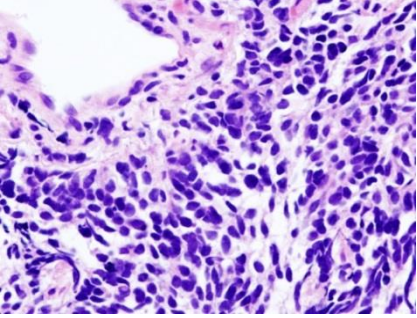




Optimisation of radiotherapy in small cell lung cancer

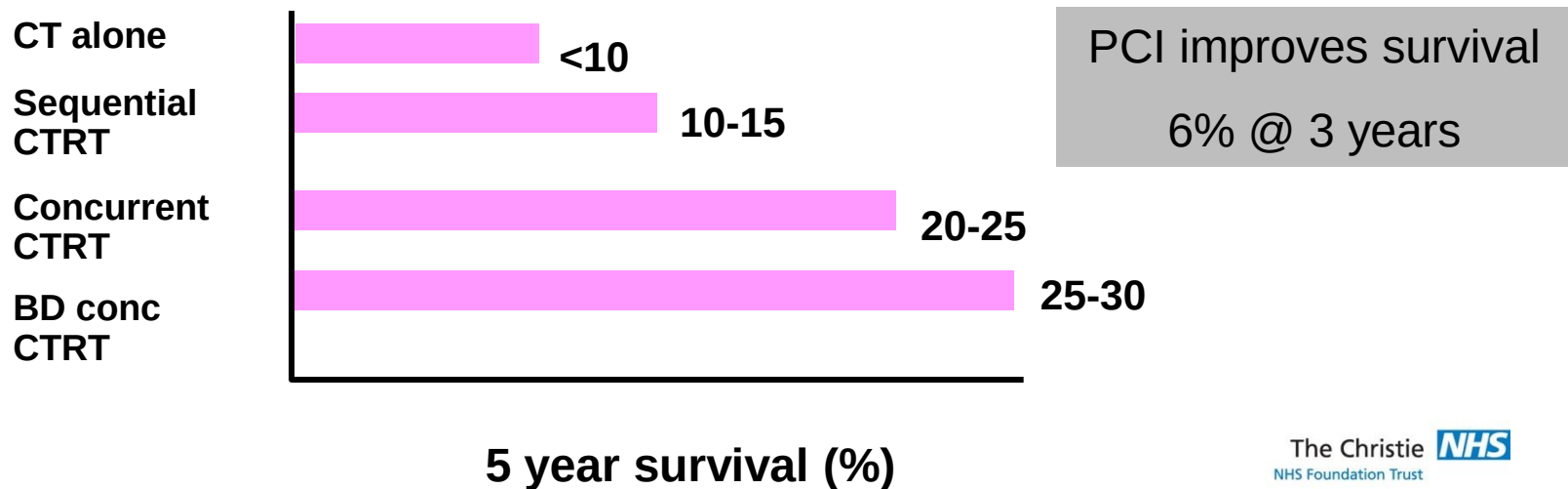
Corinne Faivre-Finn MD PhD
Manchester Lung Cancer Group
Manchester Radiotherapy Related Research Group

28th March 2014
ELCC 2014



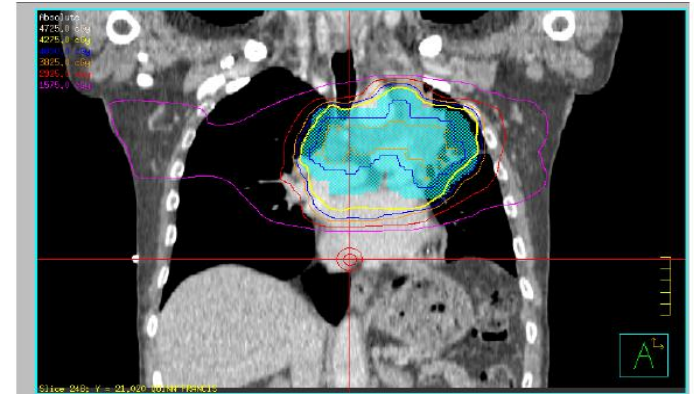
The impact of RT on survival in LS-SCLC

- No change in systemic therapy in last 20 years
 - No role for anthracyclines/pemetrexed/irinotecan
 - No role for targeted agents
- Impact of RT



Stage I-III SCLC - clinical case

- 55 year old male
- PMH HBP, ex smoker 30 PY
- PS1, MRC RS 1
- Presented with a cough and SOB on exertion
- FEV1 92% predicted, KCO 85% predicted
- Bronchoscopy-tumour obstructing the L main bronchus
- CT thorax&abdomen
 - Mass LUL
 - Station 4R, 4L, 5 and 7 lymph nodes
- CT brain clear



Treatment options

- Sequential CTRT
 - 45 Gy/15F
 - 50-55 Gy/20F
 - >60 Gy/30+F
- Concurrent CTRT
 - 45 Gy/15F
 - 45 Gy/30F BD
 - 50-55 Gy/20F
 - >60 Gy/30+F
- 3DRT or IMRT? ENI?

