



Evolving Evidence and Practical Integration of Radiation Therapy in Metastatic Non-Small Cell Lung Cancer

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Stanford Cancer Institute

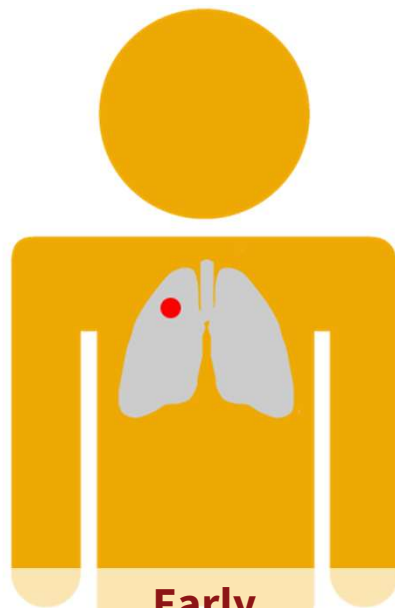


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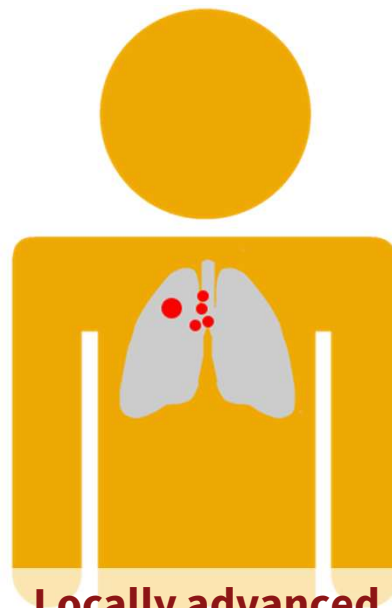
Lung Cancer Stages (Classical)



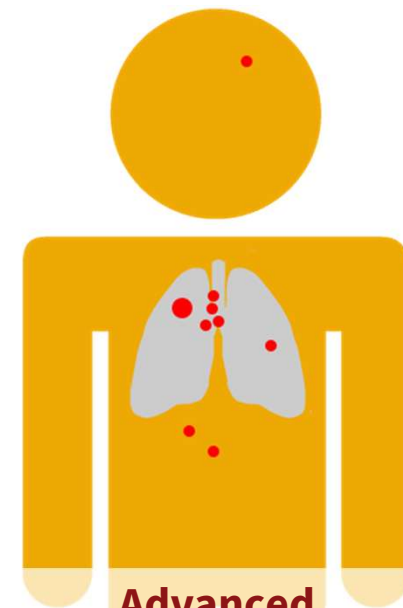
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**Early
(Localized)**
15% of patients
55% survival @ 5yr



**Locally advanced
(Regional)**
25% of patients
25% survival @ 5yr



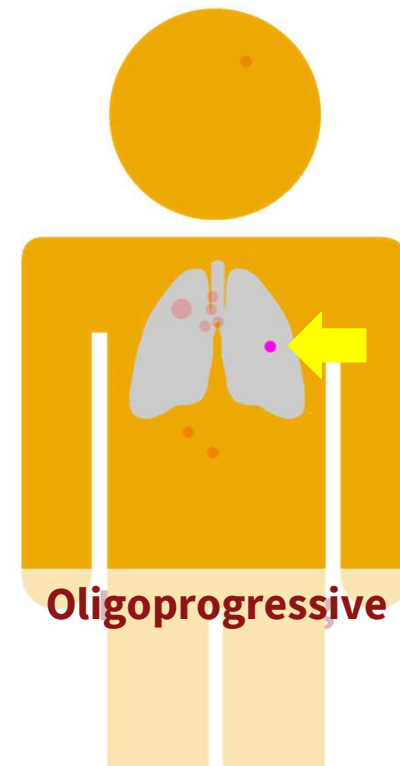
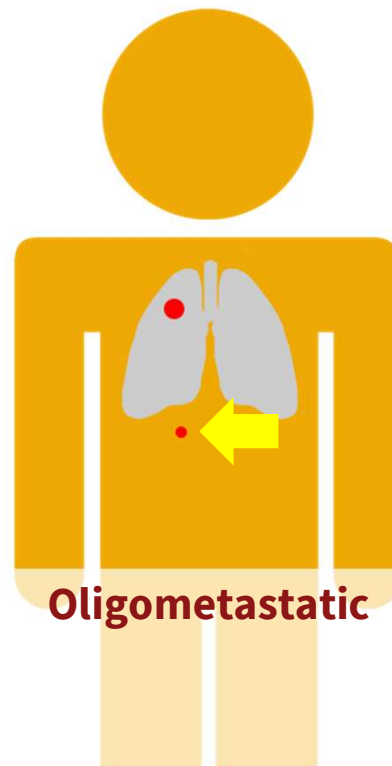
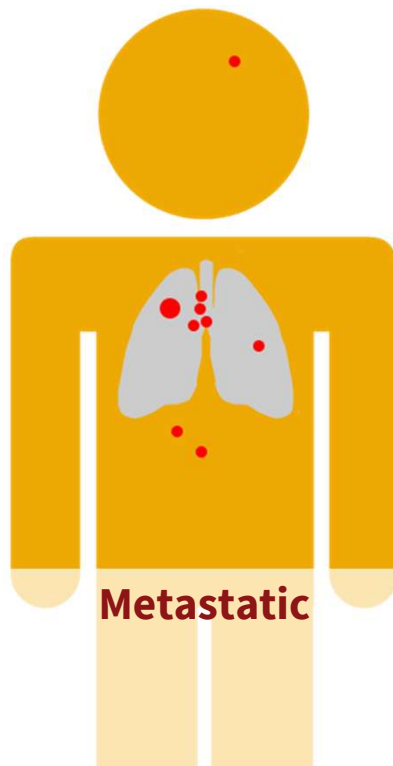
**Advanced
(Distant / Metastatic)**
60% of patients
5% survival @ 5yr

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Lung Cancer Stages (New concepts)



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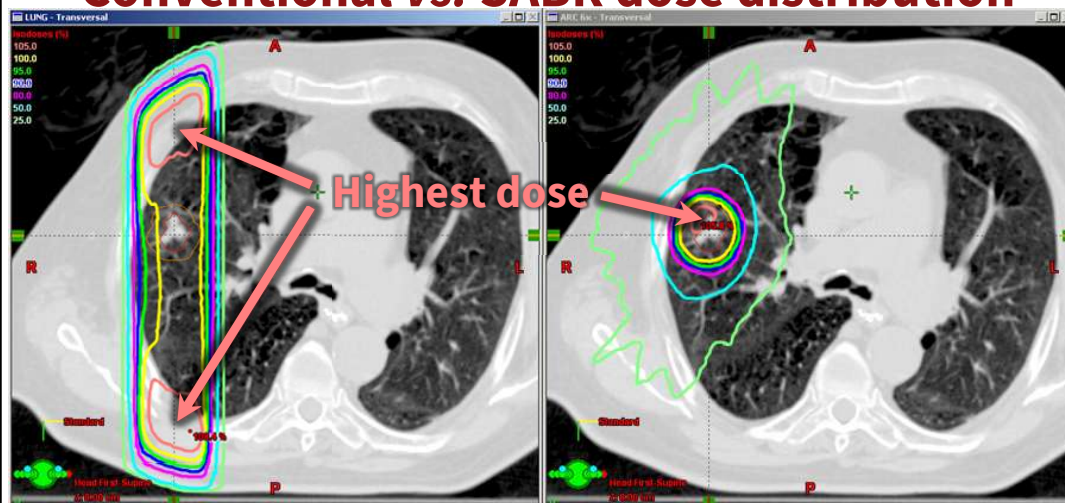
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Precision radiotherapy



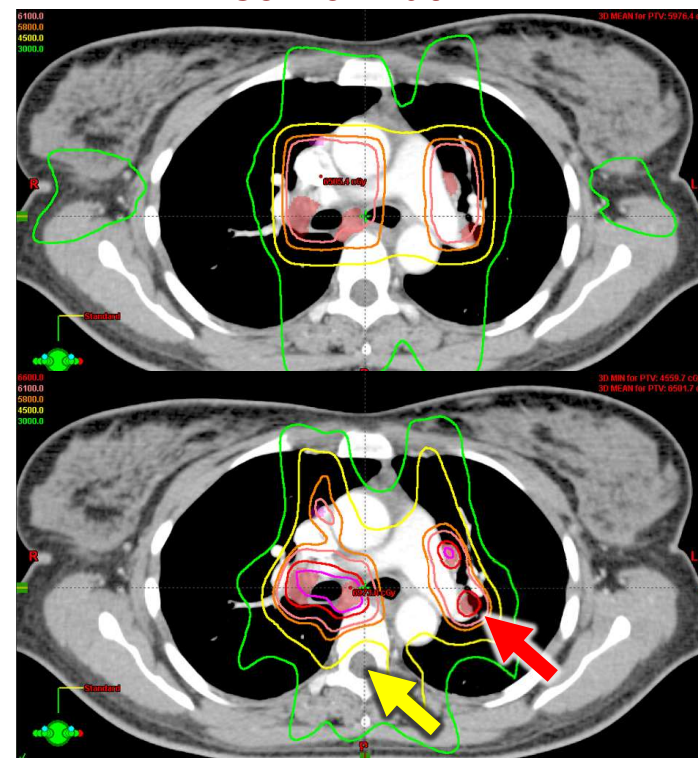
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Conventional vs. SABR dose distribution



Major improvements in **therapeutic index**
through **spatial precision**

Conformal RT



Highly conformal RT

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NSCLC case



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- 60 yo Asian man, healthy never smoker
- Active with excellent performance status
- Persistent cough and RUL consolidation on CXR despite antibiotics
- CT thorax demonstrates RUL mass and mediastinal lymphadenopathy
- CBCT-guided robotic bronchoscopy & EBUS biopsies find adenocarcinoma in RUL, 4R, 10R nodes. FNA of R SCV also +

