Therapeutics and Radiation for Small Cell Lung Cancer IASLC 19th World Conference on Lung Cancer

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ΑΝΘ ΘΕΑΓΕΝΕΙΟ

Therapeutics and Radiation for SCLC

Staging and definition of limited disease	Therapy of recurrent disease
[^{18}F]FDG PET/CT In SCLC: Analysis of the Phase III CONVERT Randomized Controlled Trial	Two Novel Immunotherapy Agents Targeting DLL3 in SCLC: Trials In Progress of AMG 757 and AMG 119 Anlotinib as third-line or further-line treatment in relapsed SCLC: a multicentre, randomized, double-blind phase 2 trial

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September 23–26, 2018 Toronto, Canada
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[^{18}F]FDG PET/CT IN SMALL-CELL LUNG CANCER (SCLC): ANALYSIS OF THE PHASE III CONVERT RANDOMIZED CONTROLLED TRIAL

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Introduction

- Standard staging for LS-SCLC is thorax & abdomen CT, brain imaging (CT/MRI) +/- bone scintigraphy **(conventional imaging)**
- The role of staging ^{18}F-FDG PET/CT in SCLC is controversial:
  - Small studies have shown that ^{18}F-FDG PET/CT upstages up to 47% of LS-SCLC patients[1]
  - Practice guidelines (e.g. ESMO, NCCN, UK NICE) **recommend** or **suggest** staging ^{18}F-FDG PET/CT[2]
  - However, PIII trials that established cCTRT in LS-SCLC were performed before ^{18}F-FDG PET/CT era[3]

Unanswered question

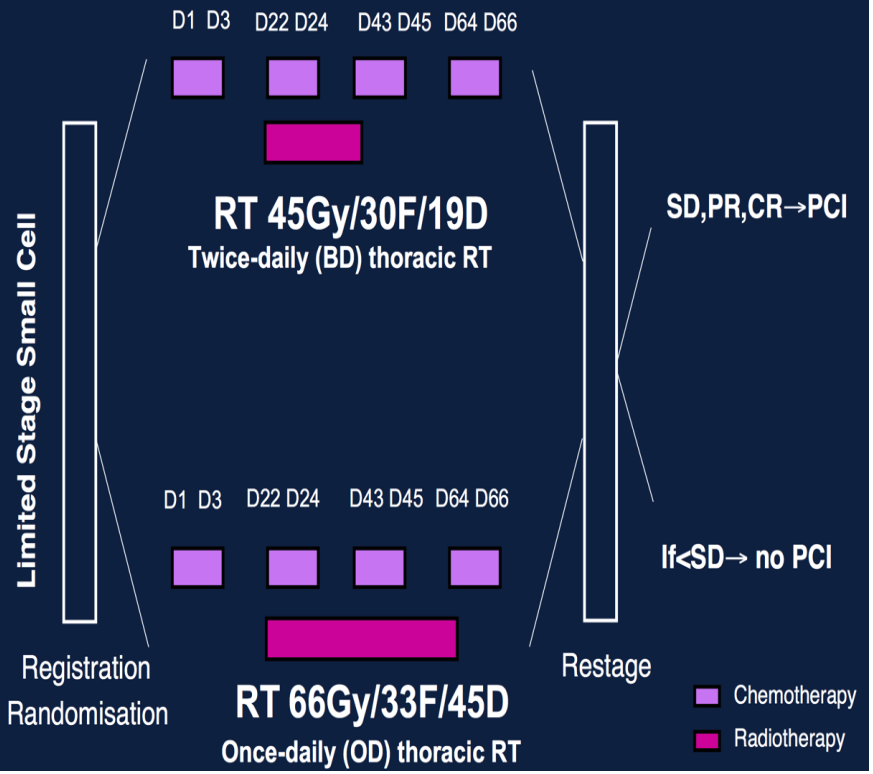
- **Is outcome of LS-SCLC staged with conventional imaging different from that of patients staged with additional ^{18}F-FDG PET/CT?**

1: Bradley JD, et al. J Clin Oncol 22:3248-54, 2004; Ruben JD, Ball DL. J Thorac Oncol 7:1015-20, 2012
2: Fruh M, et al. Ann Oncol 24 Suppl 6:vi99-105, 2013; NCCN, v1.2018; NICE, 2011
3: Turrisi AT, 3rd, et al. N Engl J Med 340:265-71, 1999

Unplanned subgroup analysis of CONVERT trial

Study design

multinational, phase III randomised study



RTP after randomisation
RT started on D22 cycle 1
- 3DCRT or IMRT
- No ENI

QA programme

Chemotherapy
4 to 6 cycles
- Cisplatin 25mg/m2 D1-3 or 75mg/m2 D1
- Etoposide 100mg/m2 D1-3

Stratification factors
- Centre
- No. of cycles chemo: 4 vs.6
- PS: 0,1 vs. 2

Patients were divided into 2 groups:

1. Patients staged with **conventional imaging** (thorax and abdomen CT, brain imaging +/- bone scintigraphy); **n=231 (43%)**
2. Patients staged with **^{18}F-FDG PET/CT** in addition; **n=309 (57%)**

CONVERT trial protocol:

- **^{18}F-FDG PET/CT** staging was allowed but **NOT** mandated
- **Bone scintigraphy** was performed if these was a specific clinical indication

Faivre-Finn. Lancet Oncol 2017

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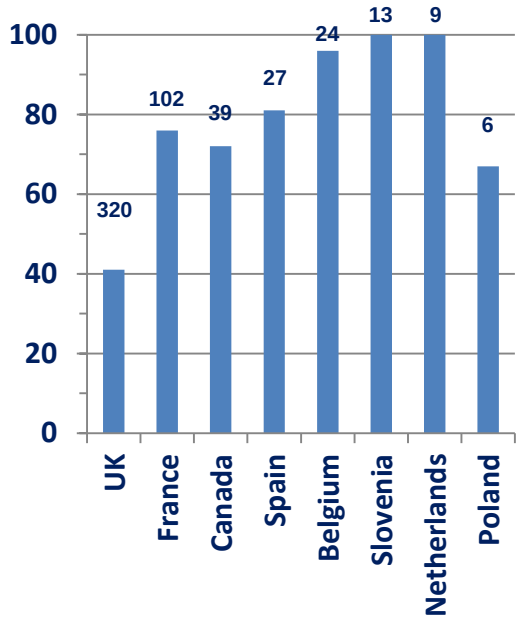
Results

% patients staged with ^{18}F-FDG PET/CT (number recruited)



	^{18}F-FDG PET/CT and conventional imaging (n=309)	Conventional imaging (n=231)	p-value
Median age (range)	62 (29-84)	62 (36-81)	0·594
ECOG PS 0	150 (49%)	98 (42%)	0·182
ECOG PS 1	148 (48%)	128 (56%)	
ECOG PS 2	11 (3%)	5 (2%)	
Adverse biochemical factors			
LDH>ULN	63 (20%)	66 (29%)	**0·035**
Hyponatremia	7 (2%)	4 (2%)	0·899
ALP>1.5xULN	68 (22%)	41 (18%)	0·267
OD radiotherapy	152 (49%)	118 (51%)	0·723
BD radiotherapy	157 (51%)	113 (49%)	
UICC/AJCC stage I	2 (1%)	2 (1%)	0·087
UICC/AJCC stage II	56 (18%)	26 (11%)	
UICC/AJCC stage III	233 (75%)	189 (82%)	
Not known	18 (6%)	14 (6%)	

	^{18}F-FDG PET/CT and conventional imaging (n=309)	Conventional imaging (n=231)	p-value
Median gross tumour volume (cc) (range)	73·3 (1·6-593)	95·7 (0·5-635·1)	**0·003**
Bone Scan			0·078
Yes	30 (10%)	35 (15%)	
No	279 (90%)	195 (84%)	
Not known	0 (0%)	1 (<1%)	
Four cycles of chemotherapy	192 (62%)	176 (76%)	**0·027**
Six cycles of chemotherapy	117 (38%)	55 (24%)	
IMRT			0·172
Yes	53 (17%)	30 (13%)	
No	226 (73%)	185 (80%)	
Not known	30 (10%)	16 (7%)	

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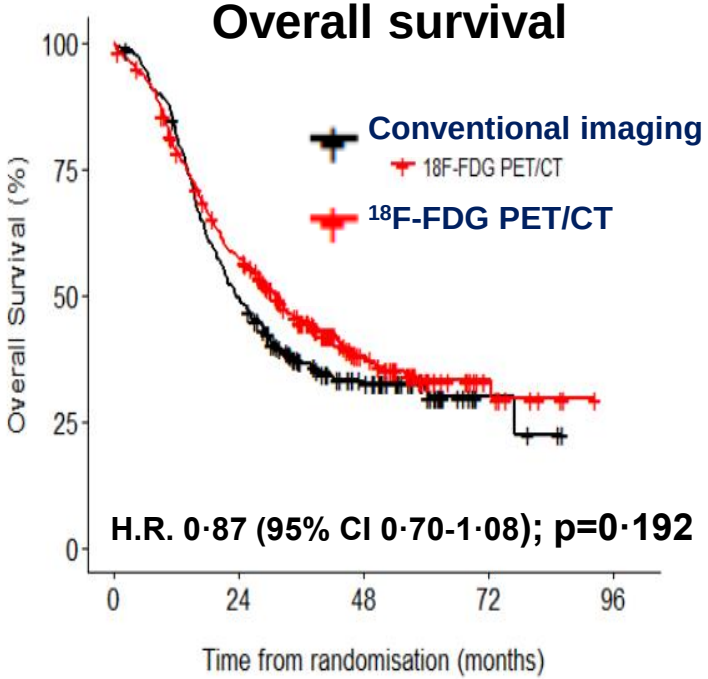
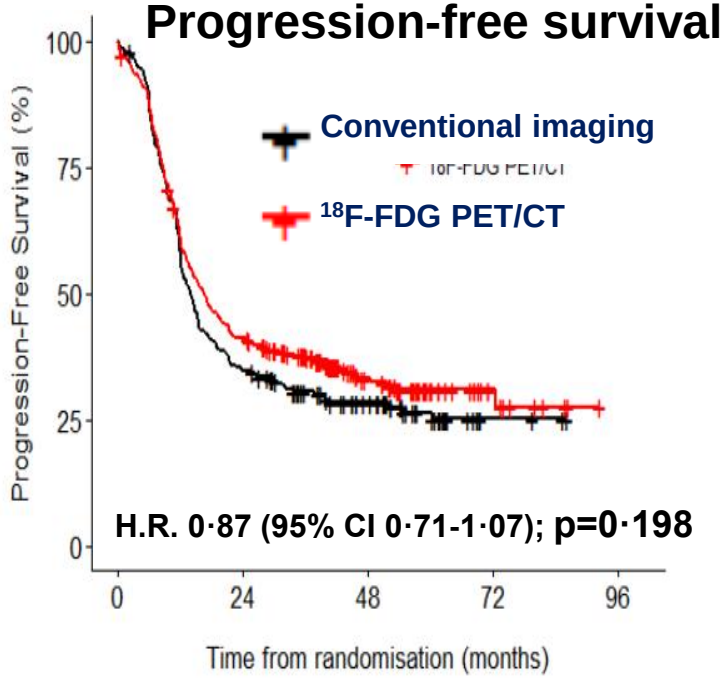
OS & PFS in patients staged with conventional imaging or with additional ^{18}F-FDG PET/CT

Overall survival



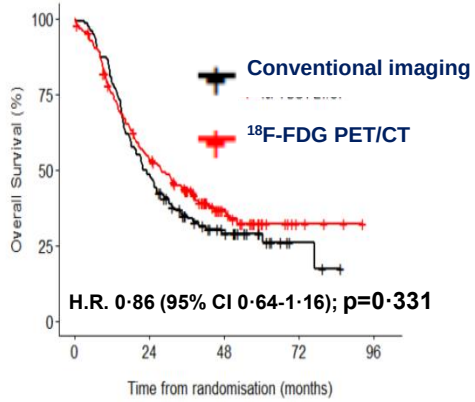
Number at risk (number censored)					
Conventional Imaging	231 (0)	113 (2)	45 (36)	4 (75)	0 (78)
18F-FDG PET/CT	309 (0)	170 (10)	55 (77)	9 (117)	0 (125)

Progression-free survival

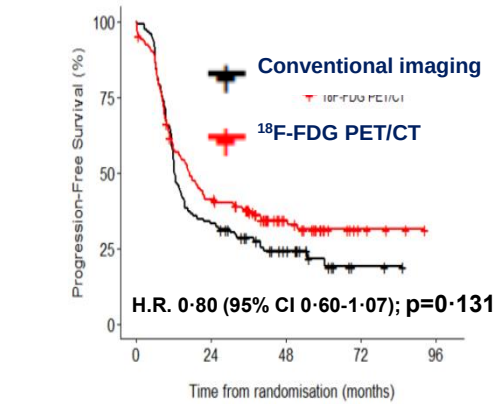


Number at risk (number censored)					
Conventional Imaging	231 (0)	80 (1)	41 (27)	3 (62)	0 (65)
18F-FDG PET/CT	309 (0)	125 (3)	49 (60)	9 (97)	0 (105)

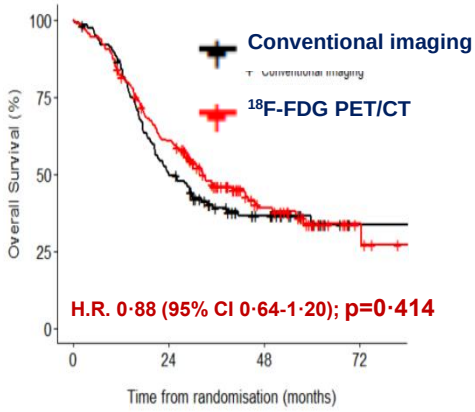
Overall survival (OD)



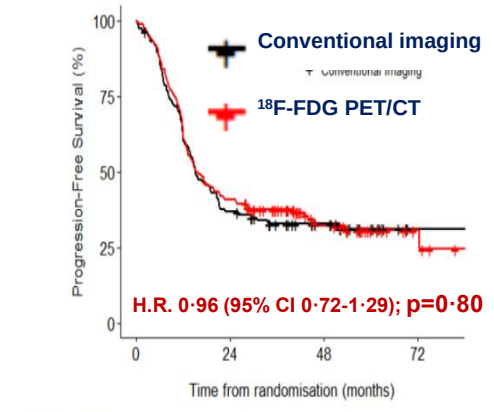
Progression-free survival (OD)



Overall survival (BD)



Progression-free survival (BD)



OS & PFS in patients staged with conventional imaging or with ^{18}F-FDG PET/CT according to treatment group (OD or BD)

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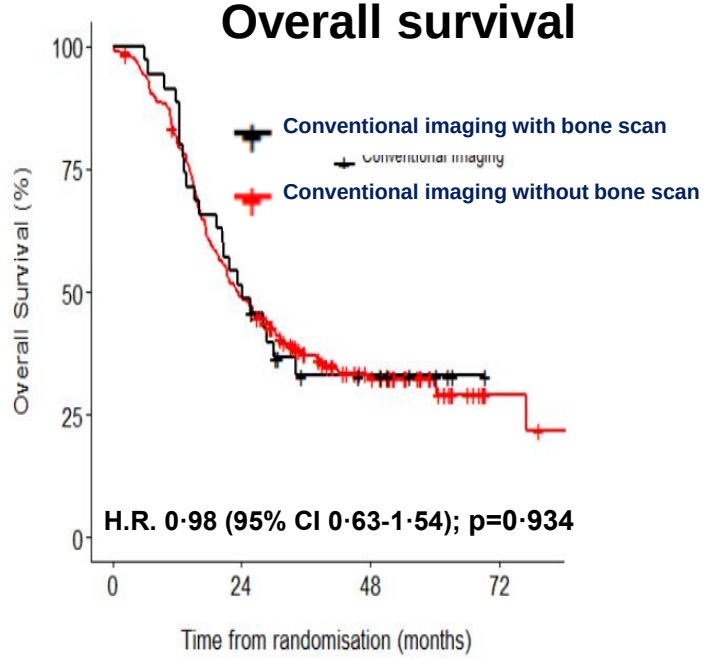
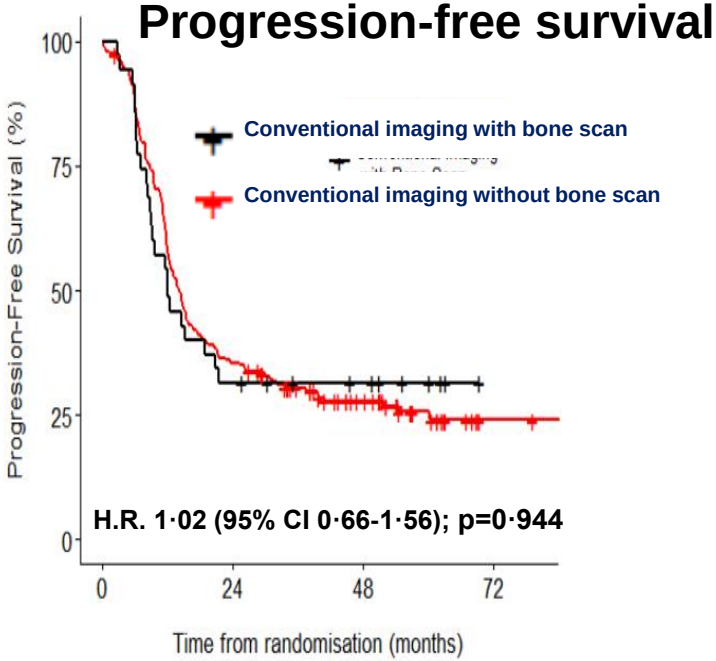
OS & PFS in patients staged using conventional imaging with or without bone scan

