RADIATION IN LOCALLY ADVANCED LUNG CANCER

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6th Annual IBCC & PO - 2022

Flow of my Talk

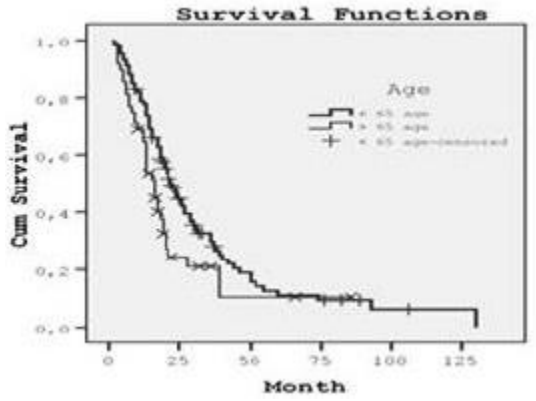
- LALC - Definition and Selection of patients
- Time, dose and fractionations
- Radiation Volumes
- OAR Constraints
- Outcome and complications

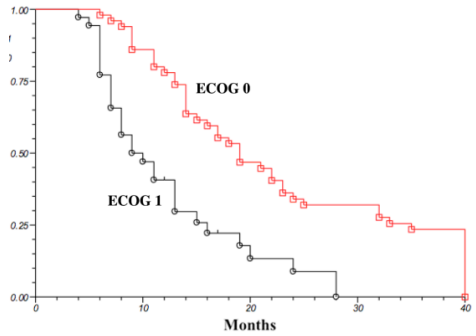
What is Locally Advanced Lung Cancer

	N0	N1	N2	N3
T1	IA	IIB	IIIA	IIIB
T2a	IB	IIB	IIIA	IIIB
T2b	IIA	IIB	IIIA	IIIB
T3	IIB	IIIA	IIIB	IIIC
T4	IIIA	IIIA	IIIB	IIIC
M1a	IVA	IVA	IVA	IVA
M1b	IVA	IVA	IVA	IVA
M1c	IVB	IVB	IVB	IVB

Patient factors

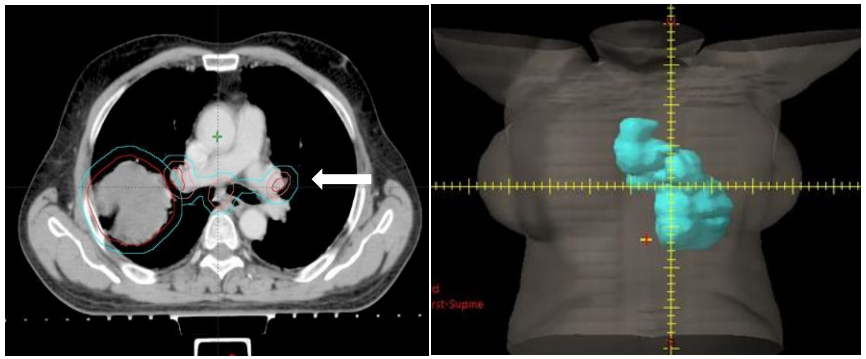
- Age - No cut-off
- Performance status (KPS/ECOG) – 70-100/0-2
- PFT parameters – FEV1>50% predicted or ≥1.0L and DLCO >40%
- Comorbidities – COPD, DM, HT
- Interstitial lung disease





Tumor factors

- T stage - T1-T4 (except nodules in different lobe)
- N3 – Crossing midline
- Size/PTV Volume - > 700cc –bad prognosis
- Location and Laterality
- Collapse: Major airway involved



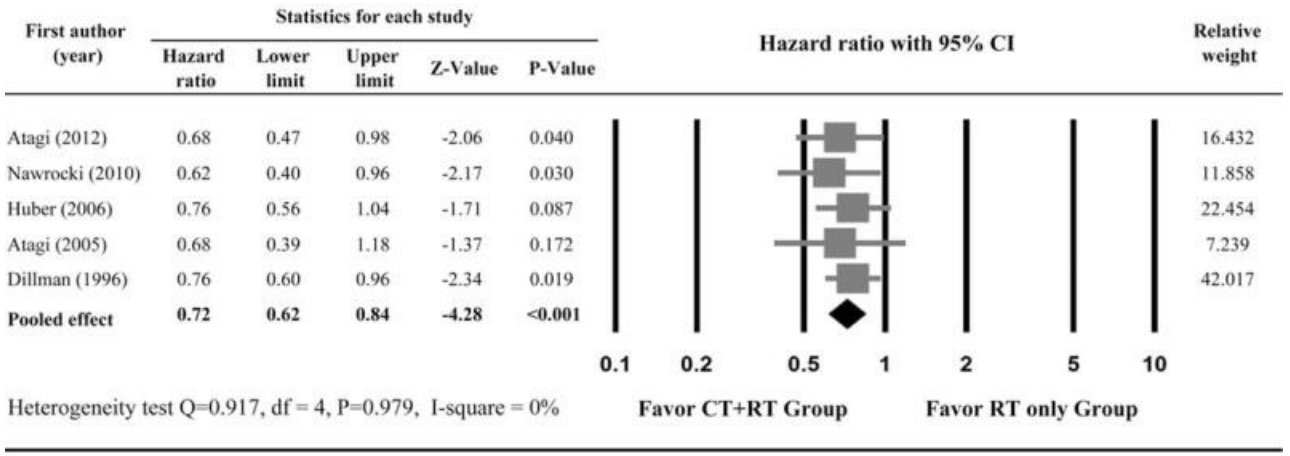
Treatment factors

- Motion management – Very essential
- Linear accelerator – Must (No Cobalt)
- Planning System – tissue heterogeneity corrections
- Pulmonary rehabilitation

