


IRCCS Azienda Ospedaliera Universitaria
San Martino – IST
Istituto Nazionale per la Ricerca sul Cancro

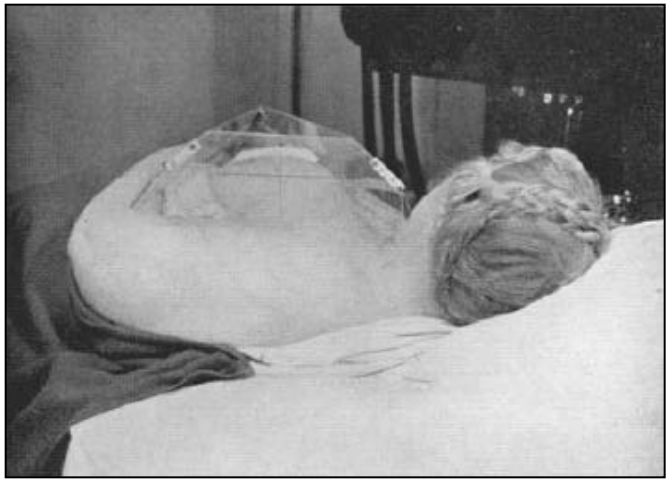
Boost simultaneo integrato (SIB): implicazioni radiobiologiche e cliniche

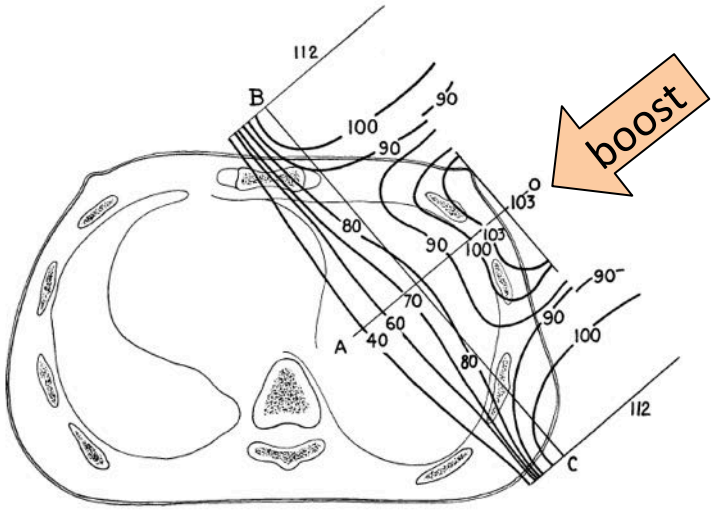
XXII Congresso Nazionale AIRO
Roma 17-20 Novembre 2012

Stefano Vagge

U.O.C. Oncologia Radioterapica

At the beginning (‘40s)





WIDTH OF ANTERIOR FIELD AND FRACTIONAL DOSE FOR VARIOUS SEPARATIONS OF THE LARGE FIELDS

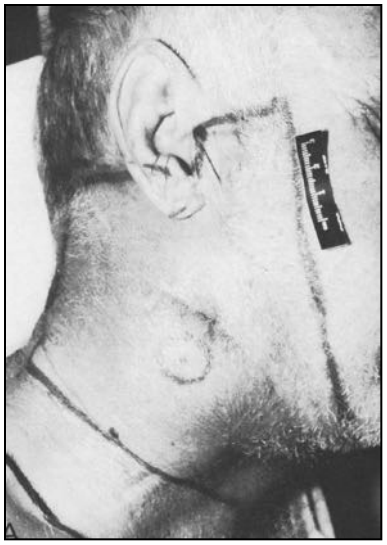
Separation of the large fields	Width of “boost” field	Dose delivered through “Boost” field as a fraction of that given each large field
18 cm.	No third field needed	—
20 cm.	8 cm.	$\frac{1}{10}$
22 cm.	8 cm.	$\frac{1}{5}$
24 cm.	8 cm.	$\frac{1}{3}$
26 cm.	10 cm.	$\frac{1}{2}$
28 cm.	12 cm.	$\frac{1}{2}$
30 cm.	15 cm.	$\frac{1}{2}$

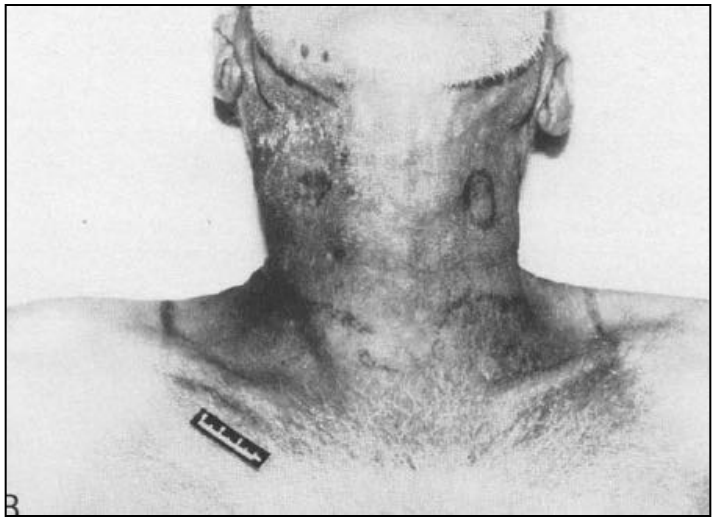
Pre-operative RT

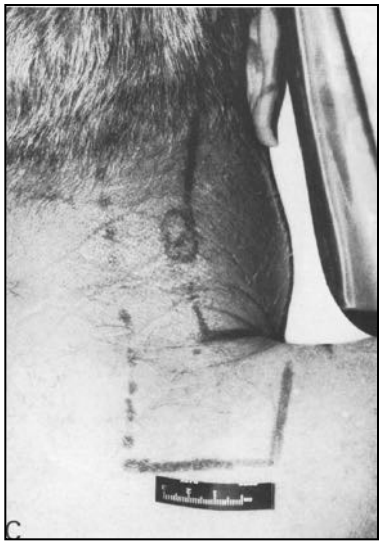
“boost” to find homogeneous dose distribution

Allchin, *BJR 1948*

Subclinical disease (‘70s)







Tumor Control Probability correlated with irradiation Dose and Volume of cancer

5000 rads

0ver 90% for subclinical
≈60% T1 lesion of Nasopharynx
≈50% 1-3 cm neck nodes

6000 rads

≈90% T1 lesion of pharynx and larynx
≈50% T3 + T4 lesion of tonsillar fossa

7000 rads

≈90% 1-3-m neck nodes
≈70% 3-5- cm neck nodes
≈90% T2 lesion of tonsillar fossa and supraglottic larynx
≈80% T3 + T4 lesion of tonsillar fossa

“Field with-in field” Technique

Different levels of dose

Fletcher

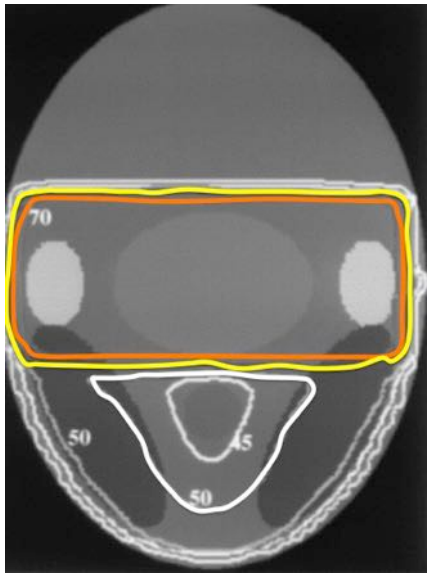
The “Boost” technique

2D
- Sequential
- Concomitant

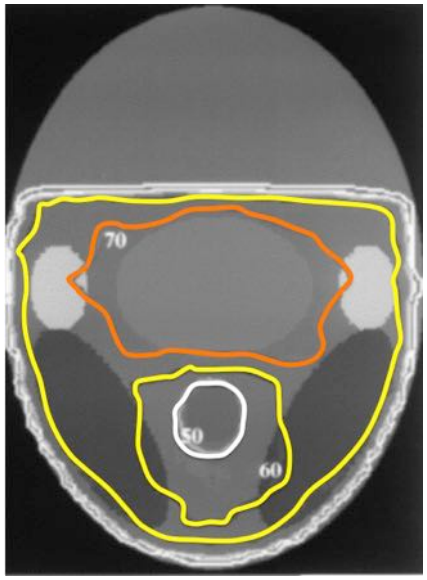
3D
- Sequential
- Concomitant
- Concomitant integrated

IMRT
- Sequential
- Simultaneous Integrated
- Simultaneous Modulated Accelerated RT

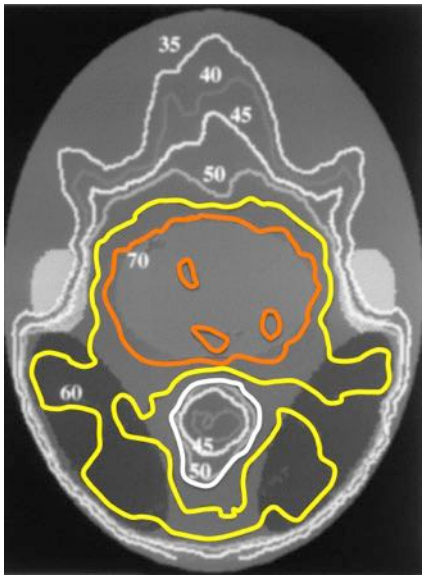
Conventional



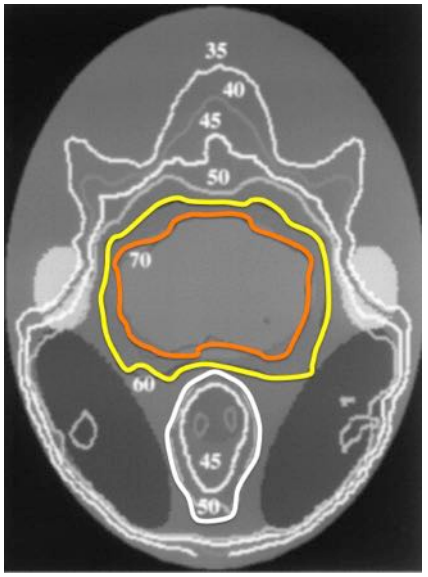
Conventional + IMRT Boost



Two-phase IMRT



SIB IMRT

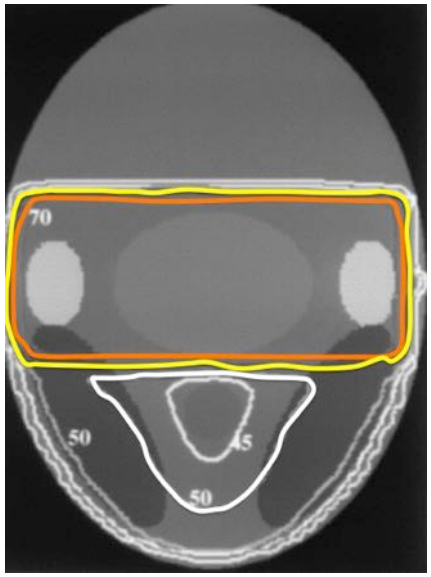


Adapted from Mohan *IJROBP 2000*

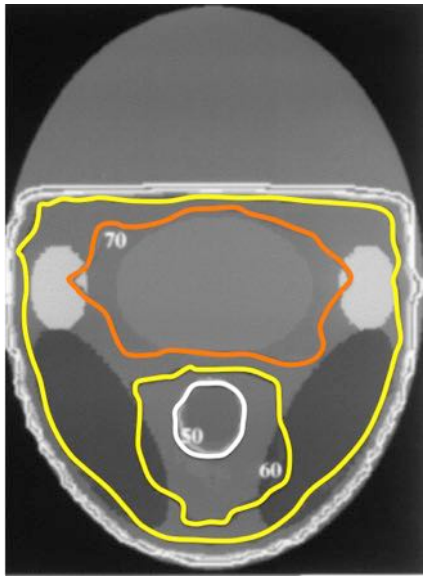
Volume (cc) outside the target regions at specified dose level or higer

Dose level (Gy)	Conventional treatment + IMRT	Two-phase IMRT	SIB	% difference between SIB IMRT and 2-phase IMRT
20	**1.447**	**1.975**	**1.941**	1.8
30	**1.355**	**1.557**	**1.459**	6.7
40	1.234	1.096	1.016	7.9
50	977	732	604	21.2
60	592	**575**	**388**	**63.0**
70	123	**83**	**62**	**33.9**

