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ORIGINAL ARTICLE

Retrospective Study

Surgical outcomes of pulmonary resection for lung cancer after neo-adjuvant treatment

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Abstract

AIM: To evaluate the outcomes of surgery for lung cancer after induction therapy.

METHODS: Using the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database (2005-2012), we identified 4063 patients who underwent a pulmonary resection for lung cancer. Two hundred and thirty-six (5.8%) received neo-adjuvant therapy prior to surgery (64 chemo-radiation, 103 radiation alone, 69 chemotherapy alone). The outcomes were compared to 3827 patients (94.2%) treated with surgery alone. Primary outcome was 30-d mortality, and secondary outcomes included length of stay, operative time and NSQIP measured postoperative complications.

RESULTS: Lung cancer patients who received pre-

operative treatment were younger (66 *vs* 69, $P < 0.001$), were more likely to have experienced recent weight loss (6.8% *vs* 3.5%; $P = 0.011$), to be active smokers (48.3 *vs* 34.9, $P < 0.001$), and had lower preoperative hematological cell counts (abnormal white blood cell: 25.6 *vs* 13.4; $P < 0.001$; low hematocrit 53% *vs* 17.3%, $P < 0.001$). On unadjusted analysis, neo-adjuvant patients had significantly higher 30-d mortality, overall and serious morbidity (all $P < 0.001$). Adjusted analysis showed similar findings, while matched cohorts comparison confirmed higher morbidity, but not higher early mortality.

CONCLUSION: Our data suggest that patients who receive neo-adjuvant therapy for lung cancer have worse early surgical outcomes. Although NSQIP does not provide stage information, this analysis shows important findings that should be considered when selecting patients for induction treatment.

Key words: Lung cancer; Pulmonary resection; Neo-adjuvant therapy; Surgical outcomes

Core tip: The aim of this retrospective study was to evaluate the results of lung cancer patients undergoing surgery after induction treatment. Using the American College of Surgeons National Surgical Quality Improvement Program database, we identified 4063 patients who underwent lung resection for cancer. Two hundred and thirty-six (5.8%) underwent neo-adjuvant therapy. The results were compared to 3827 patients (94.2%) who underwent upfront surgery. On unadjusted and adjusted analysis, neo-adjuvant patients had significantly higher 30-d mortality, overall and serious morbidity than patient treated with surgery alone. Matched cohorts comparison confirmed higher morbidity, but not higher early mortality.

Mungo B, Zogg CK, Schlottmann F, Barbetta A, Hooker CM, Molena D. Surgical outcomes of pulmonary resection for lung cancer after neo-adjuvant treatment. *World J Surg Proced* 2016; 6(2): 19-29 Available from: URL: http://www.wjgnet.com/2219-2832/full/v6/i2/19.htm DOI: http://dx.doi.org/10.5412/wjsp.v6.i2.19

INTRODUCTION

Lung cancer is among the highest reason of cancer-related mortality in the United States, including about 27% of all cancer deaths in 2014, and 224210 estimated new cases in the same year[1].

Surgery represents the mainstay of treatment for lung cancer and ongoing advancements in surgical techniques across the last two decades have led to a remarkable reduction in operative mortality[2]. Lung cancer-related mortality, however, remains disappointingly high, showing a 5-year relative survival of about 15%[3].

In an attempt to improve survival for this disease, several multimodality treatment approaches, including neo-adjuvant therapy protocols, have been developed through the years. Given its potential benefits, such as clearance of micrometastasis and tumor downstaging, the efficacy of induction treatment has been evaluated with many trials; unfortunately the results have been controversial, hence the use of neo-adjuvant therapy for locally advanced disease still represents the subject of an ongoing debate[4]. Reluctance towards the use of induction is in part due to a perceived increase in surgical risk for lung cancer patients undergoing neo-adjuvant treatment. It has in fact been reported that, in this population, induction may lead to non-negligible treatment-related mortality, and increased occurrence of post-operative adverse events such as air leaks and infectious complications[5-7]. The concern of developing life-threatening complications, prevalent and severe enough to offset the potential benefits of induction, can constitute a significant obstacle for the diffusion of neo-adjuvant protocols. In this regard, an analysis of the Society of Thoracic Surgeons (STS) General Thoracic Surgery Database has demonstrated that neo-adjuvant treatment is underutilized in the United States[8]. Only less than 10% of all major lung resections for primary lung cancer were reported to be preceded by induction treatment and, even for clinical stage ⅢA-N2, the percentage barely topped 50%. We queried the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database, to evaluate the effects of neo-adjuvant treatment on 30-d outcomes of resection for lung cancer in the United States.

MATERIALS AND METHODS

The study consisted of a retrospective research database review using the 2005-2012 ACS-NSQIP. The ACS-NSQIP is a large, nationally-validated, risk-adjusted, outcomes-based program used to measure and improve the quality of surgical care. It collects data from approximately 500 collaborating hospitals each year that vary in size and academic affiliation[9]. At participating institutions, trained surgical/clinical reviewers abstract data *via* a process of prospective systematic collection that includes information on 135 patient demographic, preoperative risk factor, laboratory value, and intraoperative factor variables in addition to 30-d measures of postoperative morbidity and mortality. Surgical cases from multiple specialties are sampled using an ACS-validated, systemic sampling protocol. Standardization of methods, data field definitions, and data collection are ensured by training and auditing protocols as well as regular assessment of inter-rater reliability. Details of the ACS-NSQIP are described elsewhere[10]. The study was deemed exempt from ethical review by the Johns Hopkins University School of Medicine Institutional Review Board.

