EUROPEAN LUNG CANCER CONFERENCE 2016

ANY ROLE OF PROPHYLACTIC CRANIAL IRRADIATION IN NSCLC

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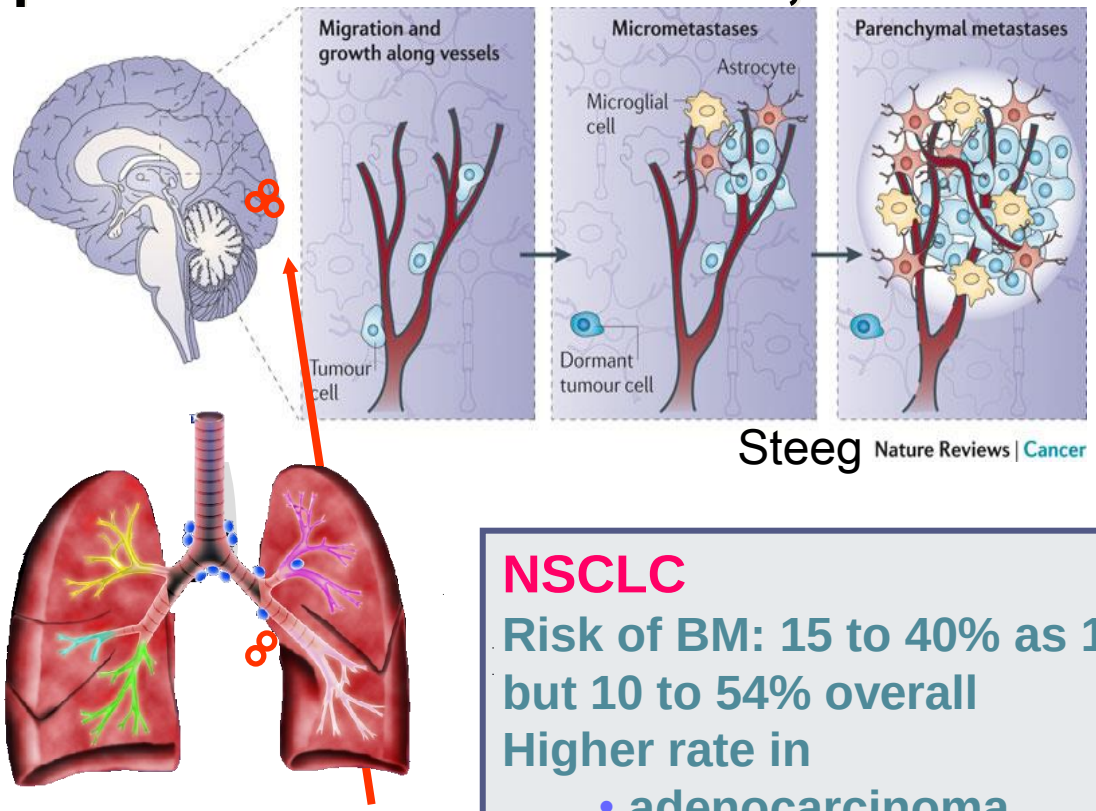
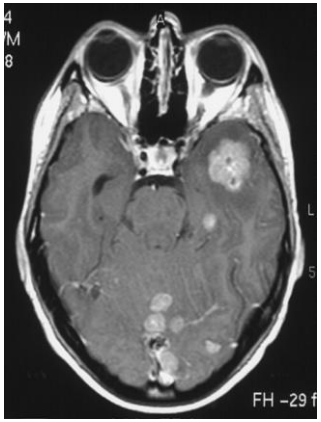
DISCLOSURE SLIDE

No disclosures to declare

Brain: Frequent site of failure in SCLC and NSCLC but BM are less frequent in NSCLC than SCLC,



Steeg Nature Reviews | Cancer 2011

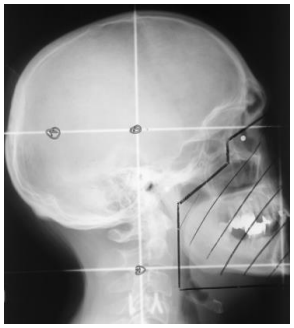


NSCLC

Risk of BM: 15 to 40% as 1st site of recurrence, but 10 to 54% overall

Higher rate in

- **adenocarcinoma**
- **Higher stage**
- **Nodal involvement**



PCI or no PCI ?
in high risk NSCLC patients

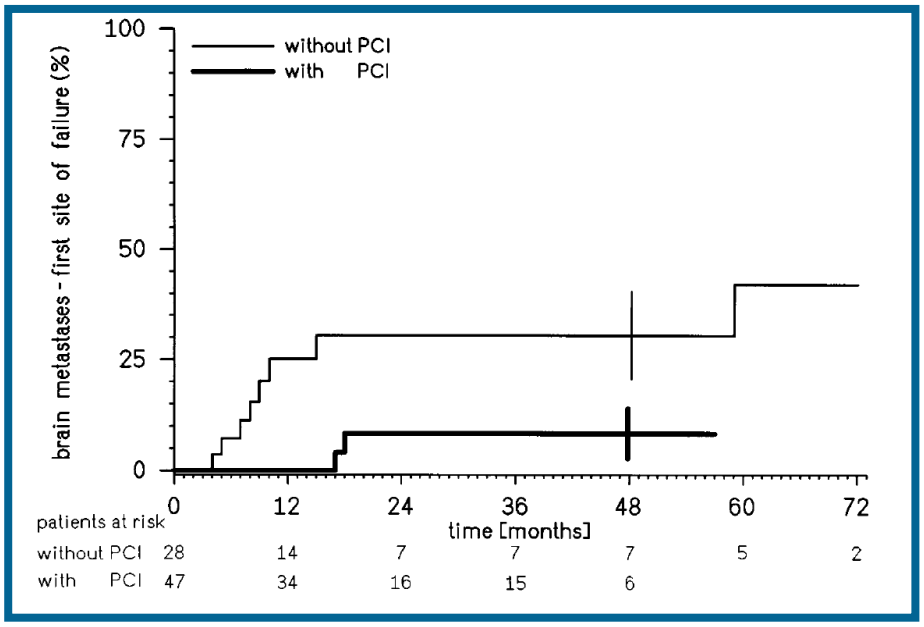
Author	Patients	Stage	Dose N fr	BM No PCI	BM PCI	p	OS No PCI	OS PCI	p
Cox 1981 VALG	281	inoperable	20/10	13%	6%	0.038	41.4 wks	35.4 wks	0.5
Umsawasdi 1984	97	I, II or III	30/10	27%	4%	0.002	-	-	-
Russel 1991 RTOG	187	II/III	30/10	19%	9%	0.1	2-yr SR 21%	2-yr SR 13%	0.36
	26	Resected Pts		25%	0%	0.06			
	161	Inop		18%	10%	0.34			

