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Salvage Pulmonary Operations Following Stereotactic Body Radiotherapy for Small Primary and Metastatic Lung Tumors: Evaluation of the Operative Procedures

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Abstract

Stereotactic body radiotherapy is an alternative treatment option for small-sized, primary lung cancers and pulmonary metastatic diseases. In the case of local relapse after stereotactic body radiotherapy, salvage pulmonary resection is considered cautiously. However, no study has described the difficulty of the salvage operations. This study aimed to assess the difficulty associated with salvage operative procedures. Eight patients who developed local relapse after stereotactic body radiotherapy and had undergone salvage pulmonary operations were enrolled in this study (stereotactic body radiotherapy group). Additionally, 439 patients who underwent video-assisted thoracoscopic lobectomy without previous stereotactic body radiotherapy were enrolled as the standard operative control group (non-stereotactic body radiotherapy group). In the stereotactic body radiotherapy group, 1 of the 8 patients had undergone lobectomy with composite resection of the third and fourth ribs. Of the 8 patients, 6 had undergone video-assisted thoracoscopic lobectomy and 1 had been inoperable because of rapid tumor progression. The operation time and the incision length of the utility port were apt to be longer in the stereotactic body radiotherapy group than in the non-stereotactic body radiotherapy group. On the contrary, the duration of drain placement and the length of hospital stay after the operation were not different. Thus, the salvage pulmonary operations were performed in the usual video-assisted thoracoscopic lobectomy approach, but slightly complicated than the standard video-assisted thoracoscopic lobectomy. Although to decide the indication of salvage operation might be difficult, it could be a feasible treatment option in local relapse after stereotactic body radiotherapy.

Keywords

lung lesions, salvage pulmonary resection, salvage surgery, stereotactic body radiotherapy, video-assisted thoracoscopic lobectomy

Abbreviations

LR, local relapse; POD, postoperative day; SBRT, stereotactic body radiotherapy; VATS, video-assisted thoracoscopic surgery

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Introduction

In recent years, stereotactic body radiotherapy (SBRT) has become a selectable treatment option for patients with high operative risk for small-sized primary and metastatic lung tumors.[1,2] However, local failure occurs in about 10% of these patients by the third year; therefore, salvage surgical resection after SBRT has been considered a treatment option for complete cure.[3] Previously, some reports stated that perioperative morbidity and local control were reasonable in patients with primary lung cancer and/or metastatic lung tumor.[4-8] However, no study has described how the operative procedure became more difficult compared to that without SBRT. In this study, we aimed to investigate our experience with pulmonary resection in patients with local persistence or relapse after SBRT. Additionally, we report on an inoperable case, in which salvage pulmonary operation for suspected local relapse (LR) was planned but not feasible because of the aggressive progression of the tumor more than that estimated.

Materials and Methods

The approval has been granted by the institutional review board of Kobe City Medical Center General Hospital for our study (zn181006). In our hospital, LR was identified basically based on radiographical examinations, and the indication of salvage operations was multidisciplinarily defined at weekly conferences among departments of thoracic surgery, respiratory medicine, medical oncology, and therapeutic radiology. Between October 2002 and September 2017, salvage surgery, after SBRT, was performed at our hospital in 14 patients with primary lung cancer and 15 patients with metastatic tumors. On the contrary, typical video-assisted thoracoscopic lobectomy approaches have been adapted for small primary and metastatic lung tumors since July 2011. After a while, the video-assisted thoracoscopic lobectomy approach in our department has been established. Therefore, data of salvage pulmonary operations after SBRT until June 2011 were not included in this study, as this study aimed to investigate the operative procedure itself. Consequently, for obtaining reference values, the operations were also limited to cases performed at the same time period. Overall, 593 patients (video-assisted thoracoscopic surgery [VATS]; lobectomy 447; segmentectomy, 94; partial resection, 34; open lobectomy, 26; segmentectomy, 0; partial resection, 2) with primary lung cancers, metastatic lung tumors, or peripheral nodular diseases underwent lung resection; however, only 8 patients were included as the SBRT group, whereas 439 patients who underwent VATS lobectomy without a history of SBRT were enrolled in the non-SBRT lobectomy group and served as the reference group. Briefly, non-SBRT lobectomy group was composed of patients with lung tumors with any total tumor size, in which 226 of 439 patients had tumors within 30 mm.

