Optimising the therapeutic ratio using novel radiotherapy technology

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Conflict of Interest

- None to declare

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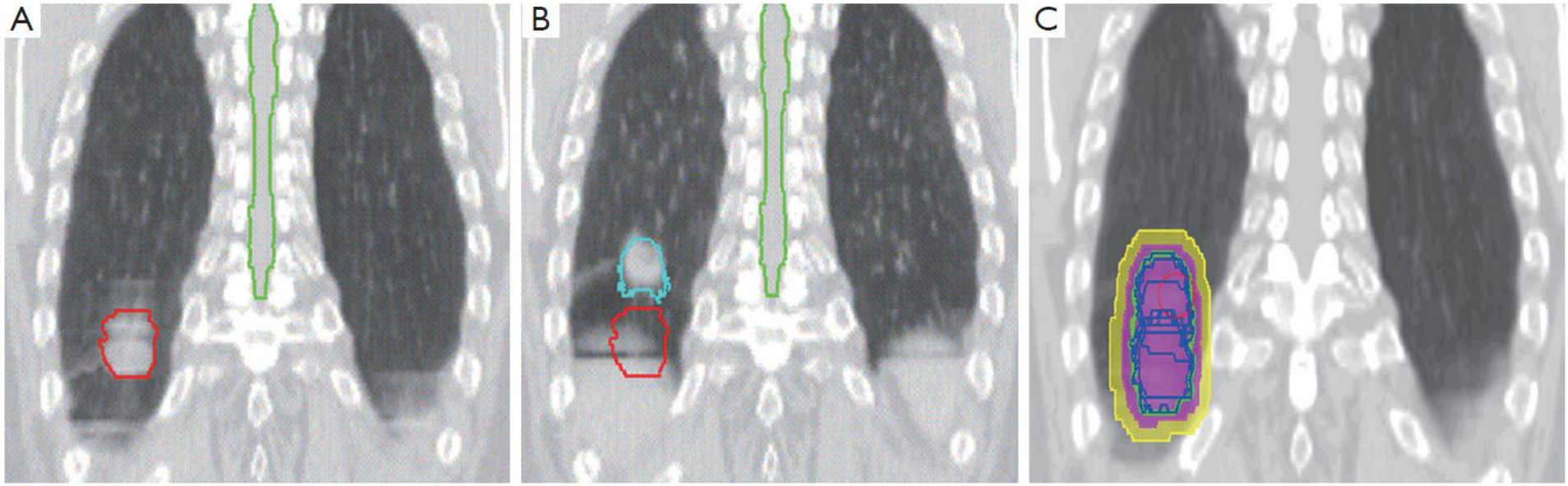
No brainers

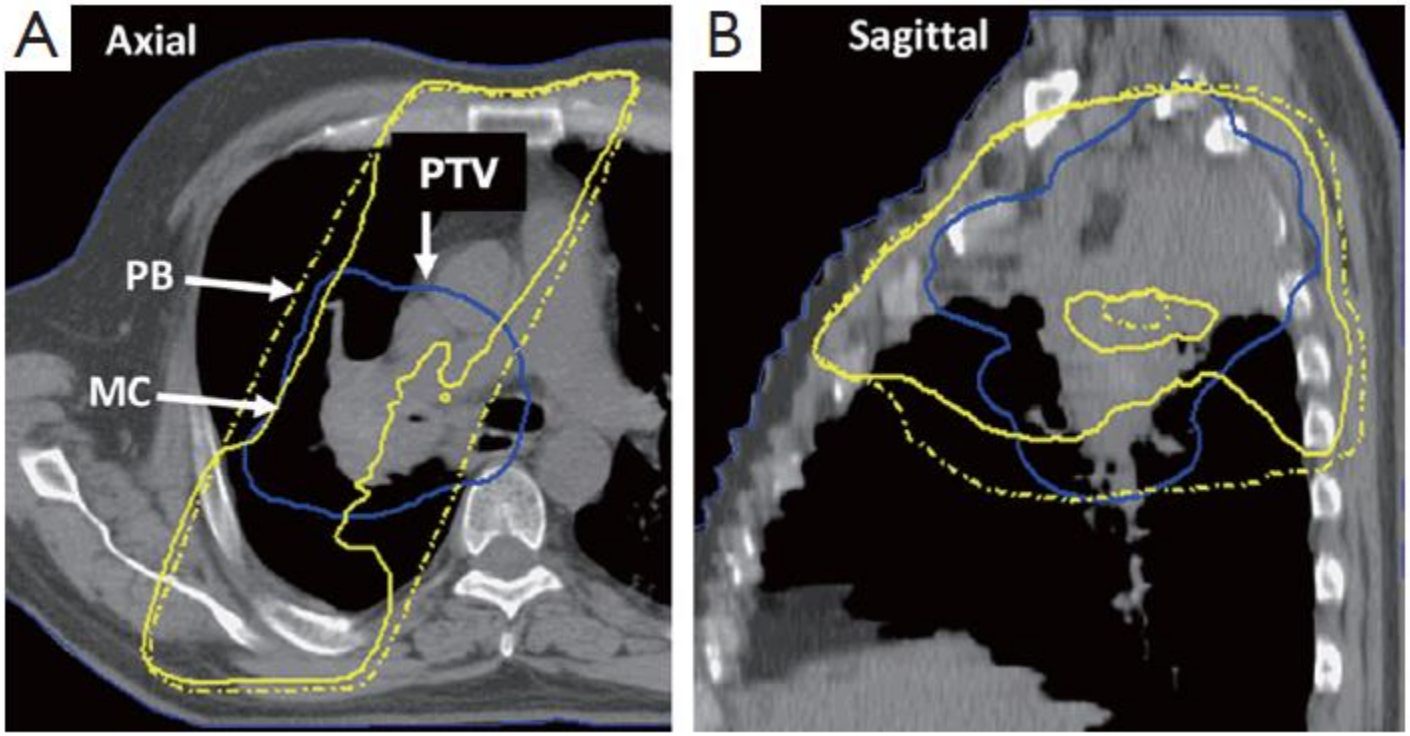
4D-CT



Glide-Hurst et al. J Thor Dis 2014

Better dose calculation algorithms:

