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Perioperative mortality and Morbidity after Lobar versus Sublobar Resection for early stage lung cancer: A post-hoc analysis of an international randomized phase III trial (CALGB/Alliance 140503)

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NA, XW, GD, RL, DM, LJK, and EV designed the study; XW, DW, RL, GW and LJK implemented the study; NA reviewed case report forms; MK performed the literature search and meta-analysis; NA, DW, ASA, DM, ML, DRJ, RK, MC, GW and EV collected data; XW, LG, DM and TS analysed data; NA, GD, DM, TS and EV interpreted data; NA, XW, DM, TS and EV wrote the manuscript; NA, DW, GD, ASA, RL, ML, DRJ, RK, MC, GW, LJK, LJV, SSR, HIP and JDM reviewed, revised and approved the manuscript

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Data sharing statement: De-identified participant data and data dictionary will be made available within 6 months after publication of the primary end-point manuscript with no end date. No related documents such as statistical analysis plan, informed consent form will be made available. The data will be made available at NCTN/NCORP Data Archive: <https://nctn-data-archive.nci.nih.gov/>. Researchers who wish to analyze the data in secondary studies, after approval of a signed Data Use Agreement (DUA)

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Abstract

Objective—The recent increased detection of small-sized peripheral non-small cell lung cancer (NSCLC) has renewed interest in sub-lobar resection *in-lieu* of lobectomy, the traditional standard of care. CALGB/ALLIANCE 140503 is a multicenter international non-inferiority phase III trial in which NSCLC patients clinically staged as T1aN0 were randomly assigned to lobar or sub-lobar resection. The primary endpoint is disease-free survival. We conducted an exploratory comparative analysis of the perioperative mortality and morbidity associated with both arms of the trial.

Patients and Methods—Between June 15/2007 and March 13/2017, 697 patients with peripheral NSCLC clinically staged as T1aN0 were intraoperatively randomized (after pathological confirmation of absence of nodal metastases in major hilar and mediastinal nodes) to either lobar (Arm A: 357) or sublobar resection (Arm B: 340; 58% wedge resections). Randomization assignment was based on a stratified permuted-block randomization scheme without concealment. Randomized was stratified according to radiographic tumor size (< 1 cm, 1–1.5 cm, and > 1.5–2.0 cm), histology (squamous carcinoma, adenocarcinoma and other) and smoking status (never, former, current). The assignment was not concealed. Perioperative mortality was defined as death from any cause within 30 and 90 days of surgical intervention and was calculated on all randomized patients. Morbidity was graded using the Common Terminology Criteria for Adverse Events (CTCAE v4.0). All analyses were done on an intention to treat basis.

Results—Overall 30 and 90-day mortality for 697 randomized patients were 0.86% (n=6) and 1.4% (n=10). Thirty and 90-day mortality were 1.1% (n=4) and 1.7% (n=6) after lobar resection and 0.6% (n=2) and 1.2% (n=4) after sub-lobar resection yielding a difference between arms of 0.5% (95%CI: –1.1,2.3) and 0.5% (95%CI: –1.5,2.6), respectively, without reaching statistical significance. No complications were observed in 47% of patients (Arm A: 46%, Arm B: 49%). Grade 3/4/5 AEs occurred in 15.2% in Arm A and 14.2% in Arm B. There were no differences between the two arms in cardiac or pulmonary complications. Grade 3 hemorrhage (requiring

transfusion) occurred in 6 patients (1.6%) in Arm A and 8 patients (2.3%) in Arm B. Prolonged air leak occurred in 9 patients (2.5%) in Arm A and 2 patients (0.6%) in Arm B.

Conclusions—In this large, multicenter randomized international trial, post-hoc analysis showed no significant differences in perioperative mortality and morbidity between lobar and sub-lobar resection in physically and functionally fit patients with clinical T1aN0 NSCLC. These data may impact the daily choices made by patients and their physicians in determining the optimal treatment approach for stage I lung cancer.

Trial registration—This trial is registered as an international standard randomized trial with [ClinicalTrials.gov](https://clinicaltrials.gov) Identifier: NCT00499330

Role of funding source—The Cancer Therapy Evaluation Program of the National Cancer Institute (CTEP) approved the trial design

Keywords

Early lung cancer; sub-lobar resection; randomized trial; minimally invasive surgery

Research in Context

Evidence before this study

The only available information on treatment related mortality and morbidity of lobar versus sub-lobar resection in patients with stage I lung cancer is derived from case series, population-based registries and administrative data-bases. More robust and contemporary data on the mortality and adverse events associated with surgical treatment for early stage lung cancer are critical for informing the debate the choice of surgical versus non-surgical therapy and as an aid in shared decision-making. We conducted a search of Ovid MEDLINE, Ovid EMBASE , and The Cochrane Library for full text articles published in all languages since 2000 that compared perioperative outcomes between matched groups of patients undergoing lobectomy or sublobar resection. Articles that compared un-matched cohorts or those that did not report any of the outcomes of interest, were excluded.

Search terms used were (Limited resection, wedge, segment*, sublobar, lobectomy, lobar, lung, match*). The quality of the selected articles and possible associated risk of bias were assessed using the Newcastle Ottawa Quality Assessment Scale for Cohort Studies. Studies with scores of 6 or more were included. Eleven and 15 studies were included in the meta-analysis of postoperative morbidity and 30-day mortality, respectively.

