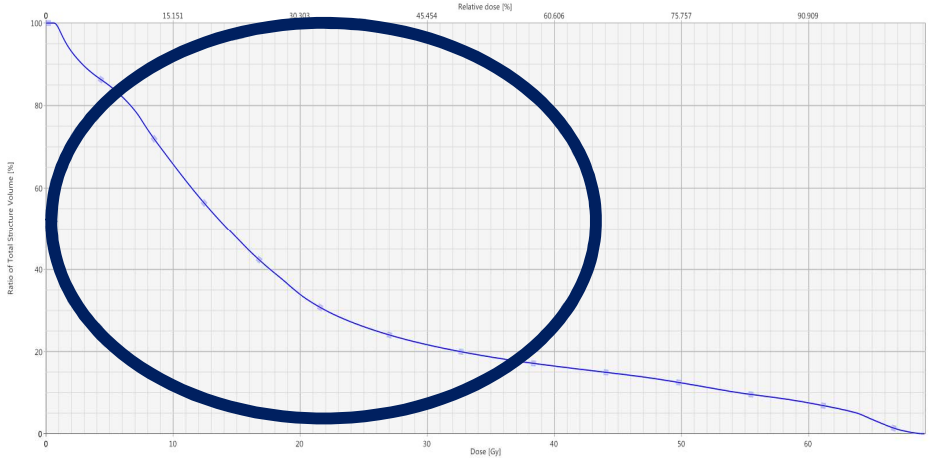
DVH & Double Trouble

- Lung cancer patient; planned treatment: 24 x 2,75 Gy = 66Gy

- Lung (– GTV) = Parallel

Constraint	24x 2,75 Gy	EQD_2	Case
D_{mean}	< 18 Gy	< 20 Gy	20 Gy



DOUBLE TROUBLE

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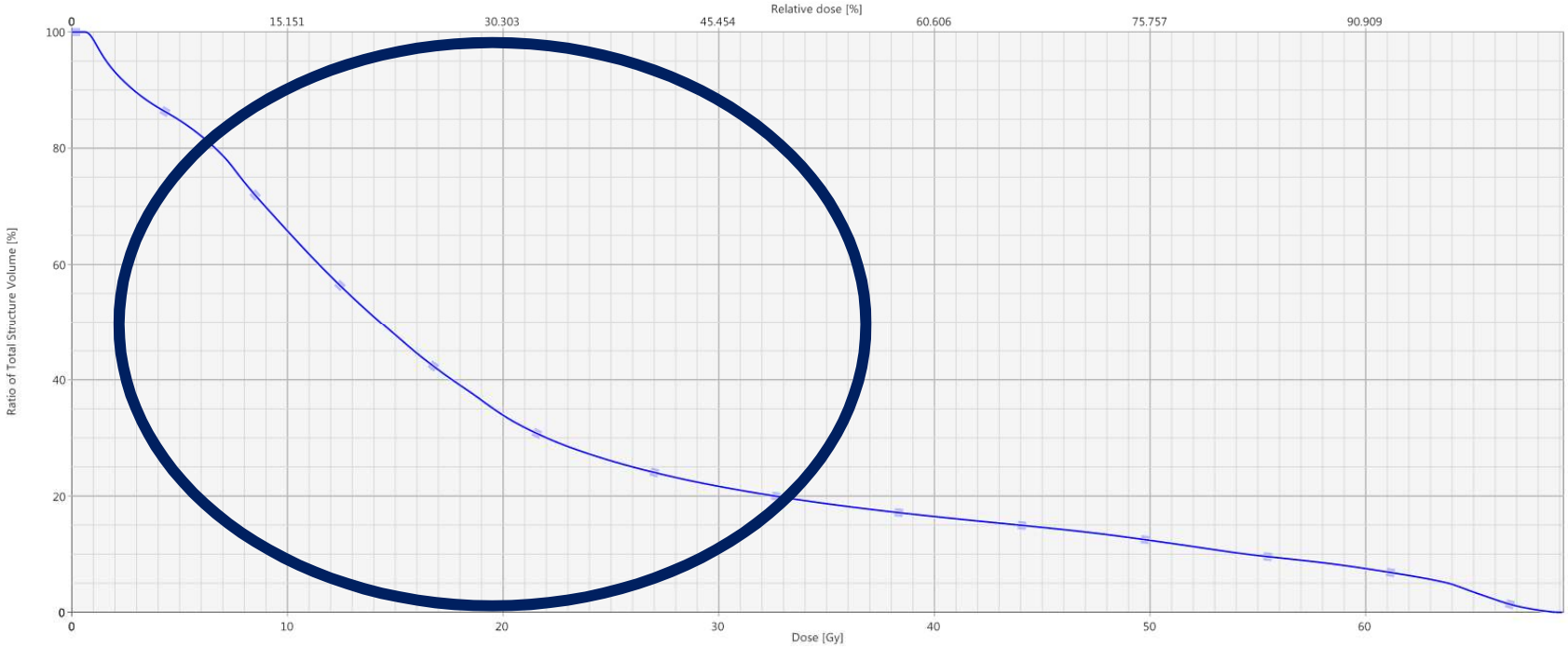
DVH & Double Trouble

- Lung (– GTV) = Parallel

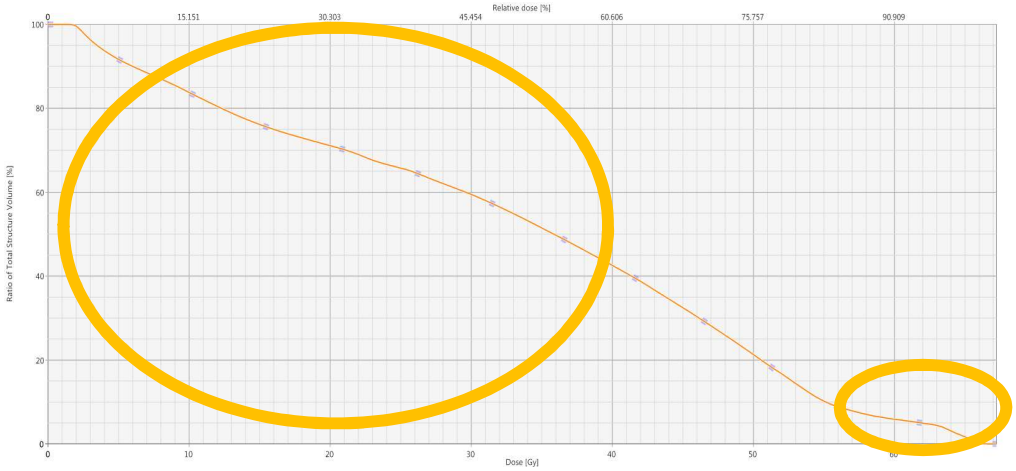


DVH & Double Trouble

- Lung cancer patient; planned treatment: 24 x 2,75 Gy = 66Gy

- Heart = Serial? Parallel?

Constraint	24x 2,75 Gy	EQD_2	Case
D_{mean}	Target < 20 Gy Max: 46 Gy	Target < 15,3 Gy Max: 45 Gy	33,2 Gy
D_{max}	66 Gy	76 Gy	66 Gy



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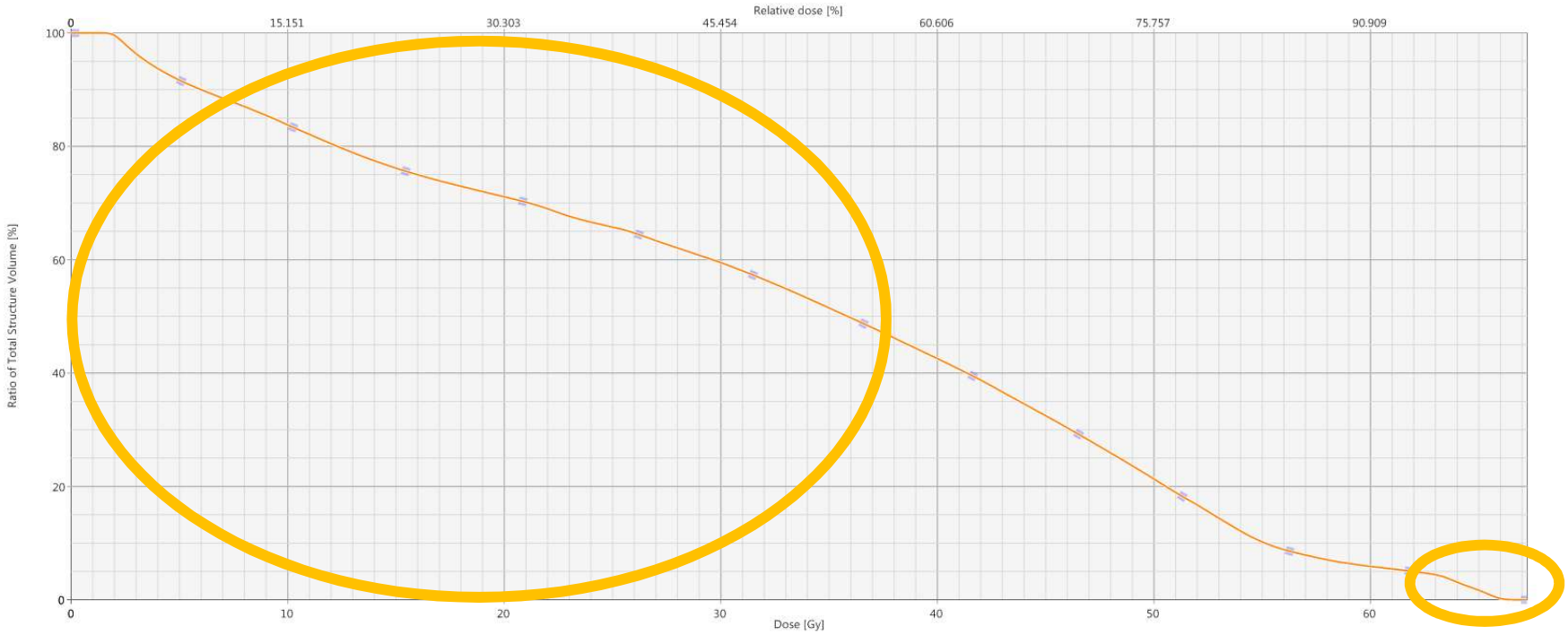
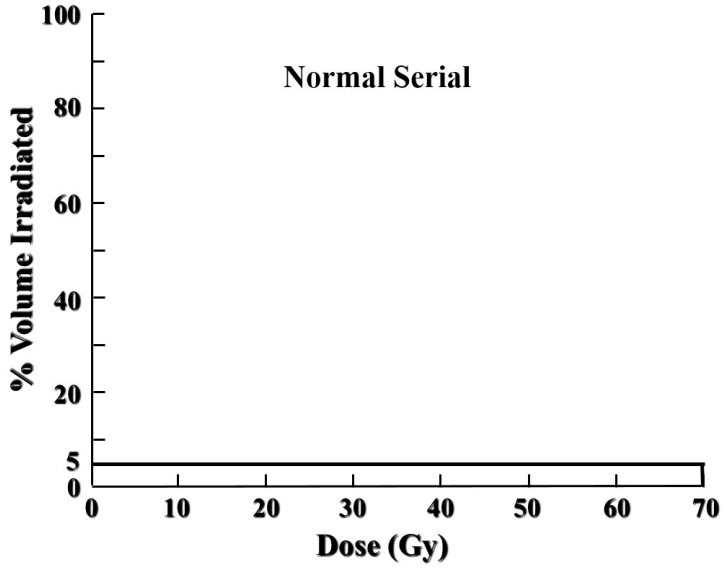
DVH & Double Trouble

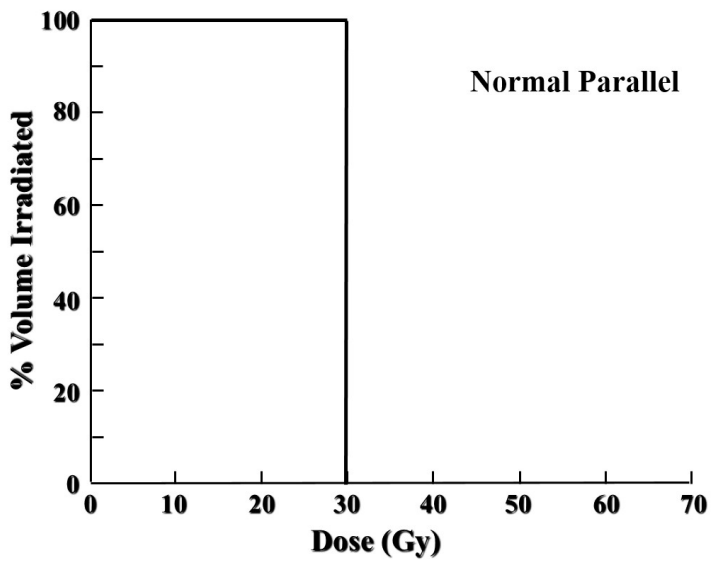
- Heart = Serial? Parallel?



DVH & Double Trouble

- Most of the DVH is irrelevant and the relevant regions (curves) are different for different tissues





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DVH & Double Trouble

- D in DVH should be biological dose
- Significance of Normal Tissue DVH is organ specific
- Most of Tumor DVH is irrelevant

Radiobiology in practice

- Power outage during start up of the linear accelerators in the morning
- 4 out of 5 machines do not start
- Waiting rooms are completely full of patients
- Other patients are on their way
- Which patients can we cancel and in which order?

Radiobiology in practice

- Which of following patients may be postponed and which patients would you irradiate today?

1) Woman, 46 y, adjuvant radiotherapy for breast cancer, day 11

2) Man, 56 y, palliative radiotherapy of 2 bone metastases, metastatic lung cancer

3) Woman, 58 y, chemoradiation treatment for cervical cancer, day 19

Radiobiology in practice

- Which of following patients may be postponed and which patients would you irradiate today?

4) Man, 62 y, esophageal cancer, preoperative chemoradiation, day 1

5) Man, 75 y, radiotherapy for primary prostate cancer, day 23

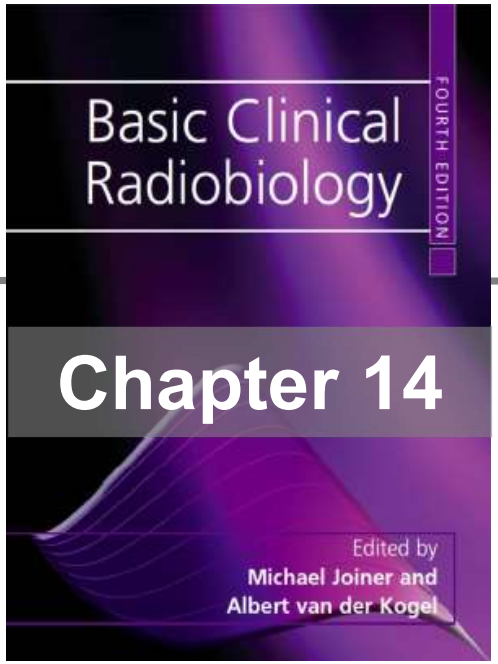
The volume effect in radiotherapy

Wolfgang Dörr

ATRAB – Applied and Translational Radiobiology

Dept. of Radiation Oncology &
RadOnc - CD Laboratory for Med.Rad.Res. for Rad.Oncol.

Medical University of Vienna, Austria



Radiotherapy and Oncology 123 (2017) 209–217

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Brain radiotherapy

Regional susceptibility to dose-dependent white matter damage after brain radiotherapy

Michael Connor [a], Roshan Karunamuni [a,e], Carrie McDonald [a,c,e], Tyler Seibert [a,e], Nathan White [b,e], Vitali Moiseenko [a], Hauke Bartsch [b,e], Nikdokht Farid [b,e], Joshua Kuperman [b,e], Anitha Krishnan [b,e], Anders Dale [b,c,d,e], Jona A. Hattangadi-Gluth [a,e,*]

[a] Department of Radiation Medicine and Applied Sciences; [b] Department of Radiology; [c] Department of Psychiatry; [d] Department of Neurosciences; and [e] Center for Multimodal Imaging and Genetics, University of California San Diego, La Jolla, California, United States

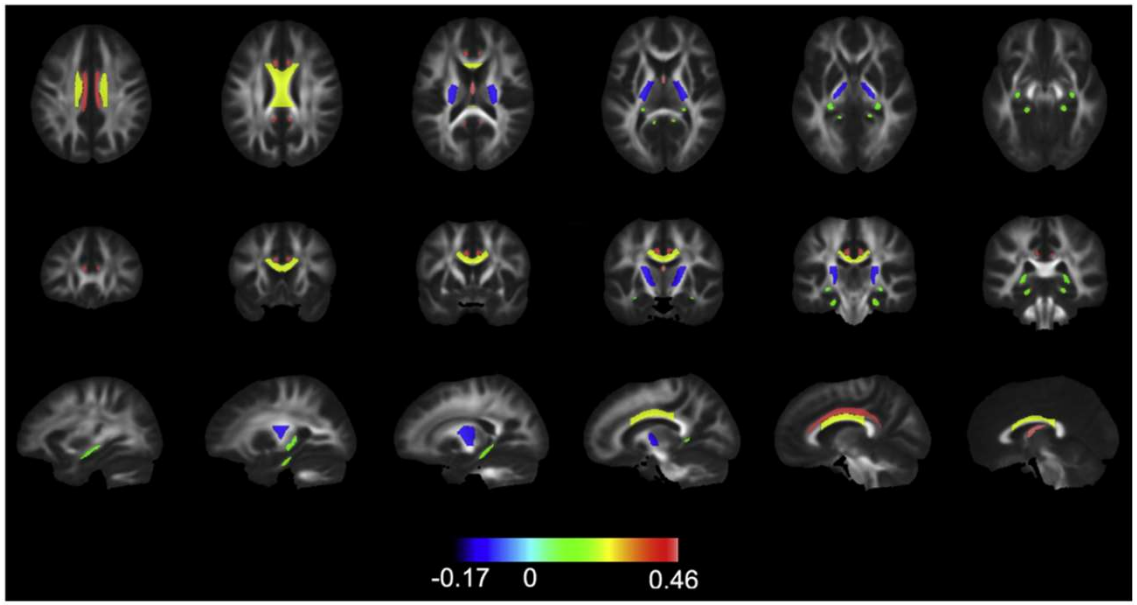


Fig. 4. Regional sensitivity to radiation. Tracts are filled with their corresponding coefficient for percent change in FA (from the model correlating mean dose to changes in the whole atlas ROI) and color coded according to value. Only statistically significant coefficients are shown. The signs for coefficients are flipped, i.e. FA is expected to decrease, so greater decreases in FA are represented by positive numbers and intensifying red color.

International Journal of Radiation Oncology biology • physics
www.redjournal.org

Physics Contribution

Modeling Urinary Dysfunction After External Beam Radiation Therapy of the Prostate Using Bladder Dose-Surface Maps: Evidence of Spatially Variable Response of the Bladder Surface

Noorazrul Yahya, PhD,*,† Martin A. Ebert, PhD,†,‡ Michael J. House, PhD,† Angel Kennedy, BSc,‡ John Matthews, FRANZCR,§ David J. Joseph, FRANZCR,‡,|| and James W. Denham, FRANZCR¶

*School of Health Sciences, National University of Malaysia, Kuala Lumpur, Malaysia; †School of Physics, University of Western Australia, Perth; ‡Department of Radiation Oncology, Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia; §Department of Radiation Oncology, Auckland City Hospital, Auckland, New Zealand; ||School of Surgery, University of Western Australia, Perth, Western Australia; and ¶School of Medicine and Public Health, University of Newcastle, Newcastle, New South Wales, Australia

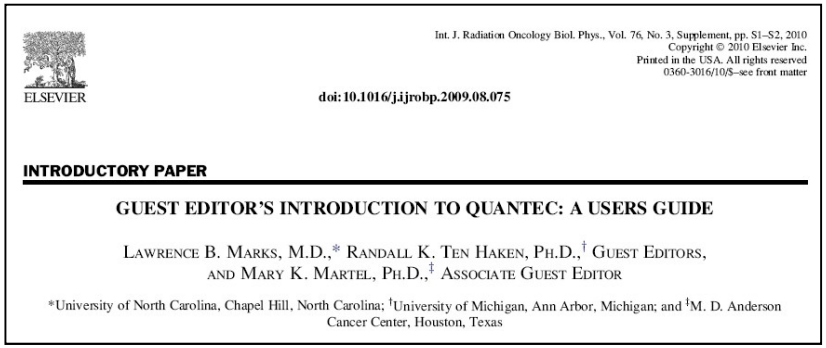
Results: The associations of the spatially specific dose measures to urinary dysfunction were dependent on the presence of specific symptoms. The doses received by the anteroinferior and, to lesser extent, posterosuperior surface of the bladder had the strongest relationship with the incidence of dysuria, hematuria, and ΔIPSS10, both with and without adjustment for clinical factors. For the doses to the posteroinferior region corresponding to the area of the trigone, the only symptom with significance was incontinence.

Radiation effects - 6 Rs of radiotherapy

Radiation sensitivity
Recovery
Redistribution
Repopulation
Reoxygenation
iRradiated volume

QUANTEC:

Quantitative Analysis of Normal Tissue Effects in the Clinic



Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S1–S2, 2010

0360-3016/10/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2009.08.075

INTRODUCTORY PAPER

GUEST EDITOR'S INTRODUCTION TO QUANTEC: A USERS GUIDE

LAWRENCE B. MARKS, M.D.,* RANDALL K. TEN HAKEN, PH.D.,† GUEST EDITORS, AND MARY K. MARTEL, PH.D.,‡ ASSOCIATE GUEST EDITOR

*University of North Carolina, Chapel Hill, North Carolina; †University of Michigan, Ann Arbor, Michigan; and ‡M. D. Anderson Cancer Center, Houston, Texas

QUANTEC

Introductory Papers

History/Overview/Scientific Issues

Application of QUANTEC metrics/models into clinical practice

Organ-Specific Papers

1. **Brain**
2. **Optic Nerve/Chiasm**
3. **Brain Stem**
4. **Spinal Cord**
5. **Ear**
6. **Parotid**
7. **Larynx/Pharynx**
8. **Lung**
9. **Heart**
10. **Esophagus**
11. **Liver**
12. **Stomach/Small Bowel**
13. **Kidney**
14. **Bladder**
15. **Rectum**
16. **Penile Bulb**

Vision Papers

True Dose

Imaging

Biomarkers

Data Sharing

Lessons of QUANTEC

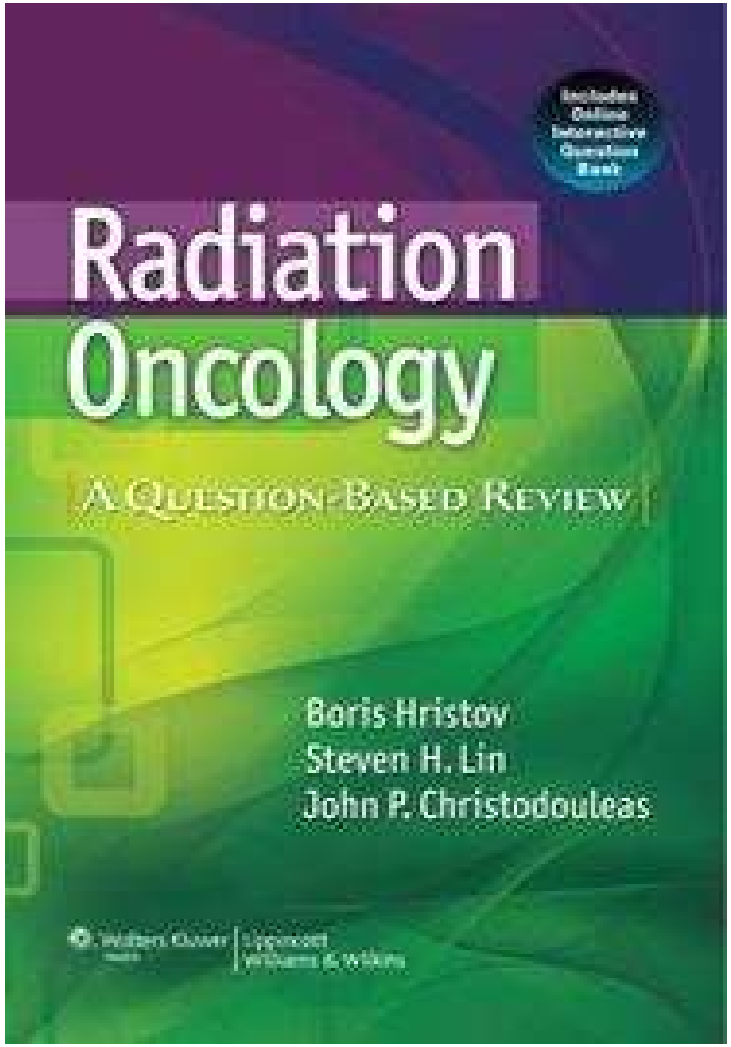
Each with 10 sections

1. **Clinical Significance**- Describes the clinical situations where the organ is irradiated, and the incidence/significance of organ injury.
2. **Endpoints**- Describes the different endpoints often considered when assessing injury, the impact of endpoint-selection on **the reported injury rates, the challenges/utilities of different endpoints, and the time course of organ injury.**
3. **Challenges Defining Volumes**- Describes how the organ is **typically defined (or segmented)** on treatment planning images. Includes a discussion of uncertainties/challenges in organ definition (e.g. changes in organ volume/shape during therapy), and the associated impact on DVH's and dose/volume/outcome analyses.
4. **Review of Dose/Volume Data**- A comprehensive summary of reported 3D dose/volume data for clinically-relevant outcomes.
5. **Factors Affecting Risk**- Other clinical factors affecting the risk of injury are noted (e.g. age, combined modality therapy, dose fractionation).
6. **Mathematical/Biological Models**- Models that have been used to relate 3D dose/volume data to clinical outcomes are summarized, along with associated model parameters, limitations and uncertainties.
7. **Special Situations**- Most of the data discussed relates to conventional fractionation. This section describes situations were the presented data/models may not apply (e.g. hypo-fractionation).
8. **Recommended Dose/Volume Limits**- The available information is condensed into meaningful dose/volume limits, with associated risk rates, to apply clinically.
9. **Future Toxicity Studies**- Describes areas in need of future study.
10. **Toxicity Scoring**- Recommendations on how to score organ injury.

BED rather than EQD2

Missing: oral cavity, skin, femoral heads, ……

QUANTEC+



APPENDIX

Normal Tissue Constraint Guidelines

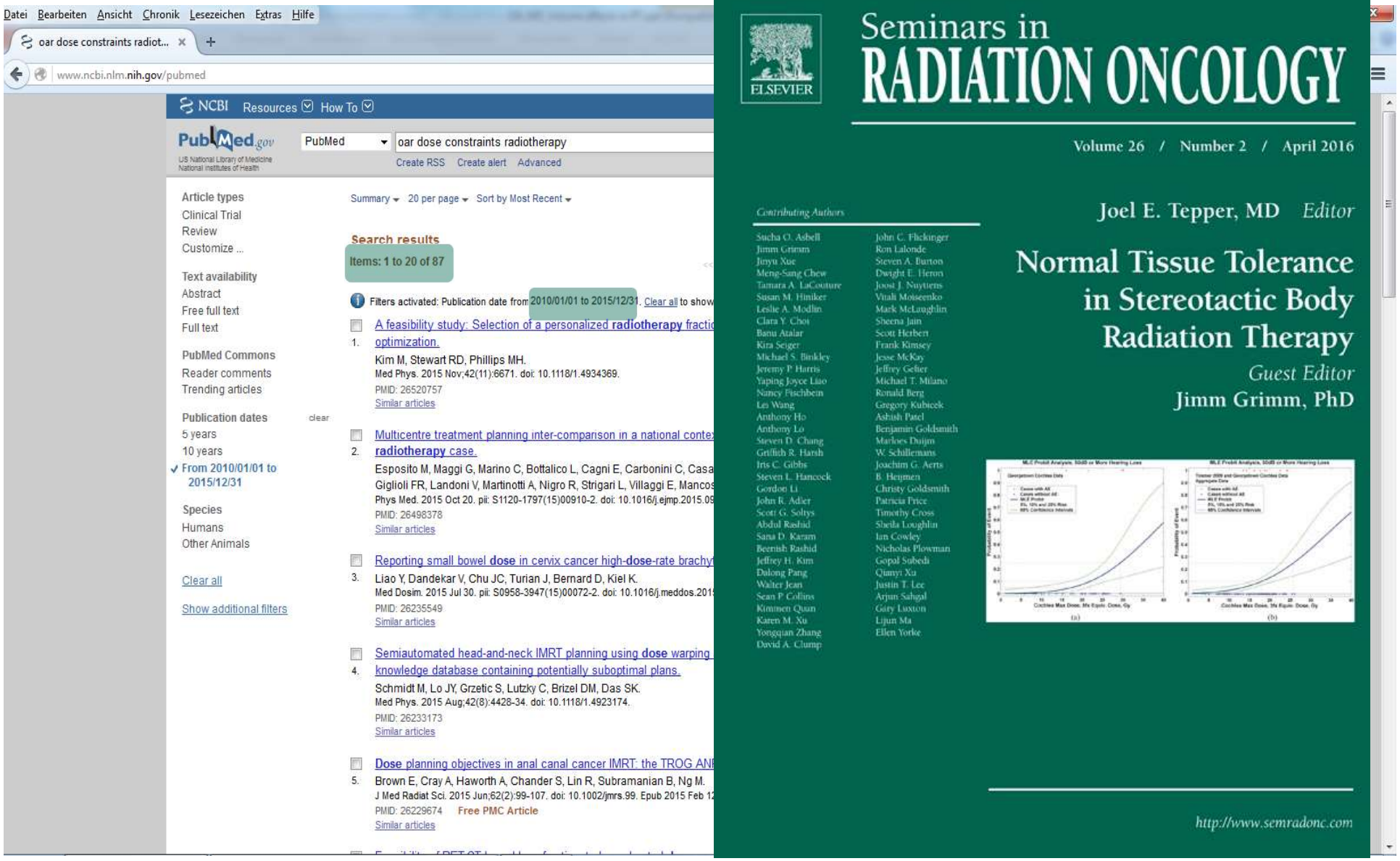
The radiation dose constraints below are meant to serve as a guide only and may not be applicable to all clinical scenarios. Most doses are derived from randomized studies or consensus guidelines and we have attempted to provide the sources for these recommendations. Please refer to the individual pediatric chapters for dose constraints in the pediatric population as these can vary greatly from protocol to protocol and tend to be particularly site- and age-dependent.

What are the recommended dose constraints for the following organs and clinical scenarios?

ORGAN	*CONSTRAINTS*
CNS (1.8-2.0 Gy/fx)	
Spinal cord	max 50 Gy (full cord cross-section); tolerance increases by 25% 6 mos after 1st course (for re-irradiation) (QUANTEC)
Brain	max 72 Gy (partial brain); avoid >2 Gy/fx or hyperfractionation (QUANTEC)
Chiasm/optic nerves	max 55 Gy (QUANTEC)
Brainstem	Entire brainstem <54 Gy, V59 Gy <1-10 cc (QUANTEC)
Eyes (globe)	Mean <35 Gy (RTOG 0225), max 54 Gy (RTOG 0615)
Lens	max 7 Gy (RTOG 0539)
Retina	max 50 Gy (RTOG 0539)
Lacrimal Gland	max 40 Gy (Parsons)
Inner ear/cochlea	mean ≤45 Gy (consider constraining to ≤35 Gy with concurrent cisplatin) (QUANTEC)
Pituitary gland	max 45 Gy (for panhypopituitarism, lower for GH deficiency) (Emami)
Cauda equina	Max 60 Gy (Emami)
CNS (single fraction)	
Spinal cord	max 13 Gy (if 3 fxs, max 20 Gy) (QUANTEC)

567

QUANTEC +++



21. Nov. 2015

NTCP models

Lyman model (power law, 4 parameters)

$$= 1/\sqrt{(2\pi)} \int^{(D - TD50(v))/(mTD50(v))} \exp(-t^2/2)dt$$

Kutcher-Burman (KB-)model

$$V_{eff} = \sum v_i (D_i/D_{max})^{1/n}$$

$$D_{eff} = \left(\sum v_i (D_i)^{1/n} \right)^n$$

Growing bone model (Krasin)

$$\mathrm{Log}(v_{post}/v_{pre}) = \beta_{time} t + \beta_{age\ group} t + \beta_{dose\text{-}age\ group} v_{Int35}$$

$$v_{Int35} = 37.5 \times v_{35-40Gy} + 42.5 \times v_{40-45Gy} + 47.5 \times v_{45-50Gy}$$
$$+ 52.5 \times v_{50-55Gy} + 57.5 \times v_{55-60Gy} + 62.5 \times v_{60-65Gy}$$

Tissue architecture models

$$NTCP(\{n_i, D_i\})$$

$$\prod_i \left(NTCP(D_i) \right)^{v_i}$$

Serial architecture/critical element

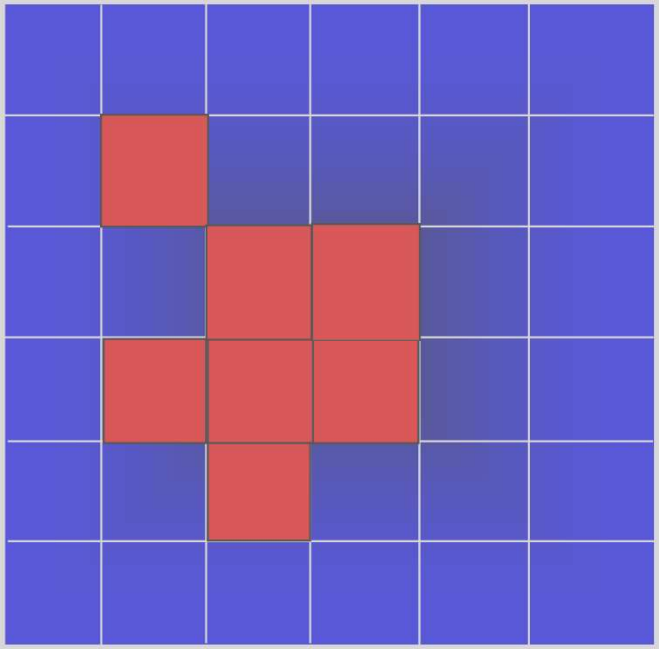
$$f_{dam} = g \sum_{lower} v_{i,lower} p_L(D_{i,lower}) + (1 - g) \sum_{upper} v_{i,upper} p_u(D_{i,upper})$$

Parallel architecture/critical volume

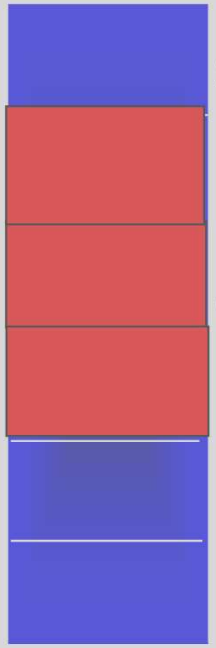
Tissue architecture

Concept of Functional Sub-Units (FSUs)

lung
liver
kidney



spinal cord
esopha-gus
intestine



parallel organisation ➔

functional damage, if a critical number of FSU's is inactivated
(threshold volume)
risk of complication ~ total dose distribution rather than on "hot spots"

serial organisation ➔

Inactivation of one subunit can lead to loss of organ function (binary response)
risk of complication strongly influenced by "hot spots"

Concept of Functional Sub-Units (FSUs)

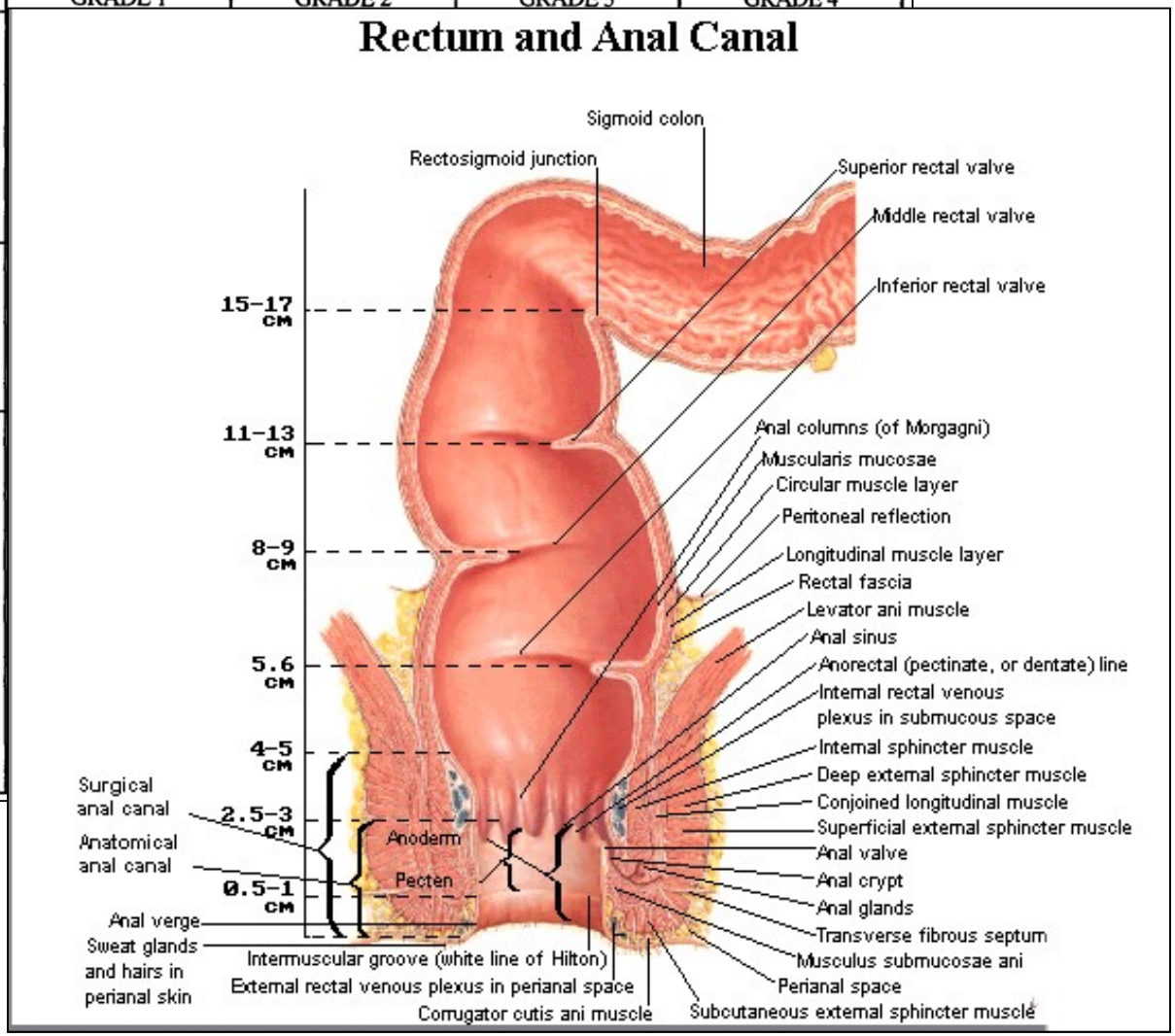
© Dörr

Endpoints and target structures

Rectum

	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Subjective	Tenesmus	Mucosal loss,	Sphincter control	Stool frequency
	Pain			
Objective	Bleeding	Ulceration	Stricture	
Management	Tenesmus & stool frequency	Pain	Bleeding	Ulceration
	Stricture	Sphincter control		

RTO 35, 1995, 17-60



Target structures/ Subvolumes

-Identification

-Dose-Effect

-Fractionation effect

-(time factor)

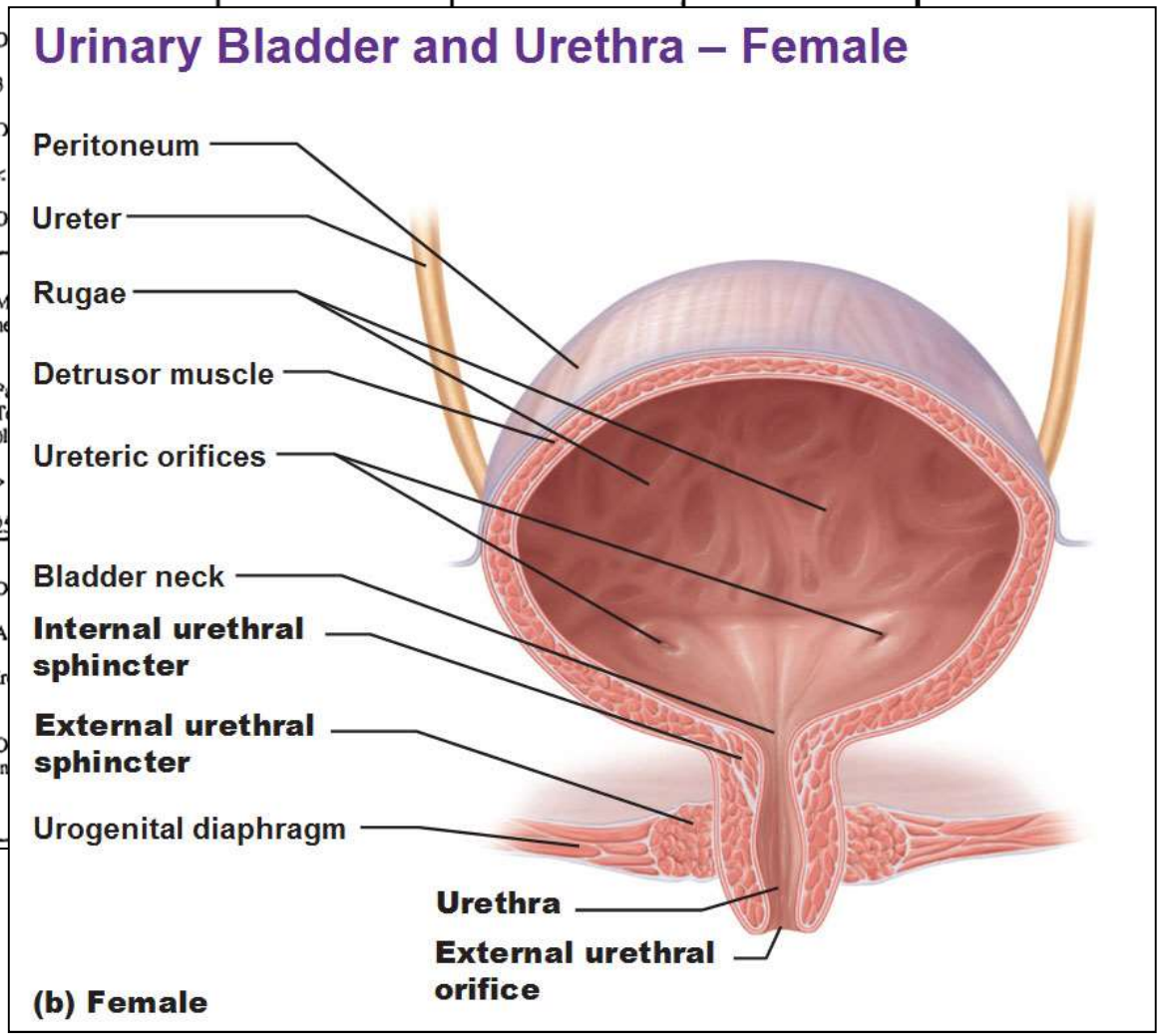
http://www.aboutcancer.com/anatomy_rectum.gif (13.05.2014)

Endpoints and target structures

Urinary bladder/Urethra

	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Subjective				
Dysuria				
Frequency				
Hematuria				
Incontinence				
Decreased stream				
Objective				
Hematuria				
Endoscopy				
Maximum volume				
Residual volume				
Management				
Dysuria				
Frequency				
Hematuria/ Telangiectasia				
Incontinence				
Decreased stream				

RTO 35, 1995, 17-60



Target structures/ Subvolumes

-Identification

-Dose-Effect

-Fractionation effect

-(time factor)

http://antranik.org/the-urinary-system-ureter-and-urinary-bladder (13.05.2014)

Endpoints and target structures

ARTICLE IN PRESS

Radiotherapy and Oncology xxx (2013) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Is there a relation between the radiation dose to the different sub-segments of the lower urinary tract and urinary morbidity aft brachytherapy of the prostate with I-125 seeds?

Marcel J. Steggerda*, Thelma Witteveen, Ferrie van den Boom, Luc M.F. Moonen

Department of Radiation Oncology, The Netherlands Cancer Institute -Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands

Results: The dose to 0.5 cm^3 of the bladder neck '$D_{0.5cc}$-blne' ($p = 0.002$ and $p = 0.005$), the prostate volume prior to treatment 'V_{pr}-0' ($p = 0.005$ and $p = 0.024$) and the pre-treatment IPSS (both $p < 0.001$) were independently correlated with mean and maximum IPSS, respectively. Of the patients with a $D_{0.5cc}$-blne $\geqslant$ 175 Gy and a V_{pr}-0 $\geqslant$ 42 cm^3, 68% suffered from enhanced LUTS, against just 30% of the other patients ($p < 0.0001$).

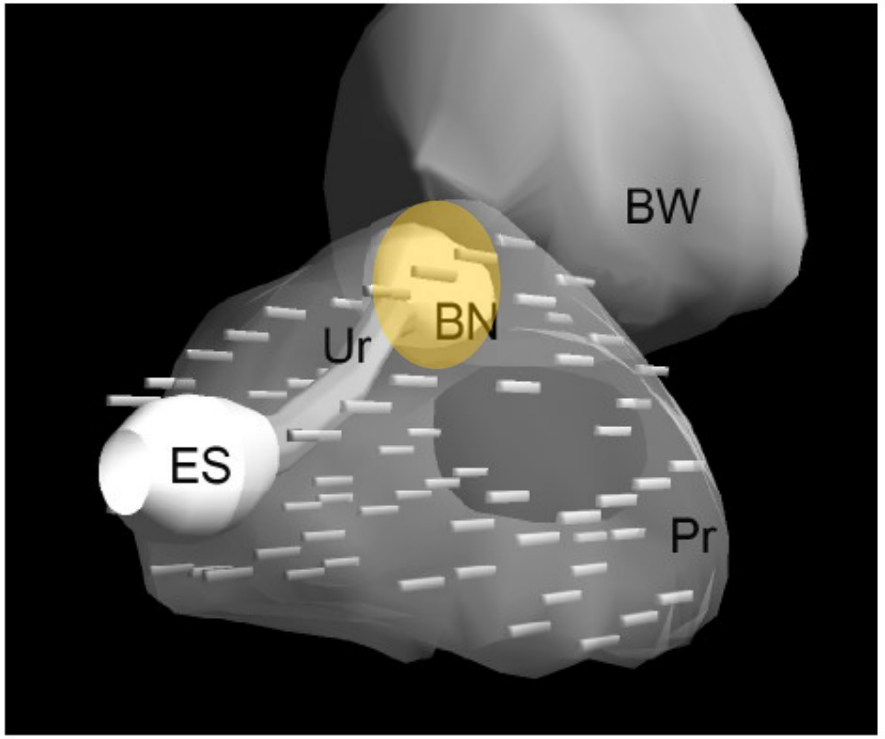
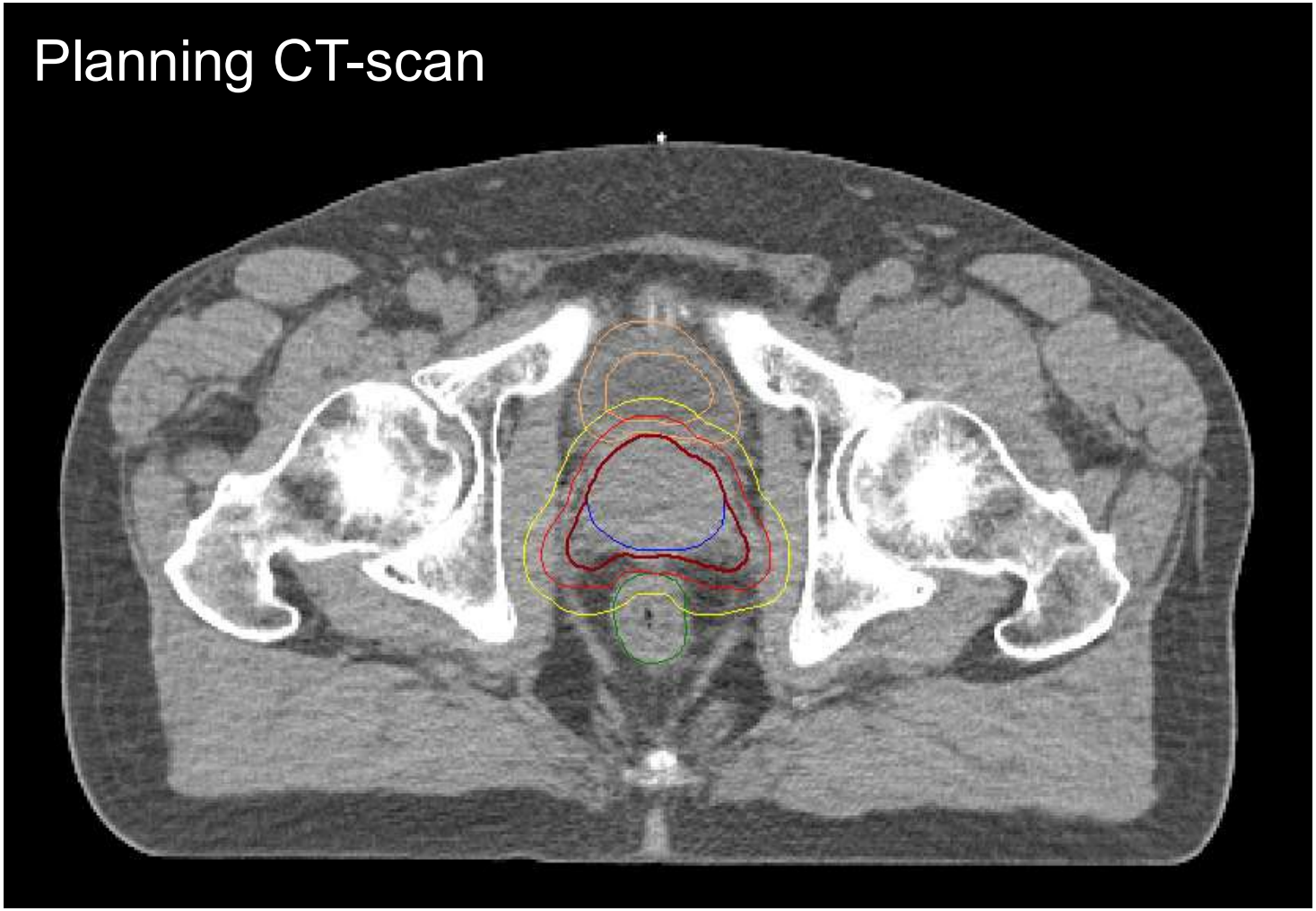


Fig. 1. 3D image of the prostate and the lower urinary tract after implantation the seeds. BW = bladder wall, BN = bladder neck, Ur = urethra, ES = external sphin ter, Pr = prostate.

Definition of volumes / volume parameters



Delineation – subjective component/department philosophy

Definition of volumes / volume parameters

Delineation – subjective component/department philosophy

Radiotherapy and Oncology 117 (2015) 542–547

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Cervical cancer radiotherapy

Variability of clinical target volume delineation for definitive radiotherapy in cervix cancer

Gemma Eminowicz *, Mary McCormack

University College Hospital, London, UK

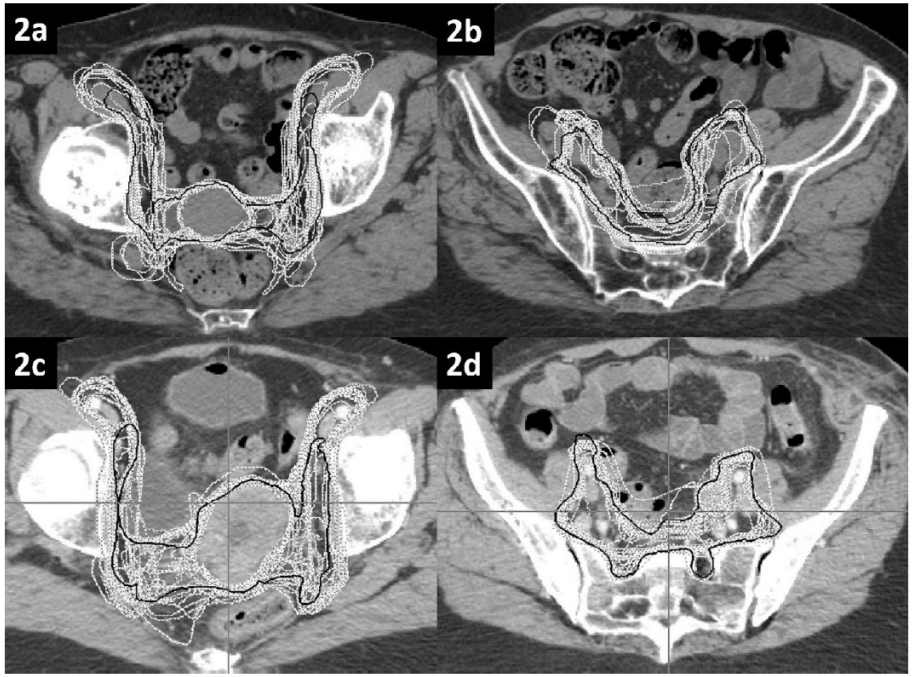
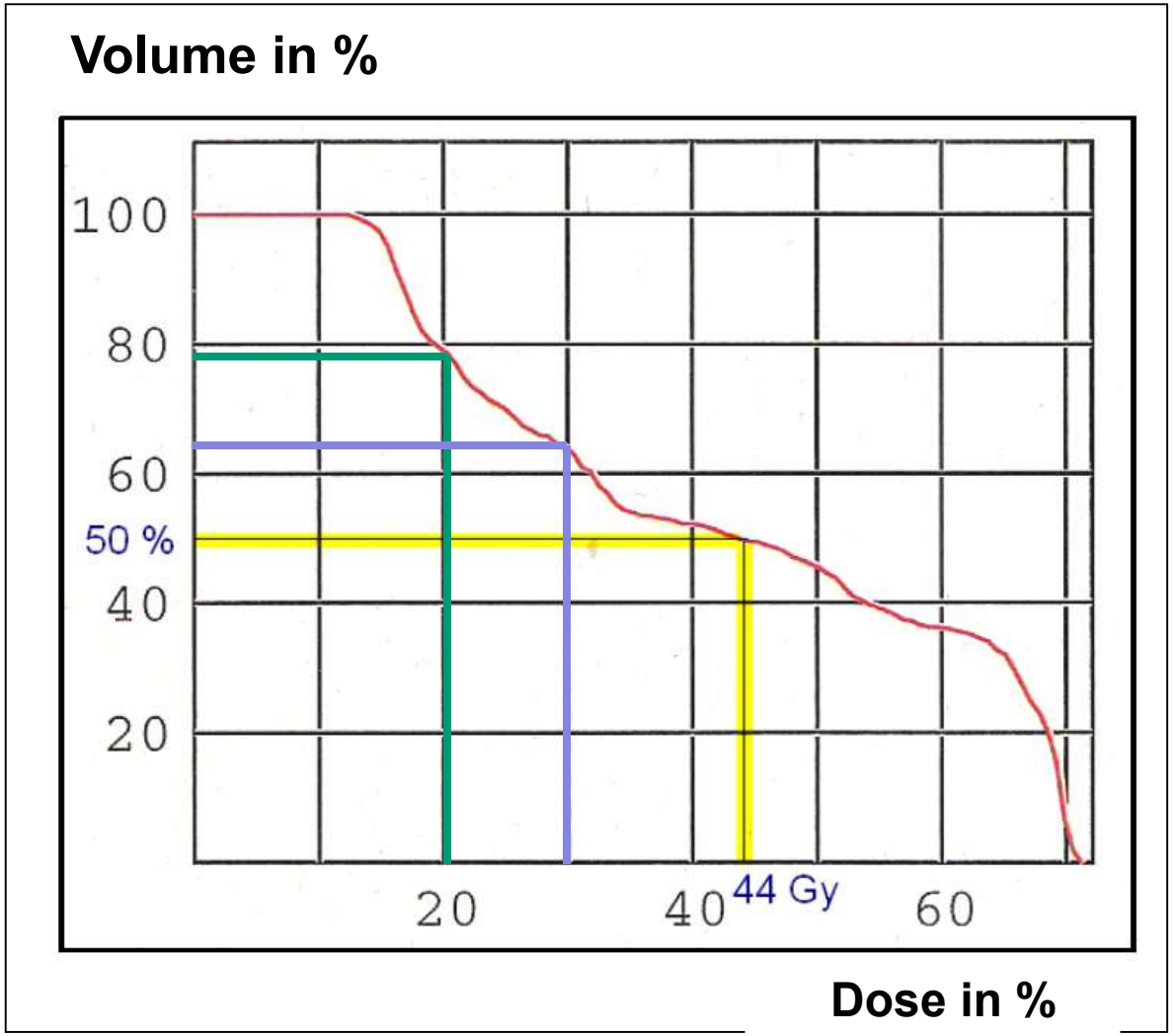


Fig. 2. Transverse CT images of CTVs(white) and GSCTV1 + 2(black) for case 1 (a and b) and 2 (c and d) at sacro-iliac level (a and c) and superior to femoral heads (b and d).

Results: 21 outlines were compared for case 1 and 22 for case 2. Volume ranged from 340 cc to 676 cc (case 1) and from 458 cc to 806 cc (case 2). A maximum 4 cm difference between outlines was observed in one direction. JCI ranged from 0.51 to 0.81 (case 1) and 0.57 to 0.81 (case 2). Variation in anatomical areas included in CTV exists between the two cases and between centres.

Conclusions: Significant inter-observer variation in cervical cancer delineation has been demonstrated. Ongoing efforts are needed to ensure inter-observer consistency through education, guidelines and multi-centre collaboration.

Dose-Volume Histogram (DVH)



Mean organ dose
44 Gy

Maximum organ dose
71 Gy

V20 79 %
V30 63%

EUD

~ Organisation of tissues (?)

Lung

Table 4. Incidence of radiation pneumonitis according to V_{dose} in patients treated with radiotherapy for lung cancer

Reference	Severity of pneumonitis	V_{dose}	Observed rate
Armstrong *et al.*, 1995 (45)	Grade ≥3	V_{25} >30%	38%
		V_{25} <30%	4%
Graham *et al.*, 1999 (46)	Grade ≥2	V_{20} <22%	0%
		V_{20} 22%–31%	7%
		V_{20} 32%–40%	13%
		V_{20} >40%	36%
Hernando *et al.*, 2001 (34)	Grade ≥1	V_{30} <22%	6%
		V_{30} 22%–31%	24%
		V_{30} 32%–40%	18%
		V_{30} >40%	29%
Claude *et al.*, 2004 (36)	Grade ≥1	V_{10} >33%	53%
		V_{20} >18%	56%
		V_{30} >13%	56%
		V_{40} >10%	56%
		V_{50} >5%	53%

Mehta et al., IJROBP 63, 2005, 5-24

Lung

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 76, No.3, Supplement, pp. S70–S76, 2010

0360-3016/10/$–see front matter

doi:10.1016/j.ijrobp.2009.06.091

QUANTEC: ORGAN-SPECIFIC PAPER Thorax Lung

RADIATION DOSE–VOLUME EFFECTS IN THE LUNG

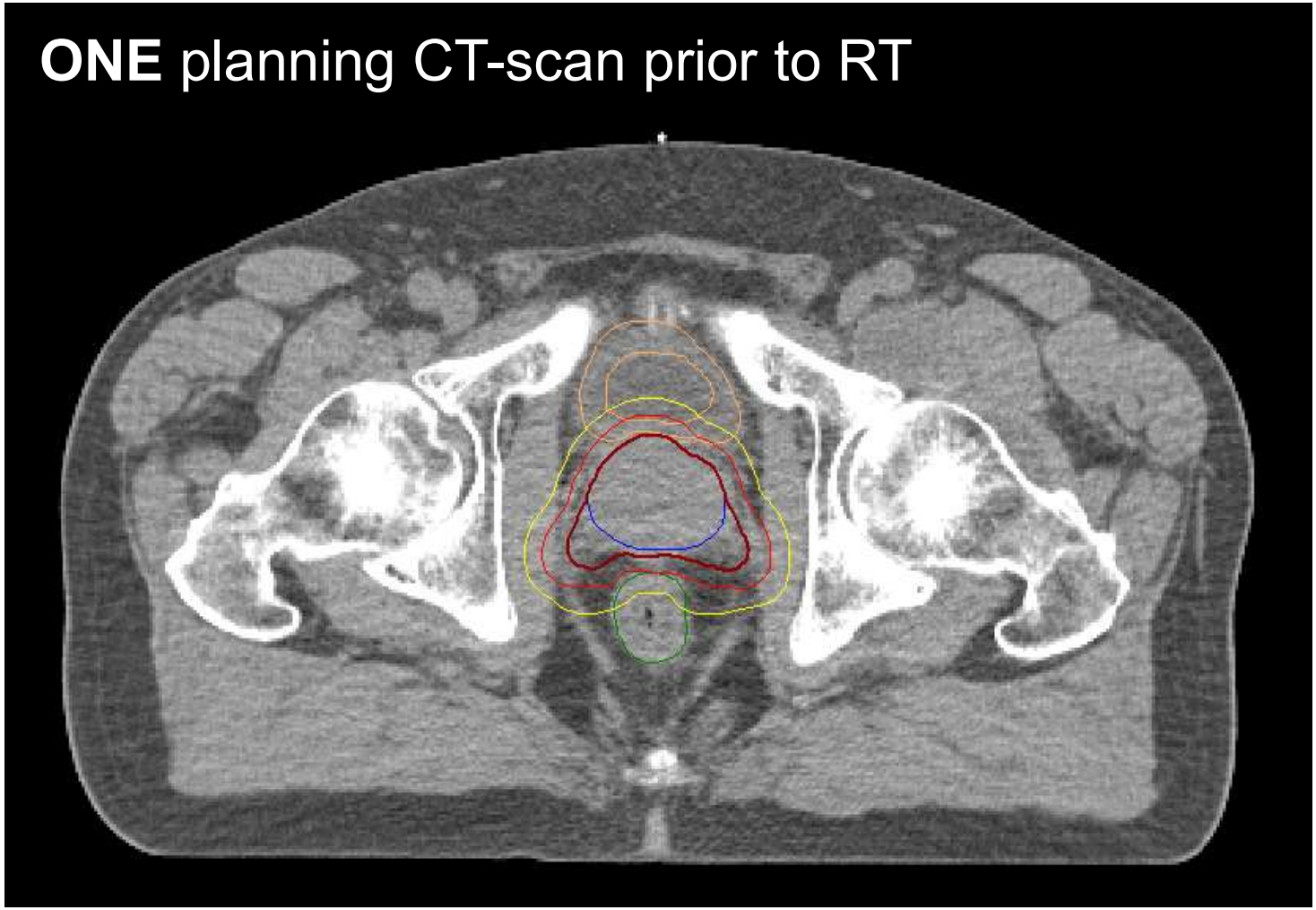
LAWRENCE B. MARKS, M.D.,* SOREN M. BENTZEN, D.Sc.,† JOSEPH O. DEASY, PH.D.,‡
FENG-MING (SPRING) KONG, M.D., PH.D.,§ JEFFREY D. BRADLEY, M.D.,‡ IVAN S. VOGELIUS, PH.D.,†
ISSAM EL NAQA, PH.D.,‡ JESSICA L. HUBBS, M.D.,‖ JOOS V. LEBESQUE, M.D., PH.D.,‖
ROBERT D. TIMMERMAN, M.D.,¶ MARIE-CATHERINE VOZENIN-MARTEL, PH.D.,# AND ANDREW JACKSON, PH.D.**

*Department of Radiation Oncology, University of North Carolina, Chapel Hill, NC; †Department of Human Oncology, University of Wisconsin School of Medicine, Madison, WI; ‡Department of Radiation Oncology, Alvin J. Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO; §Department of Radiation Oncology, University of Michigan, Ann Arbor, MI; ‖Department of Radiation Oncology, The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands; ¶Department of Radiation Oncology, University of Texas Southwestern, Dallas, TX; #Department of Radiation Physics, M. D. Anderson Cancer Center, Houston, TX; and **Department of Medical Physics, Memorial Sloan-Kettering Cancer Center, New York, NY

The three-dimensional dose, volume, and outcome data for lung are reviewed in detail. The rate of symptomatic pneumonitis is related to many dosimetric parameters, and there are no evident threshold "tolerance dose–volume" levels. There are strong volume and fractionation effects. © 2010 Elsevier Inc.

… there are no evident threshold „tolerance dose-volume" levels

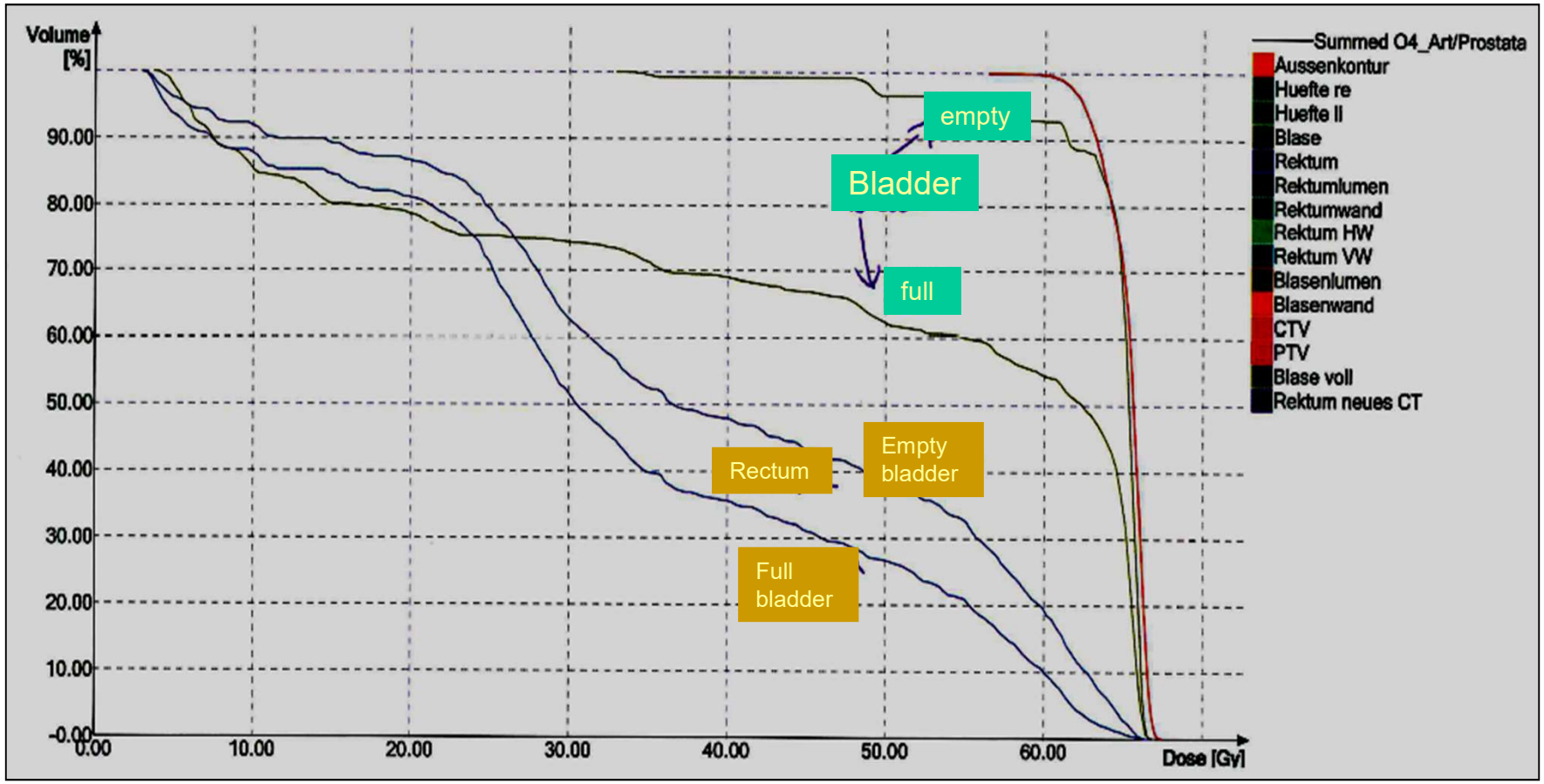
Definition of volumes / volume parameters



– „snap-shot“

– Changes in anatomy/morphology

  • physiologically



– „snap-shot“

– Changes in anatomy/morphology

- physiologically
- ~ Therapy (edema, shrinkage, weight loss, …)

Int. J. Radiation Oncology Biol. Phys., Vol. 80, No. 1, pp. 161–168, 2011

0360-3016/$–see front matter

ELSEVIER

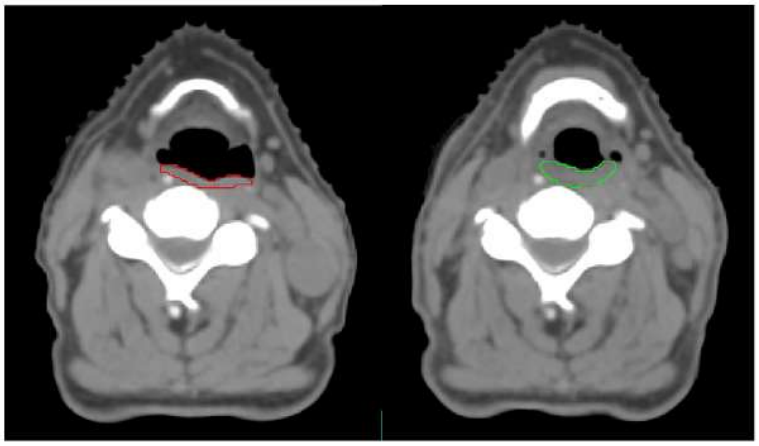
doi:10.1016/j.ijrobp.2010.01.071

CLINICAL INVESTIGATION **Head and Neck**

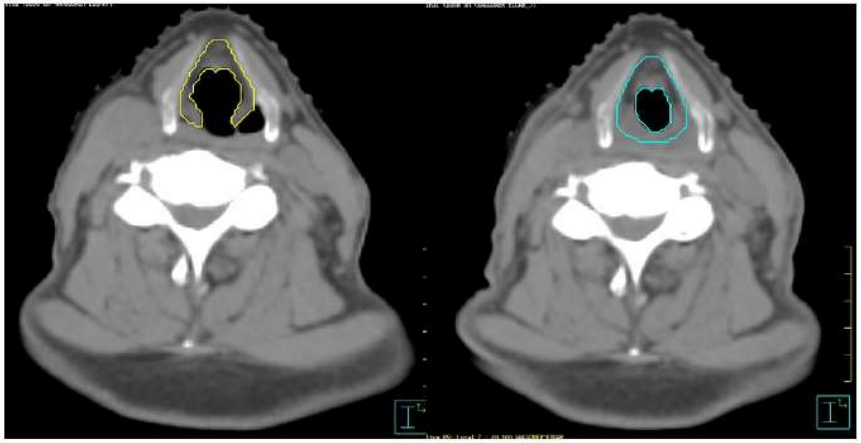
VOLUMETRIC CHANGE OF SELECTED ORGANS AT RISK DURING IMRT FOR OROPHARYNGEAL CANCER

Francesco Ricchetti, M.D.,* Binbin Wu, Ph.D.,* Todd McNutt, Ph.D.,* John Wong, Ph.D.,* Arlene Forastiere, M.D.,† Shanthi Marur, M.D.,† Heather Starmer, M.A., CCC-SLP,‡ and Giuseppe Sanguineti, M.D.*

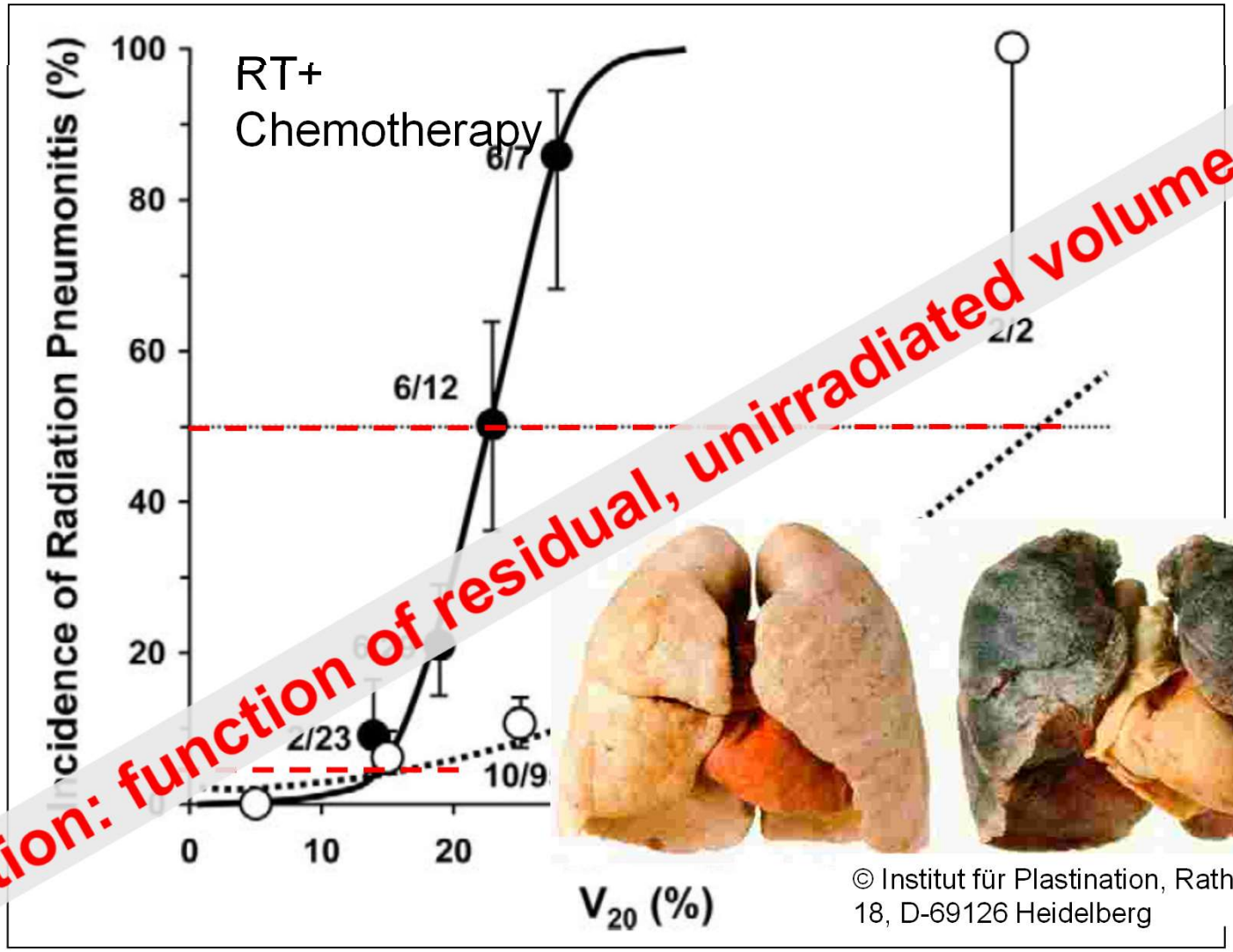
From the Departments of *Radiation Oncology and Molecular Radiation Sciences, † Oncology, and ‡Speech Therapy, Johns Hopkins University, Baltimore, MD, USA



Constrictor muscle / larynx
Planning CT vs. week 7



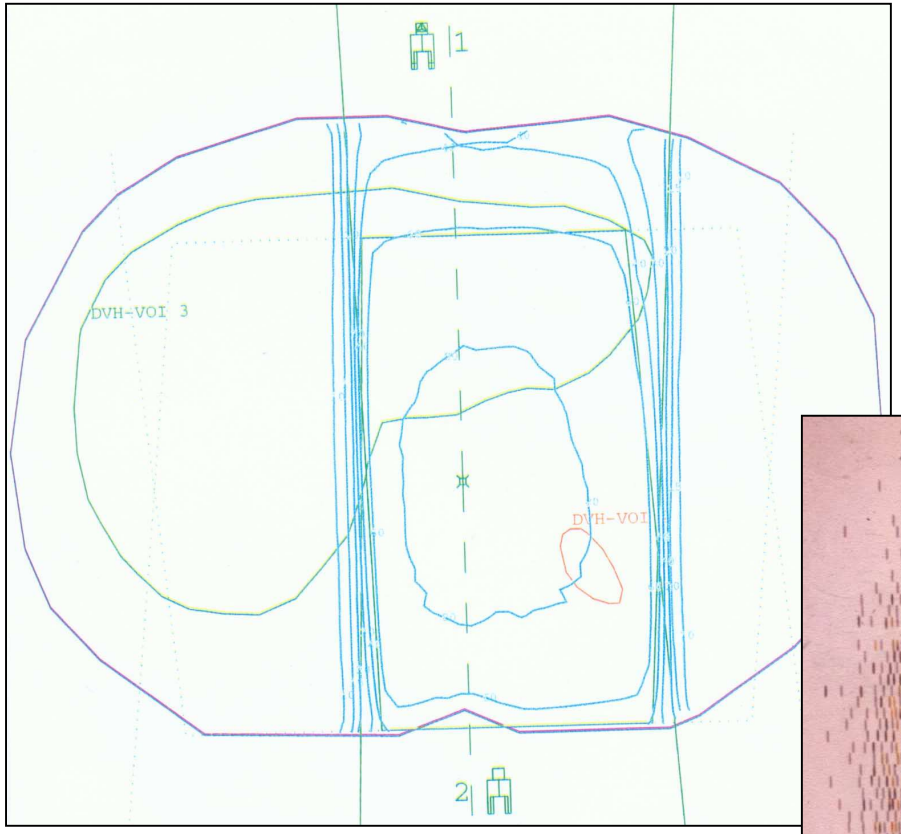
Individual tolerance levels –
Function of the unirradiated (residual) volume ?



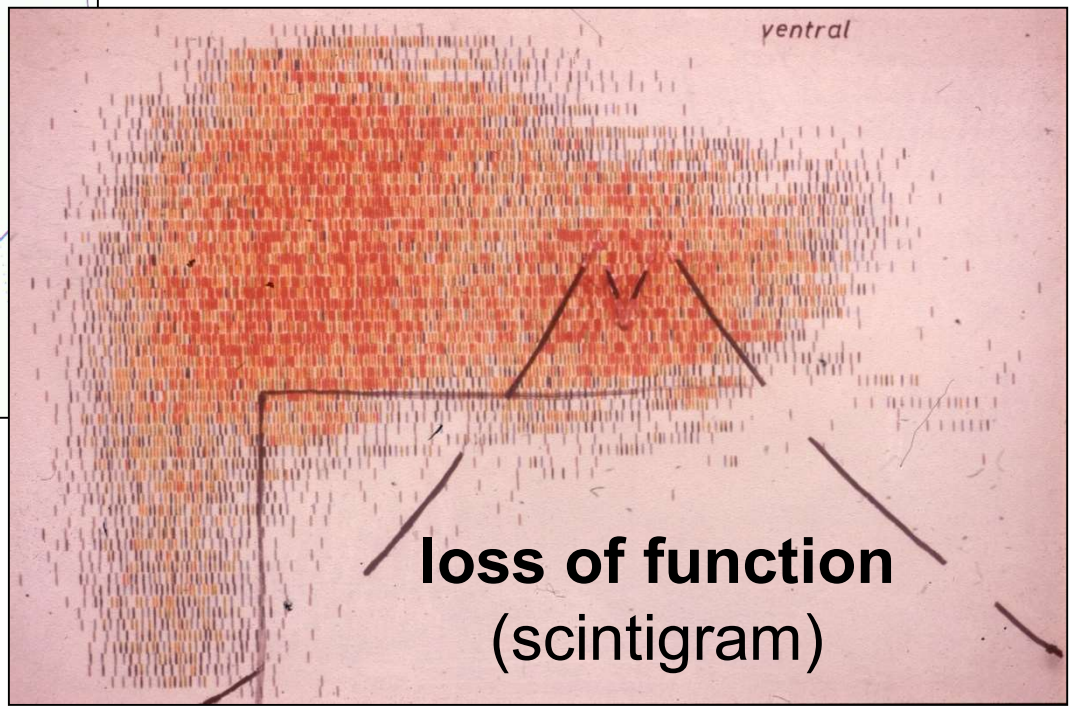
caution: function of residual, unirradiated volume ?

Mehta et al. IJROBP 63, 2005, 5-24 (reprinted from Seppenwolde et al., IJROBP 2003)

Individual tolerance levels –
Function of the unirradiated (residual) volume ?



human liver,
37 Gy



loss of function
(scintigram)

modified from
Köst et al., in preparation

Individual tolerance levels –
Function of the unirradiated (residual) volume ?

International Journal of Radiation Oncology biology • physics

www.redjournal.org

Clinical Investigation: Thoracic Cancer

Predicting Radiation Pneumonitis After Chemoradiation Therapy for Lung Cancer: An International Individual Patient Data Meta-analysis

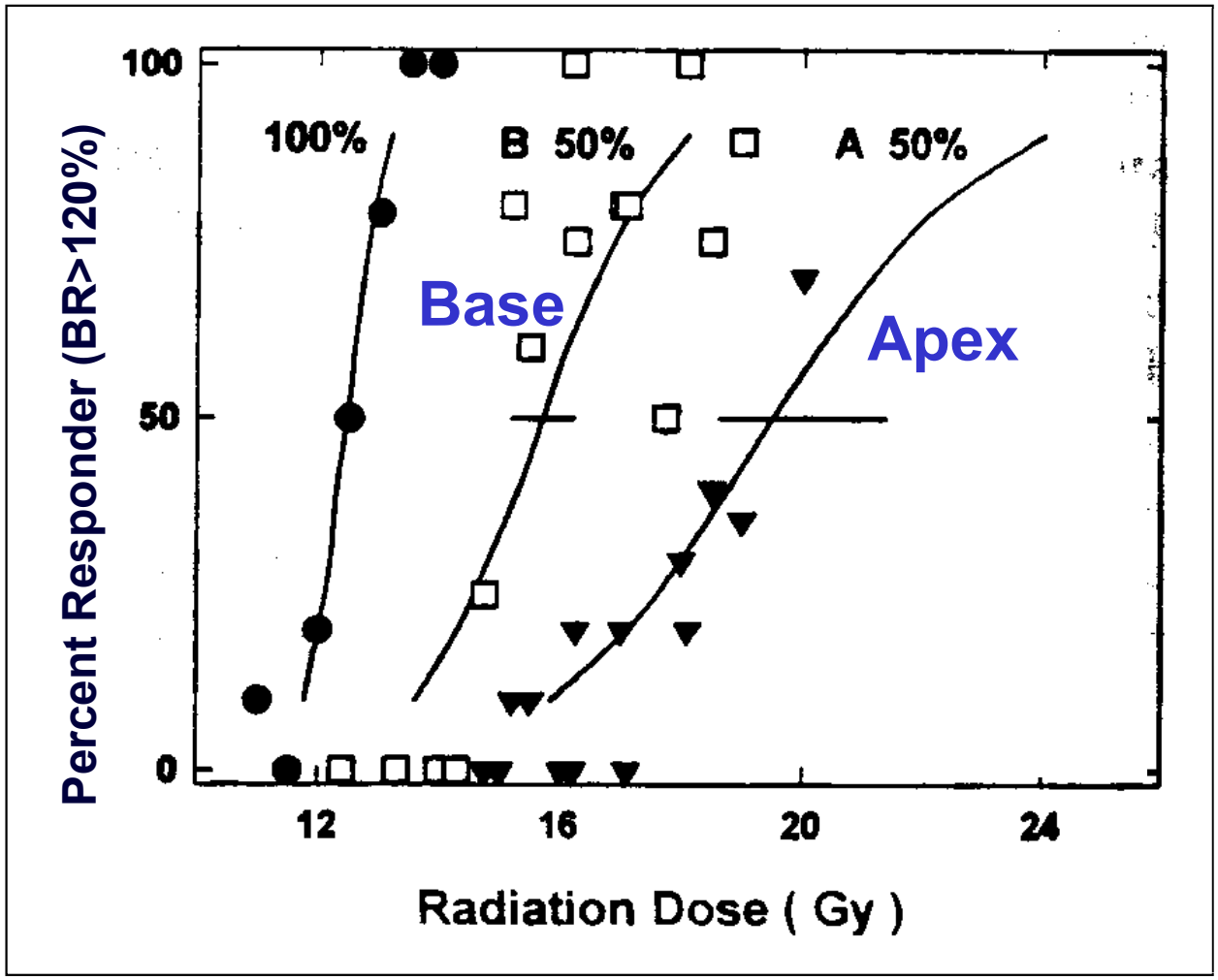
David A. Palma, MD, MSc, PhD,* Suresh Senan, MRCP, FRCR, PhD,† Kayoko Tsujino, MD,‡ Robert B. Barriger, MD,§ Ramesh Rengan, MD, PhD,‖ Marta Moreno, MD,¶ Jeffrey D. Bradley, MD,** Tae Hyun Kim, MD,†† Sara Ramella, MD,‡‡ Lawrence B. Marks, MD,§§ Luigi De Petris, MD, PhD,‖‖ Larry Stitt, MSc,¶¶ and George Rodrigues, MD, MSc*,¶¶

…le analysis of factors predictive of pneumonitis in the validation dataset

Factor	Multivariable analysis OR	95% CI	*P* value
Age (per 10-y increase)	1.38	0.95-2.01	.089
Chemotherapy regimen			<.001
Cisplatin-etoposide	1	Reference	
Carboplatin-paclitaxel	5.52	2.25-13.55	
Other	3.39	1.50-7.68	
Volume of lung receiving ≥20 Gy (V_{20})	1.07	1.03-1.11	<.001

Abbreviations: CI = confidence interval; OR = odds ratio.

Regional variations in tolerance (same endpoint)



mouse lung

modified from Liao et al., IJROBP 32, 1995, 1359-1370

Regional variations in tolerance

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 60, No. 3, pp. 748–758, 2004

0360-3016/04/$–see front matter

doi:10.1016/j.ijrobp.2004.04.037

CLINICAL INVESTIGATION **Lung**

REGIONAL DIFFERENCES IN LUNG RADIOSENSITIVITY AFTER RADIOTHERAPY FOR NON–SMALL-CELL LUNG CANCER

YVETTE SEPPENWOOLDE, PH.D., KATRIEN DE JAEGER, M.D., M.SC.,
LIESBETH J. BOERSMA, M.D., PH.D., JOSÉ S. A. BELDERBOS, M.D., AND
JOOS V. LEBESQUE, M.D., PH.D.

Radiotherapy and Oncology 122 (2017) 300–306

Contents lists available at ScienceDirect

Radiotherapy and Oncology

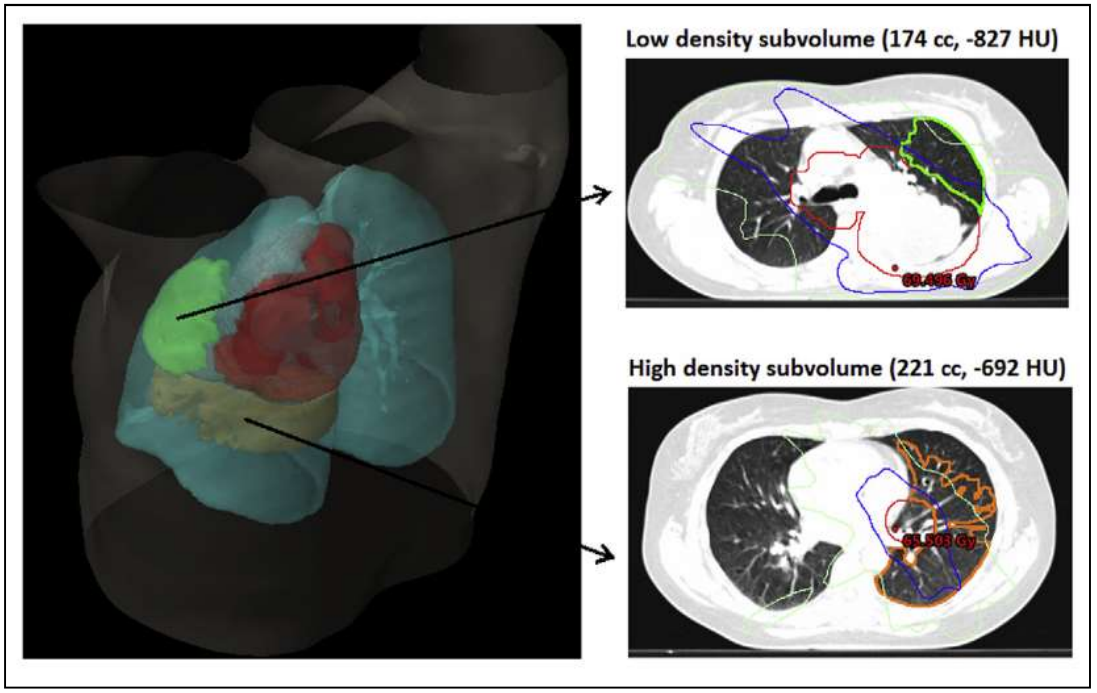
journal homepage: www.thegreenjournal.com

Morbidity of lung cancer radiotherapy

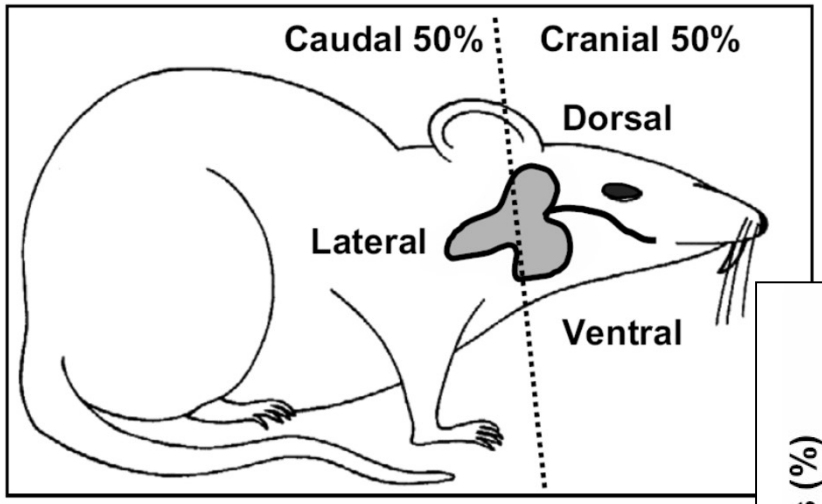
Regional variability in radiation-induced lung damage can be predicted by baseline CT numbers

Gilles Defraene [a,b,*], Wouter van Elmpt [c], Wouter Crijns [d], Dirk De Ruysscher [a,c]

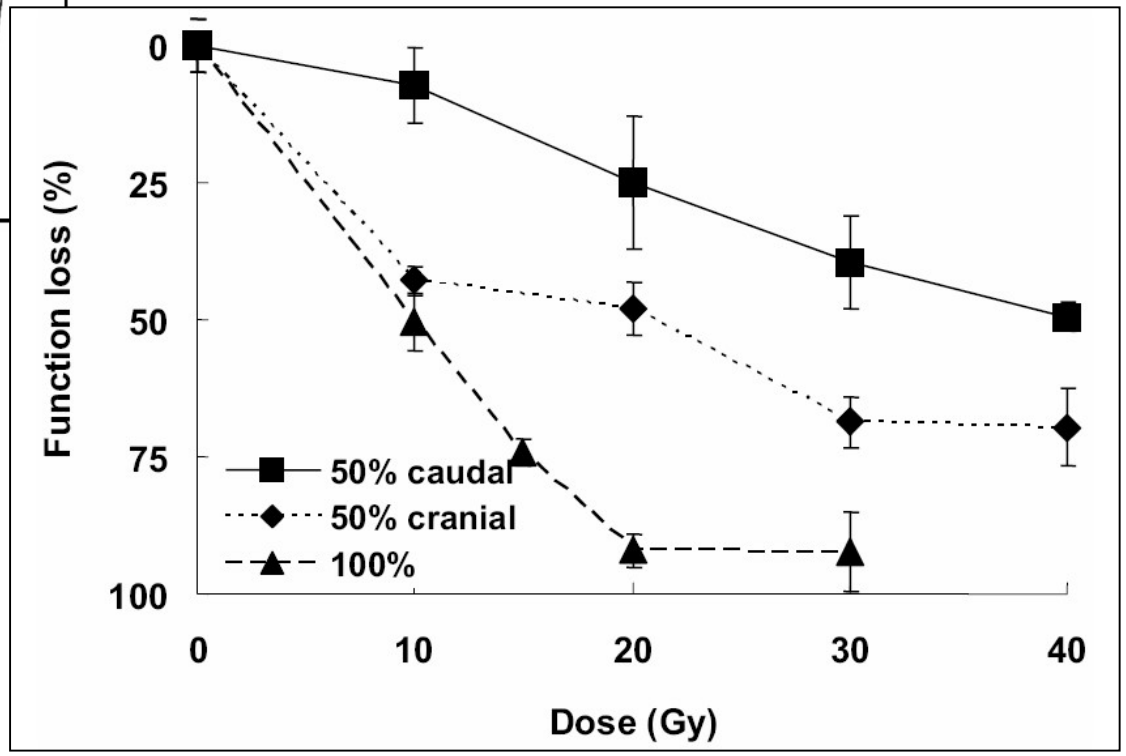
Conclusions: Limited amount of damage was observed in LD subvolumes, while the relative density increase of all subvolumes was well predictable. This could allow dose redistribution preferentially targeting low-density lung regions.



Regional variations in tolerance

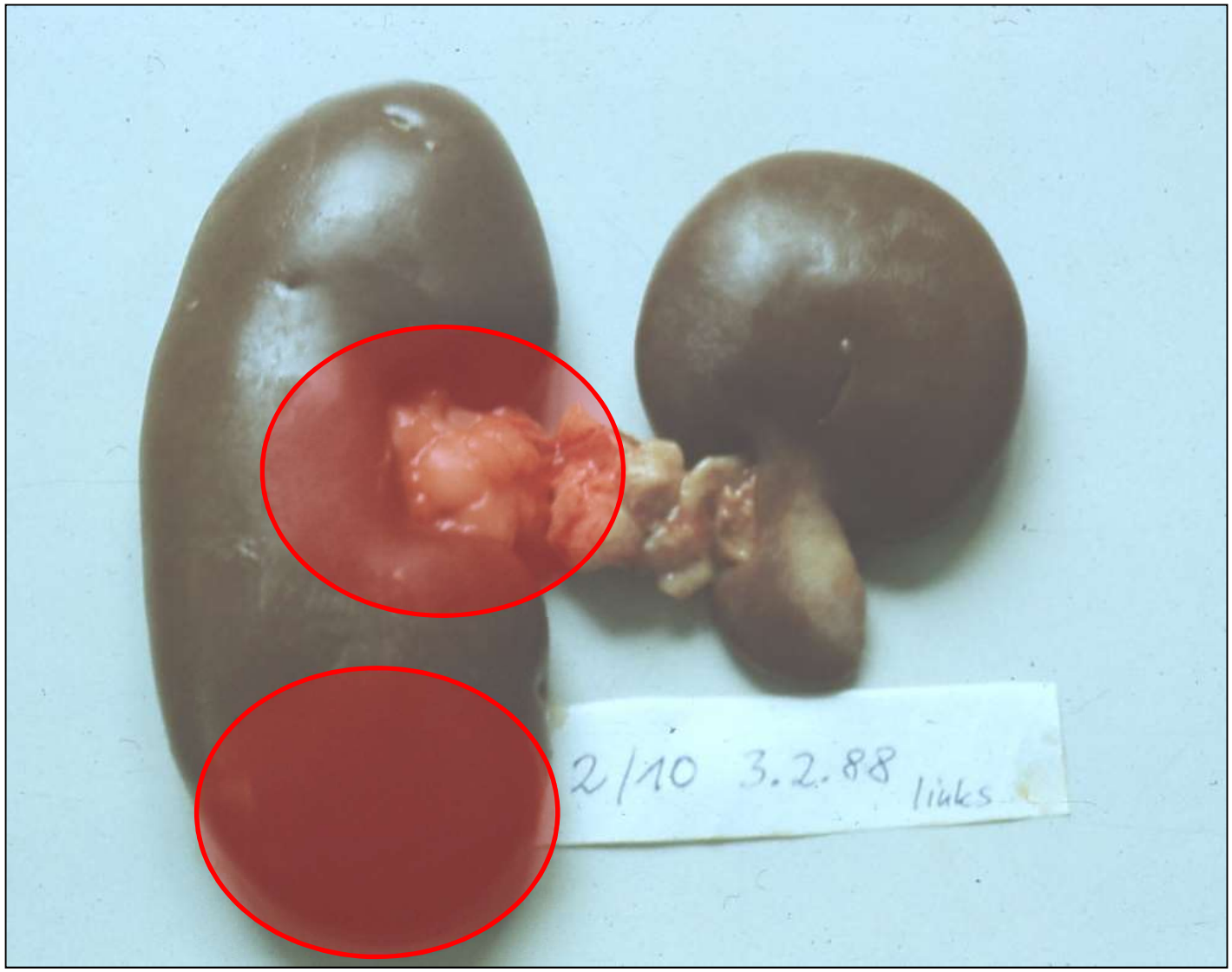


rat parotid gland



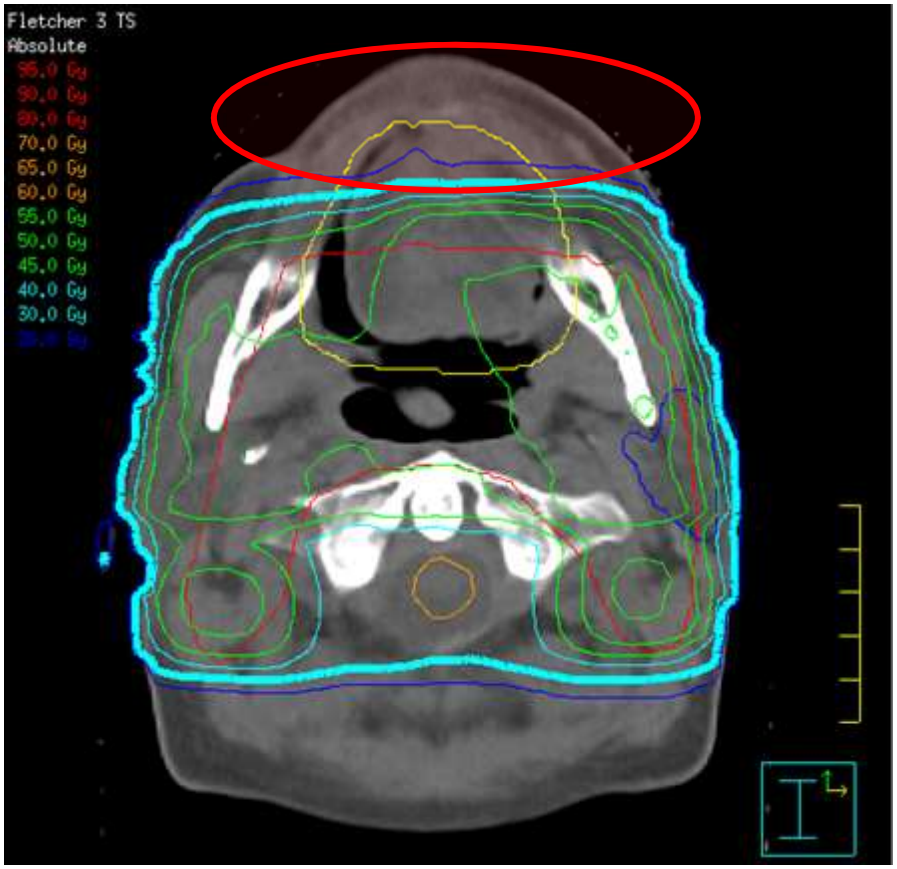
Konings et al. IJROBP 94, 2006, 98-105

Regional variations in clinical consequences



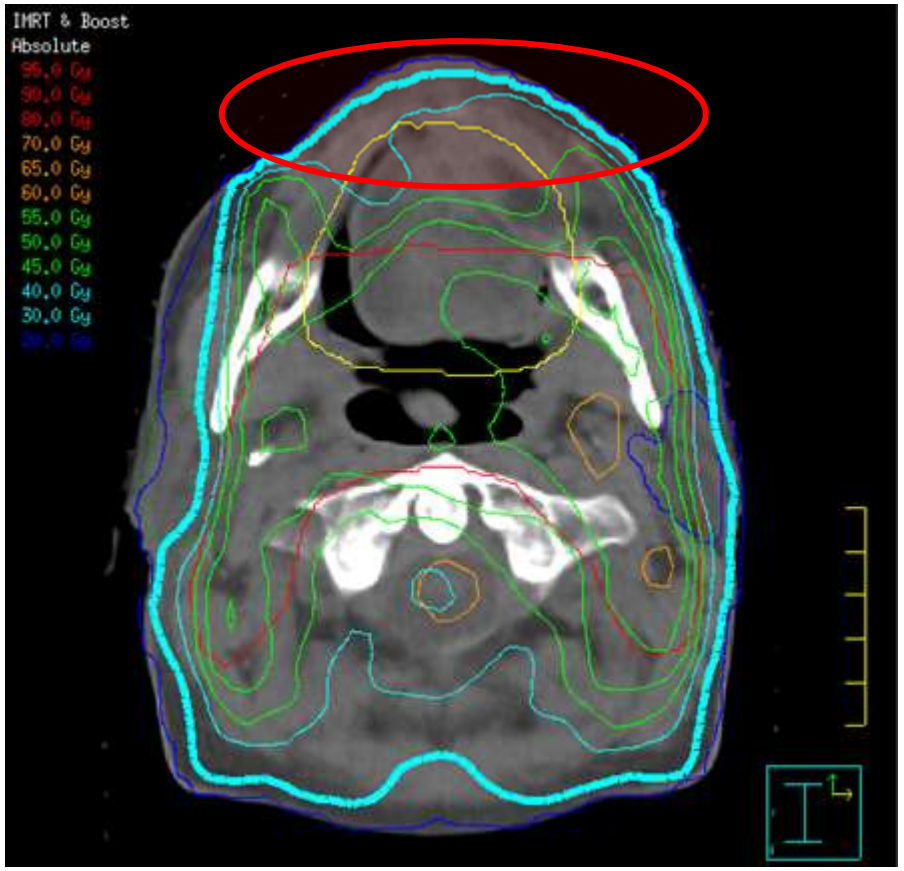
Regional variations in clinical consequences

Ca floor of the mouth, pT1 pN1

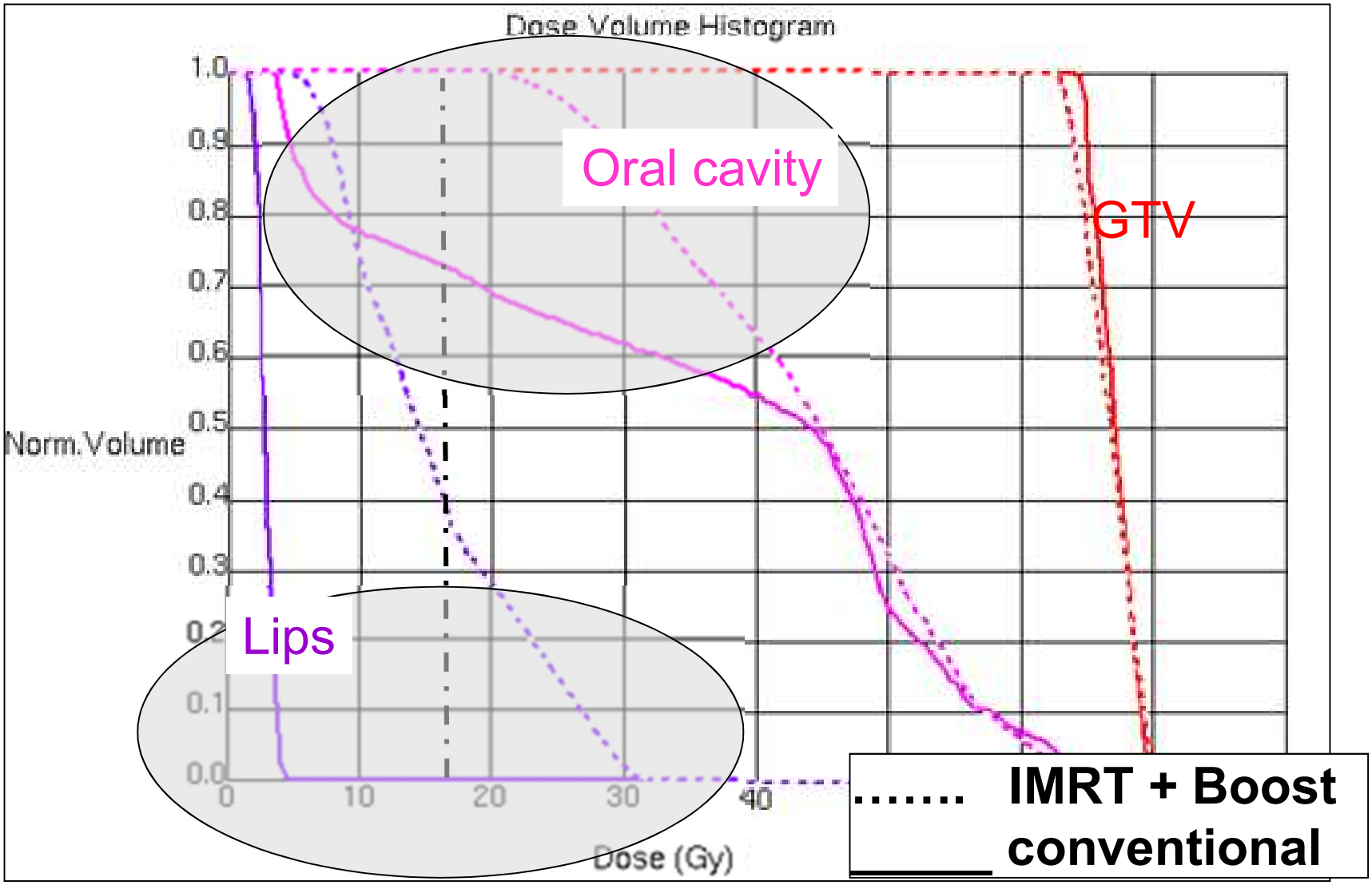


Conventional plan

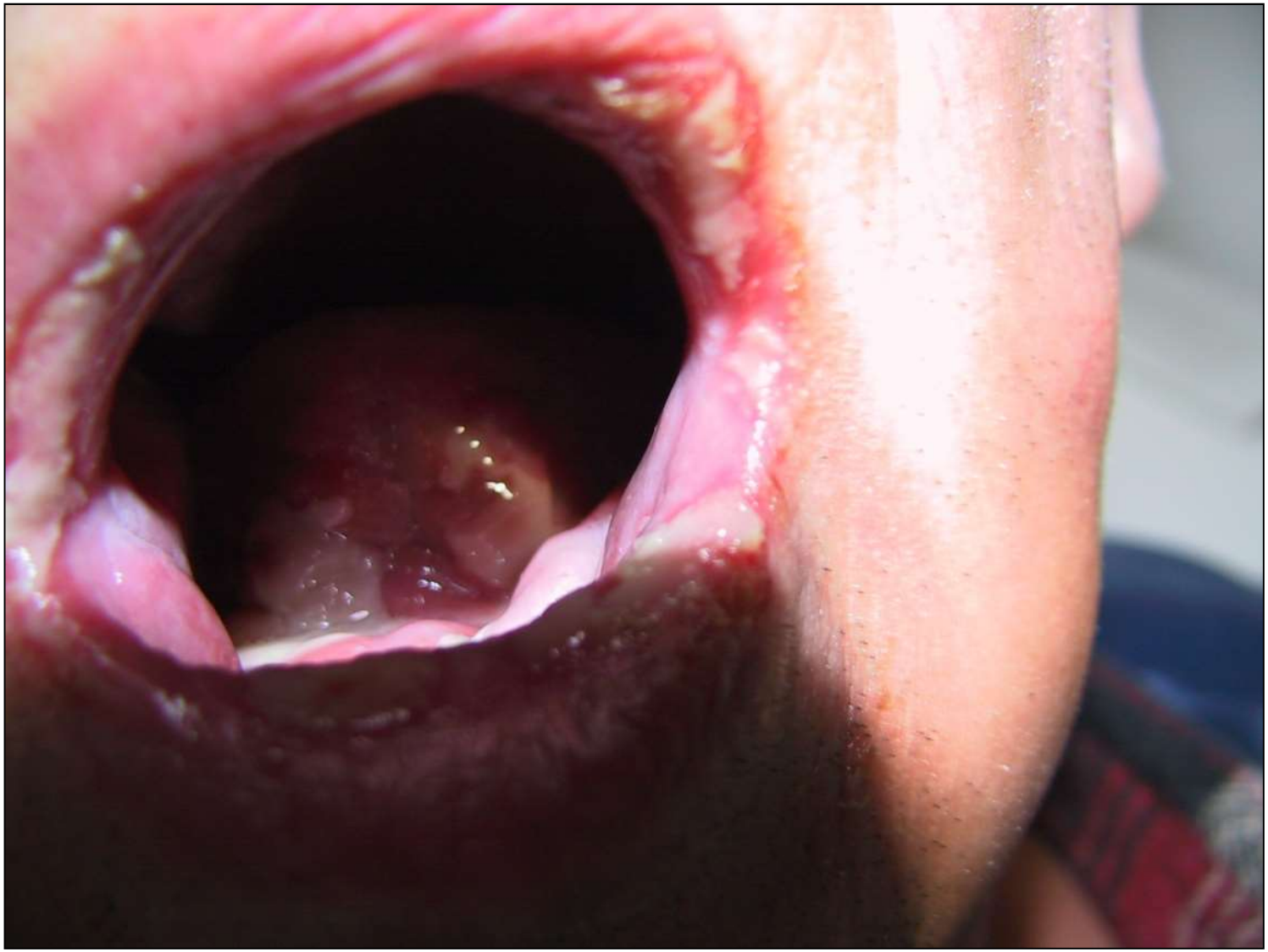
IMRT + Boost



Regional variations in clinical consequences



Regional variations in clinical consequences



Interactions between volumes/organs

Physiological Interaction of Heart and Lung in Thoracic Irradiation

International Journal of Radiation Oncology biology • physics

www.redjournal.org

Ghazaleh Ghobadi, MSc,*,† Sonja van der Veen, MD,*,† Beatrijs Bartelds, Rudolf A. de Boer, MD, PhD,§ Michael G. Dickinson, MD,‡ Johan R. de Jo Hette Faber,*,† Maarten Niemantsverdriet, PhD,*,† Sytze Brandenburg, PhD, Rolf M.F. Berger, PhD,‡ Johannes A. Langendijk, MD, PhD,* Robert P. Coppes, PhD,*,† and Peter van Luijk, PhD*

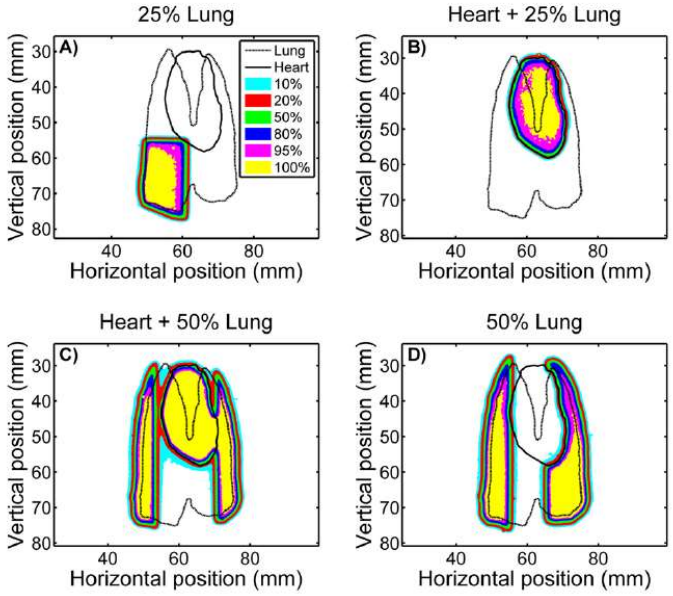


Fig. 1. Isodose contours and anatomy. Colored areas indicate dose, and the solid and dashed contour indicate the outlines of the heart and lung, respectively.

Summary

Coirradiation of the heart enhances risk and severity of radiation-induced lung toxicity through an unknown mechanism. We show that irradiation of heart, lung, or both independently induces specific cardiac dysfunction and pulmonary vascular damage, mutually enhancing each other. These results show that treatment of thoracic cancer with radiation therapy requires optimization for both pulmonary and cardiac function to reduce the risk of toxicity.

Interactions between volumes/organs

Acta Oncologica, 2014; 53: 590–596

informa
healthcare

ORIGINAL ARTICLE

Is there an impact of heart exposure on the incidence of radiation pneumonitis? Analysis of data from a large clinical cohort

SUSAN L. TUCKER[1], ZHONGXING LIAO[2], JEFFREY DINH[2], SHELLY X. BIAN[2], RADHE MOHAN[3], MARY K. MARTEL[3] & DAVID R. GROSSHANS[2]

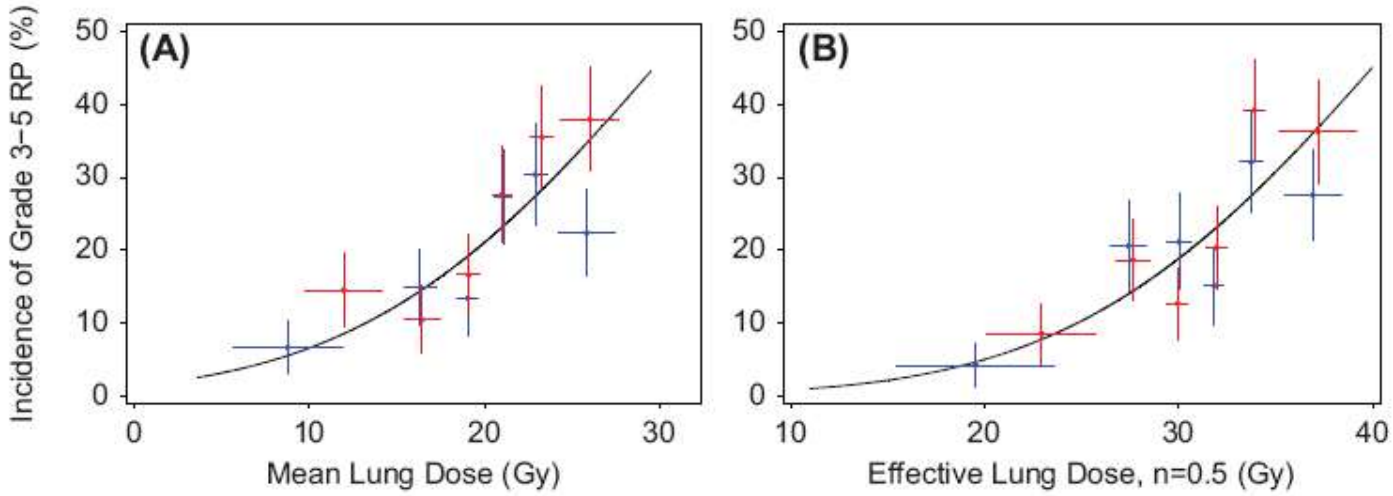


Figure 2. Kaplan-Meier incidence of Grade ≥3 radiation pneumonitis (RP) in subgroups of 52–53 patients each, plotted as a function of mean lung dose (MLD) (panel A) or effective dose to lung (D_{eff}) computed using volume parameter $n = 0.5$ (panel B). Patients were first sorted into six subgoups by lung exposure, as in Figure 1, with each group then divided in half according to smaller (blue symbols) versus larger (red symbols) heart D10 values. Points, error bars, and curves are as in Figure 1.

Interactions between volumes/organs

OPEN ACCESS Freely available online

PLOS | ONE

Complication Probability Models for Radiation-Induced Heart Valvular Dysfunction: Do Heart-Lung Interactions Play a Role?

Laura Cella[1,2]*, Giuseppe Palma[1], Joseph O. Deasy[3], Jung Hun Oh[3], Raffaele Liuzzi[1,2], Vittoria D'Avino[1], Manuel Conson[1,2], Novella Pugliese[4], Marco Picardi[4], Marco Salvatore[2], Roberto Pacelli[1,2]

1 Institute of Biostructure and Bioimaging, National Council of Research (CNR), Naples, Italy, **2** Department of Advanced Biomedical Sciences, Federico II University School of Medicine, Naples, Italy, **3** Department of Medical Physics, Memorial Sloan Kettering Cancer Center, New York, New York, United States of America, **4** Department of Clinical Medicine and Surgery, Federico II University School of Medicine, Naples, Italy

Abstract

Purpose: The purpose of this study is to compare different normal tissue complication probability (NTCP) models for predicting heart valve dysfunction (RVD) following thoracic irradiation.

Methods: All patients from our institutional Hodgkin lymphoma survivors database with analyzable datasets were included (n = 90). All patients were treated with three-dimensional conformal radiotherapy with a median total dose of 32 Gy. The cardiac toxicity profile was available for each patient. Heart and lung dose-volume histograms (DVHs) were extracted and both organs were considered for Lyman-Kutcher-Burman (LKB) and Relative Seriality (RS) NTCP model fitting using maximum likelihood estimation. Bootstrap refitting was used to test the robustness of the model fit. Model performance was estimated using the area under the receiver operating characteristic curve (AUC).

Results: Using only heart-DVHs, parameter estimates were, for the LKB model: $D_{50} = 32.8$ Gy, $n = 0.16$ and $m = 0.67$; and for the RS model: $D_{50} = 32.4$ Gy, $s = 0.99$ and $\gamma = 0.42$. AUC values were 0.67 for LKB and 0.66 for RS, respectively. Similar performance was obtained for models using only lung-DVHs (LKB: $D_{50} = 33.2$ Gy, $n = 0.01$, $m = 0.19$, AUC = 0.68; RS: $D_{50} = 24.4$ Gy, $s = 0.99$, $\gamma = 2.12$, AUC = 0.66). Bootstrap result showed that the parameter fits for lung-LKB were extremely robust. A combined heart-lung LKB model was also tested and showed a minor improvement (AUC = 0.70). However, the best performance was obtained using the previously determined multivariate regression model including maximum heart dose with increasing risk for larger heart and smaller lung volumes (AUC = 0.82).

Conclusions: The risk of radiation induced valvular disease cannot be modeled using NTCP models only based on heart dose-volume distribution. A predictive model with an improved performance can be obtained but requires the inclusion of heart and lung volume terms, indicating that heart-lung interactions are apparently important for this endpoint.

Citation: Cella L, Palma G, Deasy JO, Oh JH, Liuzzi R, et al. (2014) Complication Probability Models for Radiation-Induced Heart Valvular Dysfunction: Do Heart-Lung Interactions Play a Role? PLoS ONE 9(10): e111753. doi:10.1371/journal.pone.0111753

Normal tissue tolerance

Volume

TOLERANCE OF NORMAL TISSUE TO THERAPEUTIC IRRA

B. EMAMI, M.D.,[1] J. LYMAN, PH.D.,[5] A. BROWN, M.D.,[4] L. COIA, [illegible] H.D.,[4]
J. E. MUNZENRIDER, M.D.,[4] B. SHANK, M.D.,[2] L. J. SOLIN, [illegible]ON, M.D.[2]

[1]Mallinckrodt Institute of Radiology, Washington University School of Medi[illegible] Memorial Sloan-Kettering Cancer Center, New York, NY 10021; [3]Department of Radiation The[illegible]ania School of Medicine and the Fox Chase Cancer Center, Philadelphia, PA 19111; [illegible]Massach[illegible]partment of Radiation Medicine, Boston, MA 02114 and Harvard Medical School; an[illegible] Lawrence Berkeley Laboratory, Research Medicine and Radiati[illegible]keley, CA 94720

The importance of knowledge on tolera[illegible]o irradiation by radiation oncologists cannot be overemphasized. Unfortunatelv[illegible]s than adequate. With the increasing use of 3-D treatment planning and dose [illegible]arly volumetric information, will become even more critical. As a part of the N[illegible], a task force, chaired by the primary author, was formed and an extensive lite[illegible]out to address this issue. In this manuscript we present the updated informa[illegible]al tissues of concern in the protocols of this contract, based on available da[illegible] on partial volume effects. Due to a lack of precise and comprehensive da[illegible] [illegible] contract have also be[illegible]this is not and cannot be a comprehensive work, which is beyond the scope of this

opinion / experience of ... clinicians

-Not to be used (any more)!!!!!

Volume

QUANTEC:

Quanti… …ysis
of … …ssue
… the Clinic

Be extremely cautious !

Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S1–S2, 2010

0360-3016/10/$–see front matter

ELSEVIER

doi: 10.1016/j.ijrobp.2009.08.075

INTRODUCTORY PAPER

GUEST EDITOR'S INTRODUCTION TO QUANTEC: A USERS GUIDE

LAWRENCE B. MARKS, M.D.,* RANDALL K. TEN HAKEN, PH.D.,† GUEST EDITORS, AND MARY K. MARTEL, PH.D.,‡ ASSOCIATE GUEST EDITOR

*University of North Carolina, Chapel Hill, North Carolina; †University of Michigan, Ann Arbor, Michigan; and ‡M. D. Anderson Cancer Center, Houston, Texas

NTCP models

Lyman model (power law, 4 parameters)

$$= 1/\sqrt{(2\pi)} \int^{(D - TD50(v))/(mTD50(v))} \exp(-t^2/2)dt$$

Kutcl

Growi

Tissu

NTCP(

$$= 1 - \prod_i (1 - NTCP(Di)(D_i))^{vi}$$

$$f_{dam} = g \sum_{lower} v_{i,lower} p_L(D_{i,lower})$$

$$+ (1 - g) \sum_{upper} v_{i,upper} p_u(D_{i,upper})$$

ge group $^{fV_{Int35}}$

$\times v_{45-50Gy}$

$5 \times v_{60-65Gy}$

lement

Parallel architecture/critical volume

More quantitative data

from further (clinical) studies

for *individual endpoints*

are required !!!

Hypoxia and Tumor Microenvironment

Marianne Koritzinsky

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

Tumor hypoxia

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

Tissue hypoxia – poor oxygenation

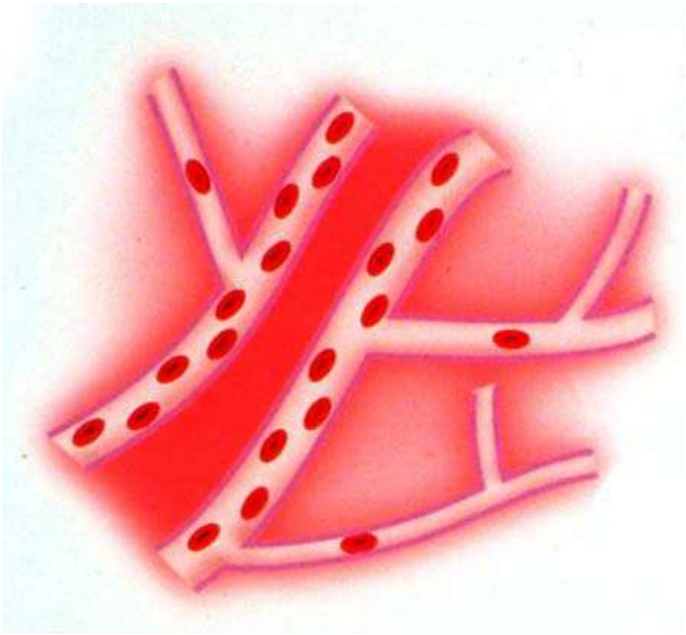
Air: 21% O2
Tissue normoxia: 5-7% O2
Tissue hypoxia: < 3% O2

Physiology

- Development
- Exercise
- Altitude

Pathology

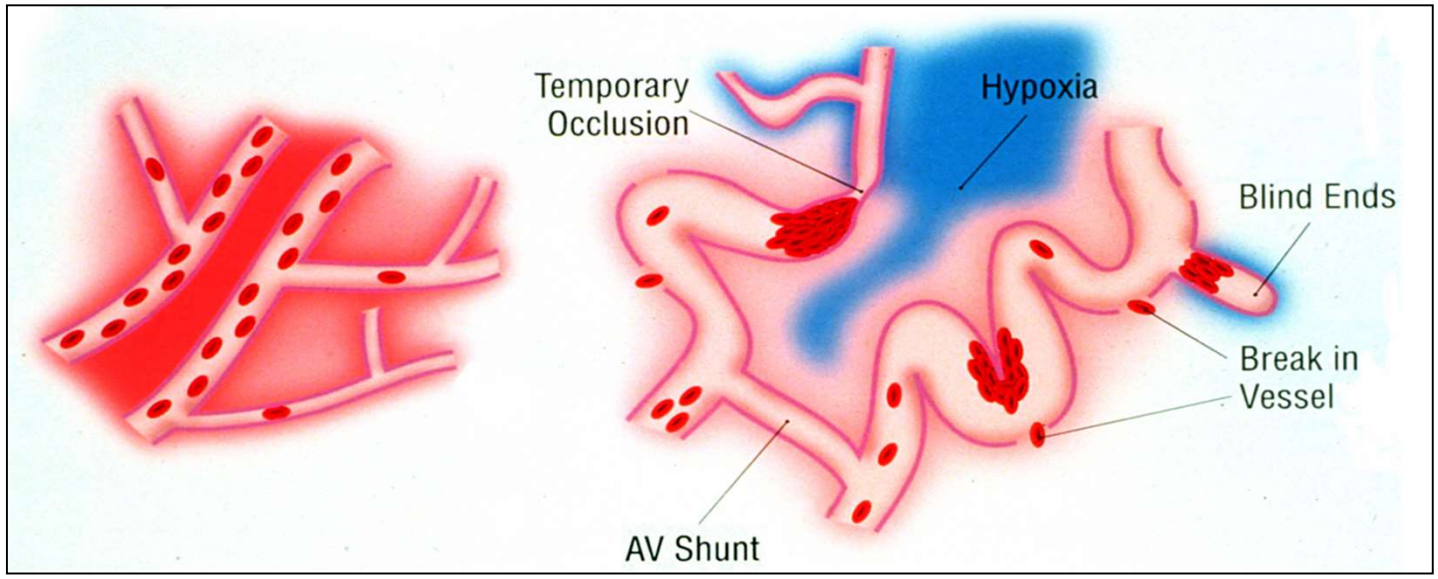
- Wound
- Stroke
- Infarctation
- Solid tumors



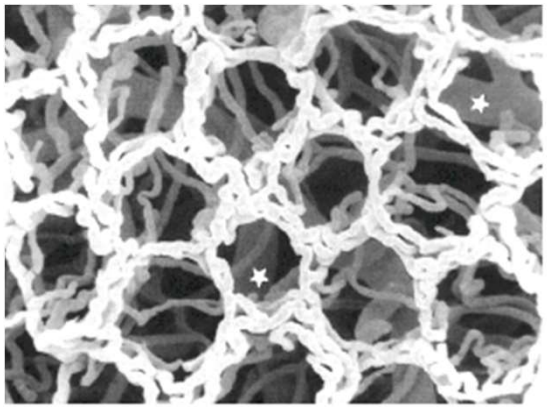
1) How and why hypoxia arises

Tumor hypoxia

Abnormal vasculature is a prime cause of hypoxia in cancer



Corrosion castings

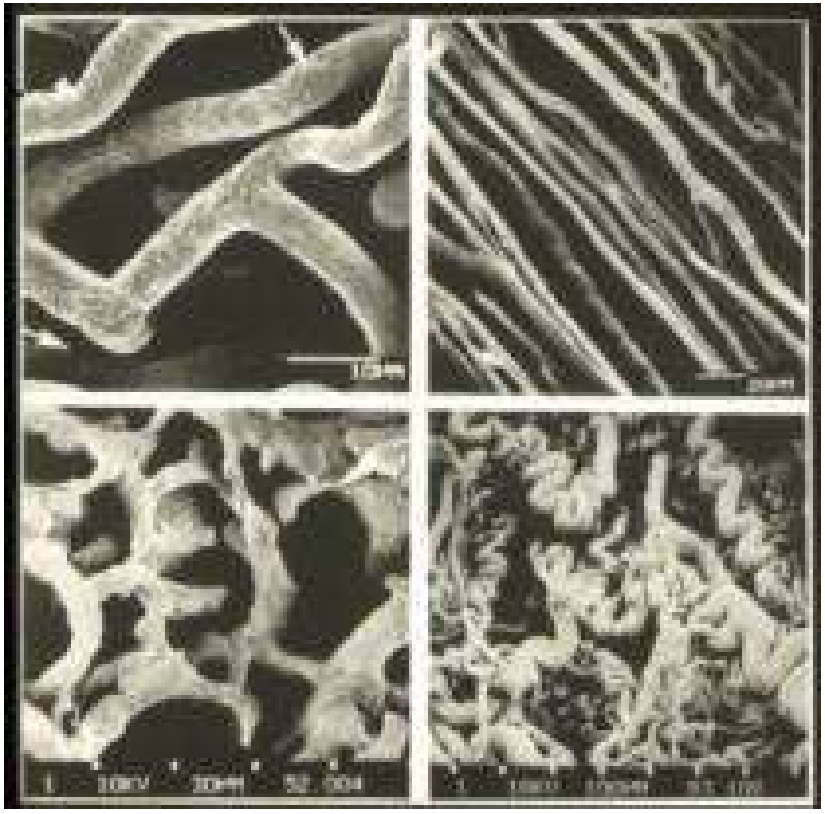


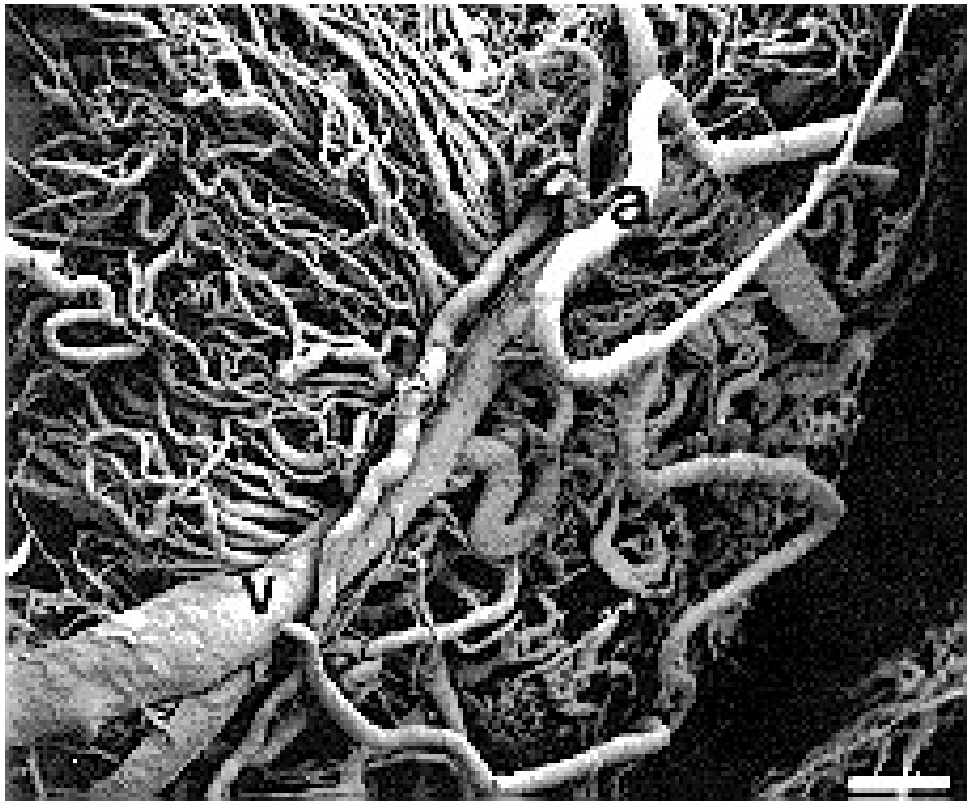
Normal colon

Colon xenograft

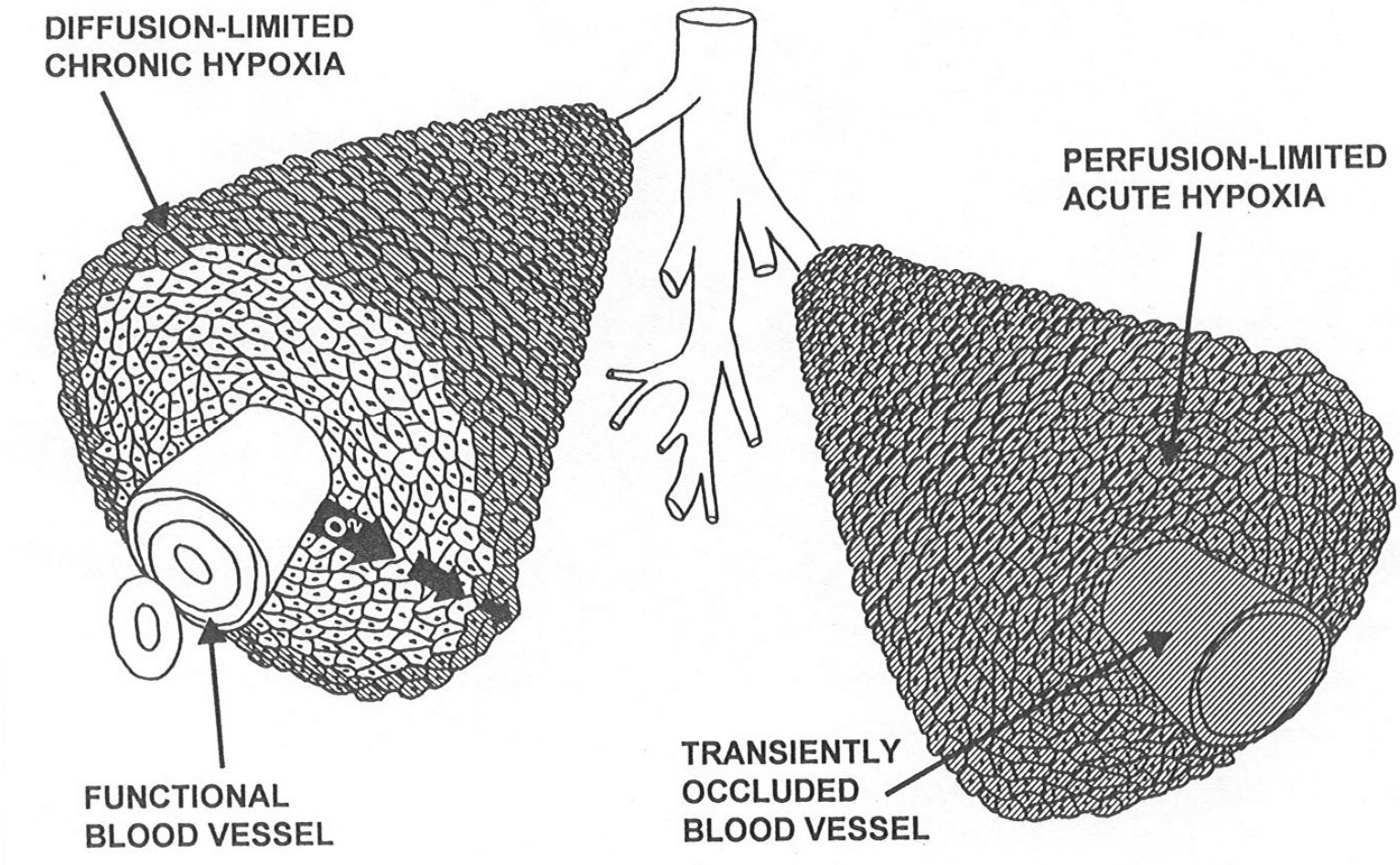
The vasculature in tumors is abnormal

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

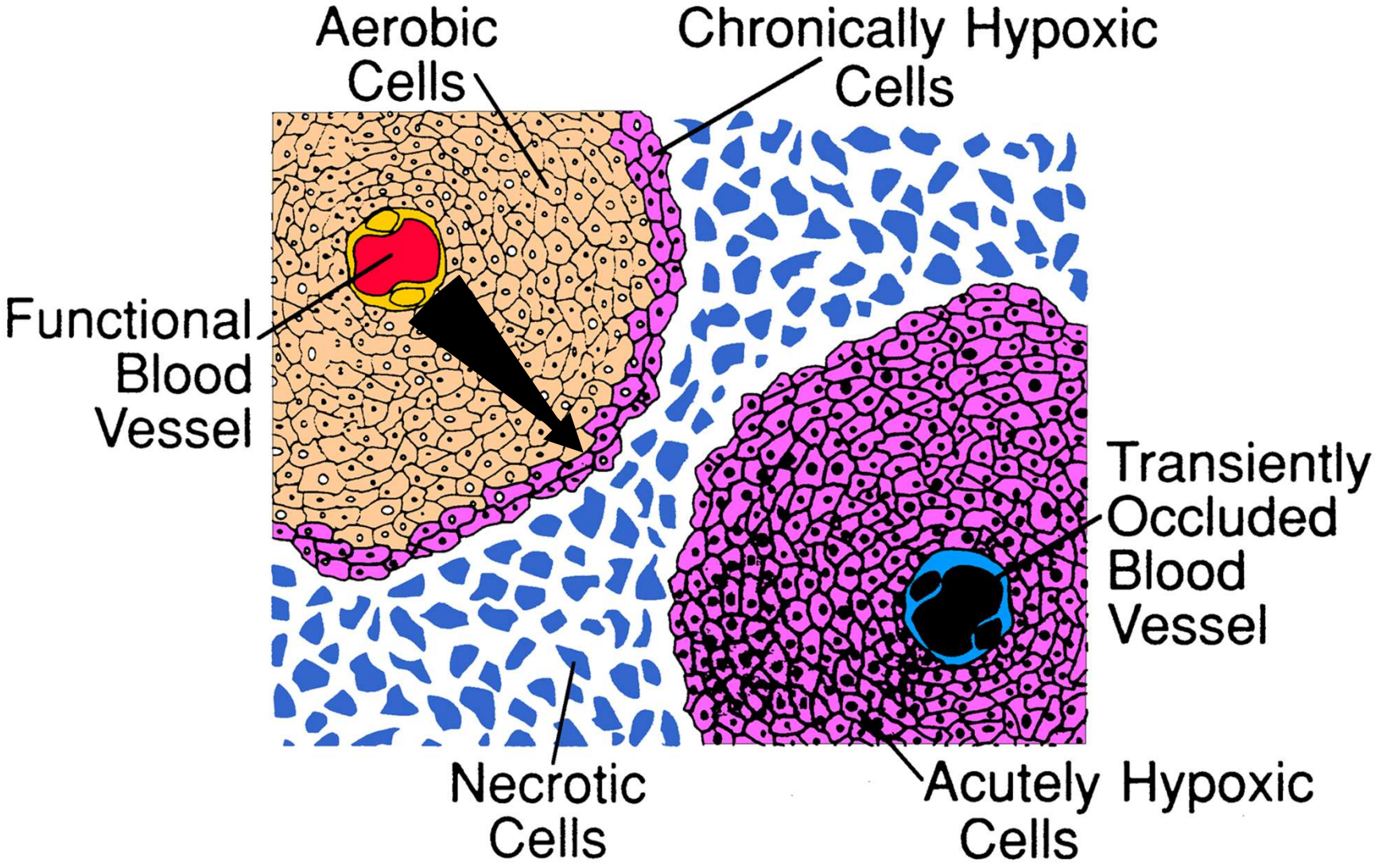




Chronic versus acute hypoxia



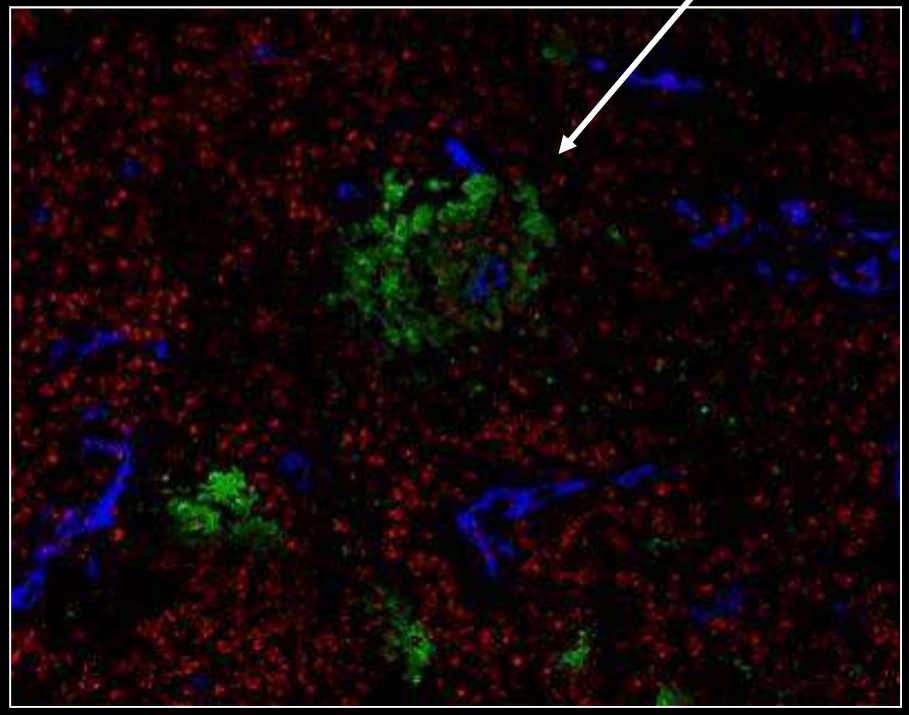
Chronic versus acute hypoxia



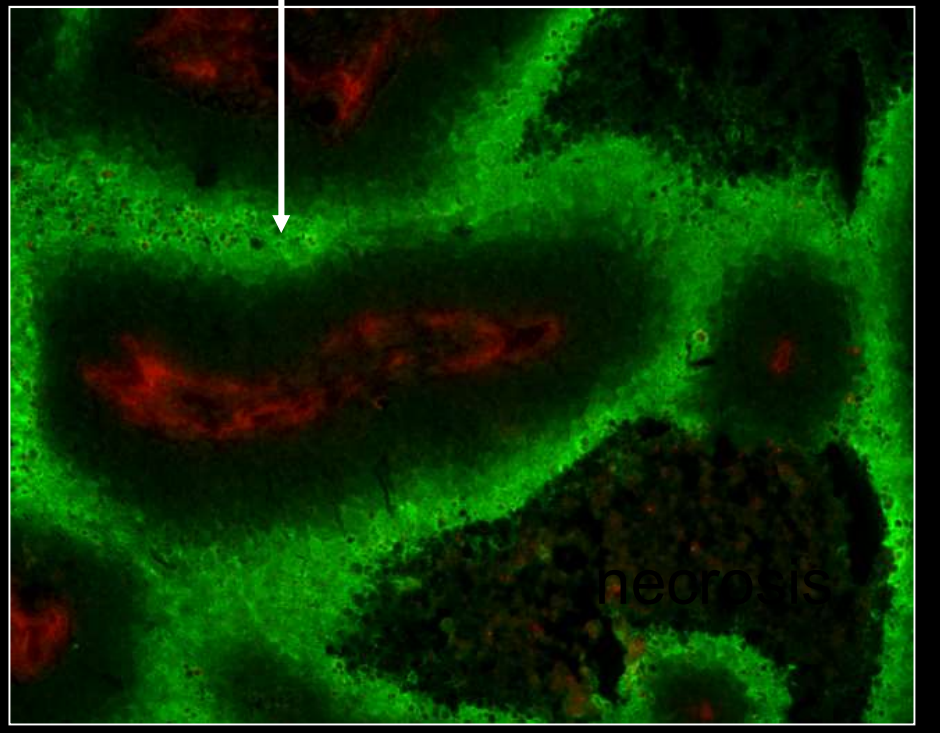
Different types of hypoxia

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

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



Hypoxia
Vessels



Hypoxia is a result of:

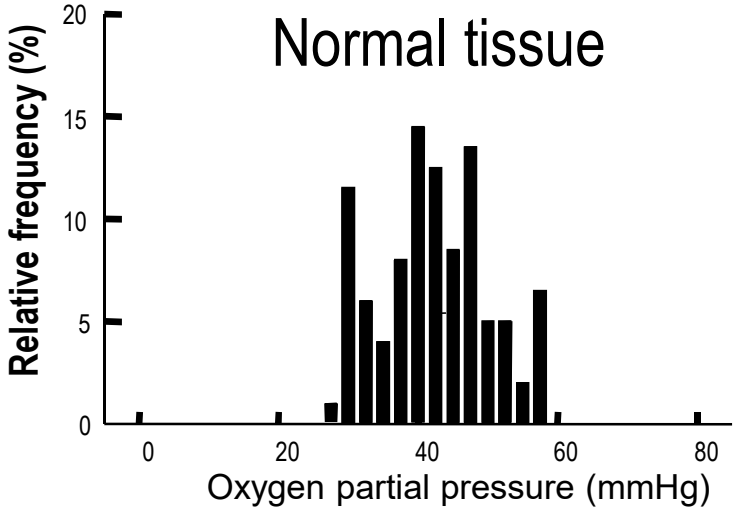
- Oxygen delivery
- Oxygen consumption
- Hypoxia tolerance

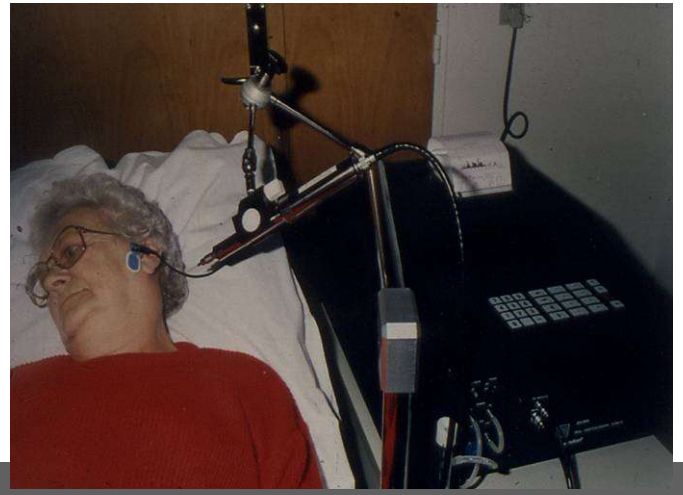
2) Heterogeneity of tumor oxygenation

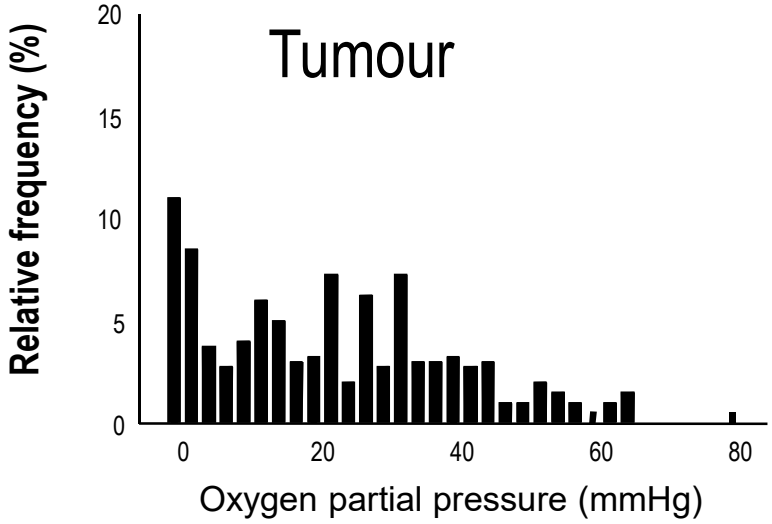
Heterogeneity in Oxygenation

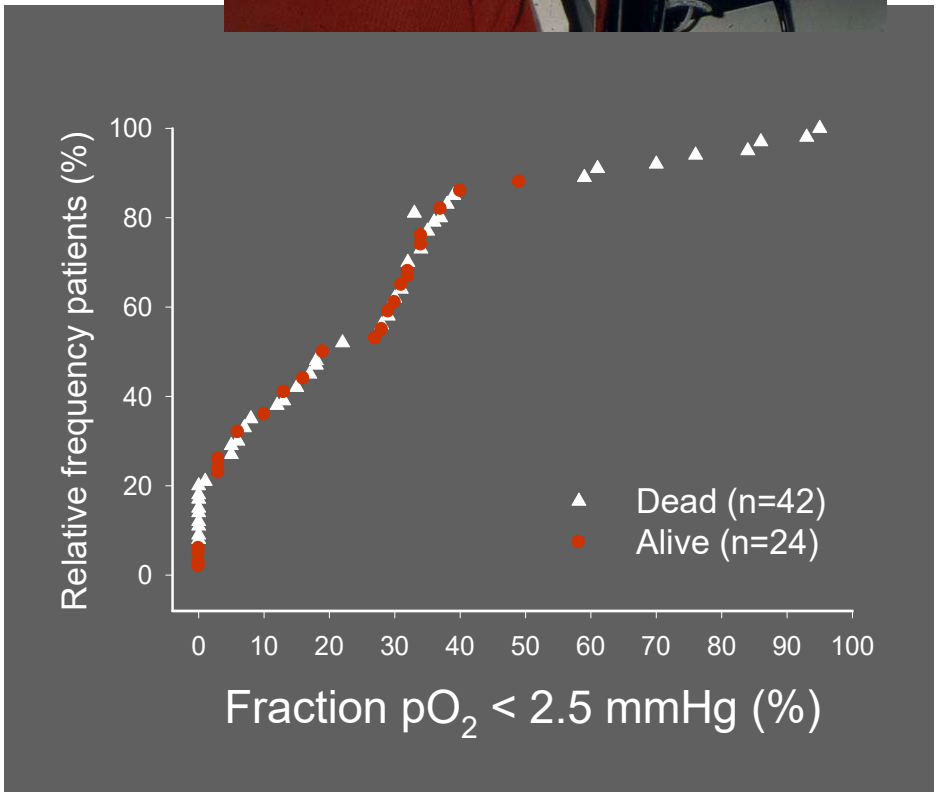
a) Amount (%) amongst patients
b) In severity
c) In space
d) In time

a) Heterogeneity in hypoxia (%) amongst patients

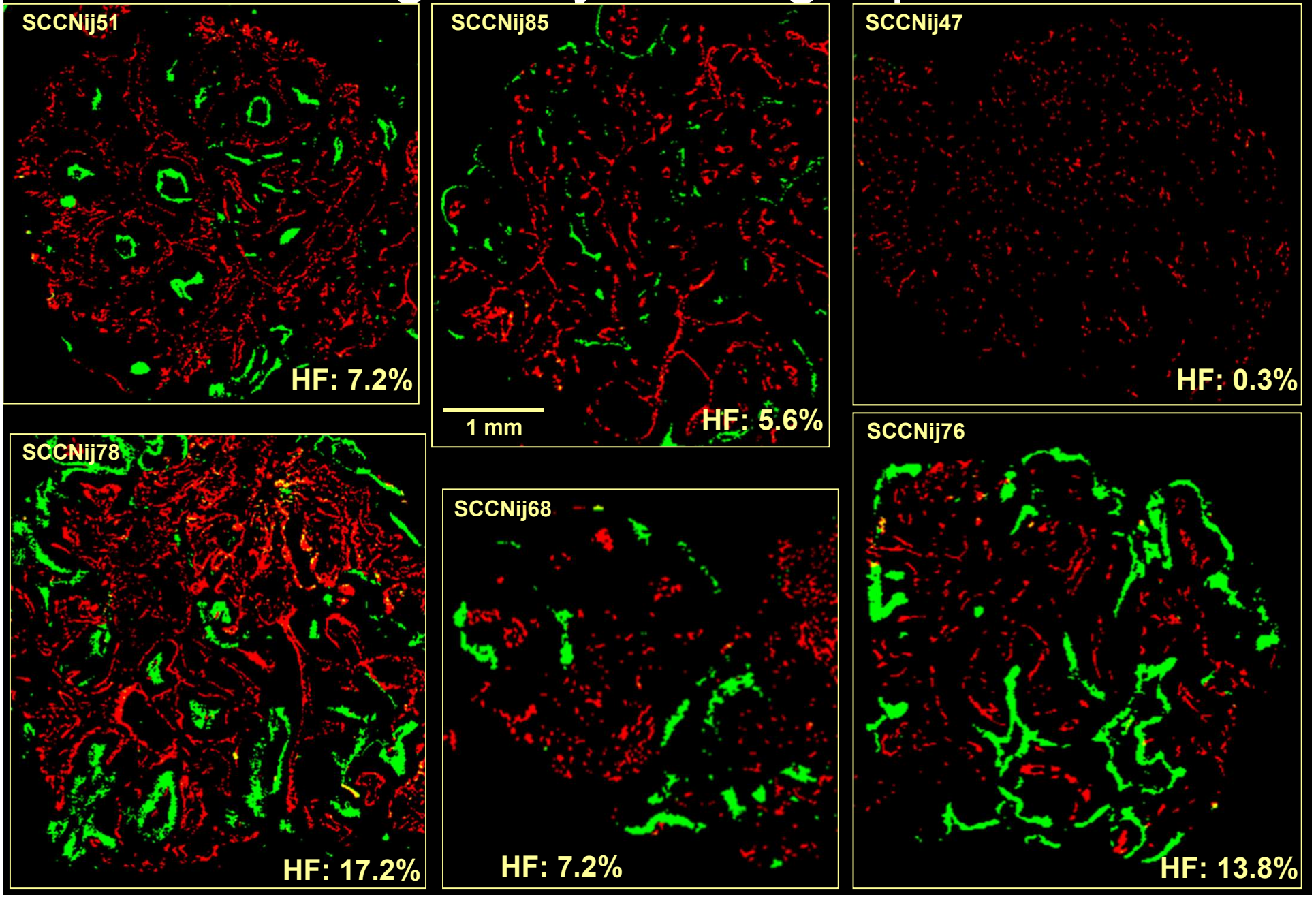








Heterogeneity amongst patients



Hypoxia predicts for poor outcome

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

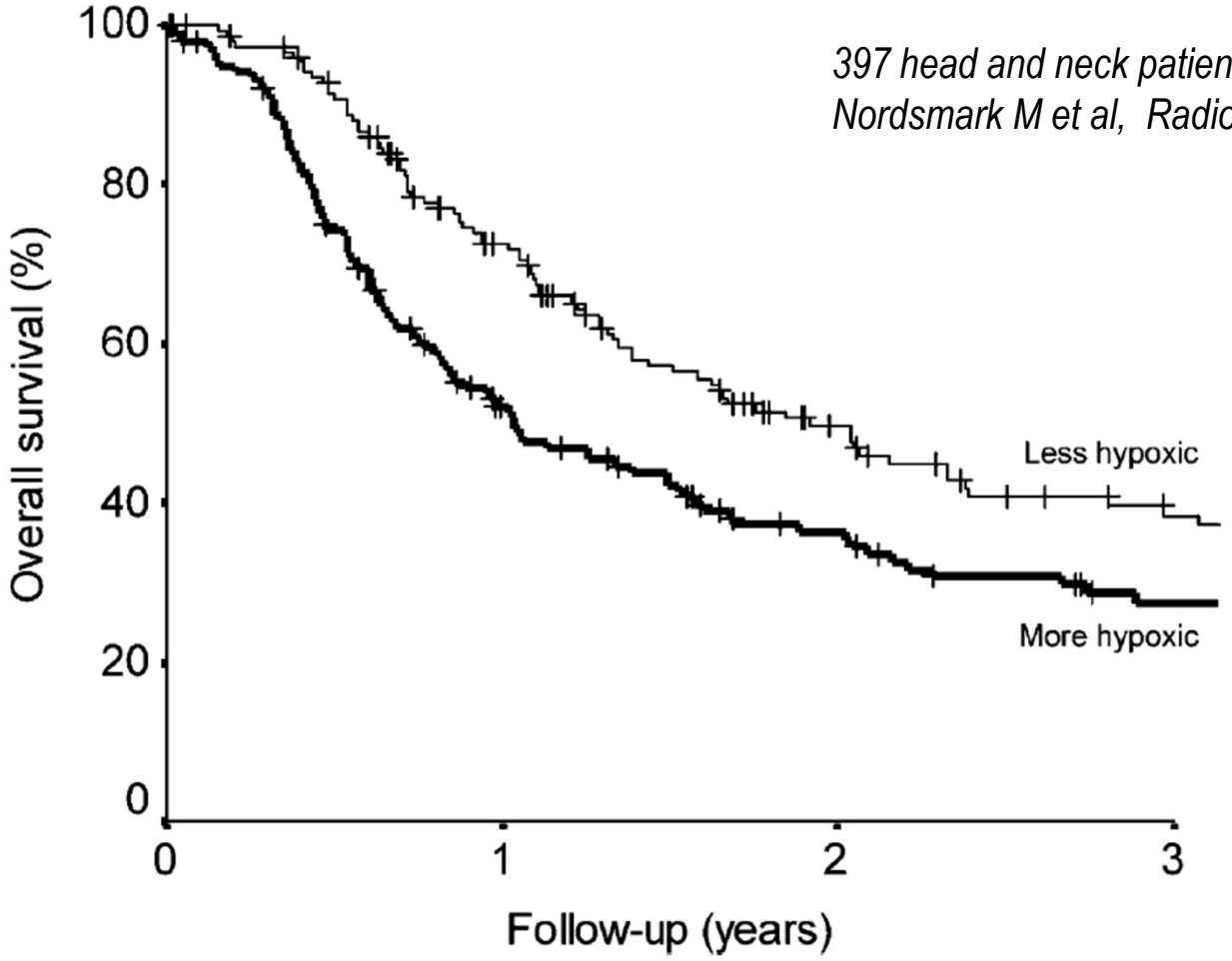
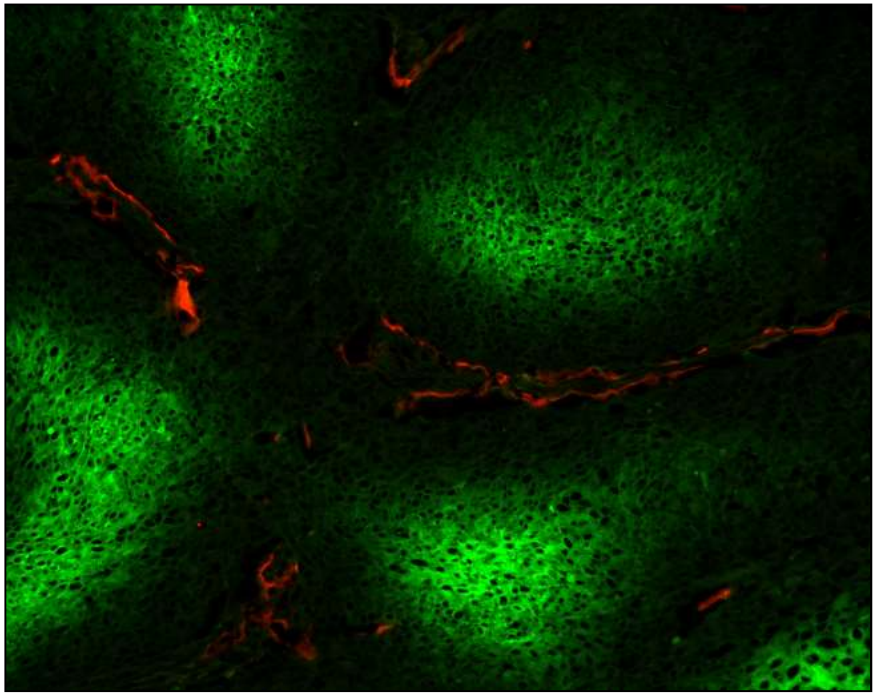
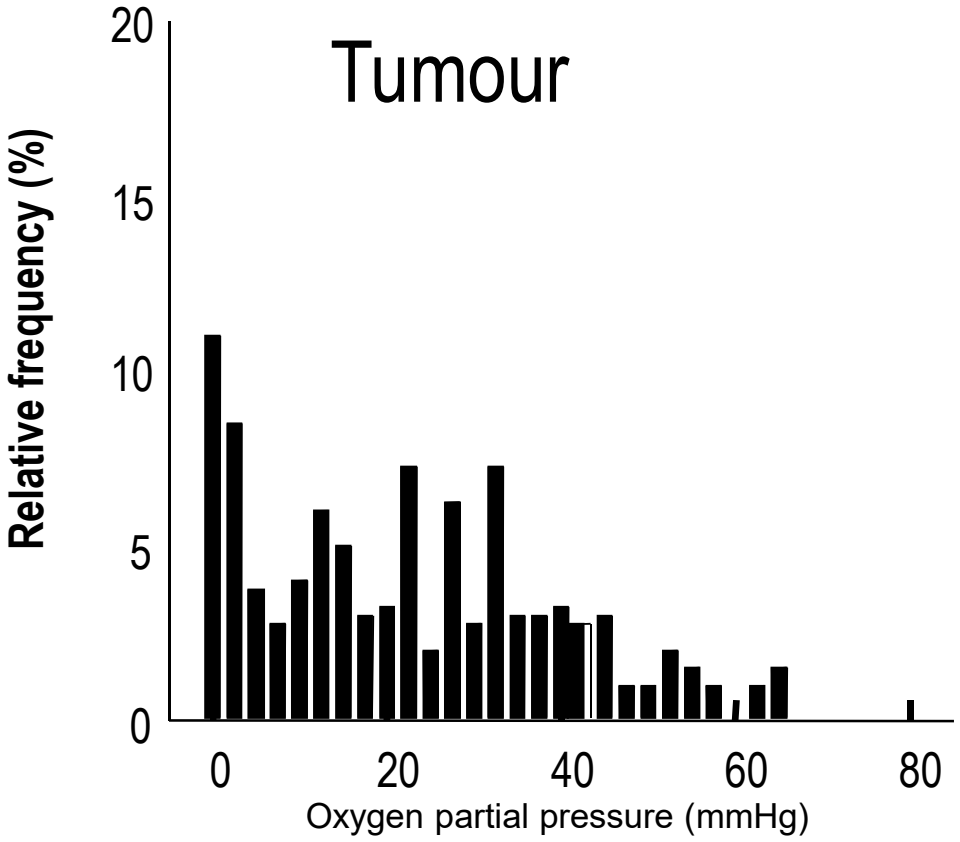


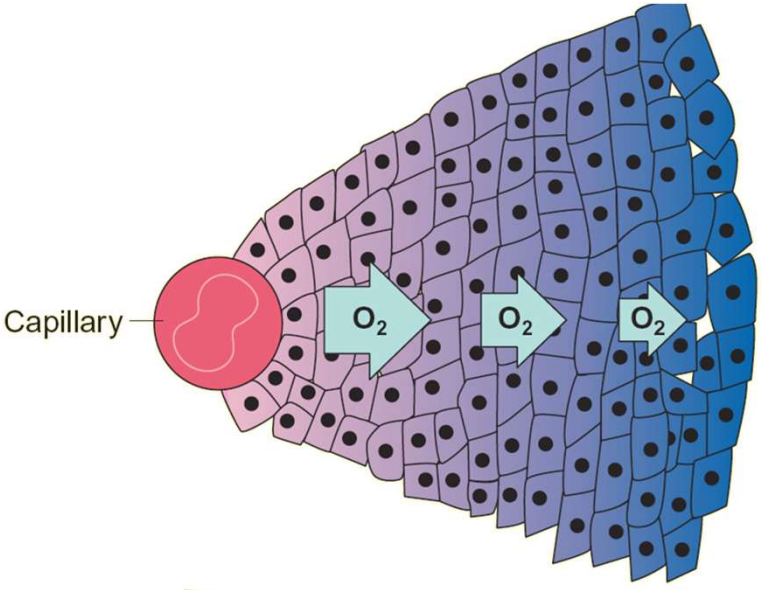
Fig. 2. Actuarial overall survival rate for patients with less hypoxic tumors ($HP_{2.5} \leq 19\%$, thin line) compared with more hypoxic tumors ($HP_{2.5} > 19\%$, bold line), $P = 0.006$.

