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SPECIAL EDITION

Diagnosis and Treatment for Early Stage Non-small Cell Lung Cancer

Surgery and stereotactic body radiotherapy for early-stage non-small cell lung cancer: prospective clinical trials of the past, the present, and the future

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Abstract
Stereotactic body radiotherapy (SBRT) may be a potential alternative to surgical resection in high-risk operable patients with early-stage non-small cell lung cancer (NSCLC). A number of clinical studies have been undertaken to answer this question, although the conclusion has remained undetermined. Although three randomized clinical trials have failed, currently several prospective clinical trials are ongoing on SBRT versus surgery for early-stage NSCLC. This review article was designed to overview the previous and ongoing clinical trials and to discuss the future perspectives in the comparisons.

Keywords Surgery · Stereotactic body radiotherapy · Lung cancer · Clinical trial

Introduction

While some researchers hypothesized equipoise between stereotactic body radiotherapy (SBRT) and surgery in low-risk or high-risk operable patients with early-stage non-small cell lung cancer (NSCLC), the definition of operability is ambiguous [1]. Given the ambiguous definition of the operability, it has been a challenge to investigate SBRT versus surgery (pulmonary resection) in operable patients. There is no high-level evidence available to address this topic, given the fact that there have been no completed randomized controlled trials on SBRT versus surgery for early-stage NSCLC.

Lobectomy with systematic lymph node dissection remains the accepted standard for low-risk patients with clinical stage I NSCLC. Specifically, the guidelines from the Japan Lung Cancer Society [2], European Society of Medical Oncology [3], and National Comprehensive Cancer Network (NCCN) [4] strongly recommend that operable patients with early-stage NSCLC should undergo lobectomy and mediastinal lymph node dissection.

In patients with early-stage NSCLC who are medically compromised but operable, treatment modalities are controversial because SBRT or stereotactic ablative radiotherapy (SABR) has been increasingly recognized as an alternative to surgical resection for early-stage NSCLC in those patients [5–7].

A majority of original studies that have sought to answer this important question are largely retrospective cohort studies [7–9] and single institutional reports [5, 10, 11]. Moreover, recently published meta-analyses performed quantitative syntheses of pooled data mostly from retrospective studies, therefore, were not free of a number of biases inherent to retrospective studies [12–17]. In terms of minimizing those biases, prospective (and ideally randomized) trials would provide fair comparisons between SBRT and surgery. In this article, we set out to review previous clinical trials, summarize ongoing ones, and discuss future perspectives.

Previous clinical trials

Before planning any well-designed clinical trials, we should learn from previous failed trials because the history of medicine may also repeat itself. Previously, three-phase 3 randomized studies have been initiated to compare SABR with surgery in patients with early-stage NSCLC (the STARS trial

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[NCT00840749], the ROSEL trial [NCT00687986], and the ACOSOG Z4099 trial [NCT01336894]), however, all were closed early because of slow accrual. In an unplanned and post hoc analysis of two randomized trials (the STARS trial and the ROSEL trial) that each closed early due to inadequate accrual, Joe Chang and colleagues compared stereotactic ablative radiotherapy (SABR) with lobectomy for stage I NSCLC in the article titled "Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomized trials." in *Lancet Oncology* in 2015 [18]. Since the publication, there have been to date no supporting results from other prospective trials for 4 years.

What were the study design and major findings?

Definition of operability (for example, in terms of comorbidities and pulmonary function test) was not described in the *Lancet Oncology* manuscript. The 28 sites in the STARS trial randomized only 36 patients, and the ten sites in the ROSEL study randomized only 22 patients. In their analysis of two studies, only 4% (58 patients) of planned patients were enrolled. The primary outcome was overall survival and the median follow-up was 40.2 months (median survival was not reached in either group). There were 6 events (deaths) in the surgery arm and one event in SABR arm. The hazard ratio for overall survival was 0.14 (95% confidence interval: 0.017–1.19), although the *p* value from log-rank test to evaluate the difference in overall survival was 0.037. The hazard ratio for recurrence-free survival was 0.69 (95% 0.21–2.29). On the basis of these results, the authors concluded that SABR could be an option for operable clinical stage I NSCLC.