The study population was restricted to include patients

Table 1 Baseline demographic and clinical characteristics

Characteristic	Total n = 4063	Neoadjuvant patients n = 236 (5.81%)	Surgery-only patients n = 3827 (94.19%)	P-value[1]
Age (yr), median (IQR)	68 (61-75)	66 (55-72)	69 (61-75)	< 0.001[2]
Male (%)	2003 (49.30)	125 (52.97)	1878 (49.07)	0.246
Race (%)				
White	3019 (74.30)	189 (80.08)	2830 (73.95)	0.173
Black	222 (5.46)	12 (5.08)	210 (5.49)	
Latino(a)	432 (10.63)	17 (7.20)	415 (10.84)	
Other or unknown	390 (9.60)	18 (7.63)	372 (9.72)	
ASA classification (%)				
1-2 no-mild disturbance	769 (18.97)	38 (16.24)	731 (19.14)	0.523
3 serious disturbance	2888 (71.24)	171 (73.08)	2717 (71.13)	
4-5 life threatening/moribund	397 (9.79)	25 (10.68)	372 (9.74)	
Functional status				
Independent	3985 (98.08)	229 (97.03)	3756 (98.14)	0.227
Partially/totally dependent	78 (1.92)	7 (2.97)	71 (1.86)	
Obese, BMI ⩾ 30 (%)	1155 (28.65)	58 (24.79)	1097 (28.88)	0.178
Diabetes (%)	598 (14.72)	27 (11.44)	571 (14.92)	0.143
Current smoker (%)	1448 (35.64)	114 (48.31)	1334 (34.86)	< 0.001[2]
Alcohol consumption (%)	221 (5.44)	15 (6.36)	206 (5.38)	0.522
Dyspnea (%)	1106 (27.22)	57 (24.15)	1049 (27.41)	0.275
History of COPD (%)	1082 (26.63)	54 (22.88)	1028 (26.86)	0.179
History of heart disease (%)	42 (1.03)	3 (1.27)	39 (1.02)	0.734
Hypertension (%)	2375 (58.45)	111 (47.03)	2264 (59.16)	< 0.001[2]
Previous cardiac surgery (%)	308 (7.58)	11 (4.66)	297 (7.76)	0.081
Weight loss (%)	152 (3.74)	16 (6.78)	136 (3.55)	0.011[2]
Steroid use (%)	161 (3.96)	22 (9.32)	139 (3.63)	< 0.001[2]
Year of operation (%)				
2005-2008	834 (20.53)	53 (22.46)	781 (20.41)	0.662
2009-2010	1794 (44.15)	105 (44.49)	1689 (44.13)	
2011-2012	1435 (35.32)	78 (33.05)	1357 (35.46)	
Preoperative WBC (%)				
Normal (4.5-11.0 × 10^9/L)	3364 (85.88)	174 (74.36)	3190 (86.61)	< 0.001[2]
Abnormal (< 4.5 or > 11.0 × 10^9/L)	553 (14.12)	60 (25.64)	493 (13.39)	
Preoperative hematocrit (%)				< 0.001[2]
Normal (⩾ 36)	3147 (80.53)	110 (47.01)	3037 (82.66)	
Abnormal (< 36)	761 (19.47)	124 (52.99)	637 (17.34)	
Surgery type (%)				< 0.001[2]
VATS	1203 (29.61)	34 (14.41)	1169 (30.55)	
Open	2860 (70.39)	202 (85.59)	2658 (69.45)	

[1]P-values taken from χ^2 tests (Fisher's exact test in cell counts less than five); [2]Two-sided values < 0.05 considered statistically significant. Wilcoxon rank-sum test used to compare rank sum differences in the non-normal distribution of age. Different denominators due to missing data: ASA (n = 4054); obese (n = 4032); WBC (n = 3917), hematocrit (n = 3908). ASA: American Society of Anesthesiology; COPD: Chronic obstructive pulmonary disease; WBC: White blood cell (count); VATS: Video-assisted thoracic surgery; BMI: Body mass index; IQR: Interquartile range.

≥ 18 years of age with a primary diagnosis of lung cancer (according to International Classification of Diseases, 9th revision, Clinical Modification), who underwent pneumonectomy [defined by Current Procedural Terminology (CPT) codes: 32440, 32442, 32445, 32488, 32671], lobectomy (32480, 32482, 32486, 32503, 32504, 32663, 32670), segmentectomy (32484, 32669), or wedge resection (32505, 32506, 32666, 32667). Patients were further excluded if they lacked reported information on administration of chemotherapy (defined by the ACS-NSQIP to be chemotherapy within 30 d pre-operation) or radiotherapy (defined by the ACS-NSQIP to be radiotherapy within 90 d pre-operation).

Collected baseline demographic and clinical characteristics are reported in Table 1. They include: Age (years), gender, race (White, Black, Latino/a, other/unknown), American Society of Anesthesiology (ASA) classification (1/2 no-mild disturbance, 3 serious disturbance, 4/5 life-threatening/moribund), functional status (independent *vs* partially/totally dependent), obesity (defined as a BMI > 29 kg/m^2), diagnosis of diabetes, current smoker within 1 year, alcohol consumption (defined as > 2 drinks/d in the 2 wk prior to admission), dyspnea, history of chronic obstructive pulmonary disease, history of heart disease (congestive heart failure and/or myocardial infarction), hypertension requiring medication, previous cardiac surgery, > 10% loss of body weight in the last 6 mo, steroid use for a chronic condition, year of operation (2005-2008, 2009-2010, 2011-2012), preoperative white blood cell (WBC) count [normal (4.5-11.0 × 10^9/L) *vs* abnormal (< 4.5 or > 11.0 × 10^9/L)], [preoperative hematocrit (normal) ⩾ 36 mg/dL *vs* abnormal (< 36 mg/dL)], and surgery type [video-assisted thoracic surgery (VATS) *vs* open]. Baseline demographic and clinical

