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Randomized phase III trial of prophylactic cranial irradiation versus observation in patients with fully resected stage IIIA–N2 nonsmall-cell lung cancer and high risk of cerebral metastases after adjuvant chemotherapy†

N. Li[1,2,‡], Z.-F. Zeng[3,‡], S.-Y. Wang[1,‡*], W. Ou[1], X. Ye[4], J. Li[5], X.-H. He[3], B.-B. Zhang[6], H. Yang[7], H.-B. Sun[8], Q. Fang[9] & B.-X. Wang[10]

Departments of [1]Thoracic Surgery; [2]Experimental Research; [3]Radiation Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou; [4]Department of Thoracic Surgery, Guangdong General Hospital, Guangzhou; [5]Department of Ultrasound, Sun Yat-sen University Cancer Center, Guangzhou; [6]Department of Thoracic Surgery, Henan Chest Hospital, Zhengzhou; [7]Department of Thyroid and Breast Surgery, The Central Hospital of Wuhan, Wuhan; [8]Department of Thoracic Surgery, Henan Cancer Hospital, Zhengzhou; [9]Department of Surgical Oncology, The Central People's Hospital of Huizhou City, Huizhou; [10]Guangzhou Medical University, Guangzhou, China

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Background: This study compared prophylactic cranial irradiation (PCI) with observation in patients with resected stage IIIA–N2 non-small-cell lung cancer (NSCLC) and high risk of cerebral metastases after adjuvant chemotherapy.

Patients and methods: In this open-label, randomized, phase III trial, patients with fully resected postoperative pathologically confirmed stage IIIA–N2 NSCLC and high cerebral metastases risk without recurrence after postoperative adjuvant chemotherapy were randomly assigned to receive PCI (30 Gy in 10 fractions) or observation. The primary end point was disease-free survival (DFS). The secondary end points included the incidence of brain metastases, overall survival (OS), toxicity and quality of life.

Results: This trial was terminated early after the random assignment of 156 patients (81 to PCI group and 75 to control group). The PCI group had significantly lengthened DFS compared with the control group, with a median DFS of 28.5 months versus 21.2 months [hazard ratio (HR), 0.67; 95% confidence interval (CI) 0.46–0.98; $P = 0.037$]. PCI was associated with a decrease in risk of brain metastases (the actuarial 5-year brain metastases rate, 20.3% versus 49.9%; HR, 0.28; 95% CI 0.14–0.57; $P < 0.001$). The median OS was 31.2 months in the PCI group and 27.4 months in the control group (HR, 0.81; 95% CI 0.56–1.16; $P = 0.310$). While main toxicities were headache, nausea/vomiting and fatigue in the PCI group, they were generally mild.

Conclusion: In patients with fully resected postoperative pathologically confirmed stage IIIA–N2 NSCLC and high risk of cerebral metastases after adjuvant chemotherapy, PCI prolongs DFS and decreases the incidence of brain metastases.

Key words: prophylactic cranial irradiation, cerebral metastases, phase III clinical trial, non-small-cell lung cancer

introduction

Annually, among nearly 1.1 million new diagnosed lung cancer cases around the world [1], non-small-cell lung cancer (NSCLC) accounts for ~85%. Stage III disease constitutes ~30% of all cases of NSCLC and the management of it, especially stage IIIA–N2 disease, remains a challenge [2]. Brain is a common site of initial failure in stage N2 NSCLC, with 14%–40% of patients developing cerebral metastases as the first site of relapse after locoregional control by multimodality therapy [3–6]. When cerebral metastases occur, even though the aggressive treatment is administered, the survival is generally disappointing, ranging from 3.1 to 11.8 months [7–11].

