The role and controversies of radiation therapy in management of small cell lung cancer

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Midwest Thoracic Symposium
October 31, 2024

No conflict of interest

Objectives:

- To review the role of radiation in management of SCLC
- To review pertinent clinical trials
- To discuss some controversies in RT for SCLC

Small cell lung cancer

- Originates from neuroendocrine cell
- Represents 10-15% of all lung cancer
- Strongly linked to smoking
- Clinically very aggressive with early development of metastases
- Highly sensitive to chemotherapy and radiation
- Very high relapse rate

LS-SCLC
Confined to a single radiation port
Ipsilateral mediastinal or supraclavicular lymph nodes
Contralateral mediastinal or supraclavicular lymph nodes
Ipsilateral pleural effusions (benign or malignant)
ES-SCLC
Not confined to a single radiation port
Metastatic disease

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Table 1 **- Definition of small cell lung cancer consists of two stages:**
(1) Limited stage: Stage I-III (T any, N any, M0) that can be safely treated with definitive radiation doses. Excludes T3-4 due to multiple lung nodules that are too extensive or have tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan.
(2) Extensive stage: Stage IV (T any, N any, M 1a/b/c), or T3-4 due to multiple lung nodules that are too extensive or have tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan.

The role of radiation therapy for limited small cell lung caner

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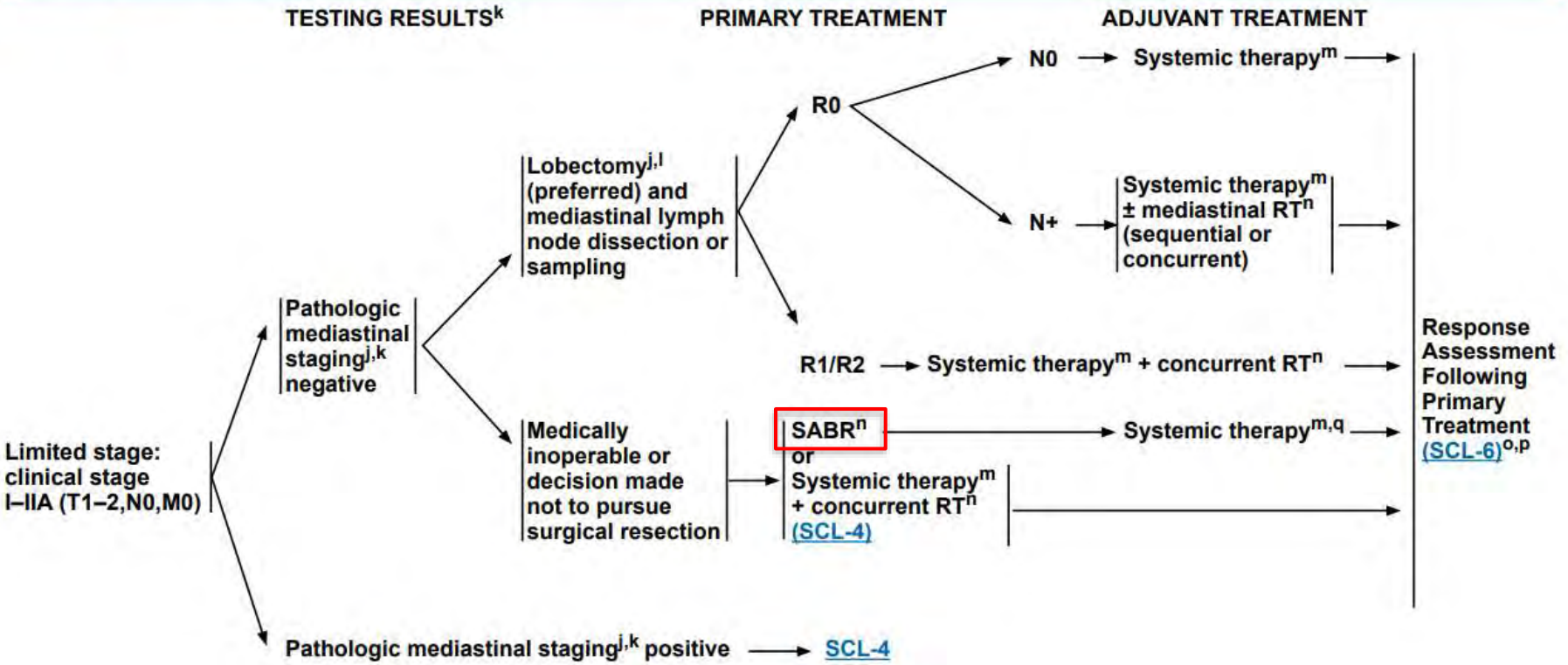


This is uncommon!

Early-Stage LS-SCLC (T1-T2N0M0)

Surgical resection with lobectomy and mediastinal nodal sampling is recommended as the preferred local therapy

For medically inoperable cT1-2 N0 patients, concurrent CRT has been the historical standard.

Ablative radiotherapy (SABR) is increasingly being utilized for well-staged medically inoperable SCLC patients.

Verma V, Hasan S, Wegner RE, Abel S, Colonias A. Stereotactic ablative radiation therapy versus conventionally fractionated radiation therapy for stage I small cell lung cancer. *Radiother Oncol.* (2019) 131:145–9. 10.1016/j.radonc.2018.12.006

Verma V, Simone CB, Allen PK, Gajjar SR, Shah C, Zhen W, et al. Multi-institutional experience of stereotactic ablative radiation therapy for stage i small cell lung cancer. *Int J Radiat Oncol.* (2017) 97:362–71. 10.1016/j.ijrobp.2016.10.041

Clinical Investigation

Multi-Institutional Experience of Stereotactic Ablative Radiation Therapy for Stage I Small Cell Lung Cancer

Vivek Verma, MD,* Charles B. Simone, II, MD,† Pamela K. Allen, PhD,‡ Sameer R. Gajjar, BS,§ Chirag Shah, MD,‖ Weining Zhen, MD,* Matthew M. Harkenrider, MD,¶ Christopher L. Hallemeier, MD,# Salma K. Jabbour, MD,** Chance L. Matthiesen, MD,†† Steve E. Braunstein, MD, PhD,‡‡ Percy Lee, MD,§§ Thomas J. Dilling, MD,‖‖ Bryan G. Allen, MD, PhD,¶¶ Elizabeth M. Nichols, MD,## Albert Attia, MD,*** Jing Zeng, MD,††† Tithi Biswas, MD,‡‡‡ Peter Paximadis, MD,§§§ Fen Wang, MD, PhD,‖‖‖ Joshua M. Walker, MD, PhD,¶¶¶ John M. Stahl, MD,### Megan E. Daly, MD,**** Roy H. Decker, MD, PhD,### Russell K. Hales, MD,†††† Henning Willers, MD,‡‡‡‡ Gregory M.M. Videtic, MD, CM, FRCPC,‖ Minesh P. Mehta, MBChB, FASTRO,§§§§ and Steven H. Lin, MD, PhD‡

**Department of Radiation Oncology, University of Nebraska Medical Center, Omaha, Nebraska; †Department of Radiation Oncology, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania; ‡Department of Radiation Oncology, University of Texas MD Anderson Cancer Center, Houston, Texas; §Baylor College of Medicine, Houston, Texas; ‖Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, Ohio; ¶Department of Radiation Oncology, Loyola University Stritch School of Medicine, Maywood, Illinois; #Department of Radiation Oncology, Mayo Clinic, Rochester, Minnesota; **Department of Radiation Oncology, Rutgers Cancer Institute of New Jersey, Rutgers University, New Brunswick, New Jersey; ††Department of Radiation Oncology, Stephenson Cancer Center, University of Oklahoma, Oklahoma City, Oklahoma; ‡‡Department of Radiation Oncology, University of California, San Francisco, School of Medicine, San Francisco, California; §§Department of Radiation Oncology, David Geffen School of Medicine at UCLA, Los Angeles, California; ‖‖Department of Radiation Oncology, Moffitt Cancer Center, Tampa, Florida; ¶¶Department of Radiation Oncology, University of Iowa Hospitals and*

Cumulative experience from 24 institutions to examine the survival outcomes, toxicities, and patterns of failure after SABR

Parameter	n (%)*
AJCC clinical T stage	
T1a	35 (46.1)
T1b	21 (27.6)
T2a	15 (19.7)
T2b	4 (5.3)
T3	1 (1.3)
Baseline staging PET performed	
Yes	67 (90.5)
No	7 (9.5)
SUV_{max} on pre-SABR PET	
Median	7.6
Range	1.3-27.7
Mediastinal nodal sampling	
Performed	19 (25.0)
Not performed	57 (75.0)
ECOG performance status at diagnosis	
0	16 (21.1)
1	36 (47.4)
2	14 (18.4)
3	9 (11.8)
Unknown	1 (1.3)

Table 2 Treatment characteristics of the study population

Parameter	n (%)
SABR dose and fractionation	
50 Gy in 5 fractions	28 (36.8)
50 Gy in 4 fractions	18 (23.9)
54 Gy in 3 fractions	8 (10.5)
60 Gy in 5 fractions	6 (7.9)
60 Gy in 3 fractions	5 (6.6)
48 Gy in 4 fractions	5 (6.6)
Other	6 (7.9)
Total SABR dose (Gy)	
Median	50
Range	30-60
SABR dose group	
≥60 Gy	12 (15.8)
50-59 Gy	55 (72.4)
40-49 Gy	8 (10.5)
<40 Gy	1 (1.3)
Biologically effective dose* (Gy)	
Median	112.5
Range	72-180
Biologically effective dose group	
<100 Gy	3 (3.9)
100-129 Gy	53 (69.7)
130-149 Gy	7 (9.2)
≥150 Gy	13 (17.1)
Receipt of PCI†	
Yes	17 (23.0)
No	53 (71.6)
Unknown	4 (5.4)
Receipt of chemotherapy	
Yes	45 (59.2)
No	27 (35.5)
Unknown, but most likely†	4 (5.3)
Type of chemotherapy	
Cisplatin/etoposide	28 (57.1)
Carboplatin/etoposide	19 (38.8)
Other/unknown	2 (4.1)

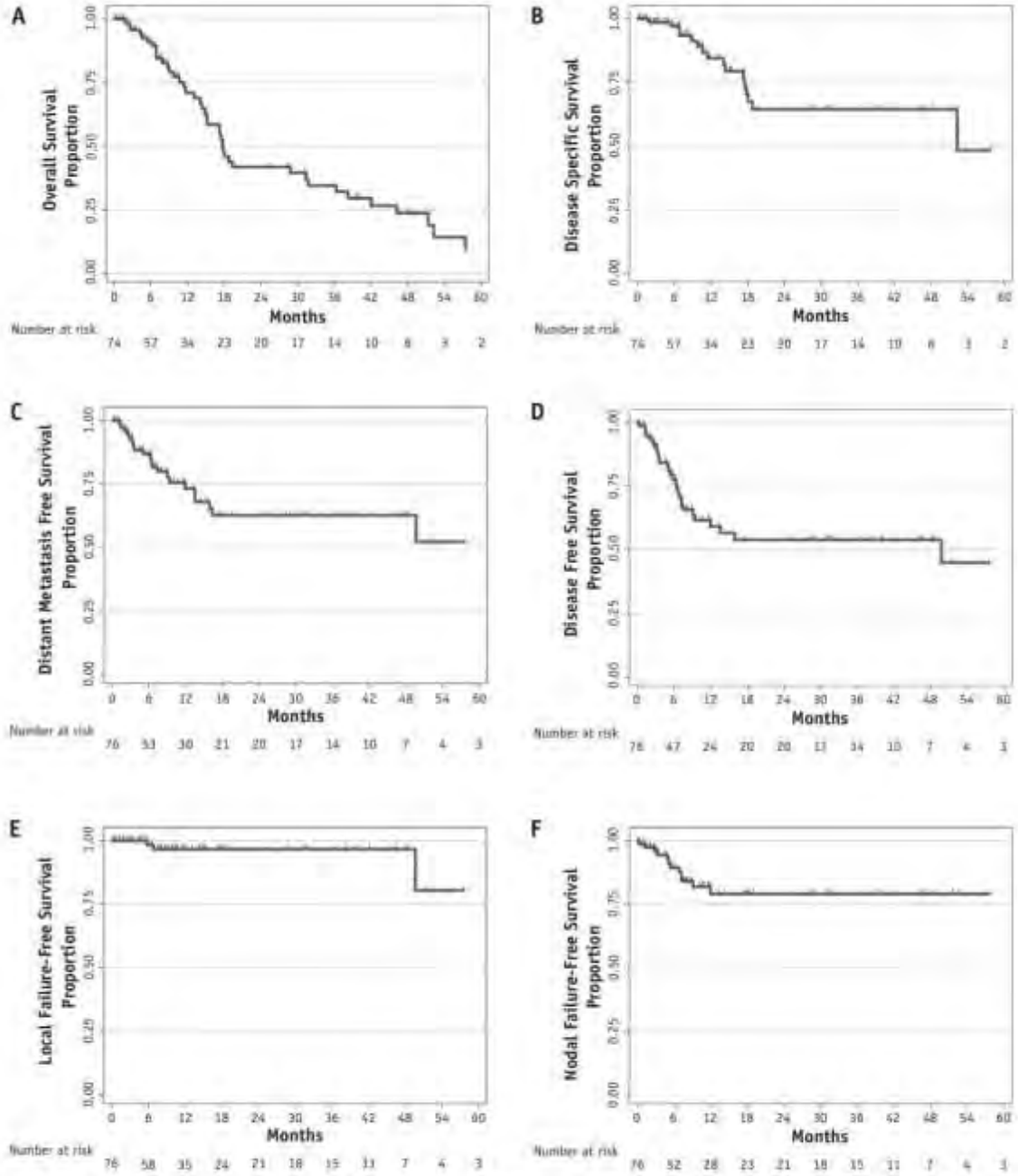


Fig. 1. Kaplan-Meier curves for the cohort illustrating overall survival (A), disease-specific survival (B), distant metastasis-free survival (C), disease-free survival (D), local failure-free survival (E), and nodal failure-free survival (F).

Table 3 Multivariate analysis using Cox proportional hazards model

Parameter	HR	95% CI	*P* value
OS			
Receipt of chemotherapy (yes vs no)	0.41	0.21-0.80	.010
Tumor size (>2 cm vs ≤2 cm)	2.80	1.32-5.94	.008
Presence of nodal failure (yes vs no)	3.88	1.73-8.75	.001
DFS			
Receipt of chemotherapy (yes vs no)	0.37	0.17-0.82	.014
Response of primary tumor (partial vs complete)	3.61	1.20-10.87	.023
LC			
Total radiation dose (continuous variable)	0.71	0.54-0.94	.018

Abbreviations: CI = confidence interval; DFS = disease-free survival; HR = hazard ratio; LC = local control; OS = overall survival.
Statistically significant variables associated with OS, DFS, and LC are listed.

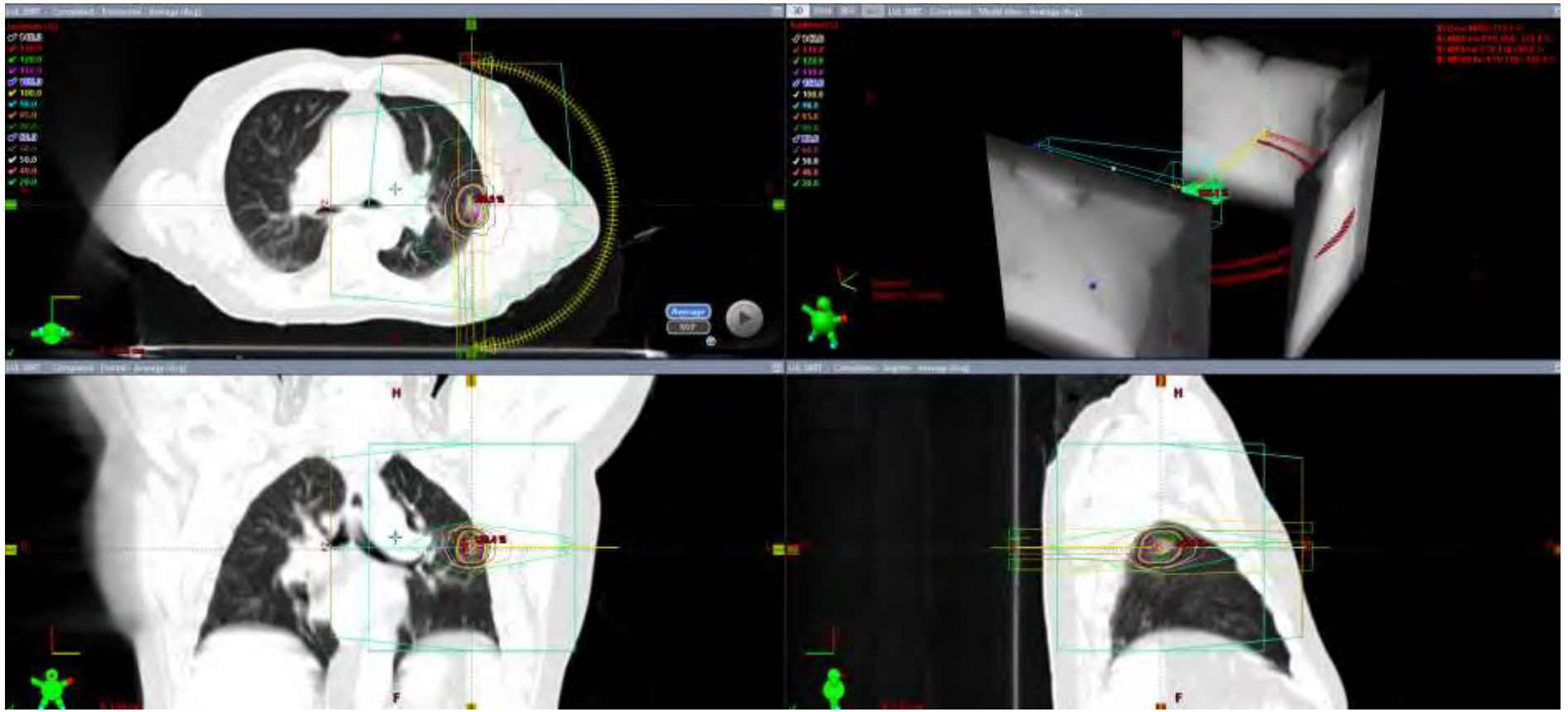
Toxicities

Overall, SABR was associated with limited toxicities. Of the 76 lesions, 9 cases (11.8%) of grade 1, 3 (3.9%) of grade 2, and 1 (1.3%) of grade 3 pneumonitis developed. Additionally, 1 case each of grade 1 dermatitis and grade 2 fatigue occurred. Also, 4 cases (5.3%) of chest wall pain (3 with grade 2 and 1 with an unknown grade) were observed, without any rib fractures. No acute or late esophageal toxicity was observed.

