Evolving Role of Radiotherapy in Lung Cancer Treatment

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No conflict of interest to disclose

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Objectives:

- To review the role of RT in NSCLC
- To review recent trials on RT
- To discuss how to improve the outcomes

Estimated New Cases

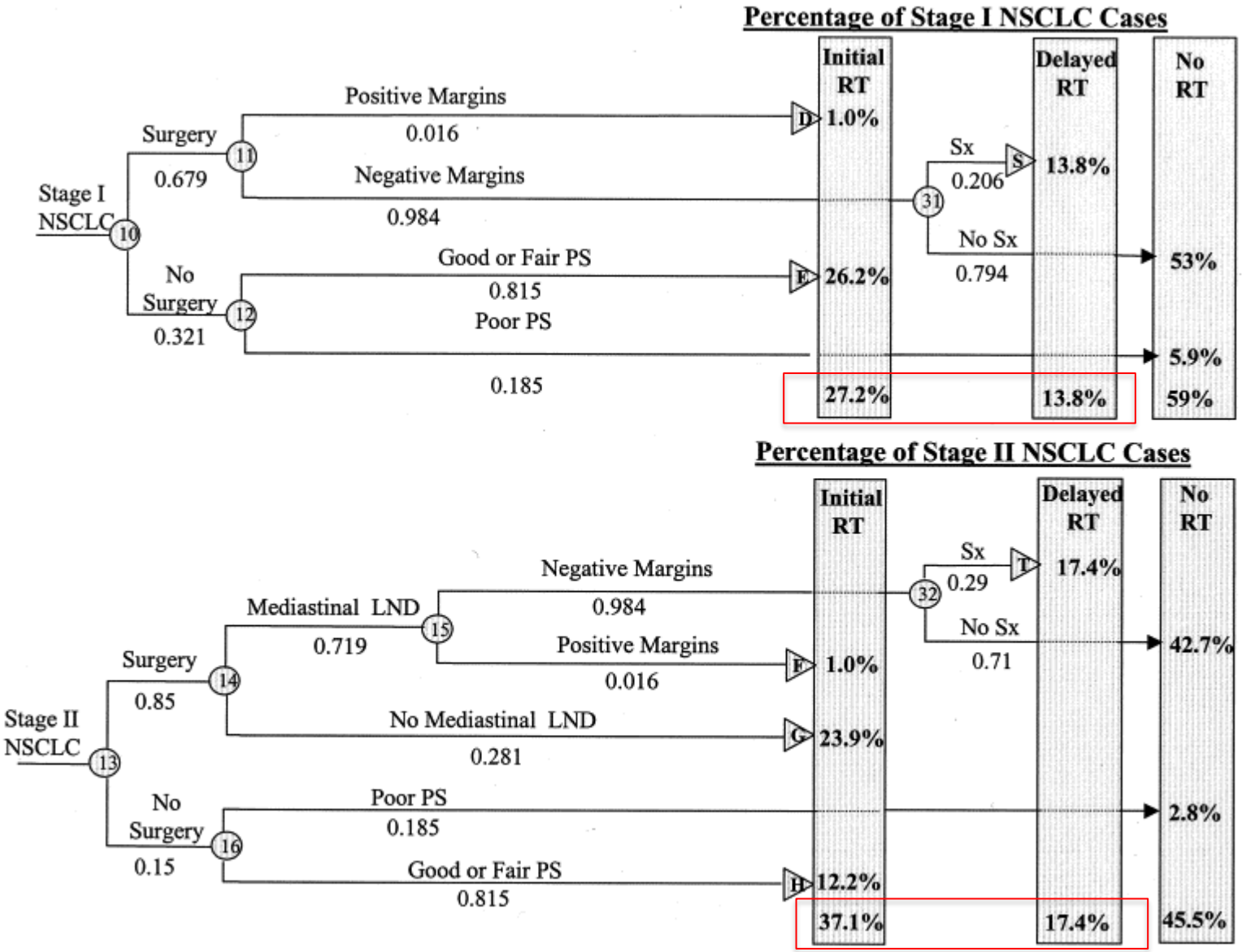
Males				Females		
Prostate	268,490	27%		Breast	287,850	31%
Lung & bronchus	117,910	12%		Lung & bronchus	118,830	13%
Colon & rectum	80,690	8%		Colon & rectum	70,340	8%
Urinary bladder	61,700	6%		Uterine corpus	65,950	7%
Melanoma of the skin	57,180	6%		Melanoma of the skin	42,600	5%
Kidney & renal pelvis	50,290	5%		Non-Hodgkin lymphoma	36,350	4%
Non-Hodgkin lymphoma	44,120	4%		Thyroid	31,940	3%
Oral cavity & pharynx	38,700	4%		Pancreas	29,240	3%
Leukemia	35,810	4%		Kidney & renal pelvis	28,710	3%
Pancreas	32,970	3%		Leukemia	24,840	3%
All Sites	**983,160**	**100%**		**All Sites**	**934,870**	**100%**

Estimated Deaths

Males				Females		
Lung & bronchus	68,820	21%		Lung & bronchus	61,360	21%
Prostate	34,500	11%		Breast	43,250	15%
Colon & rectum	28,400	9%		Colon & rectum	24,180	8%
Pancreas	25,970	8%		Pancreas	23,860	8%
Liver & intrahepatic bile duct	20,420	6%		Ovary	12,810	4%
Leukemia	14,020	4%		Uterine corpus	12,550	4%
Esophagus	13,250	4%		Liver & intrahepatic bile duct	10,100	4%
Urinary bladder	12,120	4%		Leukemia	9,980	3%
Non-Hodgkin lymphoma	11,700	4%		Non-Hodgkin lymphoma	8,550	3%
Brain & other nervous system	10,710	3%		Brain & other nervous system	7,570	3%
All Sites	**322,090**	**100%**		**All Sites**	**287,270**	**100%**

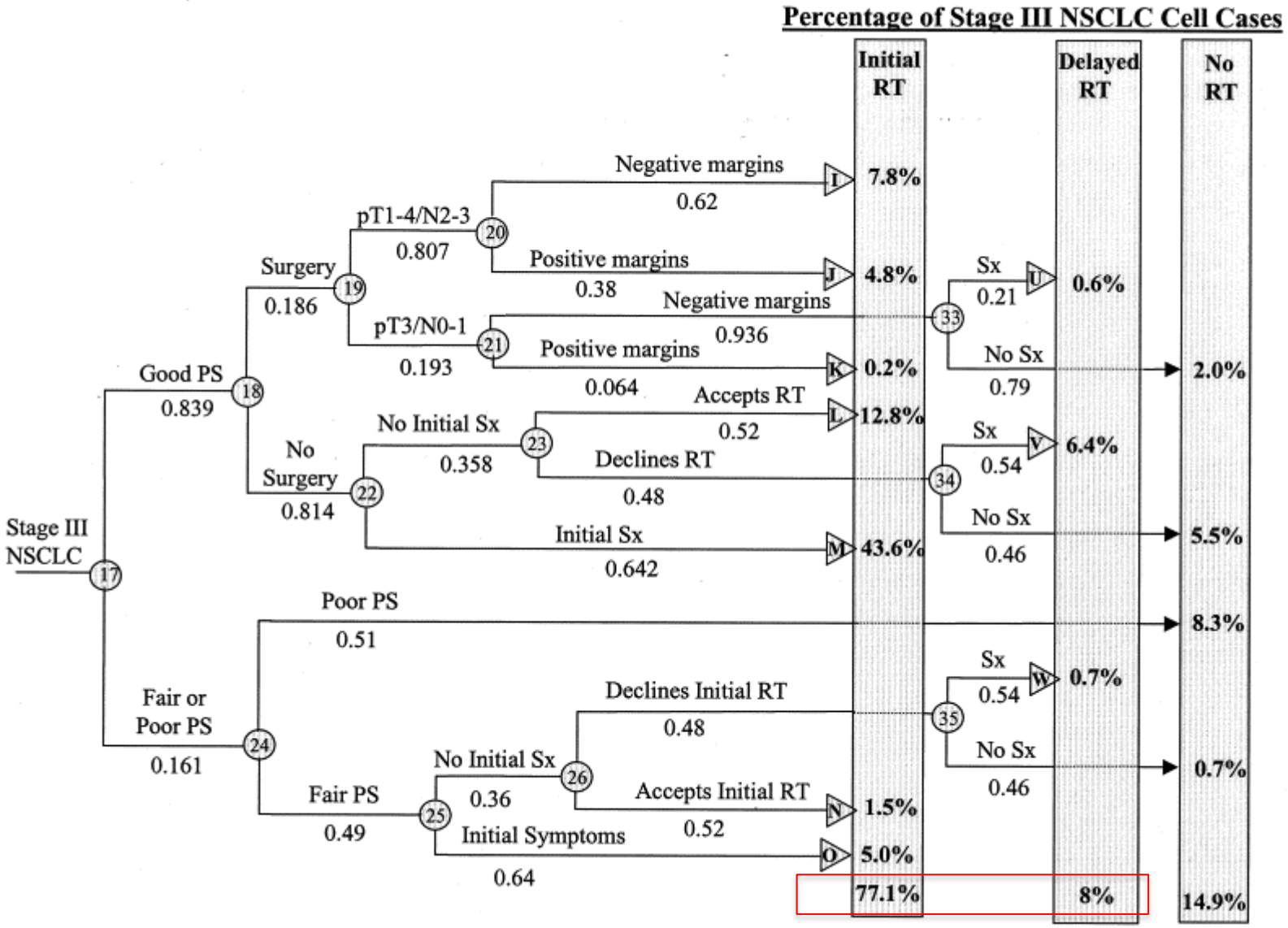
Radiotherapy (RT) is used in all stages of lung cancer treatment and is required at least once in over half of patients for either cure or palliation.

Indications for radiotherapy (RT) for Stage I and II non–small-cell lung cancer



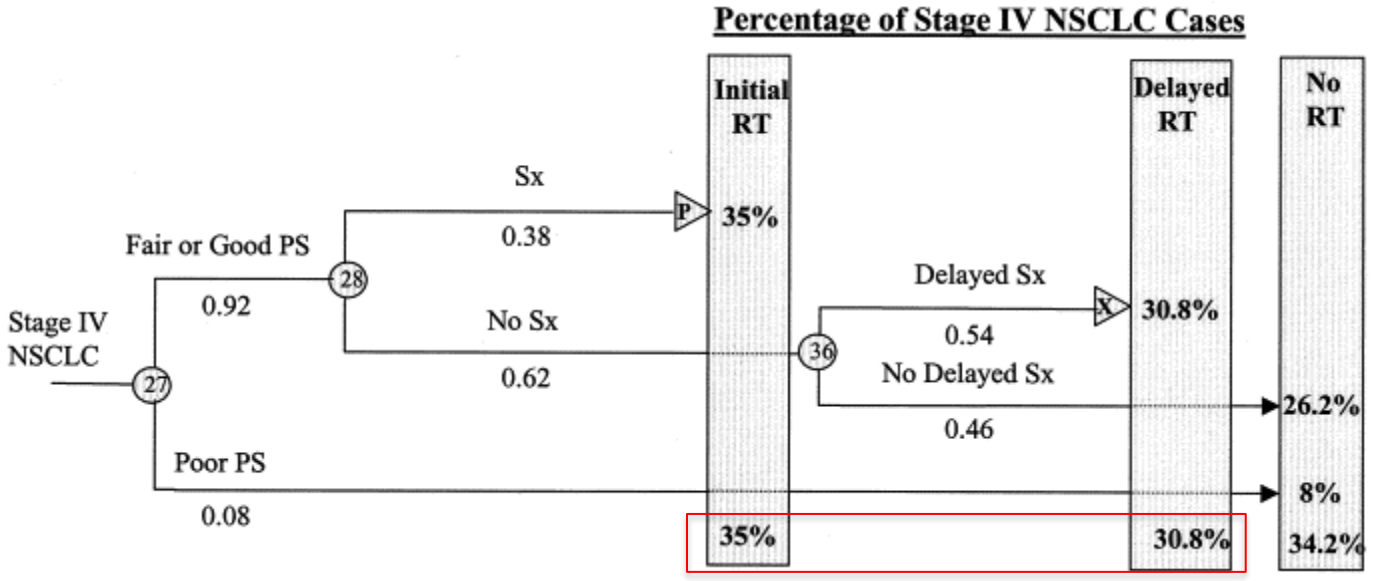
S. Tyldesley, et al Radiat Oncol Bio Phy 2001

Indications for radiotherapy (RT) for Stage III non–small-cell lung cancer



S. Tyldesley, et al Radiat Oncol Bio Phy 2001

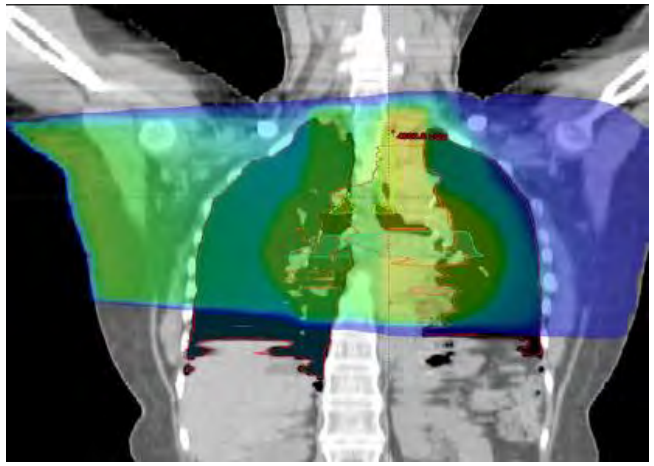
Indications for radiotherapy (RT) for Stage IV non–small-cell lung cancer



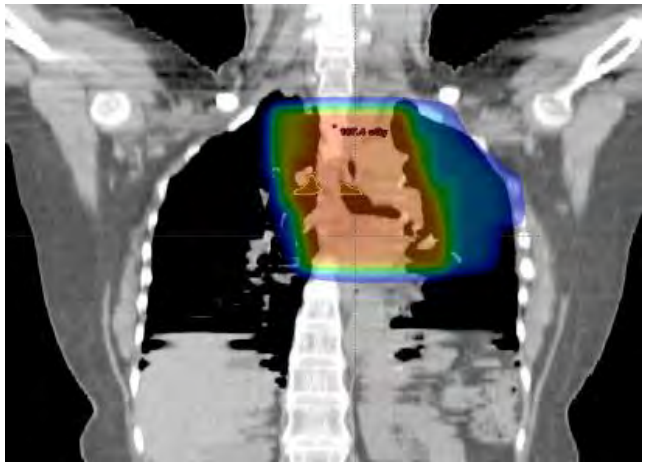
Overall, 64.3% ± 4.7% of NSCLC cases will require RT, 45.9% ± 4.3% at the time of diagnosis, and 18.3% ± 1.8% later in the course of the illness

S. Tyldesley, et al Radiat Oncol Bio Phy 2001

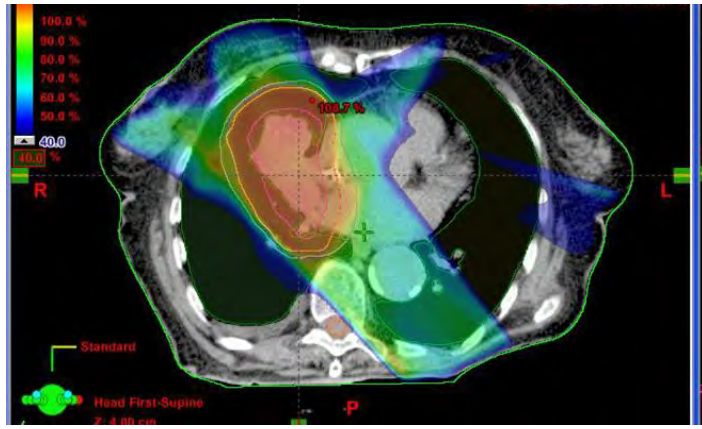
Improved radiation delivery



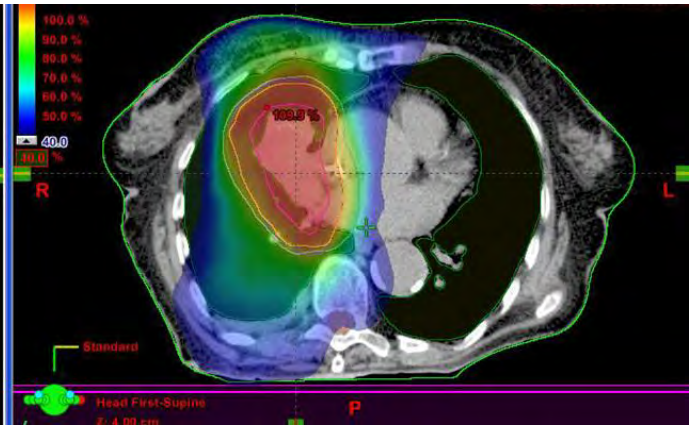
Conventional



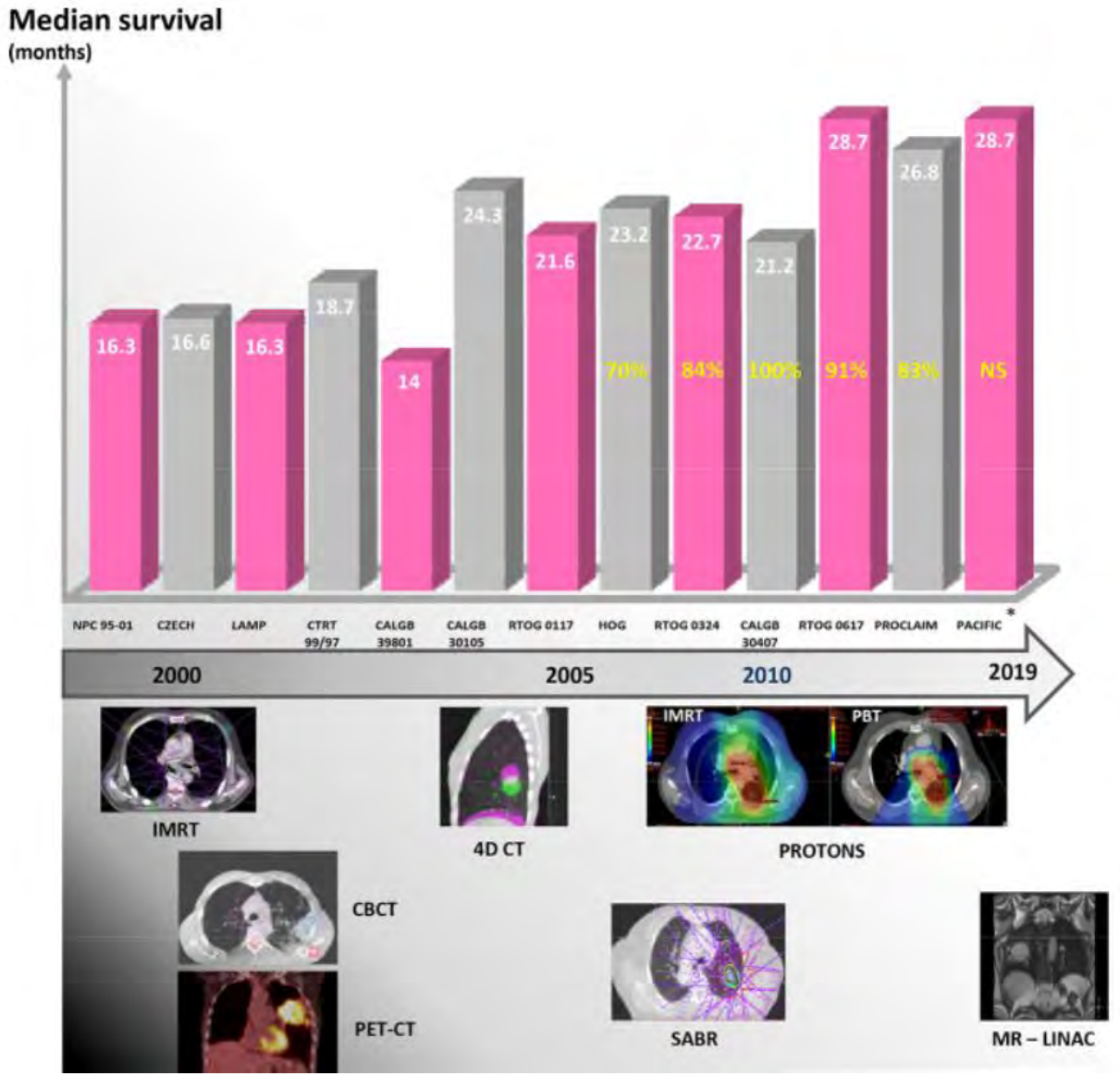
3D-CRT



IMRT



VMAT



Technical Advances in Radiation Therapy in Lung Cancer

Brown S, Banfill K, Aznar MC, Whitehurst P, Faivre Finn C. The evolving role of radiotherapy in non-small cell lung cancer. Br J Radiol. 2019;92(1104):20190524. doi:10.1259/bjr.20190524

