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

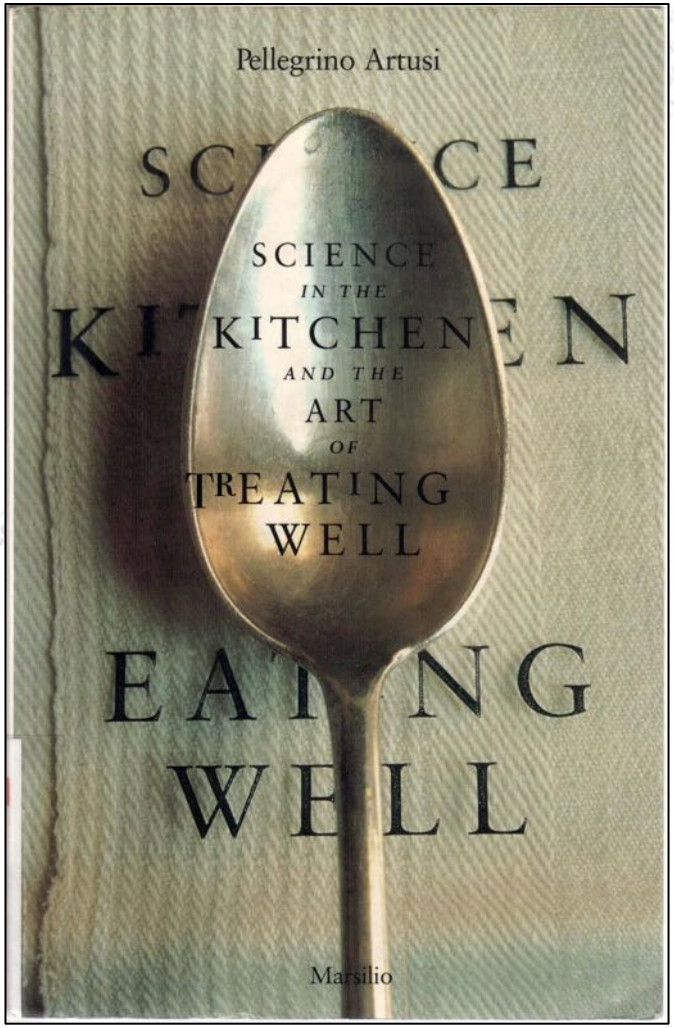
Radiochirurgia e Radioterapia Stereotassica: Non solo Tecnica

Tempi- Dosi- Volumi

Stefano Vagge MD Ph.D.

Radiation Oncology Department

Genova Marzo 2017


Pellegrino Artusi
SCIENCE
IN THE
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AND THE
ART
OF
TREATING
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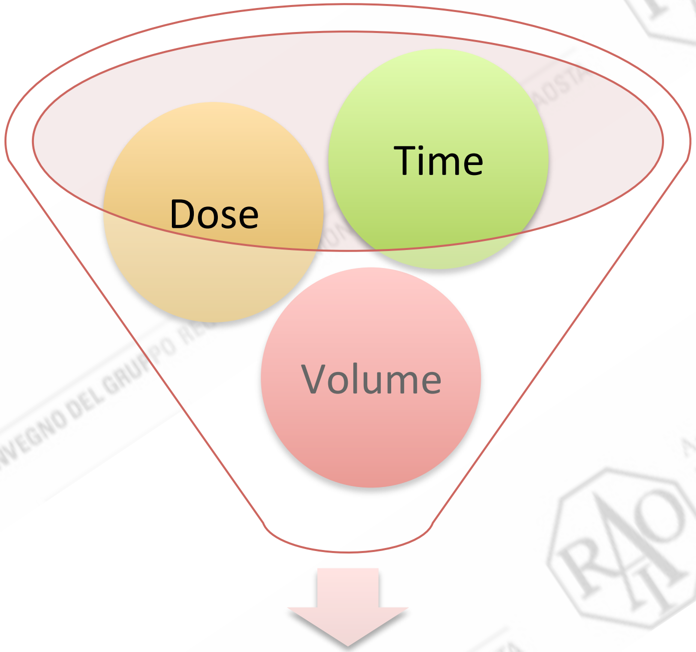
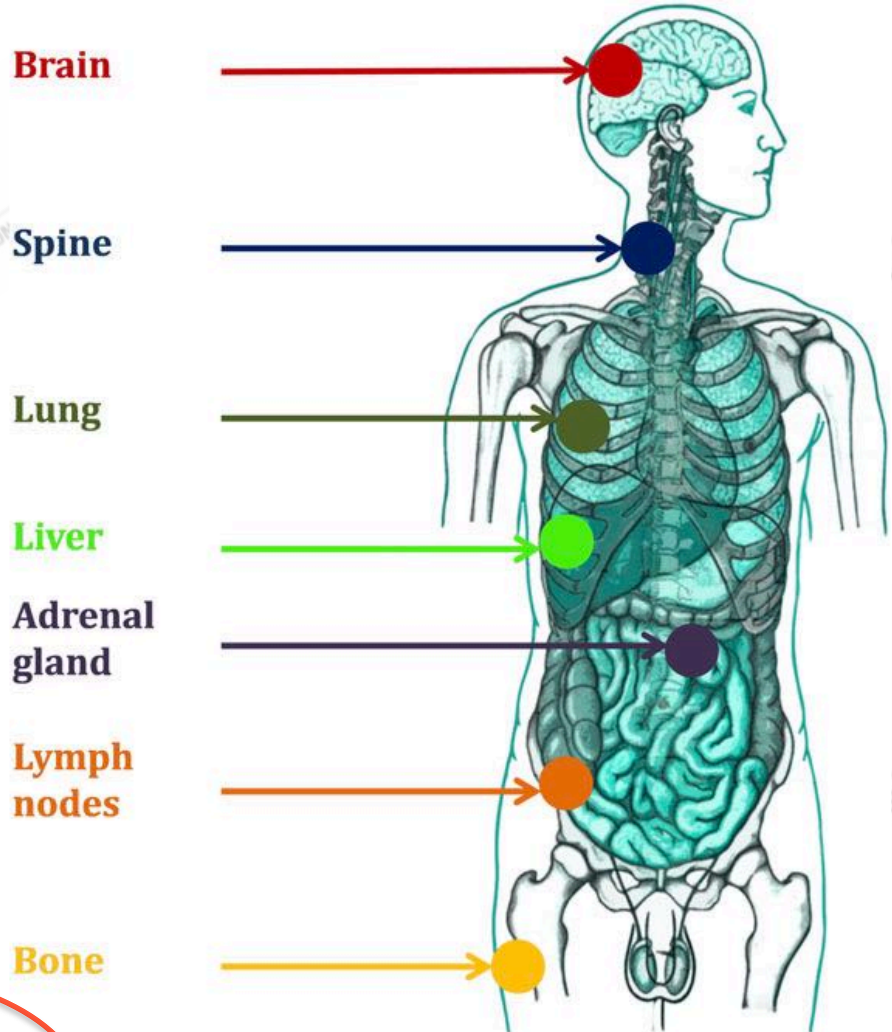
Marsilio


Dose
Time
Volume

SABR-SRS

Heterogeneity of Targets and nearby Anatomy in SABR



Ricardi et al. Journal of Radiation Research 2016

Biology of “Dose” in SABR

Martin Brown, Stanford University (editorial):

> It seems, therefore, that high-dose single-fraction radiotherapy is achieving higher local control than could be expected given what we know about radiation killing of cancer cells in a tumor.

> It is therefore possible that the antitumor effects of high single doses of radiation are not only because of direct radiation-killing of the tumor cells but also because the vascular endothelium rapidly degenerates in the tumor, thereby killing more tumor cell by a secondary response.

Brown et al. IJROBP 2008; 71(2): 324

Biology of “ Dose” in SABR– “the 4 Rs”

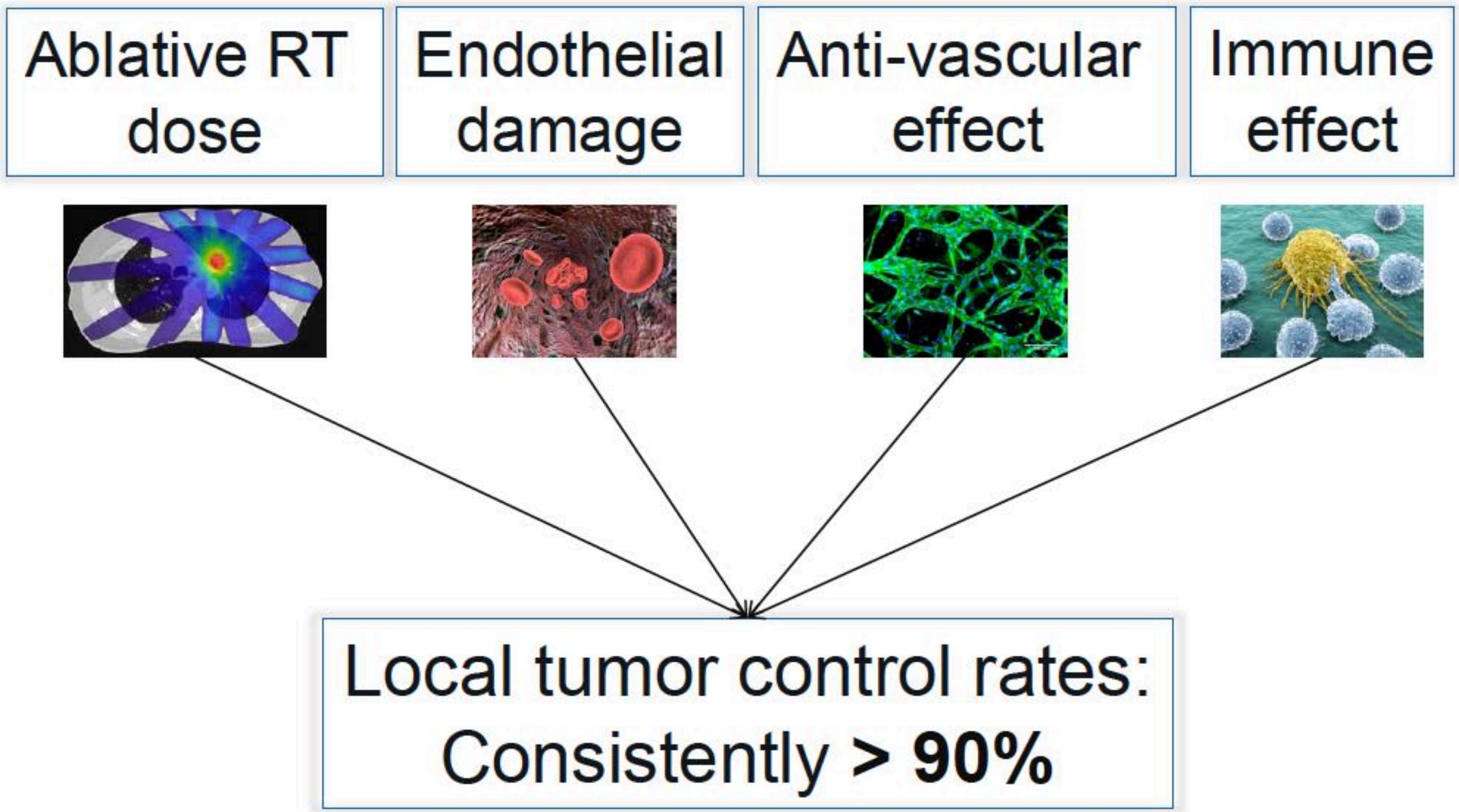
Are there specific biological responses to SBRT?

