Technology in Cancer Research & Treatment
Volume 17: 1-6

DOI: 10.1177/1533033818783904
journals.sagepub.com/home/tct
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Clinical Outcomes of Stereotactic Body Radiotherapy for Patients With Stage I Small-Cell Lung Cancer: Analysis of a Subset of the Japanese Radiological Society Multi-Institutional SBRT Study Group Database

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Abstract

Stereotactic body radiotherapy (SBRT) is widely used as a curative treatment option for stage I non-small-cell lung cancer, but for patients with stage I small-cell lung cancer, the role of stereotactic body radiotherapy is unclear. In this study, we retrospectively analyzed the outcomes of a subset of patients with stage I small-cell lung cancer treated with stereotactic body radiotherapy in the database of the Japanese Radiological Society-Multi-Institutional stereotactic body radiotherapy Study Group. The 43 patients treated with stereotactic body radiotherapy for stage I small-cell lung cancer between 2004 and 2012 at 11 Japanese institutions were studied: median age = 77 years; 32 (74%) males and 11 females; and 80% were medically inoperable. The clinical stage was IA in 31 and IB in 12. In all patients, the lung tumors were pathologically proven as small-cell lung cancer. A total dose of 48 to 60 Gy was administered in 4 to 8 fractions. The median biologically effective dose ($\alpha/\beta = 10$ Gy) was 105.6 Gy. Chemotherapy and prophylactic cranial irradiation were administered in only 8 patients, respectively. The median follow-up time was 23.2 months. The 2-year overall survival, progression-free survival, and distant metastasis-free survival rates were 72.3%, 44.6%, and 47.2%, respectively. The 2-year local control was 80.2%. Regarding the patterns of failure, distant metastasis, lymph node metastasis, and local recurrence were observed in 47%, 28%, and 16% of patients, respectively. No ≥grade 3 stereotactic body radiotherapy-

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related toxicities were observed. Although stereotactic body radiotherapy was thus revealed to be effective for the local control of stage I small-cell lung cancer, the incidence of distant metastases was high. Further investigations of larger cohorts are needed, including analyses of the effects of combined chemotherapy.

Keywords
stereotactic body radiotherapy, small-cell lung cancer, clinical stage I, JRS-SBRTSG

Abbreviations
CBDCA, chemoradiotherapy using carboplatin; CDDP, chemoradiotherapy using cisplatin; CI, confidence interval; CT, computed tomography; DMFS, distant metastasis-free survival; FDG-PET, F18-fluorodeoxyglucose positron emission tomography; Gy, Gray; HR, hazard ratio; JRS-SBRTSG, Japanese Radiological Society multi-Institutional SBRT Study Group; LD-SCLC, limited disease of stereotactic body radiotherapy; MRI, magnetic resonance imaging; MV, megavoltage; NSCLC, non-small cell lung cancer; OS, overall survival; PCI, prophylactic cranial irradiation; PFS, progression-free survival; PS, performance status; SBRT, stereotactic body radiotherapy; SCLC, small-cell lung cancer; UICC, Union for International Cancer Control

Received: February 28, 2018; Revised: April 04, 2018; Accepted: May 24, 2018.

Introduction

Among the primary lung cancers, small-cell lung cancer (SCLC) is characterized by rapid progression and early metastasis.[1] For patients with limited SCLC disease, thoracic radiotherapy combined with systemic chemotherapy has been considered the standard treatment based on the results of clinical studies.[2], [3] However, long-term favorable results have been reported for stage I patients treated with surgery as a main modality.[4-13] Therefore, surgical resection or surgical resection combined with chemotherapy have been recommended for SCLC, especially for the patients with stage I SCLC among limited-disease patients.

In contrast, for medically inoperable patients with stage I SCLC, radiotherapy and/or chemotherapy is generally considered, but the optimal treatment strategy specifically for these patients has not been established. Stereotactic body radiotherapy (SBRT) is now widely used as one of the effective radiation modalities for stage I non-small cell lung cancer (NSCLC). Considering that favorable outcomes have been obtained for early SCLC by local therapy such as surgery, it is possible that SBRT could also be an effective treatment option for stage I SCLC. However, there have been only a few reports regarding SBRT for stage I SCLC other than a single-institutional experience with a small number of cases.[14], [15,16]

Because of the small number of cases that are diagnosed clinically as stage I SCLC and the limited number of such patients that undergo SBRT, it is extremely difficult to obtain meaningful information about clinical outcomes from a single-institutional study and also difficult to conduct a clinical trial. We thus conducted the present study to retrospectively evaluate the outcomes of SBRT for patients with stage I SCLC using data extracted from a Japanese multi-institutional database.

