TOGA symposium

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Radiotherapie Iridium Netwerk

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Partner AZ Lokeren

AZ Rivierenland
Bornem – Rumst - Willebroek

AZ Voorkempen
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GZA Ziekenhuizen
Antwerpen – Mortsel – Wilrijk

UZA
Edegem

ZNA
Antwerpen - Merksem

De plaats van radiotherapie bij de behandeling van het kleincellig neuro-endocrien carcinoom.

Neuro-endocriene tumoren

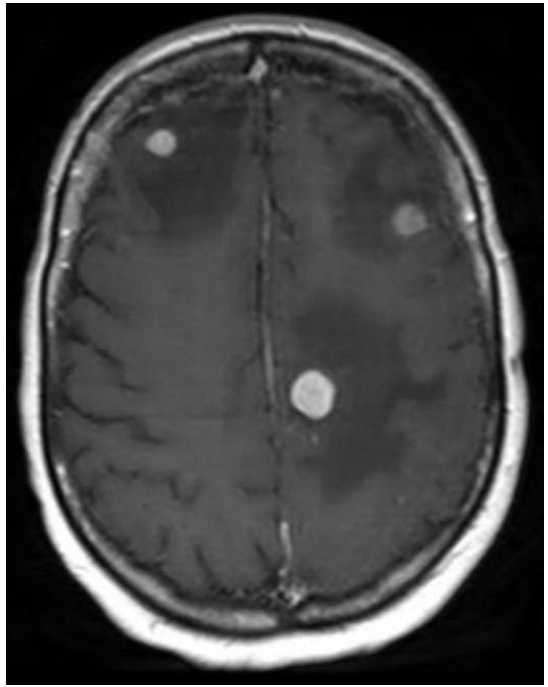
Classificatie

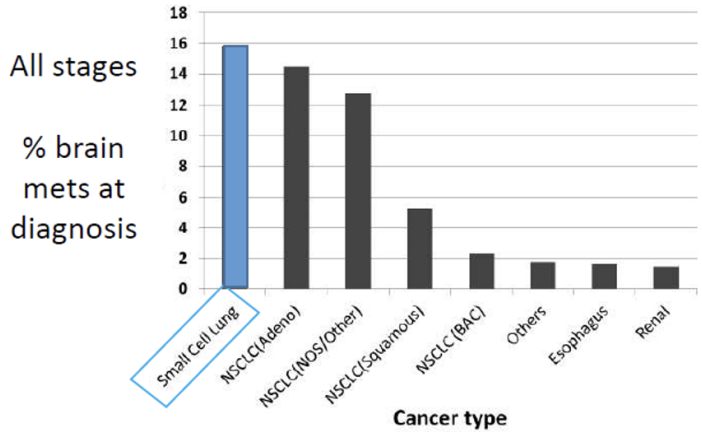
Differentiatie		Kenmerken	Maligniteitsgraad
Goed	Typisch carcinoïd	< 2 mitosen/2mm2 Geen necrose	G1, Laag
Goed	Atypisch carcinoïd	2-10 mitosen/2mm2 Of necrose	G2, Intermediair
Slecht	Gootcellig neuro-endocrien carcinoma	Grote cellen > 10 mitosen/2mm2 En necrose	G3, Hoog
Slecht	Kleincellig neuro-endocrien carcinoma	Kleine cellen > 10 mitosen/2mm2 En necrose	G3, Hoog

Kleincellig longcarcinoma (SCLC)

Hoge incidentie hersenM+:

- Bij diagnose : 15-20%
- Na 2j Fup (na CR): 50%
- Postmortem: 80%



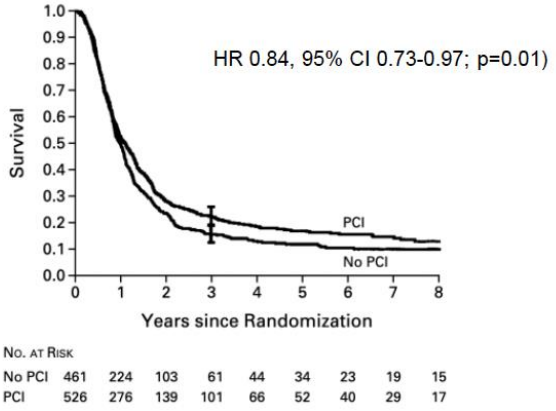


Profylactische pancraniele RT (PCI)

- Meta-analyse 1999:
  - 7 studies (PCI+ / PCI-)
  - 987 pt – CR locoregionaal
  - Limited (85%) - Extensive (15%)
  - Variabel dosis/fractionatie schema

