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Interpreting Survival Data from Clinical Trials of Surgery versus Stereotactic Body Radiation Therapy in Operable Stage I Non-Small Cell Lung Cancer Patients

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Abstract

Objectives—To identify the variability of short- and long-term survival outcomes among closed Phase III randomized controlled trials with small sample sizes comparing SBRT (stereotactic body radiation therapy) and surgical resection in operable clinical Stage I non-small cell lung cancer (NSCLC) patients.

Patients and Methods—Clinical Stage I NSCLC patients who underwent surgery at our institution meeting the inclusion/exclusion criteria for STARS (Randomized Study to Compare CyberKnife to Surgical Resection in Stage I Non-small Cell Lung Cancer), ROSEL (Trial of Either Surgery or Stereotactic Radiotherapy for Early Stage (IA) Lung Cancer), or both were identified. Bootstrapping analysis provided 10,000 iterations to depict 30-day mortality and three-year overall survival (OS) in cohorts of 16 patients (to simulate the STARS surgical arm), 27 patients (to simulate the pooled surgical arms of STARS and ROSEL), and 515 (to simulate the goal accrual for the surgical arm of STARS).

Results—From 2000 to 2012, 749/873 (86%) of clinical Stage I NSCLC patients who underwent resection were eligible for STARS only, ROSEL only, or both studies. When patients eligible for STARS only were repeatedly sampled with a cohort size of 16, the 3-year OS rates ranged from 27–100%, and 30-day mortality varied from 0–25%. When patients eligible for ROSEL or for both STARS and ROSEL underwent bootstrapping with n=27, the 3-year OS ranged from 46–100%, while 30-day mortality varied from 0–15%. Finally, when patients eligible for STARS were

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repeatedly sampled in groups of 515, 3-year OS narrowed to 70–85%, with 30-day mortality varying from 0–4%.

Conclusion—Short- and long-term survival outcomes from trials with small sample sizes are extremely variable and unreliable for extrapolation.

Keywords

lung cancer; surgery; stereotactic body radiation therapy; clinical trials

1. Introduction

For clinical Stage I non-small cell lung cancer (NSCLC) patients, lobectomy with mediastinal lymph node sampling has been the standard of care, with 5-year survival rates exceeding 80%. [1,2] Resection allows for local control and nodal sampling allows the possibility of upstaging (occurring in 15–35% of patients). [3–5] Increased use of video-assisted thoracoscopic surgery (VATS) have decreased rates of postoperative complications substantially [6,7]. For inoperable or high risk patients, stereotactic body radiation therapy (SBRT) has emerged as an alternative to surgery [8,9].

To examine SBRT's role in treating operable Stage I NSCLC patients, two Phase 3 randomized controlled trials were created: the STARS trial in the United States (Randomized Study to Compare CyberKnife to Surgical Resection in Stage I Non-small Cell Lung Cancer) and the ROSEL Trial in the Netherlands (Trial of Either Surgery or Stereotactic Radiotherapy for Early Stage (IA) Lung Cancer). To compare overall survival (OS) outcomes, STARS required 1030 randomized patients, while ROSEL called for 960 patients. [10,11] However, both trials failed to accrue and closed, with STARS randomizing 36 patients and ROSEL enrolling 22 patients.

Chang and colleagues recently published a post-hoc analysis combining enrolled patients from STARS and ROSEL including 27 surgical patients. [12] We hypothesize that this pooled analysis remains underpowered with unstable and inconclusive results. By using our institutional data from clinical Stage I NSCLC surgical patients, we evaluated whether creating similarly sized simulations of a) the pooled analysis and b) the target accrual goal would identify variable ranges of 30-day mortality and 3-year OS.

2. Patients and Methods

2.1 Patients

This study received approval by our Institutional Review Board (IRB) at Washington University in St. Louis. We used our prospectively maintained clinical Stage I NSCLC database to identify surgical patients that would have been eligible for STARS and/or ROSEL. Inclusion and exclusion criteria for these trials are listed in Table 1.

