Locally Advanced NSCLC-Radiation Therapy

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DISCLOSURES

Commercial Interest	Relationship(s)
Bristol Myers Squibb	PI – clinical trial
Merck	PI – clinical trial
BioMimetix	PI – clinical trial
Genentech	PI – clinical trial

Local Tumor Control from Selected Modern Trials

Table 1. Radiation Pneumonitis and Local Tumor Control After Concurrent Chemoradiation From a Few Selected Recent Trials

Study	Radiation Technology	Grade ≥ 3 Radiation Pneumonitis, %	2-Year Tumor Control, %
Liao et al[1]	PSPT arm: 3D, 66 or 74 Gy	11	65-66†
	IMRT arm: 66 Gy or 74 Gy	7	69-70†
RTOG 617[11]	74-Gy arm: 3D-CRT/IMRT	7	61
	60-Gy arm: 3D-CRT/IMRT	4	69
PROCLAIM[12]	Pemetrexed + cisplatin arm: RT* 60-66 Gy	< 3	63
	Etopside + cisplatin arm: RT* 60-66 Gy	< 3	54
UMCC2007123[13]	PET-guided ART; 3D-CRT; median dose, 83 Gy	7	82

Kong, JCO, 2018

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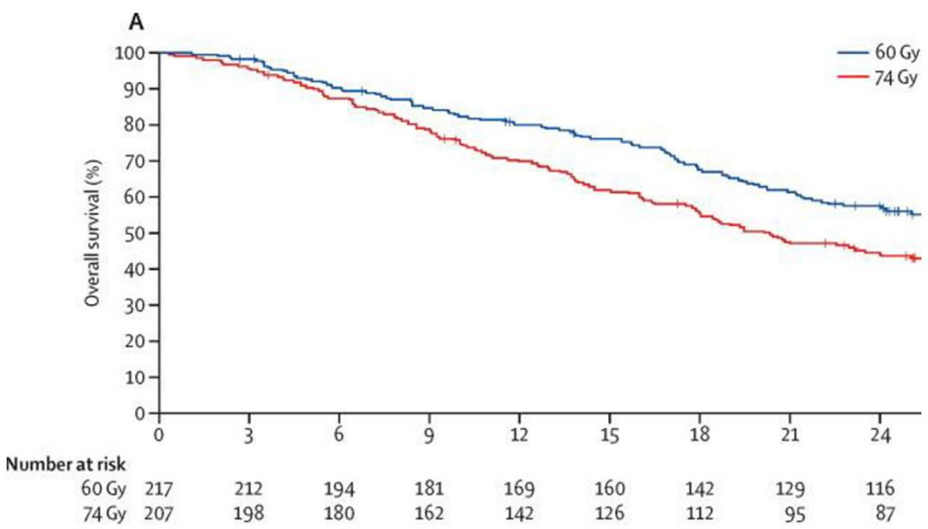
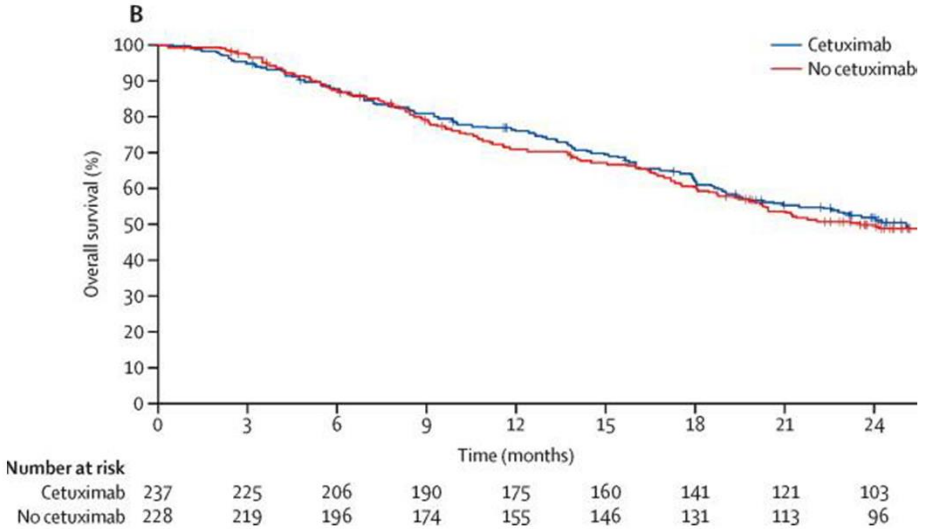
RTOG 0617: 74 Gy vs 60 Gy for NSCLC

- 74 Gy was not superior to 60 Gy
- Addition of cetuximab was not superior to chemoradiation alone

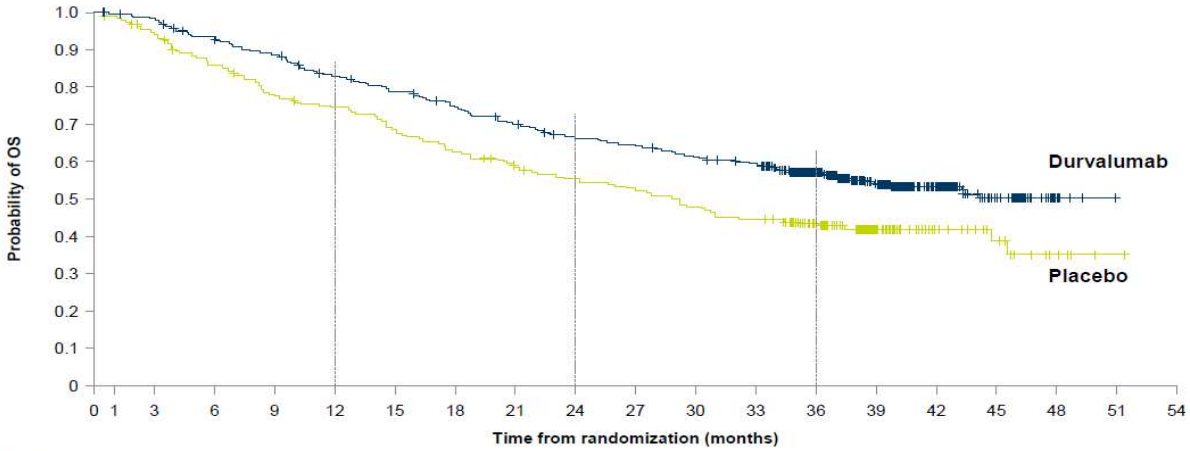




PACIFIC trial: advent of immunotherapy

	No. of events/ total no. of patients (%)	Median OS (95% CI) months	12-month OS rate (95% CI) %	24-month OS rate (95% CI) %	36-month OS rate (95% CI) %
Durvalumab	210/476 (44.1)	NR (38.4–NR)	83.1 (79.4–86.2)	66.3 (61.8–70.4)	57.0 (52.3–61.4)
Placebo	134/237 (56.5)	29.1 (22.1–35.1)	74.6 (68.5–79.7)	55.3 (48.6–61.4)	43.5 (37.0–49.9)

Stratified hazard ratio for death, 0.69 (95% CI, 0.55–0.86)
Stratified hazard ratio for death from the primary analysis,[9] 0.68 (95% CI, 0.53–0.87)



No. at risk																			
Durvalumab	476	464	431	415	385	364	343	319	298	289	274	263	205	132	73	33	7	0	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	79	49	25	13	5	1	0

- Median duration of follow-up was 33.3 mos
- 48.2% of patients have died as of 1/31/19
- 44.1% on Durva arm vs. 56.5% on placebo arm

Does radiation dose escalation matter in the wake of PACIFIC?

