A Systematic Literature Review on Salvage Radiotherapy for Local or Regional Recurrence After Previous Stereotactic Body Radiotherapy for Lung Cancer

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Abstract

Purpose: The purpose of this review article was to summarize available data on the efficacy and safety of salvage radiotherapy for isolated local or regional recurrence after prior stereotactic body radiotherapy for lung cancer. Methods: Studies were systematically searched on PubMed, following which suitable papers were selected. Reported outcomes and toxicities were qualitatively reviewed. Results: Nineteen papers, which were retrospective studies based on single institution experiences, were selected. Sixteen papers were on salvage radiotherapy for local tumor recurrence, and the remaining 3 papers evaluated radiotherapy for regional failures after stereotactic body radiotherapy for lung cancer. Patient cohorts in the selected papers seemed very frail with 2-year survival of 30% to 40% after the salvage. Local control was reported to be approximately 60% to 70%, which is worse than that after primary stereotactic body radiotherapy. Reported rates of toxicity grade 3 or worse were considered acceptable. Larger target volume and central tumor localization were suggested as risk factors for severe toxicities. Dosimetric data on patients having toxicities were found to help with considering dose constraints for organs at risk. Conclusion: Based on data from a limited number of articles, salvage radiotherapy is a reasonable treatment option for select patients with local or regional tumor recurrence after prior stereotactic body radiotherapy for lung cancer. Optimal patient selection and dose prescription can be clarified with a larger study that include more data on experiences with salvage radiotherapy.

Keywords

re-irradiation, stereotactic body radiotherapy, lung cancer, local recurrence, regional recurrence

Abbreviations

BED, biologically effective dose; CFRT, conventionally fractionated radiotherapy; CT, computed tomography; CTV, clinical target volume; EQD2, equivalent dose in 2-Gy fractions; JCOG, Japan Clinical Oncology Group; NSCLC, non-small-cell lung cancer; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group; SBRT, stereotactic body radiotherapy; VCP, vocal cord paralysis

Introduction

Stereotactic body radiotherapy (SBRT) is now an important treatment option for patients with early-stage non-small-cell lung cancer (NSCLC), especially for medically inoperable patients. Several prospective trials have proven the efficacy and safety of SBRT for early-stage NSCLC. The Japan Clinical Oncology Group (JCOG) 0403 was a prospective multi-institutional phase 2 trial for SBRT for stage I A NSCLC in both medically inoperable and operable patients. The JCOG 0403 evaluated outcomes of 100 inoperable and 64 operable patients with a median age of 78 years (range: 50-91 years). Of the 100 inoperable patients, overall survival was 59.9% and 76.5% at 3 years for the inoperable and operable patients, respectively. The local control rate at 3 years was 59.9% and 76.5% for the inoperable and operable patients, respectively.
87.3% and 85.4%, respectively. No grade 5 toxicity was observed. Other multi-institutional phase 2 trials, including the Radiation Therapy Oncology Group (RTOG) trial 0236\(^3\) and the Nordic study group trial,\(^4\) have also proven the efficacy and safety of SBRT for medically inoperable patients.

The dominant pattern of failure after lung SBRT is distant metastasis. However, a few patients develop local tumor recurrence or isolated regional lymph node metastasis. Local tumor recurrence, lymph node metastasis, and distant metastasis were observed in 20, 24, and 44 patients, respectively, in the JCOG 0403 and in 3, 2, and 11 of 59 patients in the RTOG 0236, respectively. The efficacy and safety of salvage surgery for isolated local recurrence have been recently reported by several studies.\(^5\)-\(^11\) However, the indications for salvage surgery are very limited because almost all SBRT patients are medically inoperable. Salvage SBRT is an attractive option for the medically inoperable patients with isolated local recurrence. Regarding regional failure, an international consortium of expert radiation oncologists discussed treatment recommendations for a case with recurrent node-positive NSCLC after previous SBRT for stage I disease.\(^12\) All the experts agreed that salvage chemoradiotherapy is not contraindicated in such a case. However, no consensus was made regarding radiotherapy (RT) dose and fractionation used for the patient.

Few data are available on salvage RT for local or regional failures after lung SBRT. The purpose of this review article was to search relevant papers systematically and to summarize available data from studies on efficacy and safety of salvage RT for isolated local or regional recurrence after prior SBRT for lung cancer.

