Original Study

Effect of Accurate Staging Using Positron Emission Tomography on the Outcomes of Prophylactic Cranial Irradiation in Patients With Limited Stage Small-Cell Lung Cancer

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Abstract

The effect of more accurate staging with positron emission tomography (PET) scan on the outcome of prophylactic cranial irradiation (PCI) was examined retrospectively in 280 patients with limited stage small-cell lung cancer (LS-SCLC). PCI reduced the risk of brain metastasis as the first site of relapse but had no effect on overall survival. Patients with PET-based LS-SCLC achieved long-term survival even without PCI.

Background: Prophylactic cranial irradiation (PCI) was reported to offer survival benefits in patients with limited stage small-cell lung cancer (LS-SCLC). However, earlier studies did not routinely use positron emission tomography (PET) as part of the initial evaluation, thereby reducing the accuracy of tumor staging. We examined the effect of more accurate staging with PET on the role of PCI in patients with LS-SCLC. **Patients and Methods:** We retrospectively collected data from 280 patients with LS-SCLC who had objective responses after combined chemoradiotherapy between 2001 and 2013. The outcomes of PCI were analyzed after stratifying the patients according to whether or not the initial staging included PET imaging. **Results:** The risk of brain metastasis as the first site of relapse was lower in patients who received PCI than in those who did not, only in patients without initial PET imaging (13.3% vs. 37.0%; $P = .020$), but not in patients with initial PET imaging (34.3% vs. 41.1%; $P = .243$). There was no survival difference between subgroups who received PCI or not (5-year survival rates, 34.8% vs. 34.1%; $P = .938$). Patients who had initial staging evaluation with PET achieved long-term survival even without PCI (5-year survival rates, 38.3% with PCI, 38.6% without PCI). **Conclusion:** The role of PCI needs to be critically reassessed in LS-SCLC patients whose initial staging evaluation included PET because the benefit of PCI was not apparent for them.

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Introduction

Small-cell lung cancer (SCLC) is characterized by a high risk of disease progression in the central nervous system. The risk of intracranial metastasis was >50% after successful initial treatment of SCLC in earlier studies.[1-3] The blood–brain barrier, which limits the penetration of cytotoxic agents into the brain, is considered to be the major cause of treatment failure in the central nervous system. Since prophylactic cranial irradiation (PCI) was first proposed in 1973,[4] it has been shown that PCI reduced the risk of brain metastasis and improved the overall survival in some studies of SCLC patients who responded to their initial treatment.[1-3,5-10] Currently, the National Comprehensive Cancer Network and the American College of Chest Physicians recommend PCI for patients with SCLC of all stages with complete response (CR) or partial response (PR) after induction therapy.[11,12]

Over the past 3 decades, however, there have been very few changes in the treatment of SCLC, despite dramatic changes in clinical practice, including routine use of brain magnetic resonance imaging (MRI) and positron emission tomography (PET) imaging as part of the initial staging evaluation. These imaging tools have

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been shown to be very effective in detecting asymptomatic metastases in the brain and also in the extracranial sites,[13,14] which would have been classified as having limited stage (LS) SCLC without metastasis.[15-17]

However, there has been growing concerns about the long-term neurotoxicity of PCI, since delayed neurocognitive disturbances had been reported in a number of long-term SCLC survivors who underwent PCI.[18-21] This issue is particularly important because there is a greater probability of long-term survival with accurate staging and better treatment. Using a decision-analysis statistical modeling approach, Lee et al estimated the quality-adjusted life expectancy of a theoretical cohort of SCLC patients treated with or without PCI.[22] By varying the frequency and severity of PCI-related neurotoxicity, and the survival rates, they reported that treatment with PCI is superior to no PCI under 3 conditions: low rate of neurotoxicity, mild degree of neurotoxicity, and shorter estimated survival time. However, according to this model, the risk–benefit ratio of PCI reversed when the 5-year survival rate increased beyond 40%.[22]

In our institution, PCI is recommended for carefully selected patients on the basis of the clinical decision of the treating physician and the patient's preference. In this retrospective study, we examined the risk of brain metastasis as the first site of treatment failure and overall survival according to whether or not PET was performed as part of the initial staging evaluation in LS-SCLC patients treated with or without PCI.

