MANCHESTER 1824
The University of Manchester
Manchester Cancer Research Centre

GOLF
Groupe d'Oncologie de Langue Française

LES CBNPC LOCALEMENT AVANCÉS OU INOPÉRABLES
Vu par le radiothérapeute

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Cours du Golf – 8 Octobre 2019

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Conflicts of interests

- Research grants- AZ, Elekta, MSD
- Symposium - AZ
- Advisory boards – AZ, Pfeizer

Founded in 1892, 'Cancer Pavilion and Home of the Incurables'; renamed 'The Christie Hospital & Holt Radium Institute' in 1901

- 1901 - use of X-rays for therapy
- 1905 - use of radium for therapy
- 1932 - development of the "Manchester Method" of radium treatment
- 1944 - world's first clinical trial of Stilboestrol
- 1970 - world's first clinical use of Tamoxifen
- 1986 - world's first use of cultured bone marrow for leukaemia treatment
- 1991 - world's first single harvest blood stem-cell transplant
- 1992 - world's first MLC developed with Philips
- 2002- world's first clinical use of image guided radiotherapy on a linac
- 2018-first proton facility in the UK

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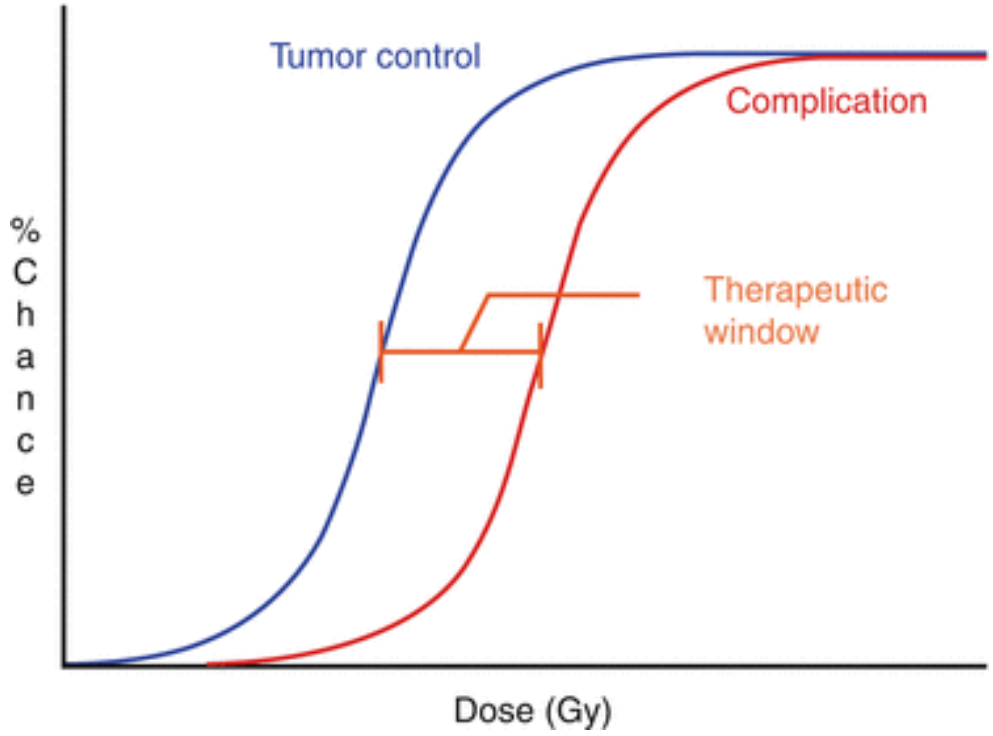
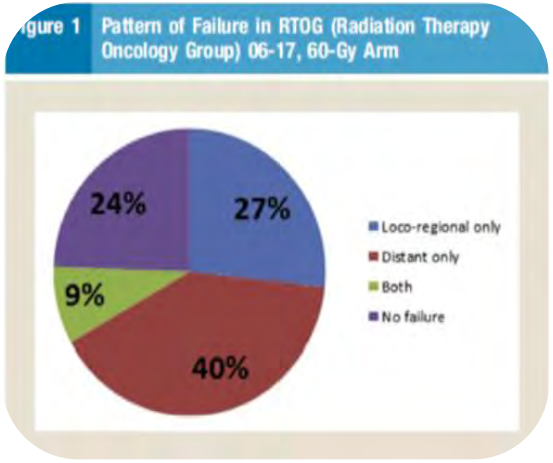
Concept of the Clinical Oncologist

Aim of radiotherapy in stage 3 - Cure



Local control

Side effects



Local relapse ~30%@2 yrs

Metastatic relapse ~50%@2 yrs

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Advanced RT=better local control=improved OS

CHART

Saunders et al. Lancet 2010

- 60 Gy/30# OD vs. 54 Gy/36# TDS
- HR death 0·76 (p=0·004, 95% CI 0·63–0·92)
- HR local progression 0·77 (p=0·027, 95% 0·61–0·97)

NSCLCCG Meta-analysis

(6 trials, 1205 patients)

Auperin et al. JCO 2010

- HR death 0.83 (p=0.04); absolute benefit survival 4.5% at 5 years
- HR loco-regional progression 0.77; 95% CI 0.62 to 0.95; p= 0.01); absolute benefit 6% at 3 years

RTOG Meta-analysis

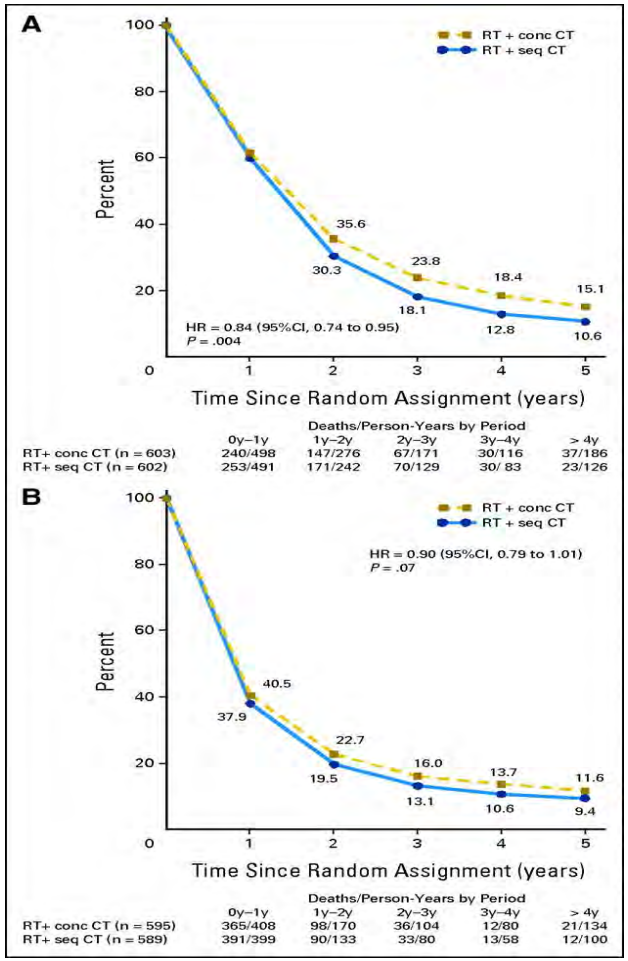
(7 trials, 1390 patients)

Machtay et al. JTO 2012

- Improved local control correlates with improved overall survival (p<0.0001)

Overall Survival

Progression-Free Survival



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Clinical Case

71 yr old female
Presented with SOB
PMH –IHD, HBP
WHO PS=1, MRC RS 2

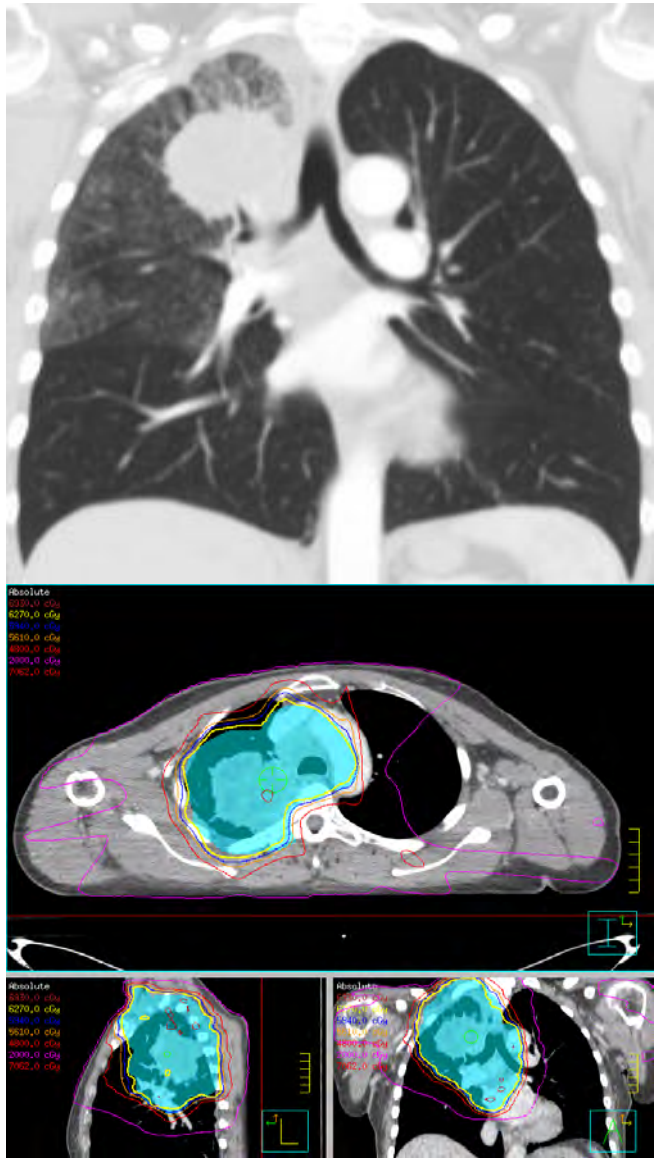
PFTs - FEV1 80% predicted KCO 105% predicted

CT - RUL tumour & enlarged 4R, 7 lymph nodes
T3 N2 M0

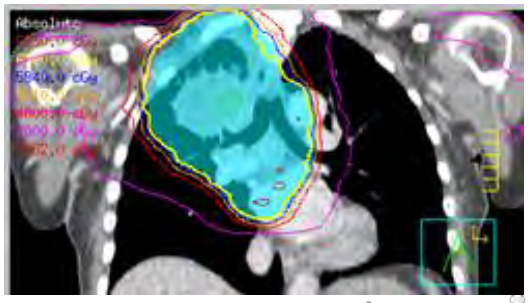
EBUS - Station 4R adenocarcinoma

PET-CT - FDG avid right supraclavicular LN T3 N3 M0

MR Brain - Clear



Is she radically treatable?
Can you consider concurrent CTRT?
What RT techniques will facilitate conc CTRT?



