Original Article

Salvage surgery to treat tumor regrowth after stereotactic body radiotherapy in primary non-small cell lung cancer

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Background: Stereotactic body radiotherapy (SBRT) is considered to be an effective and safe treatment in patients with primary lung cancer. If local recurrence is confirmed following SBRT, surgical treatment is a possibility. The present study aimed to clarify the safety and survival outcomes of salvage surgery in primary lung cancer patients with local recurrence following SBRT.

Methods: All subjects were patients with primary lung cancer who underwent surgical treatment for local recurrence following SBRT during the period from July 2005 to July 2015. We evaluated the reason for SBRT selection, the surgical procedure, postoperative complications, and prognosis.

Results: Of 932 patients underwent SBRT as treatment for primary lung cancer, 48 patients (5.2%) had local recurrence alone and 19 patients (2.0%) underwent salvage surgery. SBRT was selected in eight medically operable patients who refused surgery, and in 11 patients considered medically inoperable by their pulmonologist. Lobectomy was performed in 15 patients. Postoperative complications were documented in 4 patients (21.1%). Incomplete resection was performed in 2 patients. Stage progression was confirmed in 7 patients (36.8%). The 5-year overall survival (OS) was 72.5% and the 5-year disease-free survival (DFS) was 65.2%.

Conclusions: We evaluated patients who underwent salvage surgery due to local recurrence of lung cancer following SBRT. We found that salvage surgery could be performed safely without affecting SBRT outcomes. We further infer that cases of complete resection are likely to be associated with good prognosis, and that SBRT should be selected only after careful consideration because complete resection is not possible in all cases.

Keywords: Lung cancer; stereotactic body radiotherapy (SBRT); salvage surgery

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Introduction

Stereotactic radiotherapy was developed as a high-precision radiation technique for the treatment of intracranial tumors. In the late 1990s, stereotactic body radiotherapy (SBRT) was made possible because of image-guided radiation delivery techniques and the development of tumor motion management. Accordingly, this therapy has been applied to lung tumors. Currently, SBRT is considered to be an effective and safe treatment in patients with medically inoperable primary lung cancer (1-5), and the number of such treatments is increasing with increase in the number of SBRT-capable facilities. Recent reports have shown that the local control rate was 90% or more over three years in patients with early-stage primary lung cancer undergoing SBRT (1,2). However, the number of cases with cancer recurrence following SBRT resulting in surgical treatment (in cases with no metastasis and medically operable patients) have increased in recent years (6-9).

The present study aimed to retrospectively analyze the safety of salvage surgery in patients with local recurrence following SBRT, evaluating survival outcomes and discussing the current problems associated with this treatment. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/jtd-20-2253).

Methods

Study design

This study protocol complied with the Declaration of Helsinki (as revised in 2013). The institutional review board approved this study (approval No. 1909) and waived the requirement for informed consent because the study was a retrospective review.

All subjects were patients with primary lung cancer who underwent surgical treatment for local recurrence following SBRT at eight institutions for the Niigata Chest Surgery Research Group during the period from July 2005 to July 2015. The patients were followed-up by a radiation oncologist and a pulmonologist after SBRT, and if recurrence was suspected, the patients were referred for assessment of the possibility of salvage surgery. Local recurrence was defined as tumor regrowth seen on computed tomography (CT) scans. In addition, positron emission tomography-CT was used for supplementary diagnosis if local recurrence was suspected on CT scans. During recurrence, if the patients had no lymph node or distant metastasis, and were examined to be medically operable, surgical treatment was performed with their written consent.

Patients who were surgically treated for local recurrence following SBRT were evaluated. The data collected included the reason for SBRT selection, the time period from SBRT to salvage surgery, tumor diameter, surgical procedure, postoperative complications, and prognosis. All complications were classified into four grades of postoperative complications as per Clavien-Dindo classification criteria (10).

Each patient underwent blood tests including serum tumor marker tests and radiological examinations. A chest X-ray was performed every 2–3 months, and chest CT scans were performed every six months. Similar to usual lung cancer follow-up, the diagnosis of recurrence was confirmed based on clinical symptoms, radiologic findings, and pathological findings. An observation was censored at the last follow-up visit when the patient had either died without recurrence or was lost to follow-up.