**Materials and Methods**

Potential studies for the present review were systematically searched on PubMed using key search terms shown in Table 1. Inclusion criteria were as follows: (1) studies that included patients with primary lung cancer or a metastatic lung tumor that was treated, (2) studies with at least one patient who underwent SBRT as an initial treatment for the tumor, and (3) studies that reported on salvage RT performed for local or regional recurrence after the initial treatment. Reported outcomes and toxicities were qualitatively reviewed in the present article.

To help with the comparison of doses that had different fractionations, the prescribed doses were converted into equivalent doses in 2-Gy fractions (EQD2). The EQD2 was given by the following formula with a fractional dose of \(d\) [Gy], a number of fractions of \(n\), and an alpha-beta ratio of \(\alpha/\beta\) [Gy]:

\[
EQD2 = nd \times \frac{d + \frac{\alpha}{\beta}}{2 + \frac{\alpha}{\beta}}.
\]

We applied an \(\alpha/\beta\) of 10 Gy to calculate EQD2 [Gy\(10\)] for tumor response, and an \(\alpha/\beta\) of 3 Gy for late normal tissue toxicity EQD2 [Gy\(3\)], respectively. When biologically effective doses (BED) were provided in the article, the BED was converted into EQD2 with the formula:

\[
EQD2 = \text{BED} \times \frac{\alpha/\beta}{2 + \alpha/\beta}.
\]

### Results

Seventy-nine potential papers were identified through the PubMed search on January 31, 2018. Nineteen articles satisfied the abovementioned criteria (Figure 1). The 19 articles were all retrospective studies based on single institution experiences. Sixteen papers were on salvage RT for local tumor recurrence,
and the remaining 3 papers evaluated RT for regional failures after SBRT for lung cancer.

Salvage RT for Local Tumor Recurrence

Two papers evaluated patterns of failure after SBRT for early-stage NSCLC and the application rate of salvage treatment to patients with isolated local or regional tumor recurrence. Hamamoto et al.13 administered SBRT to 86 patients with stage I NSCLC between 2006 and 2009. With a median follow-up period of 26 months, 10 (11.6%) local failures and 3 (3.5%) regional lymph-node failures were observed. Curative-intent salvage treatment was delivered to 7 of the 10 local failures, including RT and surgery for 5 and 2 local failures, respectively. Overall survival at 1 and 2 years after the local salvage treatment was 60% and 0% for the RT group (n = 5), and 100% and 100% for the surgery group (n = 2), respectively. No patients with regional failure received curative-intent treatment. Versteegen et al.14 reviewed 855 patients who received SBRT for early-stage NSCLC. Isolated locoregional recurrence was observed in 31 (3.6%) patients. Among them, 5 patients underwent salvage surgery while 4 received RT. The median overall survival was 36 months in those who received such radical treatment.

Four papers retrospectively investigated efficacy and safety of salvage RT for local tumor recurrence in patients who had received prior definitive SBRT for primary lung cancer or metastatic lung tumors (Table 2). Peulen et al.15 from Karolinska University Hospital published the first report on salvage SBRT for local recurrence after previous SBRT. Patients in their study were given a median reirradiation EQD2 of 109 Gy. The report consisted of 29 patients with 32 lesions. Eleven lesions were centrally located. Nine patients had severe (grade 3 or worse) toxicities with a median time of 4 months (range: 1-39 months) from reirradiation. These toxicities included fatal bleeding in 3 patients. Larger clinical target volume (CTV) and central tumor localization were associated with more toxicity. Valakh et al.16 delivered salvage SBRT to 9 patients who had local recurrence in the lung periphery after prior SBRT. The

