Abstract

Objective: This study aimed to analyze the early mortality rates and patterns of relapse after stereotactic body radiotherapy (SBRT) as an initial metastasis-directed therapy.

Methods: Patients with pulmonary oligometastases initially treated with SBRT were included in this retrospective multicenter study. SBRT was performed between 2004 and 2015, and the primary lesion was controlled at the time of SBRT. Multivariate logistic regression was used for early mortality analyses.

Results: A total of 720 patients with 793 oligometastatic tumors for whom the median follow-up period was 24.6 months were enrolled. The median overall survival period was 53.2 months. The 90-, 180-, and 360-day mortality rates were 1.1% (8 deaths), 2.4% (17 deaths), and 10.8% (71 deaths), respectively. During follow up, 422 patients relapsed. Over 329 patients had single-site relapse, the most frequent site was the lung in 176; 49 had local failure; and 42 had lymph node metastases. The maximum tumor diameter was significantly related to 90-day mortality. Maximum tumor diameter, biological effective dose, and performance status were significantly related to 180-day mortality, whereas maximum tumor diameter, performance status, and pathology were significantly related to 360-day mortality.

Conclusion: Our results showed good survival outcomes and low rates of early mortality after SBRT. The patterns of relapse and factors affecting early mortality were revealed.

KEYWORDS
early mortality, initial metastasis-directed therapy, patterns of relapse, pulmonary oligometastases, stereotactic body radiotherapy
A small number of metastases are often regarded as oligometastases, for which there is potential curability with aggressive local therapy in metastatic sites. Although metastasis-directed therapy for oligometastases is sometimes performed, it is not a standard treatment, except in a few types of cancers, such as colorectal cancer. In colorectal cancer, as in other types of cancers, surgical resection of metastases is a standard strategy of metastasis-directed therapy. Stereotactic body radiotherapy (SBRT) is not recommended as an upfront metastasis-directed therapy, and is only considered in patients who are ineligible for surgery or who refuse surgery. However, the fact that SBRT is considered for patients who are ineligible for surgery indicates that most clinicians regard SBRT as a safe procedure. Indeed, SBRT for non-small cell lung cancer (NSCLC) has shown a lower rate of early mortality than surgery in some propensity score matching analyses, even in studies in which surgery was preferred. There have been doubts about the effectiveness of SBRT, but recent studies using a sophisticated SBRT technique have reported excellent outcomes. Furthermore, a prospective trial of SBRT as the first local therapy for pulmonary oligometastases from colorectal cancers showed good outcomes, with a median survival time of 46 months. Another study that compared the outcomes of SBRT and surgery for NSCLC showed that patients who received SBRT for NSCLC had significantly better survival than that in patients who underwent surgery for NSCLC, although the analysis carried out was a pooled analysis of the results of prospective trials. Some prospective trials of SBRT for oligometastases at various sites have good survival outcomes, owing to the easy accessibility to various lesions. Despite these findings, in clinical practice, clinicians tend to prefer surgery based on the results of a large number of retrospective studies evaluating the outcomes of surgery. SBRT is mainly performed in patients who are not candidates for surgery for reasons such as repeated metastasectomy and comorbidities. Recently, the results of a Japanese nationwide study on SBRT for pulmonary oligometastases in such patients were published. The current study represents a subset analysis of the nationwide study that aimed to evaluate the survival outcomes, rate of early mortality, and patterns of relapse of patients who never received metastasis-directed therapy. Although operability was not investigated in the survey, it was expected that most patients would be inoperable. Therefore, the investigation of early mortality and factors related to early mortality after SBRT is meaningful due to concerns about the factors that affect early mortality in such fragile patients, despite the reduced invasiveness of SBRT. The current study aimed to investigate the outcomes of SBRT as an initial metastasis-directed therapy for pulmonary oligometastases, and to determine the early mortality rates, patterns of relapse, and predictive factors of early mortality.