A number of studies have investigated the role of prophylactic cranial irradiation (PCI) in locally advanced NSCLC. Results of

*Correspondence to: Prof. Si-Yu Wang, Department of Thoracic Surgery, Sun Yat-sen University Cancer Center, 651 Dongfeng Road East, Guangzhou 510060, China. Tel: +86-20-87343439, Fax: +86-20-87343439. E-mail: wsysums@163.net

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‡N.L., Z.-F.Z., and S.-Y.W. contributed equally to this article.

these studies show that PCI significantly decreases the incidence of cerebral metastases in patients with NSCLC, but the impact of PCI on long-term survival is uncertain [12–16]. Several studies have shown that PCI should be administered to high-risk patients [5, 16–18], but there is no prospective study focused on patients with high risk of cerebral metastases. Previously, we built a mathematical model to predict the risk of developing cerebral metastases in patients with locally advanced NSCLC [19]. We postulated that the administration of PCI to patients with high risk of cerebral metastases would be efficacious. When the trial was started in 2005, the survival advantage of adjuvant platinum-based chemotherapy for NSCLC had been reported first by the International Adjuvant Lung Cancer Trial Collaborative Group [20], whereas postoperative radiotherapy (PORT) was reported to be detrimental (for N0 and N1 disease) or not clear (for N2 disease) [21].

The main objective of this trial was to compare the effect on disease-free survival (DFS) of PCI with that of observation in patients with completely resected stage IIIA–N2 NSCLC and high risk of cerebral metastases after adjuvant chemotherapy.

patients and methods

eligibility

Patients with fully resected stage IIIA–N2 NSCLC who had high cerebral metastases risk (supplementary File S1, available at *Annals of Oncology* online) after adjuvant chemotherapy were considered for enrollment on to the study. Patients were also required to be aged 18–75 years, have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2, have completely resected postoperative pathologically confirmed stage IIIA–N2 NSCLC and have no evidence of tumor relapse. Patients must provide written informed consent before study-related procedures.

Exclusion criteria included incomplete resection, previous radiotherapy or targeted therapy, other current or previous malignancies, any concurrent unstable disease, history of neurological or psychiatric disorders and pregnancy. Patients with N2 disease identified preoperatively were also excluded.

The interval from day 1 of the last chemotherapy cycle to randomization must be within 6 weeks. This trial was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. The Medical Ethics Committee of each center reviewed and approved the trial protocol.

study design and treatment

This was a prospective, open-label, randomized, phase III trial. Eligible patients were randomly assigned in a 1 : 1 ratio to receive either PCI or observation. Random assignment instructions were obtained through an independent provider by telephone. A minimization procedure was used with stratification according to ECOG PS (0 or 1 versus 2) and histology (squamous versus nonsquamous) and center. The schedule used for cranial irradiation was 30 Gy in 10 daily fractions of 3 Gy, 5 fractions per week. The target volume was the whole brain and radiation was administered with the use of two opposed lateral fields. The primary end point was DFS. The secondary end points included the incidence of brain metastases, overall survival (OS), toxicity and quality of life (QoL).

patient evaluations

The baseline assessment before study entry included medical history; physical examination; ECOG PS; comprehensive laboratory tests;