Pencil beam vs. Monte-Carlo



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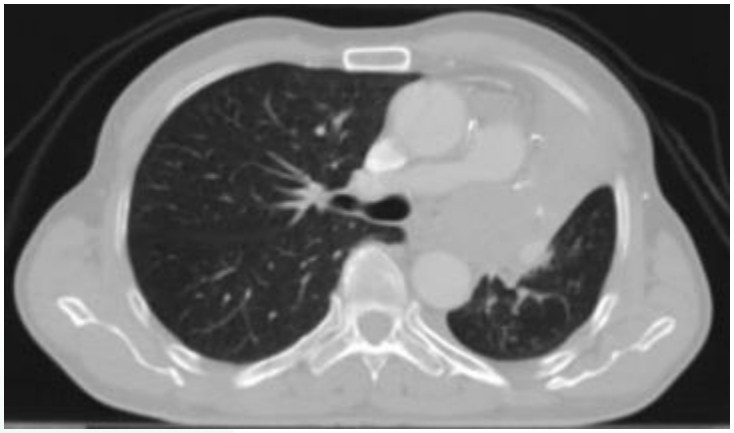
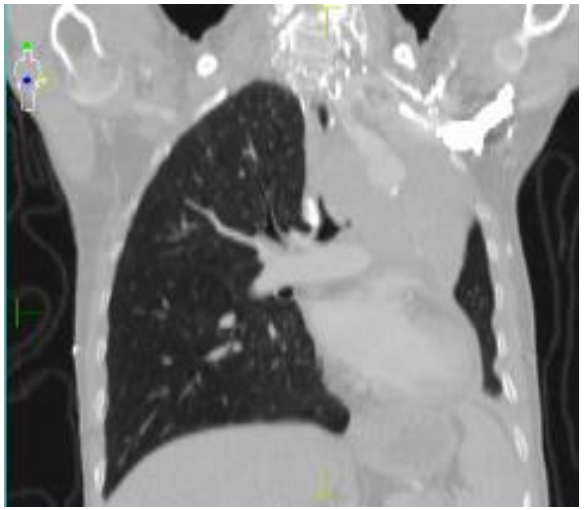
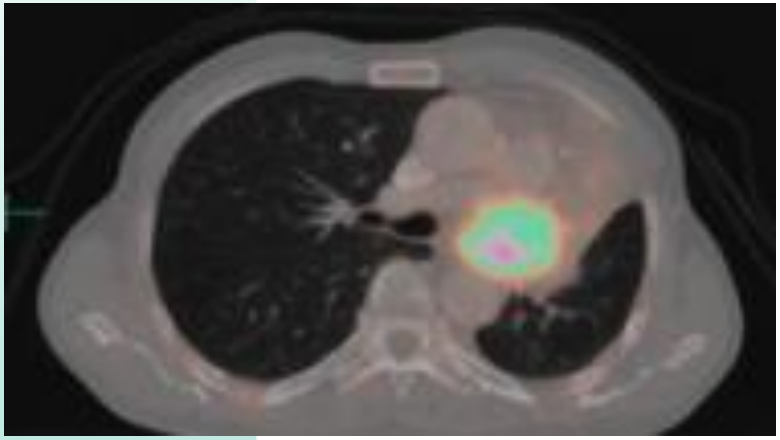
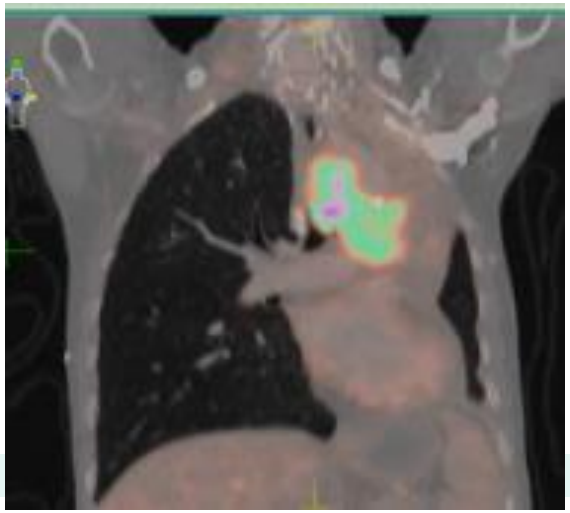
Adaptation in cases of atelectasis?









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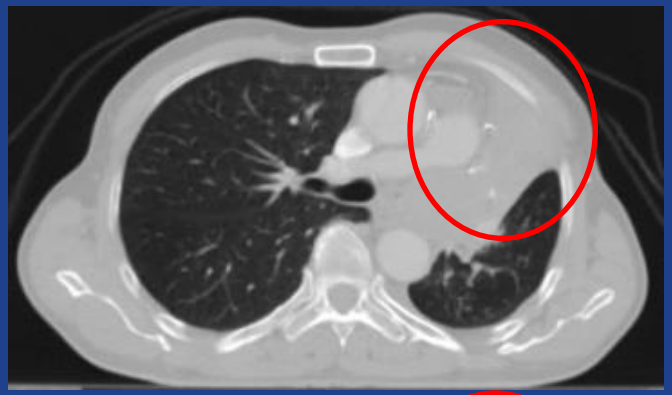
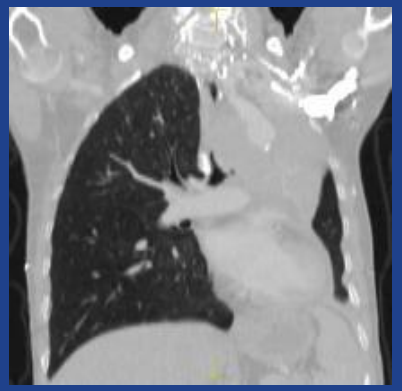
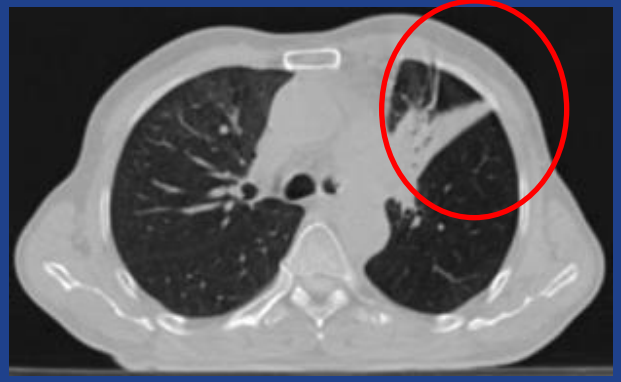
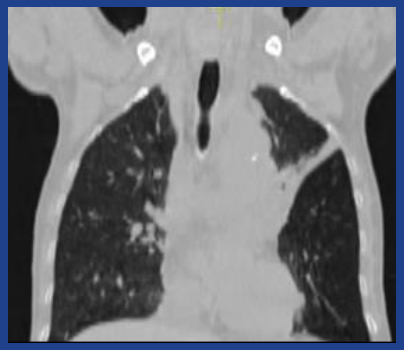
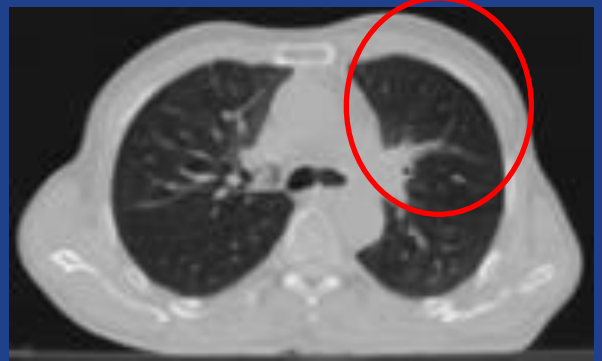
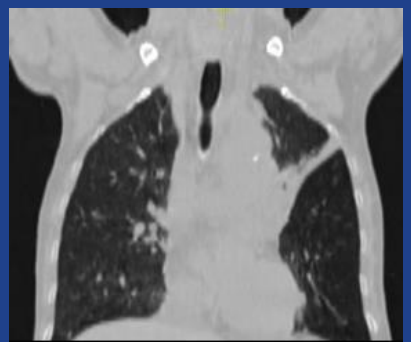
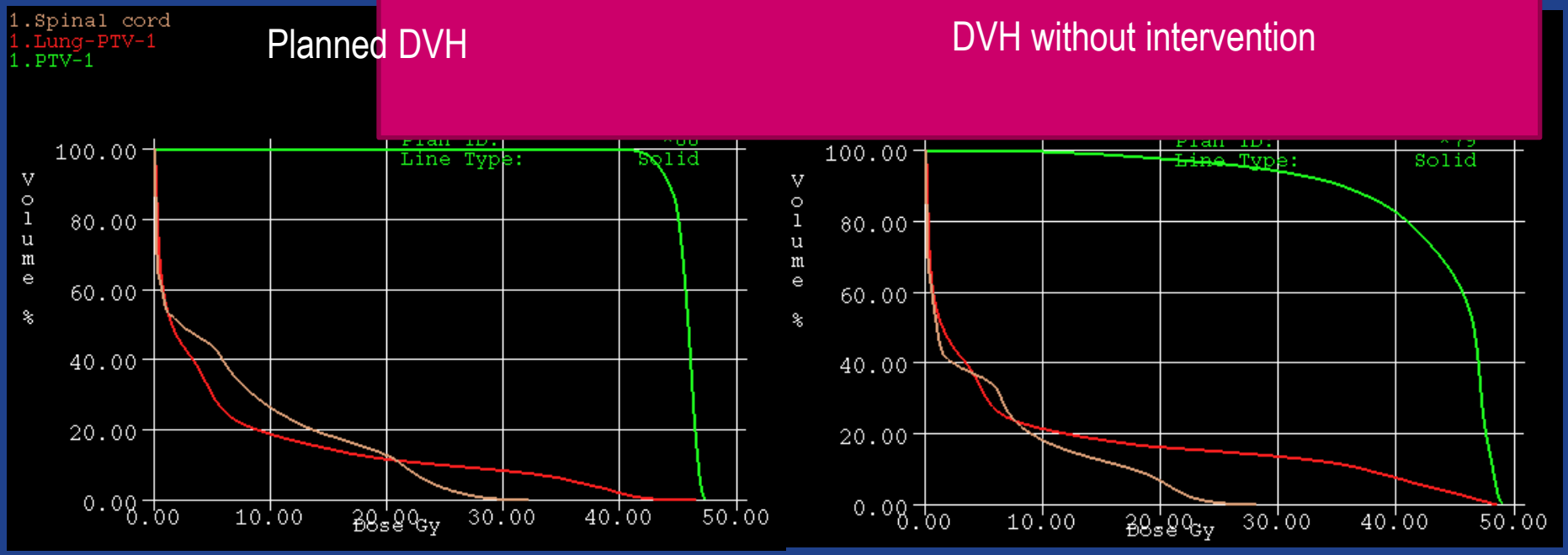
- First CT
- Second CT
  after 3 fractions
- Third CT
  after 17 fractions

