Stereotactic body radiation therapy versus surgery for patients with early-stage non–small cell lung cancer (≤ 5cm): A systematic review and meta-analysis

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Research

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Abstract

**Background:** Stereotactic body radiation therapy (SBRT) is considered as the preferred treatment method for inoperable early-stage non-small cell lung cancer (NSCLC). However, there is still a debate on the efficacy of SBRT and surgery. This meta-analysis aimed to compare survival outcomes of SBRT and surgery for early-stage NSCLC ($\leq$5cm).

**Methods:** A systematic review and meta-analysis were performed to compare survival outcomes of surgery and SBRT. And the pooled analysis was conducted with STATA 14.0 software.

**Results:** Thirty-nine comparative studies were included for systematic review and twenty-eight of which for quantitative analysis. Compared with SBRT, overall survival (OS) was superior after surgical resection, included lobectomy, sublobar resection, video-assisted thoracoscopic surgery, and thoracotomy, for patients with early-stage NSCLC ($\leq$5cm). And the results of subgroup analysis remained the support of surgery except for the OS of operable matched cohorts and the one matched cohort of age $\geq$75. However, the HR of OS showed a reduction from patients with unspecified age, $\geq$65 to $\geq$75 years old and histopathologically confirmed NSCLC to clinical NSCLC. Although cancer-specific survival and local control was superior after surgery, the recurrence rate of tumors, locoregional control, distant control, and regional control of matched patients demonstrated no significantly different outcomes between SBRT and surgery for early-stage NSCLC.

**Conclusions:** Results show that surgery has superior OS, CSS and local control compared to SBRT for early-stage NSCLC. There is still necessary to explore the survival difference between SBRT and surgery for patients with different characteristics by large-sample, long-term follow-up randomized clinical studies.

Introduction

Lung cancer is the leading cause of cancer deaths, while non-small cell lung cancer (NSCLC) accounts for the majority of lung cancer diagnoses(1). Currently, for patients with early-stage NSCLC who can tolerate surgery, lobectomy and systematic mediastinal lymph node dissection or sampling is still the standard treatment(2, 3). While for patients who cannot tolerate lobectomy, sublobar resection(SLR) could be the alternative modality for cure(4). However, some patients with poor lung function and multiple co-existing diseases cannot tolerate surgery. Stereotactic body radiation therapy (SBRT), precisely delivering few fractions of high-dose radiation per fraction to minimize toxicity and improve local control (LC), is considered as the preferred treatment method for inoperable patients with early-stage NSCLC(5-7). However, the efficacy of the SBRT and surgery remains controversial. Some studies found that there is no survival difference between surgery and SBRT(8, 9), but other studies found surgery with longer overall survival (OS) compared with SBRT(10, 11). A pooled analysis of two prematurely closed trials (STARS and ROSEL trials) suggested that the two treatments are equally effective and the SBRT may be an alternative treatment modality for operable patients(12). But there is still short of randomized controlled trials to clarify the efficacy of the two treatments. With more and more researchers exploring this puzzle, we need integrate again the newly relative studies to solve this issue from more different perspectives. As a result, this study will analyze comparative researches of surgery and SBRT for early-stage NSCLC ($\leq$5cm), and study OS of SBRT versus different resection types or surgical approaches, including lobectomy, sublobar resection (SLR), video-assisted thoracoscopic surgery (VATS) and thoracotomy. And we will try to explore the influence of age, operability, and histopathological confirmation on the survival difference between surgery and SBRT for early-stage NSCLC.

Methods

**Search strategy of literatures**

The searched electronic databases included Web of Knowledge Search, PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL), of their dates before March 11, 2021. And we combined the predefined search terms to seek all potentially relevant researches. The detail search strategies are showed in Appendix 1. Additional relevant publications were identified by hand-searched. Then, the predefined selection criteria were applied to assess all searched articles.

**Selection criteria**

The selection for eligible studies in the systematic review was according to the following standards. Inclusion criteria:(I) Early-stage NSCLC was limited to the clinical staging of T1a-T2aN0M0 (8th) with the tumor diameter $\leq$5cm;(II) comparative clinical studies with surgery and stereotactic radiotherapy as the main interventions; (III) at least included one of OS, cancer-specific survival (CSS), recurrence-free survival (RFS), disease-free survival (DFS), progression-free survival (PFS), LC, locoregional control (LRC), distant control (DC), regional control (RC); (IV) Published in English. Exclusion criteria:(I) Histologic findings other than NSCLC; (II) Unclear stage version or no relative information to judge tumor diameter; (III) non-comparative researches, and studies with incomplete data or missing information, such as letter, case analysis, review, editorial, conference abstracts, etc.; (IV) Ongoing clinical studies; (V) Duplicated publications. When the same institution published the multiple cohorts belongs to the same period, we used the following order to select a single study included in meta-analysis for the same indicators: (1) the study with the largest number of participants; (2) the recently published study. But for multiple studies from a single institution with different indicators, they were not excluded. And we also included the eligible subcohorts of studies in this analysis.

