



Plaats van de Radiotherapie bij Kleincellig Longcarcinooma (SCLC)



TOGA symposium
17/10/2014
Frederik Vandaele



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


THORACALE RT GEINDICEERD BIJ LD


RT thoracaal benefit LD

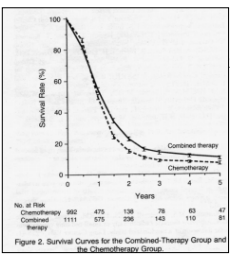
2 meta analyses

Pignon *et al*, 1992

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

↓

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



No. at Risk
Chemotherapy 952 476 138 76 63 47
Combined Therapy 1111 575 236 143 110 81

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

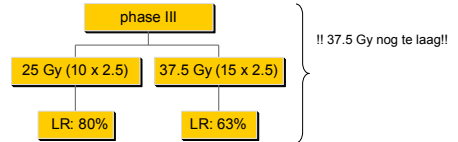

THORACALE RT GEINDICEERD BIJ LD


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

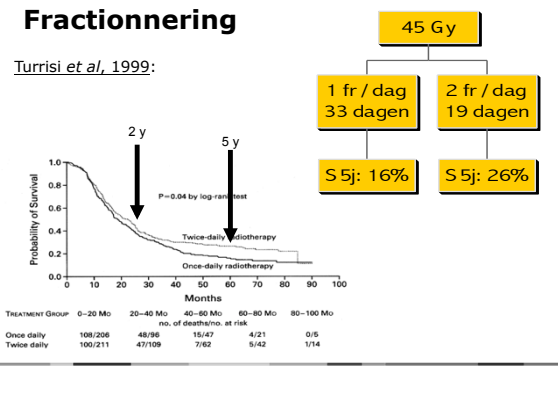
geaccelereerde hyperfractionatie:

SCLC: zeer korte verdubbelingstijd, reproductie

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

Fractionnering

Turrisi *et al*, 1999:



Fractionnering: 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

Overall no. of patients	Grade					P Value
	0	1	2	3	4	
Overall†	1 (0.5)	3 (1)	26 (16)	47 (28)	127 (68)	0.80
1	2 (1)	0	19 (9)	51 (25)	138 (65)	0.50
2	1 (0.5)	3 (1)	7 (4)	19 (9)	41 (21)	0.85
3	7 (3)	2 (1)	18 (9)	32 (16)	127 (62)	0
4	114 (56)	39 (19)	84 (41)	22 (11)	11 (5)	0
5	76 (37)	26 (13)	57 (28)	32 (16)	11 (5)	0
Other toxic effects	4 (2)	18 (9)	118 (59)	46 (23)	12 (6)	0.20
1	2 (1)	13 (6)	119 (59)	51 (26)	13 (6)	0.10

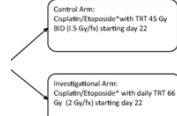
†Data were available for 200 patients receiving once-daily radiotherapy and 206 patients receiving twice-daily therapy.

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

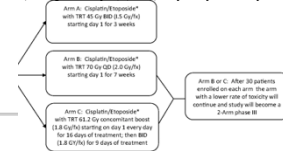
§Metastatic sites were defined as any decrease in maximum-diameter cells in the peripheral blood counts.

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 Ruyscher *et al*: SER Concept:
Interval 'Start of Any Treatment and End of Radiotherapy' moet zo kort mogelijk zijn (repopulate)

⇒ 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

isolated nodal relaps

- enkel CT-scan (pre PET)
 - Baas P *et al*. (J Cancer 2006;94:625-630): **5%**
 - De Ruyscher 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)



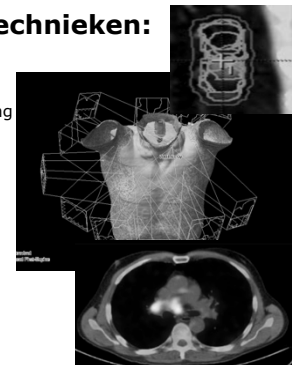
⇒ RT aangetaste klieren (pet+) prechemo, aangepast aan postchemo status

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

ES-SCLC, KPS ≥ 70 , 18-70 yrs

3 x PE

PR / CR in Thorax and CR outside Thorax

RANDOMIZE

TRT (36x1.5Gy) + daily carbo/etop

2 x PE

PCI + 2 PE

PCI + 2 PE

17 months

11 months

Jeremic et al., JCO 1999

VUmc Presented by: Ben Slotman PRESENTED AT: ASCO 50th ANNUAL MEETING (2014)

Presented By Ben Slotman at 2014 ASCO Annual Meeting

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

Ben J. Slotman, Corinne Fairclough, Joost Knegjens, John Praag, Matthew Hatton, et al.