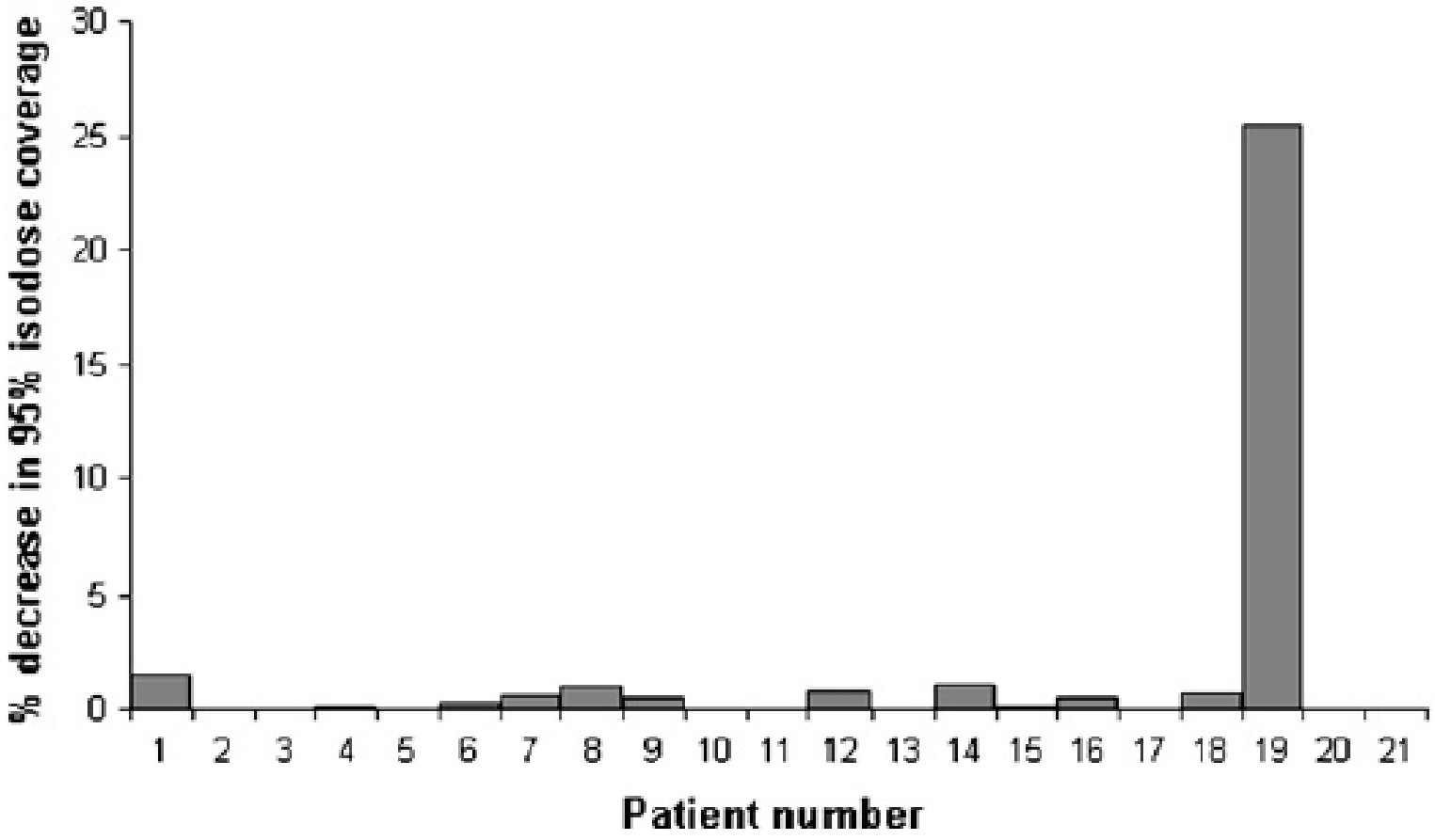
Planned DVH

DVH without intervention



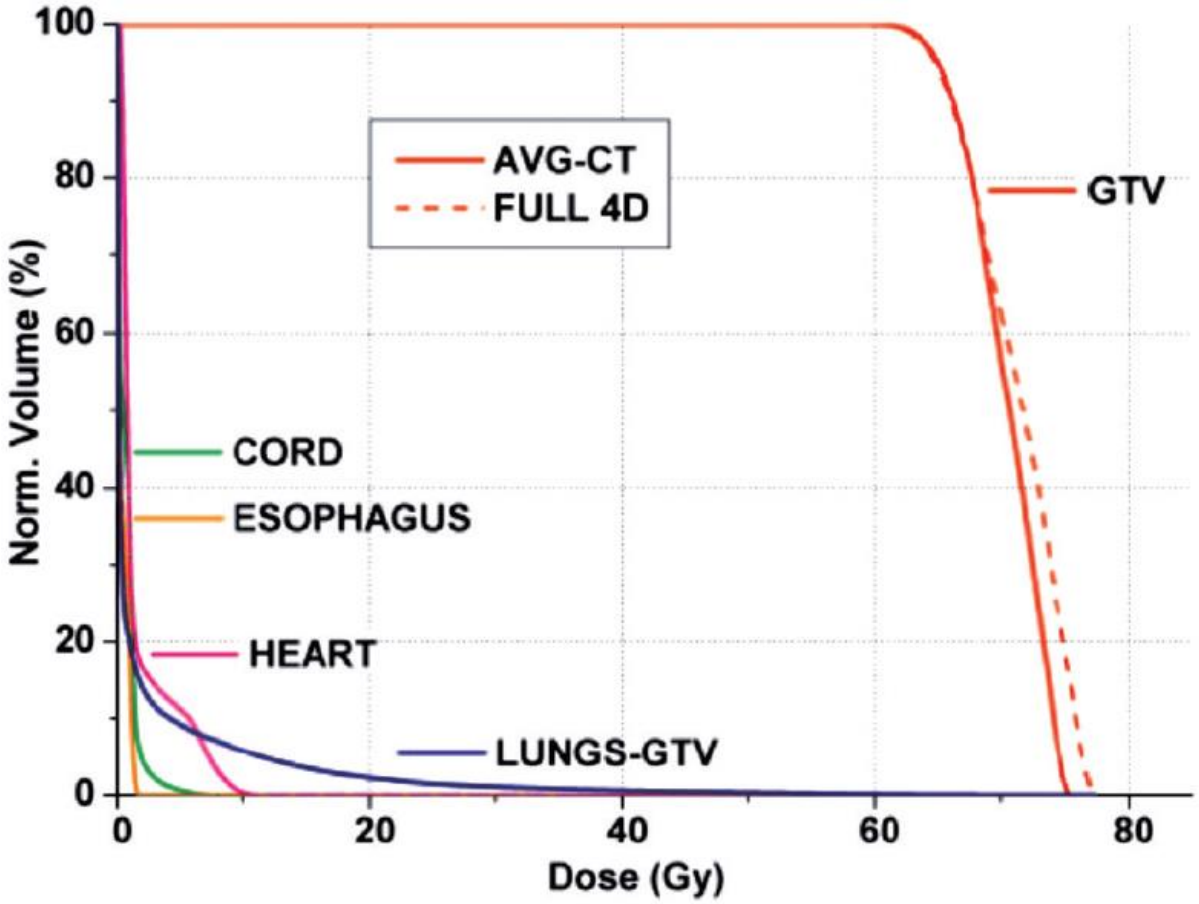
	Original Plan	Plan delivery without intervention
PTV (mean dose)	45.58 Gy	43.52 Gy
PTV coverage (volume with dose > 40.5 Gy)	99.84 %	81 %

Inter-fractional changes: Dosimetric consequences



Spoelstra et al. Int J Radiat Oncol Biol Phys 2009

But 4D dose accumulation (- - -)?



