Salvage stereotactic body radiotherapy for post-operative oligo-recurrence of non-small cell lung cancer: A single-institution analysis of 59 patients

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Received August 6, 2019; Accepted November 14, 2019

DOI: 10.3892/ol.2020.11407

Abstract. A standard treatment for patients with early-stage non-small cell lung cancer (NSCLC) who undergo surgery, and subsequently develop local failure or intrathoracic oligo-recurrence, has not yet been established. The present study aimed to assess the feasibility of stereotactic body radiotherapy (SBRT) for this subgroup of patients. Consequently, a retrospective analysis was conducted of patients with NSCLC recurrence who were treated with SBRT, and previously underwent curative surgical resection between October 2011 and October 2016. Post-SBRT survival [overall survival (OS); progression-free survival (PFS); and local control (LC)] and toxicity were analyzed. Prognostic factors for OS were identified using univariate and multivariate analysis. A total of 52 patients and 59 tumors were analyzed. The median follow-up time was 25 months (35 months for surviving patients), and median OS following salvage SBRT was 32 months. The 1- and 3-year OS rates were 84.4 and 67.8%, respectively. 1- and 3-year PFS rates were 80.8 and 58.7%, respectively. Only 4 patients (7.7%) developed local failure. Median LC was 71 months and 1- and 3-year LC rate were 97.9 and 94.9%, respectively. A total of 4 patients experienced grade 3 or higher adverse events (AEs) and two experienced grade 5 AEs (pneumonitis and hemoptysis). Central tumor location and the possibility of re-operation were independent prognostic factors for OS. The present study indicated that post-operative salvage SBRT is a promising therapeutic option for patients with NSCLC with locoregional or intrathoracic oligo-recurrence. We regard toxicity was also acceptable. However, further research is required on the appropriate selection of subjects, and stratification of the analysis by certain risk factors would increase the accuracy of the conclusions.

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Key words: salvage, stereotactic body radiotherapy, post-operative recurrence, oligo-recurrence, oligometastases, non-small cell lung cancer

Introduction

Surgery is considered the primary therapeutic option for the treatment of patients with early stage non-small cell lung cancer (NSCLC) (1-3). Although reported recurrence rates after definitive surgery vary between 28 and 60%, poor post-recurrence survival rates remain a challenge to the long-term survival of patients with NSCLC (4-7).

Standard treatment the for post-operative recurrence of NSCLC remains controversial. It is commonly systemic therapy with cytotoxic agents and/or molecular targeted agents as for metastatic stage IV disease (8,9). However, certain patients with loco-regional (only) recurrence or oligo-recurrences, that is, the state with a limited number of recurrent lesions and controlled primary lesions, a condition termed oligo-recurrence (10-13), are expected to achieve long-term survival and even cure with intensive local therapy alone (14-19).

Loco-regional recurrence of NSCLC is said to occur in 20-45% of patients during follow-up (5,14,20). If oligo-recurrence is included, >50% of patients with recurrence may be suitable for localized curative therapy (21,22). Although salvage surgery is considered to be the most promising current treatment, the majority of candidate patients do not undergo surgery because of post-operative comorbidities or poor baseline pulmonary function. Additionally, most of these patients are unable to tolerate chemotherapy, highlighting the importance of radiotherapy (23-25).

Stereotactic body radiotherapy (SBRT) is an important therapeutic option for patients with medically inoperable early-stage NSCLC or oligometastatic lung tumors (26-28). Even for patients in which operative treatment would be viable, SBRT has previously achieved results similar to those of surgery (29-31), and an increasing number of studies have reported the expansion of factors that may indicate the

selection of SBRT, including large tumors and advanced-stage NSCLC (32,33). Nevertheless, few large-scale studies have reported the effect of SBRT on post-operative oligo-recurrence of NSCLC (34,35).

Therefore, the present study aimed to retrospectively assess the efficacy and safety of salvage SBRT for post-operative oligo-recurrence following primary curative lung resection in patients with NSCLC.

Materials and methods

Case eligibility. Following Institutional Review Board approval from the Ethics Committee of the University of Tokyo (Tokyo, Japan), a retrospective review was conducted of patients treated with SBRT, admitted to University of Tokyo Hospital between September 2010 and November 2016. The patients selected had previously received pulmonary resection for a primary NSCLC, and later developed nodular lesions in the thorax, which were determined to be post-operative oligo-recurrences. The median age of patients was 74 years, ranging from 50 years to 86 years. There were 38 males and 14 females. Seven patients rejected surgery at their own discretion. Written informed consent was obtained from all patients prior to treatment initiation.