Table 2 Unadjusted intraoperative and postoperative complications

Characteristic	Total *n* = 4063	Neoadjuvant patients *n* = 236 (5.81%)	Surgery-only patients *n* = 3827 (94.19%)	*P*-value[1]
30-d mortality (%)	107 (2.63)	19 (8.05)	88 (2.30)	< 0.001[2]
Overall morbidity (%)	646 (15.90)	63 (26.69)	583 (15.23)	< 0.001[2]
Wound infection	4 (0.10)	0 (0.00)	4 (0.10)	0.787
Pneumonia	5 (0.73)	0 (0.00)	5 (0.77)	0.774
Urinary tract infection	1 (0.15)	0 (0.00)	1 (0.16)	0.956
Return to OR	201 (4.95)	22 (9.32)	179 (4.68)	< 0.001[2]
Venous thromboembolism	80 (1.97)	7 (2.97)	73 (1.91)	0.256
Cardiac complication	60 (1.48)	10 (4.24)	50 (1.31)	< 0.001[2]
Shock/sepsis	107 (2.63)	11 (4.66)	96 (2.51)	0.045[2]
Unplanned intubation	207 (5.09)	27 (11.44)	180 (4.70)	< 0.001[2]
Bleeding transfusion	178 (4.38)	28 (11.86)	150 (3.92)	<0.001[2]
Renal complication	22 (0.54)	0 (0.00)	22 (0.57)	0.636
On ventilator > 48 h	3 (0.07)	1 (0.42)	2 (0.05)	0.164
Organ space SSI	44 (1.08)	1 (0.42)	43 (1.12)	0.516
Serious morbidity (%)	469 (11.54)	44 (18.64)	425 (11.11)	< 0.001[2]
Length of stay (d), median (IQR)	6 (4-9)	6 (4-9)	6 (4-8)	0.915
Prolonged length of stay (%)	816 (20.08)	46 (19.49)	770 (20.12)	0.815
Operative time (min), median (IQR)	161 (123-216)	160 (121-214)	192 (147-250)	< 0.001[2]
Prolonged operative time (%)	1006 (24.76)	91 (38.56)	915 (23.91)	< 0.001[2]

[1]*P*-values taken from χ^2 tests (Fisher's exact test in cell counts less than five); [2]Two-sided values < 0.05 considered statistically significant. Wilcoxon rank-sum tests used to compare rank sum differences in non-normal distributions of length of stay and operative time. Overall morbidity: Wound infection, pneumonia, urinary tract infection, venous thromboembolism, bleeding transfusion, renal complication, return to OR, cardiac complication, shock/sepsis, unplanned intubation, on ventilator > 48 h, and organ space SSI. Serious morbidity: Return to OR, cardiac complication, shock/sepsis, unplanned intubation, on ventilator > 48 h, and organ space SSI. Prolonged length of stay and operative time refer to times longer than the 75th percentiles for the respective distributions; IQR: Interquartile range; SSI: Surgical site infection; OR: Operating room.

characteristics were compared between neo-adjuvant patients (receipt of chemotherapy and/or radiotherapy) and surgery-only patients (receipt of neither chemotherapy nor radiotherapy) using χ^2 tests (Fisher's exact test in cell counts less than five) for categorical variables. Two-sided *P*-values < 0.05 were considered statistically significant. To account for non-normal age distributions within the study population, Wilcoxon rank-sum tests were used to compare rank sum differences in age.

The primary outcome measure considered was 30-d postoperative mortality. Secondary intraoperative and postoperative outcomes measures included overall morbidity, serious morbidity, length of stay (LOS, days), prolonged LOS (defined as a LOS longer than the 75th percentile), operative time (min), and prolonged operative time (defined as an operative time longer than the 75th percentile). Overall morbidity was defined by presence of at least one of the following ACS-NSQIP complications: Wound infection [superficial or deep incisional surgical site infection (SSI), wound dehiscence], pneumonia, urinary tract infection (UTI), return to operating room (OR), venous thromboembolic event (VTE) (deep vein thrombosis/thrombophlebitis, pulmonary embolism), cardiac complication (cardiac arrest, myocardial infarction), shock/sepsis, unplanned intubation, bleeding requiring transfusion, renal complication (postoperative renal failure, progressive renal insufficiency), ventilator dependency > 48 h, or organ space SSI. Serious morbidity included occurrence of at least one of the following complications: Return to OR, cardiac complication, shock/sepsis, unplanned intubation, ventilator dependency for > 48 h, or organ space SSI. As with baseline characteristics, outcome measures (Table 2) were compared between neo-adjuvant and surgery-only patients using χ^2 tests (Fisher's exact test in cell counts less than five) for categorical variables and Wilcoxon rank-sum tests to compare non-normal distributions of LOS and operative times.

Unadjusted and risk-adjusted odds ratios (and corresponding 95%CI) were calculated for differences in 30-d mortality, serious and overall morbidity, constituent morbidity measures, and prolonged LOS and operative time using (multivariable) logistic regression. Risk-adjusted models accounted for potential confounding due to significant differences in baseline factors: Age, smoking, hypertension, weight loss, steroid use, abnormal WBC count, abnormal hematocrit, and type of surgery performed. Colinearity/multicolinearity was assessed for adjusted models *via* calculation of variance inflation factors all well below a critical threshold of 10.0. For the continuous right-skewed distributions of LOS and operative time, modified Park tests were used to determine the most appropriate distribution (Poisson in both cases) to be used in a generalized linear model (link log). Average marginal effects were then used to calculate predicted differences in unadjusted and adjusted mean LOS (days) and operative time (min) in a manner analogous to that described for logistic regression (Table 3).

Finally, to more robustly corroborate the findings presented in Table 3 and to bolster the weight of the low

Table 3 Intraoperative/postoperative outcomes overall and among propensity-score matched cohorts (results represent odds ratios unless otherwise indicated)

Characteristic	Unadjusted (95%CI)	*P*-value[1]	Risk-adjusted (95%CI)	*P*-value[1]	Propensity-score matched cohort[3] (95%CI)	*P*-value[1]
30-d mortality (%)	3.72 (2.22-6.22)	< 0.001[1]	2.70 (1.54-4.72)	0.001[1]	1.63 (0.77-3.45)	0.197
Overall morbidity (%)	2.02 (1.50-2.74)	< 0.001[1]	1.53 (1.12-2.11)	0.010[1]	1.68 (1.08-2.62)	0.021[1]
Return to OR	2.09 (1.32-3.33)	0.001[1]	1.77 (1.08-2.90)	0.023[1]	3.37 (1.41-8.04)	0.006[1]
Cardiac complication	3.34 (1.67-6.70)	0.001[1]	3.11 (1.47-6.57)	0.003[1]	2.57 (0.79-8.30)	0.116
Shock/sepsis	1.90 (1.00-3.60)	0.049[1]	1.53 (0.78-3.02)	0.217	3.80 (1.05-13.80)	0.043[1]
Unplanned intubation	2.62 (1.71-4.02)	< 0.001[1]	2.03 (1.28-3.22)	0.002[1]	1.66 (0.88-3.14)	0.116
Bleeding transfusion	3.30 (3.15-5.06)	< 0.001[1]	1.72 (1.08-2.73)	0.023[1]	2.31 (1.17-4.58)	0.016[1]
Serious morbidity (%)	1.83 (1.30-2.58)	0.001[1]	1.55 (1.08-2.23)	0.018[1]	1.70 (1.02-2.85)	0.042[1]
Length of stay (d)[2]						
Predicted difference in means	-0.02 (-0.38 to 0.35)	0.927	-0.93 (-1.32 to -0.55)	< 0.001[1]	-1.02 (-1.54 to -0.50)	< 0.001[1]
Prolonged length of stay (%)	0.96 (0.87-1.34)	0.815	0.67 (0.47-0.96)	0.030[1]	0.63 (0.41-0.97)	0.037[1]
Operative time (min)[2]						
Predicted difference in means	30.5 (28.8-32.1)	< 0.001[1]	26.4 (24.7-28.1)	< 0.001[1]	29.0 (26.5-31.6)	< 0.001[1]
Prolonged operative time (%)	2.00 (1.52-2.62)	< 0.001[1]	1.81 (1.36-2.41)	< 0.001[1]	1.73 (1.17-2.57)	0.006[1]

