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Surgically Managed Clinical Stage IIIA – Clinical N2 Lung Cancer in the Society of Thoracic Surgeons Database

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Abstract

Background—The role of surgery in patients with clinical stage IIIA – N2 positive (cIIIA-N2) lung cancer is controversial, in part because of variability in short and long-term outcomes. The objective of this study was to characterize the management of cIIIA-N2 lung cancer in the Society of Thoracic Surgeons General Thoracic Surgery Database (STS-GTSD).

Methods—The STS-GTSD was queried for patients that underwent surgery for cIIIA-N2 lung cancer between 2002 and 2012. A subset of patients ≥65 years of age was linked to Medicare data.

Results—3,319 surgically-managed, cIIIA-N2 patients were identified including 1,784 (54%) treated with upfront surgery (treatment naïve) and 1,535 (46%) with induction therapy. A PET scan was documented in 93% of patients, and 51% of patients were coded in STS-GTSD as having undergone invasive mediastinal staging. Nodal over-staging (cN2→pN0/N1) was observed in 43% of upfront surgery patients. Lobectomy was performed in 69% of patients and pneumonectomy in 11%. Operative mortality was similar between patients treated with upfront surgery (1.9%) and induction therapy 2.5%, p = .2583. The unadjusted Kaplan Meier estimate of 5-year survival of cIII-N2 patients treated with induction therapy then surgery was 35%.

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Conclusions—STS surgeons achieve excellent short and long-term results treating predominantly lobectomy-amenable cIIIA-N2 lung cancer. However, prevalent over-staging and abstention from induction therapy suggest either “over-coding” of false positives on imaging, or variable compliance to current guidelines for cIIIA-N2 lung cancer. Efforts are needed to improve clinical stage determination and guideline compliance in the GTSD for this cohort.

The care of the clinical stage III non-small cell lung cancer (NSCLC) with suspected or confirmed mediastinal lymph node metastases (cIII-N2) has proven to be extremely variable in the United States. Despite clear guidelines to inform the evaluation[1] and treatment[2] of this clinical scenario, observational studies have portrayed the care of cIII-N2 patients as being inconsistent and largely non-compliant with best practice standards. More specifically, induction therapy has been underutilized and a high prevalence of cIII-N2 patients have failed to be confirmed to have stage III disease at the time of resection of primary tumor[3]. We hypothesized that specialty training in thoracic surgery could mitigate some of the factors that drive variability in the evaluation and management of cIII-N2 lung cancer.

The Society of Thoracic Surgeons General Thoracic Surgery Database (STS-GTSD) represents a unique opportunity to study care patterns among a cohort of patients cared for by predominantly board-certified thoracic surgeons. By having a more uniform population of surgeons, the STS-GTSD should provide a more consistent view of the patient and tumor factors associated with care patterns in surgically managed lung cancer. Surgically-managed cIII-N2 patients in the STS- GTSD were analyzed in order to better characterize the evaluation, treatment and outcome in this population.

PATIENTS AND METHODS

Data Sources

The Society of Thoracic Surgeons-General Thoracic Surgery Database (STS- GTSD) is a comprehensive prospective database containing detailed sociodemographic, procedural and short-term outcome results of patients undergoing thoracic surgical procedures as described previously[4]. Because the STS- GTSD does not collect longitudinal data, a subset of patients ≥65 years of age in the STS- GTSD was linked to Medicare claims data from the Center of Medicaid and Medicare Services (CMS) as described previously in detail.[5]

Study Population

The STS-GTDB was queried for patients that had undergone surgical management of a lung cancer between 2002 and 2013. The study was restricted to patients with clinical stage III, N2 positive (cIII-N2) lung cancer, according to the 7th edition of the stage classification system of the American Joint Committee on Cancer[6]. Eligible procedures included lobectomy, pneumonectomy, segmentectomy, bilobectomy, wedge resection or sleeve lobectomy.

Patient Cohorts

Patient cohorts were created to align study questions with appropriately detailed populations (Figure 1).

Full cohort—All eligible patients (see above)

Linked – cohort—STS-GTSD patients >65 were evaluated for linkage with patients in CMS database to provide longitudinal follow up. A total of 1,151 patients (67% of STS-GTSD patients ≥ 65) were able to be linked to CMS data using a deterministic matching algorithm as described previously[5]. The use of commercial insurance or an HMO (rather than Medicare) was the most common reason patients were not able to be linked.