Overall survival



Number at risk (number censored)				
Conventional Imaging without Bone Scan	196 (0)	95 (2)	38 (31)	4 (63)
Conventional Imaging with Bone Scan	35 (0)	18 (0)	7 (5)	0 (12)

Progression-free survival



Number at risk (number censored)				
Conventional Imaging without Bone Scan	196 (0)	69 (1)	34 (23)	3 (51)
Conventional Imaging with Bone Scan	35 (0)	11 (0)	7 (4)	0 (11)

Pre-treatment ^{18}F-FDG PET sub-study

- After adjusting for a **multivariate clinical prognostic model** (ECOG PS, GTV & weight loss)

➢ **NONE** of the investigated ^{18}F-FDG PET parameters were independent prognostic factors for OS and PFS

Overall survival				
Parameter	**Univariate analysis (n=94, events=62)**		**Multivariate clinical prognostic model (n=73, events=44)**	
	CPE (SE)	**p-value**	**CPE (SE)**	**p-value**
Clinical prognostic model	n/a	n/a	0·64 (0·05)	n/a
SUV_{max}	0·50 (0·04)	0·83	0·64 (0·05)	0·78
SUV_{peak}	0·51 (0·04)	0·86	0·64 (0·05)	0·89
SUV_{mean}	0·50 (0·04)	0·60	0·64 (0·05)	0·86
log(metabolic tumour volume)	0·55 (0·04)	0·12	0·64 (0·05)	0·57
log(total lesion glycolysis)	0·55 (0·04)	0·13	0·64 (0·05)	0·56
CoV	0·52 (0·04)	0·91	0·64 (0·05)	0·75
Skewness	0·57 (0·04)	0·06	0·61 (0·05)	0·42

Take home message

- First prospective evidence
- Survival was **NOT** different in patients staged with or without ^{18}F-FDGPET/CT

- **Our findings suggest that conventional imaging is sufficient to select LS-SCLC patients for cCTRT**

- Better than expected outcome in both arms of CONVERT, compared to previous studies, is **NOT** explained by the use of ^{18}F-FDG PET/CT

- However ^{18}F-FDG PET/CT plays a role to guide radiation oncologists in the definition of gross tumour volume → not addressed in this study

Two Novel Immunotherapy Agents Targeting DLL3 in SCLC: Trials In Progress of AMG 757 and AMG 119

Taofeek Owonikoko,[1] Marie-Anne Damiette Smit,[2] Hossein Borghaei,[3] Ravi Salgia,[4] Michael Boyer,[5] Erik Rasmussen,[6] Lauren Averett Byers[7]

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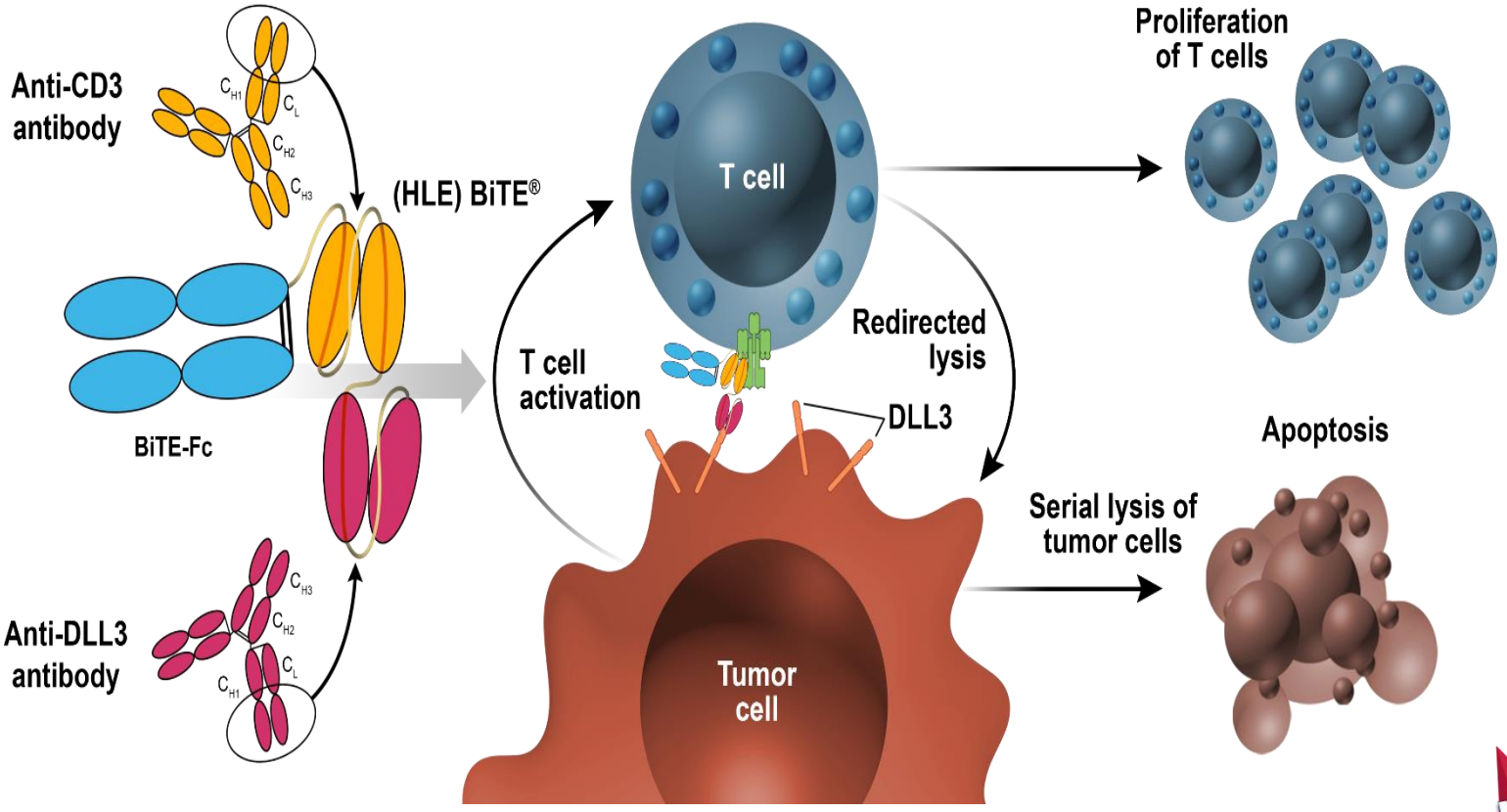
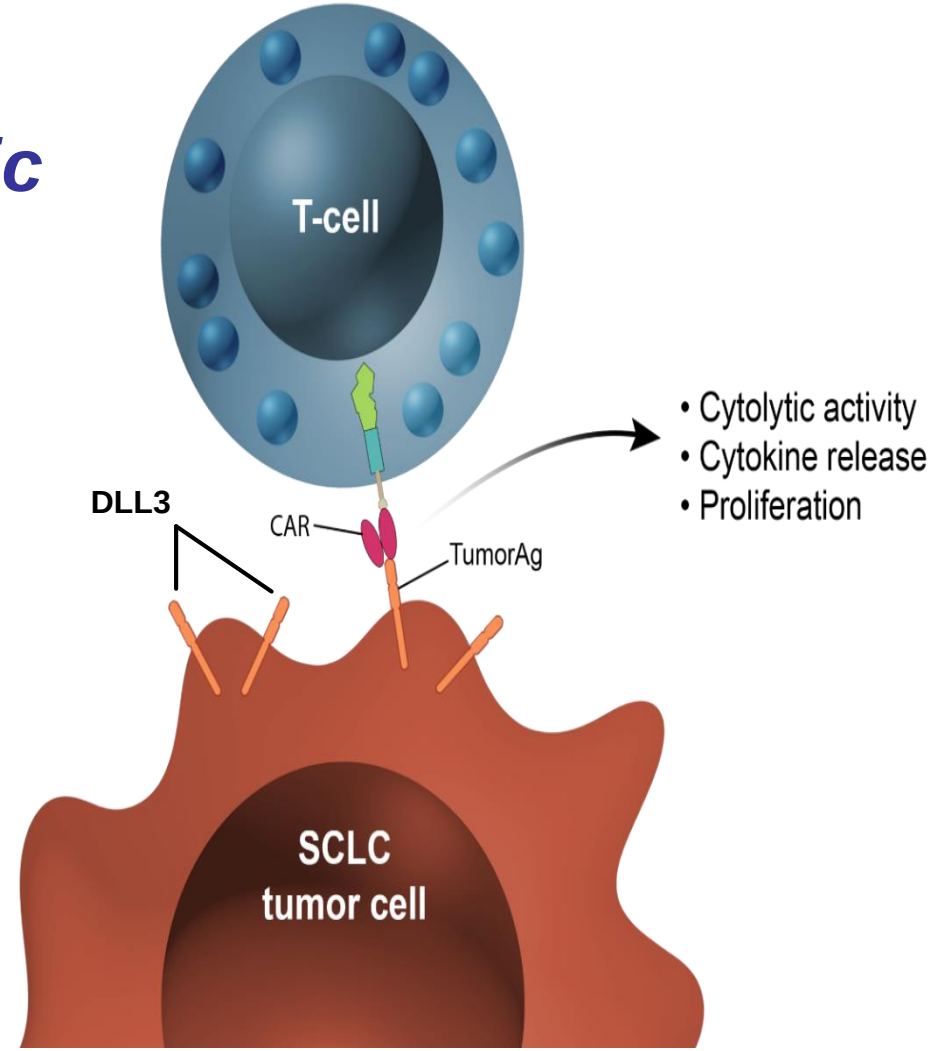
AMG 757 is a half-life extended (HLE) bi-specific T cell engager (BiTE®) antibody construct



BiTE®, bispecific T cell engager; CD, cluster of differentiation; Fc, crystallizable fragment; HLE, half-life extended.

AMG 119 is an adoptive chimeric antigen receptor (CAR) T cell therapy



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Anlotinib as third-line or further-line treatment in relapsed SCLC: a multicentre, randomized, double-blind phase 2 trial

Ying Cheng[1], Qiming Wang[2,3], Kai Li[4], Jianhua Shi[5], Lin Wu[6], Baohui Han[7], Gongyan Chen[8], Jianxing He[9], Jie Wang[10], Haifeng Qin[11], Xiaoling Li[12]

[1] Jilin Cancer Hospital, Changchun, China, [2] Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, China, [3] Henan Cancer Hospital, Zhengzhou, China, [4] Tianjin Medical University Cancer Hospital, Tianjin, China, [5] Linyi Cancer Hospital, Linyi, China, [6] Hunan Cancer Hospital, Changsha, China, [7] Shanghai Chest Hospital, Shanghai Jiaotong University, Shanghai, China, [8] Harbin Medical University Cancer Hospital, Harbin, China, [9] The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China, [10]Cancer Hospital Chinese Academy of Medical Sciences, Beijing, China, [11] The 307th Hospital of Military Chinese People's Liberation Army, [12] Liaoning Caancer Hospital & Institute, Shenyang, China

Background

- Precision Medicine has tailored cancer treatment to individuals in certain cancer types, however, there is no progression in small cell lung cancer (SCLC) yet, chemotherapy and radiotherapy have been the main, but not satisfactory approaches for over 30 years.
- Only 20% patients receive 3rd-line treatments and outcomes are poor.
  - Objective response rate (ORR) : 18%-26%;
  - Overall survival (OS) : 4.7-5.0 months;
- Anlotinib is a novel TKI with highly selective inhibition effects on multi-targets, especially on VEGFR, c-Kit, PDGFR, FGFR.
- This phase 2 randomized trial (ALTER1202, NCT03059797) was initiated to confirm the efficacy and safety of anlotinib for the third-line and further-line treatment of SCLC.

1. Clin Lung Cancer. 2016 Nov;17(6):581-587.

Study Design

A multicentre, randomized, double-blind phase 2 trial (ALTER1202; NCT03059797)

Eligibility Criteria
- 18-75 years
- Histological documentation of small cell lung cancer
- Previously received at least two chemotherapy regimens
- Measurable lesion (by RECIST1.1)
- ECOG PS: 0-2

R
2:1

Anlotinib 12 mg, qd, po
Day 1-14, 3 weeks/cycle,
N=81*

Placebo
po, qd
n=38*

PD

Primary Endpoint
- PFS

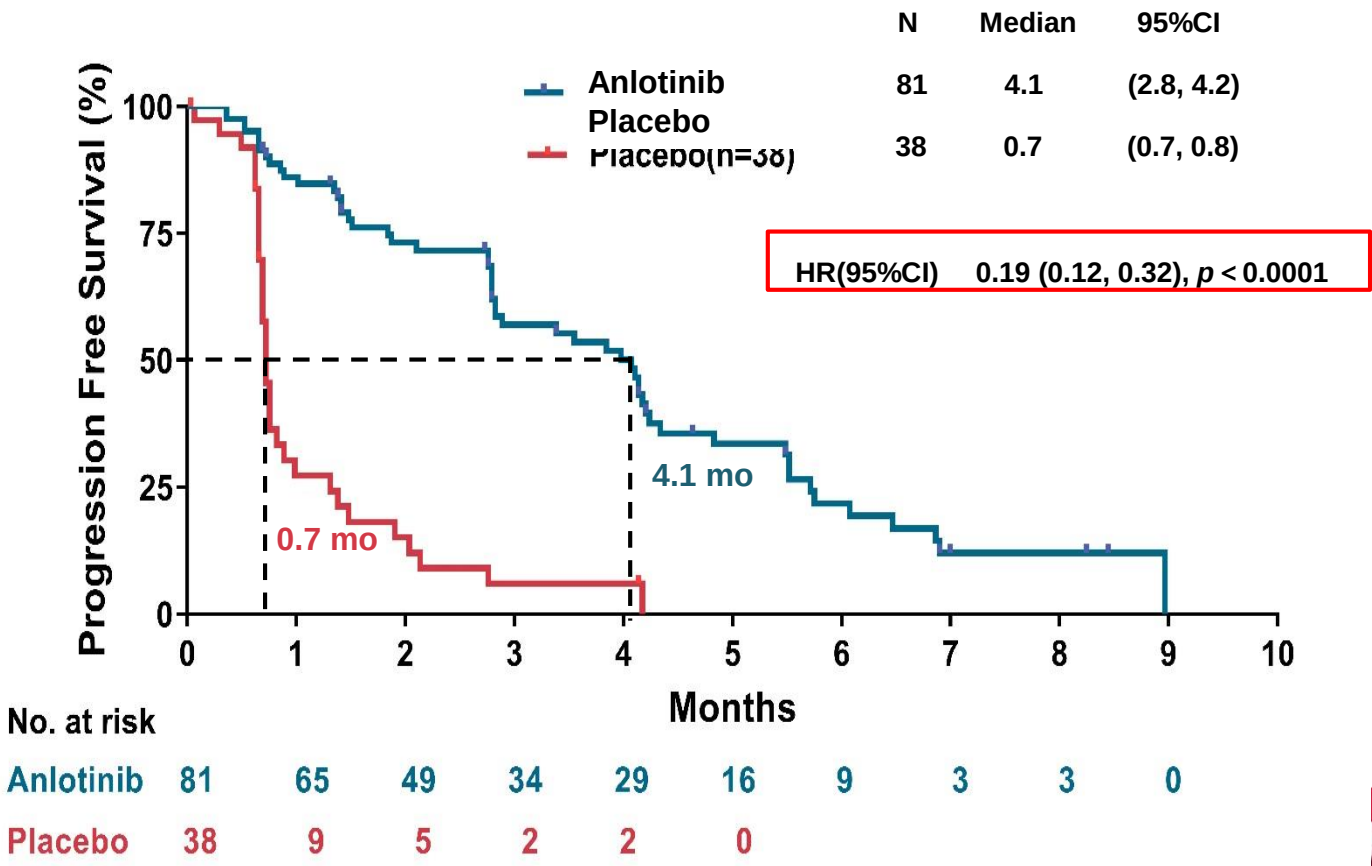
Secondary Endpoints
- OS
- ORR
- DCR
- Quality of Life
- Safety and Tolerability

- Enrollment period: March 2017 - May 2018
- 175 patients screen,120 patients randomized
- Data cutoff date: 30 Jun 2018
- **Stratified by:** Stage(Limited/ Extensive), Relapse(Sensitive / refractory)

- * In Anlotinib group, 81 patients were in full analysis dataset (FAS) and safety dataset(SS); In placebo group, 38 patients were in FAS set and 39 patients in SS.
- Randomized error patient should take anlotinib rather than placebo, this patient was included in the FAS of anlotinib arm and SS of placebo arm.
- One misdiagnosis patient was not included in the FAS of anlotinib arm.