Variables related to the operative procedures were collected from the prospectively maintained surgical database of our department. All VATS lobectomies, excluding those in the SBRT group, were performed with 1 utility port which was around 3.0 cm long and the others with 2 ports at 1.5 cm long for camera and/or assistance. The length of the utility port, operation time, total amount of bleeding, duration of drain placement, and length of hospital stay were evaluated with reference values from the non-SBRT group.

Of the patients in the reference group, cases with firm and wide range of intrapleural adhesions, composite resection, history of chemoradiotherapy, and cut-stump covering were excluded from the statistical processing, because the cases of typical lobectomy with no SBRT were the target for comparison with the SBRT group.

Statistical Analysis

The absolute values for operative variables are presented as mean (standard deviation). The pre-SBRT and presurgery tumor sizes were compared using 2-tailed paired *t* test. The operative variables between SBRT and non-SBRT groups were compared using Mann-Whitney *U* test. A *P* value <.05 was considered statistically significant. All statistical analyses were performed using Prism version 6.0h (GraphPad Software, Inc, La Jolla, California).

Table 1. Patient Characteristics and Stereotactic Body Radiotherapy Undergoing Salvage Pulmonary Operation.

Case	Gender	Age at Surgery (years)	Primary or Metastatic	Histology	Location	Initial Reason for Precluding Surgery	Radiation Dose (Gy/Fraction)
1	M	65	Primary	Adeno	RUL	Patient's choice for SBRT	48 Gy/4 fr
2	F	78	Primary	Adeno	RUL	Doctor's choice for SBRT Double primary	48 Gy/4 fr
3	F	61	Primary	Squamous	RML	Doctor's choice for SBRT Single metastasis (brain)	48 Gy/4 fr
4	F	82	Primary	Squamous	RLL	Patient's choice for SBRT	48 Gy/4 fr
5	F	62	Cervical	Squamous	LUL	Doctor's choice for SBRT Other metastasis (RML)	56 Gy/4 fr
6	M	78	Primary	Adeno	RUL	Patient's choice for SBRT	48 Gy/4 fr
7	F	66	Ovarian	Adeno	RUL	Doctor's choice for SBRT	60 Gy/8 fr
8	F	76	Primary	Adeno	RUL	Patient's choice for SBRT	56 Gy/4 fr

Abbreviations: Adeno, adenocarcinoma; F, female; fr, fraction; Gy, gray; LUL, left upper lobe; M, male; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; SBRT, stereotactic body radiotherapy; squamous, squamous cell carcinoma.

Table 2. Demographics of Patients Undergoing Salvage Pulmonary Operation After SBRT.

	Pre-SBRT			Interval From	Presurgery			Pathological Result		
Case	Tumor Size (mm)	SUVmax	Stage	SBRT to Op (months)	Tumor Size (mm)	SUVmax	Stage	Effect	Tumor Size (mm)	Stage
1	25	NA	cT1aN0M0	21	13	3.6	ycT1bN0M0	3	NA	Cryptococcosis
2	14	NA	cT1bN0M0	25	37	10.2	ycT2aN0M0	1a	21	ypT2aN0M0
3	17	NA	cT1bN0M1b	56	40	NA	ycT2aN0M0	2	32	ypT2aN1M0
4	24	8.3	cT1cN0M0	38	48	6.8	ycT3N0M0	2	40	ypT2aN0M0, pl1
5	19	18.2	Stage IV	18	52	16.2	Stage IV	NA	37	Stage IV
6	14	NA	cT1bN0M0	22	32	3.9	ycT3cN0M0	2	NA	ypT2aN0M0
7	11	0	Stage IV	16	125	NA	Stage IV	NA	NA	Stage IV
8	30	7.0	cT1cN0M0	40	55	7.0	ycT3N0M0	1a	62	ypT3N0M0
mean=(SD)	19.3 (6.5)			29.5 (13.9)	50.3 (33.0)[a]					