**Study selection and data collection**
All the potentially relevant studies were independently screened by two investigators (Y Yu and P Wen). When discrepancies between the reviewers were generated, a third investigator (Y Zhou) would intervene and resolve together with the two investigators. The data extracted included the following: institution, first author, study design, study period, patient characteristics (age, case number, tumor diameter, stage), interventions (surgery type and approach, radiation dose, biologically effective dose (BED), and fractionation schedule, adjuvant chemotherapy or radiotherapy), length of follow-up, and interest outcomes.

Risk of bias assessment

The Newcastle-Ottawa Scale (NOS) was used to assess the quality of included studies from three broad perspectives: selection, comparability, and exposure(13). A study with 0-3 stars indicated poor quality, 4-6 stars indicated moderate quality, and more than 7 stars indicated high quality. Sensitivity analysis was performed for each study to rule out its predominant influence on the pooled results. And Begg's funnel plot and Egger linear regression were used to assess the publication bias of included studies.

Statistical analysis

The comparative survival outcomes were analyzed by hazard ratio (HR) with 95% confidence interval (CI) in each included study. For studies with no HR provided, the methods described by Tierney(14) were used to calculate the corresponding outcome. And we respectively analyzed the unmatched and matched patients included in this meta-analysis for a minimized risk of selection bias. The primary analysis were survival outcomes of surgery versus SBRT. Secondary analysis was OS of different resections (lobectomy, sublobar resection, mixed resection) or different surgical approaches (VATS, thoracotomy, and mixed approaches) versus SBRT. An additional analysis was subgroup analysis for the OS of the cohort in the primary analysis. The corresponding subgroups included age subgroup of patients with unspecific age, aged ≥65 and ≥75, biopsy subgroup of histopathologically confirmed NSCLC and clinical NSCLC, and operability subgroup of operable NSCLC and not completely operable NSCLC. It should be pointed out that patients with unspecific age were partly consisted of young patients.

Heterogeneity was assessed by the I² statistic and the fixed-effects model was firstly used to calculate the pooled results. If studies with an I² of more than 50%, which is considered to have high heterogeneity, the randomized-effects model would be used to calculate again. A P-value of less than 0.05 was considered statistically significant. The pooled analysis was conducted with STATA 14.0 software.

Results

Study selection

A total of 5549 records were initially identified through the databases and 28 additional researches through other sources. After exclusion of duplicate studies and irrelevant papers, this systematic review finally included 39 studies (11, 15-52). These contained one pooled analysis of two randomized controlled trials and one pooled analysis of a randomized controlled trial and a prospective study, while the rest of 37 studies were all observational researches included 25 studies with propensity-matched data and one study with matched data. Finally, 28 studies met the selection criteria for quantitative meta-analysis. All studies included in this study at least reached moderate-quality under the assessment of Newcastle-Ottawa Scale reported scores. The select process is depicted in Figure E1 and the detailed characteristics of studies were showed in Table 1.

Patient and tumor characteristics

There are 21 unmatched studies and 19 matched studies included meta-analysis. Basic characteristics of matched and unmatched patients included for meta-analysis is showed in table E1. The commonly propensity-matched factors contained age; sex; performance status (PS); Charlson comorbidity index (CCI); respiratory function; tumor diameter, tumor stage or location, and histology. The mean age for unmatched patients is 62.0-78.3 for those who underwent surgery, 71-82.6 for those who underwent SBRT. For matched patients, the mean age is 58.7-78.3 and 60.3-78.2 respectively. The characteristics of patients and tumors in matched surgery cohorts inclined to be older or with poor pulmonary function, CCI, PS or greater clinical tumor diameter. And the histology type for matched and unmatched patients is displayed in table E2, adenocarcinoma and squamous cell carcinoma accounts for the most of NSCLC. For patients who underwent SBRT, 49.2% at most did not get a histopathologic proof of NSCLC(28). The more detailed treatment information is presented in table E3. Most patients who underwent lobectomy received mediastinal lymph node dissection or sampling(15, 31, 41, 45, 47). And for patients who underwent SLR, lymph node dissection was rarely reported. For unmatched patients who underwent surgery, there is up to 24.5% upstaged(41), 17.1% received adjuvant chemotherapy(45) and 5.4% received adjuvant radiotherapy(43). For unmatched patients who underwent SBRT, there is up to 12.1% received adjuvant chemotherapy(21). The median follow-up time is 27.5-66 months for unmatched surgery cohorts and 16-69 for months for unmatched SBRT cohorts.