Staging Cohorts—Starting in 2012, the STS-GTSD began to capture the use of imaging studies for staging (e.g. PET and CT scan), and broadened the capture of invasive mediastinal staging procedures.

Therefore, analyses of the staging evaluation were restricted to patients having surgery in either 2012 or 2013 ("*full staging cohort*" = all ages, 2012–2013). A subset of this cohort was linked to CMS ("*linked staging cohort*" = patients >65, linked to CMS, 2012–2013) in order to determine the impact of adding claims data for invasive mediastinal staging using ICD-9 codes (3422, 3426, 3425, 3429, 33.24, 88.73).

Over-staging

Over-staging was defined as a clinical stage determination that was higher than what could be confirmed by examining the surgical specimen taken at the time of primary tumor resection. This was evaluated from the perspective of summary stage (cIII→pI or II) and for mediastinal lymph node involvement (cN2→pN0/1). Pathologic "NX" (1% of cases), previously used to indicate an absence of lymph nodes in the surgical specimen, was coded as N0. Over-staging was studied in the patients that went directly to surgery without induction therapy ("Upfront Surgery"), because it is not possible to distinguish over-staging from response to therapy in the patients who received Induction.

Variables

The following independent variables were considered in the multivariable analyses: age, sex, race, year of surgery, Body mass index (BMI = kg/m2), American Society of Anesthesiologist Risk Class, Zubrod Score (= performance status, 1–5), presence of coronary artery disease, presence of cerebrovascular disease, congestive heart failure, hypertension, diabetes mellitus, steroid use, peripheral vascular disease, renal insufficiency (Creatinine >2 or hemodialysis), Forced Expiratory Volume in 1 second (FEV1) % predicted, the cigarette use, laterality, whether or not the patient had a prior thoracic surgery (i.e. thoracic reoperation), whether or not Video Assisted Surgery (VATS) was used (as defined by STS- GTSD[7]). Induction therapy was captured in the STS- GTSD as chemotherapy, radiation or both within 6 months of surgery.

Operative mortality (dependent variable) in the STS-GTSD was defined as death within 30 days of surgery, or during index hospitalization.

Missing data

Overall the rate of missing data was low (average of 3% across the data fields studied). For a number of variables (comorbidities, the use of induction therapy, whether or not the surgery represented a reoperation), failure to code the presence of a variable was considered to be a negative response (e.g. if induction therapy was not specified as given, then it was assumed not have been given). If "no" was a possible response for an independent variable (i.e. use of PET scanning), the missing cases were excluded from the calculation of prevalence.

Statistical Analyses

Descriptive analyses were performed across the varied populations with patients both combined, and stratified by the use of induction therapy or no induction therapy. Significance of differences were determined using chi-square test for categorical variables and Wilcoxon rank sum test for continuous variables. Unadjusted survival was plotted using the Kaplan Meier method.

Logistic regression was used to identify associations between the independent variables listed above (see *Variables*) and dependent outcomes including: the use of induction therapy, the presence of over-staging, and death within 90 days of surgery. The models were refined using a combination of both backwards selection (with a threshold of a p value < 0.1 used for retention in model), and consensus determination (by study team) of important inclusions.

Cox proportional hazard models were built to examine longer term survival considering the same variables above. The model was not refined for this study, but was instead evaluated using the model created for a larger STS-GTDB study set of patients ≥65 linked to CMS[5]. All analyses were run using the SAS Software 9.4 (SAS Institute, Cary, NC) with a p-value of < 0.05 determined to be significant.

RESULTS

Patients

The STS-GTSD captured 3,319 cIII-N2 patients. (Table 1). The increasing annual accrual of cStageIII-N2 patients mirrored a trend towards increased participation in the STS- GTSD (Figure 2).

Clinical Staging Evaluation

CT scanning use was documented in 84% of patients in the full staging cohort (see METHODS), PET scanning in 93% of patients, while 2% had neither study documented. Both imaging modalities were more common among patients that received induction therapy (Figure 3A).

Invasive mediastinal staging was captured by the STS-GTSD in 51% of patients in the full staging cohort, roughly half of which involved endobronchial ultrasound (EBUS) (Figure 3B). Invasive mediastinal staging was more common in patients treated with induction therapy compared to upfront surgery (69% versus 35%, $p<.0001$).

In an attempt to broaden the capture of mediastinal staging procedures, a “linked staging cohort” was evaluated containing data from both STS-GTSD and Medicare (see METHODS). The addition of Medicare claims data increased the prevalence of invasive staging procedures in the “linked staging cohort” (49% STS-GTDB → 61% STS-GTSD + CMS data).