| Table 2. Reports on Salvage Radiotherapy for Local Tumor Recurrence After Prior Stereotactic Body Radiotherapy for Primary or Metastatic Lung Tumors. |
| Author (Year) | No. of patients (lesions) | Sex (M:F) | Age, years | Tumor type (primary: metastatic) | Tumor location (central: periphery) | Initial treatment | Regimen | EQD2 [Gy10] | Time to salvage treatment, mo | SVF, 20-45 Gy/2-5fx | CTV, 109 (7-150) (cm³) | Regimen | EQD2 [Gy10] | Use of concurrent chemotherapy | Follow-up from the salvage, mo | Local control | Survival | Toxicity |
|--------------|-----------------|-----------|------------|--------------------------------|-----------------------------------|-----------------|--------|------------|------------------|----------------|----------------|--------|----------|-------------------------|------------------|-------------|----------|----------|
| Peulen et al (2011)15 | 29 (32) | 18:11 | 65 (18-87) | 6:23 | 11:21 | SBRT, 20-45 Gy/2-5fx | 2.39 (1.3-3.1) | 14 (5-54) | 11.0 (0.0-150.0) | 11 (1-25) | 109.0 (50.0-150.0) | 2.8 | 12 (41%) | 12 (1-97) | 52% at 5 mo | 59% at 1 year | Grade 2 | 12 (RP, pleural effusion, etc) |
| Yoshitake et al (2013)17 | 9 (9) | NR | 74 (59-83) | 8:1 | 0:9 | SBRT, 30-60 Gy/3-5fx | 2.8 (1.0-5.1) | 11 | 88.0 (80.0-88.0) | 12.4 (6.3-35.5) | 88.0 (80.0-88.0) | 14.8 (9.9-26.3) | 12 (1-97) | 52% at 5 mo | 59% at 1 year | Grade 2 | 12 (RP, pleural effusion, etc) |
| Hearn et al (2014)18 | 17b | 15:2 | 81 (69-88) | 17:0 | NR | SBRT, 48-60 Gy/4-10fx | 2.2 | 10 (10) | 14 (5-54) | 83.3 (83.3-124.7) | 14.8 (9.9-26.3) | 12 (1-97) | 52% at 5 mo | 59% at 1 year | Grade 2 | 12 (RP, pleural effusion, etc) |
| Versteegen et al (2011)14 | 10 (10) | 5:5 | 72 (51-78) | 10:0 | 2:8 | SBRT, 30-50 Gy/1-5fx | 2.2 | 10 (10) | 14 (5-54) | 83.3 (83.3-124.7) | 14.8 (9.9-26.3) | 12 (1-97) | 52% at 5 mo | 59% at 1 year | Grade 2 | 12 (RP, pleural effusion, etc) |

Abbreviations: BrP, brachial plexopathy; CFRT, conventionally fractionated radiotherapy; CTV, clinical target volume; CWP, chest wall pain; EQD2, equivalent dose in 2-Gy fractions; fx, fractions; LPFS, local progression-free survival; mo, months; NED, alive with no evidence of disease; NR, not reported; PTV, planning target volume; RP, radiation pneumonitis; SBRT, stereotactic body radiotherapy; SVC, superior vena cava.

aValues are shown in median (range), if unspecified.
bIncluding 4 patients who had regional or distant metastasis in addition to local recurrence.
salvage SBRT irradiation was performed under cone-beam computed tomography (CT) guidance. Local recurrence-free survival was 75% at 2 years. No grade 4-5 toxicities were observed. Yoshitake et al\(^\text{17}\) from Kyushu University used conventional fractionated RT as a salvage treatment for 17 patients with local recurrence after SBRT for primary lung cancer. Four of the 17 patients also had metastasis to regional lymph nodes or the brain. The irradiation fields were limited to the recurrent gross tumors without elective nodal irradiation with a median dose of 60 Gy in 30 fractions. Concurrent chemotherapy was administered in 4 patients. Local progression-free survival was 33.8% at 1 year after the reirradiation. No grade 2 or worse toxicity was observed except in 1 patient with a grade 2 rib fracture. Hearn et al\(^\text{18}\) reported their experience with salvage SBRT. They found that 22 patients who had isolated local recurrence after prior SBRT were not deemed candidates for the salvage therapy because of the following reasons: large tumor size (>8 cm); tumors were close to the mediastinum, chest wall, or proximal bronchus; history of overlapping conventional RT before initial SBRT; severe medical comorbidity; or persistent chest wall pain from initial SBRT. The remaining 10 patients with a recurrent tumor <5 cm received the re-SBRT with a median EQD2 of 83.3 Gy\(_{10}\) (range: 83.3-150.0 Gy\(_{10}\)). Three patients were alive without evidence of disease at the end of follow-up. There was no grade 3-5 toxicity.