Primary analysis: Results of survival outcomes of surgery versus SBRT

A total of twenty studies reported comparative OS for unmatched patients with early-stage NSCLC who underwent SBRT(N=39604) and surgery(N=179710). The pooled results showed the patients after surgery had a significantly superior OS compared those after SBRT (HR, 0.52;95% CI, 0.45-0.60; P= 0.000; I²=96.2%; Figure 1, A). In the matched cohorts, the comparative OS for patients who underwent surgery(N=19056) and SBRT(N=19060) is consistent with the unmatched cohorts (HR, 0.62; 95% CI, 0.53-0.72; P=.0000; I²=86.0%; Figure 1, B). And comparative CSS for both unmatched and matched patients who underwent SBRT or surgery, demonstrated significantly superior outcomes after surgery (Figure E2).
For DFS, RFS or PFS, we included twelve relative studies in our meta-analysis (15, 18, 21, 22, 24, 25, 30, 31, 37, 44, 45, 47). Eight studies defined DFS, RFS or PFS as the time from treatment procedure until tumor recurrence or death(15, 18, 21, 22, 31, 44, 45, 47), showing superior outcomes after surgery (matched studies: HR, 0.60,95% CI, 0.46-0.79; P=0.000; Figure E3, B). Three studies defined RFS or PFS as the time from the first day of diagnosis to the date of tumor recurrence(25, 30, 37), but the pooled outcome of matched studies demonstrated no significantly difference between SBRT and surgery (HR, 0.61,95% CI, 0.34-1.08; P=0.091; Figure E3, B).

All of the pooled results of LRC, DC and RC for unmatched patients demonstrated superior outcome for surgery (Figure E4-6, A). But the LRC, DC and RC for matched patients showed no significantly difference between SBRT and surgery (Figure E4-6, B). However, the pooled results of LC for both unmatched and matched cohorts stand by the surgery (Figure E7).

The 30-day and 90-day mortality for unmatched patients who underwent surgery was respectively 0.3-7 and 0.18-4.0, while for those who underwent SBRT is 0-0.5 and 1.3-1.4 (Table E4).

**Secondary analysis: Results of different resection types or surgical approaches versus SBRT**

Eight studies reported OS for unmatched patients who underwent lobectomy and SBRT, showing that the patients after surgery had a superior OS compared to those after SBRT (HR, 0.45,95% CI, 0.37-0.55; P=0.000; I²=87.7%; Figure E8, A). In the matched cohorts, the pooled OS is consistent with the unmatched cohorts (HR, 0.55, 95% CI, 0.37-0.82; P=0.003; I²=78.5%; Figure 2).

The HR of OS for unmatched and matched patients who underwent SLR and SBRT is lightly higher than those who underwent lobectomy and SBRT, but still showed that the patients after surgery had a significantly higher OS compared those after SBRT (unmatched cohorts: HR, 0.62,95% CI, 0.56-0.68; P=0.000; I²=83.0%; Figure E8, A. matched cohorts: HR, 0.66,95% CI, 0.61-0.71; P=.0000; =50.7%; Figure 3).

The comparative OS for both matched and unmatched patients who underwent VATS and SBRT demonstrated significantly superior outcome for patients after surgery (Figure 3 and Figure E8 B). In the subgroup of thoracotomy, the HR of comparative OS for two matched studies was slightly higher than the subgroup of VATS, but still stand by the surgery (Figure 3).

**Additional analysis and sensitivity analysis**

For the matched cohorts in the primary analysis, the HR of OS among patients with unspecific age, ≥65 and ≥75 years old showed a gradually decrease (Figure E9, B). The matched cohorts with unspecific age and ≥65 showed a significantly superior OS compared those after SBRT (HR in the subgroup with unspecific age, 0.58,95% CI, 0.49-0.70; P=.000. HR in the subgroup with ≥65 years old, 0.66,95% CI, 0.45-0.99; P=.045). The only one matched cohort with ≥75 years old included in the meta-analysis demonstrated no significant difference of OS between surgery and SBRT.

There were four studies reported OS of matched operable patients, demonstrated that surgery had same OS with SBRT (HR, 0.71,95% CI, 0.24-2.16; P=0.549; Figure 4), although the unmatched operable cohorts showed a significantly higher OS compared those after SBRT (HR, 0.42,95% CI, 0.24-0.72; P=0.002; Figure E10). For comparative OS, the pooled estimate for histopathologically confirmed NSCLC was higher than the outcome for clinical NSCLC irrespective of matching (Figure E11).