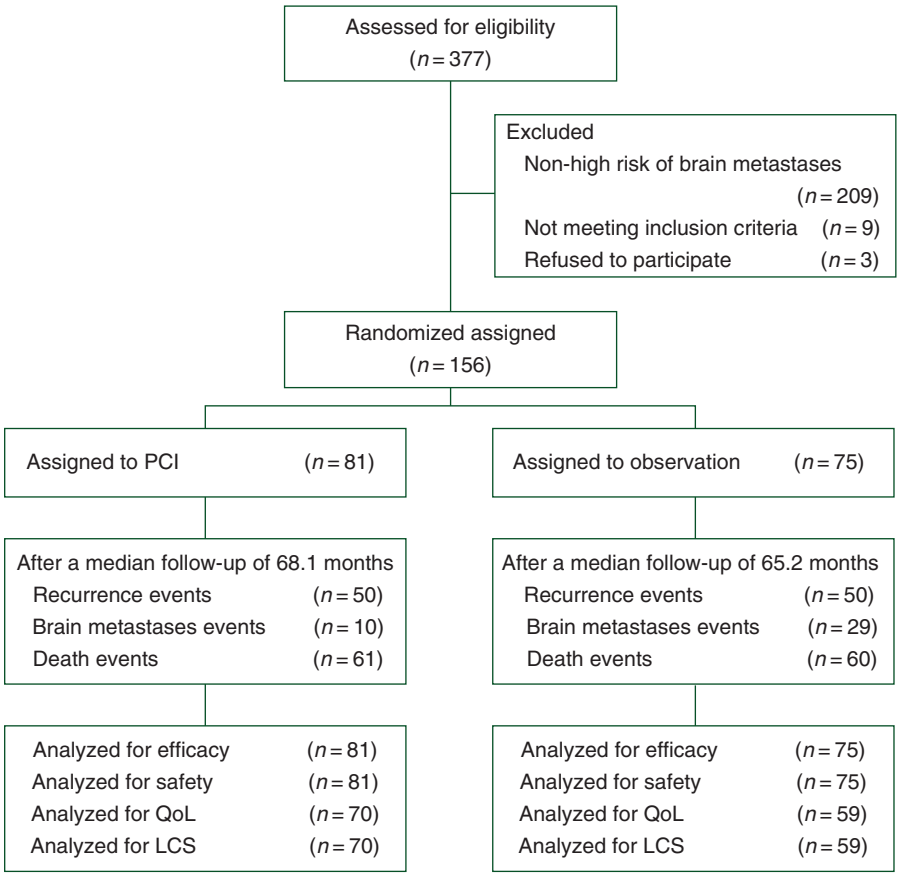

Figure 1. Flow diagram.

electrocardiogram; computed tomography (CT) scans of the chest and upper abdomen; magnetic resonance imaging (MRI) of the brain and baseline evaluation of QoL. Patients were followed up every 3 months during the first 2 years after randomization, and every 6 months thereafter. Thoracic and upper abdomen CT and brain MRI scans were scheduled every 6 months after randomization for evaluation of tumor relapse/metastasis by investigators, and repeated if clinically indicated.

DFS was defined as the time from randomization to local recurrence, brain and other metastases or death from any cause. OS was measured from the date of randomization to the date of death from any cause. Acute toxicity of PCI was assessed according to National Cancer Institute Common Terminology Criteria (NCI-CTC) for Adverse Events (version 3.0), whereas late toxicity of PCI was evaluated according to RTOG/EORTC Late Radiation Morbidity Scoring Schema. QoL was assessed by means of the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire.

statistical analysis

Based on the Adjuvant Lung Cancer Project Italy, the 5-year DFS rate of patients with stage IIIA–N2 disease in the adjuvant group was estimated to be 20% [22]. At least 254 DFS events were needed for the primary analysis to detect a 30% reduction in the hazard of recurrence with PCI versus observation [hazard ratio (HR), 0.7], with 80% power and a two-sided significance level of 5%, assuming a 36-month enrollment period and 60-month follow-up, and this trial would have needed a minimum of 254 patients to be randomized. The primary cutoff date for DFS data was January 2014.

DFS, the incidence of brain metastases and OS were estimated by the Kaplan–Meier method, with HRs and their two-sided 95% confidence intervals (CIs) estimated by Cox proportional hazards regression analysis, and the difference between the two groups was assessed by means of log-rank tests. Chi-square tests were used to compare categorical data. Patient characteristics and toxicities were analyzed descriptively. Two-sided P values of <0.05 were considered to be statistically significant.

results

baseline characteristics

From January 2005 through January 2009, 377 patients were screened, of whom 221 patients were excluded because of non-high risk of cerebral metastases ($n = 209$), disease recurrence or metastases ($n = 6$), patient refusal ($n = 3$), incomplete resection ($n = 2$) and neutropenia ($n = 1$). At last, 156 eligible patients were randomized to receive either PCI ($n = 81$) or observation ($n = 75$). This study was terminated early as a result of slow accrual. The flow diagram of this trial is shown in Figure 1. The baseline characteristics of patients are listed in Table 1.