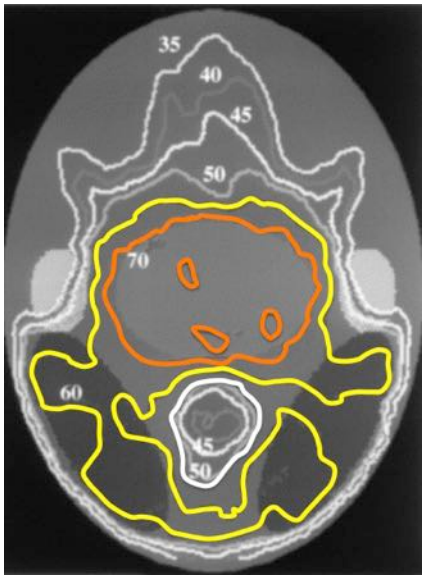
Conventional



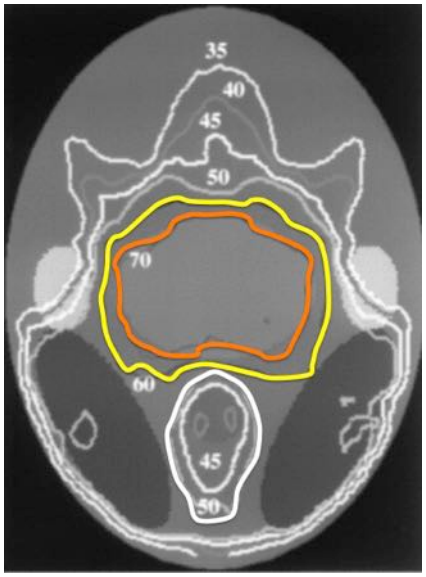
Conventional + IMRT Boost



Two-phase IMRT

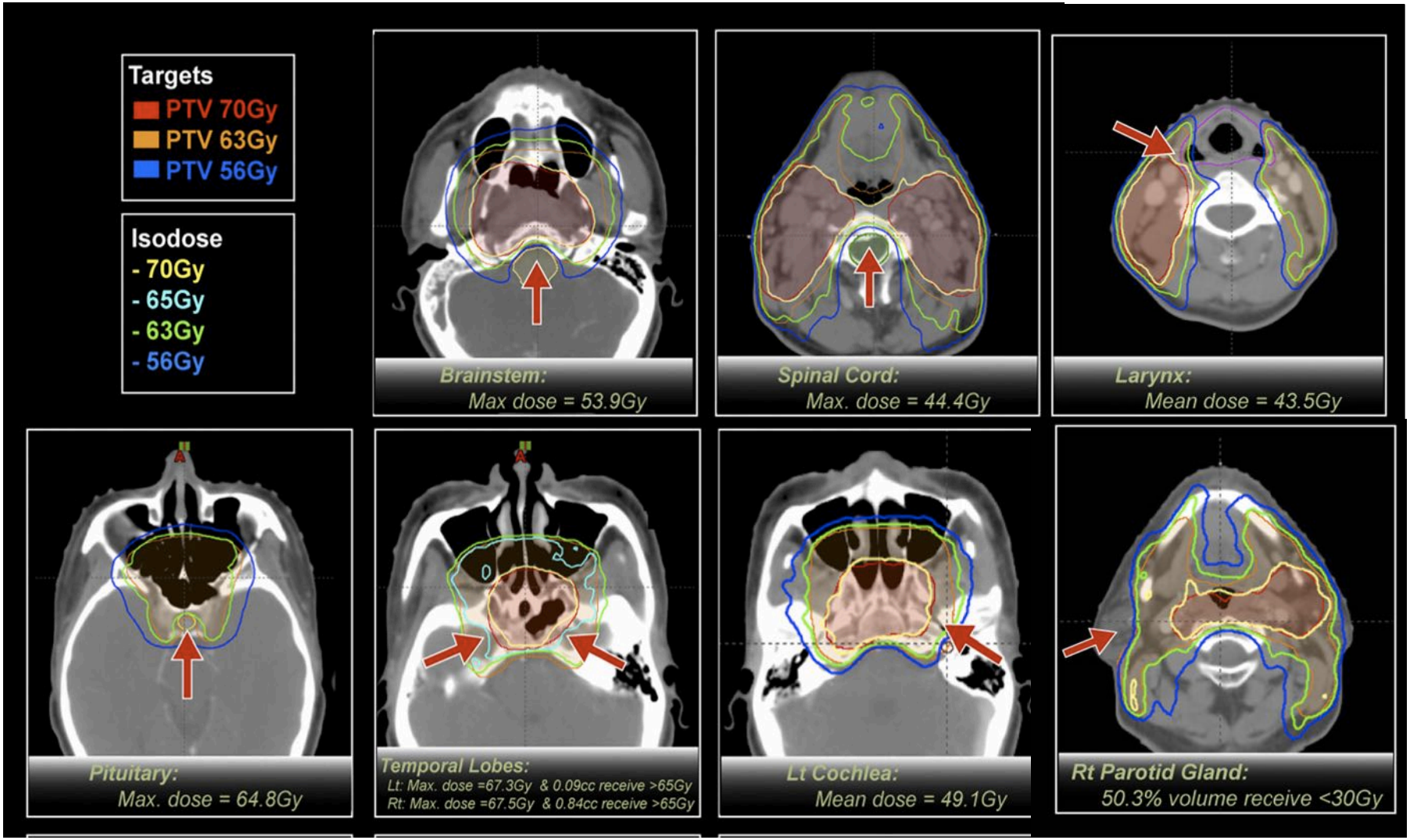


SIB IMRT



Adapted from Mohan *IJROBP 2000*

Steep and conformed dose gradients between different levels and organs at risk

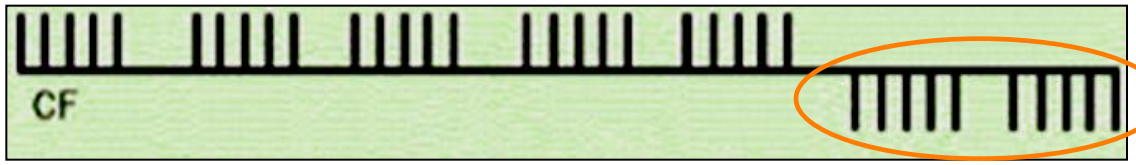


Lee , Sem Rad oncol. 2012

SIB…pro

- **Dosimetrical advantages**
  - SIB is better than IMRT sequential boost strategy
  - IMRT-SIB dose distribution can delineate the dose around multiple level of subclinical disease
  - Steep dose gradients to spare normal tissue close to targets

From evidence of conventional and altered fractionation

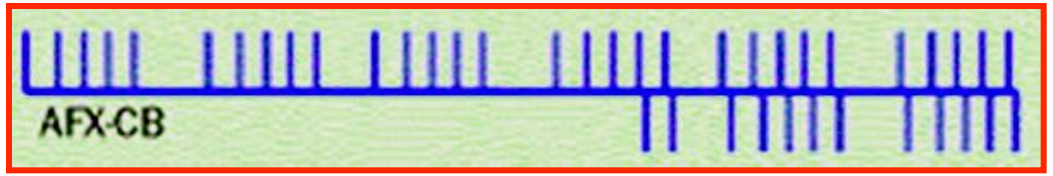


Boost fields

80.5 Gy/ 2x1.5 Gy/ 7w

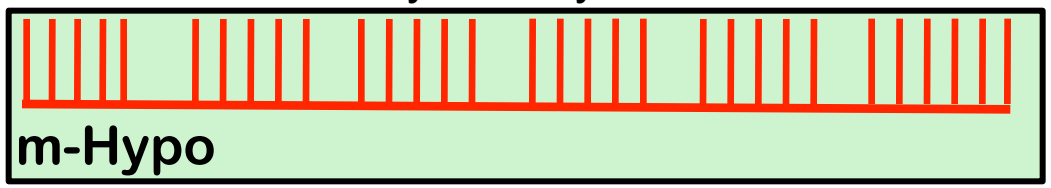
Dose escalation and increased tumor control, more severe acute toxicity

72 Gy/ 1.8 Gy x 30 + c.boost 1.5 Gy x12/ 7w



Shortened overall treatment time and increased tumor control, more severe acute toxicity

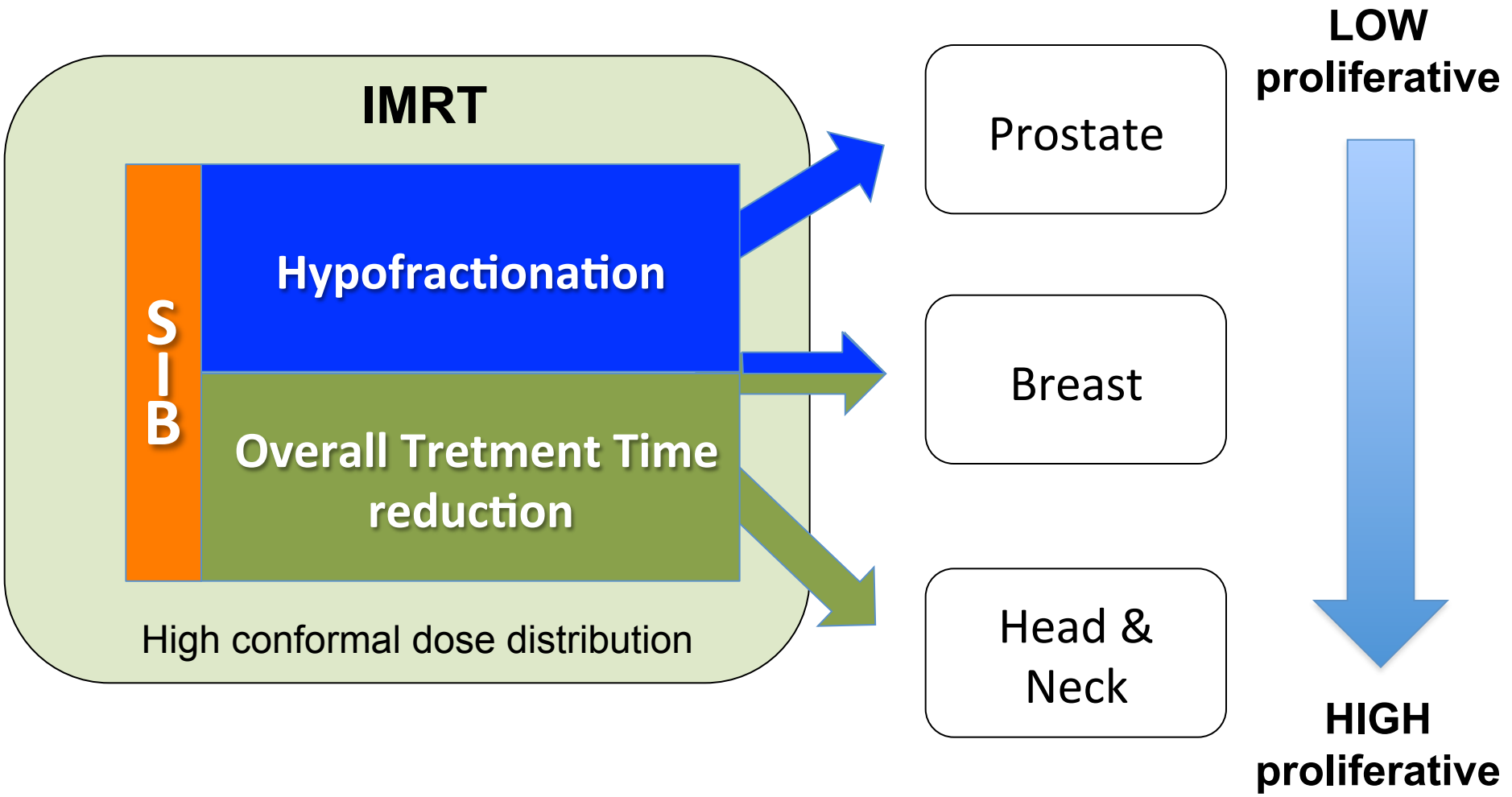
75 Gy/ 2.5 Gy / 6w



Shortened overall treatment time and increased slow proliferative tumor control, more severe late toxicity

Adapted from Linh, Lancet Oncology 2002

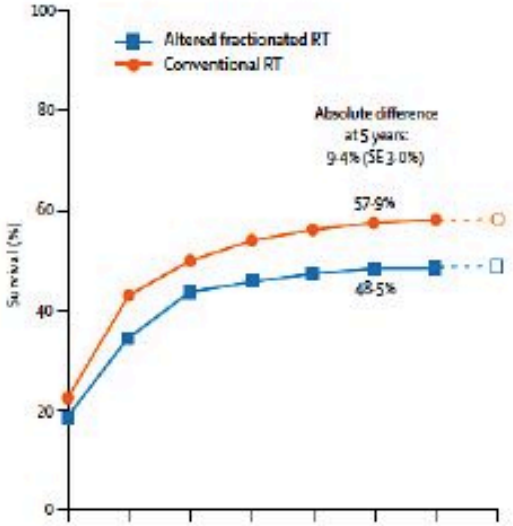
To a new design of Hybrid fractionation with two components with relative advantage in different diseases



….pact of the “accelerated” component on H&N tumor control

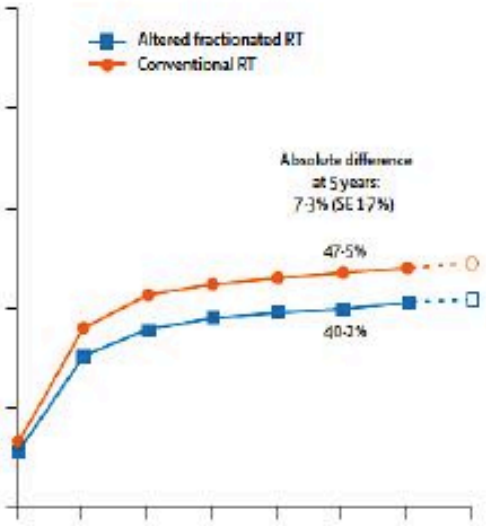
Clinical point of view

Hyperfractionation
(with moderate dose escalation)
vs. conventional fractionation