	CRT	SBRT
Repair	+	(↓)
Redistribution	+	(↓)
Repopulation	+	(↓)
Reoxygenation	+	↓↓

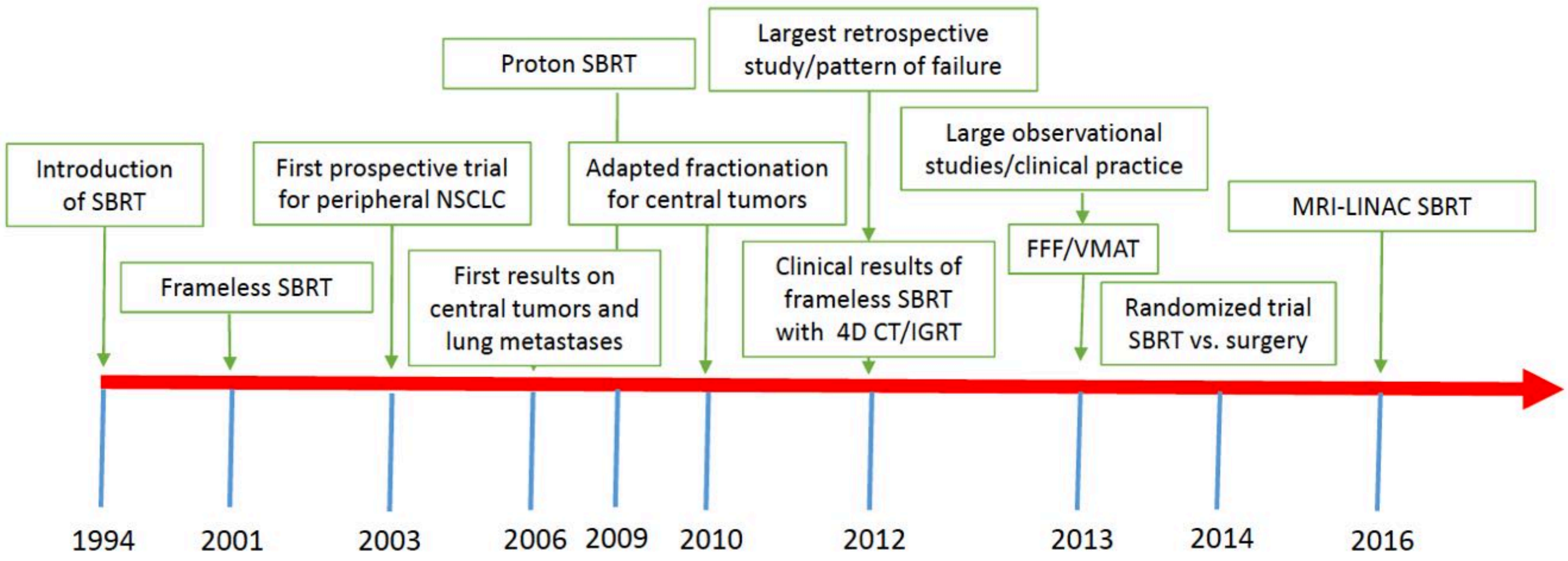
Are there additional factors?

Vascular effects	?	?
Immune responses	?	?

Biology of “Dose” in SABR over LQ model

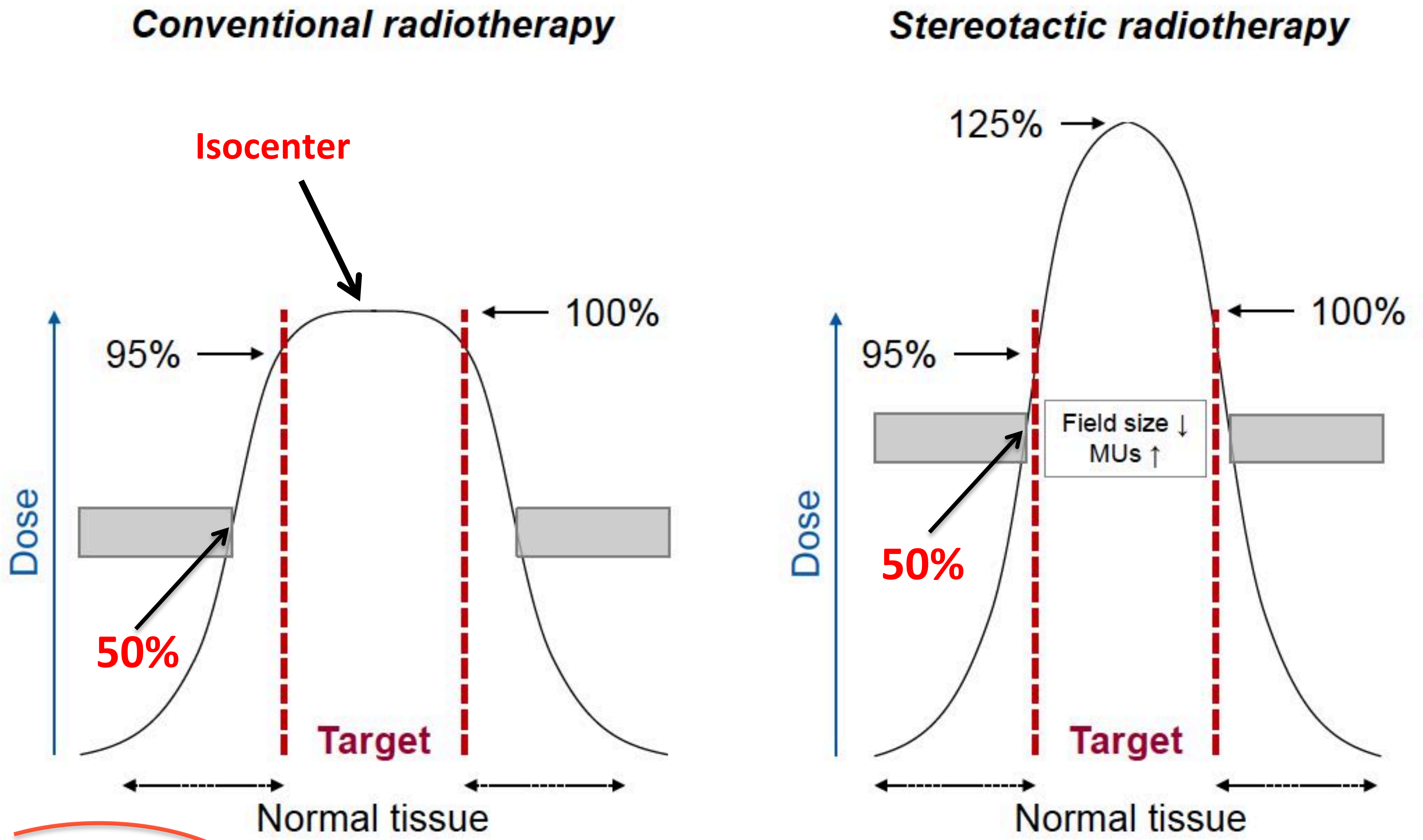


Heterogeneity of Data coming from Technical Advancement



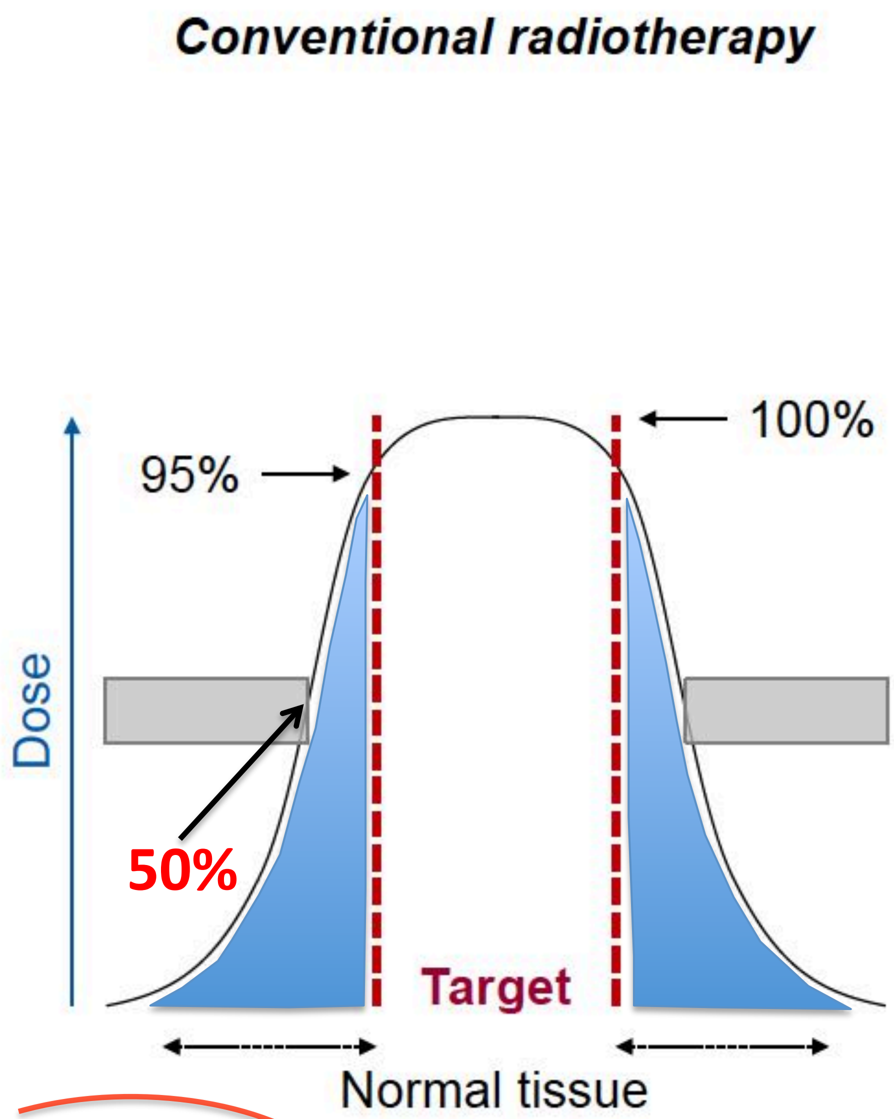
Ricardi, Badellino, Filippi, Physica Medica 2017, in press

