Original Study



# Stereotactic Body Radiotherapy for Centrally Located Primary Non–Small-Cell Lung Cancer: A Meta-Analysis

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## Abstract

**The feasibility of stereotactic body radiotherapy (SBRT) for centrally located tumors is controversial. SBRT with 100 Gy or higher biologically equivalent dose using an α/β of 10 Gy for centrally located primary NSCLC offered excellent local control (3years; 77.6% [95% confidential interval, 65.2-86.5]), comparable with that of other SBRT reports for peripheral lung tumors. The pooled rate of Grade ≥3 complications was 12.0%. This suggest that SBRT can be used in inoperable centrally located lung tumors with a curative intent.**

**Background:** The purpose of the study was to evaluate the efficacy and safety of stereotactic body radiotherapy (SBRT) for centrally located, primary non–small-cell lung cancer (NSCLC). **Materials and Methods:** Systematic search of 4 databases (PubMed, MEDLINE, EMBASE, and Cochrane Library) was performed for literature published until May 9, 2018. Primary (overall survival [OS] and local control [LC] rates) and secondary (Grade ≥3 toxicity) endpoints were reported. **Results:** Thirteen studies encompassing 599 patients with central NSCLCs were included. Median values of T1 tumor proportion, tumor size, and median survival were 55.3% (range, 0%-75%), 3.3 (range, 2.1-4.1) cm, and 26 (range, 14-68.9) months, respectively. Pooled rates of 1-, 2-, and 3-year OS rates were 84.3% (95% confidence interval [CI], 75.7-90.3), 64.0% (95% CI, 52.9-72.2), and 50.5% (95% CI, 39.4-61.5), respectively. Pooled rates of 1-, 2-, and 3-year LC rates were 89.4% (95% CI, 80.8-94.4), 82.2% (95% CI, 71.7-89.4), and 72.2% (95% CI, 55.0-84.7), respectively. Pooled rate of Grade ≥3 complication was 12.0% (95% CI, 7.3-19.0). Meta-regression analyses showed significant positive relationships between biologically equivalent dose using an α/β of 10 Gy in the linear quadratic model ($BED_{10Gy}$) and 1- and 2-year LC rates ($P < .001$ and $P < .001$), and 1- and 2-year OS rates ($P = .0178$ and $P = .032$), and Grade ≥3 complication rate ($P = .0029$). In subgroup comparisons between $BED_{10Gy}$ <100 Gy versus ≥100 Gy, 1- and 2-year LC rates were significantly different but not for OS and Grade ≥3 complication rates. **Conclusion:** Our results suggests that SBRT is potent for tumor control in central NSCLC, although complications should be further minimized through optimization of dose-fractionation scheme and accurate planning. Using $BED_{10Gy}$ ≥100 Gy yielded higher LC rates, and dose escalation was related to OS, LC, and complications.

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## Introduction

Non–small-cell lung cancer (NSCLC) is the leading cause of cancer death worldwide with an estimated 154,050 deaths for 2018 in the United States[1] and 17,399 deaths for 2016 in South Korea.[2] Surgical resection is the standard treatment modality for early-stage NSCLC, however, many patients are considered medically inoperable because of comorbidities or individual concerns.[3] Approximately 85% to 90% of untreated patients with early stage NSCLC die of cancer

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within 5 years, and conventionally fractionated external beam radiotherapy (RT) has not provided improvement of long-term survival.[3]

Stereotactic body RT (SBRT), also known as stereotactic ablative RT, is a type of radiation therapy that uses special equipment to precisely deliver high ablative-dose radiation to a tumor. SBRT uses a very high dose per fraction in low fraction numbers, mostly <10 fractions. SBRT has achieved clinical outcomes comparable with lobectomy, and has become a standard of treatment for inoperable patients with early stage NSCLC.[4,5] Local control (LC) rates of SBRT for early stage NSCLC were reported as 84% to 98% at 2 to 3 years.[6,7]

The treatment of NSCLC located near the proximal bronchial tree (PBT) or the mediastinum is challenging for the surgical and radiation treatment approaches. More extensive surgical procedures, such as pneumonectomy, might be required in central lung tumors, which could yield higher rates of complication risk.[8,9] The difficulty in the treatment of central lung tumors is also seen for SBRT, and the use of SBRT for central lung tumors is controversial. A phase II trial using SBRT for stage I NSCLC showed excessive rates of Grade ≥3 toxicity in patients with central lung tumors compared with that in patients with peripheral lung tumors treated with 60 to 66 Gy in 3 fractions.[10] Among patients with central tumors, 46% underwent Grade 3 to 5 toxicities, 2 years after the treatment, and the authors suggested not to use the SBRT regimen for central lung tumors. In contrast, recent studies using moderate fraction size or lower biologically equivalent dose (BED) showed acceptable toxicity rates.[11-13] In a systematic review of 24 publications including 315 patients with early stage NSCLC, the crude rate of Grade 3 or 4 toxicities after SBRT for central lung tumors was 8.6%.[11] In a recent report of a prospectively collected database of patients treated with lung SBRT in Princess Margaret Cancer Center, the rates of any Grade 2 or higher toxicity were 8.4% in the patients with central lung tumors.[13]

High-dose SBRT is a double-edged sword; lower radiation doses can be associated with lower toxicity rates but also lower LC and survival.[14,15] Although possible complications are not negligible, SBRT might confer a valuable chance for cure of central NSCLCs that are difficult to be treated radically. Hence, in this article, we reviewed published literature and performed a meta-analysis, to evaluate the efficacy and safety of SBRT for centrally located primary NSCLC.

## Materials and Methods

We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline. A systematic search of the literature, published to May 9, 2018 from 4 databases including PubMed, MEDLINE, EMBASE, and the Cochrane Library, was performed. The search terms, designed to identify studies on SBRT for central lung cancer fostering survival outcome, were as follows: ("lung cancer" OR "lung tumor" OR "lung tumour") AND central AND (sbrt OR stereotactic) AND survival. A period restriction was not applied because most studies with relevant subjects were recently published. A language restriction was not considered. Unpublished studies were not considered for inclusion in the present study.