Management of cStage IIIA-N2 in the STS-GTSD

Overall, 54% of cIII-N2 patients (full cohort see METHODS) went directly to surgery (Upfront Surgery). Induction therapy was used in 46% of patients, consisting of chemotherapy only (14%), both chemotherapy and radiation (31%) and radiation only (1%). Logistic Regression identified patients younger than 65 as being the most likely receive induction therapy (OR 1.41 95%CI [1.14–1.74], p = .0017), with a progressive decline in the use of induction in older subsets (Supplemental eTable 1). Declining pulmonary function (FEV1 <80% of predicted OR 0.80, 95%CI[0.67–0.95], p = .0135), left-sided tumors (OR 0.69, 95%CI[0.58–0.82], p <.0001) and active smoking status (OR 0.71, 95%CI[0.53–0.97], p = .0287) also correlated with lower prevalence of induction therapy.

A wide variety of surgical procedures were performed (Table 1). Lobectomy was the most common procedure (69% of patients), while pneumonectomy was performed in 11% of patients. Pneumonectomy was less common in patients older than 65 (7% versus 14%), while wedge resection was more common in older patients (12% versus 8%).

Over-Staging

Over-staging was evaluated in the treatment naïve, Upfront Surgery cohort (see METHODS). Overall, 39% of the clinical stage III patients had a lower pathologic summary stage (pStage I or II) and appear to have been over-staged clinically. Nodal over-staging (cN2→pN0/1) was observed in 43% of the Upfront Surgery cohort. Interestingly, the rate of nodal over-staging was similarly high (50%) in the small subset of treatment naïve patients (n = 173) that had undergone invasive mediastinal staging.

A Logistic Regression identified cigarette smoking (OR 1.81 95%CI[1.26 – 2.60], p.0013) to be associated with an increased risk of nodal over-staging (Supplemental eTable 2). Wedge resection (OR 0.58 95%CI[0.42 – 0.80], p = .0009) and left-sided tumors (OR 0.68 95%CI[0.55 – 0.85], p = .0009) were associated with a decreased risk of nodal over-staging. The VATS approach, was not associated with over-staging in this Upfront Surgery group.

Perioperative Mortality

The operative mortality (in hospital or 30-day see METHODS) for resection was 1.9% of patients who had upfront surgery and 2.5% for patients that received induction therapy (Table 1, p = 0.2583). When right pneumonectomy (n = 124) was examined, there was no difference in operative mortality between induction (5.6%) and upfront surgery (4.8%). For left pneumonectomy the operative mortality for upfront surgery (n = 81) was low (1.2%), while the induction group (n = 99) had mortality that was higher (5.7%).

The 90-day mortality was only available for patients 65 or older who comprised the “linked cohort” (see METHODS) and was 7% for patients that had upfront surgery and 6.6% for patients who received induction therapy. The 90-day mortality varied by procedure (Figure 4).

A Logistic Regression identified pneumonectomy (HR 2.42 95%CI [1.14–5.14], p = 0.0212) as being associated with an increased risk for 90-day mortality, while female gender was associated with a decreased risk (HR .53 95%CI[0.30–0.93] p = 0.0259) (Supplemental eTable 3).

Longitudinal Outcomes

Longitudinal outcomes were available in the “Linked Cohort” (n= 1,151, see METHODS). An unadjusted Kaplan Meier survival analysis was performed with a median follow-up of 1,210 days for induction patients and 1,170 for upfront surgery patients. The 5-year survival was 35% for patients treated with induction therapy and 36% for patients treated upfront surgery. The 5-year survival of the subset of Upfront Surgery patients who were confirmed to be pN2 (i.e. no clinical over-staging) was 29% (which was significantly less than the Induction group, p 0.037), yet the comparison likely biased due to an inability to eliminate over-staged (better prognosis) patients from the Induction group.

An adjusted Cox Proportional Hazards Model identified age greater 74, male gender, FEV1<80% of predicted, clinical T3 status (versus T1) and pneumonectomy to be associated with increased risk of mortality (Table 2). Performance status (Zubrod score) and the use of induction therapy were not associated with increased survival (recognizing the inability to equitably account for prevalent over-staging compromises the interpretation of the efficacy of induction therapy).