Radiation Alone or Combined with Chemo

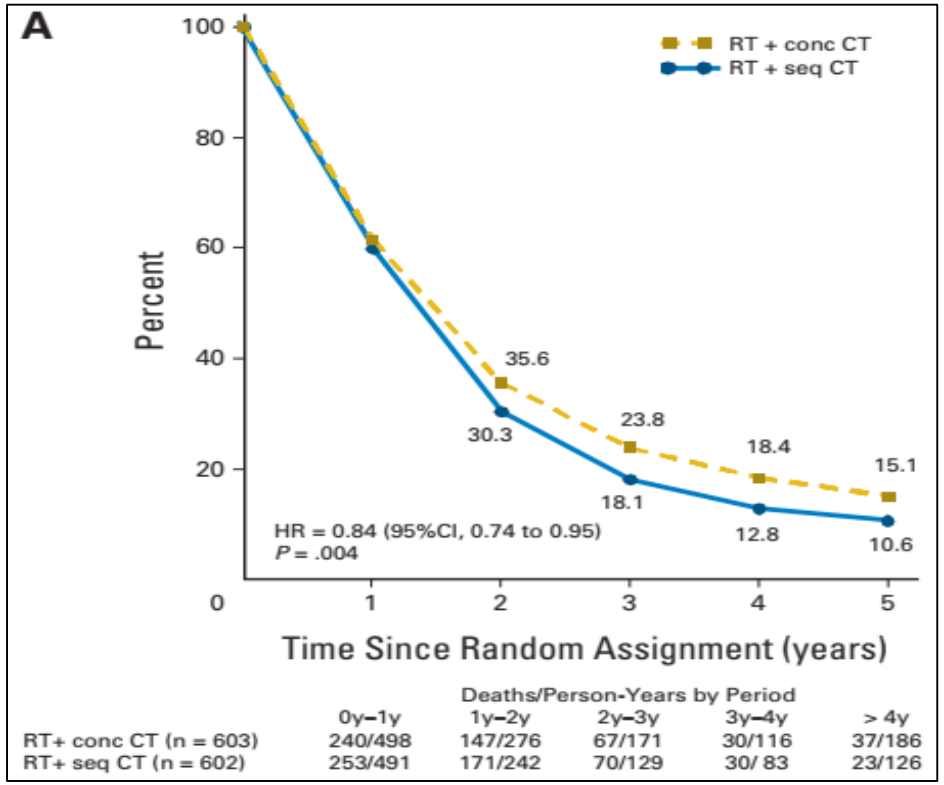
Two Year Overall Survival

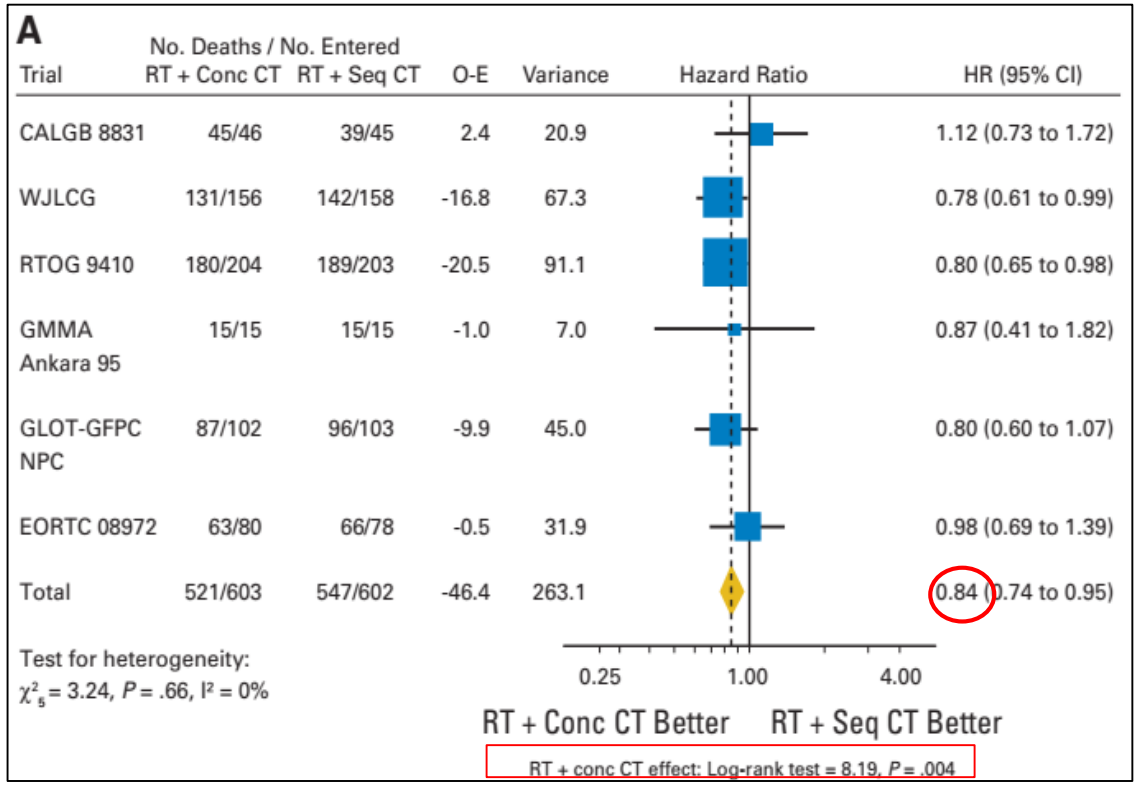
Trial	Pts	RT	CT--->RT
Finnish	238	17%	19%
NCCTG	107	16%	21%
CALGB	155	13%	26%
IGR-French	331	14%	21%



