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Effects of Delayed Surgical Resection on Short- and Long-term Outcomes in Clinical Stage I Non-Small Cell Lung Cancer

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Abstract

Background—Conflicting evidence currently exists regarding the causes and effects of delay of care in non-small cell lung cancer (NSCLC). We hypothesized that delayed surgery in early-stage NSCLC is associated with worse short- and long-term outcomes.

Methods—Treatment data of clinical stage I NSCLC patients undergoing surgical resection was obtained from the National Cancer Database (NCDB). Treatment delay was defined as resection 8 weeks or more after diagnosis. Propensity score matching for patient and tumor characteristics was performed to create comparable groups of patients receiving early (less than 8 weeks from diagnosis) and delayed surgery. Multivariable regression models were fitted to evaluate variables influencing delay of surgery.

Results—From 1998–2010, 39,995 patients with clinical stage I NSCLC received early surgery, while 15,658 patients received delayed surgery. Of these 27,022 propensity-matched patients were identified. Those with a delay in care were more likely to be pathologically upstaged (18.3% stage 2 or higher vs. 16.6%, $p < 0.001$), have an increased 30-day mortality (2.9% vs. 2.4%, $p = 0.01$), and have decreased median survival (57.7 ± 1.0 months versus 69.2 ± 1.3 months, $p < 0.001$). Delay in surgery was associated with increasing age, non-Caucasian race, treatment at an academic center, urban location, income less than \$35,000 and increasing Charlson comorbidity score ($p < 0.0001$ for all). Delayed patients were more likely to receive a sublobar resection (17.2% vs. 13.1%, $p < 0.001$).

Conclusions—Patients receiving delayed resection for clinical stage I NSCLC have higher comorbidity scores that may affect ability to perform lobectomy and result in higher peri-operative mortality. However, delay in resection is independently associated with increased rates of upstaging and decreased median survival. Strategies to minimize delay while medically optimizing higher risk patients are needed.

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Introduction

Approximately 15% of non-small-cell lung cancer (NSCLC) patients are diagnosed with Stage I disease. [1] Diagnosis at an early stage offers the best chance of survival, with overall 5-year survival rates for patients undergoing lobectomy exceeding 80%. [2] With expansions in screening for high-risk patients after the results of the National Lung Screening Trial demonstrated a relative reduction in lung cancer mortality, it is anticipated that an increasing proportion of patients may be diagnosed at an operable stage.[3,4]

Previous analysis of national data has demonstrated that delay of care in lung cancer has been associated with female gender, increasing age, African-American race, public insurance status, comorbidities, early clinical stage, diagnosis and treatment at different hospitals, and treatment at a National Cancer Institute Comprehensive Cancer Center (NCI-CCC) or Veteran Affairs Medical Center (VAMC) facility. [5] International studies demonstrating an association between early treatment and decreased overall survival have been heavily influenced by patients receiving treatment in an expedited fashion if they presented with symptoms suggestive of advanced lung cancer. [6,7,8] However, other series have not demonstrated an association between wait times and overall survival.[9,10]

To date, no study has examined what factors may influence delays of surgical resection in clinical Stage I NSCLC patients, and how this may affect overall survival. We performed both a retrospective analysis of our institutional data and a propensity matched analysis of clinical Stage I NSCLC patients from the National Cancer Data Base (NCDB) to identify associated variables as well as short-and long-term outcomes in the setting of delayed surgery.

Material and Methods

The NCDB, a joint program of the American College of Surgeons and the American Cancer Society, represents approximately seventy percent of patients receiving treatment at Commission on Cancer accredited cancer centers. De-identified patient information for clinical Stage I NSCLC patients receiving pulmonary resection from 1998 to 2010 was abstracted from the NCDB Participant User File. After initial analysis of the median time to surgery (with interquartile ranges) in 2 week blocks, delay of surgery was defined as resection 8 weeks or greater from the time of lung cancer diagnosis. In the NCDB, the number of days from either radiologic or histologic diagnosis of lung cancer to surgical resection was identified. Patient variables abstracted included age, race (coded as Caucasian versus non-Caucasian), population (or < 250,000 individuals), income (or < \$35,000 per year), facility type where surgery was performed (academic versus non-academic), Charlson-Deyo score (0, 1, or 2), and greatest circle distance of travel (in miles). Propensity score matching was performed on the basis of age at diagnosis, gender, race, income, treatment facility type, Charlson/Deyo score, tumor size, clinical T stage, surgical margin status, and type of surgical resection (sublobar, lobectomy, or pneumonectomy). Patients with propensity scores matching to the third decimal place were matched 1:1. Automated matching was performed using the Fuzzy extension command in SPSS (SPSS 21.0 for Windows, SPSS Inc, Chicago, IL).