Patients and Methods

Patients

This was a retrospective analysis of the 43 patients with stage I SCLC treated at 11 institutions extracted from the database of the Japanese Radiological Society Multi-Institutional SBRT Study Group (JRS-SBRTSG), which has surveyed 2433 patients with lung cancer treated with SBRT. In all patients, the lung tumors were pathologically confirmed as SCLC. The patients' ages were 56 to 88 (median 77) years, 32 males and 11 females. The substage by the Union for International Cancer Control seventh version (UICC seventh) was IA in 31 and IB in 12 patients. The tumor sizes (diameter) ranged from 5 to 46 mm (median 24 mm). All tumors in this series were located peripheral to the lung. The majority ($n = 34$, 79%) of the patients were medically inoperable. The performance status was 0 in 22 patients, 1 in 14 patients, 2 in 2 patients, and not available in 5 patients. F18-fluorodeoxyglucose positron emission tomography (FDG-PET) was performed in 12 patients for staging. Contrast-enhanced magnetic resonance imaging (MRI) or computed tomography (CT) of the brain were performed for staging in all patients. The patient characteristics are summarized in Table 1. Written informed consent was obtained from all patients before treatment. This study was approved by the institutional review board (Yamanashi University No. 961).

Stereotactic Body Radiotherapy Treatment

Stereotactic 3-dimensional body radiotherapy treatment was performed using noncoplanar multiple static ports or dynamic arcs. A total dose of 36.0 to 60.0 Gy was administered in 3 to 10 (median 4) fractions. The median calculated biological effective dose was 105.6 Gy (range 56.0-119.6 Gy) based on $\alpha/\beta = 10$ Gy. The prescription point was isocenter in 28 patients, 80% isodose in 7 patients, and dose covering 95% volume within the

Table 1. Characteristics of the 43 Patients With Stage I Small-Cell Lung Cancer.

Age, years	56-88 (median 77)
Females/males	11/32
Clinical stage (UICC seventh):	
IA	31
IB	12
Tumor size, mm (median)	5-46 (median 24)
Operability	
Inoperable	34
Operable	9
Performance status (ECOG)	
0	22
1	14
2	2
NA	5
FDG-PET for staging	
Yes	12
No	31
SBRT	
Total dose, Gy	36.0–60.0 (median 48.0)
No. of fractions	3–10 (median 4)
BED 10, Gy	56.0–119.6 (median 105.6)
Chemotherapy	
Yes	8
No	35
PCI	
Yes	8
No	35

Abbreviations: BED10, biological effective dose based on the assumption of $\alpha/\beta = 10$; ECOG, Eastern Cooperative Oncology Group; FDG-PET, fluorine fluorodeoxyglucose-positron emission tomography; NA, not available; PCI, prophylactic cranial irradiation; SBRT, stereotactic body radiation therapy; UICC, Union for International Cancer Control.

planning target volume in 3 patients; no data were available in 5 patients. For dose calculations, a variety of algorithms including a collapsed cone convolution, superposition algorithm, or analytical anisotropic algorithm were used.

Only 8 of the 43 patients received 3 to 4 cycles of systemic chemotherapy. The chemotherapy regimens were cisplatin or carboplatin + etoposide in 6 patients, etoposide in only 1 patient; and the regimen was unknown in 1 patient. Eight patients underwent prophylactic cranial irradiation (PCI). The dose fractionations of PCI were from 24 Gy in 10 fraction (2 cases), 30 Gy in 15 fractions (2 cases), 24 Gy in 12 fractions (1 case), and not available (3 cases).

The SBRT was performed with an X-ray beam linear accelerator of 4, 6, and 10 MV (6 MV in majority of cases). The total irradiation dose delivered was dependent on the judgment rendered at each institution.

Follow-Up

After the completion of SBRT, the patients were evaluated by examinations including CT of the chest and abdomen every 2 to 3 months for 2 years and every 6 months thereafter. Brain MRI and FDG-PET were also performed if needed.