2.2 Statistical Analysis

Univariate analysis was performed to compare patient and tumor characteristics. Chi-square and Fisher's exact tests were applied to categorical variables as appropriate based on group

size. Independent sample t-tests were applied to normally distributed continuous variables, and reported as mean and standard deviation. P values < 0.05 were considered statistically significant. Follow-up time was calculated from the date of surgery to date of death or last known follow-up. Kaplan-Meier analysis and the log-rank test was applied to determine differences in three-year OS among patient groups. All statistical analyses were performed using SAS, Version 9.3, 2011, Cary, NC.

2.3 Bootstrapping Methods

A bootstrap analysis was used to analyze the potential range of 30-day mortality and 3-year OS values. This was done by resampling our data set (with replacement to give equal probabilities of selection with each iteration) 10,000 times. Repeated simulations of 30-day mortality rates and 3-year OS of the pooled STARS and ROSEL surgical arm (n=27) and the STARS surgical arm enrollment goal (n=515) were performed. Mean values and interquartile ranges (IQR) are reported for each of the distributions generated. Bootstrapping analysis was performed in R, Version 3.1.0, R Core Team (2012), R Foundation for Statistical Computing, Vienna, Austria. [13] Normality of the three-year survival distributions was confirmed using quantile-quantile (QQ) plots.

3. Results

3.1 Patient Characteristics

From 2000 to 2012, 214/873 (24.5%) of our operative clinical Stage I patients were hypothetically eligible for both STARS and ROSEL, 508/873 (58.0%) for STARS only, and 27/873 (3.1%) for ROSEL only (Table 2). Therefore, 749/873 (85.8%) of clinical Stage I NSCLC patients at our institution would have been eligible for one or both of these trials. The most common reason for patient ineligibility from both trials was failing the pulmonary function criteria of STARS (FEV1 >40%), while also having a clinical T1b or T2 tumor (a ROSEL exclusion).

3.2 Short- and Long-Term Outcomes in Combined Surgical Arm Simulation

Patients eligible for either STARS and/or ROSEL (n=749) were sampled 10,000 times in groups of 27, to simulate the combined surgical arms of STARS and ROSEL. Here, 3-year OS rates ranged from 46% to 100%, with a mean value of 79%, IQR 73–84% (Figure 1). In groups of 27, repeated samples from this population demonstrated a 30-day mortality rate that varied from 0–15% (mean 1.6%, IQR 0–4%).

3.3 Short- and Long-Term Outcomes in Surgical Arm Target Accrual Simulation

Patients eligible for STARS or both STARS and ROSEL (n=722) were sampled 10,000 times in groups of 515, to simulate the actual accrual target for the STARS surgical arm. Here, the 3-year OS range became more narrow with values of 70% to 85%, and a mean value of 78.5%, IQR 77–80% (Figure 2). Similarly, the range of 30-day mortality rates also narrowed, varying from 0–4%, with a mean of 1.4%, IQR 1–2%.

3.4 Comparative Short- and Long-Term Survival by Treatment Arm

To evaluate for potential survival differences among patients in the 3 potential trial eligibility groups, a Kaplan-Meier analysis was performed. There was no difference among 3-year OS rates between resected patients eligible for STARS only (78.5%, 95% CI 74.6–81.8%), ROSEL only (81.5%, 95% CI 61.1–91.8%), or both STARS and ROSEL (84.6%, 95% CI 79.0–88.8%), p=0.15. There was no difference in our 30-day mortality between the three patient eligibility groups: 6/508 (1.2%) for STARS, 1/27 (3.7%) for ROSEL, and 5/214 (2.3%) for STARS and ROSEL, p=0.19.

4.0 Discussion

Our analysis demonstrates that when repeated simulations are performed using the number of surgical patients actually accrued to STARS and ROSEL, the variability of 30-day mortality and 3-year OS is so large that conclusions from these type of analyses should be considered exploratory. In the combined surgical arm simulation (n=27), possible values for 3-year OS of the 10,000 iterations ranged from 46% or 100%, depending on the specific group of patients randomly selected from our database. The mean 3-year OS of the 10,000 iterations did approach our population's actual survival rates, representing the most common survival tendency, while there was a marked reduction of the variability in bootstrap simulations of 3-year OS rates using the STARS target accrual sample size (n=515), as would be expected.

