Preliminary Report of Late Recurrences, at 5 Years or More, after Stereotactic Body Radiation Therapy for Non-small Cell Lung Cancer

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Introduction: Long-term outcomes remain unknown after stereotactic body radiation therapy (SBRT). We observed a few patients who developed disease progression late, at 5 years or more, after SBRT. In this report, we describe the characteristics of those patients with late recurrence after SBRT.

Methods: We retrospectively reviewed patients who underwent SBRT for non-small cell lung cancer with histological confirmation between January 1999 and December 2005 at our institution. During this period, 48 Gy of SBRT in four fractions at the isocenter was prescribed for all patients.

Results: In total, 66 patients were eligible. With a median follow-up period of 35.9 months, the 5-year overall survival and disease-free survival rates were 44.6% (95% confidence interval, 33.5–59.5%) and 33.8% (95% confidence interval, 23.6–48.4%), respectively. Of the patients, 16 survived without disease progression for 5 years or more after SBRT. Of these, four patients developed late recurrence at 76, 101, 108, and 109 months after SBRT. Three of the patients were females with adenocarcinomas; the other was a male with squamous cell carcinoma. The initial sites of recurrence were local in two patients, distant in one, and simultaneously local and distant in one. A total of two patients with local recurrence alone were still alive at 138 months after SBRT.

Conclusions: The rate of late recurrence was not negligible in long-term survivors after SBRT. Our experiences indicate that long-term follow-up is needed after SBRT for non-small cell lung cancer.

Key Words: Stereotactic body radiation therapy, Non-small cell lung cancer, Late recurrence.

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Stereotactic body radiation therapy (SBRT) is a recently developed and innovative radiotherapeutic technique that has been applied primarily to the lungs. SBRT is one of the more important treatment options for early non-small cell lung cancer (NSCLC), especially in inoperable or elderly patients.

Recently, initial outcomes have been reported from prospective multi-institutional trials of SBRT for early-stage NSCLC. The outcomes were satisfying and promising. In the Radiation Therapy Oncology Group (RTOG) 0236 trial, a phase II trial of SBRT for medically inoperable stage I/II NSCLC, the 3-year local control and overall survival rates were 98 and 56%, respectively.[1] In operable patients with stage IA NSCLC in the Japan Clinical Oncology Group (JCOG) 0403 trial, those rates were 86 and 76%, respectively.[2]

Long-term outcomes are still unknown for NSCLC after SBRT. We observed a few patients who developed disease progression late, at 5 years or more, after SBRT. In this report, we describe our experience with and review the characteristics of patients with late recurrence.

PATIENTS AND METHODS

We retrospectively reviewed patients who underwent SBRT for NSCLC with histological confirmation between January 1999 and December 2005 at our institution. In this period, 48 Gy of SBRT in four fractions at the isocenter was prescribed for all patients.

SBRT was performed as described previously.[3,4] The planning target volume was defined as the internal target volume, which was delineated on slow-scan computer tomography (CT), with a 5-mm margin for setup uncertainty.

Follow-up visits were every 2 to 3 months for 5 years after SBRT and every 6 months thereafter. CT was performed every 2 to 4 months during the first year, every 6 months between 1 and 5 years after treatment, and annually thereafter. 18F-fluorodeoxyglucose-positron emission tomography (FDG-PET) was not mandatory but indicated for patients suspected of recurrence.

RESULTS

In total, 66 patients were eligible. The median age was 76.5 (range, 67–86) years at the time of treatment. Of the 66 patients, 47 were males and 19 were females. According to the classification with recursive partitioning analysis pro-

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posed in our previous report,[5] 34 patients were classified in recursive partitioning analysis class I with a better prognosis; the remaining 32 patients were in class II (Table 1).

At the time of analysis, the median follow-up period was 35.9 (range, 4.2–138.2) months in the whole group and 60.0 (range, 6.9–138.2) months in the surviving patients. The median survival time was estimated to be 47.5 months (95% confidence interval [CI], 34.1–87.3 months). The 5-year overall survival and disease-free survival rates were 44.6% (95% CI, 33.5–59.5%) and 33.8% (95% CI, 23.6–48.4%), respectively.

A total of 16 patients survived without disease progression for 5 years or more after SBRT. The characteristics of these patients are shown in Table 1.

Among these 16 patients, four developed late recurrence at 76, 101, 108, and 109 months after SBRT. Table 2 summarizes the characteristics of this patient group, which included three females with adenocarcinomas and one male with squamous cell carcinoma. Surgery was contraindicated because of intercurrent diseases in all four patients. The initial site of recurrence was local in two patients, distant in one, and simultaneously local and distant in one patient. Local progression was diagnosed based on CT combined with FDG-PET in three patients. After the recurrence, best supportive care was chosen except for patient 3. Gefitinib had been temporarily administered to patient 3; however, it was stopped due to liver dysfunction. After the recurrence, two patients (patients 1 and 2) died of lung cancer. To date, at 138 months after SBRT, the other two female patients are alive with local disease (i.e., no evidence of metastasis) (Figure 1).

