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RAPID COMMUNICATION

Prophylactic Cranial Irradiation Versus Observation in Radically Treated Stage III Non–Small-Cell Lung Cancer: A Randomized Phase III NVALT-11/DLCRG-02 Study

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ABSTRACT

Purpose
The purpose of the current study was to investigate whether prophylactic cranial irradiation (PCI) reduces the incidence of symptomatic brain metastases in patients with stage III non–small-cell lung cancer (NSCLC) treated with curative intention.

Patients and Methods
Patients with stage III NSCLC—staged with a contrast-enhanced brain computed tomography or magnetic resonance imaging—were randomly assigned to either observation or PCI after concurrent/sequential chemoradiotherapy with or without surgery. The primary end point—development of symptomatic brain metastases at 24 months—was defined as one or a combination of key symptoms that suggest brain metastases—signs of increased intracranial pressure, headache, nausea and vomiting, cognitive or affective disturbances, seizures, and focal neurologic symptoms—and magnetic resonance imaging or computed tomography demonstrating the existence of brain metastasis. Adverse effects, survival, quality of life, quality-adjusted survival, and health care costs were secondary end points.

Results
Between 2009 and 2015, 175 patients were randomly assigned: 87 received PCI and 88 underwent observation only. Median follow-up was 48.5 months (95% CI, 39 to 54 months). Six (7.0%) of 86 patients in the PCI group and 24 (27.2%) of 88 patients in the control group had symptomatic brain metastases (P = .001). PCI significantly increased the time to develop symptomatic brain metastases (hazard ratio, 0.23; [95% CI, 0.09 to 0.56]; P = .0012). Median time to develop brain metastases was not reached in either arm. Overall survival was not significantly different between both arms. Grade 1 and 2 memory impairment (26 of 86 *v* seven of 88 patients) and cognitive disturbance (16 of 86 *v* three of 88 patients) were significantly increased in the PCI arm. Quality of life was only decreased 3 months post-PCI and was similar to the observation arm thereafter.

Conclusion
PCI significantly decreased the proportion of patients who developed symptomatic brain metastases with an increase of low-grade toxicity.

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INTRODUCTION

Incidence of brain metastases in patients with localized non–small-cell lung cancer (NSCLC) varies approximately from 5% to 40%.[1,2] In stage III NSCLC, the cumulative incidence of brain metastases, at present, is consistently approximately 30% at 2 years, even after adequate brain imaging at staging.[2]

In localized small-cell lung cancer, prophylactic cranial irradiation (PCI) has been shown to decrease the incidence of brain metastases by approximately 50%, with improved long-term overall survival (OS) as a result.[3,4]

PCI has also been the subject of randomized controlled trials in localized NSCLC, which have consistently demonstrated that PCI reduces the incidence of brain metastases on imaging more than 50%[5-11]; however, PCI may lead to neurocognitive

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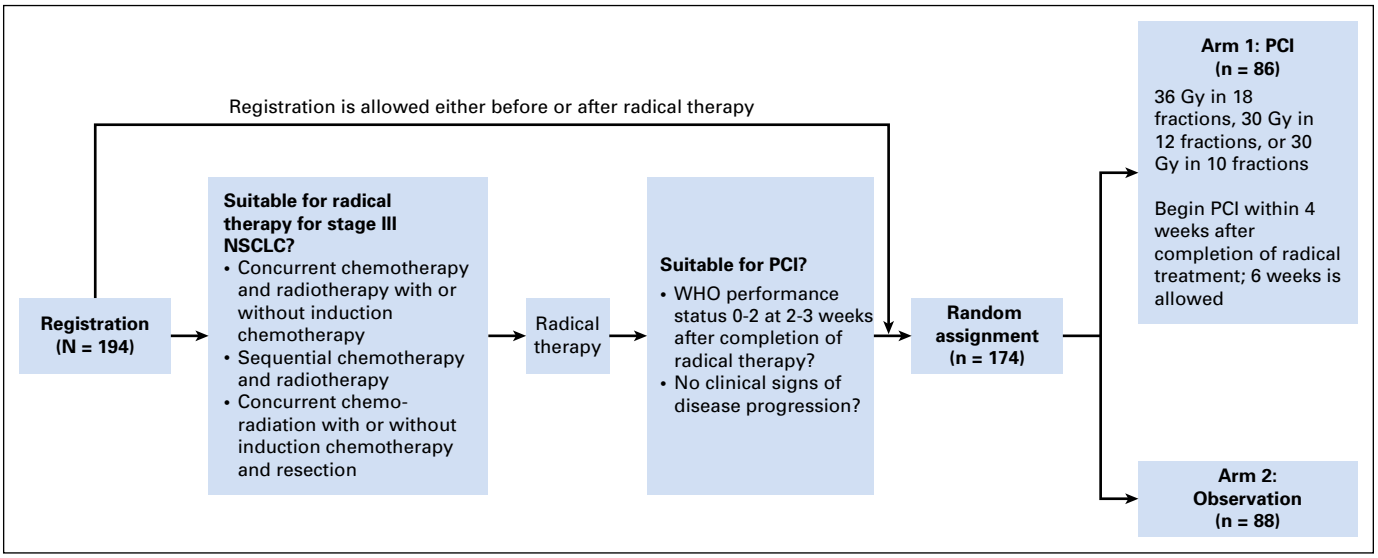

Fig 1. CONSORT diagram. NSCLC, non–small-cell lung cancer; PCI, prophylactic cranial irradiation.

decline in a significant proportion of patients,[12] and in none of the PCI studies was survival improved.

As symptomatic brain metastases are devastating for patients, impairing quality of life (QoL),[13] we have performed a randomized study to investigate whether PCI reduces the proportion of patients with symptomatic brain metastases.

