Thoracic Radiotherapy for Extensive Disease

elcc EUROPEAN LUNG CANCER CONFERENCE

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Disclosures

- No disclosures related to this subject

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Small cell lung cancer

1980s:
survival benefit
of 5% at 3 years

Thoracic RT in LS

1990s:
survival benefit
of 5% at 3 years

PCI in LS

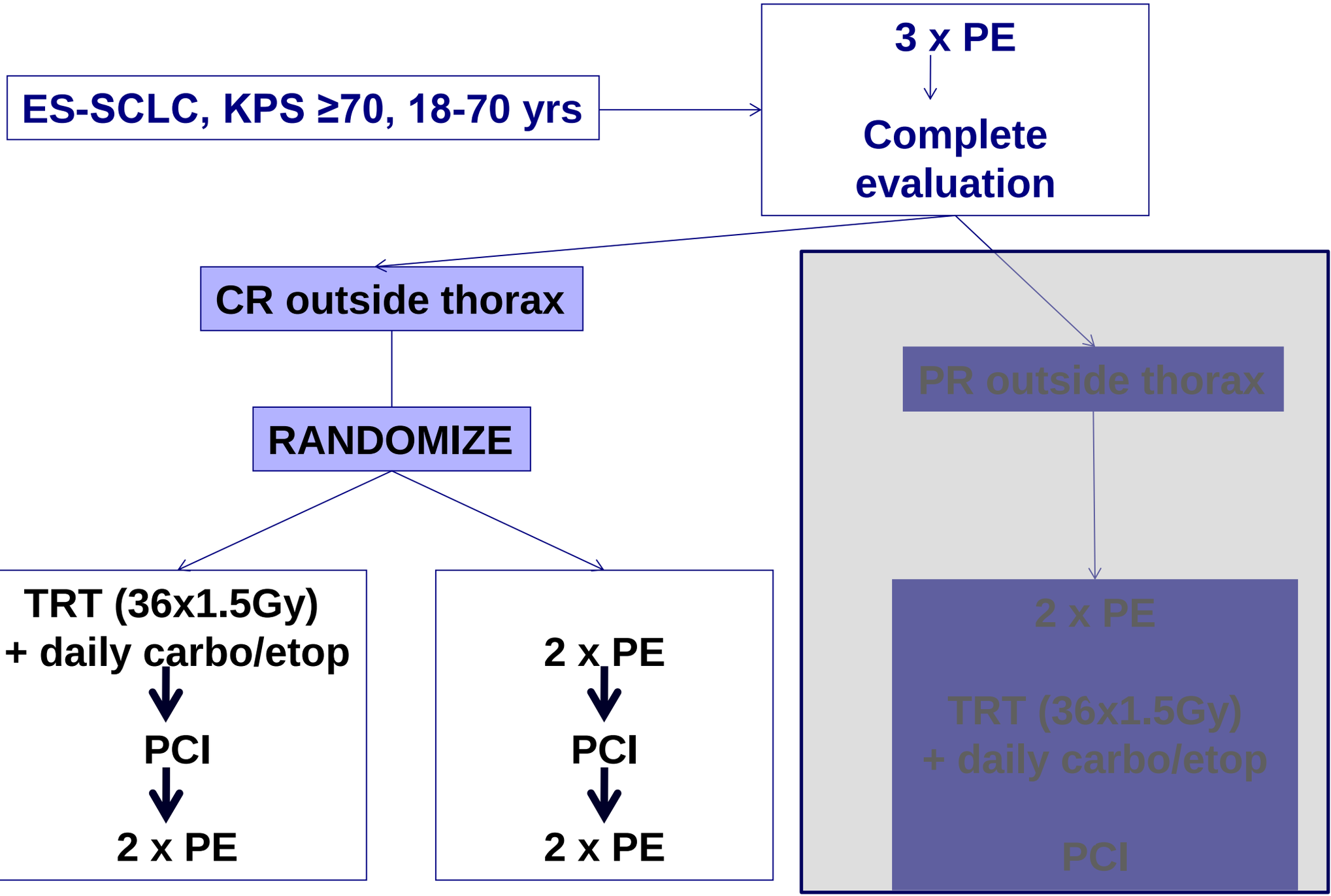
PCI in ES

Thoracic RT in ES

Does Thoracic Radiotherapy have a role in ES-SCLC as well?