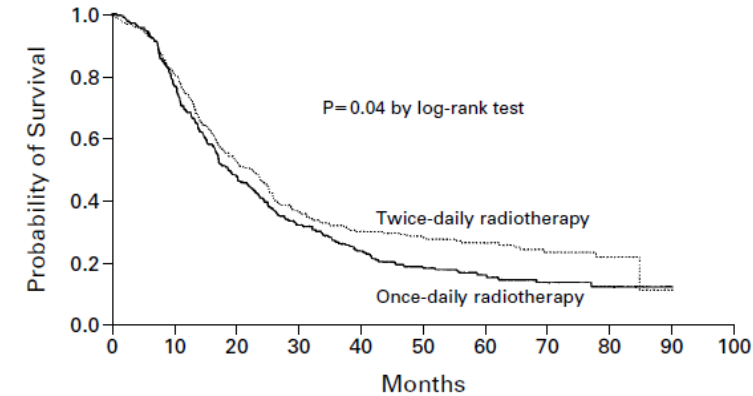
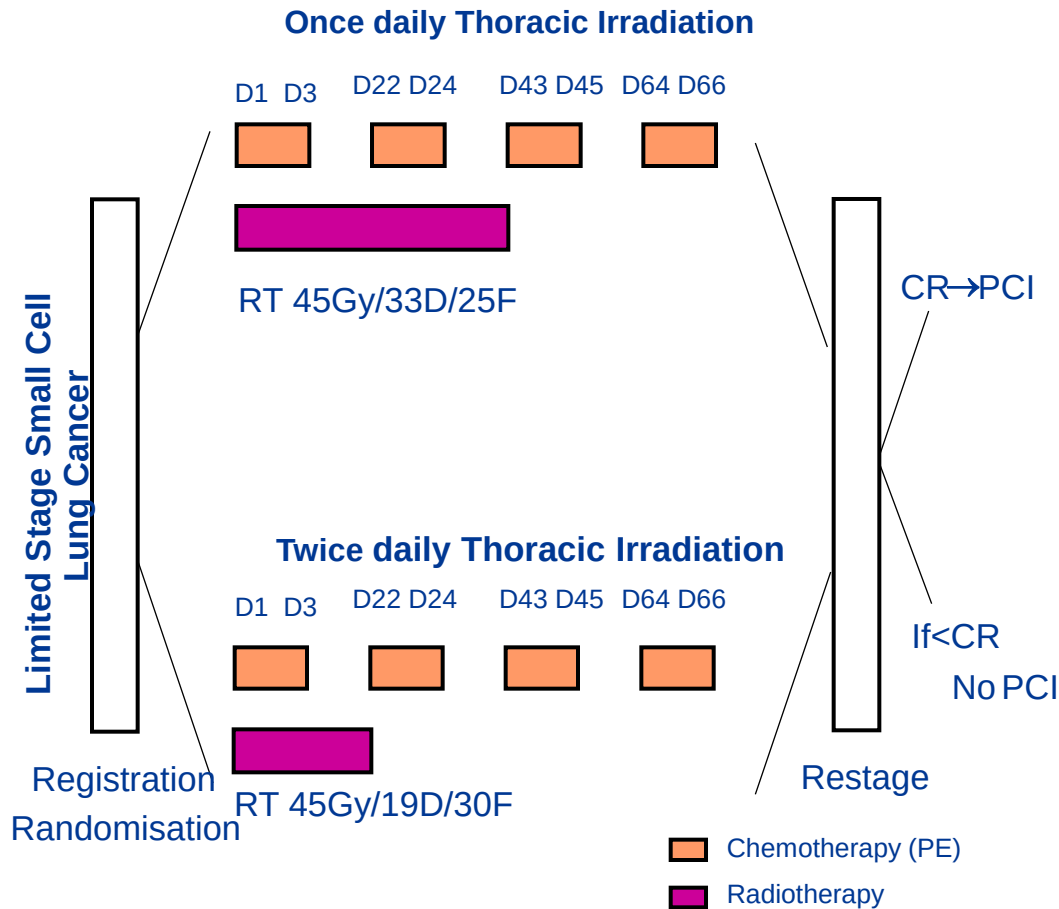


Standard of care in LS-SCLC

- CTRT >CT (*Pignon, Warde*)
- Early RT >late RT (*Fried , Cochrane review*)
- Concurrent CTRT >sequential CTRT (*Takada*)
- Best survival results achieved with early BD concurrent CTRT (*Turrisi, Jeremic*)



Standard of care for LS-SCLC Intergroup 0096



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	

Turrisi et al. N Engl J Med 1999



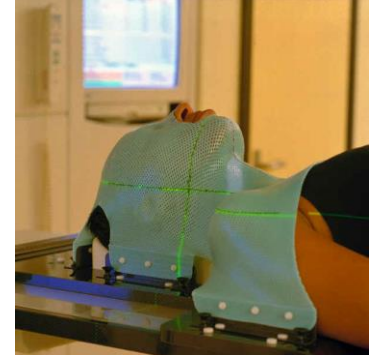
US radiation oncology survey

BD RT was used for 21% of patients in 2006-7 vs. 8% in 1998-9

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Standard of care PCI in LS-SCLC



- PCI reduces the risk of brain metastasis by ~ 50%
- PCI improves survival (6% @ 3 years)
Auperin. N Engl J Med 1999
- Standard dose 25 Gy in 10 fractions
Le Pechoux. Lancet Oncol 2009
- Benefit of PCI is maintained in the elderly population (SEER data-n=1926)
Eaton. Cancer 2013
- Significant neurocognitive impairment prior to PCI (~50%)
- Long term neurological sequelae?
Arriagada. J Natl Cancer Inst 1995
Gregor. Eur J Cancer 1997

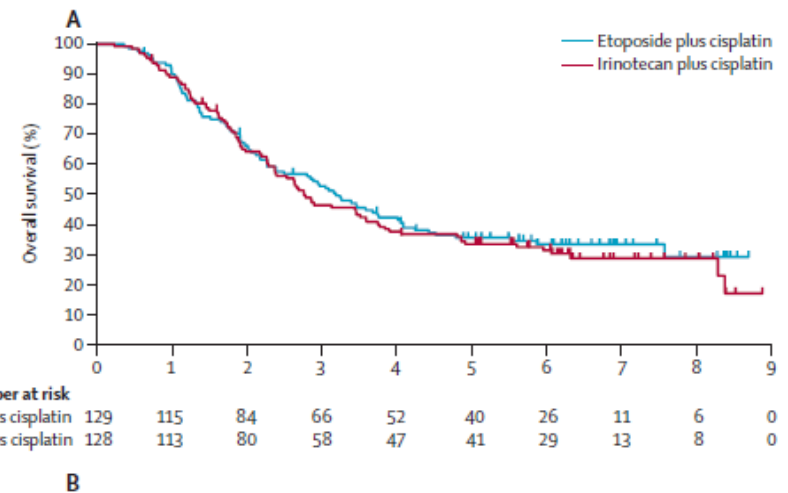
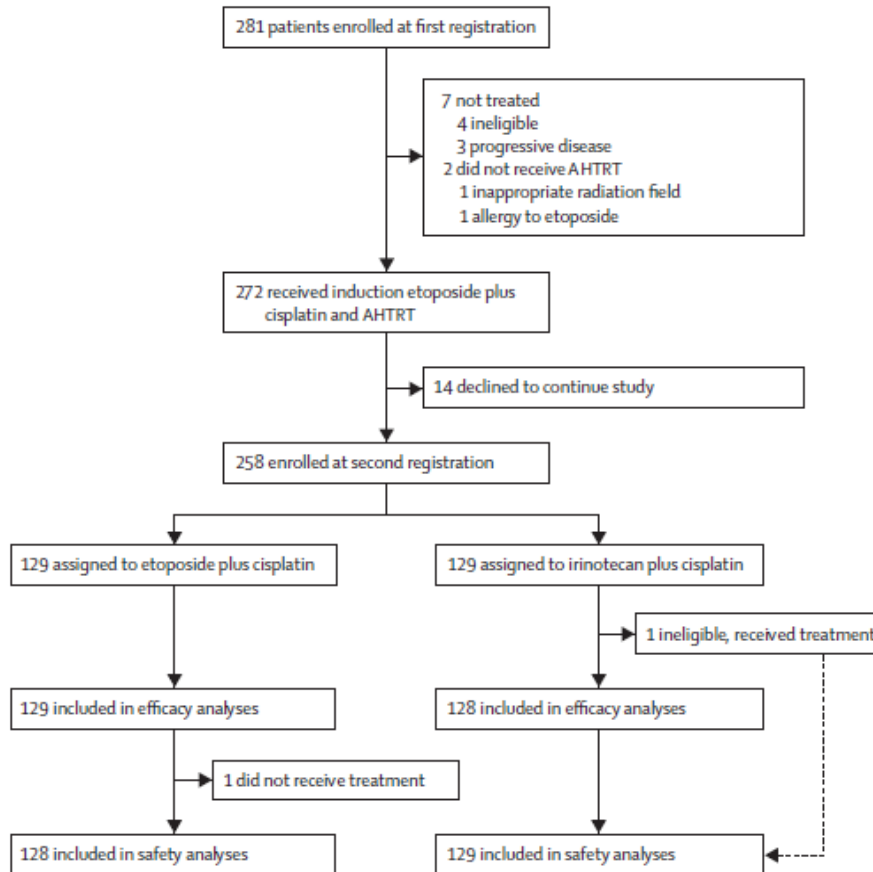