### *Selection Criteria*

The studies included in the present meta-analysis met all of the following criteria: (1) studies that included at least 10 patients with central lung cancer, treated with SBRT; (2) provision of overall survival (OS) outcome; (3) SBRT was delivered in <10 fractions; and (4) SBRT was performed for primary lung cancer, not metastatic (including oligometastatic) or recurrent cancer. Clinical studies of reirradiation were also excluded, because they might differ significantly in outcomes and toxicities from primary RT series. Studies using national databases or cancer registries, such as Surveillance, Epidemiology, and End Results, were also excluded because it might be detrimental to the independence assumption.[16]

Reviews, editorials, conference abstracts, letters, animal, or in vitro studies, and duplicated studies among databases were initially filtered by a researcher, using titles and citations. After that, 2 independent researchers reviewed the abstracts of the remaining studies to further exclude studies without relevant subjects and formats. Full text review was also performed by 2 independent researchers, to identify studies that met all inclusion criteria. For multiple studies published from single institutions, the following criteria was used in prioritizing numerical order: (1) inclusion of central lung cancer patients only, rather than with other lung cancers or malignancies; (2) those with the largest number of central lung cancer patients treated with SBRT; and (3) most recently published studies. Decisions on the final inclusion were on the basis of the mutual agreement of the 2 independent researchers.

### *Data Collection*

Data collection was performed by 2 independent researchers, using a standardized form to obtain: (1) the general information, including year of publication, name of authors, country, design of study, and the facility where study was performed; (2) clinical data, including number of patients, proportion of men, T1 tumors, age, tumor size, and dose and fractionation scheme of SBRT; and (3) treatment outcomes, including median OS rates at 1, 2, and 3 years, LC rates at 1, 2, and 3 years, and toxicity of Grade ≥3 rates. We included and presented clinical data and treatment outcomes from patients with central primary lung cancer only. We calculated the BED using an $\alpha/\beta$ of 10 Gy in the linear quadratic model ($BED_{10Gy}$) using the prescribed or median radiation dose and fractionations as well as $\alpha/\beta$ ratios of 10, which represents the biologic behavior of tumors and rapidly proliferating tissues. The equation described is as follows: $BED = D\,(1 + d/\alpha/\beta)$; where D is the total dose in Gray whereas d is the fraction dose in Gray.[17] Where tumor size was provided in volume measures (eg, cc, mL), we calculated the tumor diameter with the assumption that the tumors were spherical, using the following formula:

$$\text{tumor diameter} = 2 * \sqrt[3]{V * \frac{3}{4} * 1/\pi}$$

where V is the volume of the tumor. The primary endpoints were OS and LC rates whereas the secondary endpoint was toxicities of Grade ≥3.

### *Quality Assessment*

Because most included studies were retrospective in nature, the Newcastle–Ottawa Scale (NOS) was used to evaluate the quality of studies.[18] NOS scores of 7 to 9 and 4 to 6 indicated high-quality and medium-quality reports, respectively.

### *Statistical Analysis*

Pooled analyses were performed for primary and secondary endpoints, including time to event endpoints (survival and LC rates at 1, 2, and 3 years) and an event rate (Grade ≥3 complication rate). Survival and LC are largely affected by subject intervention and disease, which is SBRT for central NSCLC, but differences regarding tumor size, age, or treatment detail (eg, dose, target margin) might affect endpoints. Complication rates are mainly affected by subject intervention (SBRT), however, previous treatments or conditions of patients might vary among studies. Considering this, assumption to use fixed effects model so that the true effects of endpoints are homogeneous among studies is difficult to be made, and random effects model was used assuming that the true effects are heterogeneous.[19,20]

Assessment of heterogeneity among studies was performed using the Cochran Q test[21] and $I^2$ statistics,[22] and a significant heterogeneity was considered to be present if the Cochran Q $P$ value was <.1 and the $I^2$ statistic was >50%. Visual inspection of the funnel plot and quantitative analyses using Egger test of intercept[23] were used to identify publication biases. If the 2-tailed $P$ value from the Egger test was <.1, the trimmed results using the trim and fill test of Duval and Tweedie[24] were presented. For comparison among subgroups, we used a mixed effect model with a random effect to combine studies within each subgroup, and a fixed effect to combine subgroups and yield an overall effect. $P$ values derived from Q tests on the basis of analysis of variance were used and values < .05 indicated significant differences among subgroups. Meta-regressions were performed to identify relationships between primary endpoints and main clinical continuous variables, percentile of T1 patients, and $BED_{10Gy}$. The 2 variables were chosen because they were available in most of the included studies; $BED_{10Gy}$ is a treatment factor known to influence oncologic outcomes[25] in SBRT for early NSCLC, and T1 stage is a simple factor can indicate tumor size and other major anatomical prognostic factors. Two-sided $P$ values of < .05 were regarded as statistically significant. Scatter plots were generated with size of each circle indicates the size of the study (number of patients), whereas the x-axis indicates the covariate values ($BED_{10Gy}$ or T1 percentage) and the y-axis indicates logit event rates of primary endpoints (OS or LC). All statistical analyses were conducted using Comprehensive Meta-Analysis software version 3 (Biostat Inc, Englewood, NJ).

## Results

### *Study Inclusion and Characteristics*

The initial search across databases identified 751 studies. After exclusion of many reviews, editorials, letters, unpublished studies, laboratory studies, and duplicated studies among databases, 189 studies proceeded to the abstract screening stage. At abstract screening, studies with irrelevant subjects or those without clinical outcome among <10 patients with central lung cancer were excluded. Full-text review to identify studies that fully met inclusion criteria was performed for the remaining 72 studies. For studies from a single institution, we included only 1 study using selection criteria explained in the Materials and Methods section, unless those studies clearly did not include overlapped patients. There was no disagreement concerning the final inclusion of studies among researchers except with 2 studies. In one study, the fractionation scheme of SBRT ranged from 1 to 18.[26] In another study, the number of patients in 1 of the 2 cohorts included was 8.[27] For these 2 studies, all authors agreed to inclusion by agreement, through discussion. The reason for this conclusion was on the basis of most (>60%) of the patients having received SBRT in 3 or 5 fractions, and that the heterogeneity of outcomes might have been controlled through further analyses, such as subgroup analysis and meta-regression, regarding the first study. The second study provided information on 19 patients as a whole, whereas the separation into 2 cohorts was our approach. Finally, 13 studies[12,14,26-36] and 15 cohorts, encompassing 599 patients with central primary NSCLCs who underwent SBRT, were included in the present meta-analysis. The selection process is detailed in Figure 1. Of the 13 studies, 7 (53.8%) were performed in the United States, 2 in The Netherlands, and the others in Canada, China, Japan, Germany, and Austria. Eleven (84.6%) of the 13 studies were retrospectively designed. The median proportion of T1 tumors was 55.3% (range, 0%-75%). The median tumor size was 3.3 (range, 2.1-4.1) cm. According to NOS assessment, all studies were regarded to have had medium quality. The general information of the studies is summarized in Table 1.[12,14,26-29,36]

### *Overall Survival and LC*

Median survival data were available in 10 of 15 cohorts, and the median value was 26 (range, 14-68.9) months. Available 1-, 2-, and 3-year OS and LC rates are summarized in Table 2.[12,14,26-36] Calculated $BED_{10Gy}$ ranged from 72 Gy to 120.2 Gy, and the median value was 105.3 Gy.