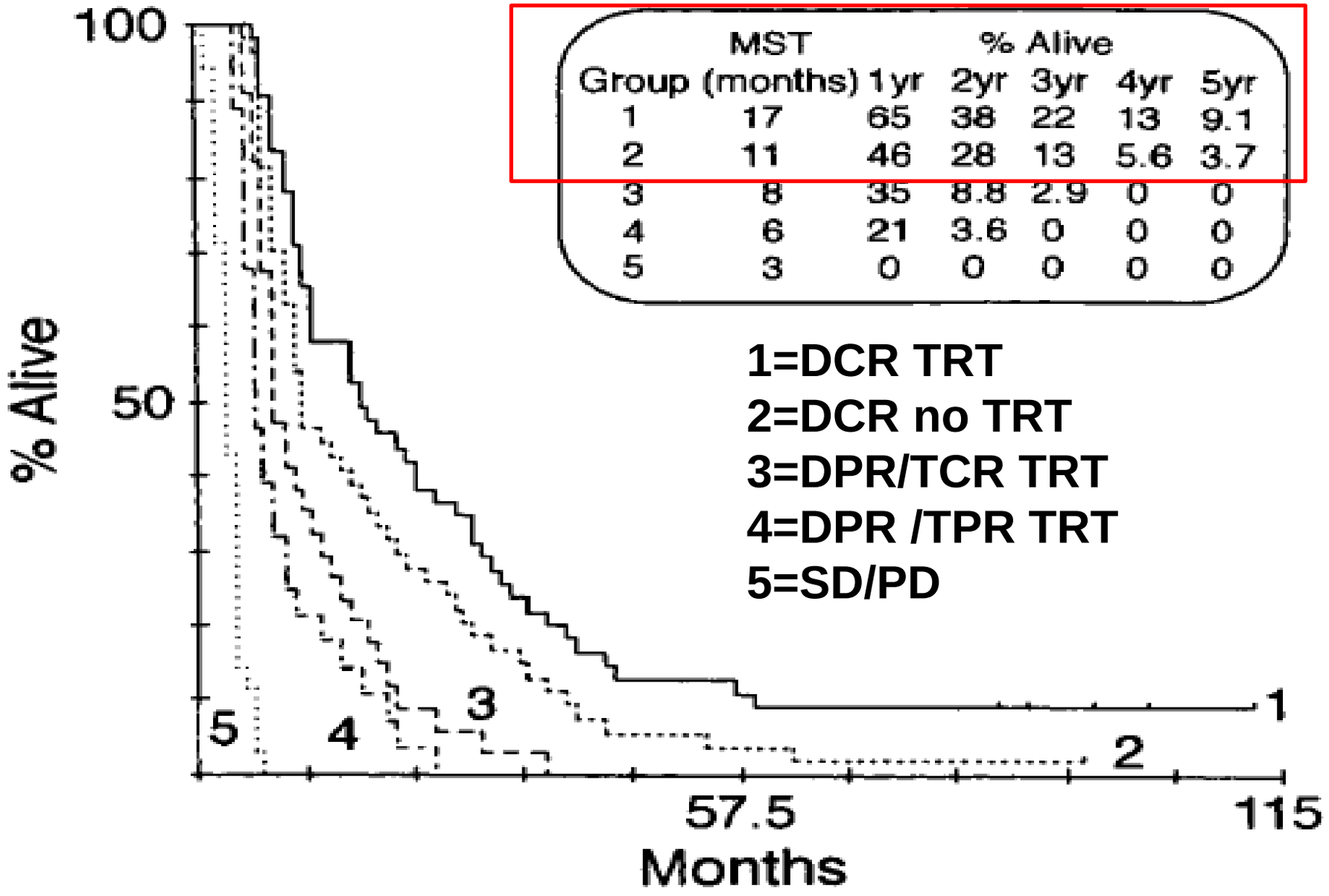
2000s:
survival benefit
of 14% at 1 year

Jeremic Study



Jeremic et al., JCO 1999

Overall 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

1=DCR TRT
2=DCR no TRT
3=DPR/TCR TRT
4=DPR /TPR TRT
5=SD/PD

Jeremic et al., JCO 1999

TRT in ES-SCLC

VUmc

Original Article

Thoracic Radiation Therapy Improves the Overall Survival of Patients With Extensive-Stage Small Cell Lung Cancer With Distant Metastasis

Hui Zhu, PhD, MD[1]; Zongmei Zhou, PhD, MD[1]; Yan Wang, PhD, MD[2]; Nan Bi, PhD, MD[1]; Qinfu Feng, MD[1]; Junling Li, MD[2]; Jima Lv, MD[1]; Dongfu Chen, MD[1]; Yuankai Shi, PhD, MD[2]; and Luhua Wang, MD[1]

Table 4. Multivariate Analysis of the Prognostic Factors for Survival in Patients With M1 Small Cell Lung Cancer

Characteristic	HR	95% CI	Chi-Square Statistic	*P*
Age, y (<65 vs ≥65)	1.284	0.719-2.292	0.713	.398
Sex (women vs men)	1.103	0.624-1.950	0.114	.735
KPS score (<80 vs ≥80)	1.281	0.718-2.288	0.702	.402
Brain metastasis (yes vs no)	1.307	0.797-2.144	1.124	.289
No. of metastatic organs (≥2 vs 1)	1.313	0.853-2.020	1.531	.216
Weight loss(≥5% vs <5%)	1.449	0.854-2.459	1.886	.170
Smoking status (yes vs no)	1.328	0.891-1.979	1.935	.164
No. of ChT cycles (≥4 vs <4)	0.532	0.342-0.830	7.758	.005
Treatment (ChT/TRT vs ChT alone)	0.658	0.449-0.965	4.594	.032

Abbreviations: ChT, chemotherapy; ChT/TRT, chemotherapy combined with thoracic radiation therapy; CI, confidence interval; HR, hazard ratio; KPS, Karnofsky performance status.