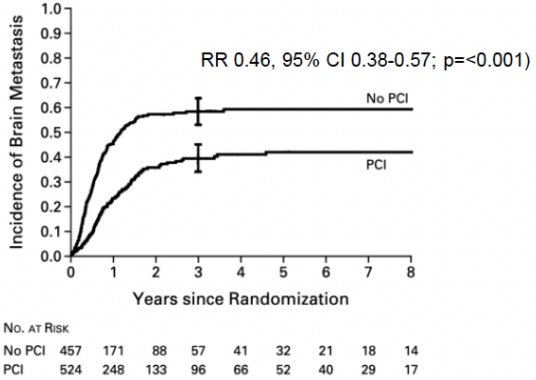
Betere overleving

15% vs 21% 3y



Minder hersenM+

59% vs 33% 3y



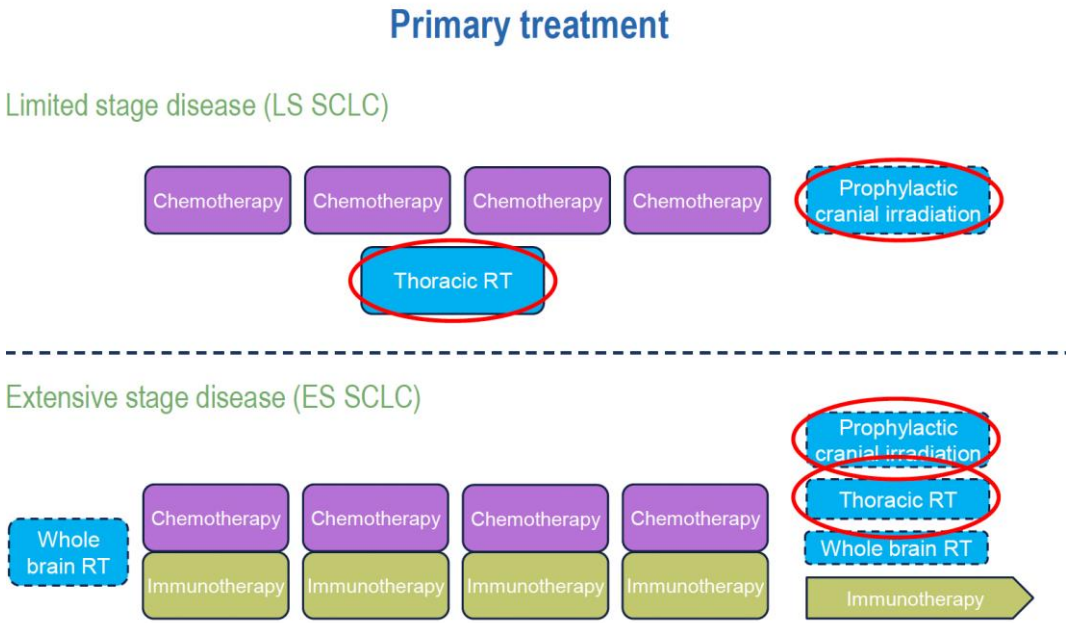
Aupérin et al. NEJM 1999; 341:476-484

Profylactische pancraniele RT (PCI)

+/- 5% OS winst na 3j → Standaardbehandeling voor LS en ES

Discussie:

- geen PET staging
- Geen MRI baseline
- Geen standaard RT schema's



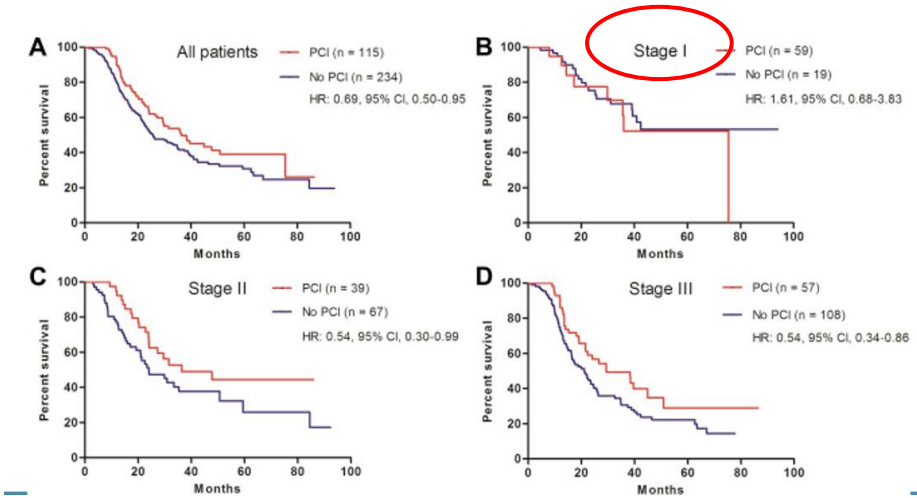
Aupérin et al. NEJM 1999; 341:476-484

EARLY stage

Benefit voor iedereen? → EARLY stage?