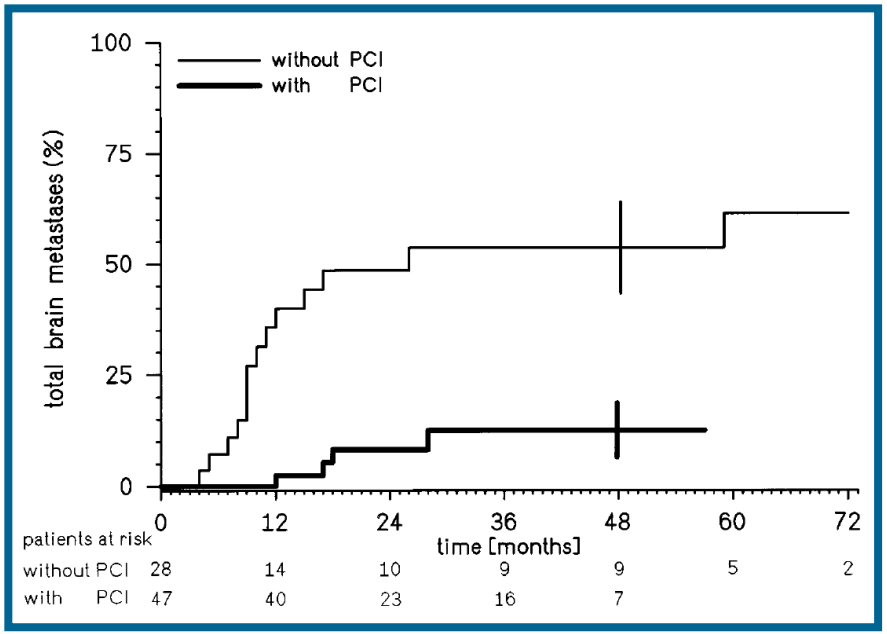
- Old trials!! No imaging …
- As systemic extra-cerebral control has improved, higher rate of BM
- Need for trials to reconsider PCI in NSCLC

RISK FACTORS OF DEVELOPMENT OF BM

- Outside of histology (adenocarcinoma), and stage (Stage III)
- Other factors have been described
- Age : Younger age or older
- Gender
- Response to treatment :
  - Good responders after Neo adjuvant CT or Neoadjuvant CTRT
  - Persistent nodal involvement after neoadjuvant treatment
- Superior sulcus location
- Genotype (patients with ALK rearrangement, EGFR mutation at higher risk)

Role of PCI in stage III treated with 3modality





- **Seventy-five patients : first 28 pts had no PCI, then following 47 pts were administered PCI (30 Gy/15 fr)**
- **PCI reduced the rate of BM as first site of relapse from 30% to 8% at 4 years (P=0.005) and that of overall brain relapse from 54% to 13% (P < .0001).**
- **Neuropsychologic testing : impairments in attention and visual memory in long-term survivors whether they received or not PCI**

elcc

Stuchke et al, JCO 1999

Evidence in favour of PCI in NSCLC?

VOLUME 25 · NUMBER 31 · NOVEMBER 1 2007

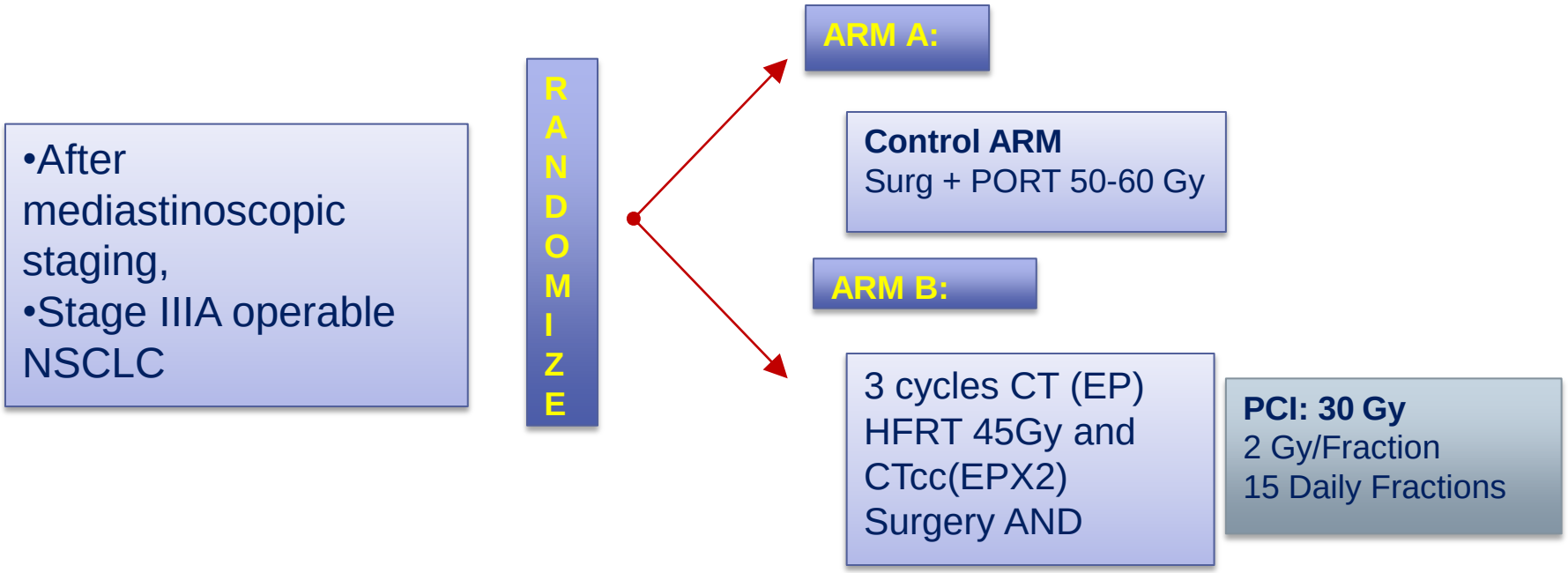
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Prophylactic Cranial Irradiation in Operable Stage IIIA Non–Small-Cell Lung Cancer Treated With Neoadjuvant Chemoradiotherapy: Results From a German Multicenter Randomized Trial