SBRT/SABR for Stage I Lung Cancer

UNMC
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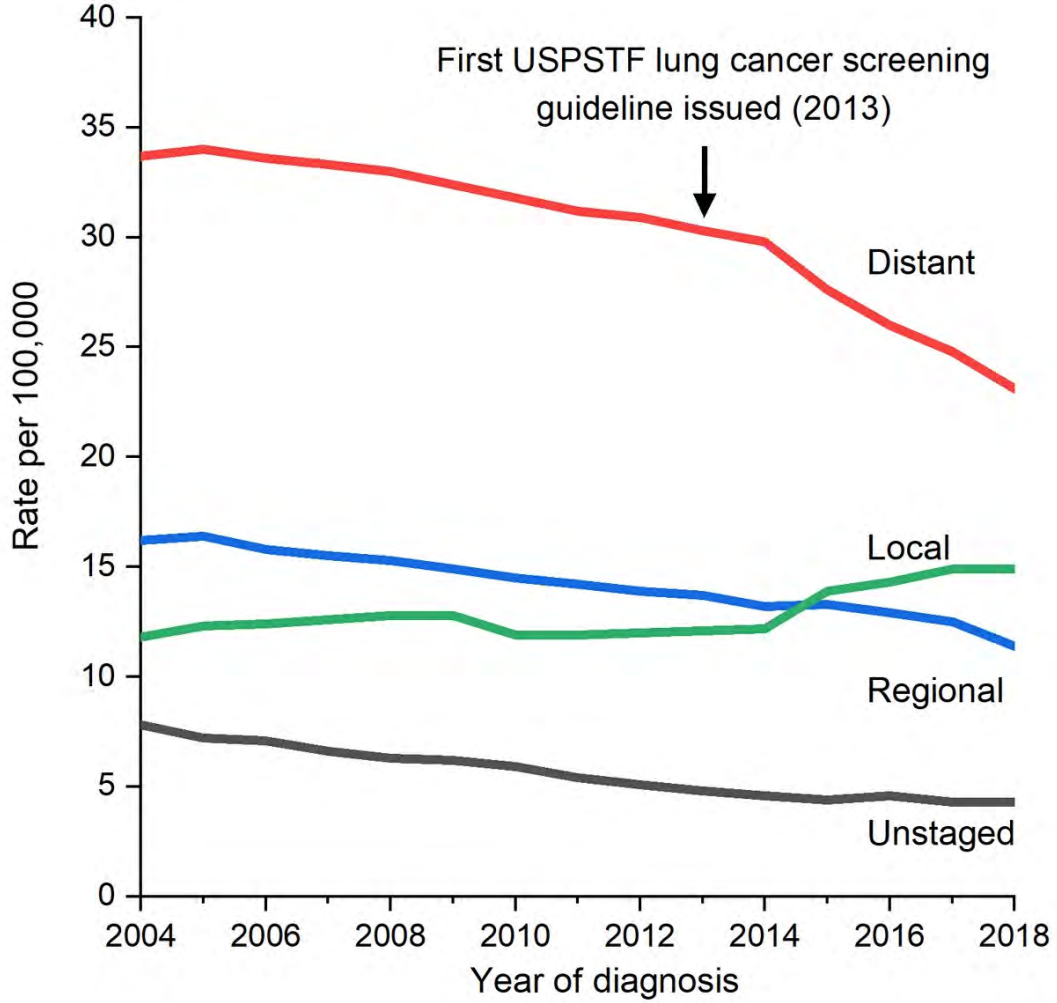


AAPC, 2014-2018 (95% CI):

-6.2[a] (-6.8 to -5.6)

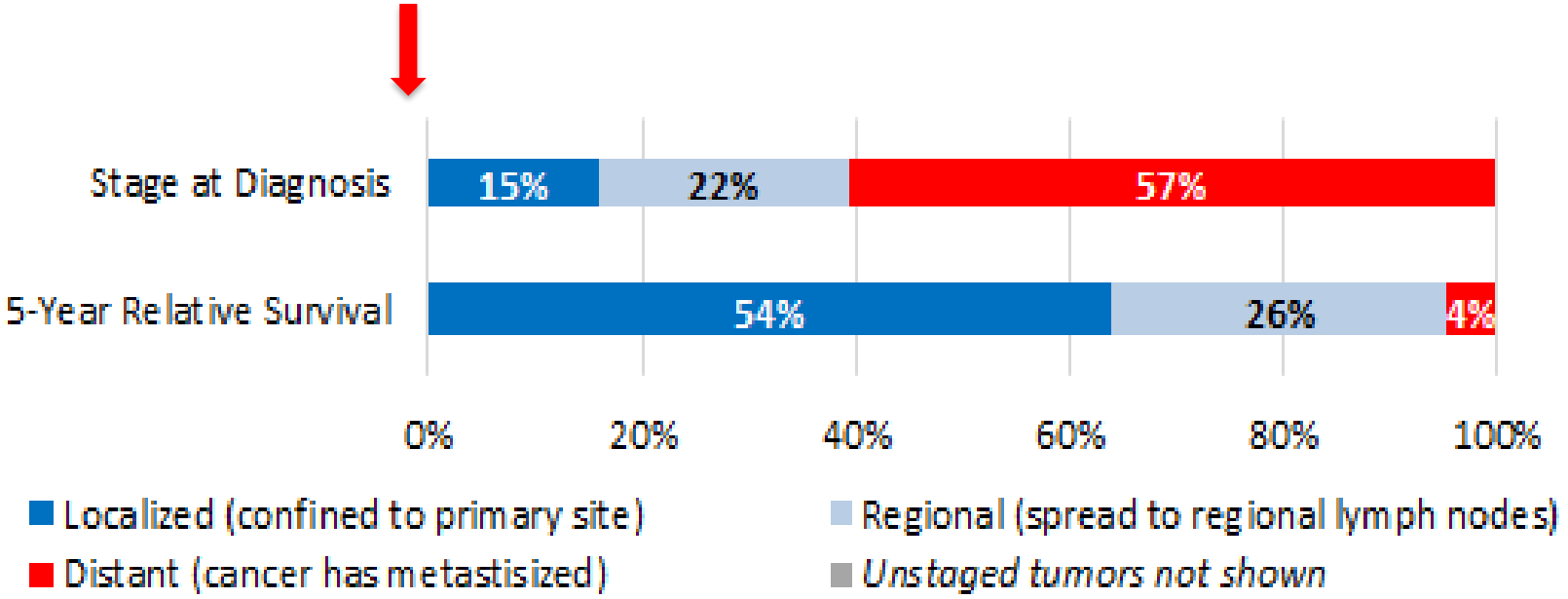
4.5[a] (3.0 to 6.0)

-3.7[a] (-5.0 to -2.3)

-2.2[a] (-4.1 to -0.3)

Percent localized stage:	17%	20%	28%
All stages, 3-yr survival:	21%	31%[b]	

Lung Cancer Diagnosis and Survival By Stage, 2003-2009



U.S. National Institutes of Health. National Cancer Institute. SEER Cancer Statistics Review, 1975-2010

Early-stage NSCLC

- Incidence is rising due to better diagnostic imaging and screening
- 90% of early-stage NSCLC patients die from lung cancer within 5 years if untreated
- Conventional fractionated RT can provide a 7-month extension of median survival

Early-stage NSCLC

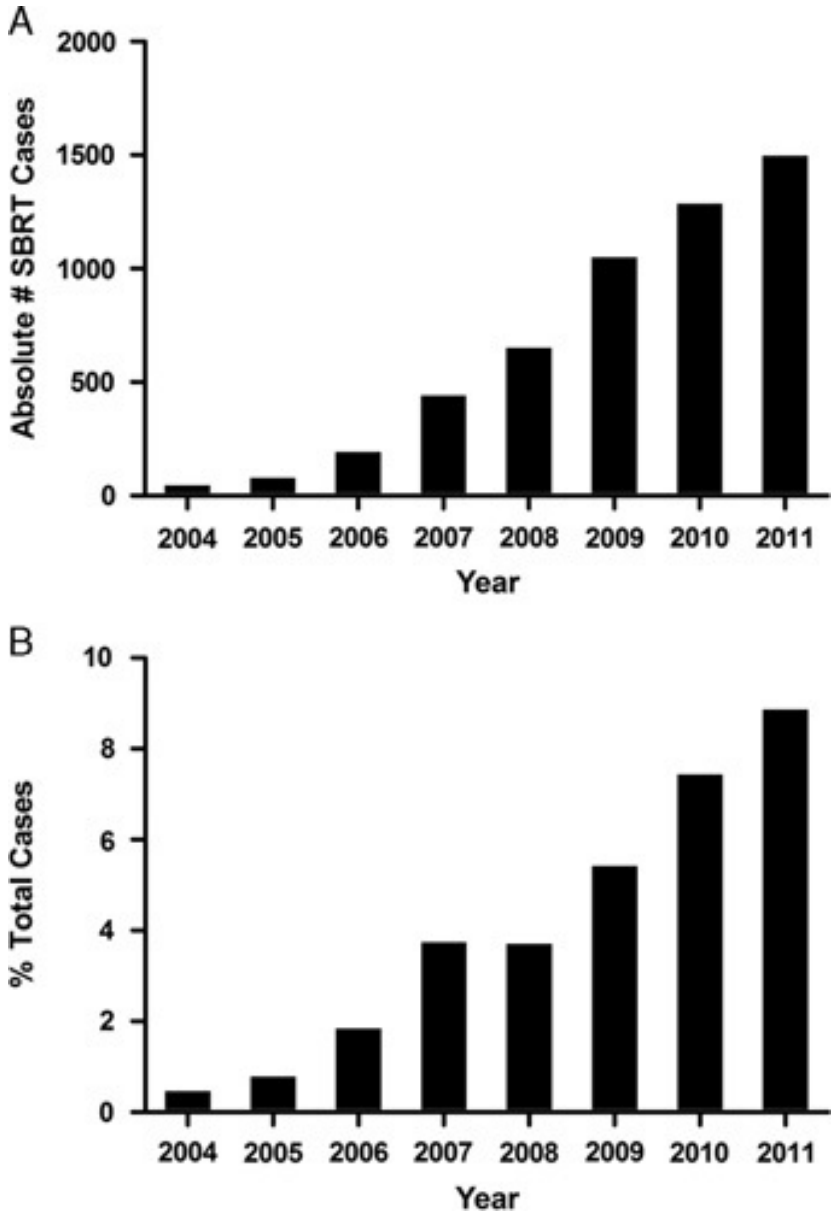
- Surgical resection is the standard treatment
- Only approximately 70% of patients receive surgical treatment.
  - ~20% of the patients are considered medically inoperable
  - ~10% patients may decline surgery due to individual concerns

Medically Inoperable Early-Stage Lung Cancers Treated with Conventional RT

Study Author	n	Dose (Gy)	5-yr survival	5-yr CSS	5-yr local
Dosoretz	152	60-69	10%		
Krol	108	60-65	15%	31%	25%
Kaskowitz	53	63	6%	13%	0%
Sibley	141	55-70	13%		
Rosenzweig	32	70.2	33%	39%	43%

There is a dramatic rise in SBRT use for patients with early-stage lung cancer.

Large-scale national database results revealed a 33-fold increase in SBRT use for early-stage NSCLC, accounting for <0.5% to 8.7% of treated cases over a 8-year span.



Trends in SBRT use. (A) Absolute number of cases by year. (B) Percentage of all stage I cases treated with SBRT by year.

American Journal of Clinical Oncology40(4):358-361, August 2017.

Stereotactic ablative radiotherapy versus standard radiotherapy in stage 1 non-small-cell lung cancer (TROG 09.02 CHISEL): a phase 3, open-label, randomised controlled trial

David Ball, G Tao Mai, Shalini Vinod, Scott Babington, Jeremy Ruben, Tomas Kron, Brent Chesson, Alan Herschtal, Marijana Vanevski, Angela Rezo, Christine Elder, Marketa Skala, Andrew Wirth, Greg Wheeler, Adeline Lim, Mark Shaw, Penelope Schofield, Louis Irving, Benjamin Solomon, on behalf of the TROG 09.02 CHISEL investigators

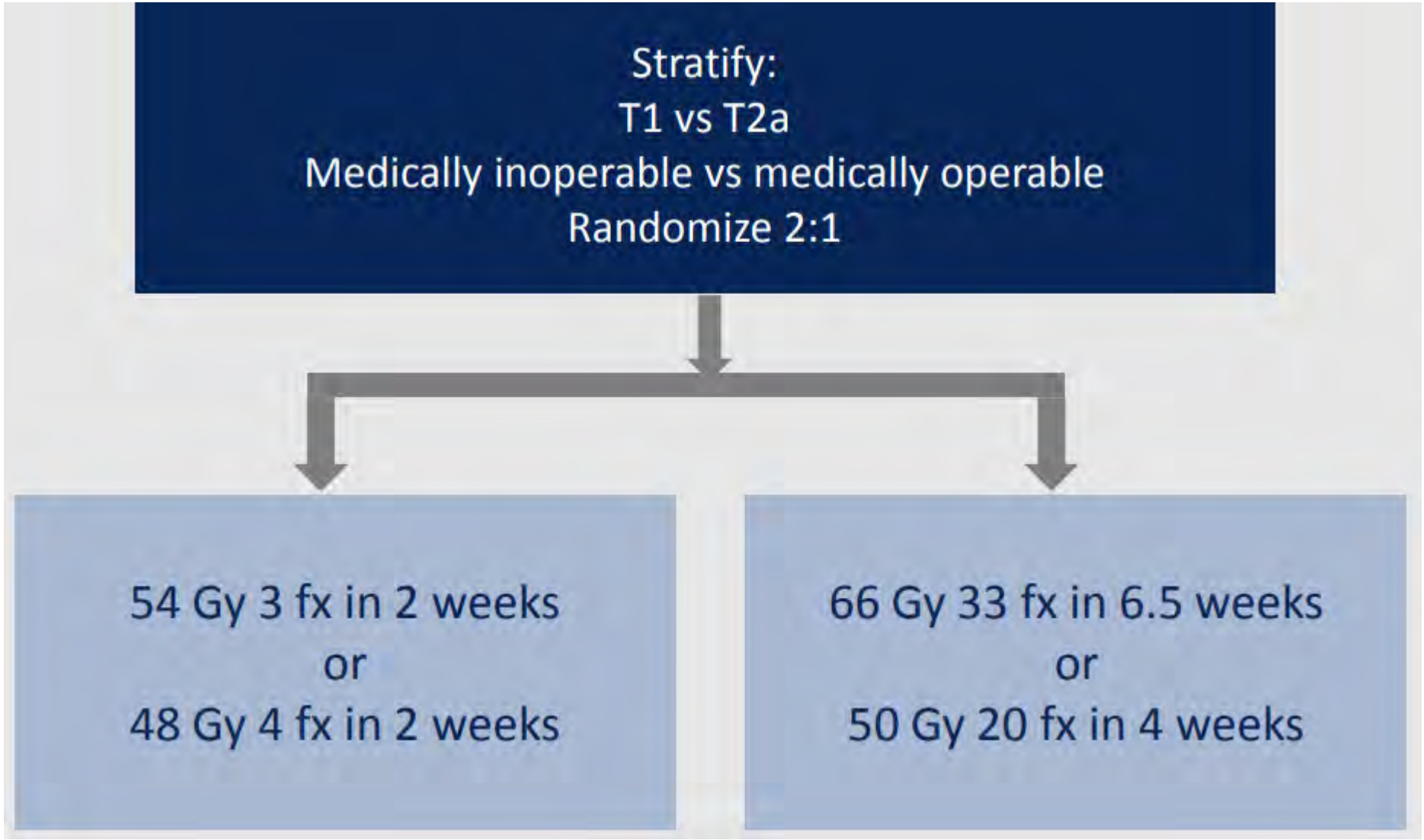
Summary

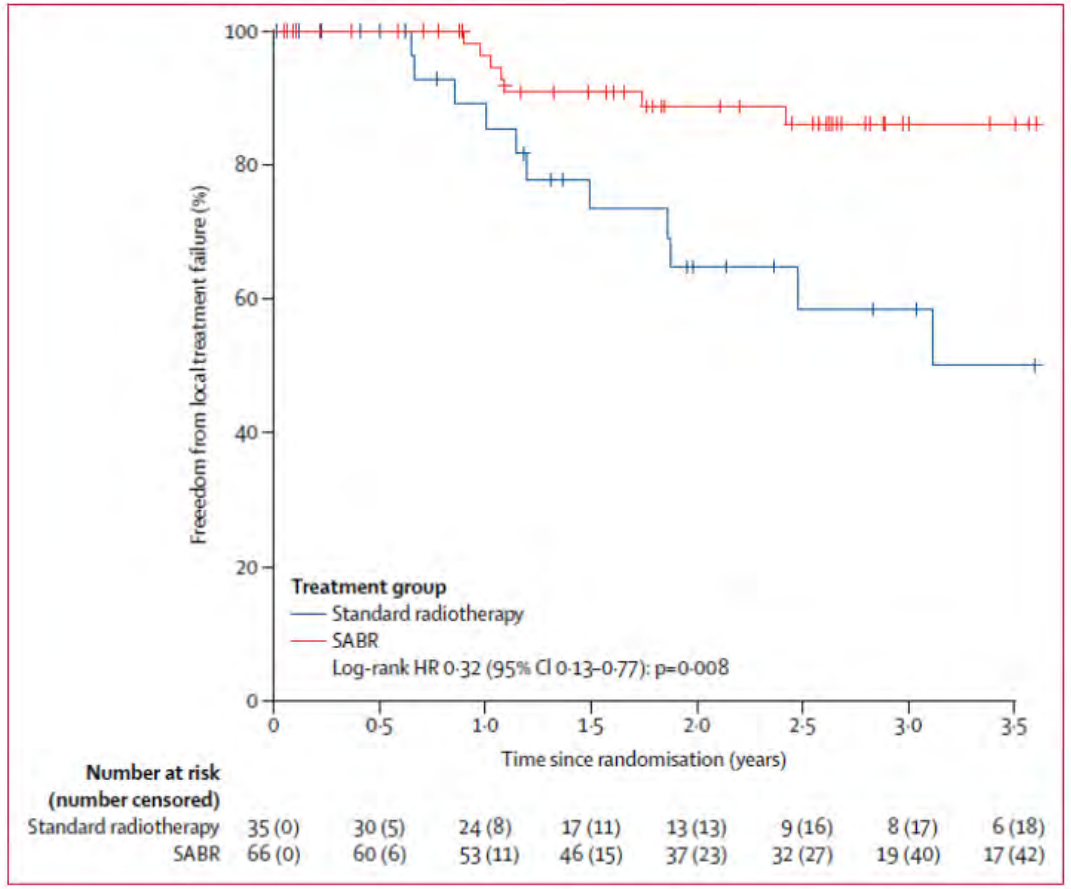
Background Stereotactic ablative body radiotherapy (SABR) is widely used to treat inoperable stage 1 non-small-cell lung cancer (NSCLC), despite the absence of prospective evidence that this type of treatment improves local control or prolongs overall survival compared with standard radiotherapy. We aimed to compare the two treatment techniques.