Strategies to optimise RT in LS-SCLC

- Optimise systemic therapy in combination with RT
 - Chemotherapy
 - Targeted agents
 - Immunotherapy
- Maintenance treatment
- Optimise RT
 - Dose
 - Fractionation
 - Volume of treatment
 - Planning, delivery, verification
- Identify patients likely to benefit from CTRT
- Reduce toxicity of PCI



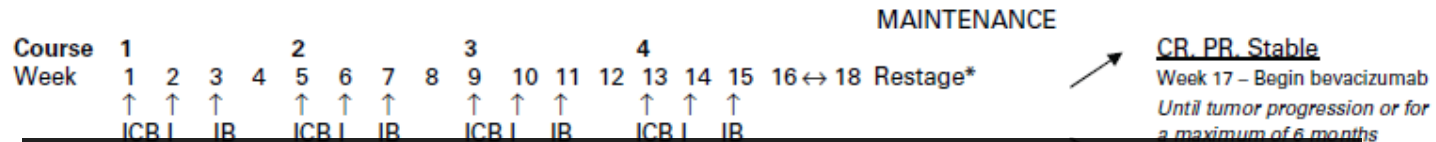
Alternative to EP in LS-SCLC?



SCLC and targeted agents

Study	Target	Agent	Design	Result
NCI-C/EORTC	MMP	Marimastat	+/- Maintenance	Negative
BAYER		BAY 12-9566	+/- Maintenance	Negative
ECOG CALGB HOG	VEGF	BEV (B)	Chemo + B Chemo + B Chemo + B	Positive Negative Negative
LLCG	Vascular stabilizer	Thalidomide	Chemo +/- T	Negative
NCI-C	VEGFR TKi	ZD 6474	+/- Maintenance	Negative
SWOG	VEGFR TKi	Sorafenib	Monotherapy	Negative
NCI	VEGFR TKi	ZD 2171	Monotherapy	Negative
Rudin	Bcl-2	Oblimersen	Chemo +/-	Negative
Langer	Bcl-2	Obatoclax	Chemo +/-	Negative
ECOG	mTOR	CCI-779	+/- Maintenance	Negative
HOG	EGFR	gefitinib	Monotherapy	Negative
Johnson Krug Dy	Kit	Imatinib	Monotherapy Monotherapy Monotherapy	Negative Negative Negative
EORTC	GD-3	BEC2/BCG	+/- Maintenance	Negative
SWOG	Proteosome	Bortezomib	Monotherapy	Negative
SWOG	RAS/VEGF	Sorafenib	Monotherapy	Negative

Radiotherapy and targeted agents



Phase II -29 LS-SCLC patients recruited

Early trial closure

Two patients developed tracheoesophageal fistulae

One patient died from an aerodigestive hemorrhage

Irinotecan (I) 60 mg/m², days 1, 8, 15

Carboplatin (C) AUC 4.0 IV, day 1

Radiation Therapy 45 Gy in 15 fractions

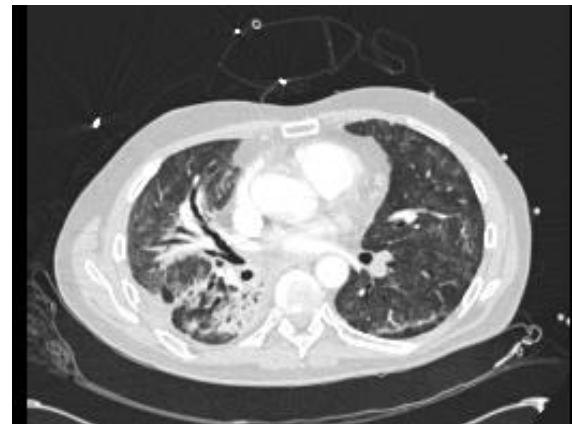
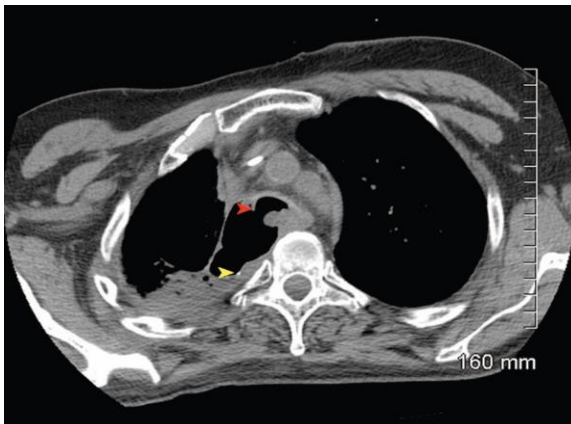
beginning with Course 1 of chemotherapy

Bevacizumab (B) 10 mg/kg IV days 1, 15

Four courses of chemotherapy administered. Courses repeated at 28-day intervals.