COMMENT

The cIII-N2 population in the STS-GTSD portrays a mixed picture of the care that is provided by STS surgeons and is captured by the current database process. The clinical stage assessment embodies the interplay between provided and documented care patterns. The STS surgeons were largely compliant with recommendations for imaging (CT and PET scanning) in the cIII-N2 population. More specifically, 84% of STS-GTDB patients were recorded to have had a CT scan and 93% had a PET scan (98% of patients had at least one of the studies, although BOTH are recommended by the American College of Chest Physicians for cIII-N2 patients[1]). The use of invasive mediastinal staging (61% when both STS and Medicare data were considered) was higher than had been previously reported for the STS-GTSD (21% across all clinical stages[4]), but still low considering that invasive mediastinal staging is recommended for all cIII-N2 patients.[1]

The current analyses also give some insight to the extent to which the STS-GTSD captures the clinical staging evaluation. For example, the addition of Medicare claims data increased the prevalence of invasive mediastinal staging from 49% to 61% in the linked staging cohort, indicating that the STS-GTDB is failing to capture invasive mediastinal staging procedures in approximately 12% of patients.

A possible explanation for a relatively low prevalence of invasive mediastinal staging in the STS-GTDB could be that STS surgeons were trusting noninvasive (imaging) studies for clinical stage determination of the mediastinal lymph nodes. Prohibitively high false positives rates have been associated with both CT scanning (42%) and integrated PET-CT scanning (37%) for mediastinal nodal metastases[1], which would make reliance of STS surgeons on imaging concerning in this context.

It is also possible that a proportion of patients are being "over-coded" as being cN2, when in fact, the treating team was not concerned about possibility of their being N2 disease. The current STS-GTDB training manual for coders indicates "All nodes > 1cm on CT or PET/CT are considered positive. All PET positive nodes are considered positive. Results of previous invasive staging (EBUS, Mediastinoscopy) should be included here.[7]" This does leave some ambiguity as to how to handle conflicting results (e.g. positive PET but negative mediastinoscopy). The fact that N2 disease could not be pathologically confirmed in 50% of treatment-naive cN2 patients that had undergone (presumably negative) invasive mediastinal staging, suggests that a proportion of patients were over-coded (i.e. the coder accepted a positive imaging result over negative invasive result). Alternatively, surgeons may have been unable to remove the positive N2 lymph nodes at the time the primary was resected, which would appear as pN0/1 (which itself may be concerning). Over-staging was not more common in the patients undergoing VATS. This differs from a prior report which noted VATS to be less likely to confirm clinically detected hilar nodal (cN1) metastases, potentially reflecting a less adequate surgical lymph node evaluation during VATS compared to open approaches[8,9].

The management of cIII-N2 patients in the STS-GTSD likewise paints a mixed picture. While the underuse of induction therapy (only 46% of cIII-N2 patients received induction therapy) is shocking, one must keep in mind that 39% of the upfront surgery patients were not confirmed to have stage III disease (and therefore would not be recommended to have induction therapy). That being said, 984 patients were cN2 and pN2 and did not receive induction therapy prior to their resection, which is concerning.

Surgical management in the STS-GTSD was predominately limited to patients with lobectomy-amenable, cIII-N2 cancer (11% had pneumonectomy). The low pneumonectomy rate fits well with the negative "pneumonectomy-prevalent" clinical trials that evaluated the role of surgery in cIII lung cancer (e.g. 36% of patients in the Intergroup 0139 trial underwent pneumonectomy), and is consistent with post-hoc analyses which have suggested the benefits of surgery in cIII lung cancer may be limited to patients with lobectomy-amenable disease.[10]

The short and long-term outcomes in this report are consistent with other studies in this population. The 30-day mortality (STS-GTSD +CMS data, Figure 4) is surprisingly similar to what has been reported in the NCDB for cIII-N2 patients (lobectomy 2.8%, pneumonectomy 7.8% and wedge 3%).[3] Roughly half of the operative mortalities occur between 30 and 90 days, which has been previously been shown for thoracic procedures[11,12]. Induction therapy does not appear increase 90-day mortality.

The estimated 5-year survival of 35% for patients with induction therapy followed by surgery compares well to the 22% 5-year survival observed in the surgery-containing arms of the prospective trials evaluating the efficacy of surgery[10,13–15]. The efficacy of induction therapy is unfortunately not able to be evaluated in this subset, because it is not possible identify accurately-staged cIII patients in both induction and upfront surgery arms.

