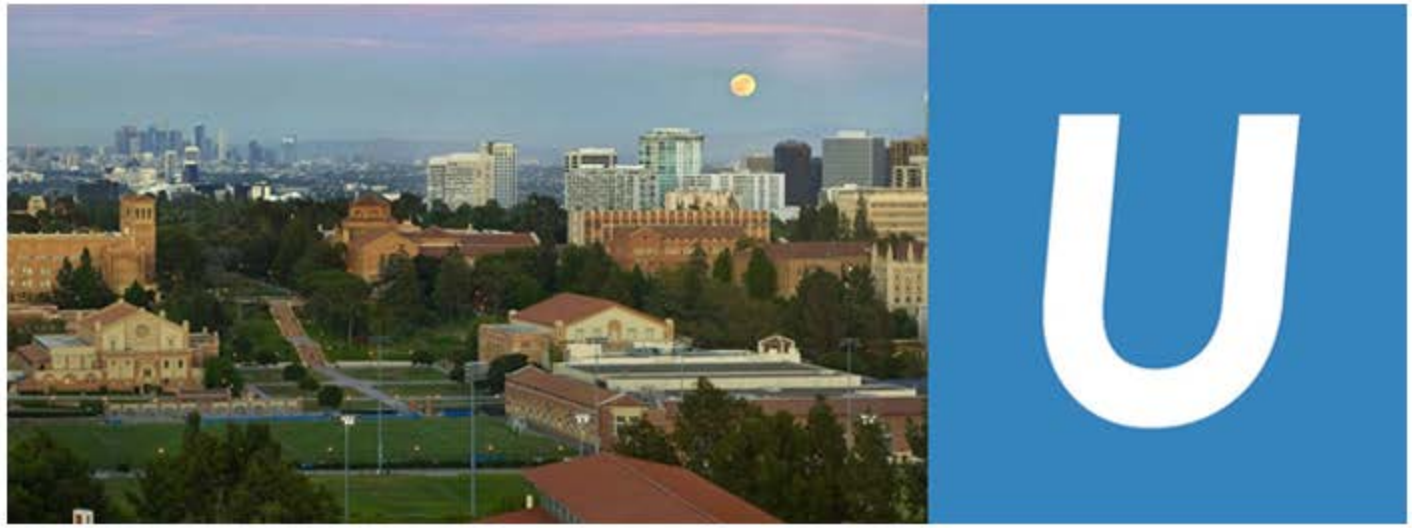
8th Annual Radiation Oncology Case-Based Education and Virtual Skills Assessment Workshop - August 14-15, 2021



Radiotherapy for the Management of Lung Cancer

Jason C. Ye, MD

Assistant Professor of Clinical Radiation Oncology

August 15, 2021

Great Job!

- Everyone did very well
- Some mistakes, likely due to stress
- Know your staging!
- Work up, think about your real patients
- Dose, and OAR constraints!

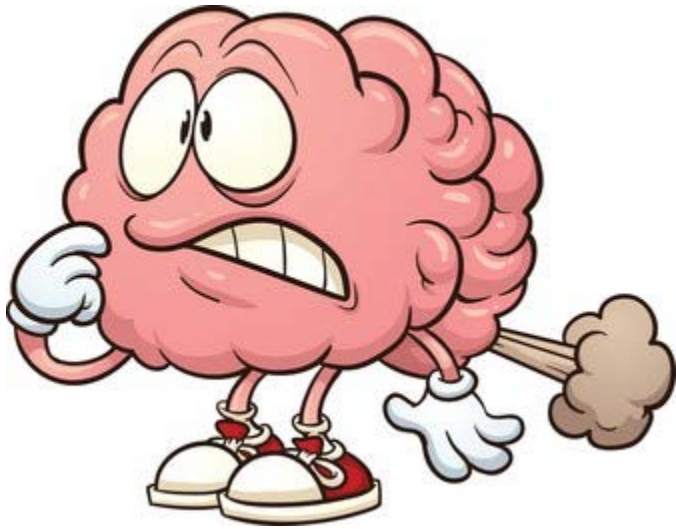


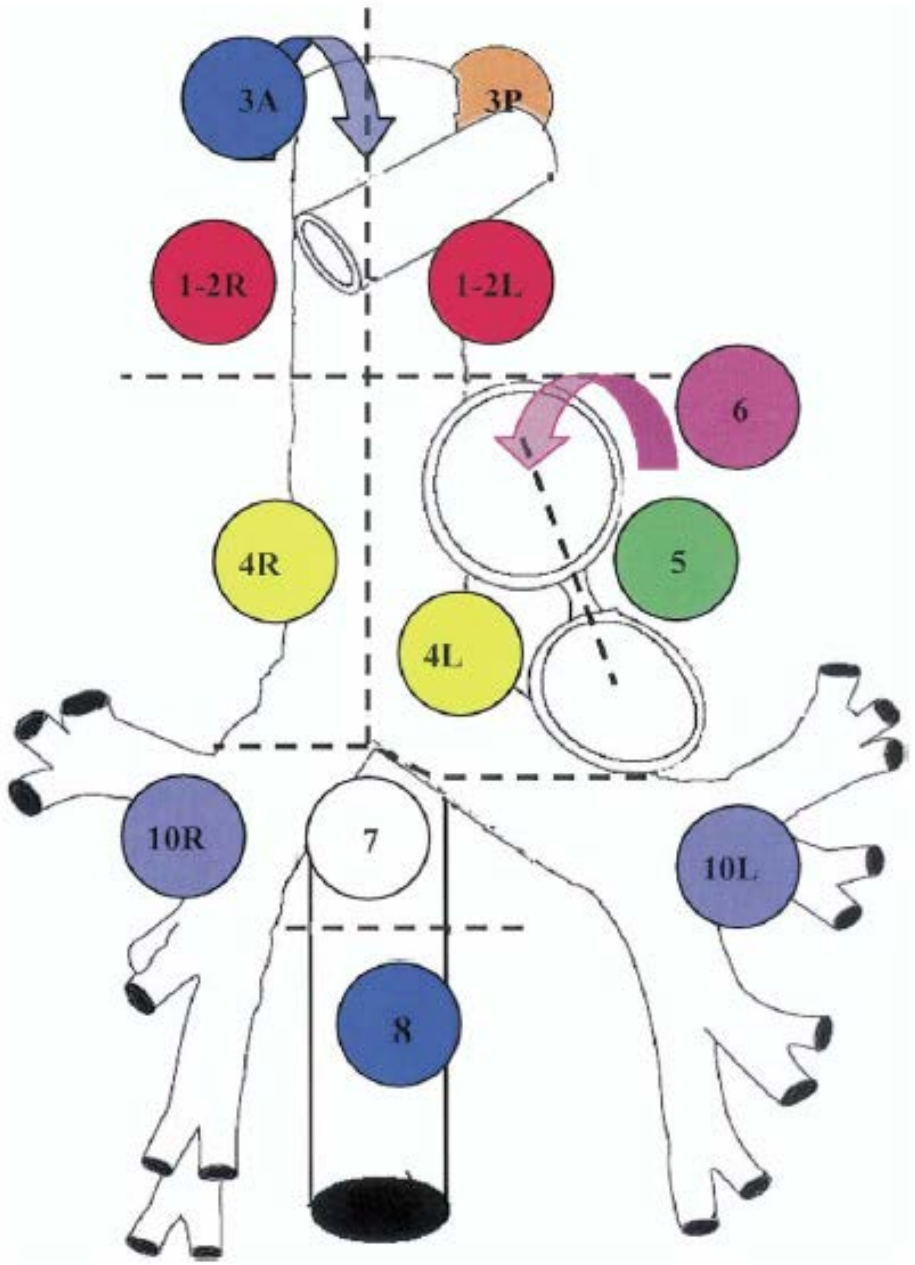
Table 1. **Definitions for T, N, M**

T		Primary Tumor
TX		Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0		No evidence of primary tumor
Tis		Carcinoma *in situ* Squamous cell carcinoma *in situ* (SCIS) Adenocarcinoma *in situ* (AIS): adenocarcinoma with pure lepidic pattern, ≤3 cm in greatest dimension
T1		Tumor ≤3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)
	T1mi	Minimally invasive adenocarcinoma: adenocarcinoma (≤3 cm in greatest dimension) with a predominantly lepidic pattern and ≤5 mm invasion in greatest dimension
	T1a	Tumor ≤1 cm in greatest dimension. A superficial, spreading tumor of any size whose invasive component is limited to the bronchial wall and may extend proximal to the main bronchus also is classified as T1a, but these tumors are uncommon.
	T1b	Tumor >1 cm but ≤2 cm in greatest dimension
	T1c	Tumor >2 cm but ≤3 cm in greatest dimension
T2		Tumor >3 cm but ≤5 cm or having any of the following features: (1) Involves the main bronchus, regardless of distance to the carina, but without involvement of the carina; (2) Invades visceral pleura (PL1 or PL2); (3) Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung
	T2a	Tumor >3 cm but ≤4 cm in greatest dimension
	T2b	Tumor >4 cm but ≤5 cm in greatest dimension
T3		Tumor >5 cm but ≤7 cm in greatest dimension or directly invading any of the following: parietal pleura (PL3), chest wall (including superior sulcus tumors), phrenic nerve, parietal pericardium; or separate tumor nodule(s) in the same lobe as the primary
T4		Tumor >7 cm or tumor of any size invading one or more of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina; separate tumor nodule(s) in an ipsilateral lobe different from that of the primary

Descriptor	7th Edition T/N/M	8th Edition T/N/M
T component		
0 cm (pure lepidic adenocarcinoma ≤3 cm in total size)	T1a if ≤2 cm; T1b if >2-3 cm	Tis (AIS)
≤0.5 cm invasive size (lepidic predominant adenocarcinoma ≤3 cm total size)	T1a if ≤2 cm; T1b if >2-3 cm	T1mi
≤1 cm	T1a	T1a
>1-2 cm	T1a	T1b
>2-3 cm	T1b	T1c
>3-4 cm	T2a	T2a
>4-5 cm	T2a	T2b
>5-7 cm	T2b	T3
>7 cm	T3	T4
Bronchus <2 cm from carina	T3	T2
Total atelectasis/pneumonitis	T3	T2
Invasion of diaphragm	T3	T4
Invasion of mediastinal pleura	T3	—
N component		
No assessment, no involvement, or involvement of regional lymph nodes	NX, N0, N1, N2, N3	No change
M component		
Metastasis within the thoracic cavity	M1a	M1a
Single extrathoracic metastasis	M1b	M1b
Multiple extrathoracic metastasis	M1b	M1c

Target Delineation: Lymph nodes

- 1 = high mediastinal
- 2 = upper paratracheal
- 3 = pre and retrotracheal
- 4 = lower paratracheal
- 5 = AP window
- 6 = paraaortic
- 7 = subcarinal
- 8 = paraesophageal below carina
- 9 = pulmonary ligament
- 10 = hilar
- 11 = interlobar
- 12 = lobar
- 13 = segmental,
- 14 = subsegmental.



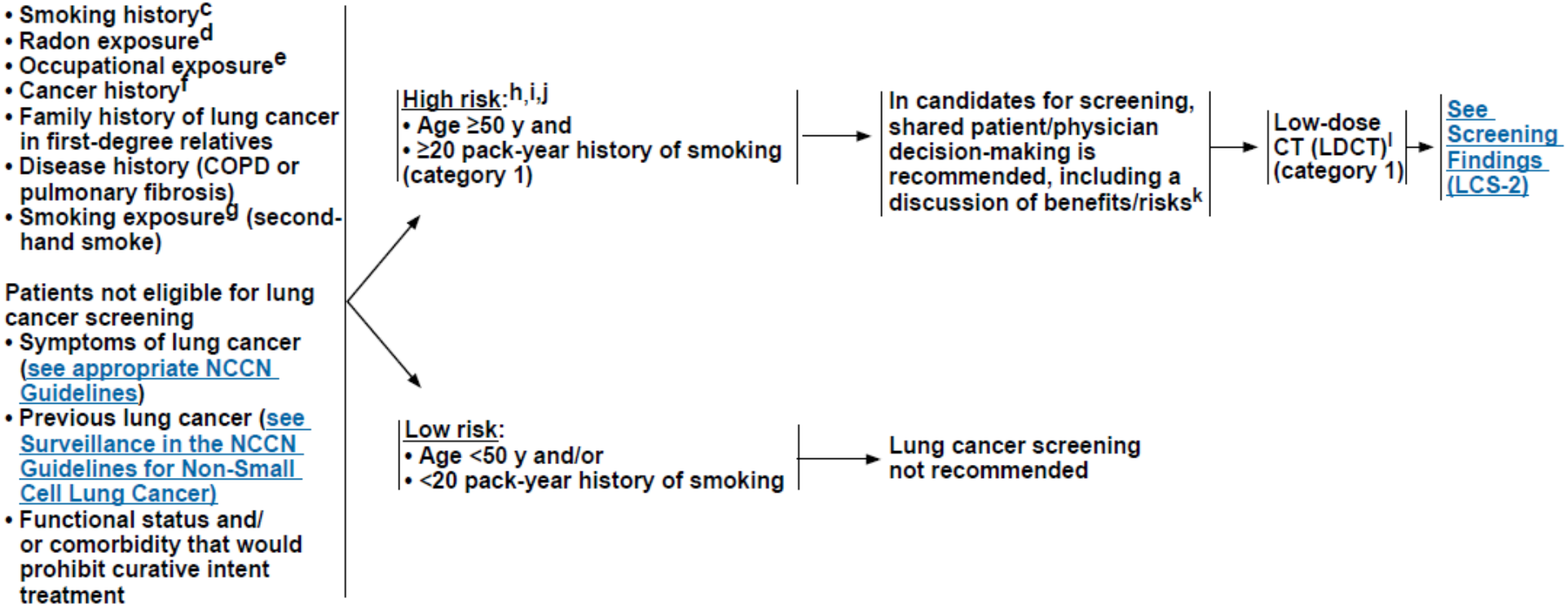
What is work-up for new diagnosis of NSCLC?

- History & Physical Exam:

HISTORY	PHYSICAL EXAM
• HPI o Further Definition of Symptoms • Social Hx o Smoking • Review of Systems o Weight Loss o Shoulder Pain	• Full Pulmonary Exam • Assess PS • Look for Brachial Plexopathy • Look for Ptosis, Meiosis, Anhydrosis

Lung Ca Screening

- National Lung Screening Trial (NEJM 2011)
  - >50,000 high risk pts (55 – 74 yrs, ≥ 30 pack yrs, active or quit < 15 yrs ago)
  - Randomized: low dose CT v. PA CXR annually x 3 years
  - Results:
    - Number needed to screen to prevent 1 cancer death: 320
    - CT screening reduced mortality by 20%
- NCCN recommends screening for high risk patients



NSCLC workup – Labs, Imaging, PFTs

Labs

- CBC
- Chem 7
- LFTs
- Alk Phos
- LDH
- Sputum Cytology

Imaging

- CXR
- CT Chest & Abdomen ***(Include Adrenals)***
- PET Scan
- *MRI Brain for Stage > IIB (N+) or Neuro Sx*
- *MRI Thoracic Inlet if Superior Sulcus*

Criteria for Medical Operability

PFTs

- FEV1/FVC: >75% Predicted
- DLCO: >40-50%
  - <40% predicted post-op associated with ↑ post-op complications
- FEV1
  - Pneumonectomy: > 2 L
  - Lobectomy: > 1.2 L
    - > 35% predicted (or > 0.8) post-op (associated with ↓ risk of death)

Additional

- Severe pulmonary htn
- Diabetes w/ severe end organ damage
- Severe vascular disease
- Severe chronic cardiac dz
- Patient refusal

RTOG 0618 – Phase II Trial of SBRT in the treatment of patients with operable Stage I/II NSCLC

(3/25/10) The patient must be considered a reasonable candidate for surgical resection of the primary tumor according to the following criteria:

- A qualified thoracic surgeon should make the determination prior to registration that there would be a high likelihood of negative surgical margins.
- baseline FEV1 > 35% predicted,
- postoperative predicted FEV1 > 30% predicted,
- diffusion capacity > 35% predicted,
- absent baseline hypoxemia (hypoxemia defined as PaO2 of $\leq$ 60 mm Hg on room air) and/or hypercapnia (hypercapnia defined as PaCO2 > 50 mm Hg),
- absent severe pulmonary hypertension,
- absent severe cerebral, cardiac, or peripheral vascular disease,
- absent severe chronic heart disease.