One patient-many questions

Standard of care
Concurrent
CTRT→IO

Limited evidence
from clinical trials

Will she benefit from high dose radiotherapy?

Is Immunotherapy right for her?

Is having chemotherapy with RT right for her?

Can she get protons instead of photons?

She has severe heart problems – will RT make them worse?

Can we track the success of her treatment?

Do genes matter for tumour response?

Should she stop statins or other drugs during RT?

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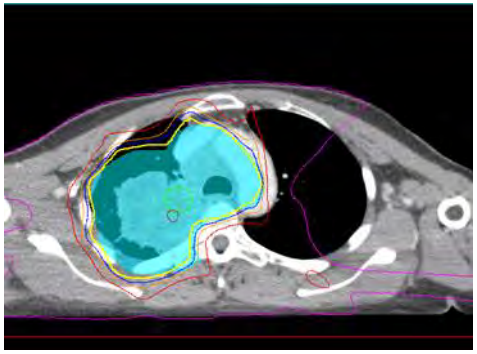
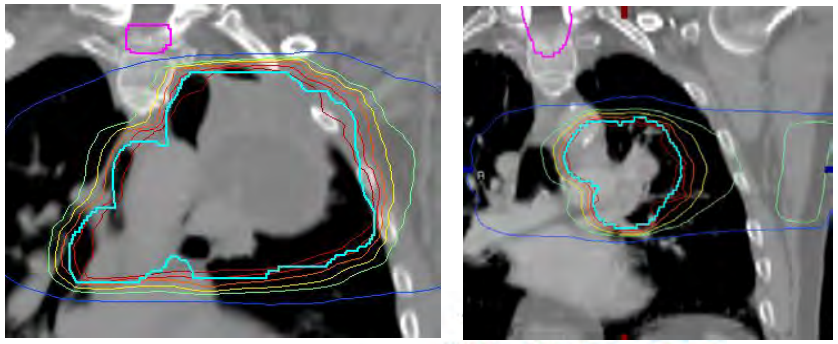
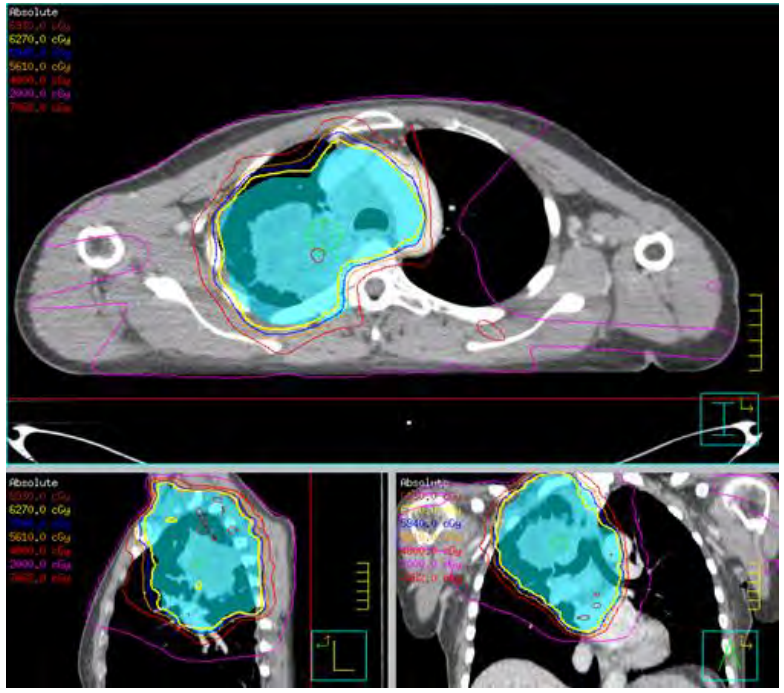
Stage III NSCLC: What is the clinical challenge?

- **Baseline patient factors:**
  - Performance status, weight loss
- **Organ at risk factors:**
  - Lung function and cardiac function
  - Influence of respiratory motion
  - Proximity of target to spinal cord, oesophagus, heart
- **Tumour factors:**
  - Histological subtype, genetic/mutational status and intra-tumour heterogeneity
  - Disease stage, primary tumour volume and location, extent of nodal involvement





What is the optimal RT treatment? Can we treat large volumes with CTRT?



The Evolution of Radiation Therapy

Drive to increase conformal delivery to irregular tumour targets
And reduce toxicity

Computerized 3D CT treatment planning

Cerrobend blocks

Image Fusion

IMRT

VMAT

4DCT

MR Linac

First Linac

1960

20

Allowing for delivery of
- Higher curative-intent radiation doses
- While limiting exposure of normal tissues
- Leading to patients are increasingly being treated with curative intent rather than palliation

Standard collimator

electron fields

Multileaf collimator

High resolution IGRT

PETCT

Stereotactic Radiotherapy

Protons

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RTOG 0617: What have we learnt?

STRATIFY	RANDOMIZE	Concurrent Treatment	Consolidation Treatment
RT Technique 1.3D-CRT 2.IMRT **Zubrod** 1.0 2.1 **PET Staging** 1.No 2.Yes **Histology** 1.Squamous 2.Non-Squamous		**Arm A** **Concurrent chemotherapy*** **RT to** 60 Gy, **5 x per wk for 6 wks**	Arm A Consolidation chemotherapy*
		Arm B **Concurrent chemotherapy*** **RT to** 74 Gy, **5 x per wk for 7.5 wks**	Arm B Consolidation chemotherapy*
		Arm C **Concurrent chemotherapy* and** Cetuximab **RT to** 60 Gy, **5 x per wk for 6 wks**	Arm C Consolidation chemotherapy* and Cetuximab
		Arm D **Concurrent chemotherapy* and** Cetuximab **RT to** 74 Gy, **5 x per wk for 7.5 wks**	Arm D Consolidation chemotherapy* and Cetuximab

*Carboplatin and paclitaxel 90% patients PET staged 185 centres
n=464 high dose vs standard dose; n=544 cetuximab vs no cetuximab

Bradley. Lancet Oncol 2015

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RTOG 0617

How not to do treatment intensification

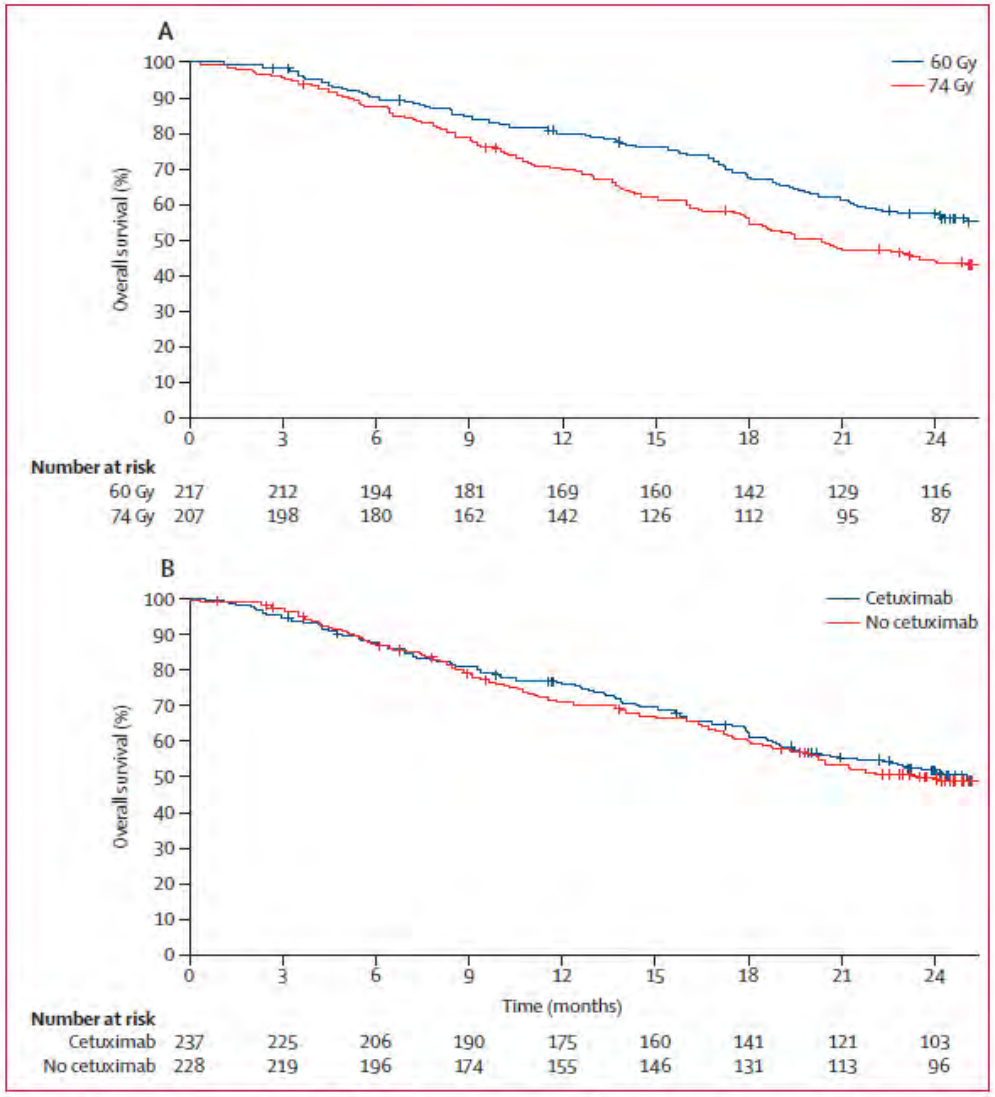

Figure 2: **Kaplan-Meier overall survival curves for radiation dose (A) and the use of cetuximab (B)**
(A) One-sided log-rank p=0·0042. (B) one-sided log-rank, p=0·2938.

