

Scientific Article

Clinical Outcome in Patients With Early-Stage Small Cell Lung Cancer Treated With Surgery or Radiation in the Absence of Prophylactic Cranial Irradiation: A Single-Center Retrospective Study



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Abstract

Purpose: As screening chest computed tomography for patients at high risk for cancer has become more widely accepted, increasing numbers of patients with early-stage small cell lung cancer (SCLC) are being diagnosed. Although surgery is an accepted option for patients with early-stage SCLC, for patients who decline or cannot undergo surgery, stereotactic body radiation treatment (SBRT) is an alternative. Although prophylactic cranial irradiation (PCI) improves survival in patients with limited-stage SCLC, PCI for early-stage SCLC (stage T1-T2) has not been explored. This study defines survival and recurrence patterns in patients with early-stage SCLC who were treated with surgery or SBRT in the absence of PCI.

Methods and Materials: In this single-institution retrospective study, 14 patients diagnosed with early-stage SCLC (stage T1-T2) between July 2015 and May 2021 at a single tertiary care hospital were treated with SBRT or surgery with no PCI. Primary outcomes were locoregional cancer recurrence, distant recurrence, recurrence-free survival, and overall survival. The secondary outcome was development of brain metastasis. Analyses included Cox regression, Kaplan-Meier survival, and log-rank tests.

Results: A total of 14 patients (5 women and 9 men) were included in the study: 9 with stage T1 and 5 with stage T2 SCLC. Six patients (43%) received SBRT and 8 (57%) had surgical treatment. All patients except 1 received adjuvant chemotherapy. Median follow-up was 14.3 months (range, 2.4-64.4 months), and the median age at diagnosis was 71.5 years (range, 54-81 years). Cox regression and log-rank tests showed no significant differences in any outcomes between the surgery and SBRT groups, and no patients developed brain metastases during the study period.

Conclusions: Data are lacking regarding the benefit of PCI in early-stage SCLC. Although the sample size in this study was too small to draw any conclusions, the findings add to the ongoing dialogue regarding the importance of PCI in this patient

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population. No difference was identified in survival and cancer recurrence in patients who received either surgery or SBRT in the absence of PCI.

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Introduction

In patients who have various types of cancer, brain metastases are a common source of morbidity and mortality. For instance, more than half of patients with small cell lung cancer (SCLC) will develop central nervous system metastases at some time during the course of their disease.¹

Prophylactic cranial irradiation (PCI) has been the standard of care when treating patients with limited-stage SCLC, and this approach has been validated in clinical studies that have shown a lower rate of brain metastasis in patients who have had PCI. Also, a meta-analysis by Aupérin et al² indicated a survival benefit in patients with SCLC who were treated with PCI.^{2,3}

However, information about the utility of PCI for patients who have early-stage SCLC is limited, as SCLC is often diagnosed at later stages. Currently, no large, nationally representative data on the risk of brain metastases in patients with early-stage SCLC are available. Additionally, very little data on the clinical outcomes for this patient population exist, and this information is necessary for defining appropriate adjuvant therapy recommendations in patients whose SCLC has been identified early.⁴

Although one might assume that improved treatments for central nervous system disease would lead to higher quality of life, prospective studies have not been done to explore this possibility.⁵ Retrospective investigations have revealed that cranial irradiation has some negative effects on brain function, in addition to increasing costs and being inconvenient to patients.⁵⁻⁷ As a result of these data and clinical experiences, defining the financial and physical toxicity profiles of PCI has become a topic of interest, and some physicians are foregoing PCI therapy for certain patients with early-stage cancers.⁸ Because physicians thoroughly discuss the risks of PCI with patients when planning a treatment strategy, some patients opt not to have PCI for various reasons, highlighting the need to define how outcomes are affected when therapies are performed in the absence of this prophylactic treatment. Therefore, our study focused on answering this question by assessing outcomes in patients with early-stage SCLC. The aim of this study was to define the outcomes of patients with early-stage SCLC in the absence of PCI therapy to determine whether stereotactic body radiation treatment (SBRT) or surgery would be associated with different survival and cancer recurrence outcomes for patients treated at our institution.

Methods and Materials

Data source and patient selection

This was a single-institution retrospective study of patients treated for early-stage SCLC (T1 and T2 N0) over a 14.3-month period between July 9, 2015, and May 19, 2021. For consistency across the group, we used the TNM Classification of Malignant Tumors from the Union for International Cancer Control 7th American Joint Committee on Cancer staging system.⁹ All patients included in the study had biopsy-confirmed SCLC and had been treated with either surgical resection or SBRT in the absence of PCI. This study was approved by Henry Ford Health.

