SACRO CUORE DON CALABRIA

IRCCS
Istituto di Ricovero e Cura a Carattere Scientifico
Sacro Cuore - Don Calabria
Ospedale Classificato e Presidio Ospedaliero Accreditato - Regione Veneto

TUMORE DEL POLMONE:
dallo screening al trattamento

Venerdì 11 novembre 2022

SEDE: *Sala Convegni "Fr. Francesco Perez"*
IRCCS Sacro Cuore - Don Calabria
Via Don Angelo Sempreboni, 5
37024 Negrar di Valpolicella - Verona

NSCLC: trattamento del NSCLC stadio I-II-III

Ruolo della Radioterapia

Niccolò Giaj Levra

Radiation Oncology, MD PhD

Advanced Radiation Oncology Department

IRCCS Sacro Cuore Don Calabria, Negrar di Valpolicella, Italy

SACRO CUORE DON CALABRIA IRCCS Cancer Care Center
ARO ADVANCED RADIATION ONCOLOGY DEPARTMENT

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AGENDA

- Comorbidity and radiotherapy
- Management of stage I and II NSCLC with radiotherapy
- Management of stage III NSCLC with radiotherapy

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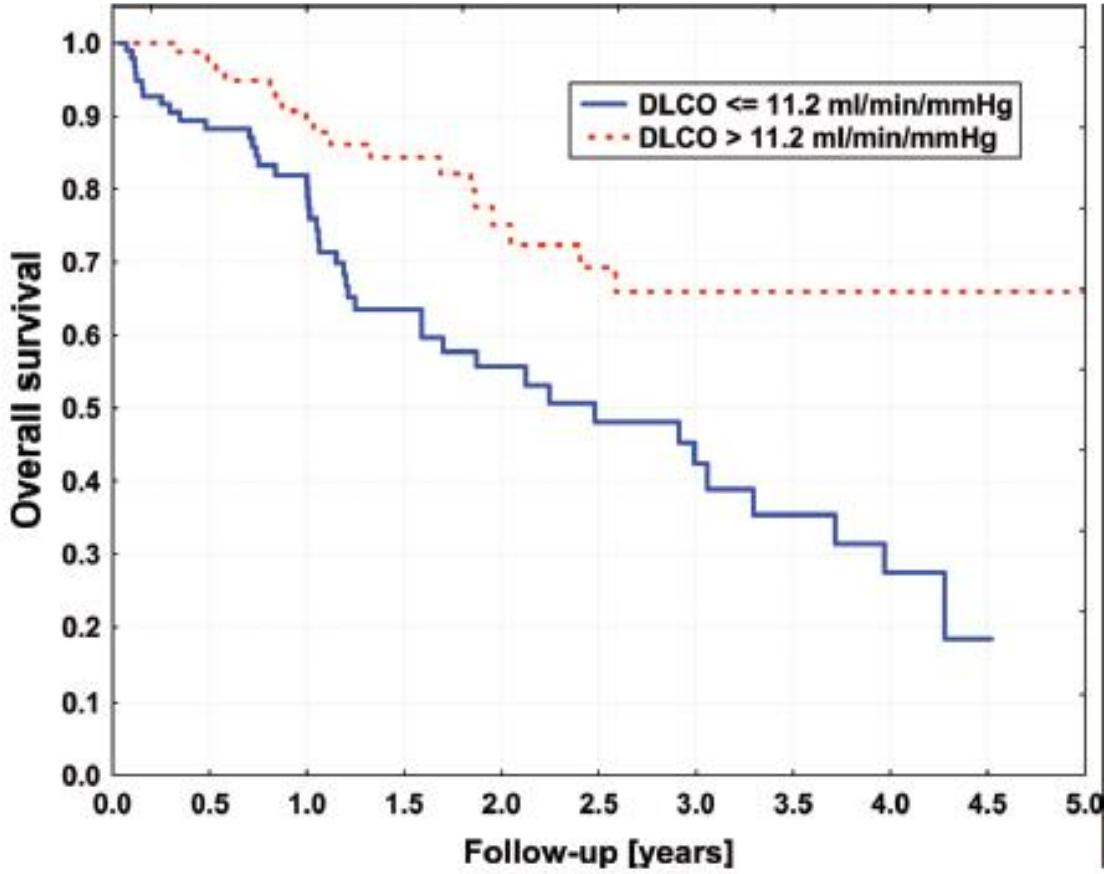
SABR AND RESPIRATORY DISEASE

Comorbidity – Pulmonary comorbidities, COPD

- About 50% of patients had COPD
- Diagnosis:
  - Tobacco smoking, environmental exposure, other
  - Symptoms: chronic cough with/without sputum
  - Understimated
- COPD and RT: increase the probability of respiratory insufficient with RT, exacerbations
- COPD impact on OS because frequently there is a concomitant chronic disease such as cardiac disease

SABR AND RESPIRATORY DISEASE

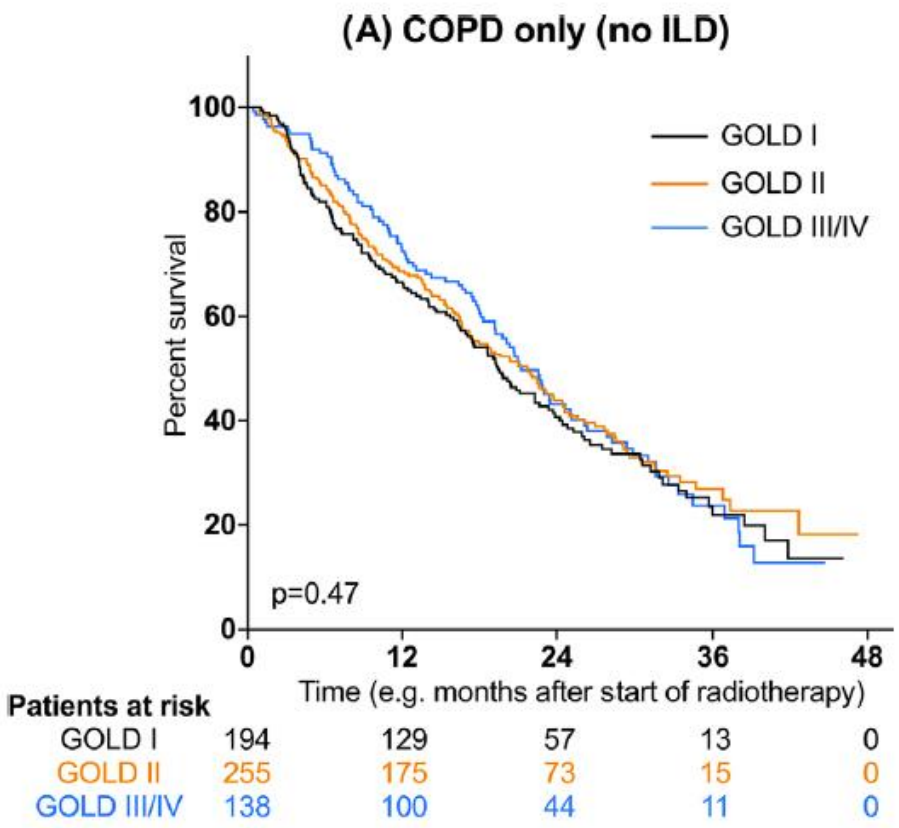
Comorbidity – Pulmonary comorbidities, COPD