Zhu et al., Cancer 2011

DUTCH CANCER SOCIETY

NCRN

CANCER RESEARCH UK

KNL

LCRQ
Dutch Lung Cancer Research Group

VUmc

Chest Radiotherapy Extensive Stage Trial

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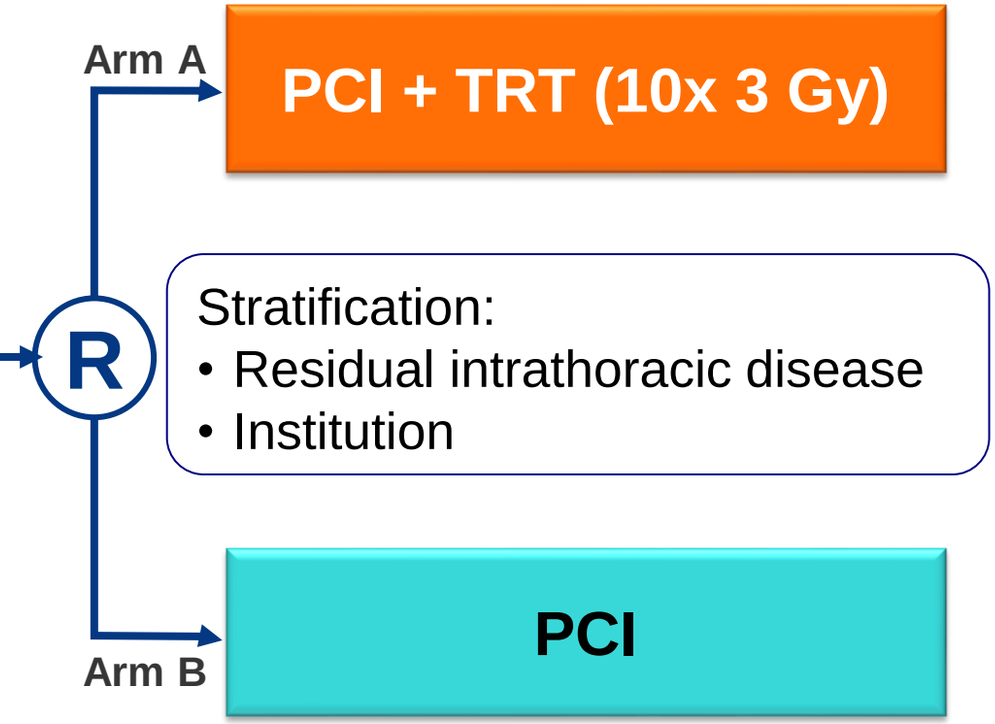
CREST Trial design

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



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

Slotman et al., Lancet 2015, 385, 36-42

Statistics

Study endoints

- Primary: overall survival
- Secondary: PFS, local control, failure pattern, toxicity

Study objectives

- The study had 80% power to detect a hazard ratio for overall survival of 0.76 at 1 year (2-sided 5% sign.)
- Accounting for 5% dropout between randomization and start of treatment, 483 patients had to be randomized

Slotman et al., Lancet 2015, 385, 36-42

Trial diagram

Randomly allocated
n=498

Thoracic RT **n=249**	**Allocation**	**Control** **n=249**
No IC/wd n=2 ***TRTcompleted n=240***	**Therapy**	**No IC/wd n=1**
ITT n=247 **PFS 231; OS 201 events**	**Analysis**	**ITT n=248** **PFS 239; OS 224 events**

Slotman et al., Lancet 2015, 385, 36-42

Patient characteristics

	(n=495)		Sign.
Median age	63	yrs	NS
Male	271	54.7	NS
Female	224	45.3	
WHO 0	167	33.7	
WHO 1	276	55.8	NS
WHO 2	52	10.5	
Complete response	25	5.1	
Partial response	350	70.7	NS
Good response	120	24.2	
Persistent intrathoracic disease	434	87.7	NS
ES only based on intrathoracic extent	34	6.9	NS

