Plaats van de Radiotherapie bij Kleincellig Longcarcinoma (SCLC)

TOGA symposium

17/10/2014

Frederik Vandaele

znа
wij zorgen voor u

Inleiding

SCLC= Systemische ziekte

Chemotherapie = hoeksteen

Radiotherapie heeft ook plaats

Inleiding

1. RT thoracaal voor Limited Stage (LD)

2. RT thoracaal voor Extensive Stage (ED)

3. PCI (voor LD en ED)

1. Thoracale RT voor LD

RT thoracaal benefit LD

2 meta analyses

Pignon *et al*, 1992

- 13 trials (2103 pt)
- CT vs CT-RT
- +RT:+ 5.4% in 3y S
- vnl bij jongere pt

Warde *et al*, 1992

- 11 trials
- CT vs CT-RT
- +RT: + 5.4% in 2y S
- +RT: + 25% in LC

RT thoracaal benefit LD

2 meta analyses

Pignon *et al,* 1992

- 13 trials (2103 pt)
- CT vs CT-RT

- +RT:+ 5.4% in 3y S
- vnl bij jongere pt

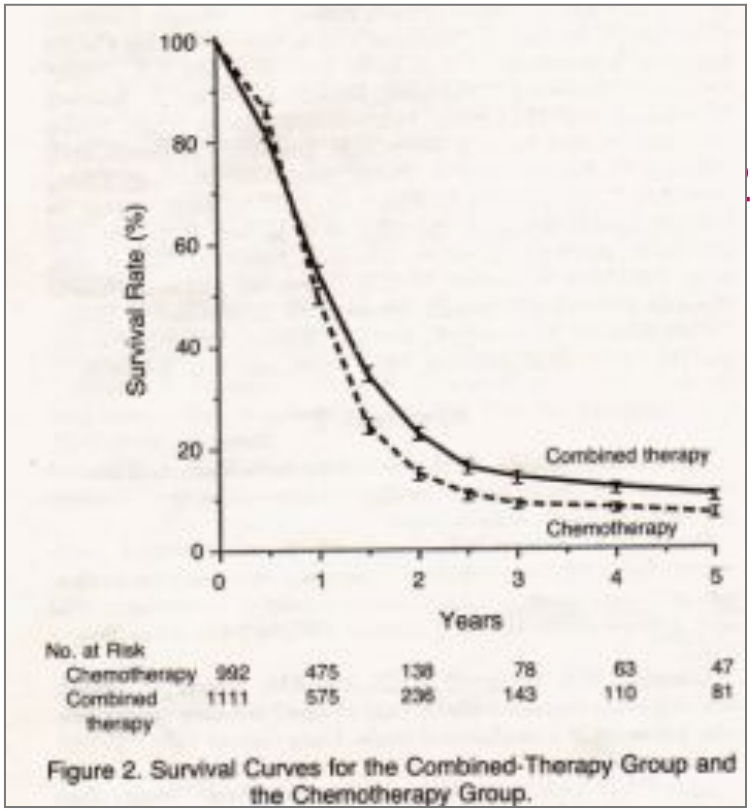


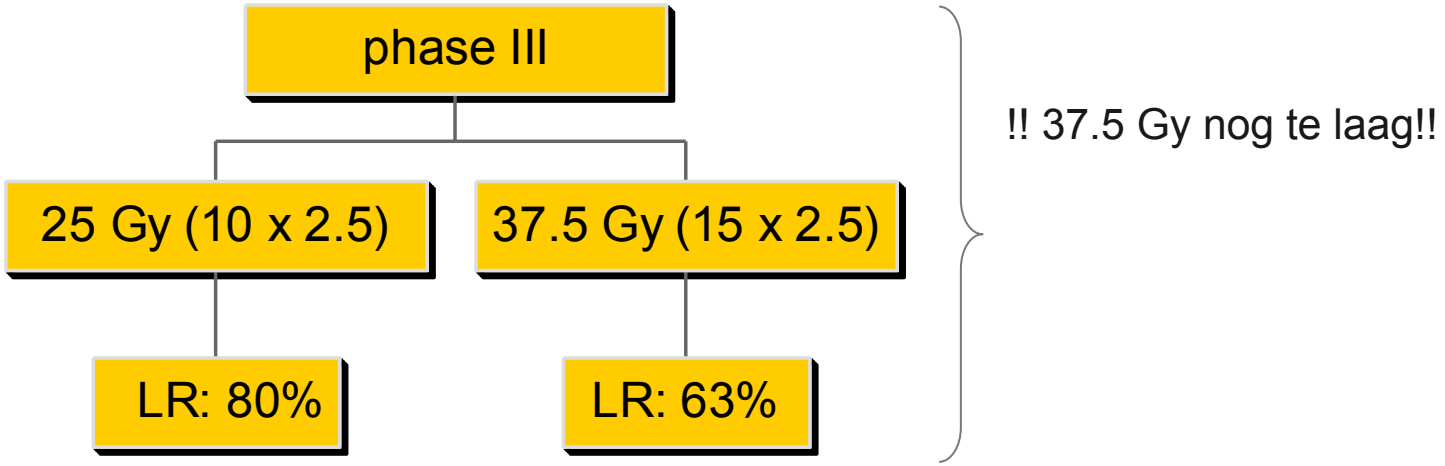
Figure 2. Survival Curves for the Combined-Therapy Group and the Chemotherapy Group.

RT thoracaal LD

- Dosis:
- Fractionatie:
- Timing:
- Volume:

Dosis

- Coy *et al,* 1988:



Dosis

Totale dosis verhogen:

- Choi et al, 1989 en Turrisi, 1989:
  - grote toename in LC van 35 naar 40 Gy
  - matige verdere toename in LC naar 50 Gy
- Arriagada et al, 1992:
  - geen betere LC bij dosissen >60 Gy
- Phase I Choi: MTD 70 Gy (1x/d) of 45 Gy (2x/d)
- Bogart CALGB : 70 Gy is mogelijk

Fractionnering

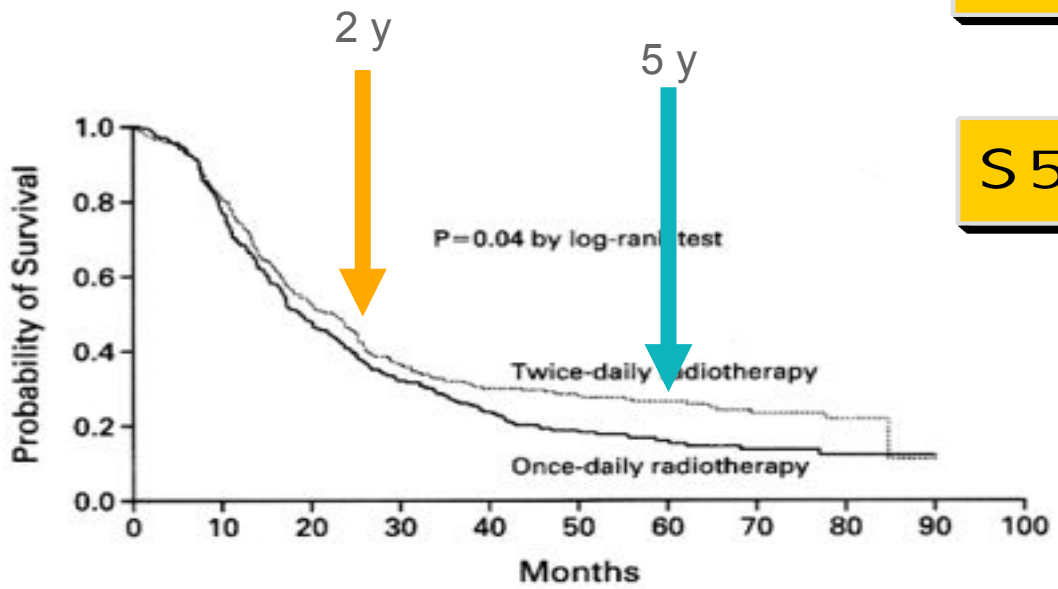
geaccelereerde hyperfractionatie:

SCLC: zeer korte verdubbelingstijd, repopulatie

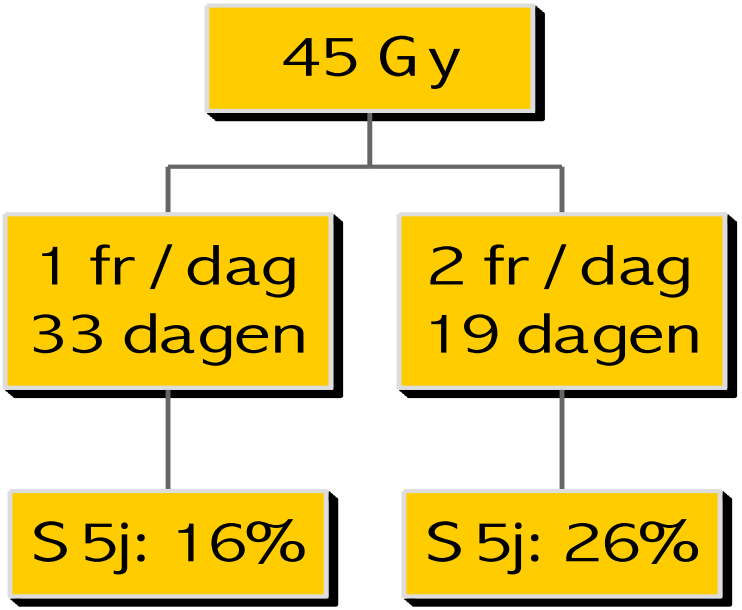
- B.i.D Turrisi & Bonner phase III studies
- B.i.D op einde van RT : RTOG Komaki 61.2 Gy in 5 wk

Fractionnering

<u>Turrisi *et al*, 1999</u>:



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



Fractionering: Turrisi

2x/d meer effectief dan 1x/d

- +: 10% toename OS op 5 jaar
- - : 15% toename graad III oesofagitis

kritiek:

- 1x/d slechts tot 45 Gy
- logistieke problemen
- ¼ doet hyperfractionatie

Complication and No. of Radiation Treatments per Day	Grade						P Value
	0	1	2	3	4	5	
	number (percent) of patients						
Overall†							0.80
1	1 (0.5)	3 (1)	20 (10)	47 (23)	127 (63)	5 (2)	
2	2 (1)	0	19 (9)	51 (25)	128 (62)	6 (3)	
Myelotoxicity‡							0.70
1	2 (1)	9 (4)	19 (9)	43 (21)	129 (64)	1 (0.5)	
2	7 (3)	2 (1)	18 (9)	52 (25)	127 (62)	0	
Esophagitis							<0.001
1	113 (56)	19 (9)	38 (19)	22 (11)	11 (5)	0	
2	76 (37)	26 (13)	37 (18)	56 (27)	11 (5)	0	
Other toxic effects							0.20
1	4 (2)	18 (9)	119 (59)	46 (23)	12 (6)	4 (2)	
2	2 (1)	13 (6)	119 (58)	53 (26)	13 (6)	6 (3)	

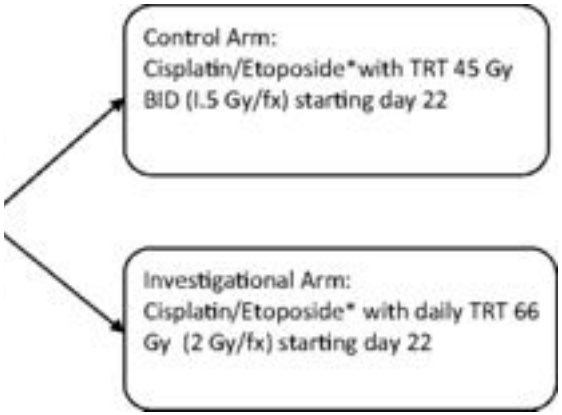
*Data were available for 203 patients receiving once-daily radiotherapy and 206 patients receiving twice-daily therapy.