Abbreviations: NA, not applicable; SBRT, stereotactic body radiotherapy; SD, standard deviation.
[a]$P < .05$.

Table 3. Details of Salvage Pulmonary Operation After SBRT.

Case	Operation Procedure	Composite Resection	Intrapleural Adhesion	Cut-Stump Covering	Utility Port (mm)	Op Time (minutes)	Total Bleeding (mL + g)	Postop Air Leak	Drain Placement (POD)	Hospital Stay (POD)
1	VATS RU lobectomy	N	Y	N	30	213	0	N	2	3
2	VATS RU lobectomy	N	N	N	30	140	0	Y	2	5
3	VATS RM lobectomy	N	N	N	50	295	95	N	4	10
4	VATS RL lobectomy	N	Y	PFT	35	288	150	N	1	5
5	VATS LU lobectomy	N	N	N	40	142	0	N	1	3
6	Open RU lobectomy	Third and fourth rib	Y	N	80	404	275	N	1	6
7	Inoperable	NA	N	NA	75	132[a]	0[a]	N	1	4
8	VATS RM&L lobectomy	Middle lobe	N	N	35	242	0	N	1	6
mean (SD)					42.1 (18.0)	246.3 (93.4)[a]	74.3 (106.9)[a]		1.63 (1.11)	5.25 (2.41)
Reference value (any tumor size)					30.2 (8.5)[b]	164.6 (60.8)[c]	26.8 (54.6)		2.08 (1.64)	5.87 (5.08)
	tumor size ≤30 mm	n = 226			28.1 (4.5)[d]	160.7 (53.0)[b]	15.7 (28.8)		2.05 (1.55)	5.57 (5.23)

Abbreviations: LU, left upper; NA, not applicable; Op time, operation time; PFT, pericardial fat tissue; POD, postoperative day; RL, right lower; RM, right middle; RM&L, right middle & lower; RU, right upper; SD, standard deviation; SBRT, stereotactic body radiotherapy; VATS, video-assisted thoracic surgery; Y, yes.
[a]The operative time and total bleeding in case 7 was excluded from the statistical analysis, because salvage surgery was not performed.
[b]$P < .001$; statistically significant; comparison between SBRT group and reference value.
[c]$P < .05$; statistically significant; comparison between SBRT group and reference value.
[d]$P < .0001$; statistically significant; comparison between SBRT group and reference value.