Inclusion criteria included patients who were diagnosed with nonmetastatic, biopsy-confirmed, clinically node-negative early-stage SCLC. Positron emission tomography was used in the staging of 93% of the patients. Brain magnetic resonance imaging (MRI) was done as per standard staging workup; all patients had initial negative brain MRI results and opted not to receive PCI. Patients who did not receive definitive treatment with surgery or SBRT and the 1 patient who was treated with PCI were excluded.

Study variables and endpoints

Demographic information, pathologic features, treatment details (surgery, radiation therapy, and chemotherapy), follow-up, recurrence patterns, and survival status at last follow-up were collected. Patients were monitored with computed tomography of the chest every 3 months after treatment. At the time of diagnosis, all patients included had negative brain MRI results. However, surveillance brain imaging was only done in 10 out of 14 patients. Primary outcomes included locoregional cancer recurrence, distant cancer recurrence, recurrence-free survival (combination of recurrence and survival), and overall survival. Secondary outcomes included brain metastasis. Brain failure was defined as evidence of brain metastasis as seen by brain MRI or computed tomography imaging.

Statistical analysis

Kaplan-Meier survival curves, log-rank tests, and Cox proportional hazards regression were used to assess the

association of treatment (surgery only vs radiation only) with the outcomes. For Cox regression analysis, median survival was computed as the time at which the Kaplan-Meier survival curve dropped below 50%. The testing level was set at .05 for significance, and all statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc, Cary, NC).

Results

Patient pathologic and treatment characteristics

A total of 14 patients had early-stage SCLC and were treated at our institution during the study period (5 women [36%] and 9 men [64%]). There were 9 patients who had clinical stage I (T1) SCLC and 5 patients who had stage IIA (T2) SCLC. All patients except 1 received adjuvant chemotherapy, with a median number of 4 cycles (range, 2-6 cycles). A total of 6 patients (43%), 66% with T1, received definitive SBRT, and 8 (57%), 62% with T1, underwent surgical resection. All 6 patients who received radiation had clinical negative nodal disease on imaging (positron emission tomography/computed tomography scan), and 3 of them had mediastinal staging–confirmed negative disease. The median follow-up for all patients was 14.3 months (range, 2.4-64.4 months). The median age for the entire group was 71.5 years (range, 54-81 years). The median tumor size was 1.6 cm (range, 1.2-5.8 cm) for the entire group (Table 1). None of the 14 patients developed brain metastases during the follow-up period.

Survival and cancer recurrence

At the last follow-up, 1 patient had locoregional recurrence, 1 patient had distant only recurrence, and 4 patients had combined locoregional and distant recurrence. None of the 14 patients developed brain metastases.

For patients with locoregional recurrence, the median survival was 12.3 months for those who received SBRT and 28.6 months for those who received surgery. For patients who had distant recurrence, median survival was 12.3 months for the SBRT group. Cox regression analysis and log-rank tests showed no statistical differences in any outcomes between patients treated with surgery versus SBRT (Fig. 1). Hazard ratios (HRs) calculated to assess surgery versus radiation did not reveal a significant association of treatment strategy with type of cancer recurrence or survival: locoregional recurrence HR, 0.54 (95% confidence interval [CI], 0.07-3.96; $P = .54$); distant recurrence HR, 0.37 (95% CI, 0.06-2.28; $P = .28$); recurrence-free survival HR, 0.37 (95% CI, 0.09-1.58; $P = .18$); and overall survival HR, 95% CI, (0.01, 1.20) ($P = .07$).

Discussion

In this study, we explored the survival and cancer recurrence outcomes of patients with early-stage SCLC who had not received PCI therapy but who were treated with either SBRT or surgery alone. We found no significant difference in types of recurrence, recurrence-free survival, or overall survival in patients who received radiation therapy versus those who had surgery. Importantly, we observed that no patients developed brain metastasis during the follow-up period.

