SCLC: Current approaches and the role of radiotherapy (thoracic and PCI) in stage IV disease

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Translationnal research- INSERM U981

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Disclosure Slide

- Consultancy fees from

→AstraZeneca, BMS, GSK, Lilly, MSD, Pfizer, Roche, Sanofi, Pierre Fabre, Merck, Boehringer.

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SCLC in 2014

- Incidence of SCLC is globally stable but its rate (10-15% of lung cancer) has decreased due to the strong increase of NSCLC and the decrease of smoking-related lung cancer where tobacco control has been developed

- Two third present with extensive stage disease

- Excellent responses to CT but few patients will be long term survivors (mostly those with limited disease)

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Extensive stage small-cell lung cancer (ES-SCLC)

- Survival is poor, and has improved little in recent decades

- 2-year survival is less than 5%
- Median time to progression is 4–6 months,
- and median survival is 7–11 months

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Most approaches have been proven unsuccessful

First Author	Regimen	No. patients	ORR (%)	Med Surv (mo)
Noda	PI vs PE	77 vs 77	84.4 vs 67.5	12.8 vs 9.4*
Natale	PI vs PE	324 vs 327	60 vs 57	9.9 vs 9.1
Hanna	PI vs PE	221 vs 110	48 vs 44	9.3 vs 10.2
Eckardt	PT vs PE	389 vs 395	63 vs 69	9.8 vs 10.0
Fink	PT vs PE	358 vs 345	56 vs 46	10.3 vs 9.4
Mavroudis	PET vs PE	62 vs 71	50 vs 48	10.5 vs 11.5
Reck	CEPac vs PEVinc	301 vs 307	72.1 vs 69	12.7 vs 11.7*
Niell	PEPac vs PE	293 vs 294	75 vs 68	10.3 vs 9.8
De Jong	CDE vs CPac	102 vs 101	60 vs 61	6.8 vs 6.7
Socinski	PemC vs EC	364 vs 369	30 vs 41	7.3 vs 9.6
Hermes	IC vs EC	105 vs 104	NR	8.5 vs 7.0
Satouchi	IP vs AP	142 vs 142	72.3 vs 77.9	17.7 vs 15.0

1st line ES-SCLC platinum/etoposide combination trials

Sponsor	IMP	Phase	MoA
Novartis	LDE225	I	Smo antagonist, inhibiting Hedgehog (Hh) signaling
National Cancer Institute	veliparib / placebo	I	PARP -1 and -2 inhibitor
National Cancer Institute	belinostat	I	HDAC inhibitor
Maastricht Radiation Oncology	chloroquine	I	Anti-autophagy
Eli Lilly	LY2940680 / placebo	Ib/II	Smo antagonist, inhibiting Hedgehog (Hh) signaling
Bayer	roniciclib	Ib/II	CDK inhibitor
Bayer	roniciclib / placebo	II	CDK inhibitor
Lund University Hospital & Sanofi	enoxaparin / placebo	III	antithrombotic
Bristol-Myers Squibb	ipilimumab / placebo	III	moAb directed against CTLA4

1st line ES-SCLC maintenance trials

Sponsor	IMP	Phase	MoA
People's Hospital of Guangxi	autologous cytokine-induced killer cell / BSC	II	immunotherapy with autologous CIK
Chinese PLA General Hospital	temozolomide	II	cytotoxic alkylating agent
Astrazeneca	olaparib	II	PARP -1 and -2 inhibitor

Systemic treatments in first line in 2014…

- Platinum-Etoposide is a standard CT regime for the treatment of SCLC,
- four to six cycles without maintenance treatment

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Second line chemotherapy

- **Relapse >3months post chemotherapy**
  → re challenge with carboplatin -etoposide

- **Relapse <3months post chemotherapy ('refractory disease')**
  → Anthracycline based chemotherapy (CAV)
  → RT or clinical trials
- **New drugs**
  - Topotecan vs BSC positive
  - Picoplatin vs BSC negative
  - Amrubicin vs topotecan (ACT1) positive RR and PFS, not OS

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SCLC has a predilection for the brain

- Approximately 10-20 % of patients present with brain metastases at the time of initial diagnosis
- Additional 40 % to 50 % will develop brain metastases at some time during the course of their disease
- It is clear that subclinical intracranial disease is likely to be present at the time of initial diagnosis and persist through treatment

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Seute T et al, cancer 2004; Quan AL et al, oncology 2004

Prophylactic cranial irradiation (PCI) in LD-SCLC

- **Reduces brain metastasis (BM)** and prolongs OS for LD-SCLC who have achieved a complete response to induction chemotherapy

- **PCI yields:**
  - a 25.3 % decreased incidence of brain metastases at 3 years (P<0.001)
  - Overall and disease-free survivals increased in PCI group by 5.4 % (P=0.01) and 8.8 % (P< 0.001), respectively at 3 years

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Aupérin A, et al. New Engl J Med 1999

Does PCI have a role in patients with ED-SCLC after chemotherapy ?

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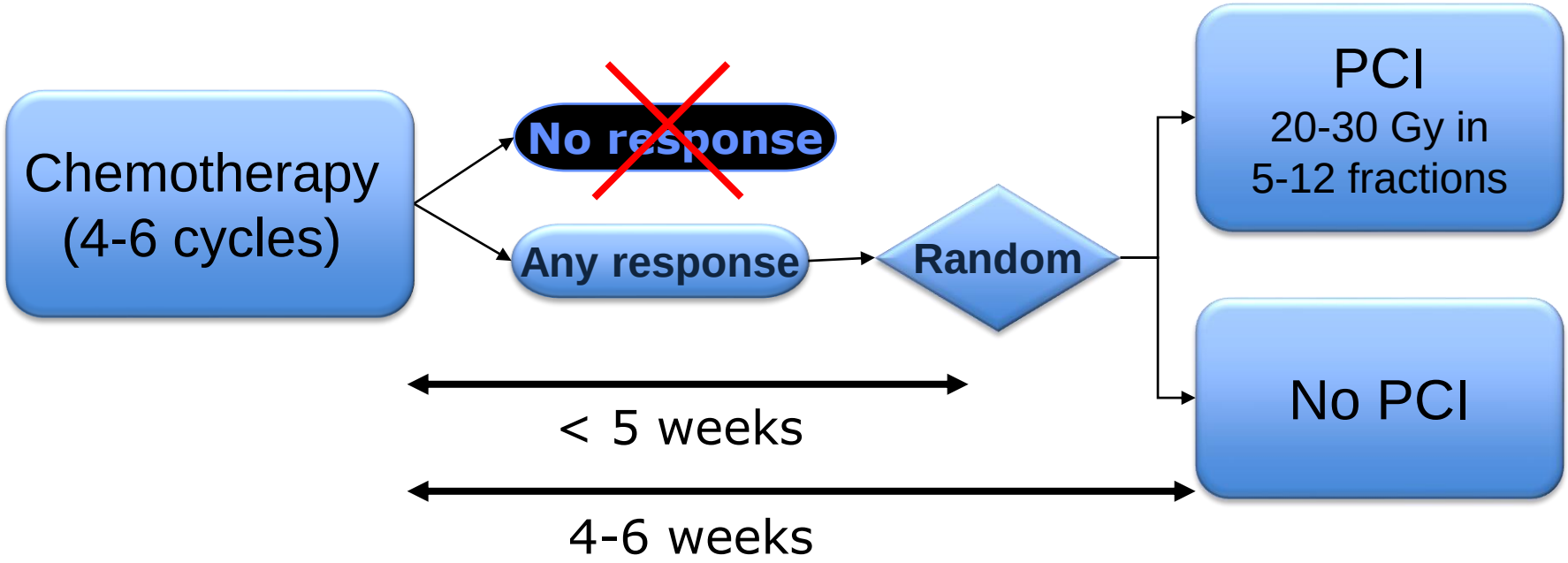
Prophylactic cranial irradiation in stage IV SCLC (EORTC 08993-22993)



- PS 0-2
- Age≤75
- No evidence of brain or leptomeningeal metastases

Presented by David. Planchard (Gustave Roussy)

Slotman et al. N Engl J Med 2007

Main Objective

- demonstrate a reduction in the risk of developing symptomatic brain metastases

Characteristics of the Patients

Variable	Prophylactic Cranial Irradiation (N=143)	Control (N=143)
Median age — yr (range)	62 (37–75)	63 (39–75)
Median time after diagnosis — mo	4.2	4.2
Sex — no. (%)		
Male	97 (67.8)	82 (57.3)
Female	46 (32.2)	61 (42.7)
WHO performance score — no. (%)†		
0	52 (36.4)	52 (36.4)
1	80 (55.9)	76 (53.1)
2	11 (7.7)	15 (10.5)

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Slotman et al. N Engl J Med 2007

Disease Status at study entry

	PCI (N=143)	Control (N=143)	Sign.
	N (%)	N (%)	
Persistent primary disease	108 (75.5)	110 (76.9)	N.S.
Presence of metastases	99 (69.2)	104 (72.7)	N.S.
- lymph nodes	50	47	
- bone	22	26	
- lung	24	25	
- other	64	82	

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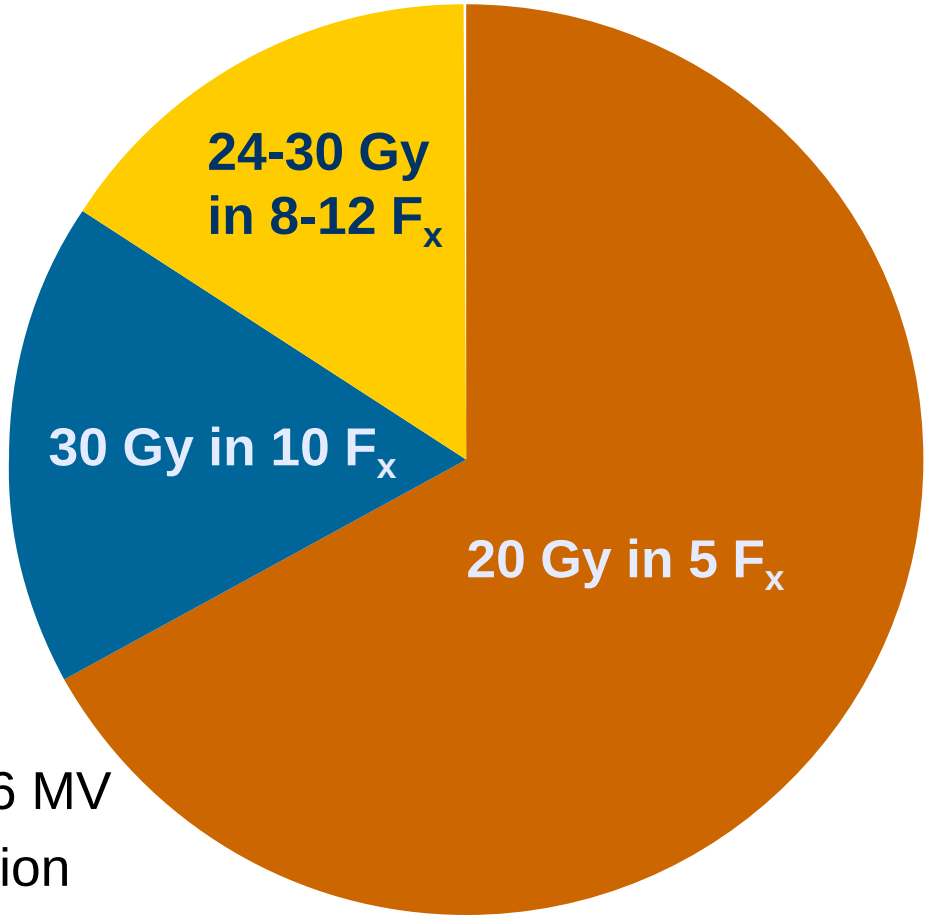
Slotman et al. N Engl J Med 2007

Radiotherapy schemes



- 2 parallel-opposed fields, most 6 MV
- 1 stopped due to early progression
- 4 treatment interruptions (3 logistical, 1 refusal)

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Slotman et al. N Engl J Med 2007