Results

Overall, 8 patients were enrolled in this study and included in the SBRT group. The characteristics of these patients are shown in Tables 1 and 2. As shown in Table 2, all patients in the SBRT group were noted to have small-sized primary and metastatic lung tumors at the initial condition, with the mean tumor size of 19.25 (6.54) mm, and they radiographically appeared to have only tumor-induced fibrosis. This meant that if the operations are performed in the initial condition, all stages of primary lung cancer should be maintained in cT1cN0Mx. In addition, those operations should have been performed by typical VATS lobectomy procedures, if surgery had been chosen. The postoperative histopathological examination of case 1 suggested cryptococcosis and radiation-induced fibrosis. However, this case was included in the SBRT group, because the final aim of this study was to assess the difficulty associated with the salvage operative procedures, not to evaluate the adverse effects after SBRT. Moreover, in the initial conditions of cases 2 and 3, SBRTs were selected instead of lung resections. In case 2, the patient had 2 primary lesions in the left upper segment and right upper lobe. The left upper segmentectomy was performed for the left lesion, and SBRT was selected for the right lesion. In case 3, brain metastasis was found on initial examination. Therefore, the surgical resection of the brain tumor and SBRT for the lung lesion was selected as initial treatment strategies. At 56 months after treatments, the primary lesion had relapsed, but no other metastatic lesion was identified. That was the reason why these cases were also enrolled in the SBRT group. The demographics of patients undergoing salvage pulmonary operation after SBRT are shown in Table 2, and the length of the utility port, operation time, total amount of bleeding, duration of drain placement, and length of hospital stay are shown in Table 3 with reference values from the non-SBRT group. Of the 8 patients, 7 underwent salvage lobectomy, and 6 of those 7 underwent VATS lobectomy. The remaining patient was inoperable because of rapid tumor progression. Of the 8 patients, 3 had tumors directly attached to the chest wall, resulting from either tumor invasion or radiation-induced fibrosis following SBRT. Two of them respectively underwent composite resections of the third and fourth ribs and the middle lobe. In 1 of the 3 patients, the bronchial cut-stump was covered with a pedicellate pericardial fat tissue. In the SBRT group, all VATS lobectomies were performed with 3 ports (1 utility port and 2 additional ports). Comparison results between the SBRT and non-SBRT groups showed that the mean length of the utility port was 42.1 (18.0) and 30.2 (8.5) mm (Figure 1), respectively; the mean duration of operation was 246.3 (93.4) and 164.6 (60.8) minutes (Figure 2), respectively; and the mean total amount of bleeding was 74.3 (106.9) and 26.8 (54.6) mL + g (Figure 3), respectively. The operation time and incision length of the utility port in the SBRT group were longer than those of the non-SBRT group ($P < .05$ and $<.01$, respectively). The total amount of bleeding was not statistically different, although the mean value of the SBRT group was 3 times higher (74.3 [106.9] and 26.8 [54.6]). The mean duration of drain placement was on postoperative day (POD) 1.63 (1.11) and 2.08 (1.64), respectively. The mean length of hospital stay after operation was POD 5.25 (2.41) and 5.87 (5.08), respectively. Both the duration of drain placement and length of hospital stay after operation were indicators of postoperative outcome metrics, but no difference was found. In the SBRT group, the mortality at both 1 month and 1 year were 0%. On the contrary, in the non-SBRT group, the mortality at 1 month was 0.2%, with one case of aspiration pneumonia, and that in 1 year was 0.9%, with 3 cases of acute exacerbation of interstitial pneumonia (4 patients were lost in 1 year). Furthermore in the SBRT group, there was no apparent complication, except for slight intercostal neuralgia

