Evidence and practice changing treatments in thoracic tumors

Cesare Guida

Ospedale del Mare

Napoli

- **SABR**
- **LA-NSCLC**
- **OLIGOMETS**

TABLE 5] Lung Cancer Stage Grouping (Eighth Edition)

T/M	Label	N0	N1	N2	N3
T1	T1a *≤1*	IA1	IIB	IIIA	IIIB
	T1b *>1-2*	IA2	IIB	IIIA	IIIB
	T1c *>2-3*	IA3	IIB	IIIA	IIIB
T2	T2a *Cent, Yisc Pl*	IB	IIB	IIIA	IIIB
	T2a *>3-4*	IB	IIB	IIIA	IIIB
	T2b *>4-5*	IIA	IIB	IIIA	IIIB
T3	T3 *>5-7*	IIB	IIIA	IIIB	IIIC
	T3 *Inv*	IIB	IIIA	IIIB	IIIC
	T3 *Satell*	IIB	IIIA	IIIB	IIIC
T4	T4 *>7*	IIIA	IIIA	IIIB	IIIC
	T4 *Inv*	IIIA	IIIA	IIIB	IIIC
	T4 *Ipsi Nod*	IIIA	IIIA	IIIB	IIIC
M1	M1a *Contr Nod*	IVA	IVA	IVA	IVA
	M1a *Pl Dissem*	IVA	IVA	IVA	IVA
	M1b *Single*	IVA	IVA	IVA	IVA
	M1c *Multi*	IVB	IVB	IVB	IVB

See Table 3 text and legend for expansion of abbreviations.

THORACIC

Discussion to: Overall survival in low-comorbidity patients with stage I non-small cell lung cancer who chose stereotactic body radiotherapy compared to surgery

Presenter: Brooks V. Udelsman, MD, MHS[a]
Invited Discussant: Andrea S. Wolf, MD, MPH[b]
Corresponding Author: Brooks V. Udelsman, MD, MHS[a]

See Article page XXX.

Presenter: Dr Brooks V. Udelsman

Dr Andrea S. Wolf *(New York, NY).* Steve Yang presented a new standard of discussion that I could probably only achieve if you'll take my suggestion to have a Springsteen session. Stereotactic body radiation therapy (SBRT) in an era when SBRT is being touted as equivalent to surgery by some and being offered even to healthy patients, your study is critically important as we need to evaluate outcomes and assess this for true equipoise. My first question is to highlight a critical point you demonstrated. Nothing is free. Although people tout the tolerability of SBRT, and patients might prefer its noninvasiveness, there are toxicities. The 30- and 90-day mortality as you showed here and in your article were 1.7% and 2.8% for surgery, respectively, but also 0.3% and 1.7% for SBRT at 90 days. We all understand perioperative mortality, but help me understand why SBRT patients die at 3 months.

Dr Brooks V. Udelsman *(New Haven, Conn).* I agree with you completely, nothing is free. We think of SBRT as incredibly safe if in the early-stage period. Now, at 30 days, the mortality is really low, but that may be due to competing risks. It can induce increased stress on the patient, cardiopulmonary risks, all of those, although these patients are fairly healthy. As you get toward 90 days, I think you do start to see more of those complications where you can get tumor necrosis, involution. And we do see some of those patients. It is not unheard of to have issues, to require tubes, and to have additional morbidity, which can lead to mortality in that group. As you said, it's not free, and we shouldn't think of it that way.

Dr Wolf. I suspect you derived your subset analysis of patients who refused surgery under the assumption that those patients were otherwise similar to those who received surgery. But the refusal of surgery may in and of itself be associated with other confounding poor prognostic clinical demographic features that are also associated with survival. Are you able to tease this out? And if not, how might it impact your results?

Dr Udelsman. That's an important point. There were some differences in these groups that we control for in the propensity match. But patients who underwent SBRT and those who refused surgery in favor of that, clearly, by their clinical teams, tended to have less wealth. They may have had other sociodemographic factors that made it more difficult for them to undergo surgery. They were caring for a disabled family member. They couldn't take time off of work. SBRT is more convenient for patients. All those factors that allow patients to undergo surgery and be able to take that time off also may affect their long-term survival. I think that's important to look at. I think it's important to look at why do patients choose SBRT? That's the next question: Why are patients choosing this over surgery when we know that they're both really safe and we think we have a lot better outcomes? We have to figure that out, and that's going to go back to the clinics and talk to our medical oncology colleagues and our radiation oncology colleagues.

Dr Wolf. That's an important point and leads to my third question about multidisciplinary discussion and

From the [a]Division of Thoracic Surgery, Department of Surgery, Yale University School of Medicine, New Haven, Conn; and [b]New York Mesothelioma Program, Department of Thoracic Surgery, The Icahn School of Medicine at Mount Sinai, New York, NY.
This discussion occurred at the 103rd AATS Annual Meeting.
Address for reprints: Brooks V. Udelsman, MD, MHS, 1510 San Pablo St, HCC1 Suite 514, Los Angeles CA 90033 (E-mail: udelsman @usc.edu).
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J Thorac Cardiovasc Surg 2023;■:1-2
0022-5223/$36.00

https://doi.org/10.1016/j.jtcvs.2023.09.041

Udelsman

Overal
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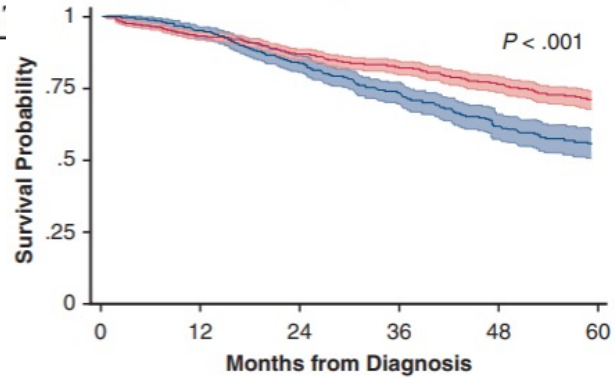
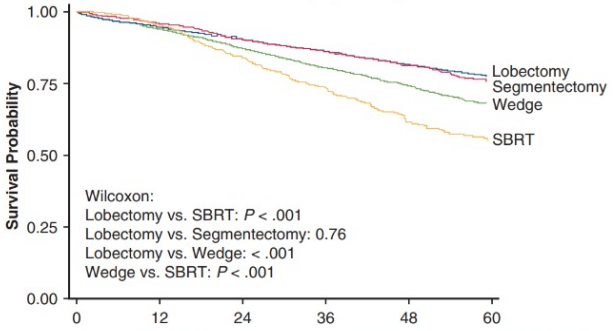
10.1016/j.jtcvs.2023.07.021

THOR

Surgery and SBRT in propensity-matched patients who refused a recommended surgery with stage I NSCLC



Stratified surgical resection and SBRT in patients who declined a recommended surgery for stage I NSCLC



SABR

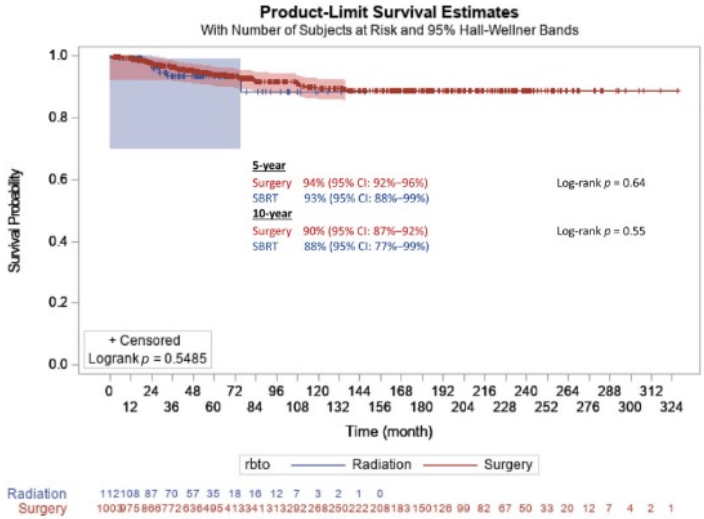
IASLC

ORIGINAL ARTICLE

Prospective Cohort Study to Compare Long-Term Lung Cancer-Specific and All-Cause Survival of Clinical Early Stage (T1a-b; ≤20 mm) NSCLC Treated by Stereotactic Body Radiation Therapy and Surgery

Journal of Thoracic Oncology Vol. ■ No. ■: ■-■

https://doi.org/10.1016/j.jtho.2023.10.002



SABR OR THERMOABLATION?

INTERNATIONAL JOURNAL OF HYPERTHERMIA
2023, VOL. 40, NO. 1, 2154577
https://doi.org/10.1080/02656736.2022.2154577

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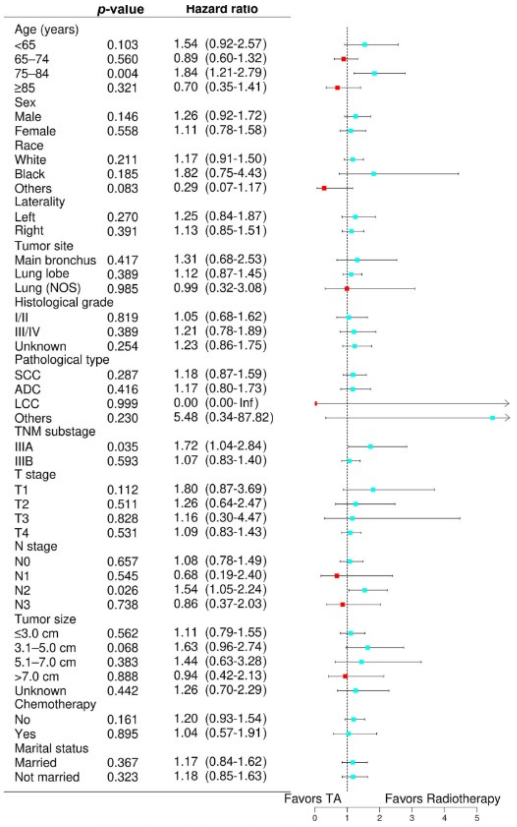
Thermal ablation versus radiotherapy for inoperable stage III non-small cell lung cancer: a propensity score matching analysis

ABSTRACT

Objective: To compare the survival benefits of thermal ablation (TA) and radiotherapy in inoperable patients with stage III non-small cell lung cancer (NSCLC).

Method: A retrospective analysis was conducted using the data from the Surveillance, Epidemiology, and End Results (SEER) program. Propensity score matching (PSM) was conducted to balance potential baseline confounding factors. Survival analyses were conducted using Kaplan–Meier and Cox regression methods.

Results: The present study included 33,393 inoperable patients with stage III NSCLC, including 106 patients treated with TA and 33,287 patients treated with radiotherapy. No statistical difference in overall survival (OS) ($p = .065$) or cancer-specific survival (CSS) ($p = .996$) was found between the patients treated with TA and those treated with radiotherapy. Using 1:3 matching, a matched cohort of 420 patients (105 patients treated with TA, 315 patients treated with radiotherapy) was identified. The differences in OS ($p = .177$) and CSS ($p = .605$) were still not significant between the radiotherapy and TA groups after PSM. According to subgroup analyses, TA showed comparable survival benefits in almost all subgroups compared to radiotherapy.



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clinical reviews

Stereotactic Body Radiotherapy for the Management of Early-Stage Non–Small-Cell Lung Cancer: A Clinical Overview

David S. Buchberger, MD[1] and Gregory M.M. Videtic, MDCM[1]

JCO® Oncology Practice
Volume 19, Issue 5 **239**

TABLE 1. Selected Studies in Lung SBRT for Early-Stage Lung Cancer

Year	Reference	Design	No. of Patients	Population	Dose Schedule	F/U	LC	OS	Toxicity
2004	Onishi et al[21]	MI RR	245	Stage I NSCLC	18-75 Gy in 1-22 fractions	Median: 24 months	LC: 85.5%	3-Year, operable, BED ≥ 100 Gy: 88.4%	Grade 3 or higher pulmonary toxicity: 2.4%
				Operable and inoperable	Median BED of 108		Local recurrence for BED ≥ 100 Gy: 8.1% (LC: 91.9%)	BED < 100 Gy: 69.4%	
2007	Onishi et al[22]	MI RR	257	Stage I NSCLC	18-75 Gy in 1-22 fractions	Median: 38 months	LC: 86.0%	5-Year, operable, BED ≥ 100 Gy: 70.8%	Grade 3 or greater pulmonary toxicity: 5.4%
				Operable and inoperable	Median BED of 111		Local recurrence for BED ≥ 100 Gy: 8.4% (LC: 91.6%)	BED < 100 Gy: 30.2%	
2003	Timmerman et al[23]	Phase I	37	T1, T2 N0M0	Dose escalation to 20 Gy in three fractions	Median: 15.2 months	LC: 83.8%	At a median F/U of 15.2 months, OS: 64.0%	G3 or higher pulmonary toxicities: 5.4%
				Medically inoperable			All LFs received < 18 Gy per fraction		No appreciable decline in cardiopulmonary function per examination, laboratory results, PFTs, imaging
2005	McGarry et al[24]	Phase I	47	T1, T2, N0M0	Dose escalation as above	T1 mean: 27.4 months	LC: 78.7% LF: 4/19 T1 LF: 6/28 T2	NA	G3 toxicity, T2 group with tumors > 5 cm: 3 of 5 patients treated with 24 Gy per fraction
				Medically inoperable		T2 mean: 19.1 months			
2006	Timmerman et al[25]	Phase II	70	T1, T2, N0M0	60-66 Gy in three fractions	Median: 17.5 months	LC, 2-year: 95.0%	OS, 2-year: 54.7%	2-Year freedom from severe toxicity in peripheral tumors 83.0%; 54.0% in central tumors G3-5: 5 of 48 with peripheral tumors, 10.4% G3-5: 6 of 22 with central tumors, 27.3%
				Medically inoperable					
2009	Fakiris et al[26]	Phase II	70	T1, T2, N0M0	60-66 Gy in three fractions	Median: 50.2 months	LC, 3-year: 88.1%	OS, 3-year: 42.7%	2-Year freedom from severe toxicity in peripheral tumors 83.0%; 54.0% in central tumors G3-5: 5 of 48 with peripheral tumors, 10.4% G3-5: 6 of 22 with central tumors, 27.3%
				Medically inoperable					
2010	RTOG 0236[27]	Phase II	55	T1, T2, N0M0	54 Gy in three fractions	Median: 34.4 months	LC, 3-year: 97.6%	OS, 3-year: 55.8%	G3/4: 16.4% (9 of 55)
				Medically inoperable					
				Peripheral					

DISCUSSION

SBRT is a safe, effective, curative, patient-friendly, and cost effective treatment for inoperable early-stage lung cancer, refined over the past 25 years through a number of studies

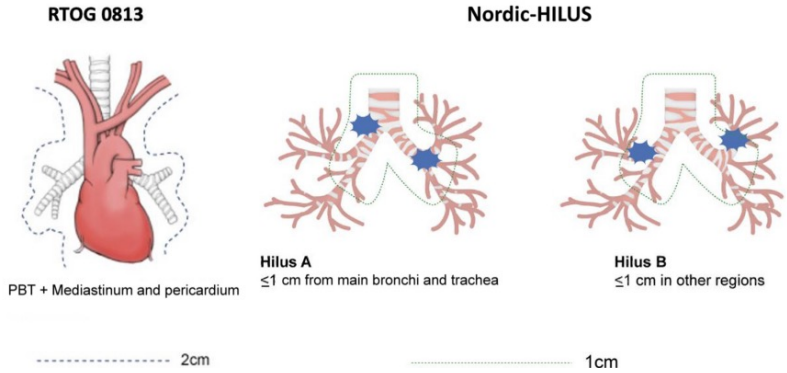
Its increasing application to the operable population and for complex clinical scenarios will continue to evolve, with integration with CT and IO

highly effective cancer cures with minimal treatment-related burden

Year	Reference	Design	Patients	Population	Dose Schedule	F/U	LC	OS	Toxicity
2018	RTOG 0236[28]	Phase II	55	T1, T2, N0M0	54 Gy in three fractions	Median: 48 months for all patients 86.4 months seven patients still living	LC, 5-year: 92.7%	OS, 5-year: 40.0%	G3/4: 30.9% (17 of 55)
				Medically inoperable					
				Peripheral					
2014	Videtic et al[29]	Institutional review	80	T1, T2, N0M0	30 Gy in one fraction (69%) 34 Gy in one fraction (31%)	Median, 30 Gy: 18.7 months 34 Gy: 17.8 months	30 Gy, LC, 1 year: 98.0% 34 Gy, LC, 1-year: 86.2%	30 Gy, OS, 1 year: 75.0% 34 Gy, OS, 1 year: 64.0%	30 Gy, no toxicity: 92.7%
				Medically inoperable					34 Gy, no toxicity: 84.0%
				Peripheral					No G3 or higher toxicity
2015	RTOG 0915[30]	Phase II	84	T1, T2, N0M0	34 Gy in one fraction 48 Gy in four fractions	Median: 30.2 months	34 Gy, 1-year LC: 97.0% 48 Gy, 1-year LC: 92.7%	34 Gy, 2-year OS: 61.3% 48 Gy, 2-year OS: 77.7%	34 Gy, G3 or higher: 10.3% 48 Gy, G3 or higher: 13.3%
				Medically inoperable					
				Peripheral					
2019	RTOG 0915[31]	Phase II	84	T1/T2 N0M0	34 Gy in one fraction 48 Gy in four fractions	Median: 4 years for all patients 6 years for those alive at analysis	34 Gy, 5-year LC: 89.4% 48 Gy, 5-year LC: 93.2%	34 Gy, 5-year OS: 29.6% 48 Gy, 5-year OS: 41.1%	34 Gy, G3 or higher: 2.6% 48 Gy, G3 or higher: 11.1%
				Medically inoperable					
				Peripheral					
2018	RTOG 0618[32]	Phase II	26	T1/T2 N0M0	54 Gy in three fractions	Median: 48.1 months	4-Year LC: 96.0%	4-Year OS: 56.0%	G3 AEs: 7.7% No G4/G5 AEs
				Medically operable					
				Peripheral					
2019	RPCI[33]	Phase II	98	T1/T2 N0M0	30 Gy in one fraction 60 Gy in three fractions	Median: 53.8 months	30 Gy, 2-year LC: 94.9% 60 Gy, 2-year LC: 97.1%	2-Year OS: 73.0% 2-Year OS: 62.0%	30 Gy, thoracic G3 AEs: 16.3%
				Medically inoperable					60 Gy, thoracic G3 AEs G3: 12.2%
				Peripheral					No grade 4/5 AEs
2019	RTOG 0813[34]	Phase I/II	100	T1/T2 N0M0	Five fractions, dose escalating, 10-12 Gy per fraction	Median: 37.9 months	2-Year LC, 10 Gy per fraction: 87.5% 2-Year LC, 12 Gy per fraction: 87.9%	2-Year OS, 10 Gy per fraction: 75.0% 2-Year OS, 12 Gy per fraction: 72.7%	12 Gy per fraction probability of DLT: 7.2%
				Medically inoperable					
				Central					
2021	Videtic et al[35]	RR	229	T1/T2 N0M0 Medically inoperable Peripheral	30 Gy in one fraction (27.9%) 34 Gy in one fraction (72.1%)	Median, 30 Gy: 36.7 months 34 Gy: 17.2 months	2-Year LC: 92.7%	Median OS: 44.1 months	G3 toxicity: 0.9% No G4/G5 AEs

SABR CENTRALI

- **Lungtech** EORTC 22113-08113
- **Sunset**
- **Expanded Hilus**



"Central tumour: tumour within 2 cm or touching the zone of the proximal bronchial tree or tumour that is immediately adjacent to the mediastinal or pericardial pleura, with a PTV expected to touch or include the pleura"

«Ultracentral tumor: tumor located within 1 cm of the proximal bronchial tree (PBT), defined as the most distal 2 cm of the trachea, the mainstem bronchi, the intermediate bronchus, and the lobar bronchi»

Lungtech EORTC 22113-08113

LungTech, an EORTC Phase II trial of stereotactic body radiotherapy for centrally located lung tumours: a clinical perspective

Br J Radiol 2015;88:20150036.

