Systematic review

Matched-pair comparisons of stereotactic body radiotherapy (SBRT) versus surgery for the treatment of early stage non-small cell lung cancer: A systematic review and meta-analysis

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A B S T R A C T

Purpose: A population-based matched-pair comparison was performed to compare the efficacy of stereotactic body radiotherapy (SBRT) versus surgery for early-stage non-small cell lung cancer (NSCLC).

Methods: All the eligible studies were searched by PubMed, Medline, Embase, and the Cochrane Library. The meta-analysis was performed to compare odds ratios (OR) for overall survival (OS), cancer-specific survival (CSS), disease-free survival (DFS), local control (LC), and distant control (DC).

Results: Six studies containing 864 matched patients were included in the meta-analysis. The surgery was associated with a better long-term OS in patients with early-stage NSCLC. The pooled OR and 95% confidence interval (CI) for 1-year, 3-year OS were 1.31 [0.90, 1.91] and 1.82 [1.38, 2.40], respectively. However, the difference in 1-year and 3-year CSS, DFS, LC and DC was not significant.

Conclusions: This systematic review found a superior 3-year OS after surgery compared with SBRT, which supports the need to compare both treatments in large prospective, randomized, controlled clinical trials.

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Lung cancer is the first and second leading cause of cancer death in males and females, accounting for 13% of the total cases and 18% of deaths in 2008 [1]. Surgery has become the recommended treatment choice for patients diagnosed with early-stage non-small cell lung cancer (NSCLC) [2], but many patients cannot undergo surgery due to comorbidities or patient preference especially in the elderly [3,4].

Stereotactic body radiotherapy (SBRT), more recently called stereotactic ablative radiotherapy (SABR), is a novel non-invasive radiation therapy modality and increasingly recognized as a favorable option in patients who are not considered operative candidates for early stage lung cancer [5–8]. Few studies also described its application in unresected hepatocellular carcinoma and benign meningioma in the elderly patients [9,10]. This approach delivers very high radiation doses to restricted tumor volumes using focused beams guided by detailed imaging [11,12]. Previous studies have revealed that SBRT could cause better survival and low rates of toxicity than conventional fractionated radiotherapy [13]. The growing evidence on SBRT outcomes has led to discussions on whether it might be equally effective as surgery for medically fit patients with NSCLC.

Currently, no randomized trials comparing surgery versus SBRT have been completed to date. The ACOSOG Z4099/Radiation Therapy Oncology Group (RTOG) 1021 trial was a phase III randomized prospective trial designed to compare outcomes in high-risk patients with stage I lung cancer treated with sublobar resection versus SBRT [14]. Unfortunately, this trial was recently closed because of poor accrual. A systematic review has showed that survival outcome in the short and medium term of patients with stage I NSCLC treated with SABR is equivalent to surgery [15]. Nevertheless, this study is an indirect comparison between the two treatment approaches, and a direct comparison should be a priority.

As far as we know, propensity score analysis allows for matching across a range of baseline factors, generating two similar groups for comparison. Therefore, we carried out a systematic review of the current literature on the clinical outcomes of SBRT for early-stage NSCLC, which mainly included propensity-matched comparative study using a large cohort of patients undergoing SBRT or surgical resection.

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Materials and methods

Literature search

We searched PubMed, Medline, Embase, and the Cochrane Library for studies published up to April 2014 by using the following keywords relating to lung cancer, surgery, radiotherapy, SBRT, and SABR.

Selection criteria

Studies were considered eligible in the meta-analysis if they met the following inclusion criteria: (1) all the patients included were stage I lung cancers; (2) study designs were prospective cohort studies or case-control studies; (3) providing data on over survival (OS), cancer-specific survival (CSS), disease-free survival (DFS), local control (LC) and (or) distant control (DC); (4) intervention: SBRT or SABR; (5) control: surgery alone. Studies were excluded based on the following reasons: (1) reviews, commentaries, editorials, case reports, and letters; (2) lacked key information for calculation with methods developed by Parmar et al. [16], Williamson et al. [17], and Tierney et al. [18]; (3) studies from one author and reported repeated samples from the same patients.

Data extraction

Studies were extracted independently by two investigators. Disagreements were resolved in consultation with a third investigator. All relevant characteristics were collected including author, publication year, country, study design, age, number of SBRT and surgery patients, tumor stage, the dose and fraction of radiation, number of events and total patients from SBRT and surgery group. Additional, CSS, DFS, LC and DC were also compared. The main outcomes were tabulated in 2 × 2 tables showing the number of events and total patients from SBRT and surgery group described by the previous research [19].