38% greater risk of death in 74 Gy arm

Heart dose (V5& V30) associated with poor survival

	60 Gy	74 Gy
MS (95% CI)	28.7 months (24·1–36·9)	20.3 months (17·7–25·0)
Oesophagitis G3+	7%	15%
Treatment related death	3	8

Bradley. Lancet Oncol 2015

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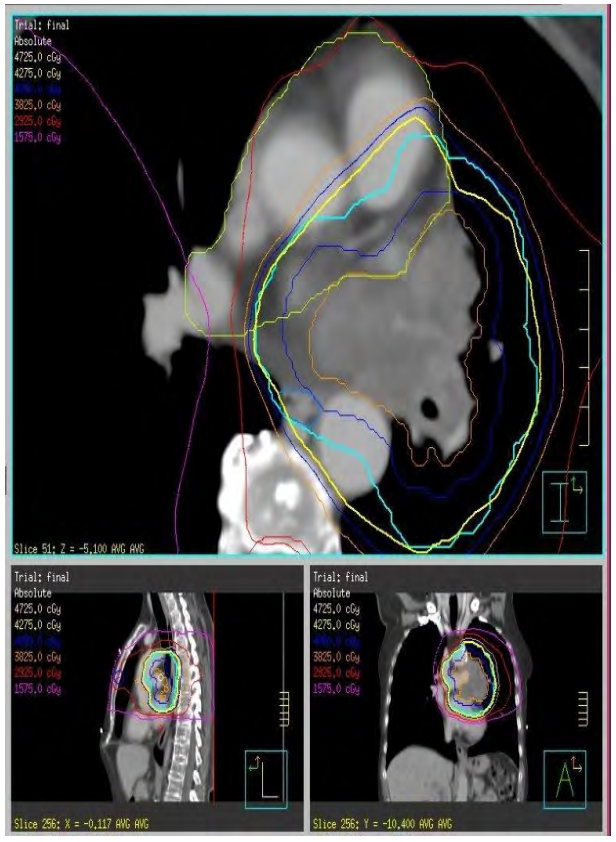
What have we learnt from RTOG0617

- Benchmark for future trials = 60 Gy in 30#
- Heart dose matters

  Bradley. Lancet Oncol 2015

- Evidence supporting IMRT

  Chun. JCO 2016



Impact of RT on heart and immune system

RTOG 0617
Heart V5, V30→ increased risk of death
Bradley. Lancet Oncol 2015

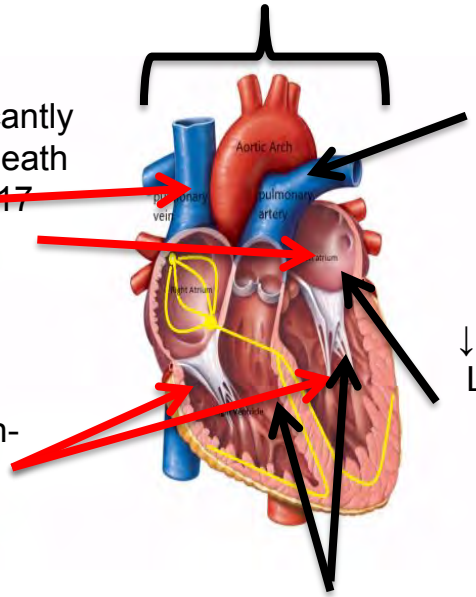
Heart

Immune system

↓OS if base of the heart dose > 8.5Gy
McWilliam et al Eur J Cancer. 2017

Impact of heart, lung, and large vessel irradiation on OS
Thor. ASTRO 2018

Max to LA and
near Min dose to SVC significantly associated with non-cancer death
Stam. Radiother Oncol. 2017



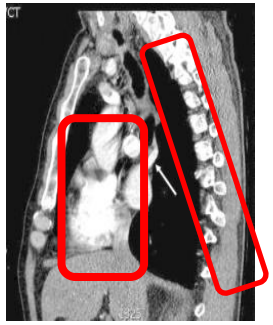
↓OS if PA V40Gy >80%
Ma et al Radiat Oncol. 2017

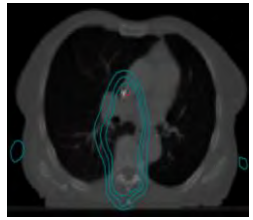
Bilateral ventricle max dose significantly associated with non-cancer death
Wong.Clin Lung Cancer. 2018

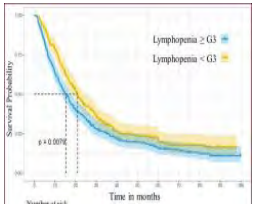
↓OS if >2.2% of LA wall received >63Gy
LA dose associated with ECG changes
Vivekanandan Int J Radiat Oncol Biol Phys. 2017

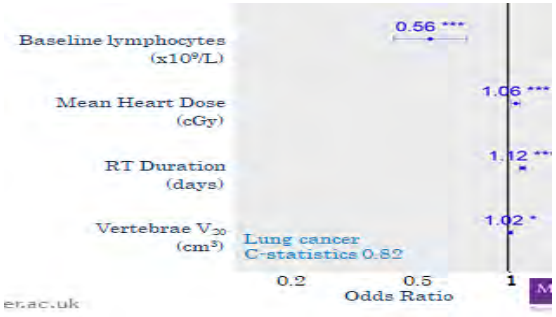
Dose to LAD, LV and RV significantly associated with CE in patients with IHD
Yegya-Raman. *J Thorac Oncol*. 2018

= Fractionated RT
= SABR









Model G3 lymphopenia
Consider prophylaxis

Need prospective data to identify sensitive substructures

RTOG 0617: benefit of IMRT

Deck Stacked Against IMRT:

Characteristic	3D-CRT	IMRT	P-value
Stage IIIB	30%	39%	0.056
PTV	427 mL	486 mL	0.005
PTV:lung ratio	0.13	0.15	0.013

Benefits of IMRT: Outcomes

Outcome	OR (95% CI)	P-value
Overall survival	1.01 (0.8, 1.28)	0.95
Progression free survival	1.12 (0.91, 1.39)	0.28
Local control	0.91 (0.67, 1.23)	0.54
Distant metastasis free	0.92 (0.71, 1.19)	0.52

Overall and progression free survival similar
in spite of more unfavorable tumors in IMRT group

Benefits of IMRT: Treatment & Toxicity

Outcome	3D-CRT	IMRT	P-value
Grade 3+ pneumonitis	8%	3.5%	0.0462
Heart V40	11.4%	6.8%	0.0026
Full consolidative chemotherapy	29%	37%	0.05

Esophagitis, weight loss, cardiovascular, neurologic adverse effects similar in IMRT and 3D-CRT

Multivariate Predictors of Grade 3+ pneumonitis

Co-variate	Comparison	OR (95% CI)	P-value
Technique	3D-CRT vs IMRT	0.44 (0.18, 1.04)	0.0621
Stage	IIIA vs. IIIB	2.35 (1.05, 5.29)	0.0385
Lung V20	Continuous	1.081 (1.02, 1.146)	0.009

Low dose bath bigger with IMRT

Lung V5 – IMRT 62% vs. 3D-CRT 55% ($P < 0.0001$)

Lung V5 did not predict pneumonitis, P = 0.14, OR 1.02, 95% CI (0.994, 1.04)

MLD did not predict pneumonitis

Chun. JCO 2016

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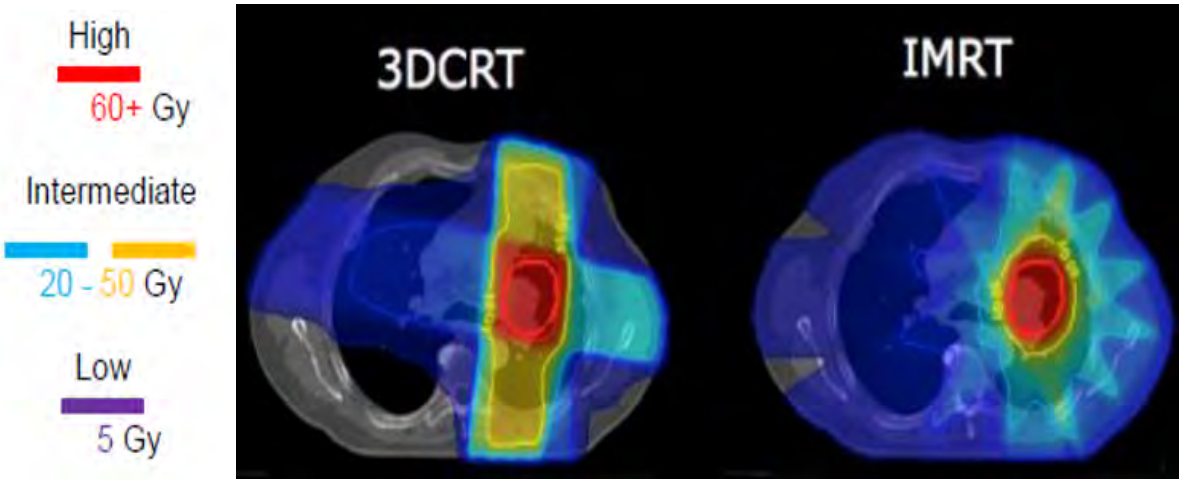
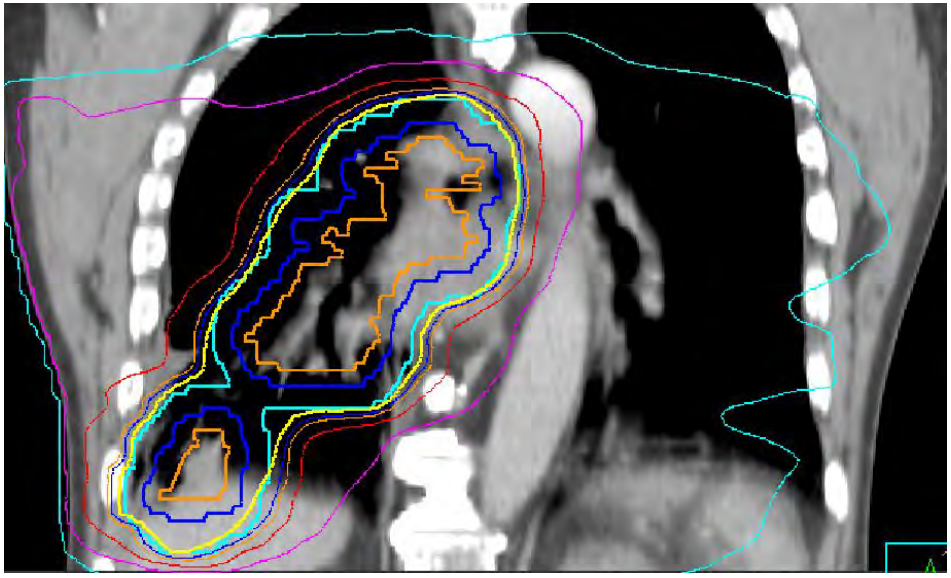
Benefit of IMRT