PATIENTS AND METHODS

Patients

Patients with stage III NSCLC—staging included contrast-enhanced brain computed tomography (CT) or magnetic resonance imaging (MRI) and a whole-body ^{18}F-labeled fluorodeoxyglucose positron emission tomography–CT scan (IASLC 7th edition staging) —were randomly assigned to either observation or PCI after concurrent/sequential chemoradiotherapy with or without surgery if they did not show tumor progression (Fig 1). PCI should start, at maximum, 6 weeks after the last chemotherapy administration. PCI dose was left to the choice of the participating hospitals—36 Gy in 18 fractions, 30 Gy in 12 fractions, or 30 Gy in 10 fractions. Patients were randomly assigned after consultation by a medical specialists to assess symptoms, toxicity according to Common Terminology Criteria for Adverse Events (version 3.0) and WHO performance status, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30, and EuroQol 5D measurement. After random assignment, follow-up was performed with similar assessments at 4, 3, 6, 12, and 24 weeks and 36 months or earlier when symptoms of brain metastasis occurred. Key symptoms were defined as one or a combination of signs of increased intracranial pressure, headache, nausea and vomiting, cognitive or affective disturbances, seizures, and/or focal neurologic symptoms. MRI or CT was then performed to prove the existence of brain metastasis. Adverse effects, OS, quality of life (Quality of Life Questionnaire C30 + BN20 and EuroQol 5D), quality-adjusted survival, and health care costs were secondary end points.

Statistical Considerations

The primary end point was the proportion of patients who developed symptomatic brain metastases within 24 months since the time of random assignment. Symptomatic brain metastases were defined by the development of new key symptoms.

The primary end point—the relationship between PCI and the incidence of symptomatic brain metastases—was assessed with Fisher exact test. P values $< .05$ were considered statistically significant.

The time to develop brain metastases—defined as time since random assignment to the first occurrence of symptomatic brain metastases—was estimated using the Fine-Gray model, using death of any cause as competing risk. Brain metastasis–free survival (time since random assignment to first occurrence of brain metastases or death), progression-free survival (time since random assignment to first occurrence of disease progression, including but not limited to brain metastases, or death), and OS (time since random assignment to death of any cause) were estimated using the Kaplan-Meier method with right censoring at the time of last follow-up in case the event of interest had not occurred. Differences in these outcomes between the groups were calculated using the log-rank test and Cox proportional hazards regression models.

To evaluate the differences in adverse effects between arms, we used the Holms-Bonferroni correction to avoid false-positive significant associations.

Table 1. Patient Characteristics

Characteristic	Treatment Arm: PCI (n = 86)	Treatment Arm: Observation (n = 88)	Total (N = 174)
Gender (male/female)	58/28	56/32	114/60
Histology, No. (%)			
Adenocarcinoma	31	41	72 (41)
Squamous-cell carcinoma	33	29	62 (36)
Large cell	19	13	32 (18)
NSCLC NOS	3	5	8 (5)
WHO performance status, No. (%)			
0	32	34	66 (38)
1	50	49	99 (57)
2	4	5	9 (5)
Stage, No. (%)			
IIIA	41	52	93 (53)
IIIB	44	36	80 (46)
Unknown	1	0	1 (1)
Median follow-up, months	48.5	48.8	48.5
95% CI, months	39 to 54	38 to 60	39 to 54

Abbreviations: NSCLC, non–small-cell lung cancer; NOS, not otherwise specified; PCI, prophylactic cranial irradiation.

Table 2. PCI Dose

PCI Dose and Fraction	No. of Patients
12 fractions of 30 Gy	38
10 fractions of 30 Gy	34
10 fractions of 25 Gy	3
18 fractions of 36 Gy	1
12 fractions of 20 Gy	1
1 fraction of 3 Gy	1
0 Gy (no PCI)	8

NOTE. Data are presented as No. unless otherwise noted.
Abbreviation: PCI, prophylactic cranial irradiation.

Random assignment was stratified for histology, WHO performance status, prior surgery and institute. Subgroup analysis within levels of the stratification factors, with the exception of institute, were planned for in the protocol.

Sample Size and Power

Approximately 1,500 patients with stage III NSCLC are treated with curative intent each year in the Netherlands. Six hundred of these 1,500 patients were expected to fulfill the inclusion criteria, and approximately 35% of 600 patients—210 patients per year—were assumed to be willing to participate in this trial. As not all hospitals in the Netherlands participated in this trial, we expected that approximately 150 patients per year would be registered in the study in our country. Of these 150, it was estimated that 30% would not reach random assignment, leaving 105 patients randomly assigned per year.

Among this group of patients with stage III NSCLC who were treated with chemoradiation, we expected to find in the control group (no PCI) that 30% of patients would have symptomatic brain metastases after 24 months.

A total of 300 patients—approximately 450 would need to be registered—would be randomly assigned in the study, 150 in each arm. When performing statistical analysis at approximately 24 months after the end of patient accrual, a total of 100 patients would have developed symptomatic brain metastases in both arms together. The study would then have 90% power—a two-sided significance level of .05—to detect a decrease to 17% in the proportion of patients who developed symptomatic brain metastases at 24 months using a log-rank test—that is, treating development of symptomatic brain metastases as a time-to-event outcome.

The estimated inclusion period would therefore be approximately 36 months. To obtain reliable 2-year data, another 2 years of follow-up would be necessary. Patients would be observed to at least 36 months after random assignment. Assuming an exponential distribution in the times to occurrence of symptomatic brain metastases, the above proportions at 2 years correspond to a hazard ratio (HR) of 0.52. In addition, the number of patients randomly assigned in the study would allow in excess of 80% to detect a more moderate HR of 0.55 between the time to develop neurologic symptoms—confirmed or not—in both treatment arms (two-sided test, .05).

However, accrual to the study was slower than expected because, after the end of chemotherapy and radiotherapy, many patients expected that the burden of additional PCI would be too high. In March 2013, it was therefore decided that the envisioned total amount of patients—450 patients registered and 300 randomly assigned—could not be reached. We thus performed a new power calculation. We now estimated that only 170 patients would be accrued after 5 years. After an additional 2 years of follow-up, assuming exponential event rates, we estimated that 75 events would have occurred. With 75 events, a two-sided log-rank test would still have 80% power to detect the above HR of 0.52 with an α of .05; however, the power to detect the more moderate HR of 0.55 would have dropped to 73%.

Ethical and Regulatory Considerations

The study was conducted in agreement with the Declaration of Helsinki—Tokyo, Venice, Hong Kong, Somerset West, and Edinburgh amendments—and the laws and regulations of the Netherlands. The study was approved by the medical ethical committees of all participating hospitals in accordance with Dutch laws and regulations. Written informed consent was obtained from all patients.

The study was registered in The Netherlands Trial Registry, number NTR1601.