The pooled estimates for morbidity were 23.8% (95% CI: 17.3–31.9%) for lobectomy and 20.5% (95% CI: 14.2–28.8%) for sublobar resection. While, the pooled estimates for 30-day mortality was 1.8% (95% CI: 1.1–2.9%) for lobectomy, and 1.5% (95% CI: 0.9–2.5%) for sublobar resection. There were no differences between lobectomy and sublobar resection in postoperative morbidity (OR:1.18, 95% CI: 0.76–1.83, P = 0.47), or in 30-day mortality (OR:1.39, 95% CI: 0.54– 3.60, P = 0.50). CALGB/ALLIANCE 140503 is a multicenter international non- inferiority phase III trial in which NSCLC patients clinically staged as T1aN0 were randomly assigned to lobar or sub-lobar resection. Since the primary endpoint

of disease-free survival has not yet matured, we conducted an exploratory analysis of the perioperative mortality and morbidity associated with both lobar and sublobar resection.

Added value of this study

The trial results show that otherwise healthy patients with stage I lung cancer can undergo surgical treatment with an expected perioperative mortality less than 2% and a serious complications rate less than 15%. The results also show a remarkable transformation in thoracic surgical practice towards more minimally invasive approaches which may have contributed to these excellent outcomes.

Implications of all the available evidence

The data would have a significant impact on the daily choices made by patients and their physicians in determining the optimal treatment approach for stage I lung cancer.

Introduction

In 1994, Ginsberg and Rubenstein published the results of the Lung Cancer Study Group's randomized trial comparing lobar (LR) and sub-lobar resection (SLR) for the surgical treatment of clinical T1N0 non-small cell lung cancer (1). The results of that trial suggested that lobectomy is the preferred therapeutic option and it has since been adopted worldwide as the surgical standard of care. Although the Lung Cancer Study Group reported only three deaths among 247 randomized patients (1.2%), there was no information provided on the morbidity associated with the surgical procedures employed in the trial. Over the past decades several investigators have reported on the mortality and morbidity of lobectomy using data from case series, large population-based registries and administrative databases (2–8). Mortality varied between a low of 1.4% in the Society of Thoracic Surgery (STS) General Thoracic Database (GTSD) to a high of 5.4% in an analysis of the National Cancer Data Base (NCDB). Similarly, major morbidity varied between 27% - 44%. This wide variability in perioperative outcomes is probably related to more granular differences in patient and tumor-related factors, variations in hospital volume, operative strategies and perhaps other potential confounders. The perception that surgical resection is associated with high mortality and morbidity may have driven, to some extent, the pursuit and development of competing therapeutic modalities such as stereotactic body radiation and other ablative approaches.

Prompted by advances in imaging and staging modalities, as well as earlier detection of smaller tumors as a result of more pervasive use of current generation computerized tomography, the Cancer and Leukemia Group B (now part of the Alliance for Clinical Trials in Oncology) and CTEP approved the design of a non-inferiority randomized trial comparing lobar (LR) with sub-lobar resection (SLR) for peripheral non-small cell lung cancer (NSCLC) two centimeters or less in size. The trial was activated in June 2007 and accrual was completed in March 2017. The primary endpoint of the trial, disease free survival, has not matured yet. Secondary endpoints included overall survival (OS), rates of loco-regional and systemic recurrence, and expiratory flow rates 6 months postoperatively. Although perioperative adverse events were not a pre-specified end-point of the trial, we

reasoned that a post-hoc comparative exploratory analysis of these events in both arms of the trial would further inform the ongoing debate regarding surgical versus emerging non-surgical therapy for early stage lung cancer. Here we report the peri-operative mortality and morbidity associated with both arms of the trial, thus providing a snapshot of modern-day perioperative outcomes associated with curative surgical resection in fit patients with clinical stage IA NSCLC.

Methods

Trial design

CALGB/ALLIANCE 140503 is a multicenter international randomized non-inferiority phase III trial in which NSCLC patients clinically staged as T1aN0 were randomly assigned to LR or SLR. Clinical staging was based on the 7th edition of the TNM staging system (9). The primary end-point is disease-free survival (DFS). Secondary endpoints included overall survival (OS), rates of loco-regional and systemic recurrence, and expiratory flow rates 6 months postoperatively. Since adverse events were not a pre-specified end-point, we conducted a post-hoc comparative exploratory analysis of mortality and morbidity in both arms of the trial. We hypothesized that in patients with peripheral NSCLC clinically staged as T1aN0, SLR will be associated with lower perioperative mortality and morbidity than LR. The protocol (NCT 0049930) was approved by the co-operative group's central institutional review board and the institutional review board at each participating institution. All patients provided written informed consent before trial enrollment.

Participants and Interventions

Inclusion and exclusion criteria are shown in Table I. Eligible patients were pre-registered (but not randomized) to the trial using a web-based system. Randomization occurred intra-operatively after confirmation of eligibility criteria. Specifically, intra-operative, confirmation of the diagnosis of NSCLC (if not obtained preoperatively) along with absence of metastatic disease in three nodal stations (one major hilar and two mediastinal) by frozen section examination were required prior to randomization. Once eligibility was confirmed, patients were randomized to either LR or SLR. The choice of the type of SLR (wedge resection or segmentectomy) was left to the discretion of the surgeon. The choice of surgical approach (thoracotomy versus video-assisted thoracoscopic surgery (VATS) or robotic assisted surgery; RATS) was also at the discretion of the surgeon. Surgeons planning to perform VATS or RATS in this trial required credentialing. All surgeons who were previously credentialed to perform VATS lobectomies from CALGB 39802 (phase II trial of VATS lobectomy) were automatically credentialed for CALGB 140503 (10). Surgeons not previously VATS credentialed were required to have performed at least 10 VATS or RATS lobectomies within the prior 12 months and submit three operative and pathology reports for central review.