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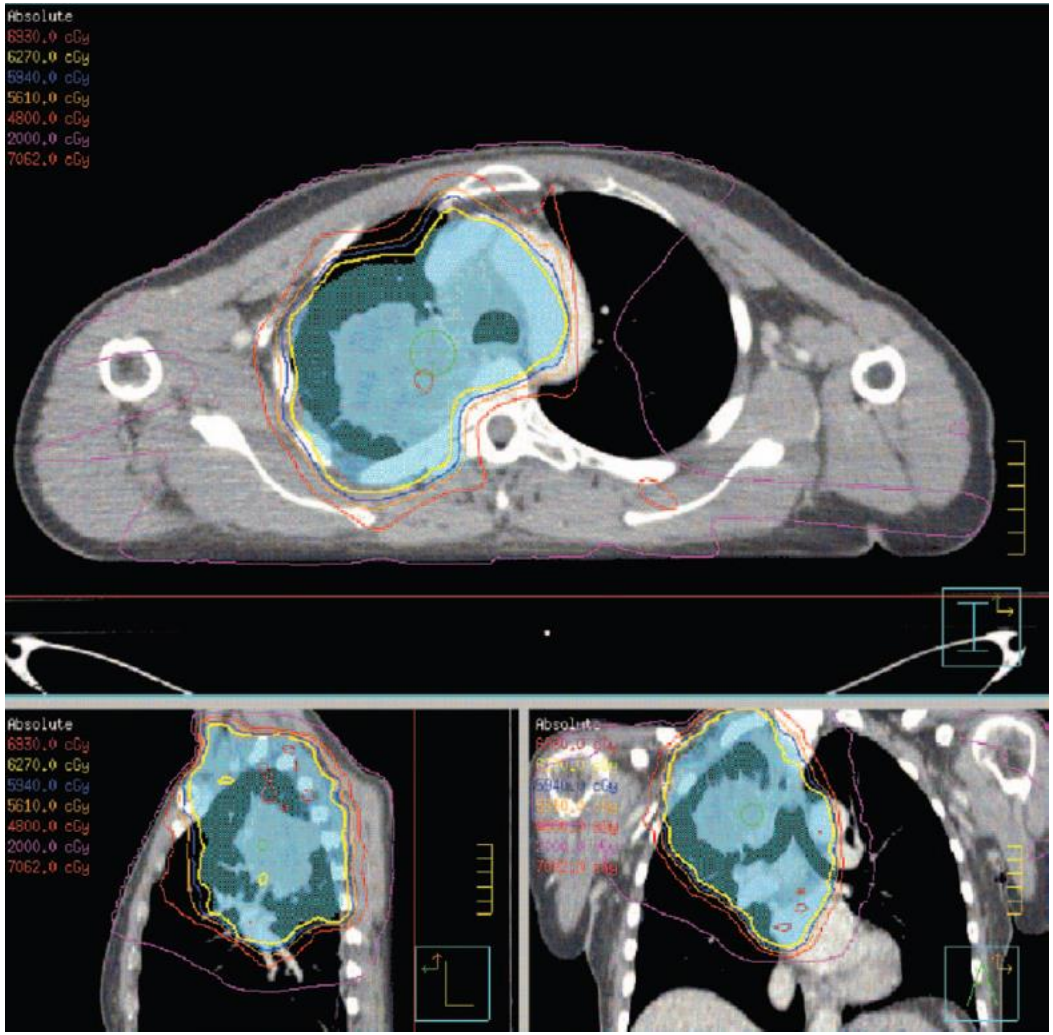
And Tracking, Gating …?

- SBRT: similar results
- Locally advanced: ?

Superior dose distributions:

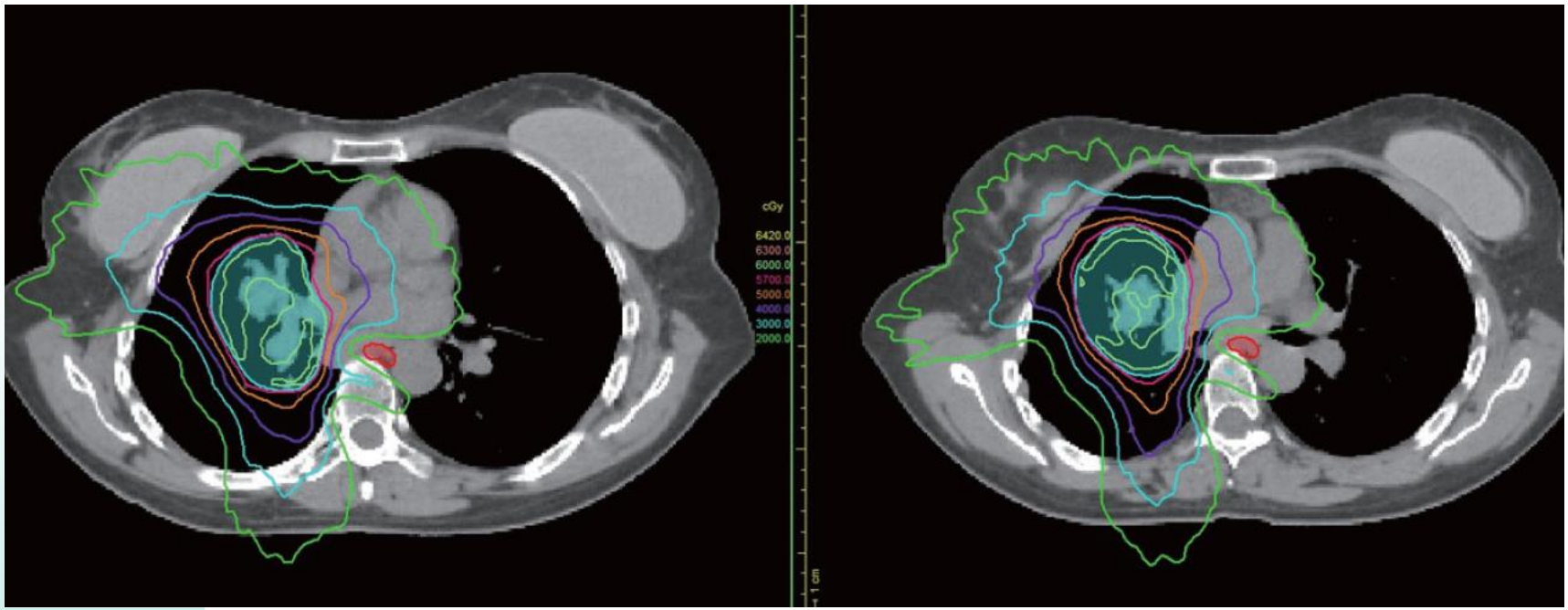
Also a no brainer?