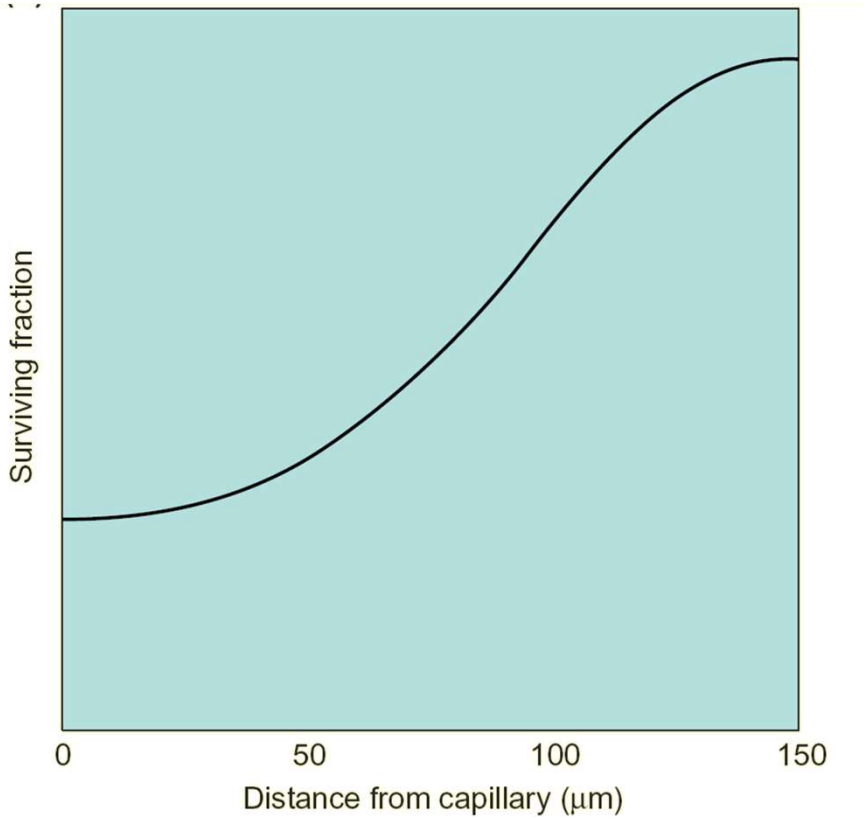
b) Heterogeneity in severity





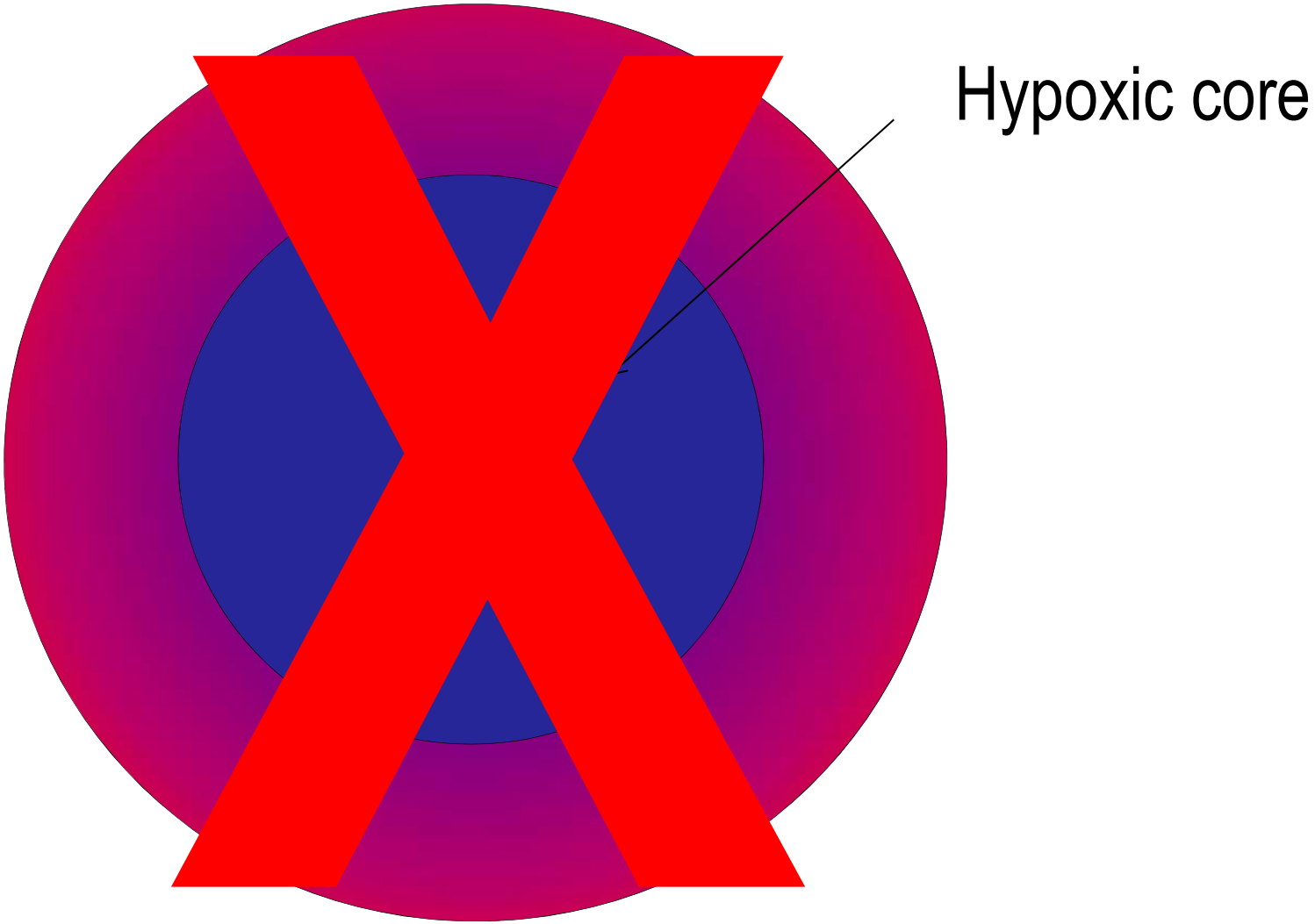
Severity and radiation response



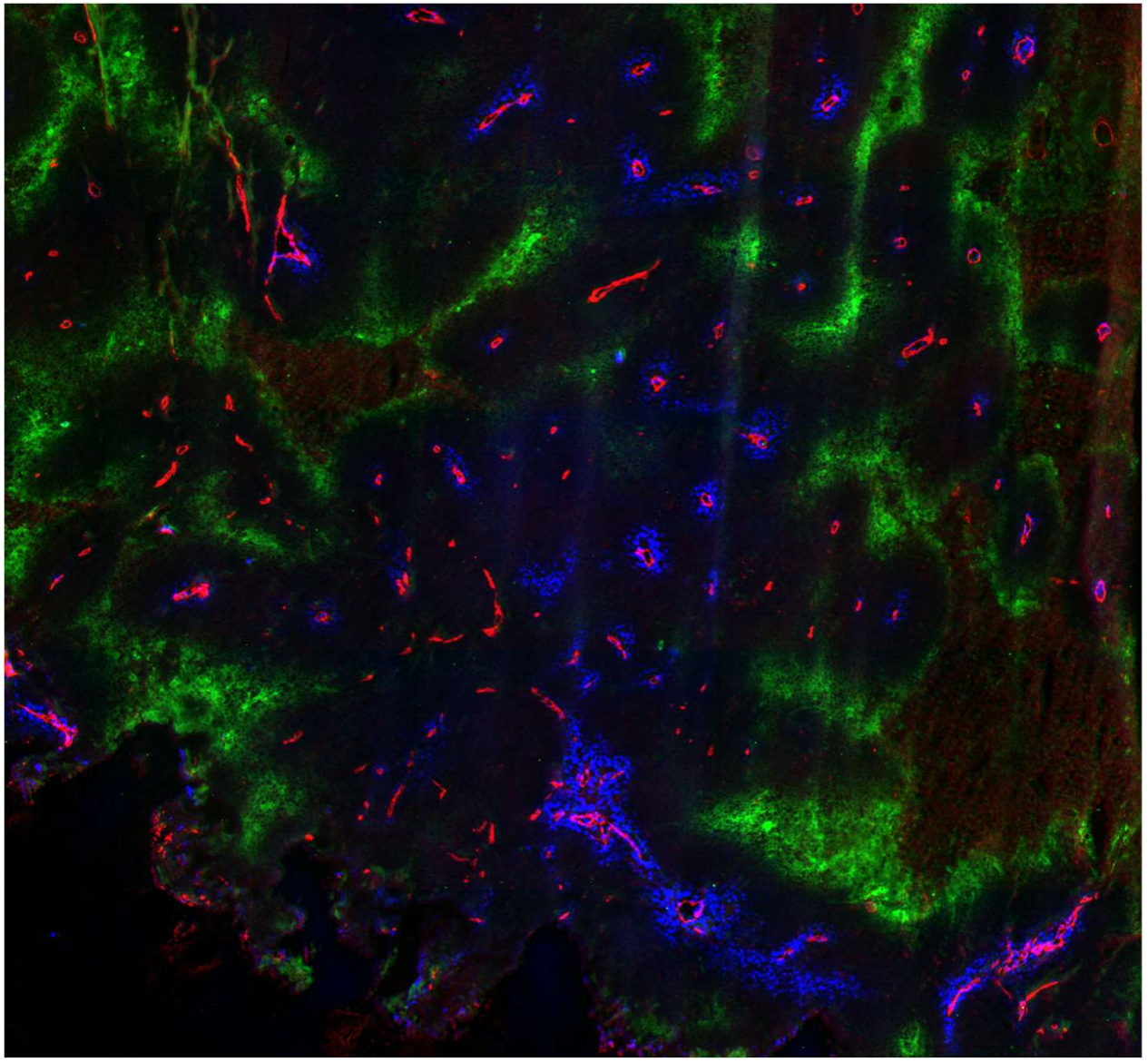


Cell killing by radiation will be reduced as a function of distance from the capillary.

c) Heterogeneity in space



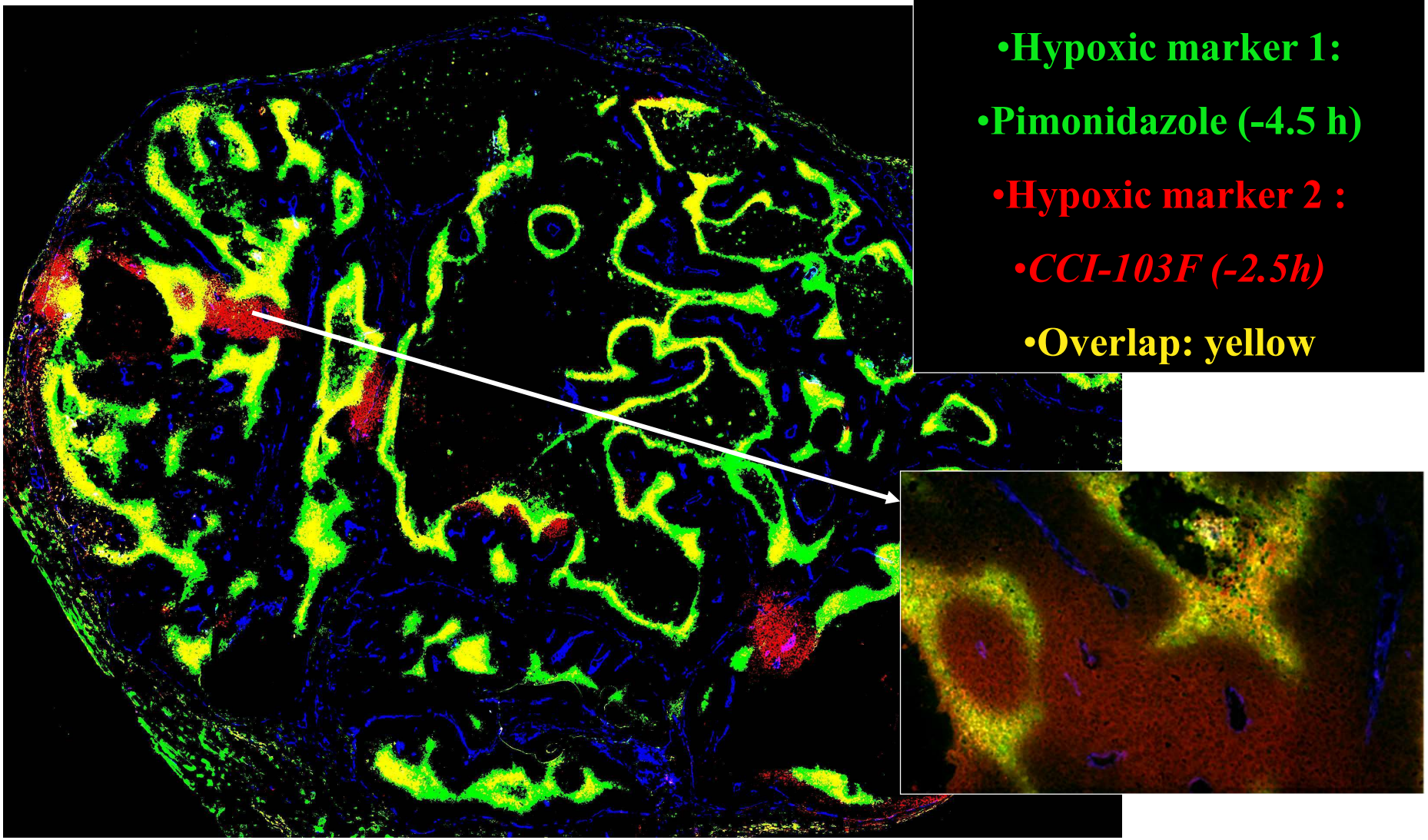
c) Heterogeneity in space



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

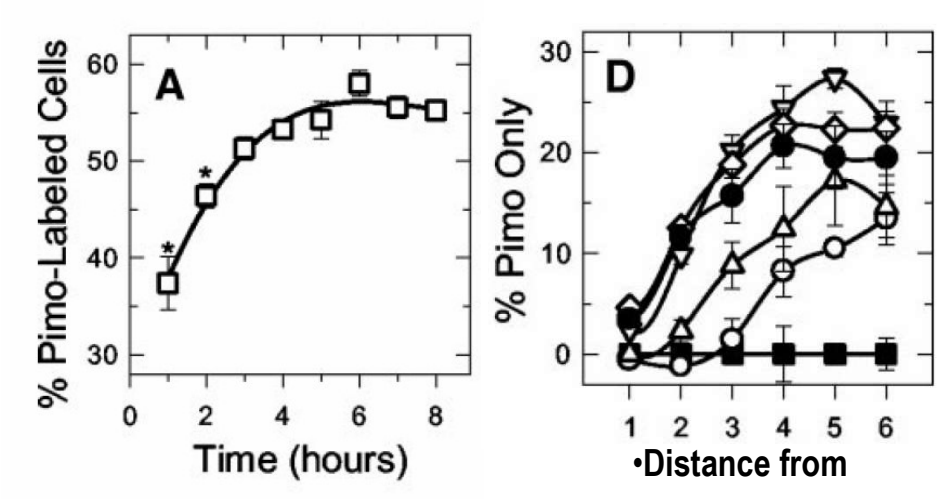
d) Heterogeneity in time

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

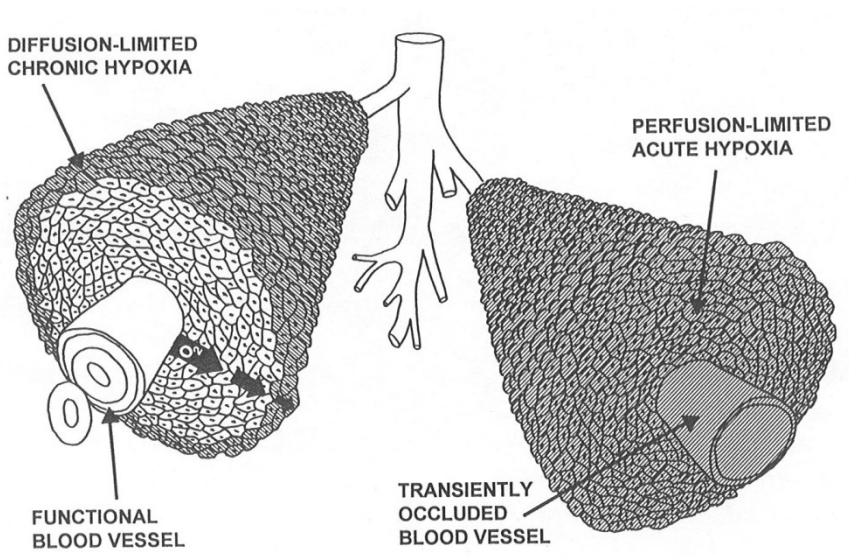
Quantifying Transient Hypoxia in Human Tumor Xenografts by Flow Cytometry

Kevin L. Bennewith and Ralph E. Durand

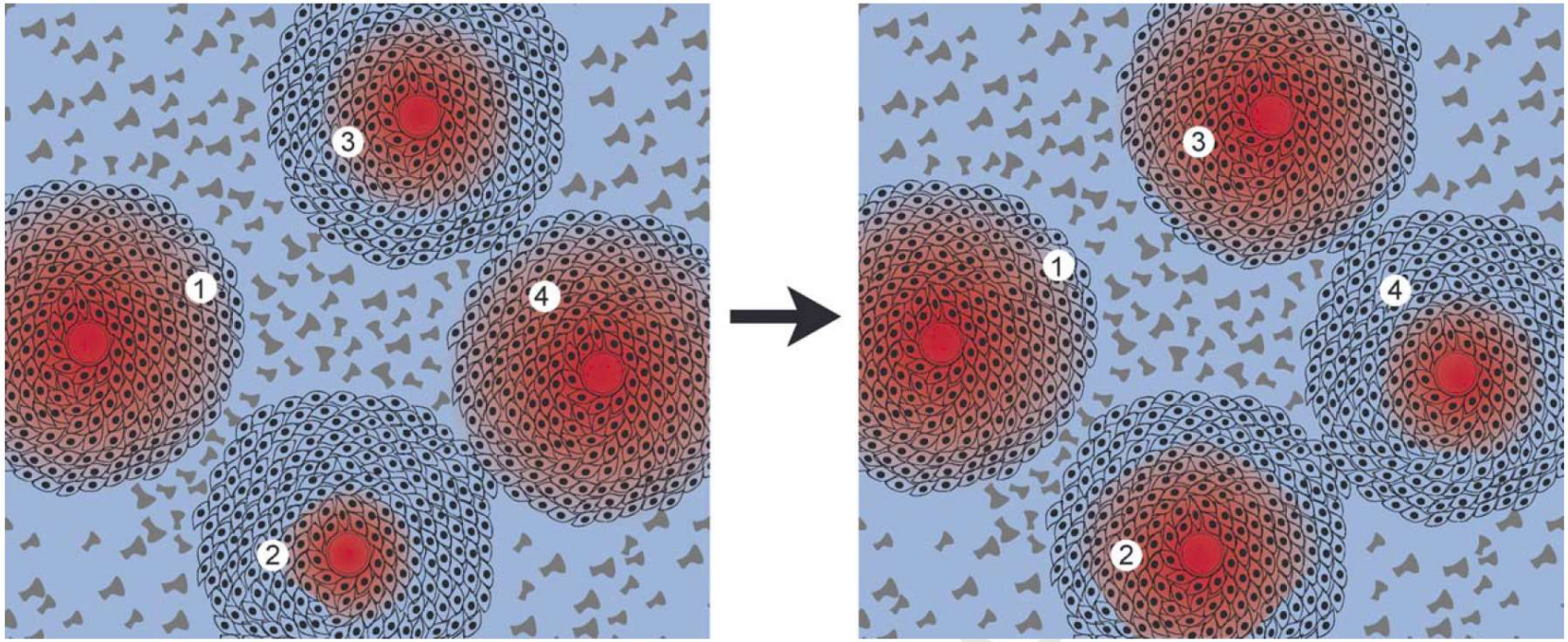
Medical Biophysics Department, British Columbia Cancer Research Centre, Vancouver, British Columbia, Canada



- Distance from
- blood vessel



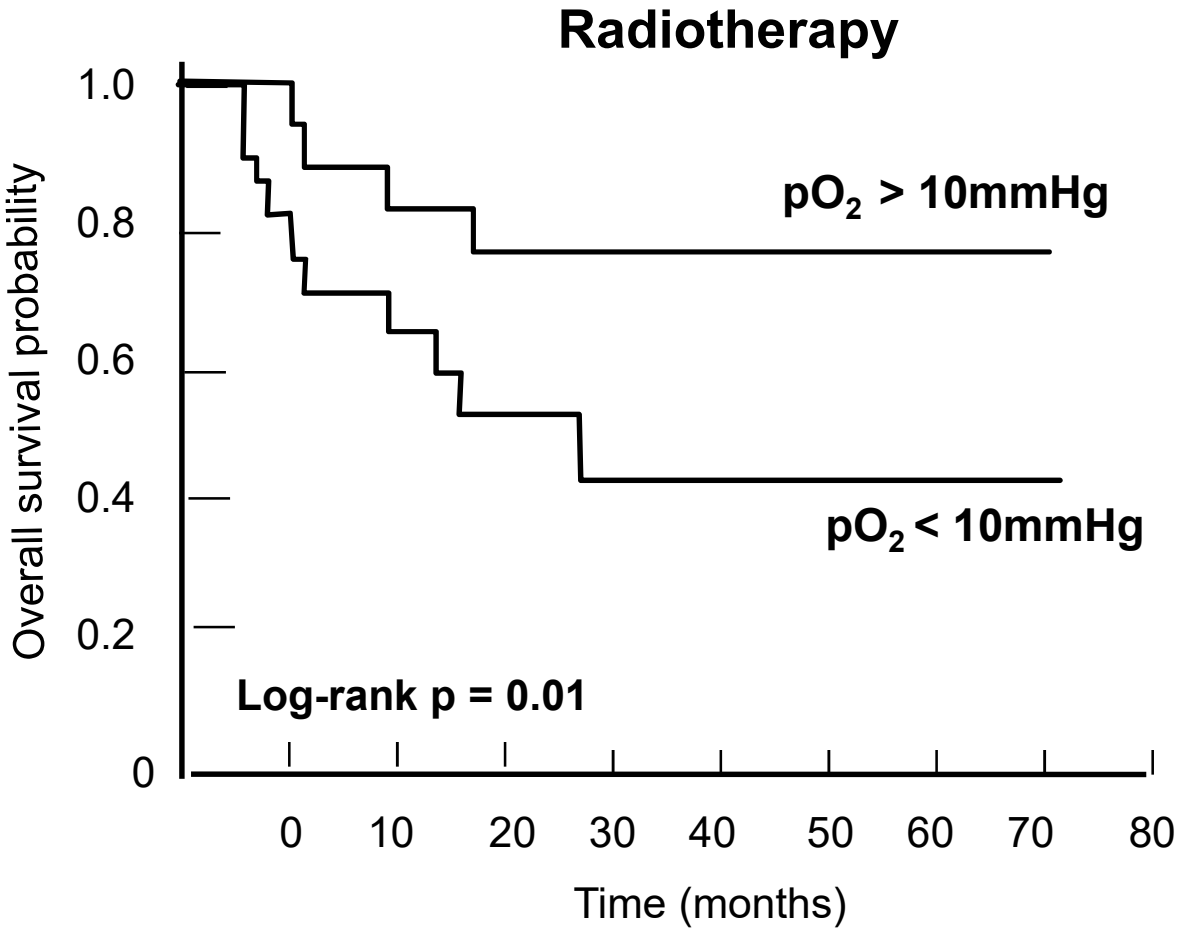
Oxygenation is dynamic



Hypoxic cells vary at every fraction

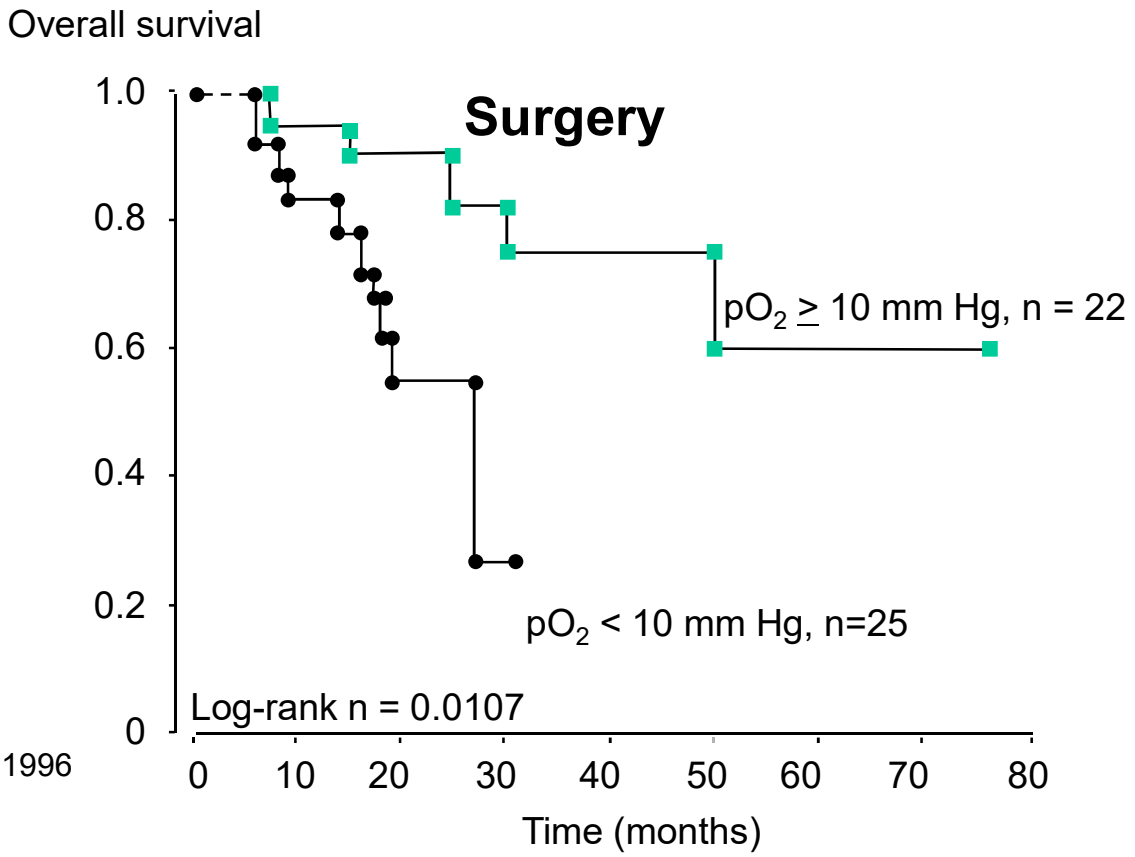
3) Cellular consequences of hypoxia

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

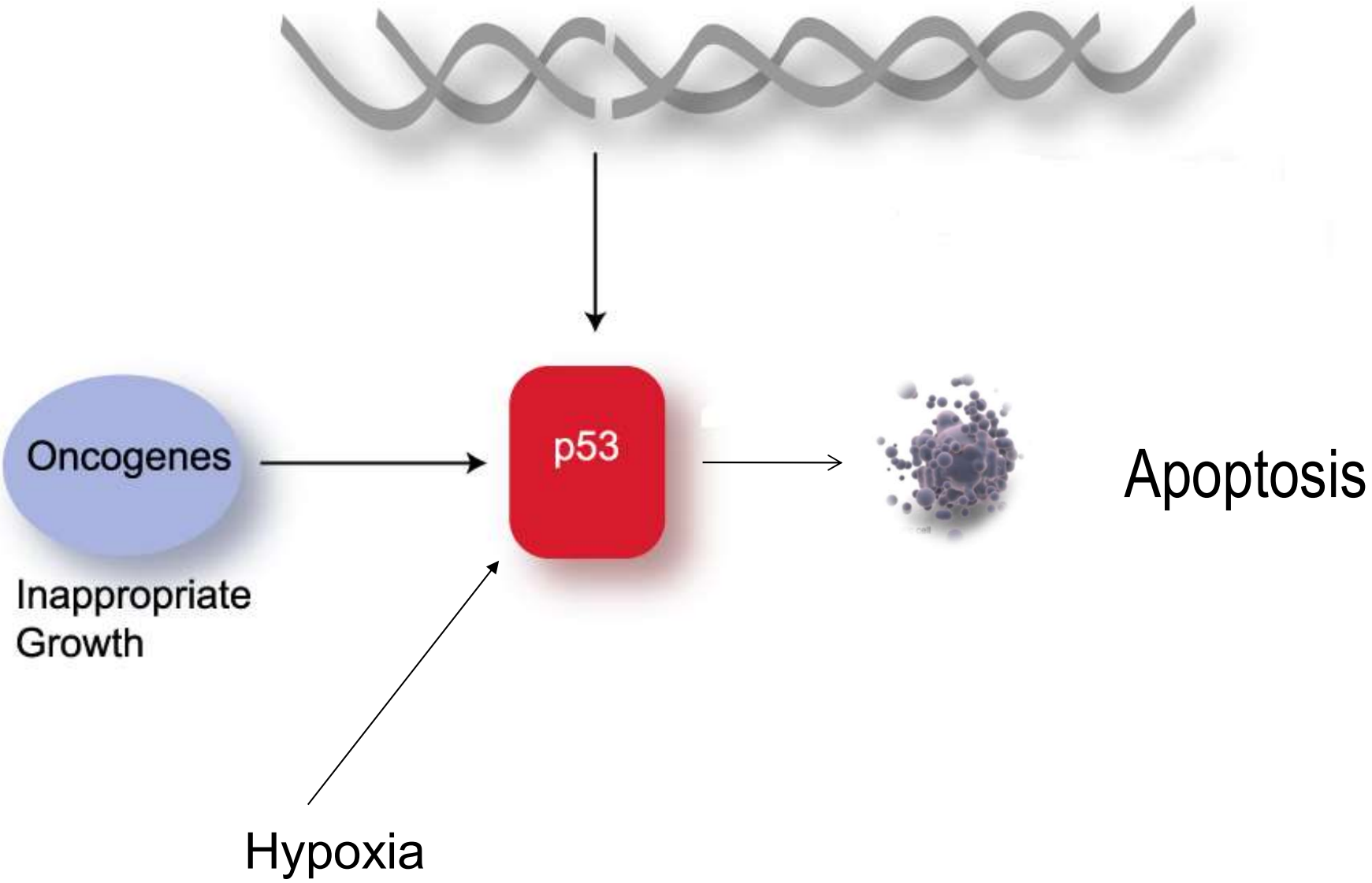
- **Hypoxic tumors are more malignant**
  - Cervix tumors have larger extensions, more frequent parametrial spread, more lymph-vascular space involvement
  - recurrent tumors are more hypoxic than primary tumors
  - predicts for the likelihood of distant metastases in soft tissue sarcomas
  - hypoxia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

Hypoxia and malignancy – mechanisms

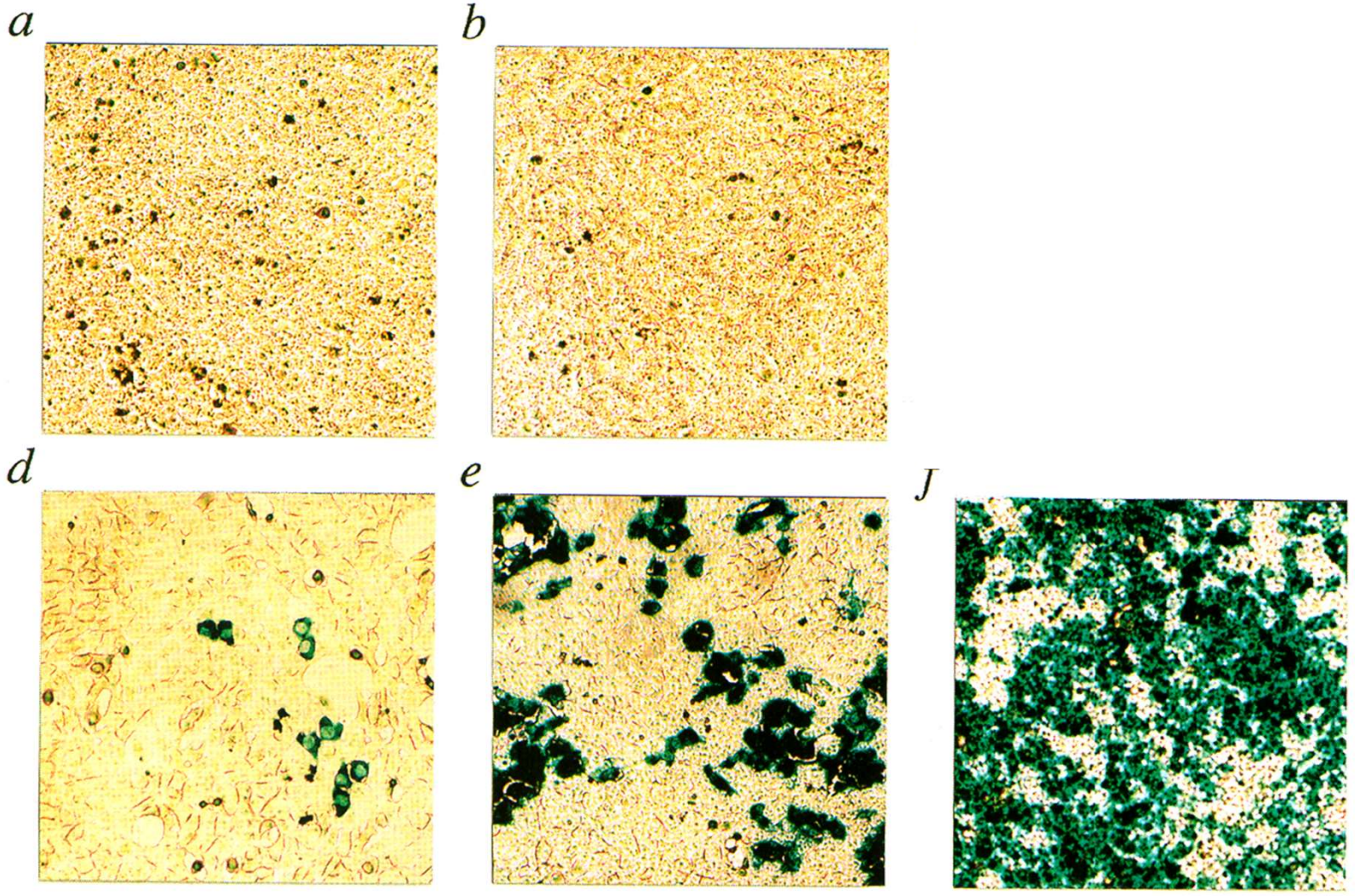
a) Tumor hypoxia can “select” for cells that are more malignant

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

Hypoxia activates p53



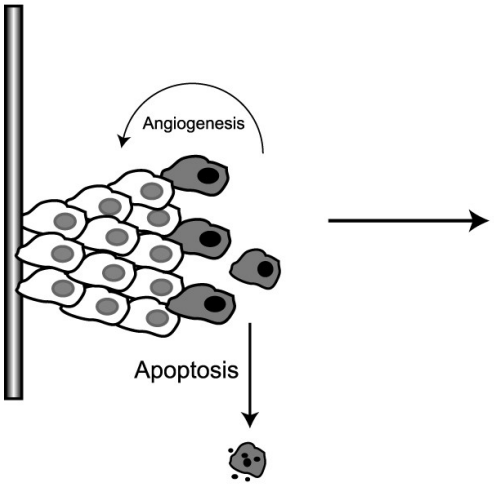
Hypoxia mediated selection of cells



Graeber, Nature 1996

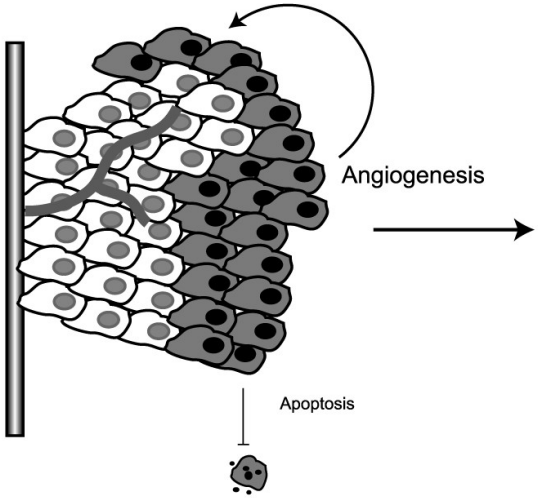
The concept of hypoxia tolerance

Early Cancer - rapid death
transient angiogenic signal



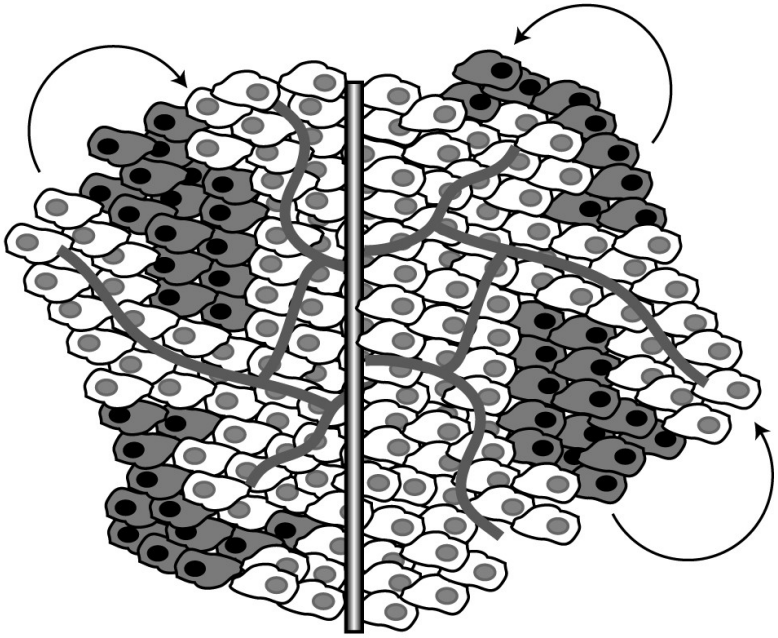
Apoptosis
Loss of energy homeostasis

Hypoxia Tolerance -delayed cell death
sustained angiogenic singal

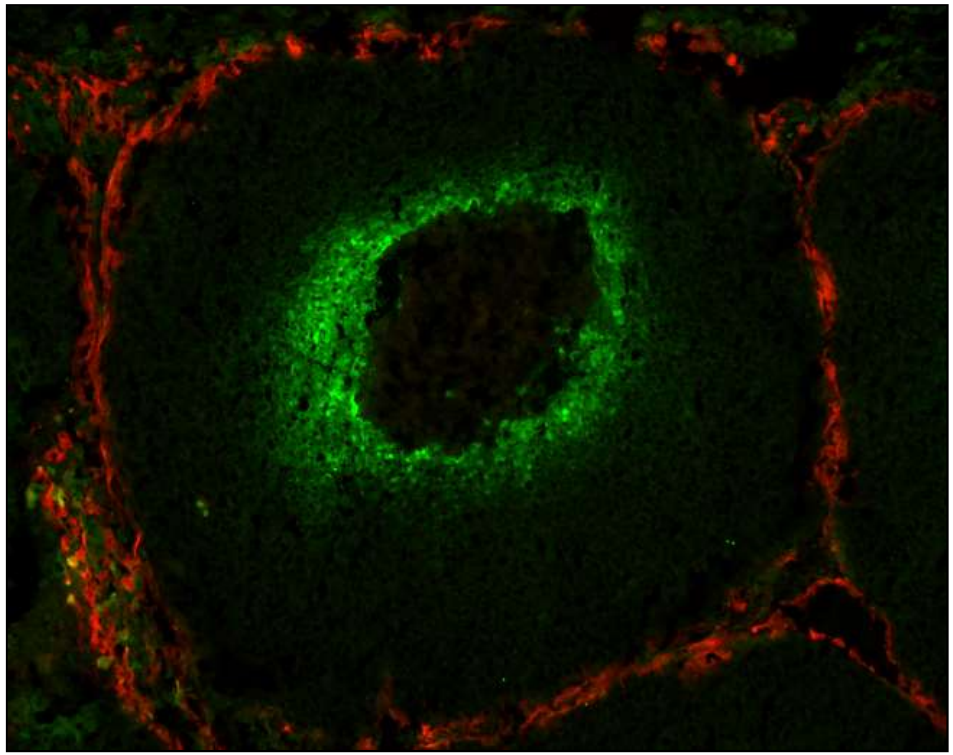


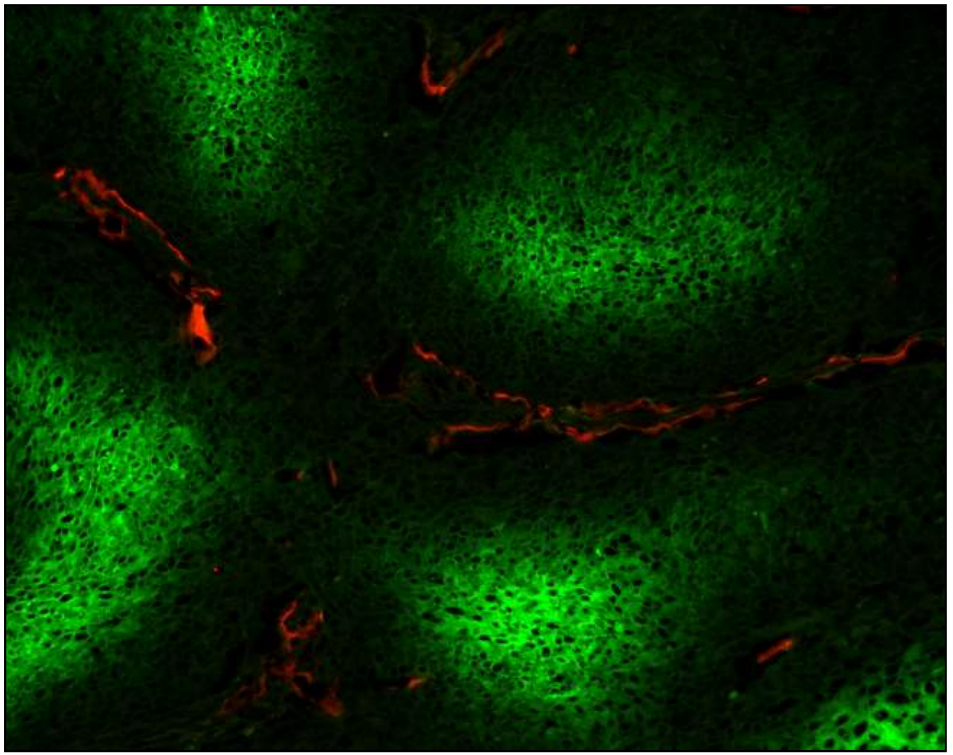
Resistance to apoptosis
Anaerobic glycolysis
Reduced protein synthesis

Mature Tumor - heterogenous hypoxia
sustained angiogenic singals



Hypoxia tolerance varies amongst tumors



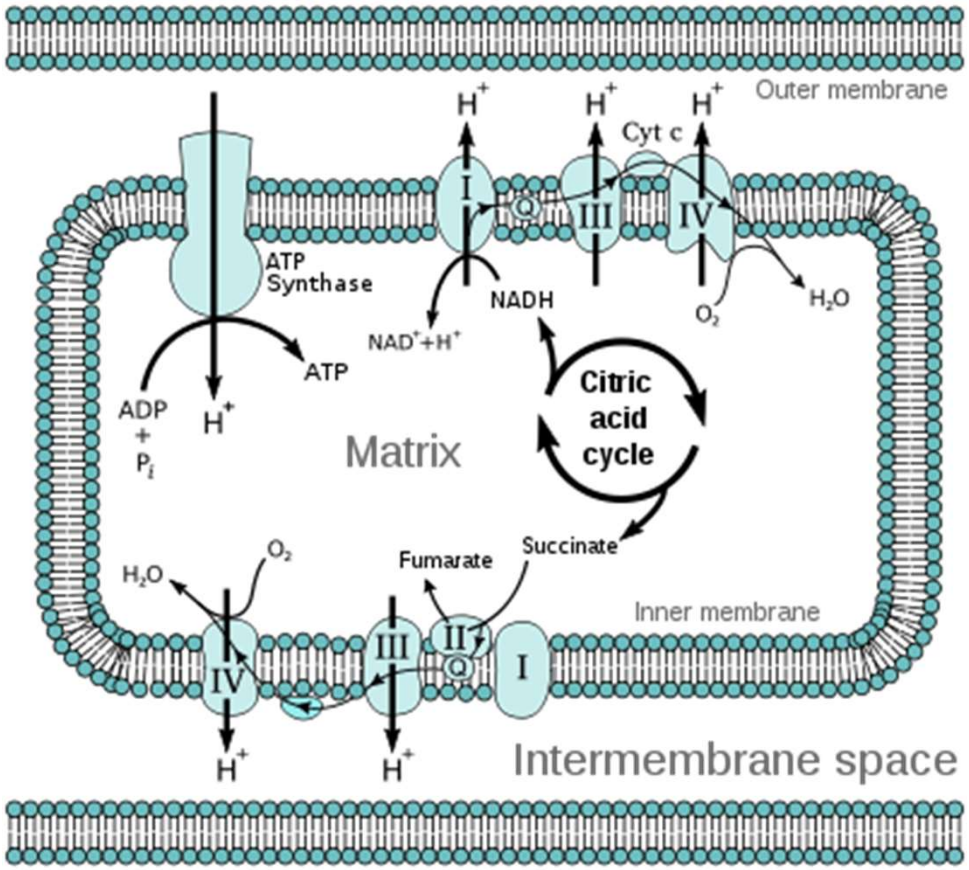


Cellular responses to hypoxia promote malignancy

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

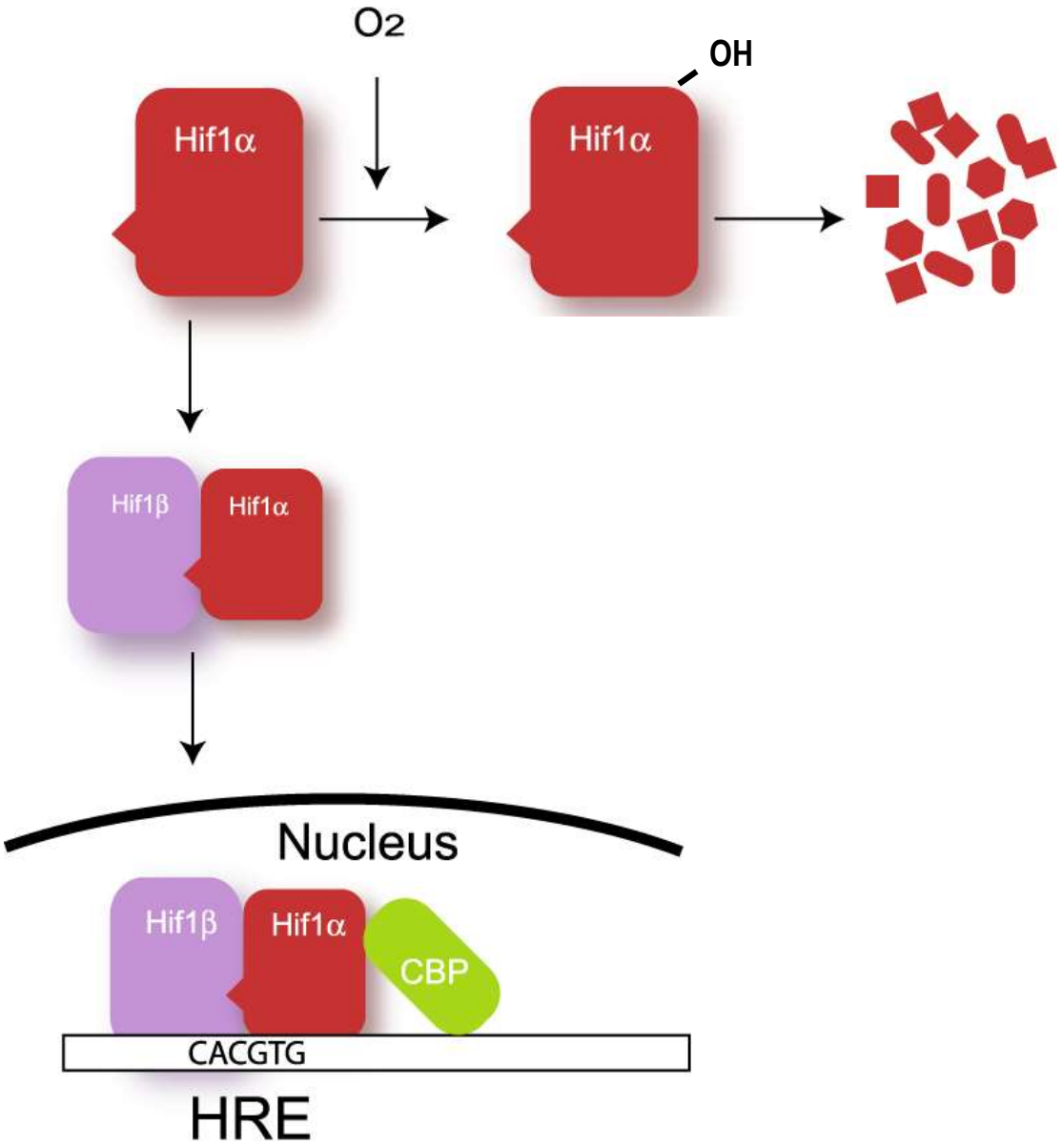
Biological changes are a consequence of altered protein activity and gene expression

Oxygen sensors: cytochrome c oxidase

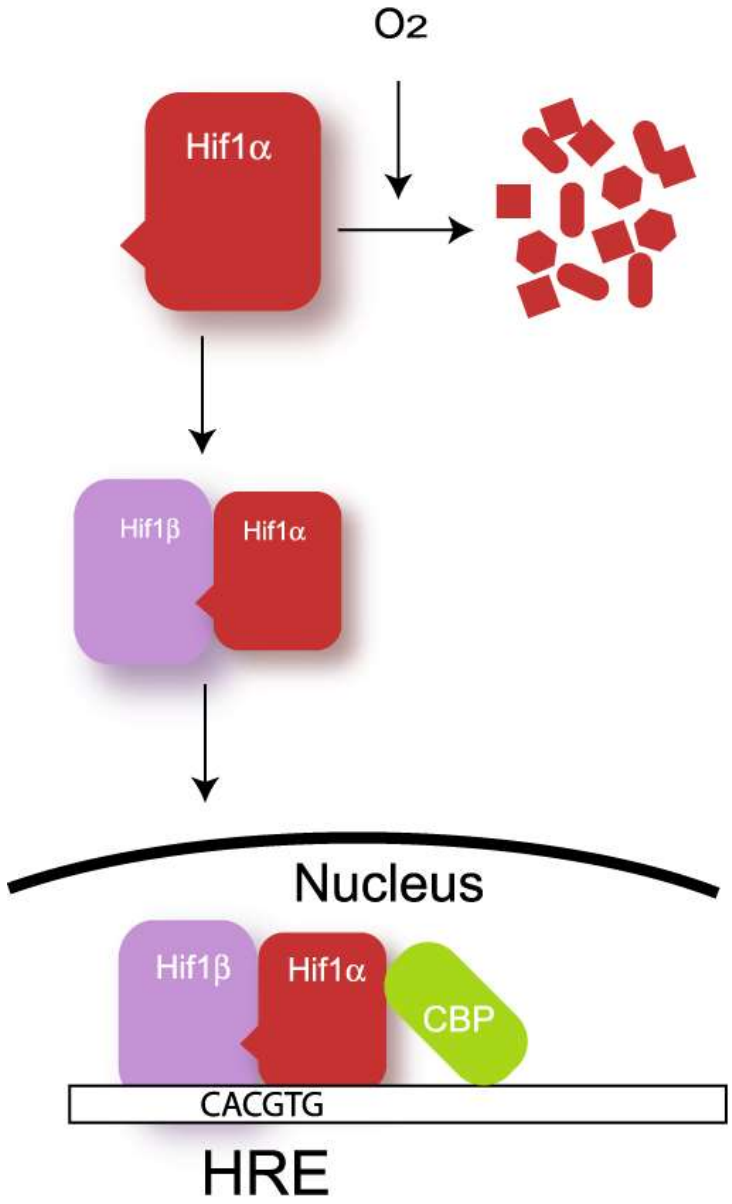


- ~80% oxygen consumption
- Reprogrammed metabolism
- ATP drop
  - Signaling pathways

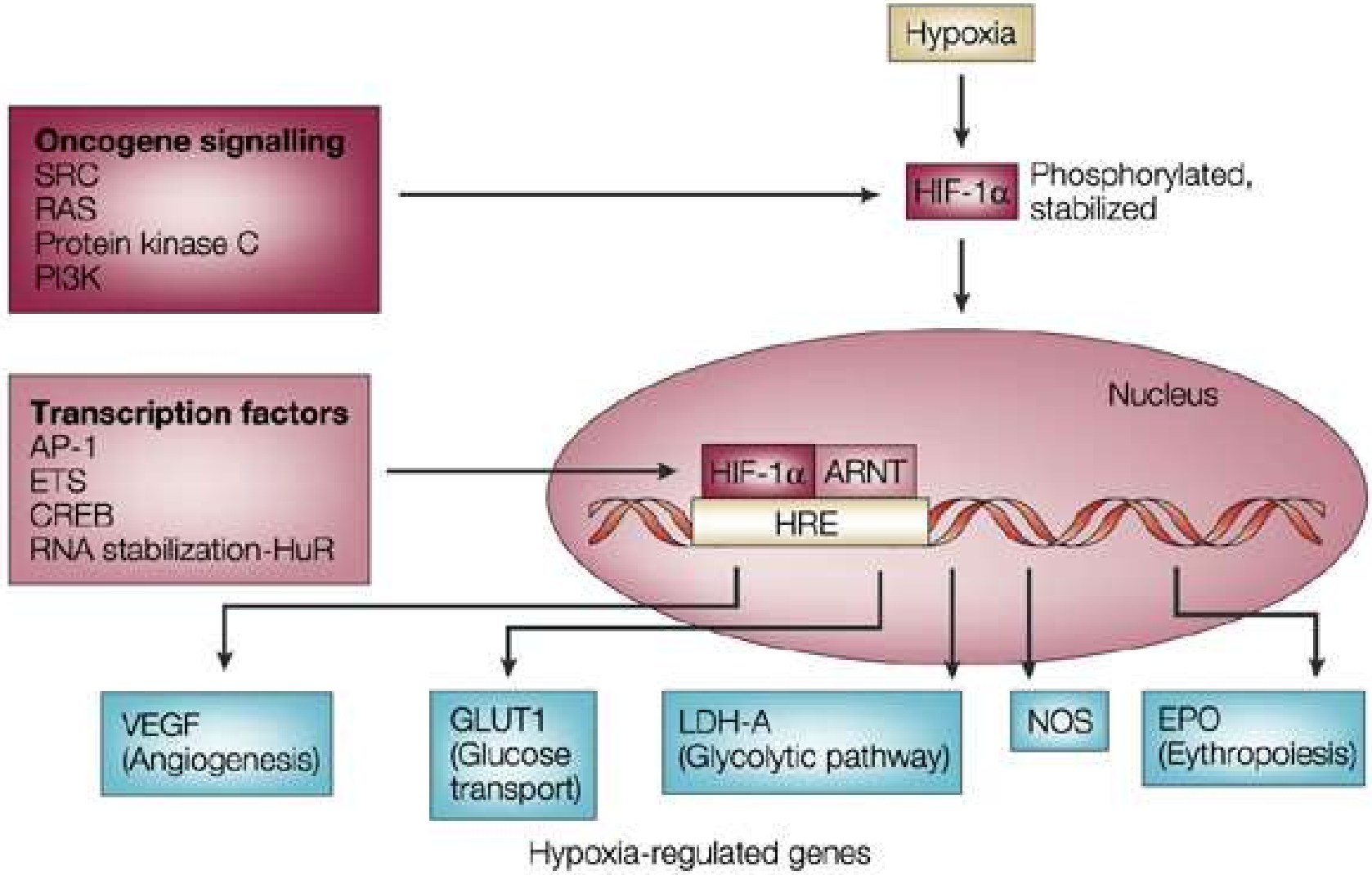
Oxygen sensors: HIF hydroxylases



HIF activation



HIF mediated pathways

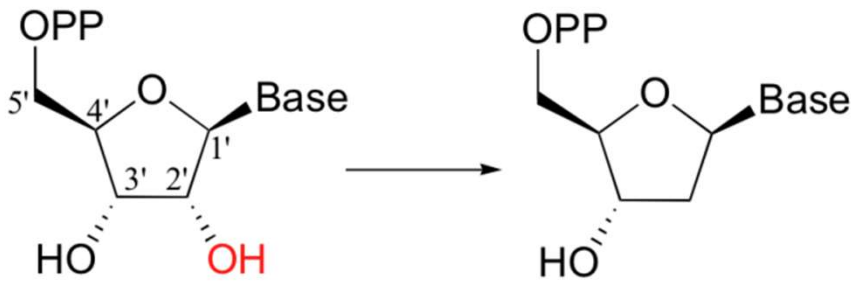


Nature Reviews | Cancer

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

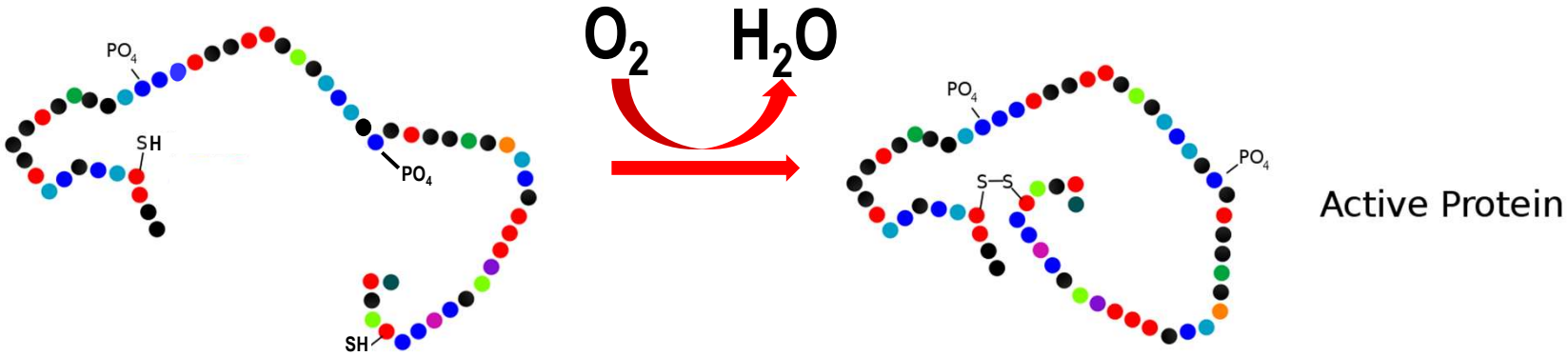


ribonucleotide diphosphate (RNA)

deoxyribonucleotide diphosphate (DNA)

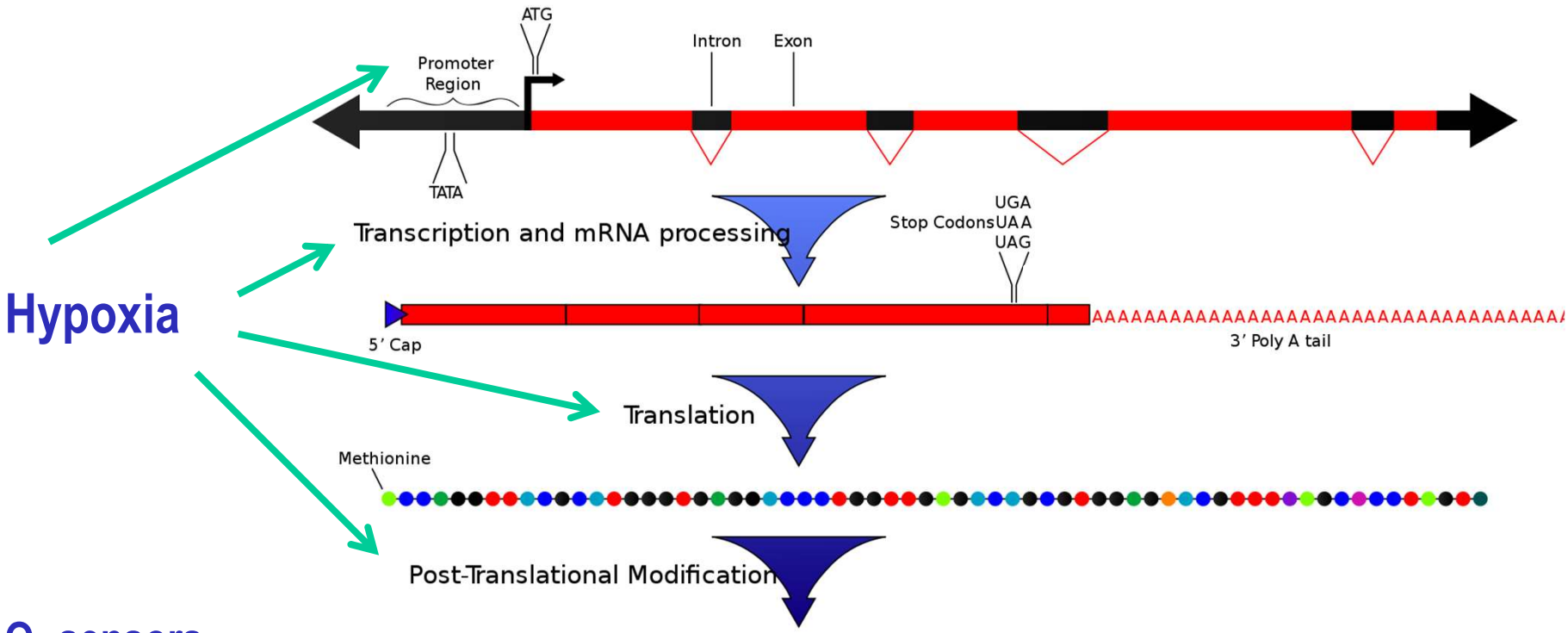
DNA synthesis

Oxygen sensors: disulfide oxidases



"Unfolded protein response"
Transcription
Translation

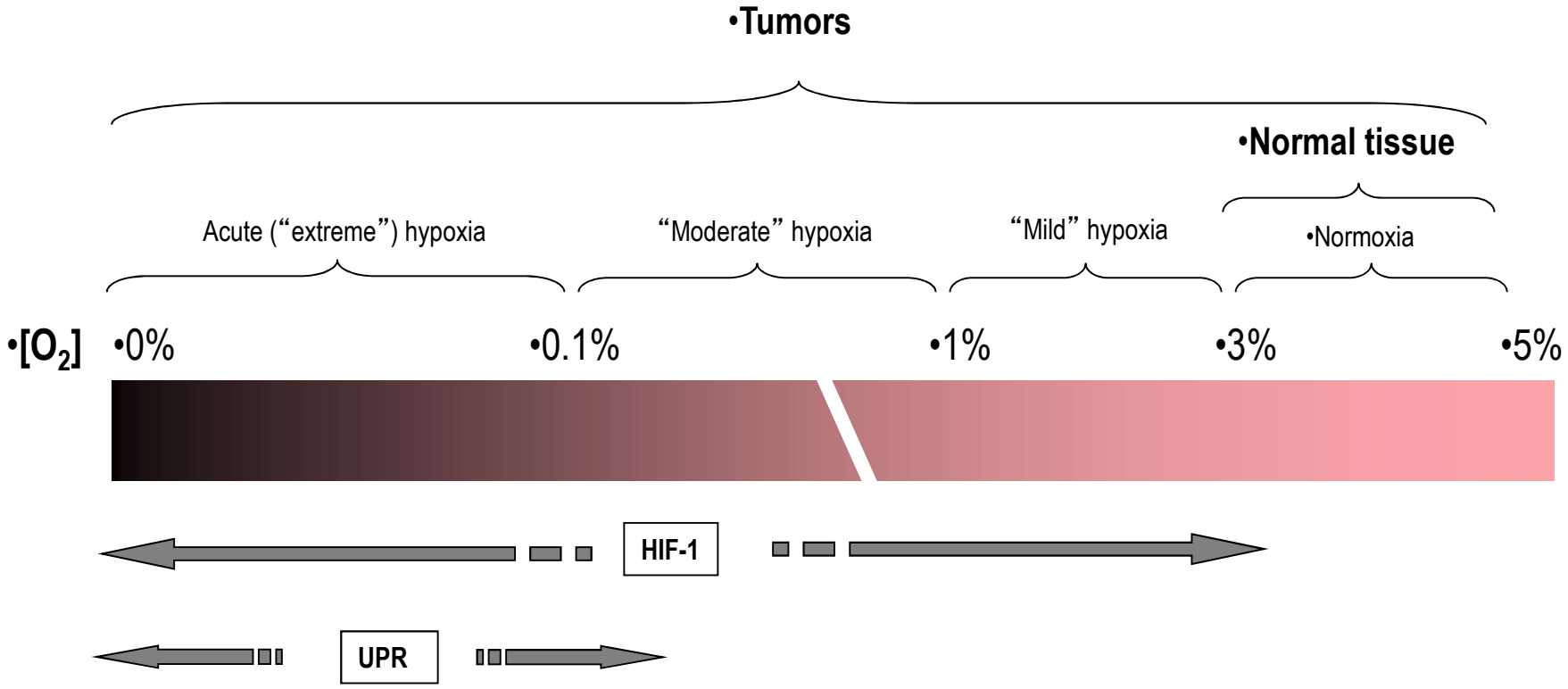
Molecular consequences of hypoxia



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

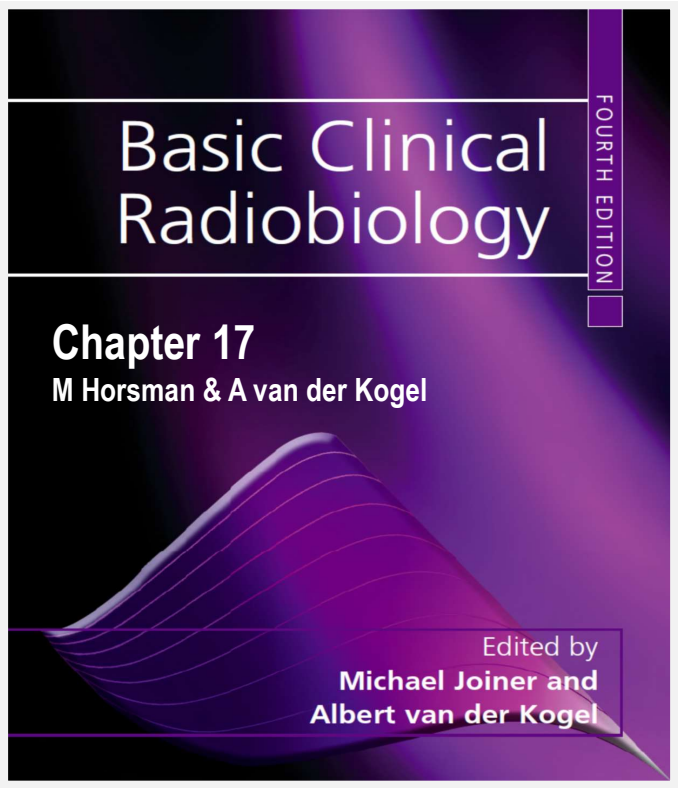
Clinical efforts to modify tumor hypoxia

Karin Haustermans

Department of Radiation Oncology, University Hospitals Leuven, Belgium

Overview

- Raising O_2 content of inspired gas
- Hypoxic cell radiosensitizers
- Increasing haemoglobin
- Overcoming acute hypoxia
- Meta-analysis
- Take home messages



Introduction

- Human tumors are hypoxic

Table 1 | **Oxygenation of tumours and the surrounding normal tissue**

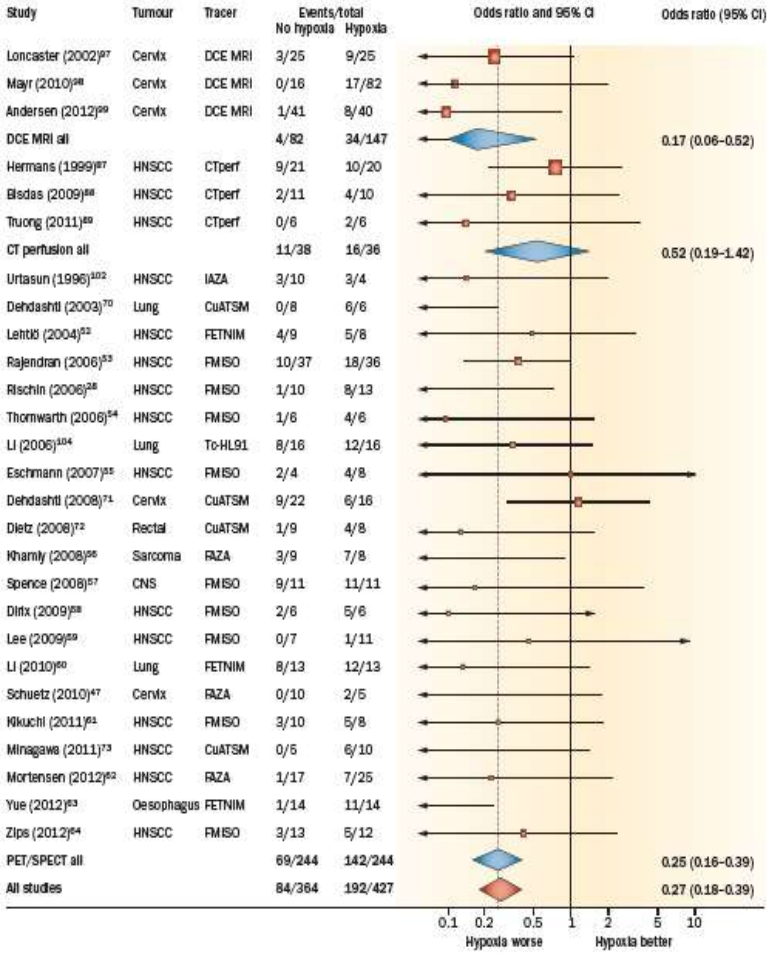
Tumour type	Median tumour pO_2* (number of patients)	Median normal pO_2* (number of patients)	References
Glioblastoma	4.9 (10) 5.6 (14)	ND ND	128 129
Head and neck carcinoma	12.2 (30) 14.7 (23) 14.6 (65)	40.0 (14) 43.8 (30) 51.2 (65)	130 131 132
Lung cancer	7.5 (17)	38.5 (17)	Q. Le (personal communication)
Breast cancer	10.0 (15)	ND	133
Pancreatic cancer	2.7 (7)	51.6 (7)	134
Cervical cancer	5.0 (8) 5.0 (74) 3 (86)	51 (8) ND ND	135 136 137
Prostate cancer	2.4 (59)	30.0 (59)	138
Soft-tissue sarcoma	6.2 (34) 18 (22)	ND ND	139 140

*$p0_2$ measured in mmHg. Measurements were made using a commercially available oxygen electrode (the 'Eppendorf' electrode). The values shown are the median of the median values for each patient. ND, not determined; pO_2, oxygen partial pressure.

Brown J. & Wilson W. Nat Rev Cancer 2004

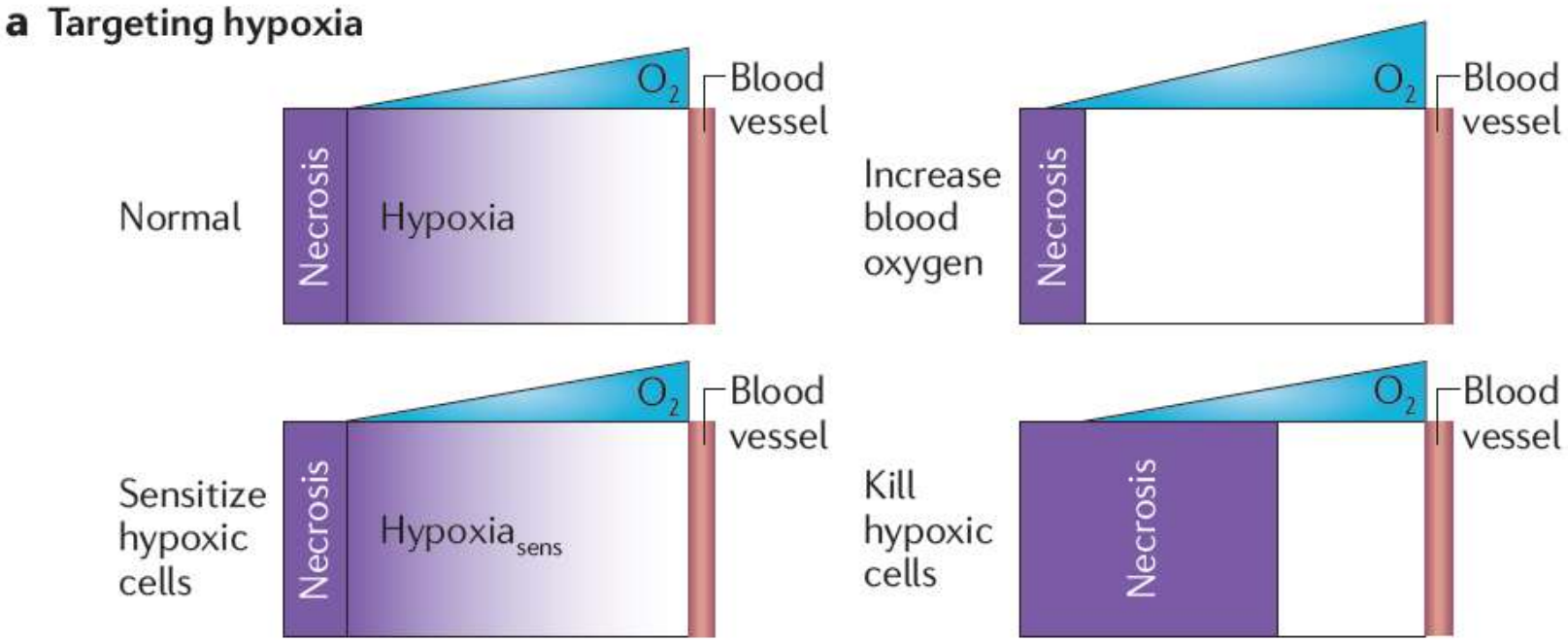
Introduction

- Hypoxia = worse outcome to radiotherapy



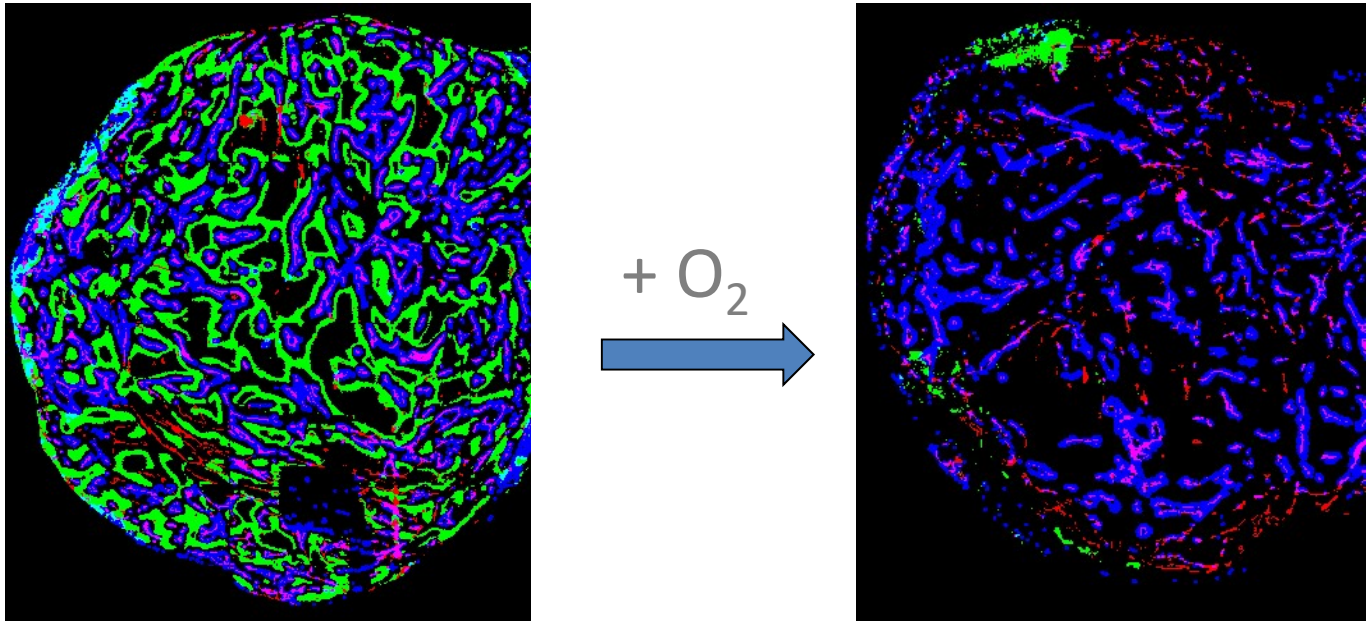
Horsman et al, Nat Rev Clin Oncol 2012

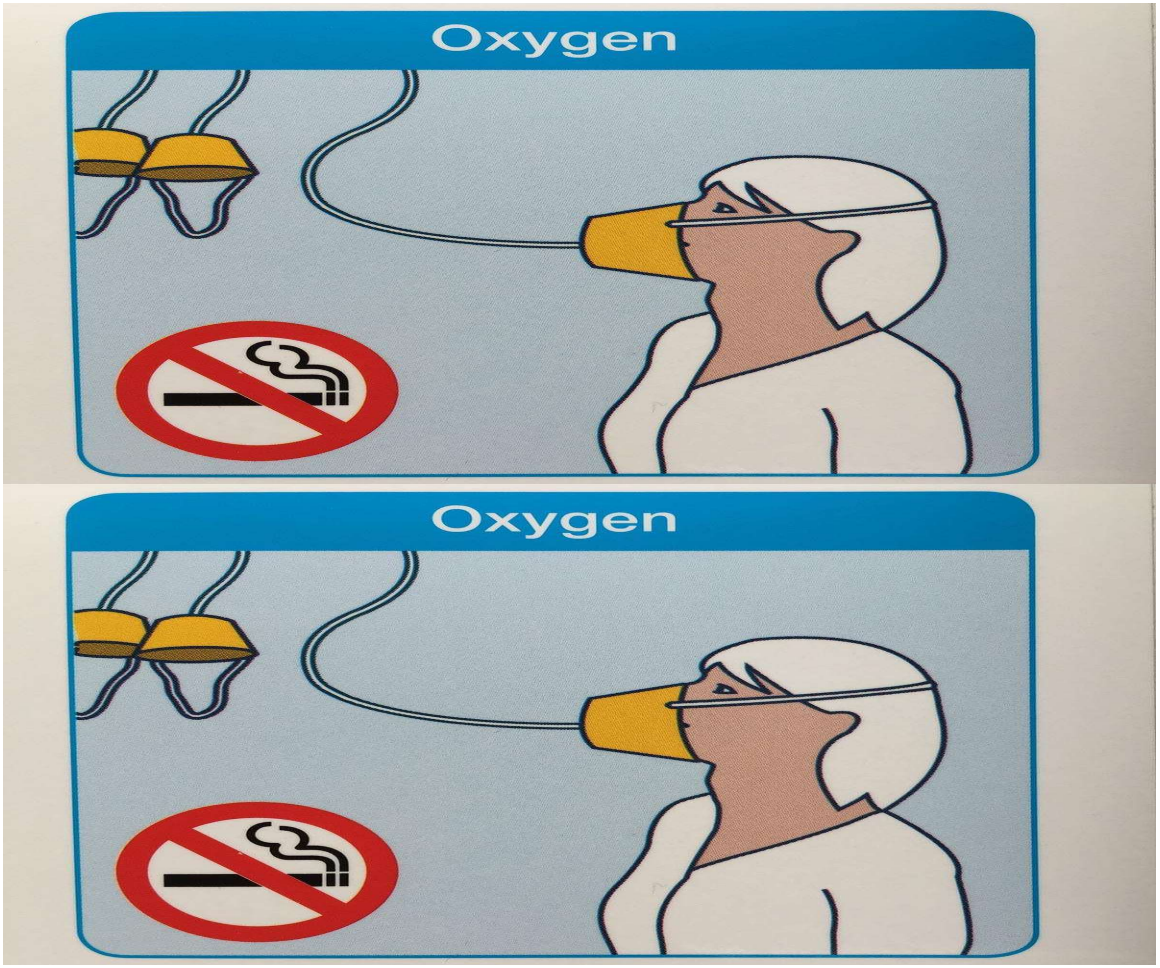
Introduction



Begg et al, Nat Rev Cancer 2011

Introduction

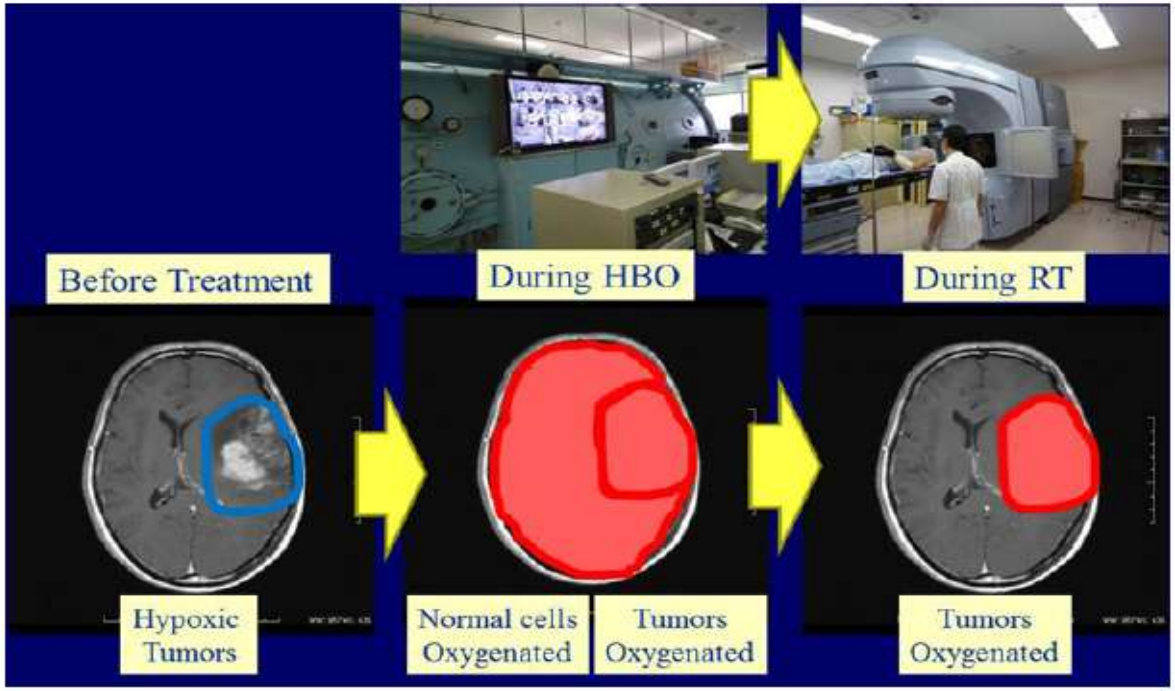




Raising O2 content of inspired gas

Hyperbaric oxygen (HBO) therapy

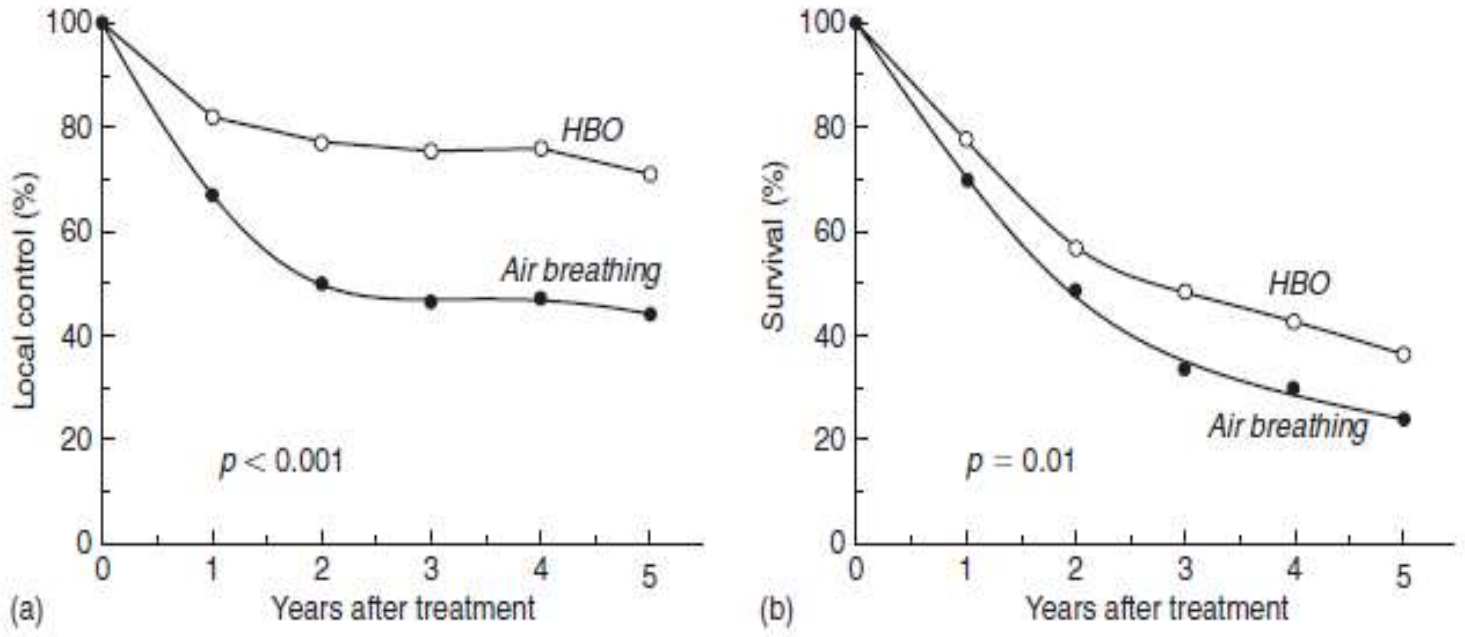
- An increase in the barometric pressure of the gas breathed by the patient during radiotherapy



Ogawa et al Int J Clin Oncol 2013

Hyperbaric oxygen (HBO) therapy

- MRC HBO trial – pts with stage III cervical cancer



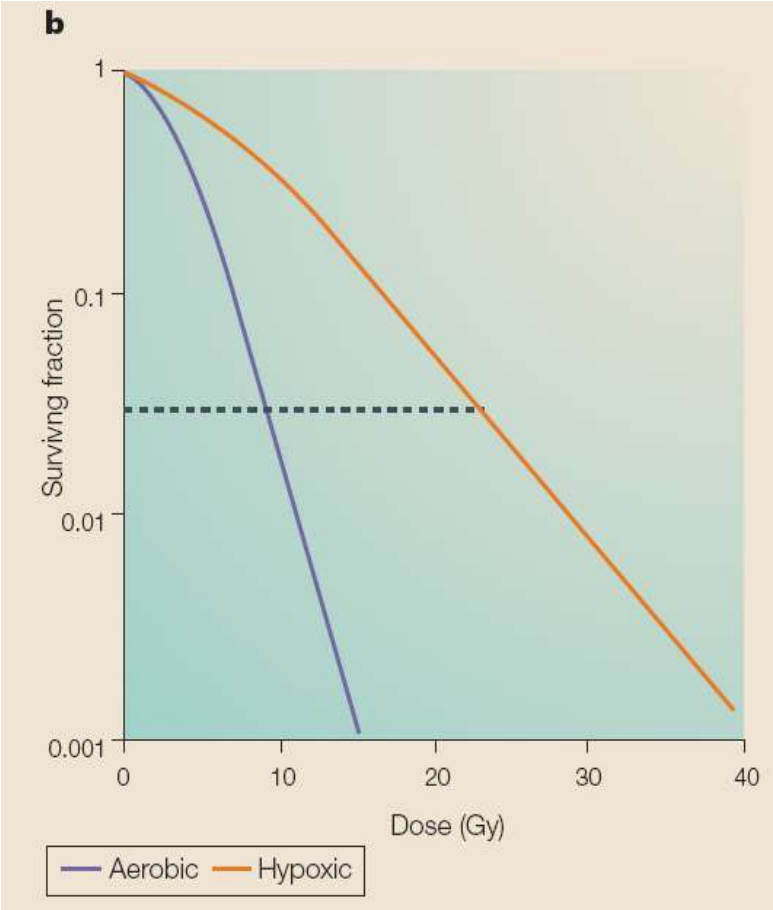
Basic Clinical Radiobiology – From Watson et al 1978

HBO 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	Endpoint[b]					Obs. time
[21]	van den Brenk	1968	30	HH	7.75 Gy x4vs7.25 Gy x4 with HBO	HBO 4 atm	L	D	S			2 + years
[22]	Evans 1	1970	40	LL	60 Gy/30 fx	Normobaric 02	L	D	S			2 + years
[23]	Tobin	1971	17	LL	60 Gy/30 fx	HBO 3 atm	L	D	S			2–3 years
[24]	Chang	1973	51	HHL	6 Gy x6+ HBO vs 6 Gy x7 or 60 Gy/30 fx	HBO 3 atm	L	D	S	M	C	5 years
[25]	Shigamats u	1973	31	HH	60–79 Gy/10 fx vs. 40–50 Gy/8–10 fx + HBO	HBO	L	D	S			2 + years
[26]	Evans 2	1975	44	LL	60 Gy/30 fx	Normobaric 02	L	D	S	M	C	2 + years
[27]	MRC 1 trial	1977	276	HH	35–45 Gy x10	HBO 3 atm	L	D	S	M	c	4 + years
[26]	MRC 3, trial	1979	24	HL	45–50/15 el 48.5–55/20 air vs. 40–45/10 HBO	HBO	L	D	S		c	5 years
[29]	RTOG 70-02	1979	254	LL	60–70 Gy/30 fx	Carbogen	L	D	S	M	c	2 + years
[30]	Sause	1979	44	HL	48 Gy/12 fx + HBO vs. 62 Gy/25 fx	HBO 3 aim	L	D	S		c	2 + years
[31]	Giaux	1962	56	II	50 Gy/16 fx	MISO	L	D	S			34 months
[32]	Sealy 1	1962	97	HH	36 Gy/6 fx/17 days	MISO	L					>1 year
[33]	B run in	1963	101	LL	72 Gy/36 fx	MISO	L	D	S			2 years
[34]	MRC 10 fx	1964	162	HH	40–45 Gy/10 fx	MISO	L	D	S		c	3 + years
[34]	MRC 20 fx	1964	89	LL	50–57 Gy/20 fx	MISO	L	D	S			3 + years
[35]	Panis	1964	52	MM	Split-course 1.1 Gy x6 daily/ 5 days – 4 weeks split-repeat	MISO	L	D	S		c	2 + years
[36,37]	EORTC 22S111	1966	330	MM	1.6 Gy x3/10 days – 3 weeks split + same to total of 67–72 Gy	MISO	L	D	S		c	5 + years
[38,39]	MRC 2, trial	1966	103	HL	64 Gy/30 fx vs. 41–44 Gy/10 fx + HBO	HBO 3 aim	L	D	S	M	c	4 + years
[40]	Sealy 2	1966	124	HL	63 Gy/30 fx (air); 36 Gy/6 fx (HBO)	HBO/MISO	L	D	S	M	c	1–2-year
[41,42]	IAEA study	1967	36	LL	70 Gy/35 fx	On ids zo e	L	D	S		c	2 + years
[43,44]	RTOG 79-15	1967	297	LL	66–74/33–37 fx	MISO	L	D	S	M	c	2 + years
[45]	Galecki	1969	35	LL	70 Gy/35 fx vs. 66 Gy/30 fx vs. 80.5 Gyx 70 fx	Metronidazole	L	D	S		c	3 + years
[46]	Dahanca 2	1969	622	LL	68-72/34–36 fx eller 61/22/9.5 weeks	MISO	L	D	S	M	c	5 + years
[47]	RTOG 79-04	1969	40	HH	4 Gy 11–13 fx	MISO	L	D	S		c	2 + years
[48]	RTOG 8S-27	1995	504	LL	66–74 Gy/33–37 fx	Etanidazole	L	D	S	M	c	5 + years
[49]	Huilgol	1996	18	LL	54 Gy/45 fx/22 days	AK-2123	L	D	S			2 + years
[50]	European trial	1997	374	LL	66–74 Gy/33–37 fx	Etanidazole	L	D	S		c	5 + years
[51,52]	Dahanca 5	1998	414	LL	66–68/33–34	Nimorazole	L	D	S	M		5 years
[53]	Haffty	1999	48	HH	12.65 Gy x2 vs. 11.50 Gy x2 + HBO	HB04 atm	L	D		M	c	5 + years
[54]	Mendenhall	2005	101	MM	76 Gy/1.2 Gy fx BID	02 Carbogen	L	D	s	M		5 + years
[55]	Ullal	2006	46	LL	60 Gy/30 fx	AK-2123	L					3 + months
[56]	ARCON	2010	345	LL	64–68 Gy/32–34 fx accelerated fx	Nicotinamide	L	D	s			2 years

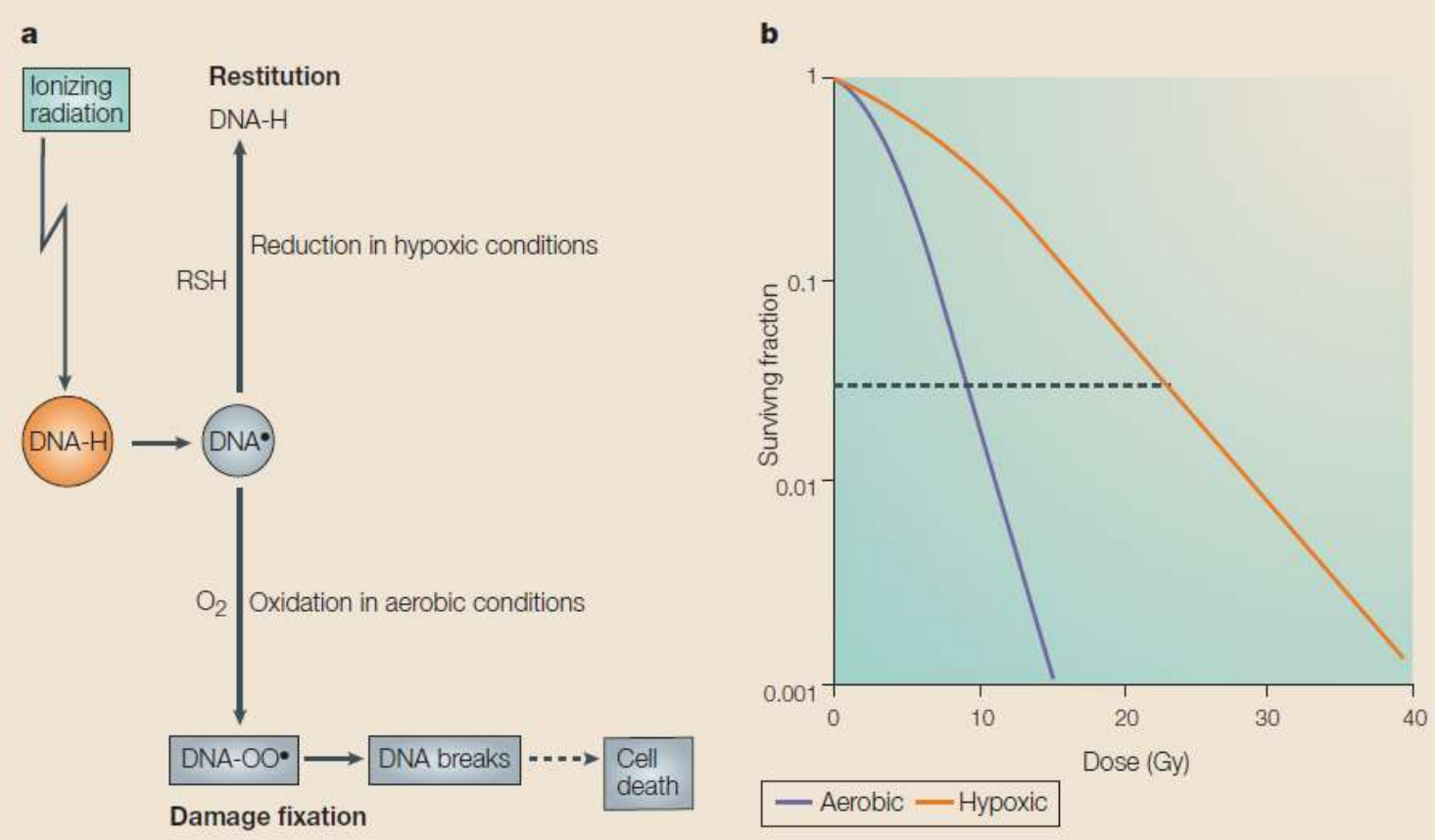
[a] H: Hypofract; L: conventional tract; M: hyperfract (multiple fx/day).
[b] L: Loco-regional failure; D: disease specific death; S: overall death; M: distant metastasis; C: complications.



Hypoxic cell radiosensitizers

Radiosensitization

- Oxygen enhancement ratio

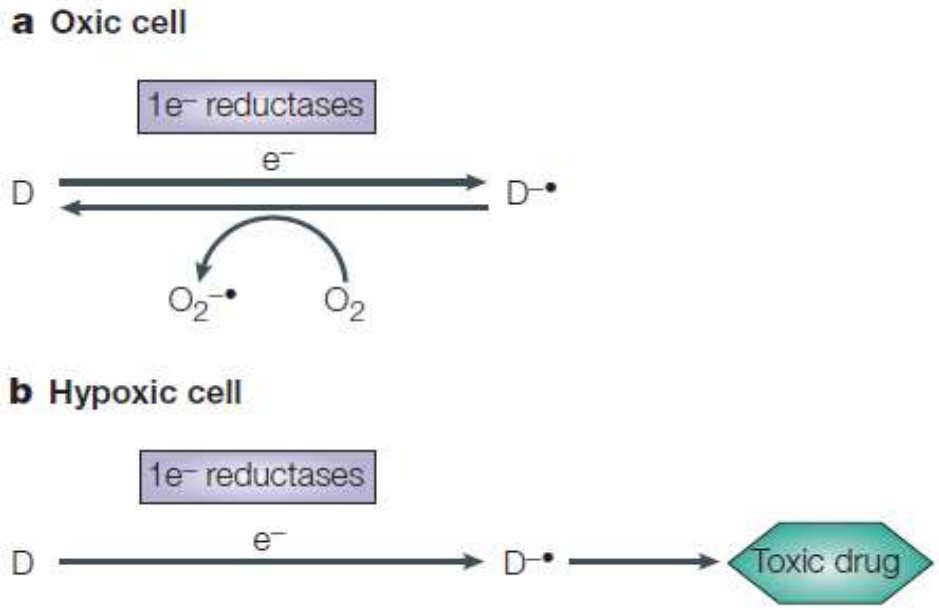


Brown J. & Wilson W. Nat Rev Cancer 2004

Bioreductive drugs

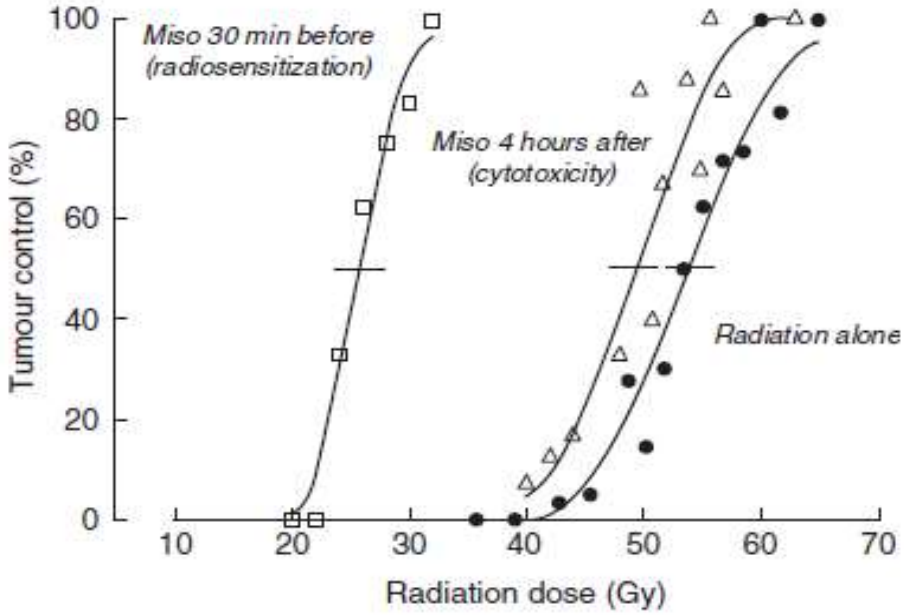
- Chemical radiosensitization of hypoxic cells by mimicking the effect of oxygen
- Nitroimidazoles

Brown J. & Wilson W. Nat Rev Cancer 2004



Hypoxic cell radiosensitizers

- Most potent is 2-nitroimidazole, misonidazole



Basic Clinical Radiobiology

DAHANCA trials

- Nimorazole in Danish HNSCC studies

Overgaard J

DAHANCA trials

- DAHANCA 5 (1986-90; 414 pts)

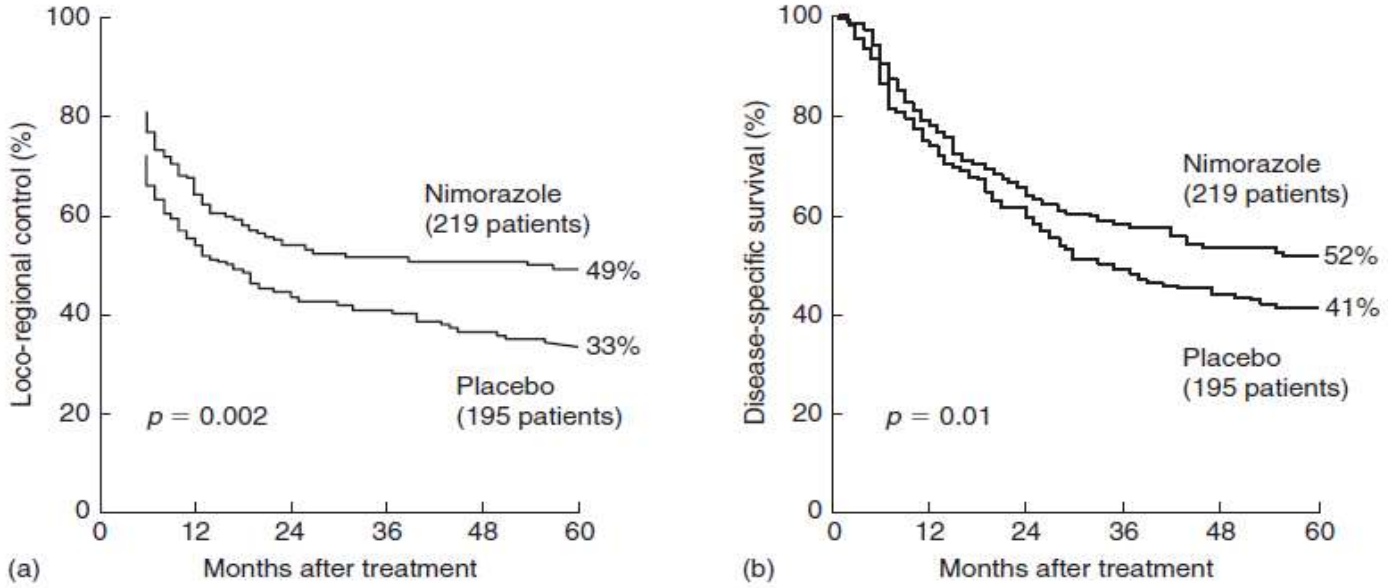
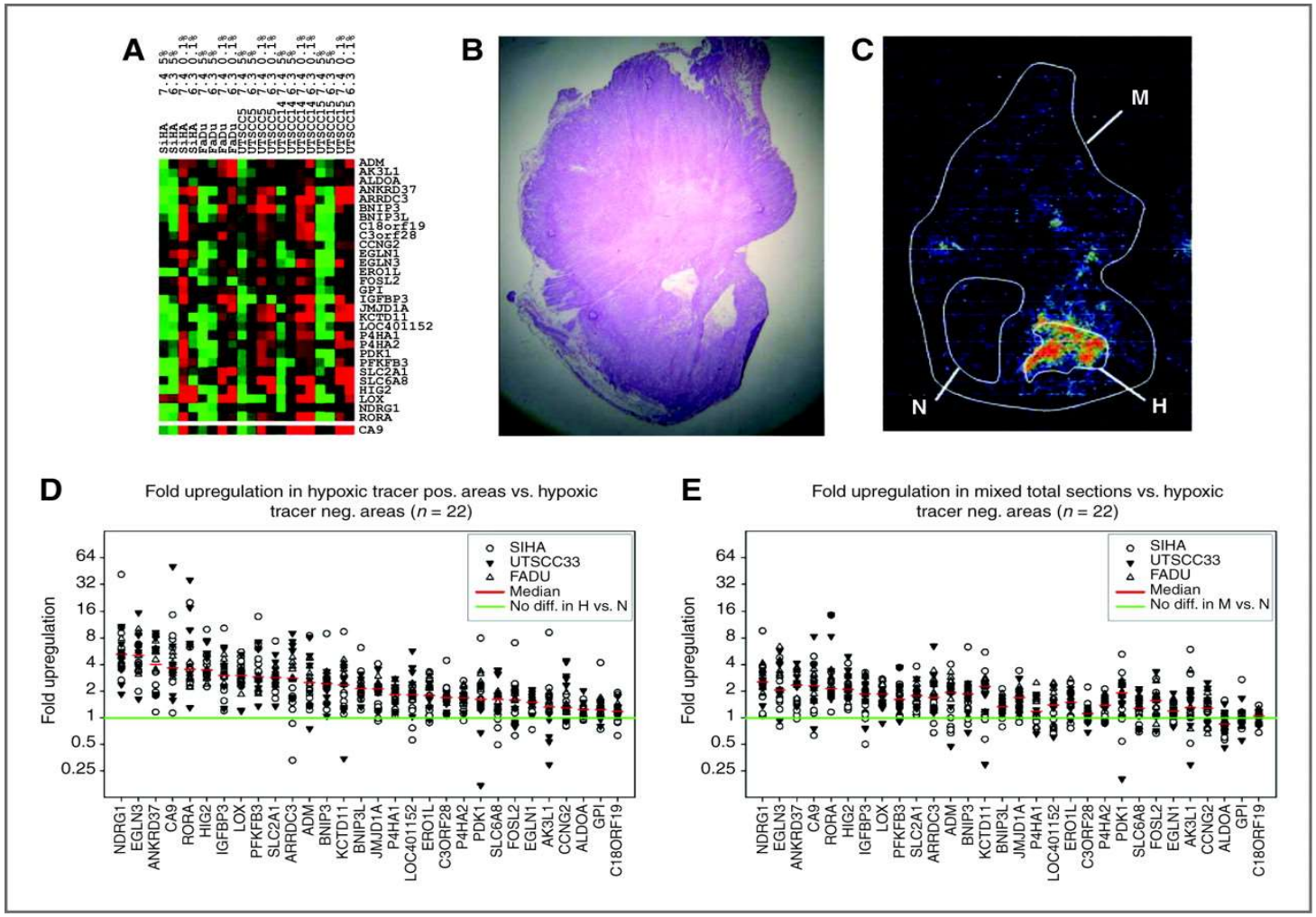


Figure 17.5 Results from the DAHANCA 5 study showing (a) actuarial estimated loco-regional tumour control and (b) disease-specific survival rate in patients randomized to receive nimorazole or placebo in conjunction with conventional radiotherapy for carcinoma of the pharynx and supraglottic larynx. From Overgaard *et al.* (1998), with permission.

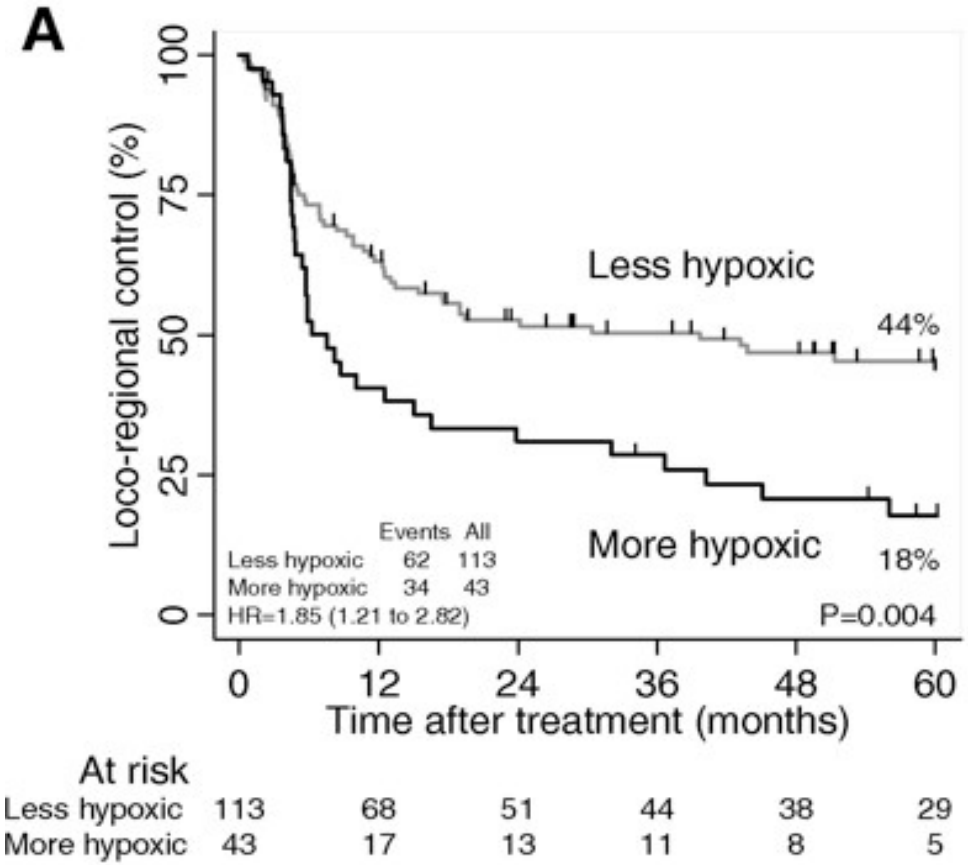
Hypoxic gene signature: toward treatment personalisation



Toustrup K et al. Cancer Res 2011;71:5923-5931

ESTRO School

Hypoxic 15 gene signature in H&N cancer



Toustrup K, Radiother Oncol, 2012

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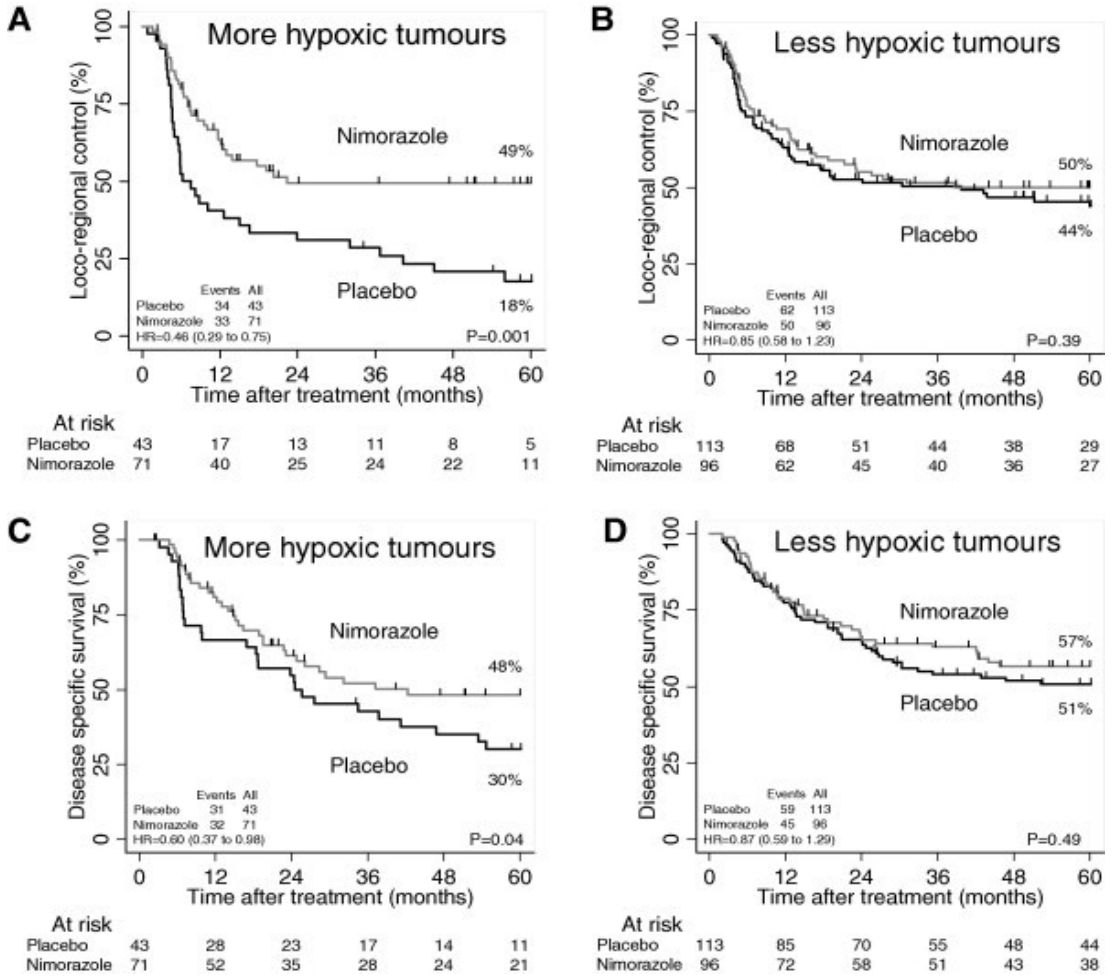
Hypoxic 15 gene signature in H&N cancer



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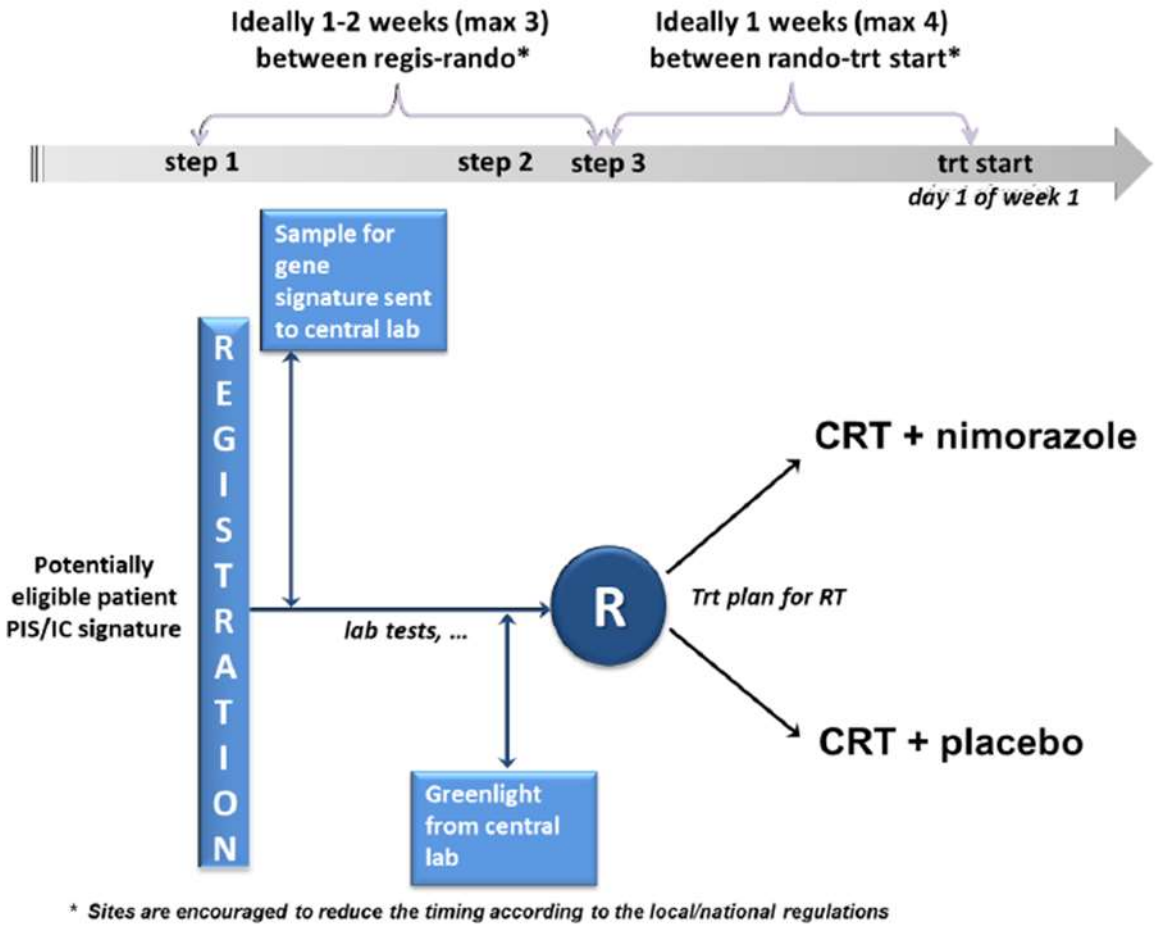
Toustrup K, Radiother Oncol, 2012

EORTC – 1219-ROG-HNCG
A blind randomized multicenter study of accelerated fractionated chemo-radiotherapy with or without the hypoxic radiosensitizer nimorazole (Nimoral), using a 15 gene signature for hypoxia in the treatment of squamous cell carcinoma of the head and neck

Pr. Vincent Grégoire, Cliniques Universitaires Saint-Luc, Brussels, Belgium

Pr. Jens Overgaard, Aarhus, Denmark

Study design



* *Sites are encouraged to reduce the timing according to the local/national regulations*

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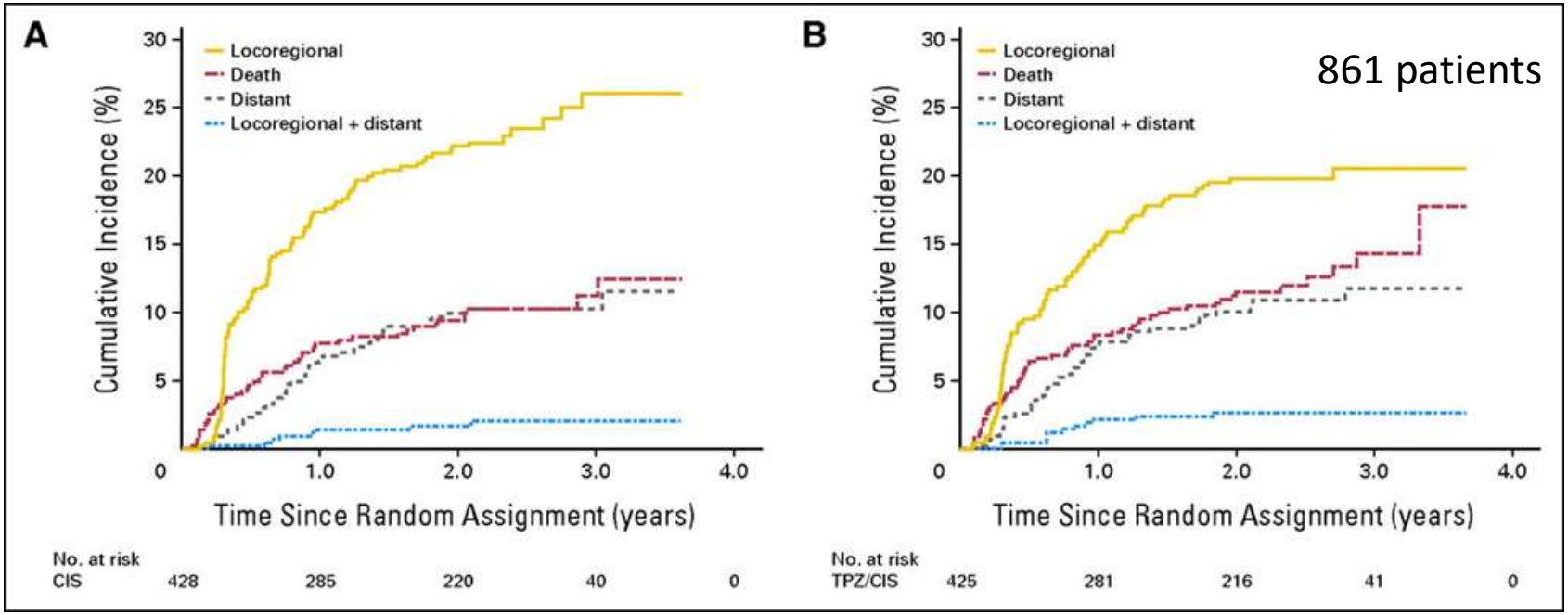
Study design

- Phase III superiority study
- Primary endpoint: loco-regional control rate
- Secondary endpoints: local control, regional control, time to distant metastases, overall survival, disease-free survival, disease-specific survival, acute and late morbidity
- Stratification for:
  - Institution
  - Localization: hypopharynx *vs* oropharynx *vs* larynx
  - T-stage: T1-2 *vs* T3-4
  - N-stage: N0-1 *vs* N2-3
  - WHO - PS: 0-1 *vs* 2
  - Hypoxic gene-profile: positive *vs* negative *vs* undetermined
- Size: 640 patients (320 in each treatment arm)
  (the recruitment will continue until 200 patients are available in the hypoxic signature positive subgroup)

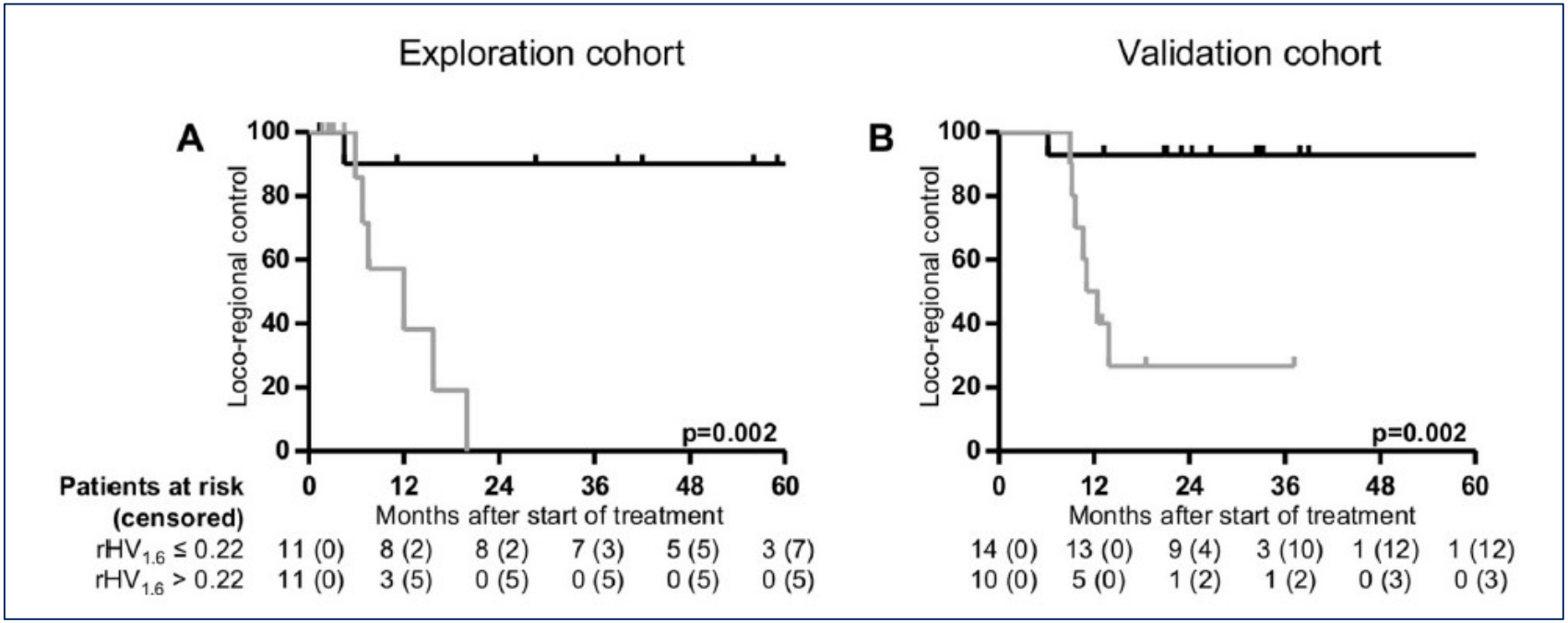
HeadSTART



Rischin et al, JCO 2010

No selection for the presence of hypoxia!

F-miso PET-CT for outcome prediction in HNSCC: residual tumor hypoxia week 2



Lock et al, Radiother Oncol 2017

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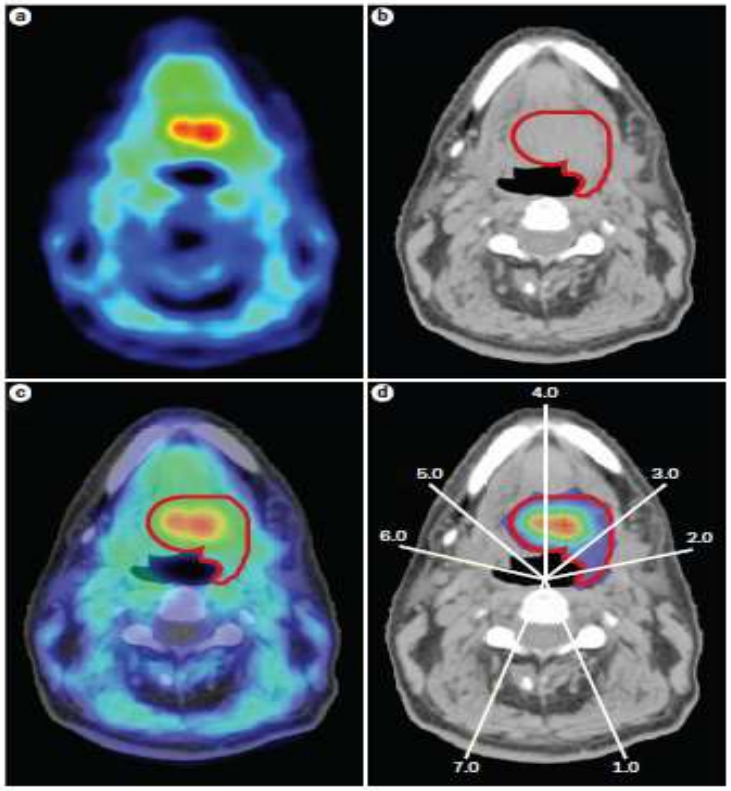
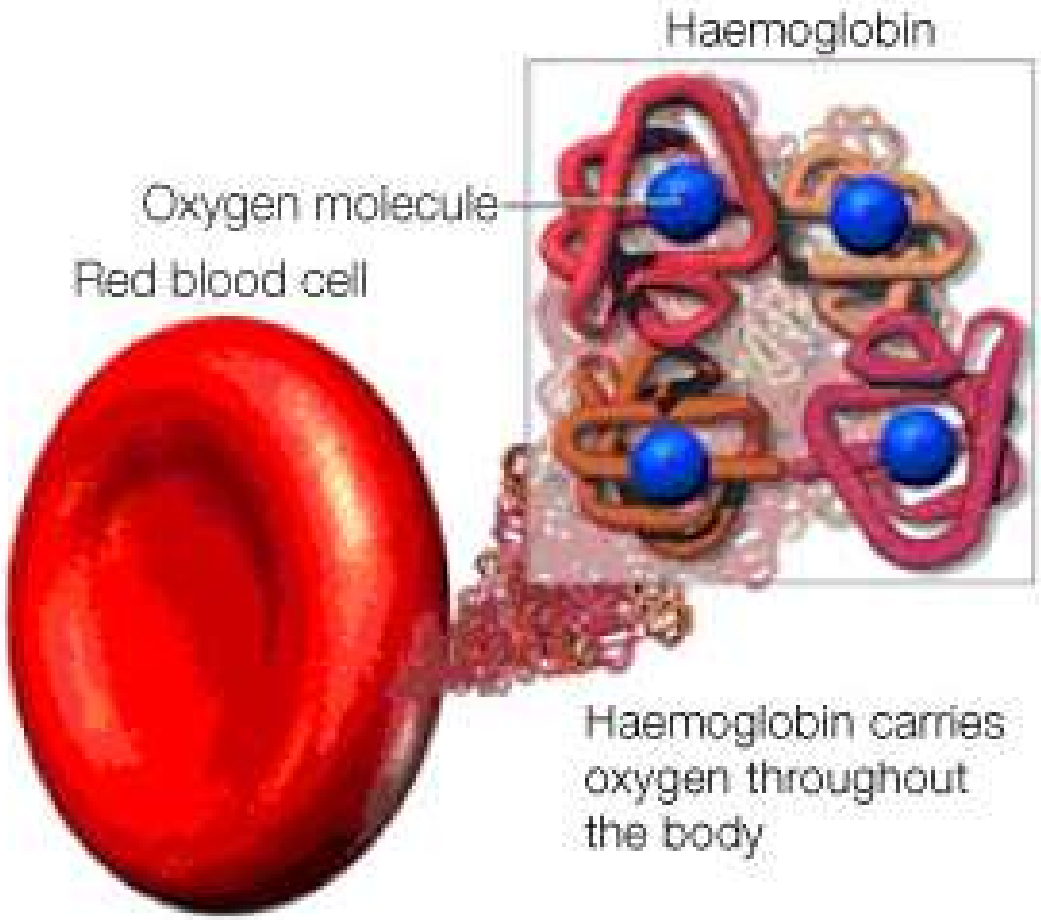
Hypoxia-mediated dose-painting

- Labelling nitroimidazole compounds with 18F for PET imaging of hypoxia → dose-painting



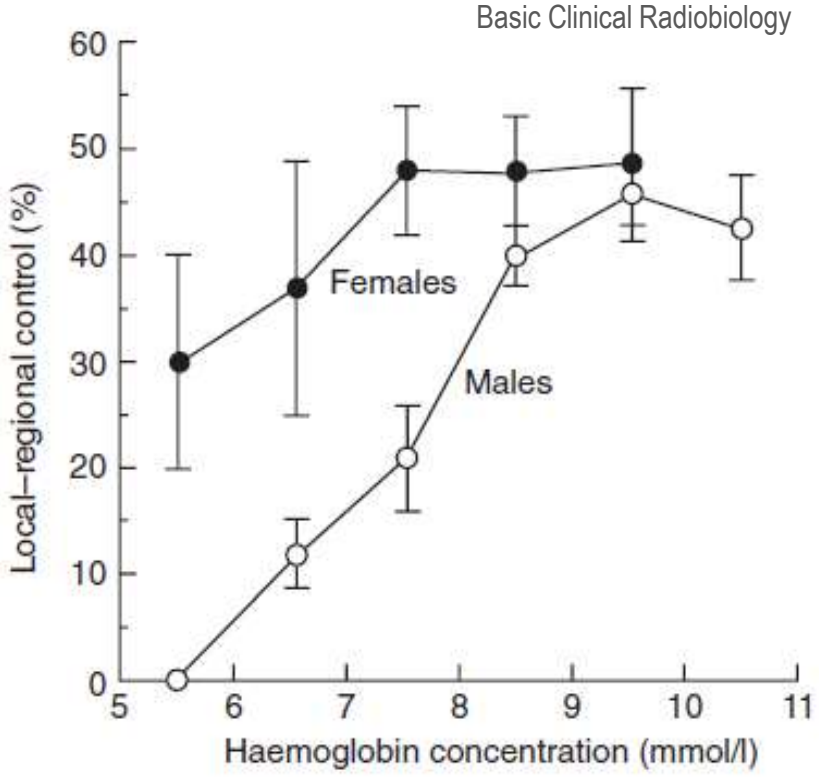
Horsman et al Nat Rev Clin Oncol 2012



Increasing haemoglobin concentration

Haemoglobin as prognostic factor

- Pts with low haemoglobin levels have a reduced local-regional tumor control



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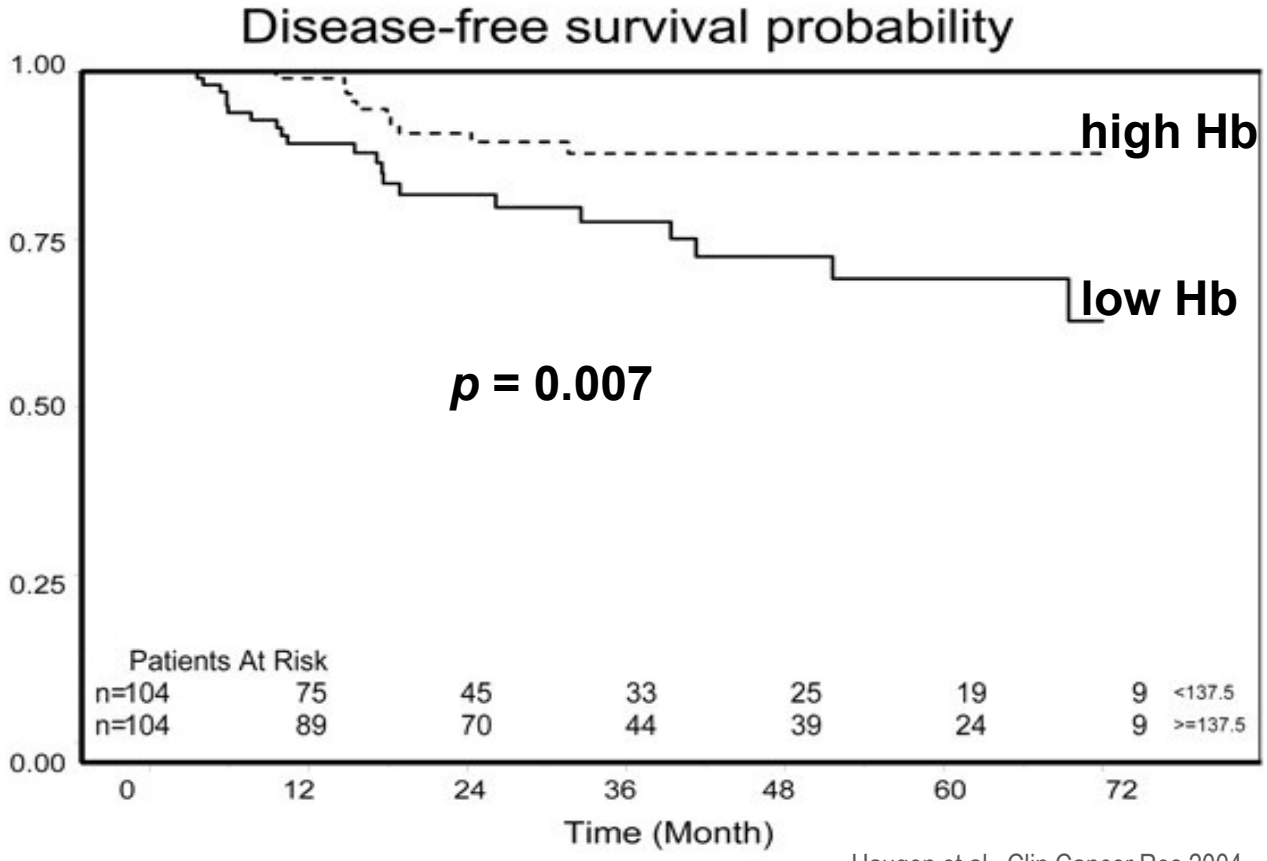
Haemoglobin as prognostic factor

- Pre-treatment Hb is associated with poor prognosis



Haugen et al., Clin Cancer Res 2004

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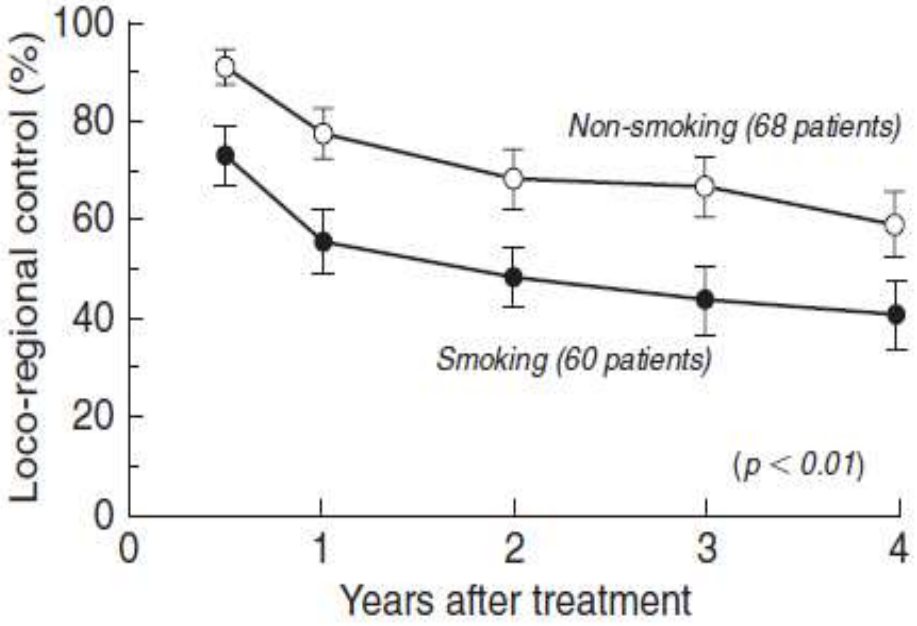
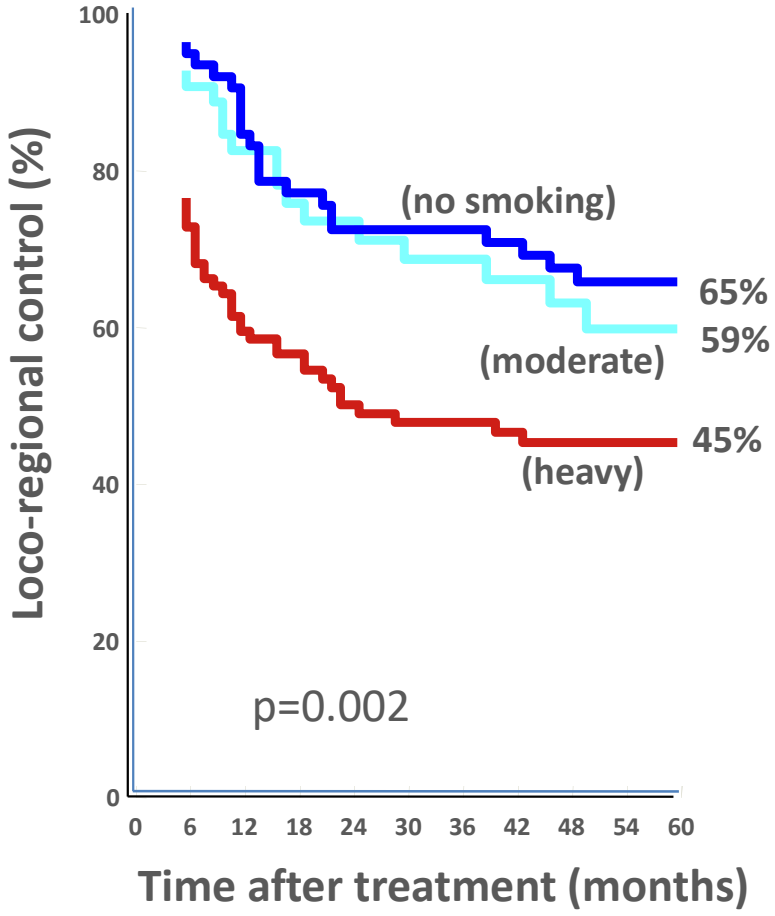
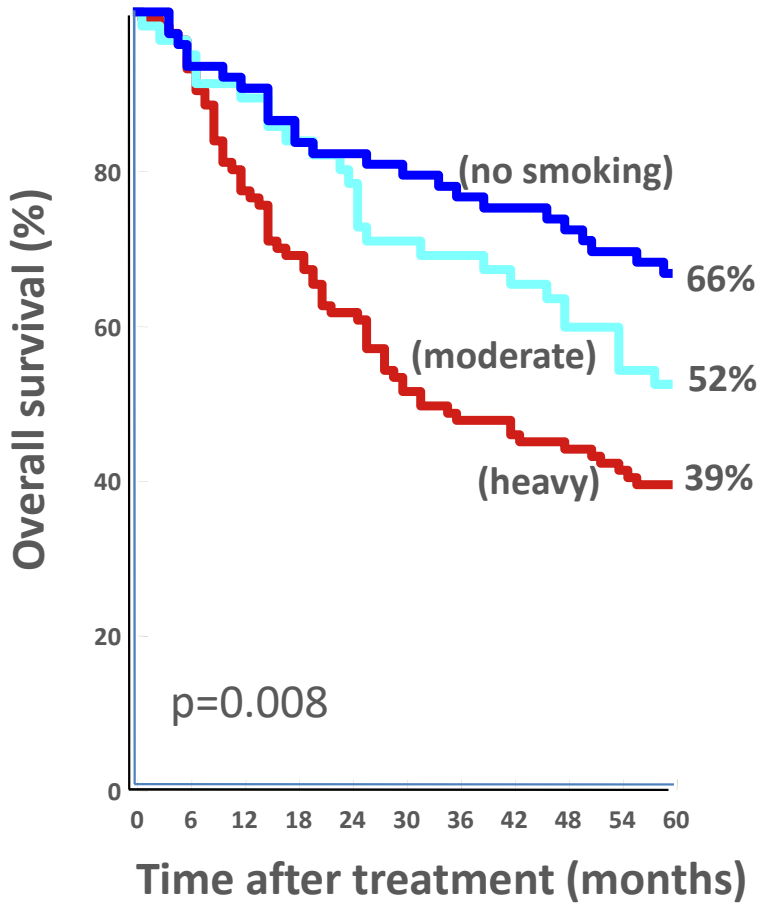
Smoking and treatment outcome

- Amount of oxygen delivered to tumors by the blood is important for a curative result!



Smoking and treatment outcome





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

ESTRO School

Effect of transfusion

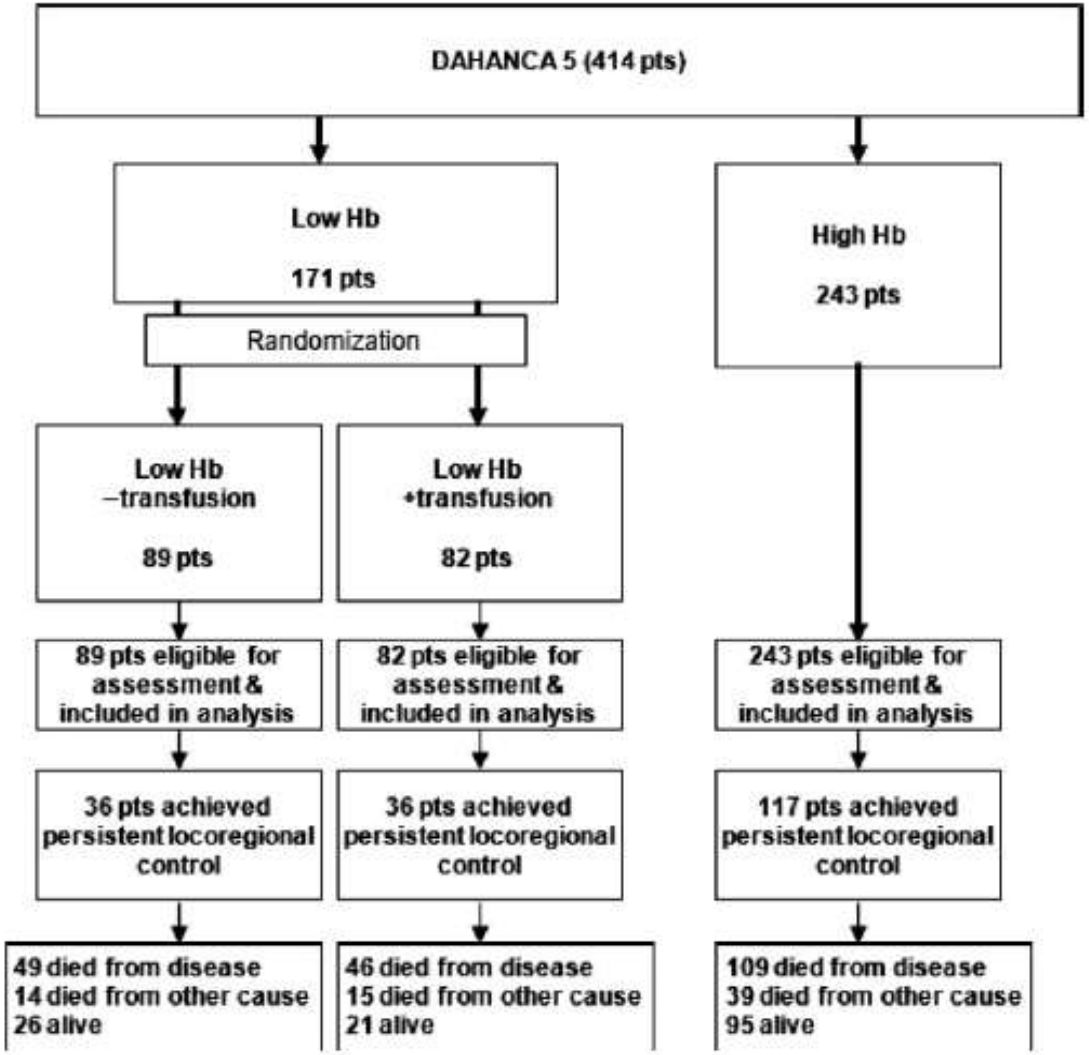


Fig. 1. Study flow chart.

Hoff et al Radiother Oncol 2010

Effect of transfusion

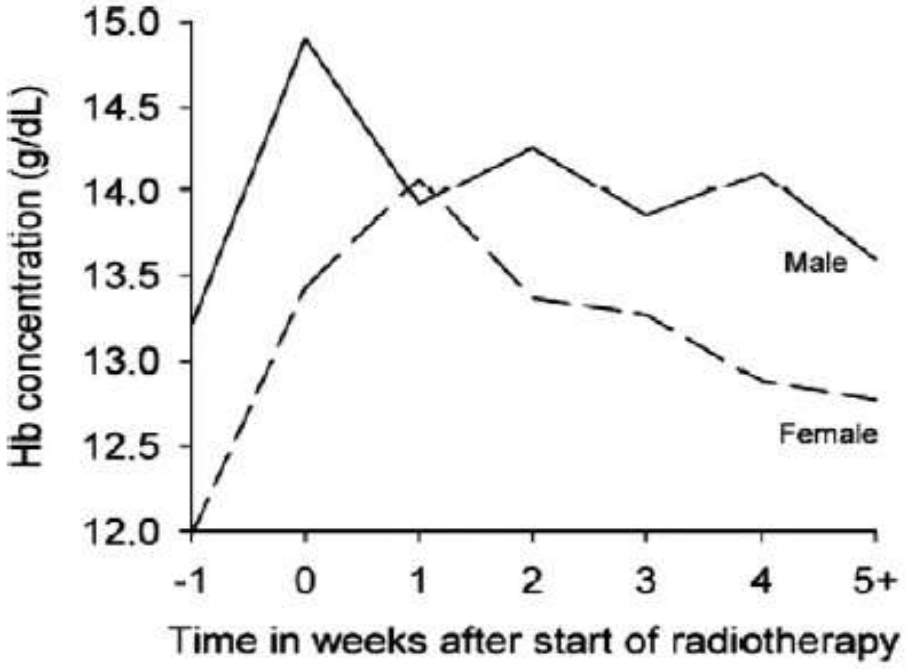
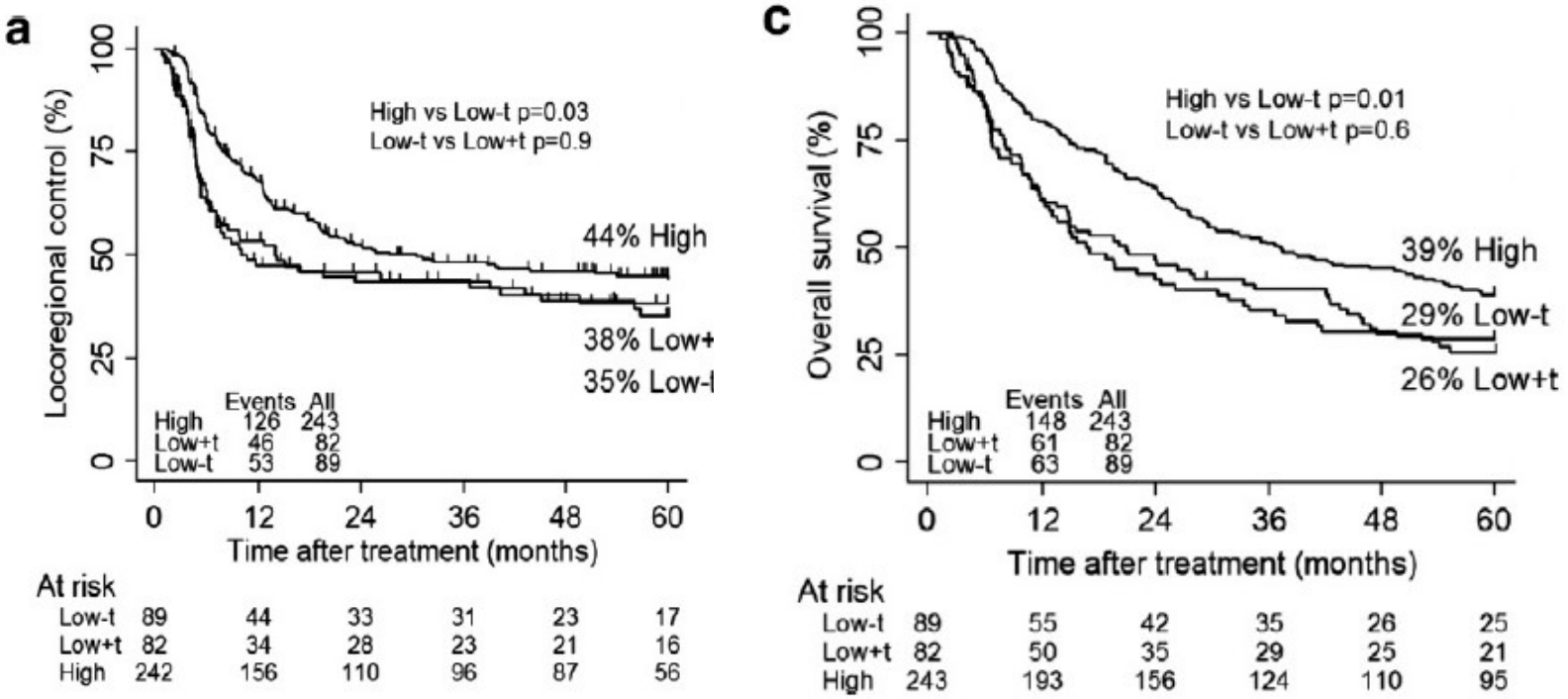


Fig. 2. Haemoglobin level during RT treatment as a function of gender.

Hoff et al Radiother Oncol 2010

Effect of transfusion



Hoff et al Radiother Oncol 2010

Conclusions from DAHANCA 5

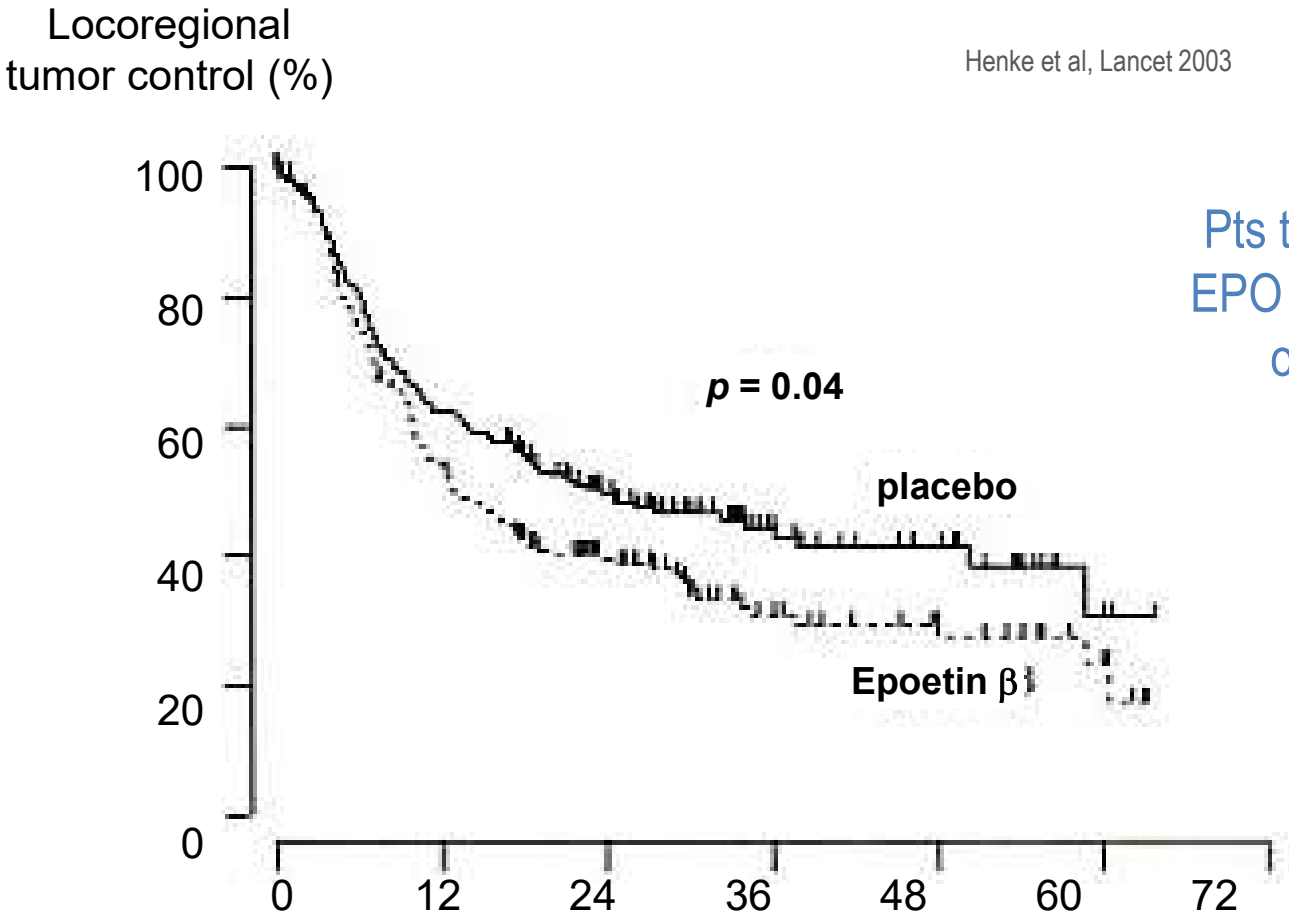
- Low hemoglobin level is associated with poor prognosis
- Hemoglobin level was raised with transfusion during radiotherapy
- Transfusion was unable to improve the effect of radiotherapy in head and neck cancer patients

Erythropoietin

- EPO is another approach to increase the haemoglobin levels
  - Gradual increase of oxygen supply over time

EPO and radiotherapy

Henke et al, Lancet 2003

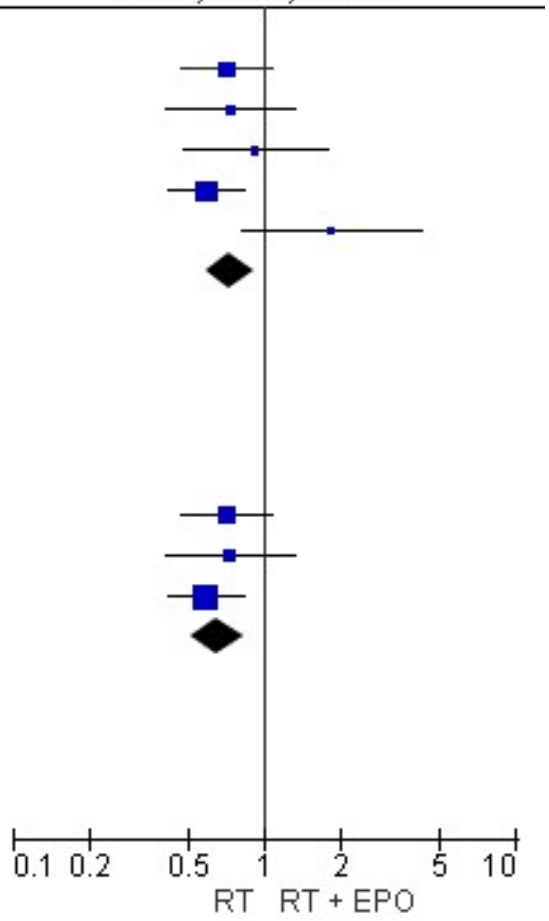


Pts treated with EPO have worse outcome

EPO and radiotherapy

Lambin P et al Cochrane review 2009

Study or Subgroup	RT + EPO Events	Total	RT Events	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)						



Conclusions from EPO trials

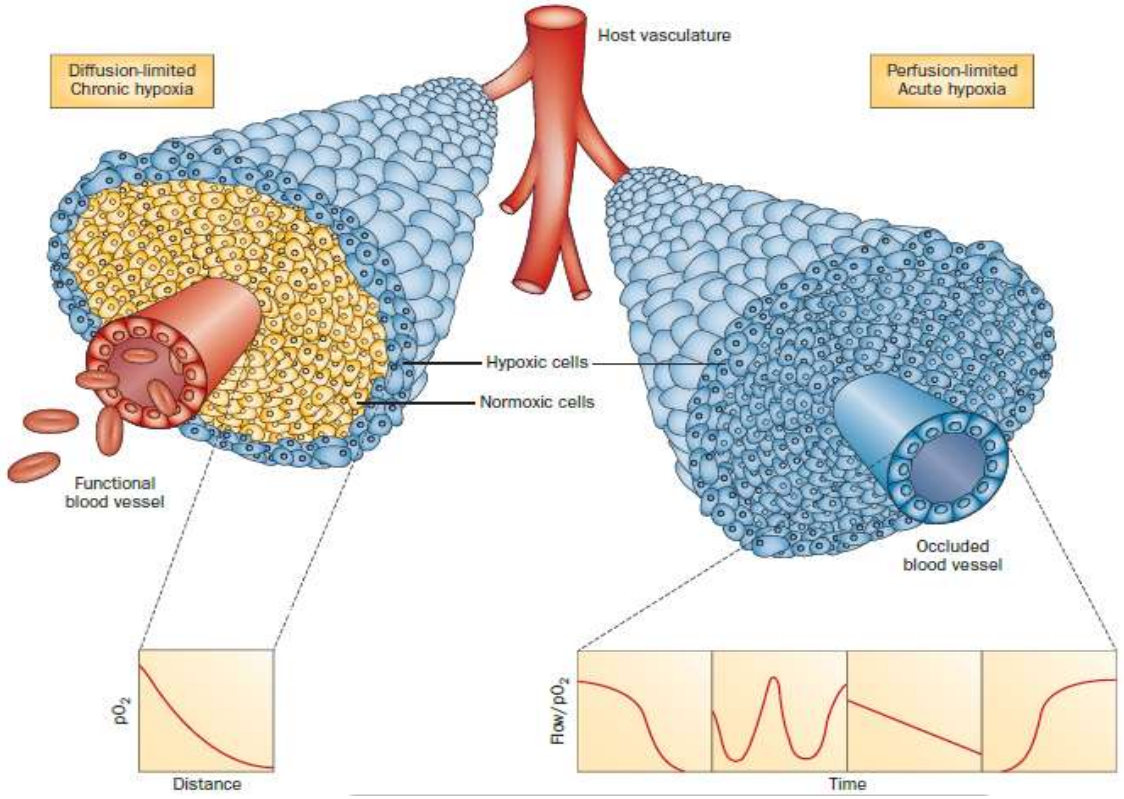
- RT plus EPO has a negative influence on outcome as opposed to RT alone (non-haemopoietic effects of EPO?)

- EPO should not be administered as an addition to RT outside the experimental setting for patients with head and neck cancer.