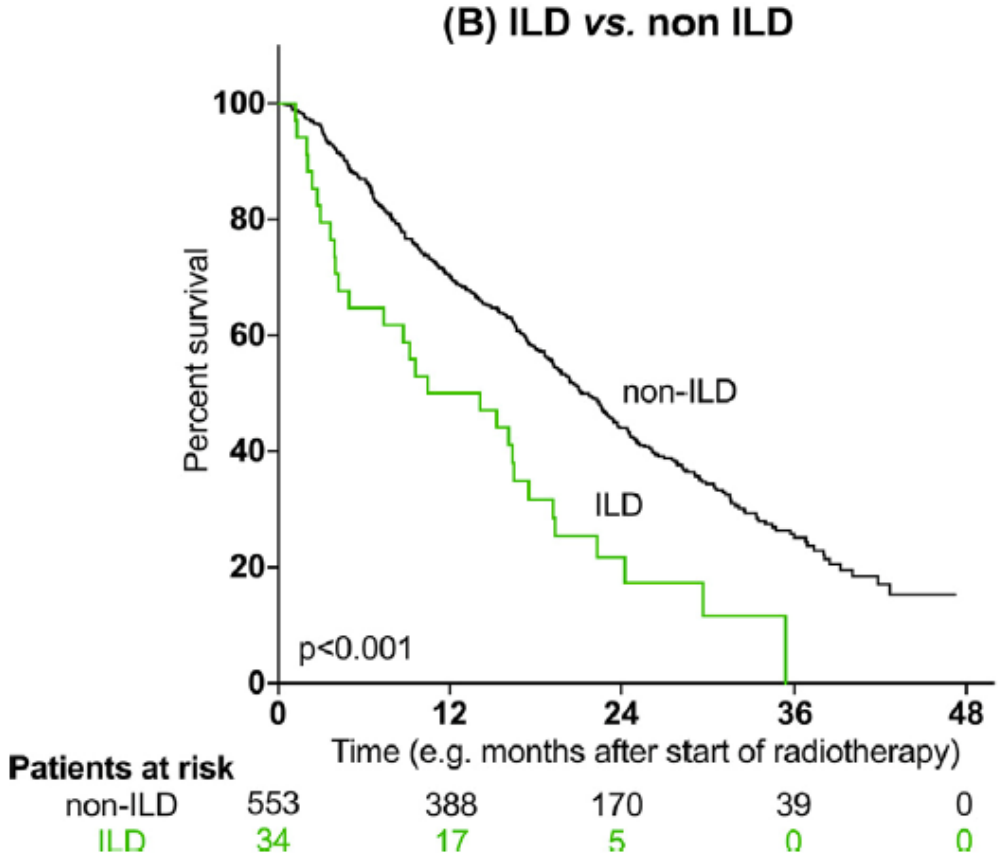


Guckenberger, et al. J Thorac Oncol. 2012

PATIENT SELECTION

Comorbidity – Pulmonary comorbidities, COPD and ILD





Tang C, et al. Radio Oncol. 2021

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Treatment:

SABR in early stage NSCLC ineligibile to surgery

ESTRO-ACROP consensus guideline

ESTRO ACROP consensus guideline on implementation and practice of stereotactic body radiotherapy for peripherally located early stage non-small cell lung cancer

Matthias Guckenberger [a,*], Nicolaus Andratschke [a], Karin Dieckmann [b], Mischa S. Hoogeman [c], Morten Hoyer [d], Coen Hurkmans [e], Stephanie Tanadini-Lang [a], Eric Lartigau [f], Alejandra Méndez Romero [c], Suresh Senan [g], Dirk Verellen [h]

[a] *Department of Radiation Oncology, University Hospital Zürich, Switzerland;* [b] *Department of Radiation Oncology, Medical University of Vienna, Austria;* [c] *Department of Radiation Oncology, Erasmus MC Cancer Institute, Rotterdam, Netherlands;* [d] *Department of Radiation Oncology, Aarhus University Hospital, Denmark;* [e] *Department of Radiation Oncology, Catharina Hospital, Eindhoven, Netherlands;* [f] *Department of Radiation Oncology, Centre Oscar Lambret, Lille, France;* [g] *Department of Radiation Oncology, VU University Medical Center, Amsterdam, Netherlands;* [h] *Department of Radiation Oncology, UZ Brussel (VUB), Belgium*

Europe

Radiothe Oncol 2017

Stereotactic Body Radiotherapy for Early-Stage Non–Small-Cell Lung Cancer: American Society of Clinical Oncology Endorsement of the American Society for Radiation Oncology Evidence-Based Guideline

Bryan J. Schneider, Megan E. Daly, Erin B. Kennedy, Mara B. Antonoff, Stephen Broderick, Jill Feldman, Shruti Jolly, Bryan Meyers, Gaetano Rocco, Chad Rusthoven, Ben J. Slotman, Daniel H. Sterman, and Brendon M. Stiles

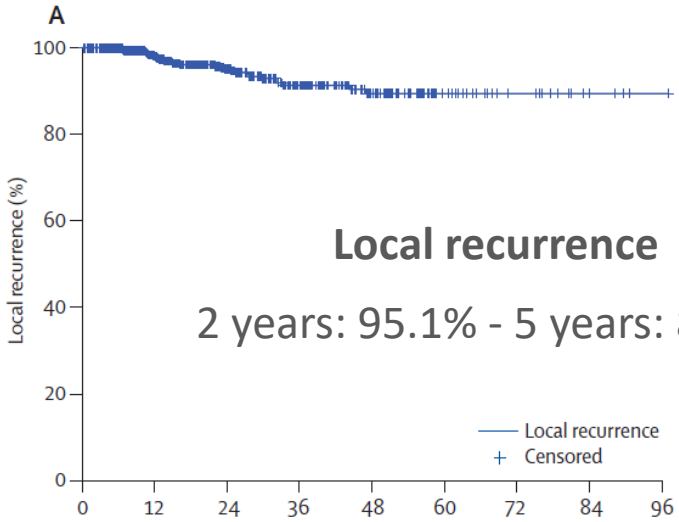
United States

JCO 2018

Treatment:

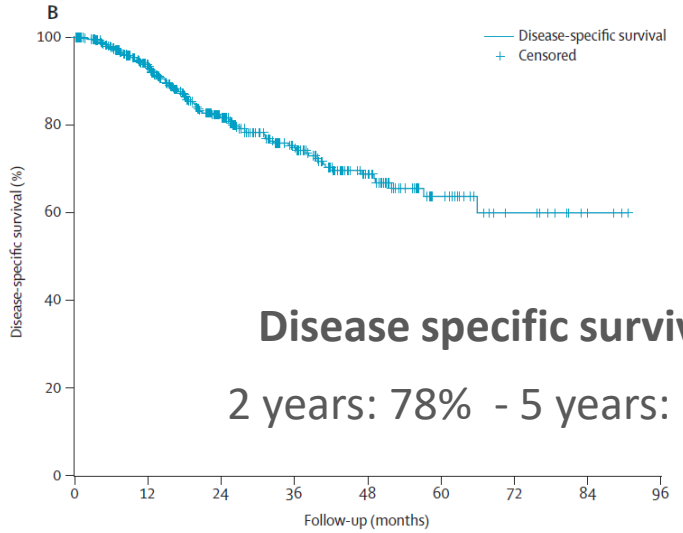
SABR in early stage NSCLC ineligibile to surgery