Chest Radiotherapy Extensive Stage Trial

VUmc PRESENTED AT: ASCO 50th ANNUAL MEETING (2014)

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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

VUmc Presented by: Ben Slotman PRESENTED AT: ASCO 50th ANNUAL MEETING (2014)

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CREST Trial Design

ES-SCLC, WHO 0-2

4-6 platinum-based chemotherapy

Any response

RANDOMIZE

TRT (30Gy in 10fx)

PCI

PCI

Stratification:

- Institute
- Presence of intrathoracic disease

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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

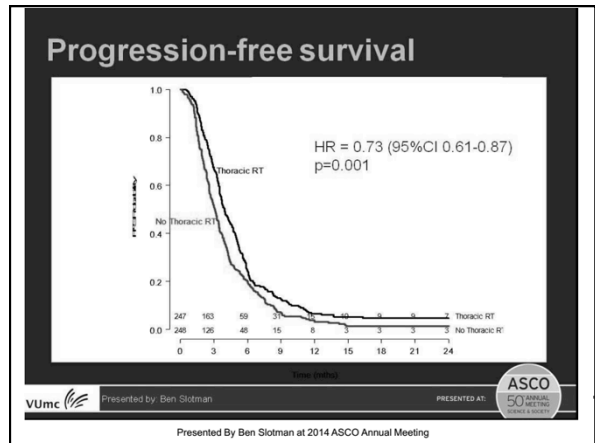
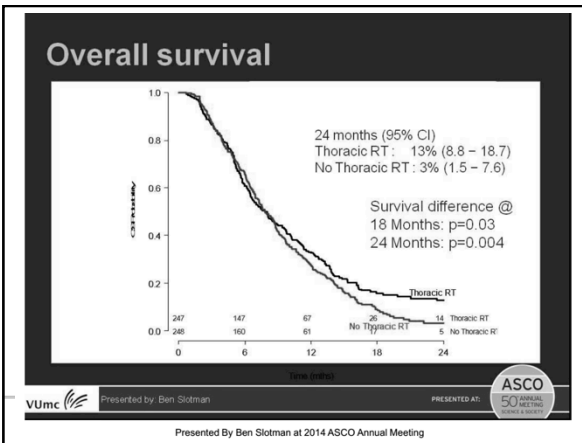
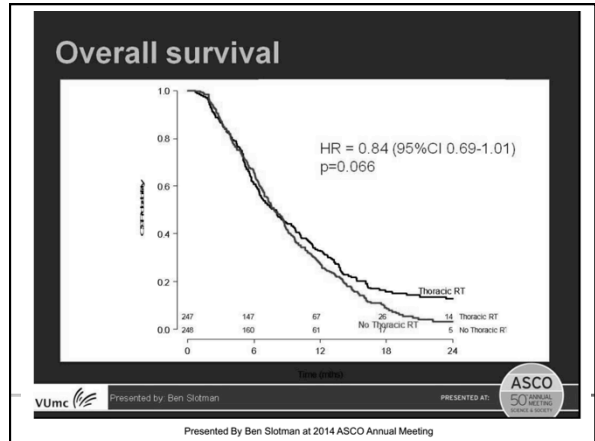
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Patient characteristics

	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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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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Toxicity (CTCAE v3) G3+

CTC Grade	TRT (n=247)		Control (n=248)	
	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

VUmc Presented by Ben Slotman ASCO 50th ANNUAL MEETING PRESENTED AT: 2014

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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