- At median followup of 25.2 months, intrathoracic progression occurred in 37% of patients in durvalumab arm and 48% of those in placebo arm

- But toxicity is more concerning in patients receiving duvalumab – increased risks of pneumonitis and patients have less reserve to tolerate subtle or overt cardiac toxicity

- Needs for more novel forms of dose escalation
- More targeted – give the dose to specific high risk subvolumes
- More personalized – give the dose to those who can tolerate it better

Why FDG-PET?

- ^{18}F-FDG uptake correlates with tumor grade, stage, cell proliferation, response to therapy, and prognosis
- Areas of high ^{18}F-FDG uptake on pretreatment scans → sites of tumor relapse in patients with non-small cell lung cancer
- Ability to identify highly metabolically active subvolumes within gross tumor masses
- Prospective phase II and III studies demonstrated ability to dose escalate with FDG-PET within organ tolerances

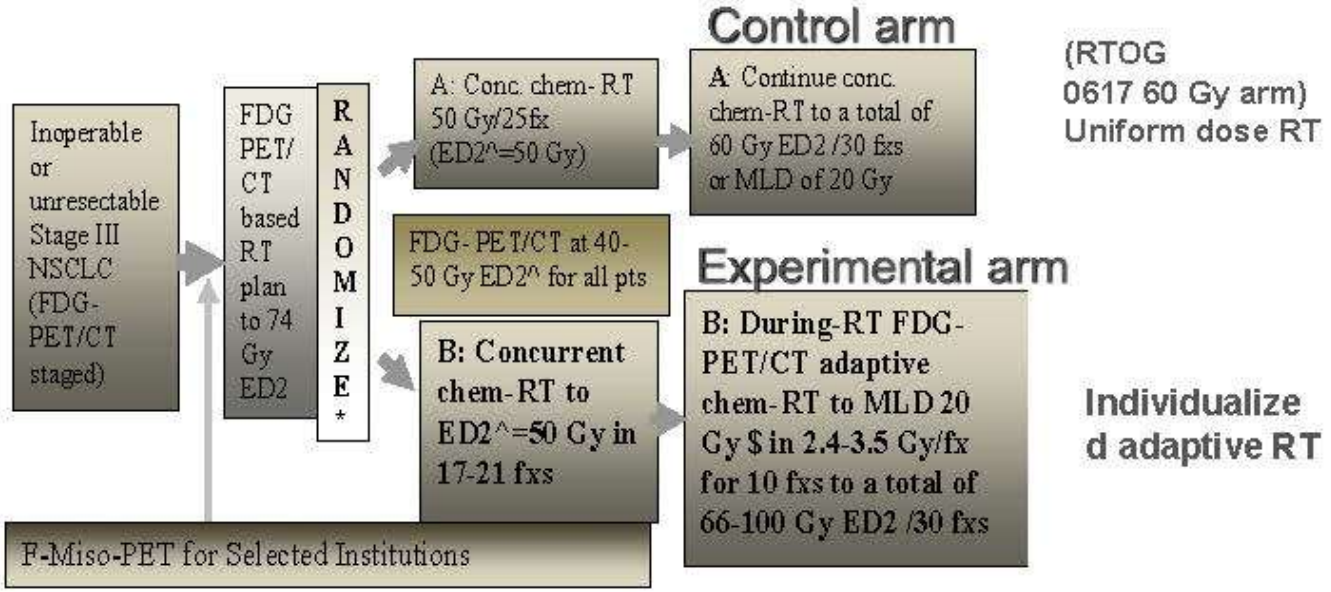
Mankoff, JAMA Oncol, 2017; Aerts, Lung Cancer, 2012; Calais, J Nuc Med, 2015; van Elmpt, Radiother Oncol 2012; Wanet Strahlenther Onkol 2017; Moller, Radiother Oncol 2017

Results of RTOG 1106/ACRIN-6697: A Randomized Phase II Trial of Individualized Adaptive Radiotherapy Using Mid-Treatment FDG-PET/CT and Modern Technology in Locally Advanced Non-Small Cell Lung Cancer (NSCLC)

Feng-Ming (Spring) Kong, MD, PhD, FACR, FAAWR, FASTRO

World Lung Cancer Congress 2020
January 28, 2021

RTOG1106 Study Schema



*Randomization: 1:2 for control and experimental arms, stratified by GTV (200 cc) and MLD (14 Gy)

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Study Statistical Considerations

- **The Primary Endpoint**: 2 year local-regional control rate based on *central review*
  - The trial did not define infield tumor control or overall control
- **Secondary endpoints**:
  - Tumor volume reduction, adaptive RT dose escalation & RT plan compliances
  - Local regional progression free survival
  - Overall survival and treatment toxicity
- **Sample size and powers**: 132 total, 44 vs 88
  According to preliminary data from U of Michigan, 1 Gy dose escalation ~20% improvement can be achieved from 20 Gy Adaptive RT dose escalation. The study was designed for 85% power.