Table 4 Patterns of failure of the study population

Incidence and proportions	Location*	Median (range) time to failure (mo)	Concomitant failure
Local failure (n=4)			
5.3% of all lesions	In-field (n=4)	28.2 (5.8-61.3)	Elsewhere lung (n=2)
8.7% of all failures			Distant (n=1)
			Nodal and elsewhere lung (n=1)
Nodal failure (n=12)			
15.8% of all lesions	Hilum (n=7)	5.2 (0.2-11.9)	Isolated nodal (n=5)
26.1% of all failures	Mediastinum (n=7)		Distant (n=3)
	Supraclavicular (n=2)		Distant and elsewhere lung (n=3)
			Elsewhere lung (n=1)
Elsewhere lung failure (n=9)			
11.8% of all lesions	Ipsilateral lobe (n=1)	10.2 (0.4-61.3)	Isolated elsewhere lung (n=2)
19.6% of all failures	Ipsilateral lung (n=2)		Nodal and distant (n=3)
	Contralateral lung (n=3)		Distant (n=1)
	Unknown (n=3)		Local (n=2)
			Local and nodal (n=1)
Distant failure (n=21)			
27.6% of all lesions	Liver (n=13)	6.4 (1.2-49.7)	Isolated distant (n=13)
45.7% of all failures	Bone (n=7)		Nodal (n=3)
	Brain (n=4)		Elsewhere lung (n=1)
	Adrenal (n=2)		Nodal and elsewhere lung (n=3)
	Pleura (n=2)		Local (n=1)

* Totals might not sum to those of the first column because many patients developed synchronous failure.



Conclusions:

- From the present multi-institutional experience of SABR for T1-T2N0 SCLC patients, the largest to date
- SABR is a safe and effective treatment modality, especially when combined with chemotherapy
- This paradigm can offer very high LC and relatively high DFS and DSS
- The OS appears numerically similar to that of previously published surgical series for operable patients

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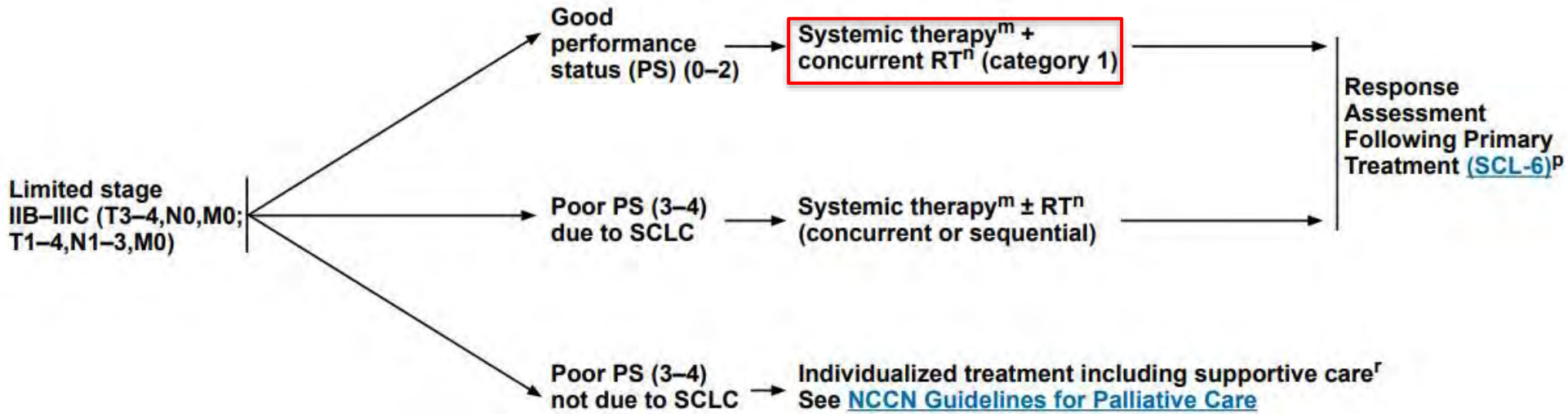
PRIMARY TREATMENT



A Meta-Analysis of Thoracic Radiotherapy for Small-Cell Lung Cancer

Authors: Jean-Pierre Pignon, M.D., Rodrigo Arriagada, M.D., Daniel C. Ihde, M.D., David H. Johnson, M.D., Michael C. Perry, M.D., Robert L. Souhami, M.D., Ola Brodin, M.D., +6, and Henry Wagner, M.D. Author Info & Affiliations

Published December 3, 1992 | N Engl J Med 1992;327:1618-1624 | DOI: 10.1056/NEJM199212033272302

VOL. 327 NO. 23

A meta-analysis of thoracic RT in LD-SCLC

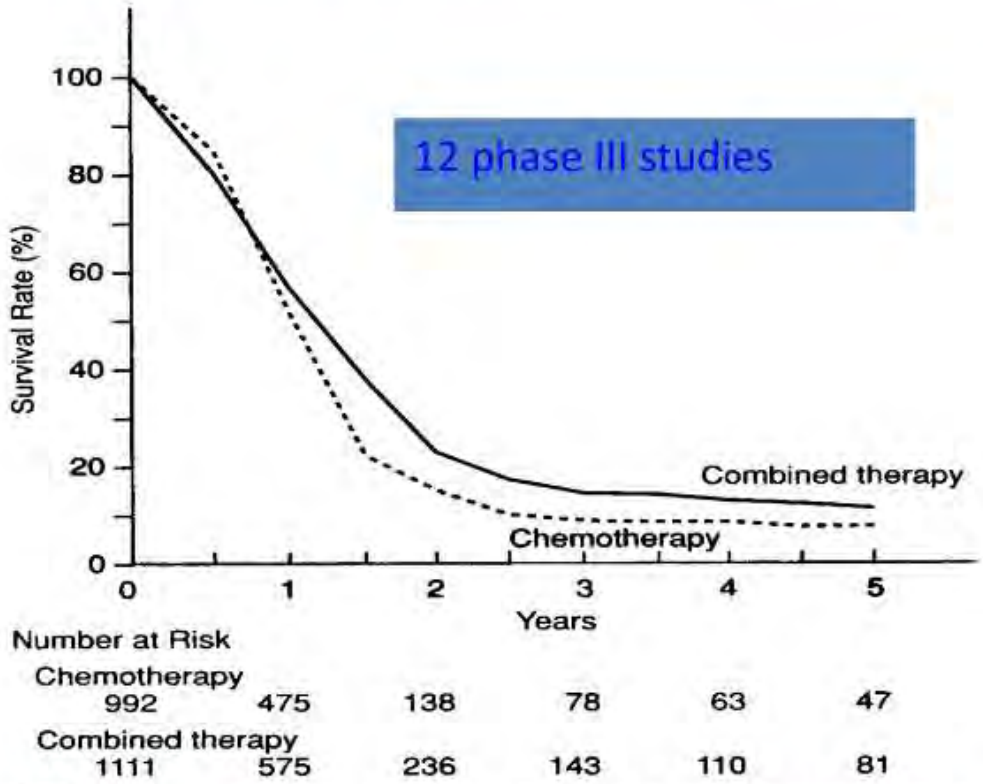


FIGURE 54.1. Survival curves for the Combined Therapy Group and the Chemotherapy Group. The three-year survival rates were 14.3% ± 1.1% in the combined-therapy group and 8.9% ± 0.9% in the chemotherapy group (for a difference of 5.4% ± 1.4%: p = 0.001 by stratified log rank test).

Pignon et al NEJM 1992

Sequence and Timing of TRT and Chemotherapy

Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal

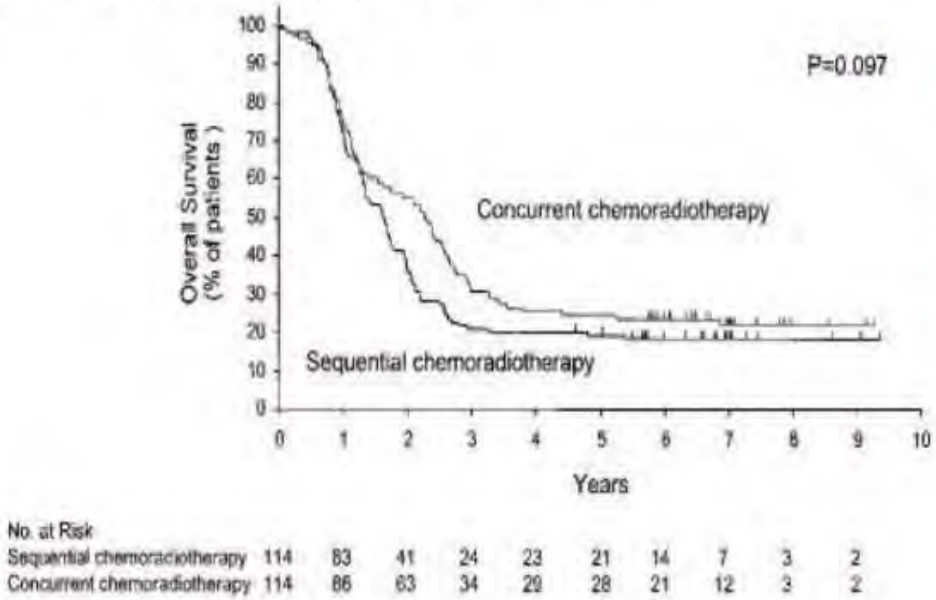
ORIGINAL REPORTS | July 15, 2002

Phase III Study of Concurrent Versus Sequential Thoracic Radiotherapy in Combination With Cisplatin and Etoposide for Limited-Stage Small-Cell Lung Cancer: Results of the Japan Clinical Oncology Group Study 9104

Authors: Minoru Takada, Masahiro Fukuoka, Masaaki Kawahara, Takahiko Sugiura, Akira Yokoyama, Soichiro Yokota, Yutaka Nishiwaki, ... SHOW ALL ...,
and for the Members of the Japan Clinical Oncology Group AUTHORS INFO & AFFILIATIONS

Publication: Journal of Clinical Oncology • Volume 20, Number 14 • https://doi.org/10.1200/JCO.2002.12.071

N=231
4 cycles PE CCRT from cycle 1 Vs Sequential RT after cycle 4 PE
RT- 45 Gy/3 wks, 1.5 Gy b.i.d



	CCRT	Sequential	P value
Median survival	27mos	19.7mos	
2-yr OS	54	35	0.097
3-yr OS	29.8	20	
5-yr OS	23	18	
Leukopenia >3	88	54	<0.001

CDDP 80mg/m2D1,
etoposide 100mg/m2 D1-3
CCRT 4qwkly, seq- 3qwkly

CONCLUSION:

This study strongly suggests that cisplatin plus etoposide and concurrent radiotherapy is more effective for the treatment of LS-SCLC than cisplatin plus etoposide and sequential radiotherapy.

review

Annals of Oncology 17: 543–552, 2006
doi:10.1093/annonc/mdj094
Published online 12 December 2005

Systematic review and meta-analysis of randomised, controlled trials of the timing of chest radiotherapy in patients with limited-stage, small-cell lung cancer

D. De Ruysscher[1,2*], M. Pijls-Johannesma[2], J. Vansteenkiste[3], A. Kester[5], I. Rutten[4] & P. Lambin[1,2]

[1]Department of Radiotherapy, GROW, University Hospital Maastricht, Maastricht, The Netherlands; [2]MAASTRO Clinic, Maastricht, The Netherlands; [3]Respiratory Oncology Unit (Dept. Pulmonology) and Leuven Lung Cancer Group, University Hospital, Leuven, Belgium; [4]Department of Radiotherapy, University Hospital Liège, Liège, Belgium; [5]Department of Methodology and Statistics, University Maastricht, Maastricht, The Netherlands

Systematic Review Evaluating the Timing of Thoracic Radiation Therapy in Combined Modality Therapy for Limited-Stage Small-Cell Lung Cancer

Daniel B. Fried, David E. Morris, Charles Poole, Julian G. Rosenman, Jan S. Halle, Frank C. Detterbeck, Thomas A. Hensing, and Mark A. Socinski

JCO(22) 2004: pp. 4837-4845

- **Early TRT**

RT initiated within 9 weeks after starting chemotherapy

- **Late TRT**

RT initiated after 9 weeks after starting chemotherapy

Survival RR for early TRT vs late TRT was 1.17

Absolute survival advantage 5.2% @2 year survival early TRT

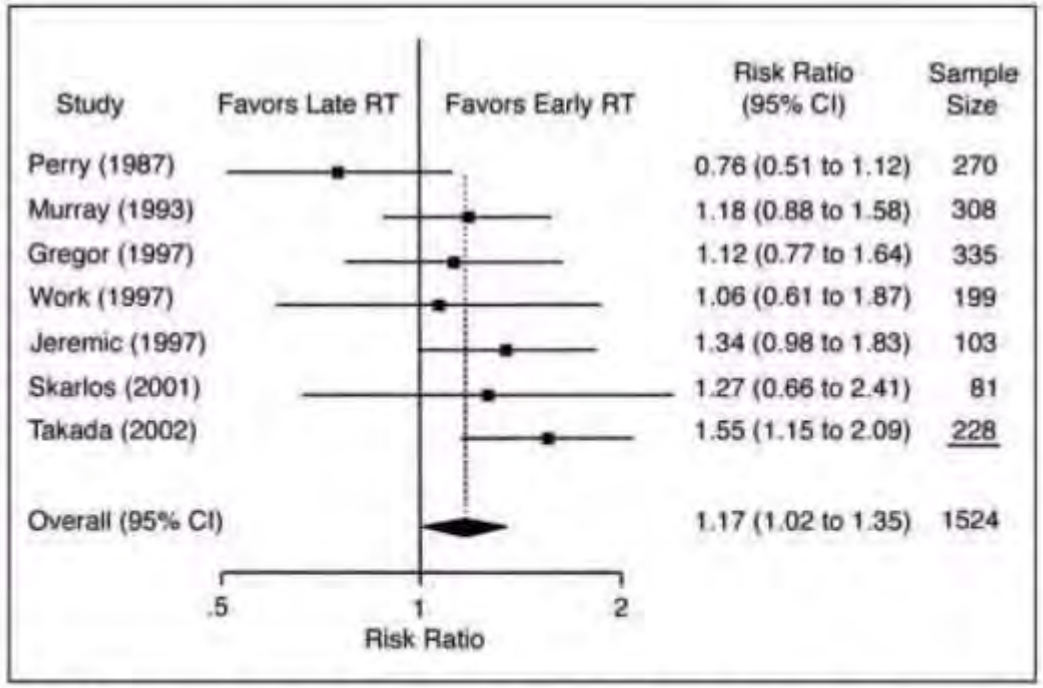


Fig 1. Two-year overall survival risk ratio forest plot for early v late thoracic radiation therapy (RT)

Conclusions:

There are indications that the 5-year survival rates of patients with LS-SCLC are in favor of early chest radiotherapy, with a significant difference if the overall treatment time of chest radiation is less than 30 days.

Impact of during of radiation (package time)

Meta-Analysis > J Clin Oncol. 2006 Mar 1;24(7):1057-63. doi: 10.1200/JCO.2005.02.9793.

Time between the first day of chemotherapy and the last day of chest radiation is the most important predictor of survival in limited-disease small-cell lung cancer

Dirk De Ruysscher [1], Madelon Pijls-Johannesma, Søren M Bentzen, André Minken, Rinus Wanders, Ludy Lutgens, Monique Hochstenbag, Liesbeth Boersma, Bradly Wouters, Guido Lammering, Johan Vansteenkiste, Philippe Lambin

Affiliations + expand

PMID: 16505424 DOI: 10.1200/JCO.2005.02.9793

Table 1. Summary of the Selected Phase III Trials Investigating Chest Radiation Schedules Combined With Chemotherapy for Limited-Stage Small-Cell Lung Cancer

Study	No. of Patients	Radiation Schedule	Day That RT Was Started	Concurrent CT	5-Year % LC*	5-Year Survival Rate (%)	Severe Pneumonitis (%)	Severe Esophagitis (%)	SER (days)	$EQD_{2,T}$ (Gy)
Murray et al[28]	155	40 Gy/15 f/19 d	21	Yes	45	20	3.2	15	40	47.13
	153	40 Gy/15 f/19 d	105	Yes	45	11	0.7	7.5	166	47.13
Jeremic et al[31]	52	54 Gy/36 f/26 d	1	Yes	58	30	1.9	28.8	26	51.75
	51	54 Gy/36 f/26 d	42	Yes	35	15	0	25.4	61	51.75
Turrisi et al[23]	211	45 Gy/30 f/19 d	1-19	Yes	64	26	NR	33	19-38	48.02
	206	45 Gy/25 f/33 d	1-19	Yes	48	16	NR	16	33-52	39.35
Takada et al[24]	114	45 Gy/30 f/19 d	2	Yes	82	24	NR	9	20	48.02
	114	45 Gy/30 f/19 d	84	No	82	18	NR	4	103	48.02

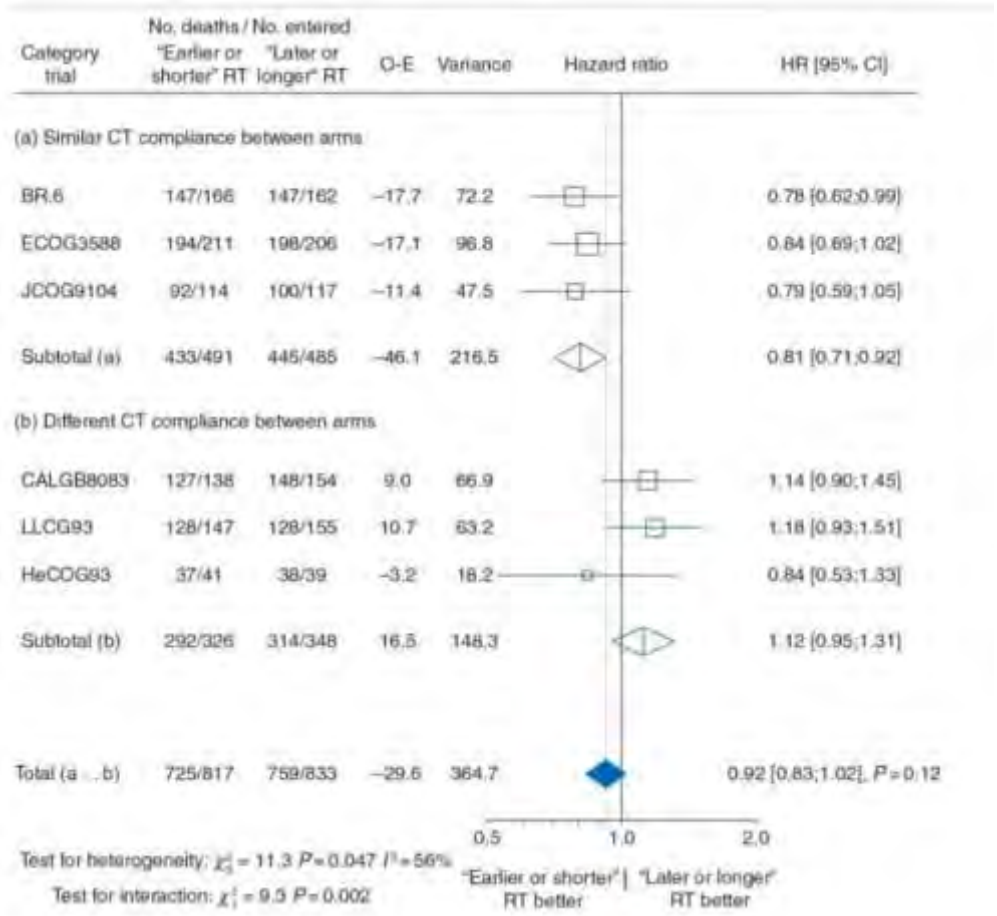
Abbreviations: RT, radiotherapy; CT, chemotherapy; LC, local tumor control; SER, the time from the start of any treatment to the end of chest irradiation; f, fractions; NR, not reported; $EQD_{2,T}$, equivalent dose at 2 Gy corrected for overall treatment time of radiotherapy.
*Cumulative % LC except for Takada et al[24] (first site of recurrence).

