Do the surgical results in the National Lung Screening Trial reflect modern thoracic surgical practice?

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ABSTRACT

Introduction: Surgical data from the National Lung Screening Trial (NLST) has yet to be closely examined. We sought to analyze surgical procedures and complications from the NLST to determine their relevance to modern surgical practice.

Methods: The NLST database was queried for patients who underwent surgical resection for confirmed lung cancer, specifically evaluating postoperative complications. Numerical variables were compared using the Mann-Whitney *U* test. Categorical variables were compared using the χ^2 test. Logistic regression univariate and multivariable analysis of independent risk factors of postoperative complications was performed.

Results: At operation, 80% of patients (*n* = 821) had lobectomy, 4.1% (*n* = 42) had pneumonectomy, and 16.1% (*n* = 166) had sublobar resection, among whom 69% (*n* = 114) had wedge resection. Only 29.6% (*n* = 305) of the cohort had a thorascopic resection. Although the overall rate of surgical patients with any complication was 31% (*n* = 318), only 15.5% of patients (*n* = 160) had major complications, most commonly prolonged air leaks (*n* = 67, 6.5%). Respiratory failure (*n* = 28, 2.7%), prolonged ventilation (*n* = 9, 0.9%), myocardial infarction or cardiac arrest (*n* = 7, 0.7%), and stroke (*n* = 2, 0.2%) were rare events. Overall 30-day mortality in patients undergoing resection was 1.7% (*n* = 18). On multivariable analysis, greater smoking pack history (odds ratio [OR], 1.01; 95% confidence interval [CI], 1.001-1.01) and pulmonary comorbidities (OR, 1.34; 95% CI, 0.98-1.82) were significant or approached significance for an association with complications/death, whereas sublobar resection (OR, 0.59; 95% CI, 0.38-0.94) and video-assisted thorascopic surgery approach (OR, 0.76; 95% CI, 0.56-1.04) were significant or approached significance for an association with decreased rates of complications/death.

Conclusions: Operative mortality and postoperative morbidity were very low in patients undergoing resection for screen-detected lung cancer. Increased use of sublobar resection and minimally invasive surgical approaches may be associated with fewer complications. (J Thorac Cardiovasc Surg 2019;157:2038-46)

Postoperative complications following resection for screen-detected lung cancer.

Central Message

In patients with screen-detected lung cancer, increased use of sublobar resection and minimally invasive approaches are associated with fewer complications. Operative mortality was very low.

Perspective

We sought to analyze surgical procedures and complications from the NLST to determine their relevance to modern surgical practice. Operative mortality was very low in patients with screen-detected lung cancer. Increased use of sublobar resection and minimally invasive surgical approaches are associated with fewer complications. The NLST may overestimate current surgical morbidity.

See Commentary on page 2047.

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The results of the National Lung Screening Trial (NLST) reported in 2011 showed a 20% reduction in lung cancer-related mortality and a 6.7% reduction in all-cause mortality for patients undergoing lung cancer screening with low-dose computed tomography (LDCT) compared with patients undergoing chest radiography.¹ Following that

Scanning this QR code will take you to the article title page to access supplementary information.

Abbreviations and Acronyms

CI	= confidence interval
IQR	= interquartile range
LDCT	= low-dose computed tomography
NLST	= National Lung Screening Trial
OR	= odds ratio
PET	= positron emission tomography
SLR	= sublobar resection
VATS	= video-assisted thoracoscopic surgery

seminal publication and numerous supporting publications, LDCT screening for lung cancer in high-risk populations was issued a national coverage determination by the Centers for Medicare and Medicaid Services in 2015.²⁻⁵ Despite this, LDCT has remained underused in potentially eligible populations.^{6,7} Using data from the National Health Interview Survey from 2010 to 2015, Jemal and Fedewa⁷ estimated that only 3.9% of eligible patients were screened for lung cancer nationwide.