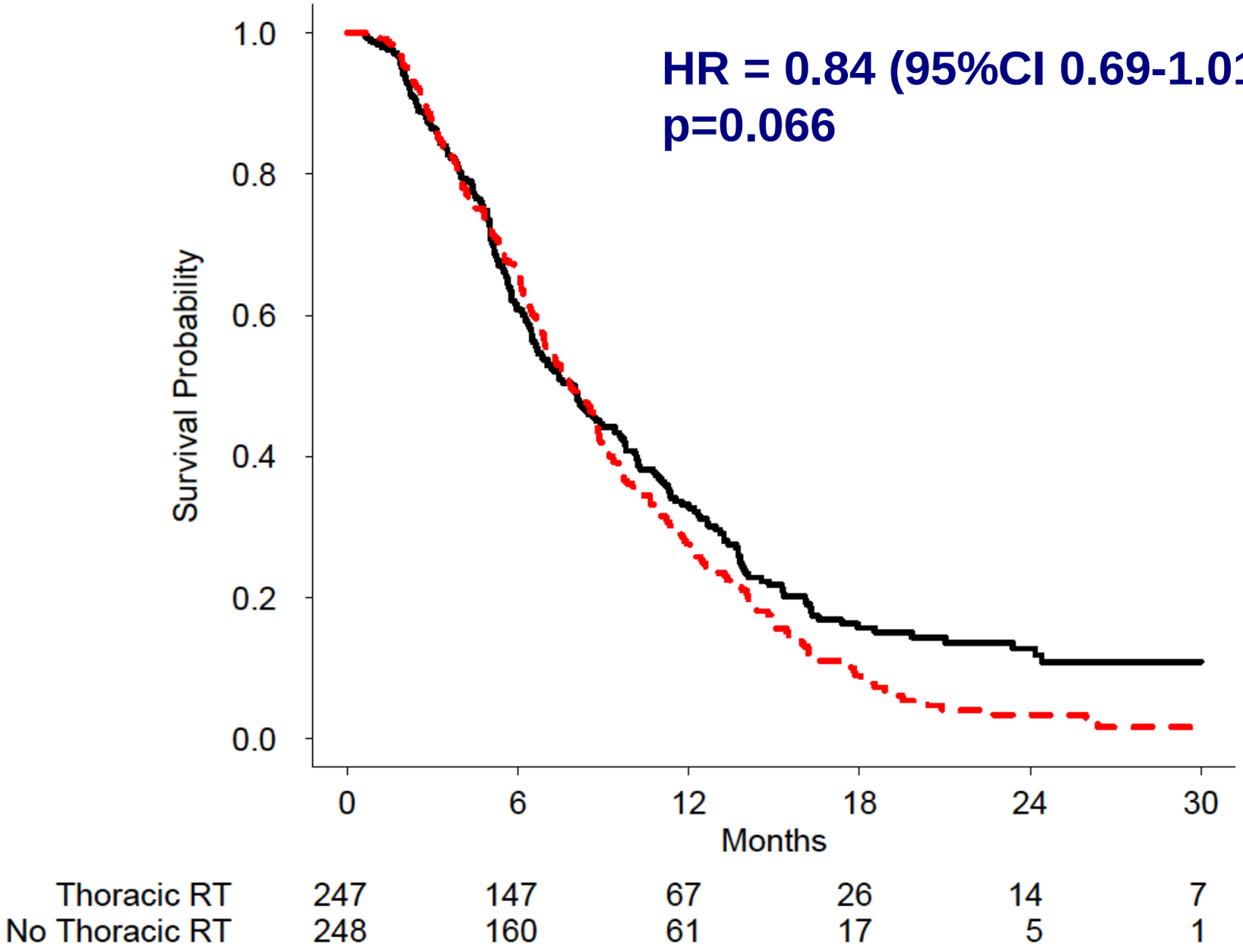
Slotman et al., Lancet 2015, 385, 36-42

Toxicity (CTCAE v3) G3+

	TRT (n=247)		Control (n=248)	
CTC Grade	G3	G4	G3	G4
Cough	0	0	1	0
Dysphagia	1	0	0	0
Dyspnoea	3	0	4	0
Esophagitis	4	0	0	0
Fatigue	11	0	8	1
Insomnia	3	0	2	0
Nausea / vomiting	1	0	0	0
Headache	3	0	2	0