With approval from the Washington University School of Medicine Institutional Review Board, a single center, retrospective review of clinical Stage I NSCLC patients undergoing resection from January 2000 to December 2012 was performed. Information was obtained from our prospectively maintained database. Delay of surgery was defined as resection 8 weeks or greater after radiologic imaging documenting findings concerning for lung cancer. Variables on patient characteristics, comorbidities (represented by the Adult Comorbidity Evaluation-27, or ACE, score), and peri-operative complications were abstracted.

Descriptive statistics were expressed as mean $\pm$ standard deviation. Independent sample t-tests and one-way ANOVA analyses were used to compare continuous variables. Chi-square tests were used to compare categorical data. Multivariable logistic regression was performed to determine variables associated with delayed surgery. Overall survival of the propensity matched patients was estimated by the Kaplan-Meier method. P values of less than 0.05 were considered statistically significant.

Results

From the NCDB, 39,995 (71.9%) clinical Stage I NSCLC patients received surgical resection less than 8 weeks from the time of diagnosis, while 15,658 (28.1%) patients underwent delayed resection. For patients receiving surgery before 8 weeks, the median time from diagnosis to surgery was 29 days (interquartile range 20-41 days), while for patients receiving surgery at 8 weeks or beyond, the interval was 77 days (interquartile range 64-102 days), thereby appropriately dichotomizing the patient groups into 'early' and 'late' timeframes. 55,067 (98.9%) of patients had a histological diagnosis of NSCLC and 568 patients (1.0%) had malignant cytologic findings.

On univariate analysis, patients with delayed surgery were significantly more likely to be older, non-Caucasian, urban, lower income, receive surgery at an academic center, travel a shorter distance for surgery, have an increased Charlson/Deyo comorbidity score, clinical T1 stage of tumor, positive surgical margins, and undergo sublobar resection (Table 1). Variables independently associated with delayed surgery included increasing age (1.01, 1.01 – 1.02), living in an urban location (1.15, 1.10 – 1.20), receiving surgery at an academic center (1.40, 1.34 – 1.46), and higher Charlson/Deyo comorbidity score (1.13, 1.09 – 1.18 for score of 1), (1.34, 1.26 – 1.42 for score of 2), all $p < 0.001$. Variables independently associated with early surgery included Caucasian race (0.70, 0.66 – 0.74) and income \$35,000 (0.89, 0.85 – 0.93), all $p < 0.001$.

Propensity matching was performed on the basis of age, gender, race, income, facility type, Charlson/Deyo score, tumor size, clinical T stage, margin status, and type of surgery performed. 13,511 matched pairs were identified for analysis (Table 2). On univariate analysis of the propensity matched patients, those receiving delayed surgery were significantly more likely to be upstaged, have a longer length of inpatient stay, and increased thirty day mortality (Table 3). For each week of delay to surgery, the hazard for mortality increased by 0.4% (1.004, 1.002 – 1.007, $p=0.001$). A Kaplan-Meier analysis demonstrated a significantly higher overall survival for patients receiving early surgery ($p<0.001$) (Figure

1). Probabilistic survival for patients receiving either early or delayed resection is shown in Table 4.

On institutional review, 971 patients received pulmonary resection for clinical stage I NSCLC from 2000 to 2012. 54% of patients (n=522) received surgery in 8 weeks or less from the time of clinical diagnosis, while 46% (n=449), received delayed surgery. Delayed patients were significantly more likely to be non-Caucasian, have a lower percent predicted FEV₁, clinically staged T1 tumor, higher ACE comorbidity scores, and have a history of congestive heart failure, hypertension, coronary artery disease, and myocardial infarction (Table 5).