Medically Inoperable Patients: Older XRT

The role of radiotherapy in treatment of stage I non-small cell lung cancer

Author	BED (acute)	Local failure alone (%)	Any local failure (%)
Krol et al. [15]		27.8	65.7
Hayakawa et al. [8]	68.1	11.1	19.4
Kaskowitz et al. [16]	65.1	41.5	43.4
Slotman et al. [9]	76.4	0	6.4
Jeremic et al. [4]	71	–	45
Sibley et al. [20]	–	16.3	19.1
Slotman et al. [17]	–	19.1	25.2
Sandler et al. [18]	62.8	42.8[a]	42.8[a]
Haffty et al. [19]	59	39	39
Noordijk et al. [13]	63.4	–	70
Morita et al. [14]	65.3	–	44.3
Gauden et al. [5]	62.5	–	–

Qiao et al, Lung Cancer 2003

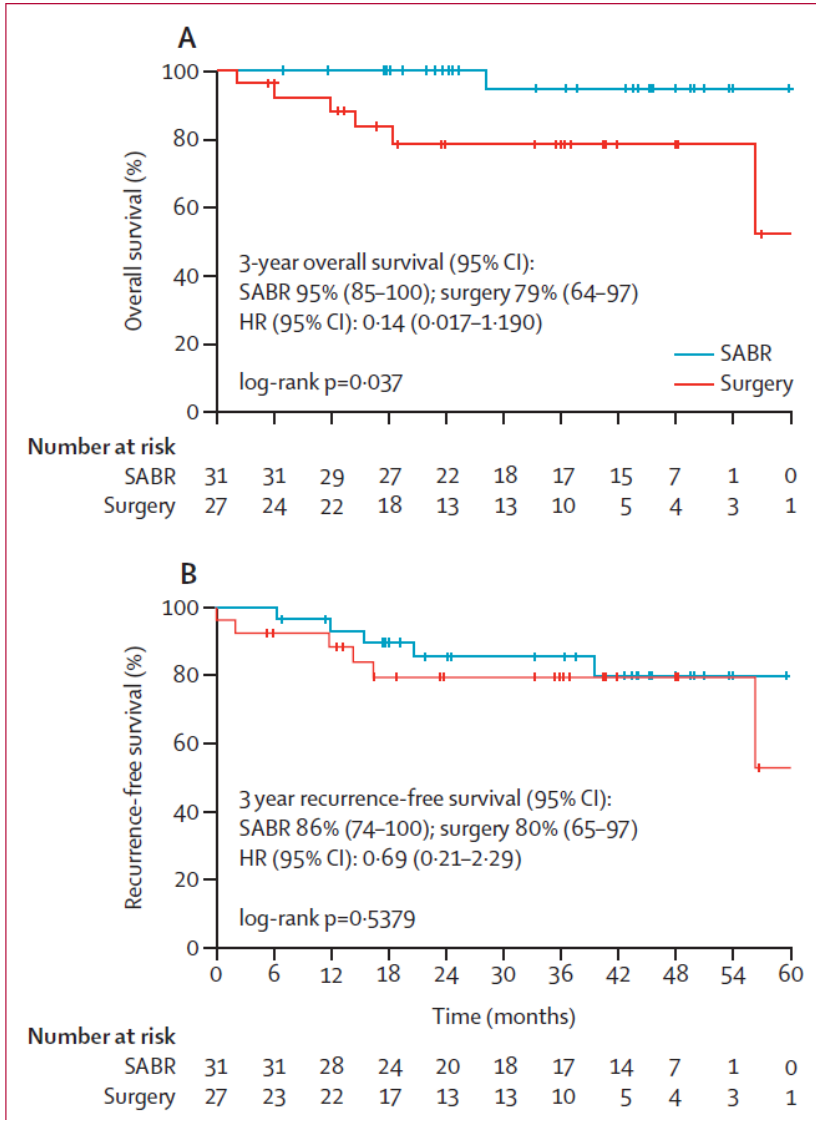
RTOG 0236, Timmerman et al. JAMA 2010

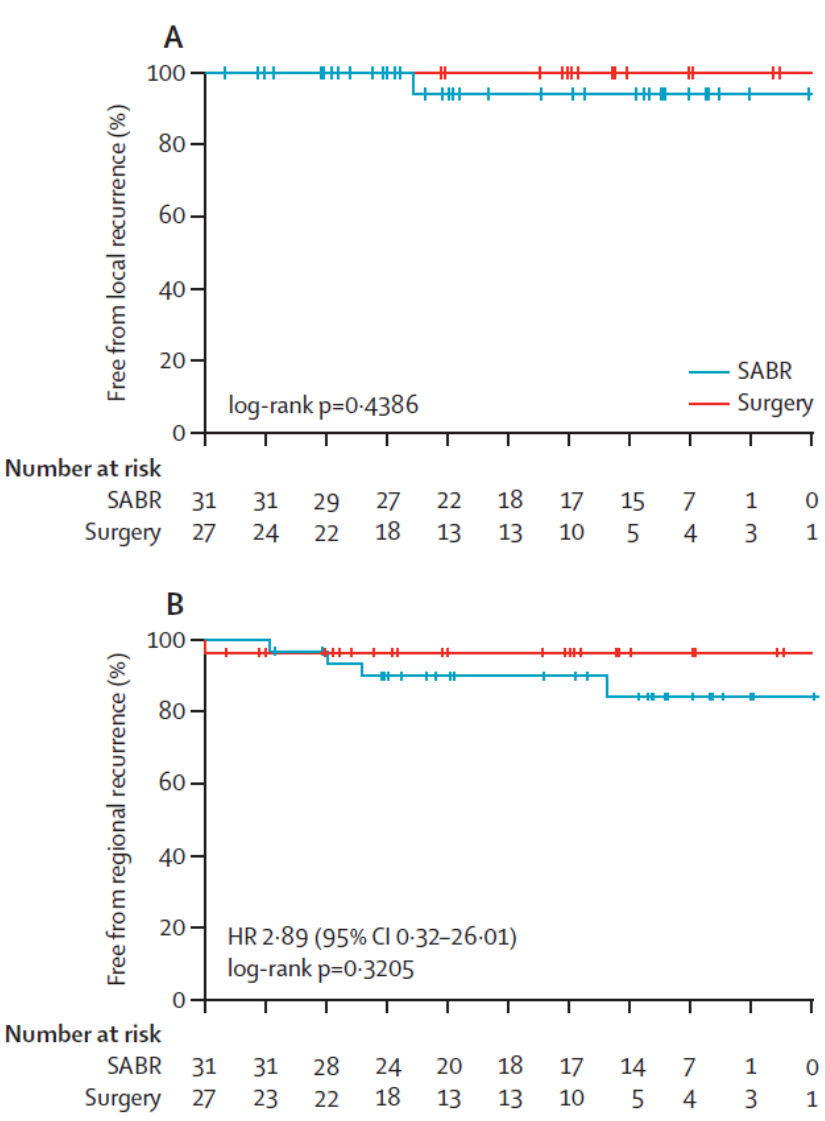
- Multi-institutional, Phase II study
- 55 evaluable patients (inoperable, T1-T2N0 NSCLC)
- 54Gy in 3fxs to PTV over 1.5-2 weeks
- Median follow-up 34.4 mo
- Only 1 primary tumor failure (97.6% control)
- 3-year DFS and OS: 48.3% (95% CI, 34.4%-60.8%) and 55.8% (95% CI, 41.6%-67.9%)
- The median overall survival was 48.1 months (95% CI, 29.6 months to not reached)
- 7 grade 3, 3 grade 4 toxicities
- 5-year outcomes: PTC 93% LC 80%, LRC 62%, DM 31%

Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials

Joe Y Chang, Suresh Senan*, Marinus A Paul, Reza J Mehran, Alexander V Louie, Peter Balter, Harry J M Groen, Stephen E McRae, Joachim Widder, Lei Feng, Ben E E M van den Borne, Mark F Munsell, Coen Hurkmans, Donald A Berry, Erik van Werkhoven, John J Kresl, Anne-Marie Dingemans, Omar Dawood, Cornelis J A Haasbeek, Larry S Carpenter, Katrien De Jaeger, Ritsuko Komaki, Ben J Slotman, Egbert F Smit†, Jack A Roth†*

- pooled analysis of two randomized controlled trials (STARS and ROSEL)
- T1-T2a (<4cm) N0M0 NSCLC in operable patients


A
Overall survival (%)
100
80
60
40
20
0
3-year overall survival (95% CI):
SABR 95% (85–100); surgery 79% (64–97)
HR (95% CI): 0·14 (0·017–1·190)
log-rank p=0·037
SABR
Surgery
Number at risk
SABR 31 31 29 27 22 18 17 15 7 1 0
Surgery 27 24 22 18 13 13 10 5 4 3 1
B
Recurrence-free survival (%)
100
80
60
40
20
0
3 year recurrence-free survival (95% CI):
SABR 86% (74–100); surgery 80% (65–97)
HR (95% CI): 0·69 (0·21–2·29)
log-rank p=0·5379
0 6 12 18 24 30 36 42 48 54 60
Time (months)
Number at risk
SABR 31 31 28 24 20 18 17 14 7 1 0
Surgery 27 23 22 17 13 13 10 5 4 3 1


A
Free from local recurrence (%)
100
80
60
40
20
0
log-rank p=0·4386
SABR
Surgery
Number at risk
SABR 31 31 29 27 22 18 17 15 7 1 0
Surgery 27 24 22 18 13 13 10 5 4 3 1
B
Free from regional recurrence (%)
100
80
60
40
20
0
HR 2·89 (95% CI 0·32–26·01)
log-rank p=0·3205
Number at risk
SABR 31 31 28 24 20 18 17 14 7 1 0
Surgery 27 23 22 18 13 13 10 5 4 3 1

SBRT for Early-Stage NSCLC

- **How would you simulate?**
  - Supine in Full Body Immobilizer
  - ABC or Abdominal Compression
  - 4D CT
  - IV Contrast not needed for N- peripheral tumors
- **What is target volume?**
  - GTV as defined by Imaging (Max IP) [free breathing CT]
    - **lung window
  - ITV [including all 10 respiratory phases, not just MIP]
  - PTV = ITV plus 5mm Margin (more in CC if no 4DCT)
  - Prescribe so
    - 95% of PTV receives 100%
    - 99% of PTV receives 90%
- **How would you plan radiation?**
  - 6-9 fields, VMAT, Conf Arc, 6 MV photons (FFF)
  - Daily target localization using, CBCT and/or kV fiducials
  - Respiratory gating (or DIBH) with fluoro

Expansions as per RTOG 0839

	Internal Margin	Set up Margin	PTV Margin
Free-breathing CT + Free-breathing delivery without daily IGRT	1 cm in superior-inferior direction and 0.5 cm in axial directions	0.5 cm uniform expansion	1.5 cm in the superior-inferior direction and 1 cm in the axial directions
Free-breathing CT + Free-breathing delivery + daily IGRT	1 cm in the superior-inferior direction and 0.5 cm in axial directions	0.2-0.3 cm uniform expansion	1.2-1.3 cm in the superior-inferior direction and 0.7-0.8 cm in axial directions
Breath-hold or gating CT + breath-hold or gating delivery without IGRT	0.5 cm in the superior-inferior direction and 0.3 cm in axial directions	0.5 cm uniform expansion	1 cm in the superior-inferior direction and 0.8 cm in axial directions
Breath-hold or gating CT + breath-hold or gating delivery + daily IGRT	0.5 cm in the superior-inferior direction and 0.3 cm in axial directions	0.2-0.3 cm uniform expansion	0.7-0.8 cm in the superior-inferior direction and 0.5-0.6 cm in axial directions
4D CT + Free-breathing delivery without daily IGRT	ITV	0.5 cm uniform expansion	ITV + 0.5 cm uniform expansion
4D CT + Free-breathing delivery + daily IGRT	ITV	0.2-0.3 cm uniform expansion	ITV + 0.2-0.3 cm uniform expansion
Abdominal compression CT + abdominal compression free-breathing delivery without IGRT	0.8 cm in the superior-inferior direction and 0.5 cm in axial directions	0.5 cm uniform expansion	1.3 cm in the superior-inferior direction and 1 cm in axial directions
Abdominal compression CT + abdominal compression free-breathing delivery + IGRT	0.8 cm in the superior-inferior direction and 0.5 cm in axial directions	0.2-0.3 cm uniform expansion	1.0-1.1 cm in the superior-inferior direction and 0.7-0.8 cm in axial directions
Abdominal compression CT + abdominal compression breath-hold or gating delivery without IGRT	0.5 cm in the superior-inferior direction and 0.3 cm in axial directions	0.5 cm uniform expansion	1 cm in the superior-inferior direction and 0.8 cm in axial directions
Abdominal compression CT + abdominal compression breath-hold or gating delivery + IGRT	0.5 cm in the superior-inferior direction and 0.3 cm in axial directions	0.2-0.3 cm uniform expansion	0.7-0.8 cm in the superior-inferior direction and 0.5-0.6 cm in axial directions

Lung SBRT: Toxicities

- Pneumonitis
- Chest wall pain/rib fracture
- Skin erythema/desquamation
- Tissue necrosis, bronchial fistula

- **Normal tissue constraints:**
  - Keep Lung V20 < 10%;
  - Conformality Index (Vol_{RX}/Vol_{PTV}): < 1.2
    - (up to 1.4 still minor variation in RTOG trials)
  - D_{2cm} (max dose 2cm from PTV in any direction: varies by size of lesion): 28.1 – 44.3
  - Chest Wall:
    - V30 Gy < 30 cc
    - Decreased risk of CW toxicity
    - Dunlap et al (IJROBP 2010)

Table 3. Maximum Dose Constraints for SABR*

OAR/Regimen	1 Fraction	3 Fractions	4 Fractions	5 Fractions
Spinal cord	14 Gy	18 Gy (6 Gy/fx)	26 Gy (6.5 Gy/fx)	30 Gy (6 Gy/fx)
Esophagus	15.4 Gy	27 Gy (9 Gy/fx)	30 Gy (7.5 Gy/fx)	105% of PTV prescription^
Brachial plexus	17.5 Gy	24 Gy (8 Gy/fx)	27.2 Gy (6.8 Gy/fx)	32 Gy (6.4 Gy/fx)
Heart/ pericardium	22 Gy	30 Gy (10 Gy/fx)	34 Gy (8.5 Gy/fx)	105% of PTV prescription^
Great vessels	37 Gy	NS	49 Gy (12.25 Gy/fx)	105% of PTV prescription^
Trachea & proximal bronchi	20.2 Gy	30 Gy (10 Gy/fx)	34.8 Gy (8.7 Gy/fx)	105% of PTV prescription^
Rib	30 Gy	30 Gy (10 Gy/fx)	40 Gy (10 Gy/fx)	NS
Skin	26 Gy	24 Gy (8 Gy/fx)	36 Gy (9 Gy/fx)	32 Gy (6.4 Gy/fx)
Stomach	12.4 Gy	NS	27.2 Gy (6.8 Gy/fx)	NS

*Based on constraints used in recent RTOG SABR trials (RTOG 0618, 0813, & 0915).
^For central tumor location. NS = not specified.

