Features of late local failure of early-stage non-small cell lung cancer treated with stereotactic body radiotherapy

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Abstract. Local failure of non-small cell lung cancer (NSCLC) treated with stereotactic body radiation therapy (SBRT) often occurs within 2 years and delayed local failure is uncommon. In the present study, features of late local failure (LLF; >2 years after SBRT) after SBRT were investigated and compared with those of early local failure (ELF; ≤2 years after SBRT) to explore whether these two local recurrence features have different prognostic implications. Patients who underwent SBRT for stage I-IIA NSCLC between July 2006 and March 2014 were retrospectively reviewed. Overall, 173 patients underwent SBRT for NSCLC. The median follow-up times after SBRT were 50 and 31 months for survival and computed tomography (CT) follow-up, respectively. LLF and ELF occurred in 7 and 13 patients, respectively. The median times to LLF and ELF were 42 months (range, 31-61 months) and 13 months (range, 4-16 months), respectively. Local-only failure occurred in 14% (1/7) of LLF cases and 77% (10/13) of ELF cases, which was significantly different (Fisher's exact test, P=0.02). Curative-intent salvage treatment was impossible in all of the LLF cases and 69% (9/13) of the ELF cases, which was significantly different (Fisher's exact test, P<0.01). The median survival times after local failure were 9 and 25 months for patients with LLF and ELF, respectively. Additionally, the 1-year overall survival rates after local failure were 29 and 83% in the LLF and ELF groups, respectively, which was significantly different (log-rank test, P<0.01 at 1-year). In summary, the prognosis after LLF was significantly unfavorable compared with after ELF. Curative-intent salvage treatment is often difficult for LLF due to metastases. Therefore, it seems reasonable to decrease the frequency of follow-up CT for detecting tumor recurrence after the first 2 years post-SBRT.

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Abbreviations: ASCO, American Society of Clinical Oncology; BED, biological effective dose; CT, computed tomography; CT-NAB, CT-guided needle aspiration biopsy; ELF, early local failure; ESMO, European Society for Medical Oncology; FDG-PET, ^{18}F-fluorodeoxyglucose-positron emission tomography; ITV, internal target volume; LLF, late local failure; NSCLC, non-small cell lung cancer; SBRT, stereotactic body radiation therapy

Key words: lung cancer, stereotactic body radiation therapy, local failure, prognosis

Introduction

In total, 10-20% of patients with early-stage non-small cell lung cancer (NSCLC) treated with stereotactic body radiation therapy (SBRT) experience local failure (1-3). Some locoregional failures, particularly local-only failures, can be salvaged with curative-intent treatment. Hence, the early detection and treatment of local failure may lead to improved clinical outcomes. The American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) guidelines for lung cancer recommend a 6-monthly computed tomography (CT) examination during the first 2 years after curative-intent treatment for detecting treatable tumor recurrence (4,5). Then, the main target of surveillance imaging shifts from detecting tumor recurrence to a new second lung cancer after the first 2 years. However, local failure in early-stage NSCLC treated with SBRT can occur even after 2 years (6). Previous studies of locally advanced NSCLC and NSCLC at various stages treated with chemoradiotherapy (7) and radiotherapy (8), respectively, have revealed that prognosis is poor for tumors that reoccur within a short period. In patients with NSCLC treated with complete resection, a short interval between initial resection and tumor recurrence remains a significant factor for poor prognosis (9,10). Therefore, curative-intent treatment for patients with NSCLC may improve prognosis. If this is also applicable to early-stage NSCLC treated with SBRT, detecting delayed local failure may be more beneficial for patient survival than detecting early recurrence after SBRT.

In the present study, features of late local failure (LLF; local failure >2 years after SBRT) for NSCLC treated with SBRT were investigated and compared with early local failure (ELF; local failure ≤2 years after SBRT).