Overcoming acute hypoxia

Overcoming acute hypoxia

- Most procedures have no or little influence on perfusion-limited acute hypoxia



Horsman et al Nat Rev Clin Oncol 2012

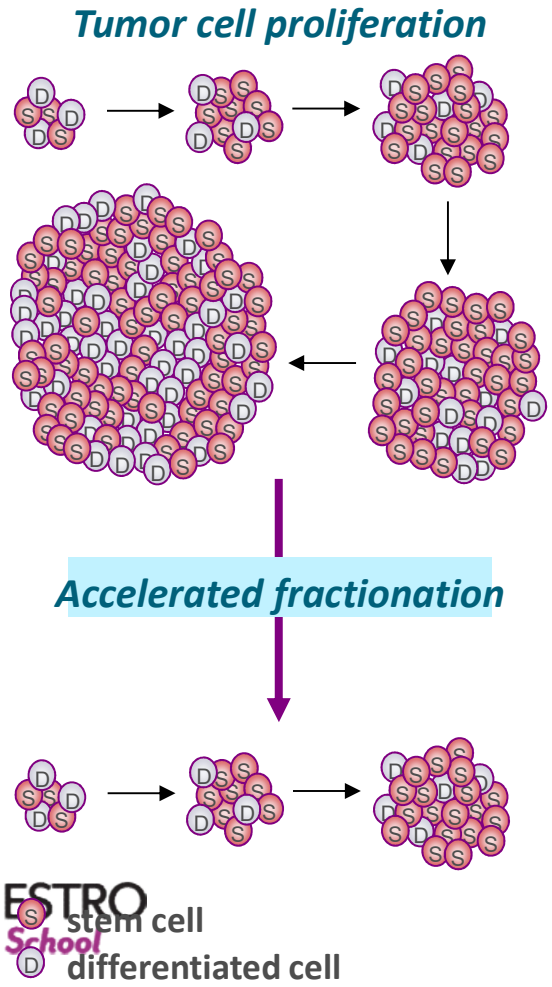
Nicotinamide

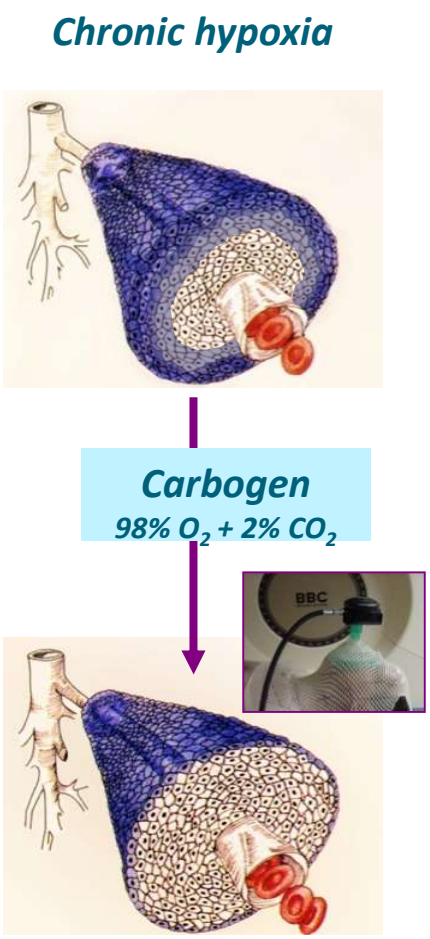
- Nicotinamide: prevents transient fluctuations in tumor blood flow that lead to development of acute hypoxia

- Hypothesis: combine nicotinamide with treatments that specifically target chronic hypoxia

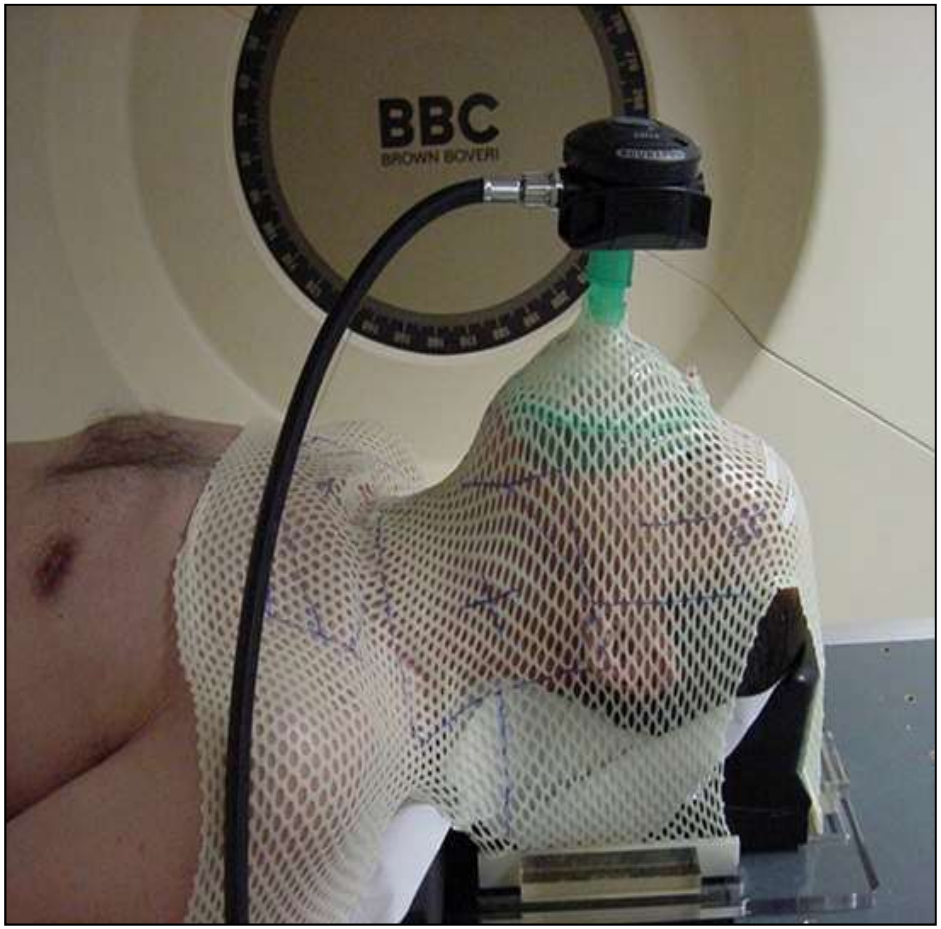
ARCON

- Accelerated Radiotherapy + CarbOgen + Nicotinamide





Carbogen



carbogen
(98% O_2 / 2% CO_2)

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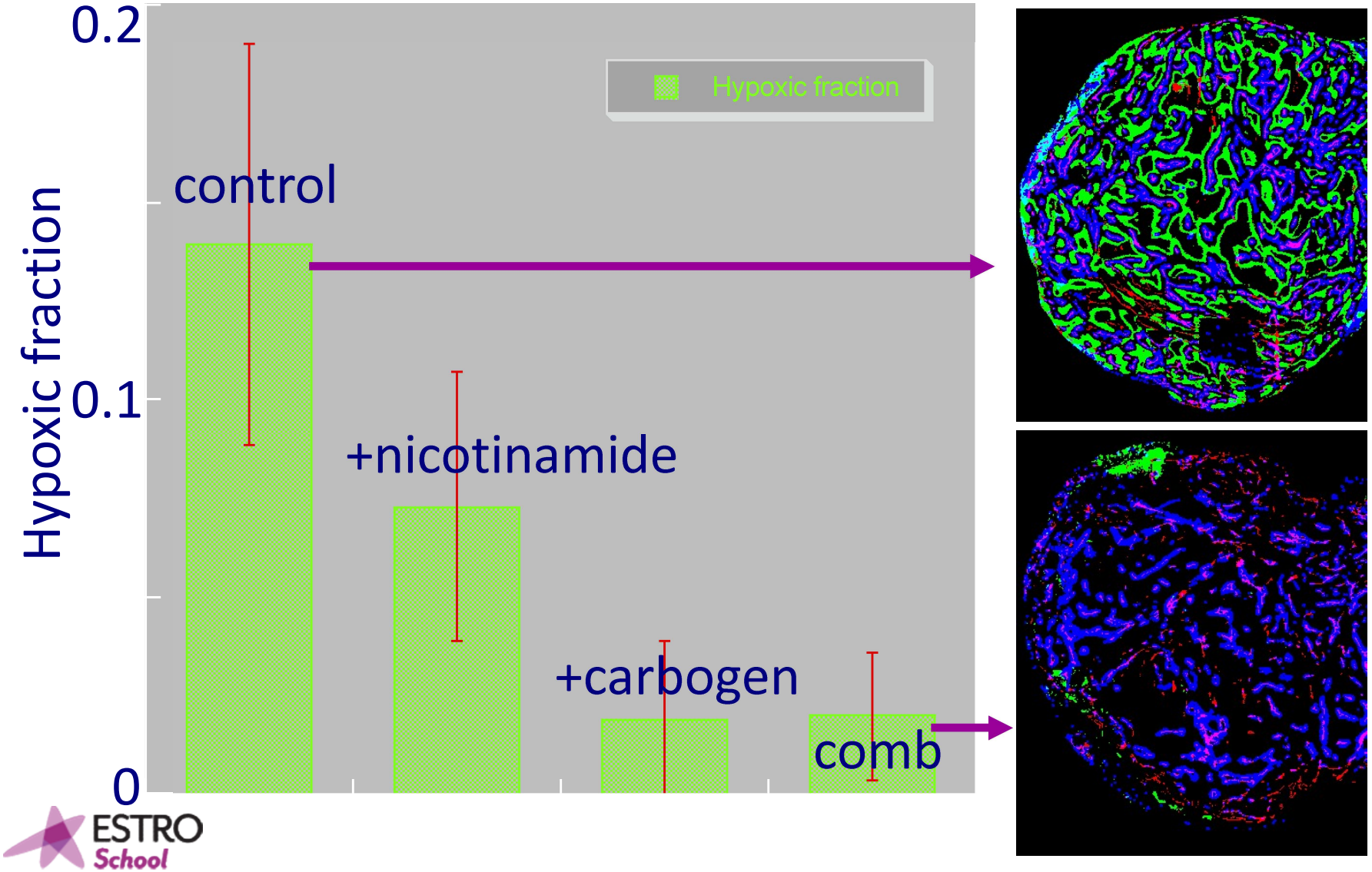
Carbogen and nicotinamide reduce hypoxia in mouse colon carcinoma



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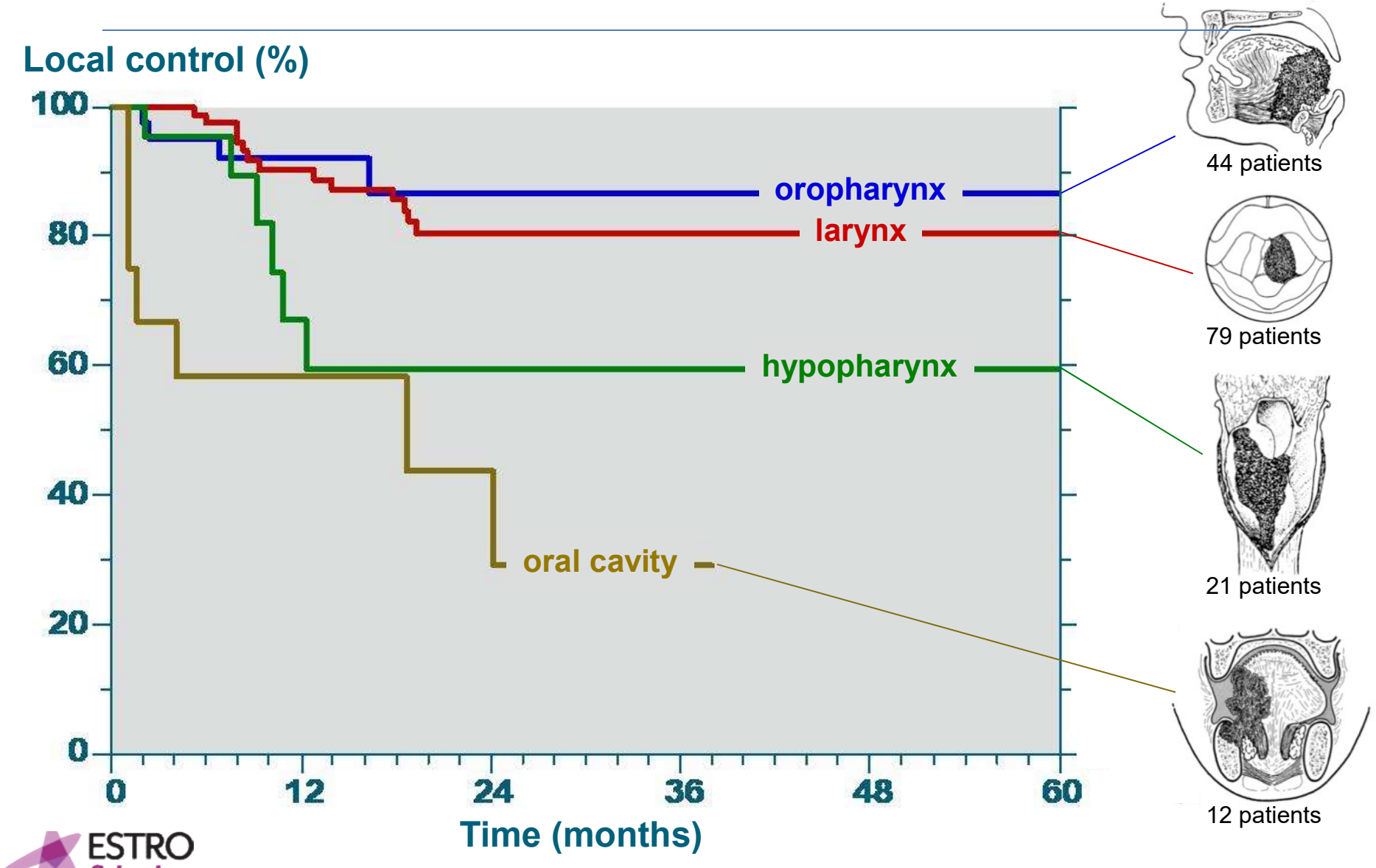
ARCON phase II trial



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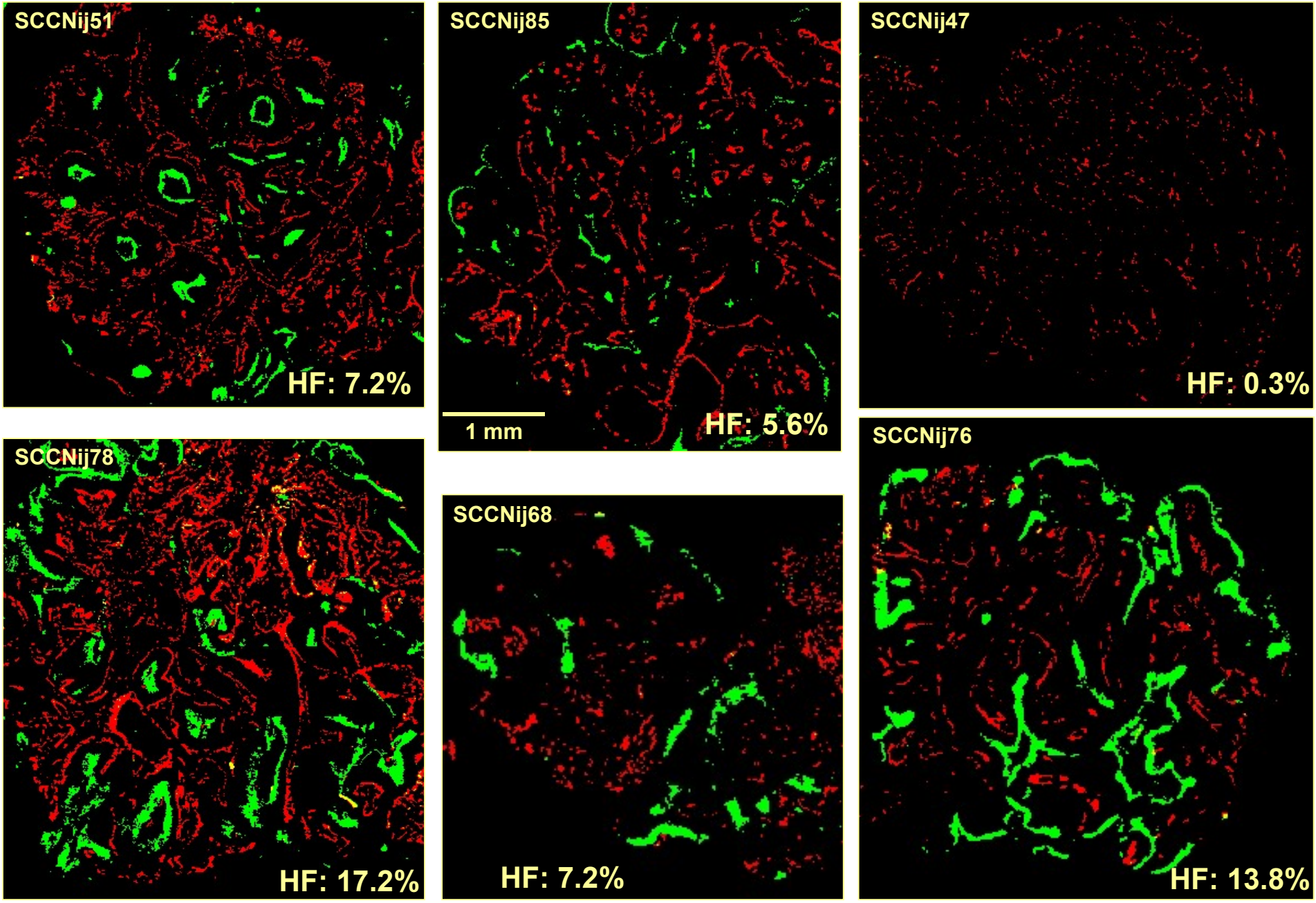
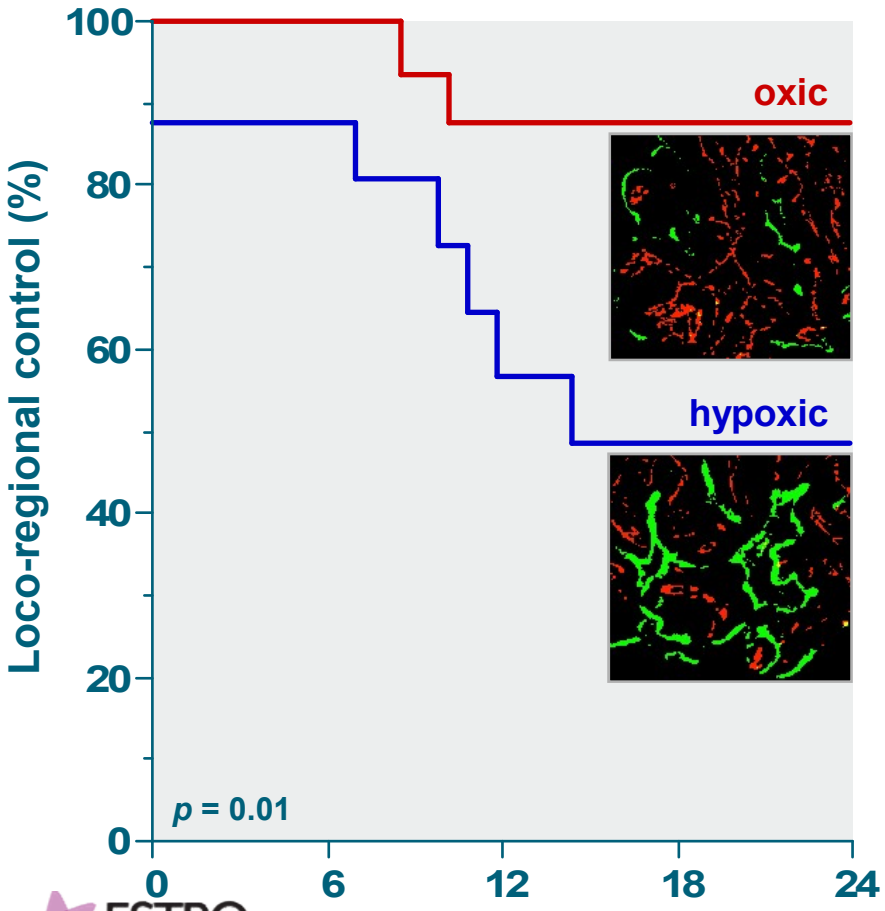
Hypoxia and vessels in H&N cancer biopsies

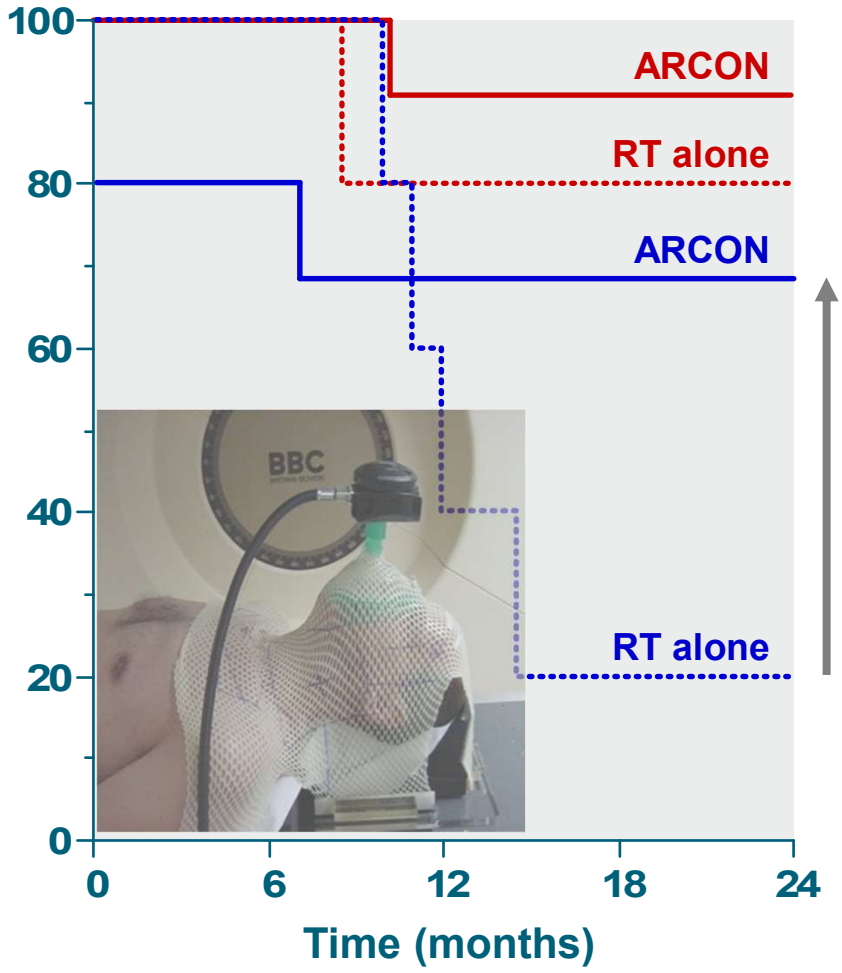


Loco-regional tumor control after RT: hypoxic vs non-hypoxic tumors

prognostic indicator



predictive assay



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Kaanders et al. Cancer Res 2002

ARCON for cT2-4 larynx carcinoma

Randomization

Accelerated Radiotherapy

Accelerated Radiotherapy + carbogen and nicotinamide

Fractionation schedule:

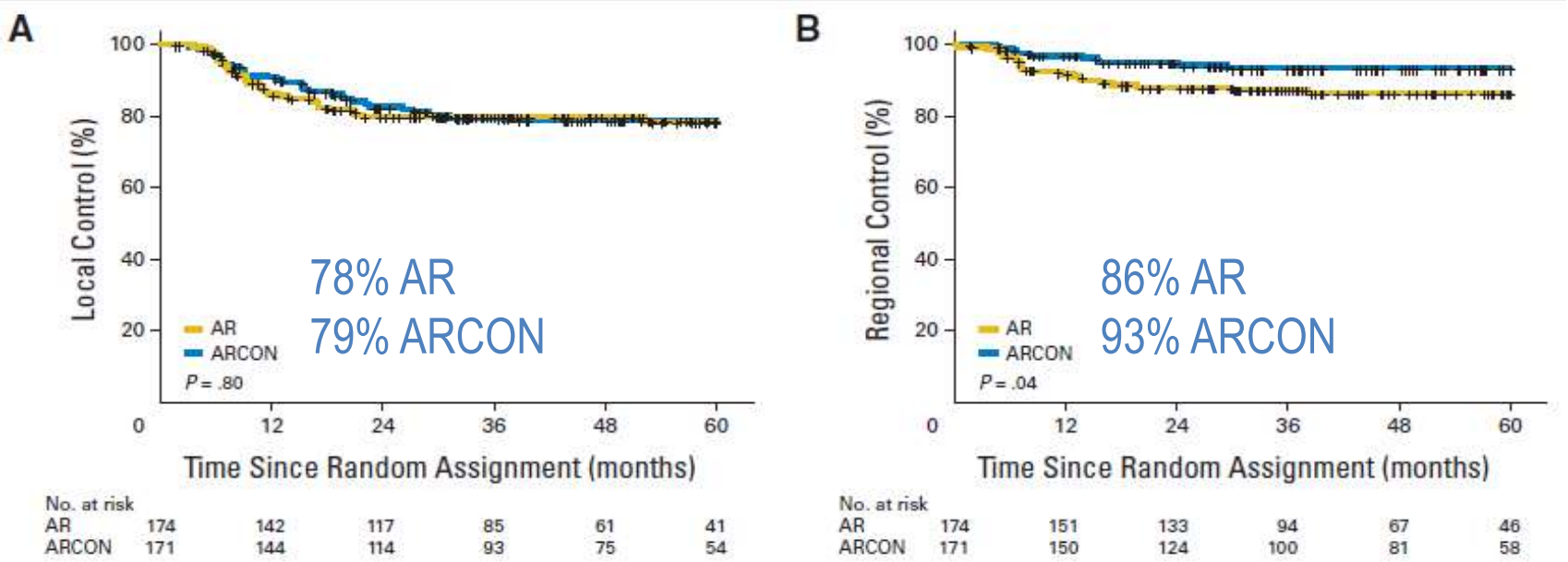
	primary	metastatic nodes
Acc. RT	68 Gy	68 Gy
ARCON	64 Gy*	68 Gy

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

Janssens et al., J Clin Oncol 2012

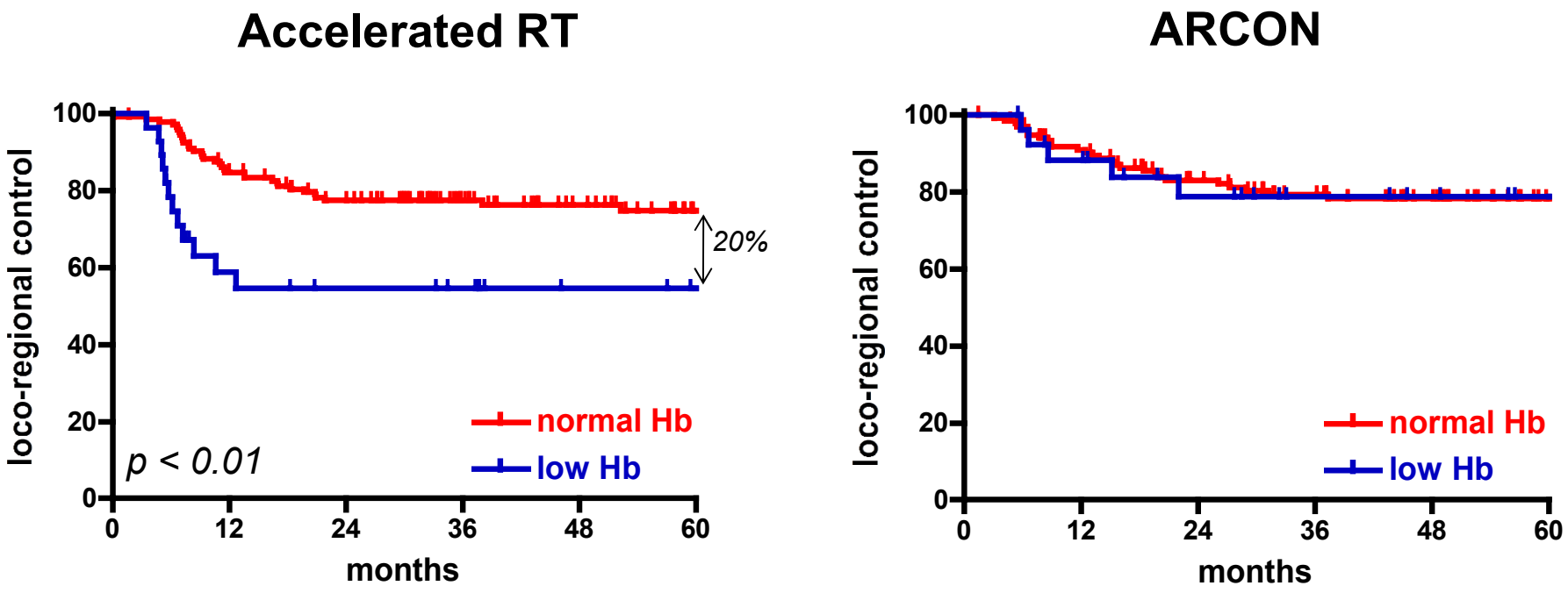
ARCON for cT2-4 larynx carcinoma

345 patients



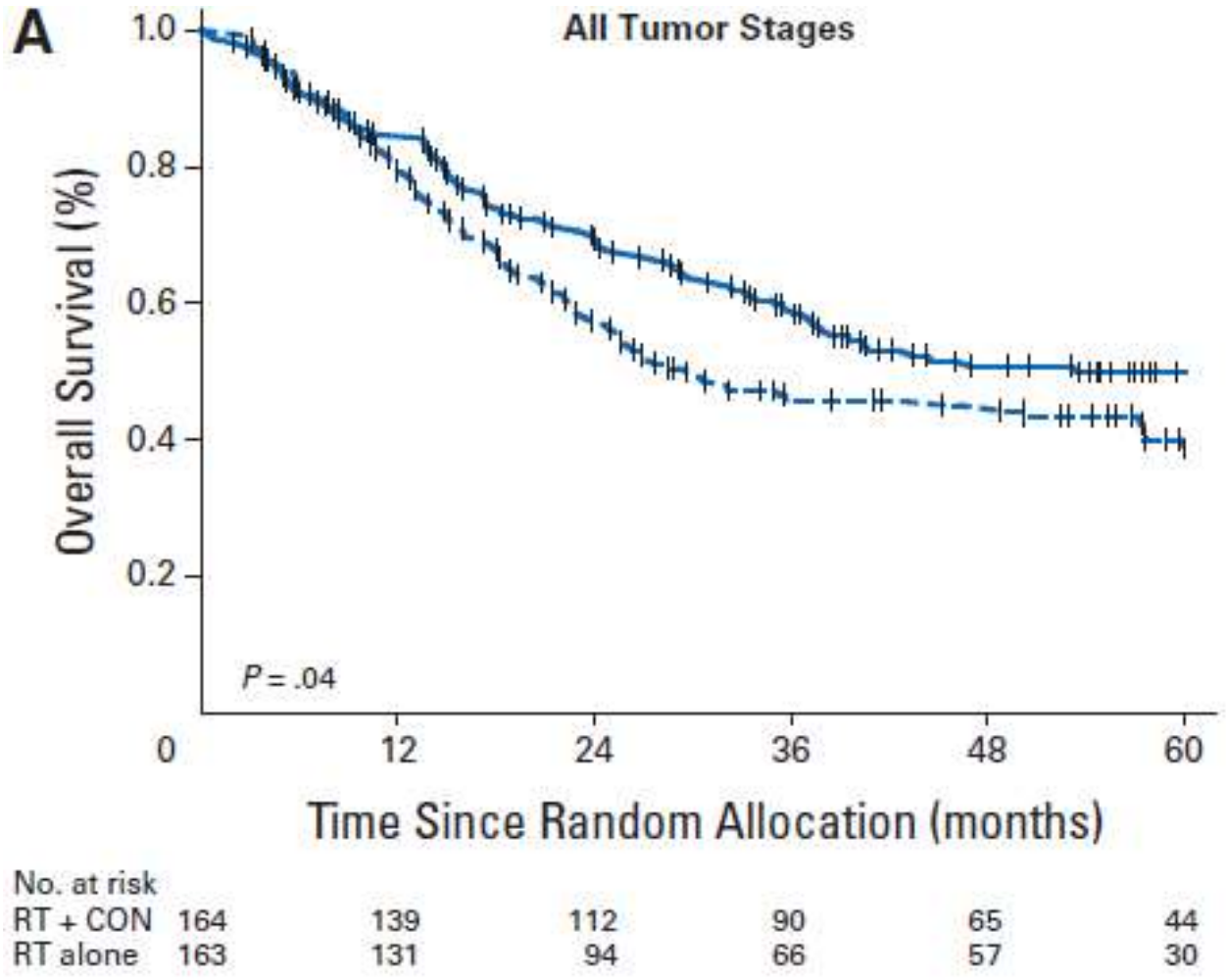
Janssens et al., J Clin Oncol 2012

ARCON improves loco-regional control in anemic patients



Kaanders ESTRO 2012

RT ± Carbogen & nicotinamide for bladder cancer

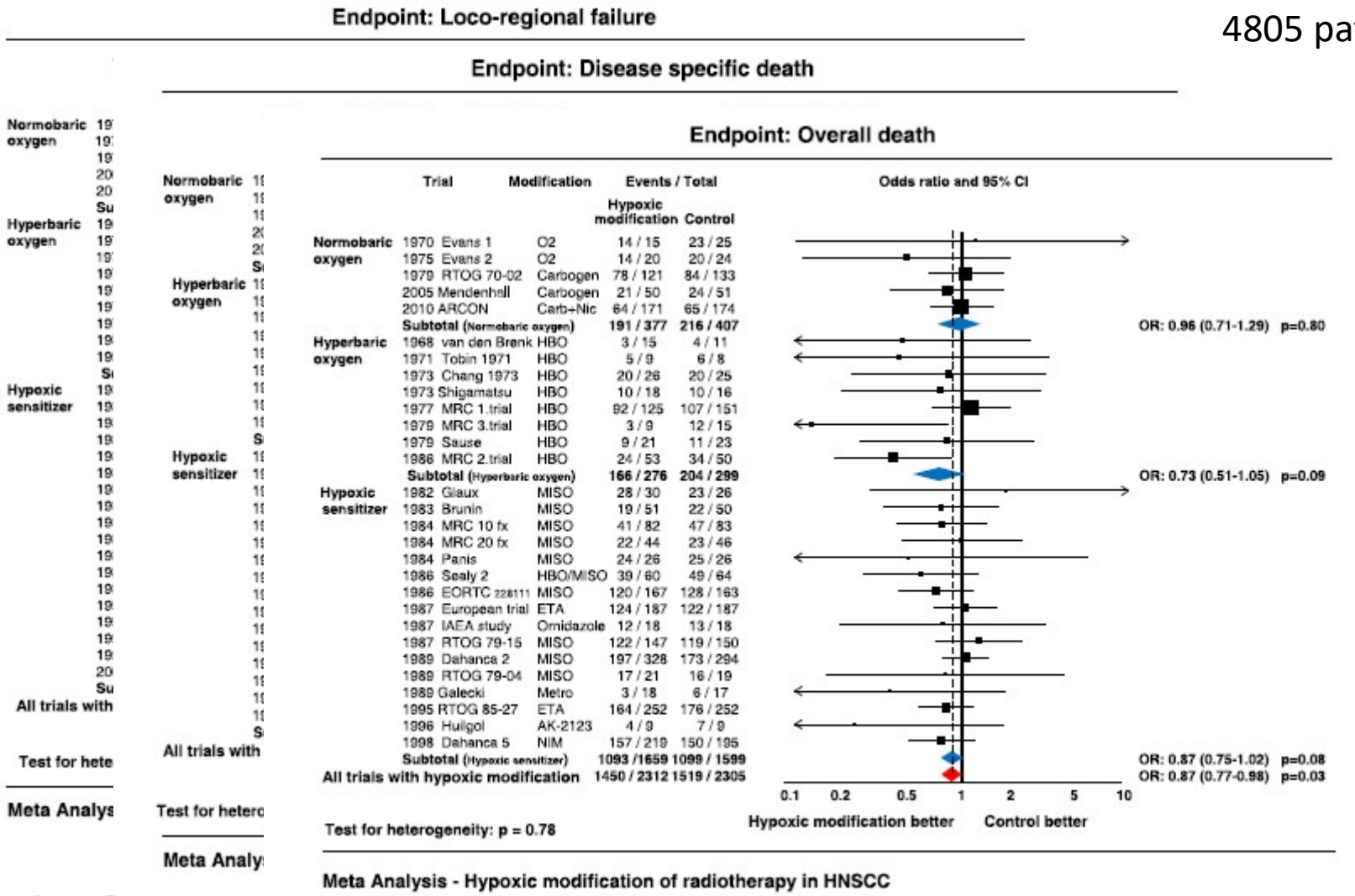


Hoskin P J et al. JCO 2010;28:4912-4918

Meta-analysis

Hypoxic modification of RT in HNSCC

4805 patients



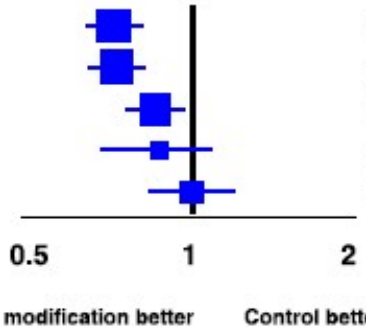
Overgaard Radiother Oncol 2011

Hypoxic modification of RT in HNSCC

Overgaard Radiother Oncol 2011

Head and neck cancer - meta analysis - summary

Endpoint	Events / Total		Odds ratio and 95% CI	Odds ratio	Risk Reduction	NNT**
	Hypoxic modification	Control				
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.

Level 1a evidence in favor of adding hypoxic modification to radiotherapy in HNSCC

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!

Back to the future: SBRT & tumor hypoxia

Table 2
Effect of hypoxic modification of radiotherapy of HNSCC given with different dose per fraction schedules.

Fractionation pattern	Endpoint and Odds Ratio (95% CI)		
	Loco-regional failure	Disease specific death	Late radiation related morbidity
Hypo-fractionation[a]	0.56 (0.40–0.77) $p > 0.001$	0.62 (0.44–0.86) $p > 0.001$	1.83 (1.05–3.18) $p > 0.03$
Conventional fractionation[a]	0.77 (0.67–0.89) $p > 0.001$	0.78 (0.67–0.90 $p > 0.001$	0.90 (0.71–1.14) $p > 0.39$

[a] The same fractionation pattern has been applied in hypoxic modification and control arms.

Overgaard Radiother Oncol 2011

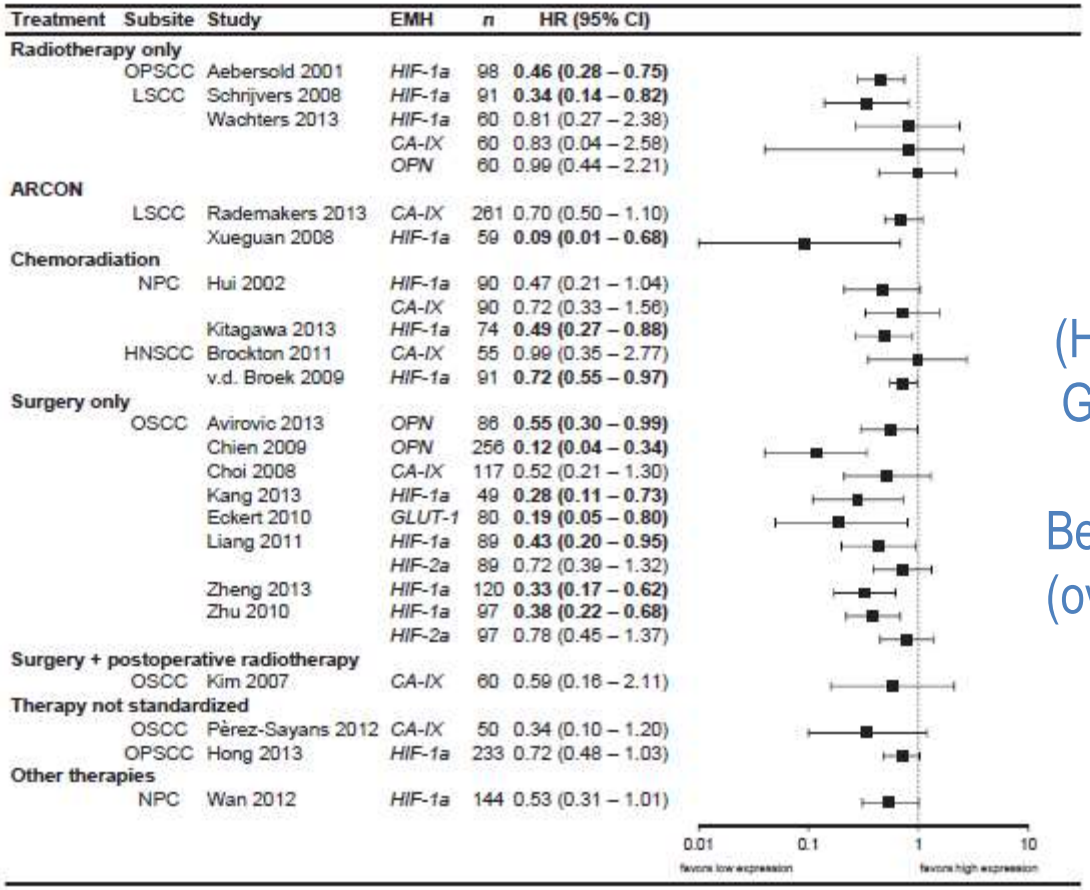
Targeting hypoxia – holy grail of radiotherapy?

- 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”

Patient selection

- Endogenous biomarkers for hypoxia

Swartz JE et al Cancer Med 2015



Low EMH expression (HIF-1a, CA-IX, GLUT-1, OPN)

-

Better prognosis (overall survival)

Favors low expression Favors high expression

Add

- Reduce oxygen consumption metformine
- Hypoxia tolerance HIF1a inhibitors

Patient selection

Swartz JE et al Cancer Med 2015

Table 2. Clinical outcome: radiotherapy/ARCON.

Study	Treatment	Stage	EMH	Pos/*n*	Cutoff	Correlations	LRC	OS	DFS	DSS
Oropharyngeal carcinoma										
Aebersold et al. [20]	XRT	Any	HIF-1a	92/98	10% N	Tumor grade		**0.46 (0.28–0.75)**	**0.50 (0.30–0.83)**	
Silva et al. [21]	XRT		HIF-1a	43/79	10%	Low Hb	**0.2 (0.1–0.42)**			
Laryngeal carcinoma										
Douglas et al. [22]	XRT	I–II	HIF-1a	124/271	10% N	None	0.96 (0.79–1.16)			LR $P = 0.23$
Kwon et al. [23]	XRT	I–II	HIF-1a	7/42	50% N	ns	**0.13 (0.02–0.82)**			
		I–II	CA-IX	17/42	30% M	ns	**0.11 (0.01–0.96)**			
Rademakers et al. [24]	ARCON/XRT[1]	III–IV	CA-IX	132/261	Med[2]	None		0.7 (0.5–1.1)		
Schrijvers et al. [25][3]	XRT	I–II	HIF-1a	46/91	0.5% N	None		**0.34 (0.14–0.82)**		
		I–II	CA-IX	53/91	1.5% M	None		0.84 (0.4–1.76)		
		I–II	GLUT-1	53/91	35% M	ns	ns			
Wachters et al. [26]	XRT	I–II	HIF-1a	11/60	0.5% N	None		0.81 (0.27–2.38)		
		I–II	CA-IX	11/60	12.5% M	None		0.83 (0.04–2.58)		
		I–II	OPN	20/60	0.5% C	ns		0.99 (0.44–2.21)		
Wildeman et al. [27]	XRT	Any	HIF-1a	59	N/M %[4]	ns	1.08 (0.91–1.29)[5]			
		Any	HIF-1a	59	Int	ns	0.92 (0.56–1.49)[5]			
		Any	CA-IX	59	int	ns	1.21 (0.96–1.52)[5]			
Nasopharyngeal carcinoma										
Xueguan et al. [28]	ARCON	Any	HIF-1a	40/59	10% N	None	0.41 (0.06–2.69)	**0.09 (0.01–0.68)[6]**	**0.26 (0.07–0.97)**	
Multiple subsites										
Nordsmark et al. [29]	XRT	Any	HIF-1a	19/59[7]	50% N	ns	**0.22 (0.06–0.81)**			
			CA-IX	26/57[7]	10% M	ns	0.35 (0.12–1.01)			
			OPN	17/57	Int D	ns	0.83 (0.35–2.00)			
Jonathan et al. [30]	ARCON	Any	CA-IX	29/58	25% M	ns	**4.23 (1.07–16.76)[6]**	ns		
			GLUT-1	29/58	Int D	ns	ns	**LR $P = 0.001$**		

The outcomes locoregional control (LRC), overall survival (OS), disease-free survival (DFS), and disease-specific survival (DSS) are shown as hazard ratio (95% confidence interval). Hazard ratios <1 indicate beneficial prognosis for nonhypoxic tumors. Significant values are shown in bold Cutoff: EMHs were scored according to nuclear (N), membranous (M), cytoplasmic (C), or diffuse (D) staining patterns. XRT: radiotherapy. ARCON; accelerated radiotherapy, carbogen gas breathing and nicotinamide. Pos: number of patients with staining above the mentioned cutoff. LR: Logrank test. ns: not specified. Multiple subsites, patients were not analyzed per subsite. EMH, endogenous markers of hypoxia; HIF-1, hypoxia-inducible factor 1.

Hypoxia-modified treatment schedules for patients with high expression of endogenous hypoxia markers

Take home messages

- 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

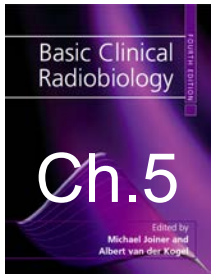
ESTRO School

Basic Clinical Radiobiology

Dose-response relationships in radiotherapy

Michael Joiner

Paris 2017

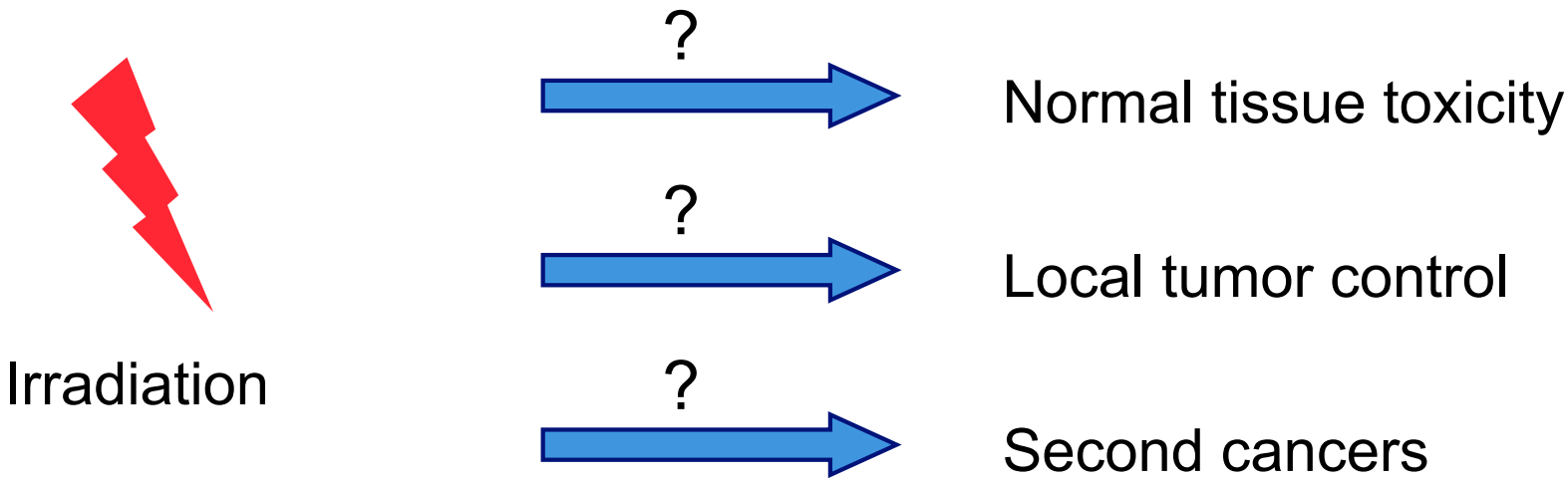


Definitions

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

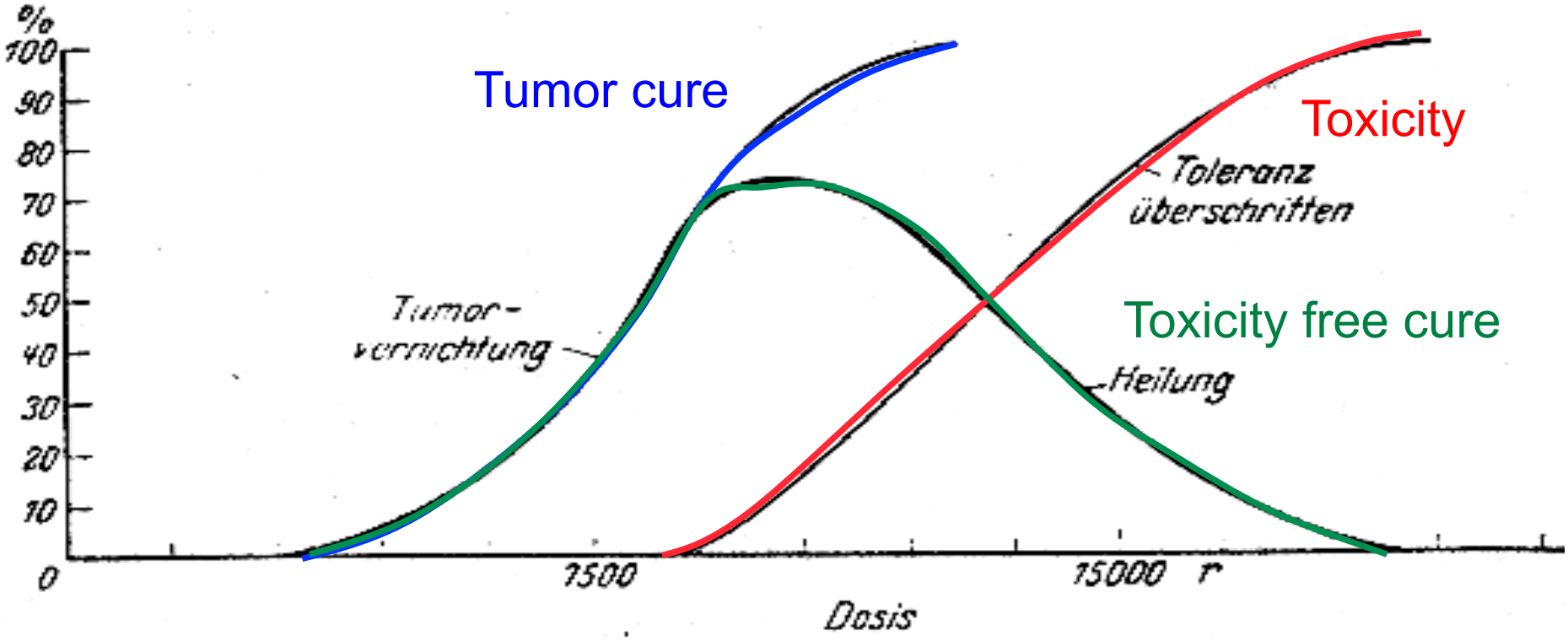


Relationship between given dose and each clinically relevant outcome needs to be defined

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

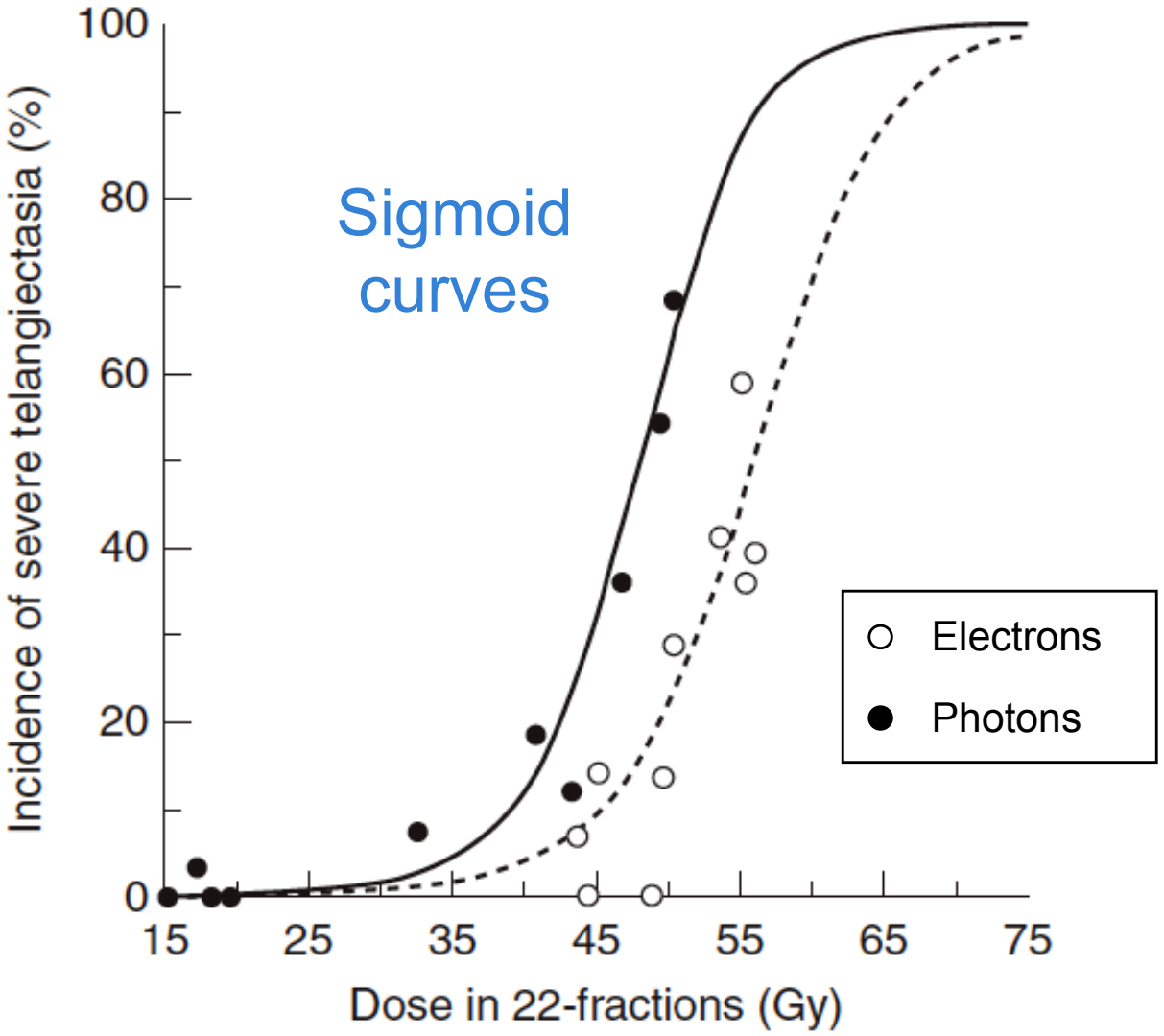
Dose response: Empirical data

Sigmoid curves indicate variability of clinical radioresponse



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

Examples of dose response relationships



Bentzen and Overgaard (1991)

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 a 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
actually in that tumor

Poisson Statistics – a reminder

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:

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

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: local 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:

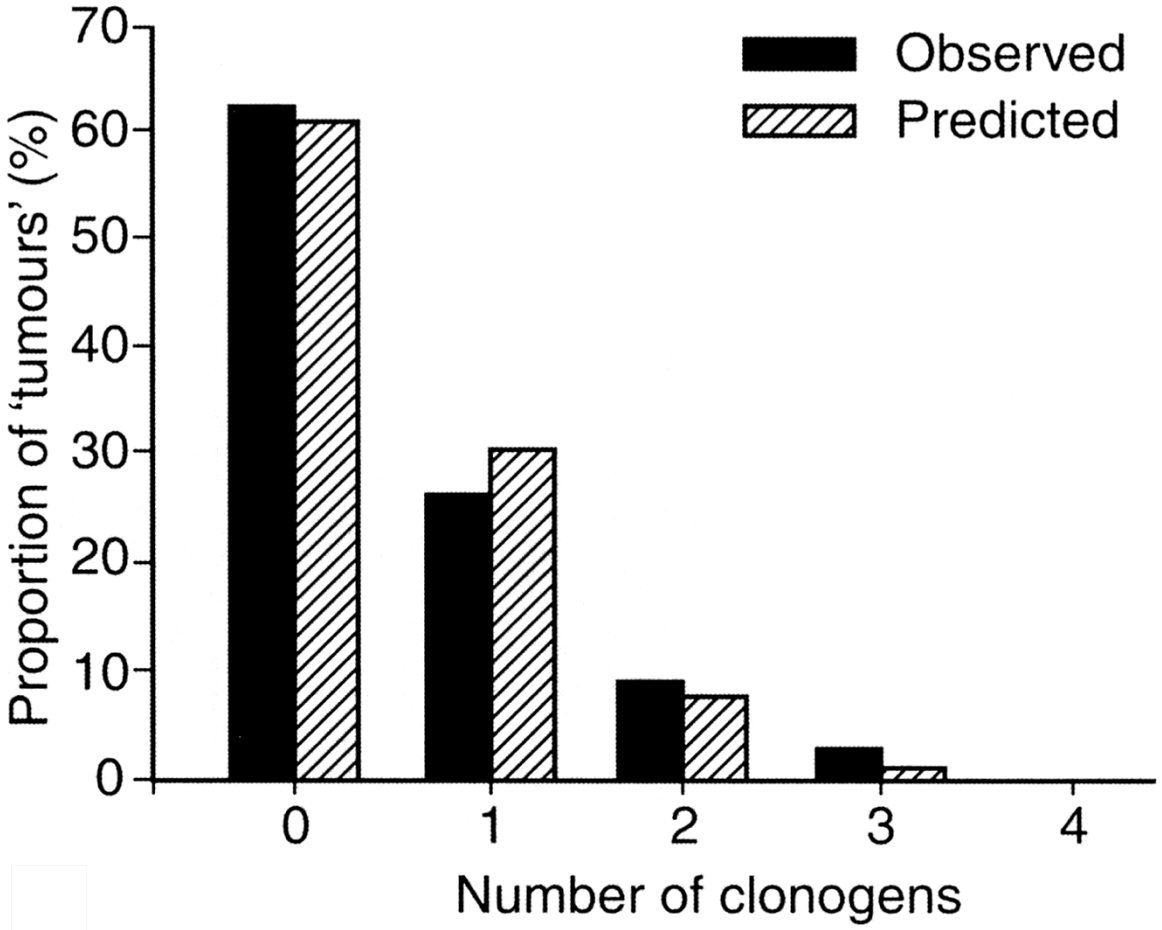
$$TCP = P(0) = \frac{e^{-\lambda}\lambda^{0}}{0!} = e^{-\lambda} = \exp\left(-\lambda\right)$$

λ is the mean number of surviving cells per tumor

Poisson “predicted” versus Monte Carlo “observed”

Average number of surviving clonogens = 0.5

Poisson distribution is confirmed by “observation”



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

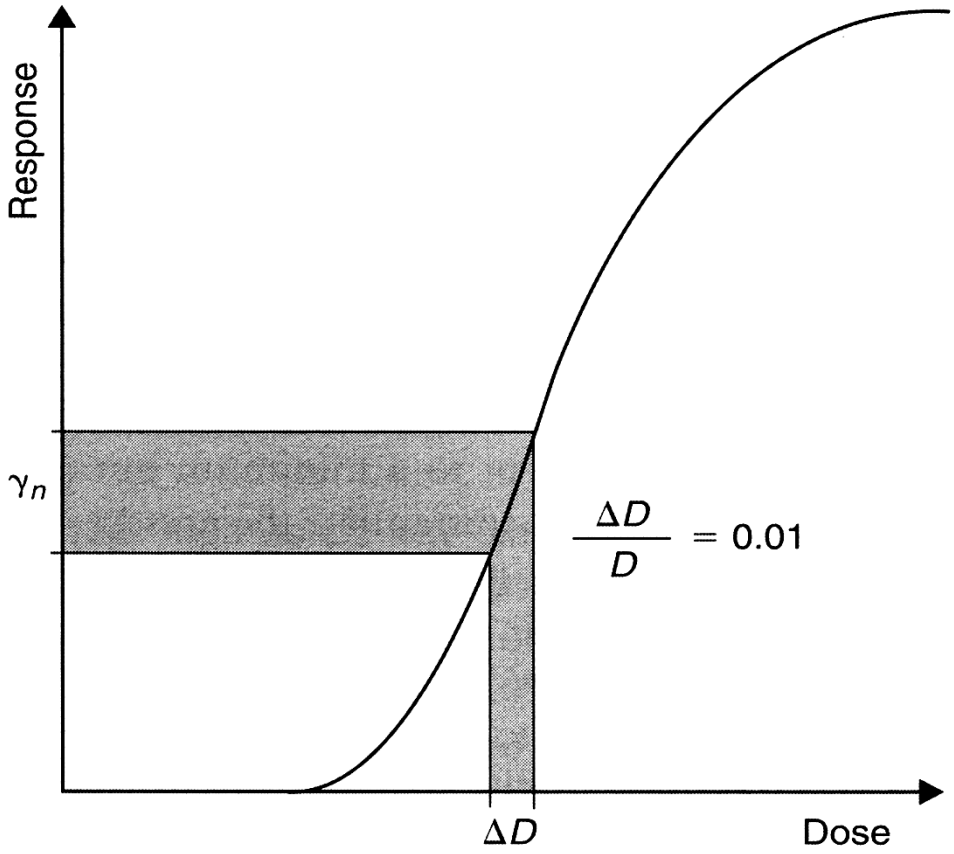
Remember that:

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

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

Interesting consequence of Poisson

It can be shown that:

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

This may be used for deducing the number of “tumor clonogens” but any 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% (*P* = 0.5, *u* = 0)

Beware: γ changes with response level

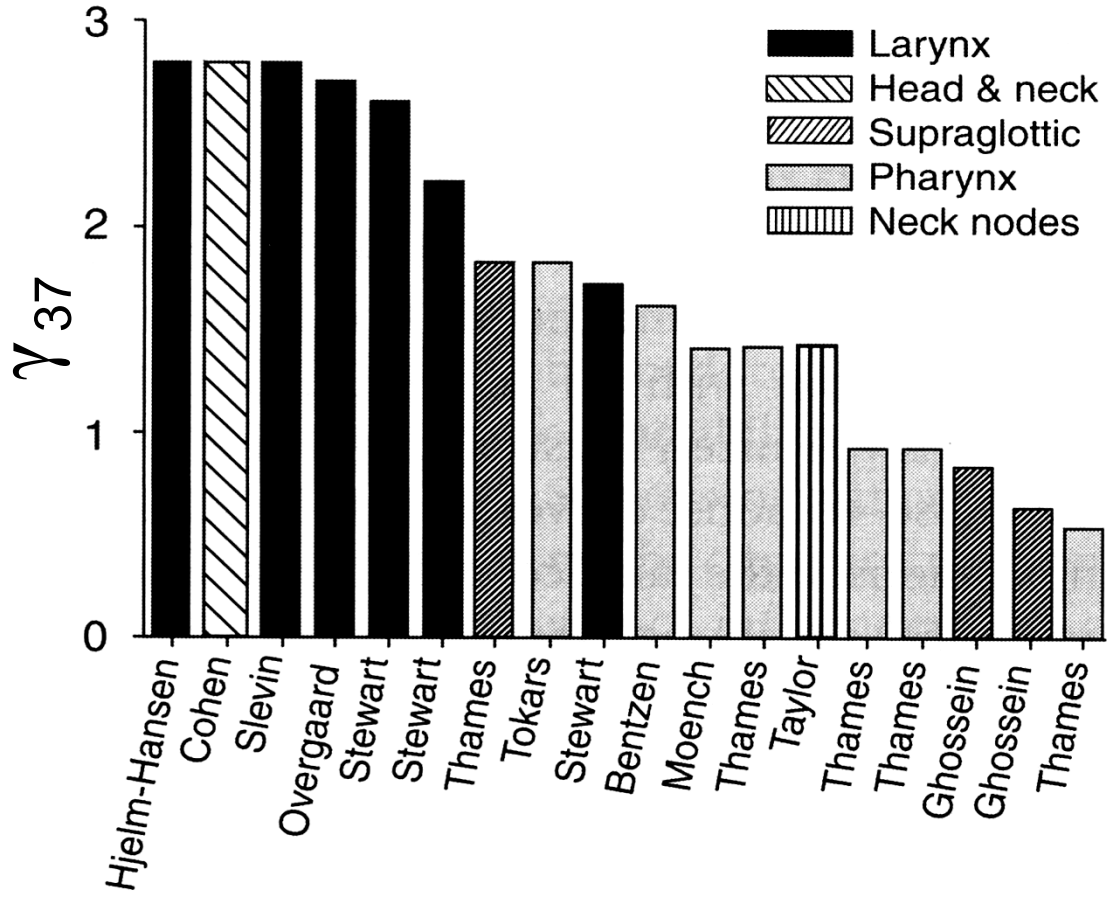
γ_{50}	Response level, %								
	10	20	30	40	50	60	70	80	90
1	0.2	0.4	0.7	0.9	1.0	1.1	1.0	0.9	0.6
2	0.5	1.1	1.5	1.8	2.0	2.0	1.9	1.5	0.9
3	0.9	1.7	2.3	2.8	3.0	3.0	2.7	2.1	1.3
4	1.2	2.3	3.2	3.7	4.0	3.9	3.5	2.8	1.6
5	1.6	3.0	4.0	4.7	5.0	4.9	4.4	3.4	2.0

γ is only useful when you are “on the curve”!

Clinical estimates of γ

Average γ_{37} for H&N ≈ 2%

From studies in which dose per fraction was fixed

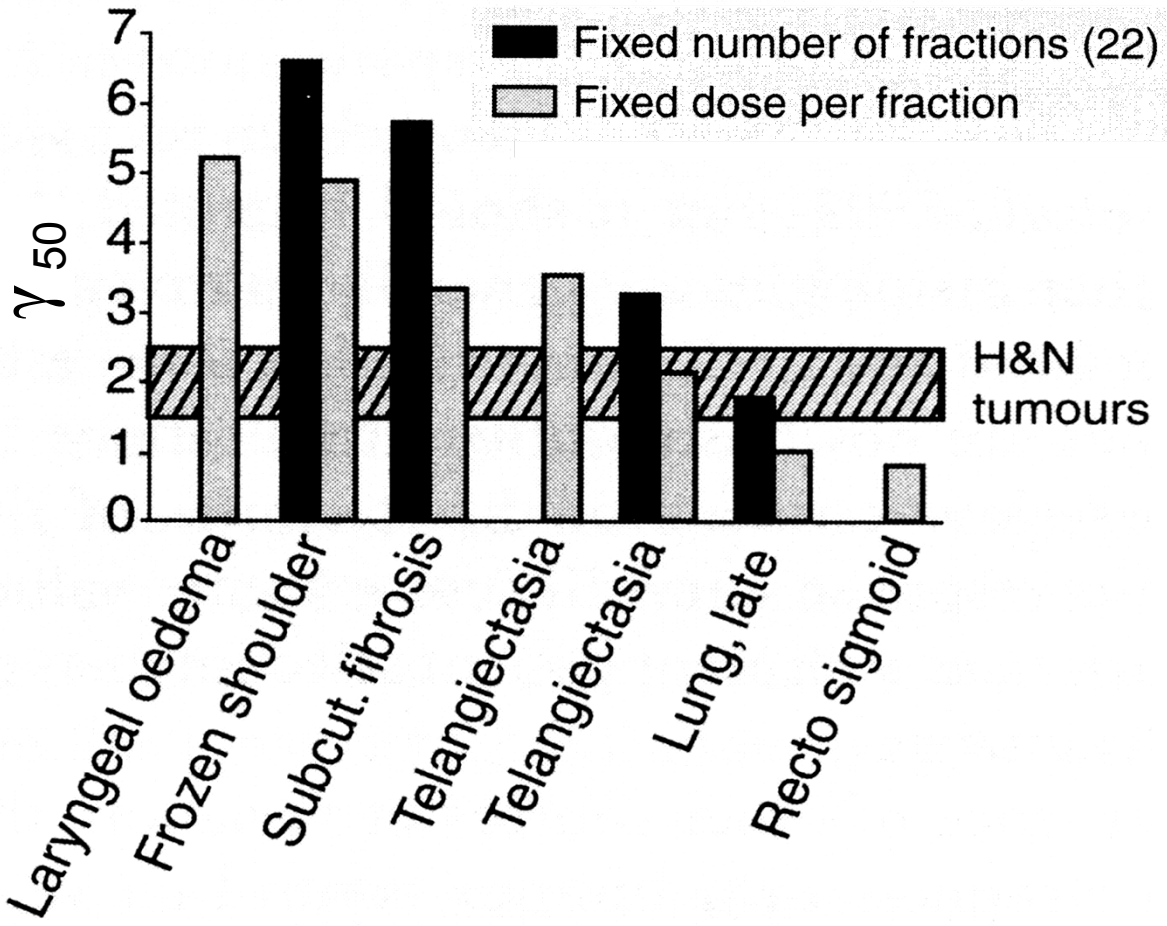


Bentzen (1994)

Value of γ in some late-reacting tissues

Compared with tumors,
γ is larger

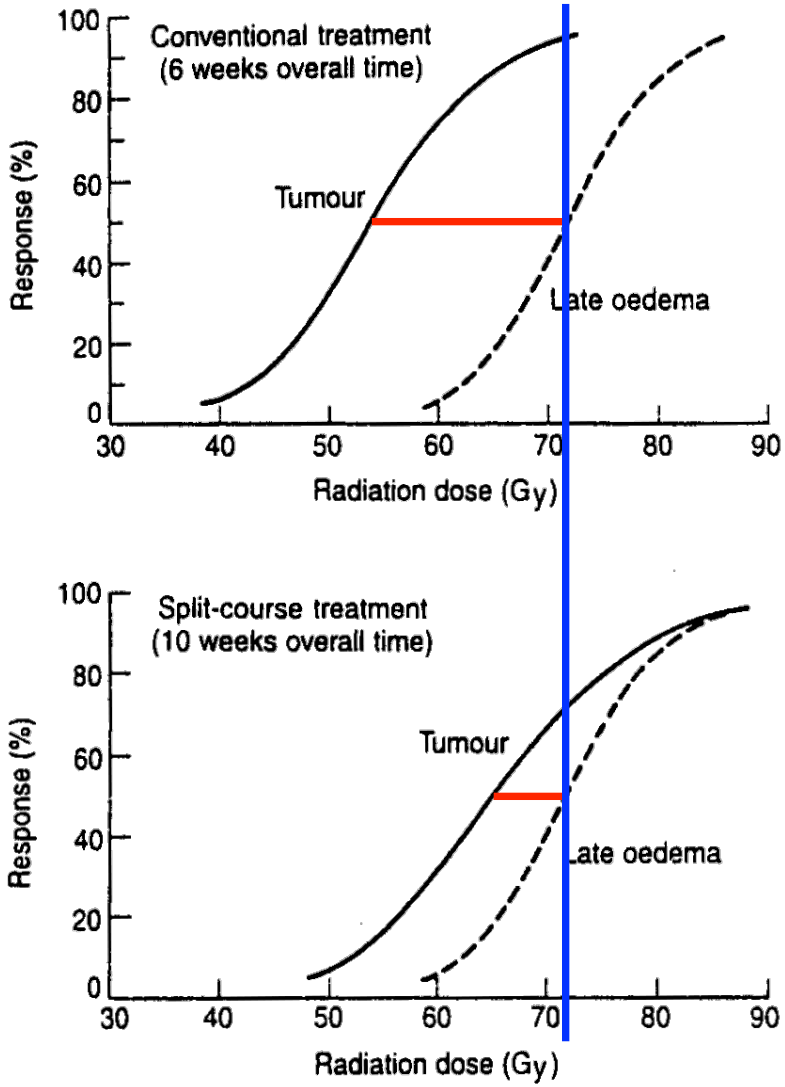
Dose response curves
can be steeper,
more so when
fixed fraction number,
i.e. higher dose per fraction



Bentzen (1994)
Bentzen and Overgaard (1996)

Balancing risks and benefits: The therapeutic window

Example: protraction of overall treatment time is detrimental!

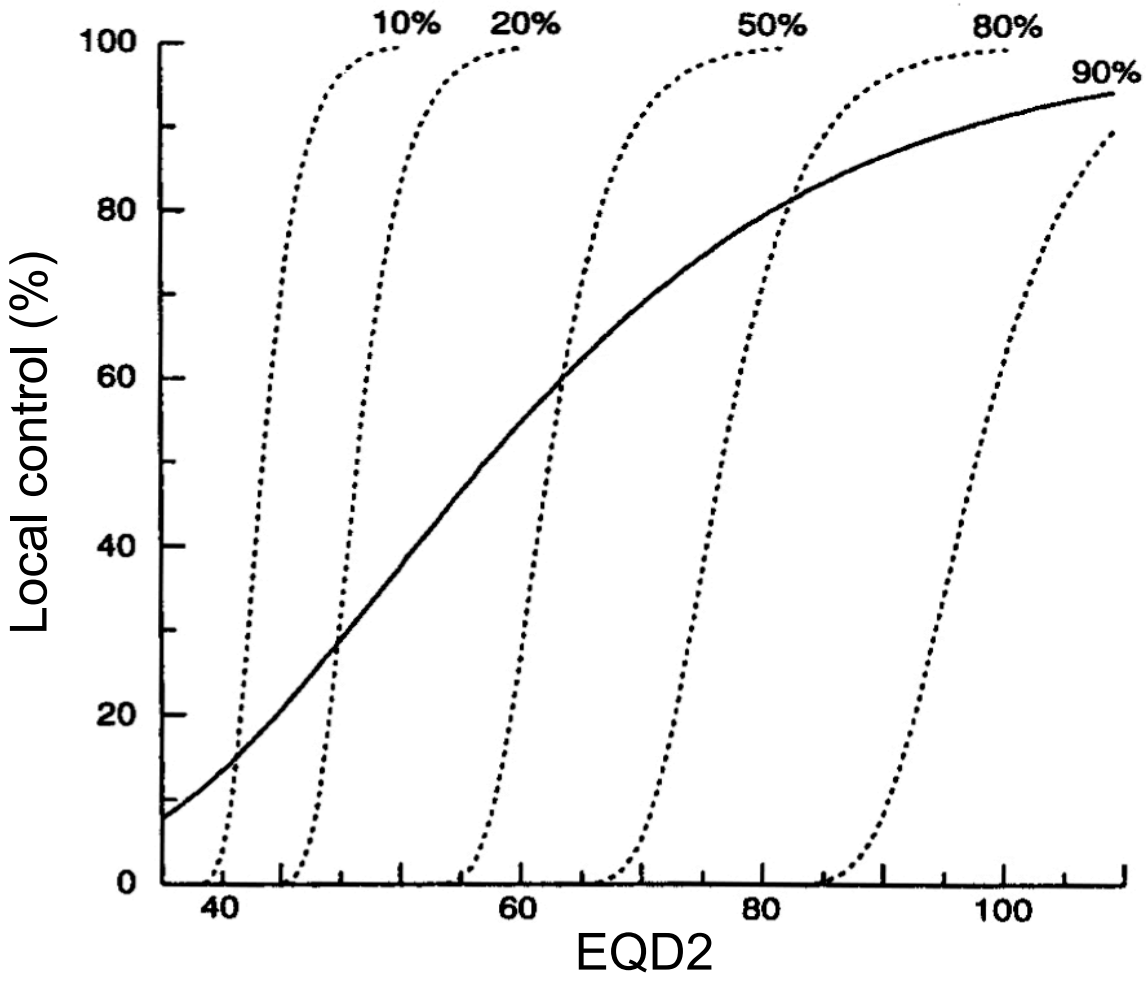


Bentzen and Overgaard (1996)

Modifying the steepness of the dose-response

Oropharyngeal cancer

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



Bentzen (1994)

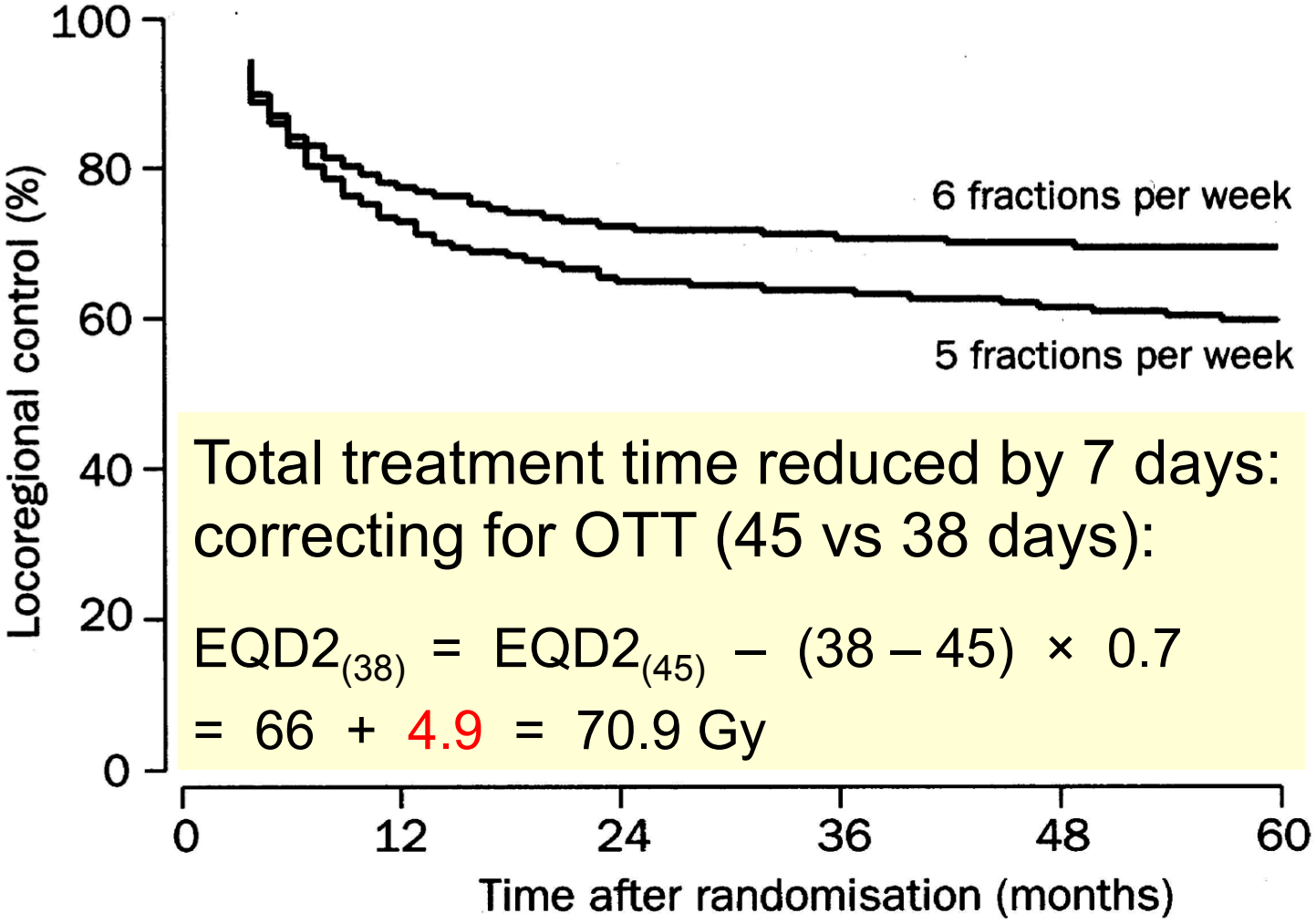
Clinical data to test modeling

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 vs 38 days):

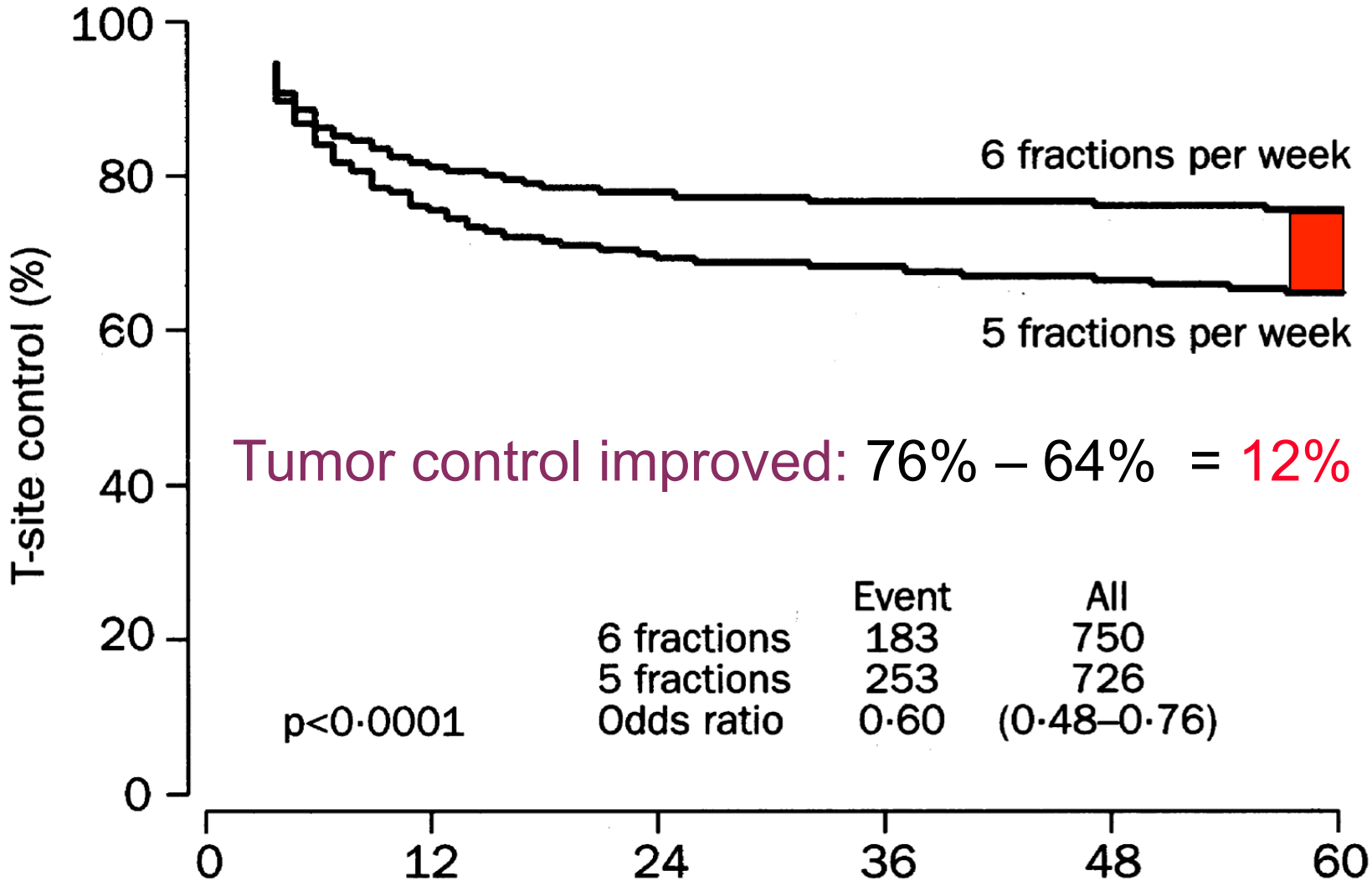
$EQD2_{(38)} = EQD2_{(45)} - (38 - 45) \times 0.7$

$= 66 + 4.9 = 70.9$ Gy

From change in dose to change in RR

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

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


100
80
60
40
20
0
T-site control (%)
6 fractions per week
5 fractions per week
Tumor control improved: 76% – 64% = 12%
Event
All
6 fractions
183
750
5 fractions
253
726
p<0·0001
Odds ratio
0·60
(0·48–0·76)
0
12
24
36
48
60

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 of dose-volume effects in normal tissue

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

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

$0 < n < 1$

Larger n, more volume effect

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

(see BCR book, Ch 5.9)

D_{50} = uniform dose producing 50% incidence of specific effect

n = denotes influence of volume effect in organ of interest

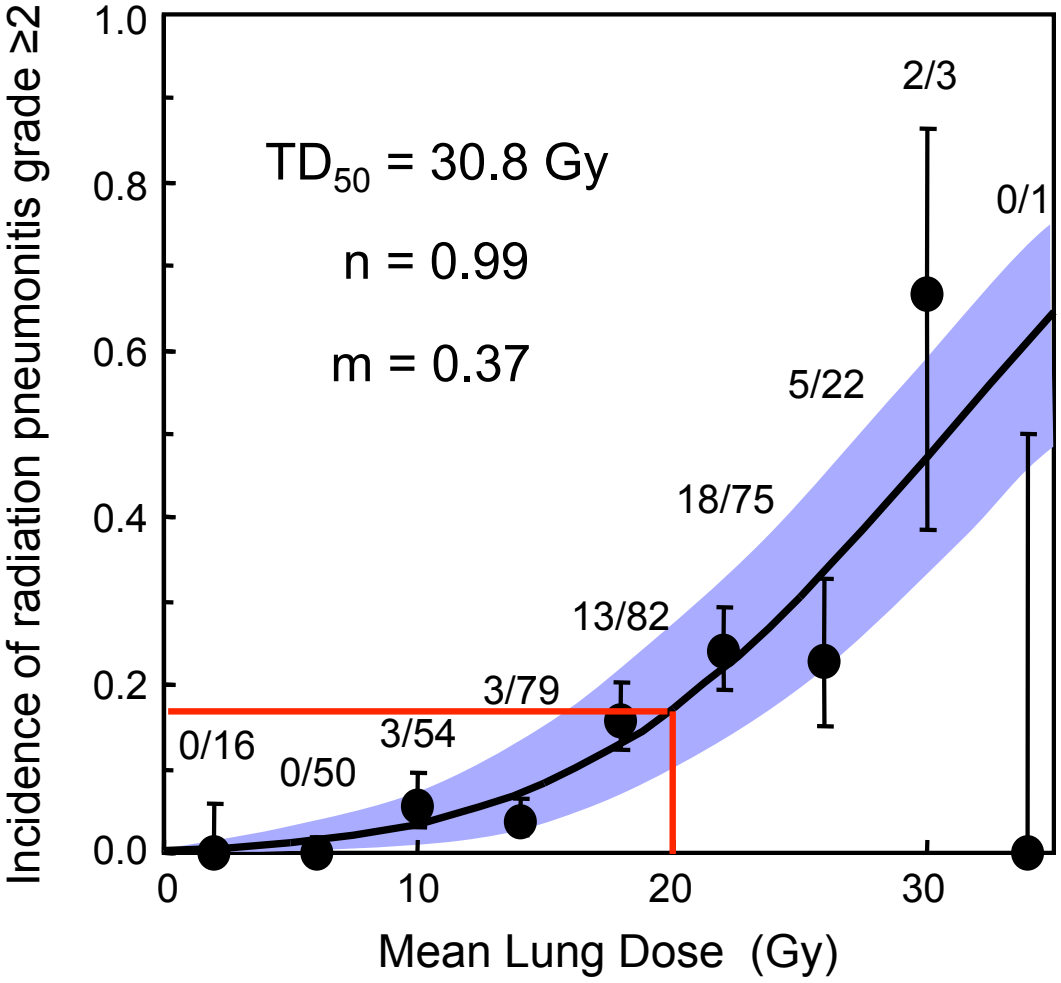
m = inverse of dose response curve gradient

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

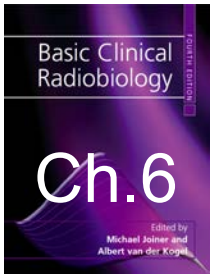
ESTRO School

Basic Clinical Radiobiology

LET and RBE

Michael Joiner

Paris 2017



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 rel
2	Moderate cluster	~100 eV within ~2 nm	DNA segment	~20–100	Charac ~repa
3	Large cluster	~400 eV within 5–10 nm	Nucleosome	~4–100	Characteristic of high-LET; ~u
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).

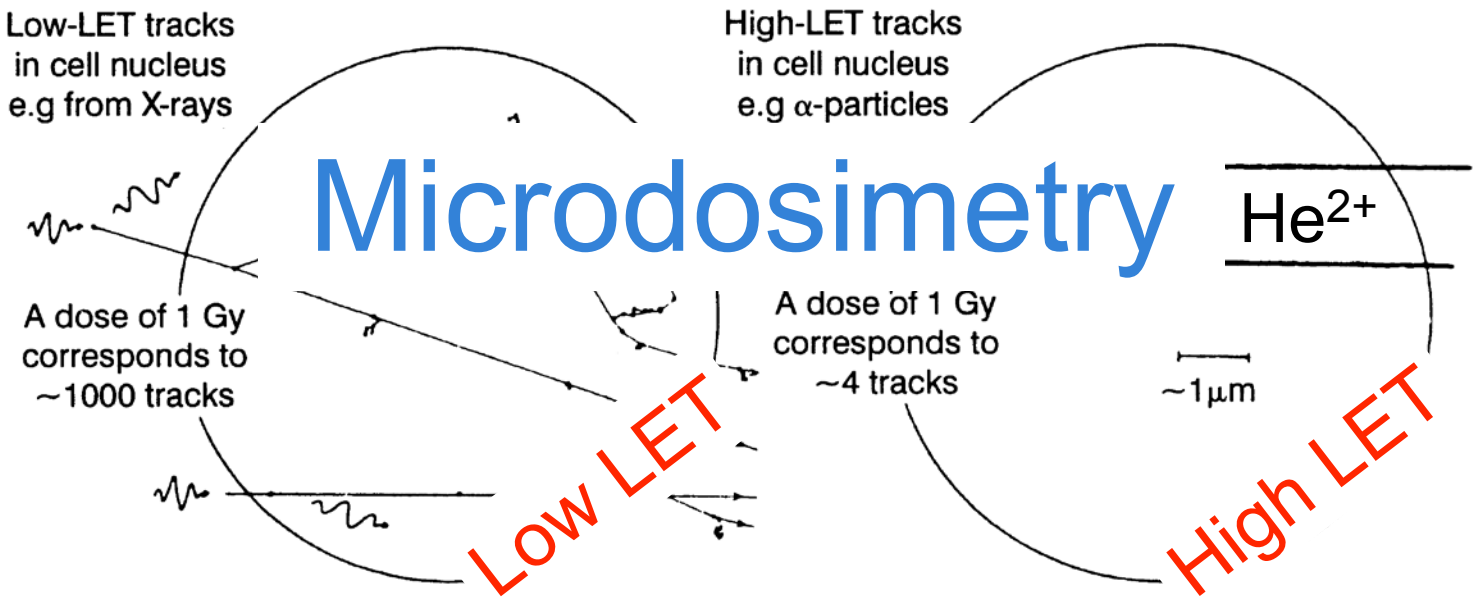
Linear Energy Transfer (LET)

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

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 keV μm^{-1} (keV/μm)



Microdosimetry

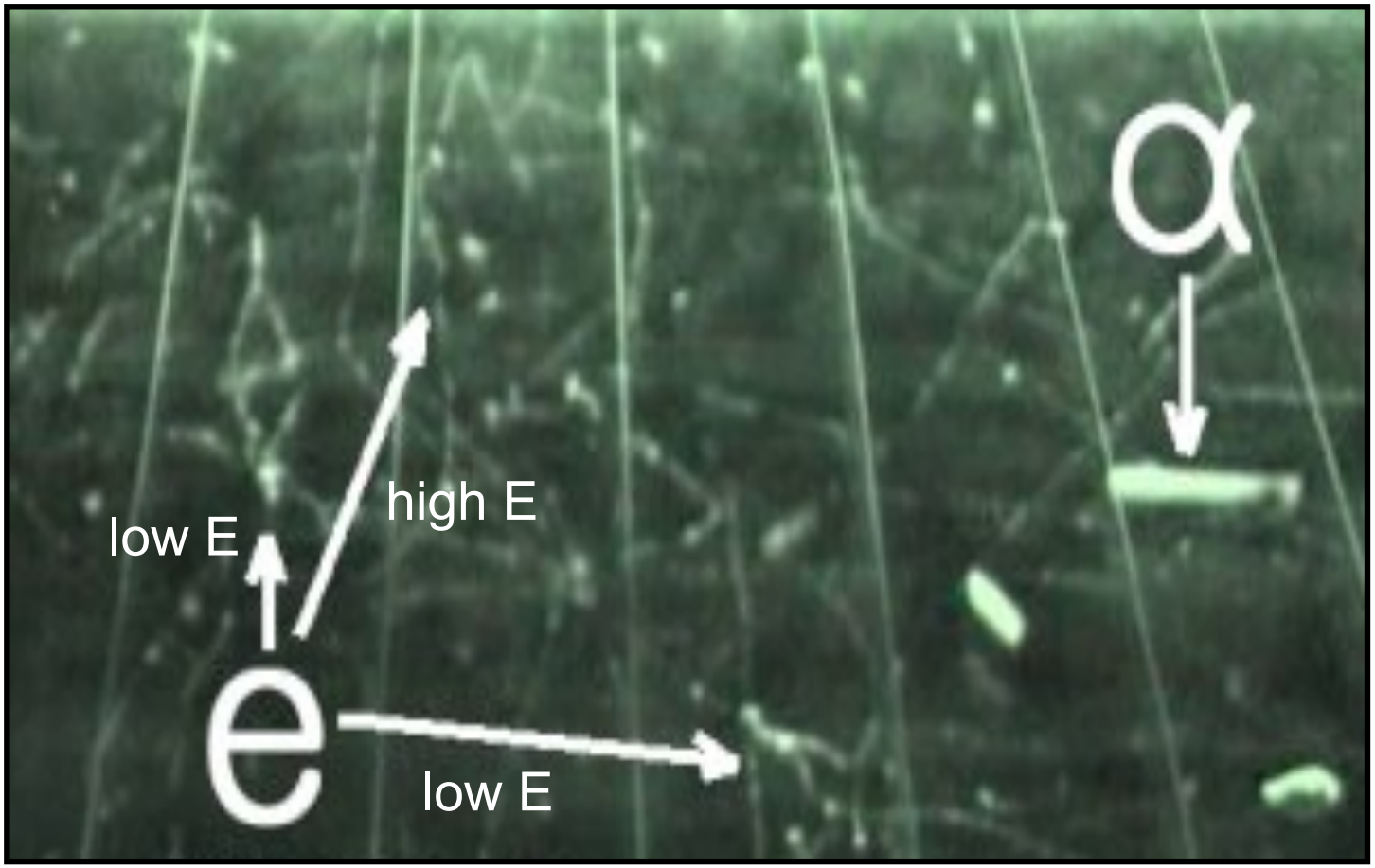
LET: Linear Energy Transfer.

A measure of average ionization density.

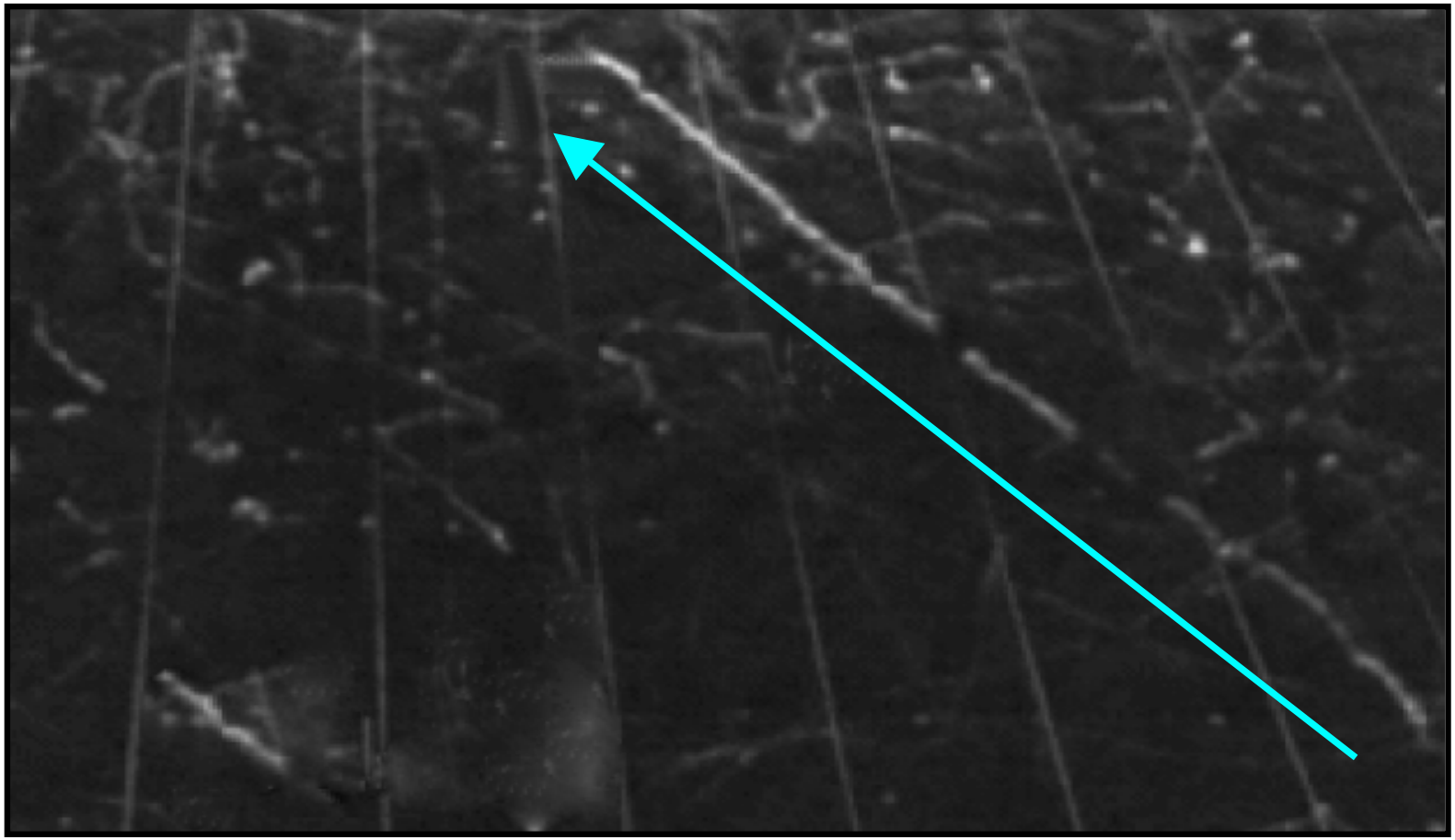
$$LET \propto \frac{charge^2}{velocity^2}$$

Charged particle tracks in a cloud chamber

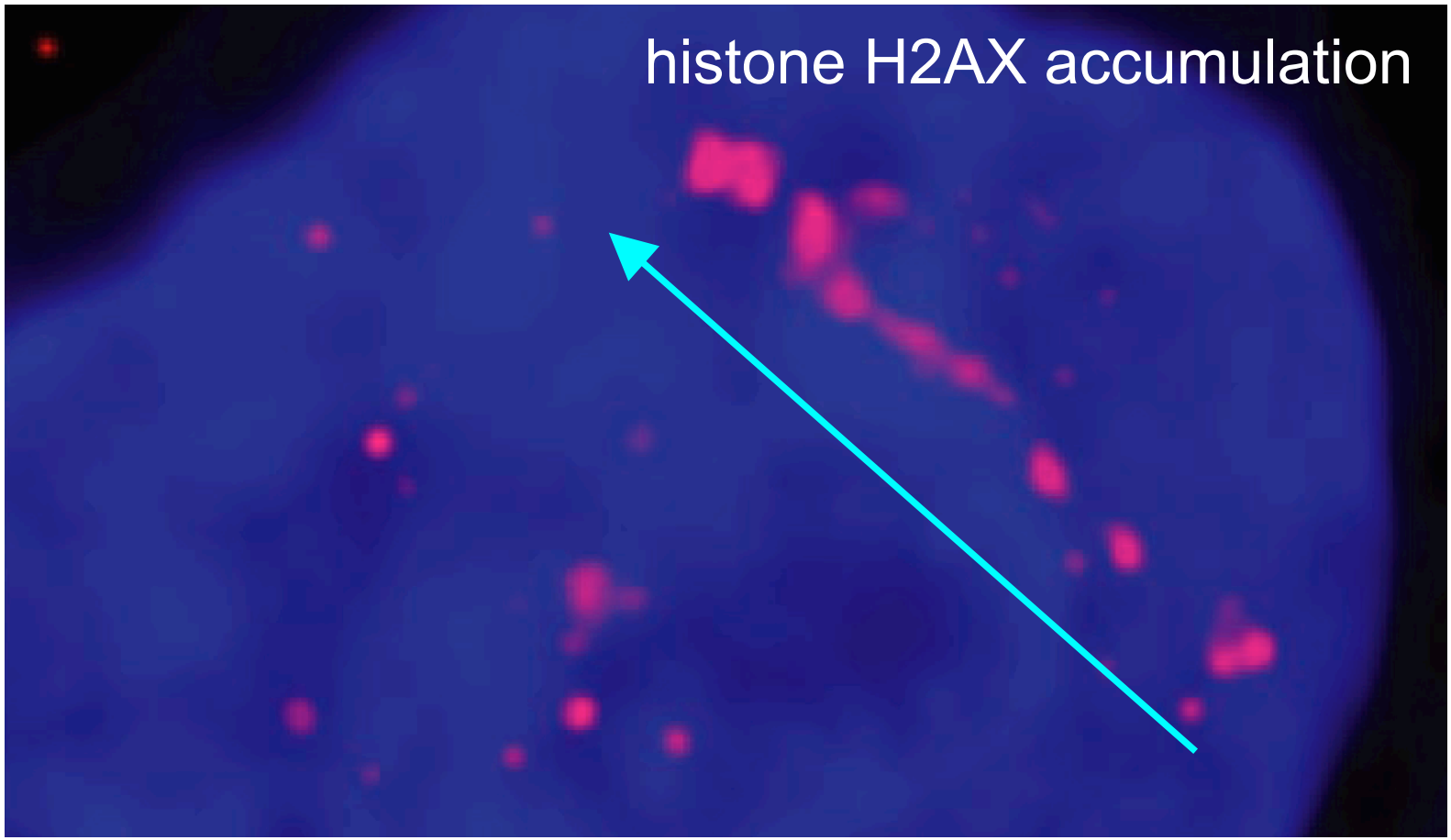
Cloud chamber photograph shows many high-energy electrons (thin tracks), low energy electrons (thicker tracks), and α particles (thickest tracks)



Charged particle slows from lower right to upper left



Initial DNA damage from an α particle



Typical LET values

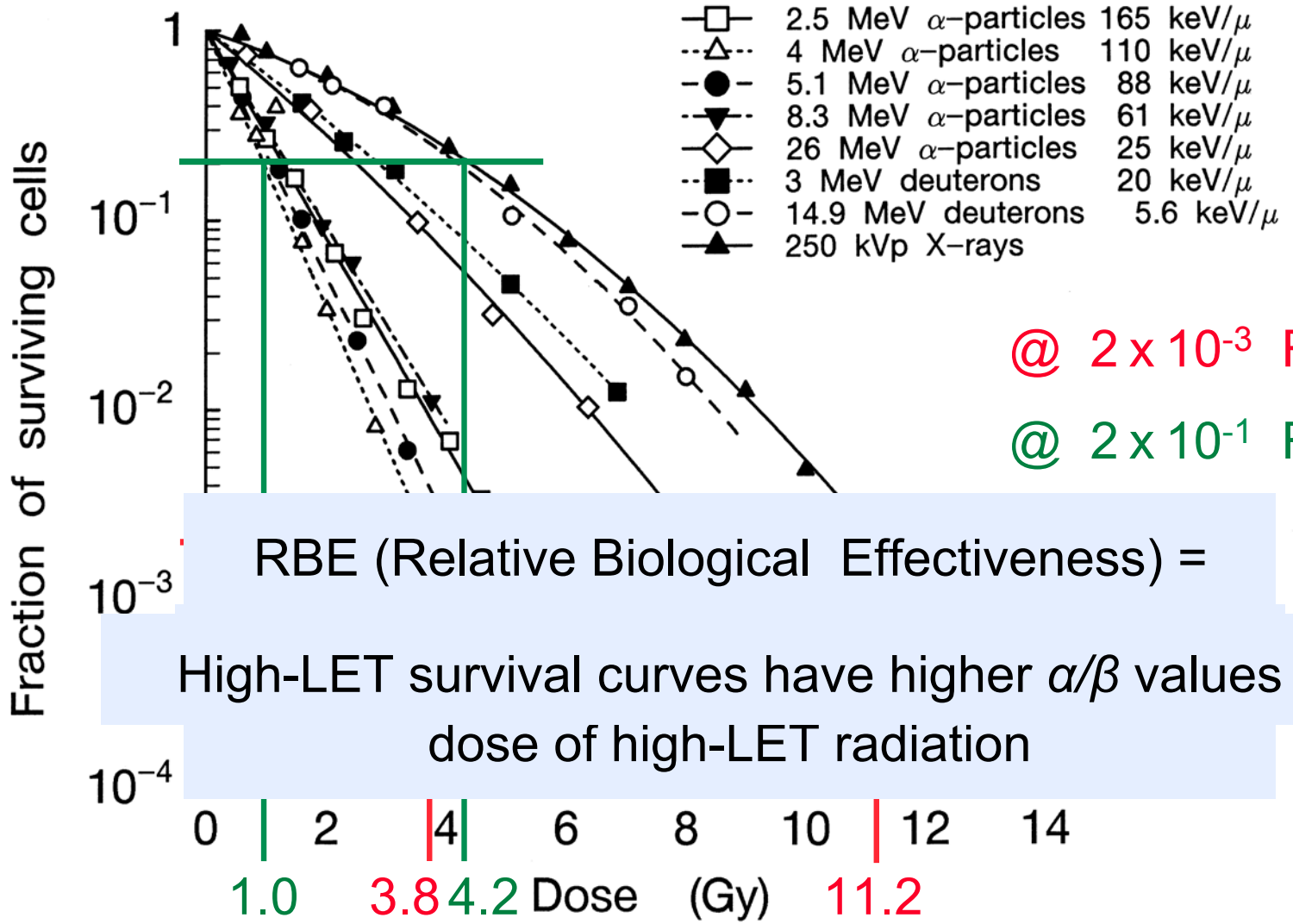
Radiation	Linear Energy Transfer, KeV/μm	
Cobalt-60 γ-rays	0.2	
250-kV x-rays	2.0	
10-MeV protons	4.7	
150-MeV protons	0.5	
	Track Avg.	Energy Avg.
14-MeV neutrons	12	100
2.5-MeV α-particles	166	
2-GeV Fe ions	1,000	

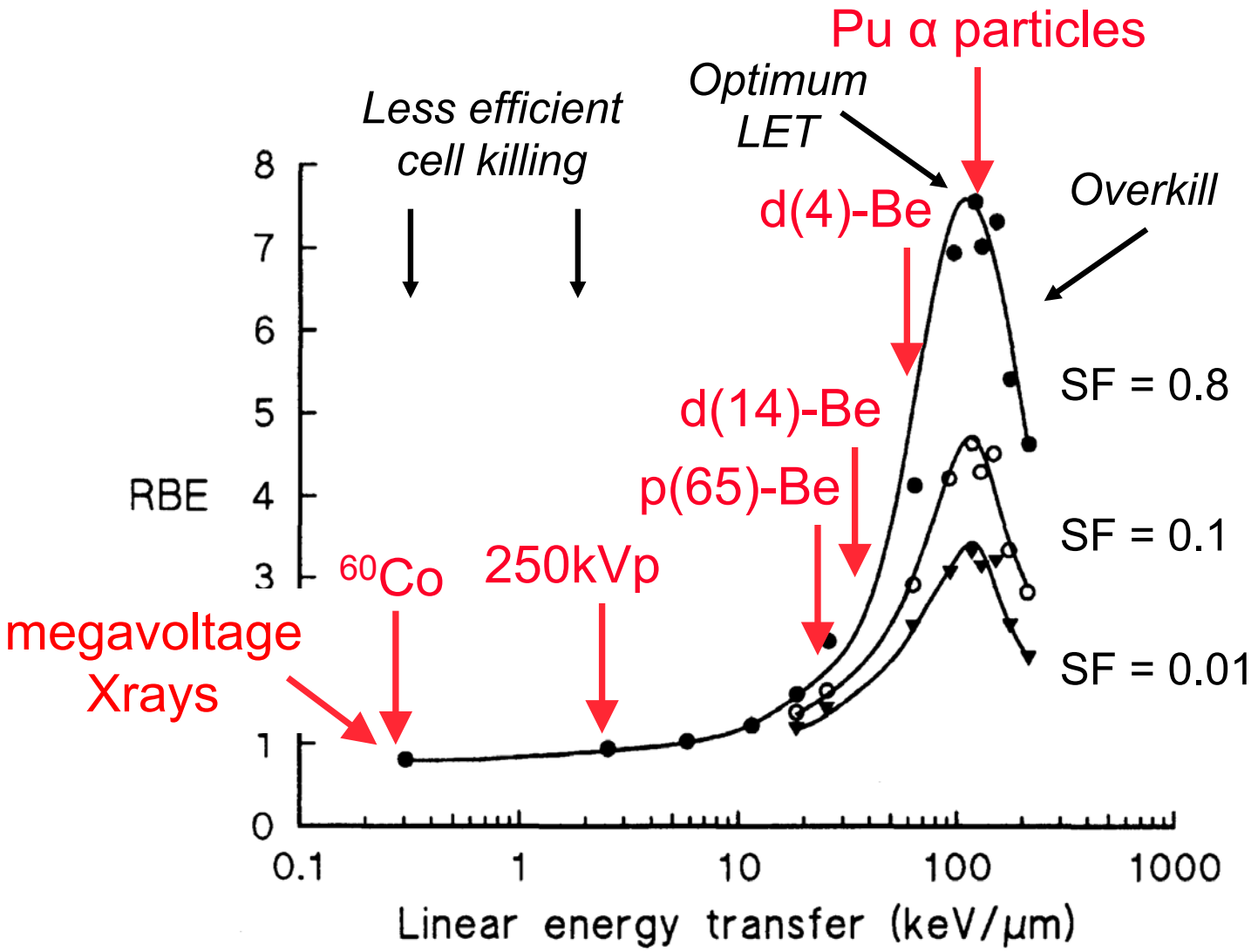
Relative Biological Effectiveness (RBE)

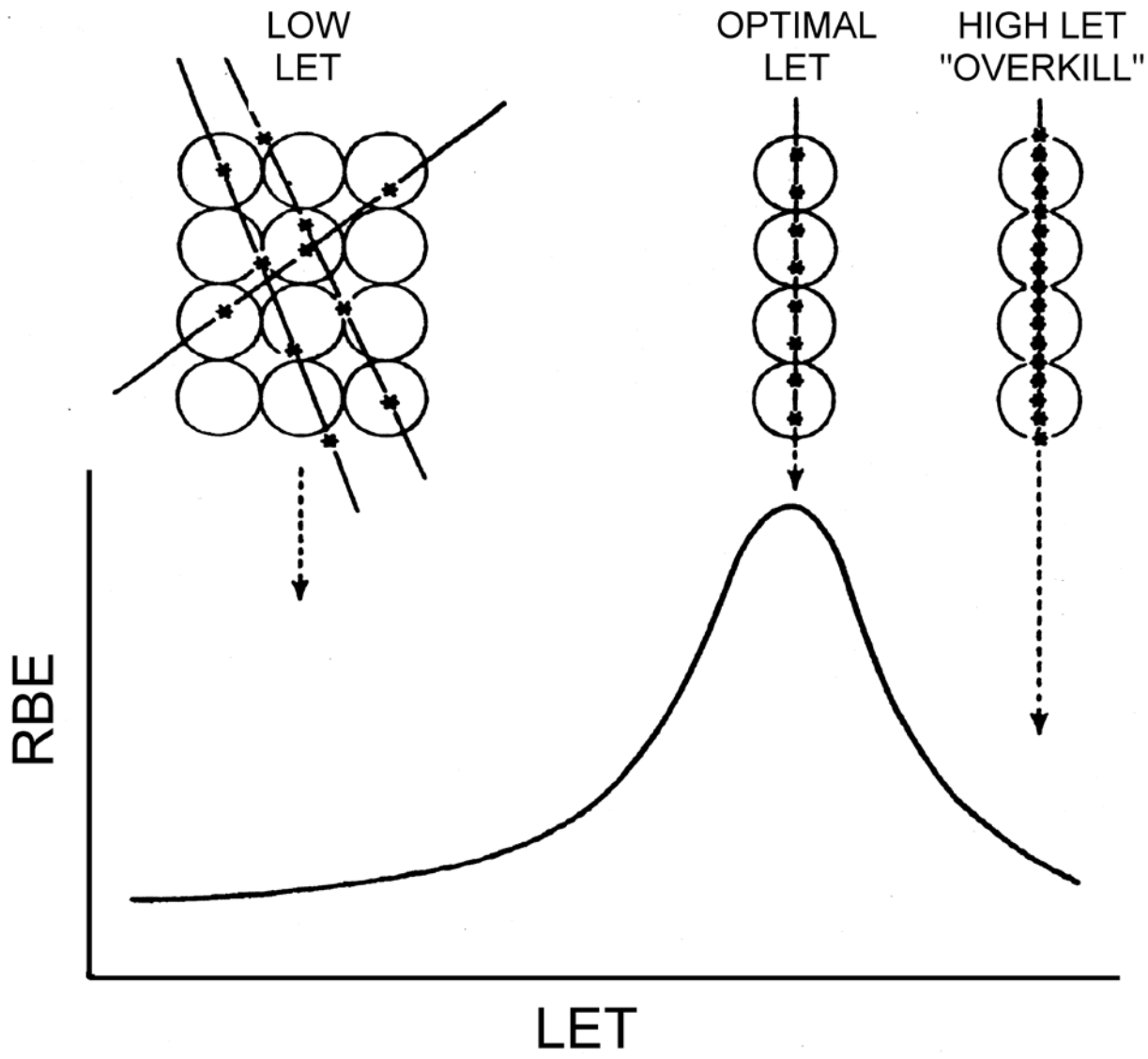
$$RBE = \frac{\textit{dose of a } \textbf{standard radiation}}{\textit{dose of the } \textbf{test radiation}}$$

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

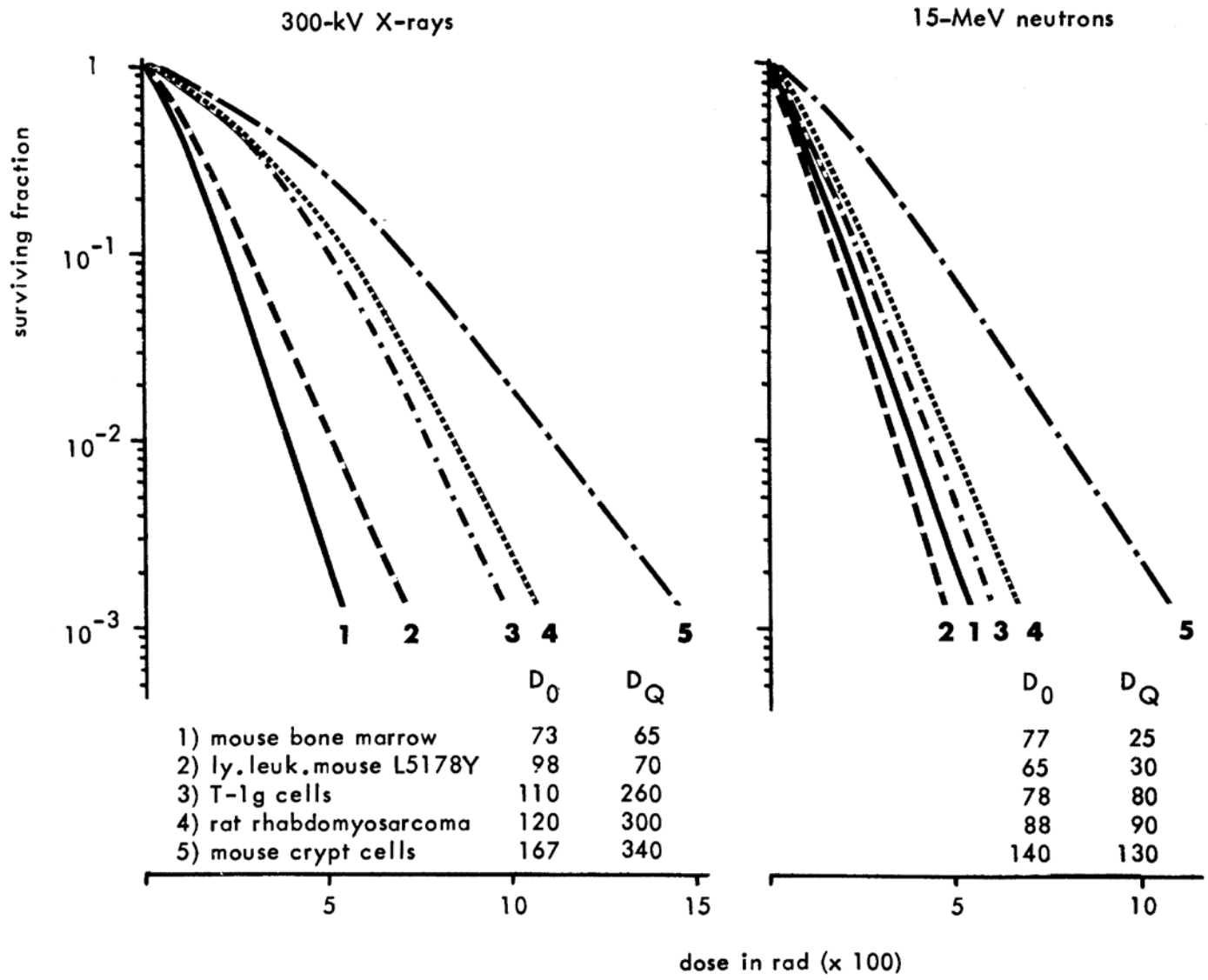
Note: The RBE between 250kVp X and ^{60}Co γ (and MV) is about 1.10–1.15 (depending on dose)


Fraction of surviving cells
1
10^{-1}
10^{-2}
10^{-3}
10^{-4}
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
@ 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

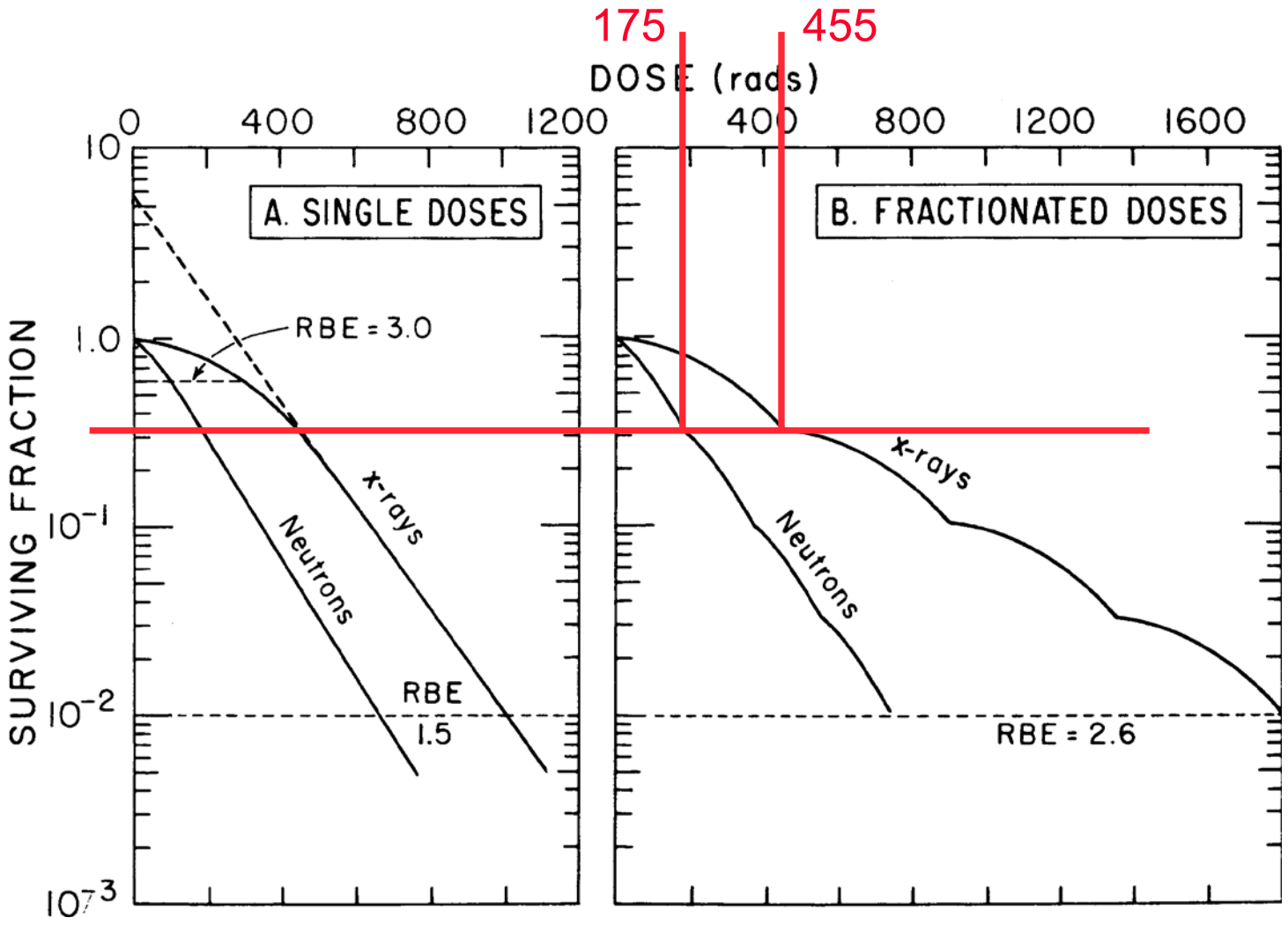
Dependence of RBE on type of cell irradiated



Dependence of RBE on the type of cell irradiated

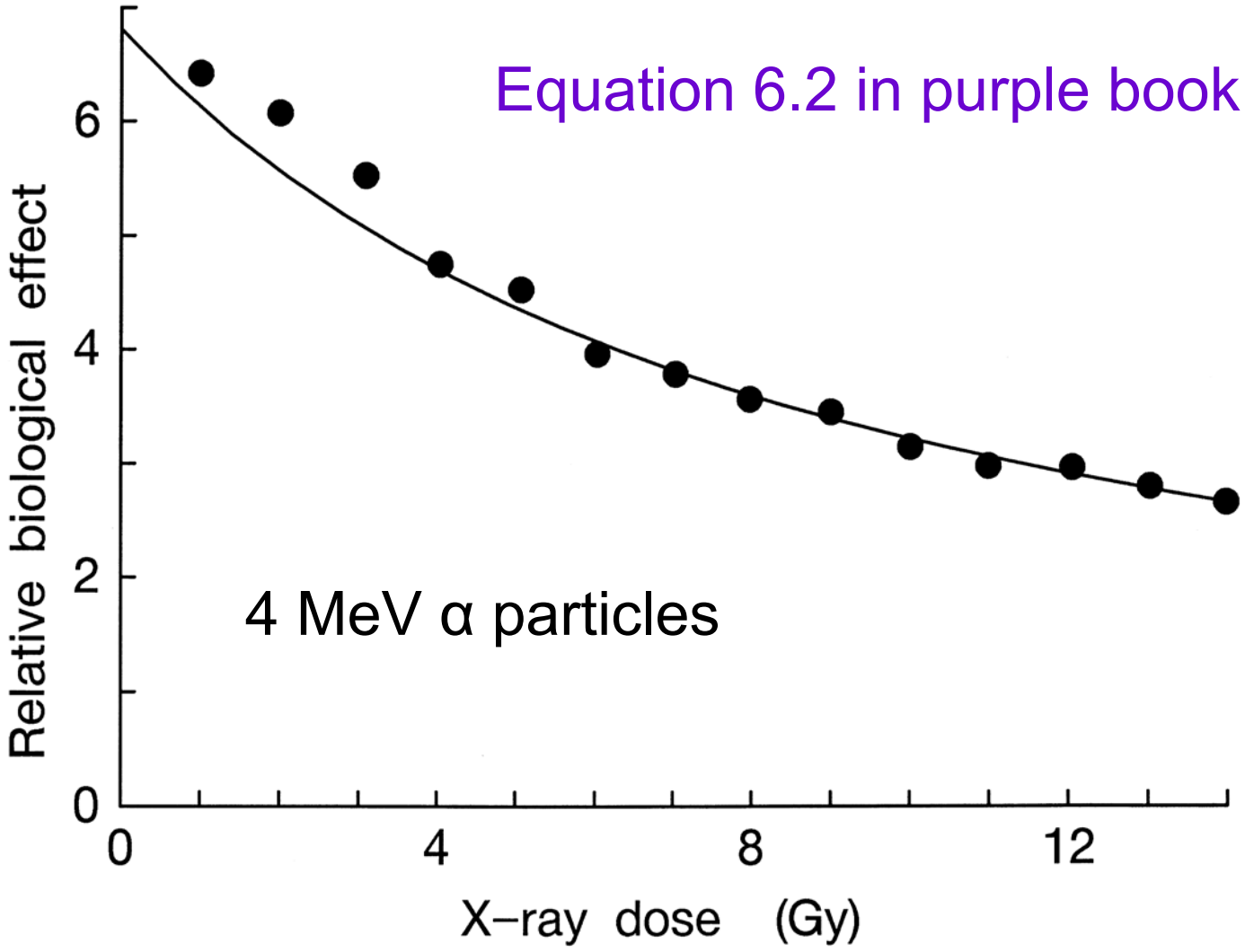
- Cells which exhibit large shoulders in their X-ray survival curves tend to have high RBEs
- Cells with *little, if any, shoulder* tend to have *low RBEs*
- There are exceptions, due to the different interaction mechanisms between low and high LET radiations *e.g.* cell-cycle effect

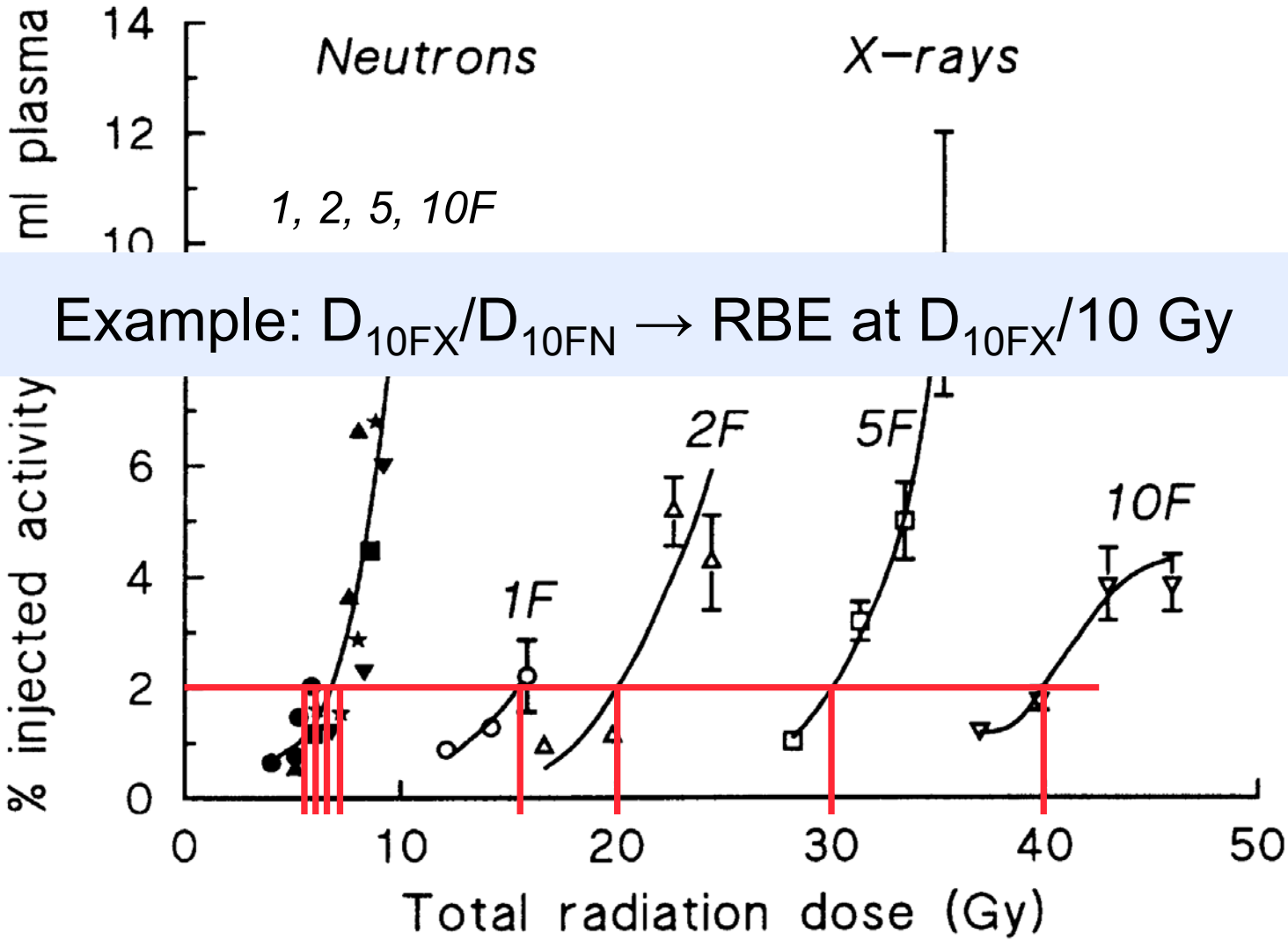
Effect of dose and dose per fraction on the RBE



Effect of dose and dose per fraction on the RBE

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

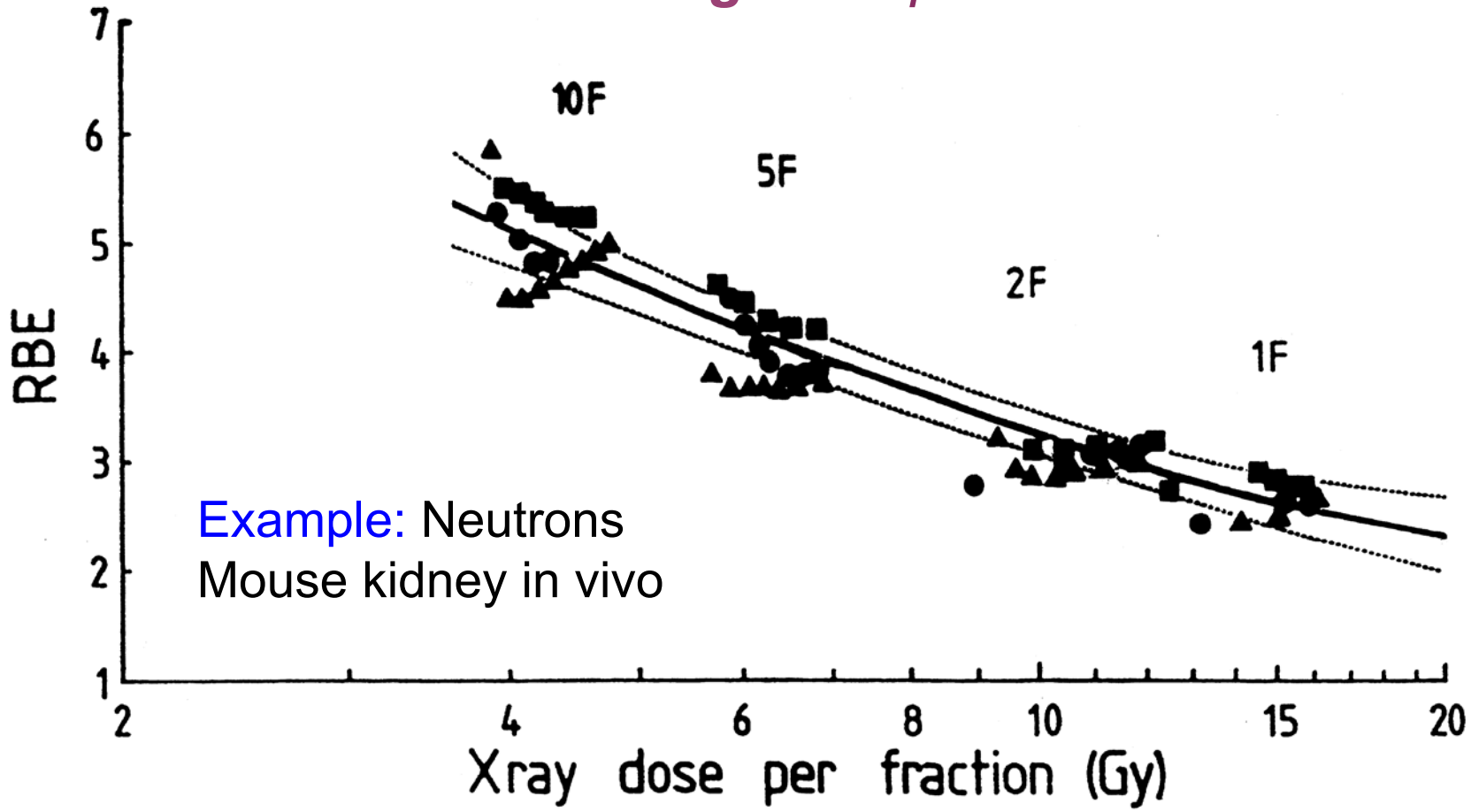

Equation 6.2 in purple book
4 MeV α particles
Relative biological effect
0
2
4
6
0
4
8
12
X–ray dose (Gy)



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 in radiation protection to cover all biological systems, doses, and endpoints.

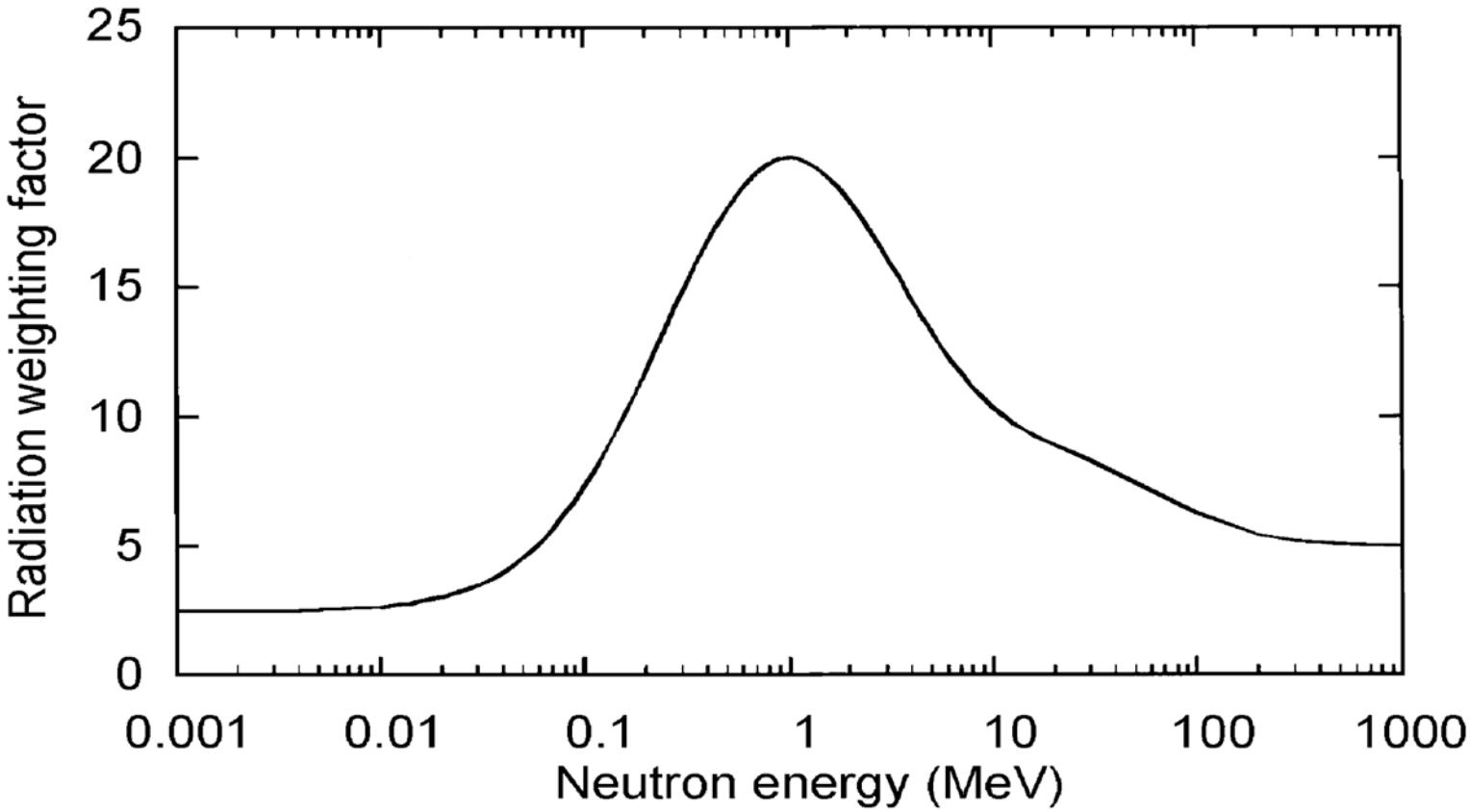
Radiation weighting factors (W_R)

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)



LET and RBE 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

LET and RBE 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

LET and RBE Conclusions 3

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

LET and RBE 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*

LET and RBE 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 LQ model in practice
A prostate cancer case

Karin Haustermans

Department of Radiation Oncology, University Hospitals Leuven, Belgium

Prostate cancer case

- A famous Belgian man 65 years old
- WHO performance status 1
- PSA 9,6 µg/l
- MR guided biopsy in the right lobe: Gleason score 3+4 in two cylinders (60% and 85%)
- Bone scan en CT scan of the pelvis negative
- cT2aN0M0

Prostate cancer case

- We proposed him 35 fractions of 2,2 Gy (TD 77 Gy) with 6 months of ADT
- What would be the chance to achieve biochemical control for this patient?
- α/β is assumed to be 1,5 Gy for prostate cancer

Prostate cancer case

- Calculation:
  - $EQD_2 = D \frac{d + (\alpha/\beta)}{2 + (\alpha/\beta)}$
  - $EQD_2 = 77 \times \frac{2{,}2 + 1{,}5}{2 + 1{,}5}$
  - $EQD_2 = 81{,}4$ Gy

- Difference = 90,4 Gy – 81,4 Gy = 9 Gy

→ 1,8% / 1 Gy = 16,2 %

Prostate cancer case

- He went to the UK for a second opinion …

CHHiP-trial

- 74 Gy / 2 Gy (37#) vs 60 Gy / 3 Gy (20#) vs 57 Gy / 3 Gy (19#)
- 3152 analysable patients
- 73% Intermediate risk; 15% Low risk; 12% High risk (NCCN)
- 97% Androgen deprivation (3-6 months)
- IMRT
- Non-inferior design (bNED or cNED -free survival ± 5% at 5 years)

Dearnaley et al. Lancet Oncol. 2016

EQD2 for prostate cancer in these 3 arms?

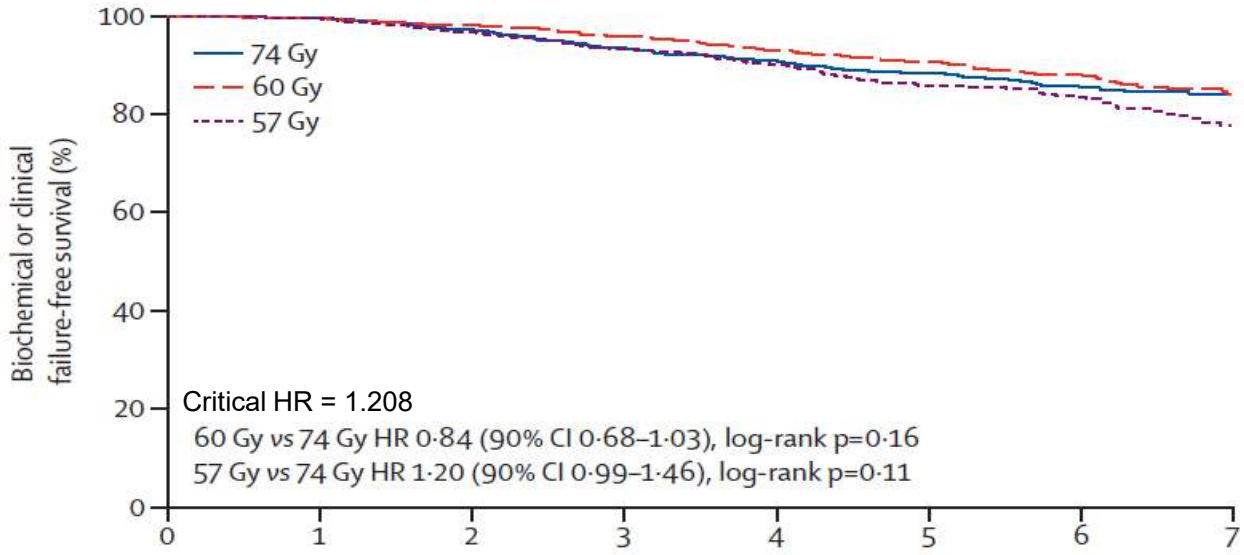
Prostate cancer case

Question 2: Which study-arm is biologically the most iso-effective with the standard-arm (74 Gy), regarding tumour control?

- Calculation: $E/\alpha = BED = D\left(1 + \frac{d}{(\alpha/\beta)}\right)$
- 74 Gy – arm $= 74\left(1 + \frac{2}{1,5}\right) = 172,67$ Gy
- 60 Gy – arm $= 60\left(1 + \frac{3}{1,5}\right) = 180$ Gy
- 57 Gy – arm $= 57\left(1 + \frac{3}{1,5}\right) = 171$ Gy

CHHiP-trial

- 60 Gy / 3 Gy (20#) = non-inferior (5y DFS)
- 57 Gy / 3 Gy (19#) = could not be claimed non-inferior (5y DFS)



Number at risk (events)								
74 Gy	1065 (4)	1037 (24)	991 (39)	926 (24)	795 (20)	495 (11)	284 (3)	167 (11*)
60 Gy	1074 (4)	1042 (15)	1011 (23)	965 (28)	816 (18)	533 (10)	280 (10)	176 (10*)
57 Gy	1077 (5)	1044 (30)	1004 (35)	944 (31)	798 (31)	492 (9)	262 (13)	151 (9*)
Number censored								
74 Gy	0	24	22	26	107	280	200	114
60 Gy	0	28	16	23	121	265	243	94
57 Gy	0	28	10	25	115	275	221	98

Dearnaley et al. Lancet Oncol. 2016

EQD2 for OAR in these 3 arms?

Acute?

Late?

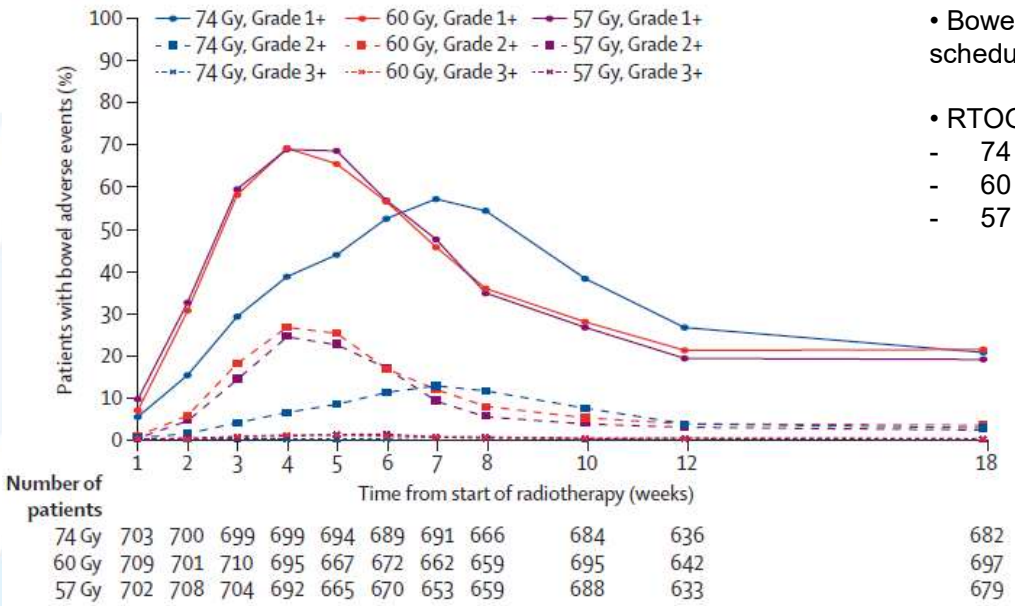
Prostate cancer case

Question 3: Which arm will cause theoretically the most late toxicity?

- Calculation: $E/\alpha = BED = D\left(1 + \frac{d}{(\alpha/\beta)}\right)$
- 74 Gy – arm: $= 74\left(1 + \frac{2}{3}\right) = 123{,}33$ Gy
- 60 Gy – arm: $= 60\left(1 + \frac{3}{3}\right) = 120$ Gy
- 57 Gy – arm: $= 57\left(1 + \frac{3}{3}\right) = 114$ Gy

CHHiP-trial

- Acute toxicity: greater peak for acute bowel toxicity
- Late toxicity: no significant differences between the 74 Gy and the 60 Gy group



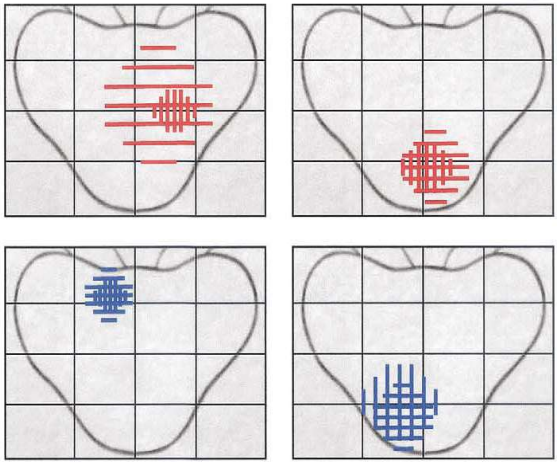
• Bowel symptoms peaked sooner in hypofractionated schedules

• RTOG grade 2 or worse bowel toxicity
- 74 Gy: 25%
- 60 Gy: 38%
- 57 Gy: 38%

Dearnaley et al. Lancet Oncol. 2016

Prostate cancer case

found out that recurrences most frequently occur at the primary tumor site …



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Cellini N et al. 2002

Universitair Medisch Centrum
Utrecht

- FLAME-trial

Randomized phase III trial

  - Standard arm: 77 Gy/2.2 Gy (35 fr) to the prostate
  - Experimental arm: additional integrated boost to macroscopically visible tumor, delineated based on 2 different imaging techniques, to a maximal total dose of 95 Gy (35 fr of 2.7 Gy)

– Primary endpoint

  - To decrease the 5-year biochemical relapse rate with at least 10%

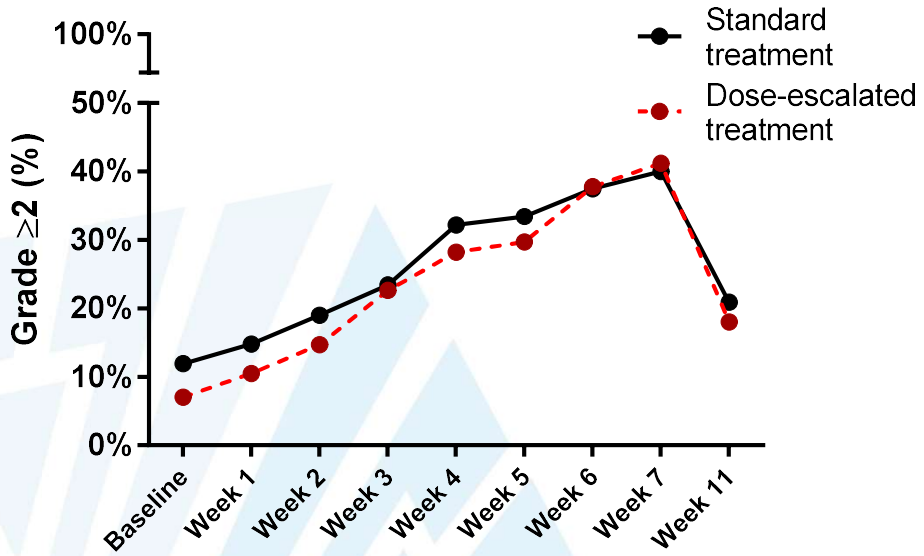
EQD2 for prostate cancer in these 2 arms?

EQD2 for OAR in these 2 arms?

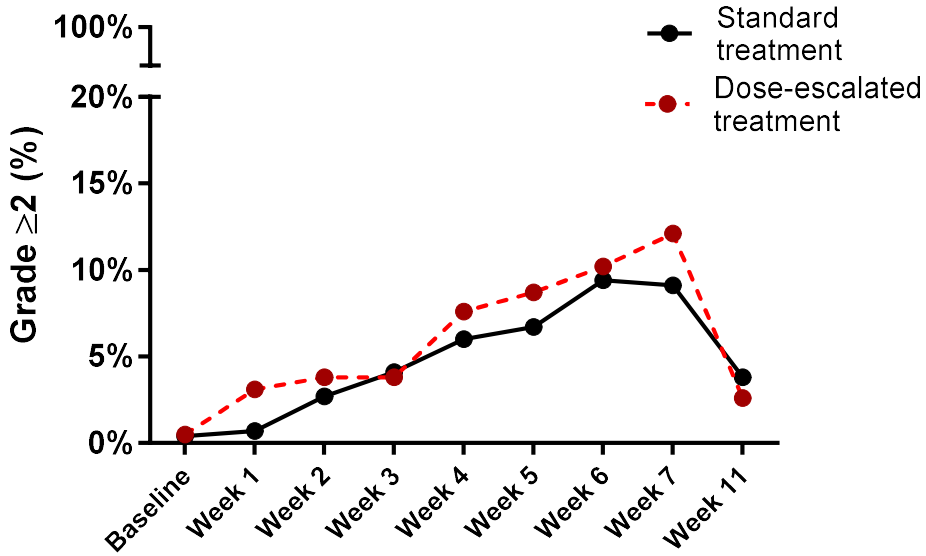
Acute?

Late?

A. Grade 2 or worse GU events over time



B. Grade 2 or worse GI events over time



Prostate cancer case

He wanted a shorter OTT due to his busy professional life …

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Extreme hypofractionation

Hypo – FLAME (phase II – trial)

- Patients are treated by external beam radiotherapy with a SBRT technique with 35 Gy in 5 weekly fractions and an additional simultaneously integrated focal boost to the tumor nodule(s) visible on MRI up to 50 Gy.

- The dose constraints for the bladder and rectum are maintained as in the Canadian SBRT PATRIOT protocol (which were proven safe and were associated with a very low rate of severe toxicity). To achieve equal or less toxicity compared to the current radiotherapy protocols, the organs at risk dose will be prioritised

Prostate cancer case

He decided to join the phase II Hypo-FLAME trial

Prostate cancer case

→ Dose constraints (GTV boost)

$D_{99\%} \geq 40$ Gy
$D_{0,1cc} < 52$ Gy

Prostate cancer case

Additional constraints corresponding to our standard dose constraints (2,2 Gy fractions) to prevent rectal toxicity

Volume	Max dose (35 fractions)
< 50%	42,9 Gy
< 70%	36,2 Gy
< 75%	28,6 Gy

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Prostate cancer case

- Extreme Hypofractionation for PCa

Calculation: $E/\alpha = BED = D\left(1 + \frac{d}{(\alpha/\beta)}\right)$

V42,9 → $BED = 42{,}9\left(1 + \frac{42{,}9/35}{3}\right) = 60$

SBRT → $BED = D\left(1 + \frac{D/5}{(\alpha/\beta)}\right)$

$60 = D\left(1 + \frac{D/5}{3}\right)$

$60 = D\left(1 + \frac{D}{15}\right)$

$\frac{1}{15}D^2 + D - 60 = 0$

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Prostate cancer case

- Extreme Hypofractionation for PCa

Calculation: $E/\alpha = BED = D\left(1 + \frac{d}{(\alpha/\beta)}\right)$

SBRT → $\frac{1}{15}D^2 + D - 60 = 0$

$$D = \frac{-1 \pm \sqrt{1^2 - 4 * \frac{1}{15} * (-60)}}{2 * \frac{1}{15}} \qquad \left(x = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a}\right)$$

$$D = \frac{-1 \pm \sqrt{1^2 + 16}}{\frac{2}{15}}$$

D = 23,4 Gy

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Prostate cancer case

Volume	Max dose (35 fractions)	Max dose (5 fractions)	BED
< 50%	42,9 Gy	23,4 Gy	60 Gy
< 70%	36,2 Gy	20,5 Gy	48,5 Gy
< 75%	28,6 Gy	16,9 Gy	36 Gy

Conventional radiotherapy

35x 2.2 Gy

How to manage uncertainties?

Incorporate uncertainties into treatment planning

Geometrical margins d
from popul

You can't anticipate everything!

rst case scenario
simulating uncertainties as dosimetric perturbations

Adapt plan in real-time to occurring events

Real-time orga
motio

You can't adapt to everything!

R ... adaptation of treatment plan to actual position

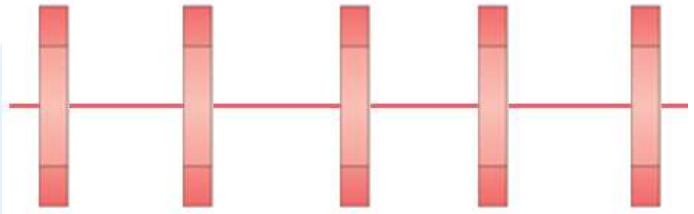
Inherent plan robustness
'Anticipate to what you expect'

Optimum?

Real-time adaptation
'Act to what you see'

'Act when necessary, anticipate as far as necessary'

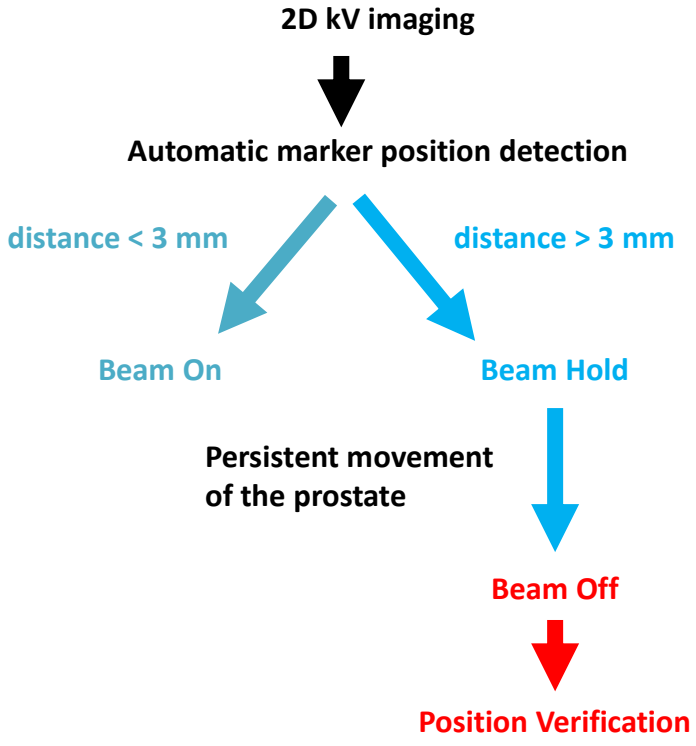
Extreme hypofractionation

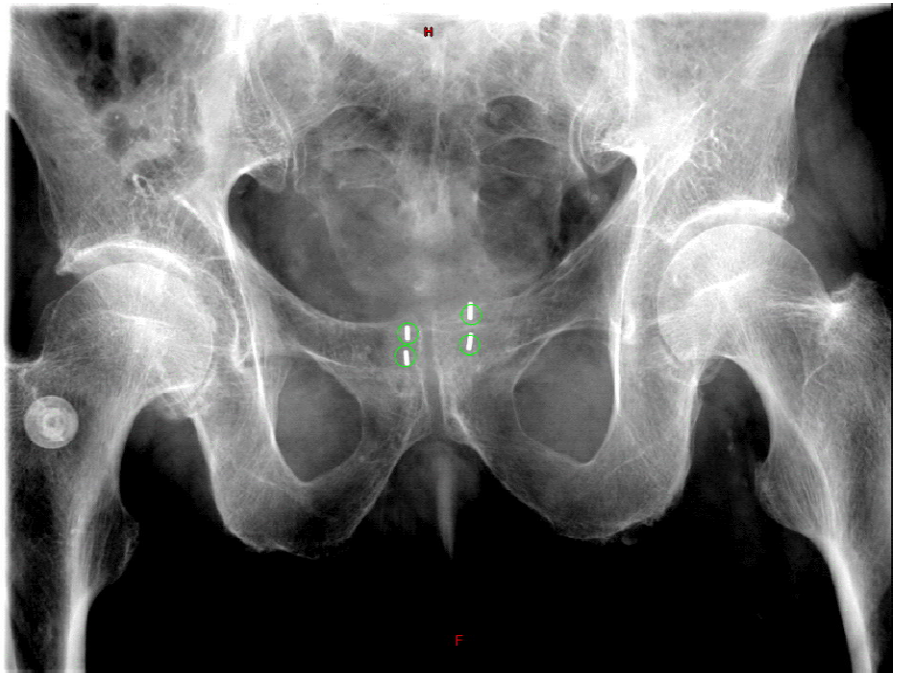


5x 7 Gy

General aspects SBRT for PCa

→ During radiation treatment: Automated Beam Hold





Prostate cancer case

- The first fraction was delivered
- We noticed a change in rectum distension when we compared CBCT before and after
- Rectum D_{max} was 9,5 Gy while Rectum D_{max} = 42 Gy (5 fractions) or 8,4 Gy / fraction

Prostate cancer case

Which dose may be delivered to the rectum in the 4 remaining fractions to not exceed Rectum D_{max}?

Prostate cancer case

- Question 5: Which dose may be delivered to the rectum in the 4 remaining fractions to not exceed Rectum D_{max}? (α/β is assumed to be 3 for late toxicity)

- Given:

	Fraction 1(Rectum)	Tolerance (Rectum)
	- D_{max} = 9,5 Gy	- D_{max} = 42 Gy
	- n = 1	- n = 5
	- d = 9,5 Gy	- d = 8,4 Gy

Prostate cancer case

- Given:

Fraction 1(Rectum)	Tolerance (Rectum)
- D_{max} = 9,5 Gy	- D_{max} = 42 Gy
- n = 1	- n = 5
- d = 9,5 Gy	- d = 8,4 Gy

- Calculation: $E/\alpha = BED = D\left(1 + \frac{d}{(\alpha/\beta)}\right)$

→ $BED_{fraction\ 1} = 9{,}5\left(1 + \frac{9{,}5}{3}\right) = 39{,}58$ Gy

→ $BED_{tolerance} = 42\left(1 + \frac{42/5}{3}\right) = 159{,}6$ Gy

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Prostate cancer case

- Calculation:

→ $BED_{fraction\ 1} = 9{,}5\ (1 + \frac{9{,}5}{3}) = 39{,}58$ Gy

→ $BED_{tolerance} = 42\ (1 + \frac{42/5}{3}) = 159{,}6$ Gy

→ $BED_{rest} = BED_{tolerance} - BED_{fraction1}$

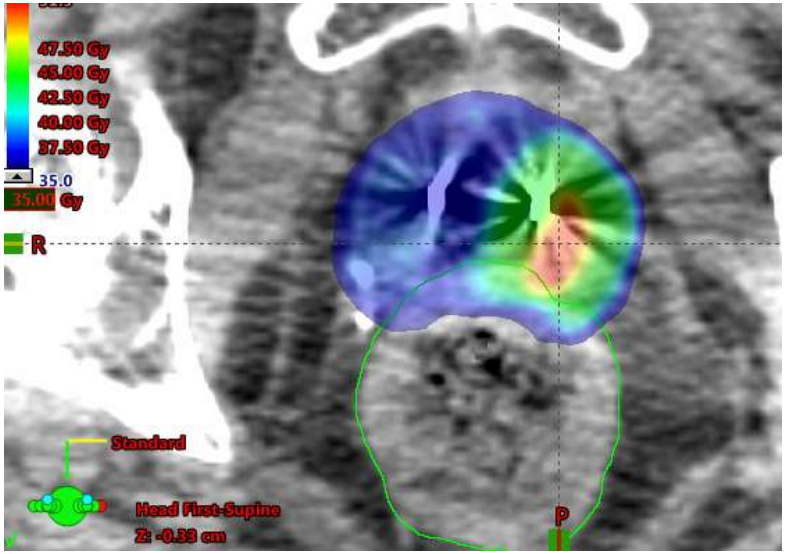
$= 159{,}6$ Gy $- 39{,}58$ Gy

$= 120{,}0$ Gy

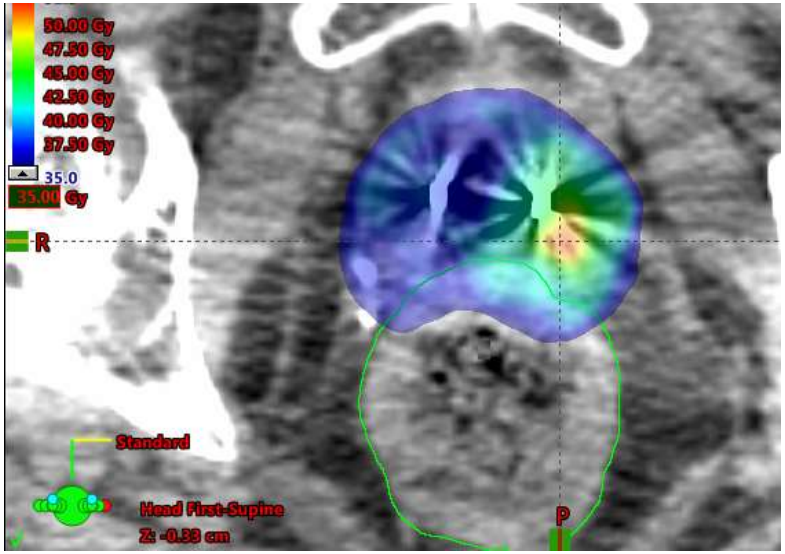
→ $BED_{rest/fraction} = 120{,}0$ Gy $/ 4 = 30{,}0$ Gy

Prostate cancer case

→ 1st plan



→ 2nd plan



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Prostate cancer case

GTV_Boost : GTV_BOOST			
Status	**Constraint**	**Result**	**Manual Check**
✓	$D_{99\%} \geq 40Gy$	43.38Gy	...
✓	$V_{40Gy} \geq 99\%$	99.93%	...
✓	$D_{0.1cc} \leq 52Gy$	51.38Gy	...

CTVp1_3500 : CTVp1_3500		
Status	**Constraint**	**Result**
✓	$V_{35Gy} \geq 99\%$	99.85%

PTVp1_04_3500 : PTVp1_04_3500		
Status	**Constraint**	**Result**
✓	$D_{99\%} \geq 33.25Gy$	33.60Gy
✓	$V_{33.25Gy} \geq 99\%$	99.55%

GTV_Boost : GTV_BOOST			
Status	**Constraint**	**Result**	**Manual Check**
✓	$D_{99\%} \geq 40Gy$	40.38Gy	...
✓	$V_{40Gy} \geq 99\%$	99.80%	...
✓	$D_{0.1cc} \leq 52Gy$	50.04Gy	...

CTVp1_3500 : CTVp1_3500		
Status	**Constraint**	**Result**
✓	$V_{35Gy} \geq 99\%$	99.84%

PTVp1_04_3500 : PTVp1_04_3500		
Status	**Constraint**	**Result**
✓	$D_{99\%} \geq 33.25Gy$	33.72Gy
✓	$V_{33.25Gy} \geq 99\%$	99.59%

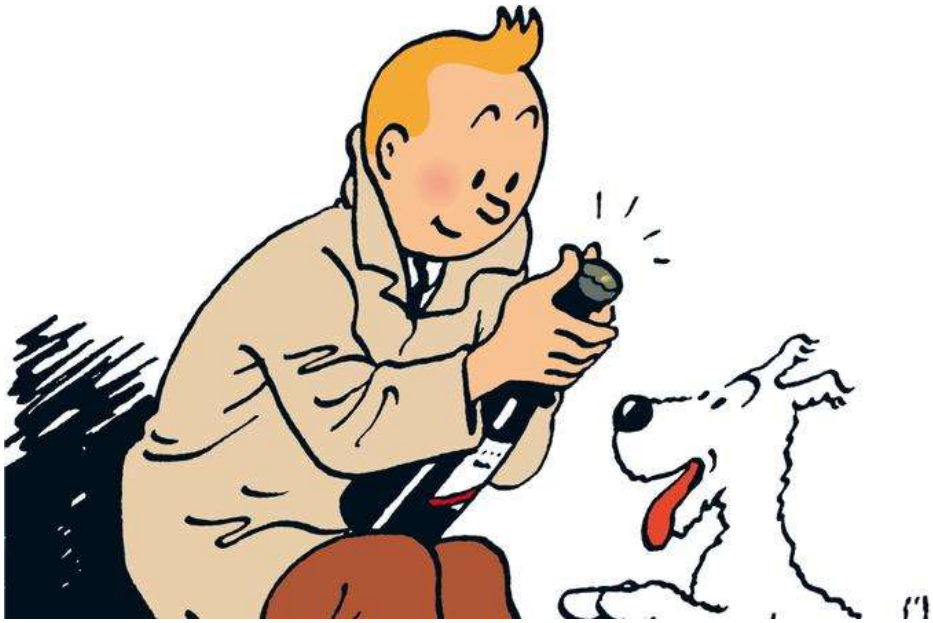
Prostate cancer case

Rectum : Rectum		
Status	**Constraint**	**Result**
✓	$D_{max} \leq 40Gy$	36.33Gy
✓	$D_{0.035cc} < 40Gy$	35.58Gy
✗	$V_{38Gy} \leq 1cc$	Not available!
✓	$V_{35Gy} \leq 1cc$ ***Softcsontraint***	0.25cc
✓	$V_{35Gy} \leq 2cc$	0.25cc
✓	$V_{32Gy} \leq 15\%$	4.14%
✓	$V_{28Gy} \leq 20\%$	8.37%
✓	$V_{23.5Gy} \leq 50\%$	13.38%
✓	$V_{20.5Gy} \leq 70\%$	17.56%
✓	$V_{17Gy} \leq 75\%$	23.76%

Prostate cancer case

Structure	Volume	Dose	Plan 1	Plan 2
PTV	Maximum dose (1 cm^3)	≤ 107 % of prescription	137,6 % (SIB)	128,1 (SIB)
	Minimum dose to 95 % of PTV	100 % of prescription	100 %	100 %
Rectum	Maximum dose (1 cm^3)	≤ 105 % of prescription	97,8 %	98,3 %
	Maximum dose (3 cm^3)	≤ 95 % of prescription	92,5 %	93,3 %
	Dose to 50 %	≤ 50 % of prescription	25,2 %	24,5 %
Bladder	Maximum dose (1 cm^3)	≤ 105 % of prescription	101,5 %	100,9 %
	Dose to 10 %	≤ 90 % of prescription	74,8 %	74,3 %
	Dose to 50 %	≤ 50 % of prescription	38,1 %	38,2 %
Penile bulb	Maximum dose (voxel)	100 % of prescription	7,1 %	7,1 %
	Maximum dose (3 cm^3)	≤ 54 % of prescription	0 %	0 %
Femoral heads	Maximum dose (voxel)	≤ 81 % of prescription	41,8 %	43 %
	Maximum dose (10 cm^3)	≤ 54 % of prescription	33,2 %	36 %
Urethra	Maximum dose (voxel)	≤ 107 % of prescription	105,8%	106,1

Thank you for your attention and enjoy Paris!



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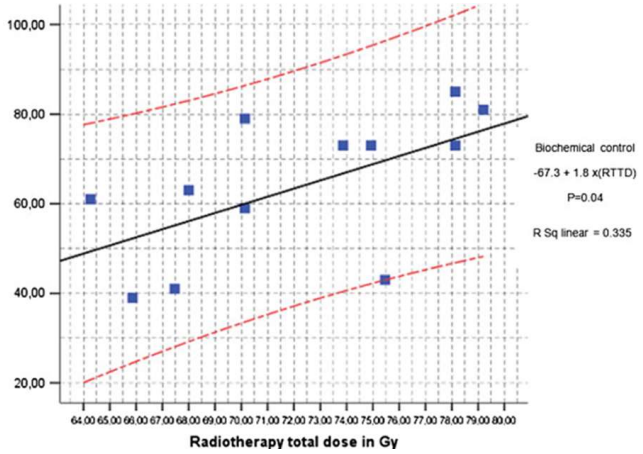
Dose Escalation = Improved Biochemical Outcome

- Reduction in biochemical relapse of 1.8% per 1 Gy
- Predicted radiation doses to achieve a 100% BC rate:

Risk	Dose (EQD2)
Low risk	86,5 Gy
Intermediate risk	90,4 Gy
High Risk	95,5 Gy



Viani et al. int J Radiat Oncol Biol Phys. 2009

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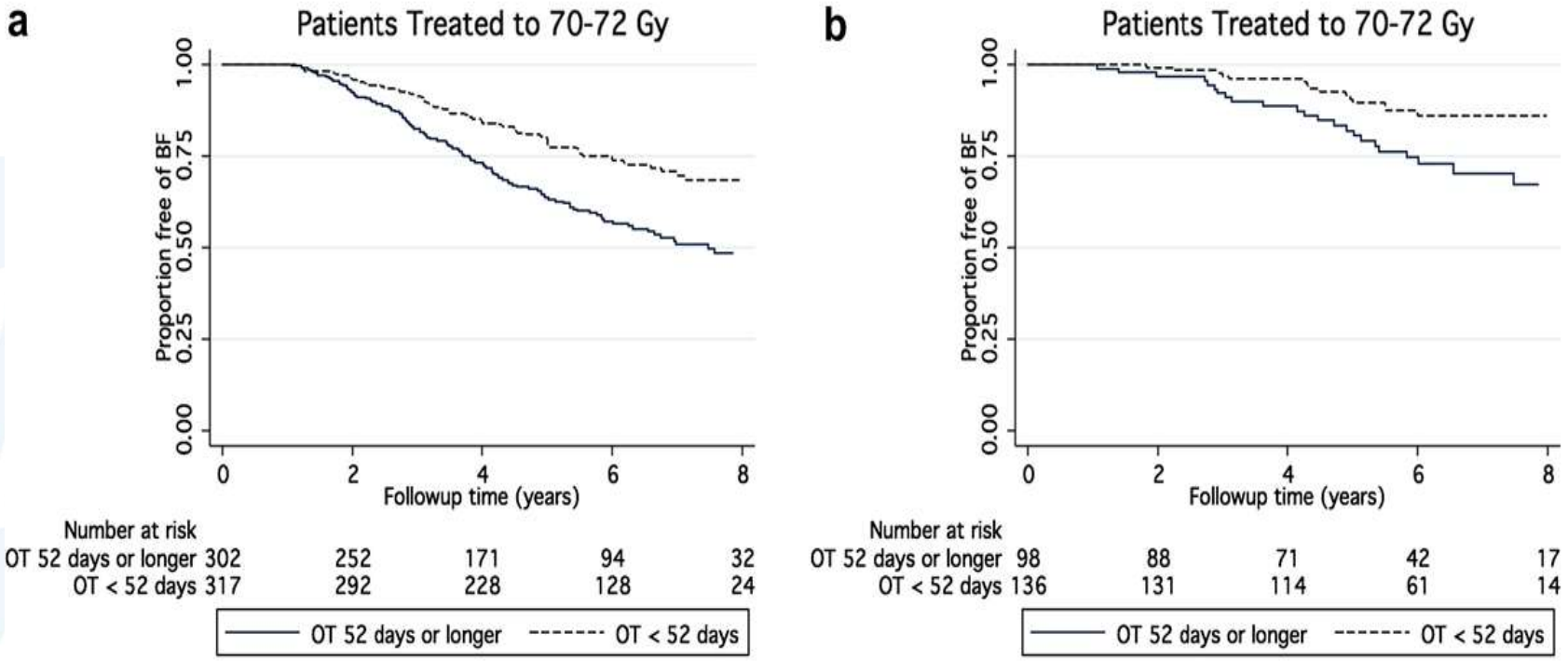
Dose escalation but …

- There is probably also an overall time factor …

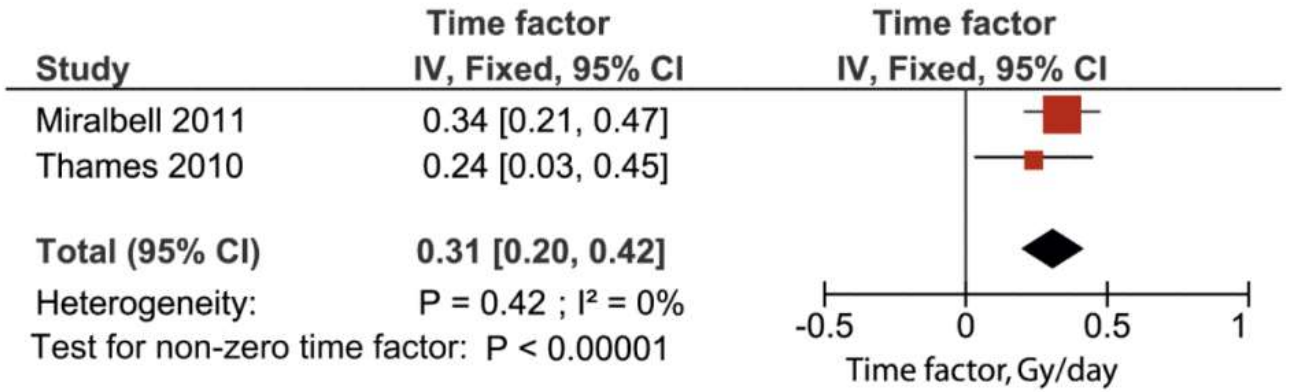
  dose equivalent of proliferation of 0.24 Gy/day



Thames et al, Radiother Oncol 2010

Dose escalation but …

- There is probably also an overall time factor …



- Could reduce the effect of some hypo-fractionated schedules

Vogelius et al. Int J Radiat Oncol Biol Phys. 2013

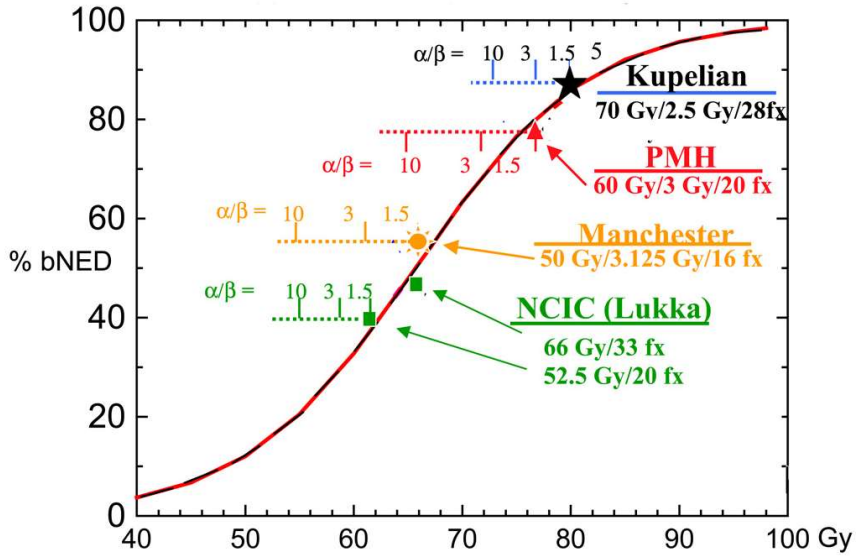
What if …

- The fractionation sensitivity of prostate cancer is uniquely high (α/β 1.5 Gy)?

- The α/β is lower than in normal tissues at risk (α/β 3 to 4 Gy)?