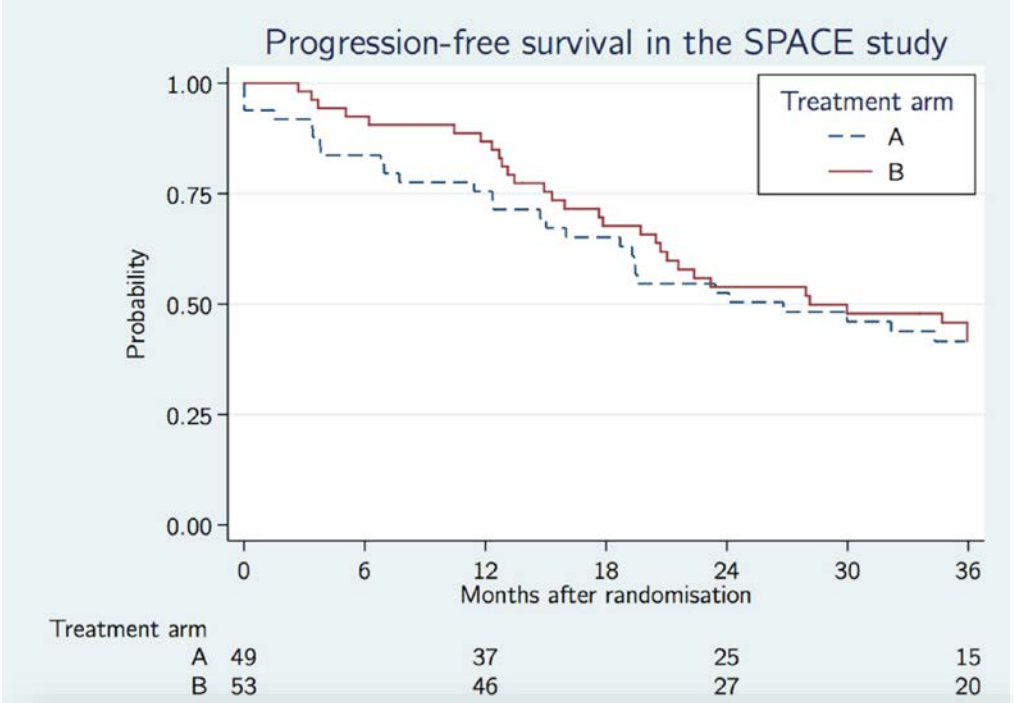
Early Stage NSCLC – SBRT

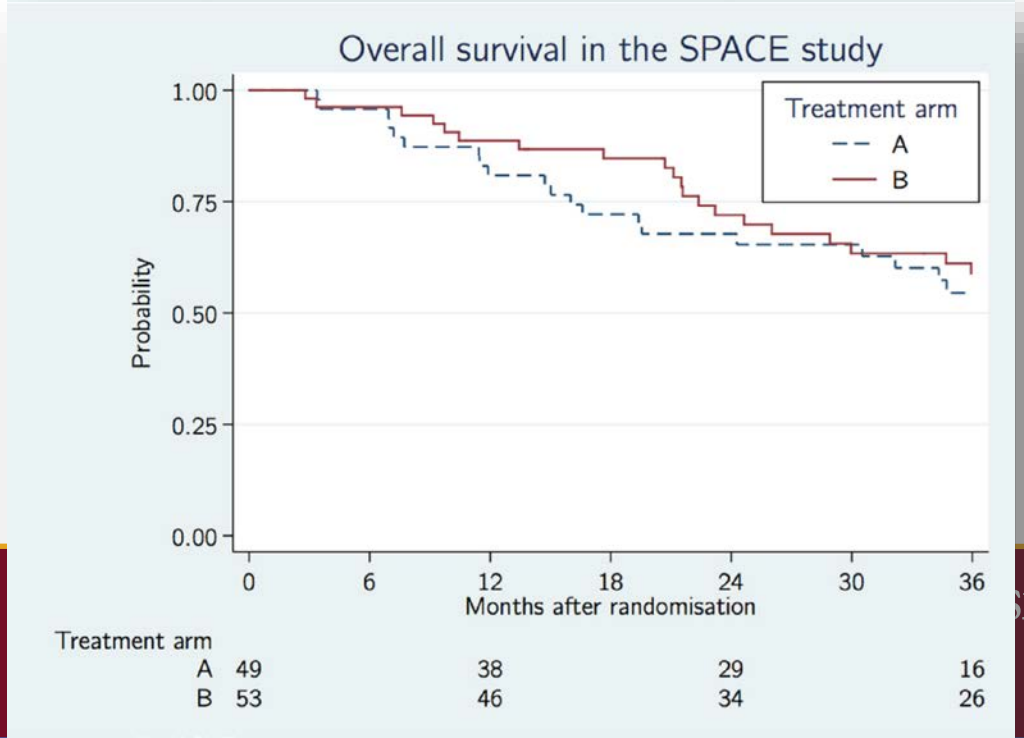
Doses acceptable for central tumors?

- 12-12.5 Gy x 4 (Onishi & MDACC)
- 10-11 Gy x 5 (RTOG 0813, this option is acceptable for central & peripheral lesions)
- 4 Gy x 15 (Canadian – Cheung et al J Natl Cancer Inst 2014)
- 7.5 Gy x 8 (VUMC – Haasbeek et al J Thor Onco 2011)
- 5Gy x 12 (VUMC – Tekatli JTO 2016), keep Dmax to 110%
- 70 Gy in 10 fx (MDACC – Chang IJROBP 2014) – if cannot meet 12.5 x 4 dose constraints
- 70 Gy in 17 fx (CALGB Bogart JCO 2010)

Nyman, SPACE trial, 2016

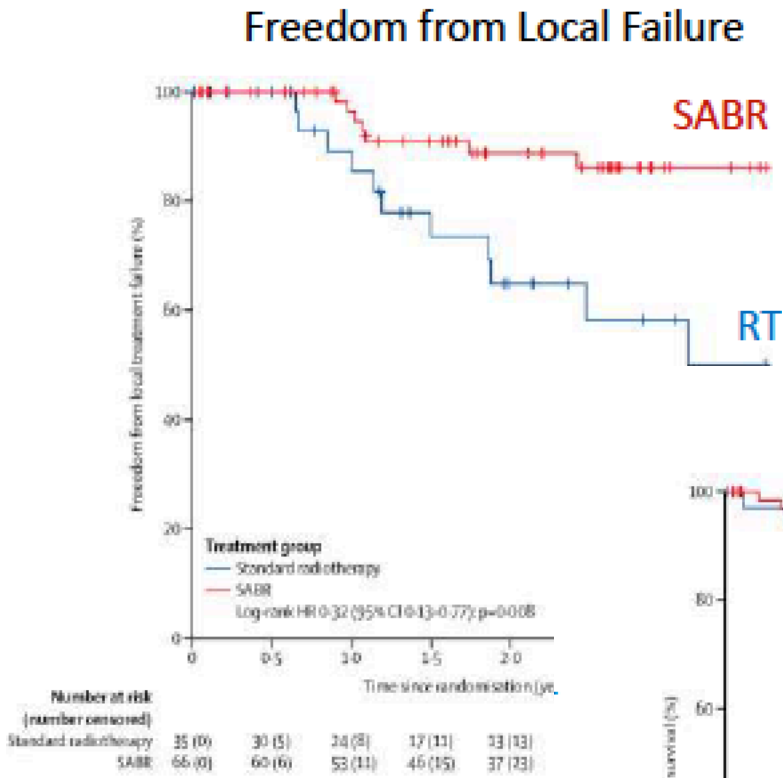
- 102 medically inoperable pts with stage I NSCLC randomized to SBRT (66Gy/3fx) vs 3D-CRT (70/35fx)
- Results
  - No difference in 1,2,3yr PFS
  - Lower toxicity with SBRT
    - Pneumonitis: 19% vs 34%
    - Esophagitis: 8% vs 30%
- **Conclusion: SBRT** with **similar disease control rate** with **lower toxicity and better QOL.** Should be standard of care.

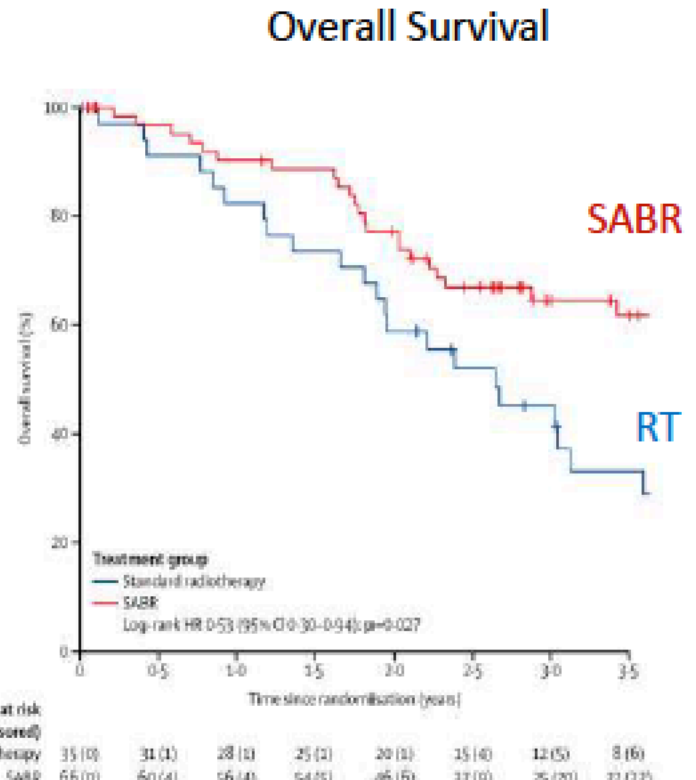




TROG 09.02 CHISEL (Ball Lancet Oncology 2019)

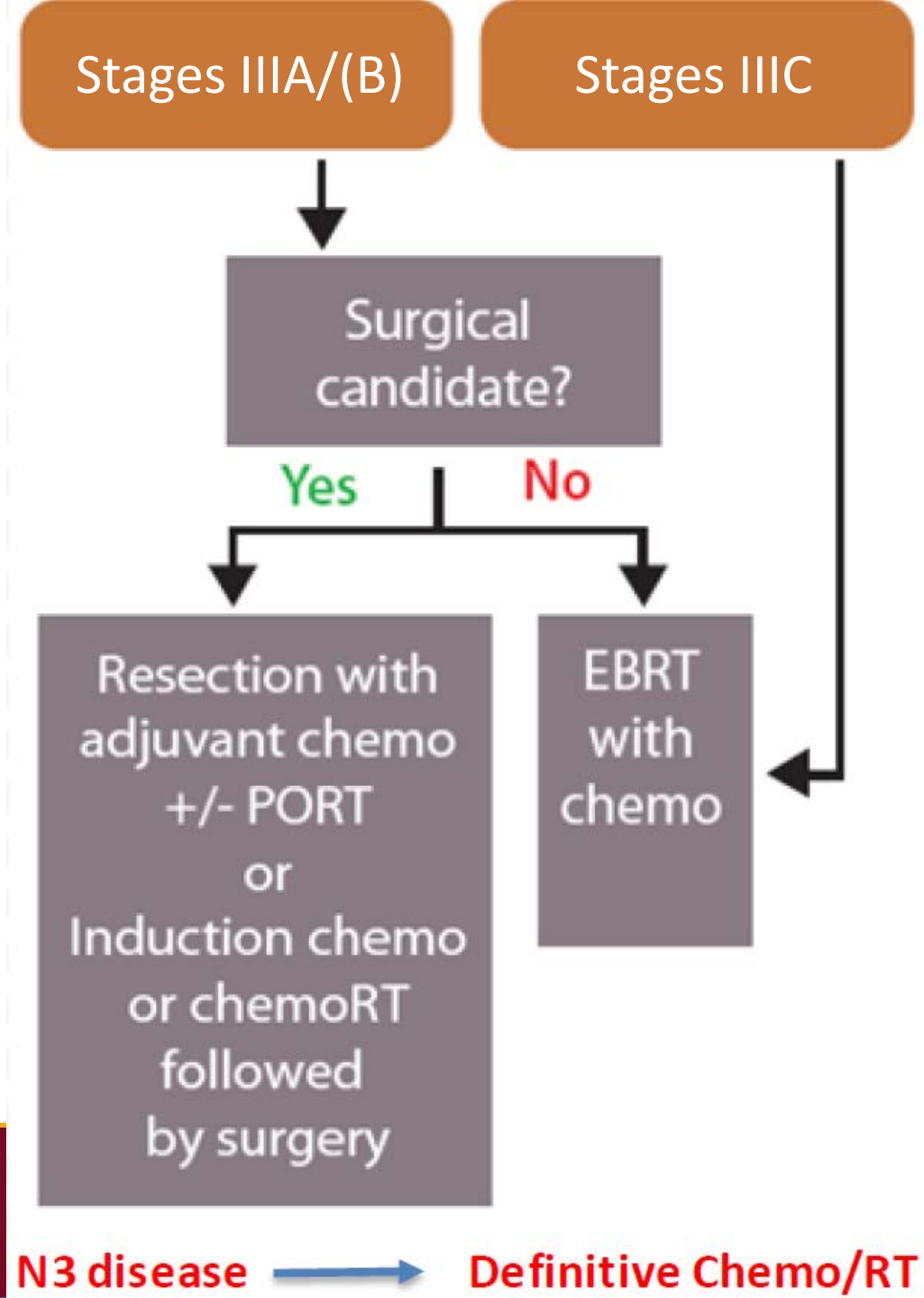
- 101 with cT1–T2aN0M0 NSCLC who where medically inoperable or had refused surgery.
  - Experimental Arm: SABR (18Gy x 3 fx or 12 Gy x 4 fx if the tumour was <2 cm from the chest wall)
  - RT (2 Gy x 33 fx or 2.5 Gy x 20 fx daily)
  - Local Progression SABR vs RT: 14 vs 31%, HR 0.32, p=0.008
  - SABR: 1 G4 AE (dyspnea) and 7 G3 AE vs RT: 2 G3 AE





LA NSCLC

- Pre-operative Chemo-RT
- Post-operative RT
- Definitive Chemo-RT

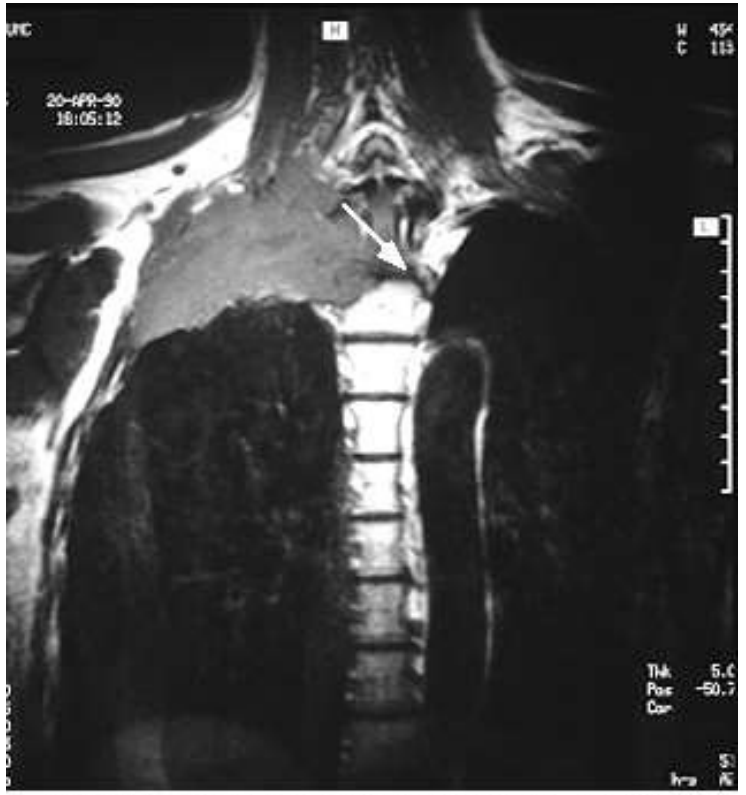


Pre-Operative Radiation

- Typically 45Gy in 25 fractions to involved areas
- Pre-op chemo-RT (vs. chemo) significantly improves downstaging at time of surgery for LA NSCLC
- Overall survival benefit unclear
- Should be performed when maximum tumor response desired
- Have a full-dose (≥ 60Gy) plan ready to avoid delay in case operability changes

Pancoast Tumor

- INT 0160 (Rusch et al. JCO 2007). Cis/etop x2c concurrent 45 Gy -> restage. If no progression, surgery -> 2c chemo.
- If still inoperable, complete 60 Gy
- Outcome?
  - **5 yr OS 44%, 56% pCR or microscopic disease**
  - **76% had complete resection, 5-yr OS 54%**



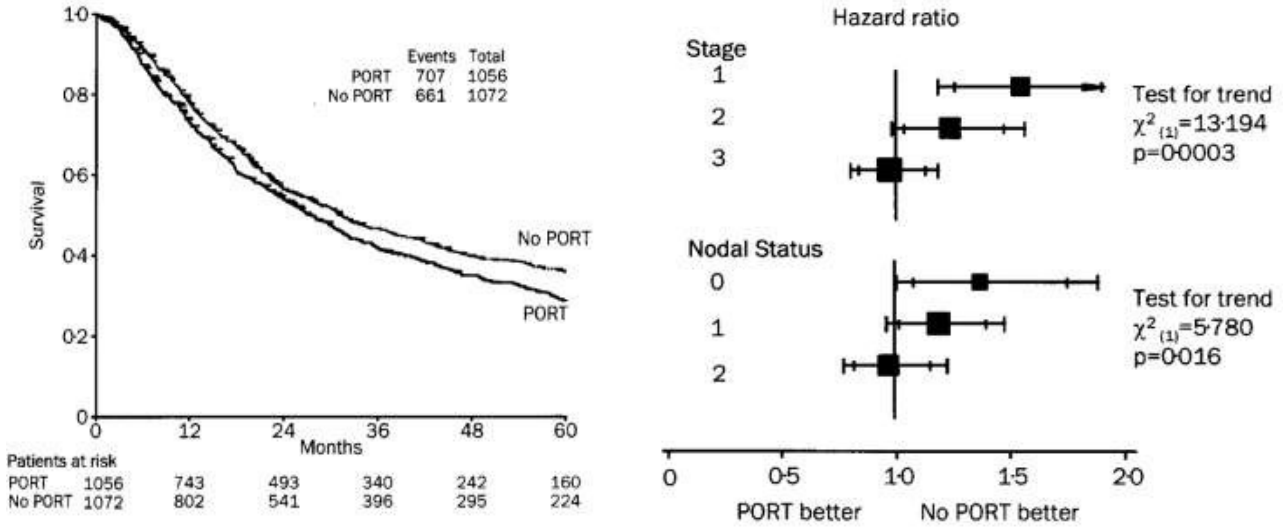
Pancoast tumor on MRI Coronal T1-weighted image shows a right-sided Pancoast tumor with vertebral destruction (arrow). Courtesy of Paul Stark, MD.