Christoph Pöttgen, Wilfried Eberhardt, Andreas Grannass, Soenke Korfee, Georg Stüben, Helmut Teschler, Georgios Stamatis, Horst Wagner, Bernward Passlick, Volker Petersen, Volker Budach, Hans Wilhelm, Isabel Wanke, Herbert Hirche, Hans-Jochen Wilke, and Martin Stuschke

SCHEMA Essen Trial Pottgen et al, JCO 07



112 patients randomized from Nov 1994 to July 2001, 43 pts had PCI

	Arm A	Arm B	p
5yr-Risk of BM(1st site)	34.7%	7.8%	0,02
5yr-Risk of BM	27,2%	9,1%	0,04

No difference in neurocognitive deficit

Brain relapse as 1st site of failure in stage III resected patients

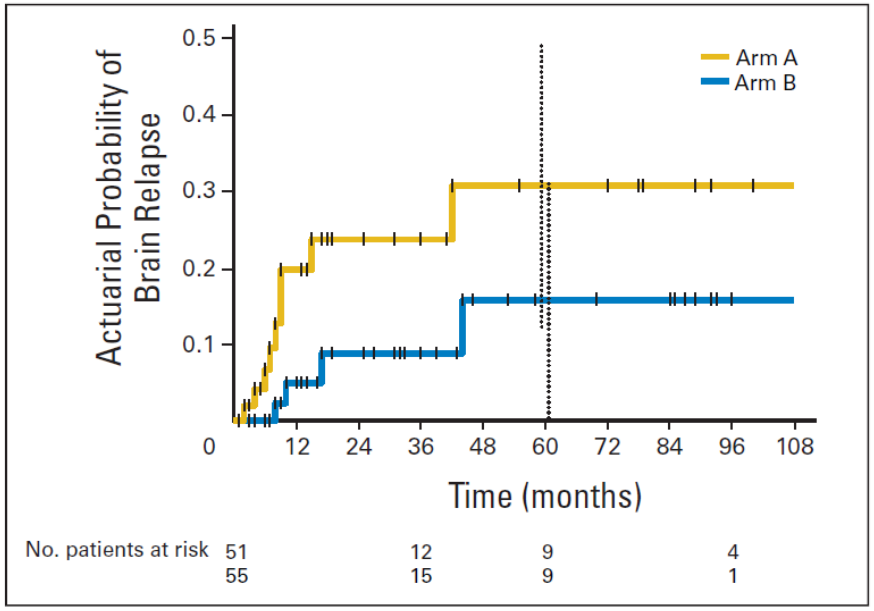


Fig 1. Actuarial probabilities of brain relapse at first site of failure by intent-to-treat analysis.