†Overall rates are based on the grade of the most severe complication of any type that occurred in each patient.

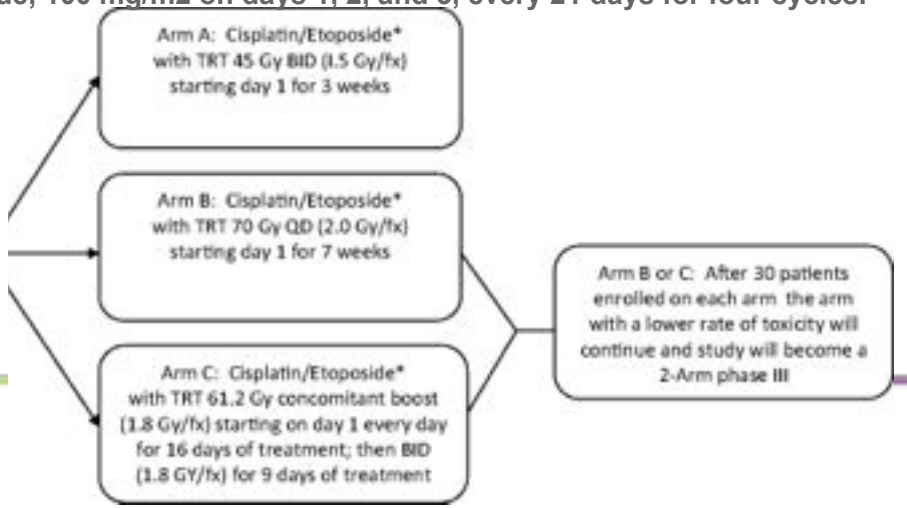
‡Myelotoxicity was defined as any decrease in marrow-derived cells in the peripheral-blood counts.[10]

2 lopende studies ivm dosis:

CONVERT:
Phase III trial of TRT in patients with limited-stage small cell lung cancer receiving cisplatin and etoposide.
All patients receive cisplatin, 25 mg/m2 on days 1–3 or 75 mg/m2 on day 1, and etoposide, 100 mg/m2 on days 1–3 for four to six cycles.



CALGB 30610/RTOG 0538:
Phase III trial of TRT regimens in patients with limited-stage small cell lung cancer receiving cisplatin and etoposide.
All patients will receive cisplatin, 80 mg/m2 on day 1 and etoposide, 100 mg/m2 on days 1, 2, and 3, every 21 days for four cycles.



Timing

- Concomitant beter dan sequentieel:
  - Gregor, J Clin Oncol. 1997
  - Takada, J Clin Oncol. 2002

- Early vs late:
  - Verschillende fase III studies/meta- analyses
    - Murray, J Clin Oncol. 1993;11(2):336.
    - Fried, J Clin Oncol. 2004;22:4837-4845
    - Pijls-Johannesma, Cancer Treat Rev. 2007;33:461-473.

Timing: early vs late

De Cochrane meta-analyse en systematische review 2005:

RT binnen de 30 dagen na de start chemotherapie leidt tot een hogere 5-jaars overleving (20,2% versus 13,8%).

D. De Ruysscher *et al*: SER Concept:

Interval 'Start of Any Treatment and End of Radiotherapy'

moet zo kort mogelijk zijn (repopulatie)

→ best vroeg starten met RT (cyclus 1 of 2)

op voorwaarde dat chemo volledig kan gegeven worden!

Volume: 'elective node irradiation'

- NSCLC: neen
- SCLC: geen duidelijke data

<u>isolated nodal relaps</u>

- enkel CT-scan (pre PET)
  - Baas P et al. (J Cancer 2006;94:625–630): **5%**
  - De Ruysscher D et al. (Oncol 2006;80:307–312): **11%**
- PET tijdperk: **3%**
  - Van Loon J et al. (Int J Radiat Oncol Biol Phys 2010;77:329–336)

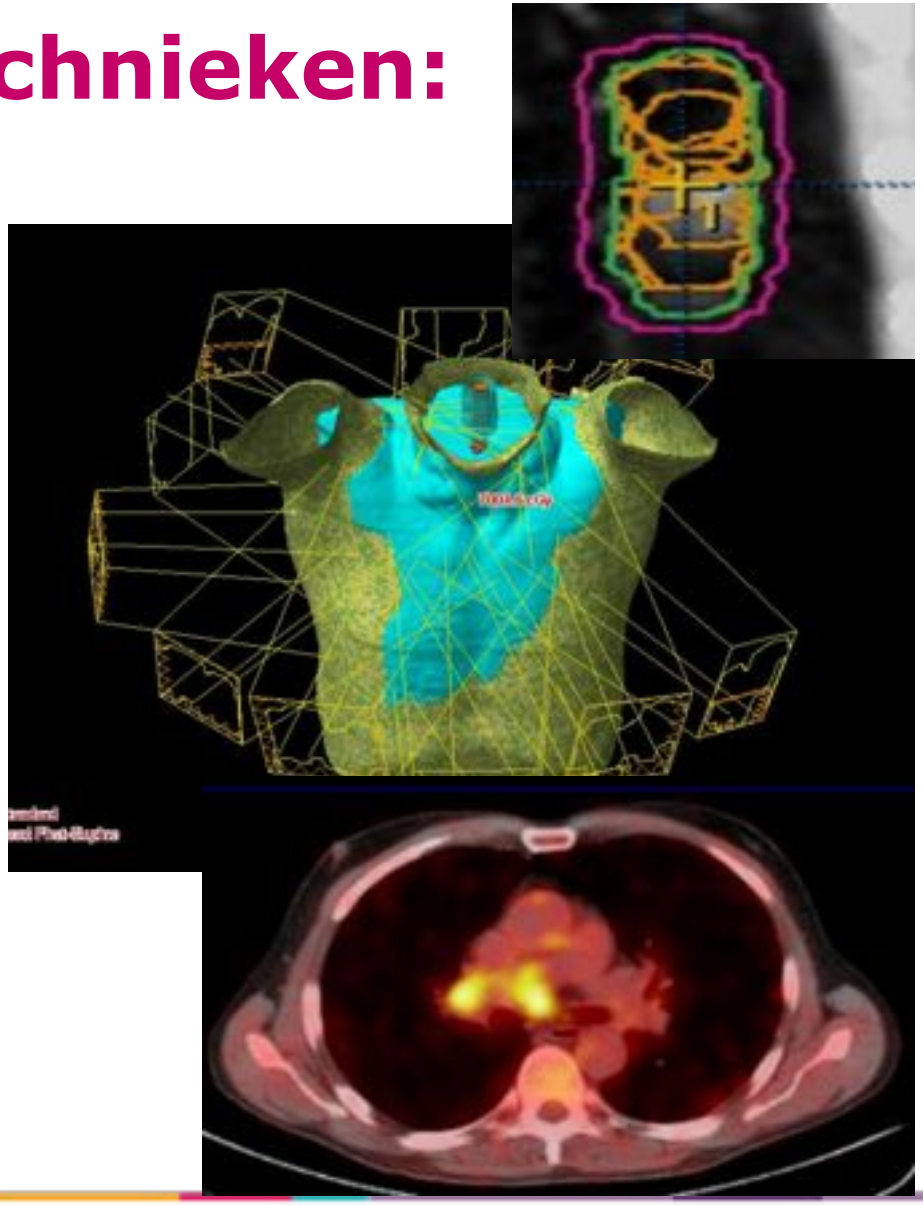
➡ **RT aangetaste klieren (pet+) prechemo, aangepast aan postchemo status**

Conclusies: RT thoracaal LD

- Chemoradiotherapie: = beste (met Cisplatinum-Etoposide)
- Dosis: 60-70 Gy 1x/d (#2Gy)
- Fractionatie: 45 Gy 2x/d over 3 weken
- Timing : concomitant of vroeg,
  liefst geen onderbrekingen + volledige chemo
- Volume: geen 'elective nodal irradiation' indien PET

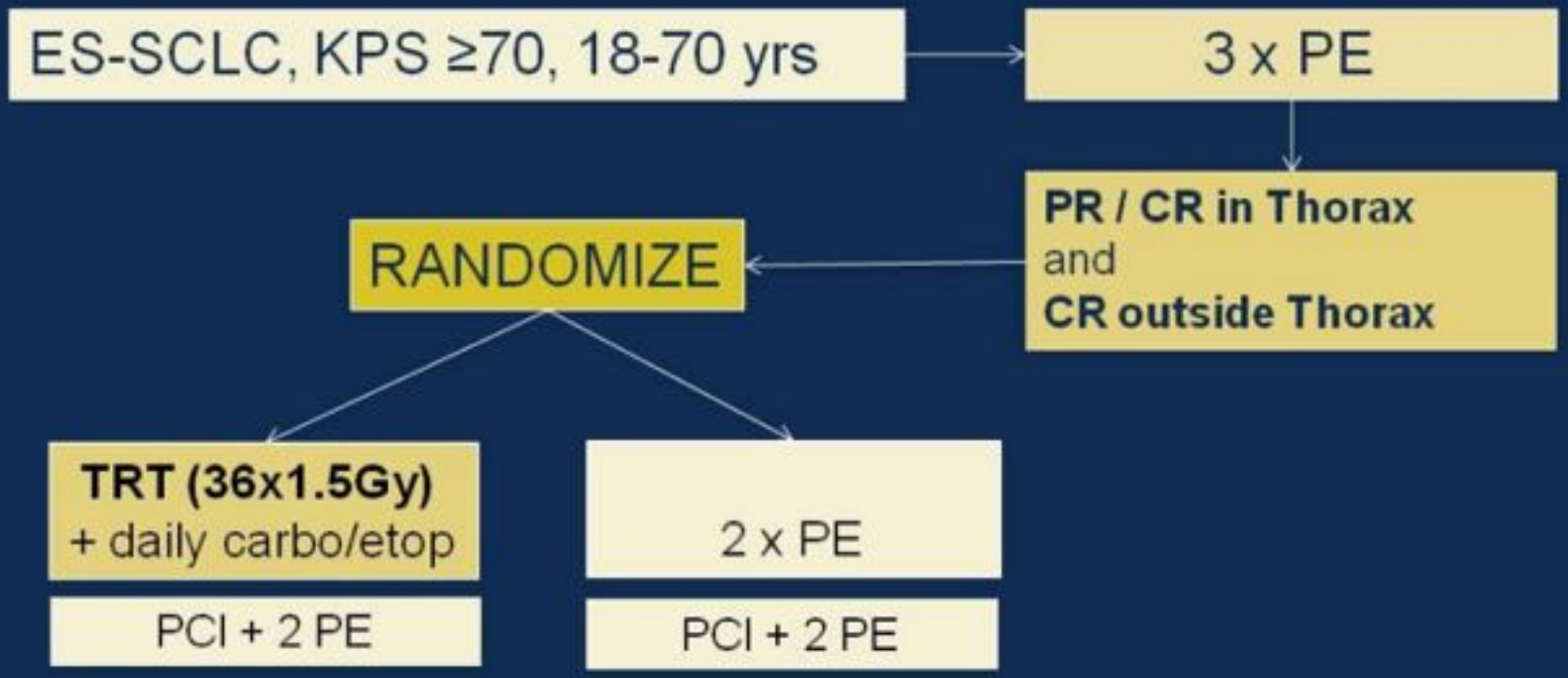
Geavanceerde technieken:

- 4D scan (ademhaling)
- betere staging/beeldvorming
- PET fusie
- IMRT
- rotationele IMRT
- image guided RT (IGRT)
- betere planningssystemen



RT thoracaal voor ED

TRT in ES-SCLC



17 months **11 months**

Jeremic et al., JCO 1999

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Randomized Trial on Thoracic Radiotherapy (TRT) in Extensive Stage SCLC