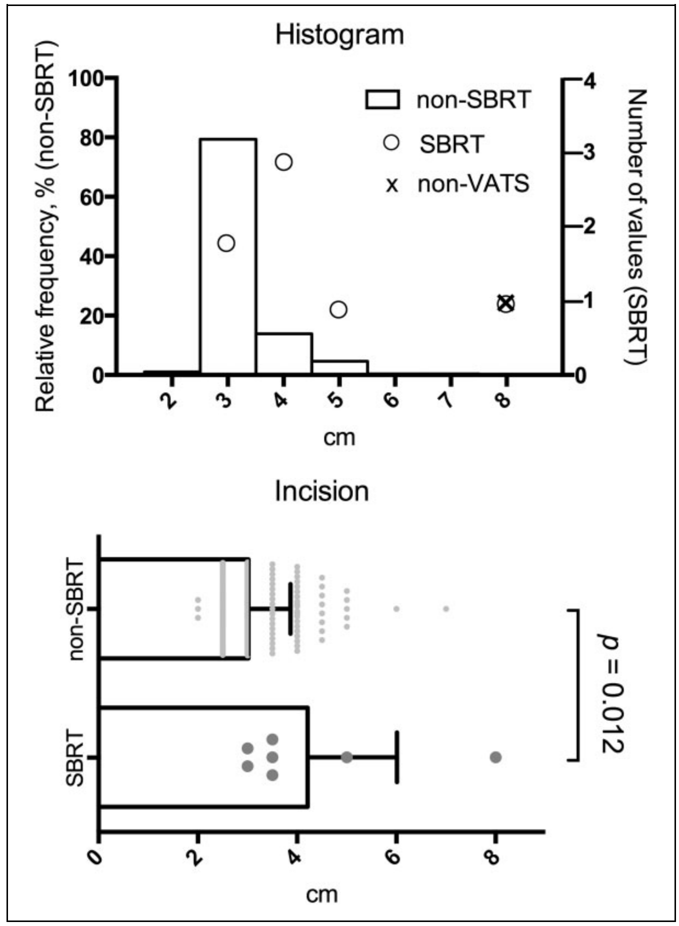

Figure 1. Skin incision and length of utility port.

and nonproductive cough, and both were less than grade 1 (CTCAE version 4.0). Consequently, with regard to postoperative conditions in hospital stay, mortality, and complications, there was nothing to be covered; thus, postoperative outcomes were not compared in this study. Finally, those results were not shown in this article.

In case 7, firm inflammatory adhesion between the interlobar surface of S2 and S4 and dense mucus accumulation in the S2 segment were noted. Furthermore, there were several newly appearing, protruding neoplastic nodules on the interlobar surface around S2 and S6a+b. The lesion of S6a+b was sufficiently large to involve the bifurcation of A6 and main trunk of the middle and basal pulmonary arteries. Therefore, right pneumonectomy was necessary to completely resect the tumor. Therefore, we decided to avoid a salvage right pneumonectomy. The clinical course of this case and changes in the images are shown in Figure 4A to F.

Discussion

Generally, although the standard treatment for stage I non-small cell lung cancer is surgical resection, SBRT is an alternative to surgical resection for small-sized lung tumors in medically compromised and/or inoperable patients.[1,2,5] In our

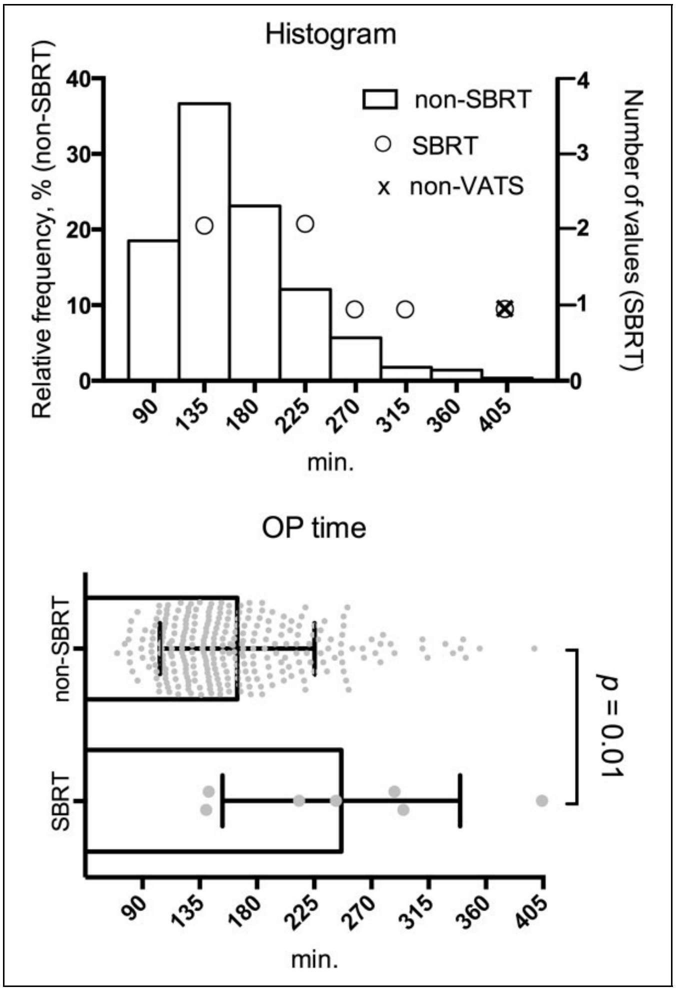

Figure 2. Operation time.

