Original Article

Stereotactic body radiotherapy for second pulmonary nodules after operation for an initial lung cancer

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Abstract

Objective: A second lung cancer is occasionally observed in patients who underwent surgical resection of the index lung cancer. The purpose of this study is to evaluate stereotactic body radiation therapy for second lung cancer.

Methods: Fifty-one medically inoperable patients who underwent stereotactic body radiation therapy for second lung cancer were the subjects: 31 cases of multiple primary lung cancer and 20 of pulmonary metastasis from the index cancer. Clinical stage was T1a in 27 patients, T1b in 13 patients and T2a in 11 patients, and 70% of subjects had impaired respiratory function. Histology of second lung cancer was adenocarcinoma in 16 patients, squamous cell carcinoma in 9 patients and not assessed in 25 patients. The interval between index cancer operation and stereotactic body radiation therapy was 31 months (range: 4–171). The total stereotactic body radiation therapy doses were 48 Gy in 4 fractions or 60 Gy in 10 fractions.

Results: With the median follow-up of 36 months, 3-year overall survival rates were 62% with the median survival time of 46 months. Cause-specific survival was 73% at 3 years. Overall survival for multiple primary lung cancer and pulmonary metastasis was quite similar: 62 and 61% at 3 years, respectively. Three-year overall survival was 77% for T1a and 43% for T1b or T2a. Grade 2 pulmonary toxicities occurred in five patients and one patient died of Grade 5 pneumonitis.

Conclusions: Even though the subjects were medically inoperable, the survival outcomes of stereotactic body radiation therapy were favorable. Furthermore, having acceptable toxicity, stereotactic body radiation therapy is feasible and could be an option for multiple primary lung cancer and pulmonary metastasis after surgical resection for the index cancer.

Key words: stereotactic body radiation therapy, second lung cancer, operation for the index lung cancer

Introduction

A second lung cancer (SLC) is occasionally detected in patients after radical surgery for lung cancer. SLC is classified into two groups: multiple primary lung cancer (MPLC) and pulmonary metastases from the resected index cancer (META). The incidence of SLC is variable. Some studies demonstrated the incidence of 4–5% (1,2) and Bodegom et al. (3) reported that, out of 1540 patients with primary carcinoma of the lung, 153 (10%) had a second primary lung tumor. A review stated that the risk of developing a second lung cancer in patients who survived resection of a non-small-cell lung cancer (NSCLC) was ~1–2%
per patient per year (4). Recently, advances in diagnosis and treatment for NSCLC have increased long-time survivors. In addition, the aggressively induced computed tomography (CT) and [18F] fluorodeoxyglucose positron emission tomography (PET) are increasing a chance to find SLC.

The mainstay for the SLC is surgical resection and it represented considerable survival achievement (4). However, a significant proportion of these patients, presenting with impaired pulmonary reserve and/or serious comorbidities, are deemed medically inoperable. Conventional radiotherapy is an alternative for medically inoperable patients. It, however, failed to yield satisfactory outcomes because of low dose to the primary lung tumor. The overall survival (OS) remained ~30–40% at 3 years even for Stage I NSCLC (5). Highly focusing to increase radiation doses to tumors, stereotactic body radiotherapy (SBRT) offers the least invasive and most tolerable approach to deliver the highest possible radiation dose to the tumor. Several studies have reported that SBRT offers outstanding local control for early-stage NSCLC (6,7). Thereby, SBRT could be expected to show efficacy for SLC patients who have insufficient cardiopulmonary reserve and/or serious comorbidities. However, the role of SBRT has rarely been discussed and should be determined. In this study, we evaluated the feasibility and efficacy of SBRT for SLC after resection of the index lung cancer.

### Patients and methods

#### Patients

Among a total of 232 patients who underwent SBRT for lung cancer at our institution from September 2006 through September 2011, 61 patients had experienced operation for prior lung cancer (the index cancer) before SBRT. Excluding 8 patients with extrathoracic metastatic lesions of the index cancer and 2 patients with other active malignancies, the remaining 51 patients with SLC were the subjects of our study. The subjects had neither regional lymph node metastasis nor distant metastasis. They presented with impaired cardiopulmonary reserve and/or other comorbidities. Consequently, most of the subjects were medically inoperable. Table 1 summarizes patient and tumor characteristics. In most patients, the index cancer was pathological Stage I (44/51, 86%) and SLC was metachronous (45/51, 88%). SLC was classified into MPLC (n = 30) or META (n = 21) from the index lung cancer according to ACCP evidence-based clinical practice guidelines, second edition (8).