SABR impact



Local recurrence

2 years: 95.1% - 5 years: 89.5%



Disease specific survival

2 years: 78% - 5 years: 63%

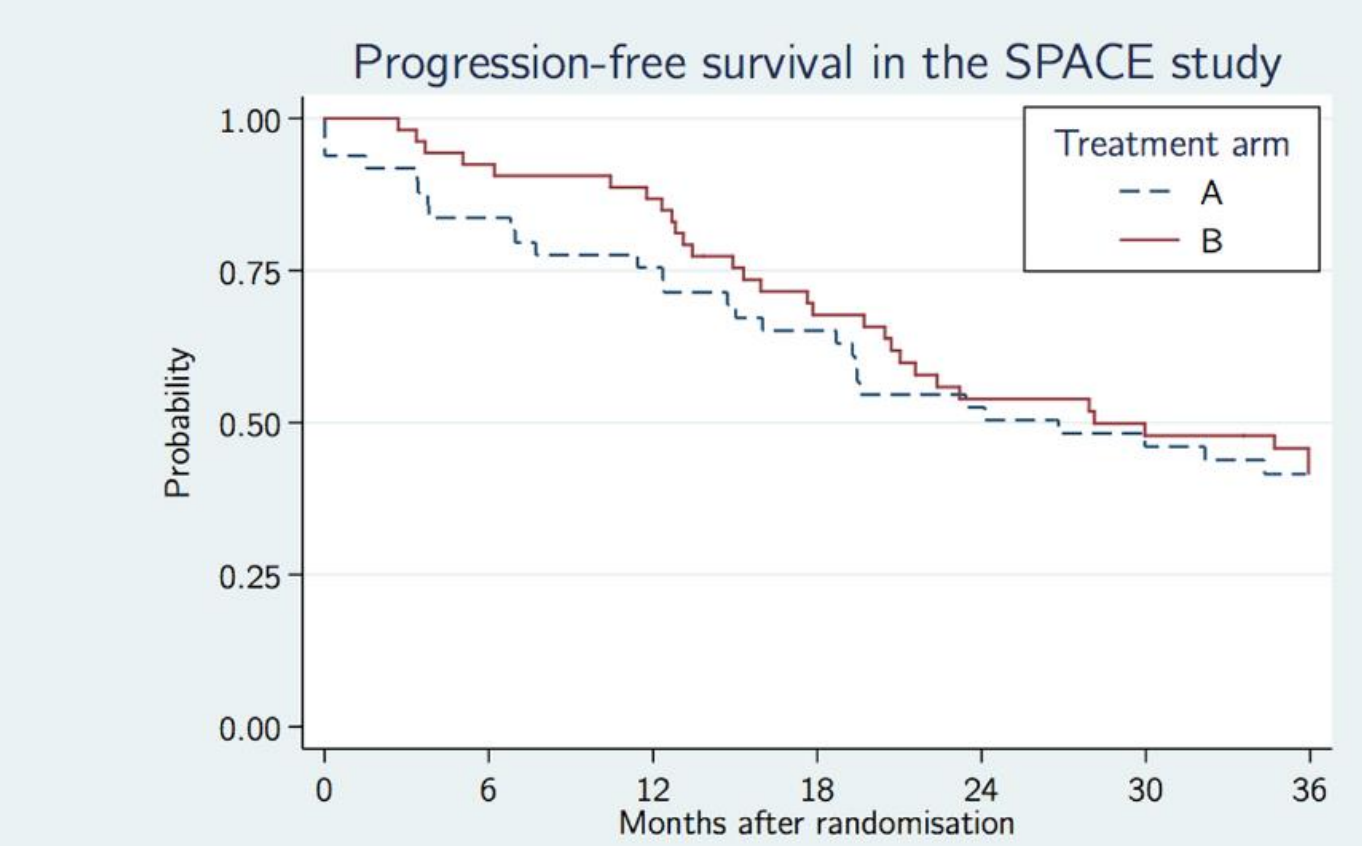
- **Retrospective study 2003-2011**
- SABR in stage I and II
- 676 patients evaluated
- Median OS: 41 months

Senthi S et al. Lancet Oncol.13:802-9, 2012

Treatment:

SABR in early stage NSCLC ineligibile to surgery

SABR impact



- **Phase II trial**
- SABR vs conventional RT in Stage I
- 102 patients
- Primary outcome: PFS

SABR less toxicity and better QoL

Nyman J, et al. Radiother Oncol.121:1, 2016

Treatment:

SABR in early stage NSCLC ineligibile to surgery

Practical Radiation Oncology (2017) 7, 295-301

practical radiation oncology
pro
www.practicalradonc.org

Special Article

Stereotactic body radiation therapy for early-stage non-small cell lung cancer: Executive Summary of an ASTRO Evidence-Based Guideline

Gregory M.M. Videtic MD, CM, FRCPC, FACR [a,*], Jessica Donington MD [b], Meredith Giuliani MBBS [c], John Heinzerling MD [d], Tomer Z. Karas MD [e], Chris R. Kelsey MD [f], Brian E. Lally MD [g], Karen Latzka [h], Simon S. Lo MB, ChB, FACR [i], Drew Moghanaki MD, MPH [j], Benjamin Movsas MD [k], Andreas Rimner MD [l], Michael Roach MD [m], George Rodrigues MD, PhD, FRCPC [n], Shervin M. Shirvani MD, MPH [o], Charles B. Simone II MD [p], Robert Timmerman MD [q], Megan E. Daly MD [r]

KQ 2: When is SBRT appropriate for medically inoperable patients with T1-2, N0 NSCLC:

- With centrally located tumors
- With tumors >5 cm in diameter
- Lacking tissue confirmation
- With synchronous primary or multifocal tumors
- Who underwent pneumonectomy and now have a new primary tumor in their remaining lung?

For patients with centrally located tumors?

Statement KQ 2A: SBRT directed toward centrally located lung tumors carries unique and significant risks when compared to treatment directed at peripherally located tumors. The use of 3-fraction regimens should be avoided in this setting.

For patients with tumors >5 cm in diameter?

Statement KQ 2C: SBRT is an appropriate option for tumors >5 cm in diameter with an acceptable therapeutic ratio. Adherence to volumetric and maximum dose constraints may optimize the safety profile of this treatment.

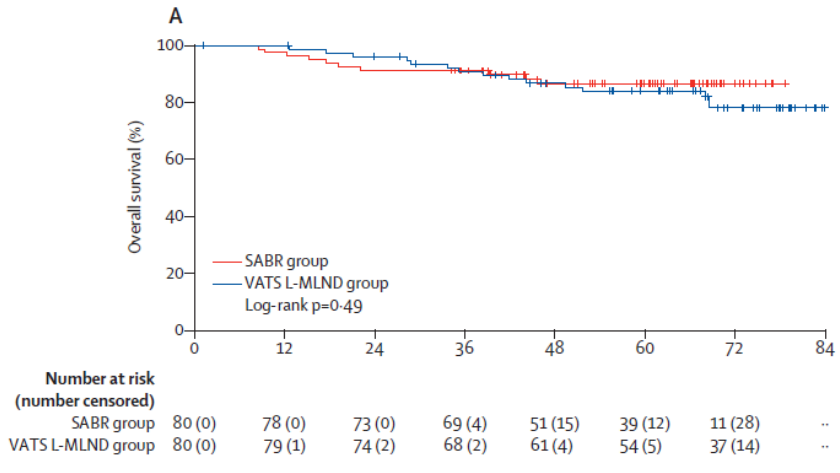
Recommendation strength: Conditional
Quality of evidence: Low
Consensus: 89%

Treatment:

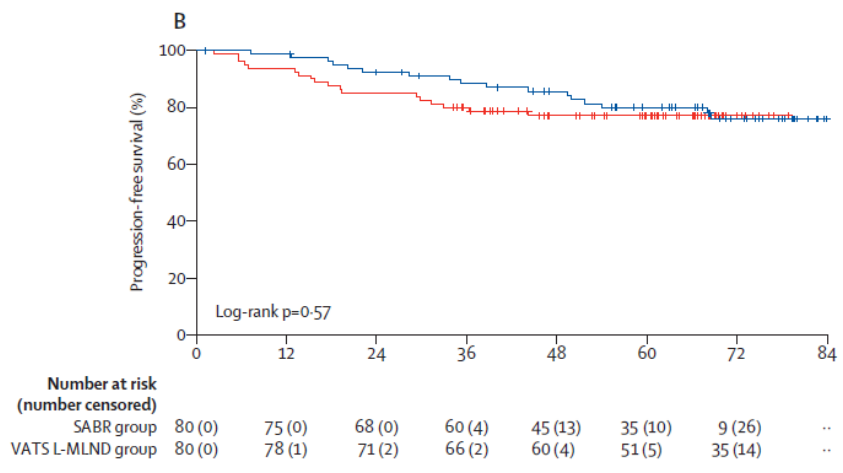
SABR in early stage NSCLC eligibile to surgery