This study has several important limitations in addition to those traditionally associated with observational studies. The results of staging evaluations are not captured by the STS-GTDB, preventing “over-staging” from being distinguishable from “over-coding.” Several details which could impact short and long-term outcome such as histology (unavailable prior to 2012) and the types and amount of chemotherapy and radiation are not captured. Finally, it is not possible to determine the extent to which the upfront surgery patients were given post-operative therapy, which may have a similar efficacy to preoperative chemotherapy. More specifically, a study of cIII-N2 NSCLC from the National Cancer Database failed to identify a survival advantage of preoperative chemotherapy, over post-operative chemotherapy.[16] Therefore, although preoperative chemotherapy is currently the standard of care, it is not possible to conclude the STS patients were undertreated, without knowing whether or not they received post-operative chemotherapy.

In conclusion, the STS-GTSD captures a substantial proportion of the surgically managed cIII-N2 patients in the United States. Although short and long-term outcomes are excellent, there are significant opportunities to enhance the care of the cIII-N2 population by STS surgeons by increasing the use of induction therapy and invasive mediastinal staging. Further study is warranted to clarify the extent to which over-coding effects the cIII-N2 population in the STS-GTDB.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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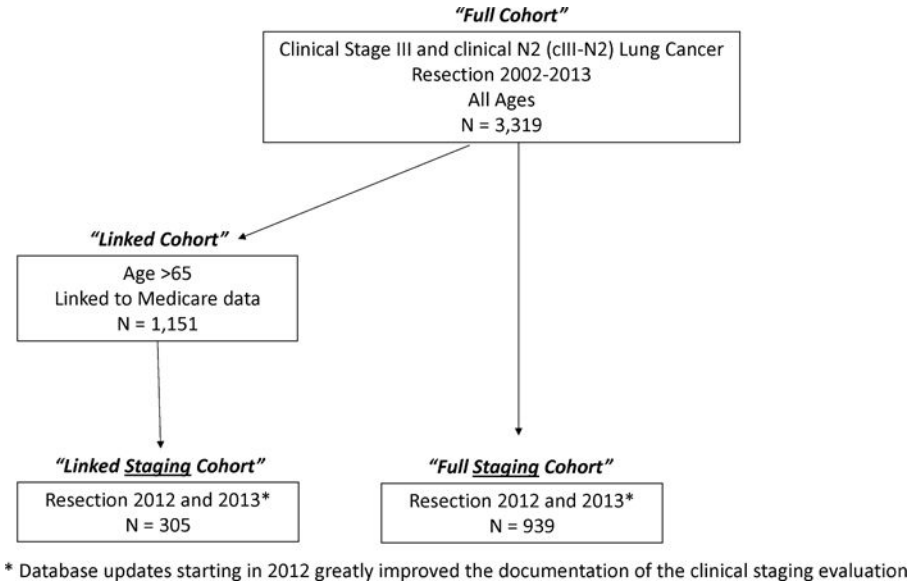

Figure 1.
Description of Cohorts.

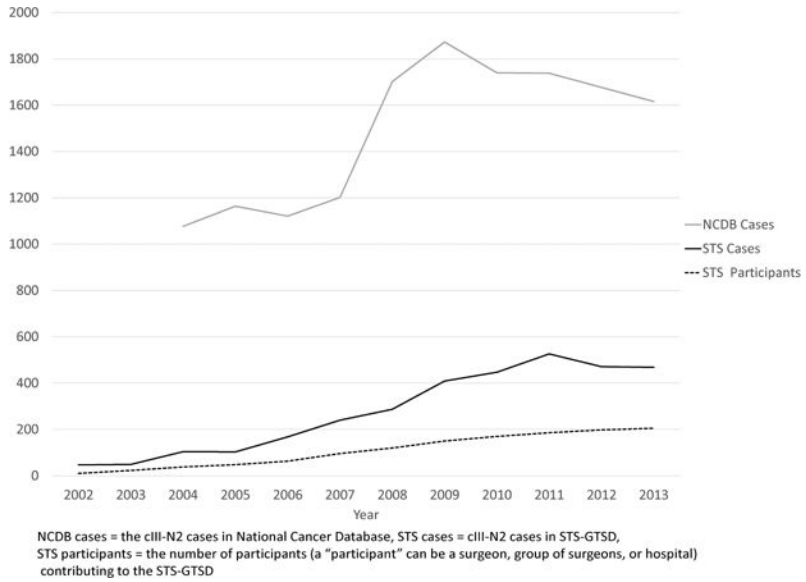

Figure 2.