RESULTS

Patients

Between 2009 and 2015, a total of 195 patients were registered; 175 were randomly assigned, 87 received PCI, and 88 patients underwent observation. Patient characteristics are listed in Table 1.

The majority of patients in both arms received definitive concurrent chemotherapy and radiotherapy—68 (77%) of 88 patients in the observation arm and 72 (84%) of 86 patients in the PCI arm. Sequential chemoradiotherapy was provided in 12 (14%) of 88 patients in the observation arm and in six (7%) of 86 patients in the PCI group. Concurrent chemoradiotherapy followed by surgery was performed in four of 88 patients in the observation group and in four of 86 patients in the PCI arm.

Eighty percent (70 of 88) of patients in the observation arm and 79% (68 of 86) in the PCI arm received a combination platinum-based therapy. Single-agent platinum was administered to 14 (16%) of 88 and 15 (17%) of 86 patients in the observation and PCI arms, respectively.

Of the 86 patients in the PCI arm, 78 (91%) completed the treatment according to the protocol. Seven patients did not begin with PCI and one patient stopped after one fraction because of migraine, nausea, and vomiting.

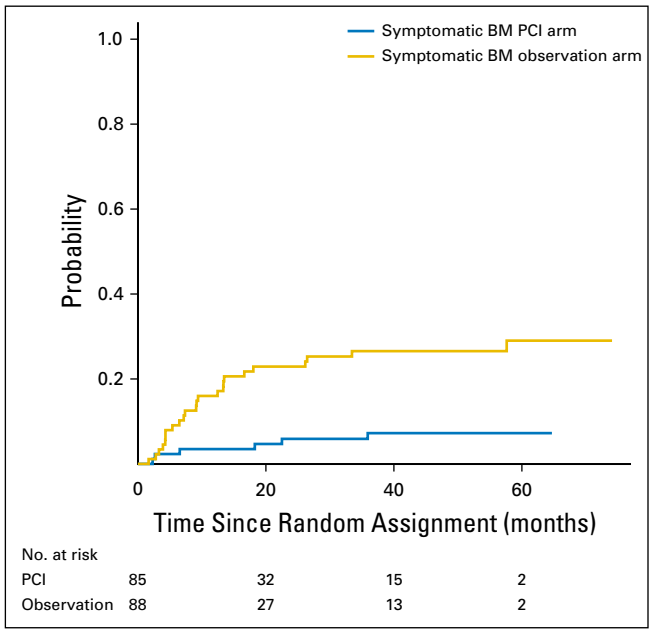

Fig 2. Cumulative incidence of symptomatic brain metastases (BM) by arm (solid lines) with death as a competing risk. Prophylactic cranial irradiation (PCI) increased the time to symptomatic BM (hazard ratio, 0.23 [95% CI, 0.09 to 0.56]; P = .0012). PCI, prophylactic cranial irradiation.

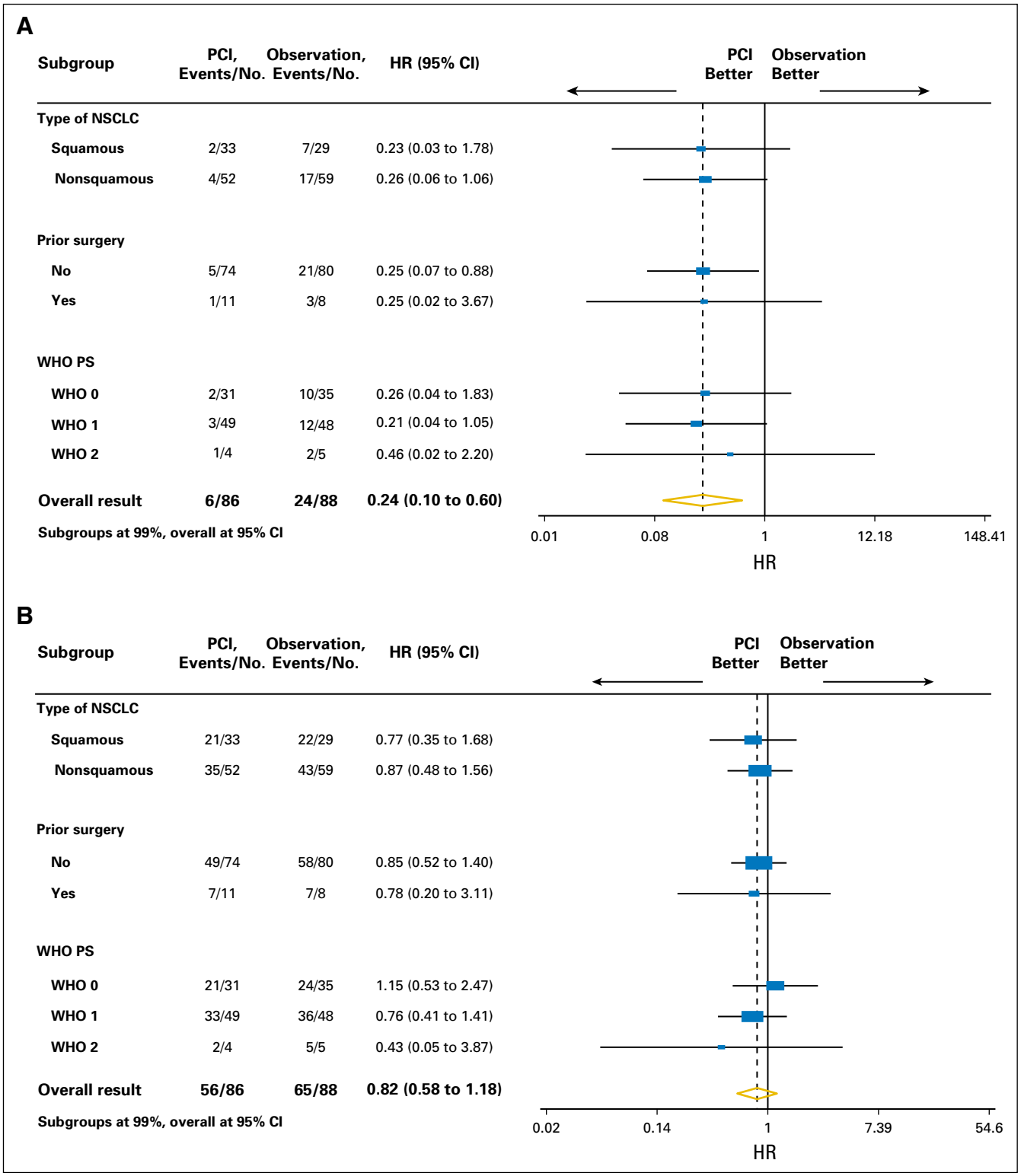

Fig 3. (A and B) Forrest plots of planned subgroup analyses: (A) time to develop symptomatic brain metastases and (B) brain metastasis–free survival. HR, hazard ratio; NSCLC, non–small-cell lung cancer; PCI, prophylactic cranial irradiation; PS, performance status.