IMRT



Chan et al. J Thorac Oncol 2014

Tomotherapy



Fey M et al. J Thor Dis 2013

Advantages and disadvantages of IMRT for lung cancer

Advantages	Disadvantages
Ability to spare organs at risk	Increased contouring, planning, and quality assurance time
Better coverage of irregular shaped targets	Increased need to accurately delineate clinical target volumes and involved nodes requiring treatment
Ability to dose escalate	Need for image guidance
Able to treat synchronous primary tumors and multiple targets simultaneously	Sharp dose gradient—may lead to under-treatment of micrometastatic disease
Enables treatment of larger radiotherapy volumes to radical dose	Potential interplay effects depending on fractionation and complexity of IMRT technique used
	Need for rigorous quality assurance programme
	Low-dose radiotherapy bath

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Evidence for IMRT, tomotherapy and VMAT: Planning studies?

TABLE 2. Planning Studies Comparing IMRT to 3DCRT

Publication	No. Patients	DiagnosesPTV Size (ccm)Prescription	3DCRT Technique	IMRT Technique	PTV	Both Lungs	Contralateral Lung	Ipsilateral Lung	Heart	Spinal Cord
Cattaneo, 2008[9]	13	Stage III NSCLC394 (215–745)34–39x1.8 Gy	3–5 fields	Tomotherapy, 2.5 cm jaw width, modulation factor <3	IMRT (V95%)	IMRT (mean, V15, V20, V30, V40)	–	–	IMRT (mean, V45, V50, V60)	NS
Chan, 2011[10]	24	Stage III NSCLC–30x2 Gy	5–7 coplanar fields	VMAT: 2 204° arcs.Hybrid-VMAT: 2 204° arcs and 2 static fields	IMRT (CI, (D5%–D95%))	IMRT (mean, V20, V10)3DCRT (V5)	–	–	IMRT (V40)	IMRT (max)
Christian, 2007[30]	10	Stages IB–IIB NSCLC197 (103–272)32 x 2 Gy	6 noncoplanar fields	3–9 coplanar fields6 noncoplanar fields	IMRT(PTV_{90}/V_{20lung})	IMRT(PTV_{90}/V_{20lung})	–	–	–	IMRT (max)
De Bree, 2012[8]	20	Inoperable NSCLC838 (407–1574)30–33x2 Gy	5 fields	VMAT, 2 arcsStatic field IMRT, 7 coplanar fields	IMRT (CI)	IMRT (mean)3DCRT (V5, V20)	–	–	IMRT (V40)	IMRT (max)
Liu, 2004[11]	10	Stages I–IIIB NSCLC403 (65–762)35x1.8 Gy	4 fields: AP/PA fields and oblique off-cord fields	SW-IMRT plans, 3–9 coplanar fields	IMRT (CI)	IMRT (V20, V30, mean)3DCRT (V5)	–	–	–	–
McGrath, 2010[29]	21	Stage IA NSCLC57 (22–125)4x12 Gy	7–10 nonopposing noncoplanar fields	1 partial arc of 180°	NS	IMRT (20 Gy, 12.5 Gy, 10 Gy, 5 Gy)	–	–	NS	NS
Murshed, 2004[12]	41	Advanced stage NSCLC—	9 equidistant coplanar 6 MV fields	SW-IMRT, 9 equidistant, coplanar fields	IMRT (CI), 3DCRT (HI)	IMRT (V10, V20)	NS	NS	IMRT (V40)	3D (max)
Ong, 2010[13]	18	Stage I NSCLC34 (3–67)8x7.5 Gy –3x 18 Gy	10 noncoplanar fields	VMAT, 2 arcs	IMRT (CI)	3DCRT (V20)	3DCRT (V5)	–	–	IMRT (max)
Simeonova, 2012[14]	20	Stages I–IV NSCLC515 (CTV)–	3–6 18 MV fields	13 coplanar fields17 noncoplanar	IMRT (min)	–	IMRT (mean, D30%)	IMRT (D30%, V20)	NS	IMRT (max)
Zhang, 2011[31]	15	Early stage LC6 (17–161)5x10 Gy	9–11 noncoplanar fields	Coplanar VMAT Noncoplanar VMATFFF VMAT	IMRT (CI, GI)	IMRT (mean, V5, V20)	–	–	–	–

Chan et al. J Thorac Oncol 2014

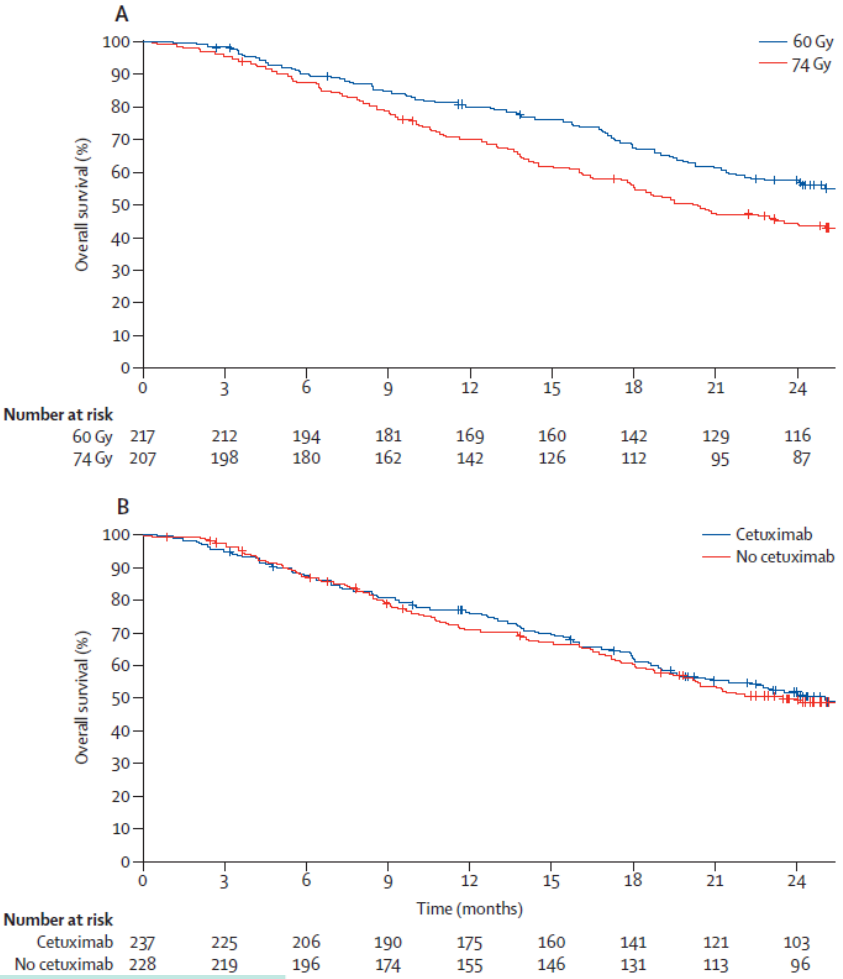
Evidence for IMRT, tomotherapy and VMAT: And Planning studies …

