Review Article

Surgery and stereotactic body radiotherapy for early stage non-small cell lung cancer: review of meta-analyses

Masatsugu Hamaji[1], Yukinori Matsuo[2], Toyofumi Fengshi Chen-Yoshikawa[1], Takashi Mizowaki[2], Hiroshi Date[1]

[1]Department of Thoracic Surgery, [2]Department of Radiation Oncology and Image-Applied Therapy, Graduate School of Medicine, Kyoto University, Sakyo-ku, Kyoto, Japan

Contributions: (I) Conception and design: All authors; (II) Administrative support: T Mizowaki, H Date; (III) Provision of study materials or patients: M Hamaji, Y Matsuo, TF Chen-Yoshikawa; (IV) Collection and assembly of data: Y Matsuo, TF Chen-Yoshikawa; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Masatsugu Hamaji, MD, PhD. Department of Thoracic Surgery, Kyoto University Hospital, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan. Email: mhamaji@kuhp.kyoto-u.ac.jp.

Abstract: Observational or randomized studies on survival outcome following surgery versus stereotactic body radiotherapy (SBRT) for early-stage non-small cell lung cancer (NSCLC) demonstrated various results, and several meta-analyses on this topic have been published. The PubMed database was queried for meta-analyses comparing surgery and SBRT for early stage NSCLC. Six meta-analyses on this comparison were identified and 4 (66.7%) suggested that surgery be associated with significantly more favorable overall survival than SBRT, using odds ratio or hazard ratio (HR) as measures of effect. Most of the included studies in the meta-analyses were observational studies and those meta-analyses should be interpreted with caution.

Keywords: Surgery; stereotactic body radiotherapy (SBRT); lung cancer; survival

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Introduction

Lobectomy with systematic lymph node dissection remains the accepted standard for good risk patients with stage I non-small cell lung cancer (NSCLC). In patients with early-stage NSCLC who are medically compromised but potentially operable, treatment modalities are controversial because stereotactic body radiotherapy (SBRT) or stereotactic ablative radiotherapy (SABR) has been increasingly recognized as a favorable alternative to surgical resection for early-stage NSCLC in those patients (1-3).

Whereas several retrospective and observational studies on potentially operable patients undergoing SBRT suggested that SBRT may be a reasonable alternative to surgical resection, the definition of operability varies or ambiguous between reports (4). Given the ambiguous definition of the operability, it has been a challenge to investigate SBRT versus pulmonary resection in operable patients.

The majority of original studies that have sought to answer this important question are largely retrospective cohort studies (2,5,6) and single institution reports (1,7,8) which analyzed relatively small sample sizes. For this reason, recently published meta-analyses have performed quantitative synthesis of pooled data from these original studies to address this question (9-14). In this review we set out to evaluate the published meta-analyses on this comparison.

Search strategy

We searched the PubMed (United States National Library of Medicine) to identify original studies published in the English language from inception to July 15th, 2018 using the terms “meta-analysis”, “surgery”, “lung cancer”, and “stereotactic body radiotherapy or stereotactic ablative