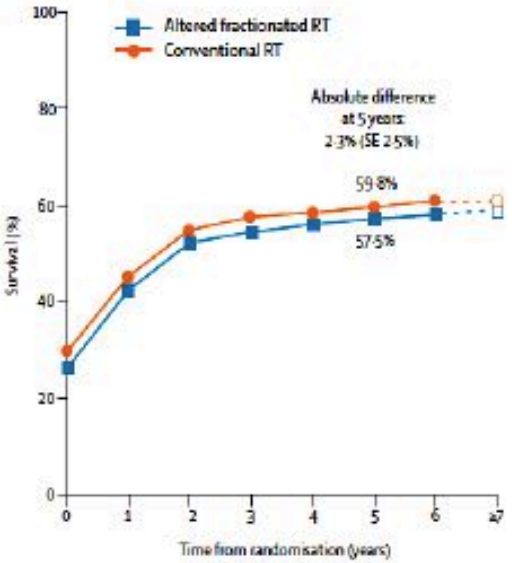
Death/person years by period	Years 0–2	Years 3–5	Years ≥6
Conventional RT	331/1313	30/483	2/261
Altered fractionated RT	288/1453	20/652	2/400

Accelerated fractionation
without decreased total dose
vs. conventional fractionation



Death/person years by period	Years 0–2	Years 3–5	Years ≥6
Conventional RT	786/4127	57/1916	13/834
Altered fractionated RT	645/4357	54/2153	13/937

Very accelerated fractionation
with decreased total dose
vs. conventional fractionation



Death/person years by period	Years 0–2	Years 3–5	Years ≥6
Conventional RT	495/1622	23/596	4/296
Altered fractionated RT	546/2097	33/848	9/430

Influence LC
Influence OS

Bourhis, Lancet 2006

….pact of the “accelerated” component on H&N tumor control

Radiobiological point of view

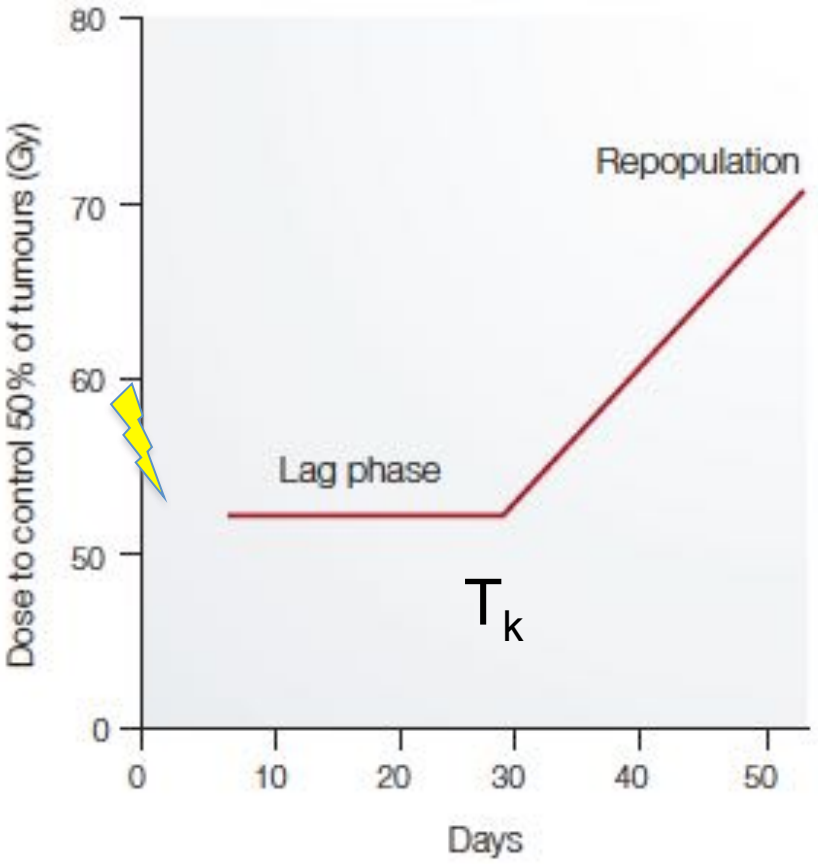
Contrasting Repopulation of cancer stem cells

- Limiting the radiotherapy effectiveness
- Might accelerate during the course of radiotherapy

T_k 4 weeks (repopulation start)

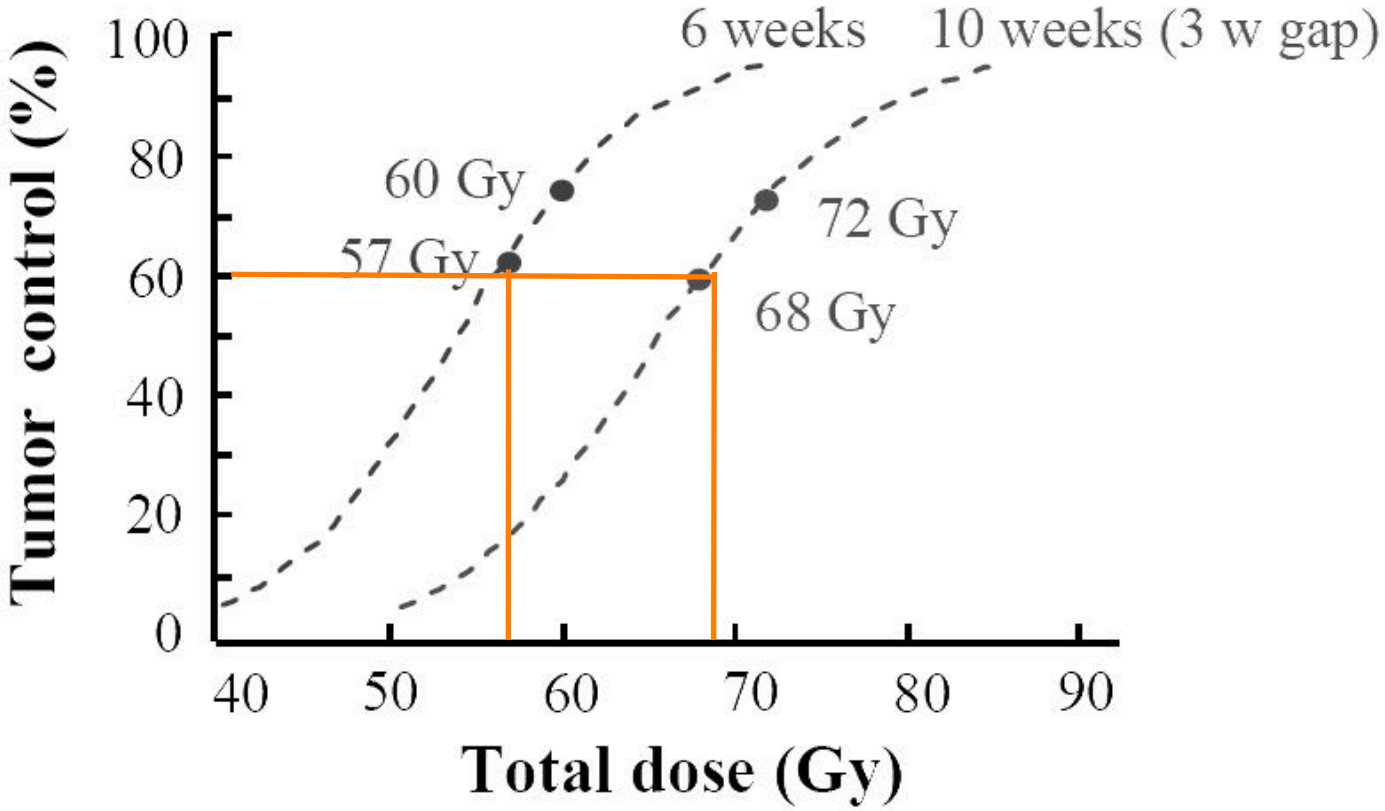
T_d 2 moths (before irradiation)

T_p 4-8 days after RT start



Kim Nature Review 2005

….pact of the “accelerated” component on H&N tumor control

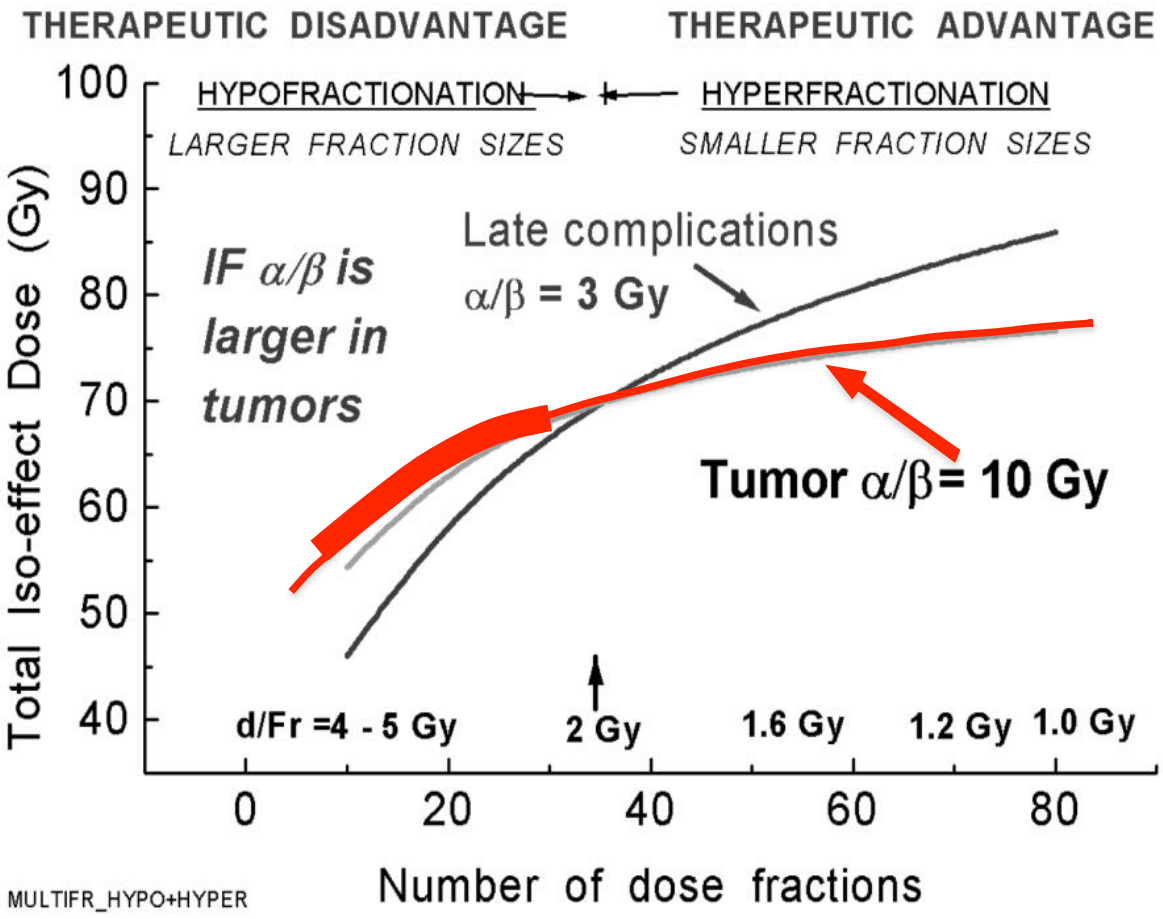


Increse TD of 0.5-1 Gy to maintain tumor control for every day of radiotherapy prolongation

Overgaard

Impact of the "Hypofractionated" component on H&N tumor control

….is not a clear benefit .. but SIB is very conformed with shape margins..