Hypofractionation in prostate cancer

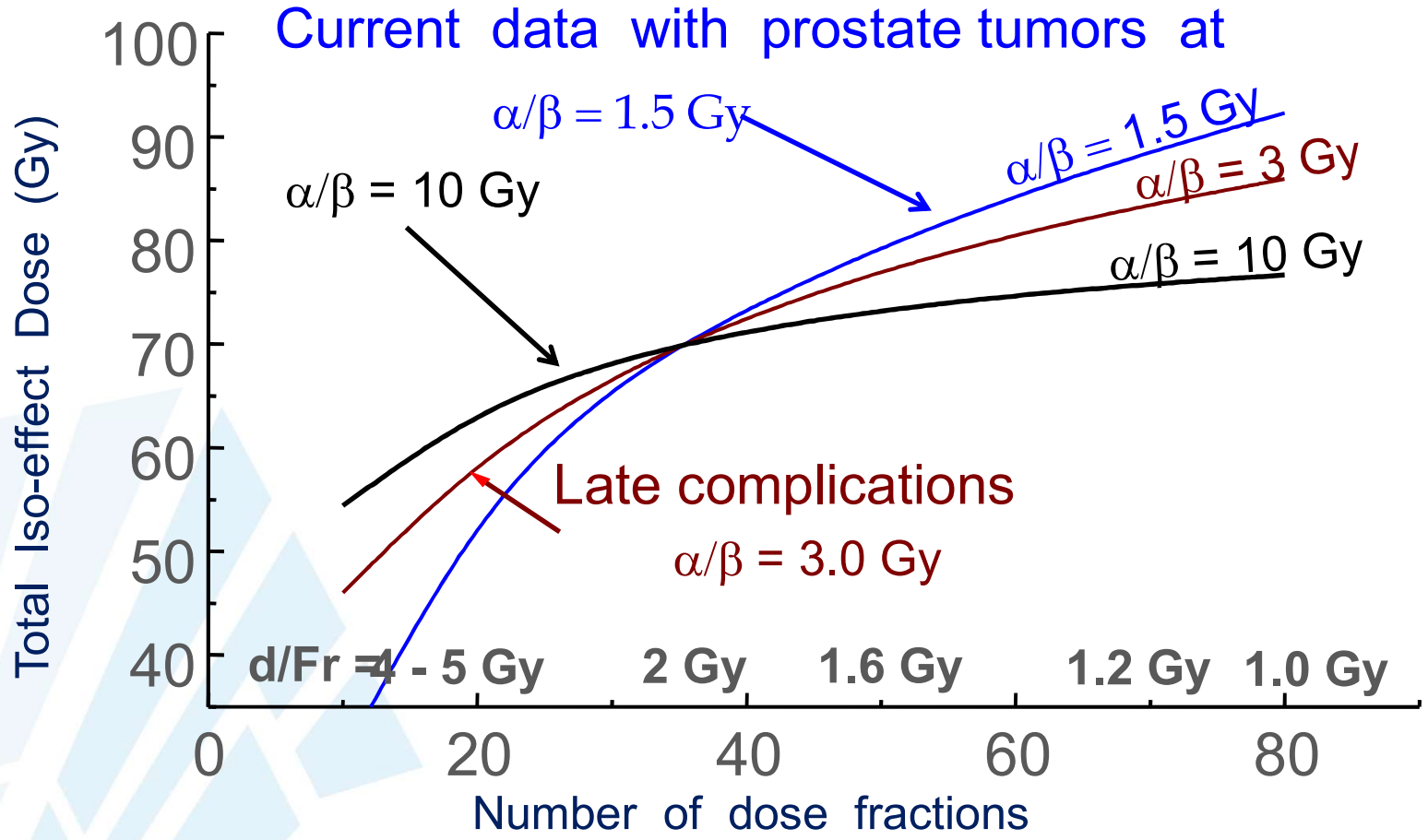
- Fractionation sensitivity of prostate tumors is uniquely high (α/β 1.5 Gy)
- The α/β is lower than normal tissues at risk (α/β 3-4 Gy)



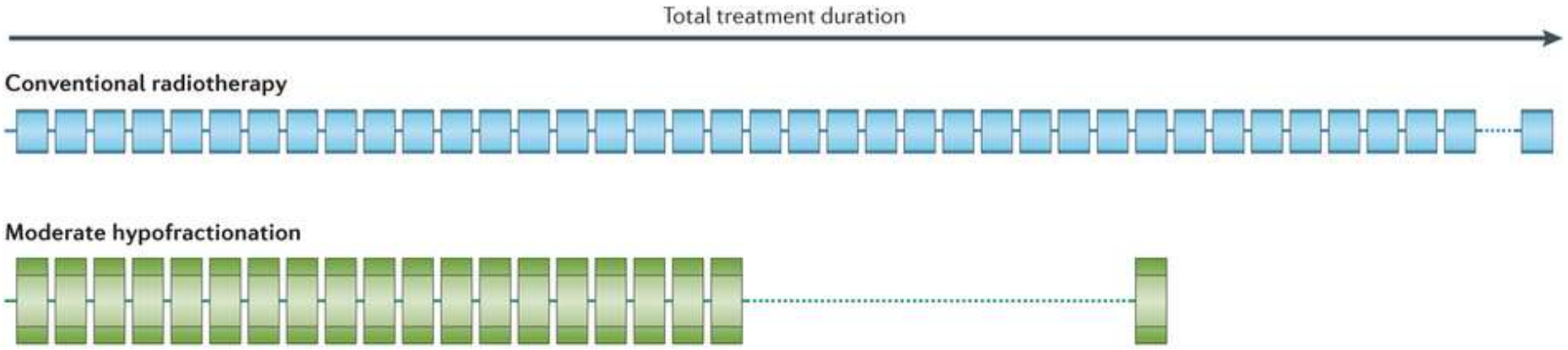
EQD2 in 2 Gy fractions with α/β 1.5 Gy

Ritter et al. Semin. Radiat. Oncol. 2008

HYPOFRACTIONATION I HYPERFRACTIONATION



Hypofractionation in prostate cancer



	Fractionation schedule		
	Conventional	Moderate	Extreme
Total dose (Gy)	76–80	57–70.2	38–50
Total treatment duration (weeks)	8–9	4–6	1–2
Number of fractions (*n*)	38–40	19–30	4–5
Dose per fraction (Gy)	1.8–2	2.4–4	6–10
Interval between fractions (days)	1	1	1–2

Arcangeli et al. Nat Rev Urol. 2016

Hypofractionation in prostate cancer

Non-disease related advantages

- Improvement in patient comfort and convenience

- Decline in workload for radiation oncology departments:

  UK: 2014-2015: Prostate cancer: 455638 attendances

  (27% workload)

  → 20-fraction schedule: - 200 000 attendances

Possible strategies

If α/β is significantly lower for prostate cancer than for rectum

- Equal tumor effect
- Equal late complications

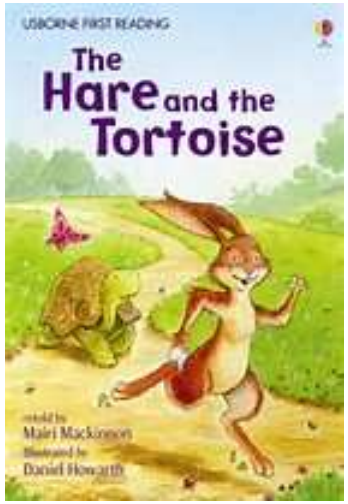
Try to keep the total dose per week below 13 Gy?

Hypofractionation – Conclusion

BUT …

“Here’s where the
alpha/beta ratio is flawed: normal tissue can be seriously injured functionally without necessarily killing the cells involved.”

“To me radiation therapy is all about the tortoise and the hare. You want to get to the destination safely, but the rapidity with which you get there is a secondary and essentially minor issue.”

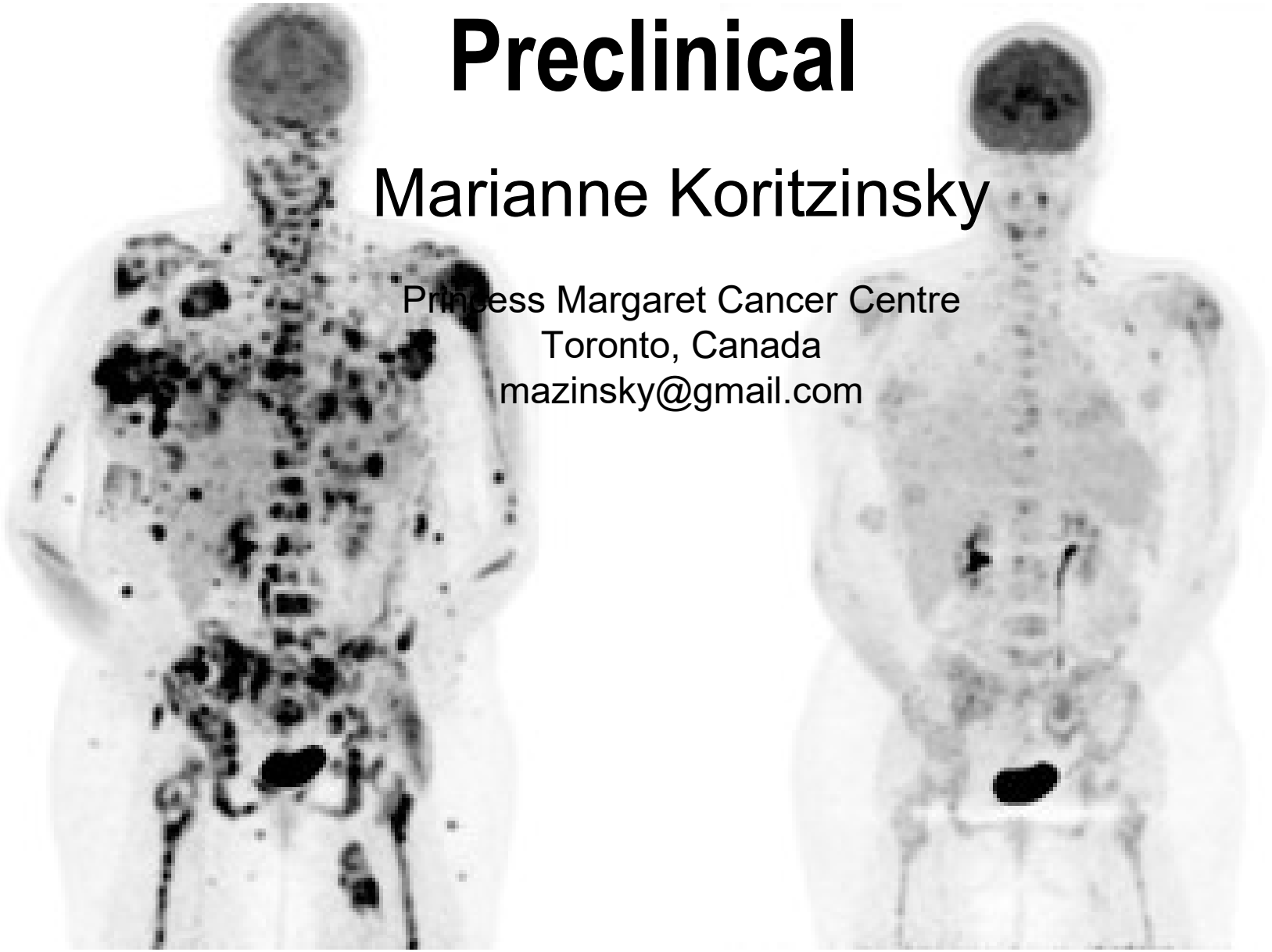


Glatstein, Int J Rad Onc Biol Phys 2008

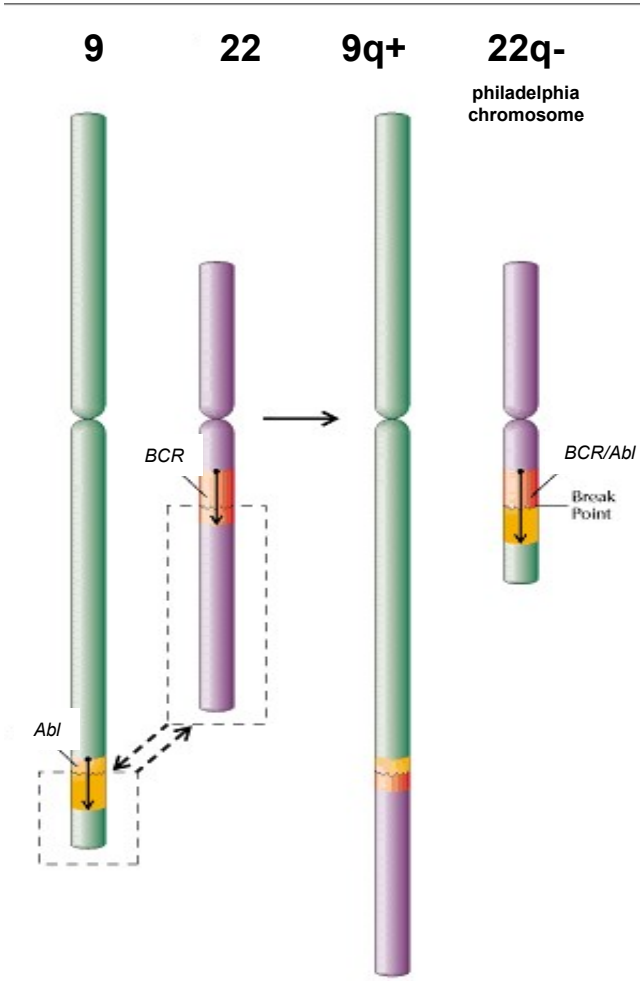
Biological response modifiers Preclinical

Marianne Koritzinsky

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



Molecular Targeting of Cancer

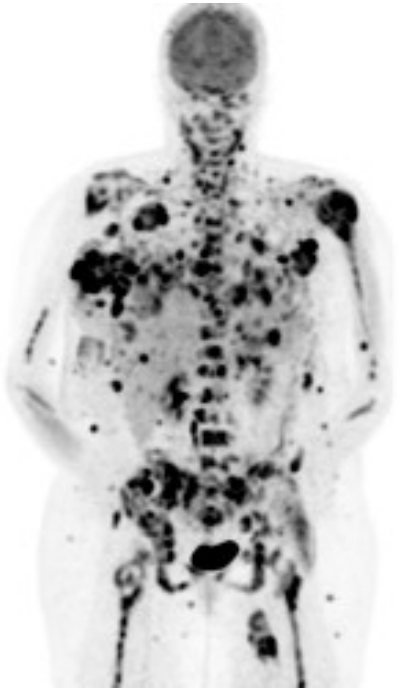


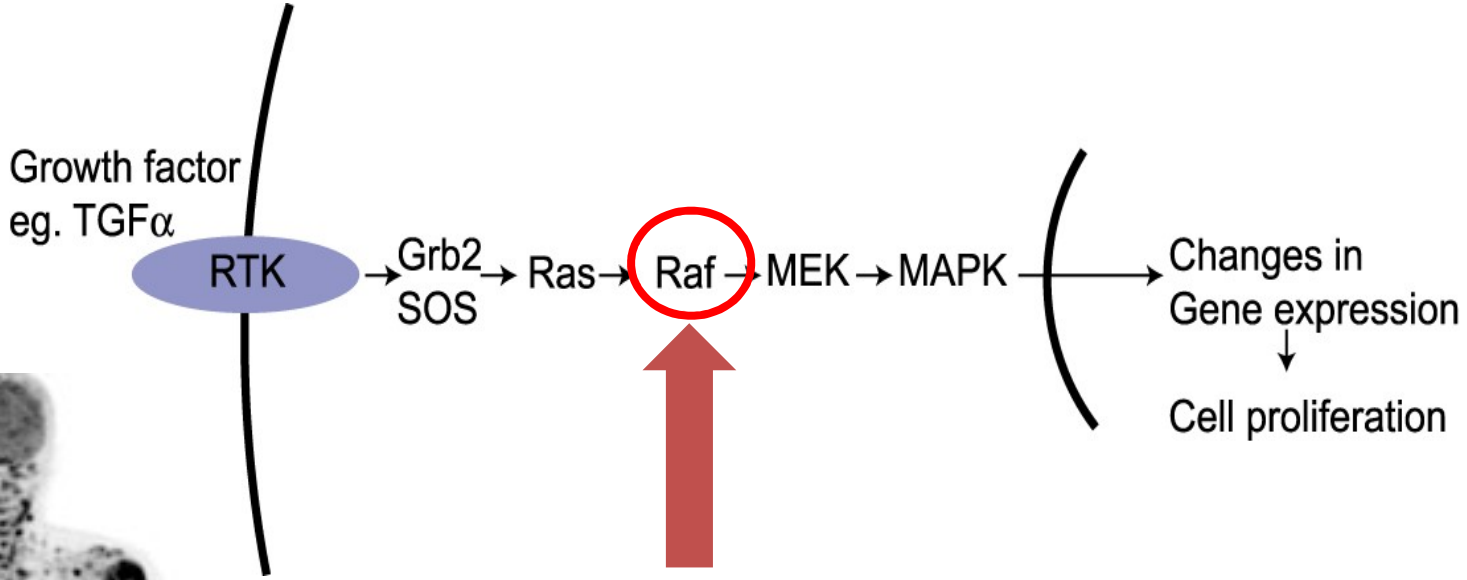
Individualization

"Here's my sequence..."

Nature, 2000

Molecular Targeting of Cancer





V600E

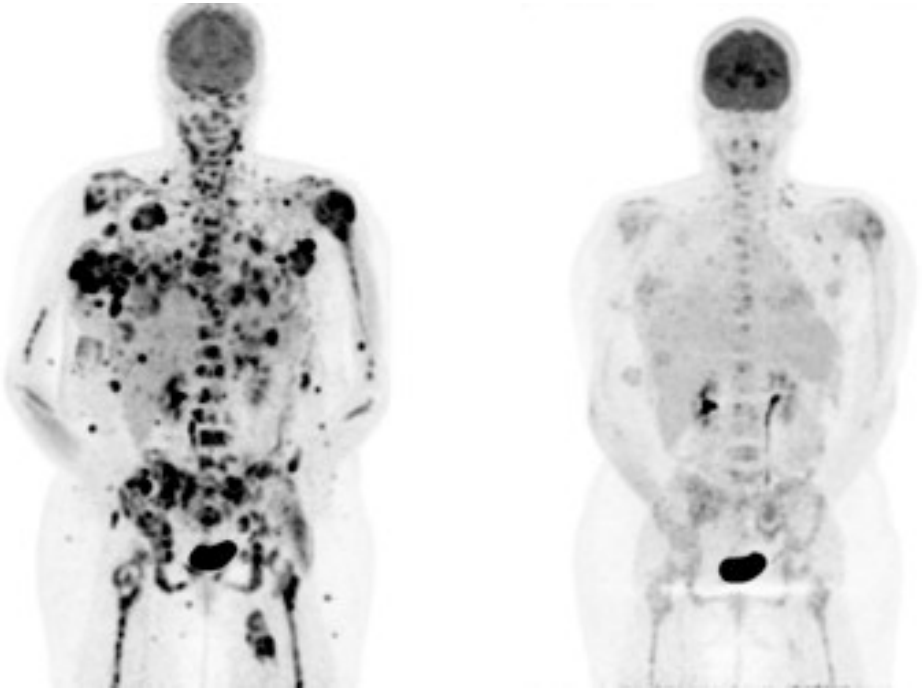
Valine – glutamic acid

non-polar–polar

Molecular Targeting of Cancer

The New York Times

February 2010



Biological response modifiers

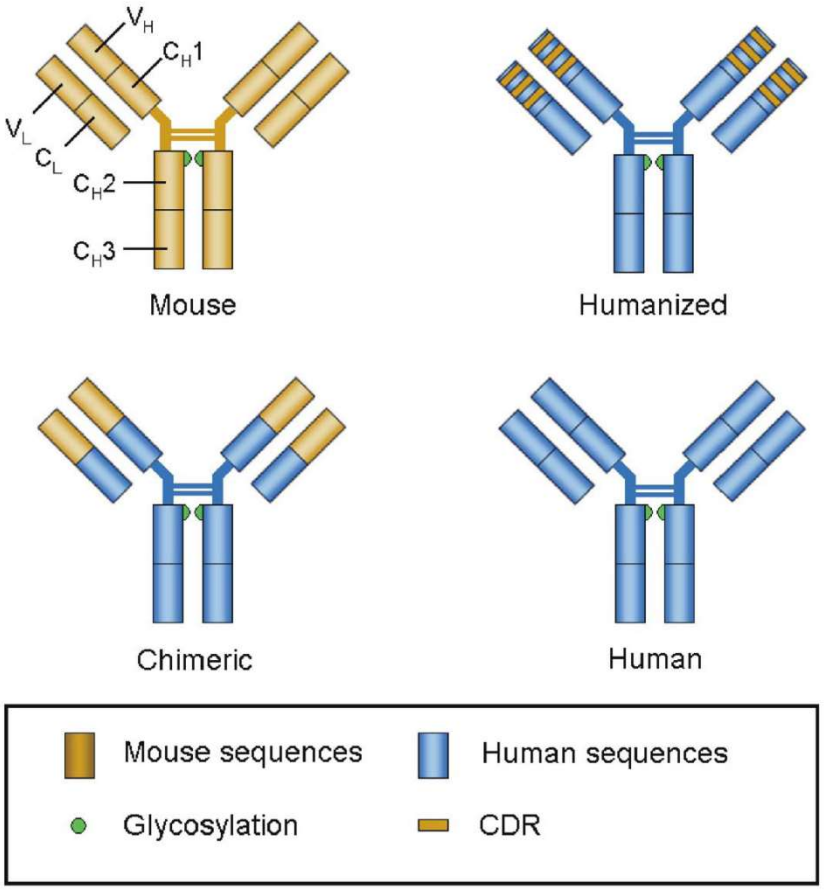
- New drugs designed to target the function of specific molecules
  - Small molecules
  - Antibodies
- Can have low toxicity
- Can have extremely high specificity

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

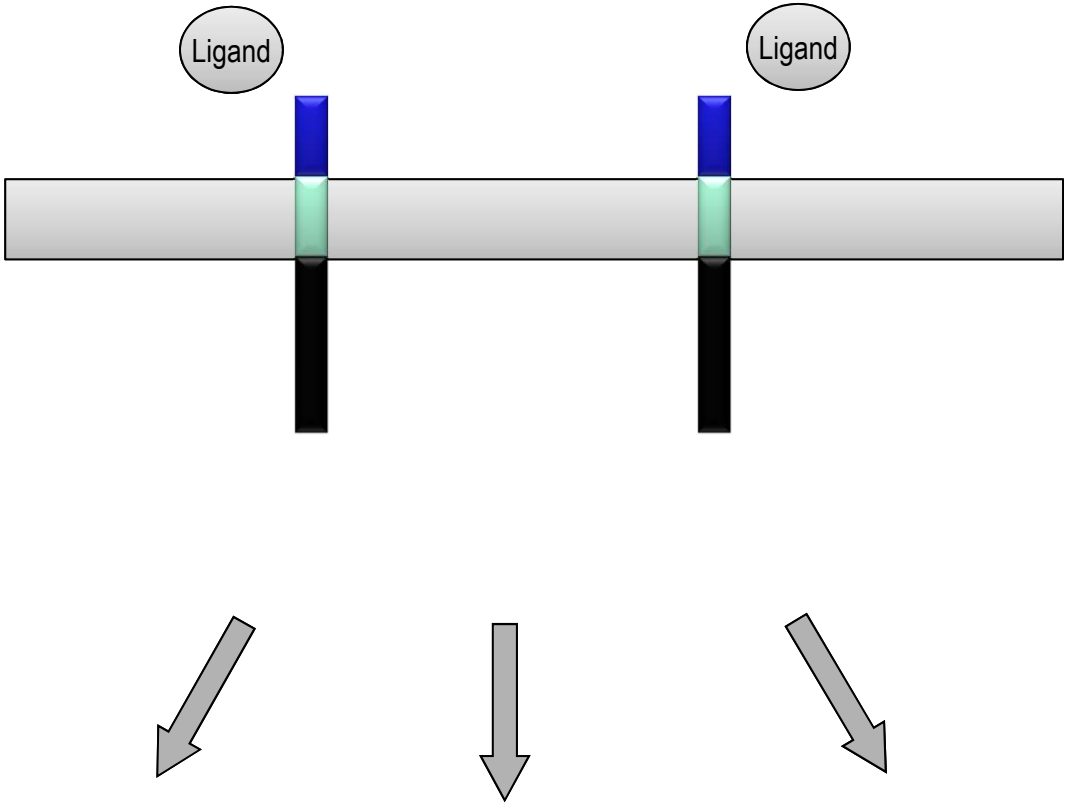
+ many more

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

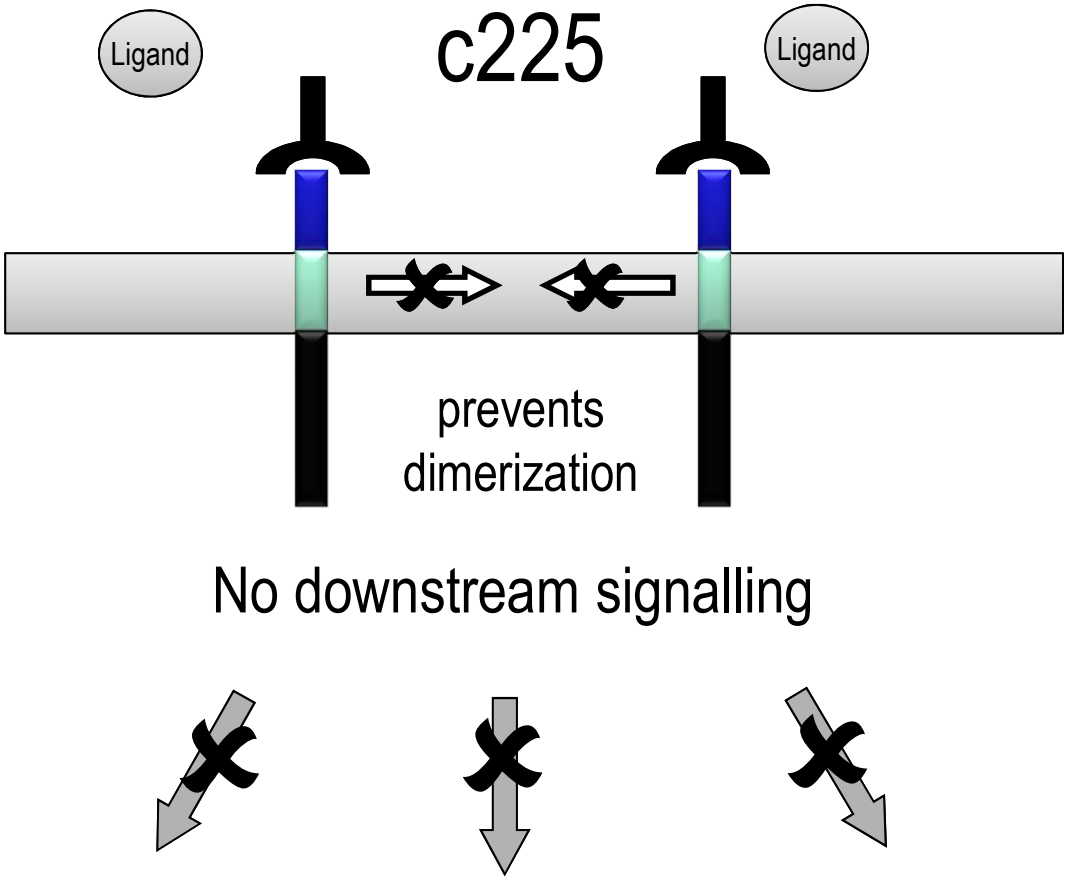


EGFR-signaling



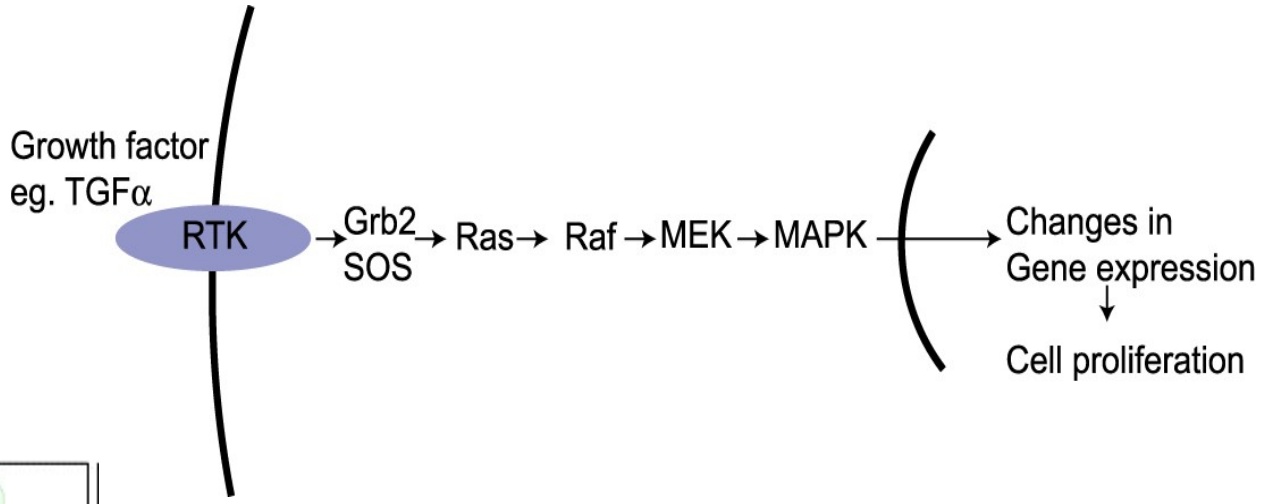
Proliferation, DNA repair, angiogenesis

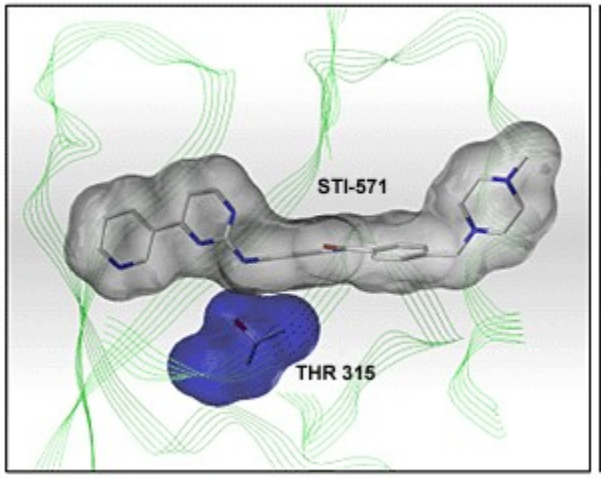
Cetuximab prevents EGFR-signaling



Proliferation, DNA repair, angiogenesis

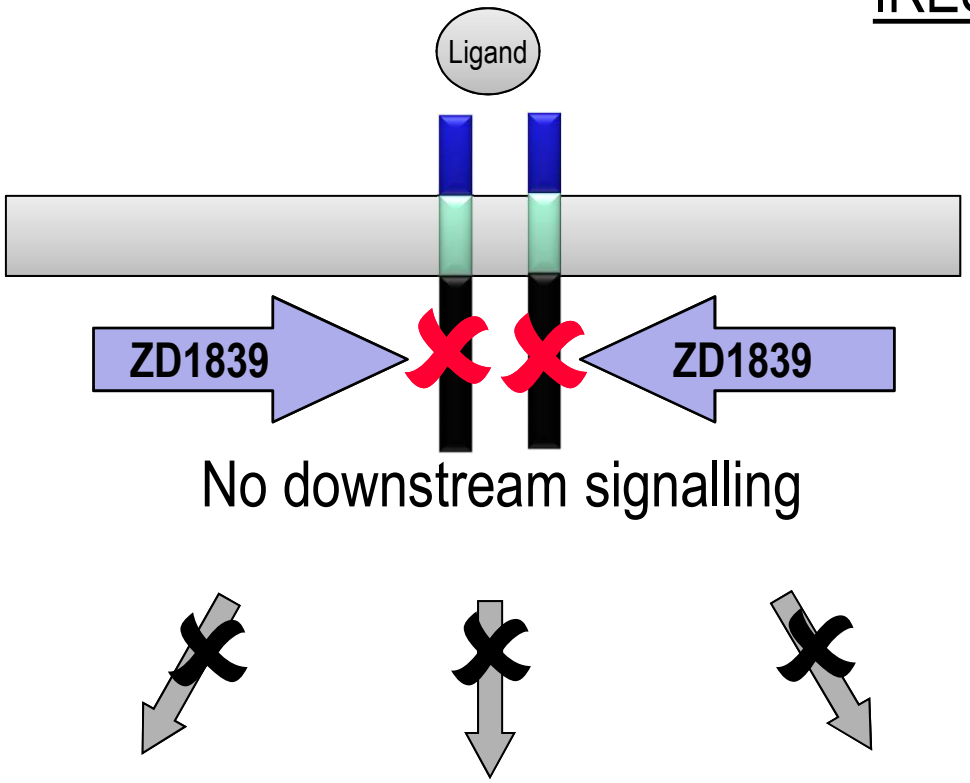
Small molecules





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

Small molecule EGFR inhibitors



IRESSA / ZD1839

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

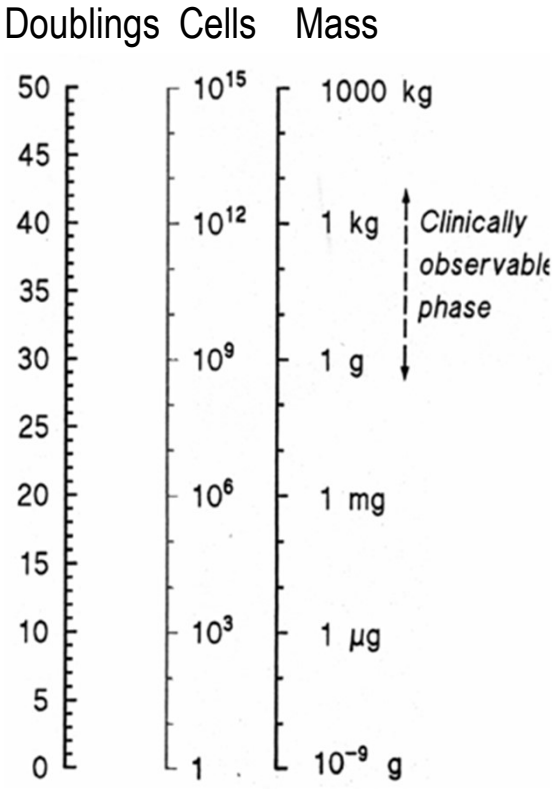
Canadian clinical trials with RT

Phase	Agent	Site	Target
I	Sorafenib	SCCHN	Raf/MEK/ERK
I	Sorafenib	Thorax, abdomen, pelvis	Raf/MEK/ERK
I	Sorafenib	Hepatocellular carcinoma	Raf/MEK/ERK
I	Sunitinib	brain met	PDGFR/VEGFR/KIT
I/II	Sorafenib	bone mets, RCC	Raf/MEK/ERK
I/II	Sorafenib	Unresectable liver mets	Raf/MEK/ERK
I/II	Sorafenib	Cervix	Raf/MEK/ERK
I/II	Nimotuzumab	NSCLC	EGFR
II	Erlotinib	NSCLC	EGFR
II	Nimotuzumab	Brain met NSCLC	EGFR
II	Vandetanib	SCCHN	VEGFR, EGFR
II/III	CDX-110	GBM	EGFRvIII
III	Cetuximab	HN	EGFR
III	Cetuximab	Esophageal	EGFR
III	Panitumumab	SCCHN	EGFR
III	Avastin	glioblastoma	VEGF-A

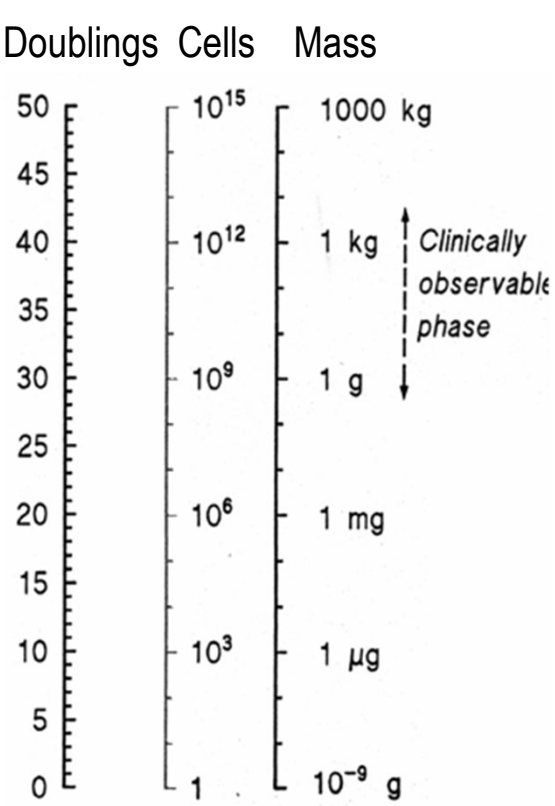
Targeting with RT: achieving cure

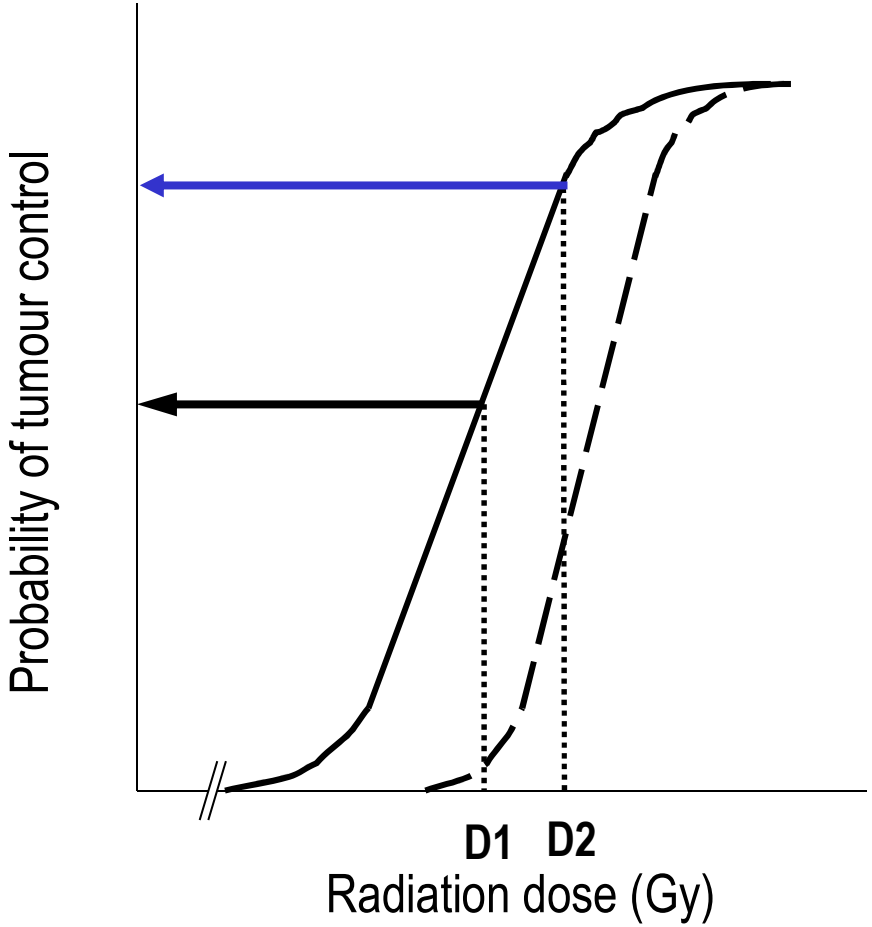
New targeted drugs unlikely to be effective stand-alone therapies

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

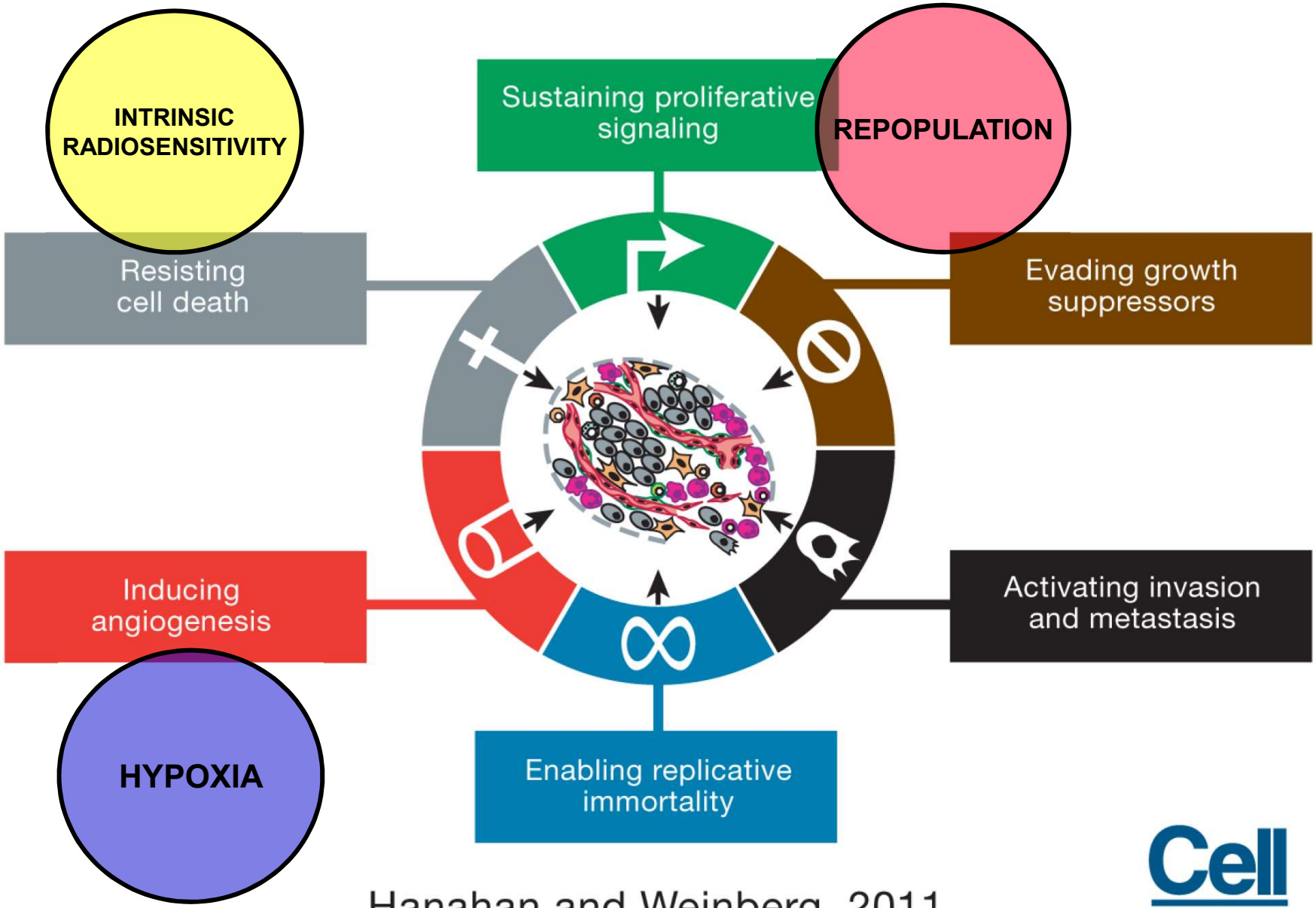


Targeting with RT: the last drop





Targeting with RT: favorable combinations

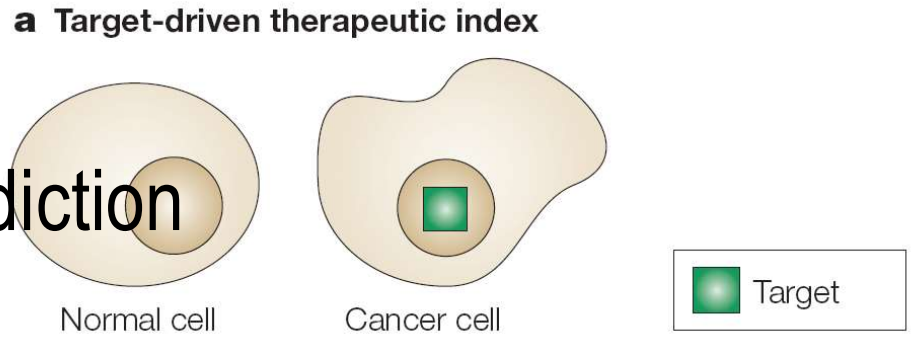


Hanahan and Weinberg, 2011

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

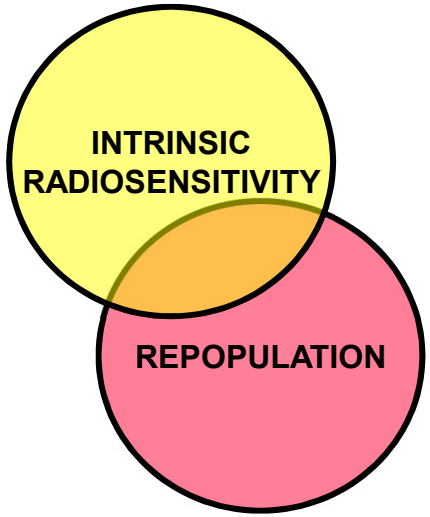
• NSCLC	40-80%
• Prostate	40-80%
• Gastric	33-74%
• Breast	14-91%
• Colorectal	25-77%
• Pancreatic	30-50%
• Ovarian	35-70%
• Bladder	31-48%
• Renal cell	50-90%
• H&N	80-100%
• Glioma	40-63%
• Esophageal	43-89%

High expression generally associated with

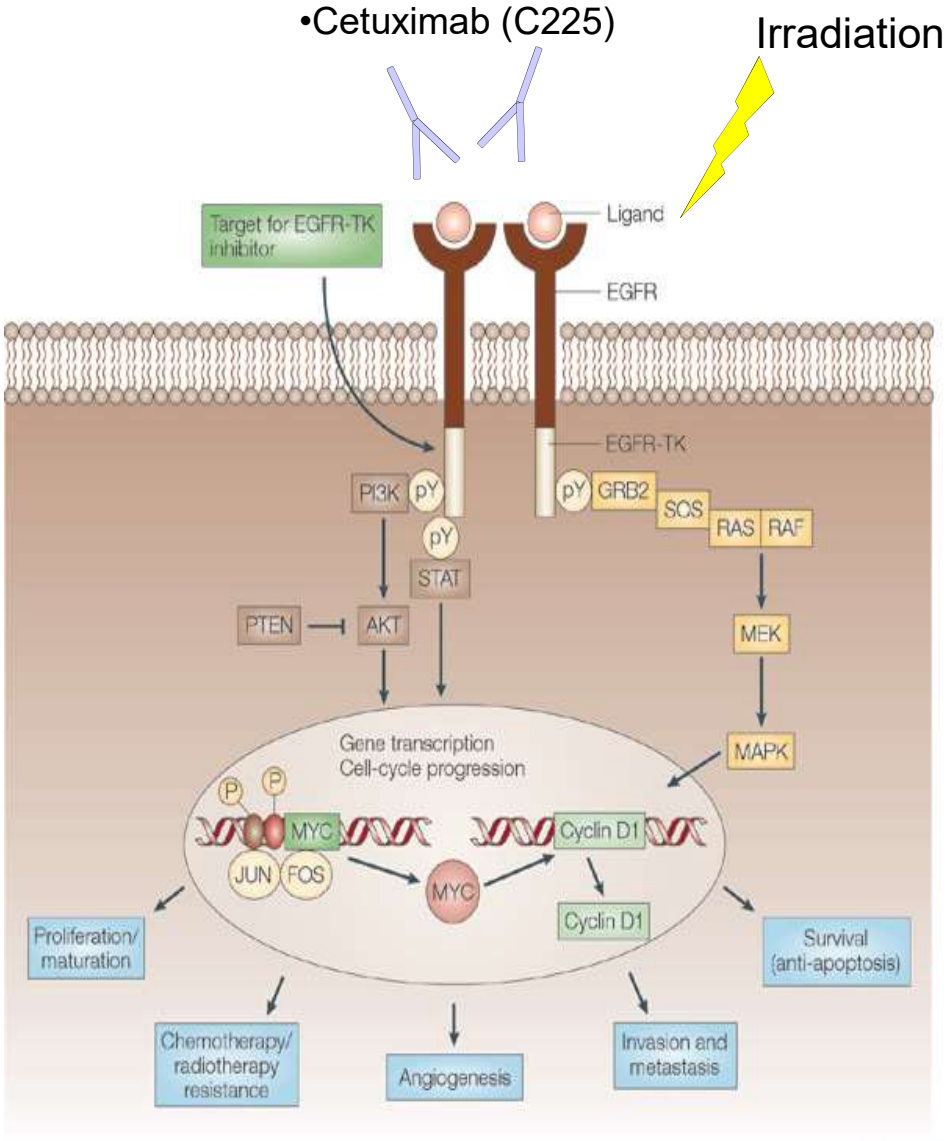
- **Invasion**
- **Metastasis**
- **Late-stage disease**
- **Chemo-/Radiotherapy resistance**
- **Poor outcome**

Example 1: Target driven lethality (EGFR)

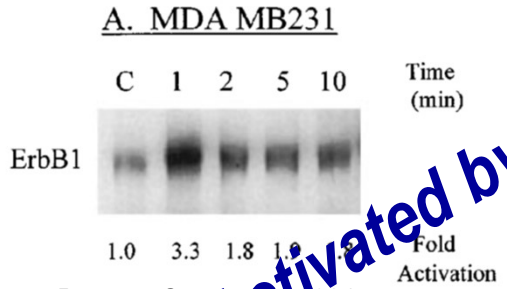
EGFR



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

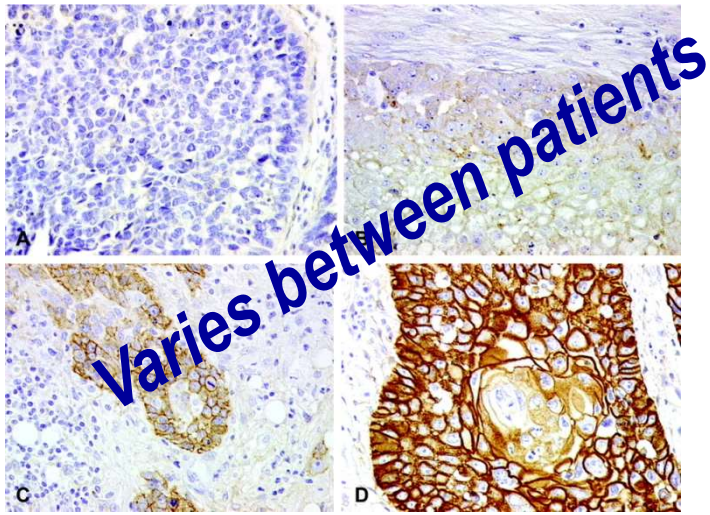


Example 1: Target driven lethality (EGFR)

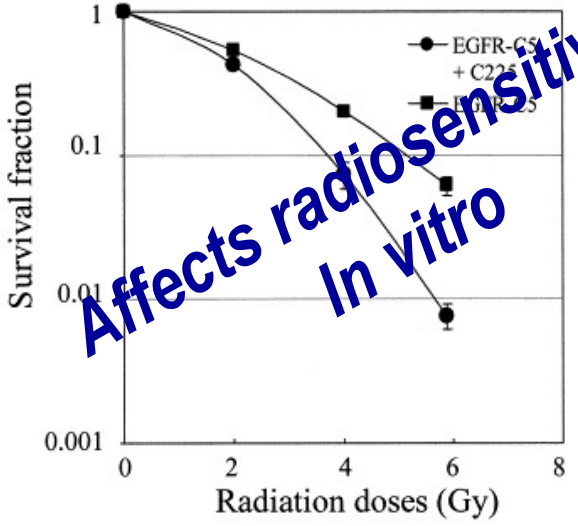


Bowers, Oncogene, 2001

Activated by radiation

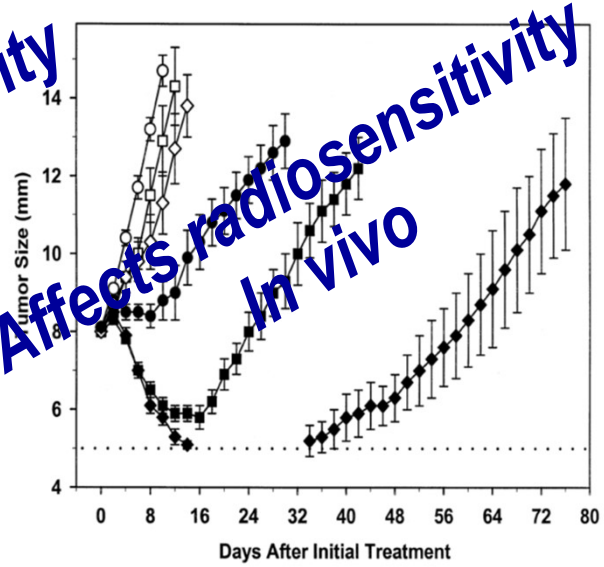


Varies between patients

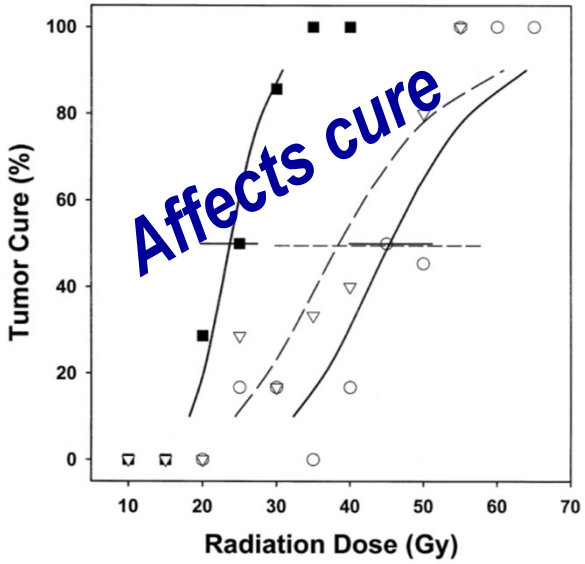


Affects radiosensitivity In vitro

Liang, IJROBP, 2003



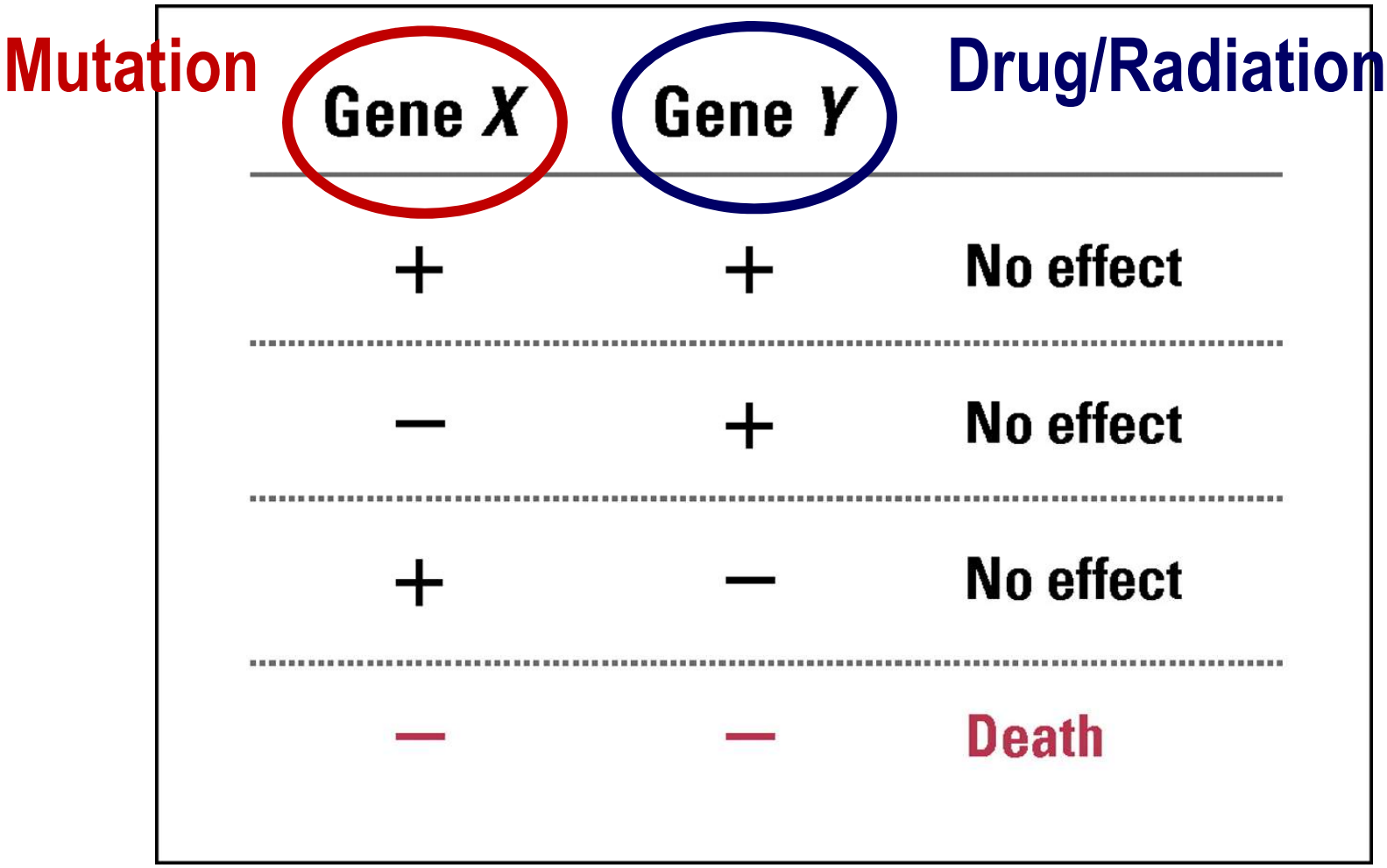
Affects radiosensitivity In vivo



Affects cure

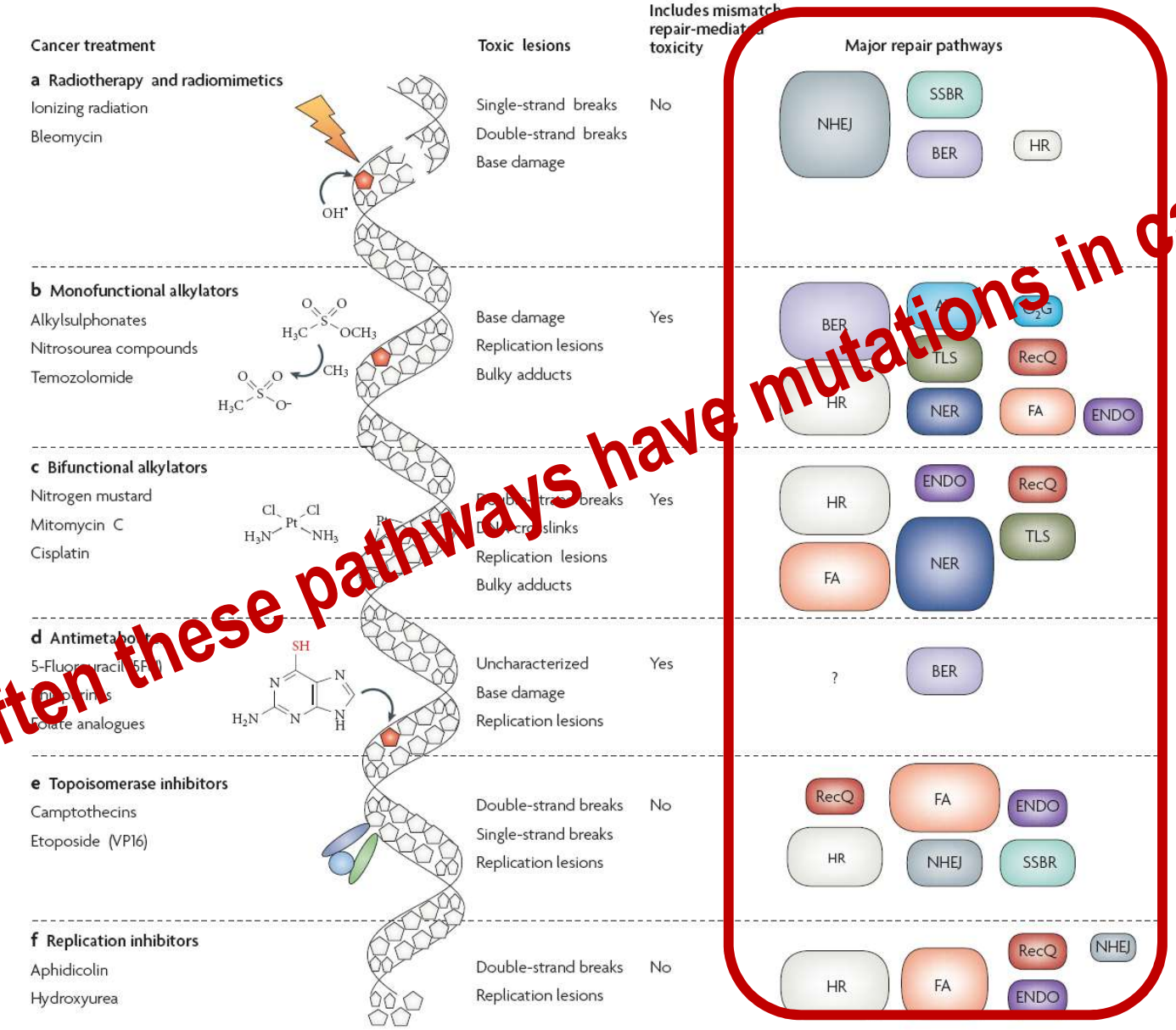
Milas, IJROBP, 2004

The Concept of Synthetic Lethality



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

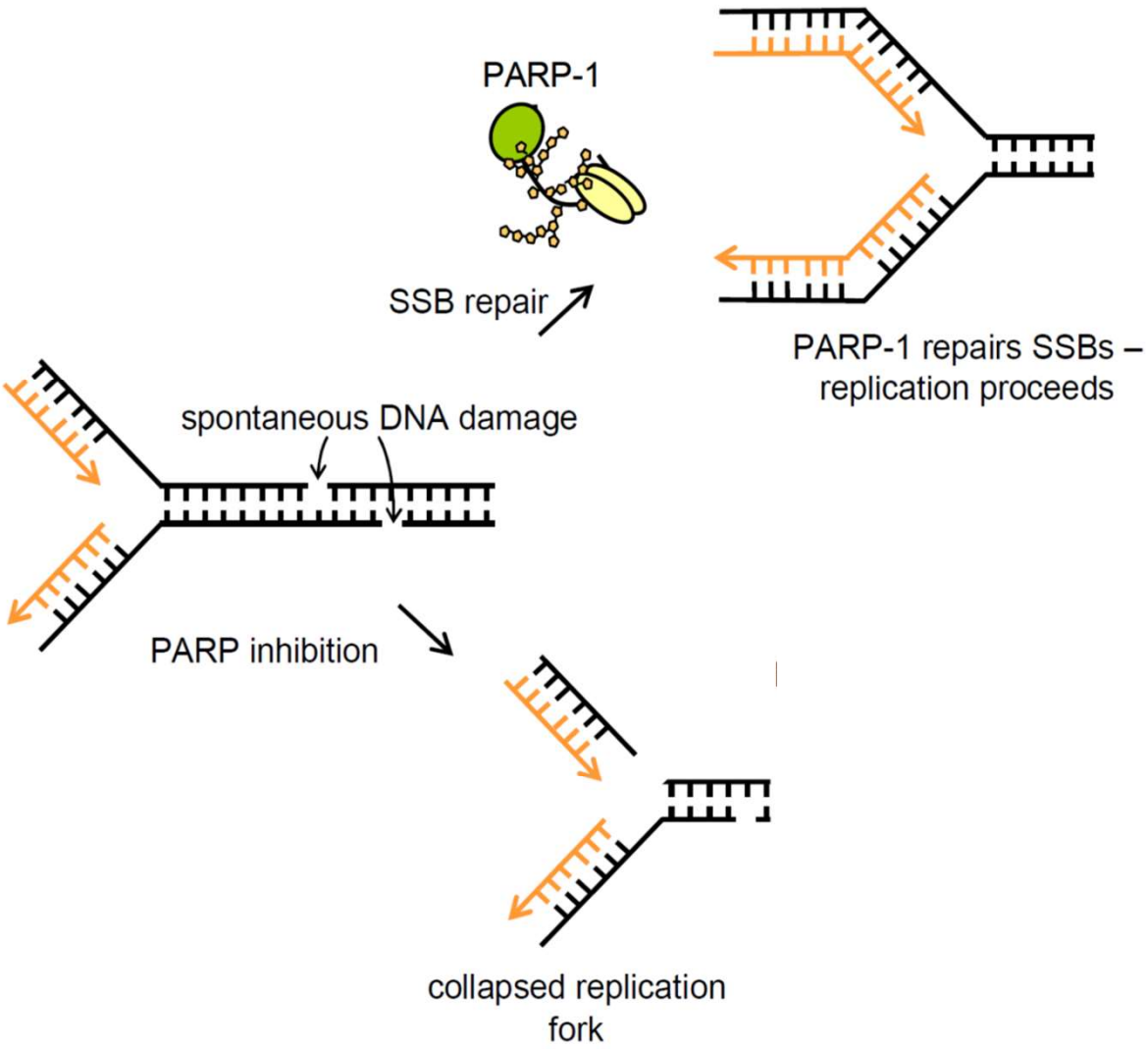
Example 2 – Synthetic lethality



INTRINSIC RADIOSENSITIVITY

Often these pathways have mutations in cancers

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



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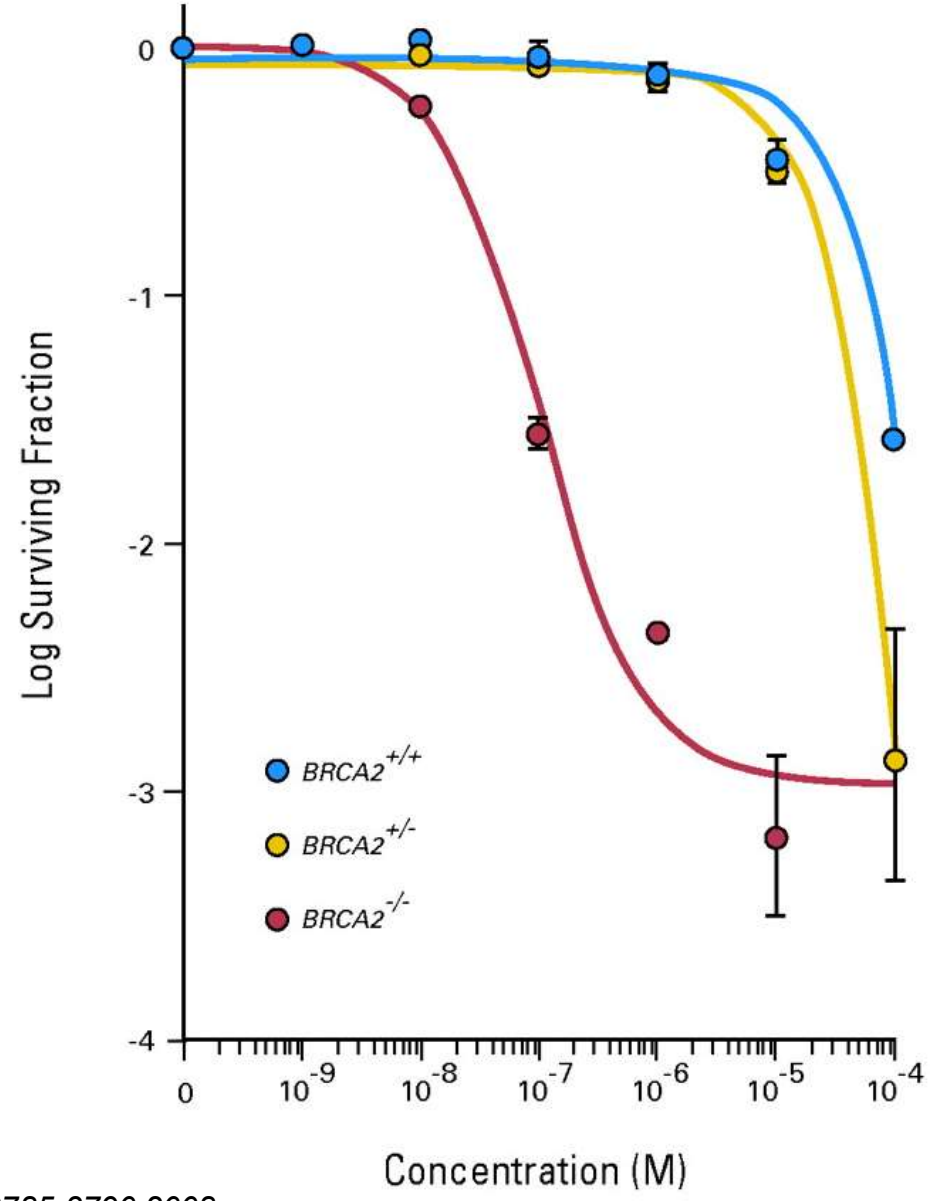


Ashworth, A. J Clin Oncol; 26:3785-3790 2008

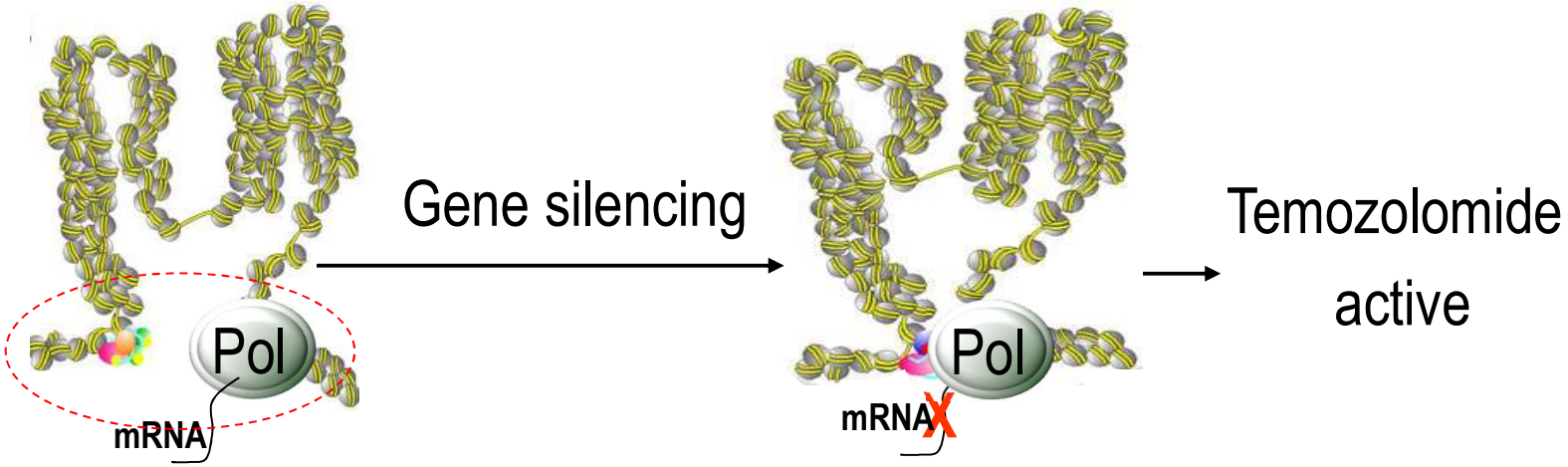
2. Synthetic lethality: Temozolomide for MGMT silencing

The NEW ENGLAND JOURNAL of MEDICINE

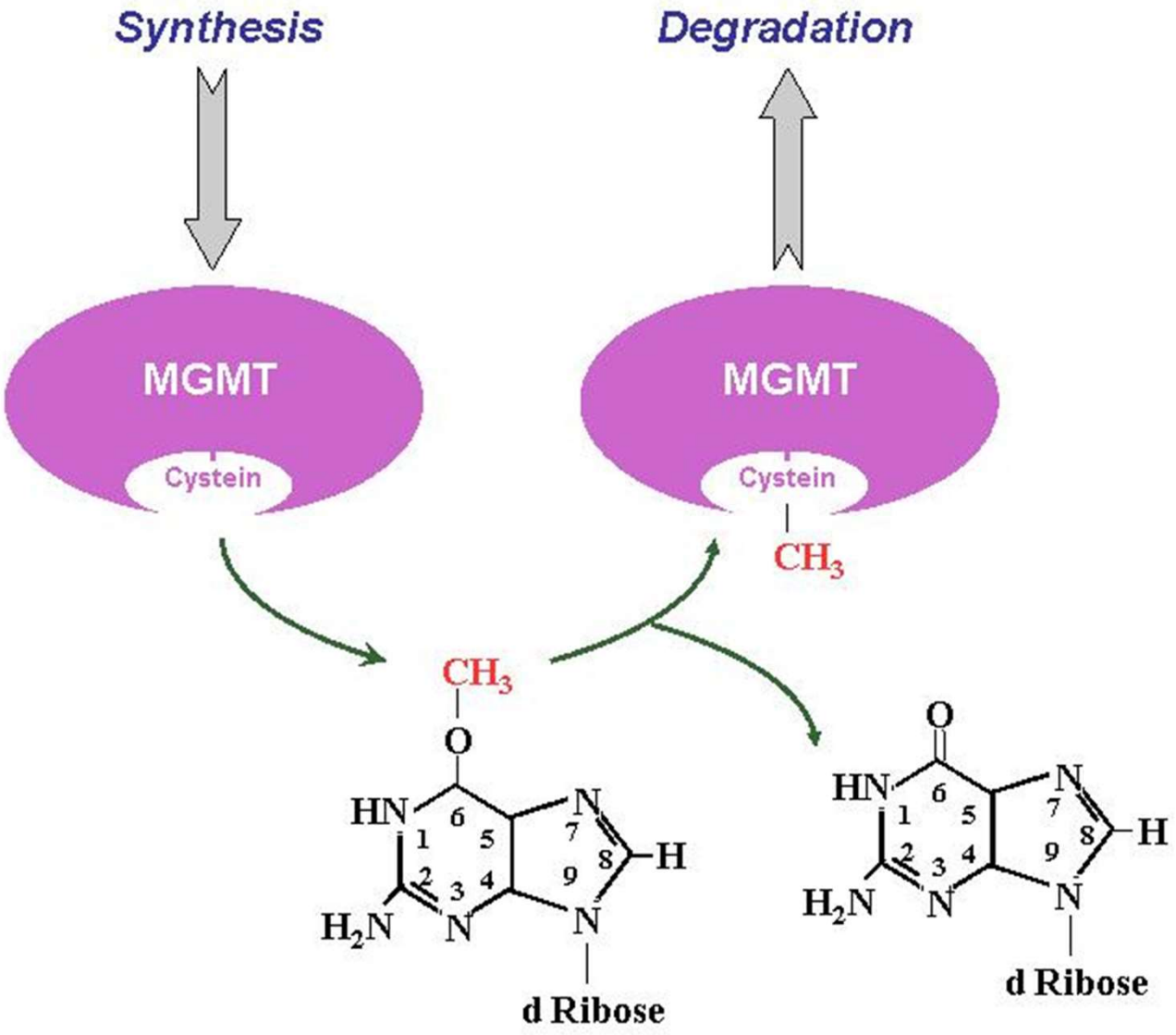
ORIGINAL ARTICLE

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.



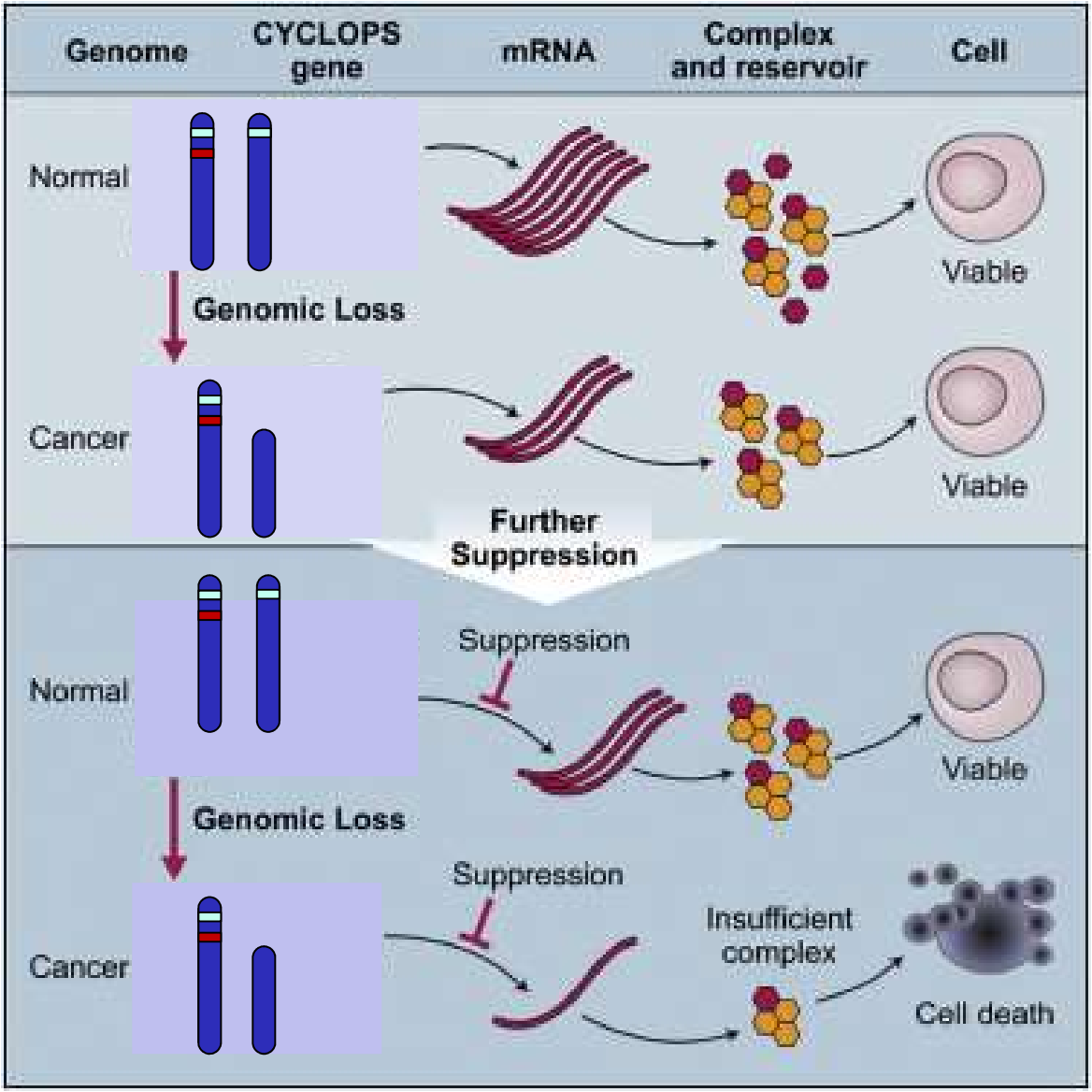
2. Synthetic lethality: Temozolomide for MGMT silencing



2. Synthetic lethality: CYCLOPS

Copy number alterations Yielding Cancer Liabilities Owing to Partial losS

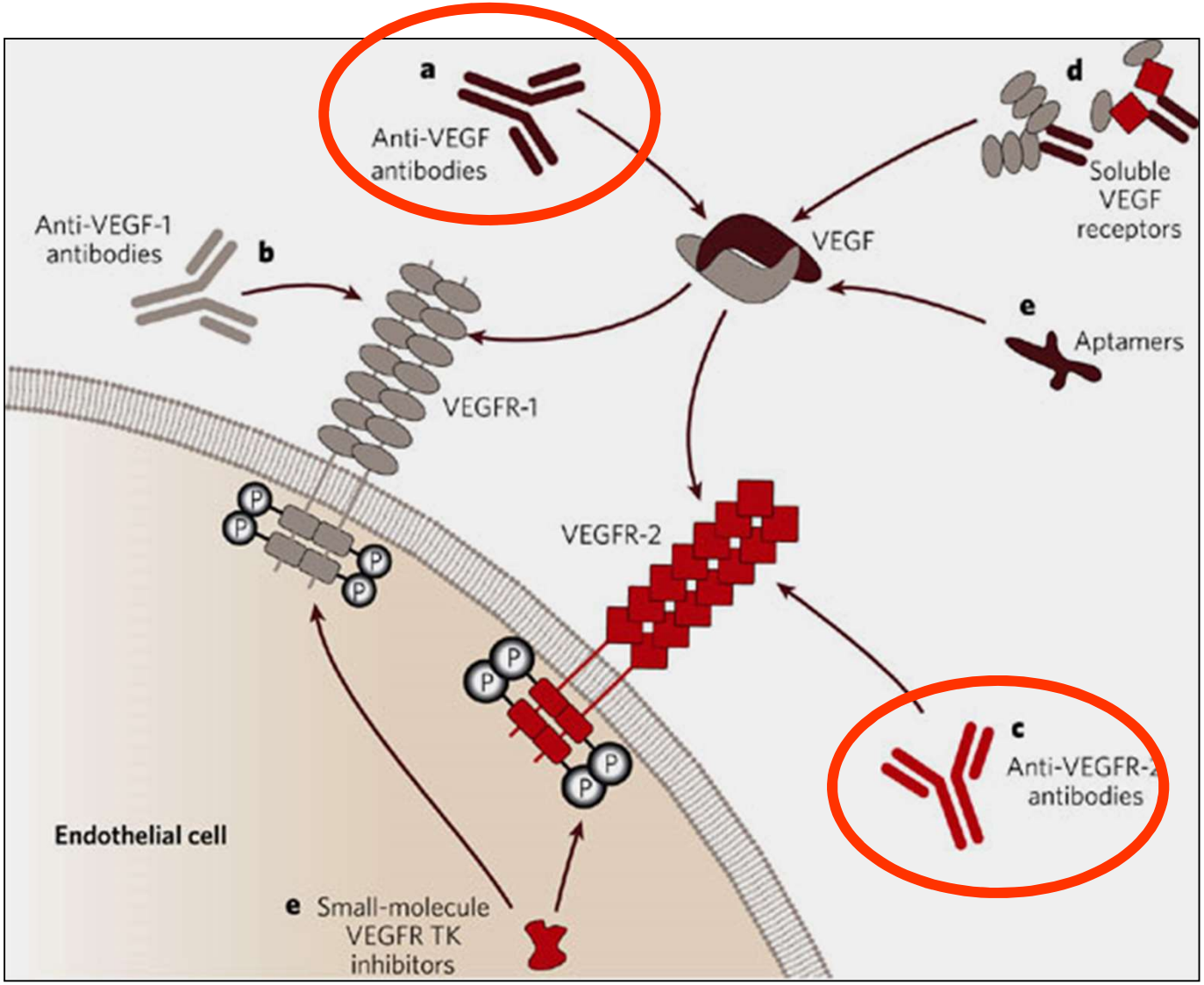
- Tumor suppressor
- CYCLOPS gene



Nijhawan et al., Cell 2012

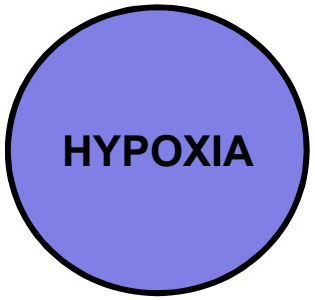
Example 3: Contextual lethality - VEGF

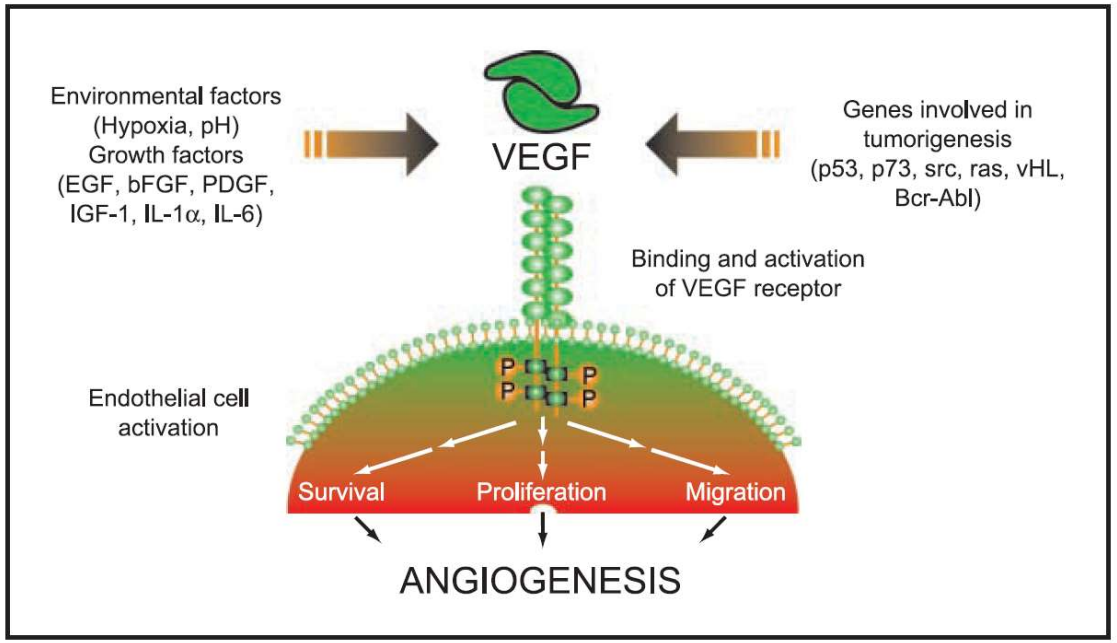
HYPOXIA



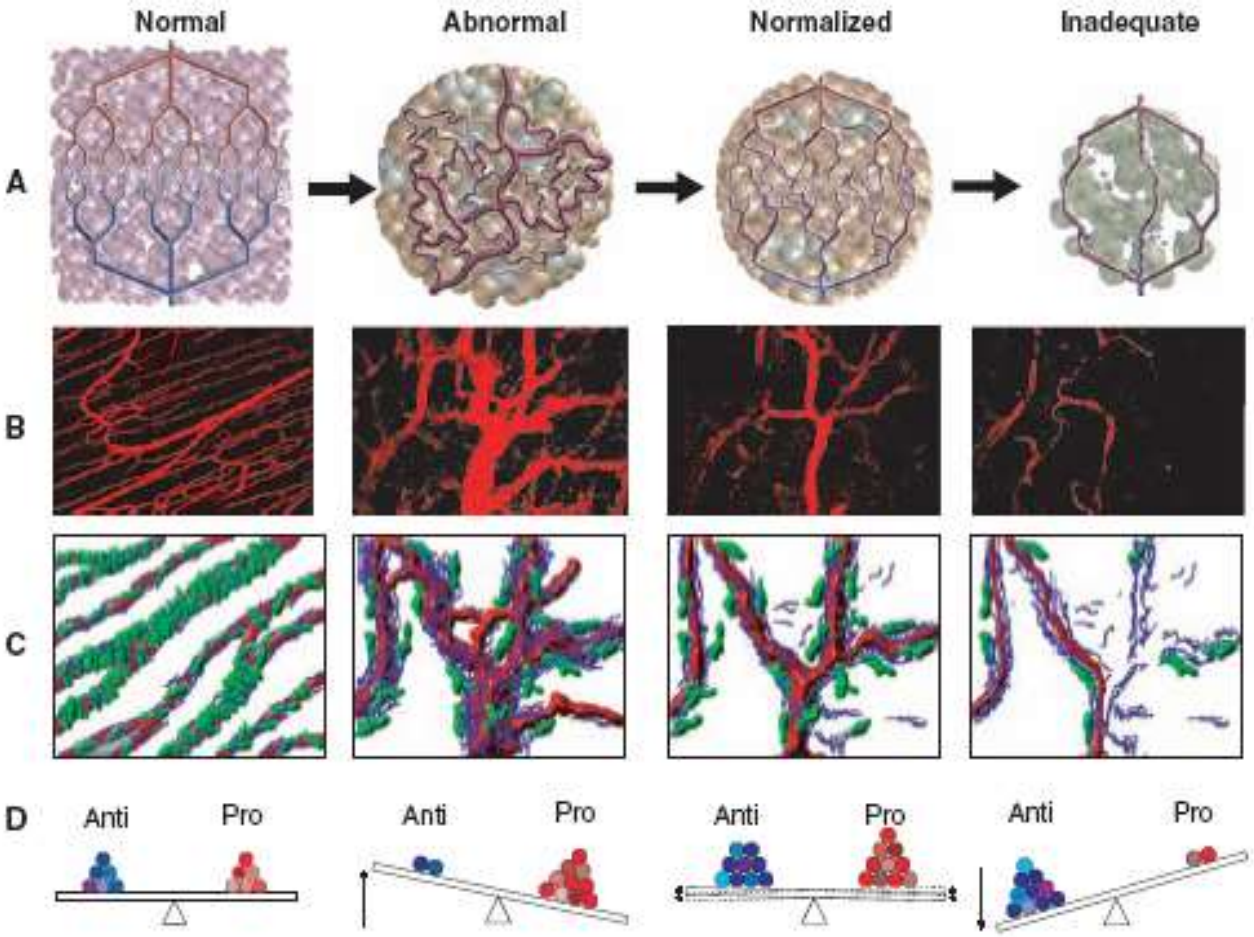
Example 3: Contextual lethality - VEGF

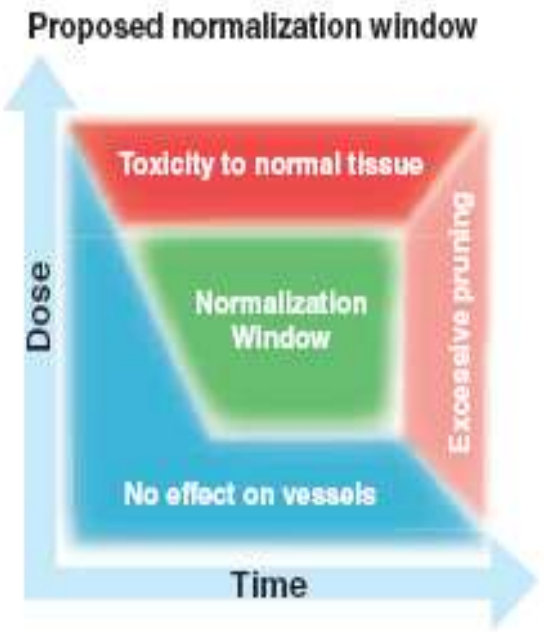
- VEGF plays central role in tumor angiogenesis
- VEGF is induced by hypoxia and expressed by many tumors
- VEGF circulates in the blood, and acts directly on endothelial cells



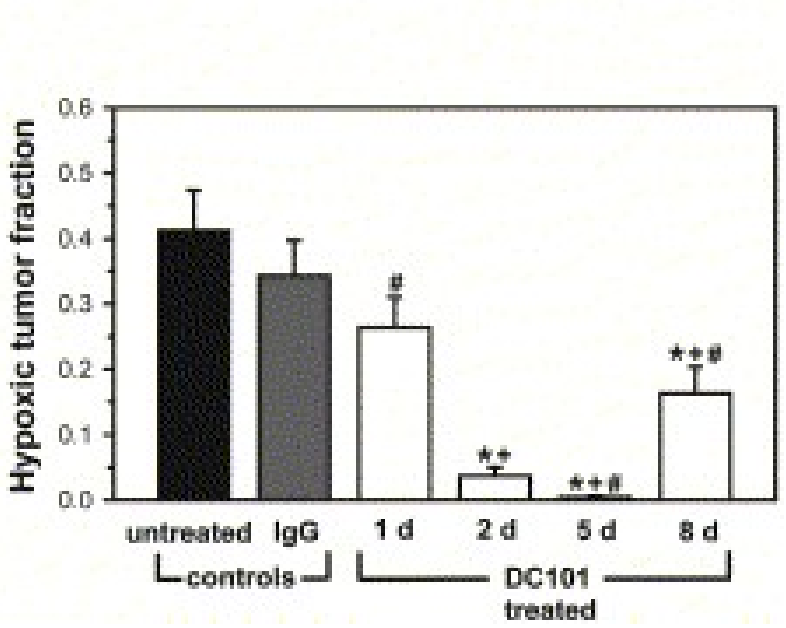


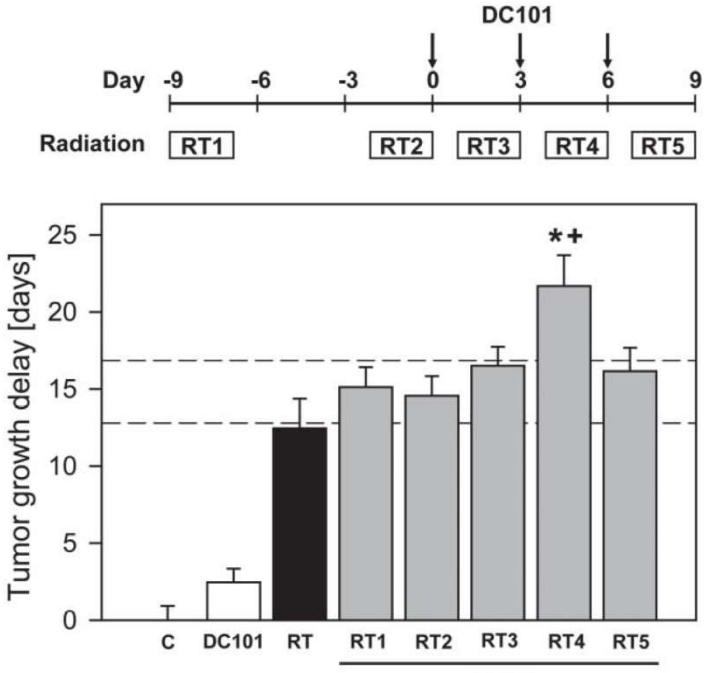
Normalisation of Tumour Vasculature

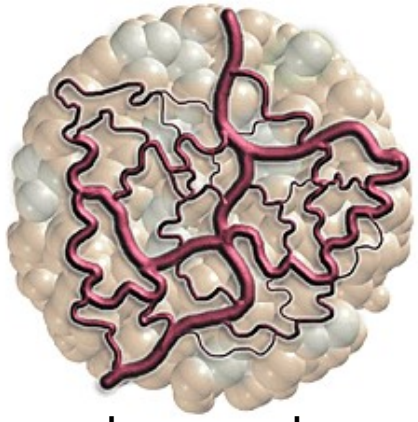




VEGF targeting can improve radiation response



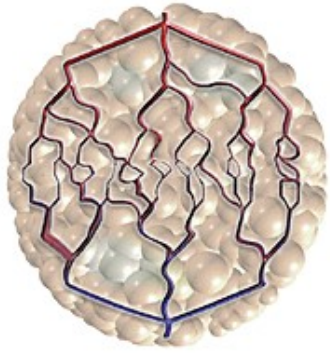




abnormal vasculature

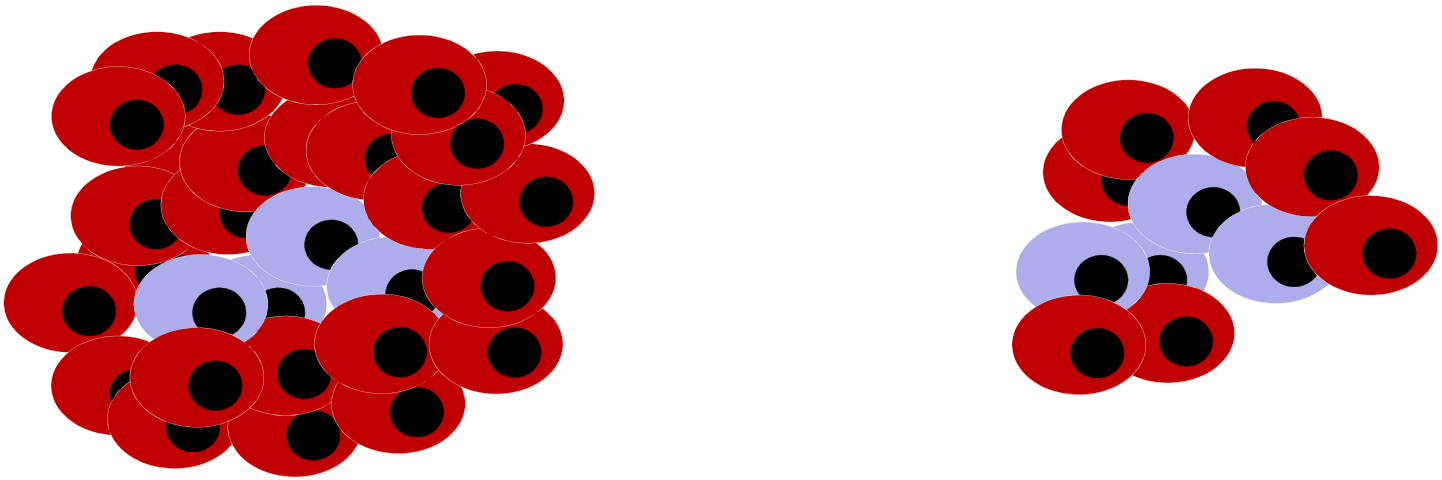
during treatment with DC101

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



normalized vasculature

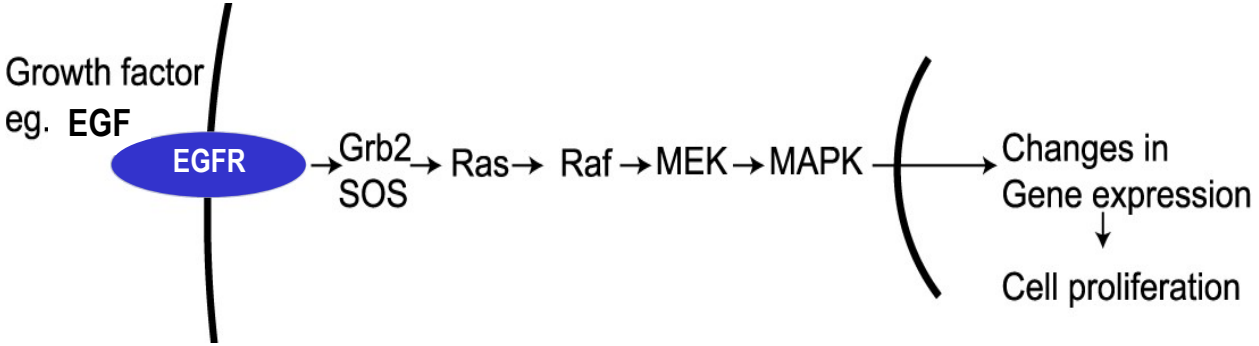
Molecular targeting: Challenges
Tumor subpopulations



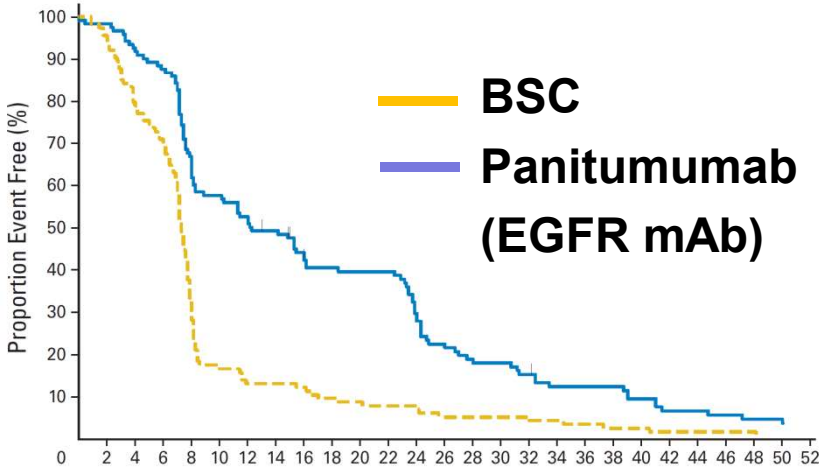
Tumor bulk, determines response

Rare cell, determines cure

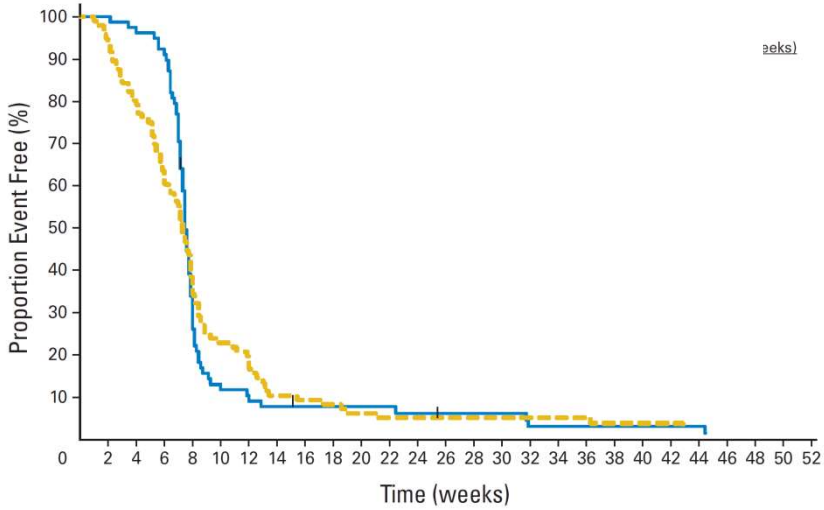
Molecular targeting: Challenges Biomarkers



Ras WT

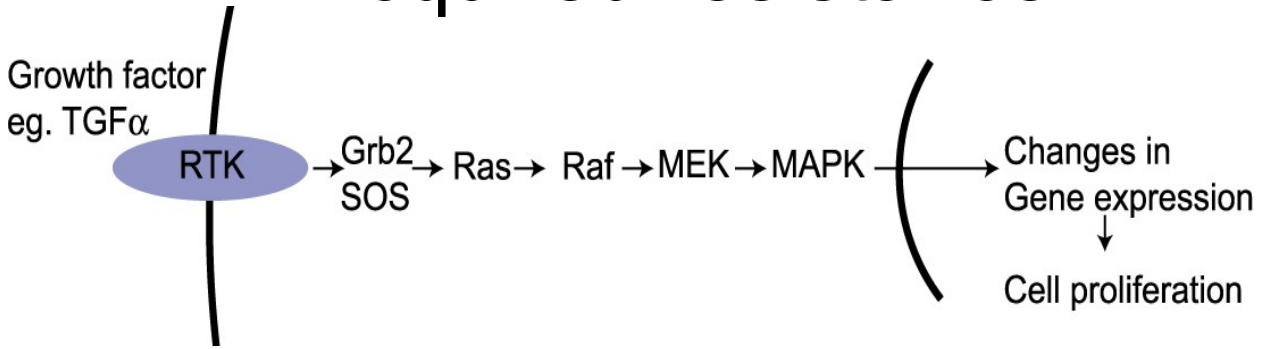


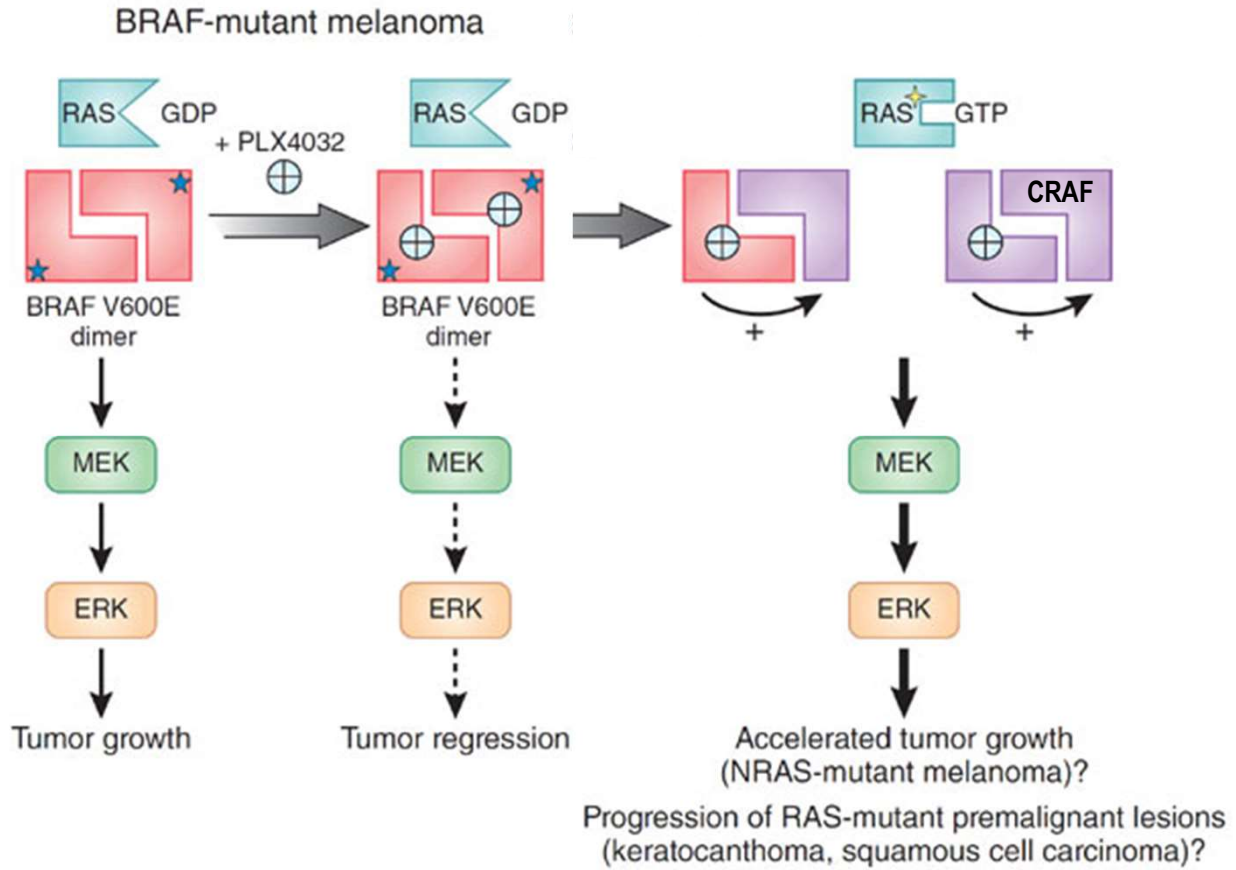
Ras MT



Amado, JCO 2008

Molecular targeting: challenges
Acquired resistance



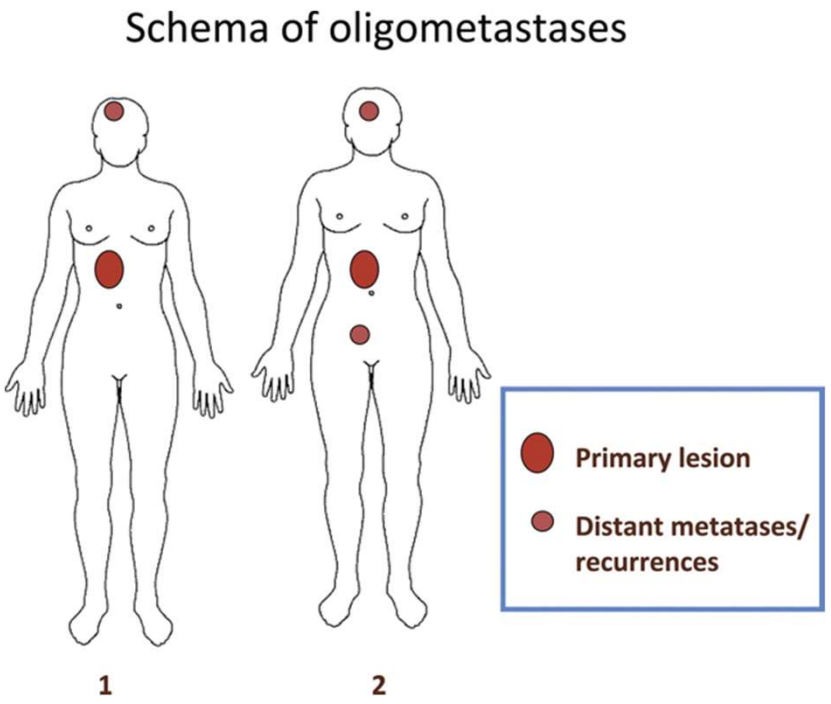


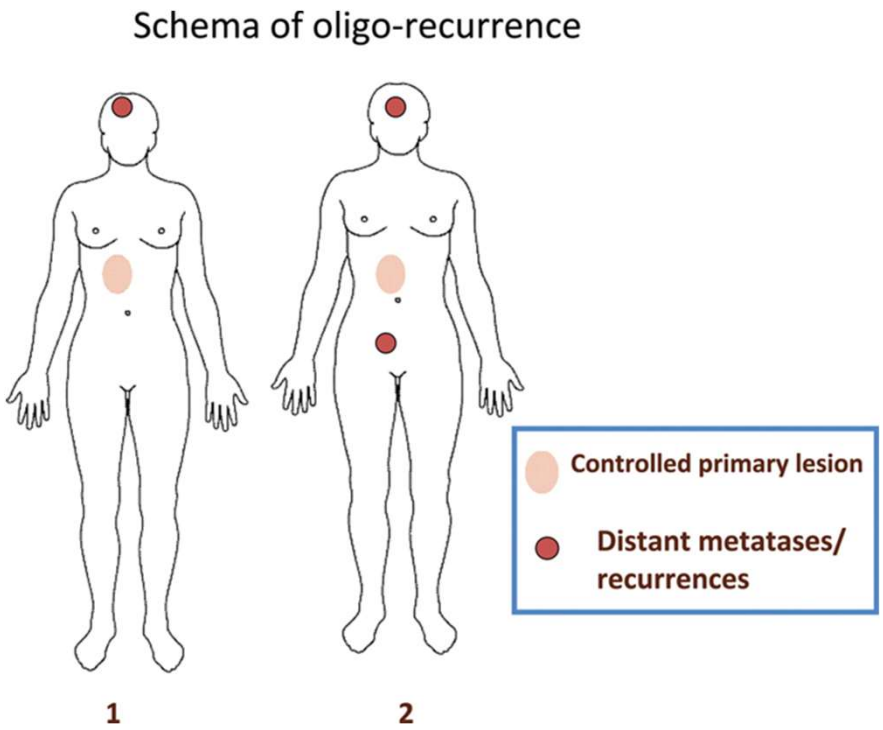
Challenge - High quality translational research

- 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

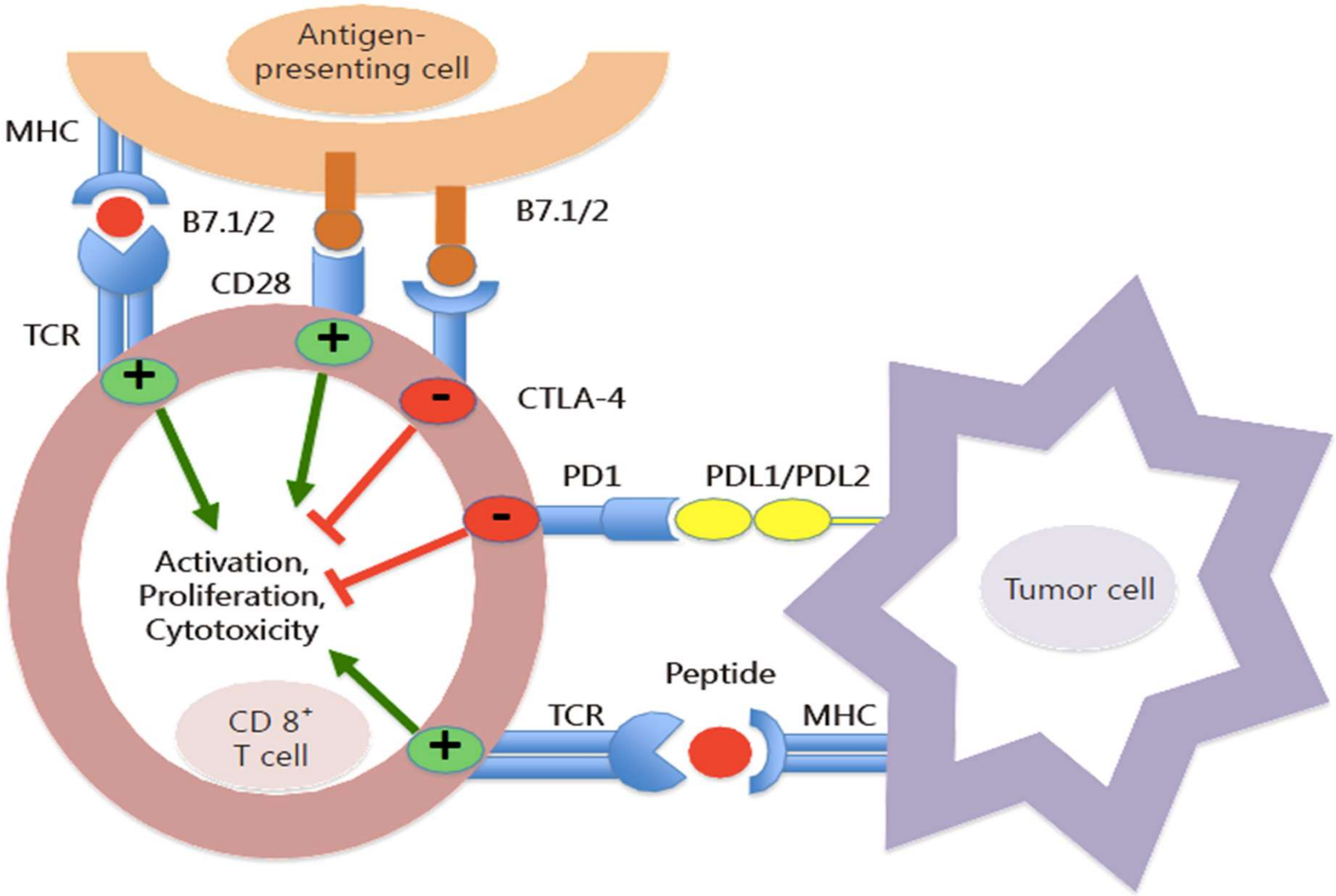
Radiation will become a part of curative systemic therapies

Oligometastases





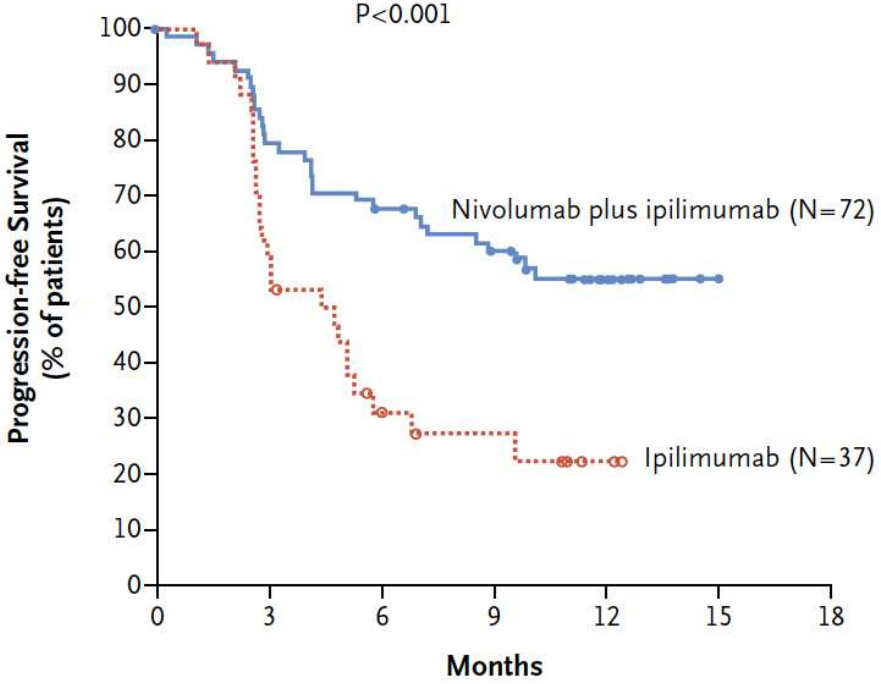
Immune therapies: Blocking CTLA4 and PD1 signaling



Immune therapy

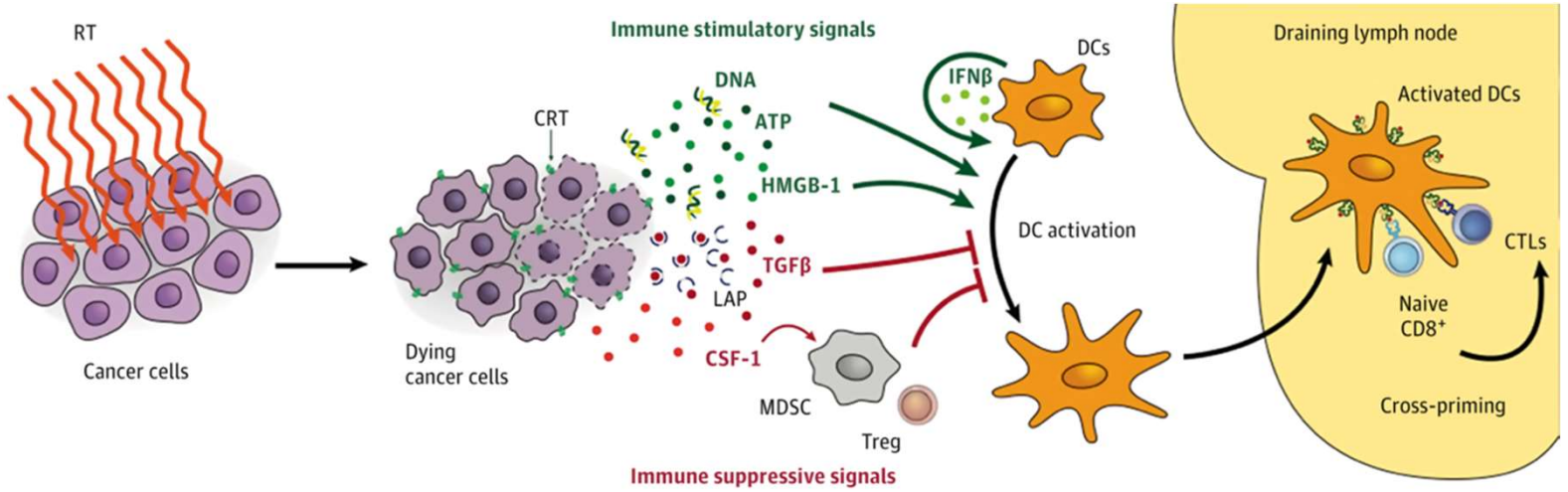
	Death or Disease Progression	Median Progression-free Survival
	no. of patients/total no.	*mo (95% CI)*
Nivolumab plus Ipilimumab	30/72	NR
Ipilimumab	25/37	4.4 (2.8–5.7)

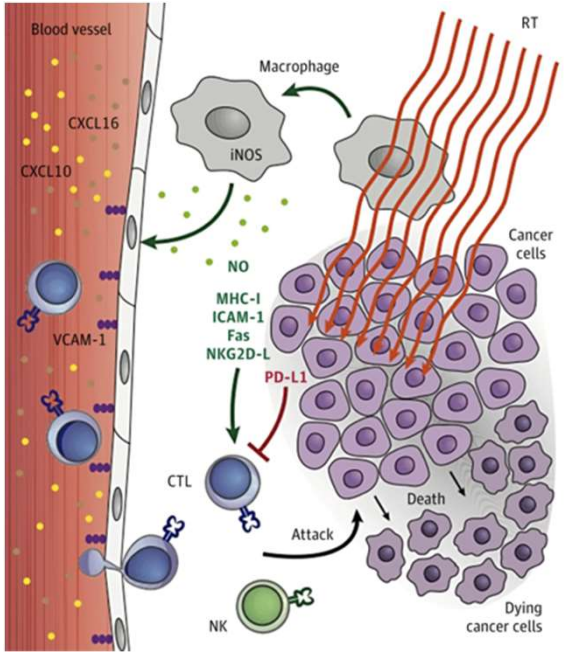
Hazard ratio, 0.40 (95% CI, 0.23–0.68)
P<0.001



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

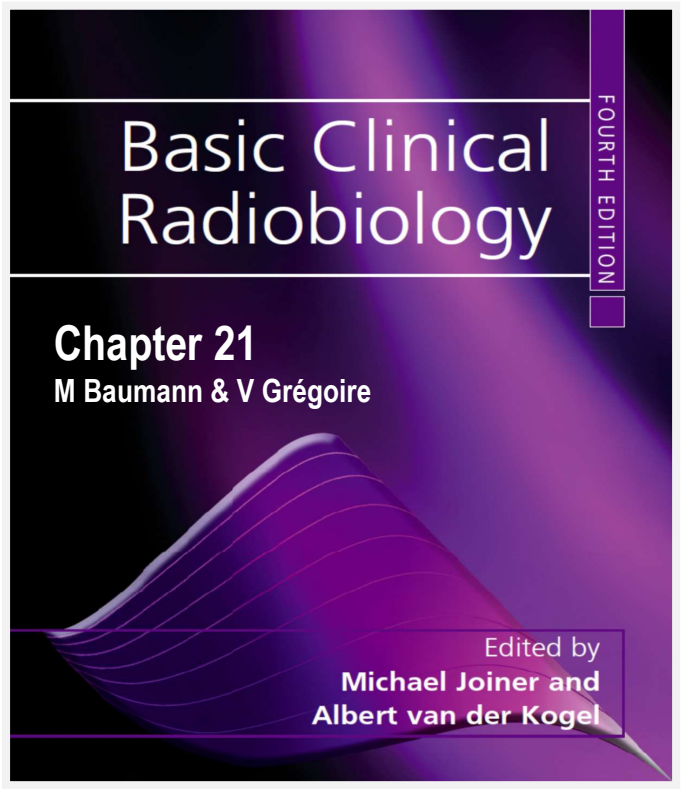
Biological response modifiers Clinical

Karin Haustermans

Department of Radiation Oncology, University Hospitals Leuven, Belgium

Overview

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

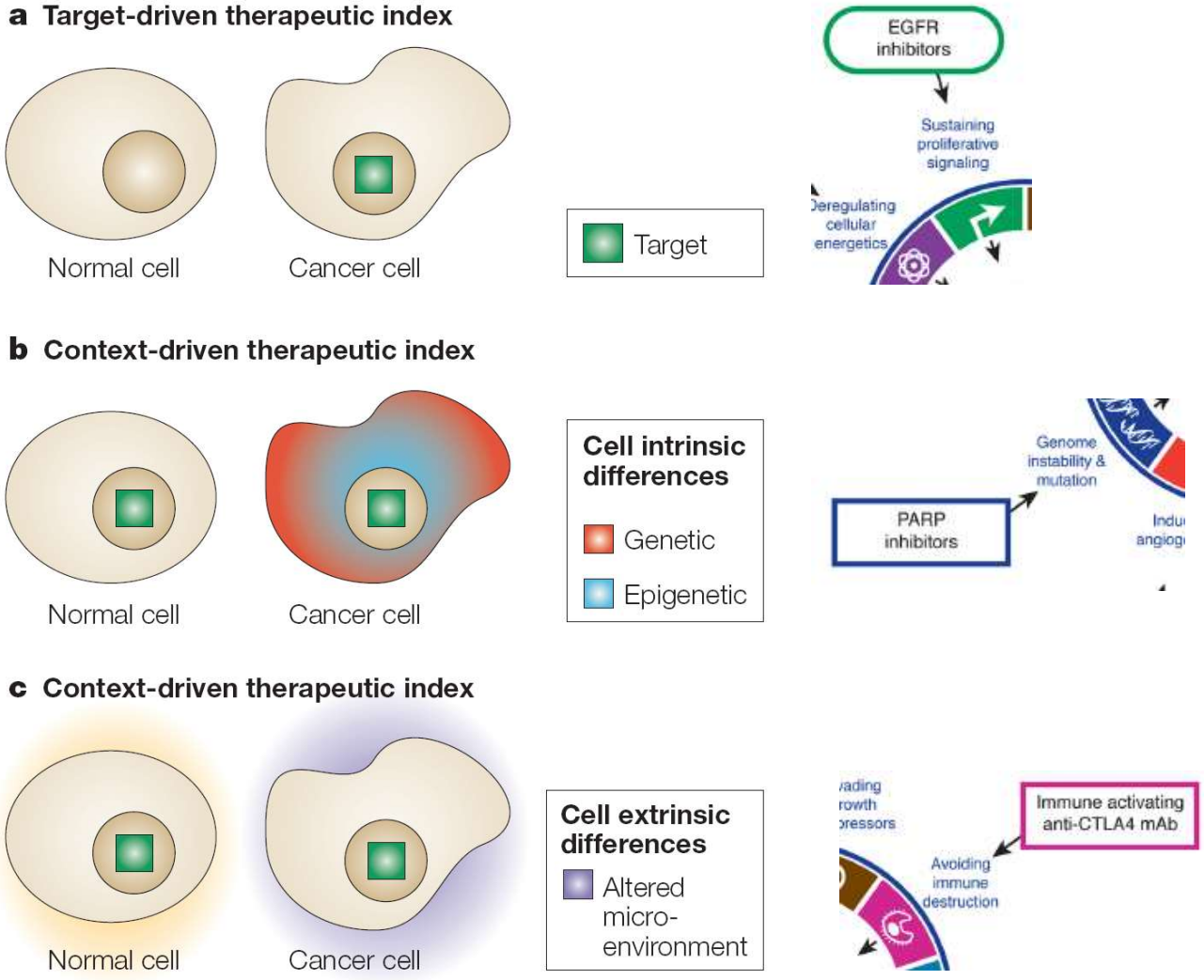


Framework

Target driven lethality
(Oncogene addiction)

Synthetic lethality

Contextual synthetic lethality

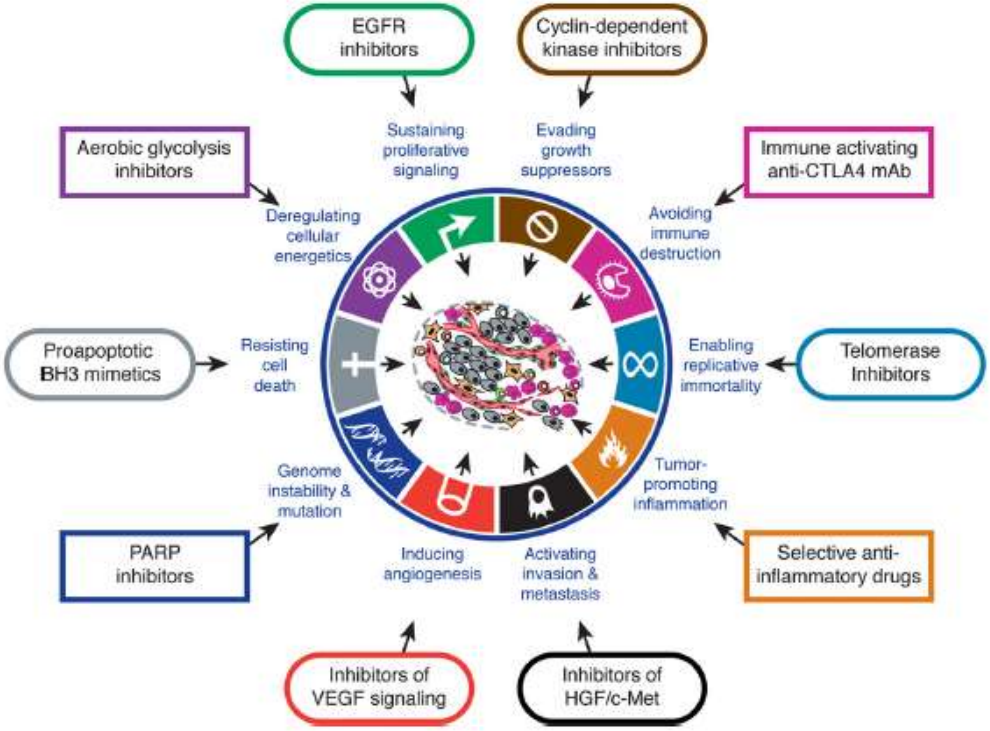


Kaelin Nat Rev 2005

Targeting the hallmarks of cancer

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

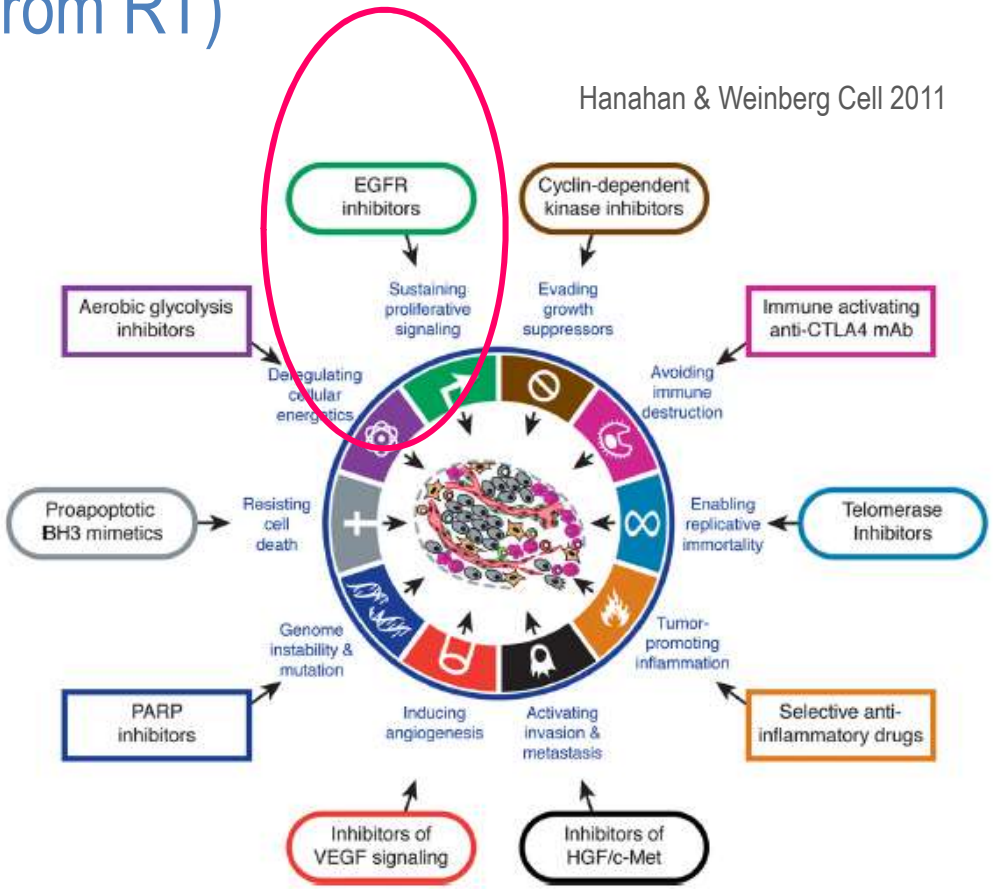
Hanahan & Weinberg Cell 2011



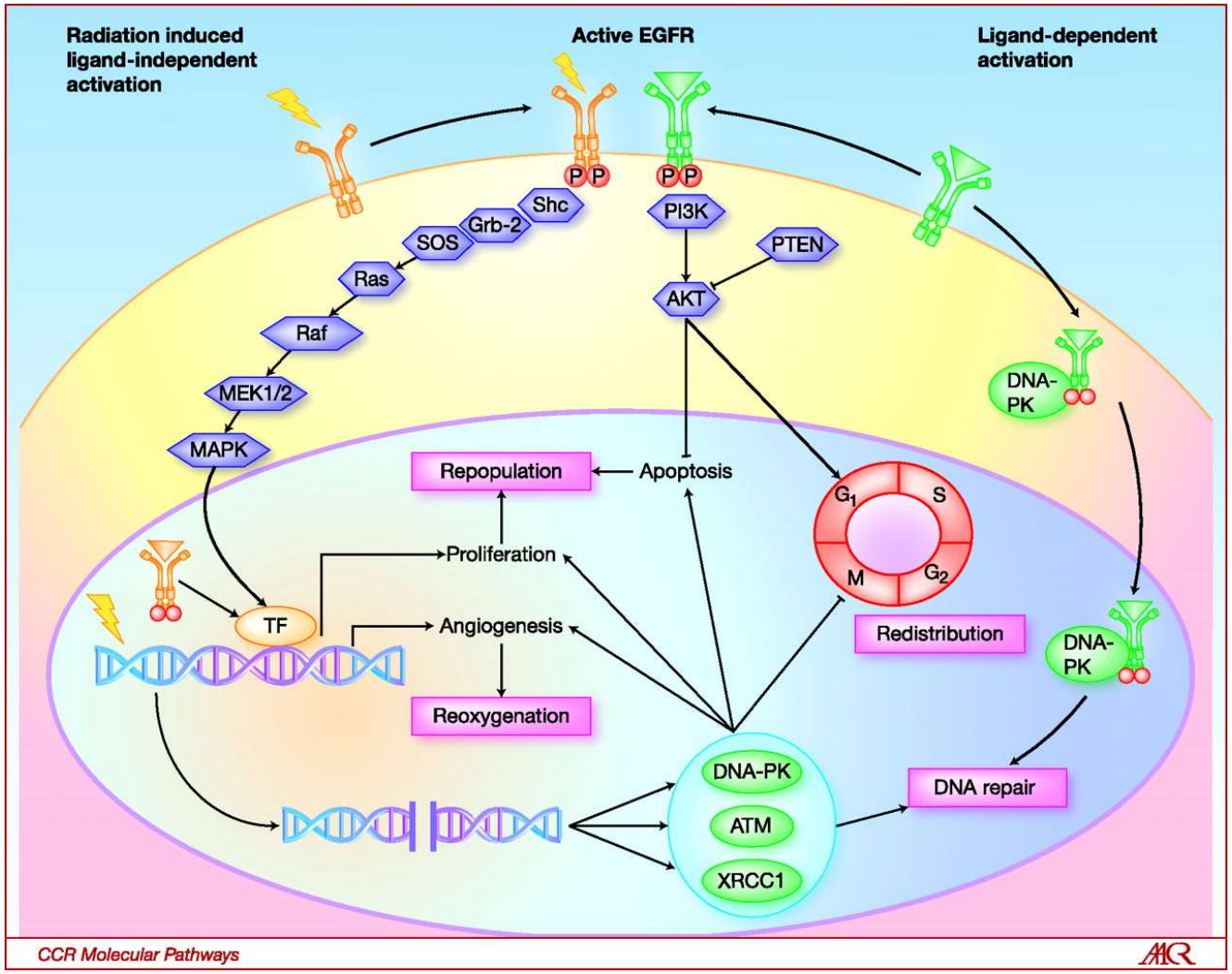
Target driven lethality

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



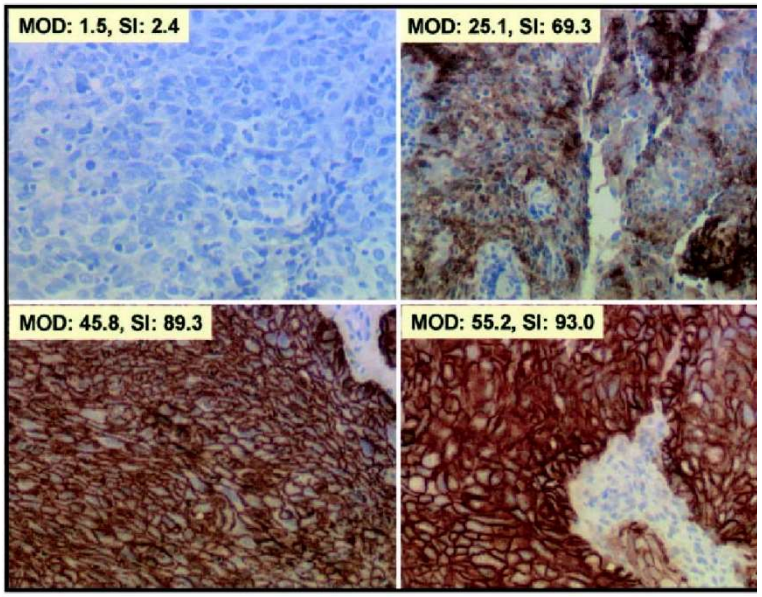
EGFR signaling



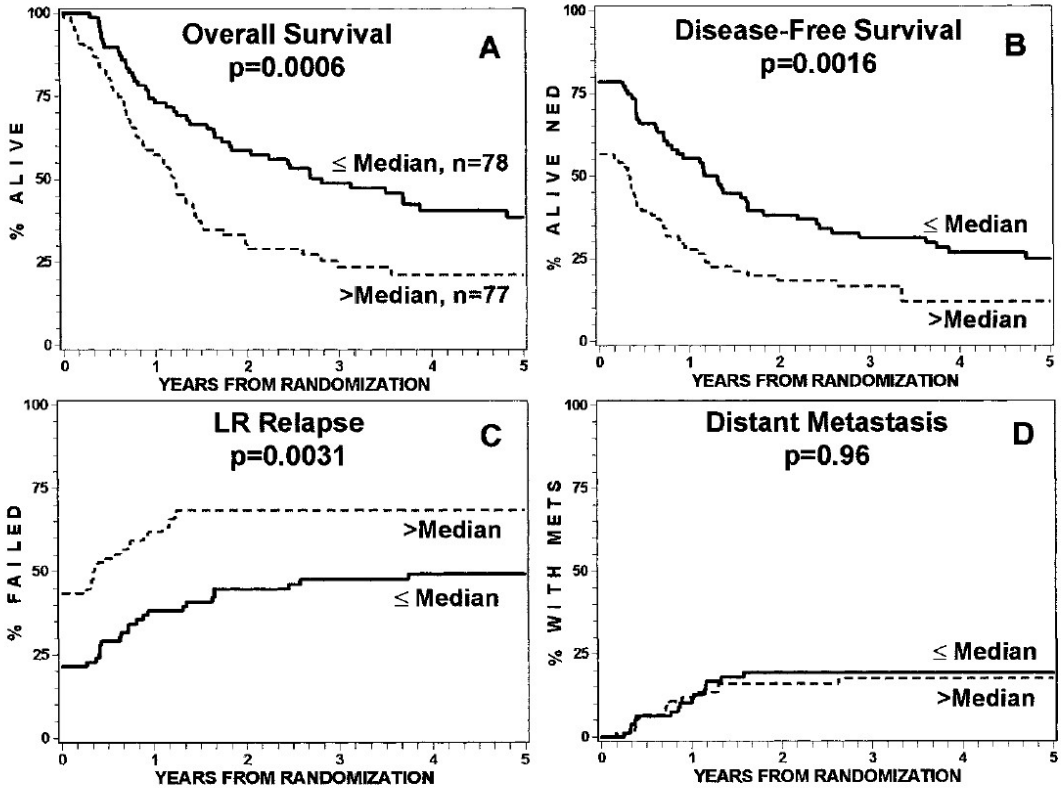
Debucquoy Clin Cancer Res 2010

EGFR expression & prognosis

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



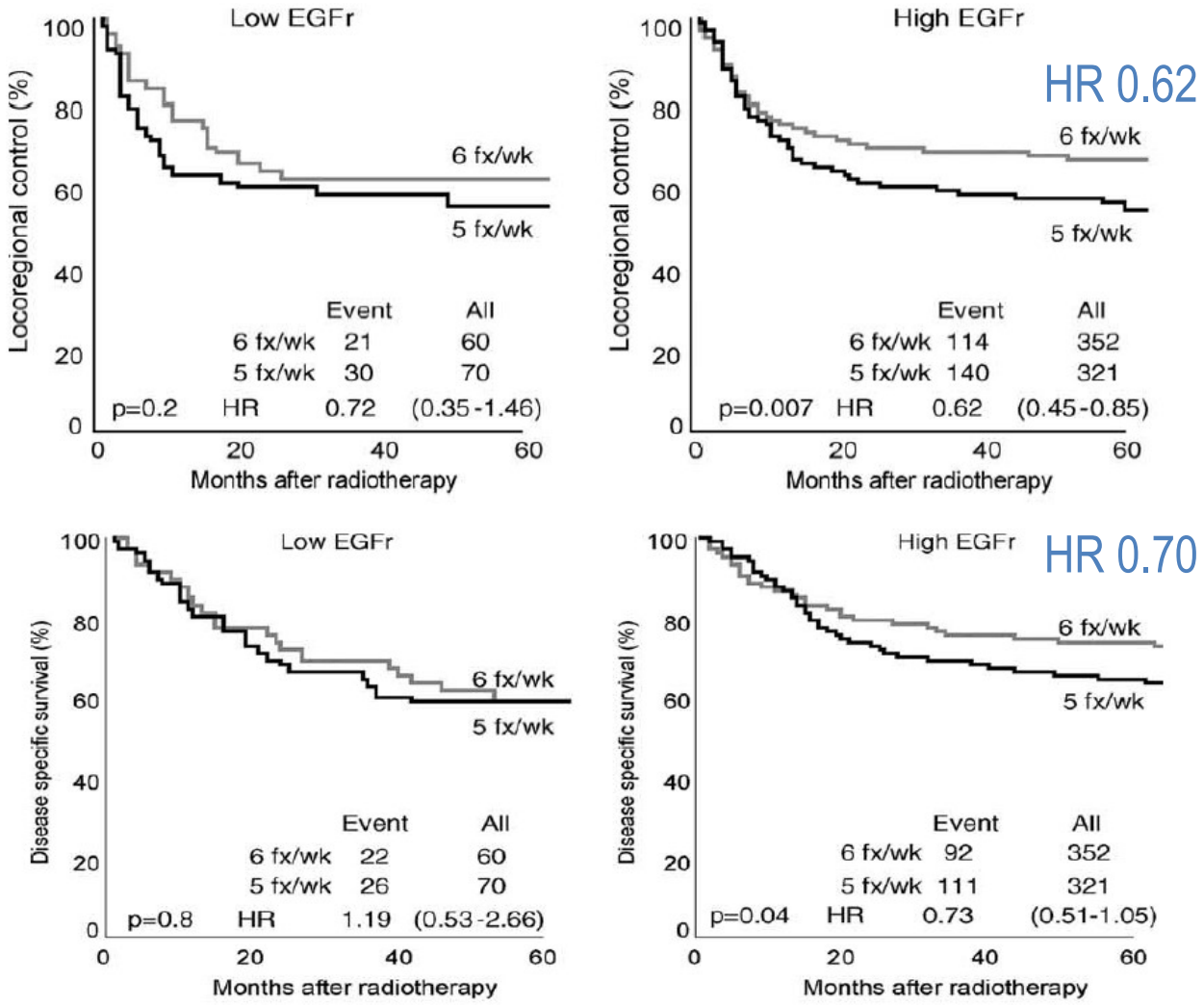
Large variation in EGFR expression in HNCSCC



Ang Cancer Res 2002

ESTRO School

EGFR expression & prognosis



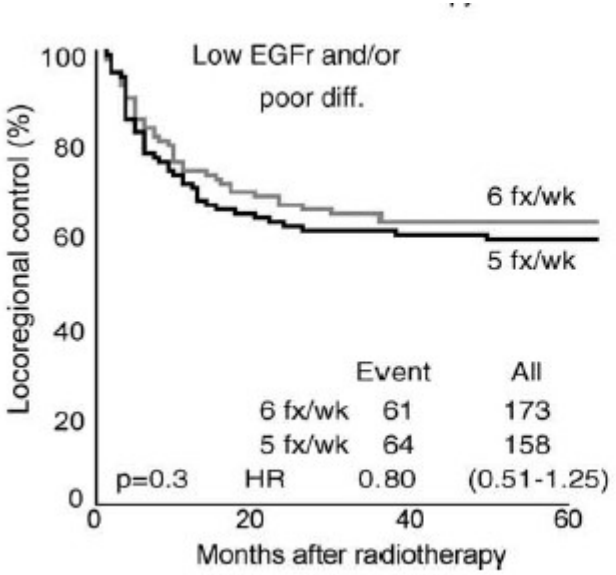
DAHANCA 6 and 7

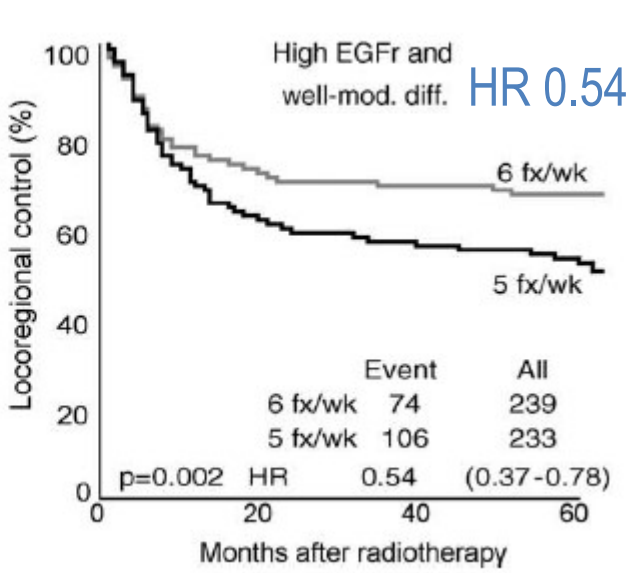
HNSCC with high EGFr expression respond better to moderately accelerated radiotherapy than tumors with low EGFr

ESTRO School

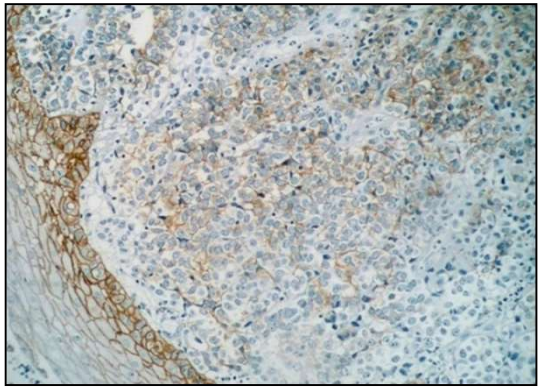
Eriksen Radiother Oncol 2005

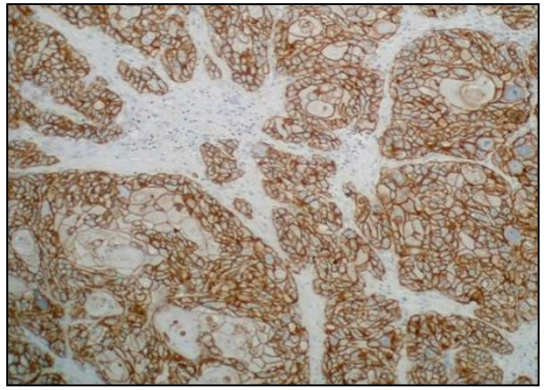
EGFR expression & prognosis





HNSCC with high EGFr and well/moderate differentiation benefit from moderately accelerated radiotherapy regarding LR control



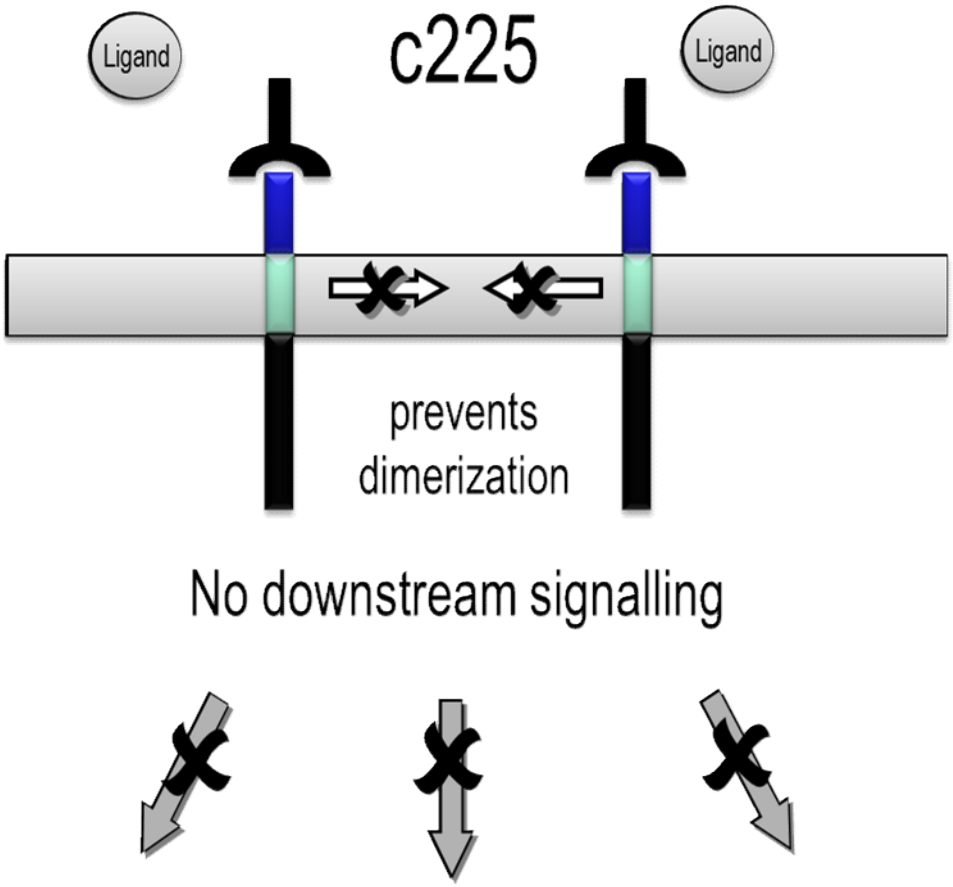


Such effect was not seen in tumors with low EGFr and/or poor differentiation

ESTRO School

Eriksen Radiother Oncol 2005

Cetuximab (c225)



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

ESTRO School

Bonner et al NEJM 2006

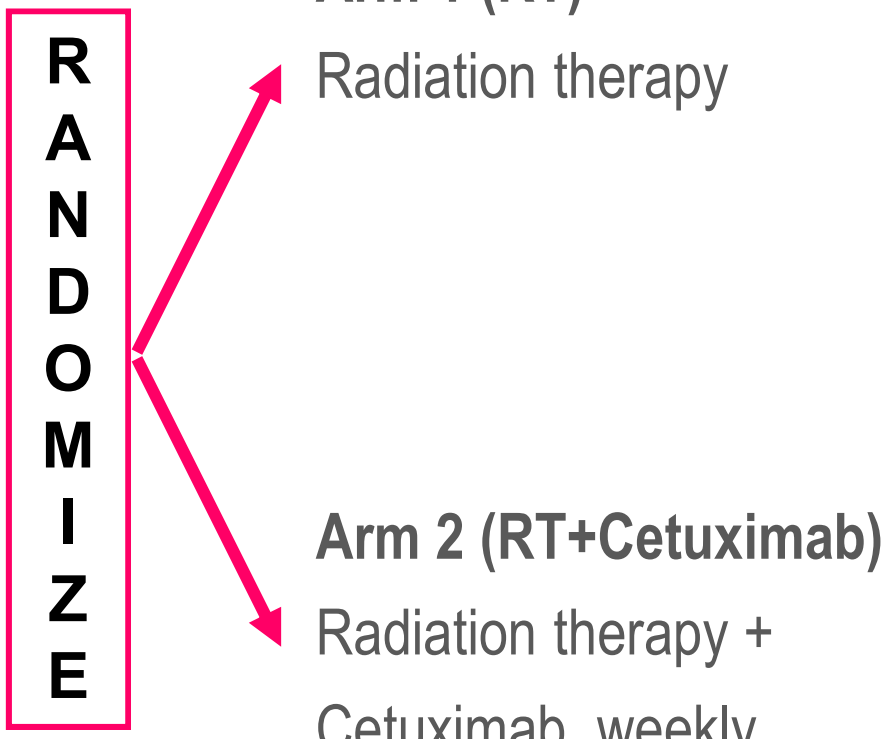
Bonner Lancet Oncol 2010

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

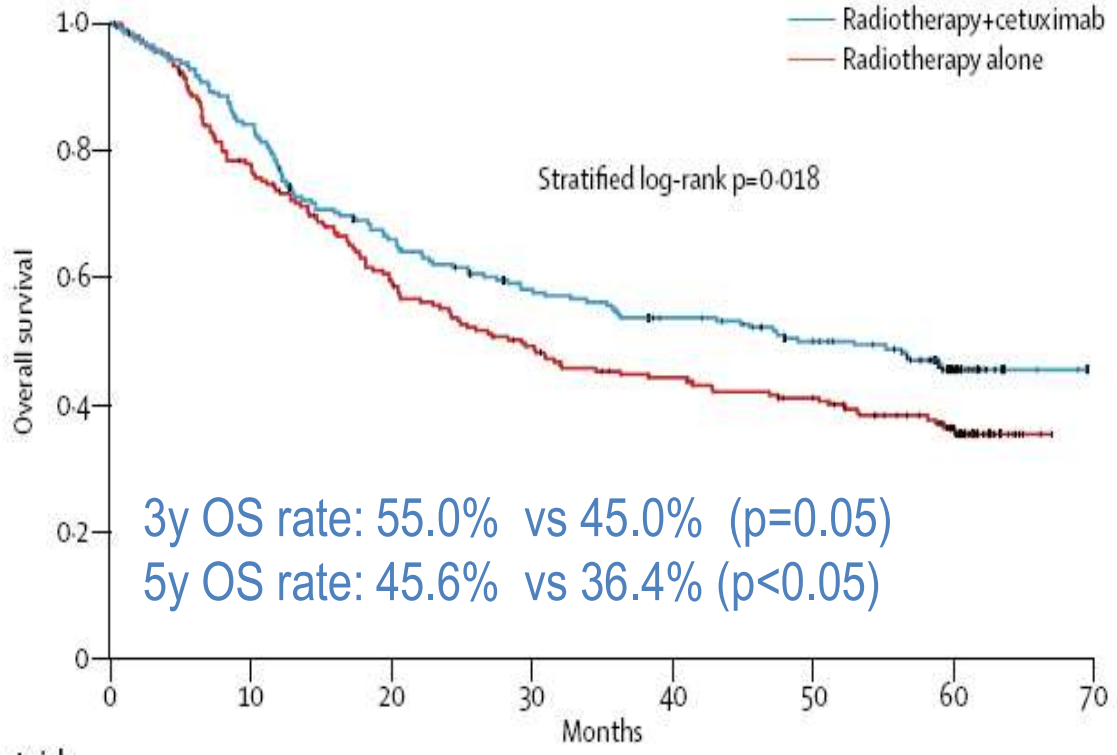


ESTRO School

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)

Bonner Lancet Oncol 2010

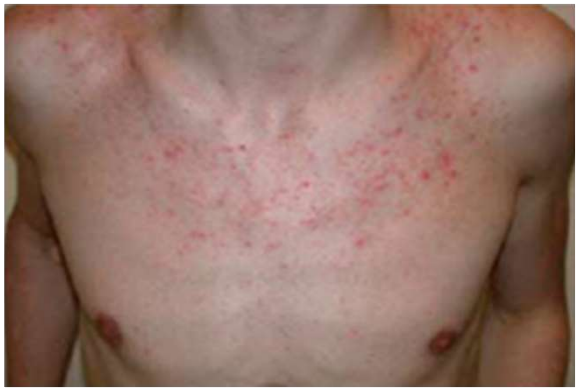
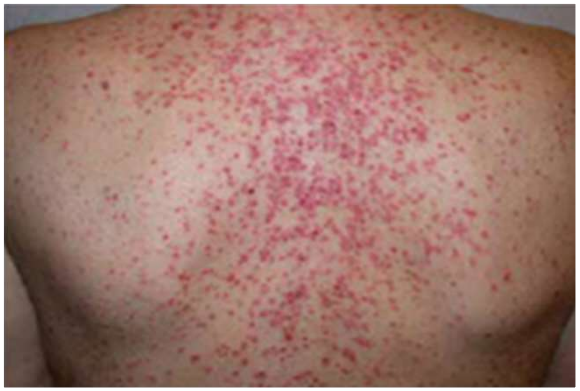
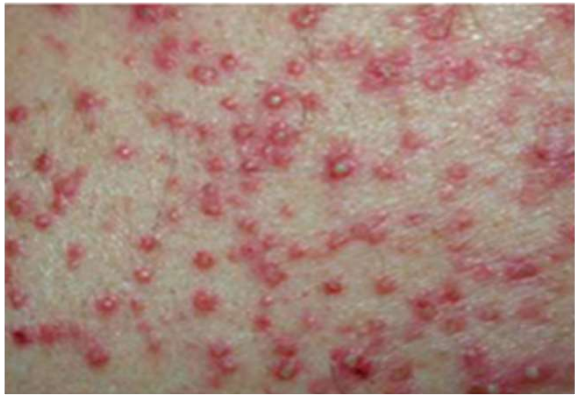
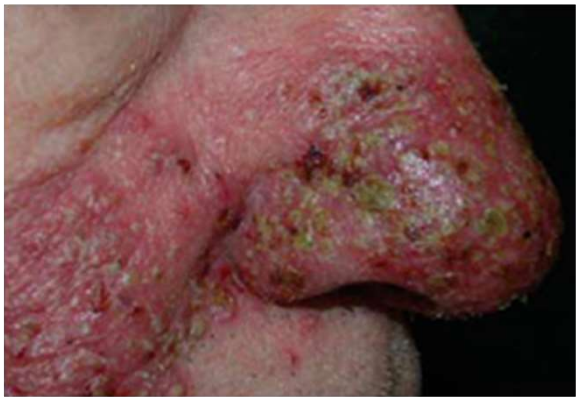
Adverse events

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

Bonner NEJM 2006

Acneiform rash

- Predictive of response to therapy?

Segaert S Ann Oncol, 2005

Acneiform rash

- Prominent cetuximab-induced rash ~ better survival

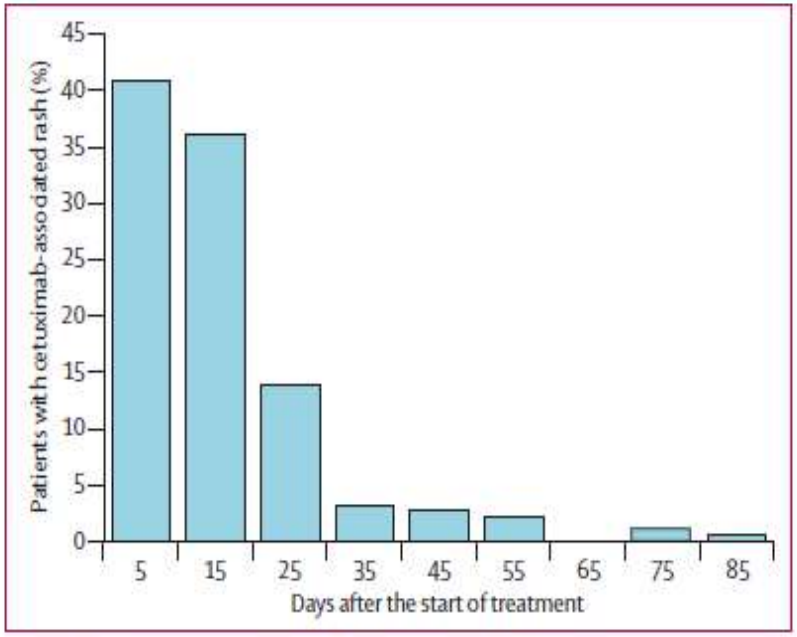


Figure 4: The onset of cetuximab-induced rash following the initiation of first treatment

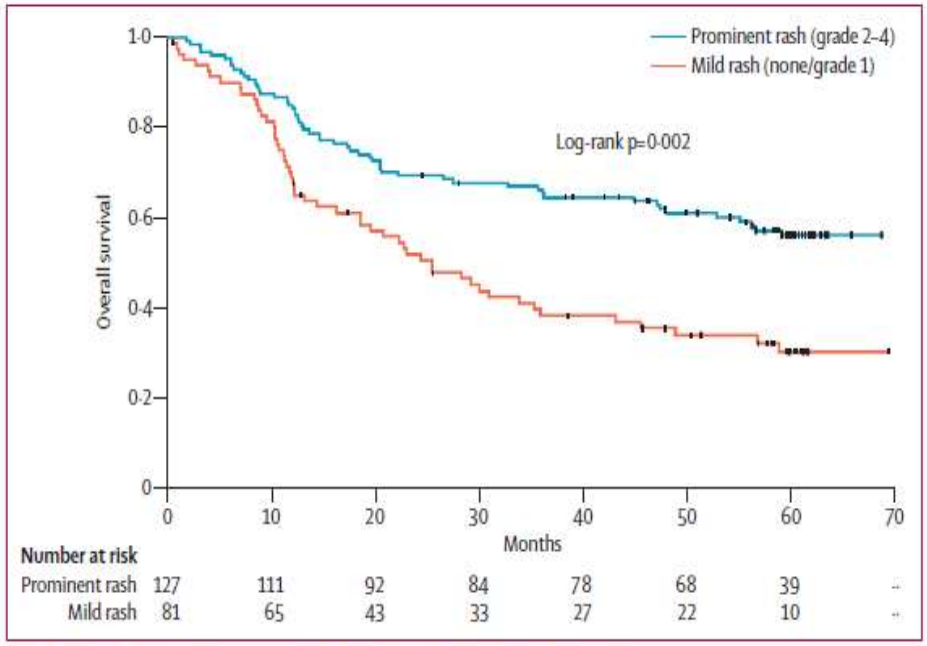


Figure 5: Overall survival by severity of rash in cetuximab-treated patients

Bonner JA, Lancet Oncol 2010

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Predictive biomarkers for cetuximab in HNSCC?

Bonner J Oncologist 2017;22:811

- p16 and HPV are not predictive for outcomes of cetuximab-containing treatment regimens in patients with locoregionally advanced or recurrent/metastatic HNSCC (despite their prognostic value)

Table 1. Trial designs for IMCL-9815 and EXTREME

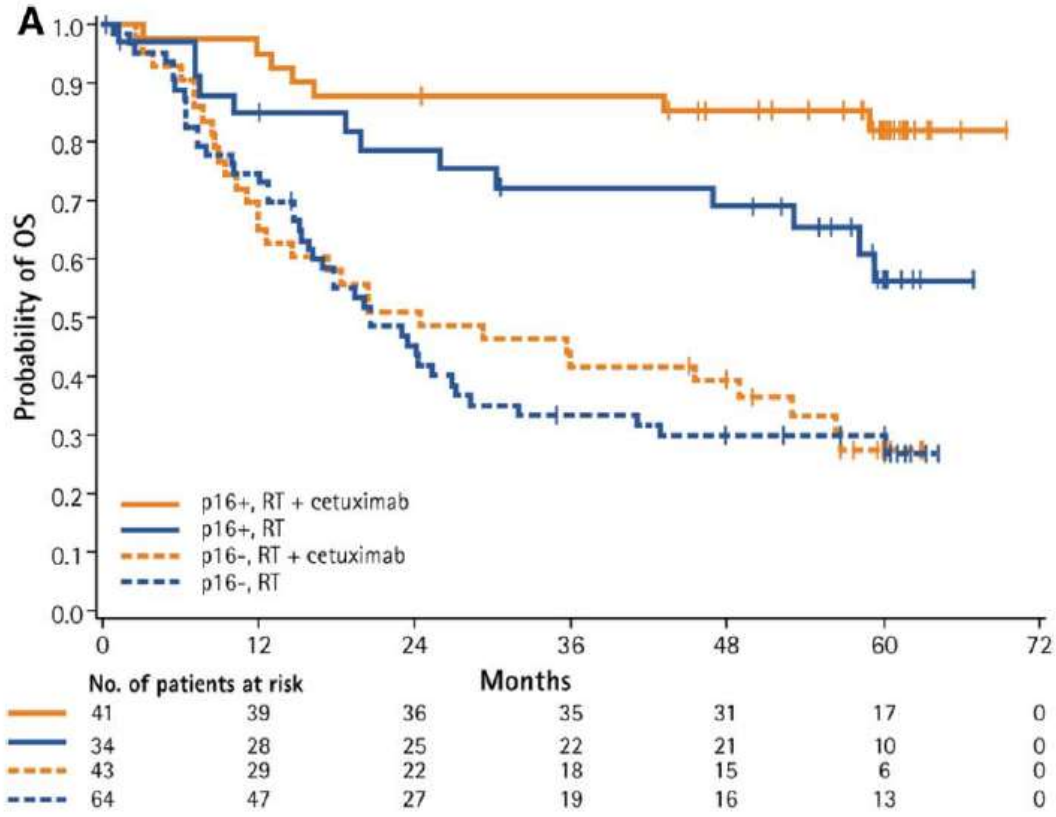
Trial, *n* Extent of disease	IMCL-9815, *n* = 424 LA SCCHN	EXTREME, *n* = 442 R/M SCCHN
Trial design	Phase III, randomized	Phase III, randomized
Arm 1	RT	Platinum + 5-FU
Arm 2	Cetuximab + RT	Cetuximab + platinum + 5-FU
Tumor sites included	• Hypopharynx • Larynx • Oropharynx	• Hypopharynx • Larynx • Oral cavity • Oropharynx
Primary endpoint	LRC	OS
Selected secondary endpoints	• OS • PFS • Safety	• PFS • Response rate • Safety

Predictive biomarkers for cetuximab in HNSCC?

Bonner J Oncologist 2017;22:811

Patients with p16+ tumors had superior OS than those with p16- tumors in both the cetuximab + RT arm and RT alone treatment arm.

Although the treatment effects were stronger in the p16+ subgroup, interaction tests revealed no significant interaction between p16 status and treatment



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EGFR inhibition + RCT in HNSCC

- Benefit with chemotherapy? RTOG0522 trial
  - Randomized Phase III, stage III and IV HNSCC
  - Concurrent accelerated radiation + cisplatin (arm A; n = 447) vs concurrent accelerated radiation + cisplatin + cetuximab (arm B; n = 444)

  - Adding cetuximab to radiation-cisplatin did not improve outcome; leads to more acute grade 3-4 toxicity

Ang KK, JCO 2014;32:2940

EGFR inhibition + RCT in HNSCC

- Benefit with chemotherapy? RTOG0522 trial

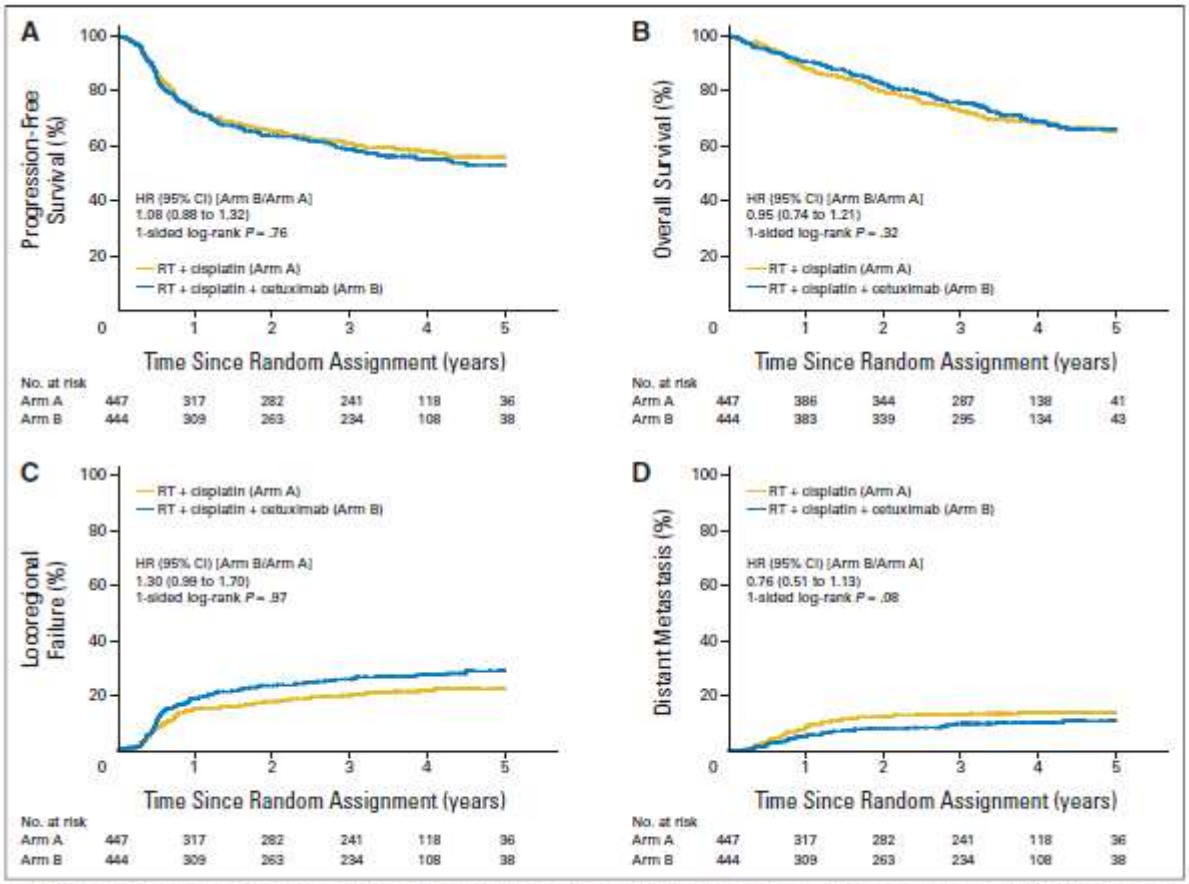

Fig 2. Kaplan-Meier estimates of (A) progression-free and (B) overall survival and cumulative incidence estimates of (C) locoregional failure and (D) distant metastasis by assigned treatment. HR, hazard ratio; RT, radiotherapy.