Inclusion and exclusion criteria. The present study included patients who met the following inclusion criteria: i) Initial resection of NSCLC with curative intent; ii) clinical diagnosis of post-operative recurrence (approved by the Tumor Board for Lung Cancer of University of Tokyo Hospital based on biopsy or image findings and clinical data); iii) recurrent disease within the thorax, including mediastinal and hilar lymph nodes; iv) absence of metastases to solid organs, or pleural seeding; and v) <10 years between initial surgery and SBRT.

The exclusion criteria were as follow: i) <6 months of follow-up completed (excluding mortality as the reason); ii) no CT confirmation of recurrence after completion of SBRT; and iii) history of adjuvant radiotherapy. SBRT was not conducted in patients with apparent interstitial pneumonitis or pulmonary fibrosis on the chest film, due to the absence of established policy regarding performance status or respiratory function in these patients.

Clinical data collected from each patient included age, sex, interval between surgery and recurrence, recurrence sites and smoking index. Staging of the primary tumor was conducted in accordance with the 7th edition of the Union for International Cancer Control staging system for lung cancer (36).

Procedure. The decision to conduct appropriated salvage therapies was approved by the Tumor Board for Lung Cancer when post-operative oligo-recurrence was suspected. SBRT was often selected as the therapeutic approach for locoregional or intrathoracic oligometastases, where it could safely be applied. In other cases, chemoradiotherapy, chemotherapy, immunotherapy, palliative therapy and best supportive care were considered. Although cases that administered chemotherapy before and/or after SBRT were not excluded, there were no cases included in which chemotherapy was performed synchronously with SBRT.

Prior to the initiation of treatment, patients were immobilized in a stereotactic body frame and underwent a four-dimensional (4D) CT scan (2-mm slice thickness). Scans were performed using an external respiratory monitoring system (AZ-733 V®; Anzai Medical Co, Ltd.) under free breathing or with abdominal compression in cases where tumor excursion was >1 cm.

Mechanistically, 4D-CT planning divides the respiratory cycle into 10 sections. Respiratory phase data were transferred to a treatment planning system (TPS; Pinnacle^{3}® version 9.1; Philips Healthcare). Gross tumor volume (GTV) was delineated in each respiratory phase using the lung window (window, 1,600 HU; level, -300 HU). The 10 GTVs were fused to form the internal target volume. A uniform 5-mm margin was then added to create the planning target volume (PTV) (37-39). The main organs at risk (OARs), namely the heart, lungs, esophagus, spinal cord, proximal tracheobronchial tree and brachial plexus, were contoured according to the guidelines outlined in the Radiation Therapy Oncology Group (RTOG) 0236 trial (40).

Patients admitted between September 2010 and March 2013 were treated using a conventional SBRT plan using 6-12 beams, whereas patients admitted from April 2013 onwards were treated using volumetric modulated arc therapy (VMAT)-SBRT with 6 or 10 MV beams using an Elekta-synergy system (Elekta Instrument AB). There was no significant difference in treatment outcome between the two methods (41). VMAT plans were designed using a single partial arc with angle ranges of -40˚ to 180˚ (left lung) or -180˚ to 40˚ (right lung), as previously detailed (37,38,41,42). Dosimetric planning and plan analysis were performed using Pinnacle^{3}. The collapsed cone convolution method (comparable to the superposition method) in the TPS was used (42,43). All final calculations were performed using a grid size of 2.0 mm. Dose distributions were calculated using CT data obtained at peak exhalation. Treatment was performed with 48-55 Gy in 4 fractions for peripheral tumors (39 lesions) or 56 Gy in 7 fractions for central tumors (17 cases) to cover 95% of the PTV ($D_{95\%}$).

The central lesion was defined as a tumor <2 cm from the proximal bronchial tree, according to the RTOG 0236 guidelines, or <2 cm in any direction from a critical mediastinal structure, including the bronchial tree, esophagus, heart, brachial plexus, major vessels, spinal cord, phrenic nerve and recurrent laryngeal nerve, as in most recent studies (44,45). For certain hilar or mediastinal tumors, or tumors invading the trachea or bronchi, a regimen with increased number of fractions (such as 50 Gy in 10 fractions) was used (46,47). The dose constraints of OARs were defined based on the protocol of the Japan Clinical Oncology Group (JCOG) 0403 trial (48). Regarding the pulmonary dose, adding to the constraints described in JCOG 0403 (V20, V15, mean lung dose, V10 (<40%) and V5 (<70%) were also restricted to reduce the volume of low dose area, which tends to be large in VMAT plans (49,50) (Table I). Furthermore, dosage deviations to organs other than those listed in Table I were permitted according to clinical benefit (51).

Follow-up and chart review. Follow-up commenced on the first day of radiotherapy initiation and ended on May 1, 2018. Patients underwent a CT scan of the chest and abdomen every

Table I. Dose constraints of organs at risk.