[1]Two-sided *P*-values < 0.05 considered statistically significant. Adjusted models controlled for age, being a current smoker within one year, hypertension requiring medication, > 10% loss of body weight in last 6 mo, steroid use for chronic condition, abnormal preoperative WBC, abnormal preoperative hematocrit, abnormal preoperative albumin, operative year, managing specialty, and type of surgery preformed; [2]Modified Park tests corresponded to a Poisson distribution. Generalized linear models (family Poisson, link log) were used to model non-normally distributed continuous data, followed by post-estimation average marginal effects to attain predicted mean differences and 95%CI. Interpretation: Patients treated with neo-adjuvant therapy had average operative times that were longer than those of surgery-only patients by 29.0 min (95%CI: 26.5-31.6 min); [3]Separate cohorts were generated for each outcome using propensity-score-based 1:1 nearest-neighbor matching without replacement, accounting for significant baseline differences in demographic and clinical characteristics. OR: Operating room.

percentage of neo-adjuvant patients observed (5.81%), rates of intraoperative and postoperative complications and corresponding adjusted odds ratios were calculated among separate cohorts generated for each outcome using propensity-score-based 1:1 nearest-neighboring matching without replacement, accounting for baseline differences in demographic and clinical factors. Within the calculated cohorts, logistic regression and modified Park tests/Poisson regression with average marginal effects were used as previously described.

Finally, in order to explore potential variations in outcomes between different neo-adjuvant regimens, a sub group analysis was performed (Tables 4-6). More specifically, outcomes of patients treated with surgery alone were compared to outcomes of patients who underwent surgical resection after neo-adjuvant chemotherapy alone, neo-adjuvant radiotherapy alone and neo-adjuvant chemo-radiotherapy. The methodology of this sub-group analysis closely reflects that of the primary analysis of the study, except for the fact that to account for non-normal age distributions within the study population, Kruskal-Wallis non-parametric one-way analysis of variance tests were used to compare rank sum differences in age. Moreover, additional variables, such as preoperative albumin level [normal (≥ 3.5 g/dL) *vs* abnormal (< 3.5 g/dL)] and managing surgical specialty (thoracic, general, other speciality) were accounted for.

All data analyses and management were performed using Stata/MP version 12 (StataCorp LP, College Station, TX, United States). The statistical review of the study was performed by a biomedical statistician.

RESULTS

We identified 4063 patients who had lung surgery from 2005 to 2012, and had information on pre-operative treatment. Induction treatment was given to 236 (5.8%) patients; of those, 64 underwent chemo-radiation, 103 radiation alone, 69 chemotherapy alone. The percentages of patients receiving induction, and the type of neo-adjuvant treatment used across the study years are shown in Figure 1. We compared the results to 3827 patients (94.2%) treated with upfront surgery. Demographic characteristics were significantly different between the two groups (Table 1). Patients who underwent induction treatment were younger (66 *vs* 69, $P < 0.001$), reported higher recent weight loss (6.8% *vs* 3.5%; $P = 0.011$), were active smokers (48.3 *vs* 34.9, $P < 0.001$), and had lower preoperative cell counts (abnormal WBC: 25.6 *vs* 13.4; $P < 0.001$; low hematocrit 53% *vs* 17.3%, $P < 0.001$). Furthermore, we observed significantly lower rates of VATS resections (14.41% *vs* 13.55%, $P < 0.001$) among neo-adjuvant patients. On unadjusted analysis, patients who received induction therapy had significantly higher 30-d mortality, overall and serious morbidity (Table 2). Odds of experiencing prolonged operative time and reoperation rates were also higher among patients in the neo-adjuvant group. Adjusted analysis showed similar findings: Patients who underwent induction had significantly higher mortality [odds ratio (OR), 2.70; 95%CI: 1.54-4.72; $P = 0.001$], overall (OR, 1.53; 95%CI: 1.12-2.11; $P = 0.010$) and serious (OR, 1.55; 95%CI: 1.08-2.23; $P = 0.018$) morbidity and higher odds of experiencing prolonged operative time (OR, 1.81; 95%CI:

Table 4 Baseline demographic and clinical characteristics among the unmatched population cohort