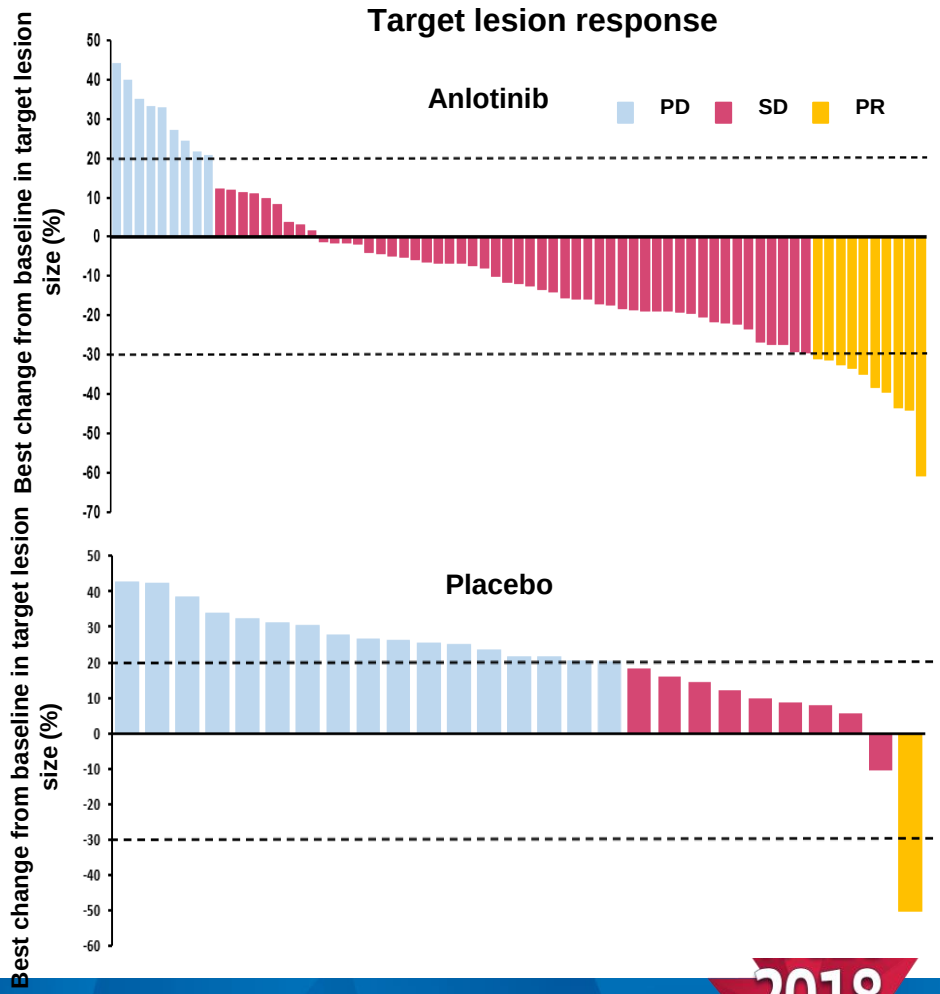
Primary Endpoint: PFS (FAS)

- Significantly prolonged median PFS in the anlotinib arm (4.1 months) vs. the placebo arm (0.7 months)



Secondary Endpoints: ORR (FAS)

	Anlotinib (n=81)	Placebo (n=38)	*P*
Complete Response, n(%)	0 (0.0)	0 (0.0)	-
Partial Response, n(%)	4 (4.9)	1 (2.6)	-
Stable Disease, n(%)	54 (66.7)	4 (10.5)	-
Progression Disease, n(%)	20 (24.7)	25 (65.8)	-
NE, n(%)	3 (3.7)	8 (21.1)	-
Objective Response Rate(%)	4.9	2.6	1.0000
95% CI	(0.2,9.7)	(0.1,13.8)	-
Disease Control Rate(%)	71.6	13.2	<0.0001
95% CI	(61.8,81.4)	(2.4,23.9)	-



Summary

- The study met its endpoints, anlotinib appears to provide significant PFS and DCR benefit for SCLC patients who failed ≥ 2 lines of chemotherapy.
  - PFS: Anlotinib vs Placebo： 4.1 vs 0.7 months (HR, 0.19; 95% CI, 0.12 to 0.32, p<0.0001)
  - DCR: Anlotinib vs Placebo： 71.6% vs 13.2%, p<0.0001
- Overall survival data were immature, but can see the benefit in anlotinib arm.
- The safety profile was consistent with the previous report and no newly adverse events were identified.
- ALTER1202 is the first randomized, placebo-controlled trial in patients with relapsed SCLC who failed ≥ 2 lines of chemotherapy in which anlotinib demonstrated robust clinical activity. Data support anlotinib as a new option for ≥ 3rd-line SCLC patients. Future studies will be further carried out including front-line treatment, combined treatment and so on.

Prophylactic cranial irradiation (PCI) for limited-stage small-cell lung (SCLC) cancer patients: results from the prospective randomised phase 3 CONVERT trial

C Le Péchoux*, A Levy*, H Mistry, I Martel-Lafay, A Bezjak, D Lerouge, L Padovani, P Taylor, C Faivre-Finn

* Department of Radiation Oncology

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TOWARDS A FUTURE WITHOUT CANCER

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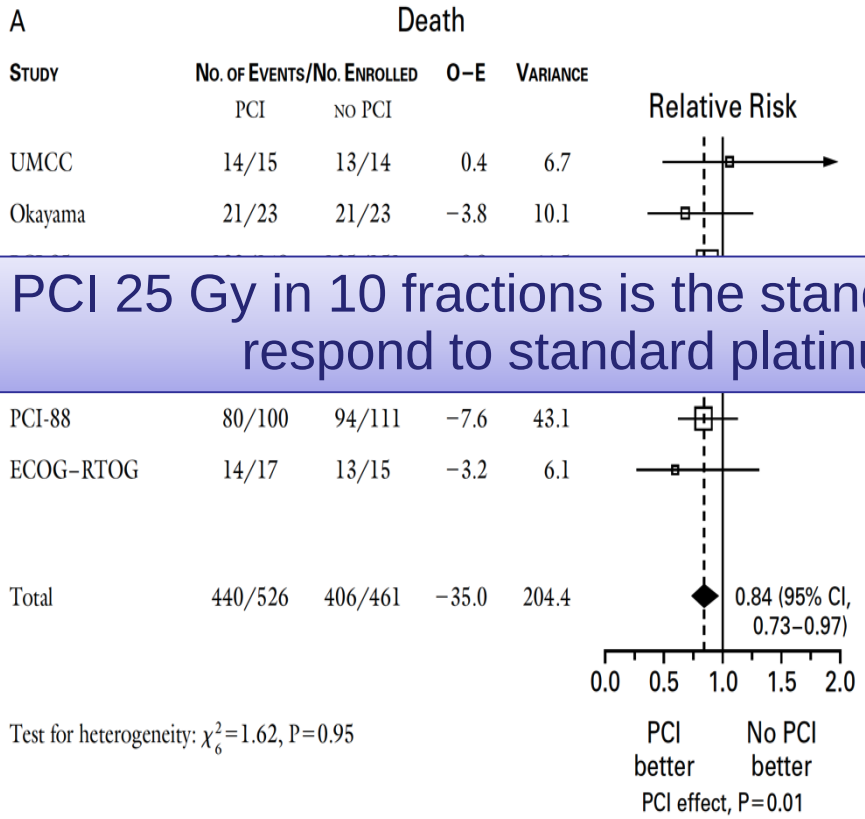
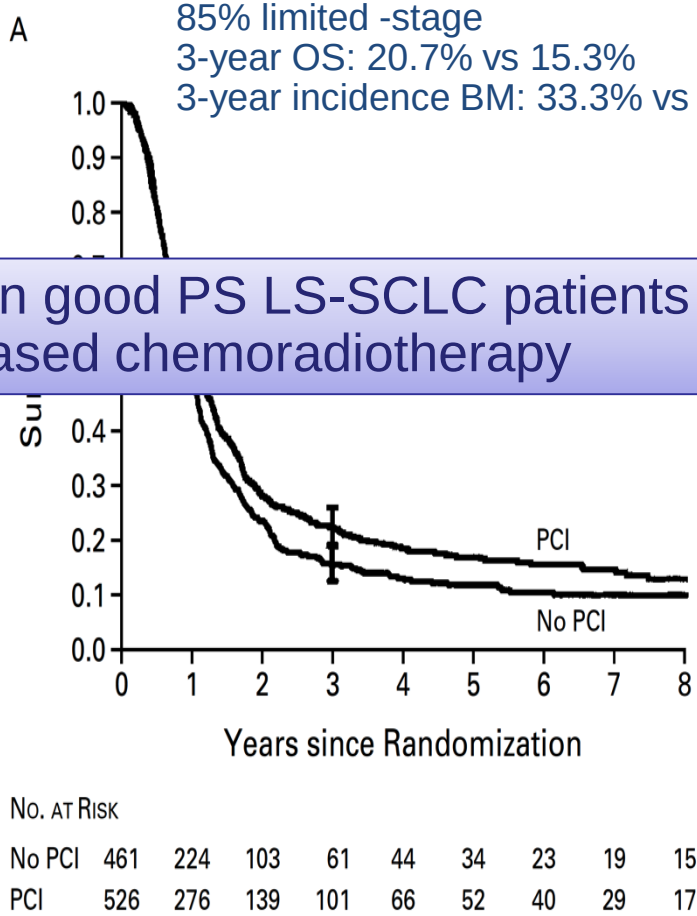
PCI in Limited-Stage SCLC



p=0.01

Aupérin, et al. NEJM 1999

85% limited -stage
3-year OS: 20.7% vs 15.3%
3-year incidence BM: 33.3% vs 58.6%



Le Péchoux, et al. Lancet Oncol 2009

PCI 25 Gy in 10 fractions is the standard in good PS LS-SCLC patients who respond to standard platinum-based chemoradiotherapy

PCI in Limited-Stage SCLC

Unsolved questions

- Optimal timing of PCI delivery after CTRT ?
  - Trend in favour of early PCI is suggested
- Impact of dose and fractionation of thoracic radiotherapy on brain relapse risk?
- Impact of magnetic resonance imaging (MRI)?
  - MRI has become a standard investigation for SCLC
  - Largest studies included in MA: Baseline CT scan
  - In PCI-99 all patients had a brain baseline imaging (74% CT scan and 26% MRI)
  - In ED, no baseline imaging in the absence of brain symptoms (Slotman study)
    Baseline MRI for all pts and then every 3 months

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

Study design

multinational, phase III randomised study

RTP after randomisation
RT started on D22 cycle 1
- 3DCRT or IMRT
- No ENI

QA programme

Chemotherapy
4 to 6 cycles
- Cisplatin 25mg/m2 D1-3 or 75mg/m2 D1
- Etoposide 100mg/m2 D1-3

Stratification factors
- Centre
- No. of cycles chemo: 4 vs.6
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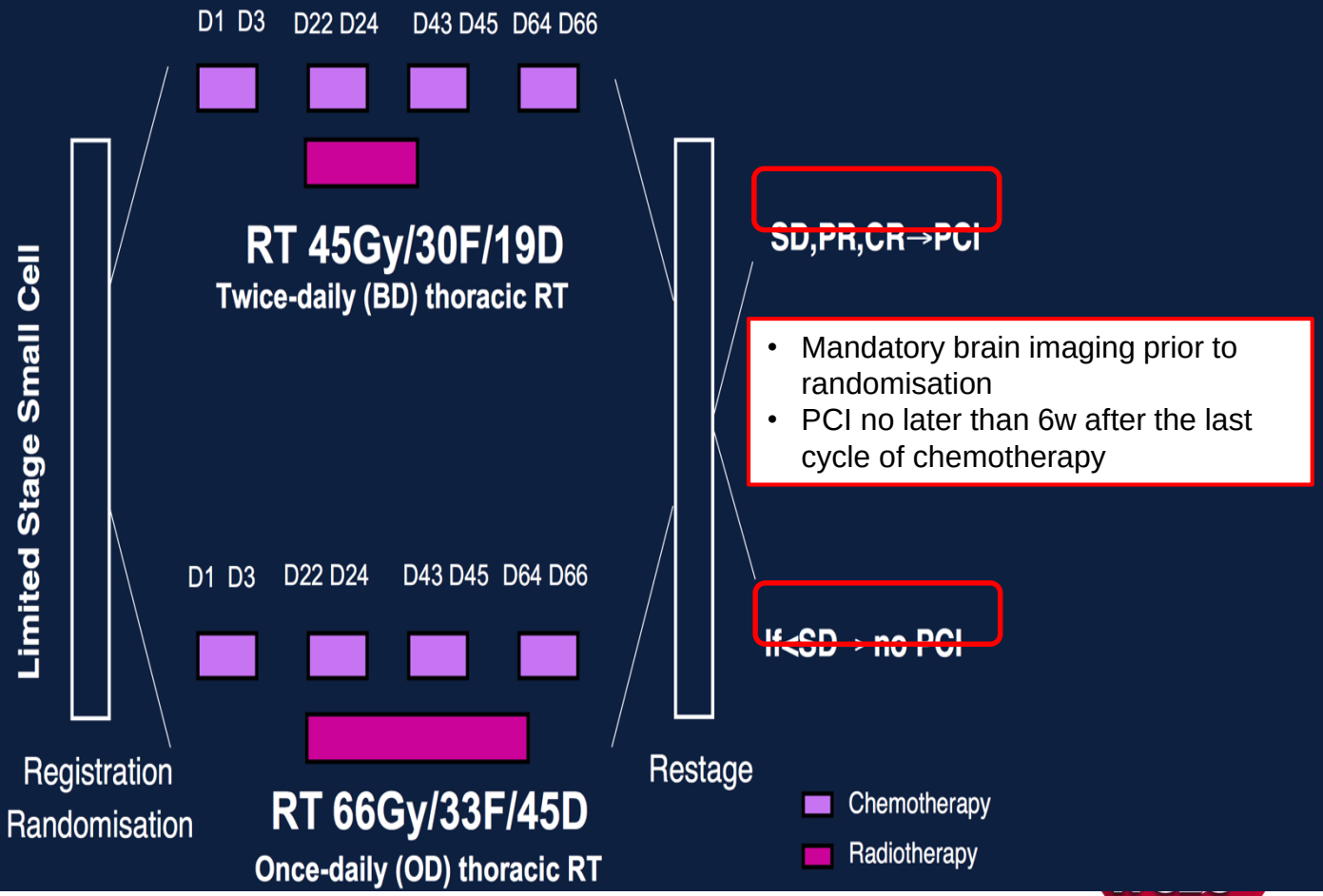


- Mandatory brain imaging prior to randomisation
- PCI no later than 6w after the last cycle of chemotherapy

Results

PCI Population

- CONVERT recruited 547 patients from 73 centres across 8 countries btw 04/2008 and 11/2013
- The modified ITT survival analysis included 543 patients (273 BD group and 270 OD group); four patients were lost to follow-up
- 449/543 (83%) received PCI after completion of CTRT
- PCI was equally delivered in both arms (p=0.49)
  - 220 (81%) of 273 in the BD group
  - 229 (85%) of 270 in the OD group
- Baseline brain imaging:
  - CT-scan : 79% (356/449 patients)
  - MRI : 18% (83/449 patients)

No PCI pts

- Older pts (p=0.01)
- Higher % of Asian patients (p=0.01)

Results

PCI delivery according to treatment groups

	Twice-daily (n=229)	Once-daily (n=220)	p-value
Total Dose (Gy); Median (Range)	25 (12.5-37.5)	25 (2.5-30)	0.741**
Total Dose (Gy) 25 >25 <25	 187 (82%) 25 (11%) 15 (7%)	 167 (76%) 32 (15%) 20 (9%)	0.278*
Days post chemotherapy ; Median (Range)	35 (9-174)	37 (25-209)	0.043**

* Chi-sq test; ** Wilcoxon Rank Sum test

no difference either when calculating from the start of chemotherapy

Results

Univariate and multivariate analyses for brain relapse (PCI patients only)

75 (17%) patients developed BM

UICC/AJCC stage of PCI pts

- **St I = 4 (1%),**
- **St II = 74 (16%),**
- **St III = 346 (77%) respectively**
- **unknown in 25 patients**

	Patients	Brain Progression from PCI initiation			
		Univariate		Multivariate	
	N/BP/Death	HR (95% CI)	p-value	HR (95% CI)	p-value
log(tGTV)	430/70/246	1.37 (1.09-1.73)	0.007	1.43 (1.11-1.85)	0.006
OD v BD (BD is referent)	449/75/263	0.95 (0.60-1.50)	0.830	0.93 (0.57-1.53)	0.770
Brain CT v MRI (MRI is referent)	438/73/255	1.17 (0.67-2.07)	0.580	1.28 (0.67-2.46)	0.450
Weight loss >10% (yes vs. no) (no is referent)	418/70/248	1.57 (0.59-4.18)	0.360	1.83 (0.69-4.89)	0.230
ECOG PS 1 or 2 vs. 0 (0 is referent)	449/75/263	0.64 (0.40-1.02)	0.059	0.54 (0.32-0.90)	0.018
log(PCI) Timing from randomisation	449/75/263	2.84 (0.82-9.82)	0.100	1.82 (0.04-8.62)	0.760
log(PCI) Timing from end of CTRT	446/74/262	1.10 (0.63-1.89)	0.750	0.83 (0.48-1.45)	0.520

Results

Univariate and multivariate analyses for OS (PCI patients only)

Median OS : 29 months (95% CI 25.8-35.7)

3-year OS rates :
- **-All: 45% (95%CI 40-50)**
- **-OD group: 42% (95%CI 36-49)**
- **-BD group: 48% (95%CI 41-55)**