Worldwide, SCLC accounts for approximately 10% to 15% of all lung cancer cases, and the overall incidence of SCLC has gone down during the past 30 years owing to lower smoking rates.^{10,11} Close to two-thirds of patients with SCLC have extensive disease at the time of diagnosis.^{10,12} Among patients who have limited disease, almost all have mediastinal involvement, either by direct tumor extension or metastases to the mediastinal lymph nodes. Approximately 10% of patients have an initial presentation with brain metastasis, and an additional 40% to 50% of these patients go on to develop metastasis sometime during their course of disease.^{13,14} Patients with SCLC who receive PCI have been shown to have higher overall survival than those who do not, with a relative risk of

Table 1 Baseline demographic, pathologic, and treatment characteristics for patients with early-stage small cell lung cancer

	All (N = 14)	SBRT (n = 6)	Surgery (n = 8)
Age at diagnosis (y), median (range)	71.5 (54-81)	74 (69-78)	70 (54-81)
Sex, no. (%)			
Female	5 (36)	3 (50)	3 (38)
Male	9 (64)	3 (50)	5 (62)
Tumor size (cm), median (range)	1.6 (1.2-5.8)	1.6 (1.4-4.8)	2.3 (1.2-5.8)
Standard uptake value, median (range)	8.9 (3.7-31.4)	9.4 (5.1-31.4)	6.3 (3.7-13.9)
<i>Abbreviation:</i> SBRT = stereotactic body radiation therapy.			

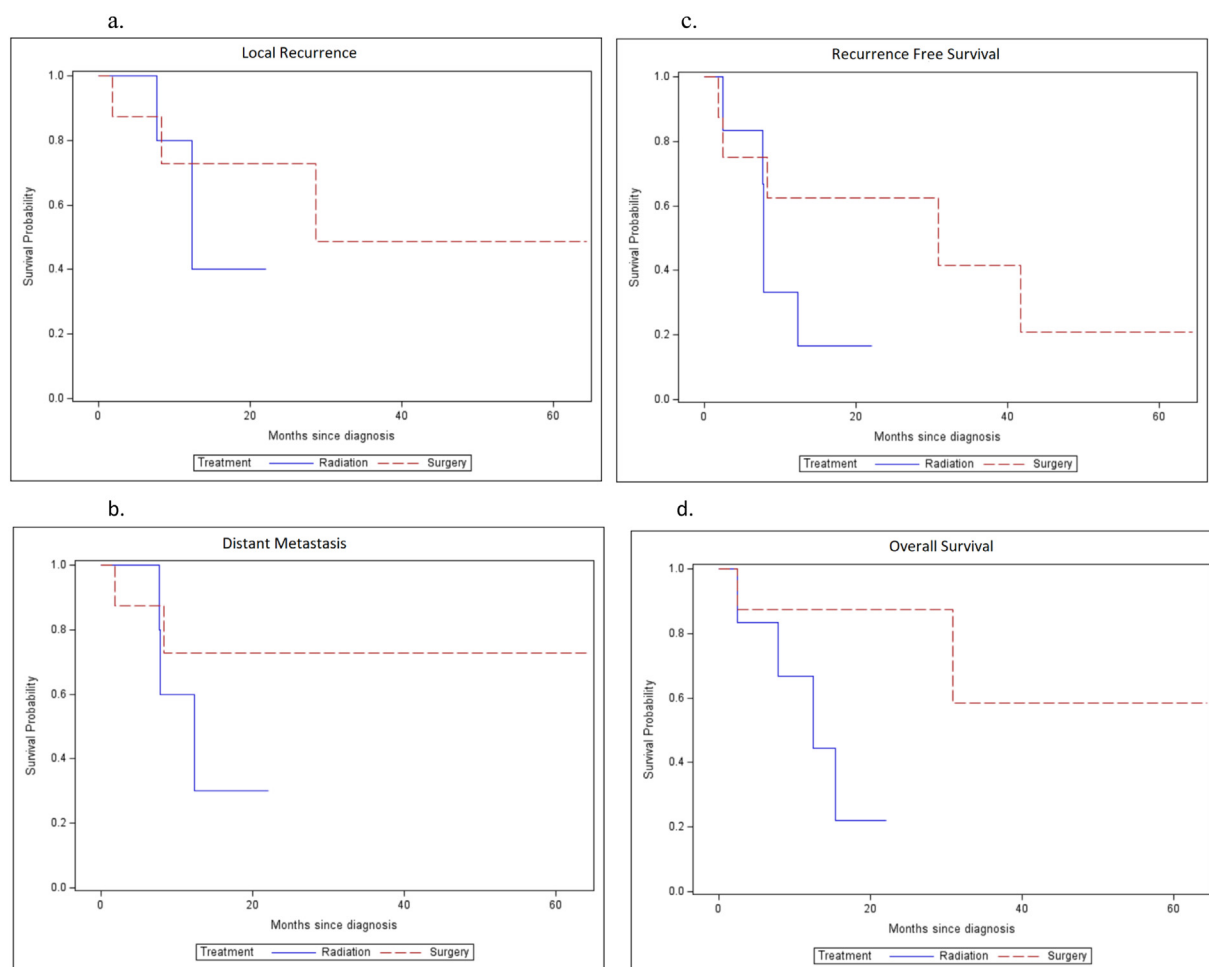


Figure 1 Kaplan-Meier and log-rank analysis of patients with early-stage small cell lung cancer who were treated with radiation therapy ($n = 6$) or surgical resection ($n = 8$). (a) Locoregional cancer recurrence. (b) Distant recurrence or metastasis. (c) Recurrence-free survival as a combination of recurrence and survival. (d) Overall survival.