2 | METHODS

2.1 | Data acquisition and inclusion criteria

This study was a retrospective, multicenter study conducted in Japan. The primary end-point of the study has already been reported, and the current study was performed as a subset analysis. The study was approved by the ethics committee of a representative facility (Ethics Committee of Toho University Omori Medical Center, reference number: 27–148). The requirement for informed consent was waived due to the retrospective nature of the study. All participating institutions had health insurance and catered to all citizens in Japan. The institutions were given the chance to opt out of this study, and were informed about the aim and significance of the study through the Internet or posters; opt-out consent was obtained from all patients.

Patients with five or fewer detectable metastases, controlled primary lesion, and controlled extrathoracic metastatic lesion at the time of SBRT; who underwent SBRT from January 2004 to June 2015; and who received a biological effective dose (BED10) of ≥75 Gy were included in the study. The following formula was used to calculate the BED10: \( \text{BED}_{10} = n \times d / (\alpha/\beta) \), where \( n \) is the number of fractions, \( d \) is dose per fraction, and the \( \alpha/\beta \) ratio is applied for 10 Gy for the tumors. A total of 1378 patients were enrolled in the study, of whom those with no history of metastasis-directed therapy were included in the final analysis.

2.2 | Patients

A total of 720 patients with 793 oligometastatic tumors were identified from the entire cohort. The characteristics of patients, oligometastatic tumors, SBRT, and chemotherapy at the time of SBRT are summarized in Table 1. The performance status (PS) and tumor diameter were also evaluated at the time of SBRT. The disease-free interval (DFI) was defined as the interval between the date that the primary site was controlled and the date that metastasis was confirmed. The DFI was measured from the day of surgery or on the last day of radiotherapy. Adjuvant chemotherapy and hormonal therapy were not considered as treatments for primary lesions. The DFI was regarded as zero in patients with simultaneous metastases at the time of initial treatment. Oligo-recurrences, sync-oligometastases, and unclassified oligometastases had DFI values of ≥6 months, 0 months, and <6 months, respectively. The majority of patients had single pulmonary oligometastases and experienced oligo-recurrence (Table 1). The BED10 ranged from 75.0 to 233.0 Gy, the dose per fraction ranged from 4 to 20 Gy, and the number of fractions ranged from 2 to 15.

2.3 | Events definitions and analyses

The time-to-event outcomes and follow-up periods were calculated from the first day of SBRT to the occurrence of the event. The 90-day, 180-day, and 360-day mortalities were defined as all-cause deaths within 90 days, 180 days, and 360 days after SBRT, respectively. The cumulative local control rate, relapse-free survival rate, and overall survival (OS) rate were calculated using the Kaplan–Meier estimator. For the univariate comparison of 90-day, 180-day, and 360-day mortalities, Fisher’s exact test was used for categorical variables, and Wilcoxon’s rank-sum test was used for continuous variables. In the multivariate analyses, stepwise selection was applied to minimize the Akaike information criterion value, and binary logistic regressions were used to
### TABLE 1  Characteristics of patients, tumors, and treatment at the time of stereotactic body radiotherapy