	Patients	Survival from PCI initiation			
		Univariate		Multivariate	
	N/BP/Death	HR (95% CI)	p-value	HR (95% CI)	p-value
log(tGTV)	430/70/246	1.37 (1.19-1.56)	<0.001	1.33 (1.16-1.54)	<0.001
OD v BD (BD is referent)	449/75/263	1.21 (0.95-1.54)	0.121	1.16 (0.89-1.51)	0.275
Brain CT v MRI (MRI is referent)	438/73/255	1.30 (0.94-1.81)	0.113	1.41 (0.99-2.00)	0.151
Weight loss >10% (yes vs. no) (no is referent)	418/70/248	2.31 (1.34-3.97)	0.002	1.98 (1.14-3.43)	0.015
ECOG PS 1 or 2 vs. 0 (0 is referent)	449/75/263	1.28 (1.00-1.63)	0.049	1.12 (0.86-1.46)	0.348
log(PCI) Timing from randomisation	449/75/263	1.07 (0.59-1.93)	0.820	0.66 (0.11-4.14)	0.659
log(PCI) Timing from end of CTRT	446/74/262	1.48 (1.12-1.96)	0.007	1.32 (0.93-1.87)	0.189

Standard v High Dose PCI: Low Dose Better

LESS Neurologic deterioration LOW DOSE

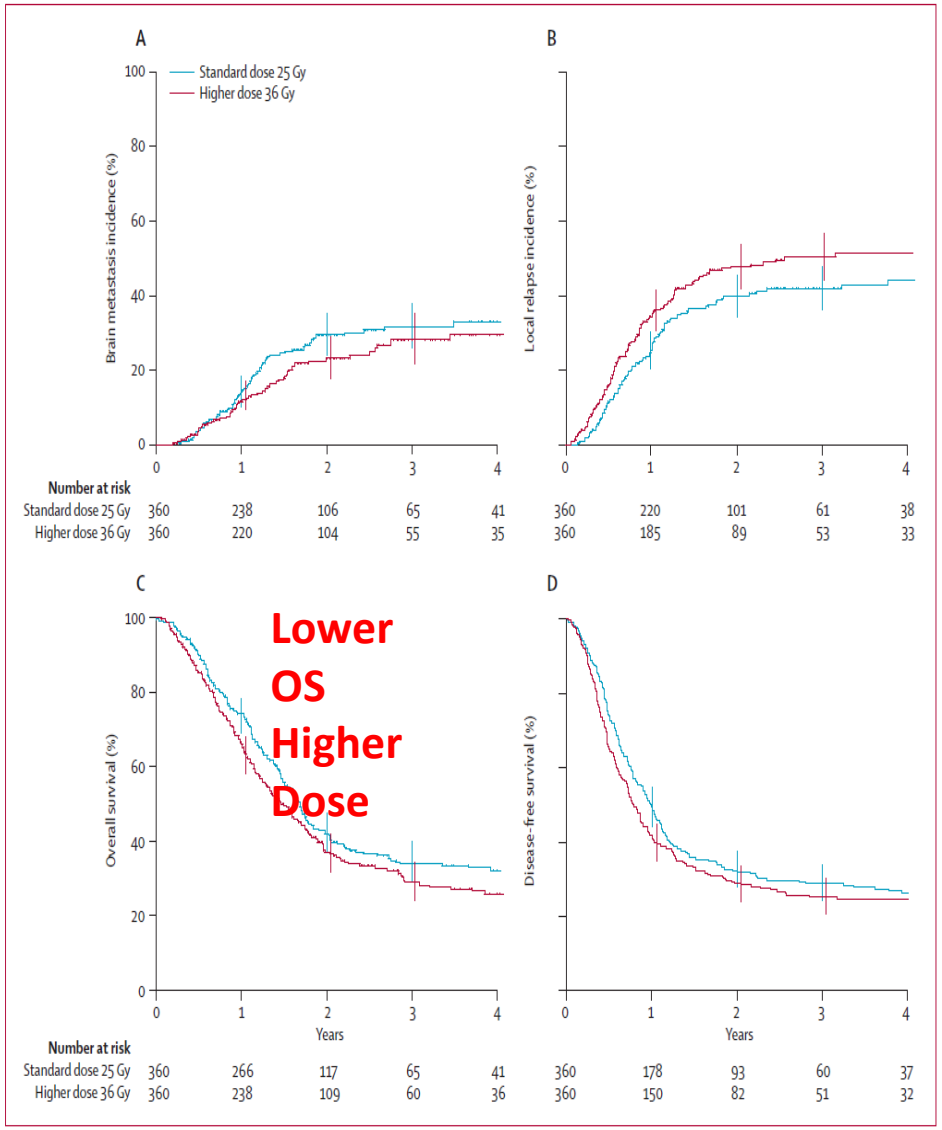


Figure 2: Kaplan-Meier curves showing total incidence of brain metastasis (A), local relapse (B), overall survival (C), and disease-free survival (D)

Table 3

The Incidence of Neurologic Deterioration and Chronic Neurotoxicity** at 12 months

		No Neurologic Deterioration		Neurologic Deterioration		95% CI of Deterioration Percentage	
Variable	**Comparison**	**n**	**%**	**n**	**%**		**p-value†**
Treatment Arm	2.5 Gy × 10	17	38	28	**62**	(50, 74)	**0.03**
	2.0 Gy × 18	3	15	17	**85**	(72, 98)	
	1.5 Gy × 24	2	11	17	**89**	(78, 100)	
Gender	Male	13	28	33	72	(61, 83)	0.64
	Female	9	24	29	76	(65, 88)	
Education Level	≤ High School	11	34	21	66	(52, 79)	0.12
	> High School	8	19	35	81	(72, 91)	
Marital Status	Married/Living as married	14	28	36	72	(62, 82)	0.59
	Single/Divorced/Widowed	7	23	24	77	(65, 90)	
Age	≤ 60 years	13	41	19	59	(45, 74)	0.02
	>60 years	9	17	43	83	(74, 91)	

		No Chronic Neurotoxicity		Chronic Neurotoxicity		95% CI of Chronic Neurotoxicity	
Variable	Category	n	%	n	%		p-value†
Treatment Arm	2.5 Gy × 10	18	40	27	**60**	(48, 72)	**0.02**
	2.0 Gy × 18	3	15	17	**85**	(72, 98)	
	1.5 Gy × 24	2	11	17	**89**	(78, 100)	
Gender	Male	13	28	33	72	(61, 83)	0.84
	Female	10	26	28	74	(62, 85)	
Education Level	≤ High School	11	34	21	66	(52, 79)	0.20
	> High School	9	21	34	79	(69, 89)	
Marital Status	Married/Living as married	14	28	36	72	(62, 82)	0.83
	Single/Divorced/Widowed	8	26	23	74	(61, 87)	
Age	≤ 60 years	14	44	18	56	(42, 71)	0.009
	>60 years	9	17	43	83	(74, 91)	

Le Pechoux Lancet Oncol 2009

Wolfson RTOG 0212

Worse if > 60y

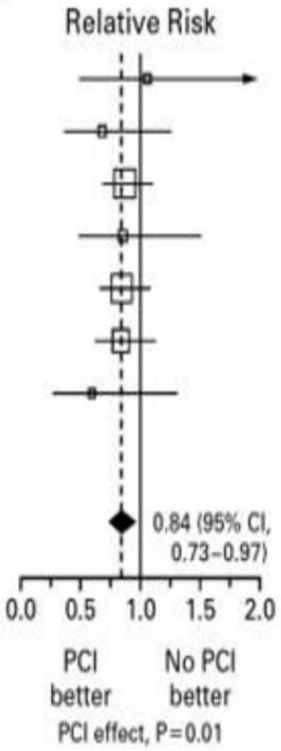
PCI in Limited-Stage SCLC

A

Death

Study	No. of Events/No. Enrolled		O−E	Variance
	PCI	no PCI		
UMCC	14/15	13/14	0.4	6.7
Okayama	21/23	21/23	−3.8	10.1
PCI-85	133/149	135/151	−8.9	66.5
Danish–NCI	24/28	24/27	−1.8	11.8
UKCCCR–EORTC	154/194	106/120	−10.1	60.3
PCI-88	80/100	94/111	−7.6	43.1
ECOG–RTOG	14/17	13/15	−3.2	6.1
Total	440/526	406/461	−35.0	204.4

Test for heterogeneity: $\chi^2_6 = 1.62$, P = 0.95

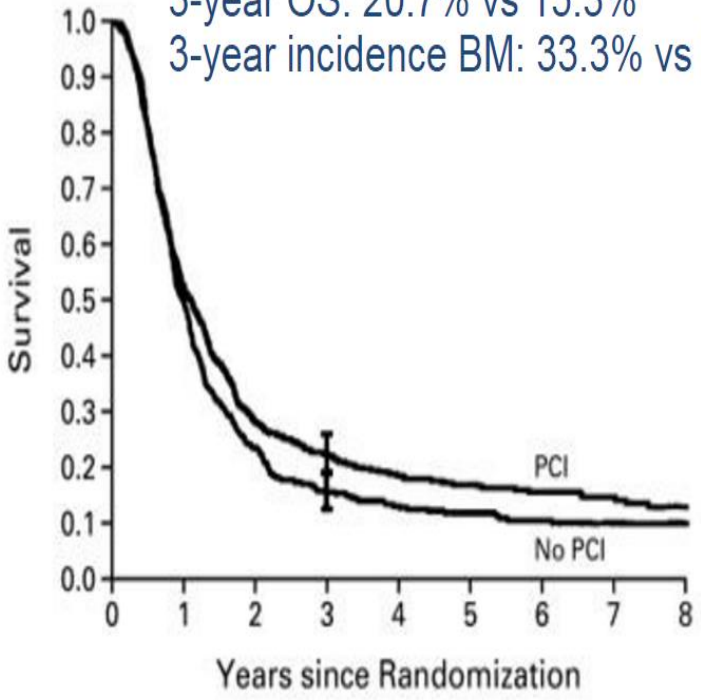


p=0.01

Aupérin, et al. NEJM 1999

A

85% limited -stage
3-year OS: 20.7% vs 15.3%
3-year incidence BM: 33.3% vs 58.6%



No. at Risk

No PCI	461	224	103	61	44	34	23	19	15
PCI	526	276	139	101	66	52	40	29	17

Le Péchoux, et al. Lancet Oncol 2009

PCI in Extensive Stage SCLC: Conflicts with LS Data

No pre-PCI Brain Imaging

Pre-PCI MRI + Surveillance

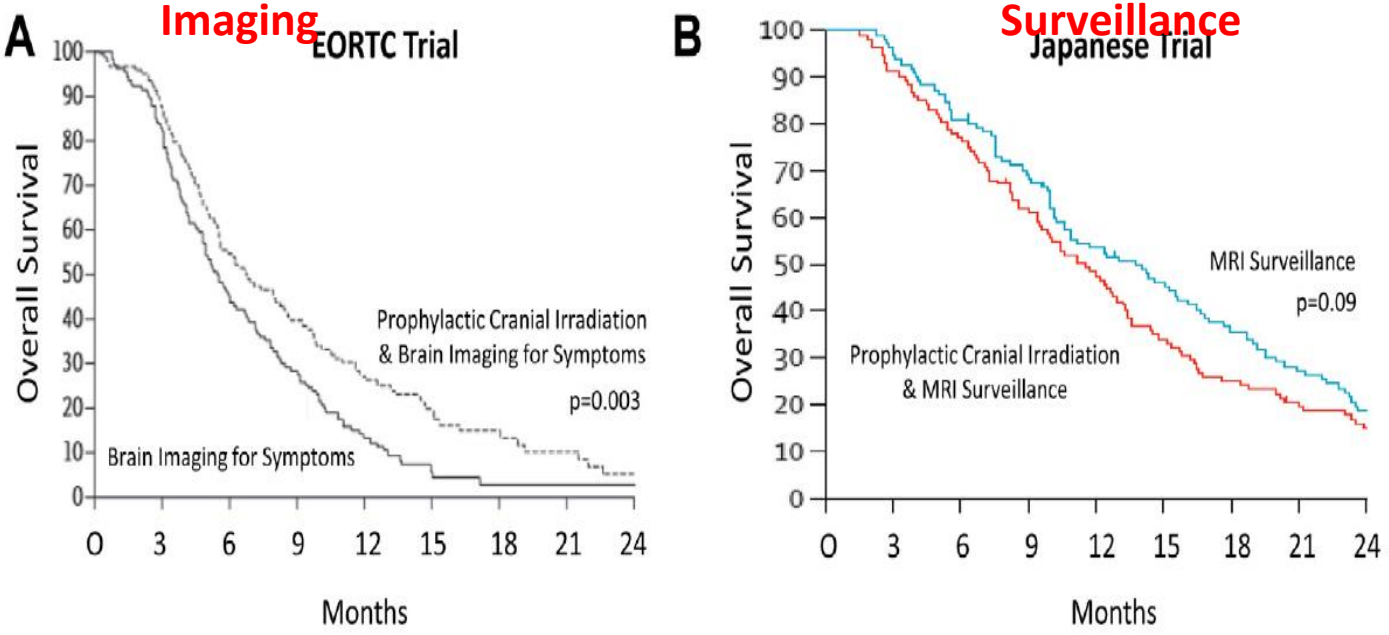


Figure 1. Overall survival in randomized trials of prophylactic cranial irradiation in extensive-stage SCLC. EORTC, European Organization for Research and Treatment of Cancer; MRI, magnetic resonance imaging. Adapted with permission from Slotman et al.[11] and Takahashi et al.[12]

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Prophylactic cranial irradiation

Prophylactic cranial irradiation after definitive chemoradiotherapy for limited-stage small cell lung cancer: Do all patients benefit? ☆

Ahsan S. Farooqi, Emma B. Holliday, Pamela K. Allen, Xiong Wei, James D. Cox, Ritsuko Komaki *

Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

- 658 pts who got Chemo at MDACC 1986-2012 Limited Stage
- 364 PCI; 294 no PCI; all thoracic RT 45-70 Gy
- CT staged to 2000; PET thereafter
- “ALL” pre-PCI brain imaging; “MOST” MRI
  - No specific numbers provided
  - No CT/MRI Surveillance data provided
- Median f/u 21 mos

Farooqi et al: Limited stage PCI

- PCI decreased risk of death HR 0.73, p=0.001
- PCI decreased risk of Brain mets 0.54, p<0.001
- Tumors >= 5 cm, increased risk brain mets HR 1.77
- If patient >= 70y and Tumor >= 5cm, PCI NOT improve OS
  - 39% v 41%, P=0.739

No PCI

PCI

No PCI

Older

Lower PS

Older RT

Table 1
Patient and treatment characteristics.

Characteristics	All patients (n = 658)	Patients who received PCI (n = 364)	Patients who did not receive PCI (n = 294)	*P* value*
Age, median (range), years	62 (27–95)	61 (34–85)	64 (27–95)	0.061
Race/Ethnicity, No. (%)				0.920
White, non-Hispanic	552 (83.9)	307 (84.3)	245 (84.3)	
While, Hispanic	31 (5.7)	18 (4.9)	13 (4.4)	
Black/African American	60 (9.1)	30 (8.2)	30 (10.2)	
Asian/Pacific Islander	10 (1.5)	6 (1.6)	4 (1.4)	
Other	5 (0.8)	3 (0.8)	2 (0.7)	
Sex, No. (%)				0.731
Male	342 (52.0)	187 (51.4)	155 (52.7)	
Female	316 (48.0)	177 (48.6)	139 (47.3)	
Karnofsky Performance Status, No. (%)				0.002
⩾80	550 (83.6)	319 (87.4)	231 (78.6)	
<80	108 (16.4)	45 (12.6)	63 (21.4)	
Treatment Era, No. (%)				0.116
<2000	320 (48.6)	167 (45.9)	153 (52.0)	
⩾2000	338 (51.4)	197 (54.1)	141 (48.0)	
Treatment Sequence, No. (%)				0.187
Concurrent CRT	394 (59.9)	229 (62.9)	165 (56.1)	
Induction chemo → CRT	137 (20.8)	72 (19.8)	65 (22.1)	
Induction chemo → RT	127 (19.3)	63 (17.3)	64 (21.8)	
Total XRT Dose, median (range)	45 (45–70)	45 (45–70)	45 (45–70)	0.750
XRT Fractionation, No. (%)				0.087
Once Daily	290 (44.1)	150 (41.2)	140 (47.6)	
Twice Daily	357 (54.3)	210 (57.7)	147 (50.0)	
Mixed	11 (1.7)	4 (1.1)	7 (2.4)	
XRT Technique, No. (%)				0.053
2D/3D	472 (71.3)	250 (68.7)	222 (75.5)	
IMRT	186 (28.7)	144 (31.3)	72 (24.4)	
Primary Tumor Size, No. (%)				0.439
<5 cm	265 (40.3)	148 (40.7)	117 (39.8)	
⩾5 cm	336 (51.1)	177 (48.6)	159 (54.1)	
Missing	57 (8.6)	39 (10.7)	18 (6.1)	
Subsequent Brain Metastases, No. (%)				0.036
Yes	139 (21.1)	66 (18.1)	73 (24.8)	
No	519 (78.9)	298 (81.9)	221 (75.2)	
Time to Brain Metastases,				<0.001
Months; median (range)	11 (2.2–73.3)	16.8 (5.6–73.3)	8.2 (2.2–36.6)	

PCI, prophylactic cranial irradiation; CRT, chemoradiotherapy; chemo, chemotherapy; RT, radiotherapy; 2D, two-dimensional radiotherapy; 3D, three-dimensional radiotherapy; IMRT, intensity-modulated radiotherapy.