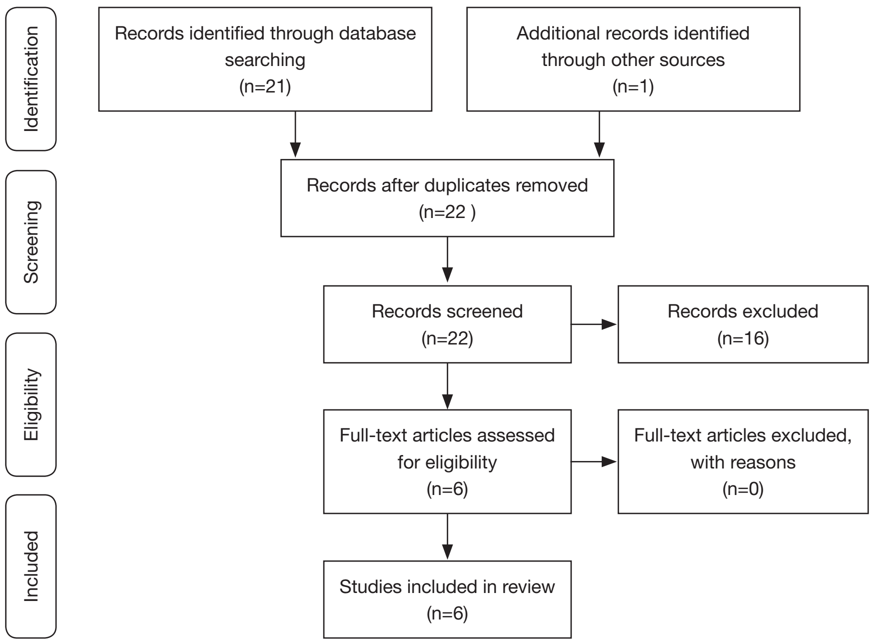

Figure 1 The workflow for selecting eligible articles according to PRISMA (preferred reporting items for systematic reviews and meta-analysis) criteria.

radiotherapy". Selection of eligible articles according to preferred reporting items for systematic reviews and meta-analysis (PRISMA) criteria is summarized as workflow in *Figure 1*. The abstracts of meta-analyses comparing between surgery and SBRT for stages I and II (early stage) NSCLC were and screened for quality, methodology, and description and then selected for full-text review.

Description of published data

In our search for meta-analyses that compare surgery and SBRT for early stage NSCLC, 22 abstracts and 6 full-text papers were evaluated. As a result, six meta-analysis articles were considered to meet eligibility for eligibility and therefore selected for review (9-14).

Six meta-analyses comparing surgery and SBRT for early stage NSCLC were comprehensively evaluated in detail (*Table 1*). Four meta-analyses were published in China, one meta-analysis published in China collaborated with Michigan group), the other published in Netherlands and Canada, between 2014 and 2018. They searched 2 to 4 databases and analyzed a median of 16 original studies, ranging from 6 to 63. The total number of patients in a meta-analysis ranged from 864 to 19,882 patients with a median of 9,675. Three meta-analyses analyzed only original studies on surgically resected stage I NSCLC, while two meta-analyses analyzed patients with surgically resected stages I and II NSCLC. Four of these meta-analyses significantly favored surgery over SBRT in terms of the outcome of overall survival in conclusion. Four meta-analyses examined publication bias and none of them reported a significant publication bias.

Two meta-analyses pooled data on surgical patients from original studies that contained only surgical patients, while pooled data on SBRT patients from another original studies that contained only SBRT patients. In other words, in the two meta-analyses, data on surgical patients and those on SBRT patients were extracted from two different sets of original studies. On the other hand, the other four meta-analyses analyzed only original studies, each of which contained data on both surgical patients and SBRT patients in their study.

Twenty-five original studies that were analyzed in the above four meta-analyses were summarized in *Table 2* (1-3,5-8,15-32). Most original studies (96%) were retrospective cohort studies and the rate of lobectomy varied from 0 to 100% with a median of 82.9%. Fourteen original studies (56%) were published in USA, 4 (16%) in Japan, 4 (16%) in Netherlands, 3 (12%) in others. The sample size ranged from 38 to 9,110 with a median

Table 1 Characteristics of reviewed meta-analyses comparing surgery versus stereotactic body radiotherapy for early-stage non-small cell lung cancer