Patients at our institution receiving delayed surgery were significantly more likely to have a sublobar resection (23% versus 14%, $p < 0.001$). In analyzing peri- and postoperative outcomes, delayed patients were more likely to have pneumonia, blood transfusion, respiratory failure, reintubation, increased 30-day mortality (Table 6). Patients receiving early surgery were significantly more likely to be pathologically upstaged (25% versus 16%, $p = 0.001$) and receive adjuvant therapy (20% versus 11%, $p < 0.0001$).

On multivariate analysis, independent predictors of delayed surgery at our institution included clinical T1 staging (1.76, 1.26 – 2.45, $p=0.001$), ACE scores of 2 or 3 (1.97, 1.16 – 3.33 and 2.044, 1.14 – 3.67, respectively, $p=0.045$), and a history of coronary artery disease (1.78, 1.23 – 2.57, $p=0.002$). Caucasian patients were independently more likely to receive surgery in 8 weeks or less (0.536, 0.353 – 0.813, $p=0.003$). In the Cox proportional hazards model for patients at our institution, delay of surgery did not significantly influence survival. Increasing age was associated with decreased survival (HR 1.05, 1.03 – 1.06, $p<0.0001$), while variables associated with increased survival included female gender (HR 0.73, 0.58 – 0.92, $p=0.008$), higher percent predicted DLCO (HR 0.52, 0.31 – 0.87, $p=0.012$), and clinical T1 stage (HR 0.73, 0.58 – 0.92, $p=0.009$).

Comment

The principal finding of our study is that delay in surgery for early-stage NSCLC patients is common and often associated with socioeconomic and clinical factors. Initial NCDB analysis revealed dichotomized means and interquartile ranges at the 8 week time point, with differences detected in survival outcomes. This threshold was used as a marker of delayed surgery for the purposes of our study, and we do not recommend it as an absolute cutoff in clinical practice. It does suggest that significant delays in care are associated with detrimental short- and long-term outcomes for early stage NSCLC patients. Patients receiving delayed surgery in both the NCDB and our institution were significantly more likely to be non-Caucasian, have higher relative comorbidity indices, present with a clinical T1 staged tumor, and undergo sublobar resection. Factors associated with increased likelihood of delayed surgery among both patient groups included increasing comorbidity scores. On the NCDB analysis, receiving surgery at an academic center was associated with the highest odds ratio for receiving delayed resection. Furthermore, NCDB patients receiving early surgical resection had improved overall survival, despite propensity matching to account for confounding variables.

Understanding factors that influence time to treatment must be understood in a geographical, political, and social context. International studies have described either no difference in mortality or improved survival among patients receiving delayed care for NSCLC. [6-13] This finding of improved survival has been attributed to advanced stage patients being triaged more quickly to treatment. [6,7,8] In the United States, an institutional review of early stage NSCLC surgical patients did not detect a significant difference in cancer-free or overall survival when 90 days was used as a threshold for delayed surgery.[14] However, this timepoint was chosen to evaluate whether 90 days of observation for indeterminate nodules would affect long term survival.[14] A retrospective study of early stage NSCLC patients in community centers referred to an NCI-designated cancer center did not detect a survival difference for a threshold of 42 days, but did demonstrate an increased hazard ratio for mortality for both the referral interval and the diagnosis to surgery interval.[15] Based on this hazard ratio, each week of delay in the diagnosis to surgery interval increased the mortality risk by 4% (adjusting for age, clinical stage, and tumor size).[15] From our NCDB analysis, although the increased mortality hazard was smaller at 0.4%, we did find an overall survival benefit for propensity matched patients receiving early surgery.