What were the responses to the article?

To my knowledge, one supportive comment to the above article and four critical comments were published in Lancet Oncology [19–23]. A majority of the comments on the publication were very critical of underpowered statistical analyses, poor surgical quality, and funding initiatives. Additionally, the issues of an unplanned publication of two underpowered clinical trials were discussed also in the *Journal of Thoracic and Cardiovascular Surgery* [24, 25]. The expert review and the comment on the review both raised the concerns for inadequate statistical power and follow-up, instability of the results, and the results not supporting the conclusion.

Ongoing clinical trials

In search of ongoing randomized trials that compare surgery and SBRT for early-stage NSCLC, the website "ClinicalTrials.gov", which is run by the United States National Library of Medicine at the National Institutes of Health, was queried with the following key words: "non-small cell lung cancer", "surgery", and "radiotherapy". In total, 244 study titles were identified with the search. After reviewing the study details, five prospective clinical trials in comparison of surgery and stereotactic body radiotherapy for patients with early-stage NSCLC were selected for review (Tables 1, 2).

Study characteristics

All the studies required the stage of the disease (stage I non-small cell lung cancer) and an eligibility (mediastinal staging) for enrollment. Among the studies varied the primary country, specialty of the principal investigator, age limit, study design, extent of pulmonary resection, primary outcome, sample size, description of cardiopulmonary function for enrollment, and follow-up periods. Among the five clinical trials, four studies (80%) required being biopsy-proven for enrollment. The primary country was United States of America in three studies and the primary investigator was a thoracic surgeon in one study (20%). Regarding the study design, three studies (60%) were randomized controlled studies, all of which are still recruiting patients. The estimated sample size of the studies ranged from 76 to 670 patients. Study results were not available in any study.

Future perspectives

In general, the study designs of ongoing prospective clinical trials still leave room to be improved. Each of PICO (patient, intervention, comparison, and outcome) that are fundamental in clinical research should be reviewed.

Eligible patients should be high-risk operable patients. It does not appear a good idea to include both low-risk operable patients and high-risk operable patients in the same "surgery" group, and I would suggest they should first focus on high-risk patients because there is no high-level evidence for such a patient group. Clinical equipoise will be of utmost importance for patient accrual. For that purpose, criteria for patient enrollment should include comorbidity information and pulmonary function test. The control group is ideally made from randomization. Given the nature of randomization, selection bias, information bias, evaluation bias, and confounding factors are presumably minimized. A sufficient sample size is a prerequisite for significant statistical analysis in randomized controlled trials. On the other hand, a small number of patients from a large number of institutions will be associated with difficult quality control.

The issues of Intervention and Comparison will be, as pointed out previously, mainly related to surgery. First, quality of surgery appears more difficult to control than that of SBRT, therefore, should be evaluated using quality

Table 1 Patient characteristics of ongoing prospective clinical trials comparing surgery versus stereotactic body radiotherapy for early-stage non-small cell lung cancer