TABLE 1. Characteristics of All Patients Reviewed in this Study and of Patients Free from Recurrence at 5 yr After SBRT

	All Patients (n = 66)	Patients Free from Recurrence at 5 yr (n = 16)
Age at SBRT (yr)		
Median (range)	76.5 (67–86)	77 (68–86)
Sex		
Male	47	11
Female	19	5
PS		
0	39	10
1	23	6
2	4	0
Histology		
Adenocarcinoma	32	10
Squamous cell carcinoma	29	6
Others	5	0
T-stage[a]		
T1a	22	8
T1b	25	5
T2a	19	3
RPA class[b]		
Class I	34	11
Class II	32	5

SBRT, stereotactic body radiation therapy; PS, performance status; RPA, recursive partitioning analysis.

[a] T-stage was retrospectively evaluated according to the 7th edition of TNM classification of Malignant Tumors.

[b] RPA class I was defined as female or T1a patients and class II as male patients with T1b-2a tumors.[5]

DISCUSSION

We previously investigated prognostic factors after SBRT for stage I NSCLC and concluded that sex and tumor diameter were the most significant factors.[5] Based on these results, we defined two prognostic classes: class I, consisting of T1a patients and female patients, and class II, consisting of male patients with T1b-2a tumors. Between the classes, significant differences were observed in local recurrence, disease progression, and overall survival after SBRT. The class II patients tended to develop early recurrence compared with the class I. In this study, 11 of 34 class I patients (32.4%) survived without disease progression for 5 years, whereas only five of 32 patients (15.6%) in the class II did. However, these prognostic factors were validated only for recurrence or death in the early period after treatment. To our best knowledge, there was no article available on late recurrence after SBRT for NSCLC. This study focused on late recurrence.

Recurrence at 5 years or later after surgery for stage I NSCLC has been reported by several authors. Thomas and Rubinstein[6] of the Lung Cancer Study Group reported late lung cancer recurrence in 22 of 308 patients (7.1%) who were clinically free of cancer 5 years or more after surgery for T1N0M0 NSCLC. Pasini et al.[7] reported that late relapse, including metachronous lung cancer, developed in 15% of patients who were disease-free at 5 years after surgery for T1–2N0M0 NSCLC. Maeda et al.[8] recently reported that late recurrence was observed in 4.8% of patients who were free from recurrence for 5 years after complete resection of stage IA NSCLC (locoregional recurrence in 2.1% and distant metastasis in 2.8%). From these reports, the rate of late recurrence after surgery is less than 10%, except for metachronous lung cancer. In our study, late recurrence was observed in four of 16 long-term survivors (25%) without disease progression for 5 years after SBRT. This seemed to be more frequent than the surgical series. When SBRT is applied to younger and operable patients, late recurrence would be expected to become an issue, similar to the patients presented here.

This study has some limitations. First, the number of long-term survivors was small. SBRT is often performed in frail patients who cannot tolerate surgery, and some of these patients die of intercurrent diseases rather than lung cancer. Indeed, 14 of the 39 patients who died in our cohort had no evidence of lung cancer recurrence. Long-term follow-up for lung cancer control would be limited in these patients. Second, this study was based on a retrospective review; thus, it was prone to selection bias. Long-term outcomes are awaited after prospective SBRT trials, such as RTOG 0236 and JCOG 0403. Third, our SBRT regimen of 48 Gy in four fractions at the isocenter, which is the same as the JCOG 0403, was lower than the doses in the United States (60 Gy in three fractions at the planning target volume periphery) as the RTOG 0236 used. A difference was observed in 3-year local control rate

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TABLE 2. Characteristics of the Four Patients Who Developed Recurrence at 5 yr or Later After SBRT

Patient	Age at SBRT (yr)	Sex	PS	Histology	T-Stage	Time of Recurrence (mo)	Site of Recurrence	Last Follow-Up (mo)	Status
1	78	F	0	Ad	T1a	76	Distant (brain)	79	Dead
2	76	M	1	Sq	T1b	101	Local and distant (lung and liver)	112	Dead
3	80	F	0	Ad	T1b	108	Local	138	Alive
4	81	F	0	Ad	T1b	109	Local	138	Alive

SBRT, stereotactic body radiation therapy; PS, performance status; Ad, adenocarcinoma; Sq, squamous cell carcinoma.