Organ at risk	Dose constraints	Dose effort targets
Lung		
MLD <18.0 Gy	MLD <18.0 Gy	
V20 <20%	V20 <20%	
V15 <25%	V15 <25%	
V10 <40%	V10 <40%	
V5 <70%	V5 <70%	
Spinal cord	25 Gy/4-10 fractions (0 cm^3)	40 Gy/4-10 fractions (0cm^3)
Heart (mean)	25 Gy/4-10 fractions (0 cm^3)	
Heart (max)	55 Gy/4-10 fractions (0 cm^3)	
Liver	30 Gy/4-10 fractions (<10 cm^3)	
Esophagus		40 Gy/4-10 fractions (0 cm^3)
pulmonary artery		40 Gy/4-10 fractions (0 cm^3)
Trachea/bronchus		40 Gy/4-10 fractions (0 cm^3)
rib, chest wall		40 Gy/4-10 fractions (0 cm^3)

MLD, mean lung dose; V20/15/10/5, percentage of the volume of an organ receiving 20, 15, 10 and 5 Gy. No constraints: Esophagus, pulmonary artery, trachea/bronchus, rib, chest wall; aimed for less than 40 Gy for these organs.

3 months for 2 years, and received ≥1 scan every 6 months thereafter.

Tumor recurrence was diagnosed as progressive and increasing by CT scan abnormalities, and confirmed by progressive and incremental increases in the standardized uptake value of a lesion, following serial PET imaging (with or without biopsy). Furthermore, locoregional recurrence was defined as disease recurrence at the surgical margin, ipsilateral hemi-thorax or regional lymph nodes. Distant metastasis was defined as metastasis to the contralateral lung and to outside of the hemi-thorax or mediastinum.

Overall survival (OS) was defined as the period from the first day of SBRT initiation to the date of mortality from any cause, or to the last follow-up visit or telephone contact prior to May 1, 2018. Progression-free survival (PFS) and local control (LC) were defined as the interval from the first day of SBRT to documented disease progression and locoregional recurrence (or mortality/follow-out), respectively. If SBRT was performed twice after surgery to treat recurrence, PFS for the first SBRT was defined as the interval between the two SBRTs.

Evaluation of toxicity. Toxicity was evaluated and graded according to the Common Terminology Criteria for Adverse Events v4.0 (52). Radiation pneumonitis (RP) was diagnosed according to clinical symptoms, including cough, shortness of breath, fever and radiologic findings in the absence of any other likely cause. All uncertain cases were discussed by the tumor board and either verified via biopsy or by consensus of the board. All hospital records, follow-up notes and images were reviewed, including all patient data regarding tumor and treatment characteristics.

Statistical analysis. The 1- and 3-year OS, RFS and LC rate were calculated using the Kaplan-Meier method; the log rank test was used for group comparisons. Survival was calculated from the end of SBRT. Cox proportional hazards models were used to assess factors associated with survival. All statistical analyses were performed using EZR version 1.36 which is a graphical interface for R (The R Foundation for Statistical Computing) (53), and the significance of univariate and multivariate analyses was set at $P<0.05$. All statistical tests were two-sided. The biologically effective dose (BED) was calculated using the BED_{10} linear-quadratic equation with an α/β value of 10 for tumors (54).

Results

Patient and treatment characteristics. A total of 61 patients (with 70 lesions among them) received chest SBRT for post-operative oligo-recurrence of NSCLC. Following exclusion of 9 patients in whom the time from surgery to SBRT was >10 years, a total of 52 patients, with 59 lesions among them, were evaluated. Patient characteristics are summarized in Table II.

Seven patients rejected surgery at their own discretion. Decreased respiratory function was the most common parameter used for selection of SBRT instead of surgery (55,56). The initial pulmonary resection was standard surgery (lobectomy with mediastinal lymph node dissection) or more in 35/52 patients (67.3%) with 41/59 lesions (69.5%), one case of which was pneumonectomy, whereas limited resection was performed for the remaining 17/52 cases (32.7%) with 18/59 lesions (30.5%). The majority of patients were unsuitable for chemotherapy, and only 8/52 (15.4%) patients received chemotherapy each before and after SBRT.

Pathological diagnosis at primary surgery was adenocarcinoma in 39/52 patients (75.0%) and squamous carcinoma in 13/52 (25.0%). Further, 9/52 patients (17.3%) exhibited pathological lymph node metastases. The epidermal growth factor receptor mutation status was detected in 4/11 of the patients in which it was tested for.

Table II. Clinicopathological characteristics.