Materials and methods

Patient selection. Medically inoperable patients with stage IA1-IIA (Union for International Cancer Control 8th Edition) (11) NSCLC treated with SBRT at the National Hospital Organization Shikoku Cancer Center (Matsuyama, Japan) between July 2006 and March 2014 were retrospectively evaluated by reviewing the medical records. Synchronous or metachronous multiple NSCLC cases in which it was difficult to identify the primary lesion that caused distant and/or regional failure were excluded from the present study. The present study was approved by the Ethics Committee of National Hospital Organization Shikoku Cancer Center (approval. no. 2021-67) and, owing to the retrospective nature of the present study, the opt-out method was applied regarding patient consent. SBRT was only performed in patients with an Eastern Cooperative Oncology Group (ECOG) performance status of ≥2 (12). Thoracic surgeons, thoracic oncologists and radiation oncologists discussed the indications for SBRT. Bronchoscopy and/or CT-guided needle aspiration biopsy (CT-NAB) were conducted for pathological diagnosis. For patients whose lung tumors were not pathologically proven, SBRT was performed only when a continuous increase in the overall tumor size, solid component size or density of ground glass were observed over time via serial CT. In all patients, the age, sex, clinical stage, pathology of tumors and SBRT dose were available from the records. However, certain basic data, including blood type, height, body weight, obesity, smoking, drinking or dietary habits, cancer-causing occupational exposure, concomitant diseases such as diabetes or hypertension and long-term medication, were unavailable.

Procedures for SBRT. For SBRT, the internal target volume (ITV) was defined as lesions that could be visualized on slow-scan CT images (4 sec, 2 mm thickness). For the planning target volume, a 5 mm margin was added to the ITV contours. For SBRT, 8-11 non-coplanar static 4 MV photon beams were used. Typical SBRT doses were 48 Gy in four fractions [biological effective dose $(BED)_{10}$=106.6] for T1 tumors and 60 Gy in five fractions (BED_{10}=132) for T2 tumors, with an isocenter prescription.

Follow-up studies. Local, regional and distant failures were diagnosed using serial follow-up CT images. Follow-up CT was conducted every 2-6 months after SBRT for the first 2-3 years. Thereafter, follow-up CT scans were performed once to thrice yearly. Follow-up CT was continued when patients were able or willing to visit the hospital. Whole-body ^{18}F-fluorodeoxyglucose-positron emission tomography/CT (FDG-PET/CT) was performed when tumor recurrence was suspected.

Table I. Characteristics of the included patients (n=173).

Characteristics	Value
Median age (range), years	79 (58-92)
Sex, n	
Male	113
Female	60
Stage, n	
Stage I	137
Stage IIA	36
Histology of tumors, n	
Adenocarcinoma	69
Squamous cell carcinoma	24
Other/unspecified non-small cell cancer	4
Unproven	76
SBRT dose (the isocenter dose), Gy	
Range	48.0-62.5
Median	48.0

SBRT, stereotactic body radiation therapy.

Salvage treatment for failure. Salvage treatment was administered whenever feasible. Typical curative-intent salvage treatments for local failure included salvage surgery or re-irradiation (SBRT or conventional three-dimensional conformal radiotherapy of ≥60 Gy for the entire lesion). Patients with distant and/or widespread regional failure were treated with supportive care to alleviate distressing symptoms.

Statistical analysis. Overall survival after local failure was calculated from the diagnosis of local failure. The Kaplan-Meier method was used to estimate the overall survival rates and local failure-free rates, and the statistical differences were evaluated using the log-rank test. Differences in the incidence of local-only, regional and distant failures were assessed using Fisher's exact test. All statistical analyses were performed using the StatView software (version 5.0; SAS Institute, Inc.).

Results

Study Population. Between July, 2006 and March, 2014, 244 NSCLC tumors from 206 patients were treated with SBRT at the National Hospital Organization Shikoku Cancer Center. Of these patients, 33 received SBRT for synchronous or metachronous multiple NSCLC and were subsequently excluded from the present study since it was difficult to identify the primary lesion that caused distant and/or regional failure. In the present study, multiple NSCLC tumors were defined as independent lung tumors that were identified metachronously or simultaneously regardless of the location and were

Table II. Characteristics of the 20 patients with local failure.

Characteristics	Early local failure, n=13	Late local failure, n=7	P-value[a]
Median age (range), years	78 (68-85)	77 (61-88)	
Age, n (%)			
≤80 years	8 (61.5)	6 (85.7)	0.35
>80 years	5 (38.5)	1 (14.3)	
Sex, n (%)			
Male	10 (76.9)	3 (42.9)	0.17
Female	3 (23.1)	4 (57.1)	
TNM[b], n (%)			
I	9 (69.2)	6 (85.7)	0.61
IIA	4 (30.8)	1 (14.3)	
Appearance, n (%)			
Solid	13 (100.0)	6 (85.7)	0.35
GGN	0 (0.0)	1 (14.3)	
History of multiple primary cancer, n (%)			
Yes	7 (53.8)	2 (28.6)	0.64
No	6 (46.2)	5 (71.4)	
Mean SBRT dose (range), Gy	52.6 (48.0-60.0)	50.1 (48.0-62.5)	
SBRT, n (%)			
48 Gy	9 (69.2)	4 (57.1)	0.65
>48 Gy	4 (30.8)	3 (42.9)	
Sq/Ad/other/UP pathology, n	6/2/1/4	1/0/0/6	
Median time to local failure (range), months	13 (4-16)	43 (31-61)	
Median interval between CT-detected local failure and the previous CT[c] (range), months	3 (1-6)	6 (4-12)	
Curative intent salvage treatment, n (%)			
Yes	9 (69.2)	0 (0.0)	<0.01
No	4 (30.8)	7 (100.0)	