Maintenance Therapy

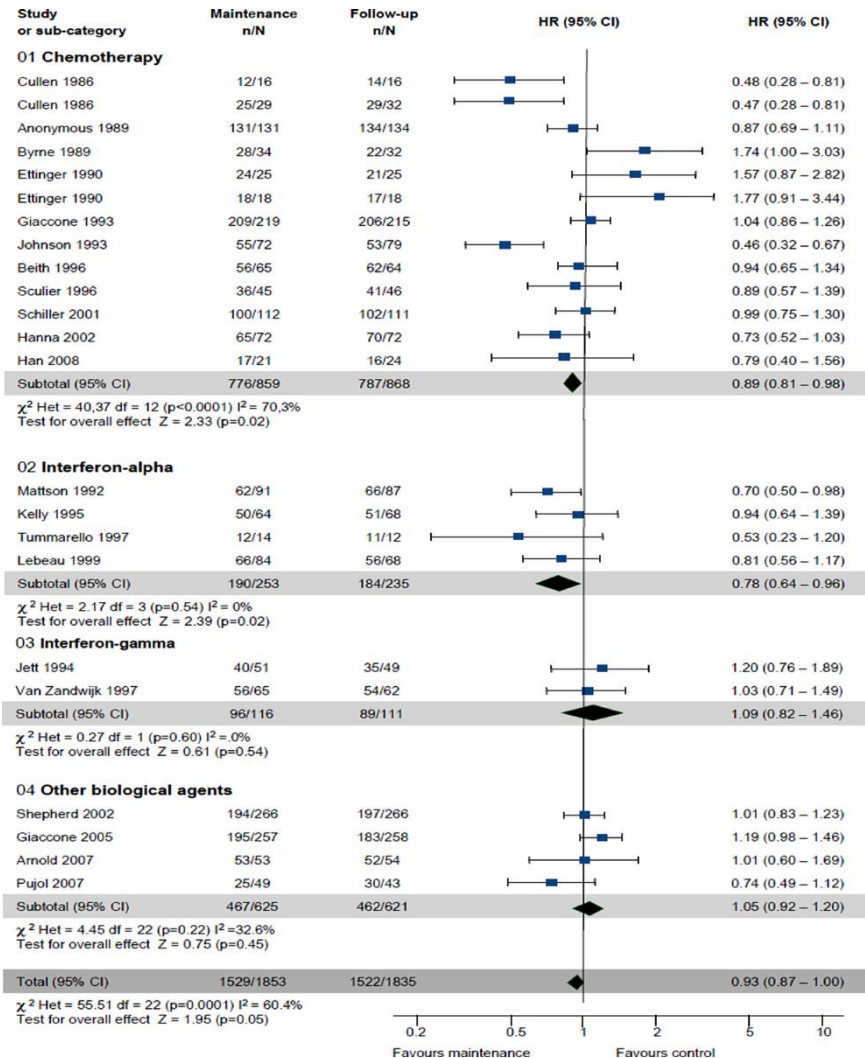
Bevacizumab (B) 10 mg/kg IV days 1, 15 until disease progression, or a maximum of six cycles (6 months)



Spigel et al. J Clin Oncol 2010

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NHS Foundation Trust

Maintenance or consolidation therapy



N = 3688, 14 RCTs

All (n=21) HR 0.93 (0.87-1.00) p=0.05

CT (n=11) HR 0.89 (0.81-0.98) p=0.02

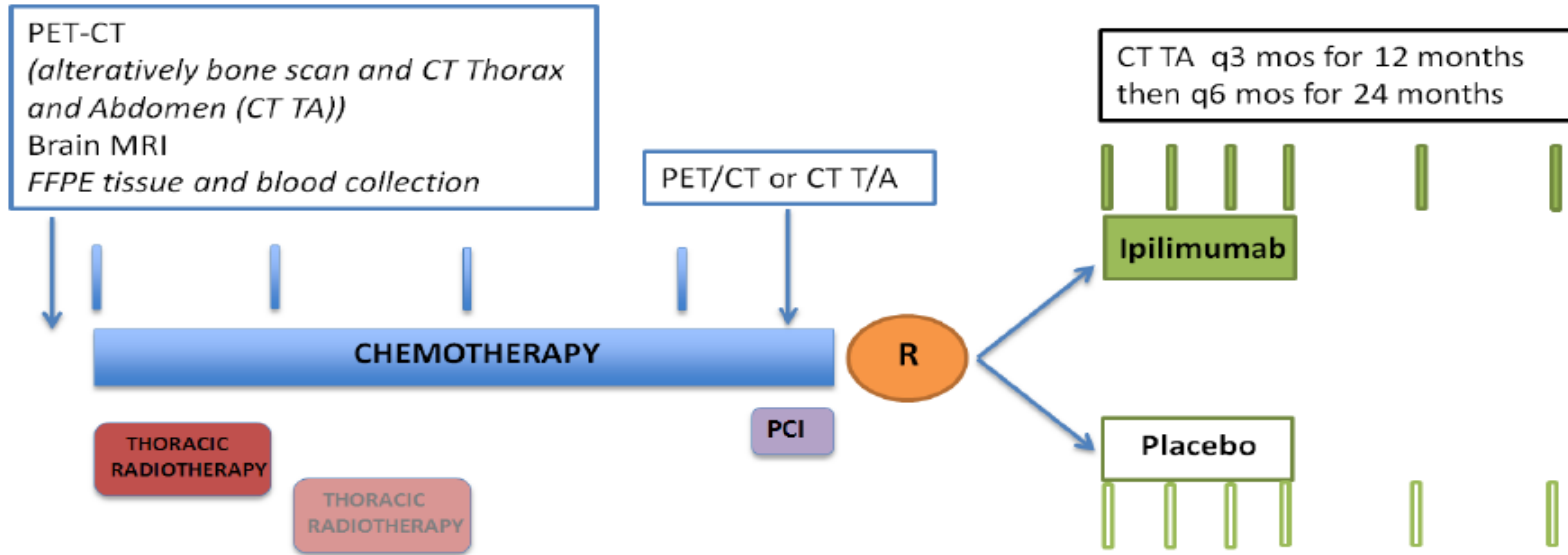
CT increased OS 1 yr by 9% , 2yr by 4%

IFN α (n=4) HR 0.78 (0.64-0.96) p=0.02

‘Clinical impact of maintenance chemotherapy needs to be confirmed by further studies’



ETOP STIMULI study



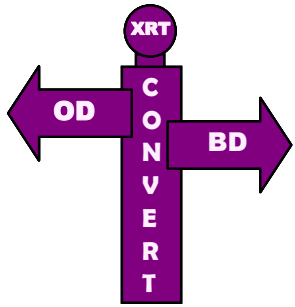
Chemotherapy: 4 cycles of Cisplatin 25 mg/m² iv D1-3 or 75 mg/m² D1 Etoposide 100 mg/m² iv D1-3 q21d.