- Veel lagere incidentie hersenM+
- Minder benefit?
- Retrospectieve analyse (Xu 2017)

Study	Year	N°	Incidence of BM
Tsuchiya et al	2005	35	11%
Nakamura et al	2004	30	7%
Ogawa et al	2011	14	0



Xu et al. NEJM 2017

EXTENSIVE stage

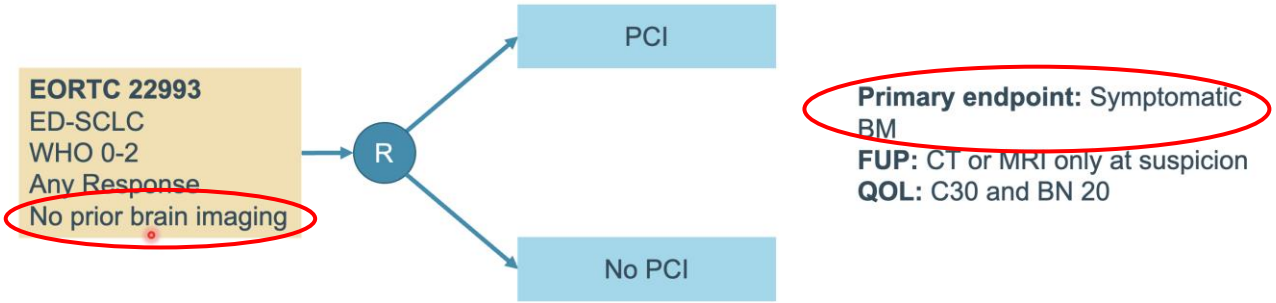
Benefit voor iedereen? → EXTENSIVE stage?

- Trial Slotman
- Eindpunt: Symptomatische hersenM
- Geen baseline staging
- Variabele RT schema's

ORIGINAL ARTICLE

Prophylactic Cranial Irradiation in Extensive Small-Cell Lung Cancer

Ben Slotman, M.D., Ph.D., Corinne Faivre-Finn, M.D., Ph.D., Gijs Kramer, M.D.,* Elaine Rankin, M.D., Michael Snee, D.M., Matthew Hatton, F.R.C.R., Pieter Postmus, M.D., Ph.D., Laurence Collette, Ph.D., Elena Musat, M.D., and Suresh Senan, Ph.D., F.R.C.R., for the EORTC Radiation Oncology Group and Lung Cancer Group†



Slotman et al. NEJM 2007

EXTENSIVE stage

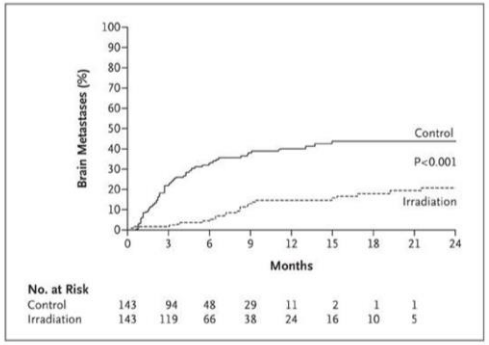
Resultaten

- 286 pt
- DFS en OS benefit

Symptomatic BM

16,8% (RT) vs 41,3% (no RT)

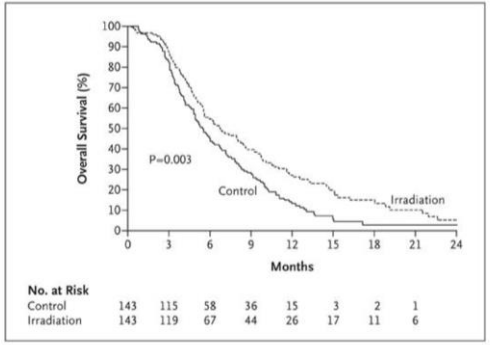
At 6 months: 4,4% (RT) vs 32% (no RT)
p<0,001



Overall Survival

Median: 6,7 m (RT) vs 5,4 m (no RT), p: 0,003

At 1 year: 27% (RT) vs 13% (no RT)



Slotman et al. NEJM 2007

EXTENSIVE stage

DISCUSSIE

- Geen baseline staging
  - asymptomatische hersenM?
- Variabele RT schema's
- Cave toxiciteit (QoL)

