Article review

Twice-daily tRT by IMRT compared with SIB-IMRT with concurrent chemotherapy for patients with LS-SCLC: A propensity-score matched analysis

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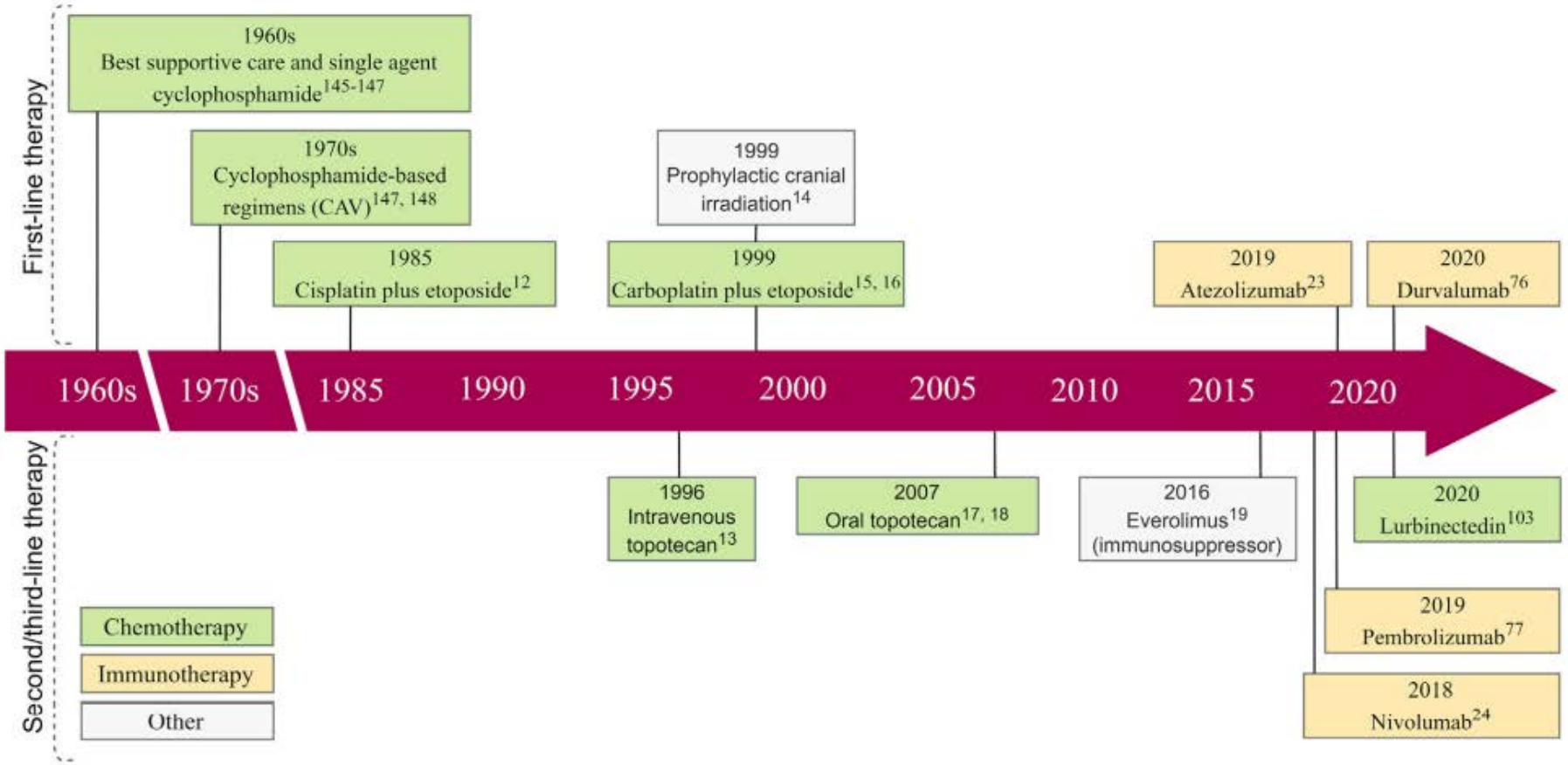
Introduction