Changes in cIII-N2 over time. The progressive increase in the number of cIII-N2 cases (black line) follows the increase in number of STS-GTDB participants (dashed line). For comparison, the number of patients having surgery for cIII-N2 lung cancer in the National Cancer Database (NCDB) is shown (gray line). The NCDB captures approximately 65% of newly diagnosed lung cancer in the United States[17]

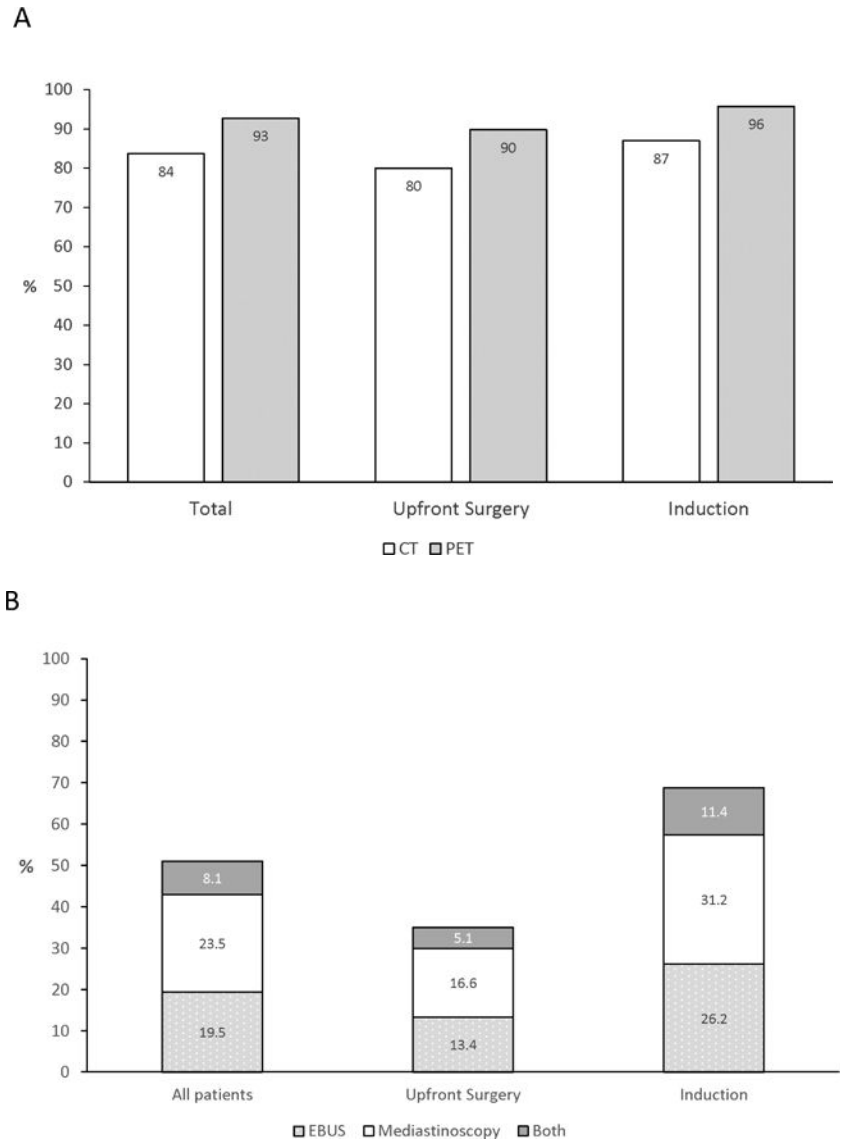

Figure 3.

Staging Evaluations. The prevalence (y-axis) of noninvasive (part A) and invasive (part B) staging evaluations are shown for patients in the “full staging cohort” (METHODS) treated with upfront surgery or with induction therapy.

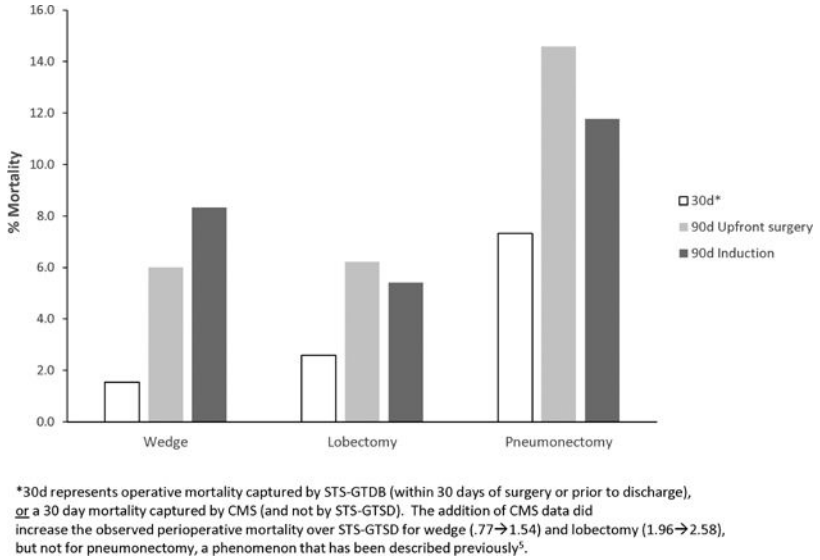

Figure 4.

