

Scientific Article

Factors influencing the utilization of prophylactic cranial irradiation in patients with limited-stage small cell lung cancer

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Abstract

Purpose: Brain metastases are common in patients with limited-stage small cell lung cancer (LS-SCLC) due to the inability of most chemotherapeutics to penetrate the blood–brain barrier. Prophylactic cranial irradiation (PCI) is therefore recommended for use in patients with a good response to concurrent chemoradiotherapy. However, PCI is not always delivered; therefore, we investigated the reasons for PCI omission in patients who underwent therapy with curative intent.

Methods and materials: We retrospectively reviewed all patients with LS-SCLC who were treated with curative intent at our institution. Overall survival and cumulative incidence of brain metastasis were estimated by the Kaplan-Meier method. The Pearson χ^2 test and Mann-Whitney U test were used to examine factors associated with PCI use, and prognostic factors were analyzed with Cox proportional hazards modeling.

Results: We examined 208 patients who were treated for LS-SCLC at our institution. A total of 115 patients (55%) received PCI. The most common documented reason for PCI omission was patient refusal due to neurotoxicity concerns (38%). Physician assessment of being medically unfit (33%) and of advanced age (8%) were the second and third most common reasons, respectively. Karnofsky performance status and clinical American Joint Committee on Cancer stage but not PCI were significantly associated with overall survival. Only clinical stage remained an independent factor on multivariate analysis.

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Conclusions: Approximately half of patients with LS-SCLC ultimately receive PCI, generally for guideline-recommended reasons. The most common reason for PCI omission was patient concerns regarding neurotoxicity. Efforts to decrease PCI neurotoxicity, including hippocampal-sparing radiation and memantine use, may increase the use of this survival-improving intervention in eligible patients with LS-SCLC.

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Introduction

Limited-stage small cell lung cancer (LS-SCLC) is typically treated with chemotherapy and radiation therapy (RT) to the primary tumor. However, the brain is a frequent site of metastasis due to the inability of most chemotherapeutics to penetrate the blood–brain barrier and may be the sole site of recurrence in patients with otherwise good responses to initial therapy. Brain metastasis is associated with significant neurocognitive symptoms and poor survival and has been observed in more than 50% of patients with SCLC.¹ Although the use of prophylactic cranial irradiation (PCI) is debated in patients with very early stage SCLC, such as T1N0M0 disease,² PCI is currently considered a standard-of-care intervention in patients with LS-SCLC who achieve a complete or partial response to initial chemotherapy.³

PCI has been studied extensively in clinical trials and was shown to improve overall survival (OS) in patients with SCLC in 2 meta-analyses of phase 2 and 3 clinical trials.^{4,5} Current National Comprehensive Cancer Network guidelines recommend the use of PCI for a limited number of patients with SCLC who respond well to initial therapy.

PCI is associated with chronic neurocognitive deficits in attention, memory, and problem-solving ability^{6,7}; however, these toxicity concerns must be weighed against the potential for neurologic deficits caused by disease progression in the brain. Currently, data on the utilization rates of PCI and the precise reasons for omission are limited. Therefore, in this study, we examined the rate of PCI use and factors associated with a lack of use in patients with LS-SCLC at a large academic institution.

Methods and materials

Patient cohort

After receiving institutional review board approval, we retrospectively reviewed all patients with LS-SCLC who were treated with curative intent at our institution from 1999 to 2013. Demographic information, stage, treatment, and disease-related outcomes were extracted from the medical record. For patients who did not receive PCI, we reviewed the clinical notes from the treating oncologists (medical, radiation, and surgical) to ascertain the reason.

Patients were staged according to the 7th Edition of the American Joint Committee on Cancer (AJCC) classification system, and all patients with up to stage IIIB disease were considered to have LS-SCLC. All patients had pathologic confirmation of disease at our institution and underwent an extent-of-disease evaluation with body computed tomography (CT) or positron emission tomography scans and a brain CT scan or magnetic resonance imaging to rule out distant metastases. Follow-up after completion of all therapy typically consisted of a history review, physical examination, CT chest scan, and magnetic resonance imaging of the brain every 3 to 6 months or as clinically indicated.

Endpoints and statistical considerations

All endpoints were calculated from the date of pathologic diagnosis. OS was calculated from the start date of chemotherapy until the date of death or last follow-up. OS was estimated with the Kaplan-Meier method and analyzed using the Cox proportional hazards regression model. Cumulative incidence of brain metastasis was analyzed by the Fine-Gray competing risks regression model, and death without brain metastasis was considered a competing risk. Pearson's χ^2 test and Mann-Whitney U test were used to examine factors associated with PCI use, and prognostic factors were analyzed by Cox proportional hazards modeling. Factors included in the analyses were age at diagnosis, Karnofsky performance status (KPS), sex, clinical AJCC stage, concurrent versus sequential delivery of RT, thoracic RT fractionation, and PCI use. PCI and factors with a *P*-value <.1 on univariate analysis were included in the multivariate analysis. All statistical tests were two-sided, and *P* <.05 was considered statistically significant.

Results

We identified 283 patients who were treated with curative intent with surgery or radiation for LS-SCLC at our institution. Surgical patients lost to follow-up with unknown chemotherapy receipt⁷ or patients who refused chemotherapy⁶ were excluded. All remaining 264 patients received systemic therapy as part of their initial therapy. Thoracic RT (TRT) was administered in 236

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