- Small-cell lung cancer is highly aggressive, lethal and widely metastatic disease
  - 15% global lung cancer incidence
  - 7% - 5-year OS
- Recalcitrant disease

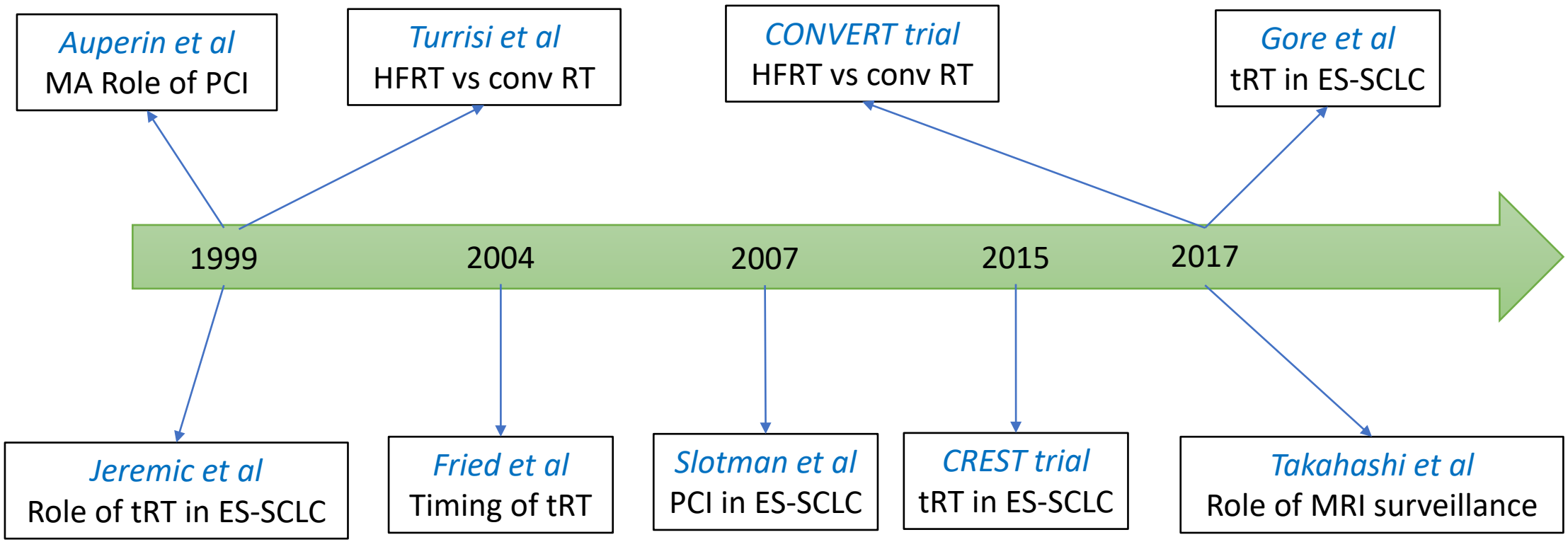
	Limited Stage	Extensive stage
Median range of survival	15-20 months	8-13 months
Survival at 2 years	20-40%	<5%
5 yr survival	10-13%	1-2%

Progress



Schwendenwein, 2021

Progress in RT



Evolution of RT in LS-SCLC

- Two meta-analysis showed significant survival advantage with addition of radiotherapy to chemotherapy.

Authors	Year	Benefit in Overall Survival
Pignon et al	1992	5.4 % (at 3 years)
Warde et al	1992	5.4 % (at 2 years)

14% reduction in mortality

Pignon, NEJM 1992
Warde, JCO 1992

- Phase 3 RCT demonstrated that concurrent treatment led to better outcomes than sequential