[1,2]S ADEBAHR, [3]S COLLETTE, [4]E SHASH, [4]M LAMBRECHT, [5]C LE PECHOUX, [6]C FAIVRE-FINN, [7]D DE RUYSSCHER, [8]H PEULEN, [8]J BELDERBOS, [9]R DZIADZIUSZKO, [10]C FINK, [11]M GUCKENBERGER, [4]C HURKMANS and [1,2]U NESTLE

Prescription ICRU 83 Isodose 80%	60 Gy/8 fr BED_{10}=105 Gy
Max dose in PTV	< 130%

Pts (2015-2017)	31 (13 sites in 6 European Country)
FFLP at 3 yr	78,6%
Median OS	46 m
Gr 5 Tox	2 (1 Lung, 1 Heart)

OAR	α/β (Gy)	D_{max} (Gy)	EqD2 (Gy)	Acceptable variation (Gy)	Acceptable variation EqD2 (Gy)	Unacceptable variation (Gy)	Unacceptable variation EqD2 (Gy)
Trachea/main bronchus	3	8 × 5.5 = 44	74.8	<8 × 5.81 = 46.68	<81.9	≥8 × 5.81 = 46.68	>81.9
Heart[a]	3						
Great vessels[a]	3						
Oesophagus	3	8 × 5 = 40	64	<8 × 5.44 = 43.52	<73.6	≥8 × 5.44 = 43.52	≥73.6
Spinal cord[b]	2	8 × 4 = 32	48			>8 × 4 = 32	>48
Brachial plexus[b]	3	8 × 4.75 = 38	58.9	<8 × 5.17 = 41.36	<67.7	≥8 × 5.17 = 41.36	≥67.7
Body-PTV[b]	3	8 × 7.5 = 60	126	<8 × 7.785 = 62.28	<134.2	≥8 × 7.785 = 62.28	≥134.2
Lung-CTV[a]	3						
Chest wall[a]	3						

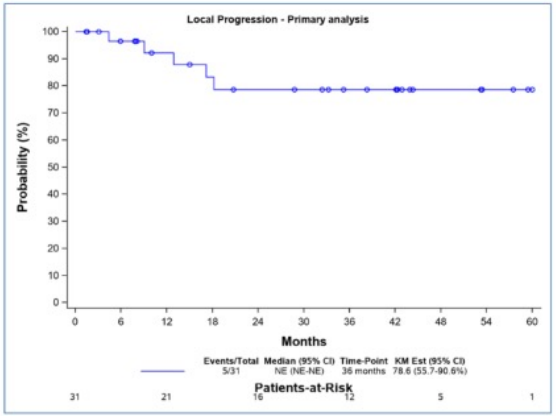


Figure 1: The probability for freedom from local progression at 36 months is 78.6% (90% CI=60.2 – 89.2%).

2023 Multidisciplinary Thoracic Cancers Symposium November 30 - December 2, 2023

Sunset

Stereotactic Radiation for Ultra-Central Non-Small Cell Lung Cancer: A Safety and Efficacy Trial (SUNSET)

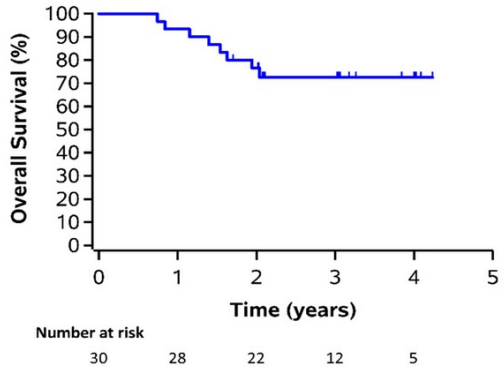
The MTD of SBRT for **ultra-central NSCLC**, using a time-to-event continual reassessment methodology (TITE-CRM).

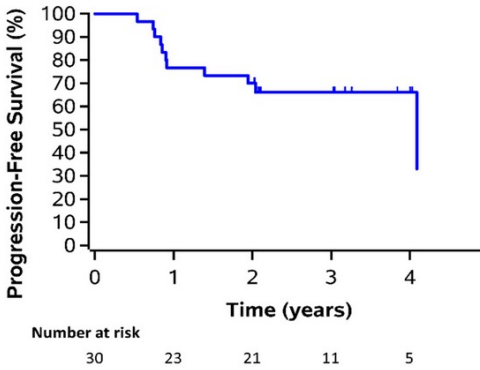
Prescription ICRU 83 Isodose 90%	• 60 Gy/8 fr • 60 Gy/10 fr • 60 Gy/15 fr
Max dose in PTV	< 120%
Pts (2018-2021)	30 (in 5 Canadian Centers)
0S	72,5%
LC	89.5%
Gr 5 Tox	2 (ILD)

Table 2 Recommended Dose Constraints

Organ	Metric	Fraction 5/6	Fraction 8/10	Fraction 15
Stomach and intestines	Max	40 Gy	45 Gy	50 Gy
	10 cc	35 Gy	40 Gy	48 Gy

OS and PFS





3-year OS: 72% (95% CI 52-85%)

3-year PFS: 66% (95% CI 46-80%)

Expanded Hilus

Int J Radiation Oncol Biol Phys, Vol. 117, No. 5, pp. 1222–1231, 2023

Expanded HILUS Trial: A Pooled Analysis of Risk Factors for Toxicity From Stereotactic Body Radiation Therapy of Central and Ultracentral Lung Tumors

Prescription Isodose encompassing PTV	• 56 Gy/8 fr
Max dose in PTV	Up to 150%
Pts (2010-2018)	230 (in 9 Nordic Center)
Gr 5 Tox	(20

Table 3 Maximum dose* in EQD_2 to the structures in the tracheobronchial tree

Structure	Median, Gy	Mean, Gy	IQR, Gy	Range, Gy
Trachea†	24	35	8-59	0-176
Mainstem bronchi†	77	76	37-107	1-211
Mainstem bronchi + intermediate bronchus†	98	96	48-132	1-228
Grade 5 bleeding: Mainstem bronchi + intermediate bronchus†,‡	119	134	103-143	92-228
Lobar bronchi§	138	129	79-184	1-301
Lobar bronchi + intermediate bronchus§	142	131	79-185	1-301
All tracheobronchial structures§	144	137	91-185	18-301

Table 5 Multivariable Cox regression of grade 5 toxicity and grade 5 bleeding

	Grade 5 toxicity				Grade 5 bleeding			
Variable	HR	95% CI	*P* value	C	HR	95% CI	*P* value	C
Tracheobronchial tumor compression, yes	2.995	1.210-7.409	.017	0.742	3.016	1.013-8.981	.047	0.764
Mainstem bronchi + intermediate bronchus, $D_{0.001cc}$ Gy^{-1}*	1.011	1.005-1.019	<.001		1.011	1.003-1.020	.009	
GTV, largest diameter, mm^{-1}	1.013	0.989-1.038	.277		1.015	0.976-1.036	.724	

INTERNATIONAL JOURNAL OF
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EDITORIAL

Beyond the HILUS Trial: How Can We Improve the Safety of SABR for Ultracentral Thoracic Tumors?

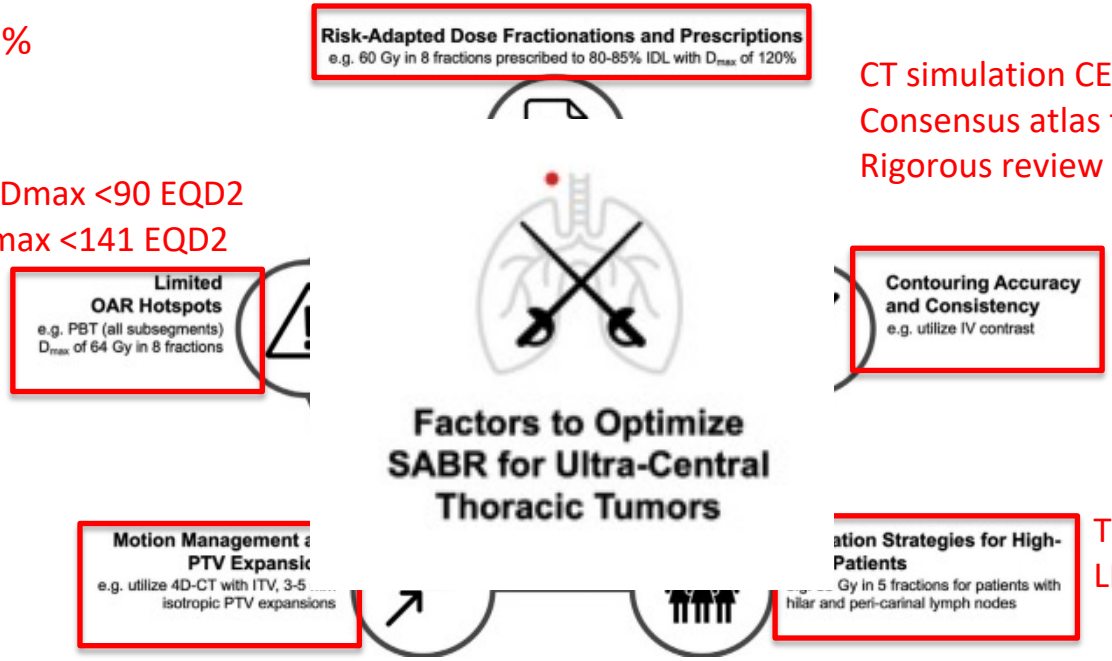
Amir H. Safavi, MD, MSc,* David A. Palma. MD. PhD.† and Meredith E. Giuliani. MBBS. PhD*,‡

Volume 117 • Number 5 • 2023

Sunset : D max < 120%

CT simulation CE (Esophagus)
Consensus atlas for OAR
Rigorous review in QA rounds

ISRS : Peribronchial Tree Dmax <90 EQD2
Sunset : Great Vessels Dmax <141 EQD2



Sunset/LungTech:
ITV-PTV: 3 -5 mm

TB inv: 60Gy/15
LN: 35 Gy/5

ORIGINAL ARTICLE

IASLC

Magnetic Resonance-Guided Stereotactic Body Radiation Therapy/Hypofractionated Radiation therapy for Metastatic and Primary Central and Ultracentral Lung Lesions

Check for updates

JTO Clinical and Research Reports Vol. 4 No. 5: 100488

Table 2. Radiation Regimen Utilized According Location of Lesion

	No. of Patients	%
54 Gy in 3 Fx		
HILUS A	0	0.0
HILUS B	1	8.3
Non-UC	3	33.3
50 Gy in 5 Fx		
HILUS A	2	7.7
HILUS B	4	33.3
Non-UC	1	11.1
60 Gy in 5 Fx		
HILUS A	3	11.5
HILUS B	1	8.3
Non-UC	3	33.3
60 Gy in 8 Fx		
HILUS A	13	50.0
HILUS B	5	41.7
Non-UC	1	11.1
50 Gy in 10 Fx		
HILUS A	1	3.8
HILUS B	1	8.3
Non-UC	0	0.0
60 Gy in 15 Fx		
HILUS A	7	26.9
HILUS B	0	0.0
Non-UC	1	11.1

Fx, fraction; Non-UC, nonultracentral.

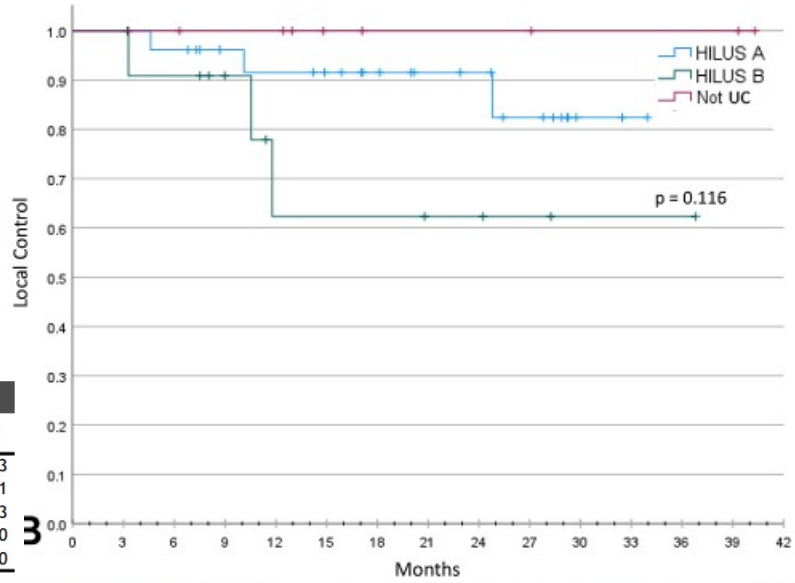


Table 3. Toxicity Profile

Acute toxicity	No. of Patients	%	Late toxicity	No. of Patients	%
Grade 1	12	25.5	Grade 1	2	4.3
Grade 2	10	21.3	Grade 2	1	2.1
Grade 3	0	0.0	Grade 3	2	4.3
Grade 4	0	0.0	Grade 4	0	0.0
Grade 5	0	0.0	Grade 5	0	0.0

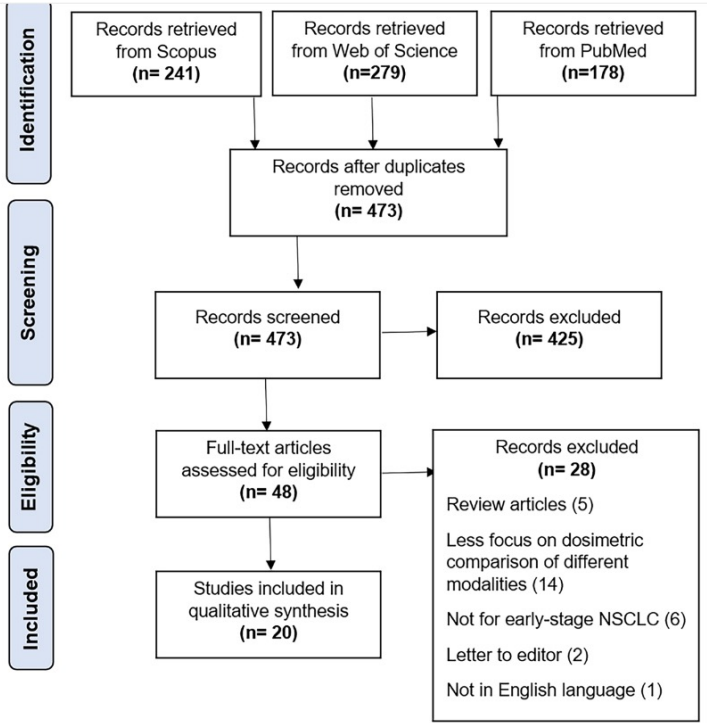
Gill *et al. Radiation Oncology* (2024) 19:1
https://doi.org/10.1186/s13014-023-02392-4

Radiation Oncology

REVIEW **Open Access**

Stereotactic body radiotherapy for early-stage lung cancer: a systematic review on the choice of photon energy and linac flattened/ unflattened beams

- Target conformity and OAR sparing (Lung) : **6MV FFF**
- Skin sparing and BOT reduction: **10MV FFF**