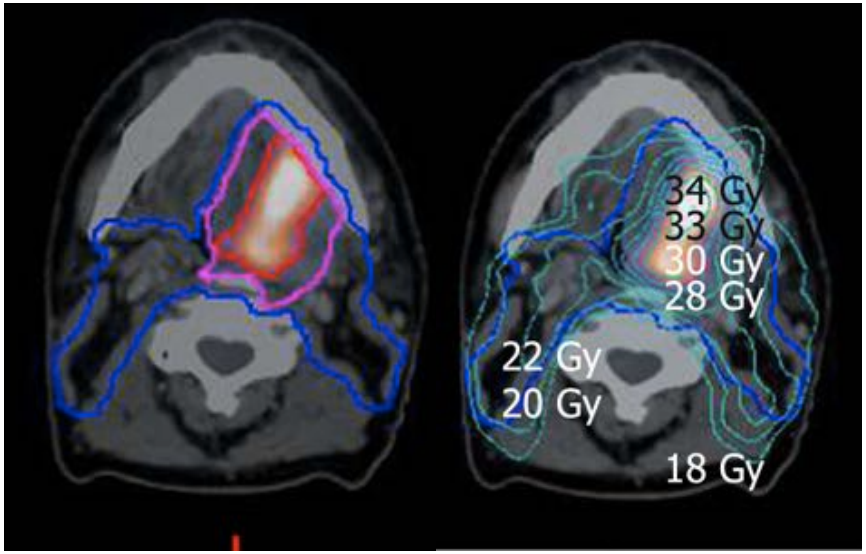
Fowler

Impact of the "Hypofractionated" component on H&N tumor control

…..so try to increase tumor control with

- Dose escalation on biologically active sub volumes

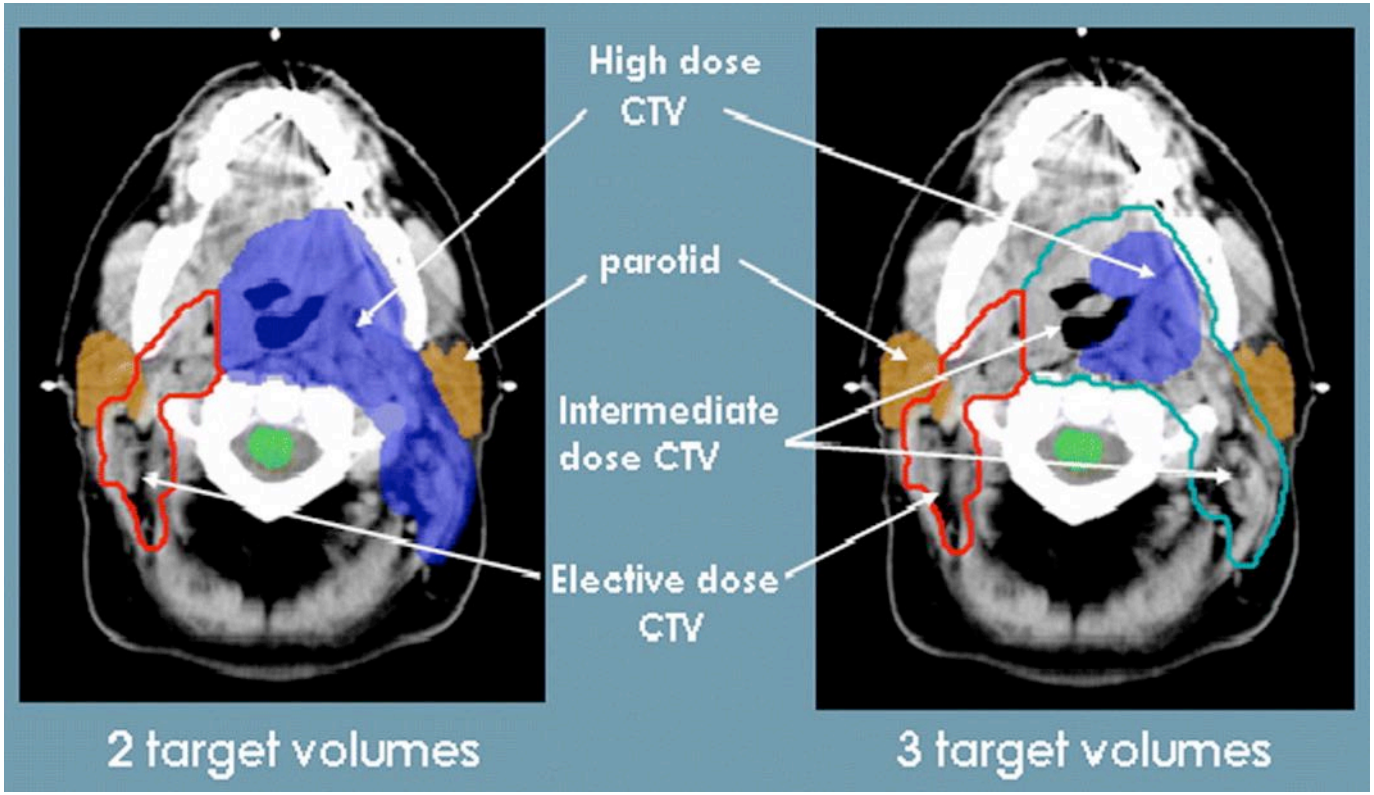
- High tumor burden areas
- Hypoxic areas (more sensitive to hypofractionation)



"dose painting"

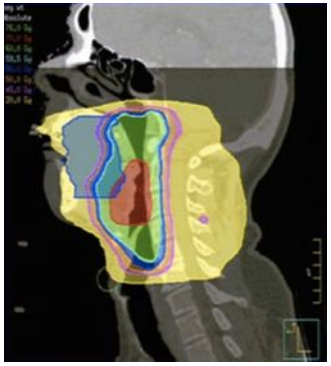
Duprez IJROBP 2011

Treating multiple levels you need to select the fraction dose in a safe "range" to reduce the risk of "late toxicity" and avoid the biological under dosage of subclinical disease



Designing a safe SIB fractionation schedule you should start from the isoeffective dose of the lower dose level

But are isodoses tight enough….to overcome Treatment dose limiting?



To reduce clinical impact of early reactions (α/β 10)

- **<u>prolong overall treatment time</u>** (enhance repopulation)
- keep interfraction interval at least of 6 h (repair sub lethal damage)
- decrease total dose (increase rate of recovery)

"gray zone" **EQD2= 49 Gy_{10} - 52.5 Gy_{10}**

To reduce clinical impact of late reaction (α/β 3)

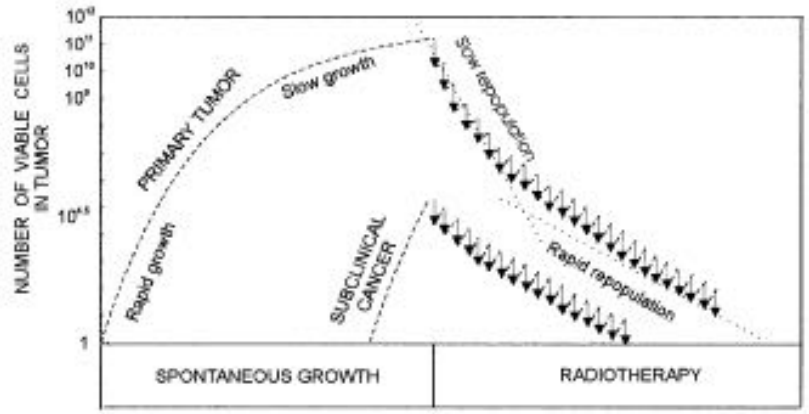
- decrease total dose
- keep interfraction interval at least of 6h
- **<u>Decrease Fx dose <2Gy</u>**

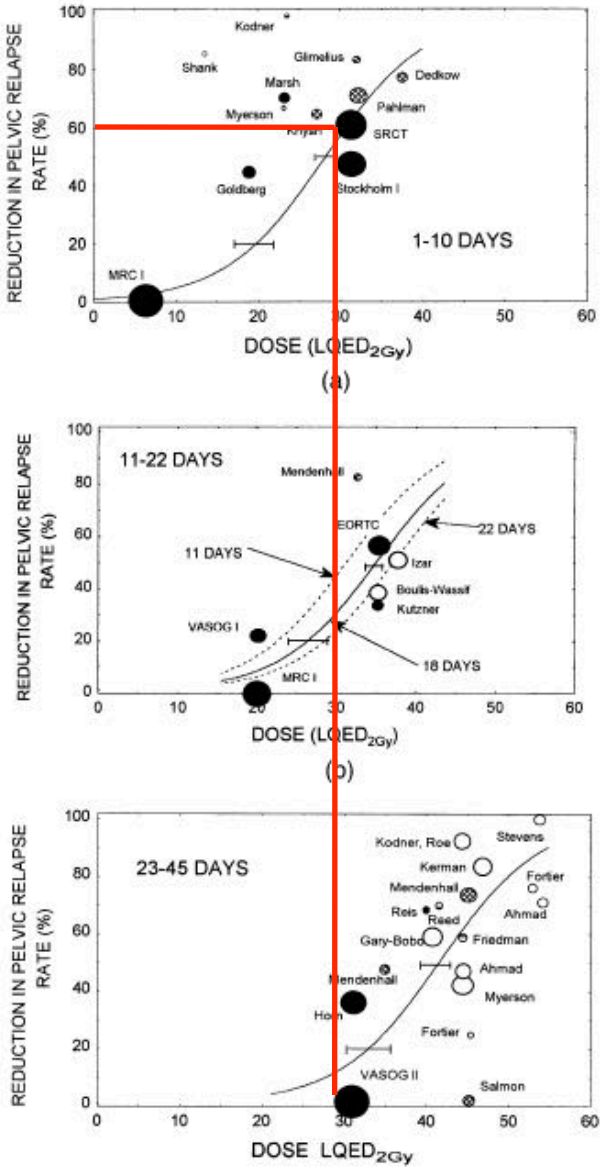
EQD2= 117 Gy_3

Marcu Cancer Traet Rew 2010

Overall treatment time and subclinical disease

- increase of about 0.5 Gy/day of RT extension to maintein LC
- approximate doubling time is about 3-4 days (Tp)
- lack of clear evidence of lag period (Tk) in contrast for primary tumors
- to overcame relapse treatment intensification is necessary (higer doses,shorter times, concomitant CT)





Suwinky IJROBP 1998

What we want to know form clinical trials with SIB

H&N

author or study	year	Type	Nº of patients	T3-T4	CT%	PTV1 D	PTV1 d	Nº Fx	PTV2 D	PTV2 d	PTV3 D	PTV3 d	Time	Local FFR(%)	Nodal FFR(%)
RTOG 0615	2012	Phase II	44	57%	100%	**70**	2.12	33	**59.4**	1.8	**54.0**	1.64	2 yy	83.7	
Bakst	2011	prospective	25	28%	100%	**70.2**	2.34	30	**..**	..	**54**	1.8	3 yy	91	91
Xiao	2011	prospective	81	100%	100%	**68**	2.27	30	**60**	2	**54**	1.8	5 yy	95	
Heming	2010	Phase II	22	73%	100%	**68.2**	2.20	31	**58.9**	1.9	**53.9**	1.7	1 yy	95.5	
RTOG 0225	2009	Phase II	68	34%	84%	**70**	2.12	33	**59.4**	1.8	**54.0**	1.64	2 yy	89.3	

Usual dose fractionation: 68-70 Gy to GTV

Fractional dose to GTV ranging from 2.12 to 2.34 per fx

“low risk” PTV ranging from 1.64 to 2 Gy per fx

NPC IMRT-SIB whole field published

Adapted from Wang, J Radiat Oncol 2012 and Lee, Sem Rad Oncol 2012

NPC IMRT-SIB whole field

H&N

author or study	year	Type	Nº of patients	T3-T4	CT%	**$EQD2_T$**	PTV1 d	Nº Fx	**$EQD2_T$**	PTV2 d	**$EQD2_T$**	PTV3 d	Time	Local FFR(%)	Nodal FFR(%)
RTOG 0615	2012	Phase II	44	57%	100%	**58**	2.12	33	**45.8**	1.8	**39.7**	1.64	2 yy	83.7	
Bakst	2011	prospective	25	28%	100%	**62.3**	2.34	30	**..**	..	**43.2**	1.8	3 yy	91	91
Xiao	2011	prospective	81	100%	100%	**60**	2.27	30	**45.8**	2	**43.2**	1.8	5 yy	95	
Heming	2010	Phase II	22	73%	100%	**59**	2.20	31	**48**	1.9	**42.2**	1.7	1 yy	95.5	
RTOG 0225	2009	Phase II	68	34%	84%	**58**	2.12	33	**45.8**	1.8	**39.7**	1.64	2 yy	89.3	

$EQD2_T$ > 58 have significantly lower locoregional failure rates

T_k = 21 days (Tumor) and 7 days (mucosal damage)
T_{pot} = 3 days (Tumor) and 2.5 days (mucosal damage)
α = 0.35 $^{-Gy}$
$Log_e 2$ = 0.693

Adapted from Wang, J Radiat Oncol 2012 and Lee, Sem Rad Oncol 2012

NPC IMRT-SIB whole field

H&N

author or study	year	Type	Nº of patients	T3-T4	CT%	**$EQD2_m$**	PTV1 d	Nº Fx	**$EQD2_m$**	PTV2 d	**Acute toxicity ≥ G3**		Local FFR(%)	Nodal FFR(%)
RTOG 0615	2012	Phase II	44	57%	100%	**46.3**	2.12	33	**32.7**	1.8	38%		83.7	
Bakst	2011	prospective	25	28%	100%	**51**	2.34	30	**..**	..	40%		91	91
Xiao	2011	prospective	81	100%	100%	**48.4**	2.27	30	**38.2**	2	**?**		95	
Heming	2010	Phase II	22	73%	100%	**47.6**	2.20	31	**36.6**	1.9	27%		95.5	
RTOG 0225	2009	Phase II	68	34%	84%	**46.3**	2.12	33	**32.7**	1.8	29.4%		89.3	

$EQD2_{mucosal}$ for acute toxicity is not safe over 51 Gy when associated to CT

T_k = 21 days (Tumor) and 7 days (mucosal damage)
T_{pot} = 3 days (Tumor) and 2.5 days (mucosal damage)
α = 0.35 $^{-Gy}$
$Log_e 2$ = 0.693