Thoracic Radiotherapy: Accelerated twice-daily, administration of 1.5 Gy x 30 over three weeks (preferred) or once-daily radiotherapy, administration 1.8-2Gy per fraction up to 55-60Gy. . Two options are allowed: start from D1 of cycle 1 or cycle 2.

Prophylactic Cranial Irradiation (PCI): 25 Gy in 10 fractions started between D5 and D10 of cycle 4

Ipilimumab (or placebo schedule): Induction course of ipilimumab, at a dose of 10 mg/kg, once every 3 weeks x4, started 4-7 weeks after cycle 4 of chemotherapy. Maintenance: 10mg/kg, once every 12 weeks, for a maximum of 3 years after randomization.





Why CONVERT?



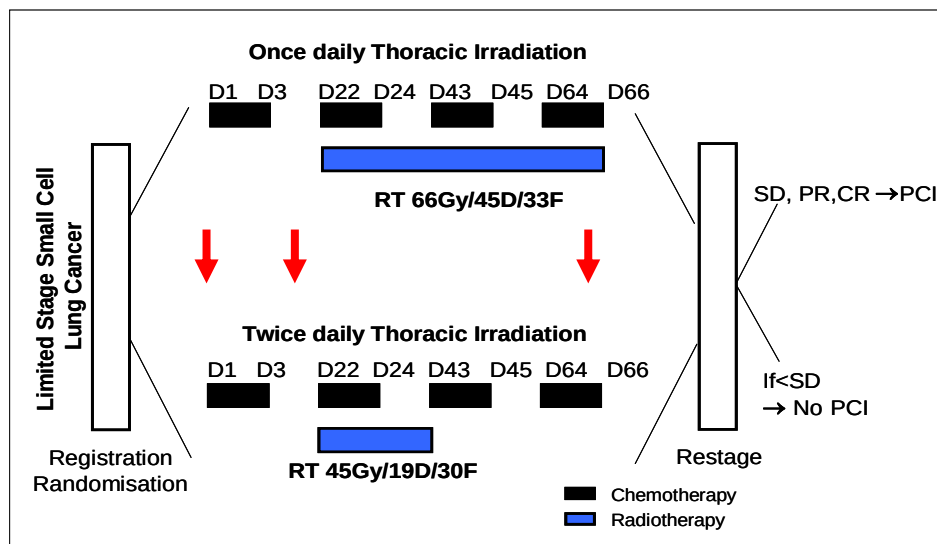
- Establish a **standard regimen** in LS-SCLC
- Importance of
 - the **RT dose**?
 - the **overall treatment time**?
- Toxicity and outcome data with **modern RT techniques**
- Can we omit ENI?
- Can G-CSF be prescribed safely in the concurrent setting?
- Can we treat elderly patients safely with CTRT?
- Can we identify patients likely to benefit from CTRT?



Randomised Ph III CONVERT Trial

Concurrent CT with once vs twice daily RT for LS-SCLC

- 547 patient, CRUK funded (NCRI, EORTC, NCIC, Spanish & French LGs)
- To establish the standard curative intent regimen for LS-SCLC
- 'The gold standard' for biomarker qualification



Timepoint	Pre	d22	End
Blood			
CTCs [Christie only]	✓		
NE/Angio/death/OPN	✓	✓	✓
Genomic DNA SNPs	✓		
Tissue			
Mcl-1, Bcl-2, CC3, Ki67, GLUT-1, HIF 1α	✓		relapse

Study Design

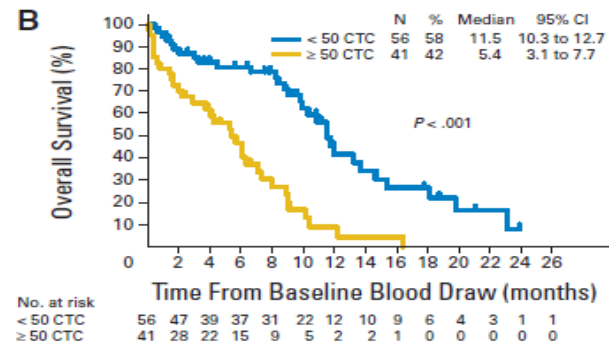
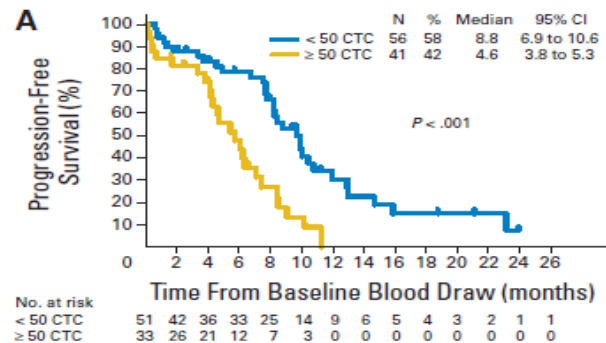
CONVERT: 12% survival benefit (HR = 0.70) at 2 years, 5% significance, 2-sided, 80% power
T-CONVERT: 90% power to detect groups separated by 13-15%, 5% significance, 2-tailed test.

Circulating tumour cells in SCLC

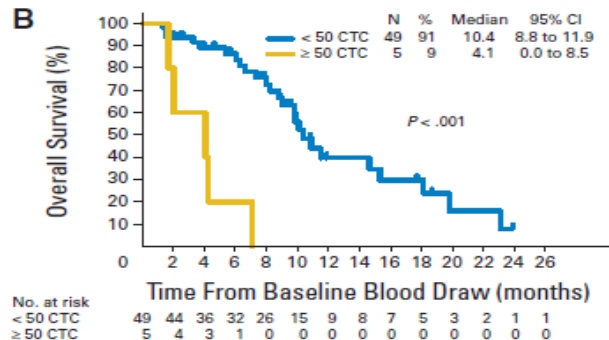
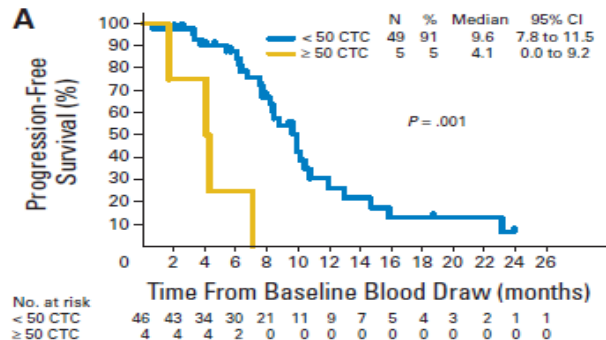
Table 1. Patient Characteristics