Ang KK, JCO 2014;32:2940

EGFR inhibition + RCT in HNSCC

- Benefit with chemotherapy? RTOG0522 trial

Table 2. Treatment-Related Adverse Events by Assigned Treatment

Adverse Event*	% of Patients					
	Arm A: RT + Cisplatin		Arm B: RT + Cisplatin + Cetuximab		*P*†	
	All Grades	Grades 3-4	All Grades	Grades 3-4	All Grades	Grades 3-4
Acute period‡						
No. of patients	447		444			
Any event	97	87	97	89	.70	.61
Dysphagia	86	57	82	52	.09	.25
Radiation mucositis	72	33	82	43	< .001	.002
Skin reaction outside portal§	14	1	82	20	< .001	< .001
Skin reaction inside portal‖	79	15	78	25	.87	< .001
Fatigue	60	9	65	14	.17	.03
[illegible]						
Anorexia	32	11	32	16	.89	.04
Salivary gland disorder NOS	31	2	27	4	.24	.67
Hypoalbuminemia	25	1	30	2	.11	.09
Oral pain	24	7	28	10	.17	.19
Hypocalcemia	16	1	26	3	< .001	.09
Hyperglycemia NOS	22	2	25	2	.48	.94
Hypokalemia	18	5	25	10	.007	.005
Constipation	24	1	24	1	.94	.75
Blood creatinine increased	24	2	17	2	.02	1.00
Platelet count decreased	21	2	22	2	.74	1.00
Lymphopenia	18	13	18	14	1.00	.63
Pyrexia	11	0	18	< 1	.003	.50
Laryngitis NOS	17	2	16	2	.59	.64
ALT increased	14	1	16	2	.35	.30
Tinnitus	16	1	15	< 1	.85	.12
Diarrhea NOS	10	1	16	2	.02	.58
Mucositis/stomatitis (clinical exam): larynx	13	5	13	5	1.00	.76
Alopecia	13	0	11	0	.40	—
AST increased	11	< 1	12	< 1	.40	1.00
Cough	11	< 1	12	1	.67	.37
Headache	4	0	12	1	< .001	.12
Laryngeal edema	11	2	10	1	.83	.77

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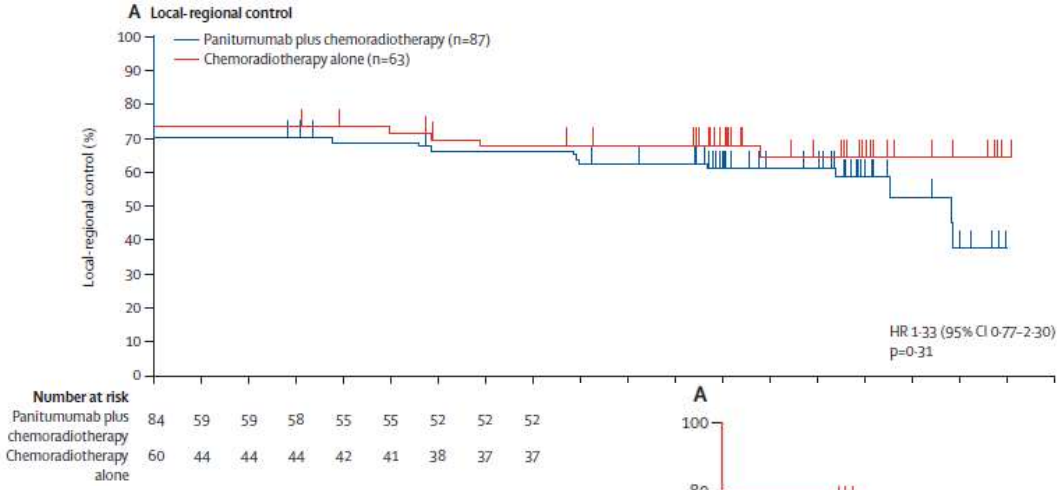
Ang KK, JCO 2014;32:2940

EGFR inhibition + RCT in HNSCC

- Other EGFR inhibitors? CONCERT trials
  - CONCERT-1
    - Open-label RCT phase II trial, stage III and IV HNSCC
    - RCT (n=63) vs R**C**T + Panitumumab (n=87)
  - CONCERT-2
    - Open-label RCT phase II trial, stage III and IV HNSCC
    - RCT (n= 61) vs **RT** + Panitumumab (n=90)

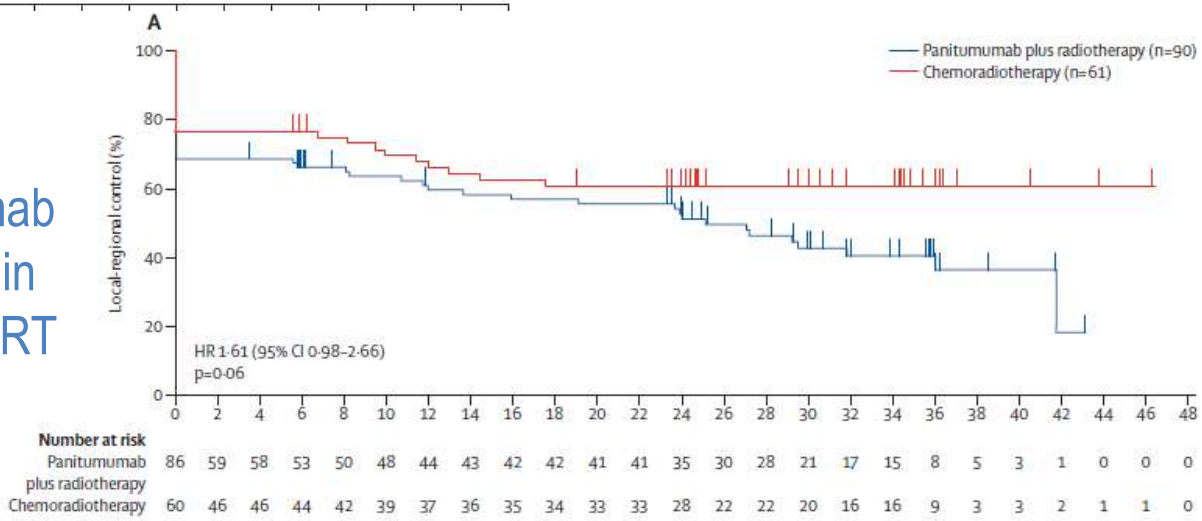
EGFR inhibition + RCT in HNSCC

- Other EGFR inhibitors? CONCERT trials



CONCERT-1: addition of panitumumab to standard fractionation radiotherapy and cisplatin did not confer any benefit

CONCERT-2: panitumumab cannot replace cisplatin in combined treatment with RT



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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

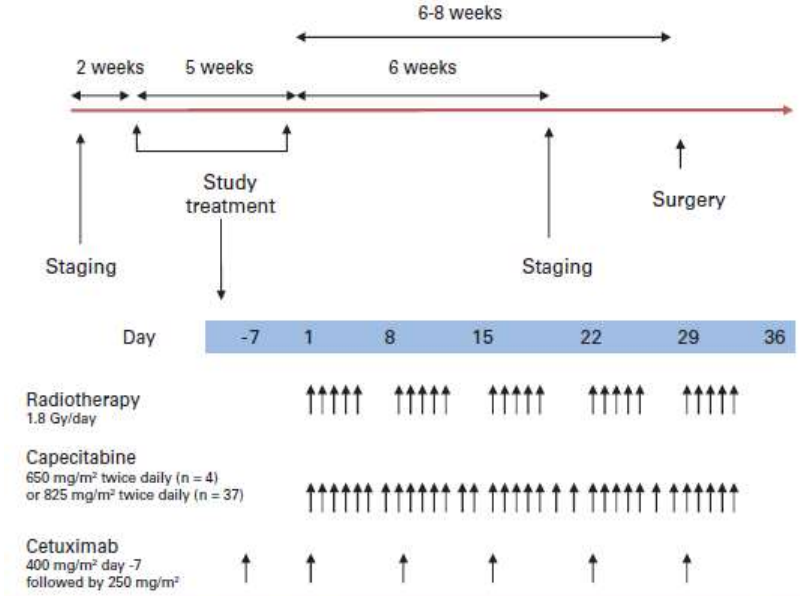
Table 4. Pathologic stage for 45 operated patients treated at recommended capecitabine dose level of 1,650 mg/m^2

	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)

EGFR inhibition + RCT in rectal cancer

- Importance of translational research

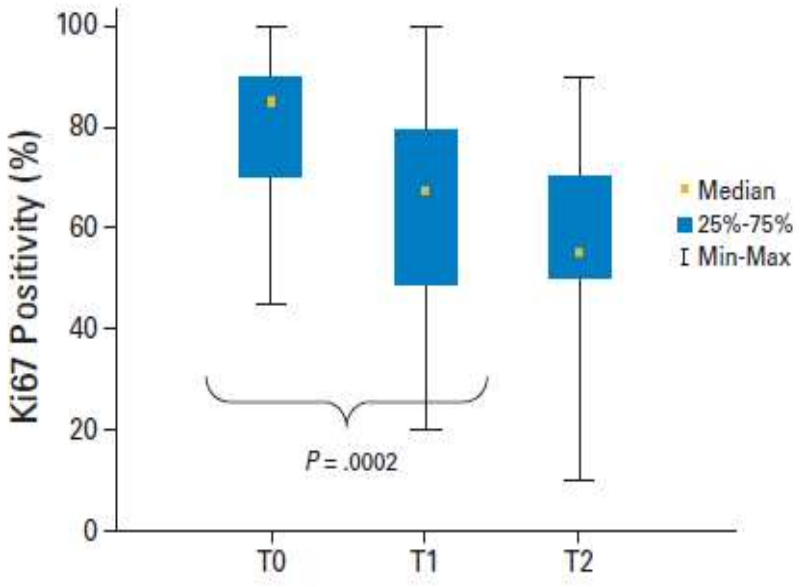


		T0	T1		T2
Tissue	*kRAS* mutations	X			
	cDNA microarrays	X	X		
	IHC: EGFR & Ki67	X	X		X
	Pathologic response				X
	Fibro-inflammation				X
Blood	Proteomics	X	X		
	ELISAs	X	X		X

Debucquoy JCO 2009

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

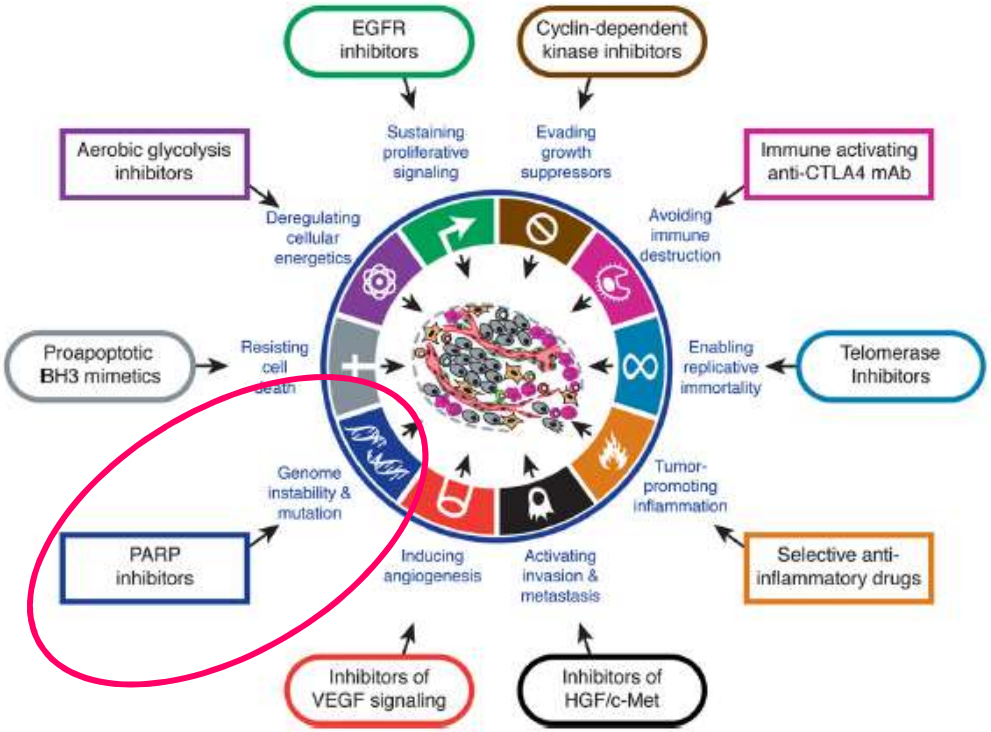


Debucquoy JCO 2009

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

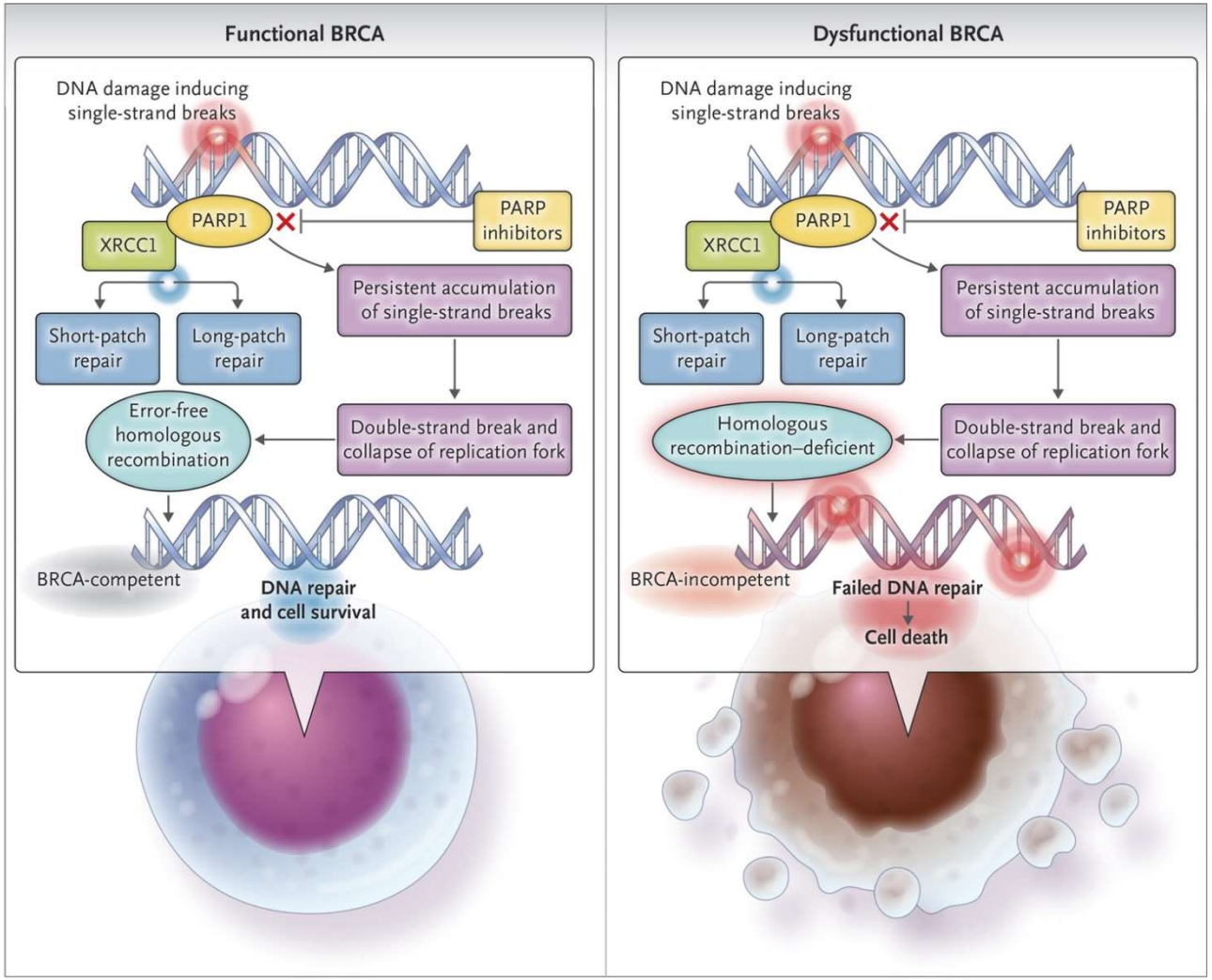
Hanahan & Weinberg Cell 2011



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

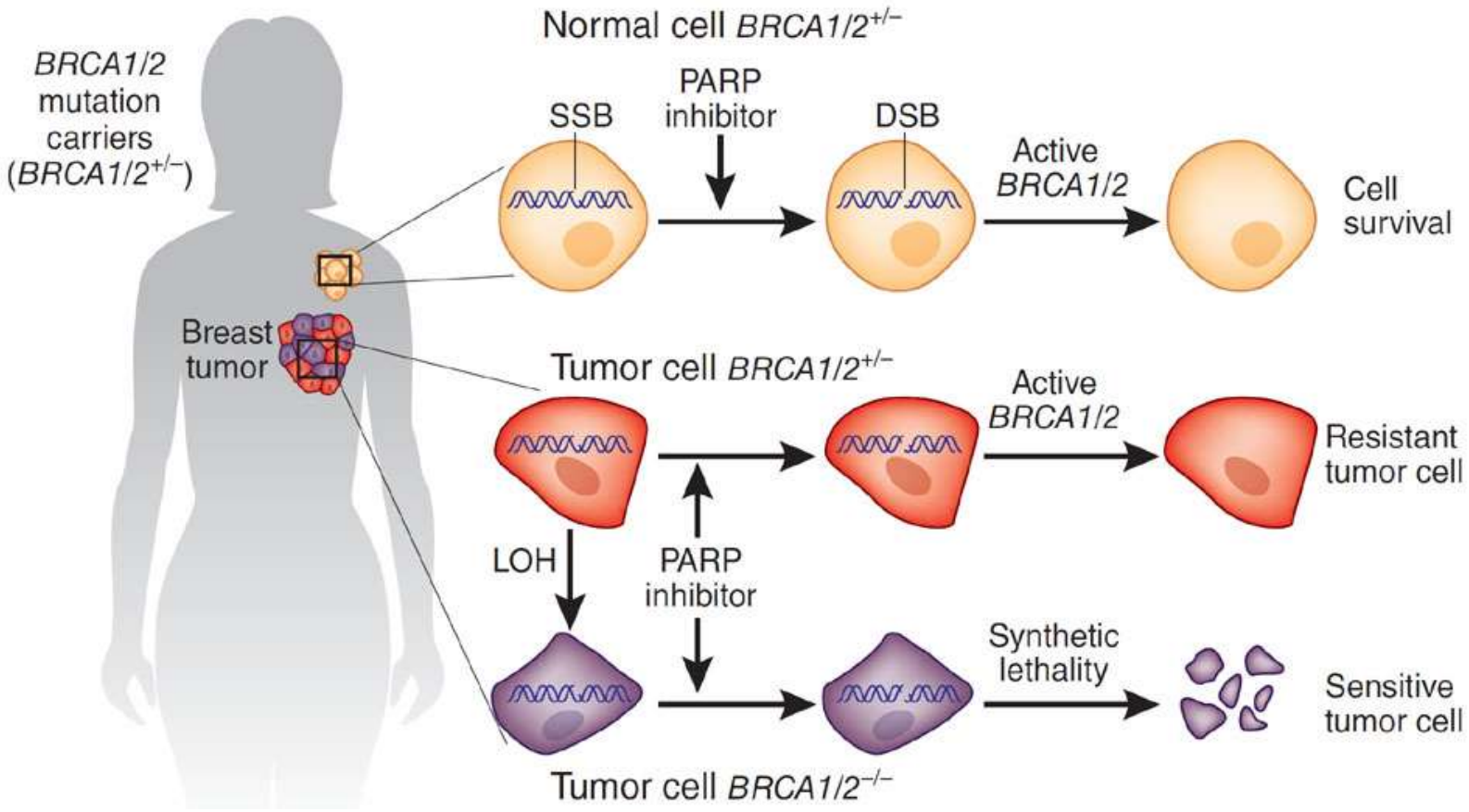
Synthetic lethality

PARP inhibition and BRCA status



McLornan NEJM 2014

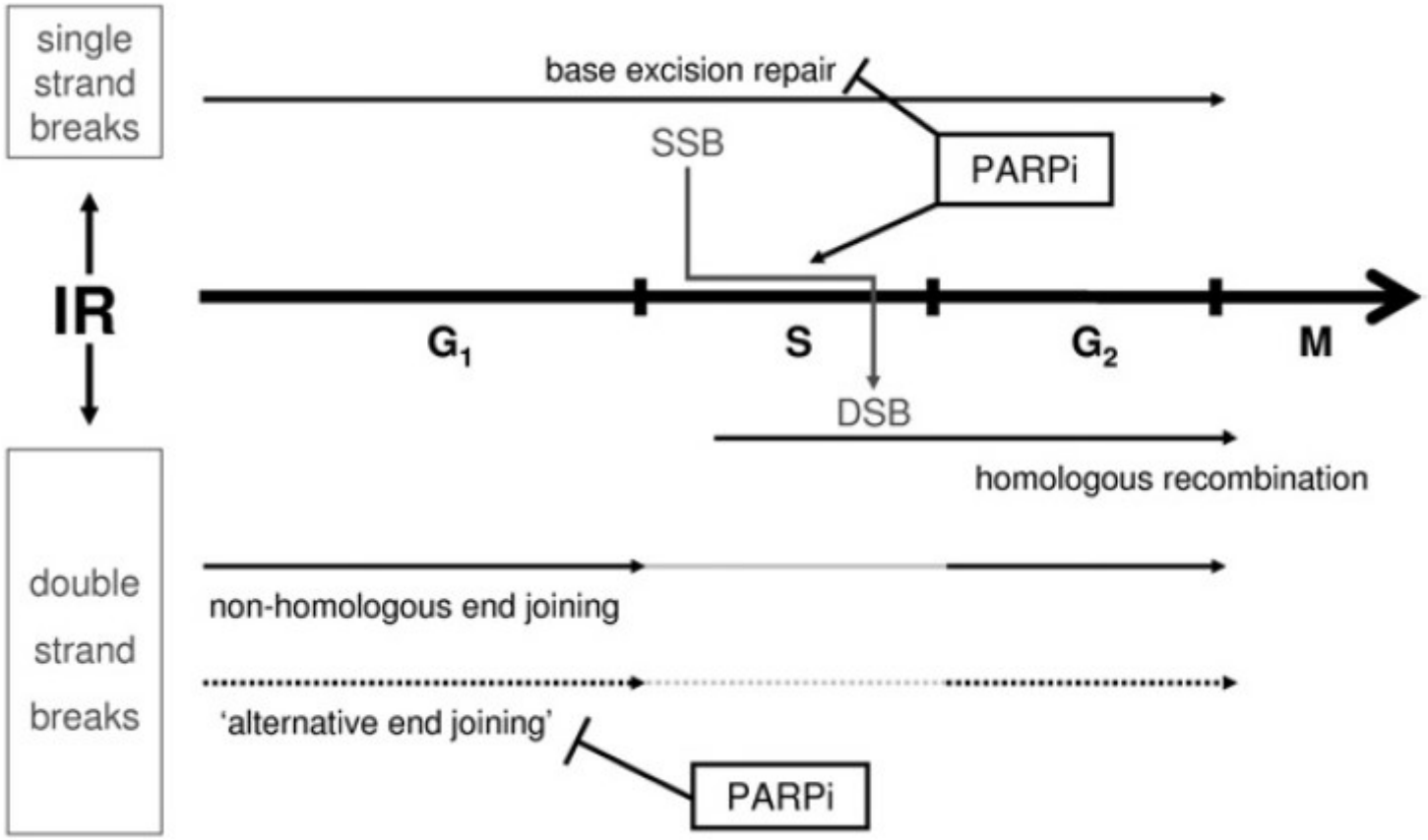
PARP inhibition and BRCA status



Polyak K Nat Med 2011

Key mechanisms of action of PARPi

Chalmers AJ et al Semin Radiat Oncol 2010



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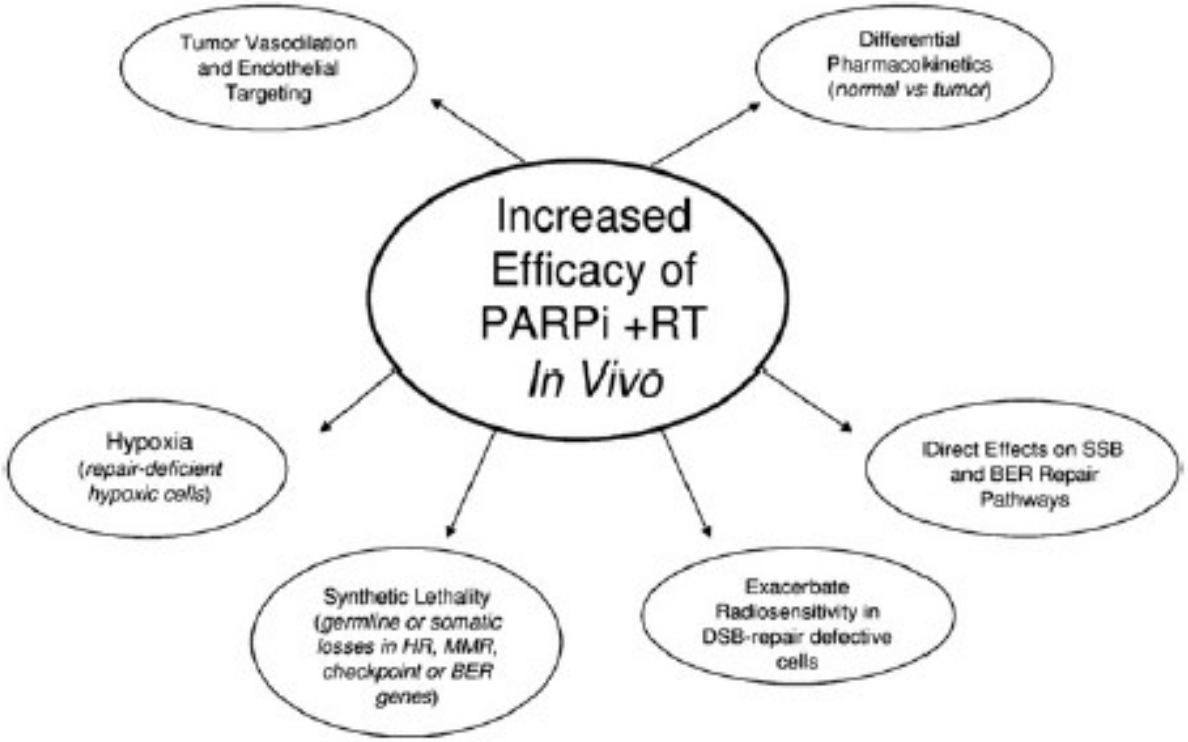
PARP inhibitors + radiotherapy

Chalmers AJ et al Semin Radiat Oncol 2010

- Mechanisms by which PARP inhibitors may increase clinical radiocurability



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PARP inhibitors + radiotherapy

Powell C et al Cancer Treat Rev 2010

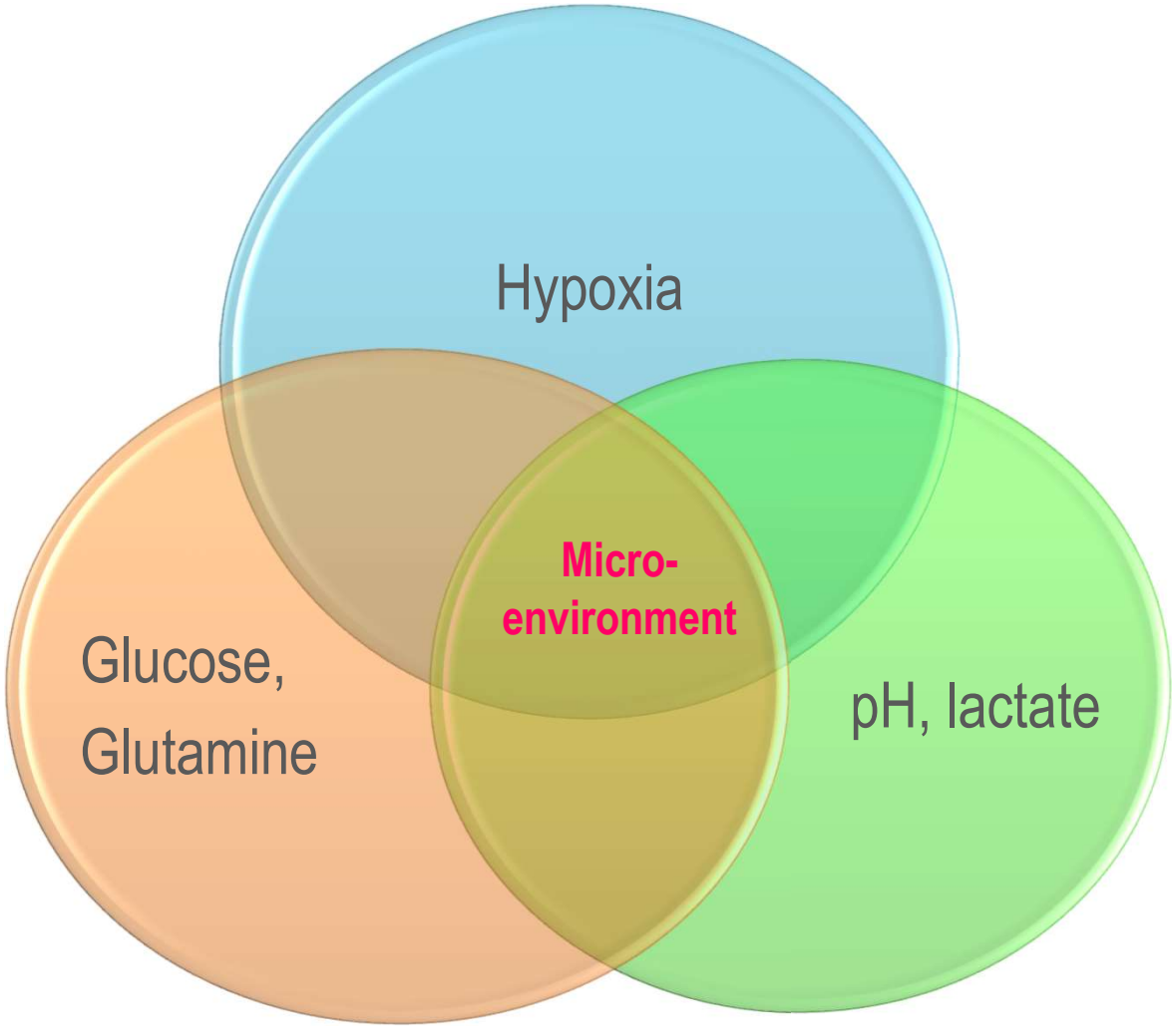
- In vivo

Table 2
Published data showing the radiosensitisation effect of PARP inhibitors *in vivo* in mouse xenograft models.

Author	PARP inhibitor	Xenograft	Efficacy with radiotherapy
Kelland and Tonkin[63]	3-Aminobenzamide	Human cervix carcinoma	Enhancement ratio
		70 cG/min	1.5–2.4
		5 cGy/min	1.02–1.37
Calabrese et al.[60]	AG14361	Colorectal cancer (LoVo and SW620)	Tumour growth delay increased by 18 days (2-fold)
Albert et al.[56]	ABT-888	Lung cancer (H460)	Tumour growth delay increased by 6.5 days (2-fold)
Khan et al.[64]	GPI-15427 (10-(4-Methyl-piperazin-1-ylmethyl)-2H-7-oxa-1,2-diaza-benzo[de]-anthracen-3-one)	Head and neck squamous cell carcinoma	Reduced tumour volume
Russo et al.[59]	E7016	Glioblastoma (U251) (in combination with temozolomide)	Tumour growth delay 10.8 days (1.5-fold)
Donawho et al.[65]	ABT-888	Colon cancer (HCT-116)	Median survival time increased by 13 days (1.5-fold)

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
  - …

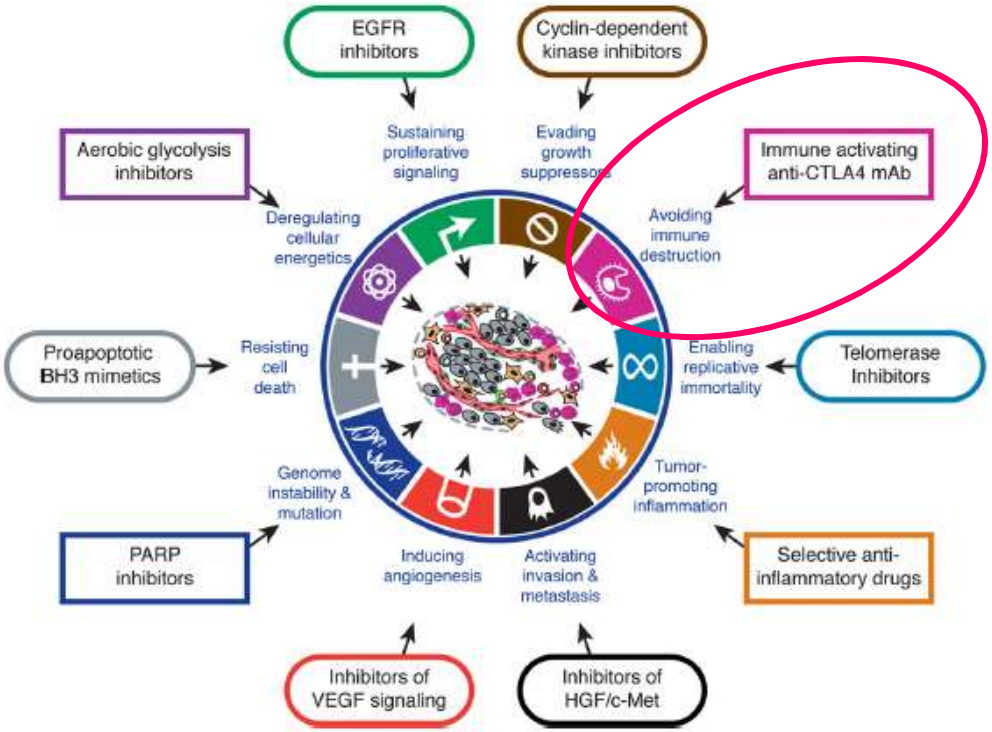


Contextual lethality

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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Immune modulation

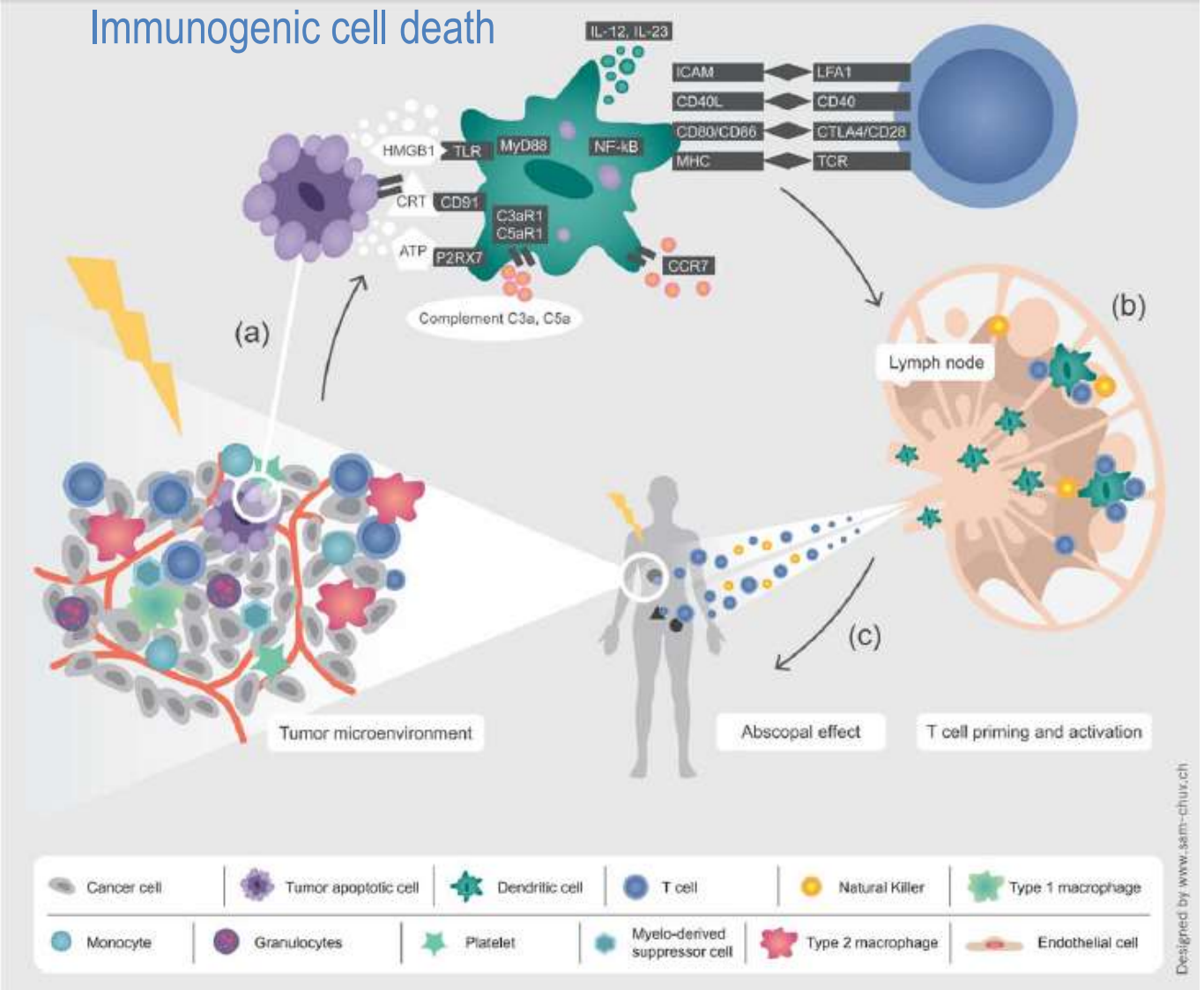
Herrera FG et al CA Cancer J Clin 2017

- Clinical efficacy of RT
  - Traditionally: local effect, through direct tumor cell death (DNA damage)
  - More recently: systemic effects on “out-of-field” tumor deposits = abscopal effect, mediated by immune mechanisms

  - RT induces ‘in situ’ vaccination
  - RT reprograms the tumor micro-environment

Immune mechanisms triggered by RT

Herrera FG et al CA Cancer J Clin 2017



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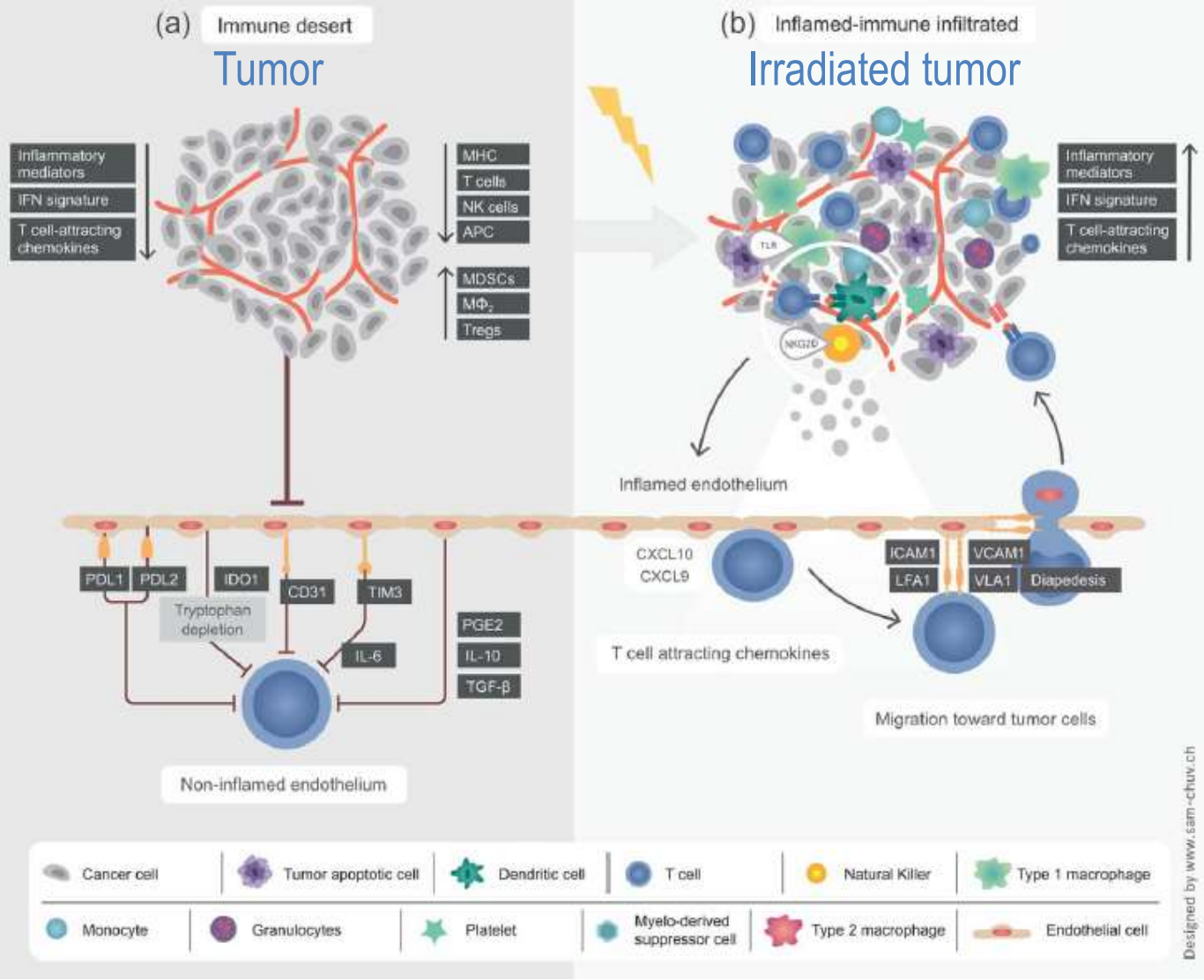
RT reprograms the tumor microenvironment

Herrera FG et al CA Cancer J Clin 2017



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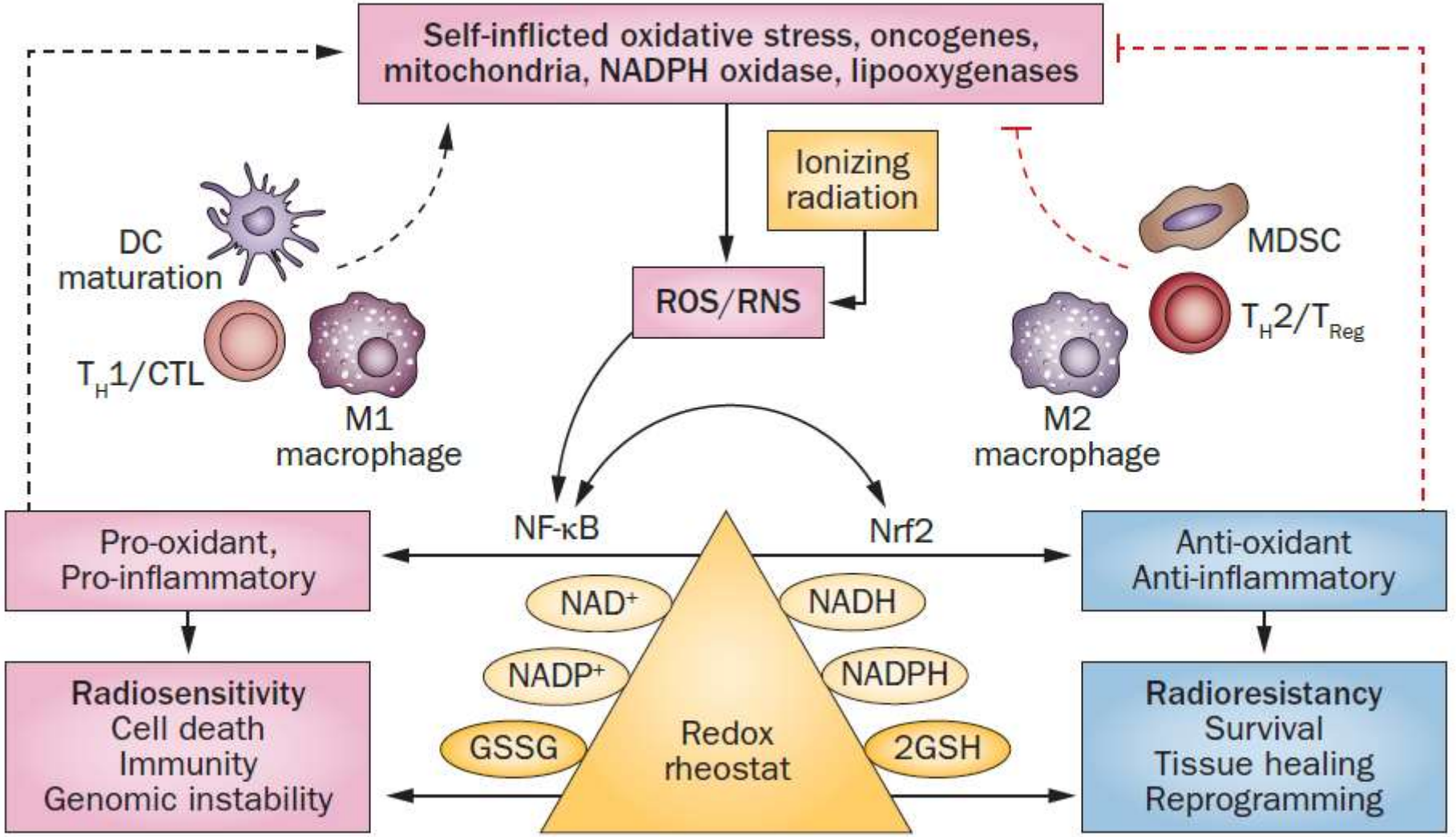
RT reprograms the tumor microenvironment



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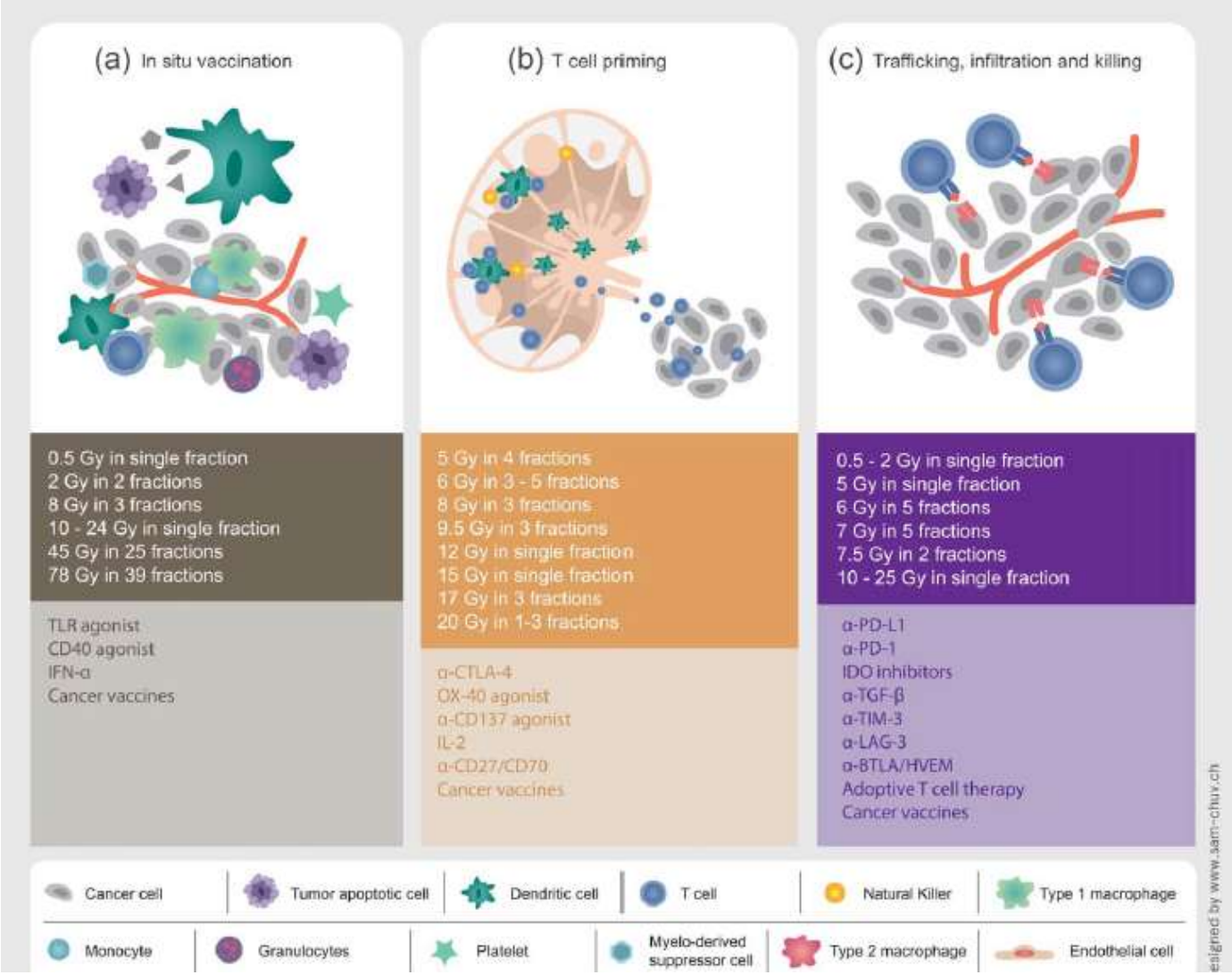
Dörthe Schaue and William H. McBride, Nature 2015

Radioimmunotherapy combinations

- 3 main clinical scenario's
  - IT + hypofractionated RT for oligometastatic disease
    - Clinical goal: reduce distant failures (effect outside radiation field)
    - Mechanism: in situ vaccination effect coupled to local and systemic effects IT
  - IT + chemoRT
    - Clinical goal: enhance efficacy of chemo-RT locally and reduce distant failures
    - Mechanism: local and distant synergies between RT and immunomodulation
  - RT + IT
    - Clinical goal: maximize efficacy of IT against specific tumor deposit (effect within radiation field)
    - Mechanism: RT = biological response modifier

Radioimmunotherapy combinations

Herrera FG et al CA Cancer J Clin 2017



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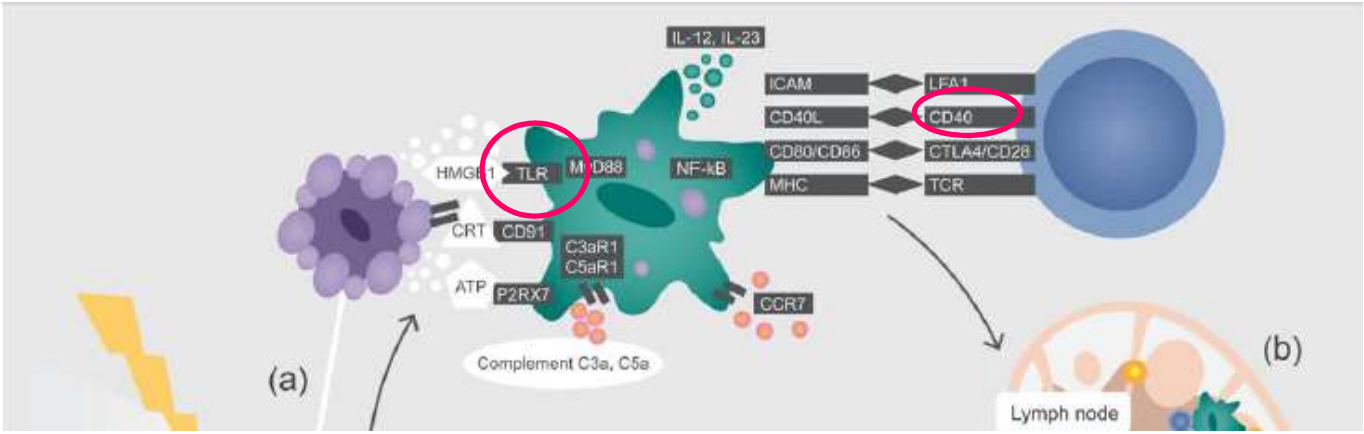
Boosting in situ vaccination effect of RT

Herrera FG et al CA Cancer J Clin 2017

- Pharmacological activation of APCs → because immunomodulatory effects of RT are often not sufficient to trigger effective antitumor immune response due to potent immune suppression in tumor micro-environment and draining lymph node
- E.g. agonists of stimulator receptor CD40 and to TLR



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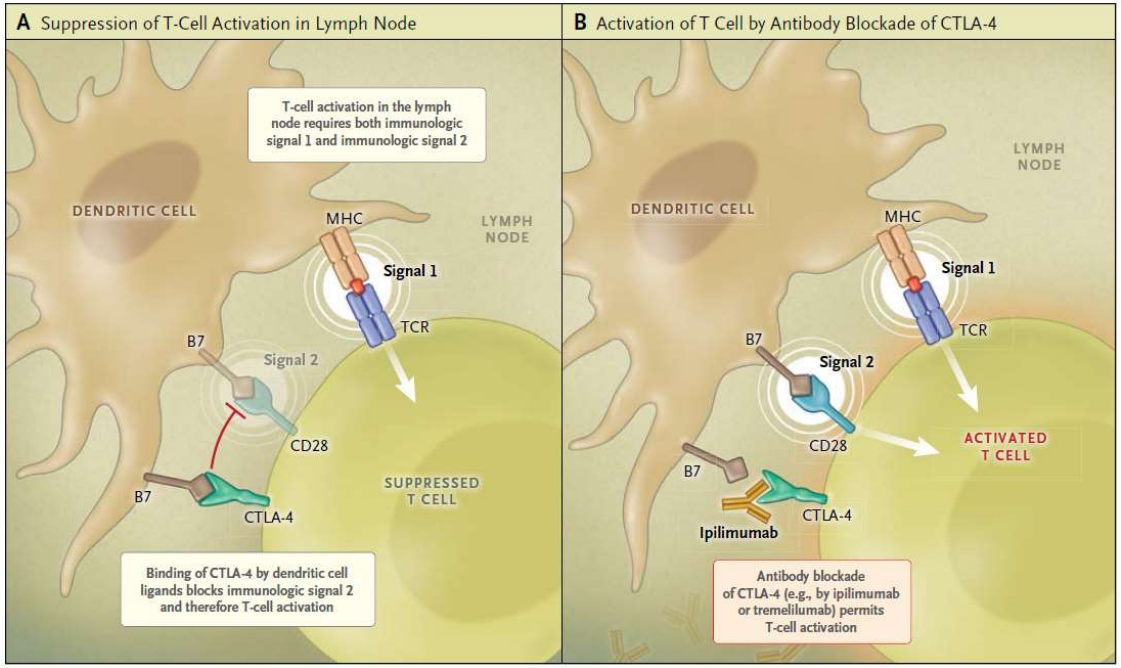
T-cell priming

Herrera FG et al CA Cancer J Clin 2017

- Agonistic antibodies directed against costimulatory molecules on T-cells and/or blocking antibodies against coinhibitory molecules to increase T-cell function
- E.g. CTLA-4 blockade (ipilimumab)



Ribas, NEJM 2015

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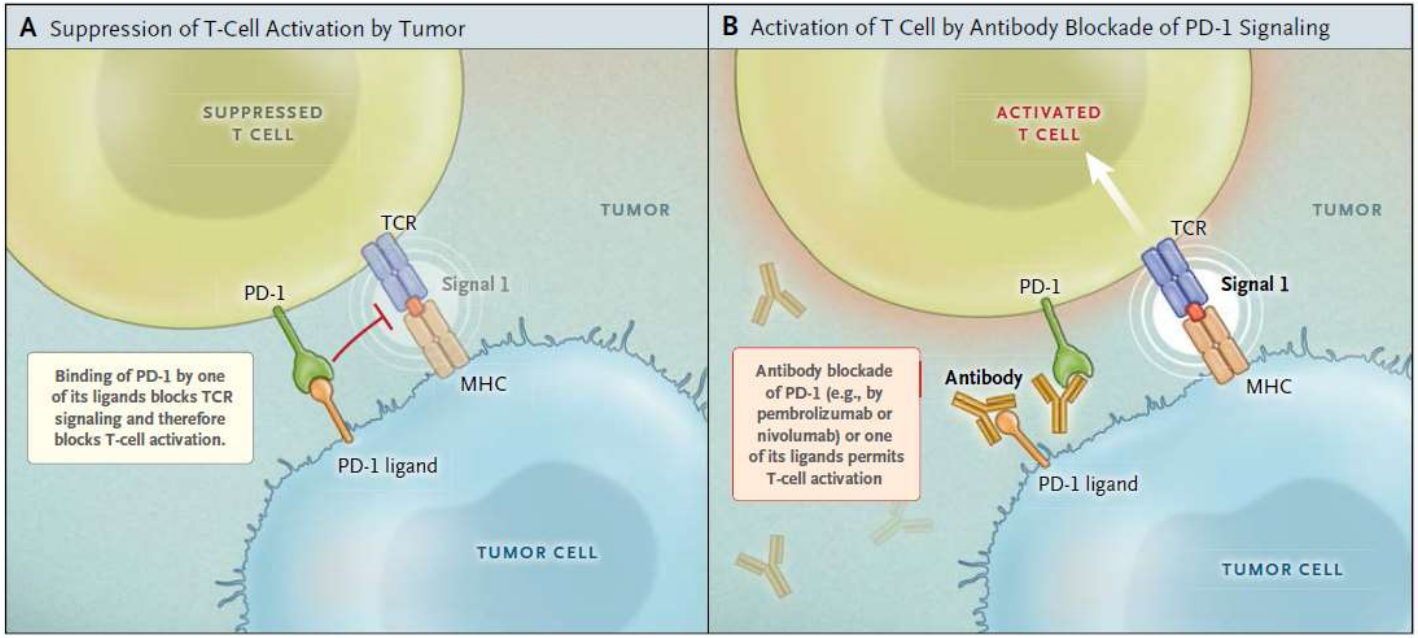
T-cell trafficking, infiltration, killing

Herrera FG et al CA Cancer J Clin 2017

- Antibodies directed against coinhibitory T-cell receptors (TCR) or TGF-blocking drugs
- E.g. PD-1 or PD-L1 antibodies (pembrolizumab, nivolumab)



Ribas, NEJM 2015

Rationale for combination with anti-PD-L1 Ab

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

Radio(chemo)-immunotherapy: 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

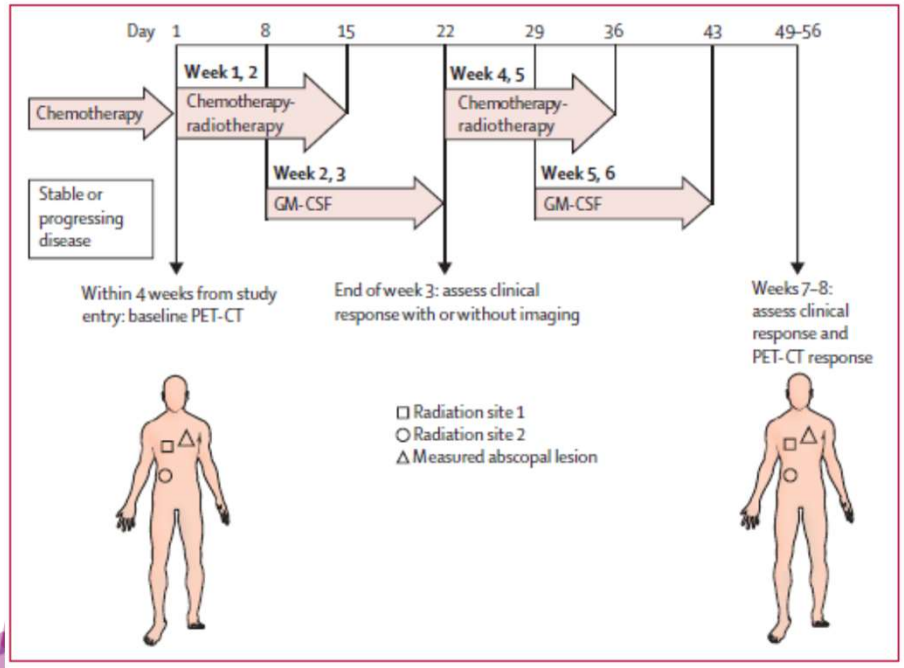
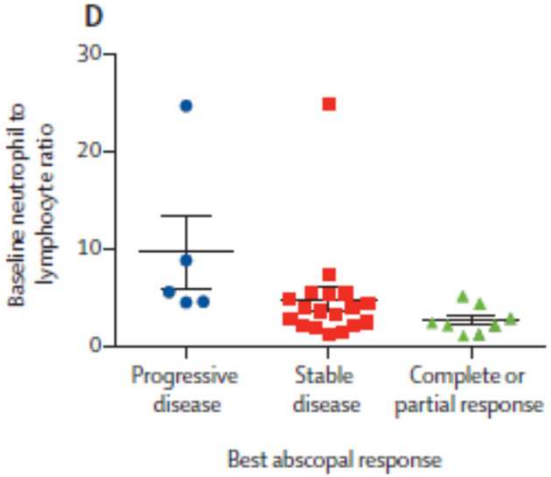


Figure 1: Treatment and assessment schema for induction and determination of abscopal responses



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

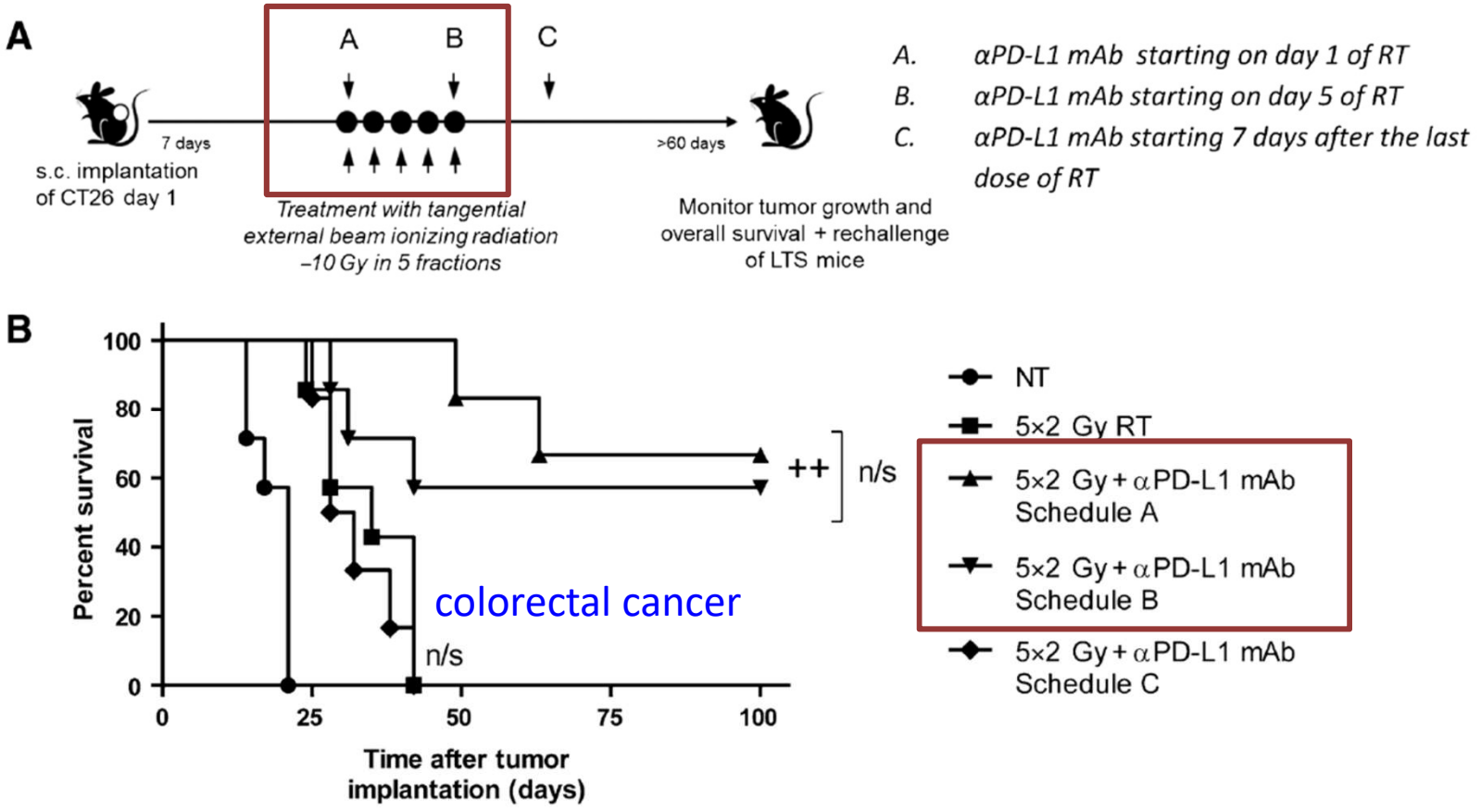
Radioimmunotherapy combinations: challenges

- Define optimal RT dose/fractionation schemes to create maximal interactions with IT
- Identify type, dose and schedule of immunogenic chemotherapy and type and schedule of immunomodulatory drugs for combination with chemo-RT
- Role of particle radiation and radionuclide therapy for their potential immunomodulatory effects

Dose scheduling for RT+IT combinations

Dovedi et al. Cancer Res 2014

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

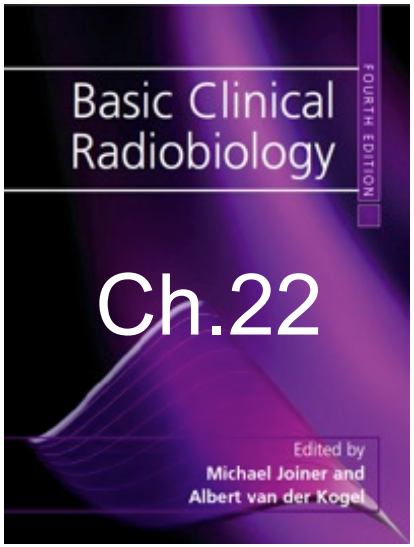


Take home messages

- 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

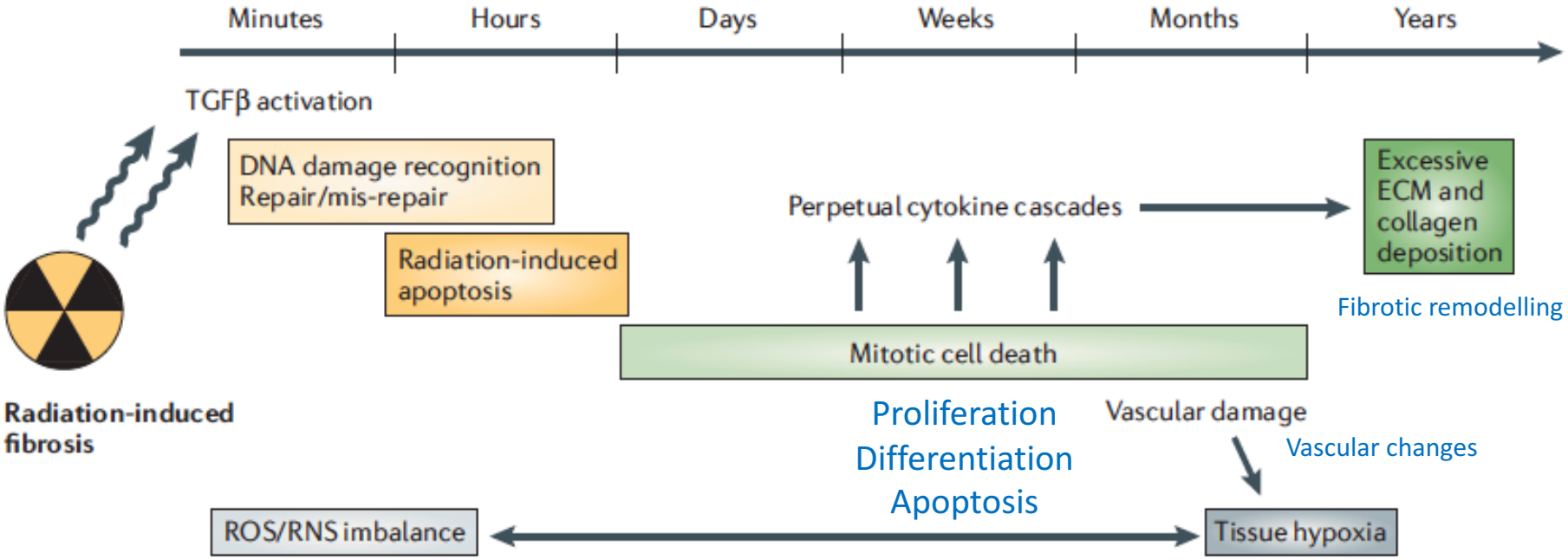


Cancer Research Center Groningen

ESTRO School

umcg

Mechanism of normal tissue damage

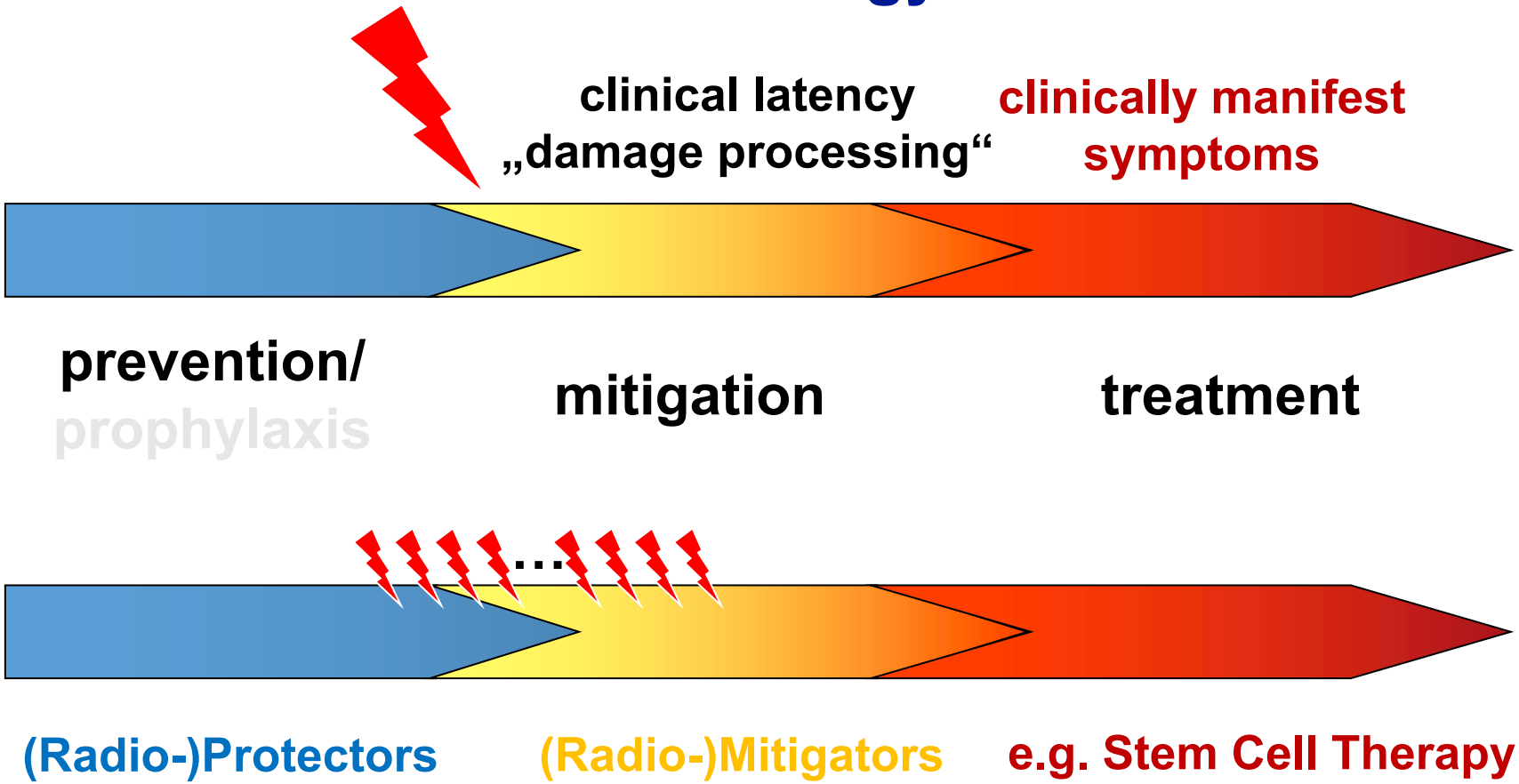


Bentzen Nature Review Cancer 2006

Parenchymal changes

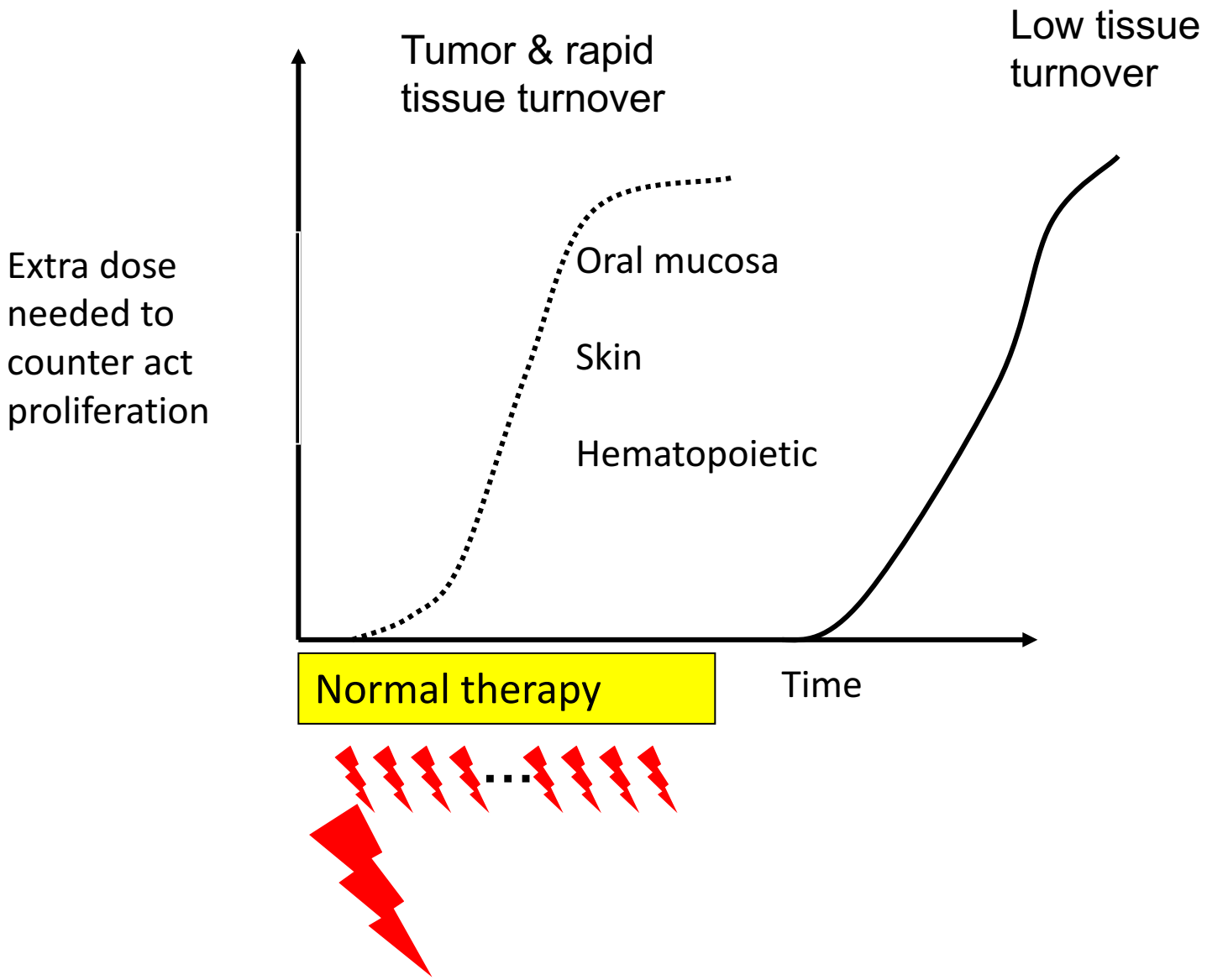
Transcription factors
Signaling chains
Inflammatory response

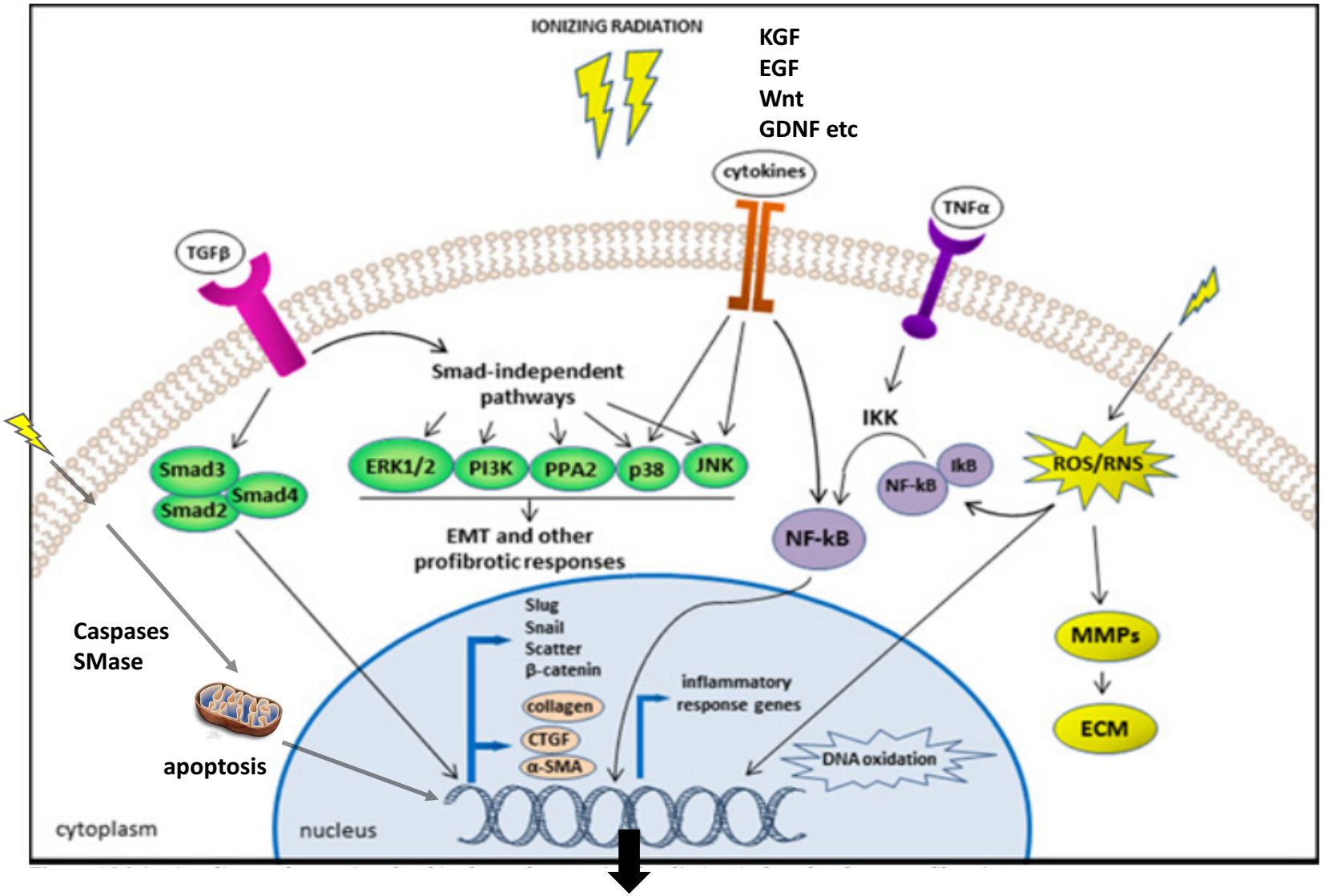
Terminology



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

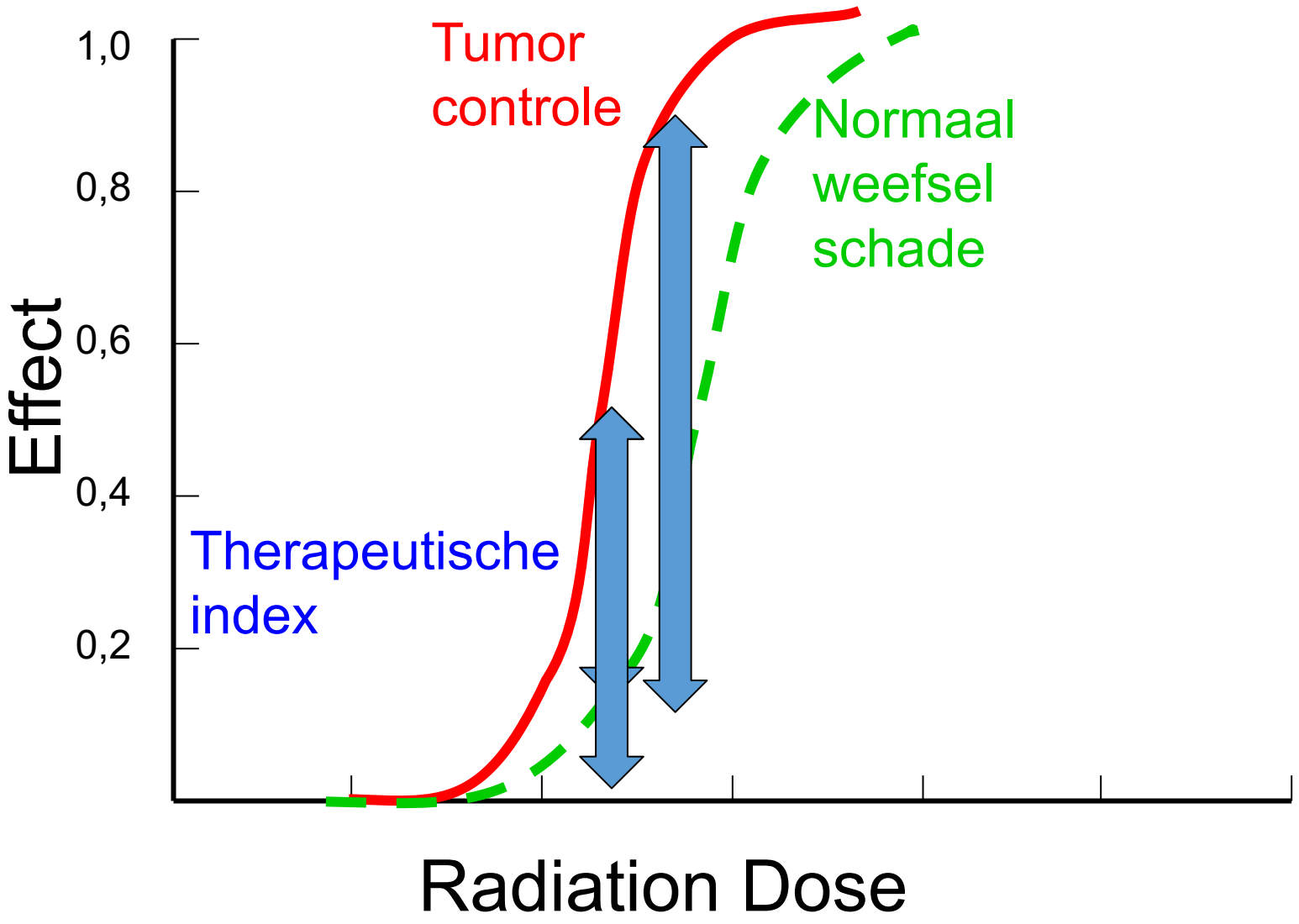
Table 1 Generalized radiation injury mechanisms and agents that target these mechanisms

Mechanism	Agents that prevent/mitigate the radiation injury mechanism	Agents that treat the radiation injury mechanism
Production of free radicals	Antioxidants	Antioxidants
	Amifostine	SOD mimetics
	Curcumin	
Activation of inflammatory pathways	ACE inhibitors/ARBs	Systemic steroids
	Statins	
	Topical steroids	
	Probiotics	
Vascular endothelial dysfunction	Pentoxifylline	Pentoxifylline
	Hyperbaric oxygen	Hyperbaric oxygen
		Bevacizumab
		Anticoagulation
Decreased normal tissue resilience and function	Memantine	Methylphenidate
	Pilocarpine	Pilocarpine
	Growth factors	PDE-5 inhibitors
	Supportive care	Supportive care

Abbreviations: ACE = angiotensin-converting enzyme; ARBs = angiotensin II receptor blockers; PDE-5 = phosphodiesterase-5; SOD = superoxide dismutase.

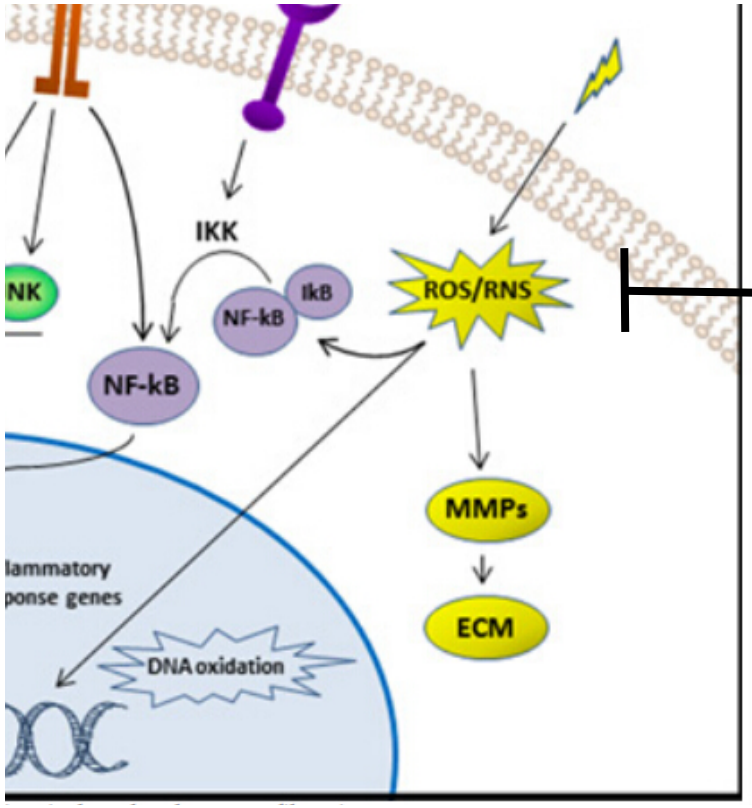
Kalman et al IJROBP 2017

Optimizing radiation oncology



Radical scavenging/detoxification

Targeting Free Radical Production



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

Endogenous: increase MnSOD production in cells

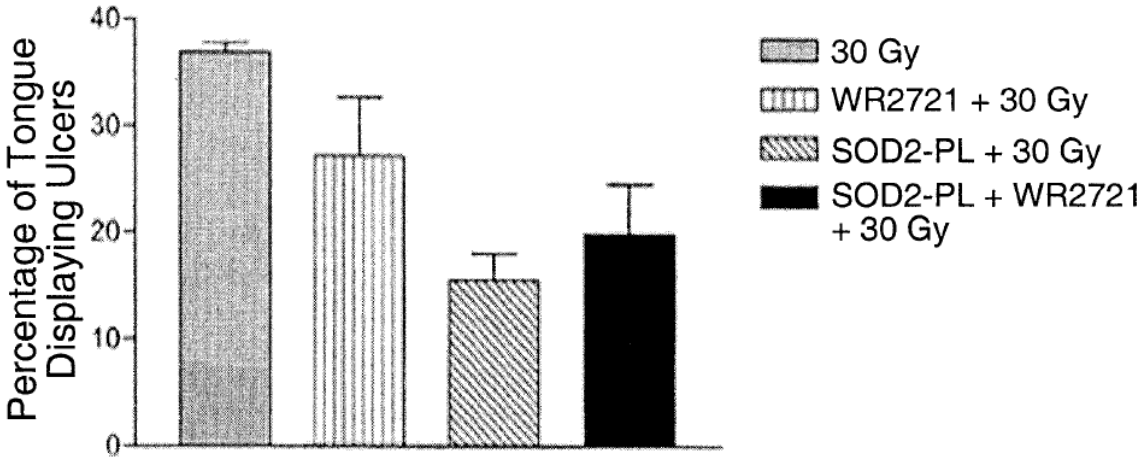
Exogenous: Add radical scavengers

Radical scavenging/detoxification

Targeting Free Radical Production

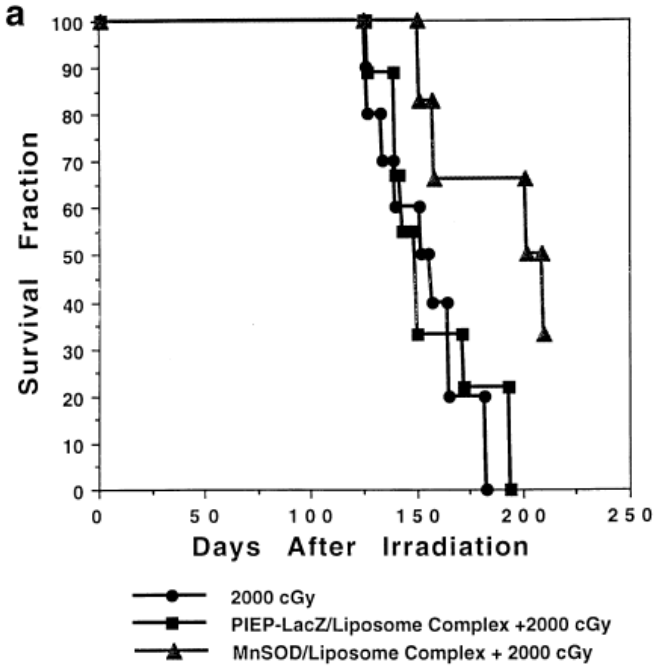
Mn-SOD gene therapy

Mouse mucosa, day 5 post irr.



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

Lung



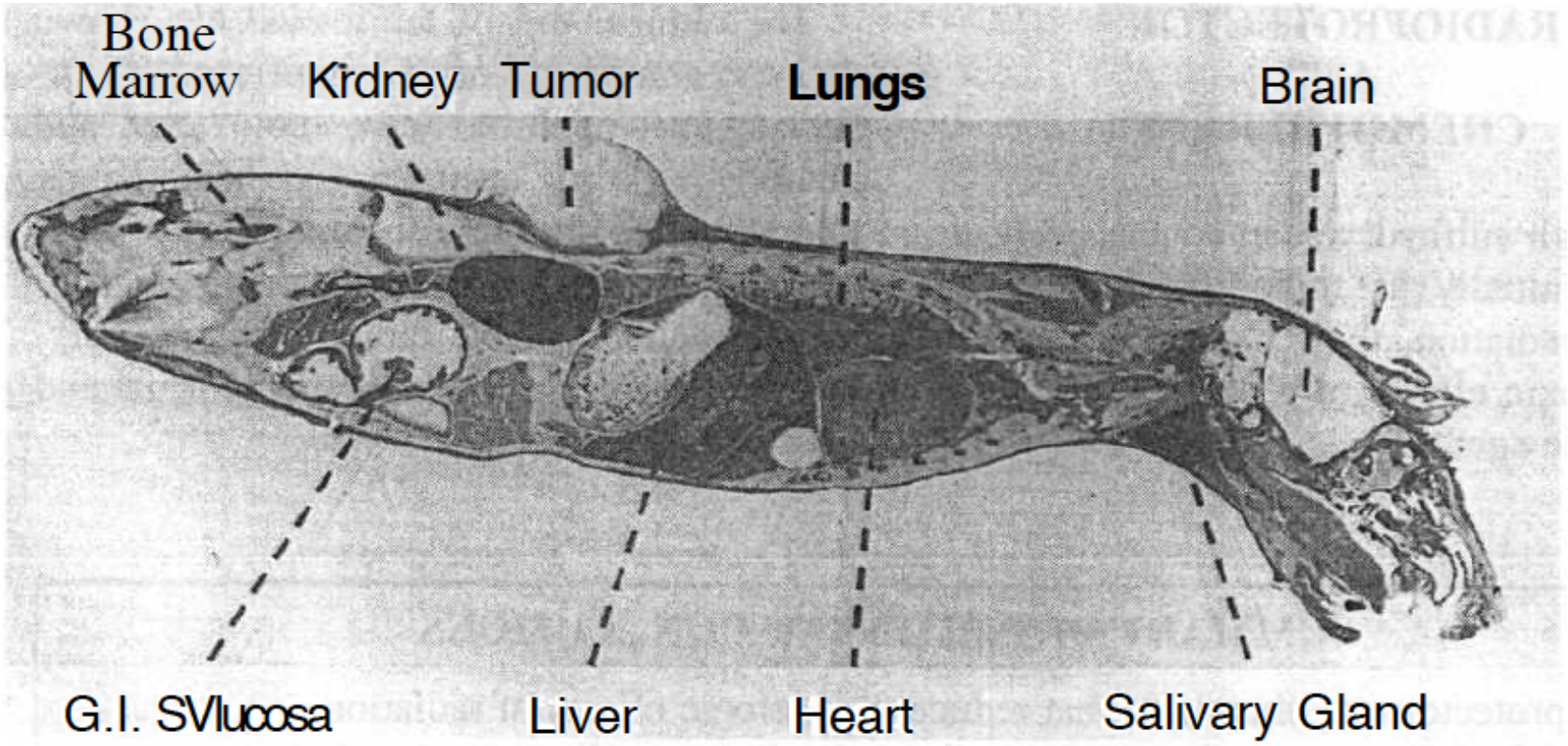
Epperly et al 1998

Radical scavenging/detoxification

Targeting Free Radical Production

Distribution

Amifostine (=WR2721)



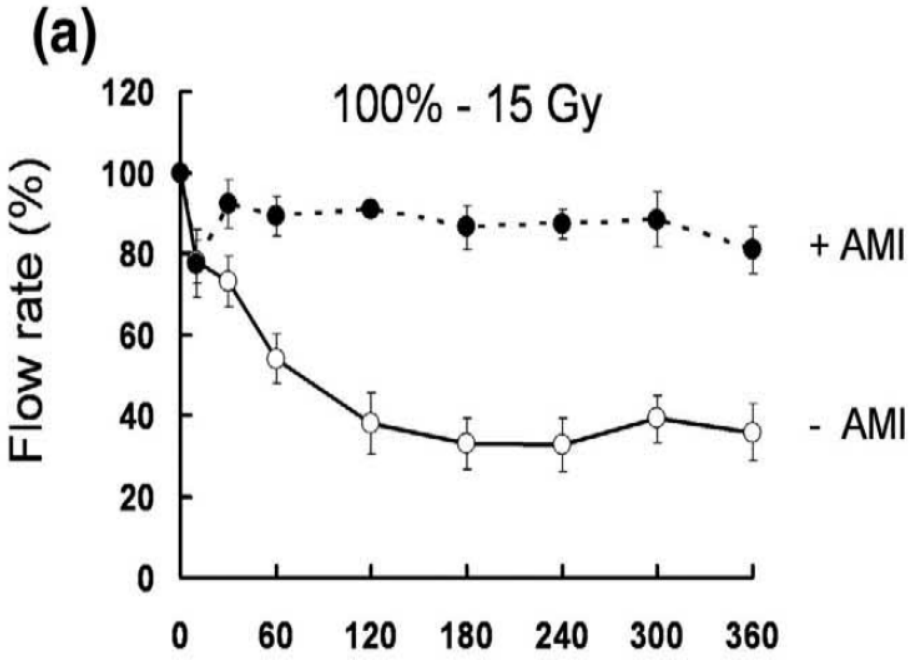
Utley et al. Rad Res 1976

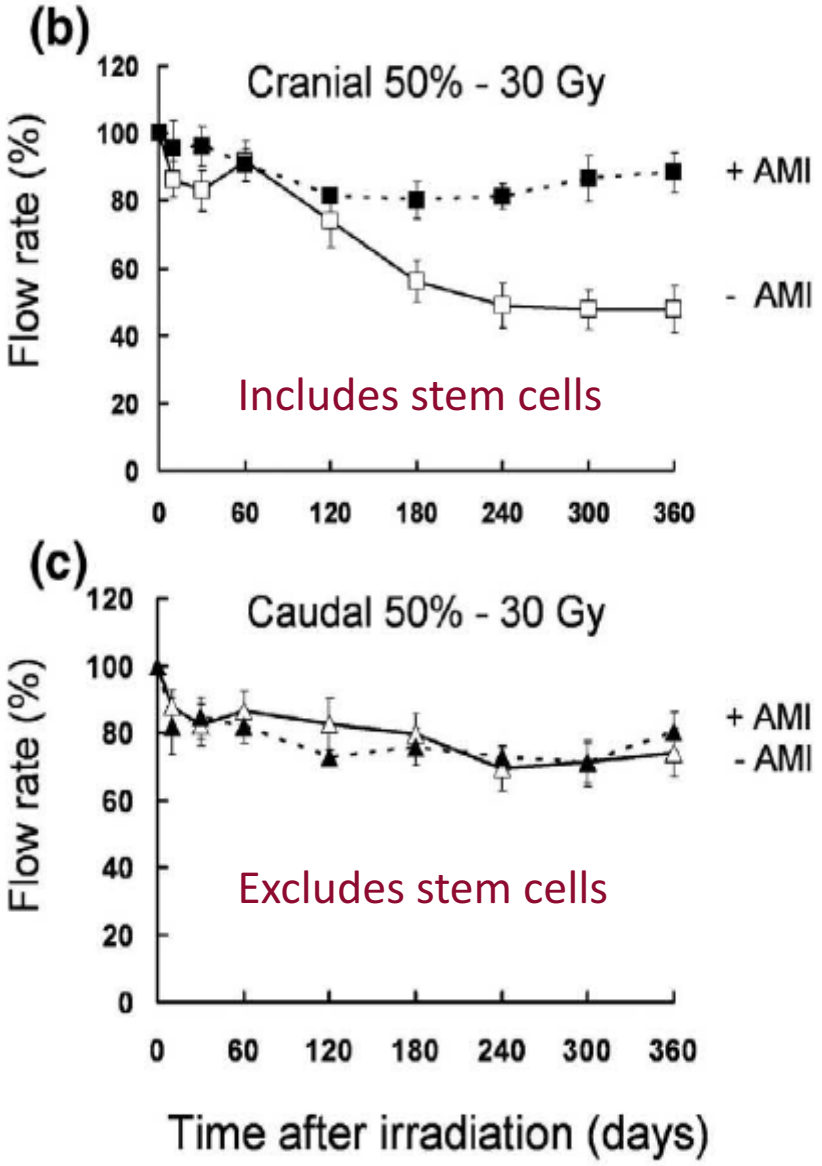
Radical scavenging/detoxification

Targeting Free Radical Production

Salivary glands

Amifostine

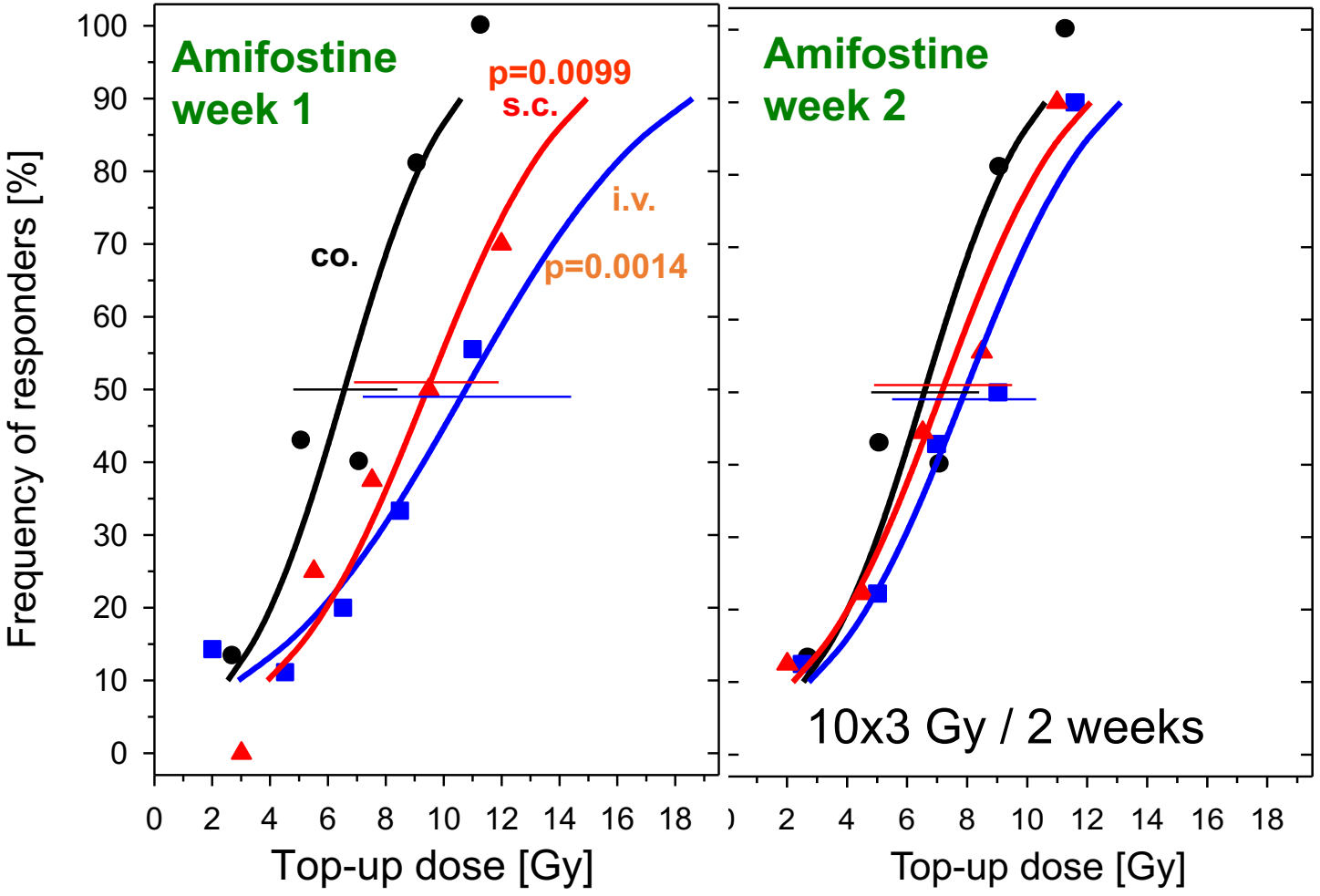




Konings et al 2005

Radical scavenging/detoxification

Targeting Free Radical Production

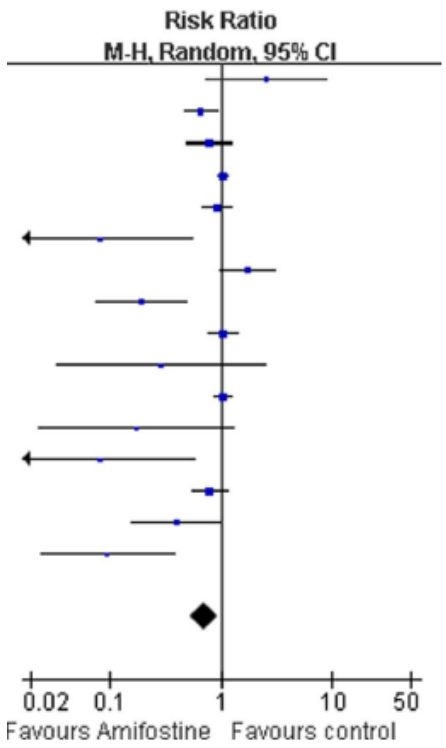


oral mucosa, mouse ulcer induction

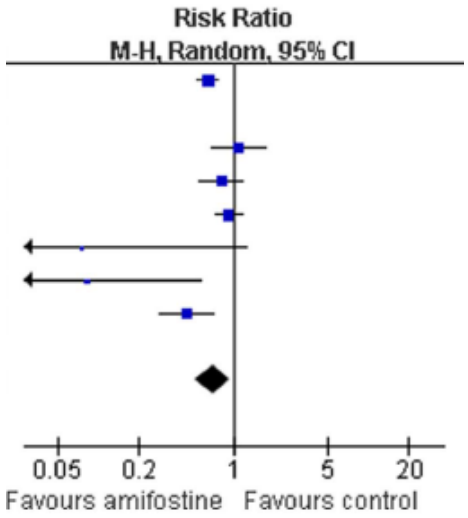
Fleischer and Dörr, Strahlenther. Onkol. 182, 2006, 567-575

Amifostine
Systematic review

Mucositis



Xerostomia

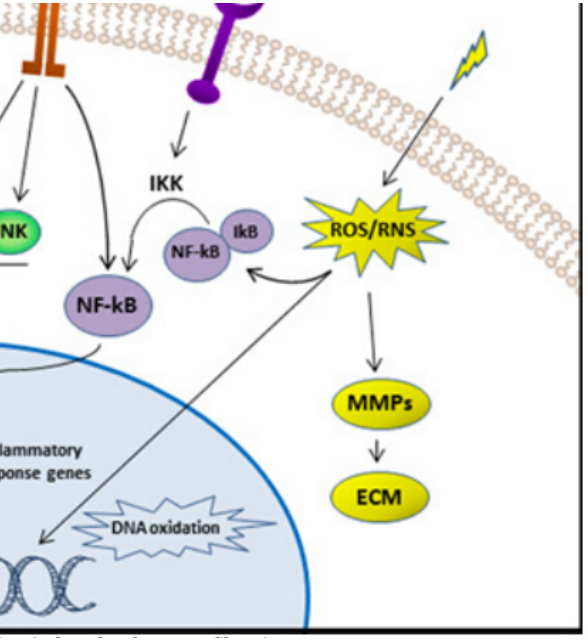


Gu et al Plos One 2014

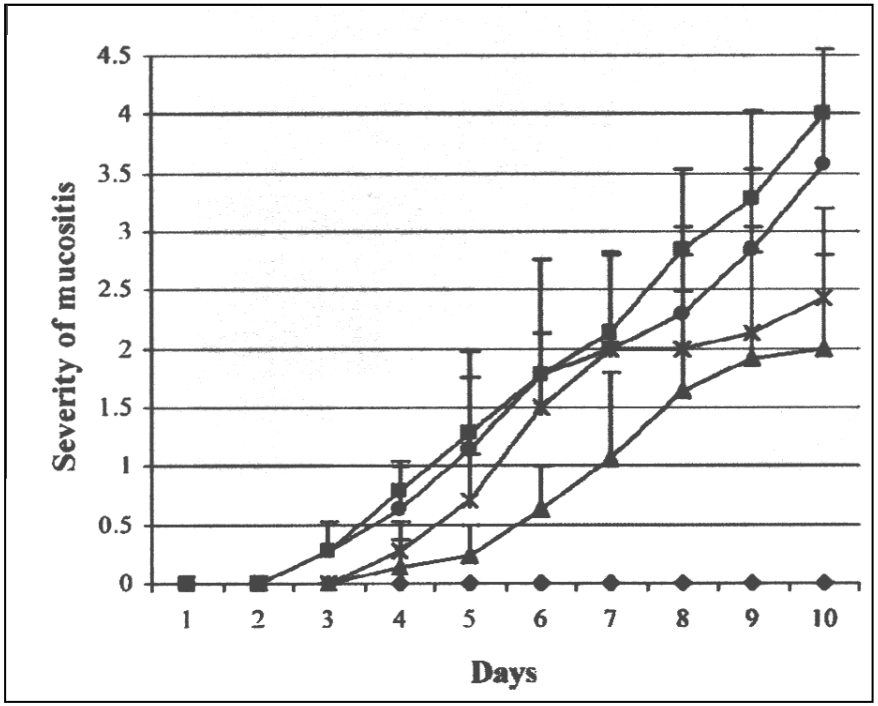
Radical scavenging/detoxification

Targeting Free Radical Production

Vitamin E



oral mucosa, rat



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

15 Gy + L-carnitine

15 Gy + Vit. E

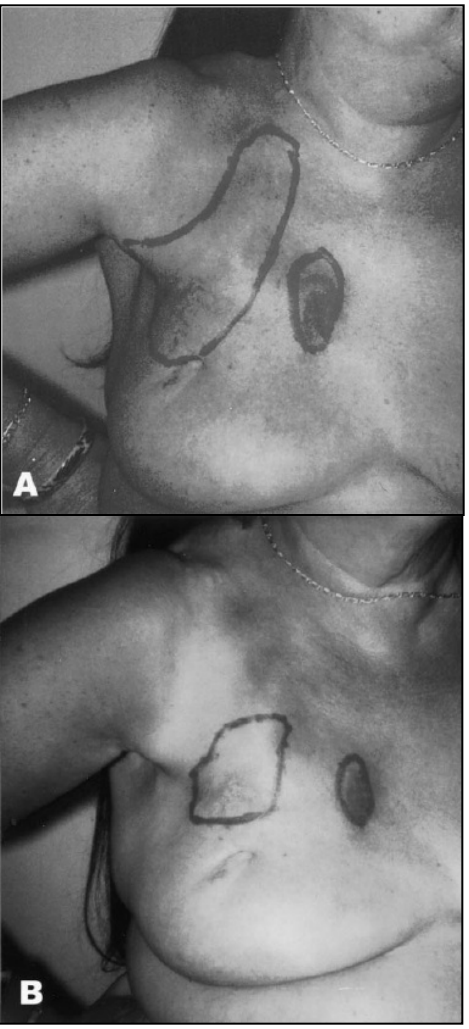
Ücüncü et al., J. Radiat. Res. 47, 2006, 91-102

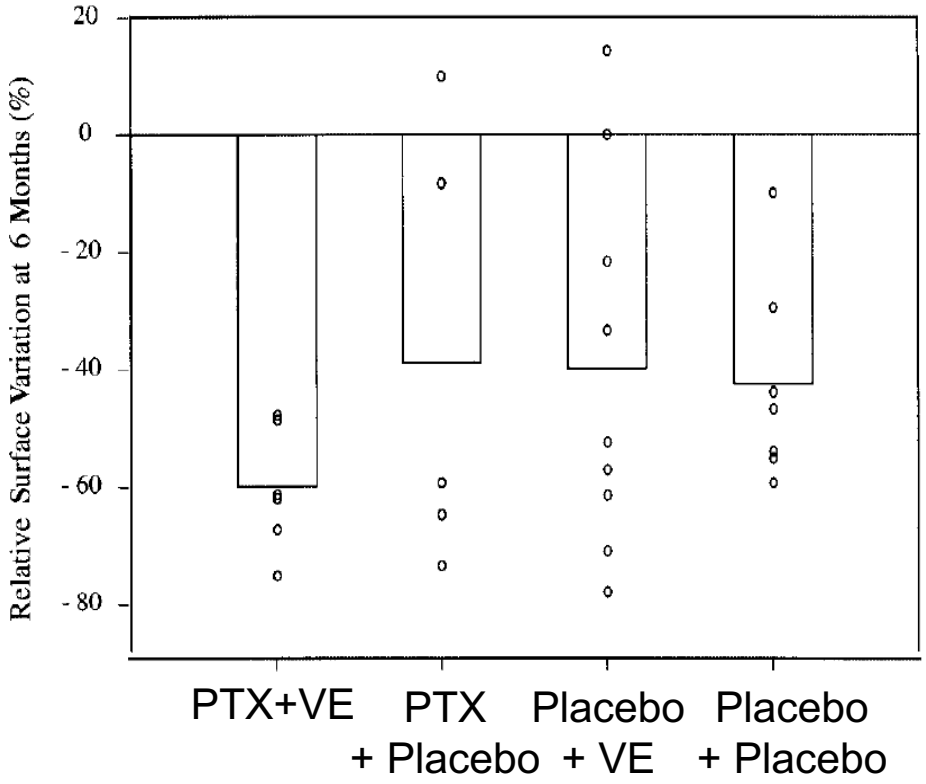
Radical scavenging/detoxification

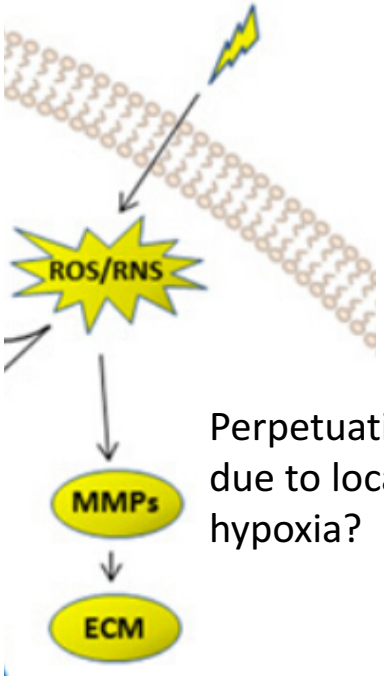
Targeting Free Radical Production

Pentoxifylline, Vitamin E

Skin fibrosis:







Perpetuating due to local hypoxia?

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

Radical scavenging/detoxification

Targeting Free Radical Production

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

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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

Table 2 Representative prevention/mitigation studies targeting free radical production

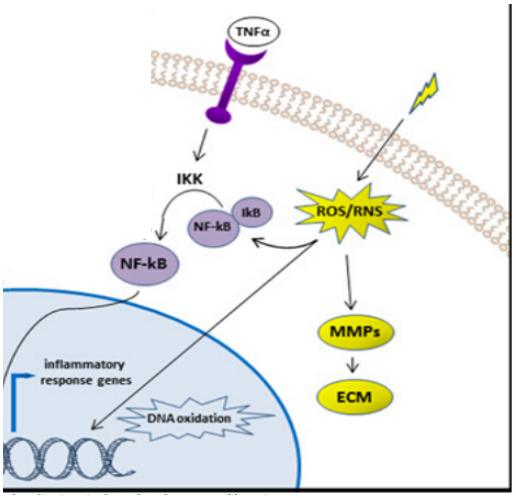
Agent	Study	Patients	Mechanism of action	Radiation therapy details	Intervention	Results (*primary endpoint[s])	Comments
Alpha-tocopherol and β-carotene (7)	Bairati et al, 2005	540 patients with Stage I-II head and neck cancer	Antioxidant	Definitive radiation therapy per treating physician	Alpha-tocopherol (400 IU/d) (vitamin E) and β-carotene (30 mg/d) (discontinued after 154 patients enrolled) during radiation and for 3 y afterwards	*Odds ratio of acute side effects with supplementation 0.72 (95% CI 0.52-1.02) If received both α-tocopherol and β-carotene, odds ratio 0.38 (95% CI 0.20-0.74) Acute grade 3-4 toxicity during radiation therapy 19% vs 25%	Odds of local recurrence higher in supplement arm (hazard ratio 1.37; 95% CI 0.93-2.02) Beta-carotene stopped after another study showed its use was associated with increased lung cancer incidence
Amifostine (8, 9)	RTOG 98-01 (Movsas et al, 2005; Lawrence et al, 2013)	242 patients stage II to IIIB NSCLC	Free radical scavenger	Induction chemotherapy then concurrent chemoradiotherapy 69.6 Gy at 1.2 Gy BID (50.4 Gy to larger volume)	Amifostine 500 mg IV 4 times per week during radiation therapy given before afternoon treatment	Acute: *Grade 3+ esophagitis 30% vs 34% ($P=.9$) Grade 2+ cardiovascular (hypotension) 16% vs 7% ($P=.0001$) Grade 2+ nausea 33% vs 21% ($P=.03$) Grade 2+ vomiting 30% vs 14% ($P=.007$) Chronic: Grade 3+ pneumonitis 8% vs 17% (NS)	During treatment, swallow scores, weight loss, and pain scores favored amifostine arm ($P=.025$, .045, and .015, respectively) No difference in overall survival
Curcumin (10)	Ryan et al, 2013	30 patients with localized breast cancer	Anti-inflammatory Antioxidant	Breast radiation to at least 42 Gy in daily fractions	Curcumin 2 g per os TID during radiation therapy	*Dermatitis at end of treatment: • *Mean grade 2.6 vs 3.4 ($P=.008$) • *Moist desquamation 29% vs 88% ($P=.002$)	No curcumin-related toxicities

Kalman et al
IJROBP 2017

Anti-inflammation/Immunomodulation

Misoprostol (PGE_2-Analogue)

Rectum



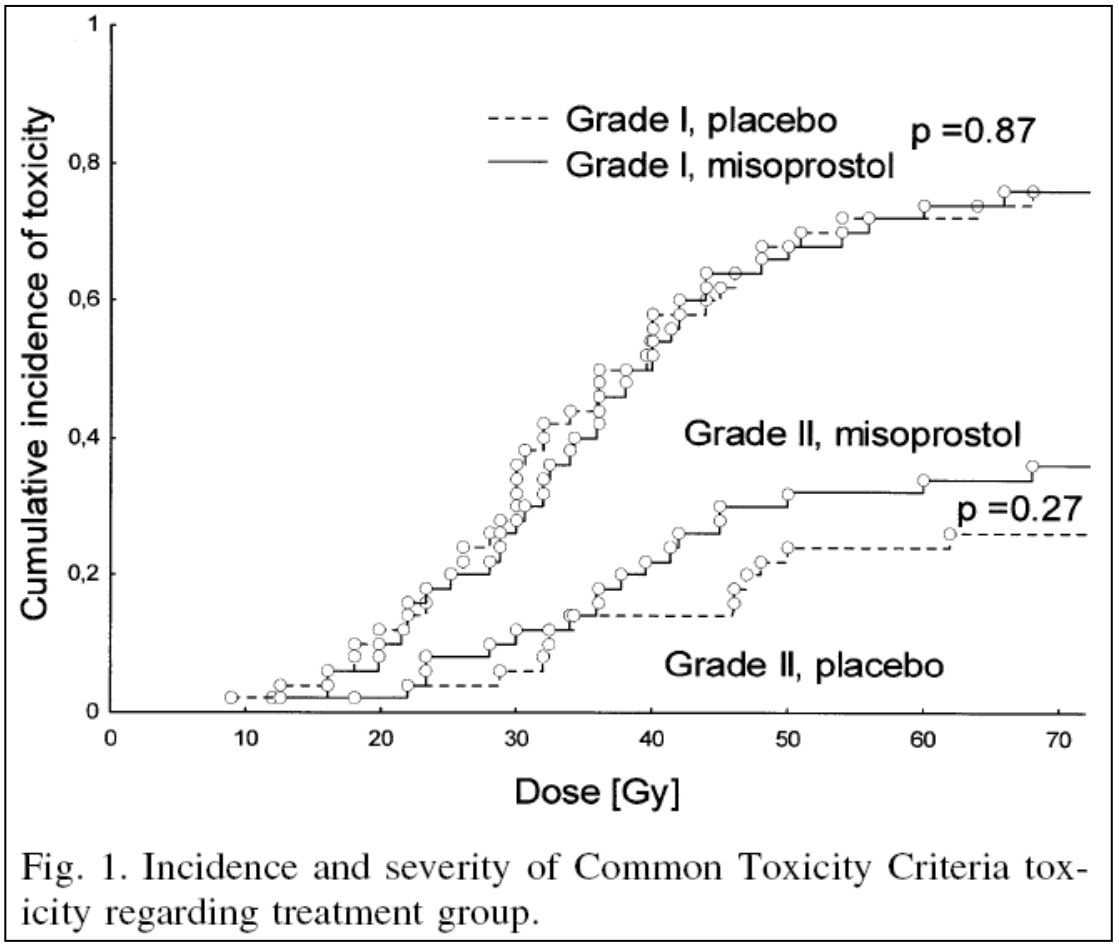


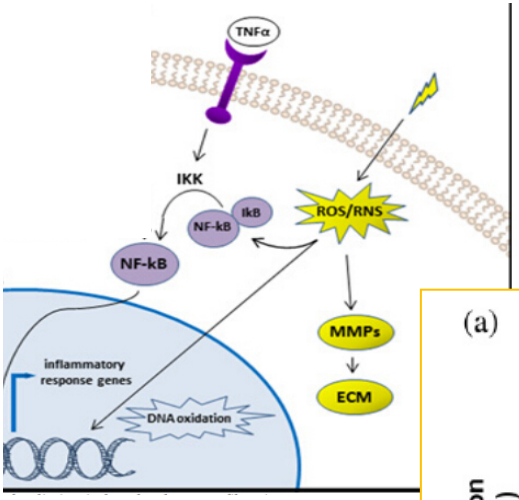
Fig. 1. Incidence and severity of Common Toxicity Criteria toxicity regarding treatment group.

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

Intervention with signaling

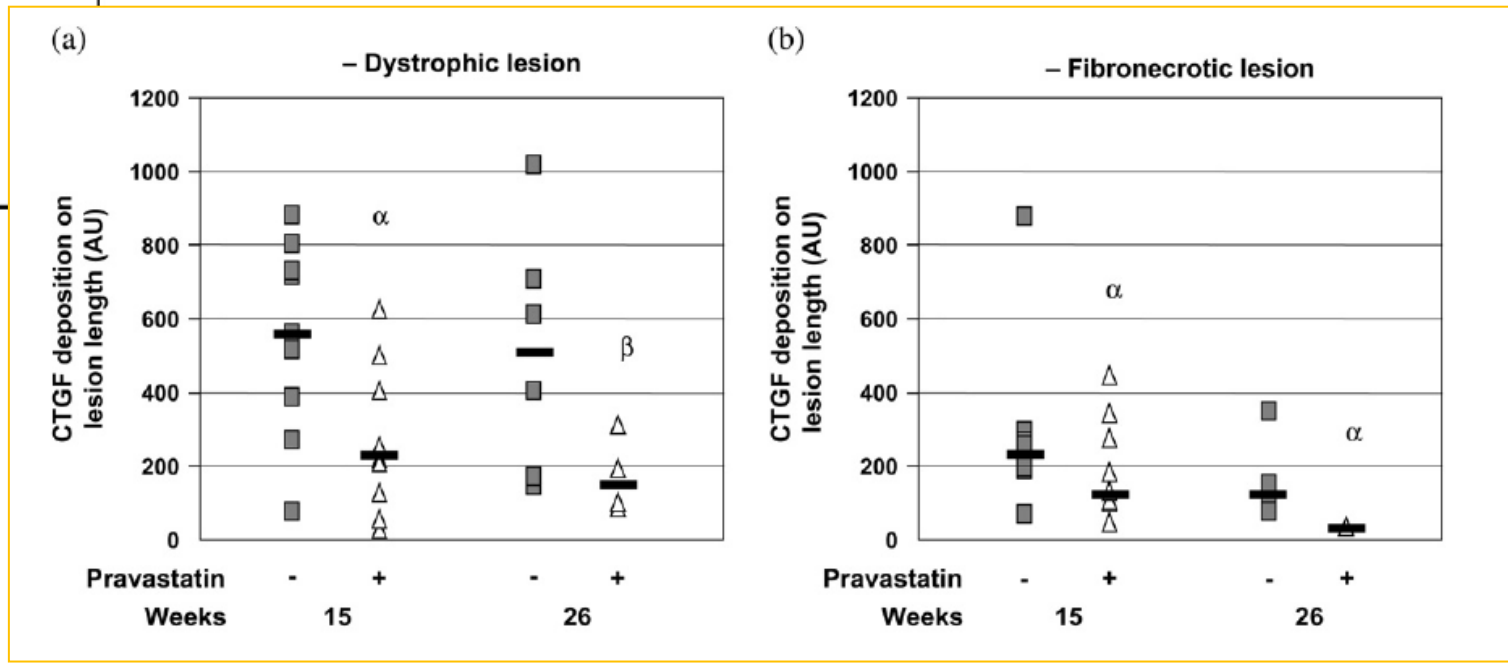
Targeting Inflammatory Pathways

Statins (or **HMG-CoA reductase inhibitors**)



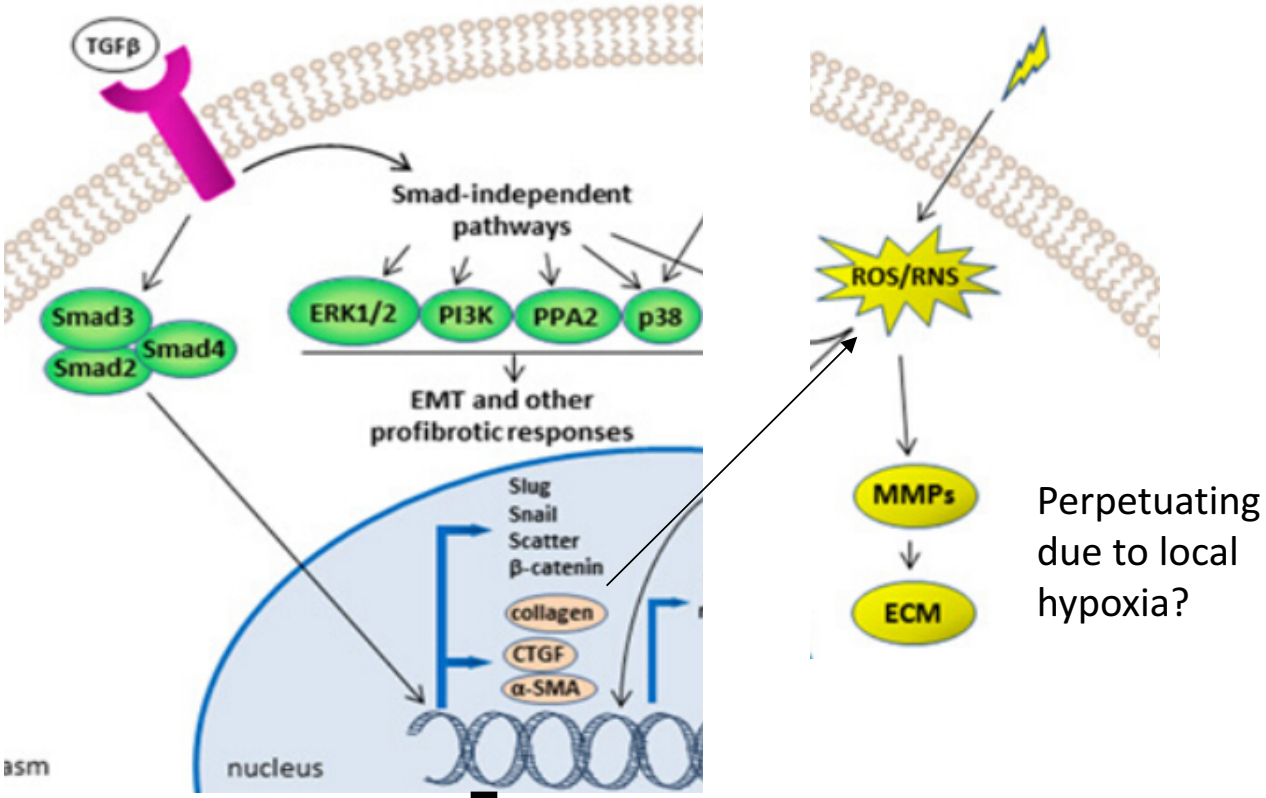
Pravastatin

Rat, intestinal fibrosis 19 Gy



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

Intervention with signaling



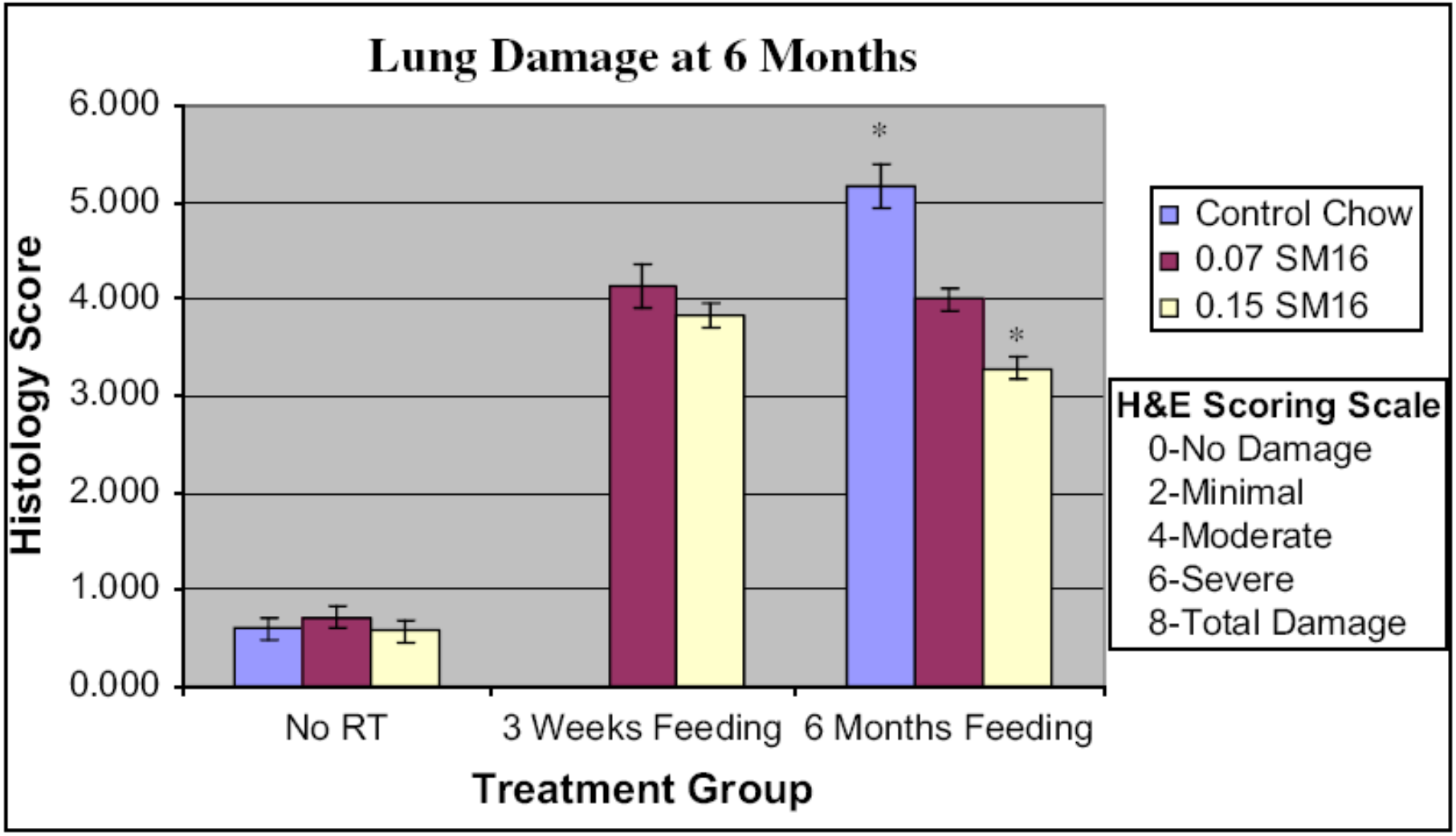
Perpetuating due to local hypoxia?

Proliferation
Differentiation
Senescence
Apoptosis
Inflammation

Adapted from Mariangela et al., 2015

Intervention with signaling

Anti-TGFß

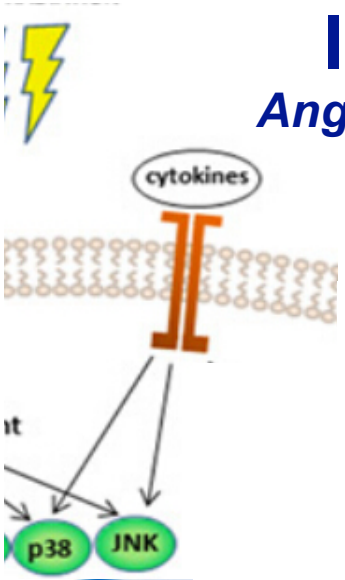


Anscher et al., IJROBP 71, 2008, 829-837

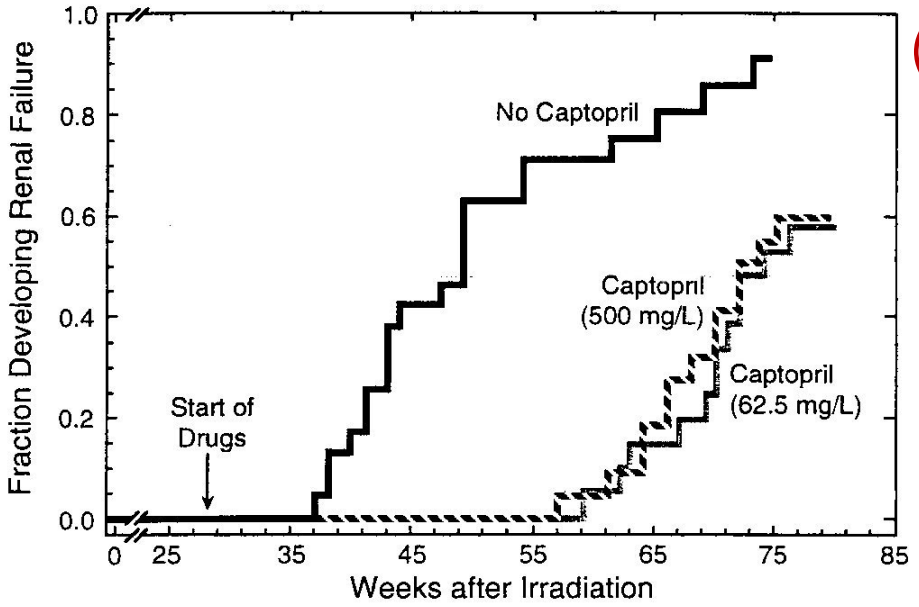
Intervention with signaling

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

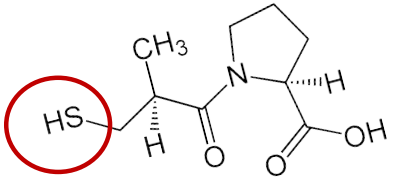
Rat kidney TBI + BMT

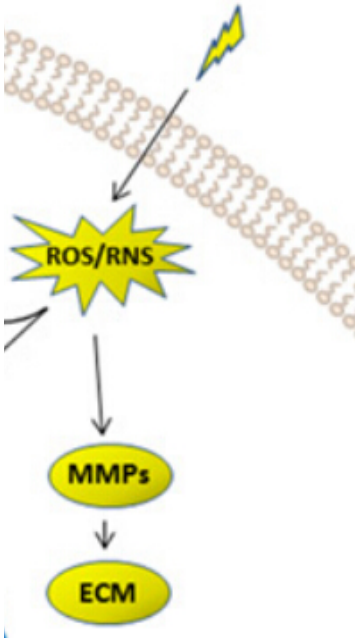


Proliferation
Differentiation
Senescence
Apoptosis
Inflammation



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





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

Table 3 Representative prevention/mitigation studies targeting inflammatory pathways

Agent	Study	Patients	Mechanism of action	Radiation therapy details
Captopril (88, 89)	Cohen et al, 2008 and 2012	55 patients undergoing stem cell transplant	↓TGF-β levels Free radical scavenger	Total body irradiation 14 Gy in 9 fractions over 3 d with at least 4 h between fractions Shielding to limit kidney dose to 9.8 Gy and lung dose to 5-7 Gy
Statins (90, 91)	Anscher et al, 2016	53 patients with prostate cancer with portion of rectum receiving >60 Gy	↓Inflammatory cytokines and pathways ↓Endothelial dysfunction and fibrosis	78-79 Gy to the prostate in 1.8- to 2-Gy fractions, or 45-46 Gy plus a brachytherapy boost, or brachytherapy monotherapy
Steroid cream (92)	Ulff et al, 2013	102 patients with breast cancer	Numerous anti-inflammatory effects	50 Gy in 2-Gy fractions to breast ± lymph nodes after breast conservation surgery or mastectomy ± lymph node dissection
Probiotic VSL#3 (lactobacilli preparation) (93)	Delia et al, 2002	190 patients with colorectal or cervical cancer	↓Inflammatory pathways Protects intestinal barrier	Postoperative radiation therapy per treating physician

Intervention	Results (*primary endpoint[s])	Comments
Captopril 6.25 mg BID (escalated to 25 mg TID if tolerated) for total of 1 y starting after neutrophil engraftment	1 y: *Serum creatinine 0.95 vs 1.10 mg/dL ($P=.2$) *Glomerular filtration rate 86 vs 77 mL/min ($P=.07$) 4 y: Chronic renal failure 11% vs 17% ($P>.2$) Pulmonary mortality 11% vs 26% ($P=.15$) 8-y survival 37% vs 22% ($P=.26$)	Average time on drug was 1.8 mo At 4 y, survival in the captopril group higher but not statistically significant ($P>.2$)
Lovastatin (20-80 mg/d) starting day 1 of radiation, for 12 mo	*Physician-reported grade 2+ rectal toxicity during first 2 y showed no difference relative to historical series Erectile function and orgasmic function declined immediately after treatment but was preserved at later time points out to 2 y	Late grade 2 rectal injury in 38% of patients
Betametasone-17-valerate cream vs 2 emollient creams, given 7 days per week for 5 wk of radiation starting first week of radiation	*Acute dermatitis better with steroid vs emollient creams: • *4 wk: $P=.003$ • *5 wk: $P=.01$ *Patient-rated itch, burn, irritation improved with steroid ($P=.048$)	Patients at greatest risk benefited more, including those postmastectomy, with lymph node irradiation, and with fair skin
VSL#3 PO TID during radiation therapy	*Any diarrhea 38% vs 55% ($P=.001$) *Grade 3-4 diarrhea 7% vs 29% ($P=.001$) *Grade 1-2 diarrhea 30% vs 21% (NS) *Mean daily BMs 5 vs 12 ($P<.05$)	No patients reported toxicity from VSL#3

Kalman et al
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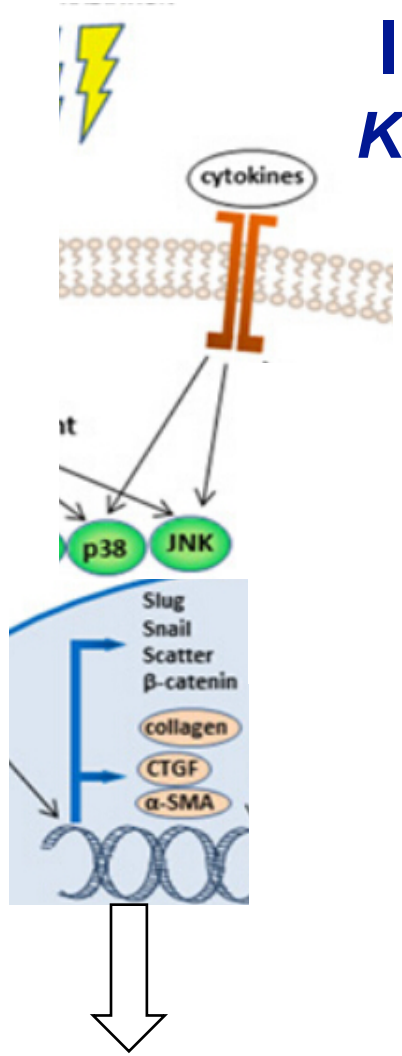
Table 4 Representative prevention/mitigation studies targeting vascular endothelial dysfunction

Agent	Study	Patients	Mechanism of action	Radiation therapy details	Intervention	Results (*primary endpoint[s])	Comments
Pentoxifylline + vitamin E (140)	Jacobson et al, 2012	53 patients with localized breast cancer	↑Microvascular blood flow Anti-inflammatory	46.8-50.4 Gy in 1.8-Gy fractions to breast/chest wall followed by a 10-Gy boost	Pentoxifylline (400 mg per os TID) and vitamin E (400 IU per os daily for 6 mo) after completion of radiation therapy	*Median difference in tissue compliance between treated and untreated breast at 18 mo: 1.0 mm vs 2.4 mm ($P=.0478$) No difference physician-reported late toxicity	Measurements were obtained using tissue compliance meter at mirror sites on treated and untreated breast
Hyperbaric oxygen (141)	Teguh et al, 2009	19 patients with oropharyngeal or nasopharyngeal cancer	↑Oxygenation of hypoxic tissue Reduction of edema Anti-inflammatory	Head and neck radiation therapy to 46-70 Gy with possible brachytherapy or Cyberknife boost	Hyperbaric oxygen 2.5 absolute atmospheres 90 min daily for 30 treatments over 6 wk starting within 2 d of completing radiation	*Improved quality of life scores at 3-18 mo: • *Swallowing ($P=.011$) • *Dry mouth ($P=.009$) • *Sticky saliva ($P=.01$) • *Eating in public ($P=.027$) • *Mouth pain visual analogue scale ($P<.0001$)	Hyperbaric oxygen is mostly used to treat radiation-induced injuries, not mitigate potential toxicity

Kalman et al IJROBP 2017

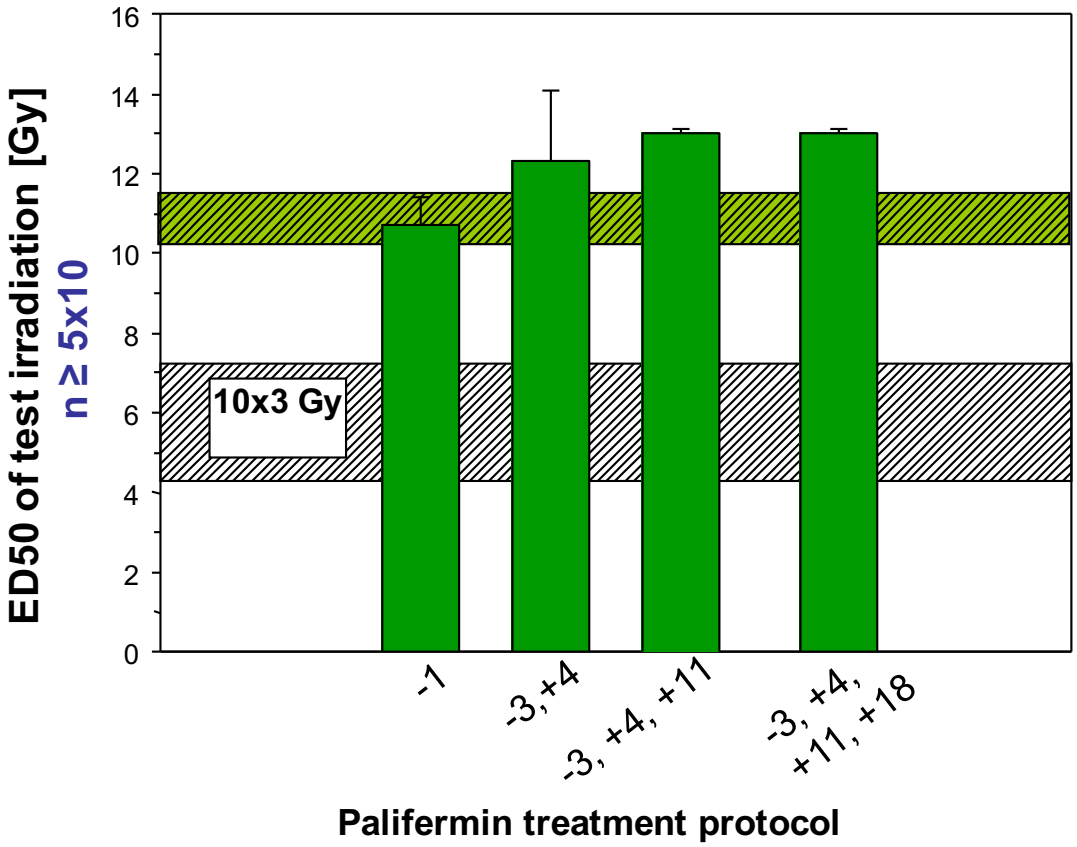
Intervention with signaling

Keratinocyte Growth Factor (Palifermin)



Proliferation
Differentiation
Senescence
Apoptosis
Inflammation

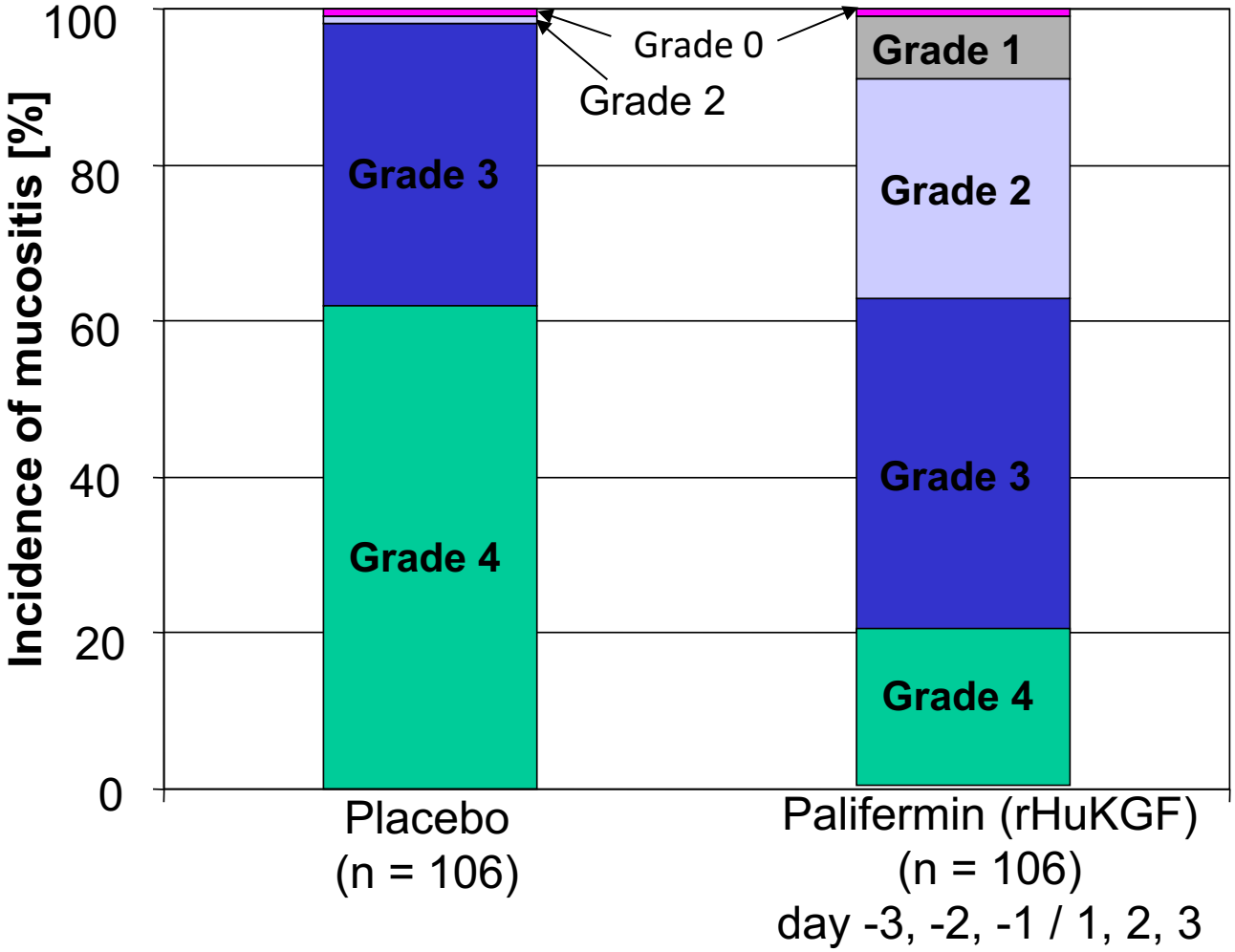
oral mucosa, mouse ulcer induction



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)

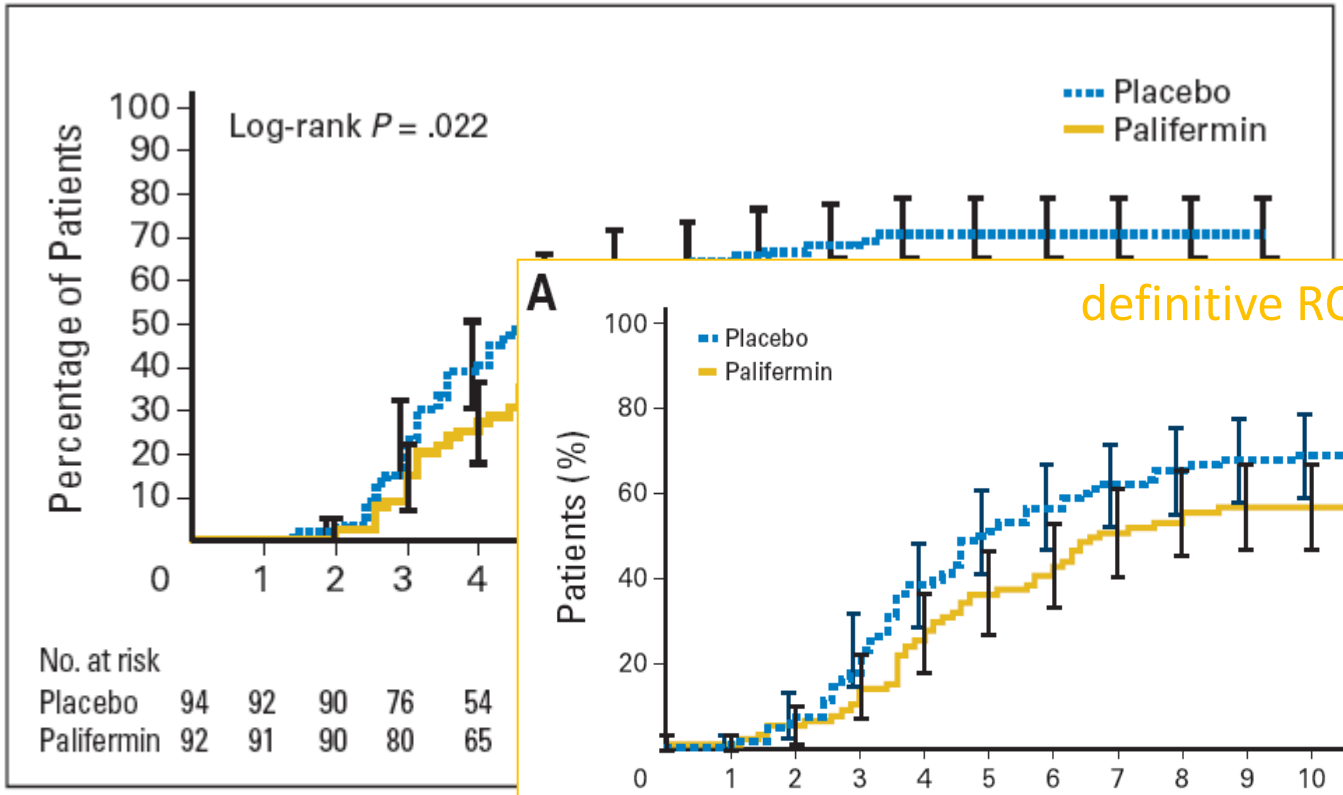
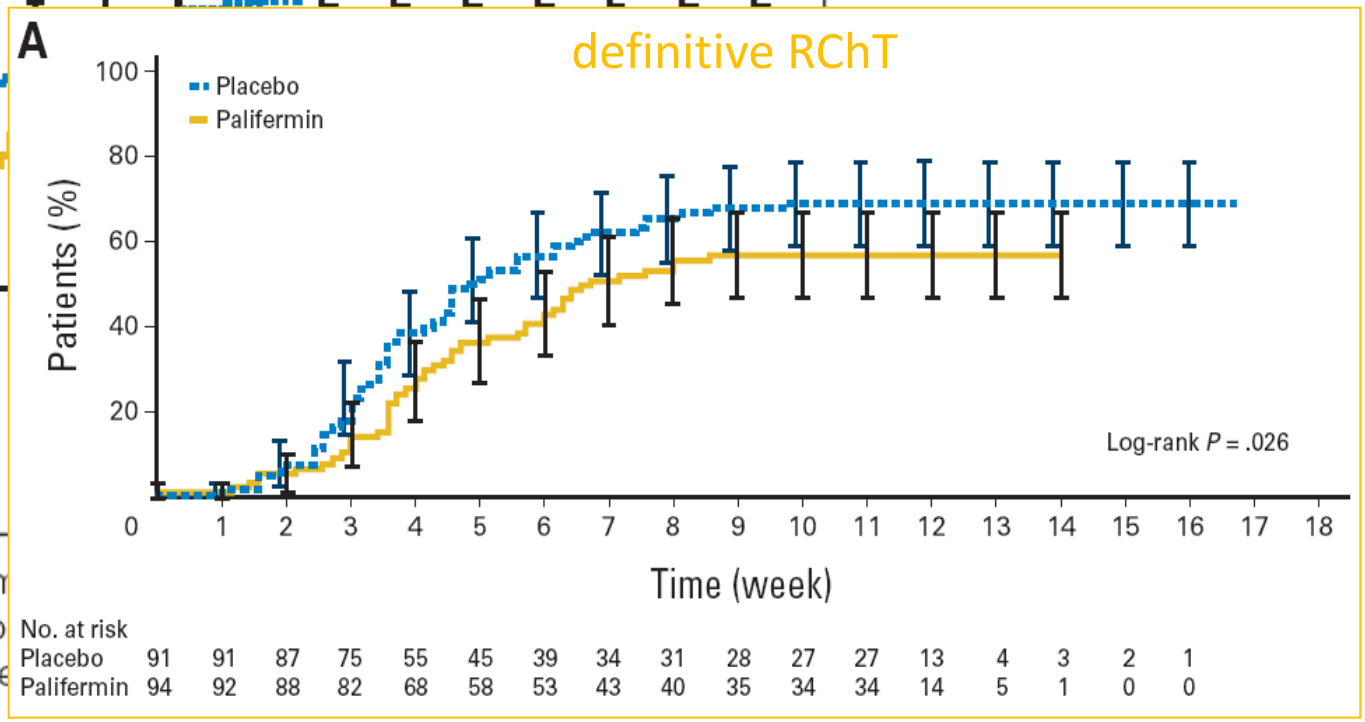


Fig 3. Kaplan-Meier plot of tim
3 to 4) during combined posto
therapy for locally advanced he



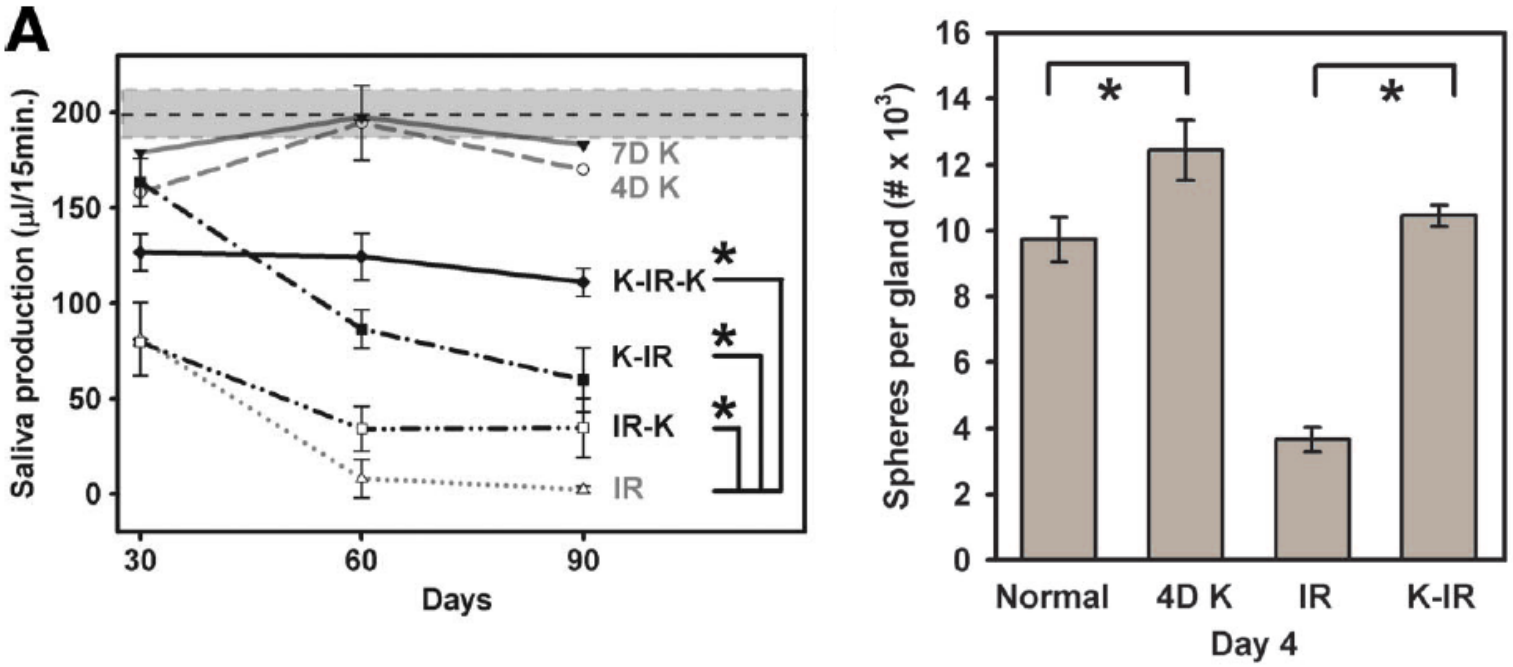
Henke et al., J Clin Oncol 2011,29:2815-2820.

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

Intervention with signaling

Keratinocyte Growth Factor (Palifermin)

Salivary gland

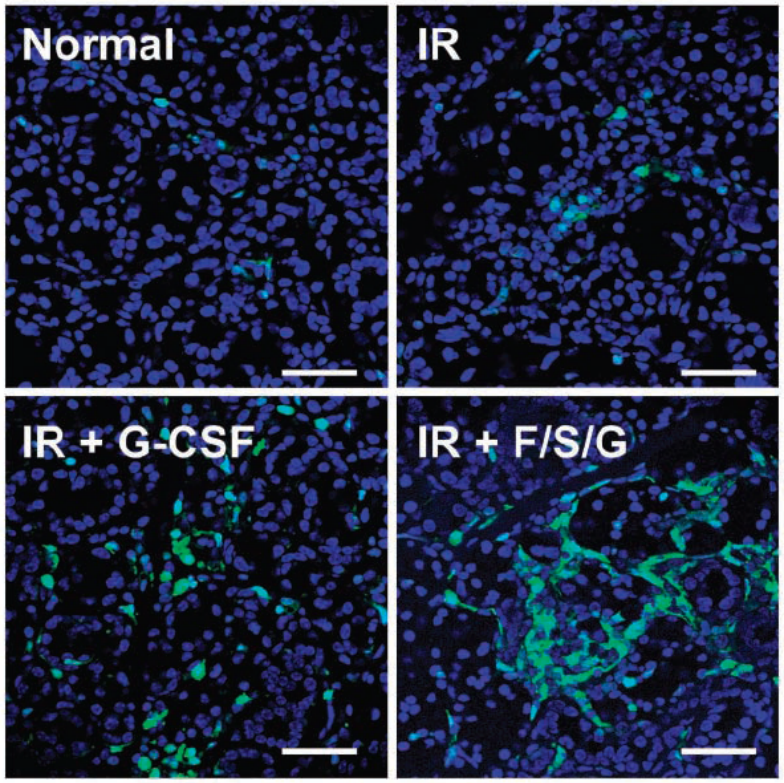


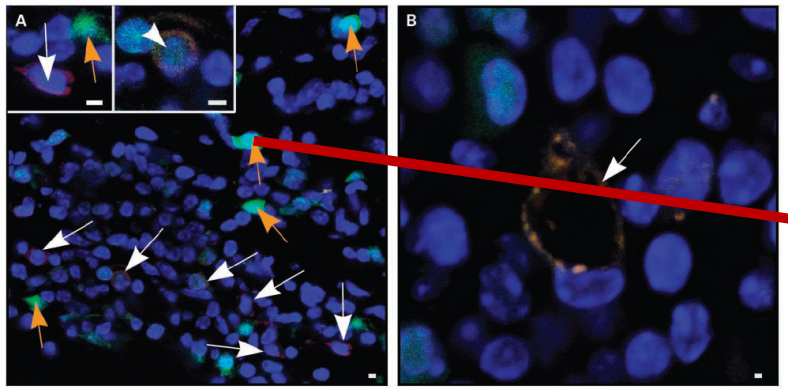
Lombaert et al Stem Cells (2008)

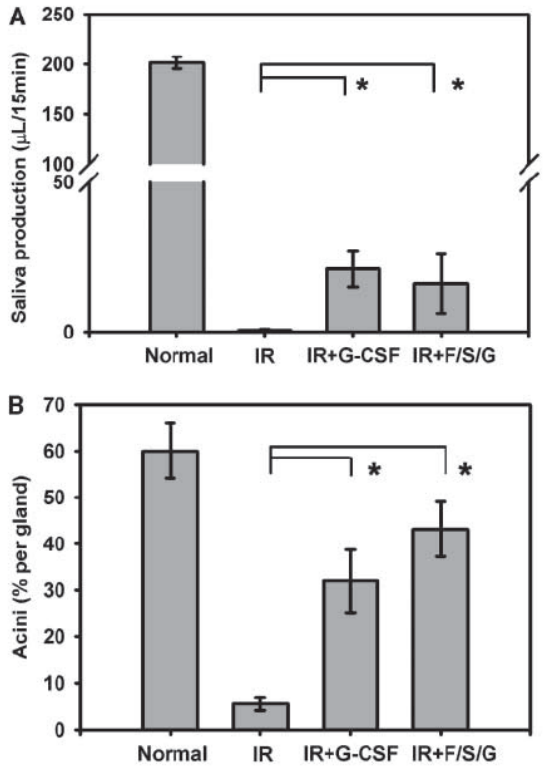
Stem Cell Expansion!!!!