| Characteristics                                      | n (%)          |
|------------------------------------------------------|----------------|
| Age (years) Median (range)                           | 72 (16–91)     |
| DFI (months) Median (range)                          | 17.9 (0–423.9) |
| Tumor diameter (cm) Median (range)                   | 1.5 (0.4–5.0)  |
| Biological effective dose (Gy) Median (range)        | 105.6 (75.0–233.0) |
| ECOG Performance Status                              |                |
| 0                                                    | 383 (53.1)     |
| 1                                                    | 245 (34.0)     |
| 2                                                    | 42 (5.8)       |
| 3                                                    | 10 (1.3)       |
| Missing                                              | 40 (5.5)       |
| No. metastases                                       |                |
| 1                                                    | 547 (75.9)     |
| 2                                                    | 134 (18.6)     |
| 3                                                    | 25 (3.4)       |
| 4–5                                                  | 7 (0.9)        |
| Missing                                              | 2 (0.2)        |
| Institution                                          |                |
| Academic                                            | 389 (54.0)     |
| Non-academic                                         | 331 (45.9)     |
| Sex                                                  |                |
| Male                                                 | 468 (65.0)     |
| Female                                               | 252 (35.0)     |
| Primary cancer sites                                 |                |
| Lung                                                 | 266 (36.9)     |
| Colorectum                                           | 129 (17.9)     |
| Esophagus                                            | 69 (9.5)       |
| Others                                               | 256 (35.5)     |
| Pathology                                            |                |
| Adenocarcinoma                                       | 363 (50.4)     |
| Squamous cell carcinoma                              | 230 (31.9)     |
| Others                                               | 87 (12.0)      |
| Not confirmed or missing                             | 40 (5.5)       |
| Methods for control of primary site                  |                |
| Surgery                                              | 566 (78.6)     |
| Other methods                                        | 152 (21.1)     |
| Missing                                              | 2 (0.2)        |
| Oligometastatic state                                |                |
| Oligo-recurrence                                    | 583 (80.9)     |
| Sync-oligometastases                                 | 51 (7.0)       |
| Unclassified oligometastases                         | 75 (10.4)      |
| Missing                                              | 11 (1.5)       |
| Irradiated tumor-located lobe                        |                |
| Upper or middle lobe                                 | 385 (53.4)     |
| Lower lobe                                           | 317 (44.0)     |
| Missing                                              | 18 (2.5)       |
| Chemotherapy before SBRT                             |                |
| Yes                                                  | 231 (32.0)     |
| No                                                   | 484 (67.2)     |
| Missing                                              | 5 (0.6)        |
| Chemotherapy concurrent with SBRT                    |                |
| Yes                                                  | 16 (2.2)       |
| No                                                   | 704 (97.7)     |
| SBRT treatment period                                |                |
| 2005–2009                                            | 257 (35.6)     |
| 2010–2015                                            | 463 (64.3)     |

The values provided under maximum tumor diameter, biological effective dose, and irradiated tumor-located lobe correspond to the number of tumors. The values indicated in other characteristics correspond to the number of patients. DFI, disease-free interval; ECOG, Eastern Cooperative Oncology Group; SBRT, stereotactic body radiotherapy.
analyze each of the mortality periods. The Holm correction for multiple testing was applied to calculate the cut-off value. The smallest \( P \)-value was \(<0.016\), the second smallest \( P \)-value was \(<0.025\), and the third smallest or highest \( P \)-value was \(<0.050\), which were all regarded as significant. EZR version 1.37 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a modified version of R commander (R Foundation for Statistical Computing, Vienna, Austria), was used for all analyses. Relapse was defined as local failure, primary lesion recurrence, or any disease progression after SBRT. The initial patterns of relapse were categorized into local failure, defined as enlargement of the irradiated tumor; primary lesion recurrence; and disease progression. Disease progression was divided into new metastases in the lung, liver, lymph node, or other distant organs. Local control was defined as the absence of local failure, whereas relapse-free survival was defined as the absence of relapse and death. Marginal field failure and involved lobe failure were not defined, and were regarded as new metastases, as considerable lung metastases were expected to emerge after SBRT.

Adverse reactions to SBRT were assessed in 689 patients. Radiation pneumonitis or hemoptysis grade \( \geq 2 \) occurred in 76 patients, grade \( \geq 3 \) occurred in 20 patients, grade \( \geq 4 \) occurred in 10 patients, and grade 5 occurred in nine patients.