Hung et al. Medicine (2019) 98:27

Timing of Radiation



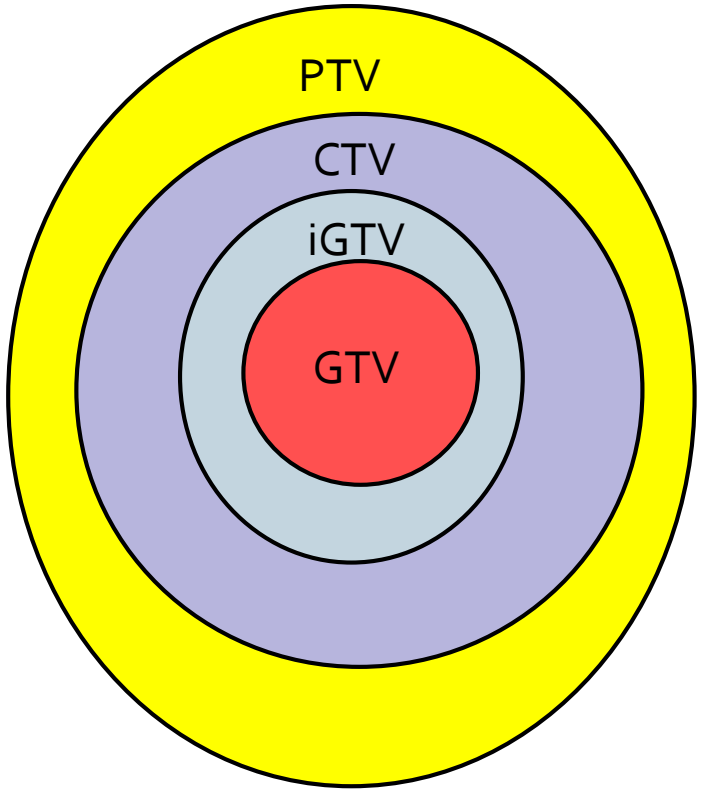


Absolute benefit of 5.7% (from 18.1% to 23.8%) at 3 years and 4.5% at 5 years

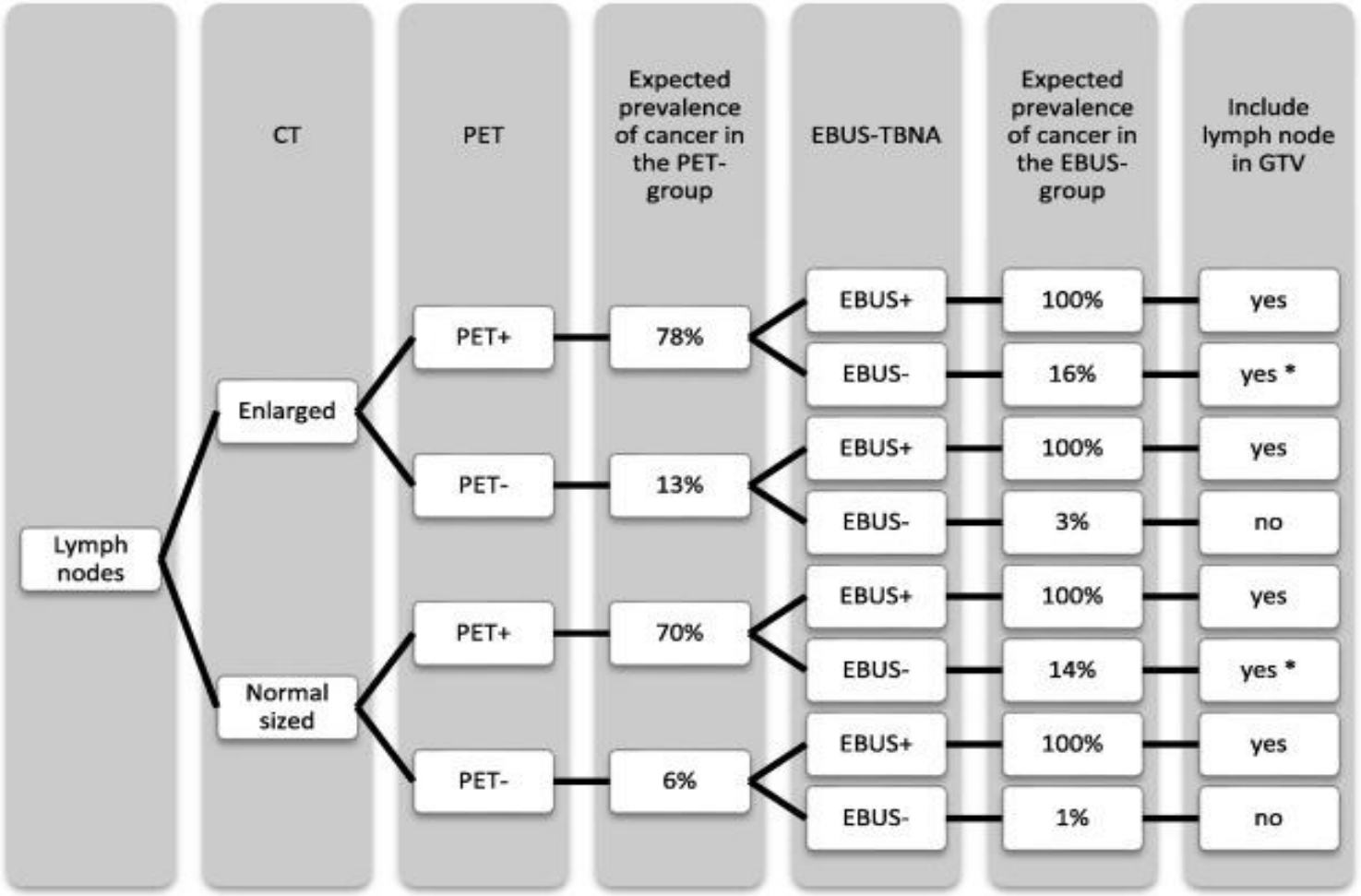
Auperin A et al. J Clin Oncol. 2010

Radiation Volumes

- GTV – Primary + Nodes (>1cm or SUV>3)
- No ENI
- ITV (iGTV) – GTV + Resp motion
- CTV – ITV + 0.7 cm
- PTV – CTV + 0.5 cm
- Prescription – Planning target volume