Intervention with signaling / stem cell therapy

Bone marrow stem cell mobilisation (G-CSF)





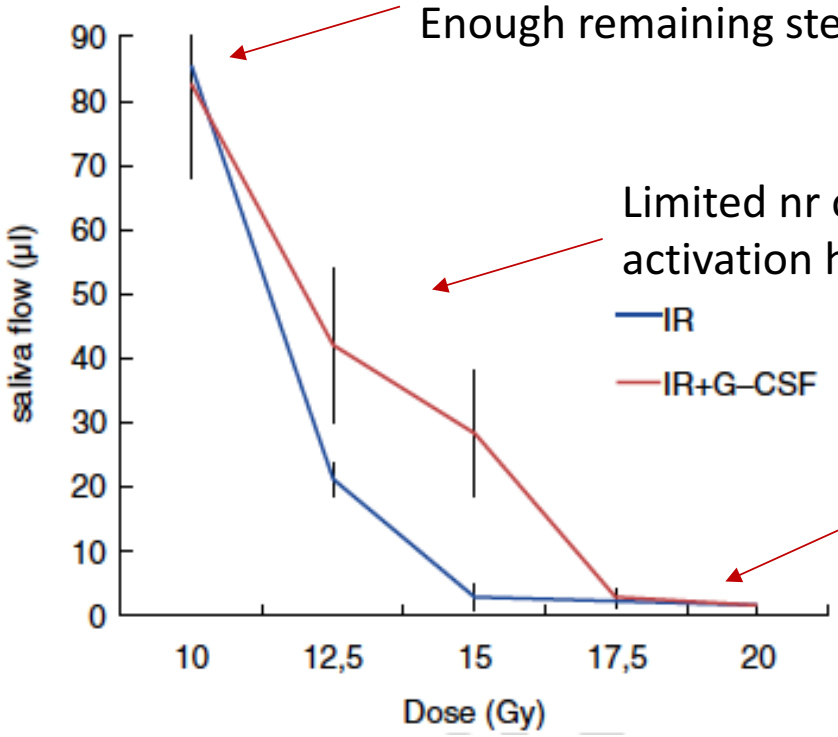


Lombaert et al Clin. Can. Res. 2008

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

Table 5 Representative prevention/mitigation studies targeting tissue resilience and function

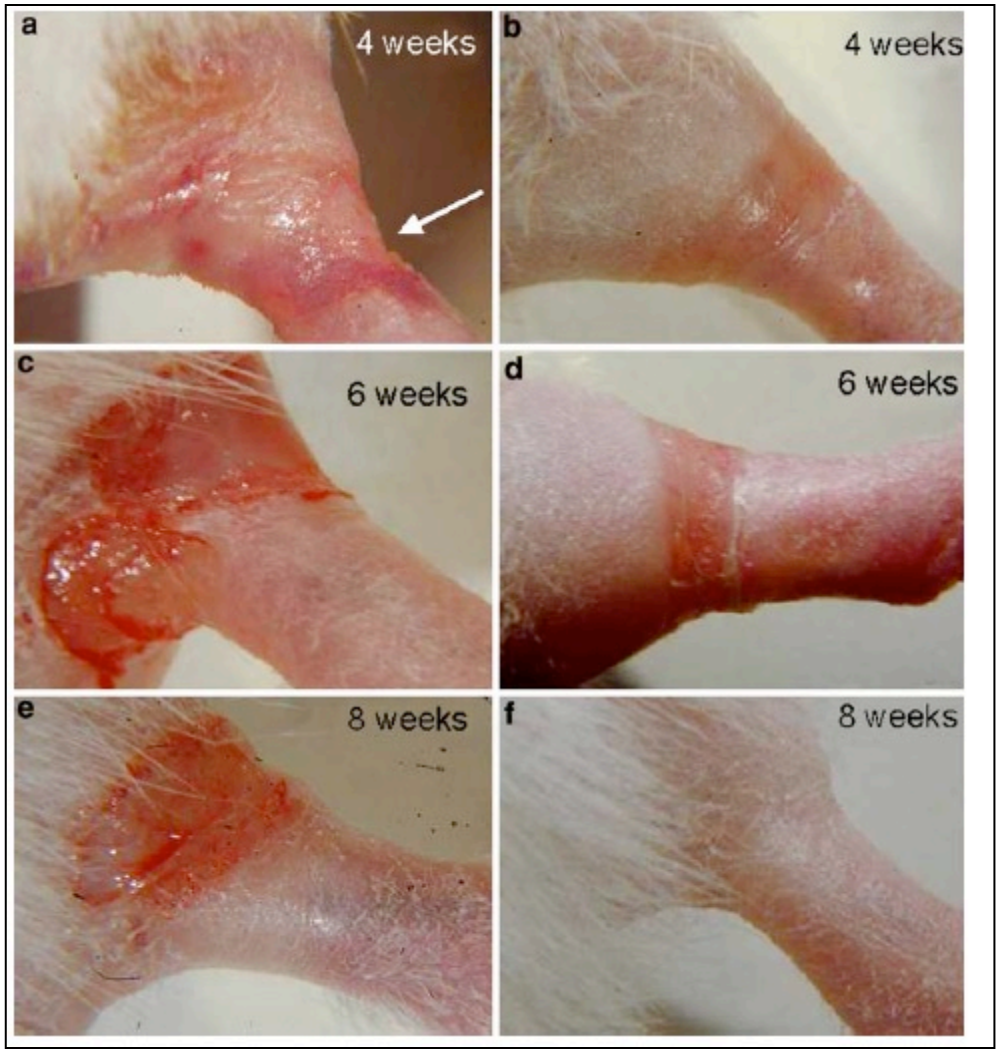
Agent	Study	Patients	Mechanism of action	Radiation therapy details
Memantine (197)	RTOG 06-14 (Brown et al, 2013)	508 patients with brain metastases	Blocks NMDA receptors to prevent neurotoxic excessive NMDA stimulation	Whole-brain radiation 37.5 Gy in 15 daily fractions of 2.5 Gy
Pilocarpine (198, 199)	RTOG 97-09 (Fisher et al, 2003; Scaratino et al, 2006)	213 patients with head and neck cancer and ≥50% of major salivary glands receiving 50 Gy	Cholinergic receptor agonists promoting salivary secretion	60-70 Gy using standard or BID fractionation without chemotherapy
Palifermin (200)	Le et al, 2011	188 patients stage III-IVB cancer of head and neck	Keratinocyte growth factor ↑cell turnover	70 Gy in 2-Gy fractions with concurrent cisplatin
Tadalafil (202)	RTOG 08-31 (Pisansky et al, 2014)	221 patients stage II prostate cancer and intact erectile function	Phosphodiesterase = 5 inhibitor ↑Nitric acid production	Prostate radiation therapy 75-79.2 Gy in daily fractions of 1.8-2 Gy or prostate brachytherapy with 145 Gy (^{125}I) or 125 Gy (^{103}Pd)
Skin washing (203)	Roy et al, 2000	99 breast cancer patients	↓Inflammatory response and damage to basal cell layers by reducing bacteria and fungi	Radiation to breast or chest wall to 45 Gy in 2.25 Gy fractions or 50 Gy in 2-Gy fractions, with electron boost to 7.5-11.25 Gy in some patients

Intervention	Results (*primary endpoint[s])	Comments
Memantine 5 mg PO daily (escalated to 10 mg BID by week 4 if tolerated) for 24 weeks starting within 3 days of initiation of radiation therapy	*HVLT-R delayed recall median decline 0.0 vs 0.9 (P=.059) at 24 wk HVLT-R delayed recognition median decline 0.0 vs 1.0 (P=.0149) at 24 wk MMSE median decline 0 vs 1 (P=.0093) at 24 wk	33% of patients died before 24 wk
Pilocarpine (5 mg per os QID for 3-6 mo) starting at time of radiation initiation	*Unstimulated salivary flow improved at end of radiation therapy, 3 mo, and 6 mo (P=.002, .047, and .093, respectively) *No difference self-reported quality of life scores in pain, chewing, swallowing, taste, saliva amount at 3 or 6 mo	Numerous previous studies have shown limited preventative effect Though objective increase in saliva, not reflected in patient's self-assessment
Palifermin (180 μg/kg IV weekly × 8 wk) starting Friday before initiation of radiation therapy	*Incidence of grade 3-4 oral mucositis 54% vs 69% (P=.041) Duration of severe oral mucositis 5 d vs 26 d (P=.112) Days to development of severe oral mucositis 47 vs 35 (P=.157) Incidence of supplemental nutrition 67% vs 55% No difference in overall survival	Similar benefit seen in postoperative patients (201)
Tadalafil (5 mg per os daily for 24 wk) starting with radiation therapy	Retained erectile function: • *At 28-30 wk, 79% vs 74% (P=.49) • At 52 wk, 72% vs 71% (P=.93)	Additionally, tadalafil did not improve overall sexual satisfaction
Gentle washing of treatment field with warm water and mild soap	*Acute skin toxicity maximum scores improved with skin washing (P=.04): • *Grade 0 0% vs 2% • *Grade 1 64% vs 41% • *Grade 2 34% vs 57% • *Grade 3 2% vs 0% Mean time to maximal toxicity score not significant: 3.3 wk vs 3.1 wk	Also trend toward decreased pain and burning

Kalman et al
IJROBP 2017

Intervention with signaling / stem cell therapy

30 Gy 30 Gy + MSC



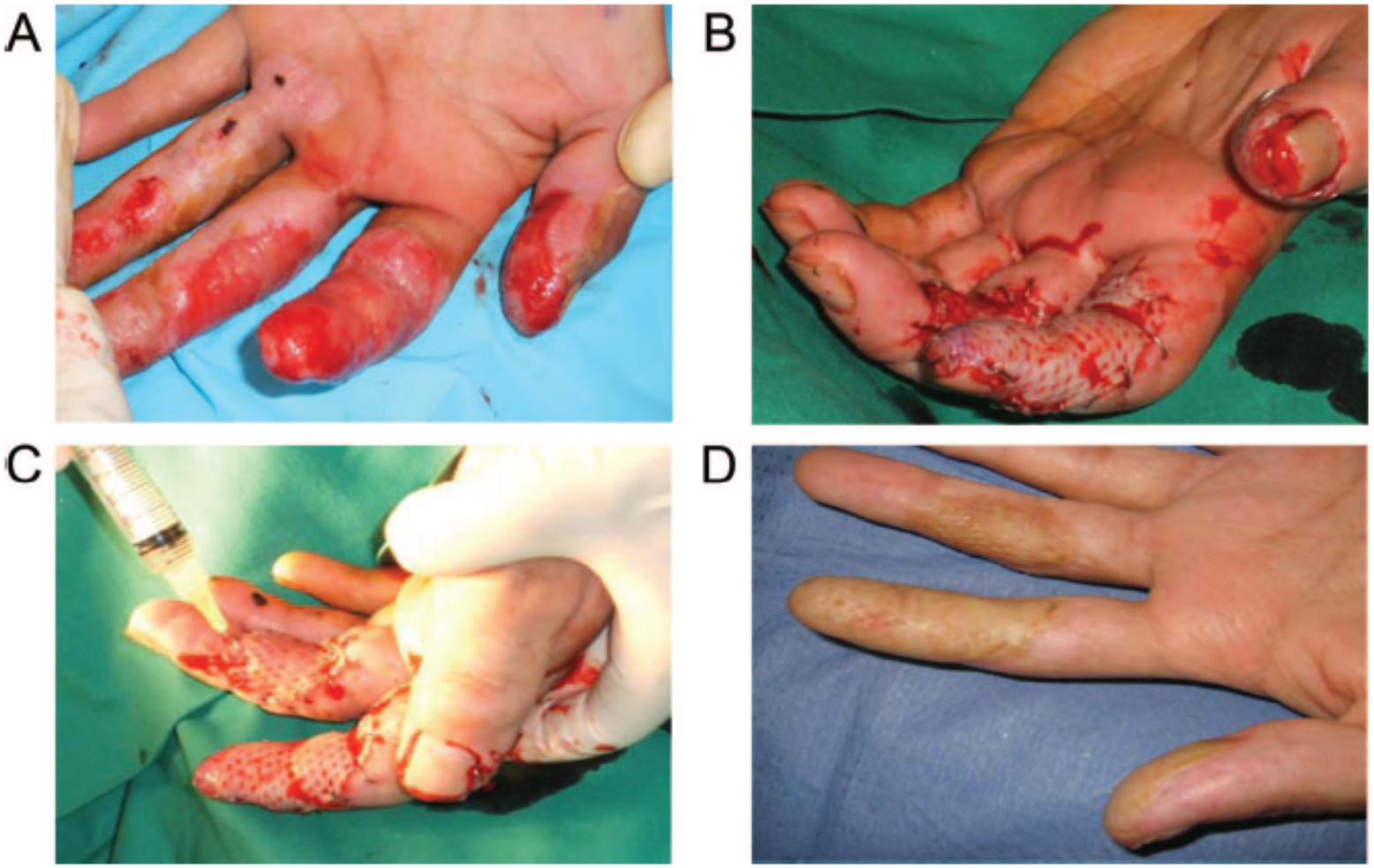
Stem cell therapy: MSC transplantation

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



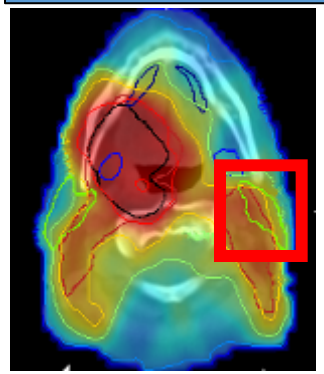
Benderitter et al 2010

Stem cell therapy

Treatment plan

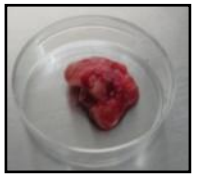
Probability of xerostomia

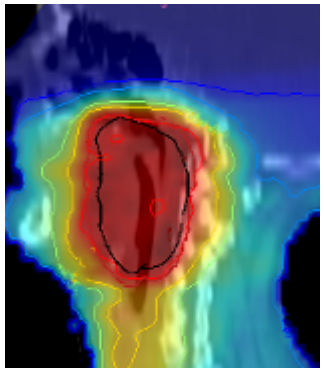
Treatment



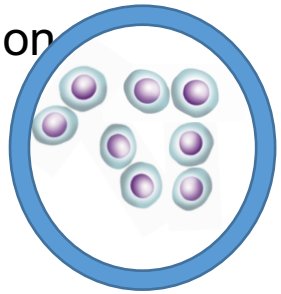
Patient with tumor

Salivary gland biopsy



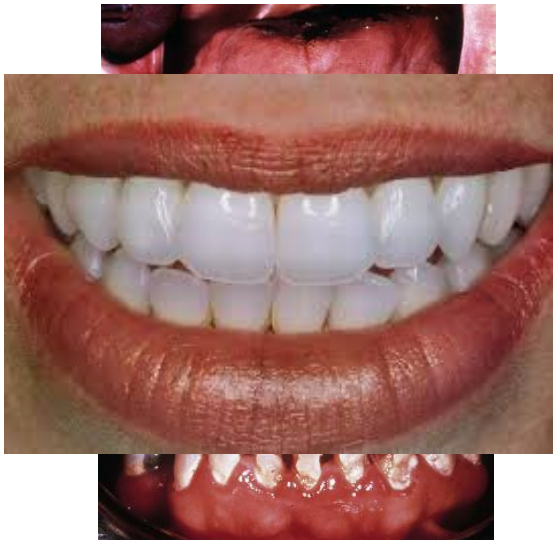


Stem cell culture and selection

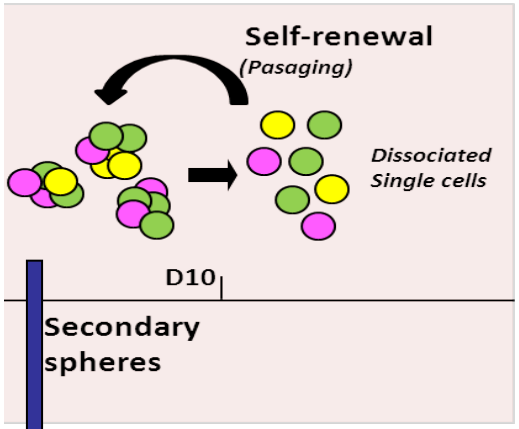


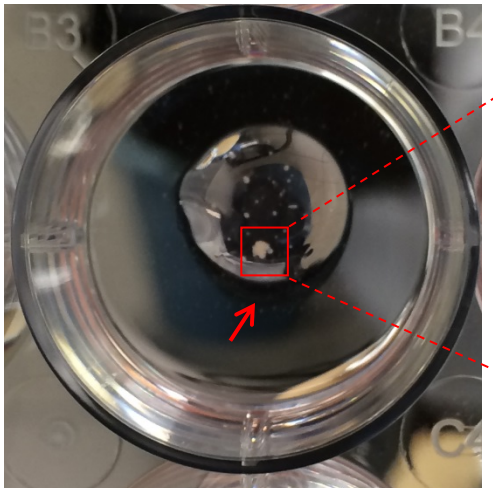
transplantation

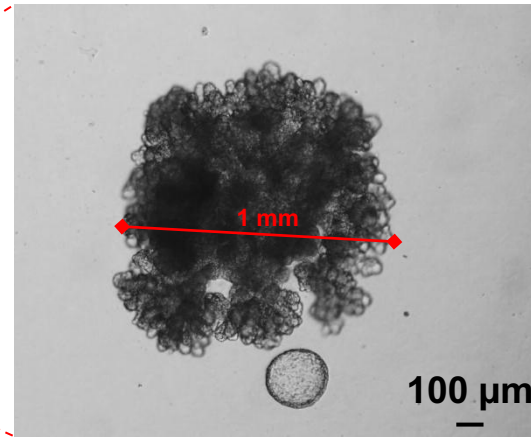
How?

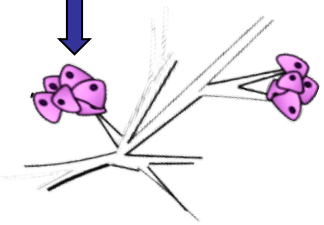


Differentiation of 1 cell to organoid

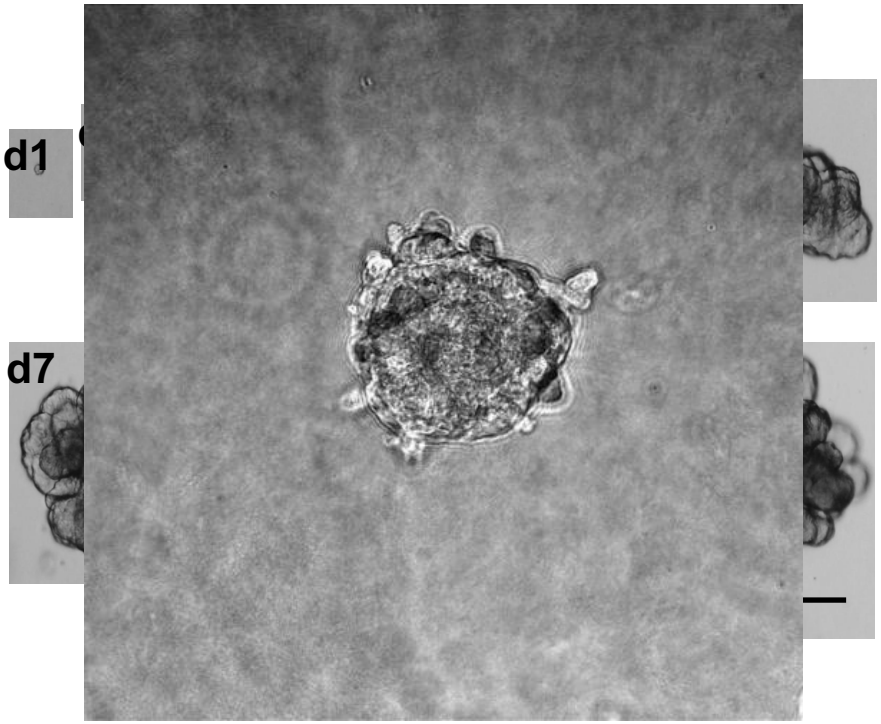








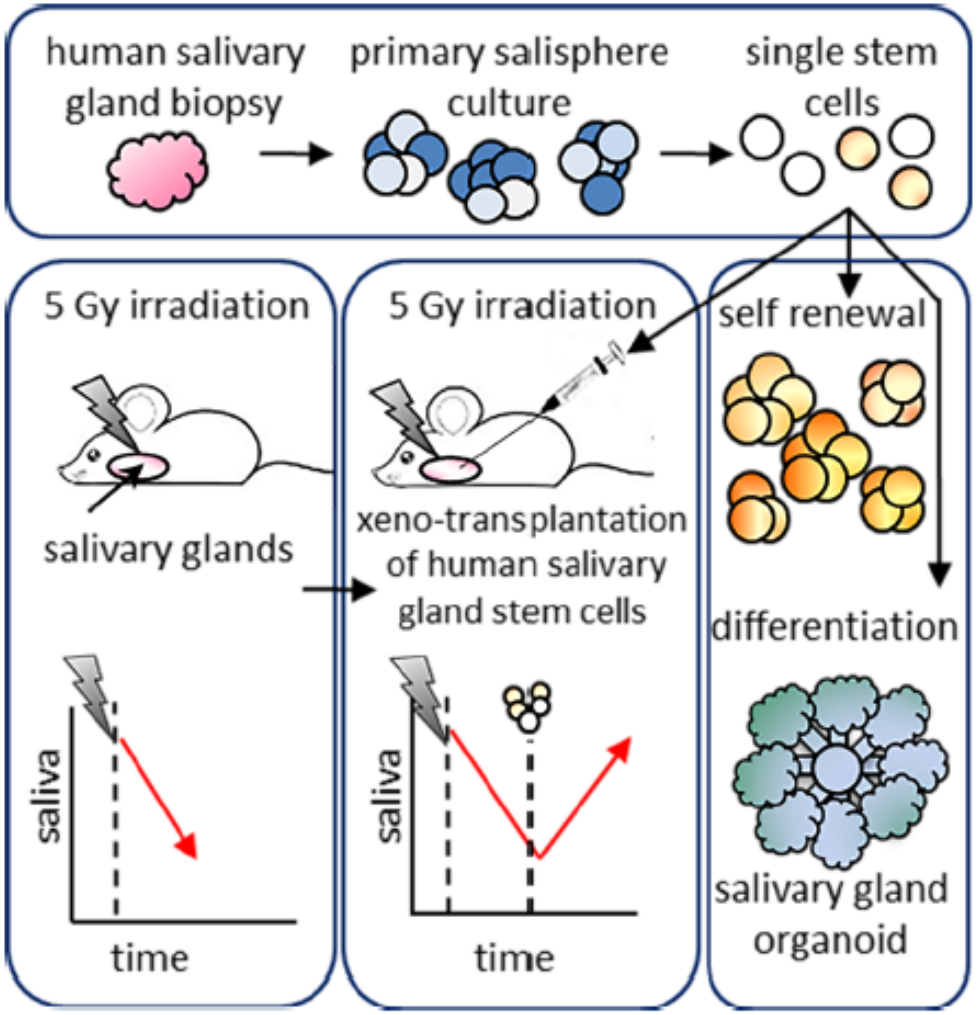
Differentiation

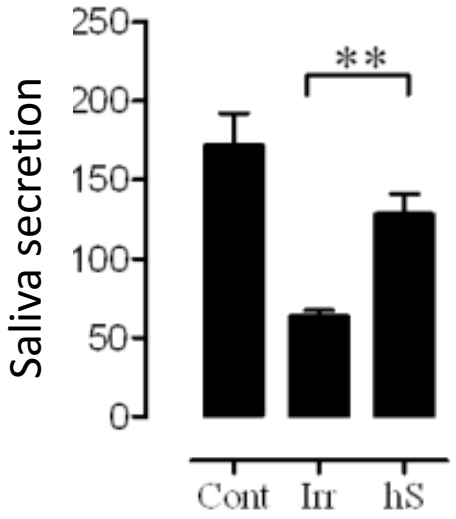


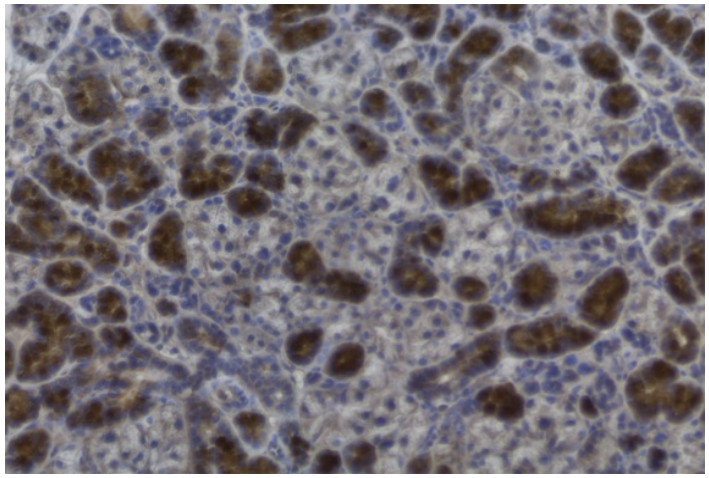
Martti Maimets et al Stem Cell Reports 2016

Johan de Rooij, UMCU

Stem cell therapy

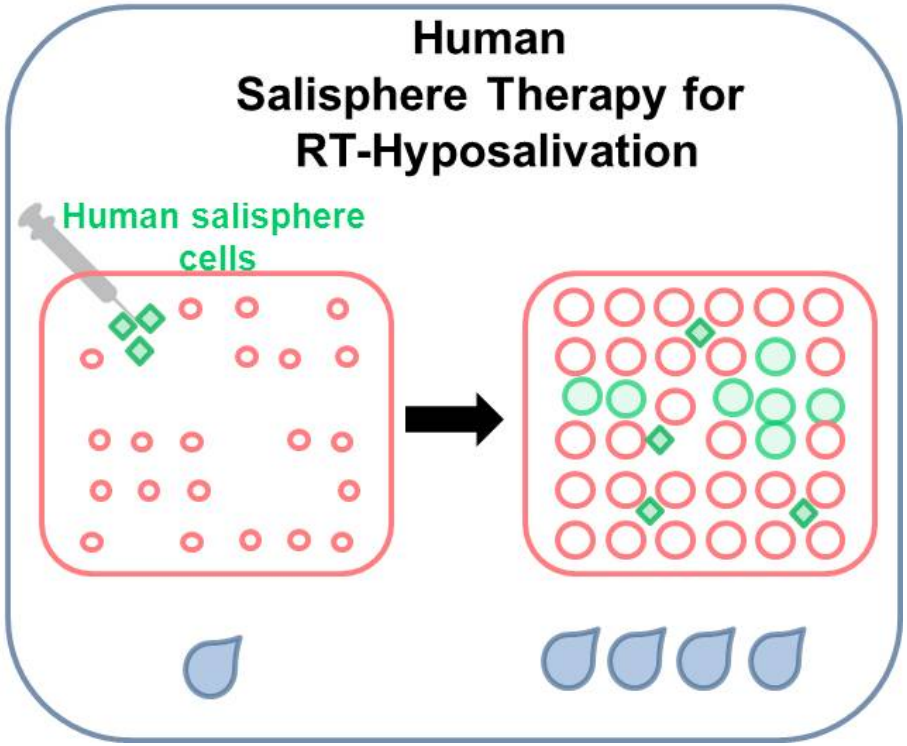




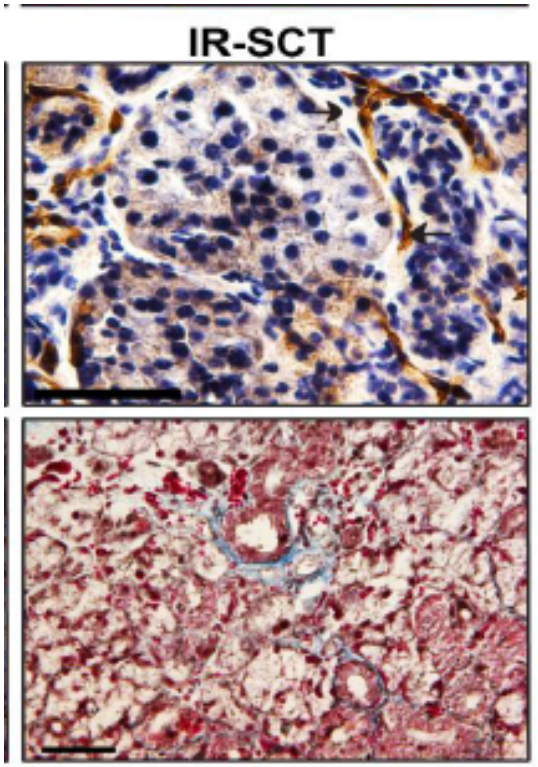


Pringle et al Stem Cells 2016

Stem cell therapy



Pringle et al Stem Cells 2016

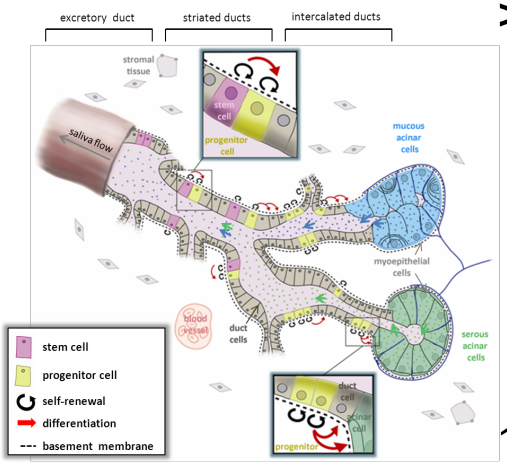


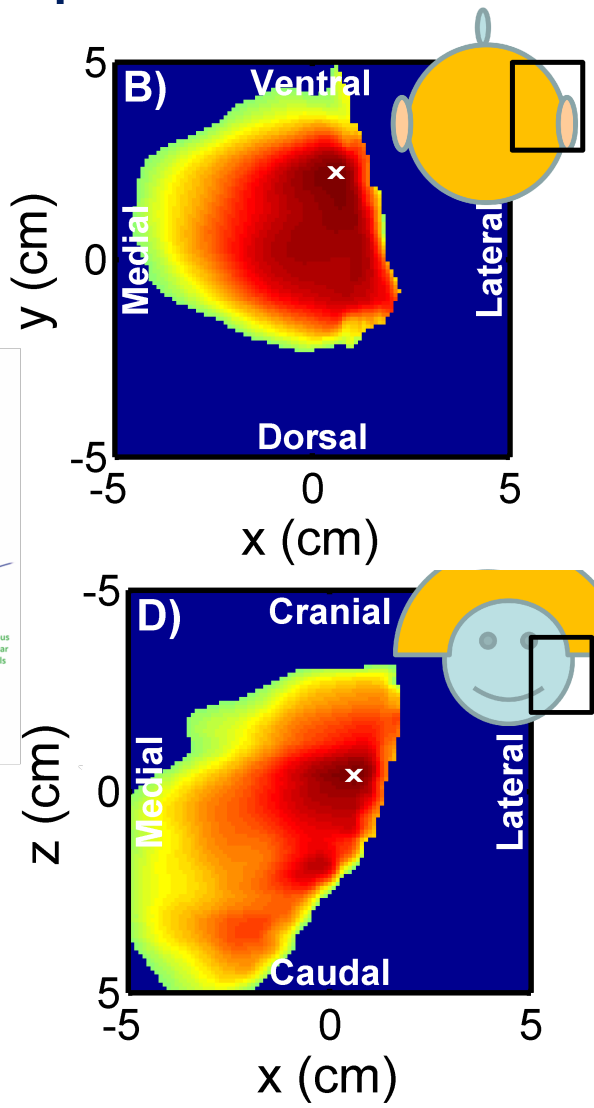
Nanduri et alRadiother & Oncol 2013

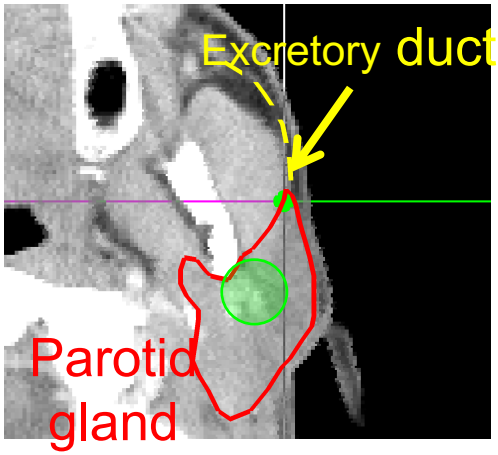
Restoration of tissue + endocrine stimulation

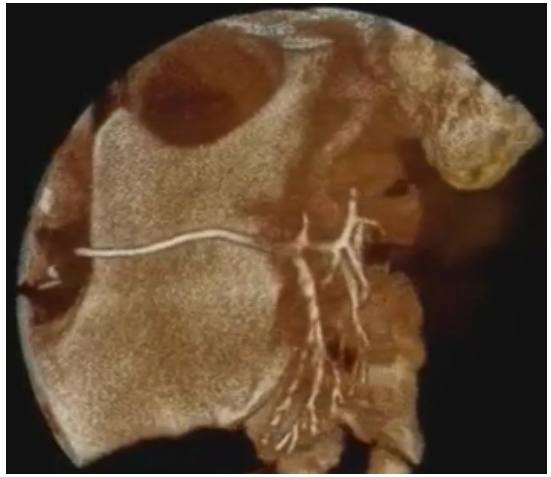
- Re-entrance in cell cycle
- ECM remodelling
- Reduction of fibrosis
- Re-vascularisation

Impact on function: human





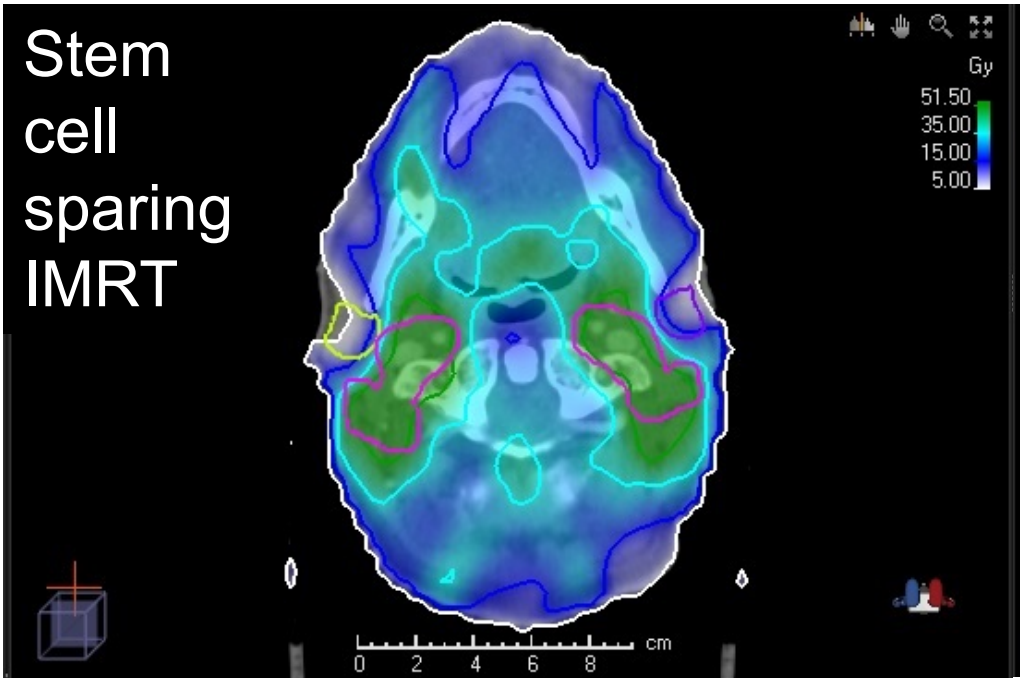


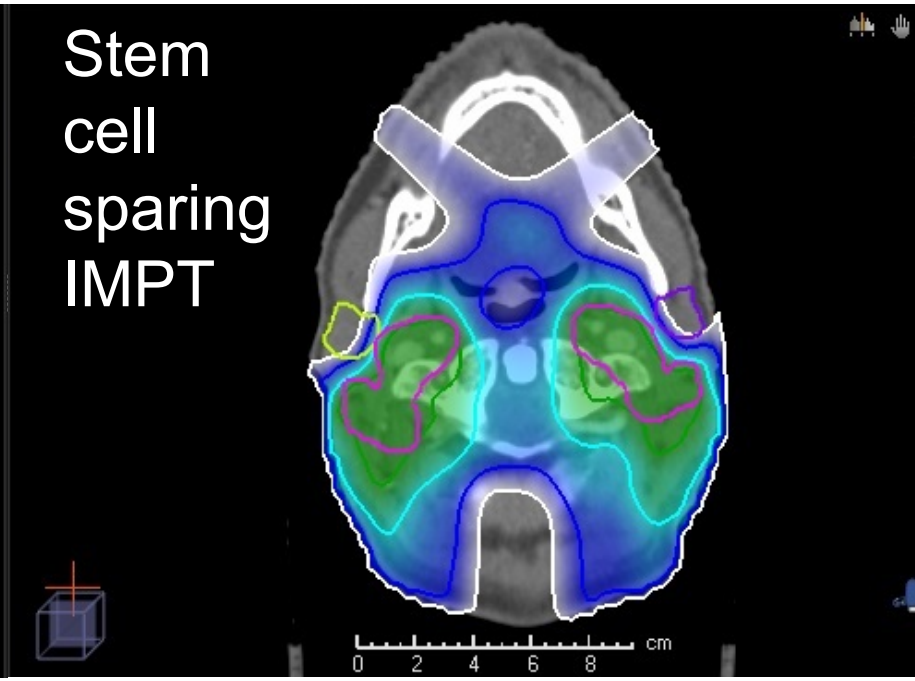


Dose to main ducts strongly determines outcome

Van Luijk et al Science Translational Medicine 2015

Protons vs. Photons

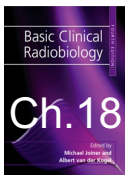




Optimum intervention strategies required

- 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

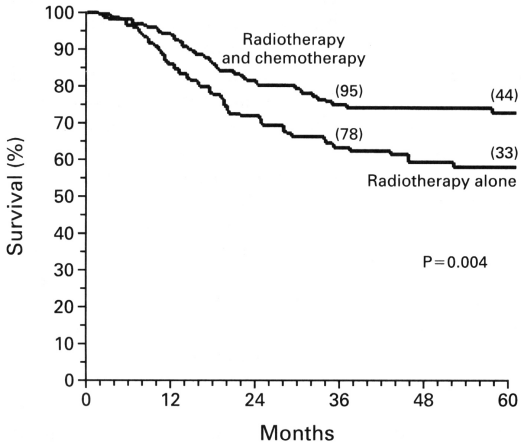


Chemo-radiation: biological basis

Vincent GREGOIRE, MD, PhD, Hon. FRCR

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)

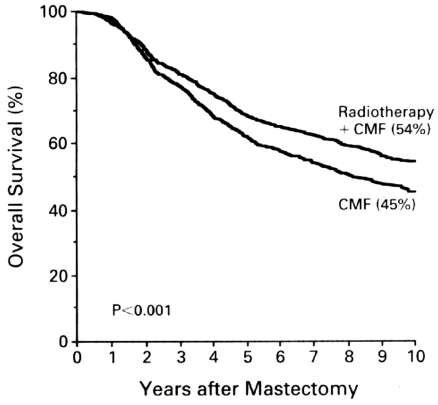
RT: 45 Gy + brachytherapy (total dose ≥ 85 Gy)
Chemo: cddp (75mg/m^2, d1), 5Fu (1g/m^2/d, d1-4), x3

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)

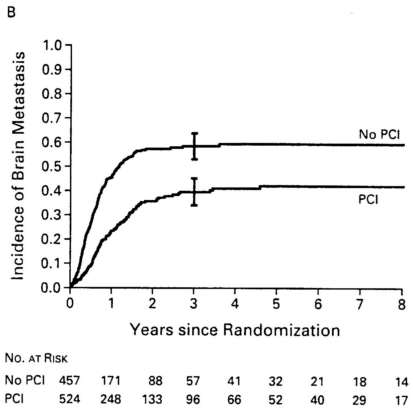
Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial

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

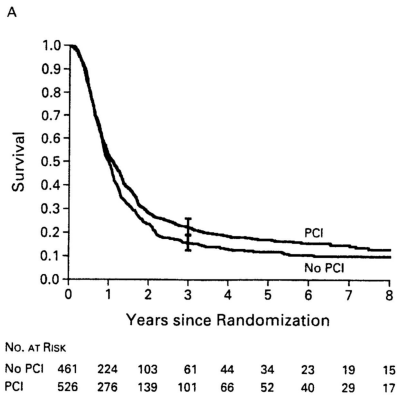


Radiotherapy + CMF	852	755	641	555	392	188
CMF	856	738	587	494	329	163

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



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



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

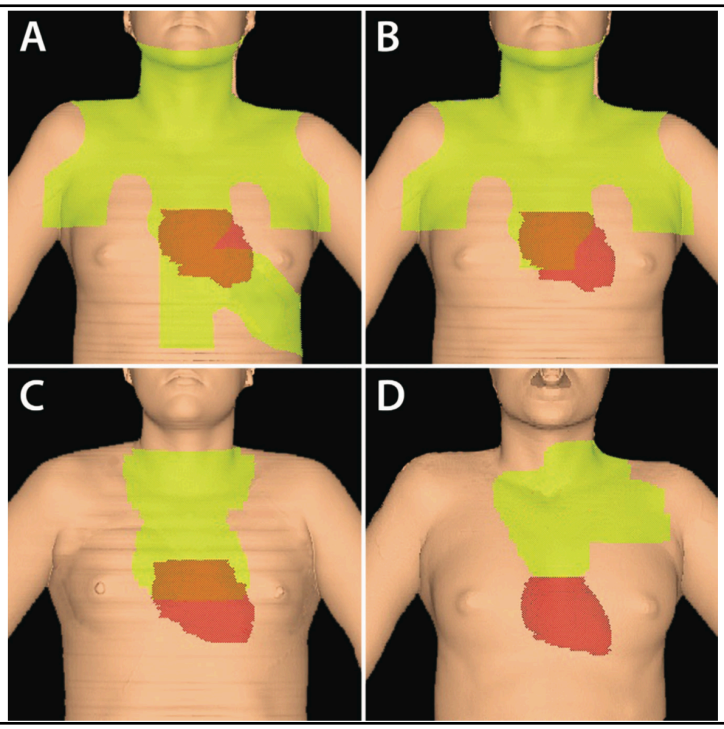
Aupérin et al., *NEJM* 341: 476, 1999

Combined chemo- and radiotherapy treatment

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

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

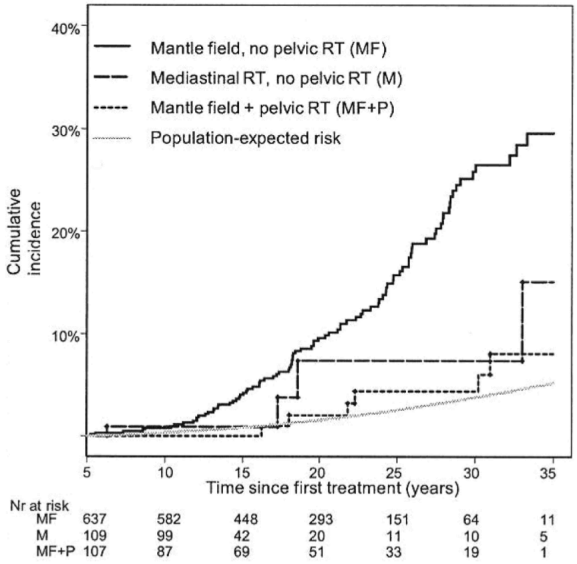
	RT (EF, 40 Gy)	CH (MOPP/ABVD)	CH+RT (IF, ≤ 40 Gy)
10 y over. survival	80-90%	80-90%	≈90%
Complications (RR)			
-leukemia	11.0	70.0	reduced
-lymphoma	21.0	22.0	reduced
-solid tumor	2.8	1.1	reduced
-cardiac	2.2-3.1	≈1.0	reduced



ESTRO 2017

Hodgson, Hematology 2011

Cumulative incidence of invasive breast cancer after RT for Hodgkin disease



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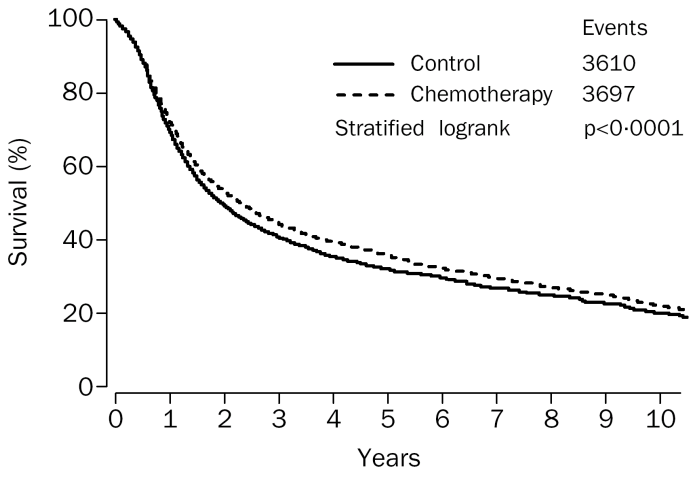
Hodgson, Hematology 2011

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)

H&N SCC: MACH-NC



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

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Meta analysis

Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients

Jean-Pierre Pignon [a,*], Aurélie le Maître [a], Emilie Maillard [a], Jean Bourhis [b], on behalf of the MACH-NC Collaborative Group [1]

[a] Department of Biostatistics and Epidemiology, Institut Gustave-Roussy, Villejuif, France
[b] Department of Radiotherapy, Institut Gustave-Roussy, Villejuif, France

Timing	No. Deaths / No. Entered LRT+CT	LRT	O-E	Variance	Hazard Ratio	HR [95% CI]
Concomitant	3171/4824	3389/4791	-326.4	1587.7		0.81 [0.78;0.86]
Induction	1877/2740	1813/2571	-40.0	900.7		0.96 [0.90;1.02]
Adjuvant	631/1244	661/1323	17.9	317.4		1.06 [0.95;1.18]
Total	**5679/8808**	**5863/8685**	**-348.5**	**2805.8**		**0.88 [0.85;0.92]**

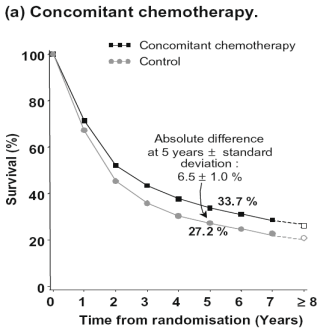
Test for heterogeneity: χ^2_{107} = 179.8 p < 0.0001, I^2 = 41%

Test for interaction: χ^2_2 = 26.60 p < 0.0001

0.5 1.0 2.0

LRT+CT better | LRT better

LRT+CT effect: p < 0.0001



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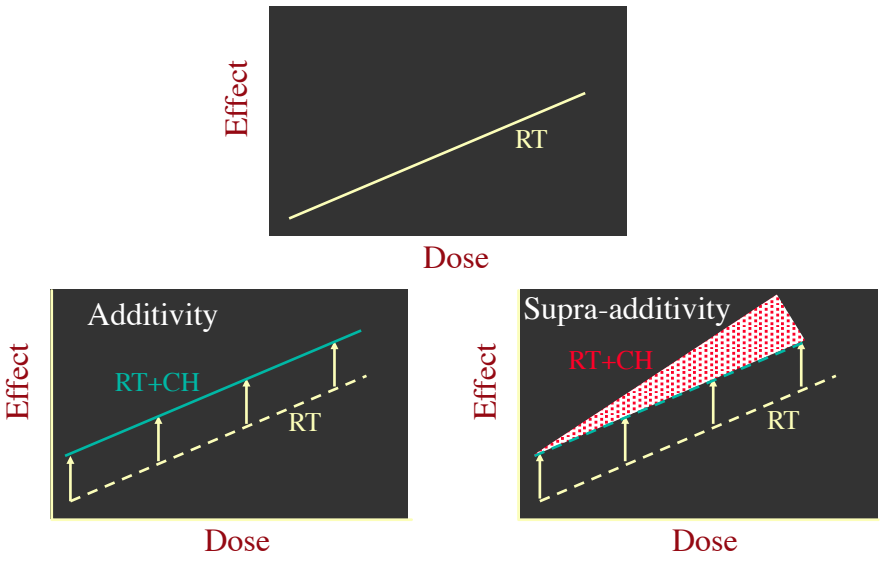
Pignon et al, Radioth Oncol 2009: 92; 4-14

Combined chemo- and radiotherapy treatment



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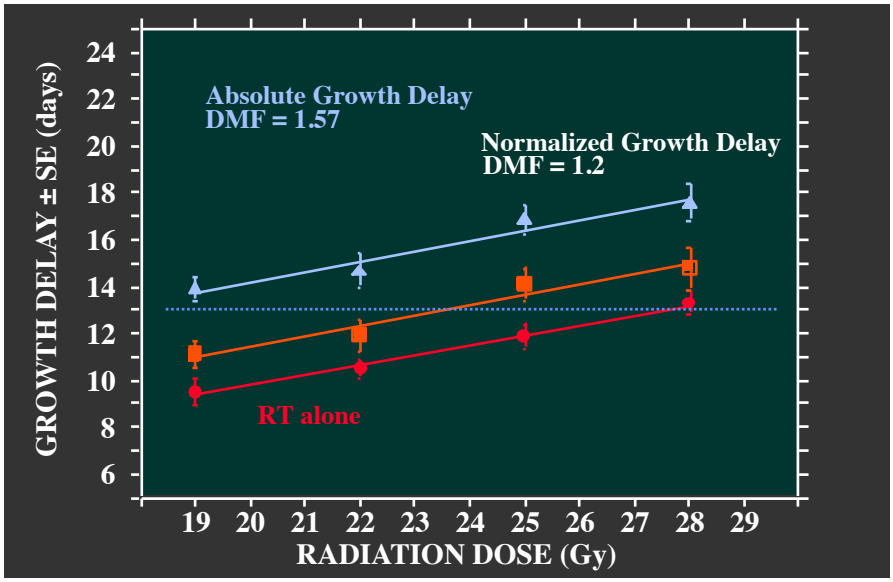
DOSE MODIFICATION FACTOR IN SA-NH TUMOR AFTER SINGLE IRRADIATION COMBINED WITH FLUDARABINE (800 mg/kg)



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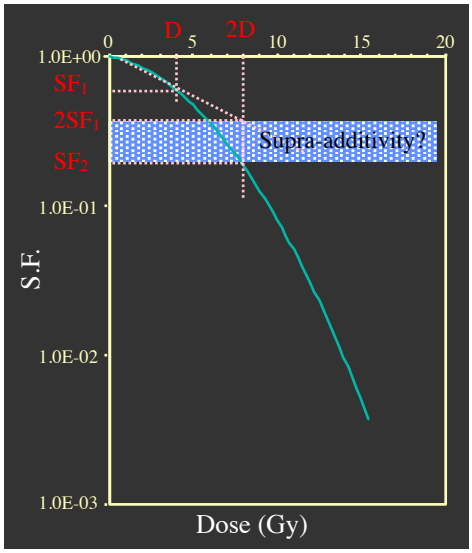
Combined chemo- and radiotherapy treatment



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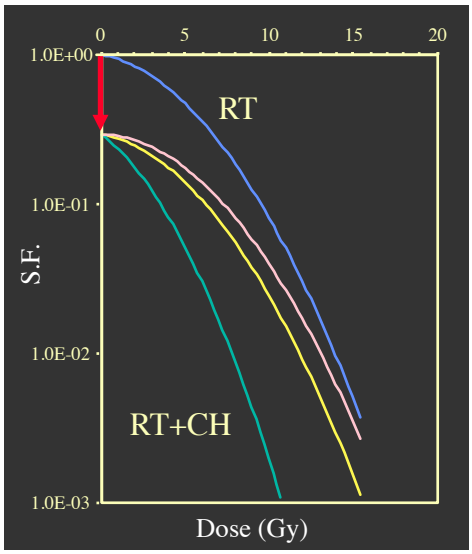
Combined chemo- and radiotherapy treatment



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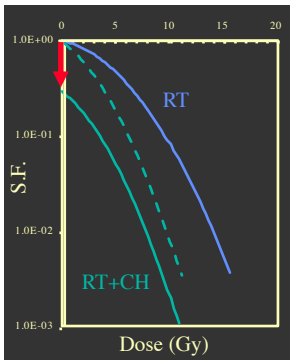
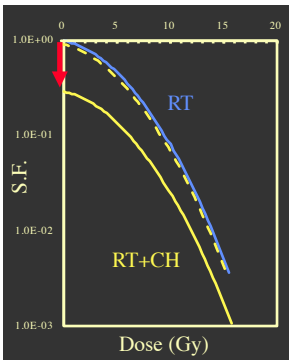
Combined chemo- and radiotherapy treatment

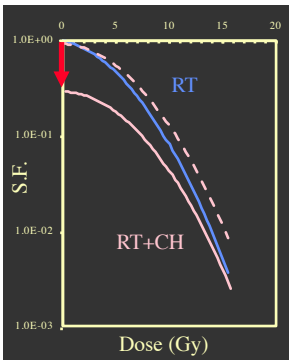
Enhancement



Non-interaction



Inhibition



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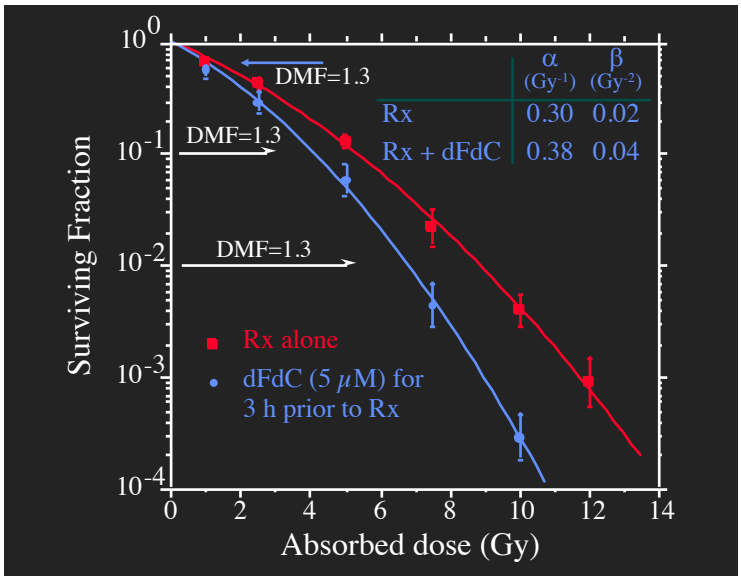
Redrawn from Steel

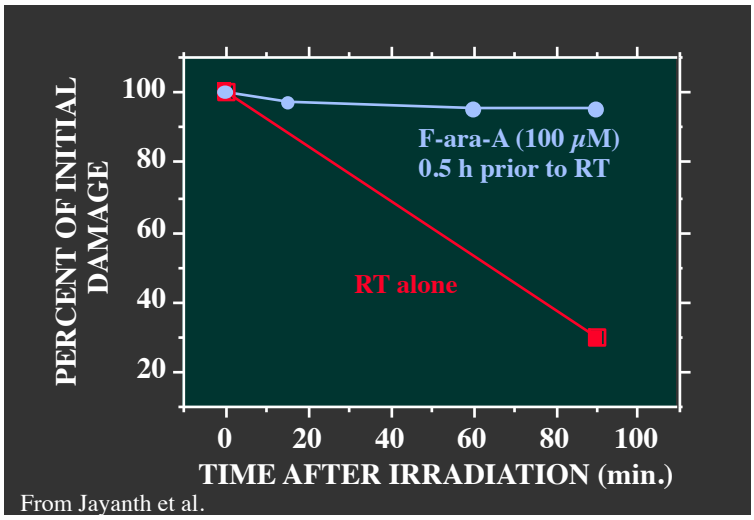
Radio-enhancement by dFdC of a human squamous cell carcinoma cell line (SQD9)



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.

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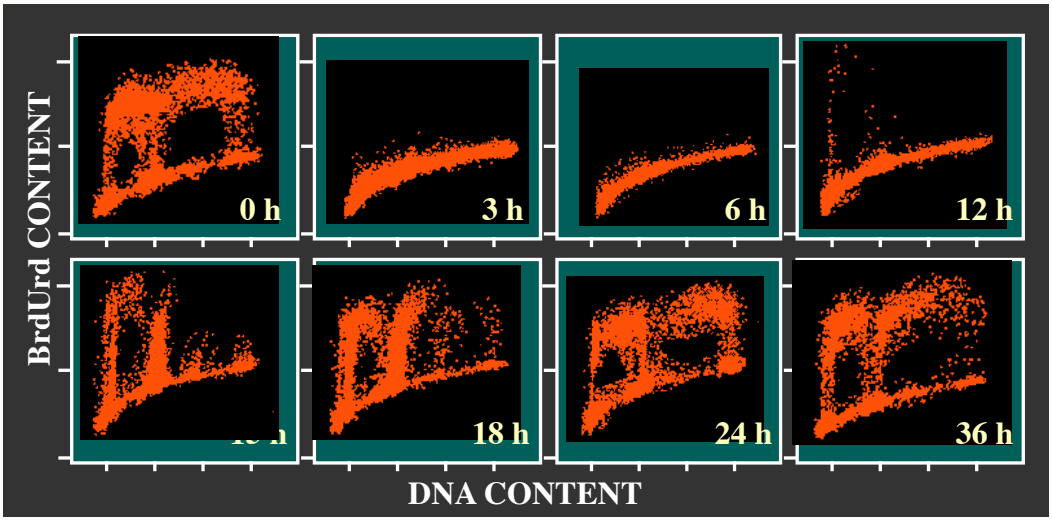
CELL CYCLE REDISTRIBUTION INDUCED BY FLUDARABINE (800 mg/kg) IN SA-NH TUMOR



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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	?	?	-	-/+	-/+

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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	?	-	+	+	+

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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	?	+?	?	?	-

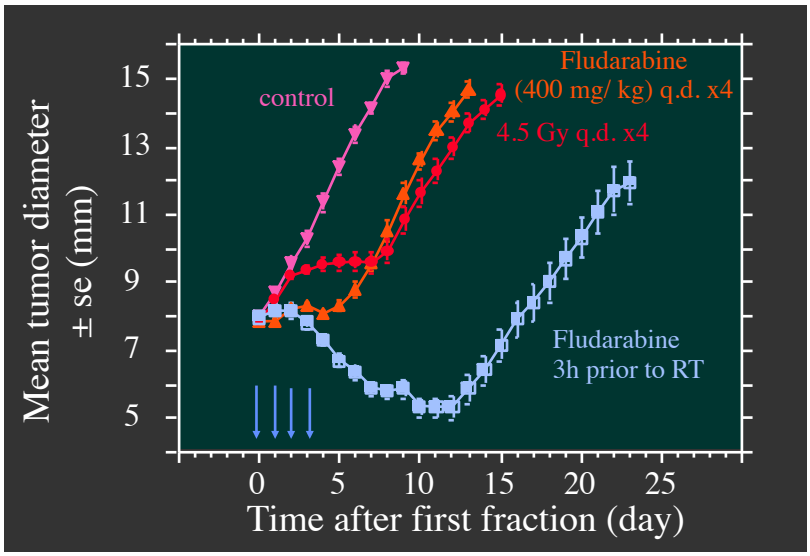
Combined chemo- and radiotherapy treatment

Cellular / molecular interaction

or

Tissular interaction ?

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



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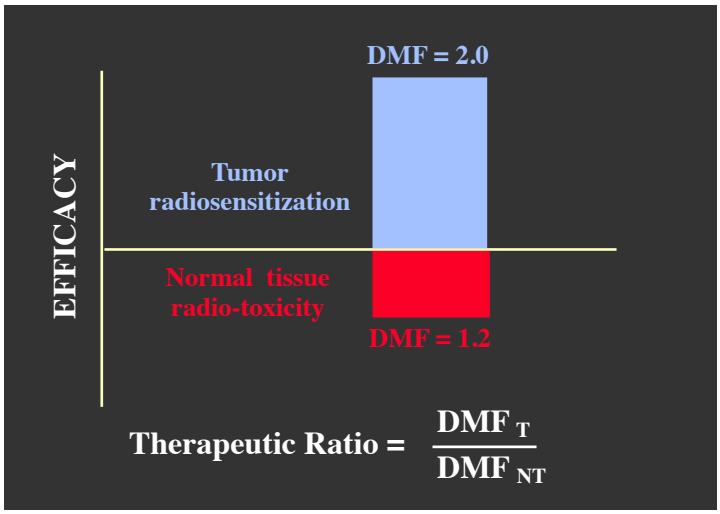
THE CONCEPT OF THERAPEUTIC RATIO



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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)	?

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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

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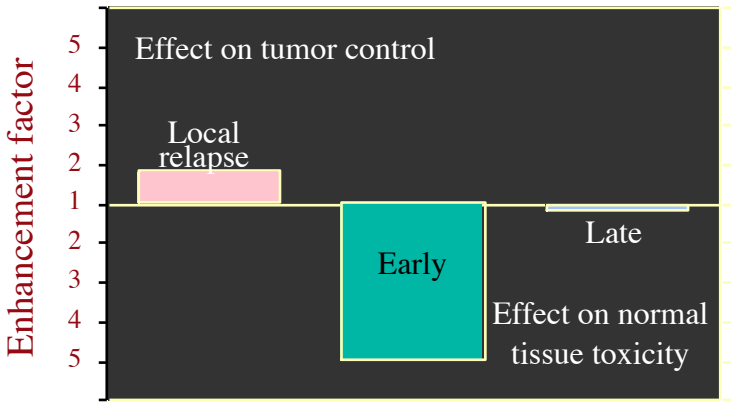
Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer.

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



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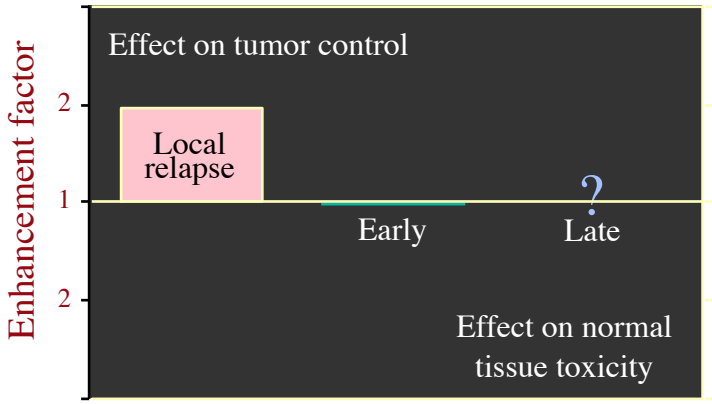
Treatment of advanced squamous-cell carcinoma of the head and neck with alternating chemotherapy and radiotherapy.

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

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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

Rob Coppes

Department of Radiation Oncology

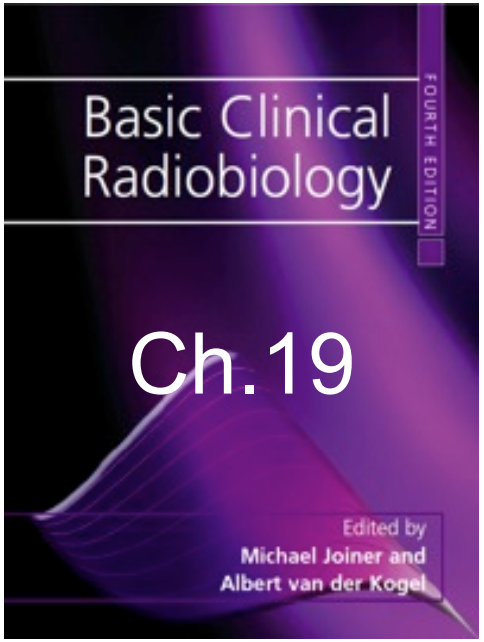
&

Department of Cell Biology

University Medical Center Groningen /
University of Groningen

Groningen

The Netherlands



Introduction

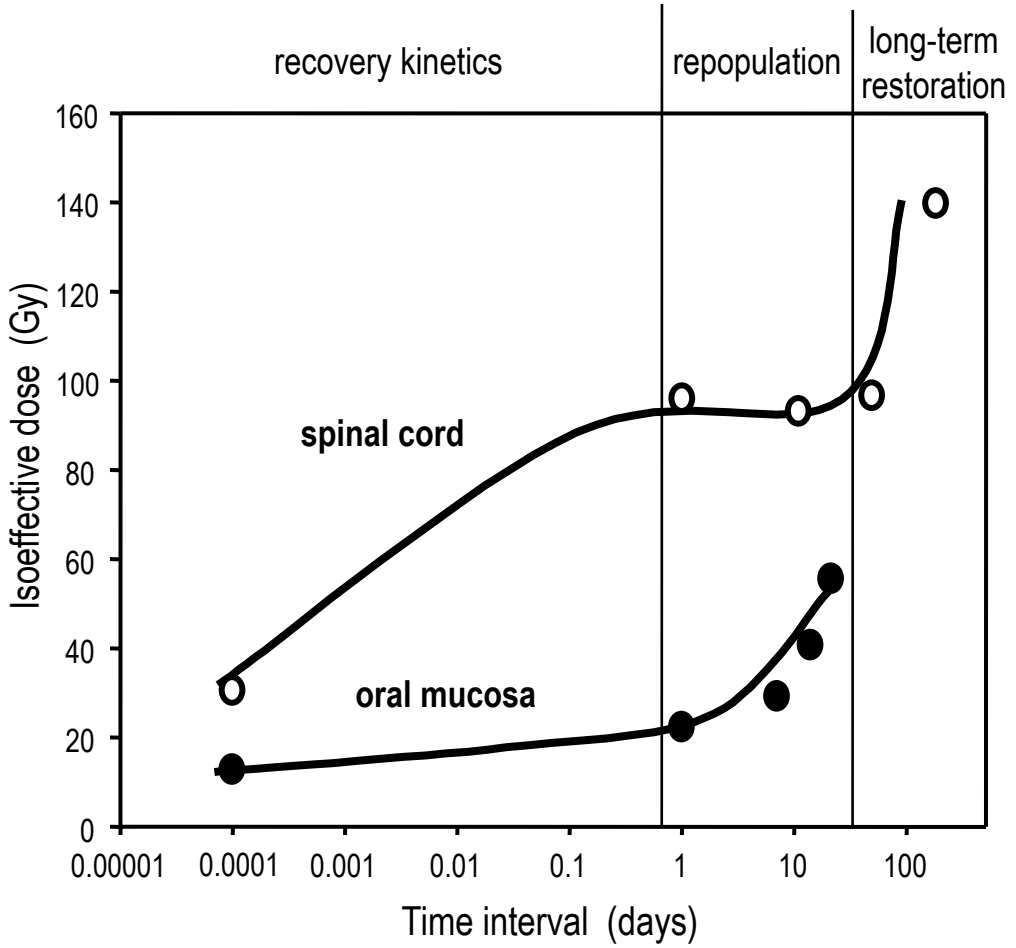
- Reirradiation of previously treated areas: why?
  - New primary tumor
    - Cancer survivors are at an increased risk of developing secondary malignancies
      - Pts still retain more risk (e.g. molecular predisposition)
      - Aetiological factors can continue (e.g. Smoking)
      - Therapy itself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

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

Introduction

- Changes in normal tissue tolerance with time



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

Introduction

No further treatment

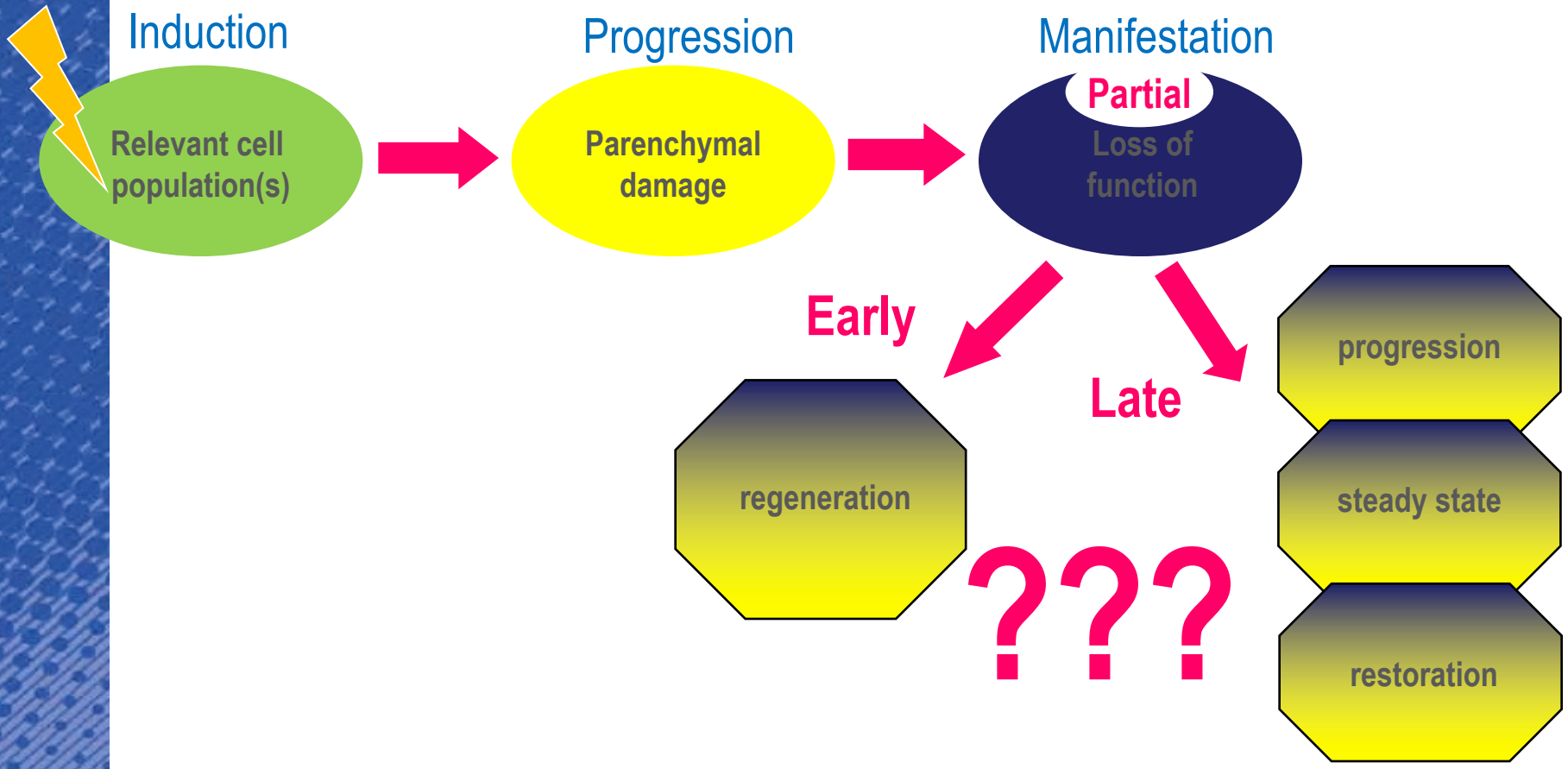
- If the radiation tolerance within a given volume or organ has already been exceeded during the first treatment
- And function is lost (or loss is to be expected)

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

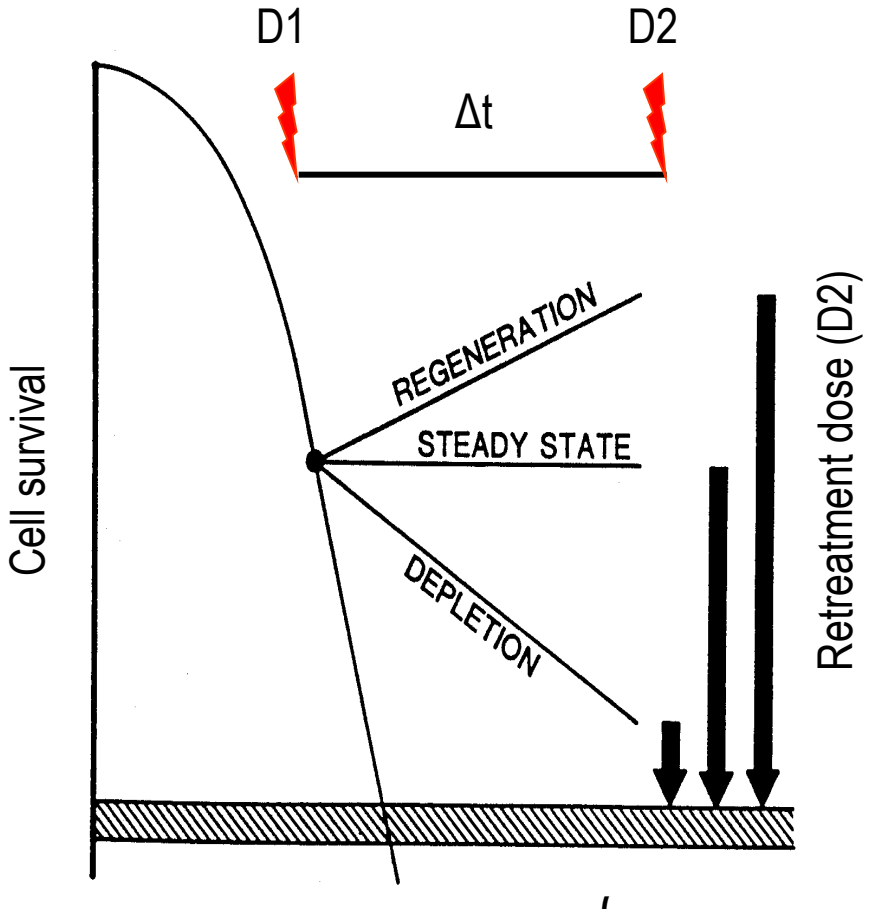
Introduction

- Pathogenesis of normal tissue radiation effects



Introduction

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



"E"

Level of cell kill
for tissue damage

Introduction

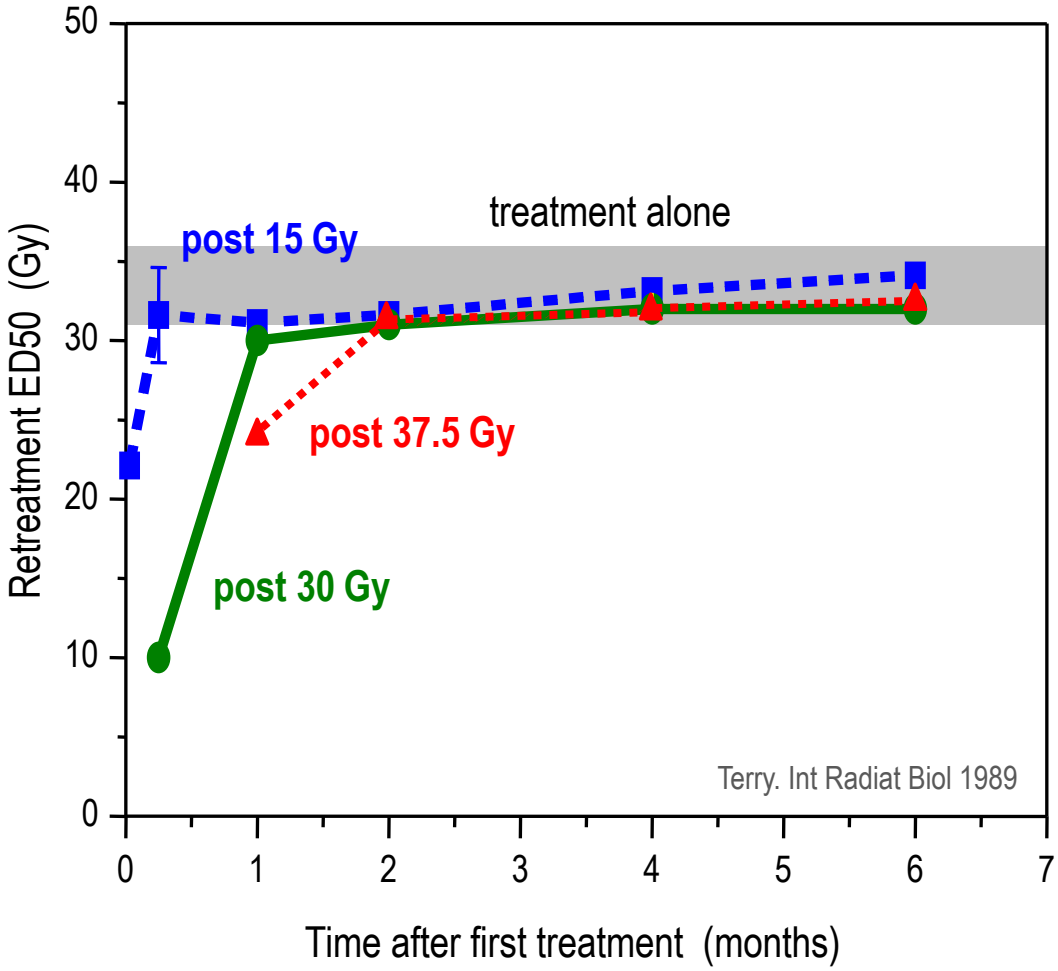
- Some concepts
  - EQD_2: equivalent dose in 2-Gy fractions
    - Calculated using LQ-model with α/β values
      - 10 Gy for early reactions
      - 3 Gy for late reactions
  - EQD_{2tol}: tolerance doses
    - Threshold doses above which defined grades of toxicity are observed
  - % EQD_{2tol}: intensity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

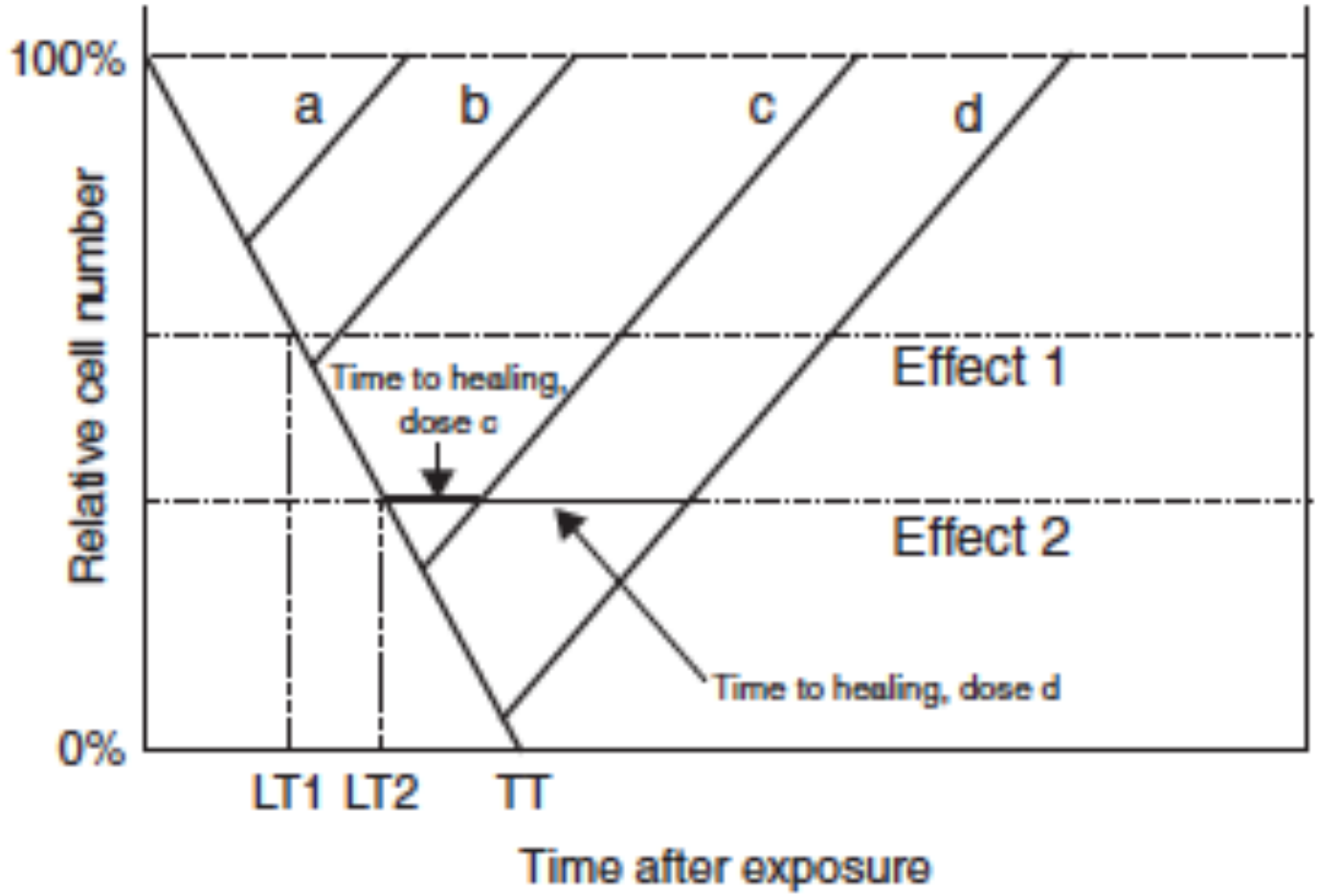
Experimental studies
Early effects

Epidermis

- Retreatment tolerance of mouse epidermis

Recovery to full tolerance within 1-2 months




100%
a
b
c
d
Relative cell number
Time to healing, dose c
Effect 1
Effect 2
Time to healing, dose d
0%
LT1
LT2
TT
Time after exposure

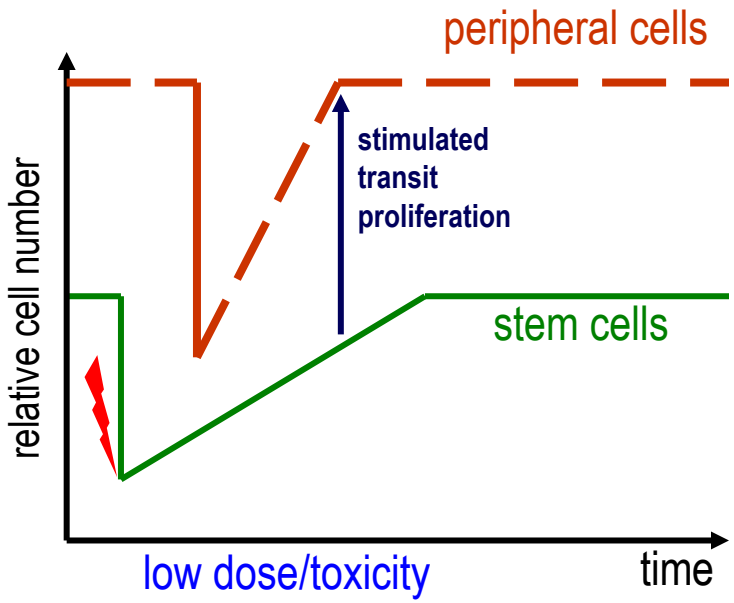
Retreatment skin and oral mucosa

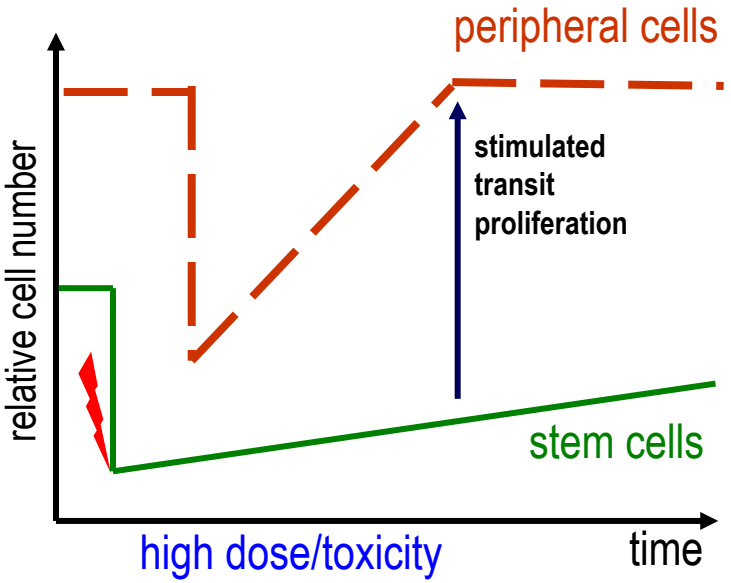
- Rapid proliferative recovery begins within 2 weeks
- Full re-irradiation tolerance for early injury is reached within 2-3 months
- Re-irradiation tolerance for late damage will be less (cfr. slides mouse limb)

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)

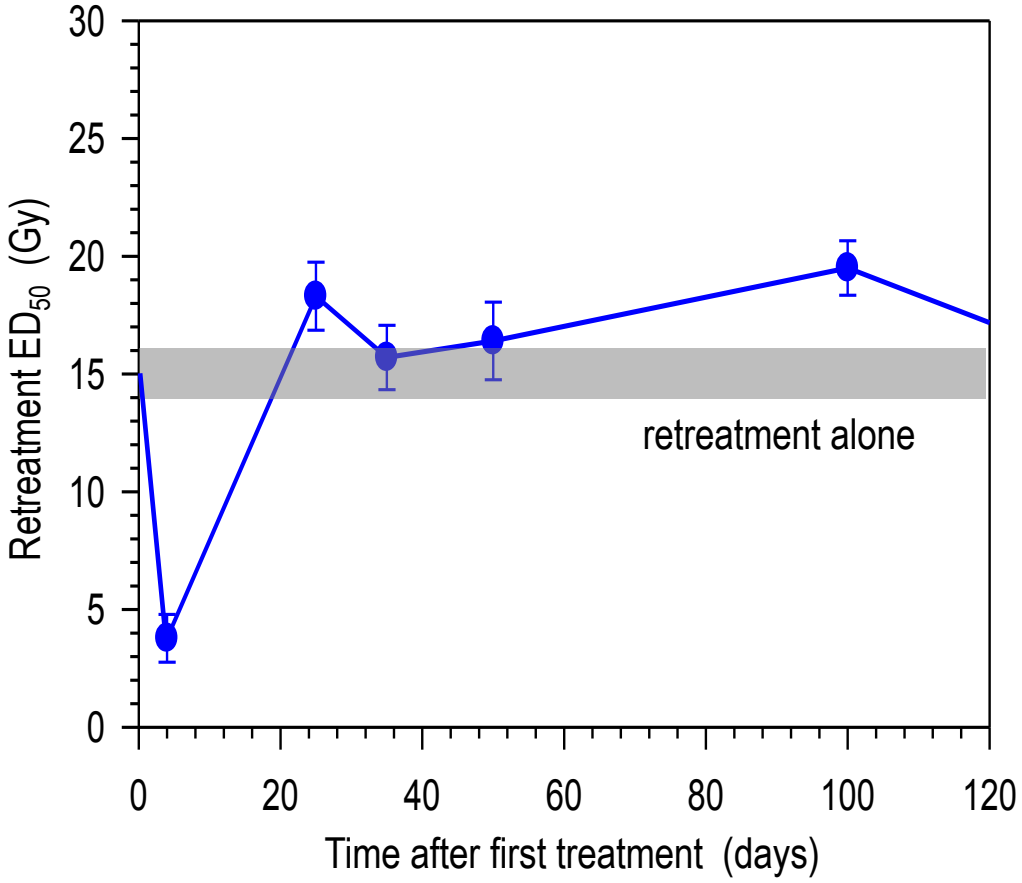




Urinary bladder (mouse)

- 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



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

Experimental studies
Late effects

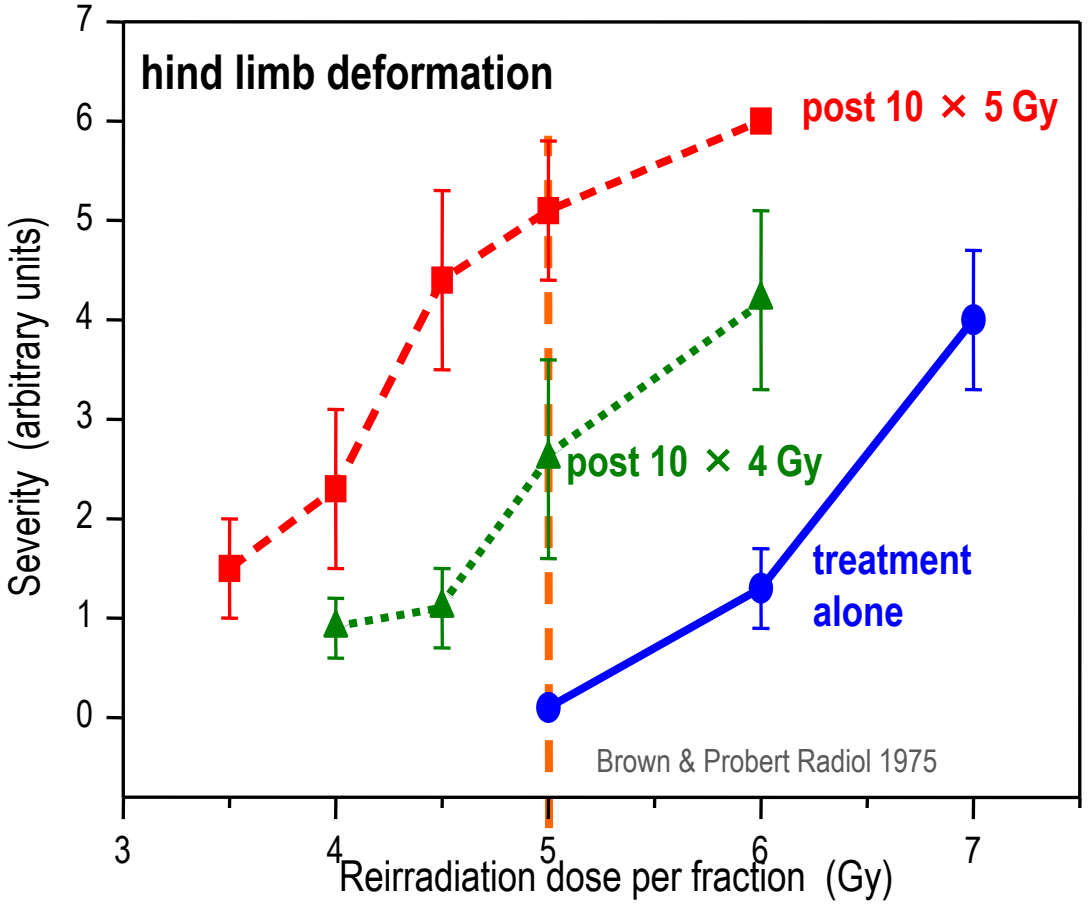
Skin

- 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



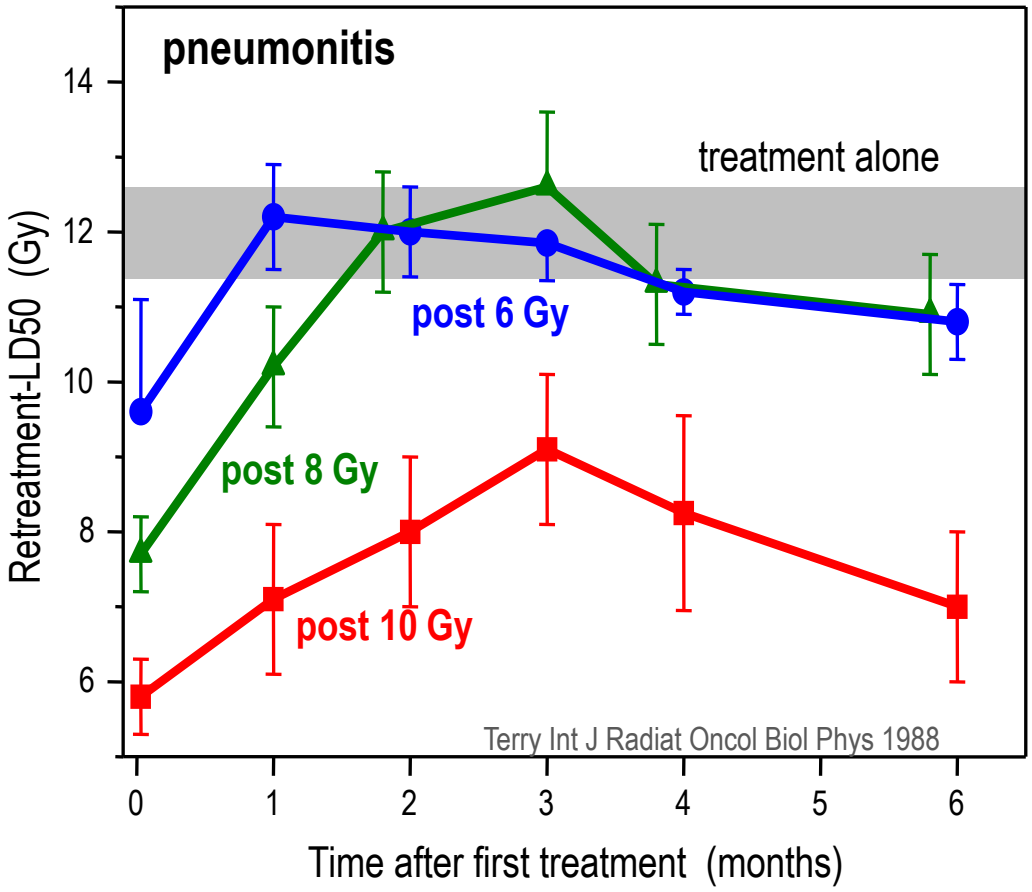
Lung

- 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



Kidney

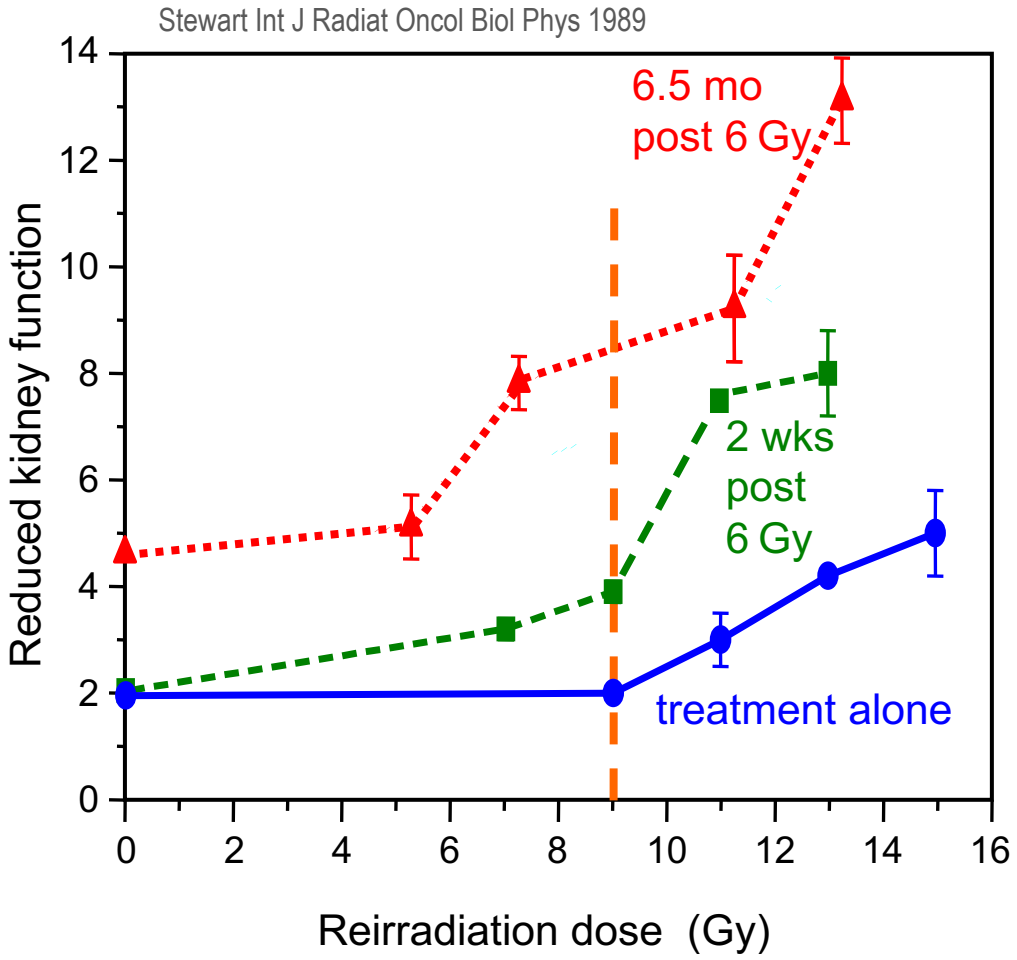
- Retreatment tolerance mouse kidney

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!



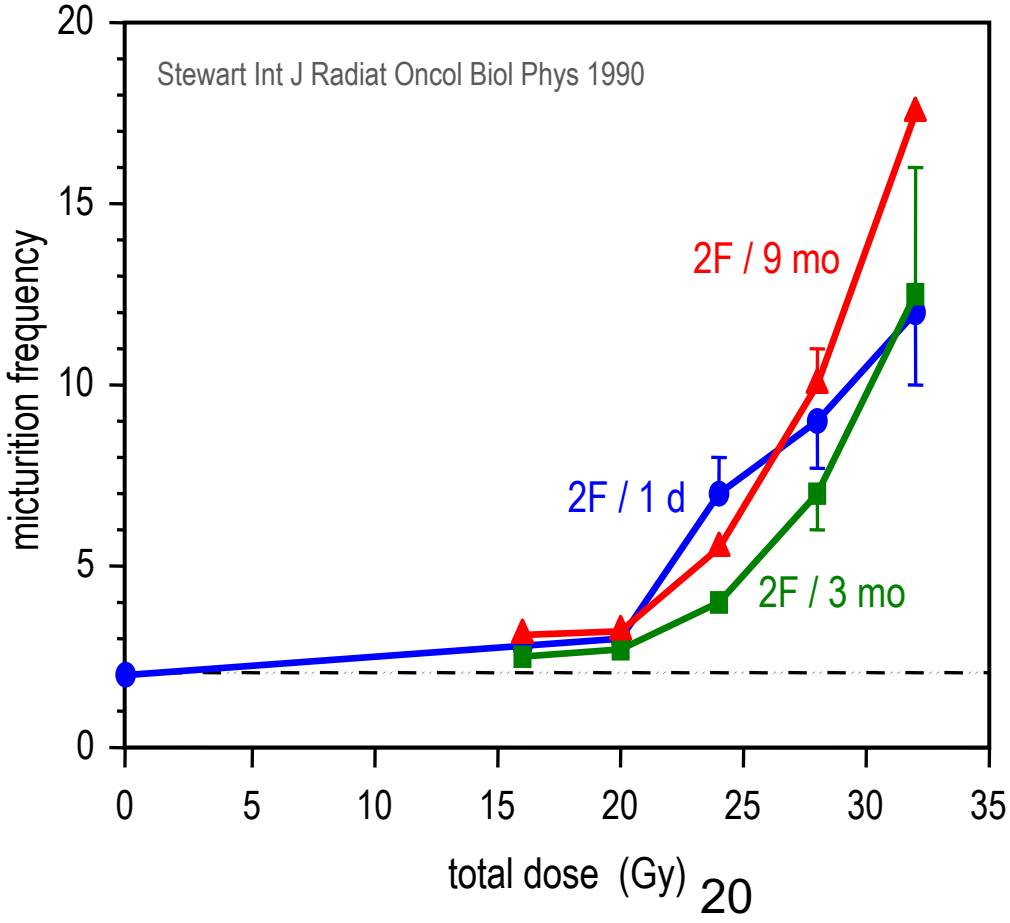
Urinary bladder

- Retreatment tolerance mouse bladder

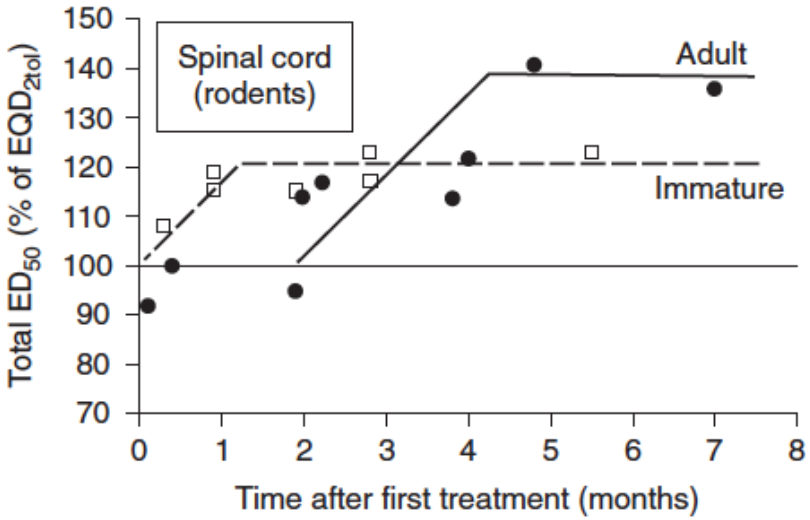
No recovery between 1 day and 9 months after initial treatment

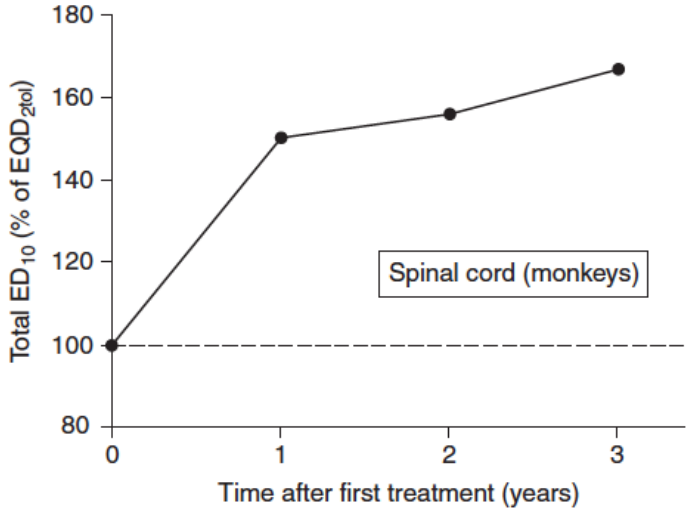
Progression of (subclinical) damage results in shortening of latent times after retreatment

Extreme caution when re-irradiating urinary bladder!

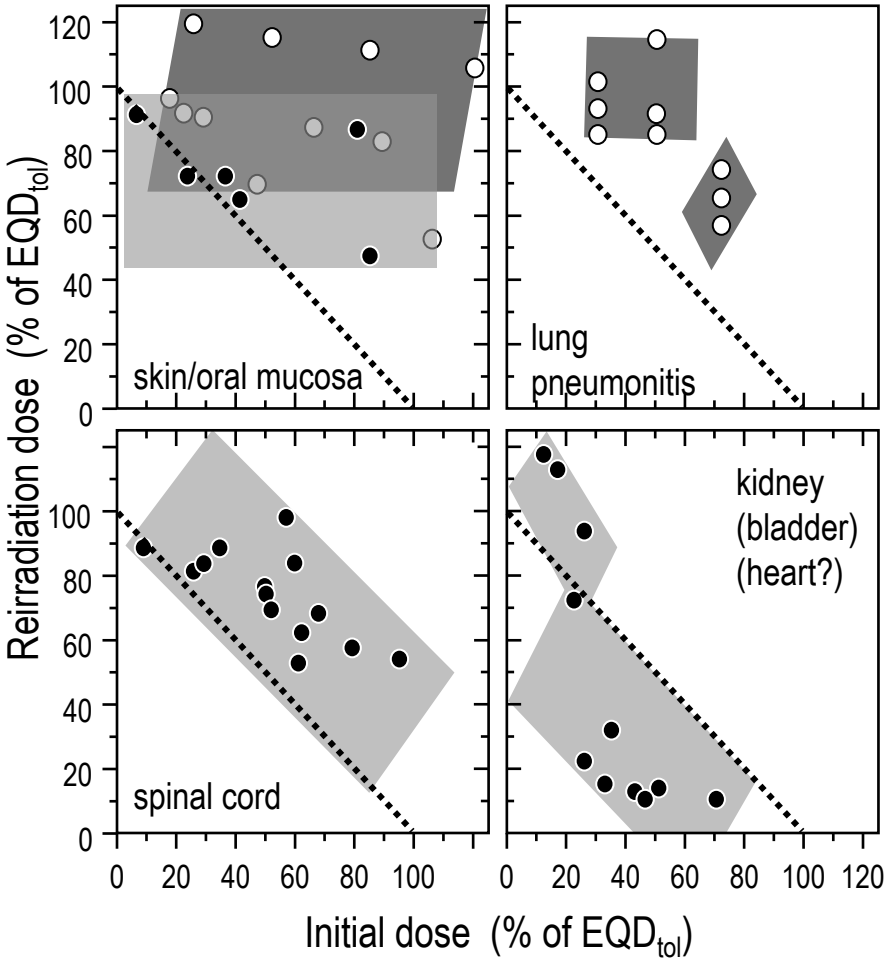


Spinal cord


Spinal cord
(rodents)
Adult
Immature
Total ED50 (% of EQD2tol)
150
140
130
120
110
100
90
80
70
0
1
2
3
4
5
6
7
8
Time after first treatment (months)


Spinal cord (monkeys)
Total ED10 (% of EQD2tol)
180
160
140
120
100
80
0
1
2
3
Time after first treatment (years)

Summary experimental data



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

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

Clinical studies

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

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

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

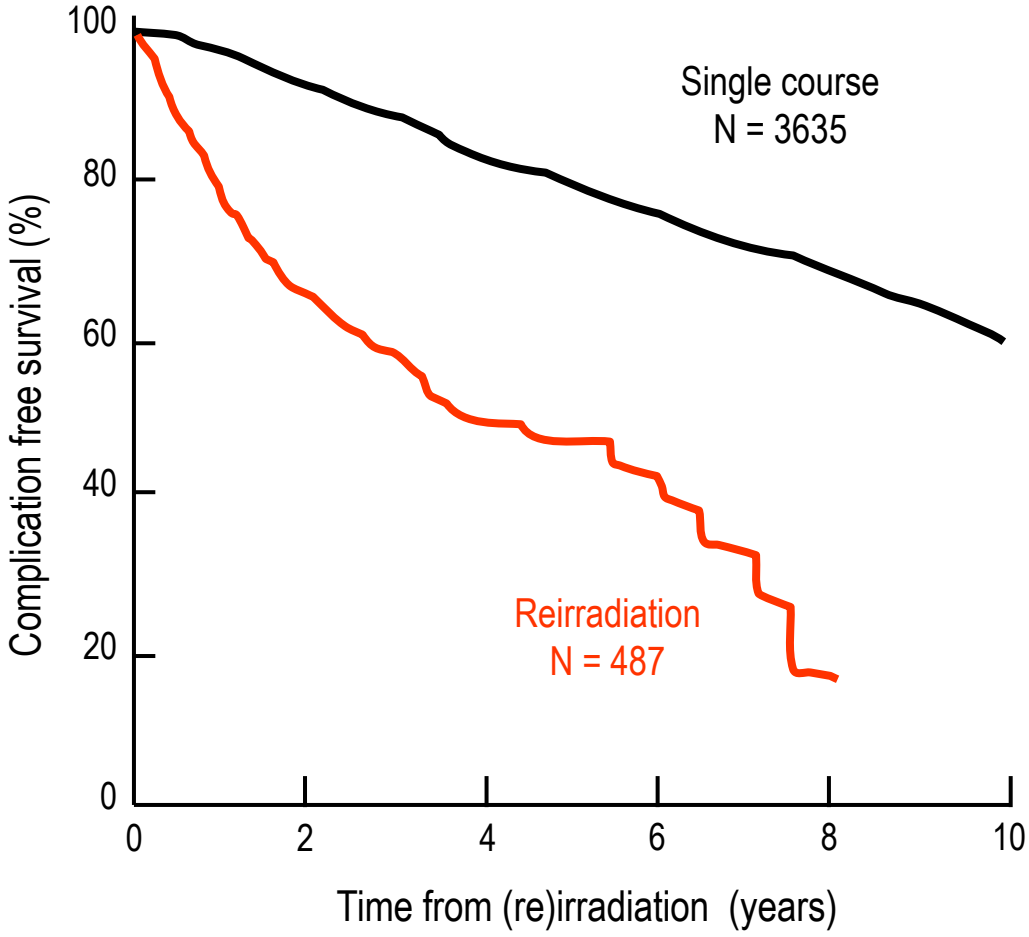
Author	Clinical response rate	Survival	Acute complications	Late complications	Treatment-related deaths
Emami[31] (1967–1985)	CR at 3 months: 81% PR at 3 months: 4%	2 years OS: 45% 5 years OS: 20%	Not reported	Marked fibrosis: 16/99 (16%)[1] Trismus: 3/99 (3%) Fistula: 3/99 (3%) Esophagal stenosis: 2/99 (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: 1pt Dry eye syndrome: 1pt	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.

Kasperts Oral Oncol 2005

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

Head & neck

115 patients
reirradiation + various CT

Initial treatment median 68 Gy
Retreatment median 65 Gy

18% LT
16% fatal

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

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)

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

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

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

Rectum

- Pre-op retreatment (hyperfractionation + chemotherapy) for rectal cancer
- Initial dose ≤55Gy; med interval 27 months
- 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.

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[a]	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[a]	PSA>1 ng/mL	NR	100
Butler et al. [35]; Teh et al. [31]	30	Au^{198}	54	17[a]	3 consecutive rises, PSA >1, metastases	NR	0
Grado et al. [23]	49	I^{125} (37) Pd^{103} (12)	64	34 [5]	3 consecutive rises above nadir	OS 56 [5] DSS 79 [5]	14
Beyer [19]	17	I^{125} (15) Pd^{103} (2)	62	53 [5]	ASTRO, clinical evidence, or ADT	OS 93 [5]	47
Koutrouvelis et al. [23]	31	I^{125} (23) Pd^{103} (8)	30	68[a]	ASTRO[b] or nadir >4 ng/mL	OS 100[a]	97
Wong et al. [34]	17	I^{125} (9) Pd^{103} (8)	44	75 [4]	ASTRO	OS 71 [4] DSS 100[a]	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[a]	52
Allen et al. [18]	12	I^{125} (4)[c] Pd^{103} (8)	45	63 [4]	ASTRO	OS 54 [4] DSS 100[a]	100
Lee et al. [27]	21	Pd^{103}	36	38 [5]	ASTRO	OS 81 [5] DSS 100[a]	57
Tharp et al. [32]	7	HDR ± EBRT	58	71[a]	ASTRO	OS 71[a]	100
Aaronson et al. [17]	24	I^{125} (19) Pd^{103} (5)	30	88[a]	Phoenix	DSS 96[a]	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[a]	ASTRO	NR	45

Prospective studies needed to better define efficacy and toxicity

Ramey World J Urol 2013

Prostate

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

- 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

Prospective studies needed to better define efficacy and toxicity

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	11
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

	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

Scarcity of high-quality data!

De Ruysscher Lancet Oncol 2014

Breast

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

Sedlmayer The Breast 2013

Table 1
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	36	50 Gy + boost (not specified)	EBRT + boost (HDR)	12	38
Hannoun-Levi 2011	22	60 Gy	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 2012	17	50 + boost (not specified)	HDR	12	80
Deutsch 2002	39	50 Gy + boost not reported	EBRT	15	120
Kraus-Tiefenbacher 2007	17	62 Gy	EBRT	36	120
Total	**315**				

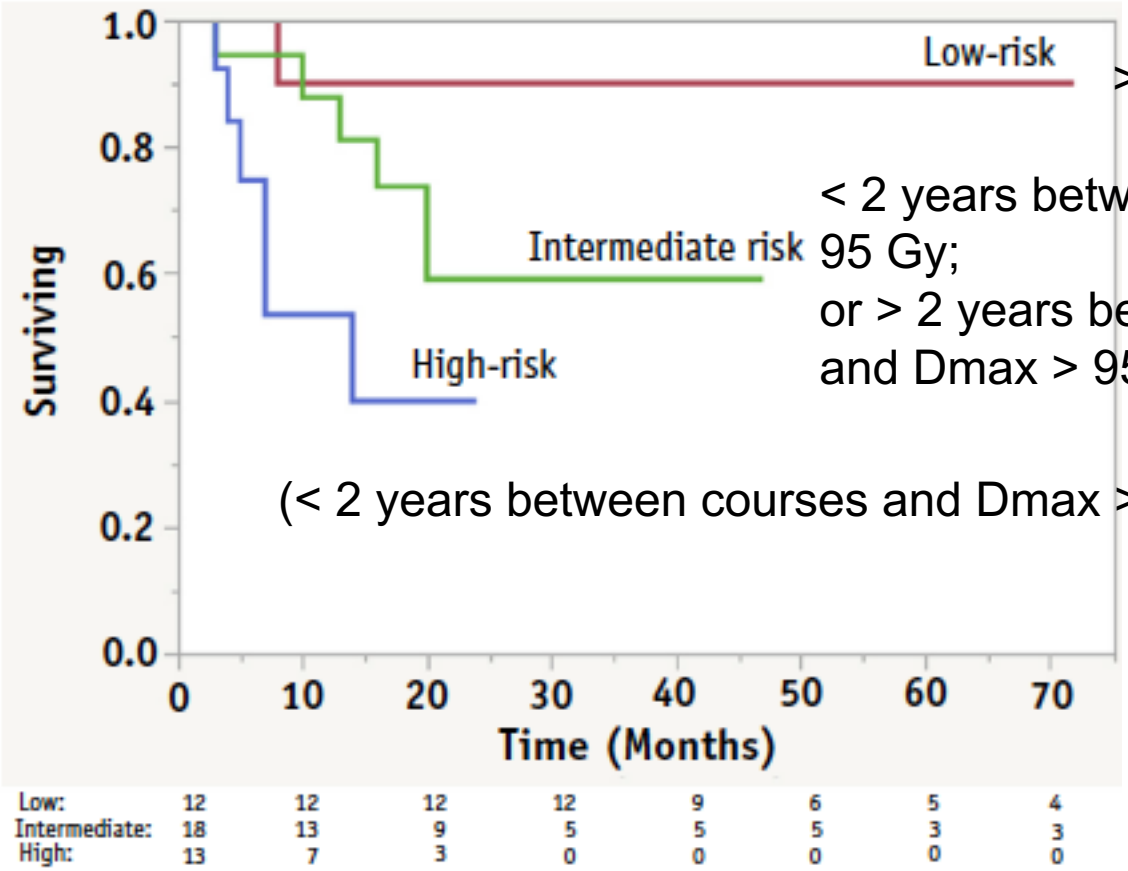
Evidence for brachytherapy more solid

Little info about effectiveness PBI via EBRT or IORT

Table 2
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

Dose tolerance of brachial plexus



> 2 years Dmax < 95 Gy

< 2 years between courses and Dmax > 95 Gy;
or > 2 years between radiation courses and Dmax > 95 Gy

(< 2 years between courses and Dmax > 95 Gy)

Chen et al. IJROBP 2017

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

Take home messages

- If tolerance has already been exceeded: no re-irradiation possible without loss of function

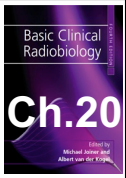
- Early effects
  - Low to moderate doses:
    - Restitution of original tolerance may be complete after tissue-specific and dose-dependent time intervals
  - High doses:
    - Residual damage may remain for longer intervals, particular at the stem cell level, which is not necessarily reflected in functional tissue compartments

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

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

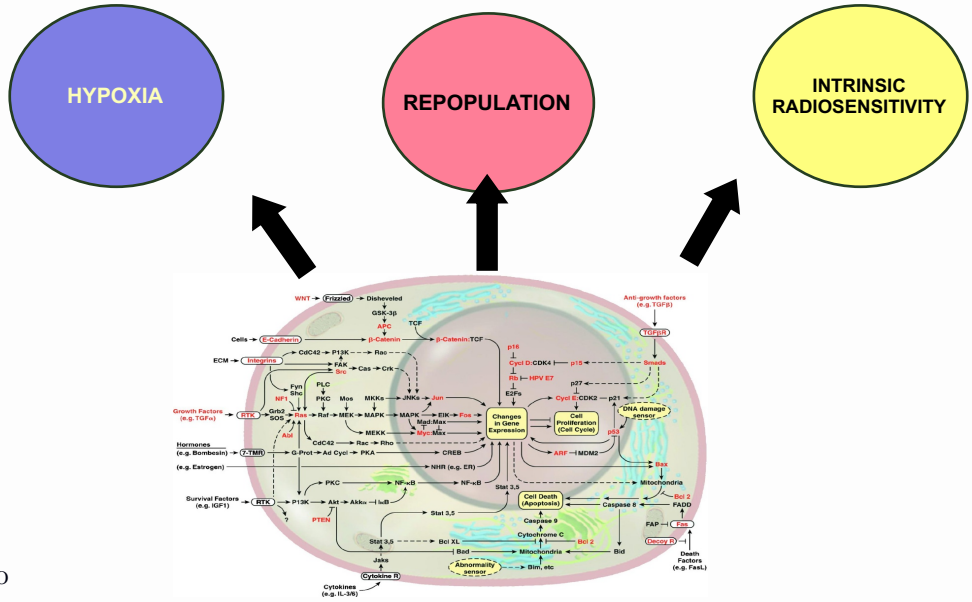


Molecular image guided radiotherapy

Vincent GREGOIRE, MD, PhD, Hon. FRCR

ESTRO 2017

Target pathways that influence radiotherapy



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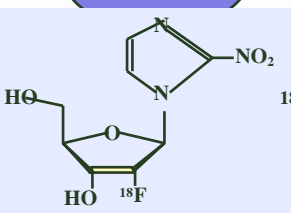
Target pathways that influence radiotherapy

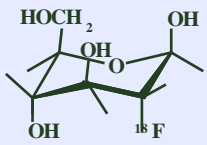
HYPOXIA

REPOPULATION

INTRINSIC RADIOSENSITIVITY

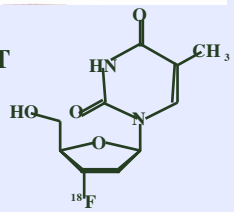


^{18}F-AZA



[^{18}F]FDG

[^{18}F]FLT



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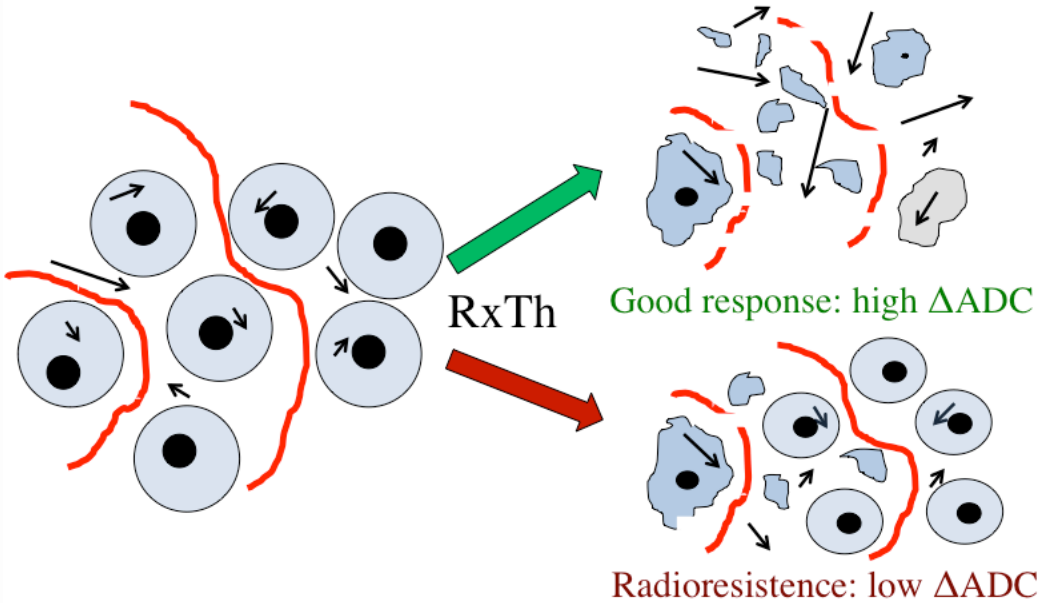
DW-MRI as surrogate of intrinsic radiosensitivity?



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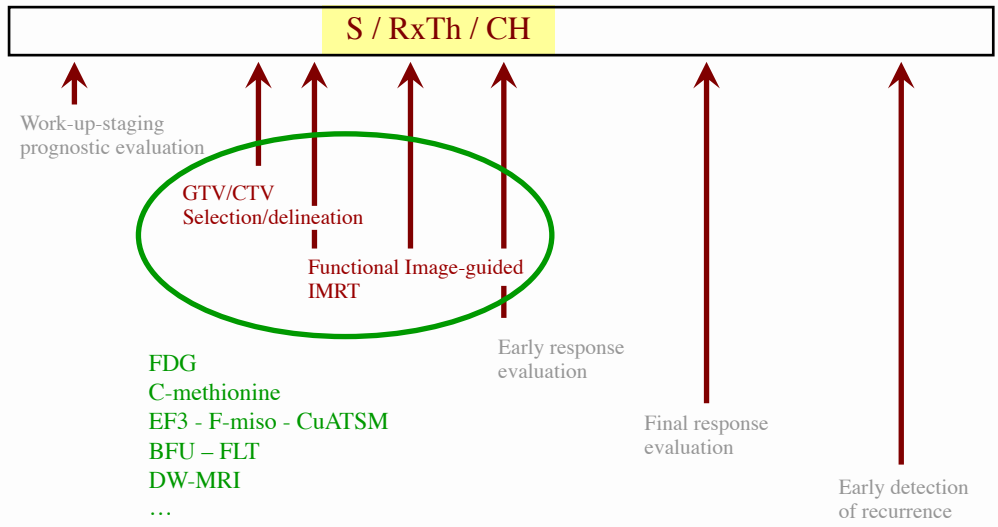
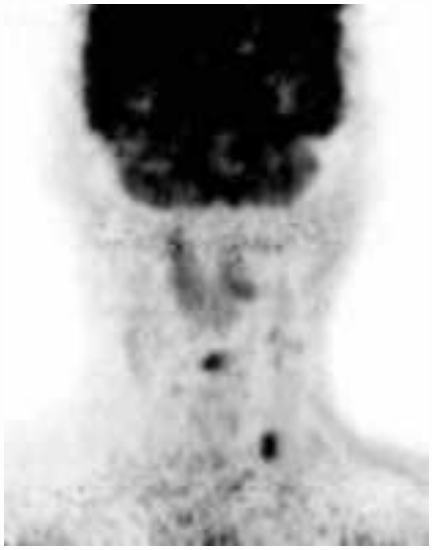
Courtesy of S. Nuyts

Potential added-value of Molecular Imaging in oncology



Could Molecular Imaging help identifying the disease?

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

ESTRO 2017

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,	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	32,36,40,43–47,49,50)	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,	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	44,47,48,51)	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.

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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

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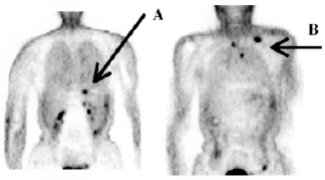
Poncelet et al. Eur J Cardiothorac Surg 2001;20:468-475
Pieterman et al. N Engl J Med 2000;343:254-261
Kernstine et al. Ann Thorac Surg 2002;73:394-402

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)

		Sensitivity		Specificity		Positive Predictive Value		Negative Predictive Value		
Study	Year	Value	95% CI	Value	95% CI	Value	95% CI	Value	95% CI	Prevalence
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

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Grégoire, 2004

Neck node staging
DW-MRI

Comparison of $ADC_{b0-1000}$ and TSE MR Findings Based on Lymph Node Size

	≥10 mm Lymph Nodes		4–9-mm Lymph Nodes	
Parameter	$ADC_{b0-1000}$	TSE MR	$ADC_{b0-1000}$	TSE MR
No. of true-positive findings	30	31	32	3
No. of false-positive findings	2	9	12	1
No. of true-negative findings	8	1	205	216
No. of false-negative findings	2	1	10	39
Sensitivity (%)	94	97	76	7
Specificity (%)	80	10	94	99.5
Accuracy (%)	90	76	92	85
PPV (%)	94	78	73	75
NPV (%)	80	50	95	85

Note.—PPV = positive predictive value.

Vandecaveye et al., Radiology 2009

Could Molecular Imaging help delineating the GTV?

Target

J. John, 1974

Target selection and delineation

Betrayal of images

This is not an apple…

R. Magritte

Image-Guided Radiation Therapy in NSCLC

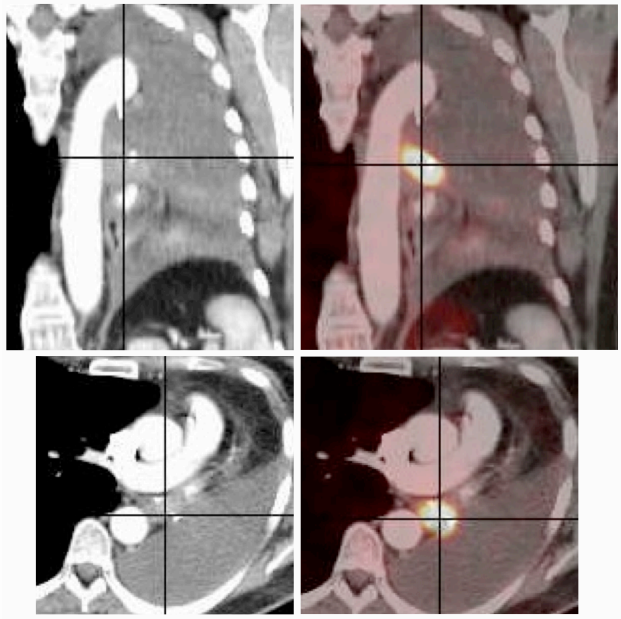

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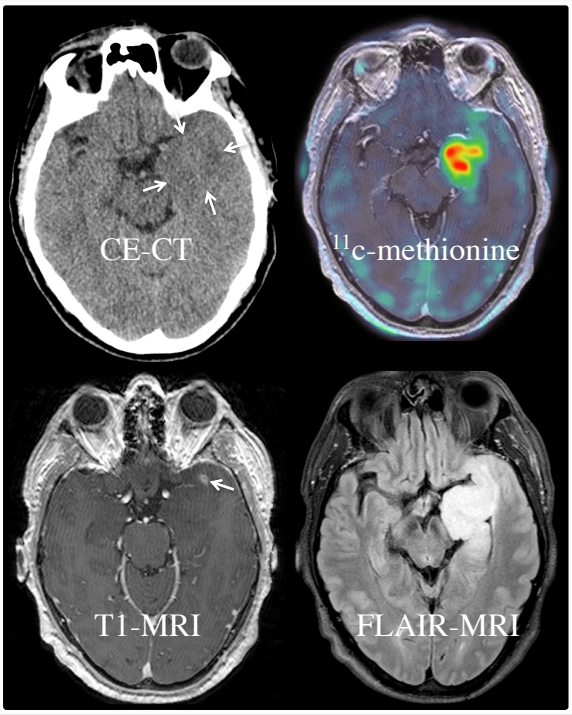
Image-Guided Radiation Therapy in grade III anaplastic astrocytoma



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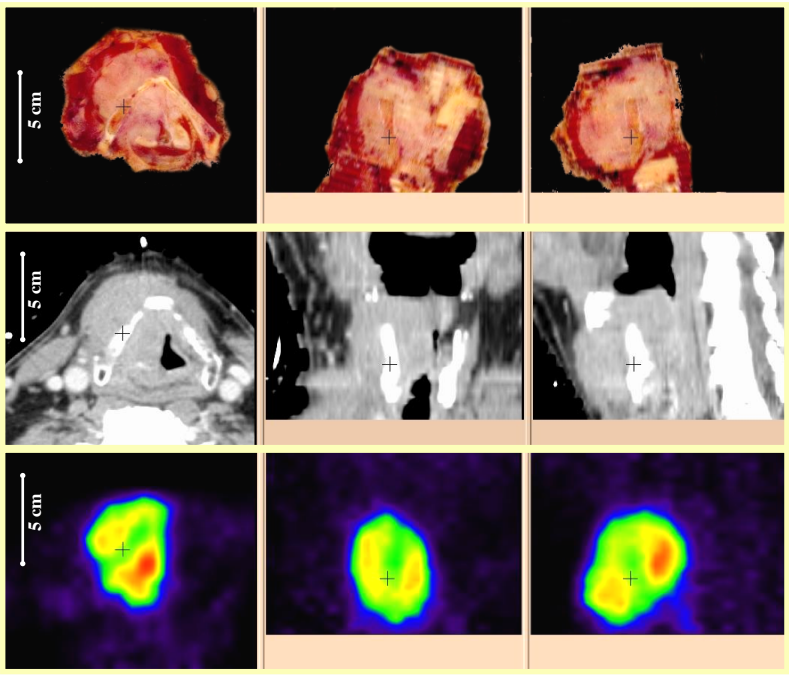
Courtesy of L. Renard



Macroscopy

CAT Scan

^{18}F-FDG PET

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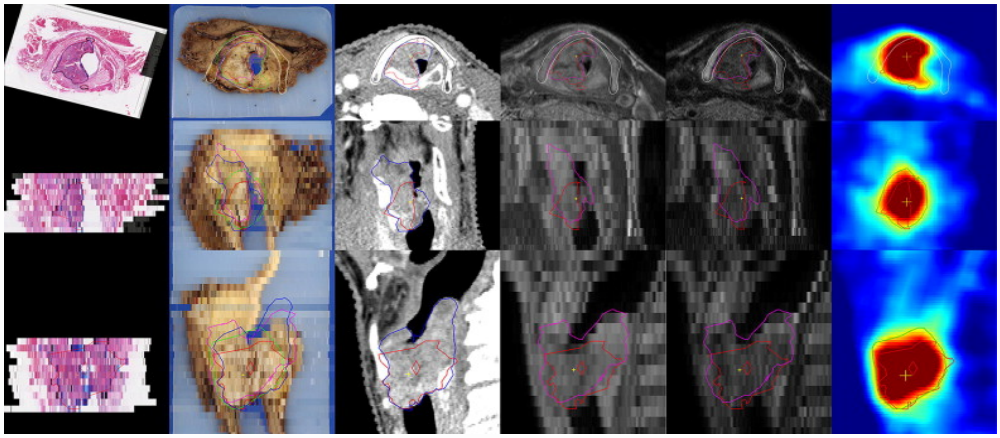
Daisne *et al*, 2004

The "ground truth" GTV



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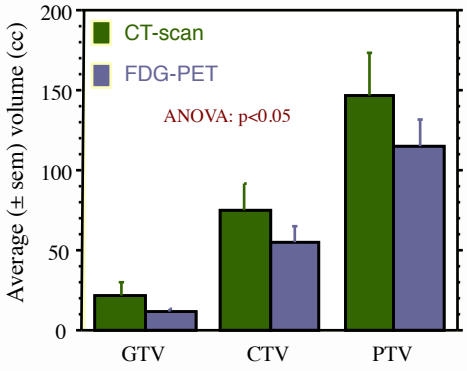
Caldas-Magalhaes, IJROBP, 2012

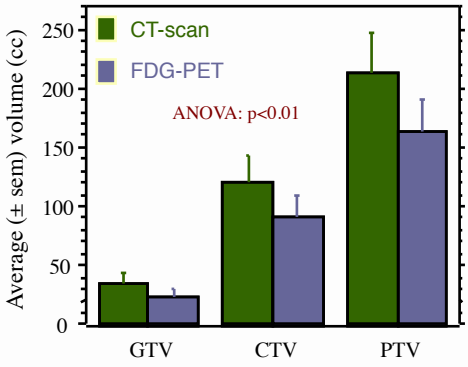
Image-Guided Radiation Therapy in HNSCC

Impact of imaging modality on CTV/PTV delineation

Larynx/hypopharynx (n=9)



Oropharynx (n=10)

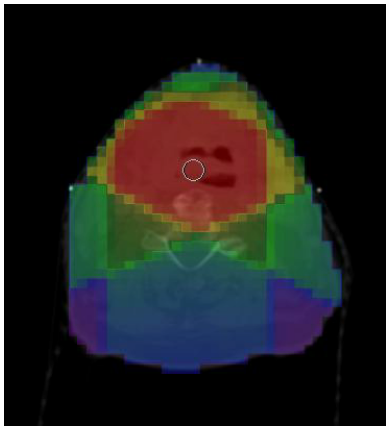


Geets *et al*, 2003

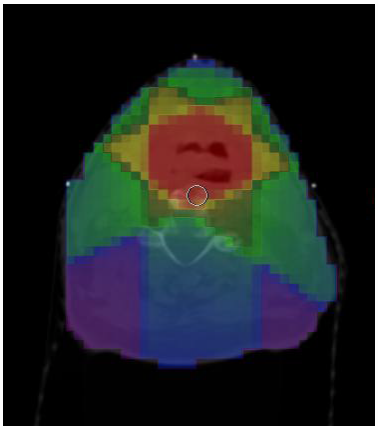
Image-Guided Radiation Therapy in HNSCC

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

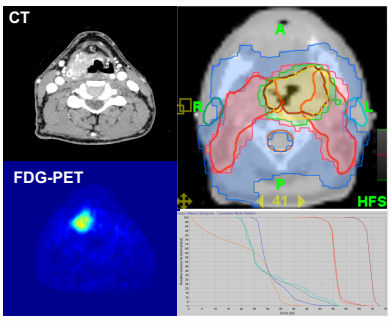
Primary objective of the study

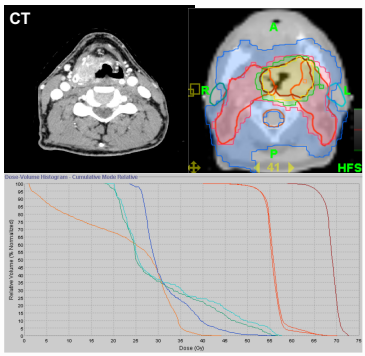
To evaluate the feasibility and safety of the use of FDG-PET for primary tumor GTV delineation in locally advanced H&N SCC patients treated by 3D-CRT and IMRT in a multicentric setting

Cliniques universitaires St-Luc, Brussels, Belgium
Centre Oscart Lambret, 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

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

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

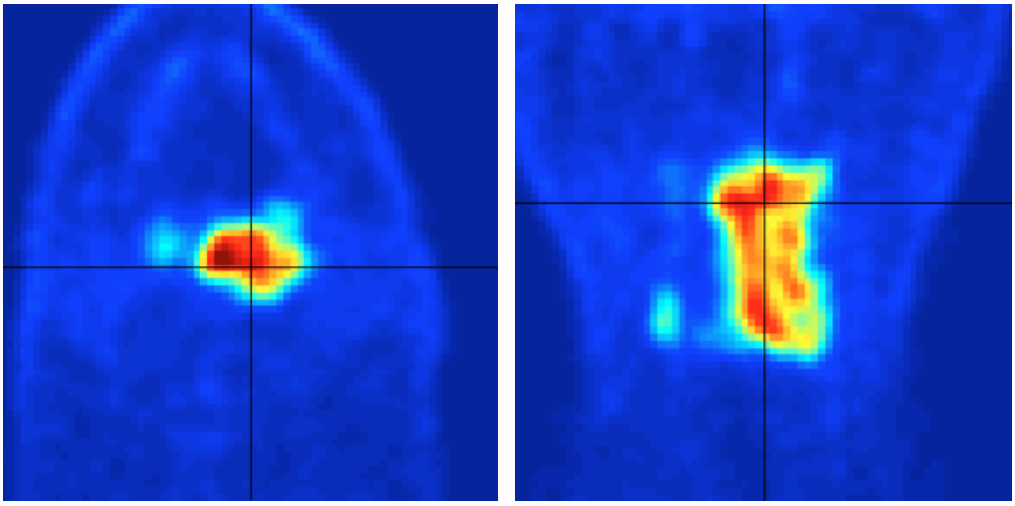
Molecular Imaging across the board

- Lung carcinoma: more accurate delineation of the NSCLC GTV with FDG-PET
- Esophageal tumor: no convincing data for FDG-PET
- Brain tumor: ^{11}C-Met in low grade glioma and meningioma
- Rectal tumor: promising data with FDG-PET, but clinical usefulness still unknown
- Cervix carcinoma: FDG-PET for delineation of mombo-aortic node GTV
- Prostate carcinoma: ^{11}C-choline for recurrent disease; MRI and DW-MRI for GTV delineation

Could Molecular Imaging help identifying tumour heterogeneity?

Dose-painting by number (DPBN)

SCC oropharynx: T4b-N0-M0



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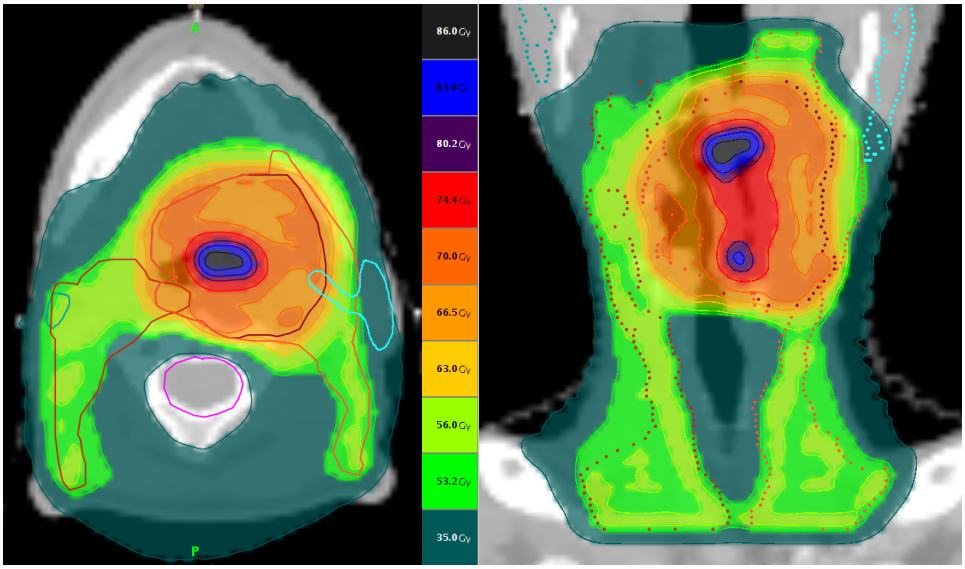
Courtesy of S. Differding, 2012

Dose-painting by number (DPBN)

SCC oropharynx: T4b-N0-M0



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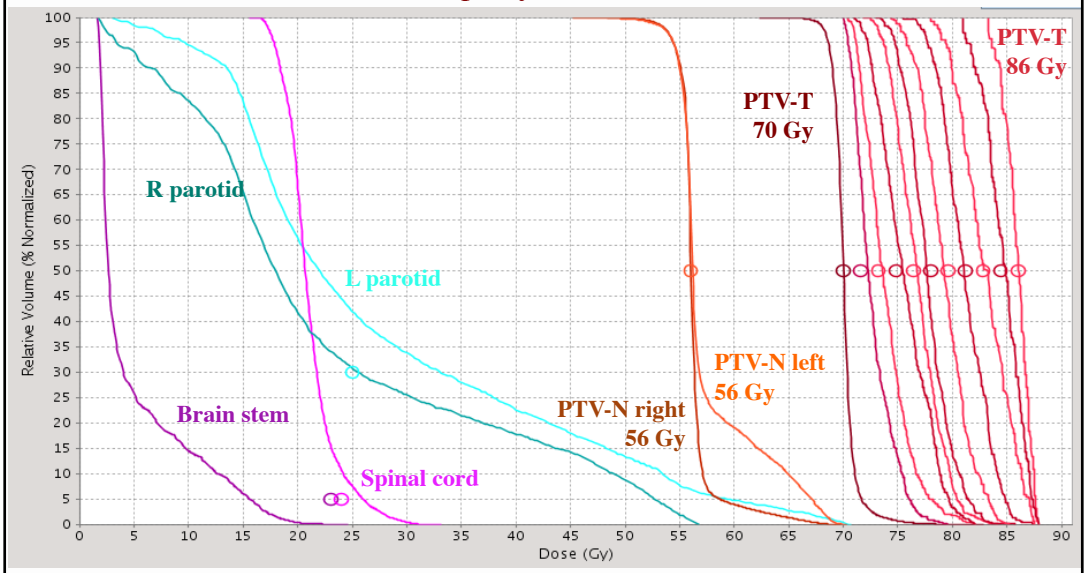
Courtesy of S. Differding, 2012

Dose-painting by number (DPBN)

SCC oropharynx: T4b-N0-M0



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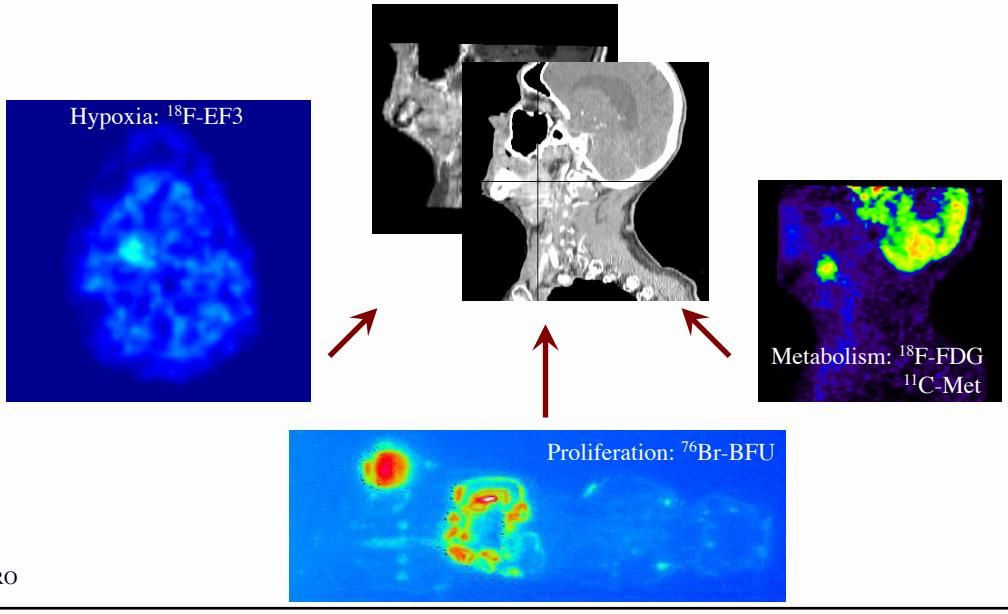
Courtesy of S. Differding, 2012

Which biological pathways? …



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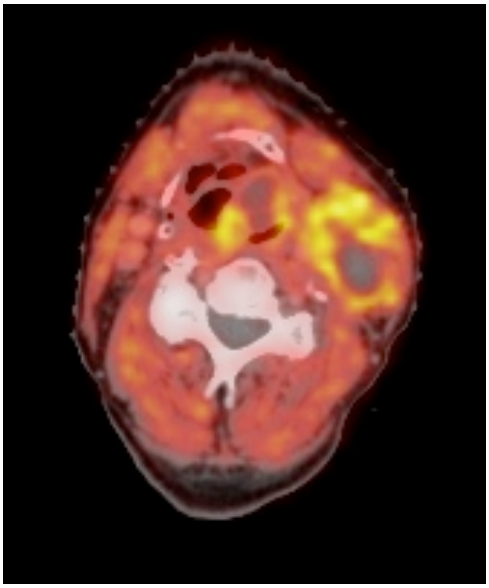
Hypoxic tracer ^{18}FAZA



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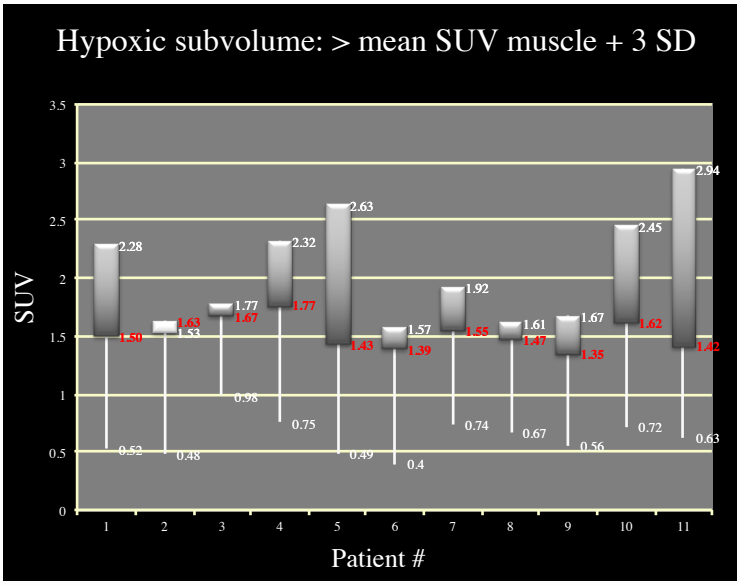
2017

^{18}F-AZA image segmentation



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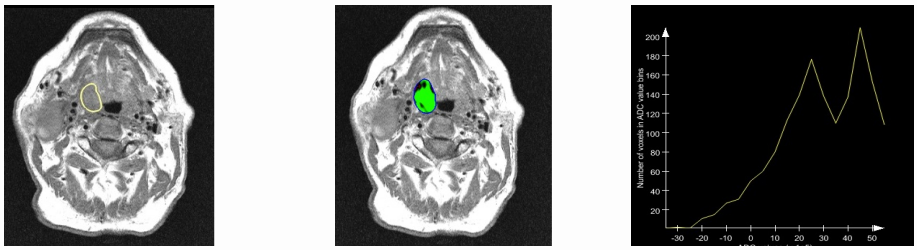
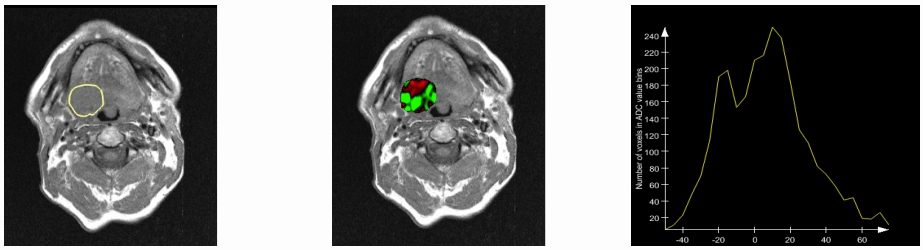
S. Servagi, 2013

Δ ADC during RT: result

2 weeks: ΔADC: +27%: no LR



2 weeks ΔADC: +9%: LR



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Courtesy of S. Nuyts

Randomized trials on dose painting / dose escalation in locally advanced HNSCC

Acronym	Stage	Molecular imaging	Design	Due date
Xuzhou Medical College, China	III-IV§	F-Miso PET and FDG-PET	RT-CH >< dose escalation on FDG >< dose escalation on F-Miso	Dec J015?
De Neve*	II-IV	FDG-PET	69 Gy IMRT >< 84 Gy IMRT	Q1 2018
Eisbruch*	III-IV	DCE-MRI	70 Gy + carbo/cddp >< 80 Gy + carbo/cddp	Dec 2020
INTELHOPE*	III-IV	FDG-PET	66 Gy + cddp >< 73.5 Gy + cddp	Dec 2020
Zips*	III-IV	F-Miso PET	70 Gy + CH >< 77 Gy +CH	Dec 2022
Escalox (Munich)	III	F-Miso PET	70 Gy + CDDP (w1, w5) >< 80.6 Gy + CDDP (w1, w5)	> July 2015

§ nasopharyngeal carcinoma
* randomized phase-II

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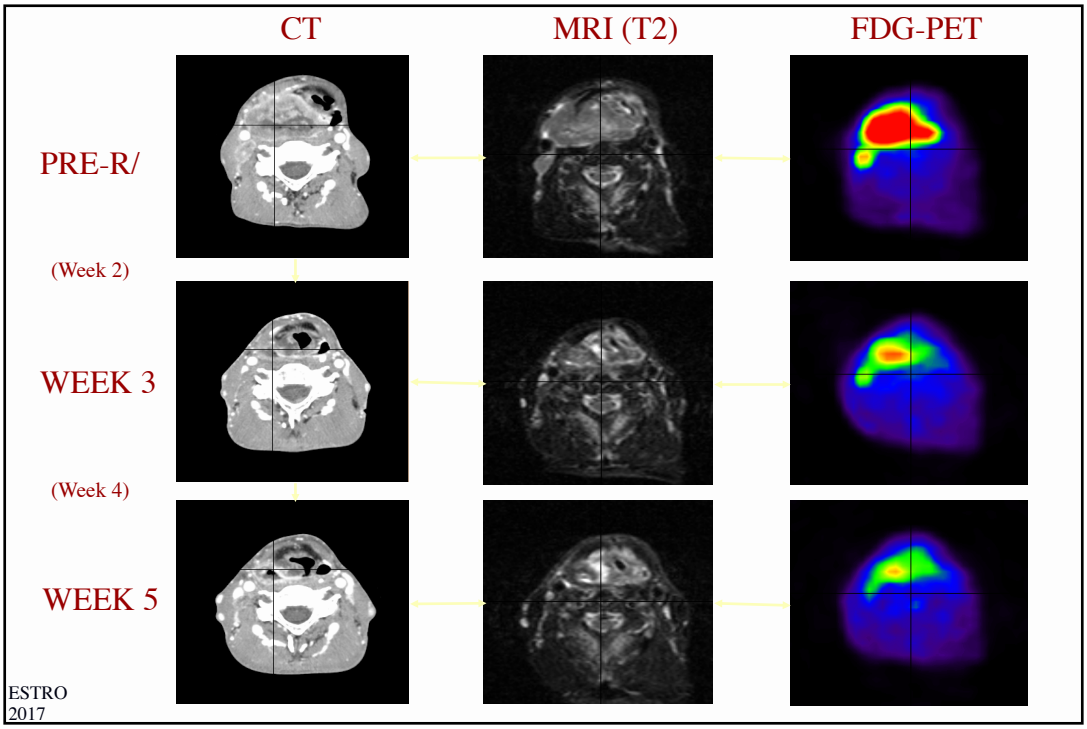
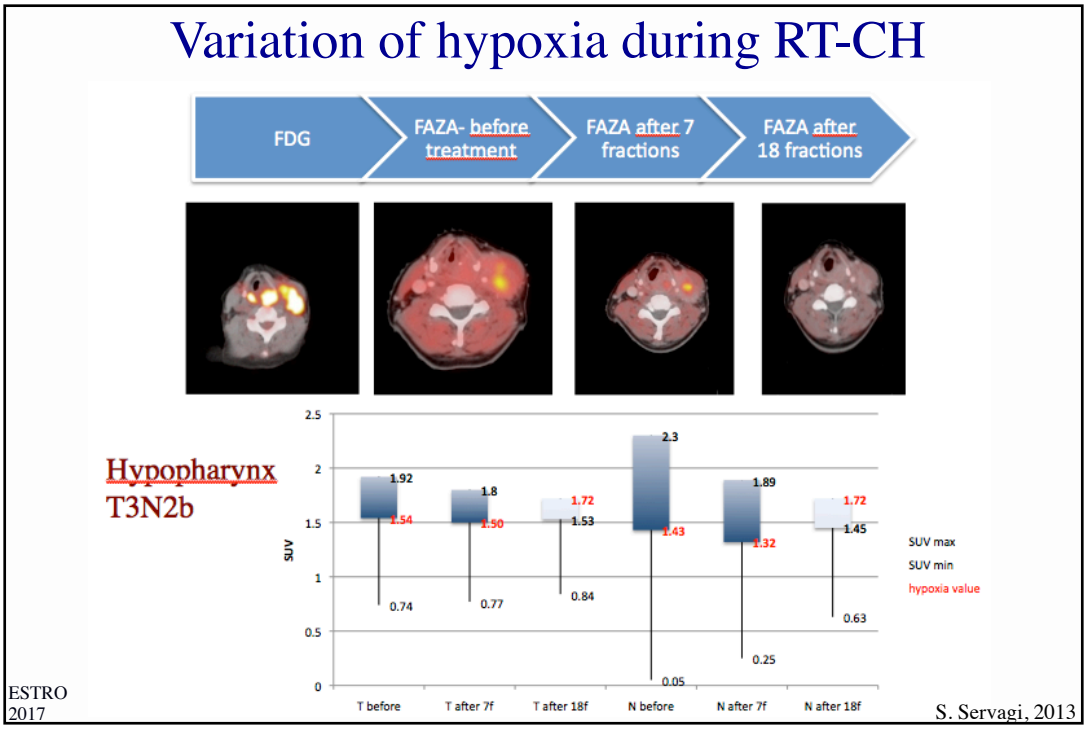
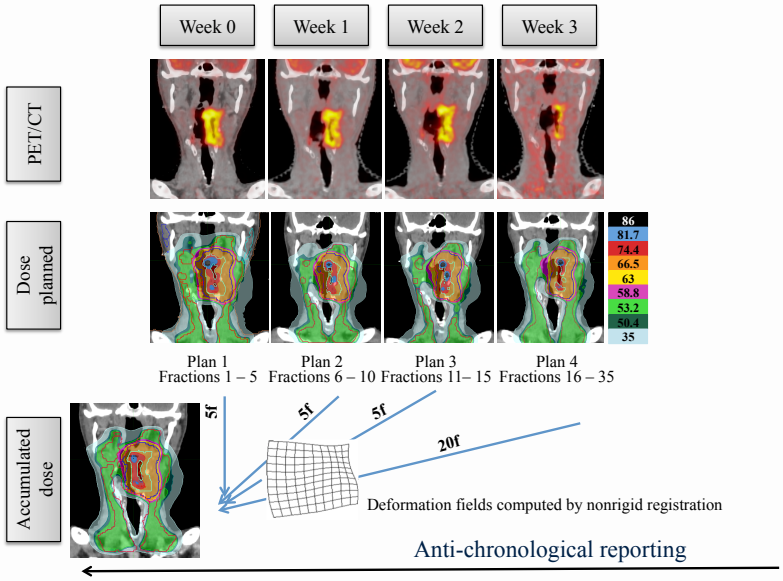
ClinicalTrials.gov, April 2017



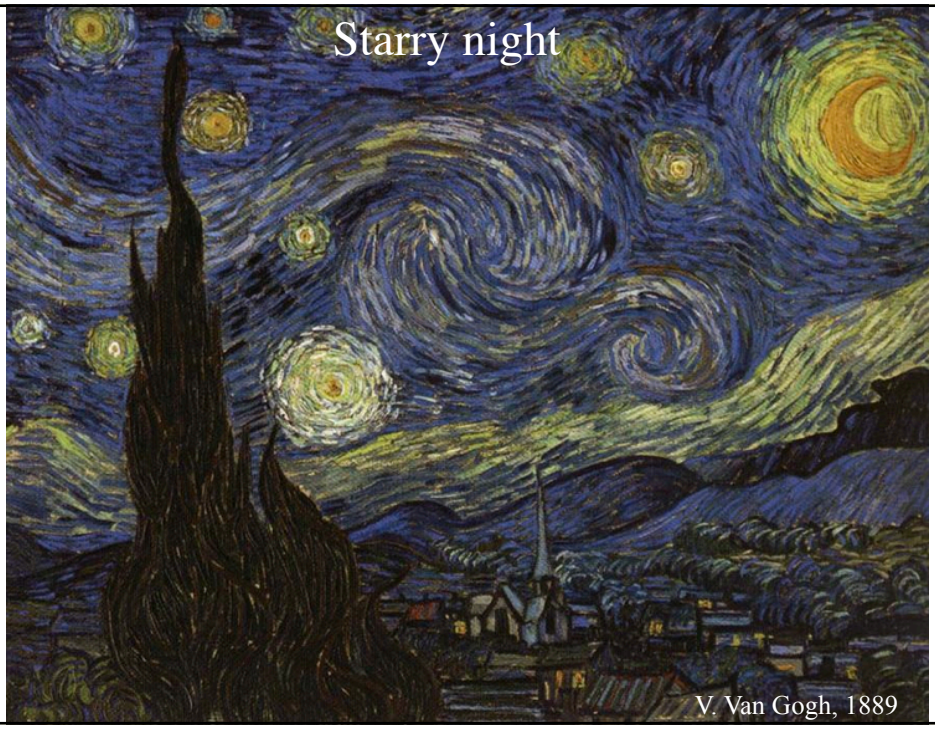
Variation of hypoxia during RT-CH



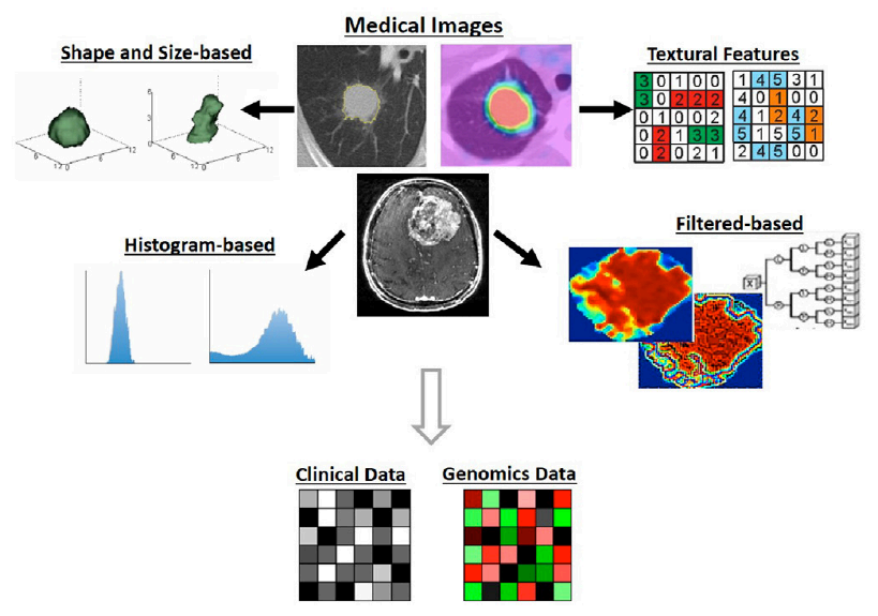
Time dependence



Differding & Grégoire, 2015



Radiomics for treatment individualization



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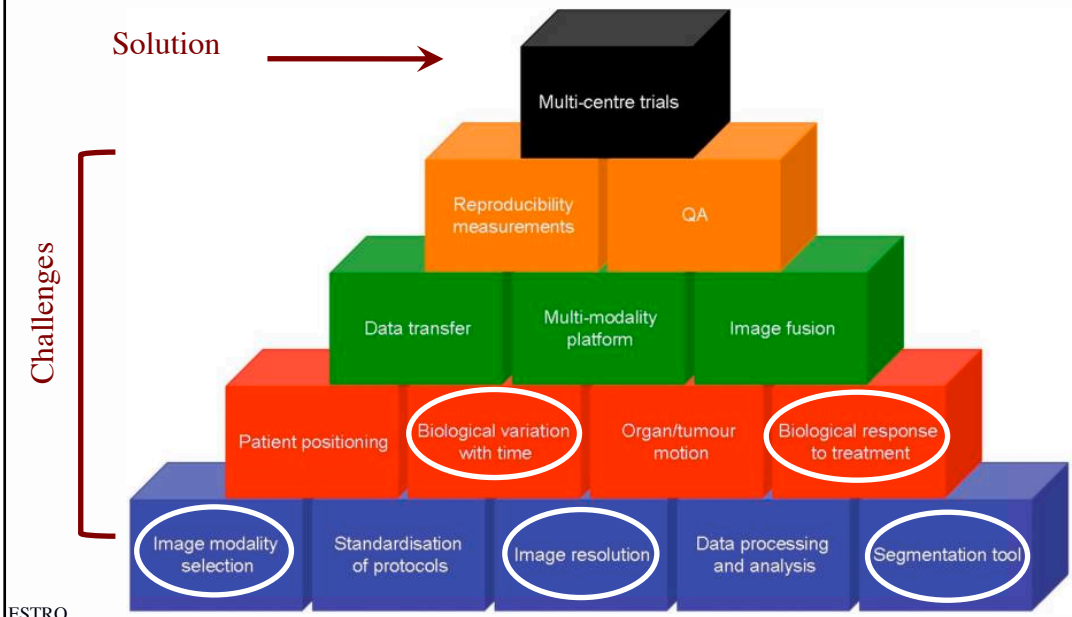
Yip, PMB, 2016

Molecular imaging in radiotherapy planning



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Newbold, 2012

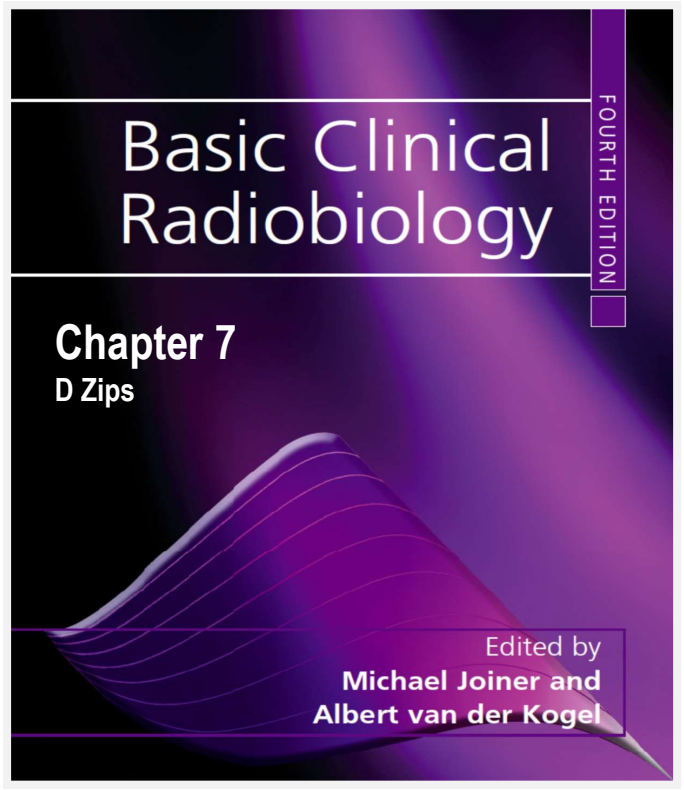
Tumor growth and response to irradiation

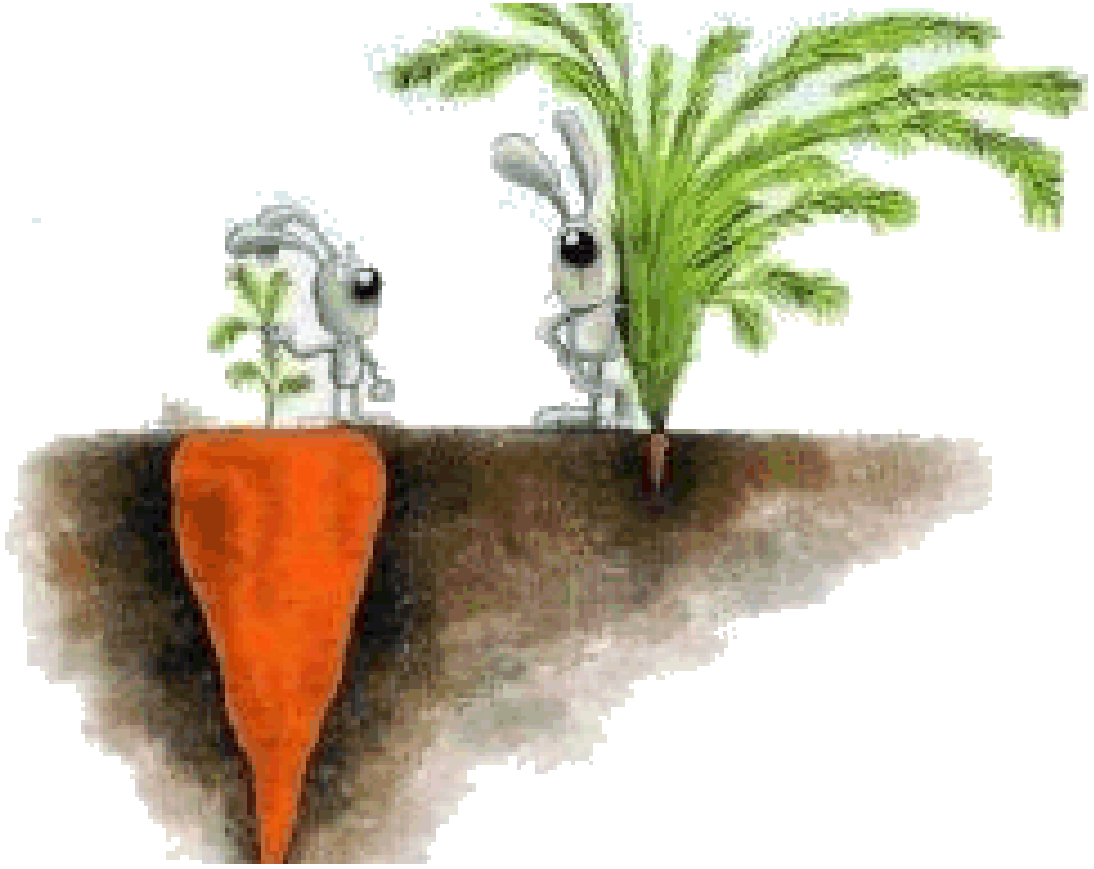
Karin Haustermans

Department of Radiation Oncology, University Hospitals Leuven, Belgium

Overview

- Tumor growth
- Tumor response to radiation
- Factors influencing local tumor control
- Take home messages





Tumor growth

Tumor growth

- Disturbed tissue homeostasis, driven by functional capabilities aquired during tumorigenesis

Hanahan and Weinberg, Cell 2011

Exponential and non-exponential growth

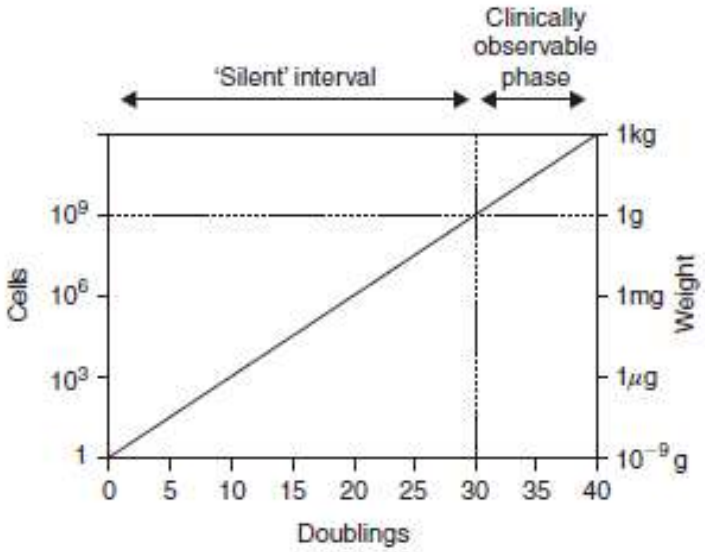


Figure 7.1 Relationship between the number of doublings from a single cell and the number of resulting cells in a tumour. To calculate the tumour weight, a cell number of 10^9 per gram was assumed. The clinically observable phase represents a minor part in the history of the tumour. Tumour weight is plotted on a logarithmic scale. If the doubling time is constant, a straight line indicates exponential tumour growth.

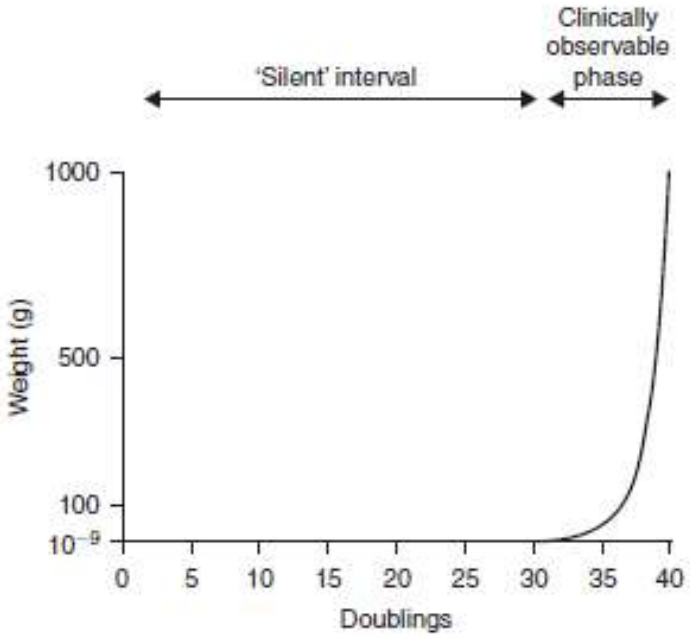


Figure 7.2 The same data as used for Fig. 7.1 but tumour weight is plotted on a linear scale. This may lead to the erroneous impression that tumour growth accelerates during the clinically observable phase.

Definitions

- Tumor volume doubling time (VDT): time required for tumor to double its volume
- Growth fraction (GF): cells in the compartment of actively dividing cells
- Cell-cycle time (Tc): time required to complete the cell cycle
- Ts: duration of S-phase
- Potential doubling time (Tpot): cell doubling time without any cell loss (Tpot = Tc/GF)
- Cell loss factor (CLF): tumor cell loss during growth

  (CLF = 1 – Tpot/VDT)

Volume doubling time

- Tumor growth rate varies considerable between tumors
- Tumors grow fast if growth fraction is high, cell-cycle time short and cell loss low

Basic clinical radiobiology

Table 7.1 Volume doubling times (VDTs) for human tumours taken from a review of early data on the growth rate of human tumours

Site and histology	Number of tumours measured	Mean VDT* (days)	Confidence limits (days)
Lung metastases			
Colon–rectum, adenocarcinoma	56	95	84–107
Breast, adenocarcinoma	44	74	56–98
Kidney, adenocarcinoma	14	60	37–98
Thyroid, adenocarcinoma	16	67	44–103
Uterus, adenocarcinoma	15	78	55–111
Head and neck, squamous cell carcinoma	27	57	43–75
Fibrosarcoma	28	65	46–93
Osteosarcoma	34	30	24–38
Teratoma	80	30	25–36
Superficial metastases			
Breast carcinoma	66	19	16–24
Primary tumours			
Lung, adenocarcinoma	64	148	121–181
Lung, squamous cell carcinoma	85	85	75–95
Lung, undifferentiated	55	79	67–93
Colon–rectum	19	632	426–938
Breast	17	96	68–134

*Geometric mean.

Data from Steel (1977).

Growth fraction

Table 7.2 Growth fractions determined by Ki67 labelling for different human tumour types

Tumour type and site	Mean/Median Ki67 LI (%)	Ki67 LI (% range)	Reference
Prostate	8.5	1–28.4	Taftachi *et al.* (2005)
Central nervous system:			
Meningeoma	4.4	0–58	Roser *et al.* (2004)
Astrocytoma	21.5	0–47.3	Rautiainen *et al.* (1998)
Head and neck	27.8	8.2–80.8	Roland *et al.* (1994)
Colorectal	37.2	18.9–71.4	Lanza *et al.* (1990)
Breast	31.6	0–99	Thor *et al.* (1999)
Lung (non-small cell)	36.7	0–93	Hommura *et al.* (2000)
Pancreas	29.7	0.5–82.1	Linder *et al.* (1997)
Soft-tissue sarcoma	12	1–85	Jensen *et al.* (1998)
Renal cell carcinoma	11	0–43	Haitel *et al.* (1997)
Bladder	35	3–55	Hoskin *et al.* (2004)
Oesophagus	33	6–95	Sarbia *et al.* (1996)

LI, labelling index.

Cell cycle kinetics

Table 7.4 Cell kinetic parameters of human tumours derived from *in vivo* labelling with iododeoxyuridine (IdUrd) or bromodeoxyuridine (BrdUrd) and measured by flow cytometry

Site	Number of patients	LI (%)	T_S (hours)	T_{pot} (days)
Head and neck	712	9.6 (6.8–20.0)	11.9 (8.8–16.1)	4.5 (1.8–5.9)
Central nervous system	193	2.6 (2.1–3.0)	10.1 (4.5–16.7)	34.3 (5.4–63.2)
Upper intestinal	183	10.5 (4.9–19.0)	13.5 (9.8–17.2)	5.8 (4.3–9.8)
Colorectal	345	13.1 (9.0–21.0)	15.3 (13.1–20.0)	4.0 (3.3–4.5)
Breast	159	3.7 (3.2–4.2)	10.4 (8.7–12.0)	10.4 (8.2–12.5)
Ovarian	55	6.7	14.7	12.5
Cervix	159	9.8	12.8	4.8 (4.0–5.5)
Melanoma	24	4.2	10.7	7.2
Haematological	106	13.3 (6.1–27.7)	14.6 (12.1–16.2)	9.6 (2.3–18.1)
Bladder	19	2.5	6.2	17.1
Renal cell carcinoma	2	4.3	9.5	11.3
Prostate	5	1.4	11.7	28.0

Fraction of cells in S phase (LI), duration of S phase (T_S) and potential doubling time (T_{pot}) were taken from Haustermans *et al.* (1997) and Rew and Wilson (2000). Ranges (in parenthesis) represent variations in median values between studies; ranges for individual tumours are considerably larger.

Basic clinical radiobiology

Cell loss factor

- Tpot is much shorter than VDT!?