Further, sensitivity analysis showed the effect of individual studies did not act any major effect on the point estimates of OS. Egger s test indicated no obvious publication bias of included studies.

**Discussion**

SBRT is more effective than conventional radiation therapy for its higher OS and LC(53, 54). In the two phase II trials of inoperable early-stage NSCLC (≤5cm) patients treated by SBRT, the 3-year LC is higher than 90% and the 3-year OS is about 60%(5, 7). And a pooled analysis of two prematurely closed trials (STARS and ROSEL trials) demonstrated that the SBRT and surgery have comparative OS, RFS, LC, DC, and RC for patients with operable stage I NSCLC(12). However, this study only included a small number of patients and there is still a lack of other finished randomized comparative trials of SBRT and surgery. Besides, with the widespread implementation of low-dose computed tomography screening, the number of patients diagnosed with early-stage NSCLC is increasing(55, 56). There is an urgent call for physicians to explore which of the two treatment modalities is more effective.

In the present study, through the systematic search and strict selection, we finally identified 39 comparative studies for this systematic review and 28 studies of which for meta-analysis. Main findings contained surgery with statistically superior outcomes of OS, CSS, LC in both unmatched and matched patients with early-stage NSCLC (≤5cm). However, it must be noted that most studies(15, 25, 41, 44, 51) demonstrated similar LC after surgery and SBRT, except for the study by Hamaji(45) showed statistically superior LC after VATS. But there were few studies reported comparative LC after VATS and SBRT to further study. However, DC and unmatched patients showed no significantly different outcomes between SBRT and surgery. And the pooled results showed there were no recurrence difference between SBRT and surgery for matched patients. However, our study showed surgery may have a lower risk of recurrence and death which is probably a connection with the superior OS of surgery. Besides, we should notice that the HR in the matched cohorts became lower than the unmatched comparisons, which is consistent with the meta-analysis of Cao(57).

It must be acknowledged that imbalanced patient or tumor characteristics may play an important role on the reduction of HR after matching, because patient survival outcomes are always associated with age, CCI or PS, lung function, or great clinical tumor diameter(26, 52, 58, 59). What’s more, the 30-
day and 90-day mortality for people who underwent surgery was apparently higher than those who underwent SBRT, while the overall mortality is lower. This may demonstrate the similar benefit of short-term survival between surgery and SBRT rather than the long-term survival(20, 28, 48).

Secondary analysis of lobectomy, SLR, VATS, or thoracotomy versus SBRT showed superior OS for surgery in both unmatched and matched cohorts. But most patients with early-stage NSCLC after lobectomy upstaged through the systematic lymph node dissection or sampling, and then timely got adjuvant chemotherapy and radiotherapy(23, 25, 28, 38, 41, 45) and thus obtain a better survival. By contrast, the patients after SLR or SBRT less received systematic lymph node dissection or sampling. In our study, the reduction of the HR of SLR versus SBRT may further confirm the survival benefit of lymph nodes dissection or sampling for patients no matter the treatment modalities. Besides, the patients who choose SLR as a treatment may be older or with high comorbidity burden than those who choose lobectomy(60-62), which could also cause the reduction of HR of OS for the patients after SLR and SBRT. However, the HR of OS of VATS and SBRT was significantly lower than thoracotomy and SBRT, which fully demonstrated the superiority of lower postoperative morbidity and mortality of VATS(63).

What's more, the results of subgroup analysis remained the support of surgery except for the OS of matched cohorts of operable patients and the only one cohort of age ≥75. It's widely acknowledged that older patients are usually with the inferior OS for poorer physical performance and comorbidity conditions(26, 64) and people with age ≥65 are more likely to develop lung cancer(65). While for patients aged ≥75 years, they less often underwent surgery, and received SBRT(26). In our present study, although the pooled results of people with unspecific age and aged ≥65 remained in favor of surgery, may show a survival benefit after SBRT for the older patients. Besides, we explored the survival influence of patient operability for it usually means patients with less comorbidities and a good physical status. The result of the same OS between surgery and SBRT for matched patients with early-stage NSCLC is consistent with the previous studies(18, 47) which suggests that the health patients may get the same survival benefit from the two treatments. What's more, we should note that a large number of studies did not completely get the histology proof of malignance(11, 20, 27, 28, 31, 32, 35, 37, 38, 45, 47). In our study, the pooled results showed SBRT had more balanced OS with surgery for the patients with histopathological confirmed NSCLC than those with clinical NSCLC irrespective of matching. The explanation for this result may include that the patients with histopathological confirmed NSCLC have better pulmonary function and PS than those with clinical NSCLC and inclined to choose surgery, thus they usually obtain preferable survival outcome(26, 41, 58, 66).

