Treatment and Prognosis of Isolated Local Relapse after Stereotactic Body Radiotherapy for Clinical Stage I Non–Small-Cell Lung Cancer

Importance of Salvage Surgery

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Introduction: Many efforts have been made to detect local relapse (LR) in the follow-up after stereotactic body radiotherapy (SBRT) for non–small-cell lung cancer (NSCLC) although limited data are available on its treatment and prognosis. We aimed to characterize treatment options and clarify long-term outcomes of isolated LR after SBRT for patients with clinical stage I NSCLC.

Methods: We reviewed our institutional database in search of patients with isolated LR after SBRT for clinical stage I NSCLC at our institution between 1999 and 2013. Patient characteristics were compared with Mann–Whitney U test, χ² test, or Fisher’s exact test as appropriate. Survival outcomes were estimated with Kaplan–Meier method. Potential prognostic factors were investigated using Cox proportional hazard model.

Results: Of 308 patients undergoing SBRT for clinical stage I NSCLC, 49 patients were identified to have isolated LR. Twelve patients underwent salvage surgery, none underwent radiotherapy, and eight patients received chemotherapy, whereas 29 patients received best supportive care. No patient characteristic except operability was significantly related with patient selection for LR treatments. Five-year overall survival (OS) rate of the whole cohort was 47.9% from SBRT and 25.7% from LR. Salvage surgery was associated with improved OS after LR (p = 0.014), and 5-year OS for patients undergoing salvage surgery was 79.5% from LR.

Conclusions: It was confirmed that our patient selection for salvage surgery for isolated LR was associated with favorable survival outcomes. Operability based on multidisciplinary conferences, rather than measurable patient characteristics, is essential for appropriate patient selection for salvage surgery.

Key Words: Non–small-cell lung cancer, Surgery, Radiotherapy, Chemotherapy.

DOI: 10.1097/JTO.0000000000000662
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ISSN: 1556-0864/15/1011-1616

Although video-assisted thoracoscopic surgery (VATS) lobectomy offers favorable survival outcome in operable patients,1 stereotactic body radiotherapy (SBRT) or stereotactic ablative radiotherapy has been increasingly recognized as a favorable alternative to surgical resection for early-stage non–small-cell lung cancer (NSCLC) in patients who are not ideal operative candidates.2–4

The rate of local relapse (LR) after SBRT for stage I NSCLC is 4% to 11.9% at 3 years5–7 and 10.5% to 28.3% at 5 years.8,9 Many efforts have been made to identify patients at higher risk of LR and, for example, previously reported risk factors of LR after SBRT included a larger tumor size10 and a lower retention index of fluorodeoxyglucose-positron emission tomography (FDG-PET).11 Moreover, to allow early detection of LR and potentially cure LR, high-risk radiologic changes in the follow-up have been identified and discussed extensively.12–14

There is a dearth of data on management of isolated LR after SBRT. Unlike local recurrence after surgical resection of NSCLC, for which local treatments (surgery or radiotherapy) are indicated,15,16 LR after SBRT for NSCLC presents a dilemma because local treatments for this patient cohort are challenging: most SBRT patients are inoperable and repeating SBRT or offering conventional radiotherapy in the same area is a safety concern and increases the risk of toxicity. One study showed that repeat SBRT for LR was safe17 and achieved reasonable local control although long-term survival outcomes remain unknown. Likewise, salvage surgery for isolated LR can be undertaken at low risk in operable patients,18–21 whereas long-term outcomes have remained to be determined. To date, no survival outcomes were reported in patients treated with chemotherapy or best supportive care (BSC) for isolated LR.

Salvage treatments for LR present a challenge; however, a portion of this patient cohort might be effectively treated, and favorably long-term survival may be achieved. In this
study, we aim to characterize treatment options and clarify long-term survival outcome in patients with isolated LR after SBRT for clinical stage I NSCLC.

**PATIENTS AND METHODS**

Approval of this study was granted by Institutional Review Board of Kyoto University Hospital. The requirement for patient consent was waived. Retrospective chart review was performed on the prospectively maintained database in Department of Radiation Oncology and Image-Applied Therapy and Department of Thoracic Surgery at Kyoto University Hospital.

Included in this study were patients who are found to have isolated LR in the follow-up after undergoing SBRT for a previously untreated, solitary, and peripheral clinical stage I (T1N0M0 or T2aN0M0) NSCLC and negative lymph node staging with PET-computed tomography (CT) at Kyoto University Hospital between January 1999 and December 2013. Selection of patients with clinical stage I NSCLC was based on American Joint Committee of Cancer 7th edition staging manual.