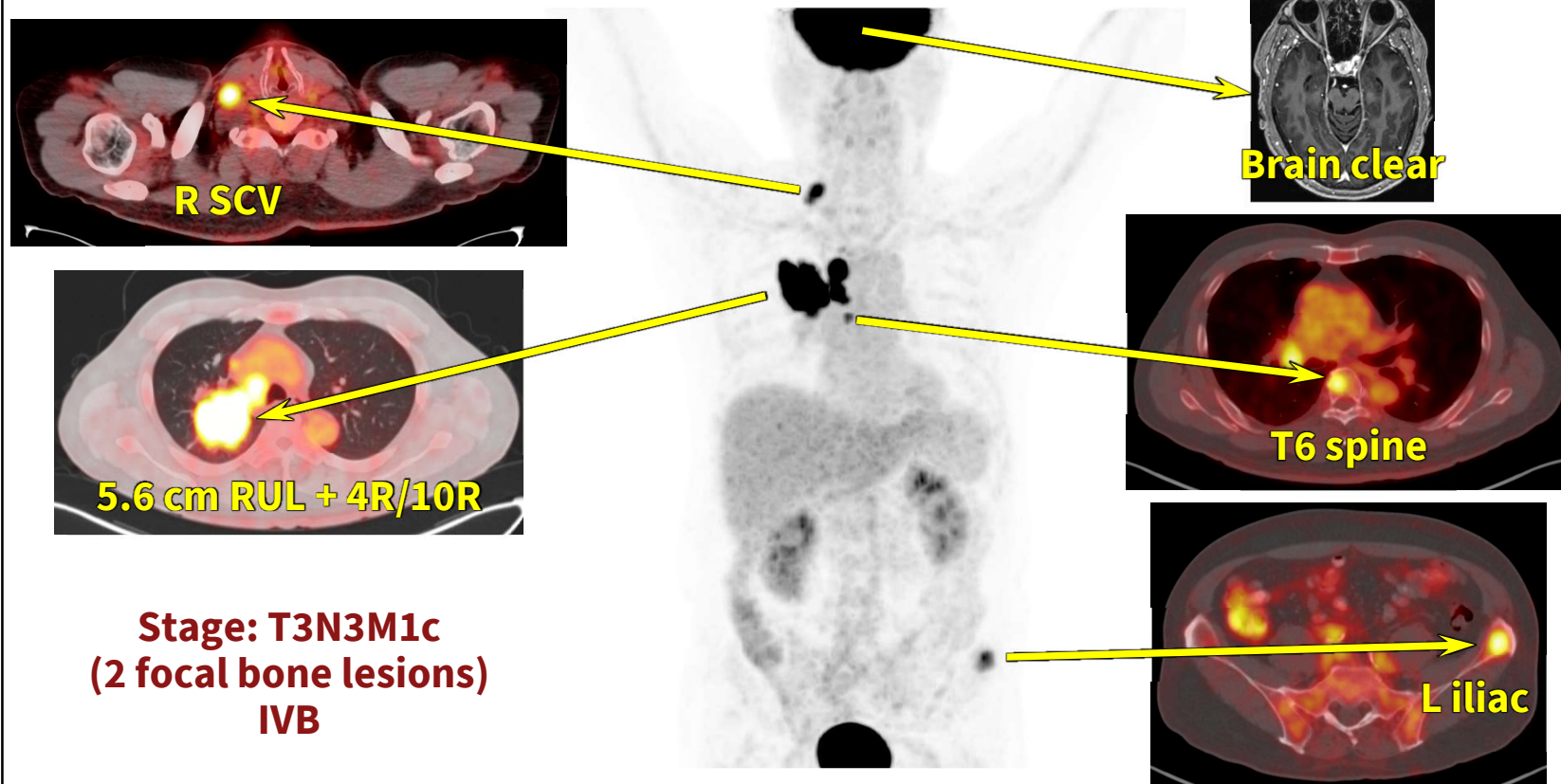
CBCT, cone beam CT; CXR, chest x-ray; EBUS, endobronchial ultrasound; FNA, fine-needle aspiration; RUL, right upper lobe; SCV, supraclavicular.

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Staging



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NCCN Guidelines Version 1.2026 Non-Small Cell Lung Cancer

CLINICAL
ASSESSMENT

PRETREATMENT EVALUATION

INITIAL TREATMENT

Broad molecular profiling:

EGFR L858R
PD-L1 80%

Stage IVA,
M1b and
Stage
IVB, M1c

- Biomarker testing (NSCL-19)
- If not previously done
- Brain MRI with and without contrast[§]
- FDG-PET/CT scan[†]
- Pathologic confirmation of metastatic lesion, if possible

PS 0–2

Solitary
or limited
metastases
confirmed^{‡‡}

Brain^{kk}

Other site

Multiple lesions

PS 3–4

Stereotactic radiosurgery (SRS) alone
or
Surgical resection,
if symptomatic or
warranted for diagnosis,
followed by SRS or whole
brain RT (WBRT)

Treatment of
Thoracic Disease
(NSCL-16)

Treatment of Thoracic
Disease (NSCL-16)

Advanced/metastatic disease
(NSCL-19)

Advanced/metastatic disease
(NSCL-19)

[†] FDG-PET/CT performed skull base to mid-thigh. Positive FDG-PET/CT scan findings for mediastinal nodal or distant disease need pathologic or other radiologic confirmation. If FDG-PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.

[§] If MRI is not possible, CT of head with contrast.

^{‡‡} Including selected patients with stage M1c and limited number and volume of metastatic lesions amenable to definitive local therapy. Clinical trials have included up to 3 to 5 metastatic sites.

^{kk} NCCN Guidelines for Central Nervous System Cancers.

Note: All recommendations are category 2A unless otherwise indicated.

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NSCL-15

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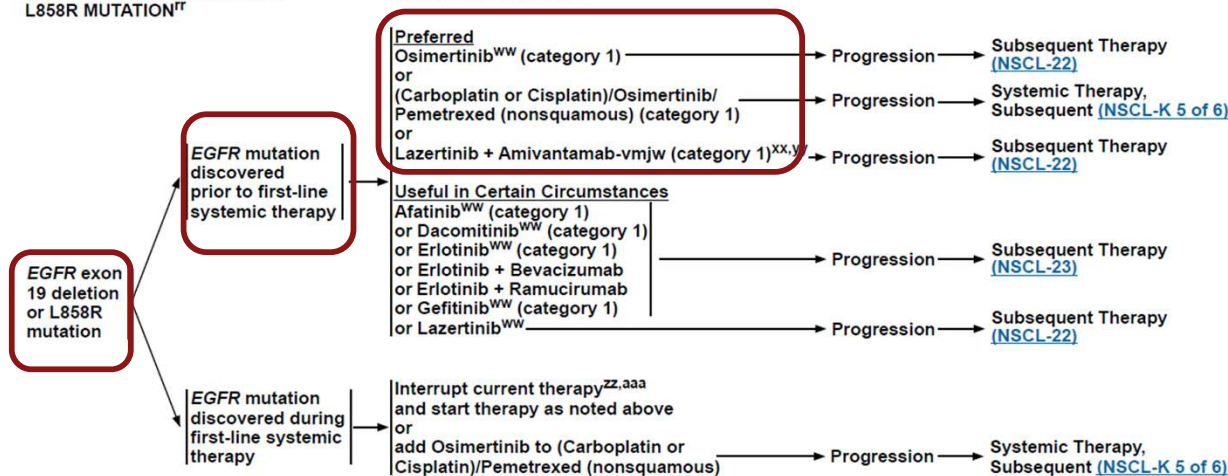


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EGFR EXON 19 DELETION OR
L858R MUTATION^{††}

FIRST-LINE THERAPY^{vv}



^{††} Principles of Biomarker Analysis (NSCL-H).

^{ww} Principles of Biomarker-Directed Therapy for Advanced or Metastatic Disease (NSCL-J).

^{ww} For performance status (PS) 0–4.

^{xx} Prophylactic anticoagulation is recommended at the time of initiation to prevent venous thromboembolic events.

^{yy} Prophylaxis with oral doxycycline or minocycline, clindamycin lotion applied to the scalp, chlorhexidine applied to nails, and a ceramide-based non-comedogenic moisturizer is recommended to reduce dermatologic adverse events. Prophylaxis with oral dexamethasone 8 mg for 2 days prior to first dose is recommended to reduce infusion-related reactions (IRRs) with amivantamab-vmjw.

Note: All recommendations are category 2A unless otherwise indicated.

^{zz} If systemic therapy regimen contains an immune checkpoint inhibitor (ICI), physicians should be aware of the long half-life of such drugs and data reporting adverse events when using osimertinib in combination with or following checkpoint inhibitors. The rate of side effects (pneumonitis) is higher within 3 months. Schoenfeld AJ, et al. Ann Oncol 2019;30:839-844; Oshima Y, et al. JAMA Oncol 2018;4:1112-1115; Oxnard GR, et al. Ann Oncol 2020;31:507-516; Gettinger S, et al. J Thorac Oncol 2018;13:1363-1372.

^{aaa} If there is a good response to current therapy, it is reasonable to continue therapy.

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NSCL-21

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TKI ± chemo for metastatic *EGFR*m



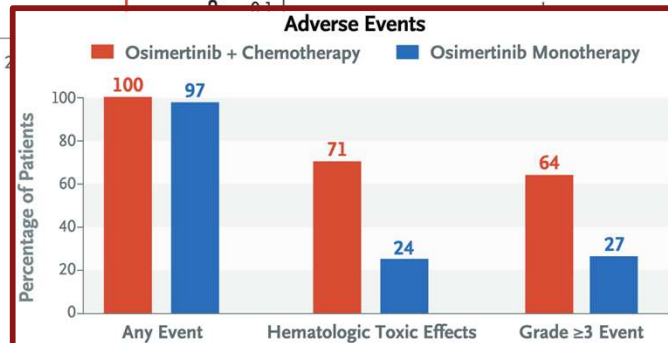
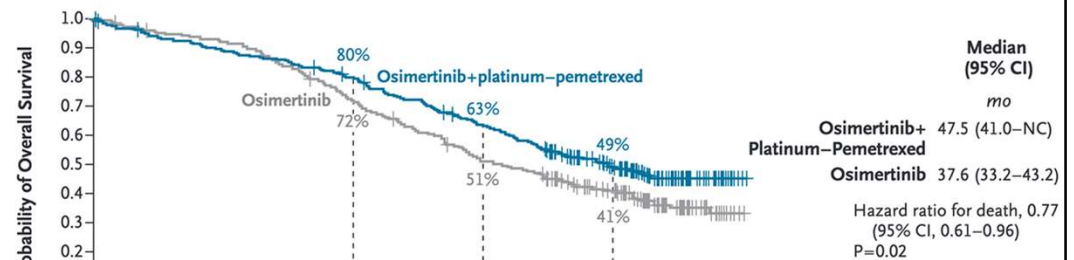
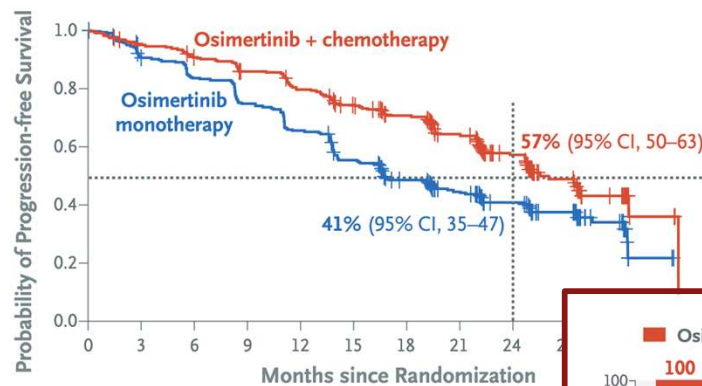
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FLAURA2: Phase III osimertinib ± platinum/pemetrexed for metastatic *EGFR*m