**Limitations**

This study still has several limitations. The short of the optimal evidence of randomized controlled trials and the unavoidable patient selection bias in present observational researches are the main limitations that we need to overcome. However, it's hard to recruit patients in randomized controlled trials for patient differed choices and many other factors(67) and the current randomized controlled trials, VALOR [NCT02984761] and STABLE-MATES [NCT02468024] in US and RAXSIA [NCT03431415] in Canada need to wait.

Secondly, there were only a few of studies reported RFS, DFS, PFS, LC, LRC, DR, and RR included in our study. We cannot clearly know the relative survival benefits for neither surgery or SBRT though this pooling analysis. And there were still only several studies available to compare the survival outcome between the SLR, VATS or thoracotomy and SBRT. What's more, there is considerable heterogeneity in the pooled estimates of survival although we made subgroup analyses.

Besides, the studies mostly consisted of patients with different patient and tumor characteristics, and treatment modalities. The biologically effective dose of SBRT in most studies were not reported and the total dose and fractions varied form one institute to another. We can hardly unit these differences of treatment, although we tried to reduce the differences of surgery types and approaches. Moreover, the definition of operability differed between studies(18, 38, 40, 47). The judge of patients who can tolerate surgery is dependent on different criterions and the opinions of pulmonologists, thoracic surgeons and radiation oncologists cannot reach an agreement(68).

Finally, we must acknowledge that there is a lot of other factors, included the histology type, tumor diameter, tumor location, the PS and pulmonary function of patients that influence the survival difference of patients with NSCLC after surgery and SBRT(52, 59, 69, 70) to further study. And the follow-up of patients who underwent SBRT is apparently shorter than those who underwent surgery which need a longer follow-up study to compare the long-term survival benefit between SBRT and surgery.

**Conclusion**

The results in this study found surgical resection, included lobectomy, SLR, VATS and thoracotomy to be associated with superior OS compared with SBRT for patients with early-stage NSCLC. And the SBRT could be an alternative treatment for the healthy patients with operable early-stage NSCLC because of the same benefit of OS with surgery. For patients with age≥65 or histopathologically confirmed early-stage NSCLC, they may obtain better OS from SBRT than younger or those with clinical early-stage NSCLC. Although CSS and LC were superior after surgery, the recurrence rate of tumors, LRC, DC, and RC for the patients with more balanced characteristics showed same outcome between SBRT and surgery. However, all of these findings need to be confirmed by more studies, especially large-sample, long-term follow-up randomized clinical studies.

**Abbreviations**

**SBRT**: stereotactic body radiation therapy

**NSCLC**: non-small cell lung cancer
OS: overall survival
SLR: sublobar resection
LC: local control
VATS: video-assisted thoracoscopic surgery
CENTRAL: Cochrane Central Register of Controlled Trials
CSS: cancer-specific survival
DFS: disease-free survival
PFS: progression-free survival
RFS: recurrence-free survival
LRC: locoregional control
DC: distant control
RC: regional control
NOS: Newcastle-Ottawa Scale
HR: hazard ratio
CI: confidence interval
CCI: Charlson comorbidity index
PS: performance status

Declarations
Ethics approval and consent to participate
All analyses in this article were based on previous published studies, thus no ethical approval and patient consent are required.

Consent for publication
All data in this article were based on previous published studies, thus no patient consent for publication is required.

Availability of supporting data
All data supporting the conclusions of this article are showed in the article and its supplementary appendix.

Competing interests
All authors declare no conflict of interest.

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Authors' contributions
YZ drafted the manuscript and contributed to article designs, study selection and data analysis. PW, and YY contributed to study selection and data collection. ZY and XL contributed to analyze the data. CW conceived of the study and participated in its design. All authors made substantial contributions to the acquisition of data and manuscript writing and approved the final manuscript.