Type of first event

	PCI (N=143)	Control (N=143)
	N (%)	N (%)
No event	14 (9.8)	6 (4.2)
Symptomatic brain metastases	**13 (9.1)**	**50 (35.0)**
- followed by extracranial progression	13	48
Extracranial disease progression	**109 (76.2)**	**85 (59.4)**
- followed by brain metastases	11	9
Death due to other causes	7 (4.9)	2 (1.4)

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Slotman et al. N Engl J Med 2007

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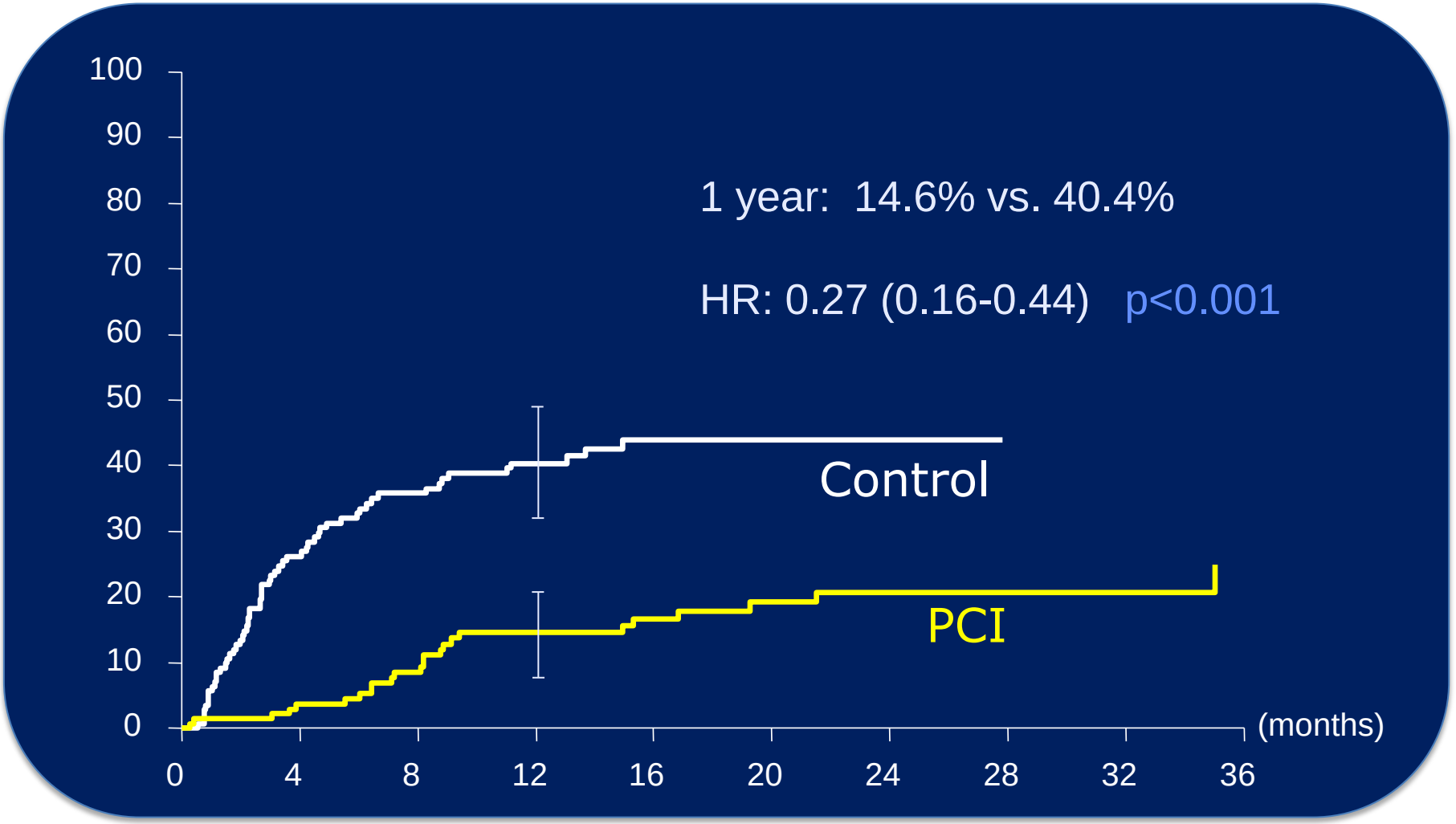
Symptomatic brain metastases



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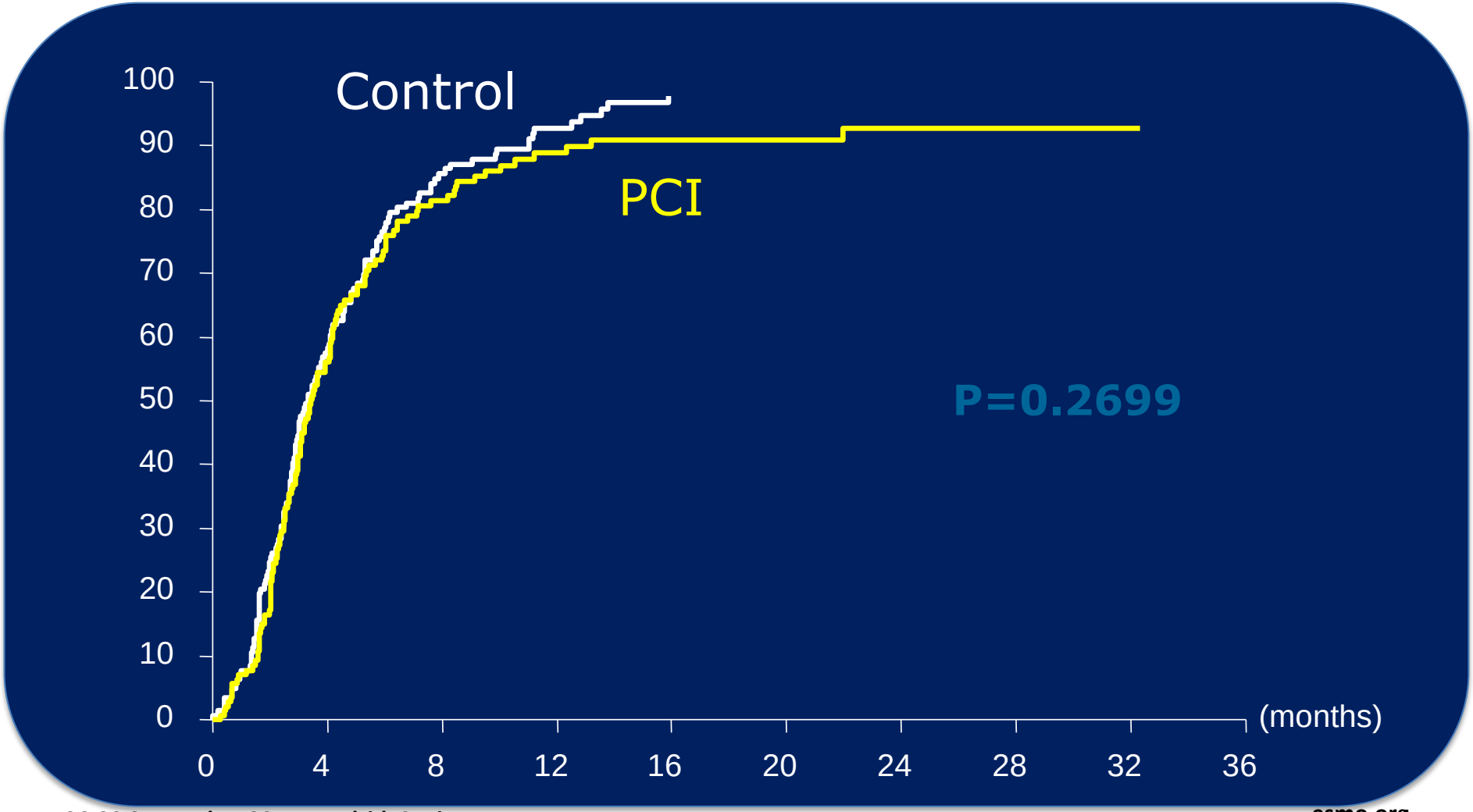
Slotman et al. N Engl J Med 2007

Extracranial progression



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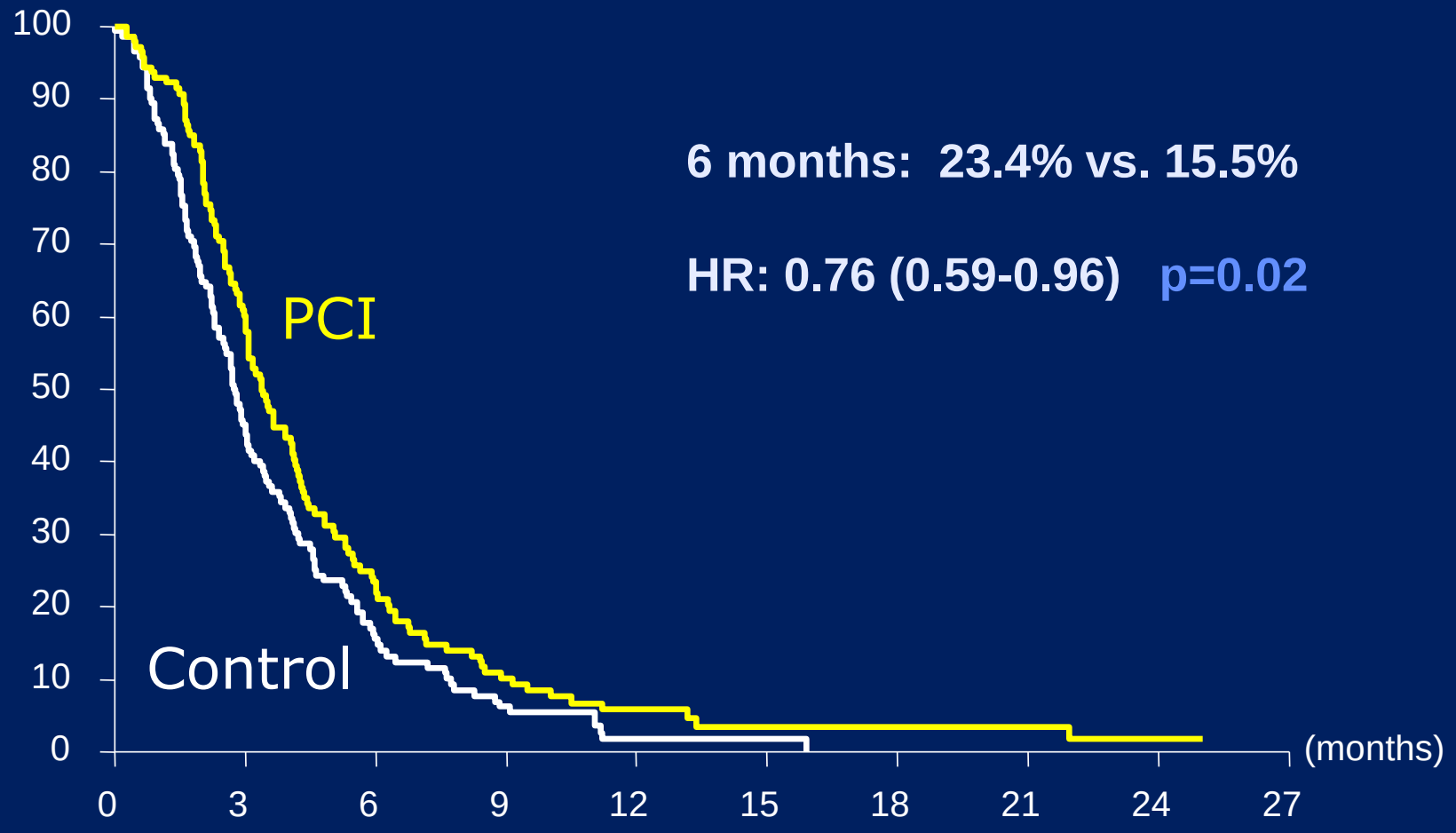
Slotman et al. N Engl J Med 2007