PORT Based on Nodal Status

Articles

Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials

*PORT Meta-analysis Trialists Group**



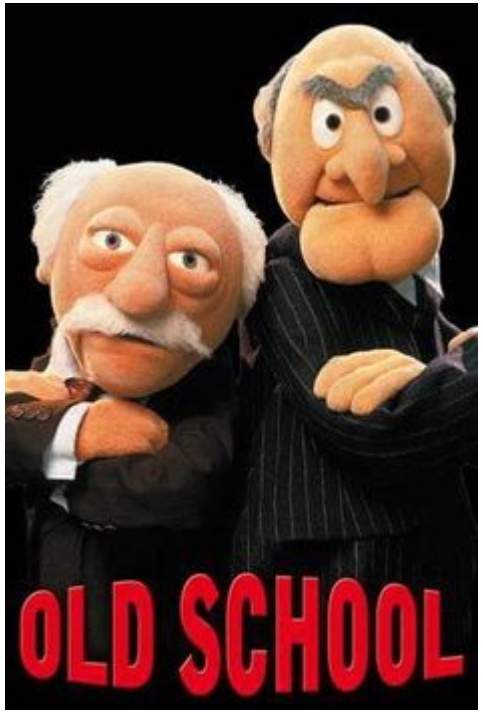
Lancet 1998

PORT = Pretty Old Radiation Therapy

- Included node negative patients
- Used ^{60}Co in many (esp. van Houtte data)
- Many used lateral fields
- 2 D treatment planning
- Patients treated in 1966
- 3 unpublished trials included
- Excess mortality with PORT may be a result of non-cancer causes of death

  471 LR: 195 PORT, 276 surgery alone

  938 deaths: 528 PORT, 410 surgery alone



PORT for NSCLC

Data to support adjuvant radiation in N2?

- **ANITA** (Douillard et al, IJROBP 2008)
  - 232 of 840 pts (Stage IB – IIIA NSCLC) received RT (unplanned analysis)
    - Trial was randomization of chemo v. obs (RT was optional, not stratified)
  - Results:
    - pN1: improved OS if didn't receive chemo, detriment if did receive chemo
    - pN2 patients benefited from RT, regardless of chemo
- **SEER analysis of PORT** *(Lally et al JCO 2006)*
  - ~7500 pts w/ stage II-III NSCLC s/p lobectomy/pneumo: PORT v. Obs
    - In N2 subset → PORT improved OS (HR 0.85; p=.008)
    - In N0-1 → PORT detrimental (HR 1.18/1.10 p=.04/.02, respectively)

PORT Modern-Era Metanalysis

Table 1
Characteristics of included studies.

Study	Year	Type	Adjuvant treatment	No PORT group (*n*)	PORT group (*n*)	Total dose	Fractionation	Comments
Mayer [13]	1997	RCT, P	RT or O	26	23	56 Gy	2 Gy/f	2-field AP or 3-field delivery; customized blocks;
Feng [12]	2000	RCT, P	RT or O	44	61	60 Gy	2 Gy/f	AP and oblique fields;
Perry [14]	2007	RCT, P	Paclitaxel and carboplatin, followed by RT or O	18	19	50 Gy	2 Gy/f	
Douillard [16]	2008	Ret	Cisplatin/vinorelbine or none, followed by RT or O	108	116	45–60 Gy	2 Gy/f	
Matsuguma [18]	2008	Ret	RT or O	46	45	25.2–63.9 Gy, 50.4 Gy median	2 Gy/f	2D and 3D based planning
Moretti [19]	2009	Ret	Cisplatin/paclitaxel or carboplatin/paclitaxel, followed by RT or O	44	39	50–60 Gy, 54 Gy median	Not reported	3-field (posterior and lateral); customized blocks.
Du [17]	2009	Ret	Variable regimen or none, followed by RT or O	255	104	50 Gy	2 Gy/f	
Scotti [20]	2010	Ret	RT or O	56	119	53 Gy median	2 Gy/f	
Zou [22]	2010	Ret	Cisplatin with either etoposide, gemcitabine or paclitaxel, followed by RT or O	79	104	48–54 Gy range, 50 Gy median	2 Gy/f	
Dai [15]	2011	Ret	Cisplatin or paclitaxel, followed by RT or O	125	96	60 Gy	2 Gy/f	
Wsinivesky [21]	2012	Ret	Platinum-based, other chemotherapy or none, followed by RT or O	597	710	N/A	N/A	SEER and Medicare analysis

Abbreviations: RCT: randomized control trial; Ret: retrospective; P: prospective; RT: radiation therapy; O: observation; 2D: 2-dimensional; 3D: 3-dimensional.

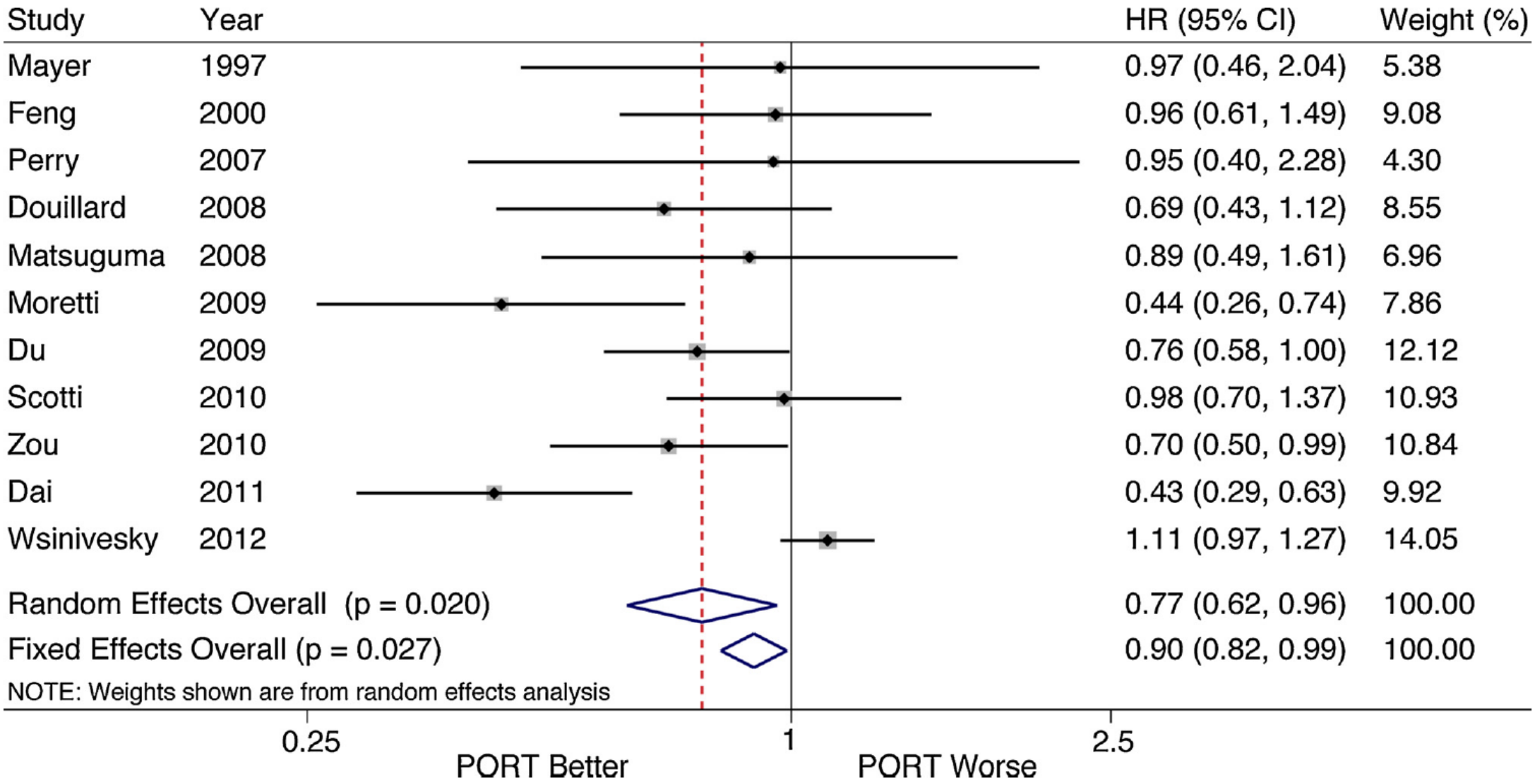


Fig. 1. Meta-analysis of OS outcomes of included studies.

PORT: Positive Margins

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Postoperative Radiation Therapy Is Associated With Improved Overall Survival in Incompletely Resected Stage II and III Non–Small-Cell Lung Cancer

Elyn H. Wang, Christopher D. Corso, Charles E. Rutter, Henry S. Park, Aileen B. Chen, Anthony W. Kim, Lynn D. Wilson, Roy H. Decker, and James Byunghoon Yu

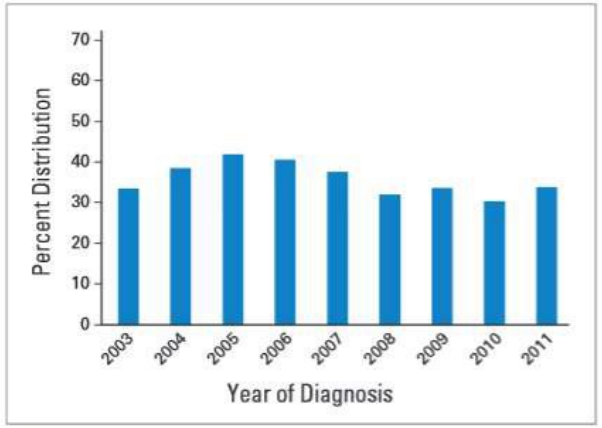
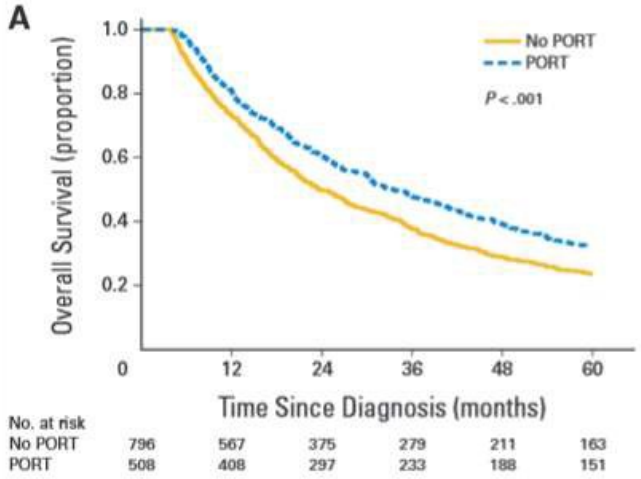


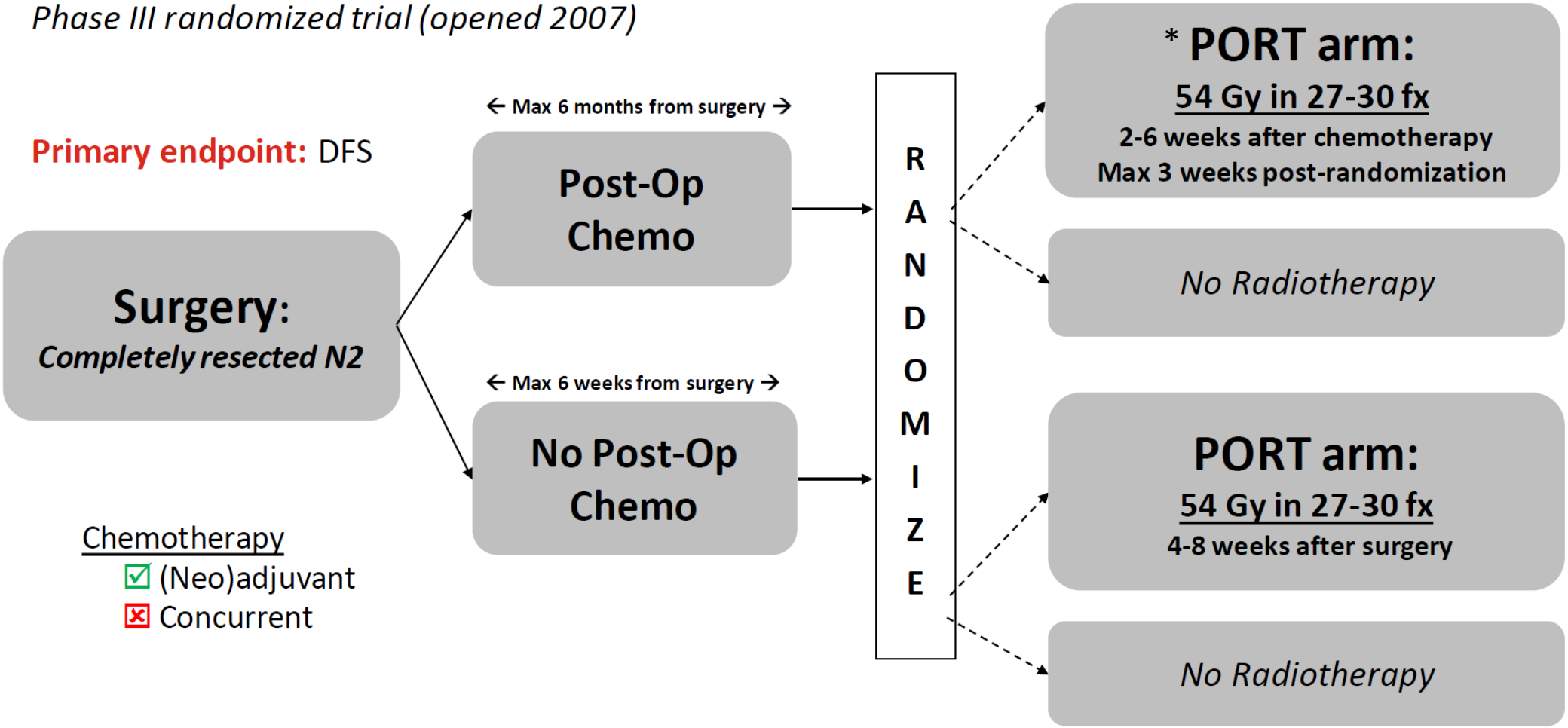
Fig 1. Percent distribution by year of diagnosis of patients receiving postoperative radiotherapy.



JCO 2015

Lung Adjuvant RT Trial (Lung ART) – EORTC 22055/08053

Phase III randomized trial (opened 2007)



*89% 3D, 11% IMRT

Source: Le Péchoux Cécile et al. "Role of Postoperative Radiotherapy in Resected Non-Small Cell Lung Cancer: A Reassessment Based on New Data." *Oncologist*, 2011. Abstract from 15th Annual BTOG.

LUNG-ART guideline

VARIATIONS IN TARGET VOLUME DEFINITION FOR POSTOPERATIVE RADIOTHERAPY IN STAGE III NON–SMALL-CELL LUNG CANCER: ANALYSIS OF AN INTERNATIONAL CONTOURING STUDY

Surgically involved mediastinal nodes	LN stations to be included in the CTV
1–2R	1–2R, 4R, 7, 10R Maximal upper limit: 1 cm above sternal notch but homolateral subclavicular node station may be treated if needed Maximal lower limit: 4 cm below the carina*
1–2L	1–2L, 4L, 7, 10L Maximal upper limit: 1 cm above the sternal notch but homolateral subclavicular node station may be treated if needed Maximal lower limit: 4 cm below the carina*
3 (Right -sided tumor)	3, 4R, 7, 10R Maximal upper limit: 1 cm above the sternal notch Maximal lower limit: 4 cm below the carina*
3 (Left-sided tumor)	3, 4L, 7, 10L Maximal upper limit: 1 cm above the sternal notch Maximal lower limit: 4 cm below the carina*
4R	2R, 4R, 7, 10R Maximal upper limit: sternal notch Maximal lower limit: 4 cm below the carina*
4L	2L, 4L, 7, 10L Maximal upper limit: sternal notch Maximal lower limit: 4 cm below the carina*
5	2L, 4L, 5, 6, 7 Maximal upper limit: top of aortic arch Maximal lower limit: 4 cm below the carina*
6	2L, 4L, 5, 6, 7 Maximal upper limit: sternal notch Maximal lower limit: 4 cm below the carina*
7 (Right-sided tumor)	4R, Maximal upper limit: top of aortic arch Maximal lower limit: 5 cm below the carina*
7 (Left-sided tumor)	4L, 5, 6, 7 Maximal upper limit: top of aortic arch Maximal lower limit: 5 cm below the carina*
8 (Right-sided tumor)	4R, 7, 8 Maximal upper limit: top of aortic arch The lower limit should be the gastroesophageal junction
8 (Left-sided tumor)	4L, 5, 6, 7 8 Maximal upper limit: top of aortic arch The lower limit should be the gastroesophageal junction

Abbreviations: LN = lymph node; CTV = clinical target volume.
* Unless other nodes are involved.

