State-of-the-art time/dose and fractionation for radio(chemo)therapy of lung cancer

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ELCC 14 april 2016

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Disclosures

None

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Introduction

- After CCRT local control ≈ 70% at 3-5 years (Auperin JCO 2010)
- RT dose conventional 60 Gy in 2 Gy +/- concurrent chemotherapy
- Dose escalation is limited by normal tissue tolerances

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Variation in the use of concurrent chemoradiation (CCRT)

Country	% CCRT
The Netherlands[1]	~70%
England[2]	~54%
Italy[3]	~17%
Canada[4]	~18%
Australia[5]	~37%
USA[6]	~35%

[1] van Reij E. Act. Onc. 2014
[2] Prewett S. Clin Onc 2012
[3] Ramella S. Tumori 2012
[4] Vinod S. JTO 2012
[5] Pramana A. AP JCO 2014
[6] Harris J. Int J Radiat Oncol Biol Phys 2014

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Options to improve locoregional control

- RT dose escalation
- Enhance RT response by targeted radiosensitization
- *Improve treatment accuracy* → Image-guided adaptive RT
- Reduce overall treatment time and Accelerated cell repopulation

↓

Hypo- or Hyperfractionation or Acceleration

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RT dose and fractionation

- Split course RT: with a several-day break
- Hyperfractionation : multiple smaller daily doses
- Acceleration : same dose in shorter period
- Hypofractionation : fewer larger fractions

BED= biological effective dose

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Influence Local Control on survival CHART trial:

R → 60 Gy / 30 fx   40 days

R → 54 Gy/ 36 fx   12 days

- 563 NSCLC patients
- 2 year OS benefit for hyperfractionation 9% (from 20 to 29%)
- For SCC 25% improved local control and a 24% reduction in risk distant metastases
- Improved LC reduced the incidence of metastases and improved survival!

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Saunders R&O 1999

Meta-analysis
Hyperfractionated / accelerated RT

- 10 trials, 2,000 NSCLC patients
- Modified fractionation improved OS as compared to conventional schedules
  (HR = 0.88, 95% CI, 0.80- 0.97; p = .009)
- Resulting in an absolute OS benefit of 2.5% (8.3% to 10.8%) at 5 years
- Similar benefit in SCLC

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Mauguen et al JCO 2012

Dose-response relation in NSCLC

The probability of sterilizing a tumor increases with increasing radiation dose to the tumor

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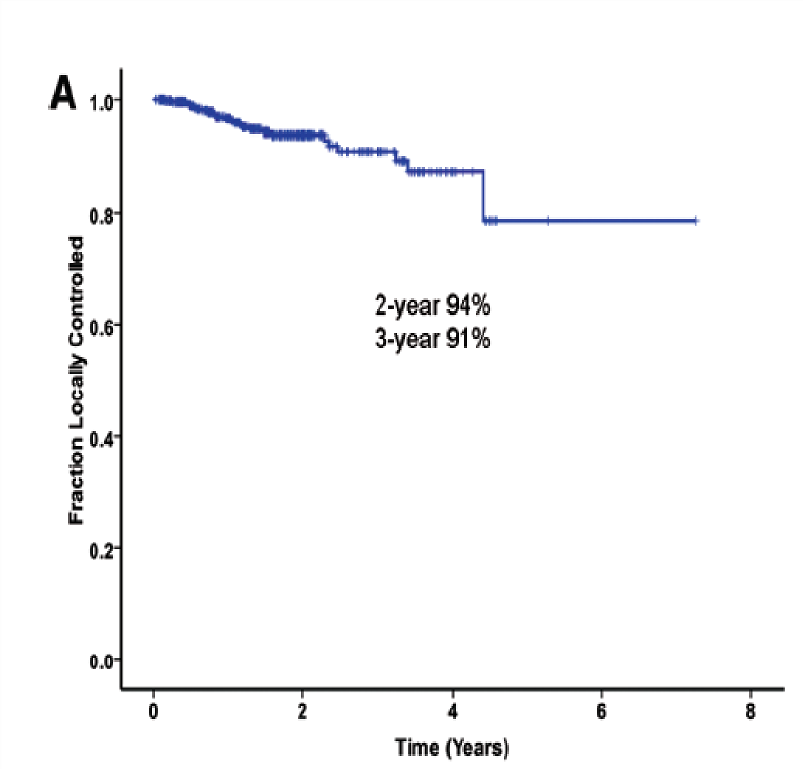
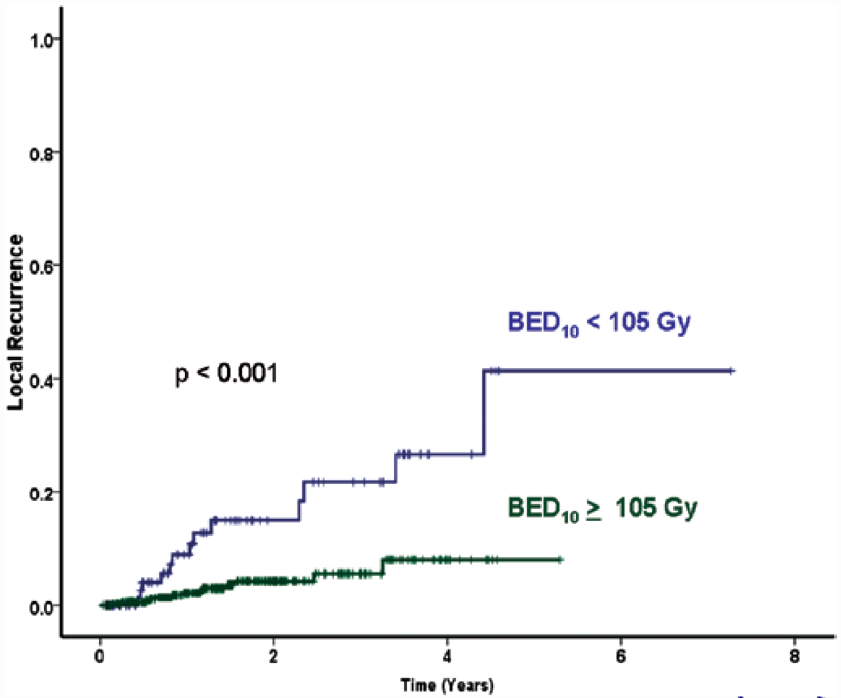
Dose-response relationship in SABR for NSCLC