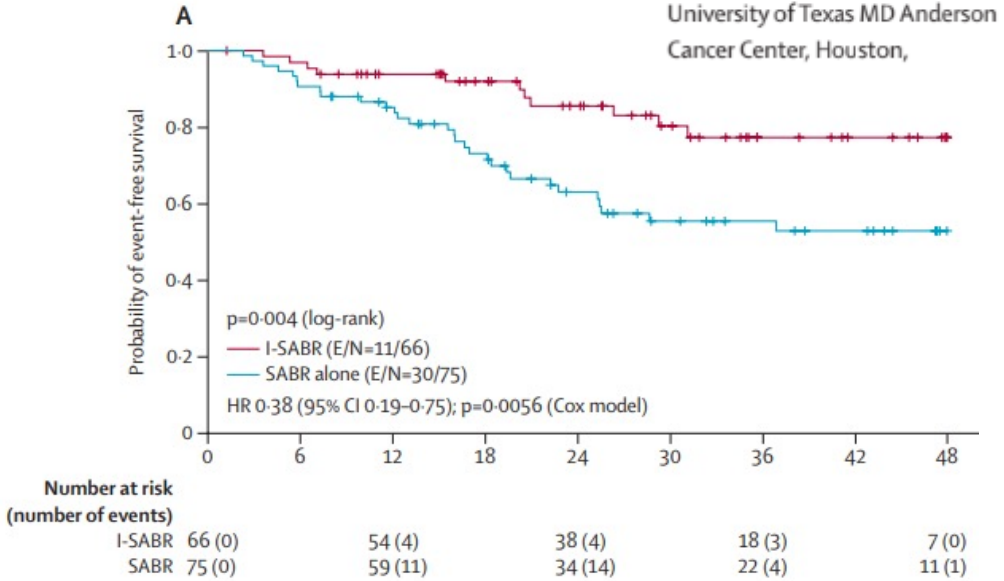
SABR + IO

Stereotactic ablative radiotherapy with or without immunotherapy for early-stage or isolated lung parenchymal recurrent node-negative non-small-cell lung cancer: an open-label, randomised, phase 2 trial *Lancet 2023; 402: 871–81*

Prof Joe Y Chang, Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston,

Phase II trial (2017-22)
141/156 PTS with GTV < 7 cm
SABR vs SABR + 4 Niv conc
Pr Endpoint : 4yr Event Free Survival

	SABR	SABR + 4 Niv
4yr EFS	**53%**	**77%**
LR	13%	0%
RR	11%	6%
DR	6%	3%
Total R	36%	12%
4 yr Mortality	12%	6%



THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

SABR + IO

Stereotactic ablative radiotherapy with or without immunotherapy for early-stage or isolated lung parenchymal recurrent node-negative non-small-cell lung cancer: an open-label, randomised, phase 2 trial

Lancet 2023; 402: 871–81

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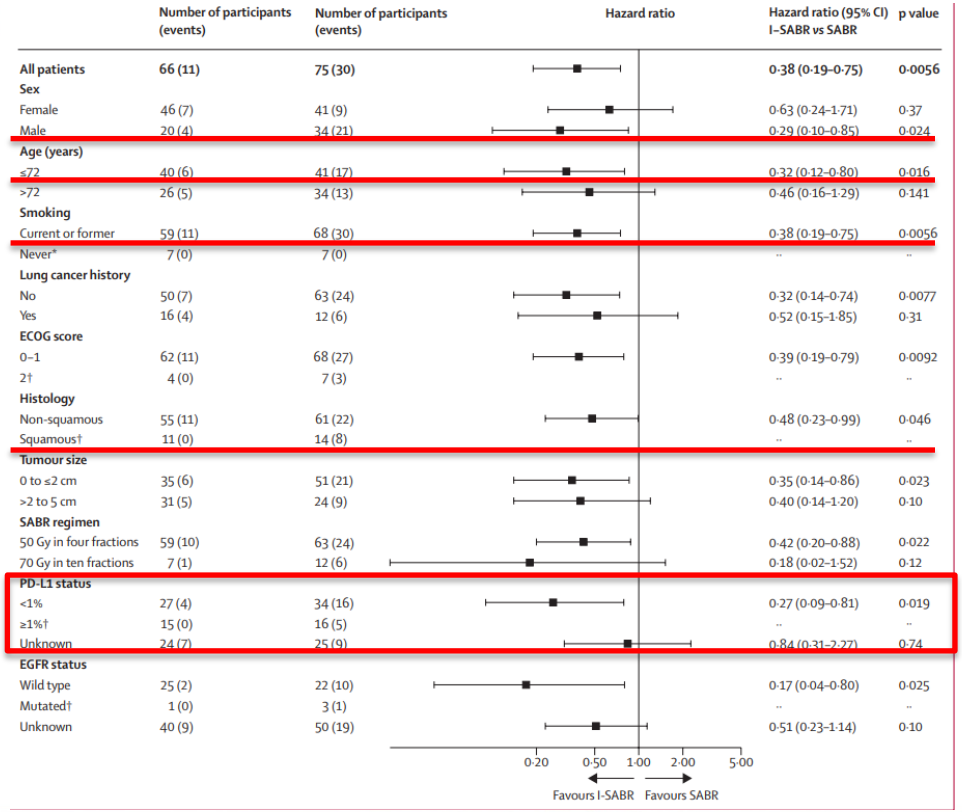


	Number of participants (events)	Number of participants (events)	Hazard ratio	Hazard ratio (95% CI) I-SABR vs SABR	p value
All patients	**66 (11)**	**75 (30)**		**0·38 (0·19–0·75)**	**0·0056**
Sex					
Female	46 (7)	41 (9)		0·63 (0·24–1·71)	0·37
Male	20 (4)	34 (21)		0·29 (0·10–0·85)	0·024
Age (years)					
≤72	40 (6)	41 (17)		0·32 (0·12–0·80)	0·016
>72	26 (5)	34 (13)		0·46 (0·16–1·29)	0·141
Smoking					
Current or former	59 (11)	68 (30)		0·38 (0·19–0·75)	0·0056
Never*	7 (0)	7 (0)		..	..
Lung cancer history					
No	50 (7)	63 (24)		0·32 (0·14–0·74)	0·0077
Yes	16 (4)	12 (6)		0·52 (0·15–1·85)	0·31
ECOG score					
0–1	62 (11)	68 (27)		0·39 (0·19–0·79)	0·0092
2†	4 (0)	7 (3)		..	..
Histology					
Non-squamous	55 (11)	61 (22)		0·48 (0·23–0·99)	0·046
Squamous†	11 (0)	14 (8)		..	..
Tumour size					
0 to ≤2 cm	35 (6)	51 (21)		0·35 (0·14–0·86)	0·023
>2 to 5 cm	31 (5)	24 (9)		0·40 (0·14–1·20)	0·10
SABR regimen					
50 Gy in four fractions	59 (10)	63 (24)		0·42 (0·20–0·88)	0·022
70 Gy in ten fractions	7 (1)	12 (6)		0·18 (0·02–1·52)	0·12
PD-L1 status					
<1%	27 (4)	34 (16)		0·27 (0·09–0·81)	0·019
≥1%†	15 (0)	16 (5)		..	..
Unknown	24 (7)	25 (9)		0·84 (0·31–2·27)	0·74
EGFR status					
Wild type	25 (2)	22 (10)		0·17 (0·04–0·80)	0·025
Mutated†	1 (0)	3 (1)		..	..
Unknown	40 (9)	50 (19)		0·51 (0·23–1·14)	0·10

0·20 0·50 1·00 2·00 5·00

Favours I-SABR Favours SABR

JAMA Oncology | Original Investigation JAMA Oncology November 2023 Volume 9, Number 11

Individualized Stereotactic Ablative Radiotherapy
The iSABR Phase 2 Nonrandomized Controlled Trial

25 Gy/1 fr = EQD2 87.5 Gy
Not for colon mets

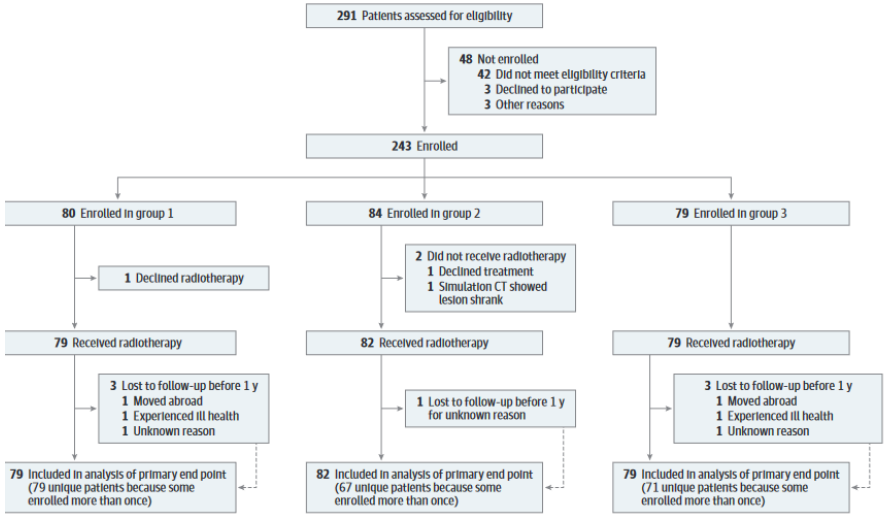
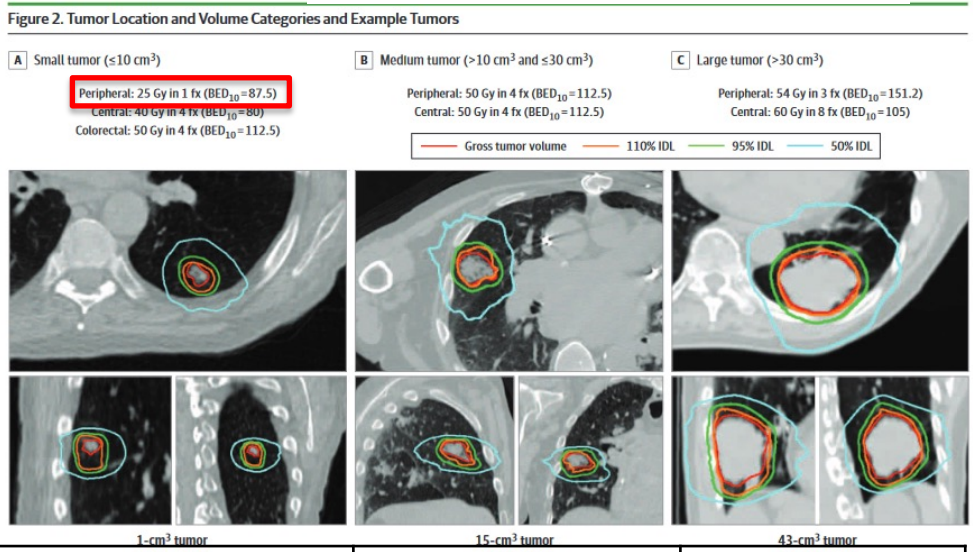


Figure 2. Tumor Location and Volume Categories and Example Tumors



Pts (2011-2018)	217 (Stanford/Hokkaido)

FFLR 1 yr	**97%**	**94%**	**96%**
FFLR 2 yr	**90%**	**92%**	**94%**

LA - NSCLC

LA - NSCLC

- **PACIFIC Trial**

- Unresectable, Stage III NSCLC without progression after definitive platinum-based cCRT (≥2 cycles)
- 18 years or older
- WHO PS score 0 or 1
- If available, archived pre-cCRT tumor tissue for PD-L1 testing*

All-comers population (i.e. irrespective of PD-L1 status)

N=713 randomized

1–42 days post-cCRT

R

2:1 randomization, stratified by age, sex, and smoking history

Durvalumab 10 mg/kg q2w for up to 12 months N=476

Placebo 10 mg/kg q2w for up to 12 months N=237

Primary endpoints

- PFS by BICR using RECIST v1.1†
- OS

Key secondary endpoints

- ORR, DoR and TTDM by BICR
- PFS2 by investigator
- Safety
- PROs

BICR, blinded independent central review; cCRT, concurrent chemoradiotherapy; DoR, duration of response; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; PFS2, time to second objective disease progression; PRO, patient-reported outcome; q2w, once every 2 weeks; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; TTDM, time to death or distant metastasis; WHO PS, World Health Organization performance status

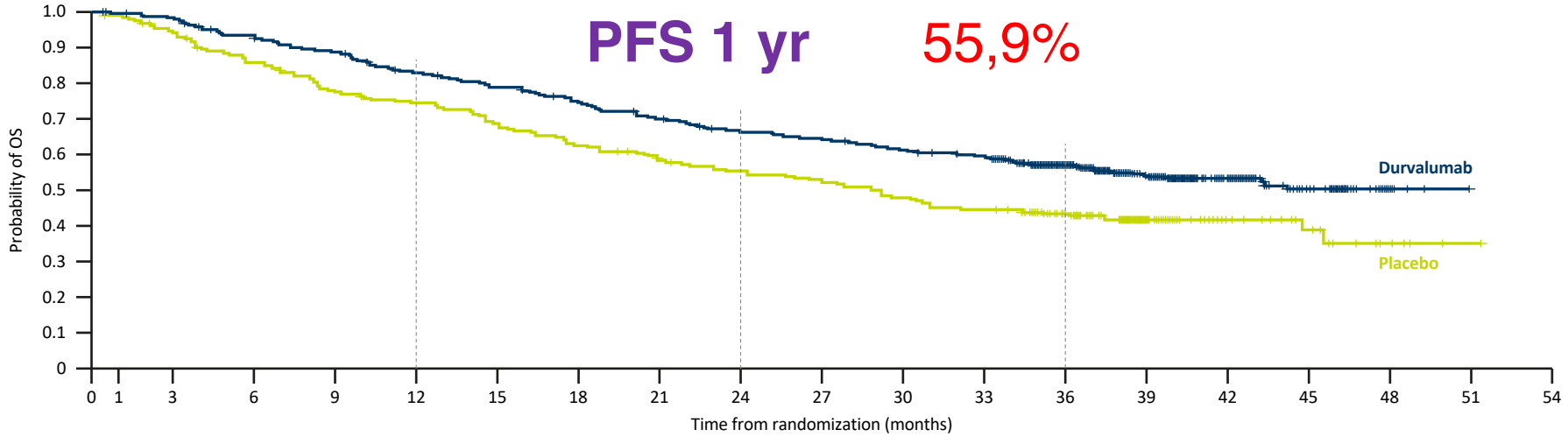
*Using the Ventana SP263 immunohistochemistry assay.

[illegible] progression or death by any cause in

1. Antonia SJ, et al. N Engl J Med. 2017;377:1919–29
2. Antonia SJ, et al. N Engl J Med. 2018;379:2342–50

Updated OS in the ITT population

	No. of events/ total no. of patients (%)	Median OS (95% CI) months	12-month OS rate (95% CI) %	24-month OS rate (95% CI) %	36-month OS rate (95% CI) %
Durvalumab	210/476 (44.1)	NR (38.4–NR)	83.1 (79.4–86.2)	66.3 (61.8–70.4)	57.0 (52.3–61.4)
Placebo	134/237 (56.5)	29.1 (22.1–35.1)	74.6 (68.5–79.7)	55.3 (48.6–61.4)	43.5 (37.0–49.9)
Stratified hazard ratio for death, 0.69 (95% CI, 0.55–0.86) Stratified hazard ratio for death from the primary analysis,[9] 0.68 (95% CI, 0.53–0.87)					

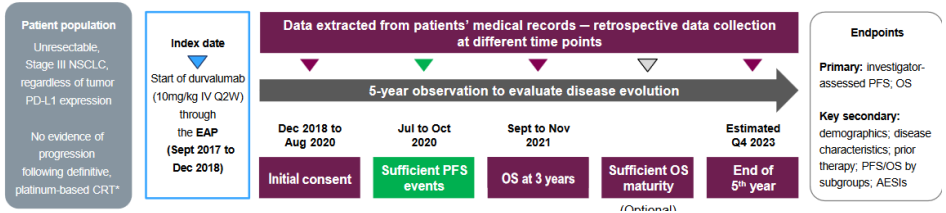


No. at risk

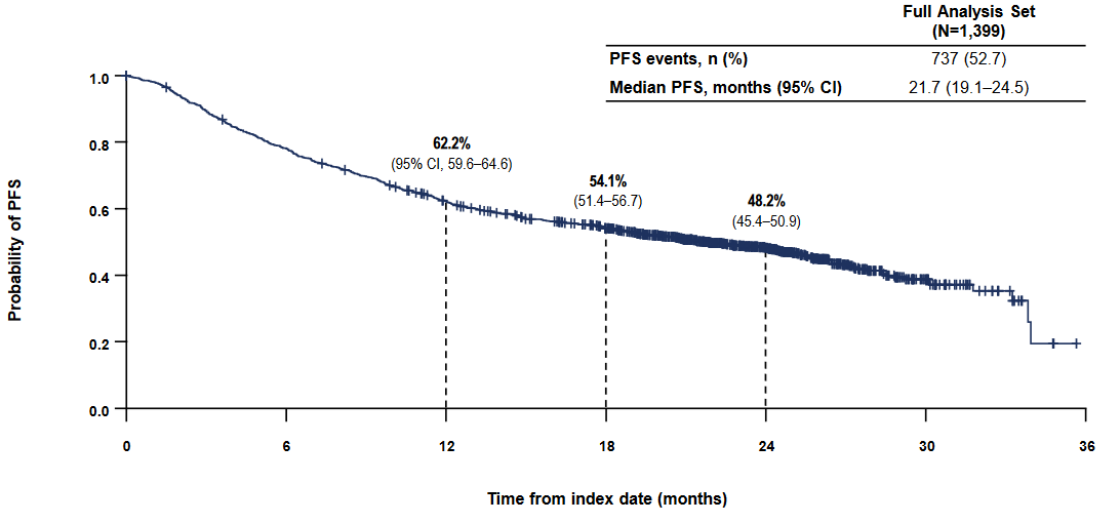
Durvalumab	476	464	431	415	385	364	343	319	298	289	274	263	205	132	73	33	7	0	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	79	49	25	13	5	1	0

Treatment Characteristics and Real-World Progression-Free Survival in Patients With Unresectable Stage III NSCLC Who Received Durvalumab After Chemoradiotherapy: Findings From the PACIFIC-R Study

Journal of Thoracic Oncology Vol. 18 No. 2: 181-193



- Pts: 1399/11 center
- Durva 11 m
- Median rwPFS 21.7 m
- Better: PD-L1 + and CCRT
- 17% Interruption x Tox (10 % Lung)



• PACIFIC Trial

- Unresectable, Stage III NSCLC without progression after definitive platinum-based cCRT (≥2 cycles)
- 18 years or older
- WHO PS score 0 or 1
- If available, archived pre-cCRT tumor tissue for PD-L1 testing*

All-comers population (i.e. irrespective of PD-L1 status)

N=713 randomized

1–42 days post-cCRT

R

Durvalumab 10 mg/kg q2w for up to 12 months N=476

2:1 randomization, stratified by age, sex, and smoking history

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*Using the Ventana SP263 immunohistochemistry assay.