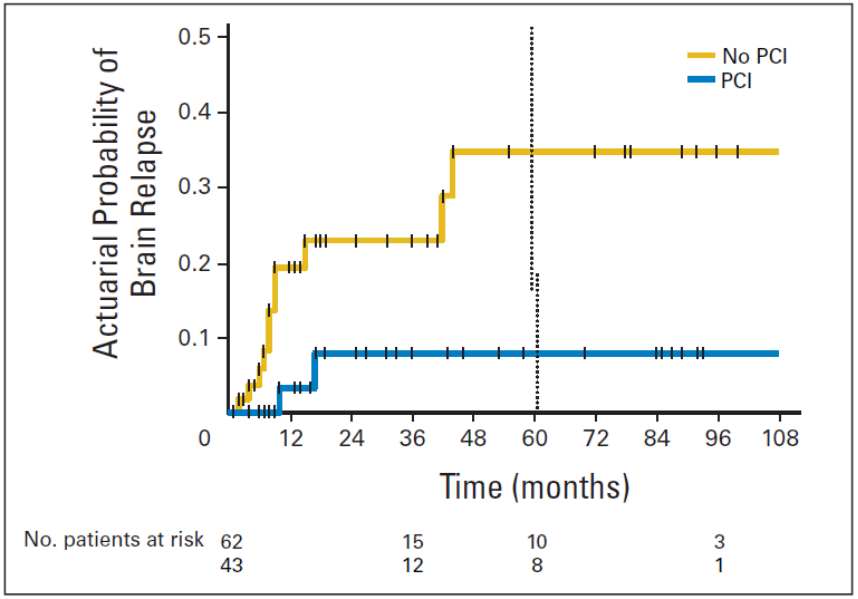
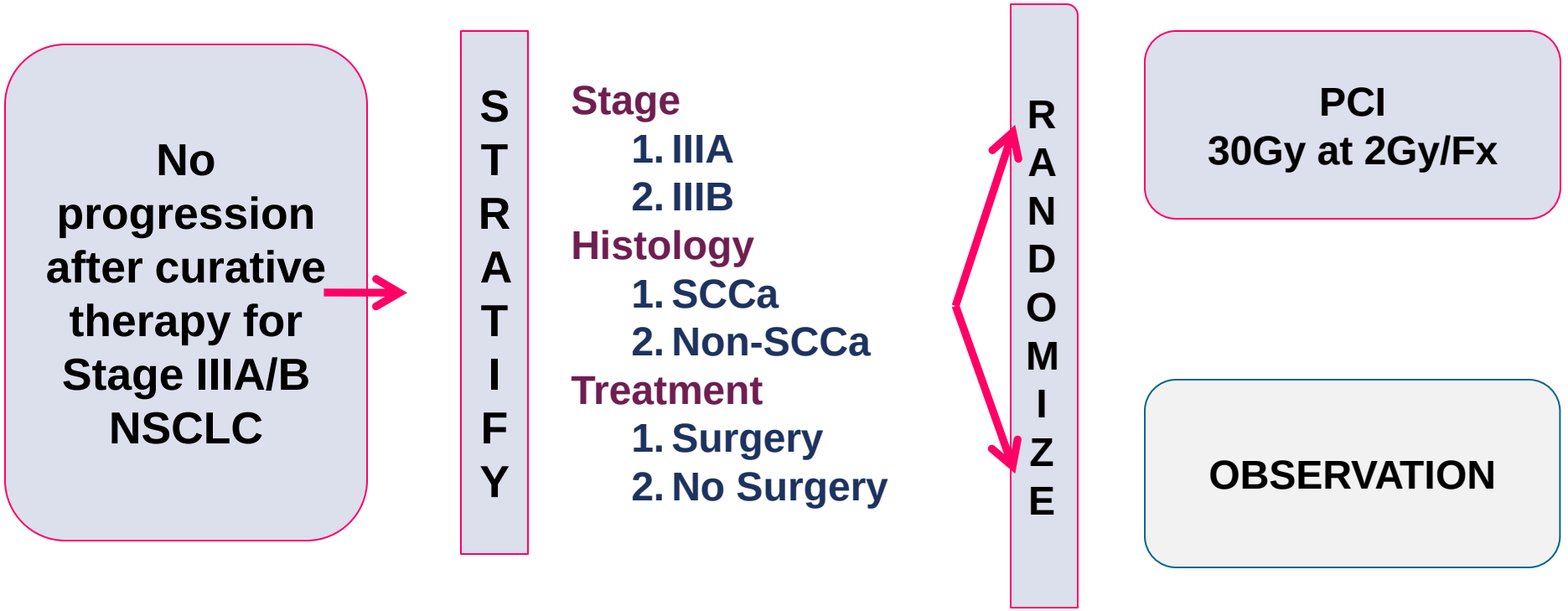


Fig 2. Actuarial probabilities of brain relapse at first site of failure according to the treatment actually administered. PCI, prophylactic cranial irradiation.

	Surg + TRT, No PCI		CTRTSurg +PCI	
2 yr Rate BM	23,7% ITA	22,8%	8,8%	7,8%
5 yr Rate BM	30,7% ITA	34,7%	15,8%	7,8%

Pottgen et al, JCO 2007

Schema of RTOG 0214



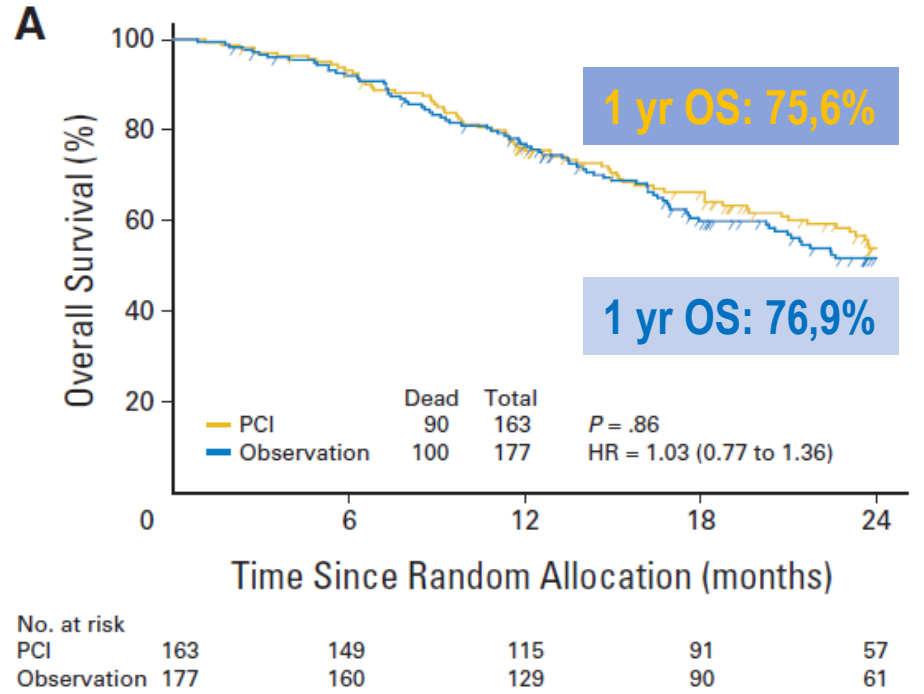
340 pts analysed / 1058 needed to show a survival improval