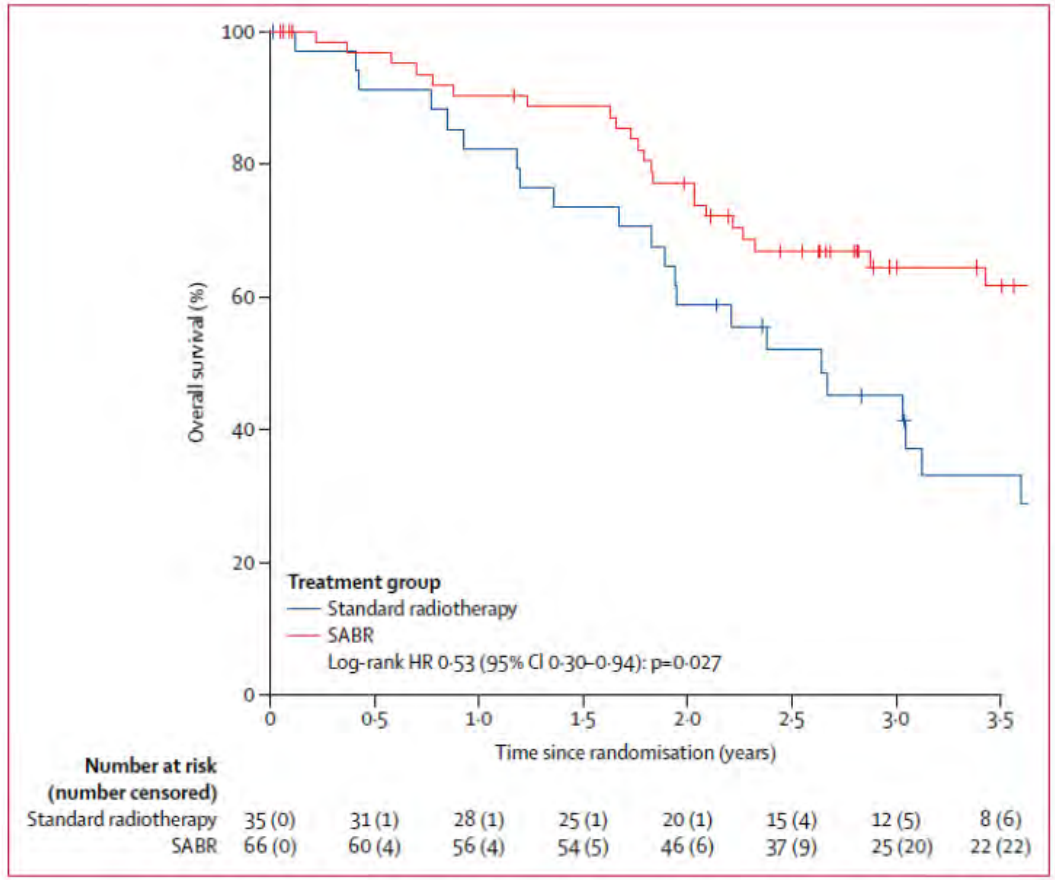
Lancet Oncol 2019

Published Online
February 12, 2019
http://dx.doi.org/10.1016/S1470-2045(18)30896-9

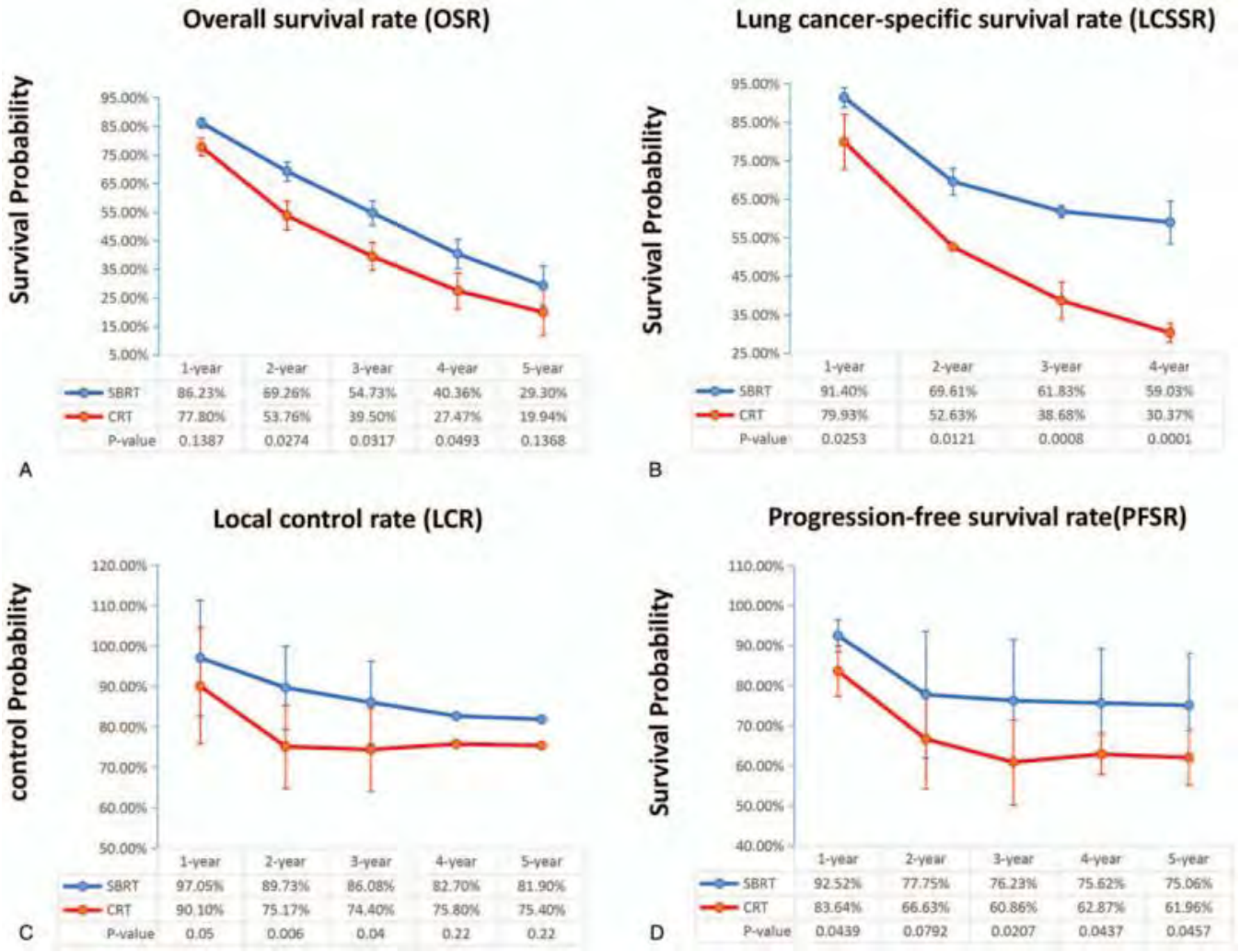
Ball et al *Lancet Oncol* 2019; 20:494


Stratify:
T1 vs T2a
Medically inoperable vs medically operable
Randomize 2:1
54 Gy 3 fx in 2 weeks
or
48 Gy 4 fx in 2 weeks
66 Gy 33 fx in 6.5 weeks
or
50 Gy 20 fx in 4 weeks


Freeedom from local treatment failure (%)
100
80
60
40
20
0
Treatment group
Standard radiotherapy
SABR
Log-rank HR 0·32 (95% CI 0·13–0·77): p=0·008
0
0·5
1·0
1·5
2·0
2·5
3·0
3·5
Time since randomisation (years)
Number at risk
(number censored)
Standard radiotherapy 35 (0) 30 (5) 24 (8) 17 (11) 13 (13) 9 (16) 8 (17) 6 (18)
SABR 66 (0) 60 (6) 53 (11) 46 (15) 37 (23) 32 (27) 19 (40) 17 (42)


Overall survival (%)
100
80
60
40
20
0
Treatment group
Standard radiotherapy
SABR
Log-rank HR 0·53 (95% CI 0·30–0·94): p=0·027
0
0·5
1·0
1·5
2·0
2·5
3·0
3·5
Time since randomisation (years)
Number at risk
(number censored)
Standard radiotherapy 35 (0) 31 (1) 28 (1) 25 (1) 20 (1) 15 (4) 12 (5) 8 (6)
SABR 66 (0) 60 (4) 56 (4) 54 (5) 46 (6) 37 (9) 25 (20) 22 (22)

SBRT compared with conventional RT (meta-analysis)



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7447473/#

Results in lung SBRT series

Author	Treatment	Primary Tumor Control	Single Fraction Equivalent Dose
North America/Europe			
Timmerman, 2006	20-22 Gy X 3	95% (2+ years)	56 – 62 Gy
Bauman, 2006	15 Gy X 3	80% (3 years)	41 Gy
Fritz, 2006	30 Gy X 1	80% (3 years)	30 Gy
Nyman, 2006	15 Gy X 3	80% (crude)	41 Gy
Zimmermann, 2005	12.5 Gy X 3	87% (3 years)	43.5 Gy
Timmerman, 2003	18-24 Gy X 3	90% (2 years)	50 – 68 Gy
Asia			
Xia, 2006	5 Gy X 10	95% (3 years)	32 Gy
Hara, 2006	30-34 Gy X 1	80% (3 years)	30 – 34 Gy
Onimaru, 2003	6 Gy X 8	70% (3 years)	35 Gy
Nagata, 2005	12 Gy X 4	94% (3 years)	43 Gy
Onimaru, 2003	7.5 Gy X 8	100% (3 years)	47 Gy

Total Dose	Reference	BED Gy10	NTD, Gy 2-Gy Fractions)	Estimated Progression-free Survival at 30 Mo. (Assuming No Hypoxia)
Conventional fractionation	—	(Fig. 1.1)	—	—
60 Gy, 30 fractions	—	72	60	15%
70 Gy, 35 fractions	—	84	70	24%
SBRT	—	(Fig. 1.2)	—	—
48 Gy, 4 fractions	(6)	106	63	34%
45 Gy, 3 fractions	(2)	113	94	95%
48 Gy, 3 fractions	(2)	125	104	99%
60 Gy, 5 fractions	(12)	132	110	>99%
60 Gy, 3 fractions	(3)	180	150	>99%
69 Gy, 3 fractions	(33)	228	190	>99%

BED, biologically equivalent dose; NTD, normalized total dose in 2-Gy fractions; SBRT, stereotactic body radiation therapy; NSCLC, non–small cell lung cancer; Tk, ; Td, ; LQ, linear–quadratic.

Fowler JF, Tome WA, Welsh JS. Estimation of the Required Doses in Stereotactic Body Radiation Therapy. In *Stereotactic Body Radiation Therapy*, Kavanagh BD and Timmerman RD, eds. Lippincott Williams & Wilkins, 2005.

*** Slide courtesy of Brian Kavanagh / University of Colorado**

Original Investigation

Lobectomy, Sublobar Resection, and Stereotactic Ablative Radiotherapy for Early-Stage Non–Small Cell Lung Cancers in the Elderly

Shervin M. Shirvani, MD, MPH; Jing Jiang, MS; Joe Y. Chang, MD, PhD; James Welsh, MD; Anna Likhacheva, MD, MPH; Thomas A. Buchholz, MD; Stephen G. Swisher, MD; Benjamin D. Smith, MD

JAMA Surg. 2014.556
Published online October 15, 2014.

Table 1. Baseline Demographic Characteristics Stratified by Treatment

Characteristic	Treatment Group, No. (%) of Patients[a]			P Value for χ^2
	Lobectomy (n = 7215)	Sublobar Resection (n = 1496)	SABR (n = 382)	
Age, y				
66-69	1515 (21.0)	235 (15.7)	39 (10.2)	<.001
70-74	2182 (30.2)	415 (27.7)	71 (18.6)	
75-79	2069 (28.7)	435 (29.1)	94 (24.6)	
≥80	1449 (20.1)	411 (27.5)	178 (46.6)	
Performance score (medical assistance)				
0	6374 (88.0)	1235 (82.6)	294 (77.0)	<.001
≥1	841 (11.7)	261 (17.4)	88 (23.0)	
Charlson comorbidity index excluding COPD				
0	4368 (60.5)	792 (52.9)	170 (44.5)	<.001
1	1700 (23.6)	379 (25.3)	108 (28.3)	
≥2	1147 (15.9)	325 (21.7)	104 (27.2)	
Oxygen supplementation				
No	6348 (88.0)	1110 (74.2)	220 (57.6)	<.001
Yes	867 (12.0)	386 (25.8)	162 (42.4)	

JAMA Surg. 2014.556
Published online October 15, 2014.

Table 2. Baseline Tumor Characteristics Stratified by Treatment

Characteristic	No. (%) of Patients[a] Lobectomy (n = 7215)	Sublobar Resection (n = 1496)	SABR (n = 382)	*P* Value for χ^2
T stage (size, cm)				
T1a (0.0-2.0)	3169 (43.9)	964 (64.4)	153 (40.1)	<.001
T1b (2.1-3.0)	2370 (32.8)	355 (23.7)	153 (40.1)	
T2a (3.1-5.0)	1676 (23.2)	177 (11.8)	76 (19.9)	
Histologic findings[b]				
NSCLC, NOS	366 (5.1)	90 (6.0)	82 (21.5)	<.001
Adenocarcinoma	4371 (60.6)	866 (57.9)	178 (46.6)	
Squamous carcinoma	2236 (31.0)	482 (32.2)	>110 (>25)	
Large cell cancer	242 (3.4)	58 (3.9)	<11 (<5)	
Laterality				
Right	4248 (58.9)	828 (55.3)	201 (52.6)	.004
Left	2967 (41.1)	668 (44.7)	181 (47.4)	
Site[b]				
Bronchus	<11 (<2)	<11 (<2)	<11 (<3)	<.001
Upper lobe	>4400 (>60)	>900 (>60)	>210 (>60)	
Middle lobe	384 (5.3)	44 (2.9)	13 (3.4)	
Lower lobe	2269 (31.4)	489 (32.7)	128 (33.5)	
Overlapping/unknown	112 (1.6)	37 (2.5)	<11 (<3)	
PET staging				
No	3329 (46.1)	701 (46.9)	92 (24.1)	<.001
Yes	3886 (53.9)	795 (53.1)	290 (75.9)	
Mediastinal sampling				
No	406 (5.6)	820 (54.8)	362 (94.8)	<.001
Yes	6809 (94.4)	676 (45.2)	20 (5.2)	

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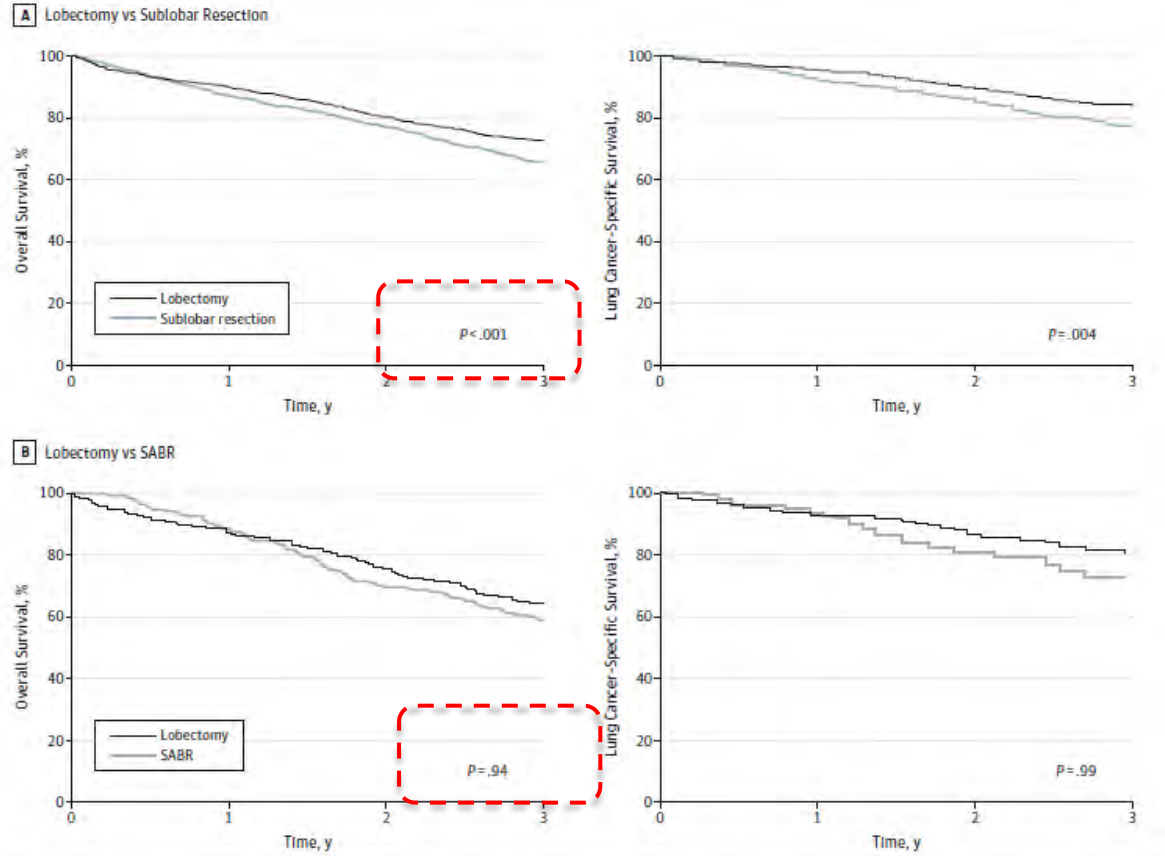
Original Investigation

Lobectomy, Sublobar Resection, and Stereotactic Ablative Radiotherapy for Early-Stage Non–Small Cell Lung Cancers in the Elderly

Figure. Outcomes for Propensity Score–Matched Cohorts



A, Comparison of groups treated with lobectomy and sublobar resection. B, Comparison of groups treated with lobectomy or stereotactic ablative radiotherapy (SABR).