The pooled analysis of STARS and ROSEL by Chang and colleagues has recently received a high level of correspondence. [14–17] A major theme of these concerned commentaries questions the conclusion that “SBRT might lead to better OS compared to surgery for operable Stage I NSCLC” despite very few follow-up events in the study populations: 6 deaths in the combined surgical arm and 1 death in the SBRT arm. [12] By comparison, ROSEL was powered for 960 participating patients, with 400 anticipated events (deaths) for analysis. [11] While we did not perform this analysis on SBRT patients (typically an inoperable or extremely high risk population at our institution, and not eligible for STARS/ROSEL), the small SBRT sample size in the pooled analysis (n=31) would lead to similar ranges of outcome variability.

The finding of a 95% 3-year OS for SBRT patients from the pooled STARS and ROSEL analysis is possibly a non-representative result. In an institutional review of over 80 operable patients receiving SBRT, the 5-year OS rates for Stage IA tumors was 72% and for Stage IB tumors 62%. [18] A recent propensity matched analysis between Stage I NSCLC patients (biopsy-proven) receiving either VATS lobectomy or SBRT demonstrated a significant improvement in 3-year OS for surgical patients (86.1% versus 60.2% for SBRT, p<0.0001), 3-year cause-specific survival (90.4% versus 71.5%, p<0.0001), and 3-year recurrence-free survival (77.0% versus 43.3%, p<0.0001). [19] Another review of operable SBRT patients from the Netherlands (from a ROSEL site) found a 3-year OS rate of 84.7%. [20] A recent propensity-matched analysis between SBRT and surgical patients found a 5-year OS of 53% versus 80% respectively, but did not reach significance (p=0.089). [21]

There are limitations to this study. While our analysis included patients eligible for STARS and/or ROSEL, this does not represent a cohort of patients that were entered into the randomization process. Hence, we cannot adjust for patients that would have declined participation in a trial. However, in STARS and ROSEL, only 58 patients were recruited over an enrollment period of 5.5 years at 38 centers, and begs the question how representative this group is. [14, 17] Of the eligible patients screened for STARS, more than half were not enrolled secondary to treatment preference (with 82% of patients opting for surgery). [12] Additionally, STARS and ROSEL (as well as our early surgical years) have a higher proportion of thoracotomy cases, while VATS has increasingly become the standard surgical approach, with improved in-hospital mortality. [22, 23]

Without reinforcing the exploratory nature of the findings of a pooled analysis, many may misinterpret the results. Few patients (and physicians) feel equipoise between these therapies, and the use of non-traditional randomization schemes to account for patient choice may be helpful.

Conclusions

Given the variability in 3-year OS and 30-day mortality in small sample sizes, the findings of equivalence between SBRT and surgery in a pooled analysis of STARS and ROSEL should be considered exploratory, and not definitive.

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Highlights

- Trials that close with poor accrual in Stage I NSCLC have variable survival rates
- Simulating trial accrual goals has survival results similar to clinical experience
- Conclusions for SBRT in operable Stage I NSCLC cannot be made from such trials