Most patients received either 30 Gy in 12 fractions or 30 Gy in 10 fractions (Table 2). Median follow-up was 48.5 months (95% CI, 39 to 54 months).

Symptomatic Brain Metastases

Six (7.0%) of 87 patients in the PCI arm and 24 (27.2%) of 88 patients in the control group ($P < .001$) had developed

Table 3. Neurologic Adverse Events (scored by the physician)

Adverse Event	All Grades			Grade 3-5		
	PCI (n = 86)	Observation (n = 88)	All (N = 174)	PCI (n = 86)	Observation (n = 88)	All (N = 174)
Ataxia	2	0	2	1	0	1
Blurred vision	1	2	3	0	0	0
Carpal tunnel syndrome	0	1	1	0	0	0
Cauda syndrome	0	1	1	0	0	0
Cerebrovascular accident	2	0	2	1	0	1
Cognitive disturbance	18	3	21	2	0	2
Concentration impairment	3	1	4	0	0	0
Confusion	4	2	6	1	1	2
Depressed level of consciousness	0	1	1	0	0	0
Dizziness	22	13	35	1	0	1
Failure arm	0	1	1	0	0	0
Fall	1	0	1	0	0	0
Hearing impaired	1	0	1	0	0	0
Insomnia	0	1	1	0	0	0
Ischemia cerebrovascular	2	0	2	1	0	1
Itching ears	1	0	1	0	0	0
Leucoencephalopathy	1	0	1	1	0	1
Memory impairment	26	7	33	0	0	0
Mental status	2	0	2	0	0	0
Mood alteration	2	0	2	0	0	0
Neuropathy	13	14	27	2	3	5
Paresis	1	0	1	0	0	0
Parkinson disease	1	0	1	0	0	0
Personality change	3	0	3	0	0	0
Personality change	1	0	1	0	0	0
Restlessness	0	1	1	0	0	0
SAB hemisphere left	1	0	1	1	0	1
Seizure	4	1	5	2	0	2
Somnolence	9	4	13	1	I	2
Speech impairment	8	2	10	2	0	2

NOTE. Data are presented as No. unless otherwise noted.
Abbreviation: PCI, prophylactic cranial irradiation; SAB, subarachnoid bleeding.

symptomatic brain metastases at 2 years after therapy. Odds ratio was 4.96 (95% CI, 1.83 to 15.7).

PCI thus decreased the cumulative incidence of symptomatic brain metastases and significantly increased the time to develop symptomatic brain metastases (HR, 0.23 [95% CI, 0.09 to 0.56]; $P = .0012$; Fig 2). Median time to develop symptomatic brain metastases was not reached in either arm, mostly as a result of the competing risk of death.

In four patients—three in the control arm and one in the PCI arm—brain metastases were found by imaging without neurologic symptoms being reported.

Planned Subgroup Analyses

The influence of the stratification factors, histologic subtype of NSCLC, WHO performance status, and prior surgery (used in the random assignment), on the effectiveness of PCI to prolong the time to develop symptomatic brain metastases and brain metastasis–free survival were assessed as shown in the forest plots in Figures 3A and 3B, respectively.

For none of the factors was the effect of PCI different between factor levels—that is, none of the tests for interaction between arm and stratification factor was significant.

Neurologic Adverse Events

Neurologic adverse events (AE) were scored by the physician. Grade 1 and 2 AEs occurred numerically more frequently in the PCI group (Table 3). Only grade 1 and 2 memory impairment (26 of 86 *v* seven of 88 patients) and cognitive disturbance (16 of 86 *v* three of 88 patients) were significantly increased in the PCI arm. The number of grade 3 to 5 toxicities was low in both arms.

Non-Neurologic AEs

Non-neurologic AEs were scored by the physician. Alopecia, fatigue, and headache were significantly more frequent in the PCI arm, occurring in 36 of 86 patients versus five of 88 patients, 55 of 86 patients versus 30 of 88 patients, and 33 of 86 patients versus 12 of 88 patients, respectively (Table 4). Severe toxicity was rare in both study arms.

Patient-Reported AEs

Patients scored dizziness, headache, hypersomnia, memory impairment, and vomiting. AEs were numerically higher in the PCI arm than in the observation arm, but only headache occurred significantly more frequent in the PCI arm (55 of 87 patients *v* 36 of 88 patients, respectively; Table 5). Grade ≥ 3 AEs were rare in both study arms.

Differences Between Patient- and Physician-Reported Incidence of AEs

As depicted in Table 6, patient and physician scoring was not always concordant. With the exception of vomiting,

Table 4. Non-Neurologic Adverse Events (scored by the physician)