Failure-free survival



6 months: 23.4% vs. 15.5%

HR: 0.76 (0.59-0.96) p=0.02

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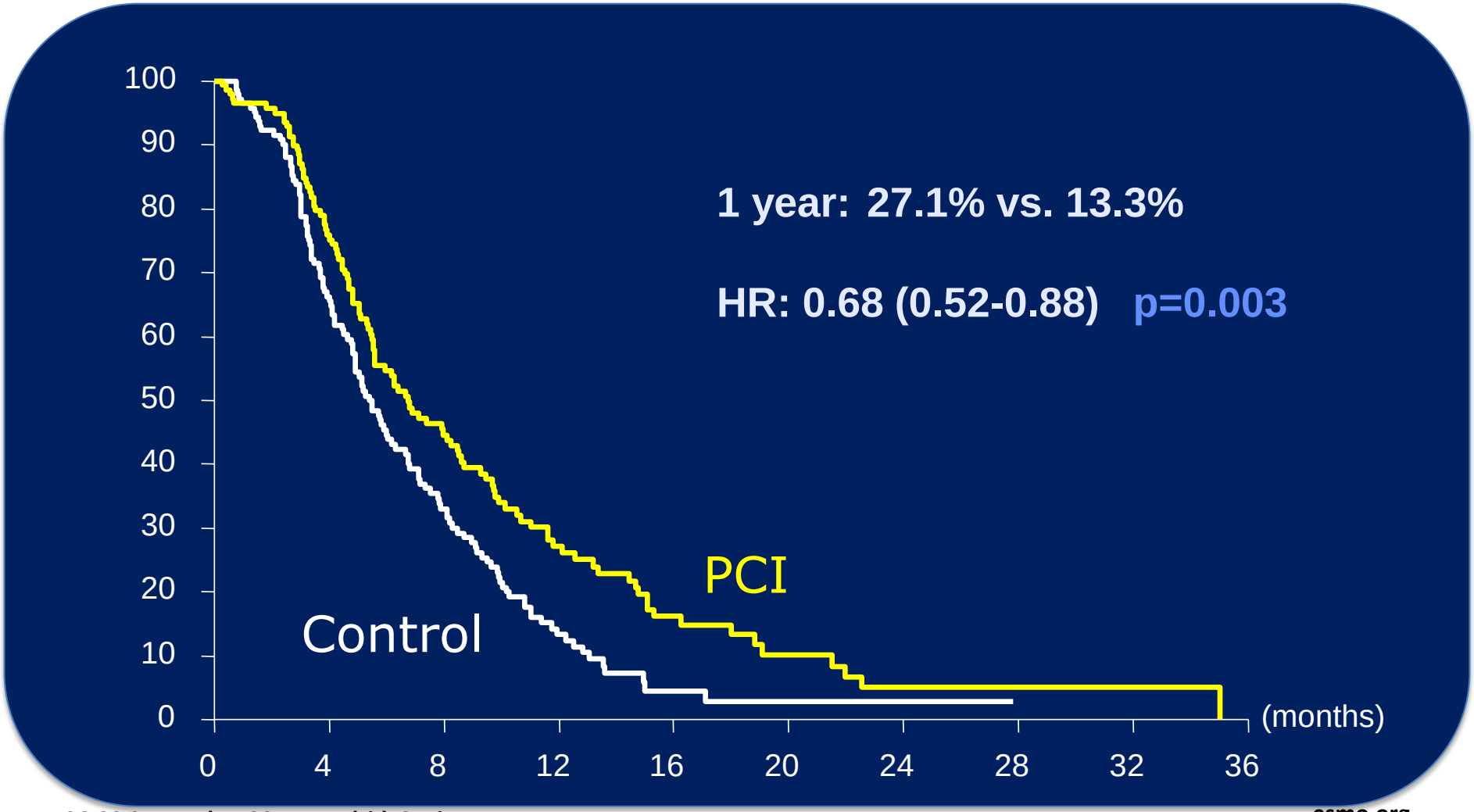
Slotman et al. N Engl J Med 2007

Overall survival



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Slotman et al. N Engl J Med 2007

Summary

- PCI reduces the **incidence of symptomatic BM** and **prolongs OS** for ED-SCLC who achieved any response to induction chemotherapy
- Patients with ED-SCLC who respond to chemotherapy should routinely be offered PCI (ESMO guidelines, levels II, B)

- Limitations of this trial:
  - Use of 1st line chemotherapy other than platinum
  - Lack of imaging assessment to confirm the absence of BM at study enrollment (Brain imaging only performed when signs and/or symptoms suggestive of brain metastases occurred)
  - Various radiation doses/fractionation in PCI treatment
  - Lack of follow-up imaging assessment for BM

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Slotman et al. N Engl J Med 2007

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Prophylactic cranial irradiation has a detrimental effect on the overall survival of patients with extensive disease small cell lung cancer: Results of a Japanese randomized phase III trial

Takashi Seto, Toshiaki Takahashi, Takeharu Yamanaka, Hideyuki Harada, Hiroshi Nokihara, Hideo Saka, Makoto Nishio, Kazuhiko Nakagawa, Koichi Takayama, Osamu Ishimoto, Koji Takeda, Hiroshige Yoshioka, Motoko Tachihara, Hiroshi Sakai, Koichi Goto, and Nobuyuki Yamamoto

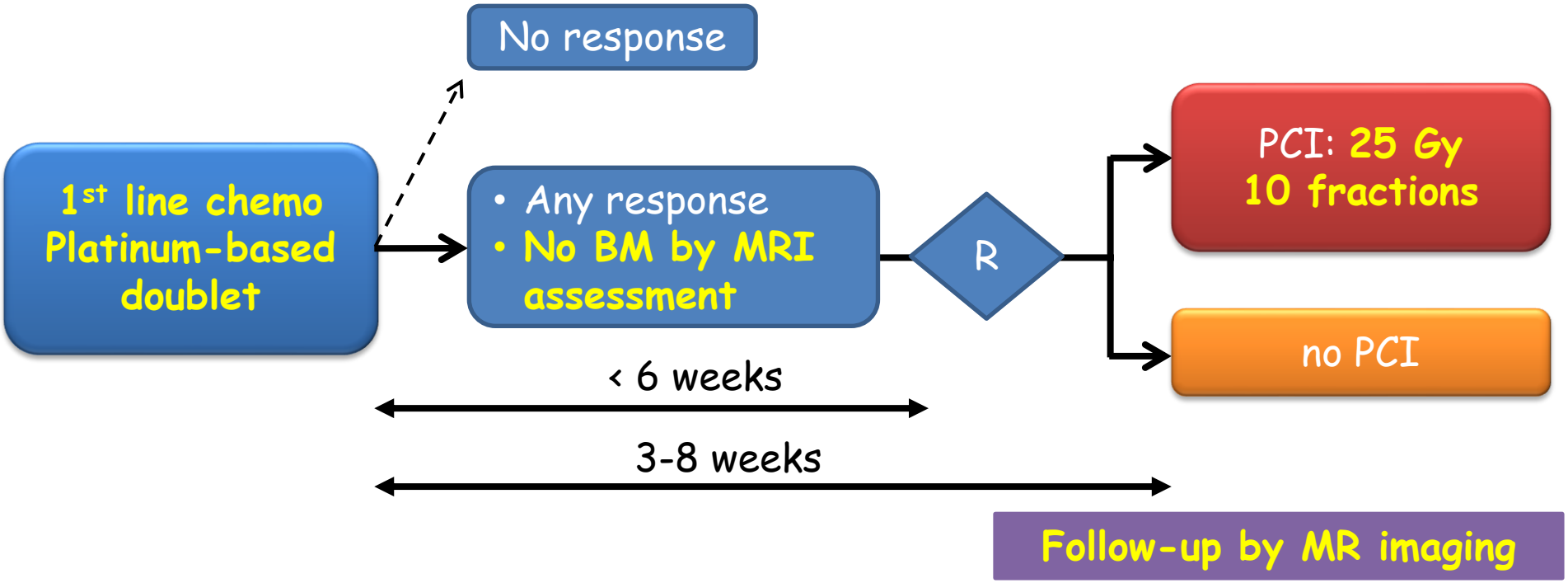
26-30 September 2014, Madrid, Spain

esmo.org

ASCO 2014

UMIN ID; 000001755

Design of this study



Stratification by Age (70≦ / <70), PS (0-1 / 2), Response (CR / PR+MR), Institutions

Primary endpoint: Overall Survival

Secondary endpoints: Time to BM (evaluated every 3 months)
Progression-Free Survival (PFS)
Safety
Mini Mental State Examination (MMSE)

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Takashi Seto et al, ASCO 2014

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Patient Characteristics

		Arm A: PCI n=84		Arm B: no PCI n=79	
Age					
	median	69		68	
	range	43-83		37-86	
Gender					
	man	68	81%	70	89%
	woman	16	19%	9	11%
ECOG PS					
	0-1	80	95%	77	97%
	2	4	5%	2	3%
Response to Chemotherapy					
	CR	10	12%	12	15%
	PR+MR	74	88%	67	85%

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Takashi Seto et al, ASCO 2014

1st line Chemotherapy

Regimen	Arm A PCI n=84	Arm B no PCI n=79	Total n=163
CDDP+irinotecan	32	26	58
CBDCA+etoposide	28	29	57
CDDP+etoposide	12	15	27
CBDCA+etoposide -> CDDP+etoposide	3	1	4
CDDP+etoposide -> CBDCA+etoposide	2	2	4
CBDCA+irinotecan	2	1	3
CBDCA+etoposide -> CDDP+irinotecan	2	1	3
CDDP+irinotecan -> CBDCA+etoposide	1	1	2
CBDCA+irinotecan -> CBDCA+etoposide	0	1	1
CDDP+irinotecan -> CBDCA+irinotecan	0	1	1
CDDP+amrubicin	1	0	1
CBDCA+amrubicin	1	0	1
CDDP+topotecan	0	1	1

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Takashi Seto et al, ASCO 2014

Adverse Events in PCI arm

	Arm A: PCI n=81 (At randomization)			Arm A: PCI n=81 (Worst Gr during PCI)		
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
alopecia	24%	0%	0%	11%	0%	0%
dermatitis	4%	0%	0%	1%	0%	0%
headache	3%	0%	0%	3%	0%	0%
anorexia	16%	6%	1%	11%	10%	1%
nausea	10%	3%	0%	9%	3%	0%
vomiting	1%	0%	0%	4%	0%	0%
dizziness	3%	1%	0%	1%	1%	0%
malaise	12%	5%	0%	13%	4%	4%
lethargy	1%	1%	0%	4%	0%	0%