Table 2. Scores on Quality-of-Life Assessment.*

Quality-of-Life Score	Assessment Time	Prophylactic Cranial Irradiation	Control	P Value†
Primary end points				
Global health status	0–9 mo‡			0.10
Role functioning	0–9 mo‡			0.17
Cognitive functioning	0–9 mo‡			0.07
Emotional functioning	0–9 mo‡			0.18
Fatigue	6 wk	43.2±2.56	29.3±2.47	<0.001
	3 mo	53.6±3.03	38.5±3.24	<0.001
Hair loss	6 wk	36.5±3.96	11.7±3.73	<0.001
Exploratory results				
Appetite loss	6 wk	28.9±3.25	10.6±3.06	<0.001
	3 mo	43.9±3.87	14.8±4.18	<0.001
Nausea and vomiting	6 wk	15.0±1.73	5.3±1.64	<0.001
	3 mo	26.9±2.92	8.2±3.15	<0.001
Leg weakness	6 wk	25.2±2.71	11.8±2.48	<0.001
	3 mo	32.2±3.62	16.0±3.93	0.003

* Plus–minus values are means ±SD. The primary quality-of-life end points were assessed with two EORTC instruments: the core quality-of-life questionnaire (QLQ-C30) and an instrument specific for brain cancer (QLQ-BN20). Scores range from 0 to 100. For functional scales, higher scores represent a higher level of functioning; for symptom scales, higher scores represent a greater severity of symptoms.
† The comparisons at each time point were considered only if the overall test was significant at the 0.01 level.
‡ The differences between the two study groups were not significant in the overall analyses at any time point.

Slotman et al. NEJM 2007

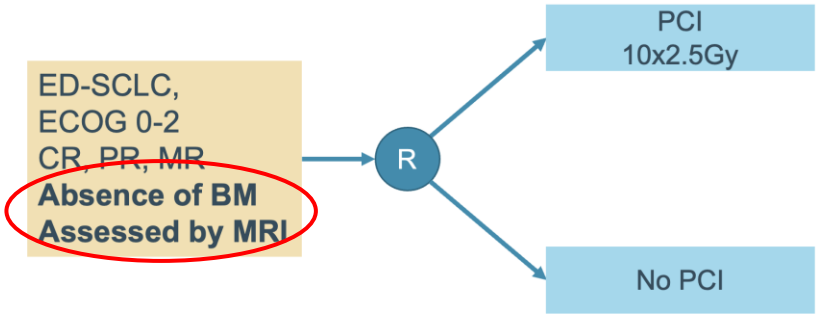
EXTENSIVE stage

Benefit voor iedereen? → EXTENSIVE stage?

- Japanese Trial
- Eindpunt: OS
- WEL baseline en follow-up MR staging
- RT schema 10x2,5 Gy

Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial

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



Primary: Overall survival
Follow-up
Brain MRI: 3-6-9-12-18-24 months
MMSE: 12 and 24 months

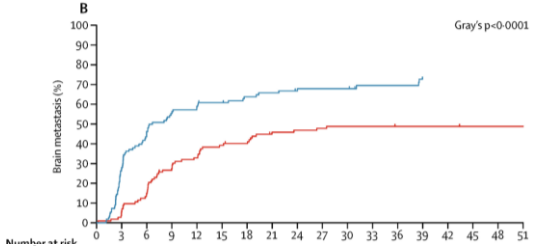
Takahashi et al. Lancet Oncol 2017

EXTENSIVE stage

RESULTATEN

- 224 pt
- Minder hersenM
- Geen OS of DFS benefit na 1j
- Geen invloed op MMSE
- Early closure study (na interim analyse)

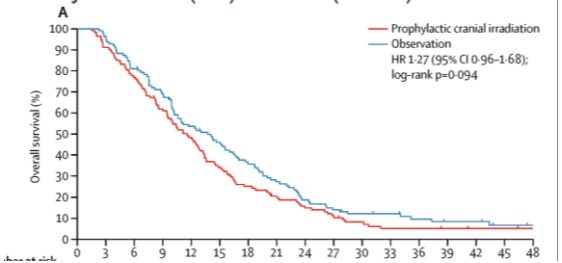
- 48% (RT) vs 69% (no RT)
- At 6 months: 15% (RT) vs 46% (no RT), p<0.001)



Overall survival

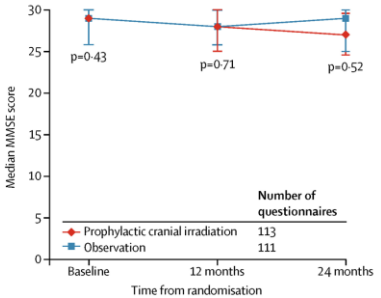
- 11.6 m (RT) vs 13.7 months (no RT)
- HR 1.27 (0.96-1.68; p:0.094)

At 1 year: 49% (RT) vs 54% (no RT)



Discussie

-> 2 studies moeilijk te vgl: andere populatie door andere staging en behandeling



Number of returned questionnaires			
Prophylactic cranial irradiation	107	37	5
Observation	105	46	8

Takahashi et al. Lancet Oncol 2017

EXTENSIVE stage

PCI in ES SCLC

-> meer controversieel in guidelines

ESMO: PCI is justified in patients <75 years of age and a PS of 0-2 who achieved a response after ChT