Annals of Oncology
Volume 27, Issue 10, October 2016, Pages 1818-1828

reviews

Impact of thoracic radiotherapy timing in limited-stage small-cell lung cancer: usefulness of the individual patient data meta-analysis †

D. De Ruysscher [1 2 ‡], B. Lueza [3 4 ‡], C. Le Péchoux [5 6], D.H. Johnson [7], M. O'Brien [8], N. Murray [9], S. Spiro [10], X. Wang [11], M. Takada [12], B. Lebeau [13], W. Blackstock [14], D. Skarlos [15], P. Baas [16], H. Choy [17], A. Price [18], L. Seymour [19], R. Arriagada [20 21], J.-P. Pignon [3 4]
on behalf of the RTT-SCLC Collaborative Group[§]



Conclusion:

'Earlier or shorter' delivery of thoracic radiotherapy with planned CT significantly improves 5-year overall survival at the expense of more acute toxicity, especially esophagitis.

Shorter period (<30 days) between the start of any treatment until the end of radiotherapy (SER) was shown to predict better 5-year OS, with decrease of 1.83% was shown for each week of SER extension beyond 30 days (20% improvement in 5-year OS if SER<30 days).

Conclusions:

- In more advanced LS-SCLC (clinical Stage II-III), concurrent CRT is the current standard of care.
- Concurrent CRT where RT starts with an early cycle (1st or 2nd) of chemotherapy is more effective compared to delayed-start RT or sequential CRT.
- Early TRT yielded better survival compared to delayed TRT (e.g., at cycle 4 of chemotherapy) in 2 meta-analyses.
- Shorter duration of TRT is more effective than protracted TRT

Optimal Dose and Fractionation?

Twice-Daily Compared with Once-Daily Thoracic Radiotherapy in Limited Small-Cell Lung Cancer Treated Concurrently with Cisplatin and Etoposide

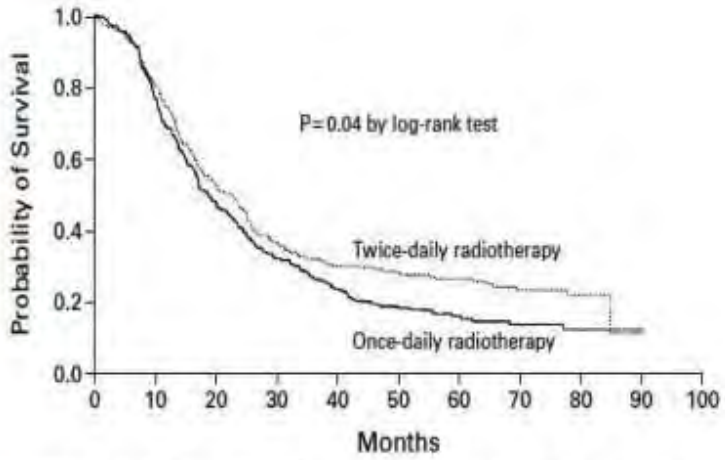
Authors: Andrew T. Turrisi, M.D., Kyungmann Kim, Ph.D., Ronald Blum, M.D., William T. Sause, M.D., Robert B. Livingston, M.D., Ritsuko Komaki, M.D., Henry Wagner, M.D., Seena Aisner, M.D., and David H. Johnson, M.D. Author Info & Affiliations

Published January 28, 1999 | N Engl J Med 1999;340:265-271 | DOI: 10.1056/NEJM199901283400403

VOL. 340 NO. 4 |

Intergroup 0096 prospective randomized controlled trial

		BD 45Gy/1.5BD/3 wks	OD 45/1.8OD/ 5wks	P value
N		211	206	
2yr OS		47	41	
5-yr OS		26%	16%	0.04
recurrence	Local	36%	52%	0.06
	L+D	6%	23%	
Osophagitis GIII		27%	11%	<0.001



Treatment Group	0–20 Mo	20–40 Mo	40–60 Mo	60–80 Mo	80–100 Mo
	no. of deaths/no. at risk				
Once daily	108/206	48/96	15/47	4/21	0/5
Twice daily	100/211	47/109	7/62	5/42	1/14

Kaplan–Meier Estimates of Overall Survival for All 417 Patients Assigned to Treatment Groups.

Chemo: CDDP 120mg/m2D1+etop 120mg/m2D1-3 CCRT C1

The current standard of care of thoracic CRT dose fractionation was established in the landmark Intergroup 0096 prospective randomized controlled trial which demonstrated superiority of concurrent BID TRT

Despite the superiority with BID fractionation, it has not been widely adapted universally for reasons:

- Inconvenience of BID treatments
- Increased toxicity (perceived?)
- A common criticism of this trial that the QD TRT arm employed a lower biologically equivalent dose (BED) compared to the BID fractionation

Selected trials of chemoradiation for LS-SCLC comparing 45 Gy/30 fractions BID regimen with QD TRT regimens.

Study	Completed	*N*	TRT in comparison group	Chemotherapy (cycles)	2-year OS (%)	Median OS (months)	*p*-value	Grade 3–4 esophagitis (%)	*p*-value
INT-0096 (29)	Yes	471	45 Gy/25 fractions QD	EP (4)	47 (BID) vs. 41 (QD)	23 (BID) vs. 19 (QD)	0.04	32 (BID) vs. 16 (QD)	<0.001
Norwegian Lung Cancer Study Group (33)	Yes	157	42 Gy/15 fractions QD	EP (4)	53 (BID) vs. 42 (QD)	25 (BID) vs. 19 (QD)	0.61	31 (BID) vs. 33 (QD)	0.80
CONVERT (34)	Yes	543	66 Gy/33 fractions QD	EP (4–6)	56 (BID) vs. 51 (QD)	30 (BID) vs. 25 (QD)	0.15	19 (BID) vs. 19 (QD)	0.85
CALGB 30610/RTOG 0538	No	729	70 Gy/35 fractions QD	EP (4)	NA	NA	NA	NA	NA

BID, twice daily treatments; QD, once daily treatments; EP, etoposide-cisplatin; OS, overall survival.

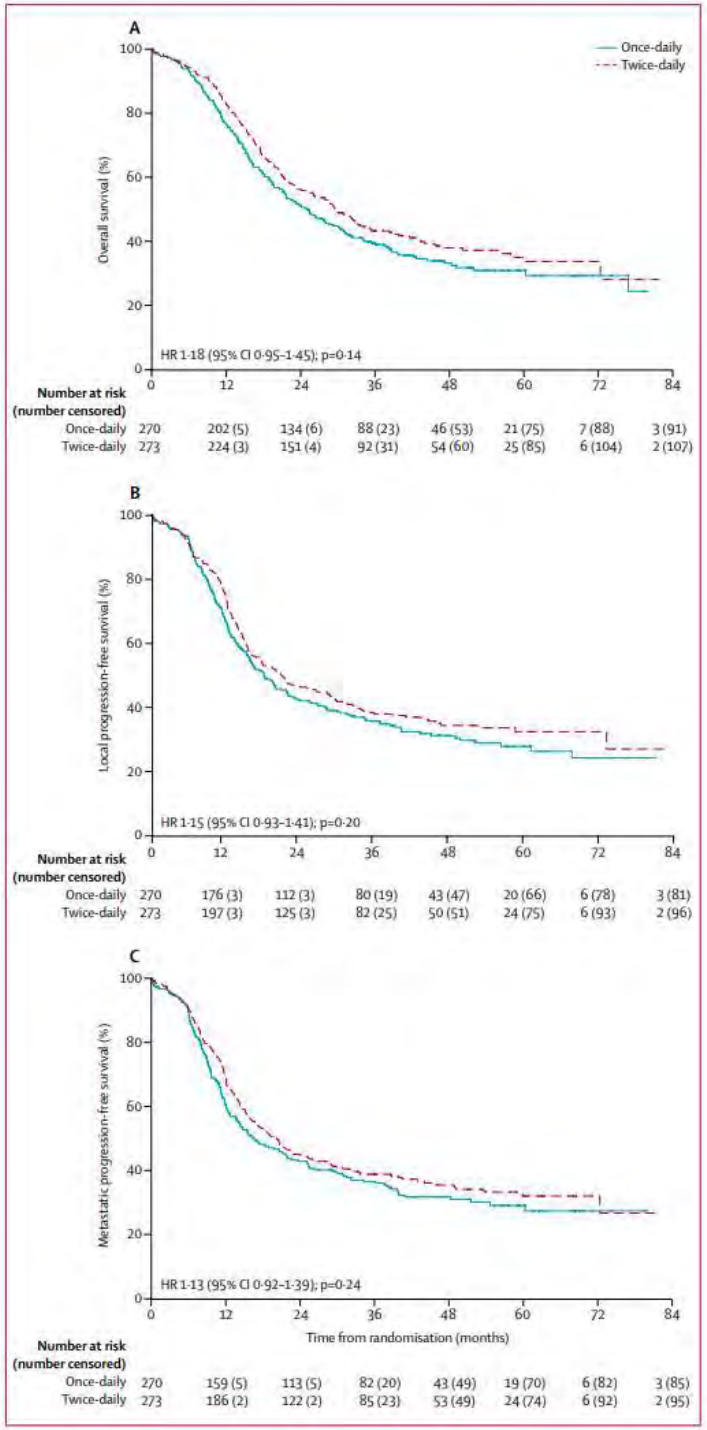
Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial

Corinne Faivre-Finn, Michael Snee, Linda Ashcroft, Wiebke Appel, Fabrice Barlesi, Adityanarayan Bhatnagar, Andrea Bezjak, Felipe Cardenal, Pierre Fournel, Susan Harden, Cecile Le Pechoux, Rhona McMenemin, Nazia Mohammed, Mary O'Brien, Jason Pantarotto, Veerle Surmont, Jan P Van Meerbeeck, Penella J Woll, Paul Lorigan, Fiona Blackhall, for the CONVERT Study Team

Lancet Oncol 2017; 18: 1116–25

2008-2013/ 73 centers/ 8 countries
Total 547 pts : 274OD arm, 273 BD arm

CCRT (cis +etop) from 2nd cycle (D22)		BD arm 45Gy/ 30#/ 1.5Gy/ 3 weeks (19 days)	OD arm 66Gy/ 33#/ 2 Gy/# 45 days	
Median FU		45 mos		
Median survival		30mos	25mos	
2- yr OS		56%	51%	
Grade 3-4	Neutropenia	74%	65%	P=0.05
	FN	49%	38%	
	esophagistis	19%	19%	
	pneumonitis	3%	2%	



	Twice-daily group (n=248)			Once-daily group (n=233)			p value*
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	
Dermatitis	15 (6%)	..	..	17 (7%)	..	..	..
Oesophagitis	29 (12%)	..	..	39 (17%)	4 (2%)	..	0·06
Oesophageal stricture or fistula	8 (3%)	..	..	6 (3%)	1 (<1%)	..	0·48
Pulmonary fibrosis	119 (48%)	3 (1%)	..	106 (46%)	2 (1%)	..	>0·99
Pneumonitis	71 (29%)	5 (2%)	1 (<1%)	70 (30%)	5 (2%)	1 (<1%)	0·90
Myelitis	1 (<1%)†	..	..	8 (3%)†	..	..	..
Other	131 (53%)	20 (8%)	3 (1%)	113 (49%)	18 (8%)	2 (1%)	0·78

Data are n (%). *p values calculated for grade 3–4 adverse events. †All cases of myelitis were grade 1 adverse events.

Table 5: **Late adverse events (>3 months after study treatment)**

- QD TRT did not improve OS in patients with LD-SCLC compared with BID TRT when given concurrently with chemotherapy.
- Both acute and late toxicities were similar and lower than expected with both regimens

OS with both regimens were higher than the survival results reported in the Intergroup 0096 study.

In CONVERT, 2-year survival for BID and QD TRT was 56% and 51%, vs 47% and 41% in the Intergroup 0096 study

Conclusion:

- BID TRT should continue to be considered standard-of-care.
- Furthermore, BID TRT concurrently with chemotherapy is well tolerated, with better compliance and shorter treatment time than QD treatment.
- From a pragmatic perspective, QD TRT could be considered when delivery of BID TRT is impossible because of departmental logistics or patient choice.

What about dose escalation

High-Dose Once-Daily Thoracic Radiotherapy in Limited-Stage Small-Cell Lung Cancer: CALGB 30610 (Alliance)/RTOG 0538

Jeffrey Bogart, MD[1]; Xiaofei Wang, MD[2]; Gregory Masters, MD[3]; Junheng Gao, MD[2]; Ritsuko Komaki, MD[4]; Laurie E. Gaspar, MD[5,6]; John Heymach, MD[4]; James Bonner, MD[7]; Charles Kuzma, MD[8]; Saiama Waqar, MD[9]; William Petty, MD[10]; Thomas E. Stinchcombe, MD[11]; Jeffrey D. Bradley, MD[12]; and Everett Vokes, MD[13]

J Clin Oncol 41:2394-2402.

METHODS This phase III trial, CALGB 30610/RTOG 0538 (ClinicalTrials.gov identifier: NCT00632853), was conducted in two stages. In the first stage, patients with limited-stage disease were randomly assigned to receive 45-Gy twice-daily, 70-Gy once-daily, or 61.2-Gy concomitant-boost radiotherapy, starting with either the first or second (of four total) chemotherapy cycles. In the second stage, allocation to the 61.2-Gy arm was discontinued following planned interim toxicity analysis, and the study continued with two remaining arms. The primary end point was overall survival (OS) in the intention-to-treat population.

TABLE 2. Radiotherapy and Chemotherapy Detail

Variable	45 Gy (N = 313), No. (%)	70 Gy (N = 325), No. (%)	Total (N = 638), No. (%)	*P*
Radiotherapy technique				.9499
Intensity modulated	188 (60.1)	196 (60.3)	384 (60.2)	
Three-dimensional conformal	125 (39.9)	129 (39.7)	254 (39.8)	
Radiotherapy start time				.7618
First cycle of chemotherapy	141 (45.0)	137 (42.2)	278 (43.6)	
Second cycle of chemotherapy	172 (54.9)	188 (57.8)	360 (56.5)	
Chemotherapy backbone				.5944
Cisplatin	252 (80.5)	267 (82.2)	519 (81.3)	
Carboplatin	61 (19.5)	58 (17.8)	119 (18.7)	

NOTE. *P* values for continuous variables are from Kruskal-Wallis test and *P* values for categorical variables are from chi-square test.