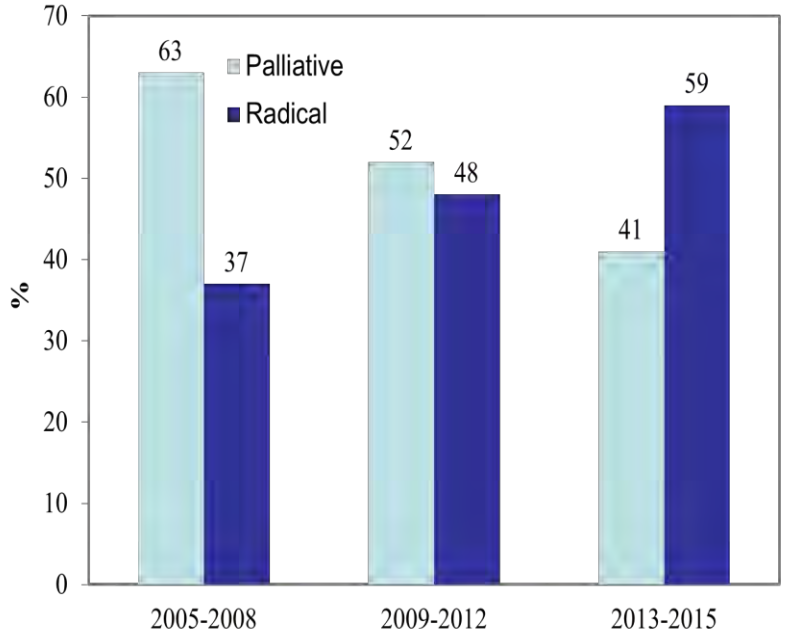
Impact of IMRT on curative-intent RT

'Big data' analysis of 8855 patients

- 2005-8: Pre IMRT partial access to IMRT (n=2872)
- 2009-12: - limited access to IMRT (n= 3344)
- 2013-2014: ~Full access to IMRT 2639



Chan et al. JTO 2014



Chan et al. BTOG 2017

What is the optimal systemic treatment with RT?

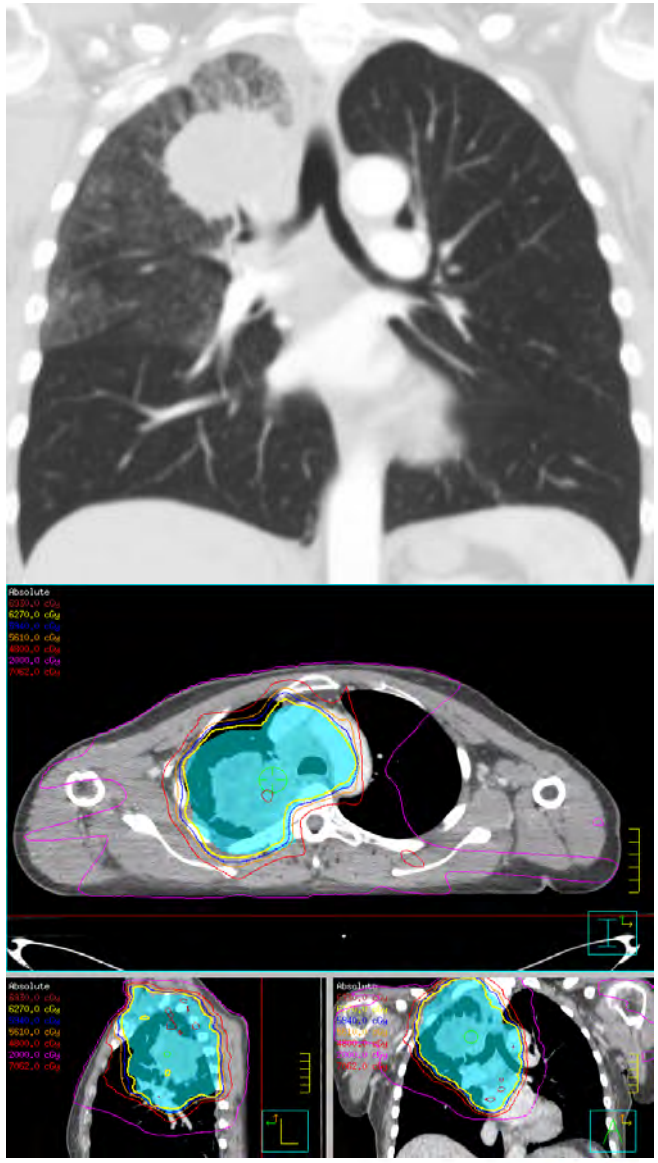
Clinical Case

71 yr old female
Presented with SOB
PMH –IHD, HBP
WHO PS=1, MRC RS 2
PDL1: <1%

60 Gy in 30 fractions
Cisplatin etoposide x 2 cycles
GTV 560 cc

2 weeks post CTRT
Grade 3 Oesophagitis
PS2

4 weeks post CTRT
Grade 2 oesophagitis
PS2



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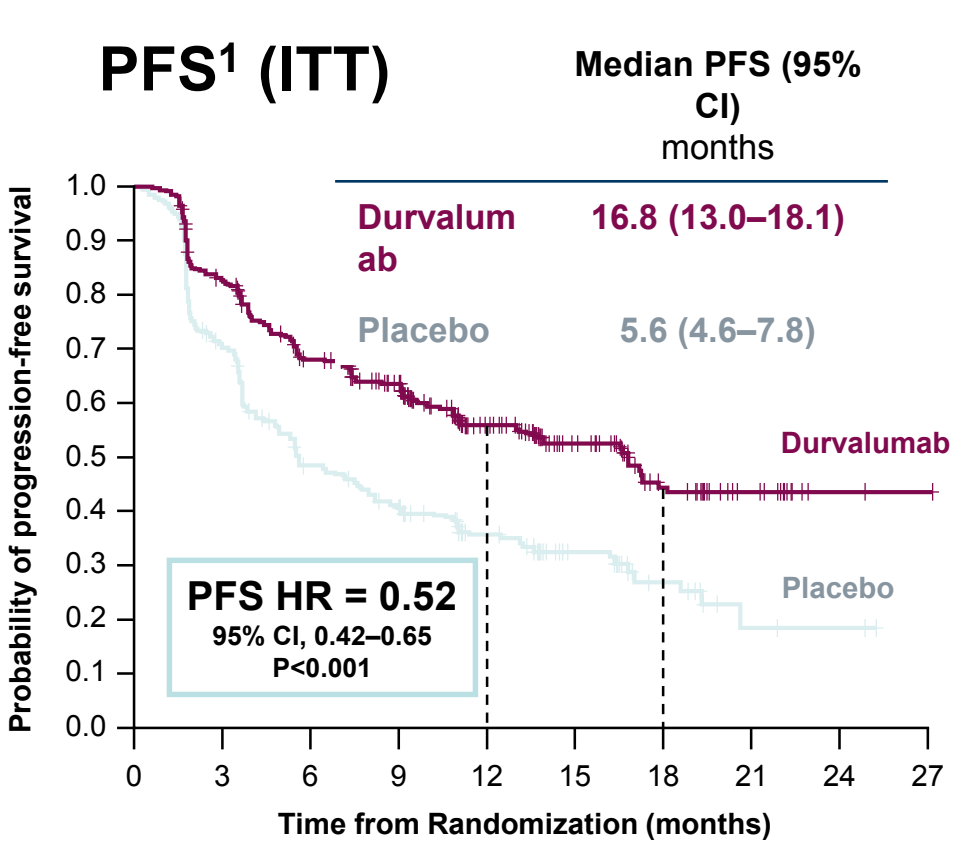
Are you comfortable treating with Durvalumab?