Characteristic	Surgery only *n* = 3593 (94.21%)	Chemotherapy *n* = 64 (1.68%)	Radiotherapy *n* = 100 (2.62%)	Chemo and radio *n* = 57 (1.49%)	*P*-value[1]
Age (yr), median (IQR)	69 (61-75)	66 (62-73)	66 (53-69)	62 (52-70)	< 0.001[2]
Male (%)	1774 (49.59)	35 (54.69)	45 (45.45)	28 (49.12)	0.662
Race (%)					
Non-Hispanic White	2678 (78.58)	48 (78.69)	83 (86.46)	46 (85.19)	0.508
Non-Hispanic Black	194 (5.69)	3 (4.92)	5 (5.21)	4 (7.41)	
Hispanic	393 (11.53)	7 (11.48)	4 (4.17)	3 (5.56)	
Other or unknown	143 (4.20)	3 (4.92)	4 (4.17)	1 (1.85)	
ASA classification (%)					
1-2 no-mild disturbance	2573 (71.61)	51 (79.69)	71 (71.00)	41 (71.93)	0.445
3 serious disturbance	665 (18.51)	10 (15.63)	19 (19.00)	7 (12.28)	
4-5 life threatening/moribund	355 (9.88)	3 (4.69)	10 (10.00)	9 (15.79)	
Functional status					
Independent	3528 (98.19)	61 (95.31)	98 (98.00)	56 (98.25)	0.413
Partially/totally dependent	65 (1.81)	3 (4.69)	2 (2.00)	1 (1.75)	
Obese, BMI ⩾ 30 (%)	1093 (30.42)	20 (31.25)	22 (22.00)	14 (24.56)	0.245
Diabetes (%)	546 (15.20)	11 (17.19)	9 (9.00)	5 (8.77)	0.178
Current smoker (%)	1223 (34.04)	29 (45.31)	48 (48.00)	30 (52.63)	< 0.001[2]
Alcohol consumption (%)	193 (5.37)	5 (7.81)	6 (6.00)	4 (7.02)	0.785
Dyspnea (%)	975 (27.14)	14 (21.88)	24 (24.00)	16 (28.07)	0.711
History of COPD (%)	962 (26.77)	19 (29.69)	21 (21.00)	11 (19.30)	0.317
History of heart disease (%)	38 (1.06)	0 (0.00)	3 (3.00)	0 (0.00)	0.186
Hypertension (%)	2134 (59.39)	31 (48.44)	48 (48.00)	25 (43.86)	0.004[2]
Previous cardiac surgery (%)	280 (7.79)	2 (3.13)	6 (6.00)	3 (5.26)	0.422
Weight loss (%)	115 (3.20)	0 (0.00)	8 (8.00)	5 (8.77)	0.003[2]
Steroid use (%)	132 (3.67)	6 (9.38)	10 (10.00)	3 (5.26)	0.001[2]
Year of operation (%)					
2005-2008	728 (20.26)	6 (9.38)	34 (34.00)	9 (15.79)	< 0.001[2]
2009-2010	1577 (43.89)	21 (32.81)	61 (61.00)	18 (31.58)	
2011-2012	1288 (35.85)	37 (57.81)	5 (5.00)	30 (52.63)	
Preoperative WBC (%)					
Normal (4.5-11.0 × 10^9/L)	2988 (83.16)	54 (84.38)	73 (73.00)	38 (66.67)	< 0.001[2]
Abnormal (< 4.5 or > 11.0 × 10^9/L)	468 (13.03)	10 (15.63)	27 (27.00)	17 (29.82)	
Preoperative hematocrit (%)					
Normal (⩾ 36)	2860 (79.60)	32 (50.00)	52 (52.00)	23 (40.35)	< 0.001[2]
Abnormal (< 36)	588 (16.37)	32 (50.00)	48 (48.00)	32 (56.14)	
Preoperative albumin (%)					
Normal (⩾ 3.5 g/dL)	3345 (93.10)	58 (90.63)	82 (82.00)	55 (96.49)	< 0.001[2]
Abnormal (< 3.5 g/dL)	248 (6.90)	6 (9.38)	18 (18.00)	2 (3.51)	
Managing specialty (%)					
Thoracic	2243 (62.43)	48 (75.00)	48 (48.00)	40 (70.18)	0.008[2]
General	991 (27.58)	11 (17.19)	42 (42.00)	11 (19.30)	
Other specialty	359 (9.99)	5 (7.81)	10 (10.00)	6 (10.53)	
Surgery type (%)					
Open	2545 (70.83)	51 (79.69)	86 (86.00)	53 (92.28)	< 0.001[2]
VATS	1048 (29.17)	13 (20.31)	14 (14.00)	4 (7.02)	

[1]Two-sided *P*-values taken from χ^2 tests (Fisher's exact test in cell counts less than five); [2]*P*< 0.05 considered statistically significant. Kruskal-Wallis one-way analysis of variance was used to compare non-normal distributions of age. ASA: American Society of Anesthesiology; COPD: Chronic obstructive pulmonary disease; CHF: Congestive heart failure; MI: Myocardial infarction; WBC: White blood cell (count); VATS: Video-assisted thoracic surgery; BMI: Body mass index; IQR: Interquartile range.

1.36-2.41; *P* < 0.001) (Table 3). Interestingly, patients treated with surgery alone had higher LOS and prolonged LOS.

Results after matching for baseline differences in demographic and clinical factors are shown in Table 7. While differences in mortality among the groups were non-significant, overall morbidity, serious morbidity and prolonged operative time remained higher in the neo-adjuvant group.

Results of the sub-group analysis comparing outcomes of surgery alone to those of different neo-adjuvant regimens did not show clinically meaningful differences between the neo-adjuvant sub groups (Tables 4-6).

DISCUSSION

The results from our analysis demonstrated globally worse postoperative outcomes in patients who received neo-adjuvant treatment before lung resection, when compared to those treated with surgery alone. Thirty-day overall and serious morbidity rates as well as operative times, were consistently higher in patients receiving induction treatment. Conversely, higher mortality in the neo-adjuvant group was statistically

Table 5 Unadjusted intraoperative/postoperative outcomes among the unmatched population cohort