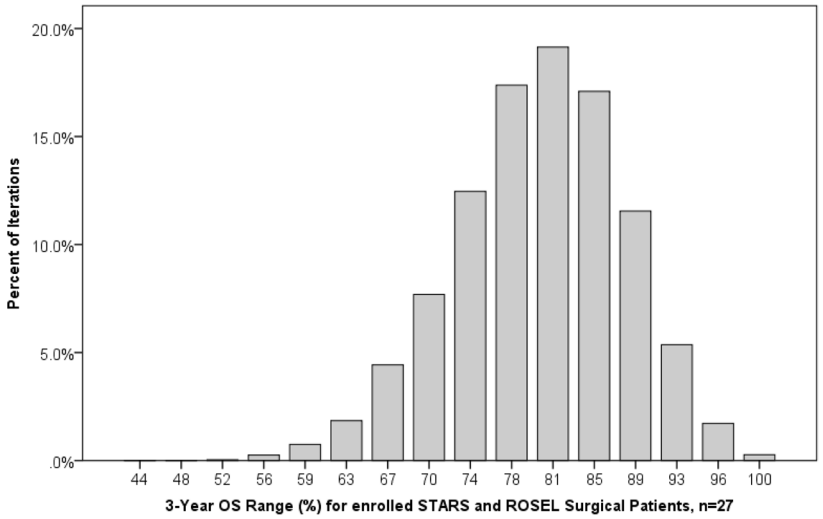

Figure 1.

Results of 3-year OS estimates when 749 clinical Stage I NSCLC patients eligible for STARS and/or ROSEL were sampled 10,000 times (with replacement) in groups of 27, to simulate the actual combined surgical enrollment arms of STARS and ROSEL.

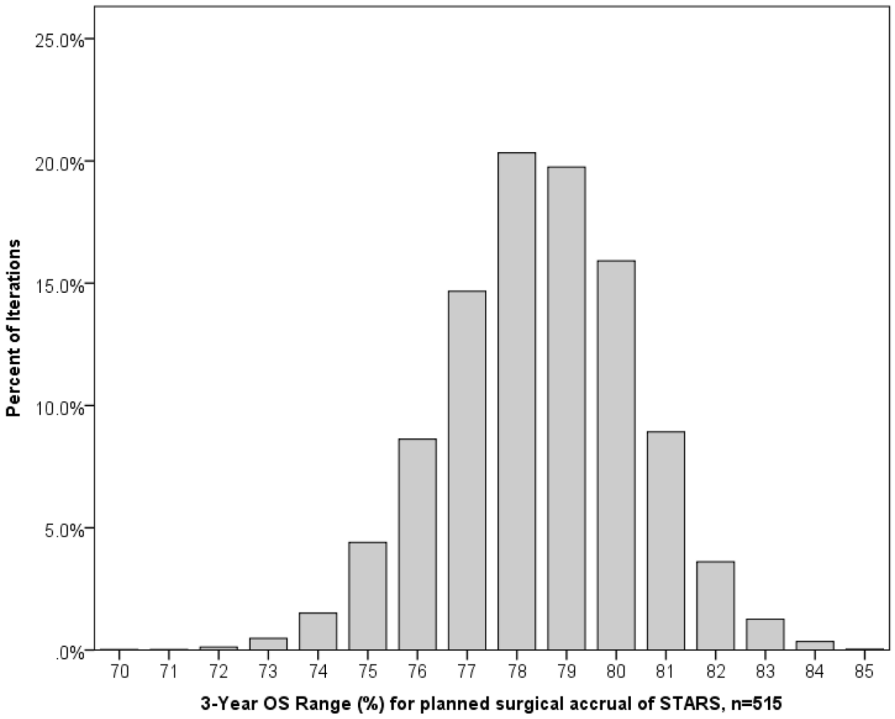

Figure 2.

Results of 3-year OS estimates when 722 clinical Stage I NSCLC patients that would have been eligible for STARS were sampled 10,000 times (with replacement) in groups of 515, to simulate the anticipated surgical enrollment arm of STARS.

Table 1

Eligibility criteria for STARS and ROSEL. [8,9].