	Median survival
Sequential RT	19.7 months
Concurrent RT	27.2 months

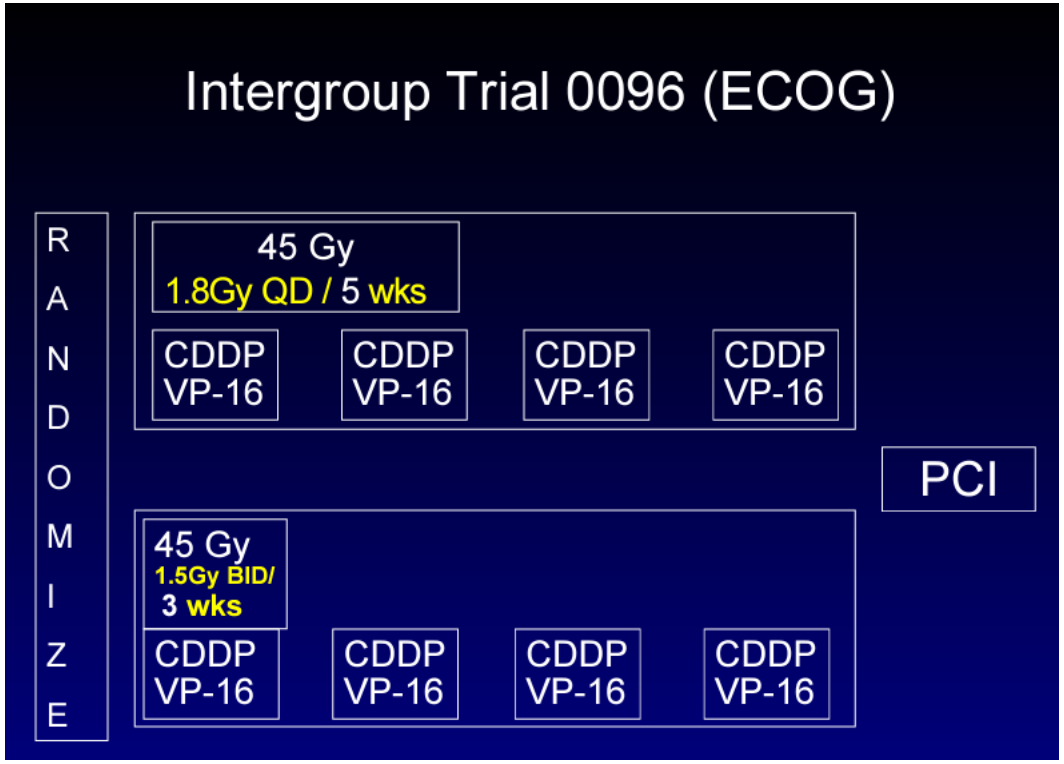
231 pts, 45Gy/3 weeks

Takada, JCO 2002

- Early vs Late concurrent RT

Fried, JCO 2004

Evidence


Intergroup Trial 0096 (ECOG)
RANDOMIZE
45 Gy