* Pearson's chi-squares tests were used for between-group comparisons of categorical variables, and medians tests were used for between-group comparisons of continuous variables. For all comparisons, $p < 0.05$ was taken to be statistically significant.

Absolute difference in Brain Met rate 6.7% PCI vs NO PCI

Doubling of Time to develop brain mets 16.8 v 8.2 mo

Annals of Oncology 23: 2919–2924, 2012
doi:10.1093/annonc/mds123
Published online 10 July 2012

Prophylactic cranial irradiation in small-cell lung cancer: Findings from a North Central Cancer Treatment Group Pooled Analysis

S. E. Schild[1*], N. R. Foster[2], J. P. Meyers[2], H. J. Ross[3], P. J. Stella[4], Y. I. Garces[5], K. R. Olivier[5], J. R. Molina[6], L. R. Past[7] & A. A. Adjei[5] on behalf of North Central Cancer Treatment Group

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Schild et al: North Central Trials

PCI associated with improved OS, **BUT**

No Data provided on Brain Staging

No Data provided on MRI Surveillance

Trials ran from 1987-1999

ES

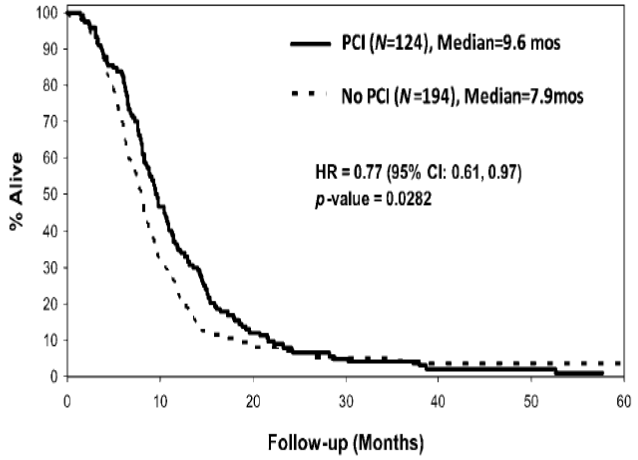

Figure 1. Survival impact of prophylactic cranial irradiation (PCI) (versus no PCI) across all extensive small-cell lung cancer patients.

LS

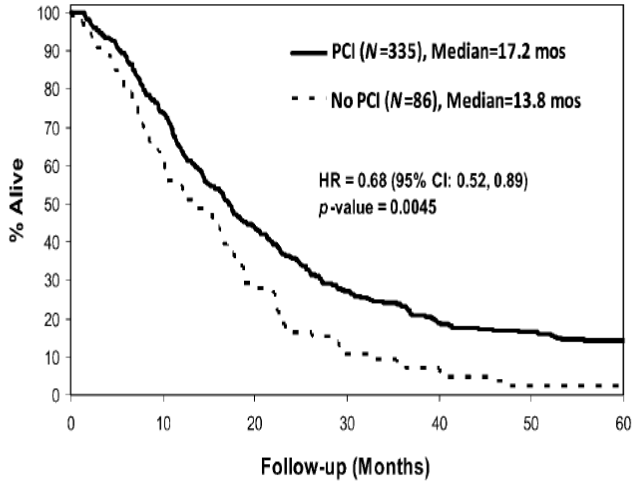

Figure 2. Survival impact of prophylactic cranial irradiation (PCI) (versus no PCI) across all limited small-cell lung cancer patients.

Table 3. Multivariate analysis of survival ($N = 739$)

Parameter	Hazard ratio (95% confidence interval)	*P* value[a,c]
PCI (versus no PCI)	0.817 (0.67, 0.99)	**0.0409**
Age (1-year increase)	1.02 (1.01, 1.03)	**0.0002**
Male (versus female)	1.17 (0.997, 1.37)	0.0543
PS 1 (versus PS 0)	0.995 (0.84, 1.18)	0.9556[a]
PS 2 (versus PS 0)	1.20 (0.93, 1.55)	0.1531[b]
ESCLC (0 or 1 metastatic site) versus LSCLC	1.72 (1.34, 2.22)	**<0.0001**[b]
ESCLC (>1 metastatic site) versus LSCLC	2.21 (1.69, 2.90)	**<0.0001**[b]
CR (versus no CR)	0.77 (0.64, 0.92)	**0.0050**

TAKE HOME MESSAGE

- In the CONVERT trial we showed that a higher risk of BM :
  - is associated with larger thoracic tumours
  - But not with the type of thoracic fractionation, baseline brain imaging, PCI and dose

- Clinical need :
  - Predictive models to achieve a more personalised management
  - New PCI trials performed in the MR imaging era

IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER
IASLC 19th World Conference on Lung Cancer
September 23–26, 2018 Toronto, Canada
WCLC2018.IASLC.ORG
#WCLC2018

Final Report of a Prospective Randomized Study on Thoracic Radiotherapy Target Volumes in Limited-stage SCLC with Radiation Dosimetric and Pathologic Analyses

Xiao Hu[1], Yong Bao[2], Yu-jin Xu[1], Hui-neng Zhu[3], Jin-shi Liu[4], Li Zhang[5], Ying Jin[6], Jin Wang[1], Hong-lian Ma[1], Xiao-ling Xu[6], Zheng-bo Song[6], Hua-rong Tang[1], Fang Peng[2], Min Fang[1], Yue Kong[1], Meng-yuan Chen[1], Bai-qiang Dong[1], Liang Zhu[3], Chang Yu[3], Xin-min Yu[6], Yun Fan[6], Yi-ping Zhang[6], Peng-cheng Chen[4], Qiang Zhao[4], You-hua Jiang[4], Xin-ming Zhou[4], Qi-xun Chen[4], Wen-yong Sun[3], Wei-min Mao[4] and Ming Chen[1*]

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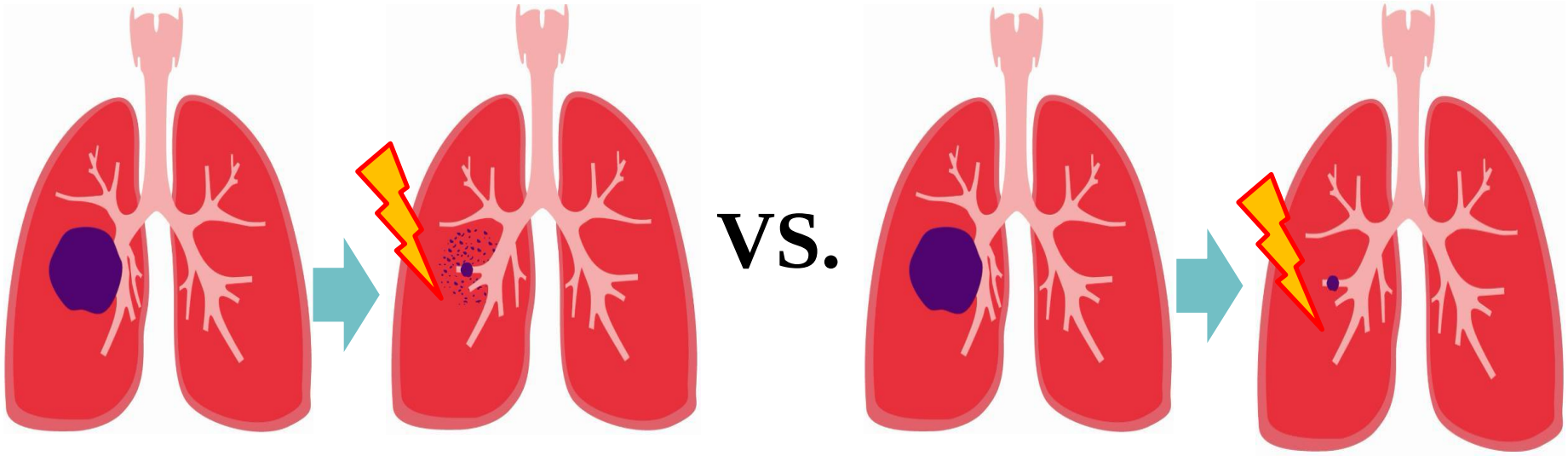
WCLC 2018

Background

- Small cell lung cancer (SCLC) accounts for approximately 13% of all bronchogenic carcinomas;
- Thoracic radiotherapy (TRT) combined with chemotherapy is the standard of care;
- TRT target volumes have been controversial for more than 20 years;
- Should we treat the post-chemotherapy or the pre-chemotherapy tumor volume？
- Is involved-field radiotherapy (IFRT) safe for limited-stage SCLC？
- Few prospective studies were available in the past two decades.

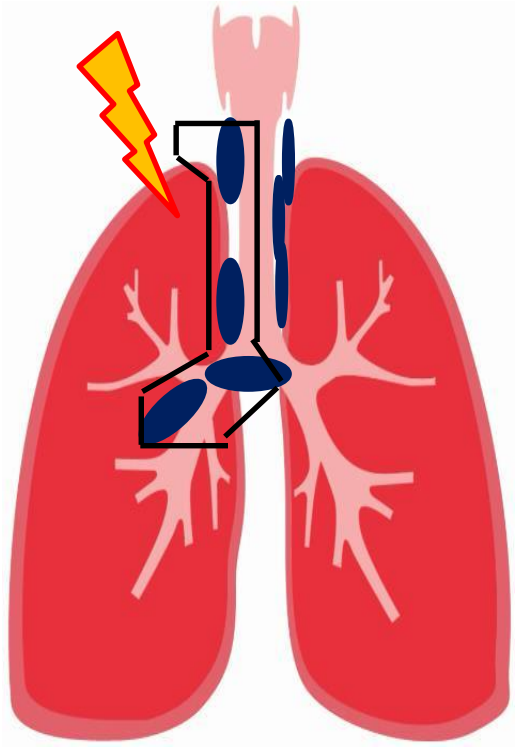
Background



Irradiate pre-chemotherapy volume?

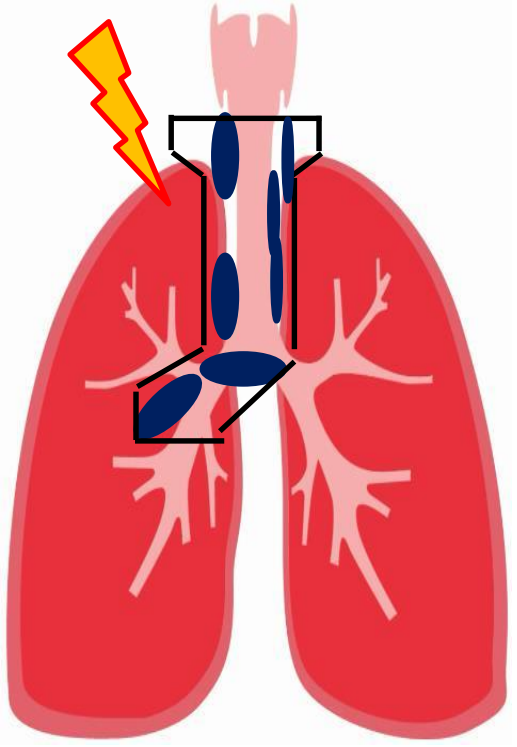
Irradiate post-chemotherapy residual tumor?

Background



Involved-filed radiotherapy (IFRT)

VS.



Elective nodal irradiation (ENI)

Patients and Methods

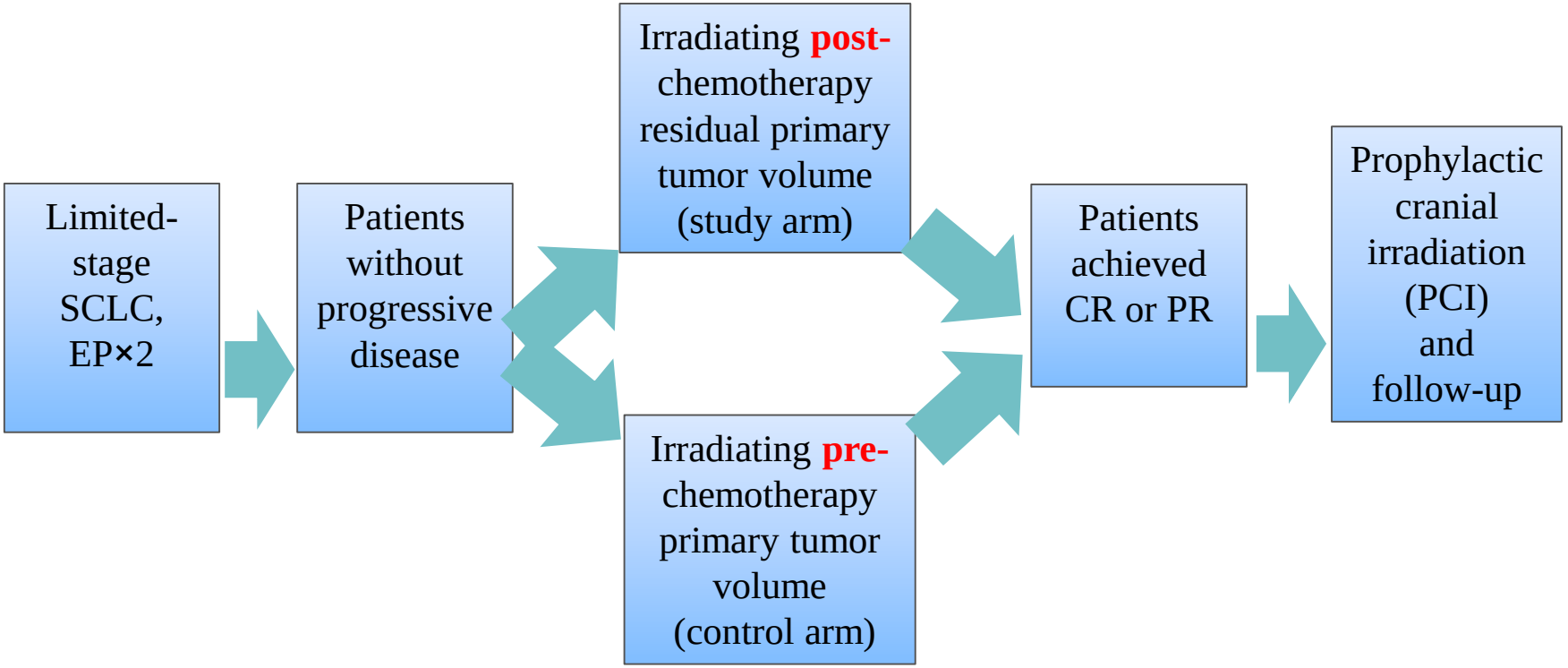
Inclusion criteria:

- Histologically or cytologically verified SCLC;
- Limited-stage disease (T1-4N0-3M0);
- No malignant pleural or pericardial effusion;
- Age ≥ 18 and ≤ 75 years old;
- Karnofsky performance status ≥ 80;
- Sufficient lung, heart, liver, kidney and bone marrow functions;
- Weight loss less than 10% within 6 months before diagnosis;
- Written informed consent was required.

Exclusion criteria:

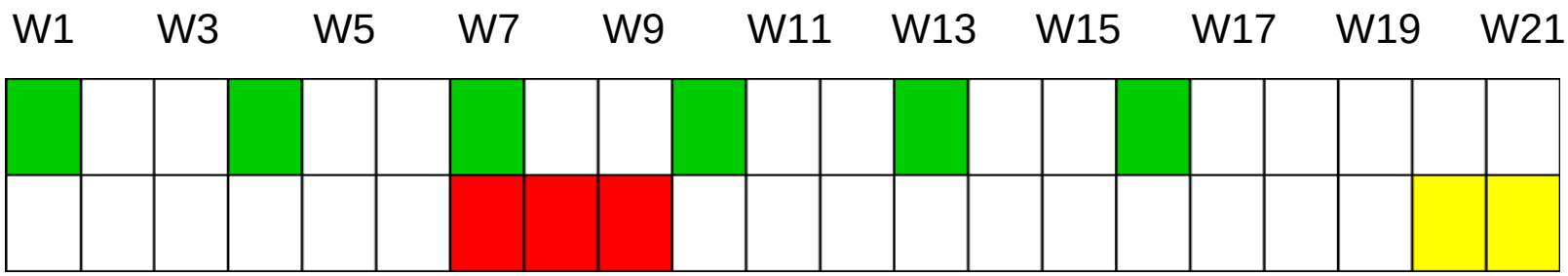
- Any contraindications for chemoradiotherapy;
- Other malignant diseases
  except: non-melanomatous skin cancer and carcinoma in situ of cervix;
- Patients during pregnancy or lactating.

Study Design



Involved-field radiotherapy was applied in both arms

Study Design



Chemotherapy consisted of etoposide (100 mg/m^2, d1-3) and cisplatin (80 mg/m^2, d1) or carboplatin (AUC=5, d1) was administered intravenously at 21-day intervals for 4 to 6 cycles.

TRT consisted of 1.5 Gy bid in 30 fractions over a 3-week period to a total dose of 45 Gy.

PCI was delivered daily to a total dose of 30 Gy or 25 Gy.