Spoelstra, IJROBP

Bronchial stump, ipsi. hilum, adjacent tumor bed mediastinal pleura also included in all cases

Outcome	No RT	PORT
3-Year DFS	43.8%	47.1%
Mediastinal Relapse	46.1%	25.0%
3-Year OS	68.5%	66.5%
Death (as the first event)	5.3%	14.6%
Total Deaths	41.5%	39.6%
Death from disease	86.1%	69.4%
Death from Cardiopulmonary	2%	16.2%
G5 RT or CT toxicity	0%	3%

PORT Summary:

- Decreases local relapse in the mediastinum, benefit vs. toxicity
- R2 (60-66Gy w/ concurrent chemo)
- R1 (54-60Gy after chemo or concurrent)
- N+ disease who are not chemo candidates (50.4Gy)
- N2? (chemo, then RT 50-54Gy, can consider boosting ECE 54-60Gy)
  - Can be omitted and save RT for salvage
  - Still included in the NCCN guidelines, weigh local control vs. distant relapse and toxicity
  - Favor in multi-station N2+ disease and other adverse features (bulky disease, multiple nodes, ECE, close margins etc.)
  - Skip in small and/or single station N2 disease
  - Skip if high dose to heart and/or lungs (Heart DMean>10Gy, Lung V20>20%?)
  - Skip if effective targeted systemic therapy available (ie. ADAURA Trial, Wu et al. NEJM 2020)

Definitive cCRT for LA Lung Ca

- Is dose-escalation still viable?
  - Not at this time (RTOG 0617). 60Gy is the standard (maybe up to 66Gy?)
  - Individualized approach in the future?
- What is the role of adjuvant immunotherapy?
  - PACIFIC Trial, 1 year of Durvalumab
- What about concurrent immunotherapy?
  - Under investigation

PACIFIC Trial

- 713 stage III NSCLC patients platinum-based chemo-RT, no POD after 2 cycles
- RT dose: 54-66Gy
- randomized 2:1 to +/- up to 1 year of Durvalumab (10mg/kg every 2 weeks)
  - immune checkpoint inhibitor
  - blocks the interaction of programmed cell death ligand 1 (PD-L1) with the PD-1 and CD80 molecules

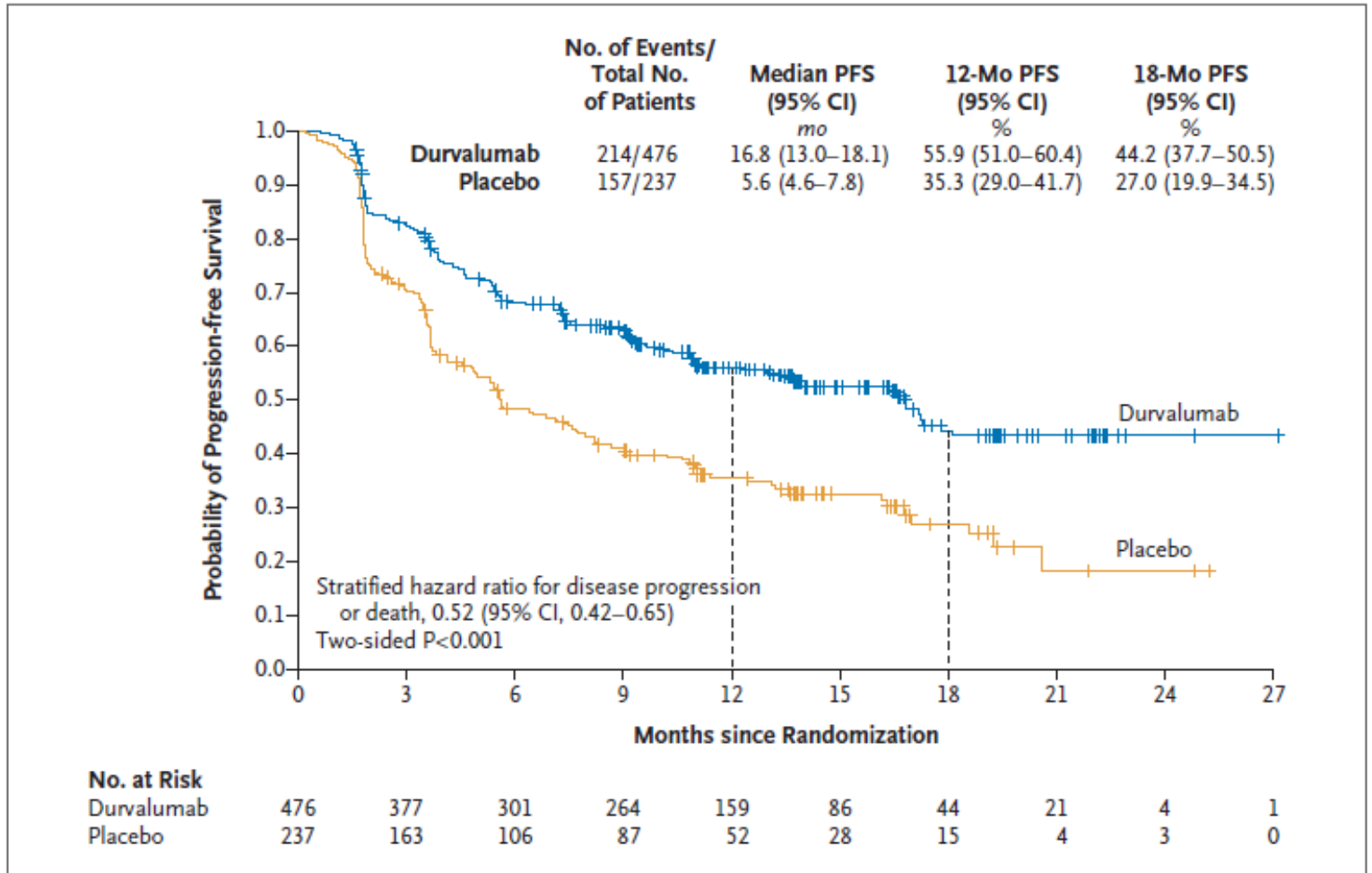
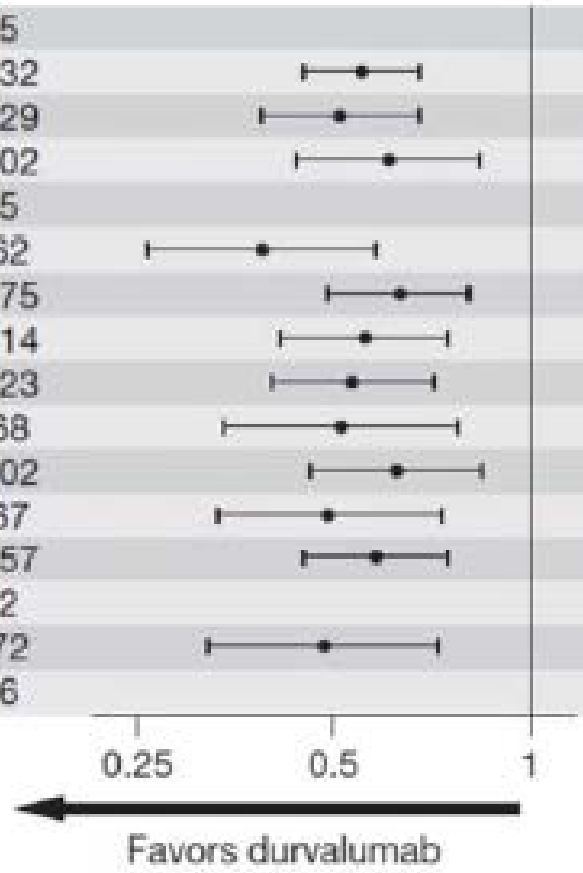


Figure 1. Progression-free Survival in the Intention-to-Treat Population.

Shown are Kaplan–Meier curves for progression-free survival (PFS), defined according to the Response Evaluation Criteria in Solid Tumors, version 1.1, and assessed by means of blinded independent central review. Tick marks indicate censored observations, and vertical lines indicate the times of landmark PFS analyses. The intention-to-treat population included all patients who underwent randomization.

Figure S2. Progression-free survival* Subgroup Analysis of Additional Factors in the Intention-to-Treat Population (BICR).

	Durvalumab No. of patients	Placebo No. of patients	Unstratified hazard ratio† (95% CI)
Type of chemotherapy gemcitabine-based	9	5	–
Type of chemotherapy non-gemcitabine-based	467	232	0.55 (0.45–0.68)
Cisplatin	266	129	0.51 (0.39–0.68)
Carboplatin	199	102	0.61 (0.44–0.83)
Cisplatin and carboplatin	8	5	–
Last radiation to randomization <14 days	120	62	0.39 (0.26–0.58)
Last radiation to randomization ≥14 days	356	175	0.63 (0.49–0.80)
Normal WHO performance status	234	114	0.56 (0.41–0.75)
Restricted WHO performance status	242	123	0.53 (0.40–0.71)
Asia	109	68	0.51 (0.34–0.77)
Europe	217	102	0.62 (0.46–0.84)
North America and South America	150	67	0.49 (0.33–0.73)
White	337	157	0.58 (0.45–0.75)
Black/African-American	12	2	–
Asian	120	72	0.48 (0.32–0.72)
Other	6	6	–



2018 NEJM update

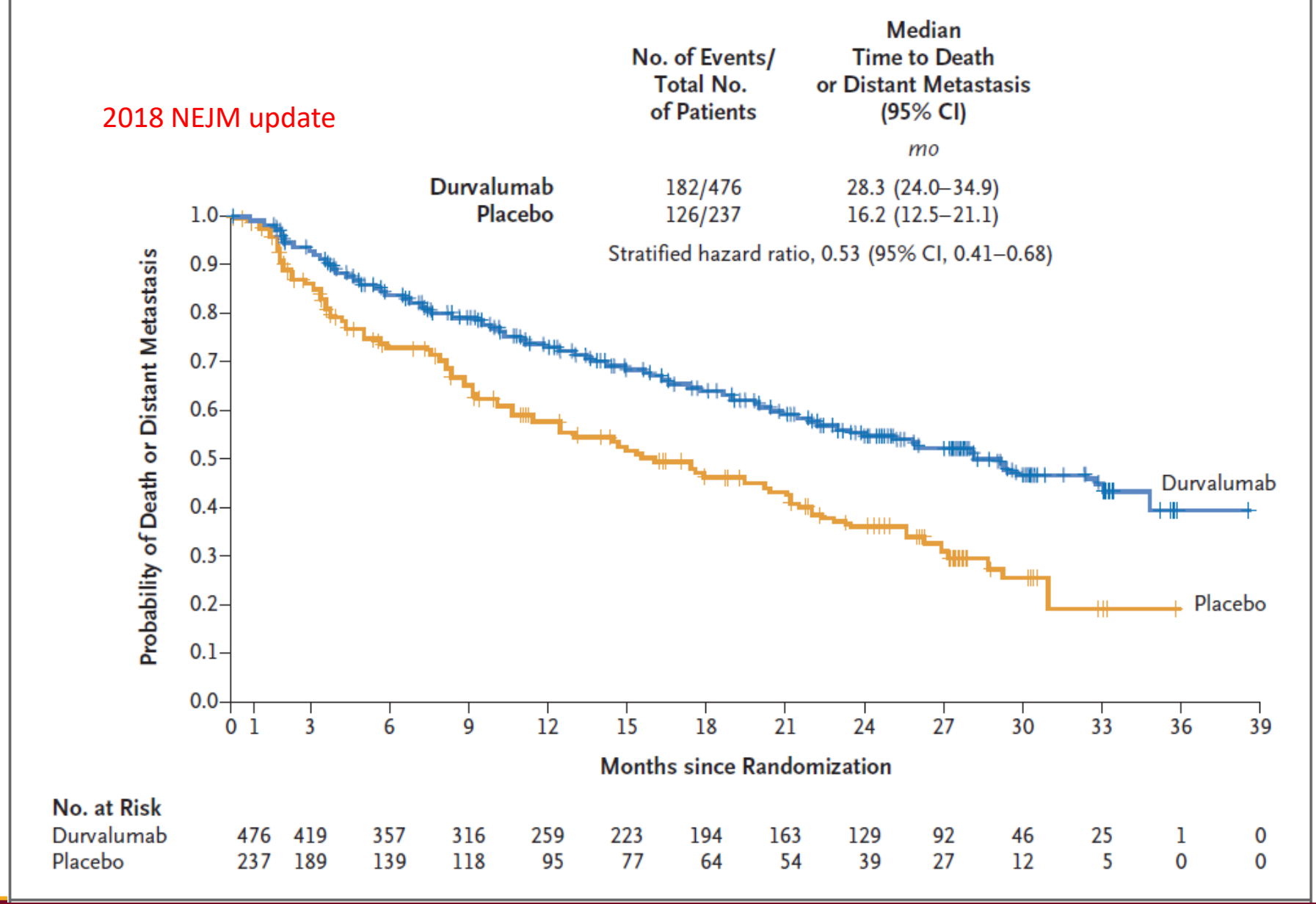
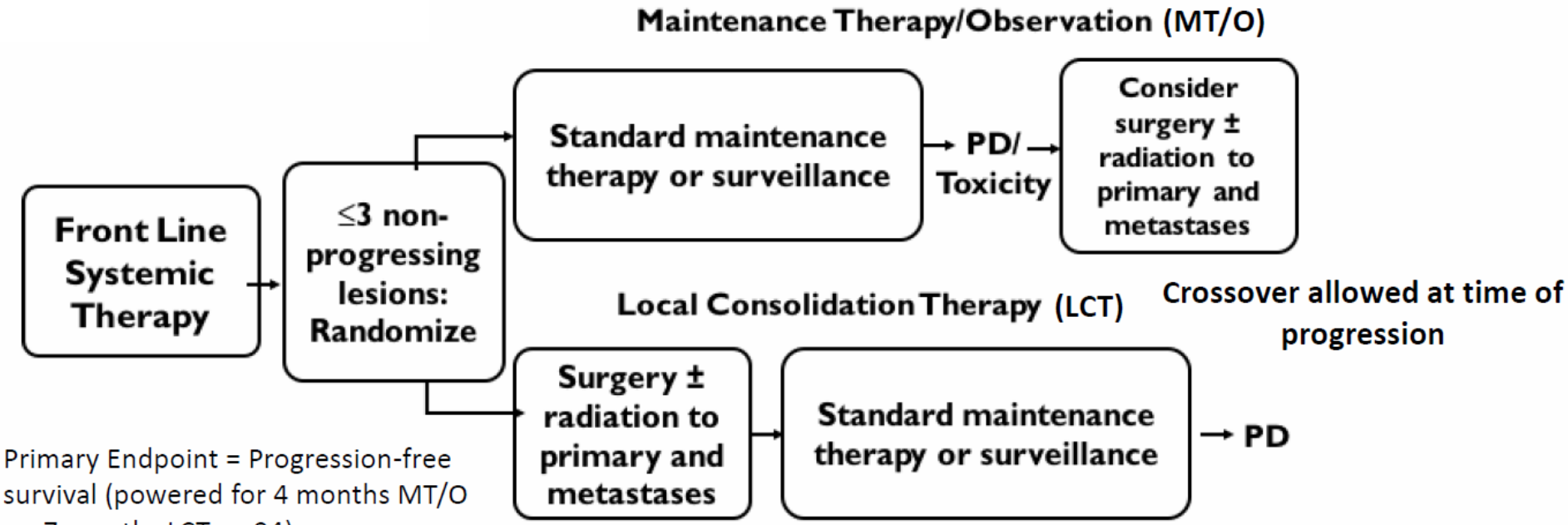


Table 5. Normal Tissue Dose-Volume Constraints for Conventionally Fractionated RT with Concurrent Chemotherapy*,‡

OAR	Constraints in 30–35 fractions
Spinal cord	Max ≤50 Gy
Lung	V20 ≤35%–40%†; MLD ≤20 Gy
Heart	V50 ≤25%; Mean ≤20 Gy
Esophagus	Mean ≤34 Gy; Max ≤105% of prescription dose; V60 ≤17%; contralateral sparing is desirable
Brachial plexus	Median dose ≤69 Gy

Oligometastatis NSCLC: MDACC Trial



Primary Endpoint = Progression-free survival (powered for 4 months MT/O vs. 7 months LCT, n=94)