Adapted from Wang, J Radiat Oncol 2012 and Lee, Sem Rad Oncol 2012

NPC IMRT-SIB whole field

H&N

author or study	year	Type	Nº of patients	T3-T4	CT%	$EQD2_I$	PTV1 d	Nº Fx	$EQD2_I$	PTV2 d	Late toxicity		Local FFR(%)	Nodal FFR(%)
RTOG 0615	2012	Phase II	44	57%	100%	**99.4**	2.12	33	**79**	1.8			83.7	
Bakst	2011	prospective	25	28%	100%	**104**	2.34	30	**..**	..	**16% TLN**		91	91
Xiao	2011	prospective	81	100%	100%	**99.5**	2.27	30	**83.4**	2			95	
Heming	2010	Phase II	22	73%	100%	**98.5**	2.20	31	**80.2**	1.9			95.5	
RTOG 0225	2009	Phase II	68	34%	84%	**99.4**	2.12	33	**79**	1.8			89.3	

2.34 Gy / Fx NOT SAFE

Adapted from Wang, J Radiat Oncol 2012 and Lee, Sem Rad Oncol 2012

SIB in Prostate Cancer

$$BED = nd\left(1 + \frac{d}{\alpha/\beta}\right) - \frac{Ln2(T - T_k)}{\alpha T_p}$$

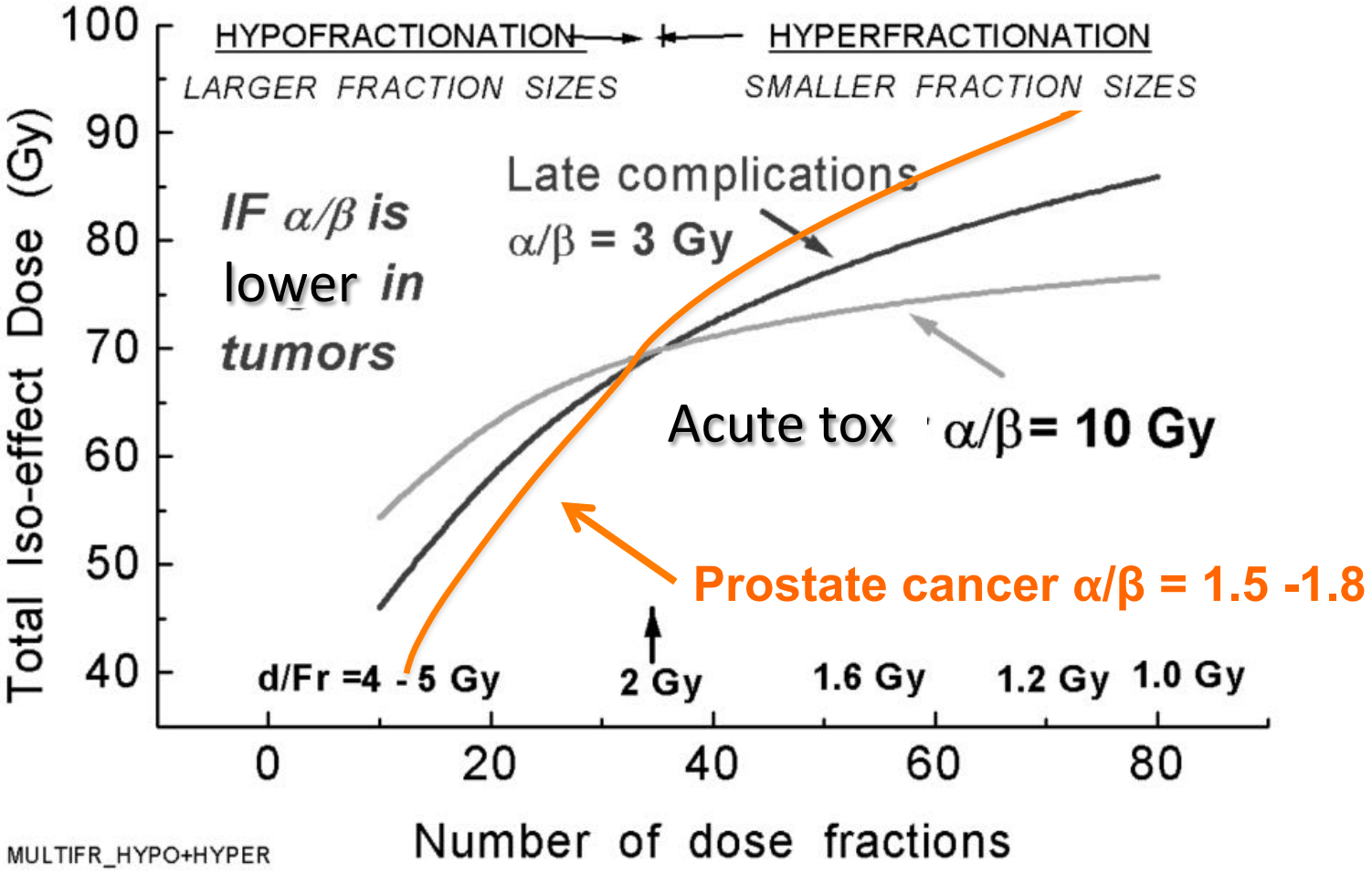
Tk = Time to compensatory repopulation of oral and pharyngeal mucosal cells after start of radiotherapy

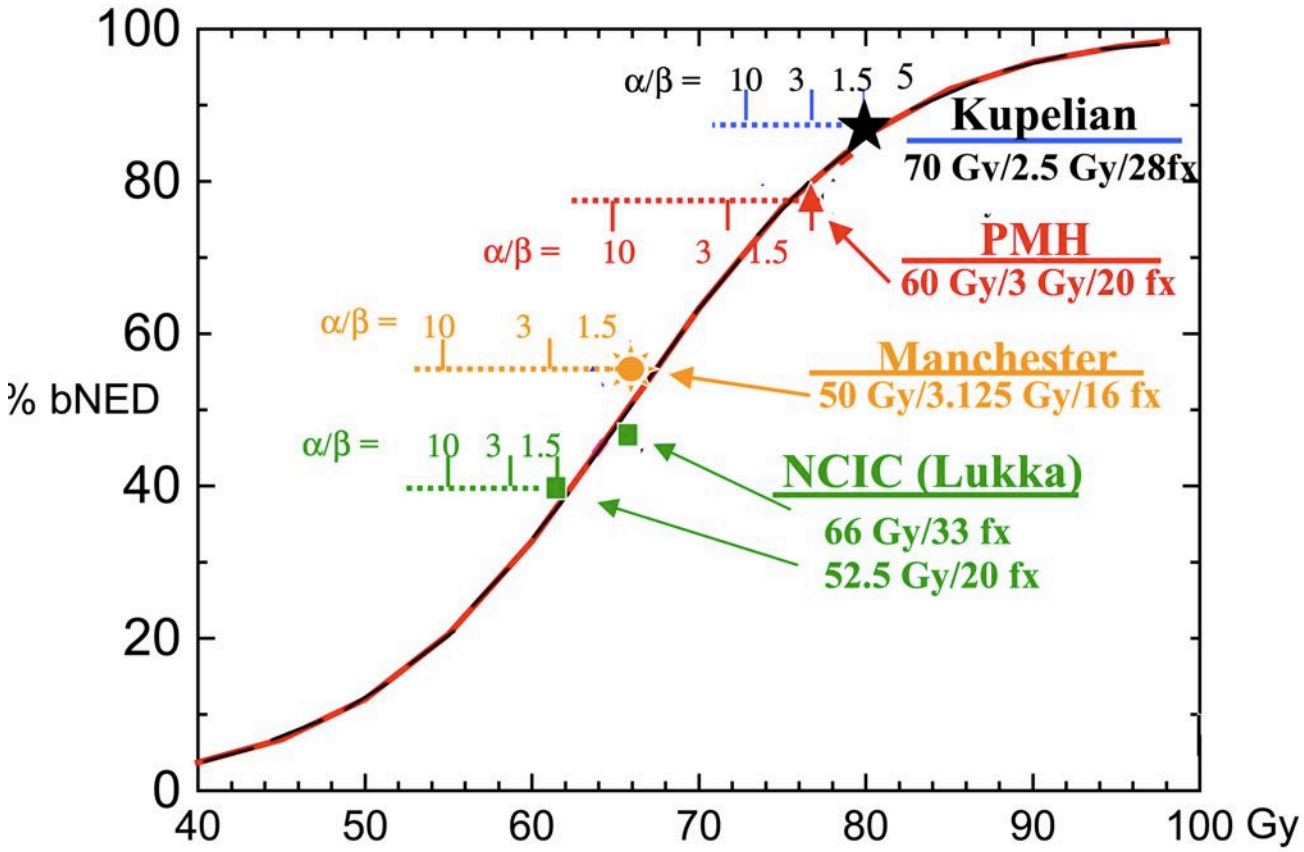
Tp = Time to double the cell population during radiotherapy

T = Overall treatment time

BED= TD * BE -BRF

Impact of the "Hypofractionated" component on Prostate cancer




100
80
60
40
20
0
% bNED
40
50
60
70
80
90
100 Gy
α/β = 10 3 1.5 5
Kupelian
70 Gv/2.5 Gy/28fx
α/β = 10 3 1.5
PMH
60 Gy/3 Gy/20 fx
α/β = 10 3 1.5
Manchester
50 Gy/3.125 Gy/16 fx
α/β = 10 3 1.5
NCIC (Lukka)
66 Gy/33 fx
52.5 Gy/20 fx
Equiv. total dose in 2 Gy fractions (α/β = 1.5)
Gy)

Prostate SIB

Phase I-II

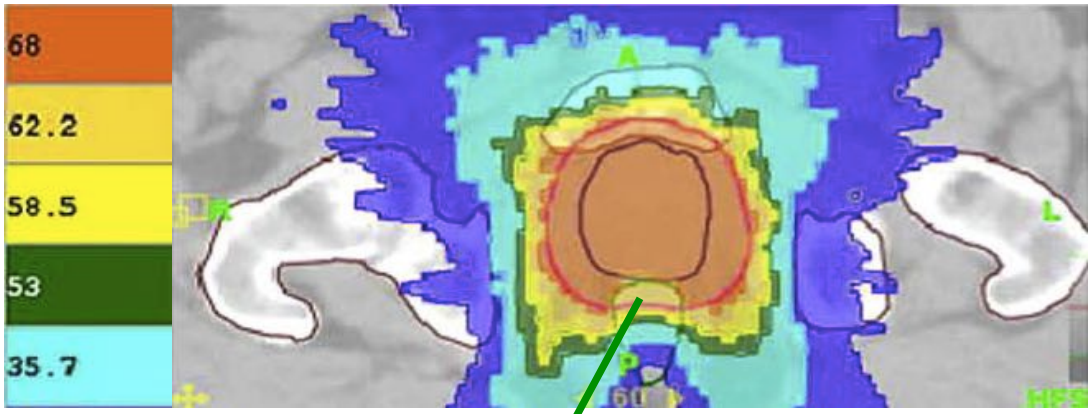
5 different levels of dose

Higher dose to prostate (intermediate and high risk patients) 2.34 x 27 fractions

-***Tailor the SIB volume to reduce the risk of unrecoverable toxicities increasing tumor biological dose***