Original Investigation

Lobectomy, Sublobar Resection, and Stereotactic Ablative Radiotherapy for Early-Stage Non–Small Cell Lung Cancers in the Elderly

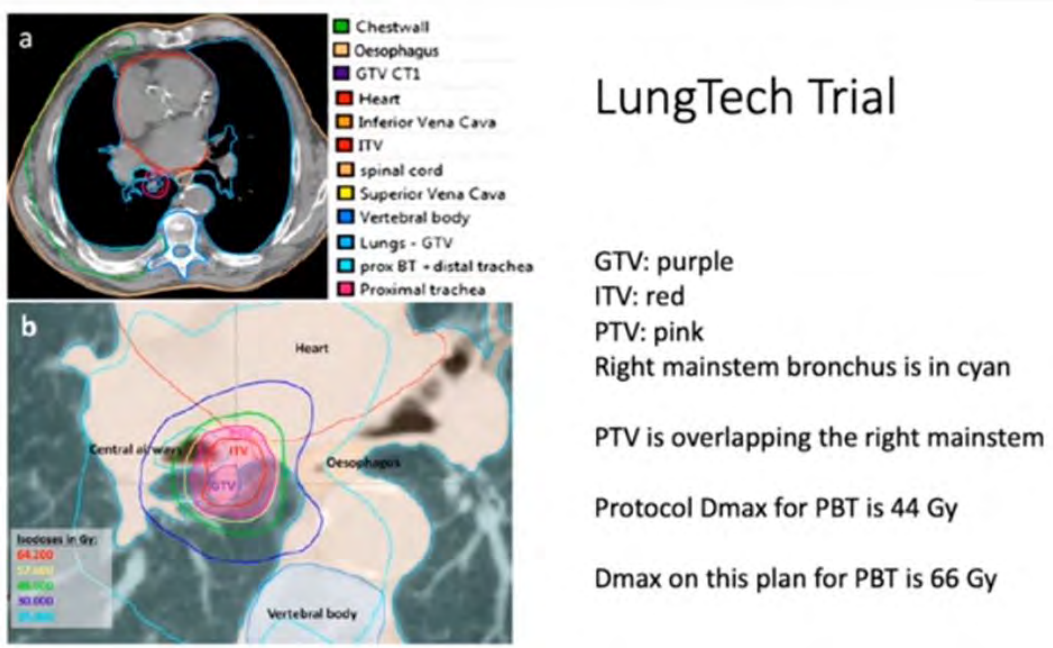
Table 5. Propensity Score–Matching Sensitivity Analysis

Comparison	Overall Survival		Lung Cancer-Specific Survival	
	AHR (95% CI)[a]	*P* Value	AHR (95% CI)[a]	*P* Value
Sublobar Resection vs Lobectomy				
Main analysis (1077 matched pairs)[b]	1.36 (1.17-1.58)	<.001	1.46 (1.13-1.90)	.004
Stricter match (1057 matched pairs)[c]	1.20 (1.03-1.39)	.02	1.30 (1.00-1.69)	.05
Less strict match (1496 matched pairs)[d]	1.25 (1.08-1.45)	.004	1.40 (1.08-1.82)	.01
SABR vs Lobectomy				
Main analysis (251 matched pairs)[b]	1.01 (0.74-1.38)	.94	1.00 (0.52-1.92)	.99
Stricter match (149 matched pairs)[c]	1.28 (0.86-1.91)	.23	1.30 (0.57-2.97)	.53
Less strict match (382 matched pairs)[d]	1.16 (0.87-1.56)	.31	1.18 (0.59-2.38)	.64

JAMA Surg. 2014.556
Published online October 15, 2014.

Trials of SABR in central lung tumors

Trial	Study population	Study design	Primary outcome	Status
LUNGTECH NCT01795521	Stage I-II NSCLC, centrally located in or abutting the 2 cm zone around the proximal bronchial tree and mediastinum),≤7 cm	Single arm Phase II study 60 Gy in eight fractions	Freedom from local progression	Closed early due to poor accrual



LungTech Trial

GTV: purple
ITV: red
PTV: pink
Right mainstem bronchus is in cyan

PTV is overlapping the right mainstem

Protocol Dmax for PBT is 44 Gy

Dmax on this plan for PBT is 66 Gy

original report

Safety and Efficacy of a Five-Fraction Stereotactic Body Radiotherapy Schedule for Centrally Located Non–Small-Cell Lung Cancer: NRG Oncology/RTOG 0813 Trial

Andrea Bezjak, MD[1]; Rebecca Paulus[2]; Laurie E. Gaspar, MD[3]; Robert D. Timmerman, MD[4]; William L. Straube, MS[5]; William F. Ryan, MD[6]; Yolanda I. Garces, MD[7]; Anthony T. Pu, MD[8]; Anurag K. Singh, MD[9]; Gregory M. Videtic, MD[10]; Ronald C. McGarry, MD, PhD[11]; Puneeth Iyengar, MD, PhD[4]; Jason R. Pantarotto, MD[12]; James J. Urbanic, MD[13]; Alexander Y. Sun, MD[1]; Megan E. Daly, MD[14]; Inga S. Grills, MD[15]; Paul Sperduto, MD[16]; Daniel P. Normolle, PhD[17]; Jeffrey D. Bradley, MD[5]; and Hak Choy, MD[4]

Escalating dose levels; at all levels, patients will receive q 2 day fractionation X 5 fractions over 1.5-2 weeks

Dose Level	Level 1	Level 2	Level 3	Level 4	**†Level 5**	Level 6	Level 7	Level 8	Level 9
Dose per Fraction	8 Gy	8.5 Gy	9 Gy	9.5 Gy	**10 Gy**	10.5 Gy	11 Gy	11.5 Gy	12 Gy
Total Dose	40 Gy	42.5 Gy	45 Gy	47.5 Gy	**50 Gy**	52.5 Gy	55 Gy	57.5 Gy	60 Gy

†Protocol treatment begins at Level 5. Levels 1-4 will be employed if dose-limiting toxicity is seen with the Level 5 (10 Gy) starting dose.

J Clin Oncol 37:1316-1325. © 2019

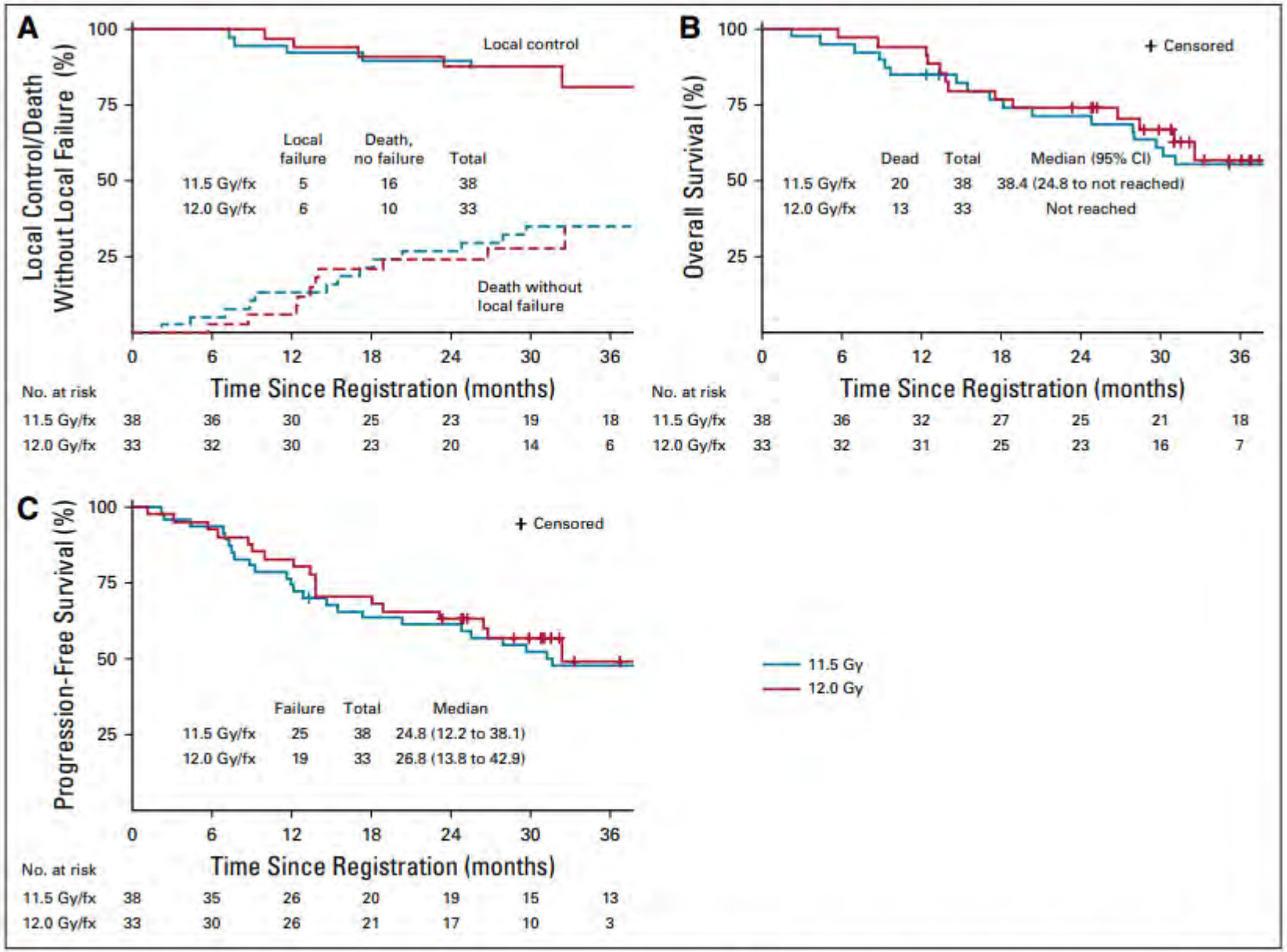


FIG 2. Outcomes for 11.5 and 12 Gy/fx cohorts. (A) Local control rates through 36 months. (B) Overall survival rates through 36 months. (C) Progression-free survival rates through 36 months. fx, fraction.

TABLE 2. DLTs by Dose Level (as Determined by Independent Review)

Treatment Arm	Evaluable Sample Size	No. of DLTs	Probability (95% CI)	DLTs	Grade	Days Since End of SBRT
Level 5: 10 Gy/fx	8	0	2.0 (0.6 to 5.1)			
Level 6: 10.5 Gy/fx	6	1	2.7 (0.8 to 6.5)	Death NOS	5	147
Level 7: 11 Gy/fx	13	1	4.3 (1.5 to 9.6)	Sinus bradycardia	5	130
Level 8: 11.5 Gy/fx	32	2	5.7 (2.1 to 12.0)	Hypoxia	3	88
				Hypoxia	3	166
Level 9: 12 Gy/fx	30	1	7.2 (2.8 to 14.5)	Pneumonitis	3	174
				Pleural effusion	3	264

Abbreviations: DLT, dose-limiting toxicity; fx, fraction; NOS, not otherwise specified; SBRT, stereotactic body radiotherapy.

CONCLUSION The MTD for this study was 12.0 Gy/fx; it was associated with 7.2% DLTs and high rates of tumor control. Outcomes in this medically inoperable group of mostly elderly patients with comorbidities were comparable with that of patients with peripheral early-stage tumors.

ORIGINAL ARTICLE

IASLC

The HILUS-Trial—a Prospective Nordic Multicenter Phase 2 Study of Ultracentral Lung Tumors Treated With Stereotactic Body Radiotherapy

Karin Lindberg, MD, PhD,[a,b,*] Vitali Grozman, MD,[c,d] Kristin Karlsson, MSc, PhD,[a,e]

Trial	Study population	Study design	Primary outcome	Status
HILUS trial	Stage I-II NSCLC or progressive metastasis from another solid tumour, centrally located (≤1 cm from the proximal bronchial tree),≤5 cm	Single arm Phase II 56 Gy in eight fractions	Assessment of toxicity	Closed

Journal of Thoracic Oncology Vol. 16 No. 7: 1200–1210, July 2021

Group A (tumors 1 cm from the main bronchi and trachea)
Group B (all other tumors)

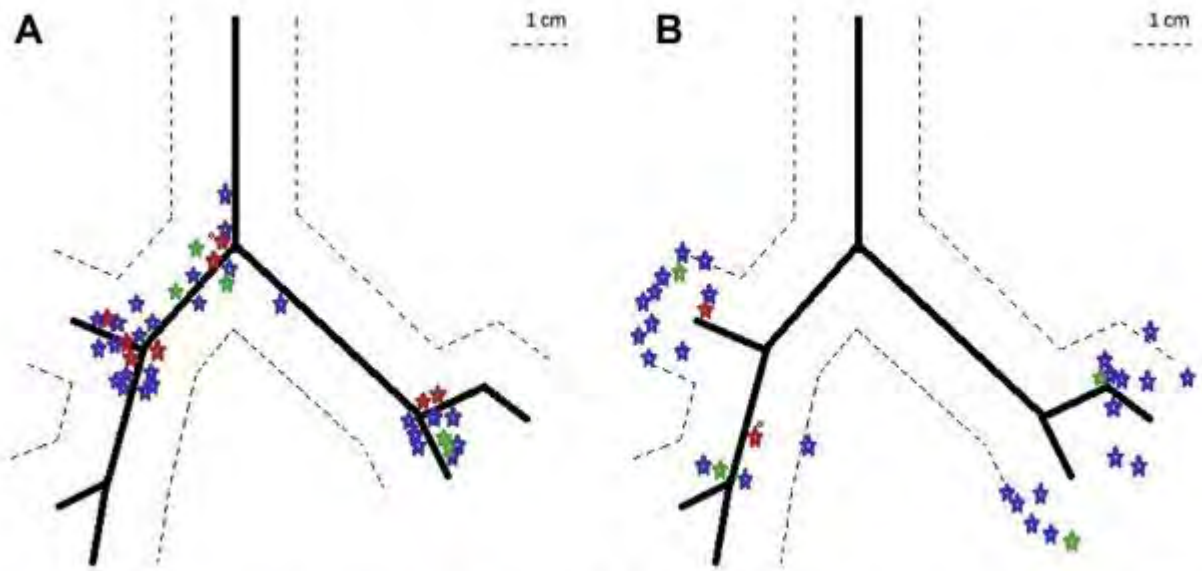


Figure 1. Localization of (*A*) tumors in group A and (*B*) tumors in group B. Red indicates grade 5 toxicity; green, local failure; blue, no grade 5 toxicity + local control.

Stereotactic body radiation therapy with 7 Gy 8 was prescribed to the 67% isodose encompassing the planning target volume.

Table 2. Maximum Recorded Toxicity Attributed to SBRT

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Toxic Symptoms	n	n	n	n	n
Prespecified toxicity					
Atelectasis	20	9			
Bronchopulmonary hemorrhage	1	2			8
Cough	16	21			
Dyspnea	16	15	7		
Fatigue	10	8	2		
Fistula					1
Fever	2	1		1	
FEV-decrease[a]	16	2			
Lung infection	1	6	1	1	1[b]
Pain	9	5	2	1	
Pericardial effusion					
Pleural effusion	12				
Pneumonitis	20	9	1	1	1
Pulmonary fibrosis	22	3			
Ventricular arrhythmia				1	
Nonprespecified toxicity					
Atrial fibrillation		1			
Atrioventricular block			1		
Bronchial obstruction		3			
Bronchial constriction		1			
COPD-exacerbation			1		
Dysphagia	3	1			
Empyema			1		
Gastric ulcer			1		
Mucous	3				
Pneumothorax				1	
Other[c]					

[a]Grade 1: 90% to 75% of baseline value; grade 2: 75% to 50% of baseline value.
[b]In addition, have grade 5 hemoptysis.
[c]Other includes dry skin grade 1 (n = 1), esophagitis grade 1 (n = 1), rib fracture grade 1 (n = 1), nausea grade 1 (n = 1), radiologic CT changes grade 1 (n = 1), rash grade 1 (n = 1) and grade 2 (n = 1), recurrence paresis grade 1 (n = 1), stridor grade 2 (n = 1), swallowing difficulties grade 1 (n = 1), and vertebral compression fracture grade 2 (n = 1).
COPD, chronic obstructive pulmonary disease; CT, computed tomography; FEV, forced expiratory volume.

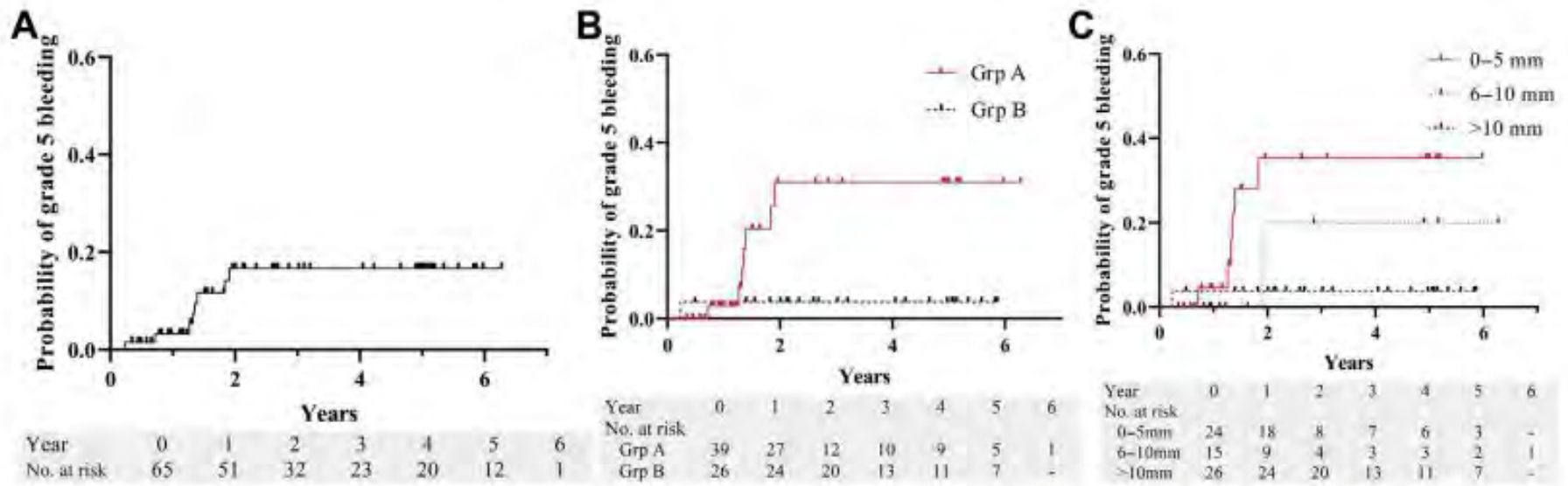


Figure 3. Time to grade 5 bleeding for (*A*) the entire cohort treated per protocol, (*B*) divided in Grps A and B ($p < 0.05$), and (*C*) divided dependent on distance between the tumor and the main bronchus ($p < 0.05$). Grp, group.