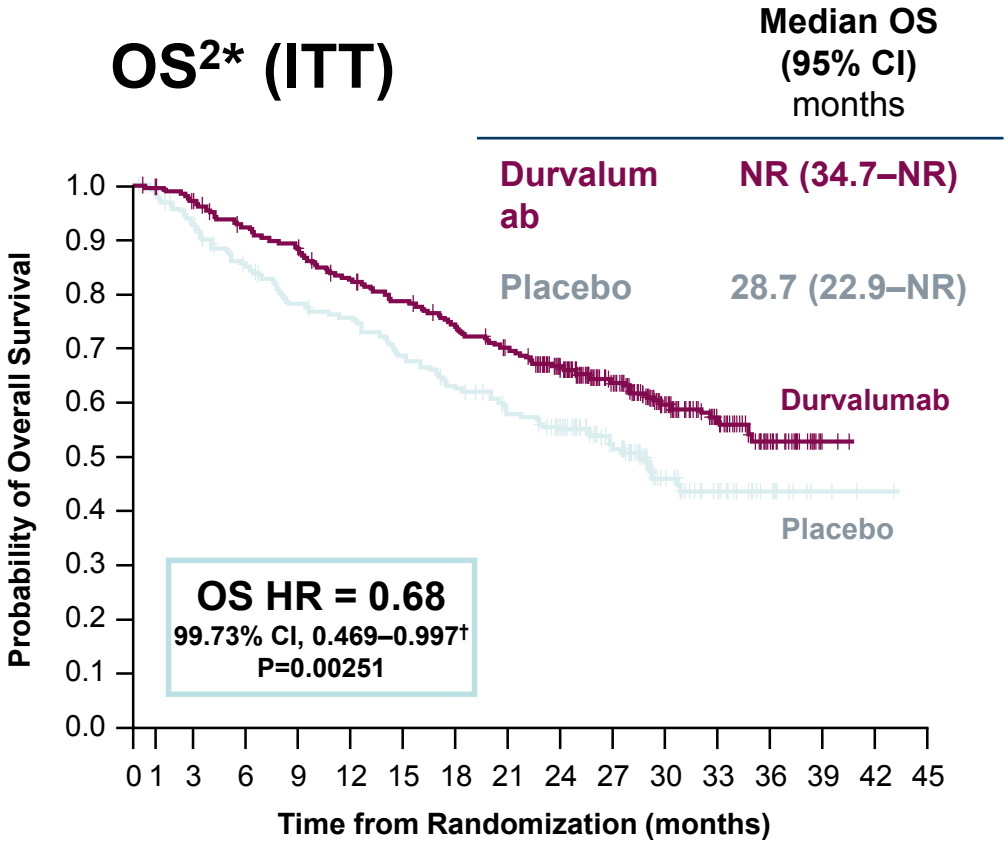
PFS AND OS IN THE ITT POPULATION

PFS[1] (ITT)



No. at Risk										
Durvalumab	476	377	301	264	159	86	44	21	4	1
Placebo	237	163	106	87	52	28	15	4	3	0

OS[2*] (ITT)



No. at Risk																	
Durvalumab	476	464	431	415	385	364	343	319	274	210	115	57	23	2	0	0
Placebo	237	220	198	178	170	155	141	130	117	78	42	21	9	3	1	0

*Median duration of follow-up was 25.2 months (range 0.2–43.1); †Adjusted for interim analysis; NR, not reached

1. Antonia SJ, et al. N Engl J Med 2017; 2. Antonia SJ, et al. N Engl J Med. 2018;

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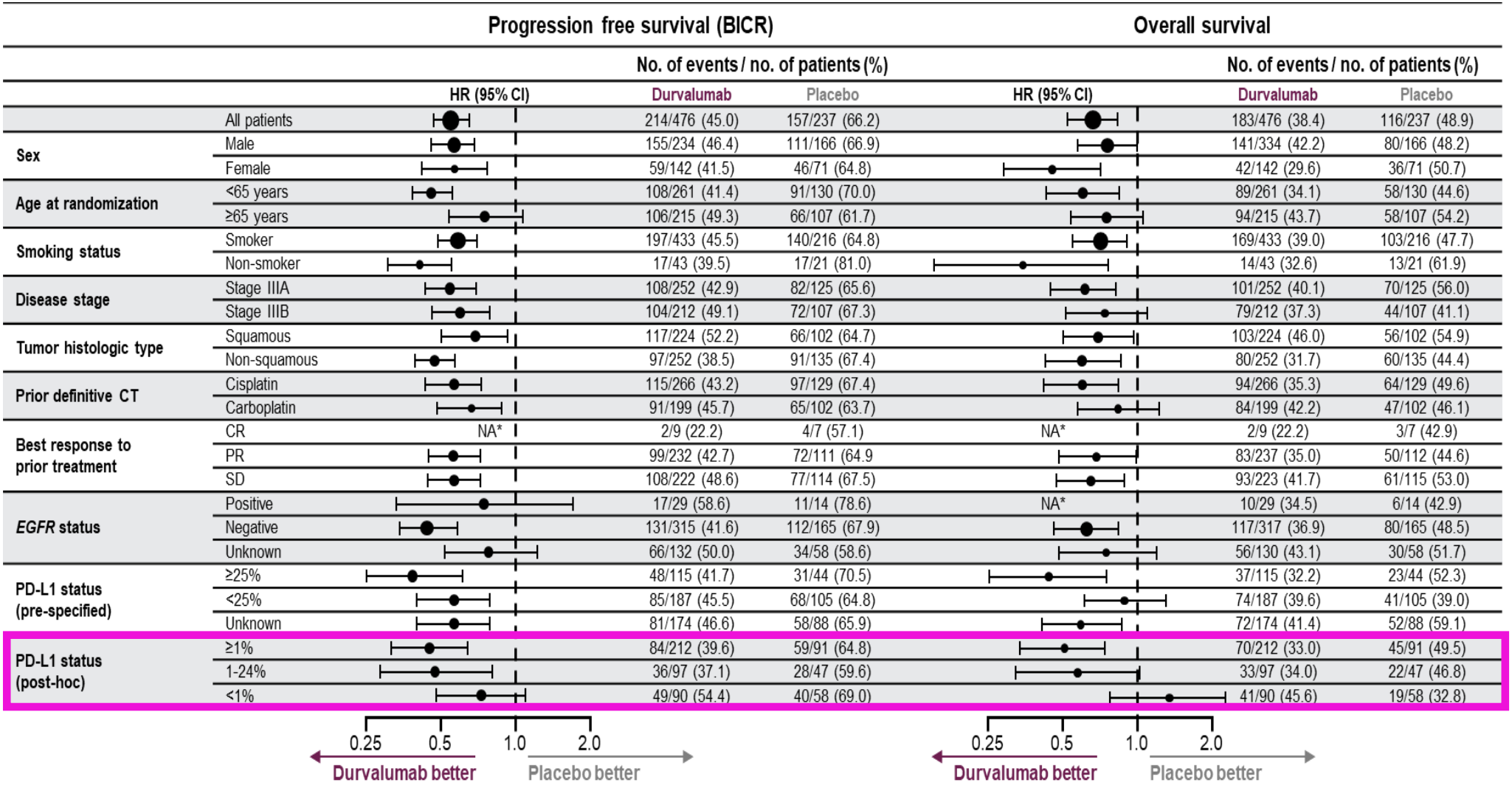
PFS AND OS BY PRE-SPECIFIED SUBGROUP (ITT)



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IMPACT OF PRECEDING CHEMOTHERAPY AND RT DOSE

	PFS (BICR)			OS		
	HR (95% CI)	No. of events / no. of patients (%)		HR (95% CI)	No. of events / no. of patients (%)	
		Durvalumab	Placebo		Durvalumab	Placebo
ITT[1,2]		214/476 (45.0)	157/237 (66.2)		183/476 (38.4)	116/237 (48.9)
Induction chemotherapy						
Yes		59/123 (48.0)	49/68 (72.1)		53/123 (43.1)	34/68 (50.0)
No		155/353 (43.9)	108/169 (63.9)		130/353 (36.8)	82/169 (48.5)
Platinum						
Cisplatin		115/266 (43.2)	87/129 (67.4)		94/266 (35.3)	64/129 (49.6)
Carboplatin		91/199 (45.7)	65/102 (63.7)		84/199 (42.2)	47/102 (46.1)
Taxane						
Yes		97/207 (46.9)	72/112 (64.3)		80/207 (38.6)	51/112 (45.5)
No		117/269 (43.5)	85/125 (68.0)		103/269 (38.3)	65/125 (52.0)
Etoposide						
Yes		49/117 (41.9)	34/52 (65.4)		43/117 (36.8)	32/52 (61.5)
No		165/359 (46.0)	123/185 (66.5)		140/359 (39.0)	84/185 (45.4)
Vinorelbine						
Yes		58/124 (46.8)	42/59 (71.2)		48/124 (38.7)	27/59 (45.8)
No		156/352 (44.3)	115/178 (64.6)		135/352 (38.4)	89/178 (50.0)
Dose of radiotherapy						
<60 Gy		16/38 (42.1)	11/15 (73.3)		15/38 (39.5)	11/15 (73.3)
60–66 Gy		187/407 (45.9)	130/202 (64.4)		160/407 (39.3)	96/202 (47.5)
>66 Gy		10/30 (33.3)	15/19 (78.9)	NA*	–	–

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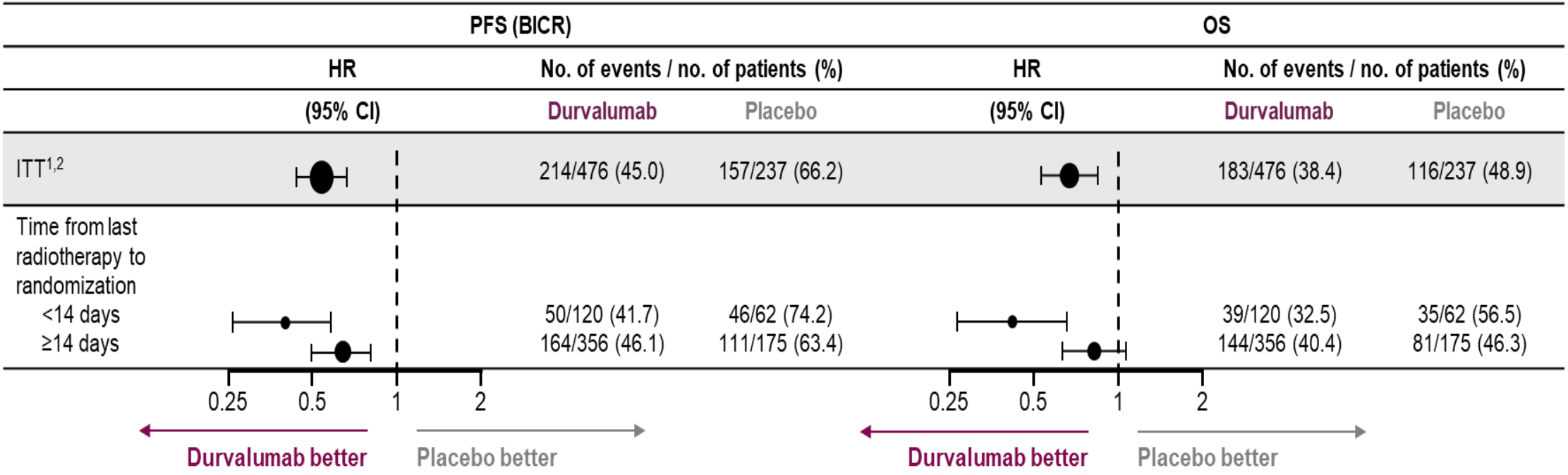
Antonia SJ, et al. N Engl J Med. 2012
Antonia SJ, et al.. N Engl J Med 2018