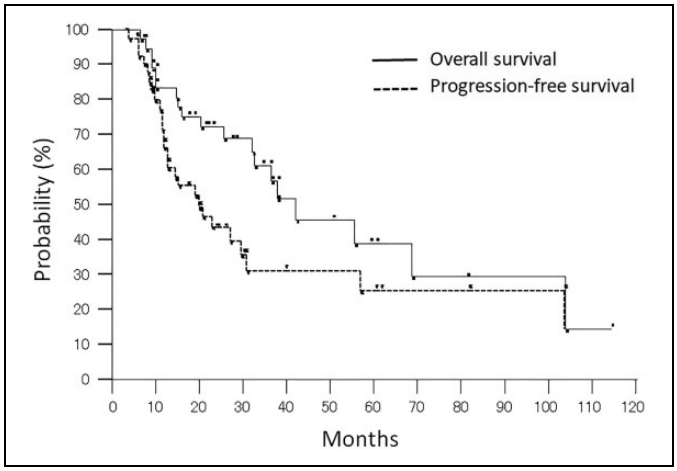

Figure 1. Kaplan-Meier curves for overall survival and progression-free survival rates for the 43 patients with stage I SCLC. SCLC indicates small-cell lung cancer.

Evaluated Outcomes and the Methods of Statistical Analysis

We evaluated the patients' overall survival (OS), progression-free survival (PFS), distant metastasis-free survival (DMFS), and local control rate after SBRT. The pattern of failures and the prognostic factors for local control and PFS were also analyzed. We used the Kaplan-Meier method to estimate the survival rates and local control rate. Log-rank testing was used to compare outcomes between the subsets of patients analyzed. The points on the survival and local control curves revealed by the Kaplan-Meier analysis were censored cases. Stereotactic body radiotherapy-related toxicities were graded according to the Common Toxicity Criteria for Adverse Effect version 4.0.

Results

Eligible Patients

The median follow-up time was 23.2 months (range 4.5-114.6 months) for all patients. Stereotactic body radiotherapy was performed as scheduled and was feasible in all patients. At the last follow-up, 24 (56%) patients had survived and 19 (44%) patients died.

Treatment Outcomes

For the 43 patients, the 2-year OS, PFS, and DMFS rates were 72.3%, 44.6%, and 47.2%, respectively. The OS and PFS survival curves are shown in Figure 1. The 2-year local control (LC) rate was 80.2% (Figure 2). Regarding the patterns of failure, distant metastasis was most frequent; distant metastasis, lymph node metastasis, and local recurrence were observed in 22 (47%), 12 (28%), and 7 (16%) patients, respectively. The sites of distant metastases were liver in 7 patients, brain in 6 patients, lung in 6 patients, bone in 4 patients, and other organs (spleen, adrenal gland, skin, colon, abdominal lymph node, and pleura in 1 patient each), including duplications in some cases.

Of the 6 patients in who brain metastases occurred, 5 patients did not undergo PCI.

In the univariate analysis of the survival rates, the 11 female patients showed significantly better OS compared to the 32 males (2-year OS: 80.0% vs 63.9%, respectively; hazard ratio [HR] 0.51, 95% confidence interval [CI] 0.24-0.90, $P = .027$). The OS curves by gender are shown in Figure 3. As shown in Table 2, the T1 stage also tended to be correlated with favorable outcome for OS (2-year OS: 77.7% for the 31 stage IA patients vs 56.3% for the 12 stage IB patients, HR 0.65, 95%CI 0.41-1.08, $P = .072$). Gender (female vs male) was also marginally significant for PFS (2-year PFS: 60.0% vs 38.5%, respectively; HR 0.62, 95%CI 0.33-1.01, $P = .069$), but T-stage was not significant for PFS. The univariate analysis for local control revealed no significant factor predicting outcomes (Table 2).