Patients found to have LR with simultaneous regional (mediastinal lymph node) or distant relapse and patients found to have LR after regional or distant relapse were excluded. Patients with the initial tumor diameter larger than 5 cm, multiple synchronous lung cancers, typical or atypical carcinoid tumors, and small-cell lung cancer were also excluded.

For SBRT, the patient was immobilized with a stereotactic body frame (Elekta, Stockholm, Sweden). The internal target volume was determined considering CT with a slow scan technique or 4D CT technique and tumor motion assessed by radiograph fluoroscopy. The planning target volume was defined as the internal target volume plus 5-mm margin. Irradiation was performed with 6-MV X-ray beams from a linear accelerator (Clinac 2300 C/D; Varian Medical Systems till April 2008: Novalis; BrainLab AG, Munich, Germany, thereafter) in multiple noncoplanar static ports.

Medical comorbidity was assessed by Charlson comorbidity index, which has been validated in patients undergoing either surgery or SBRT for lung cancer. Overall survival (OS) was calculated from the date of start of initial SBRT and from LR to death due to any cause or the last follow-up. Cancer-specific survival (CSS) was calculated from the date of start of initial SBRT and from LR to death due to recurrence of the treated NSCLC or to the last follow-up. All patients were followed up with physical examination and chest CT and/or FDG-PET (if indicated), every 2 to 4 months in the first posttreatment year, every 6 months in the second to the fifth year, and annually thereafter. LR was defined primarily as an enlargement of the local tumor on CT that continued for at least 6 months or as a maximal standardized uptake value (SUVmax) on FDG-PET greater than 5 at 6 months, occasionally with histologic confirmation. FDG-PET was obtained at the discretion of the radiologist.

**Statistical Analysis**

Continuous variables are reported as a median. Patients’ characteristics were compared using Mann–Whitney U test, \( \chi^2 \) test, or Fisher’s exact test as appropriate. The median follow-up time was calculated using the reverse Kaplan–Meier method for potential follow-up. OS and CSS were estimated with Kaplan–Meier method. Potential prognostic factors of OS and CSS from LR were analyzed with Cox proportional hazard models. The \( p \) values less than 0.05 were considered statistically significant. Variables with a significant \( p \) value in univariate analysis were included in multivariate analysis. We used JMP Version 11.0.1 (copyright 2008, SAS Institute Inc., Cary, NC) for statistical analysis.

**RESULTS**

Between 1999 and 2013, 308 patients underwent SBRT for clinical stage I NSCLC, and of these, 49 patients were found to have isolated LR during at least 1 year of follow-up. Seventeen patients (34%) of 49 patients in this study had histologically verified LR. Twelve patients underwent salvage surgery, none underwent radiotherapy, and eight patients received chemotherapy, whereas 29 patients received BSC. For reference, the median OS from SBRT of the total SBRT-treated cohort \((N = 308)\) was 48.8 months, and 5-year OS from SBRT was 43.3%. Of 308 patients, 86 were found to have distant relapse. Pretreatment patient characteristics at LR are shown in Table 1. A significant difference was found only in operability among treatment groups. Follow-up was complete in all 49 patients. The median follow-up periods for the whole patient cohort were 6.7 years from SBRT and 4.3 years from LR.

**Salvage Surgery for Isolated LR**

Salvage surgery was performed in 12 patients. Patient demographics and perioperative outcomes undergoing salvage surgery are summarized in Table 2. Nine patients were considered operable at the initial evaluation but rejected surgery upfront. Three patients were initially (at SBRT) considered inoperable for the following reasons. One patient was considered inoperable from a surgical standpoint (a history of ipsilateral thoracotomy), another from an oncological standpoint (a previous stage IV NSCLC under chemotherapy), and the other from a medical standpoint (multiple organ failures). All the three patients were considered operable at reevaluation.

Preoperative staging was performed with PET in four patients (33%), PET and brain magnetic resonance imaging in five patients (41.7%), PET and endobronchial ultrasound in one patient (8.3%; because of high SUV of mediastinal lymph nodes), and no information regarding preoperative staging was available in two patients (16.7%). In two patients, high uptake was noted in mediastinal lymph nodes on PET; in one of them, endobronchial ultrasound–transbronchial needle aspiration turned out negative on the PET-positive lymph node and the positive lymph node was considered as inflammatory in the other (biopsy was not done). Pulmonary function test was repeated preoperatively in all surgical patients. Vital capacities and forced expiratory volumes in 1 second were not statistically different from those obtained before SBRT (values not shown, \( p = 0.61 \)).