3 | RESULTS

3.1 | Treatment outcomes

A total of 720 patients with 793 pulmonary oligometastatic tumors were enrolled. The median follow-up period for all patients was 24.6 months (range 0.1–134.4 months), whereas that for survivors was 28.2 months (range 0.1–134.4 months). Chemotherapy after SBRT was administered to 114 of 717 patients (3 patients had missing data). Over 287 patients died: 207 from primary disease, 76 from non-primary disease, and 4 from unknown causes. A total of eight deaths (1.1%, \( n = 705 \), censored = 15), including five deaths from primary disease and three deaths from non-primary disease, occurred within 90 days of SBRT; 17 deaths (2.4%, \( n = 695 \), censored = 25), including nine deaths from primary disease and eight deaths from non-primary disease, occurred within 180 days of SBRT; and 71 deaths (10.8%, \( n = 654 \), censored = 66), including 49 deaths from primary disease, 21 deaths from non-primary disease, and one death from unknown causes, occurred within 360 days of SBRT. The 1-, 2-, and 3-year OS rates were 89.6% (95% confidence interval [95% CI] 87.1–91.7%), 73.2% (95% CI 69.5–76.5%), and 60.0% (95% CI 55.6–64.0%), respectively, and the median survival period was 53.2 months (95% CI 47.0–68.6 months; Figure 1). The 3-year local control rate and relapse-free survival rate were 84.1% (95% CI 80.6–87.0%) and 33.1% (95% CI 29.3–37.0%), respectively (Figure 1). Of 720 patients, adverse reactions to SBRT were assessed in 689 patients. Radiation pneumonitis or hemoptysis grade \( \geq 2 \) occurred in 76 patients, grade \( \geq 3 \) occurred in 20 patients, grade \( \geq 4 \) occurred in 10 patients, and grade 5 occurred in nine patients.

3.2 | Patterns of relapse

Over 422 events were reported, including local failure, primary lesion recurrence, and disease progression. Of the 422 events, 329 occurred
in a single organ or system. 45 occurred in multiple organs or systems, and 47 were of unknown metastases. The patterns of the first relapse in 329 patients who had a relapse in a single organ or system were as follows: local failures 14.8% (49/329), primary lesion recurrences 2.4% (8/329), lymph node metastases 12.7% (42/329), lung metastases 54.4% (176/329), liver metastases 6.3% (21/329), and other single organ or system metastases 10.0% (33/329). Furthermore, 10 patients had primary lesion recurrence (8 experienced relapse for the first time); three patients had gynecological cancers, including two who developed vaginal stump recurrence after surgery, and two had esophageal cancer recurrence after chemoradiotherapy.

### 3.3 Relevant factors for early mortality

The results of univariate analyses for 90-, 180-, and 360-day mortality rates are summarized in Table 2. Maximum irradiated oligometastatic tumor diameter was significantly related to 90-, 180-, and 360-day mortality rates ($P = 0.013$, $< 0.001$, and $< 0.001$, respectively). PS was significantly related to 180- and 360-day mortality ($P = 0.008$ and 0.003, respectively). The DFI, primary cancer site, pathology, and method of controlling primary cancer were significantly related to the 360-day mortality ($P = 0.010$, 0.009, $< 0.001$, and 0.015, respectively). The BED$_{10}$ tended to be higher in the group who died 90 and 180 days after SBRT. Results of the multivariate analyses of mortality rates are shown in Table 3. In the analysis of 90-day mortality, only maximum tumor diameter (per 1 cm increase, odds ratio [OR] 2.45, 95% CI: 1.18–5.08, $P = 0.015$) showed a significant relevance. Maximum tumor diameter (per 1 cm increase, OR 2.81, 95% CI: 1.58–4.99, $P < 0.001$), BED$_{10}$ (per 10-Gy increase, OR 1.24, 95% CI: 1.04–1.48, $P = 0.018$), and PS (PS 2–3 vs. PS 0, OR 7.91, 95% CI: 1.92–32.5, $P = 0.004$) were significantly related to the 180-day mortality. Maximum tumor diameter (per 1 cm increase, OR 2.09, 95% CI: 1.47–2.96, $P < 0.001$), PS (PS 2–3 vs. PS 0, OR 2.87, 95% CI: 1.12–7.31, $P = 0.027$), primary cancer site (esophagus or others vs. lung or colorectum, OR 1.94, 95% CI: 1.05–3.57, $P = 0.033$), and pathology (squamous cell carcinoma vs. adenocarcinoma, OR 3.28, 95% CI: 1.61–6.64, $P = 0.001$; squamous cell carcinoma vs. others, OR 3.84, 95% CI: 1.68–8.78, $P = 0.001$) were significantly related to 360-day mortality.