	All Grades			Grade 3-5		
Adverse Event	PCI (n = 86)	Observation (n = 88)	All (N = 174)	PCI (n = 86)	Observation (n = 88)	All (N = 174)
Adhesive capsulitis shoulder	0	1	1	0	0	0
Alanine aminotransferase increased	0	1	1	0	0	0
Alopecia	36	5	41	0	0	0
Anorexia	15	2	17	5	0	5
Arrhythmia	1	1	2	1	0	1
Arthritis	2	0	2	0	0	0
Ataxia	4	0	4	1	0	1
Otitis media	1	0	1	0	0	0
Atrial fibrillation	2	0	2	0	0	0
Basal cell carcinoma	1	0	1	1	0	1
Blurred vision	1	0	1	0	0	0
Bursitis	1	0	1	0	0	0
Cardiac infarction	0	1	1	0	1	1
Cataract	1	0	1	1	0	1
Constipation	1	6	7	0	0	0
Cough	32	17	49	4	1	5
Dehydration	1	1	2	1	1	2
Diarrhea	3	3	6	0	0	0
Dilatation esophagus	1	0	1	0	0	0
Dizziness	2	0	2	0	0	0
Dry eyes	0	1	1	0	0	0
Dry mouth	5	4	9	0	0	0
Dry skin	2	1	3	0	0	0
Dysgeusia	6	0	6	0	0	0
Dysphagia	17	9	26	1	0	1
Dyspnea	27	18	45	11	5	16
Edema	3	1	4	0	0	0
Erythema	2	0	2	0	0	0
Esophageal stenosis	1	0	1	0	0	0
Esophagitis	2	3	5	0	1	1
Fatigue	55	30	85	13	2	15
Fever	3	3	6	0	1	1
Flu-like symptoms	1	3	4	0	0	0
Fracture	4	1	5	1	0	1
Gait disturbance	2	0	2	0	0	0
Gastritis	1	2	3	0	0	0
Hearing impaired	8	1	9	2	0	2
Hemoglobin	11	13	24	1	0	1
Hemoptysis	0	1	1	0	1	1
Hemorrhage	2	4	6	1	2	3
Hernia	1	1	2	1	0	1
Hiccups	0	1	1	0	0	0
Hoarseness	5	3	8	0	0	0
Hyper pigmentation	4	6	10	0	0	0
Hypercalcemia	0	1	1	0	1	1
Hyperglycemia	1	0	1	1	0	1
Hypertension	0	1	1	0	0	0
Hyperthyroidism	1	1	2	0	0	0
Hypocalcemia	0	1	1	0	1	1
Hypokalemia	1	1	V	0	0	0
Hypomagnesemia	0	1	1	0	1	1
Hyponatremia	2	0	2	2	0	2
Hypotension	1	0	1	1	0	1
Hypoxia	1	1	2	0	1	1
Infection	21	11	32	7	6	13
Ischemia cerebrovascular	1	0	1	0	0	0
Itch	2	0	2	0	0	0
Joint function	0	1	1	0	0	0
Leaking mitral valve	1	0	1	1	0	1
Leukopenia	1	0	1	1	0	1
Liver dysfunction	1	0	1	0	0	0
Malaise	2	0	2	0	0	0
Melanoma	1	0	1	1	0	1
Mood alteration	1	0	1	0	0	0
Mucositis	3	1	4	0	0	0
Muscle stiffness	0	1	1	0	0	0

(continued on following page)

Table 4. Non-Neurologic Adverse Events (scored by the physician) (continued)

Adverse Event	All Grades			Grade 3-5		
	PCI (n = 86)	Observation (n = 88)	All (N = 174)	PCI (n = 86)	Observation (n = 88)	All (N = 174)
Muscle weakness	2	1	3	0	1	1
Nausea	30	15	45	4	0	4
Neutropenia	1	1	2	1	1	2
Esophagitis	2	0	2	1	0	1
Osteoporosis	1	0	1	0	0	0
Otitis externa	1	1	2	0	0	0
Pain	37	30	67	6	5	11
Pain, headache	33	12	45	1	0	1
Paresis	1	2	3	1	0	1
Pericardial effusion	0	1	1	0	0	0
Platelet count decreased	1	1	2	0	1	1
Pleural effusion	2	0	2	1	0	1
Pleuritis	1	0	1	1	0	1
Pneumonitis	6	9	15	1	2	3
Pneumothorax	0	2	2	0	0	0
Pulmonary embolism	2	2	4	2	2	4
Pulmonary fibrosis	1	0	1	0	0	0
Pulmonary infiltrates	1	0	1	0	0	0
Pyramidal tract syndrome	1	0	1	0	0	0
Pyrosis	3	2	5	0	0	0
Radiation damage	1	0	1	0	0	0
Rash	13	5	18	0	0	0
Renal function disorders	1	0	1	1	0	1
Secondary malignancy	0	1	1	0	1	1
Sensorimotor disorder	1	0	1	0	0	0
Sepsis	1	0	1	1	0	1
Sinusitis	1	1	2	0	0	0
Sputum	1	0	1	0	0	0
Syncope	1	1	2	1	1	2
Thrombocytopenia	1	0	1	1	0	1
Thrombosis	2	0	2	1	0	1
Tinnitus	3	0	3	0	0	0
Transient ischemic attacks	1	1	2	0	0	0
Urinary incontinence	1	2	3	0	0	0
Urinary tract infection	0	1	1	0	0	0
Vision impaired	2	0	2	1	0	1
Vomiting	17	9	26	1	0	1
Weakness	1	1	2	0	0	0
Weight gain	0	1	1	0	0	0
Weight loss	26	10	36	0	0	0

NOTE. Data are presented as No. unless otherwise noted.
Abbreviation: PCI, prophylactic cranial irradiation.

all AEs were under-reported by physicians. Fatigue and memory impairment were more reported by patients compared with physicians in the observation arm versus the PCI arm.

Evolution of AEs Over Time

There were striking differences in the time course of AEs, scored by physicians, between neurologic AEs (Fig 4) and non-neurologic AEs (Fig 5).

Table 5. Patient-Reported Adverse Events

Adverse Event	All Grades			Grade 3 and 4		
	PCI (n = 87)	Observation (n = 88)	All (N = 175)	PCI (n = 87)	Observation (n = 88)	All (N = 175)
Dizziness	50	36	86	1	0	1
Headache	55	36	91	4	2	6
Hypersomnia	69	70	139	3	5	8
Memory impairment	50	47	97	2	1	3
Vomiting	16	6	22	0	0	0

NOTE. Data are presented as No. unless otherwise noted.
Abbreviation: PCI, prophylactic cranial irradiation.