†Investigator assessment per RECIST v1.1 of the date of objective disease progression or death by any cause in patients without progression.

1. Antonia SJ, et al. N Engl J Med. 2017;377:1919–29
2. Antonia SJ, et al. N Engl J Med. 2018;379:2342–50

• PACIFIC 2 Trial

- Unresectable, Stage III NSCLC
- 18 years or older
- WHO PS score 0 or 1
- If available, archived tumor tissue for PD-L1

All-comers population (i.e. irrespective of PD-L1 status)

N=328 randomized

CTRT
Durvalumab
10 mg/kg q2w
Until progression

CTRT
Placebo
10 mg/kg q2w

The PACIFIC-2 Phase III trial for *Imfinzi* (durvalumab) concurrently administered with chemoradiotherapy (CRT) did not achieve statistical significance for the primary endpoint of progression-free survival (PFS) versus CRT alone for the treatment of patients with unresectable, Stage III non-small cell lung cancer (NSCLC).[1]

Primary endpoints

- PFS by BICR using RECIST v1.1†
- OS

ndary endpoints

oR and TTDM by BICR

- PFS2 by investigator
- Safety
- PROs

BICR, blinded independent central review; cCRT, concurrent chemoradiotherapy; DoR, duration of response; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; PFS2, time to second objective disease progression; PRO, patient-reported outcome; q2w, once every 2 weeks; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; TTDM, time to death or distant metastasis; WHO PS, World Health Organization performance status

*Using the Ventana SP263 immunohistochemistry assay.

†Confirmed progression per RECIST v1.1 or death by any cause in

1. Antonia SJ, et al. N Engl J Med. 2017;377:1919–29
2. Antonia SJ, et al. N Engl J Med. 2018;379:2342–50

PACIFIC ON GOING

PACIFIC-5	Phase III trial is a randomised, double-blind, placebocontrolled, multi-centre, international study assessing the efficacy and safety of durvalumab compared with placebo, as consolidation therapy in patients with unresectable Stage III NSCLC, who have not progressed following chemoradiotherapy (CRT). This is an ex-US study with a focus on patients in China
PACIFIC-8	Phase III trial is a randomised, double-blind, placebocontrolled, multi-centre, international study assessing the efficacy and safety of durvalumab and domvanalimab versus durvalumab and placebo in patients with locally advanced, unresectable NSCLC whose disease has not progressed following CRT
PACIFIC-9	Phase III trial is a randomised, double-blind, placebocontrolled, multi-centre, international study assessing the efficacy and safety of durvalumab with oleclumab or durvalumab and monalizumab in patients with locally advanced, unresectable NSCLC whose disease has not progressed following CRT

LA-NSCLC

- RT + IO without CT
  - No CT:
    - Poor PS, Comorbities, Age…
    - 20% Interruption
    - CT Immunodepressive
    - Difficulties for concomitant treatments

LA-NSCLC

RT + IO without CT: Phase II Trials

- SPIRAL-RT PFS 1 yr
- DOLPHIN PFS 1 yr
- DUART PFS 1 yr

PACIFIC CCRT PFS 1 yr 55,9%

SPIRAL RT

Original Research

A phase 2 trial of durvalumab treatment following radiation monotherapy in patients with non-small cell lung cancer ineligible for stage III chemoradiotherapy: The SPIRAL-RT study

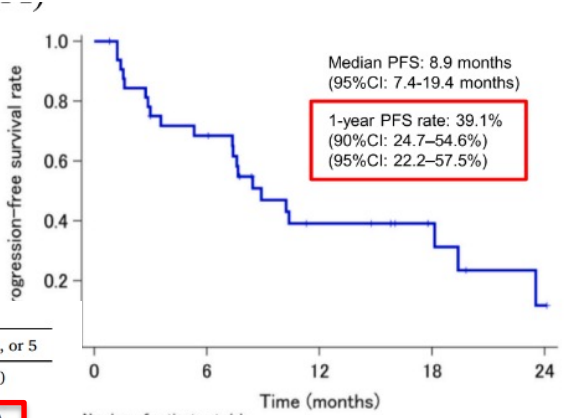
European Journal of Cancer 195 (2023) 113373

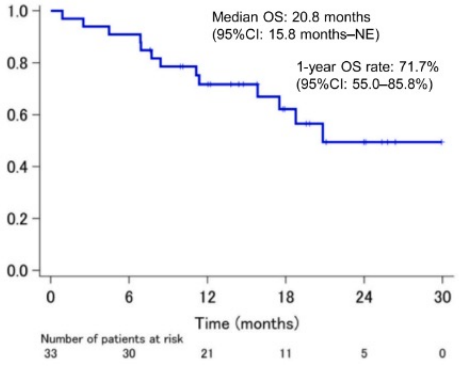
Tadaaki Yamada [a], Yasuhiro Goto [b], Hiroshi Tanaka [c], Hideharu Kimura [d], Koichi Minato [e],

Pts (2019-2021)	33 (8 Japanese Institute)
Median Age	79
Median OS	20,9 m
Gr 5 Tox	1 (1 Lung Infection)

Adverse events of any cause.

Event	Any grade[a]	Grade 3, 4, or 5
Any event	29 (87.9%)	13 (39.4%)
Radiation pneumonitis	17[b] (51.5%)	0
Lung infection	7 (21.2%)	4[c] (12.1%)
Decreased appetite	5 (15.2%)	1 (3.1%)
Pharyngitis	5 (15.2%)	0
Hypothyroidism	5 (15.2%)	0
Diarrhoea	5 (15.2%)	0
Constipation	3 (9.1%)	0
Neuralgia	3 (9.1%)	0
Infusion site extravasation	3 (9.1%)	0
Platelet count decreased	3 (9.1%)	1 (3.1%)
Fatigue	2 (6.1%)	0
Thrush	2 (6.1%)	0
Periodontal disease	2 (6.1%)	0
Hepatobiliary disorders	2 (6.1%)	1 (3.1%)
Pneumothorax	2 (6.1%)	1 (3.1%)
Chronic obstructive pulmonary disease	2 (6.1%)	1 (3.1%)
Erythema multiforme	2 (6.1%)	0
Eczema	2 (6.1%)	0
Rash maculopapular	2 (6.1%)	0
Hyperglycaemia	2 (6.1%)	0





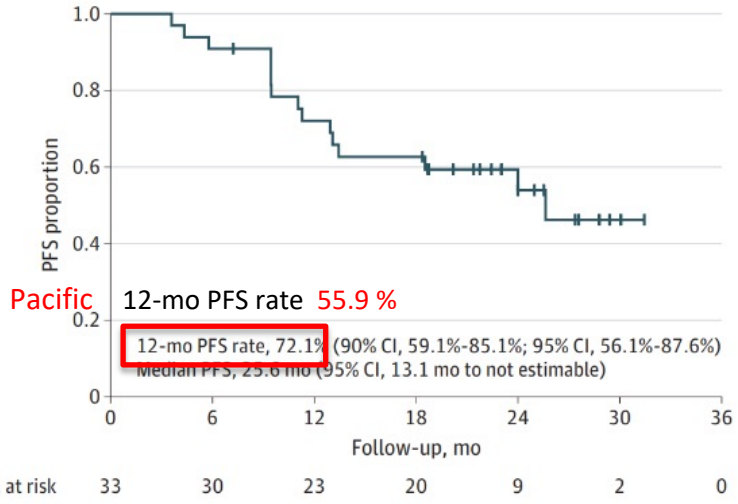
DOLPHIN

JAMA Oncology | Original Investigation

Durvalumab Plus Concurrent Radiotherapy for Treatment of Locally Advanced Non–Small Cell Lung Cancer
The DOLPHIN Phase 2 Nonrandomized Controlled Trial

JAMA Oncol. 2023;9(11):1505-1513. doi:10.1001/jamaoncol.2023.3309

Pts (2019-2022)	35 (12 Japanese Institute)
ECOG 1/2	19/16
Gr 5 Tox	2 (1 BE fistula)



Pacific 12-mo PFS rate 55.9 %

- Older patients
- Local relapses (low volume GTV)

DOLPHIN

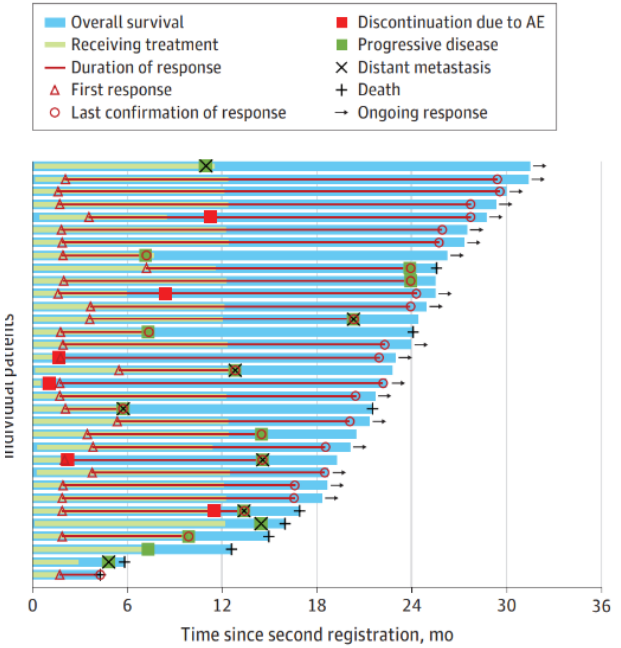
JAMA Oncology | Original Investigation

Durvalumab Plus Concurrent Radiotherapy for Treatment of Locally Advanced Non–Small Cell Lung Cancer

The DOLPHIN Phase 2 Nonrandomized Controlled Trial

JAMA Oncol. 2023;9(11):1505-1513. doi:10.1001/jamaoncol.2023.3309

AE	Participants, No. (%)
Any grade AEs	34 (100)
Grade 3 or 4	18 (52.9)
Grade 5	2 (5.9)
Leading to discontinuation of protocol treatment	6 (17.6)
Leading to discontinuation of durvalumab	7 (20.6)
Leading to discontinuation of radiotherapy	1 (2.9)
Any grade study drug-related AE	31 (91.2)
Grade 3 or 4	10 (29.4)
Grade 5	1 (2.9)
AEs of special interest	25 (73.5)
Grade 3 or 4	6 (17.6)
Grade 5	0
Corticosteroid required	7 (20.6)
Pneumonitis or radiation pneumonitis	23 (67.6)
Grade 3 or 4	4 (11.8)
Grade 5	0
Leading to discontinuation of durvalumab	3 (8.8)
Leading to discontinuation of radiotherapy	1 (2.9)



DUART

MADRID 2023 ESMO congress

Durvalumab after Radiotherapy in Patients with Unresectable Stage III NSCLC Ineligible for Chemotherapy

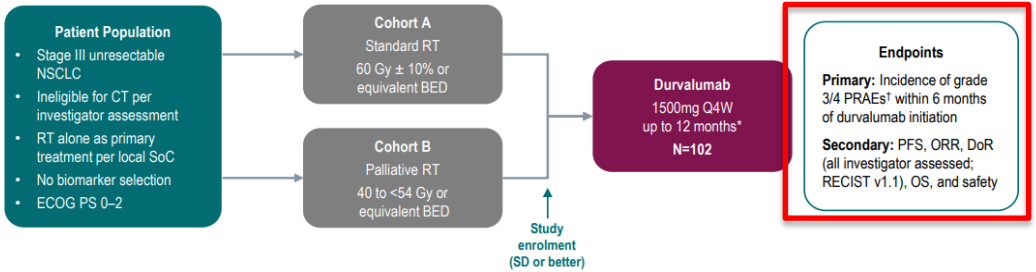
Primary Results from the DUART Study

Andrea R. Filippi,[1] Maria Rosario García Campelo,[2] Jean-Baptiste Paoli,[3] Dariusz Kowalski,[4] Chiara Bennati,[5] Paolo Borghetti,[6] Diego Cortinovis,[7] Angelo Delmonte,[8] Carlo Genova,[9] Sylvie Van Hulst,[10] Robert Mroz,[11] Sergiusz Nawrocki,[12] Ivan Toledano,[13] Giuseppe Tonini,[14] Ignacio Diaz Perez,[15] Nefeli Georgoulia,[15] Kayhan Foroutanpour,[15] Rafał Dziadziuszko[16]

Reason for ineligibility	Rate
Vascular	77
Metabolic	54
Respiratory	54
Cardiac	52

DUART Study Design

A phase 2, open-label, multicentre, international study



Characteristic		Cohort A (standard RT; n=59)	Cohort B (palliative RT; n=43)	Total (N=102)
Age	Median (range), years	78.0 (43–87)	80.0 (56–87)	79.0 (43–87)
	≥75 years, %	59.3	72.1	64.7
Sex, %	Male	69.5	74.4	71.6
	Female	30.5	25.6	28.4
Race, %*	White	94.5	95.0	94.7
	Other	1.8	0	1.1
	Unknown	3.6	5.0	4.2
ECOG PS, %*	0	27.6	7.0	18.8
	1	70.7	76.7	73.3
	2	1.7	16.3	7.9
Disease stage, %†	IIIA	61.0	60.5	60.8
	IIIB	33.9	30.2	32.4
	IIIC	5.1	7.0	5.9
PD-L1 expression, %*	TC <1%	44.2	45.2	44.6
	TC ≥1%	53.5	48.4	51.4
Smoking status, %	Current	23.7	16.3	20.6
	Former	64.4	72.1	67.6
	Never	11.9	11.6	11.8

	All-cause AEs			PRAEs*		
	Cohort A (standard RT; n=59)	Cohort B (palliative RT; n=43)	Total (N=102)	Cohort A (standard RT; n=59)	Cohort B (palliative RT; n=43)	Total (N=102)
Any AE, n (%)	56 (94.9)	43 (100)	99 (97.1)	40 (67.8)	21 (48.8)	61 (59.8)
Grade 3/4	25 (42.4)	15 (34.9)	40 (39.2)	9 (15.3)	3 (7.0)	12 (11.8)
Within 6 months	—	—	—	7 (11.9)	3 (7.0)	10 (9.8)
SAE	25 (42.4)	13 (30.2)	38 (37.3)	7 (11.9)	2 (4.7)	9 (8.8)
Outcome of death‡	5 (8.5)	2 (4.7)	7 (6.9)	1 (1.7)	0	1 (1.0)
Leading to Tx discontinuation	11 (18.6)	7 (16.3)	18 (17.6)	7 (11.9)	3 (7.0)	10 (9.8)
Leading to Tx interruption	31 (52.5)	17 (39.5)	48 (47.1)	8 (13.6)	5 (11.6)	13 (12.7)
AESI	26 (44.1)	15 (34.9)	41 (40.2)	21 (35.6)	9 (20.9)	30 (29.4)
imAE	23 (39.0)	13 (30.2)	36 (35.3)	22 (37.3)	12 (27.9)	34 (33.3)

MADRID 2023 ESMO congress

AE, adverse event; AESI, adverse event of special interest; CI, confidence interval; imAE, immune-mediated adverse event; PRAE, adverse event possibly related to treatment; SAE, serious adverse event; Tx, treatment

*PRAE is alternative nomenclature for a treatment-related AE and is used here to align with the case report form used to collect investigators' responses.
†CI calculated using the Clopper-Pearson method.
‡PRAE with outcome of death was pneumonitis (n=1) in Cohort A.

DUART

MADRID 2023 ESMO congress

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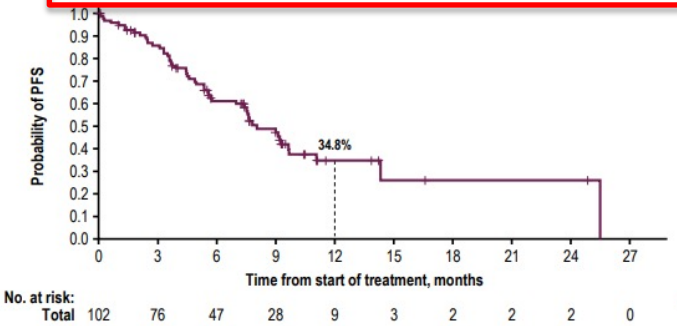
PFS

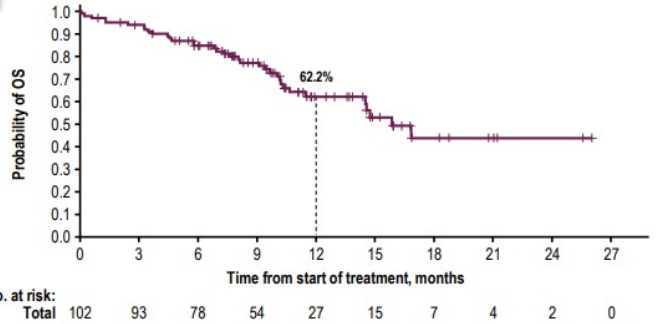
	Cohort A (standard RT)	Cohort B (palliative RT)	Total
No. events / no. patients (%)	26/59 (44.1)	25/43 (58.1)	51/102 (50.0)
Median PFS (95% CI)*, months	9.0 (5.6–NC)	7.6 (5.3–11.0)	8.0 (7.0–9.7)
12-month PFS rate (95% CI)†, %	40.2 (23.6–56.3)	29.3 (13.8–46.7)	34.8 (23.0–46.9)



Median follow-up (range) for patients censored for PFS: 7.4 months (0.0–24.9).