ASTRO: For patients with ES-SCLC who respond to chemotherapy, consultation with a radiation oncologist to enhance shared decision making on PCI versus MRI surveillance

Takahashi et al. Lancet Oncol 2017

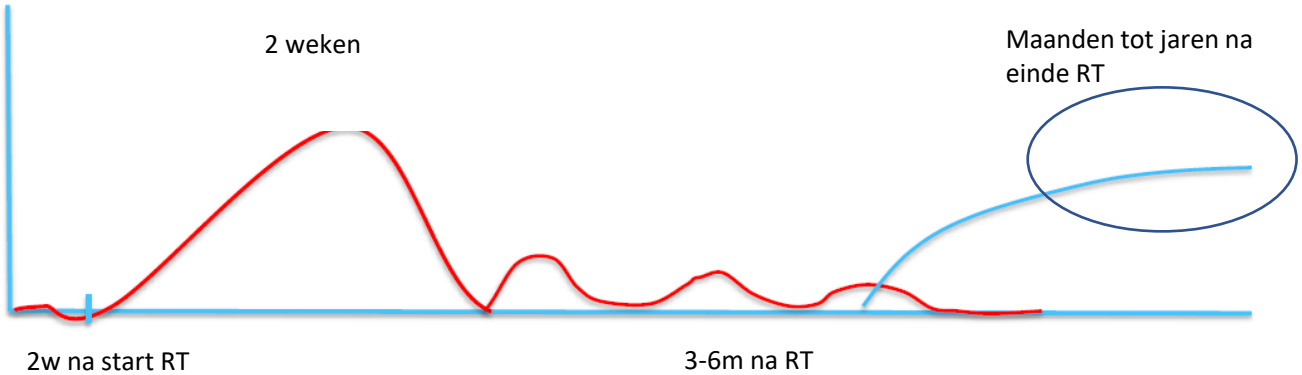
Toxiciteit

Acuut: tijdelijk

- Haaruitval – vermoeidheid - craniale overdruk – nausea – braken
- Zo nodig corticoid therapie

Laat: progressief en irreversibel

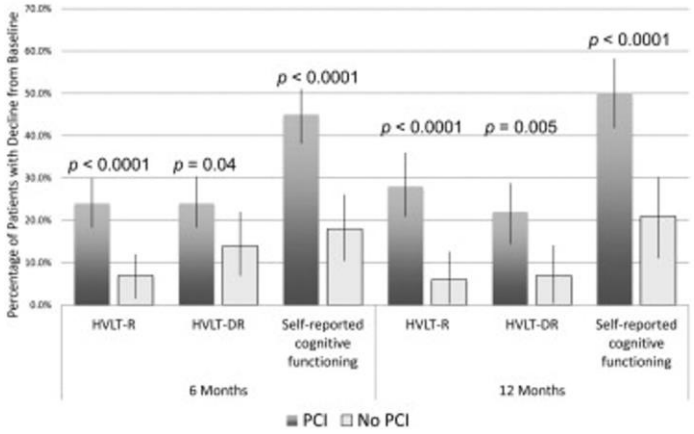
- neurotoxiciteit:
  - cognitieve dysfunctie: korte termijn geheugen - concentratie – ataxie
- Impact op QoL en dagelijks functioneren



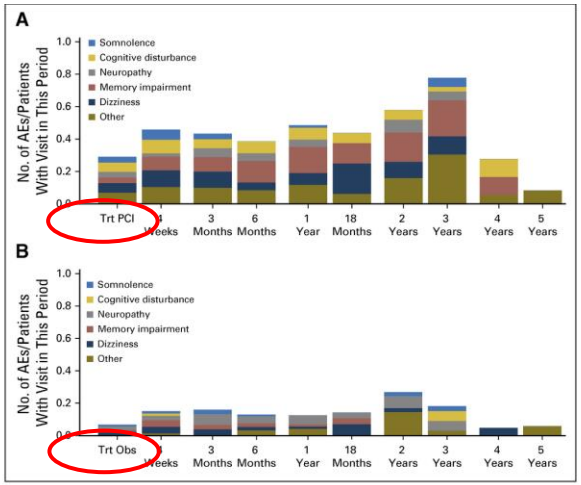
Zang et al. Cancer Treatment Rev 2020

Toxiciteit

- Neurotoxiciteit door PCI
  - Vooral low grade (1 en 2)
  - meer cogn patient-reported deterioriatie op 6 en 12m in PCI arm
- Geen verschil in QOL
  - Enkel eerste 3m na PCI



Tested and self-tested cognitive function with/Without PCI in RTOG 0212 and 0214



Neurologic toxicity with and without PCI in NVALT-11/DLCRG-02 (NSCLC)