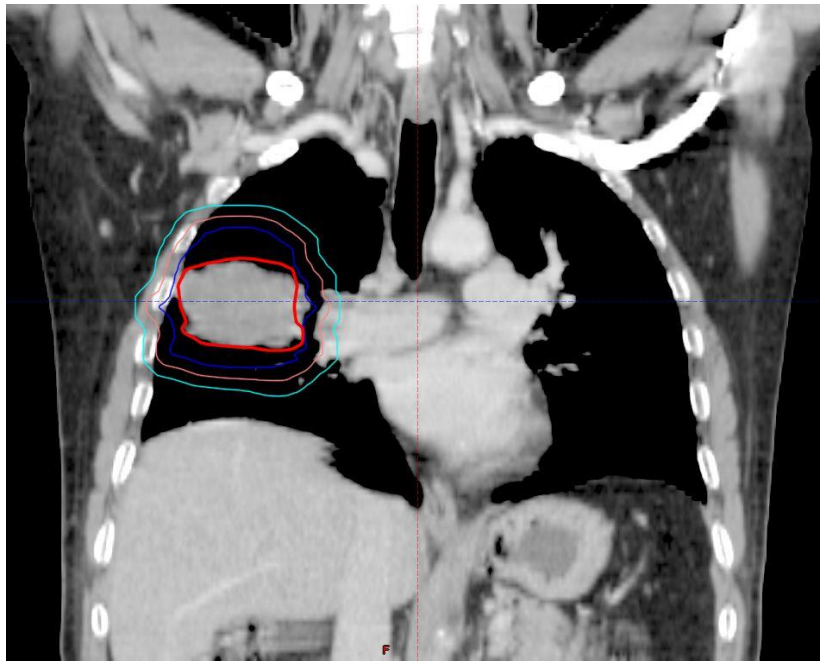
Radiation Volumes - Nodal

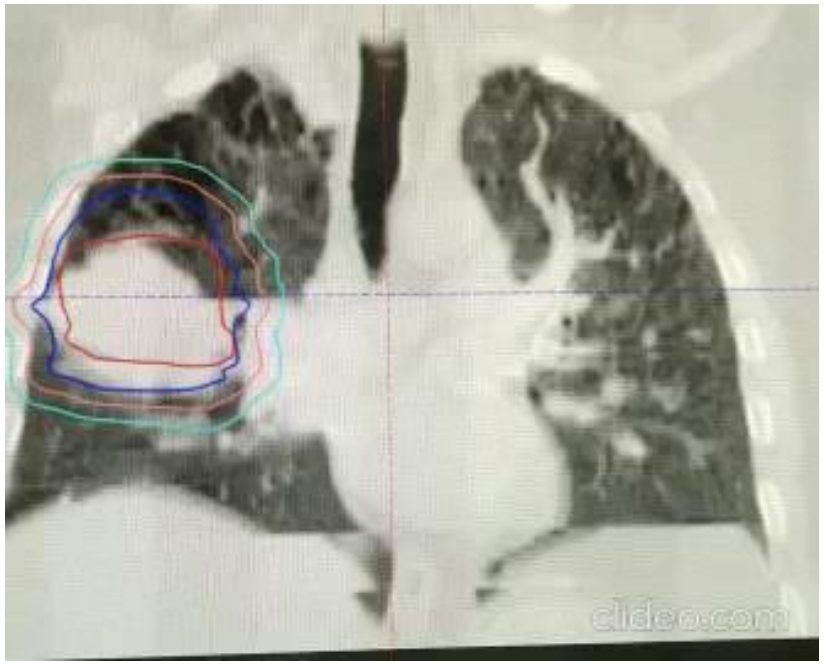


ENI is not recommended

ESTRO ACROP guidelines 2018

Motion Management

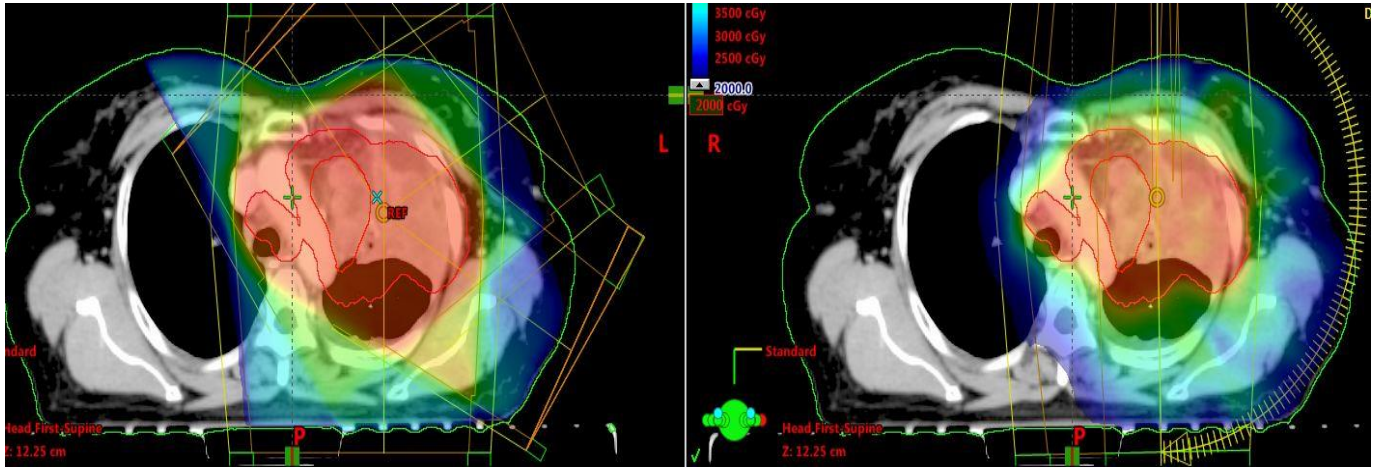




Techniques – 3D/ IMRT

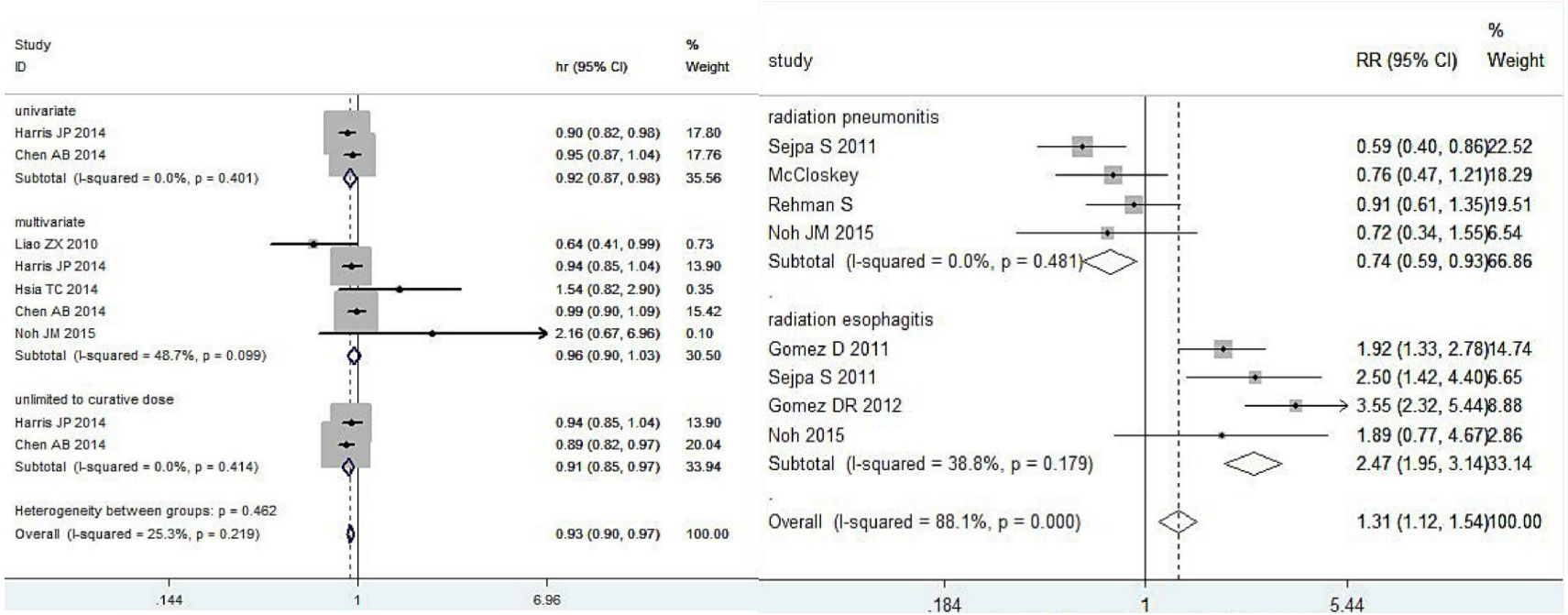
- IMRT is more conformal and reduces normal tissue doses better than 3D CRT
- In RTOG 0617 – inspite of larger volumes and more IIIB disease, IMRT reduces the risk of pneumonitis
- No difference in overall survival

Outcome	3D-CRT	IMRT,	P value
2-year OS	49.4	53.2	0.597
2-year PFS	27.0	25.2	0.595
Pneumonitis	7.9%	3.5%	0.03
Heart V40 (%)	11.4	6.8	0.003