In conclusion, treating tumors within 1 cm from the main bronchi and trachea with 56 Gy in eight fractions with inhomogeneous dose distribution implicates high risk for high-grade toxic effects, and this treatment regimen should therefore not be used for these tumors.

Going Trials of SABR in central lung tumor

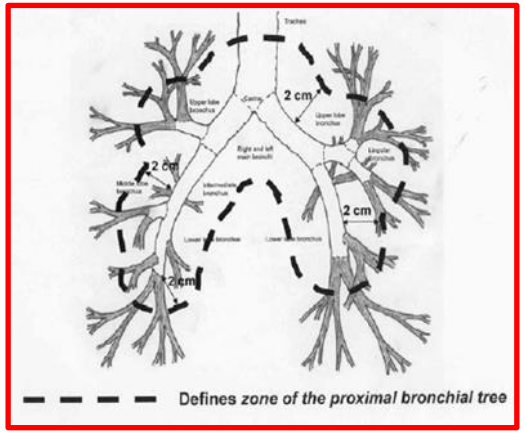
Trial	Study population	Study design	Primary outcome	Status
SUNSET NCT03306680[a]	Stage 1 NSCLC, ultra-central tumours –i.e. where PTV touches the central bronchial tree, great vessels or oesophagus	Phase I dose escalation study using a time-to-event continual re-assessment method Starting dose: 60 Gy in eight fractions Will escalate to 60 in five fractions (or de-escalate to 60 in 15 fractions if needed)	MTD i.e. dose associated with a < 30% rate of Grade 3–5 toxicity occurring within 2 years of treatment	Recruiting

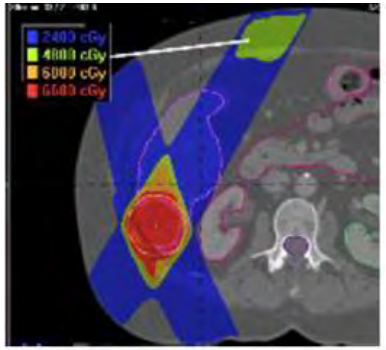
SUNSET

Table 2 Recommended Dose Constraints

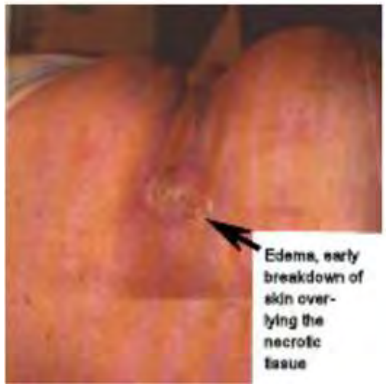
Organ	Metric	Fraction		
		5/6	8/10	15
Spinal canal	Max	30 Gy	32 Gy	39.5 Gy
Spinal canal PRV (3 mm)	Max	32 Gy	34 Gy	42 Gy
Esophagus	Max	40 Gy	45 Gy	50.5 Gy
	5 cc	35 Gy	40 Gy	48 Gy
Brachial plexus	Max	32 Gy	39 Gy	50 Gy
Heart	Max	62 Gy	64 Gy	66 Gy
	10 cc	50 Gy	60 Gy	62 Gy
Trachea	Max	62 Gy	64 Gy	66 Gy
	10 cc	50 Gy	60 Gy	62 Gy
Proximal bronchus	Max	62 Gy	64 Gy	66 Gy
	10 cc	50 Gy	60 Gy	62 Gy
Non-GTV lung	Mean	< 12 Gy	< 12 Gy	< 14 Gy
Aorta and major vessels	Max	62 Gy	64 Gy	64 Gy
	10 cc	50 Gy	60 Gy	60 Gy
Stomach and intestines	Max	40 Gy	45 Gy	50 Gy
	10 cc	35 Gy	40 Gy	48 Gy

“Zone of the proximal bronchial tree”





6-field liver SABR treatment plan showing excessive radiation near skin



Gr 3 skin reaction 8 months post SABR. From Kavanagh et al, Acta Onc 2006

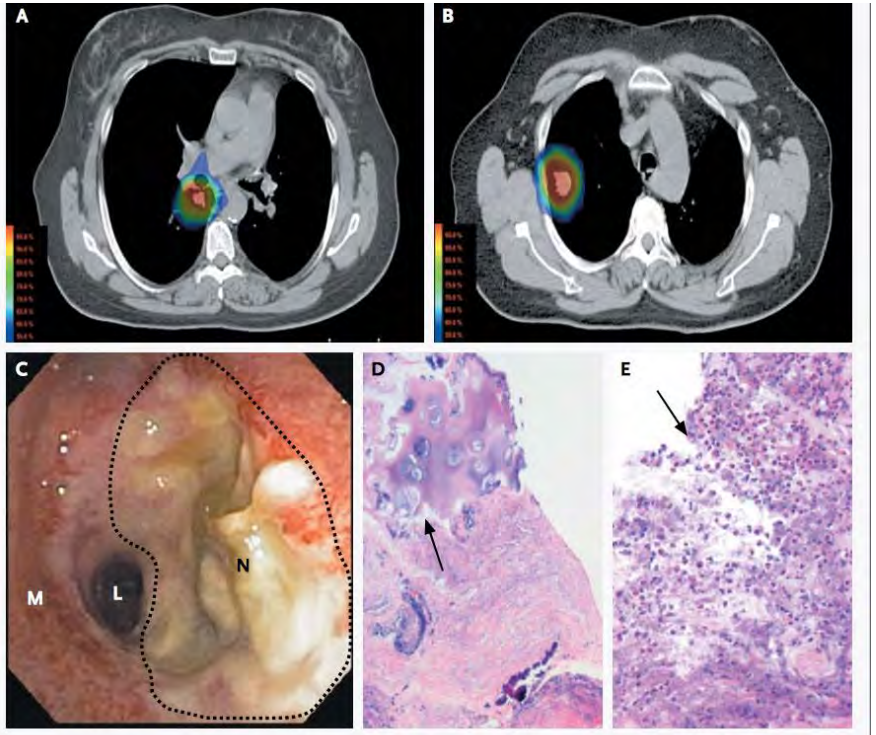
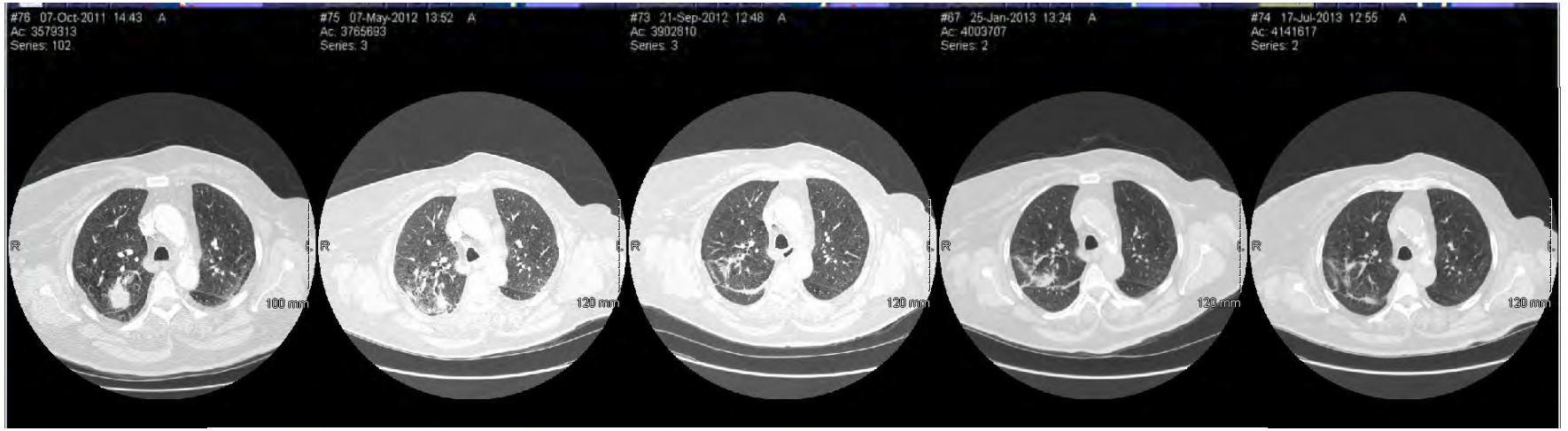


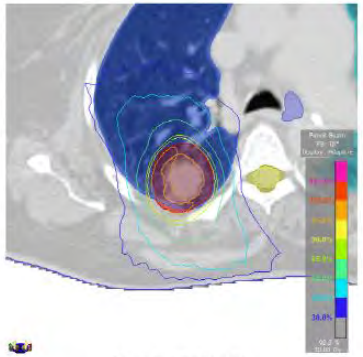
Figure 1. Initial Tumors and Post-SBRT Necrotic Tissue in a Patient with Non–Small-Cell Lung Cancer.

Panels A and B, respectively, show axial images of a central tumor in the right lower lobe of the lung and a peripheral tumor in the right upper lobe obtained at presentation with computed tomography, with overlaid treatment plans for stereotactic body-radiation therapy (SBRT). Target doses are as indicated in the color key, with blue indicating 50% of the prescribed dose and red 100%. A composite dose plan (not shown) indicated that there was no significant overlap between the two treatment fields. Endobronchial ultrasound-guided bronchoscopy, performed 8 months after SBRT, shows a plaque-like area of mucosal necrosis in the right mainstem bronchus (Panel C). The necrotic area extended from the midright mainstem bronchus to the right bronchus intermedius and right hilum along the posterolateral aspect of the airway. The necrotic area (N) is outlined and is adjacent to normal mucosa (M) and the lumen (L) of the right mainstem bronchus. Biopsy specimens stained with hematoxylin and eosin revealed cartilaginous destruction (Panel D, arrow) and parenchymal necrosis with an inflammatory infiltrate (Panel E, arrow). No viable tumor was seen, and no fungal organisms were detected with Grocott methenamine–silver nitrate staining (not shown).

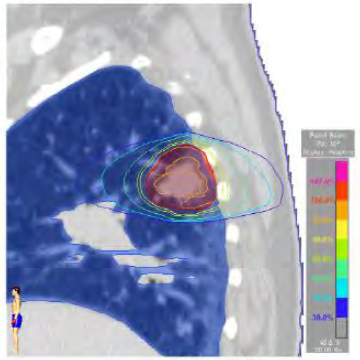
NEJM June 2012

Follow up can be challenging after SBRT

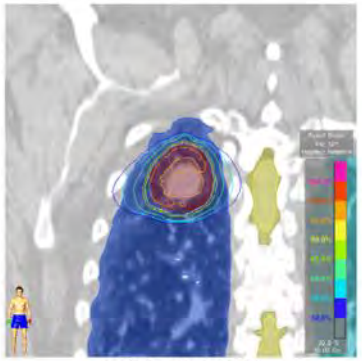




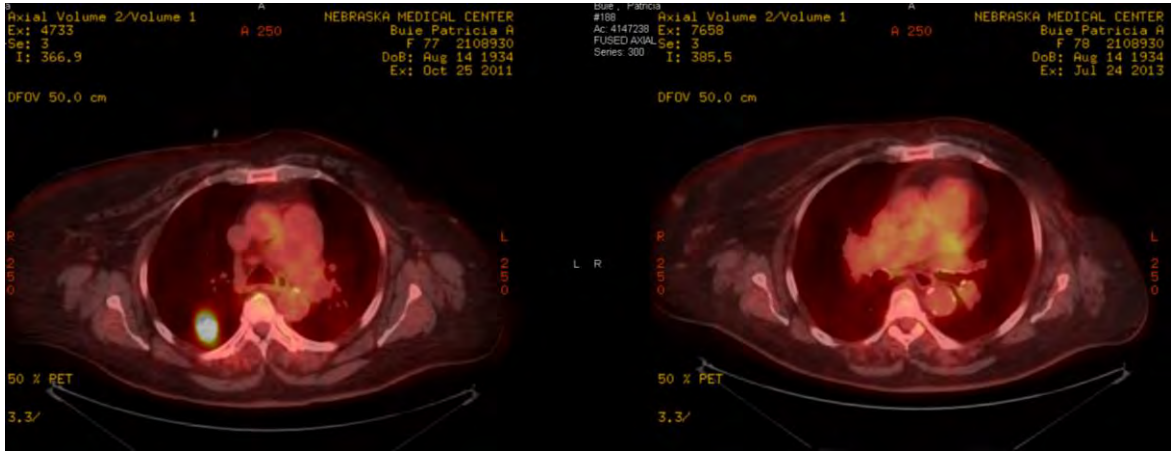
Overview Axial: PTV



Overview Sagittal: PTV



Overview Coronal: PTV



Follow-up

Definition of local control?

- CT scan every 3-4 months for 1-2 year, then every 6 months
- PET scan only when progressive consolidation on CT within or adjacent to tumor
- If PET uptake similar to pre-SBRT scan is considered as recurrent disease
- Otherwise continue to follow as NED

Definition of metabolic response according to EORTC criteria

Response	Definition
CMR	Complete resolution of FDG uptake in tumour, not distinguishable from surrounding tissue
PMR	Reduction of more than 25% in SUV
SMD	Changes of less than 25% in SUV
PMD	Increase of SUV of more than 25% or new (metastatic) lesions

CMR complete metabolic response, PMR partial metabolic response, SMD stable metabolic disease, PMD progressive metabolic disease

Eur J Nucl Med Mol Imaging. 2011 38-38(6): 1059–1063.

Conclusions:

- The use of SBRT for stage I lung cancer is rapidly expanding.
- SBRT is an effective alternative to conventional surgery or other invasive approaches.
- Improved tumor control and patient survival when compared to conventional radiotherapy.
- Ultra-central disease requires additional cautions.

Role of RT in Management of Stage III Lung Cancer

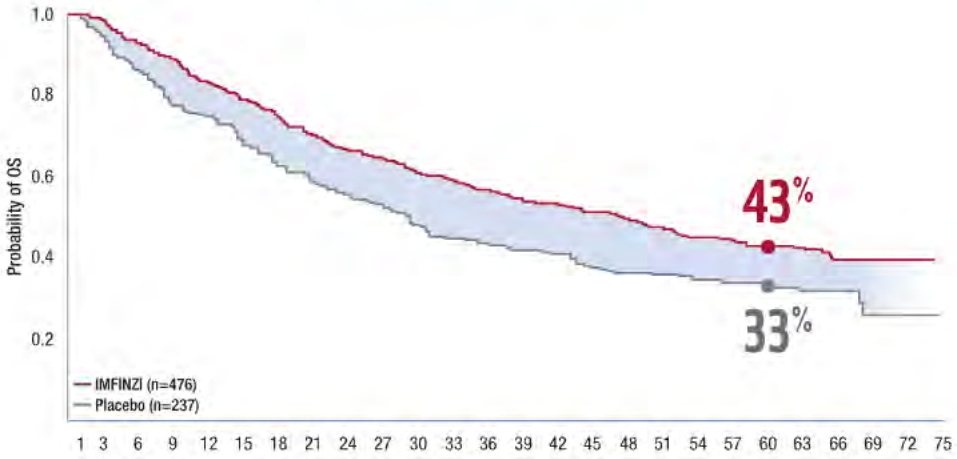
- Primarily definitive
- Neo-adjuvant
- Adjuvant

Randomized Controlled Trial > J Clin Oncol. 2022 Apr 20;40(12):1301-1311.
doi: 10.1200/JCO.21.01308. Epub 2022 Feb 2.

Five-Year Survival Outcomes From the PACIFIC Trial: Durvalumab After Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer

David R Spigel [1], Corinne Faivre-Finn [2], Jhanelle E Gray [3], David Vicente [4], David Planchard [5], Luis Paz-Ares [6], Johan F Vansteenkiste [7], Marina C Garassino [8 9], Rina Hui [10], Xavier Quantin [11], Andreas Rimner [12], Yi-Long Wu [13], Mustafa Özgüroğlu [14], Ki H Lee [15], Terufumi Kato [16], Maike de Wit [17], Takayasu Kurata [18], Martin Reck [19], Byoung C Cho [20], Suresh Senan [21], Jarushka Naidoo [22], Helen Mann [23], Michael Newton [24], Piruntha Thiyagarajah [23], Scott J Antonia [3]

5-YEAR OVERALL SURVIVAL UPDATE[3†]



Number of patients at risk

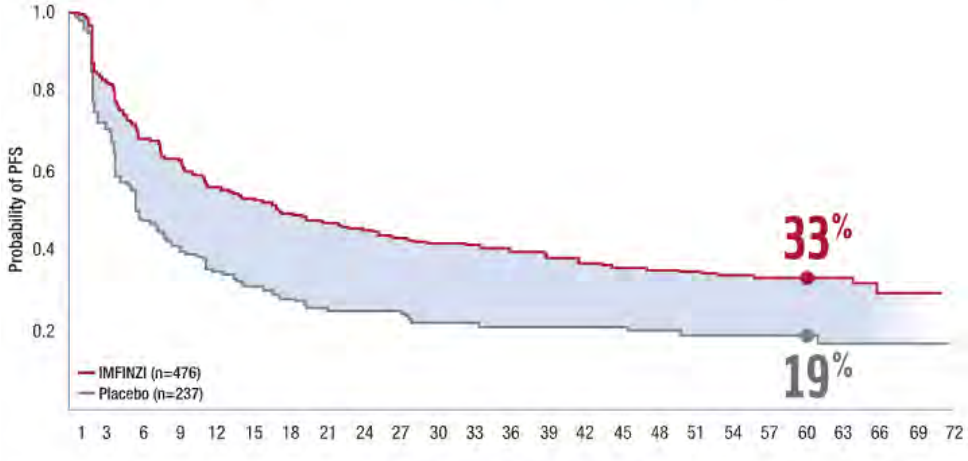
IMFINZI	476	464	431	414	385	364	343	319	298	289	273	264	252	241	236	227	218	207	196	183	134	91	40	18	2	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	97	93	91	83	78	77	74	72	56	33	16	7	2	0

5-YEAR POST-HOC OS ANALYSIS[3†] (34.2 months median follow-up)

47.5 months mOS with the PACIFIC regimen	vs	29.1 months mOS with placebo following CRT	**43%** OS with the PACIFIC regimen	vs	33% OS with placebo following CRT

HR=0.72 (95% CI, 0.59-0.89)

5-YEAR PROGRESSION-FREE SURVIVAL UPDATE[3]



Number of patients at risk

IMFINZI	476	377	301	267	215	190	165	147	137	128	119	110	103	97	92	85	81	78	67	57	34	22	11	5	0
Placebo	237	164	105	87	68	56	48	41	37	36	30	27	26	25	24	24	22	21	19	19	14	6	4	1	0

5-YEAR POST-HOC PFS ANALYSIS[3†] (34.2 months median follow-up)

16.9 months mPFS with the PACIFIC regimen	vs	5.6 months mPFS with placebo following CRT	**33%** PFS with the PACIFIC regimen	vs	19% PFS with placebo following CRT

HR=0.55 (95% CI, 0.45-0.68)

Unresectable stage III NSCLC treated with CRT and IO

What about resectable IIIA NSCLC?