De Ruysscher et al. JCO 2018; Witlox et al. R&O 2020

Toxiciteit

	Number of patients	Assessment schedule	Baseline assessment	Neuropsychological tests and other examinations	Control group*	Experimental group*	p values	Outcomes
No PCI (control) versus PCI (experimental)								
Arriagada et al (1995)[8]	229	Assessments made at baseline, and 6, 18, 30, and 48 months; 33 patients reassessed at 18 months; 23 patients reassessed at 30 months	Abnormalities in 59% of patients; brain CT scan normal in 83% of patients	Neuropsychological assessments made by neurologist: (1) orientation, memory, judgment, language, and praxis; (2) mood; (3) walking; (4) toxicity-related brain CT abnormalities	Neuropsychological changes at 2 years: (1) 36%; (2) 28%; (3) 11%; (4) 21%	Neuropsychological changes at 2 years: (1) 30%; (2) 19%; (3) 8%; (4) 27%	(1) 0·58; (2) 0·55; (3) 0·72; (4) 0·60	Impairment at baseline substantial but similar in the two groups; no significant differences between groups at 2 years
Gregor et al (1997), UKCCCR/ EORTC[14]	136	Assessments made at baseline, at 6 and 12 months, then yearly; 59 patients reassessed at 6 months, 32 patients at 1 year, and 9 patients at 2 years	Abnormalities in 24–42% of patients according to tests	(1) PASAT; (2) CFT; (3) AVLT learning; (4) AVLT retention; (5) HADS; (6) QoL assessment (tiredness)	Neuropsychological changes at 1 year: (1) 2/12 (17%); (2) 2/12 (17%); (3) 4/10 (40%); (4) 3/8 (38%); (5) 13%; (6) 6-month deterioration in QoL: 57%	Neuropsychological changes at 1 year: (1) 5/16 (31%); (2) 2/13 (15%); (3) 9/13 (69%); (4) 0/16; (5) 13%; (6) 6-month deterioration in QoL: 24%	(1–5) All NS; (6) NR	Impairment at baseline substantial but similar in the two groups; no evidence of major impairment attributable to PCI; deterioration in general symptoms reported more frequently in the no PCI group
Slotman et al (2009), EORTC[88]	268	QoL data collected at baseline, 6 weeks, and 3, 9, and 12 months; poor compliance: 54·5% at 3 months, 60·8% at 6 months, 46·3% at 9 months, and 48·9% at 1 year	..	EORTC-QLQ-BN20 and EORTC-QLQ-C30: (1) global health status; (2) fatigue; (3) cognitive functioning; (4) hair loss	Deterioration from baseline up to 3 months: (1) 22%; (2) 27%; (3) 10%; (4) 12%	Deterioration from baseline up to 3 months: (1) 35%; (2) 49%; (3) 22%; (4) 22%	NR	Limited effect of PCI for role, cognitive, and emotional functioning; effect on fatigue greater in PCI group than no PCI group at 3 months; adverse effect of PCI on fatigue (mostly), appetite loss, social functioning, future uncertainty, motor dysfunction, and weakness of legs at 6 weeks and/or at 3 months
Sun et al (2011), RTOG[89]	340	QoL and NCF data collected at baseline, and 3, 6, and 12 months; for NCF: 324 patients assessed at baseline, 144 at 6 months, and 97 at 1 year; for QoL: 309 patients assessed at baseline, 143 at 6 months, and 92 at 1 year	..	(1) MMSE; (2) HVLT recall; (3) HVLT delayed recall; (4) ADLS; EORTC-QLQ-C30: (5) global health status; (6) fatigue; (7) cognitive functioning	Deterioration from baseline at 3 months/ 6 months/ 1 year: (1) 21%/25%/18%; (2) 13%/5%/7%; (3) 10%/14%/5%; (4) no significant change; deterioration from baseline at 6 months/1 year: (5) 32%/34%; (6) 32%/28%; (7) 18%/25%	Deterioration from baseline at 3 months/ 6 months/1 year: (1) 36%/28%/23%; (2) 45%/19%/26%; (3) 44%/15%/32%; (4) no significant change; deterioration from baseline at 6 months/1 year: (5) 35%/22%; (6) 21%/34%; (7) 35%/41%	(1) 0·04 at 3 months, 0·6 at 1 year; (2) <0·001 at 3 months, 0·01 at 1 year; (3) <0·001 at 3 months, 0·003 at 1 year; (4) NS; (5) 0·76 at 6 months, 0·2 at 1 year; (6) 0·27 at 6 months, 0·52 at 1 year; (7) 0·02 at 6 months, 0·14 at 1 year	No significant differences in global cognitive function (MMSE) or QoL after PCI, but significant decline in memory (HVLT) at 1 year; good compliance at baseline (95%) and poor at 1 year (around 35%)

Beperkingen:

-heterogene tests

-geen baseline staging

-variatie in systeemtherapie

-variatie in RT dosis

Le Péchoux et al. JCO 2016

Toxiciteit

Risicofactoren neurotoxiciteit door PCI:

- Dosis per fractie >3Gy
- Hogere totaal dosis

→ Standaard schema: 10 X 2,5 Gy

- Hogere leeftijd
- Bestaande neurocognitieve achteruitgang

→ MDT overleg

- Concurrente chemotherapie
- Concurrente immunotherapie?