Characteristics	Value
Patient characteristics (n=52)	
Median age at recurrence, years (range)	74 (50-86)
Sex (male:female), n	38:14
KPS (≥90:<90), n	47:5
Smoking history (yes:no), n	30:22
Median Brinkman index, n (range)	580 (0-3,000)
Operability of recurrent tumor (operable:inoperable)	7:45
Tumor characteristics (n=59)	
Median SUVmax, n (range)	4.65 (0.87-19.5)
Histological type at primary surgery (Ad:Sq), n	45:14
pT classification (pT1:pT≥2)	27:32
pN classification (pN0:pN≥1)	50:9
pM classification (pM0:pM≥1)	59:0
Type of initial surgery (lobectomy or pneumonectomy:sublobular resection), n	41:18
Median disease-free interval prior to SBRT, months	30.5
Disease-free interval prior to SBRT (<1:≥1 years), n	12:47
Disease-free interval prior to SBRT (<5:≥5 years), n	47:12
SBRT for the recurrence tumor (n=59)	Value
Median tumor size, cm (range)	1.7 (0.1-5.6)
Tumor size (≤2:>2 cm), n	34:25
Recurrent site (central:peripheral), n	20:39
Dose prescription	
Median BED_{10}, Gy (range)	112.5 (75-130.6)
55 Gy in 4 fractions (BED_{10} 130.6 Gy)), n (%)	21 (35.6%)
50 Gy in 4 fractions (BED_{10} 112.5 Gy), n (%)	18 (30.5%)
56 Gy in 7 fractions (BED_{10} 100.8 Gy), n (%)	18 (30.5%)
50 Gy in 10 fractions (BED_{10} 75 Gy), n (%)	2 (3.4%)

KPS, Karnofsky performance status; Brinkman index, cigarettes/day x years; SUVmax, maximum standardized uptake value; Ad, adenocarcinoma; Sq, squamous cell carcinoma; SBRT, stereotactic body radiotherapy; BED_{10}, biologically effective dose (using the LQ model with the α/β=10 Gy); pT, pathological T classification; pN, pathological N classification; pM, pathological M classification.

The median interval between initial resection and salvage SBRT for recurrence was 30.5 months (range, 2.0-99.0 months). A total of 20/59 lesions (33.9%) were located in the central area, which is a greater proportion than that in the whole SBRT cohort of University of Tokyo Hospital during the same period (41).

The most common fractionation schemes were 55 Gy in 4 fractions (BED_{10}=130.6 Gy; 21 lesions, 35.6%), followed by 50 Gy in 4 fractions (BED_{10}=112.5 Gy; 18 lesions, 30.5%), and 56 Gy in 7 fractions (BED_{10}=100.8 Gy; 18 lesions, 30.5%), resulting in a median BED_{10} of 112.5 Gy (Table II).

Treatment outcomes and failure patterns. The median follow-up time for all patients was 25 months (range, 3-63 months), and for surviving patients it was 35 months (range, 10-71 months). During follow-up, 18 (34.6%) patients experienced disease progression. Among these, locoregional recurrence was observed in only 4 (7.7%) patients, all of whom suffered from intrapulmonary metastasis and/or pleural dissemination, other than local recurrence. In 8 (44.4%) patients with relapse, ≥2 lesions were found at first recurrence. The most common site of recurrent lesions was the contralateral lung (8 cases; 44.4%), followed by lymph node (6 cases; 33.3%), local and bone (4 cases; 22.2%) and brain and pleural dissemination (3 cases; 16.7%).

Survival and prognostic factors. A total of 19 patients (36.5%) died during follow-up. Median OS time was 54 months (95% CI, 51-NA; Fig. 1A), while 1- and 3-year OS rates were 84.4% (95% CI, 71.3-91.9%) and 67.8% (95% CI, 51.8-79.5%), respectively (Fig. 1A). A total of 33 patients (63.5%) remained alive at the last follow-up, while 25 (48.1%) were both alive and progression-free. Median PFS time was 51 months (95% CI, 28-60), while 1- and 3-year PFS rates were 80.8% (95% CI, 67.2-89.2) and 58.7% (95% CI, 43.2-71.3), respectively (Fig. 1B). A total of 4 patients (7.7%) developed local failure. Median LC was 71 months (range, 60 months-NA). The 1- and 3-year Kaplan-Meier-estimated LC rate was 97.9% (95% CI, 85.8-99.7) and 94.9% (95% CI, 80.8-98.7), respectively (Fig. 1C).

