Clinical Significance of Downstaging in Patients With Limited-Disease Small-Cell Lung Cancer

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Abstract

Patients with limited-disease small-cell lung cancer (LD-SCLC) who do not achieve complete response after first-line treatment have a considerable relapse rate. This study assessed the effect of downstaging in 210 patients with LD-SCLC who received first-line treatment. Downstaging resulted in longer overall survival (OS) for the entire patient group, but particularly for patients who achieved a partial response (PR).

Background: We investigated the effect of downstaging on OS in LD-SCLC patients treated with first-line treatment.

Patients and Methods: We retrospectively reviewed 210 LD-SCLC patients who were treated with first-line treatment at Seoul National University Hospital between April 1999 and November 2012. Compared with initial tumor, node, metastases (TNM) stage, cases that showed a lower TNM stage after treatment were defined as 'downstaging.' The relationship between downstaging and OS was analyzed, and a subgroup analysis on the responders was performed.

Results: After first-line treatment, 78 (37.1%) patients achieved complete response, 97 (46.2%) achieved PR, and 35 (16.7%) experienced stable disease or progressive disease. A hundred and fifty one patients (71.9%) showed downstaging of their diseases, and the remaining 59 patients (28.1%) showed no change or upstaging. The median OS for patients achieving downstaging and no change/upstaging were 32.8 months and 13.1 months, respectively ($P < .001$). Of the 97 patients who achieved PR, the OS was significantly longer in patients who showed downstaging than those who did not (25.8 months vs. 13.8 months, respectively; $P = .004$). In multivariate analyses, female sex, downstaging, lower initial TNM stage, and prophylactic cranial irradiation were independent good prognostic factors for OS. **Conclusion:** Downstaging might be an independent good prognostic factor in LD-SCLC. Specifically, downstaging is expected to be useful for stratification of patients achieving PR. Further prospective studies are warranted to verify whether patients who achieved PR without downstaging can be candidates for consolidation treatments after first-line treatment.

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Introduction

Small-cell lung cancer (SCLC) accounts for approximately 13% of all lung cancers.[1] SCLC is characterized by rapid tumor doubling time, high growth fraction, and early development of widespread metastases.[2] Prognosis is poor and median survival without treatment is only 2 to 4 months.[3] Response rates to chemotherapy with or without radiotherapy are greater in SCLC than in other malignancies, and patients achieving an objective response have more favorable outcomes than nonresponders.[4] However, patients with residual tumor after treatment have poorer outcomes than patients achieving complete response (CR), with a 2-year survival rate of only 20%, even in limited disease (LD).[5]

The extent of SCLC is classified into limited or extensive disease categories by the Veterans Administration Lung Cancer Study Group (VALSG) staging system.[6] The VALSG 2-stage system depends on whether tumors can be encompassed in the same radiation port. Recently, the tumor, node, metastases (TNM) staging system of the American Joint Committee on Cancer (AJCC) staging is applicable to SCLC.[7] TNM staging can identify subgroups of patients with distinct prognoses from LD patients, although TNM staging at diagnosis provides only limited guidance in selecting a treatment modality.[8]

We hypothesized that the change of tumor burden after treatment might be related to prognosis, and that the change of TNM

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stage might influence the treatment outcome. Also, LD-SCLC patients achieving only partial response (PR) can be classified into subgroups according to TNM stage after treatment. We investigated the effect of downstaging on overall survival (OS) in LD-SCLC patients treated with first-line treatment.

Patients and Methods

Patients and Treatment

We retrospectively reviewed records of patients who were newly diagnosed with pathologically confirmed LD-SCLC between April 1999 and November 2012 at Seoul National University Hospital (SNUH). In all, 243 patients were treated with first-line treatment. Among them, 33 patients were excluded from the study because TNM stage after treatment could not be evaluated. Computed tomography (CT) was not evaluated within 4 weeks after the completion of first-line treatment in 29 patients and surgical resection was performed during first-line treatment in 4 patients. The remaining 210 patients were included in the study and were retrospectively analyzed for patient characteristics, disease status, and treatment efficacy. Up to 6 cycles of intravenous etoposide plus either cisplatin or carboplatin in combination with definitive radiotherapy were used as first-line treatment.