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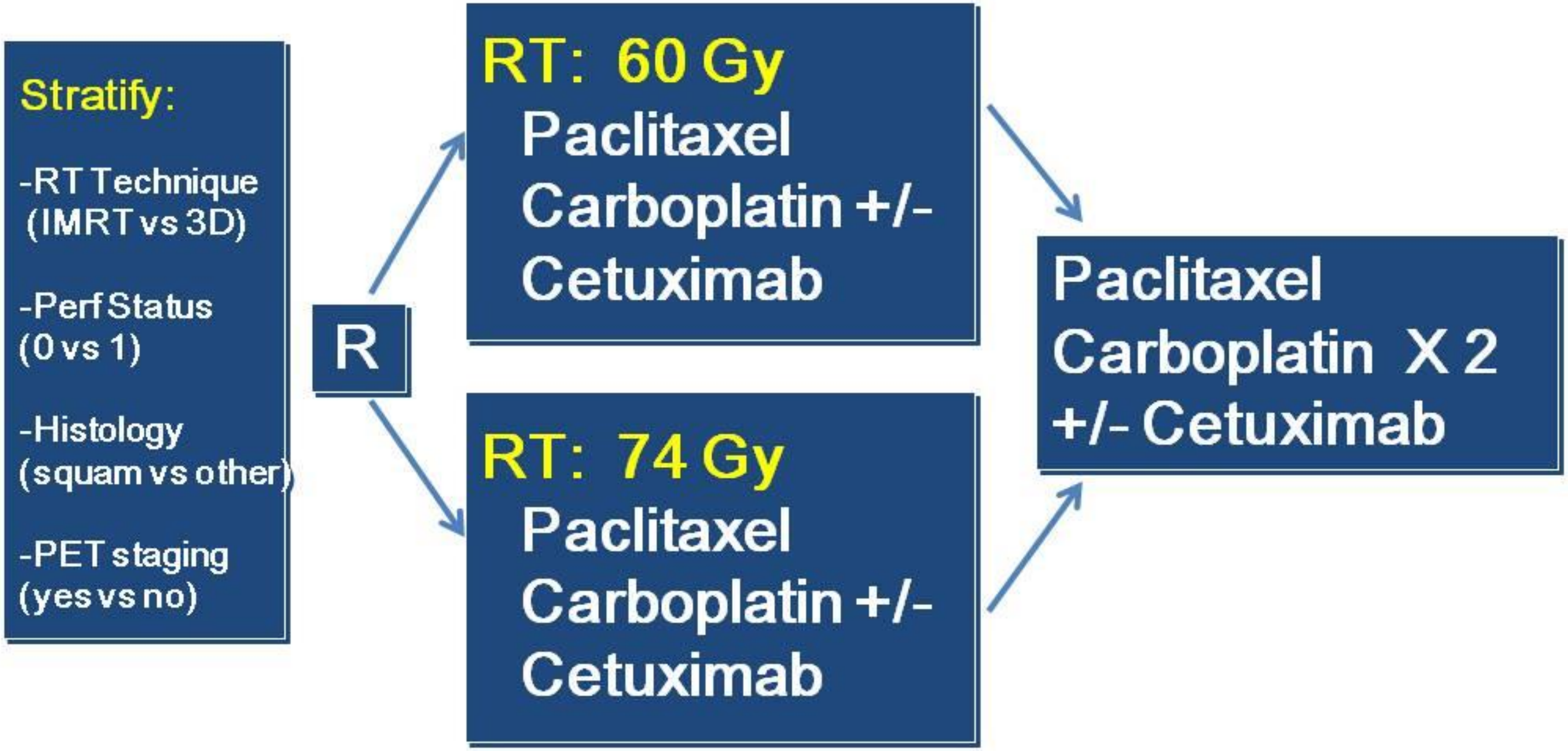
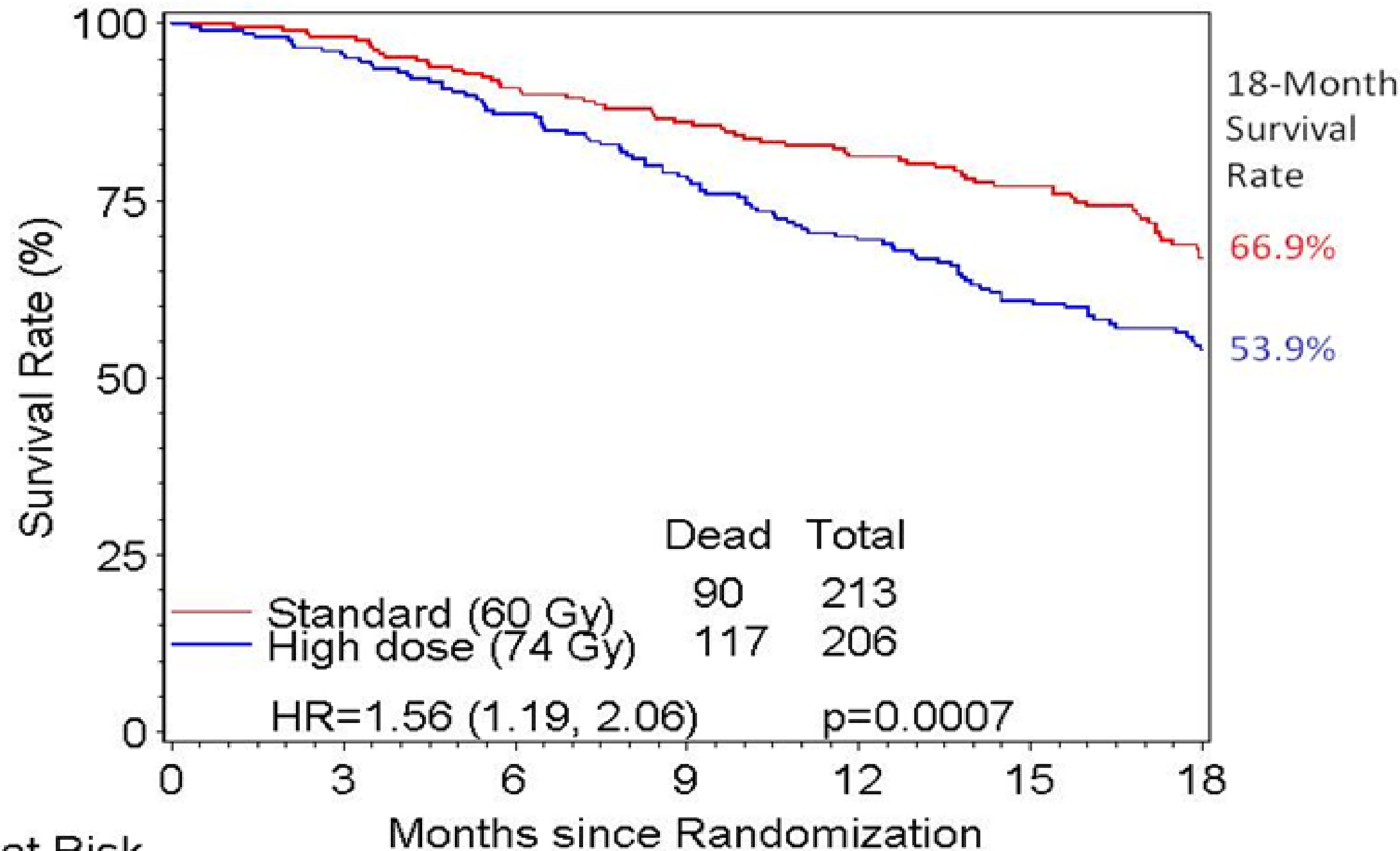
Grills JTO 2012

RTOG 0617: Trial design



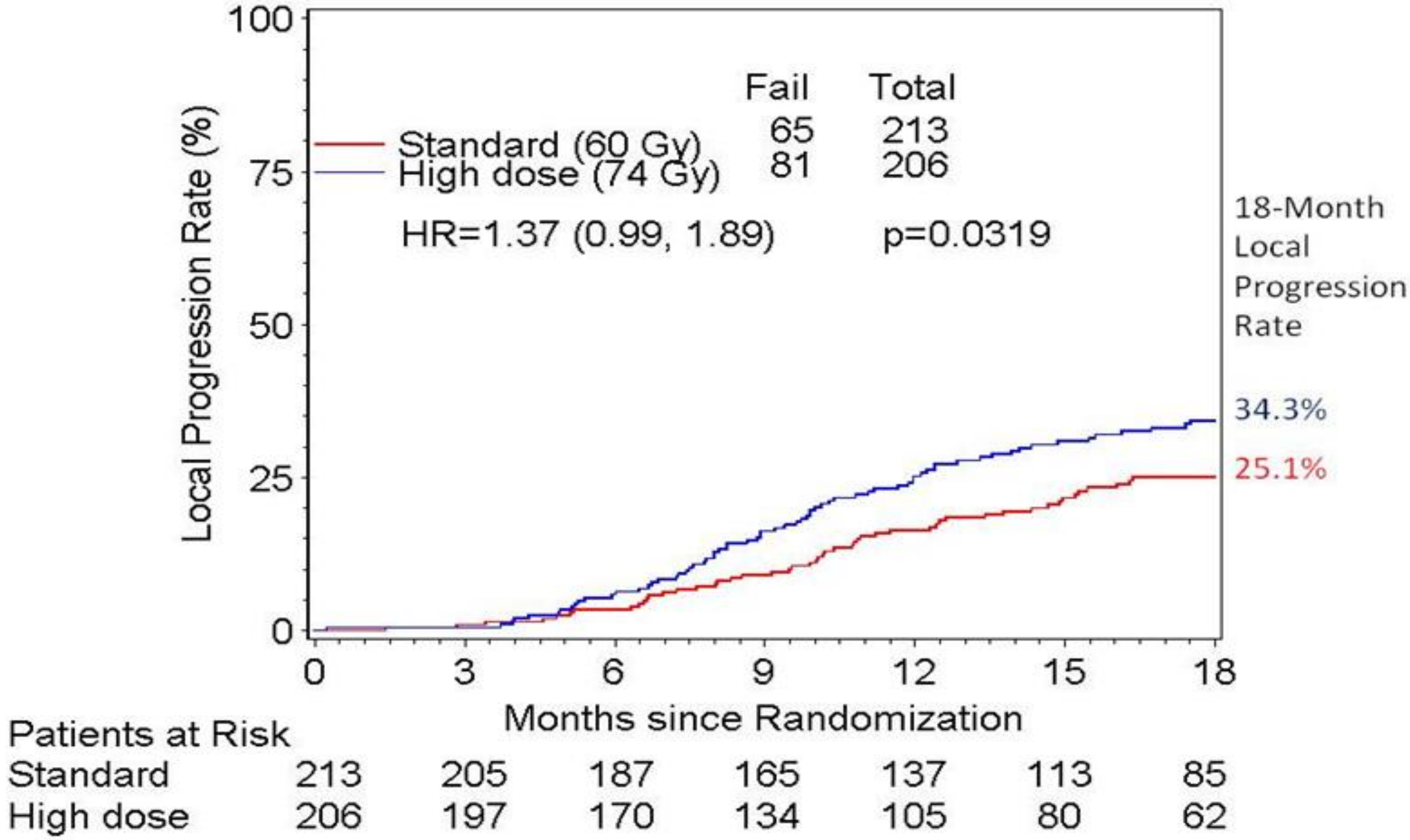
Bradley et al Lancet Oncology 2015

RTOG 0617
Survival by RT dose



Patients at Risk							
Standard	213	207	190	177	161	141	108
High dose	206	197	178	159	135	112	87