Statistical analysis

Revman 5.1 software was downloaded from the Cochrane Collaboration and used for our meta-analysis. Survival outcomes were analyzed using odd ratios (OR) with 95% CI, which can be extracted from the original article firstly. If not available, OR could be generated according to the published data including number of event patients and total patients from SBRT and surgery group. When data were only available in the figures of studies, we read the Kaplan–Meier curves by Engauge Digitizer version 4.1 and extracted the survival data to calculate ORs and its 95% CI. An observed OR > 1 considered statistically significant if the 95% CI did not overlap 1 with p < 0.05.

The heterogeneity among studies was calculated using the \( \chi^2 \) test with significance defined as p < 0.10, or quantified using \( I^2 \) with a maximum value of 30% for low heterogeneity [20–24]. For \( p > 0.10 \) or \( I^2 < 50\% \), the fixed-effects model (the Mantel–Haenszel method) was used. If not, a random effect model (the DerSimonian and Laird method) was used [24].

Begg’s test was used to assess the potential publication bias by asymmetries in the funnel [25,26]. The calculation was performed using STATA 11.0 (STATA Corporation, College Station, TX, USA), \( p > 0.05 \) was considered that there was no potential publication bias.

Results

Search results and characteristics of studies

The systematic literature search identified a total of 1477 relevant references. After screening the titles and abstracts, we excluded 199 duplicated and 1175 non-relevant studies. As shown in Supplementary Fig. 1, 96 studies were further excluded for observational study (n = 66), reviews (n = 23), insufficient data (n = 6), and duplicate data (n = 2). Finally, we identified six articles in our meta-analysis [27–33].

A propensity-matched comparison was performed in the six studies and a total of 864 matched patients were included in the review. Patients were mainly matched using propensity scores based on age, gender, tumor stage, pathology, Charlson comorbidity score, lung function and performance score. Of these included studies, 5 studies [27–31] used propensity score modeling and matched for comorbidity. Comorbidity data were not available in only one study by Palma et al. [32] where patients were matched by age, tumor stage, gender, and treatment year. The characteristics of included studies are listed in Table 1. All the patients in the six studies were diagnosed with stage I NSCLC except for one study a minority of stage II patients included [28]. The mean age of all patients was 65 years and older. The range of doses in the SBRT group was 32–60 Gy in 3–12 fractions. For patients undergoing surgery, the main operation was lobectomy that 400 (92.6%) underwent.

Survival outcome

All the studies included presented Kaplan–Meier curves, number of events and total for 1-year, 3-year OS in 864 cases, of which 432 patients were treated with surgery, and 432 patients were treated with SBRT. We compared OR for overall survival between the two groups. The pooled OR and 95% CI by comparing the treatment effect on 1-year and 3-year OS were 1.31 [0.90, 1.91] and 1.82 [1.38, 2.40] (Fig. 1), indicating that surgery was associated with better long term survival outcomes in patients with early-stage NSCLC. Three studies were noted in a sensitivity analysis contributed to a better 3-year OS of surgery patients. Of these three studies, Robinson et al. and Shirvani et al. reported the CSS data. Patients treated with SBRT died from cancer at the same rate as those undergoing surgery at 1-year (OR = 1; 95% CI 0.42–2.38; \( p = 1.00 \)) and 3-year (OR = 1.31; 95% CI 0.81–2.12; \( p = 0.27 \)) (Fig. 2).

Only the studies by Crabtree et al. and Varlotto et al. reported the DFS data. As shown in Fig. 3, there was no significant difference in the DFS. The combined OR (95% CI) for 1-year and 3-year DFS was 1.11 [0.59,2.10] and 1.19 [0.71, 1.99], suggesting that no additional survival benefit was derived from surgery in terms of DFS.

Local control and distant control

Three studies representing 392 patients reported 1-year, 3-year distant control, while two studies containing 264 patients for local control. The pooled analysis showed that compared with SBRT, surgery significantly did not decline 1-year LC (OR = 0.59; 95% CI 0.14–2.52; \( p = 0.48 \)) and 3-year LC (OR = 1.79; 95% CI 0.68–4.69; \( p = 0.24 \)) (Fig. 4). There was also no significant difference in 1-year DC (OR = 0.55; 95% CI 0.29–1.03; \( p = 0.06 \)) and 3-year DC (OR = 0.74; 95% CI 0.46–1.20; \( p = 0.22 \)) (Fig. 5).

Heterogeneity and publication bias

Heterogeneity was found in terms of 3-year DC (heterogeneity \( \chi^2 = 6.24, \ p = 0.04; \ I^2 = 68\% \) and 3-year DFS (heterogeneity \( \chi^2 = 5.76, \ p = 0.02; \ I^2 = 76\% \) 17].
X^2 = 4.01, P = 0.51; I^2 = 75\% \) in the chi-square and I-square tests. There was no evidence of heterogeneity in other survival outcomes. Begg’s funnel plot was performed to assess the publication bias in the overall survival. The funnel plot did not show any publication bias in 1-year OS (\( P = 0.573 \)) and 3-year OS (\( P = 0.573 \)) (Supplementary Fig. 2). Since no more than 3 studies were included in other survival outcomes of our study, Begg’s test and funnel were not performed.