No patients experienced acute ≧ G2

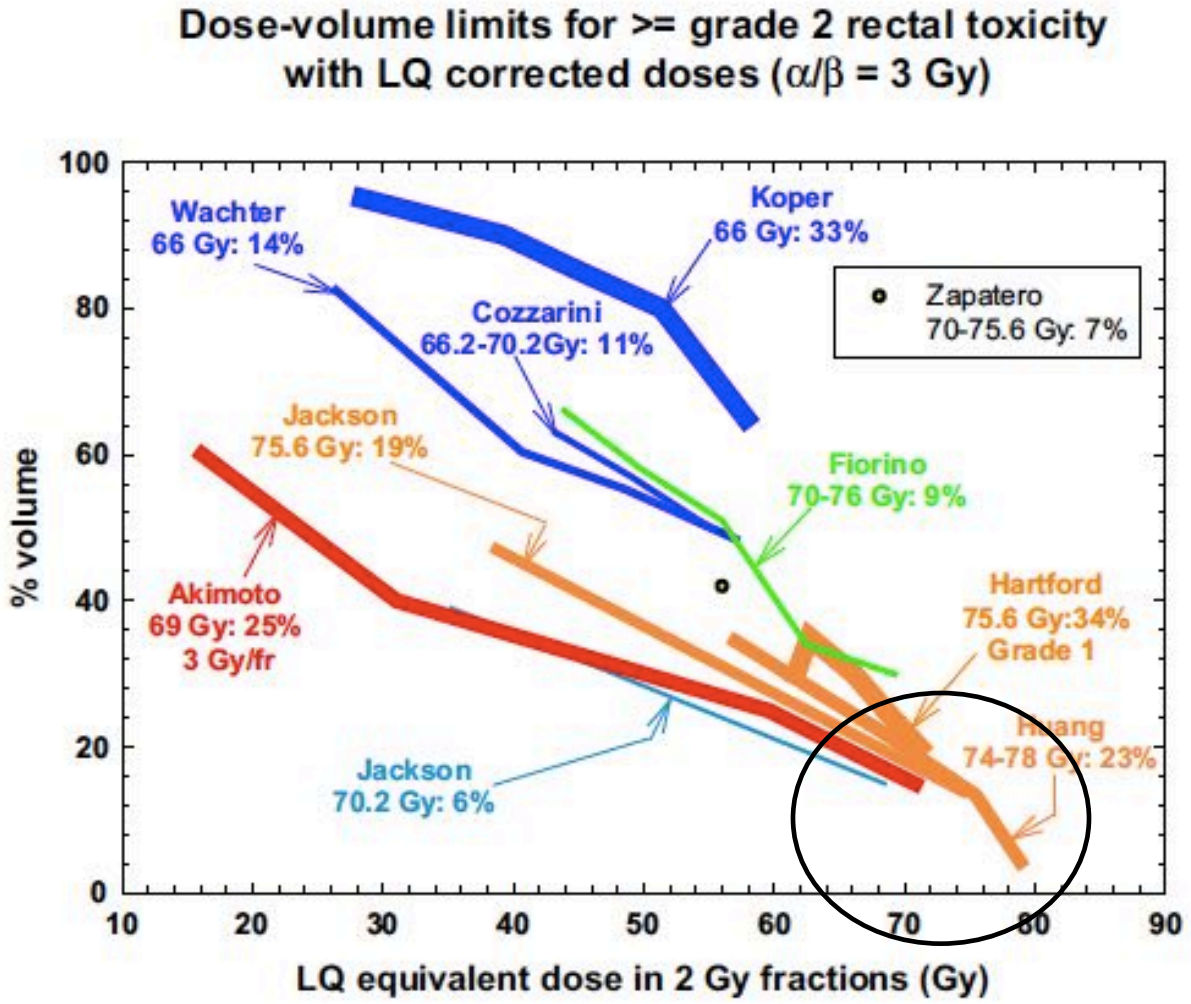
Di Muzio *IJROBP 2009*



	Low risk		Intermediate risk		High risk	
	Dose/fr.	Dose	Dose/fr.	Dose	Dose/fr.	Dose
PTV1 (LN)			1.85	51.8	1.85	51.8
PTV2 (SVc)	2	56	2.2	61.6	2.34	65.5
PTV3 ($SV_{1/3}$)	2.2	61.6	2.34	65.5	2.65	74.2
PTV4 (P)	2.55	71.4	2.65	74.2	2.65	74.2
Overlap	2.34	65.5	2.34	65.5	2.34	65.5

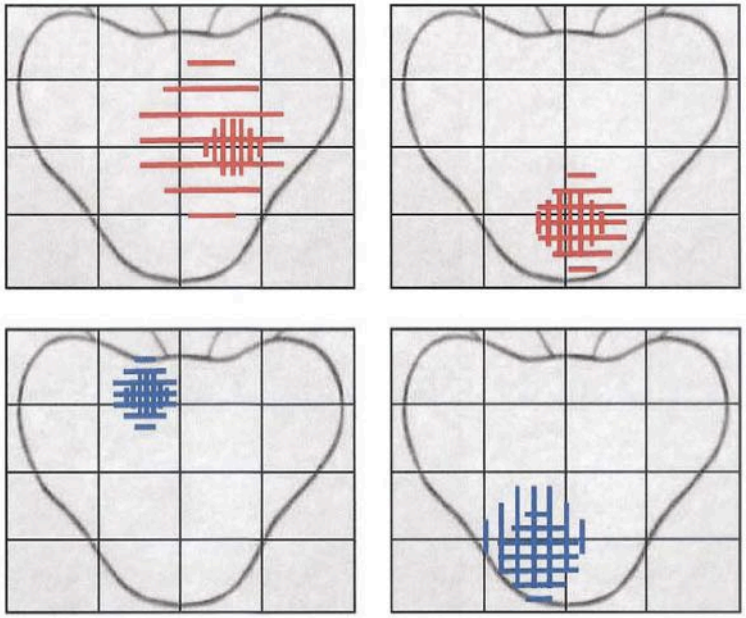
Dose/ fraction	Dose	EQD2 α/β 1.5	EQD2 α/β 3	EQD2 α/β 10	EQD2 α/β 15.5
1.85	51.8	49.6	50.2	51.1	51.4
2	56	56	56	56	56
2.2	61.6	65.1	64.1	62.6	62.3
2.34	65.5	71.9	70	67.4	66.8
2.55	71.4	82.6	79.3	74.7	73.6
2.65	74.2	88	83.8	78.2	77

Toxicity control

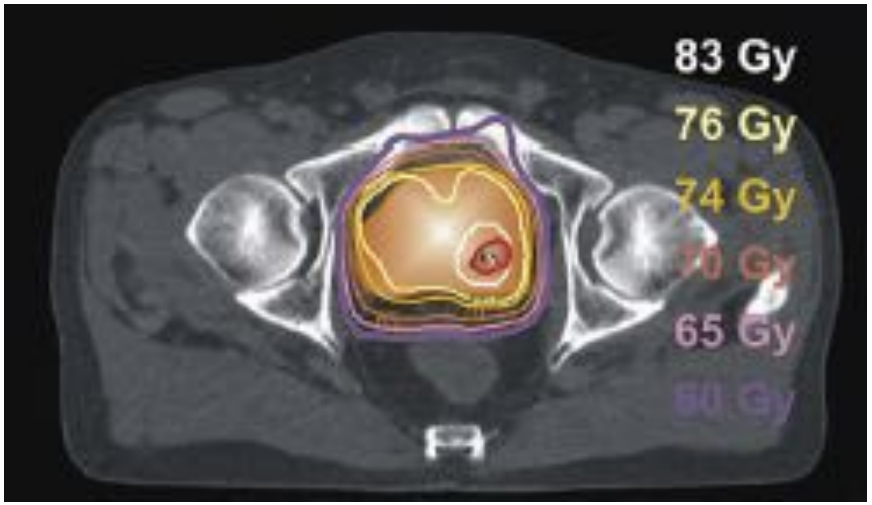


Dominant Intra-prostatic Lesions

- radioresistant cells and/or high-clonogen density volumes may be concentrated in one or more local foci



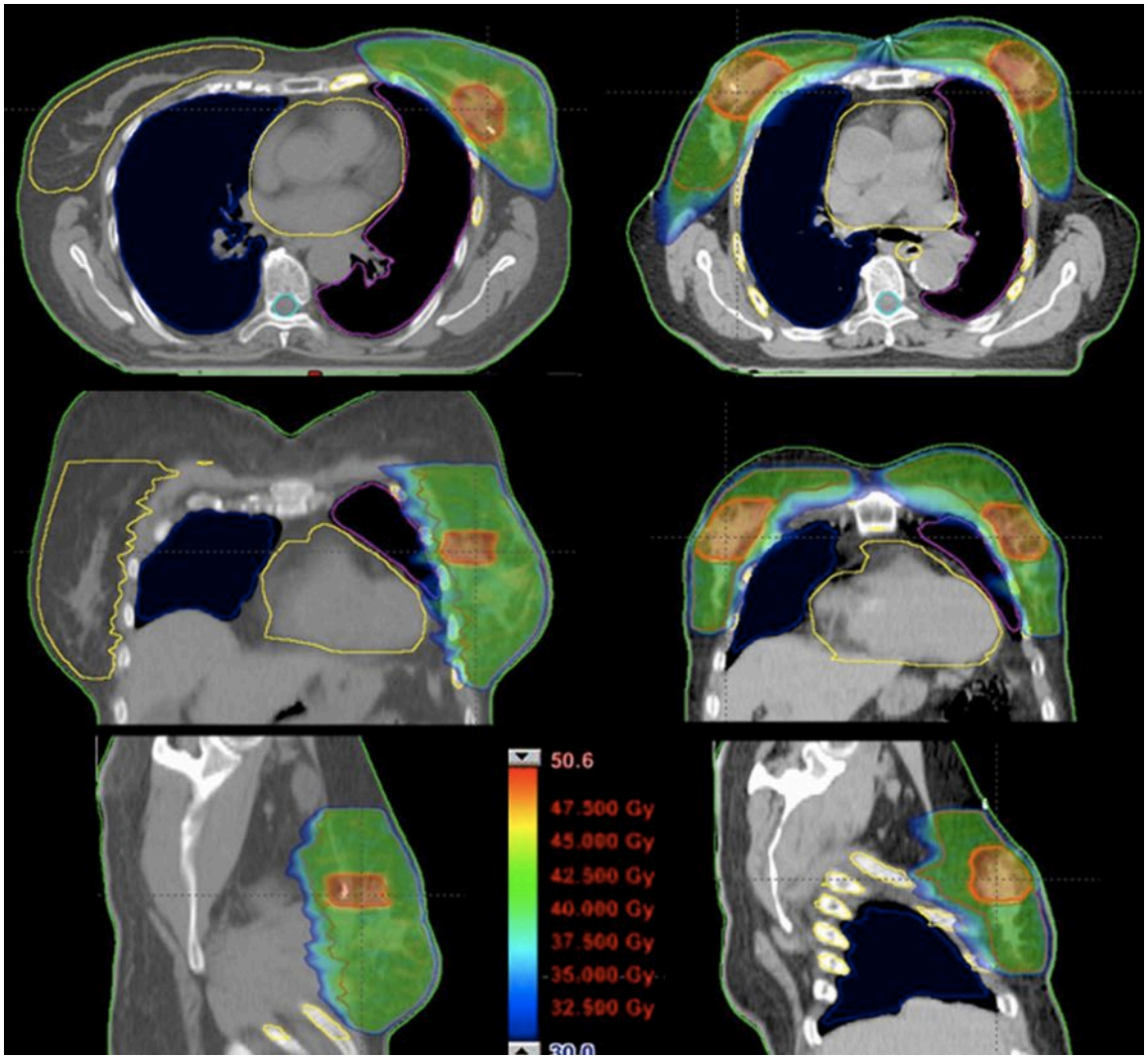
Cellini IJROBP 2002



Fonteyne IJROBP 2008

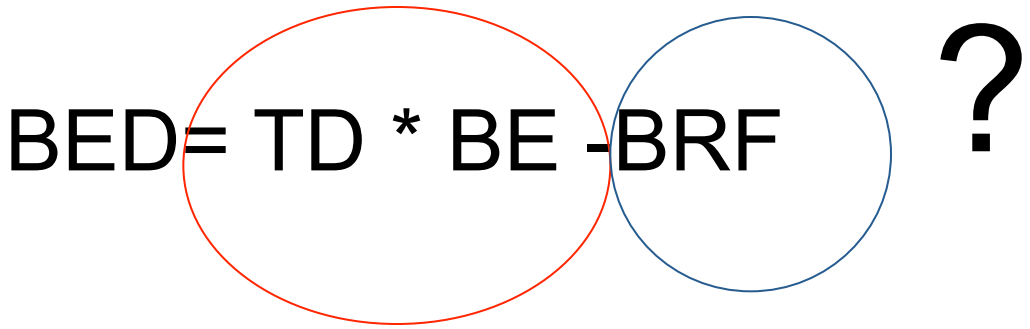
SIB in Breast Cancer

Clear dosimetric advantages



Scorsetti Radiation oncology 2012

SIB in Breast Cancer



- Boost improve LC (Bartelink, 2007)
- α/β breast cancer ≈ 4 Gy , breast normal tissue α/β (1.5-10)
- a moderate hypofractionation with isoeffective schedule is achievable (Level I)
- tumor proliferation may have been underestimated in the past and ACPI interim analysis found good cosmesis (sparing late effects)
- heterogeneous Tpot ..25 days ??? Lower for young woman?
- great importance of boost volume

Yarnold IJRBP 2011

SIB..pro

- **Dosimetrical advantage**
- **New radiobiological boundaries**
  - tailor the appropriate fraction dose over clinical and biological subvolumes
  - overcome repopulation with shortening overall treatment time