Randomization

Patient registration and randomization was done using the OPEN registration system, a web-based registration system for patient enrollment onto NCI-sponsored cooperative group

clinical trials. Patients who met the eligibility criteria were pre-registered and then randomized with equal allocation intra-operatively after confirmation of NSCLC histology and N-0 status. Randomization assignment was based on a stratified permuted-block randomization scheme with stratification for radiographic tumor size (< 1 cm, 1– 1.5 cm, and > 1.5–2.0 cm), histology (squamous cell carcinoma, adenocarcinoma and other) and smoking status (never, former, current). Assignment was not concealed to patients, surgeons, nurses and statisticians.

Sample size calculation

The primary objective of this non-inferiority trial is to determine that disease-free survival after SLR is non-inferior to that after LR and the study is powered on this primary outcome and not on the post-hoc analysis reported in this paper. The non-inferiority margin on hazard ratio scale was set at 1.306. Using a one-sided non-inferiority test with type 1 error rate of 0.05 and 80% power, the original design required that 908 eligible patients be randomized with equal allocation. To accommodate a lower-than-expected accrual rate, the trial was amended (effective 2/15/10) reducing the number of randomized patients from 908 to 692. The number of 692 patients includes the patients who were randomized at that time. In the amended design, the non-inferiority margin (a hazard ratio of 1.306), the statistical power of 80% and the type I error of 0.05 used in the original design remain unchanged, but the entire length of the amended study (accrual time + follow-up time after last enrollment) was significantly increased in order to observe the same number of events (351 events) required at the final analysis of the original design.

Outcome measures

Since neither 30 nor 90-day mortality were pre-specified end-points, we conducted a post-hoc exploratory analysis to compare perioperative 30/90 day mortality and morbidity from both arms of the trial. Perioperative mortality was defined as death from any cause within 30 and 90 days of surgical intervention. Morbidity was graded using the Common Terminology Criteria for Adverse Events (CTCAE v4.0). Since its activation, the conduct of the trial has been monitored by the Alliance Data and Safety Monitoring Board semiannually.

Statistical analysis

All perioperative data were collected and submitted to the Alliance Statistics and Data Center 30 days after the date of the surgical procedure. Patients' demographics and baseline clinical characteristics were summarized. For continuous variables, mean, standard deviation, median, interquartile range, and minimum/maximum range were calculated. For categorical variables, frequencies and percentages were provided. Morbidity within 30 days following surgery was tabulated by providing the frequencies and percentages of each adverse event by their grade regardless of attribution. The proportion differences between arms for mortality and morbidity within 30 days following surgery and their confidence intervals were estimated by the Miettinen-Nurminen method (11). A multivariable logistic regression was conducted to evaluate the association of developing grade 3/4/5 adverse events (AEs) and clinically relevant baseline variables including age, gender (Male vs. Female), race (White vs. Non-White), performance status (1–2 vs. 0), smoking status (ex-smoker vs. non-smoker, current smoker vs. non-smoker), intention to treat (ITT) surgical

procedure, and baseline predicted FEV1%. Statistical analyses were conducted by the Alliance Statistics and Data Center using SAS 9.4 for Windows. All analyses were done on an intention to treat basis. Data quality was ensured by review of data by the Alliance Statistics and Data Center and the study chairperson following Alliance policies.

Trial registration

This trial is registered as an international standard randomized trial with [ClinicalTrials.gov](https://clinicaltrials.gov) Identifier: NCT00499330

Role of funding source

The Cancer Therapy Evaluation Program of the National Cancer Institute approved the trial design but had no role in data collection, interpretation or writing of the report. The corresponding author (NA) and coauthors XW and LG had full access to the raw data and NA had the final responsibility to submit for publication.

Results

The trial was activated on June 15th 2007 and accrual was completed on March 13th 2017. One-thousand and eighty patients with cT1aN0M0 were pre-registered to the trial by 125 surgeons at sixty-nine participating institutions in the United States, Canada and Australia. Twenty-two percent of patients were treated at 29 community-based institutions including four Veterans Administration Hospitals. Twenty-one centers randomized 72.7% of all patients on the trial.

Six hundred and ninety-seven patients who met all preoperative and intraoperative eligibility criteria were randomly assigned to either LR (n=357) or SLR (n=340) (Figure 1). Among patients assigned to SLR; 200 (58%) underwent wedge resection and 129 had an anatomical segmental resection. Eleven patients (3.3%) assigned to SLR were intra-operatively converted to lobectomy mainly due to residual cancer at the resection margin. The demographic, clinical and operative characteristics are shown in Table II. The majority of patients were women and minimally invasive approaches were performed in nearly 80% of all patients. Conversion from minimally invasive approaches to open thoracotomy occurred in 6.5% of patients in each arm. Three hundred and eighty three of all 1080 registered patients were not randomized as they did not meet intraoperative eligibility criteria. These patients were treated off-protocol and were no longer followed. Failure of randomization as previously reported was due to undiagnosed benign disease (50%), under-staging of NSCLC (22.6%) or malignancy other than NSCLC (7.7%) (12).