The median follow-up was 68.1 (range, 1.1–97.3) months in the PCI group and 65.2 (range, 1.4–82.9) months in the control group. The two groups were generally balanced with respect to important variables. The adjuvant chemotherapy regimens were mainly carboplatin-based. Most patients (82.7%) completed four adjuvant cycles. The initial failure sites and postrecurrence treatment are shown in supplementary Table S1, available at *Annals of Oncology* online.

Table 1. Demographic and clinical characteristics at baseline (PCI, ECOG, PS)

Variable	PCI ($N = 81$)		Control ($N = 75$)	
	No.	%	No.	%
Age, years				
Median	55		57	
Range	31–73		24–75	
Sex				
Male	58	71.6	53	70.7
Female	23	28.4	22	29.3
ECOG PS				
0	29	35.8	28	37.3
1	50	61.7	46	61.3
2	2	2.5	1	1.3
Histology				
Adenocarcinoma	50	61.7	46	61.3
Squamous cell carcinoma	20	24.7	20	26.7
Other	11	13.6	9	12.0
Region of lymph node involvement[a]				
L1	9	11.1	10	13.3
L2	57	70.4	52	69.3
L3	15	18.5	13	17.3
Number of lymph nodes involvement				
1–3	39	48.1	34	45.3
4–6	28	34.6	27	36.0
>6	14	17.3	14	18.7
Smoking status				
Ever	63	77.8	57	76.0
Never	18	22.2	18	24.0
Surgery type				
Lobectomy	67	82.7	64	85.3
Bilobectomy	0	–	1	1.3
Pneumonectomy	14	17.3	10	13.3
Adjuvant chemotherapy regimens				
Docetaxel + carboplatin	32	39.5	26	34.7
Paclitaxel + carboplatin	18	22.2	20	26.7
Vinorelbine + carboplatin	16	19.8	13	17.3
Cisplatin-based	15	18.5	16	21.3

[a]Mediastinal lymph nodes were divided into three areas: (i) Superior mediastinal area, which included highest mediastinal node, upper paratracheal node, prevascular and retrotracheal node and lower paratracheal. (ii) Aortic area, which included subaortic node and para-aortic node. (iii) Inferior mediastinal area, which included subcarinal node, paraesophageal node and pulmonary ligament node. L1, L2 and L3 mean that lymph nodes involved one region, two regions or three regions.

PCI, prophylactic cranial irradiation; ECOG, Eastern Cooperative Oncology Group; PS, performance status.

efficacy

A total of 100 recurrence events had been recorded at data cutoff date (PCI arm, $n = 50$; control arm, $n = 50$). Both DFS and OS curves are shown in Figure 2. The PCI group had significantly lengthened DFS compared with the control group, with a median DFS of 28.5 (95% CI 21.9–35.1) months versus 21.2 (95% CI 15.0–27.4) months (HR, 0.67; 95% CI 0.46–0.98; $P = 0.037$). The 3-year and 5-year DFS were, respectively, 42.0% and 26.1% with PCI, and 29.8% and 18.5% with observation.

At data cutoff date, 39 instances of brain metastases had occurred (PCI arm, $n = 10$; control arm, $n = 29$). The actuarial 3- and 5-year brain metastases rate were 13.7% and 20.3% in the