RTOG 0617
Local failure and RT dose



RTOG 0617
Multivariate Cox Model

Covariate	**Comparison (*RL*)**	**HR (95% CI)**	**p-value**
Radiation dose	***60 Gy* v 74 Gy**	**1.51 (1.12, 2.04)**	**0.007**
Histology	*Non-squam* v Squam	1.31 (0.99, 1.75)	0.061
Max esophagitis grade	*<3* vs ≥3	1.52 (1.06, 2.20)	0.024
Heart Contour	*Per Protocol* vs. Not per protocol	0.67 (0.47, 0.96)	0.029
GTV	Continuous	1.001 (1.000, 1.002)	0.038
Heart V50(%)	**Continuous**	**1.017 (1.004, 1.030)**	**0.008**

Backwards Selection: Exit criteria p>0.10
Two-sided p-values
Removed from model: Age (continuous), overall RT review (per protocol vs. not per protocol), and lung V5 (continuous)

Dose escalation using hypofractionation (CCRT)

Study	Dose	Fraction	Dose/fx	Acute BED	Late BED	3 Year OS (%)	1 Year OS (%)	AE (%)	AP (%)	LE (%)	LP (%)
Machtay (2005)[21]	60	20	3	78.0	120.0			0	0	0	25
Belderbos (2007)[22]	66	24	2.75	84.2	126.5	29	56	17	9	5	18
Uitterhoeve (2007)[23]	66	24	2.75	84.2	126.5	31	57	NR	NR	5[a]	18[a]
Tsoutsou (2008)[24]	52.5	15	3.5	70.9	113.8		28	0	0	NR	NR
Bral (2010)[25]	67.2	30	2.24	82.3	117.4			NR	NR	NR	NR
Matsuura (2009)[26]	65	26	2.5	81.3	119.2	44	90	0	0	0	0
Casas (2011)[27]	61.6	23	2.68	78.2	116.7	34	59	6.	3	0	0
Carruthers (2011)[28]	55	20	2.75	70.1	105.4			13	3	NR	NR
Maguire (2012)[17]	55	20	2.75	70.1	105.4	38	73	NR	NR	NR	NR
Lin (2013)[29]	69	22-24	3	85.8	132.0			15	8	NR	NR
Liu (2013)[30]	75	25	3	78.0	120.0		61	15	8	8	0
Chen (2013)[31]	55	20	2.75	70.1	105.4		69	22	NR	11	NR
Donato (2013)[32]	68.4	30	2.28	82.7	118.1		77[a]	7	10[a]	0[a]	5[a]
van Den Heuvel (2013)[33]	66	24	2.75	84.2	126.5		80	NR	NR	NR	NR
Bearz (2013)[34]	60	25	2.4	74.4	108.0	24	80	3	0	0	0

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1. Kaster TS et al: Clin Lung Cancer, 2015

Dose escalation using hypofractionation

- **Prolonged overall treatment time proven disappointing**
  → accelerated repopulation[1]

- **Dose escalation using hypofractionation:**
  – EORTC phase I/II study 08912[2]:
    50 Gy/20 fx → 66 Gy /24 fx with daily cDDP was feasible

  – EORTC phase III 08972-22973[3]: concurrent vs sequential;
    66 Gy /24 fx with daily cDDP
    2-year OS 39% (concurrent) and 34% (sequential)

  – Dutch Raditux trial phase II[4]
    66 Gy /24 fx with daily cDDP, +/- Cetuximab

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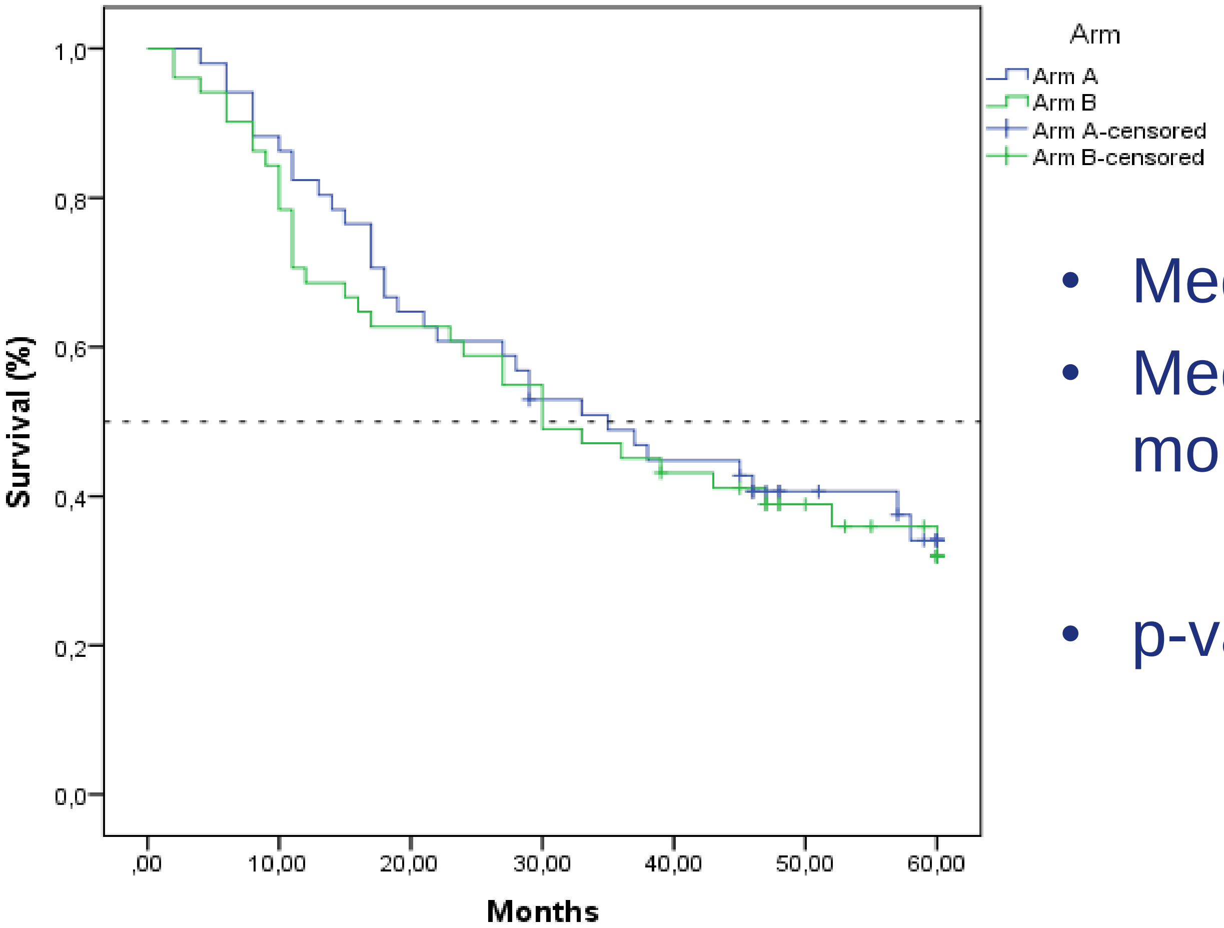
1. Bese NS et al: IJROBP 2007
2. Uitterhoeve LLJ et al: Eur J Cancer, 2000
3. Belderbos JSA et al: Eur J Cancer 2007
4. Walraven I et al:R&O 2016