Several reasons for the underuse of LDCT screening have been proposed.^{8,9} Often cited are the potential “harms” that occur in the screened population, including high rates of false-positive tests and morbidity from diagnostic and therapeutic procedures.¹⁰⁻¹² Of particular interest to surgeons is the 32% rate of surgical complications reported in the original NLST publication following diagnostic surgical procedures.¹ Such potential morbidity can certainly be framed as a harm of screening and could be used to justify observation for high-risk patients with suspicious lung nodules and recommendations of nonsurgical therapies. However, the NLST study protocol did not prespecify a standardized approach to nodule evaluation or to diagnostic or therapeutic surgical interventions. This implies that the diagnostic and therapeutic interventions used for each patient were left to the discretion of the treating physician, which makes the interpretation of the study results potentially challenging. For example, positron emission tomography (PET) for diagnosis and staging, minimally invasive surgical techniques, and limited resection were less widely used at that time. We therefore sought to examine more closely the surgical data from the NLST to describe how these patients were managed pre- and perioperatively and to determine whether the NLST surgical results can be expected to be similar to those obtained in modern surgical practice.

PATIENTS AND METHODS**The National Lung Screening Trial**

The NLST was a randomized trial comparing screening with either plain chest radiography or LDCT scan. Eligible participants included those who smoked more than 30 pack/years, were either current smokers or had quit

within the previous 15 years, and were 55 to 74 years at the time of randomization. Patients previously diagnosed with lung cancer, those who presented with symptoms, or those who were examined with computed tomography of the chest within 18 months before enrollment were excluded from the trial.

A blocked randomization stratified by age, sex, and screening center was done and analysts were blinded to personal identifiers, screening center and calendar dates. During accrual, 53,454 patients were enrolled in the study from 33 participating centers across the United States. Participant recruitment was completed in April 2004, and enrollees were followed until December 31, 2009. The primary outcome of interest of the original trial was lung cancer mortality, whereas lung cancer incidence, overall mortality, screening, and treatment-related morbidity were assessed as secondary outcomes.

Study Design and Patient Selection

The NLST dataset was reviewed for patients who underwent surgical resection for confirmed lung cancer during the study period (non-small or small cell lung cancer). In patients who underwent multiple surgical procedures, only the largest resection procedure was included in the final analysis. Variables of interests were retrieved from the NLST dataset and included demographic characteristics, smoking history, preoperative PET scan (within 6 months before surgery), preoperative/intraoperative biopsy type, clinical/pathologic stage (American Joint Committee on Cancer Seventh Ed.), surgical approach, surgical procedure, pathologic tumor size, pathologic tumor location, 90-day postoperative complications, and 30- and 90-day mortality. Complications were categorized into minor, intermediate, and major by the NLST abstractors. These definitions are listed in the NLST original publication appendix (https://www.nejm.org/doi/suppl/10.1056/NEJMoa1102873/suppl_file/nejmoa1102873_appendix.pdf). Data on death as a direct complication from surgery were retrieved from the “medical complications” dataset. Conversely, all-cause mortality data were retrieved from the main “participant” dataset. Risk factors of 90-day postoperative complications and/or death were analyzed in the whole cohort.

Statistical Analysis

Continuous variables were expressed as median (interquartile range [IQR]) and were compared using Mann-Whitney *U* test. Categorical variables were expressed as frequencies (percentages) and were compared using the 2-tailed Pearson χ^2 test.

Independent clinical risk factors of 90-day postoperative complications were explored using logistic regression analysis. The univariate model included age, sex, smoking pack/year, pulmonary comorbidity, heart disease/stroke, clinical stage, surgical approach, and extent of resection. All relevant clinical variables were included in the univariate model based on the clinical expertise of the authors. Univariate variables with probability values less than .10 were included in the multivariable model. A second multivariable model was constructed in a similar way after adjusting for clustering at the hospital level. Data analysis was performed using IBM SPSS software (Version 24.0; IBM Corp, Armonk, NY).