IMPROVED OUTCOMES IRRESPECTIVE OF TIME FROM RADIATION



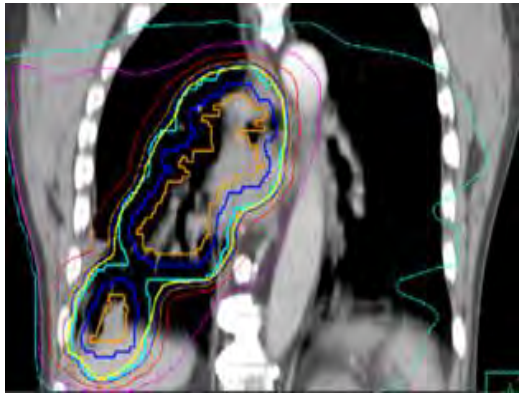
Subgroup analyses suggested that durvalumab improved PFS and OS regardless of dose of RT and time from RT to randomization

Antonia SJ, et al. N Engl J Med. 2017
Antonia SJ, et al.. N Engl J Med 2018

MY COMMENTS ON PACIFIC

- Is the PACIFIC population representative?
- No data on disease volume, dose to OARs, RT techniques
- Applicability to the sequential setting?
- Uncertainties
  - Large volume
  - Dose to OARs at the limit of tolerance
  - PS2
  - Elderly

  - Optimal duration of IO treatment?
  - Timing IO and RT?
  - Biomarkers?



What RT in combination with IO?

Conventional vs high dose per fraction?

- Preclinical studies suggest increased immunogenic cell death with higher doses
- Circulating lymphocytes highly sensitive to RT (D90 = 0.5 Gy)

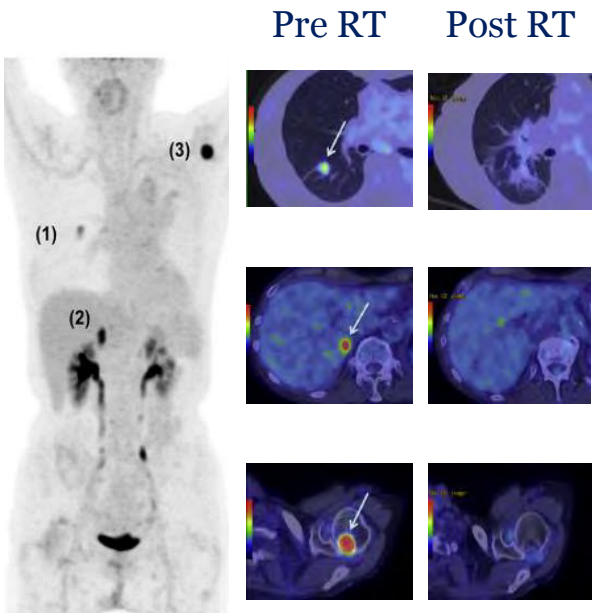
Protracted vs. short course?

- Preclinical studies suggest multiple may be better than single
- Clinical abscopal effects mainly observed following 3-5 fractions
- Protracted RT courses may induce more lymphopenia

Small vs. large fields?

- Large RT volumes may cover more lymphoid tissue & induce more lymphopenia
- Immuno-suppressive impact of conventional fields?

Treat all disease?



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Clinical Case

73 yr old female
Presented with SOB
PMH –IHD, HBP
WHO PS=1, MRC RS 2

PFTs - FEV1 80% predicted KCO 105% predicted

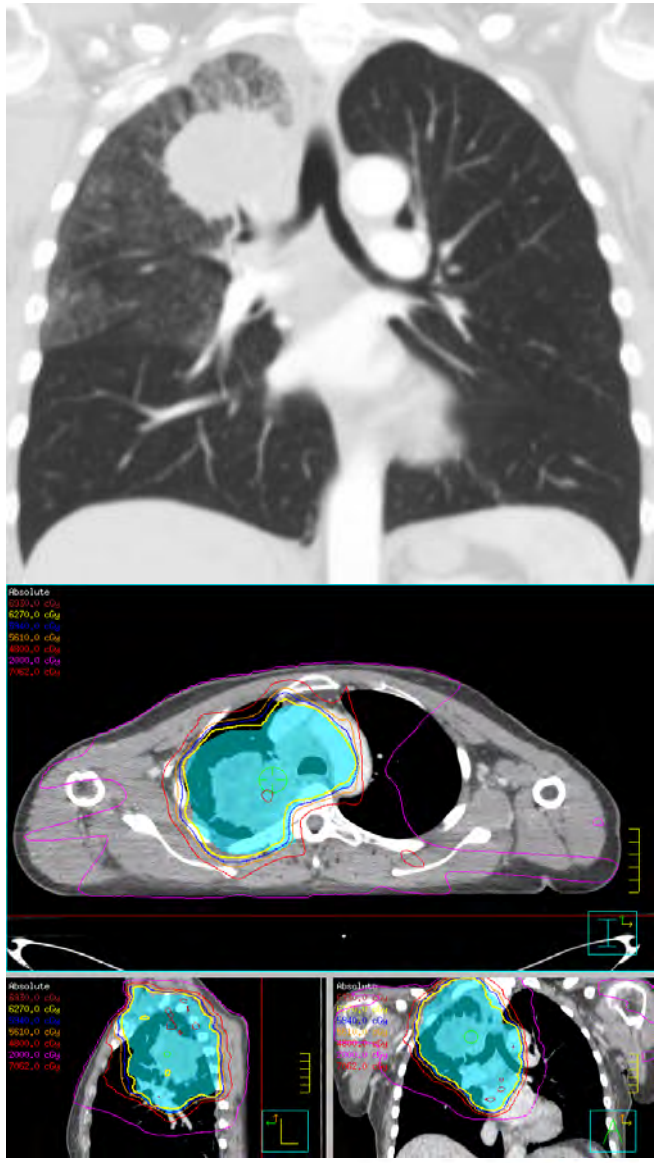
CT - RUL tumour&enlarged 4R, 7 lymph nodes, T3 N2 M0

EBUS - Station 4R EGFR+ adenocarcinoma

PET-CT - FDG avid right supraclavicular LN T3 N3 M0

MR Brain - Clear

EGFR mutation



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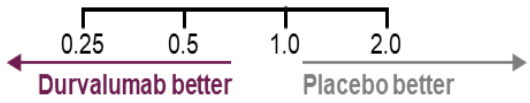
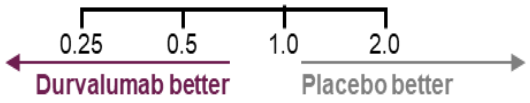
PFS AND OS BY PRE-SPECIFIED SUBGROUP (ITT)

		Progression free survival (BICR)			Overall survival		
			No. of events / no. of patients (%)			No. of events / no. of patients (%)	
		HR (95% CI)	Durvalumab	Placebo	HR (95% CI)	Durvalumab	Placebo
	All patients		214/476 (45.0)	157/237 (66.2)		183/476 (38.4)	116/237 (48.9)
Sex	Male		155/234 (46.4)	111/166 (66.9)		141/334 (42.2)	80/166 (48.2)
	Female		59/142 (41.5)	46/71 (64.8)		42/142 (29.6)	36/71 (50.7)
Age at randomization	<65 years		108/261 (41.4)	91/130 (70.0)		89/261 (34.1)	58/130 (44.6)
	≥65 years		106/215 (49.3)	66/107 (61.7)		94/215 (43.7)	58/107 (54.2)
Smoking status	Smoker		197/433 (45.5)	140/216 (64.8)		169/433 (39.0)	103/216 (47.7)
	Non-smoker		17/43 (39.5)	17/21 (81.0)		14/43 (32.6)	13/21 (61.9)
Disease stage	Stage IIIA		108/252 (42.9)	82/125 (65.6)		101/252 (40.1)	70/125 (56.0)
	Stage IIIB		104/212 (49.1)	72/107 (67.3)		79/212 (37.3)	44/107 (41.1)
Tumor histologic type	Squamous		117/224 (52.2)	66/102 (64.7)		103/224 (46.0)	56/102 (54.9)
	Non-squamous		97/252 (38.5)	91/135 (67.4)		80/252 (31.7)	60/135 (44.4)
Prior definitive CT	Cisplatin		115/266 (43.2)	97/129 (67.4)		94/266 (35.3)	64/129 (49.6)
	Carboplatin		91/199 (45.7)	65/102 (63.7)		84/199 (42.2)	47/102 (46.1)
Best response to prior treatment	CR	NA*	2/9 (22.2)	4/7 (57.1)	NA*	2/9 (22.2)	3/7 (42.9)
	PR		99/232 (42.7)	72/111 (64.9		83/237 (35.0)	50/112 (44.6)
	SD		108/222 (48.6)	77/114 (67.5)		93/223 (41.7)	61/115 (53.0)
EGFR status	Positive		17/29 (58.6)	11/14 (78.6)	NA*	10/29 (34.5)	6/14 (42.9)
	Negative		131/315 (41.6)	112/165 (67.9)		117/317 (36.9)	80/165 (48.5)
	Unknown		66/132 (50.0)	34/58 (58.6)		56/130 (43.1)	30/58 (51.7)
PD-L1 status (pre-specified)	≥25%		48/115 (41.7)	31/44 (70.5)		37/115 (32.2)	23/44 (52.3)
	<25%		85/187 (45.5)	68/105 (64.8)		74/187 (39.6)	41/105 (39.0)
	Unknown		81/174 (46.6)	58/88 (65.9)		72/174 (41.4)	52/88 (59.1)
PD-L1 status (post-hoc)	≥1%		84/212 (39.6)	59/91 (64.8)		70/212 (33.0)	45/91 (49.5)
	1-24%		36/97 (37.1)	28/47 (59.6)		33/97 (34.0)	22/47 (46.8)
	<1%		49/90 (54.4)	40/58 (69.0)		41/90 (45.6)	19/58 (32.8)