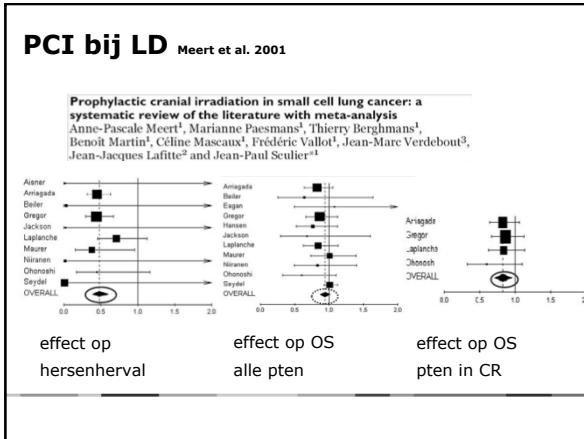
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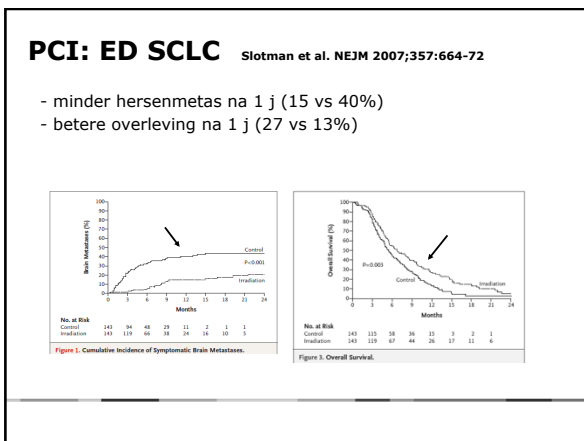
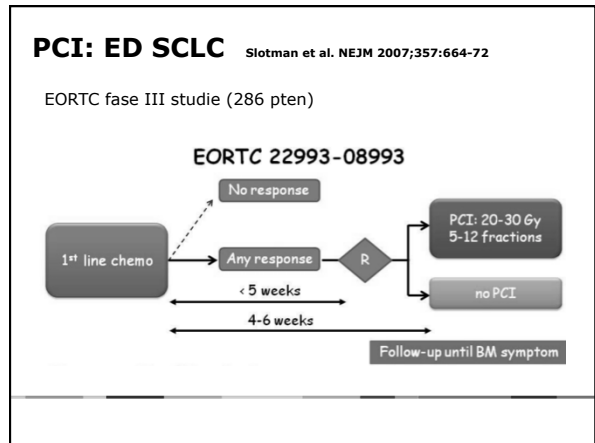
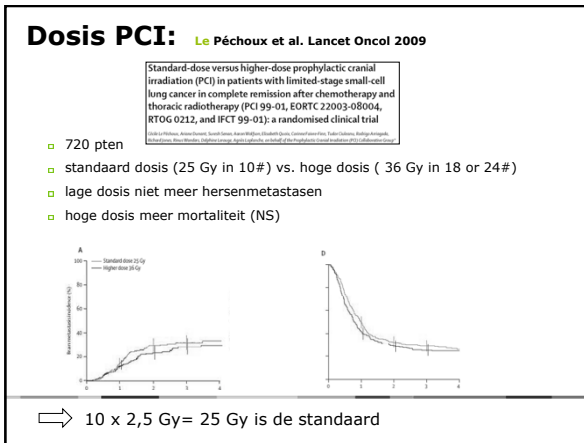
	PCI -	PCI	p
HersenM+ na 3j: %	58.6	33.3	<0.01
Levend na 3j: %	15.3	20.7	<0.01
Benefit (abs)		5.4 %	