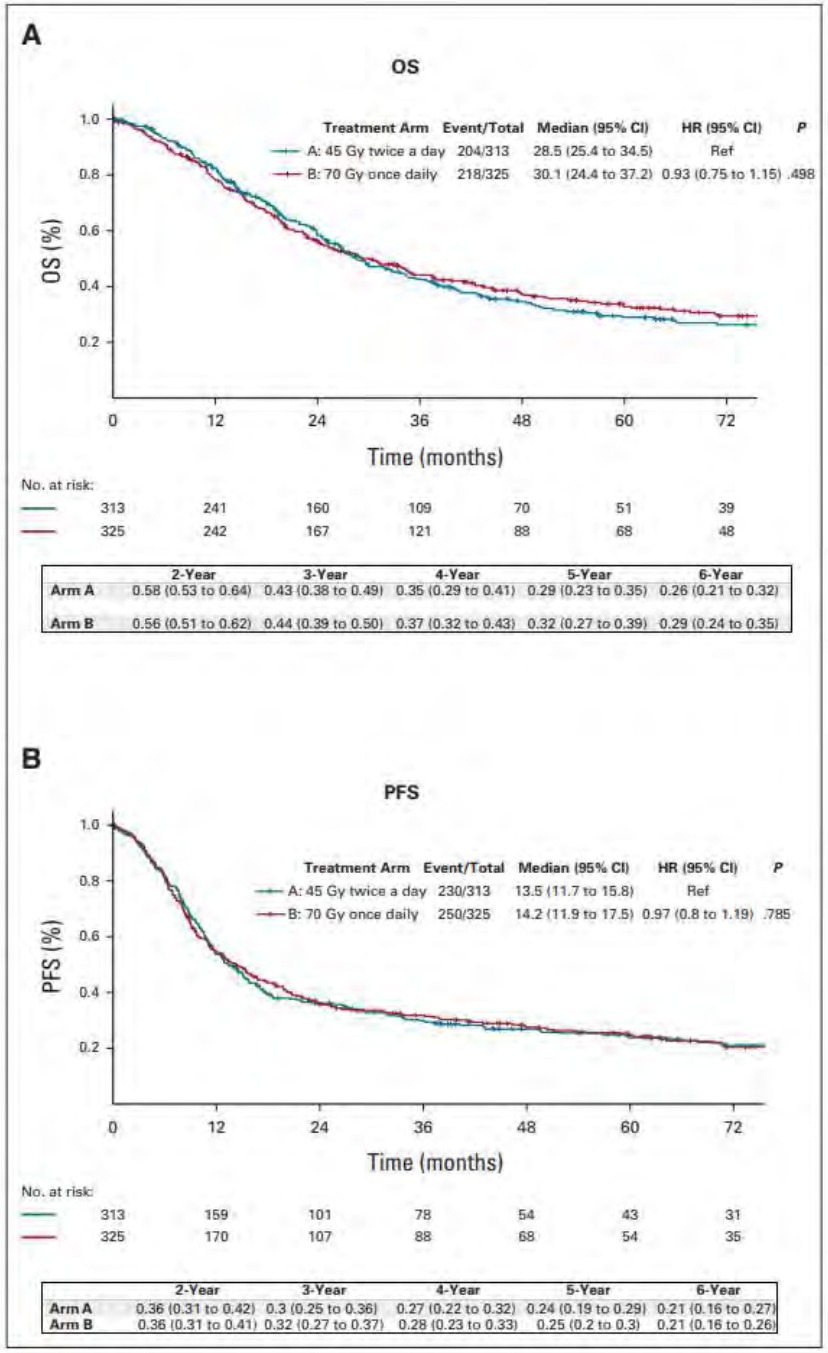


FIG 2. (A) OS and (B) investigator-assessed PFS in the intention-to treat population. *P* values are from stratified log-rank test. HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

TABLE 3. Summary of Severe (grade 3+) AEs and Commonly Occurring (> 10% on either arm) Severe AEs

AE Category	45 Gy (n = 295), No. (%)	70 Gy (n = 301), No. (%)	*P*
Overall grade 3 AE (max)	93 (29.7)	77 (23.7)	.0855
Overall grade 4 AE (max)	149 (47.6)	161 (49.5)	.6250
Overall grade 5 AE	4 (1.3)	11 (3.4)	.0792
Hematologic grade 3 AE	66 (21.1)	70 (21.5)	.8891
Hematologic grade 4 AE	140 (44.7)	157 (48.3)	.3649
Hematologic grade 5 AE	0 (0.0)	0 (0.0)	NA
Nonhematologic grade 3 AE	131 (41.9)	127 (39.1)	.4751
Nonhematologic grade 4 AE	36 (11.5)	49 (15.1)	.1840
Nonhematologic grade 5 AE	4 (1.3)	11 (3.4)	.0792
Neutrophil count decreased	186 (63.1)	198 (65.8)	.4864
Leukocyte count decreased	148 (50.2)	177 (58.8)	.0343
Hemoglobin decreased	60 (20.3)	79 (26.2)	.0882
Platelet count decreased	43 (14.6)	57 (18.9)	.1543
Dehydration	42 (14.2)	39 (13.0)	.6483
Febrile neutropenia	40 (13.6)	38 (12.6)	.7351
Lymphocyte count decreased	28 (9.5)	49 (16.3)	.0135
Esophageal pain	32 (10.8)	36 (12.0)	.6692
Dysphagia	28 (9.5)	34 (11.3)	.4707

NOTE. *P* values for continuous variables are from Kruskal-Wallis test and *P* values for categorical variables are from chi-square test. Max = patients with maximum grade toxicity, such that each patient is only counted once as having grade 3 or grade 4 toxicity.
Abbreviations: AE, adverse event; Max, maximum; NA, not available.

CONCLUSION:

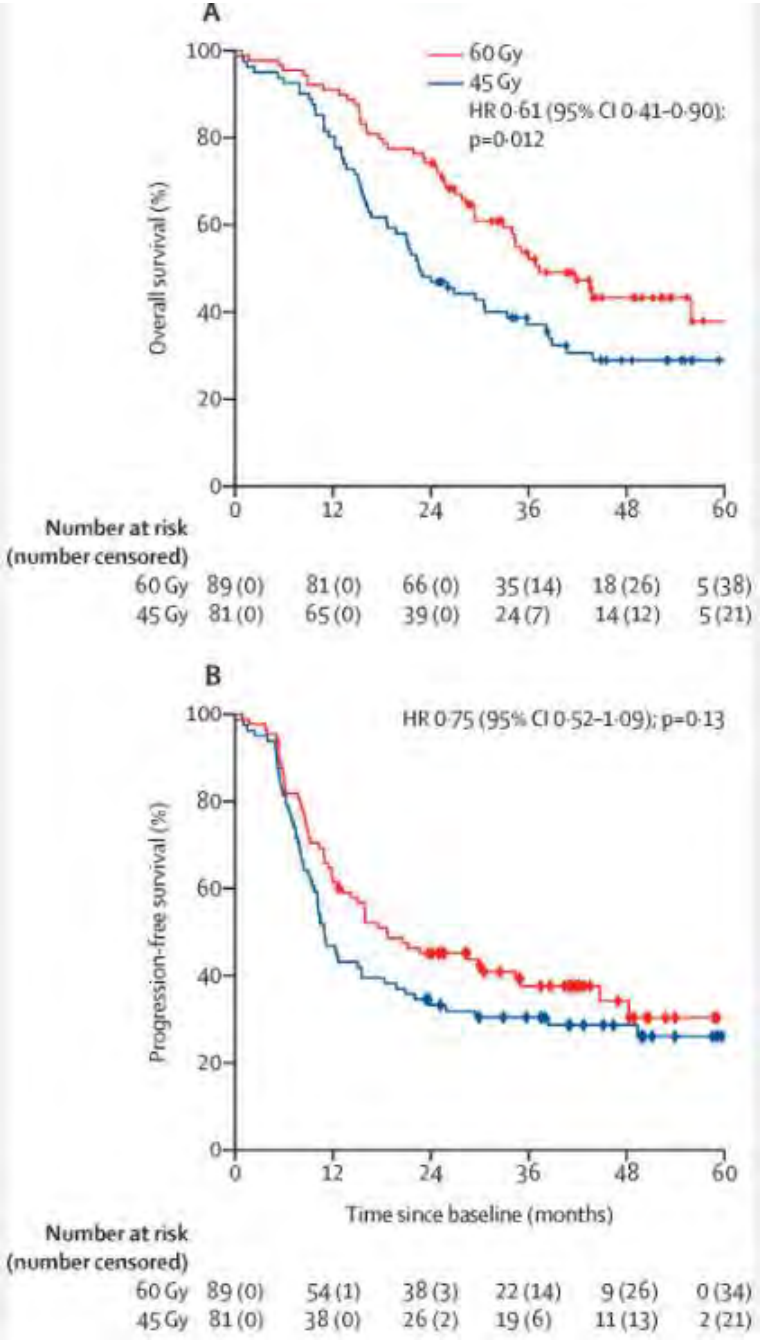
45Gy twice-daily radiotherapy remains the standard of care

THE LANCET
Oncology

High-dose versus standard-dose twice-daily thoracic radiotherapy for patients with limited stage small-cell lung cancer: an open-label, randomised, phase 2 trial

Prof Bjørn Henning Grønberg, MD [a,b] · Kristin Toftaker Killingberg, MD [a,b] · Øystein Fløtten, MD [c] · Odd Terje Brustugun, MD [d] · Kjersti Hornslien, MD [e] · Tesfaye Madebo, PhD [f] · et al. Show more

Volume 22, Issue 3p321-331March 2021



•Between May 2014 and June 2018, a total of 90 patients were randomized to the high-dose (n=45) or standard-dose (n=45) group.
•The median follow-up was 42 months.
•The 2-year OS rate was significantly higher in the high-dose group compared with the standard-dose group (56% vs. 33%; HR 0.51, 95% confidence interval 0.28–0.91).
•The 2-year PFS rate was also higher in the high-dose group (39% vs. 20%; HR 0.61, 95% confidence interval 0.36–1.04).
•There was no significant difference in toxicity or quality of life between the two groups.

PFS: median 18 months vs 10 months in favor of 60 Gy (p=0.13)

2y OS:74% vs 48% (p=0.0005), median OS 37 vs 23 mos (p=0.012 in favor of 60Gy).

Conclusion:

High-dose regimen of 60Gy in 40 fractions resulted in a substantial survival improvement without increased toxicity, suggesting that this regimen may be a more effective treatment option for patients with limited stage small-cell lung cancer.

A game changer?!

1 · Volume 117, Issue 2, Supplement , S1, October 01, 2023

High Dose Hyperfractionated Thoracic Radiotherapy vs. Standard Dose for Limited Stage Small-Cell Lung Cancer: A Multicenter, Open-Label Randomized, Phase 3 Trial

J. Yu [1] · L. Jiang [1] · L. Zhao [2] · ... · R. Yu [1] · J. Zhao [4] · A. SHI [1] ... Show more

To assess the efficacy and safety of high-dose, hyperfractionated thoracic radiotherapy of 54 Gy in 30 fractions compared with standard dose (45 Gy in 30 fractions) as a first-line treatment for LS-SCLC.

Results

Between June 30, 2017, and April 6, 2021, 224 eligible patients were enrolled and randomly assigned to 54 Gy (n = 108) or 45 Gy (n = 116). Median follow-up for the primary analysis was 45 months (IQR 41-48). Median overall survival was significantly improved in the 54 Gy group (62.4 months) compared with the 45 Gy group (43.1 months; p = 0.001). Median progression-free survival was significantly improved in the 54 Gy group (30.5 months) compared with the 45 Gy group (16.7 months; p = 0.044). The most common grade 3-4 adverse events were neutropenia (30 [28%] of 108 patients in the 54 Gy group vs 27 [23%] of 116 patients in the 45 Gy group), neutropenic infections (6 [6%] vs 2 [2%]), thrombocytopenia (13 [12%] vs 12 [10%]), anemia (6 [6%] vs 4 [3%]), and esophagitis (1 [1%] vs 3 [3%]). Treatment-related serious adverse events occurred in 9 [8%] patients in the 54 Gy group and 16 [14%] patients in the 45 Gy group. There were one treatment-related deaths in 54 Gy group (myocardial infarction).

Prophylactic Cranial Irradiation (PCI) in LS-SCLC

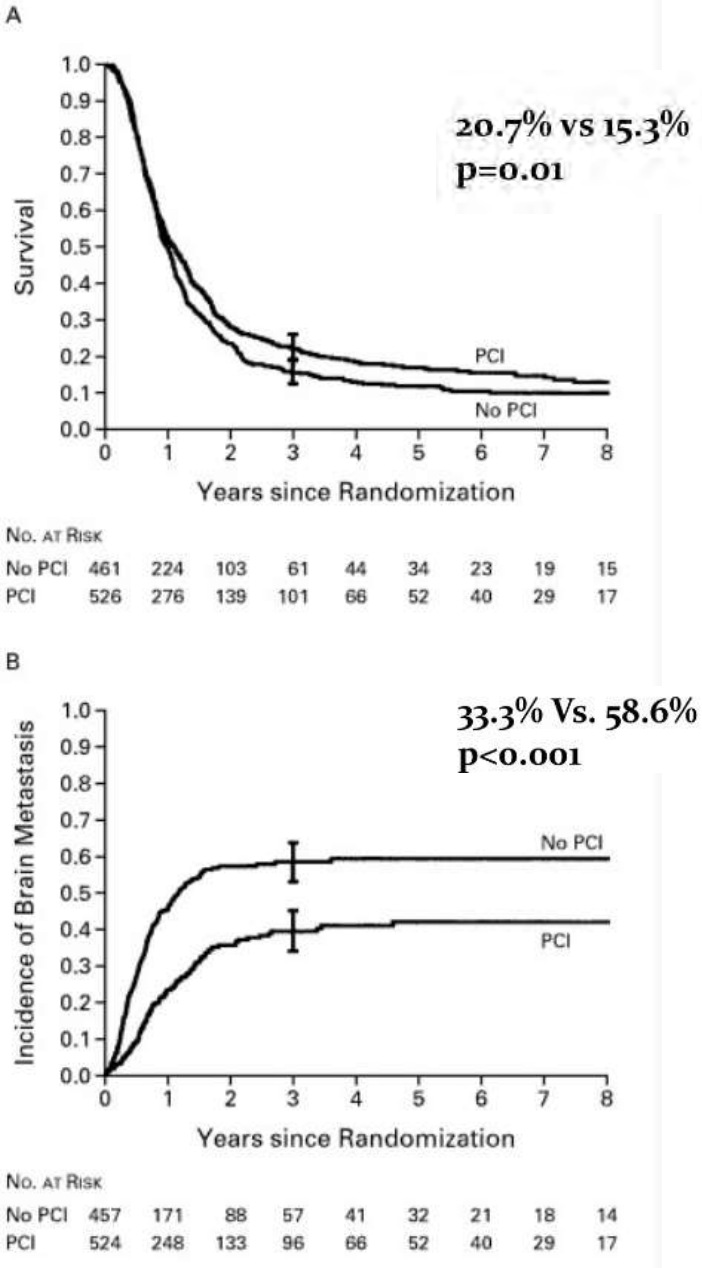
Brain metastases (BM) are the most common mode of distant spread in SCLC, with a reported 2-year incidence of approximately 50% among patients not receiving PCI

Prophylactic Cranial Irradiation for Patients with Small-Cell Lung Cancer in Complete Remission

Authors: Anne Aupérin, M.D., Rodrigo Arriagada, M.D., Jean-Pierre Pignon, M.D., Ph.D., Cécile Le Péchoux, M.D., Anna Gregor, M.D., Richard J. Stephens, Paul E.G. Kristjansen, M.D., Ph.D., Bruce E. Johnson, M.D., Hiroshi Ueoka, M.D., Henry Wagner, M.D., and Joseph Aisner, M.D., for the Prophylactic Cranial Irradiation Overview Collaborative Group* Author Info & Affiliations

Published August 12, 1999 | N Engl J Med 1999;341:476-484 | DOI: 10.1056/NEJM199908123410703

VOL. 341 NO. 7 |



The relative risk of death in the group assigned to prophylactic cranial irradiation was 0.84 (95 percent confidence interval, 0.73 to 0.97), and the relative risk of brain metastasis in this group was 0.46 (95 percent confidence interval, 0.38 to 0.57), as compared with the control group.

Absolute OS benefit of PCI was estimated to be 5.4% at 3 years.

Prophylactic cranial irradiation improves both overall survival and disease-free survival among patients with small-cell lung cancer in complete remission.

Based on current data, surgically resected p-Stage I SCLC patients aside, PCI should be offered for all LS-SCLC patients treated with reasonable performance status and no contraindications

The trials in the Auperin meta-analysis were conducted in era prior to the routine use of brain magnetic resonance imaging (MRI) in staging, with CT or clinical neurologic symptoms used to screen for BM prior to PCI

A proportion may have had BM detected. These patients, therefore, would have received whole brain radiation therapy (WBRT) for undetected, subclinical BM instead of PCI.

SWOG S1827: MRI Brain Surveillance Alone Versus MRI Surveillance and Prophylactic Cranial Irradiation (PCI): A Randomized Phase III Trial in Small-Cell Lung Cancer (MAVERICK)

Objective

This phase III trial studies magnetic resonance imaging (MRI) surveillance and prophylactic cranial irradiation (PCI) to see how well they work compared to MRI surveillance alone in treating patients with small cell lung cancer. MRI scans are used to monitor the possible spread of the cancer with an MRI machine over time. PCI is radiation therapy that is delivered to the brain in hopes of preventing spread of cancer into the brain. The use of brain MRI alone may reduce side effects of receiving PCI and prolong patients' lifespan. Monitoring with MRI scans alone (delaying radiation until the actual spread of the cancer) may be at least as good as the combination of PCI with MRI scans.

ARM I: Patients undergo conventional or hippocampal avoidance PCI over 20 minutes 5 days per week for 2 weeks. Patients also undergo MRI scan at 3, 6, 9, 12, 18, and 24 months.

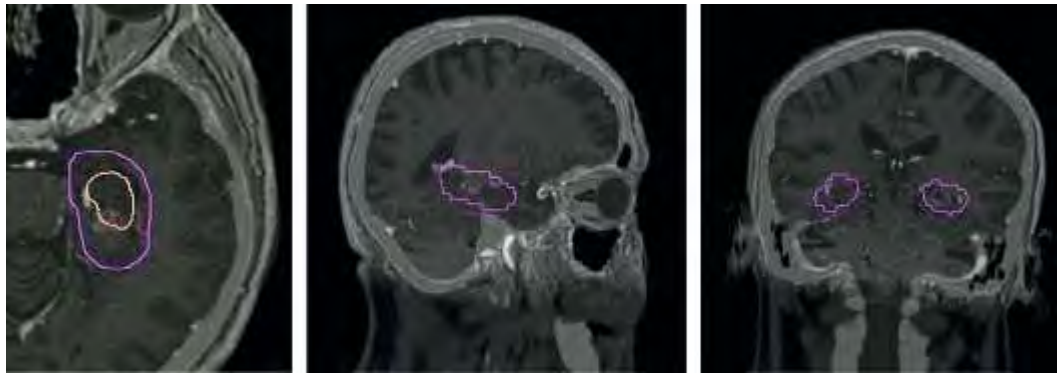
ARM II: Patients undergo MRI scan at 3, 6, 9, 12, 18, and 24 months.