**Discussion**

National Comprehensive Cancer Network (NCCN) guidelines have recommended surgery for patients able to have an operation and conventionally radiation therapy or SBRT for patients medically inoperable [33]. Patients with NSCLC are frequently older and experience a high burden of comorbid illness, so surgical resection is often precluded. In patients who are unable to undergo a surgical resection, conventional radiotherapy has been delivered as an alternative therapy with poor long-term survival of 15–30% and local failure of up to 50% [34–36]. Lately, a novel radiation therapy modality called SBRT is increasingly being considered as a preferred treatment choice in patients unfit for surgery or patients at high-risk for postoperative complications [4,37]. To date, no randomized trials comparing SBRT versus surgery have been completed.

It is the first propensity-matched comparative meta-analysis revealing the efficacy of SBRT in patients with early stage NSCLC using surgery as the control. The results of our meta-analysis, including data from six published studies with 864 patients, suggest that SBRT and surgery will likely yield the same 1-year OS. However, surgery was associated with a better 3-year OS in patients with early-stage NSCLC. Thus, despite having worse OS compared with surgery, patients treated with SBRT died from cancer at the same rate as those undergoing surgery, indicating that SBRT patients may be less healthy and many died of non-cancer causes. In addition, there was no significant difference in the 1-year and 3-year DFS, LC, and DC in such patients.
different between the two treatment groups. For patients treated with SBRT, toxicity often consisted of esophagitis, pneumonitis, hemoptysis, chest-wall pain, and no deaths were attributed to SBRT. For the other, cardiovascular and pulmonary complications were very common, including arrhythmia, myocardial infarction, pneumonia, thoracic empyema, and severe lung hemorrhage. The data as captured in individual studies do not cater for easy comparison, and may miss functional consequences of the various treatment approaches.

There are still several limitations in our study. First of all, only observational studies on SBRT for early stage NSCLC have been published, and most are retrospective or prospective Phase I–II studies. Although, we did a propensity score analysis allows for matching across a broad range of baseline factors, such as age, sex, tumor size, pathology, tumor location, and so on, creating two similar groups for comparison. Propensity score matching is still imperfect and cannot check for all biases, including confounding by indication [38]. There are still inevitably limitations to the ability of such an analysis no matter how carefully done. Only randomized comparisons between surgery and SBRT will avoid the imbalances and selection biases present in these comparisons. Secondly, the radiation dose and fractionation of SBRT mostly depended on the investigator's experience and varied because of a deficiency of biologically effective dose (BED) guideline. A system review and meta-analysis by Zhang et al. reported that the OS for the medium or medium to high BED (range, 83.2–146 Gy) groups were higher than those for the low or high BED group for SBRT in Stage I NSCLC [39]. Kestin et al. recently reported that a substantial dose–response relationship for local control of NSCLC following image-guided SBRT with optimal PTV (mean) BED10 > 125 Gy [40]. Thirdly, the individualized treatment planning is not the same, including rigorous accounting for organ motion, such as breath hold techniques, abdominal compression, and the acquisition of three and four dimensional (4D) planning CT scan. Patients with large tumor motion often have large margins to account for geometric uncertainty, resulting in an increased exposure of normal tissue to high doses. The latest research by Peulen et al. reported that mid-ventilation (MidV) based Planning Target Volumes (PTV) margins typically lead to smaller treatment volumes in SBRT [41].

Fig. 2. Forest plot of the comparison between SBRT and surgery treatment for 1-year and 3-year CSS.

Fig. 3. Forest plot of the comparison between SBRT and surgery treatment for 1-year and 3-year DFS.
lobectomy, segmentectomy, video-assisted thoracoscopic surgery (VATS) lobectomy, and pneumonectomy, which may affect the outcome of the comparison.

In summary, patients with early stage NSCLC treated with SBRT had similar DFS, LC and DC as patients treated with surgery but worse 3-year OS on a matched-pair analysis. However, we found two studies giving the significant impact on the long term survival after a sensitivity analysis conducted, in which patients treated with SBRT died from cancer at the same rate as those undergoing surgery. At present, a suggestion about SBRT or surgery might be best made at patient performance status, economic condition, comorbidity, operative mortality risk, quality of life, and patient preference. Our results support the need to enroll patients on large prospective, randomized controlled trials to accurately compare outcomes between SBRT and surgical operation for early stage NSCLC.

**Conflict of interest**

There were no conflicts of interest associated with this work for any of the authors.

**Appendix A. Supplementary data**

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2014.08.031.

**References**