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



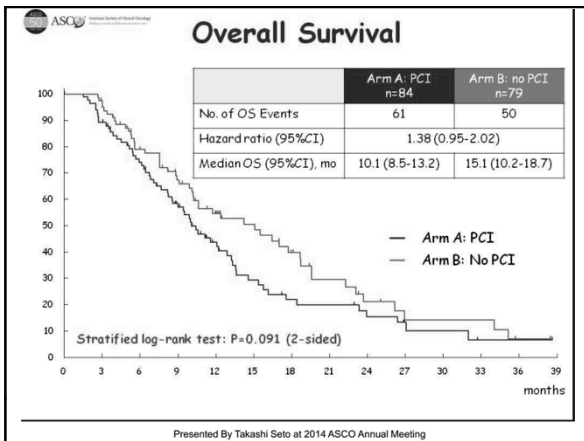
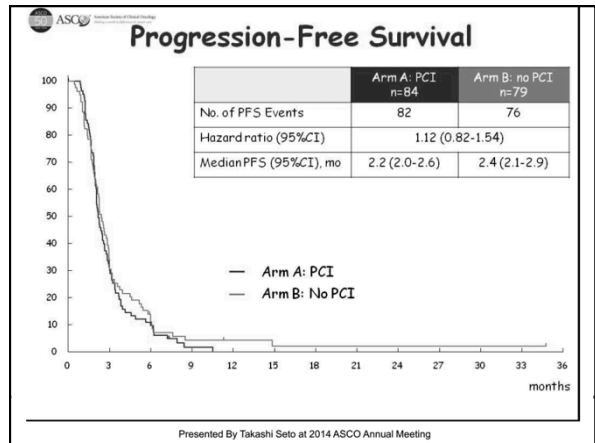
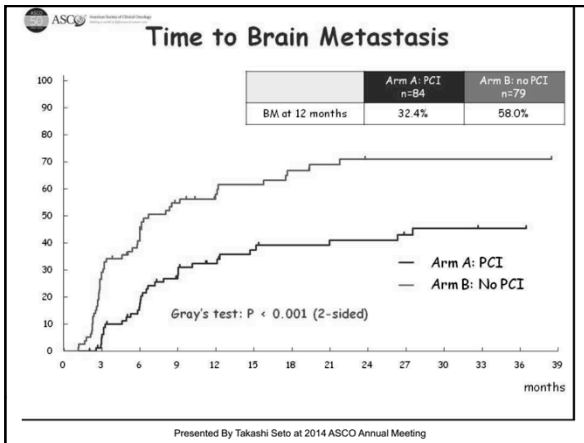
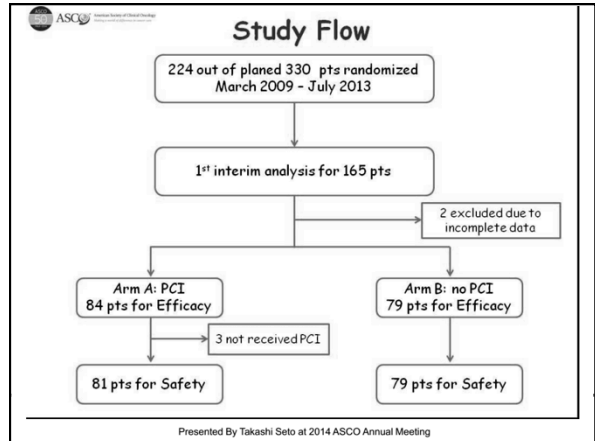
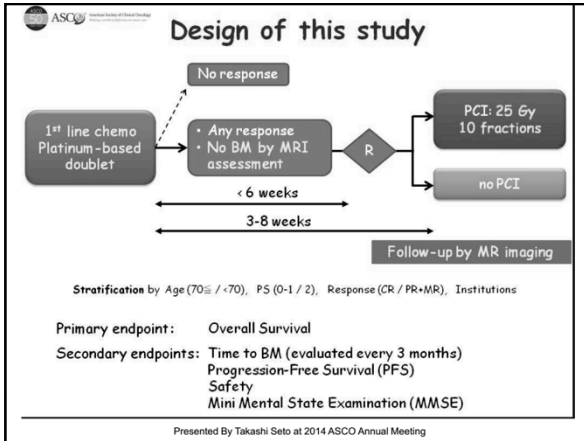
ASCO 50th Anniversary American Society of Clinical Oncology Making a world of difference in cancer care.

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

Presented by Takashi Seto at 2014 ASCO Annual Meeting



Adverse Events in PCI arm

	Arm A: PCI n=81 (All 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

Presented By Takashi Seto at 2014 ASCO Annual Meeting

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.

Presented By Takashi Seto at 2014 ASCO Annual Meeting

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

Presented By Takashi Seto at 2014 ASCO Annual Meeting

Conclusie PCI in sclc

PCI bij LD na chemo-radiotherapie = standaard

PCI bij ED bij respons na chemotherapie:

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

Dose:

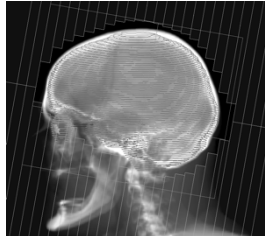
- 25 Gy/ 10 # (Le Pechoux et al. Lancet Oncol 2011)

Timing

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

PCI techniek

- 3 puntsmasker
- li- re
- ogen uitblokken



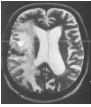
PCI toxiciteit

acuut:

- haaruitval, erytheem scalp, vermoeidheid, craniale overdruk

laat:

- neurotoxiciteit:
 - cognitieve dysfunctie,
 - motorische pb (incl pb met stappen en evenwicht)
- Neuroimaging en autopsie studies tonen leukoencefalopathie 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

Erik I. Chang, Jeffrey S. Wefel, Kenneth R. Hess, Pamela K. Allen, Frederick F. Lang, David G. Koenig, Rebecca B. Arbuskic, Michael Swint, Almon S. Shiu, Mashe H. Moax, Christine 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,¹ J.A. Kirkpatrick,¹ J.R. Yarnold,⁴ D.J. Girling,⁴ F.R. Machbeth,⁵ R. Stout⁶ and D. Machin¹