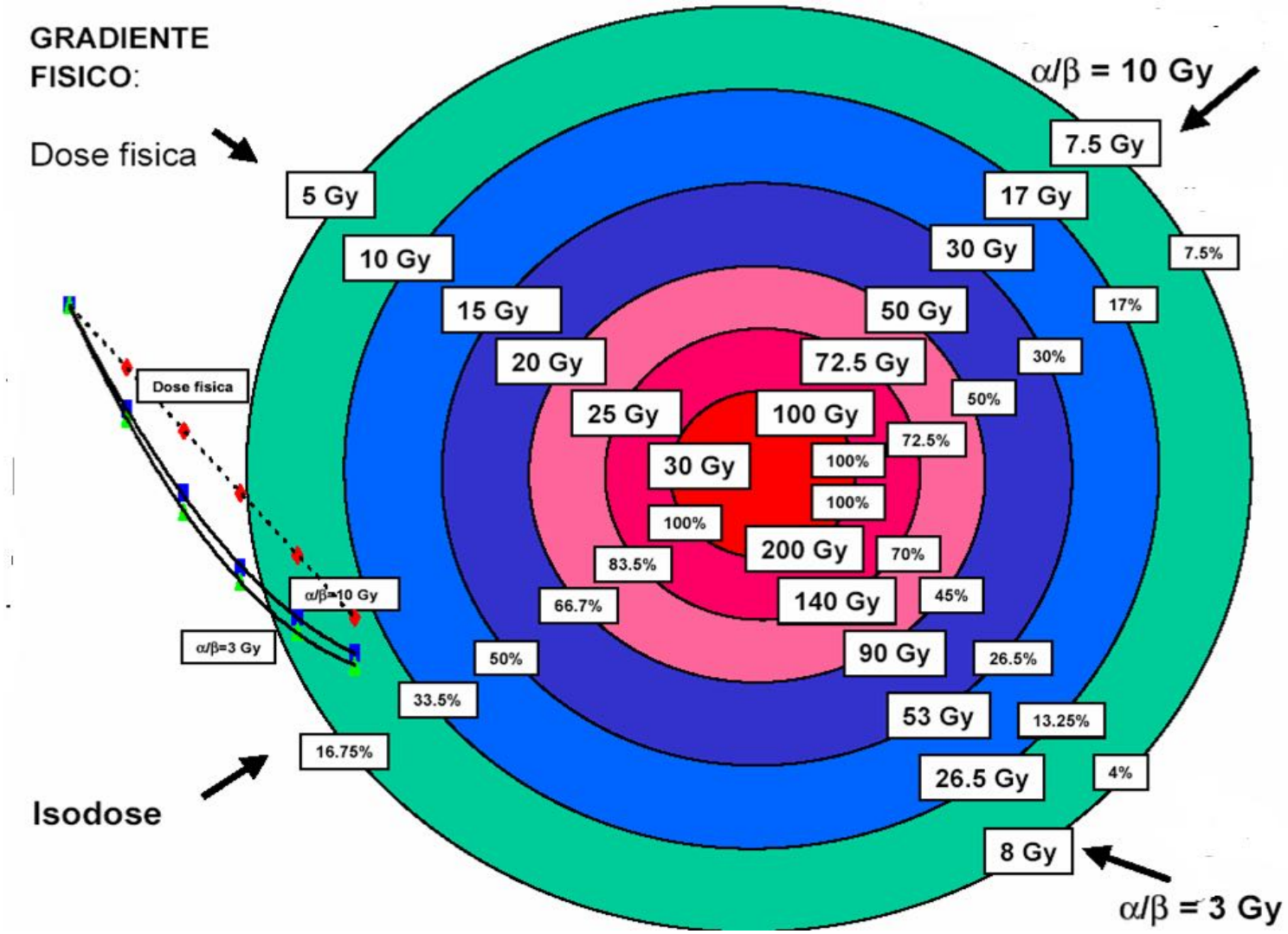
SIB..pro

- **Dosimetrical advantage**
- **New radiobiological boundaries for accelerated hypofractionadet schedule**
- **lower the risk of treatment errors with single plan treatments**
- **Positive economic considerations**

SIB….challenge

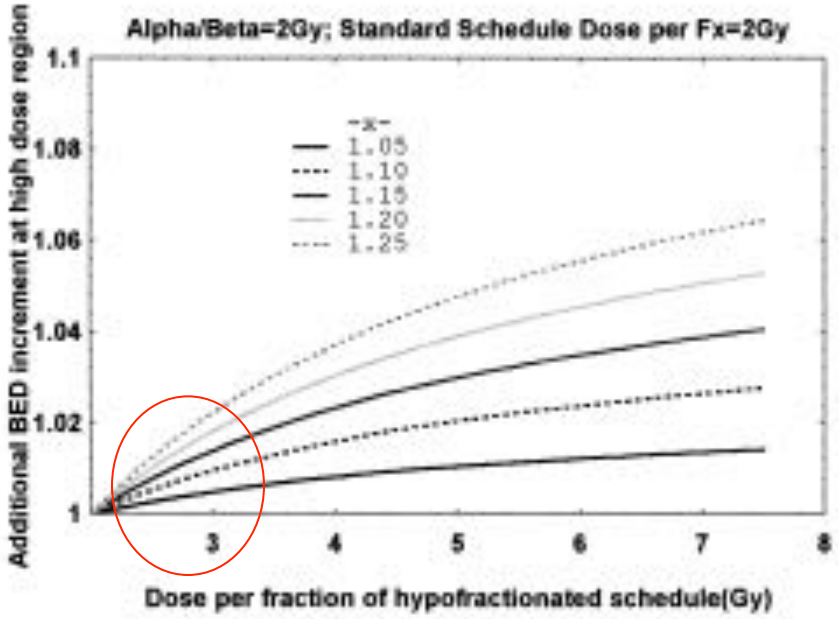
- Treble trouble with Hypofractionation
- IGRT (to avoid risk of geographically missing the target)
- manage target volume modification (Adaptive)
- Functional Imaging to define the real biological target (to manage Hypoxia-Stem Cells- prolifreration)
- Target delineation uncertainties

“Treble trouble” with Hypofractionation



Impact of dose inhomogeneities on dose intensity in hypofractionation

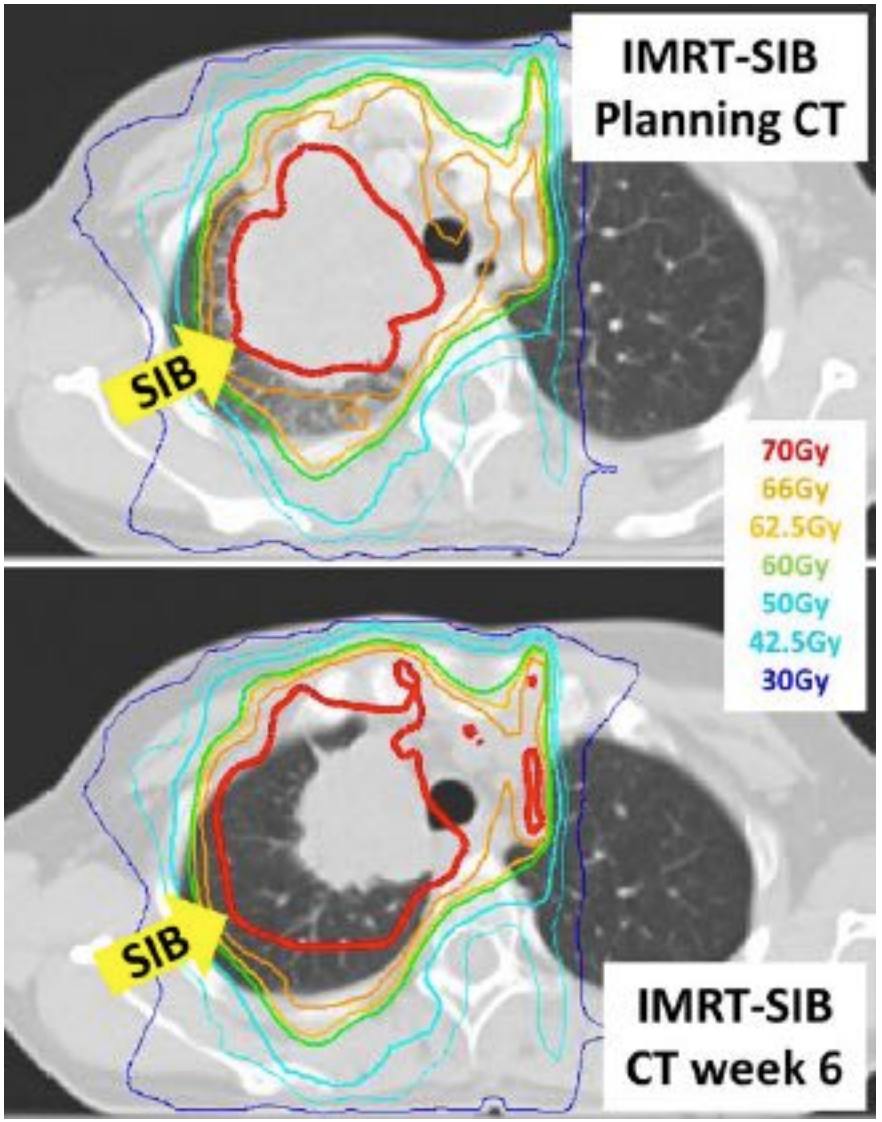
- difference between prescribed physical dose and actual delivered dose (spatial dose heterogeneity)
- variation of biological effects with different dose per fraction (biological dose heterogeneity)
- The clinical consequences of high dose to small volumes are much less than high dose to large volumes



	% equivalent dose in 2.0 Gy fractions at different fraction sizes				
Dose inhomogeneity	2 Gy	3 Gy	4 Gy	5 Gy	6 Gy
105%	107.1%	107.1%	108.0%	108.3%	108.5%
110%	114.4%	115.5%	116.3%	116.9%	117.3%
115%	121.9%	123.6%	124.9%	125.8%	126.5%

Yarnold ,IJROBP 2011 Jones, IJROBP 2000

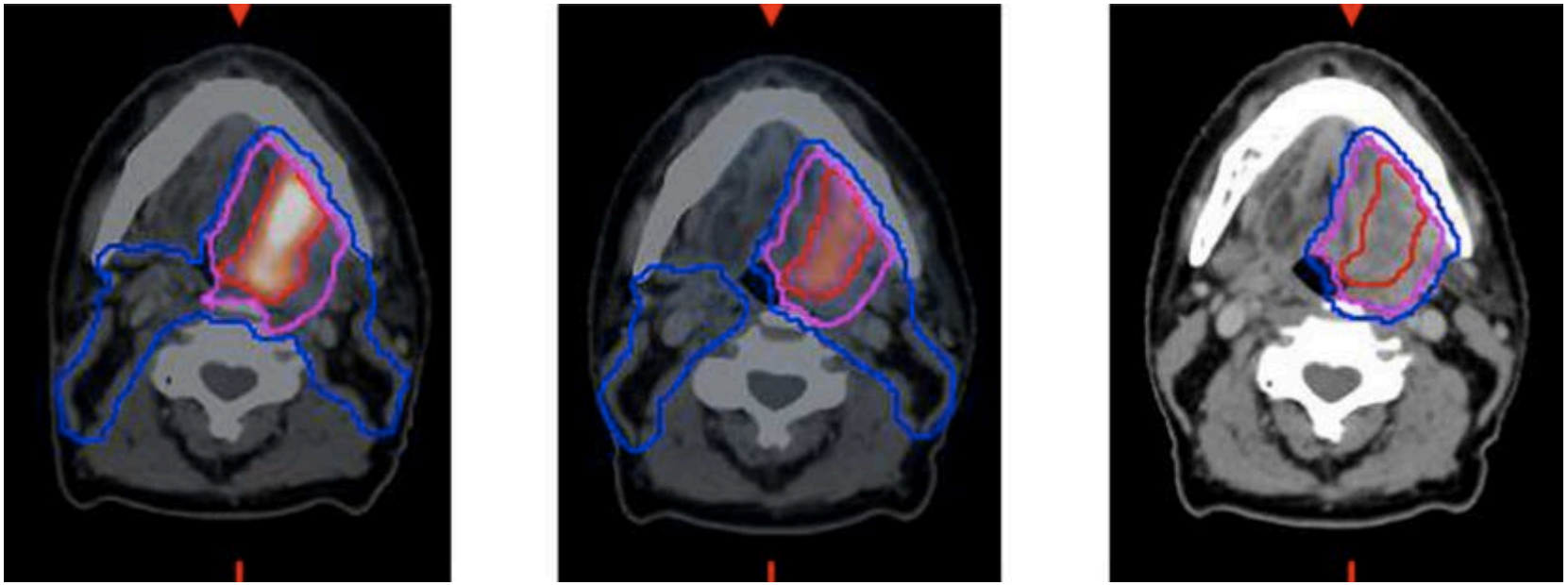
Adapt for a target ”volume” large modification to decrease toxicity



Guckenberger Strahlenther Onkol 2012

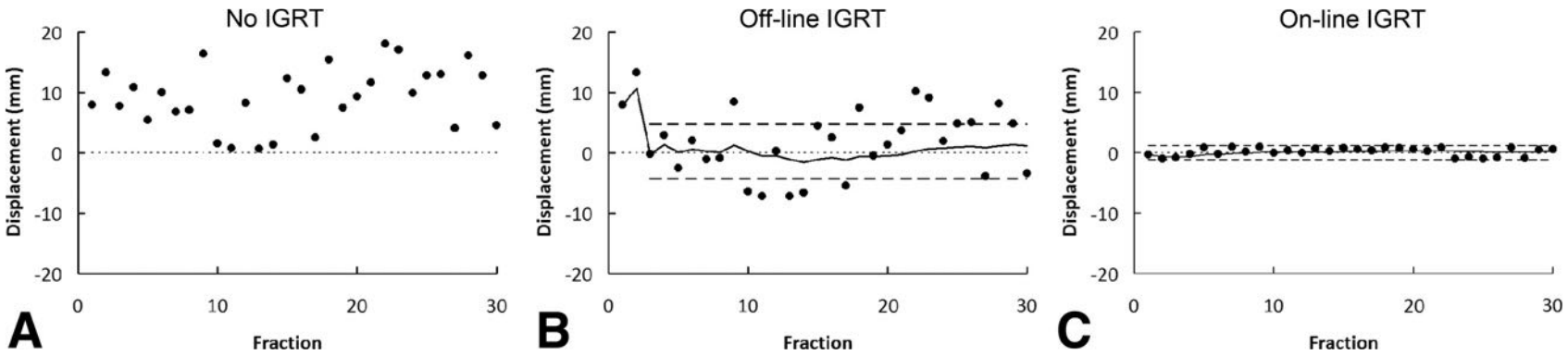
Adapt for a target “biological” modification to decrease toxicity