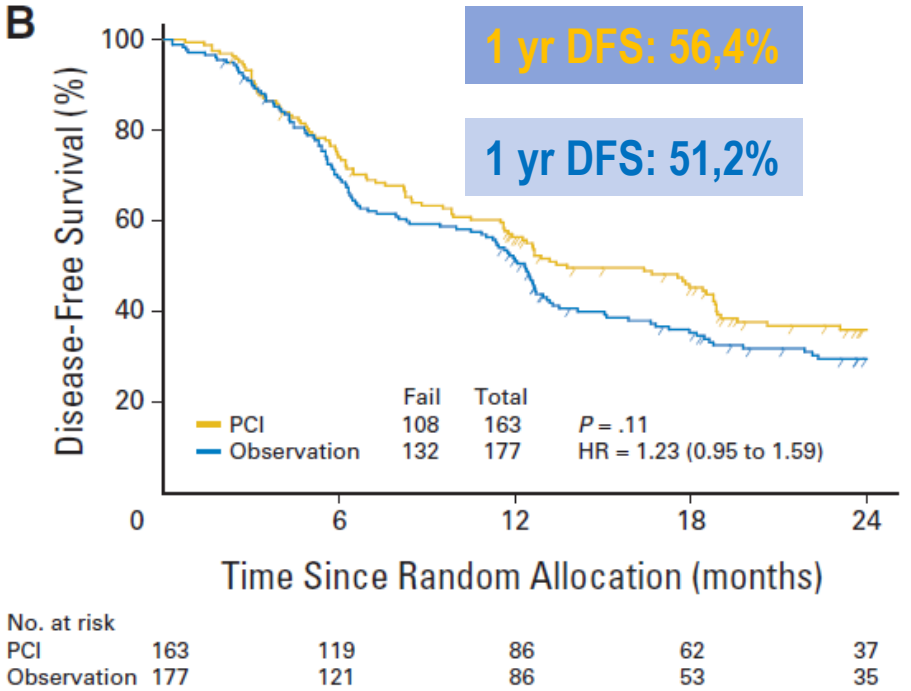
Primary objective: survival

Sary objectives: BM, DFS,QoL, Neuropsychological Function

Gore et al, JCO 2010

RTOG 0214: PCI vs no PCI in NSCLC





5 yr update will soon be published: it shows

- decreased rate of BM
- improved DFS, but no effect on OS

Gore et al, JCO 2011

Phase III Trial evalutating PCI in Locally Advanced NSCLC: Neurocognitive and Quality-of-Life Analysis.

340 pts analysed

Sun et al, JCO 2011

Table 3. Testing of Deterioration Status From Baseline in Mini-Mental Status Examination During Follow-Up Using Reliable Change Index

	Prophylactic Cranial Irradiation				Observation					

No significant differences at 1 year in

Mini mental Status Examination MMSE (P <0 .60) or

Activities of Daily Leaving scale ADLS (P <0 .88).

*From two-sample proportional test statistic comparing the percentage of people who deteriorated since baseline.

Table 4. Testing of Deterioration Status From Baseline in Hopkins Verbal Learning Test During Follow-up Using Reliable Change Index

	PCI				Observation					

Greater decline of memory (HVLT) in the PCI arm at 1 year

Immediate recall (P <0 .03)

Delayed recall (P < .008)

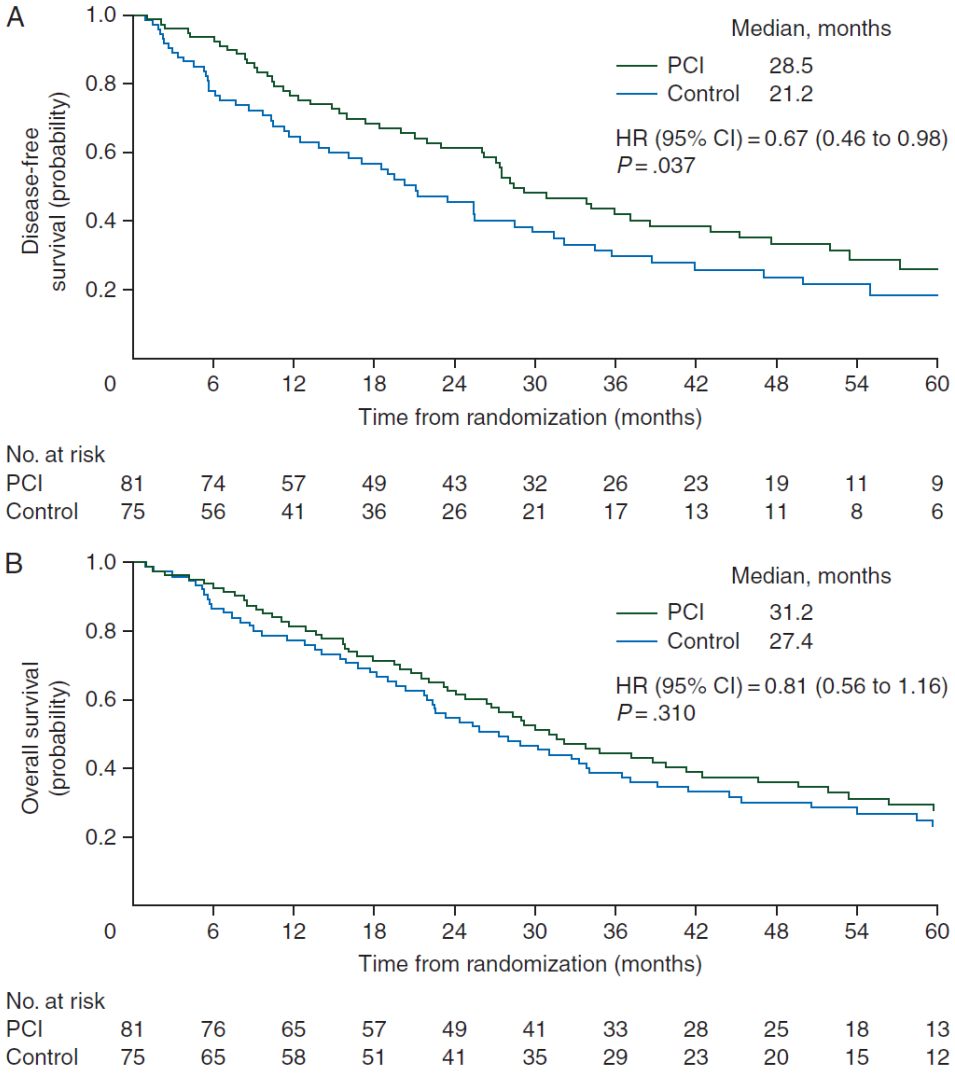
Delayed recall	8	15	44	85	8	14	50	86	.81	.81
12 months										
Recall	10	26	28	74	3	7	42	93	.01	.03
Delayed recall	10	32	21	68	2	5	38	95	.003	.008