OS

	Cohort A (standard RT)	Cohort B (palliative RT)	Total
No. events / no. patients (%)	16/59 (27.1)	19/43 (44.2)	35/102 (34.3)
Median OS (95% CI)*, months	NC (14.5–NC)	14.8 (10.1–NC)	15.9 (11.5–NC)
12-month OS rate (95% CI)†, %	67.0 (50.1–79.2)	56.3 (37.3–71.6)	62.2 (49.8–72.4)



Median follow-up (range) for patients censored for OS: 9.9 months (0.9–26.0).

frontiers | Frontiers in Immunology

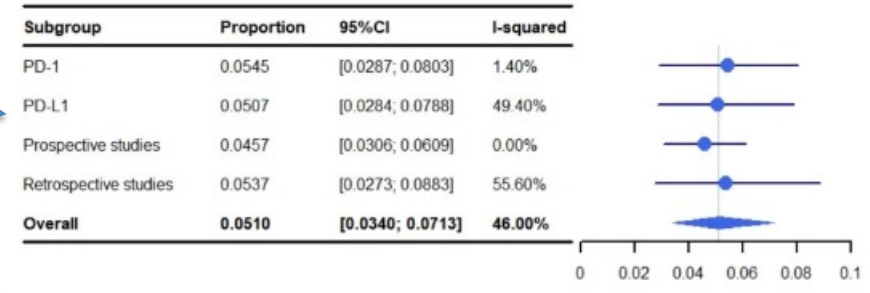
TYPE Systematic Review
PUBLISHED 13 March 2023
DOI 10.3389/fimmu.2023.1065510

Safety and efficacy of radiotherapy/chemoradiotherapy combined with immune checkpoint inhibitors for non-small cell lung cancer: A systematic review and meta-analysis

- Cardiotox < 5%
- Gr 3 Lungtox 5,82%
- SBRT better than CT-RT

TABLE 2 Non-small cell lung cancer patient survival following treatment with ICIs and RT.

	Stage II-III NSCLC	Stage IV NSCLC
1-year PFS	56.39% (95% CI: 50.66%-62.03%, I^2:39.4%)	—
2-year PFS	43.58%-45%	—
3-year PFS	39.7%	—
4-year PFS	35.0%	—
5-year PFS	33.1%	—
1-year OS	83.25% (95% CI: 79.42%-86.75%, I^2:17.6%)	50%
2-year OS	66.16% (95% CI: 62.30%-69.92%, I^2:0.0%)	25%
3-year OS	56.7%	—
4-year OS	49.7%	—
5-year OS	42.9%	—



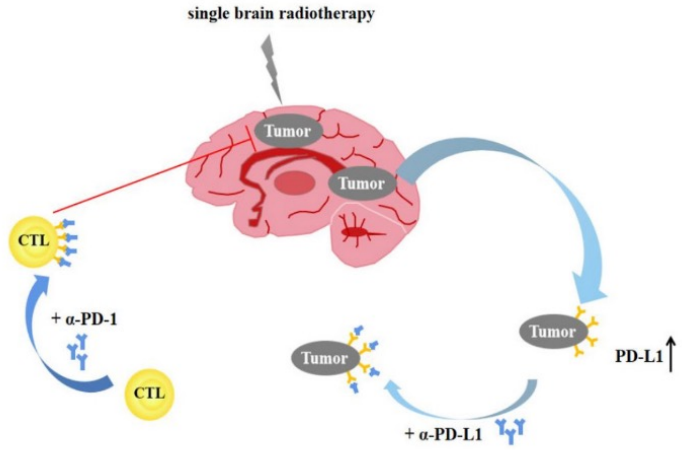
Received: 4 March 2022 | Revised: 10 June 2022 | Accepted: 29 June 2022
DOI: 10.1002/cam4.5016

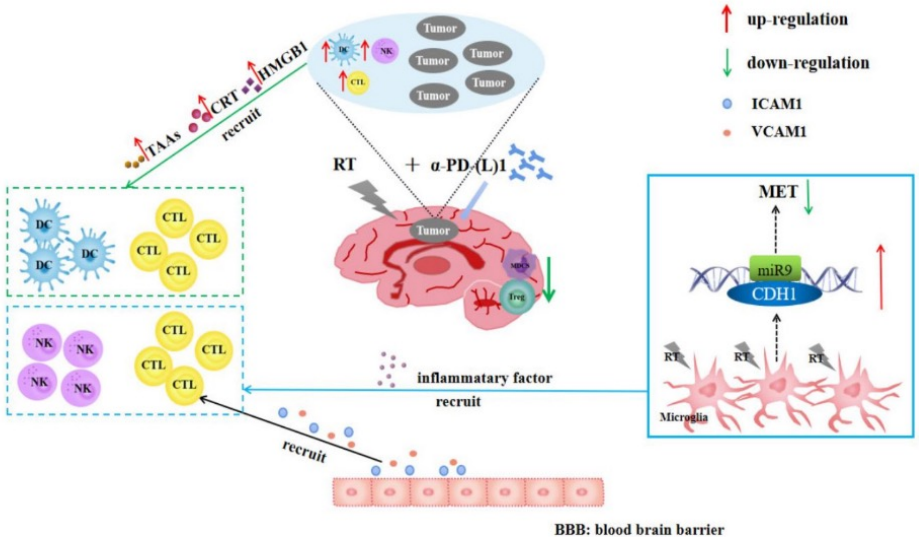
REVIEW

Cancer Medicine WILEY

Radiotherapy combined with PD-1/PD-L1 inhibitors in NSCLC brain metastases treatment: The mechanisms, advances, opportunities, and challenges

Brain SRS + IO





Received: 4 March 2022 | Revised: 10 June 2022 | Accepted: 29 June 2022
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REVIEW

Cancer Medicine WILEY

Radiotherapy combined with PD-1/PD-L1 inhibitors in NSCLC brain metastases treatment: The mechanisms, advances, opportunities, and challenges

Brain SRS + IO

TABLE 1 Advances in synergistic effects of radiotherapy and PD-1/PD-L1 inhibitors for NSCLC BMs treatment

Author (year)	Number of cases	Means of intervention	Radiotherapy plan	Immunotherapy plan	Outcome
Patruni et al (2019)[25]	13,998	RT + IO (545) vs. RT (13,545)	/	/	Median OS:13.1 vs. 9.7 months 3-year OS: 17% vs. 12%
Shaverdian et al (2017)[26]	97	Extracranial RT + IO (38) vs. IO (59)	/	Pembrolizumab (2 mg/kg or 10 mg/kg, q3w, iv; or 10 mg/kg, q2w, po)	Median PFS: 6.3 months vs. 2.0 months; 6-month PFS: 54% vs. 21%
Ahmed et al (2017)[27]	17	RT + IO	SRS or FSRT, 18–24 Gy/F or 25 Gy/5F	Nivolumab or Durvalumab	OS KM rates (6/12 months): 48%/81% (from the date of SRS); 81%/51% (from the date of cranial metastases diagnosis)
Chen et al (2018)[28]	260 (157 NSCLC)	SRS/SRT (181) vs. non-concurrent SRS/SRT + IO (51) vs. concurrent SRS/SRT + IO (28)	SRS/SRT, 15–24 Gy/1F, 18–24 Gy/3F or 25 Gy/5F	Ipilimumab, Nivolumab, or Pembrolizumab	Median OS: 12.9 months (SRS/SRT) vs. 14.5 months (non-concurrent SRS/SRT + IO) vs. 24.7 months (concurrent SRS/SRT + IO)
Pike et al (2017)[29]	85 (39 NSCLC)	SRS/WBRT + IO	WBRT (12–39 Gy)/SRS (15–30 Gy)	Pembrolizumab, Nivolumab or both (3 mg/kg)	Median OS: 192 days

TABLE 2 The optimal timing for radiotherapy combined with ICIs

Author (year)	Number of cases	Intervention time	Radiotherapy plan	Immunotherapy plan	Outcome
Li et al (2020)[30]	13	Concurrent RT + IO (SRS within 7 days of IO)	SRS	(Nivolumab, 3 mg/kg, q2w + Ipilimumab, 1 mg/kg, q6w) × 4 cycles + Nivolumab, 450 mg, q4w.	Intracranial mPFS: 9.7 months; 4-month PFS rate: 75% Extracranial ORR: 33%
Porte et al (2021)[31]	51	"SRT before IO" vs. "concurrent SRT + IO" (IO within 1 month of SRT) vs. "SRT after IO"	SRT (15–21 Gy/F, 56.0% or 18–27 Gy/3F, 41.8%)	Nivolumab (47.1%), Pembrolizumab (33.3%), Durvalumab (15.7%), or Atezolizumab (3.9%) (for a median duration of 4.9 months)	1 year R-PFI: 24.1% vs. 49.6% vs. 34.2%; 1 year OS: 67.5% vs. 70.2% vs. 69.2%; 1-year L-PFI: 70.1% vs. 78.9% vs. 77.8%
Srivastava et al (2017)[14]	50 (24 NSCLC)	RT + adjuvant IO (applying PD-1 inhibitors more than 3 weeks after SRS) (23) vs. Concurrent RT + IO (applying PD-1 inhibitors at or <3 weeks before SRS) (27)	SRS	Nivolumab/Pembrolizumab	6-month LC (76% vs. 100%) 6-month DBC (41% vs. 71%)
Imber et al (2017)[36]	45	Sequential IO + brain RT (RT >2 months after last IO) (36%) vs. Concurrent brain RT + IO (64%)	SRS (2100 cGy)/hRT (3000 cGy/5F)	Anti PD-(L)1	Median DBF:4.9 months vs. 3.9 months

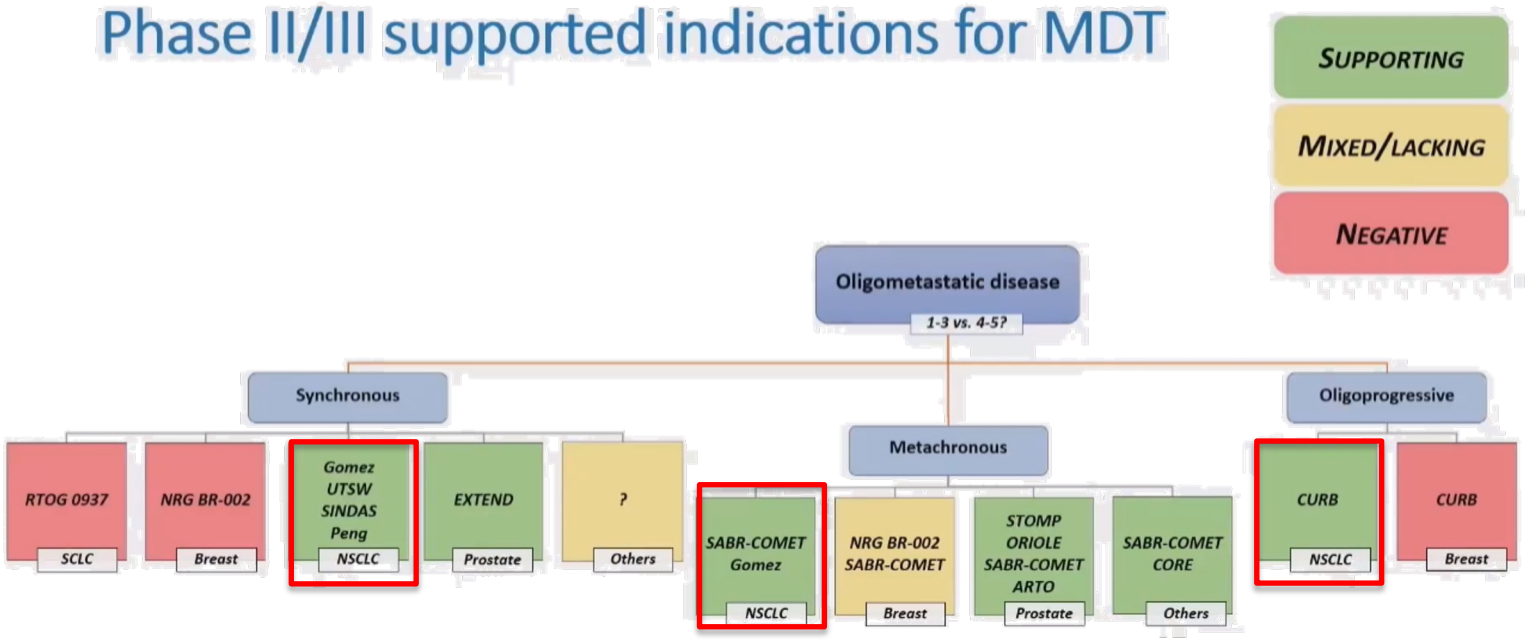
Oligomets + RT

Two Possible Ways to Define "Oligometastatic"

1. Cancers are oligometastatic when **there is a chance of cure**
   - We don't have a clear definition of cure for many cancers
   - Likely a decreasing probability of cure with increasing number of mets

2. Cancers are oligometastatic when **patients benefit from ablative treatment**
   - Might be no upper limit – patients might benefit with 15 lesions, and that is clearly not 'oligo'

Oligomets + RT



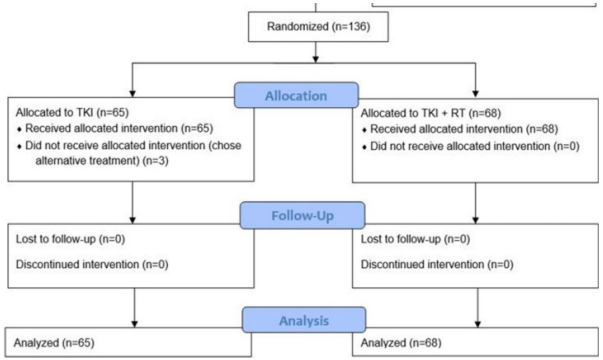
Oligomets + RT

OXFORD

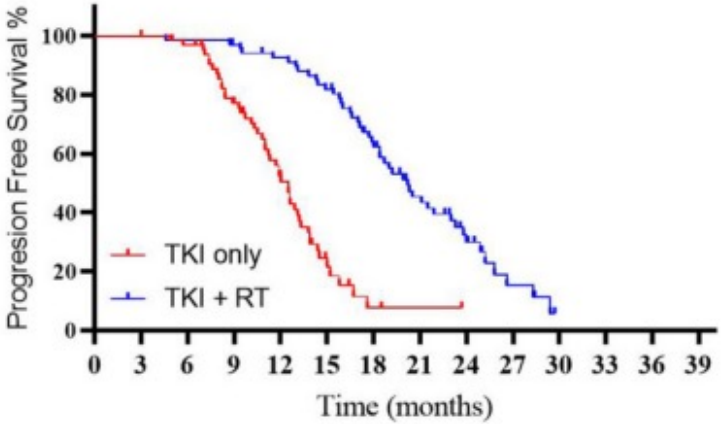
JNCI: Journal of the National Cancer Institute, 2023, 115(6), 742–748
https://doi.org/10.1093/jnci/djac015
Advance Access Publication Date: 30 January 2022
Article

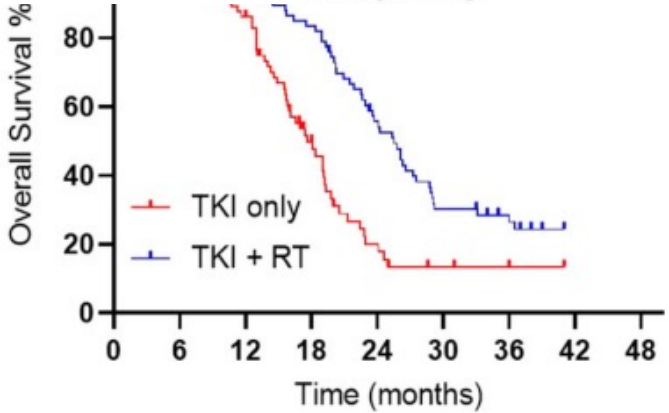
Randomized Trial of First-Line Tyrosine Kinase Inhibitor With or Without Radiotherapy for Synchronous Oligometastatic *EGFR*-Mutated Non-Small Cell Lung Cancer

Xiao-Shan Wang, MD,[1,†] Yi-Feng Bai, MD,[1,†] Vivek Verma, MD,[2] Rui-Lian Yu, MD,[1] Wei Tian, MS,[1] Rui Ao, MD,[1] Ying Deng, MD,[1]



	TKI	SABR + TKI
PFS m	12,5	20,2
OS m	17,4	25,5





Oligomets + RT

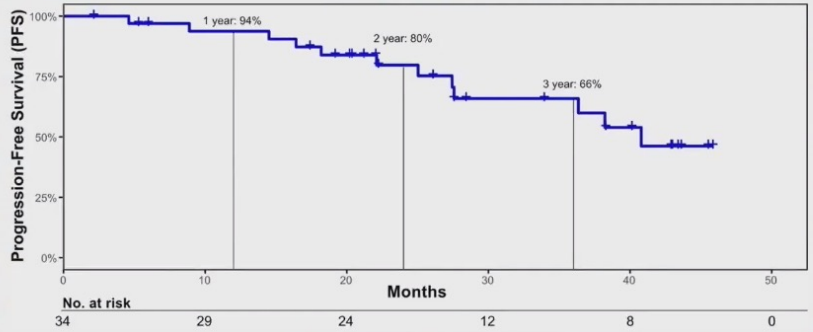
OA22.04

BRIGHTSTAR Local Consolidative Therapy with Brigatinib in Tyrosine Kinase Inhibitor-Naïve ALK-Rearranged Metastatic NSCLC

Y. Elamin,[1] S. Gandhi,[2] M. Saad,[2] S. Rehmani,[2] M.B. Antonoff,[2]

Journal of Thoracic Oncology Vol. 18 No. 11S

BRIGHTSTAR – Progression Free Survival



PFS Rate	BrightStar	ALTA 1L* (first line single agent brigatinib)
1-yr	94%	80%
2-yr	76%	56%
3-yr	66%	47%

Elamin et al. WCLC 2023

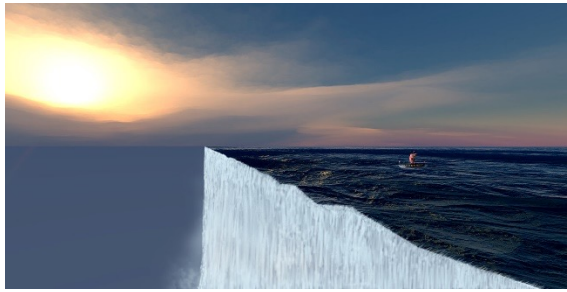
Oligomets + RT

IASLC
CONTROVERSIES IN THORACIC ONCOLOGY

Local Treatments of Oligometastatic and Oligoprogressive NSCLC Should Not Become the Standard of Care