Characteristic	Surgery only *n* = 3593 (94.21%)	Chemotherapy *n* = 64 (1.68%)	Radiotherapy *n* = 100 (2.62%)	Chemo and radio *n* = 57 (1.49%)	*P*-value[1]
30-d mortality (%)	83 (2.31)	3 (4.69)	9 (9.00)	5 (8.77)	< 0.001[2]
Overall morbidity (%)	415 (11.55)	13 (20.31)	21 (21.00)	17 (29.82)	< 0.001[2]
Wound infection	3 (0.08)	0 (0.00)	0 (0.00)	0 (0.00)	--
Pneumonia	4 (0.11)	0 (0.00)	0 (0.00)	0 (0.00)	--
Urinary tract infection	1 (0.03)	0 (0.00)	0 (0.00)	0 (0.00)	--
Return to OR	170 (4.73)	7 (10.94)	10 (10.00)	4 (7.02)	0.012[2]
Venous thromboembolism	70 (1.95)	0 (0.00)	2 (2.00)	3 (5.26)	0.212
Cardiac complication	47 (1.31)	2 (3.13)	2 (2.00)	4 (7.02)	0.002[2]
Shock/sepsis	92 (2.62)	2 (3.13)	5 (5.00)	2 (3.51)	0.513
Unplanned intubation	169 (4.70)	5 (7.81)	12 (12.00)	7 (12.28)	< 0.001[2]
Bleeding transfusion	133 (3.70)	8 (12.50)	7 (7.00)	10 (17.54)	< 0.001[2]
Renal complication	22 (0.61)	0 (0.00)	0 (0.00)	0 (0.00)	--
On ventilator > 48 h	2 (0.06)	1 (1.56)	0 (0.00)	0 (0.00)	--
Organ space SSI	38 (1.06)	0 (0.00)	1 (1.00)	0 (0.00)	--
Serious morbidity (%)	372 (10.35)	12 (18.75)	19 (19.00)	10 (17.54)	0.002[2]
Length of stay (d), median (IQR)	6 (4-8)	5 (4-7)	6 (5-9)	5 (4-8)	0.134
Prolonged length of stay (%)	899 (25.02)	10 (15.63)	28 (28.00)	13 (22.81)	0.306
Operative time (min), median (IQR)	160 (121-214)	187 (140-246)	202 (151-253)	182 (142-249)	< 0.001[2]
Prolonged operative time (%)	858 (23.44)	23 (35.94)	41 (41.00)	20 (35.09)	< 0.001[2]

[1]Two-sided *P*-values taken from χ^2 tests (Fisher's exact test in cell counts less than five); [2]$P < 0.05$ considered statistically significant. Kruskal-Wallis one-way analysis of variance was used to compare non-normal distributions of length of stay and operative time. Overall morbidity: Wound infection, pneumonia, urinary tract infection, venous thromboembolism, bleeding transfusion, renal complication, return to OR, cardiac complication, shock/sepsis, unplanned intubation, on ventilator > 48 h, and organ space SSI. Serious morbidity: Return to OR, cardiac complication, shock/sepsis, unplanned intubation, on ventilator > 48 h, and organ space SSI. Prolonged length of stay, prolonged operative time refers to times longer than the 75th percentiles for the respective distributions. OR: Operating room; SSI: Surgical site infection; IQR: Interquartile range.

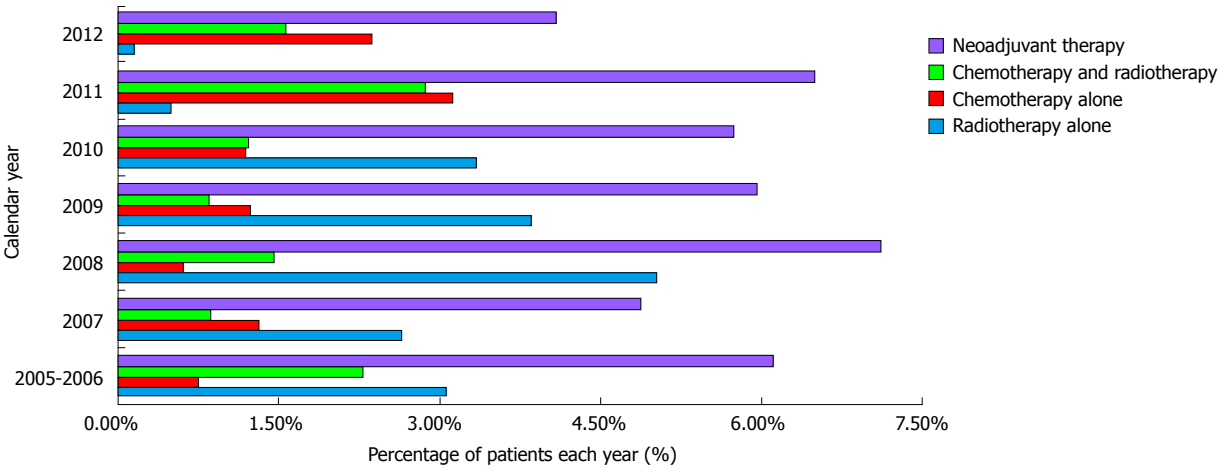

Figure 1 Percentage of patients receiving neo-adjuvant therapy across the study years. The denominations "chemotherapy alone" and "radiotherapy alone" indicate patients who underwent surgery after respectively neo-adjuvant chemotherapy not associated with neo-adjuvant radiotherapy, and neo-adjuvant radiotherapy not associated with neo-adjuvant chemotherapy.

non-significant after matching.

The two groups showed several differences at baseline, some of which likely reflected the effects of neo-adjuvant administration. Patients in the induction group, in fact, demonstrated signs of malnutrition and myelosuppression, as shown by their weight loss and lower blood cell counts. Likewise, probably some patients' characteristics such as more advanced age influenced the decision to avoid neo-adjuvant treatment.

In our population, a significantly higher percentage of patients in the neo-adjuvant group were current smokers, as defined by NSQIP (the patient has smoked cigarettes in the year prior to admission for surgery). It has been reported that continued smoking after cancer diagnosis was related to reduced treatment efficacy, increased treatment-related complications and reduced survival[11]. Even though this could have partially influenced the induction group's worse results, it is worth stressing that most differences in post-operative adverse events persisted after adjusting for smoking habits. Chronic steroid use, which was more prevalent among patients who received neo-adjuvant therapy, is

Table 6 Intraoperative/postoperative outcomes among propensity-score matched cohorts[3] relative to the surgery only group (results represent odds ratios unless otherwise indicated)