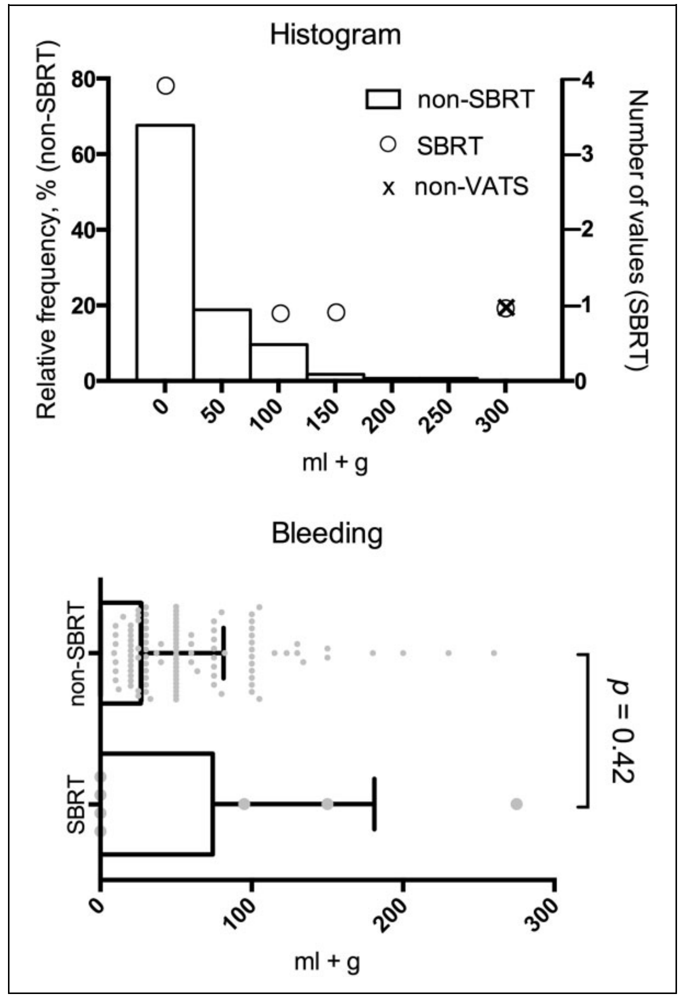

Figure 3. Total amount of bleeding.

previous study (Neri *et al* study), we had reported that SBRT might not cause intrapleural adhesions and preclude the surgical indication in LR, and close follow-ups are necessary in patients treated with SBRT.[7] In the present SBRT group, which does not overlap with the cohort in Neri *et al* study, 3 of the 8 patients had intrapleural adhesion, although we could not say whether SBRT caused such radiation-induced fibrosis. In the initial stage before SBRT, all cases reported in this study were of small-sized lung tumors, up to 30 mm in diameter ($\leq$30 mm), which cases might be the ideal target of this study. This meant that in those stages, the operative procedures should have been easier than those after SBRT. For instance, composite resection of the ribs, neighboring lobes, and other additional procedures such as covering the cut-stump of the bronchus would not have been necessary. Therefore, if all lobectomies in the SBRT group were performed at the initial stage, all operations could have been performed with 3 ports in a standard VATS approach and should be easier than those following SBRT. Subsequently, presurgery conditions of the SBRT group vary according to tumor size, intrapleural adhesion, and tumor-induced and/or radiation-induced fibrosis. With these points of view, if possible, we want to compare pre-SBRT and post-SBRT operative procedures for LR. In other words, the ideal target against post-SBRT condition was pre-SBRT condition of identical patients. Furthermore, if a propensity score analysis is used for this study, the interpretation of the results was not simple because the details of the SBRT group were varied, and enrolled patients had already been limited to only 8 cases. For those reasons, we decided to show the distributions of operative parameters derived from the SBRT group against the non-SBRT group (Figures 1–3). For more in-depth information, Table 3 shows the data extracted from the reference value, especially the values of $\leq$30 mm. To the best of our knowledge, this is the first study to shed light on the operative procedure itself.