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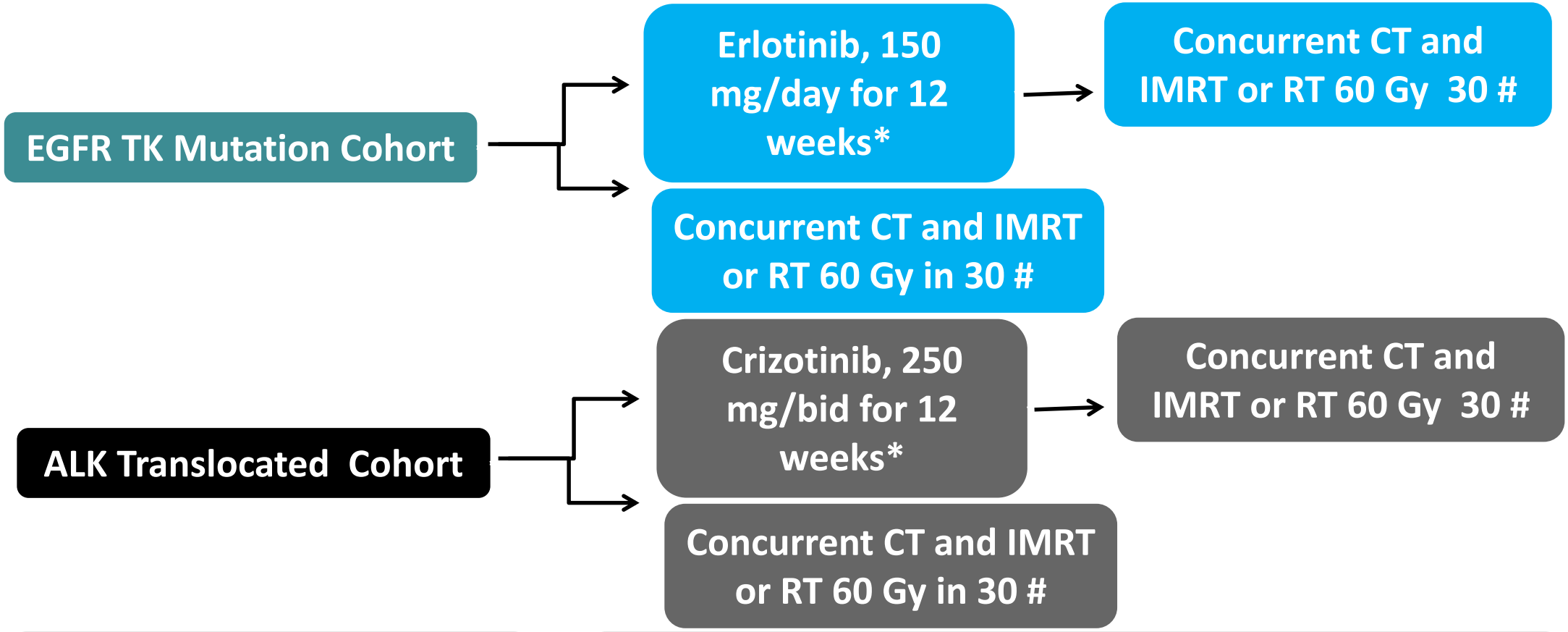
And what about the role of targeted agents in LA NSCLC?



Stratification factors:

- Stage (IIIA vs IIIB)
- CT (PE vs Carbopaclitaxel)
- Weight loss (≤ 5% vs > 5%)

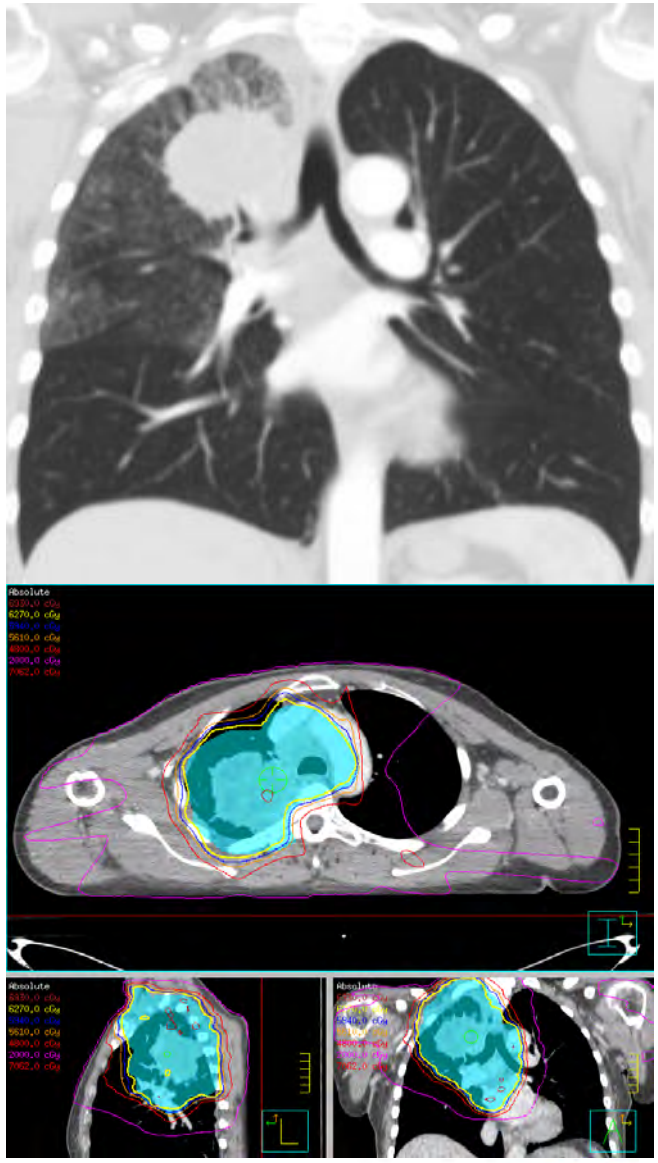
Per treating physician's discretion, a choice of 2 chemotherapy regimens:
- Cisplatin and etoposide, q 4 weeks, for 2 cycles;
- Paclitaxel and carboplatin weekly for 6 weeks followed by 2 cycles of consolidation.

***If CT at 6 weeks into induction therapy does not show at least PR, the patient will proceed directly to concurrent CT and IMRT or 3D-CRT, provided there is no PD**

Clinical Case

73 yr old female
Presented with SOB
PMH –IHD, HBP
WHO PS=1, MRC RS 2

Would she benefit from Protons, MRL?



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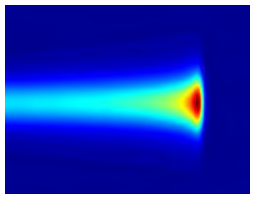
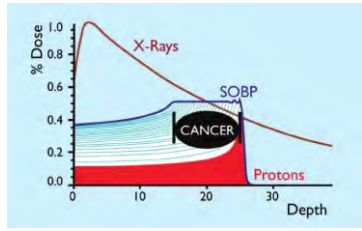
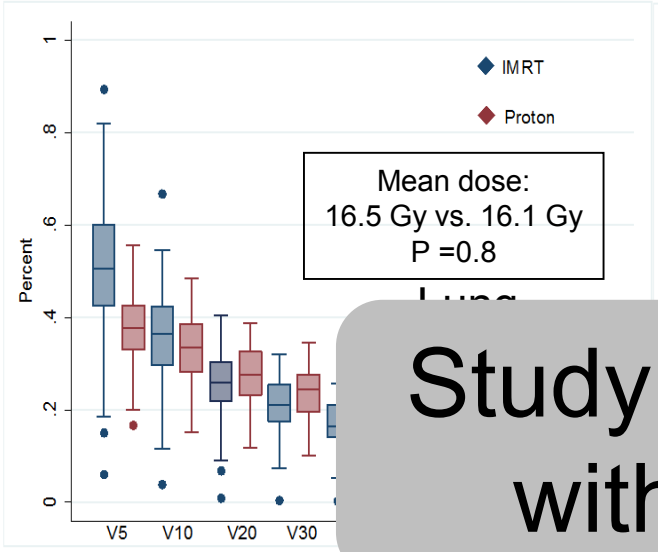
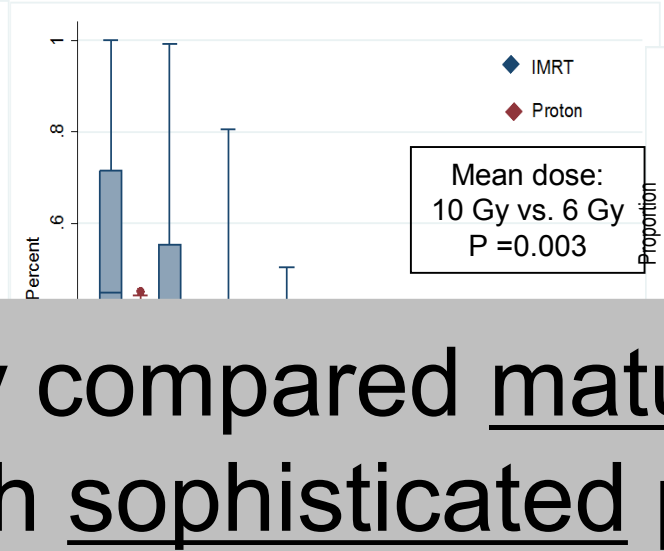
Should Protons be delivered routinely or is it the end of the story?