First author	Year	Number of searched databases	Inclusion criteria (stage and/or period)	N (studies)	N (patients)	Comparison	Measure of effect	Survival outcomes	Other outcomes	Major findings
Chen	2018	2	Stage I or II, inception to 2016	16	19,882	SABR *vs.* surgery	Hazard ratio	OS/DSS	Not applicable	OS: surgery favored (HR: 1.28, 95% CI: 1.06–1.56), DSS: not significantly different
Li	2017	3	T1–T3N0, inception to 2017	15	7,810	Surgery *vs.* SBRT	Hazard ratio	OS/RFS	Local and distant controls	OS: surgery favored (HR: 1.4, 95% CI: 1.21–1.61), locoregional and distant control: not significantly different
Wang	2017	4	Stage I, no year limitation	16	11,540	Sublobar resection *vs.* SBRT	Odds ratio	OS	Local, regional, distant controls	OS: surgery favored (OR: 2.91, 95% CI: 1.94–4.38), local control: not significantly different
Ma	2016	4	Stage I or II, 2010–2015	37	6,869	VATS *vs.* SBRT	Hazard ratio	OS/DFS	Not applicable	OS (HR: 2.02, 95% CI: 0.45–3.07) and DFS: not significantly different after adjustment
Zheng	2014	4	Stage I, 2000–2012	63	11,921	Surgery *vs.* SBRT	Hazard ratio	OS/DFS	Local control	OS (HR: 0.52, 95% CI: 0.20–1.36 for lobectomy; HR: 0.49, 95% CI: 0.19–1.3 for sublobar resection) and DFS: not significantly different after adjustment
Zhang	2014	4	Stage I, inception –2014	6	864	Surgery *vs.* SBRT	Odds ratio	OS/CSS/DFS	Local and distant controls	OS: surgery favored (OR: 1.82, 95% CI: 1.38–2.4), CSS, DFS, local control, and distant control: not significantly different

SABR, stereotactic ablative radiation therapy; SBRT, stereotactic body radiotherapy; VATS, video-assisted thoracoscopic surgery; OS, overall survival; DSS, disease specific survival; CSS, cancer specific survival; RFS, recurrence free survival; DFS, disease free survival; HR, hazard ratio; CI, confidence interval; OR, odds ratio.

Table 2 Characteristics of analyzed original studies that included both surgical patients and SBRT patients and compared surgery versus SBRT

Author	Year	Country	Study design	N	Lobectomy or more (%)
Wang	2016	China	Retrospective cohort	S: 35, SBRT: 35	No data
Rosen	2016	USA	Retrospective cohort	S: 1781, SBRT: 1781	100
Paul	2016	USA	Retrospective cohort	S: 201, SBRT: 201	0
Eba	2016	Japan	Retrospective cohort	S: 21, SBRT: 21	100
Mokhles	2015	Netherlands	Retrospective cohort	S: 73, SABR: 73	100
Ezer	2015	Canada and USA	Retrospective cohort	S: 1881, SBRT: 362	0
Hamaji	2015	Japan	Retrospective cohort	S: 41, SBRT: 41	100
van den Berg	2015	Netherlands	Retrospective cohort	S: 143, SBRT: 197	88
Chang	2015	USA	Randomized control	S: 27, SBRT: 31	100 (intention-to-treat)
Kastelijn	2015	Netherlands	Retrospective cohort	S: 175, SBRT: 53	97
Puri	2015	USA	Retrospective cohort	S: 4555, SBRT: 4555	0
Smith	2015	USA	Retrospective cohort	S: 543, SBRT: 543	55.2
Shirvani	2014	USA	Retrospective cohort	S: 251, SBRT: 251	100
Crabtree	2014	USA	Retrospective cohort	S: 56 SBRT: 56	78.6
Nakagawa	2014	Japan	Retrospective cohort	S: 183, SBRT: 35	84.1
Matsuo	2014	Japan	Retrospective cohort	S: 53, SBRT: 53	0
Port	2014	USA	Retrospective cohort	S: 76, SBRT: 12	0
Varlotto	2013	USA	Retrospective cohort	S: 77, SBRT: 77	93.5
Robinson	2013	USA	Retrospective cohort	S: 76, SBRT: 76	94.7
Verstegen	2013	Netherlands	Retrospective cohort	S: 64, SBRT: 64	100
Shirvani	2012	USA	Retrospective cohort	S: 99, SBRT: 99	100
Palma	2011	Canada	Retrospective cohort	S: 60, SBRT: 60	81.7
Grills	2010	USA	Retrospective cohort	S: 69, SBRT: 58	0
Parashar	2010	USA	Retrospective cohort	S: 123, SBRT: 97	0
Forquer	2009	USA	Retrospective cohort	S: 19, SBRT: 19	0

