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Prophylactic cranial irradiation

Prophylactic cranial irradiation after definitive chemoradiotherapy for limited-stage small cell lung cancer: Do all patients benefit? ☆

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ABSTRACT

Purpose: Prophylactic cranial irradiation (PCI) can improve overall survival (OS) and suppress brain metastases (BM) in patients with limited-stage small cell lung cancer (LS-SCLC) after complete response to primary therapy. However, PCI can be toxic. We sought to identify characteristics of patients who may not benefit from PCI.

Methods: We identified 658 patients who received chemoradiotherapy at MD Anderson in 1986–2012; 364 received PCI and 294 did not. Median follow-up time was 21.2 months (range 1.2–240.8 months). Cox proportional hazards regression, competing-risk regression, and Kaplan–Meier analyses were used to identify factors influencing OS and BM.

Results: PCI reduced risks of death [HR 0.73, 95% CI 0.61–0.88, $P = 0.001$] and BM [HR 0.54, 95% CI 0.39–0.76, $P < 0.001$]. Having tumors $\geqslant 5$ cm increased the risk of BM [HR 1.77, 95% CI 1.22–2.55, $P = 0.002$] but not death [HR 1.16, 95% CI 0.96–1.40, $P = 0.114$]. Among patients $\geqslant 70$ years with $\geqslant 5$-cm tumors, PCI did not improve OS [2-year rates 39.4% vs 40.9%, $P = 0.739$].

Conclusions: PCI remains standard therapy after complete response to chemoradiotherapy for LS-SCLC. However, older patients may be at risk from comorbidity or extracranial disease. Further work is warranted to identify patients who may not benefit from PCI.

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Lung cancer is the leading cause of mortality from cancer worldwide [1,2]. Small cell lung cancer (SCLC) is a neuroendocrine tumor that accounts for 15%-20% of all lung cancers, and is well known for its rapid doubling time and potential for widespread metastases [3,4]. Although SCLC initially responds to chemoradiation therapy, the central nervous system is a frequent site of relapse, with a 2-year cumulative risk of developing brain metastases (BM) of >50% and approximately 65% of patients having detectable BM on autopsy [5–7].

The role of prophylactic cranial irradiation (PCI) in reducing the risk of developing BM has been extensively studied in patients with limited-stage SCLC that responds completely to definitive chemoradiotherapy. A seminal meta-analysis of 7 randomized trials conducted in 1977–1995 showed that PCI not only decreased the incidence of BM among such patients but also increased their overall survival (OS) rates by approximately 5% at 3 years [8]. A second meta-analysis with nearly identical results confirmed that PCI reduced the incidence of BM and provided a survival advantage [9]. However, neither of these studies addressed its potential toxicity.

PCI is known to be associated with acute toxic effects including alopecia, nausea, headache, and fatigue [10]. However, these symptoms are typically self-limited and resolve over time. Long-term toxic effects have been more difficult to assess and quantify, and thus reports are limited. However, in an early retrospective study of 20 long-term survivors of SCLC (18 of whom had received PCI), 15 patients (75%) showed impaired neurocognitive function manifesting as memory loss, ataxia, and weakness [11]. Other studies have identified factors that increase the risk of neurotoxicity after PCI, including age >60 years, total dose >30 Gy, and receipt of chemotherapy concurrent with the PCI [12–15]. In RTOG 0212, approximately 62% of patients who received 25 Gy of PCI went on to develop chronic neurotoxicity, and age was the most significant risk factor [16,17].

A recent large retrospective analysis of patients aged >70 years with limited-stage SCLC from the National Cancer Database showed that chemoradiotherapy conferred an OS benefit over chemotherapy alone [18]. These findings suggest that, for elderly patients who can tolerate the toxicity of combined chemoradio-

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therapy, the intent of treatment should be achievement of complete response. However, the role of PCI for such patients has yet to be addressed. In this study, we sought to identify factors that correlate with brain recurrence and survival in patients with limited-stage SCLC who received definitive chemoradiotherapy and to identify subgroups of such patients for whom PCI may be more (or less) beneficial. We hypothesized that patients who were $\geqslant$70 years old may not show a survival benefit after PCI owing to their susceptibility to severe toxicity from PCI and possibly also greater risks of death from other comorbid conditions.

Patients and methods

Patient selection and data collection

After obtaining institutional review board approval, we identified 658 patients with limited-stage SCLC who had received definitive chemoradiotherapy at The University of Texas MD Anderson Cancer Center from 1986 through 2012. Information on patient demographics, diagnostic and staging work-up, treatment, and treatment response was extracted from medical records. Primary tumor size at the time of treatment initiation was measured by a radiologist on diagnostic images (when available) as the largest dimension of the primary parenchymal tumor or, if the primary tumor could not be visualized, the largest regional node.