Patients and Methods

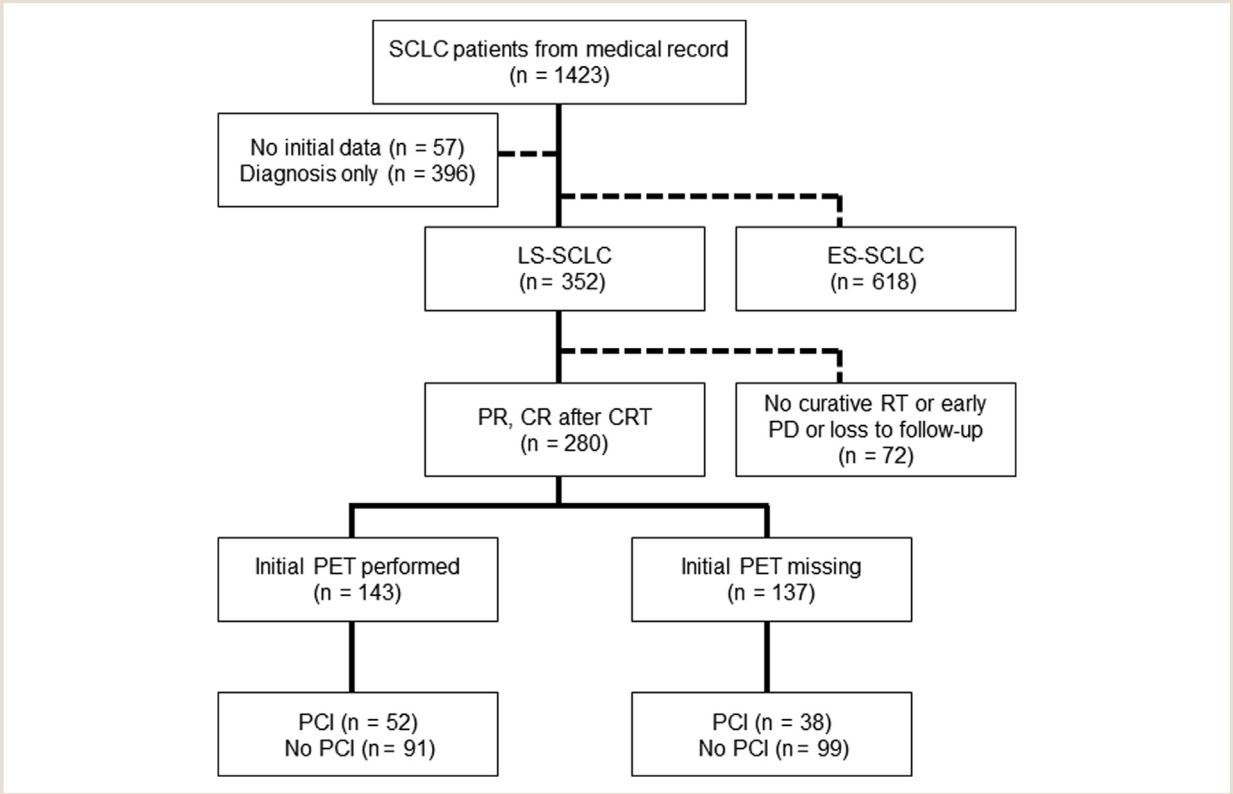
Patient Selection

We reviewed the institutional database and identified 1423 patients with a histologically or cytologically confirmed diagnosis of SCLC between April 2001 and April 2013 at the National Cancer Center Hospital, South Korea. Of these, 280 patients with LS-SCLC who achieved objective responses after chemoradiotherapy with a curative intent were eligible for the present analyses (Figure 1). In the usual clinical setting, these patients are potential candidates for PCI.

Limited stage SCLC was defined as a tumor confined to the hemithorax of origin, including the mediastinum and the ipsilateral supraclavicular nodes, but without pleural effusion. Tumor, node, metastases (TNM) staging (Seventh Edition of the American Joint Committee on Cancer Staging Manual) was also used to subdivide and analyze the study population.

Curative treatment was specified as initial platinum-based chemotherapy with sequential and/or concurrent thoracic radiotherapy with a total radiation dose of ≥45 Gy. Objective response was defined as PR or CR, in accordance with Response Evaluation Criteria In Solid Tumors version 1.1. To be specific, PR stands for

Figure 1 Patient Selection and Disposition



Abbreviations: CR = complete response; CRT = chemoradiotherapy; ES-SCLC = extensive stage small-cell lung cancer; LS-SCLC = limited stage small-cell lung cancer; PCI = prophylactic cranial irradiation; PET = positron emission tomography; RT = radiotherapy; SCLC = small-cell lung cancer.

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