Identifying barriers to early surgical resection that are within an institution's control may help reduce the percentage of patients receiving delayed care. In a NCDB analysis from 1995 to 2005 examining lung cancer patients receiving chemotherapy, radiation, and/or surgery, approximately 43% of patients received treatment within thirty days of diagnosis. [5] Variables associated with delayed treatment included female gender, increasing age, African-American ethnicity, public insurance status, clinical Stage I diagnosis, and receiving diagnosis and treatment at different hospitals.[5] Specifically, the odds ratio for delayed treatment at an NCI-CCC was 1.22 (1.15 – 1.30), academic centers 1.05 (1.00 – 1.09), and VAMC 3.03 (2.57 – 3.57).[5] A review of VAMC NSCLC cases found associations between delays in the imaging to treatment interval and early clinical stage, lack of symptoms, presence of comorbidities, and history of depression.[16]

In our institutional study, approximately 46% of Stage I NSCLC patients received delayed resection, which is higher than the NCDB dataset (28%). The 'start time' of diagnosis at our institution was from the time of initial radiologic evaluation, versus time from histologic diagnosis in the NCDB. At our institution, many patients undergo a diagnostic wedge resection with completion lobectomy at the same operation. It is difficult to estimate how this may influence our analysis –while we start the interval earlier, it is possible that time to surgery is shortened by not performing a biopsy for preoperative diagnosis. We cannot make a strong recommendation for either radiologic or histologic diagnosis as a start date, since institutional practices may vary regarding the need for tissue diagnosis prior to surgery.

The comorbidities associated with delayed surgery included cardiac factors (congestive heart failure, hypertension, coronary artery disease, and history of myocardial infarction), while other comorbidities did not reach significance despite their prevalence. At our institution, all patients undergoing resection receive an anesthesia consult, but the need for subspecialist referral may be variable. Although we are not able to identify exact causes for delay, it is plausible that patients with elevated comorbidity scores and cardiac comorbidities experienced additional evaluation prior to surgery. Detecting the need for specialist

evaluation and scheduling this as part of a multidisciplinary process could help expedite this process.

Patients in both our institutional study and the NCDB analysis were significantly more likely to receive a sublobar resection. This is likely related to the significantly higher comorbidities and lower functional status of patients receiving delayed surgery. Although reducing the interval from diagnosis to surgery would likely not affect the surgical approach, it can be argued that treating these patients in an expeditious manner is even more prudent as they will have higher potential for close or positive margins.[17,18]

Limitations of our study include the retrospective nature of both our institutional study and the NCDB analysis. Although both databases demonstrate a large number of patients with robust perioperative and outcome variables, there are potential confounders that may not be captured. Prospective monitoring of time to treatment intervals could better capture reasons for delay and identify potential intervention points. It is unknown from either our institutional study or the NCDB what proportion of academic center patients presented as community referrals or second opinions. If a significant percentage of patients had received an assessment for treatment at another location, this could inflate the time from diagnosis to treatment.

Formal recommendations for referring suspected lung cancer patients do exist in other countries. In the United Kingdom, specific guidelines include chest imaging interpretation within 5 days of ordering an urgent radiologic evaluation. [19] In Canada, recommendations state that patients with clinical signs or symptoms of lung cancer should receive a chest x-ray within 48 hours, interpretation within one week, and evaluation within two weeks. [20] In the United States, one center demonstrated that allowing a coordinator to schedule subspecialist appointments and tests reduced the time from diagnosis to treatment.[21] Implementation of a Cancer Care Coordination Program at a VAMC utilizing both a nurse practitioner coordinator and a 'cancer alert' in the medical record decreased the interval between radiologic diagnosis and treatment (126 to 101 days, $p=0.015$). [16] However, a randomized controlled trial examining the effect of nurse navigators for newly diagnosed lung, colon, or breast cancer patients showed an increase in the time to surgery interval compared to usual care patients. [22] Two additional randomized clinical trials evaluating patient navigator programs also failed to improve time to treatment. [23,24]

Efforts to facilitate care should be sensitive to medically marginalized communities, as non-Caucasian ethnicity, lower income, and urban patients were more likely to receive delayed surgery. Previous studies have documented how disparities in receiving care according to practice guidelines can persist at academic centers. [25] Prospective tracking of patients from the time of initial suspicion of lung cancer could help define which intervals in the surgical evaluation process are associated with delays in an institution specific manner. With an anticipated increase in early stage lung cancer diagnoses through expanded screening coverage, ensuring timely surgical care for the patients will become even more pressing.