Long-term FU of NSCLC pts receiving concurrent hypofractionated CCRT +/-cetuximab



- Median FU 60 months
- Median OS= 33 and 30 months
- p-value 0.722

Walraven et al., Radiother Oncol, Feb 2016

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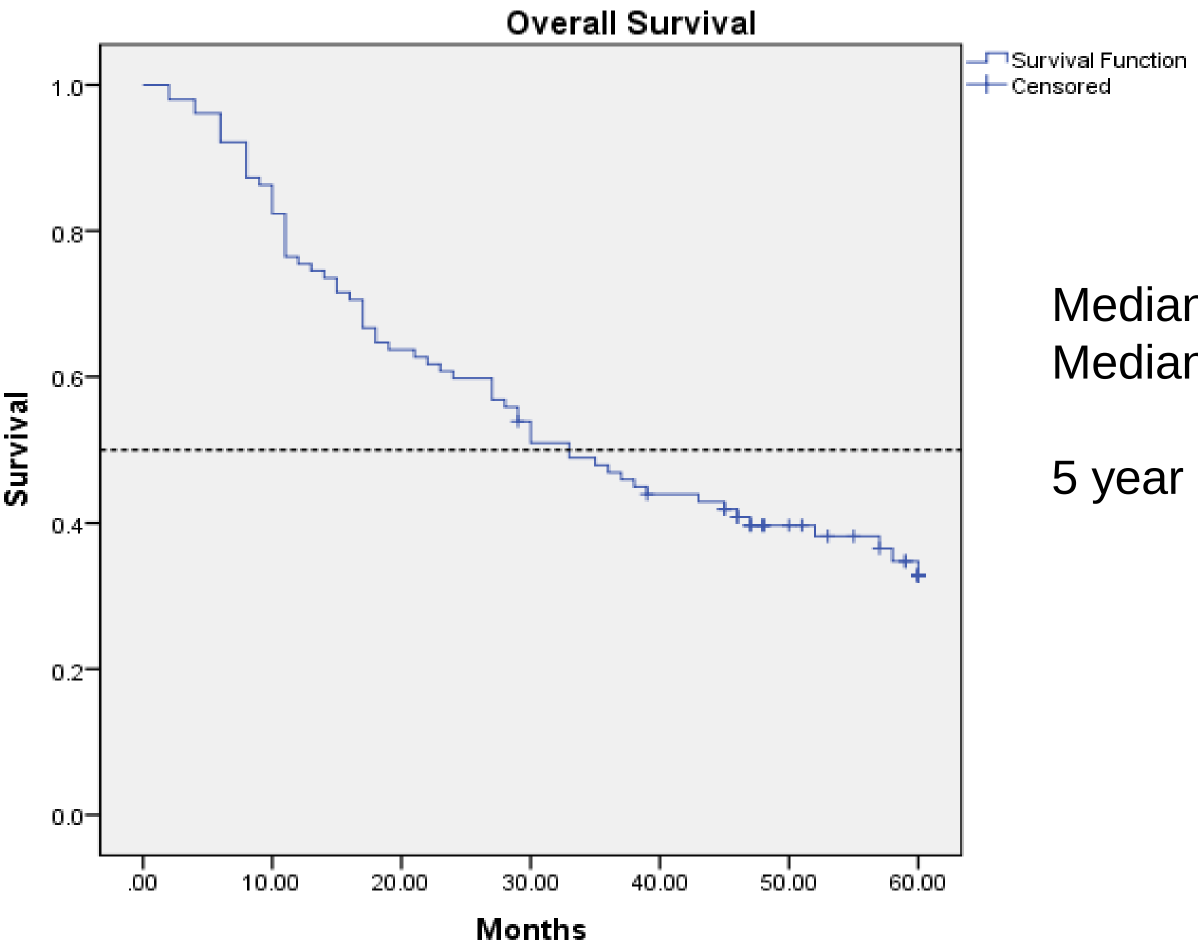
Raditux trial phase II n=102



Median FU 60 months
Median OS= 32 months

5 year OS 37%

Walraven et al., Radiother Oncol, Feb 2016

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Overall survival Raditux vs RTOG 0617

	Raditux trial	RTOG 0617 60 Gy	RTOG 0617 74 Gy
Mortality	64%*	58%[a]	67%[a]
1-year OS (%)	75%	78%	69%
2-year OS (%)	60%	53%	42%
5-year OS (%)	37%	-	-
Median OS (months)	32 months	29 months	20 months

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*based on 5-years of follow-up
[a]based on 2-years of follow-up

Baseline characteristics Raditux vs RTOG 0617

	Raditux trial 66 Gy	RTOG 0617 60 Gy	RTOG 0617 74 Gy
Age	62 years	64 years	64 years
Stage II	8%	-	-
Stage IIIA	52%	66%	63%
Stage IIIB	40%	34%	37%
GTV	119 cc	93 cc	110 cc
PTV	499 cc	481 cc	478 cc
PET staged	92%	90%	90%

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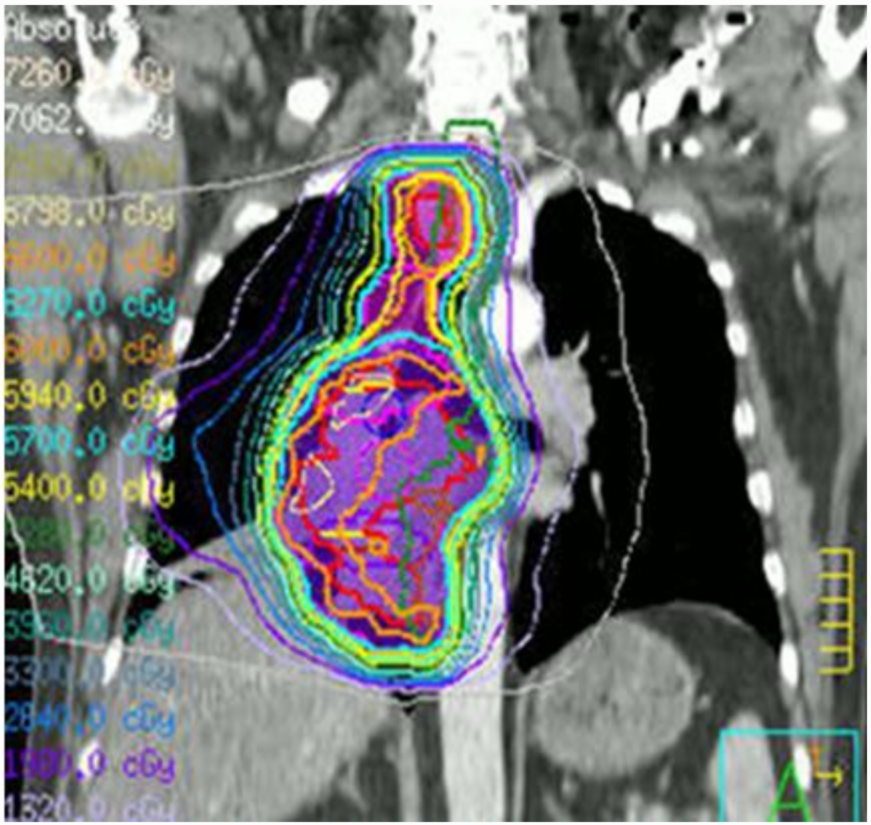
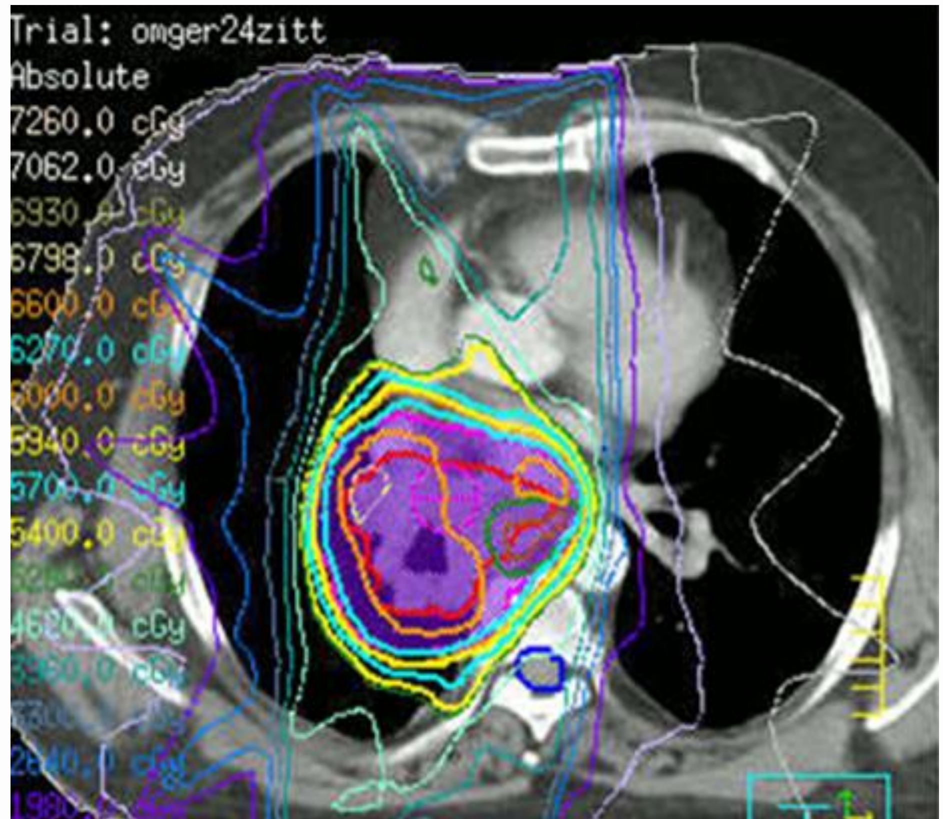
Treatment characteristics Raditux vs RTOG 0617