Table 6. Differences Between Patient- and Physician-Reported Adverse Events

Adverse Event	PCI	Observation	Total
Dizziness			
Reported by patient, not by physician	31	28	59
Reported by physician, not by patient	4	5	9
Reported by both, same (highest) grade	12	5	17
Reported by both, patient reports higher grade	6	1	7
Reported by both, physician reports higher grade	1	2	3
Sum	54	41	95
Headache			
Reported by patient, not by physician	28	29	57
Reported by physician, not by patient	6	5	11
Reported by both, same (highest) grade	19	4	23
Reported by both, patient reports higher grade	6	1	7
Reported by both, physician reports higher grade	2	2	4
Sum	61	41	102
Hypersomnia/fatigue			
Reported by patient, not by physician	23	44	67
Reported by physician, not by patient	9	4	13
Reported by both, same (highest) grade	16	15	31
Reported by both, patient reports higher grade	13	7	20
Reported by both, physician reports higher grade	17	4	21
Sum	78	74	152
Memory impairment			
Reported by patient, not by physician	27	40	67
Reported by physician, not by patient	3	0	3
Reported by both, same (highest) grade	15	6	21
Reported by both, patient reports higher grade	2	0	2
Reported by both, physician reports higher grade	6	1	7
Sum	53	47	100
Vomiting			
Reported by patient, not by physician	9	4	13
Reported by physician, not by patient	10	7	17
Reported by both, same (highest) grade	3	1	4
Reported by both, patient reports higher grade	2	0	2
Reported by both, physician reports higher grade	2	1	3
Sum	26	13	39

NOTE. Data are presented as No. unless otherwise noted.
Abbreviation: PCI, prophylactic cranial irradiation.

Although both neurologic and non-neurologic AEs were more frequent in PCI-treated patients than in the observation arm, neurologic AEs tended to increase over time after PCI, whereas non-neurologic AEs were the highest during PCI and decreased continuously over time.

OS, Symptomatic Brain Metastasis–Free Survival, and Progression-Free Survival

After a median follow-up time of 51.3 months (95% CI, 47.5 to 60.2 months), there was no difference in OS between the arms (HR, 0.9 [95% CI, 0.62 to 1.29; Fig 6A]). Median OS was slightly longer in the PCI arm than in the control arm (24.2 months [95% CI, 20.3 to 38.7 months] *v* 21.9 months [95% CI, 18.1 to 33.7 months], respectively), but this difference was not statistically significantly different ($P = .56$).

PCI significantly increased the time to develop brain metastases in all patients treated, but this was not the case for brain metastasis–free survival (HR, 0.81 [95% CI, 0.57 to 1.16]).

Median progression-free survival was slightly longer in the PCI arm than in the control arm (12.3 months [95% CI, 9.4 to 21.2 months] *v* 11.5 months [95% CI, 7.8 to 15.8 months], respectively), but this difference was not statistically significantly different ($P = .17$; Fig 6B). HR was 0.79 (95% CI, 0.56 to 1.11).

QoL

QoL was similar between both arms at baseline. At 3 months after PCI, QoL was worse in the PCI arm, particularly in physical functioning (median scores: PCI, 73; observation, 87; $P = .0017$). At 6, 12, and 18 months, QoL was similar between both arms, but long term—24, 36, and 48 months—there was a slight, non-significant advantage in QoL in the observation arm.

DISCUSSION

Brain metastases are common in locally advanced NSCLC.[1,13] Patients with brain metastases have impaired QoL and decreased neurocognitive functioning that may improve with successful therapy of brain metastases.[14] Overall prognosis for these patients remains poor.[15]

It is therefore logical that PCI, which decreases the incidence of brain metastases in localized small-cell lung cancer and can lead to improved long-term survival,[3] has also been investigated in the treatment of localized NSCLC.[5-11] All these phase III studies have consistently shown a decrease of the incidence of brain metastases detected with imaging, but none has shown increased OS.

We therefore started a randomized phase III study to investigate the influence of PCI on symptomatic brain metastases. Incidence of

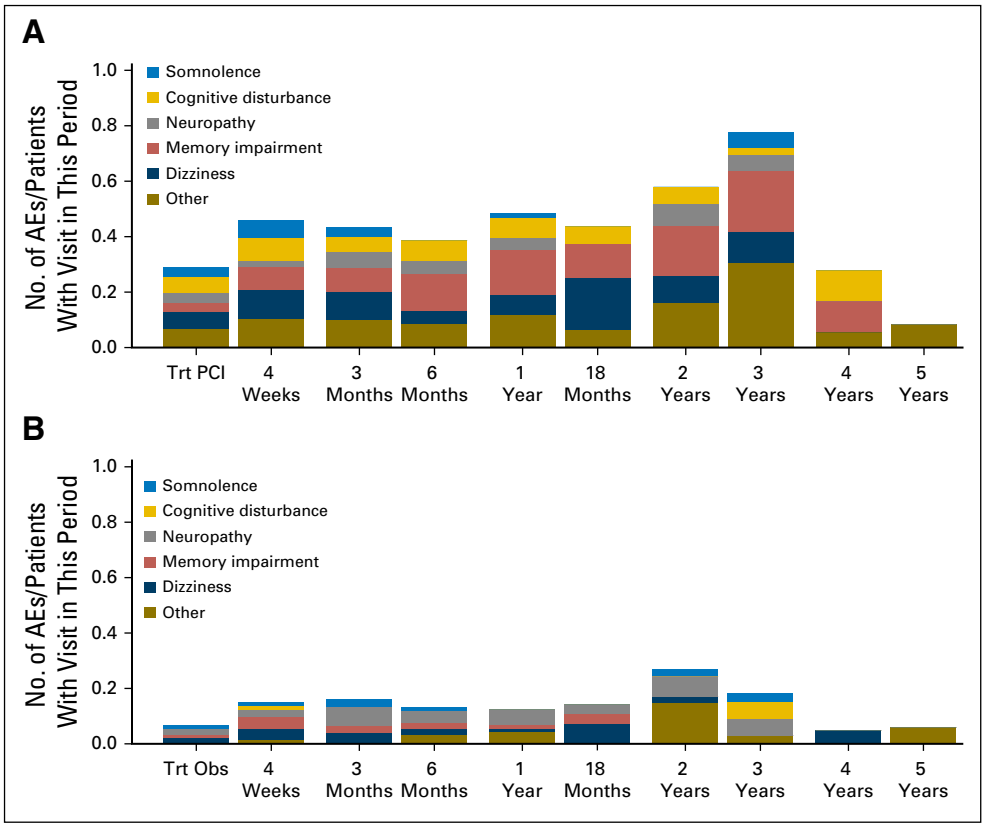

Fig 4. Number of neurologic adverse events (AEs) over time. (A) Prophylactic cranial irradiation (PCI) arm only. (B) Observation arm only. Trt, before initiation.

symptomatic brain metastases at 2 years was chosen as this was deemed to be an end point that is important for the patient.