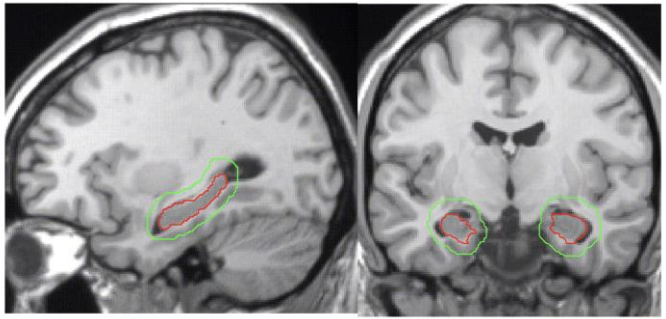
→ Toxiciteitsdata
IMpower133 study - KEYNOTE-604

Le Pechoux et al. Lancet Oncol 2009;

Hippocampal avoidance PCI

Hippocampus

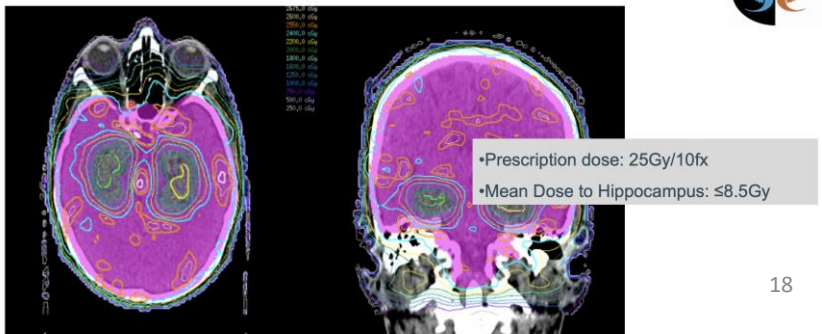
- Geheugen functie
- Gevoelig aan RT



Hypothese: Dosis reductie op hippocampus

Beperken van nevenwerkingen

= Hippocampal avoidance PCI



Hippocampal avoidance PCI

2 Random Phase III trials (LS en ES beide)

- **1 positieve trial:** (*Brown et al 2020*)

- Minder cognitieve achteruitgang in HA-RT groep en betere QoL

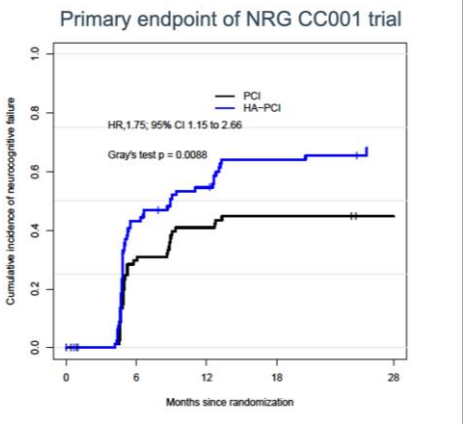
- **1 negatieve trial:** (*Belderbos et al 2021*)

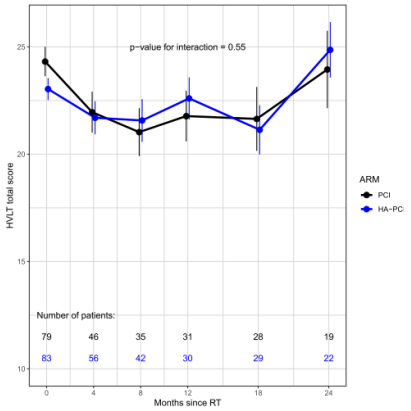
- Geen verschil in beide groepen
- Prim eindpunt: vermindering cogn 4m na RT op Hopkins test (=specif hippocampal related test)

- **Verklaring?**

- Verschillende neurocogn testing
- Studie underpowered? (n=168 en 150 resp)

-> **Voorlopig geen standaard therapie**





Brownet al. J Clin Oncol 2020; Belderbos et al J Thorac Oncol 2021

Samenvatting

<u>Huidige standaard</u>

- Limited SCLC (stadium I): ➡ geen PCI
- Limited SCLC (stadium II-III- <70j -ECOG 0- 2) met respons op chemoradiotherapie locoregionaal: ➡ Standaard PCI
- Andere limited + alle extensive SCLC (<70j -ECOG 0- 2) met respons op chemoradiotherapie locoregionaal: ➡ shared decision making
- HOE: RT 10x2,5 Gy (Hippocampal avoidance niet standaard)
- Timing: NA chemotherapie - <6 weken na einde