3D-CRT **IMRT**

Meta Analysis of 3DCRT Vs IMRT

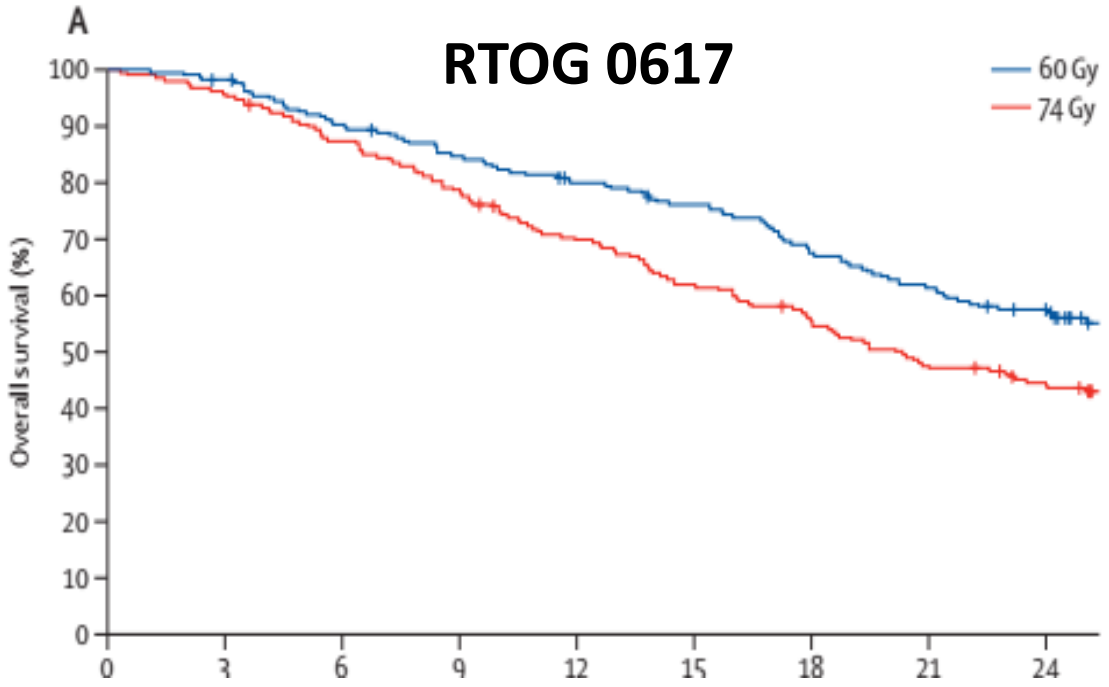


No difference in OS, significantly reduced the risk of pneumonitis

Hu et al

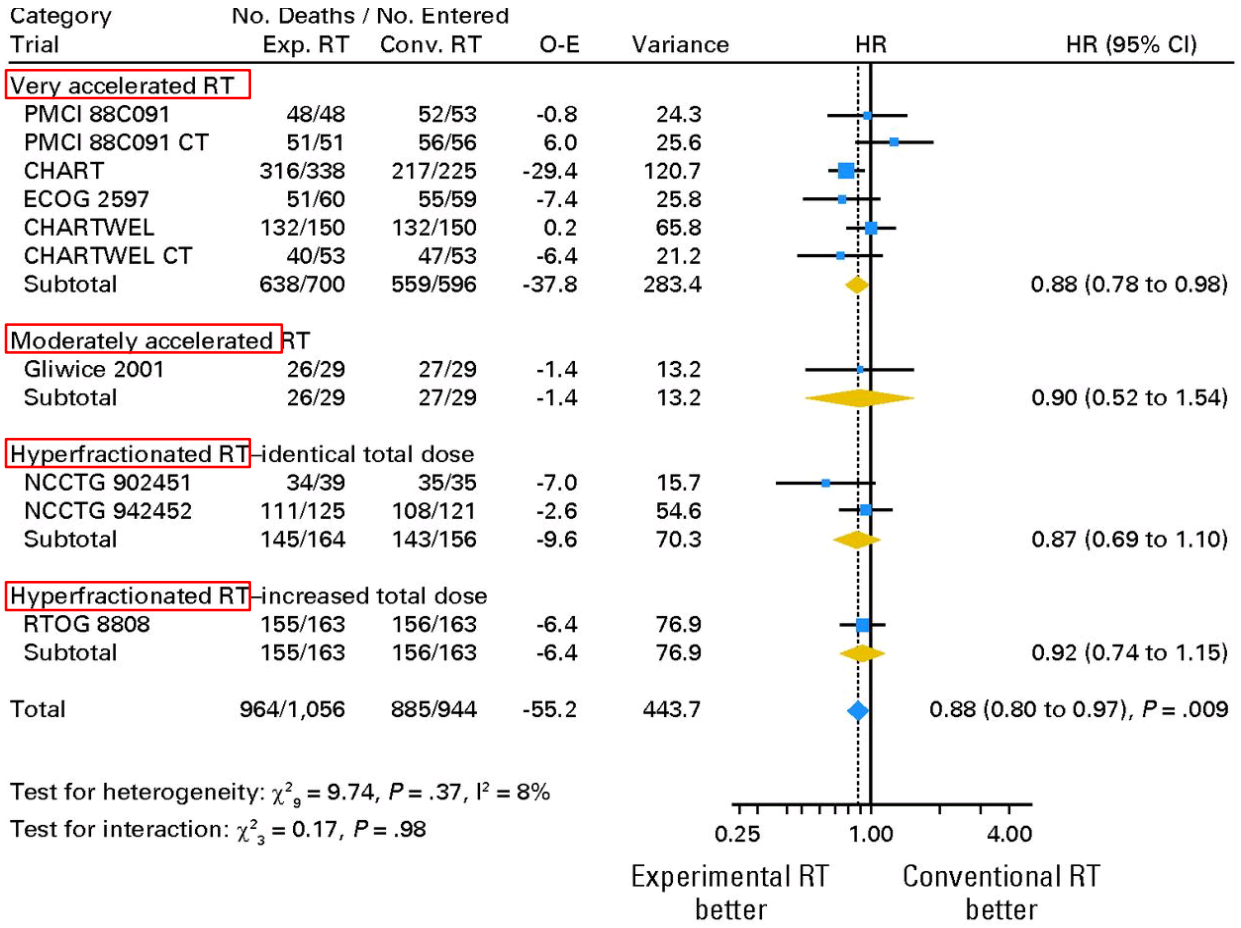
Dose and Fractionation

- Standard - 60-66 Gy in 30-33 fractions
- No proven role of uniform dose escalation



Outcome	60 Gy	74 Gy	P value
Med OS	28.7	20.3	0.007
5 yr OS	32.1%	23%	0.004
5 yr PFS	18.3%	13%	0.055

Accelerated fractionation schedules



- 5-yr absolute benefit in OS of 2.5%
- Esophagitis rate significantly higher with hyper fractionation

Mauguen A et al. J Clin Oncol 2012 Aug 1;30(22):2788-97

Outcome of CTRT

Trial (CTRT Arm)	Median OS (months)	3 year OS
INT 0139 (2009)	22.2	30%
RTOG 0617 (2015)	28.7	32% (5yr)
Proclaim (2016)	25	37%
PACIFIC (2020)	29.1	50% (4yr)

Patterns of failure

- Predominant site of failure – local and distant

RTOG 9410

- Arm 1 – Sequential
- Arm 2 – Concurrent 60 Gy
- Arm 3 – Concurrent 69.2 Gy

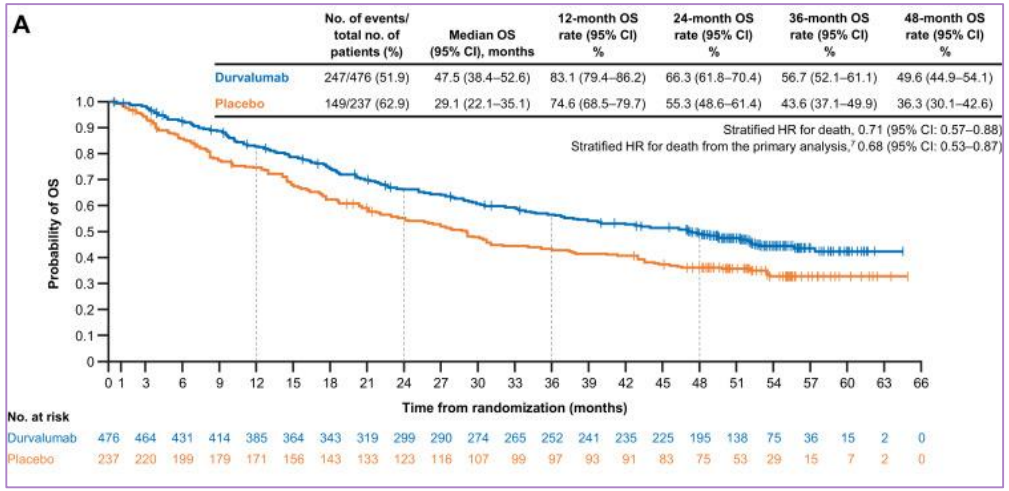
Table 3. Patterns of failure*

Component of first failure	No. (%) Arm 1 (n = 195)	Arm 2 (n = 195)	Arm 3 (n = 187)
Primary tumor	65 (33)	56 (29)	47 (25)
Thoracic lymph nodes (infield)	34 (17)	24 (12)	18 (10)
Thoracic lymph nodes (out of field)	4 (2)	8 (4)	3 (2)
Brain metastases	24 (12)	28 (14)	24 (13)
Other metastases	65 (33)	64 (33)	60 (32)
Infield only	59 (30)	49 (25)	38 (20)
Out of field only	67 (34)	73 (37)	69 (37)
Both infield and out of field	22 (11)	20 (10)	16 (9)

PROCLAIM	Arm A		Arm B	
Relapse Site	**Pts No.**	**%**	**Pts No.**	**%**
Within RT field	60	37.3	80	45.8
Outside RT field	34	20.5	31	16.3
Distant Relapse	83	50	87	45.8
Brain Mets	31	18.7	37	19.5

Immunotherapy with CTRT

- PACIFIC Trial - Consolidation Durvalumab improved 5 yr OS
- Concurrent Durvalumab (Ongoing)
- Neo-adjuvant Durvalumab (Ongoing)
- Adjuvant Pembrolizumab (Ongoing)