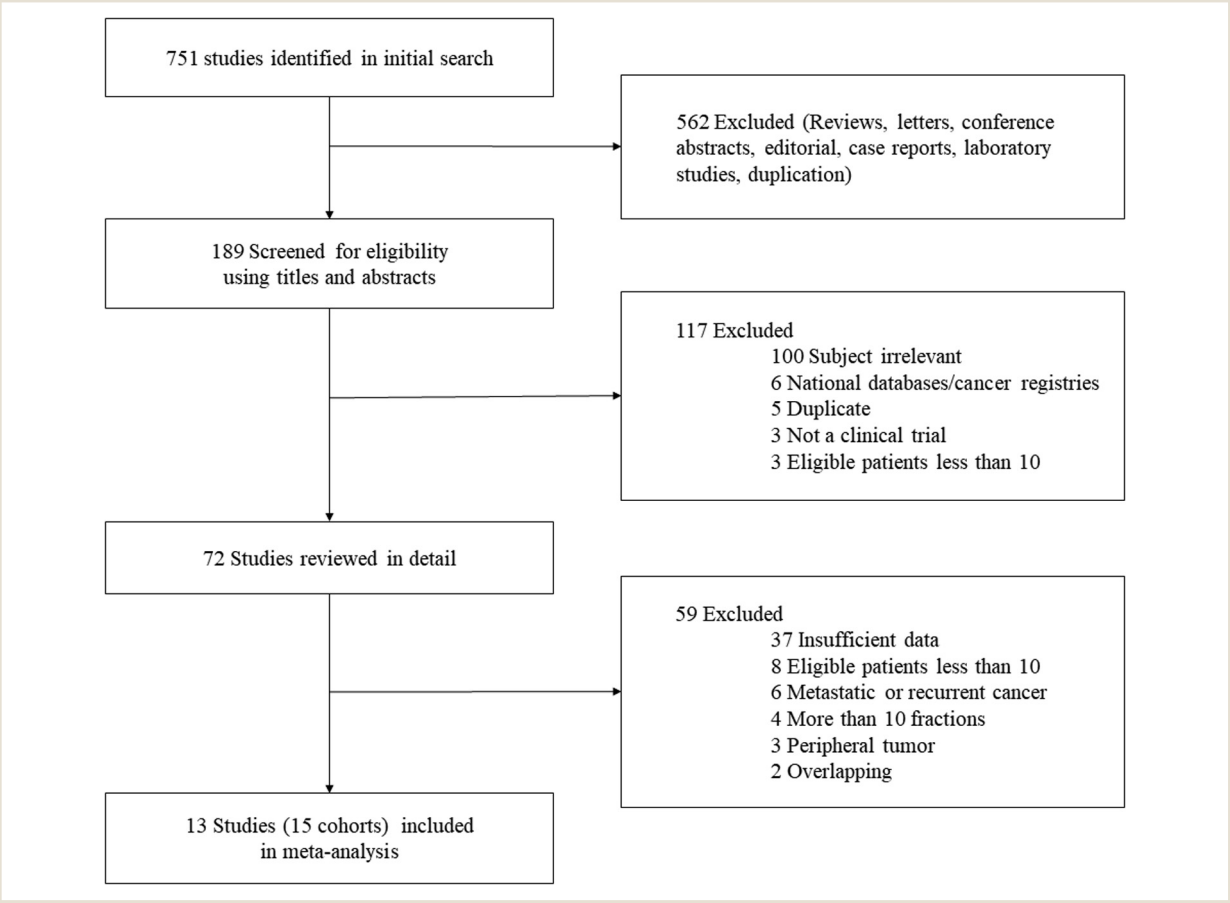
Pooled rates of 1-, 2-, and 3-year OS rates were 86.1% (95% confidence interval [CI], 78.2-91.4), 64.0% (95% CI, 52.9-72.2), and 50.5% (95% CI, 39.4-61.5), respectively. The 2-tailed $P$ value from the Egger test of 1-year OS rate was 0.049, and the trimmed value was 84.3% (95% CI, 75.7-90.3). No significant publication biases were noted regarding 2- and 3- year OS rates. Significant heterogeneities were observed in all 3 OS rates ($P$ = .002, .002, and <.001, and $I^2$ = 63.8%, 65.7%, and 75.5%, respectively). Pooled rates of 1-, 2-, and 3-year LC rates were 91.3% (95% CI, 83.2-95.7), 82.2% (95% CI, 71.7-89.4), and 72.2% (95% CI, 55.0-84.7), respectively. The 2-tailed $P$ value from the Egger test of 1-year LC rate was 0.039, and the trimmed value was 89.4% (95% CI, 80.8-94.4). No significant publication biases were identified regarding 2- and 3- year LC rates. Significant heterogeneities were observed in all 3 LC rates ($P$ = .002, <.001, and <.001, and $I^2$ = 66.9%, 74.3%, and 83.3%, respectively)

### *Treatment-Related Complications*

The complication rates of Grade ≥3 were available in 11 of 15 cohorts, and ranged from 0% to 27.3%. The pooled rate of Grade ≥3 complication was 9.1% (95% CI, 5.4-15.0). The 2-tailed $P$ value from the Egger test was 0.048, and the trimmed value was 12.0% (95% CI, 7.3-19.0). Significant heterogeneity was not observed among studies ($P$ = .107, $I^2$ = 36.6%).