Statistical analysis

Overall survival (OS) was defined as the time from the day of salvage surgery to the day of death or the end of follow-up, with disease-free survival (DFS) defined as the time from the day of salvage surgery to the day of recurrence or the end of follow-up. Cumulative survival rates were calculated by the Kaplan-Meier method. Survival differences were compared using the log-rank test. Differences showing a value of $P<0.05$ were considered significant. SPSS for Windows version 24 (SPSS Japan, an IBM company, Tokyo, Japan) was used for the statistical analyses.

Results

A total of 932 patients underwent SBRT as treatment for primary lung cancer during the period from July 2005 to July 2015 (*Figure 1*). Before SBRT, 511 (54.8%) patients had histological 87 confirmation, and the remaining 421 patients 88 were clinically diagnosed with primary lung cancer on 89 radiographic imaging. Of these, 81 patients (8.7%) were found to have lung cancer recurrence and 48 patients (5.2%) had local recurrence alone. Nineteen patients (2.0%) underwent salvage surgery, and none of them were evaluated by a thoracic surgeon before SBRT. The characteristics of the patients are shown in *Table 1*. The reasons for SBRT selection were surgery refusal by eight

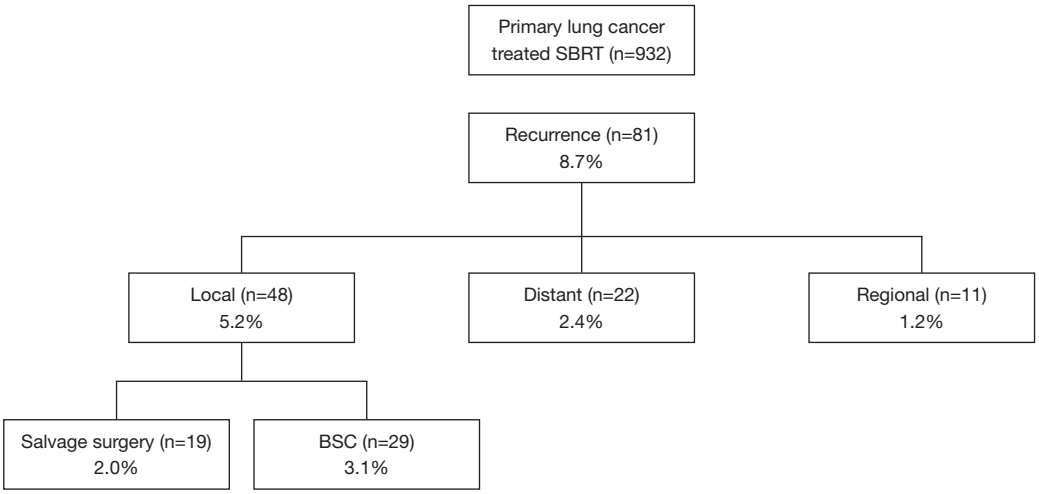

Figure 1 Patterns of disease recurrence after stereotactic body radiotherapy for non-small-cell lung cancer. SBRT, stereotactic body radiotherapy; BSC, best supportive care.

Table 1 Patient characteristics at SBRT

Variable	Value
Age (years)	77 [59–83]
Gender (M/F)	18/1
Performance status (ECOG)	
0	10
1	9
Reason for SBRT	
Patient's choice	8
Inoperable	11
Old age	5
COPD	3
Comorbidities	3
Histology	
Squamous cell	15
Adenocarcinoma	4
yc-Stage	
T1aN0M0	7
T1bN0M0	9
T2aN0M0	3
Tumor size (mm)	23 [12–48]

SBRT, stereotactic body radiotherapy.

medically operable patients during initial evaluation, and medically inoperable status of eleven patients as judged by their pulmonologist because they were elderly (n=5), had low pulmonary function (n=3), or had other comorbidities (n=3). Histologically, 15 patients were diagnosed with squamous cell carcinoma and four patients were diagnosed with adenocarcinoma. The patient characteristics at time of surgery are shown in *Table 2*. The median (range) time period from SBRT to salvage surgery was 17.3 (7.6–58.3) months, the tumor size increased from a median of 23 [12–48] mm at SBRT to 38 [15–55] mm at the time of recurrence.

None of the patients showed intrapleural adhesion due to SBRT during salvage surgery. Complete resection was performed in 17 patients and incomplete resection was performed in two patients. In those with incomplete resection, one patient was found to have malignant pleural effusion and the other patient was found to have descending aorta invasion during surgery. Lobectomy was performed in 15 patients (pneumonectomy with aortic resection in one patient), segmentectomy in three patients, and wedge resection in one patient. Lymph node dissection was performed in all patients, except for the one who underwent wedge resection, and pathology examinations showed lymph node metastasis in two patients (*Tables 3*,*4*).