Study title	Specialty of primary investigator	Country	Start year	Study design	Study status	Age of subject	Sample size	Tumor stage	Cardiopulmonary function	Mediastinal staging	Biopsy-proven?
Surgery versus stereotactic body radiation therapy for stage up to IA2 (T1a or T1b) non-small cell lung cancer (RAXSIA)	Thoracic surgery	Canada	2018	Non-randomized	Recruiting	18–75 years	160, estimated	T1aN0M0 or T1bN0M0	No description	EBUS or mediastinoscopy if lymph node > 1 cm on CT or PET-CT	Yes
Radical resection versus ablative stereotactic radiotherapy in patients with operable Stage I NSCLC (POSTILV)	Radiology	China	2012	Randomized	Recruiting	18 years or older	76, estimated	Stage I NSCLC (AJCC, 7th ed.)	Described	Biopsy if lymph node > 1 cm on CT or PET-CT	Yes
SBRT (stereotactic body radiation therapy) versus surgery in high-risk patients with early-stage lung cancer	Radiation Oncology	USA	2015	Non-randomized	Active, not recruiting	18 years or older	217, enrolled	T1 or T2, N0, M0	No description	Clinical stage I NSCLC (T1 or T2, N0, M0)	No
JoLT-Ca sublobar resection (SR) versus stereotactic ablative radiotherapy (SAbR) for lung cancer (STABLE-MATES)	Radiation Oncology	USA	2015	Randomized	Recruiting	18 years or older	272, estimated	Tumor ≤ 4 cm maximum diameter	No detailed description	Biopsy if lymph node > 1 cm on CT or PET-CT	Yes
Veterans affairs lung cancer surgery or stereotactic radiotherapy (VALOR)	Radiation Oncology	USA	2017	Randomized	Recruiting	18 years or older	670, estimated	Stage I NSCLC	No description	Biopsy if lymph node > 1 cm on CT or PET-CT	Yes

EBUS endobronchial ultrasound, *CT* computed tomography, *PET* positron emission tomography, *NSCLC* non-small cell lung cancer, *AJCC* American Joint Committee on Cancer

Table 2 Treatment characteristics of ongoing prospective clinical trials comparing surgery versus stereotactic body radiotherapy for early-stage non-small cell lung cancer

Study title	Dose of SBRT	Surgical procedure	Follow-up period	Primary outcome	Secondary outcomes
Surgery versus stereotactic body radiation therapy for stage up to IA2 (T1a or T1b) non-small cell lung cancer (RAXSIA)	Not described	Anatomical segmentectomy, lobectomy, or bilobectomy	5 years	Disease-free survival	Overall survival, efficacy, morbidity included
Radical resection versus ablative stereotactic radiotherapy in patients with operable Stage I NSCLC (POSTILV)	55 Gy	Complete resection	2 years	Loco-regional control	Overall survival
SBRT (stereotactic body radiation therapy) versus surgery in high-risk patients with early-stage lung cancer	Not described	Not described	Not applicable	Treatment selection model for high-risk early-stage NSCLC patient population	Not applicable
JoLT-Ca sublobar resection (SR) versus stereotactic ablative radiotherapy (SAbR) for lung cancer (STABLE-MATES)	54 Gy	Sublobar resection	3 years	Overall survival	Disease-free survival
Veterans affairs lung cancer surgery or stereotactic radiotherapy (VALOR)	50–57.5 Gy	Anatomical resection	5 years	Overall survival	QOL, respiratory function

SBRT stereotactic body radiotherapy, *QOL* quality of life

indicators of pulmonary resection [26]. Another issue in this setting would be a more complex post-treatment management in surgical patients. Thoracic surgical patients require inpatient and outpatient managements following pulmonary resection, whereas healthy SBRT patients will probably be managed on an outpatient basis. Third, advantages of minimally invasive approaches such as (uniport or multi-port) video-assisted thoracoscopic surgery and robotic-assisted thoracoscopic surgery should be recognized in contrast to conventional open thoracotomy. The extent of pulmonary resection also varied between lobectomy, segmentectomy, and wedge resection and should be specified in each clinical trial. Ideally, surgical patients in randomized controlled studies should be operated on by certified thoracic surgeons if SBRT patients are treated using qualified SBRT devices.

In conclusion, we should strive to develop and perform a well-designed prospective clinical trial. High-risk operable patients should first be focused on. Patients, intervention, comparison, and outcomes should be carefully discussed in developing research protocols.

Compliance with ethical standards

Conflict of interest Masatsugu Hamaji declares that he has no conflict of interest.

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