Detailed information concerning the occurrence of severe toxicities was provided in 4 studies.[12,26,30,31] Among 11 patients with high-grade toxicities in the 4 studies, 5 patients experienced Grade 3 radiation pneumonitis and 1 patient died from Grade 5 radiation pneumonitis. One patient who experienced Grade 5 radiation

**Figure 1** Study Screening and Inclusion Process




pneumonitis, and who was reported by Schanne et al[26] had stage IB disease and a maximum tumor diameter of 3 cm. The patient received 48 Gy in 8 fractions and died 2 months after the treatment without reported bronchial stenosis or bleeding. The other 5 patients experienced Grade 3 or 4 toxicities including bronchopulmonary hemorrhage, vocal cord palsy, pleural effusion, pulmonary embolism, and bronchial obstruction, respectively.

### *Subgroup Comparisons*

We performed subgroup comparisons for the primary and secondary endpoints with reference to $BED10_{Gy}$ = 100 Gy, which affected the survival and tumor control rates significantly, in a previously large study.[25] Of 13 available studies, 10 studies were categorized as $BED_{10Gy}$ ≥100 Gy. Because the number of studies categorized as $BED_{10Gy}$ <100 Gy was only 3, we mainly considered heterogeneity among studies with $BED_{10Gy}$ ≥100 Gy after subgroup comparisons.

One-, 2-, and 3-year OS rates for $BED_{10Gy}$ <100 Gy were 75.4% (95% CI, 52.0-89.7), 62.5% (95% CI, 32.0-85.5), and 51.4% (95% CI, 12.7-88.5); and ≥100 Gy were 88.4% (95% CI, 80.3-93.5), 66.9% (95% CI, 59.1-73.9), and 53.0% (95% CI, 44.1-61.8), respectively. Intergroup comparison *P* values were not significant for all 3 comparisons. Among $BED_{10Gy}$ ≥100 Gy subgroup studies, heterogeneities were significant for 1-year OS rate ($P = .039$; $I^2 = 54.8\%$), and not significant for 2-year ($P = .132$; $I^2 = 41.0\%$) and 3-year OS rates ($P = .133$; $I^2 = 46.5\%$).

One-, 2-, and 3- year LC rates for $BED_{10Gy}$ <100 Gy were 75.9% (95% CI, 66.5-83.4), 62.8% (95% CI, 52.8-71.8), and 66.3% (95% CI, 34.7-87.9); and ≥100 Gy were 93.6% (95% CI, 89.7-96.0), 86.7% (95% CI, 82.2-90.3), and 77.6% (95% CI, 65.2-86.5), respectively. Intergroup comparison *P* values were significant for 1- and 2-year LC rates ($P < .001$ and $< .001$) and not for 3-year LC rate. Among $BED_{10Gy}$ ≥100 Gy subgroup studies, significant heterogeneity was not found for all 3 analyses.

Complication for Grade ≥3 rates of $BED_{10Gy}$ <100 Gy was 2.8% (95% CI, 0.4-16.4), and for ≥100 Gy was 10.8% (95% CI, 6.2-18.1). The intergroup comparison was not significant ($P = .162$). The heterogeneity among studies in the subgroup of $BED_{10Gy}$ ≥100 Gy was not significant ($P = .09$; $I^2 = 45.3\%$). All subgroup comparisons results are summarized in Table 3.

### *Meta-Regression*

Meta-regression analyses were performed for the primary and secondary endpoints with $BED_{10Gy}$ and T1 percentage as covariates. Analyses for the 3-year OS and LC rates were not performed because the number of available studies was few.

**Table 1** General Characteristics of Included Studies

| Reference | Study Design | Affiliation | Year | Nationality | n | Male Sex, % | T1, % | Median Age (Range), Years | Median Follow-up Period (Range), Months | Tumor Size (Range), cm[a] |
|---|---|---|---|---|---|---|---|---|---|---|
| Bowers et al[29] | R | Riverside Regional Hospital | 2017 | USA | 50 | | 46 | | 12.3 (0.6-66.8) | |
| Ma et al[30] group 1 | R | Roswell Park Cancer Institute | 2018 | USA | 11 | 82 | 55 | 78 (56-84) | 12 (1.4-41.2) | 2.6 (0.1-3.9) |
| Ma et al[30] group 2 | | | | | 31 | 45 | 64 | 74 (50-89) | 17 (0-60.7) | 2.1 (0.7-4) |
| Verma et al[31] | R | 12 Centers | 2016 | USA | 26 | | 0 | | 12 | |
| Bahig et al[32] | R | Montreal Univ | 2014 | Canada | 39 | | | | 22 | |
| He et al[33] | R | Fudan Univ | 2015 | China | 18 | 83.3 | 55.6 | 74.5 (61-87) | 38.1 | 4.1; 35 $cm^3$ (2-118)[b] |
| Tekatli et al[12] | R | VU Univ | 2015 | Netherlands | 80 | 66 | 35 | 73 (45-94) | 47 | 3.8; 28 $cm^3$ (2-165)[b] |
| Chaudhuri et al[34] | R | Stanford Univ | 2015 | USA | 34 | 44.1 | 63 | 74 (30-90) | 18.5 (3-56) | 2.9; 13.2 $cm^3$ (2.4-80)[b] |
| Nuyttens et al[14] | R | Erasmus MC Cancer Institute | 2012 | Netherlands | 39 | | | 73 (34-88) | 23 | |
| Olsen et al[27] group 1 | R | Washington Univ | 2011 | USA | 8 | 62.5 | 37.5 | 78 (63-84) | 11 | 3.72; 27 $cm^3$ (7-72)[b] |
| Olsen et al[27] group 2 | | | | | 11 | 54.5 | 75 | 74 (54-87) | 16 | 3.25; 18 $cm^3$ (1-76)[b] |
| Baba et al[35] | P | Nagoya City Univ | 2010 | Japan | 29 | | 62.1 | | 26 (7-66) | |
| Fakiris et al[28] | P | Indiana Univ | 2009 | USA | 22 | | | | 50.2 (1.4-64.8) | |
| Park et al[36] | R | Yale Univ | 2015 | USA | 111 | 57.7 | 72.1 | m75.8 ± 0.8 | 31.2 | m, 2.5 cm ± 0.1 |
| Schanne et al[26] | R | 13 Centers | 2015 | Germany, Austria | 90 | 69 | 36 | 71.6 (50-90) | 14 | m, 3.3 cm |

Abbreviations: m = mean; P = prospective; R = retrospective; Univ = university; USA = United States of America.
[a]Tumor size is median except where otherwise stated.
[b]Calculated value from volume.