RESULTS**Patients/Diagnostic Procedures**

We identified 1029 patients who underwent surgery for lung cancer after screening with either LDCT or chest radiograph in the NLST cohort (Table 1). Surgeries were performed in 33 hospitals and the number of procedures performed per institution ranged from 4 to 127. Patients studied were predominantly male ($n = 593$, 58%), with a median age of 63 years (IQR 59-68), and a median smoking

TABLE 1. Patient demographics (n = 1029)

Characteristic	Number	% or IQR
Median age	63	IQR 59-68
Sex		
Male	593	58%
Female	436	42%
Race		
White	948	92%
Black	44	4%
Others/unknown	37	2%
Smoking pack years, median	57	IQR 45-80
Clinical Stage (American Joint Committee on Cancer Seventh Ed.) (n = 972)		
cStage I	764	79%
cStage II	91	9%
cStage III	99	10%
cStage IV	18	2%
Histology		
Adenocarcinoma	568	55%
BAC	96	9%
Other subtypes	472	46%
Squamous	267	26%
Other	194	19%

IQR, Interquartile range; cStage, clinical stage; BAC, bronchioloalveolar carcinoma.

pack history of 57 pack years (IQR 45-80). The majority (n = 568, 55%) of patients had adenocarcinoma and upper-lobe tumors (n = 613, 60%), with a median tumor size of 1.9 cm (IQR 1.3-3 cm).

Regarding preoperative workup, only 71% of patients (n = 729) had a PET scan performed within 6 months preoperatively. We were also able to determine the method of preoperative invasive diagnostic procedures in a subset of patients (n = 717). The remaining 312 patients did not have data entered regarding preoperative biopsy. On the 717 patients, 1172 invasive diagnostic procedures were performed. Surgical biopsy was performed in 266 patients, of whom 249 patients had the surgical biopsy performed on the same date as the definitive surgery. Computed tomography-guided biopsy was performed in 309 patients. Stand-alone lymphadenectomy or lymph node sampling was performed in 100 patients. Endobronchial or transbronchial biopsy was performed on 250 patients. Mediastinoscopy was performed in 192 patients, of whom 117 patients had other types of invasive diagnostic procedures done as well. For the remaining 55 patients, a biopsy procedure was performed but without details recorded regarding the type of the biopsy. The most invasive diagnostic procedures performed on the 717 patients are summarized in Table 2.

Surgical Approaches and Extent of Resection

We next evaluated the extent of resection and the surgical approach in the 1029 patients. The majority of patients

TABLE 2. The most invasive preoperative diagnostic procedures

Most invasive diagnostic procedure (n = 717)*	Number (%)
Surgical Bx	266 (37)
Mediastinoscopy	141 (19.5)
Lymphadenectomy, lymph node sampling/biopsy	19 (2.5)
CT-guided biopsy	188 (26)
Endobronchial/transbronchial biopsy	91 (13)
Others	12 (2)

Bx, Biopsy; CT, computed tomography. *A total of 717 patients had data on preoperative invasive diagnostic procedures.

(n = 821, 79.8%) underwent lobectomy (including bilobectomy in 48 patients, 4.7%), whereas 42 patients (4.1%) underwent pneumonectomy, and 166 patients (16.1%) underwent sublobar resection (SLR), including wedge resection in 114 patients and segmentectomy in 52 patients (Figure 1, A). Most patients (n = 630, 61%) undergoing cancer resection had an open thoracotomy approach, whereas only 305 patients (29.6%) had a minimally invasive thoracoscopic (video-assisted thoracoscopic surgery [VATS]) approach (Figure 1, B). The other 94 patients (9.1%) had missing data for the surgical approach. Postoperative morbidity and mortality for patients with and without reported surgical approach were compared (Table E1). Lymph node sampling and/or dissection was performed in 890 patients (86.5%) and was more commonly performed during thoracotomy (91% vs 81% for VATS, $P < .001$) and during lobectomy (92% vs 55% for SLR, $P < .001$). The pathologic stage distribution of the resected cancers is shown in Figure 2. The majority of cancers were stage IA (55%), whereas 18% were stage IB and the remaining 27% were higher pathologic stage. Among the patients who had both clinical and pathologic stages recorded (n = 813), the rate of pathologic upstaging after resection was 25.5% (n = 207), including 11% of patients (n = 89) with clinically unsuspected nodal disease.