**Characterize Treatment Options for Patients with NSCLC**

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The surgical approach was determined at the surgeon’s discretion. The VATS approach was initially attempted in six patients (50%), but conversion to open thoracotomy was necessitated because of intraoperative bleeding in one. The bronchial stump was covered with pericardial fat pad in two patients (16.7%) and intercostal muscle in one patient (8.3%). Mediastinal lymph node dissection was performed in all patients but one. Postoperatively, prolonged air leak (>5 d) was seen in three patients (25%), but otherwise no postoperative complication was noted. Two
patients (16.7%) with positive mediastinal lymph nodes on preoperative PET were positive on mediastinal lymph nodes on final pathology and were offered adjuvant chemotherapy (cisplatin and vinorelbine, two and four cycles, respectively), 5 and 8 weeks postoperatively, respectively. Viable tumor cells were found in the specimens of all 12 patients.

Chemotherapy as Systemic Antitumor Therapy for Isolated LR

Chemotherapy as systemic antitumor therapy was performed in eight patients: cytotoxic chemotherapy only in three patients and gefitinib in five patients. Patient demographics and survival outcomes receiving cytotoxic chemotherapy only or gefitinib are summarized in Table 3. Three patients (patients F, G, and H) were considered operable both at SBRT and at LR. Among five patients on gefitinib, two patients (patients D and H) were found to have epidermal growth factor receptor (EGFR) gene mutations: an exon 19 E746-A750 deletion in one and an exon 21 L858R mutation in the other. No information on EGFR status was obtained in the other three patients.

Treatment Options for Patients Who Were Operable at SBRT

Seventeen of 49 patients in this study were considered operable at initial SBRT. Of them, nine patients underwent salvage surgery at LR, five persistently rejected salvage surgery, preferring cytotoxic chemotherapy or gefitinib (N = 3) or BSC (N = 2). The rest of the three patients became inoperable at LR because of aggravated performance status (N = 2) or a postoperative complication of interim bladder cancer (N = 1). Survival outcomes in patients (N = 5) who were operable at SBRT and received BSC at LR were summarized in Table 4.

Survival Outcomes

OS from LR and that from SBRT are shown in Figure 1A and B, respectively. Five-year OS of the whole patient cohort, patients undergoing salvage surgery, those
undergoing chemotherapy, and those receiving BSC was 47.9% (95% confidence interval [CI]: 32.9–62.9), 79.5% (95% CI: 44.6–94.9), 60.0% (95% CI: 25.4–86.9), and 31.5% (95% CI: 13.6–49.6), from initial SBRT. Median OS of the whole patient cohort, patients undergoing salvage surgery, those undergoing chemotherapy, and those receiving BSC was 50.8 months, not reached, 68.5 months, and 31.9 months, from initial SBRT.

Five-year OS of the whole patient cohort, patients undergoing salvage surgery, those undergoing chemotherapy, and those receiving BSC was 25.7% (95% CI: 11.1–40.3), 79.5% (95% CI: 44.6–94.9), 0%, and not reached, from LR. Median OS of the whole patient cohort, patients undergoing salvage surgery, those undergoing chemotherapy, and those receiving BSC was 25.0, 82.7, 43.9, and 12.0 months, from LR.

CSS from LR and that from SBRT are shown in Figure 2A and B, respectively. Five-year CSS of the whole patient cohort, patients undergoing salvage surgery, those undergoing chemotherapy, and those receiving BSC was 56.9% (95% CI: 42.2–71.7), 90.9% (95% CI: 56.1–98.7), 75.0% (95% CI: 37.7–93.7), and 36.1% (95% CI: 16.7–55.4) from initial SBRT. Median CSS of the whole patient cohort, patients undergoing salvage surgery, those undergoing chemotherapy, and those receiving BSC was 29.7, 82.7, 43.9, and 12.0 months, from LR.

Hazard ratios, 95% confidence intervals, and p values of potential prognostic factors of survival outcomes (OS and CSS) from LR in univariate and multivariate analyses are shown in Table 5. In multivariate analysis, salvage surgery was a significant prognostic factor of OS and CSS from LR.