[a]Differences in the incidence of local failures were assessed using Fisher's exact test. [b]Union for International Cancer Control 8th Edition. [c]There was 1 case each of early and late local failure without information on the CT acquisition interval. SBRT, stereotactic body radiotherapy; GGN, Ground-Glass Opacity Nodule; Sq, squamous cell carcinoma; Ad, adenocarcinoma; UP, unproven; CT, computed tomography.

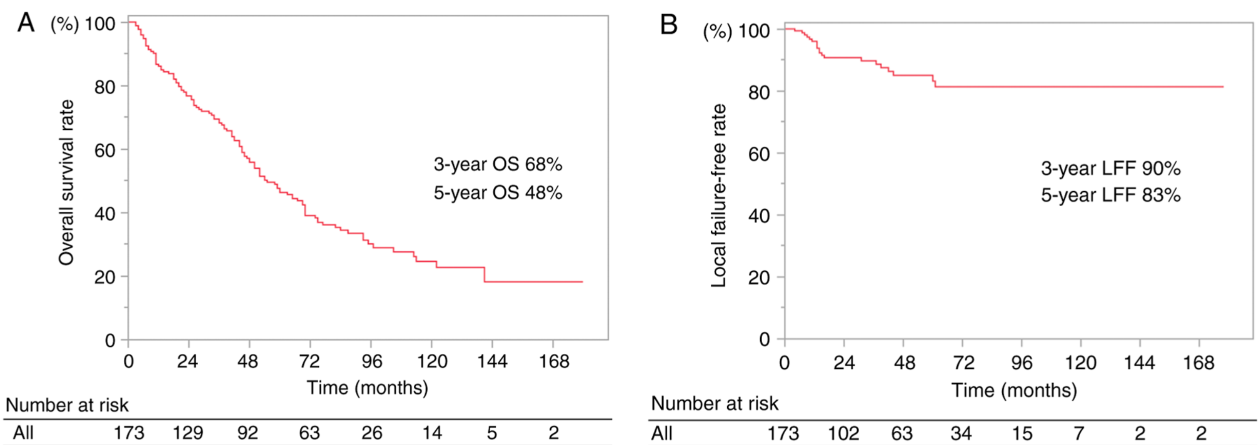

Figure 1. OS and LFF rates. (A) OS and (B) LFF rates. OS, overall survival; LFF, local failure-free.

diagnosed as primary NSCLC by two radiologists based on the imaging findings, disease course and medical history. The remaining 173 patients (173 tumors) were included in the present study (Table I).

Table III. Patterns of failure in patients who experienced local failure.

Failure patterns	ELF, n=13	LLF, n=7	P-value[a]
Local only, n (%)	10 (77)	1 (14)	0.02
Local + regional, n (%)	1 (8)	2 (29)	0.27
Local + distant, n (%)	2 (15)	1 (14)	>0.99
Local + regional + distant, n (%)	0 (0)	3 (43)	0.03
Distant, n (%)	2 (15)	4 (57)	0.12
Regional, n (%)	1 (8)	5 (71)	0.01

[a]Differences in the incidence of local failures were assessed using Fisher's exact test. ELF, early local failure (local failure ≤2 years from SBRT); LLF, late local failure (local failure >2 years after SBRT; SBRT, stereotactic body radiotherapy.

The median follow-up time from SBRT was 50 months (range, 3-180 months) for survival and 31 months (1-178 months) for CT follow-up. The median and mean doses of SBRT were 48.0 and 50.1 Gy, respectively (range, 48.0-62.5 Gy). The 3- and 5-year overall survival rates were 68 and 48%, respectively and the 3- and 5-year local failure-free rates were 90 and 83%, respectively (Fig. 1).