Surgical Morbidity and Mortality

Among the 53,454 patients who were enrolled in the NLST trial, 2585 patients (4.8%) underwent 1 or more invasive procedures during the trial period. Of those patients, the incidence of having 1 or more postprocedural complications by 90 days was 18% (n = 465) (0.9% of all the screened population), and the incidence of having at least 1 major postprocedural complication at 90 days was 6.5% (n = 168) (0.3% of all the screened population).

One hundred eighty-seven patients had resection for non-cancer-related diagnoses. Postoperative complications occurred in (n = 26, 14%) of these patients, among whom only 3% (n = 6) had major complications. The 90-day postoperative mortality rate was 1% (n = 2).

Next, we evaluated the rates and the magnitude of postoperative complications among patients with cancer and

FIGURE 1. A and B, Extent of resection and surgical approach in patients undergoing resection for lung cancer in the National Lung Screening Trial cohort. VATS, Video-assisted thoracoscopic surgery.

determined their relationship to the extent of resection and surgical approach. The NLST reported a 32.1% rate of complications for patients with lung cancer following diagnostic thoracotomy, thoracoscopy, or mediastinoscopy.¹ In the NLST cohort of patients undergoing resection for lung cancer, the rate of complications was 30.8% ($n = 318$), including minor complications in 2.7% (95% confidence interval [CI], 2%-4%) ($n = 28$), moderate complications in 12.6% (95% CI, 11%-15%) of patients ($n = 130$), and major complications in 15.5% (95% C, 13%-18%) of patients ($n = 160$) (Table 3). The most common major

complication was a prolonged air leak/bronchial stump leak ($n = 67$, 6.5% [95% CI, 5%-8%] of cohort and 42% of major complications). Respiratory failure ($n = 28$, 2.7% [95% CI, 2%-4%]) and major cardiac events ($n = 8$, 0.8% [95% CI, 0.3%-1.5%]) were rare. Death recorded as a complication of surgery at 90 days was less than 1% ($n = 9$, 0.87% [95% CI, 0.43%-1.7%]), although overall 30-day mortality rate was 1.7% ($n = 18$) and overall 90-day mortality rate was 2.8% (95% CI, 2%-4%) ($n = 29$).

Interestingly, patients who had preoperative surgical biopsy ($n = 266$) had a trend toward greater rates of all complications following therapeutic procedures (35% vs 29.5%, $P = .096$) and specifically had greater rates of major complications (21.1% vs 13.6%, $P = .03$). Among patients undergoing SLR ($n = 166$), the rate of minor/moderate complications (9%) was significantly lower compared with patients undergoing lobectomy (16.6%, $P = .048$). The rate of major complications was also lower but not statistically different between SLR and lobectomy (13.3% vs 15.8%, $P = .574$). Similarly, the rate of minor/moderate complications among patients undergoing VATS was lower than among those undergoing thoracotomy (12.8% vs 17.6%, $P = .059$), whereas the rate of major complications was lower but again statistically not different (14.4% vs 17%, $P = .319$).

On univariate analysis, both VATS approach (odds ratio [OR], 0.71; 95% CI, 0.52-0.96, reference thoracotomy) and SLR (OR, 0.60; 95% CI, 0.4-0.89, reference lobectomy) were associated with lower rates of complications or death (Table 4). On multivariable analysis, greater smoking pack history (OR, 1.01; 95% CI, 1.001-1.01) and pulmonary comorbidities (OR, 1.34;

FIGURE 2. Pathologic stage distribution of patients undergoing resection for lung cancer in the National Lung Screening Trial cohort.