Ben J. Slotman,

Corinne Faiv ren, John Praag,
Joost Knegj Matthew Hatton,
enan

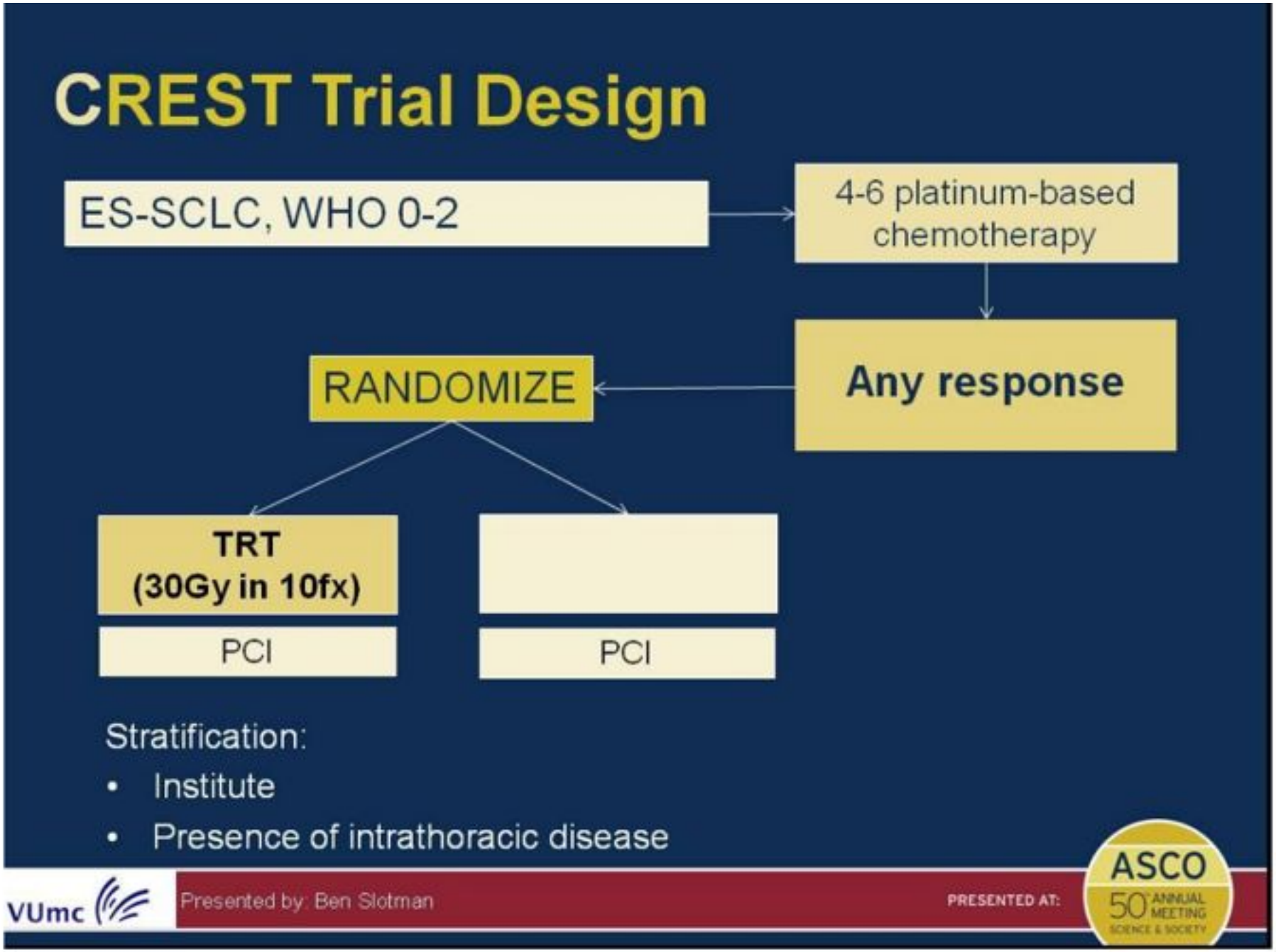
Chest
Radiotherapy
Extensive
Stage
Trial

PCI in ES-SCLC

	PCI	Control	p-value
Symptomatic brain metastases @ 1yr	14.6%	40.4%	p<0.001
Overall survival @ 1 yr	27.1%	13.3%	p=0.003

Persistent intrathoracic disease in 76% of patients and intrathoracic progression in 89% of patients

Slotman et al., NEJM 2007



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Endpoints & Objectives

Study endpoints:

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

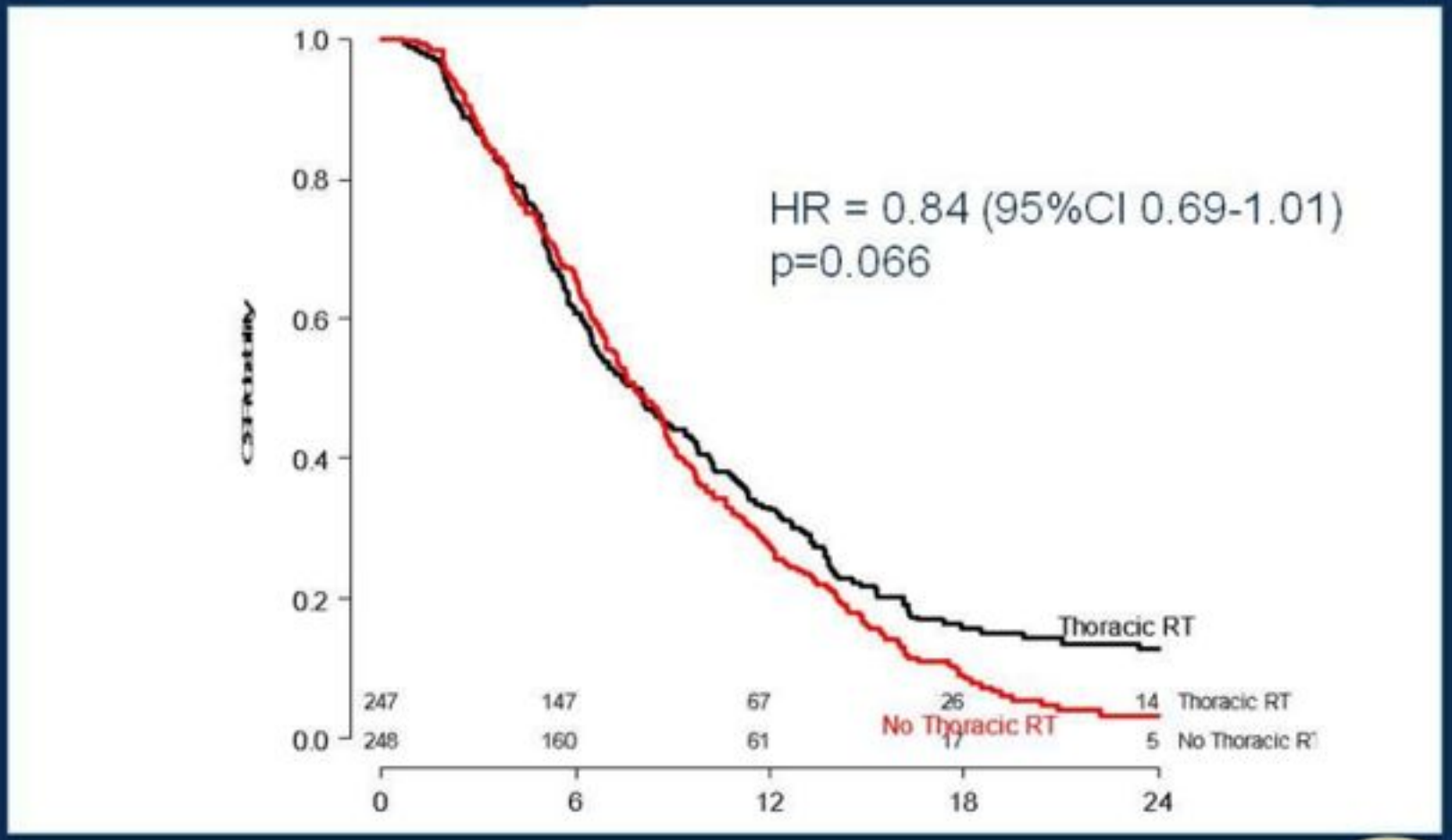
Study objectives:

- 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

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)

Overall survival



VUmc

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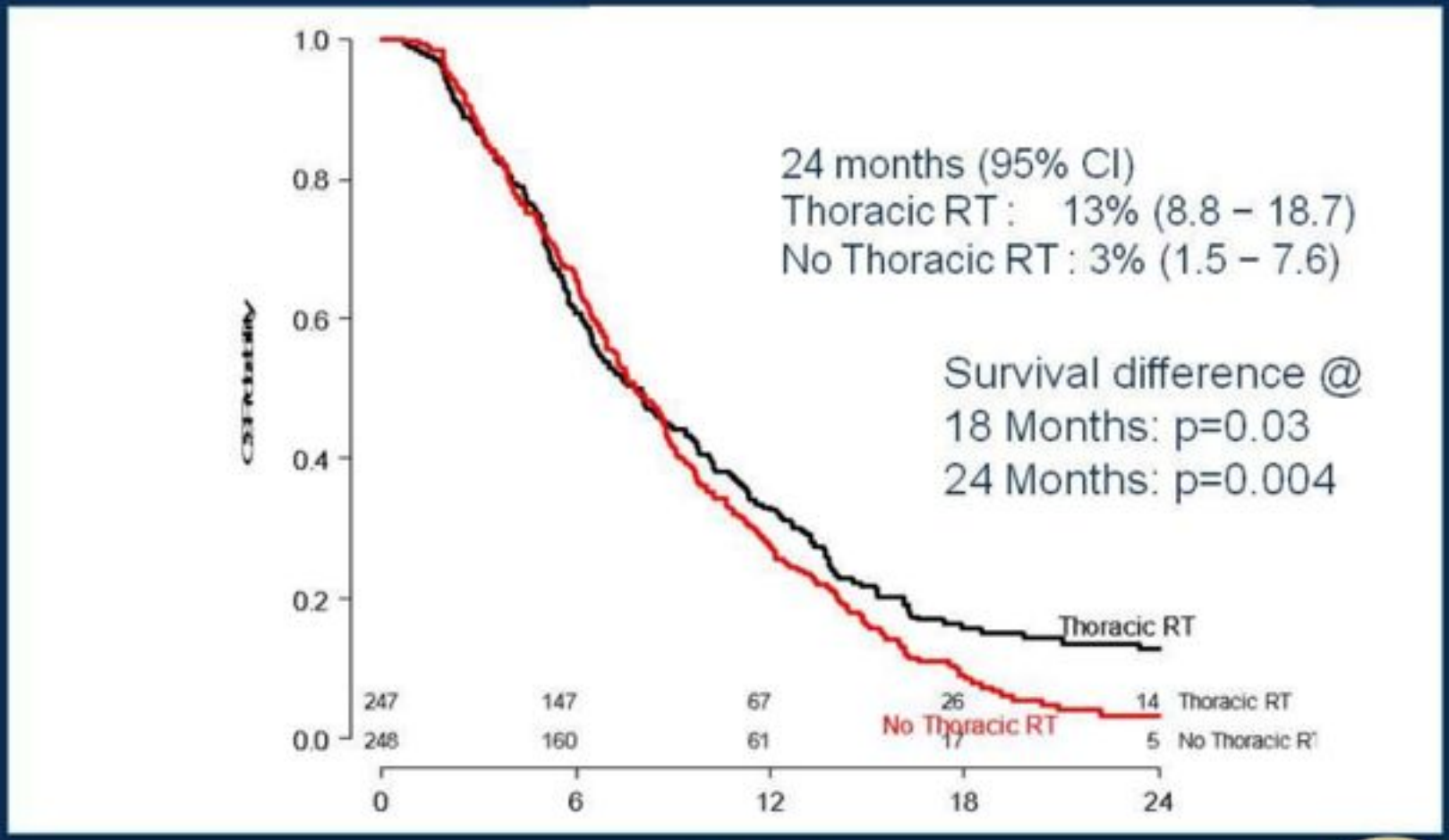
Overall survival