### 4 DISCUSSION

The present study is one of the largest-scale analyses of SBRT as an initial metastasis-directed therapy for pulmonary oligometastases under a controlled primary site (oligo-recurrence) and a simultaneous control of the primary site (sync-oligometastases). The results showed extremely low 90- and 180-day mortality rates (1.1% and 2.4%, respectively), as expected from the experience of SBRT for NSCLC. In a pulmonary oligometastases setting, high safety and low mortality soon after SBRT were confirmed, although some patients received chemotherapy during the course of SBRT (Table 1). At 360 days after SBRT, the mortality rate increased to 10.8%, and the number of deaths from primary disease doubled compared with that from non-primary disease (49 vs. 21 deaths). This finding suggested that primary disease progression contributed greatly to the 360-day mortality after SBRT. The number of deaths from primary disease and non-primary disease finally increased to 207 and 76, respectively. Good OS was also observed 360 days after SBRT, and the median survival period of 53.2 months was comparable to that after surgery. Pastorino et al. reported a median survival period of 35 months after complete metastasectomy, and Casiraghi et al. reported a 5-year OS rate of 46% in patients who underwent R0 resection. These results clearly indicate that SBRT is an effective alternative treatment to metastasectomy, and that the choice of method for metastasis-directed therapy should be judged appropriately by considering the very low early mortality rate after SBRT, as well as the different routes of access to the metastatic lesions in SBRT and metastasectomy.

Maximum metastatic tumor diameter was significantly related to 90-, 180-, and 360-day mortality rates. The maximum tumor diameter is a well-known factor related to survival after SBRT for pulmonary metastases or other oligometastases. Tumor diameter also affects the early mortality rate, as there is a tendency in patients with a larger tumor diameter to have a larger SBRT-treated volume; this might result in a greater irradiated lung volume and affect other organs, thus causing radiation pneumonitis and other toxicities. However, the number of pulmonary metastases is not related to early mortality. Therefore, the number of pulmonary metastases might make a lower contribution to early mortality compared with the maximum tumor diameter. The number of metastases might have a lesser effect on a few patients with three or more oligometastases or all patients with metastases limited to the lung.

The results related to BED$_{10}$ were interesting. In SBRT for metastatic targets, a higher BED resulted in a higher local control rate. However, as for early mortality, a higher BED resulted in a significantly higher rate of 180-day mortality, a trend that was also observed in the 90-day mortality. Although the date of SBRT toxicity was not investigated in this survey, reports of previous studies could explain the possible association between 180-day mortality and the timing of emergence of radiation-induced lung toxicity. As an abnormal shadow in the lung caused by SBRT occurred within 6 months in most patients (i.e., radiation pneumonitis), and early radiation pneumonitis was reported to correlate with severe radiation pneumonitis, SBRT toxicity may influence early mortality. Actually, two of 20 patients with grade ≥3 radiation pneumonitis died within 180 days after SBRT, although a grade 5 radiation pneumonitis did not occur within 180 days after SBRT. In SBRT for NSCLC, the percentage of lung volume receiving ≥20 Gy and the mean lung dose were associated with lung toxicity. Furthermore, patients with central lung tumors treated with high doses of SBRT showed a high rate of toxicity. Thus, it is possible that higher doses provide better local control, but do not always contribute to lower early mortality. However, considering the very low 90- and 180-day mortality rates, and the importance of metastasis-directed therapy, this is a risk–benefit problem, and excessive hesitation to deliver ablative radiation doses would be over-cautious.
## TABLE 2  Results of univariate analyses for 90-, 180-, and 360-day mortality rates