It is important to weigh the potential benefits and risks of PCI in the context of individual patient characteristics and preferences. Strategies for reducing neurotoxicity risk, such as lower radiation doses or hippocampus-sparing techniques, are actively being investigated.

original reports

Randomized Phase III Trial of Prophylactic Cranial Irradiation With or Without Hippocampal Avoidance for Small-Cell Lung Cancer (PREMER): A GICOR-GOECP-SEOR Study

Núria Rodríguez de Dios, MD, PhD[1,2,3]; Felipe Couñago, MD, PhD[4]; Mauricio Murcia-Mejía, MD[5]; Mikel Rico-Oses, MD, PhD[6]; Patricia Calvo-Crespo, MD[7]; Pilar Samper, MD[8]; Carmen Vallejo, MD, PhD[9]; Javier Luna, MD[10]; Itziar Trueba, MD[11]; Amalia Sotoca, MD[12]; Cristina Cigarral, MD[13]; Núria Farré, MD[14]; Rosa M. Manero, Psy[15]; Xavier Durán, MStat, PhD[2]; Juan Domigo Gispert, MD, PhD[2,3,16,17]; Gonzalo Sánchez-Benavides, PhD[2,16,18]; Teresa Rognoni, Psy[19]; Margarita Torrente, PhD[20,21]; Jaume Capellades, MD[22]; Mar Jiménez, MD[23]; Teresa Cabada, MD, PhD[24]; Miguel Blanco, MD[25]; Ana Alonso, MD[26]; Juan Martínez-San Millán, MD[27]; José Escribano, MD[28]; Beatriz González, Psy[13]; and José Luis López-Guerra, MD, PhD[29]



Journal of Clinical Oncology
Volume 39, Number 28
https://doi.org/10.1200/JCO.21.00639

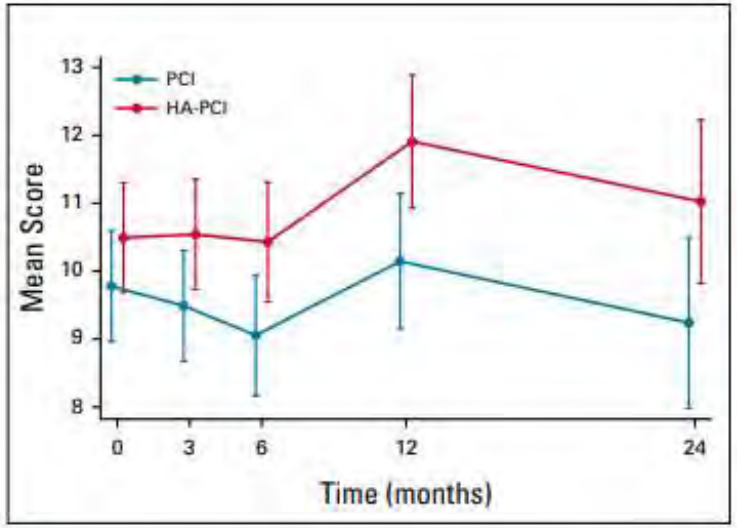


FIG 2. Mean scores of FCSRT-delayed free recall over time. FCSRT, Free and Cued Selective Reminding Test. HA, hippocampal avoidance; PCI, prophylactic cranial irradiation.

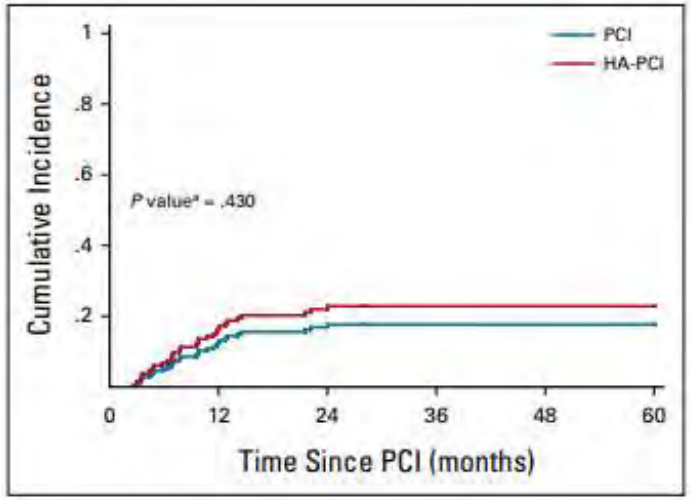


FIG 3. Cumulative incidence of brain metastases. [a]Pepe and Mori test comparing the cumulative incidence of two groups of arm. HA, hippocampal avoidance; PCI, prophylactic cranial irradiation.

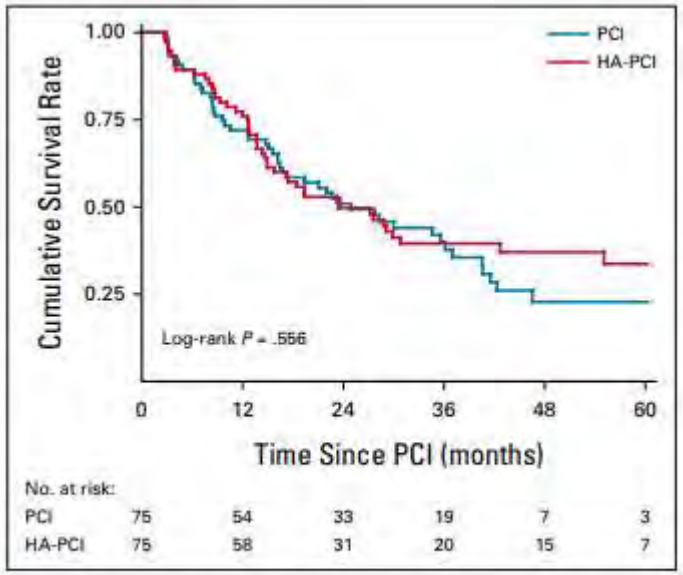


FIG 5. Overall survival for all randomly assigned patients. HA, hippocampal avoidance; PCI, prophylactic cranial irradiation.

CONCLUSION:

HA-PCI better preserves cognitive function in patients with SCLC. No differences were observed in brain failure, OS, and QoL compared with standard PCI

Neuro-Oncology

25(1), 167–176, 2023 | https://doi.org/10.1093/neuonc/noac148 | Advance Access date 31 May 2022

Hippocampal avoidance prophylactic cranial irradiation (HA-PCI) for small cell lung cancer reduces hippocampal atrophy compared to conventional PCI

Michiel B. de Ruiter, Paul F. C. Groot, Sabine Deprez, Pim Pullens, Stefan Sunaert, Dirk de Ruysscher, Sanne B. Schagen†, and José Belderbos†

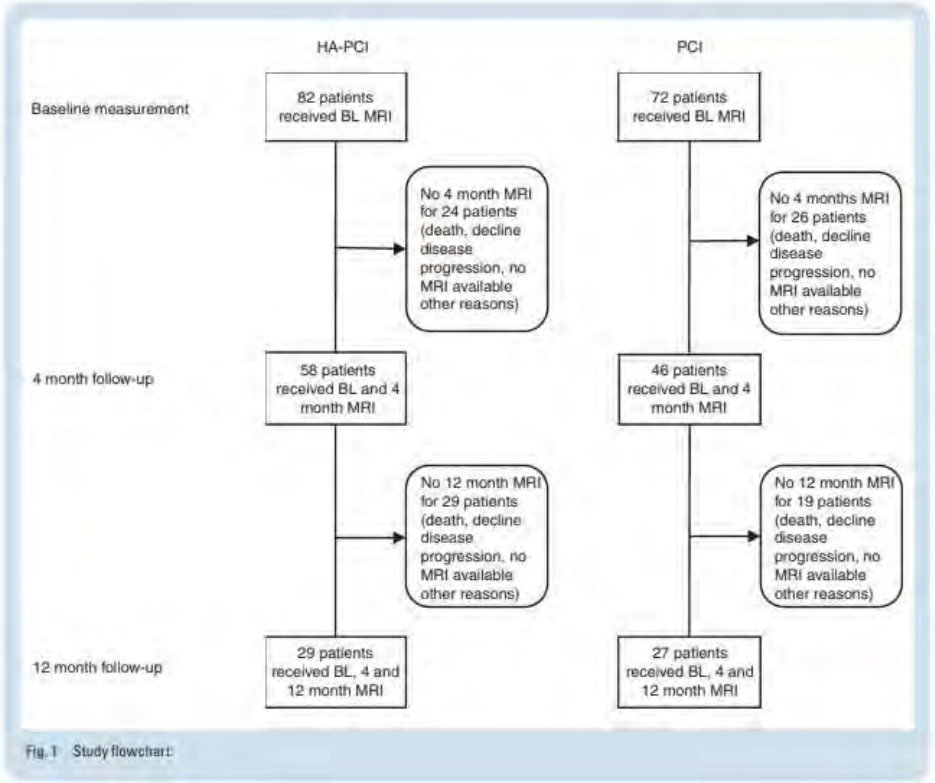


Fig. 1 Study flowchart:

Conclusion:

- HA-PCI reduces hippocampal atrophy compared to regular PCI whereas both techniques are associated with considerable brain injury as shown by various MRI indices.

- The neurocognitive benefit of sparing the hippocampus in the context of PCI is still subject to debate

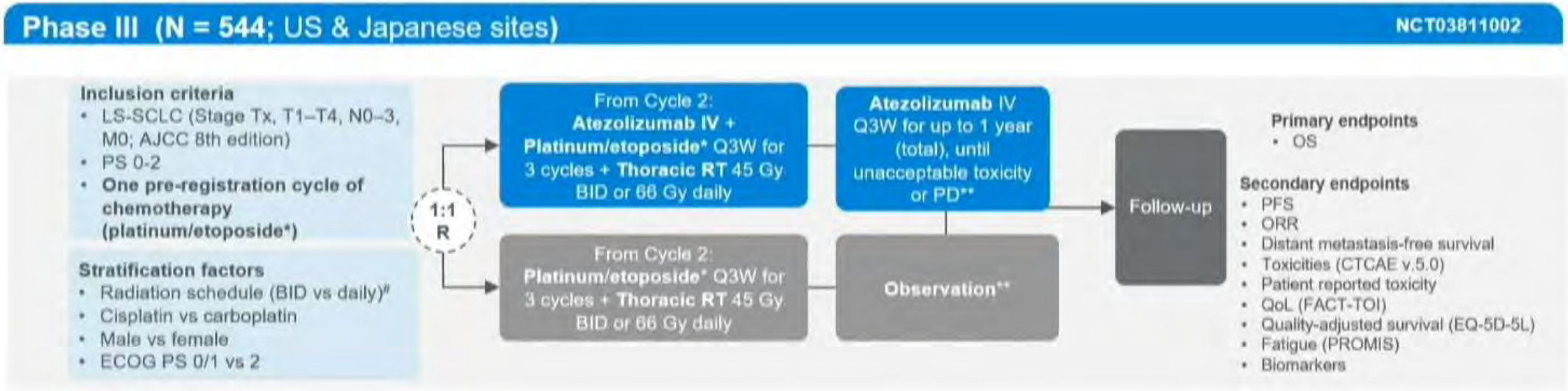
International Journal of Radiation Oncology*Biology*Physics
Volume 117, Issue 4, 15 November 2023, Page e3

LBA 04

Primary Endpoint Results of NRG CC003: Phase IIR/III Trial of Prophylactic Cranial Irradiation (PCI) with or without Hippocampal Avoidance (HA) for Small Cell Lung Cancer (SCLC)

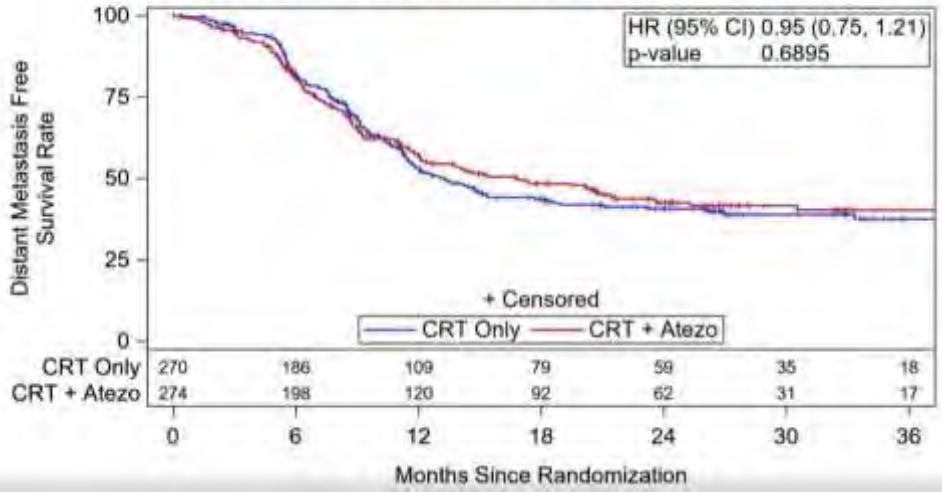
V. Gondi [1], S. Pugh [2], M.P. Mehta [3], J.S. Wefel [4], W.A. Tome [5], A. Sun [6], G.M. Videtic [7], B.H. Lok [8], H.A. Yoon [9], J.H. Heinzerling II [10], A.S. DeNittis [11], R.C. McGarry [12], K. Devisetty [13], V. Kundapur [14], A.J. Wu [15], R. Paulus [16], L.A. Kachnic [17]

NRG LU005 Schema

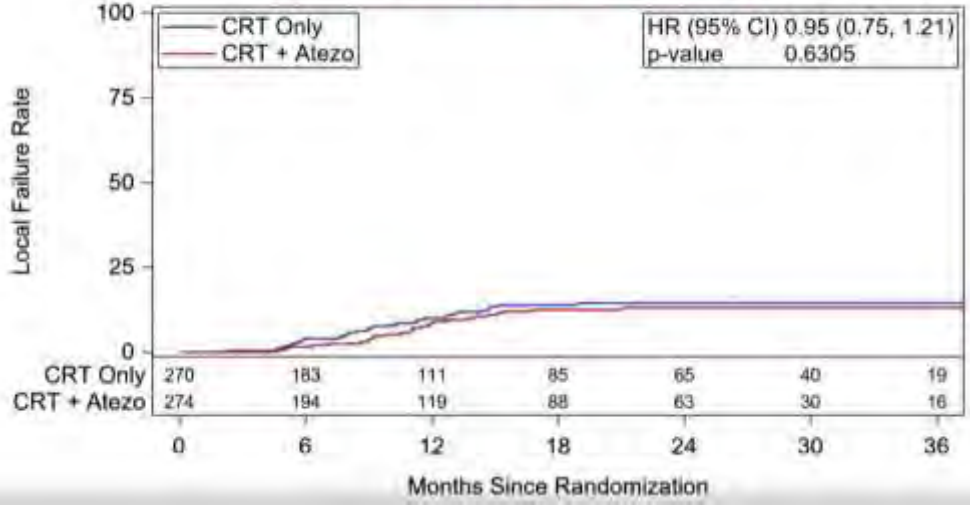


#Thoracic RT 45 Gy BID (1.5 Gy x 30 fractions ->3 weeks) or 66 Gy daily (2 Gy x 33 fractions ->6.5 weeks) beginning with cycle 2 of chemotherapy; *cisplatin (preferred) or carboplatin; first cycle of chemotherapy given prior to study entry, 3 given on study (for a total of 4 cycles); **All patients with a CR or near CR are strongly recommended to receive prophylactic cranial irradiation (PCI; 25 Gy)