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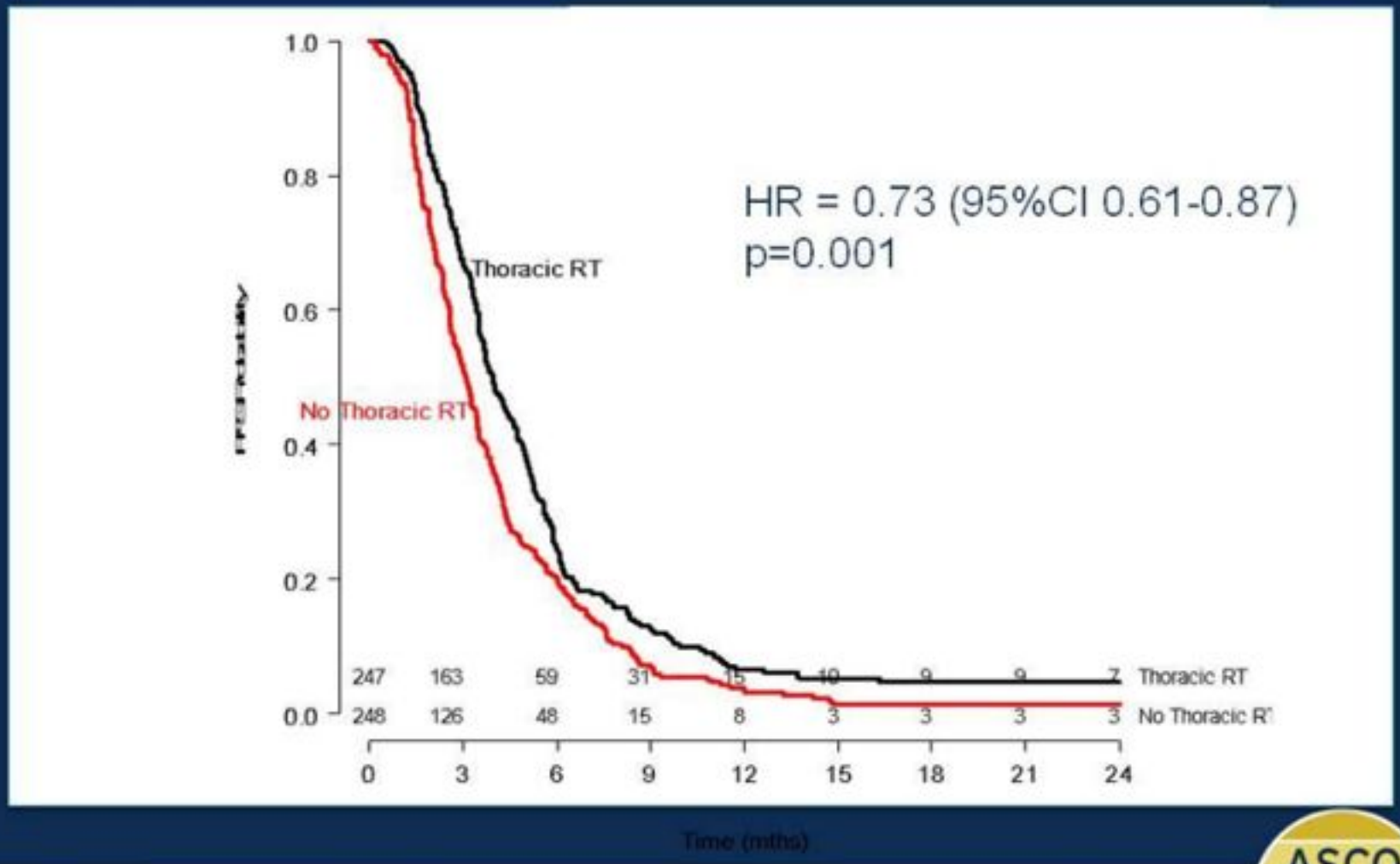
Progression-free survival



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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.

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

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Conclusions

Thoracic radiotherapy (30 Gy in 10 fx) in ES-SCLC

- Improves overall survival
- Improves progression-free survival
- Improves intrathoracic control

Thoracic radiotherapy should be offered in addition to PCI to all ES-SCLC patients responding to initial chemotherapy

PCI

Prophylactic Cranial Irradiation

PCI

- Bij diagnose : 20% hersenM+
- Na CR binnen 2j FUP: 50% hersenM+
- Postmortem: 80% hersenM+
- chemo werkt niet preventief

PCI bij LD

2 meta-analyses:

Aupérin et al. NEJM 1999;

7 RCT en 987 pten

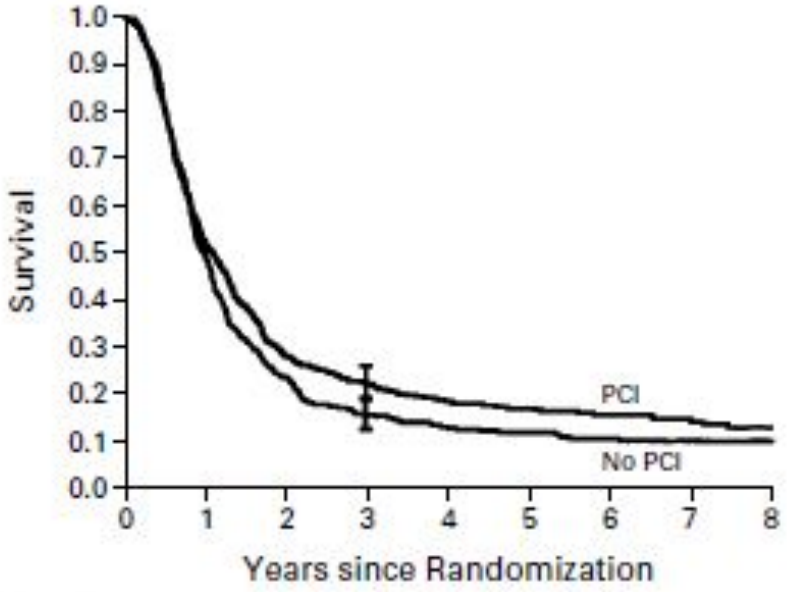
Meert et al. BMC Cancer 2001; 1:5

12 RCT en 1547 pten

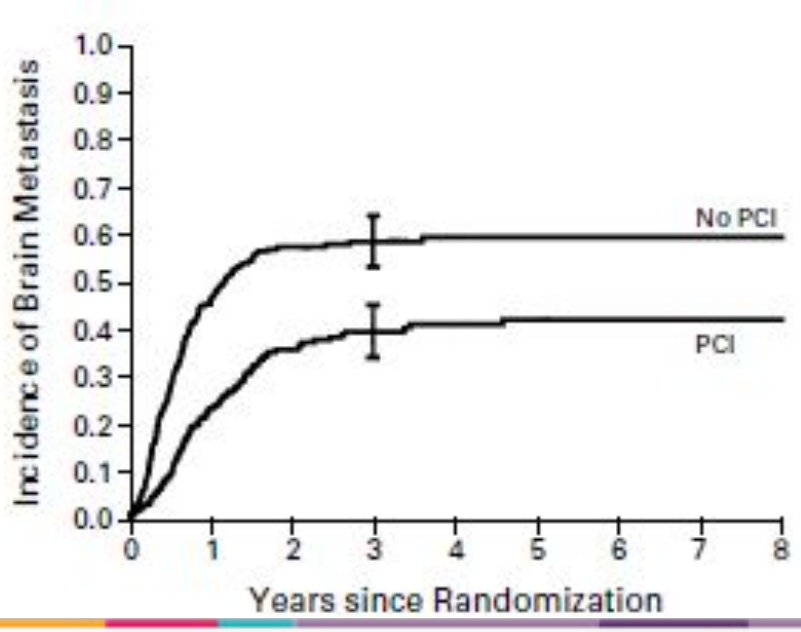
PCI bij LD Aupérin et al. NEJM 1999; 341:476-484

- Meta-analyse 7 studies (PCI+ / PCI-)
- 987 pten in CR op RX thorax

betere overleving



minder hersenmetas

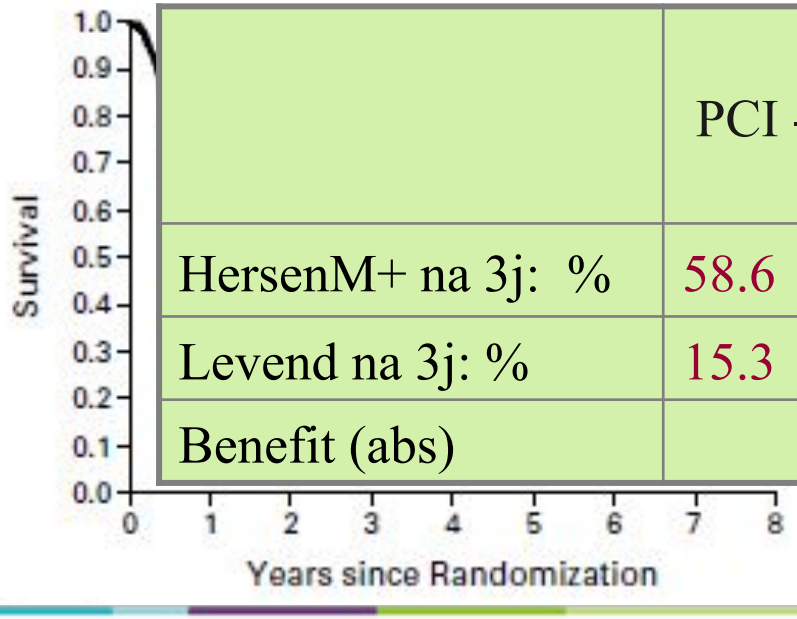


PCI bij LD Aupérin et al. NEJM 1999; 341:476-484

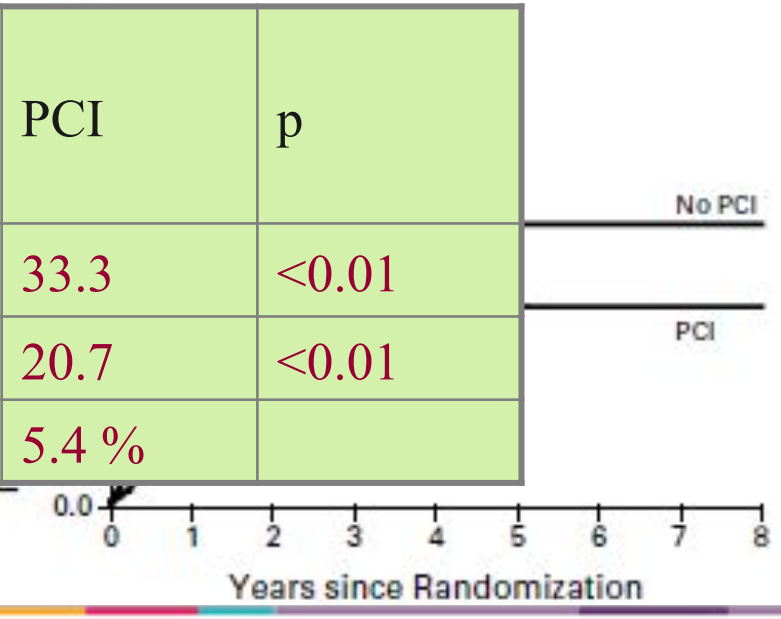
- Meta-analyse 7 studies (PCI+ / PCI-)
- 987 pten in CR op RX thorax

betere overleving

	PCI -	PCI	p
HersenM+ na 3j: %	58.6	33.3	<0.01
Levend na 3j: %	15.3	20.7	<0.01
Benefit (abs)		5.4 %	