Seven articles evaluated salvage RT for patients with local recurrence after previous thoracic irradiation that included not only SBRT but also conventionally fractionated RT (CFRT; Table 3).\(^\text{19-25}\) Prescribed dose and fractionation varied among the articles. Trakul et al\(^\text{19}\) assessed treatment outcomes for SBRT reirradiation for in-field recurrences after prior SBRT or CFRT. With a median BED of 80 Gy\(_{10}\) (EQD2, 66.7 Gy\(_{10}\)), the local control rate was 65.5% at 12 months. Improved local control was also associated with an interval time longer than 16 months between the treatments (\(P = .042\)). Ester et al\(^\text{21}\) also reported SBRT salvage for isolated local recurrence after prior thoracic irradiation. Local control was 92% with a median survival of 24 months. Patel et al\(^\text{22}\) evaluated treatment of in-field lung cancer recurrence with SBRT re-irradiation after CFRT or SBRT. SBRT reirradiation was delivered with a low median EQD2 of 40 Gy\(_{10}\). The reirradiation resulted in no severe toxicities, and there was an acceptable crude local control rate of 80%. Ceylan et al\(^\text{25}\) also reported on SBRT salvage for 28 patients with isolated local recurrence. They found a significant difference in local control between patients treated with BED \(\geq 48\) Gy\(_{10}\) (ECD2, 40 Gy\(_{10}\)) and those with BED <48 Gy (median local control, 48 months vs 13 months; \(P = .007\)). Meijneme et al\(^\text{20}\) assessed accumulated dose and toxicity after reirradiation in 20 patients. There was no grade 3-5 toxicity observed. Median accumulated V20 (volume receiving 20 Gy or more) of the lungs was 15.2% (range: 3%-47%). In patients who received an accumulated dose higher than 70 Gy\(_3\), a median EQD2 of the maximal dose was 115 Gy\(_3\), 89 Gy\(_3\), and 85 Gy\(_3\) in the heart, the trachea and the esophagus, respectively. Kilburn et al\(^\text{22}\) reported on their experience of thoracic reirradiation for local recurrence after prior RT. One patient developed an aortoesophageal fistula which is considered a grade 5 toxicity. The EQD2 in the aorta was estimated to be 200 Gy\(_3\). Binkley et al\(^\text{24}\) reported dose–volume data (D\(_{\text{max}}\)cm\(^3\), dose to the most exposed x cm\(^3\)) in patients who developed toxicities after thoracic reirradiation. The data included esophagitis \(\geq 2\) grade 2 (D\(_{\text{max}}\)cm\(^3\), 41.0-100.6 Gy\(_3\)), chest wall \(\geq 2\) grade 2 (D\(_{\text{max}}\)cm\(^3\), 35.0-117.2 Gy\(_3\)), lung grade 2 (V20, 4.7%-21.7%), vocal cord paralysis (VCP; vagal nerve D0.2 cm\(^3\), 207.5-302.2 Gy\(_3\)), and Horner syndrome (sympathetic trunk D0.2 cm\(^3\), 130.8 Gy\(_3\)).

Regarding toxicity, 2 articles provided additional information. Shultz et al\(^\text{26}\) reported clinical and dosimetric factors associated with VCP in patients treated with SBRT. They identified 2 patients who developed VCP; the first underwent repeat SBRT for a recurrent tumor in the left lung apex. Cumulative single fraction equivalent doses with an \(\alpha/\beta\) of 3 (SFED3) to the vagal nerve and the recurrent nerve were 37.4 Gy\(_3\) and 13.7 Gy\(_3\), respectively. The second patient, who had connective tissue disease, received SFED3 of 16 Gy\(_3\) and 19.5 Gy\(_3\) to the vagal and recurrent nerves, respectively. They concluded that reirradiation and connective tissue disease are risk factors for VCP after SBRT for the lung. Nonaka et al\(^\text{27}\) from the University of Yamanashi reported a case that demonstrated how 2 treatments with SBRT resulted in fatal gastric perforation. The patient in this case was an 83-year-old man who had T2N0M0 lung cancer in the base of the left lung. For the first treatment, SBRT was delivered with a dose of 40 Gy in 4 fractions. He developed a gastric ulcer at 3 months and was treated with medication. Following this, local tumor recurrence was observed at 8 months after the first treatment with SBRT. Re-irradiation with SBRT of 50 Gy in 4 fractions was delivered to the recurrent tumor with the patient well informed about the possibility of serious toxicity by the second treatment with SBRT. At 2 months after the second treatment with SBRT, fatal gastric perforation occurred. The maximal dose to the stomach was estimated to be 83.5 Gy in the nominal dose. Regarding optimal dose prescription for salvage SBRT, Nishimura et al\(^\text{28}\) suggested that efficacy of SBRT with escalated dose to the tumor through a report of 2 cases. Two patients developed local recurrence in their lung periphery after prior SBRT with a prescription of 50 Gy in 5 fractions to an 80% isodose line. The salvage SBRT was performed with a dose of 60 Gy in 5 fractions prescribed to a 60% isodose line, which resulted in a higher dose at the tumor center with a steeper dose falloff outside the target volume than the prior prescription. Both patients in these cases achieved local control without severe toxicity.