Postoperative complications were documented in 4 patients (21.1%), including prolonged air leak (more than

Table 2 Patient characteristics at time of surgery

Variable	Value
Interval from SBRT to surgery (months)	17.3 (7.6–58.3)
Diagnostic imaging	
CT	9
PET-CT	10
Tumor size at recurrence (mm)	38 [15–55]
yc-Stage	
T1aN0M0	3
T1bN0M0	4
T2aN0M0	8
T2bN0M0	3
T3N0M0	1
Surgical procedure	
Lobectomy [pneumonectomy with aortic resection]	15 [1]; aortic invasion: 1
Segmentectomy	3; aortic invasion: 1
Wedge resection	1
Operative findings	
Aortic invasion	2
Malignant pleural effusion	1
Postoperative complication	
Pulmonary fistula	2
Heart failure	1
Pleuritis	1
Tumor size at surgery (mm)	28 [15–47]
p-Stage	
T1aN0M0	1
T1bN0M0	8
T2aN0M0	6
T2aN2M0	1
T4N0M0	1
T4N1M0	1
T2aN2M1a	1
Observation period (months)	30.2 (9.4–120.1)
Outcome	
Alive	8
Alive with recurrence	4
cancer death	3
Death due to other disease	4 (other cancer: 2; pneumonia: 2)

SBRT, stereotactic body radiotherapy.

5 days) in two patients, pleuritis in one, and heart failure in the other. The Clavien-Dindo scores were I or II in all 4 patients.

Over a median follow-up period of 34.8 months in patients who underwent salvage surgery, The 5-year OS and DFS was 72.5% and 65.2%, respectively (*Figure 2A,B*). The 3-year OS in patients with lobectomy and limited resection after SBRT were 84.6% and 0%, respectively (P=0.039), and the 3-year DFS were 65.6% and 0%, respectively (P=0.853) (*Figure 2C,D*). In addition, eight patients survived without recurrence, four patients survived with recurrence, three patients died from recurrence, and 4 patients died from other diseases (2 from other cancers and 2 from pneumonia).

Of the four patients who survived with recurrence, two underwent a second SBRT. One of these patients had isolated pleural nodule recurrence, and the other had bronchial stump recurrence. The third patient had isolated contralateral lung metastasis recurrence, resulting in lung resection. The fourth patient who survived with recurrence experienced brain metastasis, had an epidermal growth factor receptor (EGFR) mutation, and received EGFR-tyrosine kinase inhibitor therapy. Three patients died from lung cancer recurrence; one patient underwent wedge resection, one had lymph node metastasis, and the other one underwent incomplete resection because of a descending aortic invasion.

Discussion

As previously demonstrated, SBRT therapy results in high local cancer control rates and low toxicity in medically inoperable patients with early stage, non-small cell lung cancer (1-5). However, the definition of "medically inoperable" differs based on facilities and research, and no clear criteria have been outlined. In the present study, 19 patients underwent salvage surgery to treat local recurrence following SBRT. Of these, 11 were diagnosed to be medically inoperable by a pulmonologist (no thoracic surgeon made diagnoses in this regard). To objectively determine the status of medical operability, careful consideration by a multidisciplinary tumor board is required (6).

Although SBRT results in a high local control rate, lung cancer recurrence can occur. In the present study, 932 patients underwent SBRT; of these, 81 patients (8.7%) were found to have lung cancer recurrence and 48 patients (5.2%) had local recurrence alone. Senthi *et al.* (11) reported a local

Table 3 Patient demographics

Case	Age (y)	Gender	Reason for SBRT	Histology	cTNM	Tumor size at SBRT (mm)	DFI (Mo)	Tumor size (mm)
1	78	M	COPD	Sq	T1bN0M0	24	8.6	45
2	60	M	COPD	Sq	T1bN0M0	22	10.8	48
3	83	M	High age	Sq	T2aN0M0	46	7.6	35
4	81	M	Patient's choice	Sq	T1bN0M0	23	28.3	31
5	82	F	COPD	Sq	T1aN0M0	13	15.4	20
6	68	M	Comorbidity	Sq	T1bN0M0	25	26.2	45
7	80	M	Comorbidity	Sq	T1bN0M0	26	14.5	55
8	78	M	Patient's choice	Sq	T1bN0M0	24	13.3	31
9	83	M	High age	Sq	T2aN0M0	48	8.5	52
10	84	M	High age	Sq	T1bN0M0	21	17.3	31
11	79	M	Comorbidity	Ad	T1aN0M0	15	39	15
12	86	M	Patient's choice	Ad	T1bN0M0	26	58.3	38
13	80	M	Patient's choice	Sq	T1aN0M0	13	50.3	42
14	83	M	High age	Ad	T1aN0M0	16	20	51
15	74	M	Patient's choice	Sq	T2aN0M0	37	10.8	31
16	83	M	Patient's choice	Sq	T1aN0M0	16	31.4	38
17	85	M	High age	Ad	T1bN0M0	27	25	42
18	67	M	Patient's choice	Sq	T1aN0M0	16	9.5	26
19	77	M	Patient's choice	Sq	T1aN0M0	12	36	45