- Adjuvant chemotherapy improves both overall survival and disease-free survival (level 1 evidence)
- The role for postoperative radiation therapy (PORT) remains controversial as retrospective studies demonstrate conflicting results regarding improvement in OS and locoregional control
- PORT in patients with positive margins, or mediastinal lymph node (LN) involvement (pN2 disease, not incidental N2) may improve locoregional control and potentially OS.

VOLUME 24 · NUMBER 19 · JULY 1 2006

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Postoperative Radiotherapy for Stage II or III Non–Small-Cell Lung Cancer Using the Surveillance, Epidemiology, and End Results Database

Brian E. Lally, Daniel Zelterman, Joseph M. Colasanto, Bruce G. Haffty, Frank C. Detterbeck, and Lynn D. Wilson

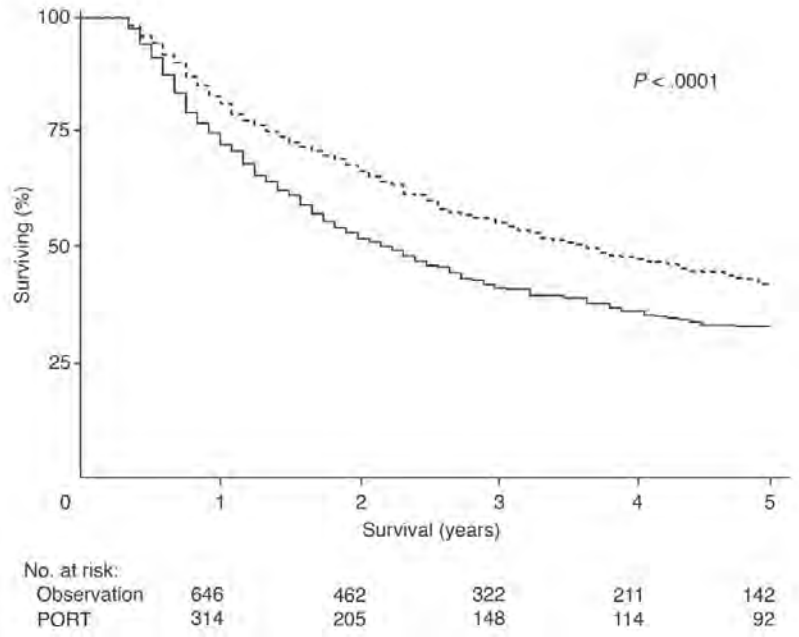


Fig 3. Plot of overall survival for N0 patients stratified by postoperative radiotherapy (PORT) use. The solid line represents patients who received PORT, and the dashed line represents patients who did not receive PORT.

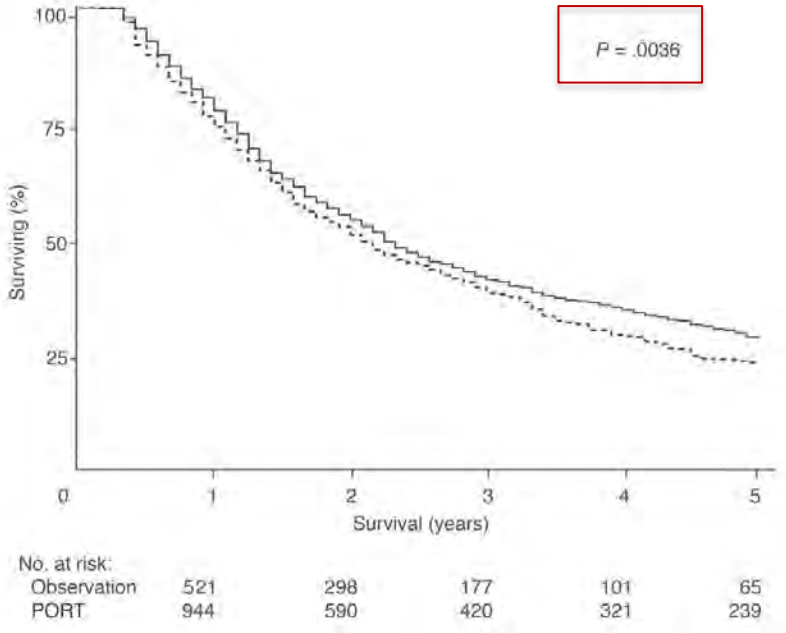


Fig 5. Plot of overall survival for N2 patients stratified by postoperative radiotherapy (PORT) use. The solid line represents patients who received PORT, and the dashed line represents patients who did not receive PORT.

Meeting Abstract | 2022 ASCO Annual Meeting I

LUNG CANCER—NON-SMALL CELL LOCAL-REGIONAL/SMALL CELL/OTHER THORACIC CANCERS

The Lung ART adjuvant radiotherapy phase 3 randomized trial: Impact of quality of resection in stage IIIAN2 patients.

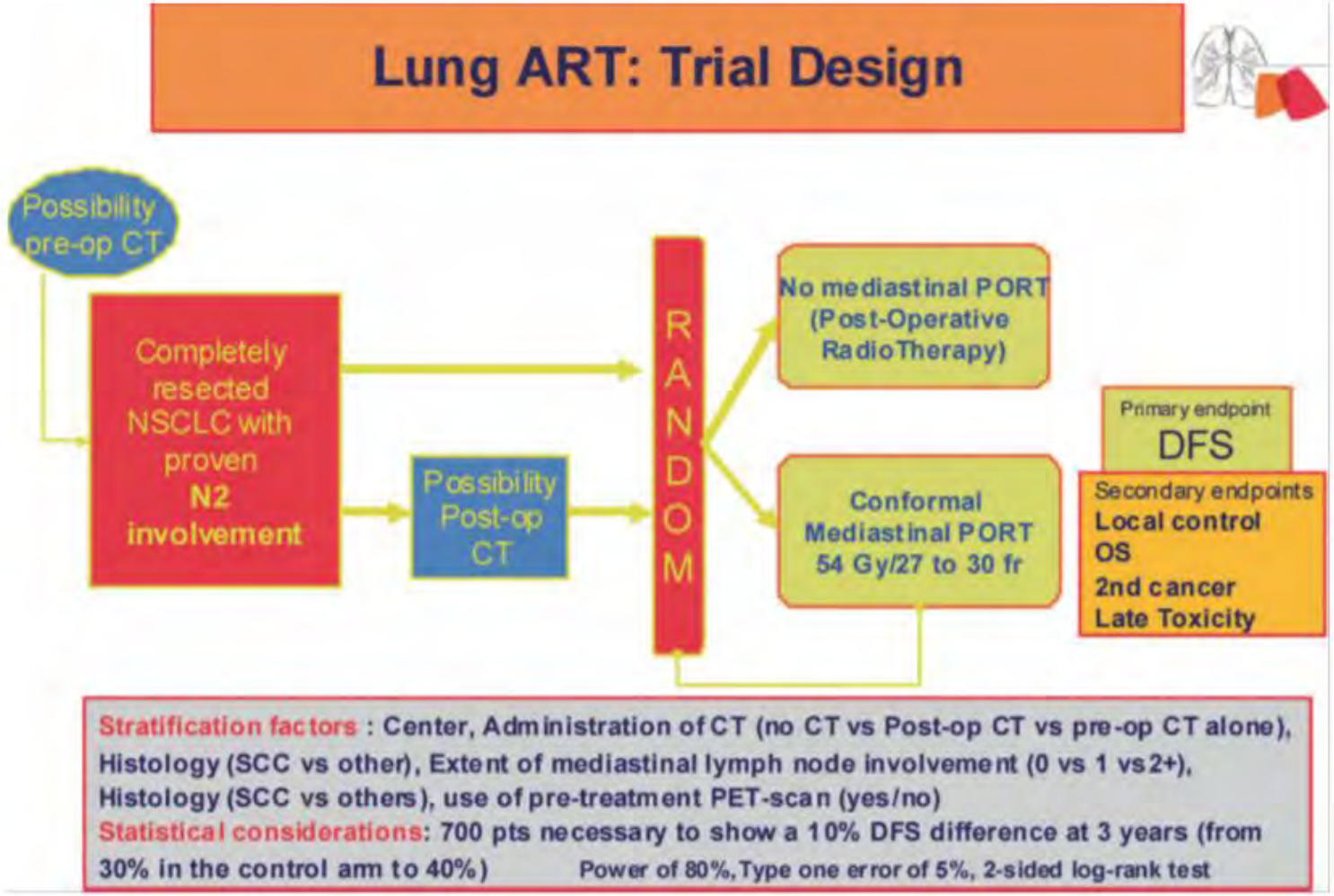


Figure 1 Lung adjuvant radiotherapy trial (ART) design. CT, computed tomography; DFS, disease-free survival; NSCLC: non-small cell lung cancer; PET, positron emission tomography; PORT, postoperative radiation therapy; post-op, postoperative; pre-op, preoperative; SCC, squamous cell carcinoma

VIRTUAL 2020 ESMO congress

Results: Patient flow chart

Data cut-off = 31 May 2019 (n_{events} = 296)

501 pts included (08/07 to 07/18)

ITT population 85% France, 10% United-Kingdom

249 control + 252 PORT

- 11 PORT patients not treated
- 3 patients in the CA with no FU
- 0 patients in the CA had PORT

487 patients analysed for safety

Safety population

Site country	Total	
n	501	
Belgium	1	0.2%
France IFCT 0503	427	85.2%
Germany	15	3.0%
Switzerland SAKK	8	1.6%
United Kingdom	50	10.0%

Median follow-up = 4.8 years (IQR = [2.9 ; 7.0])

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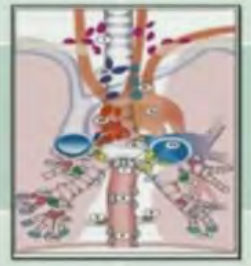
Baseline Characteristics : Surgery

	Control arm (n = 249)	PORT arm (n = 252)
Type of surgery (n(%))		
- Lobectomy	81%	78%
- Bilobectomy	7%	8%
- Pneumonectomy	10%	12%
- Sublobar resection	2%	2%
Largest T size (Median [min;max],mm	34 [0;110]	33 [5;150]
pTNM		
pN0/pN1 (down staging after preop CT)	pN0: 1% pN1: 2%	pN0: 2% pN1: 1%
pN2	pN2: 98%	pN2: 96%
In pN2 patients		
N2 stations most frequently involved on Surgical pathological exam 4R / 5 / 7	St4 R: 66% / St 5 L: 43% St7 R Tum: 66% / L Tum: 34%	St 4R: 55% / St 5 L: 31% St7 R Tum: 65% / L Tum: 35%



IASLC Nodal Map (Rusch et al, JTO 2009 TNM 7)

45% of patients had a single N2 station involved and 52% had two or more (not clear how may incidental N2 disease)

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Radiotherapy

	PORT arm (n = 252)
Thoracic irradiation (n(%))	241 (96%)
Early termination (n(%))	7 (3%) (3 progressions, 2 toxicities)
Total received dose (in Gy) (median (min;max))	54 Gy (21;70)
Main parameters regarding Dose to lungs and Heart*	Dosimetric parameters / Median (min - max) Lungs V20: 23% (3 – 36) MLD: 12.7 Gy (2.5 – 22) Mean heart dose: 13.4Gy (0.7 – 36,2) Heart V35: 15% (0 – 50)
PORT technique	3DRT : 201 (89%) IMRT: 25 (11%) 26 Unspecified

* Lung V20 should not exceed 31% after lobectomy and 22% after pneumonectomy; dose to 30% of the cardiac volume should not exceed 35 Gy

89% received 3DRT

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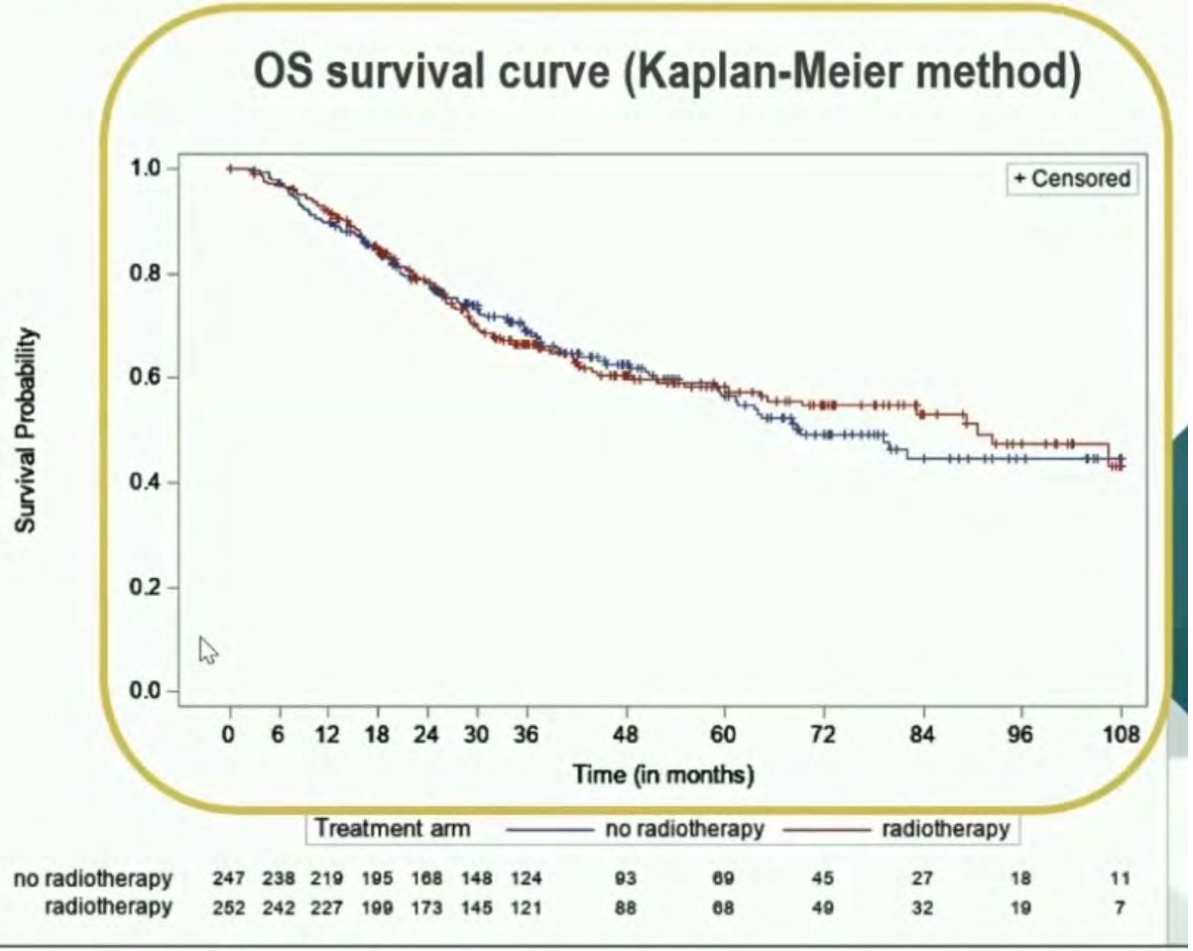
Overall Survival (Secondary Endpoint; ITT)

n_{events} = 201 events

Overall Survival rates at 3 years

Control arm: 68.5% (95% CI = [61;75])

PORT arm: 66.5% (95% CI = [59;73])



Mean follow up: 4.8 years

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Disease-Free Survival 1/3 (Primary Endpoint; ITT)

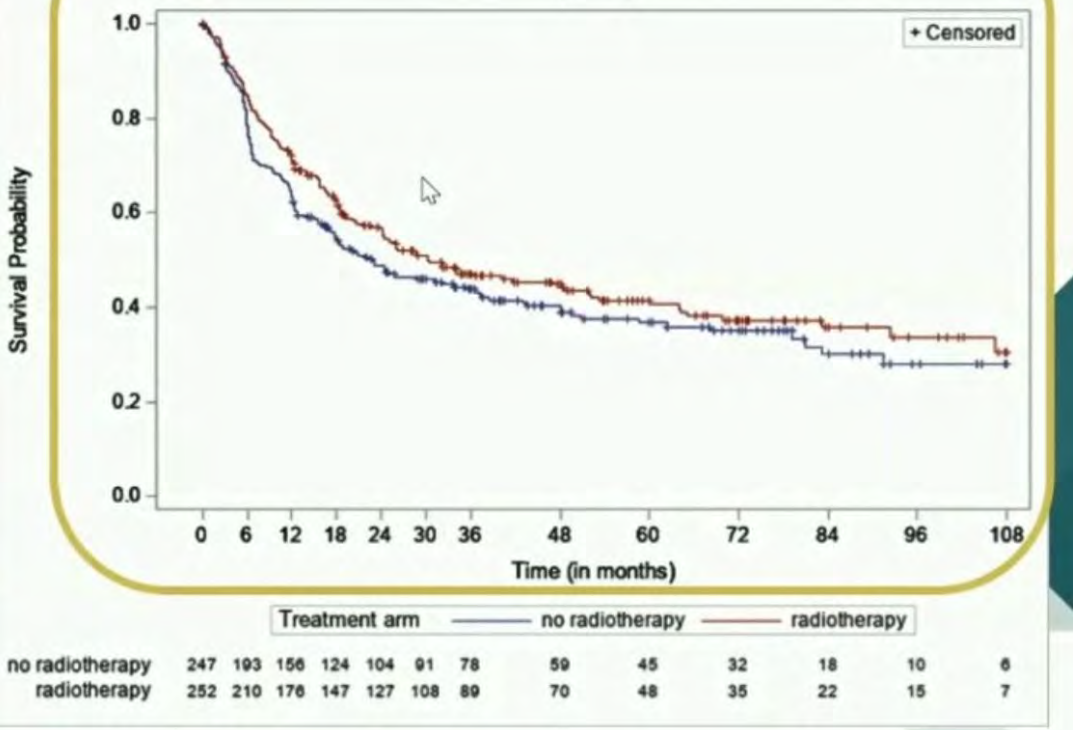
Main analysis (Adjusted Cox Model)