**Management of Regional Recurrence**

We identified 3 articles that discussed management of regional recurrence after SBRT for the lung\(^\text{29-31}\) (Table 4). Manabe et al\(^\text{29}\) from Nagoya City University reported on their experience with salvage RT for hilar or mediastinal lymph node metastasis. The patient cohort consisted of not only post-SBRT (n = 13) but also postproton beam therapy (n = 1) and postsurgery
| Author (Year) | No. of patients (lesions) | Sex (M:F) | Age, years | Tumor type (primary:metastatic) | Tumor location (central:peripheral) | Initial treatment | Salvage treatment | Toxicity Grade 2 | Toxicity Grade 3 | Toxicity Grade 4 | Toxicity Grade 5 |
|---------------|---------------------------|-----------|------------|-------------------------------|----------------------------------|------------------|------------------|-----------------|----------------|----------------|----------------|
| Trakul et al (2012) | 15 (17) | 7:10 | 66 (49-92) | 12:5 | 6:11 | NR | SBRT (n = 4), 25-50 Gy/1-4fx; CFRT (n = 11) | 14.2 (2-57.7) | 14.2 (2-57.7) | None | None |
| Meijneke et al (2013) | 20 (20) | 14:6 | 71 (50-80) | 17:3 | NR | 26.5 (0.2-240) | SBRT (n = 14), 30-60 Gy/1-6fx; CFRT (n = 8), 45-60 Gy/15-25fx | 66.7 (50.0-93.8) | 66.7 (50.0-93.8) | None | None |
| Ester et al (2013) | 12 (13) | 8:4 | 67.9 (45.9-86.7) | 11:1 | NR | 4.6 (1.0-28.4) | SBRT, 45-50 Gy/6fx | 71.3 (71.3-83.3) | 71.3 (71.3-83.3) | None | None |
| Kilburn et al (2014) | 33 | 19:14 | 66 (45-80) | NR | NR | 2.5 (0.6-5.4) (cm) | SBRT (n = 30), 20-54 Gy/1-10fx; CFRT (n = 3), 60-70.2 Gy/26-35fx | 40 (16.3-93.8) | 40 (16.3-93.8) | None | None |
| Patel et al (2015) | 26 (29) | 19:7 | 68 (42-87) | NR | NR | 3.2 (1.2-9.5) (cm) | SBRT, 15-50 Gy/3-5fx | 72.9 (50.0-93.8) | 72.9 (50.0-93.8) | None | None |
| Binkley et al (2016) | 38 (44) | 23:15 | 66 (35-94) | NR | NR | 9.1 (0.5-87.5) | SBRT (n = 21), 25-54 Gy; CFRT (n = 17), 45-71.6 Gy | 24.2 (23.3-150.0) | 24.2 (23.3-150.0) | None | None |
| Ceylan et al (2017) | 28 (34) | 25:3 | 64 (48-90) | NR | NR | 72.9 (43.1-126) NR | SBRT: 83.3; CFRT: 66 | 16 (4-65) | 16 (4-65) | None | None |

Abbreviations: BrP, brachial plexopathy; CFRT, conventionally fractionated radiotherapy; CWP, chest wall pain; EQD2, equivalent dose in 2-Gy fractions; fx, fractions; GTV, gross tumor volume; NR, not reported; SBRT, stereotactic body radiotherapy; SVC, superior vena cava; syn., syndrome; RP, radiation pneumonitis; VCP, vocal cord paralysis.

aValues are shown in median (range), if unspecified.
Table 4. Reports on Salvage Radiotherapy for Isolated Regional Recurrence After Prior Treatment of Non-small-cell Lung Cancer.