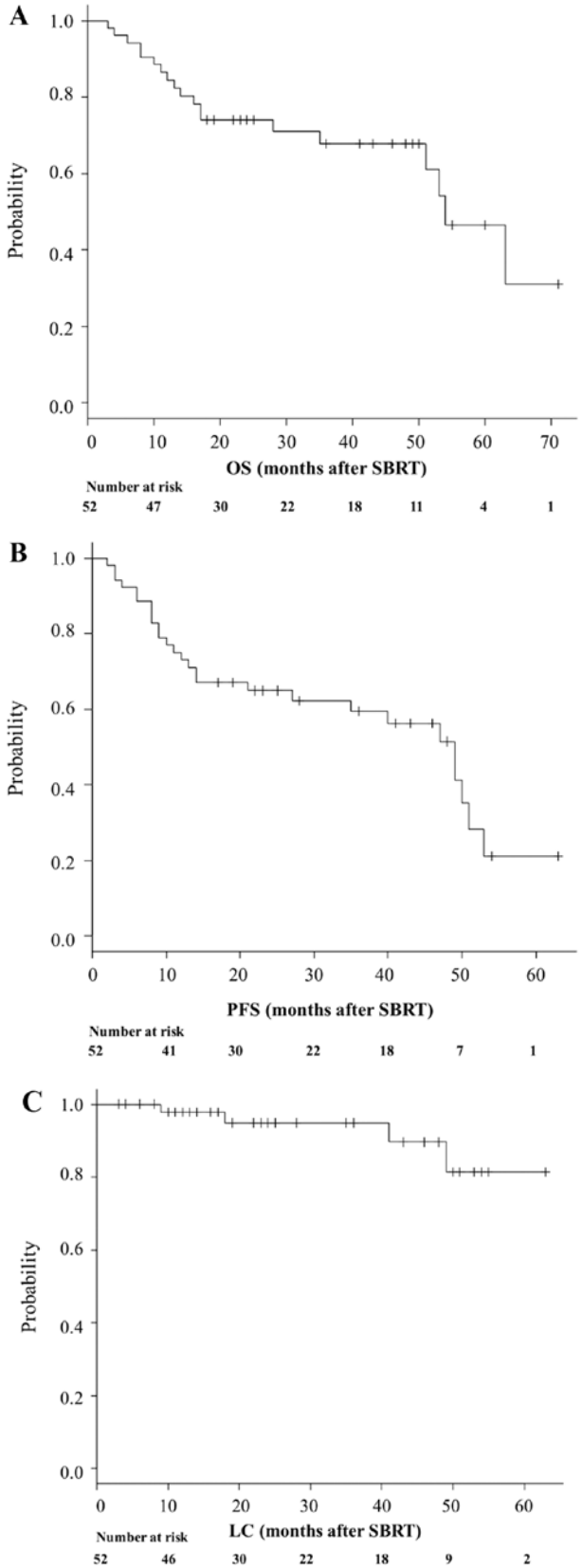

Figure 1. Prognosis of patients who underwent SBRT. Kaplan-Meier estimates of (A) OS, (B) PFS and (C) LC for patients who underwent SBRT. OS, overall survival; PFS, progression-free survival; LC, local control; SBRT, stereotactic body radiotherapy.

Predictive factors for OS. Table III provides the results of univariate and multivariate analyses for OS. Sex, possibility of re-operation, disease-free interval between initial surgery and local recurrence (≥1 vs. <1 years) and location (central or peripheral) and dose prescription were revealed to be significant prognostic factors for OS, following univariate analysis. By contrast, multivariate analysis indicated that location (central vs. peripheral; P=0.0012) and possibility of re-operation (impossible vs. possible; P=0.00092) were significant prognostic factors for OS. Fig. 2 illustrates the Kaplan-Meier curves according to these factors.

Regarding PFS, in addition to these factors, age (≥75 years; P=0.037), type of prior surgery (limited surgery; P=0.0046), diameter of the primary tumor (pT ≥2; P=0.014) and recurrent lesion (≥2 cm; P=0.039) were also significant prognostic factors.

Toxicity. In total, 9 patients (17.3%) developed grade 2 adverse events (AEs), and 4 patients (7.7%) developed grade 3 or greater AEs. Of these, two patients (3.8%) developed grade 5 AEs, meaning mortality due to toxicity. One grade 5 case was radiation pneumonitis and the second was hemoptysis. The prescribed dose for both patients was 56 Gy in 7 fractions. Further details of the two aforementioned cases have been reported by the present authors in a previous study (33).

The doses for OARs in these two cases were summarized in Table IV. In both cases, dose-restricted organs were not irradiated above the limit, but some unrestricted OARs were being given higher doses than the effort target (in other words, the indicators to achieve if possible). The other common features of the two cases were having recurrence following lung lobectomy, central lesions and presence of a smoking history.

Discussion

Post-operative recurrence of NSCLC is commonly treated using a multifaceted treatment program, including systemic therapy, as with metastatic stage IV disease (8,9). However, certain recurrent cases with local lesions alone or a limited number of metastatic lesions (termed oligo-recurrence), may occasionally be cured using localized therapy alone (11-14).