**DISCUSSION**

SBRT is a reasonable alternative to surgical resection for early-stage NSCLC in medically compromised or inoperable patients.2,3 Our previous studies suggested that the role of SBRT in low-risk operable patients tolerating a lobectomy has remained to be determined,25 whereas SBRT may be a promising alternative in patients at high risk for a lobectomy,1 which is consistent with other international data.5,6

Any improvement in salvage treatments for relapse after SBRT can contribute to more favorable survival outcomes in patients undergoing SBRT for early-stage NSCLC. The most frequent pattern of relapse after SBRT for early-stage NSCLC is reported to be distant with LR being less common than regional or distant relapse.9,26,27 The definition and detection of LR seem more challenging than detection of regional or distant relapse because LR is seen in previously irradiated areas. The definition of LR varies across institutions. Biopsy confirmation is not a common practice (the reported rate of biopsy confirmation in presumable LR ranges from 17.6% to

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**TABLE 3.** Demographics and Outcomes in Patients Undergoing Chemotherapy (Cytotoxic Chemotherapy Only or Gefitinib) for Isolated Local Relapse after SBRT

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Sex</th>
<th>Histology</th>
<th>CCI</th>
<th>DFI (mo)</th>
<th>Treatment</th>
<th>Toxocities</th>
<th>Subsequent Tx</th>
<th>Survival from Local Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 73</td>
<td>M</td>
<td>Ad</td>
<td>3</td>
<td>24.5</td>
<td>Gefitinib</td>
<td>NI</td>
<td>NI</td>
<td>Cancer death (44 mo)</td>
</tr>
<tr>
<td>B 78</td>
<td>F</td>
<td>Ad</td>
<td>4</td>
<td>55.1</td>
<td>Gefitinib</td>
<td>Eczema</td>
<td>PEM</td>
<td>Cancer death (24 mo)</td>
</tr>
<tr>
<td>C 75</td>
<td>M</td>
<td>Sq</td>
<td>2</td>
<td>12.8</td>
<td>CBDCA + PTX</td>
<td>None</td>
<td>DTX, VNR, Erlotinib</td>
<td>Cancer death (29 mo)</td>
</tr>
<tr>
<td>D 78</td>
<td>F</td>
<td>Ad</td>
<td>0</td>
<td>41.0</td>
<td>Gefitinib</td>
<td>None</td>
<td>no</td>
<td>Alive (39 mo)</td>
</tr>
<tr>
<td>E 66</td>
<td>M</td>
<td>UK</td>
<td>0</td>
<td>20.8</td>
<td>DTX</td>
<td>NI</td>
<td>NI</td>
<td>Noncancer death (38 mo)</td>
</tr>
<tr>
<td>F 89</td>
<td>F</td>
<td>Ad</td>
<td>1</td>
<td>108.3</td>
<td>Gefitinib</td>
<td>NI</td>
<td>NI</td>
<td>Cancer death (51 mo)</td>
</tr>
<tr>
<td>G 77</td>
<td>M</td>
<td>Sq</td>
<td>0</td>
<td>8.8</td>
<td>DTX</td>
<td>BM suppression</td>
<td>NI</td>
<td>Cancer death (22 mo)</td>
</tr>
<tr>
<td>H 78</td>
<td>M</td>
<td>Ad</td>
<td>0</td>
<td>20.9</td>
<td>Gefitinib</td>
<td>None</td>
<td>No</td>
<td>Alive (25 mo)</td>
</tr>
</tbody>
</table>

SBRT, stereotactic body radiotherapy; His, histology; CCI, Charlson comorbidity index; DFI, disease-free interval; Tx, treatment; inop, inoperable; His, history; M, male; F, female; Ad, adenocarcinoma; Sq, squamous cell carcinoma; UK, unknown; NI, no information; CBDCA, carboplatin; PTX, paclitaxel; DTX, docetaxel; BM, bone marrow; PEM, pemetrexed; VNR, vinorelbine.