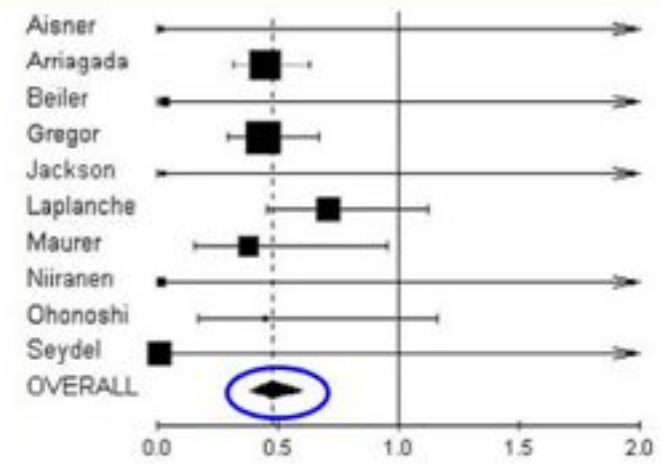
minder hersenmetas



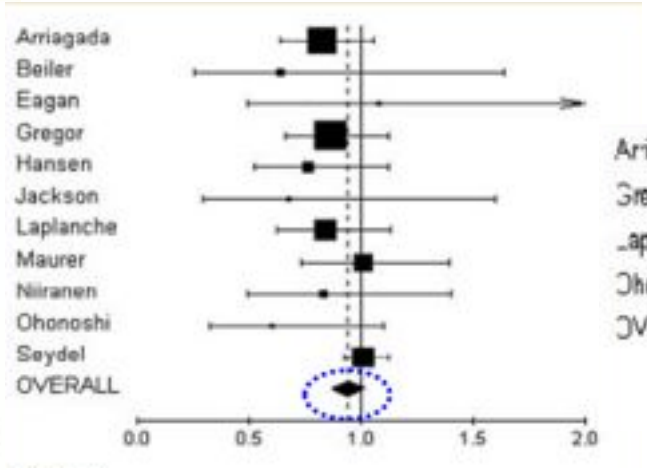
PCI bij LD Meert et al. 2001

Prophylactic cranial irradiation in small cell lung cancer: a systematic review of the literature with meta-analysis

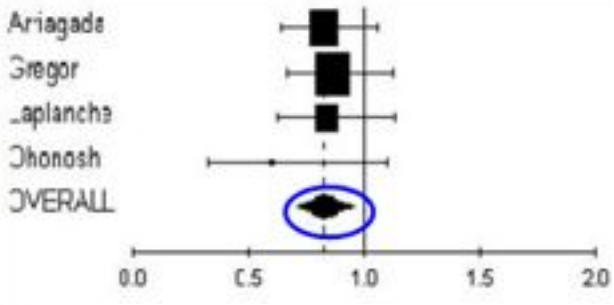
Anne-Pascale Meert[1], Marianne Paesmans[1], Thierry Berghmans[1], Benoît Martin[1], Céline Mascaux[1], Frédéric Vallot[1], Jean-Marc Verdebout[3], Jean-Jacques Lafitte[2] and Jean-Paul Sculier*[1]



effect op hersenherval



effect op OS alle pten



effect op OS pten in CR

Timing PCI

- Geen gerandomiseerde studies
- ASCO, 1999, Gregor

  Zo vroeg mogelijk NA CT : PCI <4 weken beter dan late PCI (p<0.01))

  GEEN concomitante CT! neurotoxiciteit

  > 6m na diagnose: ↓ effectiviteit

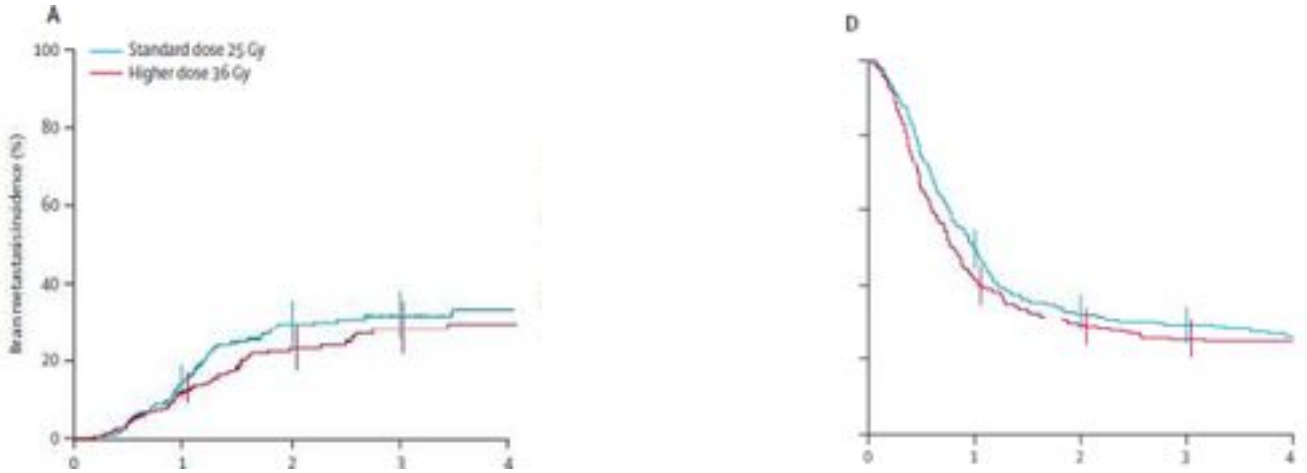
→ PCI aan het einde van de CT, 3-5 maanden na diagnose

Dosis PCI: Le Péchoux et al. Lancet Oncol 2009

Standard-dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic radiotherapy (PCI 99-01, EORTC 22003-08004, RTOG 0212, and IFCT 99-01): a randomised clinical trial

*Cécile Le Péchoux, Ariane Dunant, Suresh Senan, Aaron Wolfson, Elisabeth Quoix, Corinne Faivre-Finn, Tudor Ciuleanu, Rodrigo Arriagada, Richard Jones, Klaus Wanders, Delphine Lerouge, Agnès Laplanche, on behalf of the Prophylactic Cranial Irradiation (PCI) Collaborative Group**

- 720 pten
- standaard dosis (25 Gy in 10#) vs. hoge dosis (36 Gy in 18 or 24#)
- lage dosis niet meer hersenmetastasen
- hoge dosis meer mortaliteit (NS)

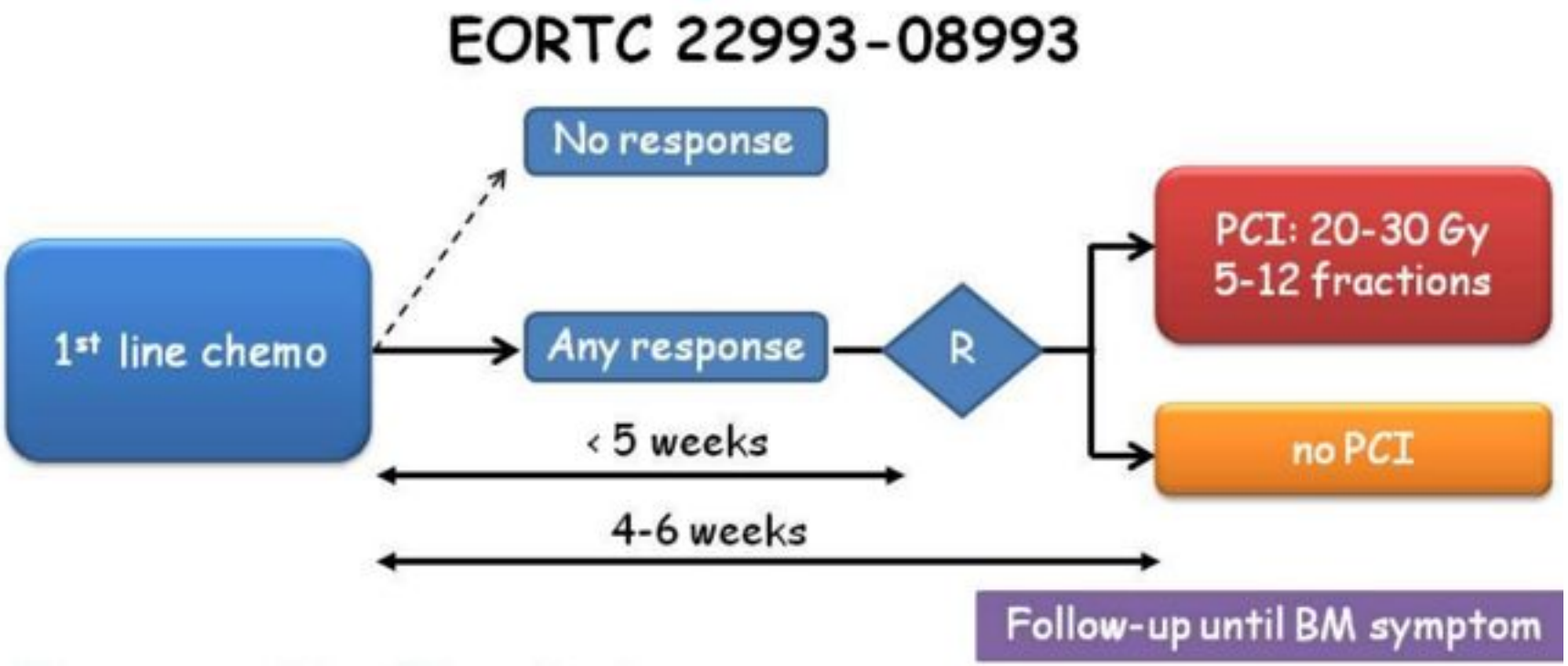


10 x 2,5 Gy= 25 Gy is de standaard

PCI: ED SCLC

Slotman et al. NEJM 2007;357:664-72

EORTC fase III studie (286 pten)



PCI: ED SCLC

Slotman et al. NEJM 2007;357:664-72

- minder hersenmetas na 1 j (15 vs 40%)
- betere overleving na 1 j (27 vs 13%)

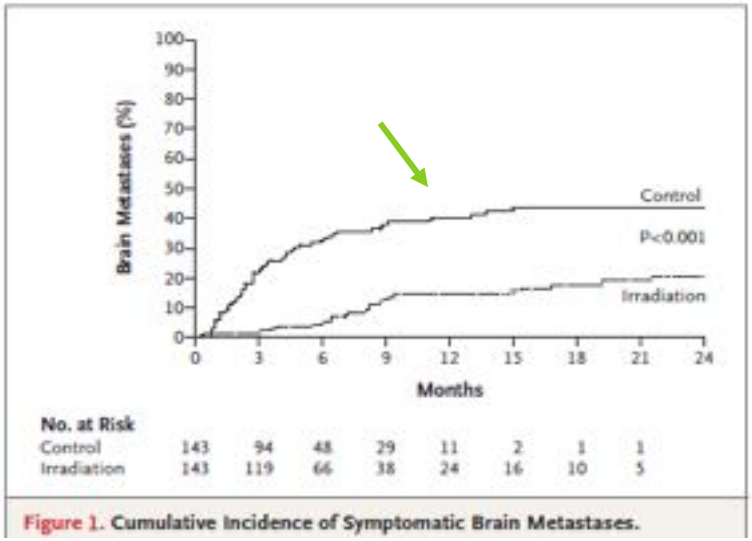


Figure 1. Cumulative Incidence of Symptomatic Brain Metastases.