Histological diagnostic results of the index lung cancer and SLC are presented in Table 2. A histological diagnosis of the index cancer had been given for every case. On the contrary, SLC was not pathologically confirmed for half cases (n = 25) because of difficulty to take biopsy of a small lesion or risk to take biopsy from compromised patients. Before SBRT, patients were restaged using history, physical examination, chest and abdominal CT and brain magnetic resonance imaging. Forty-six patients (90%) underwent PET and these diagnostic images revealed no regional lymph node and distant metastasis. Every patient except one who underwent total laryngectomy underwent respiratory function tests. The clinical stage of SLC was T1a in 27 patients, T1b in 13 patients, T2a in 11 patients and N0M0 in all patients.

#### SBRT technique

Patients were immobilized with the BodyFix double-vacuum immobilization system (Medical Intelligence, Schwabmuenchen, Germany) and underwent four-dimensional CT (4D-CT) of the whole lung under free-breathing using a GE LightSpeed instrument (16 slices, General Electric Co., Waukesha, WI) equipped with a real-time position management system (Varian Medical Systems, Palo Alto, CA) that...
providing a patient breathing signal. 4D-CT generated 10 respiratory bins. Radiotherapy planning was performed on average intensity projection created from 4D-CT and the tumor on maximum intensity projection was defined as internal target volume (ITV). Planning target volume (PTV) was ITV plus three-dimensional isotropic margins of 5 mm.

Treatment was delivered with a Varian 23EX linear accelerator equipped with a 60-leaf collimator, an aS 1000 EPID and a gantry-mounted on-board imager (Varian Medical Systems). Before every treatment, free-breathing cone beam CT was taken as verification image for image-guided radiation therapy. Treatment beams were 6 MV X-ray via seven non-coplanar portals. In most patients (n = 46), total delivered dose was 48 Gy at the isocenter in four consecutive working days. For the other five patients whose SLC was centrally located, 60 Gy in 10 fractions was selected. When α/β is assumed to be 10 for tumors, biologic effective doses (BED) defined by a linear-quadratic model were 105.6 Gy for 48 Gy in 4 fractions and 96 Gy for 60 Gy in 10 fractions. Any subjects received neither neoadjuvant, adjuvant, nor concomitant chemotherapy.

Follow-up and statistics
Patients were followed up on an outpatient basis with monthly interviews during the first 6 months, bimonthly during the next 6 months and thrice or quarter per year thereafter. All patients were followed up until the date of analysis (30 June 2013) or death. The median follow-up for all patients was 36 months with potential range of 21–81 months. Follow-up chest CT was performed once a year at least. The primary outcomes were OS, cancer-specific survival (CSS) and toxicities that were classified by Common Terminology Criteria for Adverse Events, version 4.0.

Using the Kaplan–Meier method, OS and CSS were calculated from the date of first SBRT fraction to the date of death or the date of analysis for living patients. Log-rank test was used to determine whether a statistically significant difference was present between patient groups. Statistical analyses were performed using GraphPad Prism 5.0 (GraphPad Software, La Jolla, CA), and a P value <0.05 was considered statistically significant.

Results
Patients
Before SBRT, 25 patients (50%) had experienced treatment of malignancy other than the index lung cancer. The most frequent malignancy was lung cancer (n = 10) followed by gastric (n = 5), esophageal (n = 3) and rectal cancer (n = 3). Among them, four patients with lung cancer or one with esophageal cancer had undergone thoracic radiotherapy. SLC was ipsilateral to the index cancer in 31 patients and contralateral in 20 patients. Respiratory function tests at SBRT revealed that 32 patients (n = 64) had impaired respiratory function: obstructive in 15 (30%), restrictive in 11 (22%) and mixed pattern in 6 (12%) patients. During SBRT, two patients had required home oxygen therapy (HOT) due to hypoxia after lung resection of the index cancer. The remaining patients, however, met eligibility criteria of respiratory function tests for SBRT at our institute: >0.6 l of forced expiratory volume in 1 s. Dosimetric parameters of SBRT are shown in Table 3. Median gross tumor volume (GTV) was 4.39 cm³. The median PTV was 25.3 cm³ and was >40 cm³ in 11 patients. After SBRT for SLC, eight patients underwent repeated SBRT for new MPLC in four patients and for a new metastatic lesion in the other four patients.