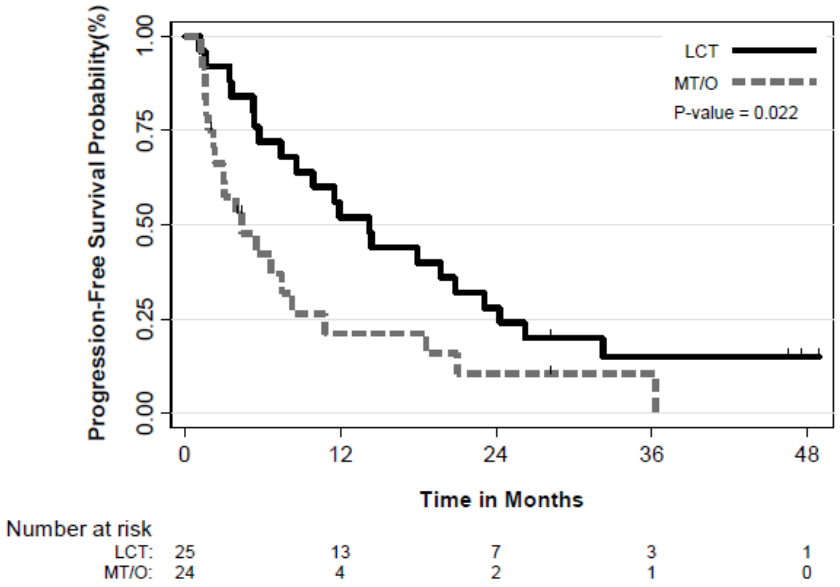
Secondary Endpoints: Overall survival, safety/toxicity, time to appearance of new lesions

Balanced randomization: 1) Number of metastases (0-1 vs. 2-3), 2) Response to first-line systemic therapy (stable disease vs. partial response), 3) N0-N1 vs. N2-N3, 4) CNS vs. no CNS metastases, 5) EGFR/ALK alteration vs. wild type

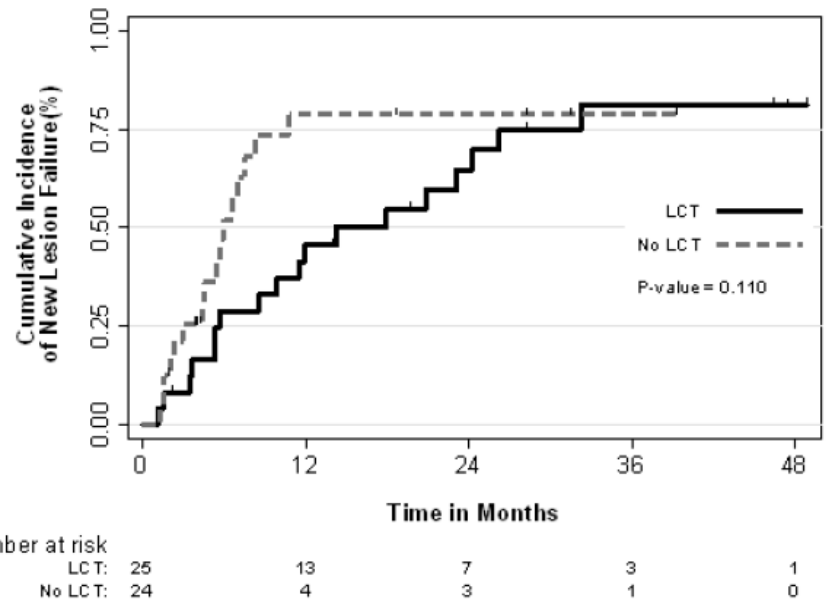
Gomez et al., *Lancet Oncol* 2016

PFS and Time to New Lesion Failure

PFS

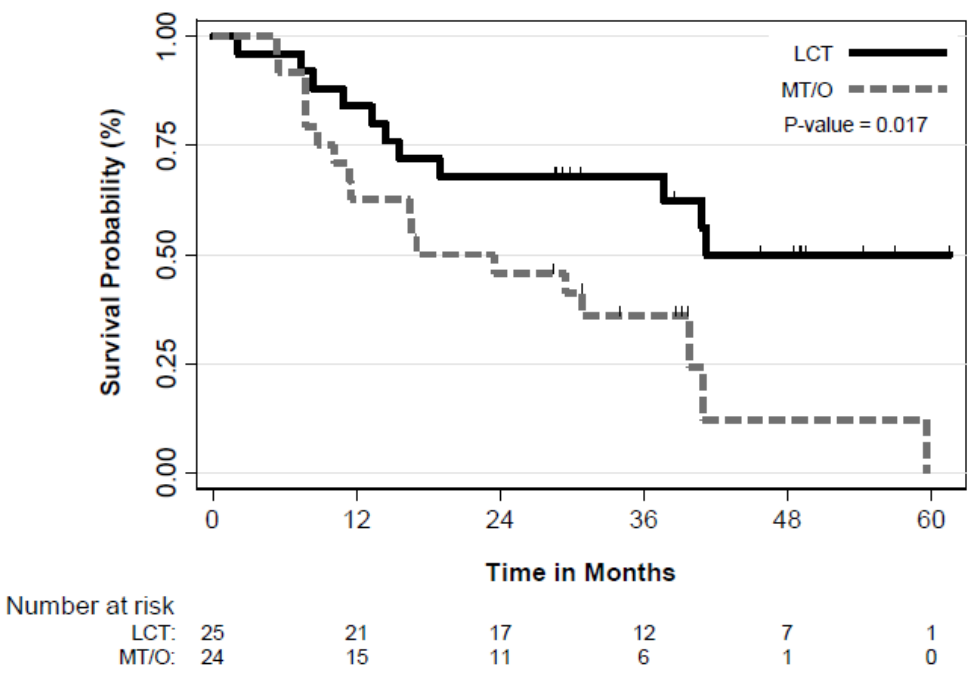


Time to New Lesion Failure



No additional Grade 3 or higher adverse events in either arm

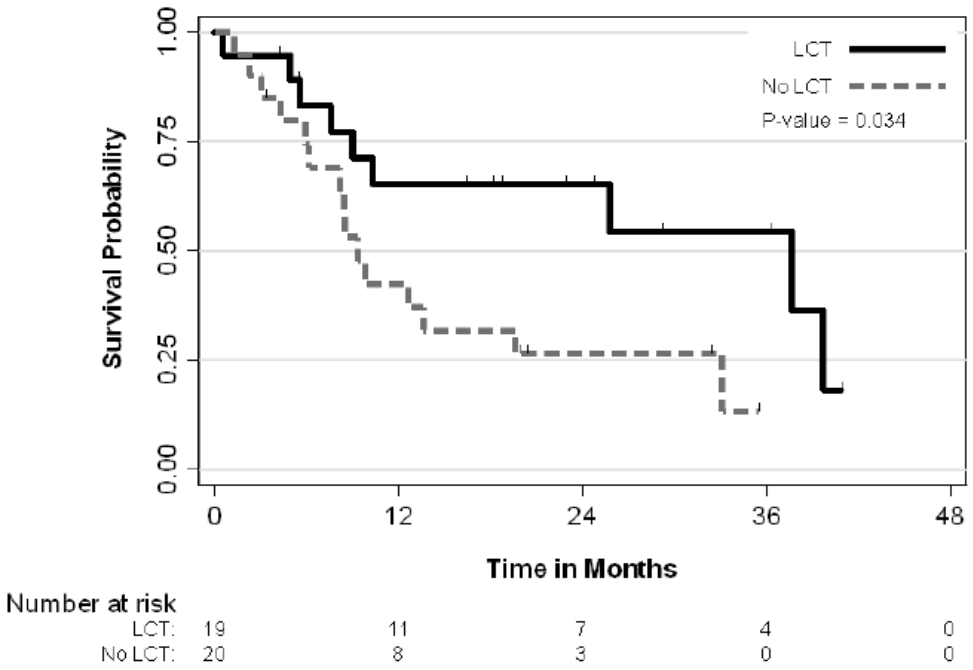
Overall Survival



Median 17.0 months MT/O [HR=0.40, 95% CI 10.1–39.8, *P*=0.017] vs. 41.2 months LCT [95% CI 18.9–not reached]

Gomez et al, ASTRO 2018 Update

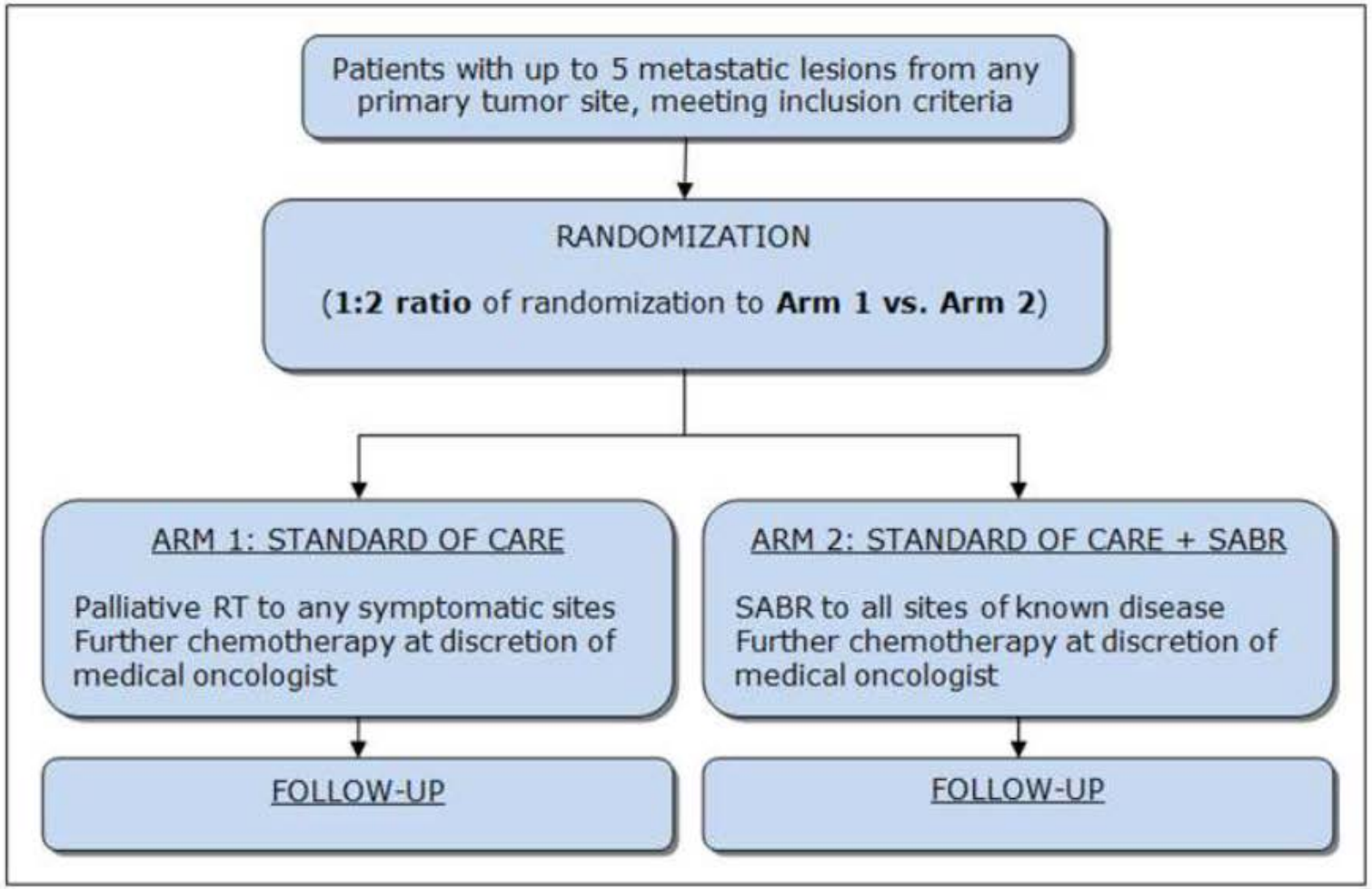
Survival After Progression



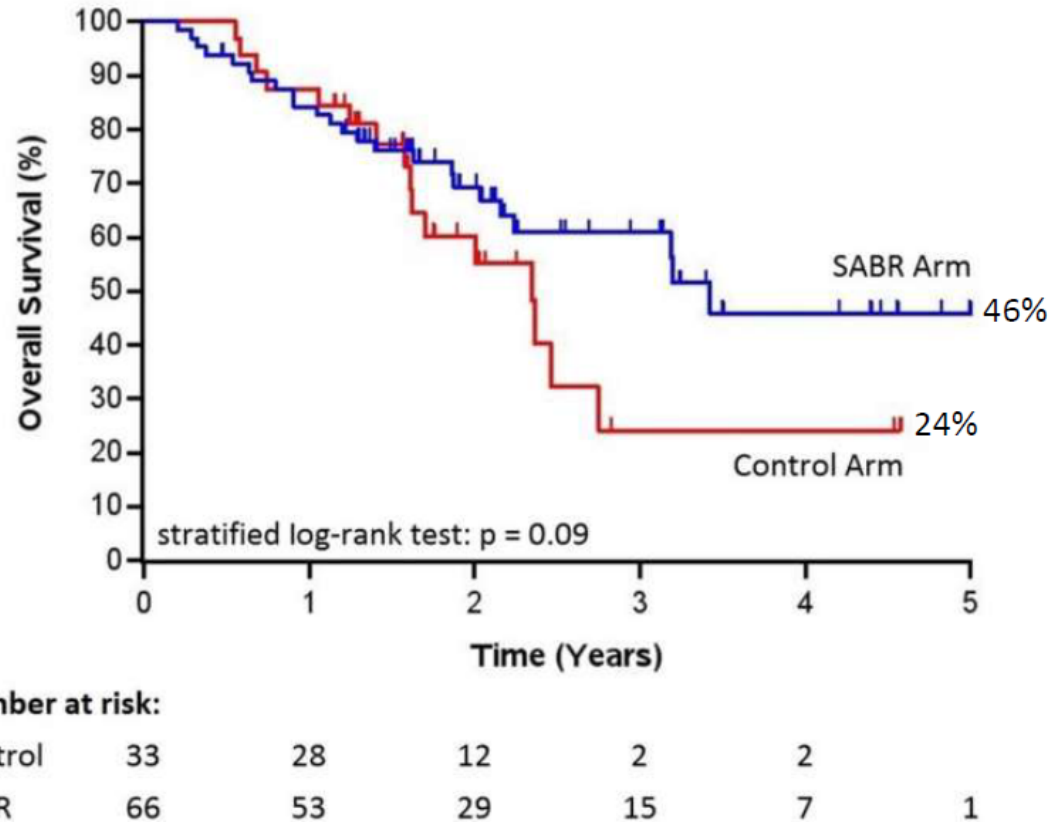
Median 37.6 months LCT [95% CI 9.0-not reached] vs. 9.4 months MT/O [95% CI 5.9–19.6, *P*=0.034]

Gomez et al, ASTRO 2018 Update

SABR-COMET Schema



Overall Survival



Number at risk:

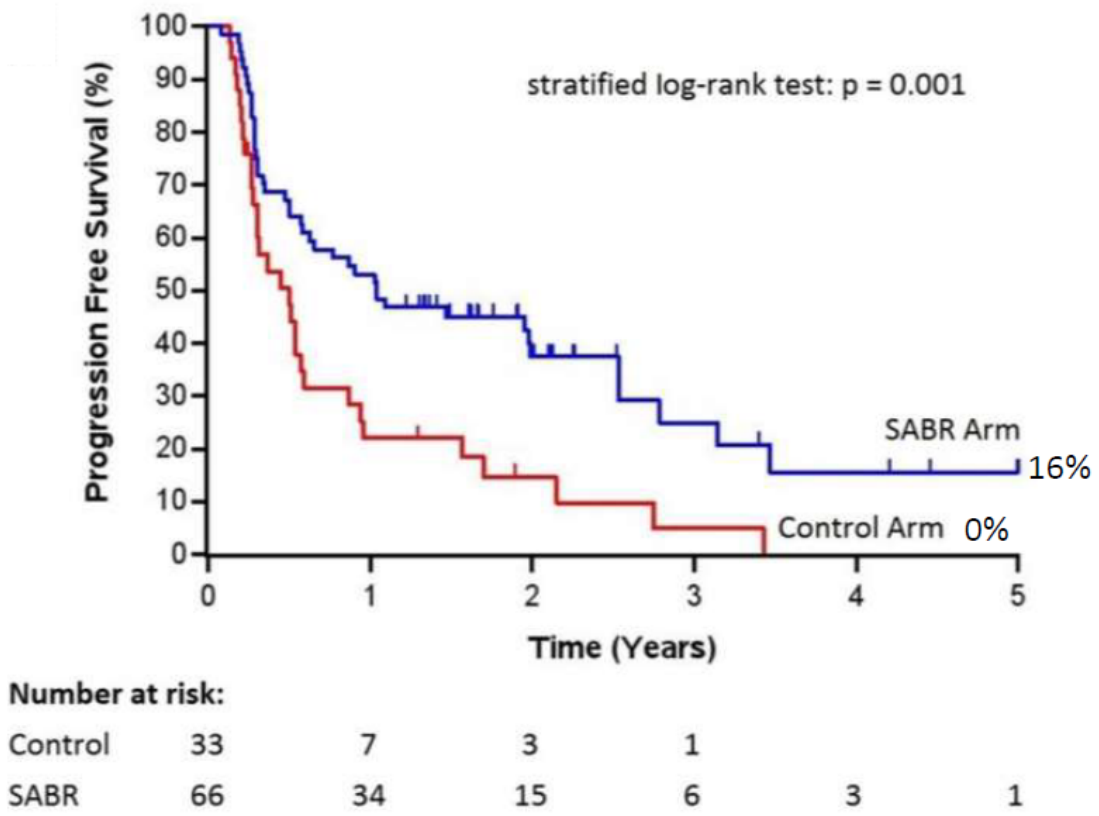
Control	33	28	12	2	2	
SABR	66	53	29	15	7	1

