Original Study

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Prophylactic Cranial Irradiation for Patients With Locally Advanced Non−Small-Cell Lung Cancer at High Risk for Brain Metastases

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Abstract

We evaluated the effect of prophylactic cranial irradiation on survival among high-risk subgroups of locally advanced non−small-cell lung cancer patients on a national scale. Our population-based analysis suggests no overall survival benefit of prophylactic cranial irradiation for these patients, even among a group of patients who were at higher risk for brain metastases (age < 60 years, adenocarcinoma, bulky disease).

Background: Although there is no proven survival benefit of prophylactic cranial irradiation (PCI) for patients with locally advanced (LA) non−small-cell lung cancer (NSCLC), some speculate that PCI might be helpful for certain subpopulations at higher risk of brain metastases (< 60 years, adenocarcinoma, or stage IIIB). In this study we evaluated the effect of PCI on survival among these high-risk LA-NSCLC patients on a national scale. **Materials and Methods:** Using the Surveillance, Epidemiology, and End Results database, we included all adult patients with primary stage III NSCLC, diagnosed from 1988 to 1997 (years during which PCI was recorded) with follow-up until 2008. The Kaplan−Meier estimator, log-rank test, and Cox proportional hazard regression were used to evaluate the survival effect of PCI. Sequential landmark analysis excluding patients from 1 to 6 months after diagnosis was used to account for immortal time bias. **Results:** A total of 17,852 patients were included in the analysis, among whom 326 (1.8%) received PCI. Patients younger than 60 years and those with adenocarcinoma were significantly more likely to receive PCI. After adjustment for available covariates, there was no statistically significant survival difference between PCI and non-PCI patients (hazard ratio, 1.04; 95% confidence interval, 0.93-1.16). Similar results were found in all subgroup analyses of high-risk patients. Sequential landmark analysis suggested a potential survival detriment associated with PCI when analyzing only patients who survived at least 3 months after diagnosis. **Conclusion:** Our population-based analysis suggested no overall survival benefit of PCI for LA-NSCLC patients, even among a group of patients who were at higher risk for brain metastases.

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Introduction

Primary cancer of the lung and bronchus is associated with approximately 221,000 new diagnoses and 157,000 deaths in 2011, representing 15% of cancer diagnoses and 28% of cancer deaths

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per year.[1] Approximately 85% of lung cancers are classified as non−small-cell lung cancer (NSCLC), which can be further subdivided according to specific histologies such as adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, and the remaining 15% are classified as small cell lung cancer (SCLC). Brain metastases (BM) occur frequently in patients with NSCLC, presenting as the first site of recurrence in 15% to 40% of patients with an incidence proportion of 17% to 54% at some point during the course of the disease,[2-8] and in those with SCLC, they present in 15% to 20% of patients at the time of SCLC diagnosis and occur considerably more frequently with longer follow-up.[9-11] Therefore, serious consideration has been given to the use of prophylactic cranial irradiation (PCI) in the initial management of patients with either NSCLC or SCLC who are at high risk of BM to prevent or delay central nervous system relapse.

Two meta-analyses, multiple clinical trials, and a large observational population-based analysis have demonstrated a significant benefit of PCI in decreasing BM incidence and improving survival in patients with limited-stage SCLC with a complete response or extensive-stage SCLC with at least a partial response after initial treatment.[12-16] However, the prospective evidence has been more mixed regarding PCI for well-controlled locally advanced (LA) NSCLC. Four randomized clinical trials published in the 1980s and 1990s and 1 published in 2011 (Radiation Therapy Oncology Group [RTOG] 0214) have consistently demonstrated a cumulative decrease in brain metastasis incidence but no significant benefit in overall survival or progression-free survival for these patients.[17-21]

Despite the lack of survival benefit shown by these trials when all LA NSCLC patients were included, controversy still persists as to whether PCI has a greater survival benefit for certain subpopulations at higher risk for BM, particularly for younger patients, patients who have adenocarcinoma, or patients who have bulkier disease.[2,3,5,6,22-25] Using a large US national cancer registry, the goal of this study was to evaluate the effect of PCI on survival among these high-risk LA NSCLC subgroups on a population scale.