To identify LR is basically based on radiographical examinations (eg, computed tomography and fluorodeoxyglucose positron emission tomography), and the indication of salvage operations is multidisciplinarily defined at weekly conferences among departments of thoracic surgery, respiratory medicine, medical oncology, and therapeutic radiology. In case 1, the final pathological diagnosis was Ef3 and a lesion with an abnormal fluorodeoxyglucose uptake; the maximum standardized uptake value was 3.6 (Table 2), which was caused by

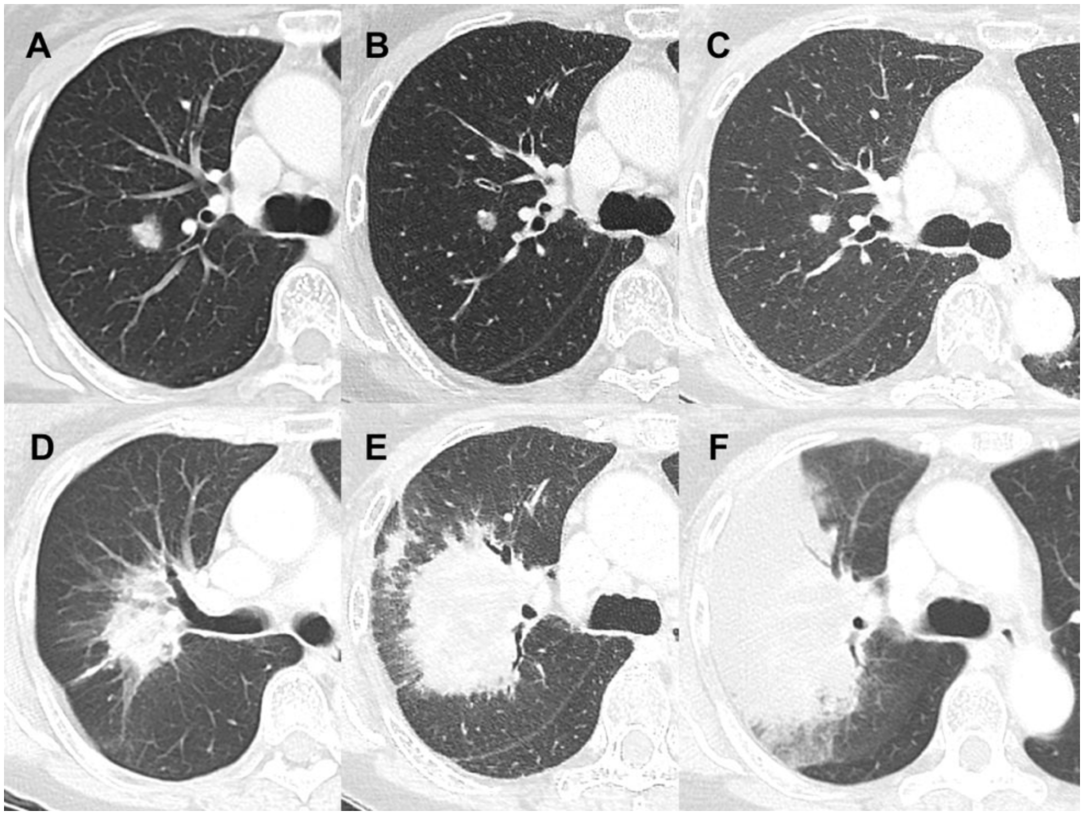

Figure 4. A, Chest computed tomography scan in case 7 at the start of stereotactic body radiotherapy shows a mass sized 11 mm in the right upper lobe. B, The scan at 4 months after stereotactic body radiotherapy shows the shrunken tumor. C, Follow-up scan at 8 months shows slight tumor regrowth. D, Follow-up scan at 10 months showed apparent tumor regrowth. Follow-up scan (E) at 13 and (F) 14 months showed rapid tumor regrowth. At 16 months, after stereotactic body radiotherapy, salvage operation was attempted, but it resulted in an inoperable state, because the tumor progression area was more extensive than what was estimated.

cryptococcosis forming a small round nodule in the fibrotic area after SBRT. Therefore, we could not make further follow-up. Thus, it is very difficult to distinguish the benign nodule from LR of the tumor. Following salvage operations, small discontinuous air leak on gentle respiration was observed only in case 2, but it had stopped on the first POD. In cases 6 and 8, peripheral tumors after SBRT were involved with the neighboring structures, the former was firmly adhered to the chest wall along with a postradiation bone fracture, and the latter had radiation and tumor-induced fibrosis that was firm enough so that S4 and S6 segments could not be divided and the entire aspect of A7-10 was unclear, which resulted in additional resection of the nearby structures. Case 7 was inoperable because of the rate of tumor progression. In the aforementioned cases, it was difficult to determine the indication of salvage operation and the time to perform the operation.

Comparison results between SBRT and non-SBRT groups showed that the operation time and incision length of utility port were longer in the SBRT group. These results should be derived from tumor enlargement and radiation-induced fibrosis. Moreover, no difference was found between the 2 groups in terms of duration of drain placement, length of hospital stay, mortality, and complication. Considering the aforementioned aspects, the operative procedures for the SBRT group appeared to be more complicated than those for the non-SBRT group. However, the most important thing is that salvage VATS lobectomy could be performed without worsening postoperative outcomes, and the patients in the SBRT group had neither serious complication nor death related to salvage operation.