	Raditux trial 66 Gy	RTOG 0617 60 Gy	RTOG 0617 74 Gy
RT OTT **Total treatment duration**	32 32	40 82	51 93
IMRT	76%	46%	47%
EQD2T (time corrected equivalent RT dose)	59,6 Gy	49.7 Gy	58.8 Gy
Chemotherapy concurrent	cisplatin	paclitaxel and carboplatin	paclitaxel and carboplatin
Consolidation CT	_	paclitaxel and carboplatin	paclitaxel and carboplatin
Protocol adherence	86%	83%	74%
Low-volume centers (< 4 pts per year)	_	2/3	2/3

Improve accuracy: Intensity Modulated RT
Reduce Heart dose





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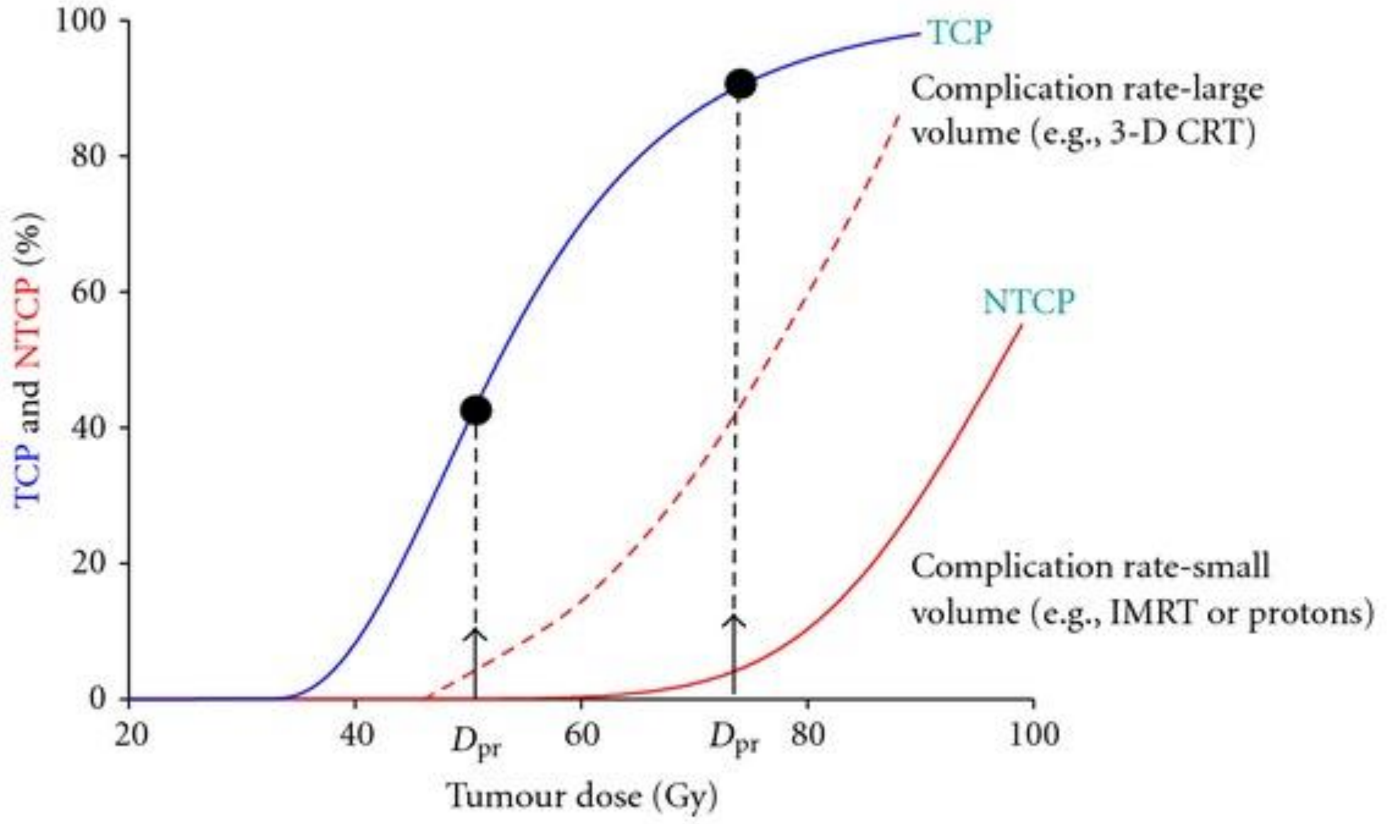
Radiobiological Optimization of External-Beam RT