Investigator-Assessed Progression-free Survival

Median, 25.5 mo vs. 16.7 mo; difference, 8.8 mo

HR for disease progression or death, 0.62 (95% CI, 0.49–0.79); $P < 0.001$



Planchard *NEJM* 2023; Jänne *NEJM* 2025

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NSCL-15

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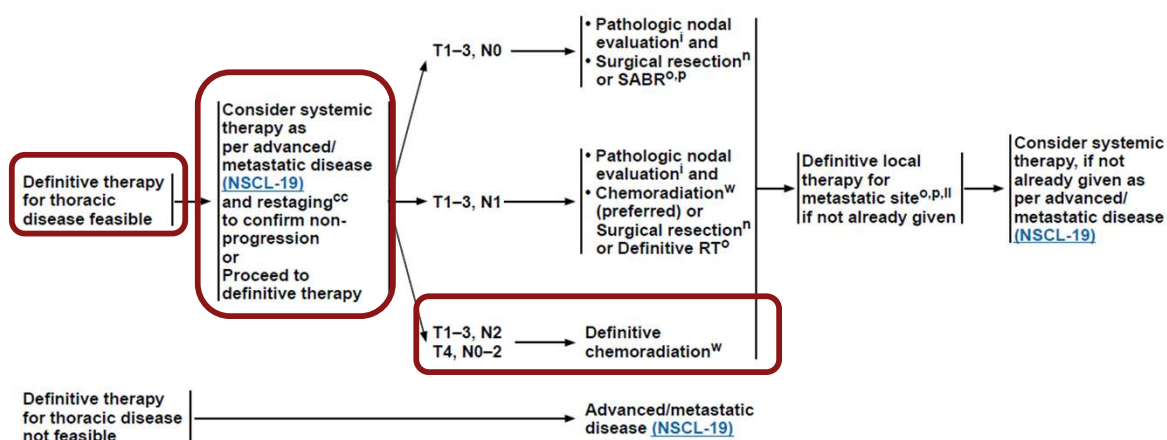
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TREATMENT OF THORACIC DISEASE



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

ⁿ [Principles of Surgical Therapy \(NSCL-B\)](#).

^o [Principles of Radiation Therapy \(NSCL-C\)](#).

^p IGTA therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients. [Principles of Image-Guided Thermal Ablation Therapy \(NSCL-D\)](#).

^w [Concurrent Chemoradiation Regimens \(NSCL-F\)](#).

^{cc} Chest CT with contrast and/or FDG-PET/CT to evaluate progression.

ⁱⁱ Typically, RT (including SABR) or surgical resection.

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NSCL-16



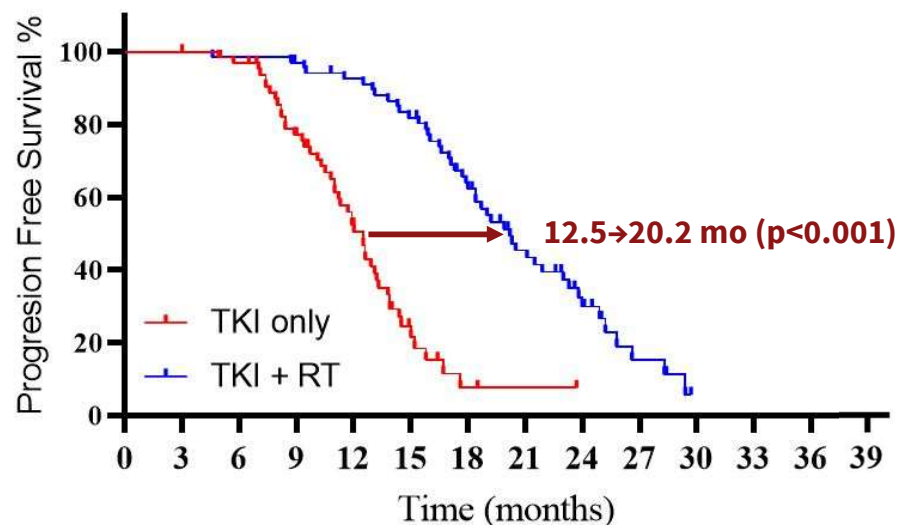
Radical RT for oligometastatic *EGFR*m



Thoracic Rad Onc @Stanford

SINDAS: Phase III TKI ± up front SABR for synchronous oligometastatic *EGFR*m

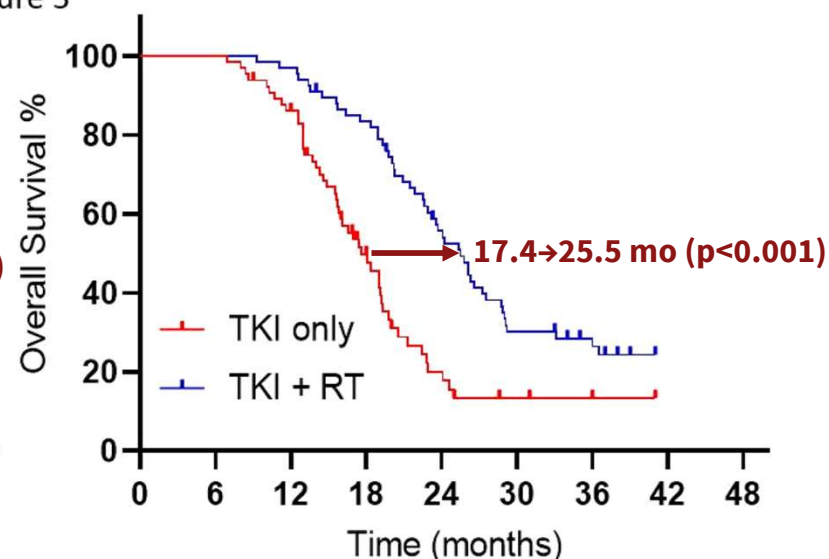
Figure 2



TKI only	65	65	62	48	28	8	3	2	1	0	0
TKI + RT	68	67	67	65	60	51	37	22	12	5	1

SABR, stereotactic ablative radiotherapy; TKI, tyrosine kinase inhibitor; RT, radiation therapy.

Figure 3



TKI only	65	65	55	26	9	5	3	2
TKI + RT	68	68	66	56	36	20	14	9

Wang *JNCI* 2022

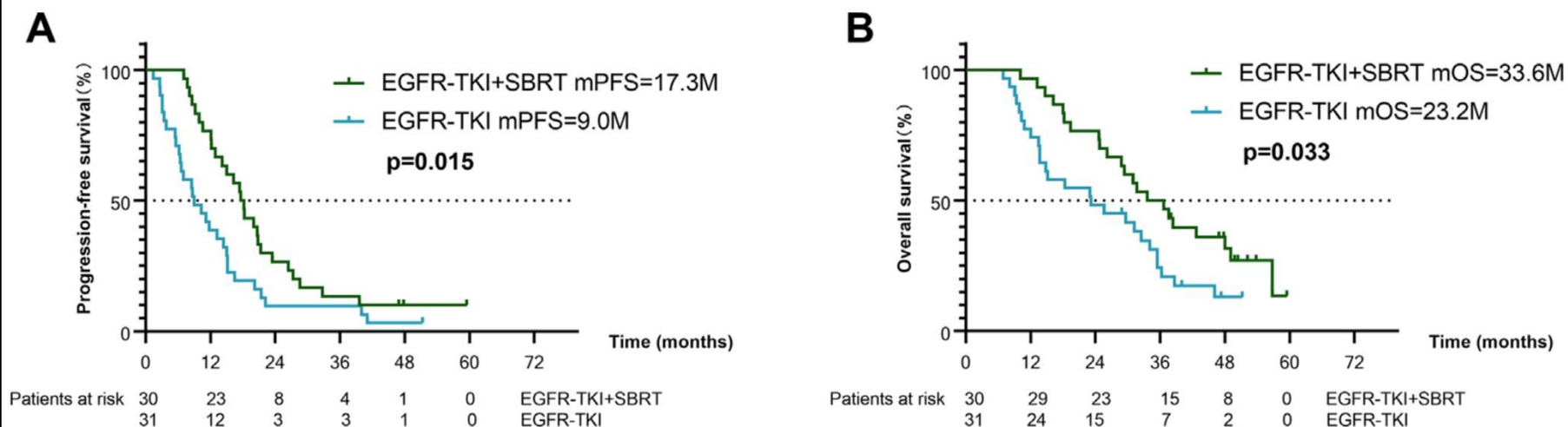
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Radical RT for oligometastatic *EGFR*m



Thoracic Rad Onc @Stanford

Wuhan: Phase IIR TKI ± SABR* for synchronous oligometastatic *EGFR*m *after 3 mo PR/SD on TKI



PR, partial response; SBRT, stereotactic body radiation therapy; SD, stable disease.