HR = 0.85
95% CI = [0.67;1.07]
p value = 0.16

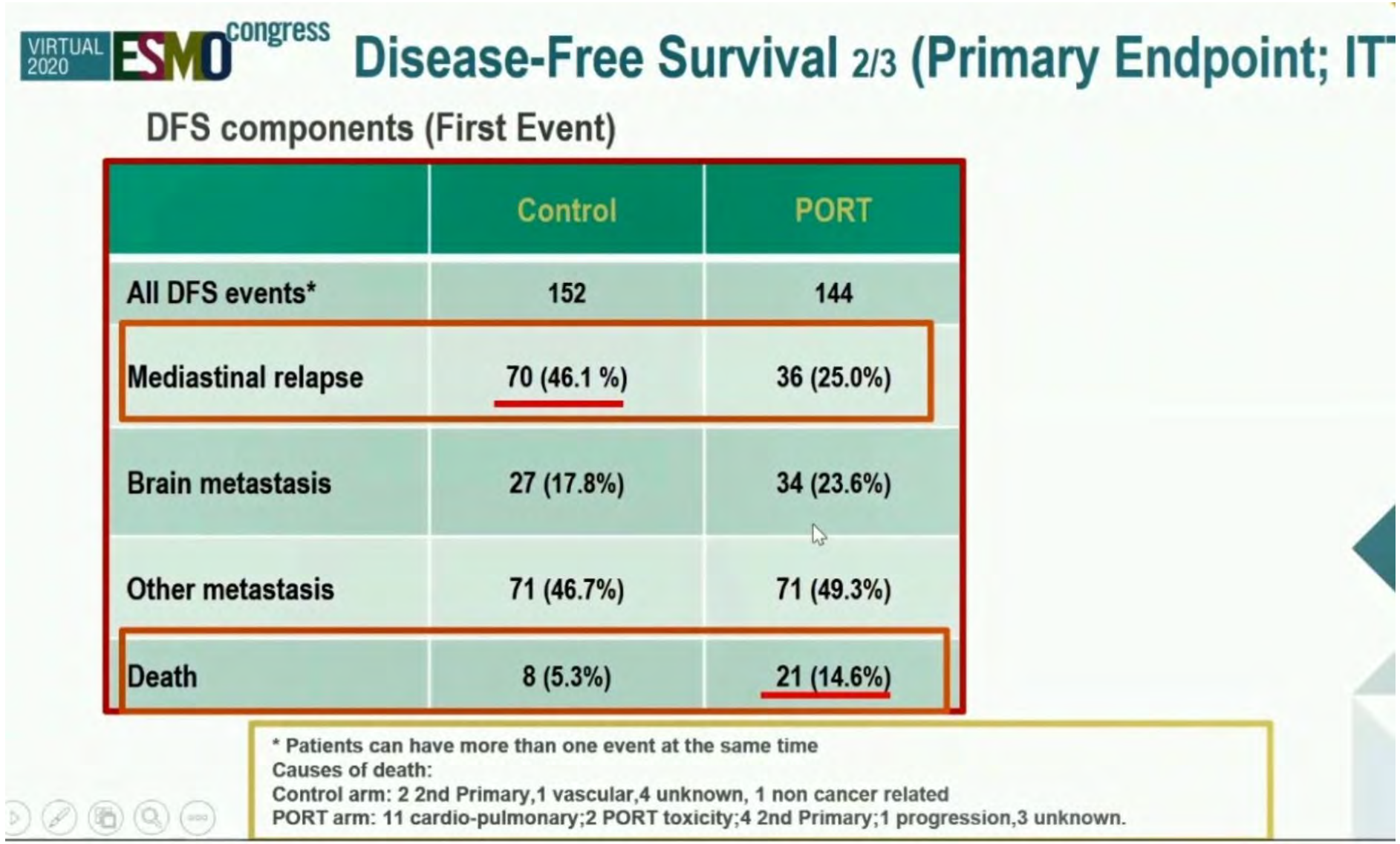
	Control	PORT
Median DFS	22.8 mo (95% CI = [17;37])	30.5 mo (95% CI = [24;49])
3-yr DFS	43.8% (95% CI = [37;51])	47.1 % (95% CI = [40;54])

95%CI = 95% bilateral Confidence Interval

DFS survival curve (Kaplan-Meier method)



PORT was associated with a non-statistically significant 15% increase in DFS among stage IIIAN2 pts.



PORT reduces mediastinal relapse by 46%

PORT patients were less likely to experience mediastinal relapse as a first DFS event than controls (25.0 vs 46.1%)

PORT patients were more likely to experience grade 3–4 early toxicity than controls (11.6 vs 7.7%) and at least one late toxicity at this severity (14.6 vs 8.9%)

Although the mortality rates were comparable in the PORT and control groups (39.6 vs 41.5%), the causes of death differed; PORT was associated with higher rates of death from cardiopulmonary causes (16.2 vs 2.0%) and a lower rate of death from disease progression or recurrence (69.4 vs 86.1%).

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Conclusion

- LungART is the first European randomized study evaluating modern PORT after complete resection, in patients selected predominantly with PET scan and having received (neo)adjuvant CT.
- 3-year DFS (43.8% in the control arm and 47.1% in the PORT arm) was higher than expected in both arms. Mediastinal relapse was reduced (46% in CA vs 25% in PORT)
- PORT was associated with a non-statistically significant 15% increase in DFS among stage IIIAN2 pts.
- Safety issues: More toxicities were observed in the PORT arm, especially cardio-pulmonary that need to be further explored
- Conformal PORT cannot be recommended as Standard of Care in all completely resected Stage IIIAN2 NSCLC patients.
- Further analyses are planned (QA surgery and PORT, Patterns of failure, TR...)

JAMA Oncology | Original Investigation

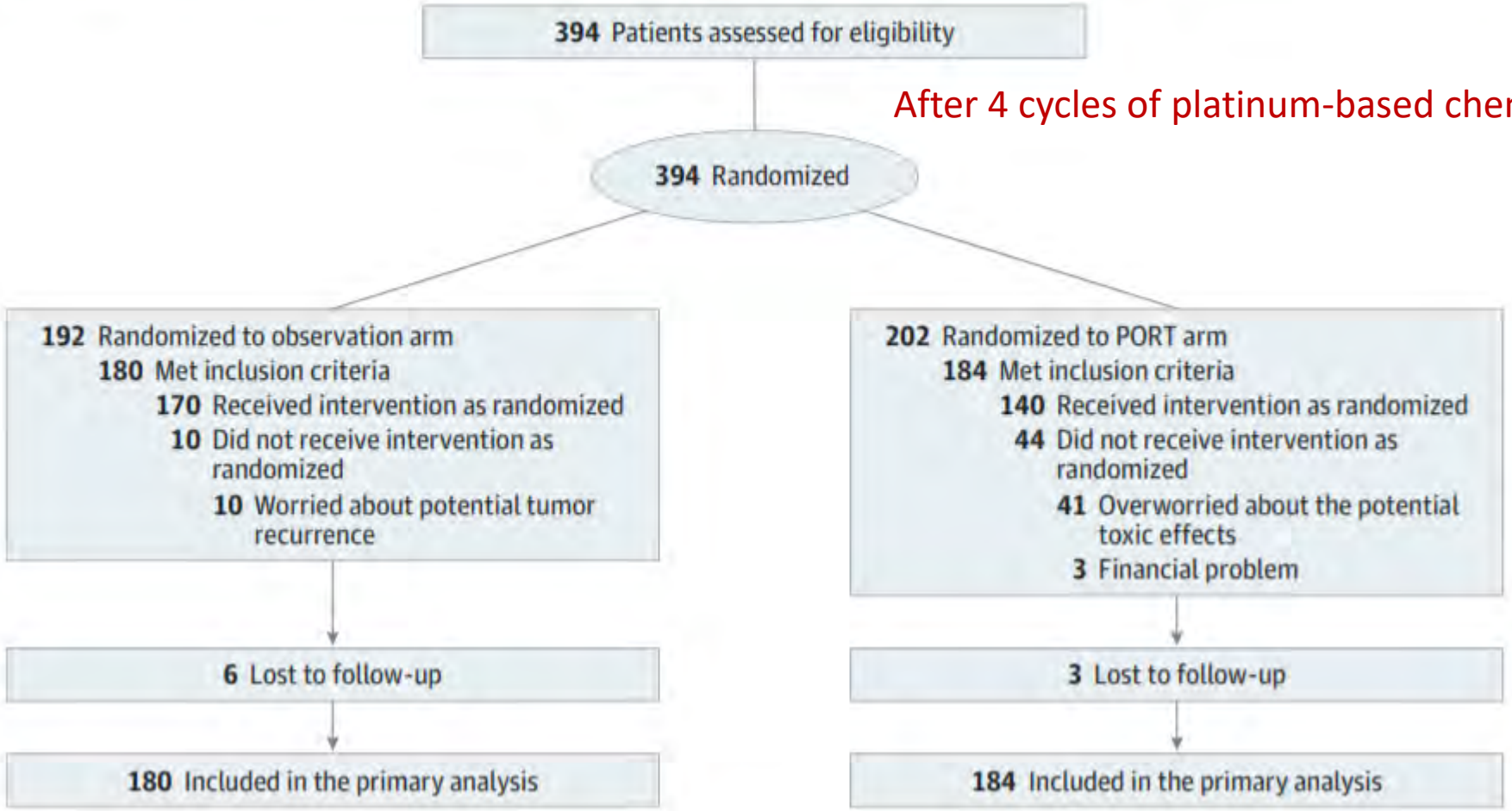
Effect of Postoperative Radiotherapy for Patients With pIIIA-N2 Non–Small Cell Lung Cancer After Complete Resection and Adjuvant Chemotherapy
The Phase 3 PORT-C Randomized Clinical Trial

Zhouguang Hui, MD; Yu Men, MD; Chen Hu, PhD; Jingjing Kang, MD; Xin Sun, MD; Nan Bi, MD, PhD; Zongmei Zhou, MD; Jun Liang, MD; Jima Lv, MD; Qinfu Feng, MD; Zefen Xiao, MD; Dongfu Chen, MD; Yan Wang, MD; Junling Li, MD; Jie Wang, MD; Shugeng Gao, MD; Luhua Wang, MD; Jie He, MD

Single institution trial

JAMA Oncol. 2021;7(8):1178-1185.

Figure 1. Participant Flow in the Randomized Clinical Trial

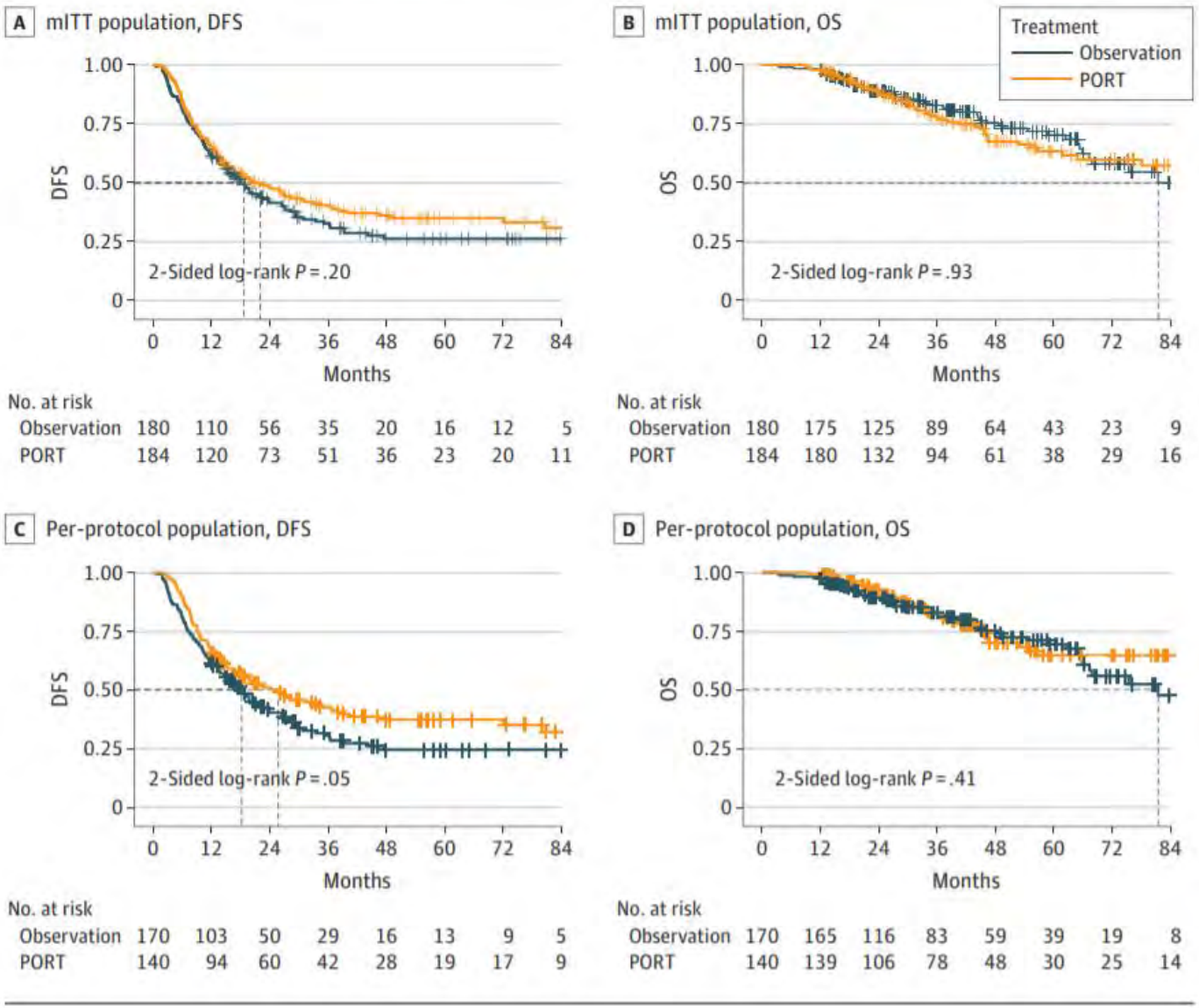


After 4 cycles of platinum-based chemotherapy

44 of 184 patients (21.7%) in the PORT arm refused PORT

10 of 180 patients (5.6%) in the observation arm actually received PORT

Figure 2. Kaplan-Meier Curves by Arm for Survivals Using Modified Intent-to-Treat (mITT) and Per-Protocol Populations



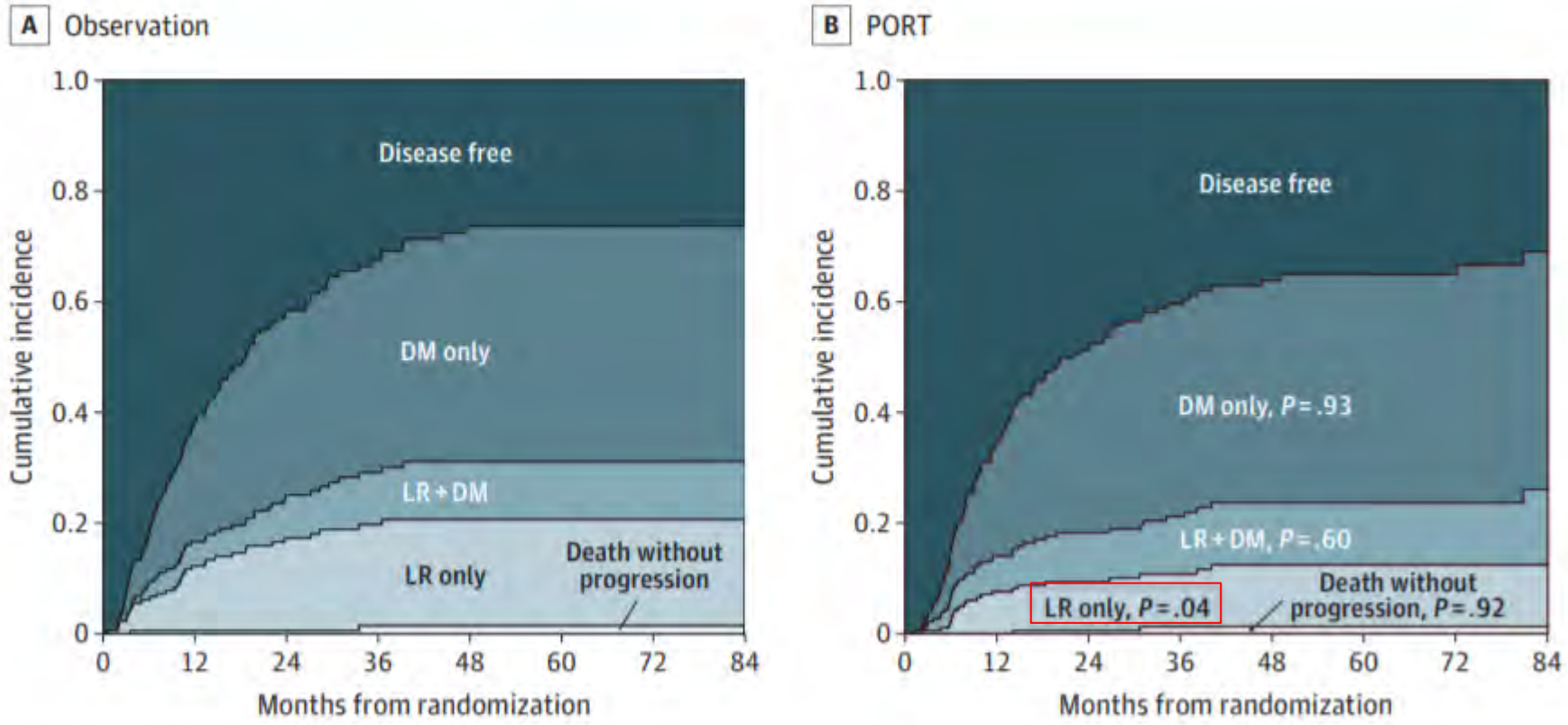
A, Disease-free survival (DFS) of mITT analysis; B, Overall survival (OS) of mITT analysis; C, DFS of per-protocol analysis; D, OS of per-protocol analysis. PORT indicates postoperative radiotherapy.

Table 2. Summary of Efficacy Results

	mITT analysis		PP analysis		AT analysis	
Outcome	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
DFS	0.84 (0.65-1.09)	.20	0.75 (0.57-1.00)	.05	0.73 (0.56-0.96)	.02
OS	1.02 (0.68-1.52)	.93	0.83 (0.53-1.30)	.41	0.72 (0.48-1.09)	.12
LRFS	0.71 (0.51-0.97)	.03	0.56 (0.39-0.80)	.002	0.52 (0.37-0.74)	<.001
DMFS	0.94 (0.72-1.22)	.62	0.85 (0.63-1.14)	.28	0.82 (0.62-1.08)	.15

Abbreviations: AT, as-treated; DFS, disease-free survival; DMFS, distant metastasis-free survival; HR, hazard ratio; LRFS, locoregional recurrence-free survival; mITT, modified intent-to-treat; OS, overall survival; PP, per-protocol.

Figure 3. Failure Pattern, Modified Intent-to-Treat Population



DM indicates distant metastasis; LR, locoregional recurrence; PORT, postoperative radiotherapy.

What can we conclude from two randomized trials?

1. PORT cannot be recommended for all patients who receive systemic therapy
2. PORT significantly improves LR control
3. PORT increases cardiopulmanry toxicities
4. Despite adjuvant chemotherapy, DM remains high (>70% of all failures)
5. More effective systemic therapy is needed
6. Better patient selection and improved RT delivery may improve treatment outcomes

Role for postoperative radiation for N2 disease?