Nahum AE.
Comput Math Methods Med. 2012

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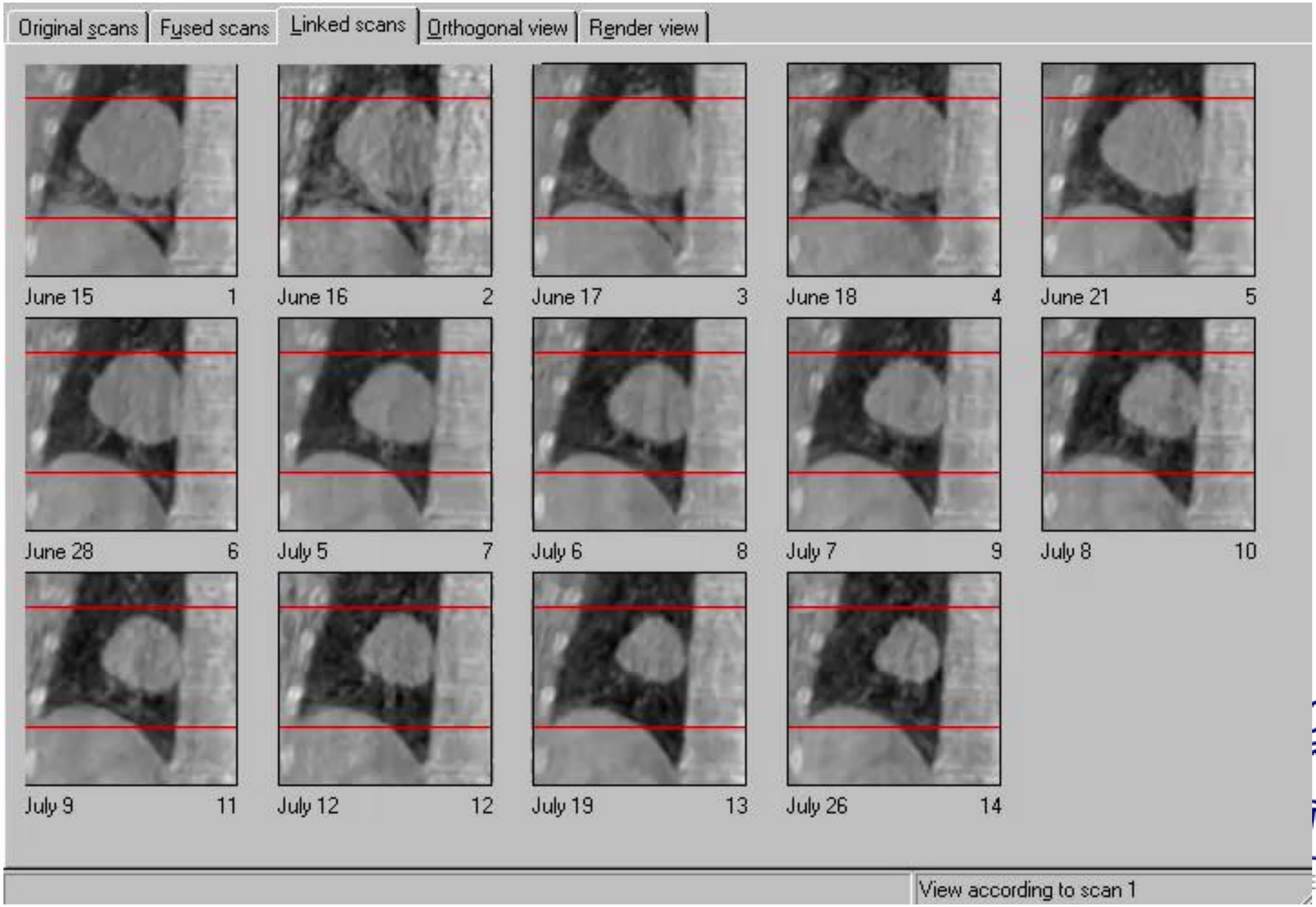
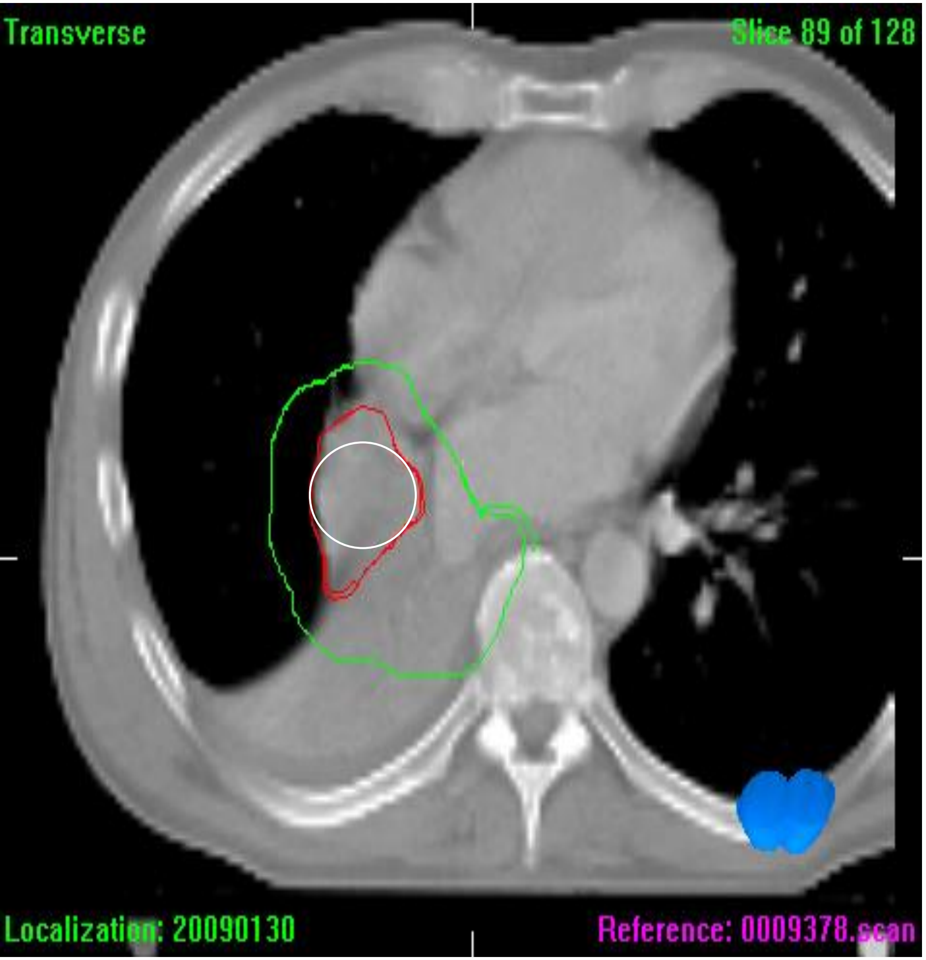
Improve accuracy:
Image-guided RT: Linear accelerator with Cone beam CT