SBRT, stereotactic body radiotherapy; DFI, disease-free interval; M, male; F, female; COPD, chronic obstructive pulmonary disease; Sq, squamous cell carcinoma; Ad, adenocarcinoma.

recurrence rate of 4.9% in patients with stage T1–2 non-small cell lung cancer (NSCLC) at 2 years, and Lagerwaard *et al.* (12) reported a local recurrence rate of 5.1% in medically operable patients with stage I NSCLC at three years. Similarly, a recurrence rate of 5.2% was obtained in the present study.

Recently, the number of reports on salvage surgery to treat local recurrence following SBRT has been increasing (6-9). As in the present study, a few instances of adhesion have been previously reported due to the effect of SBRT. In the present study, surgical treatment for local recurrence following SBRT resulted in a 5-year survival rate of 72.5% in cases of complete resection. At the time of suspected local recurrence following SBRT, if the patients are diagnosed as being medically operable, aggressive salvage surgery should be considered because complete resection can result in good long-term prognosis.

The current standard treatment for stage I primary lung cancer is lobectomy and mediastinal lymph node dissection. Surgical treatment for lung cancer has a perioperative mortality of 0.7–1.4% and has been established as the treatment of choice (13-15). In addition to a high local control rate, SBRT is associated with no serious complications and very few cases of treatment-related death (<0.0–0.7%), and is recognized as a minimally invasive treatment (12,13). Therefore, SBRT may be selected in the absence of careful consideration or because of patient refusal to undergo surgery. In recent years, the number of reports regarding SBRT to treat medically operable patients with lung cancer has been increasing (12,16). However, few reports have shown successful outcomes of SBRT over more than three years, whereas others have reported insufficient long-term outcomes; therefore, SBRT has not been used as a definitive treatment (17) and cannot be used as a standard of care in medically operable patients with lung cancer.

Before the introduction of SBRT, limited surgery was

Table 4 Surgical procedures and postoperative outcomes

Case	Lobectomy or limited surgery	Findings	Postoperative complications	Clavien-Dindo classification	pTNM	Tumor size in history (mm)	Outcome	Recurrence
1	Right upper lobectomy	–	–	–	T1bN0M0	24	Alive with recurrence	Lung metastasis
2	Right upper lobectomy	–	–	–	T1bN0M0	28	Alive	–
3	Left upper lobectomy	–	–	–	T2aN0M0	25	Death from other disease	–
4	Right S6 segmentectomy	–	–	–	T1bN0M0	30	Death from other disease	–
5	RUL wedge resection	–	–	–	T1bN0M0	28	Cancer death	Local recurrence
6	Left upper lobectomy	–	–	–	T2aN0M0	47	Death from other disease	–
7	Left upper lobectomy	–	–	–	T2aN0M0	38	Alive	–
8	Right upper lobectomy	–	–	–	T1bN0M0	25	Alive with recurrence	Pleural metastasis
9	Left upper division segmentectomy	Aortic invasion	–	–	T4N0M0	40	Cancer death	Incomplete resection
10	Right lower lobectomy	–	–	–	T2aN0M0	26	Alive	–
11	Left upper lobectomy	–	–	–	T1aN0M0	15	Alive	–
12	Left upper lobectomy	–	Pulmonary fistula	I	T2aN0M0	38	Death from other disease	–
13	Right lower lobectomy	–	Heart failure	II	T2aN0M0	30	Alive with recurrence	Bronchial stump
14	Left upper lobectomy	Malignant pleural effusion	Pulmonary fistula	I	T2aN2M1a	35	Cancer death	Incomplete resection
15	Right upper lobectomy	–	–	–	T1bN0M0	22	Alive	–
16	Left upper lobectomy	–	Pleuritis	II	T1bN0M0	25	Alive	–
17	Right middle and lower lobectomy	–	–	–	T2aN2M0	28	Alive with recurrence	Brain metastasis
18	Right S6 segmentectomy	–	–	–	T1bN0M0	22	Alive	–
19	Left pneumonectomy with aortic resection	Aortic invasion	–	–	T4N1M0	45	Alive	–

RUL, right upper lobe.