- Vast majority of newly produced cells are lost from the GF (e.g. by differentiation, necrosis, metastasis), explaining the slow growth rate of tumors

Cell loss factor

Table 7.5 Calculation of cell loss factors (CLFs) for human tumours based on labelling with radiolabelled thymidine or thymidine analogues and volume doubling times (VDTs) in separate series

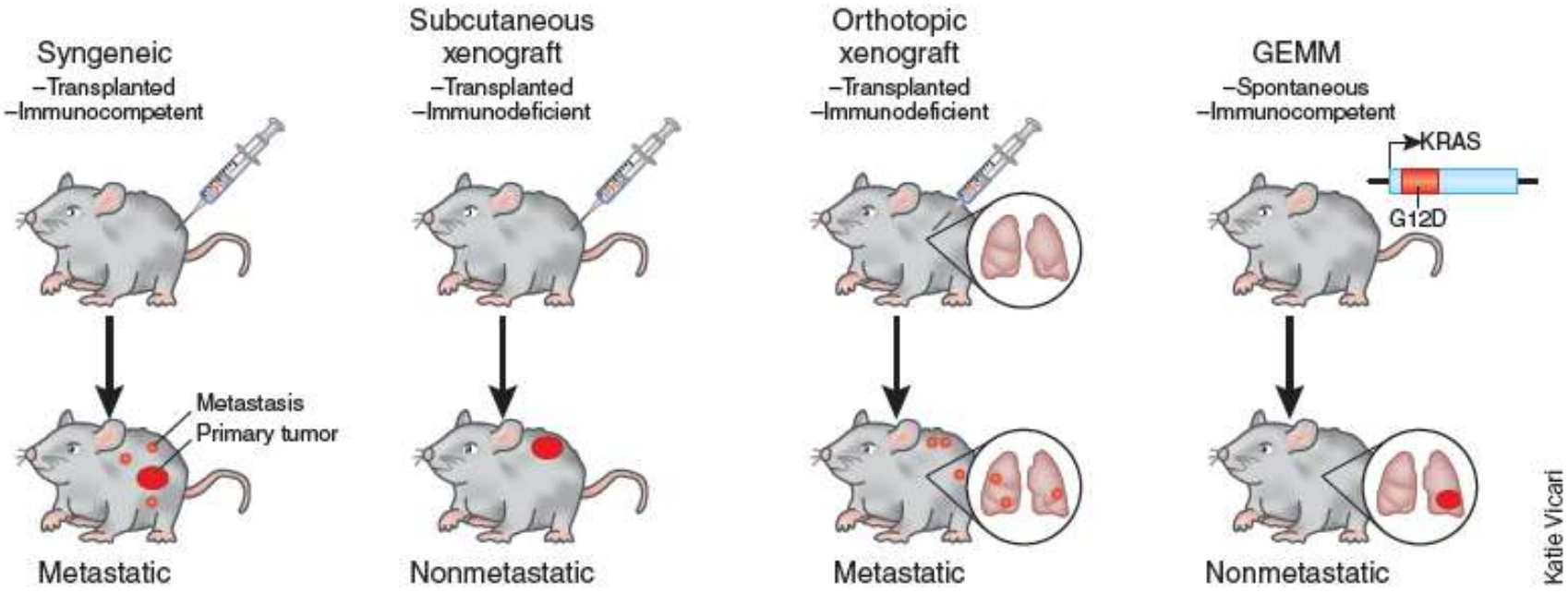
Site	LI (%)	T_{pot} (days)	VDT (days)	CLF (%)
Undifferentiated bronchus carcinoma*,[1]	19.0	2.5	90	97
Sarcoma*,[1]	2.0	23.3	39	40
Childhood tumours*,[1]	13.0	3.6	20	82
Lymphoma*,[1]	3.0	15.6	22	29
Head and neck**,[2]	9.6	4.1	45	91
Colorectal**,[2]	13.1	3.9	90	96
Melanoma**,[2]	4.2	8.5	52	84
Breast**,[2,3]	3.7	9.4	82	89
Prostate**[2,4]	1.4	28.0	1100	97

*,**Labelling with radiolabelled thymidine or thymidine analogues, respectively.
[1]From Steel (1977), calculations assume $T_S = 14$ hours, $\lambda = 0.8$.
[2]Fraction of cells in S phase (LI) and potential doubling time (T_{pot}) from Haustermans *et al.* (1997) and Rew and Wilson (2000); calculations assume $\lambda = 0.8$ (Steel, 1977).
[3]VDT values for pulmonary metastases from Spratt *et al.* (1996).
[4]VDT from PSA doubling times from Schmid *et al.* (1993), Fowler *et al.* (1994) and Lee *et al.* (1995).

Basic clinical radiobiology

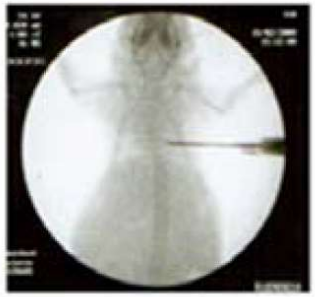
Tumor growth in animal models

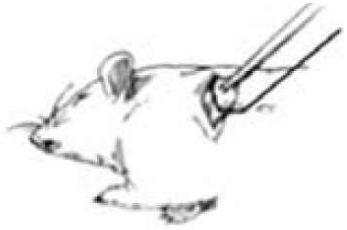
- Types of mouse model used to test new cancer therapies

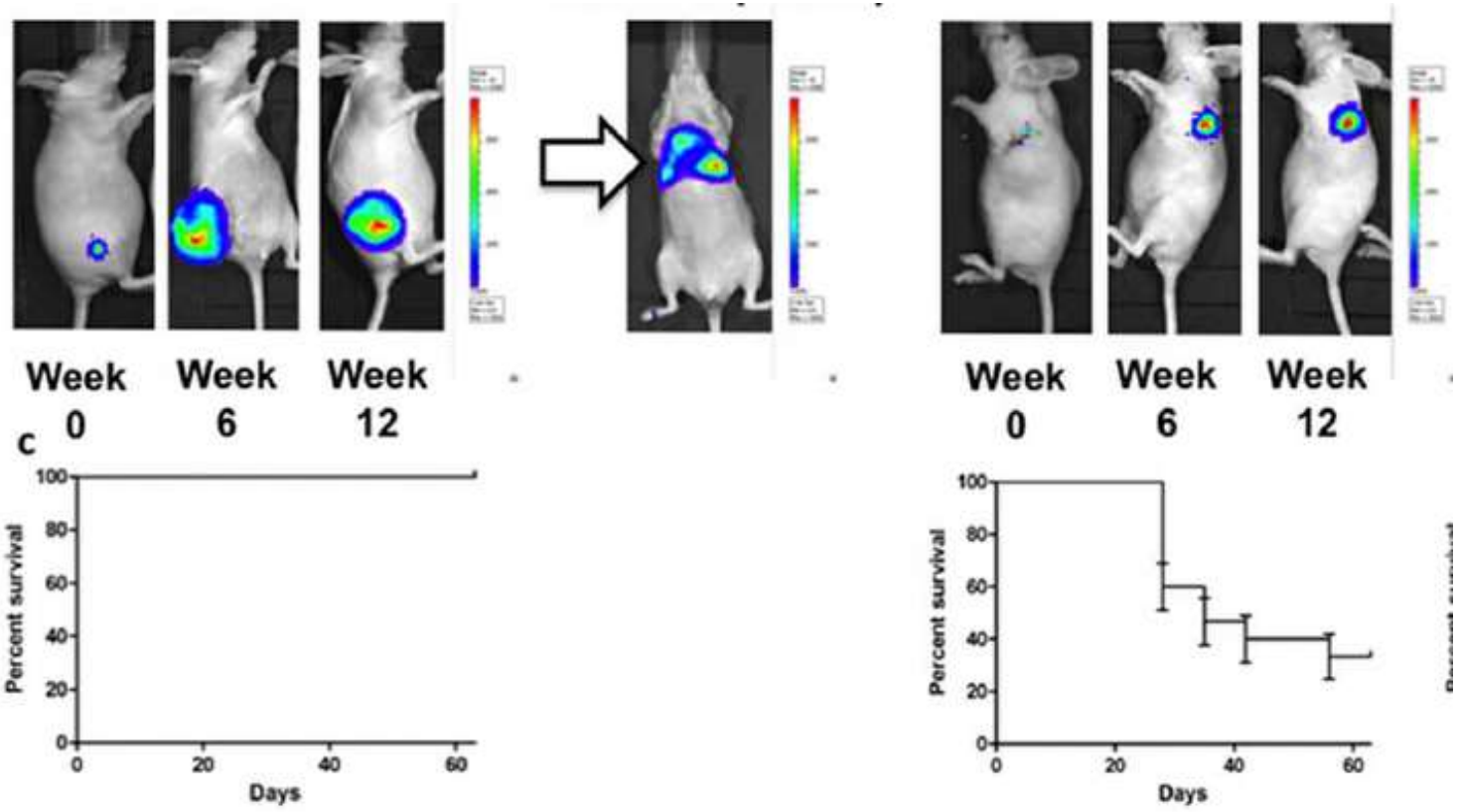


Francia et al Nat Biotech 2010

Orthotopic tumors: lung
bioluminescence imaging





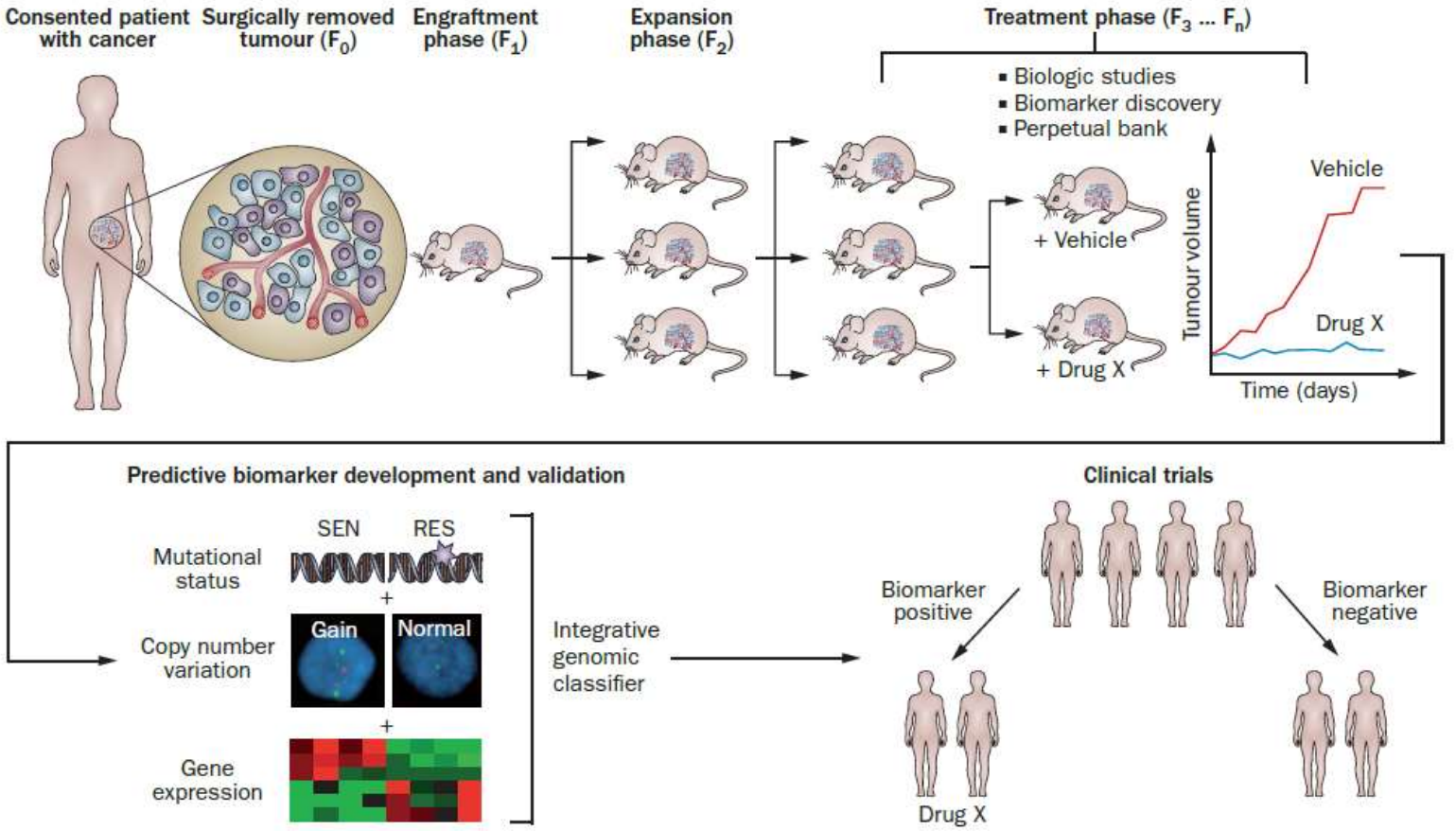


Mordant et al, Plos One 2011

Tumor growth in animal models

- Patient-derived xenografts

Tentler et al Nat Rev Clin Oncol 2012



Tumor response to radiation

Endpoints

- Tumor regression → non-specific endpoint
- Tumor regrowth delay → difficult or impossible to accurately estimate cell kill
- Local tumor control
  - Aim of curative RT → improvements in LC often translate into prolonged survival
  - When all clonogenic cells (i.e. cells with the capacity to proliferate and to cause recurrence after RT) have been inactivated

Clonogenic cell survival after RT

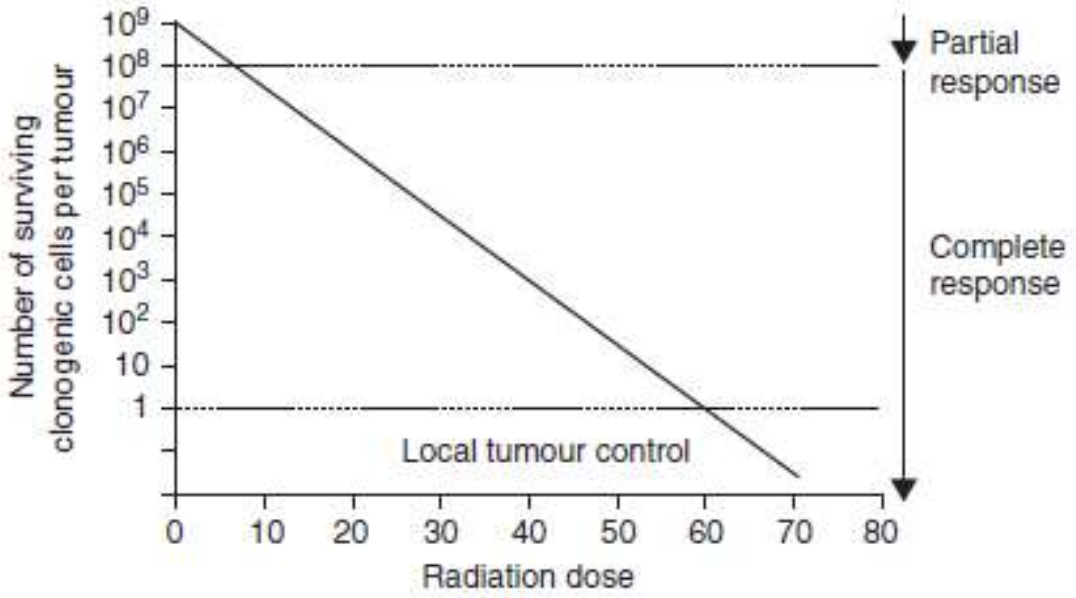


Figure 7.3 Relationship between clonogenic cell survival, radiation dose and different endpoints to assay tumour response, assuming a tumour consisting of 10^9 clonogenic cells and a surviving fraction after 2 Gy of 50 per cent.

Basic clinical radiobiology

Local tumor control

- TCP as a function of radiation dose – Poisson distribution
- Random distribution of radiation-induced cell kill within a population of clonogenic cells

1				1	2
2	3	1	2	1	
	1		2		1
1	1	2		4	1
1		1		3	1
	2	1	1		

Figure 7.4 A model tumour consisting of 36 clonogenic tumour cells (each square represents one clonogenic cell) after irradiation with a dose sufficient to inflict an average of one 'lethal hit' per clonogenic cell. Owing to random distribution of the 'lethal hits' among the tumour, some clonogenic cells received one (1), two (2), three (3) or four (4) lethal hits. These cells subsequently die (grey shadow). According to Poisson statistics (SF = $exp(-m)$, see text) 37 per cent of the clonogenic cells (i.e. a total of 13 cells (received no 'lethal hit' and survived white background). The tumour control probability (TCP) after this 'treatment' can be calculated as TCP = $exp(-13) = 2.3 \times 10^{-7}$. This means that only 1 out of 23 million tumours will be locally controlled in this situation. In Table 7.6 and Fig. 7.5, the dose effects on surviving cell fraction (SF) and TCP are illustrated.

Local tumor control

Table 7.6 Relationship between radiation dose, fraction of surviving clonogenic tumour cells (SF) and local tumour control probability (TCP) according to Poisson statistics for the 'treatment' of a model tumour consisting of 36 clonogenic tumour cells.

Radiation dose (relative units)	Number of 'lethal hits' per clonogenic cell (m)	SF = $\exp^{(-m)}$ (%)	Number of surviving clonogenic tumour cells (N = SF × 36)	TCP = $\exp^{(-N)}$ (%)
1	36/36 = 1	37	13	<0.0001
2	72/36 = 2	14	5	1
3	108/36 = 3	5	2	17
4	144/36 = 4	1.8	0.7	52
5	180/36 = 5	0.7	0.2	78
6	216/36 = 6	0.25	0.09	91
7	252/36 = 7	0.09	0.03	97
8	288/36 = 8	0.03	0.01	99

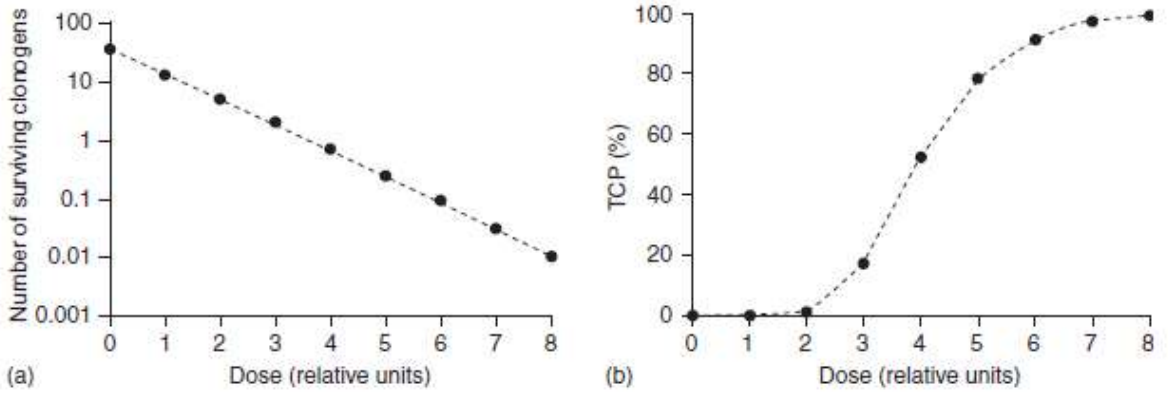
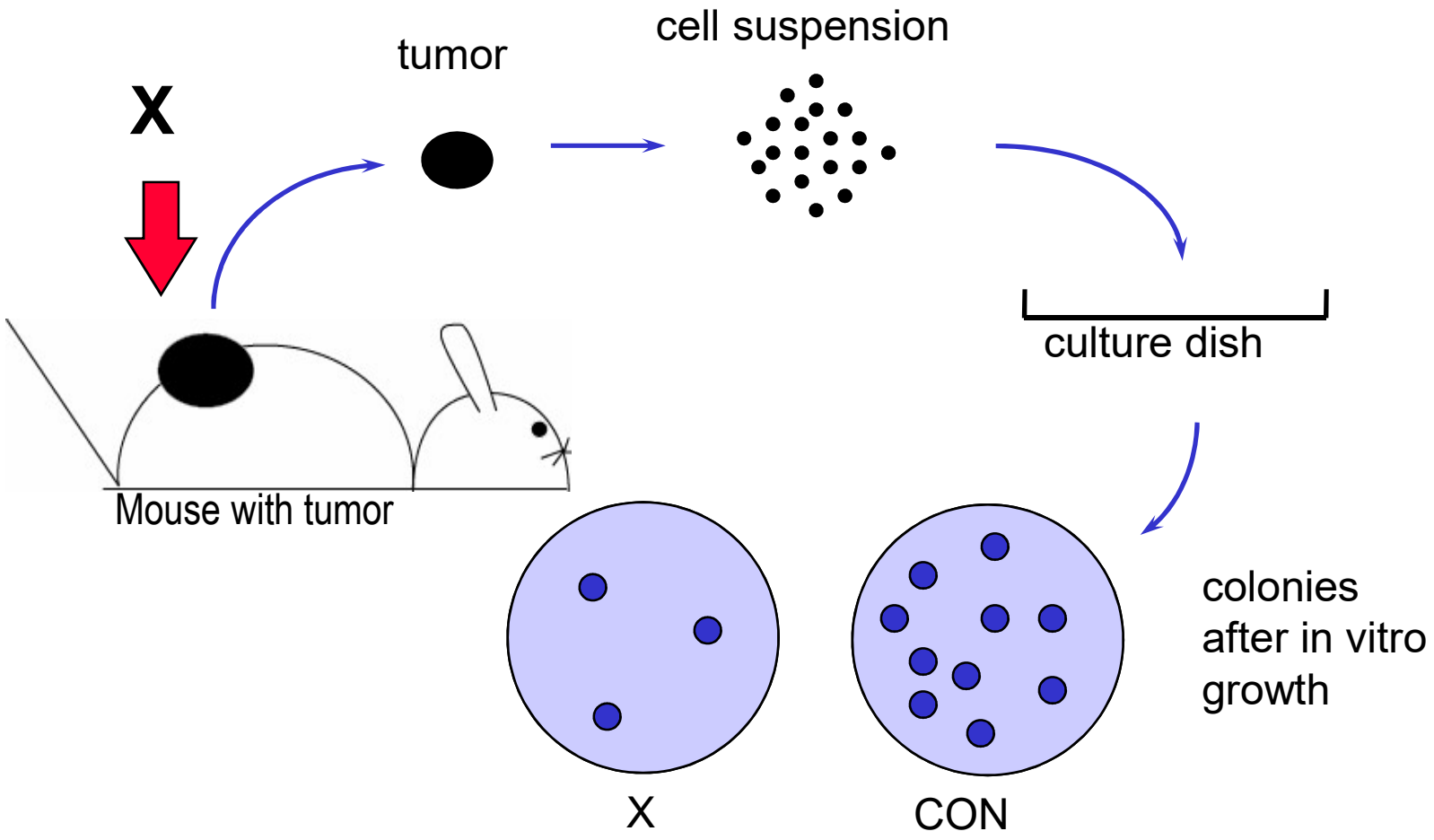


Figure 7.5 Illustration of the 'treatment effects' on the model tumour consisting of 36 clonogenic cells (compare Fig. 7.4 and Table 7.6). Values for the number of surviving clonogens and tumour control probability (TCP) were taken from Table 7.6.

Ex-vivo assays

- 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.

Clonogenic cell survival: ex vivo

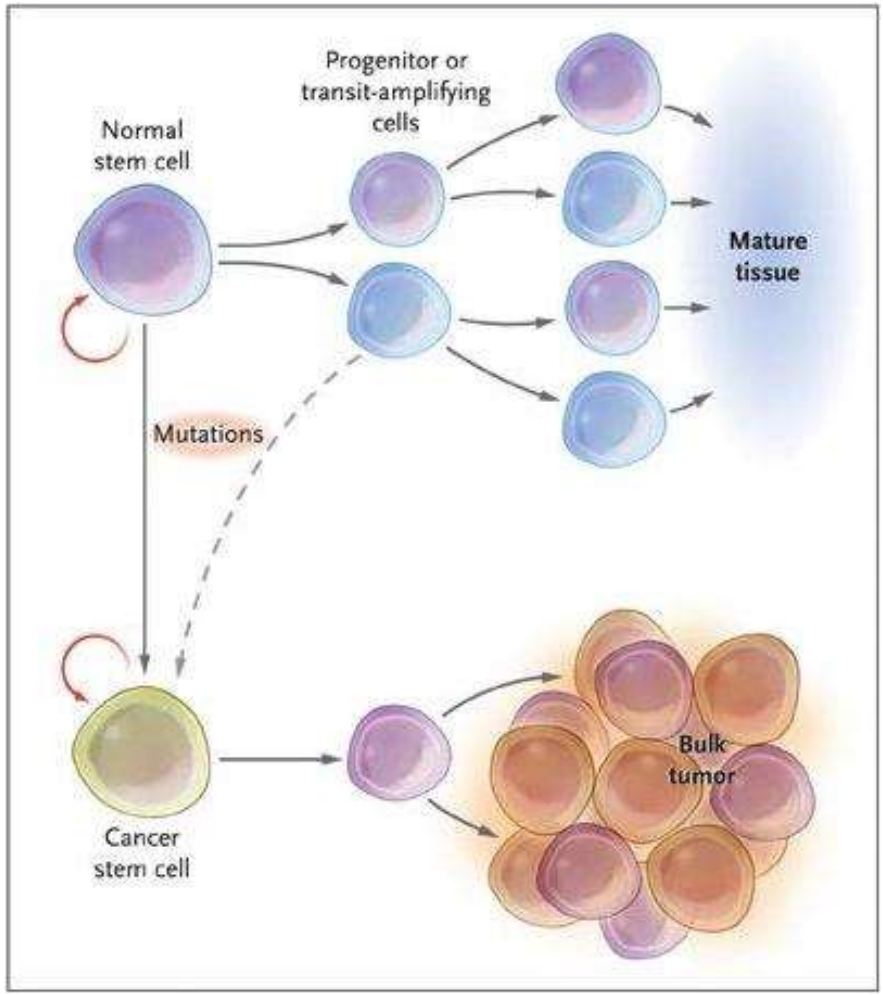


Ex-vivo assays

- 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 and vascularisation

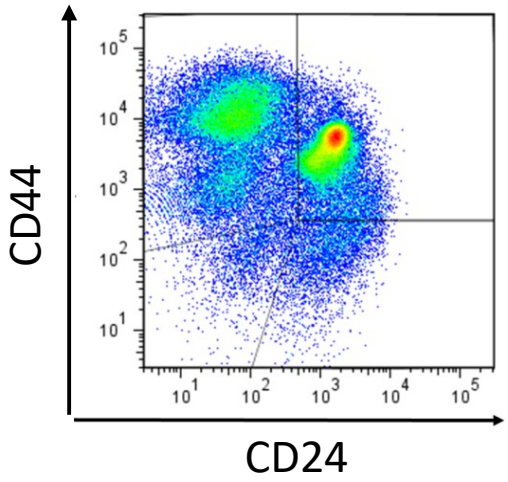
Cancer Stem Cells (CSCs)

- 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

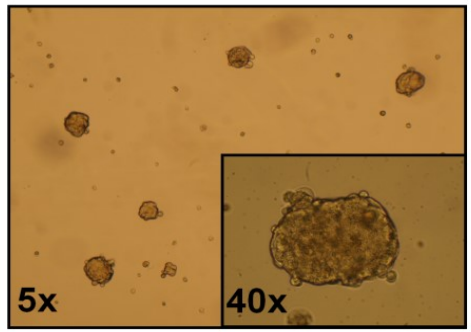


Jordan et. al. NEJM 2006

Measuring CSC content

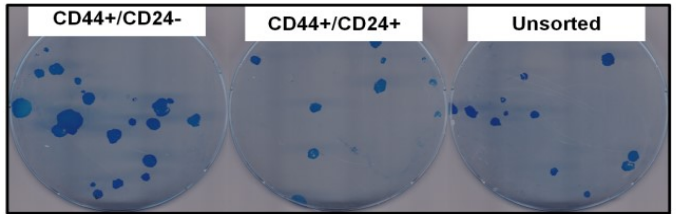


B

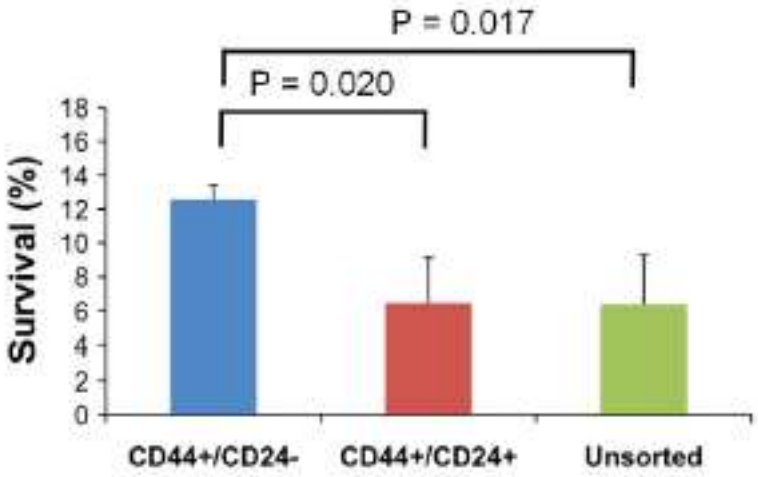


Stem Cells

C



Clonogenics



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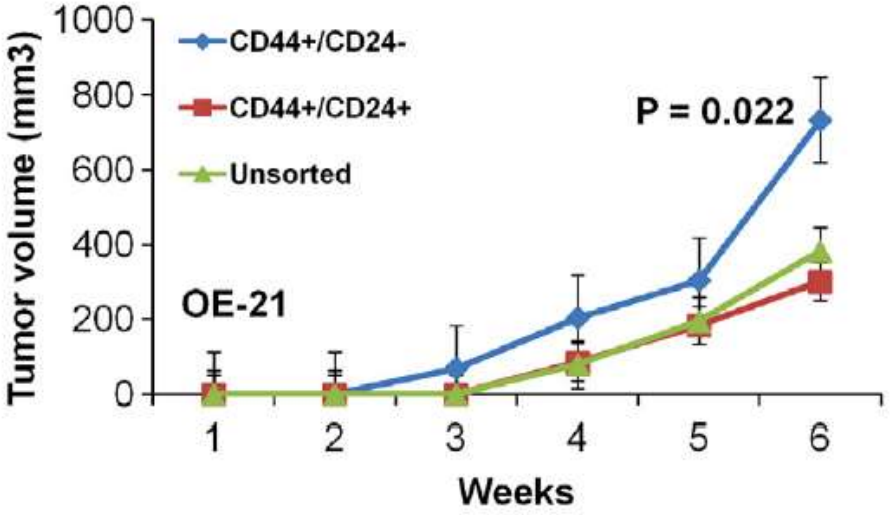
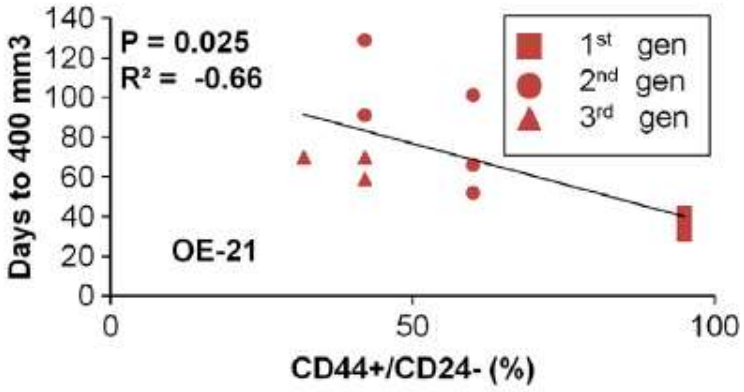
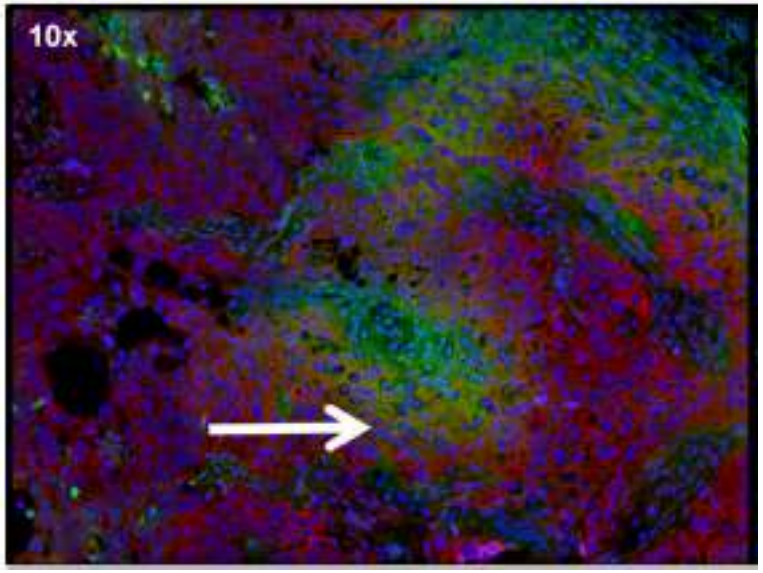
Smit et. al. Radiother Oncol 2013

Cancer stem cells

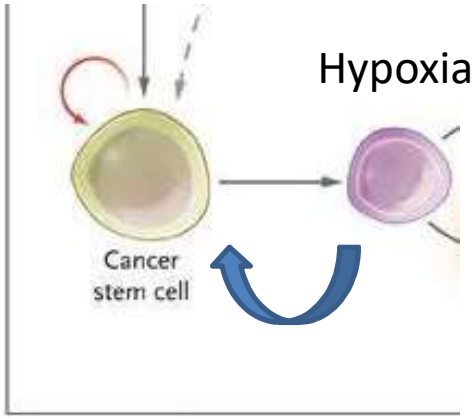






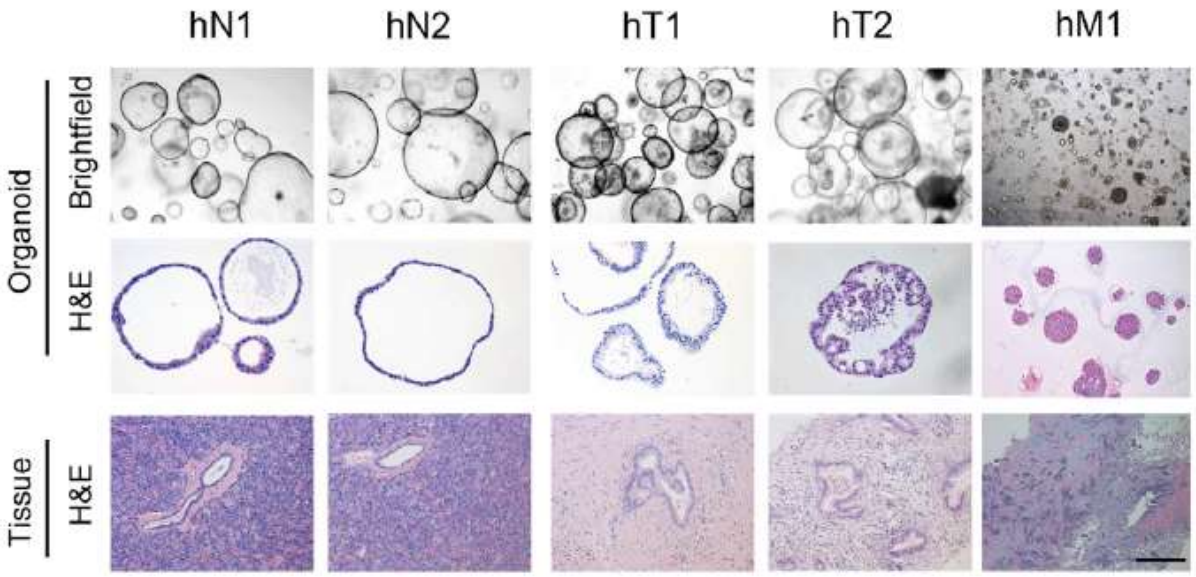
Red is CD44

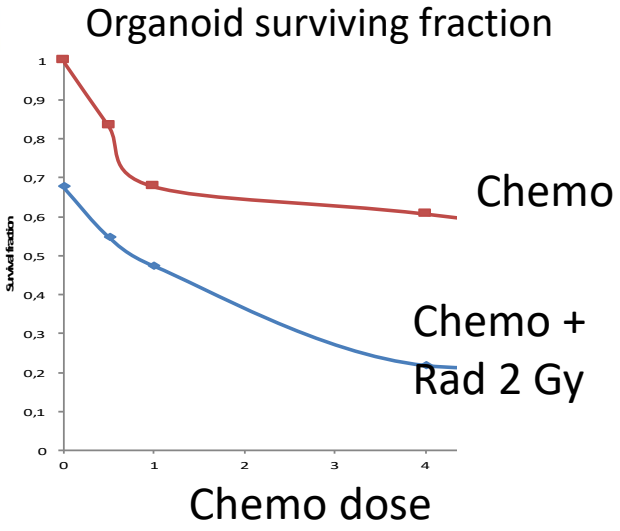
Green is pimonidazole



Smit et. al. Radiother Oncol 2013

CSC derived organoids?



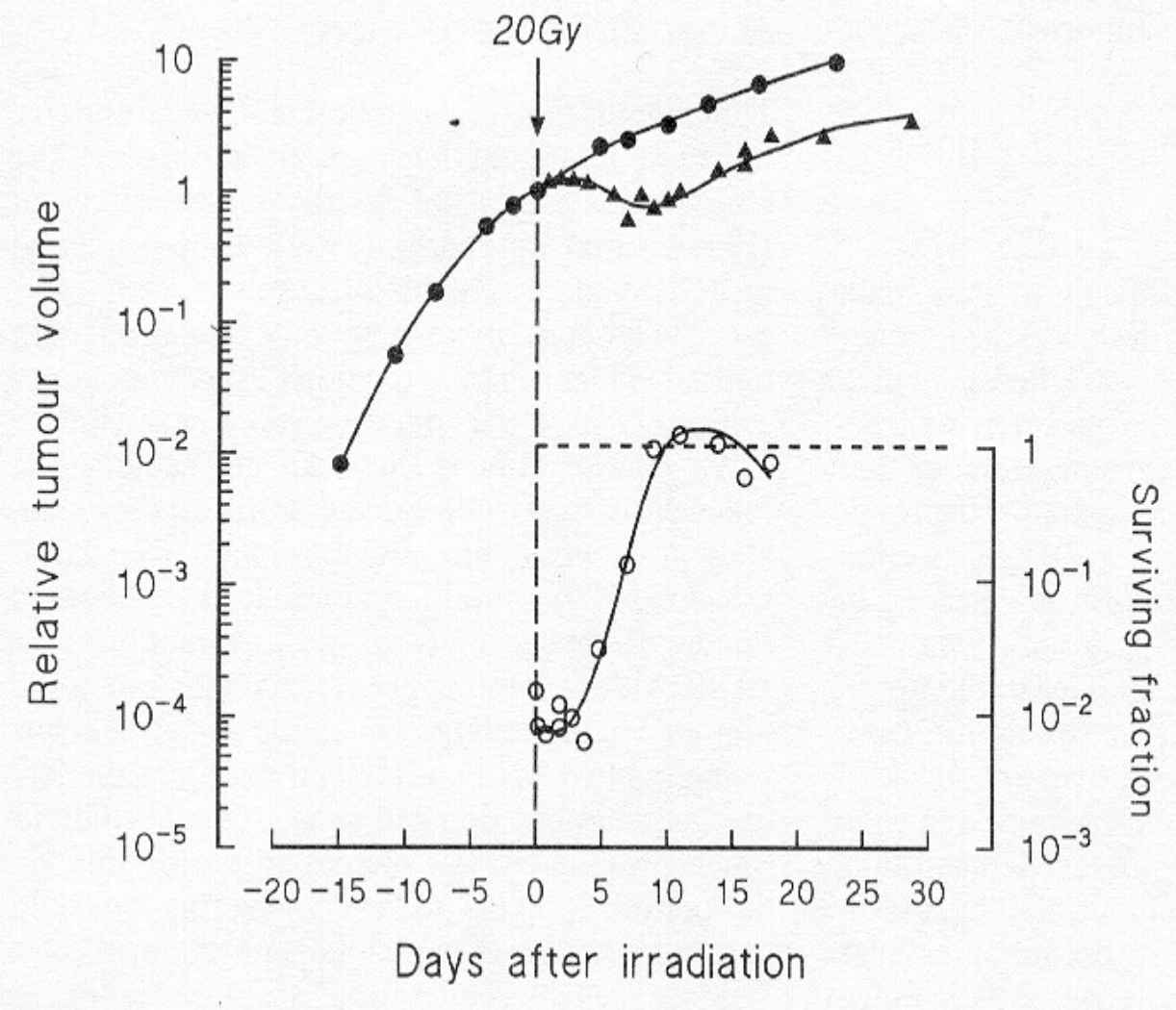


Boj et al Cell 2015

In situ assays

- In Situ assays (growth delay, tumor control):
  - Tumors left in place
  - Measure response of effective and potential stem cells
  - Limitation: no quantification of stem cells; surviving fraction is difficult to assess

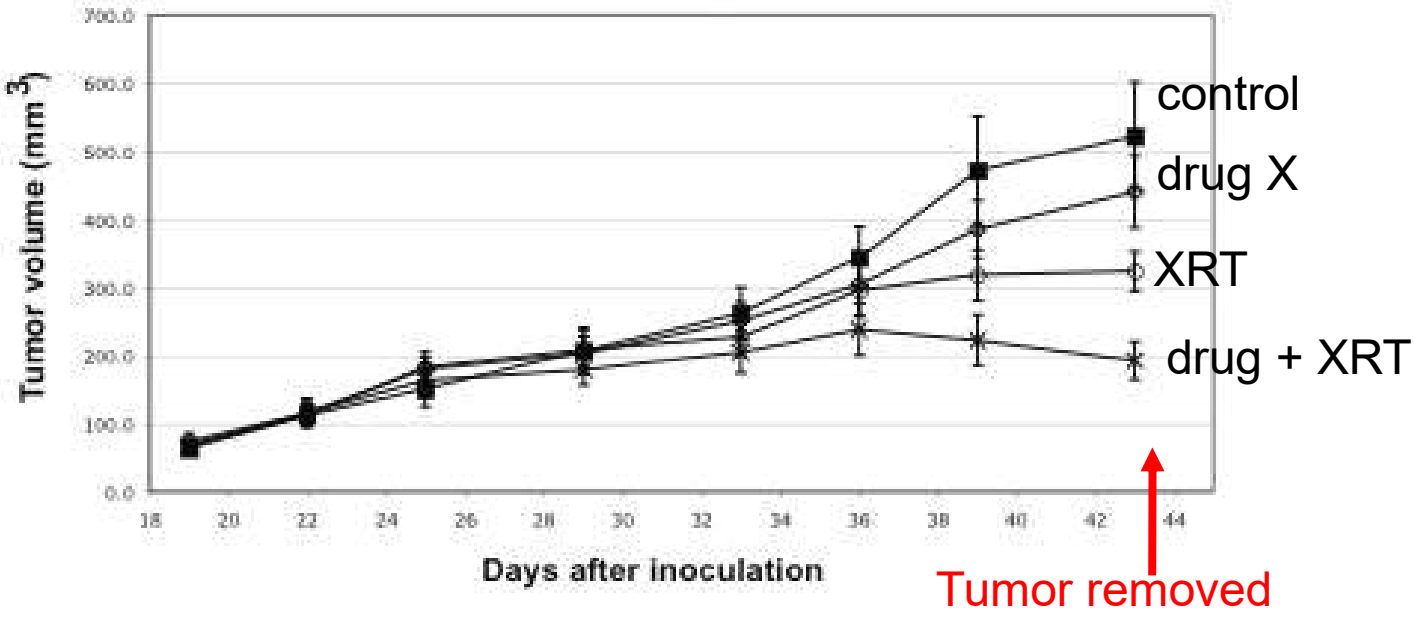
Tumor regression ≠ cell survival



Hermens and Barendsen, *Eur. J. Cancer* 1969

Tumor regression ≠ cell survival

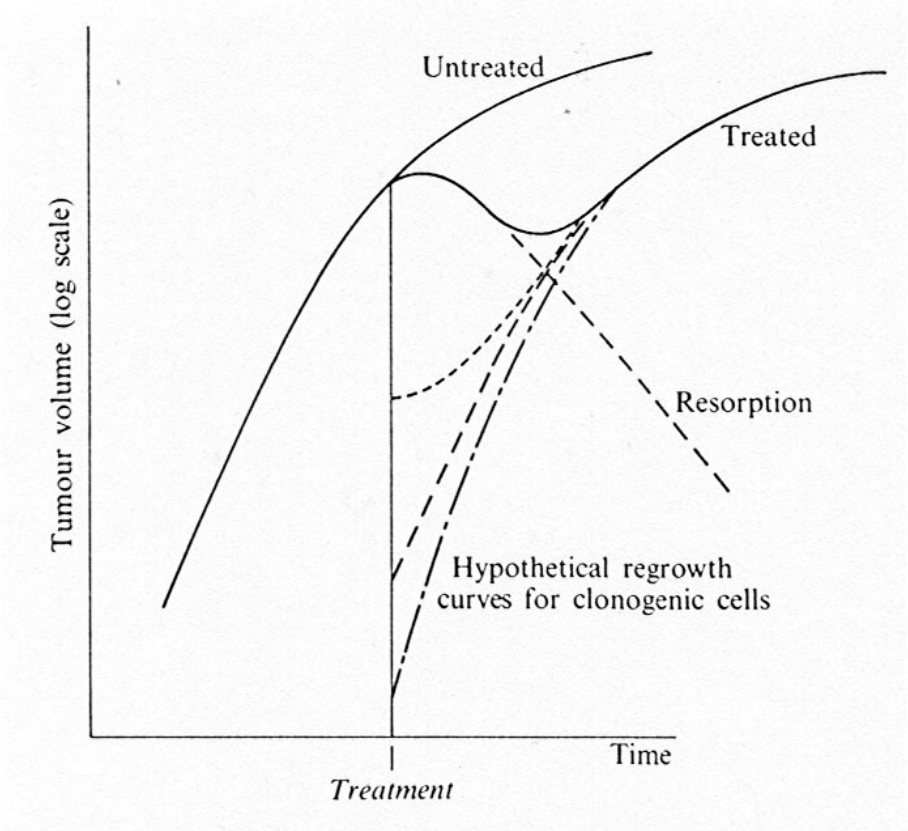
Human s.c.c. xenograft treated with 8 X 3 Gy / 4 wks



drug X = VEGFR2 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

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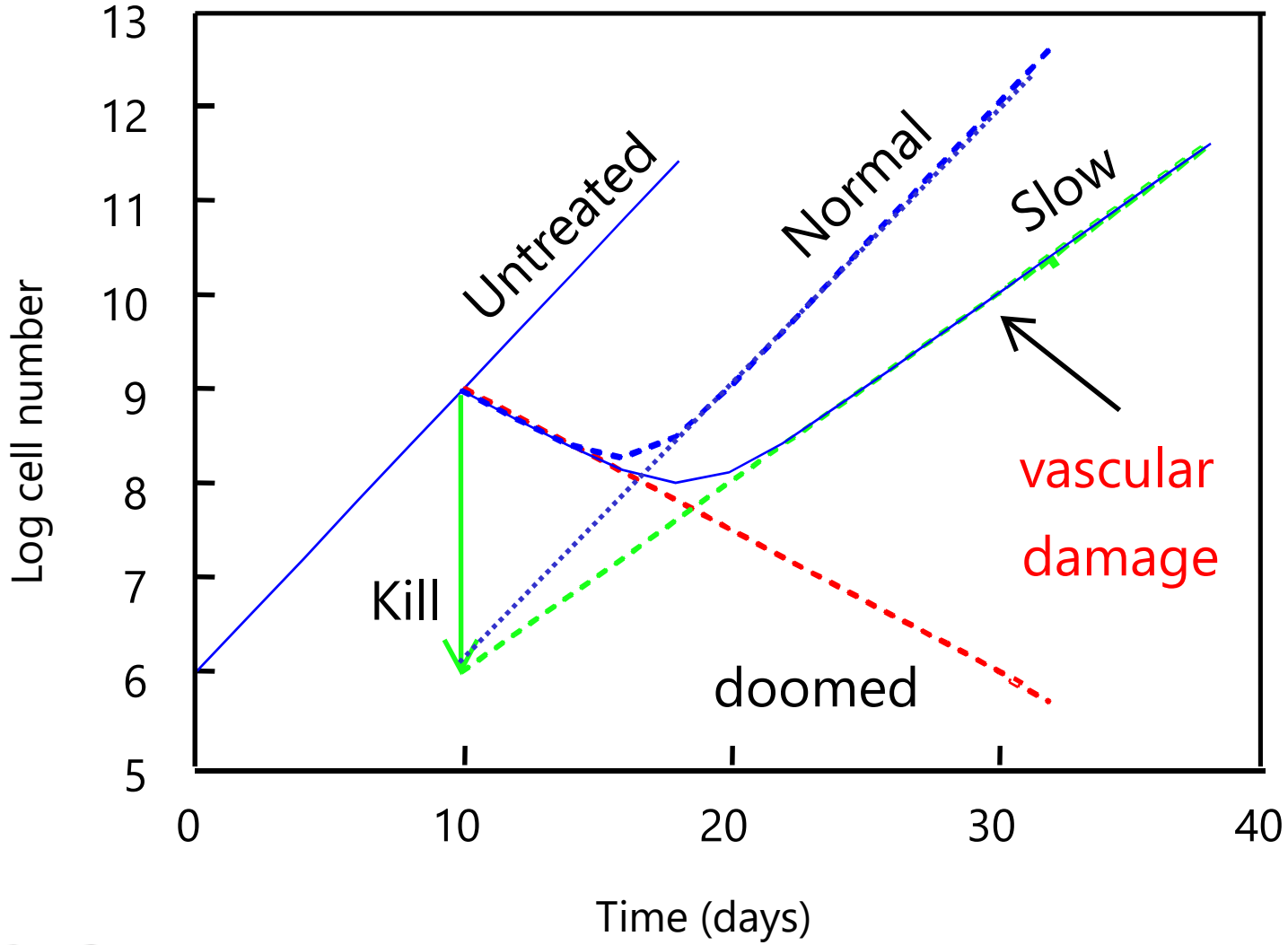
Vascular damage: tumor bed effect



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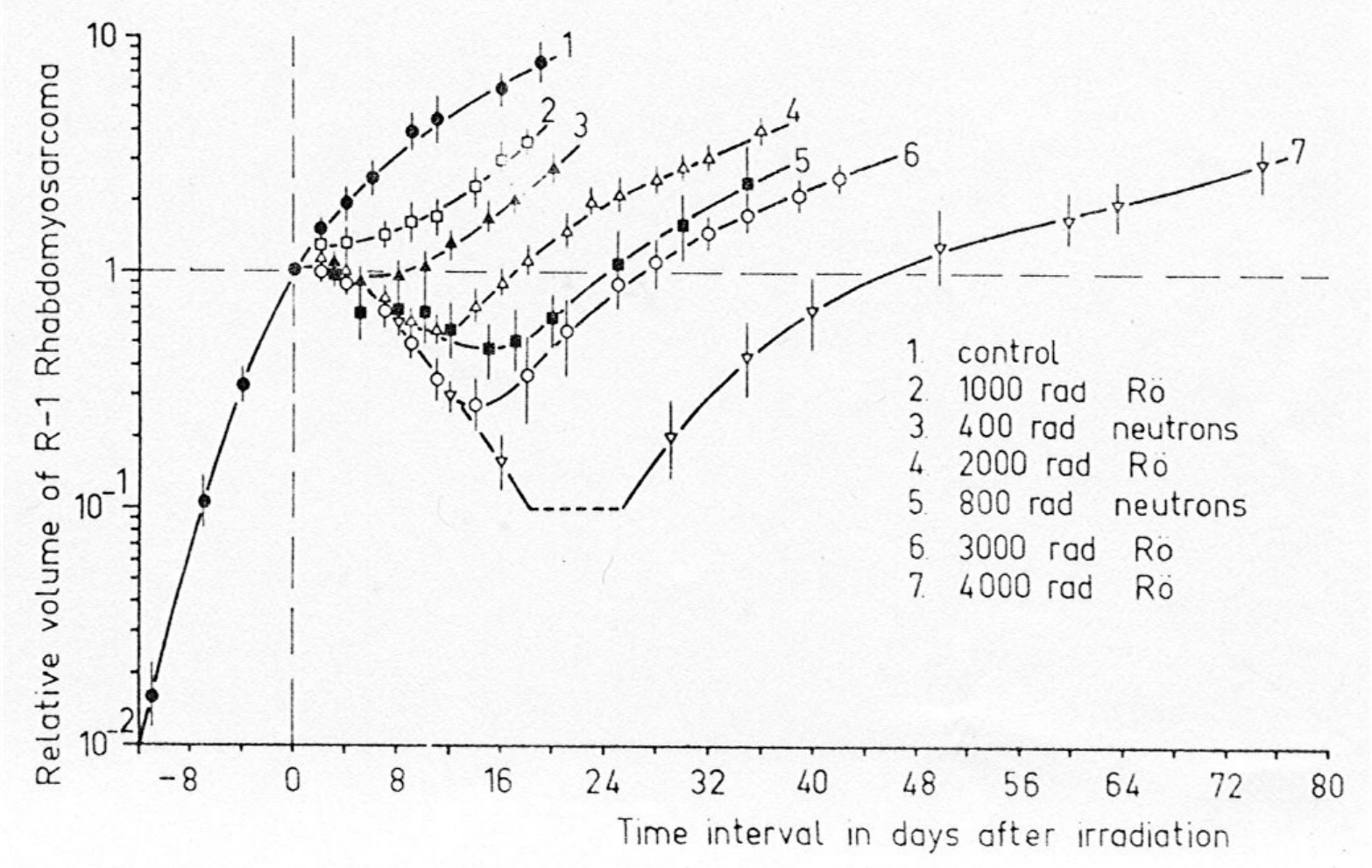
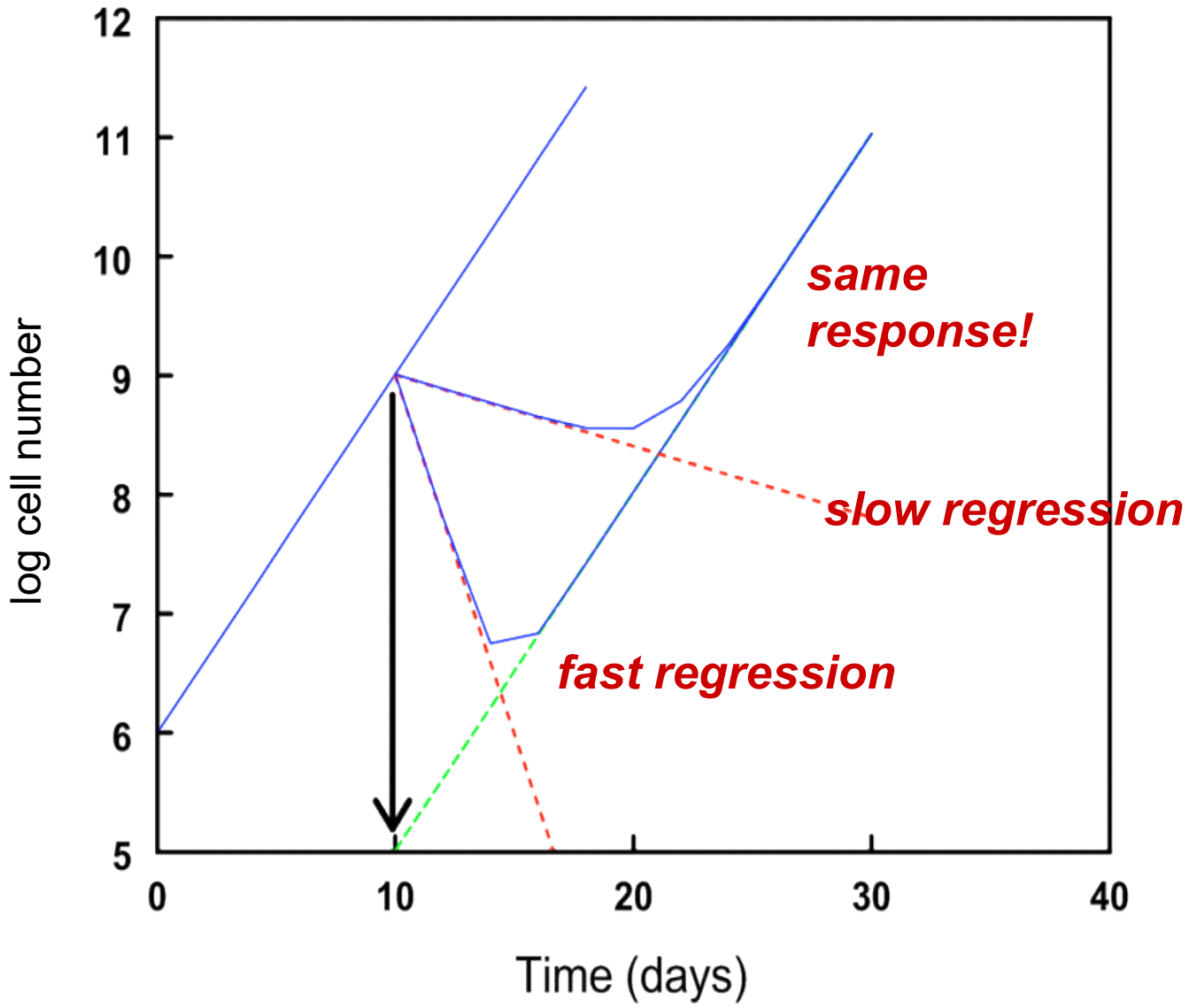
Application of Regrowth Delay Assay
Comparison of different treatments

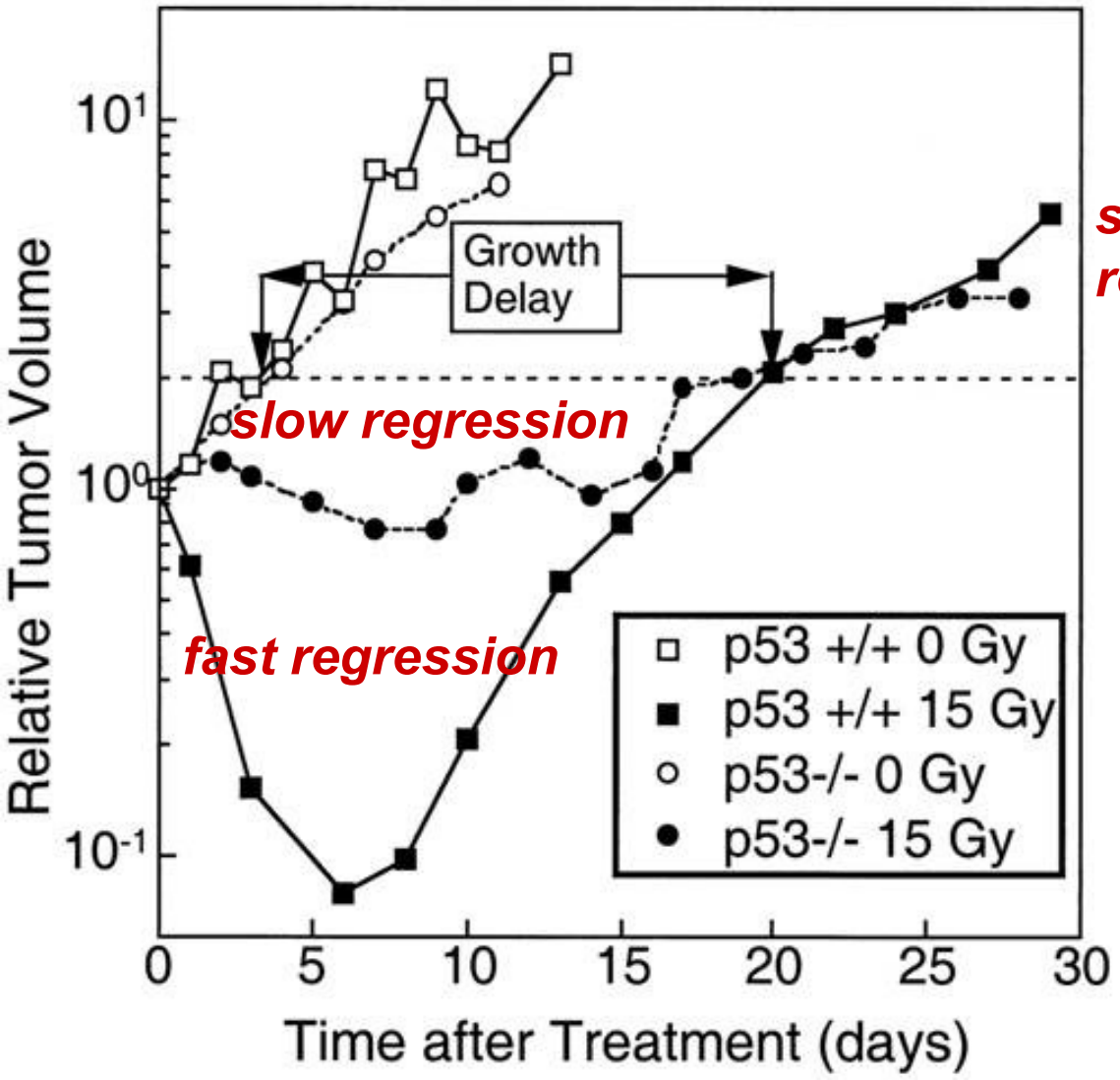


Barendsen and Broerse, Eur. J. Cancer 1969.

Delay independent of regression rate



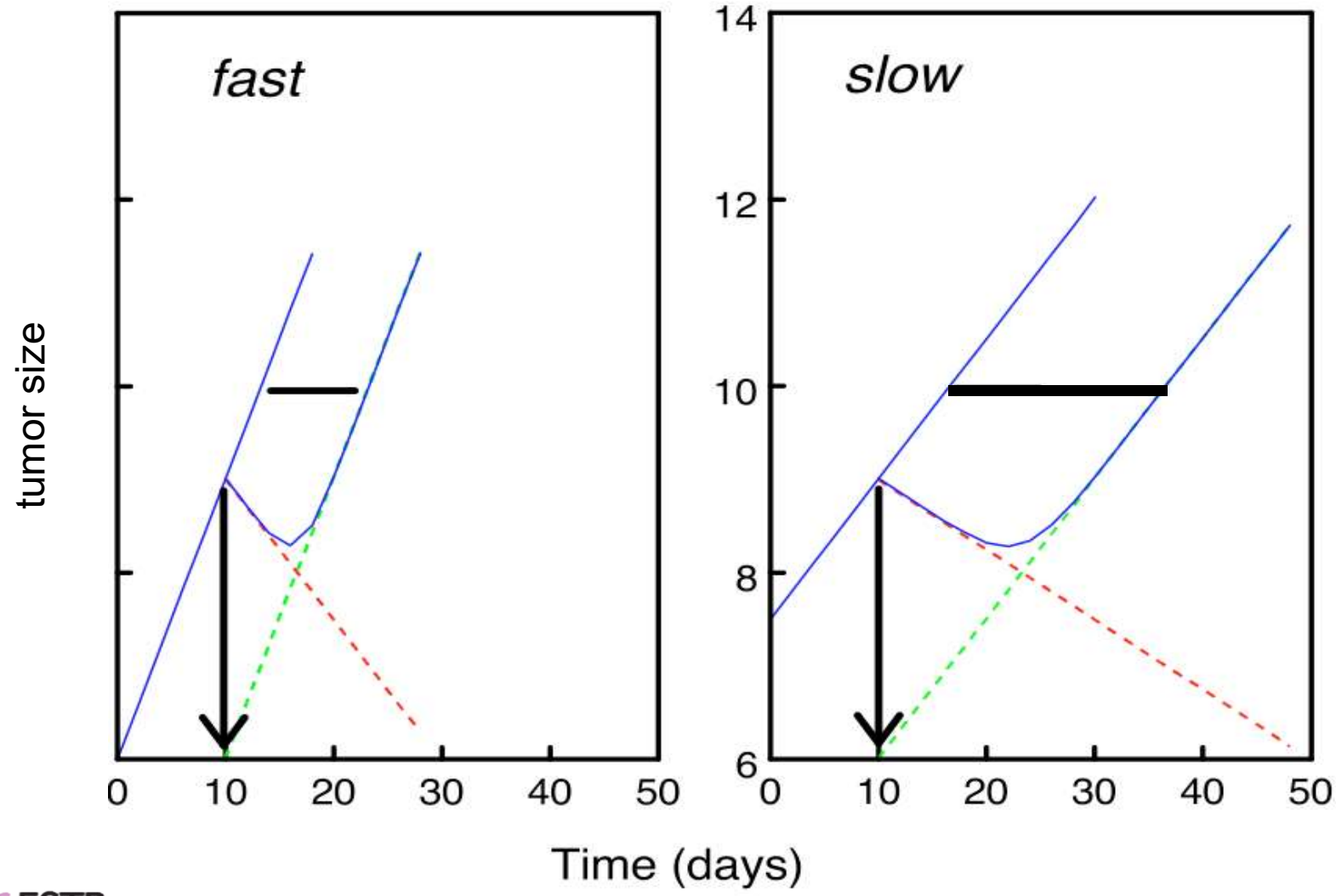
Delay independent of regression rate



same response!

Wouters & Brown, 1999

Growth delay depends on doubling time



Summary growth delay assay

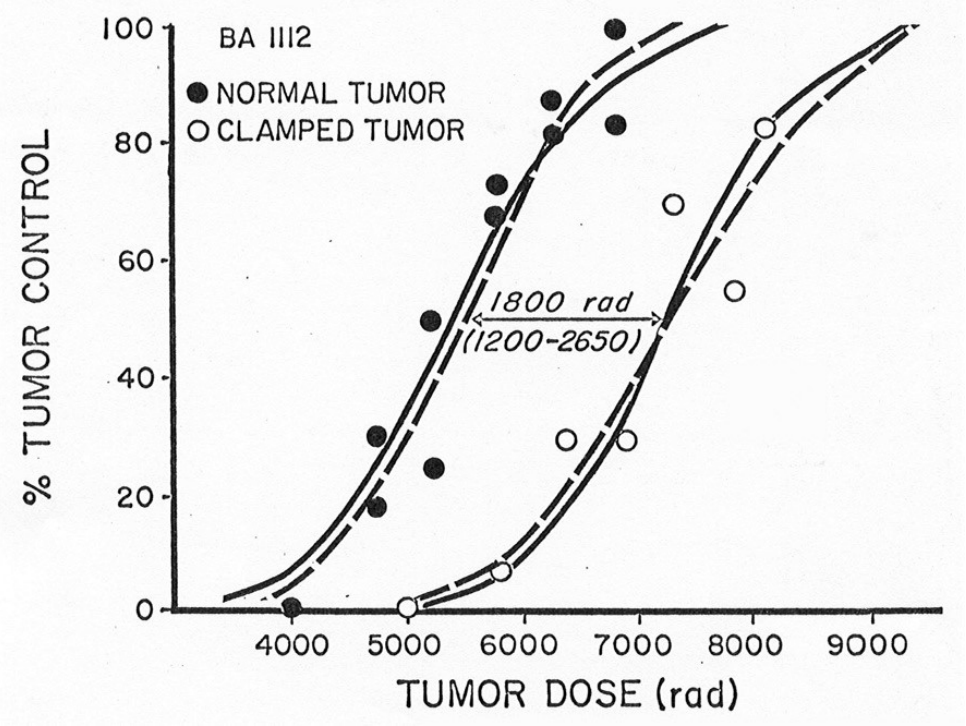
- Dependent on reliable volume measurement (difficult!)
  - with ultrasound imaging or bioluminescence more reliable than manual caliper
- Only suitable for few logs of tumor cells (selection)
- Reflects growth rate of clonogenic and non-clonogenic cells
- Dependent on growth rate of tumor
  - comparison 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)

Local tumor control 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) – TCD50

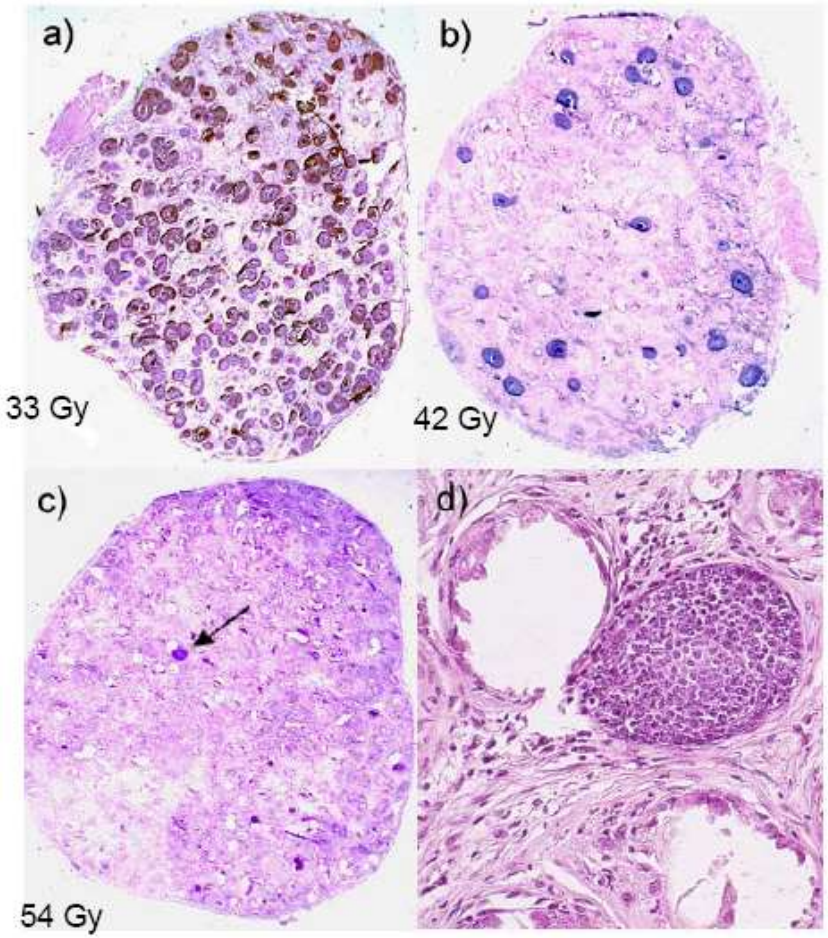
- The radiation dose which cures 50% of a homogeneous population of tumors (TCD50) is estimated.
- This assay most directly assesses the sensitivity of the stem cell population in the tumor.

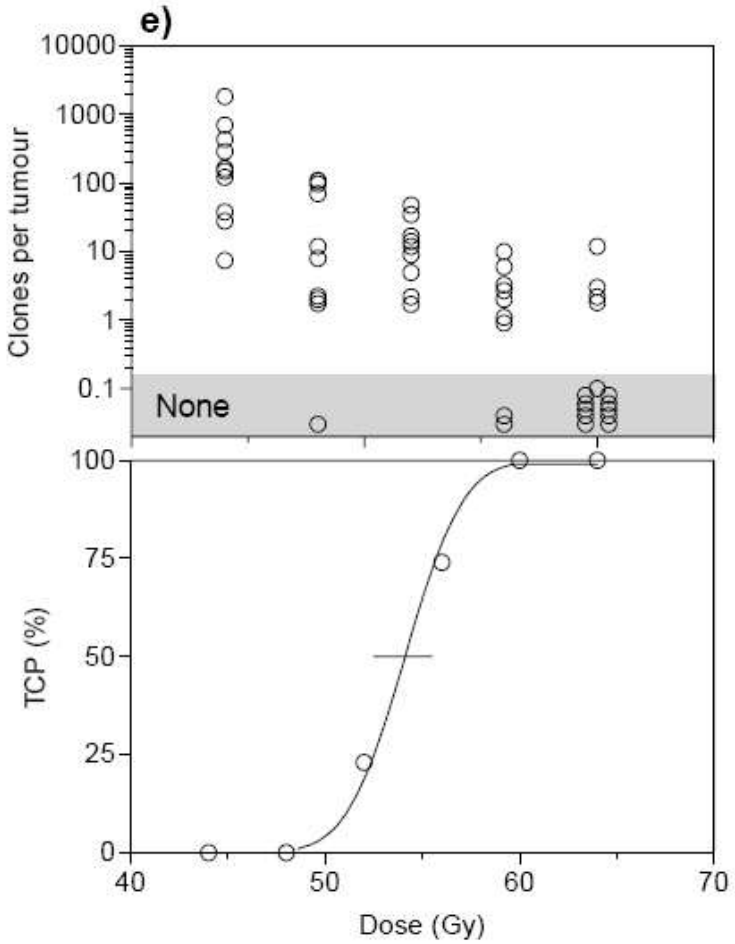


Moulder & Rockwell, IJROBP 1984

ESTRO School

Local tumor control





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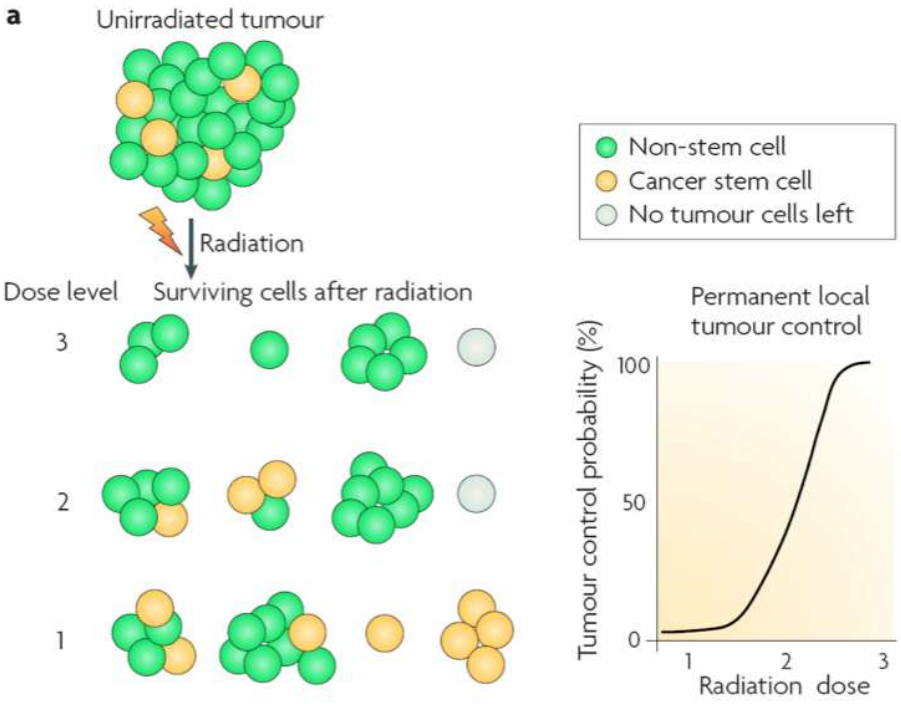
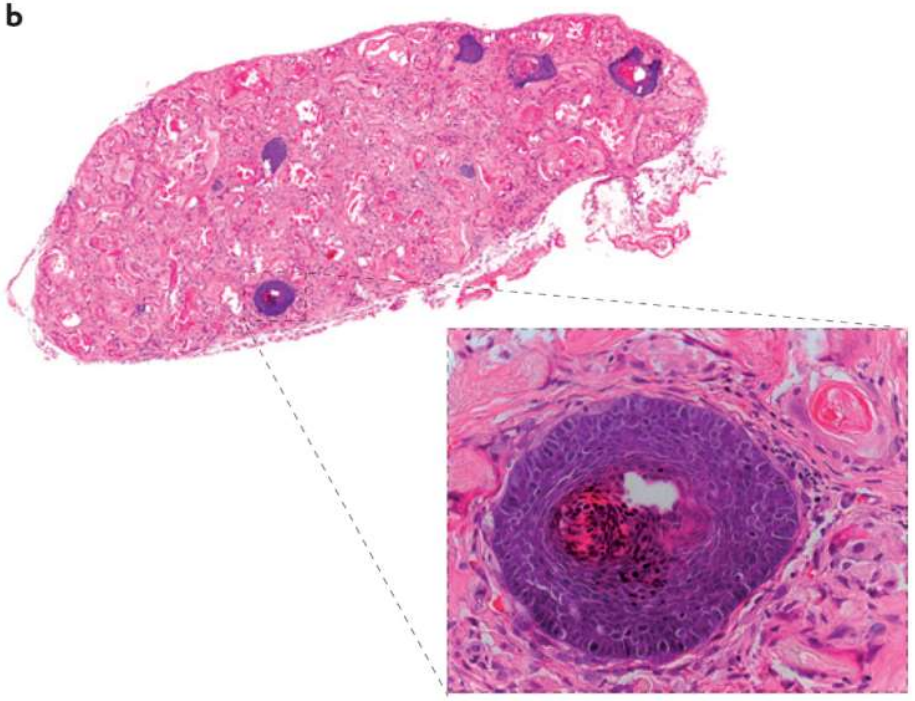
Killing all cancer stem cells is necessary for local tumour control





Baumann, Krause, Hill, Nature Rev Cancer 545-554, 2008

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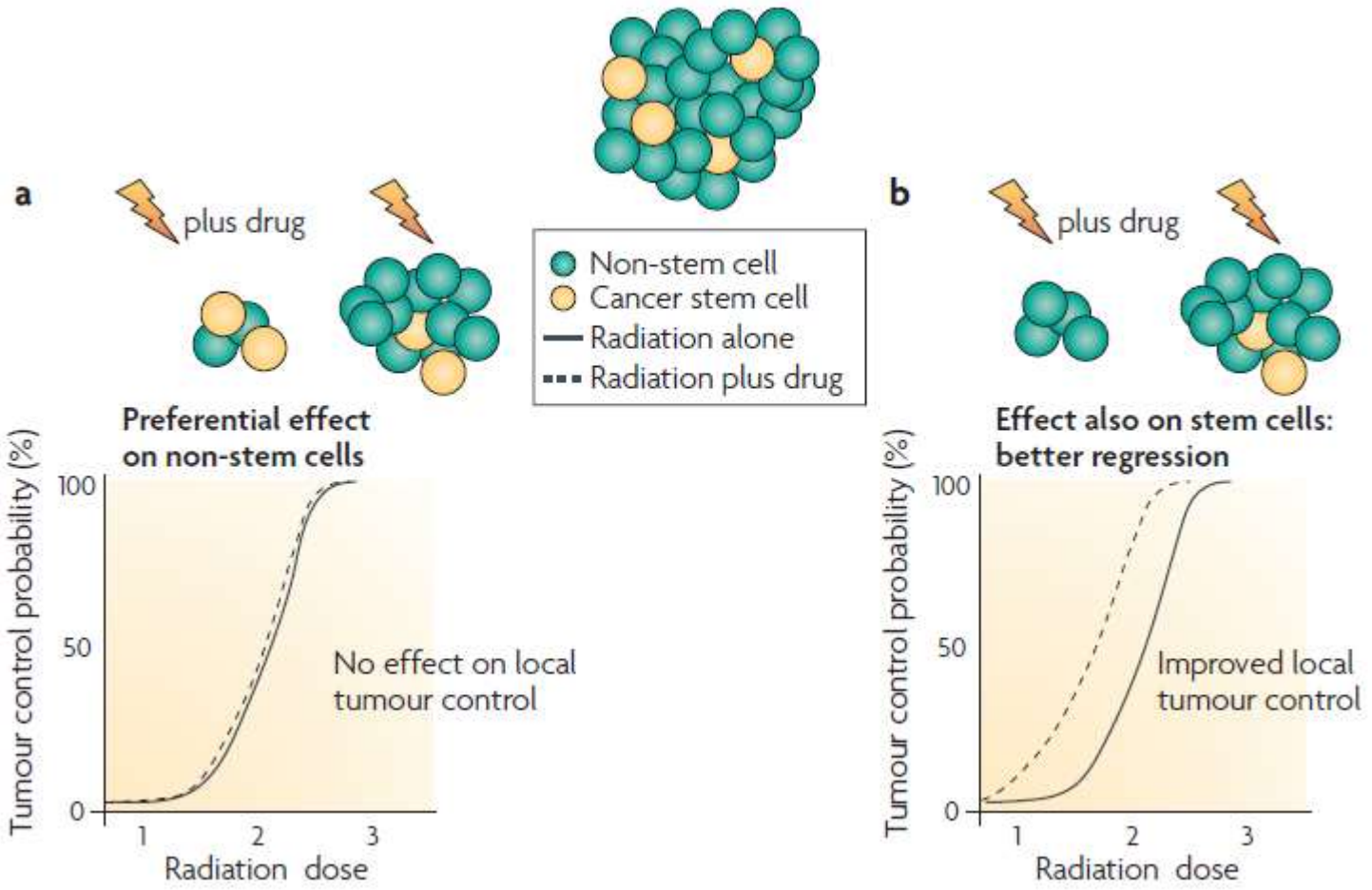
Killing all cancer stem cells is necessary for local tumour control



Baumann, Krause, Hill, Nature Rev Cancer 545-554, 2008

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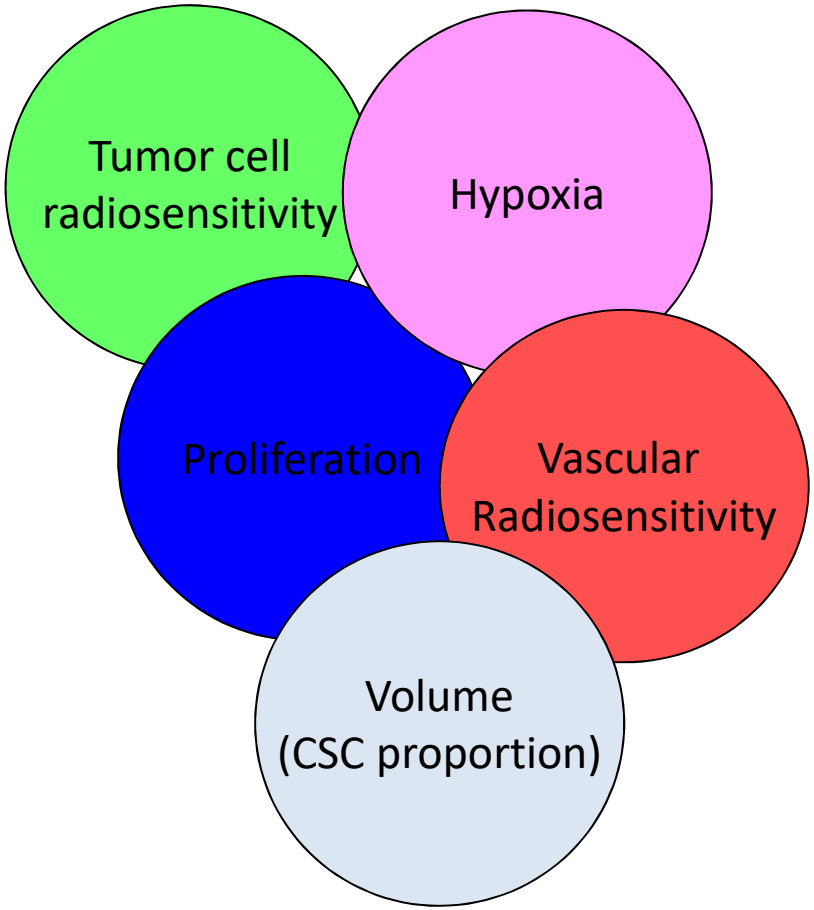
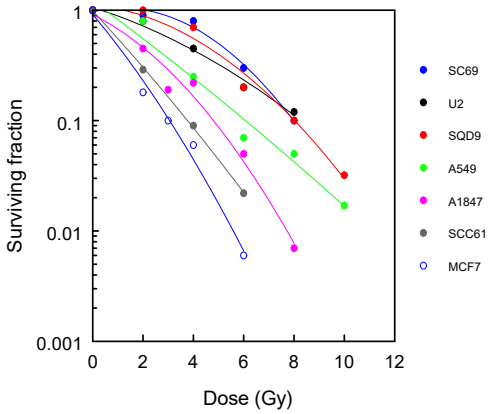
Summary TCD50 assay

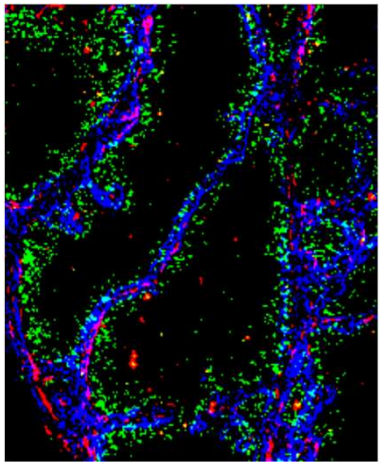
- Best assay available for experimental radiotherapy
- Most relevant for clinical practice
- Tumour cells remain in situ
- Dependent only on clonogenic cells
- All clonogenic cells are assayed, not only some logs
  - Thus also survival of small resistant subgroups of clonogens can be assayed
- Good for radiobiological modelling

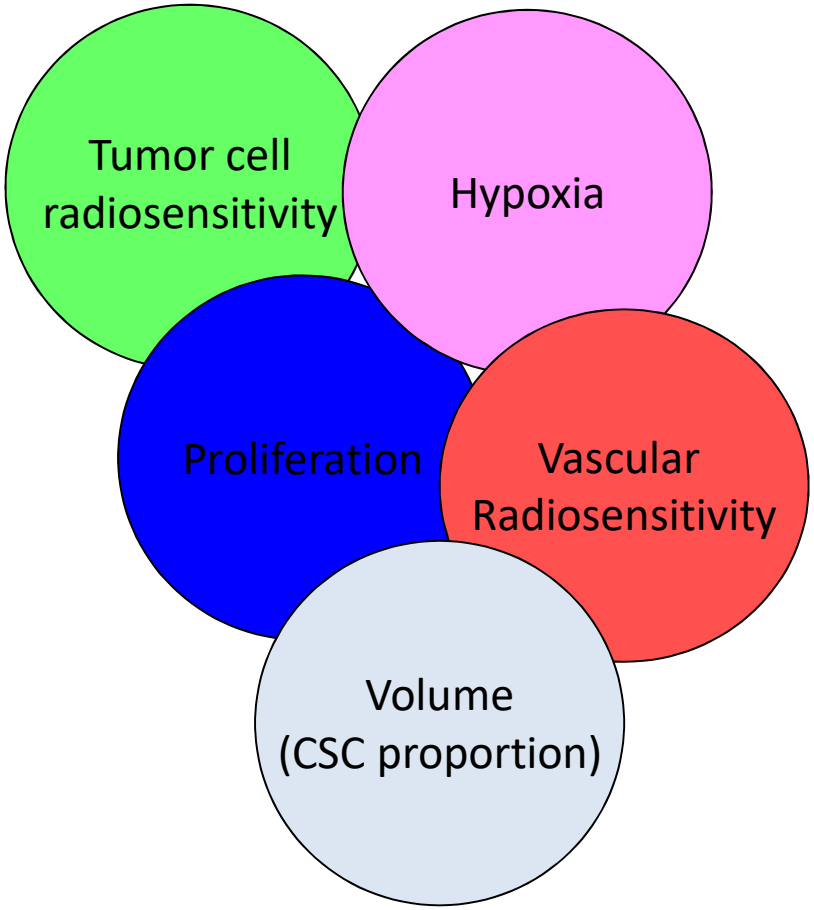


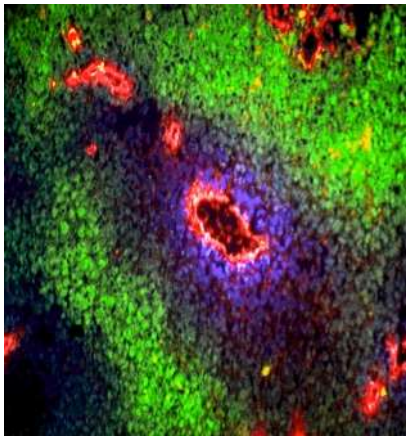
Factors influencing local tumor control

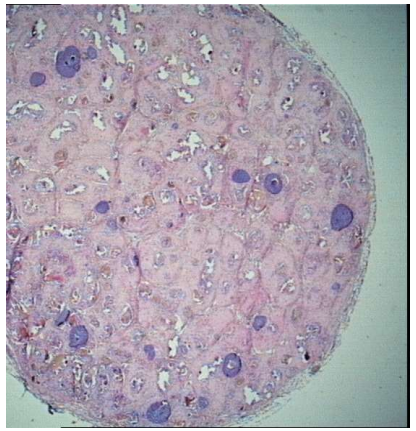
Biological contributors to outcome











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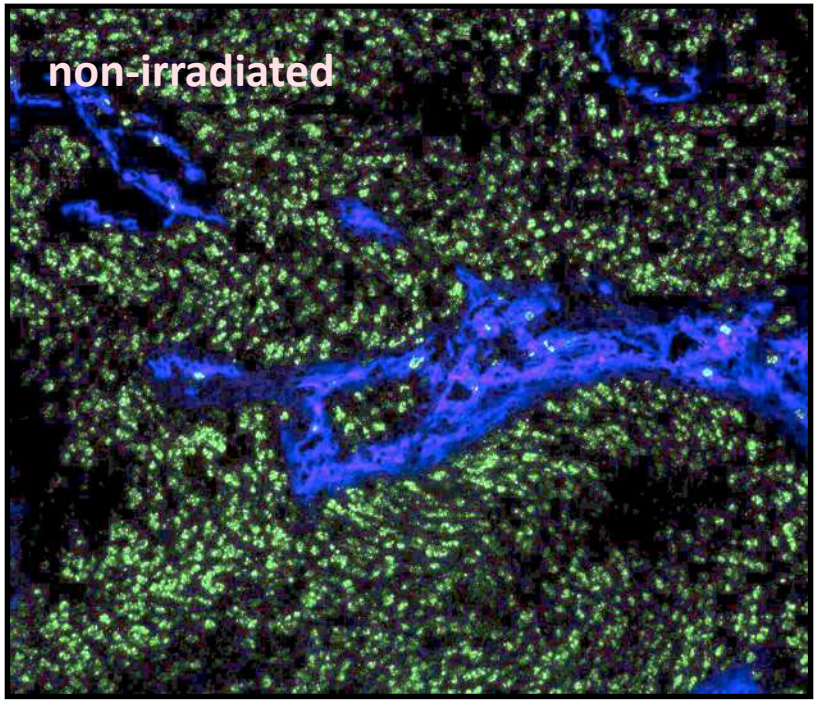
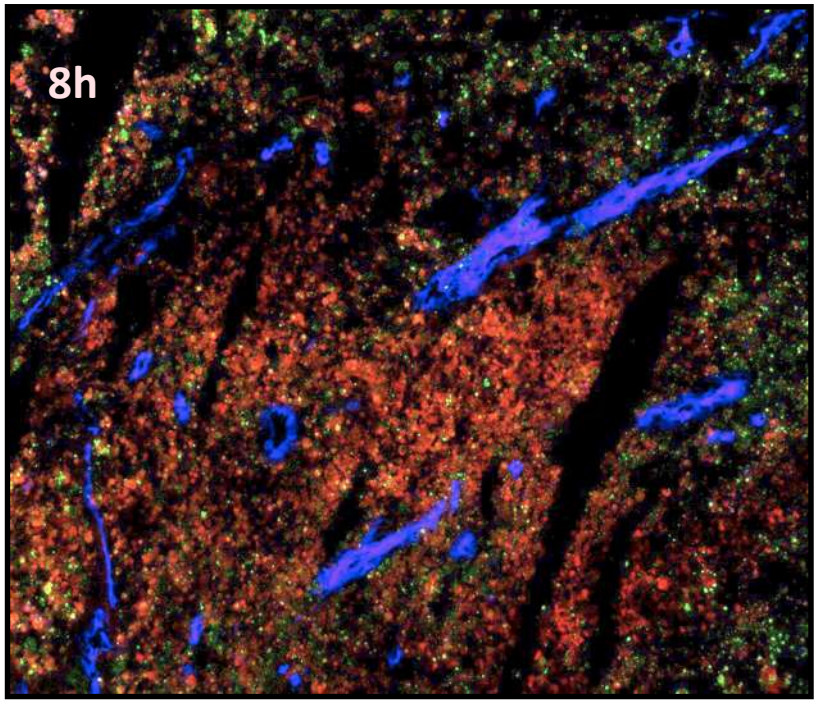
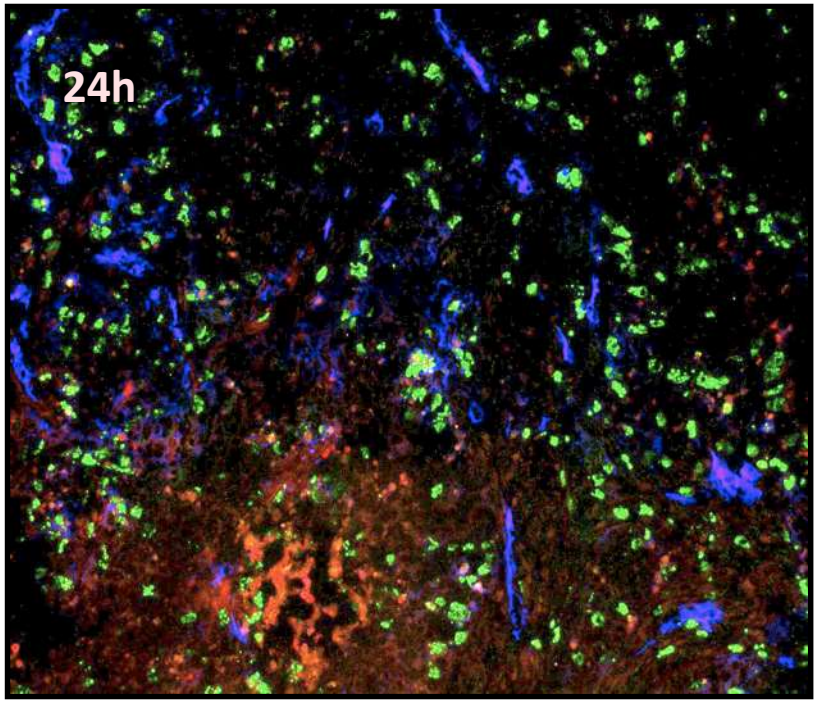
Effect of irradiation on tumors: cell death and proliferation







Proliferating cells
Apoptotic cells
Blood vessels

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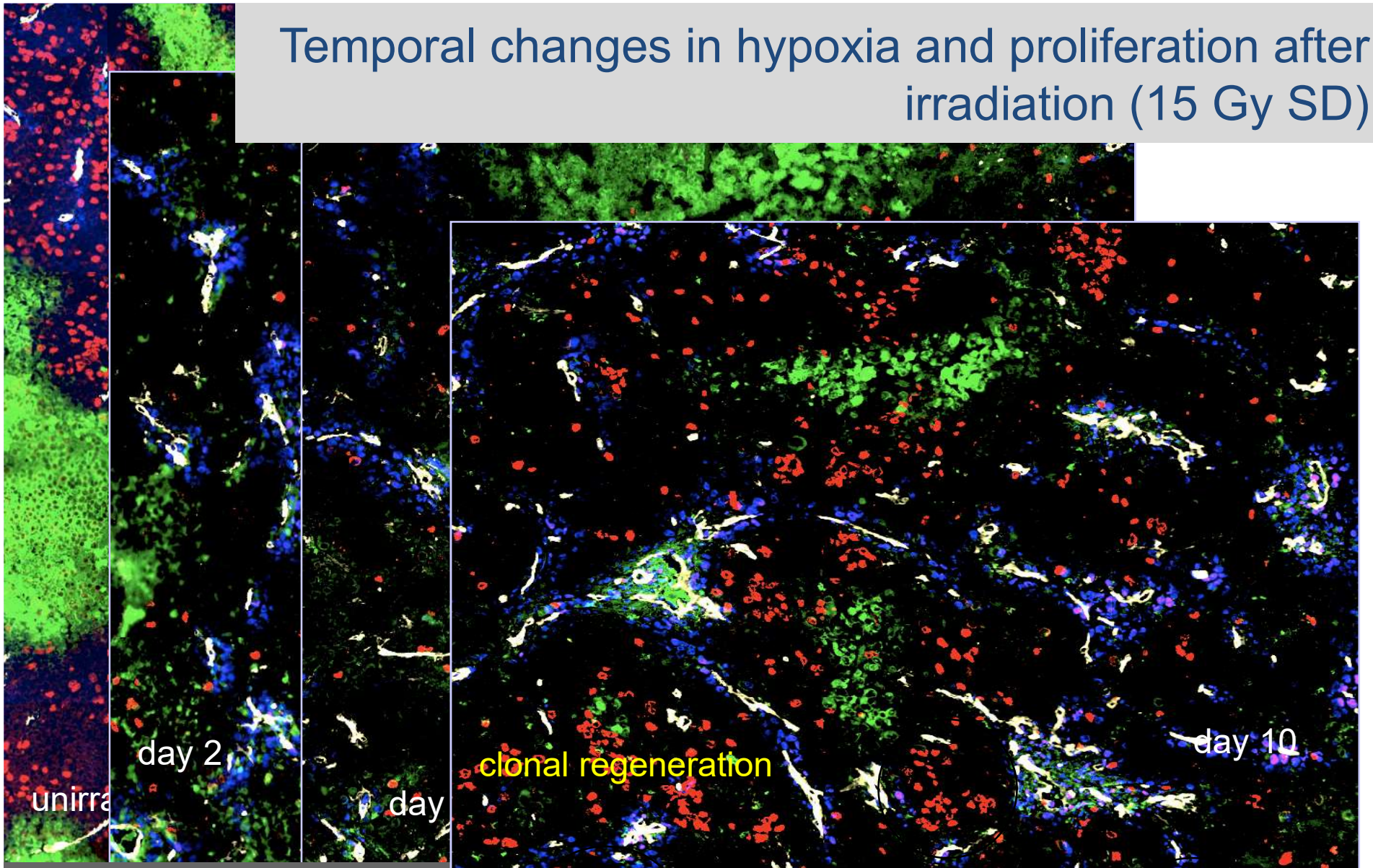
Temporal changes in hypoxia and proliferation after irradiation (15 Gy SD)

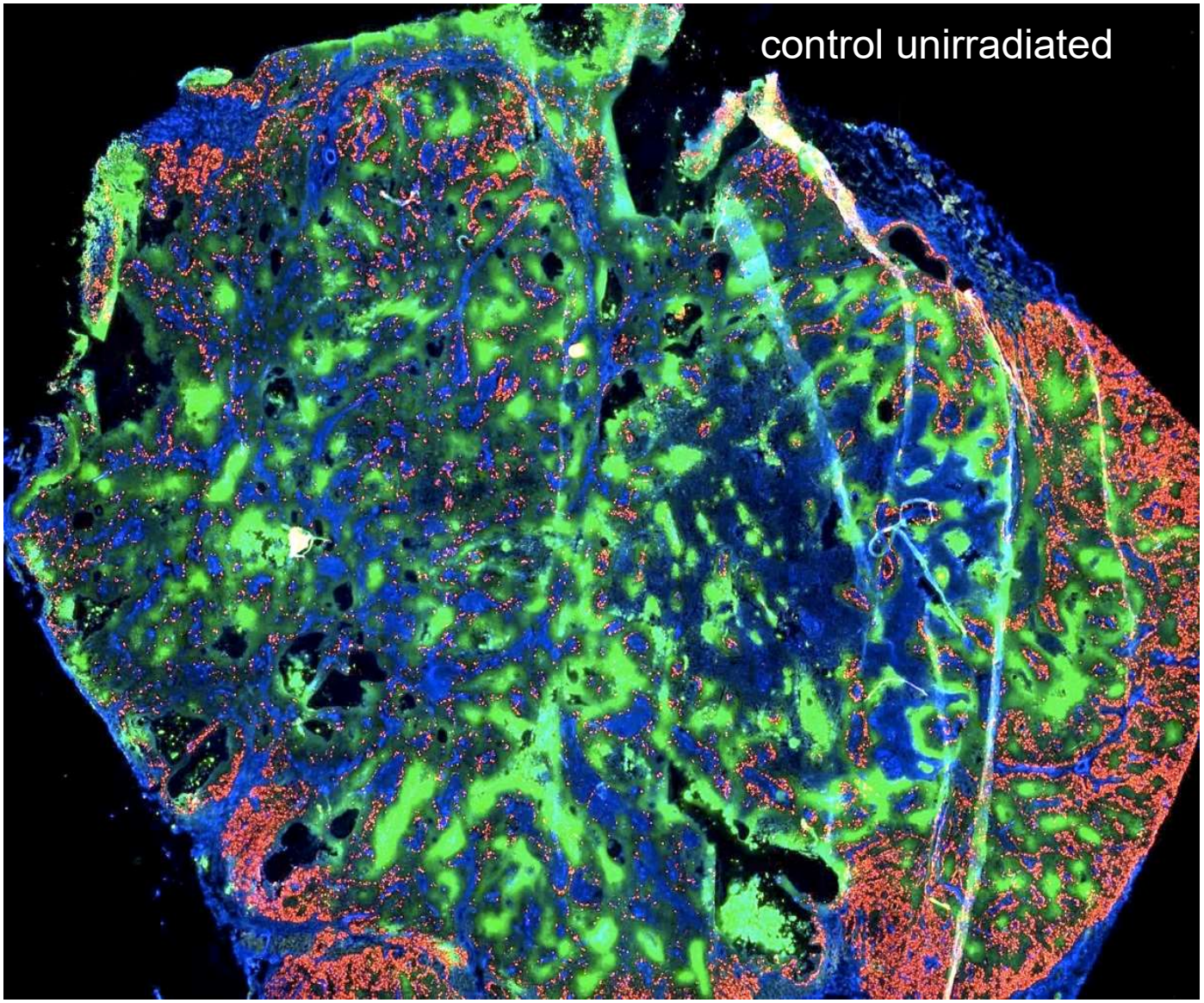


green: hypoxic cells

red: proliferating cells

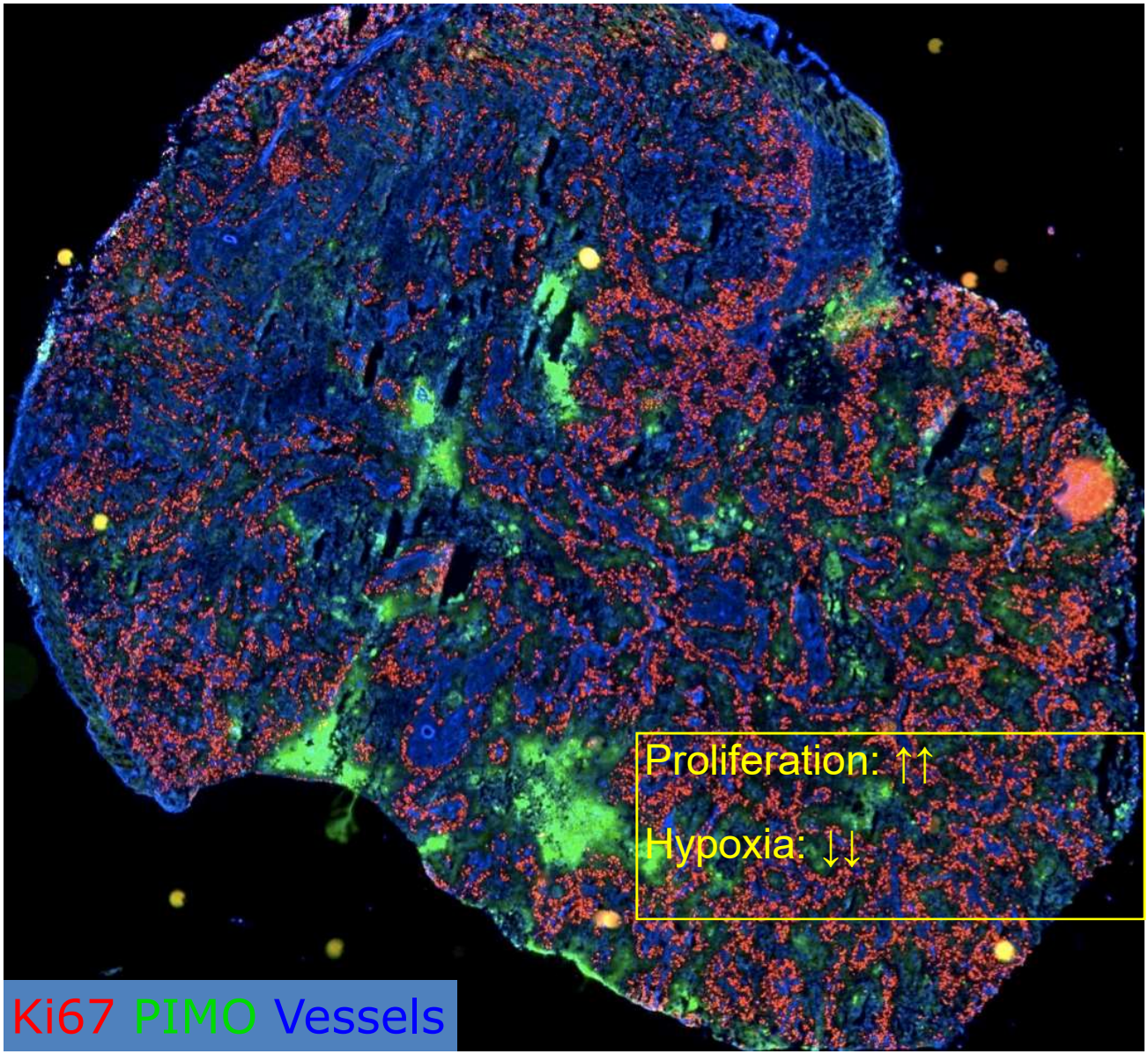
blue / white: blood vessels

Proliferation & hypoxia in s.c.c. xenograft



Ki67 PIMO Vessels

Proliferation & hypoxia in s.c.c. xenograft after 8 X 3 Gy/4 weeks



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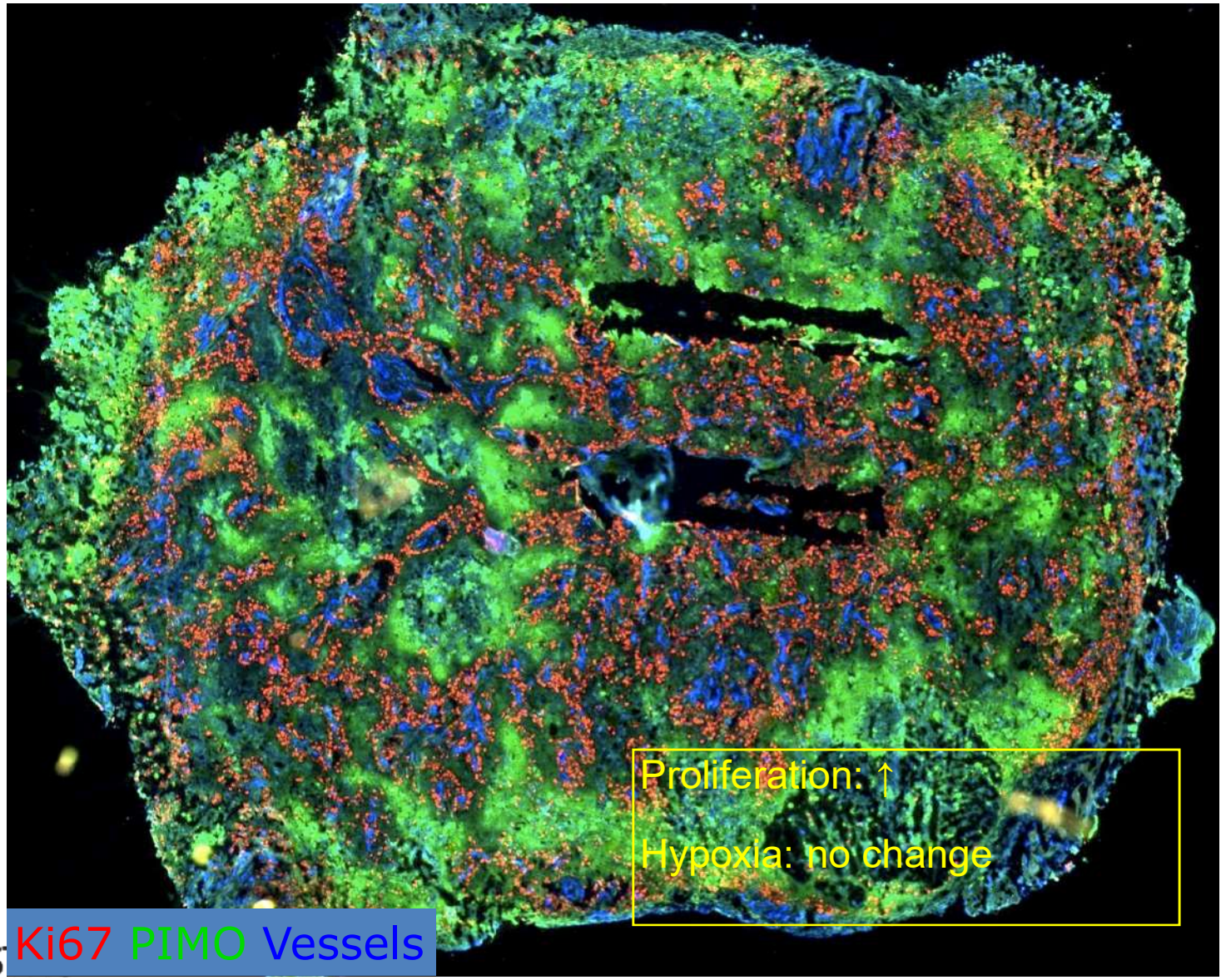
Proliferation & hypoxia in s.c.c. xenograft after 8 X 3 Gy/4 weeks + VEGFR-inhibitor



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Repopulation of clonogenic tumor cells

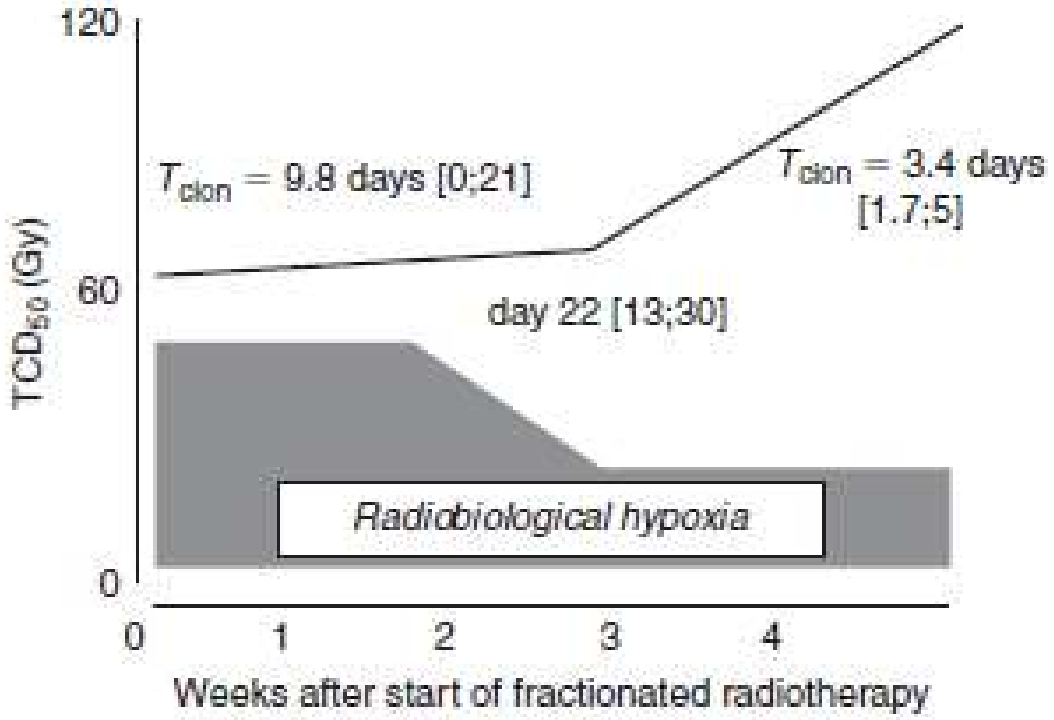
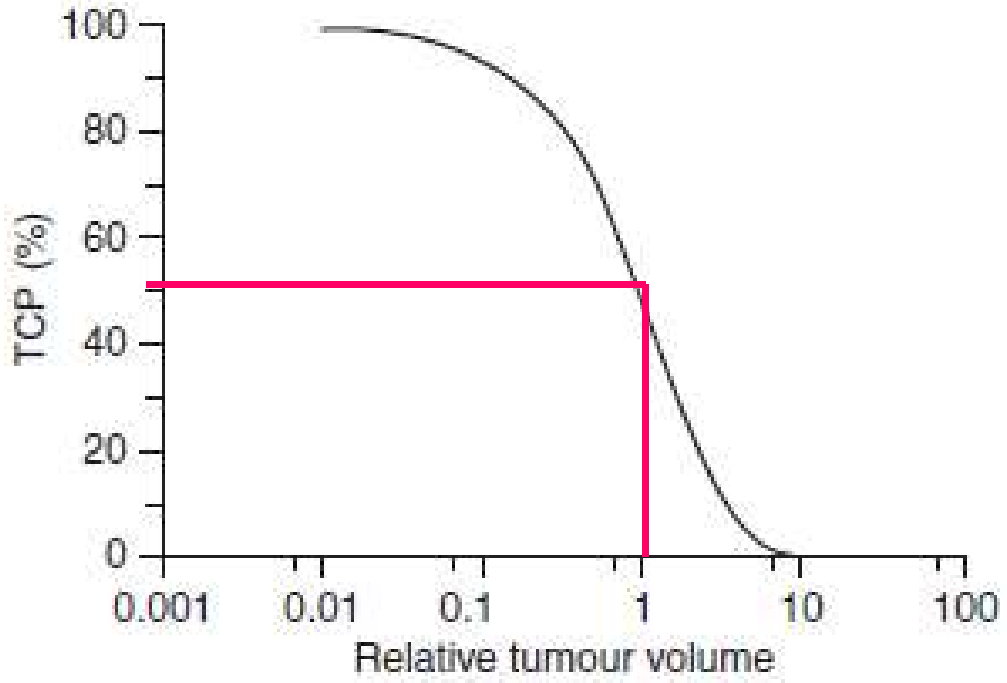


Figure 7.13 Rate, kinetics and underlying mechanism of repopulation of clonogenic tumour cells in FaDu squamous cell carcinoma growing in nude mice

Tumor volume

- Important determinant of local tumor control!



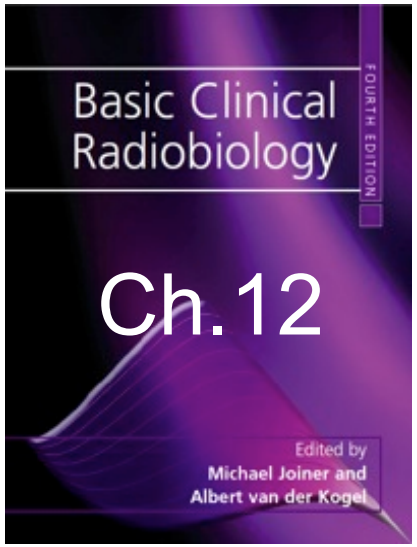
Summary

- Tumor response to radiation depends on
  - Intrinsic cellular radiosensitivity
  - Stromal interactions (vasculature)
  - Microenvironment (hypoxia)
  - Tumour volume (stem cell number)
  - Cellular proliferation (repopulation)

Take home messages

- 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



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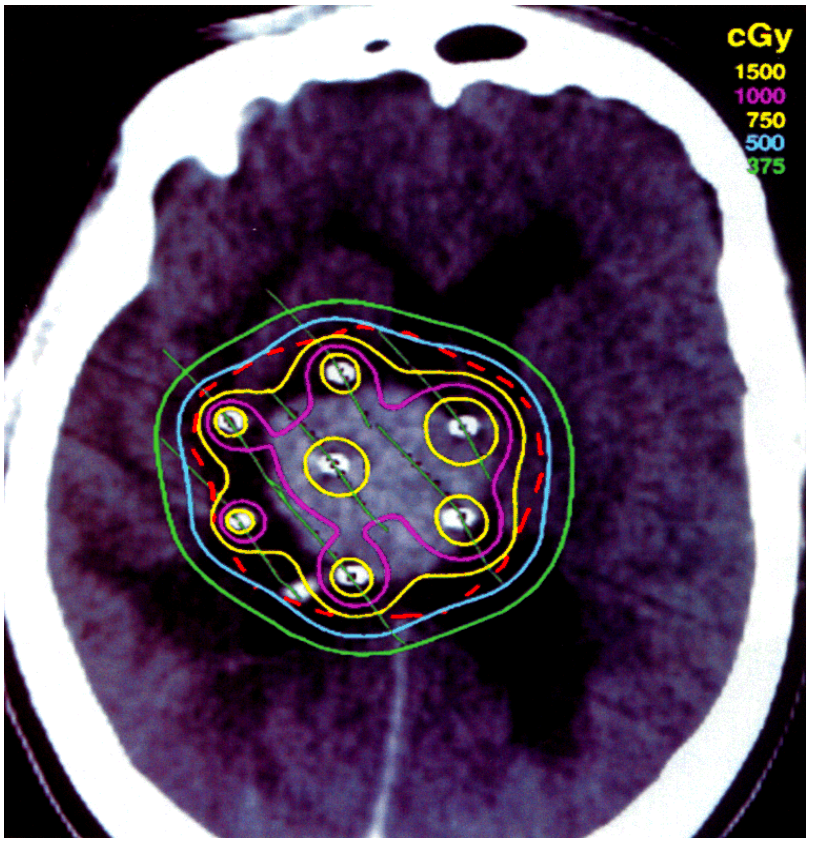
University of Groningen,
The Netherlands

*many thanks to **Bert van der Kogel** for his slides*



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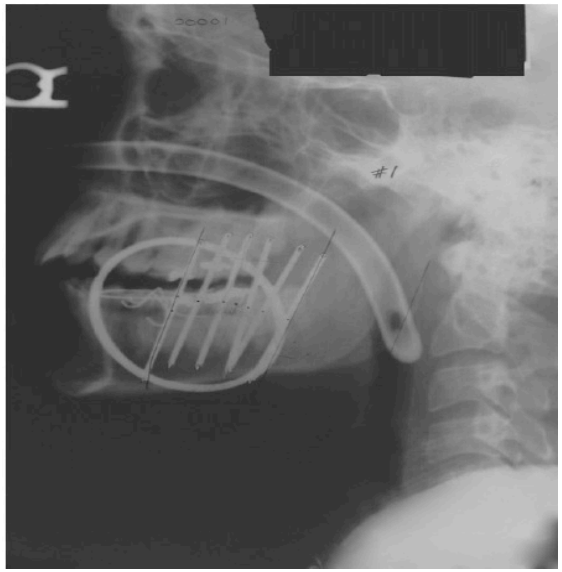
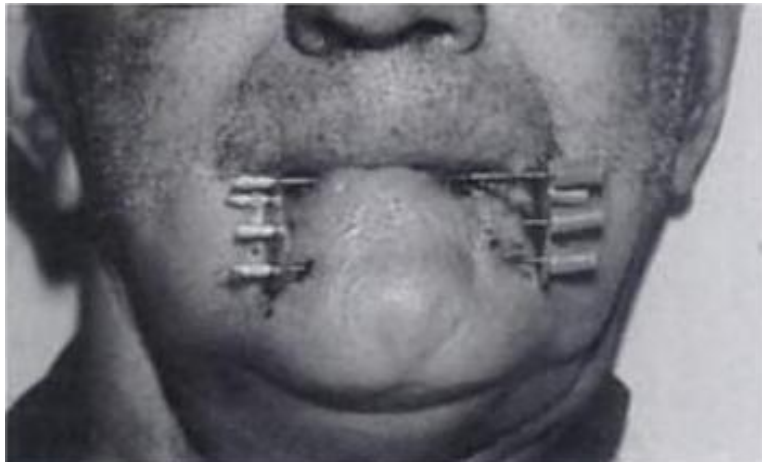
umcg

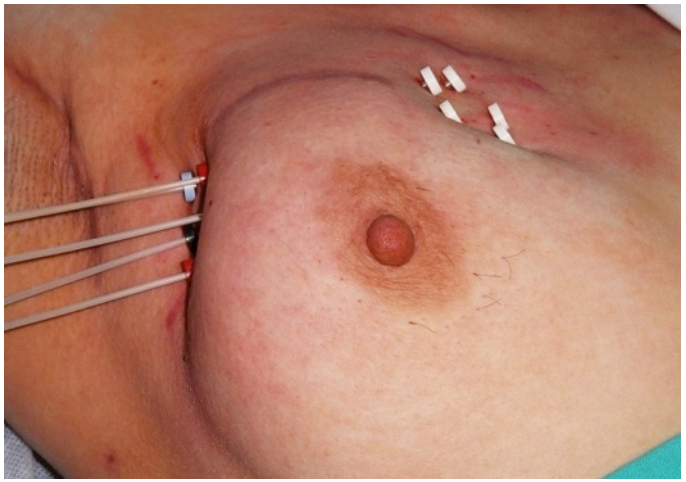
Cancer Research Center Groningen

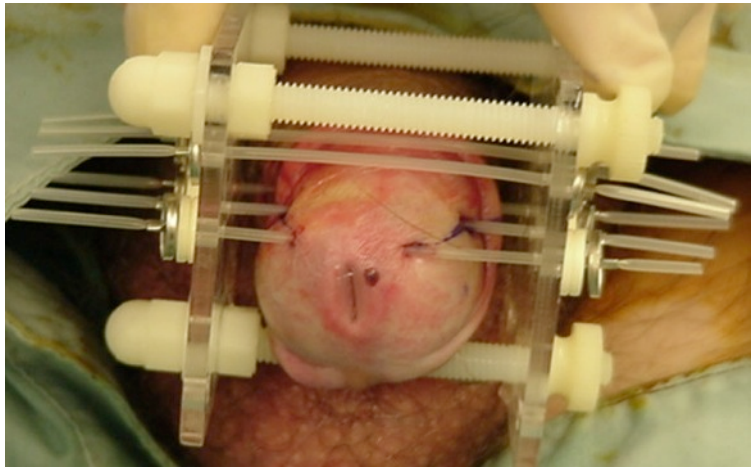

Claudius Regaud 1870-1940
Father of Fractionation
Low Dose Rate Radium Treatment of Tongue and Cervical Cancer 1918

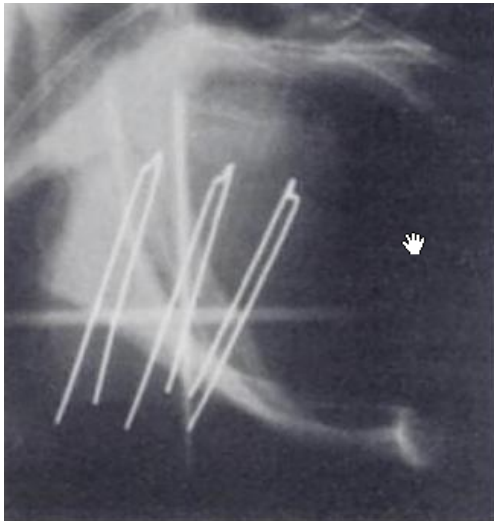
LDR Brachytherapy

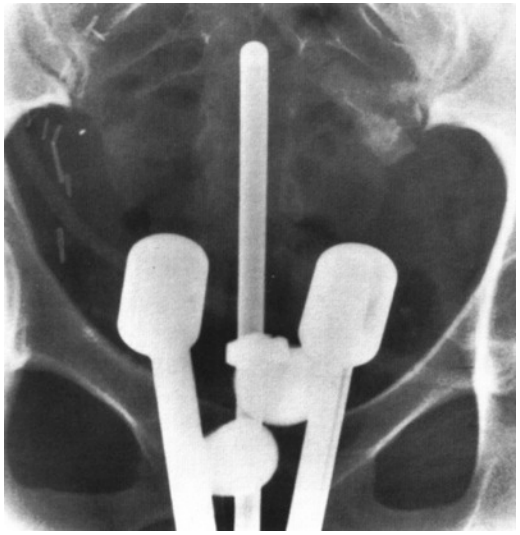




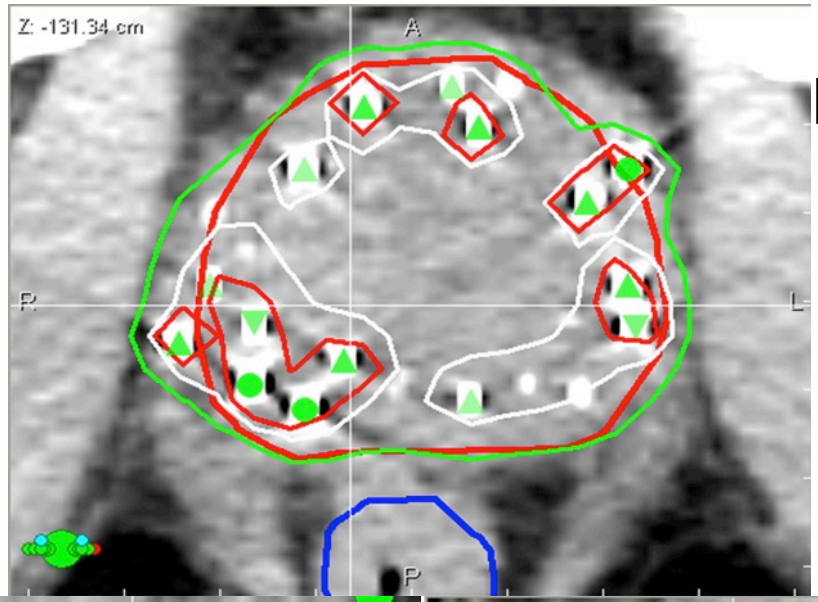


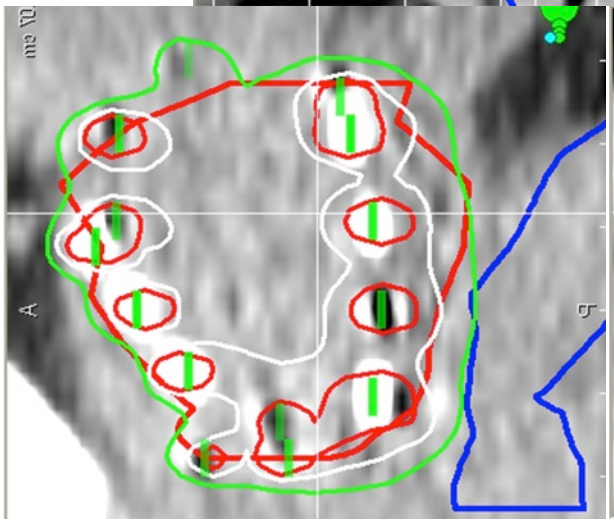


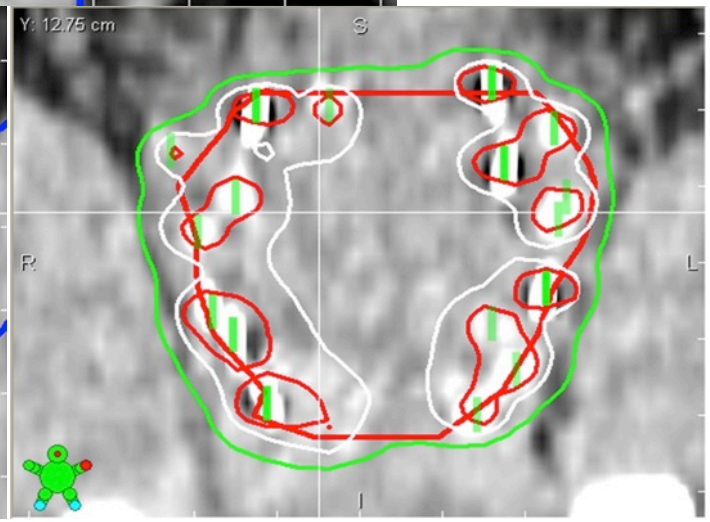




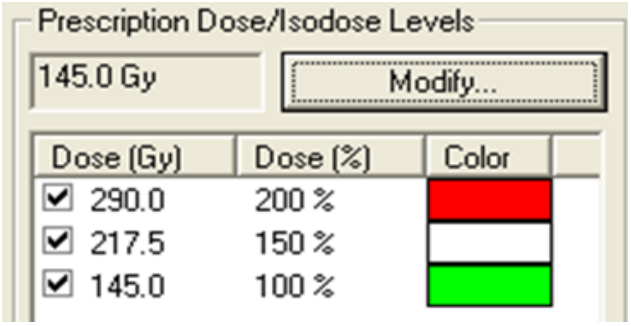
Prostate Brachytherapy





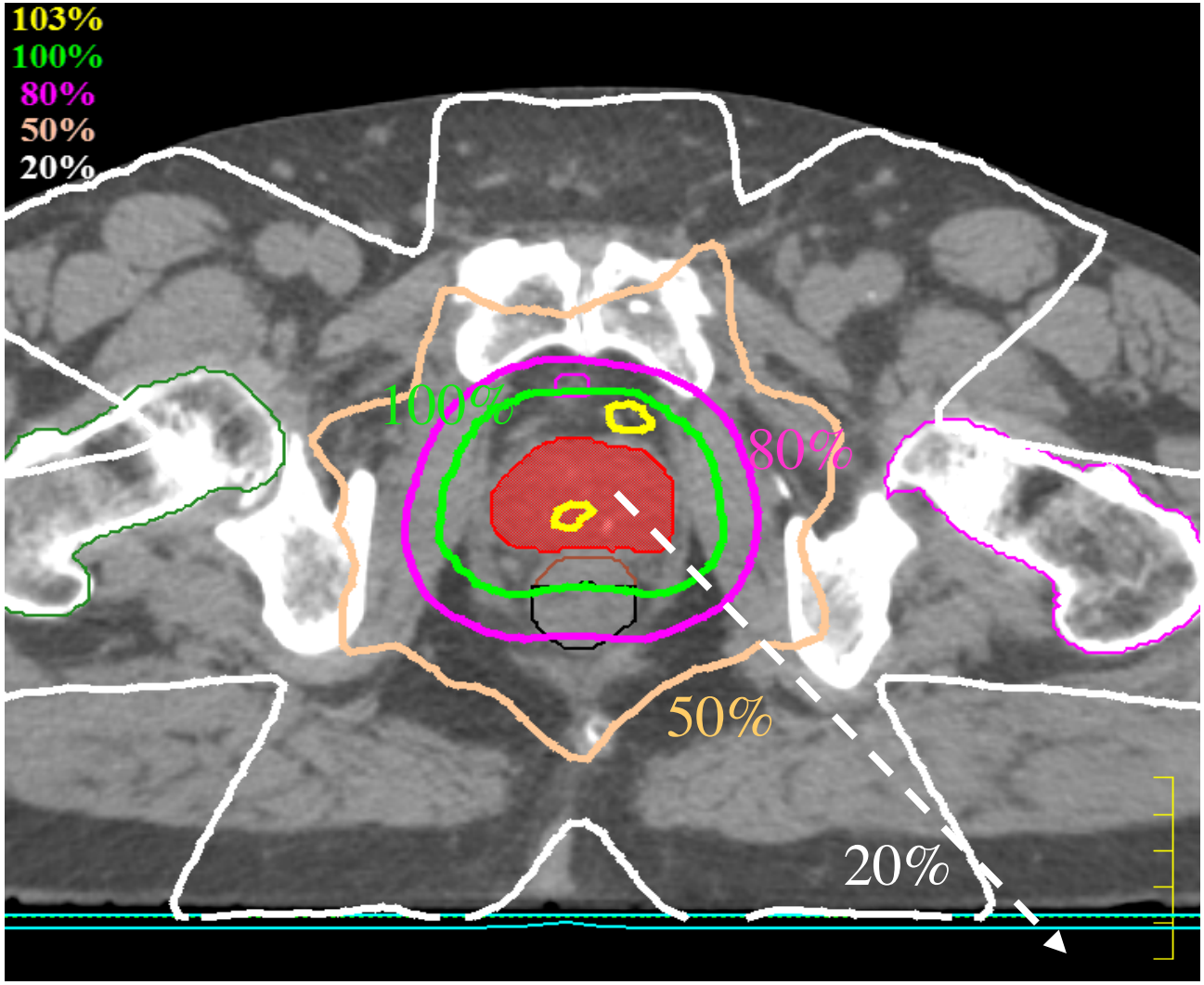


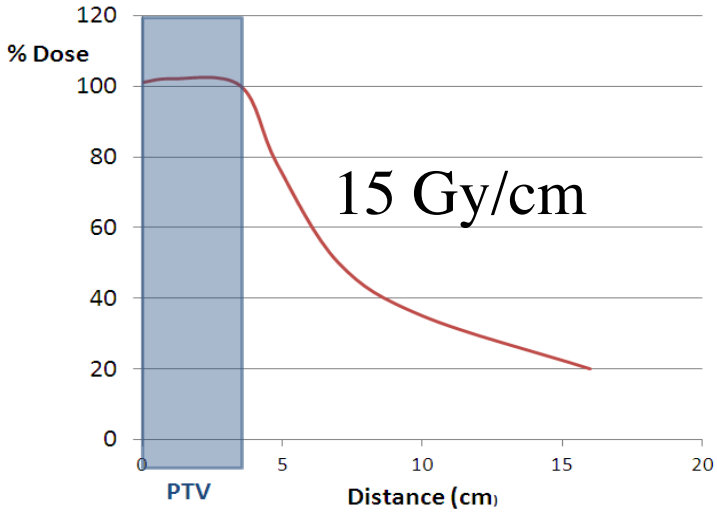
Prescribed Dose = 145 Gy (100%)
Mean Dose = 245 Gy (170%)



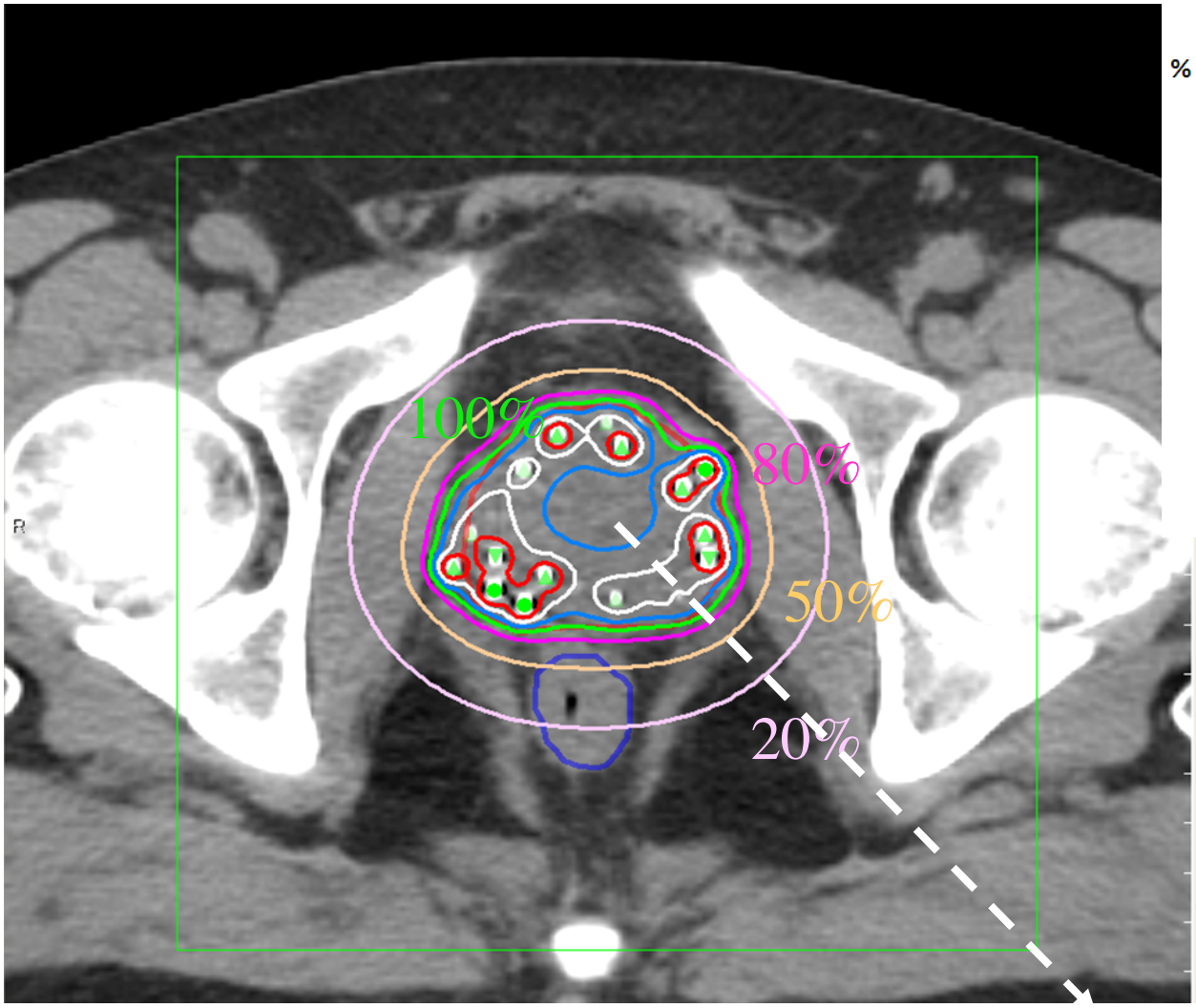
Much greater dose inhomogeneity within the target. What dose is actually given?

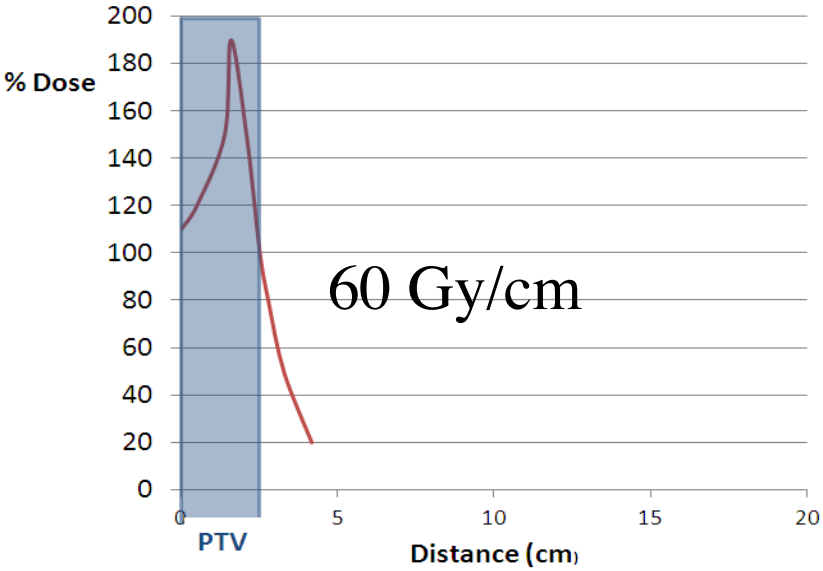
Prostate External Beam RT





Prostate Brachytherapy

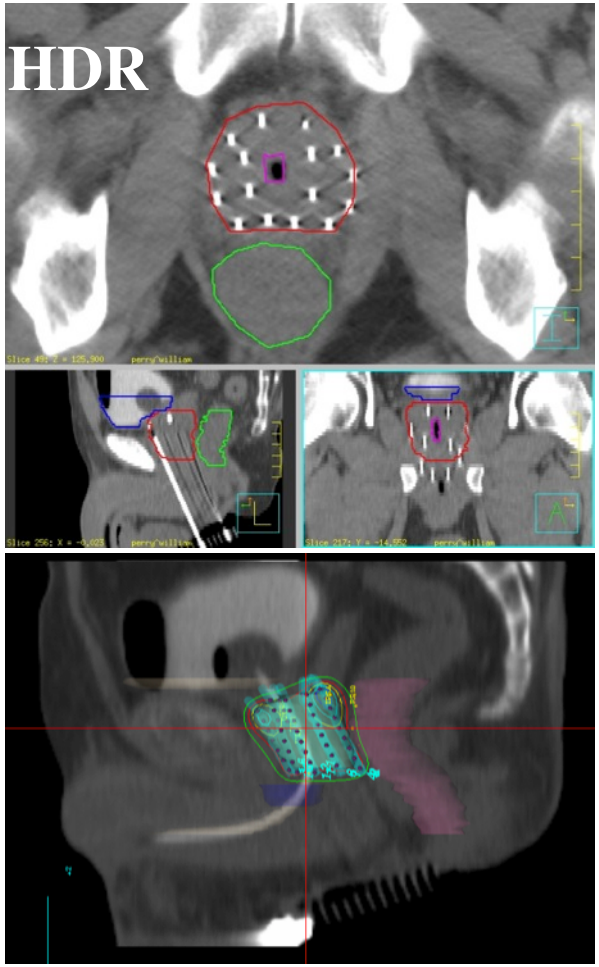




Dose (Gy)	Dose (%)	Color
☑ 290.0	200 %	
☑ 217.5	150 %	
☑ 174.0	120 %	
☑ 145.0	100 %	
☐ 137.7	95 %	
☑ 116.0	80 %	
☑ 72.5	50 %	
☑ 29.0	20 %	

Prostate Brachytherapy

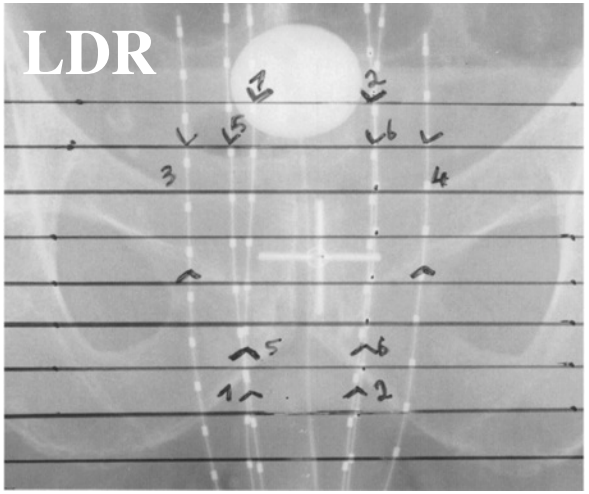
HDR (^{192}Ir)

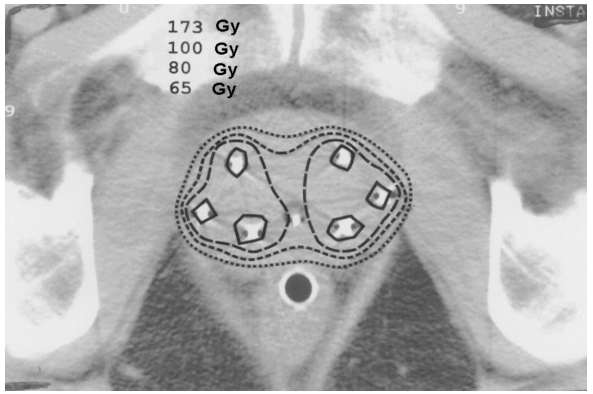


38 Gy/4 f in 2 days

> 60 Gy/hr

LDR (^{192}Ir, ^{137}Cs)

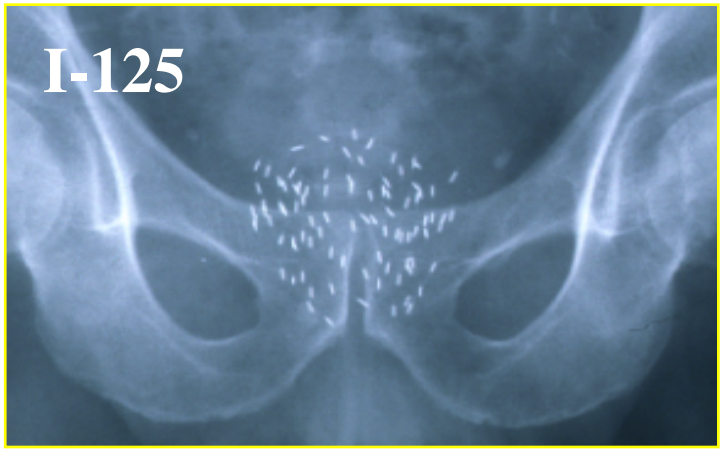


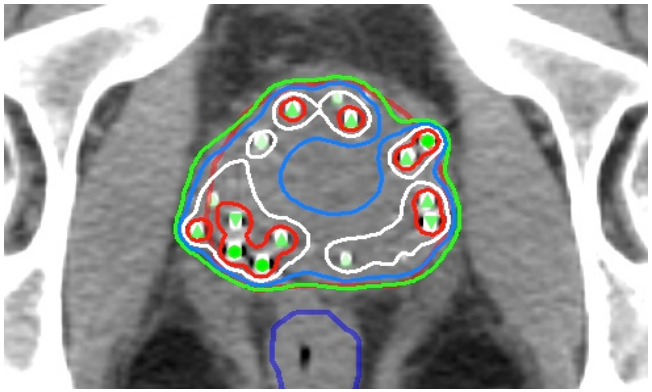


80 Gy ~ 6 days

0.6 Gy/hr

I-125 seeds

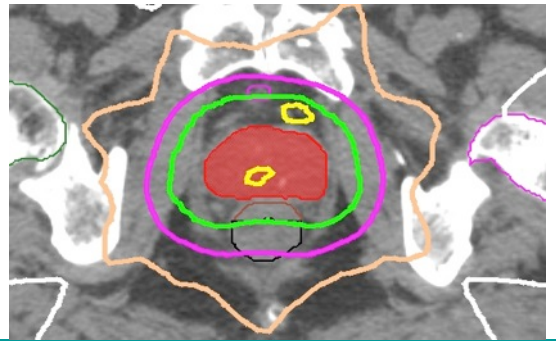


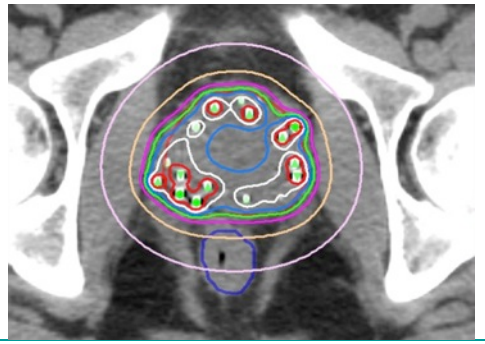


145 Gy Permanent

< 0.1 Gy/hr

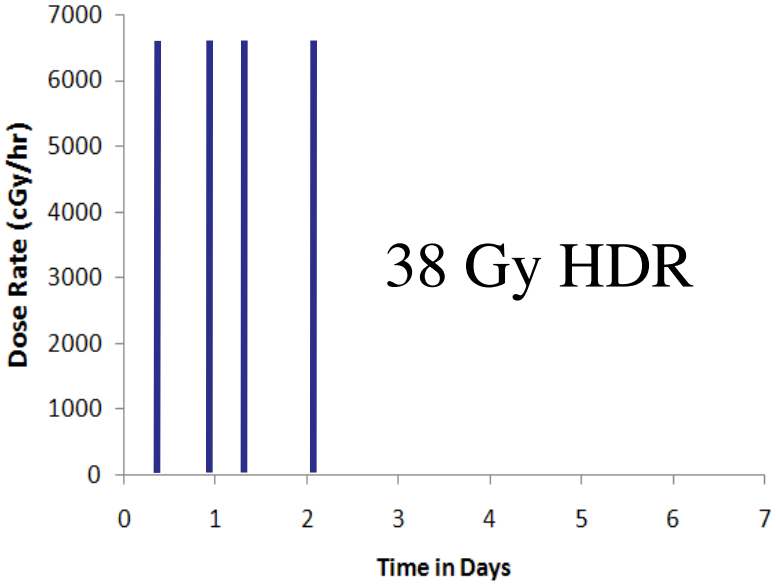
External Beam vs Brachytherapy



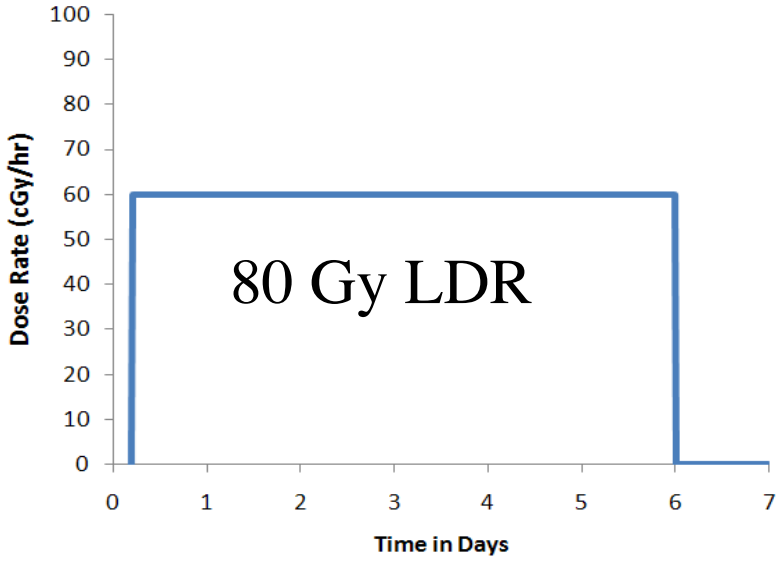


	EBRT	Brachytherapy
Homogeneity	Tight	Huge hot areas
Dose	High	Very High
Volume	Variable	Small
Dose Fall-Off	Moderate	Very Rapid
Dose Rate	High	Variable
Duration	5-8 weeks	days - months

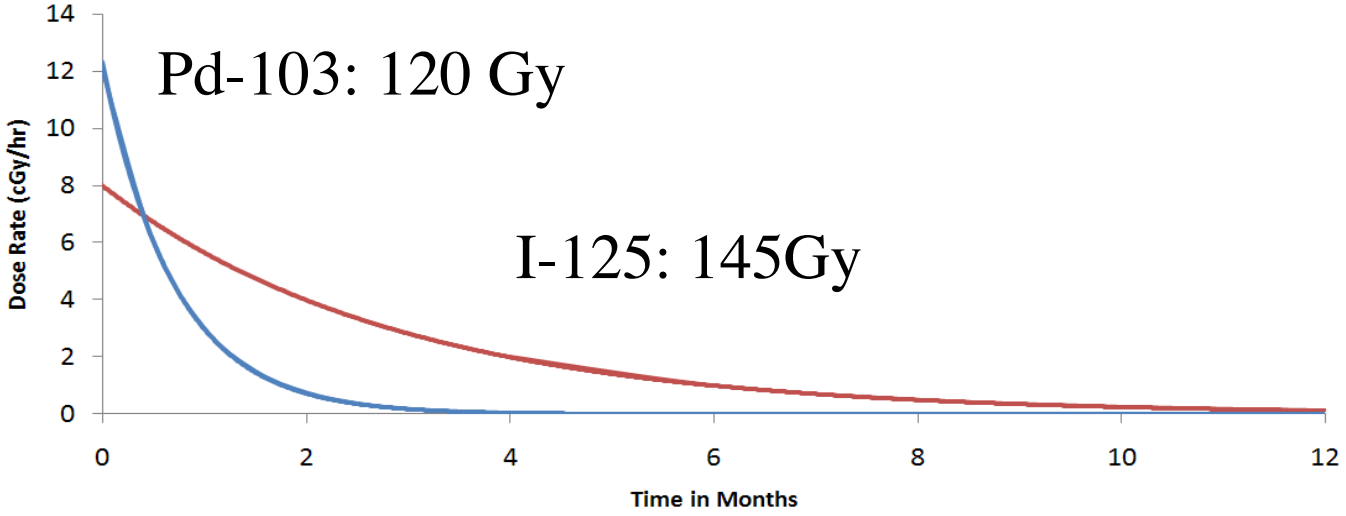
Schedules & dose rates for (prostate) brachytherapy



38 Gy HDR

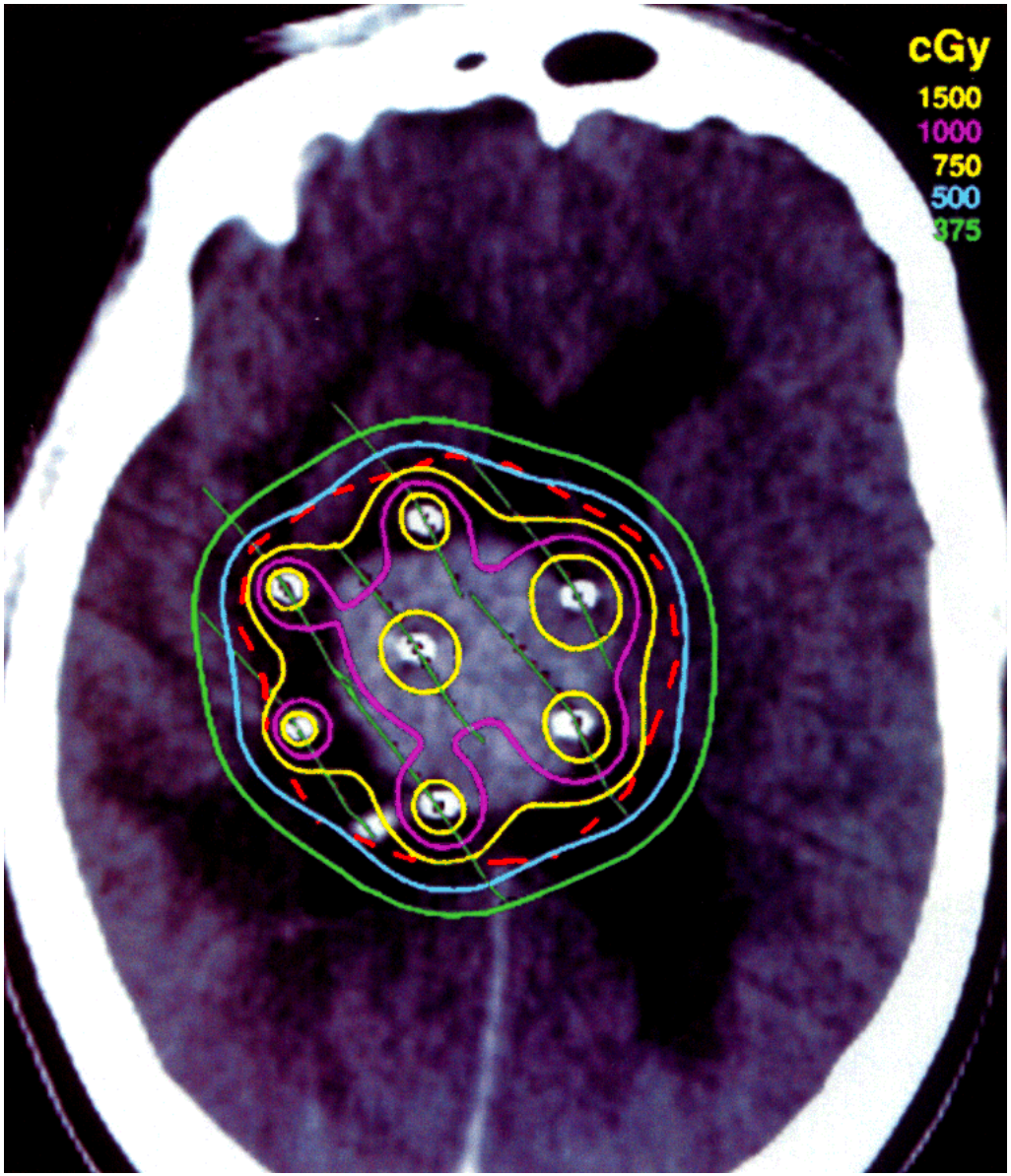


80 Gy LDR



Pd-103: 120 Gy

I-125: 145Gy



Treatment plan for brain implant

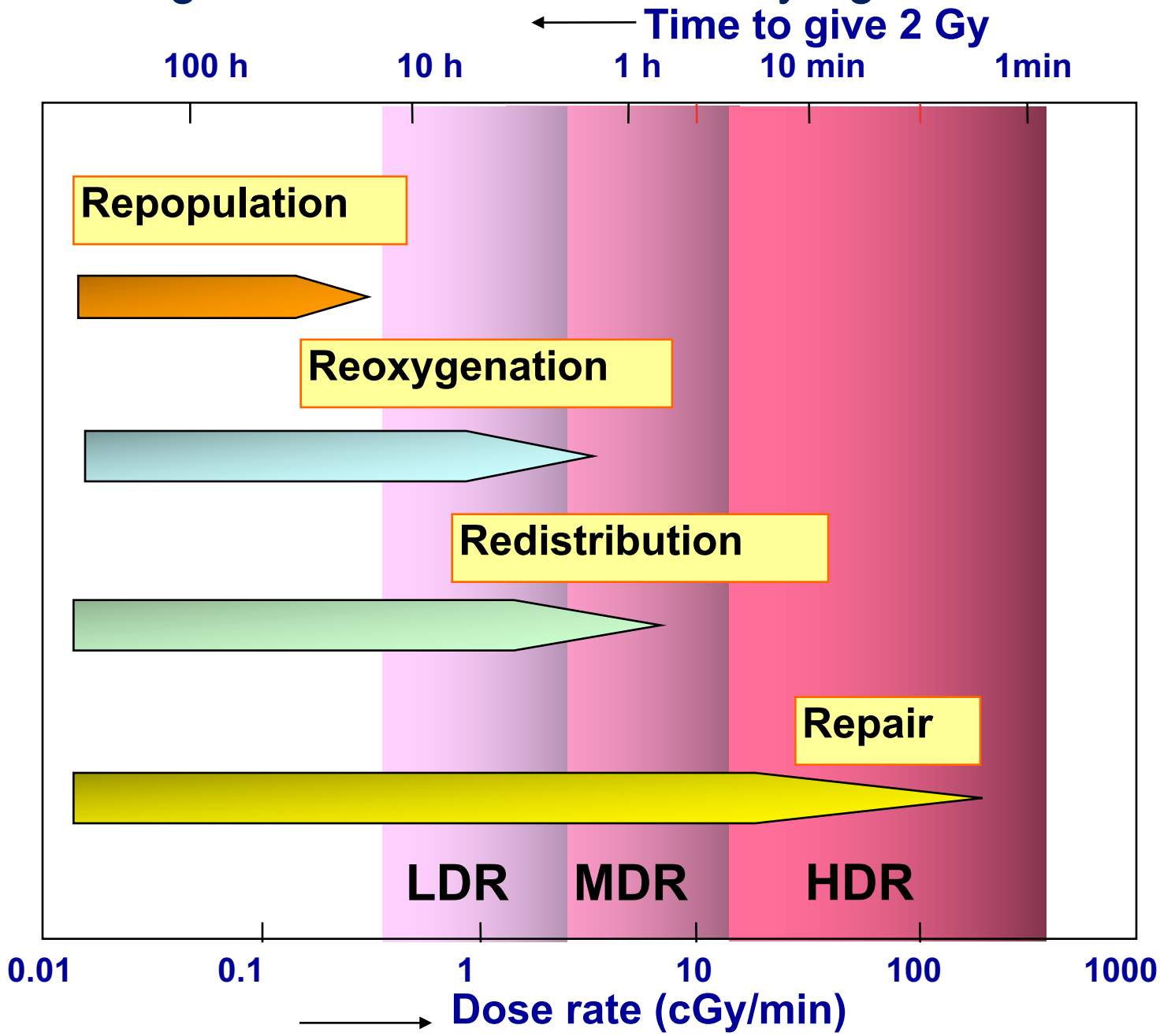
Inverse of “double trouble” at a distance from implants:

- decreasing dose rates
- decreasing total dose

In addition:

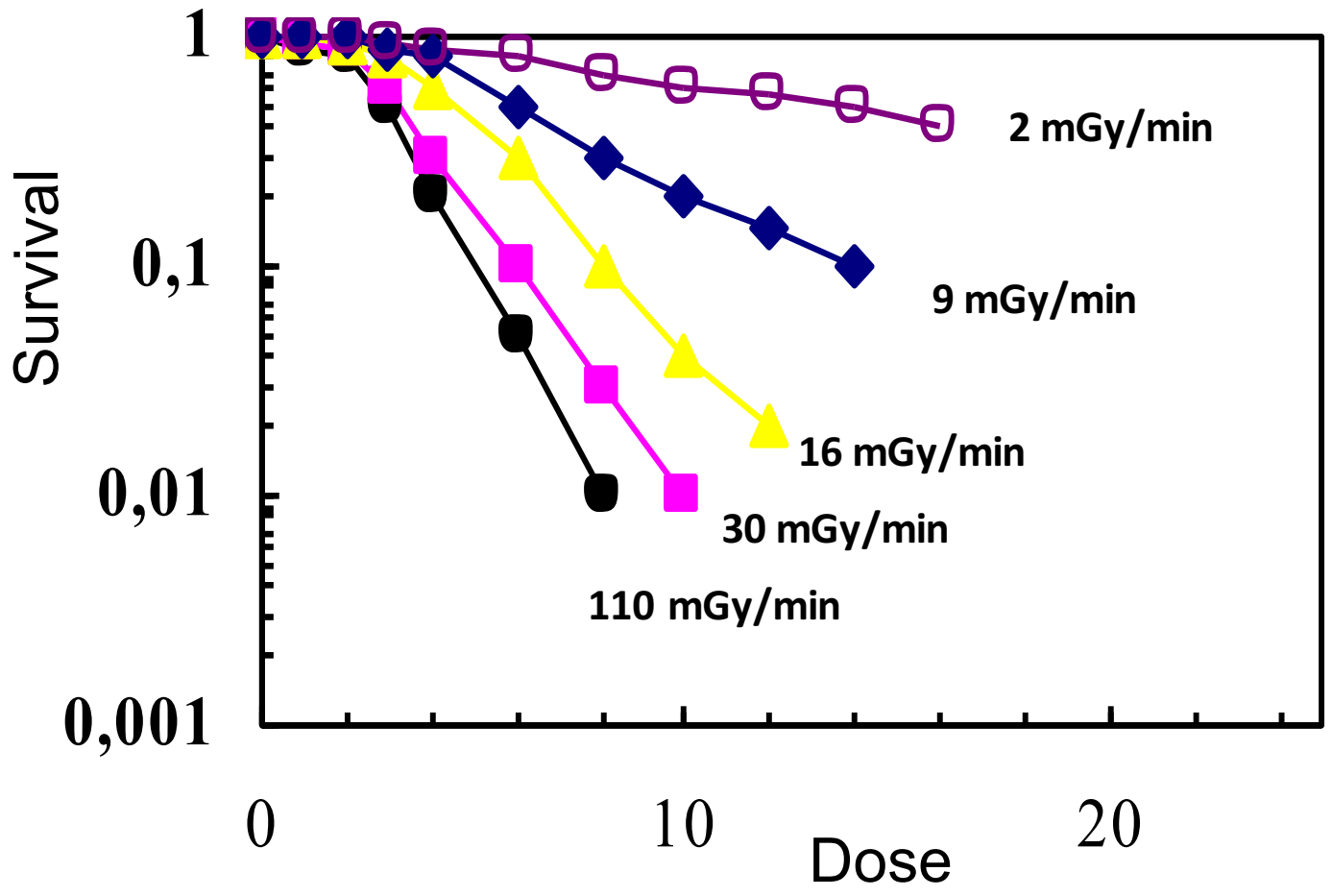
Small volumes

Radiobiological mechanisms underlying the dose rate effect

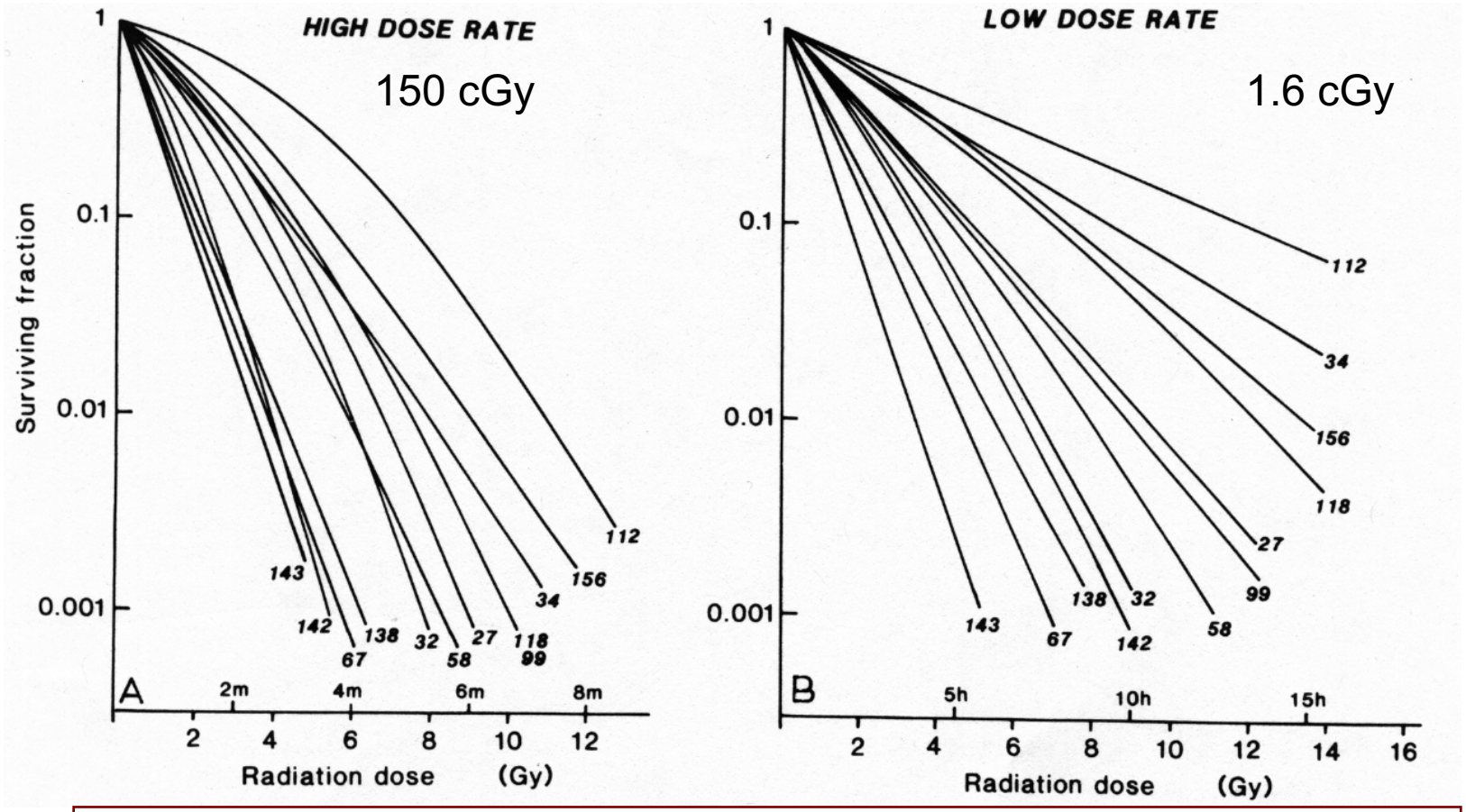


Modified from *Steel et al* (1986)

Cell survival curves for different dose rates



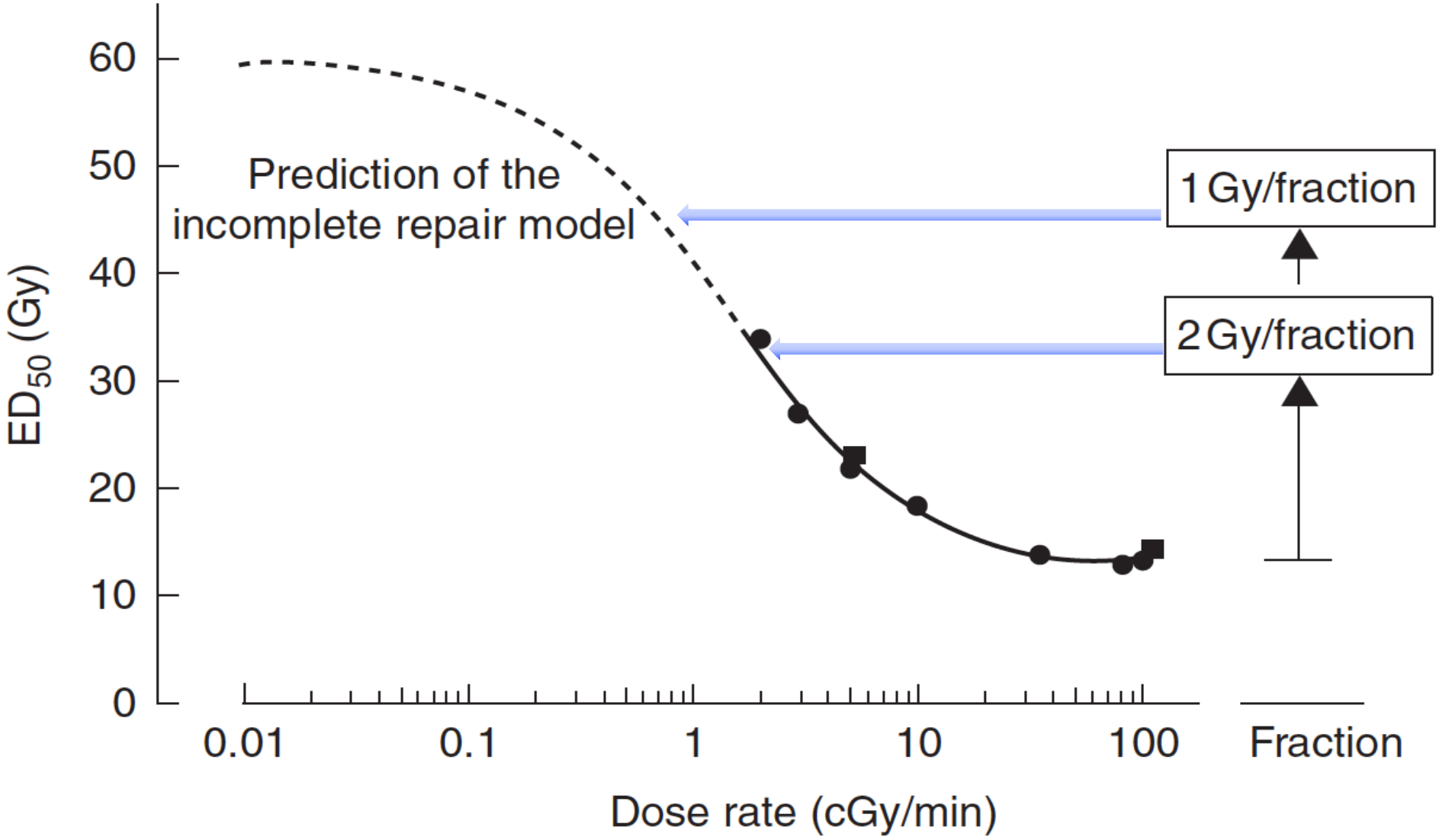
Cell survival curves for human cell lines



low dose rate: better discrimination between cells with different radiosensitivity

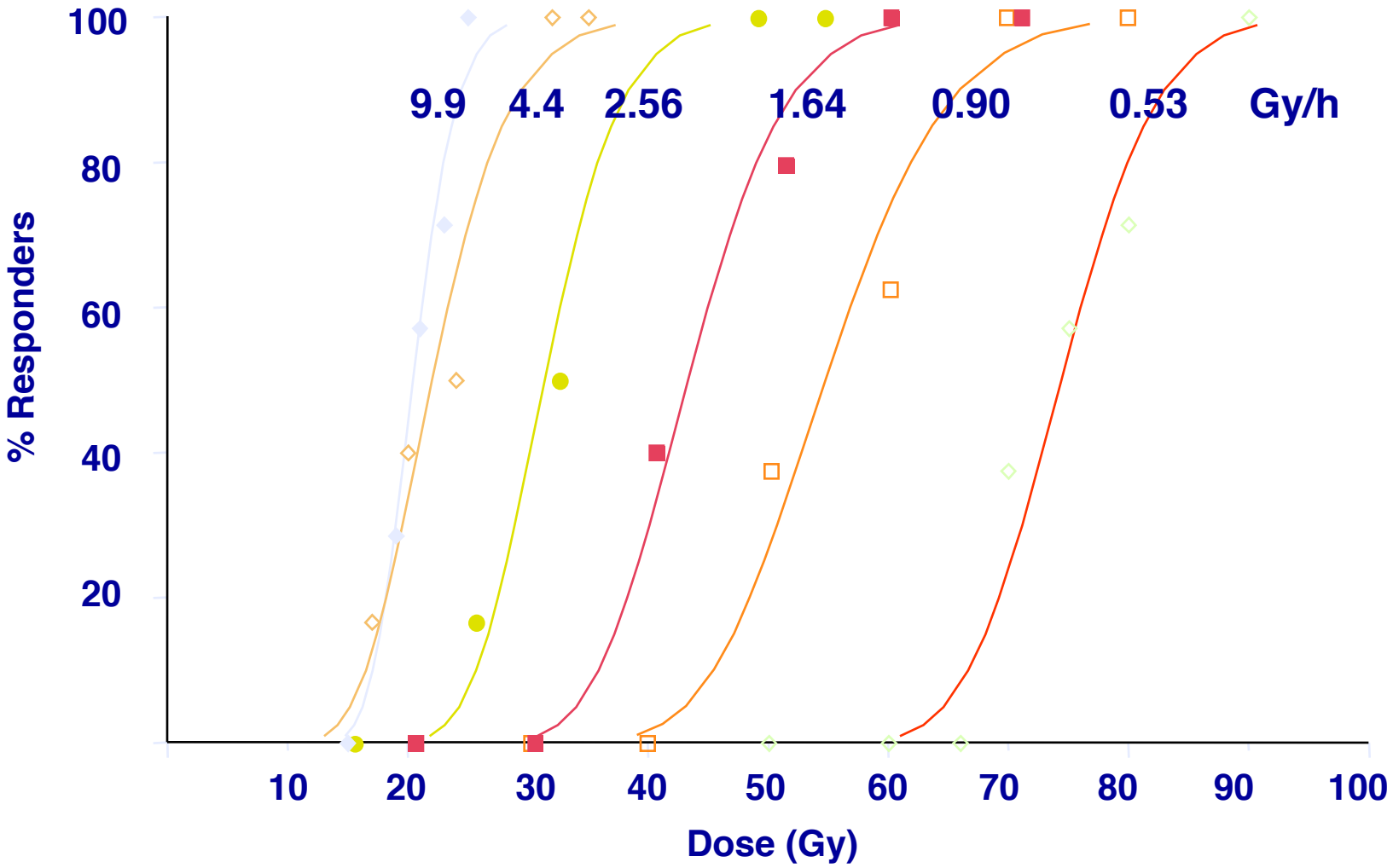
Dose rate effects in normal tissues

Dose-rate effect for pneumonitis in mice

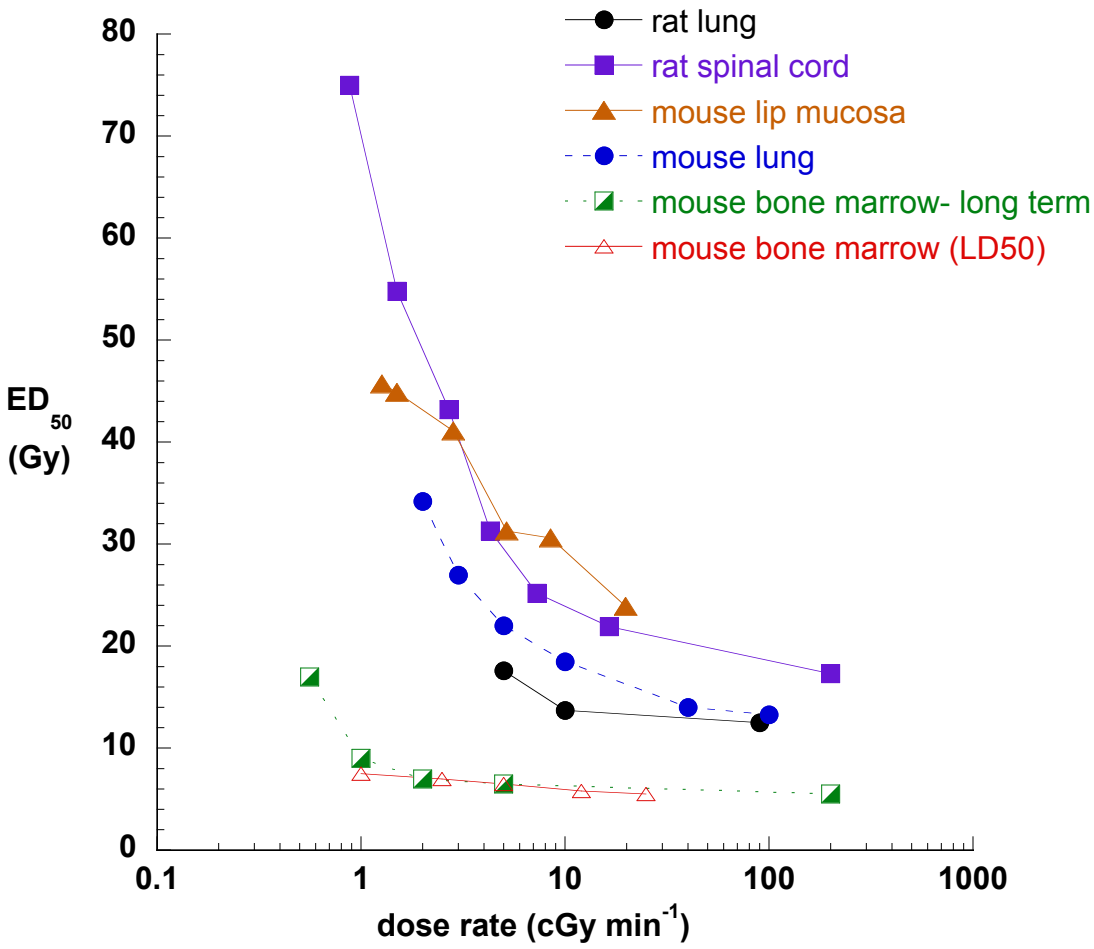


Down *et al.* (1986)

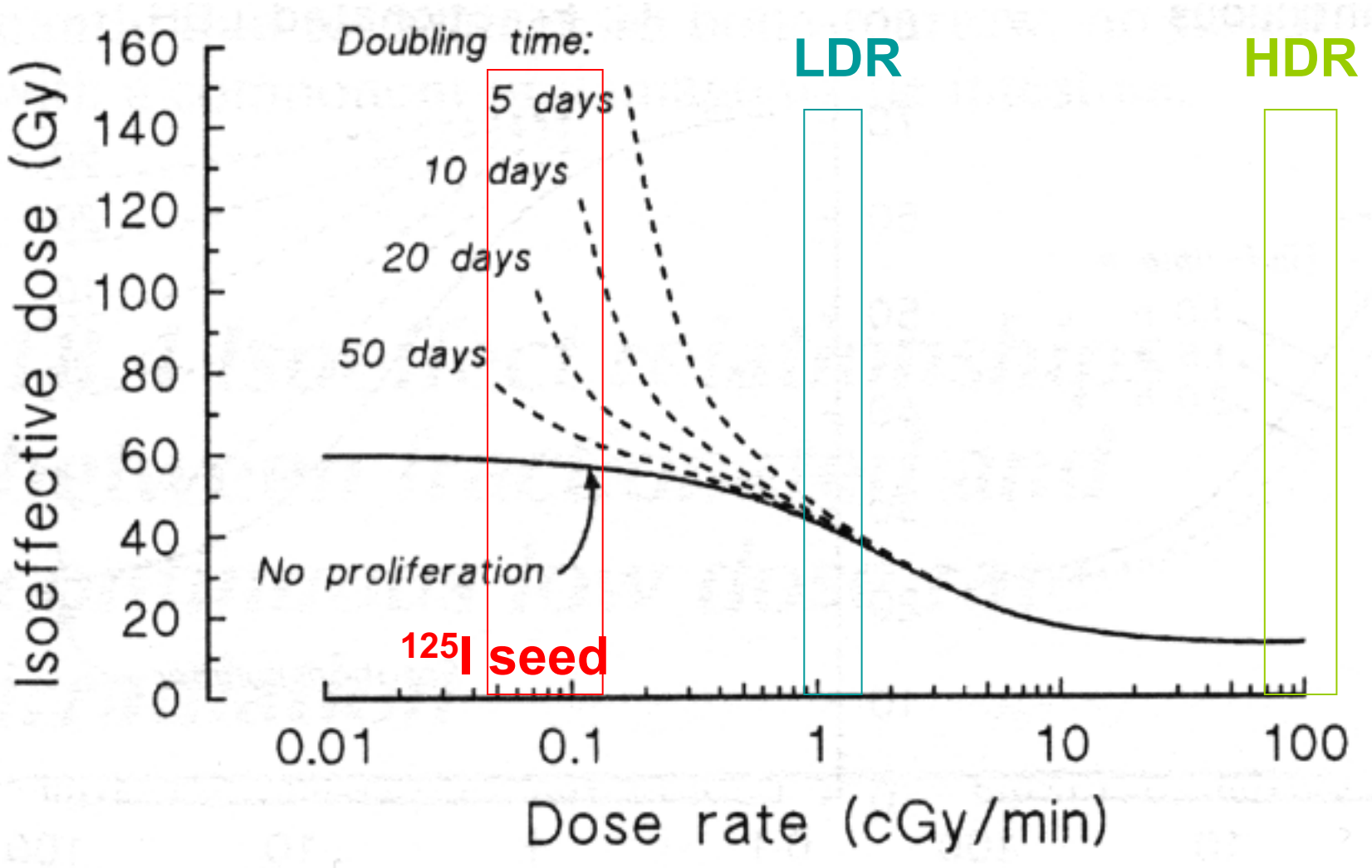
Dose-rate effects in rat spinal cord: continuous irradiation using ^{192}Ir- wires (= 6 different constant dose rates)



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.