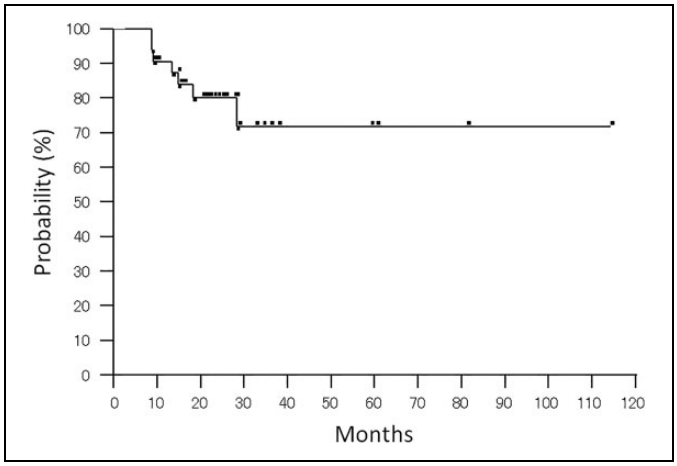

Figure 2. Kaplan-Meier curve for local control.

Treatment-Related Toxicities

All of the SBRT regimens for lung were completed without toxicity during the radiotherapy period. There was no grade 4 or 5 toxicity. After the SBRT period, 3 (6.9%) patients experienced grade 3 radiation pneumonitis. The incidence of ≥grade 2 radiation pneumonitis was 11.6% (5 patients). Other SBRT-related ≥grade 2 toxicities were not observed. No information was available with regard to hematological toxicity in the 8 patients who underwent chemotherapy.

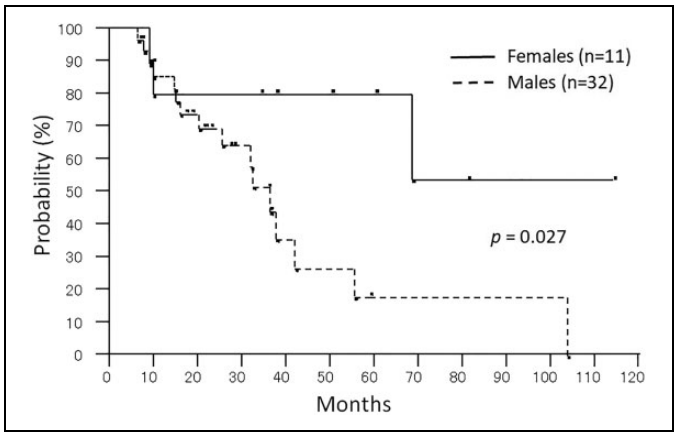

Figure 3. Overall survival curves by females versus males.

Discussion

This was a retrospective study of data extracted from the database of the JRS-SBRTSG for 43 patients with stage I SCLC treated with SBRT. Several reports have been published regarding the favorable outcomes of surgery with or without

Table 2. Univariate Analysis of Overall Survival, Progression-Free Survival, and Local Control.

Variables	n	2-Year OS	*P* Value	2-Year PFS	*P* Value	2-Year LC	*P* Value
Female	11	80.0%	.027	60.0%	.069	77.1%	.886
Male	32	69.3%		38.5%		81.0%	
Age (years)							
≥77	22	64.6%	.667	47.6%	.514	73.3%	.507
<77	21	74.7%		39.9%		86.6%	
Stage							
IA	31	77.7%	.072	47.2%	.287	79.5%	.506
IB	12	56.3%		38.2%		80.0%	
BED10							
≥100 Gy	33	71.6%	.435	37.4%	.492	76.1%	.234
<100 Gy	10	71.4%		65.6%		100%	
Chemotherapy							
Yes	8	100%	.615	70.0%	.341	100%	.704
No	35	66.8%		44.6%		75.1%	
PCI							
Yes	8	85.7%	.791	43.8%	.785	100%	.433
No	35	76.7%		45.1%		73.9%	

Abbreviations: BED10, biological effective dose based on the assumption of $\alpha/\beta = 10$; LC, local control; OS, overall survival; PCI, prophylactic cranial irradiation; PFS, progression-free survival.

chemotherapy for patients with stage I SCLC.[7-13] It is difficult to directly compare this SBRT result with the outcomes of surgery mainly because of the difference between pathological stage and clinical stage. However, the OS of 72.3% in the present study's patients at 2 years after SBRT might be considered satisfactory considering that 80% of the patients included in this series were medically inoperable and that a significant portion of the patients (64.6%) were ≥77 years old (Table 2).