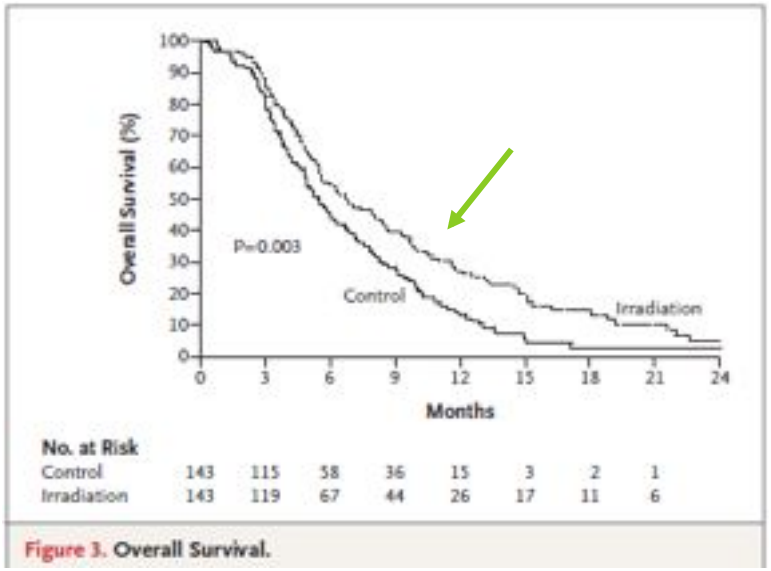


Figure 3. Overall Survival.

ASCO 50 1964-2014
ASCO American Society of Clinical Oncology
Making a world of difference in cancer care

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

UMIN ID; 000001755

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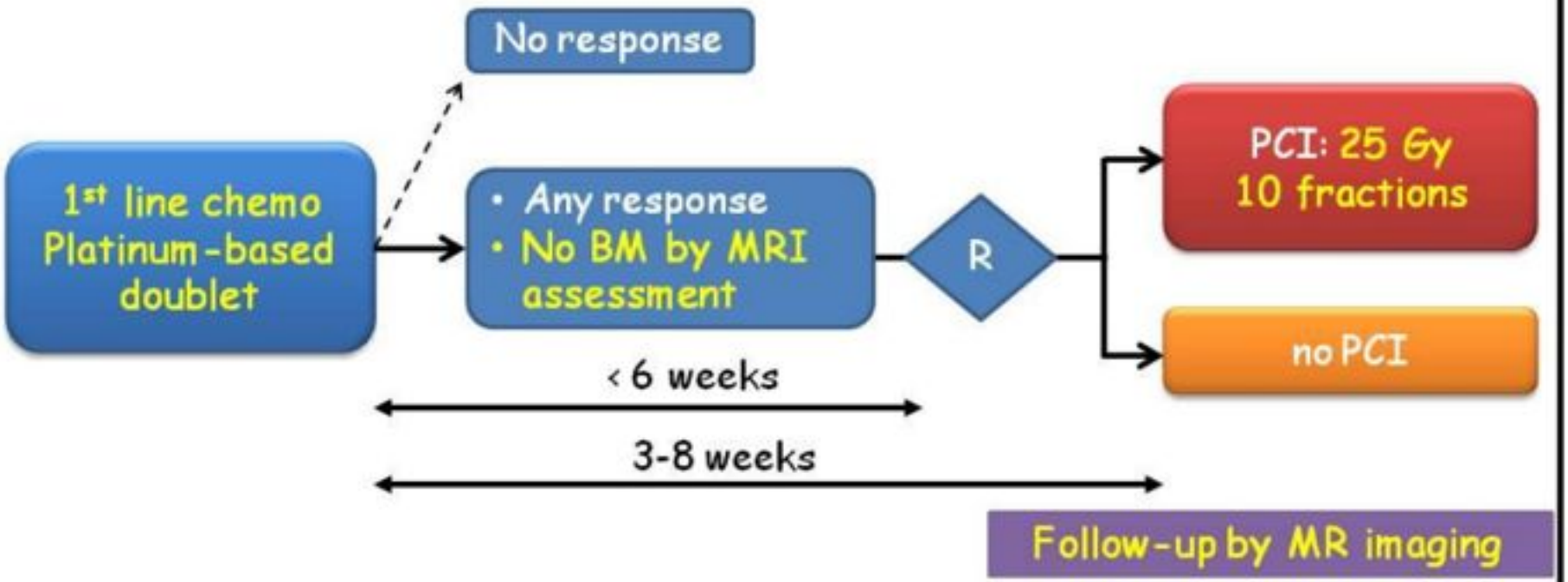
Design of this study

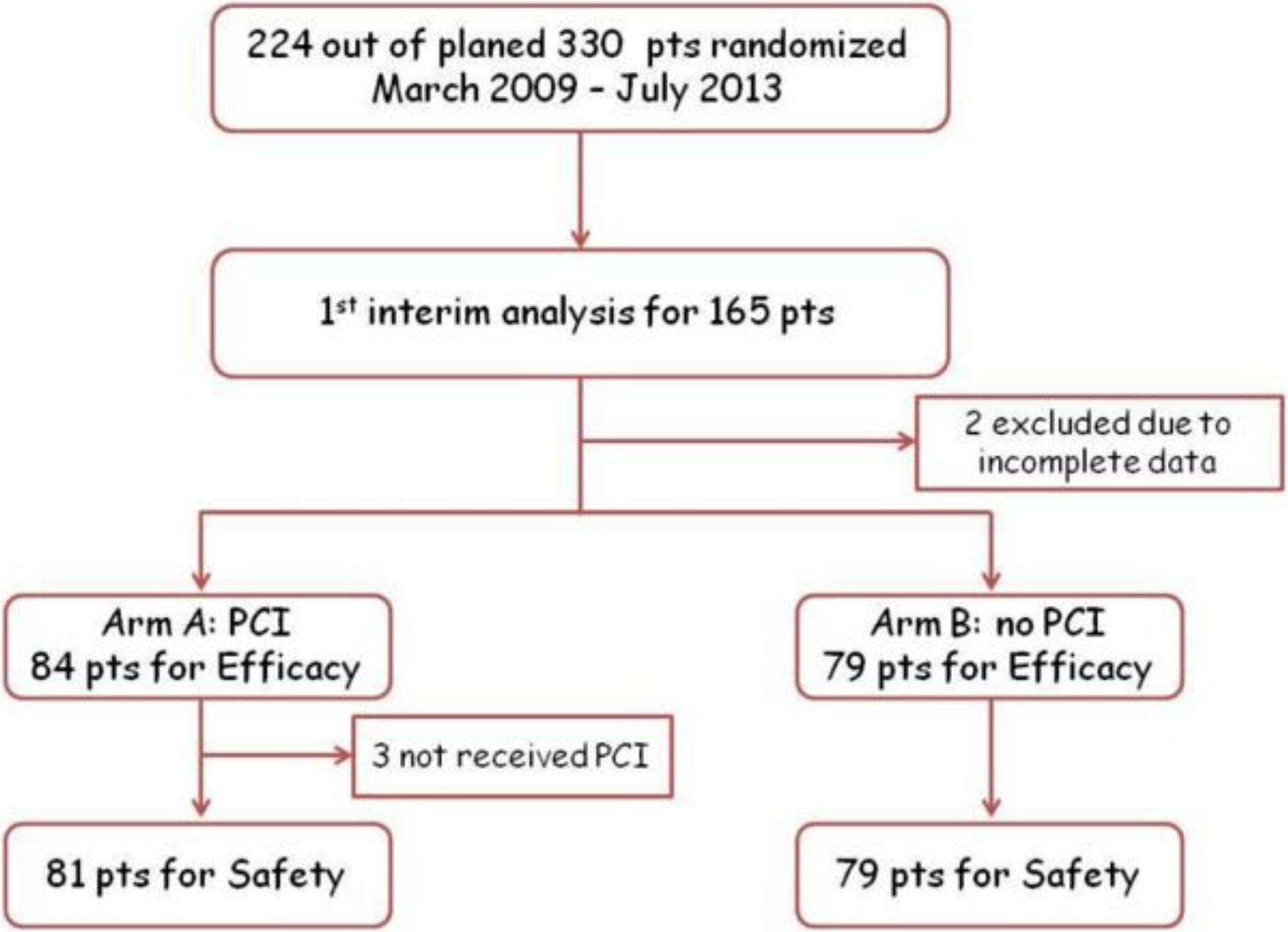


Stratification by Age (70≦ / <70), PS (0-1 / 2), Response (CR / PR+MR), Institutions

Primary endpoint: Overall Survival

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

Study Flow



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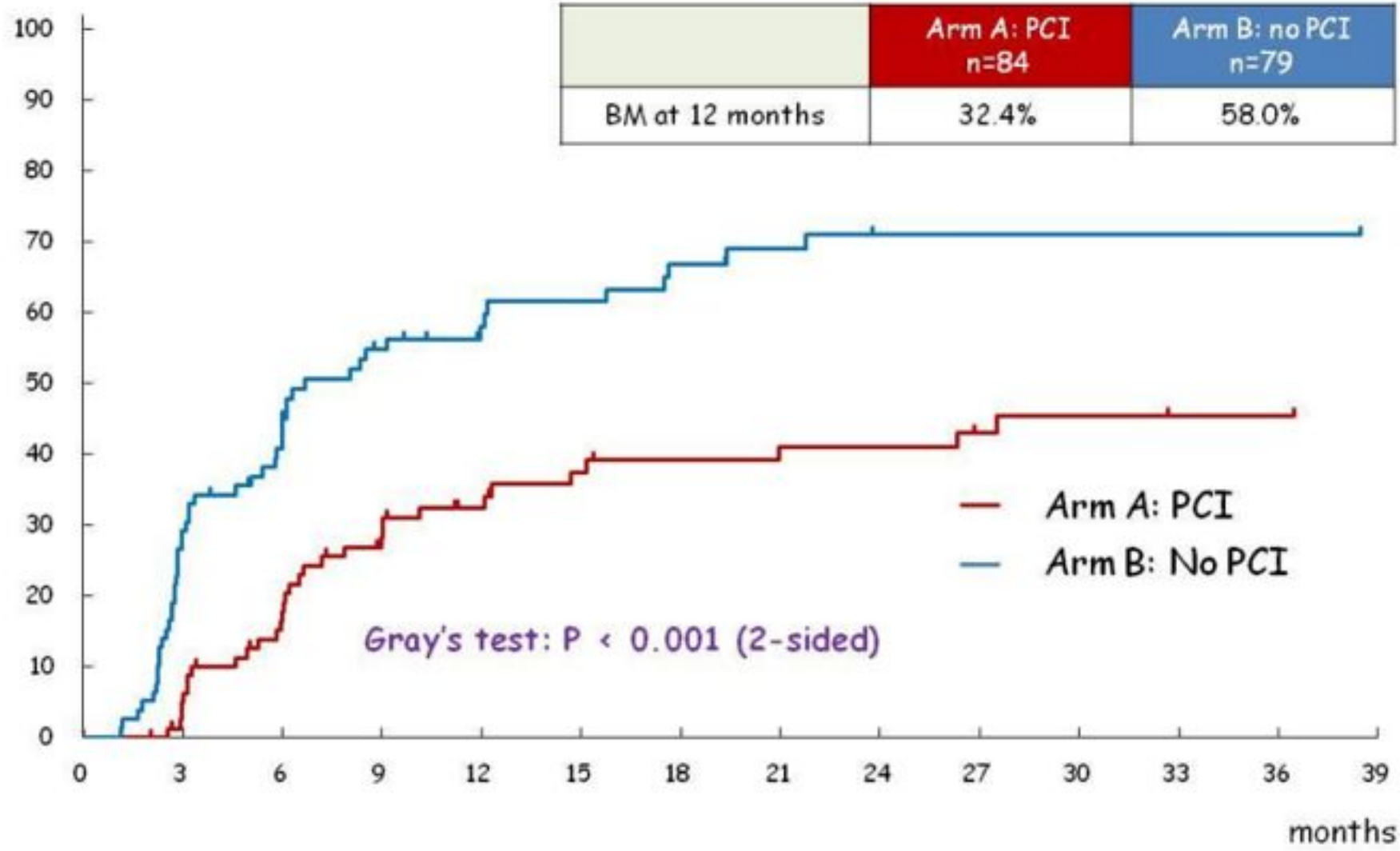
Time to Brain Metastasis