**Table 2 Clinical Results and Radiation Doses in Included Studies**

| Reference | n | Dose/Fractions | $BED_{10Gy}$ | MS (Months) | 1-Year OS (%) | 2-Year OS (%) | 3-Year OS (%) | 1-Year LC (%) | 2-yr LC (%) | 3-Year LC (%) | Toxicities Grade ≥3, % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Bowers et al[29] | 50 | 20-60/2-5 | | 68.9 | | | | 87.7[a] | 82.5 | | NA |
| Ma et al[30] group 1 | 11 | 26/1, 30/1 | M, 120 (93.6-120) | 27 | 82 | | | 100 | | | 18 |
| Ma et al[30] group 2 | 31 | 50-60/5 | M, 115.5 (100-132) | 25 | 87 | | | 96 | | | 6 |
| Verma et al[31] | 26 | 50/5, 60/5, 48/4, 54/3 | 72-132 | 18 | | | | | | | 3.8 |
| Bahig et al[32] | 39 | 50/5, 50/4, 60/3 | M, 113 (106-180) | | | 74 | | | 89 | | NA |
| He et al[33] | 18 | 50/10, 60/10 | M, 85.5 (75-96) | 47.7 | 100 | 88.8[a] | 75.6 | | | 94.4 | 0 |
| Tekatli et al[12] | 80 | 60/8 | 105 | 38 | 81 | 62 | 53 | | | | 6.4 |
| Chaudhuri et al[34] | 34 | 50/4, 50/5 | M, 112.5 (100-112.5) | | 100 | 67.6 | | 94.2 | 91.2 | | 3 |
| Nuyttens et al[14] | 39 | 48/8, 45/5, 50/5, 60/5 | M, 100 (76.8-132) | | 82.1[a] | 53 | 48.5[a] | 100 | 85 | 76.9[a] | NA |
| Olsen et al[27] group 1 | 8 | 45/5 | 85.5 | 14 | 62.5 | 50[a] | | 75 | 50 | 50[a] | 0 |
| Olsen et al[27] group 2 | 11 | 50/5 | 100 | | 90.9 | 90.9[a] | | 100 | 100 | | 0 |
| Baba et al[35] | 29 | 48/4, 52/4 | M, 105.6 (105.6-119.6) | | | | 72 | | | 66 | NA |
| Fakiris et al[28] | 22 | T1 60/3, T2 66/3 | 180 (T1), 211.2 (T2) | 24.4 | 90.9[a] | 54.5[a] | 40.9[a] | | | | 27.3 |
| Park et al[36] | 111 | 54/3, 50/4, 50/5 | m, 120.2 ± 2.5 | 34.8 | 96[a] | 71.6 | 47.2[a] | 95.4[a] | 87.1 | 84.6[a] | 12.6 |
| Schanne et al[26] | 90 | 37.5 (24-60)/5 (1-18) | M, 72 | 21 | 72 | 46.0[a] | 29 | 76 | 64 | 52 | 1.1 |

Abbreviations: $BED_{10Gy}$ = biologically equivalent dose using an $\alpha/\beta$ of 10 Gy in the linear quadratic model; LC = local control; M = median; m = mean; MS = median survival; OS = overall survival; T1 = tumor stage 1, tumors <3 cm; T2 = tumor stage 2, tumors that is between 3 cm and 5 cm across.
[a]Calculated value from graph.

**Table 3 Pooled Rates of Endpoints**

| Outcome | Cohorts, n | Patients, n | *P*, Heterogeneity | $I^2$, % | Egger Test, *P* | Events, % (95% CI) | Trimmed Value[a] | *P* Between |
|---|---|---|---|---|---|---|---|---|
| **1-Year OS Rate** | | | | | | | | |
| All | 11 | 455 | .002 | 63.8 | .049 | 86.1 (78.2-91.4) | 84.3 (75.7-90.3) | |
| $BED_{10Gy}$ <100 | 3 | 116 | .149 | 47.4 | .208 | 75.4 (52.0-89.7) | | |
| $BED_{10Gy}$ ≥100 | 7 | 317 | .039 | 54.8 | .622 | 88.4 (80.3-93.5) | | .142 |
| **2-Year OS Rate** | | | | | | | | |
| All | 10 | 452 | .002 | 65.7 | .279 | 64.0 (52.9-72.2) | | |
| $BED_{10Gy}$ <100 | 3 | 116 | .016 | 75.8 | .467 | 62.5 (32.0-85.5) | | |
| $BED_{10Gy}$ ≥100 | 6 | 314 | .132 | 41.0 | .469 | 66.9 (59.1-73.9) | | .517 |
| **3-Year OS Rate** | | | | | | | | |
| All | 7 | 389 | <.001 | 75.5 | .258 | 50.5 (39.4-61.5) | | |
| $BED_{10Gy}$ <100 | 2 | 108 | .001 | 91.4 | N/A | 51.4 (12.7-88.5) | | |
| $BED_{10Gy}$ ≥100 | 4 | 259 | .133 | 46.5 | .229 | 53.0 (44.1-61.8) | | .949 |
| **1-Year LC Rate** | | | | | | | | |
| All | 9 | 385 | .002 | 66.9 | .039 | 91.3 (83.2-95.7) | 89.4 (80.8-94.4) | |
| $BED_{10Gy}$ <100 | 2 | 98 | .949 | ~0.0 | N/A | 75.9 (66.5-83.4) | | |
| $BED_{10Gy}$ ≥100 | 7 | 287 | .507 | ~0.0 | .147 | 93.6 (89.7-96.0) | | <.001 |
| **2-Year LC Rate** | | | | | | | | |
| All | 8 | 382 | <.001 | 74.3 | .260 | 82.2 (71.7-89.4) | | |
| $BED_{10Gy}$ <100 | 2 | 98 | .437 | ~0.0 | N/A | 62.8 (52.8-71.8) | | |
| $BED_{10Gy}$ ≥100 | 6 | 284 | .792 | ~0.0 | .149 | 86.7 (82.2-90.3) | | <.001 |
| **3-Year LC Rate** | | | | | | | | |
| All | 6 | 295 | <.001 | 83.3 | .539 | 72.2 (55.0-84.7) | | |
| $BED_{10Gy}$ <100 | 3 | 116 | .031 | 71.2 | .496 | 66.3 (34.7-87.9) | | |
| $BED_{10Gy}$ ≥100 | 3 | 179 | .081 | 60.2 | .247 | 77.6 (65.2-86.5) | | .441 |
| **Complication Grade ≥3** | | | | | | | | |
| All | 11 | 442 | .107 | 36.6 | .048 | 9.1 (5.4-15.0) | 12.0 (7.3-19.0) | |
| $BED_{10Gy}$ <100 | 3 | 116 | .533 | ~0.0 | .233 | 2.8 (0.4-16.4) | | |
| $BED_{10Gy}$ ≥100 | 7 | 300 | .09 | 45.3 | .404 | 10.8 (6.2-18.1) | | .162 |

Abbreviations: $BED_{10Gy}$ = biologically equivalent dose using an $\alpha/\beta$ of 10 Gy in the linear quadratic model; LC = local control; OS = overall survival.
[a]Trimmed for possible publication biases.