Fergus Macbeth, DM,[a] Tom Treasure, MD[b,*]

- Ashworth : Metanalysis of 45 studies: «no control data»
- No III ph Trials (Iyengar/Gomez early closed)
  - Not correct PFS as surrogate
  - OS : not reported or late reported (95% CI overlap)
- Lim: III phase Trial (up to 4 brain mets) : No diff in OS
- 2 small II ph Trials in CCMet
  - CCLOC (imbalanced arms)
  - SABR-COMET (OS advantage not significant imbalanced arms)



Oligomets + RT

CONTROVERSIES IN THORACIC ONCOLOGY

IASLC

Check for updates

Local Treatments of Oligometastatic and Oligoprogressive NSCLC Should Become the Standard of Care

Gregory M. M. Videtic, MDCM, FRCPC, FACR, FASTRO*

- No III ph Trials (Iyengar/Gomez early closed)
- But..Gomez : Systemic vs Systemic + Local therapy

PFS	4.4 m	vs	14.2 m
OS	17.2 m	vs	41.1 m

- SABR-COMET(18p) Palliative vs Palliative + Local therapy

5 yr OS	17.7 %	vs	42,3 % (p<0.006)

In OMD, LC by SABR/S reduces deaths and prevents the risk of new mets

www.thelancet.com/oncology Vol 22 August 2021

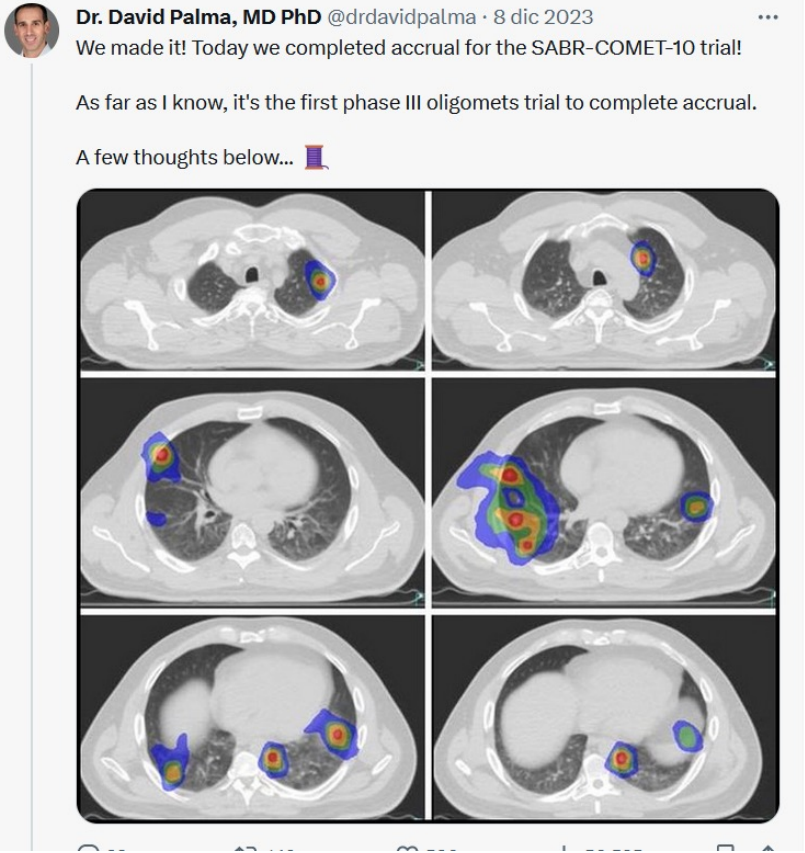
Spotlight

Should stereotactic radiotherapy be the preferred treatment for oligometastatic disease?

Opening opinion: Yes

*David Palma, Alison Tree

- No surgery advantages in OMD III Phase Trial
- Excellent Local Control
- Low Toxicity
- No interruption systemic treatment
- Contemporary treatment of multiple lesions



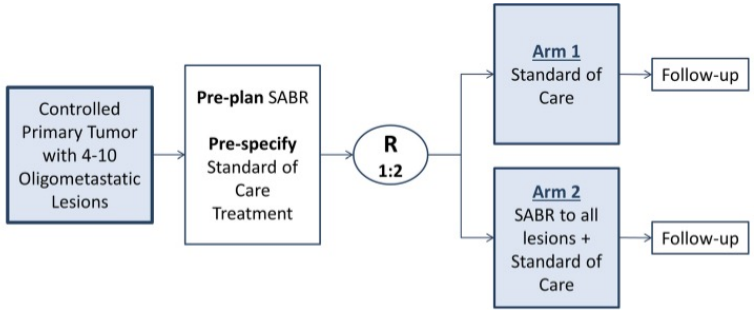
Stereotactic ablative radiotherapy for the comprehensive treatment of 4–10 oligometastatic tumors (SABR-COMET-10): study protocol for a randomized phase III trial

Palma *et al. BMC Cancer* (2019) 19:816
https://doi.org/10.1186/s12885-019-5977-6

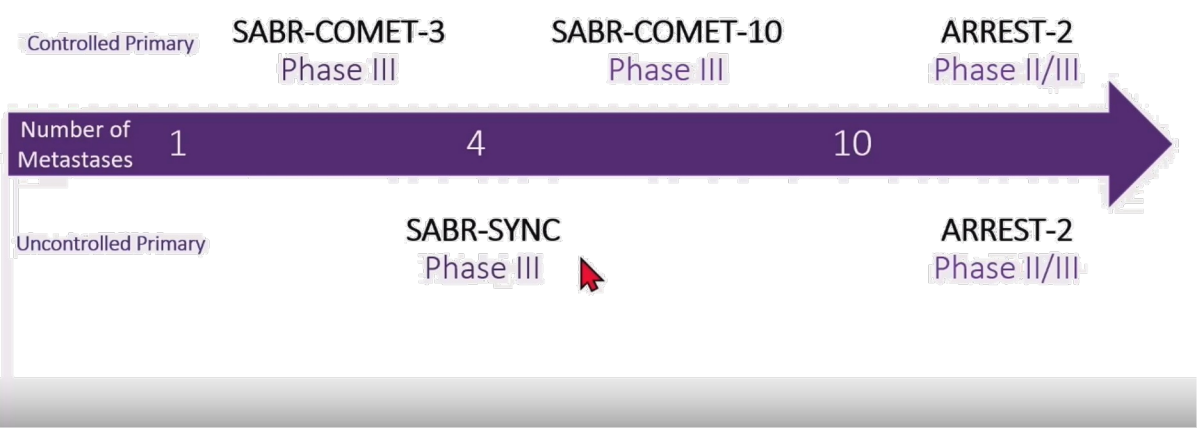
David A. Palma, Robert Olson, Stephen Harrow, Rohann J. M. Correa, Famke Schneiders, Cornelis J. A.

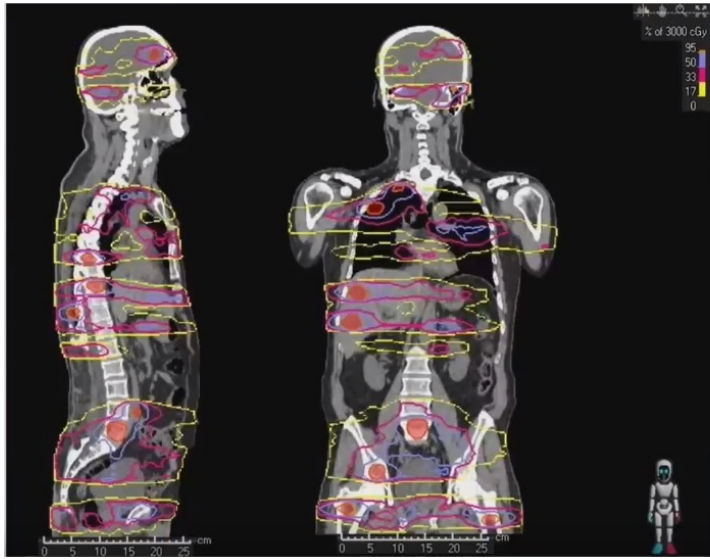
195 pts
Stratification :
Histology
Systemic Therapy

SABR:20/1,30/3,35/5
Pr. EP: OS
Sec.EP: PFS,QoL, Tox



Looking Ahead: Phase III Data Coming





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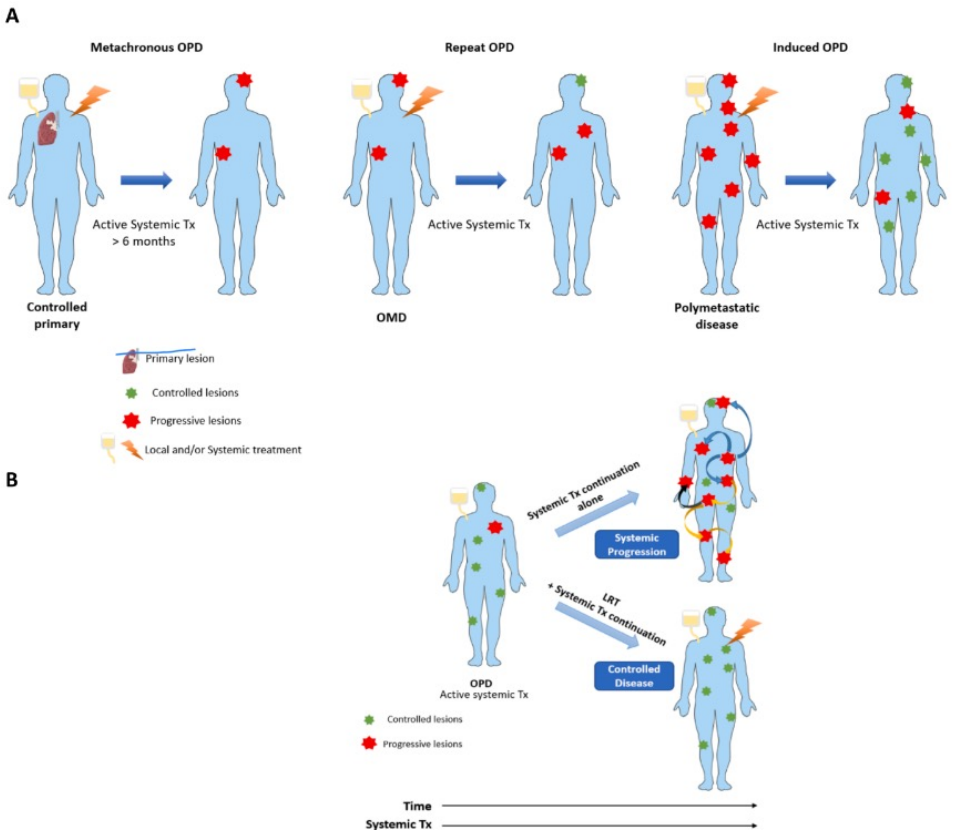
Anti-tumour Treatment

Local control strategies for management of NSCLC with oligoprogressive disease

Cancer Treatment Reviews 120 (2023) 102621

Antoine Mavrikios [a], Jordi Remon [b], Clément Ouevrin [c], Olaf Mercier [d,e], Lambros Tselikas [d,f].



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Anti-tumour Treatment

Local control strategies for management of NSCLC with oligoprogressive disease

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Antoine Mavrikios[a], Jordi Remon[b], Clément Ouevrin[c], Olaf Mercier[d,e], Lambros Tselikas[d,f].

Table 1
LRT strategies for NSCLC with OPD receiving ICB.

Trial	Design	N NSCLC	MUT+	N OPD	Brain mets	mFU	Drug	Type of LRT	mPFS2	mOS	% ≥ G3 AE
Selected Retrospective											
Schoenfeld et al. [10]		57	0/57	≤ 3	Yes	16	Anti-PD(L)1 ICB	XRT, Surgery, RE	NA	NA	NA
Wang et al. [31]		24	7/24: 4 KRASm, 3 EGFRm	≤ 2	Yes	28	Anti-PD(L)1 ICB	SRT	11	34	8%
Mahmood et al. [32]		59/120	34/59: 29 KRASm, 4 EGFRm, 1 ALKm	≤ 5	Yes	16 (whole cohort)	ICB +/- Various Tx	SRT, XRT	6.4 (whole cohort)	29.8 (whole cohort)	0.8%
Prospective											
Chicas-Sett et al. [33]	Single arm phase 2	31/50	4/50	≤ 5	Yes	33 (whole cohort)	Anti-PD1 ICB	SRT	14.2* (whole cohort)	37.4 (whole cohort)	0%
CURB [35] [NCT03808662]	Randomized phase 2	59/102 (stopped, 160 planned)	8/59	≤ 5	No	52	Various	SRT	10.1 (SRT) vs 2.1	NA	0.9%
Ongoing											
STOP [NCT02756793]	Randomized phase 3	90	NA	≤ 5	Yes	NA	Various	SRT	NA	NA	NA
SUPPRESS-NSCLC [NCT04405401]	Randomized phase 2	68	NA	≤ 5	No	NA	Various ICB or TKI	SRT	NA	NA	NA

Table 2
LRT results in oncogene-addicted NSCLC with OPD receiving TKI.

Trial	Design	N NSCLC	MUT+	N OPD	Brain mets	mFU	Drug	Type of LRT	mPFS2	mOS	% ≥ G3 AE
Selected Retrospective											
Weickhardt et al. [36]		25	15 ALKm, 10 EGFRm	≤ 4	Yes	9	Crizotinib, Erlotinib	SRT, XRT, Surgery	6.2	NA	8%
Gan et al. [37]		14	ALKm	≤ 4	No	12	Crizotinib	SRT, HRT, Surgery	5.5	NA	0%
Hu et al. [38]		33	EGFRm	≤ 5	Yes	18	Erlotinib, Gefitinib, Icotinib	SRT, XRT	6.5	21.8	0%
Mok et al. [39]		55	EGFRm	≤ 5	Yes	13	Erlotinib, Gefitinib, Afatinib, Osimertinib	SRT	6.9	25.1	1.8%
Yu et al. [40]		18	EGFRm	< 5	No	NA	Erlotinib, Gefinitib	Surgery, XRT, RFA	10	41	NA
Hubbeling et al. [41]		61	37 ALKm, 12 ROS1, 12 RET	57/61 ≤ 5	Yes	28	Various TKI	XRT, Surgery, PTA	6.8	34	11%
Li et al. [42]		15	EGFRm	1	No	NA	Erlotinib, Gefitinib	PTA	8	23	0%
Prospective											
Weiss et al. [43]	Single arm phase 2	25 (stopped, 40 planned)	EGFRm	≤ 3	Yes	NA	Erlotinib	SRT	6	29	0%
Kim et al. [44] [NCT02759835]	Single arm phase 2	8 (ongoing)	EGFRm	≤ 5	Yes	NA	Osimertinib	XRT, Surgery	2.3	NA	NA
Ongoing											
LAT-FLOSI [NCT04216121]	Single arm phase 2	39	EGFRm	≤ 3	Yes	NA	Osimertinib	SRT	NA	NA	NA
HALT [NCT03256981]	Randomized phase 2–3	110	Mutated (Various)	≤ 3	No	NA	Various TKI	SRT	NA	NA	NA

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CANCER TREATMENT

STOP Ph2

Various Systemic Tx
≤ 5 intra- and extracranial OPD

N=90

SoC + SRT

SoC

PFS

SUPPRESS (Registry)

ICB or TKI
≤ 5 extracranial OPD

R

N=68

Continue ICB or TKI + SRT

SoC

PFS/OS

HALT Ph2/3

EORTC

TKI
≤ 3 extracranial OPD

R 2:1

N=110

Continue TKI + SRT

Continue TKI

PFS

LAT-FLOSI Ph2

1st line Osi
≤ 5 intra- and extracranial OPD

N=39

Continue Osi + SRT

PFS2

The Stereotactic Ablative Radiotherapy for Oligo-Progressive Cancers (STOP) Trial

Results from a Phase II, Multicentre, Randomized Trial

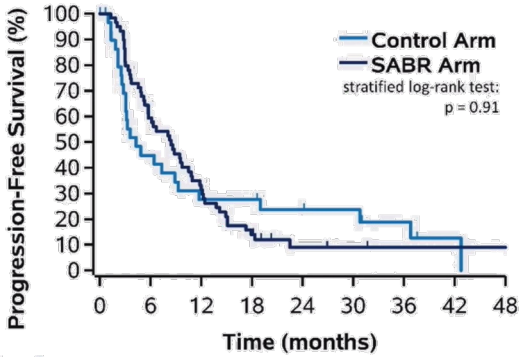
Results – Patient Demographics

- Mean age of 67
- 43% were Female
- 95% were ECOG 0/1
- 14% - cytotoxic chemo
- 27% immunotherapy

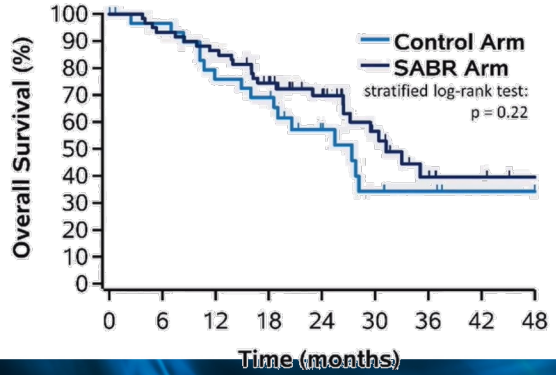
ASTRO - 2023

Characteristic	Control (31)	SABR (59)
Primary Histology (%)		
Lung	58	37
Breast	10	15
Gastrointestinal	13	10
GU Kidney	6	12
GU Prostate	6	12
...(others)		
Radiated Site (%)		
Lung	55	44
Bone	13	25
Liver	10	14
Adrenal	10	5
Lymphnode	13	22
Brain	0	3
Number of Progressing lesions (%)		
1	73	67
2	20	26
3	7	2
4	0	4
5	0	2

Progression Free Survival



Overall Survival



BC CANCER

UBC · UHN Princess Margaret Cancer Centre · CAPRI

The Stereotactic Ablative Radiotherapy for Oligo-Progressive Cancers (STOP) Trial

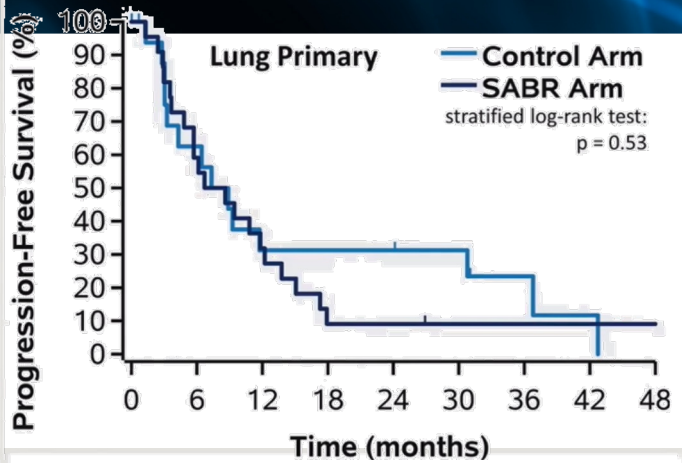
Results from a Phase II, Multicentre, Randomized Trial

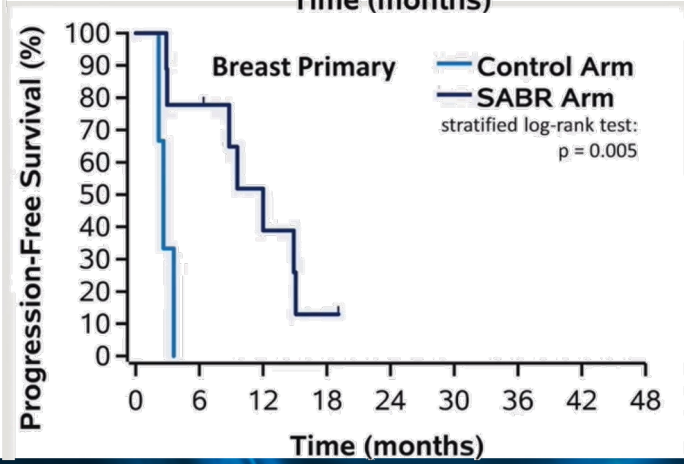
Every time you present a subgroup analysis

ASTRO – 2023
Devin Schellenberg
BC Cancer

Justin Bieber writes a new song

So you want to do this cautiously and interpret these results carefully.