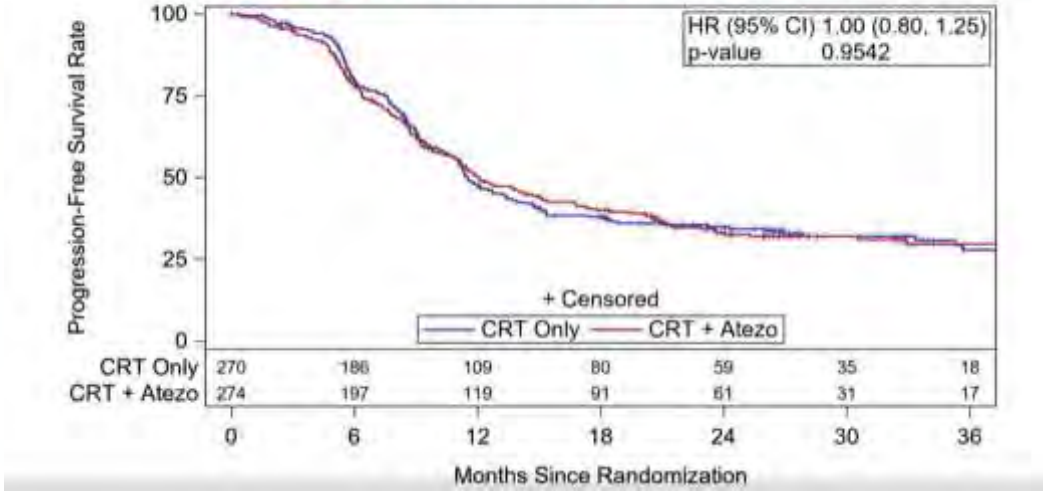
Distant Metastasis Free Survival



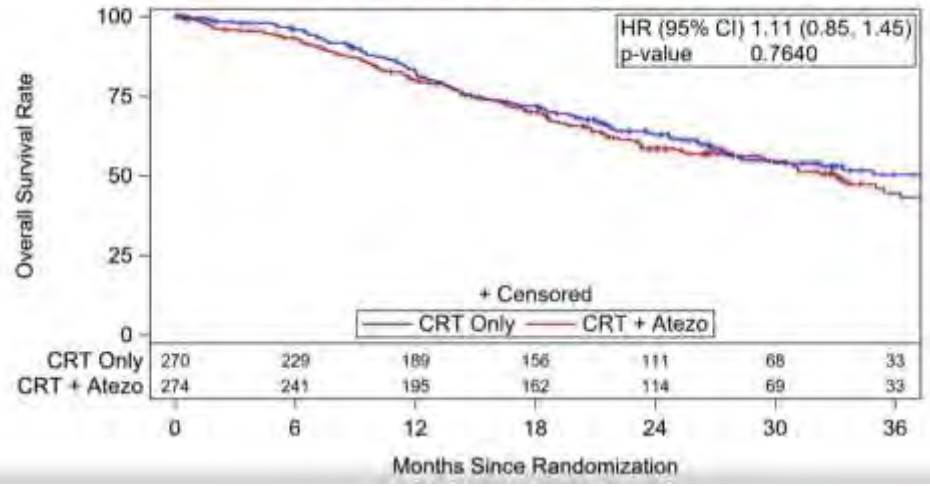
Time to Local Failure



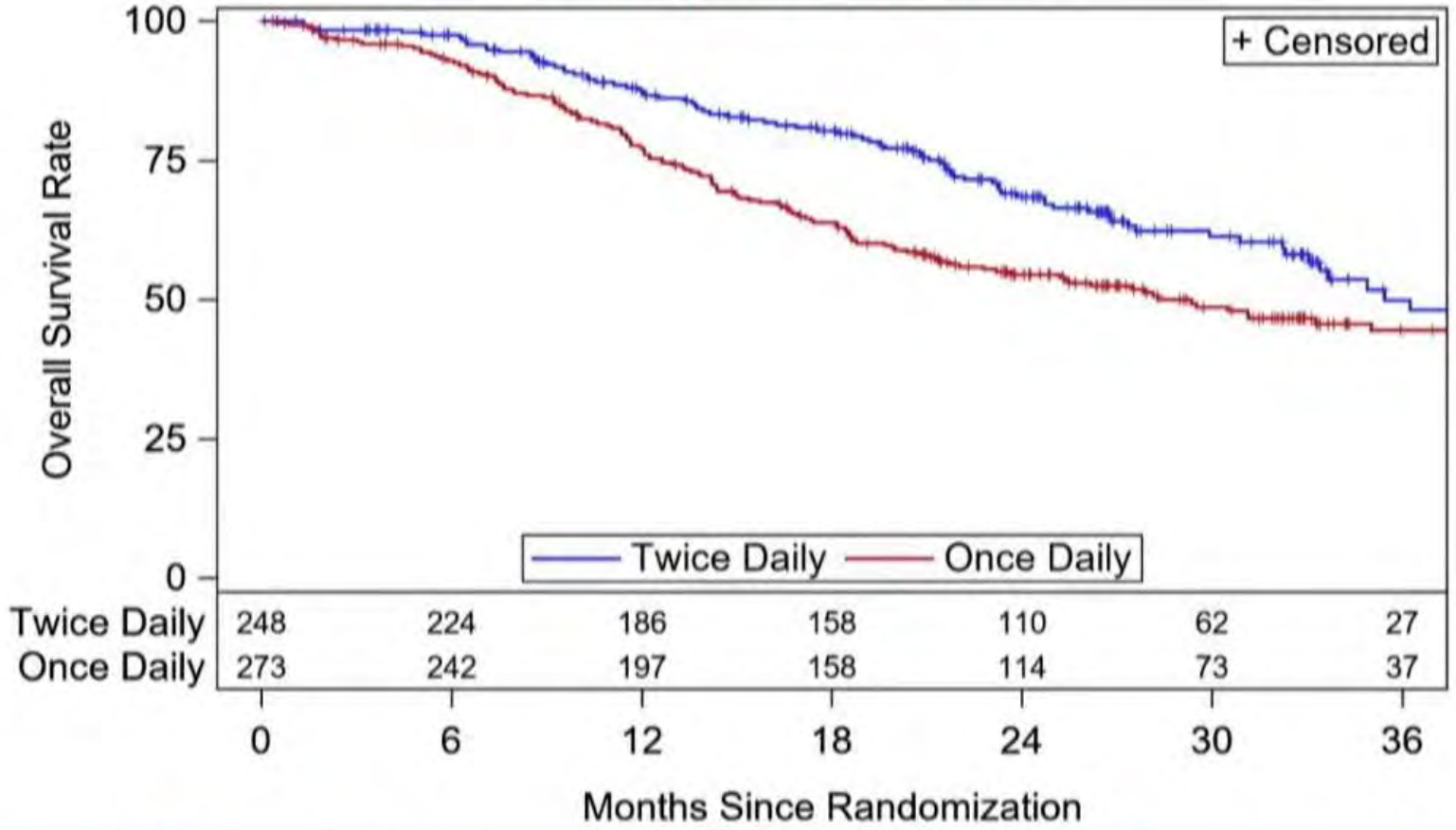
Progression Free Survival



Overall Survival



Overall Survival: Unadjusted RT Schedule Comparison



Note: Preliminary findings. Patients may have received twice daily RT over once daily for a number of reasons, including better performance status. Excludes patients who received no RT.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Durvalumab after Chemoradiotherapy in Limited-Stage Small-Cell Lung Cancer

Authors: Ying Cheng, M.D., David R. Spigel, M.D., Byoung Chul Cho, M.D., Ph.D., Konstantin K. Laktionov, M.D., Jian Fang, M.D., Yuanbin Chen, M.D., Yoshitaka Zenke, M.D., Ph.D., +17, for the ADRIATIC Investigators* Author Info & Affiliations

Published September 13, 2024 | N Engl J Med 2024;391:1313-1327 | DOI: 10.1056/NEJMoa2404873

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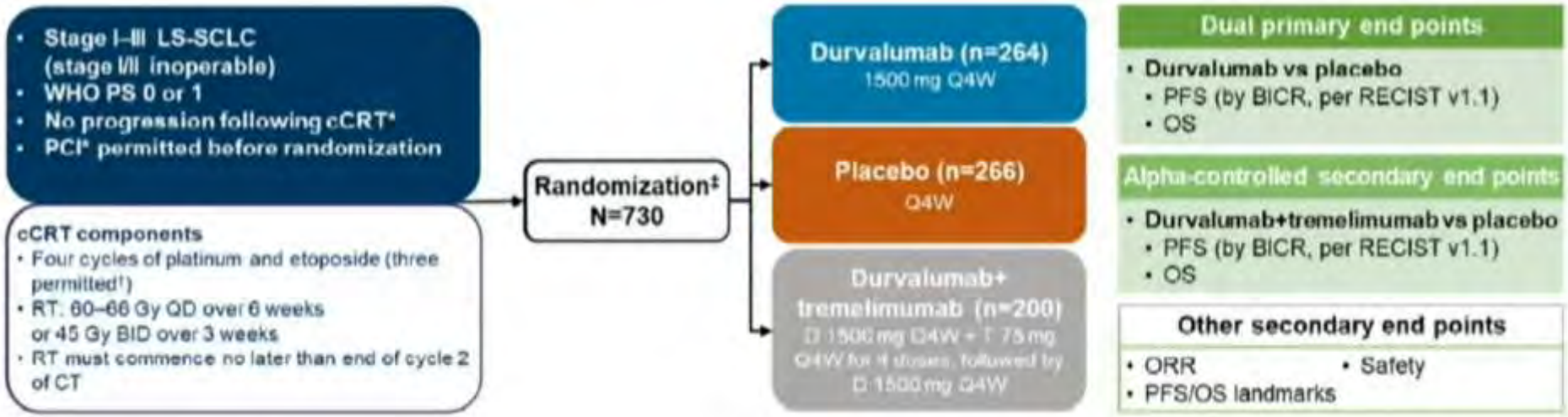
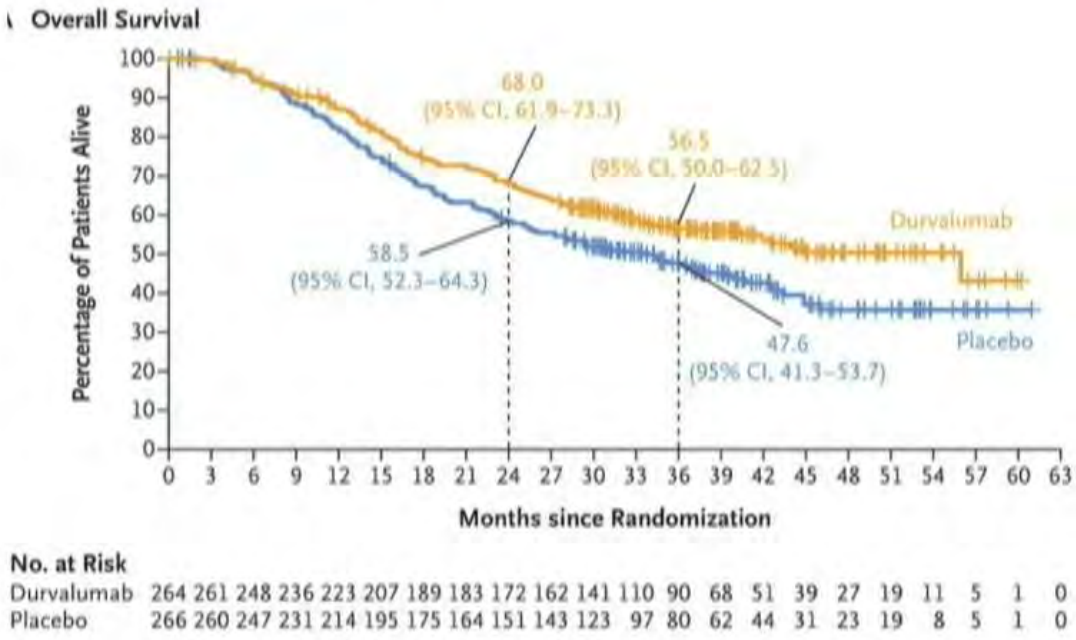
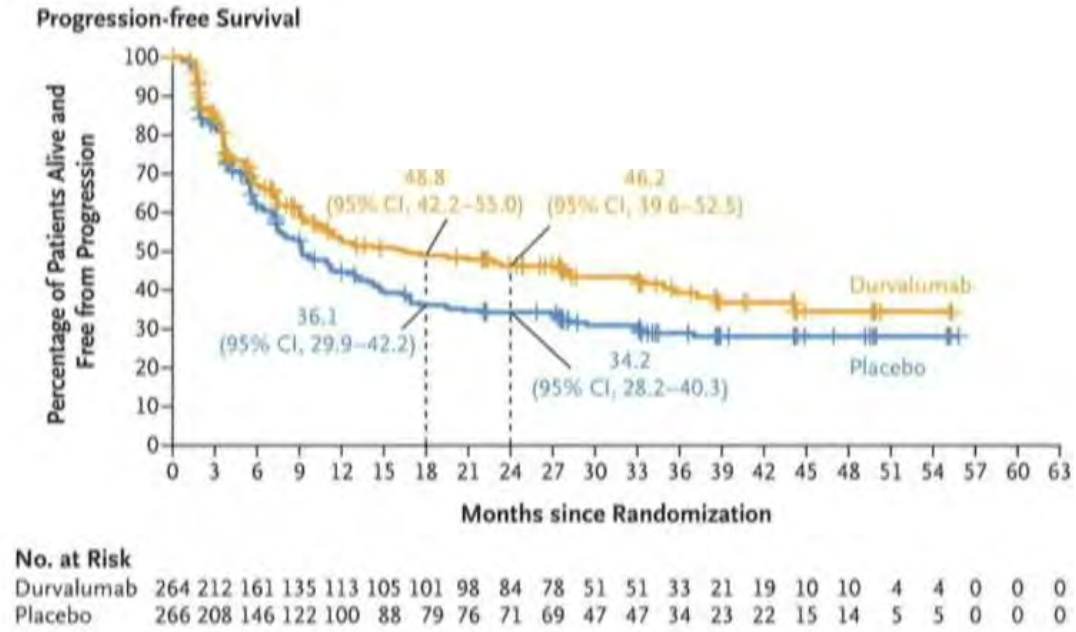
ADRIATIC study design



ADRIATIC study





Median OS of 55.9m vs 33.4m
HR 0.73 (98.321% CI, 0.54 to 0.98; P=0.01)

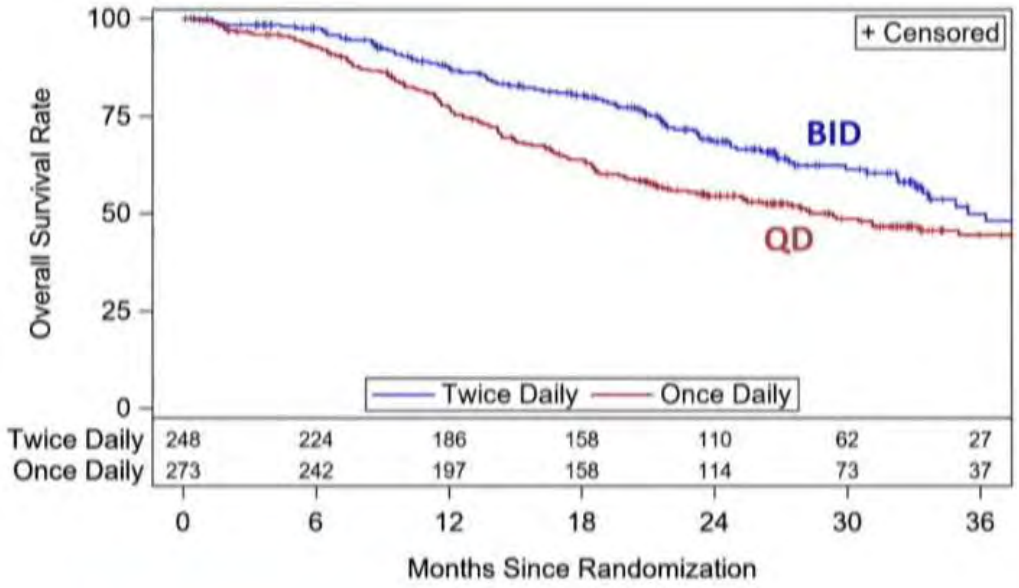
Median PFS of 16.6m vs 9.2m
HR 0.76 (97.195% CI, 0.59 to 0.98; P=0.02)

Ching et al, NEJM 2024

Fractionation- Is BID superior?

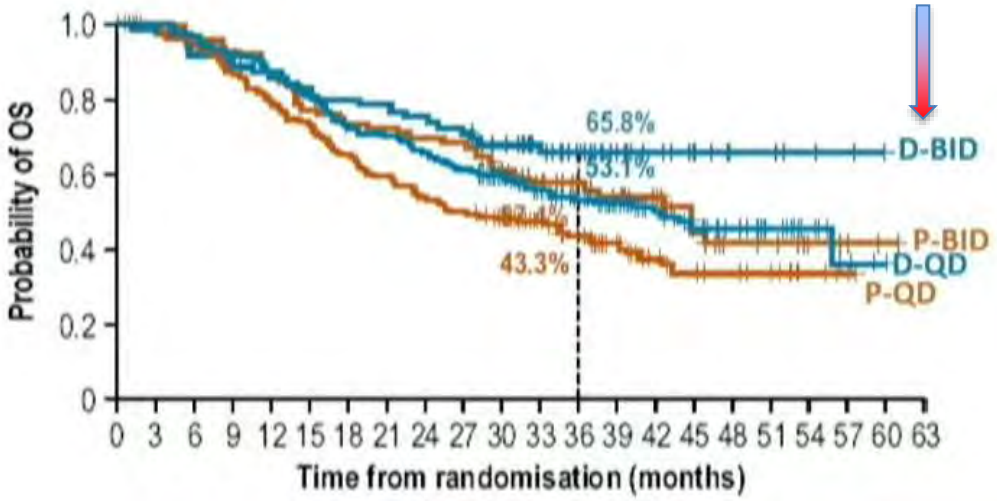
BID correlated with PCI and <14 from CRT

LU005



Not randomized data
Inherent selection bias

ADRIATIC

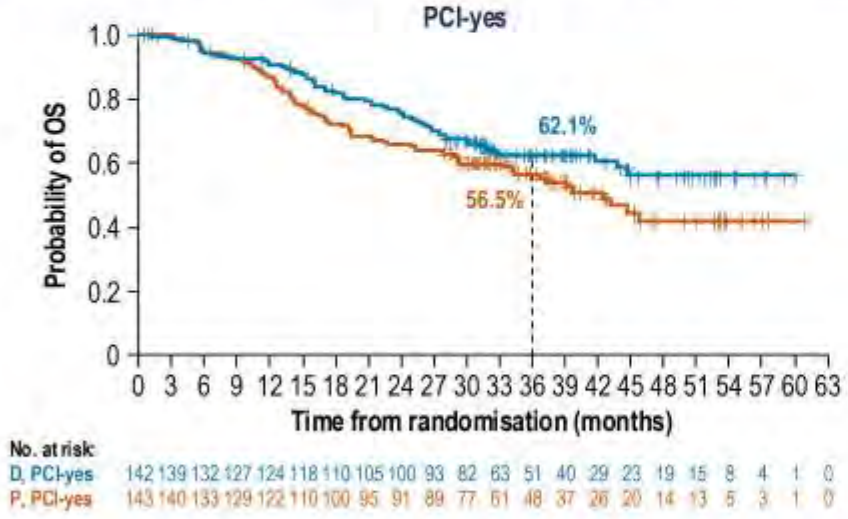


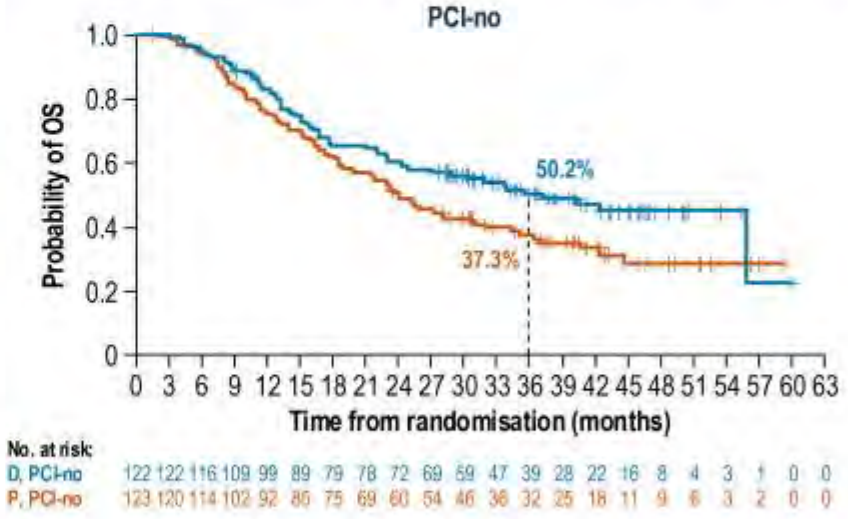
	BID RT		QD RT	
	D (n = 69)	P (n = 79)	D (n = 195)	P (n = 187)
Median OS (95% CI), months	NR (NE–NE)	44.8 (29.4–NE)	41.9 (32.0–NE)	26.1 (21.7–36.8)
3-year OS, %	65.8	57.4	53.1	43.3
HR (95% CI)	0.68 (0.40–1.14)*		0.72 (0.55–0.96)*	
Multivariable HR (95% CI)	0.71 (0.42–1.18)‡		0.73 (0.55–0.96)‡	

Modified from Senan et al. ESMO 2024

PCI-Yes and PCI-No Subgroups – OS

	PCI-yes		PCI-no		ITT	
	D (n = 142)	P (n = 143)	D (n = 122)	P (n = 123)	D (n = 264)	P (n = 266)
Median OS (95% CI), months	NR (43.9–NE)	42.5 (33.4–NE)	37.3 (24.3–NE)	24.1 (18.8–31.1)	55.9 (37.3–NE)	33.4 (25.5–39.9)
3-year OS, %	62.1	56.5	50.2	37.3	56.5	47.6
HR (95% CI)	0.75 (0.52–1.07)*		0.71 (0.51–0.99)*		0.73 (0.57–0.93)†	
Multivariable HR (95% CI)	0.72 (0.50–1.03)‡		0.73 (0.52–1.02)‡		–	





CI, confidence interval; NE, not estimable; NR, not reached; yr, year.

*Subgroup HRs and CIs calculated using an unstratified Cox proportional hazards model.†ITT HR and CIs calculated using a Cox proportional hazards model stratified by receipt of PCI.‡Multivariable analysis interaction p-value 0.96.

The patients who received PCI had longer absolute OS and PFS than those who did not, regardless of treatment arm.

Is this going to be a new standard of care?!