Treatment characteristics

All patients had received radiotherapy doses of at least 45 Gy to the primary intrathoracic disease. Most patients received concurrent chemotherapy with the radiation. However, some patients (generally those with poor performance status or large lesions) were given induction chemotherapy before concurrent chemoradiotherapy, and others received induction chemotherapy followed by radiotherapy. Radiotherapy typically consisted of 45 Gy in 30 fractions delivered twice daily to the entire involved field; 70 Gy in 35 fractions delivered once daily; or 61.2 Gy delivered in 34 fractions, with the first 18 fractions delivered daily to the involved field followed by 16 fractions delivered twice daily to a reduced field based on response. Patients who received surgery as part of treatment were excluded from this analysis. Disease was staged in all cases with computed tomography (CT) and, after 2000, with positron emission tomography (PET) or PET/CT. All patients underwent brain scanning as part of the staging process, most with magnetic resonance imaging except for a few patients who underwent brain CT because of having claustrophobia or a cardiac pacemaker.

The standard practice at the authors' institution is to recommend PCI for all patients with limited-stage SCLC whose intrathoracic disease has responded to local therapy and who do not have evidence of distant metastasis. PCI typically consisted of 25 Gy delivered in 10 daily fractions to the whole brain using opposed lateral or left anterior oblique/right anterior oblique beams. PCI was typically initiated 4–6 weeks after completion of primary chemoradiotherapy if disease restaging examinations at that time showed response of intrathoracic disease and no evidence of distant metastasis.

Statistical analysis

Pearson's chi-square tests were used to assess measures of association in frequency tables, and a nonparametric test of medians was used for between-group comparisons of continuous variables. We compared demographic and treatment-related characteristics between patients who received PCI and those who did not. Next, we used the Kaplan–Meier method to calculate cumulative freedom from BM and OS over time. The time points in this study were calculated from the date of treatment initiation to the date BM was diagnosed, or the date of death or last clinic follow-up visit, as applicable. Cox proportional hazards regression analyses were used to identify factors potentially associated with OS. To analyze freedom from BM, competing-risks regression analysis was used, with the endpoint being development of BM and the competing risk being development of extracranial metastasis. Log-rank tests were used to compare freedom from BM and OS between various groups. Data were analyzed with Stata/MP 14.0 (StataCorp LP, College Station, TX), and $p < 0.05$ was considered to indicate statistically significant differences.

Results

Of the 658 patients who received definitive chemoradiotherapy for limited-stage SCLC included in this analysis, 364 (55.3%) received PCI and 294 (44.7%) did not. Those who did not receive PCI showed no response or early disease progression, had poor performance status, or chose to decline PCI against medical advice. The median age of all patients was 62 years (range 27–95 years), and 151 (22.9%) were $\geqslant$70 years old at when treatment was begun. Tumor size was known for most patients (601 [91.3%]); 265 (44.1%) had primary intrathoracic disease that was <5 cm in diameter at the time of treatment initiation, and 336 (55.9%) had disease $\geqslant$5 cm. When demographic and treatment characteristics were compared between patients who received PCI and those who did not, patients who received PCI were more likely to have had a Karnofsky performance status (KPS) score of 80 or higher (87.4% vs. 78.6%; $p = 0.002$). Patient and treatment characteristics are summarized in Table 1.

The median follow-up time for all patients was 21.2 months (range 1.2–240.8 months); the median OS time was 24.5 months; the 2-year OS rate was 51.3%; and the 5-year OS rate was 23.7%. Rates of disease-free survival (DFS), local recurrence-free survival (LRFS), distant metastasis-free survival (DMFS), and BM-free survival (BMFS) at 2 years and 5 years were: DFS 38.1% and 30.9%; LRFS 59.9% and 51.5%; DMFS 48.9% and 39.5%; and BMFS 76.3% and 71.4%.

On univariate competing risk regression analysis, where the primary outcome was development of BM and the competing risk was development of extracranial metastatic disease, the only factor associated with increased risk of BM was primary tumor size $\geqslant$5 cm (subdistribution hazard ratio [SHR] 1.66, 95% confidence interval [CI] 1.15–2.40, $p = 0.007$ vs. size <5 cm). On the other hand, being treated with 2D or 3D conformal radiotherapy techniques (rather than intensity-modulated radiotherapy [IMRT]), being treated after 2000, and receipt of PCI were all associated with *reduced* risk of developing BM (Table 2). On multivariate competing risk regression analysis, only receipt of PCI (SHR 0.57, 95% CI 0.41–0.79, $p = 0.001$ vs. no PCI) and use of 2D or 3D radiation techniques (SHR 0.46, 95% CI 0.30–0.73, $p = 0.001$ vs. IMRT) were associated with a reduced risk of developing BM.

On univariate Cox regression analysis, where the primary outcome was mortality from any cause, factors associated with increased overall mortality included age $\geqslant$ 70, KPS < 80, and the use of induction chemotherapy followed by sequential radiotherapy. Factors associated with reduced risk of overall mortality were treatment with 2D or 3D conformal radiotherapy techniques (vs. IMRT), treatment after 2000, and receipt of PCI (Table 2). On multivariate analysis, treatment with 2D or 3D radiotherapy techniques (SHR 0.79, 95% CI 0.64–0.99, $p = 0.037$ vs. IMRT) and receipt of PCI (SHR 0.76, 95% CI 0.63–0.91, $p = 0.003$ vs. no PCI) remained associated with reduced overall mortality.

In considering both the total incidence of BM and the time to diagnosis of BM, patients who received PCI developed BM less