Mortality

Six of 697 patients died within 30 days of surgical resection for an overall 30-day mortality of 0.86%. Four patients died after LR and 2 after SLR (one patient each after wedge resection and segmentectomy). Four additional deaths occurred between 31 and 90 days (two after LR and one each after wedge resection and segmentectomy) yielding a 90-day mortality of 1.4%. Thirty and 90-day mortality were 1.1% (n=4) and 1.7% (n=6) after LR and 0.6% (n=2) and 1.2% (n=4) after SLR, yielding a non-statistically significant difference

between arms of 0.5% (95% CI: -1.1, 2.3) and 0.5% (95%CI: -1.5,2.6), respectively. Ninety-day mortality in patients 80 years old was less than 2% regardless of the extent of resection (Table III). There was one death in 17 octogenarians after LR and none after SLR. Causes of deaths in all ten patients are shown in Table IV.

Morbidity

Morbidity data was available on 692 (99.2%) patients (355 LR; 337 SLR). Forty-seven percent of patients experienced no adverse events [162 (46%) after LR and 165 (49%) after SLR]. An adverse event of any grade occurred in 193 patients (54%) after LR and 172 patients (51%) after SLR. The difference in proportions between the two arms was 3.3% (95% CI: -4.1, 10.7). Importantly, grade 3 and 4 AEs occurred in 37 (10.4%) and 13 patients (3.7%) after LR and 41 (12.2%) and 5 patients (1.5%) after SLR respectively (Table V). The difference in proportions of grade 3/4 AEs between the two arms was 0.4% (95% CI: -4.8, 5.6). Since SLR was not stratified based on the extent of resection (wedge or segment), comparison of adverse events between segmentectomies, wedge resections and LR was based on procedure actually performed. Grades 3/4/5 AEs were slightly more frequent after segmentectomy (18.6%) compared to LR (15.6%) and wedge resections (11.0%); the difference in AE proportion was not statistically significant (0.133 Fisher's exact) (data not shown). All grade adverse events developing in at least 5% of patients regardless of attribution are shown in Table VI.

The most common cardiovascular AE in both arms was supraventricular tachyarrhythmias which occurred in 42 patients (11.8%) after LR and 25 patients (7%) after SLR. The difference in proportion of supraventricular arrhythmia between the two arms was 4.4% (95% CI: 0, 8.9). In the majority of patients, the arrhythmias were asymptomatic and either resolved spontaneously or required non-urgent pharmacological intervention (Grade 1/2). In four (1%) patients after LR and three (0.9%) after SLR, the arrhythmias were symptomatic and incompletely controlled by simple medical measures thus requiring additional interventions (Grade 3). In only one patient, who had a SLR, was the arrhythmia life threatening requiring immediate intervention (Grade 4). Grade 3 and 4 cardiac ischemia occurred in three (0.8%) and two (0.5%) patients respectively all of whom had LR. Collectively, any grade 3/4 cardiovascular AE developed in 8 (2.2%) and 4 (1.2%) patients after LR and SLR respectively. The difference in proportions of grade 3/4 cardiovascular AEs between the two arms was 1.1% (95% CI: -1.0, 3.3).

The most common pulmonary AE was atelectasis that occurred in 19% of patients in each arm (LR: 68 patients;SLR: 64 patients). The majority (80%) were asymptomatic and required no intervention (Grade 1) and the remainder required chest physiotherapy or suctioning (Grade 2). Pleural effusions were observed in 38 patients after LR and 37 patients after SLR. Replacement of the chest tube with or without pleurodesis was necessary in 2 patients after LR and 3 after SLR. Pneumothoraces or post-resection air spaces were reported after 12% of (44 patients) and 10% of SLR (36 patients). Replacement of the chest tube with or without sclerosis was required in 12 (3%) and 8 (2%) patients after LR and SLR respectively. Air-leak from the chest tube beyond five days occurred in 9% of patients after LR and 7% after SLR. Interventions to control air-leak were required in nine (2.5%) and two

(0.5%) patients and SLR respectively. Overall, grade 3/4 pulmonary morbidity occurred in 36 (10%) and 23 patients (6.8%) after LR and SLR respectively. The difference in proportions of grade 3/4 pulmonary AEs between the two arms was 3.3% (95% CI: -0.9, 7.6). Pulmonary emboli developed in 1% of patients and were likely the cause of death in one patient after LR. The number of patients with other grade 3/4 AEs of interest such as perioperative transfusions, neurological events and infectious complications are shown in Table VI.

Multivariate predictors of grade 3/4/5 AEs in all patients

Multivariate analysis was performed on 595 patients, on whom all data points were available, to determine the predictors of grade 3/4/5 AEs in all patients. Clinically relevant variables included in the analysis included age, gender, race, smoking history, performance status, predicted forced expiratory volume and type of resection on an intention to treat basis. The only significant predictors for any grade 3/4/5 AE were age and baseline FEV1% (Table VII). The odds of experiencing any grade 3/4/5 AEs were increased by 30% with each 10-year increment in age (Odds Ratio [every 10 years], 1.308, 95% CI, 1.001, 1.709, $p=0.049$). Not surprisingly, higher FEV1% predicted a lower probability of serious AEs (Odds Ratio, 0.98; 95% CI, 0.97, 0.99, $p<0.001$).