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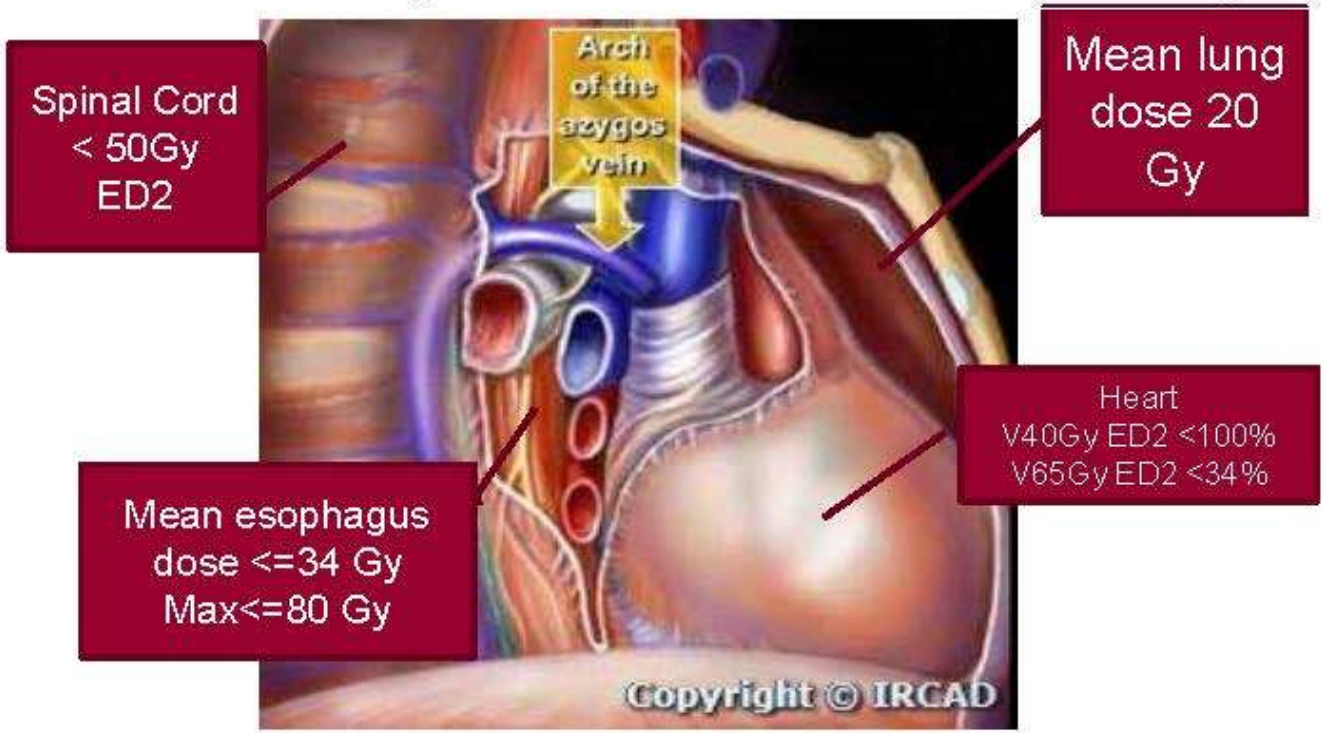
OAR Limits (Similar to RTOG617)



- Lower prescription dose and greater dose heterogeneity were allowed to reach the dose limits of OARs.

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Results-1: Patients and Doses

- A total of 138 patients enrolled between February 22, 2012 and March 8, 2017
- Minimum follow-up 3.6 years
- Patient characteristics were balanced between two arms
- 7/84 patients did not receive protocol RT in ART arm (5 no RT, 2 no ART)
- Adaptive RT dose escalation was 11 Gy

Radiation Therapy Delivery Summary

	Standard RT (n=43)	Adaptive RT (n=84)
Received RT		
No	1 (2.3%)	5 (6.0%)
Yes	42 (97.7%)	79 (94.0%)
Reason for no RT	(n=1)	(n=5)
Patient withdrawal prior to beginning protocol treatment	1 (100.0%)	3 (60.0%)
Adverse events	0 (0.0%)	1 (20.0%)
Other (Plan could not be made to meet protocol requirements)	0 (0.0%)	1 (20.0%)
Total dose (Gy)	(n=42)	(n=79)
Median	60	70.95
Min - Max	8 - 60	3.96 - 85.5
Q1 - Q3	60 - 60	67.8 - 76.08

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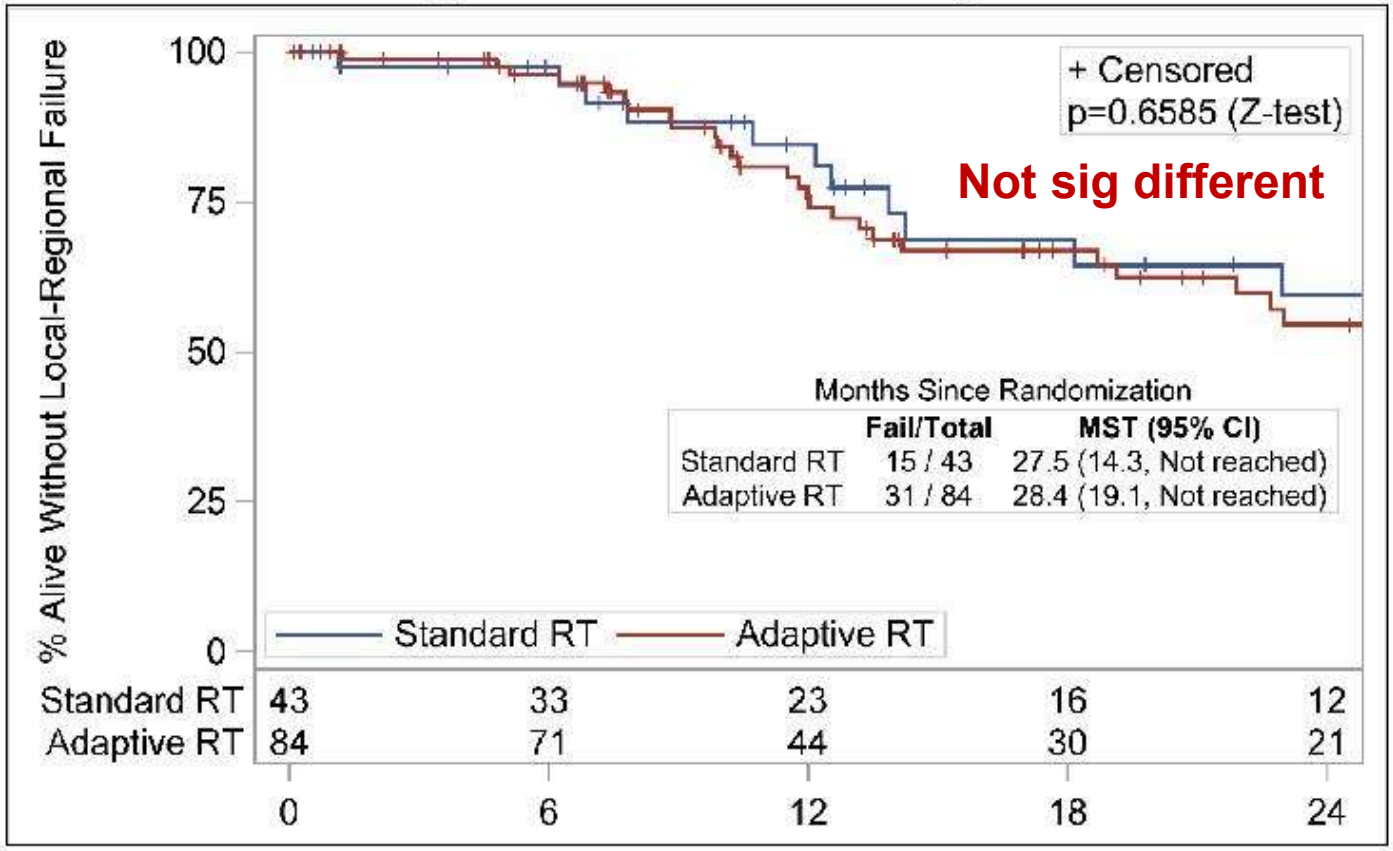
BigART →11 Gy of escalation, did not achieve study goal of 20 Gy