Table 3. Dosimetric parameters

<table>
<thead>
<tr>
<th>GTV (cm³)</th>
<th>ITV (GTV) (cm³)</th>
<th>PTV (GTV) (cm³)</th>
<th>D95 (Gy)</th>
<th>D2 (Gy)</th>
<th>V20 (%)</th>
<th>Mean lung dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>4.39</td>
<td>7.56</td>
<td>25.5</td>
<td>93.7</td>
<td>101.8</td>
<td>4.1</td>
</tr>
<tr>
<td>SD</td>
<td>8.6</td>
<td>10.3</td>
<td>22.3</td>
<td>4.9</td>
<td>1.8</td>
<td>2.3</td>
</tr>
<tr>
<td>Max.</td>
<td>45.1</td>
<td>57.7</td>
<td>132</td>
<td>99.4</td>
<td>109.3</td>
<td>11.3</td>
</tr>
<tr>
<td>Min.</td>
<td>0.63</td>
<td>0.96</td>
<td>10</td>
<td>79.7</td>
<td>99.3</td>
<td>1.5</td>
</tr>
</tbody>
</table>

GTV, gross tumor volume; ITV, internal target volume; CTV, clinical target volume; PTV, planning target volume; D95, dose to 95% of PTV; D2, dose to 2% of PTV; V20, % lung volume that receives 20 Gy or more; SD, standard deviation.

Survival
Three- and 5-year OS for all patients was 62% (95% confidence interval [CI]: 74–47%) and 38% (95% CI: 54–23%), respectively, with the median survival time of 46 months (Fig. 1A). Twenty-three patients were alive at the time of analysis. Of these, 22 patients were alive with no evidence of disease and the other one alive with disease. Because some patients who died had a history of malignancy other than the index cancer and SLC, it was difficult to specify the cause of death in such a case. We assumed that the cause of death was SLC for all patients who died of unspecified malignancy. Eighteen patients died of SLC. Nine patients died of intercurrent diseases and six of them died of pulmonary disorders such as pneumonia irrelevant to radiation toxicities. One patient who had been receiving HOT at SBRT died of Grade 5 radiation pneumonitis (treatment-related death). CSS was 73% (95% CI: 84–57%) at 3 years and 55% (95% CI: 70–36%) at 5 years (Fig. 1A).

OS for MPLC and META was quite similar: 62% (95% CI: 75–44%) and 61% (95% CI: 78–38%) at 3 years, respectively (Fig. 1B). Classified by tumor size of SLC, 3-year OS and median survival were 77% (95% CI: 89–56%) and 53 months for T1a and 43% (95% CI: 63–21%) and 33 months for T1b and T2a. The difference in survival between two groups was insignificant (P = 0.17) (Fig. 1C). A half of our subjects had non-biopsied lesions that might be non-malignant. OS at 3-year for patients with and without a pathological confirmation was 59 and 65%, respectively (P = 0.65) (Fig. 1D).

Toxicities
Five patients developed the following Grade 2 pulmonary toxicities (Table 4): hypoxia requiring intermittent HOT in four patients and dyspnea with limiting instrumental activities of daily living in the other four patients. These patients were 75 years and older and T1b or T2a except one case of T1. In four out of the five patients, GTV and PTV were above the median values of total subjects. In particular, in four patients, PTV was <40 cm³ that was in only 11 patients out of a total of 51 subjects. In the other 40 subjects whose PTV was >40 cm³, only one patient developed Grade 2 pulmonary toxicity. Consequently, the incidence of Grade 2 pulmonary toxicities could highly develop in patients with a large PTV. Among these five patients, two patients died of SLC and one patient died of pneumonia. The other two patients survived without evidence of SLC for 24–58 months. One patient had developed Grade 5 radiation pneumonitis in 5 months and died in 11 months after SBRT. This patient had had mixed respiratory impairment and had been undergoing HOT at SBRT.
Discussion

Our study analyzed the outcome of SBRT for SLC after resection of the index lung cancer. The SLC in our study included both of MPLC and META. However, most studies on this issue analyzed solely MPLC excluding META. The differential diagnosis of MPLC and META in routine practice is usually not easy, and there is a potential conflict to diagnose them. Furthermore, SBRT often treats metastatic lung tumor. These were the reasons why our study added META to the subjects. Wulf et al. reported clinical outcomes of SBRT for lung metastases of 41 patients. In this study, the origin of metastases was lung cancer in nearly half of the patients and 2-year OS was 33%. In another study on SBRT for lung metastases by Ricardi et al., metastases of lung cancer also accounted for 47.5% and 3-year OS was 52.5%. In our study, 3-year OS for META was 61%, which was very similar to that for MPLC (62%). We basically classified SLC detected within 2 years after index LC operation into META. However, a part of those SLC might be MPLC. This could be a reason of the fairly good survival of META and we supposed that SBRT should also be considered for such patients.