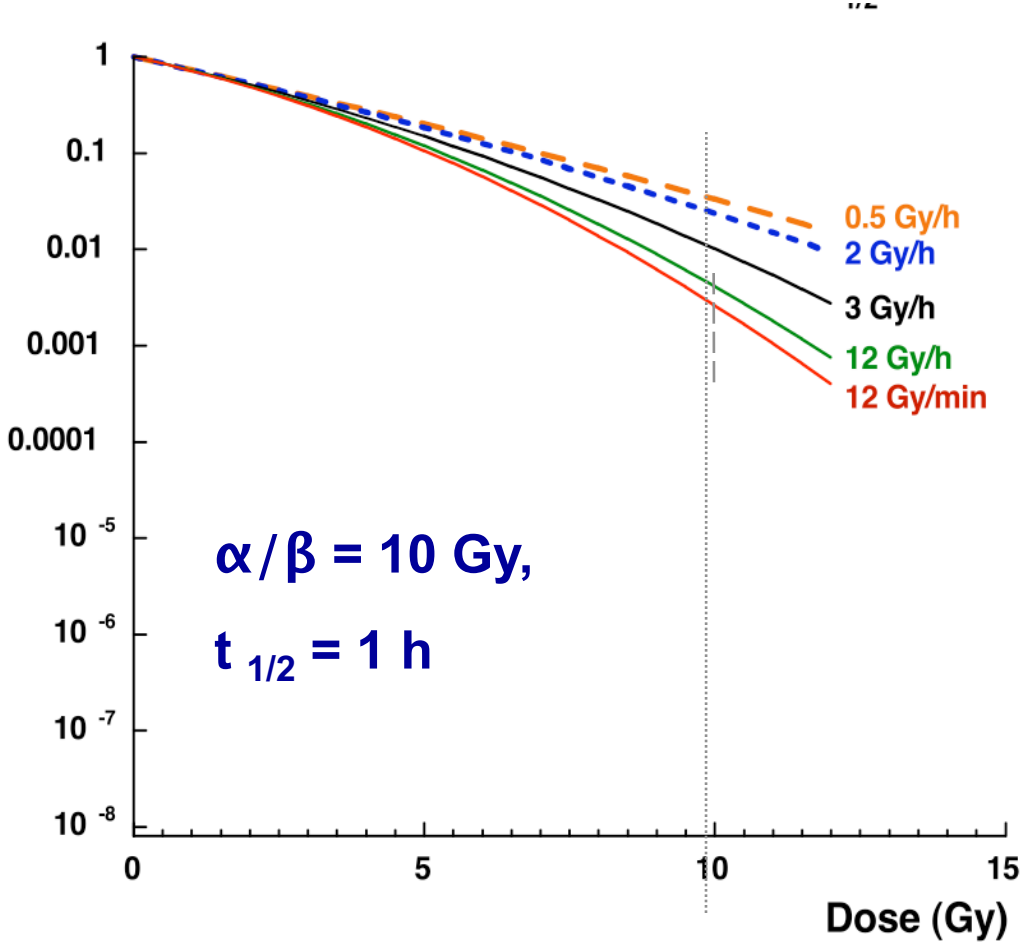
[#] continuous low dose rate; F, acute dose fractions; FLDR, fractionated low dose rate.

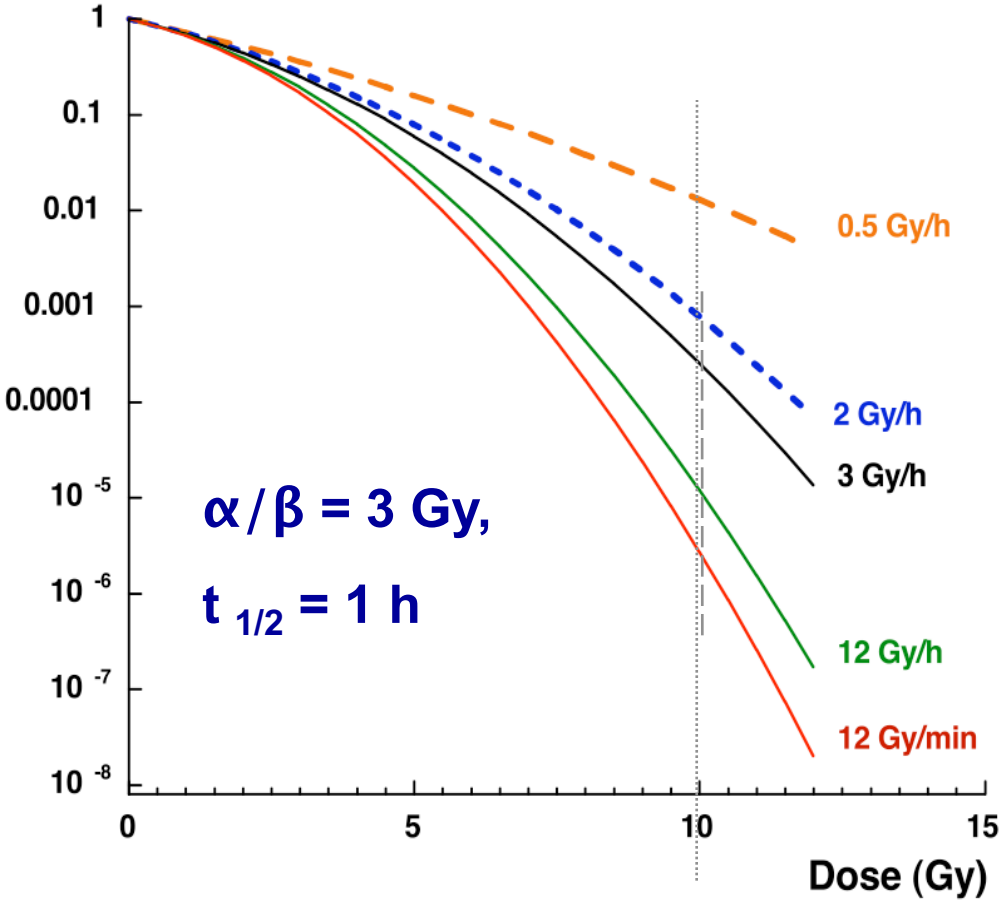
$T_{1/2}$ for late-responding human tissues

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)

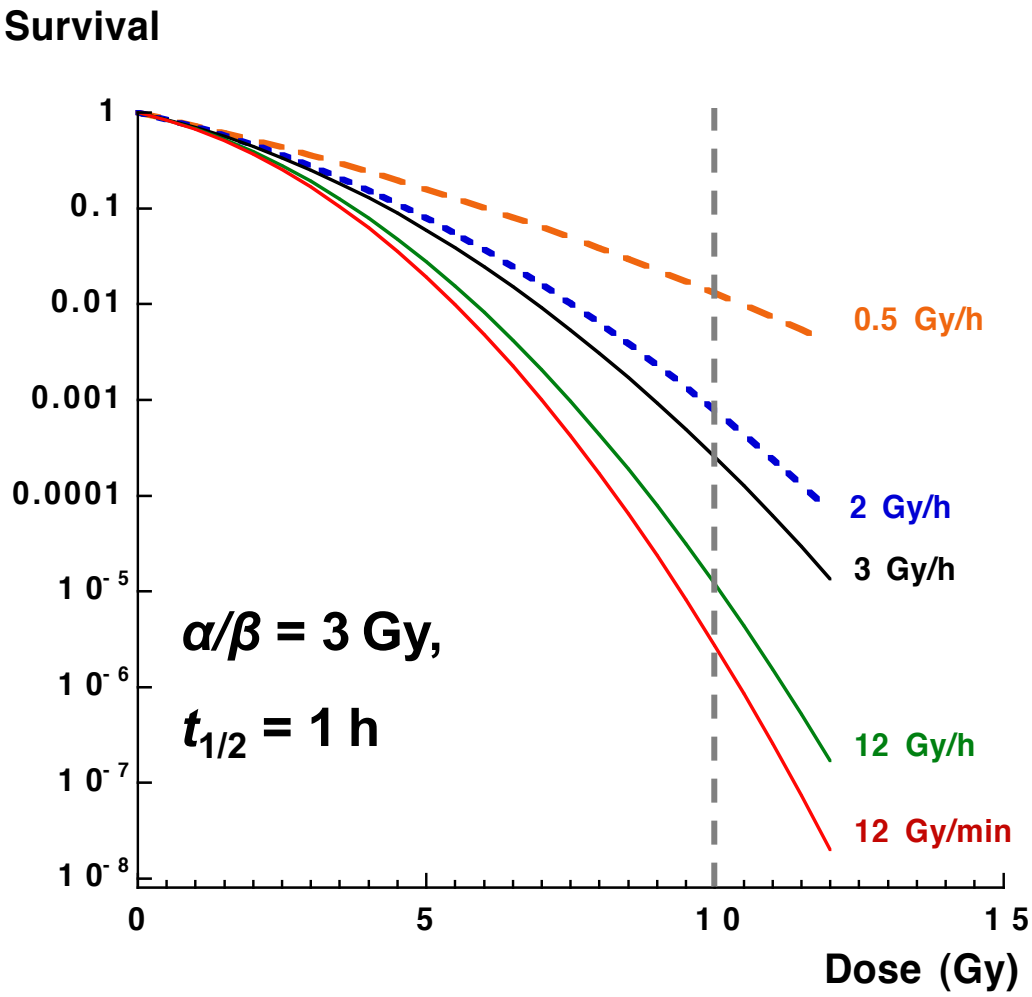
Effects at different dose rates: variation in α/β ratio

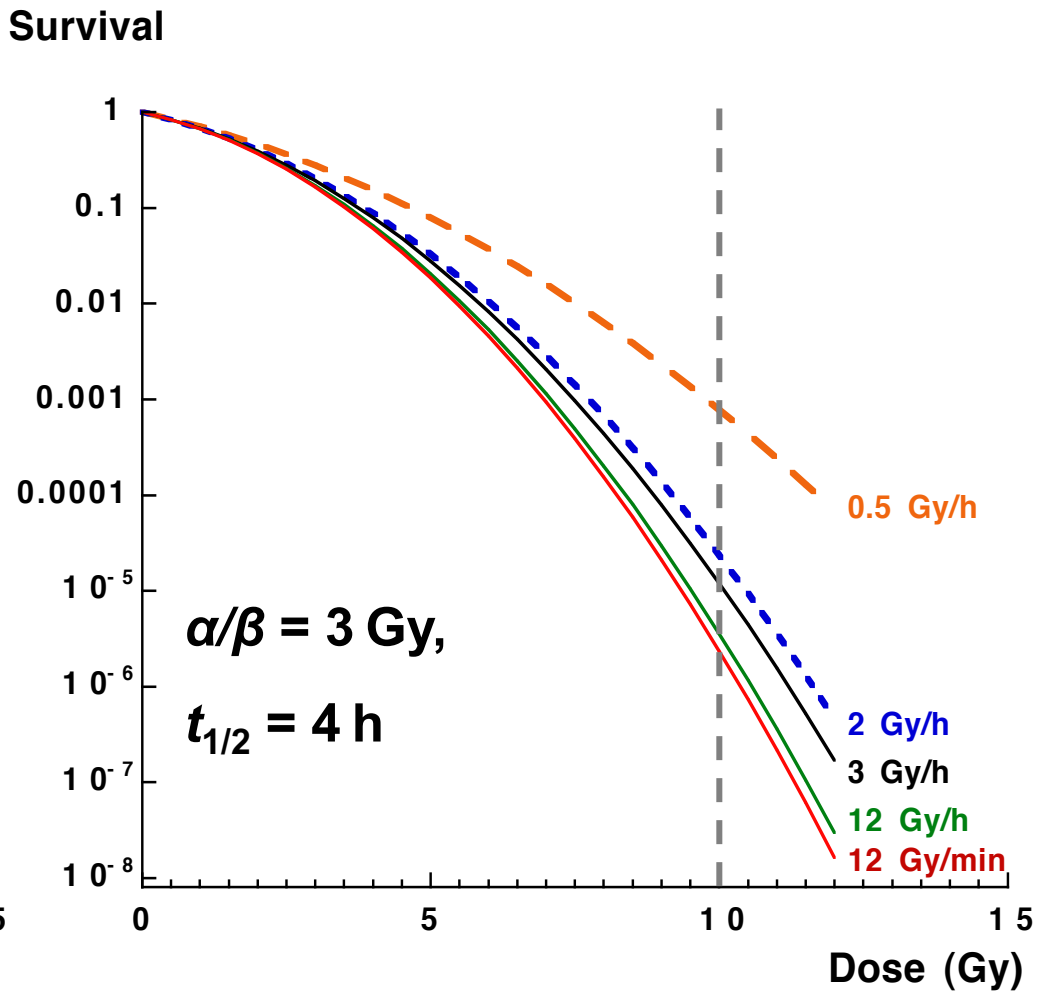




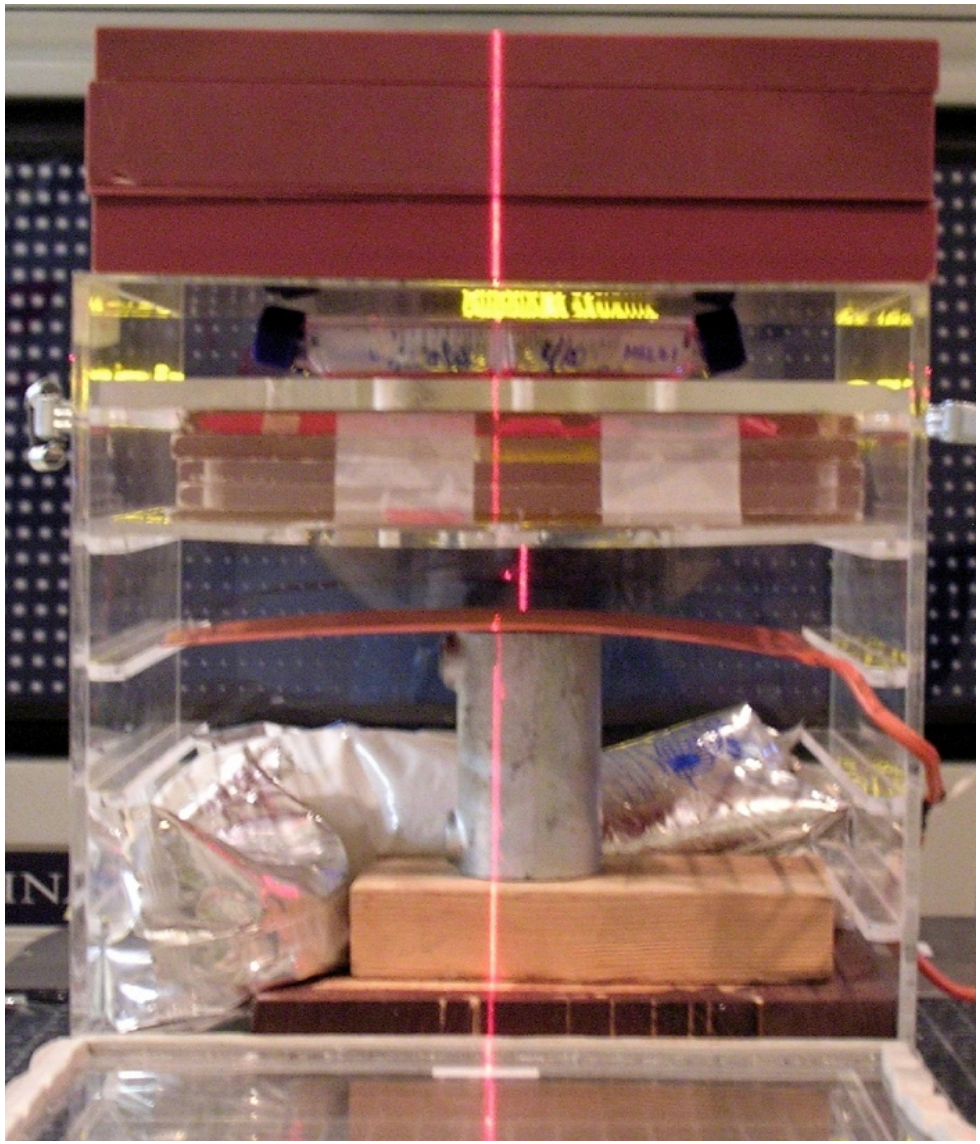
Tissue with low α/β more sensitive to change in dose rate

Low α/β values: variation in repair half-times ($t_{1/2}$)



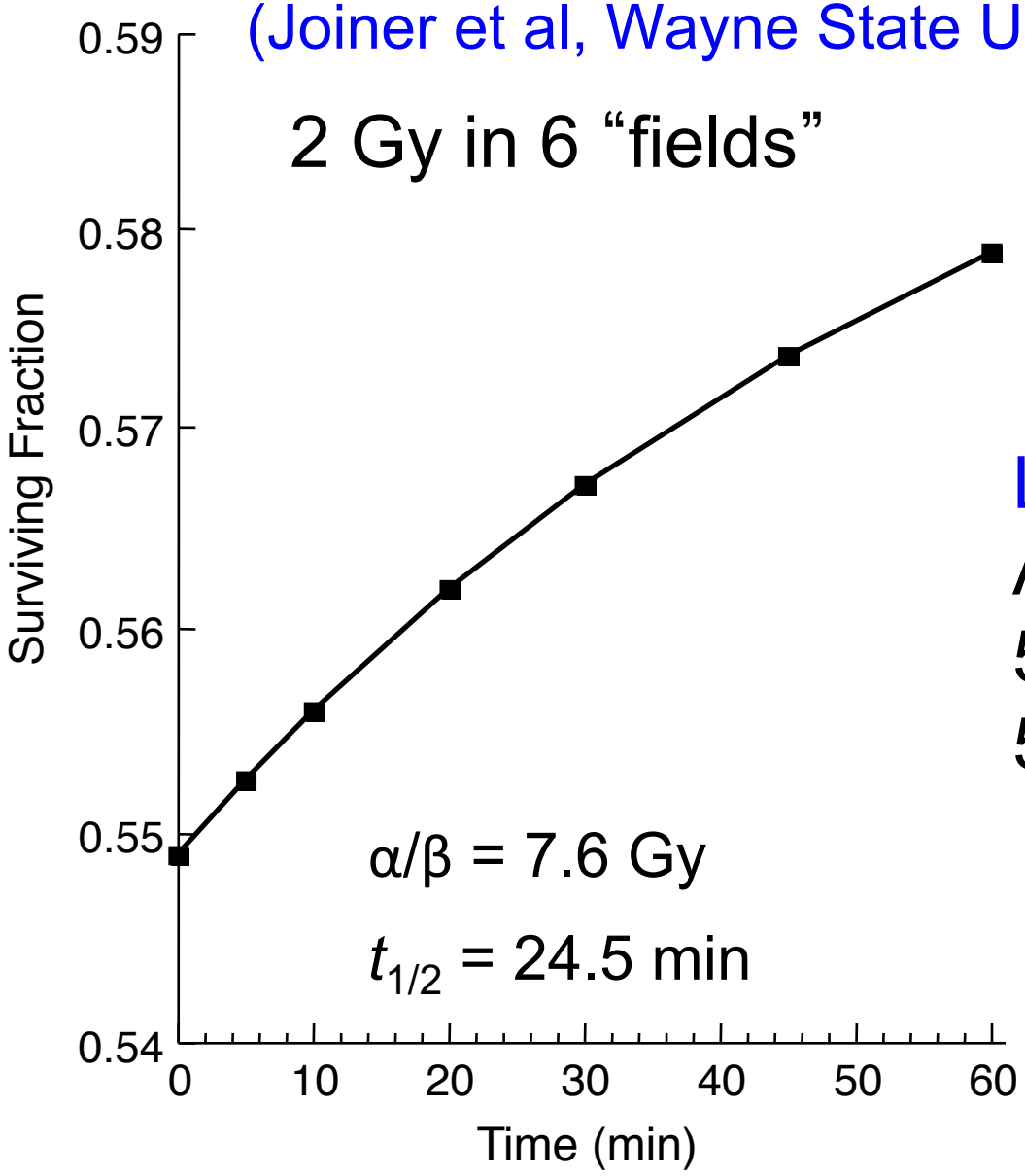


Loss of effect with increased treatment time in IMRT?



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:

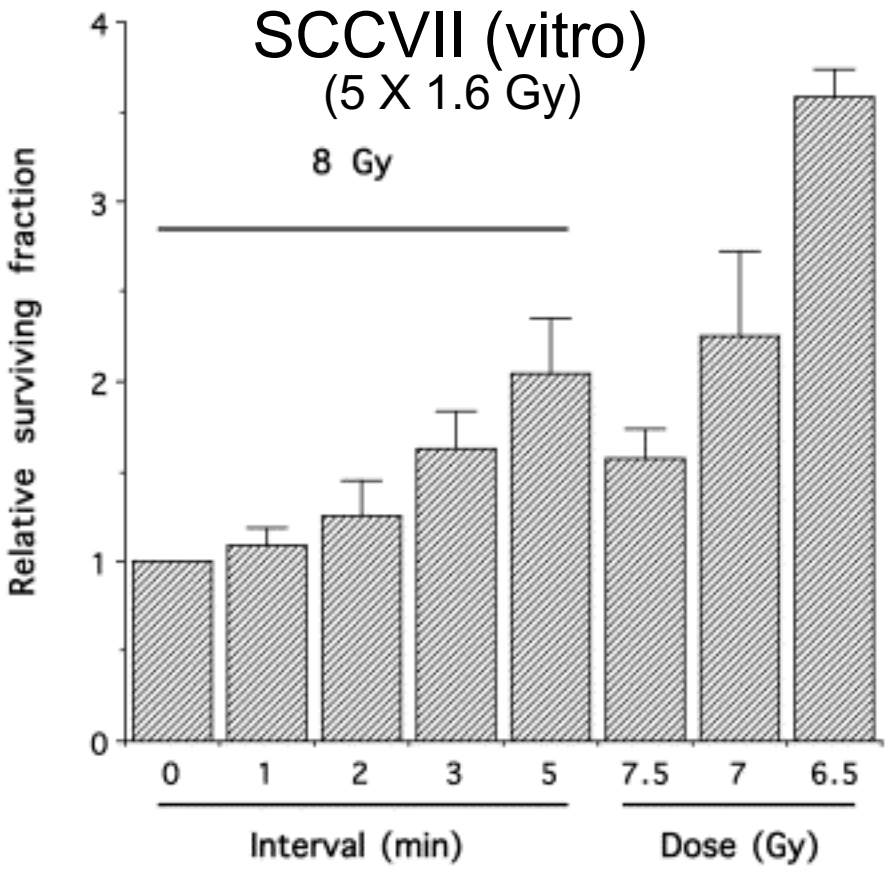
Acute to 60 min: 9%

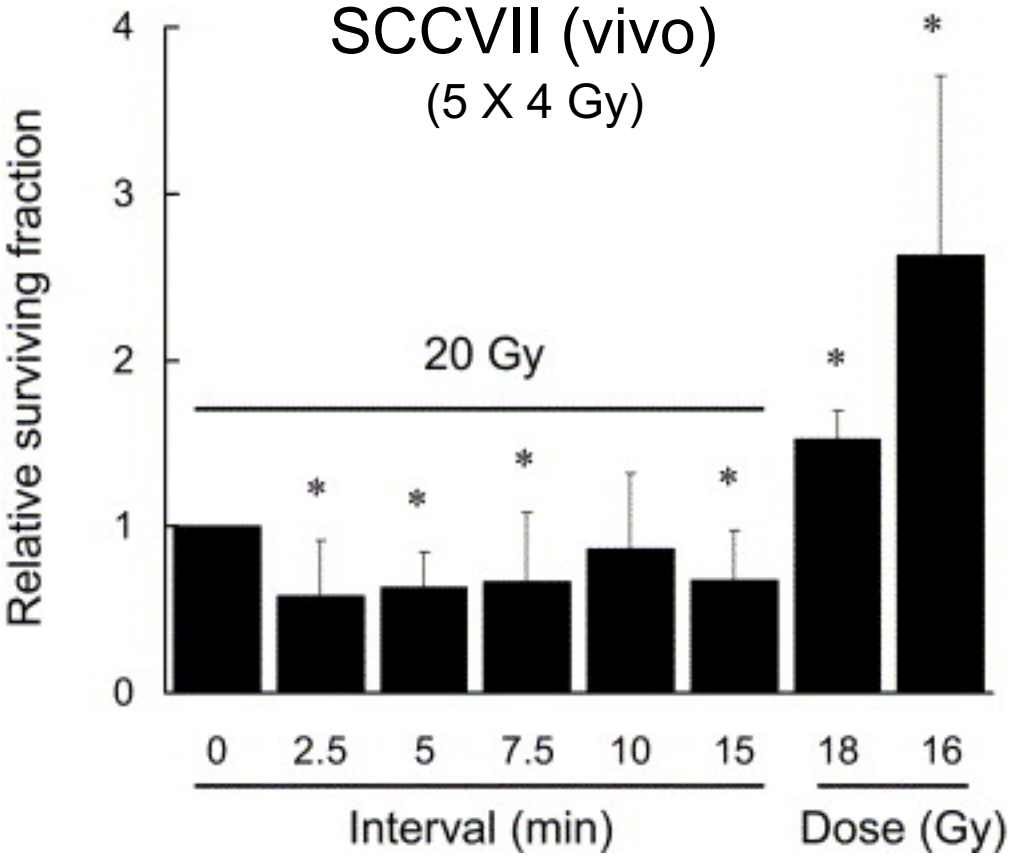
5 min to 45 min: 6%

5 min to 30 min: 4%

Joiner et al, Med. Phys. 2010

intermittent irradiation: loss of effect?

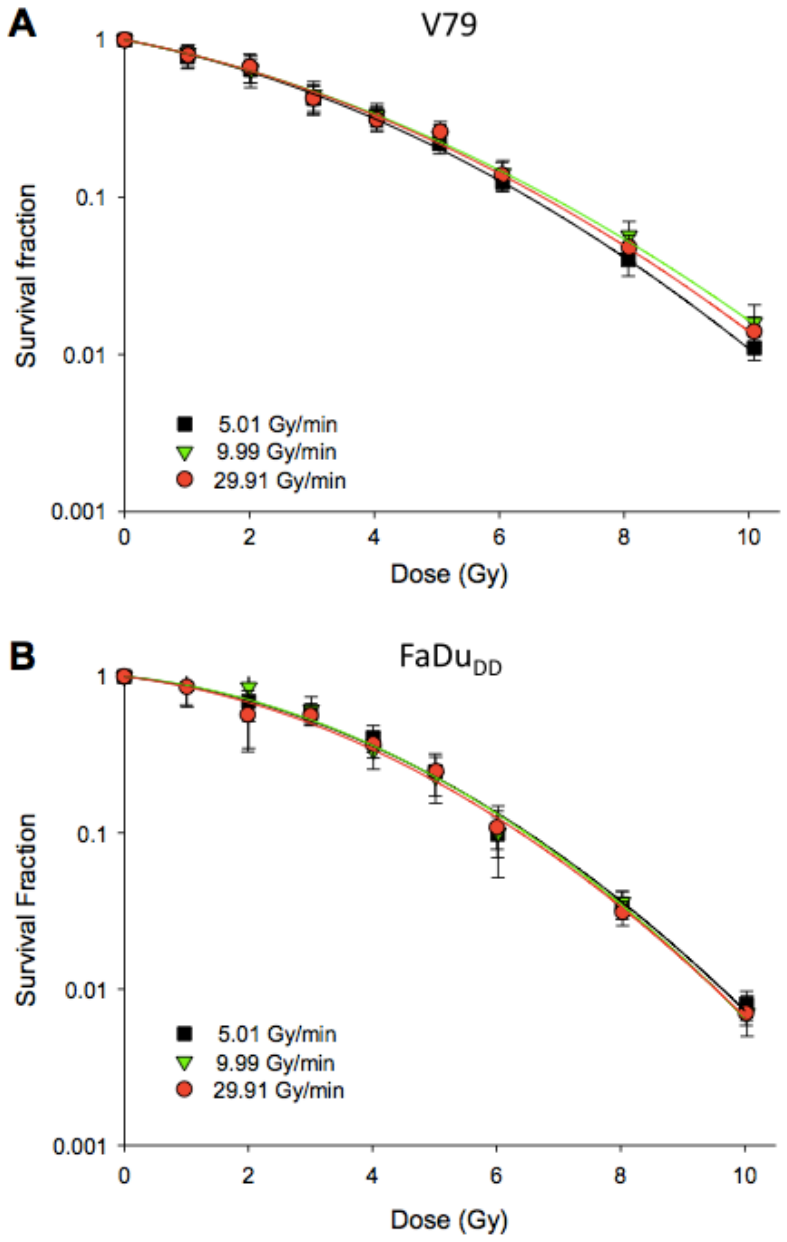




in vitro: loss of effect with short intervals

in vivo: recovery of sublethal damage compensated by reoxygenation

(Tomita et al, 2008)

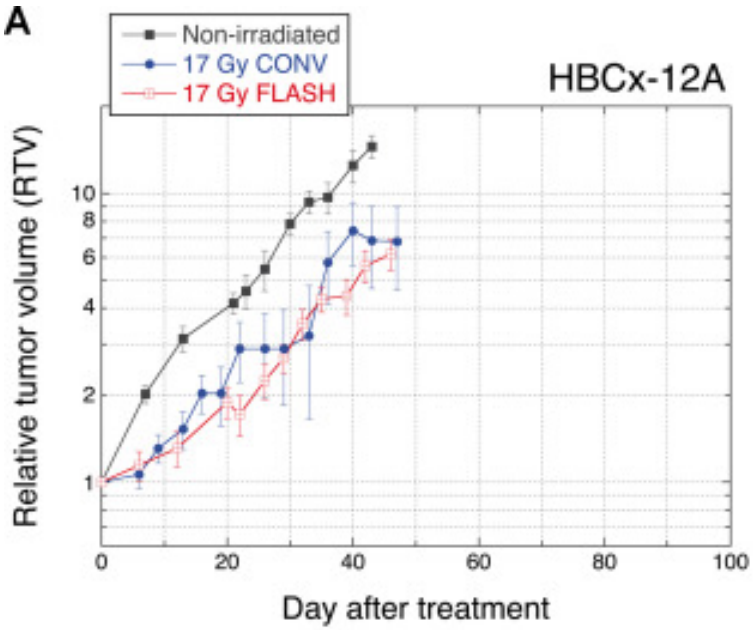


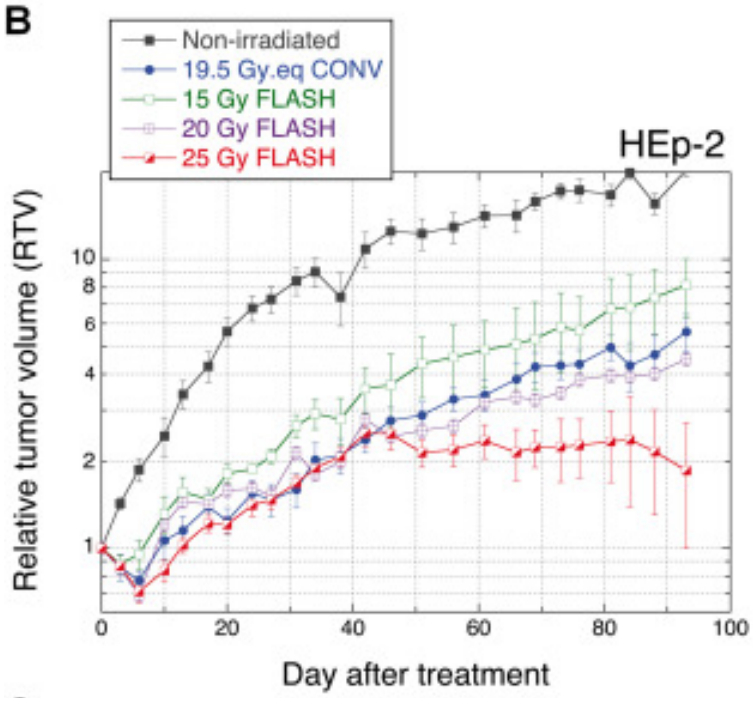
Effectiveness of very high dose rate

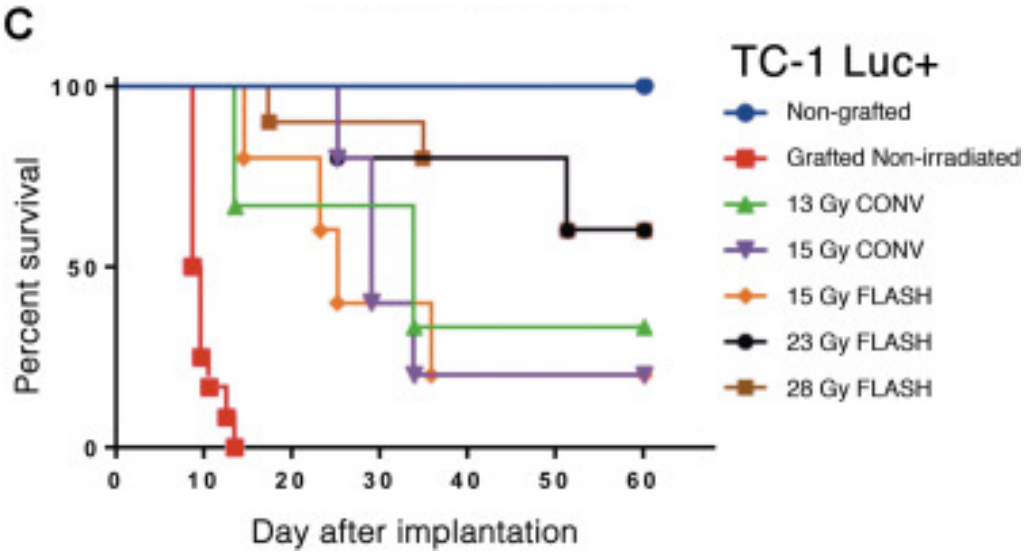
With the development of flattening filter-free linear accelerators for radiotherapy, the instantaneous dose rate has increased by approximately a factor 4.
The present study investigates the radiobiological effect of this high instantaneous dose rate on two cell lines

B.S. Sørensen et al. Radiother & Oncol 101 (2011) 223–225

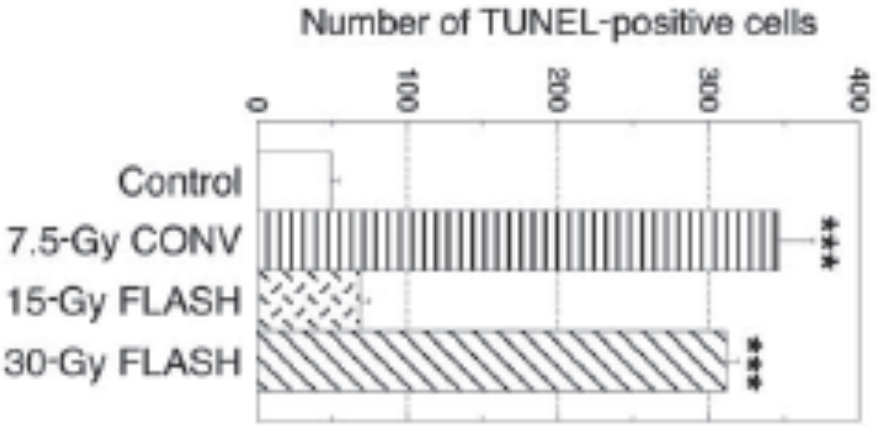
Effectiveness of very high dose rate Flash: 40 Gy/s

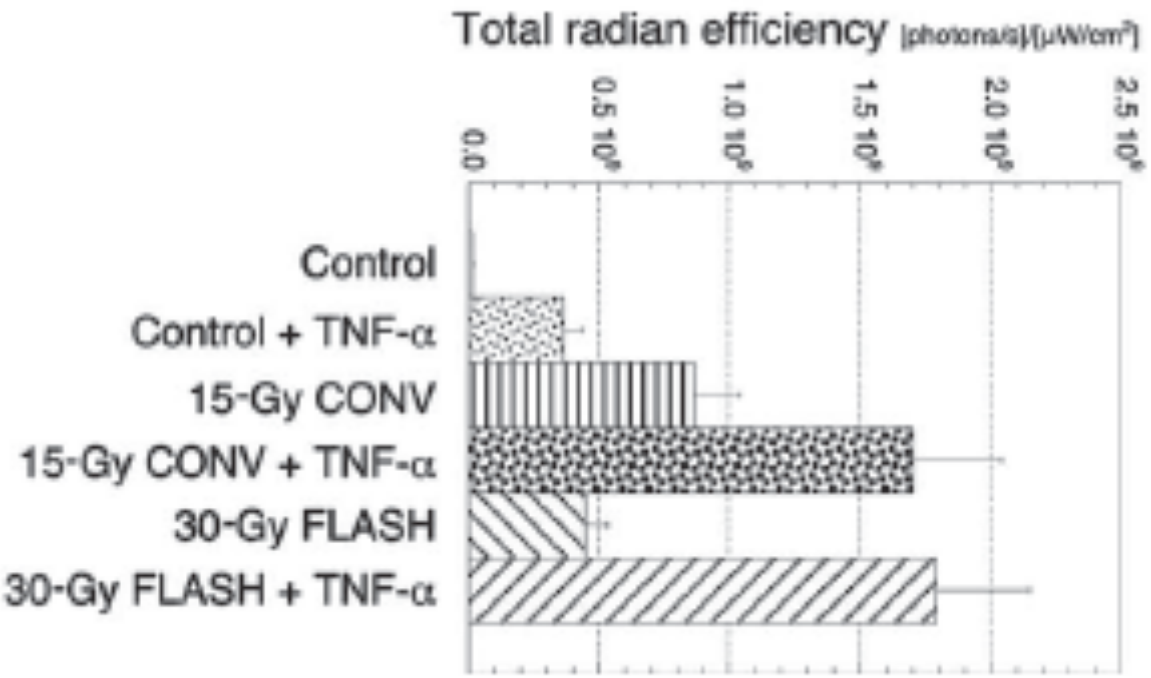






Fauvodon et al. Sci Transl Med. 2014





Fauvodon et al. Sci Transl Med. 2014

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 value)
- 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

Vincent GREGOIRE, MD, PhD, Hon. FRCR

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Radiotherapy and Oncology 95 (2010) 3–22

Contents lists available at ScienceDirect

Radiotherapy and Oncology

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

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Radiotherapy and Oncology 103 (2012) 5–7

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Systematic review

Charged particles in radiotherapy: A 5-year update of a systematic review

Dirk De Ruysscher [a,*], M. Mark Lodge [b], Bleddyn Jones [c], Michael Brada [d], Alastair Munro [e], Thomas Jefferson [f], Madelon Pijls-Johannesma [a]

[a] Department of Radiation Oncology (MAASTRO), Maastricht University Medical Center, The Netherlands; [b] International Network for Cancer Treatment and Research, Oxford; [c] Gray Institute for Radiation Oncology and Biology, University of Oxford; [d] Institute of Cancer Research, Sutton; [e] Department of Radiotherapy, University of Dundee, UK; [f] Independent Epidemiologist, Rome, Italy

ESTRO 2017

VOLUME 32 · NUMBER 26 · SEPTEMBER 10 2014

JOURNAL OF CLINICAL ONCOLOGY | REVIEW ARTICLE

Promise and Pitfalls of Heavy-Particle Therapy

Timur Mitin and Anthony L. Zietman

A B S T R A C T

Proton beam therapy, the most common form of heavy-particle radiation therapy, is not a new invention, but it has gained considerable public attention because of the high cost of installing and operating the rapidly increasing number of treatment centers. This article reviews the physical properties of proton beam therapy and focuses on the up-to-date clinical evidence comparing proton beam therapy with the more standard and widely available radiation therapy treatment alternatives. In a cost-conscious era of health care, the hypothetical benefits of proton beam therapy will have to be supported by demonstrable clinical gains. Proton beam therapy represents, through its scale and its cost, a battleground for the policy debate around managing expensive technology in modern medicine.

J Clin Oncol 32:2855-2863. © 2014 by American Society of Clinical Oncology

ESTRO 2017

Advanced Drug Delivery Reviews 109 (2017) 26–44

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Proton therapy – Present and future☆

Radhe Mohan [a,*], David Grosshans [b]

[a] Department of Radiation Physics, MD Anderson Cancer Center, Houston, TX 77030, United States
[b] Department of Radiation Oncology, MD Anderson Cancer Center, Houston, TX 77030, United States

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Mohan et al. 2017

Uncharged	Charged	
X rays γ rays	e^- p^+ He^{2+}	Low LET
Neutrons	C^{6+} Ne^{10+} Si^{14+} Ar^{18+}	High LET

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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)

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Improvement of **ballistic selectivity**

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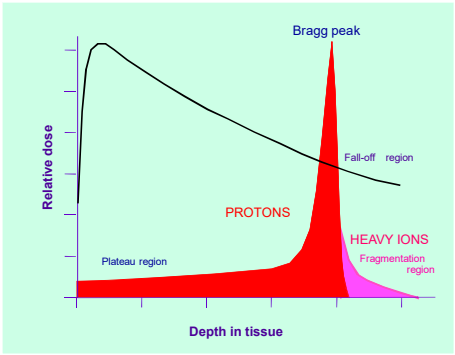

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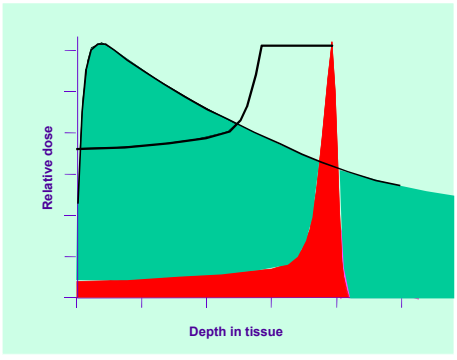

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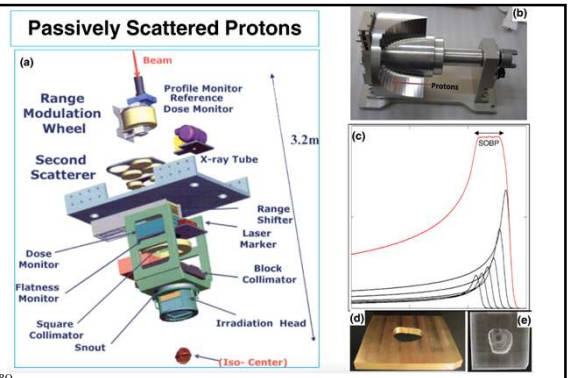

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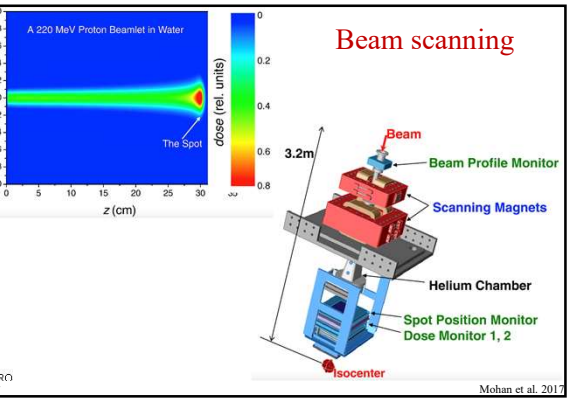
Mohan et al. 2017



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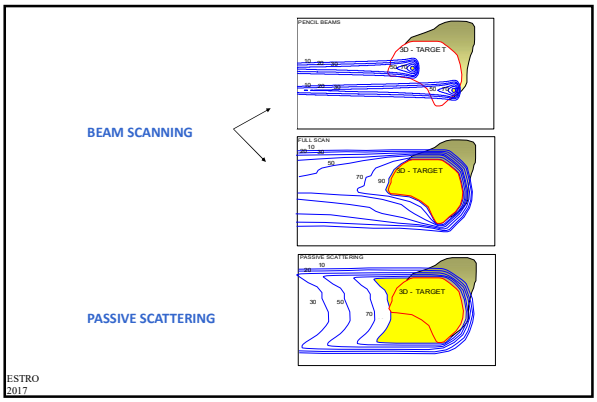
Mohan et al. 2017



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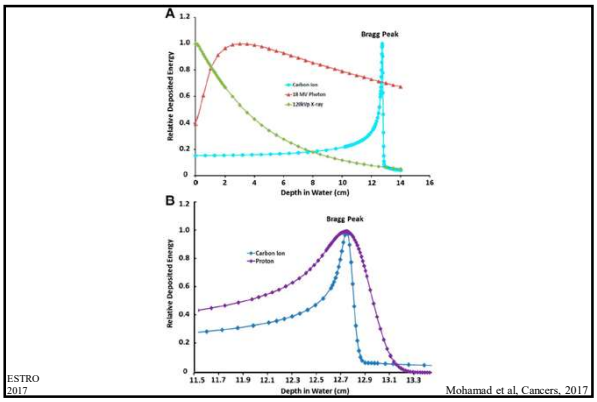

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Mohamad et al, Cancers, 2017

Improvement of **differential effect**

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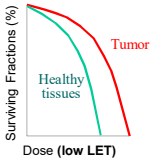
Reduction of radiosensitivity differences :

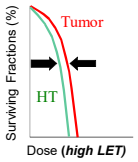
Potential therapeutic advantage

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*

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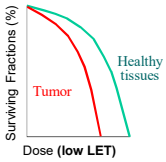
Reduction of radiosensitivity differences :

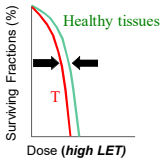
contra-indication

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*

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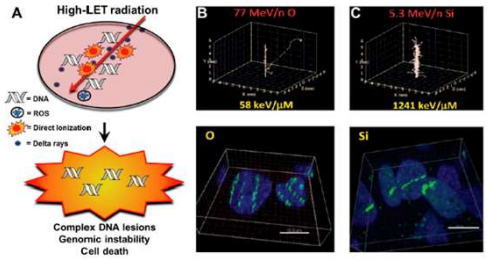
Ion beam therapy: clusters of DNA damages



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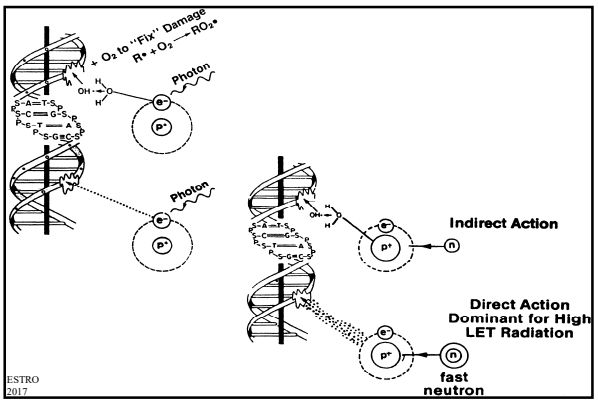
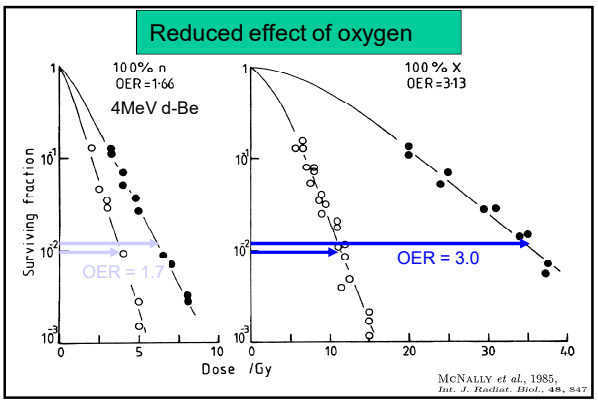
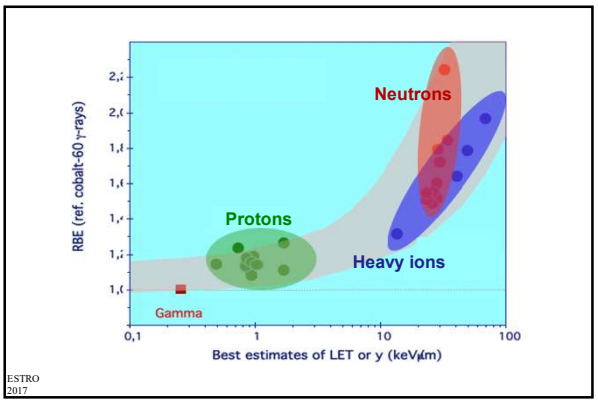
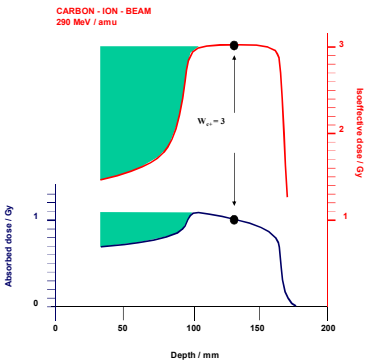
Mohamad et al, Cancers, 2017


O_2 to "Fix" Damage
$R\bullet + O_2 \rightarrow RO_2\bullet$
Photon
Photon
Indirect Action
Direct Action
Dominant for High
LET Radiation
fast
neutron
ESTRO
2017


Reduced effect of oxygen
100% n
OER=1·66
4MeV d-Be
100 % X
OER=3·13
Surviving fraction
OER = 1.7
OER = 3.0
Dose /Gy
McNally et al., 1985,
Int. J. Radiat. Biol., 48, 847

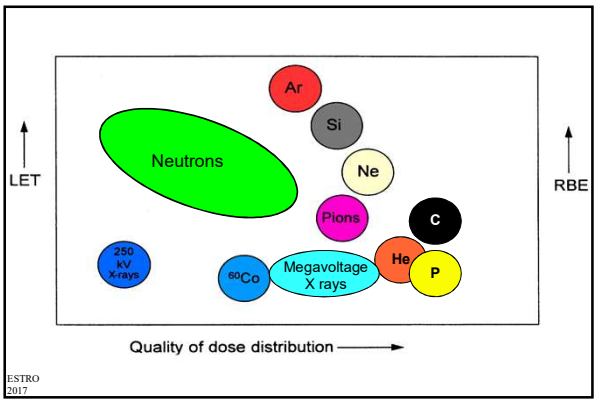

Neutrons
Protons
Heavy ions
Gamma
RBE (ref. cobalt-60 γ-rays)
Best estimates of LET or y (keV/µm)
ESTRO
2017



ESTRO 2017

Potential **clinical benefit** of Protons

ESTRO 2017



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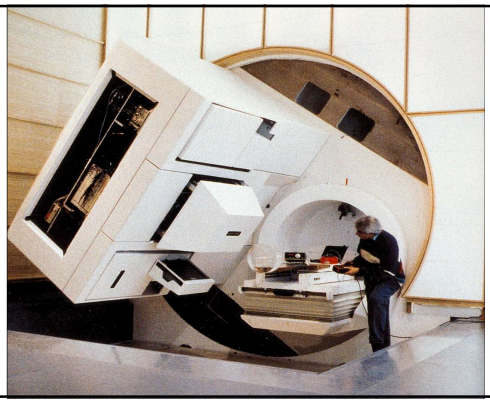

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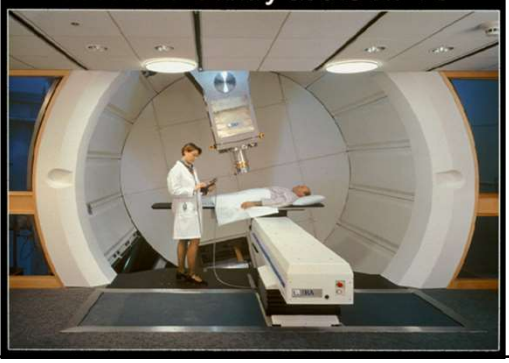
Isocentric Gantry at the NPTC



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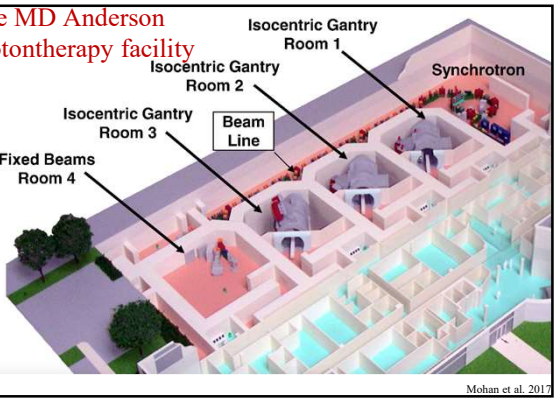
The MD Anderson protontherapy facility

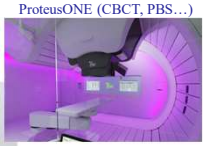


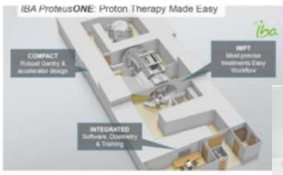
ESTRO 2017

Mohan et al. 2017

The KUL-UCL protontherapy facility

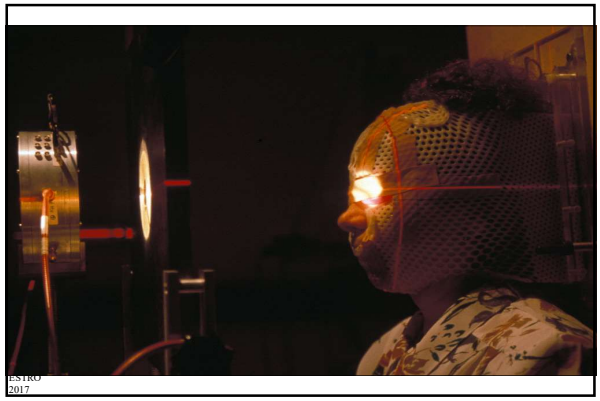
ProteusONE (CBCT, PBS…)

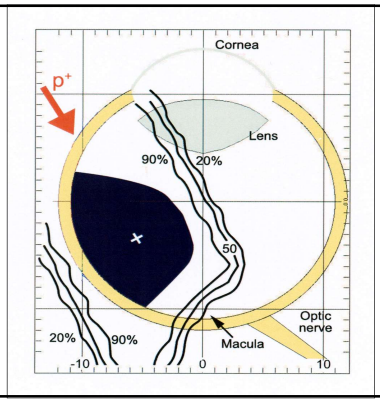


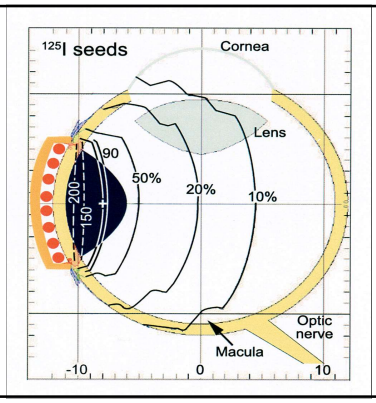


Siemens in-room dual energy CT on-rails

RayStation TPS







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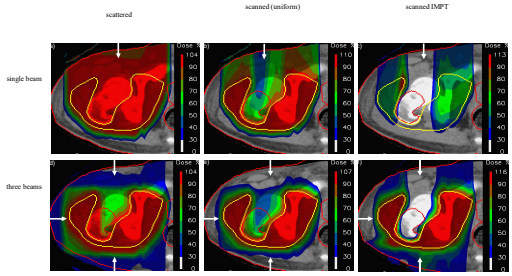
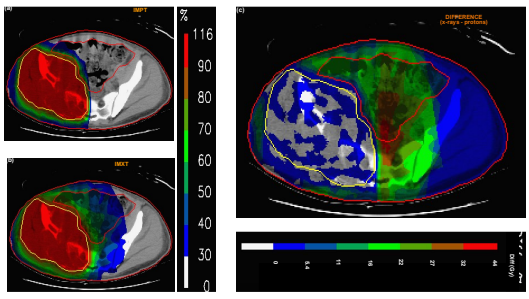
Proton beam, IMPT, … for a bone sarcoma



ESTRO 2017

Image from M. Goitein, Radiation Oncology: A physicist's-eye-view Springer, 2007.

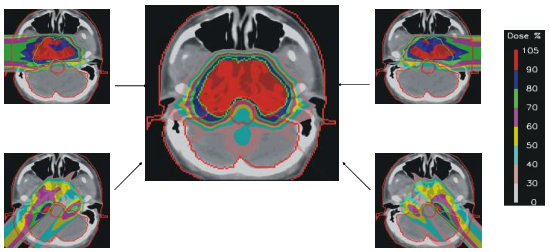
IMRT and IMPT for Ewing sarcoma



ESTRO 2017

Image from M. Goitein, Radiation Oncology: A physicist's-eye-view Springer, 2007.

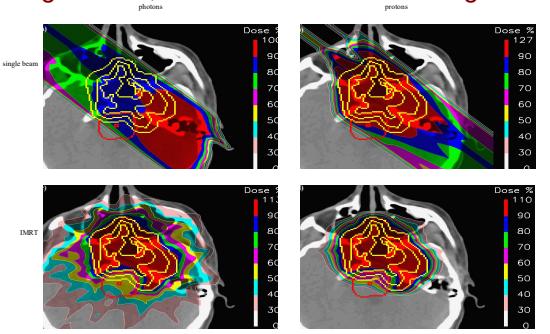
IMPT for a nasopharyngeal carcinoma



ESTRO 2017

Image from M. Goitein, Radiation Oncology: A physicist's-eye-view Springer, 2007.

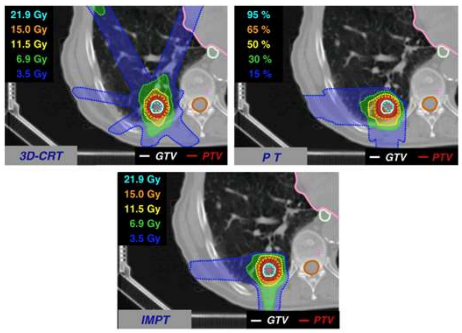
Single beam, IMRT and IMPT for meningioma



ESTRO 2017

Image from M. Goitein, Radiation Oncology: A physicist's-eye-view Springer, 2007.

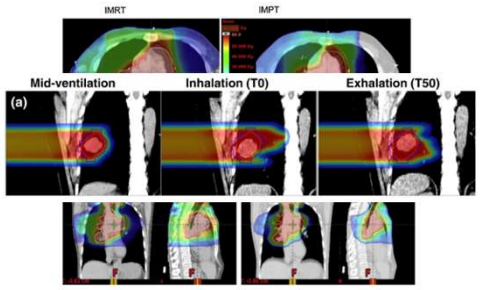
IMRT and IMPT for lung non-small cell carcinoma



ESTRO 2017

Dietmar et al. 2008

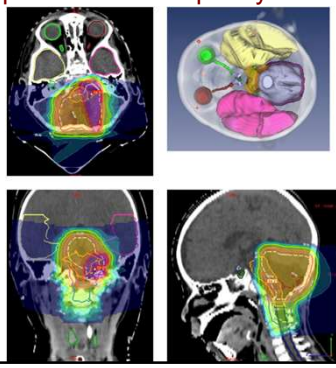
IMRT and IMPT for lung non-small cell carcinoma



ESTRO 2017

Mohan et al. 2017

IMPT for posterior fossa ependymoma in children

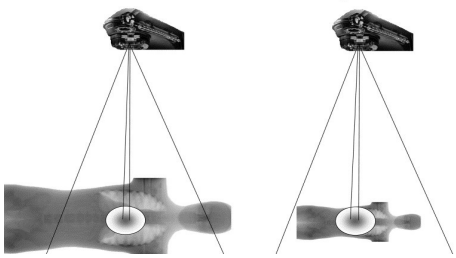


ESTRO 2017

Laprie et al. 2015

IRRADIATION OF CHILD

Same Leakage for Adult RT vs. Pediatric RT — But in Pediatric RT Scatter from the Treatment Volume Is More Significant



ESTRO 2017

Hall, 2006

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

ESTRO 2017

Suit, 2010

Comparison between CRT and SBRT for stage I NSCLC

Retrospective single arm studies: 1994-2008

30 studies included (2611 patients, published data)

Treatment	#pts	$EQD_{2,T}$ (Gy)	#Fractions
CRT	1326	42-63	20-43
SBRT	895	33-176	3-10
Protons	180	63-111	2-6

Treatment	2-year overall survival	(95% CI)	p-Value**	
			SBRT	Protons
CRT	0.531	(0.464–0.599)	<0.001	0.310
SBRT	0.702	(0.633–0.770)		0.262
Protons	0.612	(0.474–0.750)		
	2-year disease-specific survival			
CRT	0.674	(0.587–0.761)	0.006	0.430
SBRT	0.834	(0.751–0.917)		0.246
Protons	0.740	(0.607–0.874)		

ESTRO 2017

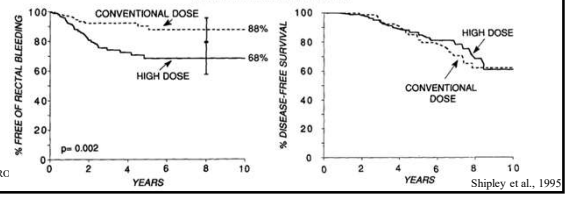
Grutters et al., 2009

Randomized phase III trials with proton therapy published as of August 2017

ADVANCED PROSTATE CANCER: THE RESULTS OF A RANDOMIZED COMPARATIVE TRIAL OF HIGH DOSE IRRADIATION BOOSTING WITH CONFORMAL PROTONS COMPARED WITH CONVENTIONAL DOSE IRRADIATION USING PHOTONS ALONE

WILLIAM U. SHIPLEY, M.D.,* LYNN J. VERHEY, PH.D.,* JOHN E. MUNZENRIDER, M.D.,* HERMAN D. SUIT, M.D.,* MARCIA M. URIE, PH.D.,* PATRICIA L. MCMANUS, B.S.N., O.C.N.,* ROBERT H. YOUNG, M.D.,† JENOT W. SHIPLEY, B.S.,* ANTHONY L. ZIETMAN, M.D., F.R.C.R.,* PETER J. BIGGS, PH.D.,* NIALL M. HENEY, M.D.‡ AND MICHAEL GOITEIN, PH.D.*

Departments of *Radiation Oncology, †Pathology, ‡Urology, and the Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA 02114



ESTRO 2017

Shipley et al., 1995

Randomized phase III trials with proton therapy (August 2017)

Keywords: proton therapy / Cancer / phase III

Row	Saved	Status	Study Title	Conditions	Interventions
1		Recruiting	Proton Therapy vs. IMRT for Low or Intermediate Risk Prostate Cancer	Prostate Cancer	Radiation: Proton Beam Therapy; Radiation: Intensity Modulated Radiation Therapy
2		Recruiting	Randomized Trial of Intensity-Modulated Proton Beam Therapy (IMPT) Versus Intensity-Modulated Photon Therapy (IMRT) for the Treatment of Oropharyngeal Cancer of the Head and Neck	Head And Neck Cancer	Radiation: Intensity-Modulated X-Ray Therapy (IMRT); Radiation: Intensity-Modulated Proton Beam Therapy (IMPT); Procedure: Modified barium swallow (MBS); Behavioral: Questionnaires
3		Recruiting	Comparing Photon Therapy To Proton Therapy To Treat Patients With Lung Cancer	Stage IIA Non-small Cell Lung Cancer; Stage IIB Non-small Cell Lung Cancer; Stage IIIA Non-small Cell Lung Cancer; Stage IIIB Non-small Cell Lung Cancer	Radiation: photon beam radiation therapy; Radiation: proton beam radiation therapy; Drug: paclitaxel; Drug: carboplatin; Drug: etoposide; Drug: cisplatin; Procedure: quality-of-life assessment; Other: questionnaire administration
4		Active, not recruiting	Proton Therapy for High Risk Prostate Cancer	Prostate Cancer	Radiation: Radiation therapy (XRT); Other: Androgen Deprivation Therapy (ADT); Other: Chemotherapy
5		Not yet recruiting	Randomized Carbon Ions vs Standard Radiotherapy for Radioresistant Tumors	Malignant Tumors as Chordoma; Adenoid Cystic Carcinoma and Sarcoma	Radiation: Carbon ions therapy; Radiation: Advanced external radiotherapy by Xrays or protons
6		Not yet recruiting	Prevention of Neovascular Glaucoma by Intravitreal Injections of Anti-VEGF in Patients Treated With Proton Therapy for a Large Choroidal Melanoma	Ocular Melanoma	Drug: Aflibercept Injection; Drug: Faloe injection
7		Recruiting	Proton Radiotherapy Versus Radiofrequency Ablation for Patients With Medium or Large Hepatocellular Carcinoma	Carcinoma, Hepatocellular	Radiation: Proton radiotherapy; Procedure: Radiofrequency Ablation
8		Recruiting	Pragmatic Randomized Trial of Proton vs. Photon Therapy for Patients With Non-Metastatic Breast Cancer: A Radiotherapy Comparative Effectiveness (RADCOMP) Consortium Trial	Breast Cancer	Radiation: Photon; Radiation: Proton
9		Recruiting	Trial of Proton Versus Carbon Ion Radiation Therapy in Patients With Chordoma of the Skull Base	Chordoma; Tumor; Treatment	Radiation: Carbon ion; Radiation: Protons
10		Recruiting	Trial of Proton Versus Carbon Ion Radiation Therapy in Patients With Low and Inter-mediate Grade Chondrosarcoma of the Skull Base	Chondrosarcoma	Radiation: carbon ion therapy; Radiation: proton therapy

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ClinicalTrials.gov

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*

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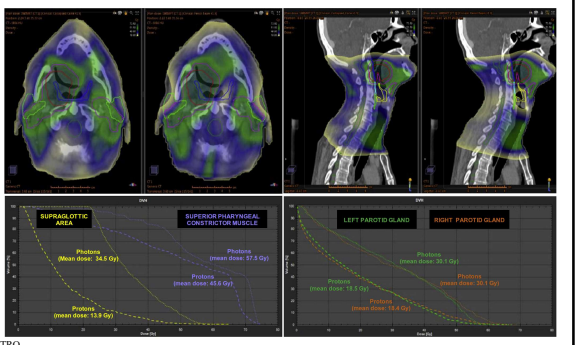
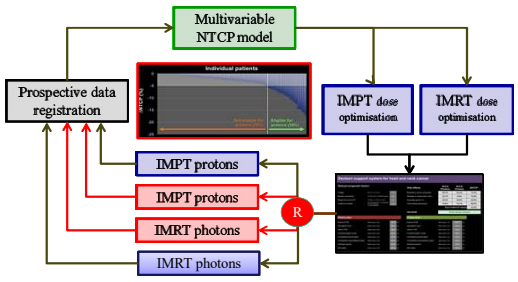
PROTON THERAPY INDICATIONS: in silico studies



ESTRO 2017

Courtesy of Langendijk

The "Biomarkers" of hadrontherapy?



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Courtesy of Langendijk, 2016

Potential **clinical benefit** of ions

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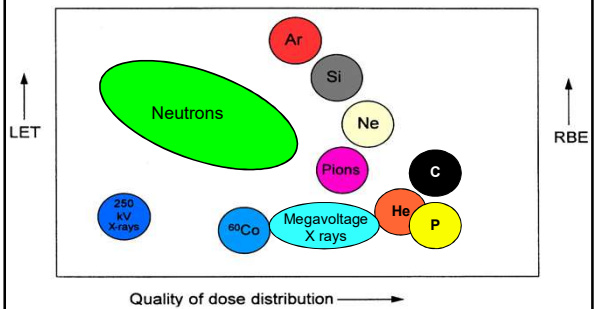

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Salivary gland tumors

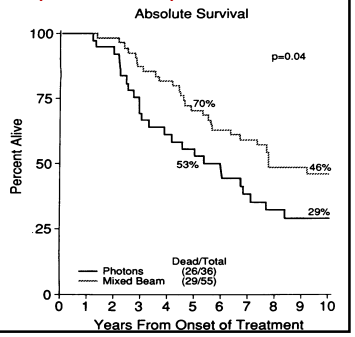
STUDY RESULTS

	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.



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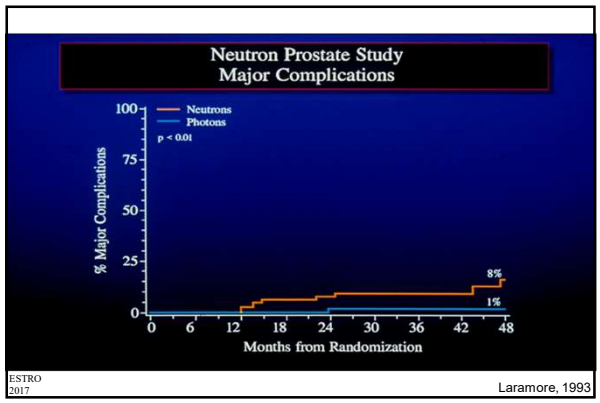
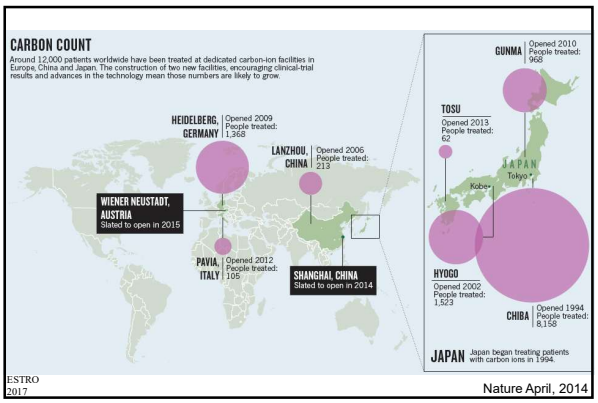


ESTRO 2017

Laramore, 1993



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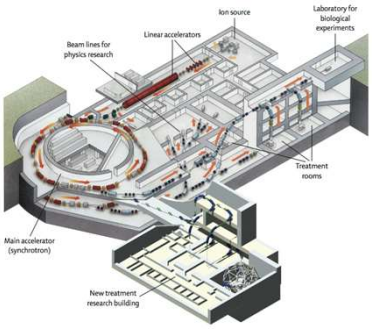
Nature April, 2014

Carbon Ion Therapy facility at NIRS



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Kamada et al, Lancet Oncol.

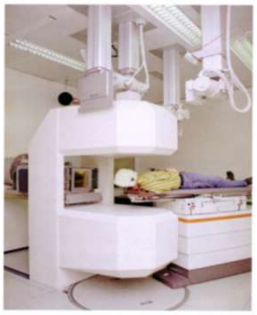

Fig.12: Patient positioned in front of the exit-window before irradiation. The X-ray equipment is removed and positioned at the ceiling. The two heads of the PET-camera are above and below the patient's head.

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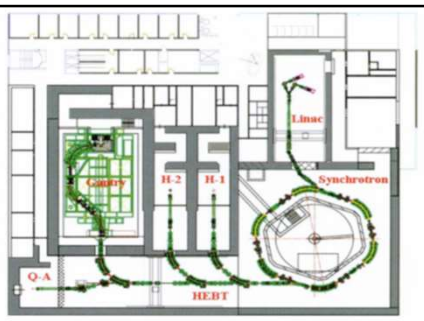

Fig.38: Ground plan of the layout of the HIT facility showing the ion source and the synchrotron from where the beam is guided to the two medical areas with fixed horizontal beam and to the gantry room.

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View of the accelerating synchrotron. Dipole magnets (in red) at the left and right hold the beam on its duty cycle while the quadrupoles (yellow) focus the beam.

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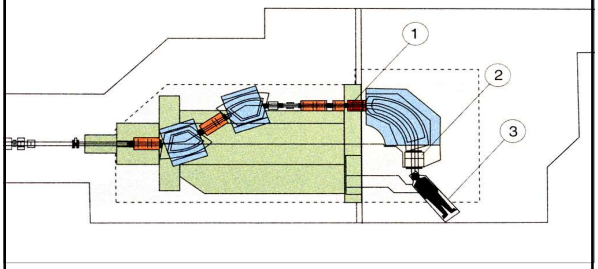

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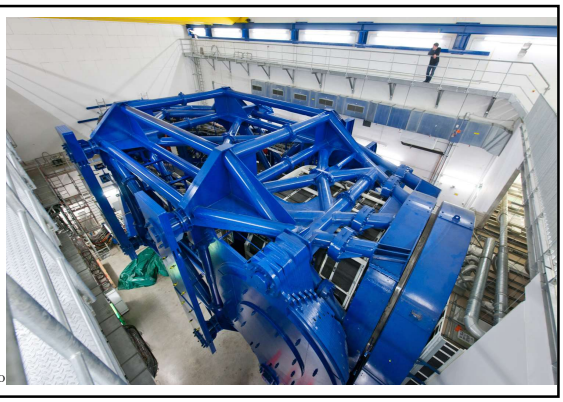

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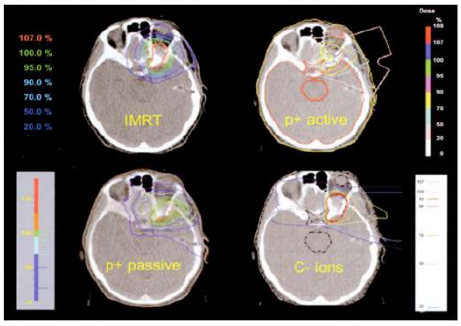
IMRT, protons, IMPT and Carbon Ions



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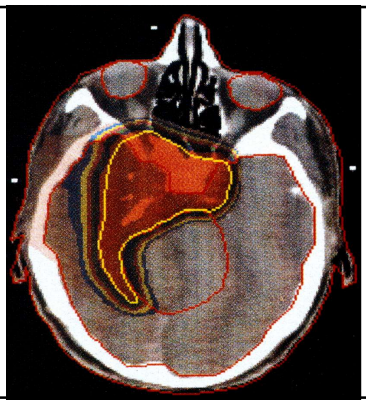

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Carbon Ion Therapy for Chordoma

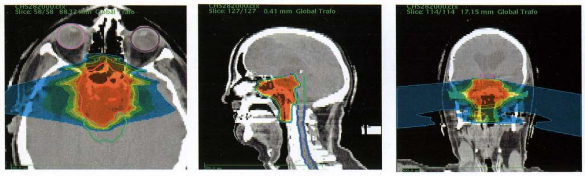

Figure 5 Three-dimensional biologically optimized dose distribution in a patient with skull-base chordoma treated with carbon ion RT, total dose 60 CGE in 20 fractions within 3 weeks. Red line = target volume, orange line = 90% isodose, yellow line = 70% isodose, green line = 50% isodose, blue line = 20% isodose line. Two opposed lateral fields were used.

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Carbon Ions versus IMRT

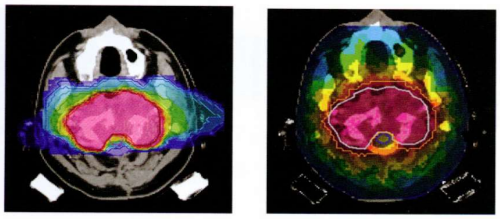

Fig. 4: Comparison of carbon irradiation (left) and photon irradiation (right). For photon IMRT, nine channels are used which distribute the dose to the normal tissue. For carbon therapy with a scanned beam, the dose in the only two entrance channels is much smaller than for IMRT.

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Carbon Ion Therapy in Japan

	Total number of patients (%)	Clinical practice
Prostate	1731 (22%)	1399
Bone and soft tissue	1033 (13%)	780
Head and neck	854 (11%)	529
Lung	795 (10%)	207
Liver	485 (6%)	250
Post-operative rectum	408 (5%)	338
Pancreas	353 (4%)	113
Gynaecological	207 (3%)	10
Eye	128 (2%)	86
CNS	106 (1%)	0
Para aortic lymph node	94 (1%)	87
Skull base	85 (1%)	56
Oesophagus	71 (1%)	0
Lacrimal gland	24 (<1%)	1
Scanning	11 (<1%)	0
Miscellaneous	1547 (20%)	715

Kamada et al, Lancet Oncol.

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

Taylor & Francis

Acta Oncologica

ISSN: 0284-186X (Print) 1651-226X (Online) Journal homepage: http://www.tandfonline.com/loi/ionc20

Treatment with heavy charged particles: Systematic review of clinical data and current clinical (comparative) trials

Stephanie E. Combs & Jürgen Debus

To cite this article: Stephanie E. Combs & Jürgen Debus (2013) Treatment with heavy charged particles: Systematic review of clinical data and current clinical (comparative) trials, Acta Oncologica, 52:7, 1272-1286, DOI: 10.3109/0284186X.2013.818254

To link to this article: http://dx.doi.org/10.3109/0284186X.2013.818254

Carbon Ion Therapy for Head & Neck cancers

Publication	Number of patients	Tumour	Treatment	Median follow-up	Local control	Overall survival
Jingo et al., 2012	27	Head-and-neck sarcoma	70.4 Gy E/16 fractions	37 months (range 4.1–73 months)	91.8% at 3 years	74.1% at 3 years
Schulz-Ertner et al., 2005	29	Adenoid-cystic-carcinoma	Photon 50 Gy E, Carbon Boost 18 Gy E/6 fractions	16 months (2–60 months)	78% at 5 years	76% at 5 years
Yanagi et al., 2009	102	Mucosal melanoma	Carbon ions	49.2 months (range 16.8–108.5)	84.1% at 5 years	27% at 5 years
Mizoe et al., 2012	236	Malignant melanoma, adenocarcinoma, squamous cell carcinoma, adenoid-cystic carcinoma	Carbon ion radiotherapy	54 months (mean; range 3–162 months)	5-years: 75% for malignant melanoma, 73% for adenoid cystic carcinoma, 73% for adenocarcinoma, 61% for papillary adenocarcinoma, 61% for squamous cell carcinoma and 24% for the 14 with sarcomas	5-years: 68% for adenoid cystic carcinoma, 56% for adenocarcinoma, 35% for malignant melanoma

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Combs, Acta Oncol., 2013

Carbon Ion Therapy for lung cancers

Publication	Number of patients	Tumor	Treatment	Median follow-up	Local control	Overall survival
Miyamoto et al., 2003	81	NSCLC	Carbon ion 59.4–95.4 Gy E/18 fractions/6 weeks 68.4–79.2 Gy E/9 fractions	52.6 months (minimum 30 months)	59% at 5 years	42% at 5 years
Miyamoto et al., 2007	50	NSCLC	Carbon ion 72 Gy E/9 fractions/3 weeks	59.2 months (range 6–83 months)	95% at 5 years	50% at 5 years
Miyamoto et al., 2007	79	NSCLC	Carbon ion T1: 52.8 Gy E/4 fractions/1 week T2: 60 Gy E/4 fractions/1 week	38.6 months (range 2.5–72.2 months)	T1: 98% at 5 years T2: 80% at 5 years	45% at 5 years
Iwata et al., 2013	27	NSCLC	60 Gy E/10 fractions; 52.8 Gy E/4 fractions; 66 Gy E/10 fractions; 80 Gy E/20 fractions	51 months (range 24–103 months)	75% at 4 years	58% at 4 years
Yamamoto et al., 2012	91	Metastatic lung tumors	40–80 Gy E, 1–16 fractions	2.3 years (range 0.3–13.1 years)	91.9% at 2 years	71.2% at 2 years

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Combs, Acta Oncol., 2013

Comparison between photons, protons and carbon for stage I NSCLC

Retrospective single arm studies: 1994-2008

30 studies included (2611 patients, published data)

Treatment	#pts	$EQD_{2,T}$ (Gy)	#Fractions
CRT	1326	42-63	20-43
SBRT	895	33-176	3-10
Protons	180	63-111	2-6
Carbon ions	210	53-125	4-9

Treatment	2-year overall survival	(95% CI)	p-Value**		
			SBRT	Protons	Carbon-ions
CRT	0.531	(0.464–0.599)	<0.001	0.310	0.006
SBRT	0.702	(0.633–0.770)		0.262	0.638
Protons	0.612	(0.474–0.750)			0.180
Carbon-ions	0.737	(0.609–0.864)			
	2-year disease-specific survival				
CRT	0.674	(0.587–0.761)	0.006	0.430	0.065
SBRT	0.834	(0.751–0.917)		0.246	0.797
Protons	0.740	(0.607–0.874)			0.391
Carbon-ions	0.815	(0.700–0.930)			

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Grutters et al., 2009

Randomized phase III trials with carbon therapy (August 2017

Keywords: carbon therapy / Cancer / phase III

Row	Saved	Status	Study Title	Conditions	Interventions
1	☐	Recruiting	Trial of Proton Versus Carbon Ion Radiation Therapy in Patients With Chordoma of the Skull Base	Chordoma; Tumor; Treatment	Radiation: Carbon ion; Radiation: Protons
2	☐	Not yet recruiting	Randomized Carbon Ions vs Standard Radiotherapy for Radioresistant Tumors	Malignant Tumors as Chordoma, Adenoid Cystic Carcinoma and Sarcoma	Radiation: Carbon ions therapy; Radiation: Advanced external radiotherapy by Xrays or protons
3	☐	Recruiting	Trial of Proton Versus Carbon Ion Radiation Therapy in Patients With Low and Inter-mediate Grade Chondrosarcoma of the Skull Base	Chondrosarcoma	Radiation: carbon ion therapy; Radiation: proton therapy

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ClinicalTrials.gov

Potential indications of ions…?

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Pending questions…
Are hadrons really needed?

- For which patients?
- With which setting?
- For which money?

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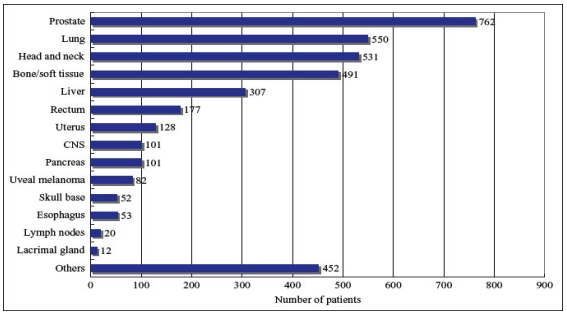
Carbon Ion Therapy at NIRS



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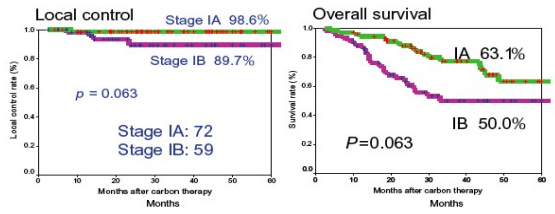
Tsujii, 2008

Carbon Ion Therapy for stage I NSCLC at NIRS (4 or 9 fractions)



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Tsujii, 2008

Carbon Ion Therapy for chordomas and chondrosarcomas

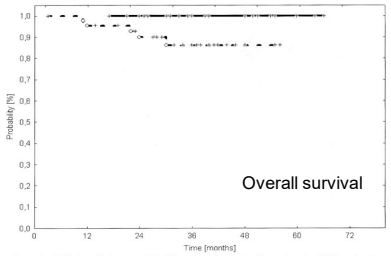

Figure 2. Actuarial overall survival (Kaplan Meier curve) for 67 patients treated with carbon ion RT for chordomas (dotted line, n=44) and low grade chondrosarcomas (solid line, n=23) of the skull base.

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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

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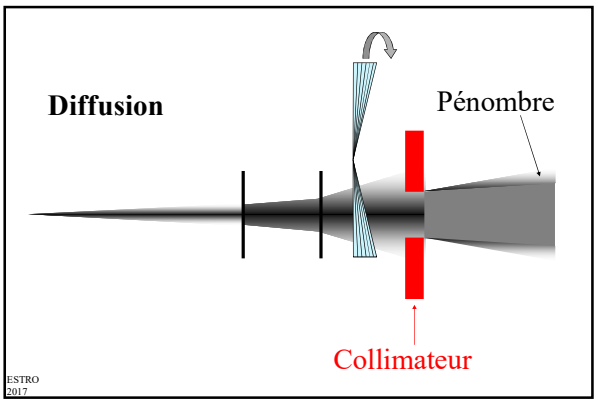

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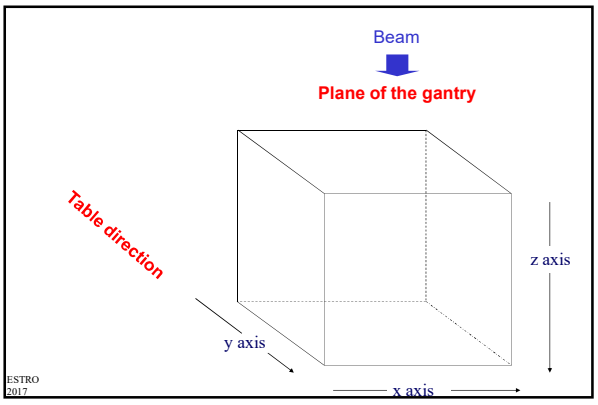

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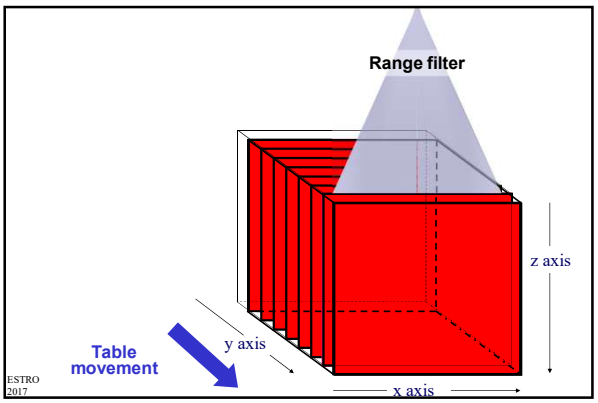

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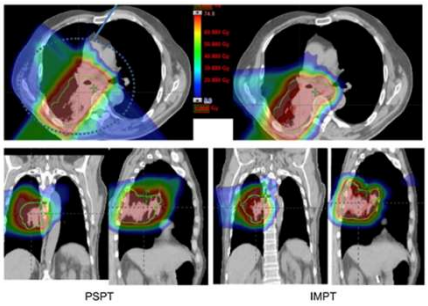
IMRT and IMPT for lung non-small cell carcinoma



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Mohan et al. 2017

Row	Saved	Status	Study Title	Conditions	Interventions
1	☐	Recruiting	Proton Therapy vs. IMRT for Low or Intermediate Risk Prostate Cancer	Prostate Cancer	Radiation: Proton Beam Therapy; Radiation: Intensity Modulated Radiation Therapy
2	☐	Recruiting	Randomized Trial of Intensity-Modulated Proton Beam Therapy (IMPT) Versus Intensity-Modulated Photon Therapy (IMRT) for the Treatment of Oropharyngeal Cancer of the Head and Neck	Head And Neck Cancer	Radiation: Intensity-Modulated X-Ray Therapy (IMRT); Radiation: Intensity-Modulated Proton Beam Therapy (IMPT); Procedure: Modified barium swallow (MBS); Behavioral: Questionnaires
3	☐	Recruiting	Comparing Photon Therapy To Proton Therapy To Treat Patients With Lung Cancer	Stage IIA Non-small Cell Lung Cancer; Stage IIB Non-small Cell Lung Cancer; Stage IIIA Non-small Cell Lung Cancer; Stage IIIB Non-small Cell Lung Cancer	Radiation: photon beam radiation therapy; Radiation: proton beam radiation therapy; Drug: paclitaxel; Drug: carboplatin; Drug: etoposide; Drug: cisplatin; Procedure: quality-of-life assessment; Other: questionnaire administration
4	☐	Active, not recruiting	Proton Therapy for High Risk Prostate Cancer	Prostate Cancer	Radiation: Radiation therapy (XRT); Other: Androgen Deprivation Therapy (ADT); Other: Chemotherapy
5	☐	Not yet recruiting	Randomized Carbon Ions vs Standard Radiotherapy for Radioresistant Tumors	Malignant Tumors as Chordoma, Adenoid Cystic Carcinoma and Sarcoma	Radiation: Carbon ions therapy; Radiation: Advanced external radiotherapy by Xrays or protons
6	☐	Not yet recruiting	Prevention of Neovascular Glaucoma by Intravitreal Injections of Anti-VEGF in Patients Treated With Proton Therapy for a Large Choroidal Melanoma	Ocular Melanoma	Drug: Aflibercept Injection; Drug: Falso injection
7	☐	Recruiting	Proton Radiotherapy Versus Radiofrequency Ablation for Patients With Medium or Large Hepatocellular Carcinoma	Carcinoma, Hepatocellular	Radiation: Proton radiotherapy; Procedure: Radiofrequency Ablation
8	☐	Recruiting	Pragmatic Randomized Trial of Proton vs. Photon Therapy for Patients With Non-Metastatic Breast Cancer: A Radiotherapy Comparative Effectiveness (RADCOMP) Consortium Trial	Breast Cancer	Radiation: Photon; Radiation: Proton
9	☐	Recruiting	Trial of Proton Versus Carbon Ion Radiation Therapy in Patients With Chordoma of the Skull Base	Chordoma; Tumor; Treatment	Radiation: Carbon ion; Radiation: Protons
10	☐	Recruiting	Trial of Proton Versus Carbon Ion Radiation Therapy in Patients With Low and Inter-mediate Grade Chondrosarcoma of the Skull Base	Chondrosarcoma	Radiation: carbon ion therapy; Radiation: proton therapy

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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 T1a - 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)

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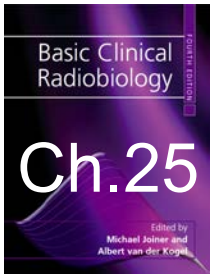
ESTRO School

Basic Clinical Radiobiology

Radiation-induced malignancies

Michael Joiner



Paris 2017

Radiation
induced cancers

Radiotherapy
induced cancers

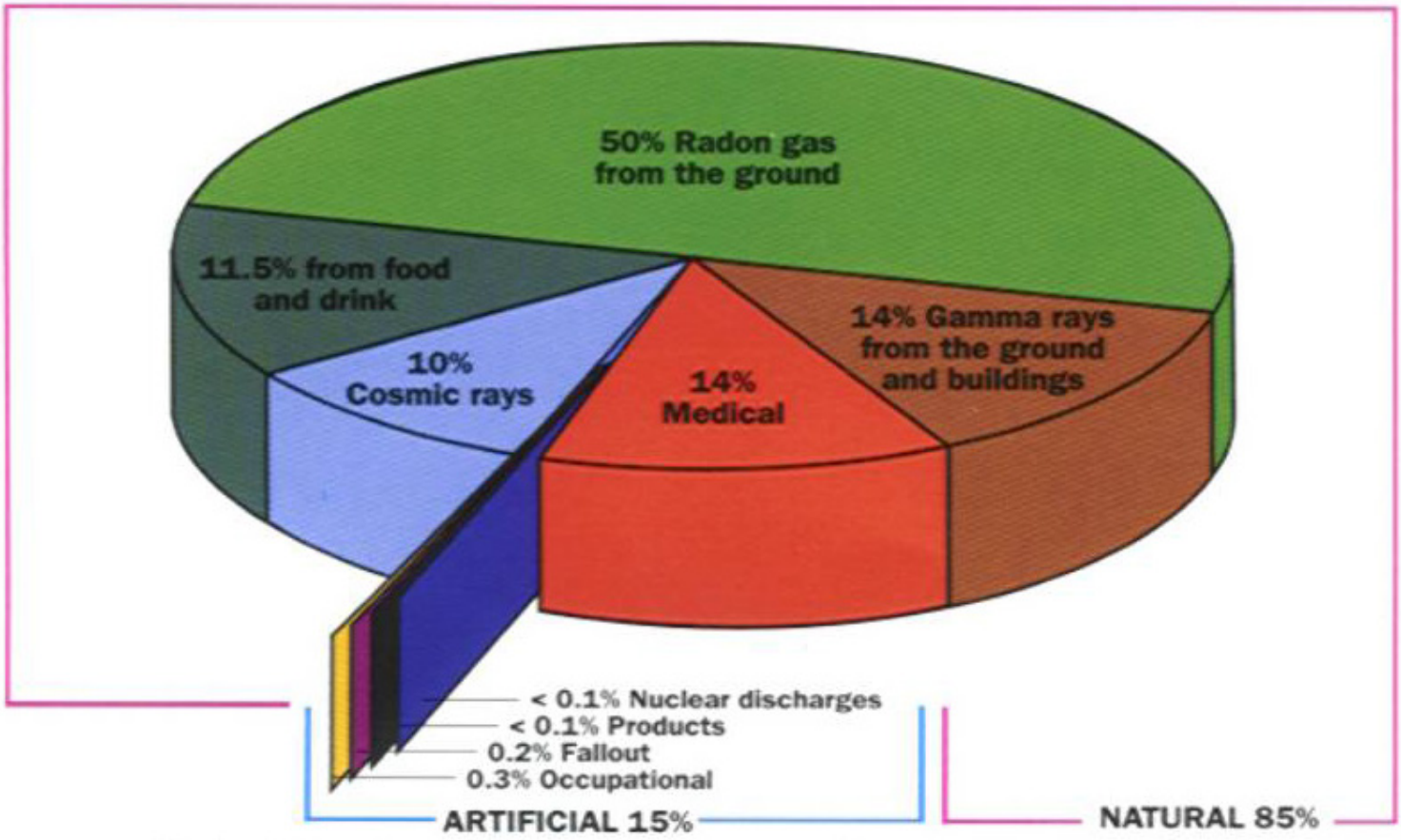
BED = Banana Equivalent Dose

0.5 g potassium per banana, 15 Bq radioactivity

37 MBq = 1 mCi

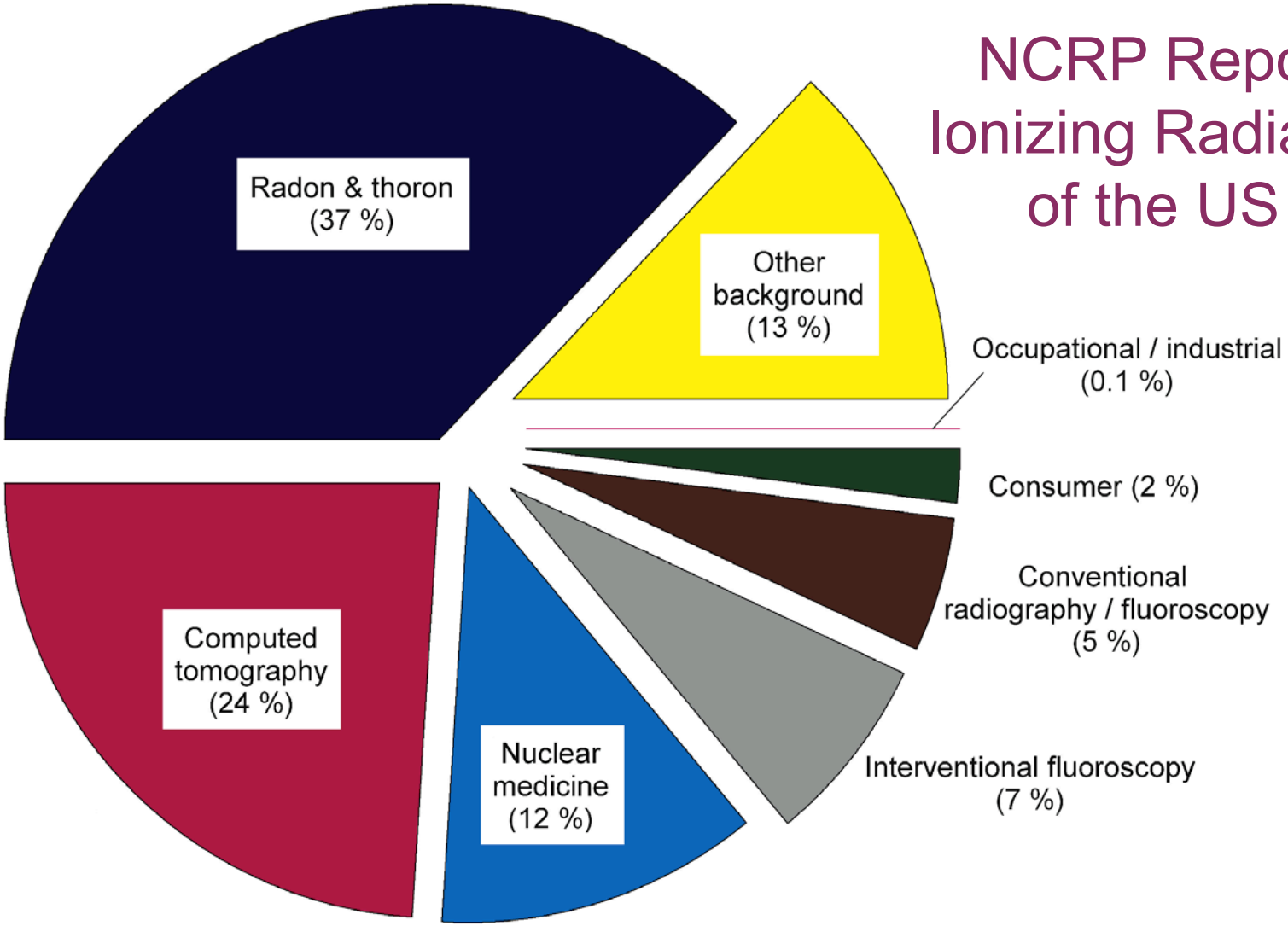
http://en.wikipedia.org/wiki/Banana_equivalent_dose

Sources of radiation dose to the general population in **1980**



http://www.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

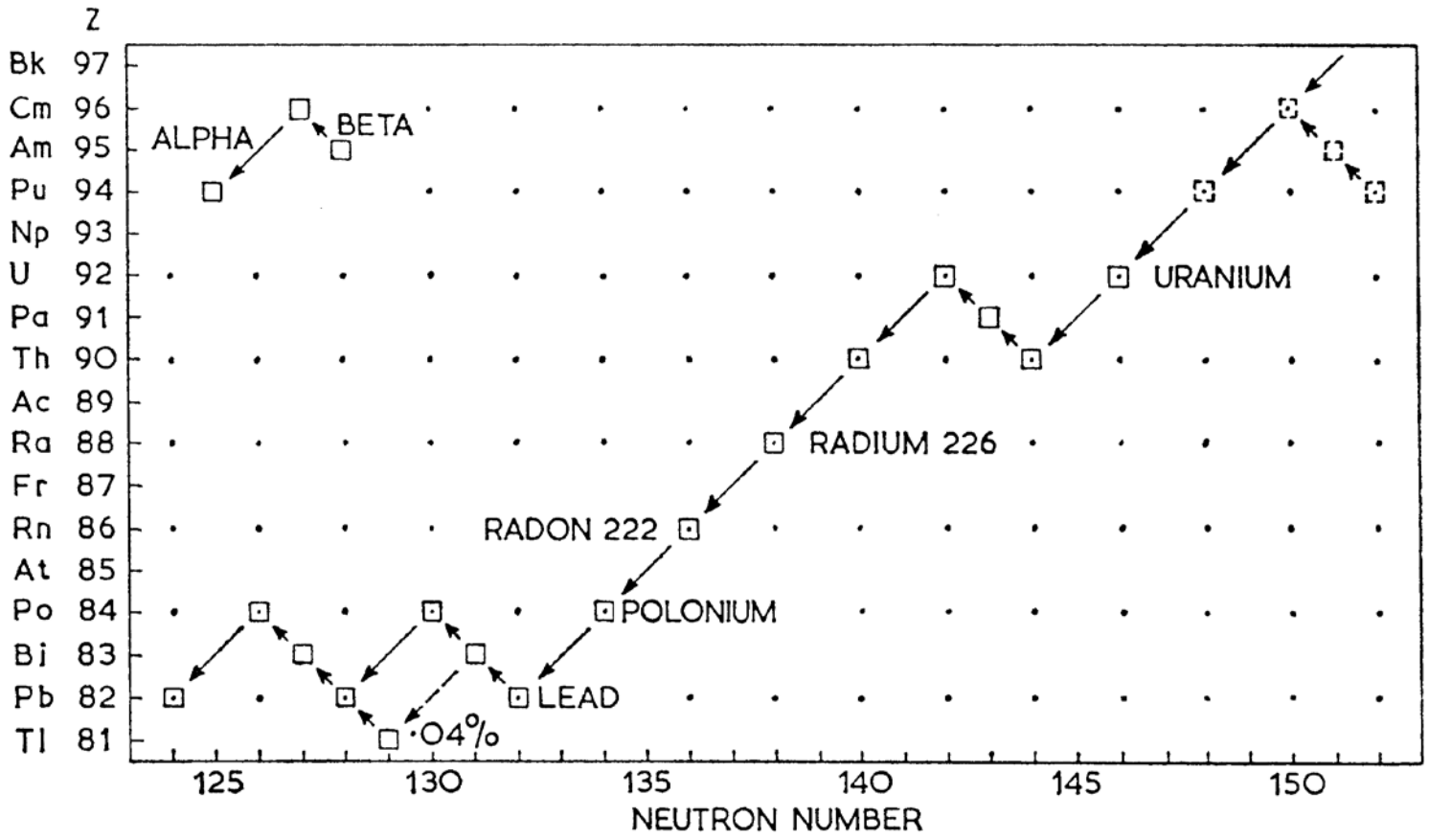
1920s: *bone cancer* in radium dial painters

1930s: *liver cancer and leukemia* from Thorotrast

1940s: excess *leukemia* in first radiologists

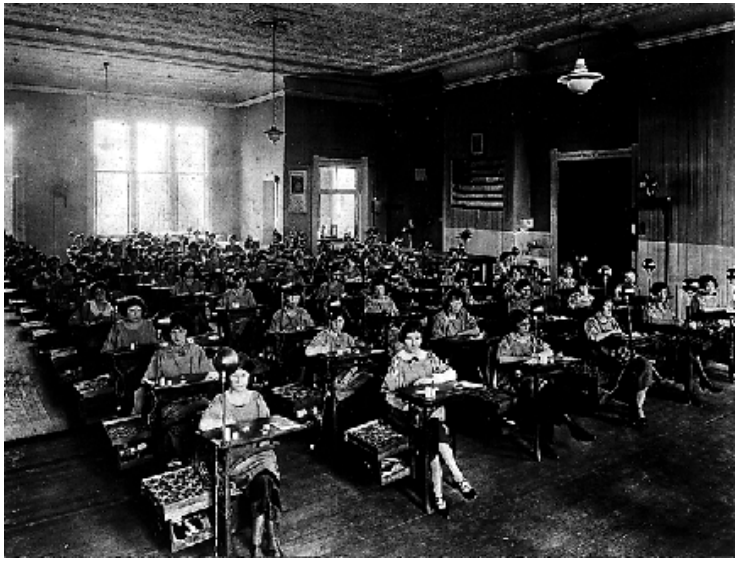
www.curie.fr

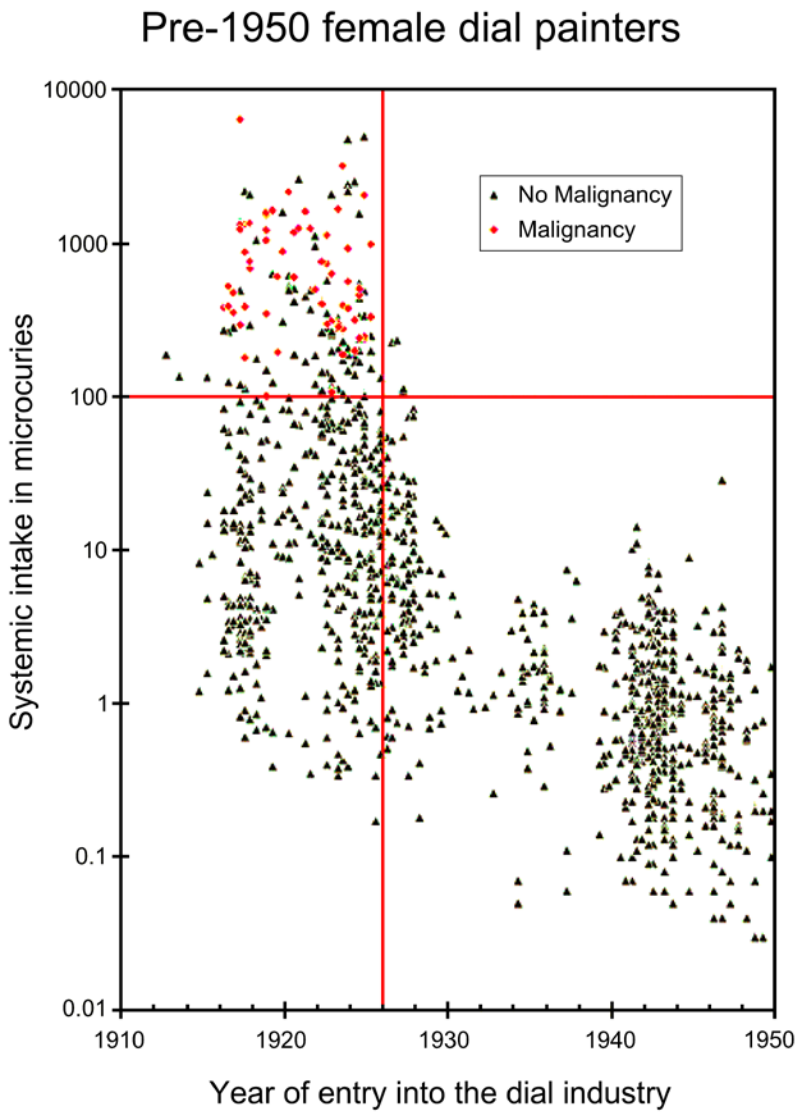
Lewicki AM, *Radiology* **223:**299-303, 2002



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.

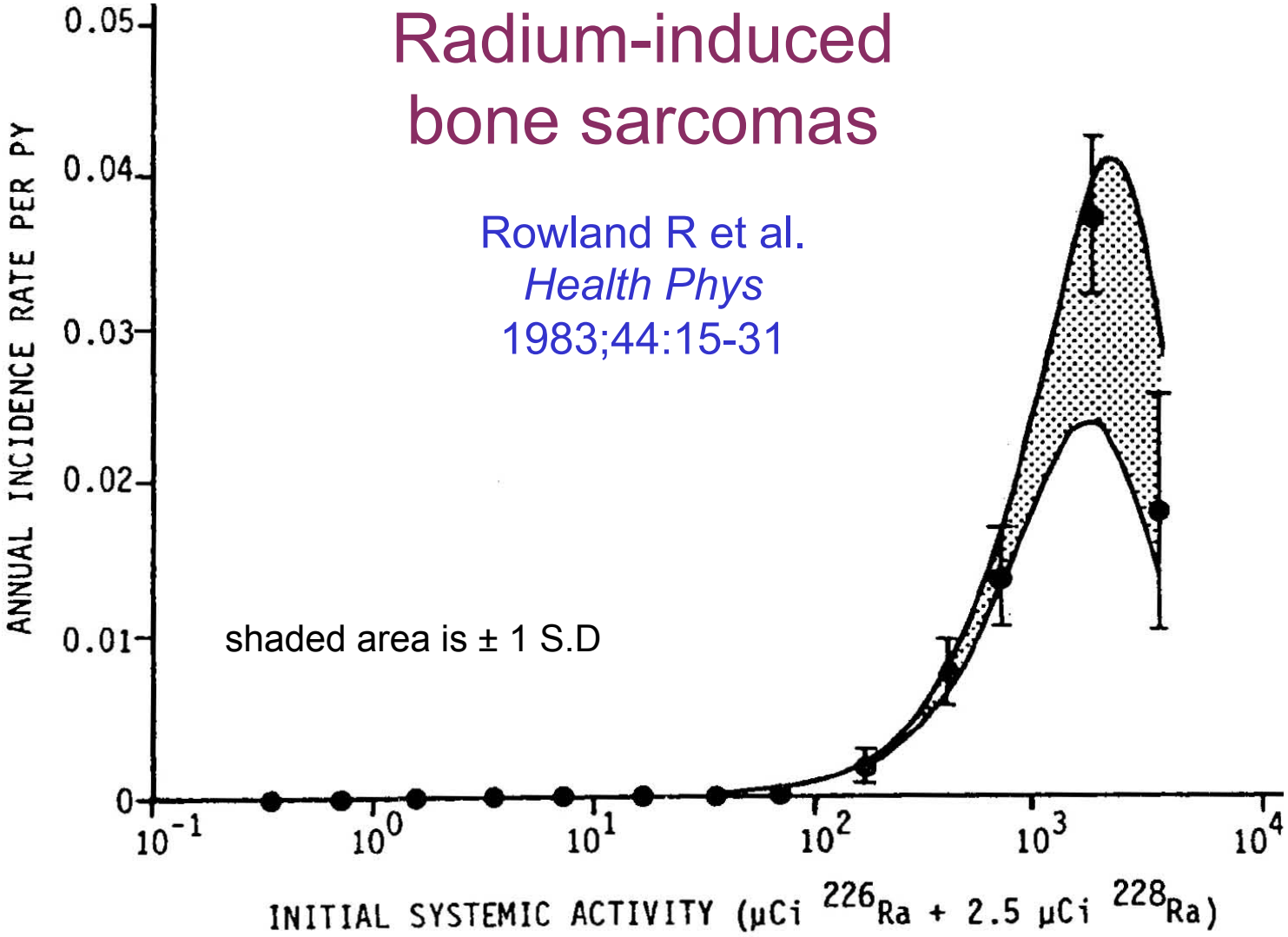


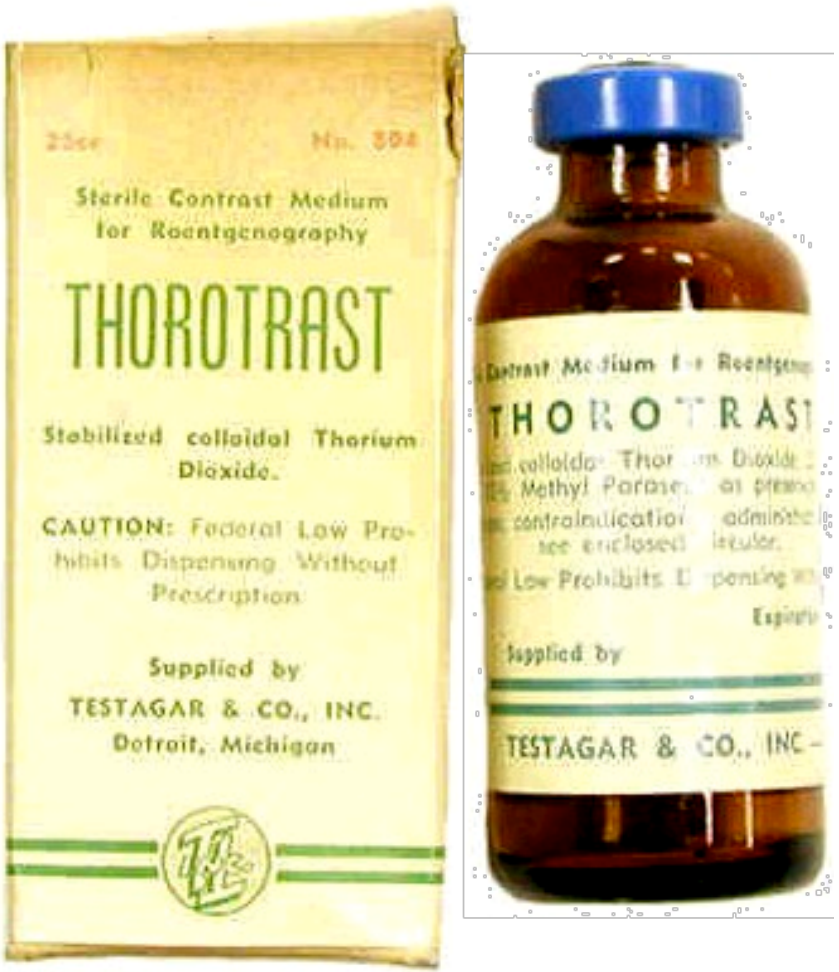


Rowland RE.
Radium in Humans:
A Review of U.S. Studies.
Argonne National Lab,
Argonne Ill, 1994

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

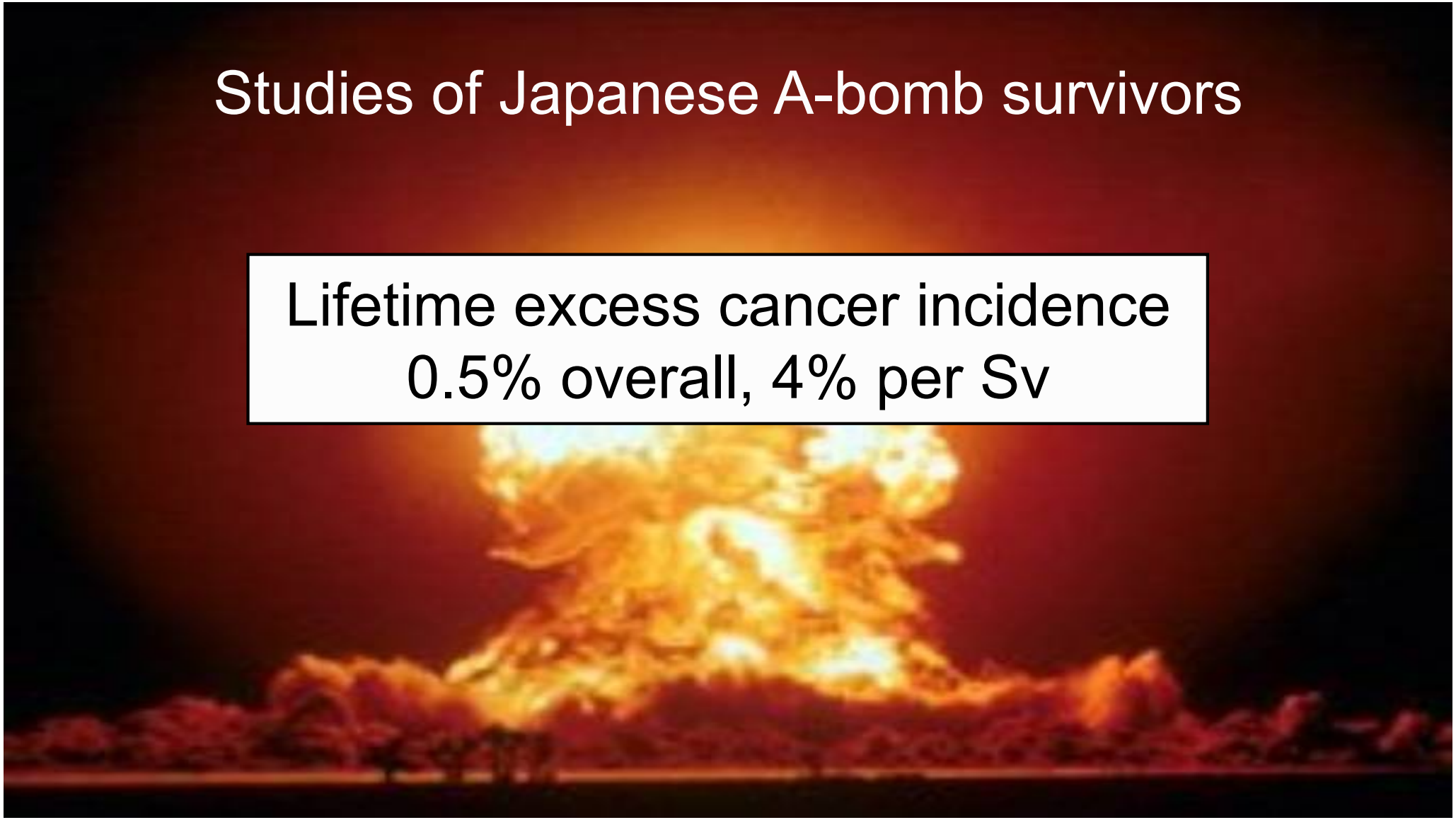
Travis LB et al. *Radiat Res* 2003;160:691-706

Relative risk is preferred to ***Absolute risk***

- ***Relative risk (RR)***
  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***
  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

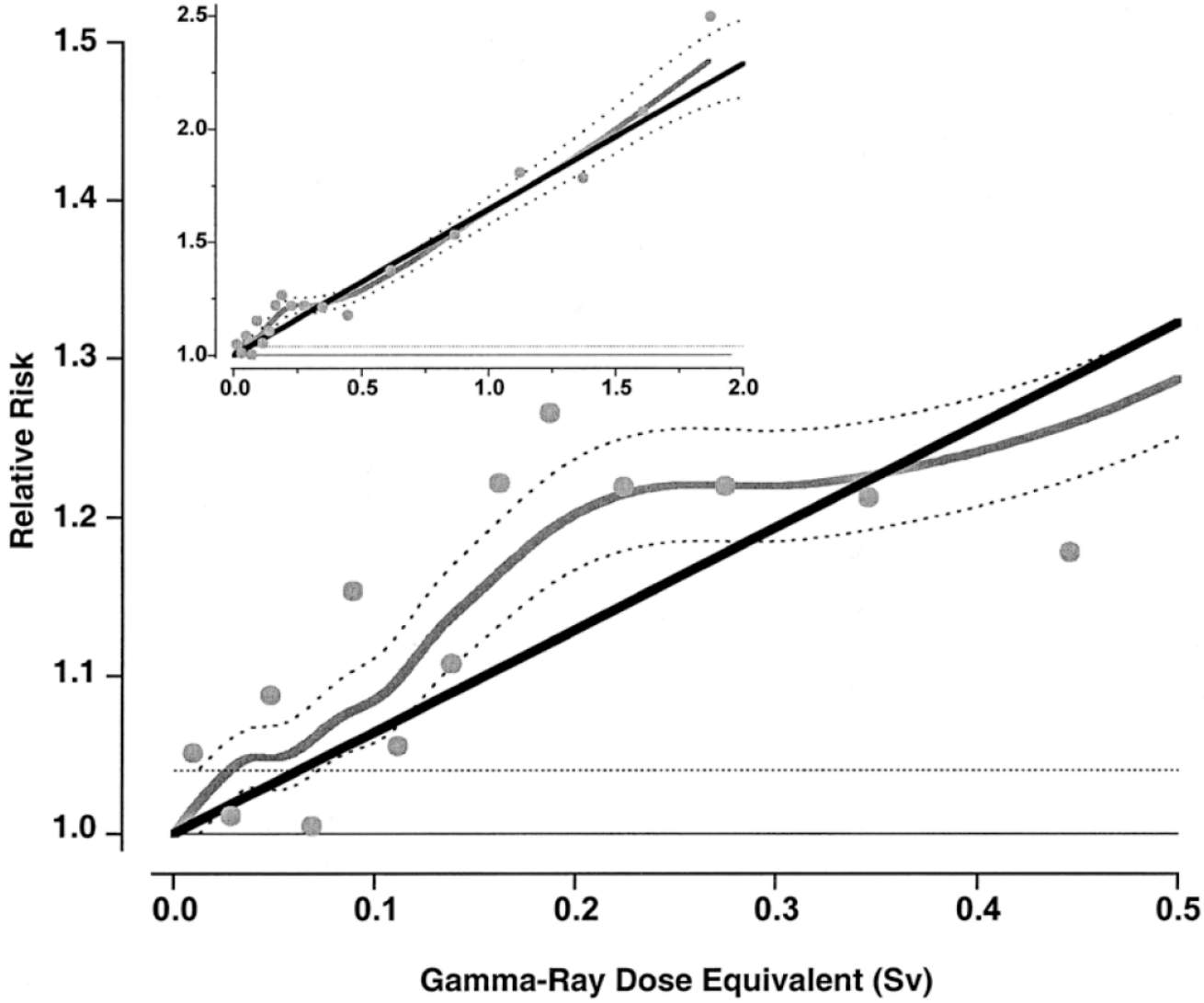
Pierce DA and Preston DL. *Radiat Res* 2000;154:178-86

Excess cancer mortality

Lifetime risk per 100,000 at 0.1 Sv

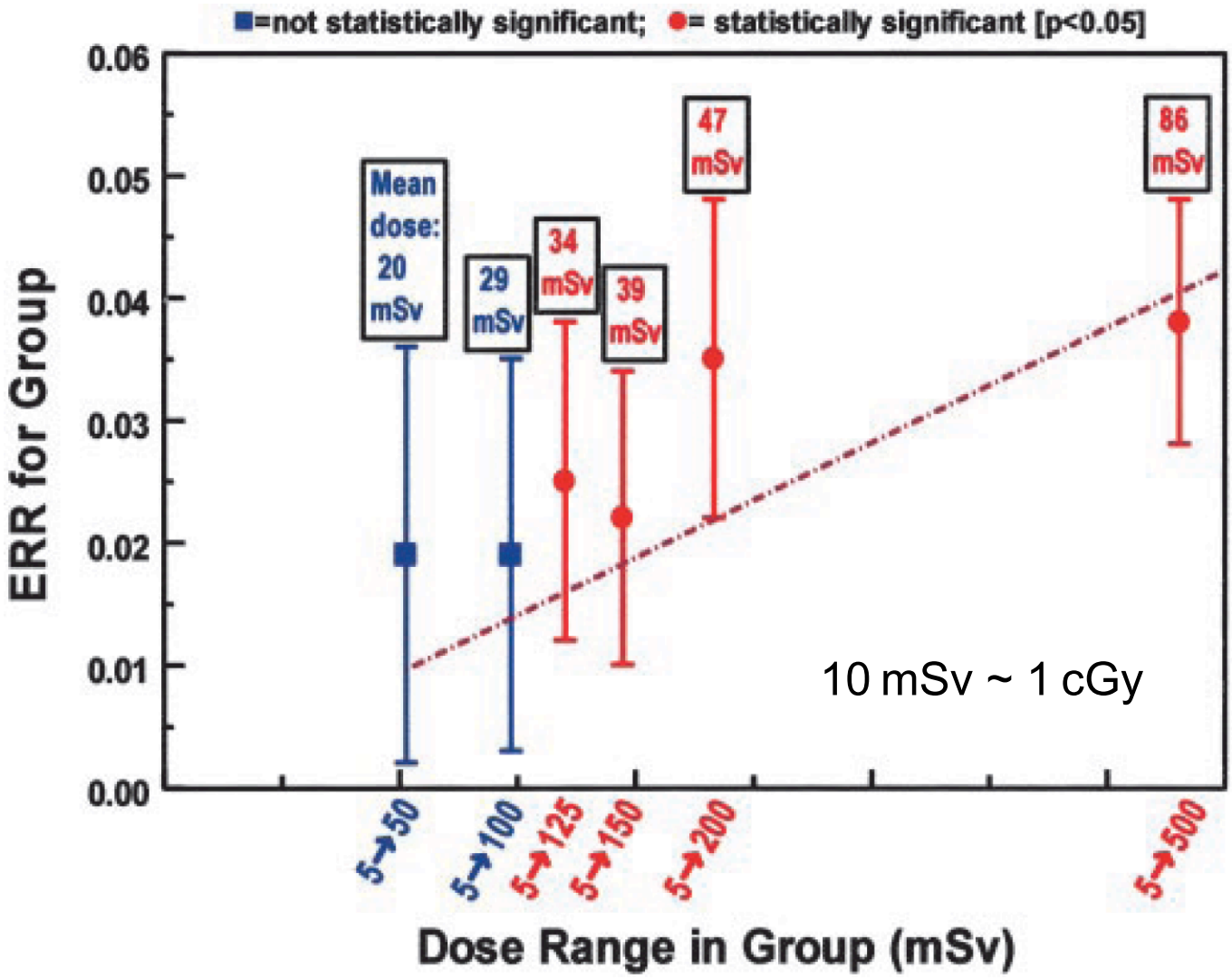
	BEIR V (U.S. Population)			
	Males	Females	UNSCEAR 88 (Japanese Population)	
Breast	—	70	Breast	60
Respiratory	190	150	Lung	151
Digestive system	170	290	Stomach	126
			Colon	79
Other solid	300	220	Other solid	194
Leukemia	110	80	Leukemia	100
Total	770	810	Total	710

Radiation related cancer risk: A bomb survivors



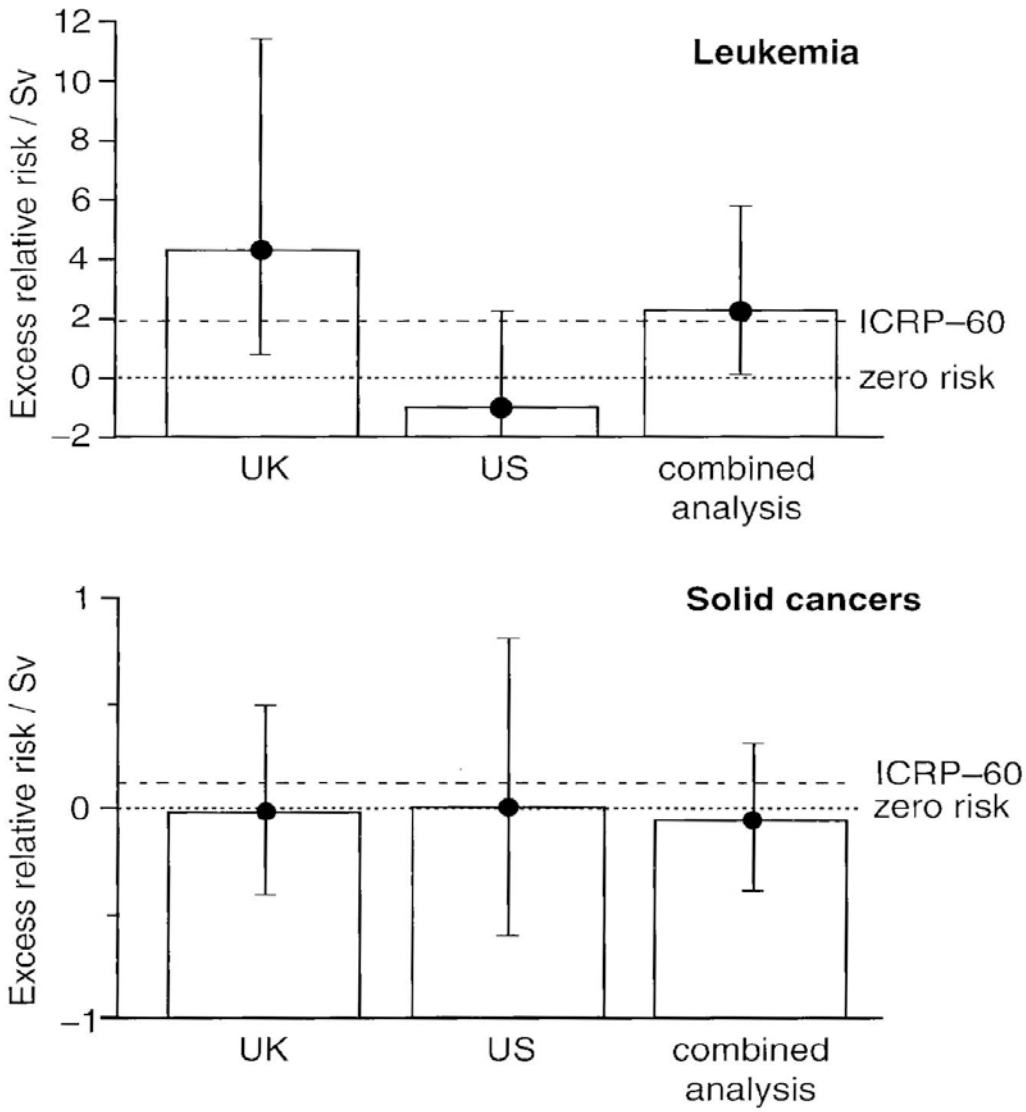
Pierce DA and Preston DL.
Radiat Res 2000;154:178-86

Solid cancer mortality from A bomb



Brenner DJ et al.
PNAS 2003;100:13761-6

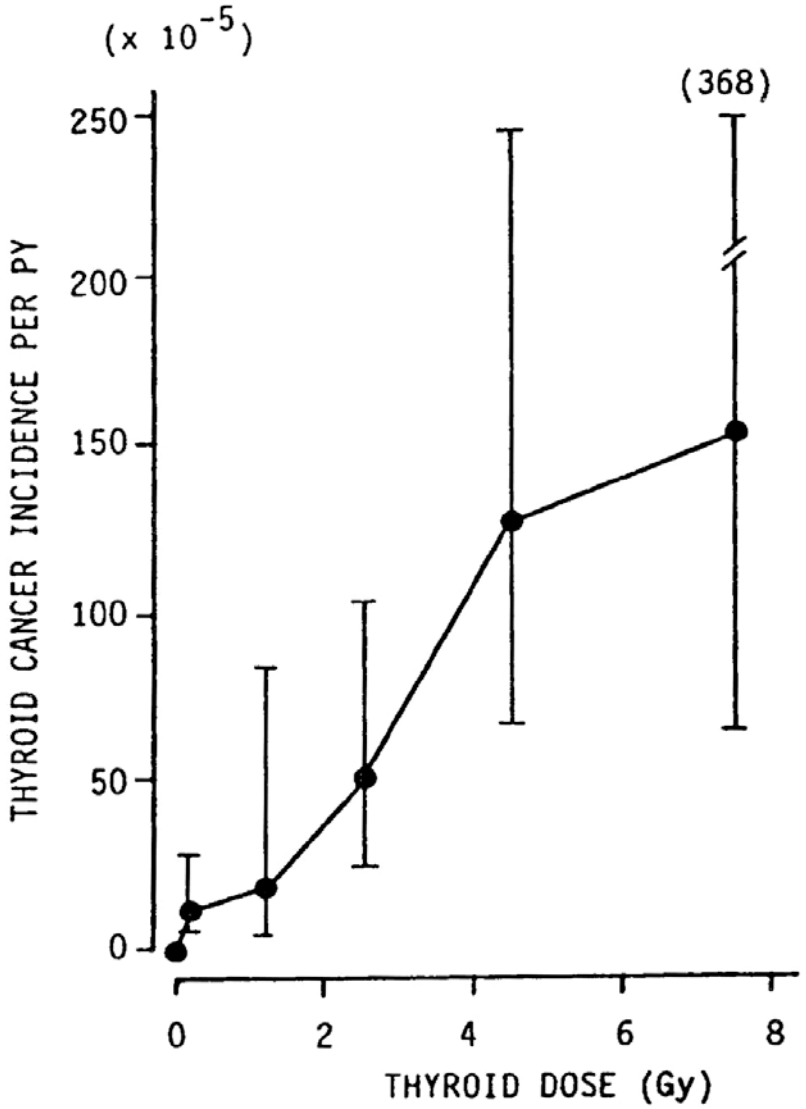
Cancer risk in 95,000 nuclear industry workers



From DJ Brenner

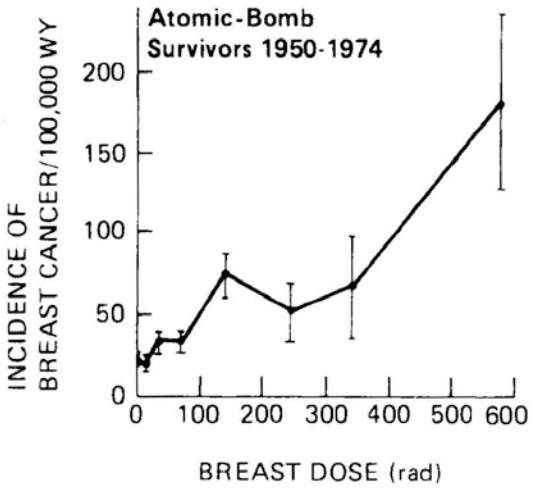
Thyroid tumors following thymus irradiation

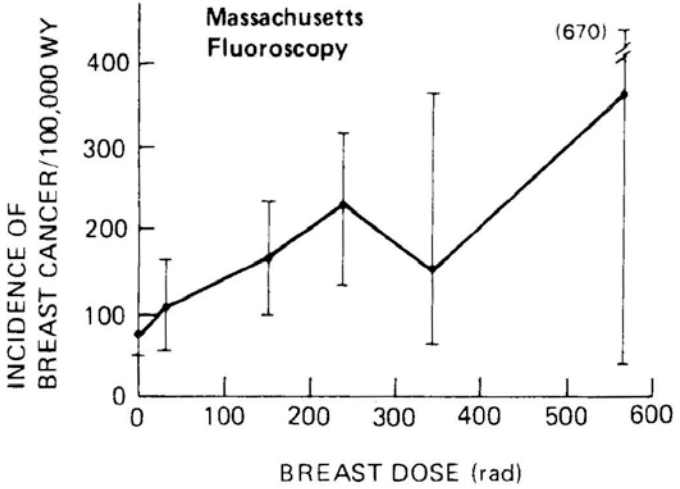
0.1%

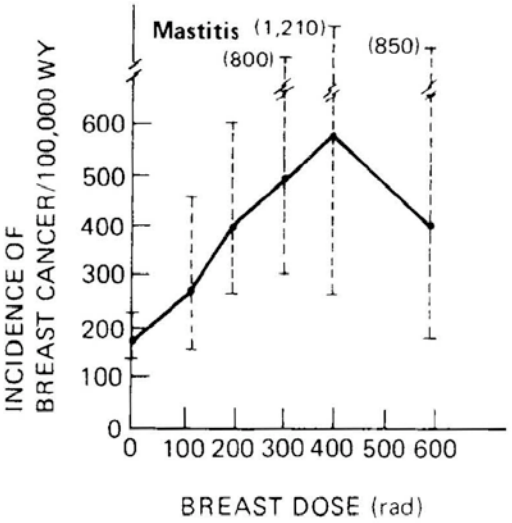


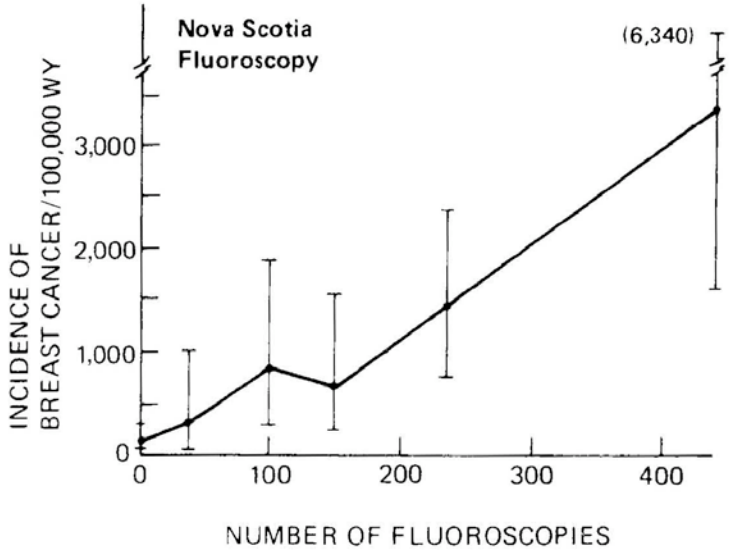
Shore RE et al. *JNCI* 1985;74:1177-84

Breast cancer following fluoroscopy



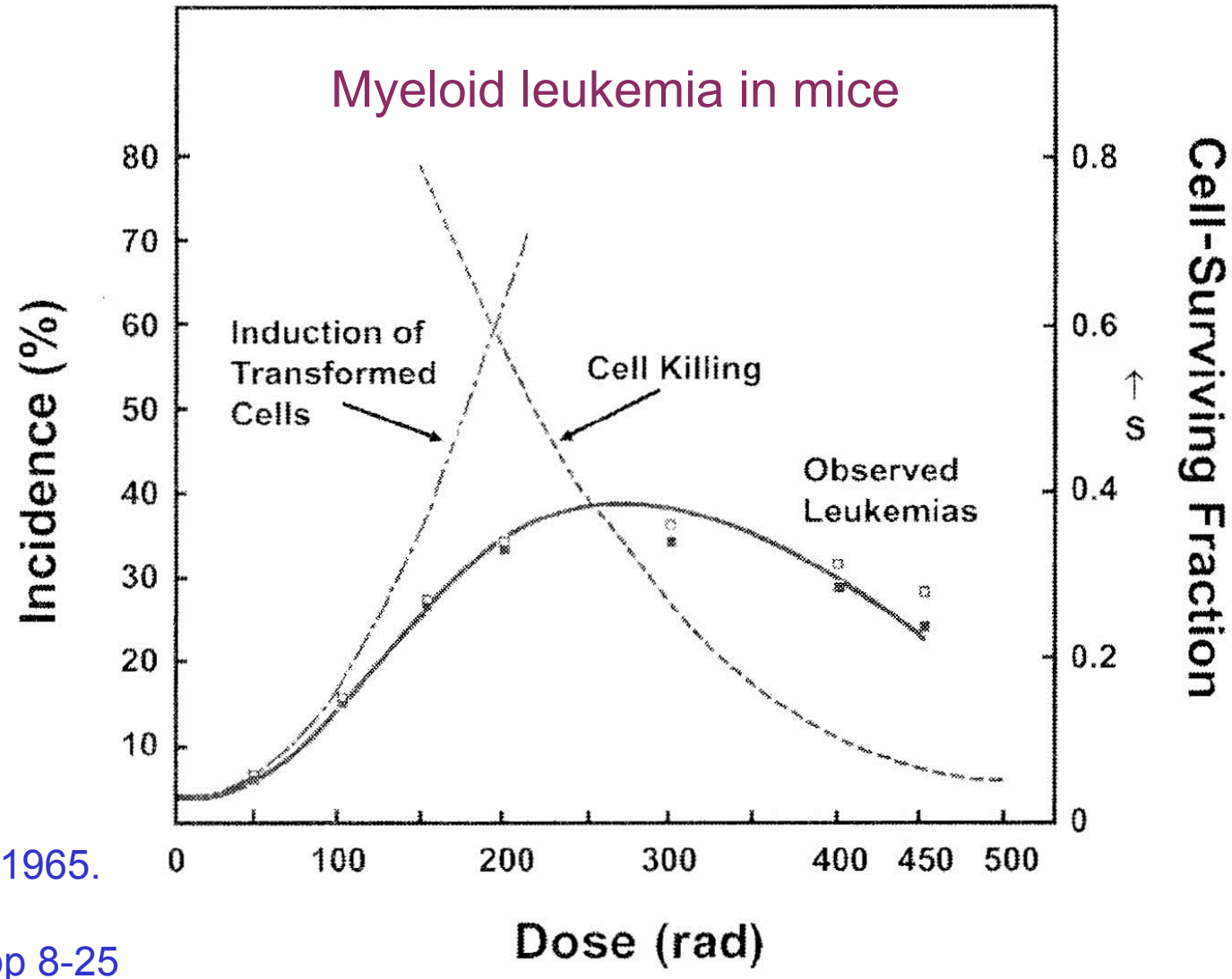






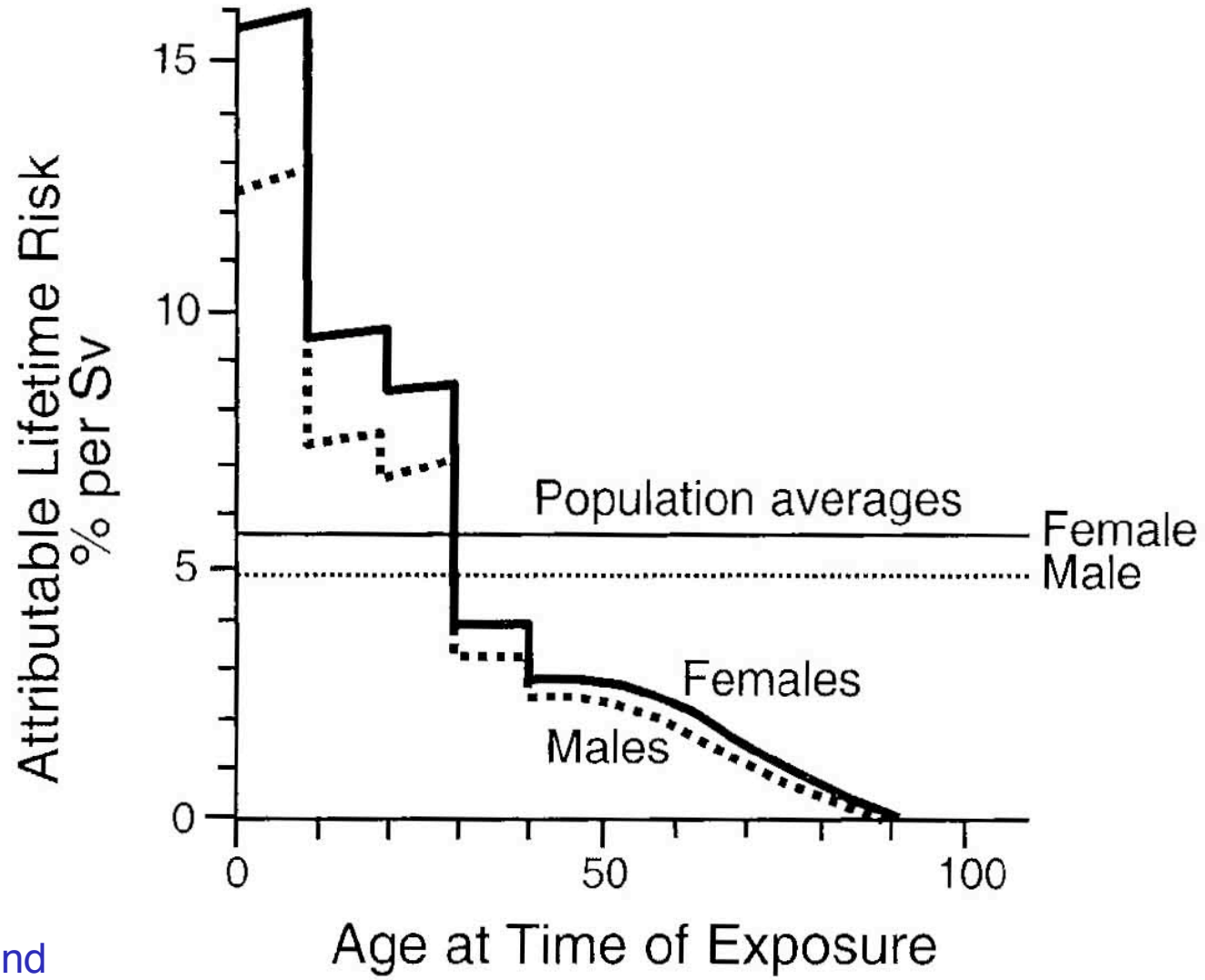
Boice JD et al.
Radiology 1979;131:589-97

Bell-shaped Cancer incidence curve



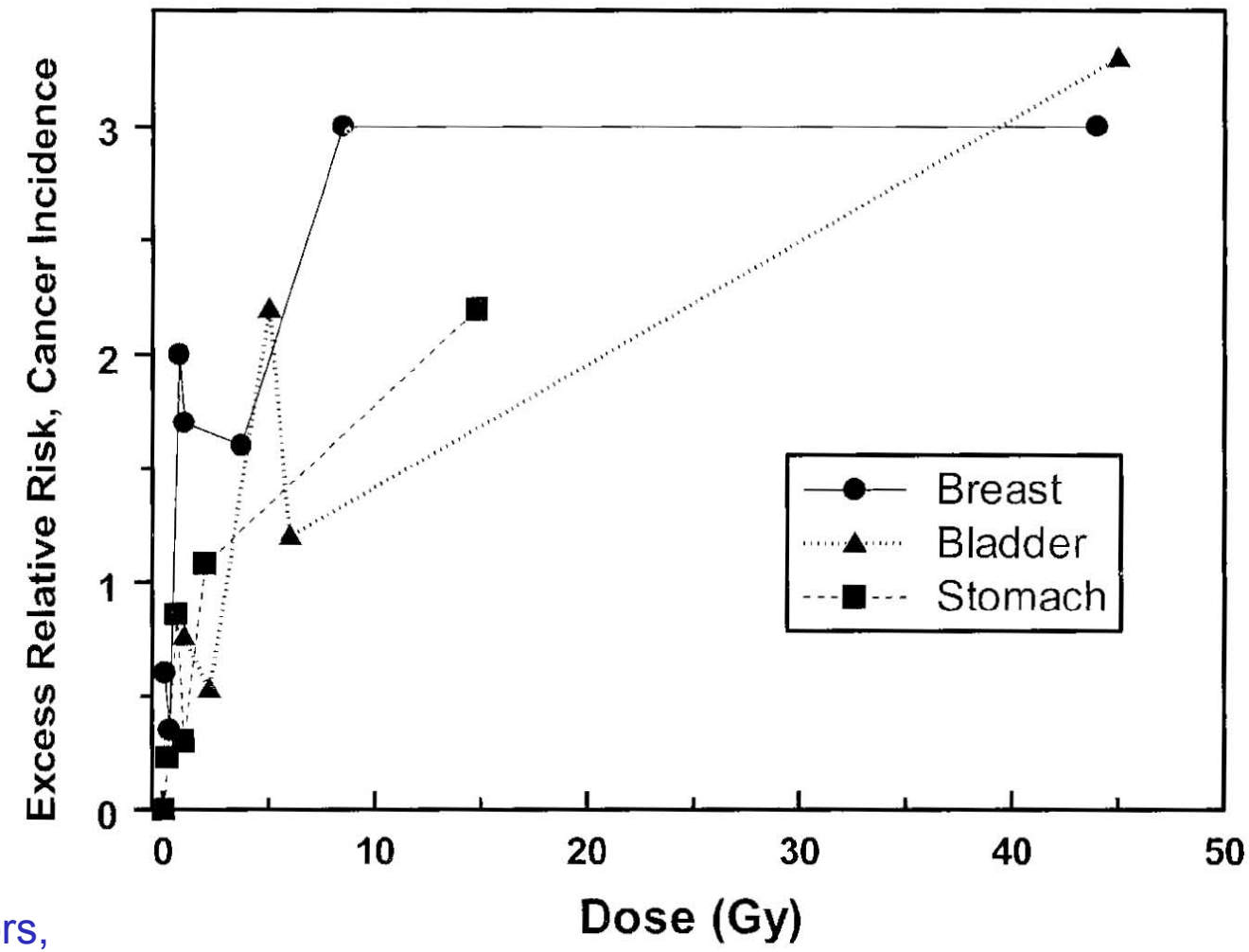
Gray LH.
Radiation biology and cancer, 1965.
In: *Cellular Radiation Biology,*
William & Wilkins, Baltimore, pp 8-25

Age dependence of cancer risk



ICRP. *Ann ICRP Pub* 1990;60: Pergamon Press, Oxford, England

Dose response for carcinogenesis



Compiled by 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

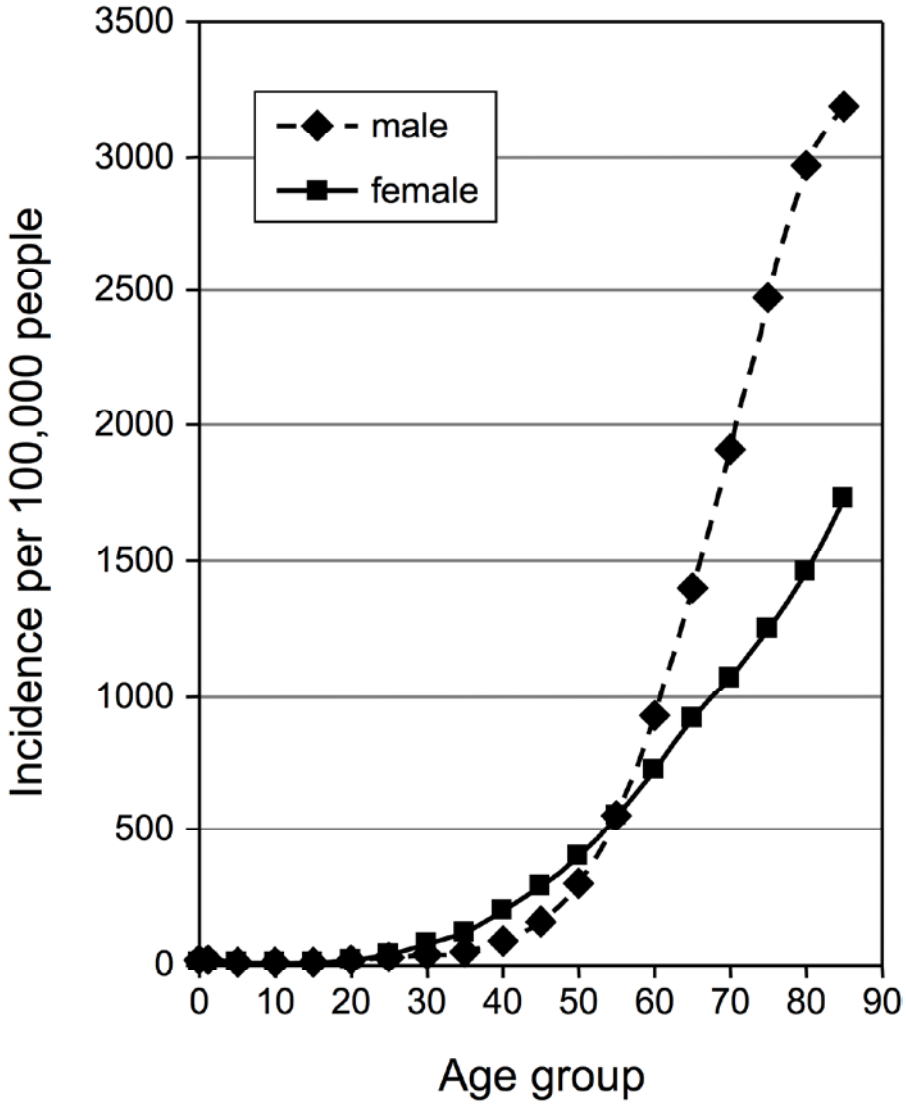
Radiation weighting factors (W_R)

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

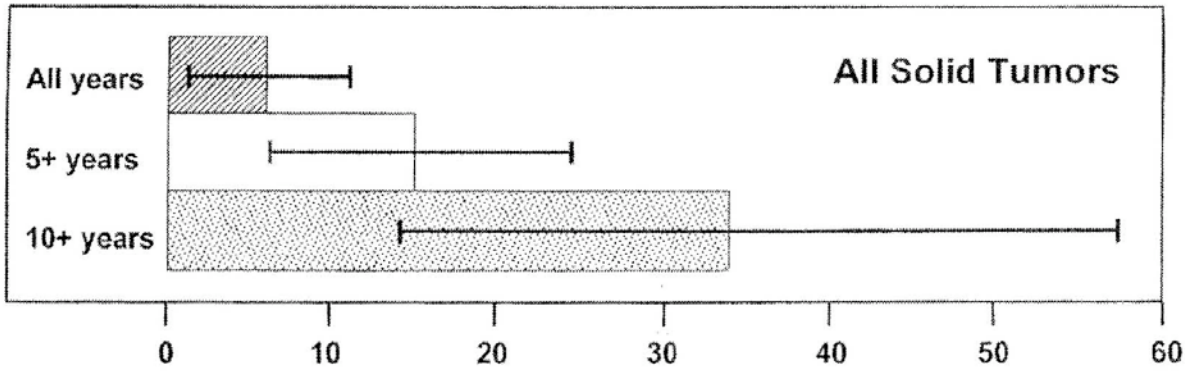
2nd cancers after RT of prostate Ca

	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

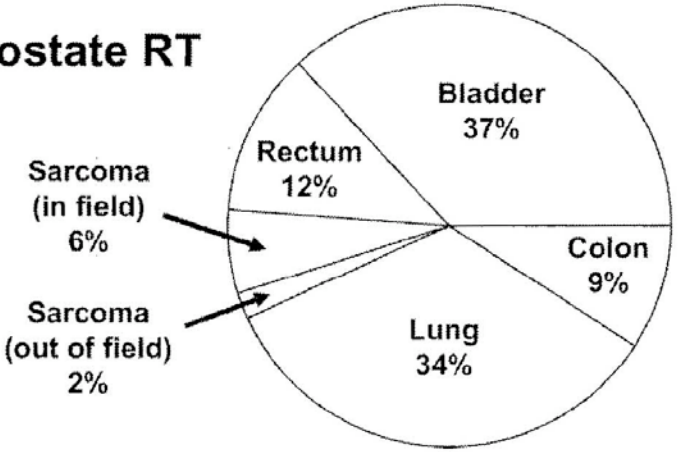
2nd cancers after RT of prostate Ca

Percentage Increase in Relative risk for RT vs. Surgery %



Second Cancers after Prostate RT

% contribution to total number of radiation-induced second cancers

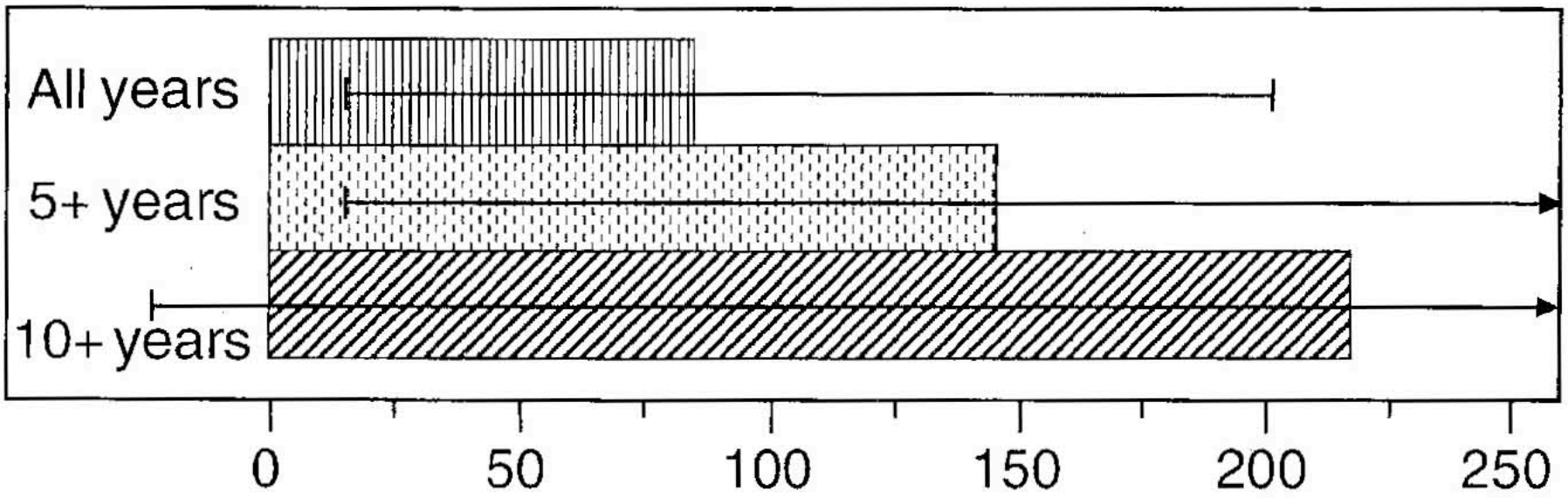


Brenner DJ et al. *Cancer* 2000;88:398-406

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 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 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, which peaks 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 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 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 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 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