Results-5: Thoracic Adverse Events

	Standard RT (n=42)	Adaptive RT (n=80)
Any Grade 2+ Adverse Event	37 (88.1%)	78 (97.5%)
Grade 2+ Esophagitis	13 (31.0%)	34 (42.5%)
Grade 2+ Respiratory, Thoracic, and Mediastinal Disorders	19 (45.2%)	35 (43.8%)
Grade 2+ Cardiac Disorders	2 (4.8%)	4 (5.0%)

*Adverse events graded per CTCAE v4.0 criteria and reported as possibly, probably, or definitely related to treatment

Results-6: Local-Regional Control (Central Review)



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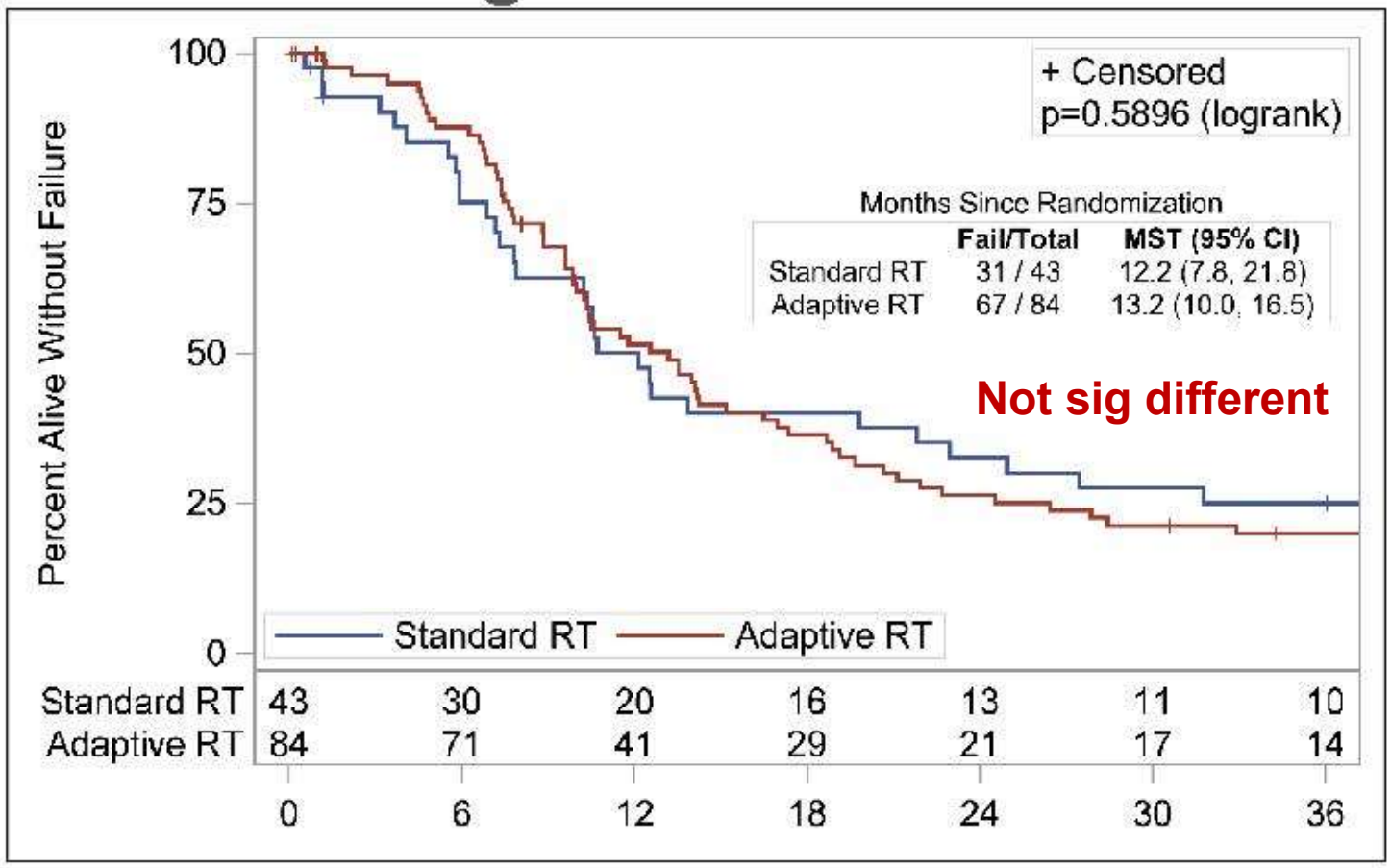
Failure based on central review of imaging

Results-10: Progression Free Survival



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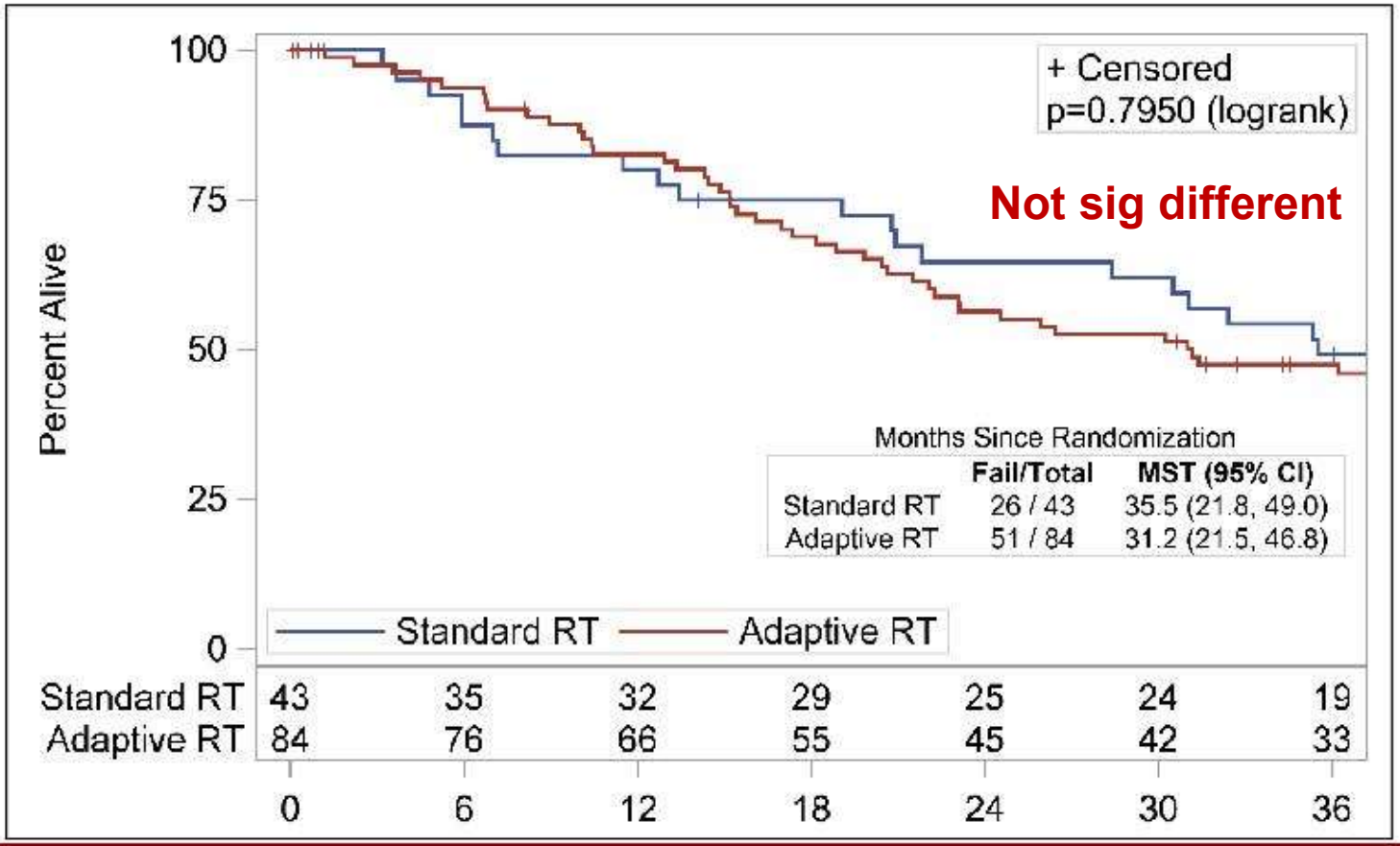
Results-11: Overall Survival