The $BED_{10Gy}$ showed strong relationships with 1- and 2-year LC rates ($P < .001$ and $P < .001$, respectively), and significant relationships with 1-year and 2-year OS rates ($P = .0178$ and $P = .032$, respectively). The relationship was significant for complication of Grade ≥3 rate ($P = .0229$). Similarly, T1 percentage showed a strong relationship with 1- and 2- year LC rates ($P < .001$ and $P = .0004$), significant relationship with 1-year OS rate ($P = .0002$), and borderline significance with 2-year OS rate ($P = .0744$). The relationship was not significant for the complication of Grade ≥3 rate ($P = .1728$).

The results of the meta-regression are shown as scatter plots in Figures 2 and 3.

### *Publication Biases*

Publication biases were identified using visual inspection of funnel plots and Egger tests, and trimmed results are presented for the 1-year OS rate, 1-year LC rate, and complications of Grade ≥3 rate.

## Discussion

In the present study, we showed comparable treatment outcomes of SBRT for patients with centrally located NSCLC in 13 studies involving 599 patients. This study showed that SBRT with a $BED_{10Gy}$ of 100 Gy or higher offered excellent LC (3-year, 77.6%), comparable to that of other SBRT reports for peripheral lung tumors.[37] Not surprisingly, the pooled rate of 3-year OS was 50.5% in this study, which is lower than other reports after surgery.[38] The trials included in this meta-analysis had inoperable patients and few operable patients and the percentage of operability is a strong predictor for OS as shown in previous studies.[37,39]

Statistically significant heterogeneity was shown in the analyses of the OS and LC in the present study. We assumed the main factor of the heterogeneity might be different dose-fractionation schemes. Therefore, to assess whether any differences in survival were because of differing dose fractionation, we used a meta-regression model. From the model, higher BED was significantly associated with higher OS and LC rates, but complications of Grade ≥3 also had a positive relationship with BED. The finding that the OS and LC rates can be increased with dose escalation and the LC rate of BED ≥100 Gy can be achieved as high as that in peripheral lung tumors is quite encouraging. This suggests that SBRT can be used in inoperable centrally located lung tumors as a curative intent.

The use of higher BED to achieve a better tumor control in central lung tumors has been widely suggested.[14,15,27] Nuyttens et al reported that the 2-year LC rate was 85% for tumors treated with a $BED_{10Gy}$ >100 Gy compared with 60% for tumors treated with a $BED_{10Gy}$ ≤100 Gy.[14] According to a retrospective report by Rowe et al, the 2-year LC rate in patients who received BED ≥100 Gy was 100%, whereas the rate in those who received <100 Gy was 80%.[15] In our meta-analysis, the pooled rates of 1- and 2-year LC rates in studies using $BED_{10Gy}$ ≥100 Gy versus $BED_{10Gy}$ <100 Gy were 93.6% versus 75.9% ($P < .001$) and 86.7% versus 62.8% ($P < .001$), respectively, which corresponds with the clinical trends in other studies.

We divided the subgroups on the basis of the radiation dose ($BED_{10Gy} = 100$ Gy) because the relationship between SBRT dose and oncologic outcome is an emerging clinical interest. The main reason that the heterogeneities were not fully resolved by the subgroup analyses might be that the number of studies included is still limited. Because LC was more affected by the radiation dose, heterogeneities were relatively well resolved at 1 year and 2 years; however, heterogeneities of OS were less resolved probably because OS was affected by several patient factors besides radiation dose and other previous or consequent treatments. Future research should be performed to investigate factors affecting OS other than tumor control related to high-dose SBRT.

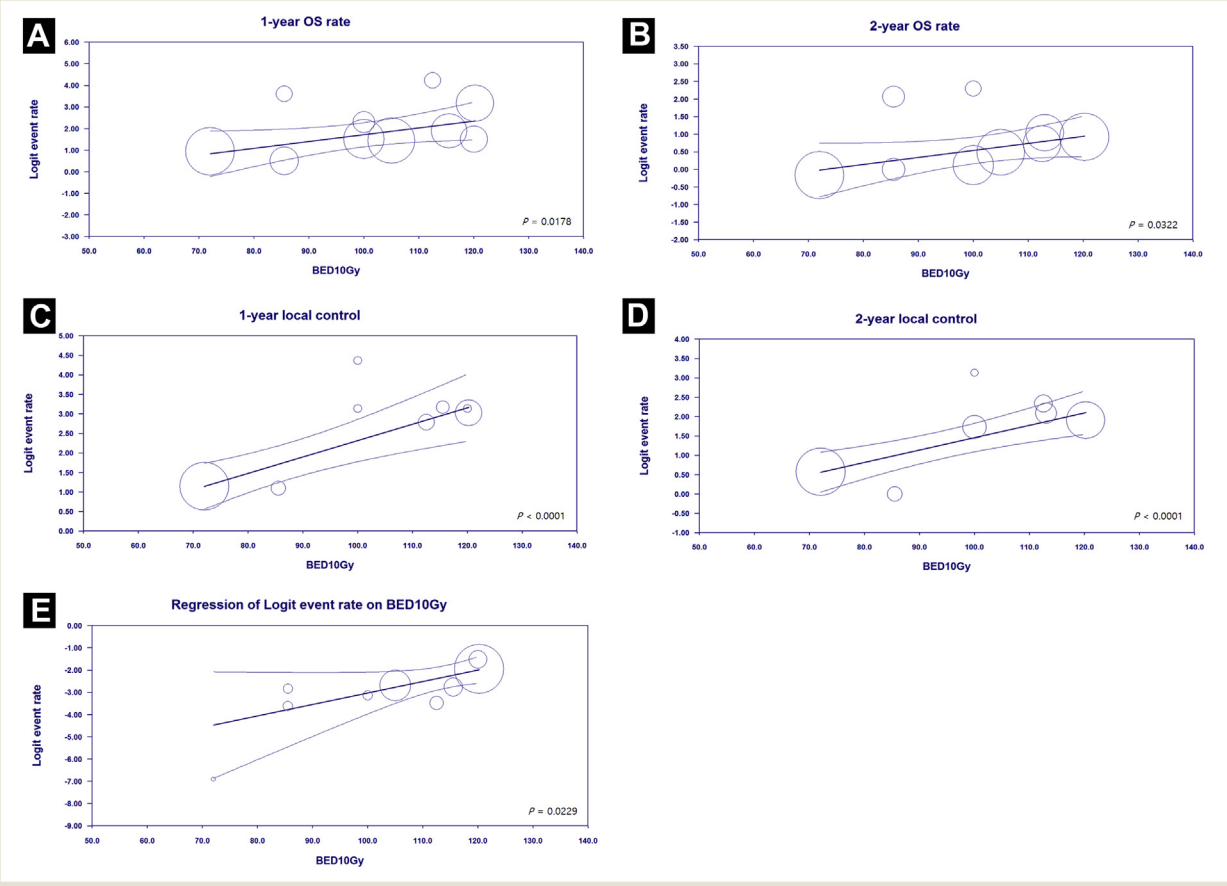
Twelve percent of the estimated rate of Grade ≥3 toxicity in this study might not be negligible. The most common toxicity among the studies that provided detailed information of Grade ≥3 toxicities was radiation pneumonitis (5/11), for which central location was not a significant factor in a previous pooled analysis of lung SBRT studies.[40] Predictive values for radiation pneumonitis in central lung SBRT are not different from those in peripheral lung SBRT. Chang et al reported that the predictive values for radiation pneumonitis among patients who received SBRT for central NSCLC were for total lung dose >6 Gy, the lung volume receiving ≥20 Gy >12%, and ipsilateral lung volume receiving ≥30 Gy (V30) >15%.[41]