Peng *Radiother Oncol* 2023

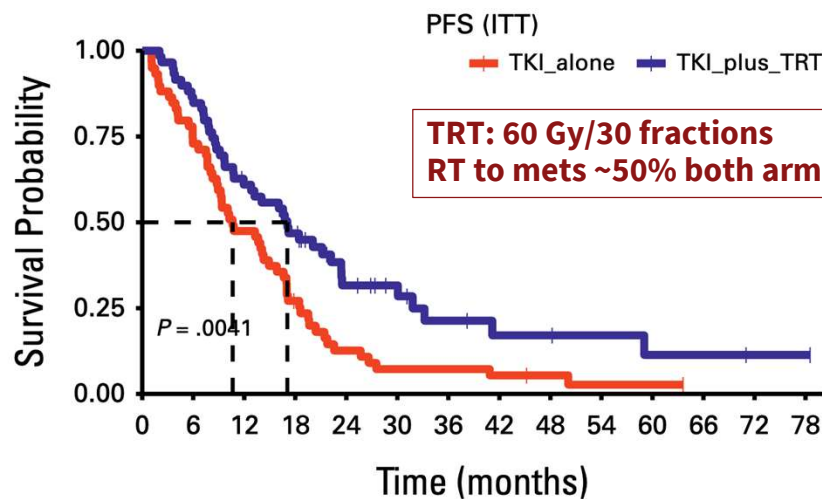
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Thoracic RT for oligo-organ *EGFR*m



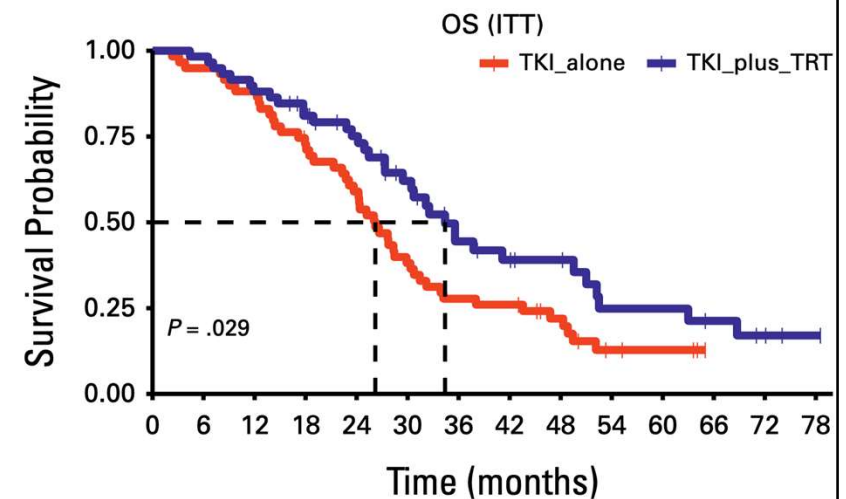
Thoracic Rad Onc @Stanford

Northern Radiation Oncology Group of China 002 Trial: Phase III TKI ± thoracic RT (TRT) for synchronous *oligo-organ* metastatic *EGFR*m



Number at risk

TKI_alone	59	43	28	15	7	4	4	3	2	1	1	0	0	0
TKI_plus_TRT	59	51	35	26	14	10	6	4	4	3	2	2	1	1



Number at risk

TKI_alone	59	56	52	42	34	22	16	15	10	4	3	0	0	0
TKI_plus_TRT	59	58	51	45	37	26	17	14	12	7	7	5	3	1

Sun J Clin Oncol 2025

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Treatment plan



Thoracic Rad Onc @Stanford

(Caveat: the 3 trials above used 1st gen EGFR TKIs)

- Definitive thoracic RT with concurrent platinum/pemetrexed
 - 60-66 Gy to RUL mass, involved mediastinal & SCV nodes
 - Include T6 metastasis in thoracic treatment volume
- Stereotactic ablative radiotherapy (SABR) to L iliac bone metastasis
- Adjuvant/maintenance Osimertinib

Takeaway: radical RT has the potential to improve survival in oligometastatic NSCLC in addition to systemic therapy

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NorthStar: A Phase II Randomized Study of Osimertinib (OSI) With or Without Local Consolidative Therapy (LCT) for Metastatic EGFR-Mutant Non-Small Cell Lung Cancer (NSCLC)

Yasir Y. Elamin, Saumil J. Gandhi, Mara B. Antonoff, Enoch Chang, George Blumenschein Jr, Zhongxing Liao, Daniel R. Gomez, Joe Y. Chang, Steven H. Lin, Tina Cascone, Carl Gay, Janet Tu, Xiuning Le, Anne Tsao, Michael S. O'Reilly, Matthew S. Ning, Collin Blakely, Chad G. Rusthoven, Jia Wu, Ara A. Vaporciyan, Stephen G. Swisher, John V. Heymach

Courtesy J Chang MDACC

NorthStar Study Design

Randomized, multicenter, phase II trial, NCT03410043

Key Eligibility

- Locally advanced or metastatic NSCLC
 - ECOG PS 0 or 1
 - Measurable disease
 - TKI naïve *EGFR* Ex19del or L858R
- or
- Acquired T790 no prior 3rd gen TKI

Stratification Factors

- TKI naïve vs prior 1/2 gen TKI
- Number of metastases (≤3 vs >3)
- PR vs SD
- Brain metastases

Induction
osimertinib
6-12 weeks

Non-PD
R 1:1
N=120

Osimertinib*

Osimertinib* plus
LCT

Primary Endpoint

- PFS

Key Secondary Endpoints

- Safety of osimertinib and LCT
- OS
- PFS in ≤3 mets
- PFS in TKI naïve

*Osimertinib continued until disease progression or unacceptable toxicity

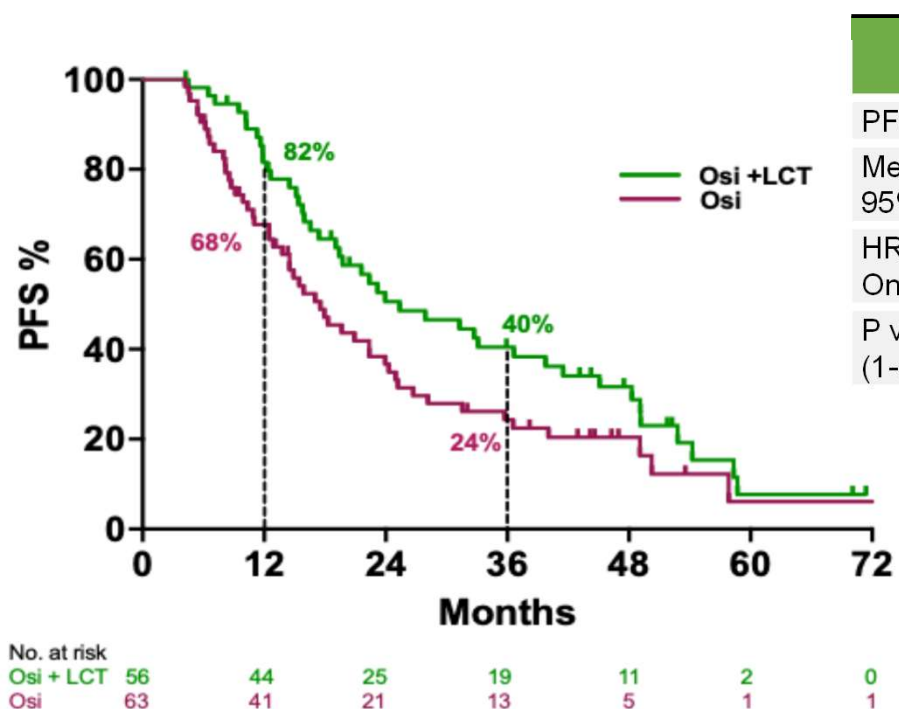
Yasir Elamin, MD

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Courtesy J Chang MDACC



Progression-Free Survival



	Osimertinib (n=63)	Osimertinib plus LCT (n=56)
PFS events, n (%)	50 (79.3%)	42 (75%)
Median PFS month	17.5	25.3
95% CI	(14.5, 24.3)	(19.4, 45.0)
HR		0.66
One-sided 90% CI		0.50 - 0.87
P value (1-sided log rank)		0.025

Yasir Elamin, MD

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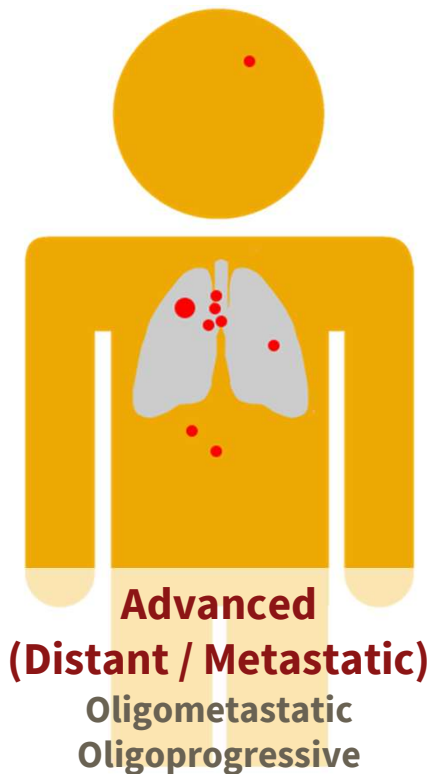
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Advanced lung cancer



Thoracic Rad Onc @Stanford



- Standard treatment is systemic drugs: chemo, mutation targeted, immunotherapy
- More focused radiation allows safe ablation of more tumors
- More effective drug therapy **increases** the potential of effective local therapy to **achieve cures or improve survival**

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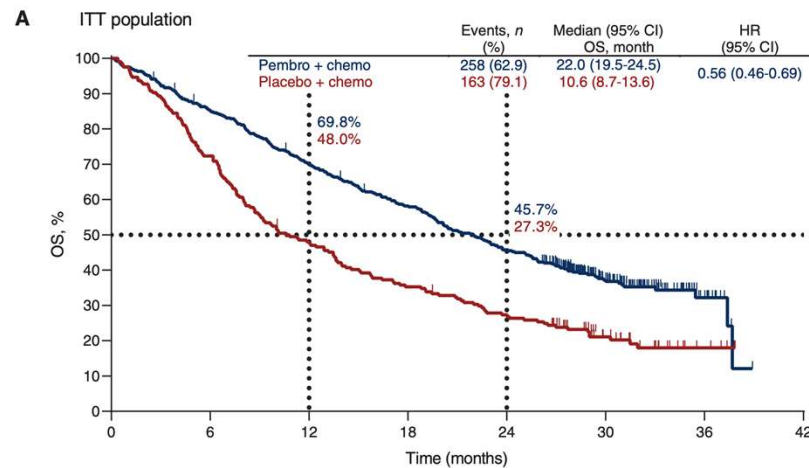
Standard: chemo and/or immuno



Thoracic Rad Onc @Stanford

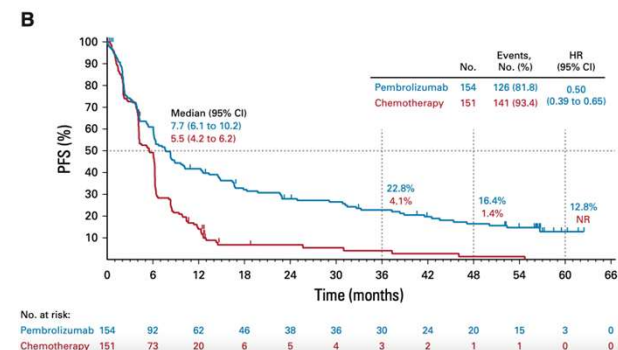
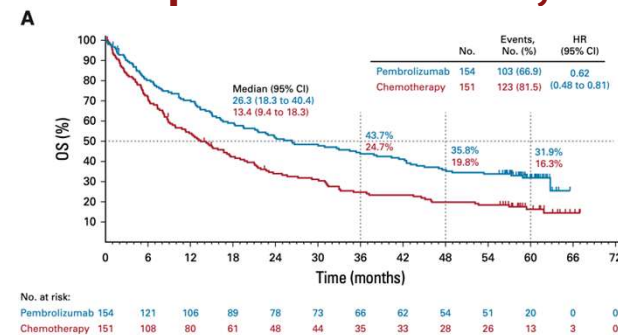
KEYNOTE-189: chemo ± pembro