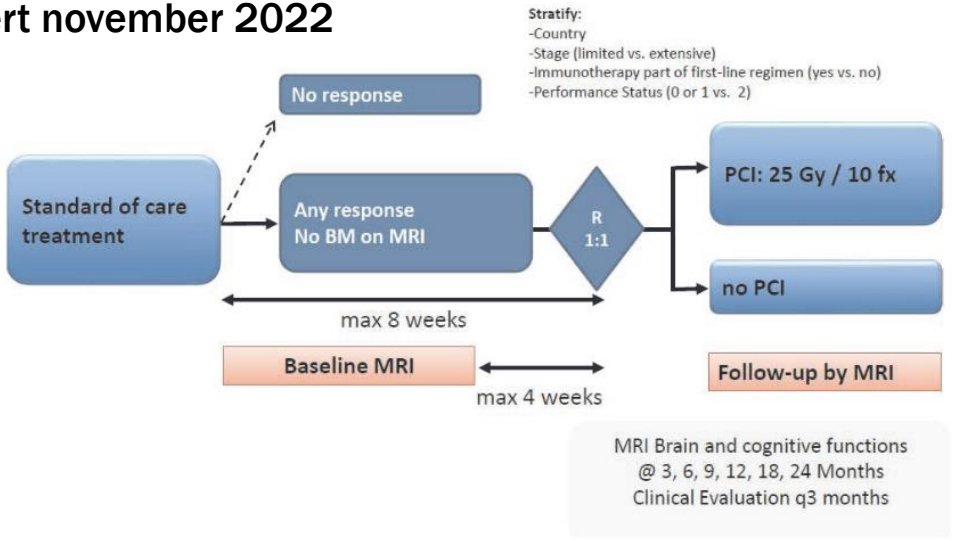
Samenvatting

Discussie:

- Effectiviteit? (extensive disease)
- Angst voor lange termijn neurotoxiciteit
- Neurotoxiciteit moeilijk beoordeelbaar
- Wat met combinatie immunotherapie?
- Verbeterde systeemtherapie -> minder hersenmetastasen –> nog nood aan PCI?
- Verbeterde imaging en staging: MRI surveillance als alternatief?
- Verbeterde RT technieken: stereotactische RT ipv WBRT?

PRIMALung studie

- EORTC studie
  - Fase 3 non inferiority design
  - Hypothese: OS met MRI surveillance is non-inferior aan PCI met MRI surveillance
  - Secund eindpunten: PFS, incid hersenM, QoL, neurocogn testing
  - Optie voor HA-RT
  - Studie lopende in GZA en UZA sedert november 2022



PRIMALung studie

- Inclusie criteria:
  - Age ≥ 18 years
  - Limited and extensive stage proven diagnosis of SCLC
  - Completed standard therapy prior to randomization:
    - For patients with LS-SCLC, this includes a combination of 4-6 cycles of platinum-based doublet chemotherapy and either definitive thoracic radiotherapy (including SBRT for early-stage T1-2 N0 M0 disease who do not undergo surgery) or definitive surgical resection; thoracic radiation in addition to definitive surgical resection is allowed at the discretion of the treating physician, but is not mandated.
    - For patients with ES-SCLC, this includes 4-6 cycles of platinum-based doublet chemotherapy either with or without thoracic radiotherapy
  - Immunotherapy concurrent with and/or adjuvant to standard therapy is allowed at the discretion of the treating physician.
  - Absence of progressive disease after completed standard therapy on systemic imaging (computed tomography (CT) or magnetic resonance imaging (MRI) of Chest/Abdomen/Pelvis), 42 days before randomization.
  - Absence of brain metastases or leptomeningeal disease after completed standard therapy on systemic imaging (brain MRI), within 28 days before randomization.
  - Interval from day 1 of last cycle of chemotherapy to randomization of ≤ 16 weeks
  - ECOG PS ≤ 2
  - Estimated creatinine clearance ≥ 30 mL/min as calculated using the MDRD formula
  - Women of child-bearing potential (WOCBP) must have a negative serum pregnancy test

Toekomst perspectieven

- Verschillende fase 3 trials PCI vs surveillance lopende (MAVERICK – PRIMER, NCI trial)
- Alternatieven: stereotactische RT voor beperkte asympomatische hersenM = FIRE SCLC trial (retrospectieve cohort studie)
- Subgroepen selecteren wie benefit van PCI:
  - vb Vooral pt met CR locoregionaal vaak meer kans op herval cerebraal
  - -> tot 1/3 pt

Bedankt!