Features of local failure according to the failure time. Of the 173 included patients, 20 experienced local failure. LLF and ELF occurred in 7 and 13 patients, respectively (Table II). The differences in baseline factors between the ELF and LLF groups were not statistically significant (Table II). The proportions of squamous cell carcinoma and adenocarcinoma were 38 and 23%, respectively, in the ELF cases and 14 and 29%, respectively, in the LLF cases (Table SI). In addition, pathologically unproven tumors were 31% in the ELF and 57% in the LLF (Table SI). The median time to local failure was 14 months (range, 4-61 months), 42 months (range, 31-61 months) and 13 months (range, 4-16 months) for all local failure, LLF and ELF cases, respectively.

The incidence of local-only failure was lower in the LLF than in the ELF cases (Table III). Among the 20 local failures, local-only failure was observed in 14% (1/7) of LLF cases and 77% (10/13) of ELF cases, which was statistically significant (Fisher's exact test, P=0.02). When local failure was detected by CT, regional failure was observed in 71% (5/7) of LLF cases and 8% (1/13) of ELF cases (Fisher's exact test, P=0.01), whereas distant failure was observed in 57% (4/7) and 15% (2/13) of LLF and ELF cases respectively (Fisher's exact test, P=0.12).

The median survival times after local failure were 9 months (range, 1-16 months) and 25 months (range, 2-87 months) for patients with LLF and ELF, respectively (Fig. 2). The 1- and 2-year overall survival rates after local failure were 29 and 0%, respectively, in LLF cases, and 83 and 56%, respectively, in ELF cases (log-rank test, P<0.01 at 1-year; Fig. 2).

Curative-intent salvage treatment, including salvage surgery and salvage radiotherapy with ≥60 Gy for the entire lesion, was not performed for any patients with LLF (0/7), but was performed in 69% (9/13) of patients with ELF (Fisher's exact test, P<0.01; Table II). Of the 9 patients with ELF in which curative-intent salvage therapy was performed, surgery was performed for 3 patients and ≥60 Gy radiotherapy of the entire lesion was administered for 6 patients.

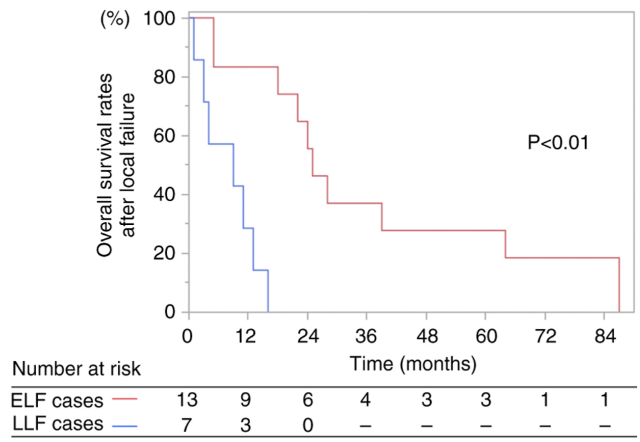

Figure 2. Overall survival rates after local failure according to time to local failure in patients who experienced local failure after stereotactic body radiotherapy for non-small cell lung cancer. ELF, early local failure; LLF, late local failure.

Discussion

To the best of our knowledge, the present study is the first to show the poor prognosis of patients after LLF following the treatment of NSCLC with SBRT. The median survival time after local failure was significantly shorter in the LLF compared with the ELF cases (6.5 vs. 25 months). The incidence of local-only failure was also significantly lower in the LLF compared with the ELF cases (14 vs. 77%). Reportedly, in outcomes of NSCLC treated with conventionally fractionated radiotherapy or surgery, delayed failure (>6-12 months from treatment) may be associated with an improved prognosis compared with early failure (5-8). However, LLF after SBRT was shown to be associated with poor prognosis in the present study.

In the present study, most LLF cases had distant and/or regional metastases when local failure was detected. Curative-intent salvage treatment is often difficult among LLF cases due to these metastases. After SBRT, radiation fibrosis of the lungs often masks signs of local failure (13). We hypothesize that LLF tumors grow latently in the radiation fibrosis of the lung and continue to be a seed for metastasis for a relatively long period before local recurrence becomes apparent. The benefit of surveillance imaging for detection compared with ELF may be relatively small since the potential for curative-intent salvage treatment remains relatively small for LLF. The frequency of follow-up CT scans after the first 2 years may also be decreased for patients with NSCLC treated with SBRT, as recommended by the ASCO and ESMO guidelines (4,5).