SABR in Stage I NSCLC

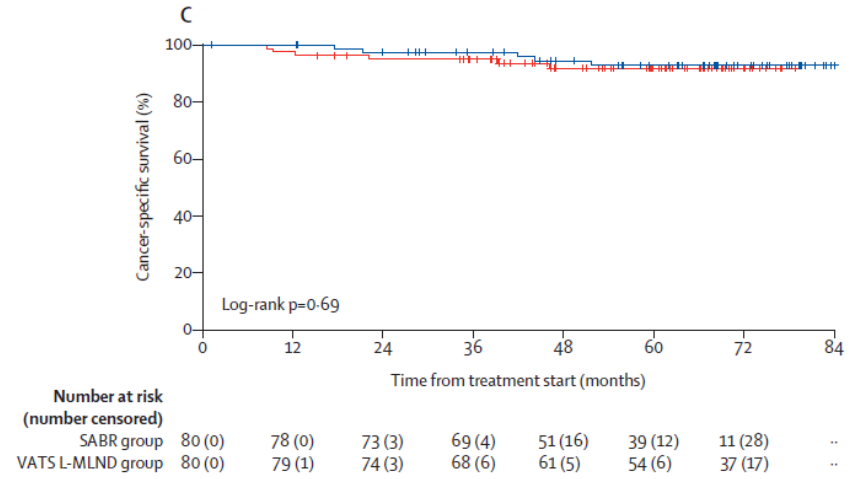
Median follow-up 5.1 years



Overall survival



Progression free survival



Lung cancer specific survival

Long-term survival after SABR is non-inferior to VATS L-MLND for operable stage IA NSCLC. SABR remains promising for such cases. Multidisciplinary management is strongly recommended

Chang YL, et al. Lancet Oncol.22:1448-57, 2021

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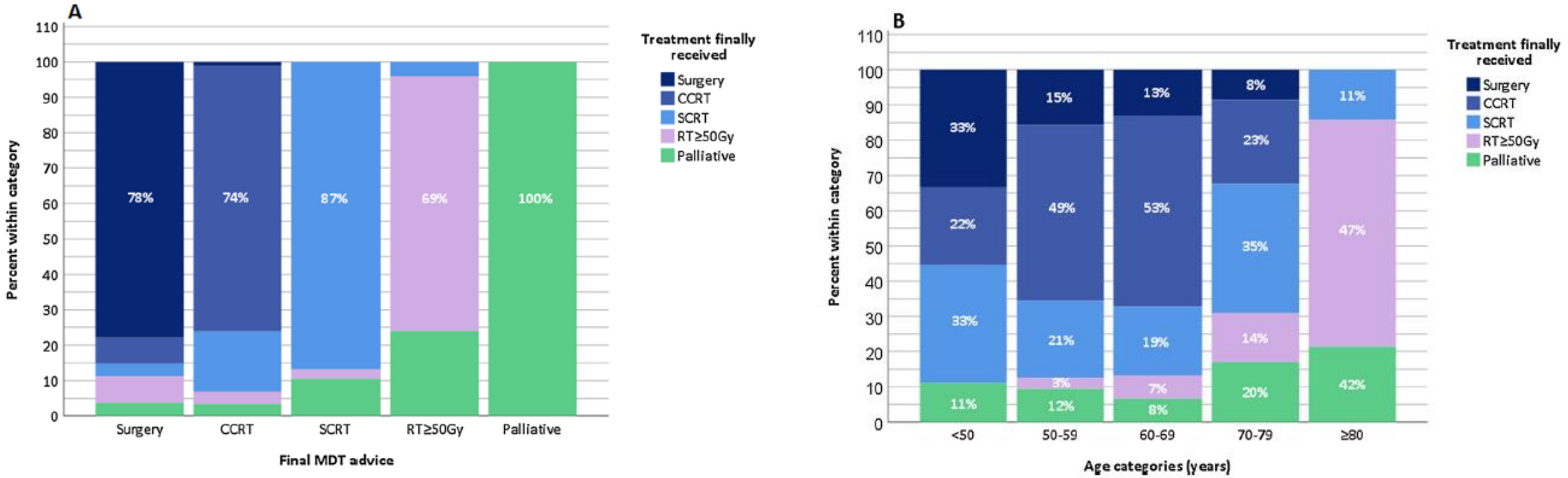
PATIENT SELECTION

Thoracic multidisciplinary tumor boards – Age and comorbidities in NSCLC radical treatment

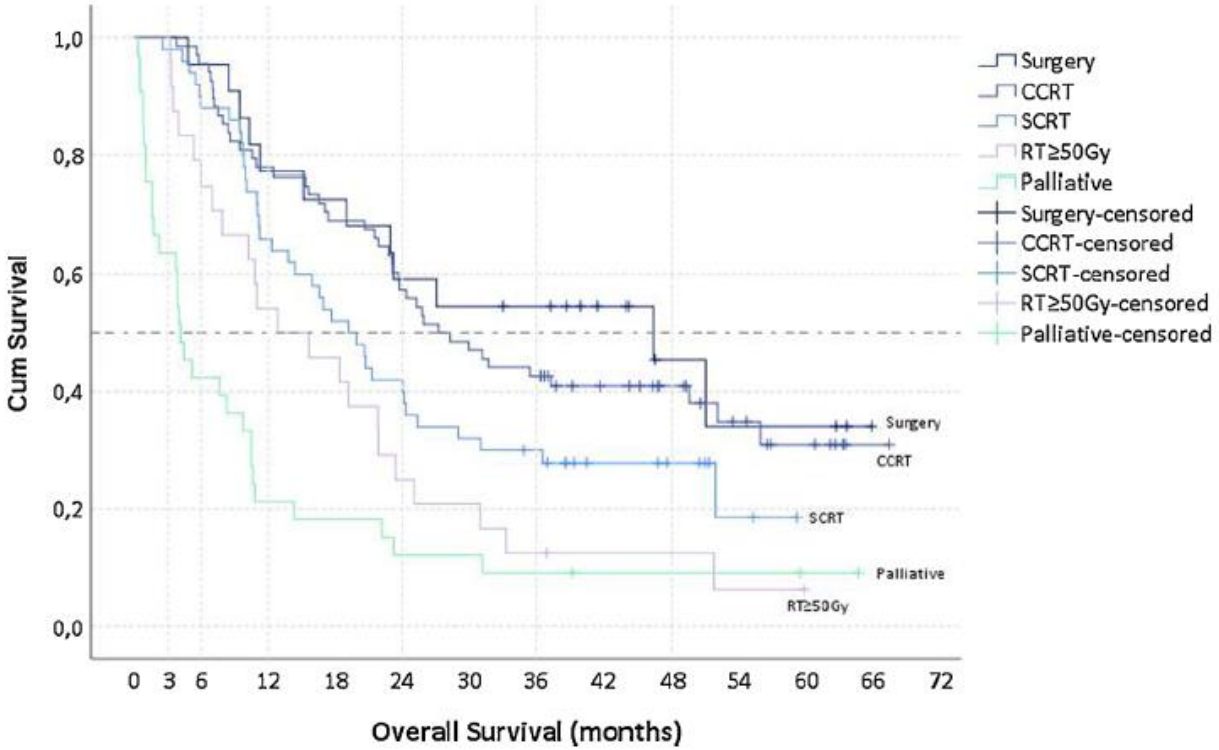


Dutch register of 197 NSCLC locally advanced

Ronden MI et al. Lung Cancer. 2021

PATIENT SELECTION

Thoracic multidisciplinary tumor boards – Age and comorbidities in NSCLC radical treatment



RIT were recommended in 61 % of patients, but only 48 % finally received RIT

Ronden MI et al. Lung Cancer.2021

THERAPEUTIC APPROACH

Close liason between LC and OS

CHART, Saunders et al. Lancet 1997

- 60 Gy in 30 fractionts vs. 54 Gy in 36 fractions (hyperfractionated)
- HR death 0.76 (p=0.0042)
- HR loco-regional progression 0.77 (p=0.027)

NSCLCCG Meta-analysis (6 trials, 1205 patients), Auperin et al. JCO 2010

- HR death 0.83 (p=0.04), absolute benefit survival 4.5% @ 5 years
- HR loco-regional progression 0.77 (p=0.01); absolute benefit 6% @ 3 years