Although surgical resection is not a standard of care for pulmonary metastases of lung cancer, MPLC is often treated with operation. The survival outcomes of MPLC treated with surgery varied widely. A study of 54 cases of resected MPLC reported the 3- and 5-year OS of 26 and 18%, respectively (1). For 33 patients of Stage I, which was the identical stage to ours, OS was 28.3% at 3 years and 19% at 5 years. Adebonojo et al. (2) analyzed metachronous MPLC treated mostly with surgery and demonstrated a 5-year OS of 39% with 36 months of median survival for 29 Stage I patients. A report of surgical treatment for metachronous MPLC by Battafarano et al. (9) described a 5-year OS of 42% for 50 patients of Stage I. Recently, outstanding surgical results for metachronous MPLC at Mayo Clinic were reported.

Table 4. Toxicities

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Age/ gender</th>
<th>Index cancer operation</th>
<th>SLC T stage</th>
<th>GTV (cm³)</th>
<th>PTV (cm³)</th>
<th>V20 (%)</th>
<th>MLD (Gy)</th>
<th>Survival time (months)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>77M</td>
<td>Lobectomy</td>
<td>1a</td>
<td>2.8</td>
<td>13.3</td>
<td>2.8</td>
<td>2.7</td>
<td>53M</td>
<td>DID</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>80M</td>
<td>Lobectomy</td>
<td>2a</td>
<td>4.9</td>
<td>44.2</td>
<td>9.4</td>
<td>5.6</td>
<td>58M</td>
<td>NED</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>80M</td>
<td>Sublobectomy</td>
<td>2a</td>
<td>33.9</td>
<td>91.4</td>
<td>8.1</td>
<td>5.8</td>
<td>33M</td>
<td>DT</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>77M</td>
<td>Lobectomy</td>
<td>1b</td>
<td>12.7</td>
<td>40.2</td>
<td>5.3</td>
<td>4.8</td>
<td>32M</td>
<td>DT</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>75M</td>
<td>Sublobectomy</td>
<td>2a</td>
<td>45.1</td>
<td>132</td>
<td>8.4</td>
<td>6</td>
<td>24M</td>
<td>NED</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>71M</td>
<td>Lobectomy</td>
<td>1a</td>
<td>5.86</td>
<td>25.21</td>
<td>5.6</td>
<td>5.1</td>
<td>11M</td>
<td>DID</td>
</tr>
</tbody>
</table>

MLD, mean lung dose; DID, death from intercurrent diseases; NED, no evidence of disease; DT, death from second lung cancer.

Figure 1. (A) Overall survival (OS) and cause-specific survival (CSS) after SBRT for SLC. (B) OS: MPLC vs. META. (C) OS by T stage. (D) OS by pathological confirmation. SBRT, stereotactic body radiation therapy; SLC, second lung cancer; MPLC, multiple primary lung cancer; META, pulmonary metastasis.
(10). This retrospective study assessed 161 patients including 124 cases (77%) of Stage I and demonstrated 5-year OS of 60.8% with the median survival of 72.9 months for all patients. The 3-year OS for Stages IA and IB was 73.4 and 66.7%, respectively. These outcomes were excellent and this compared favorably with patients with single lung cancers when matched to stage. However, the follow-up time was somewhat short (28.7 months at median) and the authors stated that the patients were highly selected from a cohort of single institution.

There have been few studies that evaluated the role of SBRT for MPLIC after surgical resection of the index lung cancer. Creach et al. (11) assessed SBRT for MPLIC of 63 patients, 46 patients of whom had operation for the index lung cancer. OS at 2 years for the entire cohort was 58.5% with the median survival time of 20.0 months. Another study by Chang et al. (12) analyzed clinical outcomes of 101 patients with MPLIC treated with SBRT, 47 of whom had undergone operation for the index lung cancer. Four-year OS for all patients was 47.5% with the median survival of 46 months. Thus, the results of these studies were similar to ours. SBRT for MPLIC could achieve equivalent survival outcomes to surgery, even though most of the subjects treated with SBRT were medically inoperable.

We compared our results with those of SBRT for NSCLC patients without previous pulmonary resection for lung cancer. A Japanese multi-institutional investigation on SBRT for early-stage NSCLC demonstrated a 3-year OS of 56% (13). The 3-year OS was 60% and the median survival was 40.6 months in a prospective study by Baumann et al. (14). The similarity between these survival outcomes and ours (62% of 3-year OS with the median survival of 46 months) suggested that previous operation for lung cancer did not have a significant negative impact on the prognosis of SLC treated with SBRT.