Repeat 4D Cone Beam CT: Tumor regression during RT



Shows respiration, tumor shrinkage and baseline position variation

Image-guided adaptive RT Using Cone-Beam CT
e.g. dissolving of atelectases



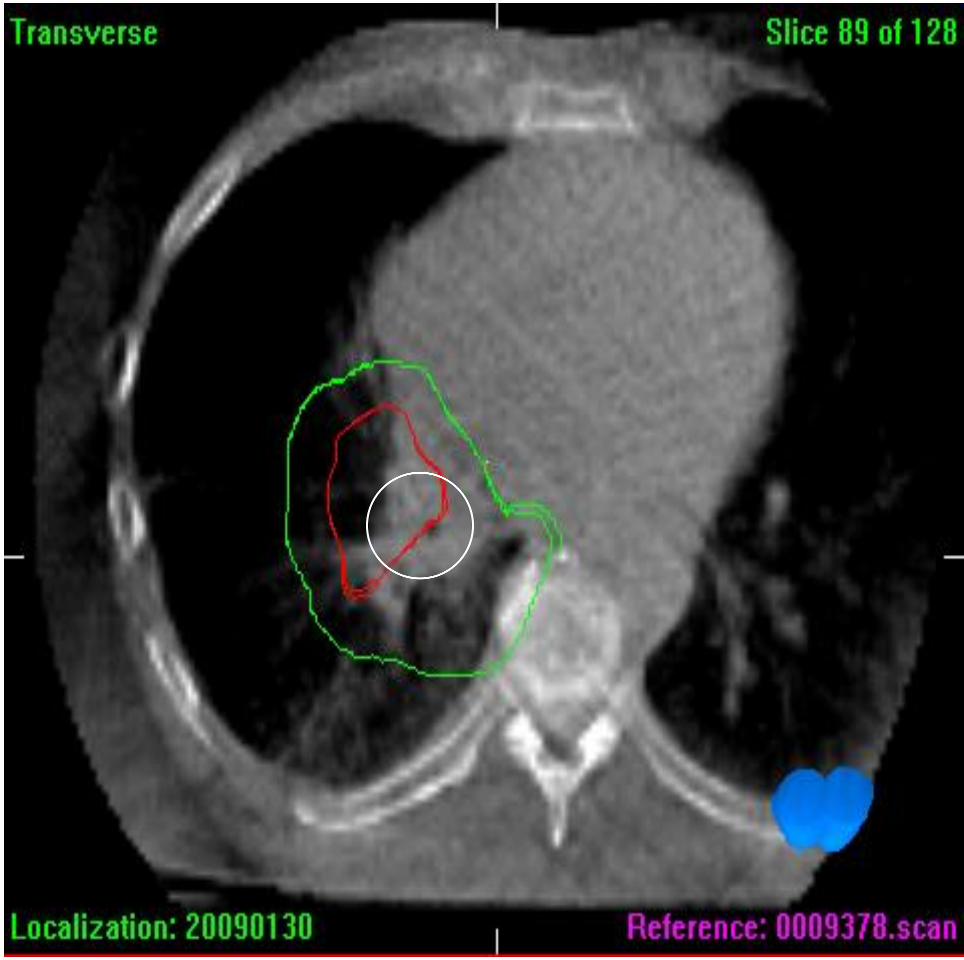


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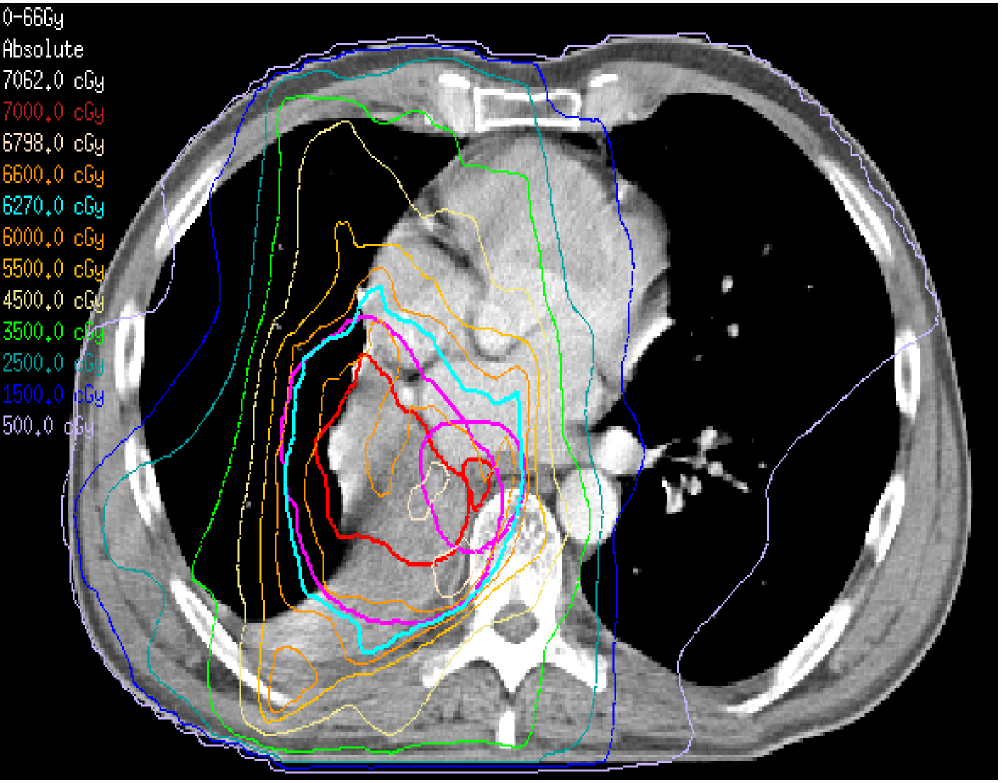
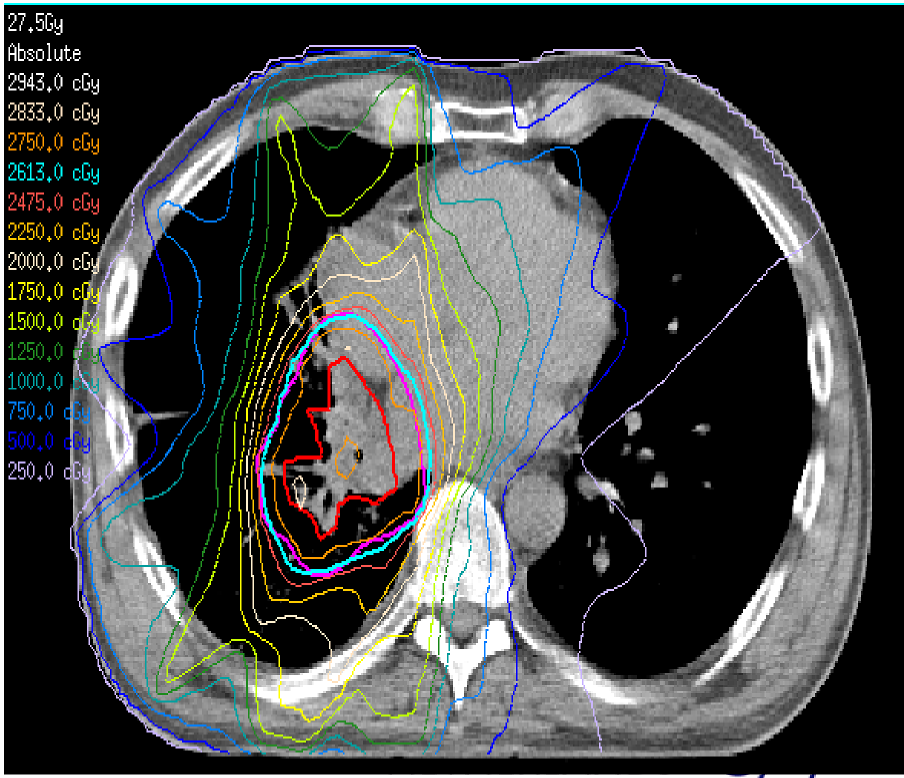
Image-guided adaptive RT:
Dose distribution before and after replanning





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Current-Future developments

Combining high precision RT with targeted agents in a preclinical setting

Novel PET tracers (proliferation-hypoxia)

Evolving role of Radio-immunotherapy

Possibillities to predict RT respons in serum

Protontherapy/Heavy Ions

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Image-guided radiotherapy for small animals (µIGRT)

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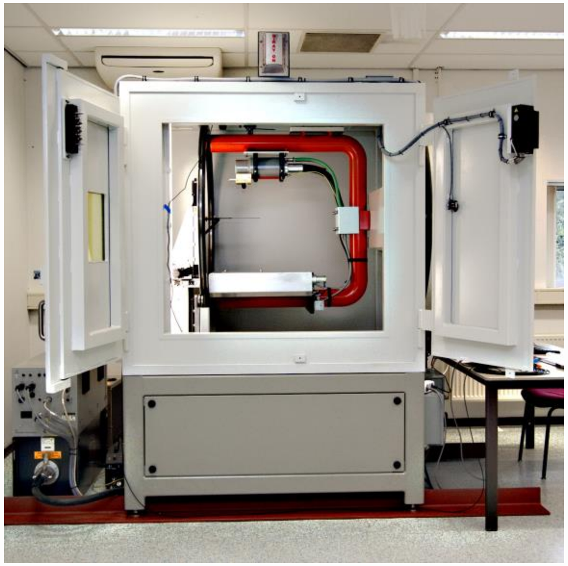
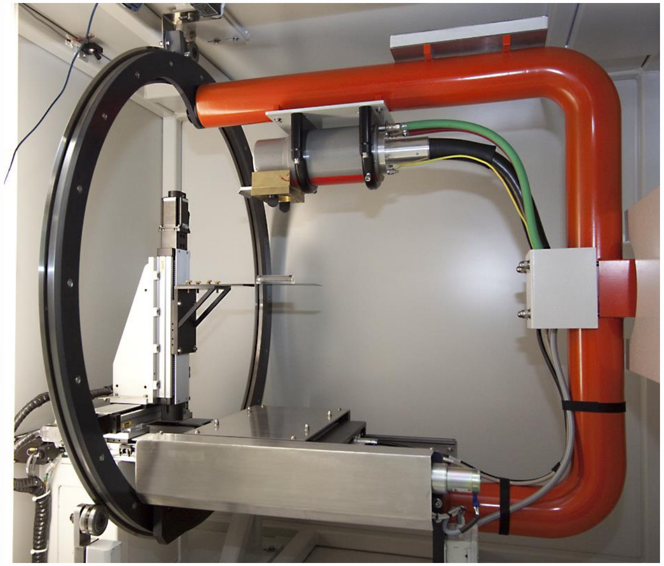
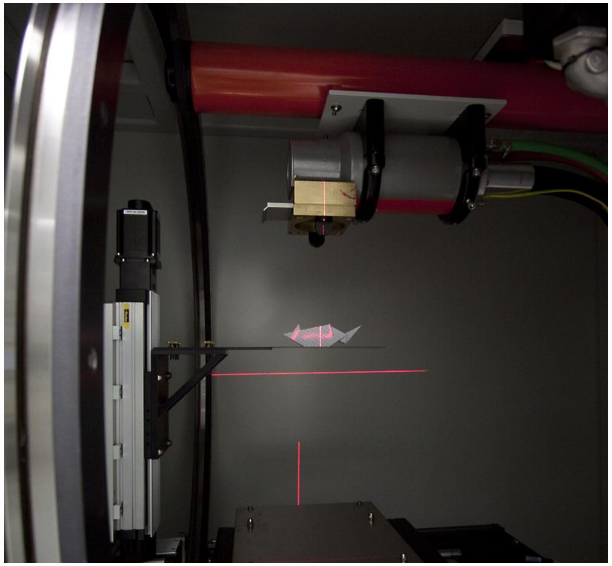
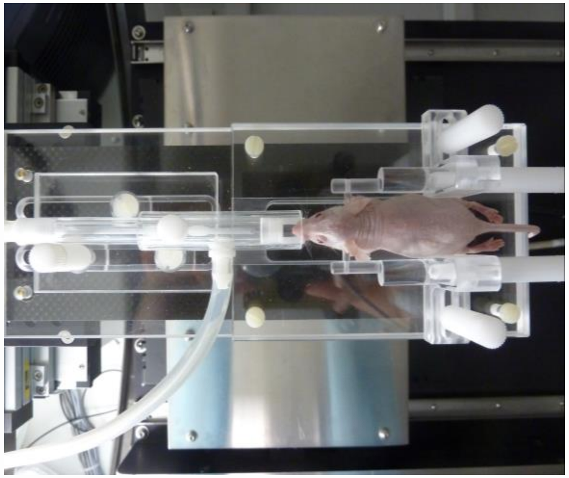
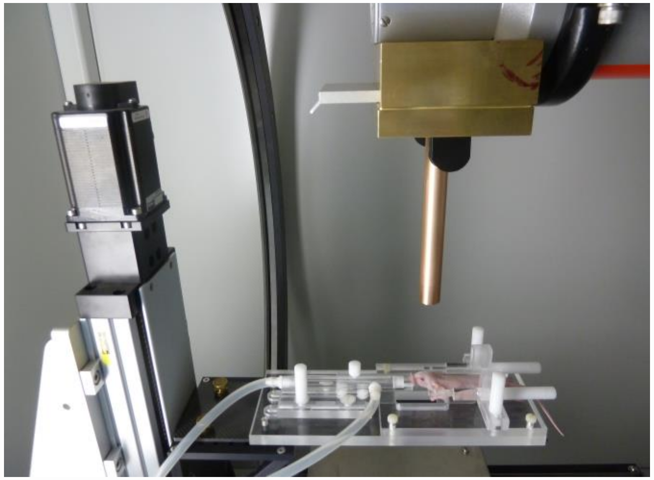
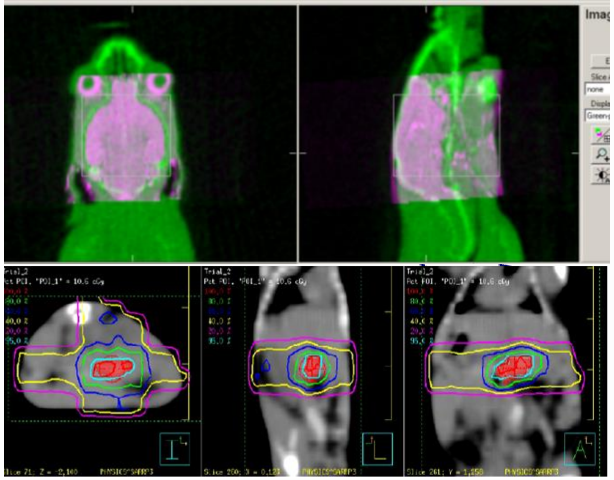
Image-guided radiotherapy for small animals (µIGRT)