Gender was suggested to be a prognostic factor for the OS ($P = .027$) and PFS ($P = .069$) of patients with stage I SCLC in this study; the prognoses of the female patients were significantly better than those of the males. The significance of the gender as a prognostic factor has been reported in resected NSCLC.[17-19] In a series of radiotherapy for NSCLC, female gender was shown to be a favorable prognostic factor.[20,21] Several studies have investigated prognostic factors in patients with SCLC. A retrospective analysis of 243 patients from the Japanese Lung Cancer Registry performed by The Japanese Joint Committee of Lung Cancer Registry suggested gender is one of the independent prognostic factors.[22] In a patient cohort with limited disease SCLC treated with definitive chemoradiotherapy, female gender was significantly associated with longer OS and brain metastasis-free survival.[23]

In the present series, the prescribed dose with 48 Gy in 4 fractions or 50 Gy in 5 fractions was generally used. These dose fractions have been commonly used for patients with stage I NSCLC.[24] This result suggests that many of the institutions in Japan have also been choosing the same SBRT protocol for their patients with SCLC because the optimal dose of SBRT for SCLC has not yet been determined. As SCLC is considered to be generally radiosensitive, its local control rate might be expected to be more favorable compared to that of NSCLC. In this study, however, the local control rate (80.2% at 2 years) is not considered better compared to the results of several NSCLC series.[25-27] Consequently, there is room to consider a dose escalation for SCLC as well as NSCLC.

There was no significant difference in local control between the present patients with T1 and T2 diseases. T-stage has been reported to be a prognostic factor for local control as well as OS and PFS in patients with stage I NSCLC.[20] Our result may suggest that the local control for T2 disease of SCLC would be easier than that of T2 disease of NSCLC.

Our findings that the PFS was 44.6% at 2 years and that significant populations of patients had distant metastases (47%) and lymph node metastases (28%) are not satisfactory. In the treatment of SCLC, chemotherapy has played an important role because of SCLCs' biological behavior characterized by rapid growth and early dissemination. Generally, concurrent chemoradiotherapy using cisplatin (CDDP) or carboplatin (CBDCA) plus etoposide (VP16) has been recommended for limited disease of SCLC (LD-SCLC). In the present study, only a small number of patients (7, 16%) received chemotherapy using standard regimens (CDDP or CBDCA + VP16), and the majority (35; 81%) of the patients were treated with SBRT alone. Although the difference is not significant, the PFS of the patients who received chemotherapy combined with SBRT tended to be better compared to that of patients treated with SBRT alone (70.0% vs 44.6%). This may be the main reason why the rates of distant metastases and lymph node metastases were relatively high in this study. As another reason, there would be staging migrations in some cases considering that the proportion of patients who underwent FDG-PET as a pretreatment evaluation was low (12 patients, 28%) in this series. However, further investigations of larger cohorts are needed to determine whether chemotherapy is essential for patients with stage I SCLC.

The role of PCI has been established for LD-SCLC patients in who a complete response is obtained by initial therapy.[28,29] A small retrospective study indicated that PCI was a significant predictor of survival in patients with stage I to II SCLC treated with chemoradiotherapy.[30] However, it has not been established whether PCI is essential, especially for stage I patients. In our series, distant metastases were a major pattern of recurrence, and the brain was one of the frequent sites of distant metastases (as was the liver). Therefore, PCI may also be effective for patients with stage I SCLC. Unfortunately, it is difficult to discuss the role of PCI because of the small number of patients who received PCI. Further investigations regarding the role of PCI in larger cohorts of stage I patients are needed.

Our study has several limitations. It was a retrospective and small cohort study as a part of a multi-institutional series with a relatively short follow-up period (median 23 months). The irradiation dose and follow-up methods were not uniform. The calculation algorithms and prescription methods differed among the 11 participating institutions. A national survey of SBRT for stage I SCLC has been performed by Japanese Radiation Oncology Study Group, and the results based on a larger cohort will be reported in the near future.

Conclusion

Our retrospective analysis of 43 patients with stage I SCLC indicates that SBRT is a safe and effective therapy for inoperable patients with stage I SCLC. However, in view of the high incidence of distant metastases and lymph node metastases, the combination of SBRT and chemotherapy may be essential. Regarding the role of PCI for stage I patients, further investigations are needed in larger cohorts.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by Japan Society for the Promotion of science (JSPS) KAKENHI, Grant Number JP16H05389.

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