Study Objectives

- Primary endpoint:

  3-year local/regional control probability

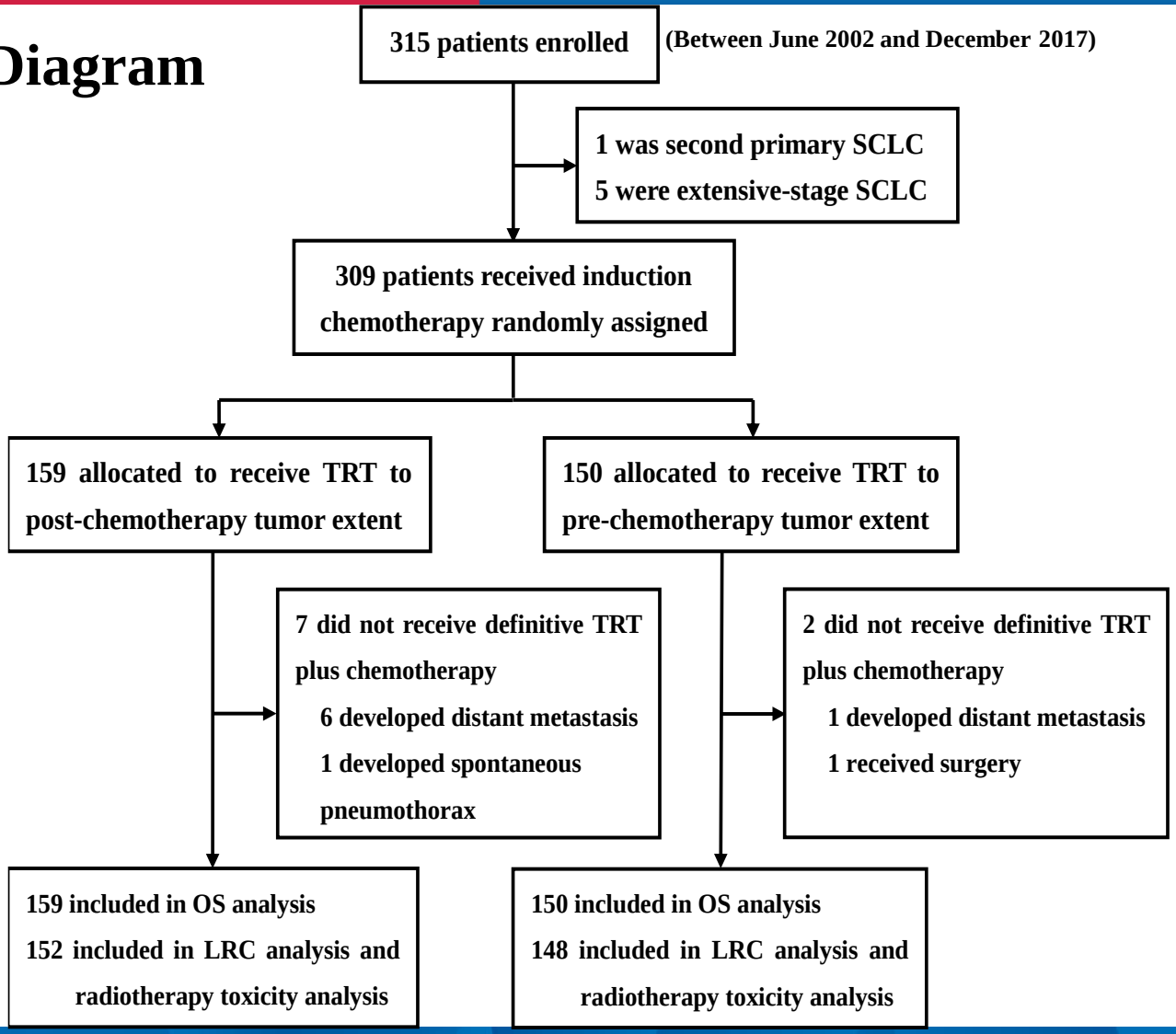
- Secondary endpoints:

  Overall survival

  Failure patterns

  Treatment related toxicities (CTCAE v3.0 and RTOG criteria)

Consort Diagram



Baseline Characteristics

Characteristics	Study Arm (n=159)		Control Arm (n=150)		*P*
	No. of Patients	%	No. of Patients	%	
Age (years)					
Median	59		58		
Range	34-75		32-75		
Sex					
Male	130	81.8	131	87.3	0.20
Female	29	18.2	19	12.7	
KPS					
90	107	67.3	111	74.0	0.21
80	52	32.7	39	26.0	
Mean FEV1 (L)	2.15		2.23		0.32
Weight loss					
< 5%	135	84.9	130	86.7	0.74
5%-10%	24	15.1	20	13.3	
Tumor type					
Central	123	77.4	117	78.0	1.0
Peripheral	36	22.6	33	22.0	
AJCC Staging					
I	2	1.3	2	1.4	0.51
II	8	5.0	10	6.6	
IIIA	43	27.0	48	32.0	
IIIB	106	66.7	90	60.0	
PET/CT examination	34	21.4	25	19.1	0.31

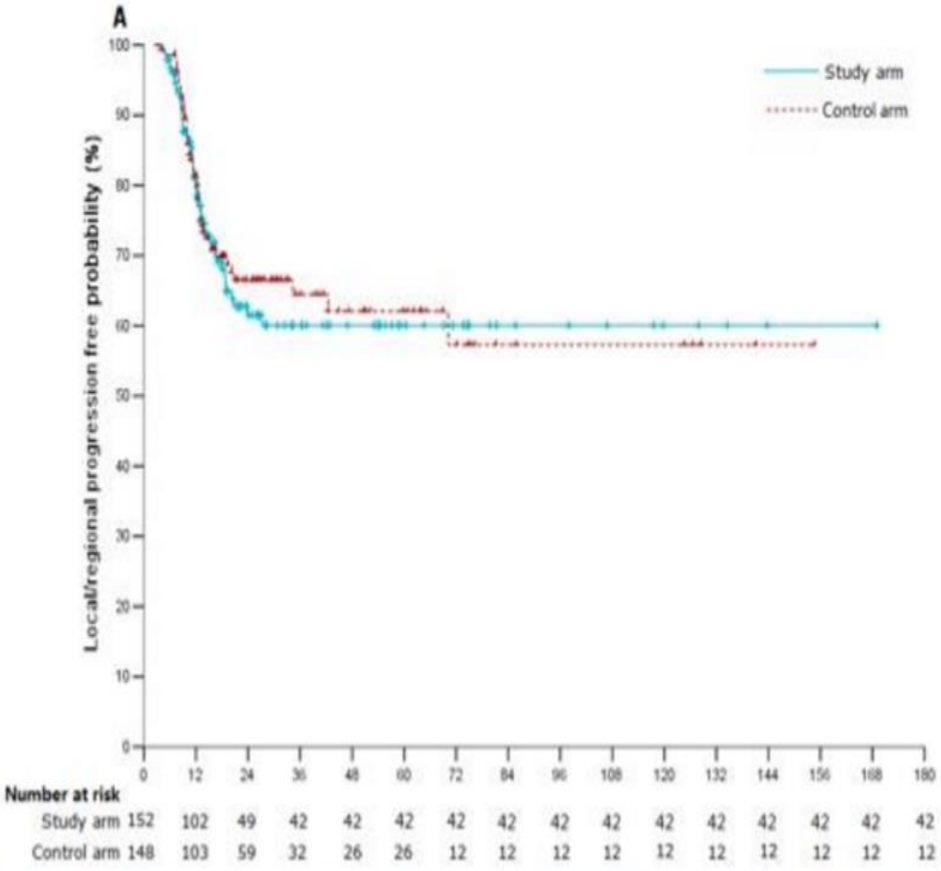
Treatment Delivery

Chemotherapy	Study arm N=159 (%)	Control arm N=150 (%)
Cycles		
0	2 (1.3)	0 (0)
2	6 (3.8)	2 (1.3)
3	9 (5.7)	12 (8.0)
4	94 (59.1)	83 (55.3)
5	17 (10.7)	23 (15.3)
6	31 (19.5)	30 (20.0)

Radiotherapy	Study arm N=159 (%)	Control arm N=150 (%)
No TRT	7 (4.4)	2 (1.3)
IMRT	81 (53.3)	66 (44.6)
Not complete TRT	3 (1.9)	3 (2.0)
PCI	98 (64.5)	97(65.5)
30 Gy/15 F	12 (12.2)	11 (11.3)
25 Gy/10 F	83 (84.7)	83 (85.6)
Other doses	3 (3.1)	3 (3.1)

Equivalent Locoregional Recurrence 1-5y

Local/regional Progression Free Probability (per-protocol)



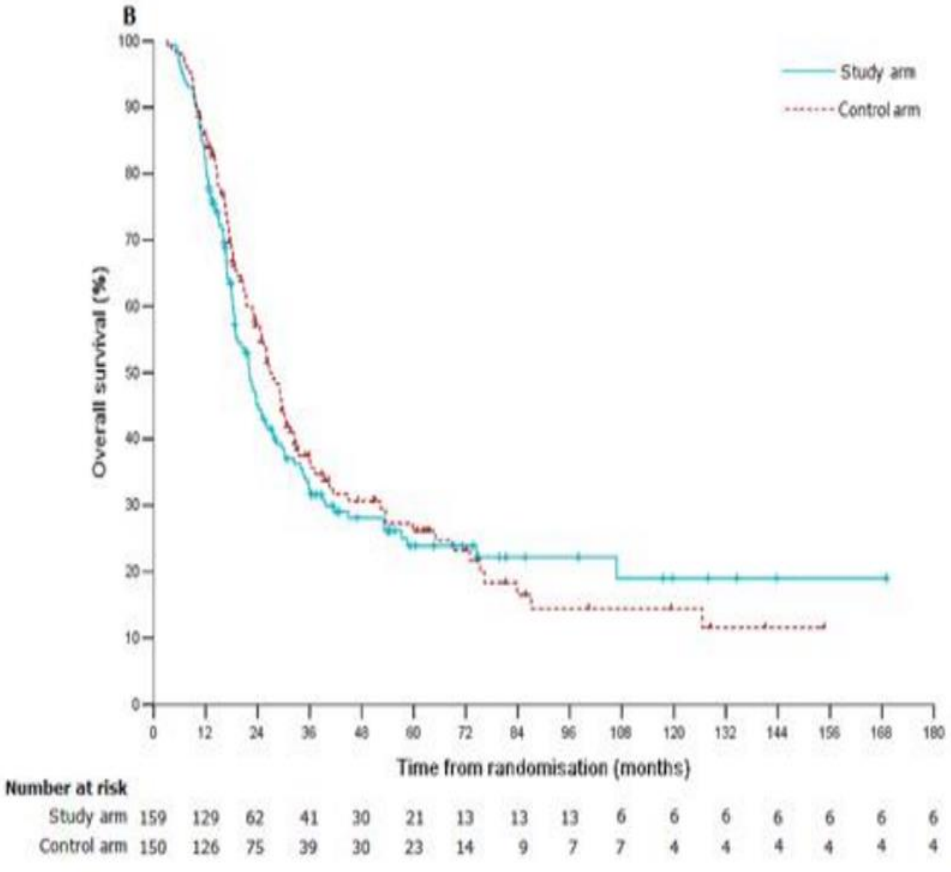
Median follow-up: 35.4 (6.6-165) months in survivors

LRPFP	Study arm N=152	Control arm N=148	*P*
1-year	79.4%	79.8%	
3-year	60.1%	64.5%	0.74
5-year	60.1%	57.3%	

HR: 0.93, 95% CI: 0.62-1.39

Equivalent Overall Survival 1-5y

Overall Survival (intention-to-treat)



OS	Study arm N=159	Control arm N=150	*P*
Median (months)	22.1 (18.2-26.0)	26.9 (23.5-30.3)	
1-year	81.1%	85.3%	0.51
3-year	31.6%	36.6%	
5-year	23.9%	26.1%	

HR: 0.91, 95% CI: 0.70-1.19

Adverse Events (acute)

Toxic Effect/Grade	Study Arm		Control Arm		*P*
	No.	%	No.	%	
Acute Toxic Haematologic toxicity ≥ grade 3					
Leucopenia					
III	59	37.1	55	36.7	0.35
IV	13	8.2	10	6.7	
Neutropenia					
III	59	37.1	56	37.3	0.72
IV	41	25.8	34	22.7	
Thrombocytopenia					
III	32	20.1	19	12.7	0.34
IV	16	10.1	12	8.0	
V	1	0.6	0	0	
Anemia					
III	34	21.4	29	19.3	0.59
IV	15	9.4	8	5.3	

Toxic Effect/Grade	Study Arm		Control Arm		*P*
	No.	%	No.	%	
Radiotherapy related toxicities					
Pneumonitis					
I-II	60	39.4	65	43.9	0.40
III	2	1.3	1	0.7	
IV	0	0	0	0	
V	2	1.3	0	0	
Esophagitis					
I	87	57.2	63	42.6	**0.01**
II	41	27.0	41	27.7	
III	9	5.9	23	15.5	
Weight loss					
I	30	19.7	43	29.1	0.16
II	12	7.9	9	6.1	

Adverse events (late)

Toxic Effect/Grade	Study Arm		Control Arm		*P*
	No.	%	No.	%	
Late toxicities					
Pulmonary fibrosis					
I	33	21.7	29	19.6	0.01
II	3	2.0	14	9.5	
III	0	0	2	1.4	
Esophageal stricture					
I	8	5.3	6	4.1	0.53
II	0	0	1	0.7	

Lung Cancer 76 (2012) 72–77

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Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

UK Trial

Omitting elective nodal irradiation during thoracic irradiation in limited-stage small cell lung cancer – Evidence from a phase II trial

Rovel Colaco[a], Hamid Sheikh[a], Paul Lorigan[b], Fiona Blackhall[b], Paul Hulse[d], Raffaele Califano[b], Linda Ashcroft[b], Paul Taylor[b,c], Nicholas Thatcher[b], Corinne Faivre-Finn[a,*]

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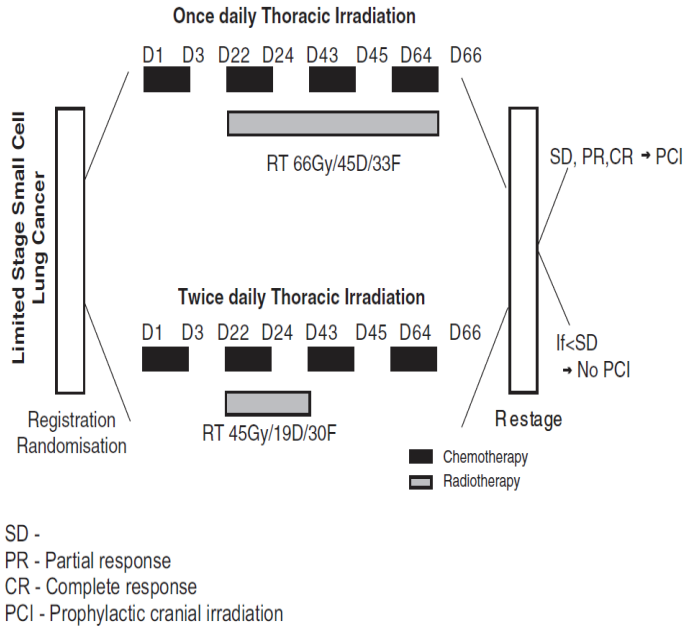


Fig. 1. ACTOR trial – phase II comparison of accelerated twice-daily compared with once-daily thoracic radiotherapy in limited stage small-cell lung cancer treated concurrently with etoposide and cisplatin.

Colaco et al: Phase II trial of concurrent chemoRT that omitted ENI based on CT imaging

No excess isolated recurrences out of field

Table 2

Patterns of recurrence.

	No patients (%)	Once-daily RT (n, %)	Twice-daily RT (n, %)
Isolated NR outside PTV	0	0	0
NR outside PTV + other recurrence	2 (6)	1 (3.8)	1 (10)
Isolated PTV recurrence	2 (6)	1 (3.8)	1 (10)
PTV recurrence + other recurrence	4 (11)	2 (7.7)	2 (20)
DM only	6 (17)	6 (23.1)	0
No recurrence	17 (47)	12 (46.2)	5 (50)
Non-evaluable	5 (13)	4 (15.4)	1 (10)
Total	36 (100)	26 (100)	10 (100)

NR, nodal recurrence; DM, distant metastasis; PTV, planning target volume; RT, radiotherapy.