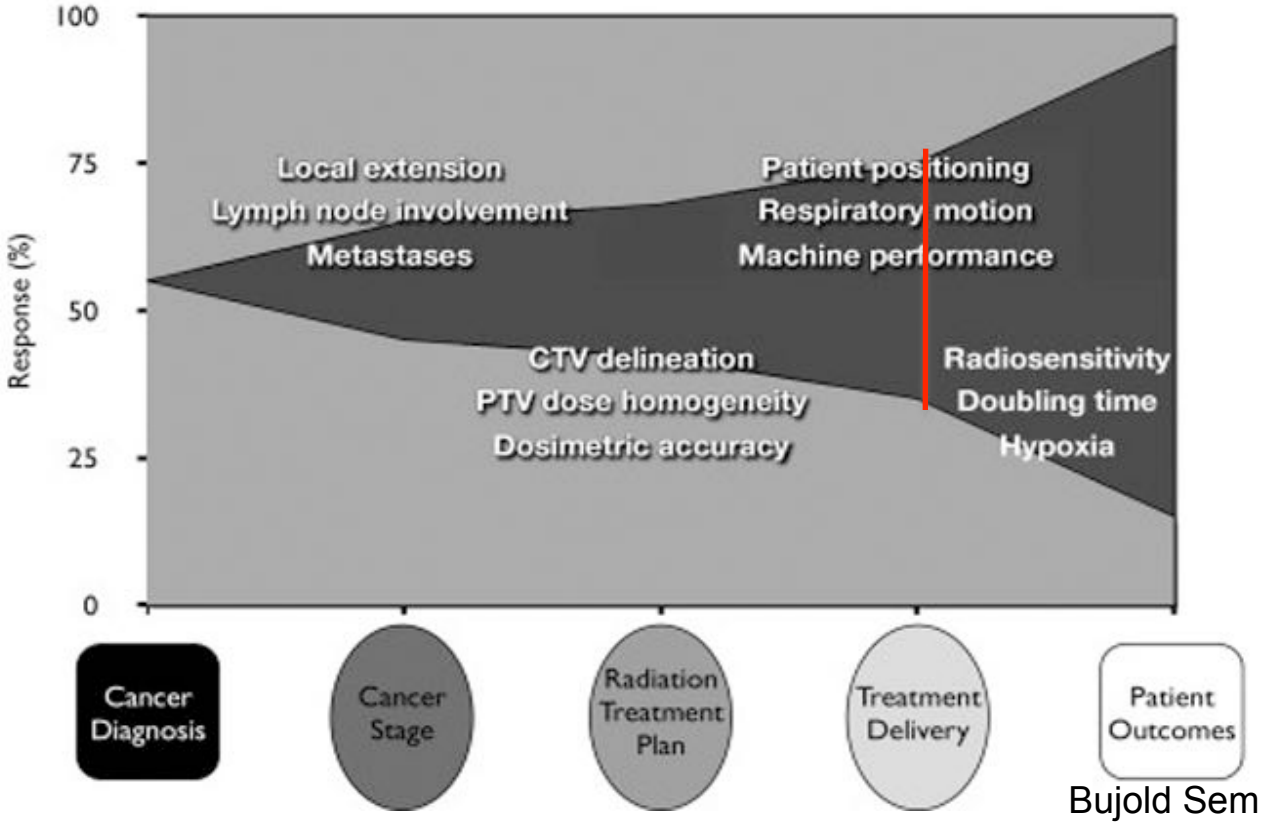
Treatment weeks



Duprez IJROBP 2011

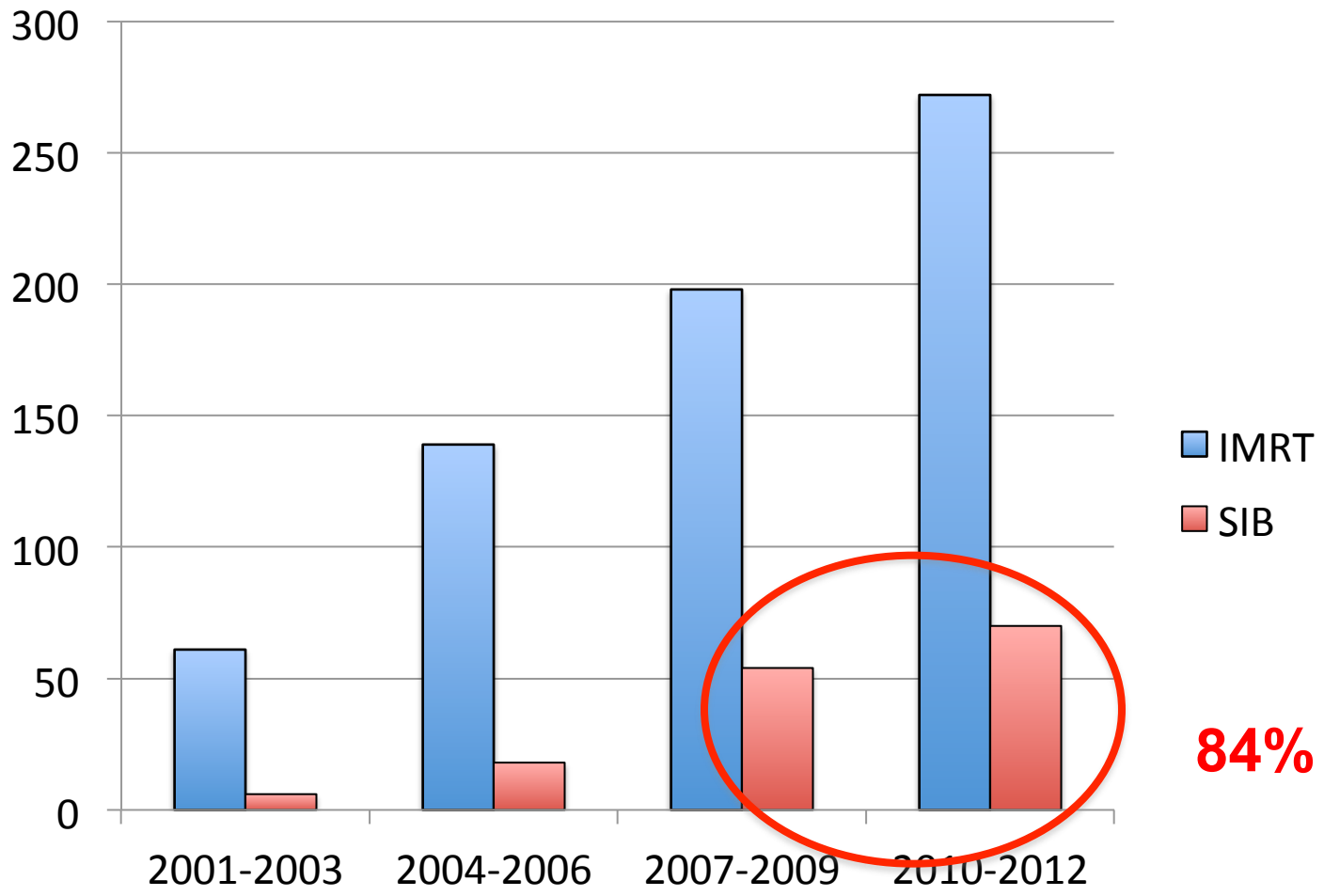
IGRT influence the outomes





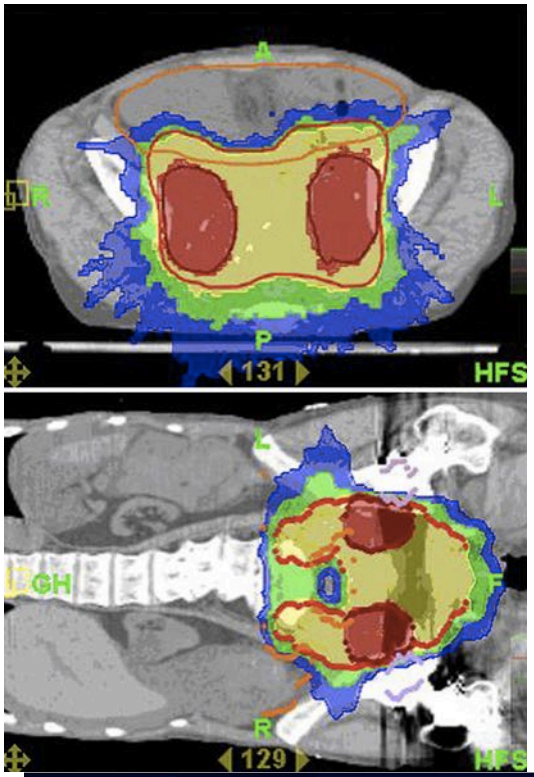
Bujold Sem Rad Oncol 2012

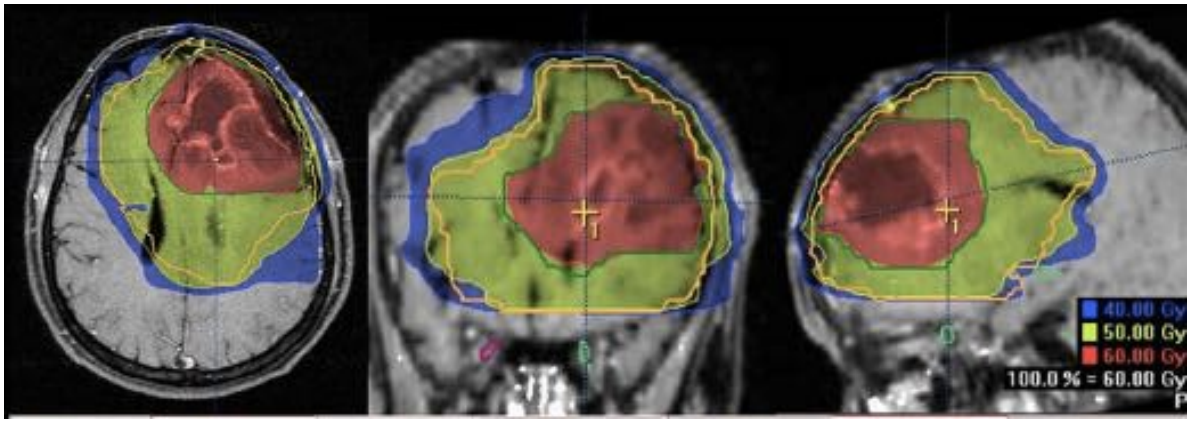
Published clinical trials on SIB-IMRT



Less afraid with the help of technology ?!?

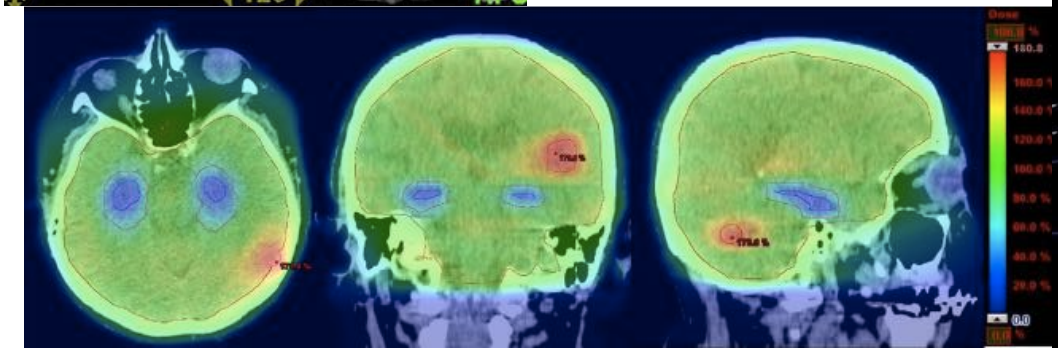
various



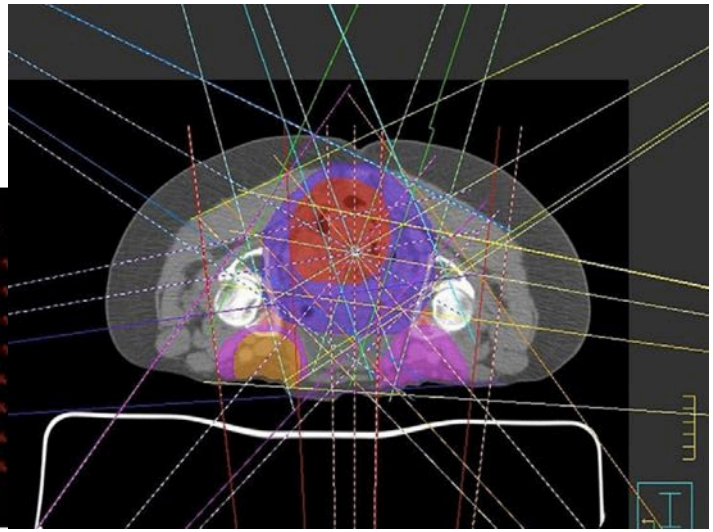


SIB in high grade gliomasIJROBP 2010

Gynecological



Whole brain irradiation - ippocampal sparing -SIB on multiple metastases. IJROBP in press



Anal canal JROBP 2012

Conclusions and remarks

- SIB introduce into a new therapeutic landscape..but lack of evidence
- LQ model can give “only” the direction in the design of a treatment schedule
- Patients and tumors are heterogeneous (predictive models, genomics..)
- Technology improvement can make the radiation oncologist feel safe in treatment delivery, but the margins of “risk” for tumor control and toxicities are very narrow in many districts

Be careful!