**TABLE 4.** Demographics and Survival Outcomes in Patients (N = 5) Who Were Operable at SBRT but Received Best Supportive Care at LR

<table>
<thead>
<tr>
<th>Age/Sex</th>
<th>DFI (mo)</th>
<th>CCI</th>
<th>Operability at LR</th>
<th>Comment</th>
<th>Survival from SBRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>78/male</td>
<td>28</td>
<td>1</td>
<td>Inoperable</td>
<td>Performance status aggravated</td>
<td>Died, 29 mo</td>
</tr>
<tr>
<td>76/male</td>
<td>29</td>
<td>1</td>
<td>Operable</td>
<td>Rejected surgery again</td>
<td>Died, 37 mo</td>
</tr>
<tr>
<td>79/male</td>
<td>15</td>
<td>3</td>
<td>Inoperable</td>
<td>Another malignancy</td>
<td>Died, 16 mo</td>
</tr>
<tr>
<td>81/female</td>
<td>7</td>
<td>1</td>
<td>Inoperable</td>
<td>Performance status aggravated</td>
<td>Died, 37 mo</td>
</tr>
<tr>
<td>85/female</td>
<td>31</td>
<td>1</td>
<td>Operable</td>
<td>Rejected surgery again</td>
<td>Alive, 47 mo</td>
</tr>
</tbody>
</table>

SBRT, stereotactic body radiotherapy; DFI, disease-free interval; CCI, Charlson comorbidity index; LR, local relapse.
87.5%\(^{13,28–30}\), or not reported in other studies.\(^{31–35}\) LR is usually diagnosed by radiological studies, and PET-CT is more specific in this setting than CT alone.\(^{13,28,29,32}\) On PET, an \(\text{SUV}_{\text{max}}\) of greater than 5 is more likely associated with LR rather than radiation pneumonitis after SBRT,\(^{14,28,30}\) and this association has been validated in another study.\(^{11}\)

As discussed above, many efforts have been made to detect LR after SBRT; however, little is known about long-term outcomes of salvage treatments or BSC. Any salvage treatment for LR would be challenging for presumably compromised patients undergoing SBRT. Reported percentages of patients with LR after SBRT who undergo salvage treatment range widely from 24% to 100%.\(^{17,20}\) Previously reported salvage treatments for isolated LR after SBRT for early-stage NSCLC included salvage surgery\(^{18–21}\) and repeated SBRT.\(^{17}\)

**FIGURE 1.** Kaplan–Meier estimates of overall survival (OS) from local relapse (LR) (A) and from SBRT (B). Black solid line, patients undergoing salvage surgery; grey solid line, those undergoing chemotherapy; black dotted line, those receiving best supportive care.

**FIGURE 2.** Kaplan–Meier estimates of cancer-specific survival (CSS) from local relapse (LR) (A) and from SBRT (B): Black solid line, patients undergoing salvage surgery; grey solid line, those undergoing chemotherapy; black dotted line, those receiving best supportive care.
By comparing patient demographics and tumor characteristics between salvage treatment groups, we attempted to identify significant measurable factors that may guide treatment. The only significant preoperative factor was operability at SBRT and at LR. However, operability is an unmeasurable factor difficult to define and presumably a factor that largely derives from multidisciplinary conferences between radiation oncologists and thoracic surgeons. It should be emphasized that operability be discussed multiple times, not only at SBRT but also at LR because operability is not always constant or fixed as in our series. In our series, 25% of the patients undergoing salvage surgery had a bronchial stump coverage at different standpoints but became operable at reevaluation. Conversely, as in our patients, a portion of operable patients at SBRT can become inoperable at LR, which is inevitable over the course of time.

One technical factor that makes us hesitant to proceed with salvage surgery is potential intrapleural adhesions that are presumably derived from SBRT and may preclude a minimally invasive approach, among previous reports on salvage surgery after SBRT. There was no intrapleural adhesion in either case in Neri et al.'s report, there is no description on adhesions in Taira et al.'s report, or intrapleural adhesions were noted in two patients (16.7%) in our series, whereas adhesions were reported in all patients in Allibhai et al.'s study. In our series, 5 of 12 (41.7%) of patients were operated on through VATS in contrast to the report of Allibhai et al. Selection of the surgical approach in our series was largely dependent on the surgeon's discretion, and our findings suggest that minimally invasive thoracic surgery or VATS seems feasible at least in a subset of patients undergoing salvage surgery after SBRT, which would be an advantage in perioperative outcomes, especially in cardiopulmonary-compromised patients when comparable with open thoracotomy. Previous irradiation can delay bronchial healing after anatomical pulmonary resections, but no information on coverage of the bronchial stump in salvage surgery was available in previous studies. In our series, 25% of the patients undergoing salvage surgery had a bronchial stump coverage at the discretion of the surgeon. A majority of patients undergoing induction therapy and surgical resection for advanced NSCLC had a bronchial stump coverage to prevent bronchopleural fistulae, but whether bronchial stump coverage is required in salvage surgery remains unknown given the differences in time since irradiation and peripheral locations of tumors.