KEYNOTE-024: pembro vs. chemo, PD-L1 50%



No. at risk:								
Pembro + chemo	410	347	283	234	184	86	12	0
Placebo + chemo	206	149	98	72	55	25	5	0

Rodriguez-Abreu *Ann Oncol* 2021



Reck *J Clin Oncol* 2021

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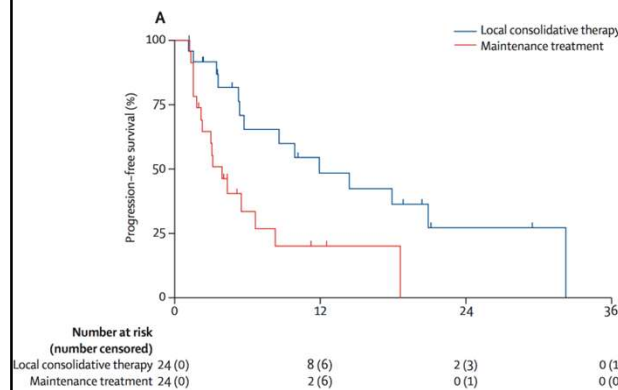
Randomized data for oligometastasis



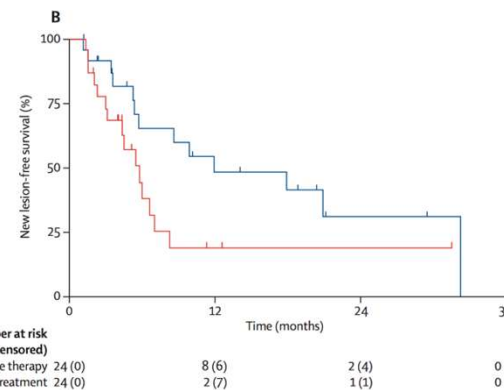
Thoracic Rad Onc @Stanford

Consolidative ablation of synchronous oligometastases extends progression free survival (Phase IIR)

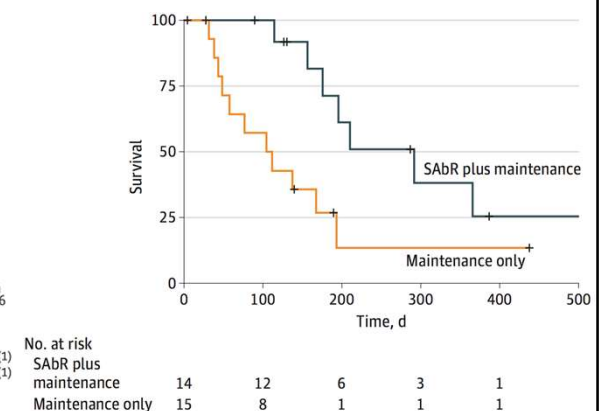
PFS



New lesions



PFS



Gomez *Lancet Oncol* 2016

Iyengar *JAMA Oncol* 2017

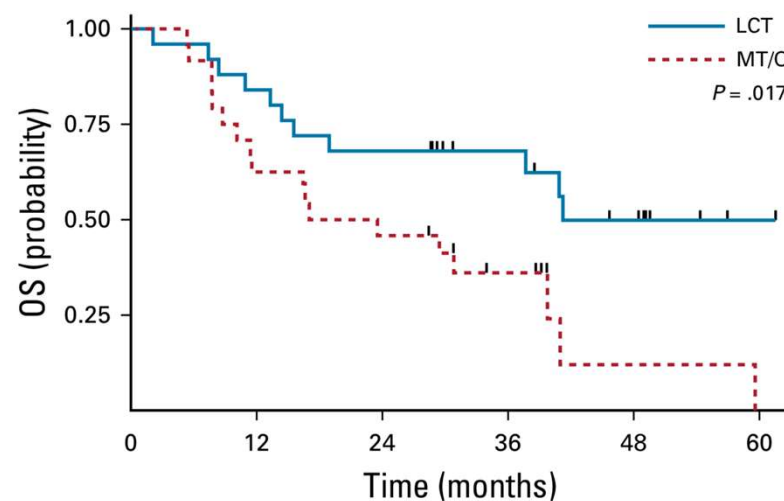
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Radical RT for oligometastatic cancer



Thoracic Rad Onc @Stanford

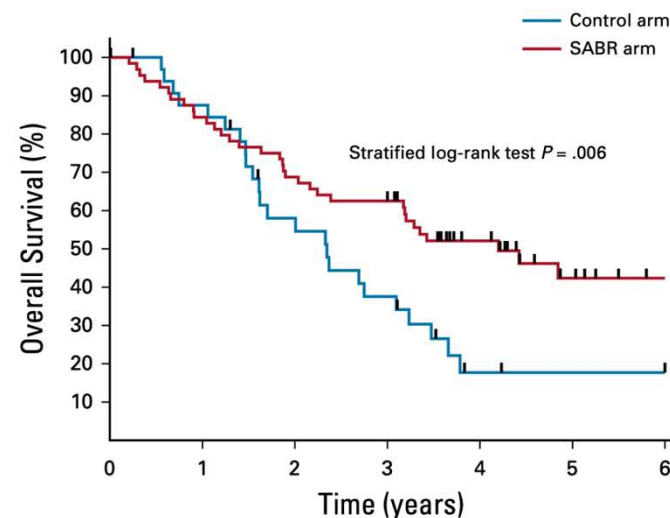
LCT vs. maintenance/obs for synchronous oligometastatic lung cancer (“OliGomez”)



No. at risk						
LCT:	25	21	17	12	7	1
MT/O:	24	15	11	6	1	0

Gomez *J Clin Oncol* 2019

SABR vs. SOC for metachronous oligometastatic cancer (SABR-COMET)



No. at risk							
Control	33	28	17	11	3	2	2
SABR	66	54	44	40	21	10	5

Palma *J Clin Oncol* 2020

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NRG-LU002: Randomized Phase II/III Trial Of Maintenance Systemic Therapy Versus Local Consolidative Therapy (LCT) Plus Maintenance Systemic Therapy For Limited Metastatic Non-Small Cell Lung Cancer (NSCLC)

Puneeth Iyengar, MD, PhD, Chen Hu, PhD, Daniel Gomez, MD, Robert Timmerman, MD, Charles Simone, MD, Clifford Robinson, MD, David Gerber, MD, Saiama N Waqar, MBBS, MSCI, Jessica S Donington, MD, Stephen G Swisher, MD, Michael Weldon, MSc, Jackie Wu, PhD, Bryan Faller, MD, Sawsan Rashdan, MD, Kevin L Stephans, MD, Pamela Samson, MD, Kristin A Higgins, MD, Ryan Nowak, MD, Jessica A Lyness, MS, Jeffrey D Bradley, MD

Puneeth Iyengar, MD, PhD; Attending and Director, Metastatic Service,
Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center



@IyengarPuneeth

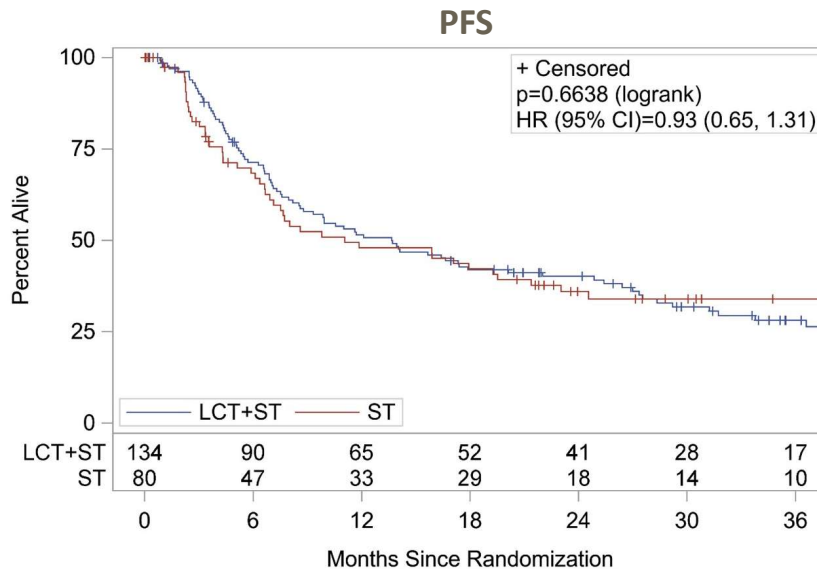
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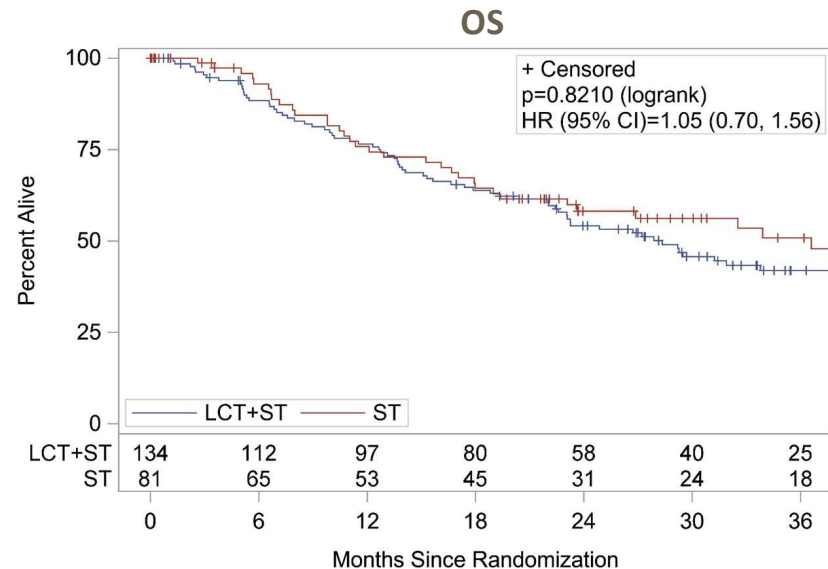


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NRG LU002



	Fail/Total	1yr PFS Rate (95% CI)	2yr PFS Rate (95% CI)
ST	49 / 80	48.0% (35.9, 59.0)	35.9% (24.8, 47.2)
LCT+ST	89 / 134	51.5% (42.5, 59.8)	40.1% (31.5, 48.6)



	Fail/Total	1yr OS Rate (95% CI)	2yr OS Rate (95% CI)
ST	37 / 81	75.8% (64.0, 84.2)	58.1% (45.6, 68.8)
LCT+ST	70 / 134	76.5% (68.1, 82.9)	54.1% (44.9, 62.5)

Median Follow-up:

All patients – 21.9 mo

Surviving patients – 29.4 mo

Of 185/215 patients treated with IO-containing systemic therapy regimens, the PFS HR was 0.90 (95% CI: 0.61, 1.32).