TABLE 3. Planning Studies Comparing Different Types of IMRT Technique

Publication	No. Patients	DiagnosisPTV Size (ccm)Prescription	IMRT Technique	PTV	Both Lungs	Contralateral Lung	Ipsilateral Lung	Heart	Spinal Cord	Treatment Time
Bertelsen, 2012[32]	15	NSCLC252 (77–509) 33 x 2Gy	SS-IMRT 7–9 fields Single arc VMAT	NS	VMAT (V20)	–	–	–	–	VMAT
Chan, 2011[10]	24	Stage III NSCLC-30x2 Gy	VMAT: 2 204° arcs. Hybrid-VMAT: 2 204° arcs and 2 static fields	Hybrid-VMAT (D5%–D95%)	Hybrid-VMAT (mean, V20, V10, V5)	–	–	VMAT (V40)	NS	VMAT
Holt, 2011[33]	27	Early-stage LC45 (14–102)3x18Gy	Noncoplanar IMRT (NC-IMRT) Coplanar VMAT	NC-IMRT	VMAT & NC-IMRT (mean, V5, V20)	–	–	VMAT (max)	NCP-IMRT (max)	VMAT
Jiang, 2011[34]	12	Locally advanced NSCLC34x2Gy	SS-IMRT: 5–7 beams VMAT (1 full arc) P-VMAT (200° partial arc)	VMAT (CI, HI)	IMRT (V5, V10)VMAT & P-VMAT(V30, V20, mean)	IMRT (V5, V10) P-VMAT (V30, V20, mean)	NS	NS	NS	P-VMAT
Ong, 2010[13]	9	Stage I NSCLC34 (3–67)8x7.5G –3x 18Gy	VMAT, 2 arcs 9–10 coplanar FF-IMRT fields	VMAT (CI)	NS	NS	–	–	–	VMAT
Simeonova, 2012[14]	20	Stages I–IV NSCLC515 (CTV)-	13 coplanar FF-IMRT fields17 noncoplanar FF IMRT fields	NS	–	17F-IMRT (mean, D30%)	NS	NS	NS	13F-IMRT
Weyh, 2012[35]	8	Stages I + II NSCLC–4 x 12 Gy	Helical tomotherapy (HT)FF-IMRT VMAT	HT (CI)	NS	–	–	NS	NS	VMAT
Zhang, 2011[31]	15	Early stage LC6 (17–161)5x10 Gy	Coplanar VMAT Noncoplanar VMATFFF VMAT	FFF VMAT (mean target dose)	NS	–	–	–	–	–

Chan et al. J Thorac Oncol 2014

Evidence for IMRT?



No difference in the outcome between 3D-CRT and IMRT (stratification factor)

Bradley et al. Lancet Oncol 2015

IMRT, VMAT: A tool for dose-escalation and dose painting

TABLE 4. Examples of Ongoing Clinical Trials Utilizing IMRT for Dose Escalation

Trials Evaluating Personalized Dose Escalation Based on Dose Delivered to OARs	Trials Evaluating an Increased Dose to Selected Parts Within the Tumor, Defined by Functional Imaging (Dose Painting)
Isotoxic IMRT (NCT01836692)	**PET boost (NCT01024829)**
Prospective multicenter single arm feasibility study	Randomized multicenter phase II study
Stage III NSCLC	T2-4, N0-3, M0 inoperable, NSCLC
Sequential chemoradiotherapy	RT alone, sequential, or concurrent chemoradiotherapy
Hyperfractionated, accelerated, and dose-escalated radiotherapy with IMRT and image guidance. Dose based on prespecified normal tissue doses	66 Gy given in 24 fractions of 2.75 Gy delivered with IMRT +/- integrated boost to whole tumor, or the FDG PET-CT 50% SUV_{max} area of the primary individualized to meditational organs at risk (with or without chemotherapy)
Maximum dose 79.4 Gy in 39 twice-daily (BD) fractionsPrimary outcome: delivery of isotoxic IMRT to dose >60 Gy EQD2 (total biologically equivalent in 2 Gy fraction)Proceed to phase II if dose escalation possible in >80% patients	Primary outcome: local progression-free survival at 1 yearThe planning results of the first 20 patients have been published. It was possible to dose escalate 75% of patients to 72Gy, with dose-limiting organs being the mediastinal structures and the brachial plexus[80]
Maastro study (NCT01166204)	**RTOG (NCT01507428)**
Nonrandomized monocenter phase II study	Randomized multicenter phase II study
Stages I–III NSCLC	Stage III NSCLC
Concurrent chemoradiotherapy	Concurrent chemoradiotherapy
Radiotherapy delivered with IMRT to an individualized mean lung dose of 20 Gy +/-1	60 Gy in 30 daily fractions delivered with IMRT +/- adaptive radiotherapy based on FDG-PET/CT scan between fractions 18 and 19
45Gy/30 BD fractions for first 3 weeks followed by once daily fractions of 2 Gy until the target dose has been reached	Max dose 80.4 Gy in 30 daily fractions, individualized to mean lung dose 20 Gy
Primary outcome: overall survival	Primary outcome: local progression-free survival

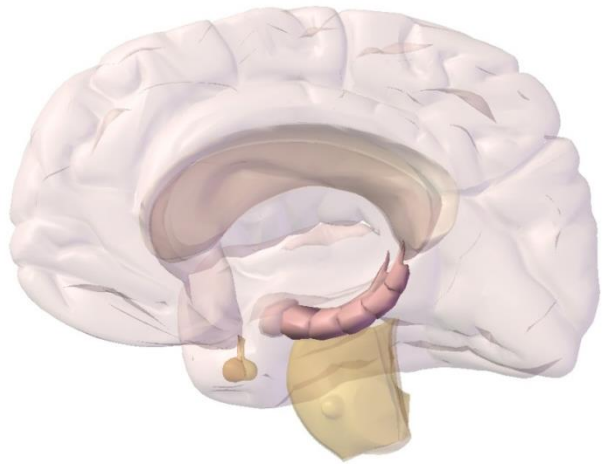
Chan et al. J Thorac Oncol 2014

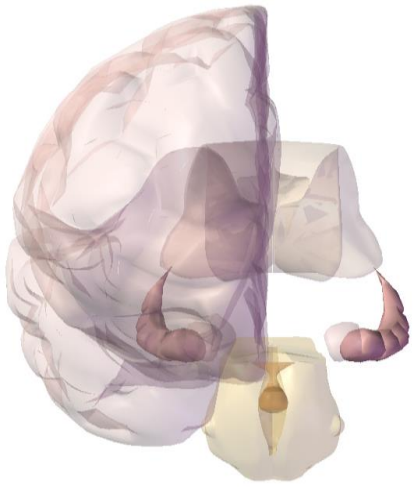
UZ LEUVEN

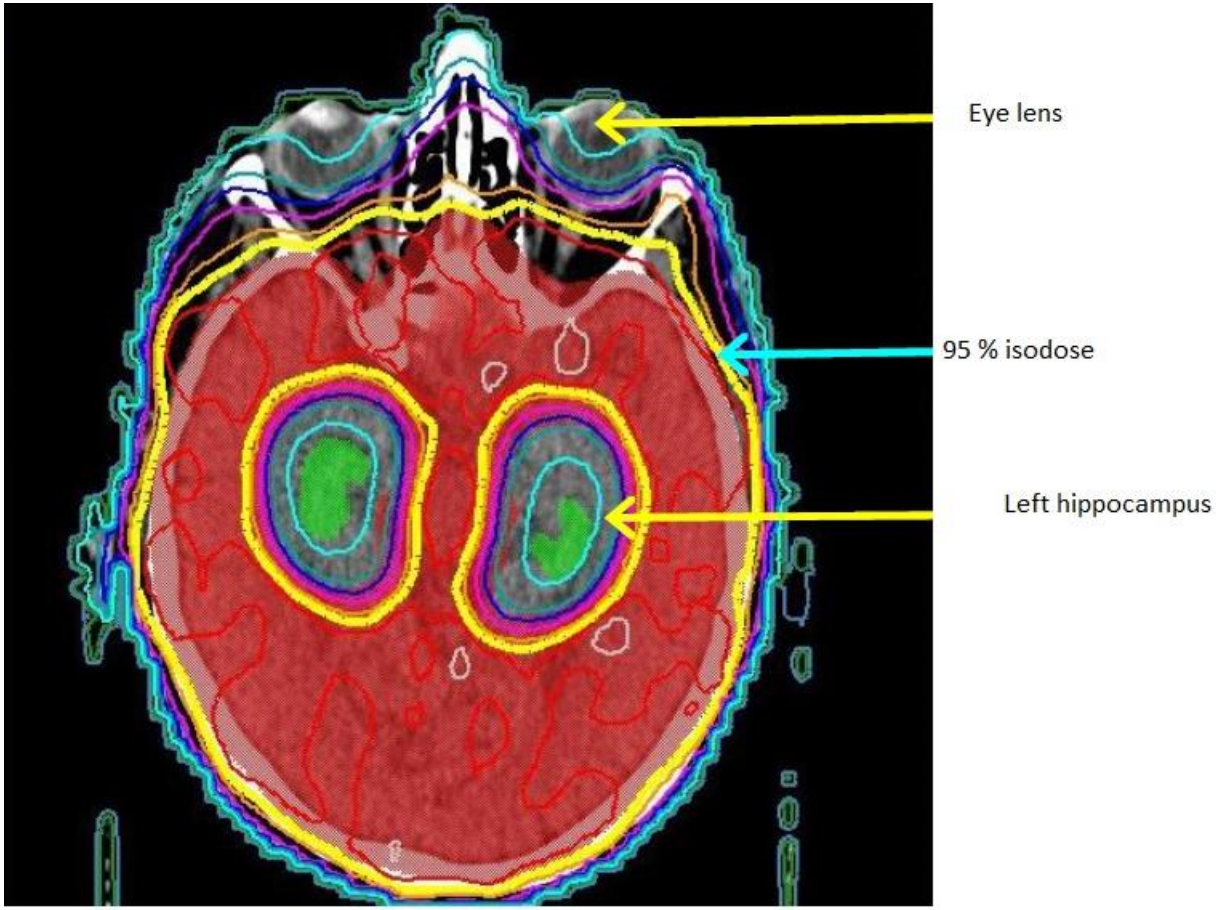
NKI-AVL
Het Nederlands Kanker Instituut
Antoni van Leeuwenhoek Ziekenhuis