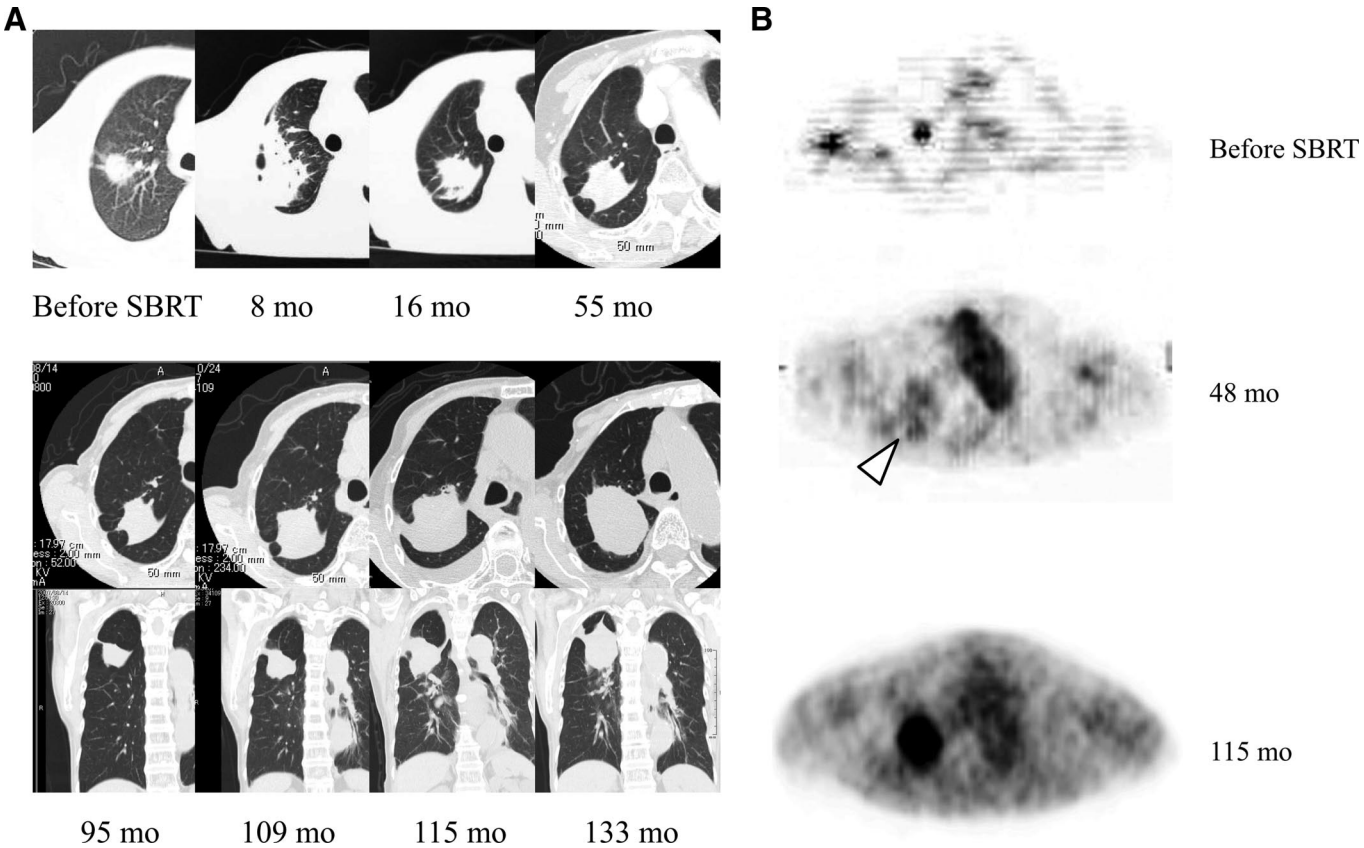

FIGURE 1. Computer tomography (CT) (*A*) and fluorodeoxyglucose-positron emission tomography (FDG-PET) (*B*) images for patient 4. *A*, CT images: A 21-mm tumor was located in the right upper lobe in an 81-year-old woman. Stereotactic body radiation therapy (SBRT) was performed for the tumor, with 48 Gy in four fractions. Radiation pneumonitis was observed at 8 months after SBRT. It shrank into a mass-like consolidation by 16 months after SBRT and persisted at a stable size for 95 months. The consolidation showed regrowth at 109 months. After that, the tumor gradually enlarged. *B*, FDG-PET images: Before SBRT, the tumor had a localized uptake with a maximum standardized uptake value (SUVmax) of 3.6. At 48 months after SBRT, uptake by the tumor was ill defined, with an SUVmax of 2.1 (arrowhead). At 115 months, the FDG uptake of the tumor became intense and well defined, with an SUVmax of 6.6.

between the JCOG 0403 and the RTOG 0236 (86 versus 98%). The possibility might exist that such a lower prescription dose causes late recurrence of local tumor. Another limitation was that local progression was not histologically confirmed but was diagnosed based on imaging. There are some difficulties in the radiological diagnosis of local recurrence after SBRT. A mass-like consolidation prevents us from evaluating local tumors on CT after SBRT. In our previous report, enlargement of the consolidation at 12 months or more after SBRT indicated local recurrence.[9] Our study of FDG-PET revealed that moderate to intense FDG uptake observed soon after SBRT did not always indicate a residual tumor.[10] From these experiences, we suspect local progression when a local consolidation enlarges continuously on CT, especially at 1 year or more after treatment. A well-defined and intense FDG uptake will support the CT findings in the late period after SBRT. Although the local tumor was properly diagnosed as a malignancy based on imaging, we could not determine whether the local tumor was due to regrowth of the residual cancer or a secondary cancer.

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These issues will be addressed in prospective trials of SBRT for operable patients with NSCLC (e.g., RTOG 0618).

In conclusion, the rate of late recurrence was not negligible in long-term survivors after SBRT. Our experiences indicate that long-term follow-up after SBRT for NSCLC is needed.

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