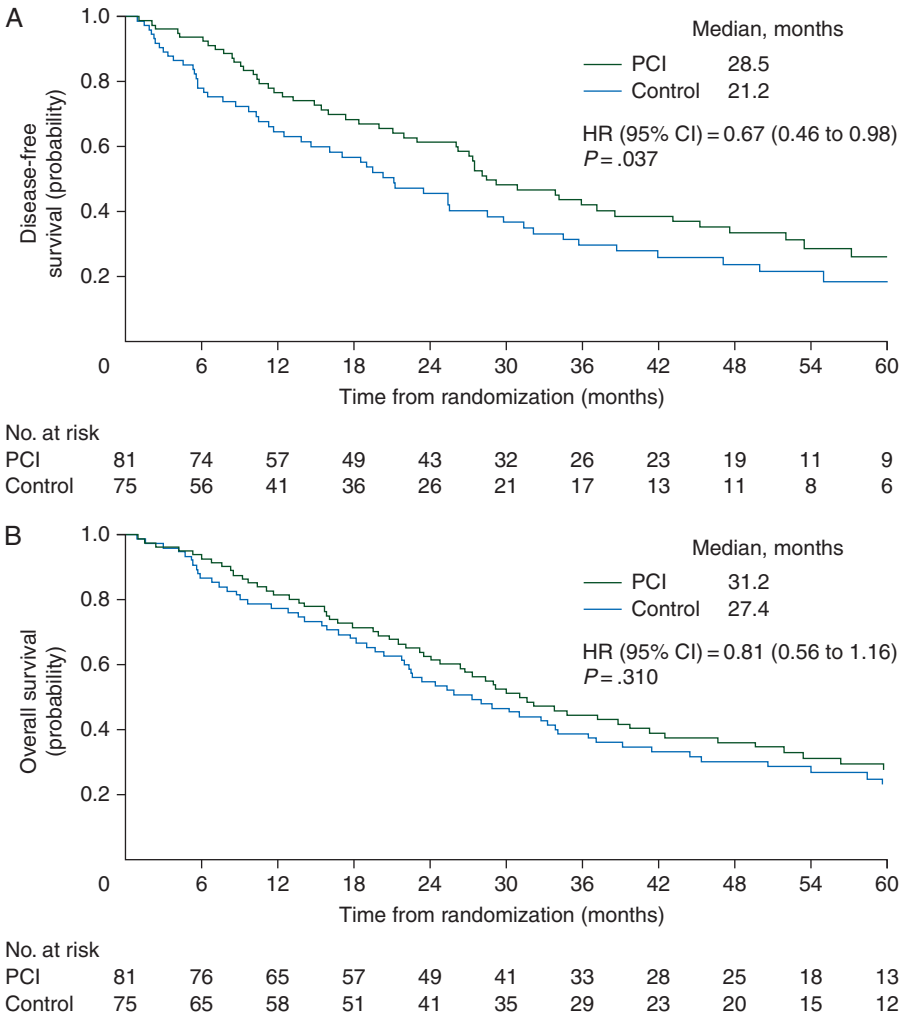

Figure 2. Kaplan–Meier curves for (A) disease-free survival and (B) overall survival.

PCI arm versus 44.2% and 49.9% in the control arm (HR, 0.28; 95% CI 0.14–0.57; $P < 0.001$). Supplementary Figure S1, available at *Annals of Oncology* online shows the Kaplan–Meier curves for brain metastases. The odds ratio of the incidence of brain metastases at 5 years for PCI versus control group was 0.25 (95% CI 0.12–0.51; $P < 0.001$). The actuarial 3- and 5-year brain relapse as the first site of recurrence rate were 11.8% and 15.6% versus 39.2% and 45.3%, respectively (HR, 0.26; 95% CI 0.12–0.57; $P = 0.001$). The crude 5-year brain relapse as the first site of recurrence rate was 9.9% versus 33.3% (OR, 0.22; 95% CI 0.91–0.53; $P < 0.001$).

A total of 121 death events had occurred at data cutoff (PCI, $n = 61$; control, $n = 60$). The median OS was 31.2 (95% CI 24.2–38.2) months in the PCI group and 27.4 (95% CI 19.4–35.4) months in the control group (HR, 0.81; 95% CI 0.56–1.16; $P = 0.310$). The 3-year and 5-year OS were, respectively, 44.5% and 27.4% with PCI, and 38.7% and 22.8% with observation.

toxicity

For patients in the PCI arm, the main acute toxicities (within 90 days) included: headache in 27% (grade 1, 20%; grade 2, 6%; grade 3, 1%), nausea or vomiting in 23% (grade 1, 17%; grade 2, 6%), fatigue in 22% (grade 1, 11%; grade 2, 9%; grade 3, 2%), skin toxicity in 5% (grade 1, 1%; grade 2, 4%) and insomnia in 2% (grade 2). The main late toxicities (after 90 days) of the brain included: mild headache or slight lethargy (22.2%), moderate headache or great lethargy (11.1%) and severe headaches (2.5%). Other grade 3 late toxicities included skin atrophy in one patient and fatigue in one patient.