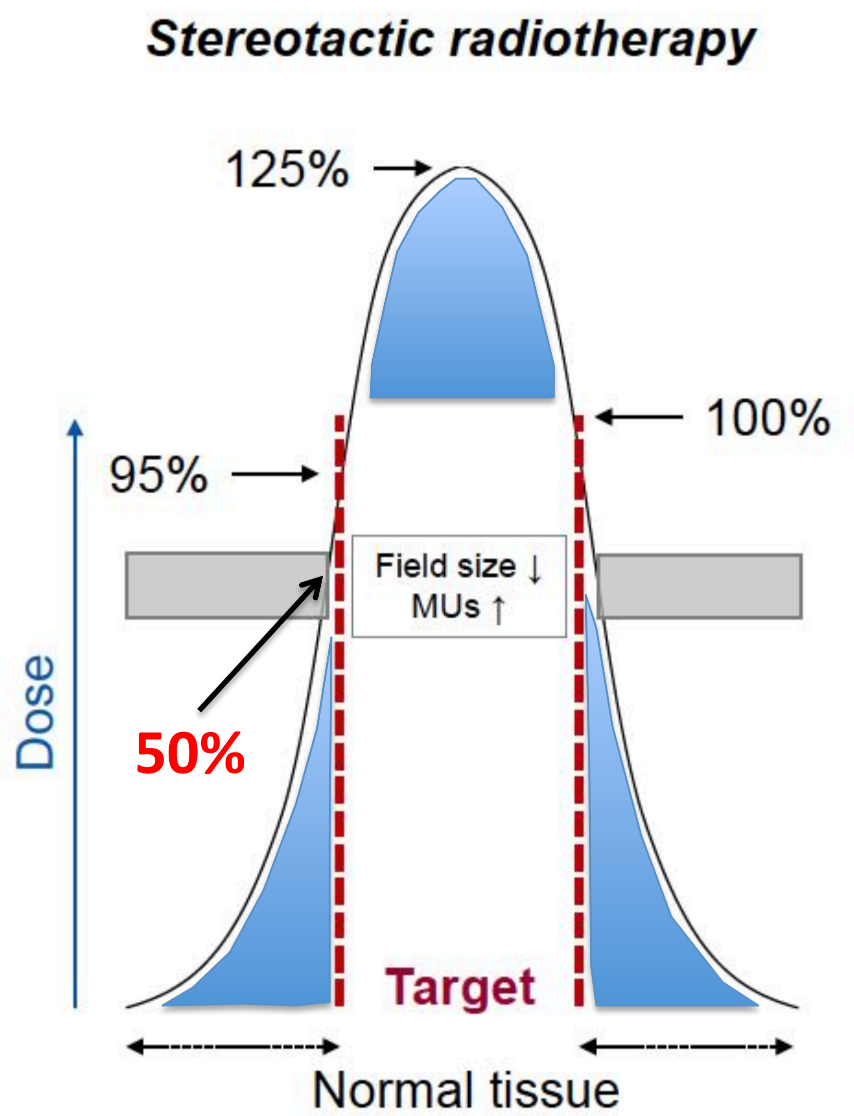
Dose in SABR– "dose prescription"



Adapted from Guckenberger

Dose in SABR– "dose prescription"





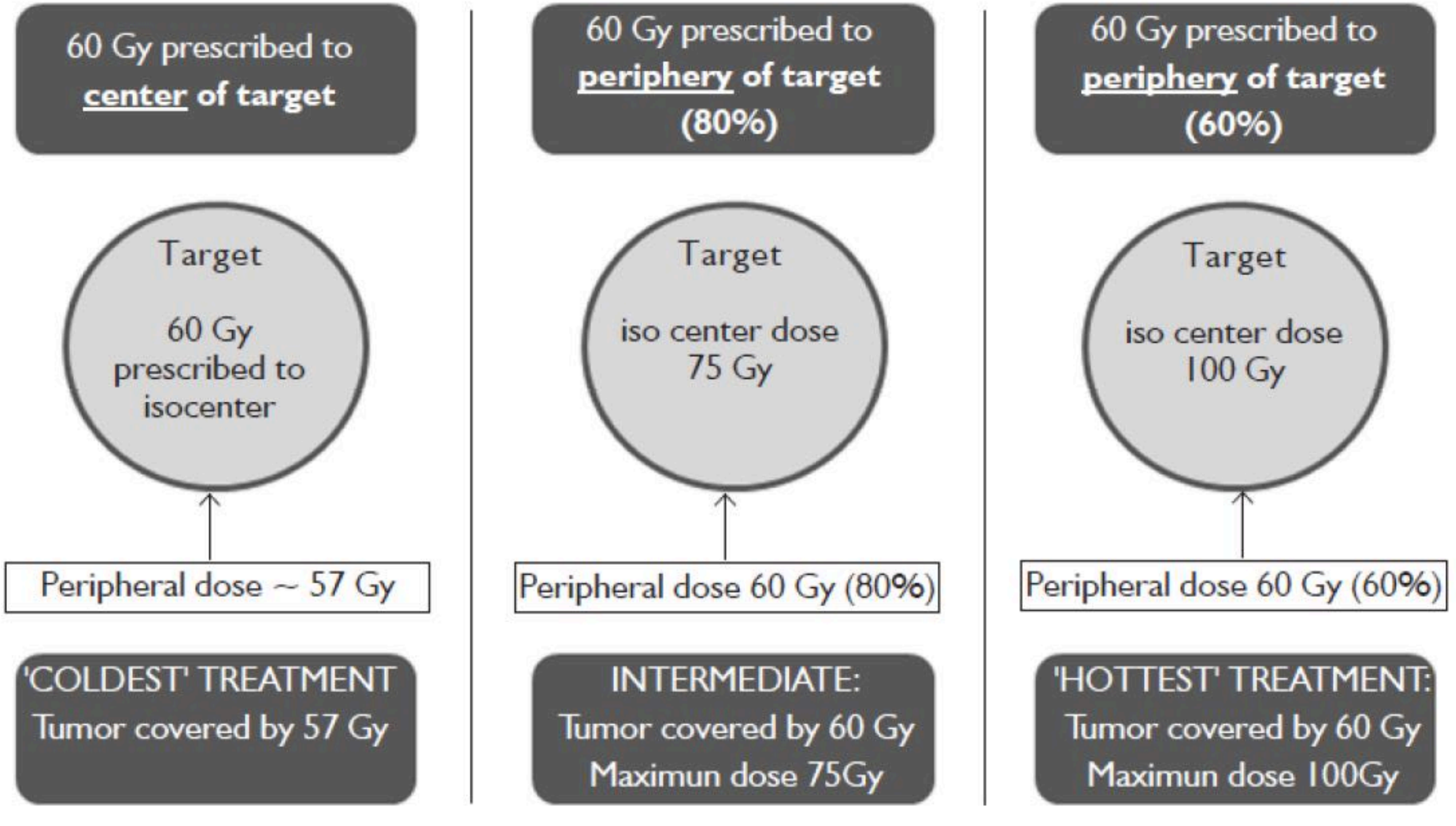
Adapted from Guckenberger

Conventional RT

#% Isodose prescribed SBRT

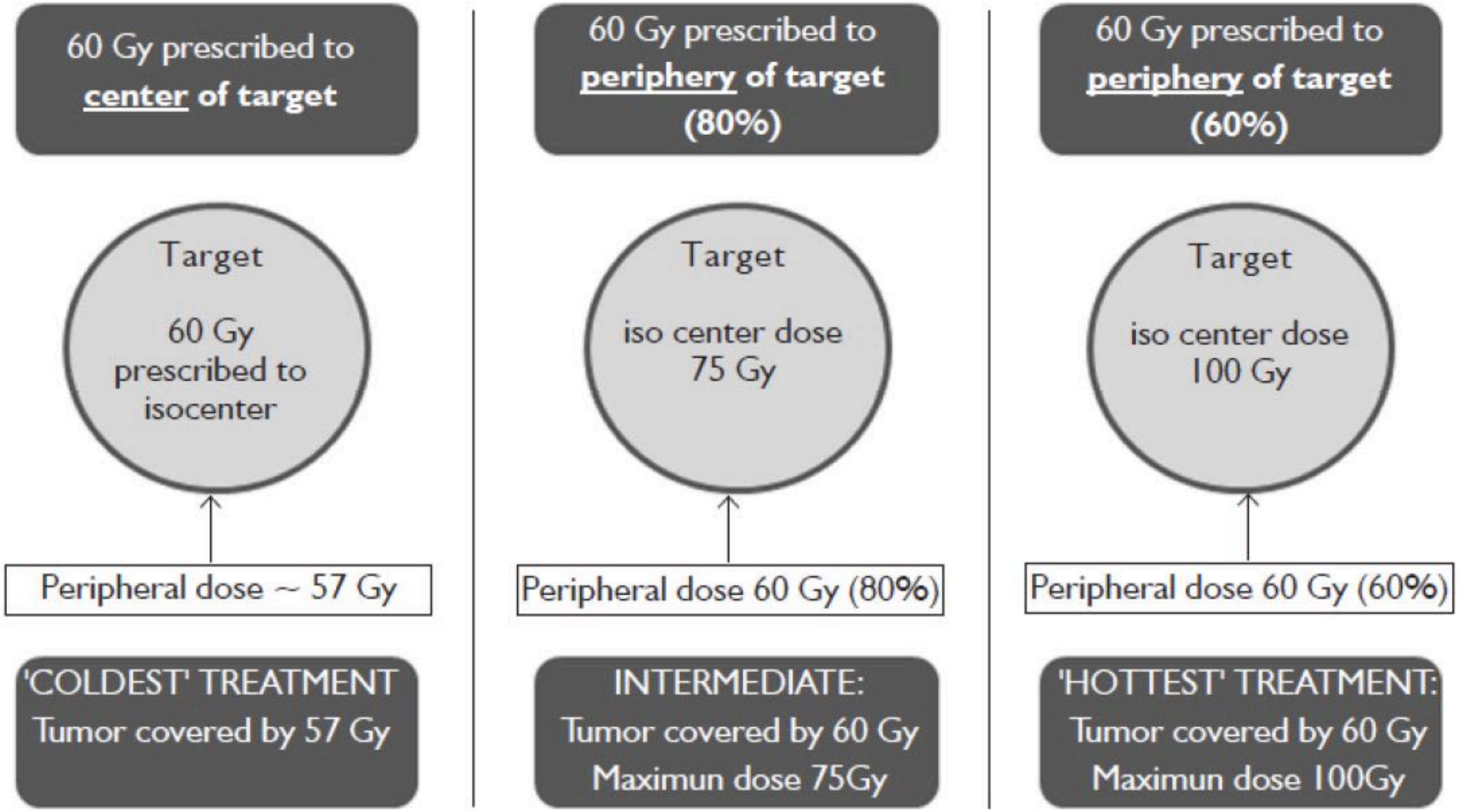
IMRT SBRT

Dose in SABR– heterogeneity in "dose prescription"



Senan S, J Thorac Dis 2011; 3:189-196

Dose in SABR– heterogeneity in "dose prescription"



Dis 2011; 3:189-196

<u>ICRU 100</u> will be helpful

Dose calculation algorithms

- Type A models (the VUmc model falls into this category): Models primarily based on electronic path length (EPL) scaling for inhomogeneity corrections. Changes in lateral transport of electrons are not modelled. The algorithms in this group are e.g. Eclipse/ModBatho and Eclipse/ETAR, OMP/PB, PrecisePLAN, Plato ETAR, Brainscan, I-plan Dose/PB and XiO/Convolution.