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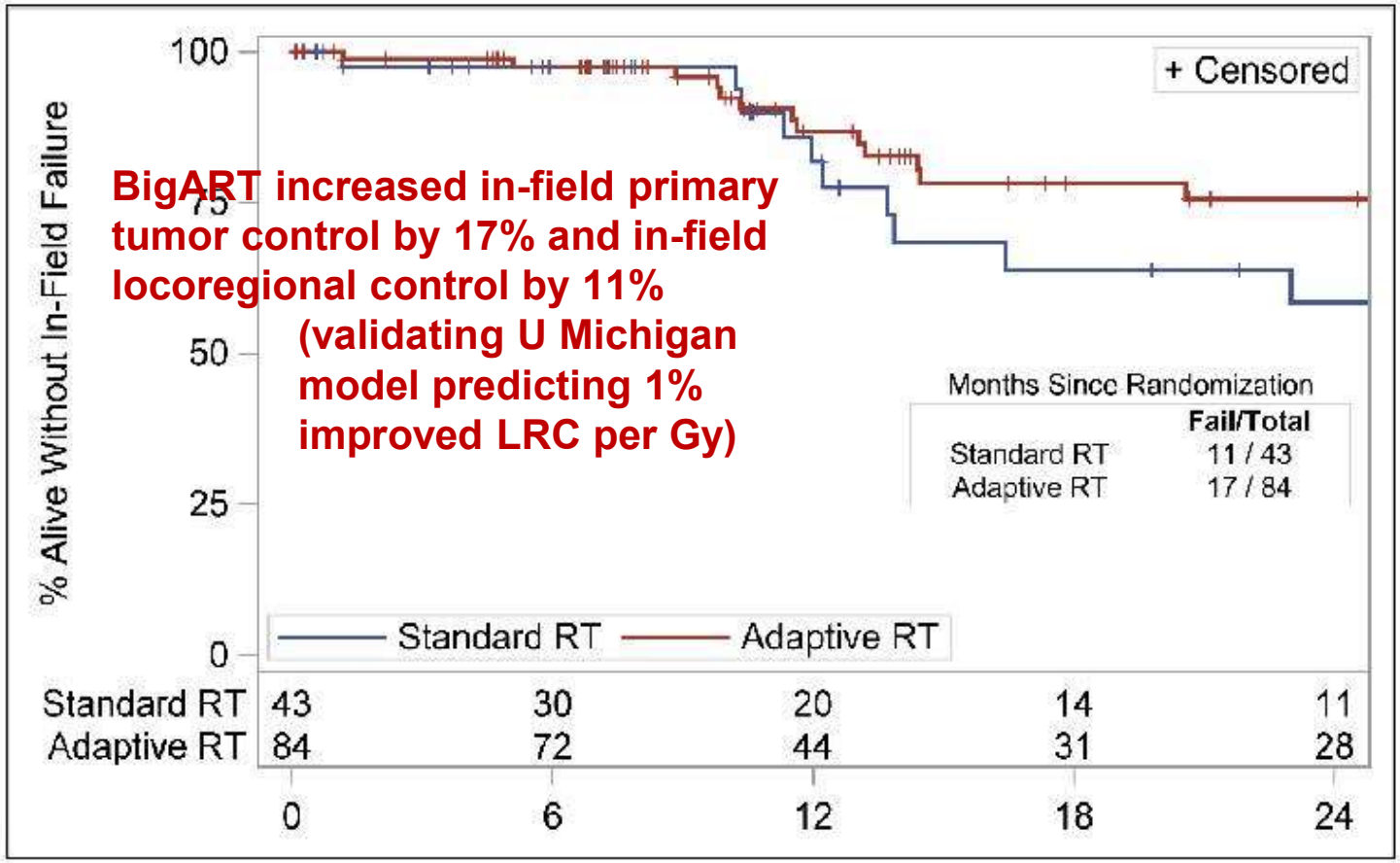
Results-9: In-field Local Tumor Control (Site Reported)



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Exploratory analysis

Local, regional and pulmonary failures in the randomised PET-Boost trial for NSCLC patients

S.A. Cooke
The Netherlands Cancer Institute - Antoni van Leeuwenhoek
Amsterdam, The Netherlands

D. de Ruysscher, B. Reymen, M. Lambrecht, G. Fredberg Persson, C. Faivre-Finn, E. Dieleman, J. van Diessen, K. Sikorska, F. Lalezari, J-J. Sonke, J. Belderbos.

NETHERLANDS CANCER INSTITUTE
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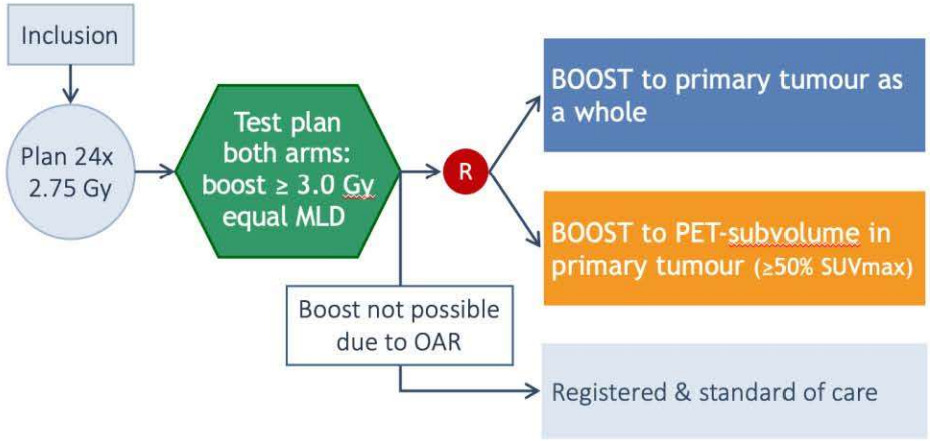
PET-Boost Study Design