Neoadjuvant Chemo-Radiation

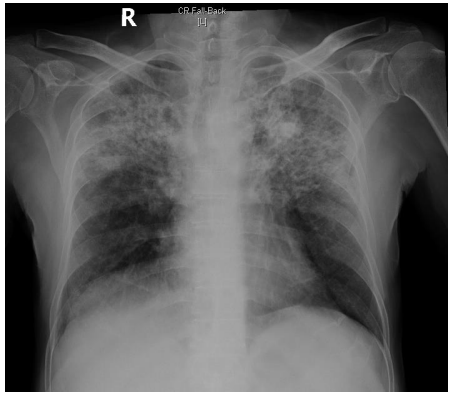
Study	Arms	Median OS (months)	OS	Median PFS	Downstaging
RTOG 8901	NACT-Sx	19.4	70% (1yr)		
	NACT-CTRT	17.4	66% (1yr)		
INT 0139	**CTRT (45Gy)-Sx**	23.6	27% (5yr)	12.8 (5yr – 22%)	
	CTRT (61Gy)	22.2	20% (5yr)	10.5 (5yr – 12%)	
ESPATAUE (2015 JCO)	**NACT-CTRT(bid)-Sx**	-	44% (5yr)	(5yr – 35%)	R0-81%
	NACT-CTRT	-	40% (5yr)	(5yr – 32%)	
Pless et al (2015 Lancet)	**NACT-RT-Sx**	37.1		12.8	R0-91%
	NACT-Sx	26.2		11.6	R0-81%
Katakami et al (2012 Cancer)	**CTRT(40Gy)-Sx**	39.6	52% (3yr)	12.4 (3yr – 34%)	40%
	NACT-Sx	29.9	39% (3yr)	9.7 (3yr – 18%)	21%
Thomas et al (2008 Lancet)	NACT-Sx ± RT	33	31% (5yr)	21 (5yr – 25%)	20%
	NACT-CTRT(bid)-Sx	32.4	39% (5yr)	20 (5yr – 30%)	60%

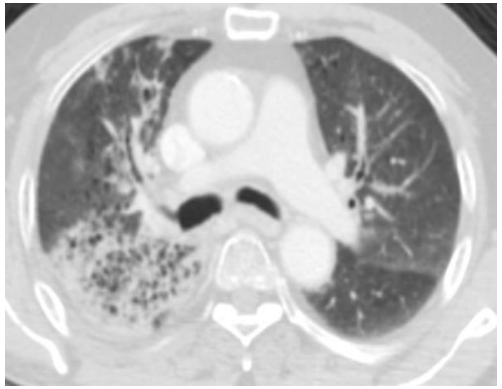
Downstaging - Significance

	Yes	No
INT 0139	34.4 months (pN0)	
Katakami et al (2012 Cancer)	72 months	31 months
Thomas et al (2008 Lancet)	50 months	20 months

Complications of CRT

- Radiation Pneumonitis – ≥ Gr 3 - 15-20 %
- Oesophagitis – length of oesophagus and Etoposide
- Radiation Induced Heart Disease – RTOG 0617 attributed poorer OS





Factors impacting RIP

Age > 65 yrs
Lung Doses (MLD>20Gy, V20>35%)
PFT
Smoking
Taxanes CT

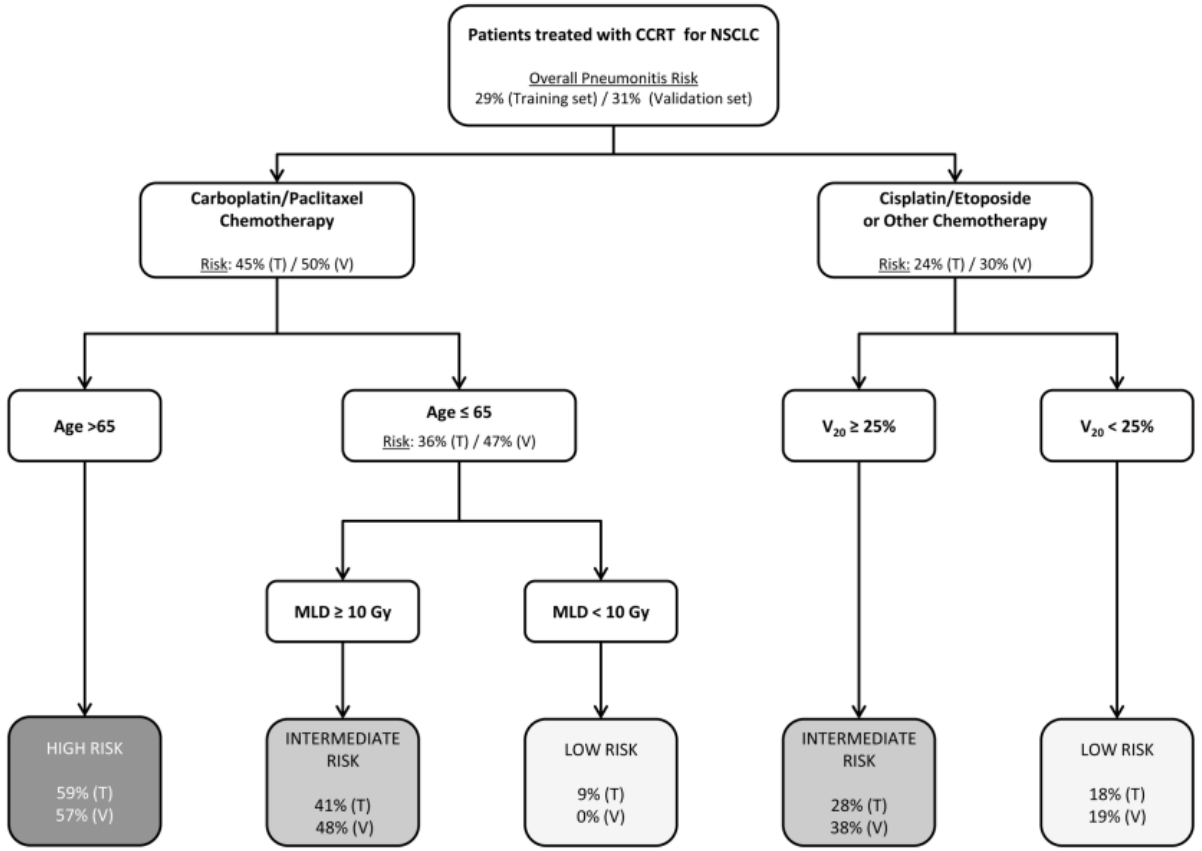
Treatment - Short course steroids

CTCAE Scale

PFT	Cutoff point	No Pneumonitis	Pneumonitis	HR	95% CI	*P* value
FEV1	<1.9	2 (9.1%)	7 (46.7%)	3.21	0.93–11.16	**0.017**
	≥1.9	20 (90.9%)	8 (53.3%)			
FeNO	<17.5	13 (59.1%)	3 (20%)	1.90	1.10–3.28	**0.041**
	≥17.5	9 (40.9%)	12 (80%)			
DLCO	<18.9	7 (31.2%)	12 (80%)	2.26	1.21–4.22	**0.007**
	≥18.9	15 (68.2%)	3 (20%)			

Bouscoulet et al. Respiratory Research (2018) 19:72

Risk stratification for RP



V20 Gy	Symptomatic pneumonitis (≥ Gr 2)	Fatal Pneumonitis
<20%	18.4%	0.0%
20-29.99%	30.3%	1.0%
30-39.99%	32.6%	2.9%
≥ 40%	35.9%	3.5%