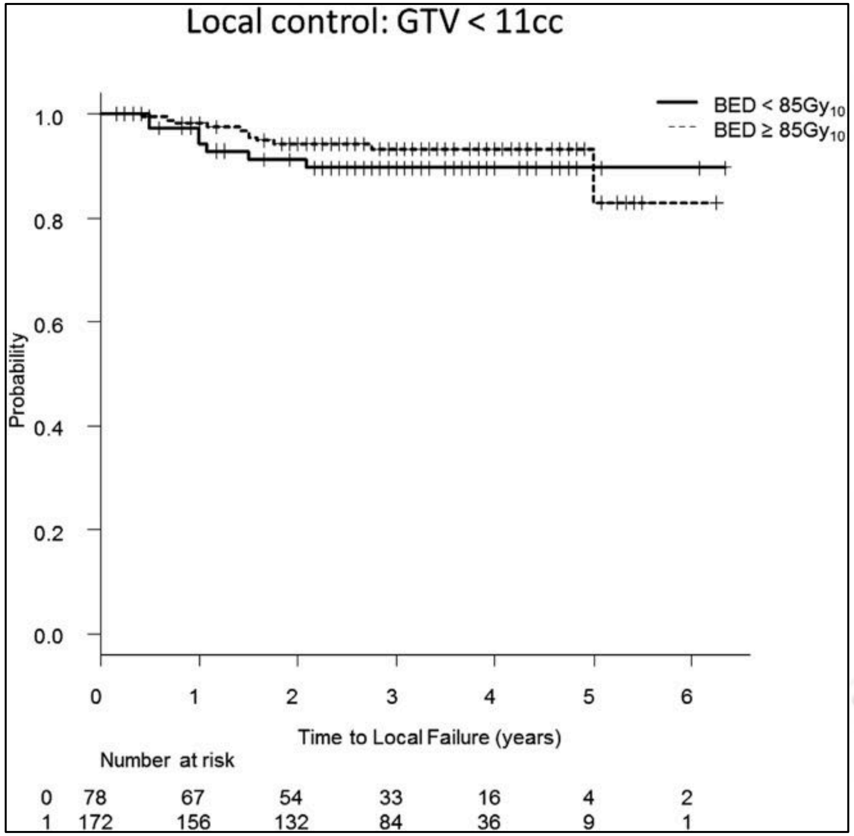
- Type B models: Models that in an approximate way consider changes in lateral electron transport. The models in this group are e.g. Pinnacle/CC, Eclipse/AAA, OMP/CC, I-Plan-dose with Monte-Carlo algorithm and XiO/Superposition.

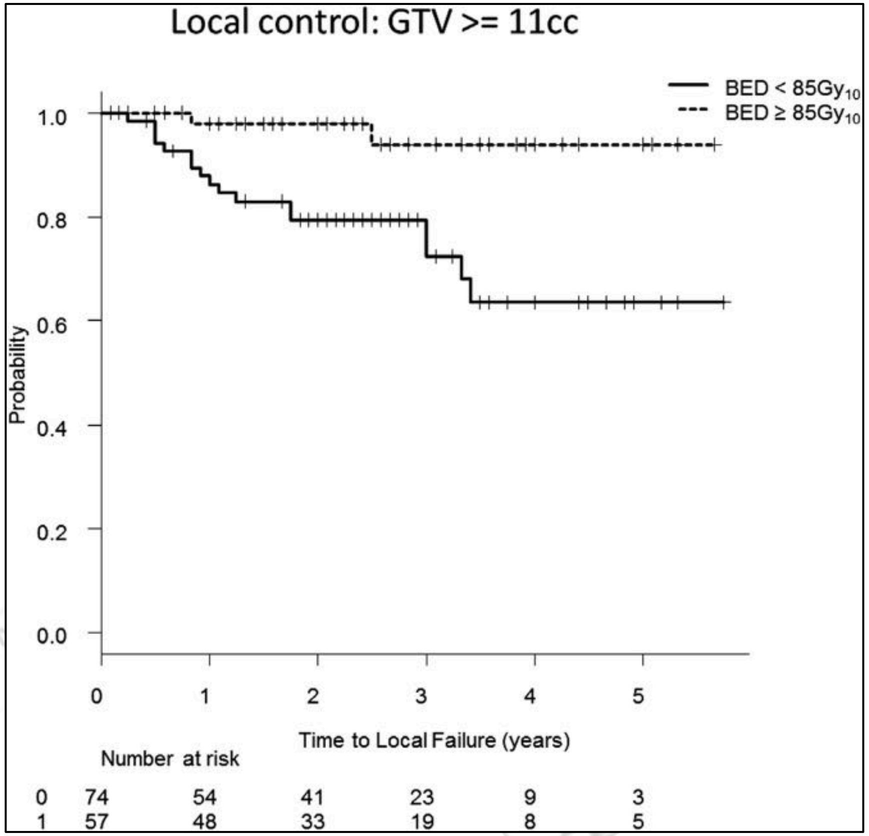
Knöös, PMB 51 (2006) 5785

Dose-Volume-Response analysis in stereotactic Radiotherapy for Early Lung Cancer

***Osamu S**. Radiotherapy and Oncology 2014*

- To render actually given doses comparable between two different approaches (Japanese & Western) "a Gy in Japan is not a Gy in Western series"
- Japanese prescription to PTV isocenter vs peripheral PTV for Western
- Western type A algorithm vs type B for Japanese
- Different fractionation
- Replanning with same peripheral prescription & LC analysis





Western (isodose 80%) prescription

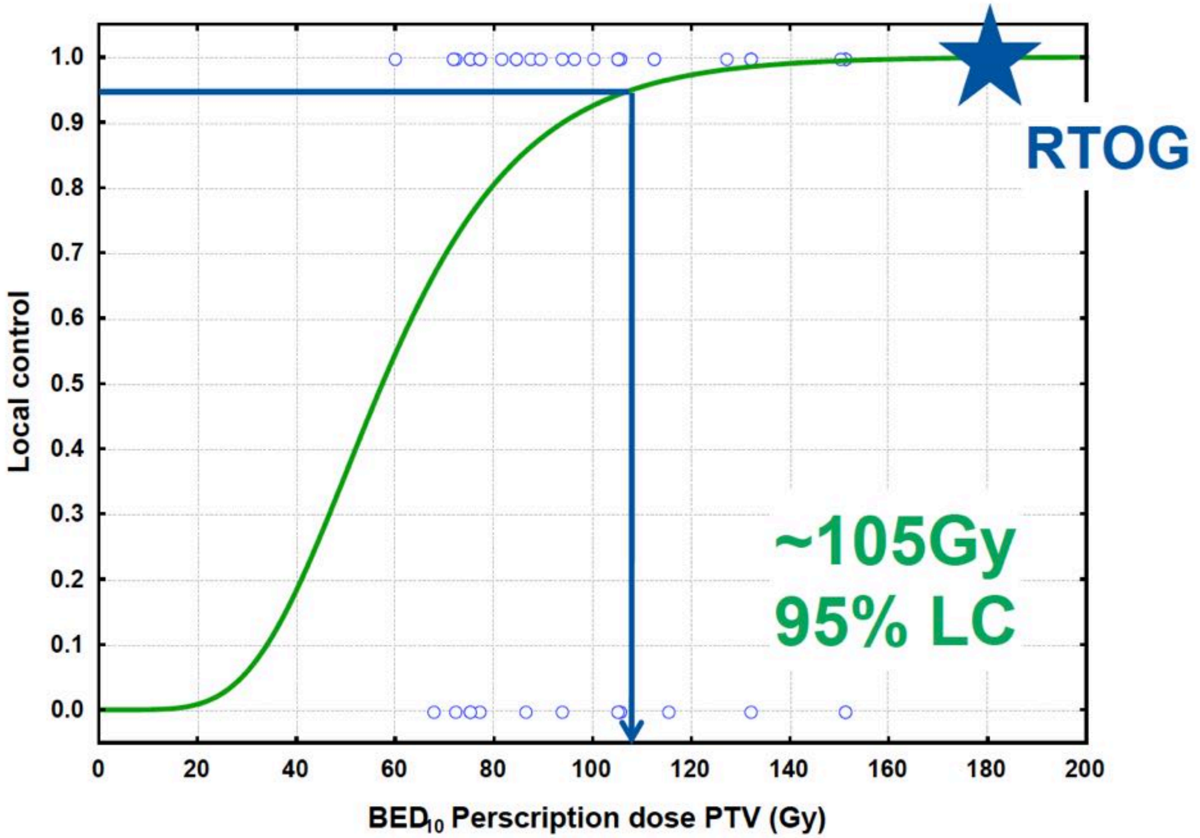
- 20 Gy x 3 (i.e. 75 Gy to isocentre)
- 12 Gy x 5
- 7.5 Gy x 8 or 5 Gy x 12

Japanese (isocentre) prescription

- 12 Gy x 4 (i.e. 48 Gy to isocentre)
- 6 Gy x 10

Dose & Local Tumor Control

Guckenberger IJROBP 2008
Kerstin ASTRO Meeting 2010



Plateau of dose-response relationship at ~100Gy BED

Limit of Dose ?

- *Onishi et al*: LC was significantly improved with **BED greater than 100 Gy** (prescription dose at isocenter), with 5-year LC rate of 84% for BED10 > 100 Gy vs. 37% for BED10 < 100 Gy (p < 0.001).

- *Kestin et al* : a significant correlation between **BED10 > 105 Gy** (prescription to the edge of the PTV, with 60%–90% of the isocenter dose) and higher local control.