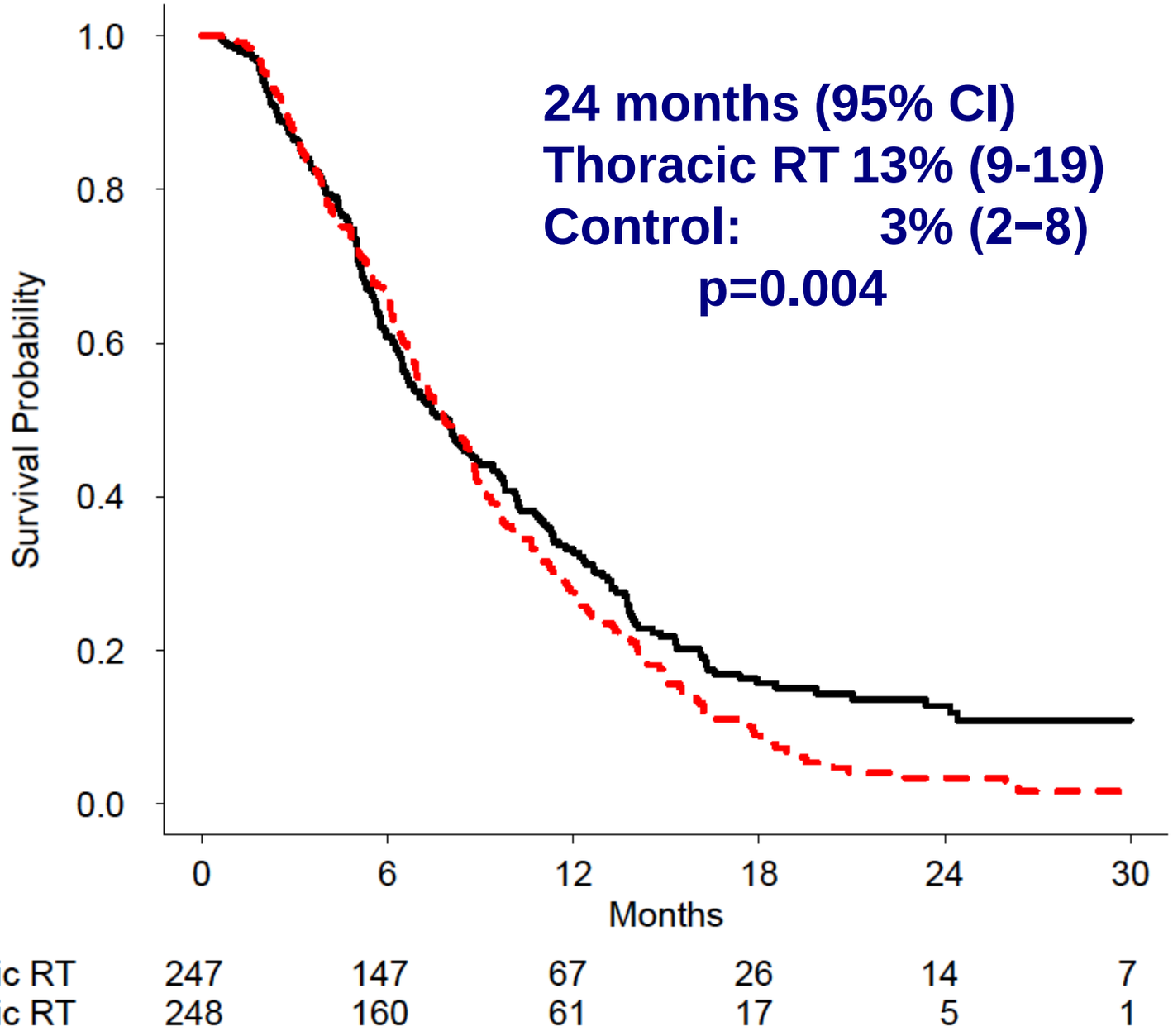
Slotman et al., Lancet 2015, 385, 36-42

Overall survival



Slotman et al., Lancet 2015, 385, 36-42

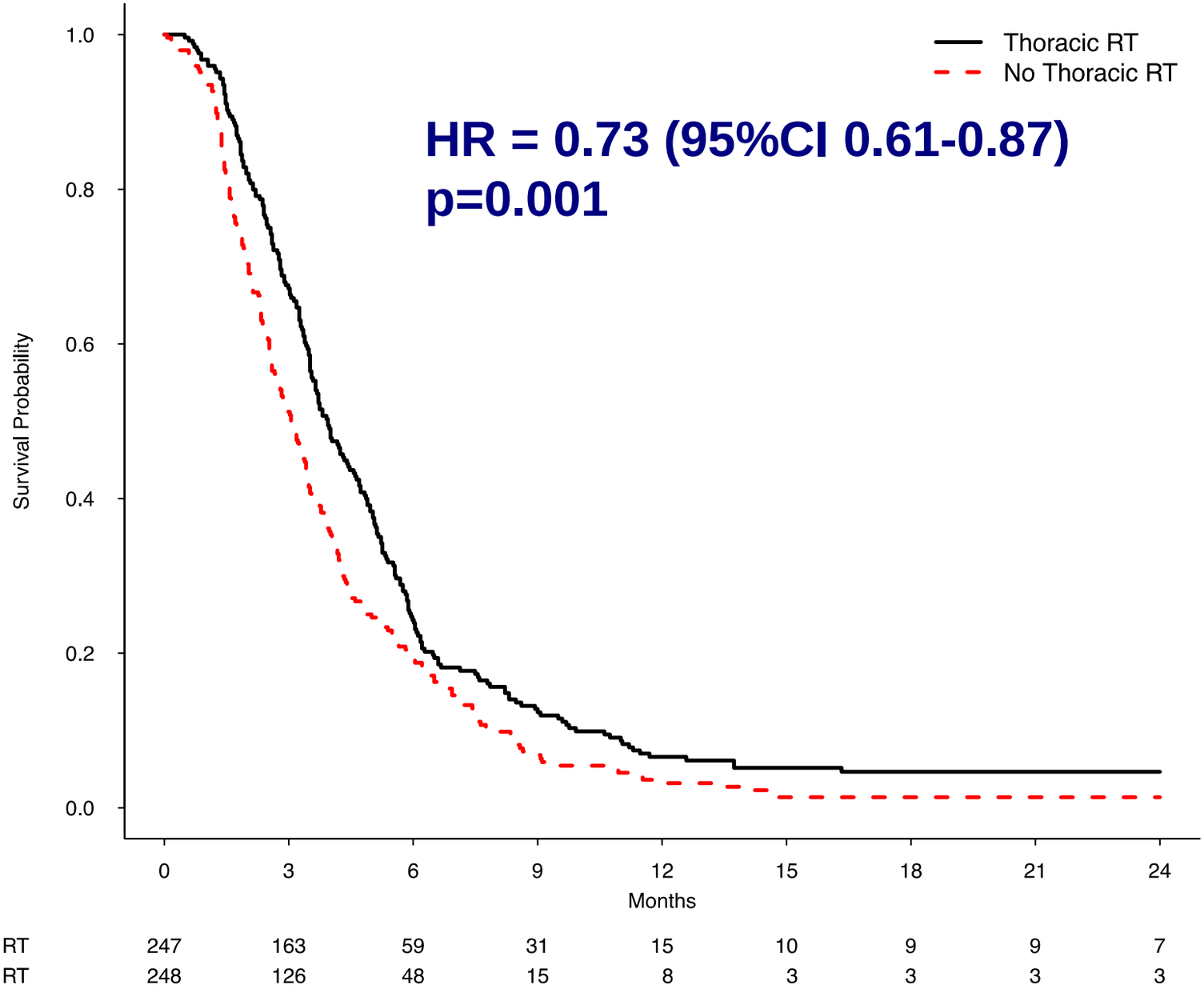
Overall survival



24 months (95% CI)
Thoracic RT 13% (9-19)
Control: 3% (2−8)
p=0.004