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Figure 1.

Kaplan-Meier curve for propensity matched clinical stage I NSCLC patients with delayed versus non-delayed surgical resection.

Table 1

Characteristics of clinical Stage I NSCLC patients receiving either early or delayed pulmonary resection from the NCDB.

n=55,653	Surgery < 8 weeks n= 39,995	Surgery ≥ 8 weeks n= 15,658	P value
Age at diagnosis	67.63 ±10.1	68.73 ±9.8	<0.001
Caucasian	36,094 (90.2%)	13,509 (86.3%)	<0.001
Population < 250,000	25,547 (63.9%)	10,509 (67.1%)	<0.001
Income < \$35,000	25,548 (67.6%)	9,713 (65.5%)	<0.001
Facility: Academic	13,606 (34.5%)	6,483 (41.9%)	<0.001
Non-academic	25,843 (65.5%)	9,002 (58.1%)	
Charlson Score: 0	20,744 (51.9%)	7,469 (47.7%)	<0.001
1	14,149 (35.4%)	5,699 (36.4%)	
2	5,102 (12.8%)	2,490 (15.9%)	
Size of tumor (mm)	30.3 ± 22.2	29.91 ± 21.0	<0.01
Negative surgical margins	96.5%	96.1%	0.046
Type of surgery performed: Sublobar (wedge or segment)	5223 (13.1%)	2688 (17.2%)	<0.001
Lobectomy	33270 (83.2%)	12471 (79.6%)	
Pneumonectomy	1502 (3.8%)	499 (3.2%)	

Table 2

Clinical Stage I NSCLC patients receiving either early or delayed resection after 1:1 propensity matching.

Patient characteristics		Surgery < 8 weeks n=13,511	Surgery >8 weeks n=13,511	P value
Age at diagnosis		68.7 ± 9.8	68.8 ± 9.7	0.581
Male gender		48.1% (6505)	48.6% (6564)	0.473
Caucasian		87.1% (11,765)	87.2% (11,787)	0.689
Income \$35,000		65.3% (8823)	66.2% (8946)	0.118
Treatment Facility Type	Non-Academic	59.0% (7969)	58.8% (7951)	0.834
	Academic	41.0% (5542)	41.2% (5560)	
Charlson Score	0	47.8% (6459)	48.0% (6490)	0.205
	1	37.1% (5011)	36.2% (4895)	
	2	15.1% (2041)	15.7% (2126)	
Size of tumor		30.1 ± 22.6	30.5 ± 21.3	0.103
AJCC Clinical T stage	1	63.7% (8608)	64.1% (8656)	0.552
	2	36.3% (4903)	35.9% (4855)	
Surgical Margins	No residual tumor	96.3% (13005)	96.2% (12,999)	0.848
	Residual tumor present	3.7% (506)	3.8% (512)	
Type of operation	Sublobar	16.1% (2170)	15.8% (2130)	0.750
	Lobectomy	80.8% (10918)	81.0% (10946)	
	Pneumonectomy	3.1% (423)	3.2% (435)	

Table 3

Post-operative and survival outcomes for propensity matched clinical Stage I NSCLC patients from the NCDB receiving either early or delayed pulmonary resection.

n=27,022	Surgery < 8 weeks n= 13,511	Surgery ≥ 8 weeks n= 13,511	P value
Pathologic Stage 1	11,266 (83.4%)	11,040 (81.7%)	0.002
2	1,359 (10.1%)	1,519 (11.2%)	
3	813 (6.0%)	857 (6.3%)	
4	73 (0.5%)	95 (0.7%)	
Unplanned readmission within 30 days of discharge	612 (4.6%)	562 (4.3%)	0.001
Length of Stay	7.33 ±6.8	7.72 ±7.3	<0.001
Thirty Day Mortality	322 (2.4%)	391 (2.9%)	0.010
Median Survival (months)	69.16 ±1.3	57.69 ±1.0	

Table 4

Propensity matched patients at risk by year in Kaplan-Meier analysis, receiving either early or delayed surgical resection.