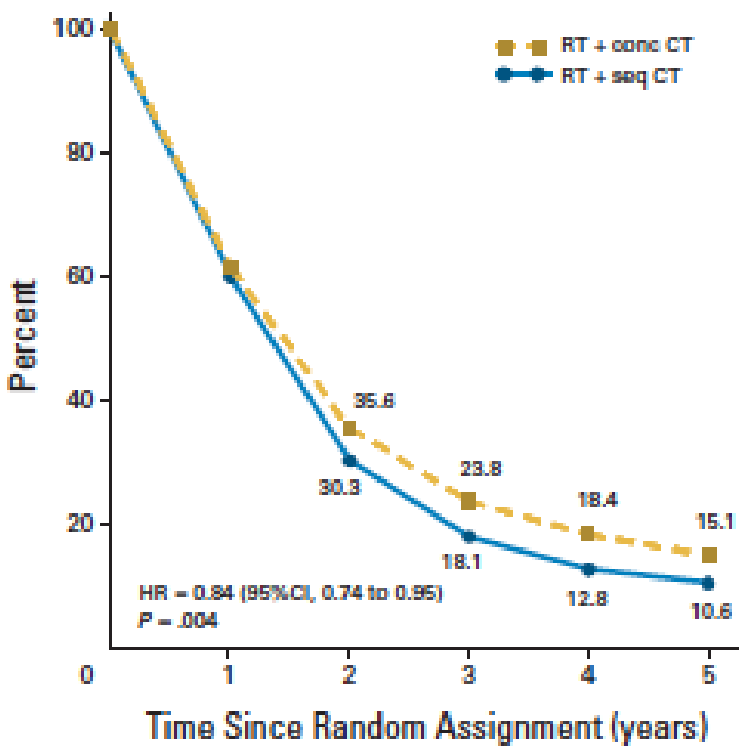
RTOG Meta-analysis (7 trials, 1390 patients), Machtay et al. JTO 2012

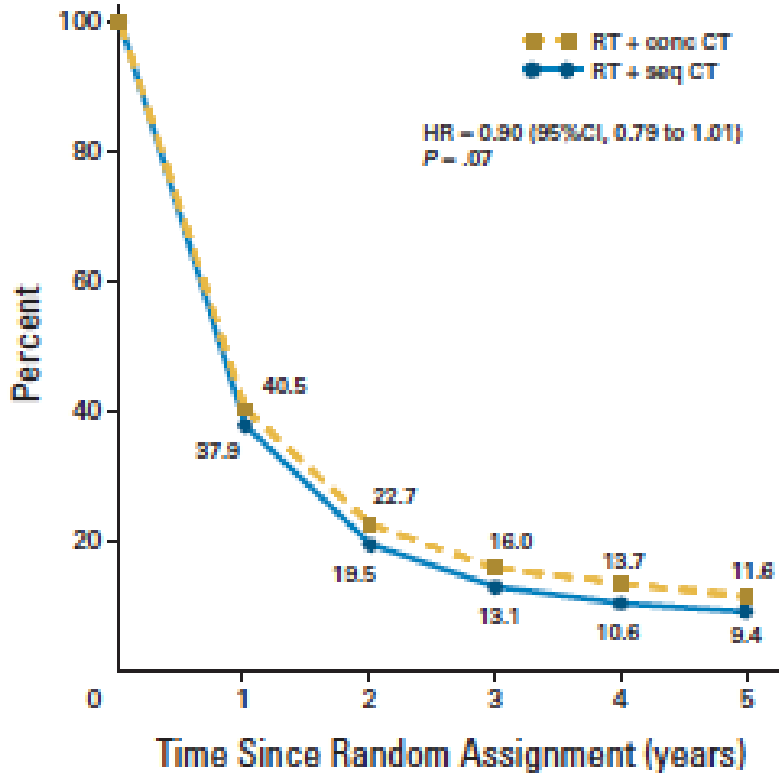
- Improved local control correlated with improved overall survival (p<0.001)

THERAPEUTIC APPROACH

Therapeutic approach

Concurrent CT-RT versus sequential CT and RT





HR death 0.83 (p=0.04), absolute benefit survival 4.5% @ 5 years
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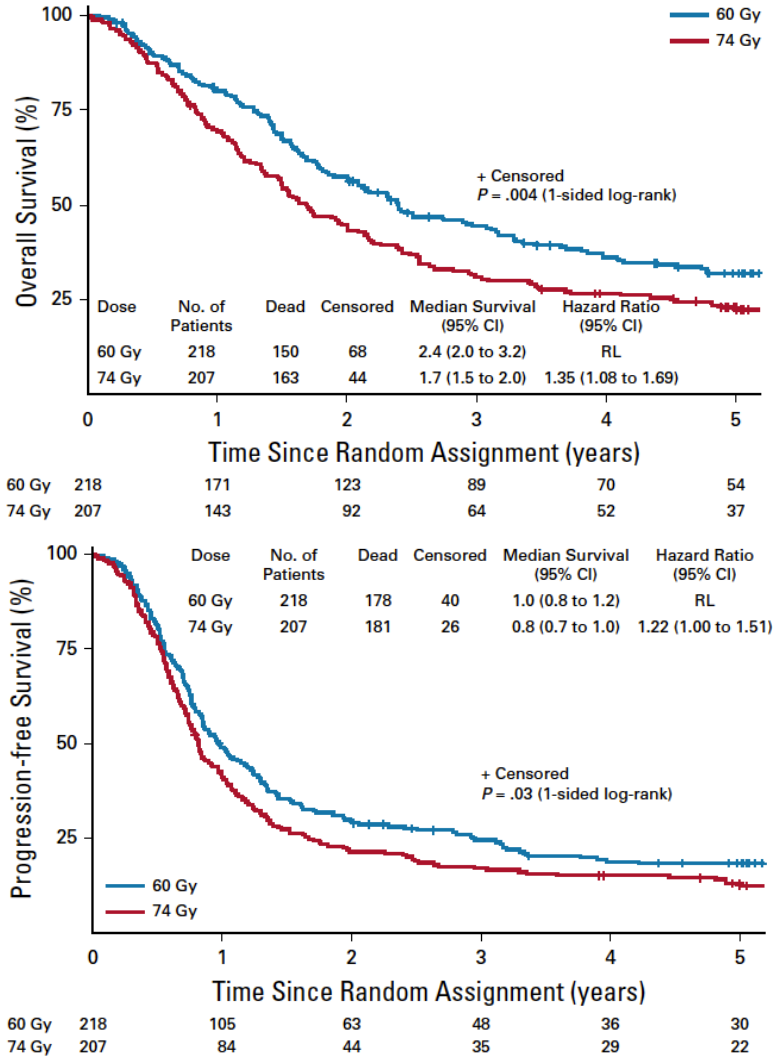
Auperin et al. JCO 2010

THERAPEUTIC APPROACH



Higher risk of death in 74 Gy arm

	60 Gy	74 Gy
MS (95% CI)	28.7 months (24.1-36.9)	20.3 months (17.7-25.0)
Esophagitis G3+	7%	15%
OS @ 5 years	32.1%	23%
Local failure @ 5 years	38.2% (31.7-44.8)	45.7% (38.7-52.4)