A number of studies have evaluated second resection for local recurrence or intrathoracic oligo-recurrence in patients who received surgery as initial treatment (6,57-59). Hung *et al* (6) reported 1- and 2-year post-recurrence OS rates of 48.7 and 17.6%, respectively, in their study of 74 patients with local recurrence. Notably, Kim *et al* (57) reported a 5-year OS rate after second resection of 33.4% with an operative mortality for the second resection of 5.8%. Previously, Yukiue *et al* (58) achieved 2- and 5-year OS rates after second resection of 87.8 and 62.9%, respectively. However, 9 patients (23%) exhibited serious post-operative complications and 1 (2.6%) died during surgery, raising concerns regarding the safety of the operation (58). Alternative reports on post-operative recurrence have also indicated that re-operation may represent an effective treatment for post-operative lung cancer recurrence, in certain patients in which the oncological benefits outweigh the surgical risk (14,59).

By contrast, SBRT has been recently recognized as an alternative therapy for patients with inoperable early-stage NSCLC or those who refuse surgery (26,28,31). Regarding post-operative oligo-recurrence, SBRT is not an established

Table III. Analysis of clinical and dosimetric variables associated with OS (patients, n=52; tumors, n=59).

	Univariate		Multivariate	
Variable	HR (95% CI)	P-value	HR (95% CI)	P-value
Patient				
Age at recurrences, years (≤75 vs. >75)	1.81 (0.22-1.48)	0.74		
Sex (male vs. female)	1.72 (4.31-6.90)	0.0062	3.94 (0.80-19.37)	0.091
Smoking history (yes vs. no)	1.11 (0.01-1.05)	0.55		
Initial surgery for primary NSCLC				
Histology (adenocarcinoma vs. alternative subtypes)	1.19 (0.0038-3.73)	0.23		
Extent of pulmonary resection (sublobular resection vs. lobectomy or pneumonectomy)	4.16 (0.048-3.61)	0.43		
T status (pT2 vs. pT1)	6.38 (0.10-3.93)	0.63		
Lymphatic invasion (present vs. absent)	3.51 (0.023-5.32)	0.45		
Lymph node metastasis (pN≥1 vs. pN0)	1.37 (0.73-2.56)	0.080		
Disease-free interval, years (≥1 vs. <1)	4.76 (1.99-1.14)	0.017	0.92 (4.26-19.52)	0.062
Disease-free interval, years (≥5 vs. <5)	2.50 (0.24-2.55)	0.44		
SBRT for recurrent tumors				
Possibility of re-operation (impossible vs. possible)	2.46 (29.07-2.08)	<0.0010	9.53 (2.51-36.15)	<0.001
Tumor size (≤2 cm vs. >2 cm)	6.05 (0.043-8.52)	0.71		
Tumor size (≤3 cm vs. >3 cm)	2.38 (0.0058-9.77)	0.45		
SUVmax (≥5.0 vs. <5.0)	1.57 (0.17-1.43)	0.69		
Location (lower or mediastinum vs. upper or middle)	1.18 (0.29-4.86)	0.82		
Central lesion (central vs. peripheral)	1.22 (0.37-4.050)	0.011	5.51 (1.96-15.49)	0.0012
Dose prescription (55 Gy 4 Fr vs. the others (50 Gy, 4 Fr; 56 Gy, 7 Fr; 50 Gy, 10 Fr)	2.52 (2.10-3.00)	0.011	0.03 (0.27-2.31)	0.23
Chemotherapy after SBRT (present vs. absent)	7.97 (0.035-1.82)	0.89		

P-values were calculated using *Cox* regression analysis for univariate and multivariate analysis. OS, overall survival; HR, hazard ratio; SBRT, stereotactic body radiotherapy; SUVmax, maximum standardized uptake value; Fr, fraction.

standard therapy and no large prospective clinical trials have been conducted. Takeda *et al* (60) analyzed the outcomes of SBRT in 23 patients with isolated post-surgical local recurrence. LC and OS rates were revealed to be 94.7 and 86.8% at 1 year and 84.0 and 76.4% at 2 years, respectively. Regarding AEs, 3 patients (13.0%) suffered from RP grade ≥3 and the authors concluded that SBRT, when used to treat isolated postsurgical local recurrence, achieves high LC with limited toxicity (60). Nishiyama *et al* (61) subsequently investigated 41 patients with medically inoperable diseases who underwent SBRT for second pulmonary nodules arising from different types of cancer and reported that grade 2 RP AEs occurred in five patients and one succumbed to grade 5 RP.

In the present study, the 3-year OS, PFS and LC rates of all included patients were 67.8, 58.7 and 94.9%, respectively, and these results are comparable not only to previous studies on SBRT (4,16,17), but also on re-operation. Considering that More than two thirds of patients (≥67.3%) in the present analysis were regarded as ineligible for surgery or chemotherapy, the survival outcomes for salvage SBRT as a therapeutic technique are promising.