quality of life

No significant differences were noted in deterioration rate for QoL and symptoms between the two groups (supplementary File S2, available at *Annals of Oncology* online).

discussion

This trial examined the efficacy and safety of PCI in patients with resected stage IIIA–N2 NSCLC and high risk of cerebral metastases after adjuvant chemotherapy. Although the enrollment stopped early, which is the limitation of our study, overall results demonstrated a positive effect of PCI. The primary end point of this trial, DFS, was significantly prolonged among patients who were assigned to PCI (median DFS, 28.5 months; $P = 0.037$).

Our study shows that PCI provides significantly lengthened DFS in patients with curatively resected postoperative pathologically confirmed stage IIIA–N2 NSCLC who received adjuvant chemotherapy, prolonging median DFS by 7.3 months. This study can be compared with the RTOG 0214, which investigated PCI in patients with stage III NSCLC without progression after locoregional control [16]. Although the decrease in the rate of brain metastases with PCI was shown in RTOG 0214, PCI did not yield a benefit of OS or PFS. The negative result in survival of RTOG 0214 can be explained by the unintended selection of patients with low risk of cerebral metastases. In our study, all patients were presented with NSCLC with high risk of brain metastases according to the mathematical model [19]. These patients are prone to develop brain metastases.

Our study also shows a benefit of PCI in decreasing the risk of cerebral metastases (an absolute decrease of 29.6% at 5 years). The reduction in risk of cerebral metastases observed in our study is similar in magnitude to risk reduction observed in previous randomized studies [12–14, 16]. Accordingly, the incidence of cerebral metastases of patients in the control group is as high as that of patients with locally advanced NSCLC who were treated with resection-containing therapy, whose overall brain metastases rate ranged from about 30% to 50% [3, 23, 24]. The notable reduction in the incidence of cerebral metastases from PCI did not increase extracranial metastases, resulting in a DFS benefit from PCI.

The DFS benefit in our study did not translate into a significant OS benefit. This may be largely related to the early termination. Welsh et al. reported a phase II trial of erlotinib plus whole-brain radiotherapy followed by maintenance erlotinib in treating patients with brain metastases from NSCLC [11]. Results of the trial demonstrated that the erlotinib-containing approach yielded an excellent median survival of 19.1 months for patients harboring EGFR mutations. In light of the high incidence of EGFR mutations (~30%) among patients with resected NSCLC in China [25], the OS results in our study may be slightly confounded by the postrecurrence therapy of target therapy. Nonetheless, the OS curves separate from the beginning without crossover in favor of PCI. PCI conferred an absolute increase of 4.6% at 5 years. The efficacy of PCI seen in this trial was along with the presence of acute and late toxicities. However, no severe adverse effects or PCI-related death were observed and these adverse effects from PCI did not affect the QoL assessment significantly, suggesting that the PCI of 30 Gy in 10 fractions is well tolerated. The optimal schedule of PCI remains undetermined. We chose the dose of 30 Gy in 10 fractions of 3 Gy based on two previous randomized studies [13, 14].

It is noteworthy that the majority of adjuvant chemotherapy regimens consisted of carboplatin-based doublets, which were testified to have similar efficacy compared with cisplatin-based regimens [26], with less toxicity and better compliance. Since the role of PORT for N2 NSCLC was not clear when this trial was initiated [21], all patients in this trial did not receive PORT. Based on the results of several subsequent studies, PORT is associated with a positive effect on survival in N2 NSCLC [27]. So in further studies, PORT should not be excluded in this cohort of patients.

In conclusion, this trial shows that PCI prolongs DFS, decreases the rate of cerebral metastases among selected patients with fully resected pathologically confirmed stage IIIA–N2 NSCLC after adjuvant chemotherapy. Selection of lung cancer individuals with high risk of brain metastases is recommended.

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disclosure

The authors have declared no conflicts of interest.

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