| Factors | 90-day (n = 705, censored = 15) | 180-day, n = 695, censored = 25 | 360-day, n = 654, censored = 66 |
|---------|---------------------------------|-------------------------------|-------------------------------|
|         | Alive (n) | Death (n) | P-value | Alive (n) | Death (n) | P-value | Alive (n) | Death (n) | P-value |
| Age     | 692 | 7 | | 673 | 16 | 0.768 | 579 | 69 | |
| Median (years) | 72 | 73 | 0.768 | 72 | 73 | 0.672 | 72 | 72 | 0.952 |
| Missing | 5 | 1 | | 5 | 1 | | 4 | 2 |
| Disease-free interval | 688 | 8 | 0.705 | 669 | 17 | 0.220 | 18.5 | 14.0 | 0.010 |
| Median (months) | 17.8 | 16.8 | 0.705 | 17.9 | 13.6 | | 18.5 | 14.0 | 0.010 |
| Missing | 9 | 0 | | 9 | 0 | | 6 | 2 |
| Maximum tumor diameter | 661 | 8 | 0.013 | 644 | 16 | | 555 | 67 | |
| Median (cm) | 1.5 | 2.5 | | 1.5 | 2.5 | 0.001 | 1.5 | 2.1 | 0.001 |
| Missing | 36 | 0 | | 34 | 1 | | 28 | 4 |
| Biological effective dose | 630 | 7 | 0.167 | 613 | 15 | 0.043 | 105.6 | 105.6 | 0.681 |
| Median (Gy) | 105.6 | 112.5 | | 105.6 | 119.6 | | 105.6 | 105.6 | 0.681 |
| Missing | 67 | 1 | | 65 | 2 | | 57 | 6 |
| Performance status | | | | | | | | | |
| 0 | 371 | 3 | | 363 | 6 | | 324 | 26 |
| 1 | 239 | 3 | | 232 | 6 | | 193 | 31 |
| 2-3 | 49 | 2 | 0.162 | 45 | 5 | 0.008 | 38 | 10 | 0.003 |
| Missing | 38 | 0 | | 38 | 0 | | 28 | 4 |
| No. metastases | | | | | | | | | |
| 1 | 531 | 6 | | 515 | 15 | | 442 | 57 |
| 2 | 129 | 2 | | 126 | 2 | | 110 | 11 |
| 3-5 | 36 | 0 | 0.776 | 36 | 0 | 0.640 | 30 | 3 | 0.813 |
| Missing | 1 | 0 | | 1 | 0 | | 1 | 0 |
| Institution | | | | | | | | | |
| Academic | 375 | 5 | | 364 | 9 | | 315 | 41 |
| Non-academic | 322 | 3 | 0.732 | 314 | 8 | 1.000 | 268 | 30 | 0.614 |
| Sex | | | | | | | | | |
| Male | 454 | 7 | | 438 | 15 | | 377 | 53 |
| Female | 243 | 1 | 0.274 | 240 | 2 | 0.067 | 206 | 18 | 0.112 |
| Primary cancer sites | | | | | | | | | |
| Lung | 259 | 2 | | 252 | 5 | | 227 | 20 |
| Colorectum | 124 | 0 | | 119 | 4 | | 109 | 7 |
| Esophagus | 66 | 2 | | 63 | 4 | | 51 | 12 |
| Others | 248 | 4 | 0.178 | 244 | 4 | 0.179 | 196 | 32 | 0.009 |
| Pathology | | | | | | | | | |
| Adenocarcinoma | 354 | 2 | | 347 | 5 | | 314 | 20 |
| Squamous cell carcinoma | 222 | 3 | | 213 | 7 | | 171 | 29 |
| Others | 84 | 2 | 0.194 | 83 | 2 | 0.347 | 67 | 16 | <0.001 |
| Missing | 37 | 1 | | 35 | 3 | | 31 | 6 |
| Control of primary sites | | | | | | | | | |
| Surgery | 549 | 4 | | 532 | 12 | | 462 | 47 |
| Other methods | 146 | 4 | 0.068 | 144 | 5 | 0.383 | 120 | 24 | 0.015 |
| Missing | 2 | 0 | | 2 | 0 | | 1 | 0 |