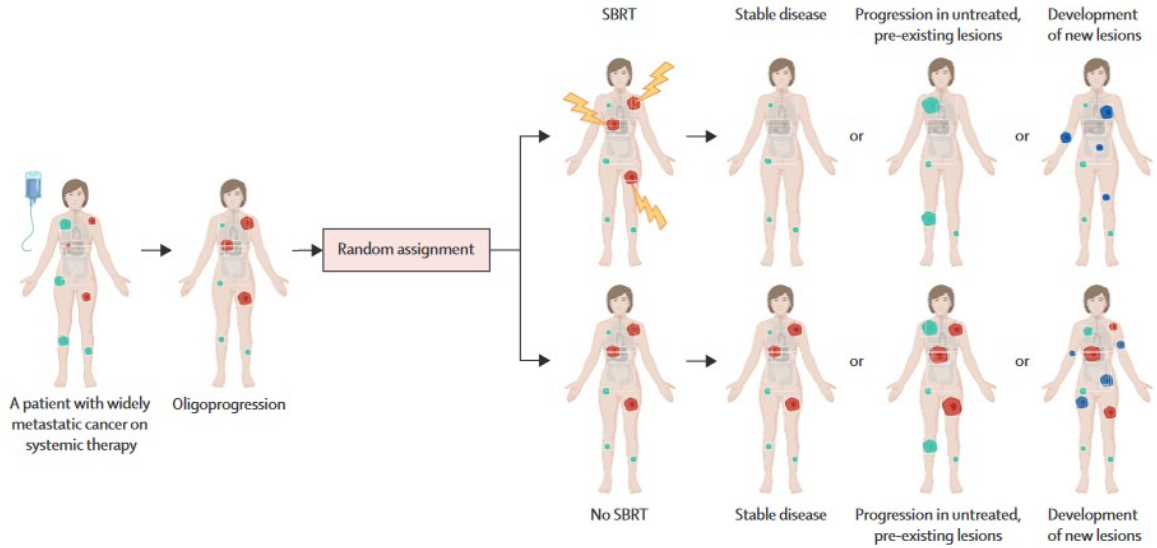




Standard-of-care systemic therapy with or without stereotactic body radiotherapy in patients with oligoprogressive breast cancer or non-small-cell lung cancer (Consolidative Use of Radiotherapy to Block [CURB] oligoprogression): an open-label, randomised, controlled, phase 2 study

Lancet 2024; 403: 171–82

Chiaojung Jillian Tsai, Jonathan T Yang, Narek Shaverdian, Juber Patel, Annemarie F Shepherd, Juliana Eng, David Guttmann, Randy Yeh,

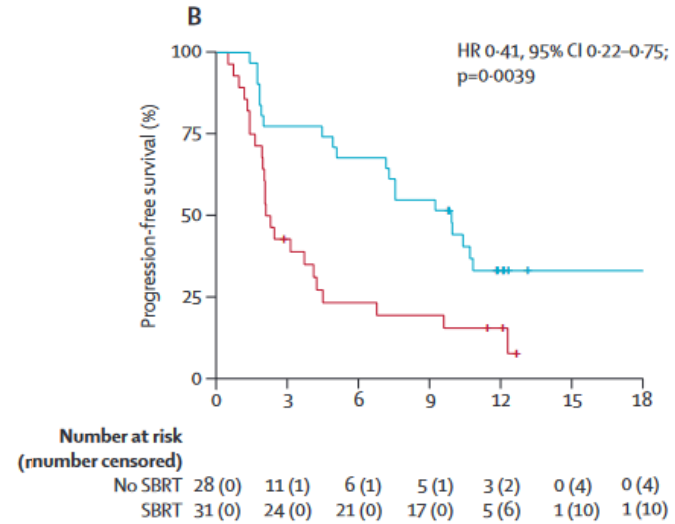


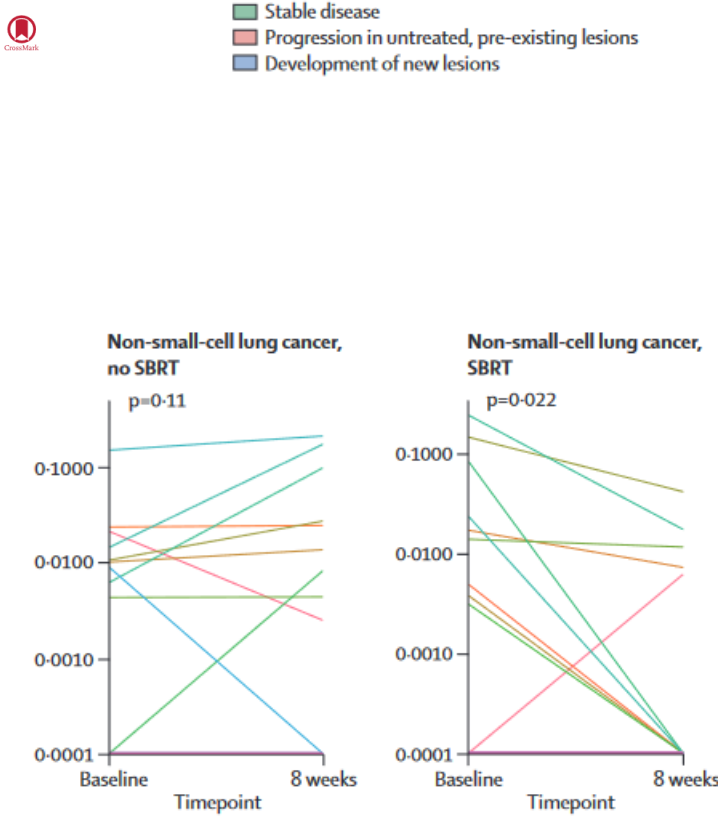
	Non-small-cell lung cancer	
	SOC (n=28)	SBRT (n=31)
Median age, years	70 (65–74)	71 (62–76)
Sex		
Female	12 (43%)	19 (61%)
Male	16 (57%)	12 (39%)
Received immunotherapy		
Yes	23 (82%)	24 (77%)
No	5 (18%)	7 (23%)
Number of oligoprogressive lesions		
1	8 (29%)	9 (29%)
2–5	20 (71%)	22 (71%)
Marker status		
Driver mutation	3 (11%)	5 (16%)
No driver mutation	25 (89%)	26 (84%)
Triple-negative breast cancer	NA	NA
Non-triple-negative breast cancer	NA	NA
Total number of metastatic sites		
1	4 (14%)	2 (6%)
2–5	15 (54%)	17 (55%)
>5	9 (32%)	12 (39%)
Had brain metastases		
Yes	5 (18%)	4 (13%)
No	23 (82%)	27 (87%)
Number of lines of systemic therapies received	1 (1–2)	2 (1–2)
Synchronous metastasis at initial cancer diagnosis	14 (50%)	17 (55%)

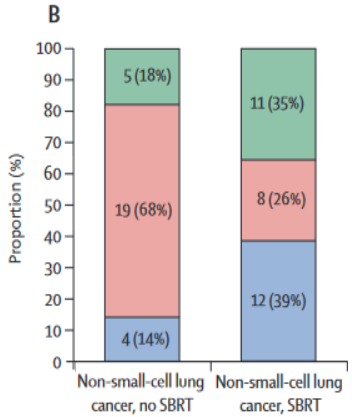
Standard-of-care systemic therapy with or without stereotactic body radiotherapy in patients with oligoprogressive breast cancer or non-small-cell lung cancer (Consolidative Use of Radiotherapy to Block [CURB] oligoprogression): an open-label, randomised, controlled, phase 2 study

Lancet 2024; 403: 171–82

Chiaojung Jillian Tsai, Jonathan T Yang, Narek Shaverdian, Juber Patel, Annemarie F Shepherd, Juliana Eng, David Guttmann, Randy Yeh,

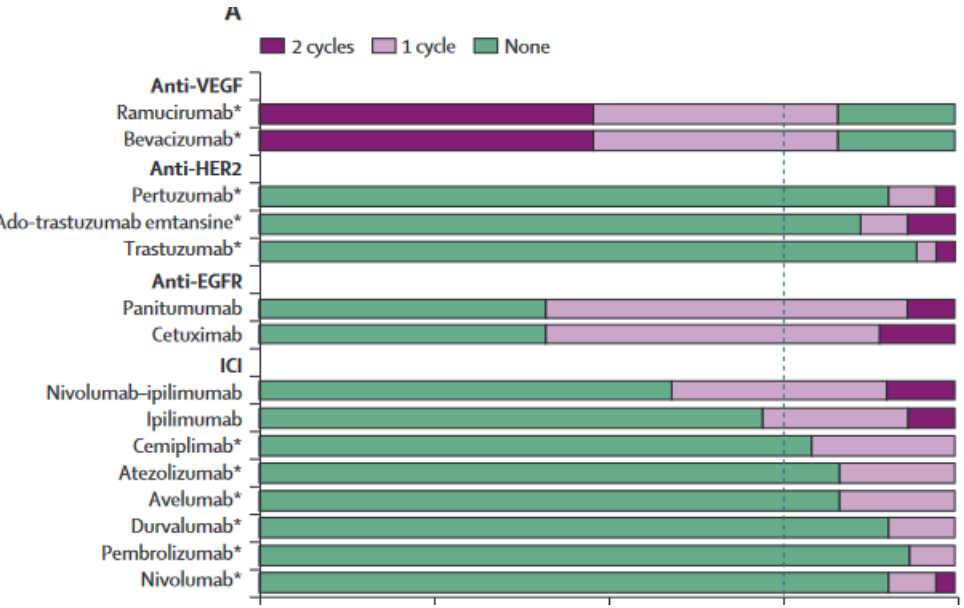


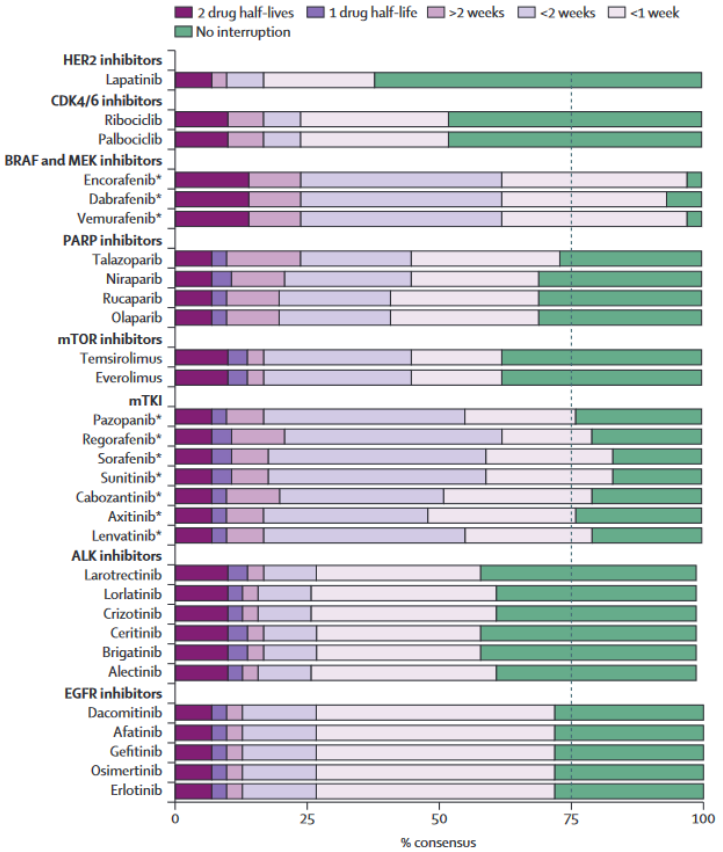




Metastases-directed stereotactic body radiotherapy in combination with targeted therapy or immunotherapy: systematic review and consensus recommendations by the EORTC–ESTRO OligoCare consortium

Lancet Oncol 2023; 24: e121–3





Metastases-directed stereotactic body radiotherapy in combination with targeted therapy or immunotherapy: systematic review and consensus recommendations by the EORTC–ESTRO OligoCare consortium

Lancet Oncol 2023; 24: e121–37

Table 1 Summary of suggested approaches

Agents	Drug	Suggestions
BRAF and MEK inhibitor	Vemurafenib and dabrafenib; trametinib	Suspend 3 d before and after RT. Suspend 1-2 d before and after RT.
EGFR and ALK inhibitor	Cetuximab; erlotinib and gefitinib; crizotinib and osimertinib	Suspend the week of radiation if SBRT. Suspend 1-2 d before and after RT. Suspend ≥2 d before and after RT.
VEGF inhibitor	Bevacizumab; sorafenib and sunitinib	Suspend 4 weeks before and after RT. Suspend 5-10 d before and after RT.
Cyclin-dependent kinase (CDK) inhibitors 4-6	Palbociclib and ribociclib	Suspend 3 d before and after RT.
Immunotherapy	Ipilimumab; other	Suspend 2 d before and after RT if 8 Gy in single fraction to bone. Insufficient data to recommend with moderate and ultrafractionation RT; caution suggested on an individual basis.
HER2 target therapy	Trastuzumab and pertuzumab; lapatinib; T-DM1	Generally safe to use concomitantly with RT. Insufficient data to recommend with moderate and ultrafractionation RT; caution suggested on an individual basis. Insufficient data to recommend with moderate and ultrafractionation RT; caution suggested on an individual basis.

Abbreviations: ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; RT = radiation therapy; SBRT = stereotactic body RT; VEGF = vascular endothelial growth factor; CDK = cyclin-dependent kinase; TDM1 = trastuzumab emtansine.

Guimond E, Tsai CJ, Hosni A, O'Kane G, Yang J, Barry A. Safety and Tolerability of Metastasis-Directed Radiation Therapy in the Era of Evolving Systemic, Immune, and Targeted Therapies. Adv Radiat Oncol. 2022 Jul 14;7(6):101022.