Previous reports have shown an association between the pathological subtypes of NSCLC and the incidence of LLF after SBRT, in which there is a trend towards a higher incidence of LLF in adenocarcinoma than in squamous cell carcinoma. Specifically, Shintani *et al* (6) reported that the median time to local failure was 1.3 and 2.1 years for squamous cell carcinoma and adenocarcinoma, respectively. The study mentioned that frequent follow-up in the first 2 years is necessitated for squamous cell carcinoma, whereas careful follow-up beyond the first 2 years is warranted for adenocarcinoma. Woody *et al* (14) reported that the time to local failure was 14.9 and 18.9 months for squamous cell carcinoma and adenocarcinoma, respectively. In the present study, the proportions of squamous cell carcinoma and adenocarcinoma were 38 and 23%, respectively, in the ELF cases and 14 and 29%, respectively, in the LLF cases. Despite the relatively high and low proportion of adenocarcinomas in the LLF and ELF cases, respectively, 57% of LLF and 31% of ELF cases had pathologically unproven tumors. Hence, the pathological features of LLF and ELF could not be adequately analyzed in the present study due to the low number of available cases.

The present study had certain limitations. First, this was a retrospective study using obsolete medical records from a single institution with a limited sample size; the available data, including blood type, height, body weight, obesity, smoking, drinking or dietary habits, cancer-causing occupational exposure, concomitant diseases such as diabetes or hypertension and long-term medication, were also limited; hence, further studies are warranted to confirm the differences in the features of LLF and ELF. Second, it is often difficult to assess local recurrence after SBRT. To address this issue, in the present study, an initial diagnosis was based on a single CT image. However, CT imaging findings, such as increased consolidation or the loss of an air-bronchogram in the treated area over time, were also considered. Additionally, these findings were combined with clinical symptoms, elevated tumor markers and increased FDG accumulation via FDG/PET-CT to make a more comprehensive decision. Although local recurrence was diagnosed with as much care as possible, careful interpretation is still required. However, in the present study, local recurrence was not proven in the majority of cases as tumors with inflammation also showed increased FDG uptake even in the absence of local recurrence (15,16). Therefore, careful interpretation will be required regarding the results of FDG uptake as an indicator of local recurrence after SBRT. Third, pathological confirmation could not be obtained for most tumors reviewed in the present study as some patients did not undergo CT-NAB for pathological confirmation. For these patients, the diagnosis of lung cancer was based on careful CT observations over time (FDG-PET/CT was performed when necessary). The treatment outcomes of clinically diagnosed lung cancer are comparable to those of pathologically proven NSCLC when various clinical findings are integrated and carefully diagnosed (17). Since careful CT follow-up was performed before SBRT, we consider that the diagnosis of lung cancer was reliable. Furthermore, since follow-up CT was performed more frequently in the first 2 years after SBRT compared with later years, an effect similar to 'lead-time bias' may potentially contribute to generating differences in survival time after local failure between the LLF and ELF cases. However, the median interval between CT-detected local failure and previous CT was 6 and 3 months for the LLF and ELF cases, respectively, which was not a significant difference. Finally, information regarding the cause of death was unavailable since information on the date of death was obtained from the cancer registry database for a number of patients.

In conclusion, for patients with stage I-IIA NSCLC treated with SBRT, the prognosis after local failure was significantly improved in the ELF cases compared with the LLF cases. Curative-intent treatment is often not performed in patients with LLF due to the frequent distant and/or regional failure. Considering the features of LLF cases, it seems reasonable to decrease the frequency of follow-up CT for detecting tumor recurrence after the first 2 years post-SBRT, as recommended by the ASCO and ESMO guidelines.

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Availability of data and materials

The data generated in the present study are not publicly available to preserve individuals' privacy under 'the Personal Information Protection Law' but may be requested from the corresponding author.

Authors' contributions

KM and YH designed the study. KM and YH confirm the authenticity of all the raw data. YH analyzed the data. KM, YH, HK, KN, TU, HS, DH, TN, YK, YS, TK and MY collected the patient data and drafted the article. All authors collaborated in writing the discussion section and in discussing the interpretation of the results. KM prepared the manuscript and YH edited the manuscript. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

All procedures involving human participants were performed in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This retrospective study was approved by the Ethics Committee of National Hospital Organization Shikoku Cancer Center (Matsuyama, Japan; approval. no. 2021-67). The opt-out method was applied regarding patient consent due to the retrospective nature of the present study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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