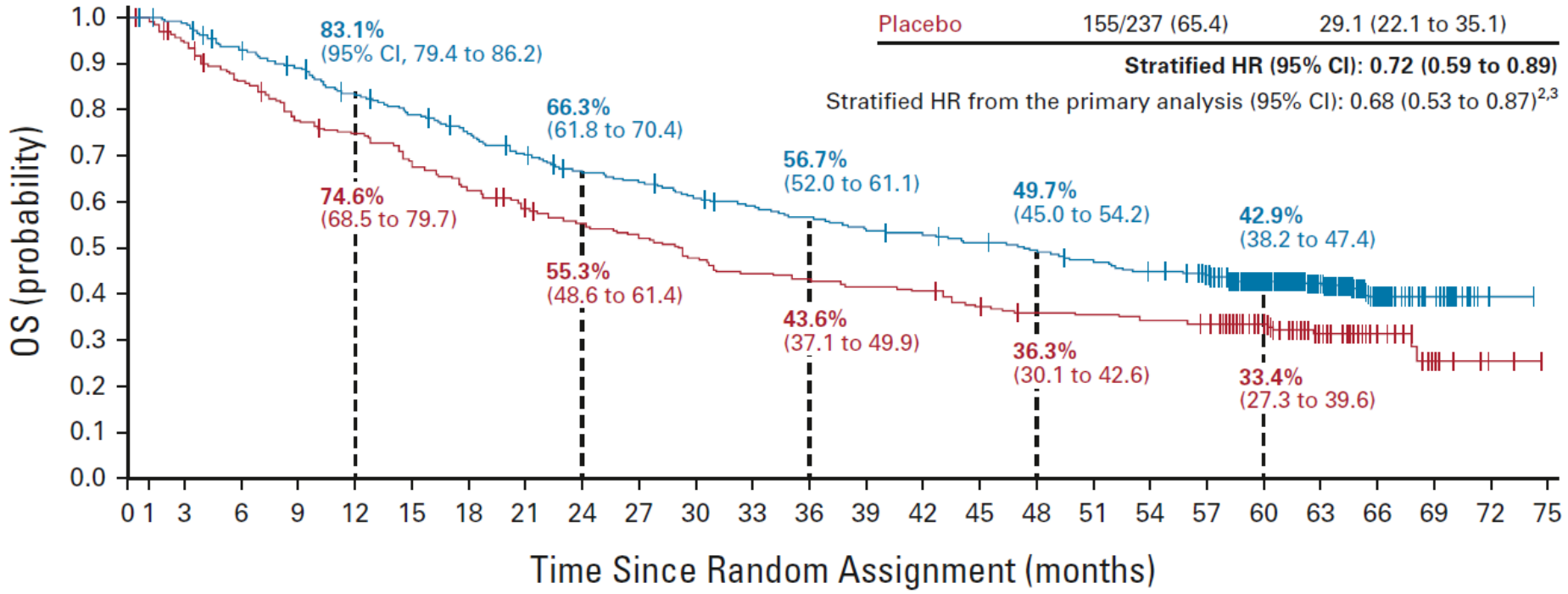
Bradley JD et al. J Clin Oncol, 2020

THERAPEUTIC APPROACH

Arm	No. of Events/ Total No. of Patients (%)	Median OS (95% CI), Months
Durvalumab	264/476 (55.5)	47.5 (38.1 to 52.9)
Placebo	155/237 (65.4)	29.1 (22.1 to 35.1)

Stratified HR (95% CI): 0.72 (0.59 to 0.89)

Stratified HR from the primary analysis (95% CI): 0.68 (0.53 to 0.87)[2,3]



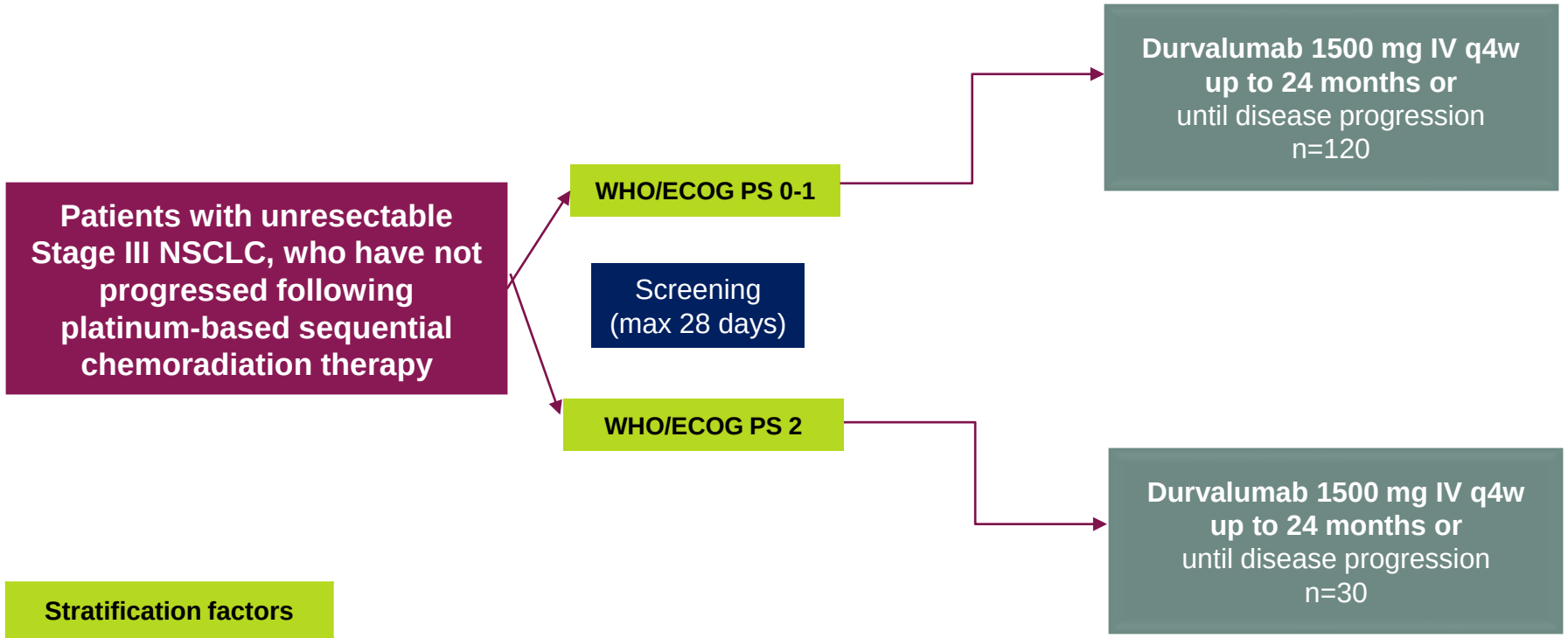
No. at risk:

Durvalumab	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

Spigel DR et al. J Clin Oncol 2022

PACIFIC 6 Study Design

Phase 2, open-label, multicenter study



Stratification factors

- WHO/ECOG PS 0-2
- Histological subtype

[a]Investigator-assessed.

Primary endpoints

- Safety and tolerability (occurrence of Grade 3 and Grade 4 TRAEs)

Key Secondary endpoints

- mPFS[a] (per RECIST v1.1), PFS12, PFS24
- mOS, OS12, OS24, OS36
- ORR[a] (per RECIST 1.1)
- DoR[a] (per RECIST 1.1)
- Number of patients with AE, SAEs, AESIs, imAEs
- Other safety and tolerability parameters

THERAPEUTIC APPROACH

PACIFIC 6 Study

Table 3. Safety Summary

	ECOG PS 0 or 1 (n = 114)		ECOG PS 2 (n = 3)		All Patients (N = 117)	
AE Category, n (%)	Any Cause	PRAE[a]	Any Cause	PRAE[a]	Any Cause	PRAE[a]
Any	108 (94.7)	87 (76.3)	3 (100)	3 (100)	111 (94.9)	90 (76.9)
Grade 3 or 4	22 (19.3)	5 (4.4)	0	0	22 (18.8)	5 (4.3)
Serious	23 (20.2)	6 (5.3)	0	0	23 (19.7)	6 (5.1)
Fatal	2 (1.8)	1 (0.9)	0	0	2 (1.7)	1 (0.9)
Leading to discontinuation of durvalumab	25 (21.9)	19 (16.7)	0	0	25 (21.4)	19 (16.2)
Immune mediated	46 (40.4)	42 (36.8)	2 (66.7)	2 (66.7)	48 (41.0)	44 (37.6)