The absence of perioperative mortality and the low perioperative morbidity rate of 25% in our study suggest that upfront SBRT followed by salvage surgery in cases of LR is a viable option in patients with multiple comorbidities or in those hesitant to undergo primary surgery. The short-term outcomes of salvage surgery seem comparable to those of lobectomy for NSCLC as a first treatment and far better than those of reoperative pulmonary resection. Despite the small sample size, long-term survival outcomes of our surgical patients seem comparable to those of lobectomy as a first treatment.

Salvage surgery plays a diagnostic role as well to judge if radiologic features really reflect a local recurrence after SBRT because comprehensive histopathological examination of the whole tumor (to detect viable cells) is only possible after surgical resection of the tumor. All our patients undergoing

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**TABLE 5.** Hazard Ratios and 95% CI of Potential Prognostic Factors of OS and CSS from LR in Univariate and Multivariate Analysis

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>P Value</th>
<th>HR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at LR (per 1 year)</td>
<td>1.05</td>
<td>1.00–1.10</td>
<td>0.043</td>
<td>1.06</td>
<td>1.00–1.13</td>
<td>0.038</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.07</td>
<td>0.44–1.33</td>
<td>0.73</td>
<td>1.007</td>
<td>0.57–1.52</td>
<td>0.069</td>
</tr>
<tr>
<td>Disease-free interval (per 1 year)</td>
<td>1.06</td>
<td>0.75–1.08</td>
<td>0.42</td>
<td>1.65</td>
<td>1.023–1.84</td>
<td>0.014</td>
</tr>
<tr>
<td>Tumor histology (Ad vs. non-Ad)</td>
<td>1.06</td>
<td>0.27–1.22</td>
<td>0.21</td>
<td>4.1</td>
<td>0.85–15.9</td>
<td>0.08</td>
</tr>
<tr>
<td>Initial tumor size</td>
<td>1.02</td>
<td>0.97–1.07</td>
<td>0.39</td>
<td>1.02</td>
<td>0.97–1.07</td>
<td>0.39</td>
</tr>
<tr>
<td>Tumor location (upper and middle vs. lower lobes)</td>
<td>0.53</td>
<td>0.24–1.22</td>
<td>0.13</td>
<td>0.66</td>
<td>0.27–1.79</td>
<td>0.40</td>
</tr>
<tr>
<td>Performance status (2–3 vs. 0–1)</td>
<td>1.1</td>
<td>0.38–1.61</td>
<td>0.74</td>
<td>1.01</td>
<td>0.1–1.37</td>
<td>0.97</td>
</tr>
<tr>
<td>Charlson comorbidity index (per one)</td>
<td>1.06</td>
<td>0.78–1.31</td>
<td>0.67</td>
<td>1.006</td>
<td>0.69–1.29</td>
<td>0.97</td>
</tr>
<tr>
<td>Vital capacity (per 1%)</td>
<td>0.99</td>
<td>0.98–1.02</td>
<td>0.68</td>
<td>1.007</td>
<td>0.99–1.03</td>
<td>0.51</td>
</tr>
<tr>
<td>FEV1 (per 1%)</td>
<td>0.99</td>
<td>0.96–1.02</td>
<td>0.50</td>
<td>1.004</td>
<td>0.71–1.04</td>
<td>0.80</td>
</tr>
<tr>
<td>Smoking history (never vs. current)</td>
<td>1.96</td>
<td>0.33–37.4</td>
<td>0.50</td>
<td>1.36</td>
<td>0.20–26.9</td>
<td>0.94</td>
</tr>
<tr>
<td>Pack-year (per 1)</td>
<td>1.01</td>
<td>0.99–1.02</td>
<td>0.20</td>
<td>1.01</td>
<td>0.99–1.02</td>
<td>0.057</td>
</tr>
<tr>
<td>Inoperable</td>
<td>2.36</td>
<td>1.29–3.94</td>
<td>0.0001</td>
<td>1.83</td>
<td>1.27–2.57</td>
<td>0.03</td>
</tr>
<tr>
<td>Treatment (nonsurgical vs. surgery)</td>
<td>2.23</td>
<td>1.58–3.2</td>
<td>&lt;0.0001</td>
<td>36.3</td>
<td>6.04–740</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Multivariate analysis**