Extensive stage small cell lung cancer

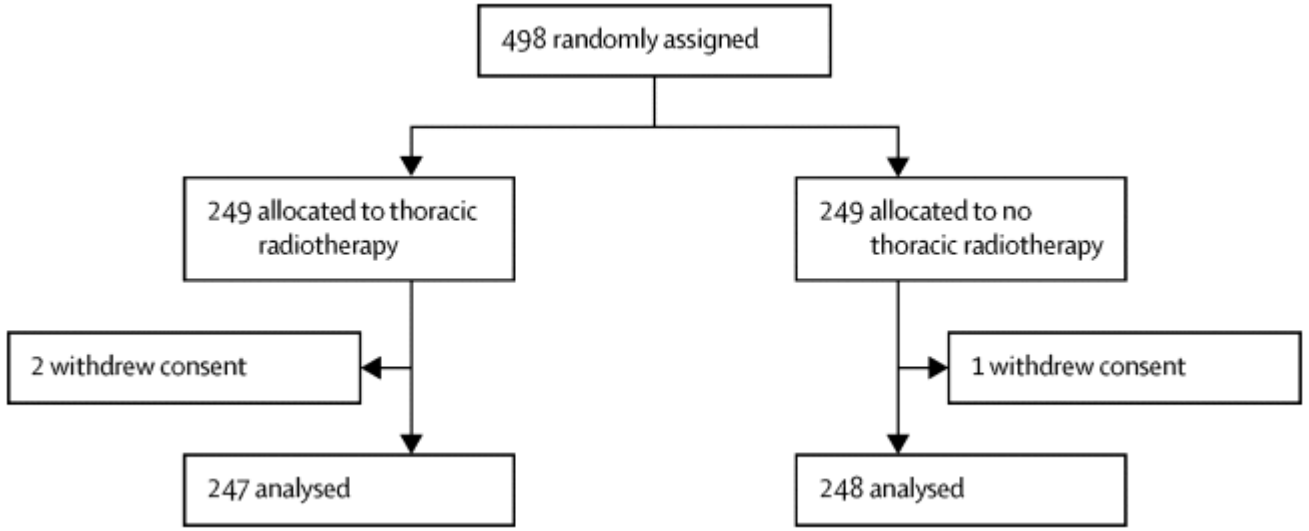
- ES_SCLC accounts for 65-70% of all newly diagnosed SCLC
- About 70-90% of patients have residual intrathoracic disease after chemotherapy
- Most of residual disease will progress within the first year

CREST RCT

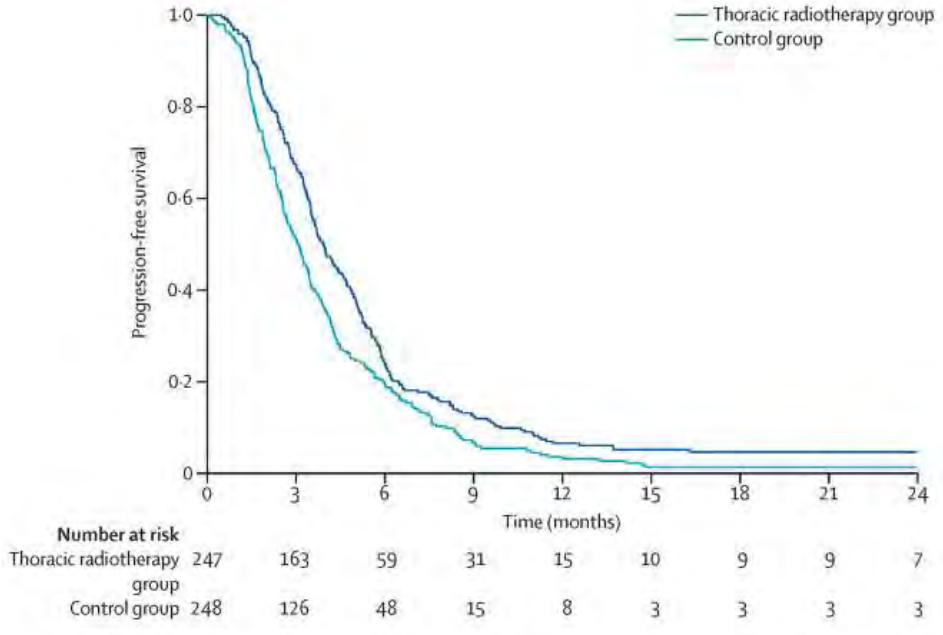
Clinical Trial > Lancet 2015 Jan 3;385(9962):36-42. doi: 10.1016/S0140-6736(14)61085-0. Epub 2014 Sep 14.

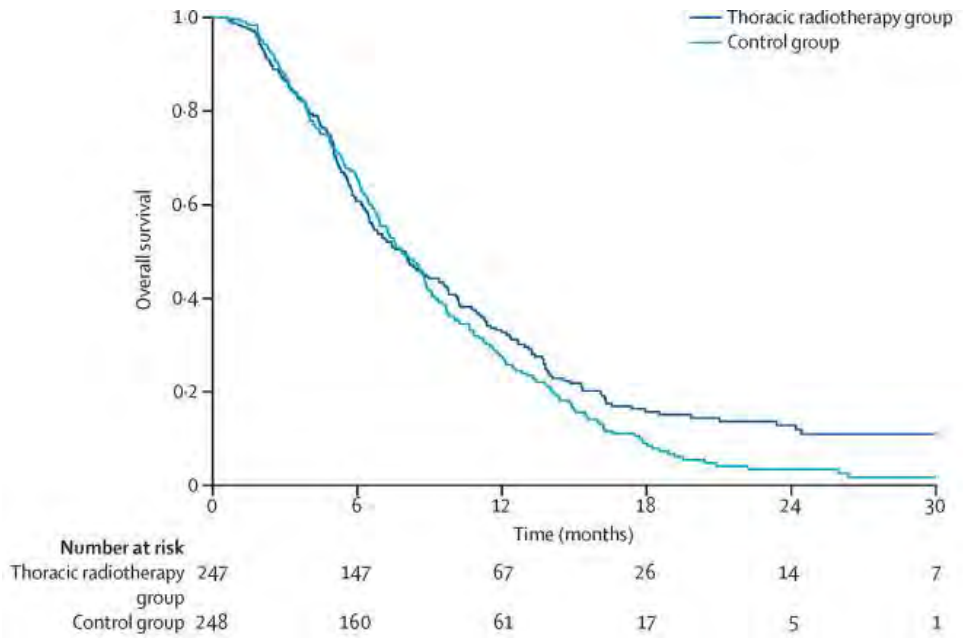
Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial

Ben J Slotman [1], Harm van Tinteren [2], John O Praag [3], Joost L Knegjens [4], Sherif Y El Sharouni [5], Matthew Hatton [6], Astrid Keijser [7], Corinne Faivre-Finn [8], Suresh Senan [9]



ES-SCLC patients with any response to 4–6 cycles of EP were randomized to either consolidative TRT (with 30 Gy in 10 fractions) and PCI or PCI alone





- Although the primary endpoint of 1-year OS was not significantly different between the groups, on secondary analysis, 2-year OS was significantly improved in consolidative TRT patients (13 vs. 3%; p = 0.004).
- Patients receiving consolidative TRT had a near 50% reduction in intrathoracic progression (43.7 vs. 79.8%; p < 0.0001) with no significant toxic effects reported

Who may benefit from consolidative TRT?

- Patients with residual intrathoracic disease
- patients with 2 or fewer metastases
- Absence of liver and bone metastasis

Thoracic radiotherapy improves long-term survival. Therefore, thoracic radiotherapy should be considered for patients with extensive stage small-cell lung cancer who have responded to chemotherapy.

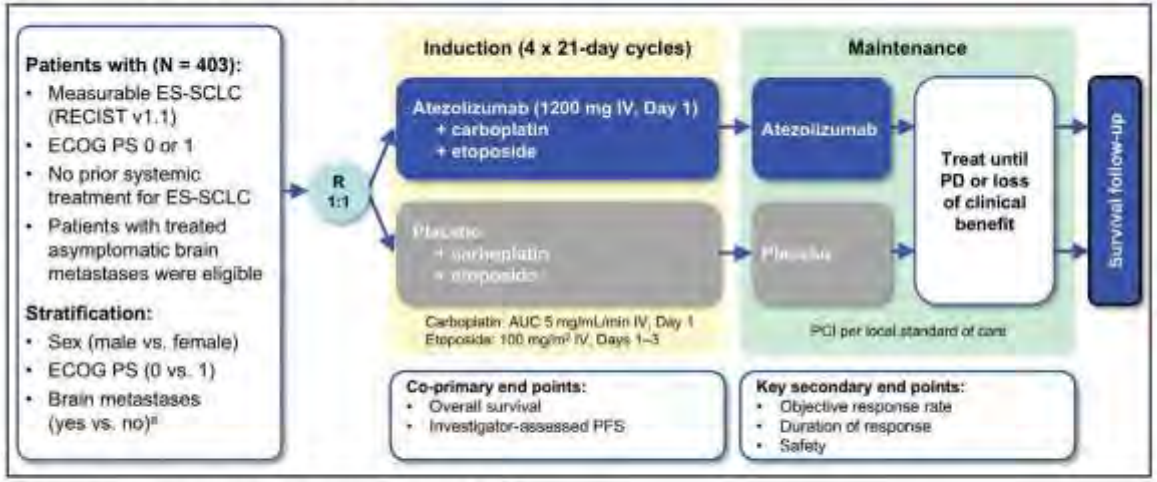
IMpower133

First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer

Authors: Leora Horn, M.D., Aaron S. Mansfield, M.D., Aleksandra Szczęsna, M.D., Libor Havel, M.D., Maciej Krzakowski, M.D., Ph.D., Maximilian J. Hochmair, M.D., Florian Huemer, M.D., +14, for the IMpower133 Study Group* Author Info & Affiliations

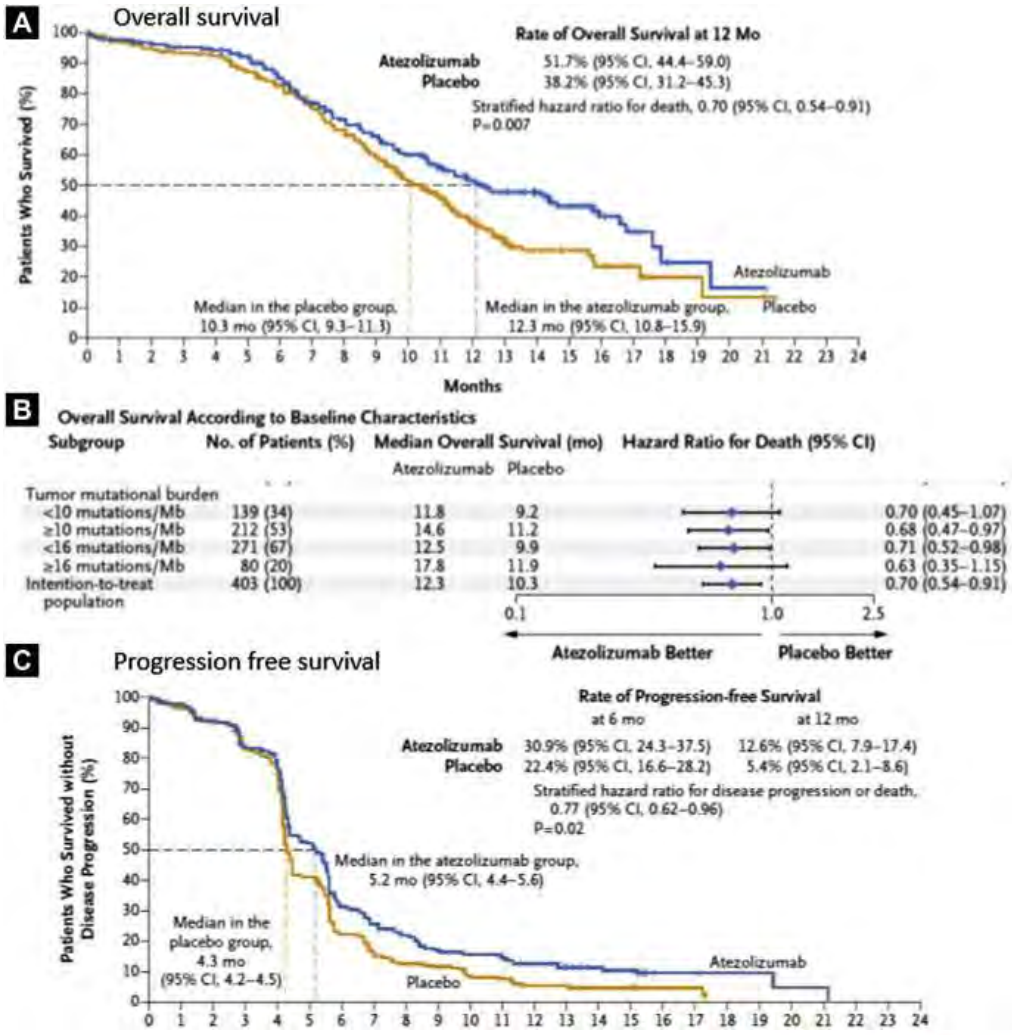
Published September 25, 2018 | N Engl J Med 2018;379:2220-2229 | DOI: 10.1056/NEJMoa1809064
VOL. 379 NO. 23 | Copyright © 2018

Fig. 1. Study Design of IMpower133



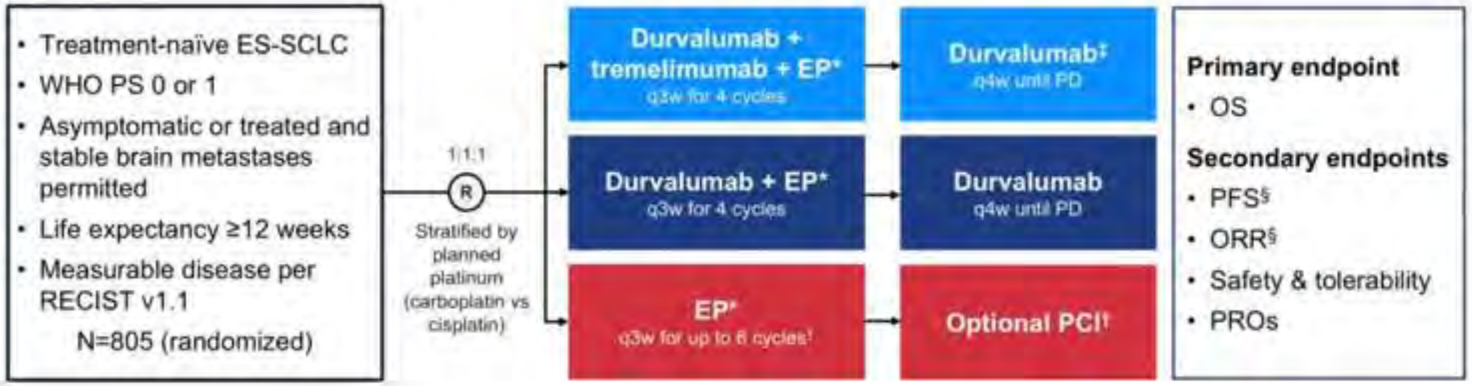
[a]Only patients with treated brain metastases were eligible.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; IV, intravenous; PCI, prophylactic cranial irradiation; PD, progressive disease; PFS, progression-free survival; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors.



Durvalumab plus platinum–etoposide versus platinum–etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial

Phase 3, global, randomized, open-label, active-controlled, multicenter study



13-MONTH mOS with IMFINZI + EP vs 10.3-MONTH mOS with EP alone

HR=0.73 (95% CI, 0.59-0.91; *P*=0.0047)

OVERALL SURVIVAL AT 3-YEAR PLANNED EXPLORATORY ANALYSIS[1†]

(median duration of follow-up: 39.4 months)

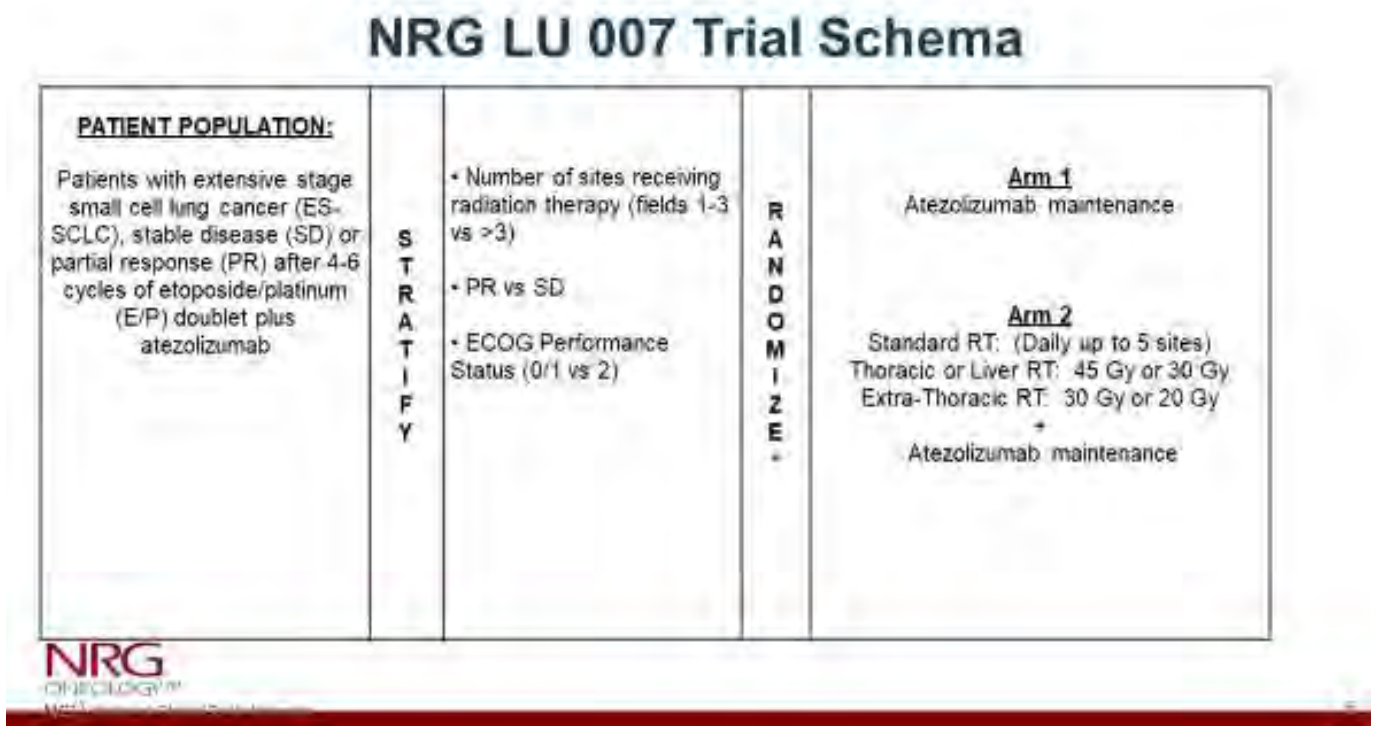
3X more patients were estimated to be alive at **3 YEARS**