Comparison of operative mortality in the linked subset of patients. 90-day mortality was available for the subset of patients ≥65 that were able to linked to Medicare data. The 90-day mortality is shown across three procedures, stratified according to whether patients were treated with upfront surgery (gray bars) or induction therapy (black bars). For comparison, the 30-day mortality (a composite of STS-GTSD and Medicare data) is shown (white bars).

Table 1

Description of the cIII-N2 population in the GTSD (N = 3,319)

Variable*		Upfront Surgery N=1784	Induction N=1535	P-Value**
Age (years)	Median (IQR)	67 (59, 74)	63 (55, 69)	<.0001
Gender	Male	930 (52.1%)	767 (50.0%)	0.2211
Race	White/Caucasian	1,549 (86.8%)	1,305 (85.0%)	0.1580
	Black/African American	156 (8.7%)	141 (9.2%)	.
	Other	11 (0.6%)	3 (0.2%)	.
Year of Surgery	2002	32 (1.8%)	15 (1.0%)	<.0001
	2003	18 (1.0%)	31 (2.0%)	.
	2004	50 (2.8%)	54 (3.5%)	.
	2005	50 (2.8%)	53 (3.5%)	.
	2006	75 (4.2%)	93 (6.1%)	.
	2007	98 (5.5%)	142 (9.3%)	.
	2008	138 (7.7%)	149 (9.7%)	.
	2009	261 (14.6%)	148 (9.6%)	.
	2010	275 (15.4%)	172 (11.2%)	.
	2011	294 (16.5%)	232 (15.1%)	.
	2012	256 (14.3%)	215 (14.0%)	.
	2013	237 (13.3%)	231 (15.0%)	.
Coronary Artery Disease	Yes	386 (21.6%)	205 (13.4%)	<.0001
Cerebrovascular Disease	Yes	138 (7.7%)	88 (5.7%)	0.0082
Congestive Heart Failure	Yes	51 (2.9%)	28 (1.8%)	0.0173
Hypertension	Yes	999 (56.0%)	703 (45.8%)	<.0001
Diabetes Mellitus	Yes	296 (16.6%)	193 (12.6%)	0.0001
Peripheral Vascular Disease	Yes	168 (9.4%)	81 (5.3%)	<.0001
Chronic Kidney Disease	Yes	32 (1.8%)	14 (0.9%)	0.0243
DLCO % Predicted	Median (IQR)	68.0 (55.0, 83.0)	70.0 (57.0, 83.0)	0.4952
FEV1 % Predicted	Median (IQR)	79.0 (66.0, 92.0)	82.0 (69.0, 94.0)	0.0005
	Missing	14 (0.9%)	12 (0.9%)	.
Induction Therapy	None	1,609 (90.2%)	0 (0.0%)	<.0001
	Chemotherapy Only	0 (0.0%)	472 (30.7%)	.
	Radiation Therapy Only	0 (0.0%)	28 (1.8%)	.
	Chemotherapy and Radiation	0 (0.0%)	1,035 (67.4%)	.
Pathological Stage	Stage I	381 (21.4%)	397 (25.9%)	0.0118
	Stage II	284 (15.9%)	225 (14.7%)	.
	Stage III	1,035 (58.0%)	837 (54.5%)	.
	Stage IV	36 (2.0%)	23 (1.5%)	.
PET or PET/CT$	Yes	396 (80.3%)	427 (95.7%)	0.0006