Trials evaluating PCI in resected St III NSCLC

- 156 patients (81 to PCI group and 75 to control group).
- DFS PCI group > control group
  - median DFS of 28.5 mo vs 21.2 mo [HR 0.67; P= 0.037]
- Decrease in risk of brain metastases
  - 5-year BM rate, 20.3% versus 49.9%; HR, 0.28;P < 0.001).
- No difference in Median OS
  - 31.2 months in the PCI group and 27.4 months in the control group (HR, 0.81; 95% CI 0.56-1.16; P = 0.310).

Trials evaluating PCI in resected St III NSCLC

Li et al, Ann Onc 2015



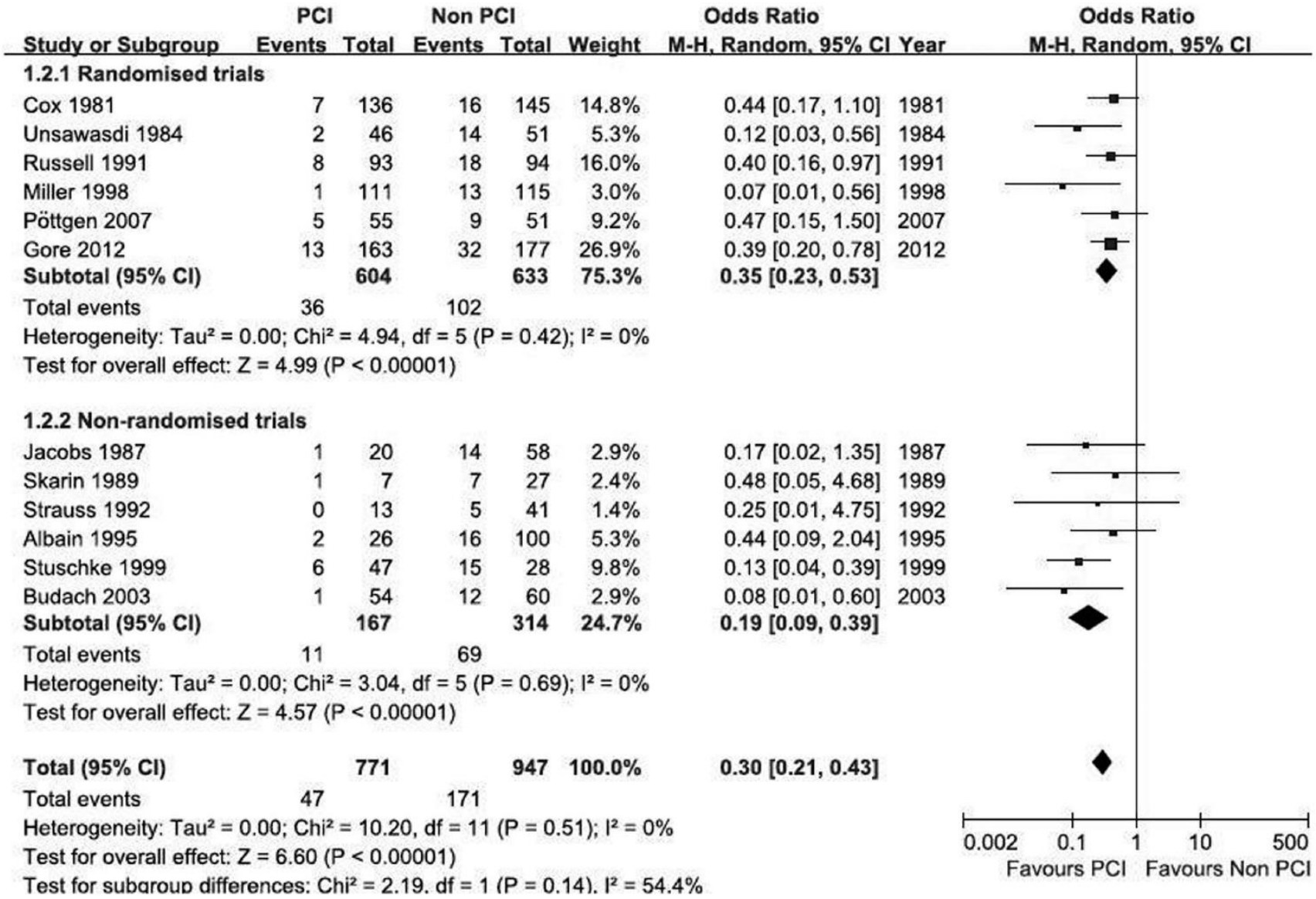


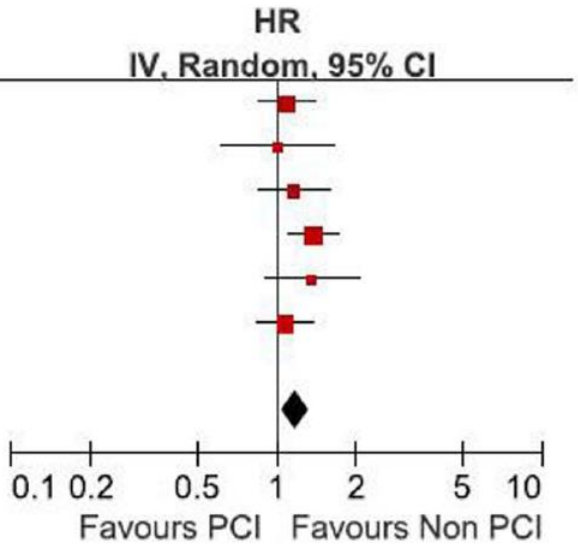
Figure 2. Results of the meta-analysis on studies evaluating the effect of PCI on brain metastases: OR: 0.30 (95% CI: 0.21–0.43).