Improvement of memory function after Prophylactic Cranial Irradiation (PCI) by avoidance of the hippocampus: A randomized phase III study in small cell lung cancer patients

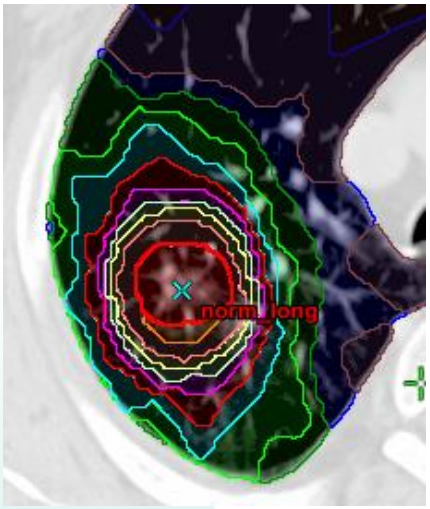
Dirk De Ruysscher, MD, PhD, on behalf of the HA-PCI working group

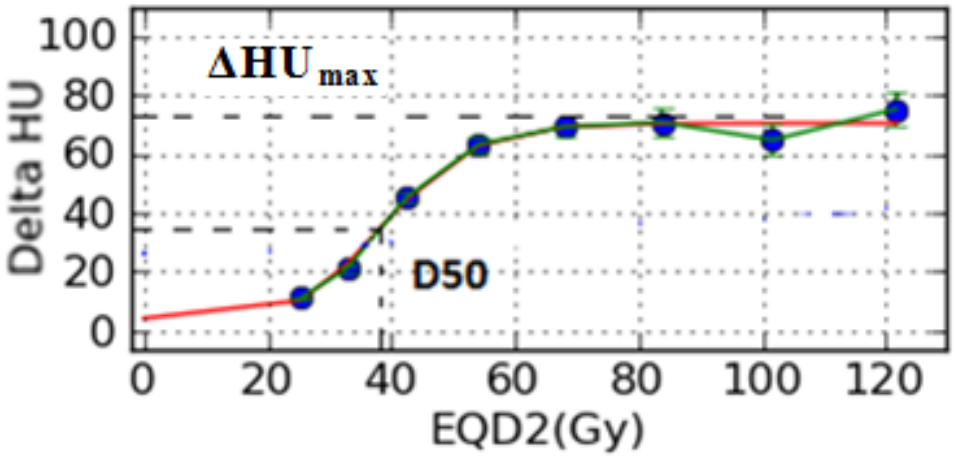


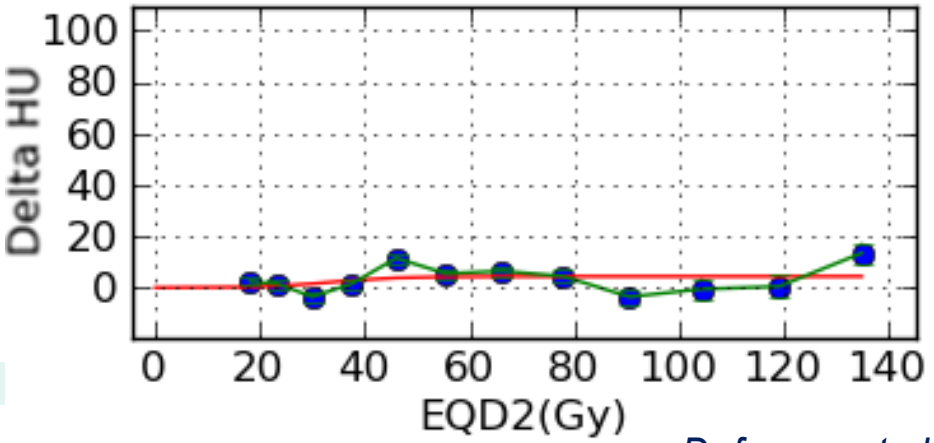



Eye lens
95 % isodose
Left hippocampus

Individual dose-response relation for radiation-induced lung damage on the basis of a single pre-treatment CT scan