Discussion

The results of this large randomized trial showed that there is no significant difference in combined 30 and 90-day mortality between LR and SLR (1.4% vs 0.9%). Furthermore, major morbidity (Grade 3/4) was similar in both arms of the trial occurring in 14.1% after LR and 13.7% after SLR. The treatment-related mortality reported here is remarkable given the wide participation in the trial of a large number of thoracic surgeons from both academic and community-based institutions. The 30-day mortality of 1.1% after LR in this trial is lower than the 30-day mortality reported in the large randomized ACOSOG Z030 trial (1.3%) although the majority of LR in the latter trial were done using open thoracotomy (13). A more recent snapshot provided by an analysis of the STS-GTSD, showed a 30-day mortality of 1.5% after LR; 1.8% after open lobectomy and 1.3% after VATS lobectomy (14). Although comparison of the present results with those of other trials or registries can be problematic, it should be noted that the demographic and clinical characteristics of the patients in the ACOSOG Z030 trial, the STS-GTSD and national registries are largely identical to those reported here (13–16).

Our interest in reporting 90-day postoperative mortality is based on the emerging recognition that it is an important (though often under-reported) metric of surgical outcomes (17–20). An increase in mortality between 31 and 90 days has previously been reported by other investigators in several solid tumors including esophageal, pancreatic and lung cancer (17–20). While most deaths beyond thirty days are usually treatment-related, the contribution of competing causes of death including disease progression warrants further investigation. However, It is noteworthy that in the current trial, disease progression did not contribute to any death within 90-day of surgical intervention. As is evident from our data, 90-day mortality after LR increased from 1.1% at 30 days to 1.7% at 90 days. Similarly,

mortality doubled at 90 days after SLR, from 0.6% to 1.2%. It is our opinion, that regardless of the modality of treatment delivered, it should be customary to present data that reflect treatment-related mortality both at the end of treatment and 90 days after treatment has been completed. Such information is necessary if one is to compare the impact of different treatment strategies in a population of patients, though nominally healthy, is often older with multiple preexistent co- morbidities. For example, in an analysis of the NCDB, Stokes and colleagues recently reported that 30 and 90-day mortality were significantly higher after LR and SLR compared to SBRT (21). Specifically, 30-day mortality was 2% and 1.8% after LR and SLR respectively and 0.8% after SBRT. At 90-days, mortality estimates were 3.4% and 3.3% after LR and SLR respectively and 2.9% after SBRT. Clearly, the short-term advantage of SBRT in that analysis is driven by a surgical mortality that far exceeds mortality rates representative of the modern standard of care. Accurate representation of short-term risks (30/90 mortality) and long-term disease specific outcomes is an essential ingredient of shared decision-making.

The morbidity of lung resection has been the subject of numerous investigations and reported “major morbidity” generally ranges between 9% and 45%. This wide range is most likely attributable to variations in patients’ clinical characteristics but also possibly due to variations in definitions and the often-subjective grading of the severity of complications. The results of the current trial represent the most exhaustive compilation of adverse events following curative lung resection for early stage NSCLC. The data on complications are presented using the Common Toxicity Criteria of Adverse Events (CTCAE) that, unlike conventional surgical reporting, provide some objectivity in the determination of the severity of adverse events.

While the use of the Clavien-Dindo classification may bring more precision to the assessment of the severity of surgical complications, it is not readily translatable to other treatment modalities (22). In contrast, adverse events reporting using CTCAE allows appropriate comparisons of AEs among various disciplines and is already widely used in neoadjuvant clinical trials. The adverse events profile reported in the current trial clearly shows that while slightly over 50% of patients in each arm experience at least one adverse event, the great majority are either not clinically significant or are easily managed with minimal or no sequelae. The prevalence of specific adverse events such as supraventricular tachyarrhythmias, pneumonia, atelectasis, and air-leaks is consistent with results previously reported from various case series and analysis of the STS-GTSD. Significantly, however, the data show that major adverse events that are likely to prolong hospitalization or are life threatening occurred in less than 15% of patients regardless of the extent of resection. In this context, our data on morbidity is somewhat limited by lack of data on length of hospital stay and frequency of readmission which, at the time of trial design, were not considered pertinent to the primary end-point.

Nonetheless, the low 30 and 90-day mortality and Grades 3/4 AEs should be considered a new benchmark for achievable surgical results in patients with early stage NSCLC. In that regard, it is notable that almost 80% of patients in each arm of the trial had their lung resection performed by minimally invasive video-assisted or robotic techniques. This rate of minimally invasive resection for lung cancer surpasses the rate of 60% VATS utilization in

the STS-GTSD as recently reported by Seder *et al* (23) and far exceeds the 20% penetrance of VATS reported in the national registries (24,25). This transformation in thoracic surgical practice over the past decade has been truly remarkable and bodes well for further improvements in operative and peri-operative outcomes.

Finally, a distinguishing feature of our trial design is that the SLR arm allowed for both wedge resections and anatomical segmentectomies. That trial design was driven by practical sample size considerations as well as a desire to design a trial that reflects “real world” practice patterns. Although a three arm trial that randomizes patients to either lobectomy, segmentectomy or wedge resection would have more precisely answered the posited research question, the sample size required for such a design would have been prohibitively large. Conventional wisdom based largely on retrospective case series holds that an anatomical segmentectomy that involves individual ligation of segmental vessels and bronchi and wider parenchymal resection is oncologically superior to non-anatomic wedge resections. Despite the well-known anatomical differences between both types of SLR, it is noteworthy that studies from the national databases report that nearly 80% of SLR performed in the United States are wedge resections (15–16). In an attempt to mirror prevailing practice patterns in our trial design, we opted to leave the choice of the type of SLR to the surgeon. Interestingly our results show that even among dedicated well-trained general thoracic surgeons as many as 58% of patients underwent wedge resections.

Limitations.