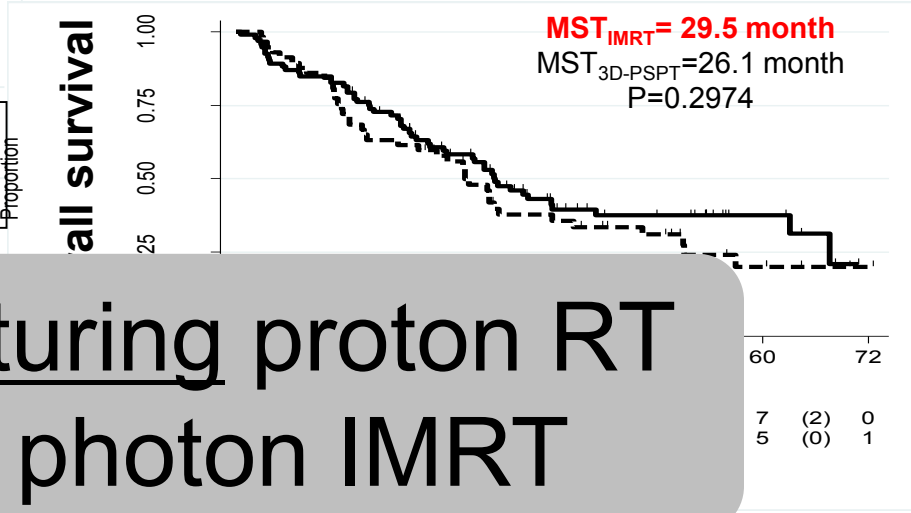
RCT photon IMRT vs Passive Scattering protons (70Gy/35f)





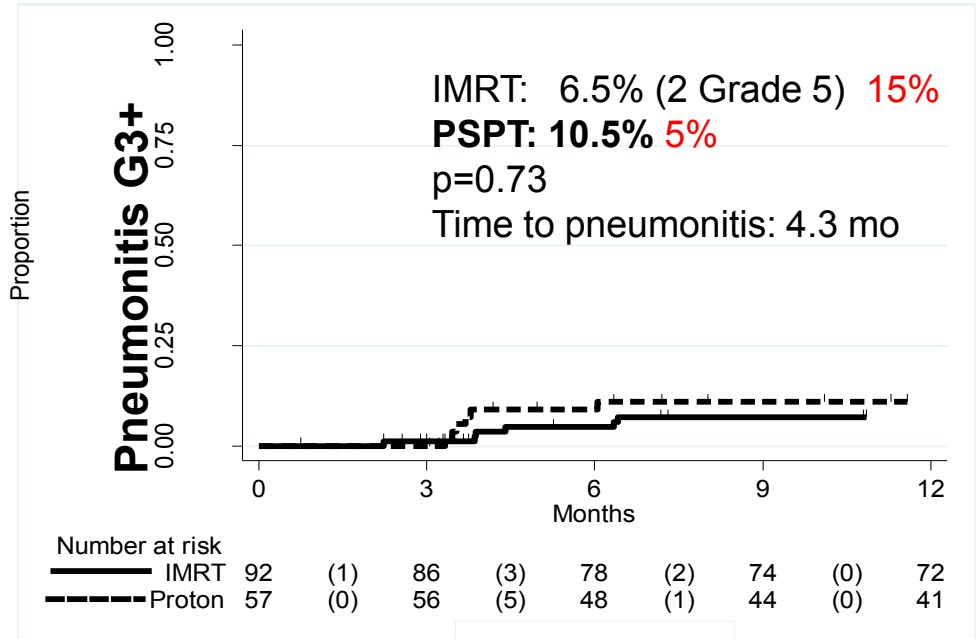


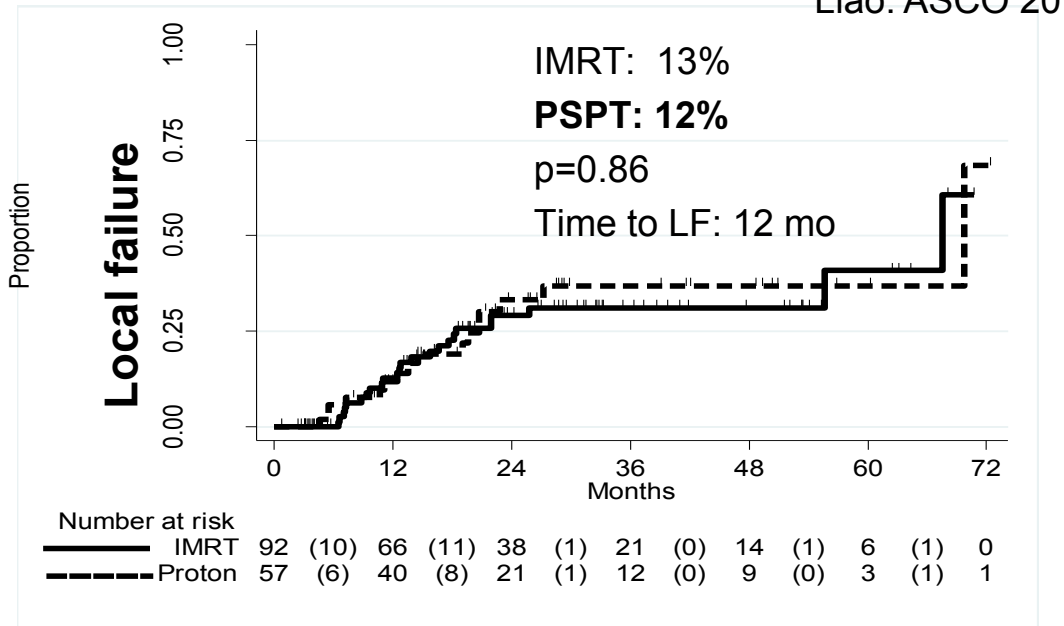




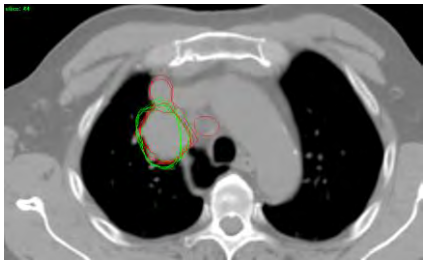
Study compared maturing proton RT with sophisticated photon IMRT

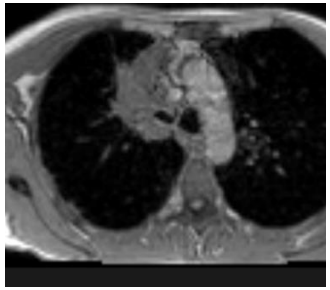
Liao. ASCO 2016

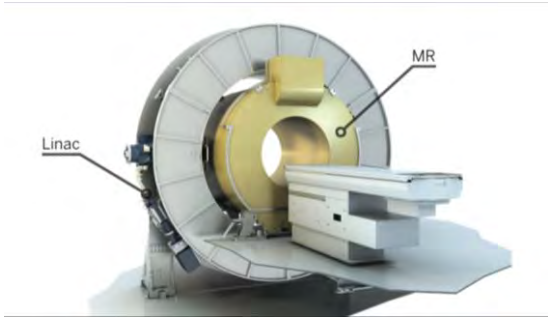




Opportunities for strengthening the current workflow with MRL
'See while you treat'







Improved soft tissue information for tumour & OAR delineation

Reduced margins

On-treatment imaging

Localisation imaging

Treatment planning

Treatment Verification

Treatment delivery

Assessment of effect of respiratory motion

Real time adaptive treatment

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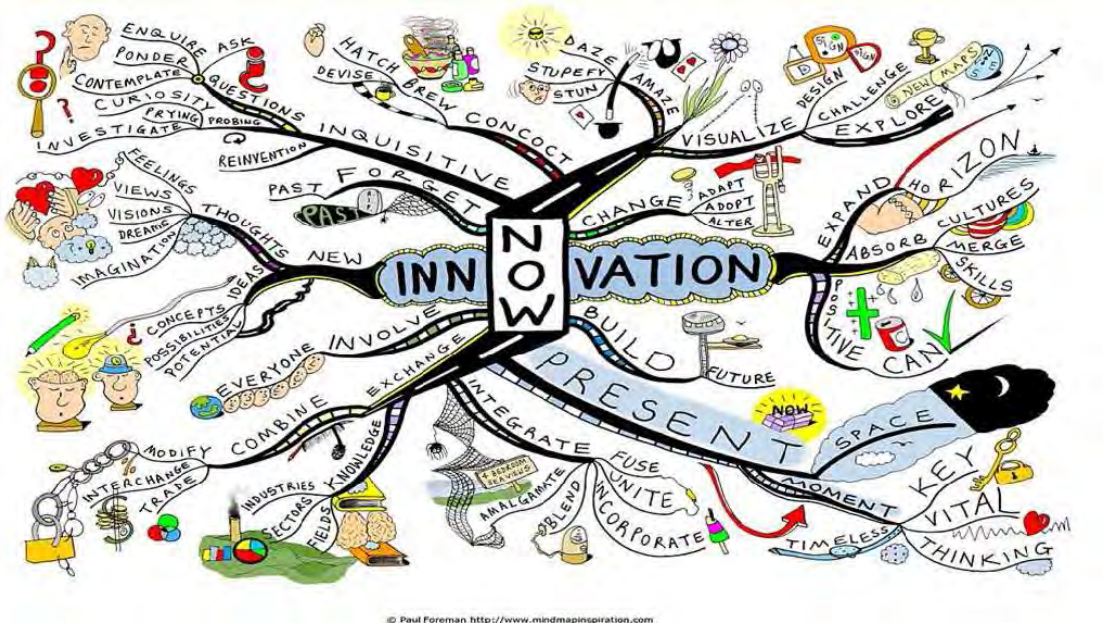
Integration of RT innovations in the multimodality treatment of LA-NSCLC

- **Big changes in the field of advanced RT**
- **Facilitating safer drug-RT combinations**
- **Challenge** – evaluate, demonstrate the impact



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