1.8Gy QD / 5 wks
CDDP VP-16
CDDP VP-16
CDDP VP-16
CDDP VP-16
PCI
45 Gy
1.5Gy BID/
3 wks
CDDP VP-16
CDDP VP-16
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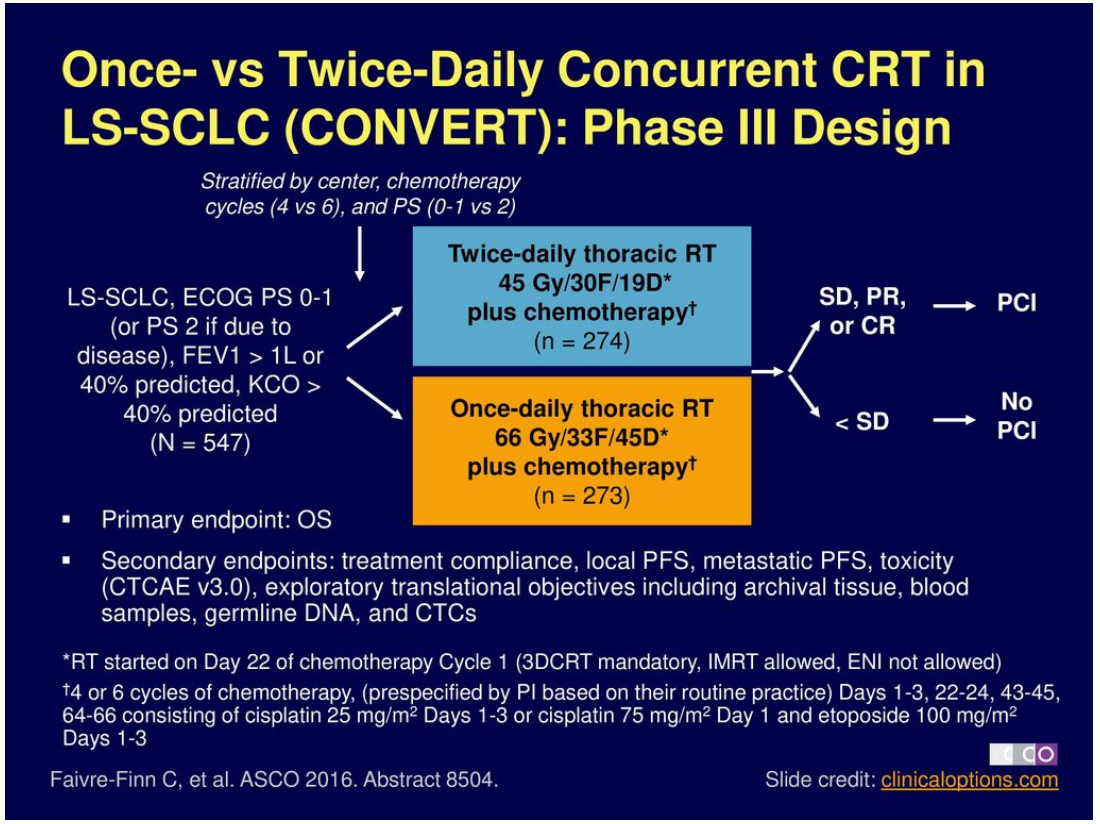
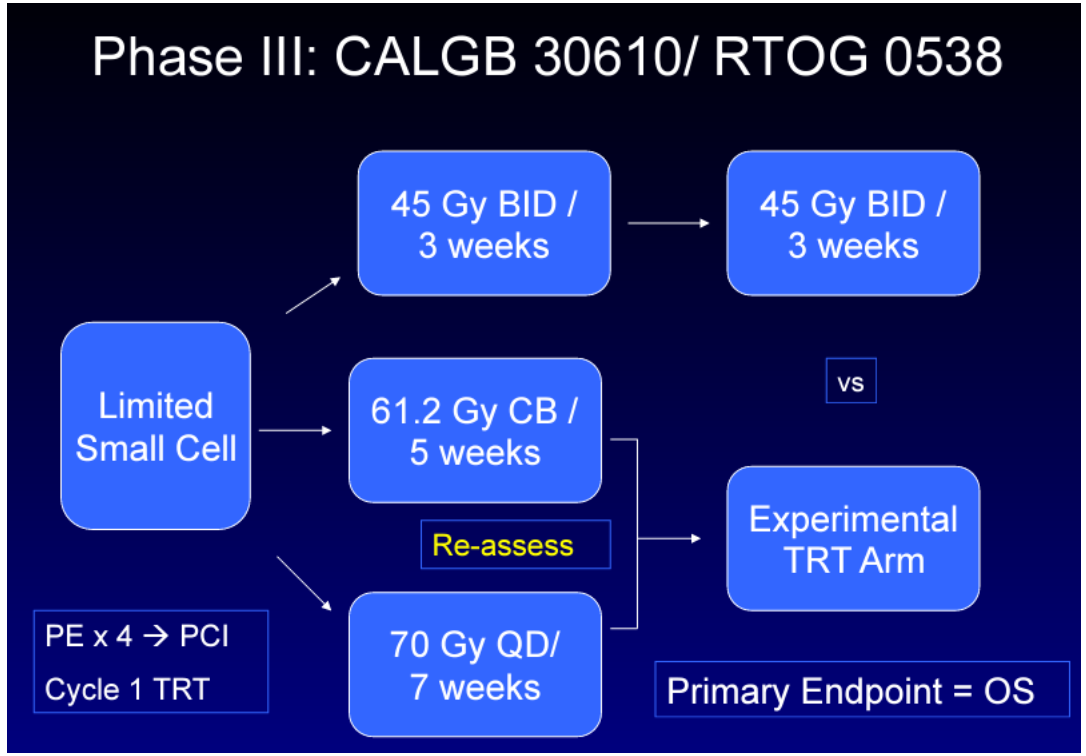
CDDP VP-16