Iyengar ASCO 2024

Of 185/215 patients treated with IO-containing systemic therapy regimens, the OS HR remained 1.05 (95% CI: 0.68, 1.63).

RT enhances immunotherapy



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Pooled PEMBRO-RT & MDACC: Phase 1/2R pembro ± accelerated RT/SABR

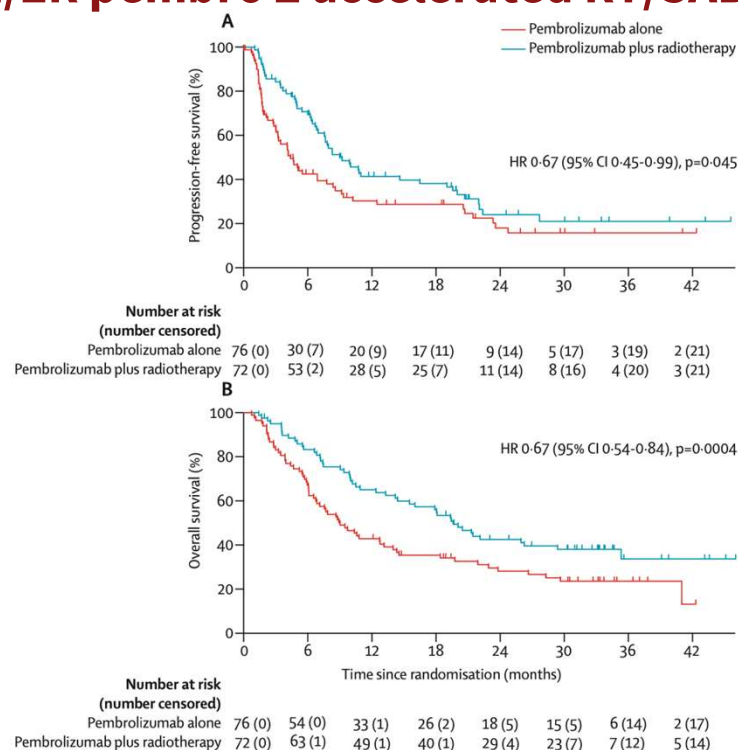
Abscopal effects

	Pembrolizumab alone (n=76)	Pembrolizumab plus radiotherapy (n=72)	Number needed to treat	Odds ratio (95% CI)	p value
Best overall response					
Abscopal response rate	15/76 (19.7%)	30/72 (41.7%)	2.00	2.96 (1.42-6.20)	0.0039
Abscopal control rate	33/76 (43.4%)	47/72 (65.3%)	4.58	2.51 (1.28-4.91)	0.0071
PD-L1 status					
<1%	6/36 (16.7%)	11/29 (37.9%)	4.69	3.00 (0.96-10.00)	0.080
1-49%	3/14 (21.4%)	9/19 (47.4%)	3.85	3.30 (0.96-16.70)	0.16
≥50%	5/15 (33.3%)	6/13 (46.2%)	16.13	1.72 (0.37-7.69)	0.70
Objective response at 12 weeks					
Abscopal response rate	14/76 (18.4%)	25/72 (34.7%)	5.26	1.95 (0.91-4.20)	0.086
Abscopal control rate	29/76 (38.2%)	45/72 (62.5%)	4.09	2.71 (1.39-5.28)	0.0033

Data are n (%), unless otherwise stated.

Table 2: Response to treatment

Theelen/Chen *Lancet Respir Med* 2020



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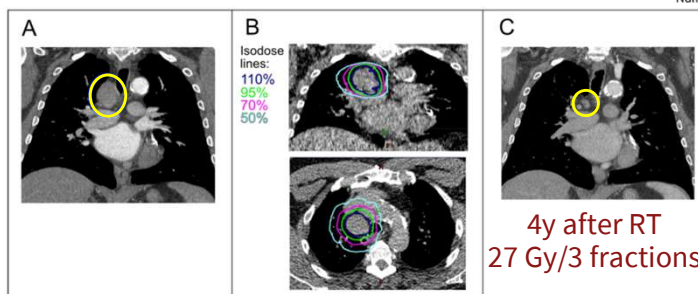
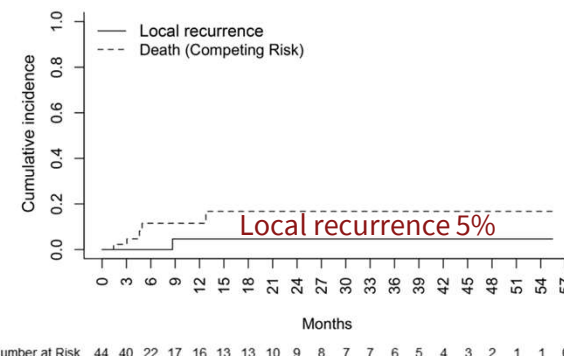
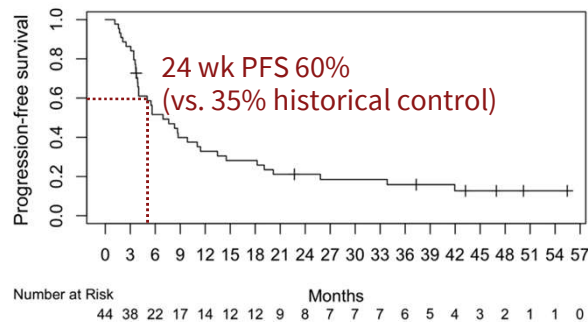
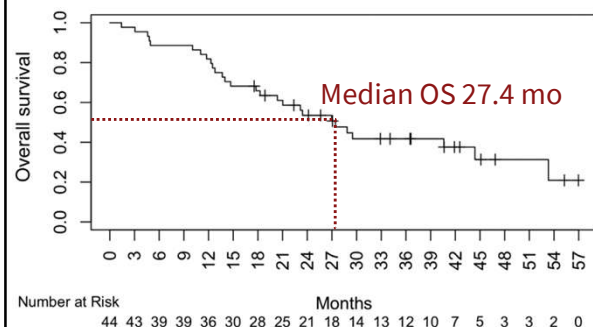
RT enhances immunotherapy



Thoracic Rad Onc @Stanford

Stanford Radical RADiotherapy and Immunotherapy for metastatic CAncer of the Lung (RRADICAL) trial

Radical dose radiotherapy to 1-4 extracranial tumors in patients with metastatic NSCLC responding to or mildly progressing on ICI, with goal of maximal cytoreduction



Gensheimer *IJROBP* 2025

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SABR for oligoprogressive cancer

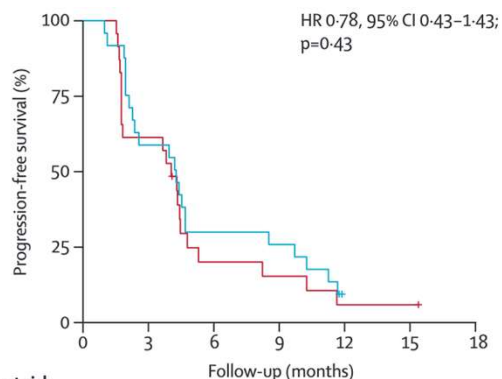


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CURB: Phase IIR SOC systemic $\pm$ SABR* for oligoprogressive breast/lung cancer

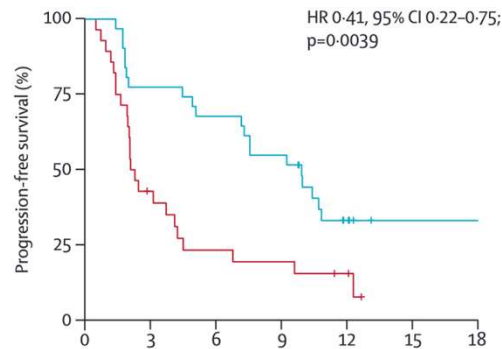
*to all progressive sites (up to 5), no limit on total # non-progressing metastases

Progression-free survival
(breast cancer)



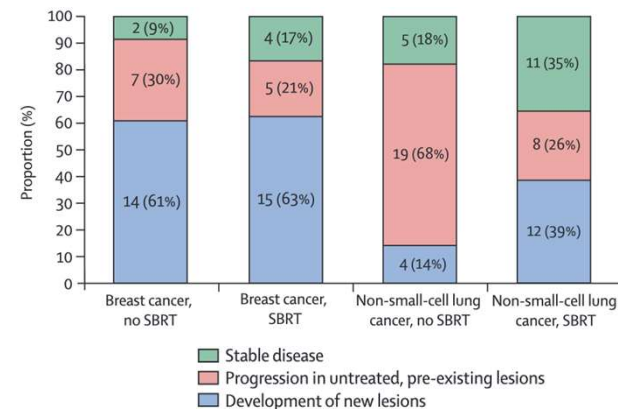
Number at risk (number censored)		Follow-up (months)						
No SBRT	23 (0)	14 (0)	4 (1)	3 (1)	1 (1)	1 (1)	0 (2)	
SBRT	24 (0)	14 (0)	7 (0)	6 (0)	2 (0)	0 (2)	0 (2)	

Progression-free survival
(lung cancer)



Number at risk (number censored)							
No SBRT	28 (0)	11 (1)	6 (1)	5 (1)	3 (2)	0 (4)	0 (4)
SBRT	31 (0)	24 (0)	21 (0)	17 (0)	5 (6)	1 (10)	1 (10)

Patterns of recurrence



Tsai *Lancet* 2024

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Phase II individualized SABR (iSABR)



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Tumor volume/location/histology adapted dosing

A Small tumor ($\leq 10 \text{ cm}^3$)

Peripheral: 25 Gy in 1 fx ($\text{BED}_{10}=87.5$)
Central: 40 Gy in 4 fx ($\text{BED}_{10}=80$)
Colorectal: 50 Gy in 4 fx ($\text{BED}_{10}=112.5$)