TABLE 3. Surgical morbidity and mortality

Category/specific complications (90 d)	Number (n = 1029)	Percentage (95% CI)
No complications	711	69% (66%-72%)
Mortality (90-d)	29	2.8% (2%-4%)
Major complications		
Any	160	15.5% (13%-18%)
Bronchial stump leak/air leak requiring tube >4 d	67	6.5% (5%-8%)
Acute respiratory failure/prolonged ventilation/respiratory arrest	38	3.7% (3%-5%)
Empyema/BP fistula/hemothorax/wound dehiscence/injury to vital organ	35	3.4% (2%-5%)
CVA/thromboembolic events	11	1% (0.5%-2%)
MI/cardiac arrest/CHF	8	0.8% (0.3%-1.5%)
Moderate complications		
Arrhythmia/pneumothorax requiring tube/infections/other	130	12.6% (11%-15%)
Minor complications		
Subcutaneous emphysema/atelectasis/other	28	2.7% (2%-4%)

CI, Confidence interval; BP, bronchopleural; CVA, cerebrovascular accident; MI, myocardial infarction; CHF, congestive heart failure.

95% CI, 0.98-1.82) were significant or approached significance for an association with complications/death, whereas SLR (OR, 0.59; 95% CI, 0.38-0.94) and VATS approach (OR, 0.76; 95% CI, 0.56-1.04) were significant or approached significance for an association with decreased rates of complications/death. After we adjusted for clustering at the hospital level, only the type of the surgical procedure (SLR: OR, 0.54; 95% CI, 0.34-0.87) and pulmonary comorbidity (OR, 1.48; 95% CI, 1.06-2.06) were associated with postoperative complications/death.

DISCUSSION

The surgical results for patients with non-small cell lung cancer enrolled in the NLST have not been closely examined. In the original publication, it was reported that in patients with lung cancer confirmed, the rate of complications after thoracotomy, thoracoscopy, or mediastinoscopy was 32.4%.¹ However, specific surgical procedures and approaches were not described, nor were specific complications. The high potential incidence of complications secondary to invasive procedures is frequently described as a potential harm of LDCT lung cancer screening. Indeed, in the “Patient and Physician Guide: National Lung Screening Trial (NLST)” published on the National Cancer Institute’s cancer.gov Web site, the benefit of LDCT

screening is described as “3 in 1000 fewer died from lung cancer,” which immediately contrasted with the harm that “2 in 1000 had a major complication from invasive procedures.”¹³ With such narrow risk/benefit, it is little wonder that LDCT screening has yet to be widely embraced by patients and primary care physicians.⁶⁻⁹ Yet the magnitude of those complications and their relationship to the underlying lung cancer, extent of surgery, or surgical approaches has not been described. Because the NLST enrolled patients over a decade ago, we hypothesized that the surgical management of screen-detected cancers in the NLST may potentially differ from modern surgical practice.

In the NLST cohort, there was relatively low use of preoperative PET and nonsurgical biopsy. This is perhaps not surprising, as no specific nodule evaluation approach was mandated in the NLST. In the current cohort, 29% of surgical patients with lung cancer did not have PET scans performed preoperatively. A more routine use of PET scan may also help to avoid pathologic upstaging and potential surgical morbidity. Furthermore, given the exceedingly high number of false-positive nodules in the NLST, the risk of surgically overtreating patients without biopsy is significant. Many individuals with screen-detected nodules will not have lung cancer. In the previously reported NLST cohort, 23% of the surgical procedures described (thoracotomy, thoracoscopy, or mediastinoscopy) were performed for benign lesions.¹ Although these procedures were performed in less than 1% of patients without lung cancer but with positive screening tests, it would obviously be preferable to avoid invasive surgical procedures when possible. The NLST data presented here suggest that diagnostic surgical biopsies may be associated with increased surgical complications after resection. At our institution, we have generally relied on preoperative nonsurgical biopsies to confirm tissue diagnosis before surgery, obtained either with radiologic guidance or by bronchoscopic guidance.