approximately 0.84 ($P = .01$); thus, PCI has become the standard of care for patients with SCLC, including those who have limited-stage SCLC.²

Notwithstanding the aggressive character of SCLC, a small percentage of patients have an initial presentation or are diagnosed with early-stage, clinical T1-T2a disease, with no involvement of regional lymph nodes and no distant metastases. As more screening programs are introduced, the number of people diagnosed with early-stage SCLC is expected to rise. Although SCLC accounts for 10% of lung cancers detected during screening, it often presents as symptomatic disease in between annual screenings, because it is a fast-growing malignancy. As a result, annual low-dose computed tomography imaging has not become an effective screening tool for detecting early-stage SCLC.¹⁵

Although PCI has been shown to improve survival in patients with SCLC, some health care practitioners have been reluctant to use PCI because they are concerned about radiation-induced central nervous system injury. Additionally, staging and imaging practices have evolved since the initial, main findings on SCLC were published, and close

surveillance with MRI is being actively studied as an alternative to PCI. The SWOG 1827 trial is now evaluating the use of MRI screening every 3 months instead of PCI for all patients with limited-stage SCLC.^{16–18} Thus, how patients who are diagnosed with early-stage SCLC respond to treatments in the absence of PCI will need to be assessed, and our study begins to fill that gap.

In patients with stage I-IIA SCLC who were treated with surgery or SBRT, no patients showed evidence of brain metastases during the study period, nor did we find that surgery and SBRT in the absence of PCI differed regarding overall survival or cancer recurrence. In a meta-analysis by Yang et al,¹⁹ which investigated the effects of PCI in patients who had surgical resection for SCLC, the authors concluded that addition of PCI to surgical treatment might lead to an overall survival advantage, but not for those with early-stage disease. The meta-analysis also revealed that of the 3 studies that assessed brain metastasis in patients with SCLC who had surgical resection, only 1 study looked at patients with early-stage disease, and it revealed no significant difference in brain metastases

between the PCI and non-PCI groups.¹⁹ Furthermore, a quantitative meta-analysis of brain metastasis incidence rates in patients with p-stage I cancer revealed that approximately 10% of patients with stage I SCLC developed brain metastasis, suggesting that the lack of a survival benefit from PCI in this population could simply be due to the low incidence.^{20,21} It is also worth noting that patients with advanced-stage SCLC have an 18% to 25% probability of developing brain metastasis, and PCI has been shown to have no effect on overall survival or disease-free survival while lowering the risk of brain metastasis.^{22,23} The current SWOG study (MRI Brain Surveillance Alone Versus MRI Surveillance with PCI) is enrolling patients who have limited- and extensive-stage SCLC, and this larger controlled study will provide a better understanding of the role for PCI in patients with SCLC.¹⁶ Individualization of treatment may be important to consider, and health care providers should balance the potential benefits and morbidity risks of PCI.

Some limitations of this study should be noted. Although this is the largest series to date assessing only patients with early-stage SCLC, our sample size was still too small. The main study limitation is also the retrospective nature of the study with its inherited bias. Another limitation is that despite surveillance brain imaging being performed for 10 patients (70%), routine MRI brain surveillance is still not available for all patients.

Conclusion

PCI has been frequently used to avert brain metastasis in patients who have SCLC. However, the benefit of PCI for early-stage SCLC is not clear. In some circumstances, MRI surveillance may be preferable. Individualized risk assessment is necessary, and patients should be involved in the decision-making process. This cohort, despite being too small to draw any conclusions, concurs with the most recent American Society for Radiation Oncology recommendations to defer routine PCI treatment for stage I SCLC.²⁴ Until we have the results of the ongoing SWOG trial, we recommend that health care providers have a comprehensive discussion with patients regarding the risks and benefits of PCI within the setting of limited, early-stage SCLC; randomized clinical trials and more extensive studies exploring the utility of PCI in patients with early-stage cancers are needed.

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