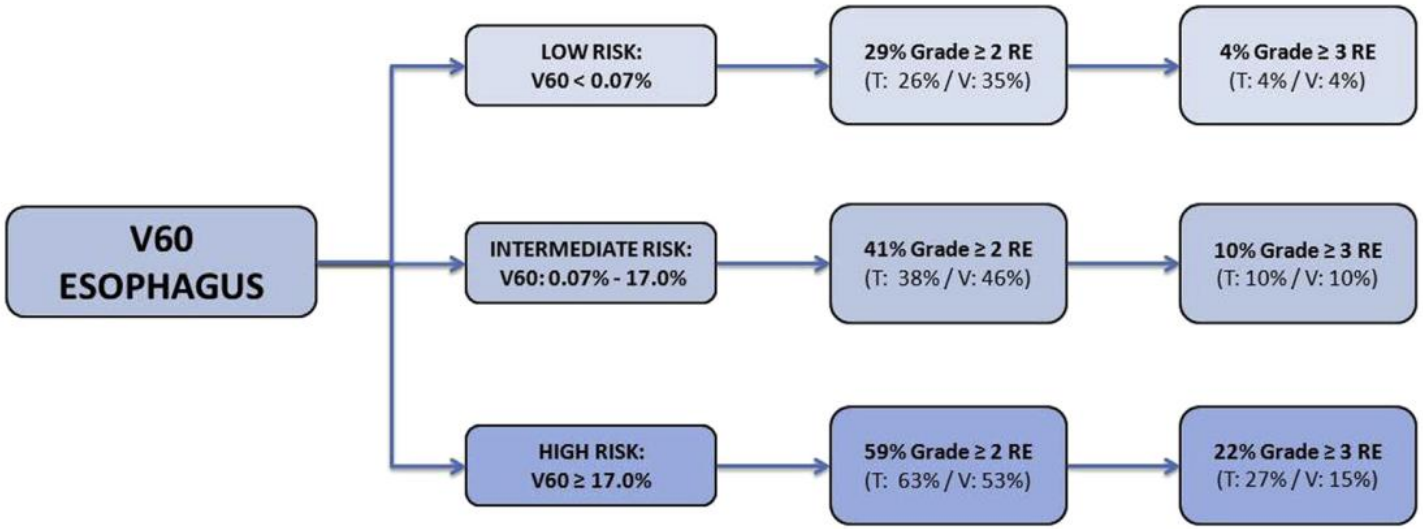
Palma et al; IJROBP: 2014

Predictors of Esophagitis

- Usually starts from 4-5th week
- Etoposide
- V60
- SUVpeak

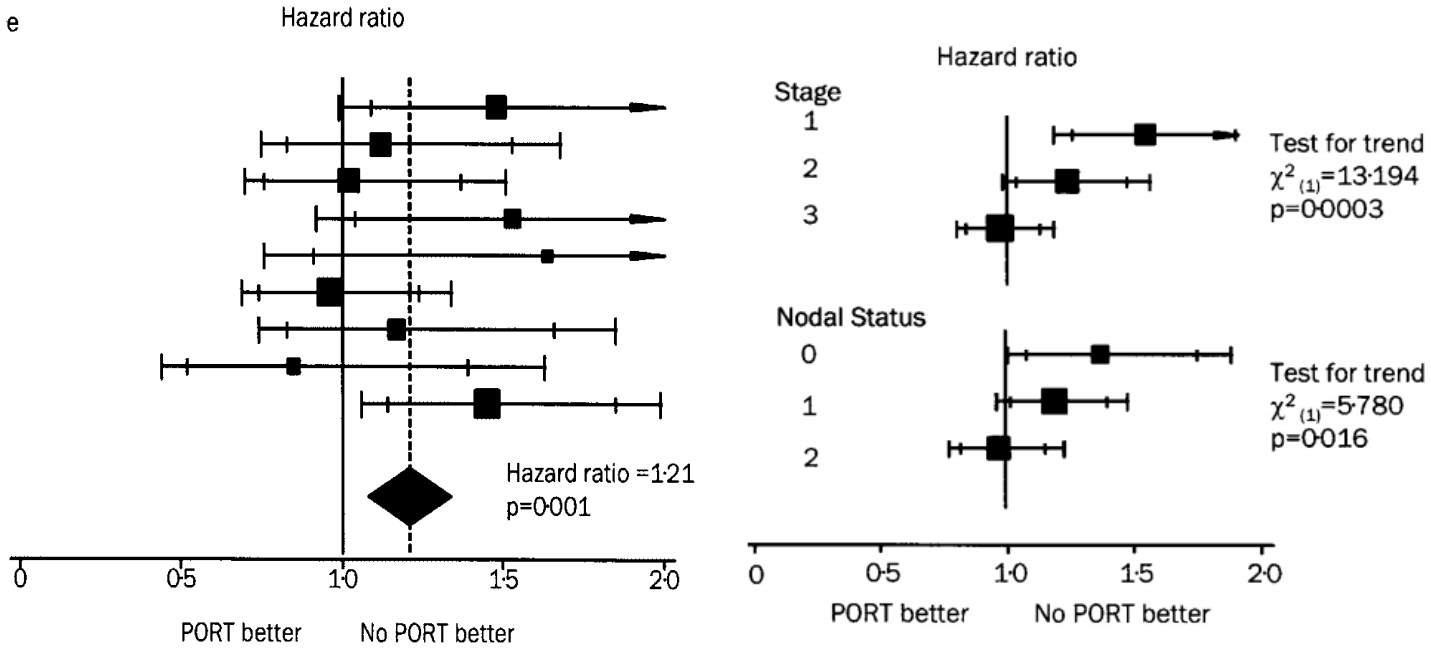
CLINICAL INVESTIGATION | VOLUME 87, ISSUE 4, P690-696, NOVEMBER 15, 2013

Predicting Esophagitis After Chemoradiation Therapy for Non-Small Cell Lung Cancer: An Individual Patient Data Meta-Analysis