- mimicking clinical RT protocols -

Radio-Immunotherapy

- RT complements the effects of Immunotherapy
- RT can sensitize unresponsive tumors to
  anti CTLA-4
- Antitumor responses of RT and blocking of PD1 or PD-L1

NKI Trials RT + immuntherapy NSCLC

- *RT + Selectikine (NHS-IL2LT) Phase Ib* **Completed***
- *SABR+ Pembrolizumab vs. Pembrolizumab Phase I-II* **Recruiting**

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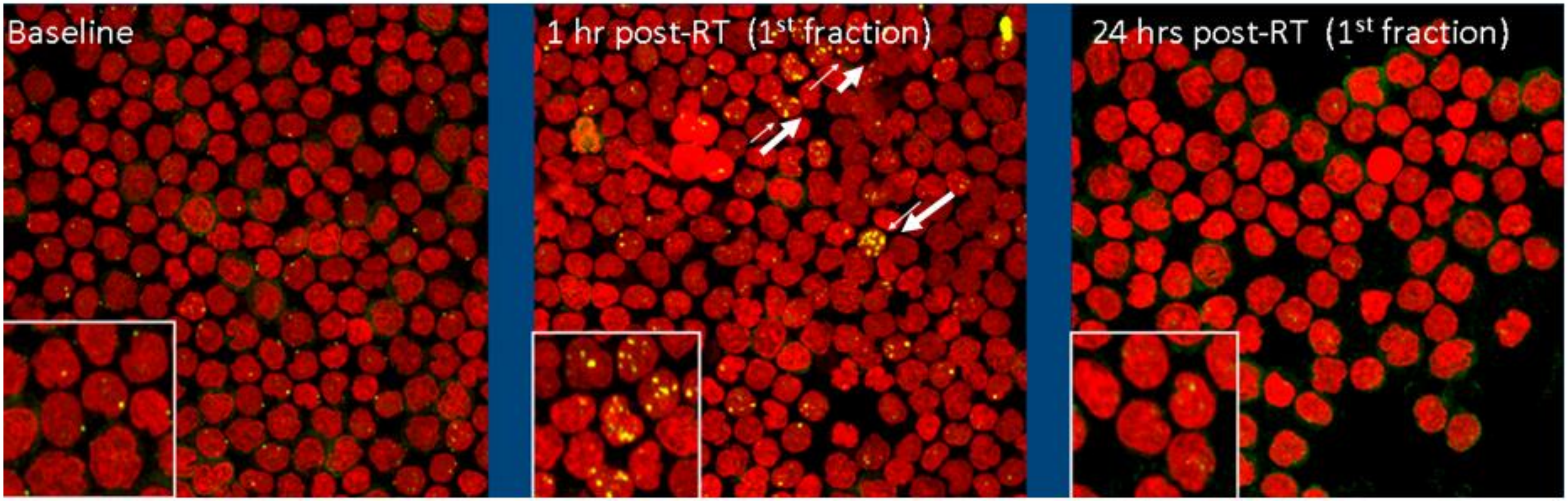
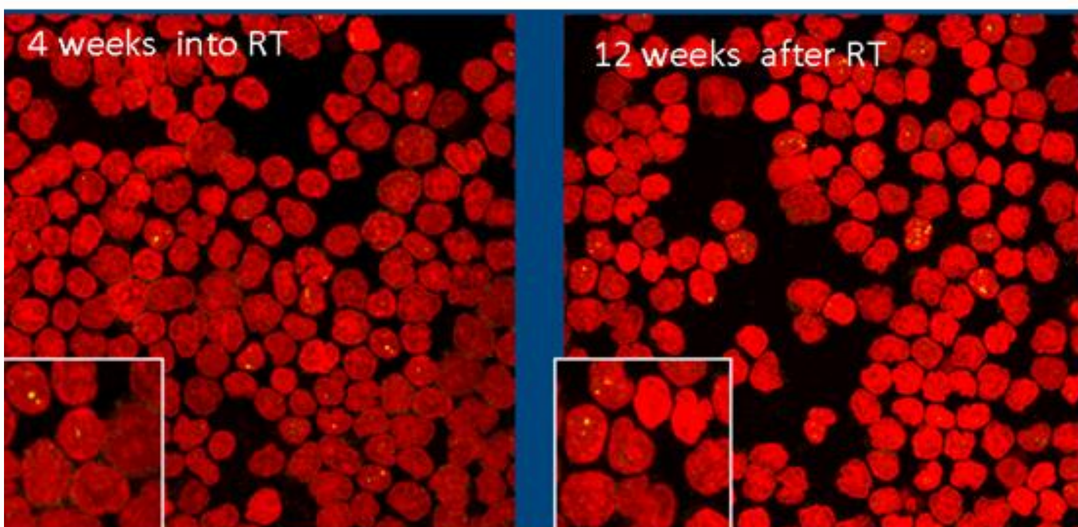
*Van den Heuvel M J Transl Med 2015

γ-H2AX assay *to detect DSB secondary to ionising radiation*





- Increased signal shortly after RT, lymphocytes with multiple foci
- Back to baseline levels at 24-hours and beyond

Courtesy of Shankar Siva

Take home messages

- The optimum dose and fractionation for NSCLC remains uncertain.
- The RT dose-response relationship remains a sound basis for further randomized studies making use of Image-guided adaptive RT
- Dose escalation: avoid long overall treatment time:

  hypofractionation or hyperfractionation
- Use of high precision RT: more personalized prescription

Meet NKI RT team ……