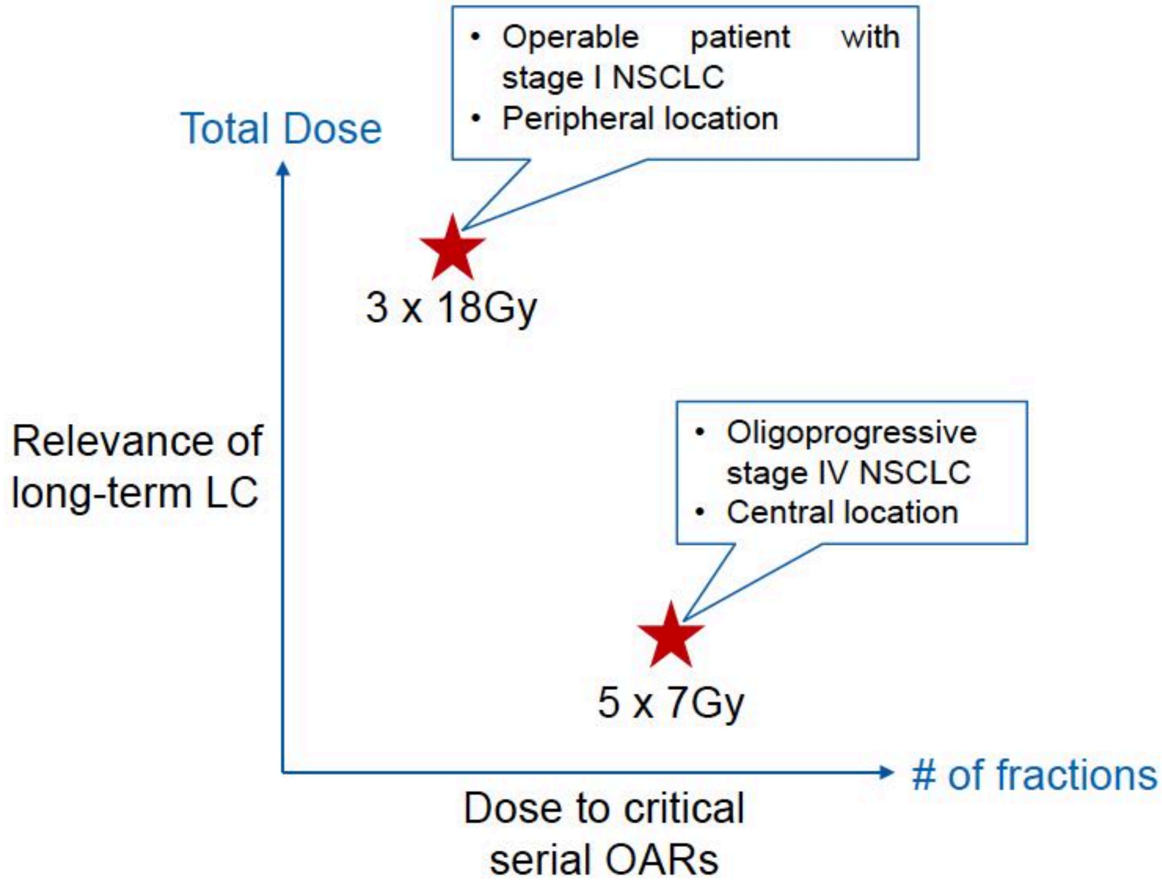
- *Zhang et al*: based on the BED quartiles (low, medium, medium–high, and high), **outcome got worse for BED below 83.2 Gy and for BED exceeding 146 Gy.**

- *Koshy et al*: T2 tumors treated with **a BED10 > 150 Gy** (roughly equal to 54 Gy in 3 fractions) **had a significantly improved survival** compared with patients treated with a BED10 < 150 Gy [22].

Onishi H, et al. Cancer 2004.
Kestin L, et al. Radiother Oncol 2014.
Zhang J, et al. Int J Radiat Oncol Biol Phys 2011.
Koshy, et al Int J Radiat Oncol Biol Phys 2015

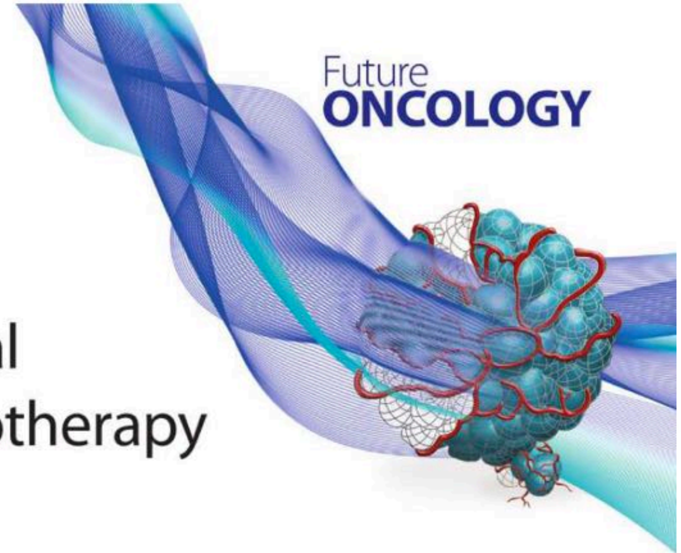
Courtesy from Alongi

Risk adapted fractionation



SBRT
Practical Survey for
DOSE and FRACTIONATION

RESEARCH ARTICLE
For reprint orders, please contact: reprints@futuremedicine.com



A multinational report of technical factors on stereotactic body radiotherapy for oligometastases

Kristin J Redmond*[,1], Simon S Lo[2], Roi Dagan[3], Ian Poon[4], Matthew C Foote[5], Darby Erler[4], Young Lee[4], Frank Lohr[6], Tithi Biswas[7], Umberto Ricardi[8] & Arjun Sahgal[4]

Suggested adequate Imaging

Table 1. Imaging for gross tumor volume delineation by disease site.

Modality	Lung metastasis	Liver metastasis	Adrenal metastasis	Nodal metastasis	Spinal metastasis	Bone metastasis
Imaging technique	CT with and without contrast (strong) ± PET/CT (low)	Triphasic CT or MRI (strong)	CT with and without contrast (moderate) ± PET/CT (low)	CT with and without contrast (moderate) ± PET/CT (low)	CT with and without contrast (strong) MRI with and without gadolinium (strong)	CT with and without contrast (strong) MRI with and without gadolinium (strong) ± PET/CT (low)

Volumes Expansion

Table 2. Gross tumor volume expansions by disease site.

Target volume	Lung metastasis	Liver metastasis	Adrenal metastasis	Nodal metastasis	Spinal metastasis	Bone metastasis
CTV	N/A	5 mm depending on bowel (strong)	5 mm (strong)	N/A	Anatomic margin† (strong)	3 mm (moderate)
ITV	Defined on 4D-CT (strong)	Defined on 4D-CT (strong)	N/A	N/A	N/A	N/A
PTV‡	5 mm (strong)	5 mm (strong)	3–5 mm (strong)	3–5 mm (strong)	1–2 mm (moderate)	3 mm (strong)

Dose prescriptions

Table 3. Reasonable prescription doses for disease sites utilized by participating institutions.

Disease site	1 fraction	2 fractions	3 fractions	4 fractions	5 fractions
Lung (strong)	26 Gy	N/A	45–54 Gy	48–60 Gy	50–60 Gy
Liver (moderate)	N/A	N/A	45–75 Gy	N/A	30–60 Gy
Adrenal (moderate)	N/A	N/A	N/A	20–40 Gy	35–50 Gy
Lymph node (moderate)	N/A	N/A	N/A	N/A	35–50 Gy
Spine (strong)	16–24 Gy	24–28 Gy	24–30 Gy	24–30 Gy	25–50 Gy
Bone (moderate)	20 Gy	24–28 Gy	24–27 Gy	N/A	30–50 Gy

Note that these are not intended to be precise indications, but rather we present the results of our survey to serve as a foundation for future investigations. They are not data driven and must be validated in future studies. The most appropriate prescription doses are dependent upon the unique patient and clinical scenario. The level of agreement is noted in parenthesis.
N/A: Not applicable.

Dose coverage parameters

Table 6. Acceptable dosimetric parameters used for plan acceptance by disease site.

Target volume	Lung metastasis	Liver metastasis	Adrenal metastasis	Nodal metastasis	Spinal metastasis	Bone metastasis
Coverage of PTV	≥95% volume receiving 95–100% of prescribed dose (strong)	≥90% Volume receiving 90–100% of prescribed dose (strong)	≥95% volume receiving 80–95% prescribed dose (strong)	≥95% volume receiving 95–100% of prescribed dose (moderate)	>85–90% volume receiving 95–100% of prescribed dose. Lower coverage accepted in retreatment setting or in multi level SBRT (strong)	≥90% volume receiving 100% of prescribed dose (strong)
Coverage of ITV	100% volume receiving ≥95% of prescribed dose (strong)	100% volume receiving ≥95% of prescribed dose (strong)	100% volume receiving ≥95% of prescribed dose (strong)	N/A	N/A	N/A
Coverage of GTV	100% volume receiving 100% prescribed dose (strong)	100% volume receiving 100% prescribed dose (strong)	100% volume receiving 100% prescribed dose (strong)	100% volume receiving ≥95% of prescribed dose (strong)	N/A	100% volume receiving ≥95% of prescribed dose (strong)

Dose constraints

Table 4. Reasonable normal tissue constraints utilized by participating institutions.

Normal structure	1 fraction	2 fractions	3 fractions	4 fractions	5 fractions
Spinal cord[†] (moderate)	12–12.5 Gy Dmax	17 Gy Dmax	18–21 Gy Dmax	23 Gy Dmax	25–30 Gy Dmax
Brachial plexus (moderate)	16–17.5 Gy Dmax	18–20 Gy Dmax	24 Gy Dmax	27–30.5 Gy Dmax	30–32 Gy Dmax
Cauda equina[‡] (moderate)	12–16 Gy Dmax	17 Gy Dmax	21–24 Gy Dmax	24–28 Gy Dmax	30–32 Gy Dmax
Esophagus (moderate)	14–15.4 Gy Dmax	16–20 Gy Dmax	25.2 Gy Dmax	26–30 Gy Dmax	30–35 Gy Dmax
Small bowel/stomach (moderate)	12–14 Gy Dmax	16–20 Gy Dmax	12–16 Gy <10 cc; 21–22 Gy Dmax	14 Gy<10 cc; 24–30 Gy Dmax	16–18 Gy <10 cc; 28–35 Gy Dmax
Heart (low)	18–22 Gy Dmax	20–24 Gy Dmax	30 Gy Dmax	34–38 Gy Dmax treated on non-consecutive days	38–40 Dmax
Lungs (per individual lung) (low)	7 Gy <1500 cc; V20 <30%	V10 <10%, v5 <3–5%, V20 <30%, mean lung dose ≤5 Gy	12.5 Gy <1000 cc; 20 Gy <10%; V20 <30%	V10 <10%, v5 <3–5%, V20 <30%, mean lung dose ≤5 Gy	13–13.5 Gy <1000 cc; 12.5 Gy <1500 cc; V20 <30%
Liver[†] (low)	9–15 Gy <700 cc	14 Gy <700 cc	15 Gy <700 cc	19 Gy <700 cc	20–21 Gy <700 cc
Kidney (low)	10 Gy <200 cc	12 Gy <200 cc	12–14 Gy <200 cc	16 Gy <200 cc	17.5 Gy <200 cc; 2/3 volume <15–23 Gy
Large airway (low)	20 Gy Dmax	N/A	30 Gy Dmax	34.8 Gy Dmax	36–40 Gy Dmax
Large vessels (low)	37 Gy Dmax	N/A	30–45 Gy Dmax	49 Gy Dmax	V47 Gy <10 cc; 40–53 Dmax