High-risk features:

- Positive surgical margin
- Multistation nodal disease or bulky disease
- Subcarinal involvement for an upper-lobe cancer
- Extracapsular nodal disease in the involved N2 station
- Highest node resected involvement
- Inadequate nodal resection at surgery

How to improve the potential survival benefit of PORT for patients with N2 disease?

- Better patient selection
- Minimizing RT toxicities

Radiation-induced heart disease covers a wide range of conditions that can occur following thoracic radiation. These conditions arise because of acute inflammation leading to microvascular damage, chronic inflammation, and fibrosis of cardiac substructures. The resulting pathology depends on which cardiac substructure is damage

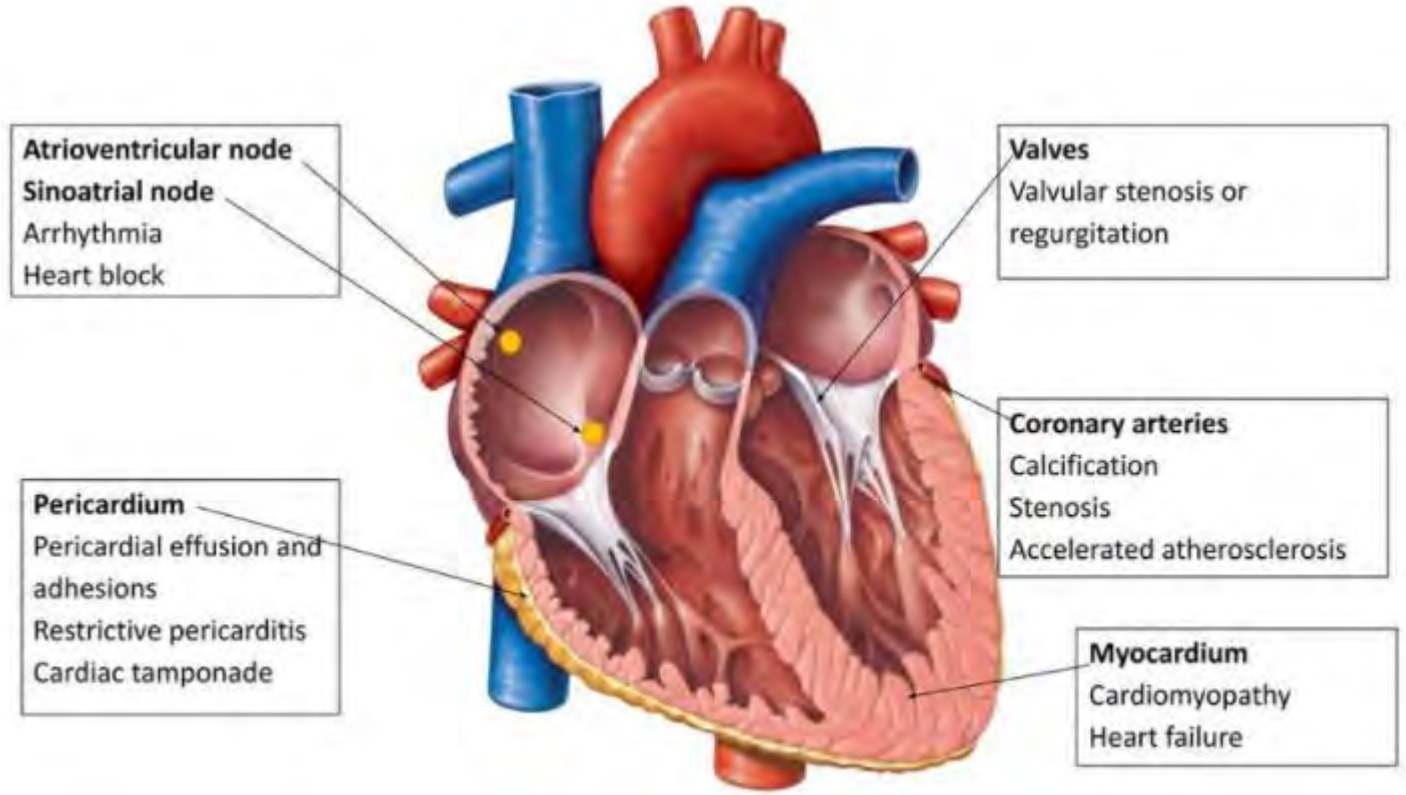


Figure. Potential Radiotherapy-Induced Complications, by Cardiac Substructure

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ORIGINAL REPORT

Cardiac Toxicity After Radiotherapy for Stage III Non–Small-Cell Lung Cancer: Pooled Analysis of Dose-Escalation Trials Delivering 70 to 90 Gy

Kyle Wang, Michael J. Eblan, Allison M. Deal, Matthew Lipner, Timothy M. Zagar, Yue Wang, Panayiotis Mavroidis, Carrie B. Lee, Brian C. Jensen, Julian G. Rosenman, Mark A. Socinski, Thomas E. Stinchcombe, and Lawrence B. Marks

Table 1. Trials Included and the No. of Patients Treated at UNC and Included in the Final Analysis

Trial Abbreviation	Trial Title	No. of Patients	Chemotherapy	Radiation
LCCC 9603	Phase I/II Trial of Induction Carboplatin/Paclitaxel Followed by Concurrent Escalating Dose Conformal Radiotherapy and Carboplatin/Paclitaxel in Locally Advanced NSCLC	26	Induction carboplatin plus paclitaxel *and* concurrent carboplatin plus paclitaxel	70-74 Gy (2 Gy once daily)
LCCC 9732	Phase I Dose Escalation Research Study of Radiotherapy Using Three-Dimensional Treatment Planning Following Neoadjuvant Chemotherapy for Stage IIB/III NSCLC	11	Induction carboplatin plus paclitaxel *or* induction carboplatin plus vinorelbine*	73.6-86.4 Gy (1.6 Gy twice a day)
LCCC 2001	Phase I Trial of Induction Chemotherapy Using Paclitaxel, Carboplatin, and Irinotecan with Filgrastim Support Followed by Concurrent Escalating Dose Conformal Radiotherapy and Paclitaxel/Carboplatin in Locally Advanced Unresectable Stage IIIA/B NSCLC	18	Induction carboplatin plus irinotecan plus paclitaxel *and* concurrent carboplatin plus paclitaxel	78-90 Gy (2 Gy once daily)
CALGB 30105	Induction/Concurrent Chemotherapy and Dose-Escalated Three Dimensional Thoracic Radiation for Patients With Stage III NSCLC: A Randomized Phase II Study	10	Induction and concurrent carboplatin plus paclitaxel *or* induction carboplatin plus gemcitabine and concurrent gemcitabine	74 Gy (2 Gy once daily)
LCCC 0215	Induction Chemotherapy Using Paclitaxel, Carboplatin, Irinotecan with Pegfilgrastim Support Followed by Conformal Radiotherapy and Paclitaxel/Carboplatin/ Gefitinib in Locally Advanced Unresectable Stage IIIA/B NSCLC	19	Induction carboplatin plus irinotecan plus paclitaxel *and* concurrent carboplatin plus paclitaxel plus gefitinib	74 Gy (2 Gy once daily)
LCCC 0511	Phase I/II Trial of Induction Carboplatin/Paclitaxel With Bevacizumab Followed by Concurrent Thoracic Conformal Radiation Therapy With Carboplatin/ Paclitaxel, Bevacizumab and Erlotinib in Stage IIIA/B NSCLC	28	Induction carboplatin plus paclitaxel plus bevacizumab *and* concurrent carboplatin plus paclitaxel plus bevacizumab with or without erlotinib *and* consolidation bevacizumab plus erlotinib	74 Gy (2 Gy once daily)

Abbreviations: CALGB, Cancer and Leukemia Group B; LCCC, Lineberger Comprehensive Cancer Center; NSCLC, non–small-cell lung cancer; UNC, University of North Carolina.

*No concurrent chemotherapy was used in this trial.

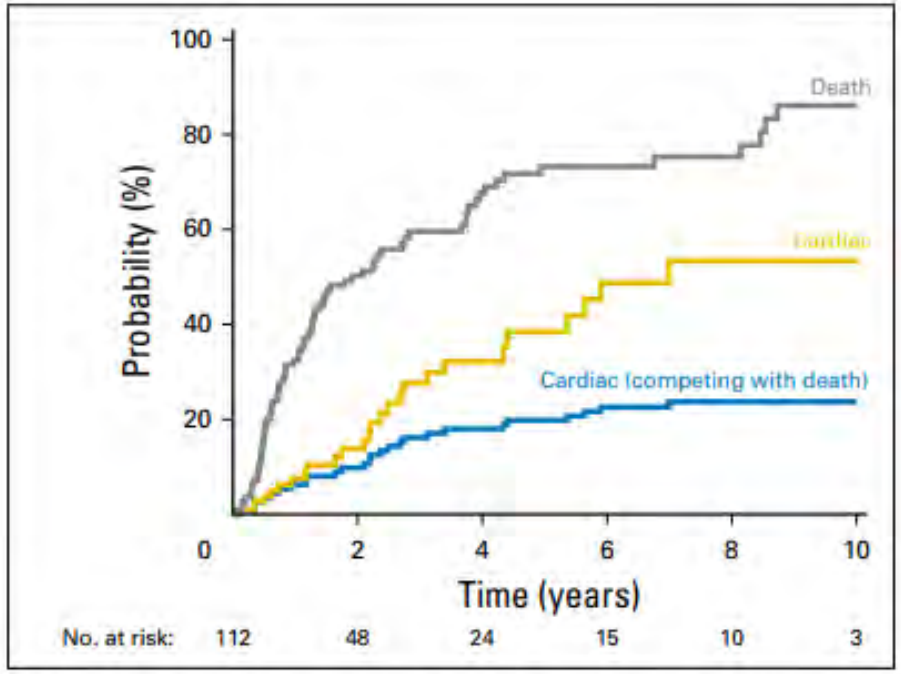


Fig 1. Cumulative incidence plot of death (gray), symptomatic cardiac events (gold), and symptomatic cardiac events adjusted for the competing risk of death (blue).

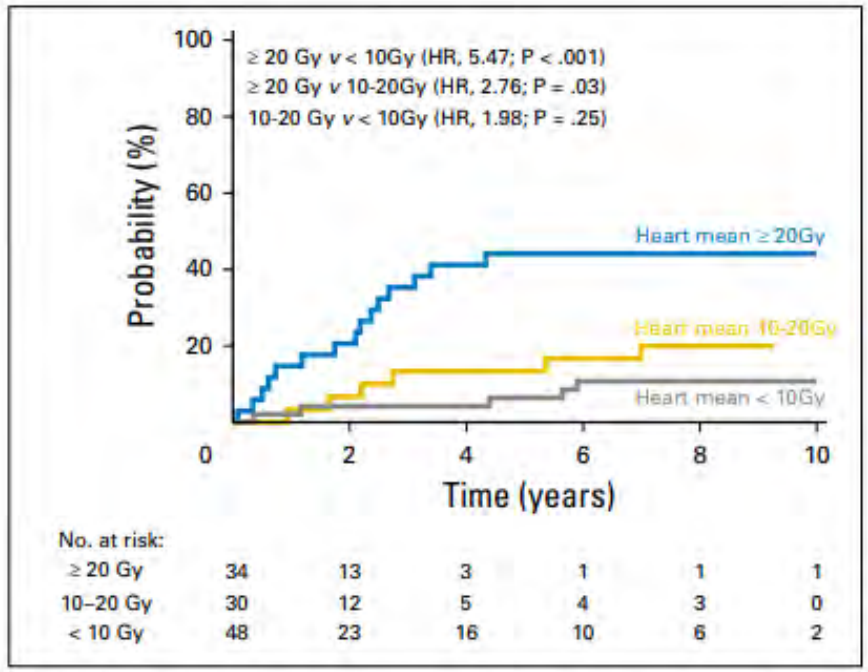


Fig 2. Cumulative incidence of competing risk–adjusted symptomatic cardiac events in patients with heart mean dose ≥ 20 Gy (blue), 10 to 20 Gy (gold), and < 10 Gy (gray).

Clinically significant cardiac events after high dose thoracic RT for stage III NSCLC were associated with heart dose and cardiac risk and occurred fairly early after treatment. Consistent with the current emphasis on reducing radiation heart exposure for other malignancies, heart doses should be similarly minimized in patients with stage III NSCLC.

In Summary:

Role for adjuvant radiation therapy for N2 disease

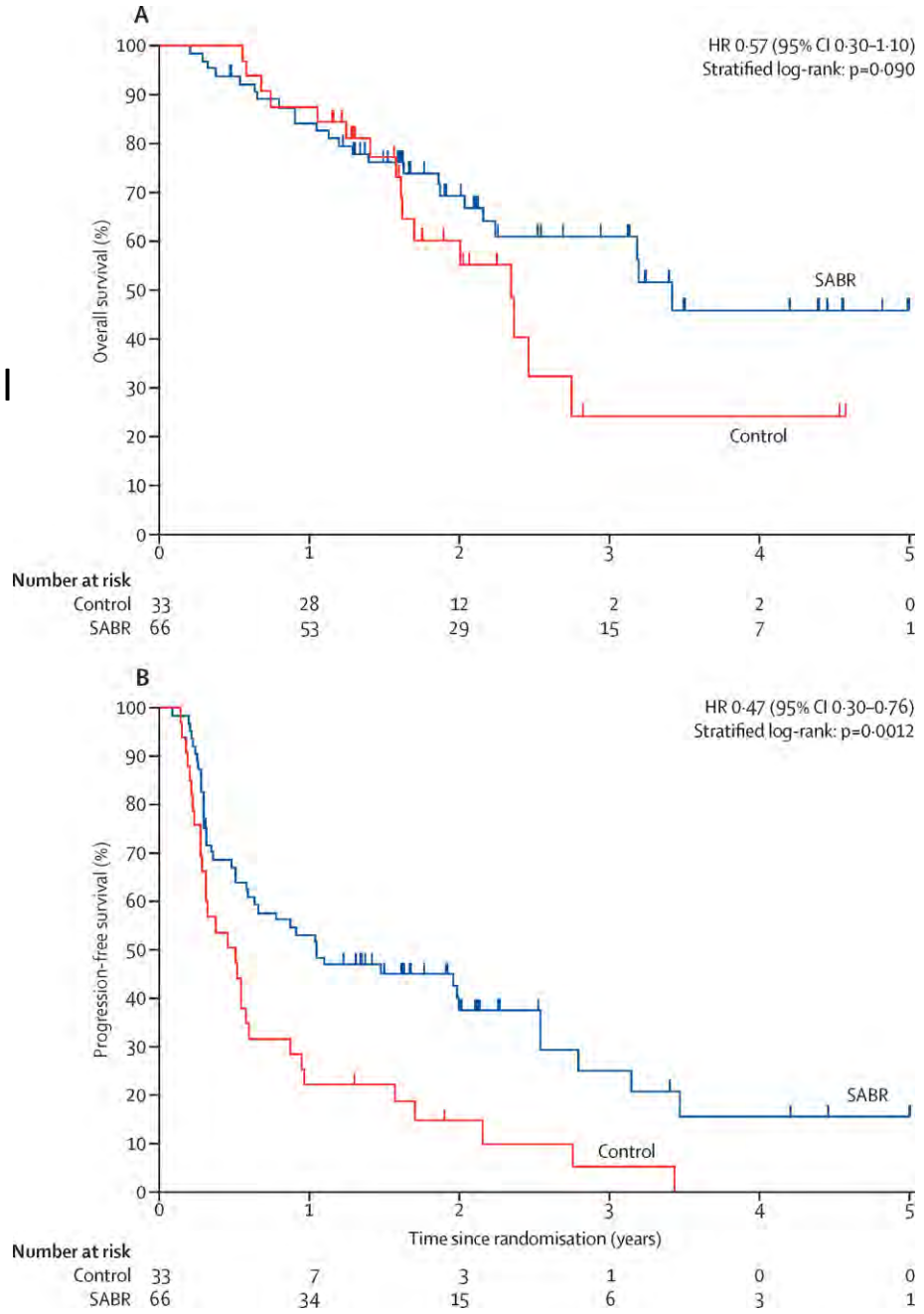
- Available level 1 evidence does not support routine use of PORT
- Randomized trial findings cannot be generalized yet
- More trials on PORT for NSCLC would be unlikely
- We should consider PORT for patients with multiple high-risk factors
- It is critical to minimize PORT related cardiopulmonary toxicity and mortality

Radiation therapy for stage IV disease

- One of the most effective palliative modality
- Potentially enhancing systemic therapy?

Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial

D. Palma et al.
Lancet 2019



Median overall survival was 28 months (95% CI 19–33) in the control group versus 41 months (26–not reached) in the SABR group (hazard ratio 0·57, 95% CI 0·30–1·10; p=0·090).

Adverse events of grade 2 or worse occurred in three (9%) of 33 controls and 19 (29%) of 66 patients in the SABR group (p=0·026), an absolute increase of 20% (95% CI 5–34). Treatment-related deaths occurred in three (4·5%) of 66 patients after SABR, compared with none in the control group.

Published Phase II trials: SBRT for oligomets

Phase II study	Inclusion criteria	Number Pts- SBRT	Median FU	SBRT Fractionation	Outcome	Grade 3+ Toxicity
Iyengar, JAMA Onc 2018	NSCLC, <=5 mets	14	9m	21-27Gy/1fx 26.5-33Gy/3fx 30-37.5Gy/5fx	Median PFS 9.7m	28%
SABR-COMET Palma, Lancet 2019	Any primary, <=5 mets	66	25m	54Gy/3fx 35Gy/5fx 60Gy/8fx	Median PFS 12m	11%
Rusthoven, JCO 2009	Any primary, <=3 lung mets	38	15m	60Gy/3fx	Median PFS 8.4m	8%
Collen, Ann Oncol 2014	NSCLC, <=5 mets	26	16m	50Gy/10fx	Median PFS 11.2m	8%
SAFFRON II	Any primary, <=3 lung mets	87		28Gy/1fx 48Gy/4fx	1yr DFS 60%	3.4%

NRG LU 002

Patients with metastatic NSCLC having completed 4 cycles or courses of first-line/induction systemic therapy Restaging studies reveal no evidence of progression and limited (≤ 3 discrete sites) metastatic disease, all of which must be amenable to SBRT +/- Surgery	STRATIFY	Histology: Squamous vs. Non-squamous Systemic Therapy: Immunotherapy vs Cytotoxic Chemotherapy	RANDOMIZE	Arm 1: Maintenance systemic therapy alone Arm 2: SBRT or SBRT and Surgery to all sites of metastases (≤ 3 discrete sites) plus irradiation (SBRT or hypofractionated RT) of the primary site followed by maintenance systemic therapy. All Arm 2 patients, even if treated with Surgery, must have one site of disease (metastasis or primary) treated with radiation.

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In Summary

- Radiotherapy is a main treatment modality for lung cancer (only modality being used for all stages I-IV)
- Primary modality in locally advanced stage III disease
- Increased role in stage I and stage IV
- PORT may be considered for selected high-risk patients
- Advances in radiobiology and technology will improve the treatment outcomes

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