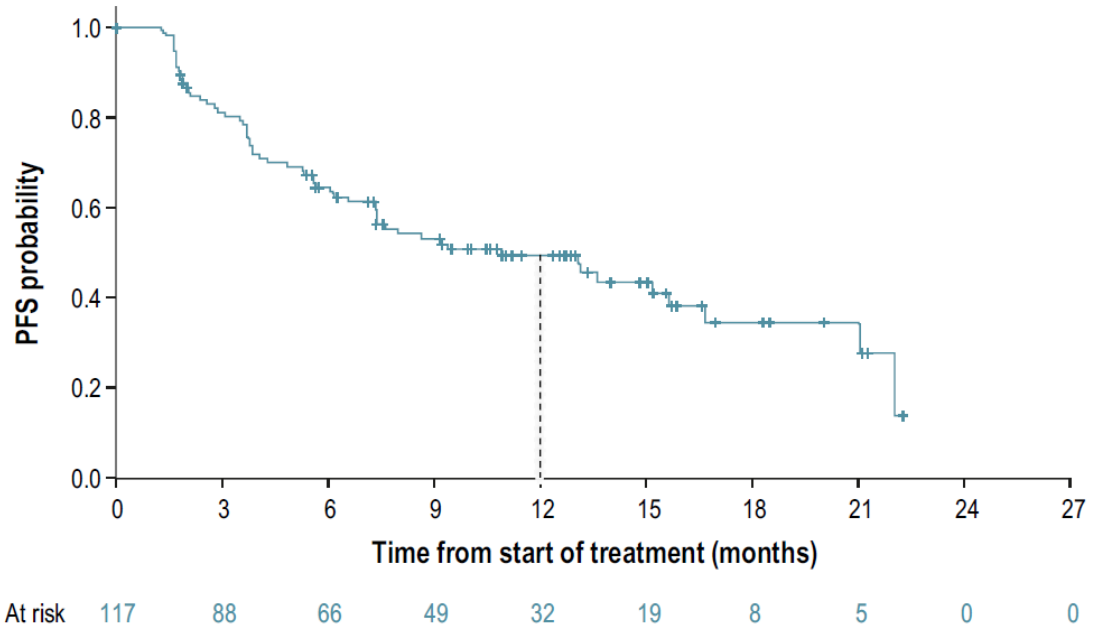
Table 5. Summary of Pneumonitis, Interstitial Lung Disease, and Radiation Pneumonitis Events by Severity

	Max. CTCAE Grade (N = 117)					Action Taken With Durvalumab (N = 117)	
AE Preferred Term, n (%)	Any AE	Grade 1	Grade 2	Grade 3 or 4	Grade 5	Interrupted	Discontinued
Pneumonitis	22 (18.8)	2 (1.7)	17 (14.5)	2 (1.7)	1 (0.9)	8 (6.8)	12 (10.3)
Interstitial lung disease	3 (2.6)	1 (0.9)	2 (1.7)	0	0	0	3 (2.6)
Radiation pneumonitis	4 (3.4)	1 (0.9)	1 (0.9)	2 (1.7)	0	0	3 (2.6)

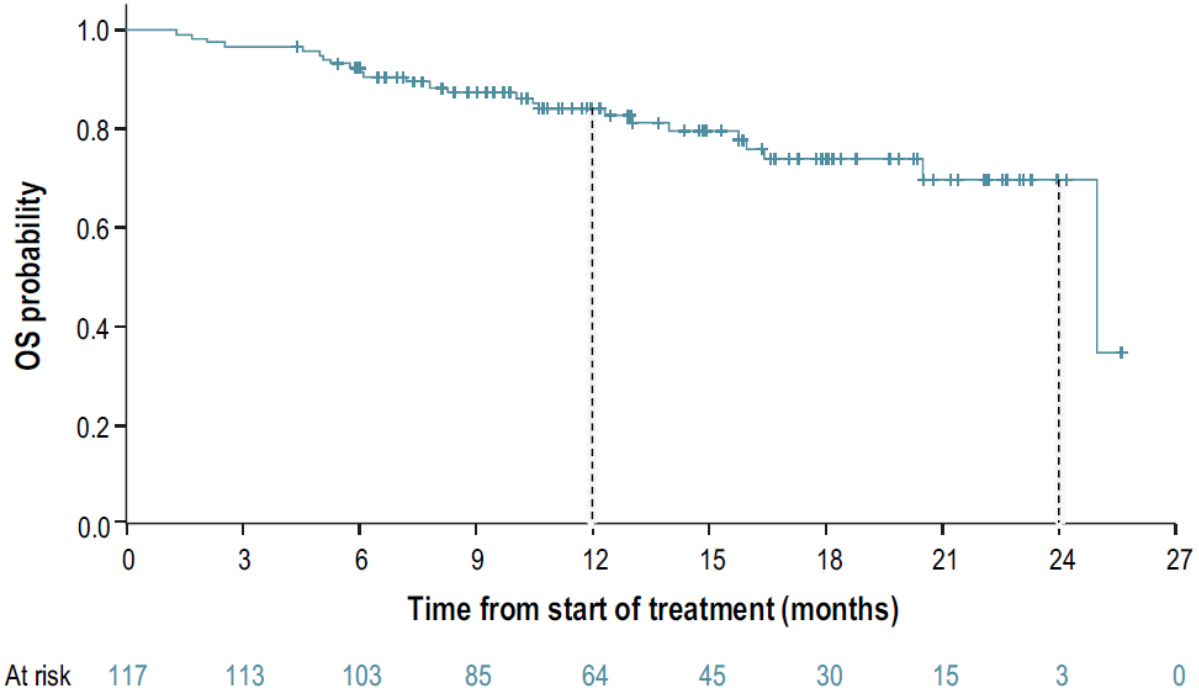
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; Max., maximum.

Garassino MC. et al. J Thorac Oncol 2022

PACIFIC 6 Study Design



	All patients (N = 117)
Total progression events, n (%)	61 (52.1)
Median PFS, months (95% CI)	10.9 (7.3–15.6)
12-month PFS rate, % (95% CI)	49.6 (39.5–58.9)
24-month PFS rate, % (95% CI)	NR (NE–NE)

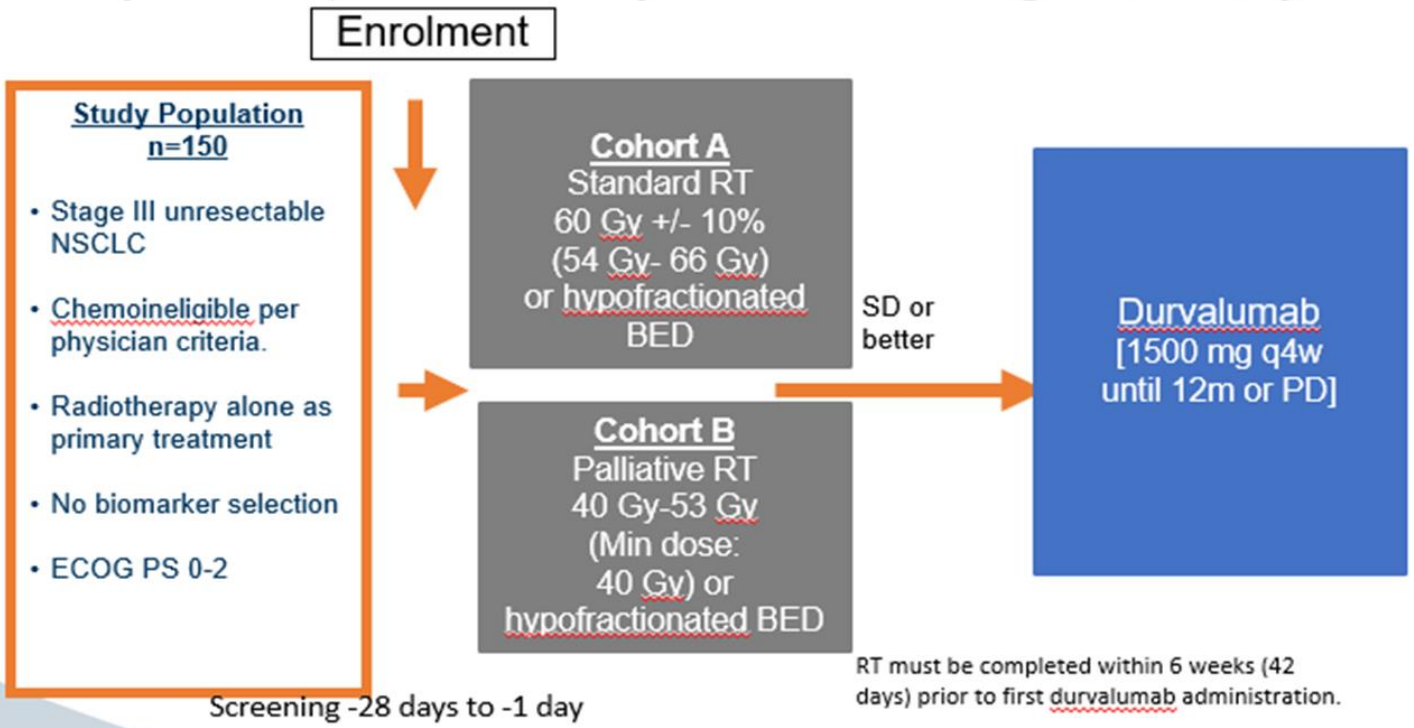


	All patients (N = 117)
Deaths, n (%)	25 (21.4)
Median OS, months (95% CI)	25.0 (25.0–NE)
12-month OS rate, % (95% CI)	84.1 (75.6–89.9)
24-month OS rate, % (95% CI)	69.8 (55.8–80.2)