Once- vs Twice-Daily Concurrent CRT in LS-SCLC (CONVERT): Phase III Design
Stratified by center, chemotherapy cycles (4 vs 6), and PS (0-1 vs 2)
LS-SCLC, ECOG PS 0-1 (or PS 2 if due to disease), FEV1 > 1L or 40% predicted, KCO > 40% predicted (N = 547)
Twice-daily thoracic RT 45 Gy/30F/19D* plus chemotherapy† (n = 274)
Once-daily thoracic RT 66 Gy/33F/45D* plus chemotherapy† (n = 273)
SD, PR, or CR → PCI
< SD → No PCI
Primary endpoint: OS
Secondary endpoints: treatment compliance, local PFS, metastatic PFS, toxicity (CTCAE v3.0), exploratory translational objectives including archival tissue, blood samples, germline DNA, and CTCs
*RT started on Day 22 of chemotherapy Cycle 1 (3DCRT mandatory, IMRT allowed, ENI not allowed)
†4 or 6 cycles of chemotherapy, (prespecified by PI based on their routine practice) Days 1-3, 22-24, 43-45, 64-66 consisting of cisplatin 25 mg/m² Days 1-3 or cisplatin 75 mg/m² Day 1 and etoposide 100 mg/m² Days 1-3
Faivre-Finn C, et al. ASCO 2016. Abstract 8504.
Slide credit: clinicaloptions.com

HFRT in SCLC

Study	Turrisi (INT 0096)
Year	1999
Statistics	Superiority (BD exp. arm)
Baseline staging	CT or MRI (%NR), radionuclide bone scanning, bilateral iliac-crest BM sample
N pt.	417
RT	45 Gy BD (3w) *vs.* 45 Gy OD (5w)
Chemo.	4 CDDP Etop
PCI	If indicated (% NR)
Median OS	23 *vs.* 19 m*, P=0.004
2y PFS	29 *vs.* 24%* (NS)
G3-4 esophagitis	32 *vs.* 16%* (P<0.001)
G3-4 pneumonitis	1 *vs.* 2%* (NS)

HFRT



	45Gy BID	70Gy QD	61.2Gy CB
2-yr OS	59%	56%	57%
4-yr OS	35%	39%	5-yr: 28%
Median OS	28.7 mo	30.5 mo	32.3 mo