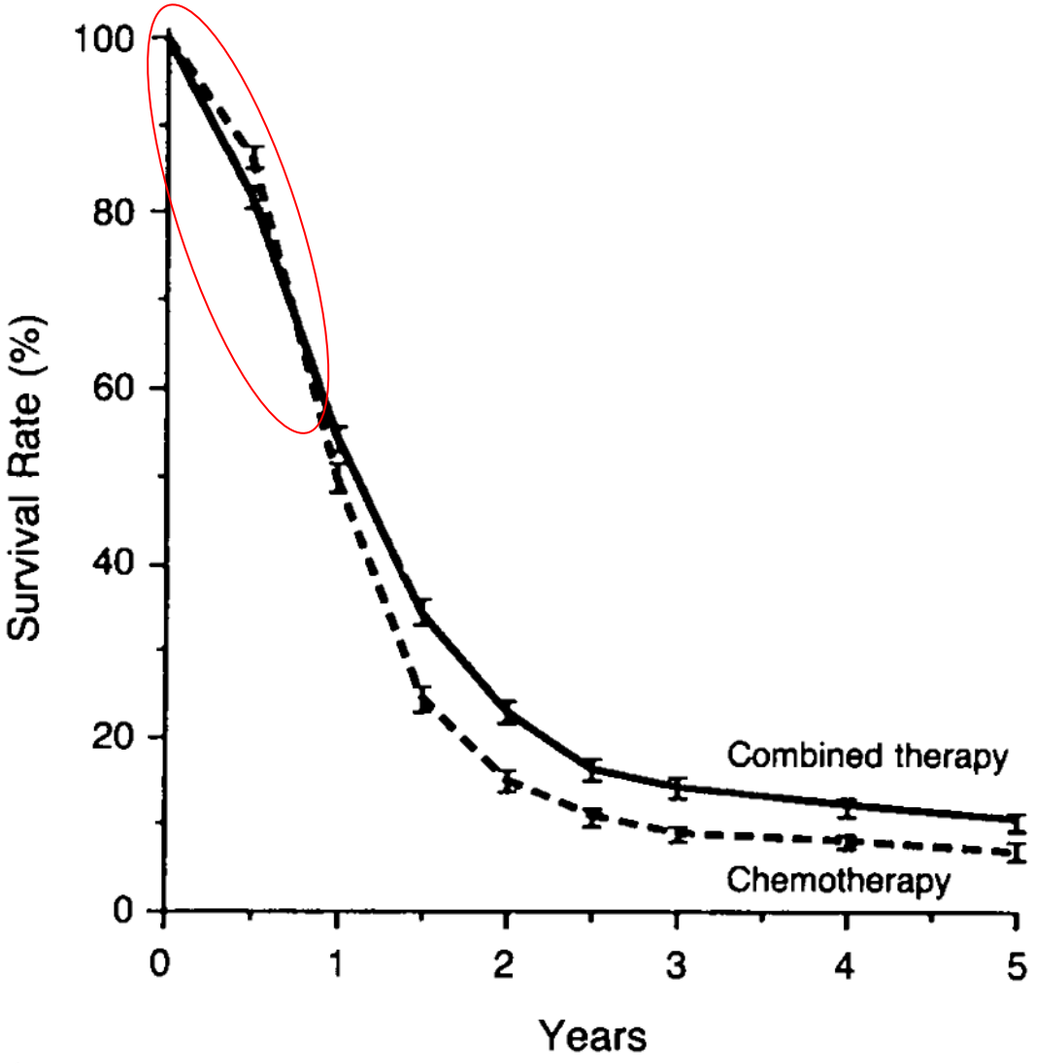
Slotman et al., Lancet 2015, 385, 36-42

Progression-free survival



Slotman et al., Lancet 2015, 385, 36-42

Benefit of TRT in SCLC



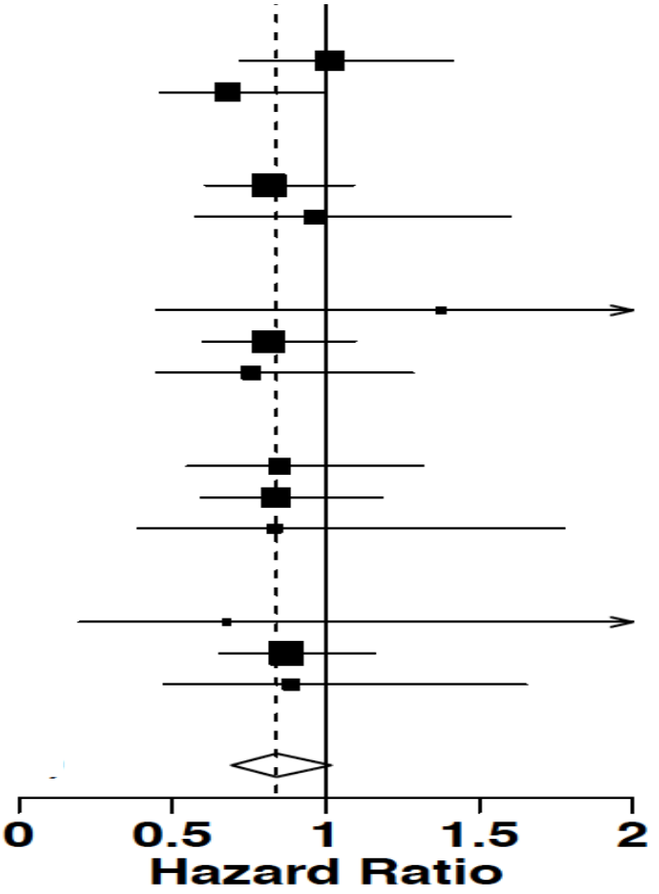
No. at Risk						
Chemotherapy	992	475	138	78	63	47
Combined therapy	1111	575	236	143	110	81