Garassini MC. et al. J Thorac Oncol 2022

DUART
Durvalumab after RT in Unresectable Stage III NSCLC Ineligible for Chemo

Ph 2 open-label, multi-center practice informing GMA study



BED: bioequivalent dose; DoR: Duration of response; Durva: durvalumab; ECOG: Eastern Cooperative Oncology Group; Gy: gray; m: Month; mOS: median overall survival; mPFS: median progression-free survival; NSCLC: Non small-cell lung cancer; ORR: Overall response rate; OS12: Overall survival at 12 months; PD: Progressive disease; PFS6, PFS12: Progression-free survival at 6, 12 months, respectively; PRAE: Possibly related adverse event; PS: Performance status; q4w: Every 4 weeks; RT: radiation therapy

PRIMARY ENDPOINT
- Safety and tolerability (occurrence of Grade 3 & 4 PRAEs) within 6 months from the initiation of durvalumab

SECONDARY ENDPOINTS
- mPFS (per RECIST v1.1), PFS6 and PFS12
- ORR (per RECIST v1.1)
- DoR (per RECIST v1.1)
- mOS, OS12
- Lung cancer mortality
- Number of patients with AE, SAEs, AESIs, imAEs
- Other safety and tolerability parameters

EXPLORATORY ENDPOINTS
- QoL
- Tumor PD-L1
- Potential TMB and other ctDNA Circulating soluble factors

Treatment:
Post-operative radiotherapy?

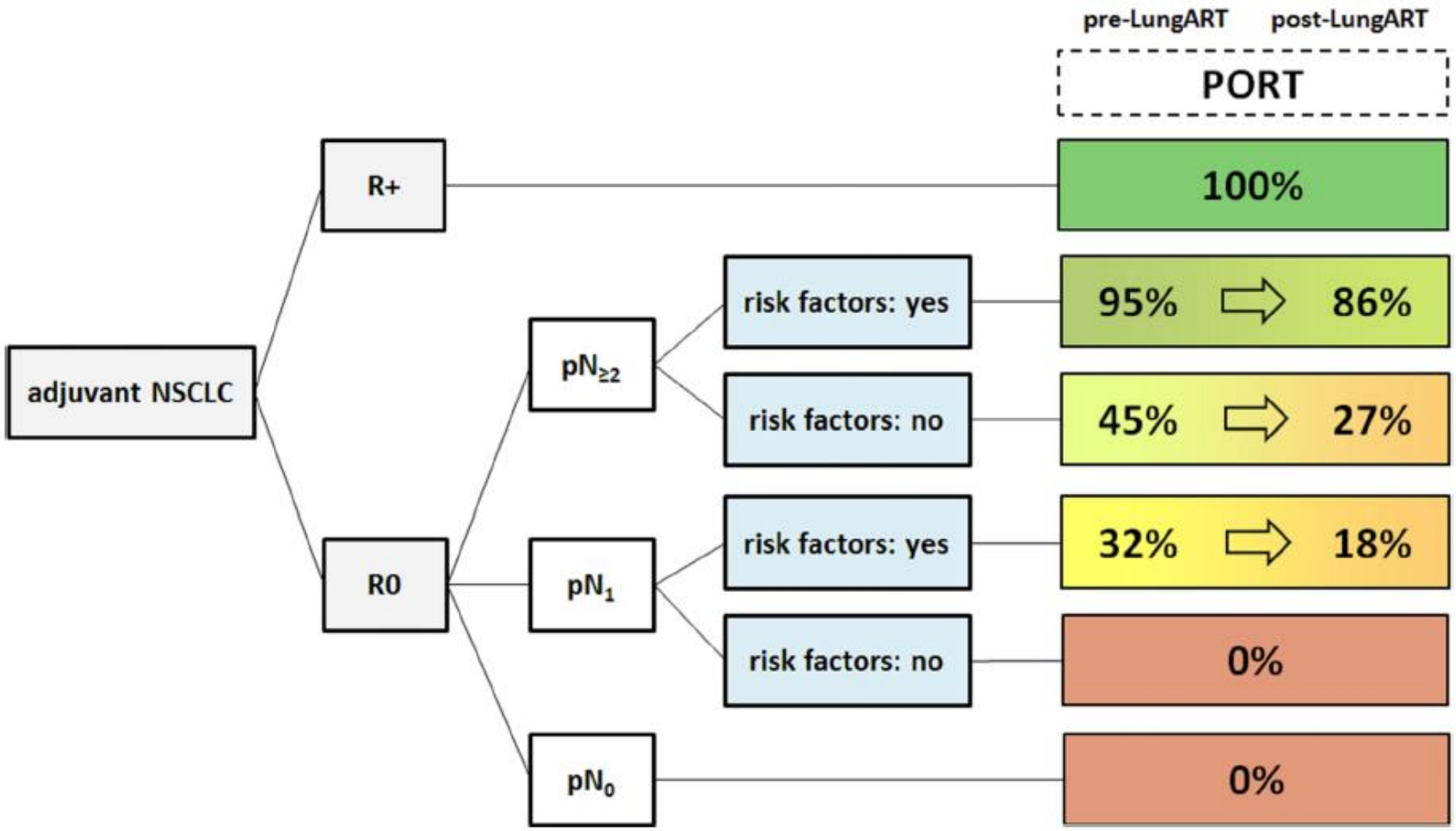
Postoperative radiotherapy versus no postoperative radiotherapy in patients with completely resected non-small-cell lung cancer and proven mediastinal N2 involvement (Lung ART, IFCT 0503): an open-label, randomised, phase 3 trial

Cecile Le Pechoux, Nicolas Pourel, Fabrice Barlesi, Delphine Lerouge, Delphine Antoni, Bruno Lamezec, Ursula Nestle, Pierre Boisselier, Eric Dansin, Amaury Paumier, Karine Peignaux, François Thillays, Gerard Zalcman, Jeannick Madelaine, Eric Pichon, Anne Larrouy, Armelle Lavole, Delphine Argo-Leignel, Marc Derollez, Corinne Faivre-Finn, Matthew Q Hatton, Oliver Riesterer, Emilie Bouvier-Morel, Ariane Dunant, John G Edwards, Pascal Alexandre Thomas, Olaf Mercier, Aurelie Bardet, on behalf of IFCT, UK NCRI, and SAKK

Interpretation Lung ART evaluated 3D conformal PORT after complete resection in patients who predominantly had been staged using (^{18}F-FDG PET-CT and received neoadjuvant or adjuvant chemotherapy. 3-year disease-free survival was higher than expected in both groups, but PORT was not associated with an increased disease-free survival compared with no PORT. Conformal PORT cannot be recommended as the standard of care in patients with stage IIIAN2 NSCLC.

Lancet Oncol. 23:104-114, 2022

Treatment:
Post-operative radiotherapy?



Süveg K, et al. Clin Lung Cancer. 2021.

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CONCLUSIONS

- SABR is the standard of care in patients with early stage NSCLC not eligible to surgery
- Concomitant chemo-radiotherapy ± immunotherapy is the treatment choice in unresectable locally advanced NSCLC
- Good tolerance has been observed in sequencial chemo-radiotherapy followed by immunotherapy
- PORT should be prescribed in select pN2 patients