Characteristic	Evaluable Patients (n = 97)	
	No.	%
Age at baseline, years		
Median	68	
Range	28-84	
Sex		
Female	54	56
Male	43	44
Stage at diagnosis		
Limited	31	32
Extensive	66	68

baseline



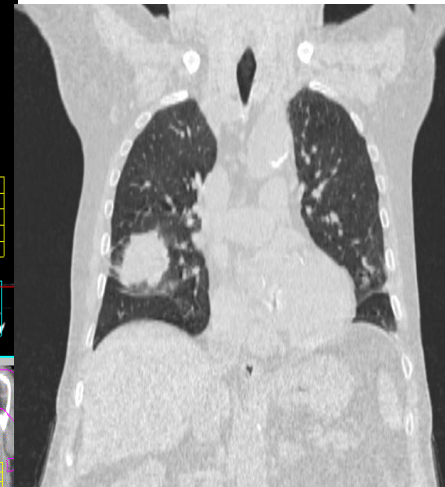
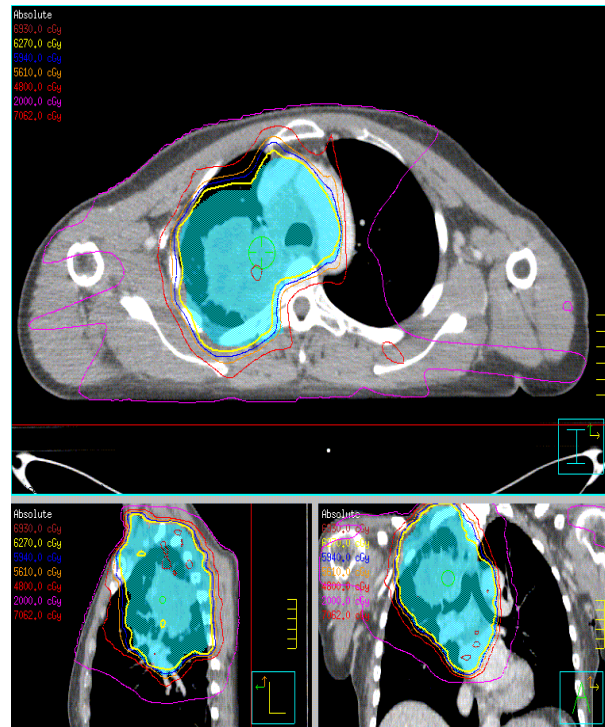
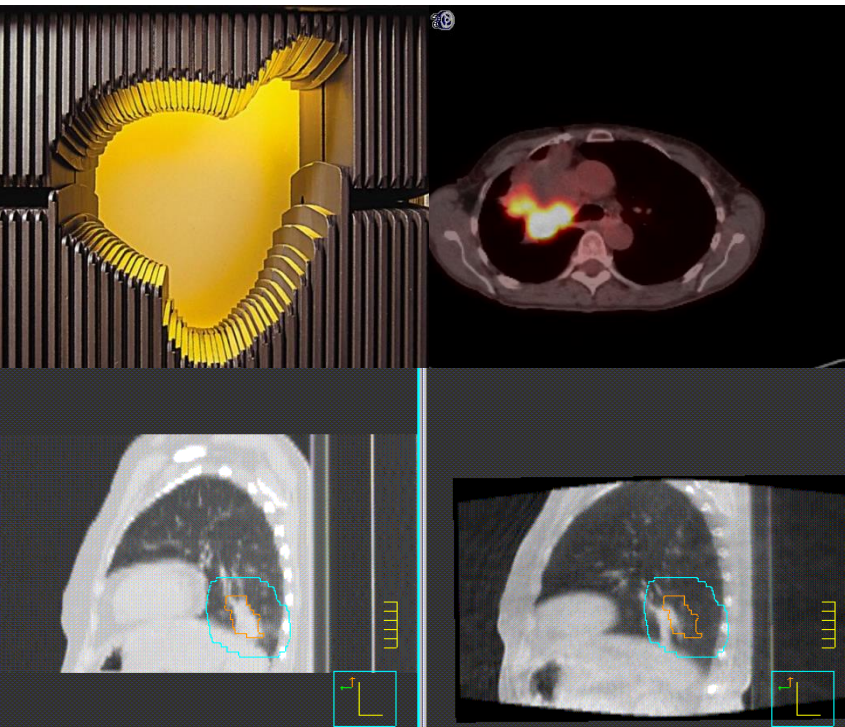
After cycle 1