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>P Value</th>
<th>HR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at LR (per 1 year)</td>
<td>1.03</td>
<td>0.97–1.08</td>
<td>0.31</td>
<td>1.05</td>
<td>0.99–1.34</td>
<td>0.0095</td>
</tr>
<tr>
<td>Inoperable</td>
<td>1.36</td>
<td>0.83–2.04</td>
<td>0.19</td>
<td>1.06</td>
<td>0.51–1.80</td>
<td>0.84</td>
</tr>
<tr>
<td>Disease-free interval (per 1 year)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1.3</td>
<td>1.12–1.91</td>
<td>0.0033</td>
</tr>
<tr>
<td>Treatment (nonsurgical vs. surgery)</td>
<td>2.23</td>
<td>1.58–3.2</td>
<td>0.014</td>
<td>63</td>
<td>6.2–218.1</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval; LR, local relapse; LLL, left lower lobe; LUL, left upper lobe; RUL, right upper lobe; FEV1, forced expiratory volume in one second; BSC, best supportive care; Chemo, chemotherapy; NA, not applicable; OS, overall survival; CCS, cancer-specific survival.
salvage surgery had viable tumor cells in the specimens. Taira et al. reported salvage surgery for two cases with low SUVmax (2.7 and 1.9) resulting in no viable cells in the resected tumor. In Neri et al. report, two patients were noted to have high SUVmax (9.4 and 12.2) along with viable cells in the resected mass. Of interest, one patient from Allibhai et al. report had high SUVmax (8.9) but no viable cells in the resected mass. Future studies from other institutions are expected to add to the information on the relationship between SUVmax and viable cells.

To date, cytotoxic chemotherapy or EGFR-tyrosine kinase inhibitor treatment for isolated LR after SBRT for early-stage NSCLC has not been reported. To date, chemotherapy after SBRT has been discussed only in the adjuvant setting for large or centrally located tumors treated with SBRT. In Chen et al. study, 17 patients were offered adjuvant chemotherapy with three to four cycles of cisplatin-based regimens 1 week after SBRT. Patients older than 75 years and those with comorbidities were not administered adjuvant chemotherapy. As a result, toxicities were mild, of grade 2 or lower severity. Song and Zhang suggested gefitinib as a salvage treatment in patients with EGFR mutation who failed to respond to radiotherapy for brain metastases of NSCLC. Imai et al. study suggested that these patients benefit more from EGFR-tyrosine kinase inhibitors than from radiotherapy. Although data are limited, it seems reasonable to consider EGFR-tyrosine kinase inhibitors for patients with EGFR mutation because no serious complication was noted in our study.

No patient in our study underwent repeat SBRT or other radioablative procedures for LR of NSCLC, and there is a paucity of literature regarding repeat SBRT for LR of NSCLC. Each study contained a small patient cohort undergoing repeat SBRT more than 12 months after first SBRT, with a short follow-up period ranging from 12 to 22 months (median). The toxicities ranged from grades 2 to 5. As suggested by the authors, further studies are required to evaluate the outcomes and the indications. Once long-term survival outcomes are available, we may consider repeat SBRT, especially for select inoperable patients with LR.

The limitations of this study included its retrospective study design and the single center experience. Our study is also limited by the relatively small sample size. Another limitation would be that biopsy confirmation was not possible in all SBRT-treated patients in other studies. More importantly, the majority of LR in our study were biopsy proven and there may be false-positives in our patients managed nonsurgically. Although most patients of the entire cohort underwent PET, SUVmax was unavailable in most of these patients.

Despite these limitations, our results are based on the largest data set to date, with a long follow-up period after salvage treatments for isolated LR after SBRT. To obtain a larger sample size and identify significant prognostic factors after salvage surgery, a multi-institutional study of either a retrospective or prospective design is required.

CONCLUSIONS

We characterized salvage treatment options for isolated LR after SBRT for early-stage NSCLC. Our results suggest salvage surgery for isolated LR can be undertaken safely with favorable survival outcomes and that it is recommended to select patients with isolated LR. It should be emphasized that operability at LR be discussed at multidisciplinary conferences. Long-term and continued follow-up is required especially for patients with reasonable functional status undergoing SBRT for NSCLC.

REFERENCES

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