Additionally, it was revealed that the major failure pattern after radical radiotherapy was distant metastasis. This finding is consistent with the results of a study by Kelsey *et al* (62), in which 50% of patients developed distant metastases following salvage radiotherapy. SBRT, which can achieve good local control, may be expected to improve recurrence-free survival by combination with recently developed immunotherapy.

Several retrospective studies have investigated prognostic factors for OS time in patients with local recurrence (62-64); the reported factors associated with prolonged OS time were female, young age, long disease-free interval between initial surgery and local recurrence (5,28,62-65), early stage of primary tumor (5,66) and high prescribed radiation dose (67,68). In the present study, female and disease-free interval were significantly associated with OS time only in univariate analysis. In multivariate analysis, central lesions and re-operative lesions (operative refusal by patients) were significantly associated with poor survival prognosis.

Similar to previous findings (47-49,69-72), central lesions exhibited a worse prognosis than peripheral lesions in the present study. One possible reason for this may be an increase in the number of AEs, which are associated with central SBRT (44,46). Among the included patients, all 4 cases of AEs graded ≥3 (including a grade 5 case) occurred in patients with central lesions.

Additionally, relatively low doses for central tumors may also contribute to the inferior outcomes; higher radiation

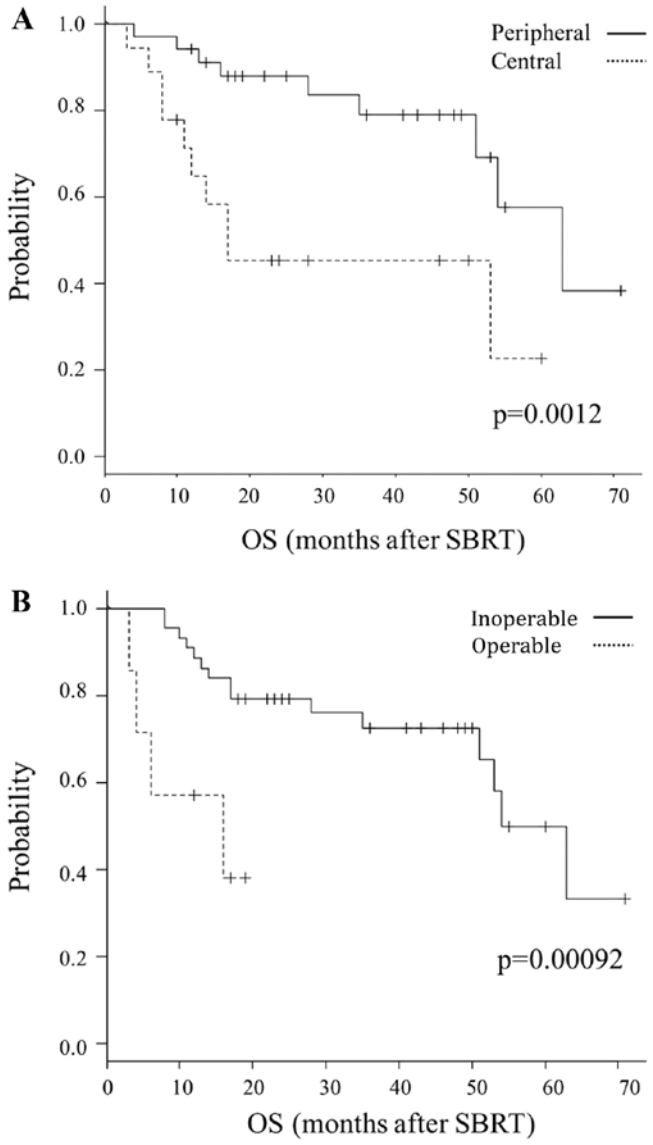

Figure 2. Comparison of OS by prognostic factors. OS according to (A) tumor location (peripheral vs. central) and (B) possibility of re-operation (operable vs. inoperable). OS, overall survival; SBRT, stereotactic body radiotherapy.

doses have been reported to be associated with prolonged OS time, even in patients with post-operative recurrence (67,68), although there was no indication of a survival difference between high and low BED (above and below BED_{10} ≤130.6), in the present study. It was concluded that the cause was that most patients treated at University of Tokyo Hospital have been treated with BED_{10} 100 Gy or higher. Notably, in a study by Kim *et al* (4), it was suggested that determining whether increasing radiation alone improves survival may be difficult in a situation where high doses were administered and irradiation technology was developed (4).

In the present study, patients who underwent sublobular resection exhibited an improved prognosis compared with those who received lobectomy or pneumonectomy. The prognosis of initial surgery itself is considered to be improved with lobectomy compared with sublobular resection (73,74), indicating that the results are reversed in cases of post-operative oligo-recurrence. The current findings may be a result of the limited number of cases that were considered as appropriate (based on invasion characteristics) reduce the ablation range, or even the small population size, especially in the operable group.