Considerations for radiotherapy techniques

Modern techniques

- 3D CRT/IMRT
- 4DCT and PETCT for RT planning
- IGRT



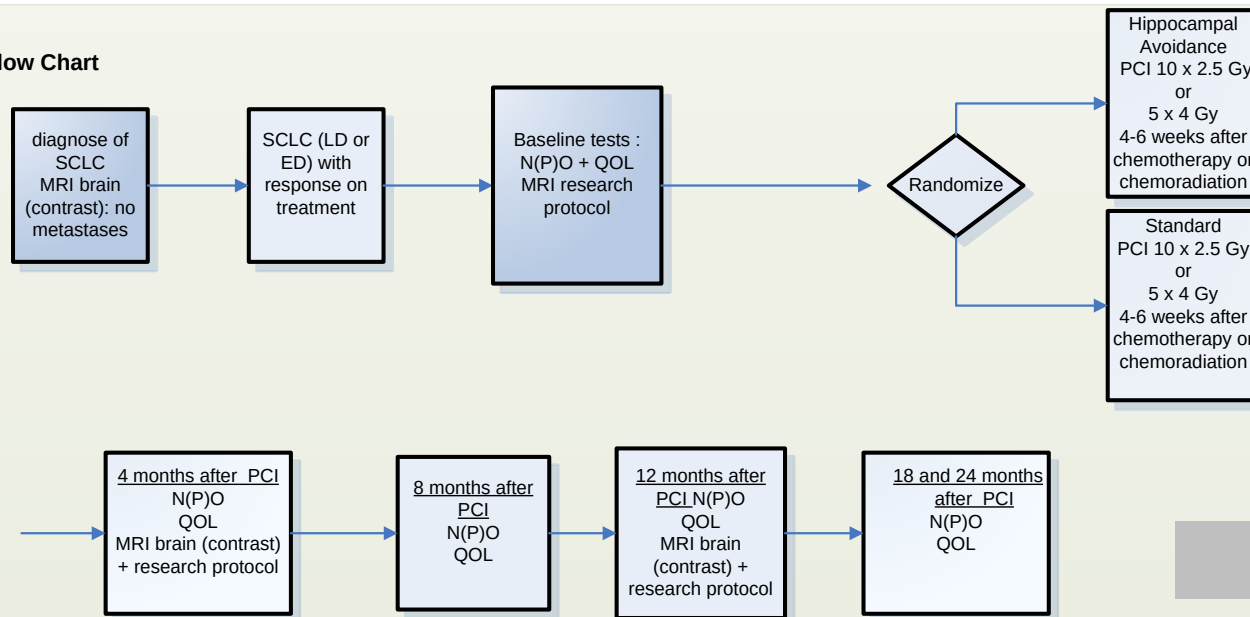
CONVERT facility questionnaire

Lung planning techniques	2008	2013
FDG-PET imaging for GTV delineation	20	28
Intensity Modulated Radiotherapy	3	14
Volumetric Arc Therapy	0	2
Use of 4DCT	3	14
Treatment planning algorithms		
•Type A treatment planning algorithm	9	1
•Type B treatment planning algorithm	24	33
•Clarkson algorithm	1	0
•Monte Carlo algorithm	0	2
Treatment verification		
•Megavoltage electronic portal imaging	17	17
•Cone beam CT (CBCT)	6	17
•Kilovoltage planar imaging	2	8
•Radiographic portal films	4	0



PCI hippocampus sparing

Flow Chart



Inclusion criteria

- Patients with either limited disease (LD) or extensive disease (ED) small cell lung cancer (SCLC) candidate for PCI after a partial or complete response to chemotherapy or chemoradiation
- WHO-performance status ≤ 2 (see Appendix IV).
- Sufficient proficiency in Dutch language
- No evidence of progressive extracranial metastatic disease

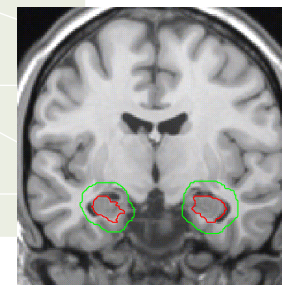
Exclusion criteria

- Prior radiotherapy to the brain
- Patients receiving any systemic anticancer treatment during PCI
- Pregnancy or lactation

Randomization

- ☐ The patient had chemoradiation or chemotherapy less than 6 weeks prior the randomization
- ☐ The patient will receive PCI within 2 weeks after randomization
- ☐ No signs of progressive disease after chemotherapy
- ☐ Signed informed consent

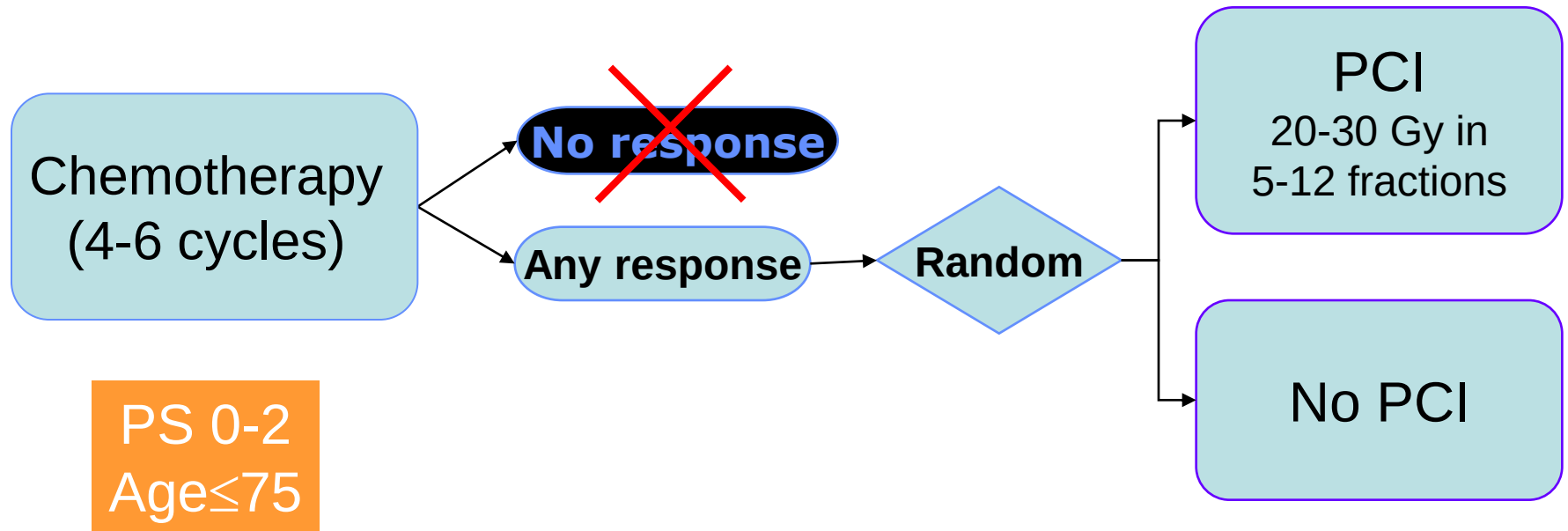
Primary objective
To reduce memory function loss 4 months after PCI