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

Cognitive function test	Impairment at			
	6 months		1 year	
	PCI (%)	No PCI (%)	PCI (%)	No PCI (%)
FAMT	576 (29)	921 (44)	518 (21)	212 (7)
CFP	418 (22)	1108 (51)	213 (9)	212 (7)
AVLT learning	721 (36)	917 (43)	913 (38)	419 (16)
AVLT constant	426 (22)	917 (43)	616 (26)	18 (0)

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

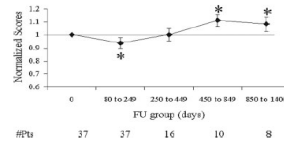
Eur J Cancer 1997;33:1752-8

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, PhD¹
Christina A. Meyers, PhD²
Pamela K. Adkins, PhD²
Samuel D. Davenport²
Ritsuko Komaki, MD¹

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

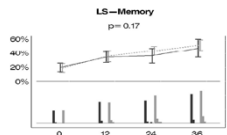
PCI toxiciteit

Le Pécoux 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

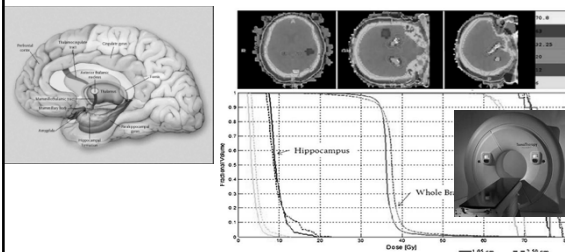


PCI toxiciteit

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

General information

Date
Saturday, 17 January 2015

Venue
BNP Paribas Fortis
Auditorium Hélène Fourment, Meer 48, ringweg Via Wapper
2000 Antwerpen

Accreditation
Accredited with ECR/ECMEC is pending, last year 3.5 points
Accreditation application NMAI is pending

Target audience
This symposium will be of special interest for pulmonologists, radiation oncologists,
oncologic surgeons, medical oncologists, pathologists, and investigators
interested in thoracic oncology

Registration
Please register on-line via the congress calendar on www.congresscare.com.
Registration fee is EUR 50 (EUR 30 for AGO), and is including admission to
the meeting, programme/abstract book, breaks, lunch buffet and certificate of
attendance.
Delegates registering before Thursday, 15 January 2015 will receive a
confirmation e-mail with route description.

Cancellation
Written cancellations received before Tuesday, 6 January 2014 will be
refunded less EUR 15 administration costs.

11th Thoracic Oncology Winter symposium

A Fair of the Future

Saturday 17 January 2015
Auditorium Hélène Fourment, BNP Paribas Fortis, Antwerp

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 reason for not attending this year. So, spend January 17 in and 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 Meerbeek
Coordinator Thoracic oncology
MICA USA

Prof. Dr. V. Surmont
Coordinator Lung
MICA USA

Programme

11th Thoracic Oncology Winter Symposium
Saturday 17 January 2015

09:00 Registration
welcome
Jan van Meerbeek, UZ Antwerpen, Belgium

09:35 Research lecture
Chair: Jan van Meerbeek, UZ Antwerpen, Belgium
Volunteers in Lung cancer diagnosis
Kenta Kaneko, UZ Gent, Belgium

09:55 - 11:00 Session 1: Can local therapy benefit a systemic disease?
Chair: Roland Liewers, UZ Gent & Bepko Hiddinga, UZ Antwerpen, Belgium
09:55 Consolidation Thoracic radiotherapy in NSCLC
Bert Skrymgeour, Middelheim, Antwerpen, the Netherlands
10:30 Prophylactic cranial irradiation in NSCLC
Masahiro Goto, National Cancer Center, Fukuoka, Japan
10:45 Interactive Q & A with voting
Thomas Maatso, UZ Gent, Belgium

11:00 Break

11:30 - 11:00 Session 2: The winding road to cure in metastatic NSCLC
Chair: Gilbert Lin, National, Amsterdam, the Netherlands &
Henric Surmont, UZ Gent, Belgium
11:30 Targeting tank tyrosin for survival or for bone recovery?
Suzanne Peters, DHE (academic), Switzerland
11:50 2nd generation ALK inhibitors: busy or redundancy?
Christian Kahl, UZ Antwerpen, Belgium
12:00 James King, Sigph, France
12:45 3rd generation EGFR-TKI: slowing the hot
Bryant Brown, KCR, Paris, France
12:45 Will we ever cure NSCLC?
Gilbert Lin, NCI/NIH, Amsterdam, the Netherlands

13:00 Luncheon
Jan van Meerbeek, UZ Antwerpen, Belgium

13:45 Buffet

Bedankt voor uw aandacht!

Who said cigarette kills ?

I'm 48 and still feeling good.