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Table

Table 1. Characteristics of studies included in systematic review.
| Institution | Author | NOS | Study period | N  | Age | Op (%) | Biopsy (%) | Technique (%) | The main outcome of interest |
|-------------|--------|-----|--------------|----|-----|--------|------------|---------------|----------------------------|
| US          |        |     |              |    |     |        |            |               |                            |
| US          |        |     |              |    |     |        |            |               |                            |
| NCDB        | Raman  | 6   | 2004-2015    | NR | NR  | NR     | NR         | NR            | OS                         |
| Wu         |        | 7   | 2004-2014    | 30451 | 22134 | NR | NR | NR | NR | NR | NR | OS |
| Wu*        |        | 7   | 2004-2014*   | 9967 | 9967 | NR | NR | NR | NR | NR | NR | OS* |
| Wu*        |        | 7   | 2004-2014*   | 2807 | 9967 | NR | NR | NR | NR | 100 | 0 | OS* |
| Wu*        |        | 7   | 2004-2014*   | 4097 | 9967 | NR | NR | NR | NR | 0 | 100 | OS* |
| Razi       |        | 7   | 2004-2015    | 8964 | 286 | ≥80 | 100 | 94 | NR | NR | Mt | OS |
| Razi*      |        | 7   | 2004-2015*   | 266 | 266 | ≥80 | 100 | NR | NR | NR | Mt | OS* |
| Mayne      |        | 6   | 2004-2015    | 570 | 475 | NR | 100 | 100 | NR | NR | Mt | OS |
| Mayne*     |        | 6   | 2004-2015*   | 279 | 279 | NR | 100 | 100 | NR | NR | Mt | OS* |
| Khorfan*   |        | 7   | 2004-2015*   | 794 | 753 | NR | 100 | NR | NR | NR | OS* |
| Chi        |        | 7   | 2004-2015    | 1571 | 89 | ≥75 | 100 | 100 | NR | NR | OS |
| Chi        |        | 7   | 2004-2015    | 3796 | 89 | ≥75 | 100 | 100 | NR | NR | OS |
| Arnold      |        | 7   | 2004–2012    | 75 | 127 | ≥90 | NR | NR | NR | NR | Mt | OS |
| Ajmani*    |        | 7   | 2005-2013*   | 3867 | 3867 | NR | NR | 100 | 100 | NR | NR | OS* |
| Yerokun*   |        | 7   | 2008-2011*   | 1584 | 1584 | NR | NR | 100 | 100 | NR | NR | OS* |
| Yerokun*   |        | 7   | 2008-2011*   | 319 | 319 | ≥80 | NR | 100 | 100 | NR | NR | OS* |
| Rosen      |        | 7   | 2008-2012    | 13652 | 1781 | NR | 100 | 100 | NR | NR | Mt | OS |
| Rosen*     |        | 7   | 2008-2012*   | 1781 | 1781 | NR | 100 | 100 | NR | NR | Mt | OS* |
| Puri        |        | 6   | 1998-2010    | 111731 | 5887 | NR | NR | NR | NR | NR | Mt | OS |
| Puri        |        | 6   | 1998-2010    | 26292 | 5887 | NR | NR | NR | NR | NR | Mt | OS |
| Puri*       |        | 6   | 1998-2010*   | 5355 | 5355 | NR | NR | NR | NR | NR | Mt | OS* |
| Puri*       |        | 6   | 1998-2010*   | 4555 | 4555 | NR | NR | NR | NR | NR | Mt | OS* |
| SEER        | Paul   | 6   | 2007-2012    | 415 | 275  | ≥66 | NR | 100 | 100 | 100 | 0 | OS, CSS |
| Paul        |        | 6   | 2007-2012    | 2253 | 714  | ≥66 | NR | 100 | 100 | 100 | 0 | OS, CSS |
| Paul        |        | 6   | 2007-2012    | 2854 | 714  | ≥66 | NR | 100 | 100 | 0 | 100 | OS, CSS |
| Paul*       |        | 6   | 2007-2012*   | 201 | 201 | ≥66 | NR | 100 | 100 | 0 | 100 | OS, CSS* |
| Name          | Years       | Cases | Mortality | 30-day Mortality | 90-day Mortality | 1-year Mortality | 5-year Mortality | Country                     | Location                      |
|---------------|-------------|-------|-----------|------------------|------------------|------------------|------------------|---------------------------|-------------------------------|
| Paul*         | 2007-2012*  | 643   | ≥66       | NR               | 100              | 100              | 0               | OS, CSS                   |                               |