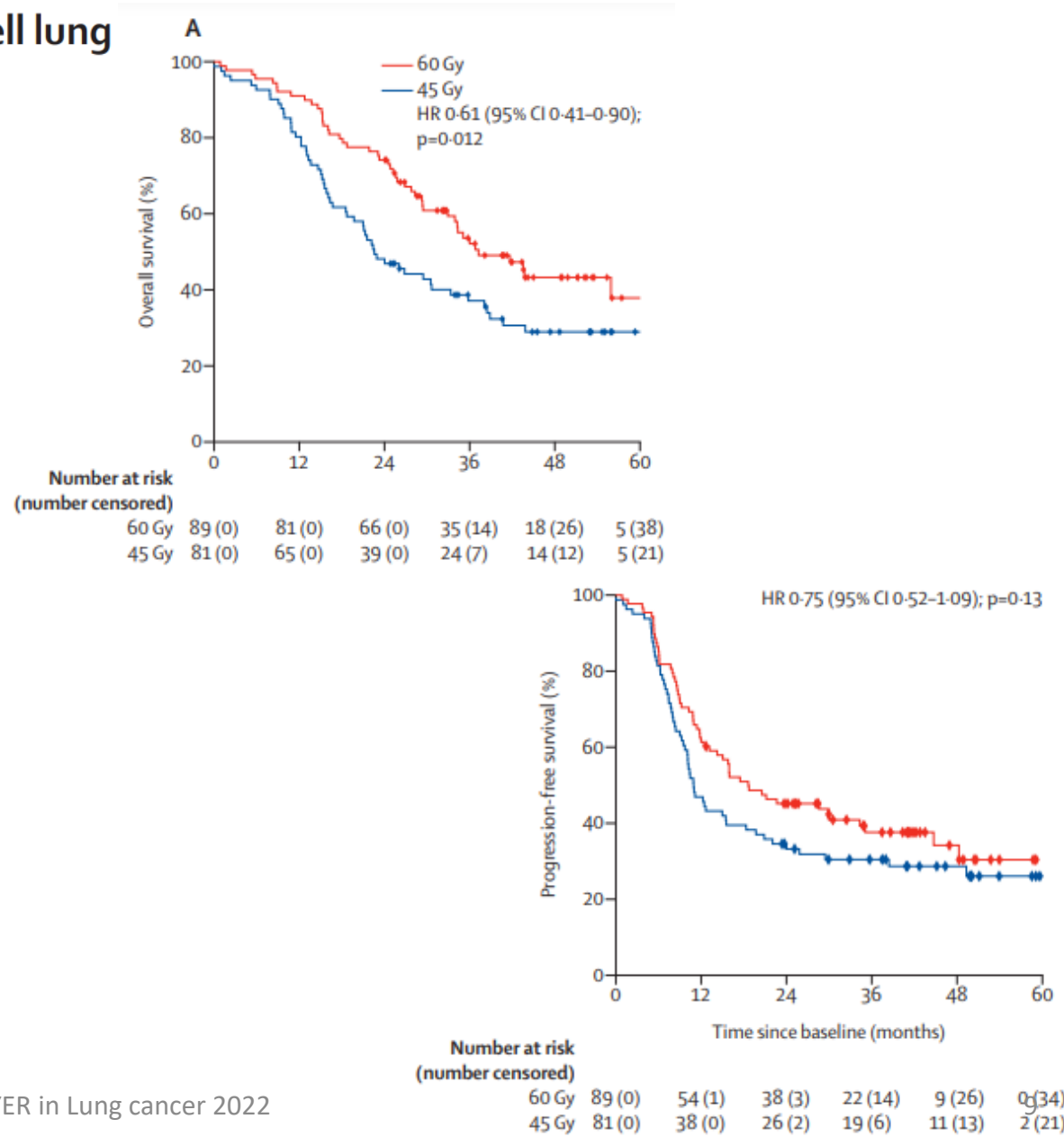
ASCO 2021, 2022

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

Bjørn Henning Grønberg, Kristin Toftaker Killingberg, Øystein Fløtten, Odd Terje Brustugun, Kjersti Hornslien, Tesfaye Madebo, Seppo Wang Langer, Tine Schytte, Jan Nyman, Signe Risum, Georgios Tsakonas, Jens Engleson, Tarje Onsøien Halvorsen

- Phase II RCT
- 170 patients
- Primary end point – 2-yr OS
- Standard arm: 45 Gy in 30#
- Test arm: 60 Gy in 40#

Lancet Oncology 2021



Clinical practice of HFRT

- Despite the evidence – poor clinical integration
  - High volume centres – scheduling conflicts
  - Inconvenient for patients – waiting
- Once daily dose/#
  - US – 85%
  - Europe – 60%

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Twice-daily thoracic radiotherapy by intensity-modulated radiation therapy (IMRT) compared with simultaneous integrated boost IMRT (SIB-IMRT) with concurrent chemotherapy for patients with limited-stage small cell lung cancer. A propensity-score matched analysis

Hongfu Sun [a,b,1], Chengxin Liu [a,b,1], Jing Zhang [a], Guanghui Yang [a], Dan Han [a,b], Tingting Liu [b], Wei Huang [a,b,*], Baosheng Li [a,b,*]

[a] *Department of Radiation Oncology, Shandong Cancer Hospital Affiliated to Shandong University, Jinan; and* [b] *Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan*

Radiother Oncol. 2022 Jul;172:140-146.

doi: 10.1016/j.radonc.2022.01.022. Epub 2022 Jan 29.