Clinical Practice Guideline

Treatment of Oligometastatic Non-Small Cell Lung Cancer: An ASTRO/ESTRO Clinical Practice Guideline

Practical Radiation Oncology® (2023) 13, 393–412

Check for updates

Evidence in KQs based on PICOTS

Population, Intervention, Comparator, Outcome, Timing, Setting framework

Table 2 KQs in PICO format

KQ	Population	Intervention	Comparator	Outcomes
1.	**What are the optimal patient/disease characteristics to select patients with oligometastatic NSCLC for definitive treatment combining systemic and local therapies?**			
	Adult patients with oligometastatic NSCLC	• Definitive local treatment of all disease sites, locoregional primary and metastases, with or without concurrent systemic therapy consisting of: ○ Surgical excision ○ Minimally invasive ablation (eg, RFA) ○ RT (including conventionally fractionated, SABR, SBRT and SRS)	• Standard of care systemic therapy or best supportive care	• Overall survival • PFS • Local control • Toxicity/QoL • DMFS • Time-to-switch to another systemic therapy
2.	**What are the selection criteria for choice of local treatment modality in the management of patients with oligometastatic NSCLC?**			
	Adult patients with oligometastatic NSCLC	• Definitive local treatment of all disease sites, locoregional primary and metastases, with or without concurrent systemic therapy consisting of: ○ Surgical excision ○ Minimally invasive ablation ○ RT (including conventionally fractionated, SABR, SBRT and SRS)	None	• Overall survival • PFS • Local control • Toxicity/QoL • DMFS • Time-to-switch to another systemic therapy
3.	**What are the appropriate sequencing and timing of systemic therapy and definitive local therapies for patients with oligometastatic NSCLC?**			
	Adult patients with oligometastatic NSCLC	• Definitive local treatment of all disease sites, locoregional primary and metastases, including surgical excision, minimally invasive ablation, and RT • Systemic therapy (including targeted therapy, immunotherapy, chemotherapy, and combinations)	None	• Overall survival • PFS • Local control • Toxicity/QoL • DMFS • Time-to-switch to another systemic therapy
4.	**What are the optimal dose-fractionation regimens, planning, and delivery technique of RT for patients with oligometastatic NSCLC?**			
	Adult patients with oligometastatic NSCLC receiving RT	• Definitive local treatment of all disease sites, locoregional primary and metastases, specifically as it relates to RT • RT (including SBRT/SBRT-like, hypofractionation, conventionally-fractionated RT)	None	• Overall survival • PFS • Local control • Toxicity/QoL • DMFS • Time-to-switch to another systemic therapy
5.	**After a definitive local therapy approach for oligometastatic NSCLC, what are the indications for additional local therapy upon disease progression?**			
	Adult patients with oligoprogression or oligorecurrence after definitive local therapy for NSCLC	• Local therapy (definitive RT or surgery) of all new or progressive disease sites, locoregional primary and metastases	• Standard of care systemic therapy or best supportive care	• Overall survival • PFS • Local control • Toxicity/QoL • DMFS • Time-to-switch to another systemic therapy

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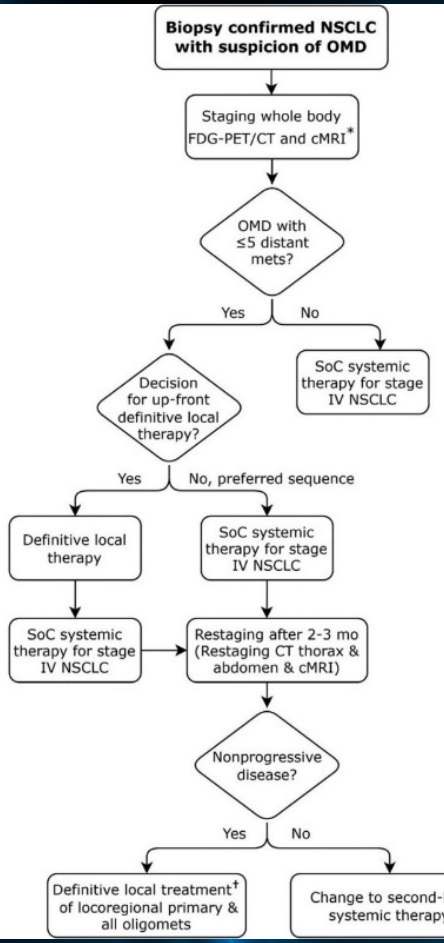
Table 3 Patient/disease characteristics for definitive systemic and local therapies

KQ1 Recommendations	Strength of Recommendation	Quality of Evidence (refs)
1. For patients with oligometastatic NSCLC, treatment decisions should be made using a patient-centered multidisciplinary team approach.	Strong	Expert Opinion
2. For patients with oligometastatic NSCLC, the integration of definitive local therapy is only recommended if technically feasible and clinically safe for all disease sites.	Strong	Moderate 8-10
3. For patients with oligometastatic NSCLC, a discussion of definitive local therapy as a component of multimodality treatment approach is recommended irrespective of presence of activating driver mutations.	Strong	Moderate 7-9
4. For oligometastatic NSCLC, definitive local therapy is recommended only for patients having up to 5 distant metastases, diagnosed with appropriate imaging. Implementation remark: Despite some prospective trials including patients with up to 5 extracranial metastases, most patients enrolled had 1-2 treated oligometastatic lesions, which should be factored into decision-making.	Strong	Moderate 7-10
5. For patients with synchronous oligometastatic NSCLC, definitive local therapy to all cancer sites in addition to standard of care systemic therapy is conditionally recommended.	Conditional	Moderate 7-9
6. For patients with metachronous oligorecurrent NSCLC, definitive local therapy to all oligorecurrent cancer sites in addition to standard of care systemic therapy is conditionally recommended.	Conditional	Low 10
7. For patients with induced oligopersistent NSCLC, definitive local therapy to all persistent cancer sites in addition to standard of care systemic therapy is conditionally recommended.	Conditional	Low 8,9
8. For patients with induced oligoprogressive NSCLC receiving systemic therapy, definitive local therapy to all progressive cancer sites is conditionally recommended while continuing the current line of systemic therapy.	Conditional	Expert Opinion



Clinical Practice Guideline

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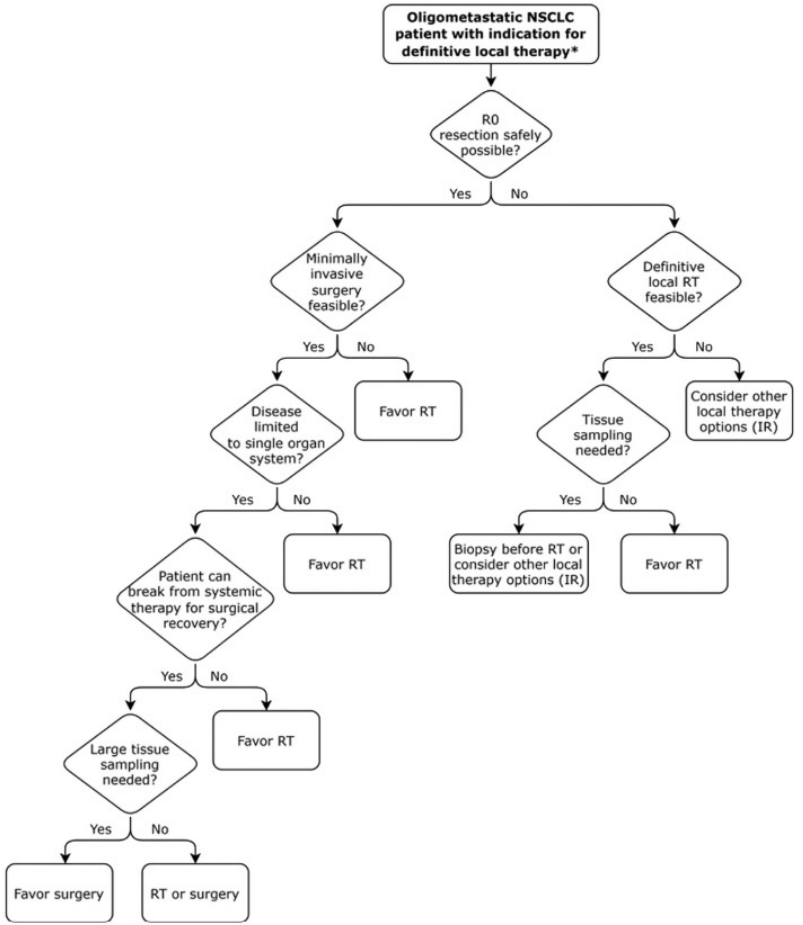
Practical Radiation Oncology® (2023) 13, 393–412

Table 4 Local treatment modality selection criteria for oligometastatic NSCLC

KQ2 Recommendations	Strength of Recommendation	Quality of Evidence (refs)
1. For patients with oligometastatic NSCLC, a patient-centered multidisciplinary discussion of the most appropriate local treatment strategy of RT and/or surgery either alone or in combination are recommended.	Strong	Moderate 35
2. For patients with oligometastatic NSCLC, RT and/or surgery are recommended as definitive local treatment modalities for the locoregional primary and all oligometastases.	Strong	Moderate* 7,8,10,35-40
3. For patients with oligometastatic NSCLC, highly conformal RT approaches and minimally invasive techniques for surgery are recommended to minimize morbidity.	Strong	Moderate 8-10,37,41,42
4. For patients with oligometastatic NSCLC, deciding between RT and surgery as the definitive local treatment modality should: • Favor RT when multiple organ systems are being treated • Favor RT when the clinical prioritization is to minimize breaks from systemic therapy • Favor surgery when large tissue sampling is needed for molecular testing, to guide systemic therapy.	Strong	Expert Opinion



Clinical Practice Guideline

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10. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy for the comprehensive treatment of oligometastatic cancers: Long-term results of the SABR-COMET phase II randomized trial. *J Clin Oncol.* 2020;38:2830-2838.

Table 6 RT dose-fractionation regimens, planning, and deliver

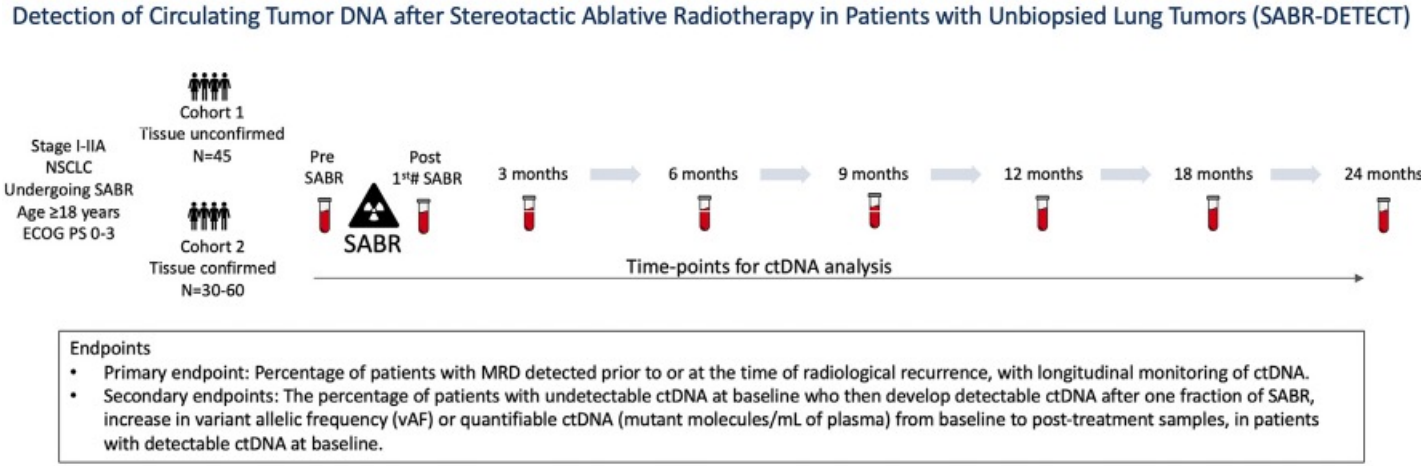
KQ4 Recommendations
1. For patients with oligometastatic NSCLC, appropriate staging with MRI, and MRI in cases of suspect or proven spine or liver metastas recommended.
2. For patients with oligometastatic NSCLC, individual assessment of for targets in the lungs and upper abdomen using 4-D CT, fluorosc with appropriate motion compensation is recommended.
3. For patients with oligometastatic NSCLC, highly conformal RT usi planning, appropriate motion management strategies and image-gu are recommended.
4. For patients with oligometastatic NSCLC, a risk adapted approach RT (preferred), hypofractionated RT, or alternatively definitive che on the location and burden of disease is recommended.
5. For patients with oligometastatic NSCLC, definitive local RT shoul fractionations which achieve durable local control. Implementation remarks: ○ Durable local control defined as minimum 85% local control at ○ Higher BED[10] (typically >75 Gy) with SBRT alone is associated control. ○ Lower BED[10] (50-75 Gy range) is associated with acceptable local control, typically in the setting of combination systemic therapy and SBRT.

rogression (after definitive local therapy approach)

	Strength of Recommendation	Quality of Evidence (refs)
gometastatic NSCLC urrence, systemic	Strong	Expert Opinion
gometastatic NSCLC additional local therapy	Strong	Expert Opinion
gometastatic NSCLC local therapy is	Conditional	Low [10]
gometastatic NSCLC at sites previously nded if systemic with toxicity acceptable	Conditional	Expert Opinion

Detection of Circulating Tumor DNA After Stereotactic Ablative Radiotherapy in Patients With Unbiopsied Lung Tumors (SABR-DETECT)

Saurav Verma,[1,3] Sympascho Young,[2,3] Thomas A.C. Kennedy,[4] Ilda Carvalhana,[4]



Washington University in St. Louis
School of Medicine

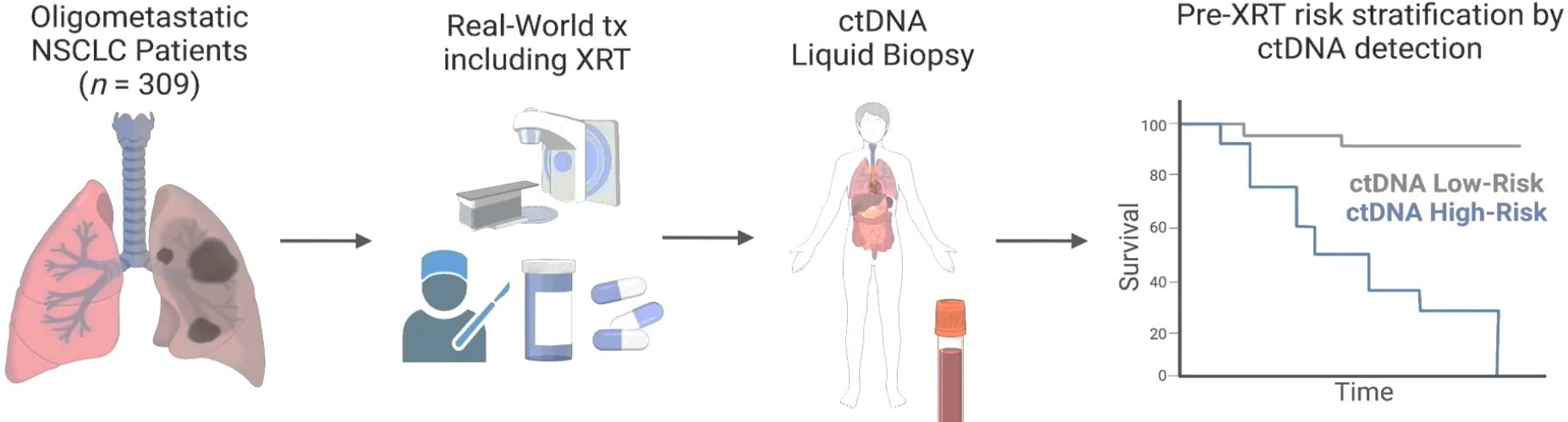
Department of Genetics

Circulating Tumor DNA for Early Risk Stratification of Oligometastatic Lung Cancer

WashU

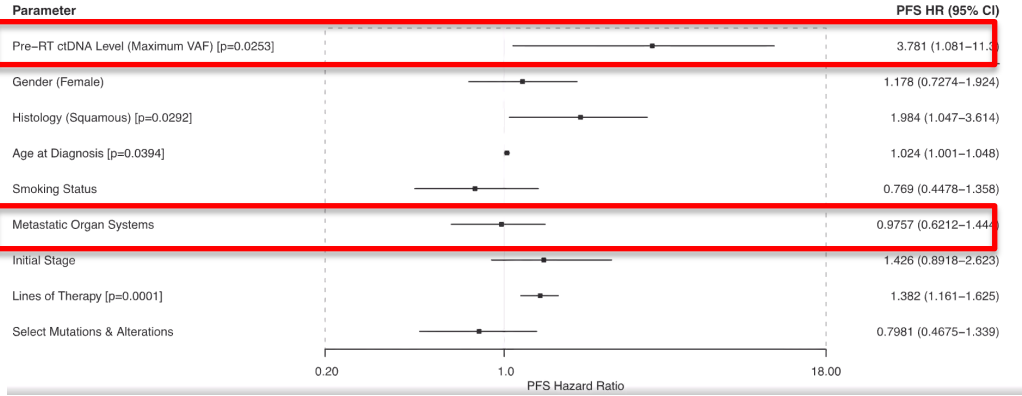
Aadel Chaudhuri, MD PhD

Radiation Oncology

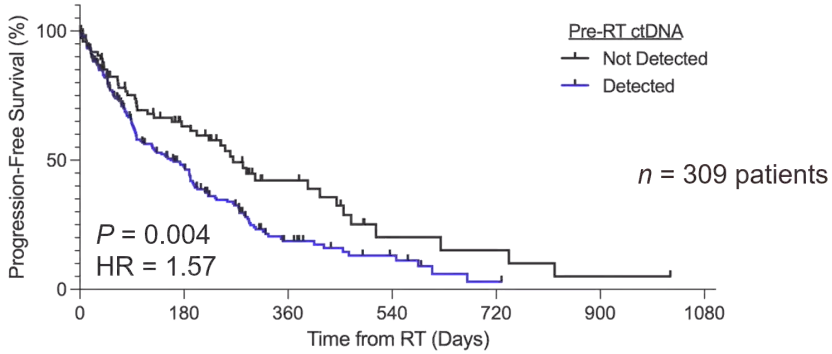


Circulating Tumor DNA for Early Risk Stratification of Oligometastatic Lung Cancer

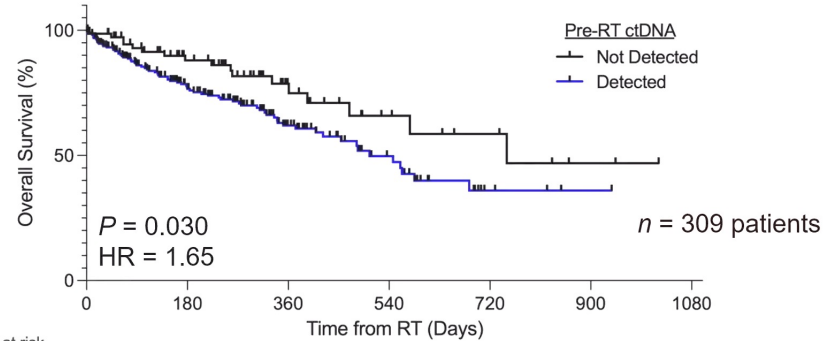
Multivariate Cox regression for PFS



ctDNA detection pre-XRT predicts PFS



ctDNA detection pre-XRT predicts OS



Conclusions & Future Directions

- We have exciting real-world data suggesting that ctDNA detection and levels can risk-stratify oligometastatic NSCLC
- Oligometastatic patients with low or undetectable ctDNA had improved survival outcomes with radiotherapy
- While ctDNA correlated with survival outcomes, the number of metastatic disease sites did not
- It will be fascinating to analyze ctDNA correlatives in ongoing oligometastatic SABR/SBRT studies
- We need to test ctDNA-based decision frameworks for consolidation SABR/SBRT for oligometastatic disease in