ES or Stage IV SCLC



Prophylactic cranial irradiation in stage IV SCLC EORTC 08993-22993



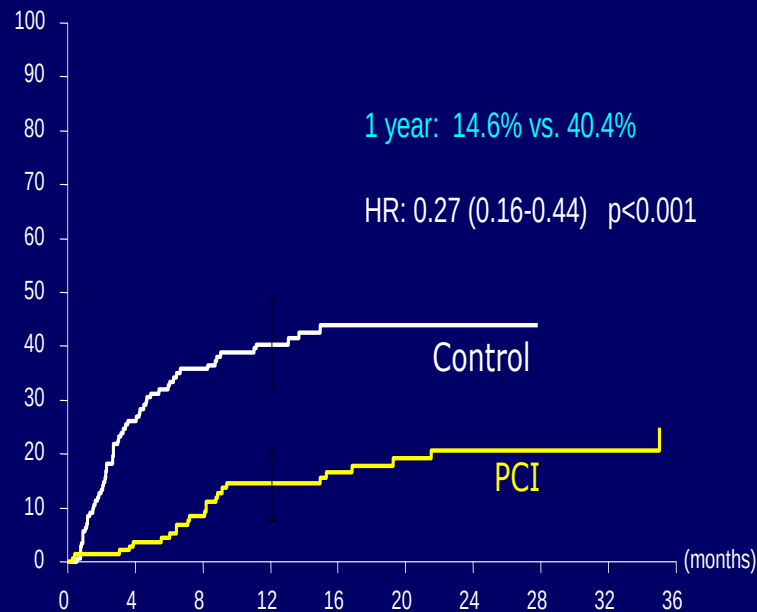
Slotman et al. N Engl J Med 2007



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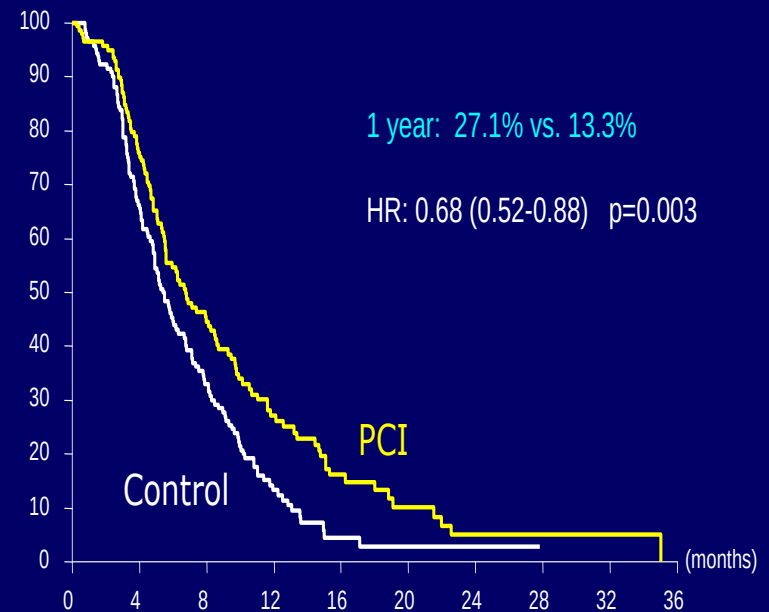
Prophylactic cranial irradiation in stage IV SCLC EORTC 08993-22993

Symptomatic brain metastases



Slotman et al. *N Engl J Med* 2007; 357: 664-72

Overall survival



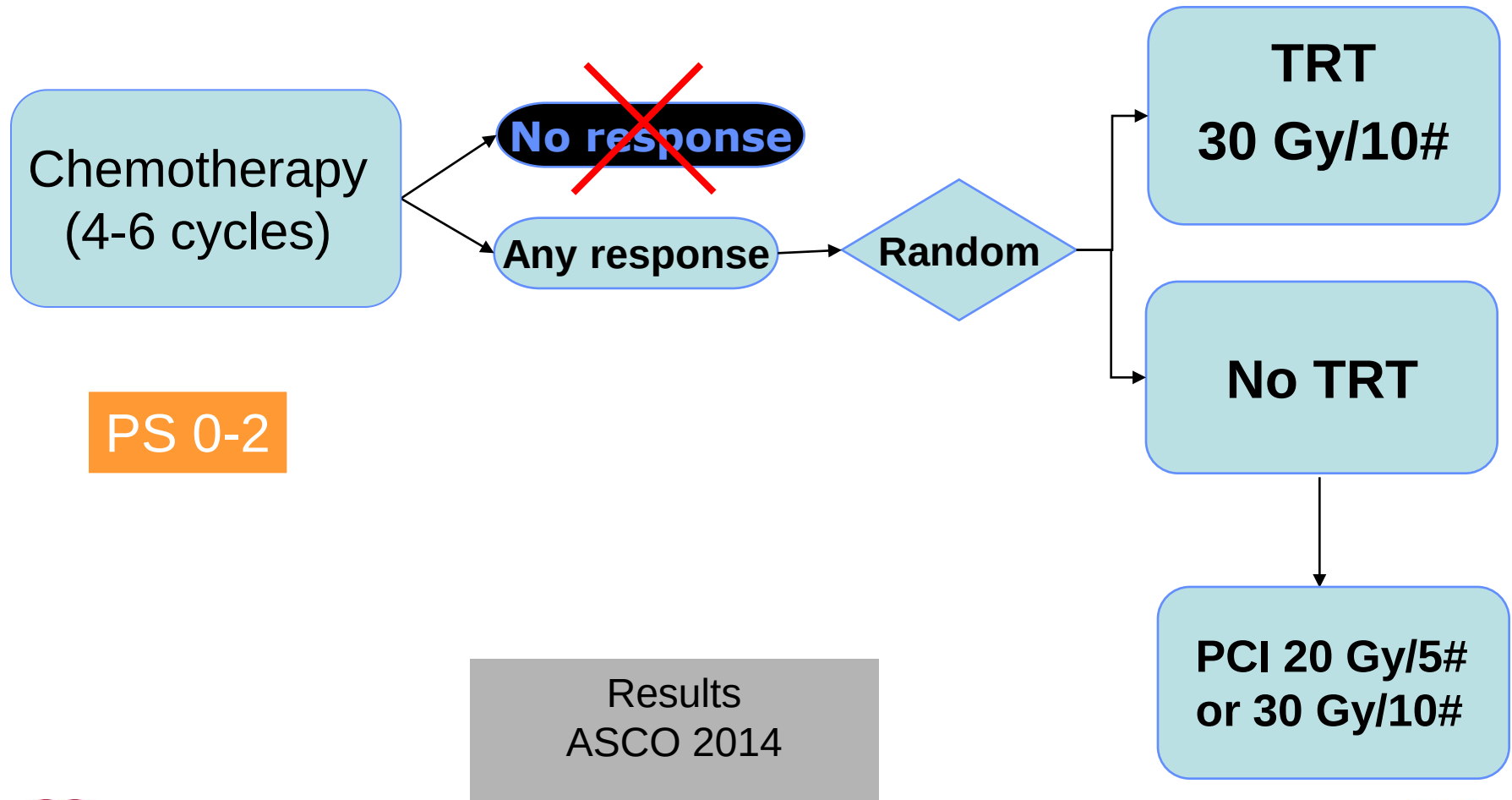
Slotman et al. *N Engl J Med* 2007; 357: 664-72



Slotman et al. *N Engl J Med* 2007

CREST

Dutch-UK thoracic RT study in stage IV SCLC



Conclusions

- Major progress in LS-SCLC in the last two decades **with RT**
 - Progress translating into improvements in both local control and survival
 - RT is the **only targeted treatment** that currently works in SCLC
- PCI improves survival in both LS and ES
- The CONVERT and CREST trial will establish new standards of care
- Need to understand the biology!