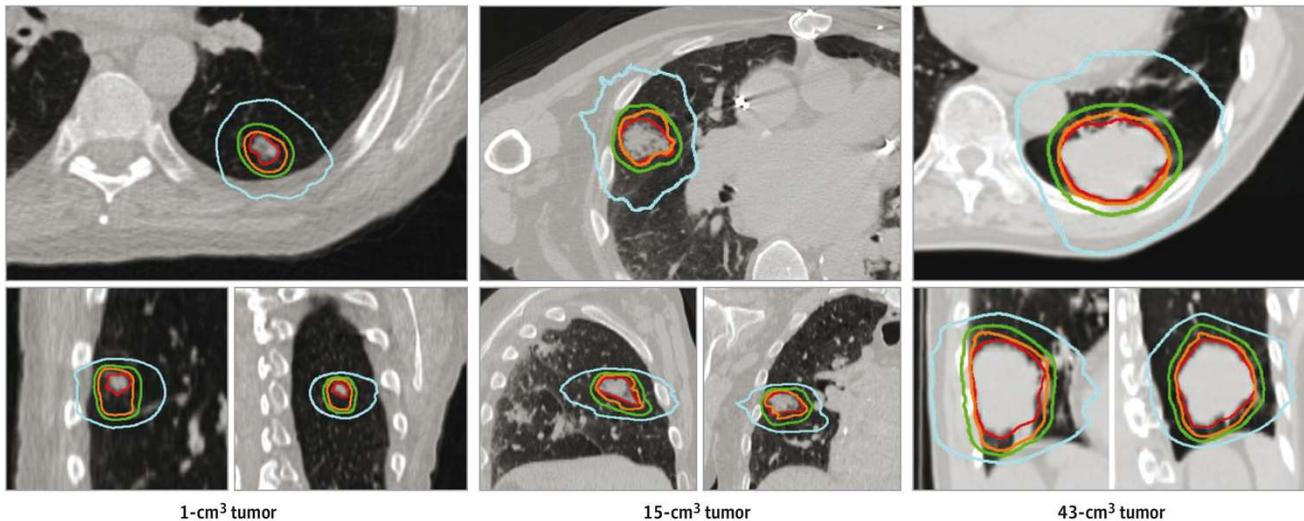
B Medium tumor ($>10 \text{ cm}^3$ and $\leq 30 \text{ cm}^3$)

Peripheral: 50 Gy in 4 fx ($\text{BED}_{10}=112.5$)
Central: 50 Gy in 4 fx ($\text{BED}_{10}=112.5$)

C Large tumor ($>30 \text{ cm}^3$)

Peripheral: 54 Gy in 3 fx ($\text{BED}_{10}=151.2$)
Central: 60 Gy in 8 fx ($\text{BED}_{10}=105$)

— Gross tumor volume — 110% IDL — 95% IDL — 50% IDL



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MEDICINE



Gensheimer *JAMA Oncol* 2023

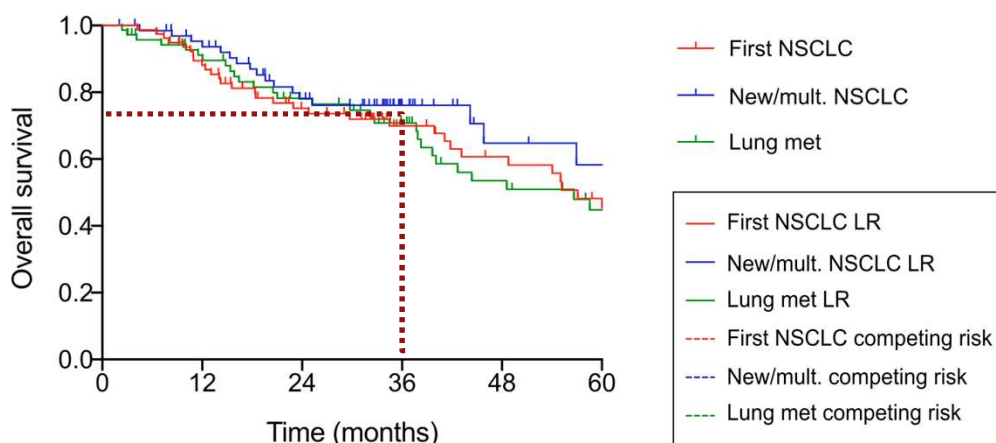
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Phase II individualized SABR (iSABR)



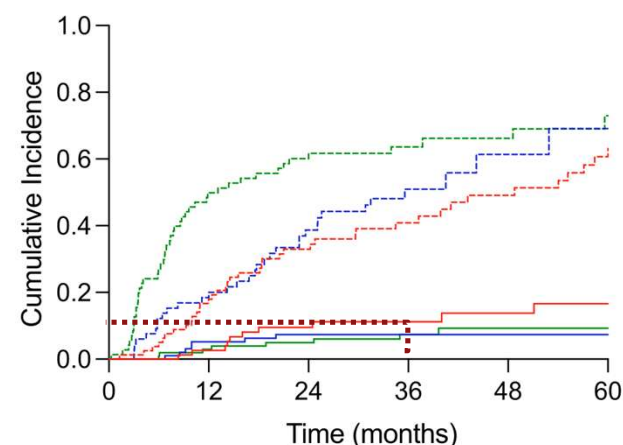
Thoracic Rad Onc @Stanford

Overall survival



No. at risk						
First NSCLC	79	66	48	33	26	18
New/mult. NSCLC	67	60	44	24	12	10
Lung met	71	59	45	34	22	15

Local recurrence (LR)



No. at risk						
First NSCLC	79	59	39	25	18	13
New/mult. NSCLC	103	70	50	22	12	10
Lung met	103	53	37	24	13	11

Gensheimer *JAMA Oncol* 2023

B Loo – Stanford Radiation Oncology

Stereotactic radiation (SRS/SRT) versus hippocampal avoidance whole brain radiation (HA-WBRT) in patients with 5-20 brain metastases: A multicenter, phase 3 randomized trial

Ayal Aizer MD MHS, Shyam Tanguturi MD, Grant Benham, Paul Brown MD, Daniel Cagney MD, Paul Catalano ScD, Fallon Chipidza MD, Daphne Haas-Kogan MD, Jaroslaw Hepel MD, Monica Krishnan MD, Marciana Johnson BA MPH, Nayan Lamba MD, Jennifer Nosker PhD, Michael Parsons PhD, Luke Peng MD ScM, Ivy Ricca BA, Diana Shi MD, Kee-Young Shin MS, Patrick Wen MD, Rifaquat Rahman MD

Ayal Aizer MD, MHS

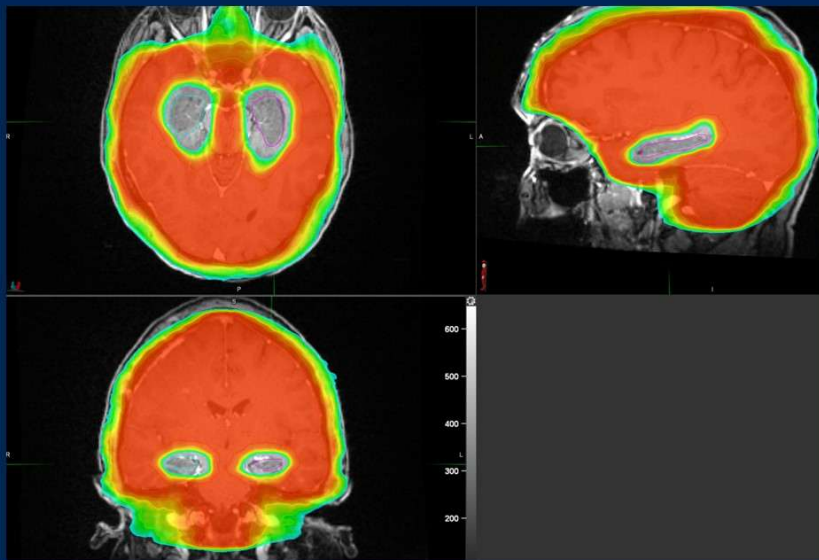
Director of Central Nervous System Radiation Oncology

Brigham and Women's Hospital / Dana-Farber Cancer Institute

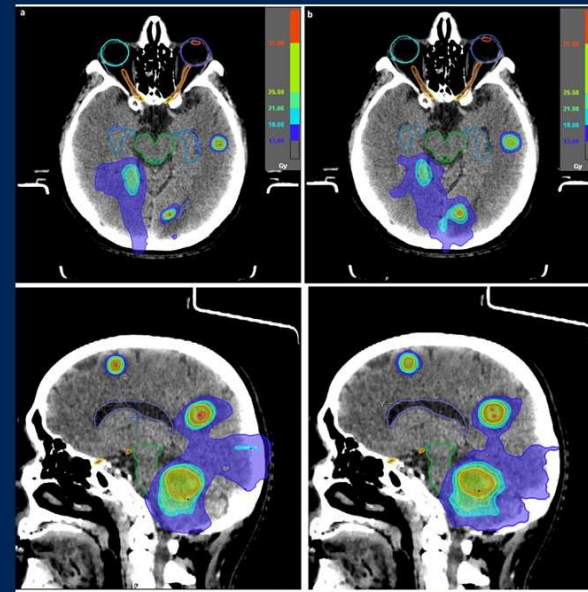
Associate Professor, Harvard Medical School

Conclusion: SRS is standard of care

Is LESS MORE?



Ayer, A



Cancers 2021, 13(14), 3458

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#ASCO25

PRESENTED BY: Iris C. Gibbs, MD | Radiation for Multiple (5-20) Brain Metastases: Is Less More?