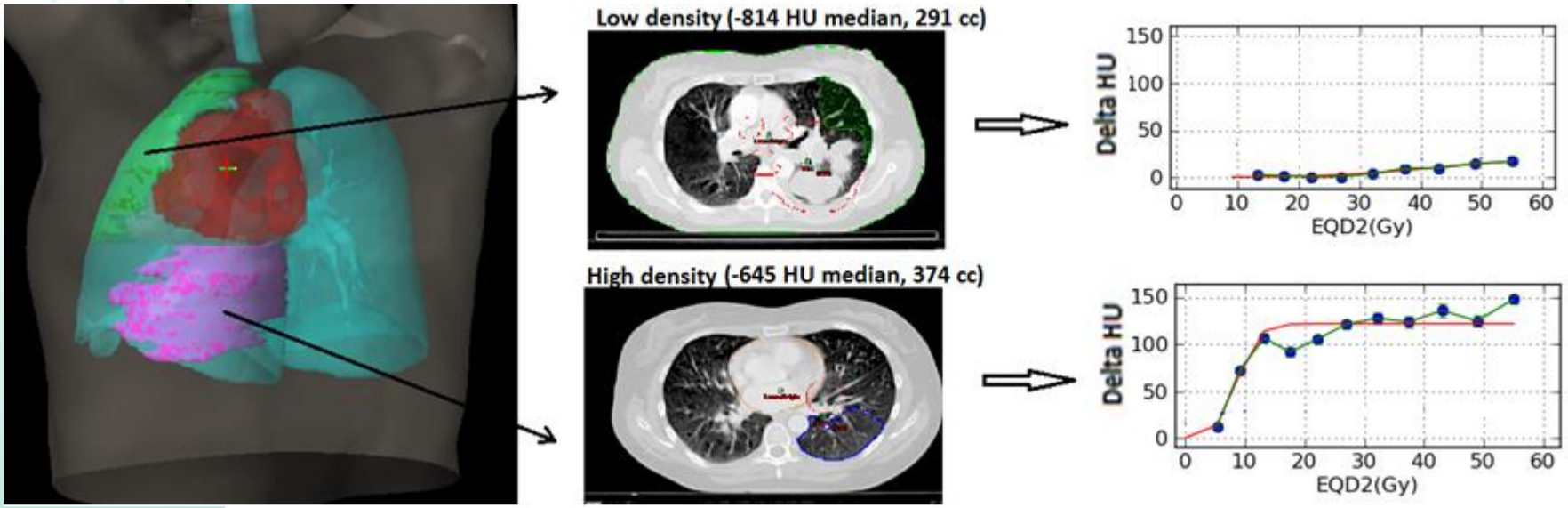




Defraene et al. Radiother Oncol 2015

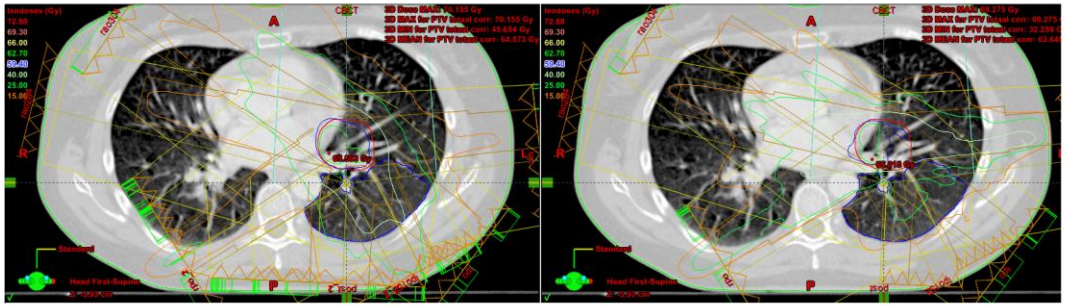
Heterogeneity within one lung

- Concept
  - Hypothesis: denser regions more prone to damage
  - Manually defined subregions maximally differing in density on planning CT
  - Lower lobe more radiosensitive



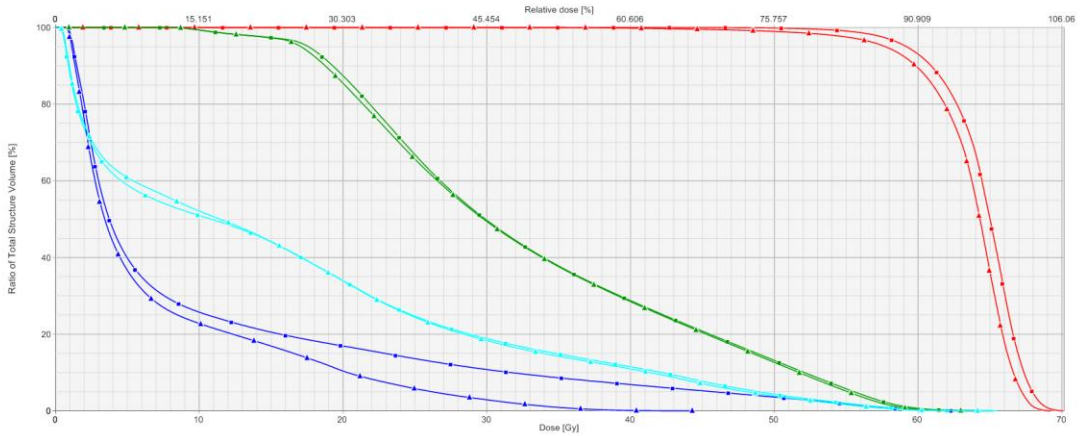
Redistribution of radiation dose

- Maximally sparing high-risk subregion
- Same PTV and OAR constraints (identical MLD!)



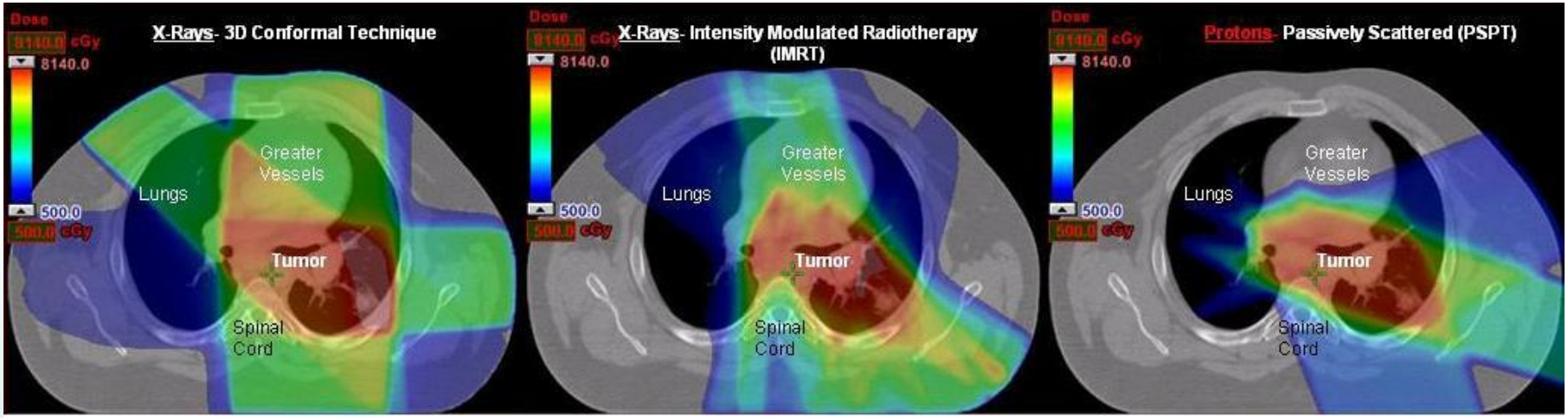
Delivered IMRT plan

Redistribution IMRT plan: avoiding high density structure



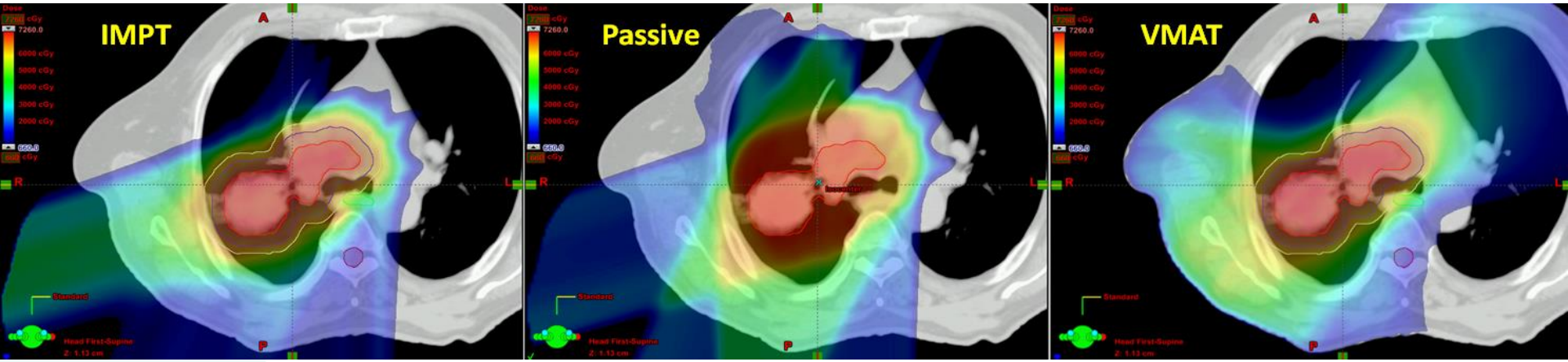
High-risk subregion: mean dose reduction of 6.6 Gy

Proton Therapy: Superior dose distributions



De Ruysscher D, Chang JY. Sem Radiat Oncol 2013

Proton Therapy: Superior dose distributions



Comparison of IMPT vs. PSPT and VMAT in stage III NSCLC.

IMPT achieves the best sparing of all critical strictures. PSPT spares more heart and contralateral lung but not esophagus or ipsilateral lung as compared with VMAT.

Chang JY et al. Int J Radiat Oncol Biol Phys 2016

Conclusions

- New technologies lead to a better dose distribution
- More patients can receive a radical radiotherapy dose
- Lack of evidence for improved survival/ local control/ less side effects (new NTCP models!)
- Huge potential for re-distribution studies
- Need for refinement of adaptive strategies