CTCAE ver. 3.0

Takashi Seto et al, ASCO 2014

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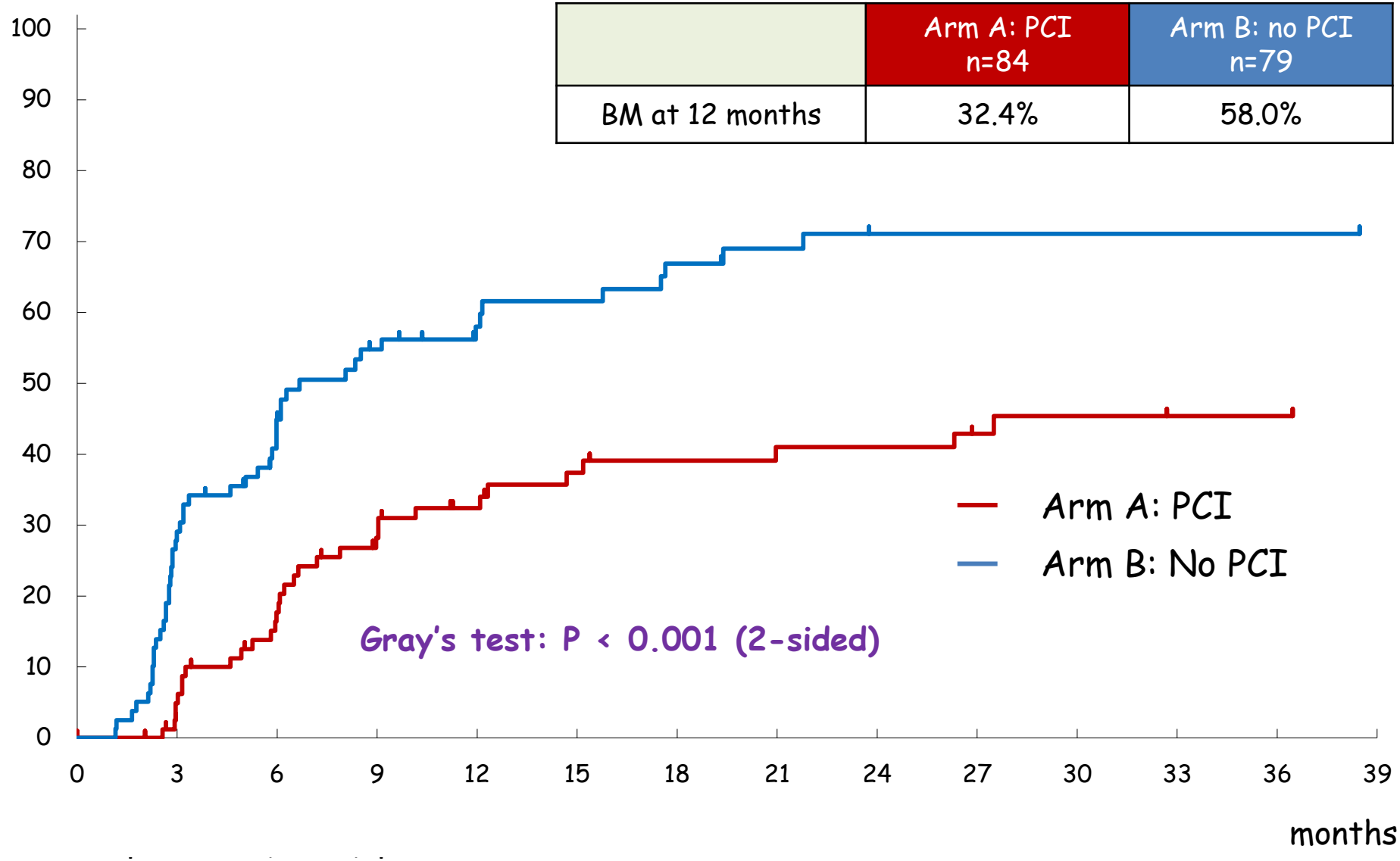
Time to Brain Metastasis

	Arm A: PCI n=84	Arm B: no PCI n=79
BM at 12 months	32.4%	58.0%



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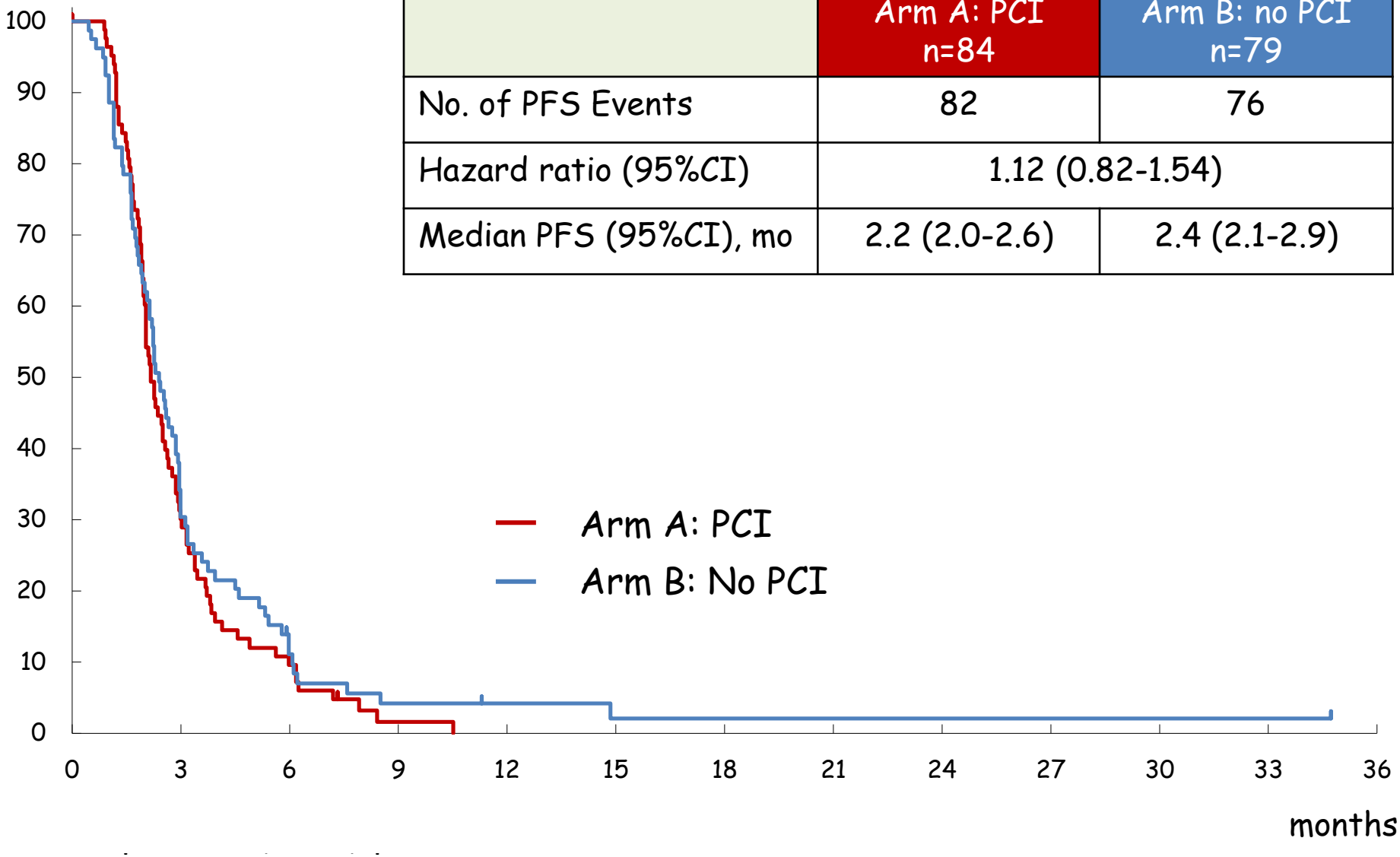
Takashi Seto et al, ASCO 2014

Progression-Free Survival

	Arm A: PCI n=84	Arm B: no PCI n=79
No. of PFS Events	82	76
Hazard ratio (95%CI)	1.12 (0.82-1.54)	
Median PFS (95%CI), mo	2.2 (2.0-2.6)	2.4 (2.1-2.9)



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Takashi Seto et al, ASCO 2014

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Post-Study Chemotherapy After PD

	Arm A: PCI	Arm B: no PCI
2nd line chemotherapy	68 (82%)	70 (89%)
Single agent	48	49
Platinum-based doublet	15	18
Cisplatin + irinotecan + etoposide	4	3
Other	1	0
3rd line chemotherapy	36 (43%)	42 (53%)
Single agent	24	29
Platinum-based doublet	9	13
Other	3	0
4th line chemotherapy	13 (16%)	21 (27%)
Single agent	6	13
Platinum-based doublet	7	7
CODE	0	1

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Takashi Seto et al, ASCO 2014

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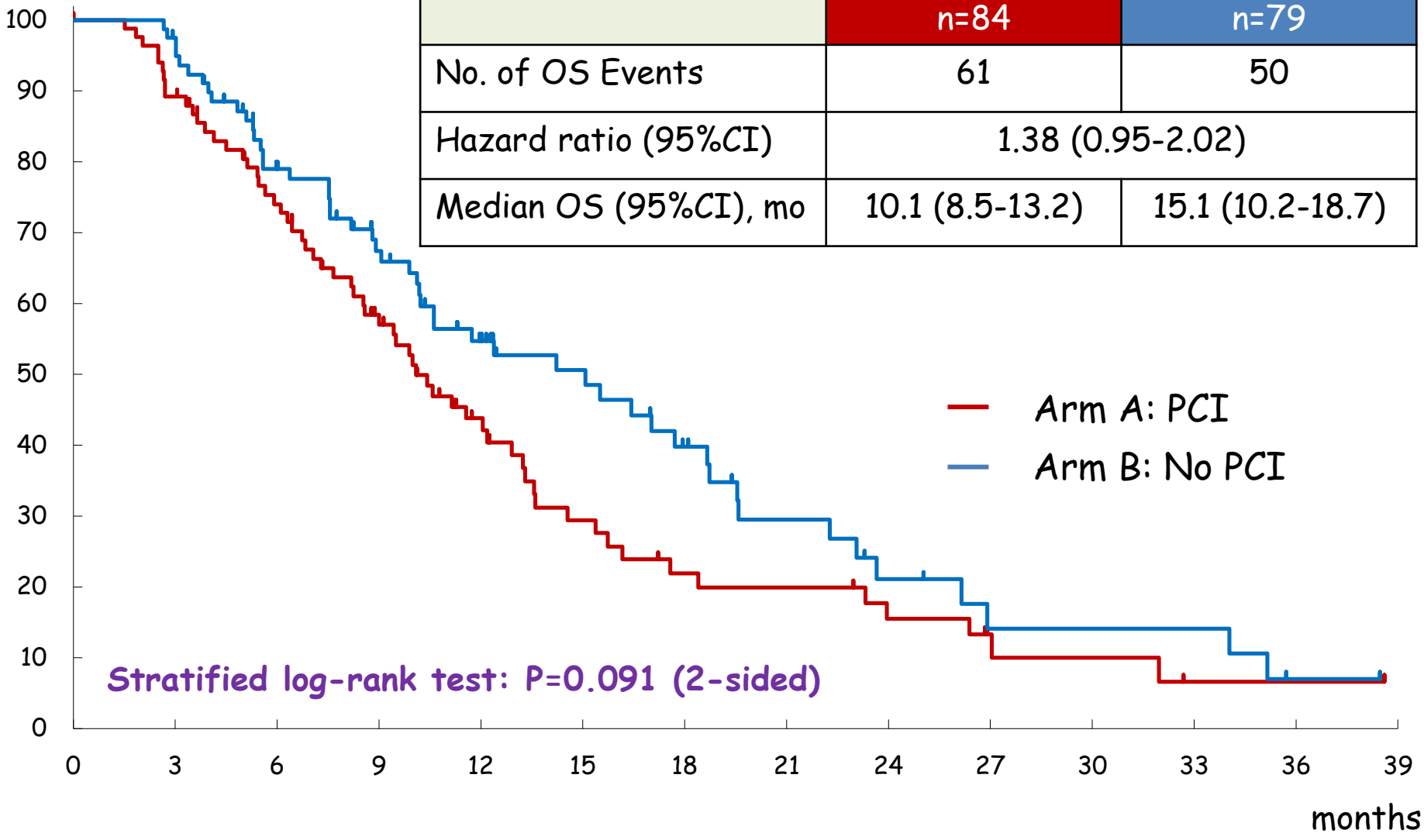
Overall Survival

	Arm A: PCI n=84	Arm B: no PCI n=79
No. of OS Events	61	50
Hazard ratio (95%CI)	1.38 (0.95-2.02)	
Median OS (95%CI), mo	10.1 (8.5-13.2)	15.1 (10.2-18.7)



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Takashi Seto et al, ASCO 2014

Summary

- PCI significantly reduced the risk of BM.
  - 32.4% vs 58.0% at 12 months in the PCI and no PCI arms
- PFS was comparable between the two arms.
  - The median was 2.2 vs. 2.4 months. HR=1.12 (0.82-1.54)
- Increase of AEs greater than Gr 2 was not observed in PCI arm except anorexia and malaise.
- PCI did not show the survival benefit for ED-SCLC patients with a confirmed absence of BM.