Figure 2. Survival Curves for the Combined-Therapy Group and the Chemotherapy Group.

Pignon et al., Meta-analysis of TRT in SCLC. N Engl J Med. 1992,327, 1618-24

Overall survival

Subgroup	Thoracic RT Events/N	No Thoracic RT Events/N	HR
Sex			
1= male	115/135	122/136	1.01 (0.72 – 1.41)
2= female	86/112	102/112	0.68 (0.46 – 1.00)
Age			
[36,70)	152/193	170/189	0.82 (0.61 – 1.09)
[70,85]	49/54	54/59	0.96 (0.58 – 1.60)
Response CT			
1 = CR	10/13	12/13	1.38 (0.45 – 4.22)
2 = PR	148/179	153/170	0.81 (0.60 – 1.10)
3 = good response	43/55	59/65	0.76 (0.45 – 1.28)
WHO Perf status			
ps 0	74/97	65/70	0.85 (0.55 – 1.32)
ps 1	101/121	136/155	0.84 (0.60 – 1.18)
ps 2	26/29	23/23	0.83 (0.39 – 1.78)
ED based on			
intrathor.dis	11/19	9/15	0.68 (0.20 – 2.31)
distant mets	161/190	172/188	0.87 (0.66 – 1.16)
both	29/38	43/45	0.89 (0.48 – 1.65)



Subgroups at 99%, overall at 95% confidence

Slotman et al., Lancet 2015, 385, 36-42

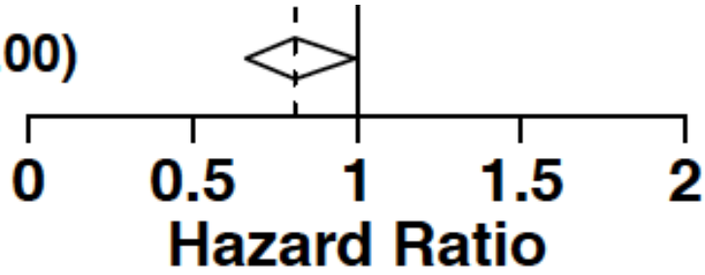
Overall survival

95% CI

Overall Survival

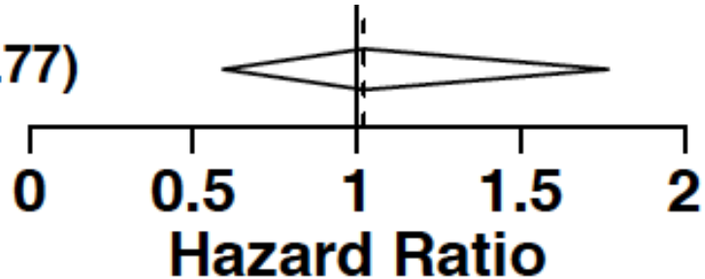
With Residual intrathoracic disease (p<0.05)

Overall result 176/215 197/219 0.81 (0.66 – 1.00)



Without Residual intrathoracic disease (NS)

Overall result 25/32 27/29 1.02 (0.59 – 1.77)



Slotman et al., Lancet 2015, 385, 1292-3

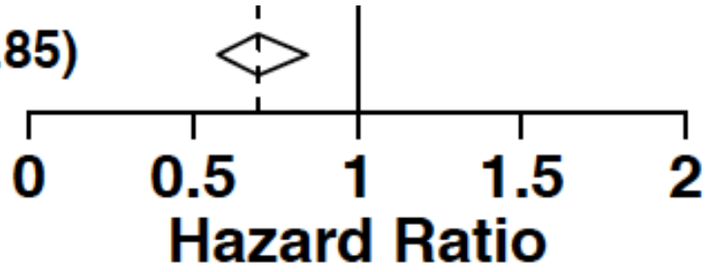
Progression-free survival

95% CI

Progr-free Survival

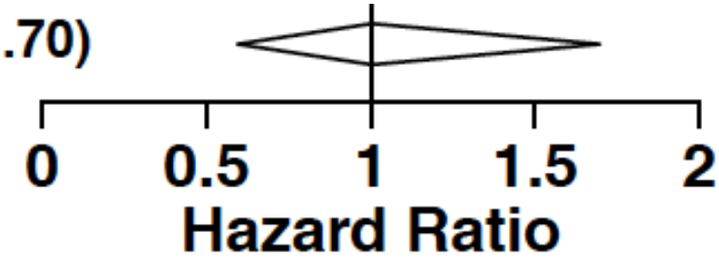
With residual intrathoracic disease (p=0.002)