Median OS

Control Arm: 28 months
(95% CI: 19-33 months)

SABR Arm: 41 months
(95% CI: 26 months to 'not reached')

Progression-Free Survival



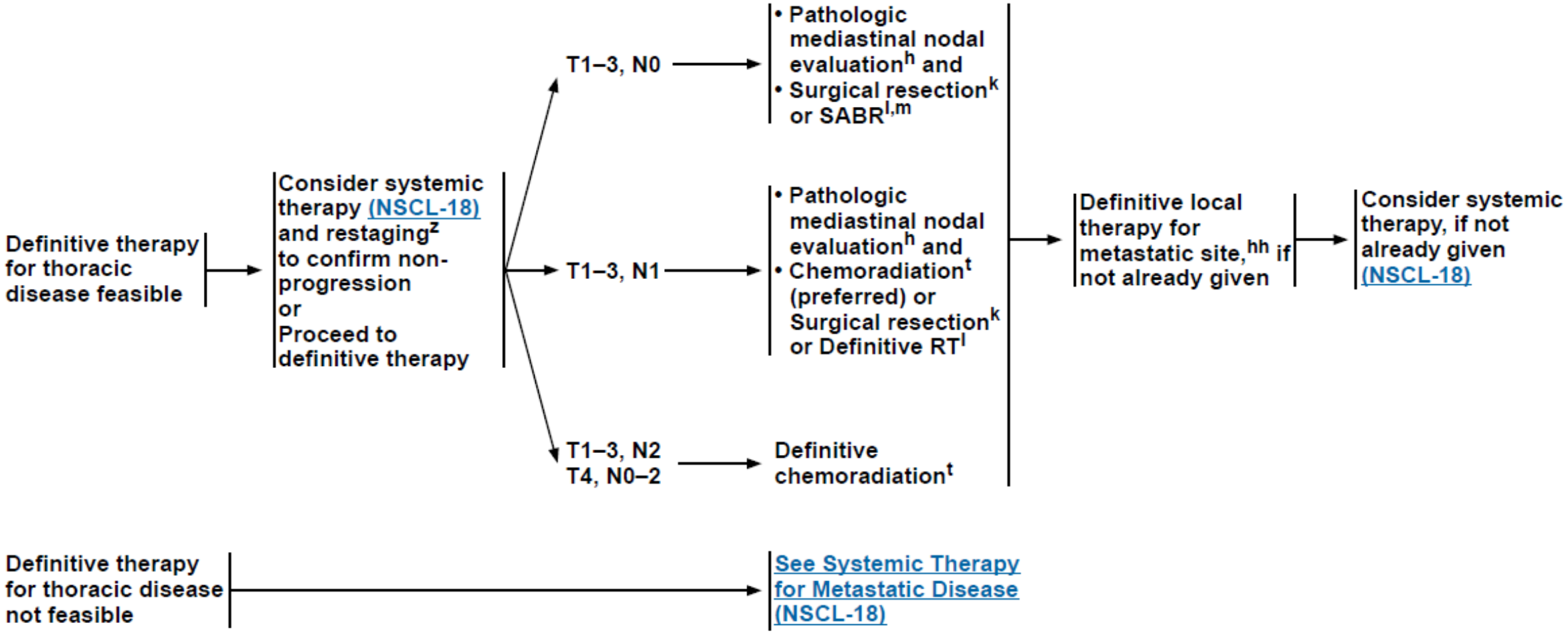
Median PFS

Control Arm: 6 months
(95% CI: 3.4-7.1 months)

SABR Arm: 12 months
(95% CI: 6.9-30 months)

8 patients on SABR Arm received salvage SABR after progression

TREATMENT OF THORACIC DISEASE



[h] Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS, and CT-guided biopsy. An EBUS-TBNA negative for malignancy in a clinically (PET and/or CT) positive mediastinum should undergo subsequent mediastinoscopy prior to surgical resection.

[k] See Principles of Surgical Therapy (NSCL-B).

[l] See Principles of Radiation Therapy (NSCL-C).

[m] Image-guided thermal ablation therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients not receiving SABR or definitive RT. See Principles of Image-Guided Thermal Ablation Therapy (NSCL-D).

[t] See Concurrent Chemoradiation Regimens (NSCL-F).

[z] Chest CT with contrast and/or PET/CT to evaluate progression.

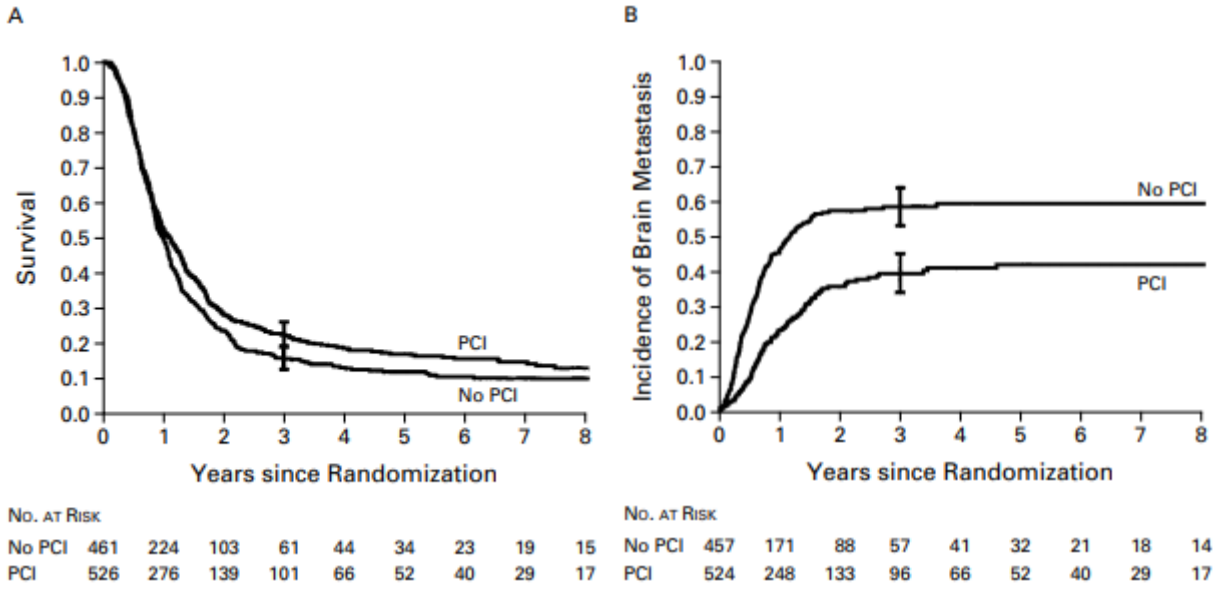
[hh] Typically, RT (including SABR) or surgical resection. Image-guided thermal ablation therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients not receiving RT or surgery.

What about SCLC?

- Standard: cCRT 45Gy in 30fxs BID over 3 weeks w/ Cis/Etoposide
  - OS: 47% @ 2yr, 26% @ 5yr, median 23mo
  - Esophagitis: G3 27% (vs. 11%), G4 5% (vs. 5%)
  - Spinal Cord <36Gy (up to 41Gy OK)
- Alternative: cCRT 66Gy in 33Fxs per CONVERT trial (60-70Gy OK)
  - OS: 56% (BID) vs. 51% (QD) @ 2 yr), 34% (BID) vs. 31% (QD) @ 5yr, Median 30mo (BID) vs. 25mo (QD)
  - Esophagitis: G3 18% (BID) vs. 19% (QD), only single patient w/ G4 (BID)
- Start early w/ Cycle 1 or 2 of chemo
  - Treat pre-chemo nodal stations and post-chemo tumor volume

Auperin PCI Meta-analysis (mostly LS)

7 trials, 1965-1995 (most >1985), had to be in CR pre PCI, 83-88% were LS, median f/u 5.5 years



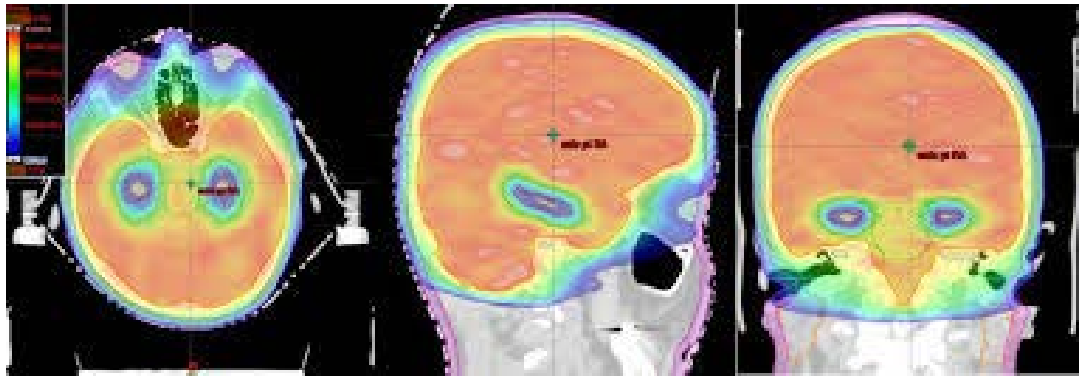
End Point	No. of Patients		Relative Risk (95% CI)	P Value	Heterogeneity (P Value)	Rate in the Control Group over a 3-Yr Period	Absolute Benefit at 3 Yr
	Treatment Group	Control Group				percent	
Overall survival	526	461	0.84 (0.73–0.97)	0.01	0.95	15.3	+5.4
Disease-free survival	526	461	0.75 (0.65–0.86)	<0.001	0.96	13.5	+8.8
Cumulative incidence of brain metastasis	524	457	0.46 (0.38–0.57)	<0.001	0.14	58.6	−25.3

These trials did not compare PCI against MRI surveillance

3-year incidence of brain mets 33% vs. 59%

Auperin et al. NEJM 1999

Ongoing studies



- NRG CC-003
  - Patients: all SCLC
    - Stratified by LS-SCLC vs ES-SCLC, age, and memantine use
  - 25 Gy in 10 fractions +/- hippocampal avoidance
- **PREMER (JCO 2021)
  - HA-PCI better for cognitive decline, no diff. in mets, OS, and QoL
- SWOG 1827, MAVERICK
  - LS or ES SCLC, PCI or no PCI (HA-PCI allowed)
- NRG CC-009
  - SCLC w/ limited brain mets, HA-WBRT vs. SRS

Japanese Trial (PCI vs Surveillance in ES)

- Ph III, 2009-2013, n=224, ES, any response to platinum-based doublet chemo
- No brain mets on pre-PCI MRI
- Had surveillance MRI q3mo x 1 year, then 18 and 24 months
  - Arm 1: PCI 25Gy/10fx
  - Arm 2: no PCI
- Study closed early 2/2 futility
- Median OS 11.6 vs 13.7 months favor obs (HR 1.27 p=0.094)
- Arm 2: brain mets 32% vs 59% at 1 year
- Conclusion of study "PCI not essential for ES-SCLC"

OS is not affected if patients have routine MRI surveillance, but many of these patients will ultimately need whole brain radiation.