EORTC vs Japanese PCI Trials

	EORTC (Slotman)	Japan (Seto)
Nb Patients	286	163
PCI Dose/Fx	Variable	25 gy/10 fr
Pre-enrollment neuro-imaging	Not required	No BM by MRI assessment
Follow up imaging	Not required	Brain Required
Neuro function data	Limited	Limited

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Few data on neurological impact

- **In EORTC trial (Quality of Life Questionnaire C30 and Quality of Life Questionnaire Brain Cancer Module):**
  - Few pts experiencing Grade 3 acute and/or late toxicity
  - Acute side effects negatively influenced some quality-of-life scales immediately after treatment
  - no overall effect on global quality of life at up to 9 months
  - HRQOL assessment was 93.7% at baseline and dropped to 60% at 6 weeks and 46,3% at 9 months…
  - Largest mean difference between two arms observed for fatigue and hair loss

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Ben Slotman et al, NEJM 2007

Late radiation reactions

	PCI (N=134) N	(%)
No change from baseline	87	(64.9)
Grade 1. Mild headache, slight lethargy	29	(21.6)
Grade 2. Moderate headache, great lethargy	15	(11.2)
Grade 3. Severe headache, severe CNS dysfunction	3	(2.2)

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Slotman et al. N Engl J Med 2007

To be discussed…

- Are results from the asian trial transposable to non asian subjects?
- Asian study clearly raises the question of the benefit of PCI in patients with brain radiological monitoring

- EORTC trial probably closer to «real life» in patients with no systematic brain evaluation

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Slotman BJ et al, JCO 2009

What we learn about PCI in LS-SCLC

- PCI has the potential for inducing neurotoxicity:
  - Avoidance of concurrent chemotherapy
  - Use of low fraction dose schedules have reduced this risk considerably
- **Late neuropsychological side effects** observed both in patients who received PCI and those who did not.
  - For both groups, risk in 2-year survivors about 5–10%
- **Neuropsychological late sequelae** have been attributed to radiation-induced hippocampal dysfunction
  - Benefit by avoiding hippocampal area ?

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Arriagada R, et al, JNCI 1995, Gregor A et al, Eur J cancer 1997

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Benefit to increase dose of PCI LS-SCLC

- **Increase in dose from 25 Gy (10 fractions) to 36 Gy (18 once-daily or 24 twice-daily fractions):**
  - did not result in significant decrease in risk of BM (HR= 0.80, P=0.18)
  - no significant difference between two groups in terms of QoL and neurological and cognitive functions
  - in both groups a mild deterioration across time of communication deficit, weakness of legs, intellectual deficit and memory
  - Few patients had severe deterioration of neuropsychological and cognitive functions over the first 3 years

- **Recommended PCI dose in LS-disease patients remains 25 Gy in 10 fractions**

QLQ-C30/BN20 questionnaires at 6 and 12 months and The LS scale

Presented by David. Planchard (Gustave Roussy)

Le Pechoux et al, Annals of onco 2010 LePechoux C, et al, lancet onco 2009

PCI in NSCLC (stage III) RTOG 0214

- After treatment with surgery and/or radiation therapy with or without chemotherapy
- PCI (30 Gy in 15 fractions) or observation
- PCI decreased rate of BM but did not improve OS or DFS
- Neurocognitive and Quality-of-Life Analysis:
  - no significant differences in global cognitive function (MMSE) or QOL after PCI
  - but a significant decline in memory (HVLT) at 1 year

Neurocognitive Function: Mini-Mental Status Examination (MMSE), Activities of Daily Living Scale (ADLS), and Hopkins Verbal Learning Test (HVLT). QOL: EORTC core tool (QOL Questionnaire-QLQC30) and brain module (QLQBN20)

Presented by David. Planchard (Gustave Roussy)

Elizabeth M. Gore et al, JCO 2011

Alexander Sun et al, JCO 2011

If we do a PCI

- **Still a standard of care in ES-SCLC:**
  - Guidelines ESMO 2013: “Patients with any response to first-line treatment and who have a reasonably good PS should be evaluated for PCI [II, B].”

- **PCI schemes for this group of patients should preferably be short** (not more than 25Gy in 10 fraction: 25 Gy in 10 daily fractions or 20 Gy in 5 fractions.)
- **Caution in older and frail patients**

- **Patients should be told** of the benefits of PCI and of its possible negative impact on intellectual deficit, memory…
- **Brain evaluation not mandatory** if no clinical specific signs

II: Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality)

B:Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended

Intrathoracic tumour control remains a major challenge for ED-SCLC

- **EORTC 08993-22993 PCI:**
  - 75% of patients had persisting intrathoracic disease after chemotherapy
  - 90% had intrathoracic disease progression within the first year after diagnosis

- **In ES-SCLC, thoracic RT has traditionally been reserved to patients who required local palliation**

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External-beam RT is particularly useful for

- **Patients with loco-regional disease causing symptoms such as**
  - dyspnea, cough, hemoptysis,
  - post-obstructive pneumonia,
  - Pain (bone metastasis…),
  - and neurologic disease…

Presented by David. Planchard (Gustave Roussy)

1st retrospective review

- ES-SCLC who received consolidation TRT 30Gy identified
- SCLC treated from January 2005 to July 2009

- Ninety-nine patients (46%) of all ES-SCLC patients received TRT, either palliative or consolidative
  - Nineteen patients (9%) identified as receiving consolidative TRT

- Most patients (n =16) had metastatic disease in only one organ site at presentation and no patient had more than two sites of metastases

Presented by David. Planchard (Gustave Roussy)

Meredith E. Giuliani et al, clinical lung cancer 2011

Main results

- Incidence of LR failure was 26% and 39% at 1 and 2 years
- Incidence of distant failure was 58% and 74% at 1 and 2 years
- Median OS : 14 months

Distant failure remained a significant problem

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Meredith E. Giuliani et al, clinical lung cancer 2011

2nd Retrospective study

- January 2003 and December 2006,
- records of 119 patients diagnosed with ED-SCLC

- Sixty patients received chemotherapy (ChT) and TRT (ChT/TRT)
- metastasis involved in 1 organ in 51 pts and 2 organs in 9 pts
- RT ≥50 Gy received by 46 pts (76.7%)

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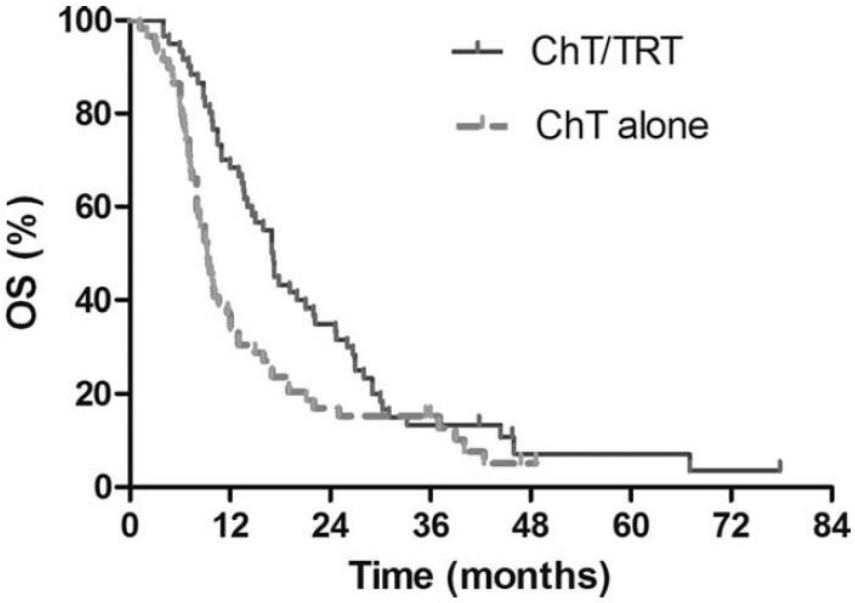
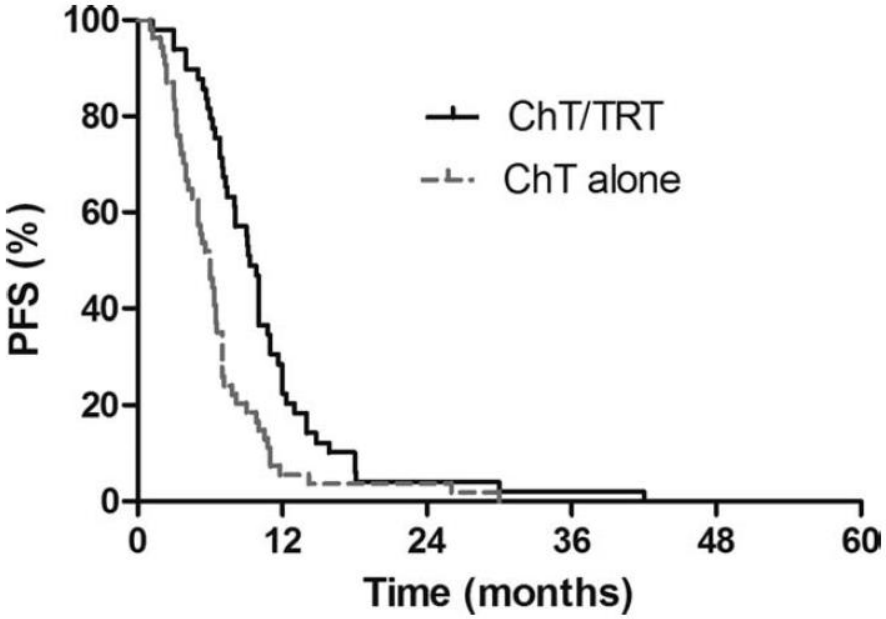
Hui Zhu et al, Cancer 2011

Main results



median OS 17 vs 9.3 months



PFS 10 vs 6,2 months

Retrospective results needed to be confirmed in prospective studies

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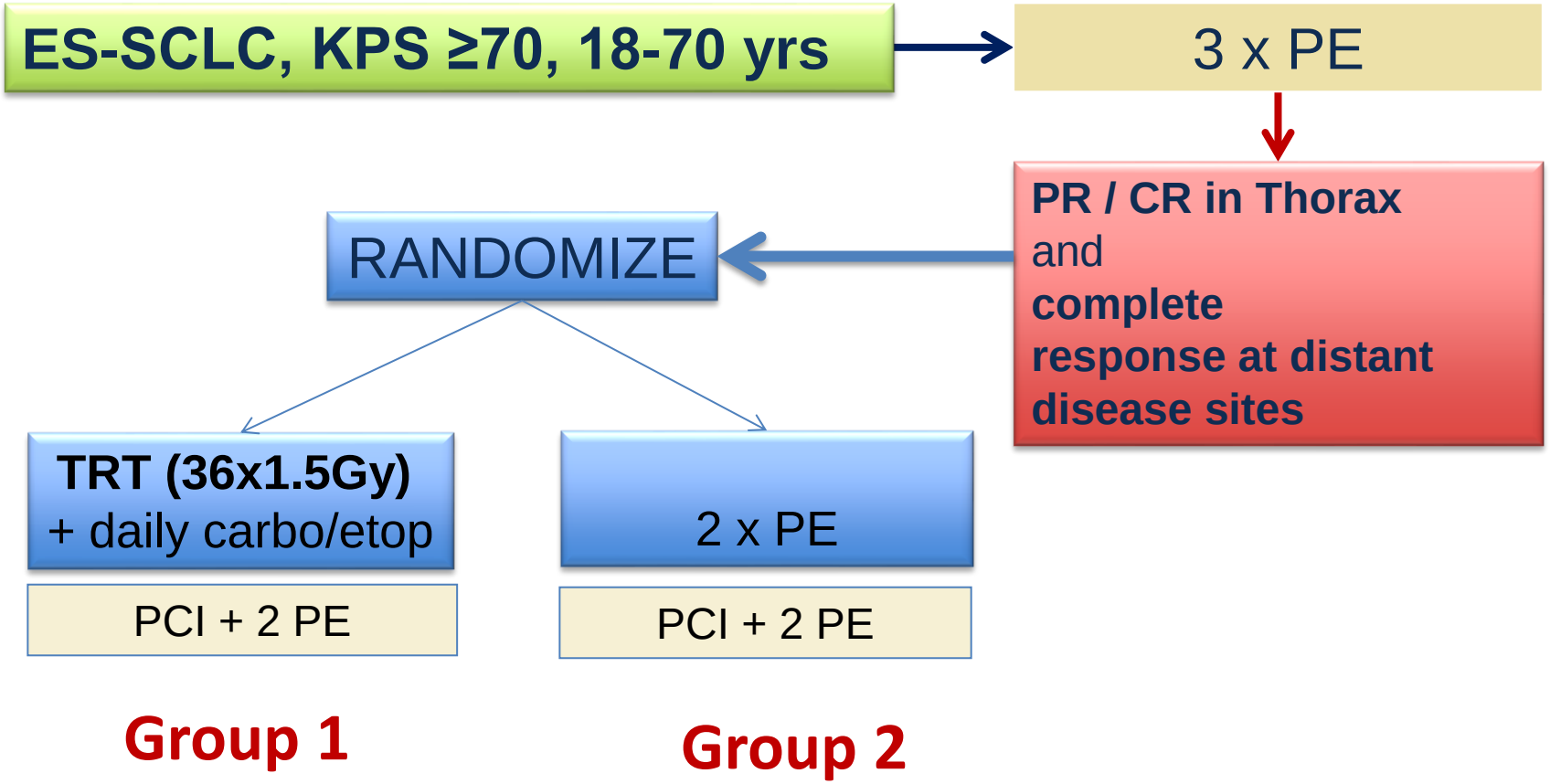
First study to address the role of thoracic RT for ES-SCLC systematically