Design — phase 2, randomised, international trial for stage II-III NSCLC patients

Goal — improve freedom from local failure (FFLF) rate at 1 year from 70% to 85%

Inclusion criteria
- Stage IB - III NSCLC
- Primary tumour ≥ 4 cm
- SUVmax ≥ 5.0
- WHO PS 0 - 2
- No tumour growth into large blood vessels or >50% encasement vessels

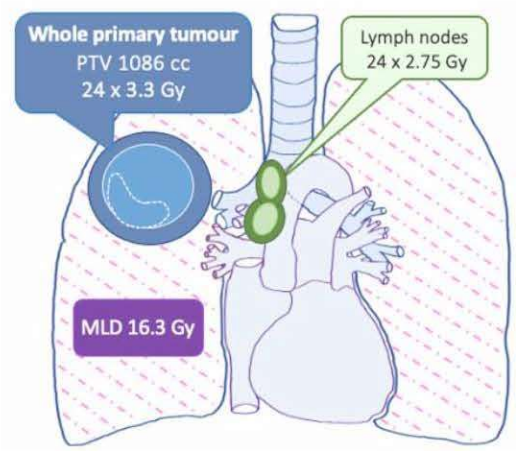


RT with concurrent, sequential or no chemotherapy.

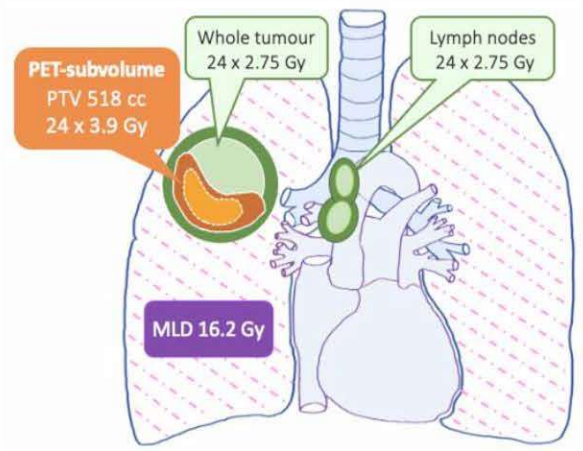
Subvolume defined as ≥50% SUVmax

Two isotoxic dose escalation treatment arms

Boost homogeneous to whole primary tumour



Boost PET-subvolume within primary tumour



Two plans for one example patient

Primary endpoint
- Freedom from local failure at 1 year by central review of CT-scans

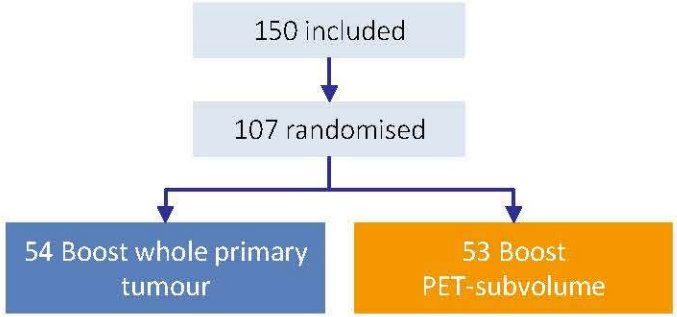
Secondary endpoints
- Overall survival
- Toxicity†
- Local and regional failures outside PTV
- Distant metastasis
- Quality of life

†*Van Diessen et al. Rad & Onc 2019*

Methods

Trial was open Apr 2010 to Sep 2017:

- 7 European institutes
- Due to slow accrual trial was closed after inclusion of 150 patients



Central review of follow-up CT-imaging by radiologist.

Site of *first* intrathoracic recurrence

- Local recurrence
- Regional recurrences: in-field or out-of-field
- New pulmonary lesions

Phase 2 trial design in which arms are not compared → no p-values reported.

Patient & Treatment Characteristics

	Boost whole primary tumour (n=54)	Boost PET-subvolume (n=53)
Male	69 %	58 %
Age median	66 yrs	69 yrs
WHO 0 – 1 WHO 2	91% 9 %	96 % 4 %
Stage II Stage IIIA Stage IIIB	9 % 56 % 35 %	15 % 62 % 23 %
Concurrent chemo Sequential None	76 % 7 % 17 %	68 % 11 % 21 %
Non-squamous Squamous	65 % 31 %	55 % 45 %