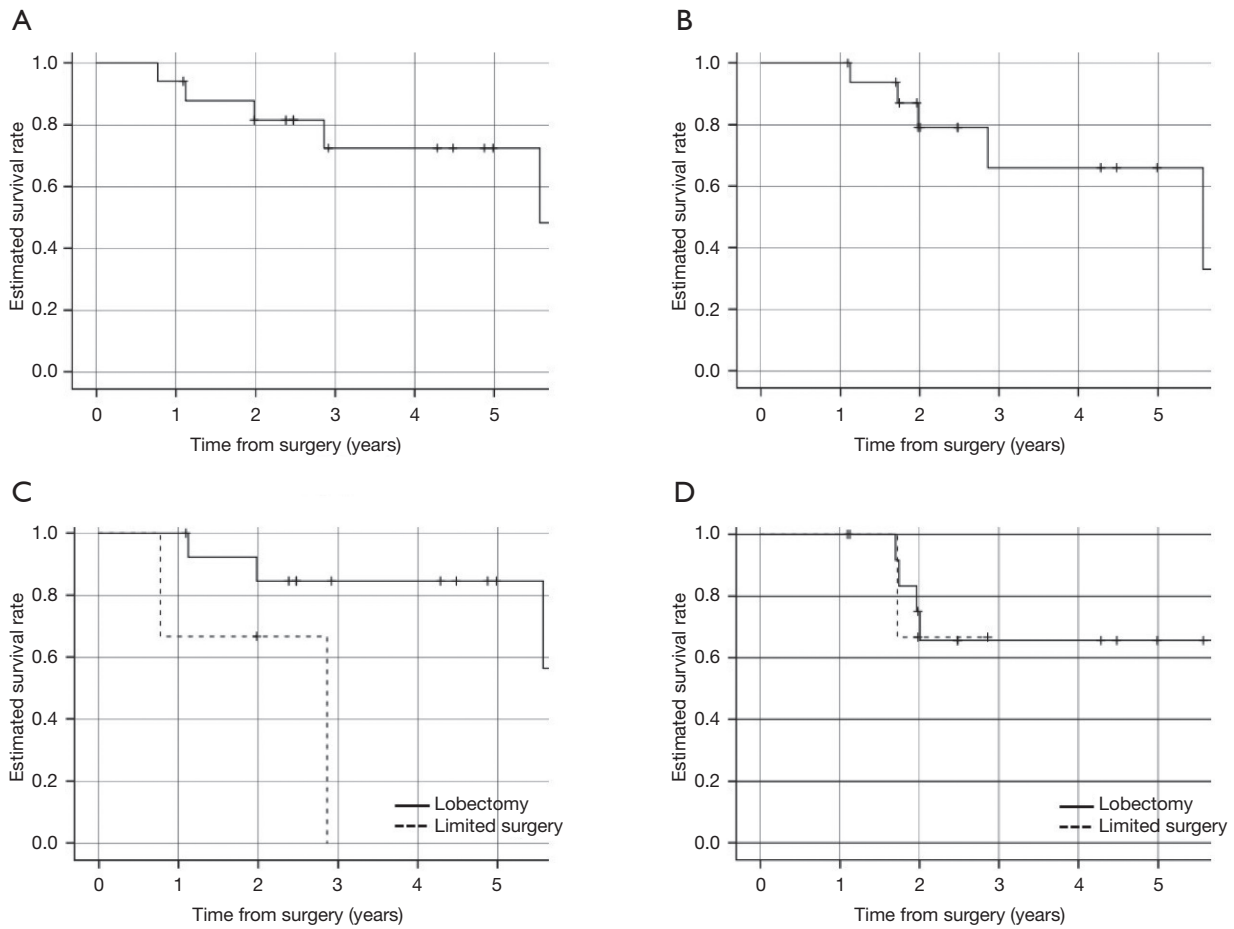

Figure 2 Overall survival (A) and disease-free survival (B) curves for patients who underwent salvage surgery after SBRT. Overall survival (C) and disease-free survival (D) curves for patients who underwent salvage surgery after SBRT, comparing the lobectomy and limited surgery. SBRT, stereotactic body radiotherapy.