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Jeremic et al., JCO 1999

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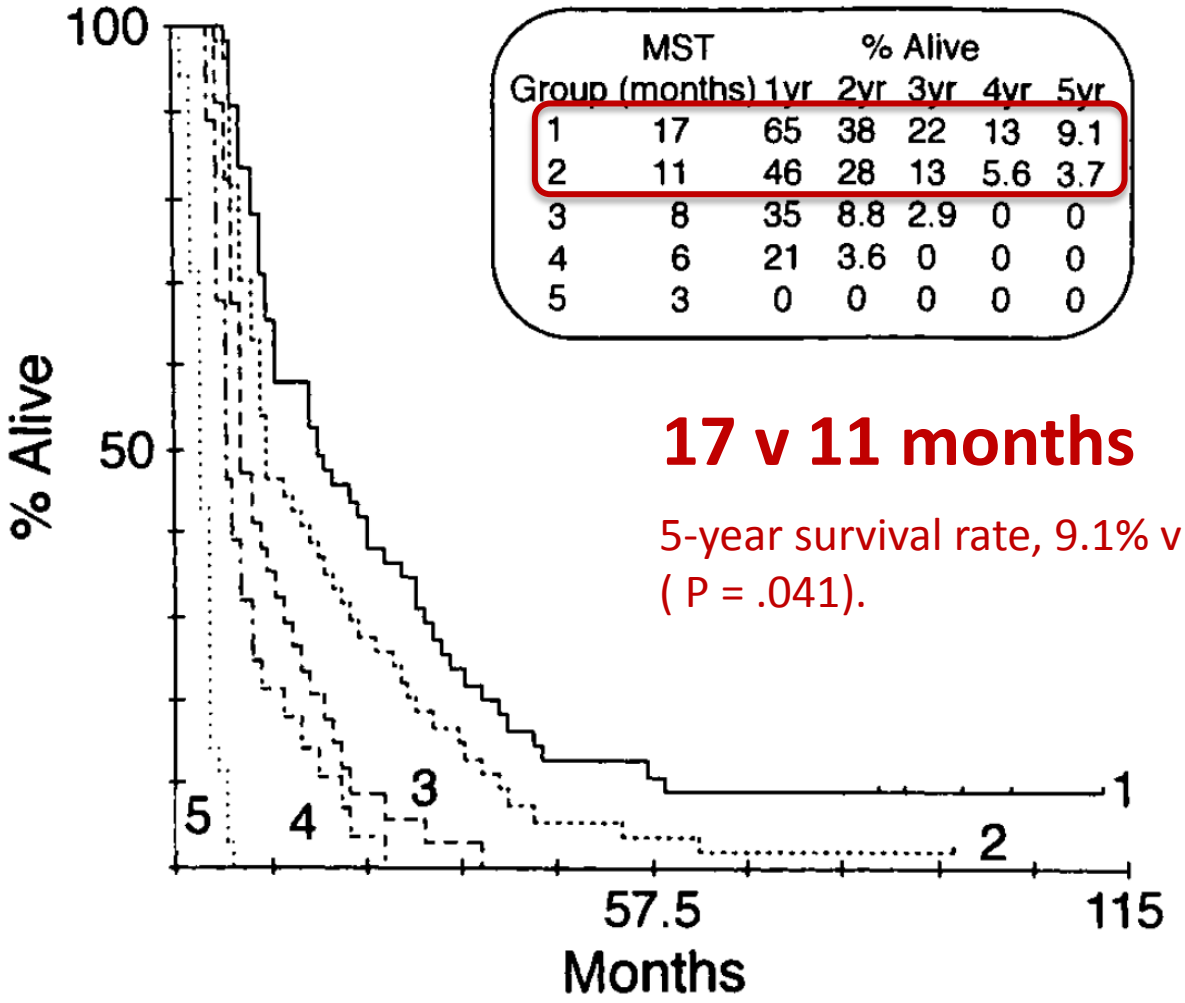
Overall survival

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

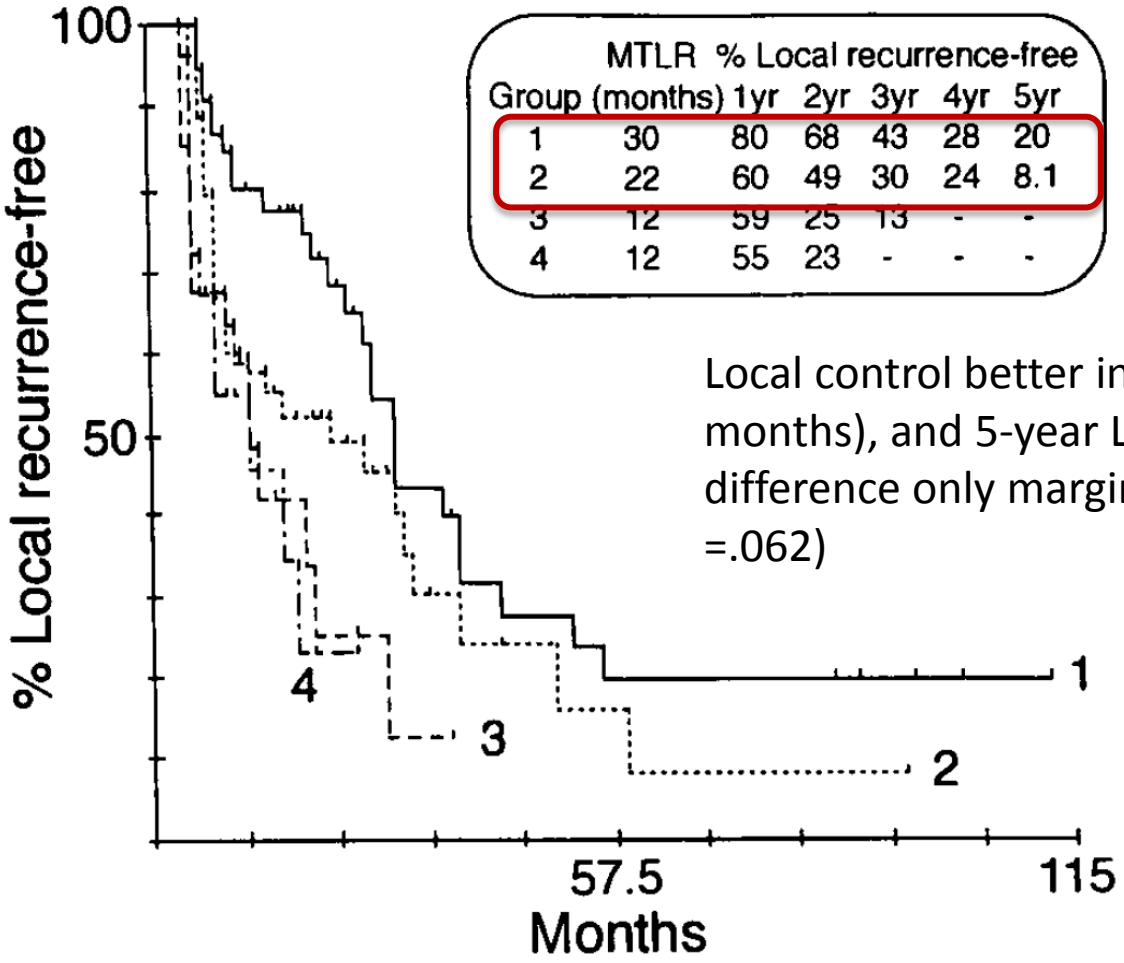


17 v 11 months

5-year survival rate, 9.1% v 3.7%, (P = .041).

Patients in group 1 achieved best results that were significantly better than those in the other treatment groups.

Local recurrence-free survival



Group	MTLR (months)	% Local recurrence-free 1yr	2yr	3yr	4yr	5yr
1	30	80	68	43	28	20
2	22	60	49	30	24	8.1
3	12	59	25	13	-	-
4	12	55	23	-	-	-

Local control better in group 1 (30 and 22 months), and 5-year LRFS of 20% and 8.1% but difference only marginally not significant (P =.062)

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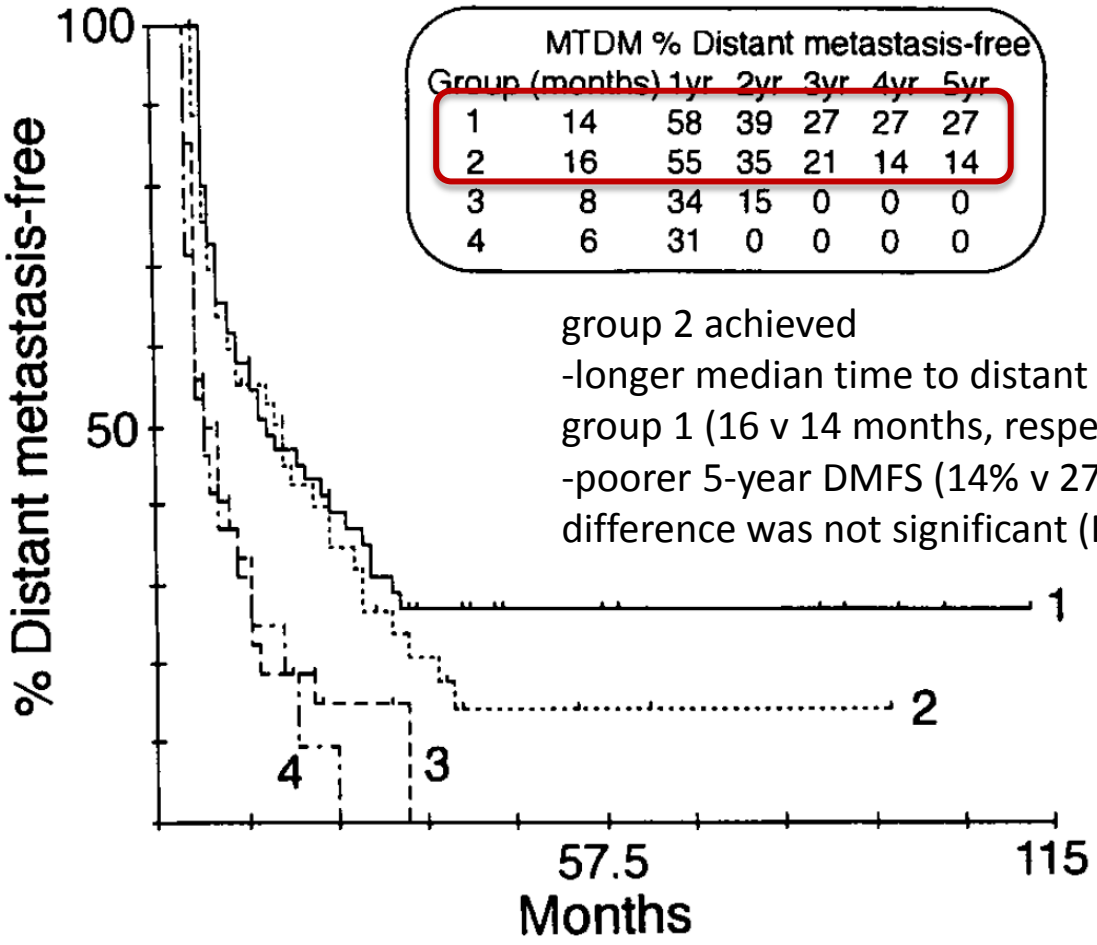
Distant metastasis-free survival

Group	MTDM (months)	% Distant metastasis-free 1yr	2yr	3yr	4yr	5yr
1	14	58	39	27	27	27
2	16	55	35	21	14	14
3	8	34	15	0	0	0
4	6	31	0	0	0	0



group 2 achieved
-longer median time to distant metastasis than group 1 (16 v 14 months, respectively),
-poorer 5-year DMFS (14% v 27%, respectively), difference was not significant (P = .35).