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



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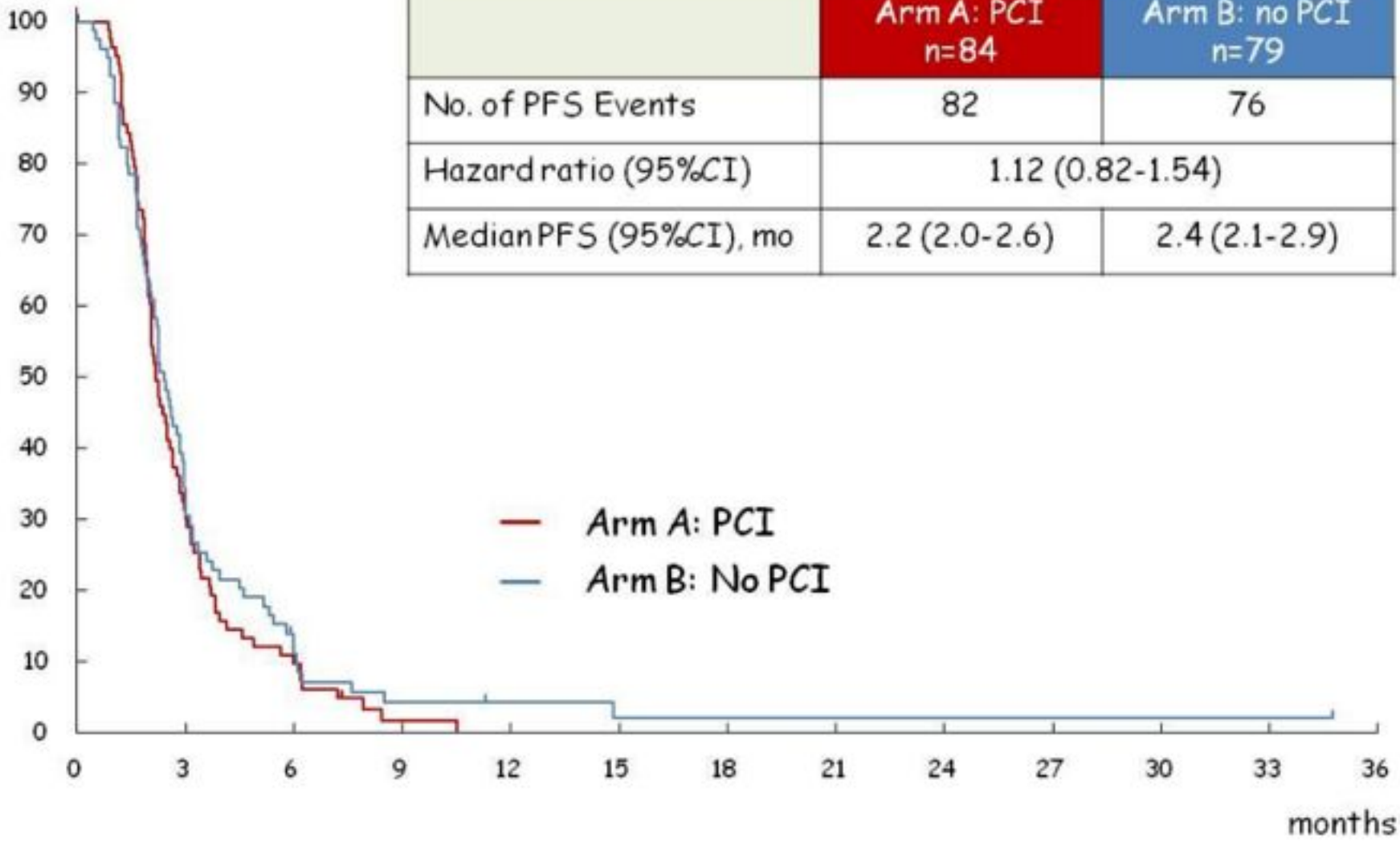
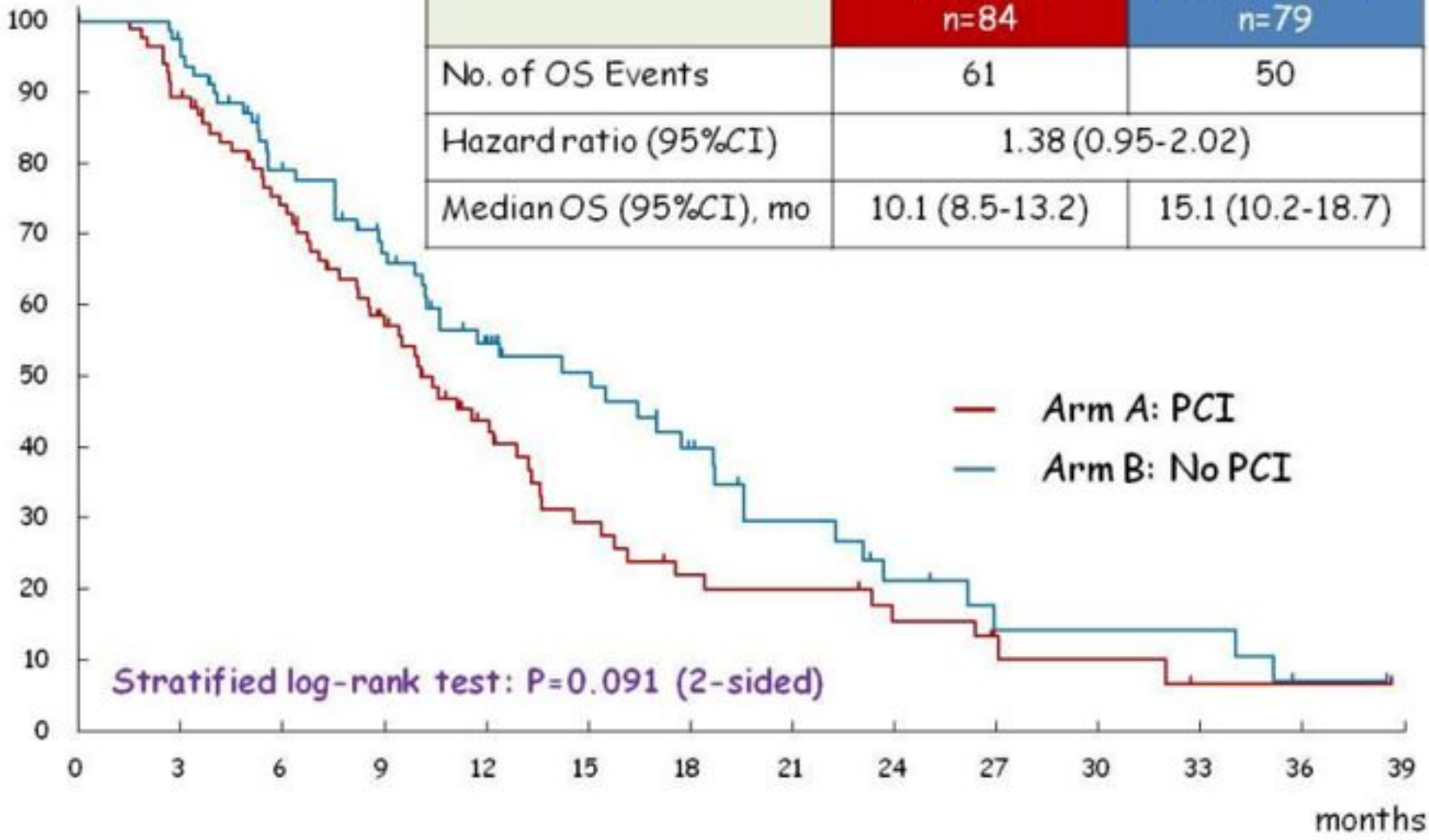
Progression-Free Survival

	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)



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)



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

Summary

- This study was early terminated because of futility based on the results of 1st interim analysis.
  - Bayesian predictive probability of showing superiority of PCI over no PCI was < 0.1%
- 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.

Conclusion

PCI did not show the survival benefit for ED-SCLC patients with a confirmed absence of BM.

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

Conclusie PCI in sclc

PCI bij LD na chemo-radiotherapy = standaard

PCI bij ED bij respons na chemotherapie:

- minder hersenmetastasen
- effect op overleving??
- enkel bij CR of zeer goede PR?

Dose:

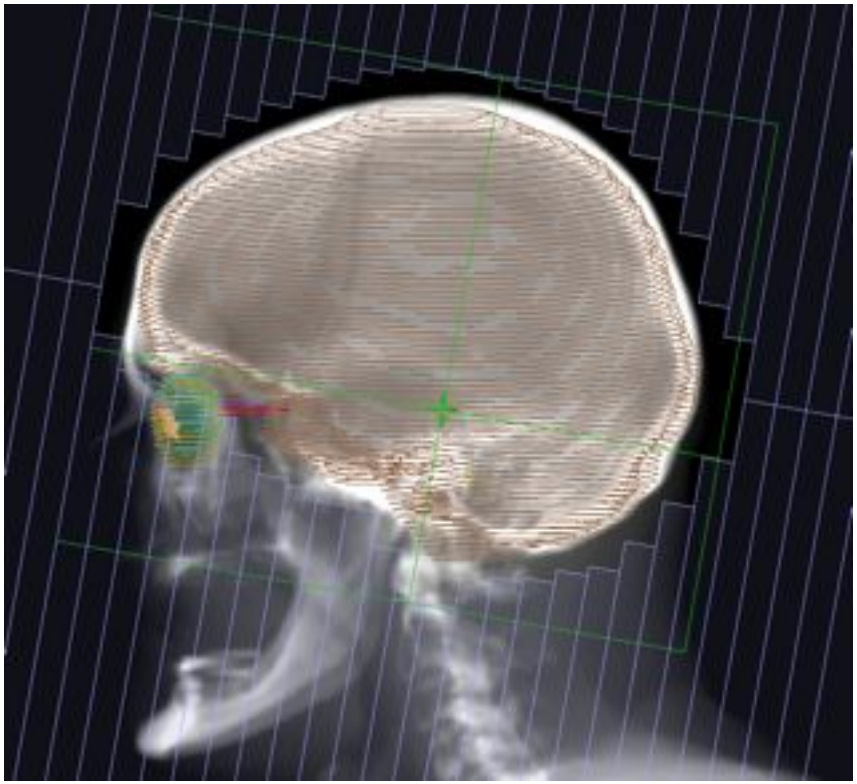
- 25 Gy/ 10 # *(Le Pechoux et al. Lancet Oncol 2011)*

Timing

- best binnen 4 wk na de laatste chemotherapie toediening (niet cyclus)

PCI techniek

- 3 puntsmasker
- li- re
- ogen uitblokken



PCI toxiciteit

acuut:

- haaruitval, erytheem scalp, vermoeidheid, craniale overdruk

laat:

- neurotoxiciteit:
  - cognitieve dysfunctie,
  - motorische pb (incl pb met stappen en evenwicht)

  - Neuroimaging en autopsie studies tonen leukoencephalopathie en hersenatrofie, progressief in tijd

PCI toxiciteit

Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial

Eric L Chang, Jeffrey S Wefel, Kenneth R Hess, Pamela K Allen, Frederick F Lang, David G Kornguth, Rebecca B Arbuckle, J Michael Swint, Almon S Shiu, Moshe H Maor, Christina A Meyers

Chang et al, Lancet Oncol 2009;10:1037

- RS vs RS + WBRT, 58 pten
- Primair eindpunt : neurocognitief!
- pten met WBRT significante achteruitgang van leer- en geheugenfunctie na 4 maand.