There have been reported some parameters that have effects on the prognosis of lung cancer treated with SBRT. Onishi et al. (13) demonstrated that BED ≥ 100 Gy at the isocenter was necessary for optimal control of operable patients. A total given doses in most of our patients was 105.6 Gy. Primary tumor volume was reported as an indicator of clinical outcome of SBRT. Beitler et al. (15) investigated tumor volume and the prognosis in a study on SBRT for NSCLC and showed that patients with a GTV < 65 cm³ revealed a longer median survival than those with GTVs > 65 cm³. A study on NSCLC patients treated with definitive three-dimensional conformal radiation therapy indicated that the GTV in cubic centimeter was most highly correlated with OS, cause-specific survival and local tumor control (16). In a report on the surgical outcome of MPLIC by Hamaji et al. (10), the multivariate analysis showed that only tumor size > 2 cm was a significant negative prognostic factor for progression ($P = 0.003$) (5-year OS: 76.2% for the tumor ≤ 2 cm [T1a] and 37.4% for the tumor > 2 cm [T1b or more]). Although the difference was not significant ($P = 0.17$), in our study, T1a had a better 3-year OS (77%) than T1b and T2a (43%).

Regarding toxicities, surgical resection of MPLIC occasionally developed mortal complication. Battafarano et al. (9) evaluated resection for metachronous lung cancer and reported operative mortality of 5.8%. Among studies on surgery for MPLIC, mortality ranged from 5.4 to 7.4% (2,9,17). On the other hand, severe toxicities of SBRT toxicity are infrequent. In RTOG0236 on SBRT for inoperable NSCLC ($n = 55$), Grade 3 late toxicities developed in 12.7% and Grade 4 in 3.6% (7). A Japanese multi-institutional investigation demonstrated that the incidence of Grade 3 and 4 pneumonitis was 2.4%. In these reports, no Grade 5 adverse events were reported. In spite of previous pulmonary resection, our study presented similar low incidence of respiratory complication (12%). Although one case developed Grade 5 pneumonitis, this patient had been receiving HOT at SBRT. Thereby, SBRT could be a feasible option for MPLIC, if properly indicated.

Relevance between irradiated lung volume and toxicity could exist in SBRT for NSCLC. Matsuo et al. (18) investigated dosimetric factors associated with symptomatic radiation pneumonitis (Grade ≥ 2) after SBRT for 74 patients and observed Grade 2 pneumonitis in 15 patients and Grade 3 in 1 patient. They demonstrated that the PTV (ml), V25 (%) and V20 (%) were significant dosimetric factors and the optimal cutoffs were 37.7 ml, 4.2% and 5.8%, respectively. In our study, T stage was T1b or T2a in four patients out of six patients developing pulmonary complications. PTV (ml), V20 (%) and mean lung dose mostly exceeded the cutoffs in Matsuo’s study. We agree to Matsuo’s conclusion that the tumor size is a significant risk factor for symptomatic radiation pneumonitis after SBRT. Furthermore, we find that elder patients also had a tendency of pulmonary complication.

In our study, there is an important shortcoming that half of the patients did not have pathologic confirmation of SLC. Because of patient’s comorbidities precluding pathologic diagnosis from being attained, SBRT for lung cancer is often performed without pathologic confirmation. These patients ranged from 34 to 66% in literatures (19–22). Verstegen et al. (21) performed a large-sized study ($n = 591$) comparing clinically diagnosed disease with pathologically proven disease. No significant differences were observed between both groups in OS and regional and distant recurrence rates. Other studies including ours also demonstrated no differences in prognosis between two groups, and Takeda et al. (22) stated that clinically diagnosed patients were mostly estimated to have NSCLC and seems to include quite a small number of benign lesions, if any.

**Conclusions**

We evaluated SBRT for SLC after surgical resection of the index cancer. Even though the subjects were medically inoperable, the survival outcomes of SBRT were comparable with those of surgery. SBRT for SLC achieved similar survival outcomes to SBRT for NSCLC without previous surgery for lung cancer and the previous surgery did not seem to have a significantly negative impact on SBRT for SLC. Patients with META achieved similar survival outcomes to MPLC. Moreover, SBRT developed no more severe toxicities than surgery. Thereby, SBRT could be a treatment option for SLC: MPLC and META.

**Conflict of interest statement**

None declared.

**References**