Damage in central organs at risk such as esophagus, trachea, bronchi, and heart occurred in 2 patients (1 bronchopulmonary hemorrhage and 1 bronchial obstruction) among the 11 patients with detailed information on Grade ≥3 toxicities. Central tumor location itself is also a significant factor for the risk of fatal hemoptysis.[42] Fatal hemoptysis was reported in 13% to 14% of patients with endobronchial tumors after conventional RT in the older literature.[43,44] Nishimura et al reported that fatal hemoptysis can occur when the pulmonary artery or bronchus receive a dose of >50 Gy in a 5-fraction scheme.[45] In a normal tissue complication probability analysis, any grade of radiographic bronchial toxicity in the main stem or intermediate bronchus was significantly associated with maximum point doses delivered to the bronchus, with a 25% probability, at a maximum equivalent dose in 2 Gy of 193 Gy, which corresponds to 63 Gy in 5 fractions.[46] Accurate planning considering the tolerable doses to OAR referring to this information could further minimize complications of SBRT for central lung tumors.

Among the studies included in this meta-analysis, 2 cohorts reported conspicuously high toxicity rates of >15% and both cohorts used fraction size ≥20 Gy per fraction. One cohort included in a study by Ma et al[30] was a patient group treated with 26 to 30 Gy in 1 fraction, and the rate of Grade ≥3 toxicities was 18%. In the other cohort, reported by Fakiris et al,[28] 60 to 66 Gy in 3 fractions was used, and the rate of Grade ≥3 toxicities in patients with central tumors was 27.3%.

The toxicity and survival outcome vary depending on the dose fractionation scheme, but there is still no consensus on what dose and fraction should be used in central lung tumors. The Radiation Therapy Oncology Group (RTOG) performed a phase I/II trial (0813) to find the maximum tolerable dose for patients with centrally located early-stage NSCLC. The phase I report of the trial revealed that 60 Gy in 5 fractions, the highest dose level of the study, was tolerable and the second report for efficacy showed that 2-year OS in 12 Gy per fraction cohort was 72.7% (90% CI, 54.1%-84.8%).[47,48] Although it is one of the largest series of SBRT for central NSCLC, conferring oncologic outcomes, the study was not included in the present analysis because it is available in abstract

**Figure 2** Meta-Regression of Radiation Dose ($BED_{10Gy}$) With Overall Survival and Local Control. (A) One-Year Overall Survival Rates. (B) Two-Year Overall Survival Rates. (C) One-Year Local Control Rates. (D) Two-Year Local Control Rates. (E) Rates of Complications of Grade 3 or Higher