However, the biggest limitation of this study is that the real operative data of SBRT group before exposure to radiation were not attainable, because these comparisons could be performed only in virtual reality condition. This is why non-SBRT group was considered the reference for SBRT group before exposure to radiation. In many cases of non-SBRT group, exfoliation of hilar structures and encircling of pulmonary vessels could be easier than in the SBRT cohort, because of lesser fibrosis and small range of tumor progression. All operations were also performed in a single center and by a team of thoracic surgeons, which could have caused several unavoidable biases. As a major limitation, the number of patients in the SBRT group was small, which may cause some different results. Essentially, between the first and second halves of the study in our hospital, intrapleural adhesions were encountered in 3 of 8 patients at the salvage operation, but there was no adhesion in either case in Neri *et al* patient group.[7] However, Hamaji *et al* reported intrapleural adhesions in 2 of 12 patients.[8] Thus, the small sample size always has a possibility to cause different results. Furthermore, VATS lobectomies in the non-SBRT group mainly consisted of patients with primary lung cancer between stages IA and IIIA, which meant that the condition was not always advantageous for comparison with the SBRT group. Nevertheless, the operative procedures in the non-SBRT group could be easier than those in the SBRT group.

In conclusion, this study suggested that the salvage VATS lobectomy following SBRT could be performed in a usual VATS approach for lung tumors without negative postoperative outcome, except for the difficulty of surgical procedure during operation. For patients who were operable even after SBRT, it was not necessary to avoid surgical indication. However, in cases 1 and 7, when and/or how the surgical indication should be decided for the patients with LR after SBRT are difficult. Similarly, as we reported previously, when LR is suspected, it is important to determine the time to perform the operation. Further studies are still needed to establish treatment algorithms for patients who exhibit LR after SBRT.

Declaration of Conflicting Interests

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