Radiotherapy and Oncology 80 (2006) 307–312
www.thegreenjournal.com

Phase II trial

Netherlands Trial

Omission of elective node irradiation on basis of CT-scans in patients with limited disease small cell lung cancer: A phase II trial

Dirk De Ruysscher[a,b,*], Robert-Harm Bremer[a], Friederike Koppe[a,1], Stofferinus Wanders[a], Erik van Haren[c], Monique Hochstenbag[d], Wiel Geeraedts[e], Cordula Pitz[f], Jean Simons[g], Guul ten Velde[d], Jo Dohmen[h], Gabriel Snoep[i], Liesbeth Boersma[a], Tom Verschueren[a], Angela van Baardwijk[a], Cary Dehing[a], Madelon Pijls[a], Andre Minken[a], Philippe Lambin[a,b]

[a]*MAASTRO Clinic, Maastricht, The Netherlands,* [b]*Department of Radiation Oncology (MAASTRO), GROW, U.H. Maastricht, Maastricht, The Netherlands,* [c]*Department of Lung Diseases, Atrium Medical Centre, Heerlen, The Netherlands,* [d]*Department of Lung Diseases, University Hospital Maastricht, Maastricht, The Netherlands,* [e]*Department of Lung Diseases, Maasland Hospital, Sittard, The Netherlands,* [f]*Department of Lung Diseases, Sint Laurentius Hospital, Roermond, The Netherlands,* [g]*Department of Lung Diseases, and* [h]*Department of Radiology, Sint Jans Gasthuis, Weert, The Netherlands,* [i]*Department of Radiology, University Hospital Maastricht, Maastricht, The Netherlands*

JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2012;42(10)948–954
doi:10.1093/jjco/hys114
Advance Access Publication 17 July 2012

Comparison of Treatment Outcomes Between Involved-field and Elective Nodal Irradiation in Limited-stage Small Cell Lung Cancer

Tae Jin Han[1], Hak Jae Kim[1,2,3,*], Hong-Gyun Wu[1,2,3], Dae-Seog Heo[2,4], Young Whan Kim[2,4] and Se-Hoon Lee[2,4]

[1]Department of Radiation Oncology, Seoul National University College of Medicine, [2]Cancer Research Institute, Seoul National University College of Medicine, [3]Medical Research Center, Institute of Radiation Medicine, Seoul National University and [4]Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea

Retrospective study
80 pts chemoRT for LS-SCLC
n=50 IF RT; n=30 ENI
6% Isolated nodal failure IF RT group; 0% ENI

Improved outcomes with ENI if NO PET
3y OS 56% vs 29%, p=0.02

Published in final edited form as:
Int J Radiat Oncol Biol Phys. 2012 January 1; 82(1): e91–e97. doi:10.1016/j.ijrobp.2010.12.072.

POSITRON EMISSION TOMOGRAPHY/COMPUTED TOMOGRAPHY-GUIDED INTENSITY-MODULATED RADIOTHERAPY FOR LIMITED-STAGE SMALL-CELL LUNG CANCER

Shervin M. Shirvani, M.D.[*], **Ritsuko Komaki, M.D.**[*], **John V. Heymach, M.D., Ph.D.**[†], **Frank V. Fossella, M.D.**[†], and **Joe Y. Chang, M.D., Ph.D.**[*]

[*]Department of Radiation Oncology, University of Texas M.D. Anderson Cancer Center, Houston, TX

[†]Department of Thoracic/Head and Neck Medical Oncology, University of Texas M.D. Anderson Cancer Center, Houston, TX

Retrospective
60 pts
LS-SCLC underwent **PET** and IMRT including 4D planning **omitting ENI**
Median f/u 21 mos
30/60 pts recurred
1/30 isolated nodal recurrence

Summary of the Clinical Study

- This is the only randomized trial regarding radiotherapy target volumes using modern radiotherapy techniques;
- With a median follow-up of 35.4 months (for survivors), the 3-year LRPFP was 60.1% in study arm vs. 64.5% in control arm (HR: 0.93, 95% CI: 0.62-1.39, *P*=0.74);
- Although ＞ 90% patient were stage III, 5-year OS of 23.9% in study arm vs. 26.1% in control arm was achieved (HR: 0.91, 95% CI: 0.70-1.19, *P*=0.51);
- No out-field recurrence of the primary tumor was developed in the study arm;
- No out-field recurrence of mediastinal lymph node was observed in both arms when IFRT was used;
- Treatment related toxicities were comparable in the two arms, except for significantly more acute esophagitis and pulmonary fibrosis in the control arm.

Conclusions

- Irradiation to the post-chemotherapy tumor volume and application of IFRT did not increase local/regional failure;
- Less patients suffered from acute esophagitis and late pulmonary toxicity;
- TRT can be limited to post-chemotherapy tumor extent IFRT can be routinely applied in daily practice for patients with limited-stage SCLC.

JOURNAL OF CLINICAL ONCOLOGY
Official Journal of the American Society of Clinical Oncology

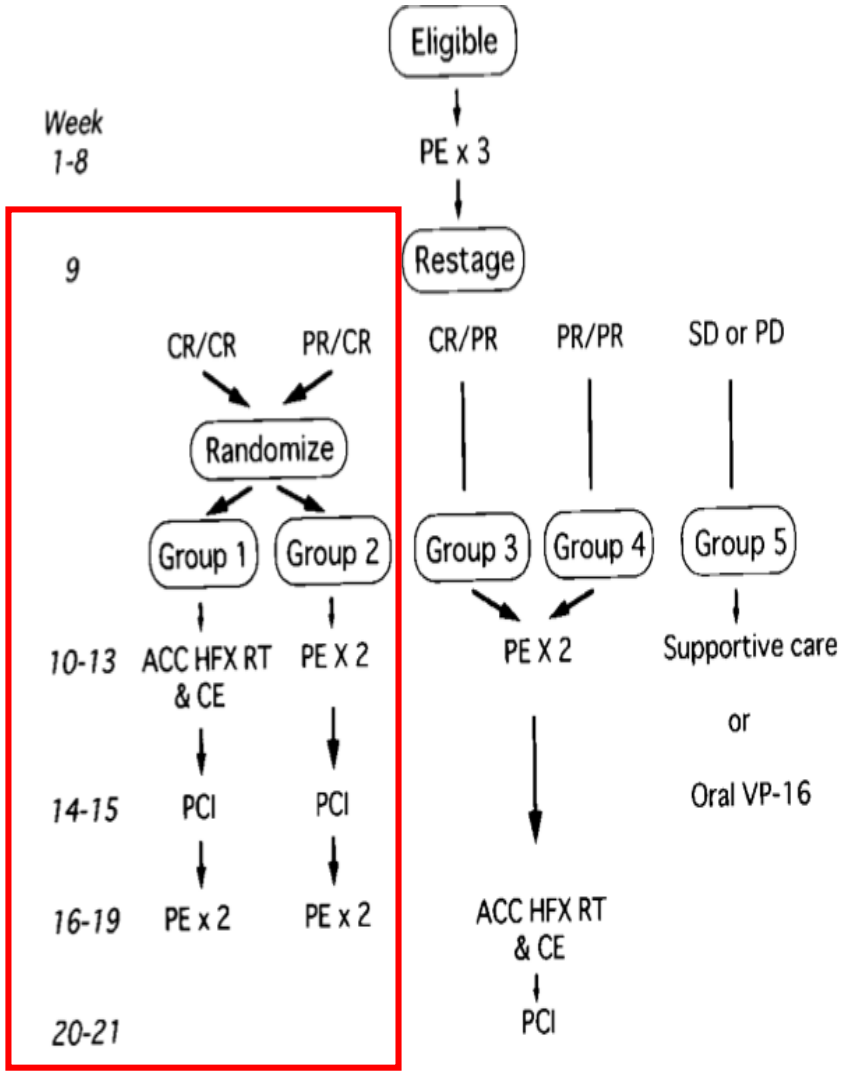
Role of Radiation Therapy in the Combined-Modality Treatment of Patients With Extensive Disease Small-Cell Lung Cancer: A Randomized Study

By Branislav Jeremic, Yuta Shibamoto, Nebojsa Nikolic, Biljana Milicic, Slobodan Milisavljevic, Aleksandar Dagovic, Jasna Aleksandrovic, and Gordana Radosavljevic-Asic

PE +/- Acc Fx RT for ED-SCLC

- 210 patients
- ED SCLC
- KPS >/= 70
- Staging
  - CXR and tomography
  - Bronchoscopy
  - BMbx
  - Brain, bone, liver radionuclide scans
  - abd US
  - CT brain and chest ---after 1989

No. of metastatic sites							
1	97	23	25	18	14	17	.91
2	87	27	23	12	11	14	
3	17	4	5	3	2	3	
4	4	1	1	1	0	1	
5	1	0	0	0	1	0	

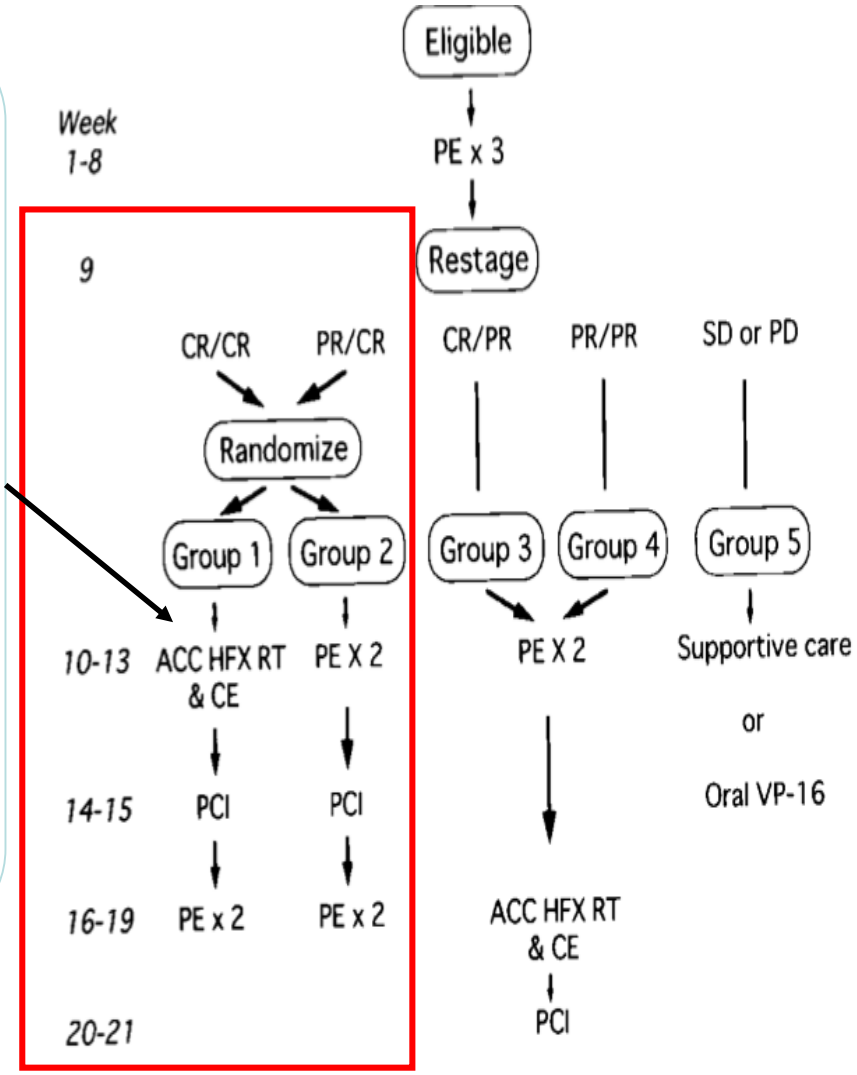


Jeremic et al. J Clin Oncol 17:2092-2099, 1999

Radiation
AP/PA : 36 Gy in 24 fx
Oblique fields: 18 Gy in 12 fx

Fields
Gross disease
Ipsi +2cm
Mediastinum +1 cm
Bilat supraclav

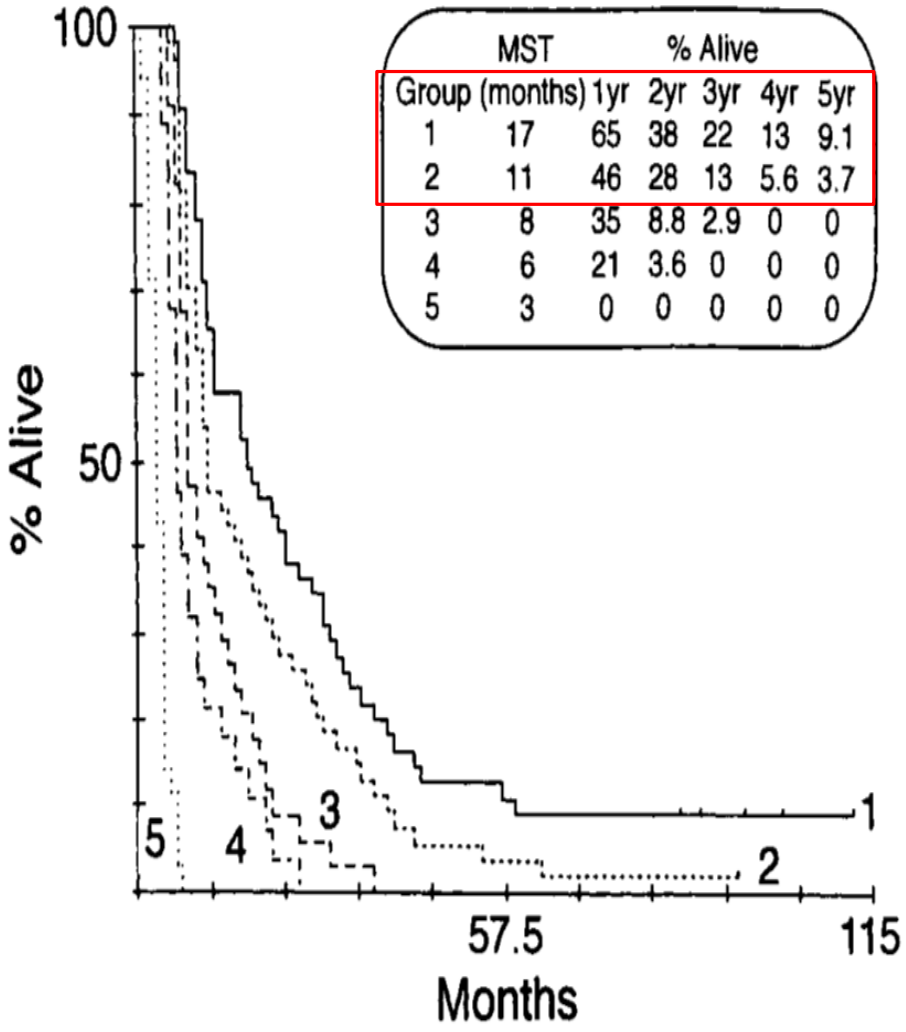
Concurent ChT
Carbo 50 mg/Etoposide 50mg
Daily



Jeremic et al. J Clin Oncol 17:2092-2099, 1999

Survival

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



Jeremic et al. J Clin Oncol 17:2092-2099, 1999

Conclusion

The addition of ACC HFX RT to the treatment of the most favorable subset of patients led to improved survival over that obtained with ChT alone

THE LANCET

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

Ben J Slotman, Harm van Tinteren, John O Praag, Joost L Knegjens, Sherif Y El Sharouni, Matthew Hatton, Astrid Keijser, Corinne Faivre-Finn, Suresh Senan**

CREST Trial design

Chest
Radiotherapy
Extensive
Stage
Trial

ES-SCLC

No brain- /leptomeningeal mets
No pleural mets
No previous RTX brain/thorax
Any response after 4-6 cycles of platinum-based chemotherapy
WHO 0-2
Age 18+
Encompassable volume

R

Arm A: PCI + TRT (10 x 3 Gy)

Stratification:
- Residual intrathoracic disease
- Institution

Arm B: PCI

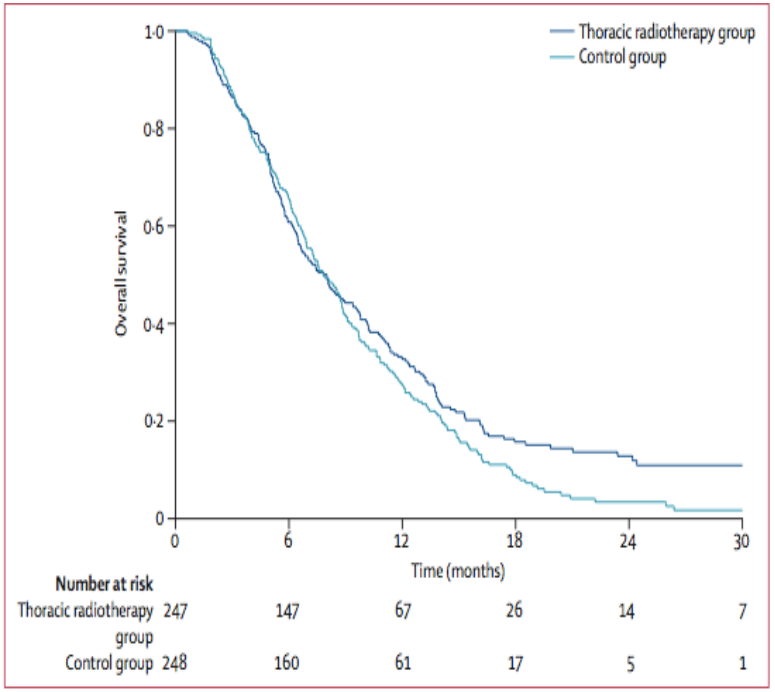
Study treatment should start between 2 and 7 weeks after last chemotherapy