Study conduct

- December 2009 to December 2017
- IRB approved retrospective study
- Inclusion criteria:
  - Histologically or cytologically confirmed SCLC
  - Age 18 years or older; ECOG 0-1
  - Stage I-III according to 2009 TNM classification
  - Received twice-daily tRT by IMRT or SIB-IMRT with concurrent chemotherapy
  - More than or equal to 2 cycles of chemotherapy
    - EP/EC

RT details

- Target volumes
  - GTV – Post chemo primary volume & Pre chemo nodal extent
  - CTV – 0.5 cm GTV expansion
  - PTV – 0.5 cm CTV expansion
- Dose/fractionation
  - IMRT group – 45Gy in 30# BID of 1.5Gy to PTV
  - SIB-IMRT group :
    - 57 Gy in 30# BID of 1.9 Gy to GTV
    - 51 Gy in 30# BID of 1.9 Gy to CTV and
    - 45 Gy in 30# BID of 1.9 Gy to PTV

Propensity score matching

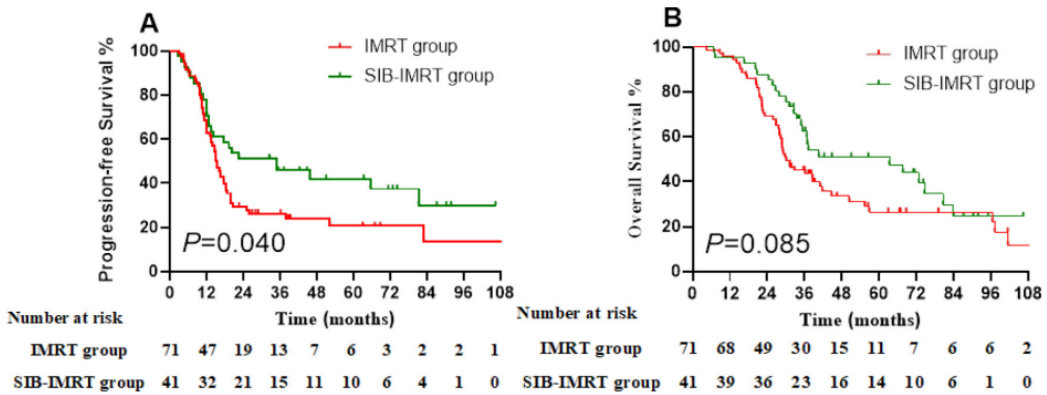
- 1:1 PSM approach was used according to PS: to reduce the effects of potential confounding factors between groups
- PS was identified by
  - Two demographic variables - sex and age
  - Four disease characteristics - laterality, T stage, N stage, and TNM stage, and
  - Three treatment-related covariates - chemo regimens, cycles, and the timing of tRT
- Propensity scores were calculated with logistic regression – nearest neighbor algorithm
- Primary objective: PFS; Secondary objective: OS, ORR, toxicity
- Time to event calculated for date of diagnosis

Results

	After propensity score matching No. (%) (n = 74)		
	IMRT group(n = 37)	SIB-IMRT group(n = 37)	P
Sex			0.790
Male	27 (73.0)	28(75.7)	
Female	10(27.0)	9(24.3)	
Age (years)			0.814
<60	22(59.5)	21(56.8)	
≥60	15(40.5)	16(43.2)	
Laterality			0.642
right	17(45.9)	19(51.4)	
left	20(54.1)	18(48.6)	
T-stage			0.812
T1-2	14(37.8)	15(40.5)	
T3-4	23(62.2)	22(59.5)	
N-stage			0.425
N0-1	8(21.6)	11(29.7)	
N2-3	29(78.4)	26(70.3)	
TNM-stage			0.174
I-II	3(8.1)	7(18.9)	
III	34(91.9)	30(81.1)	
Chemotherapy Regimens			1.000
EP	35(94.6)	35(94.6)	
EC	2(5.4)	2(5.4)	
Chemotherapy Cycles delivered			0.451
2–4	15(40.5)	17(45.9)	
5–6	21(56.8)	17(45.9)	
>6	1(2.7)	3(8.1)	
TTRT			0.572
early TRT	30(81.1)	28(75.7)	
late TRT	7(18.9)	9(24.3)	