Characteristic	Surgery only varied size with cohort	Chemotherapy *n* = 64 matched patients	Radiotherapy *n* = 100 matched patients	Chemo and radio *n* = 57 matched patients
30-d mortality (%)	1.00 (reference)	0.74 (0.16-3.43)	1.24 (0.73-2.13)	1.38 (0.79-2.43)
Overall morbidity (%)	1.00 (reference)	1.10 (0.46-2.65)	1.14 (0.80-1.62)	1.38 (1.01-1.89)[1]
Serious morbidity (%)	1.00 (reference)	1.25 (0.50-3.13)	1.00 (0.70-1.42)	1.00 (0.72-1.38)
Length of stay (d)[2]				
Predicted mean difference	0.00 (reference)	-1.43 (-2.19 to -0.68)[1]	0.34 (0.08-0.60)[1]	-0.04 (-0.28-0.21)
Prolonged length of stay (%)	1.00 (reference)	0.56 (0.21-1.46)	0.95 (0.68-1.31)	0.78 (0.57-1.06)
Operative time (min)[2]				
Predicted mean difference	0.00 (reference)	13.8 (10.7-17.0)[1]	19.9 (18.7-21.1)[1]	9.49 (8.41-10.6)[1]
Prolonged operative time (%)	1.00 (reference)	2.20 (1.00-4.87)[1]	1.56 (1.15-2.11)[1]	1.03 (0.79-1.34)

[1]Two-sided *P*-values < 0.05 considered statistically significant; [2]Modified Park tests corresponded to a Poisson distribution. Generalized linear models (family Poisson, link log) were used to model non-normally distributed continuous data, followed by post-estimation average marginal effects to attain predicted mean differences and 95%CI. Interpretation: Patients treated with chemotherapy had average operative times that were longer than those of surgery-only patients by 13.8 min (95%CI: 10.7-17.0); [3]Separate cohorts were generated for each outcome using propensity-score-based 1:1 nearest-neighbor matching without replacement, accounting for significant baseline differences in demographic and clinical characteristics.

Table 7 Rates of intraoperative and postoperative complications in cohorts matched for each outcome

Characteristic	Neoadjuvant patients *n* = 234 (50.00%)[3]	Surgery-only patients *n* = 234 (50.00%)[3]	Odds ratio (95%CI)	*P*-value[1]
30-d mortality (%)	19 (8.12)	12 (5.13)	1.63 (0.77-3.45)	0.197
Overall morbidity (%)	63 (26.92)	42 (17.95)	1.68 (1.08-2.62)	0.021[1]
Return to OR	22 (9.40)	7 (2.99)	3.37 (1.41-8.04)	0.006[1]
Cardiac complication	10 (4.27)	4 (1.71)	2.57 (0.79-8.30)	0.116
Shock/sepsis	11 (4.70)	3 (1.28)	3.80 (1.05-13.80)	0.043[1]
Unplanned intubation	27 (11.54)	17 (7.26)	1.66 (0.88-3.14)	0.116
Bleeding transfusion	28 (11.97)	13 (5.56)	2.31 (1.17-4.58)	0.016[1]
Serious morbidity (%)	44 (18.80)	28 (11.97)	1.70 (1.02-2.85)	0.042[1]
Length of stay (d)[2]				
Predicted difference in means	--	--	-1.02 (-1.54 to -0.50)	< 0.001[1]
Prolonged length of stay (%)	44 (18.80)	63 (26.92)	0.63 (0.41-0.97)	0.037[1]
Operative time (min)[2]				
Predicted difference in means	--	--	29.0 (26.5-31.6)	< 0.001[1]
Prolonged operative time (%)	90 (38.46)	62 (26.50)	1.73 (1.17-2.57)	0.006[1]

[1]Two-sided values < 0.05 considered statistically significant; [2]Modified Park test found Poisson most appropriate distribution to account for non-normality of the count data; average marginal effects used to calculate predicted difference in the mean; [3]Separate cohorts were generated for each outcome using propensity-score-based 1:1 nearest-neighbor matching without replacement, accounting for baseline differences in demographic and clinical characteristics. While all cohorts had an equal distribution of matched neoadjuvant and surgery-only patients (*n* = 234) by design, no two cohorts necessarily contain the same patients in order to account for cohorts appropriately weighted to each outcome. OR: Operating room.

another factor that has previously been associated with worse surgical outcomes[12]. Of note, the higher rates of steroid use observed in the induction group could in part represent therapy for drug- and radiation-induced pulmonary toxicity, which is routinely treated with high dose of steroids[13,14]. Yet, only prolonged steroid treatment would meet the requirements to be collected by the NSQIP under the "steroid" variable.

The occurrence of some of the adverse events observed more frequently in the induction group can be directly related to neo-adjuvant therapy. Thrombocytopenia induced by myelotoxic drugs, for example, might worsen bleeding risk, regardless the chemotherapy used[15]. Similarly, lower leukocyte counts can certainly predispose to the development of sepsis. Moreover, some authors have expressed concern that induction therapy may promote pleural adhesion and vascular fragility, resulting in anatomic disruptions detrimental for surgical outcomes[5]. Analogously, radiation-induced fibrosis can result in a more complex-hence prone to structural damage-dissection between the anatomical planes, which can easily account for lengthier operative times and higher bleeding rates, as observed in the neo-adjuvant patients. Of note, in the NSQIP database the "postoperative bleeding" variable is recorded by using the number of transfusions given as a surrogate; since patients who received induction treatment had a higher chance for myelosuppression, they intuitively had higher probability of developing a significant postoperative anemia requiring transfusion.

On adjusted analysis, patients who underwent neo-adjuvant therapy appeared to have shorter LOS and reduced odds of experiencing prolonged LOS than patients treated with surgery alone; this is counterintuitive, give the globally worse outcomes of the induction group. Nevertheless it is worth recalling that the NSQIP variable "discharge destination" was included in 2011. Understanding the destination after discharge is important to evaluate if the LOS for neo-adjuvant patients was actually shorter due to early discharge home or an artifact attributable to a transfer to another facility.