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RT seems to improve

- **Time to local recurrence**
- **and median survival**
- However, that single-center study has not been reproduced so far and has not resulted in the routine use of thoracic RT for ES-SCLC

- Two studies invetigating the role of thoracic RT for ES-SCLC have recently been initiated (CREST, RTOG 0937)

MADRID 2014 ESMO congress

Dutch Lung Cancer Study Group

UK NCRI Clinical Study Group

CRESTT

Chest
Radiotherapy
Extensive
Stage
Trial

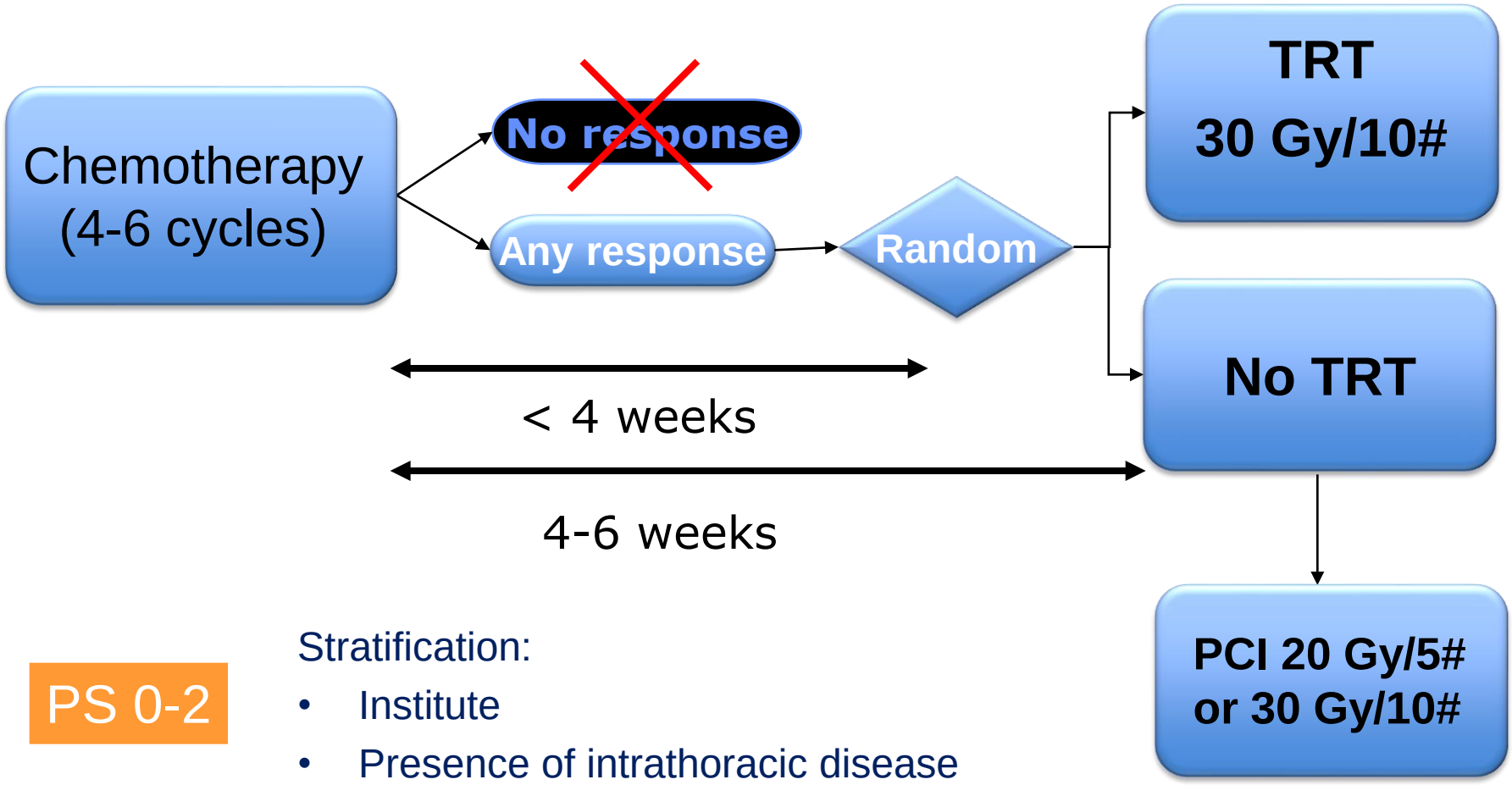
DUTCH CANCER SOCIETY · NCRN · CANCER RESEARCH UK · iKNL · I.C.R.G. · VUmc

26-30 September 2014, Madrid, Spain

esmo.org

Ben Slotman et al, ASCO 2014

CREST Trial Design



PS 0-2

Stratification:

- Institute
- Presence of intrathoracic disease

Ben J Slotman et al, ASCO 2014

Ben J Slotman at al, lancet 2014

Endpoints & Objectives

Study endpoints:

- Primary: overall survival
- Secondary: 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% significance)
- Accounting for 5% dropout between randomization and start of treatment, 483 patients had to be randomized

Ben J Slotman et al, lancet 2014

Patient characteristics

	TRT (n=247)		Control (n=248)	
Extensive stage based on				
distant metastasis	190	(76.9)	188	(75.8)
extent of intrathoracic disease	19	(7.7)	15	(6.1)
both	38	(15.4)	45	(18.1)

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Ben J Slotman, lancet 2014

Patient characteristics

	TRT (n=247)		Control (n=248)	
Response				
Complete response	12	(4.9)	13	(5.2)
Partial response	180	(72.8)	170	(68.6)
Good response	55	(22.3)	65	(26.2)
Persistent intrathor. disease				
Yes	215	(87.0)	219	(88.3)
No	32	(13.0)	29	(11.7)

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Toxicity Grade 3 and higher

	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

95% of patients completing protocol-specified thoracic radiotherapy without interruption

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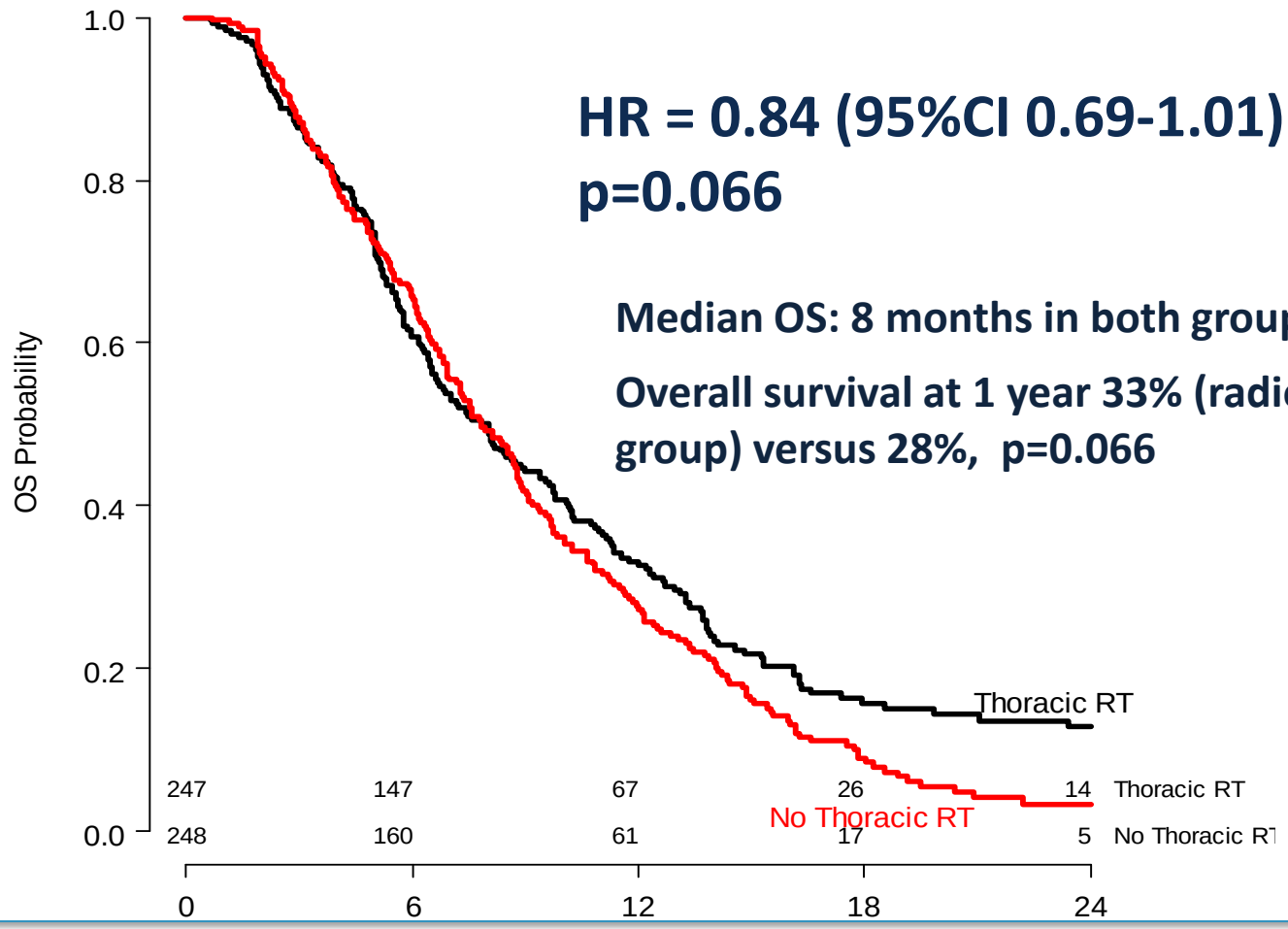
Overall survival