Follow-up Year	< 8 weeks (Early Surgery)	8 weeks (Delayed Surgery)
Year 1	89.6% (10,227)	89.1% (10,263)
Year 2	79.1% (6,811)	77.0% (6,789)
Year 3	69.6% (4,332)	65.3% (4,220)
Year 4	61.7% (2,767)	56.0% (2,590)
Year 5	54.8% (1,790)	48.7% (1,682)
Year 6	48.8% (1,022)	41.9% (933)
Year 7	41.2% (441)	34.1% (404)
Year 8	35.3% (126)	27.9% (66)

Table 5

Preoperative characteristics and comorbidities of patients receiving surgery at our institution for clinical Stage I NSCLC at early versus delayed time points.

Patient Characteristics	Surgery < 8 weeks (n=544), 54%	Surgery ≥ 8 weeks (n=449), 46%	P value
Female gender	276 (53%)	232 (52%)	0.747
Mean age (years)	66.0 ± 10.1	66.9 ± 9.7	0.151
Caucasian race	466 (89%)	368 (82%)	0.001
Mean annual income (US dollars)	50,637 ± 19,733	51,606 ± 22,798	0.480
FEV1 (L)	2.13 ± 0.73	2.05 ± 0.73	0.086
FEV1% predicted	80 ± 19	78 ± 21	0.040
DLCO (L)	16.44 ± 5.9	15.40 ± 5.6	0.009
DLCO% predicted	72 ± 23	71 ± 24	0.505
Clinical T1 stage	338 (65%)	342 (76%)	<0.0001
Smoking history			
Never smoker	50 (10%)	41 (9%)	0.432
Past smoker	302 (58%)	244 (54%)	
Current smoker	170 (33%)	164 (37%)	
ACE Score			
0	83 (16%)	37 (8%)	<0.0001
1	211 (40%)	156 (35%)	
2	125 (24%)	125 (28%)	
3	63 (12%)	79 (18%)	
Unknown	40 (8%)	52 (12%)	
Diabetes Mellitus	87 (17%)	72 (16%)	0.227
Congestive Heart Failure	7 (1%)	15 (3%)	0.029
Hypertension	270 (52%)	282 (63%)	0.001
Coronary Artery Disease	84 (16%)	117 (26%)	<0.0001
Chronic Renal Insufficiency	21 (4%)	18 (4%)	0.600
Pulmonary Hypertension	3 (0.6%)	7 (1.6%)	0.194
History of Myocardial Infarction	46 (9%)	57 (13%)	0.044

Table 6

Peri- and postoperative outcomes of patients receiving surgery at our institution for clinical Stage I NSCLC at early versus delayed time points.

Outcomes	Surgery < 8 weeks (n=522, 54%)	Surgery ≥ 8 weeks (n=449, 46%)	P value
Resection type			
Sublobar	74 (14%)	103 (23%)	0.001
Lobectomy	403 (77%)	324 (72%)	
Bilobectomy	25 (5%)	12 (3%)	
Pneumonectomy	20 (4%)	10 (2%)	
Air leak	59 (11%)	43 (10%)	0.402
Pneumonia	33 (6%)	51 (11%)	0.006
Arrhythmia	94 (18%)	79 (18%)	0.933
Deep Vein Thrombosis	8 (2%)	13 (3%)	0.185
Blood transfusion	18 (3%)	39 (9%)	0.001
Myocardial infarction	5 (1%)	1 (0.2%)	0.225
Wound infection	4 (1%)	5 (1%)	0.740
Respiratory failure	27 (5%)	44 (10%)	0.006
Reintubation	23 (4%)	34 (8%)	0.040
Renal failure	9 (2%)	11 (2%)	0.500
Mean length of stay, days	6.2 ± 5.8	7 ± 9.3	0.083
Mortality	6 (1.1%)	14 (3.1%)	0.040
Readmission 30 days from discharge	26 (5%)	32 (7%)	0.221
Median survival, months	97.5 (0.2 – 168.6)	90.5 (0-172.8)	