| Author (Year)      | Manabe et al (2012) | Kilburn et al (2014) | Ward et al (2016) |
|--------------------|---------------------|----------------------|-------------------|
| No. of patients    | 26                  | 12                   | 15                |
| Sex (M:F)          | 18:8                | 4:8                  | 7:8               |
| Age, years         | 75 (29-87)          | 66 (53-85)           | 77 (56-87)        |
| Initial treatment  | SBRT (n = 13), 48-52 Gy/4fx; Proton (n = 1), 60 GyE/10fx; Surgery (n = 12) | SBRT (n = 9), 50-60 Gy/3-5fx; AHRT (n = 2), 70.2 Gy/26fx; SBRT + AHRT (n = 1) | SBRT, 34-60 Gy/1-7fx |
| EQD2 [Gy10]        | 90.9 (80.0-99.7)    | 83.3 (71.3-150.0)    | 85.7 (76.6-150.0) |
| Time to salvage    | 12 (1-62)           | 15 (2-57)            | 11.1 (1.8-39.0)   |
| salvage treatment  | CFRT, 54-66 Gy/27-33fx | CFRT, 60-70.2 Gy/23-36fx | CFRT, 17-60.4 Gy/2-33fx |
| EQD2 [Gy10]        | 64 (54-66)          | 66 (60-74.3)         | 48.8 (26.2-60.0)  |
| Use of concurrent  | 3                   | 2                    | 2                 |
| chemotherapy       |                     |                      |                   |
| Follow-up from the | 35 (7-62)b          | 10 (2-49)            | NR                |
| salvage, mo        |                     |                      |                   |
| Locoregional control | 76% at 1 year (in-field) | 100% at 2 years; 92% at 5 years | 84.4% at 1 year |
| Survival           | 36% at 3 years (14% at 3 years for post-SBRT) | 58% at 1 year; 29% at 2 years | 73.3% at 1 year |
| Toxicity grade 2   | 8 RP, 2 esophagitis, 1 dermatitis | 4 (esophagitis, dysphagia) | 6 (5 esophagitis, 1 dyspnea) |
| Toxicity grade 3   | 1 dermatitis        | 1 (dyspnea)          | None              |
| Toxicity grade 4   | None                | None                 | None              |
| Toxicity grade 5   | 1 RP                | None                 | None              |

Abbreviations: AHRT, accelerated hypofraction radiotherapy; CFRT, conventionally fractionated radiotherapy; EQD2, equivalent dose in 2-Gy fractions; fx, fractions; NR, not reported; RP, radiation pneumonitis; SBRT, stereotactic body radiotherapy.

*nValues are shown in median (range), if unspecified.

*bFollow-up period for surviving patients.

They delivered a median of 64 Gy to recurrent tumors and 26 to 46 Gy for prophylactic therapy to the mediastinal lymph node area, respectively. The salvage RT resulted in in-field control of 76% at 1 year. Overall survival was 36% at 3 years for the whole cohort, and 14% for post-SBRT. One patient in the post-SBRT cohort had grade 5 radiation pneumonitis. Kilburn et al.\textsuperscript{30} retrospectively reviewed 12 patients who received salvage CFRT for isolated mediastinal failure after SBRT or hypofractionated RT. The median salvage dose was 66 Gy (range: 60-70 Gy) to the gross disease without elective nodal irradiation. The locoregional failure-free survival was 100% and 92% at 2 and 5 years, respectively. One patient developed grade 3 dyspnea, but no grade 4 or 5 toxicity was observed. The authors suggested that the omission of elective nodal irradiation resulted in a low toxicity rate. Ward et al.\textsuperscript{31} evaluated salvage RT for isolated nodal failure after SBRT. They used various dose regimens ranging from 17 Gy in 2 fractions to 60.4 Gy in 33 fractions. The most common regimen was 45 Gy in 15 fractions, which was used for 53% of the patients. The authors suggested that 45 Gy in 15 fractions might be ideal for many medically inoperable patients, but 60 Gy in 30 fractions with chemotherapy would be an option only for select patients.