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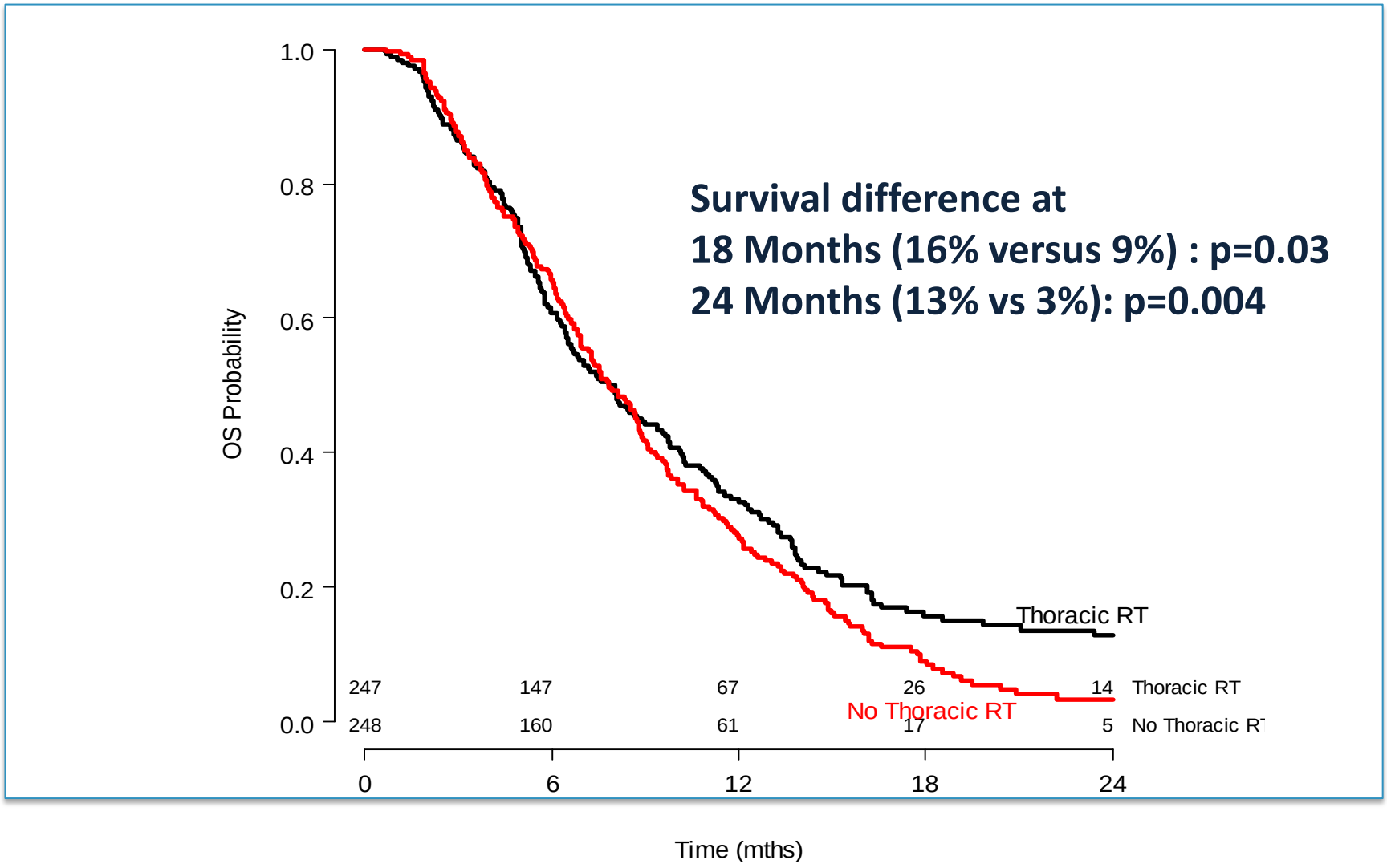
Overall survival



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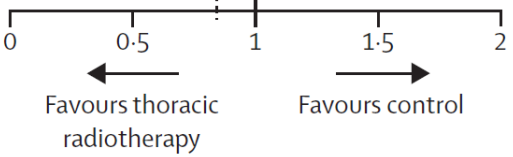
OS: subgroup analysis

	Thoracic radiotherapy	Control	Hazard ratio (CI)*	p value
	Events/patients	Events/patients		
Intrathoracic disease				0·35
Yes	175/213	195/215	0·80 (0·61–1·05)	
No	26/34	29/33	1·09 (0·54–2·18)	
Sex				0·06
Men	115/135	122/136	1·01 (0·72–1·41)	
Women	86/112	102/112	0·68 (0·46–1·00)	
Age (years)				0·58
36–70	152/193	170/189	0·82 (0·61–1·09)	
71–85	49/54	54/59	0·96 (0·58–1·60)	
Response to chemotherapy				0·58
CR	10/13	12/13	1·38 (0·45–4·22)	
PR	148/179	153/170	0·81 (0·60–1·10)	
Good response	43/55	59/65	0·76 (0·45–1·28)	
WHO performance status				1·00
0	74/97	65/70	0·85 (0·55–1·32)	
1	101/121	136/155	0·84 (0·60–1·18)	
2	26/29	23/23	0·83 (0·39–1·78)	
Extensive disease based on				0·86
Intrathoracic disease	11/19	9/15	0·68 (0·20–2·31)	
Distant metastases	161/190	172/188	0·87 (0·66 –1·16)	
Both	29/38	43/45	0·89 (0·48–1·65)	
Total	**201/247**	**224/248**	**0·84 (0·69–1·02)**	



no significant differences in overall survival in subgroups

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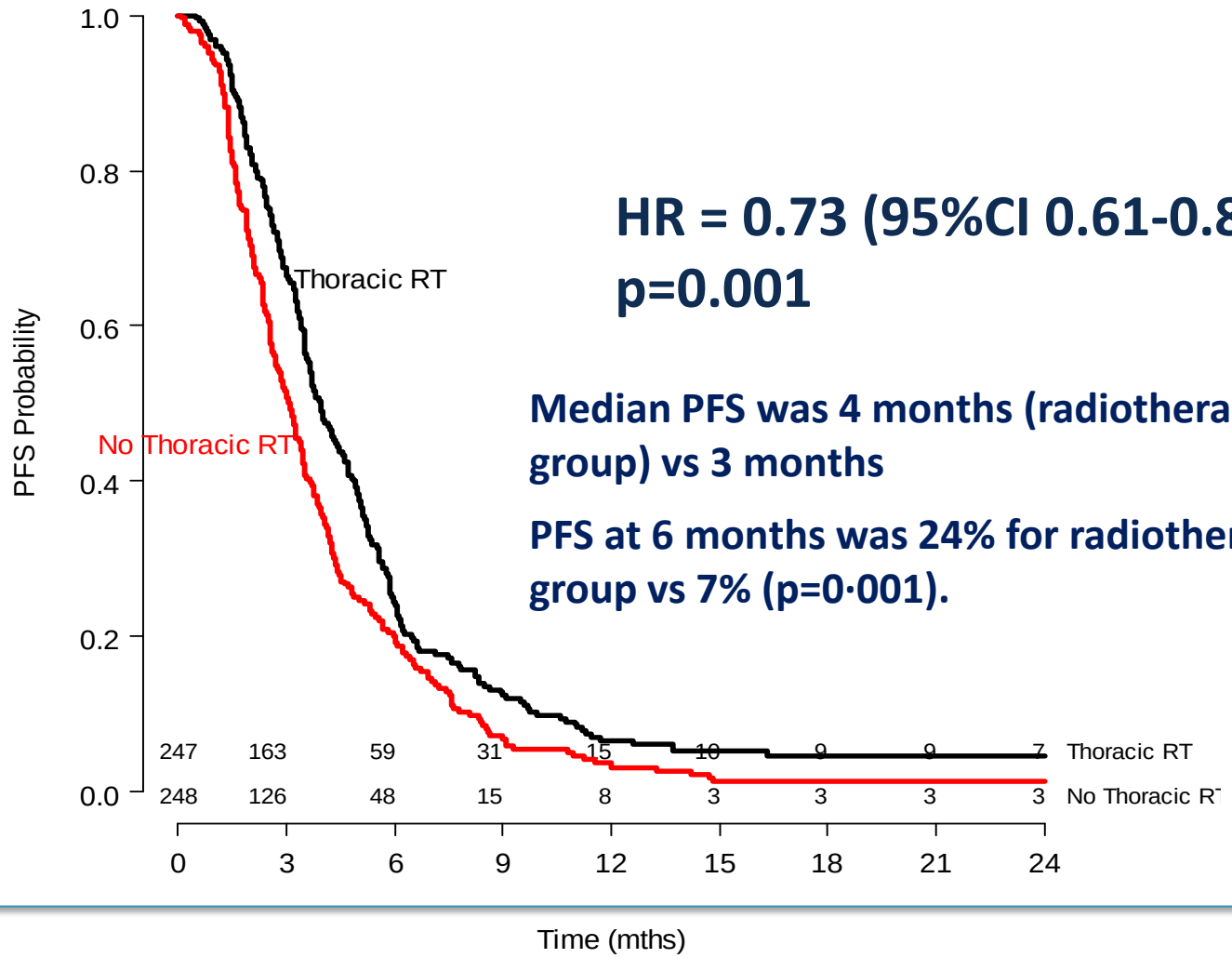
Progression-free survival

Progression was less likely in the thoracic radiotherapy group



HR = 0.73 (95%CI 0.61-0.87)
p=0.001

Median PFS was 4 months (radiotherapy group) vs 3 months

PFS at 6 months was 24% for radiotherapy group vs 7% (p=0·001).

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Progression free survival

Analysis of interaction of factors with treatment

Factor	Sign.
Sex	p=0.12
Age (in groups)	p=0.19
WHO performance score	p=0.94
Type of ES (distant, intrathoracic or both)	p=0.78
Response after chemotherapy	p=0.94
Presence of intrathoracic disease at randomization	p=0.11

No significant difference in the effect of thoracic radiotherapy on PFS

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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.

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Recurrences

	Thoracic radiotherapy group (n=247)	Control group (n=248)
Any site	213 (86·2%)	223 (89·9%)
Thorax only	49 (19·8%)	114 (46·0%)
Thorax and brain	5 (2·0%)	3 (1·2%)
Thorax and other sites	50 (20·2%)	77 (31·0%)
Thorax, brain, and other sites	4 (1·6%)	4 (1·6%)
Brain only	10 (4·0%)	6 (2·4%)
Brain and other sites	5 (2·0%)	0 (0·0%)
Other sites only	90 (36·4%)	19 (7·6%)

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

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Should thoracic radiotherapy be considered for all patients with ES-SCLC who have responded to chemotherapy ?

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What the study has shown

- Results show that thoracic radiotherapy improves long-term survival (benefit at 18 and 24 months)

- **Trial's primary aim** was to detect a difference in survival of 10% at 12 months, which the study did not do (HR 0.84, 95% CI 0.69–1.01)
- **Benefit in PFS** HR = 0.73 (p=0.001)
- Greater % of extrathoracic evolution in Thoracic arm

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*Jan P van Meerbeeck, David Ball, lancet 2014

To be discussed….

- Should we consider thoracic radiotherapy in all responders with extensive disease ?
- Non-curative setting (benefit /toxicities, QoL…)
- Information about patient-related outcomes would have helped
- Only for selected patients ?
  - For example, would thoracic radiotherapy be appropriate in a responder who still has large volume liver metastases, adrenal metastases and minimal intrathoracic disease burden?
  - “Debulking” chemo-resistance disease

*Jan P van Meerbeeck, David Ball, lancet 2014

To be discussed…

- Should we bring forward thoracic radiotherapy and administer it at an accelerated schedule and during chemotherapy?
- Benefit of addition of radiotherapy to sites of extrathoracic disease ?
  - Phase II (RTOG), prophylactic cranial irradiation and thoracic radiotherapy are combined with radiotherapy to up to four extrathoracic metastases
- Combination of molecular targeted with radiotherapy ?
- Combination of immunotherapy with RT ?

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RTOG 0937 Protocol
Randomized Phase II Study Comparing Prophylactic Cranial Irradiation Alone To Prophylactic Cranial Irradiation And Consolidative Extra-Cranial Irradiation For Extensive Disease Small Cell Lung Cancer (ED-SCLC)

- **Primary Objective**: 1-year overall median survival rate
- **Extensive disease small cell lung cancer**, excluding CNS metastases

- Radiographic evidence of 1-4 extra-cranial metastatic lesions prior to platinum-based chemotherapy AND have had radiographic partial or complete response to chemotherapy in a minimum of one site of disease and no progression in any site.

- 45 Gy in 15 fractions or 40 Gy in 10 fractions
- **Target Accrual: 154**
- **Status: Open to Accrual**

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Thoracic irradiation for ED-SCLC

- Await results from the RTOG trial
- Not currently a standard but a strong option to discuss case by case
- Would be more comfortable to irradiate patient in good PS:
  - either with symptomatic thoracic lesion: centrally located primary tumours, symptoms such as dyspnoea, infections due to atelectasis, chest pain or superior vena cava syndrome
  - and/or low volume (or control) of extra-thoracic metastases ?
- ESMO recommendations 2013 (II, C): pending CREST study

Presented by David. Planchard (Gustave Roussy)

*Jan P van Meerbeeck, David Ball, lancet 2014

TAKE HOME MESSAGE

- Treatment of stage IV SCLC is palliative
- **Etoposide–cisplatin (4–6 cycles)** is the standard treatment regimen
- **Radiotherapy should be preferred as palliative** treatment in case of symptoms such as dyspnea due to atelectasis, pain due to born metastases, neurologic trouble due to BM, superior vena cava syndrome…
- Patients with any response to first-line treatment and who have a reasonably **good PS should be evaluated for PCI and TR**

Presented by David. Planchard (Gustave Roussy)

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