(Continues)
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The DFI and oligo-recurrences, which are common prognostic factors after SBRT for oligometastases, were not independent significant factors for early mortality.\(^{27-29}\) It is likely that these factors reflect the state of malignancies, including the aggressiveness of the primary disease and the tendency for the primary disease to spread throughout the body. These factors may be used to determine the effectiveness of metastasis-directed therapy, but they do not have significant relevance to early mortality, given the relatively low ratio of deaths from primary disease in the early period after SBRT. Control of primary lesions and true single organ oligometastases with no history of prior metastasis-directed therapy, which resulted in the first relapse of cancer in the lung (the most common site of relapse), contributed to the prolongation of survival and reduction in the rate of early mortality. Furthermore, successful control of the primary lesion, which led to the recurrences of eight primary lesions at first relapse, also contributed to the excellent survival outcomes and minimized the effect of oligo-recurrence; conversely, the effectiveness of metastasis-directed therapy was maximized. DFI and oligo-recurrences showed prognostic significance, as deaths from primary disease increased; these factors are useful to identify long-term survivors and long-term relapse-free survivors after metastasis-directed therapy.

The present retrospective study had several limitations. The retrospective nature of the study has inherent selection biases. Furthermore, some missing data were reported, various or short follow-up procedures were performed, and various treatment protocols in addition to SBRT were used, all of which may have affected the results. Possible factors, such as comorbidity and operability, were not investigated. Finally, the 90-day and 180-day mortality rates were low.

In conclusion, SBRT for pulmonary oligometastases resulted in good OS with a median survival of 53.2 months, which is comparable to that after surgical resection. Furthermore, the rate of early mortality after SBRT was very low (1.1% at 90 days and 2.4% at 180 days after SBRT), even in patients who were not candidates for surgery. SBRT is a good alternative to metastasectomy considering its effectiveness and reduced invasiveness. Some factors affecting the early mortality rate and patterns of failure were reported; these findings will be helpful in the selection and follow up of patients after SBRT.

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TABLE 3  Results of multivariate logistic analyses for 90-, 180-, and 360-day mortality using stepwise selection

| Factors                          | OR   | 95% CI   | P     |
|----------------------------------|------|----------|-------|
| **90-day mortality**             |      |          |       |
| Maximum tumor diameter           |      |          |       |
| Per 1-cm increase                | 2.45 | 1.18–5.08| 0.015 |
| Control of primary site          |      |          |       |
| Surgery vs. other methods        | 0.24 | 0.24–1.00| 0.050 |
| **180-day mortality**            |      |          |       |
| Maximum tumor diameter           |      |          |       |
| Per 1-cm increase                | 2.81 | 1.58–4.99| <0.001|
| Biological effective dose        |      |          |       |
| Per 10 Gy increase               | 1.24 | 1.04–1.48| 0.018 |
| Performance status               |      |          |       |
| 1 vs. 0                          | 1.36 | 0.38–4.78| 0.627 |
| 2−3 vs. 0                        | 7.91 | 1.92–32.5| 0.004 |
| Pathology                        |      |          |       |
| SqCC vs. adenocarcinoma          | 3.28 | 1.61–6.64| 0.001 |
| SqCC vs. others                  | 3.84 | 1.68–8.78| 0.001 |
| Disease-free interval            |      |          |       |
| Per 1-month increase             | 0.99 | 0.97–1.00| 0.187 |
| Located lobe                     |      |          |       |
| Upper or middle vs. lower        | 0.606| 0.33–1.11| 0.104 |

SqCC, squamous cell carcinoma.

CONFLICT OF INTEREST
YN has received lecturer fees from Janssen Pharmaceutical K.K.
TY, MA, HO, KY, TS, HY, MK, RO, and KJ have no conflicts of interest to declare.

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