Palma et al; IJROBP: 2013

PORT in LALC



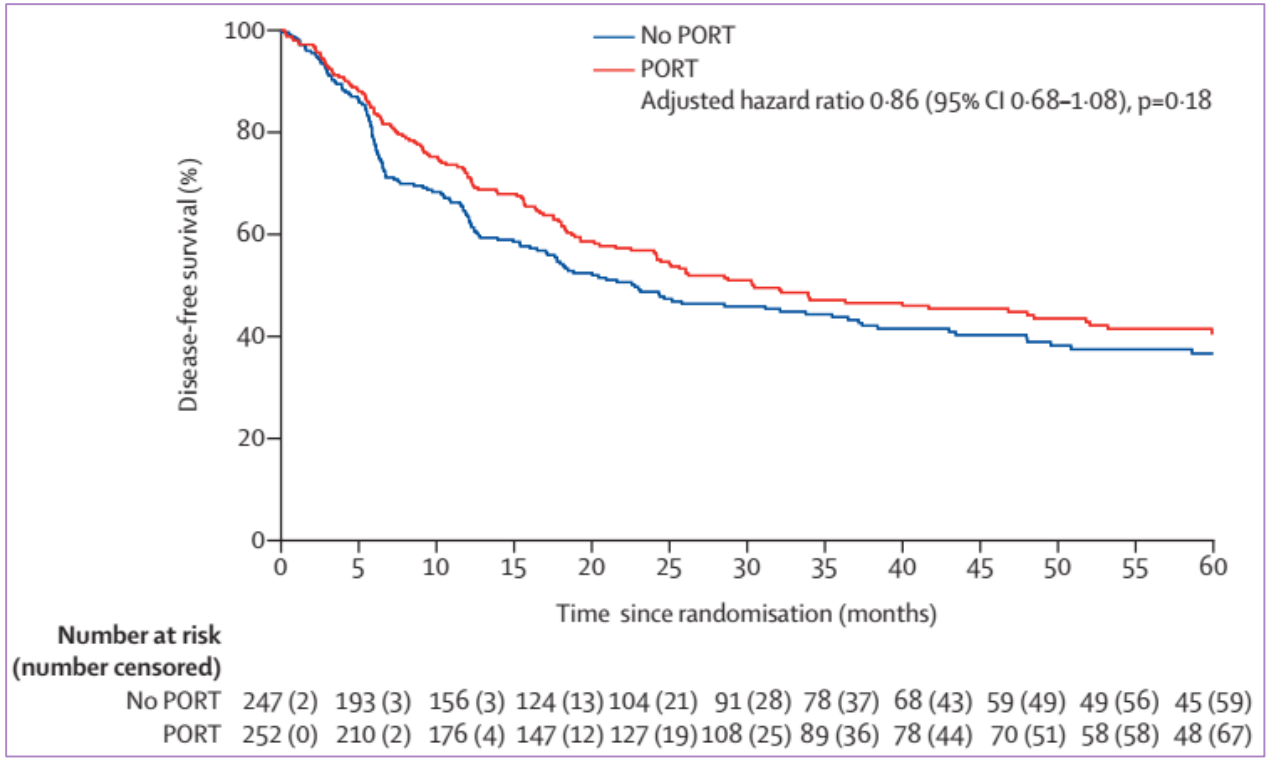
PORT Meta Analysis; Lancet - 1998

Table 3. ANITA trial results: Percentage of patients with 5-year survival, according to treatment received by nodal status

Treatment group	pN0	pN1	pN2
Observation (%)	62.3	31.4	16.6
Observation + PORT (%)	43.8	42.6	21.3
Chemotherapy* (%)	59.7	56.3	34.0
Chemotherapy* + PORT (%)	44.4	40.0	47.4

Douillard et al. IJROBP.2008;72:695-701

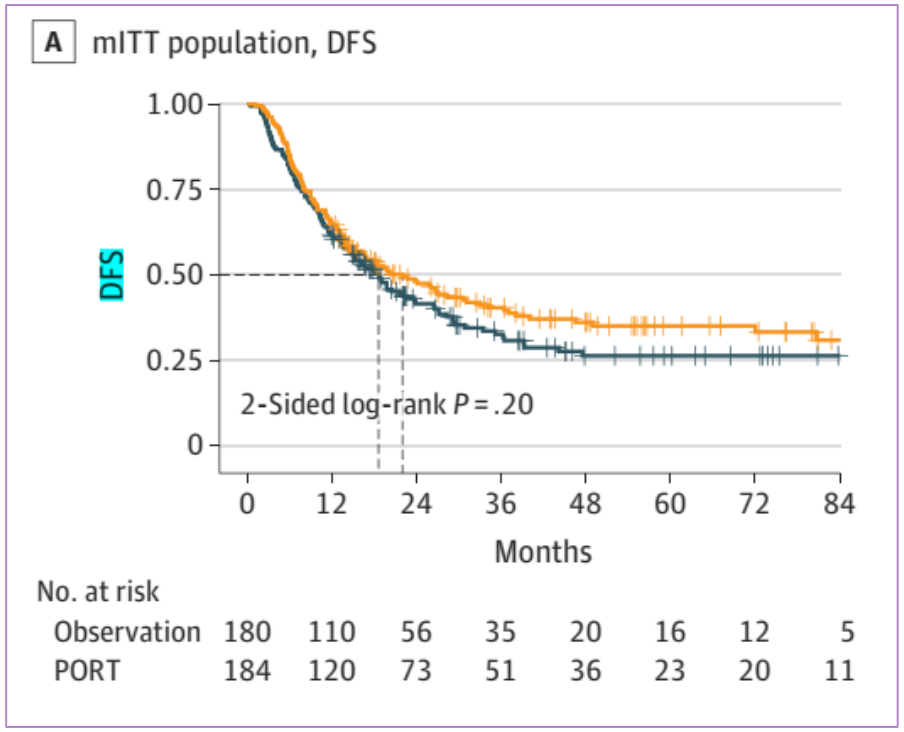
Postoperative radiotherapy versus no postoperative radiotherapy in patients with completely resected non-small-cell lung cancer and proven mediastinal N2 involvement (Lung ART): an open-label, randomised, phase 3 trial

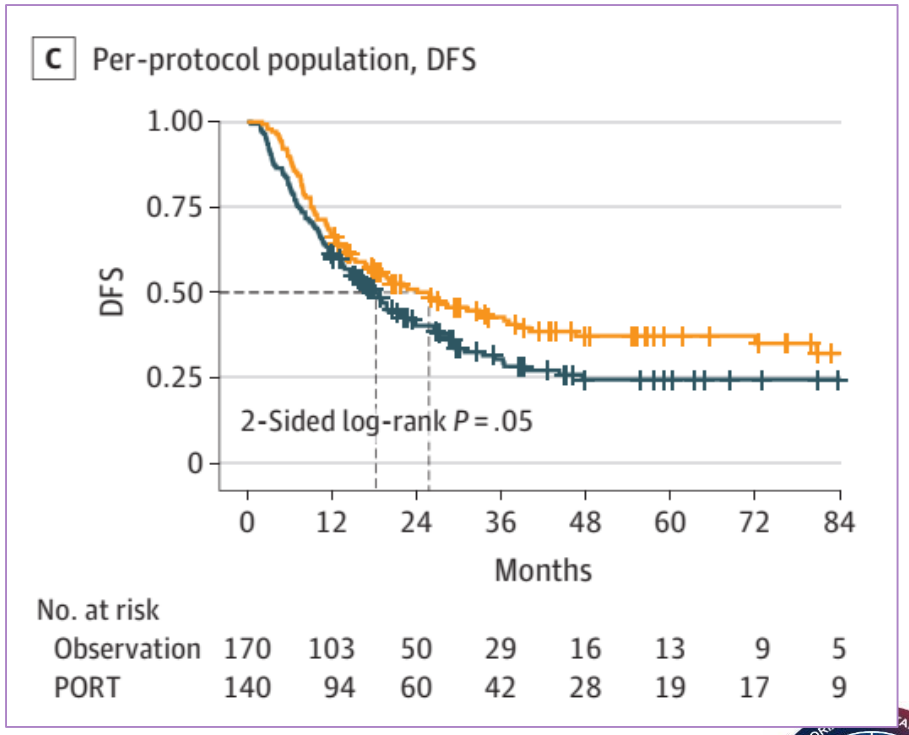


JAMA Oncology | Original Investigation

Effect of Postoperative Radiotherapy for Patients With pIIIA-N2 Non–Small Cell Lung Cancer After Complete Resection and Adjuvant Chemotherapy

The Phase 3 PORT-C Randomized Clinical Trial





Take Home Message

- Radiation therapy is the standard treatment for LALC
- Patient selection is very crucial
- Concurrent chemotherapy – improves OS
- Radiation volume and Planning – utmost consideration
- Immunotherapy with CTRT – Promising results

THANK YOU

Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomised trial in stage III non-small-cell lung cancer

Thomas et al 2008

Histopathological response in patients with complete resection* (n=182), n (%)		
>90%	59 (60)	17 (20)
<90%	30 (31)	60 (71)
Unknown or not done	9 (9)	7 (8)