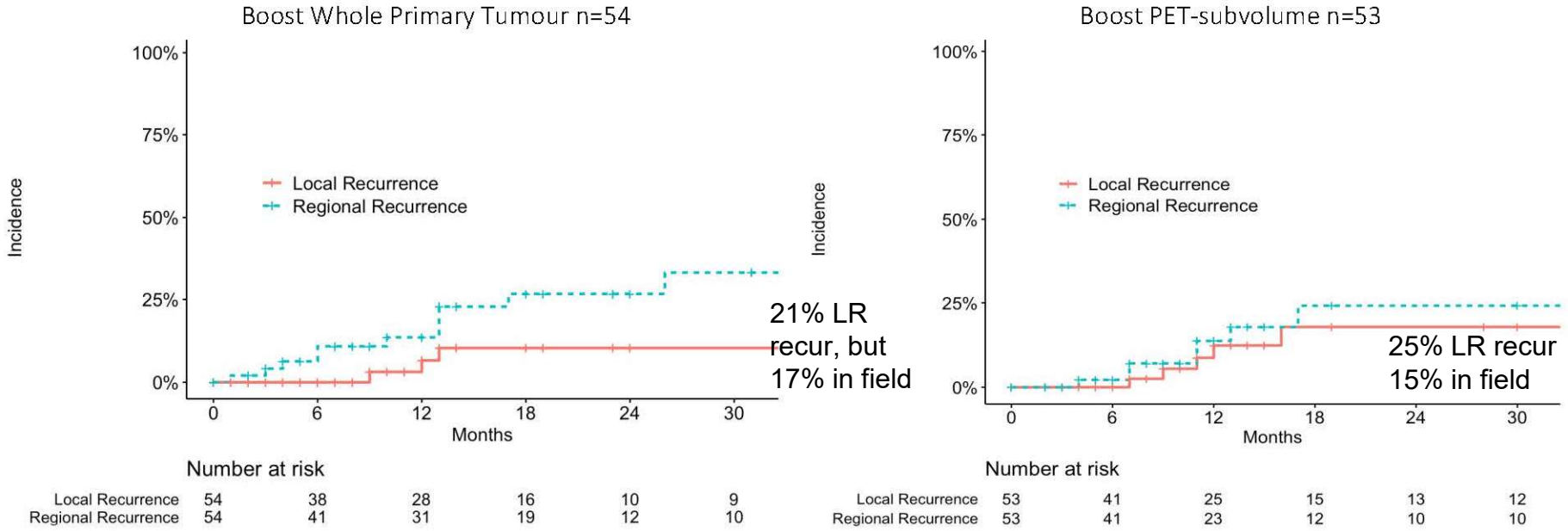
Planning Results

			Boost whole primary tumour (n=54)	Boost PET-subvolume (n=53)
GTV_{prim}	(cm^3)	median + IQR	100 (66 -178)	115 (61-180)
$GTV_{PET\text{-}subvolume}$	(cm^3)	median + IQR	n.a.	29 (14 - 52)
PTV_total	(cm^3)	median + IQR	499 (401-643)	497 (344 – 665)
Dose per fraction		median	3.3 Gy	3.5 Gy
Total physical dose		median	78 Gy	84 Gy
Mean Lung Dose (Gy)	EQD2 (α/β=3 Gy)	mean + SD	16.6 ± 2.8	15.6 ± 3.8
Heart Mean Dose (Gy) Heart Max Dose (Gy)	EQD2 (α/β=3 Gy) EQD2 (α/β=3 Gy)	median + IQR median + IQR	8 (3 – 18) 67 (53-75)	11 (2.4 – 17) 68 (38 – 73)
Oes V36 (Gy)		median + IQR	36 (27 – 47)	36 (19 – 47)

Very high doses were achieved to the primary tumor!

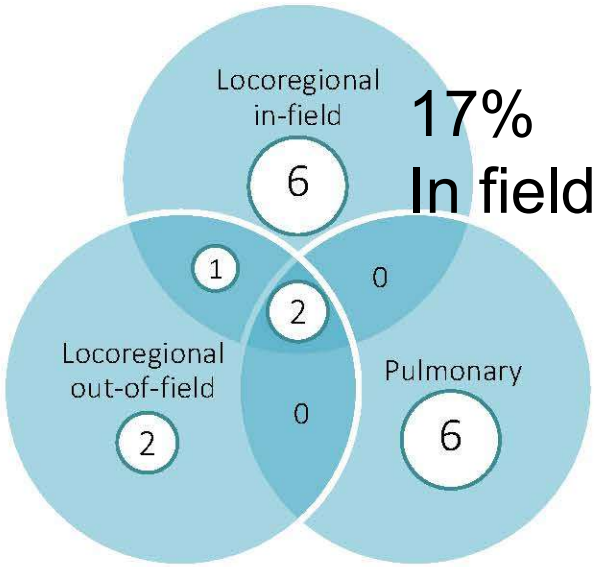
Local and Regional Recurrences

Median FU time 12.6 months



Site of First Intrathoracic Progression

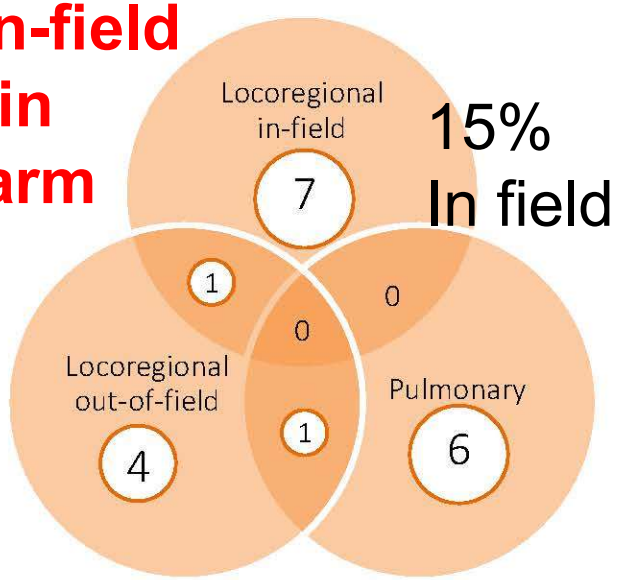
Boost Whole Primary Tumour n=54



21% LR recur rate overall

<20% in-field failure in either arm

Boost PET-subvolume n=53



25% LR recur rate overall

Higher the biological effective dose (BED) better the local-control

When BED 101-125Gy, projected tumor control of 70%-80%

Kong's Study (Abstract #3790)

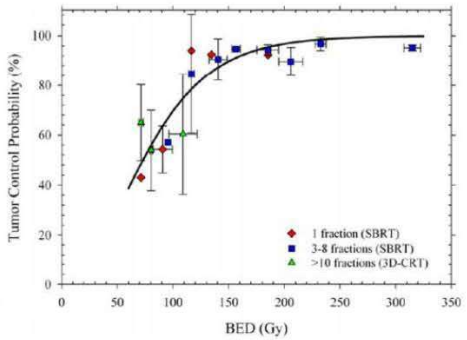
- Adaptive arm BED median (α/β=10) = **95.8Gy**

Cooke's study (Abstract # 2266)

- Boost PET-subvolume BED median (α/β=10) = **113.4 Gy**

BED–Gy	Projected tumor control: LQ
50-75 Gy	44%-58%
76-100 Gy	58%-70%
101-125 Gy	70%-80%
126-150 Gy	80%-88%
151-175 Gy	86%-92%
176-200 Gy	92%-95%
200-225 Gy	95%-97%
225-250 Gy	97%-98%
>250 Gy	≥ 98%

BED versus tumor control for linear quadratic (LQ) model

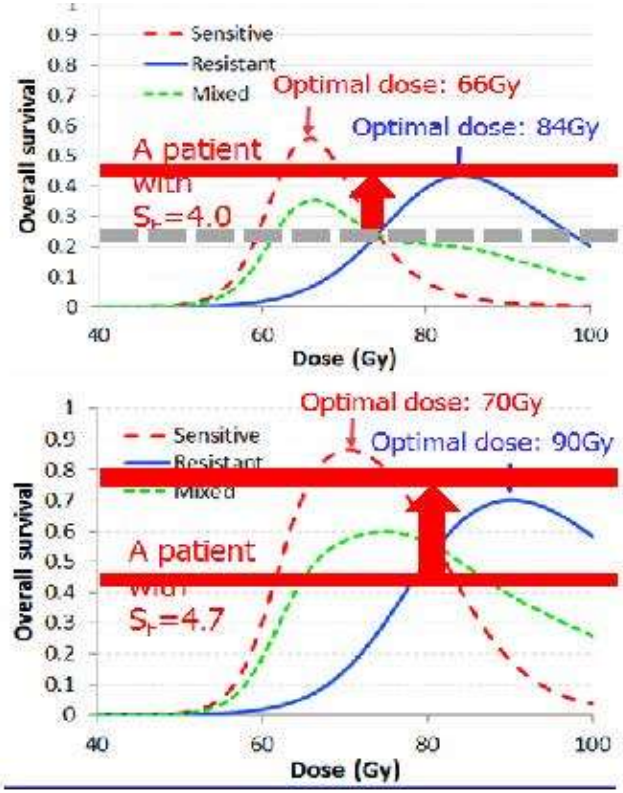


Tumor control probability (TCP) as a function of BED for stage I NSCLC

(for reference - SBRT 50 Gy in 5 fractions = BED 100 Gy)

Mehta N. Practical Radiat Oncol 2012
Brown. JM. Int J Radiat Oncol Biol Phys, 2013

Future directions: individualized radiosensitivity or other biologically based selection principles?