| Ezer          | 2002-2009*  | 1881S | ≥66       | NR               | 100              | NR               | NR               | OS, CSS                   |                               |
| Ezer          | 2002-2009*  | NR    | > 75      | NR               | 100              | NR               | NR               | OS, CSS                   |                               |
| Ezer*         | 2002-2009*  | NR    | ≥66       | NR               | 100              | NR               | NR               | OS, CSS                   |                               |
| Smith         | 2003-2009   | 1496S | ≥66       | NR               | 100              | NR               | NR               | OS, CSS                   |                               |
| Smith         | 2003-2009   | 7215S | ≥66       | NR               | 100              | NR               | NR               | OS, CSS                   |                               |
| Smith*        | 2003-2009*  | 300S  | ≥66       | NR               | 100              | 100              | 40              | OS*                       |                               |
| Smith*        | 2003-2009*  | 243L* | ≥66       | NR               | 100              | 100              | 27              | 73*                       | OS*                           |
| Shirvani      | 2003-2009   | 7215S | ≥66       | NR               | 100              | NR               | NR               | Mt, OS, CSS*              |                               |
| Shirvani      | 2003-2009   | 1496S | ≥66       | NR               | 100              | NR               | NR               | Mt, CSS                   |                               |
| Shirvani*     | 2003-2009*  | 251L* | ≥66       | NR               | 100              | 100              | 27              | 73*                       | OS*                           |
| Shirvani      | 2001-2007   | 6531L | ≥66       | NR               | 100              | NR               | NR               | OS, CSS                   |                               |
| Shirvani      | 2001-2007   | 1277S | ≥66       | NR               | 100              | NR               | NR               | OS, CSS                   |                               |
| Shirvani*     | 2001-2007*  | 99L*  | ≥66       | NR               | 100              | 100              | 27              | 73*                       | OS*                           |
| Shirvani*     | 2001-2007*  | 112S* | ≥66       | NR               | 100              | 100              | 27              | 73*                       | OS*                           |
| Michael E. DeBakey VAMC | 2009-2014 | 127L | 56        | NR               | 100              | 100              | 0               | NR                       |                               |
| Cornwell      | 2009-2014   | 127L  | 56        | NR               | 100              | 100              | 0               | NR                       |                               |
| Cornwell*     | 2009-2014*  | 37L*  | 37        | NR               | 100              | 100              | 100             | 0*                       | Mt, Cc, OS, RFS, CSS*        |
| VINCI         | Bryant      | 2006-2015 | 634S | 449 | NR | NR | 100 | NR | Mt, OS, CSS |
| Bryant        | 2006-2015   | 2986L | 449 | NR | NR | 100 | NR | Mt, OS, CSS |
| Weill Cornell Medical Center | Parashar | 1993-2012 | 123W | 97W | 40-96 | 0 | NR | NR | NR | Cc, OS, DFS, LC, DC |
| Washington University | Crabbtree | 2000-2007 | 288 | 57 | NR | NR | 100 | NR | DFS, LC |