Notably, we report a 30-day surgical mortality of only 1.7% (including a rate of 0.68% for mortalities specifically recorded as a complication of surgery) in this cohort of patients with lung cancer. This is compared with the 30-day surgical mortality 0.9% previously reported by the International Early Lung Cancer Action Program,¹⁴ of 0% reported in the Danish Lung Cancer Screening trial,¹⁵ and of 0% reported in the Dutch Belgian randomized lung cancer screening trial.¹⁶ The number of patients in the current NLST study exceeds that of the other 3 studies combined (1029 vs 597) and should establish a new standard for the surgical mortality of screen-detected lung cancer in the United States. The overall mortality at 90 days was 2.8%, including a rate of 0.87% for death specifically reported as a complication of surgery. Despite including a high proportion of heavy smokers, surgical mortality in this randomized prospective cohort is less than that recently reported among all stage I surgical cases in the National Cancer

TABLE 4. Risk factors associated with surgical morbidity and/or death

Independent variables	No. of events/ no. of patients (318/1029)	Univariate		Multivariable*		Multivariable* adjusted for clustering at hospital level	
		OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Age, y	318/1029	1.02 (0.99-1.05)	.077	1.02 (0.99-1.05)	.125	1.02 (0.99-1.02)	.214
Sex							
Female	120/436	Reference		Reference		Reference	
Male	198/593	1.32 (1.01-1.73)	.044	1.20 (0.89-1.62)	.229	1.26 (0.91-1.75)	.163
Race							
White	297/948	Reference					
Others	21/81	0.77 (0.46-1.29)	.314				
Smoking pack/year	318/1029	1.01 (1.002-1.01)	.005	1.01 (1.001-1.01)	.020	1.005 (0.99-1.01)	.110
Pulmonary comorbidity							
No	218/741	Reference		Reference			
Yes	100/288	1.28 (0.96-1.07)	.099	1.34 (0.98-1.82)	.064	1.48 (1.06-2.06)	.021
Cardiovascular/cerebrovascular comorbidity			.409				
No	259/853	Reference					
Yes	59/176	1.16 (0.82-1.63)					
NLST randomization arm							
CXR	274/397	Reference					
Spiral CT	195/632	0.99 (0.76-1.30)	.966				
Histology							
Adenocarcinoma	164/568	Reference					
Squamous cell cancer	90/267	1.25 (0.92-1.71)	.157				
Others	64/194	1.21 (0.86-1.72)	.280				
Tumor location (n = 969)							
Upper/middle lobe	203/663	Reference					
Lower lobe	94/306	1.005 (0.75-1.35)	.975				
Clinical stage (n = 972)							
cStage I/II	260/855	Reference					
cStage III/IV	39/117	1.14 (0.76-1.73)	.521				
No. of surgeries performed at the facility							
≥44 surgeries, median	175/557	Reference					
<44 surgeries	143/472	0.95 (0.73-1.24)	.698				
Surgical approach (n = 935)							
Open	218/630	Reference		Reference		Reference	
VATS	83/305	0.71 (0.52-0.96)	.024	0.76 (0.56-1.04)	.091	0.77 (0.55-1.08)	.135
Extent of resection (n = 987)							
Bi (lobectomy)	266/821	Reference		Reference		Reference	
Sublobar resection	37/166	0.60 (0.40-0.89)	.011	0.59 (0.38-0.94)	.024	0.54 (0.34-0.87)	.011

OR, Odds ratio; CI, confidence interval; NLST, National Lung Screening Trial; CXR, chest radiograph; CT, computed tomography; cStage, clinical stage; VATS, video-assisted thoracoscopic surgery. *Univariate variables with P value <.1 were included in the multivariable model. In total, 935 patients were included in the multivariable model, of whom 301 patients had postoperative morbidity.