Several different protocols of neo-adjuvant therapy have been designed and tested for lung cancer, and their overall benefit varies according to tumor stage and type of induction used. Results of a recent systematic review and meta-analysis of randomized controlled trials, showed that patients affected by non-small-cell lung cancer who underwent preoperative chemotherapy had significantly improved overall survival, time to distant recurrence, and recurrence-free survival in resectable non small cell lung cancer (NSCLC)[16]. Analysis of data from the National Cancer Database suggested that neo-adjuvant chemo-radiation followed by lobectomy, was associated with an improved survival in patients with advanced NSCLC[17]. A large randomized trial showed that the addition of pre-operative chemo-radiation to chemotherapy, in patients with resectable stage Ⅲ NSCLC increases pathological response and mediastinal downstaging, without however affecting survival[18]. The same study showed a remarkable increased in treatment-related mortality in patients who underwent pneumonectomy after having received chemo-radiation, to the point that the risk outweighed the benefit of therapy. Shah *et al*[19] reported that the addition of induction radiotherapy to induction regimens granted no benefit in survival and discouraged its routinely use, given the potential harmful effects of radiation itself. On the other hand, Toyooka *et al*[20] indeed suggested that induction chemo-radiotherapy could be superior to induction chemotherapy alone in selected groups of patients, such as those with mediastinal lymph node metastasis. There are fewer studies on the use of neo-adjuvant therapy for early stage lung cancer; some data have suggested potential advantages of induction, showing a trend towards better survival, which, however, did not reach statistical significance[21]. Even though the NSQIP database does not allow us to study oncologic outcomes, it still provides valuable and reliable information about surgical outcomes. The assessment of mortality and morbidity in patients undergoing neo-adjuvant therapy for lung cancer is timely and relevant, given the concerns raised by the potential harms of induction protocols. Several authors have described increased post-operative adverse events after neo-adjuvant therapy, with global complication rates as high as 43.5% in patients who underwent chemo-radiotherapy[22]. Our results correlate well with the STS database analysis performed by Kozower *et al*[23]. These authors developed a large risk model for morbidity and mortality after lobectomy, sleeve lobectomy, bilobectomy, pneumonectomy, segmentectomy, and wedge resection for primary lung cancer, and observed that induction chemo-radiation therapy is an independent predictor of mortality and major morbidity. However, our work also showed some interesting differences from similar studies in the literature. Evans *et al*[8] queried the STS General Thoracic Surgery Database in order to examine outcomes of patients undergoing lung resections after neo-adjuvant treatment. According to their analysis, induction therapy did not increase the odds of discharge mortality, prolonged LOS, or major morbidity. Several differences, which may account for this discrepancy in results, are worth being stressed. First of all Evans *et al*[8] only focused on major resections, such as lobectomies and pneumonectomies. Secondarily, our two studies present some differences in the types of statistical analysis chosen, as well as in the morbidities selected as outcomes. Finally, it is important to recall that NSQIP has the potential of capturing more data from general surgery units than STS, which is more specialty-oriented. Our data, in fact, showed that almost 40% of the pulmonary resection in our study where not performed by thoracic surgeons (Table 4). It is indeed known that general surgeons perform the majority of lung resections in the United States (more than 50%), even though they have on average significantly lower median thoracic surgical procedure case volumes compared with general thoracic and cardiac surgeons[24]. In parallel, it has been reported that thoracic surgeons, in high-volume personal and hospital settings, achieve the best outcomes for lung resections[25]. As a consequence, it is reasonable to postulate that also differences in the distribution of surgeons' specializations across the two datasets might be one of the underlying causes of the observed discrepancies in outcomes.

Our study has several limitations in part related to the type of dataset used. NSQIP in fact, collects data only for 30 and 90 d before surgery for chemotherapy and radiation therapy respectively. Therefore if a patient received any treatment before this period of time, the patient could have been mislabeled as never receiving treatment at all. Moreover all patients without information regarding induction therapy were excluded from the study. Also, patients who were not surgical candidate due to unexpected complications of induction therapy were not recorded in this dataset and therefore excluded from this study. Information about drugs type and dosage as well a radiation planning were not available to us to optimize our analysis. Furthermore, in order to achieve greater statistical power, we grouped different neo-adjuvant regimens together under the broader group of "surgery following neo-adjuvant therapy". While this approach necessarily leads to some loss of insight within the single neo-adjuvant regimens, we believe that it was appropriate for the purpose of the present study; in fact it is worth stressing that our sub-group analysis did not show clinically meaningful differences among the various neo-adjuvant sub-groups. Patients' baseline

and tumor's characteristics (including stage) might have influenced the decision to give induction therapy. NSQIP however does not provide this information and therefore we can't comment on the indication for neo-adjuvant therapy. We found significantly more open cases in the induction group, yet, it is not possible to determine if those procedures started as open procedures or were conversions from VATS, since both these events are recorded as open in NSQIP. In addition only few hospitals voluntarily participate in the NSQIP database and therefore our results might not apply to all hospitals and the general population. Finally, this database records data only for 30 d after surgery and a longer follow-up cannot be evaluated, especially in regards to oncologic results.

Although with some limitations, our study shows important results to consider when treating a patient with lung cancer who underwent induction therapy.

This study shows that induction treatment for lung cancer leads to worse early post-operative outcomes after lung resection. Further research will be necessary in order to individuate subgroups of patients particularly susceptible to develop complications. With these assumptions, since the evidence in favor of neo-adjuvant therapy for lung cancer is not as compelling as for other cancers, we believe that the indication for induction should be weighted carefully for every patient against its possible downsides, in order to exploit its benefits while minimizing the potential harm.

COMMENTS

Background

Induction therapy for lung cancer has been reported to modestly improve survival in locally advanced disease. However, the impact of treatment on surgical outcomes has not been extensively studied.

Research frontiers

In an attempt to improve survival for this disease, several multimodality treatment approaches, including neo-adjuvant therapy protocols, have been developed through the years. The concern of developing life-threatening complications, prevalent and severe enough to offset the potential benefits of induction, can constitute a significant obstacle for the diffusion of neo-adjuvant protocols.

Innovations and breakthroughs

In this study, results showed globally worse postoperative outcomes in patients who underwent neo-adjuvant therapy prior to lung resection, when compared to those treated with surgery alone.

Applications

Indication for induction therapy should be weighted carefully for every patient against its possible downsides, in order to exploit its benefits while minimizing the potential harm.

Terminology

American College of Surgeons National Surgical Quality Improvement Project (ACS-NSQIP) is a large, nationally-validated, risk-adjusted, outcomes-based program used to measure and improve the quality of surgical care.

Peer-review

Well-prepared and discussed review on affects of treatment and/or surgery of lung cancer. While it is hard to believe that similar studies were not performed in past, particularly considering the wide occurrence of this type of tumor, the results are interesting and clinically important.

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