Assessments of Treatment Outcome

Treatment efficacy was evaluated using clinical exam, chest X-ray, and chest CT every 2 to 3 cycles, and after the completion of the planned treatment. Tumor response was assessed according to the revised Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[9] 'No response' (NR) was defined as a case that showed stable disease or progressive disease according to RECIST 1.1 criteria. We evaluated TNM staging according to AJCC 7th edition[7] before and after first-line treatment. Posttreatment response and posttreatment TNM stage were defined as response and stage evaluated within 4 weeks after completion of first-line treatment. Compared with initial TNM stage, cases that showed a lower TNM stage after treatment were categorized as 'downstaging.' For example, an initial TNM stage IIIB changed to a post-treatment TNM stage of IA, IB, IIA, IIB, or IIIA. Cases that were classified as the same stage and cases that were classified as a higher stage after treatment were categorized as 'no change' and 'upstaging,' respectively. After completion of treatment among patients who were node-positive at diagnosis, we assessed 'nodal clearance,' which was defined as the reduction of any pathological lymph nodes to less than 10 mm on the short axis, in accordance with RECIST 1.1.

The study was reviewed and approved by the Institutional Review Board of SNUH (approval number: H-1206-012-412). The study was also conducted in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

Overall survival was measured from the start date of first-line treatment to the date of death. A subgroup analysis for OS, stratified according to treatment response and change of TNM stage after treatment, was also performed. Progression-free survival (PFS) was measured from the start date of first-line treatment to the date of disease progression or to the date of death. A subgroup analysis for PFS was performed in a manner similar to that for OS. We used the Kaplan-Meier method to estimate the median time to OS and PFS. Survival plots were compared using the log-rank test. Cox proportional hazards regression was used for multivariate analysis. A 2-sided $P < .05$ was considered statistically significant. All statistical analyses were performed using SPSS for Windows, version 19.0 (IBM Corporation).

Results

Study Population and Patterns of Treatment

The baseline characteristics of the 210 patients are shown in Table 1. A hundred and eighty patients (85.7%) were male and smokers (177, 84.3%). Twenty seven patients (12.9%) had a poor performance status, indicated by an Eastern Cooperative Oncology Group performance status $\geq$ 2. One hundred seventy patients (81.0%) were diagnosed as TNM stage III and no patients were diagnosed as stage IV. Approximately two-thirds of the patients were eligible to receive prophylactic cranial irradiation (PCI) after first-line treatment. Radiotherapy was applied concurrently with and without induction chemotherapy in 148 patients (70.5%) and 6 patients (2.9%), respectively. Twenty-nine patients (13.8%) received sequential radiotherapy after 6 cycles of chemotherapy. Planned radiotherapy was not performed and chemotherapy alone was

Table 1 Baseline Characteristics of Patients

Characteristic	Total (n = 210)
Sex, n (%)	
Male	180 (85.7)
Female	30 (14.3)
Median Age, Years (Range)	62 (42-86)
Smoking, n (%)	
Ex- or current smoker	177 (84.3)
Never smoker	21 (10.0)
Unknown	12 (5.7)
ECOG PS, n (%)	
0-1	174 (82.9)
2 or more	27 (12.9)
Unknown	9 (4.3)
TNM Stage at Diagnosis, n (%)	
IA / IB	8 (3.8) / 10 (4.8)
IIA / IIB	17 (8.1) / 5 (2.4)
IIIA / IIIB	76 (36.2) / 94 (44.8)
Chemotherapy Regimen, n (%)	
Etoposide with cisplatin	158 (75.2)
Etoposide with carboplatin	44 (21.0)
Others	8 (3.8)
Radiotherapy Sequence, n (%)	
Concurrent	154 (73.3)
After chemotherapy	29 (13.8)
No radiation	27 (12.9)
Prophylactic Cranial Irradiation, n (%)	
Yes	139 (66.2)
No	71 (33.8)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; TNM = tumor, node, metastases.