Materials and Methods

The Surveillance, Epidemiology, and End Results (SEER) registry of the National Cancer Institute is the largest cancer database in the United States and was comprised of 13 SEER regions (Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Utah, Los Angeles, San Jose-Monterey, Alaska, rural Georgia) at the time of the study period. Each of the SEER registries is required to collect data on all patients diagnosed with cancer who are residents of the geographic area covered by the registry at the time of diagnosis. The SEER population is comparable with the general US population with regard to poverty and education level, but is more urban and has a higher proportion of foreign-born persons.[26]

In our study sample, we included all adult patients in the SEER registry diagnosed from 1988 to 1997 with primary stage IIIA or IIIB NSCLC (International Classification of Diseases, 3rd edition, primary site code C340-349), no evidence of metastases, and no other lifetime malignancies. Patients were excluded if their tumor histology was small cell, large cell, sarcoma, lymphoma, or unknown; if there was incomplete PCI information; or if their source documents were from autopsy or death certificate only. Receipt of PCI was determined according to a specific variable in the database for only lung and leukemia cases that coded for radiation given to the central nervous system as part of the first course of therapy. This variable was only available during our study period, 1988 to 1997. Follow-up data were available until December 31, 2008.

Independent demographic variables included age at diagnosis (< 60, 60-69, 70-79, vs. ≥ 80), sex, race/ethnicity (white vs. black vs. Asian/Pacific Islander vs. other), Hispanic origin, marital status, and geography (Northeast vs. Midwest vs. South vs. West). Clinical and pathologic variables included cancer-directed surgical resection (pneumonectomy vs. lobectomy vs. other vs. none), tumor histology (adenocarcinoma vs. squamous cell carcinoma vs. other), tumor stage (IIIA vs. IIIB), and central nervous system radiation therapy.

Differences in patient demographic and clinical characteristics between patients who did or did not receive PCI were evaluated using χ^2 statistical analysis. The Kaplan−Meier estimator was used to measure the effect of PCI on overall survival for each of the high-risk subgroups, and the Mantel−Cox log-rank test was used to assess for potential significant differences in overall survival. Cox proportional hazards regression was used to identify the explanatory variables that predict for survival after adjusting for available covariates and to calculate hazard ratios (HRs) for death and 95% confidence intervals (CIs). Sequential landmark analysis including only patients who had survived until a predetermined landmark (from 1 to 6 months after diagnosis) was used as a sensitivity analysis to account for immortal time bias, because including patients who died soon after diagnosis might artificially bias the results in favor of the cohort that received radiation therapy.[27]

Data analysis and management were performed using SAS version 9.2 (SAS Institute, Cary, NC). All tests were 2-sided, with

Table 1	Demographic and Clinical Characteristics of All Patients (n = 17,852) and Those Who Received PCI (n = 326) for Locally Advanced Non−Small-Cell Lung Cancer		
Characteristic	**All, n**	**PCI, n (%)**	**P**
Age, Years			<.001
<60[a]	4125	129 (3.1)	
60-69	6018	109 (1.8)	
70-79	5712	74 (1.3)	
≥80	1997	14 (0.7)	
Sex			.118
Male	11,361	194 (1.7)	
Female	6491	132 (2.0)	
Race			.034
White[a]	14,349	247 (1.7)	
Black	2173	59 (2.7)	
Asian	1219	19 (1.6)	
Other	111	1 (0.9)	
Hispanic Origin			.475
Hispanic	560	8 (1.4)	
Non-Hispanic	17,292	318 (1.8)	
Marital Status			.146
Married	10,675	207 (1.9)	
Not married	6722	110 (1.6)	
Tumor Histology			.032
Adenocarcinoma[a]	8694	178 (2.0)	
Squamous cell carcinoma	8499	134 (1.6)	
Other	659	14 (2.1)	
Tumor Stage			.328
IIIA	6873	117 (1.7)	
IIIB	10,979	209 (1.9)	
Cancer-Directed Surgery			.276
Pneumonectomy	963	14 (1.5)	
Lobectomy	2085	31 (1.5)	
Other	785	17 (2.2)	
None[a]	14,019	264 (1.9)	

Abbreviation: PCI = prophylactic cranial irradiation.
[a]Reference comparison for χ^2 test.