UK

NLCA

Khakwani | 2015 | 1897 | 476 | NR | NR | 99 | 52 | NR | NR | Mt, OS | Netherand

NCR
de Ruiter | 2012-2016 | 5042 | 3722 | ≥18 | NR | NR | 48 | 78 | 22 | NR |
de Ruiter | 2012-2016 | 4646L | 3722 | ≥18 | NR | NR | 78 | 22 | Mt, OS |

Driessen | 2010-2016 | 2299 | 3049 | ≥65 | NR | NR | 100 | 0 | OS |
| Institution                                      | Start Date | End Date | Number | Median | 5th | 95th | 5th | 95th | 5th | 95th | 5th | 95th | 5th | 95th | 5th | 95th | Country |
|-------------------------------------------------|------------|----------|--------|--------|-----|------|-----|------|-----|------|-----|------|-----|------|-----|------|---------|
| Driessen                                        | 2010-2015  |          | 414L   | 378    | ≥65 | NR   | 100 | 52   | 100 | 0    | OS  |
| Detillon                                        | 2010-2015  |          | 159L*  | 159*   | ≥65 | NR*  | 100*| 0*   | OS* |
| University of Groningen                         | 2007-2010  |          | 143    | 197    | 40-93| NR   | 41   | 22   | 6    | 94   | OS  | LRC, LC, DC
| Japan                                           |            |          |        |        |     |      |     |      |     |      |     |      |     |      |         |
| Nagoya City University Graduate School of Medical Sciences | 2004-2014  |          | 574    | 182    | 22-89| NR   | 100 | 100  | NR  | NR  | Mt, OS, DFS, CSS, LC |
| Tomita                                          | 2004-2015* |          | 120*   | 120*   | 29-89*| NR*  | 100*| 100* | NR* | NR* | Cc, OS, DFS, CSS, LC* |
| Okayama University Medical School               | 2002-2014  |          | 193S   | 58     | 25-89| NR   | 100 | 100  | 100 | 0   | Mt, Cc, OS, PFS |
| Kanazawa University and Fukui Prefectural Hospital | 2006-2013  |          | 141S   | 106    | NR   | NR   | 100 | 100  | 53  | 48  | NR  |
| Tamura                                          | 2006-2013* |          | 78*    | 78*    | NR*  | NR*  | 100*| 100* | NR* | NR* | OS, CSS, DFS* |
| Tamura*                                         | 2006-2013* |          | 37*    | 35*    | NR*  | NR*  | 100*| 100* | NR* | NR* | OS, CSS, DFS* |
| Miyazaki University hospital                    | 2008-2014  |          | 57     | 41     | ≥80  | NR*  | NR  | 59   | NR  | NR  | Mt, Cc, OS, CSS |
| Miyazaki*                                       | 2008-2014* |          | 27*    | 27*    | ≥80* | NR*  | NR* | NR*  | NR* | NR* | Mt, Cc, OS, CSS* |
| Kyoto University                                | 2003-2009  |          | 413L   | 104L   | 23-88| NR   | 100 | 88   | 100 | 0   | Mt, OS, CSS, DFS, LC, DC |
| Hamaji                                          | 2003-2009* |          | 41L*   | 41*    | 58-86*| NR*  | 100*| 93*  | 100*| 0*  | Mt, OS, CSS, DFS, LC, DC* |
| Tenri and Kurashiki Hospital                    | 2001-2011  |          | 183    | 35     | ≥75  | 37   | 100 | 100  | NR  | NR  | Mt, Cc, OS |
| Chinese                                         |            |          |        |        |     |      |     |      |     |      |     |      |     |      |         |
| Li* Gansu Provincial Hospital                   | 2014-2016* |          | 53L*   | 53*    | NR*  | 100*| 100*| 100* | 100*| 0*  | Cc, OS, DFS* |
| Zhejiang Cancer Hospital                       | 2011-2016  |          | 246L   | 70     | 39-88| NR   | 20  | 73   | 72  | 28  | Mt, Cc, OS, DFS, CSS, LC, RC, DC |
| Lin*                                            | 2011-2016* |          | 45L*   | 45*    | NR*  | NR*  | NR* | NR*  | NR* | NR* | Mt, Cc, OS, DFS, CSS, LR, RC, DC* |
| Dong                                            | 2012-2016  |          | 121S   | 109    | NR   | NR   | 100 | 86   | 100 | 0   | Mt, Cc, OS, DFS, |
| Author        | Year       | Techniques    | Mortality | RC | MT | OS | CSS | LRC |
|--------------|------------|---------------|-----------|----|----|----|-----|-----|
| Dong*        | 2012-2016* | 40*           | NR*       | 100*| NR*|    |     |     |
| Dong         | 2012-2017  | 106           | 99        | ≥70 | NR | 100| 87  | 79  |
| Zhongshan Hospital Ye | 2010-2016  | 325           | 100       | NR | NR | 100| 81  | 89  |
| Ye*          | 2010-2016* | 76*           | 76*       | NR*| NR*| 100| 85* | NR* |
| PLAGH Wang   | 2002-2010  | 106           | 74        | >60 | 19 | 100| 90  | 51  |
| Wang*        | 2002-2010* | 35*           | 35*       | >60 | NR*| NR*|     |     |
| multi-institutional Eba | 2002-2007  | 219*          | 40*       | NR | 100| 100| 100 | NR  |
| Eba*         | 2002-2007* | 21*           | 21*       | NR*| 100*| 100*|     |     |
| Chang*       | 2008-2013* | 27*           | 31*       | 43-85*| 100*| 100*| 74* |     |

Sy, surgery; SBRT, stereotactic body radiation therapy; NOS, Newcastle-Ottawa Scale; Op, operability; VATS, video-assisted thoracoscopic surgery; Ty, thoracotomy; NCDB, National Cancer Database; NR: not reported; OS, overall survival; S, sublobar resection; L, lobectomy; Mt, mortality; W, wedge; SEER, Surveillance, Epidemiology, and End Results; CSS, cancer-specific survival; VAMC, Veterans Affairs Medical Center; Cc, Complication; VINCI, VA Informatics and Computing Infrastructure; RFS, recurrence-free survival; DFS, disease-specific survival; LC, local control; DC, distant control; NLCA, National Lung Cancer Audit; NCR, Netherlands Cancer Registry; PFS, progression-free survival; RC, regional control; LRC, locoregional control; PLACH, Chinese People's Liberation Army General Hospital.

**Figures**
Figure 1

Forest plot of overall survival in unmatched patients (A) and overall survival in matched patients (B). HR, hazard ratio; CI, confidence interval.

Figure 2

Forest plot of overall survival in matched patients after different resections versus stereotactic body radiation therapy. HR, hazard ratio; CI, confidence interval; SLR, sublobar resection.
Figure 3

Forest plot of overall survival in matched patients, after different surgical approaches versus stereotactic body radiation therapy. HR, hazard ratio; CI, confidence interval; VATS, video-assisted thoracoscopic surgery.

Figure 4

Forest plot of the overall survival for matched operable and not completely operable patients. HR, hazard ratio; CI, confidence interval; VATS, video-assisted thoracoscopic surgery.

Supplementary Files

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