Although the generalizability of our results may be inferred from the large number of participating surgeons and the wide array of contributing academic and community-based institutions, there are a number of important limitations worth considering. First, our results reflect a post-hoc exploratory analysis of end-points not previously prespecified in the protocol and should therefore be regarded as hypothesis generating rather than hypothesis testing. However, it is important to emphasize that the decision to report the data on 30 and 90-day mortality and morbidity was made prior to data analysis and thus the results may reflect an unbiased representation of perioperative outcomes. Therefore, we consider that the results of the current analysis represent the best available evidence for current surgical outcomes in this setting. Another limitation is whether outcomes achievable in patients enrolled in randomized trials such as this, can be readily generalized to the broader population of patients with lung cancer. Although patients enrolled in randomized trials may certainly be highly selected, a comparison of the demographics and clinical characteristics of our patients with studies reported from STS-GTSD and from national registries such as the NCDB, SEER (Surveillance, Epidemiology and End Results Program) and the Nationwide Inpatient Sample database, suggest that the groups are not markedly dissimilar (7,23,24). This trial was also limited to patients with peripheral small (*** 2 centimeters) tumors that were anatomically suitable for either lobar or sub-lobar resection. The patients were further intra-operatively selected based on the absence of metastatic nodal disease in the mediastinal or hilar nodes. The results may not therefore be extrapolated to patients with larger or more central tumors for whom lobectomy is the only reasonable option or to patients with metastases to the major hilar or mediastinal nodes. Finally, all participants in this trial had cardiopulmonary functions and performance status sufficiently adequate to undergo a lobar

resection. Notwithstanding these limitations, our results represent the expected modern day outcomes of surgical treatment of early stage lung cancer in patients with adequate cardiopulmonary function.

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Figure 1:
Consort diagram

Table I.**Eligibility Criteria**

Pre-registration Eligibility Criteria	
1. Peripheral lung nodule	2 cm on preoperative CT scan and presumed to be lung cancer.
2. The center of the tumor, as seen on CT, must be located in the outer third of the lung in either the transverse, coronal or sagittal plane. Patients with pure ground glass opacities or pathologically confirmed N1 or N2 disease are not eligible.	
3. The tumor location must be suitable for either lobar or sublobar resection (wedge or segment).	
4. ECOG performance status of 0–2.	
5. No prior malignancy within 3 years other than non-melanoma skin cancer, superficial bladder cancer, or CIS of the cervix.	
6. No prior chemotherapy or radiation therapy for this malignancy.	
7. No evidence of locally advanced or metastatic disease.	
8. Age	18 years.
Intra-operative Randomization Eligibility Criteria	
1. Histologic confirmation of NSCLC (if not already obtained).	
2. Confirmation of N0 status by frozen section examination. Right sided tumors require that node levels 4, 7, and 10 diagnosed as negative on frozen section. Left sided tumors require that node levels 5 or 6, 7 and 10 diagnosed as negative on frozen section. Nodes previously sampled by mediastinoscopy, EBUS and/or EUS within 6 weeks of the definitive surgical procedure do not need to be resampled.	

Table II.

Demographics, Baseline Clinical Characteristics, and Type of Surgery

	LR (N=357)	SLR (N=340)	Total (N=697)
Age			
Mean (SD)	66.6 (8.7)	66.7 (8.7)	66.7 (8.7)
Median	67.0	68.0	67.0
IQR	61.0, 73.0	61.0, 72.5	61.0, 73.0
Range	43.0, 88.0	37.0, 89.0	37.0, 89.0
Race, n (%)			
Unknown	8 (2.2%)	6 (1.8%)	14 (2.0%)
White	313 (87.7%)	314 (92.4%)	627 (90.0%)
Black or African American	29 (8.1%)	16 (4.7%)	45 (6.5%)
Asian	4 (1.1%)	2 (0.6%)	6 (0.9%)
American Indian/Alaska Native	1 (0.3%)	0 (0.0%)	1 (0.1%)
Not Reported	1 (0.3%)	1 (0.3%)	2 (0.3%)
More than One Race	1 (0.3%)	1 (0.3%)	2 (0.3%)
Sex, n (%)			
Male	147 (41.2%)	150 (44.1%)	297 (42.6%)
Female	210 (58.8%)	190 (55.9%)	400 (57.4%)
Performance Status, n (%)			
0	250 (70.0%)	263 (77.4%)	513 (73.6%)
1	102 (28.6%)	72 (21.2%)	174 (25.0%)
2	5 (1.4%)	5 (1.5%)	10 (1.4%)
Smoking History, n (%)			
Never	35 (9.8%)	30 (8.8%)	65 (9.3%)
Former	171 (47.9%)	167 (49.1%)	338 (48.5%)
Current	151 (42.3%)	143 (42.1%)	294 (42.2%)
Histology, n (%)			
Adenocarcinoma	258 (72.3%)	257 (75.6%)	515 (73.9%)
Squamous cell	68 (19.0%)	57 (16.8%)	125 (17.9%)
Carcinoid	1 (0.3%)	5 (1.5%)	6 (0.9%)
Other	30 (8.4%)	21 (6.2%)	51 (7.3%)
Tumor Location, n (%)			
RUL	128 (35.9%)	120 (35.3%)	248 (35.6%)
RML	16 (4.5%)	19 (5.6%)	35 (5.0%)
RLL	43 (12.0%)	55 (16.2%)	98 (14.1%)
LUL	107 (29.8%)	90 (26.5%)	197 (28.3%)
LLL	63 (17.6%)	56 (16.5%)	119 (17.1%)

	LR (N=357)	SLR (N=340)	Total (N=697)
% Predicted FEV1			
Mean (SD)	83.1 (22.1)	84.1 (19.2)	83.6 (20.7)
Median	83.0	83.5	83.0
IQR	72.0, 97.0	73.0, 96.0	72.0, 96.0
Range	-2.0, 146.0	-2.0, 138.0	-2.0, 146.0
Surgery Type, n (%)			
Thoracotomy	51 (14.3%)	42 (12.4%)	93 (13.3%)
VATS	283 (79.3%)	276 (81.2%)	559 (80.2%)
VATS w/ conversion to thoracotomy	23 (6.4%)	22 (6.5%)	45 (6.5%)

Table III.