Variable*		Upfront Surgery N=1784	Induction N=1535	P-Value**
CT$	Yes	354 (71.8%)	387 (86.8%)	0.0087
EBUS and/or Mediastinoscopy$	None	320 (64.9%)	139 (31.2%)	<.0001
	EBUS only	66 (13.4%)	117 (26.2%)	.
	Mediastinoscopy/Chamberlain only	82 (16.6%)	139 (31.2%)	.
	Both EBUS and Mediastinoscopy/ Chamberlain	25 (5.1%)	51 (11.4%)	.
Pathological N	1	210 (11.8%)	187(12.2%)	<.0001
	2	984 (55.2%)	662 (43.1%)	.
	3	6 (0.3%)	6 (0.4%)	.
	X	12 (0.7%)	21 (1.4%)	.
	O	537 (30.1%)	623 (40.6%)	.
Cigarette Use	Never smoked	221 (12.4%)	169 (11.0%)	0.0288
	Past smoker	1,106 (62.0%)	1,053 (68.6%)	.
	Current smoker	457 (25.6%)	310 (20.2%)	.
Laterality	Right	925 (51.8%)	956 (62.3%)	<.0001
	Left	696 (39.0%)	502 (32.7%)	.
	Bilateral	3 (0.2%)	3 (0.2%)	.
General Thoracic Reoperation	Yes	137 (7.7%)	101 (6.6%)	0.1842
Primary Procedure	Wedge Resection	274 (15.4%)	66 (4.3%)	<.0001
	Segmentectomy	52 (2.9%)	19 (1.2%)	.
	Lobectomy	1,179 (66.1%)	1,112 (72.4%)	.
	Sleeve Lobectomy	32 (1.8%)	41 (2.7%)	.
	Bilobectomy	86 (4.8%)	106 (6.9%)	.
	Pneumonectomy	161 (9.0%)	191 (12.4%)	.
VATS for Primary Procedure	Yes	633 (35.5%)	276 (18.0%)	
Operative Mortality (D) (STS)	Yes	34 (1.9%)	38 (2.5%)	0.2583

*Variables that were evenly distributed were not show in table (BMI, American Society of Anesthesia Class, Zubrod score)

**P-values values only include non-missing row values

$All clinical staging evaluations performed on full staging cohort (see METHODS)

Missing cases not shown, but full table with missing cases available upon request

Table 2

Cox Proportional Hazards Model (Linked Cohort, n = 1040 [*]).

Variable[&]	*Unadjusted HR (95% CI)*	*Unadjusted P*	*Adjusted HR (95% CI)*	*Adjusted P*	*Overall P*
Upfront Surgery	Reference		Reference		
Induction Therapy	1.01 (0.85,1.19)	0.9312	1.06 (0.87,1.28)	0.5833	
Clinical Stage T1			Reference		0.0648
Clinical Stage T2			0.99 (0.81,1.22)	0.9402	
Clinical Stage T3			1.34 (1.01,1.77)	0.0429	
Age Group (years) 65–69			Reference		0.0697
Age Group (years) 70–74		.	1.11 (0.88,1.39)	0.3898	
Age Group (years) 75–79		.	1.33 (1.05,1.70)	0.0196	
Age Group (years) 80 and older		.	1.35 (1.00,1.83)	0.0525	
Male			Reference		
Female		.	0.75 (0.62,0.90)	0.0026	
ASA group I – II			Reference		0.1146
ASA group III		.	0.75 (0.57,0.99)	0.0395	
ASA group IV – V		.	0.82 (0.56,1.18)	0.2844	
Peripheral Vascular Disease		.	1.34 (1.02,1.75)	0.0343	
FEV Predicted < 40%		.	2.34 (1.27,4.31)	0.0065	0.0047
FEV Predicted (40–60%)		.	1.34 (1.01,1.79)	0.0419	
FEV Predicted (60–80%)		.	1.30 (1.06,1.59)	0.0104	
FEV Predicted 80% or More			Reference		
Primary Procedure Lobectomy			Reference		0.0163
Primary Procedure Bilobectomy		.	1.49 (1.01,2.21)	0.0461	
Primary Procedure Pneumonectomy		.	1.53 (1.11,2.11)	0.0092	
Primary Procedure Segmentectomy		.	1.24 (0.77,2.00)	0.3839	
Primary Procedure Sleeve Lobectomy		.	1.52 (0.89,2.59)	0.1249	

Variable[&]	*Unadjusted HR (95% CI)*	*Unadjusted P*	*Adjusted HR (95% CI)*	*Adjusted P*	*Overall P*
Primary Procedure Wedge Resection		.	1.34 (1.00,1.81)	0.0530	
VATS for primary procedure		.	0.93 (0.74,1.18)	0.5652	

ASA = American Society of Anesthesiology Class

[*] A total of 1,040 of the potential 1,151 linked cases (90%) contained sufficiently complete data to be considered in the final Cox Proportional Hazards model.

[&] variables included in final model that were not significant were not shown (BMI, smoking status, reoperation, comorbidities