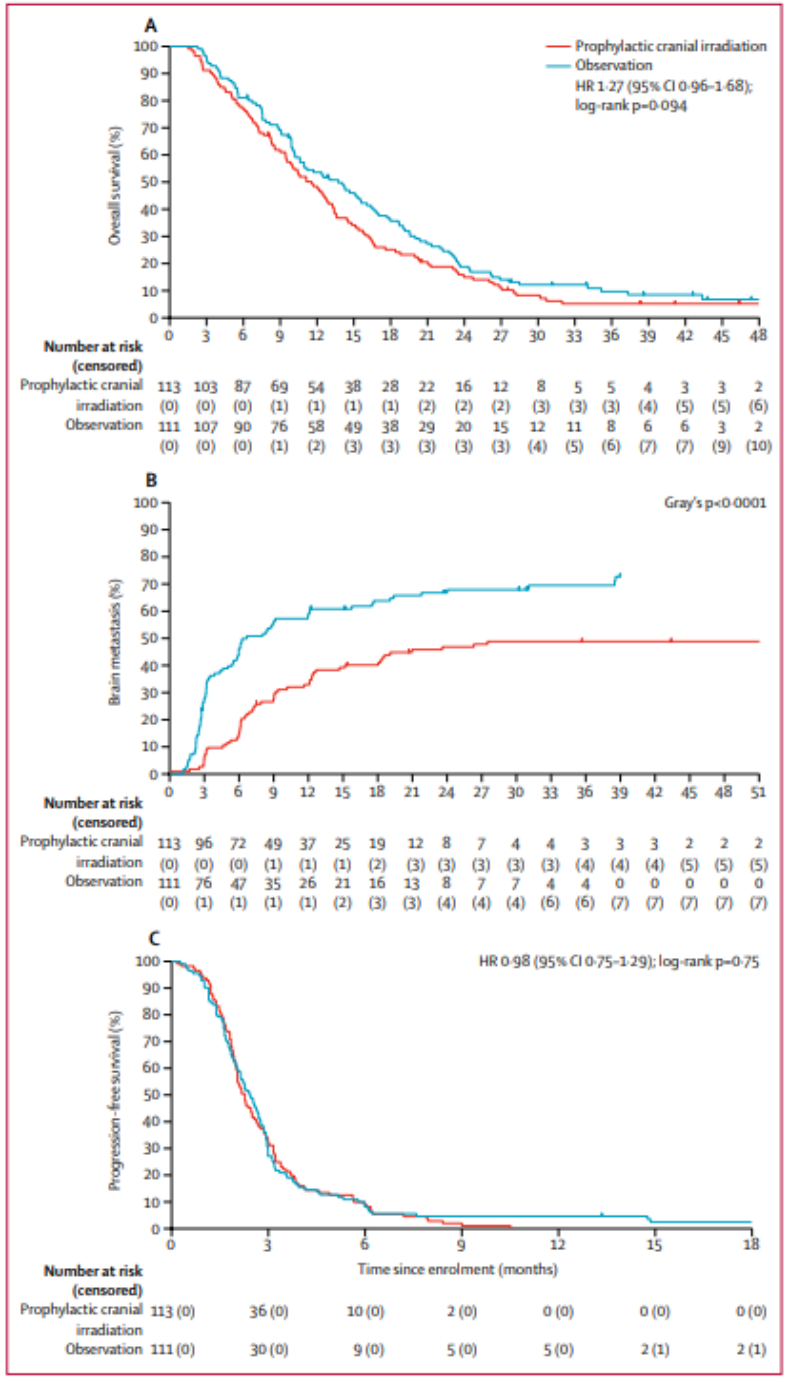


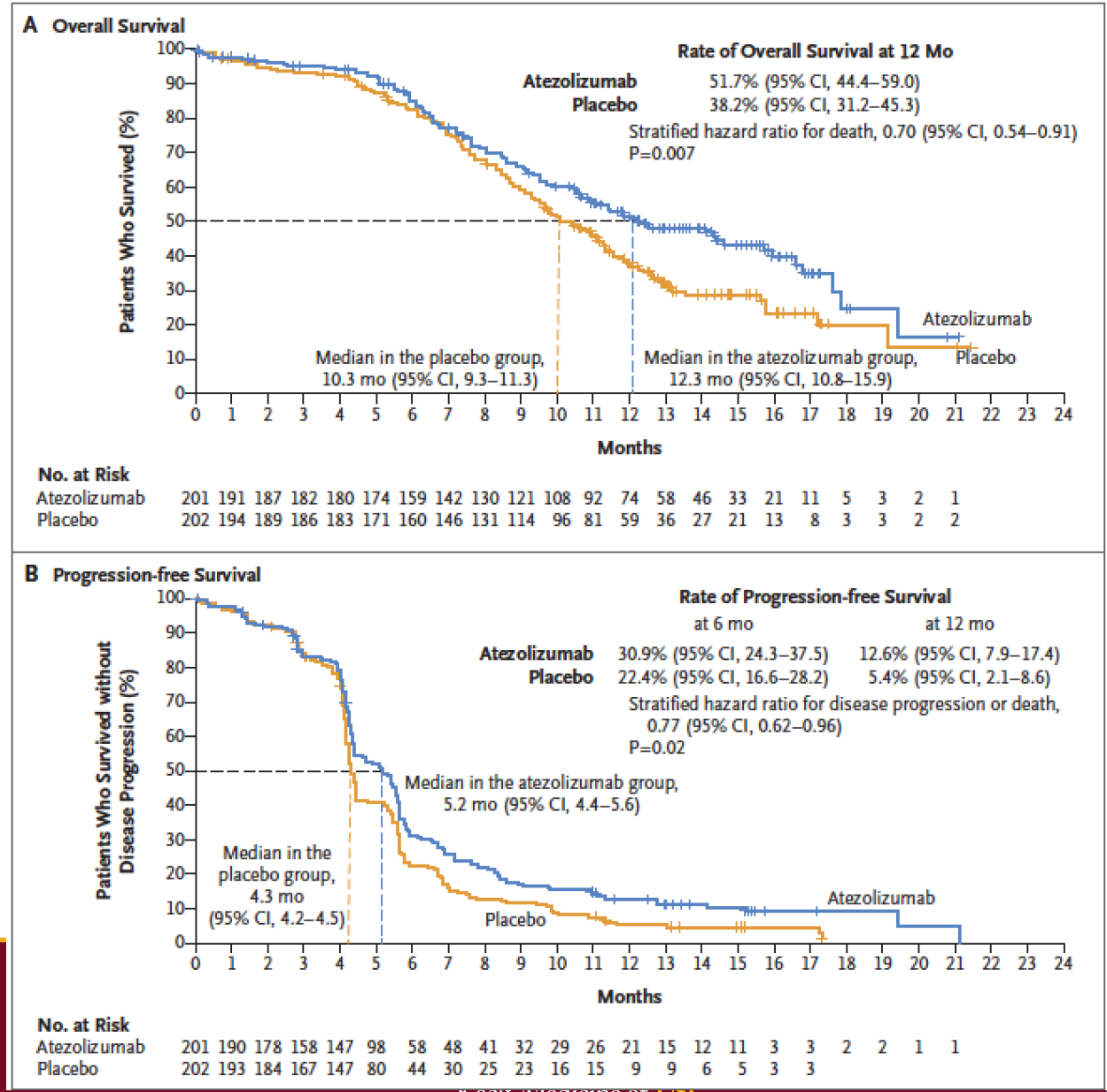
Figure 2: **Overall survival (A), cumulative incidence of brain metastases (B), and progression-free survival (C)**
HR=hazard ratio.

Takahashi, Lancet Onc 2017

Immunotherapy for ES-SCLC (Horn et al. NEJM 2018) IMpower133

Double-blind, 403 patients

- Carboplatin and Etoposide x 4 cycles
  - Concurrent induction then Maintenance Atezolizumab (anti PD-L1)
  - Placebo
- Outcomes:
  - Median follow-up of 13.9 months
  - Median OS 12.3 mo vs 10.3 mo (HR 0.70; P = 0.007).
  - Median PFS 5.2 mo vs 4.3 mo (P = 0.02)
  - Similar toxicity except immune related events 40% versus 25%

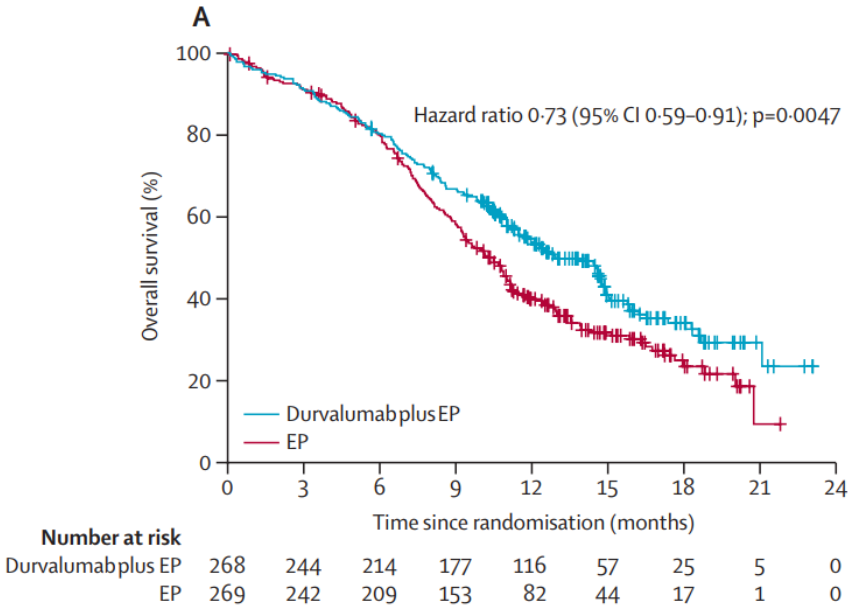


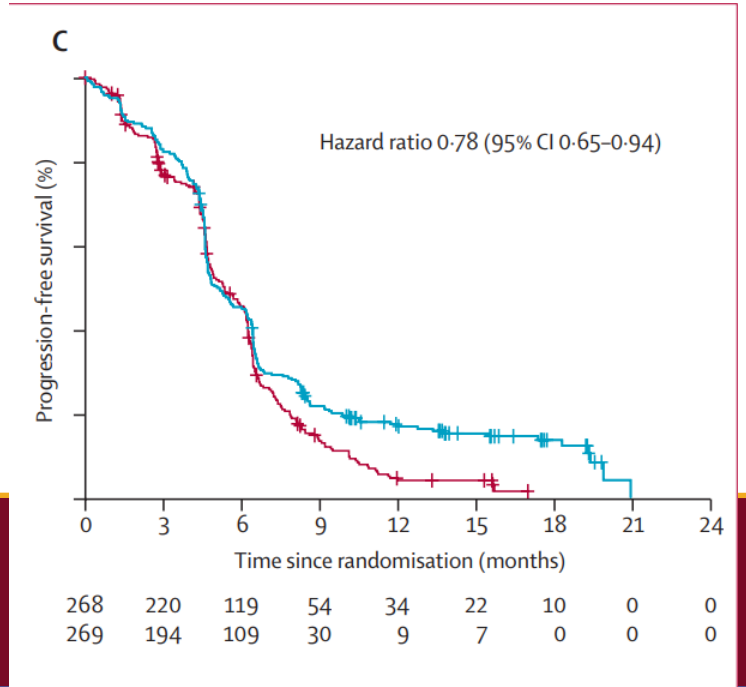
Immunotherapy for ES-SCLC (Paz-Ares et al. Lancet 2019) CASPIAN

Open phase III RCT, 805 tx-naive patients, randomized:

- 1) Platinum-etoposide + durvalumab
- 2) Platinum-etoposide + durvalumab + tramelimumab
- 3) Platinum-etoposide alone +/- PCI (discretion, 8%)

- Outcomes (Interim for Arms 1 and 3)
  - Median follow-up of 14.2 months
  - Median OS 13 mo vs 10.3 mo (HR 0.73; P = 0.005).
  - 18m OS: 34% vs 25%
  - Median PFS 5.1 mo vs 5.4 mo (HR 0.78)
  - 12m PFS: 18% vs 5%
  - Similar toxicity except immune related events 20% versus 3% (mostly G1-2)





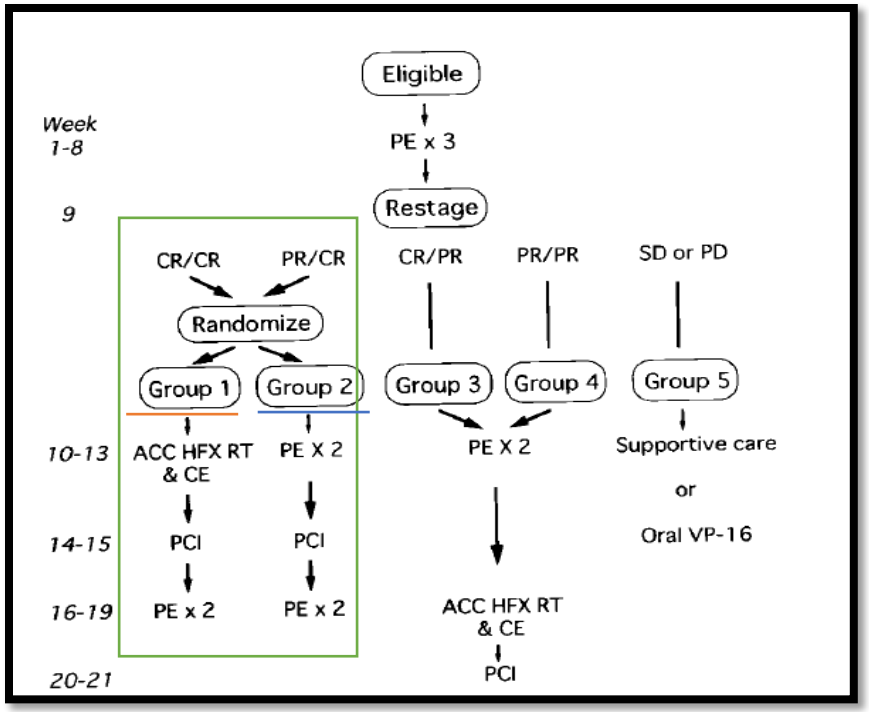
Thoracic RT in Extensive Stage (Yugoslavia)

- RCT, 1988-1993, n=210, single institution
  - No CNS mets allowed
- 3 cycles Cisplatin/Etoposide upfront
- If CR at distant met and CR/PR at local level:

  -Arm 1: **CRT** with Carbo/Etop and 54 Gy in 36 fx BID (36 Gy AP/PA, remainder off cord), then PE x2

  -Arm 2: PE x 4 (**no TRT**)

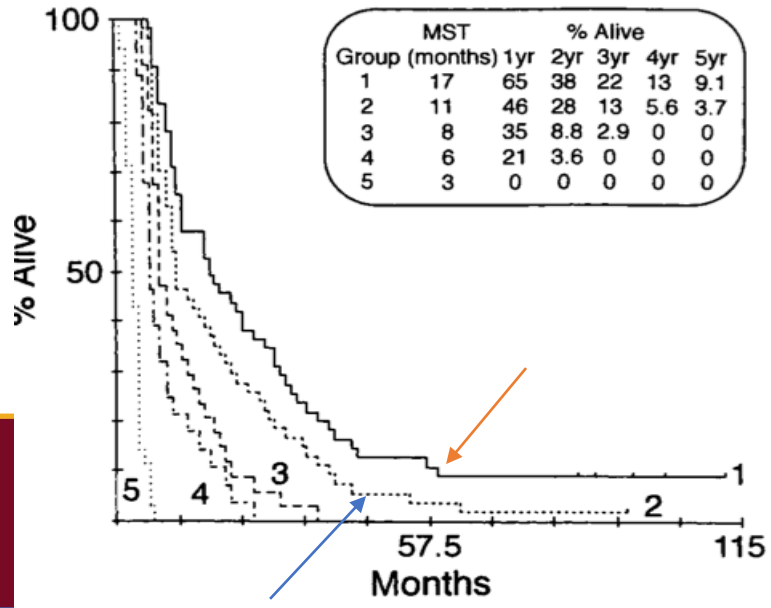
  -All got PCI



Results:

Survival favored by XRT (p<0.05)

- **MST 17 vs 11 months**
- **5yrOS 9 vs 4%**
- Only XRT had ≥ Grade 3 esophagitis (27%)



Group	MST (months)	% Alive 1yr	2yr	3yr	4yr	5yr
1	17	65	38	22	13	9.1
2	11	46	28	13	5.6	3.7
3	8	35	8.8	2.9	0	0
4	6	21	3.6	0	0	0
5	3	0	0	0	0	0

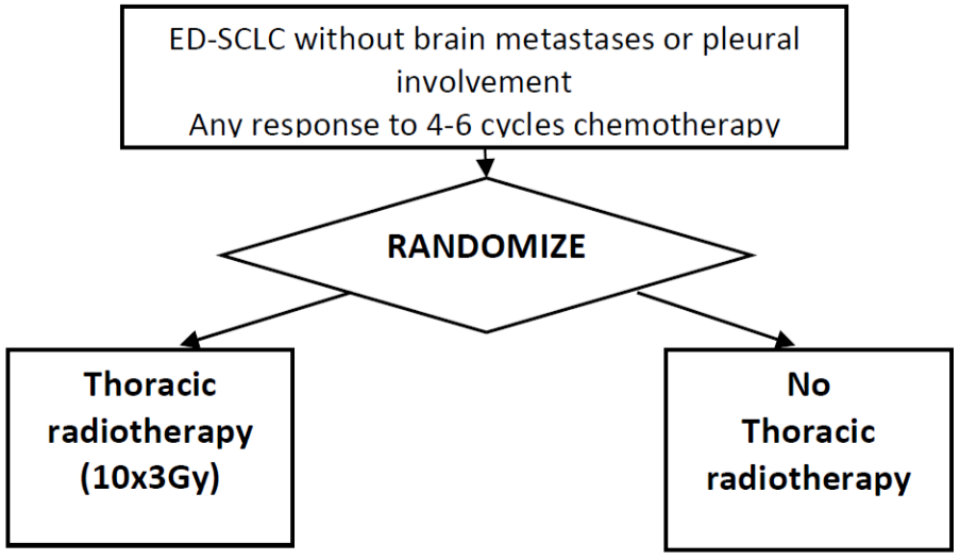
Jeremic, JCO 1999

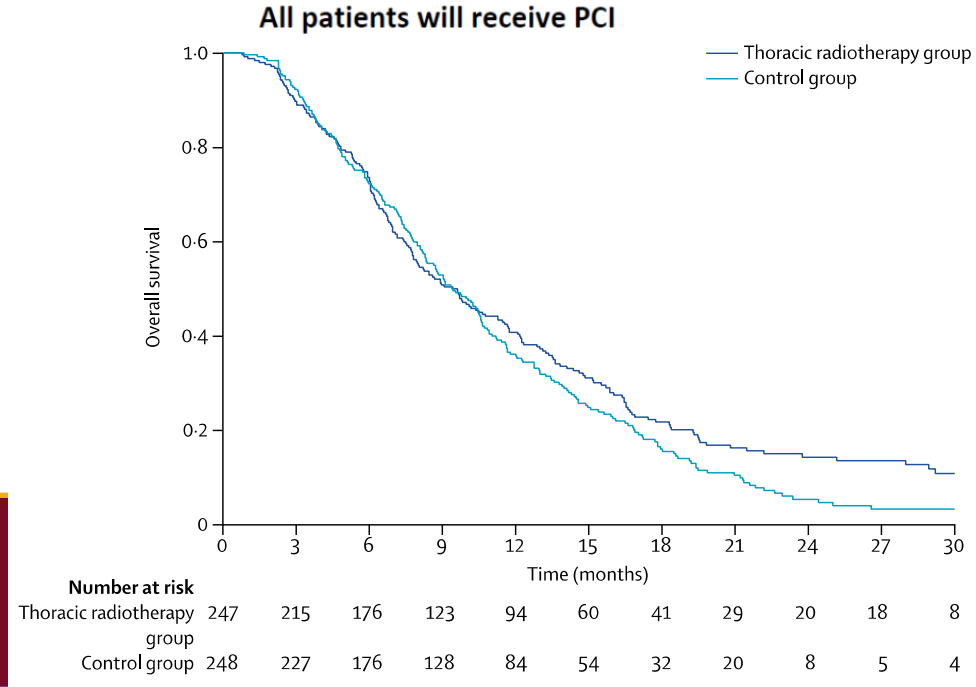
Thoracic RT in Extensive Stage (Dutch CREST trial)

- Phase III, 2009-2012, n=498
- ECOG 0-2, ES, 4-6 cycles EP, chemo responders
- 30Gy/10fx TRT vs no TRT
- all got PCI

Results:

- 1º endpoint: 1yr OS 33% v 28% **(NS)**
- **2º endpoint: 2yr OS 13% v 3% (p=0.004)**
- 6mo PFS 24% vs 7%, p=0.001
- No severe tox
- The benefits were limited to patients with residual intrathoracic disease based upon CT following chemotherapy, and not in those with a complete response





Slotman, Lancet 2015

ES SCLC Summary

- Chemo-immunotherapy is the first line
- Always get brain MRI!
- PCI benefit unclear (consider enrolling on MAVERICK)
- Consolidative RT?
  - 30Gy in 10fx standard to thoracic disease
  - Higher dose in select patients?
  - Safety and outcome with immunotherapy?
  - LU-007 RAPTOR Trial (30 or 45Gy to thorax&liver, 30 or 20Gy to other)

Good Luck!!!

Questions?