**Discussion**

This review article aimed to summarize data from studies on the efficacy and safety of salvage RT for isolated local or regional recurrence after prior SBRT for lung cancer. The available articles were retrospective studies based on single institution settings. Patient characteristics and treatment regimens varied among the papers. Therefore, rigorous quantitative analysis of the data was impossible. Patient cohorts in the selected articles seemed very frail with 2-year survival of 40 to 70% as Trakul et al.\textsuperscript{19} pointed out. Because local recurrent tumors are thought possibly to be radioresistant, higher doses than the initial treatment might be needed to control the recurrent tumor. However, we also need to consider that the higher dose would result in a higher risk of severe toxicities. Although SBRT can be safely applied to recurrence in the lung periphery, those with central tumor recurrence or regional lymph node recurrence are not good candidates for salvage SBRT because of the risk of toxicities. All the 3 articles that discussed salvage RT for regional recurrence did not use SBRT but CFRT with or without chemotherapy.\textsuperscript{29-31}

Toxicities after the salvage RT were found to be acceptable except for a few studies that reported grade 5 toxicities. To reduce the toxicity risk, we need to consider the 2 risk factors that include larger CTV and central tumor localization proposed by Peulen et al.\textsuperscript{15} Dosimetric data provided by several
authors also help us to consider dose constraints for organs at risk (Table 5).

Surgery is also an important treatment option to salvage isolated local recurrence, if indicated. Neri et al.2 and Chen et al.6 made the first reports on salvage surgery for 7 and 5 patients, respectively, with local recurrence after SBRT. Both the articles reported that SBRT did not cause any difficulties in the surgical process. The efficacy and safety of salvage surgery for isolated local recurrence have been recently reported by several studies.7-9 Taira et al.10 reported 2 patients who underwent salvage lung resection for suspected local recurrence after SBRT, which turned out to be no viable tumor. The report suggested difficulties in distinguishing local recurrence from post-SBRT changes. Hamaji et al.11 suggested that such a radical local treatment might result in better prognosis after local recurrence. They reviewed 49 patients with isolated local recurrence after SBRT, and 12 of them underwent salvage surgery. The results suggested that salvage surgery was associated with an improved overall survival of 79.5% at 5 years after the surgery (P = .014). Based on the report by Hamaji et al., surgery might be preferable as salvage treatment of local recurrence in the aspect of long-term survival. However, the indications for salvage surgery are very limited because most SBRT patients are medically inoperable.

Early diagnosis of local tumor recurrence is a key to reducing target volumes, which leads to a reduction in toxicity risk. However, it is not easy to distinguish local tumor recurrence from radiation-induced lung injury. Huang and Palma32 recommends the following schedule of imaging for follow-up: serial CT imaging at 3 to 6 months for the initial year, then every 6 to 12 months for an additional 3 years, and annually thereafter. If local tumor recurrence is suspected, a multidisciplinary team discussion is recommended to evaluate the suspicious lesion based on the use of high-risk CT features and the uptake of 18-fluorodeoxyglucose on positron emission tomography. The high-risk CT features include (1) enlarging opacity at the primary site, (2) sequential enlarging opacity, (3) enlarging opacity after 12 months, (4) a bulging margin, (5) loss of linear margin, (6) air bronchogram loss, and (7) crano-caudal growth.

In conclusion, based on data from a limited number of articles, salvage RT is a reasonable treatment option for select patients with local or regional recurrence after prior SBRT for lung cancer. Optimal patient selection and dose prescription can be clarified with a larger study that includes more data on experiences with salvage RT.

### Table 5. Dosimetric Data in Patients Having Severe Toxicities After Reirradiation.

| Toxicities                        | Organs At Risk | Maximal Dose in EQD2 [Gy] | Author (Year) |
|-----------------------------------|----------------|---------------------------|---------------|
| Aortaesophageal fistula grade 5   | Aorta          | 200.0 (nominal dose)      | Kilburn et al (2014) |
| Gastric perforation grade 5       | Stomach        | 83.5 (nominal dose)       | Nonaka et al (2017) |
| Esophagitis grade 3               | Esophagus      | D1 cm³; 60.6              | Binkley et al (2016) |
| Chest wall grade 3                | Chest wall     | D30 cm³; 89.5, 124.6      | Binkley et al (2016) |
| Vocal cord paralysis              | Vagal nerve    | D0.2 cm³; 207.5, 302.2    | Binkley et al (2016) |
|                                  | Recurrent nerve| 37.4, 16 (SFED)           | Shultz et al (2014) |
| Brachial plexopathy               | Brachial plexus| D0.2 cm³; 242.5           | Binkley et al (2016) |
| Horner’s syndrome                 | Sympathetic trunk| D0.2 cm³; 130.8       | Binkley et al (2016) |

Abbreviations: Dxm³, dose to the most exposed x cm³; EQD2, equivalent dose in 2-Gy fractions; SFED, single fraction equivalent dose.

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