Xie et al, PLOS1 2014

Study or Subgroup	log[HR]	SE	Weight	HR IV, Random, 95% CI	Year
Cox 1981	0.0862	0.1273	21.7%	1.09 [0.85, 1.40]	1981
Unsawasdi 1984	0.01	0.2554	5.4%	1.01 [0.61, 1.67]	1984
Russell 1991	0.1484	0.1581	14.1%	1.16 [0.85, 1.58]	1991
Miller 1998	0.3185	0.1106	28.8%	1.38 [1.11, 1.71]	1998
Pöttgen 2007	0.3023	0.21	8.0%	1.35 [0.90, 2.04]	2007
Gore 2012	0.0677	0.1266	22.0%	1.07 [0.83, 1.37]	2012
Total (95% CI)			**100.0%**	**1.19 [1.06, 1.33]**	

Heterogeneity: Tau² = 0.00; Chi² = 3.70, df = 5 (P = 0.59); I² = 0%

Test for overall effect: Z = 2.88 (P = 0.004)



Xie et al, PLOS1 2014

SEER Data base study

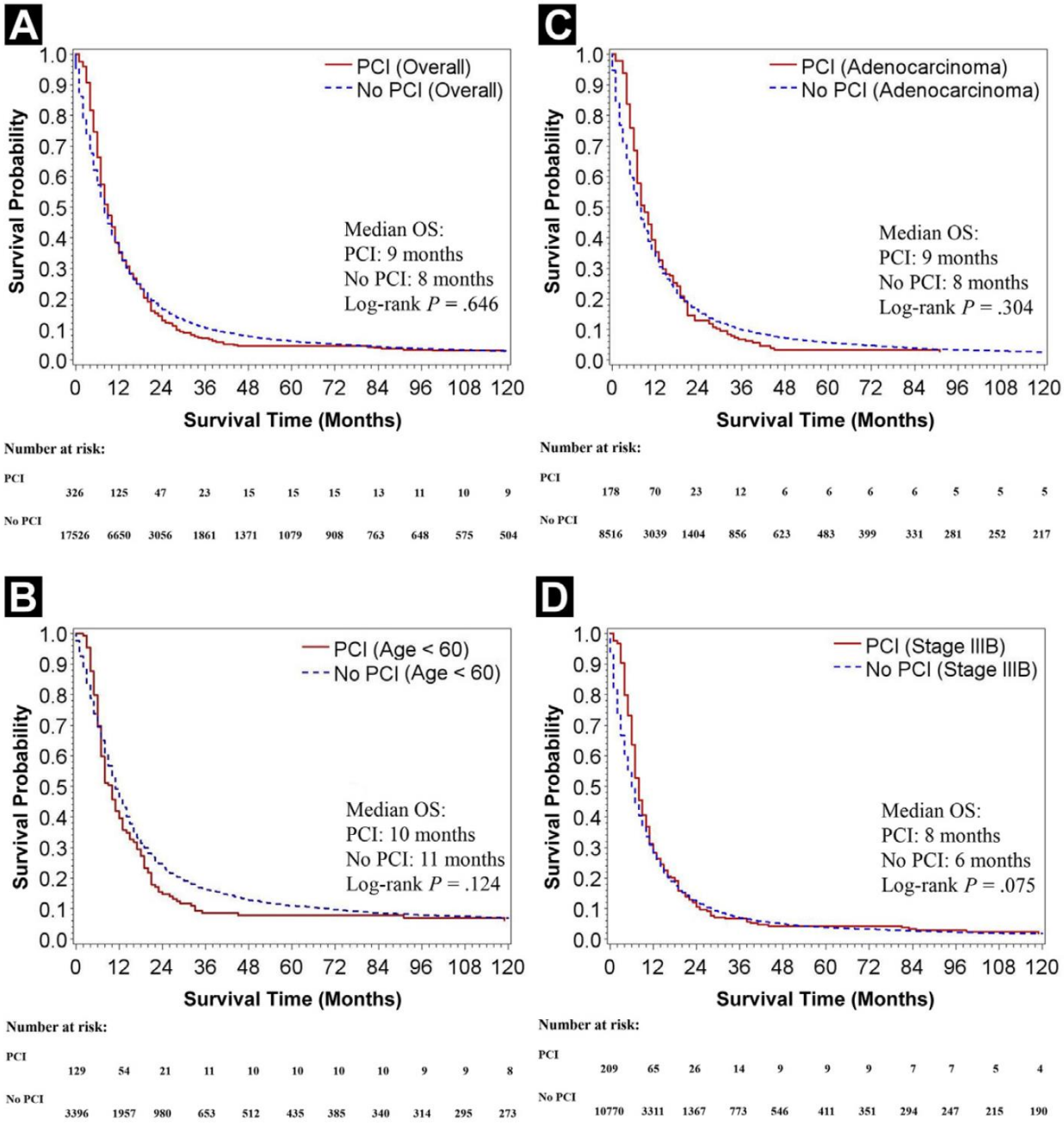
17852 Stage III NSCLC pts diagnosed 1988-1997