In the present study, the irradiated dose for the OARs of two patients with grade 5 AEs were reviewed. As described in the results section, the dose delivered to restricted OARs in these two cases did not exceed the constraints, but certain

Table IV. Irradiated dose for organs at risk of two patients who exhibited grade 5 AEs.

OAR	Patient 1	Patient 2
ITV, cm^2	5.0	9.6
PTV, cm^2	19.4	33.0
Lung	5.0	9.6
V5 (%)	16.6	31.2
V10 (%)	6.1	22.8
V20 (%)	3.8	11.3
Mean (cGy)	355.8	703.9
Trachea		
Max (cGy; point)	628.7	162.4
Max (cGy; 5cc)	226.1	122.3
Carina		
Max (cGy; point)	6,109.3	4,644.6
Max (cGy; 5cc)	-	489.3
Esophagus		
Max (cGy; point)	3,402.0	5,364.6
Max (cGy; 5cc)	1,809.0	1,223.2
Pulmonary artery		
Max (cGy; point)	5,583.2	4,654.9
Max (cGy; 5cc)	226.1	1,467.8
Pulmonary veins		
Max (cGy; point)	2,412.2	5,610.4
Max (cGy; 5cc)	-	-
Aorta		
Max (cGy; point)	2,818.5	3,834.4
Max (cGy; 5cc)	2,366.8	2477
Superior vena cava		
Max (cGy; point)	3,641.2	5,770.8
Max (cGy; 5cc)	2,788.9	3,914.3
Heart		
Mean (cGy)	274.3	879
V_{30} (%)	1.3	5.7
Spine		
Max (cGy; point)	1,387.5	2,034.8
Chest wall		
Max (cGy; point)	-	4,084.6

Dose prescription; 56 Gy in 7 fractions, Patient1; hemoptysis, Patient 2; pneumonitis. AE, adverse events; OAR, organ at risk; ITV, internal target volume; PTV, planning target volume; V5/10/20/30, percentage of the volume of an organ receiving 5, 10, 20 and 30 Gy; 5cc, cubic centimeter; cGy, centi Gy.

unrestricted OARs were being treated with a higher dosage than the effort target (48). The present results indicated dose restrictions on certain OARs, such as blood vessels and trachea, which have not currently been restricted.

In addition, patient factors, such as smoking history (75) and interstitial lung disease (76,77), have been reported as risk factors too. The occurrence of severe AEs may be associated with the clinicopathological factors of patients and tumors as well as the radiation dose. All these factors act synergistically and it is difficult to accurately quantify the relative contribution of each factor. Although a conclusion was not reached in the present study, risk stratification combining both patient and radiation factors should be performed in future research. Collecting and analyzing data of serious AEs is difficult for a single institution; thus, risk analyses will require multi-center, long-term data accumulation to improve their statistical power.

The present study had several limitations. Primarily, it was conducted at a single institution and using a retrospective design. Therefore, a degree of intrinsic bias may remain, and information regarding clinical examinations (respiratory function, PET and status of gene expression) was insufficient in some cases, so that it was not possible to examine the associations between treatment outcomes. Additionally, the number of patients was low, which may have limited the statistical confidence of the results. Further research is necessary, including prospective studies with a large sample size, in order to support the conclusions of the present study. Finally, it is difficult to distinguish between post-operative recurrence and multiple primary lung cancers, even when pathological examinations are performed.

Furthermore, it is difficult to compare AE risk in cases of different prescriptions, because dose division for each dose restriction has not yet been established. This is an issue to be clarified in future research.

The present study suggested that salvage SBRT represents a promising treatment for patients with NSCLC exhibiting post-operative locoregional or intrathoracic oligo-recurrence, particularly in LC. Independent risk factors associated with a decreased OS were a central lesion and the possibility of re-operation. The AEs were also considered as tolerable. However, further research is required on the selection of subjects and stratification by risk factors.

Acknowledgements

The authors would like to thank Dr Libby Cone for editing the drafts of this manuscript.

Funding

The present study was supported by a Grant-in-Aid from Japan Society for the Promotion of Science, KAKENHI JP Scientific Research (C) (grant no. 18K07667).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

SA, HY, WT, JNa, MS, OA and KeN participated in research design. Acquisition of the data was performed by SA, TI, SO and TK. Evaluation of the images was conducted by SA, KaN, TO and YN. Interpretation of the data was conducted by SA, MA and JNi. The manuscript was prepared by SA, HY and WT, and written by SA and HY. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Research Ethics Committee, University of Tokyo Hospital [Tokyo, Japan; 3372-(3)/2016]. Written informed consent for data collection and analysis was obtained from the respective patients.

Patient consent for publication

Patients provided written consent for the publication of their data.

Competing interests

The authors declare that they have no competing interests.

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