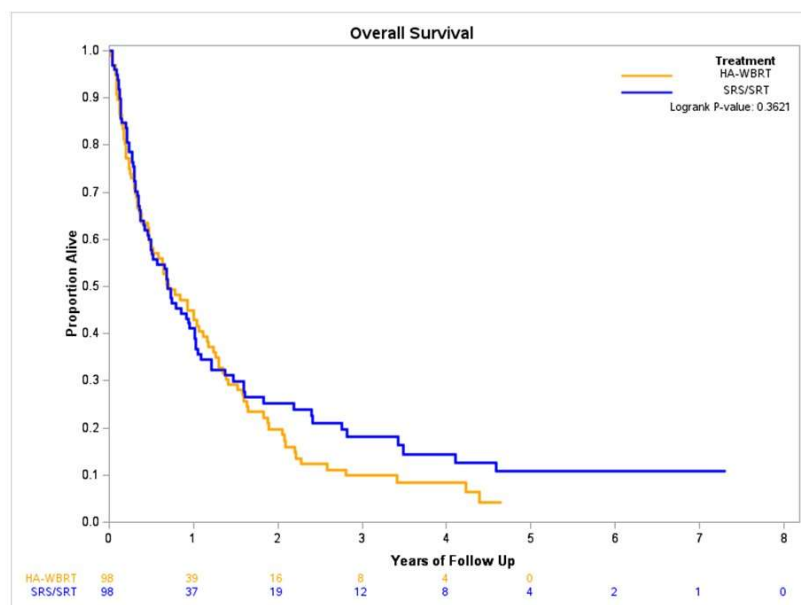
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Gibbs ASCO 2025

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Overall Survival



	SRS/SRT	HA-WBRT
Median Survival, mo (95% CI)	8.3 (5.9 -12.3)	8.5 (5.9 - 13.9)
12 Month Survival (95% CI)	41.1% (31.3% - 50.7%)	42.8% (32.7% - 52.6%)
Median # brain mets	15	13
% NSCLC	47%	43%

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Primary Outcome

MDASI-BT Symptom Severity			
	SRS/SRT	HA-WBRT	p
Baseline (mean)	2.19	1.90	0.20
Post baseline minus baseline (weighted, mean)	-0.03	0.59	
Difference	-0.62		<0.001

MDASI-BT Symptom Interference			
	SRS/SRT	HA-WBRT	p
Baseline (mean)	3.49	3.18	0.40
Post baseline minus baseline (weighted, mean)	-0.62	0.89	
Difference	-1.50		<0.001

Averaged Severity + Interference (N=172): -1.06 (95% CI -1.54, -0.58), indicating lower symptom burden and interference with daily function with SRS/SRT (p<0.001)

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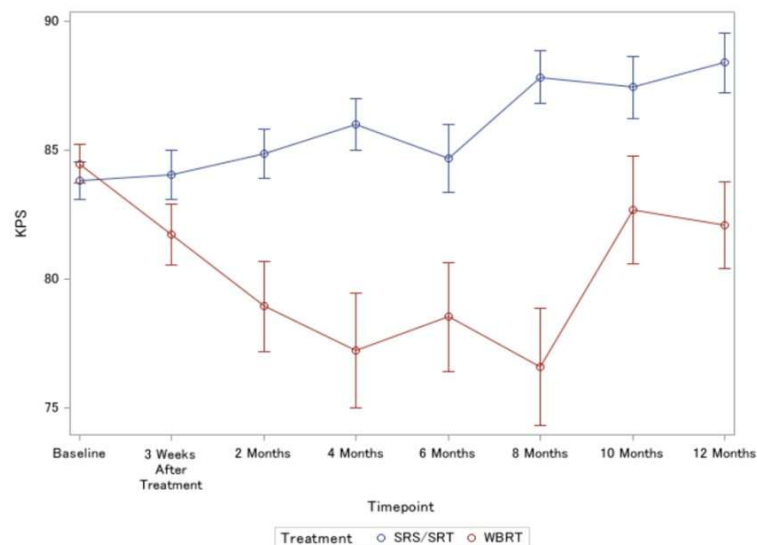
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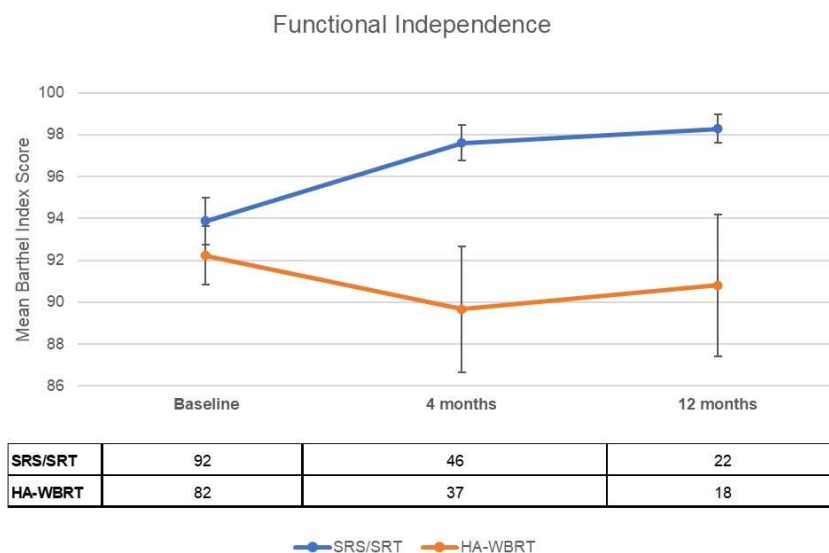
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Performance Status



	BL	3 wk	2 mo	4 mo	6 mo	8 mo	10 mo	12 mo
SRS/SRT	97	79	70	55	45	37	35	31
HA-WBRT	92	76	65	50	47	35	30	29

Functional Independence



SRS/SRT	92	46	22
HA-WBRT	82	37	18

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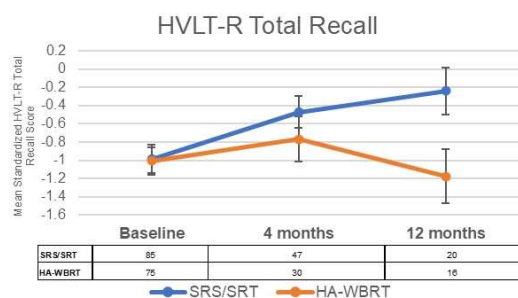
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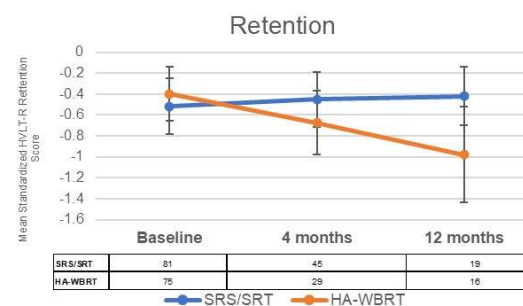
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Neurocognitive Testing - HVL



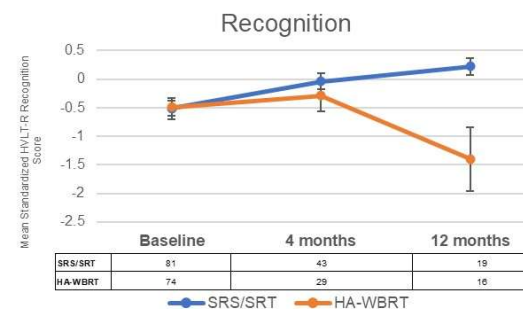
Timepoint	p
Baseline	0.39
4 Months	0.20
12 Months	0.03



Timepoint	p
Baseline	0.77
4 Months	0.69
12 Months	0.31



Timepoint	p
Baseline	0.82
4 Months	0.19
12 Months	0.01



Timepoint	p
Baseline	0.91
4 Months	0.43
12 Months	0.004

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Take-home points



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- Systemic therapies for NSCLC are (finally) becoming more effective
- Ablative local therapy has an emerging role in metastatic lung cancer
- Radical RT has the potential to improve survival in oligometastatic or oligoprogressive NSCLC, and even polymetastatic NSCLC, in addition to systemic therapy
- As systemic therapies improve, the impact of effective local therapies is likely to increase

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Stanford Thoracic Radiation Oncology Service



Bill Loo, MD PhD
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Alex Chin, MD
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Lucas Vitzthum, MD
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Heather Wakelee
Millie Das
Nathaniel Myall
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Joseph Shrager
Leah Backhus
Mark Berry
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Interventional Pulmonology

Harmeet Bedi
Kevin Duong
Meghan Ramsey
Brian Shaller
Arthur Sung

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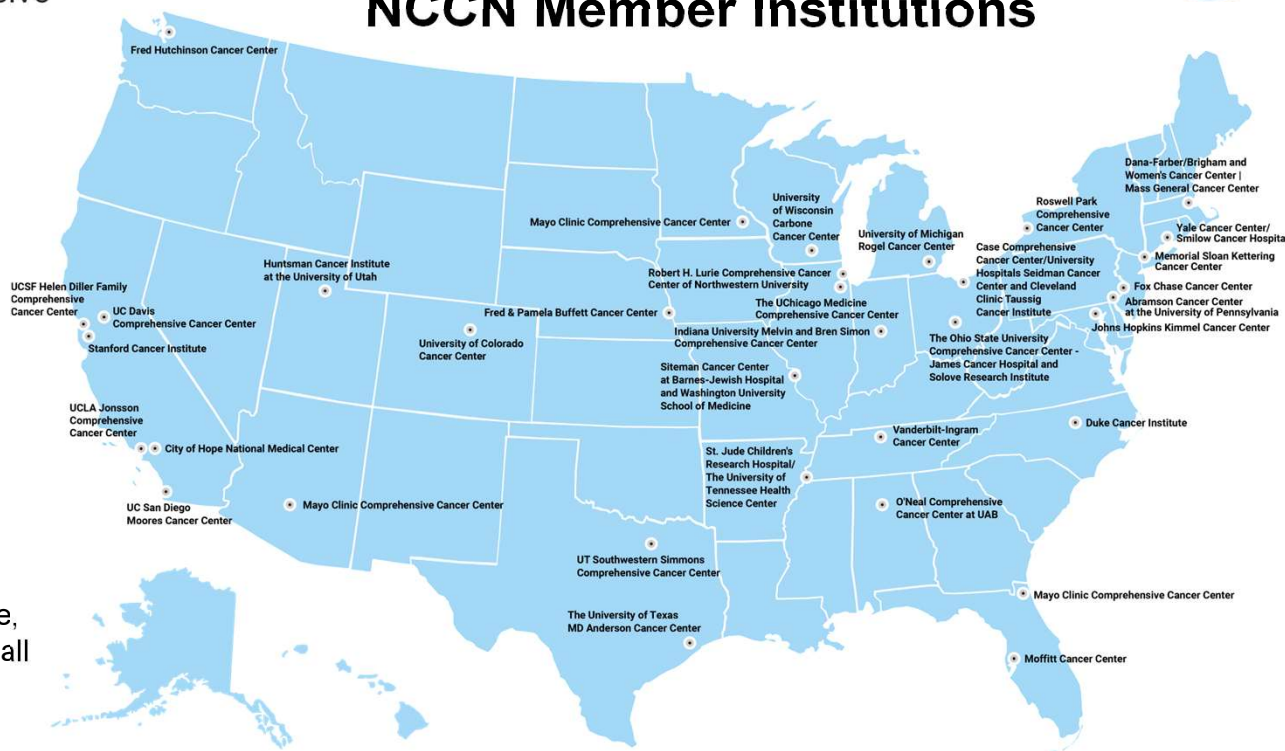
An alliance of leading cancer centers devoted to patient care, research, and education

Our Mission

To define and advance quality, effective, equitable, and accessible cancer care and prevention so all people can live better lives

Our Vision

Access to high-quality, high-value, patient-centered cancer care for all people globally



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