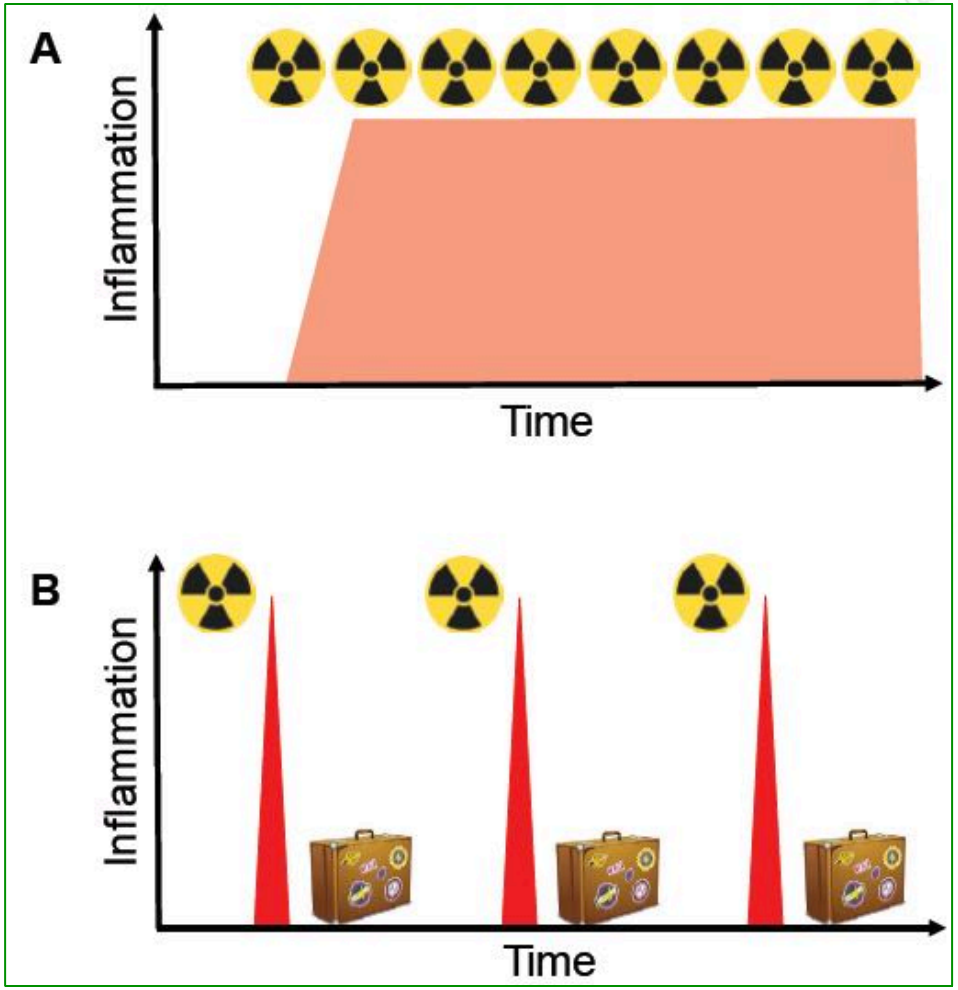
Is there a role for TIME or TIMING?

www.impactjournals.com/oncotarget/ Oncotarget, Vol. 6, No. 18

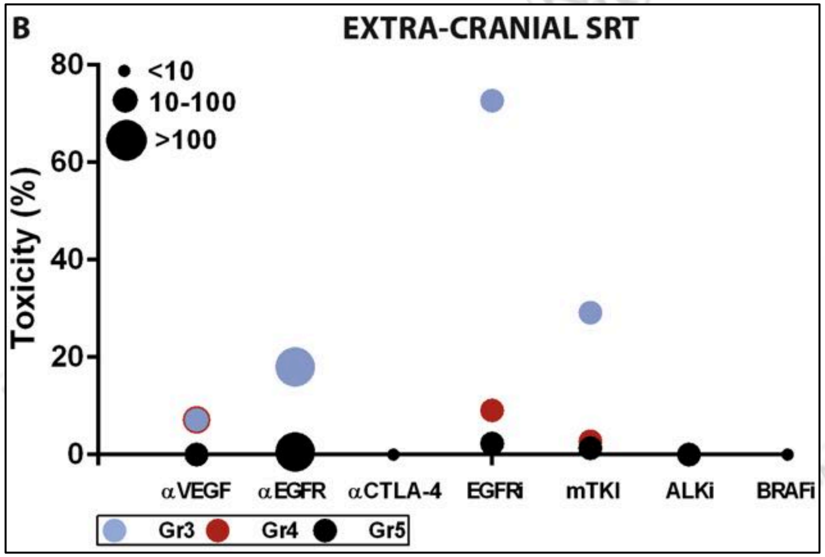
Editorial

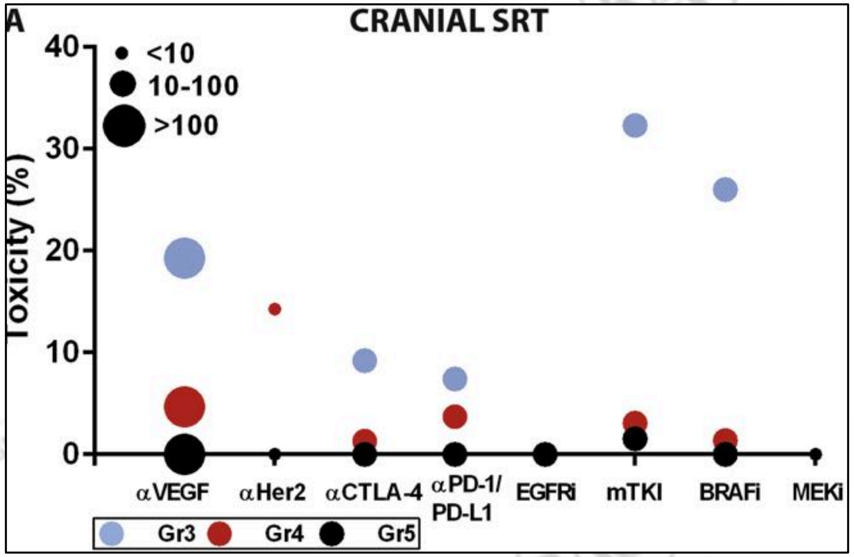
Radiation holidays stimulate tumor immunity

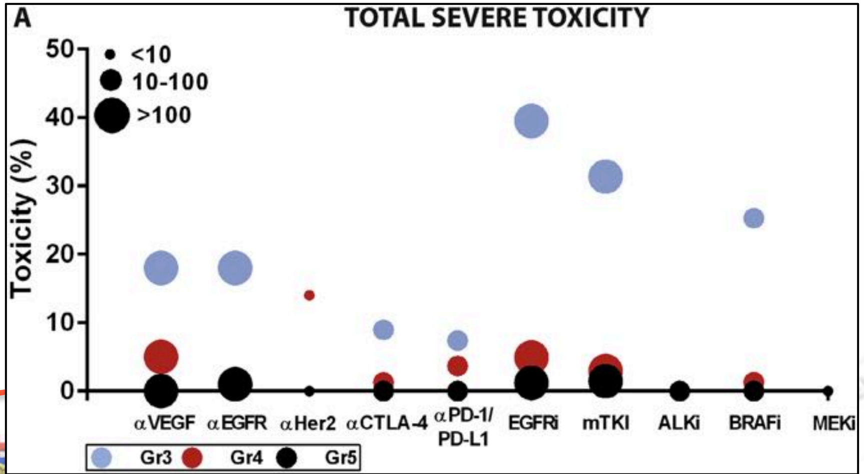
Laura Surace, Matthias Guckenberger and Maries van den Broek

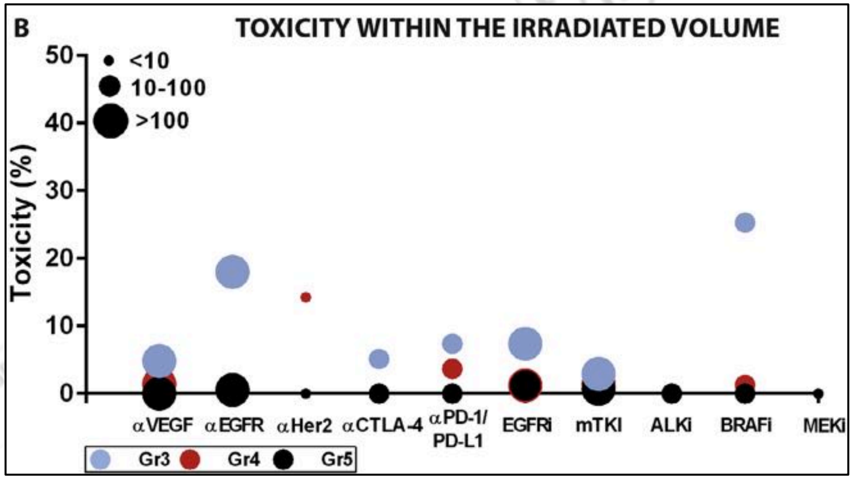


Concurrent Stereotactic Radiotherapy and target therapy or immunotherapy







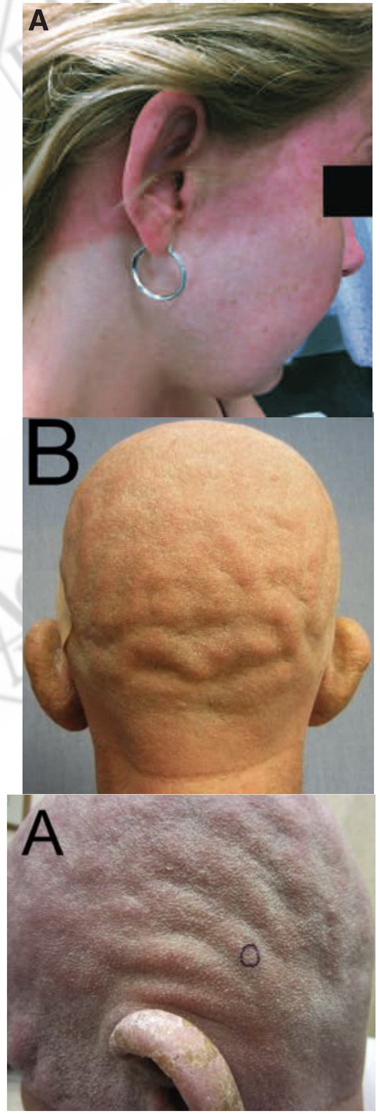


Kroeze et al. Cancer Treat Rev 2017

“Timing” to avoid toxicity

Avoiding Severe Toxicity From Combined BRAF Inhibitor and Radiation Treatment: Consensus Guidelines from ECOG

- Combination of BRAFi and RT for melanoma 27 pubblications
- 7 pubblications noted potential intracranial neurotoxicity
- Rates of radionecrosis, hemorrhage from WBRT, SRS, or both do not appear increased with concurrent or sequential administration of BRAFi