Patient Characteristics

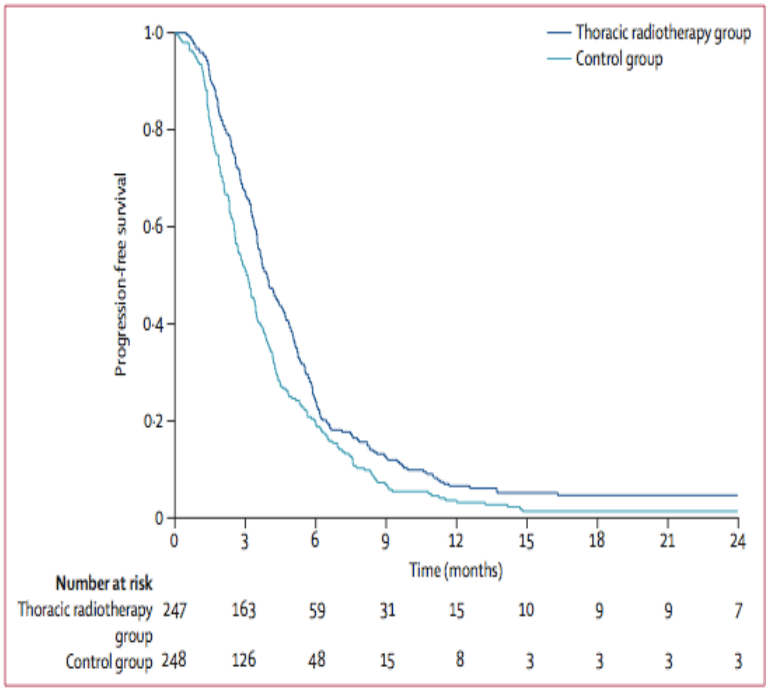
Patient characteristics	(n=495)
Median age	63 yrs
Male : Female	54.7: 45.3
WHO 0 : 1 : 2	33.7 : 55.8 : 5.1
Response (CR : PR : Good response)	5.1 : 70.7 : 24.2
Persistent intrathoracic disease (yes : no)	87.7 : 12.3
ES with M_0 ; M_1	6.9 ; 93.1

Slotman et al. Lancet 2015; 385: 36–42

Overall and Progression-Free Survival



Overall survival
HR = 0.84 (95%CI 0.69-1.01) p=0.066
12 m: 33% vs. 28%
24 m: 13% vs. 3% (p=0.004)



Progression-free survival 6 mos
24% (95% CI 19-30) vs 20% (95% CI 16-26) p=0.001

Progression was less likely in the RT group
HR = 0.73 (95%CI 0.61-0.87) p=0.001

Slotman et al. Lancet 2015; 385: 36–42

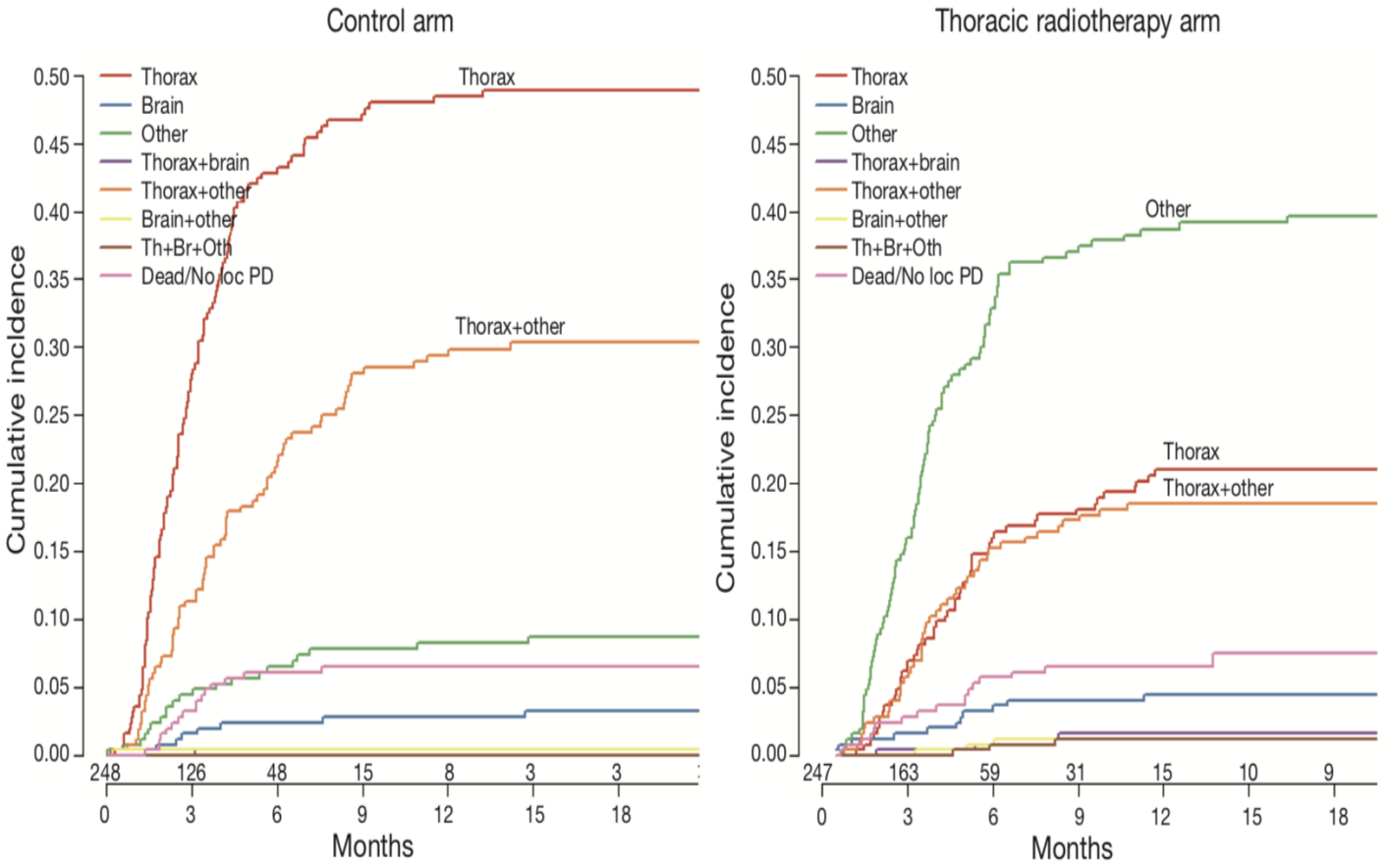
Conclusion

Thoracic radiotherapy (30Gy in 10fx)

- Improves overall survival
- Improves progression-free survival
- Improves intrathoracic control
- TRT should be offered in addition to PCI to patients with a response but residual intrathoracic disease after chemotherapy

Slotman et al. Lancet 2015; 385: 36–42

CREST



Recurrences occurred later and were more often in extra-thoracic and extra-cranial sites

Survival outcomes after whole brain radiotherapy for brain metastases in elderly patients with newly diagnosed metastatic small cell carcinoma

Paul Renz[1], Shaakir Hasan[2], and Rodney Wegner[2]

WVU Cancer Institute[1]

Allegheny Health Network Cancer Institute[2]

Background

- Small Cell Lung Cancer (SCLC)
  - Advanced age at diagnosis
  - High incidence of brain metastases
  - Treatment consists of whole brain radiotherapy (WBRT) or best supportive care

WBRT

- Effective treatment
  - SCLC radiosensitive
- Tolerated poorly by the elderly
  - Short and long term toxicity (i.e., fatigue and neurocognition)
  - No proven survival benefit

WBRT Toxicity

- Chang et al. Lancet Oncol. 2009 Nov;10(11):1037-44
  - "*SRS plus WBRT were at a greater risk of a significant decline in learning and memory function by 4 months compared with the group that received SRS alone"*
- Brown et al. JAMA 2016 Jul 26;316(4):401-409
  - *"compared with SRS combined with WBRT, resulted in less cognitive deterioration at 3 months. In the absence of a difference in overall survival, these findings suggest that for patients with 1 to 3 brain metastases amenable to radiosurgery, SRS alone may be a preferred strategy"*

Survival benefit unclear in elderly

- QUARTZ Trial
  - Mulveena et al. Lancet 2016 Oct 22;388(10055):2004-2014.
    - *"the combination of the small difference in QALYs and the absence of a difference in survival and quality of life between the two groups suggests that WBRT provides little additional clinically significant benefit for this patient group"*

Does WBRT improve survival in an exclusively elderly population with SCLC brain metastases?

National Cancer Database Study

- 1615 patients ≥75 years old with SCLC brain metastases at diagnosis
  - chemotherapy+WBRT (n=576)
  - chemotherapy alone (n=238)
  - WBRT alone (n=360)
  - no treatment (n=441).
- Clinical and demographic characteristics reported
- Multivariable regression analysis for survival
- Propensity score-matching was utilized

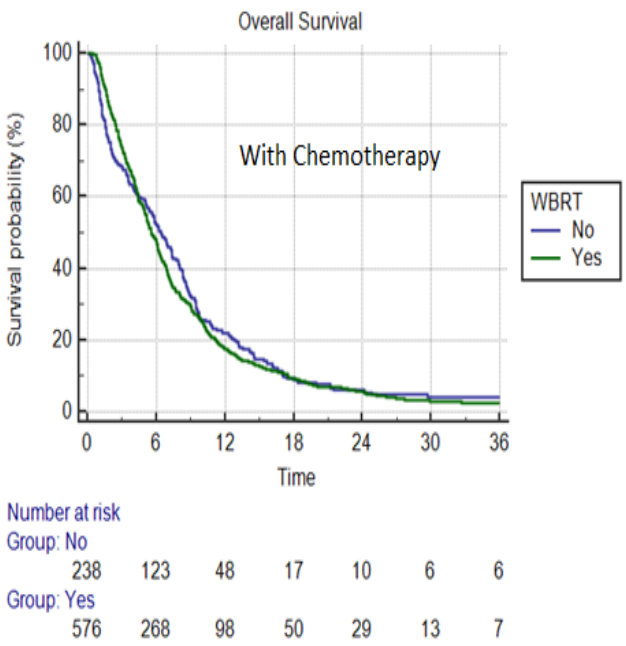
Results

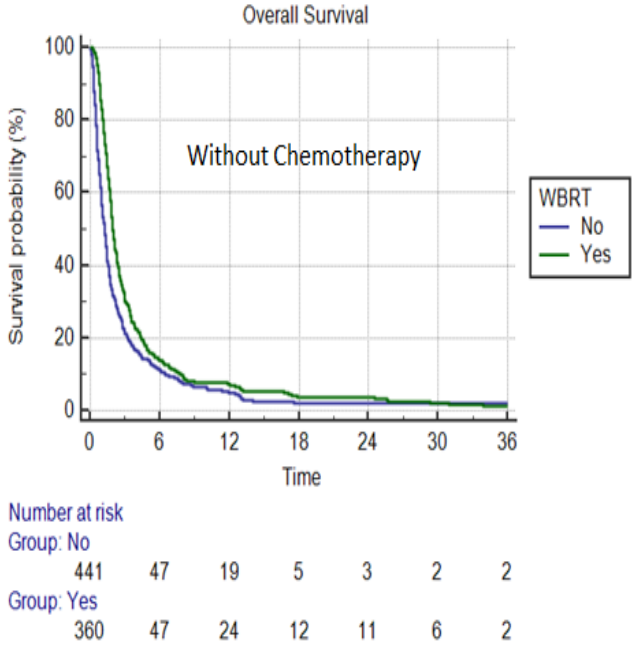
- Median age 79 years
- WBRT median dose 30 Gy
- Median OS of 2.9 months

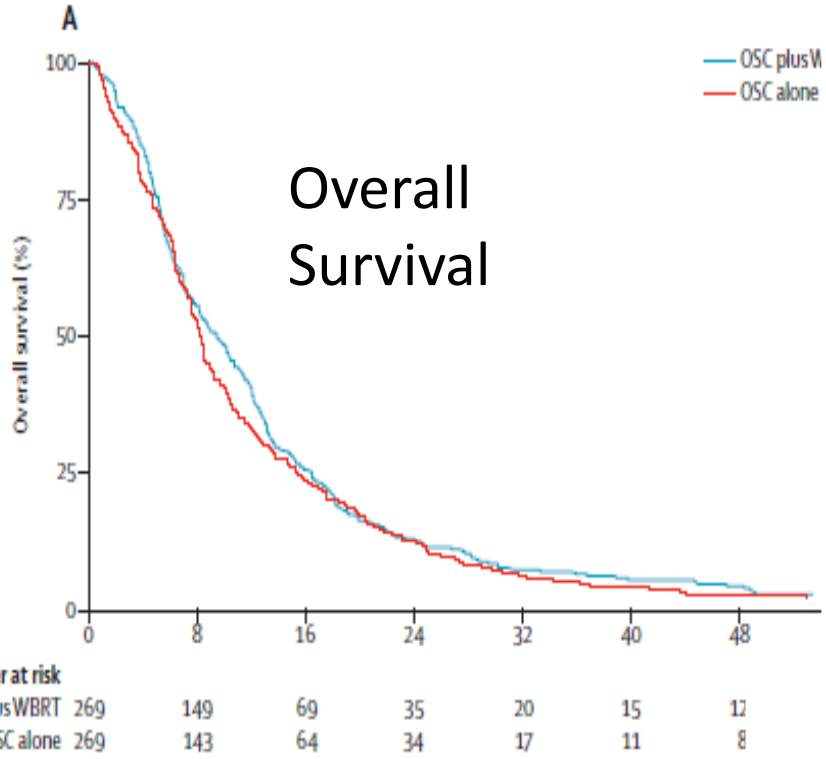
- OS for patients receiving chemotherapy
  - WBRT 5.6 months vs no WBRT 6.4 months (p=0.43)
- OS for patients without chemotherapy
  - WBRT 1.9 months vs no WBRT 1.2 months (p<0.0001)

- Multivariable cox regression revealed age >80, extracranial disease, male sex, and rural location as predictors of increased risk of death.

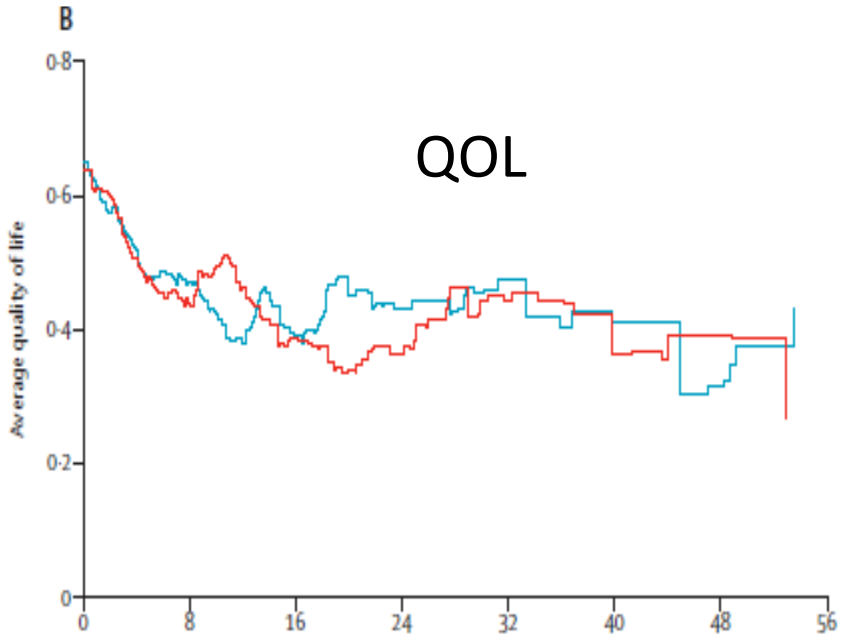
Figure 1. Overall Survival With WBRT in Elderly Patients With and Without Chemotherapy







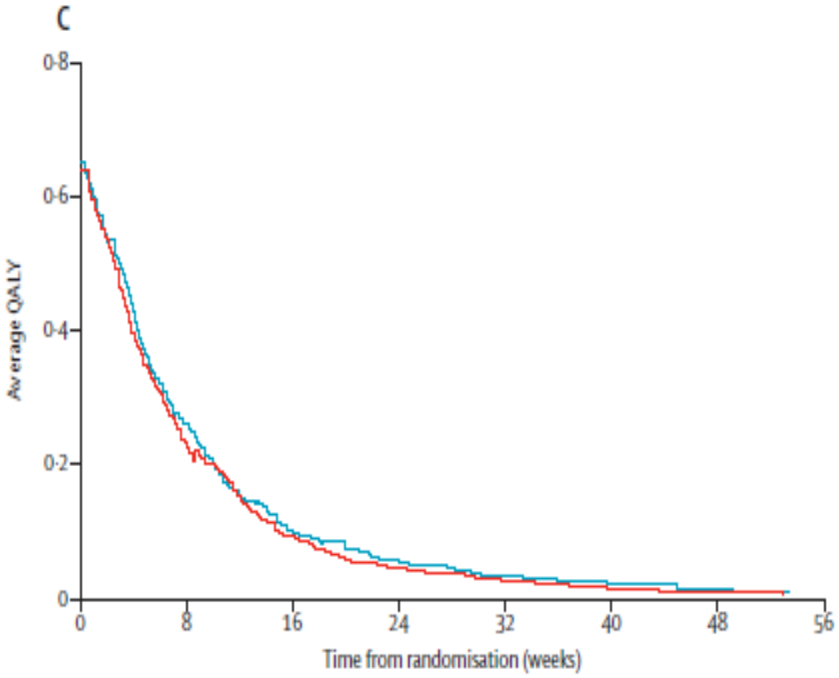
Overall Survival



QOL

QUARTZ Trial:

Failure to demonstrate OS or QOL benefit with 20 Gy in 5 fx WBRT compared to Decadron + Supportive Care alone



Conclusions

- WBRT for SCLC brain metastasis in the elderly should be administered with caution
  - Lack of clear survival benefit
  - Clear toxicity
  - Other options: SRS, Chemotherapy, BSC

ΙΣΝ SNF

ΙΔΡΥΜΑ ΣΤΑΥΡΟΣ ΝΙΑΡΧΟΣ
STAVROS NIARCHOS
FOUNDATION