Database (3.59%) and is at the low end of the range of several of the surgical studies (2.7%-9.5%) frequently cited in literature from other specialties.¹⁷⁻¹⁹

Despite the low mortality, postoperative complications are relatively common after surgical resection of screen-detected lung cancer.^{1,15,16} However, we believe that the 32% overall rate of complications reported in the original

NLST publication and the harm estimation reported in the “Patient and Physician Guide: National Lung Screening Trial (NLST)” have overly amplified concerns about surgical complications. As reported in the original NLST publication, major complications only occurred after 0.06% of positive LDCT screening studies in patients ultimately found not to have cancer, compared with the

greater rates of complications in patients found to have lung cancer.¹ Clearly, it is the patients with lung cancer who are most at risk for procedural complications, a fact that has perhaps been lost on the general public. Even among the “major” complications in these patients with cancer, by far the most common (in 6.5% of all patients and accounting for more than one third of major complications) was an air leak requiring a chest tube for >4 days, perhaps not surprising in a population expected to have a high rate of emphysema. However, this complication often requires no further treatment and is generally self-limited. Complications with potential long-term adverse consequences, such as significant respiratory, cardiac, and thromboembolic events were rare, generally occurring in less than 2% to 3% of patients. Similarly, among non-major complications cardiac arrhythmias requiring medication, pneumothorax requiring reinsertion of a chest tube, and infections requiring antibiotics, all generally complications from which long-term effects can be expected to be minimal, accounted for more than 75% of the moderate-grade complications.

It is also important to note that surgical morbidity has steadily decreased since the time of the NLST enrollment, likely in part due to the more widespread use of minimally invasive surgical techniques and to the more frequent adoption of SLR for greater-risk patients or for those with small peripheral lung cancers (Table 5).^{20,21} In the NLST surgical cohort, minimally invasive VATS approaches were used in only 29.6% of cases and SLR in only 16.1% of cases. The NLST data suggest that both strategies may be associated with a decrease in surgical morbidity. This is consistent with previous reports in the literature.^{21,22-25} Minimally invasive approaches are certainly feasible for screen-detected lung cancers, as previously described in the DLCST surgical data, in which 84% of resections performed on patients in the computed tomography–screened arm were performed via VATS.¹⁵ In the most recent analysis of the Society of Thoracic Surgeons database, 62% of all lung cancers were resected via a minimally invasive approach.²² Interestingly, SLR was performed in 19.8% of those patients and in 20% of patients with early-stage lung cancer in the National Cancer Database between 2004 and 2013.^{17,22} Although survival results from randomized trials evaluating the oncologic efficacy of SLR versus lobectomy (A Phase III Randomized Trial of Lobectomy Versus Limited Resection for Small-sized Peripheral Non-small Cell Lung Cancer [JCOG0802] and Cancer and Leukemia Group B [CALGB] 140503) are still pending, several large series and reviews have shown SLR to be equivalent to lobectomy in carefully selected patients.²⁶⁻²⁸ Data from the International Early Lung Cancer Action Program (I-ELCAP) cohort have also suggested that SLR and lobectomy have equivalent 10-year survival rates (85% vs 86%) for screen-detected lung cancers.¹⁴

TABLE 5. The use of sublobar resection and VATS approach in large modern lung cancer studies

Study (year)	Number	% Sublobar resection
Sublobar resection		
NLST (2002-2008)	1029	16
STS GTSD (2012-2014) ²²	17,153	20
NCDB (2004-2013) ¹⁷	76,623	20
SEER-Medicare (stage IA <2 cm; 2007-2012)*	3986	31
% VATS		
VATS resection		
NLST (2002-2008)	1029	30
DLCST (2004-2011) ¹⁵	51	84
STS GTSD (2012-2014) ²²	17,153	62
CALGB 140503 (2007-2017) ⁴³	697	80

NLST, National Lung Screening Trial; STS GTSD, Society of Thoracic Surgeons General Thoracic Surgery Database; NCDB, National Cancer Database; SEER, Surveillance, Epidemiology, and End Results; VATS, video-assisted thoracoscopic surgery; DLCST, Danish Lung Cancer Screening Trial; CALGB, Cancer and Leukemia Group B. *Unpublished data (Stiles BM, et al, 2018).