S, surgery; SBRT, stereotactic body radiotherapy.

of 152. Among 24 retrospective cohort studies, 19 studies (79.2%) utilized propensity-score matching, 3 studies (12.5%) utilized multivariable analysis, and 2 studies (8.3%) compared surgery and SBRT with no adjustment for potential confounding factors.

Discussion

A meta-analysis is a quantitative synthesis of measured outcomes from multiple (prospective or retrospective) original studies, attempting to produce a weighted average of the included outcomes. Meta-analyses in general have several advantages that include increasing the statistical power of the analyses which are common to the individual studies and improving estimates of the size of the effect. On the other hand, they also have disadvantages and limitations in relying only on data from previously published studies. For example, it may be impossible to include all relevant studies, either because some studies are not published or because others do not include the outcome of interest, which could be associated with publication bias or selective outcome reporting bias. What is most important is that meta-analyses may inherit the limitations inherent to the original studies including selection bias, information bias, and study designs other than intention-to-treat.

In this review, six meta-analyses were summarized and discussed. Of interest, the measure of effect was not consistent among the reviewed meta-analyses. If primary outcomes in meta-analyses of original studies are related to time-to-event, special considerations are required. Time-to-event outcomes are supposed to take account of not only whether an event takes place but also when the event occurs, therefore both the event itself and the timing of the event are important. Survival outcome such as overall survival is a typical example of a time-to-event outcome. In (prospective or retrospective) cohort studies, it is most appropriate to analyze time-to-event outcomes using hazard ratios (HRs) because HRs appropriately account for both the number and timing of events, and the time until last follow-up for each patient who has not experienced an event (censored) (33,34). Odds ratio and relative risk, however, account only for the number of events and do not take into account when these events occur. It should be noted that odds ratio and relative risk could be measures of effect for survival outcome if all subjects are followed up for a certain period of observation. Specifically, if odds ratio is used for 5-year overall survival, all subjects should be followed up for more than 5 years. Those measures of effect are occasionally reported as survival outcome in several published meta-analyses although other measures of effect, such as HRs were used in the analyzed original studies. Using those measures of effect will introduce inaccuracies in meta-analyses of original studies whose primary outcomes are time-dependent variables such as overall survival and recurrence free survival.

A majority of the original studies comprising the reviewed meta-analyses were retrospective cohort studies. Prospective studies are typically expected to have fewer biases than retrospective studies, whereas even randomized studies, unless properly designed, may add little evidence to pre-existing dataset except for the erroneous conclusion (24). Study designs, whether prospective or retrospective, are of utmost importance when compare surgery and SBRT. In an attempt to perform a meta-analysis, selection of original studies will determine the quality of the meta-analysis. Especially for surgical patients, the approach (open thoracotomy, video-assisted thoracoscopic surgery, or robotic-assisted thoracoscopic surgery), the extent of resection (lobectomy or more, segmentectomy, or wedge resection), and stages of NSCLC should also be as consistent as possible among the included studies.

In conclusion, our review of meta-analyses suggested that surgery, compared with SBRT, may be associated with more favorable overall survival in patients with early stage NSCLC, whereas the results of those meta-analyses should be interpreted with caution due to the above discussions. However, inclusion of appropriate original studies and use of appropriate measures of effect would be associated with more meaningful and more relevant meta-analyses in the future.

In the future, we should seek for metrics, with surgery and SBRT in our view, to select optimal treatment options in individual patients with early stage NSCLC.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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