Overall result **202/215** **212/219** **0.70 (0.57 – 0.85)**



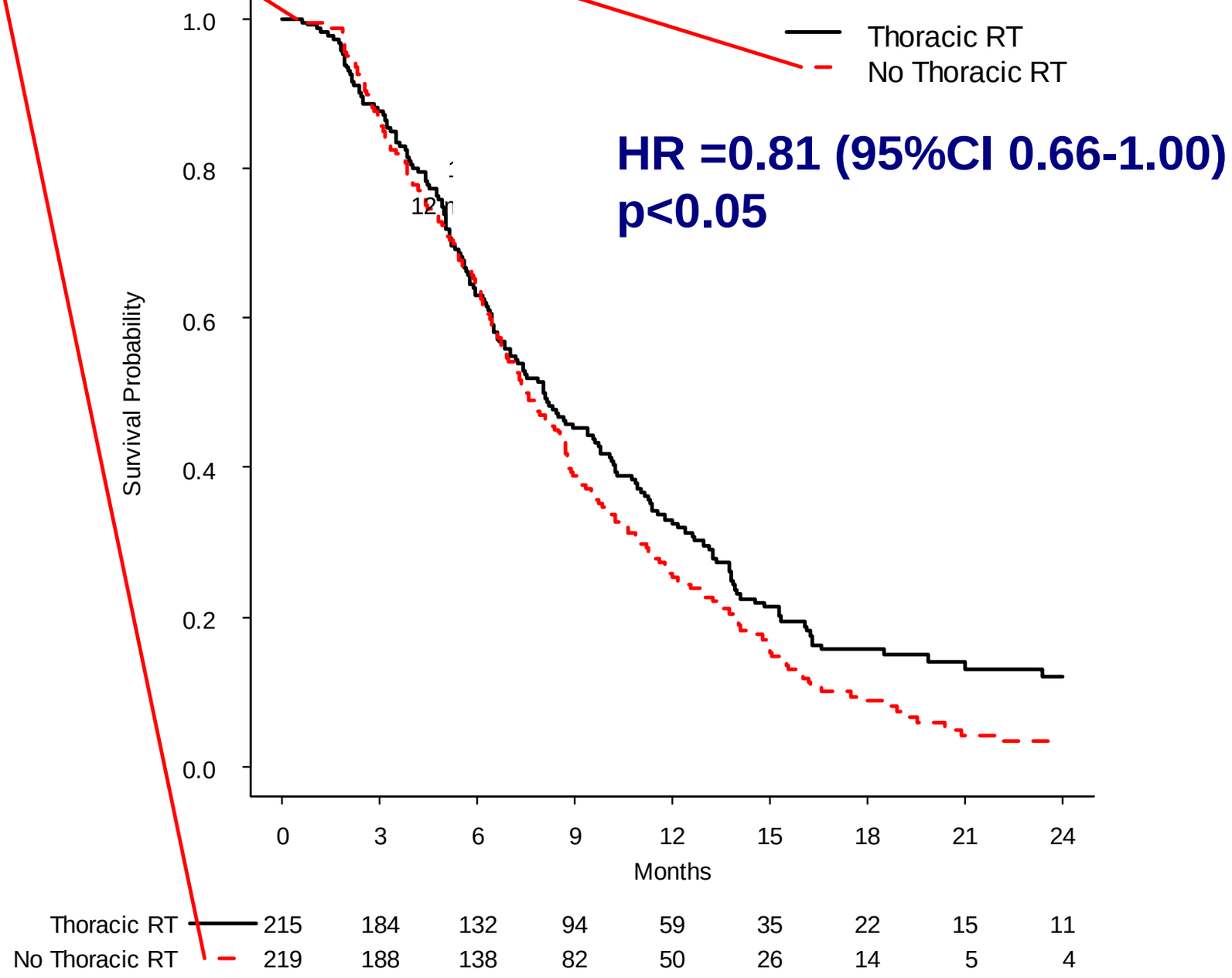
Without Rresidual intrathoracic disease (NS)

Overall result **29/32** **27/29** **1.00 (0.59 – 1.70)**



Slotman et al., Lancet 2015, 385, 1292-3

Overall survival (Pts with RITD)



Intrathoracic progression

	TRT	Control	p-value
All	43.7%	79.8%	p<0.001
As first site of relapse	41.7%	77.8%	p<0.001
As only site of relapse	19.8%	46.0%	p<0.001

Progression occurring at different organ sites within 30 days was considered as simultaneous progression.

Conclusions

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

The next step in ES-SCLC

RTOG 0937

Phase II trial of PCI plus extracranial consolidative RTX

Objectives

- To determine the overall median survival and 1-year survival
- Evaluation of recurrence patterns and time to failure

CLOSED

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site

PCI
25Gy / 10 fx

+

Thoracic RT
45 Gy / 15 fx

+

RT metastatic lesions
45Gy / 15 fx

Alternatives: 20x2.5 Gy;
10x4 Gy; 7x5 Gy; 5x6 Gy

Thank you for your attention