often selected for treatment in high-risk patients with comorbidities or poor pulmonary function. Limited surgery has a minimal effect on pulmonary function, and if a sufficient margin (≥1 cm) of the tumor diameter can be secured, it is considered safe and effective (18). Ginsberg *et al.* (19) reported that the locoregional recurrence rate after wedge resection was three-fold higher than lobectomy, with poor prognosis. In addition, Crabtree *et al.* (13) compared local recurrence after surgery with that after SBRT, demonstrating that SBRT was associated with higher local recurrence rates. Further, Yerokun *et al.* (20) compared the OS after limited surgery with SBRT, and revealed that SBRT was associated with a significantly poorer prognosis; this tendency was more pronounced in elderly patients or those with comorbidities. Because SBRT may be selected in the absence of careful consideration, lobectomy and mediastinal lymph node dissection should be performed in medically operable patients.

Some reports have stated that local recurrence during follow-up after SBRT defined as continuous increase of the tumor in size or increase FDG avidity (6-8). But, one of the issues with recurrent lung cancer after SBRT is the difficulty to correctly diagnose recurrence based on imaging. Fibrotic changes often develop after SBRT and tumor shadow becomes indistinguishable from the fibrotic shadow (21). Ogawa *et al.* (22) reported positive FDG-PET (SUVmax ≥5) finding does not necessarily indicate tumor recurrence because they experienced a number of false positive cases. It has been reported that late fibrotic changes or mass-like fibrosis can occur over more than two years and

is considered to be a normal change following SBRT (9,23), possible delaying the recurrence diagnosis. Therefore there are no criteria to diagnose recurrence after SBRT in primary lung cancer. We defined local recurrence after SBRT as continuous increase of the tumor in size. Further, we found that the increase in tumor size ranged from 23 [12–48] to 38 [15–55] mm. And, we defined the time period from SBRT to salvage surgery as from the start of SBRT to the date of salvage surgery. We found the time period from SBRT to salvage surgery ranges 17.3 (7.6–58.3) months. This result was similar to previous report (range between 10 and 17 months) (6-8). Careful follow-up is important to detect disease progression and to implement timely intervention.

We found stage progression in seven out of 19 patients who underwent salvage surgery (36.8%). Other reports have shown variable results in terms of stage progression; Antonoff *et al.* (6) reported stage progression in 11 out of 15 patients (73.3%) and Hamaji *et al.* (9) in 6 out of 12 patients (50%), with some patients requiring additional treatment with an anticancer drug. In some cases, salvage surgery could be performed during recurrence following SBRT. Considering cancer stage progression and advancing age, SBRT must be avoided in the absence of careful consideration.

The 5-year OS rate of 72.5% found in the present study was lower than that of 79.5% in the report by Hamaji *et al.* (9). The reason was thought to be that there are some cases of death from other diseases in the present study, but this comparison is unconfirmed due to the small number of cases analyzed.

The primary limitations of the present study include its retrospective design and small sample size. However, considering available literature regarding local recurrence after SBRT in patients with primary lung cancer, the sample size of 19 patients used here is the largest reported to-date. Further, there was no pathology diagnosis before SBRT in 42.5% of the cases, which may have contributed to low local recurrence rate following SBRT.

Conclusions

We evaluated patients who underwent salvage surgery to treat local recurrence of lung cancer following SBRT. Salvage surgery could be performed safely without affecting SBRT outcomes. In cases of complete resection, salvage surgery can lead to good long-term prognosis. Our evaluation suggested that SBRT was selected in medically operable patients without careful consideration. The standard treatment for patients with stage I NSCLC is lobectomy and mediastinal lymph node dissection. To provide optimal assessment and treatment, careful consideration by a multidisciplinary tumor board is required. Because of the recurrence rate following SBRT, unknown long-term outcomes, and stage progression during recurrence, we recommend that cursory SBRT selection should be avoided.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/jtd-20-2253

Data Sharing Statement: Available at http://dx.doi.org/10.21037/jtd-20-2253

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (Available at http://dx.doi.org/10.21037/jtd-20-2253). The authors have no conflicts of interest to declare.

Ethics Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study protocol complied with the Declaration of Helsinki (as revised in 2013) and was approved by the institutional review board at Nishi-Niigata Chuo National Hospital (approval No.1909). The requirement for informed consent was waived because all data in this study were completely anonymized.

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