HR=0.71 (95% CI, 0.60-0.86)

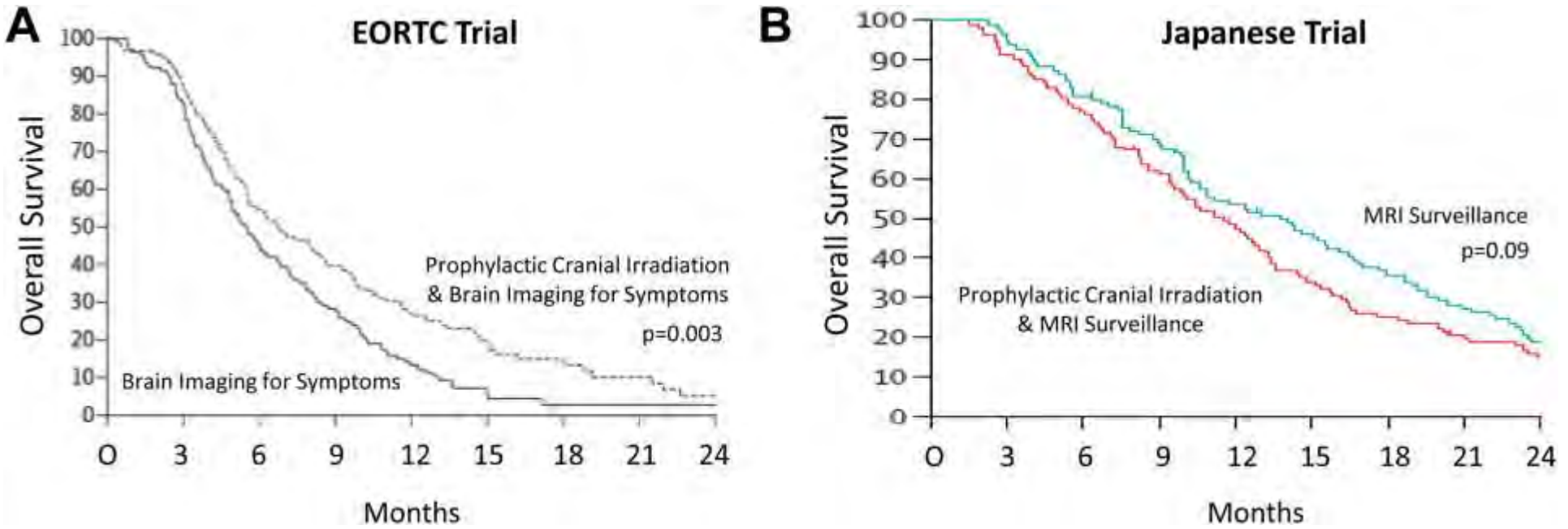
Number of patients at risk

IMFINZI + EP	268	244	214	177	140	109	85	70	60	54	50	46	39	25	13	3	0	0
EP	269	243	212	156	104	82	64	51	36	24	19	17	13	10	3	0	0	0

Combining Radiotherapy and Immunotherapy in Patients with Extensive Stage Small Cell Lung Cancer (NRG-LU007, “the RAPTOR Trial”)



Prophylactic Cranial Irradiation in ES-SCLC



- The EORTC trial did not require CNS imaging before randomization, and subsequent imaging was acquired only for neurologic symptoms.
- The Japanese trial mandated CNS imaging before randomization and at 3, 6, 9, 12, 18, and 24 months in both arms.
- Therefore, whereas the EORTC trial included an arm of PCI omission, the Japanese trial included PCI omission with active MRI surveillance.

Radiosurgery and SCLC

Evaluation of First-line Radiosurgery vs Whole-Brain Radiotherapy for Small Cell Lung Cancer Brain Metastases

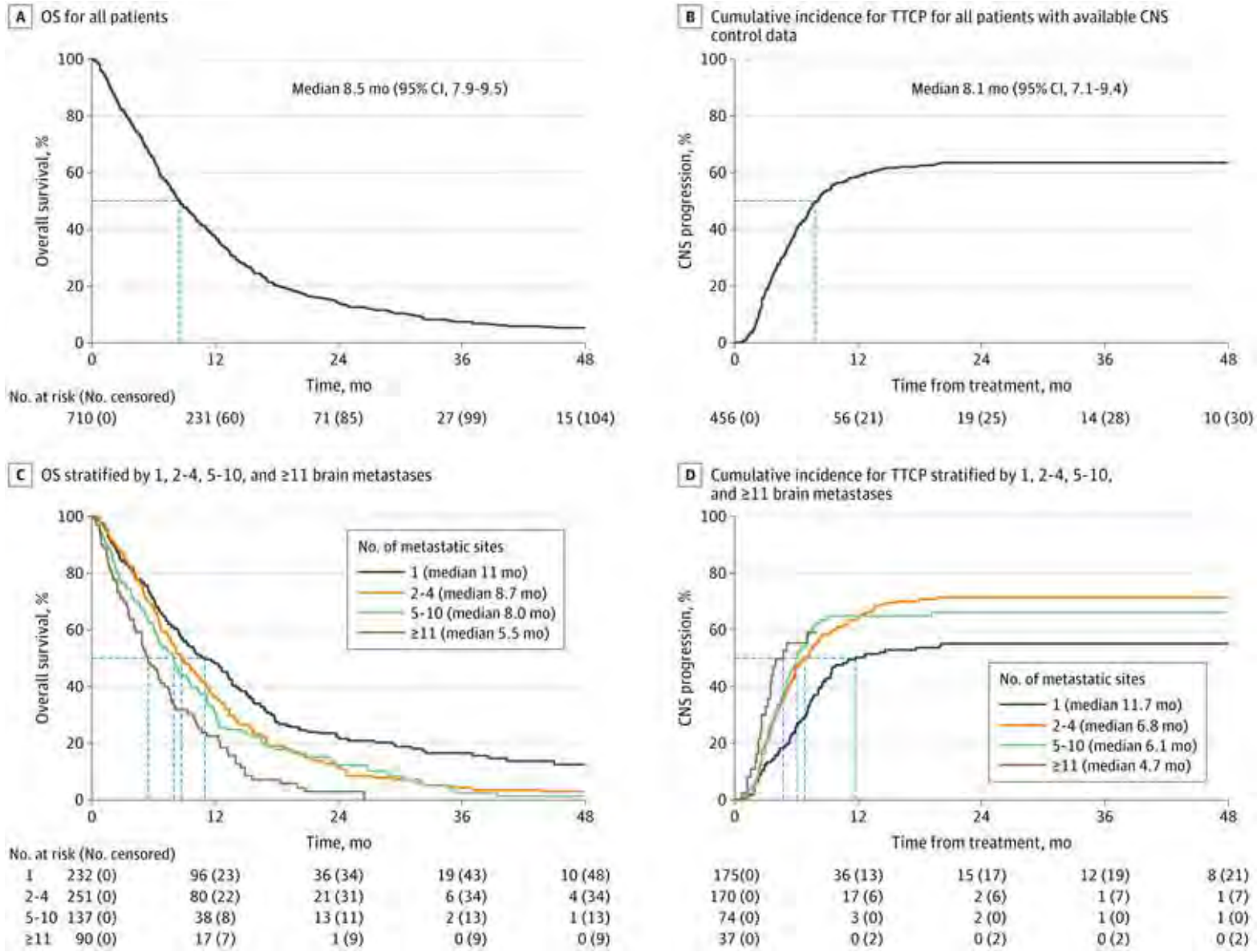
The FIRE-SCLC Cohort Study

Chad G. Rusthoven, MD[1]; Masaaki Yamamoto, MD, PhD[2]; Denise Bernhardt, MD[3]; et al

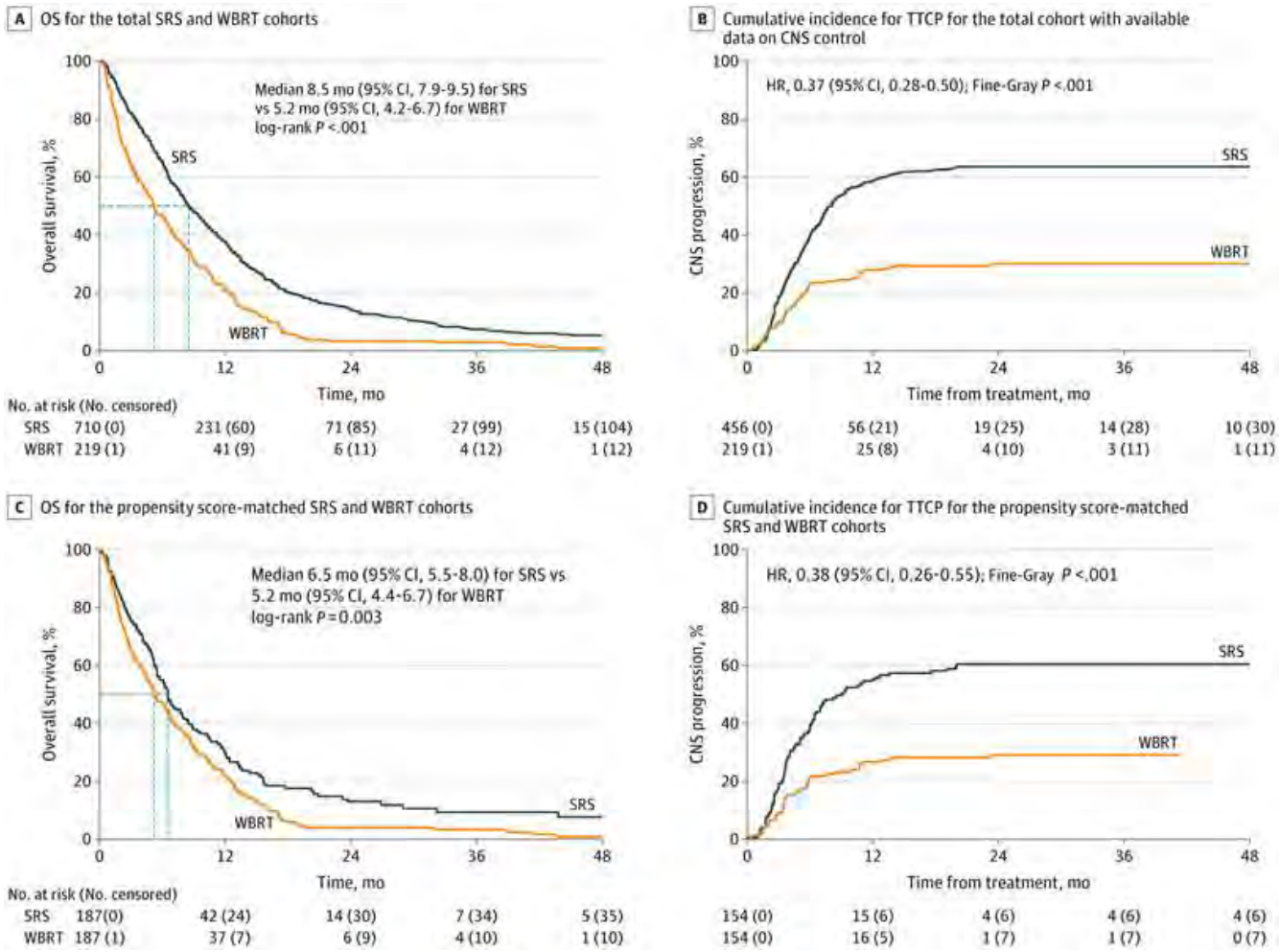
» Author Affiliations | Article Information

JAMA Oncol. 2020;6(7):1028-1037. doi:10.1001/jamaoncol.2020.1271

OS and Time to Central Nervous System Progression (TTCP) After First-line SRS



Overall Survival and Time to Central Nervous System Progression (TTCP) After First-line SRS vs WBRT



Conclusion:

First-line SRS is an appropriate treatment option in carefully selected small cell lung cancer patients with CNS metastasis.

PRINCIPLES OF RADIATION THERAPY

General Principles:

- General principles of RT for lung cancer—including commonly used abbreviations; standards for clinical and technologic expertise and quality assurance; and principles of RT simulation, planning, and delivery—are provided in the NCCN Guidelines for Non-Small Cell Lung Cancer (NSCL-C) and are applicable to RT for SCLC.
- RT has a potential role in all stages of SCLC, as part of either definitive or palliative therapy. Radiation oncology input, as part of a multidisciplinary evaluation or discussion, should be provided for all patients early in the determination of the treatment strategy.
- To maximize tumor control and to minimize treatment toxicity, critical components of modern RT include appropriate simulation, accurate target definition, conformal RT (CRT) planning, and ensuring accurate delivery of the planned treatment. A minimum standard is CT-planned 3D-CRT conformal RT. Multiple fields should be used, with all fields treated daily.
- Use of more advanced technologies is appropriate when needed to deliver adequate tumor doses while respecting normal tissue dose constraints. Such technologies include (but are not limited to) 4D-CT and/or FDG-PET/CT simulation, intensity-modulated RT (IMRT)/volumetric modulated arc therapy (VMAT), image-guided RT (IGRT), and motion management strategies. IMRT is preferred over 3D conformal EBRT on the basis of reduced toxicity in the setting of concurrent chemotherapy/RT.[1] Quality assurance measures are essential and are covered in the NCCN Guidelines for Non-Small Cell Lung Cancer (NSCL-C).
- Useful references include the ASTRO Guidelines and the American Radium Society.[2,3,4]

General Treatment Information:

Limited Stage:

- In patients with clinical stage I–IIA (T1–2, N0, M0) who have undergone lobectomy and are found to have regional nodal involvement on final pathology, postoperative RT is recommended in pathologic N2[5] and may be considered in pathologic N1 stage, either sequentially or concurrently with chemotherapy. Principles of postoperative RT for NSCLC, including target volumes and doses, are recommended.
- Selected patients with stage I–IIA (T1–2, N0, M0) SCLC who are medically inoperable or in whom a decision is made not to pursue surgery may be candidates for stereotactic ablative radiotherapy (SABR), also known as stereotactic body RT (SBRT), to the primary tumor followed by adjuvant systemic therapy. Principles of SABR for SCLC are similar to those for NSCLC (see NCCN Guidelines for Non-Small Cell Lung Cancer: NSCL-C).[6-8]
- Timing: RT concurrent with systemic therapy is standard and preferred to sequential chemo/RT.[9] RT should start early, with cycle 1 or 2 of systemic therapy (category 1).[10] A shorter time from the start of any therapy to the end of RT (SER) is significantly associated with improved survival.[11]
- Target definition: RT target volumes should be defined based on the pretreatment FDG-PET scan and CT scan obtained at the time of RT planning, as well as any positive biopsies. FDG-PET/CT is recommended, preferably within 4 weeks and no more than 8 weeks, before treatment. Ideally, FDG-PET/CT should be obtained in the treatment position.

PRINCIPLES OF RADIATION THERAPY

Limited Stage (continued):

- Historically, clinically uninvolved mediastinal nodes have been included in the RT target volume, whereas uninvolved supraclavicular nodes generally have not been included. Several more modern series, both retrospective and prospective, suggest that omission of elective nodal irradiation (ENI) results in low rates of isolated nodal recurrences (0%–11%, most <5%), particularly when incorporating FDG-PET staging/target definition (1.7%–3%).[12-17] ENI has been omitted in recent prospective clinical trials (including CALGB 30610/RTOG 0538 and the EORTC 08072 [CONVERT] trial). Inclusion of the ipsilateral hilum in the target volume, even if not grossly involved, differs between these trials but may be reasonable.
- In patients who start systemic therapy before RT, the gross tumor volume (GTV) can be limited to the post-induction systemic therapy volume to avoid excessive toxicity. Initially involved nodal regions (but not their entire pre-systemic therapy volume) should be covered.[14,18]
- Dose and schedule: For limited-stage SCLC, the optimal dose and schedule of RT have not been established.
  - Based on the randomized phase III trial, INT 0096, 45 Gy in 3 weeks (1.5 Gy twice daily [BID]) is superior (category 1) to 45 Gy in 5 weeks (1.8 Gy daily).[19,20] When BID fractionation is used, there should be at least a 6-hour interfraction interval to allow for repair of normal tissue.
  - Retrospective and randomized phase II studies from Norway and Canada suggest that similarly accelerated doses of 40–42 Gy in 3 weeks but given in once-daily fractionation produce similar outcomes as 45 Gy in 3 weeks in BID fractionation, though regional practice between daily and twice daily fractionation has diverged between those countries after subsequent experience.[21,22,23]
  - If using once-daily conventionally fractionated RT, higher doses of 66–70 Gy are preferred.[24-27] Two randomized phase III trials did not demonstrate superiority of 66 Gy in 6.5 weeks/2 Gy daily (the European CONVERT trial) or 70 Gy in 7 weeks/2 Gy daily (CALGB 30610/RTOG 0538) over 45 Gy in 3 weeks/1.5 Gy BID, but overall survival and toxicity were similar.[28,29,30]
  - Recent randomized phase II trials suggest that higher dose accelerated RT of 60–65 Gy in 4–5 weeks given in BID or daily fractionation may produce increased overall or progression-free survival compared to 45 Gy in 3 weeks in BID fractionation.[31,32]

Extensive Stage:

- Consolidative thoracic RT is beneficial for selected patients with ES-SCLC with complete response or good response to systemic therapy before immunotherapy, especially with residual thoracic disease and low-bulk extrathoracic metastatic disease. Studies have demonstrated that consolidative thoracic RT up to definitive doses is well-tolerated, results in fewer symptomatic chest recurrences, and improves long-term survival in some patients.[33,34] The Dutch CREST randomized trial of modest-dose thoracic RT (30 Gy in 10 fractions) in patients with ES-SCLC that responded to chemotherapy (without immunotherapy) demonstrated significantly improved 2-year overall survival and 6-month progression-free survival, although the protocol-defined primary endpoint of 1-year overall survival was not significantly improved.[32] Subsequent exploratory analysis found the benefit of consolidative thoracic RT is limited to the majority of patients who had residual thoracic disease after systemic therapy.[36]
- Dosing and fractionation of consolidative thoracic RT should be individualized within the range of 30 Gy in 10 daily fractions up to definitive dosing regimens in patients with a longer life expectancy.

Thank you