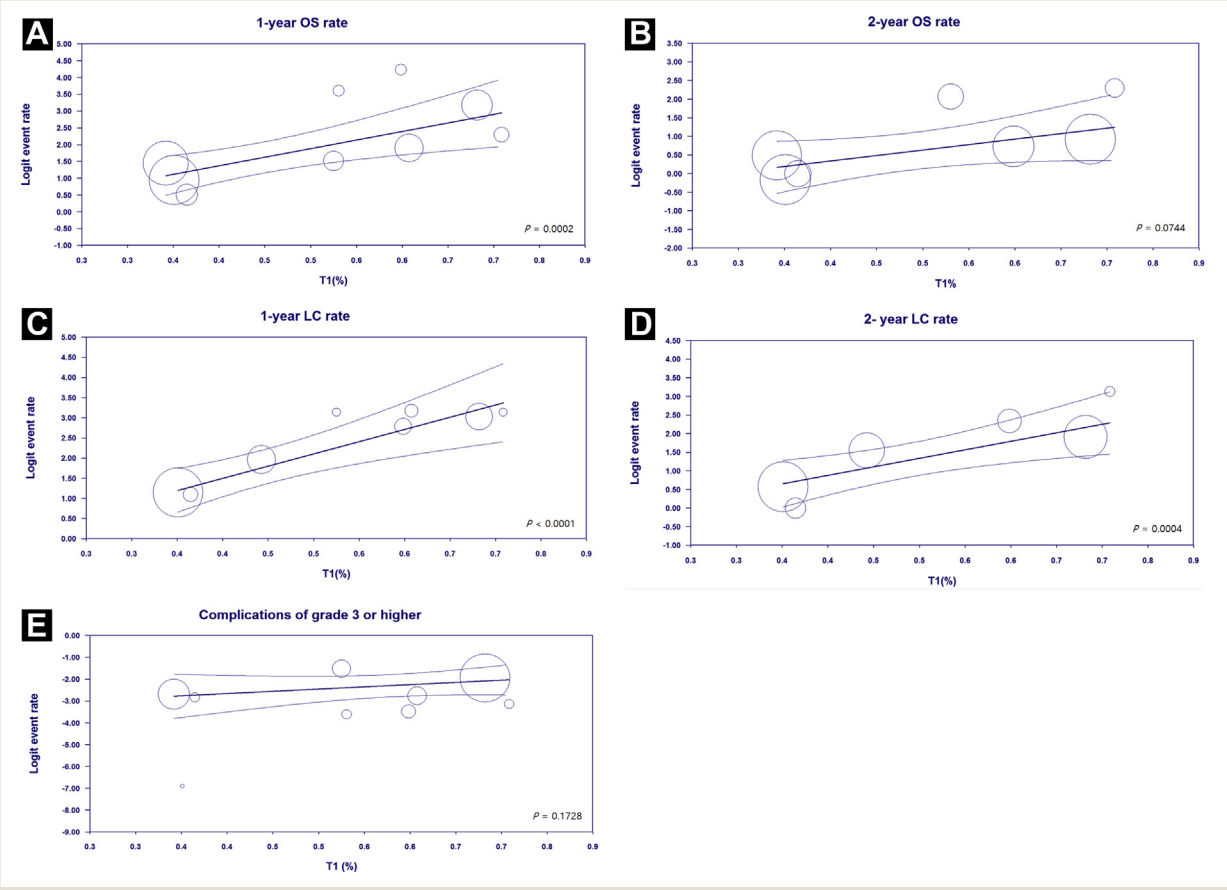

Abbreviation: $BED_{10Gy}$ = biologically equivalent dose using an $\alpha/\beta$ of 10 Gy in the linear quadratic model.

form and pending publication. The RTOG 0813 trial is ongoing to confirm the long-term safety and efficacy of 5-fraction SBRT. Similarly, a Swedish group is performing a phase II trial with 56 Gy in 8 fractions for central lung tumors, and the first toxicity analysis showed that 21 patients (28%) underwent Grade 3 to 5 toxicities.[49] Because firm safety recommendations are yet to be established for central NSCLCs SBRT, all the information described should be comprehensively considered.

A systematic review was previously published by Senthi et al,[11] which had subjects similar to our present study. Although 20 publications and 563 central lung tumors were included, approximately half of the patients had metastatic lung tumors. In our study, to estimate the treatment outcome only for primary NSCLC, we excluded metastatic or recurrent tumors and limited included studies to involve at least 10 patients with primary central NSCLC treated with SBRT, which might have yielded more homogeneous oncologic outcome and clinical interests.

The current study has several limitations. Meta-analyses using observational studies are controversial, because the heterogeneity among studies might affect pooled estimates.[50] However, oncology does not always have the best evidence, and in many situations, limited data from multiple smaller trials, retrospective studies, or clinical observations might only be available.[51] SBRT for central lung cancer is an emerging option, however, evidence is yet to be cumulated and it is not suggested as the primary standard in most clinical guidelines. So the meta-analysis of published observational studies could be one of the few options for assessing feasibility and efficacy.[50] In this study, we could not avoid the limitation of including mostly medium-quality studies. The comparability is considered to be highly important in NOS, and most of the studies are commonly regarded to have medium quality unless they have an adequate control or nonexposed group. As mentioned previously, SBRT has not been commonly proposed as a primary standard and has been reserved for patients who are not candidates for surgery. That is why we could not avoid the limitation, because most studies were mainly focused on retrospective reporting of their clinical experiences. Nonetheless, because clinicians will only see the analyzed results and quality assessments, we believe that strict evaluations of individual studies is a way to increase the validity of the study, as meta-analysts. Exclusion of unpublished studies might yield

**Figure 3** Meta-Regression of T1 Percentage With Overall Survival and Local Control. (A) One-Year Overall Survival Rates. (B) Two-Year Overall Survival Rates. (C) One-Year Local Control Rates. (D) Two-Year Local Control Rates. (E) Rates of Complications of Grade 3 or Higher




publication bias, and unpublished studies such as dissertations might not have inferior quality than published studies.[20] However, most unpublished studies in our searches were in abstract form, often with short follow-up or insufficient clinical data. Considering both, we decided not to include unpublished studies but to compensate possible publication bias with Duval and Tweedie's trim and fill method.[24] Finally, studies included in our analyses used a variety of definitions for "central lung tumors." Most of the studies[12,14,31,32,34] were on the basis of the RTOG 0813 definition (tumors within 2 cm from the PBT, or immediately adjacent to the mediastinal or pericardial pleura).[45] Another 4 studies[26-28,30] used the definition suggested in RTOG 0236 (tumors within 2 cm in all directions around the PBT).[7] In 2 other studies[29,36] tumors within 2 cm from the PBT as well as critical mediastinal structures (brachial plexus or vertebral body), were included as "central lung tumors."

To our knowledge, this study is the first and largest meta-analysis to evaluate SBRT for centrally located primary NSCLC. The present study suggests that tumor controllability of SBRT for central NSCLC was potent, although complications should be further minimized by optimization of dose-fractionation scheme and accurate treatment planning. The studies using $BED_{10Gy}$ ≥100 Gy yielded higher LC rates, and dose escalation was related to OS, LC, and complications.

### *Clinical Practice Points*

- Stereotactic body RT has become a standard of treatment for inoperable patients with early stage NSCLC, but feasibility is controversial for centrally located tumors.
- We performed meta-analysis with 13 studies encompassing 599 patients who received SBRT for centrally located primary NSCLC.
- This study showed that SBRT with $BED_{10Gy}$ ≥100 Gy for centrally located primary NSCLC offered excellent LC (3 years, 77.6%), comparable with that of other SBRT reports for peripheral lung tumors.
- The pooled rate of Grade ≥3 complications was 12.0%, which should be further minimized with optimization of dose fractionation scheme and accurate planning.
- Using $BED_{10Gy}$ ≥100 Gy yielded higher LC rates, and dose escalation was related to OS, LC, and complications.
- This suggests that SBRT can be used in inoperable centrally located lung tumors as a curative intent.

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## Disclosure

The authors have stated that they have no conflicts of interest.

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