PCI toxiciteit

Prophylactic Cranial Irradiation is Indicated Following Complete Response to Induction Therapy in Small Cell Lung Cancer: Results of a Multicentre Randomised Trial

A. Gregor,[1] A. Cull,[1] R.J. Stephens,[2] J.A. Kirkpatrick,[3] J.R. Yarnold,[4] D.J. Girling,[2] F.R. Macbeth,[5] R. Stout[6] and D. Machin[2]

Table 3. Occurrence of cognitive function impairment in patients without impairment at baseline

	Impairment at			
	6 months		1 year	
Cognitive function test	PCI (%)	No PCI (%)	PCI (%)	No PCI (%)
PASAT	5/26 (19)	3/21 (14)	5/16 (31)	2/12 (17)
CFT	4/18 (22)	1/19 (5)	2/13 (15)	2/12 (17)
AVLT learning	7/23 (30)	5/17 (29)	9/13 (69)	4/10 (40)
AVLT retention	4/26 (15)	3/17 (18)	0/16 (0)	3/8 (38)

- bij baseline: 24% cognitief probleem
- bij follow-up: geen significant verschil cognitieve functie

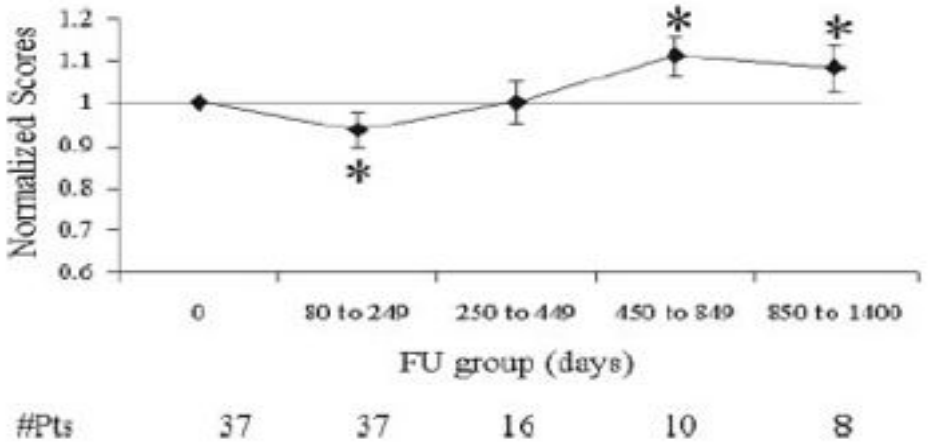
Eur J Cancer 1997;33:1752-8

PCI toxiciteit

Neurocognitive Function in Patients With Small Cell Lung Cancer

Effect of Prophylactic Cranial Irradiation

Cancer 2008;112:589–95.



David R. Grosshans, MD, PhD[1]
Christina A. Meyers, PhD[2]
Pamela K. Allen, PhD[1]
Samuel D. Davenport[2]
Ritsuko Komaki, MD[1]

- na PCI, tijdelijke vermindering vd mentale scores
- nadien terug blijvende verbetering

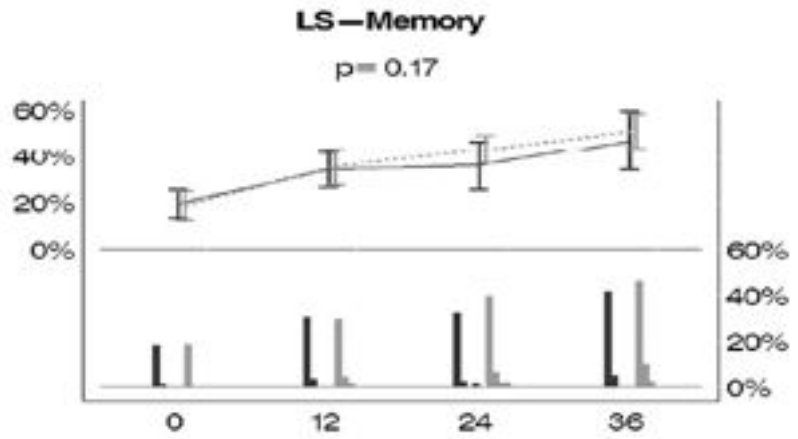
PCI toxiciteit

Le Péchoux et al Ann Oncol 2010;22:1154-63

PCI « Hi-Lo » Trial (LD SC)

QOL en neurocognitieve functie

- geen significante achteruitgang hiervan
- wel 'milde' achteruitgang van communicatie, zwakte OLM, intellect en geheugen

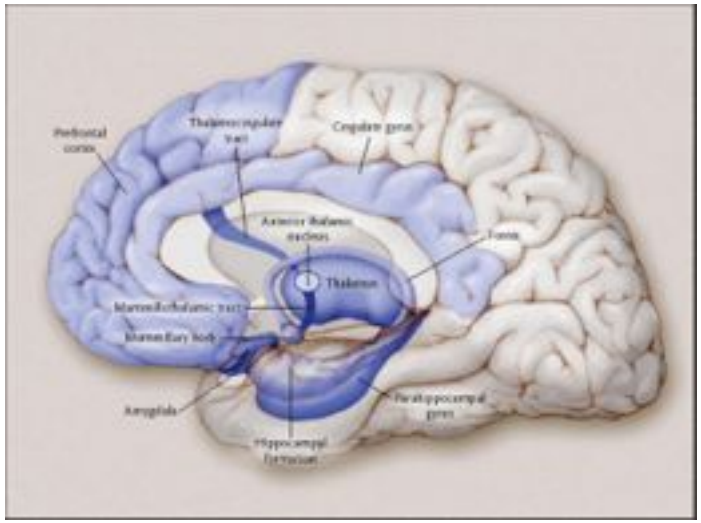


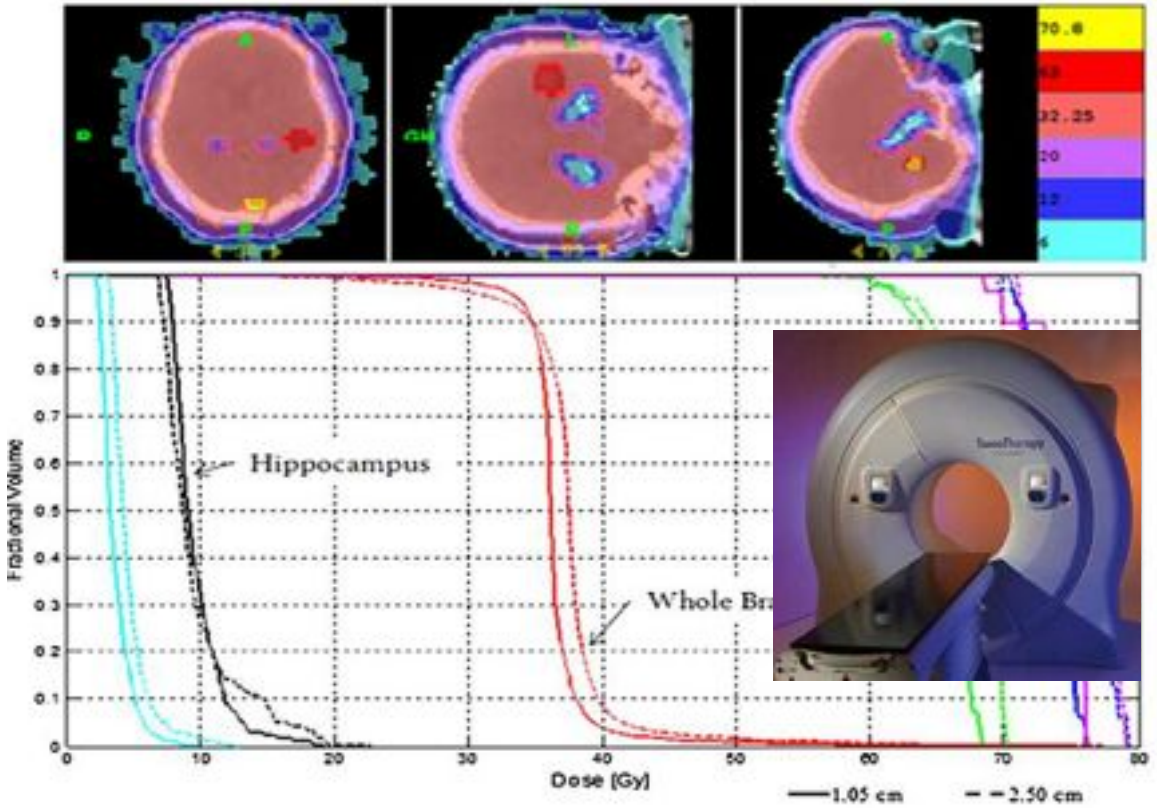
PCI toxiciteit

RTOG 0212 Wolfson, 2010

- vergelijkt neurotoxiciteit PCI bij LD SCLC bij verschillende doses
- Neuropsychologische testen en QOL:
- na 1 jaar: bij 73% cognitieve achteruitgang van minstens 1 vd 6 metingen (geheugen, vloeiend spreken, aandacht en executief functioneren).
- meer bij hogere dosis PCI.

Hippocampus sparende RT





Take home messages

1. RT thoracaal VOOR LD = is standaard
   (concomitant)

2. RT thoracaal VOOR ED = bij respons op chemo
   (sequentieel)

3. PCI :

- voor LD: standaard na chemoradiotherapie
- voor ED: enkel bij CR na therapie?
- Toxiciteit: hippocampus sparende PCI?

Wintersymposium

Wintersymposium

Introduction

Dear colleague
As per January 2015, the annual Thoracic Oncology Wintersymposium will be held alternately in Antwerp and Ghent. It is hence my pleasure to welcome you in the heart of the capital of diamonds. We have composed a scientific programme which is only matched by your ambition to learn the latest in Thoracic Oncology. There will be an animated debate on radiotherapy in extensive stage small cell lung cancer and experts will critically question the new developments in targeted treatment in advanced non-small cell lung cancer.

As we will gather in an auditorium located in front of Rubens' house and close to the main downtown boutique area, the gap between science, culture and shopping is no excuse for not attending this year. So, pencil January 17 in red in your 2015 agenda today! We look forward to meet and greet you in the New Year.

On behalf of the Comprehensive Thoracic Oncology Clusters of Ghent and Antwerp University Hospitals,

Prof. Dr . J. van Meerbeeck
Coördinator Thoraxoncologie
MOCA UZA

Prof. Dr . V. Surmont
Coördinator LONG

Programme

11th Thoracic Oncology Winter Symposium
Saturday 17 January 2015

09:00 **Registration**
09:30 Welcome
Jan van Meerbeeck, UZ Antwerpen, Belgium

09:35 **Research lecture**
Chair: Jan van Meerbeeck, UZ Antwerpen, Belgium
Volatomics in (lung) cancer diagnosis
Kevin Lamote, UZ Gent, Belgium

09:55 – 11.00 Session 1: Can local therapy benefit a systemic disease?
Chairs: Yolande Lievens, UZ Gent & Birgitta Hiddinga, UZ Antwerpen, Belgium
09:55 Consolidation thoracic radiotherapy in ES SCLC
Ben Slotman, VUmc, Amsterdam, the Netherlands
10:20 Prophylactic cranial irradiation in ES SCLC
Takashi Seto, National Kyushu Cancer Center, Fukuoka, Japan
10:45 Interactive Q & A with voting
Thomas Malfait, UZ Gent, Belgium

11:00 Break

11:30 – 13.00 Session 2: The winding road to cure in metastatic NSCLC
Chairs: Egbert Smit, NKI-AvL, Amsterdam, the Netherlands & Veerle Surmont, UZ Gent, Belgium
11:30 Targeting rank ligand for survival or for bone recovery?
Solange Peters, CHU Lausanne, Switzerland
11:50 2nd generation ALK-inhibitors: luxury or necessity?
Christian Rolfo, UZ Antwerpen, Belgium
12:05 2nd generation EGFR-TKI: progress or redundancy?
James Yang, Taipeh, Taiwan
12:25 3rd generation EGFR-TKI's: drowning the fish?
Benjamin Besse, IGR, Paris, France
12:45 Will we ever cure mNSCLC?
Egbert Smit, NKI-AvL, Amsterdam, the Netherlands

13:00 Adjourn
Jan van Meerbeeck, UZ Antwerpen, Belgium

13:05 Buffet

Bedankt voor uw aandacht!