326 pts (1,8%) had PCI

No difference in OS

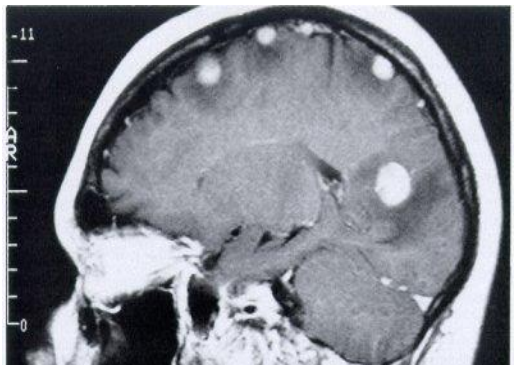
No difference in subgroups of pts at higher risk

Park, Clin Lung Cancer 2015



Potential toxicity of PCI to be discussed with pts

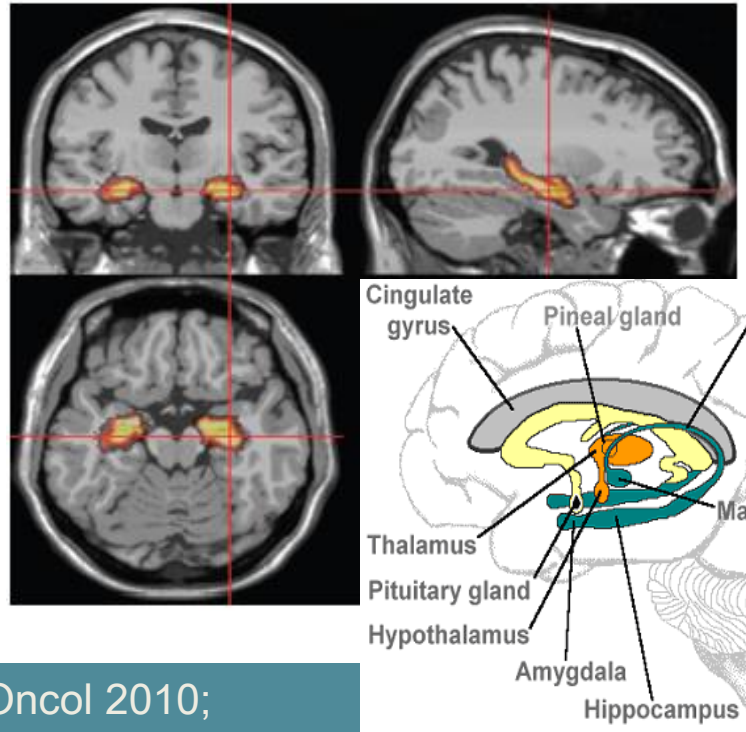
Beneficial effects of PCI on survival and incidence of BM.



Deterioration generally mild, of cognitive functions

Rationale of hippocampus sparing to reduce possible neurotoxicity

- Hippocampus primarily involved in the consolidation of new memories and “good humour”.
- Contains neural stem cells involved in the repair of damage to the CNS
- Hippocampal involvement by metastatic disease is rare in NSCLC (5-12%)
- Hippocampus sparing may result in lower rates of memory loss to be evaluated in PCI prospective trials with close follow-up++ in terms of BM
- Phase II trial showed less NC decline/historical series
- Ongoing trials



Monje Nat Med 2002; Marsh et al, 2010; Gondi, Rad&Oncol 2010; Ghia IJROBP 2007; Guttierez IJROBP 2007; Gondi et al 2014

Trials in PDQ ClinicalTrials.gov

NCT01282437 Netherland	**Prophylactic Cranial Irradiation (PCI) vs Observation in Stage III NSCLC (NVALT11) completed trial**
NCT00745797 China	Prophylactic Cranial Irradiation (PCI) Versus no PCI in Non Small Cell Lung Cancer After a Response to Chemotherapy (PCI) Closed because of slow accrual
NCT02448992 China	**Hippocampal-Sparing Prophylactic Cranial Irradiation in Pathologically Nodal Positive Non-Small-Cell Lung Cancer ?**
NCT01158170 China	**Prophylactic Cranial Irradiation in Erlotinib/Gefitinib-responders With Non-small Cell Lung Cancer (NSCLC) (RT1001) ?**
NCT01603849 Mexico	**Prophylactic Cranial Irradiation in Patients With Lung Adenocarcinoma With High Risk of Brain Metastasis (PCI) ?**
NCT00955695 **Korea**	A Randomized, Phase III Trial of **Prophylactic Cranial Irradiation** (PCI) in Patients With Advanced Non-small Cell **Lung Cancer** (NSCLC) Who Are Nonprogressive on Gefitinib or Erlotinib ?
NCT02341170 Germany	A Phase III Trial of Hippocampal-sparing **Prophylactic Cranial Irradiation** (HS-PCI) in Locally Advanced (Stage IIIA/IIIB) Adenocarcinoma of the **Lung (not yet started, 438 pts planned)**

Conclusion

- PCI reduces the incidence of BM (18% at 1 yr vs 8%)
- No effect on survival:
- Updated results are awaited from RTOG 0214
- PCI in NSCLC is not recommended
- New MA?? With new generation of randomized trials…
- Hippocampus sparing PCI may contribute to reduce neurotoxicity