30/90 Day Mortality by Age Group

	30-day		90-day		Total Patients	
	LR	SLR	LR	SLR	LR	SLR
<= 60	1 (1.1%)	0	1 (1.1%)	0	87	81
61–70	1 (0.7%)	0	2 (1.4%)	2 (1.4%)	142	141
71–80	1 (0.9%)	2 (1.9%)	2 (1.8%)	2 (1.9%)	111	103
>=81	1 (5.9%)	0	1 (5.9%)	0	17	15

Table IV.

Deaths at 30 Day and 90 Day

	LR (n=357)	SLR (n=340)	Difference (95% CI)*	Total (n=697)
30-day mortality	4 (1.1%) - ARDS (2) - Ischemic bowel (1) - Probable PE (1)	2 (0.6%) - ARDS (1 on segment) - Heart failure (1 on wedge)	0.5% (1.1, 2.3)	6 (0.9%)
90-day mortality	6 (1.7%) - ARDS (2) - Bradycardia (1) - Pneumonia (1) - Probable PE(1) - Ischemic bowel (1)	4 (1.2%) - ARDS (1 on segment) - Heart failure (1 on wedge) - Multi organ failure (1 on wedge) - Lung disease (1 on segment)	0.5% (1.5, 2.6)	10 (1.4%)

*
Miettinen-Nurminen method

Table V:

Summary of all adverse events reported within 30 days of surgery, by grade and regardless of cause

	Lobar resection (n=355) *	Sublobar resection (n=337) *	Difference (95% CI)
Grade 1 event	64 (18%)	75(22%)	-4.2% (-10.2 to 1.8)
Grade 2 event	75(21%)	49 (15%)	6.6% (0.9 to 12.3)
Grade 3 event	37 (10%)	41(12%)	-1.7% (-6.6 to 30)
Grade 4 event	13 (4%)	5(1%)	2.2% (-0.2 to 4.9)
Grade 5 event	4 (1%)	2(1%)	0.5% (-1.1 to 2.3)

* Adverse events were not submitted by time of analysis for two patients assigned lobar resection and three patients assigned sublobar resection.

Table VI:

Listing of Adverse Events within 30 Days of Surgery (regardless of attribution)

Listing of Grade 1+ Adverse Events Max Grade Per Patient Per Event Regardless of Attribution Number of Evaluable Patients: LR (Arm A)=355* SLR (Arm B)=337*											
Grade of Adverse Event											
	Arm	1- Mild		2- Mod		3-Severe		4-LifeThr		5-Lethal	
		n	(%)	N	(%)	n	(%)	n	(%)	n	(%)
Cardiovascular											
Atrioventricular heart block	A	1	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
	B	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Cardiac ischemia/infarction	A	0	(0%)	0	(0%)	3	(1%)	2	(1%)	0	(0%)
	B	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(0%)
Hypertension	A	4	(1%)	2	(1%)	1	(0%)	0	(0%)	0	(0%)
	B	0	(0%)	2	(1%)	0	(0%)	0	(0%)	0	(0%)
Hypotension	A	3	(1%)	10	(3%)	1	(0%)	0	(0%)	0	(0%)
	B	2	(1%)	6	(2%)	4	(1%)	0	(0%)	0	(0%)
Left ventricular diastolic dysfunction	A	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
	B	1	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Pulmonary hypertension	A	1	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
	B	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Supraventricular and nodal arrhythmia	A	5	(2%)	33	(9.2%)	4	(1%)	0	(0%)	0	(0%)
	B	5	(2%)	16	(5%)	3	(1%)	1	(0%)	0	(0%)
Vasovagal episode	A	0	(0%)	1	(0%)	0	(0%)	0	(0%)	0	(0%)
	B	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Ventricular arrhythmia	A	1	(0%)	1	(0%)	0	(0%)	0	(0%)	0	(0%)
	B	0	(0%)	1	(0%)	0	(0%)	0	(0%)	0	(0%)
	B	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Hemorrhage											
Hemorrhage assoc w/surg, intra-op/postop	A	0	(0%)	1	(0%)	6	(1.6%)	0	(0%)	0	(0%)
	B	1	(0%)	0	(0%)	8	(2.3%)	0	(0%)	0	(0%)
Hemorrhage, CNS	A	0	(0%)	0	(0%)	0	(0%)	1	(0%)	0	(0%)
	B	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Infection/Febrile Neutropenia											
Colitis, infectious	A	0	(0%)	1	(0%)	0	(0%)	0	(0%)	0	(0%)
	B	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Septicemia	A	0	(0%)	0	(0%)	0	(0%)	1	(0%)	0	(0%)
	B	0	(0%)	0	(0%)	0	(0%)	1	(0%)	0	(0%)
Urinary tract infection	A	0	(0%)	12	(3.3%)	10	(2.8%)	1	(0%)	0	(0%)
	B	1	(0%)	4	(1%)	8	(2.3%)	0	(0%)	0	(0%)
Pneumonia	A	0	(0%)	7	(2%)	13	(3.6%)	0	(0%)	0	(0%)