Patients with such excellent survival are at risk for second primary lung cancers, of which the 10-year risk may be as high as 14.3%.²⁹ By preservation of lung parenchyma and pulmonary function, minimally invasive approaches and SLR may improve quality of life in this cohort and may also not preclude the possibility of future surgical treatment of new cancers. However, as conflicting data exist, SLR should only be used in carefully selected patients until clinical trial results are mature.³⁰⁻³³

One final note of caution should be sounded. There has been growing enthusiasm for the use of stereotactic body radiation therapy for screen-detected lung cancers.^{19,34,35} This is despite several population-based retrospective studies that have demonstrated markedly worse long-term survival for patients treated with stereotactic radiation compared with surgery, even when comparing healthy, medically operable patients.³⁶⁻³⁸ The rationale for stereotactic radiation is based largely on the suggestion that surgery carries too much risk of morbidity and mortality, a concept that are largely based on older, single-institution surgical studies. However, the 90-day mortality reported in this NLST surgical cohort is actually less than that reported following stereotactic body radiation therapy (2.8% vs 2.93%) in the National Cancer Database.¹⁷ In addition, although others have suggested that screen-detected lung cancers have a lower incidence of unexpected nodal metastases, in this NLST surgical lung cancer cohort 19% of patients had nodal metastases, including 13% with positive nodes that were not suspected clinically.³⁹ This percentage, as well as the 25% overall rate of pathologic upstaging, is similar to previous reports

from the surgical literature^{40,41} and provides further evidence of the need for accurate pathologic staging, which cannot be obtained with stereotactic radiation therapy. The risk of overtreatment is also a significant concern with stereotactic radiation, as many centers do not routinely biopsy suspicious lung nodules. In a screening cohort in which 96.4% of detected nodules are not actually lung cancer, such a strategy could lead to the overtreatment of many patients with benign lung nodules. For all of these reasons, we strongly favor surgical resection in medically operable patients with screen-detected lung cancers, ideally after confirmation with nonsurgical biopsy. In addition, thoracic surgeons should preferably follow well-established national guidelines in the diagnosis and management of lung cancer. The National Comprehensive Cancer Network guidelines recommend repeat radiologic assessment of small screen-detected nodules, imaging with PET as part of the workup for diagnosed lung cancers, and a preference for minimally invasive surgical approaches.⁴²

The study has several limitations. Post hoc analysis and interpretation of data drawn from large clinical trials can be challenging. Patients in the NLST were relatively healthy, young (median age 64 years), and were generally white and well educated. Future research should assess whether the postoperative morbidity data presented here can be applied to older, more diverse patient populations with greater comorbidities and should attempt to assess whether lung cancer screening outside of NLST centers yields similar proportions of lung nodules and cancers detected. In addition, the inability to control for other possible confounding factors that were not included in the NLST database (ie, information on surgeon and hospital characteristics) may have influenced the results of the study.

In conclusion, we provide for the first time a detailed analysis of the surgical cohort of patients with lung cancer from the NLST. Surgical mortality and complications with long-term detrimental effects to the patient are relatively rare. Because of the relatively low use of SLR and VATS in the NLST, we believe that the original publication likely overestimates the current surgical morbidity of screen-detected early-stage lung cancer.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: lung cancer, screening, low-dose computed tomography, minimally invasive surgery, sublobar resection

TABLE E1. Differences in patients' characteristics and postoperative morbidity based on availability of data on surgical approach

Variable	Missing surgical approach (n = 94)	Reported surgical approach (n = 935)	P value
Age	63 (59-67)	63 (59-68)	.832
Sex (male)	57 (61%)	536 (57%)	.536
Race			.172
White	90 (96%)	858 (92%)	
Others	4 (4%)	77 (8%)	
Packs/year	56 (44-80)	57 (45-79)	.554
Clinical stage (n = 972)			.096
cStage I/II	70 (82%)	785 (88.5%)	
cStage III/IV	15 (18%)	102 (11.5%)	
Postoperative complications	17 (18%)	301 (32%)	.005
30-d postoperative mortality	1 (1%)	17 (2%)	1*
90-d postoperative mortality	2 (2%)	27 (3%)	1*

cStage, Clinical stage. *P value calculated using the Fisher exact test.