Hold BRAFi 3 days before & after fractionated RT

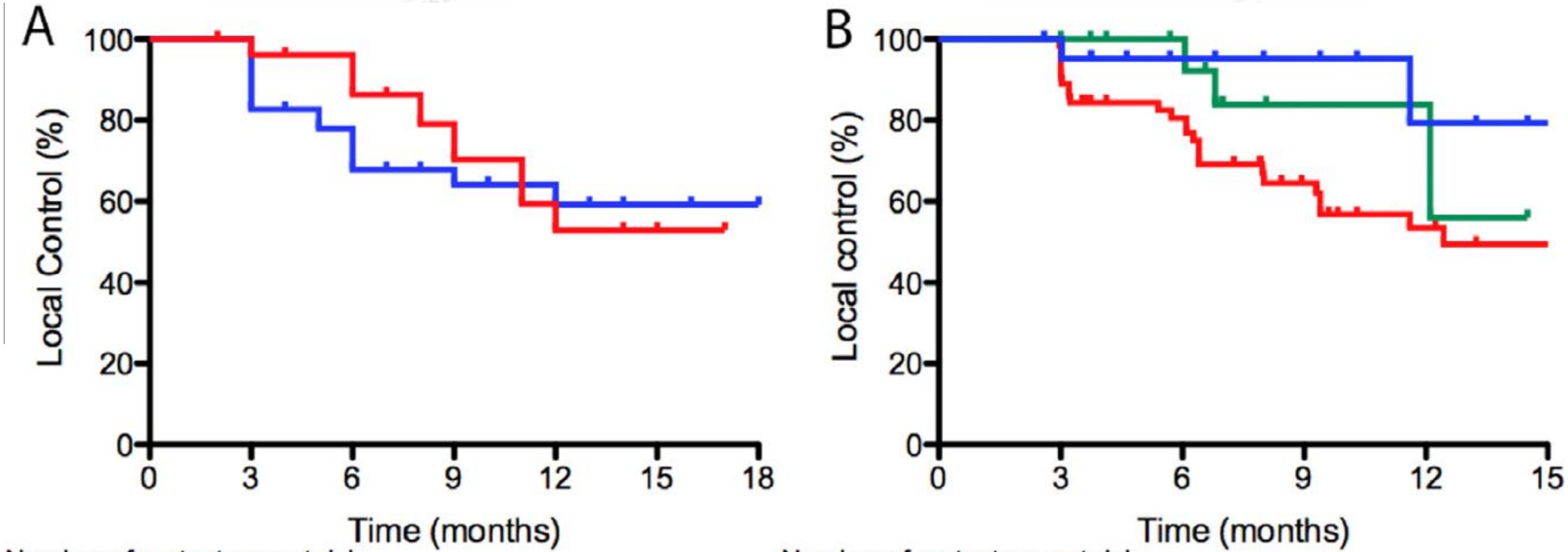
Hold BRAFi 1 day before and after SRS

Int J Radiation Oncol Biol Phys, Vol. 95, No. 2, pp. 632–646, 2016

Journal of Clinical Oncology, Vol 34, No 3 (January 20), 2016: pp e17-e20

VOLUME managed by the Technique

Movement can influence the outcomes?



Number of metastases at risk

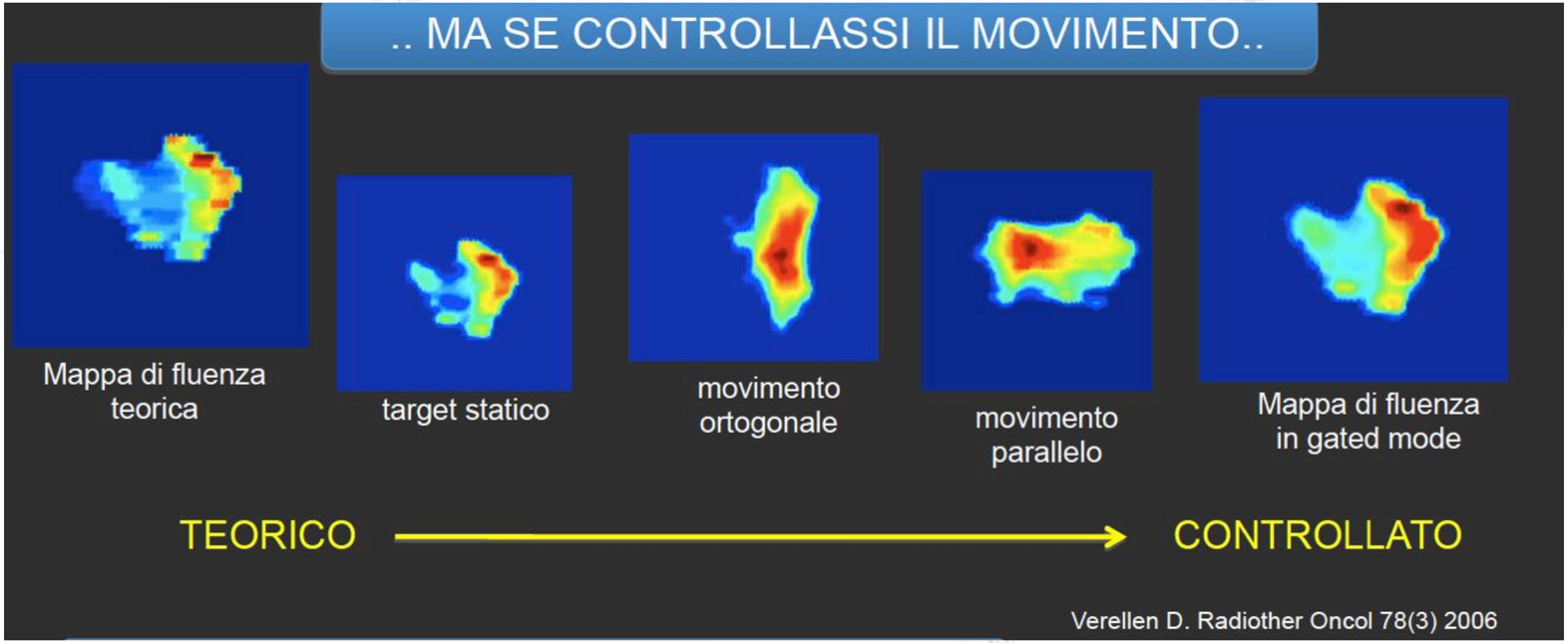
10x4Gy	52	52	31	18	13	10	6
10x5Gy	53	52	39	18	9	5	2

Number of metastases at risk

Lymphnodes	22	22	15	9	6	4
Liver/lung	64	63	44	27	17	12
Other	19	19	14	5	5	2

Van Den Begin Radiother Oncol 2014

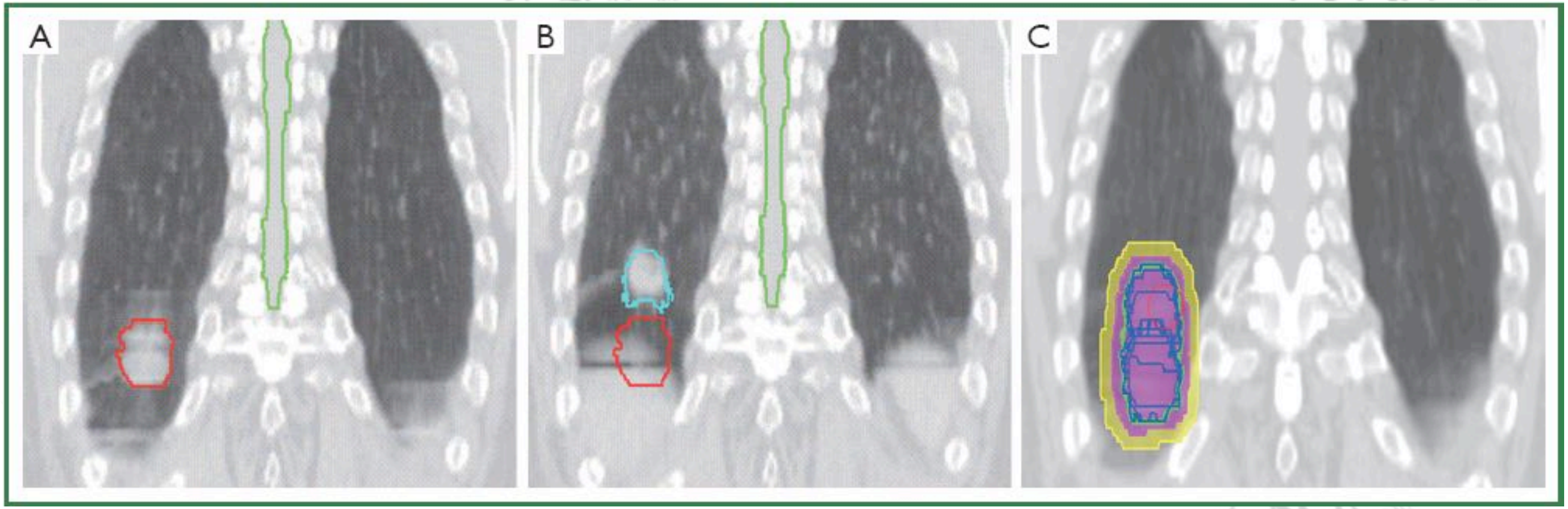
Movement and IMRT



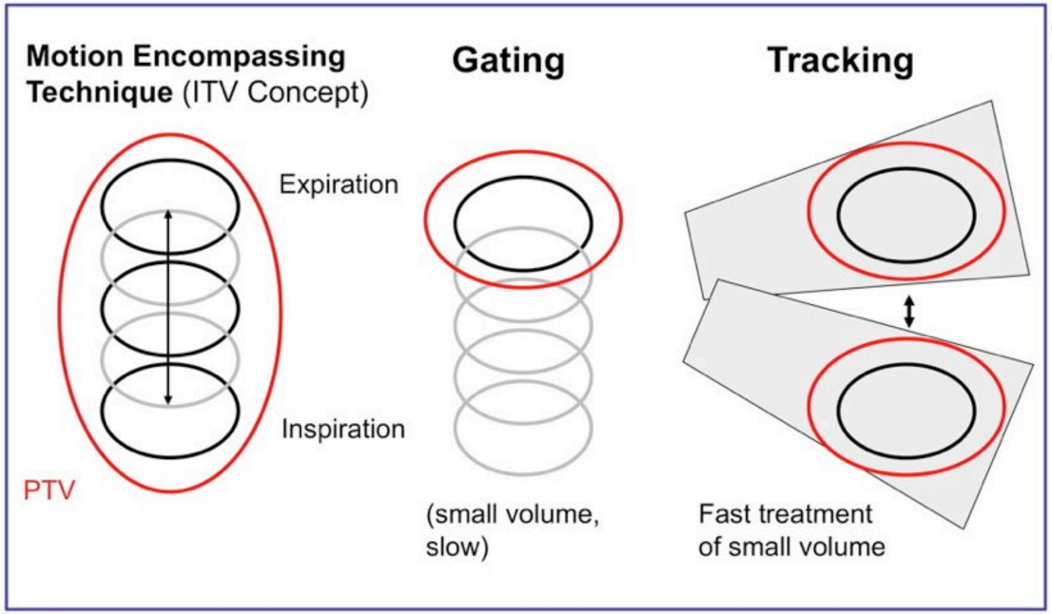
Strategies

How	Technique	Comments
Incorporate all movement	4DCT or slow CT in quiet respiration	Individualized approach, but no reduction of Target Volume
Reduce movement	Abdominal Belt suppressor	Reproducibility / Residual movement
Freeze movement	Breath-hold	Not feasible in most stage I patients Reproducibility / Residual movement
Dosimetric Averaging of respiratory movement	Mean tumor position with margins that account for dose blurring	- Requires knowledge of full motion pattern - Imaging artefacts of bin @ mean position - Margin depends on penumbra shape - Margin is spatial dependent - Moderate reduction of Target Volume
Intercept movement / **'gated'** radiotherapy	Treat in phase when tumor is immobile	- Use of an internal or external surrogate for tumor motion - Treatment less efficient
Track or **chase** tumor	Implanted radio-opaque and specialized equipment (eg Cyberknife)	(1) difficult endobronchial marker insertion (2) CT-guided insertion risks pneumothorax (3) markers migrate after insertion (4) difficult to predict normal tissues doses (5) Relies on a good relation between external marker and internal tumor motion