Listing of Grade 1+ Adverse Events Max Grade Per Patient Per Event Regardless of Attribution Number of Evaluable Patients: LR (Arm A)=355* SLR (Arm B)=337*											
Grade of Adverse Event											
	Arm	1- Mild		2- Mod		3-Severe		4-LifeThr		5-Lethal	
		n	(%)	N	(%)	n	(%)	n	(%)	n	(%)
Wound infection	B	0	(0%)	2	(0.6%)	11	(3.2%)	0	(0%)	0	(0%)
	A	0	(0%)	6	(1.6%)	0	(0%)	0	(0%)	0	(0%)
	B	1	(0%)	2	(0%)	1	(0%)	1	(0%)	0	(0%)
Neurology											
Confusion	A	8	(3%)	6	(2%)	3	(1%)	0	(0%)	0	(0%)
	B	9	(3%)	3	(1%)	0	(0%)	1	(0%)	0	(0%)
Pain											
Pain	A	10	(3%)	11	(4%)	3	(1%)	0	(0%)	0	(0%)
	B	11	(4%)	13	(4%)	4	(1%)	0	(0%)	0	(0%)
Pulmonary											
Adult Respiratory Distress Syndrome	A	1	(0%)	0	(0%)	0	(0%)	5	(2%)	2	(1%)
	B	0	(0%)	0	(0%)	1	(0%)	1	(0%)	1	(0%)
Aspiration	A	0	(0%)	0	(0%)	0	(0%)	2	(1%)	0	(0%)
	B	0	(0%)	1	(0%)	0	(0%)	0	(0%)	0	(0%)
Atelectasis	A	54	(18%)	13	(4%)	1	(0%)	0	(0%)	0	(0%)
	B	53	(18%)	10	(3%)	1	(0%)	0	(0%)	0	(0%)
Chylothorax	A	0	(0%)	1	(0%)	1	(0%)	0	(0%)	0	(0%)
	B	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Cough	A	4	(1%)	2	(1%)	0	(0%)	0	(0%)	0	(0%)
	B	2	(1%)	3	(1%)	0	(0%)	0	(0%)	0	(0%)
Dyspnea (shortness of breath)	A	3	(1%)	2	(1%)	3	(1%)	1	(0%)	0	(0%)
	B	3	(0%)	2	(1%)	1	(0%)	0	(0%)	0	(0%)
Fistula, pulmonary/upper respiratory	A	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
	B	0	(0%)	0	(0%)	1	(0%)	0	(0%)	0	(0%)
Hypoxia	A	0	(0%)	5	(2%)	4	(1%)	2	(1%)	0	(0%)
	B	0	(0%)	3	(1%)	11	(4%)	1	(0%)	0	(0%)
Obstruction/stenosis of airway	A	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
	B	0	(0%)	0	(0%)	0	(0%)	1	(0%)	0	(0%)
Pleural effusion (non-malignant)	A	35	(12%)	1	(0%)	2	(1%)	0	(0%)	0	(0%)
	B	31	(10%)	3	(1%)	3	(1%)	0	(0%)	0	(0%)
Pneumothorax	A	32	(11%)	11	(4%)	1	(0%)	0	(0%)	0	(0%)
	B	28	(9%)	8	(3%)	0	(0%)	0	(0%)	0	(0%)
Airleak	A	14	(5%)	10	(35%)	9	(3%)	0	(0%)	0	(0%)
	B	16	(5%)	7	(2%)	2	(1%)	0	(0%)	0	(0%)
Voice changes/dysarthria	A	1	(0%)	0	(0%)	1	(0%)	0	(0%)	0	(0%)
	B	0	(0%)	1	(0%)	0	(0%)	0	(0%)	0	(0%)
Surgery/Intra-Op Injury											

Listing of Grade 1+ Adverse Events Max Grade Per Patient Per Event Regardless of Attribution Number of Evaluable Patients: LR (Arm A)=355* SLR (Arm B)=337*											
Grade of Adverse Event											
	Arm	1- Mild		2- Mod		3-Severe		4-LifeThr		5-Lethal	
		n	(%)	N	(%)	n	(%)	n	(%)	n	(%)
Intra-operative injury	A	1	(0%)	0	(0%)	1	(0%)	0	(0%)	0	(0%)
	B	1	(0%)	0	(0%)	1	(0%)	0	(0%)	0	(0%)
Vascular											
Thrombosis/thrombus/embolism	A	0	(0%)	1	(0%)	2	(1%)	1	(0%)	1	(0%)
	B	0	(0%)	0	(0%)	1	(0%)	3	(1%)	0	(0%)

*
Two patients in LR and three patients in SLR failed to submit AE data by the time of the analysis

Table VII.

Multivariate logistic regression of grade 3/4/5 AEs (n=595)

	Odds Ratio	95% Confidence Limits		P-value
SLR vs LR (ITT)	0.871	0.562	1.349	0.537
Age (unit=10yrs)	1.308	1.001	1.709	0.049
Male vs Female	0.817	0.523	1.276	0.375
White vs Non-White	1.758	0.750	4.120	0.194
PS 1–2 vs 0	0.971	0.591	1.596	0.908
Ex-smoker vs Non-smoker	1.355	0.538	3.416	0.519
Current-smoker vs Non-smoker	1.577	0.619	4.013	0.340
FEV1 predicted (%)	0.980	0.970	0.991	<.001