Trial name	Inclusion Criteria	Exclusion Criteria
STARS	• Histologic or cytologic confirmation of NSCLC • Clinically staged as T1N0M0 or T2 (≤4cm)N0M0 • PET/CT with no clinically positive nodes • FEV_1> 40% predicted, postoperative FEV_1>30% predicted, and DLCO >40% predicted • ≥18 years of age • Zubrod 0-2	• Primary tumor >4cm • Neuroendocrine tumor • Evidence of regional or distant metastasis • Previous lung radiation • Pregnancy • Severe vascular, cerebrovascular, or heart disease
ROSEL	• Either histologic/cytologic confirmation of NSCLC *or* evidence of a new or growing pulmonary lesions with radiologic features which is PET-avid • Clinical Stage IA tumor with no evidence of regional or distant metastases • Tumor is at least 2cm away from main and lobar bronchi, and at least 1.5cm away from aorta and main pulmonary artery • ECOG performance score ≤2	• History of any active malignancy (other than NSCLC) unless treated > 3 years with no evidence of recurrence or is non-melanoma skin cancer or in- situ cervical cancer • Unstable comorbidities (congestive heart failure, myocardial infarction in the past year) • Pregnancy

Table 2

Clinical characteristics of clinical stage I NSCLC patients that received surgical resection from 2000–2012, that were eligible for either STARS only, or both STARS and ROSEL.

Patient Characteristics	Patients eligible for STARS only (n = 508)	Patients eligible for STARS and ROSEL (n = 214)	P Value
Age	66.64 (± 10.10)	65.81 (± 10.07)	0.39
ACE (Adult Comorbidity Evaluation) Score			
0	59 (7.7%)	26 (16.9%)	0.95
1	199 (35.2%)	77 (41.4%)	
2	129 (30.2%)	55 (20.3%)	
3	75 (17.0%)	32 (12.3%)	
Gender			
Male	241 (47.4%)	94 (43.9%)	0.39
Female	267 (52.6%)	120 (56.1%)	
Race			
Caucasian	435 (85.6%)	186 (86.9%)	0.58
Other	73 (14.4%)	27 (12.6%)	
Prior Malignancy			
No	314 (61.8%)	154 (72.0%)	0.01
Yes	193 (38.0%)	59 (27.6%)	
FEV_1 % Predicted	81.79 (± 0.19)	80.53 (± 0.20)	0.40
DLCO % Predicted	74.79 (± 0.23)	74.90 (± 0.19)	0.43
Smoking History			
Current	174 (34.3%)	76 (35.5%)	0.92
Never	54 (10.6%)	21 (9.8%)	
Past	280 (55.1%)	117 (54.7%)	
Number of Comorbidities			
0	154 (30.3%)	70 (32.7%)	0.94
1	184 (36.2%)	74 (34.6%)	
2	98 (19.3%)	40 (18.7%)	
≥3	72 (14.2%)	30 (14.0%)	
Tumor Location			
Left lower lobe	70 (13.8%)	33 (15.4%)	0.71
Left upper lobe	150 (29.5%)	65 (30.4%)	
Right lower lobe	86 (16.9%)	30 (14.0%)	
Right upper lobe	172 (33.9%)	77 (36.0%)	
Right middle	30 (5.9%)	9 (4.2%)	
Parenchymal Location			

Patient Characteristics	Patients eligible for STARS only (n = 508)	Patients eligible for STARS and ROSEL (n = 214)	P Value
Central	182 (35.8%)	0 (0.00%)	<0.01
Peripheral	326 (64.2%)	214 (100%)	
Clinical T stage			
T1a	132 (26.0%)	214 (100%)	<0.01
T1b	257 (50.6%)	0 (0.00%)	
T2	119 (23.4%)	0 (0.00%)	
Pathology			
Adenocarcinoma	310 (61.0%)	144 (67.3%)	0.05
Squamous	143 (28.2%)	42 (19.6%)	
Other	55 (10.8%)	28 (13.1%)	
Preoperative Lesion Size (cm)	2.55 (± 0.79)	1.56 (± 0.37)	<0.01
Resection type			
Bilobectomy or pneumonectomy	29 (5.7%)	1 (0.5%)	<0.01
Lobectomy	400 (78.7%)	163 (76.2%)	
Segmentectomy	31 (6.1%)	9 (4.2%)	
Wedge	48 (9.5%)	41 (19.2%)	
Surgical approach			
Thoracotomy	303 (59.7%)	126 (58.9%)	0.70
VATS	203 (40.0%)	86 (40.2%)	
Sternotomy	2 (0.4%)	2 (0.9%)	