We have indeed shown that PCI significantly reduced the incidence of symptomatic brain metastases from 27.2% in the observation arm to 7.0% in the PCI arm ($P < .001$). The number needed to treat is therefore 4.95; therefore, by treating approximately five patients with PCI we can prevent one case of symptomatic brain metastasis.

Patients who received PCI had more neurologic AEs, but most of them were low grade (grade 1 and 2). Only grade 1 and 2 memory impairment (30% *v* 8%, respectively) and cognitive disturbance (19% *v* 3%, respectively) were significantly increased in the PCI arm compared with the observation arm.

The non-neurological AEs, alopecia, fatigue, and headache. were significantly more frequent in the PCI arm, occurring in 42% versus 6%, 64% versus 34%, and 38% versus 14% of patients. Severe toxicity was rare in both study arms.

When assessing patient-reported AEs, only low-grade headache occurred significantly more frequently in the PCI arm (63% *v* 41%, respectively).

With the exception of vomiting, all AEs were under-reported by physicians compared with patients. Fatigue and memory impairment were much more under-reported by physicians in the observation arm than in the PCI arm. Considering the results of patient reports, memory impairment would not seem different between the two study arms, for it was reported by 57% and 54% of patients in the PCI arm and observation arm, respectively. According to physicians, the same AE would only be observed in 8% of patients in the observation arm and in 30% of patients in the PCI arm. This may be a result of a priori bias of physicians and underscores the need for assessment of patient-reported outcomes and objective tests.

The timelines of neurologic AEs are different from non-neurologic AEs: the former increased over time, whereas the latter were the highest during PCI and decreased thereafter.

Three months after PCI, QoL was worse in the PCI arm, but thereafter returned to the same level as that of the observation arm. After ≥ 2 years, QoL was slightly better in the observation arm, but this did not reach statistical significance up to 48 months after PCI. More detailed information for QoL items is needed to include this in the evaluation of the beneficial and deleterious effects of PCI.

OS and progression-free survival were similar in both arms; this is the key element in the controversy that surrounds PCI. PCI is clearly efficacious in reducing the incidence of brain metastases in all randomized studies. In a meta-analysis on the basis of on published data from phase III trials, the relative risk to decrease brain metastases was 0.33 (95% CI, 0.24 to 0.45; summarized in Fig 7); however, at present, no single study has demonstrated an effect on OS. In the current study, at 2 years, approximately 67% of patients in the PCI arm and 72% in the observation arm showed a recurrence. As the absolute reduction in brain metastases was 20%, it is clear that the majority of patients developed extracranial recurrences, thus lowering the potential effect of PCI on OS.

The absence of an effect—either beneficial or deleterious—on OS may be explained by the large extent of extracranial metastases that develop, a lack of statistical power in the current studies, the too-short follow-up time in some trials, or only a marginal effect. Another explanation for the absence of improvement in OS may be the effect of subsequent treatment of (a)symptomatic brain metastases in the observation arm—for instance, by radiosurgery. The

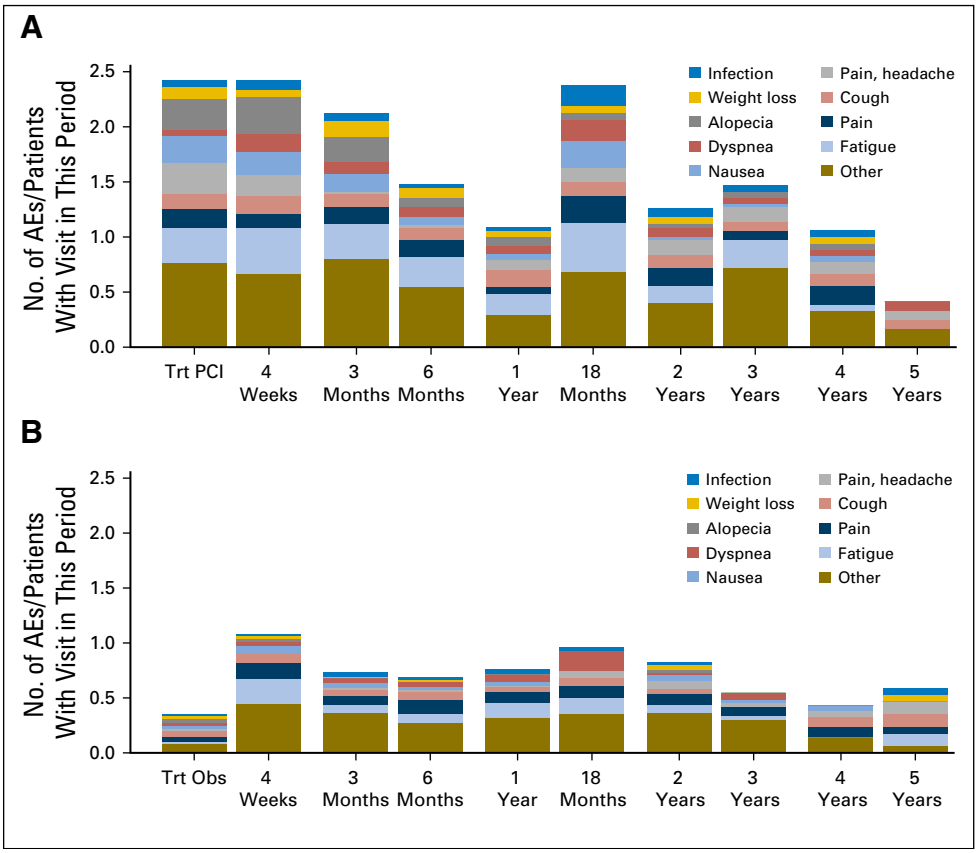

Fig 5. Number of non-neurologic adverse events (AEs) over time. (A) Prophylactic cranial irradiation (PCI) arm only. (B) Observation arm only. Trt, before initiation.

neurocognitive AEs of PCI may be reduced by, for example, sparing of the hippocampus, pharmacologic interventions, or MRI follow-up with radiosurgery for recurrences[12]; however, these strategies, at present, are experimental.