RTOG617 study revealed 2/3 patients had sensitive genotype, will not benefit from RT dose escalation. Dose optimization may improve survival. *~Kong et al ASTRO 2020*

ART can increase normal tissue sparing factor (Sp) to improve survival on top of dose optimization in each individual.

Prospective study on ART dose optimization is needed.

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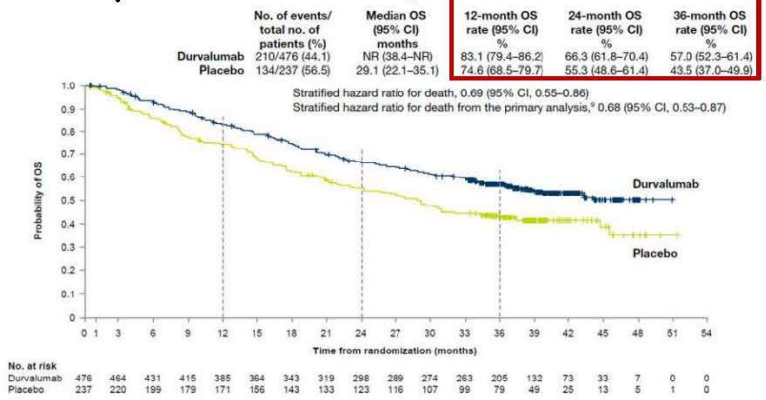
Our aim at increasing the cure rate in LA-NSCLC

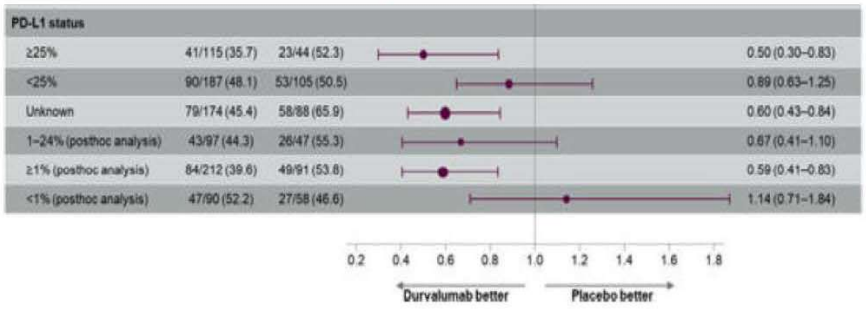
Other biological predictive indictors (eg. PD-L1)?

- Improved LC & OS by ICI Consolidation in PACIFIC study

3 Survival Update **Δ1, 2, and 3-ys= 8% 11% 13.5%**



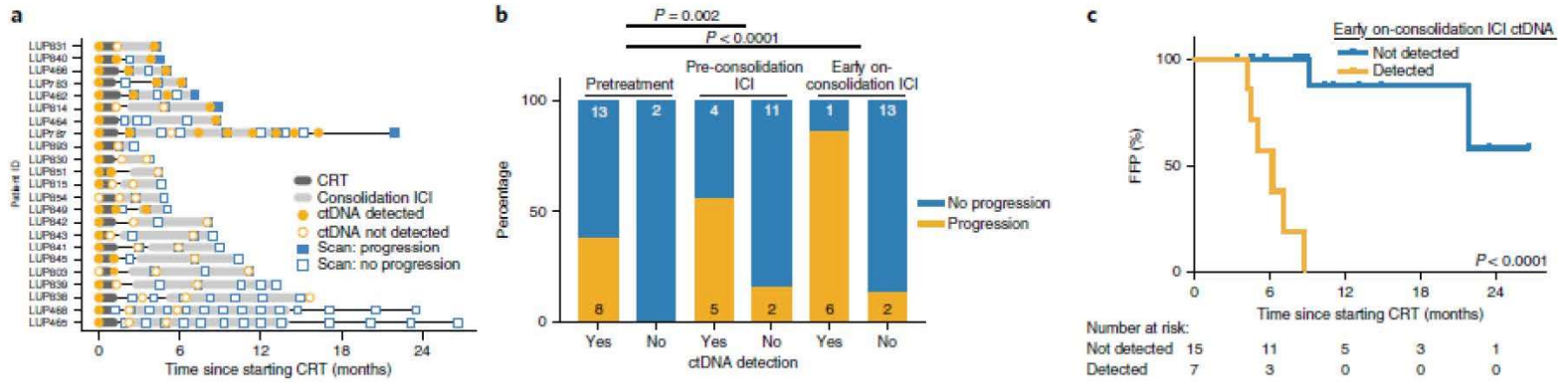
PD-L1 status: > 25%



Gray JE, et al. J Thora Oncol. 2020
Antonia SJ, et al, N Engl J Med 2017

Beyond the high FDG-uptake Region by PET and expression of PD-L1

- Circulating tumor DNA dynamics predict benefit from consolidation IO in LA-NSCLC



ctDNA changes during therapy are associated with outcomes in LA-NSCLC patients treated with CRT and consolidation ICI.

Everett J. Moding, et al. Nature Cancer. 2020

Future directions: more frequent or continuous adaptive replanning of radiation?

- For ^{18}F-FDG, radiation causes decrease of tracer uptake and tumor SUV_{max} but increases background uptake due to radiation-induced inflammation
- → When is best time to adapt? second vs fourth week of treatment?

- Image-guided radiotherapy systems allow increasing automation
- CBCT-Linac systems: daily delineation of target volumes and automated daily dose evaluation
- MRI-Linac systems: daily assessment of functional parameters derived from perfusion, diffusion, and spectroscopy imaging
- PET-Linac systems: clinical use has not yet been fully reported

Future directions: PET tracers targeting hypoxia?

- ^{18}F-FMISO = most extensively studied PET tracer for imaging hypoxia
- high lipophilicity and slow plasma clearance, low tumor-to-background ratio
- F-MISO results have not yet been reported from RTOG 1106

- Second-generation nitroimidazole derivatives: more hydrophilic, lower lipophilicity, higher tumor-to-background ratio
- ^{18}F-fluoroazatiomycin arabinoside (^{18}F-FAZA)
- ^{18}F-fluoroerythronitroimidazole (^{18}F-FETNIM)
- ^{18}F-flortanidazole (^{18}F-HX4)

- ^{4}Cu-ATSM
- bioreductive enzymes reduce Cu (II) to Cu (I) in hypoxic conditions, which dissociates from ATSM and is trapped within the hypoxic cell

- Locoregional relapse is frequent after chemoradiation even when adjuvant immunotherapy is given
- RTOG 1106 and PET-Boost endpoints of LRC not met, but dose escalation does clearly improve in-field control
- Still looking for better selection principles
- Still need to optimize when to adapt and possibly ? which tracer(s) to use