Technical goal in lung SABR: reduce ITV



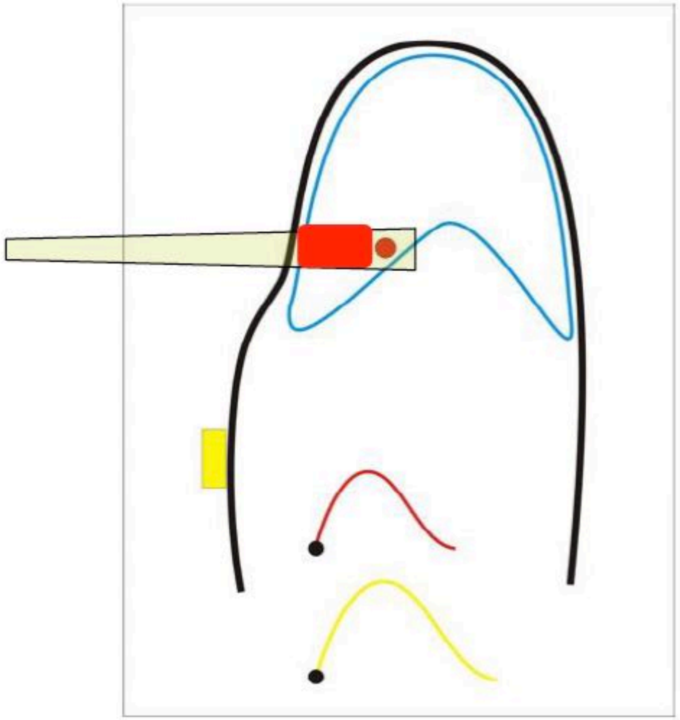
Carry K. J Tor Dis 2014



Lung S. SPS

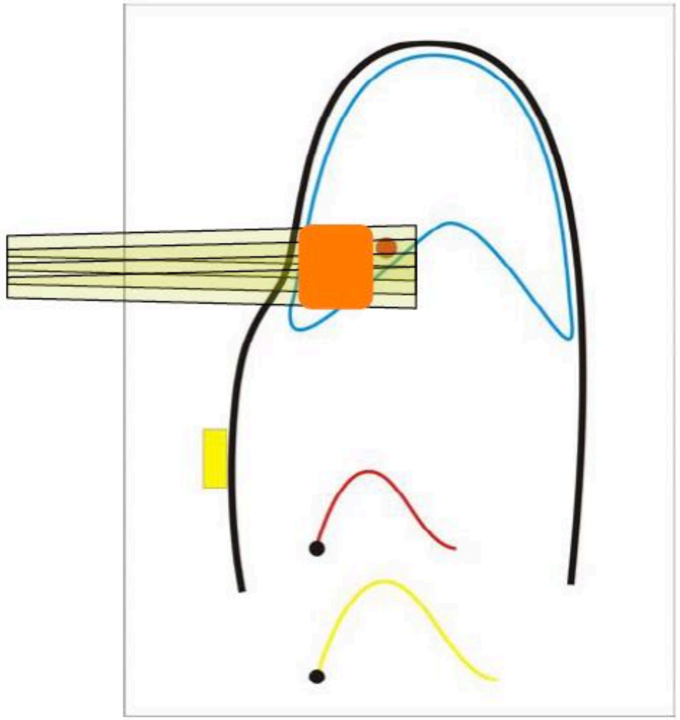
Tracking vs Gating

- Gating



➤ Higher dose, concentrated

- Tracking



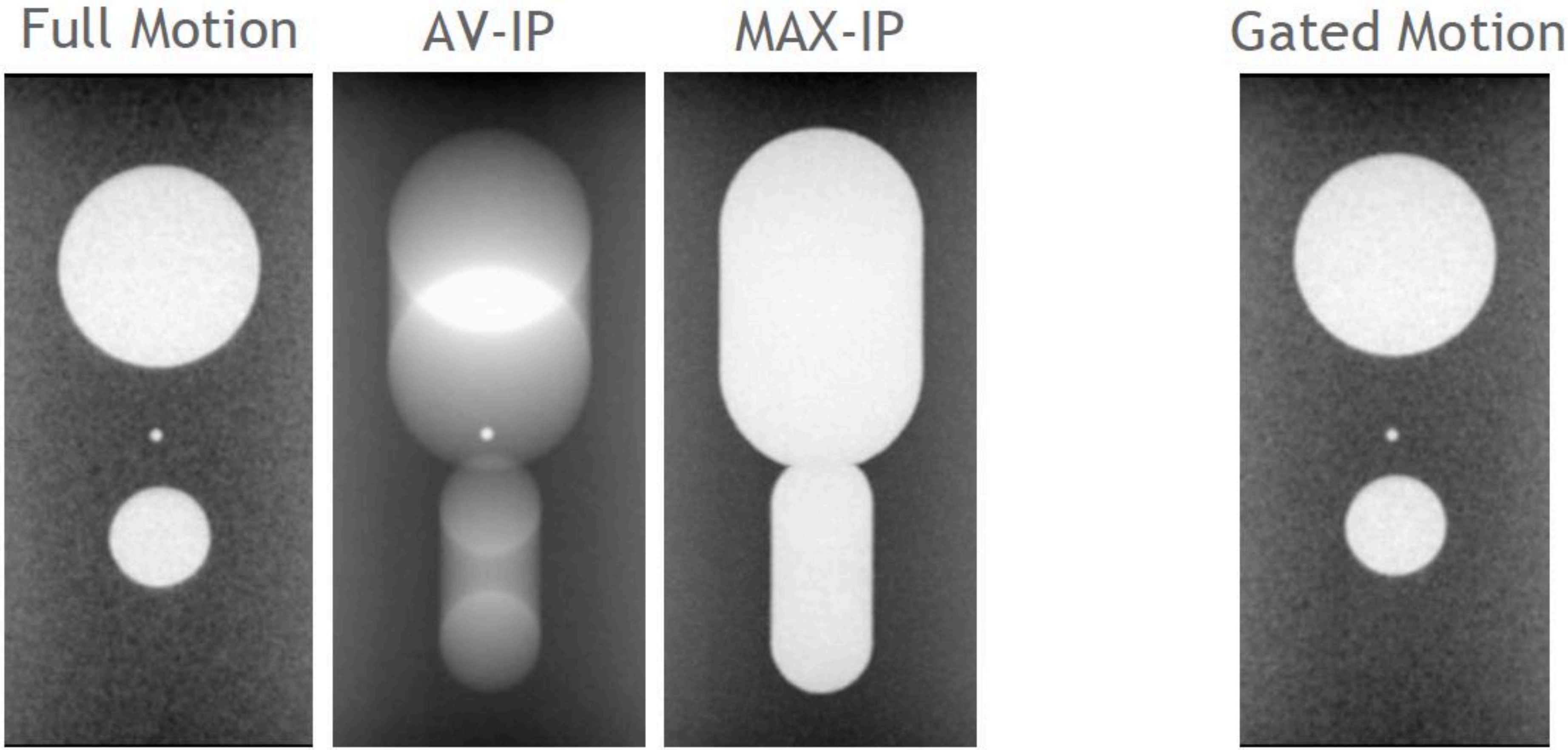
➤ Lower dose, larger volume

Courtesy from Verellen

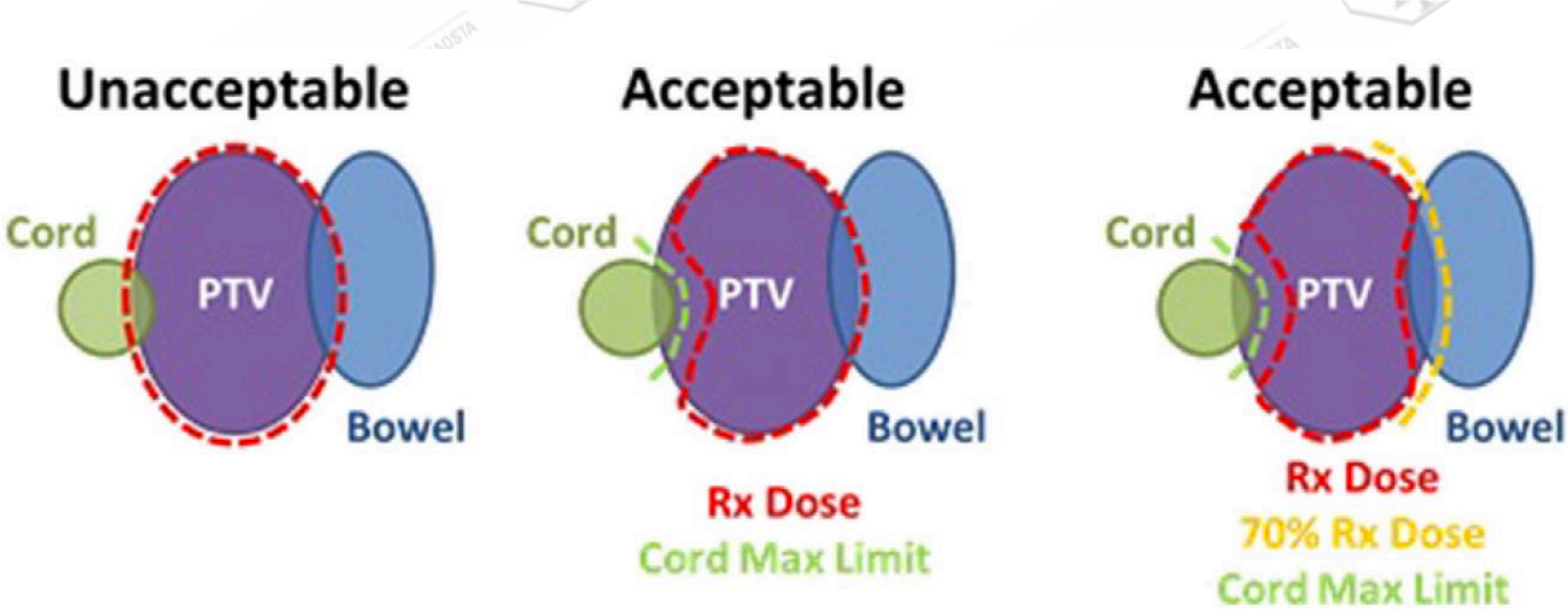
“Volume” delineation

- Creating ITV
  - using 4DCT bins
    - All 10 bins
      - Contour propagation on 4DCT phase bins
    - EE or EI
    - MIP
  - Hands on session Eclipse afternoon
- Using dosimetric margins

4DCT –"Volume" (composite) recostruction



"Volume" delineation



The first NCI- Trial for treatment of Multiple metastases
NRG-BR001

Practical in Radiation Oncology 2017

THANKS ...!!!