The type of chemotherapy that is used presently does not influence the incidence of brain metastases[16]; however, the first results with the programmed death-ligand 1 inhibitor, durvalumab, when administered after concurrent chemotherapy and

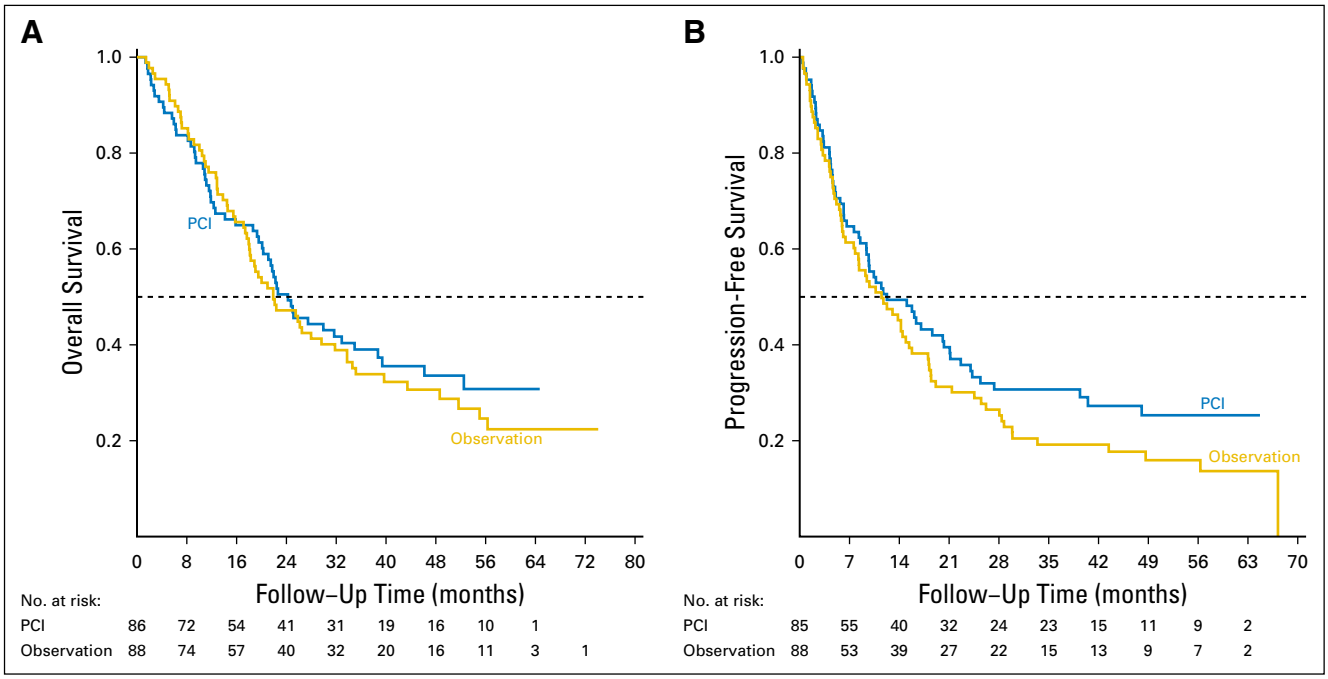

Fig 6. Overall survival and progression-free survival. (A) Overall survival. There is no significant difference in overall survival between the two arms (hazard ratio, 0.9 [95% CI, 0.62 to 1.29]). (B) Progression-free survival. There is no significant difference in progression-free survival between the two arms (hazard ratio, 0.79 [95% CI, 0.56 to 1.11]). PCI, prophylactic cranial irradiation.

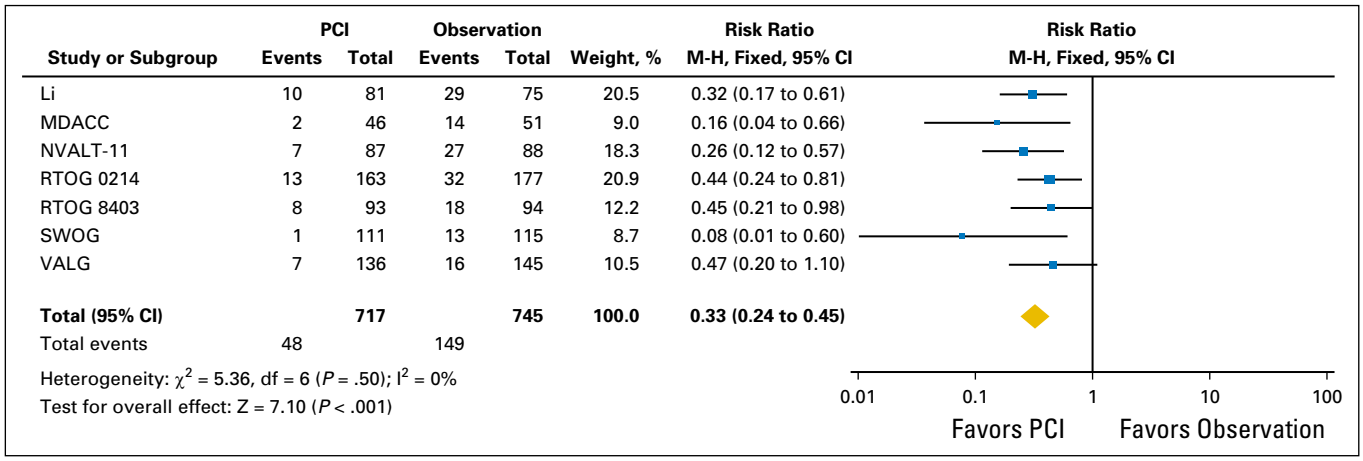

Fig 7. Meta-analysis on the basis of published data from phase III trials on the incidence of brain metastases on the basis of imaging Data from Li et al,[10] Cox et al,[5] NVALT-11 (current series), Gore et al,[9] Russell et al,[7] Mira et al,[8] and Umsawasdi et al.[6] PCI, prophylactic cranial irradiation.

radiotherapy in stage III NSCLC suggest a decrease in the incidence of brain metastases.[17] If these results are confirmed, the proportion of patients who may experience a beneficial effect from PCI will decrease, whereas, in contrast, PCI may nearly abolish brain metastases.

In conclusion, we show that PCI decreases symptomatic brain metastases with an increase of low-grade AEs, a decrease of QoL only after 3 months, and without affecting OS. We therefore believe that the pros and cons of PCI necessitates a shared decision process between patients and physicians about its use.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Prophylactic Cranial Irradiation Versus Observation in Radically Treated Stage III Non–Small-Cell Lung Cancer: A Randomized Phase III NVALT-11/DLCRG-02 Study

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