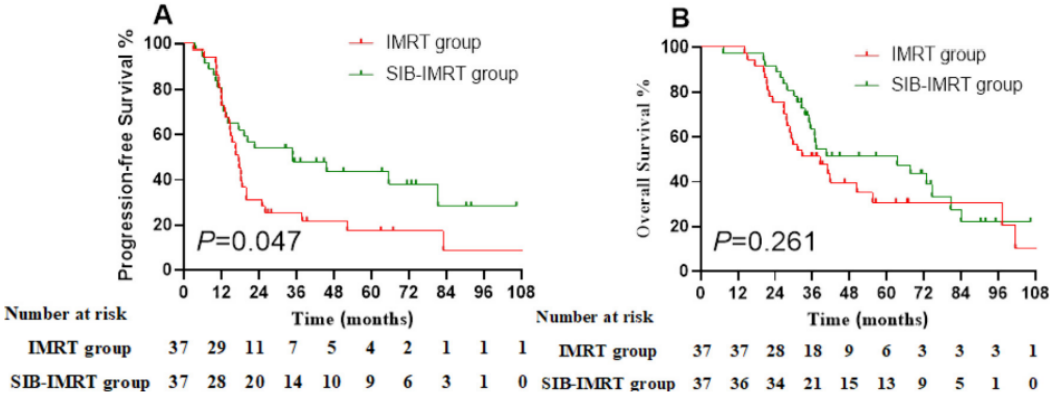
Results

Before PSM



	PFS		OS	
	IMRT	SIB	IMRT	SIB
Median	15.4 mo	34.9 mo	30.1 mo	63.4 mo
1-yr	67%	78%	96%	95%
3-yr	26%	46%	45%	63%
5-yr	21%	42%	27%	51%
9-yr	14%	30%	12%	25%

After PSM



	PFS		OS	
	IMRT	SIB	IMRT	SIB
Median	17.5 mo	34.9 mo	38.5 mo	63.4 mo
1-yr	78%	81%	100%	97%
3-yr	26%	48%	51%	64%
5-yr	18%	44%	31%	52%
9-yr	9%	29%	10%	22%

Results

- Higher RT dose was associated with better PFS
- SIB was associated with better LRR but not DM
- Toxicity

	Before propensity score matching No. (%) (n = 112)			After propensity score matching No. (%) (n = 74)		
	IMRT group(n = 71)	SIB-IMRT group(n = 41)	P	IMRT group(n = 37)	SIB-IMRT group(n = 37)	P
Treatment-related toxicity			0.949			0.639
0–2	42(59.2)	24(58.5)		22(59.5)	20(54.1)	
3–4	29(40.8)	17(41.5)		15(40.5)	17(45.9)	
Neutropenia			0.972			0.806
0–2	50(70.4)	29(70.7)		24(64.9)	25(67.6)	
3–4	21(29.6)	12(29.3)		13(35.1)	12(32.4)	
Gastrointestinal toxicity			0.366			1.000
0–2	71(100.0)	40(97.6)		37(100.0)	36(97.3)	
3–4	0(0.0)	1(2.4)		0(0.0)	1(2.7)	
Radiation oesophagitis			0.230			0.207
0–2	63(88.7)	33(80.5)		33(89.2)	29(78.4)	
3–4	8(11.3)	8(19.5)		4(10.8)	8(21.6)	
Radiation pneumonitis			0.921			1.000
0–2	64(90.1)	38(92.7)		34(91.9)	34(91.9)	
3	7(9.9)	3(7.3)		3(8.1)	3(8.1)	

My take

- Role of RT in SCLC is pivotal, but still evolving
- SCLC serves as the best example to demonstrate the importance of RT dose/fractionation on outcomes
  - Survival benefit of HFRT vs Conventional RT
  - Dose response in SCLC
- HFRT
  - Survival benefit
  - Clinical practice remains thin
- Modern technology allows safer use of HFRT
- Onus lies on us to identify suitable, convenient and practical way of delivering HFRT in our setup.