Invasive mediastinal staging for resected non–small cell lung cancer in a population-based cohort

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ABSTRACT

Objectives: Invasive mediastinal nodal staging is recommended before curative-intent resection in patients with non–small cell lung cancer deemed at risk for mediastinal lymph node involvement. We evaluated the use and survival effect of preoperative invasive mediastinal nodal staging in a population-based non–small cell lung cancer cohort.

Methods: We analyzed all curative-intent resections for non–small cell lung cancer from 2009 to 2018 in 11 hospitals in 4 contiguous Dartmouth Hospital Referral Regions, comparing patients who did not have invasive mediastinal nodal staging with those who did.

Results: Preoperative invasive nodal staging was used in 22% of 2916 patients, including mediastinoscopy only in 13%, minimally invasive procedures only in 6%, and both approaches in 3%. Sixty-three percent of patients at risk for nodal disease (tumor size ≥ 3.0 cm/T2–T4; N1–N3 by computed tomography or positron-emission tomography-computerized tomography criterion) did not undergo invasive staging; among those who did not have invasive testing, 47% had at least 1 of the 3 clinical indications. Mediastinoscopy yielded a median of 3 lymph nodes and 2 nodal stations; 17% of mediastinoscopies and 31% of endobronchial ultrasound procedures yielded no lymph node material. Patients not invasively staged were more likely to have no nodes (6% vs 2%; $P < .0001$) and no mediastinal nodes (20% vs 11%; $P < .0001$) examined at surgery. Invasive staging was associated with significantly better survival ($P = .0157$).

Conclusions: More than a decade after the 2001 American College of Surgeons Patient Care Evaluation report, preoperative invasive nodal staging remains underused and of variable quality, but was associated with survival benefit in high-risk patients. (J Thorac Cardiovasc Surg 2019;158:1220–9)

Survival of NSCLC resection cohort stratified by number of risk features for nodal disease.

Central Message

Preoperative invasive mediastinal nodal staging remains underused in patients with NSCLC at high risk for nodal disease, even though use was associated with improved survival.

Perspective

Preoperative invasive mediastinal nodal staging is recommended for patients with NSCLC deemed at high risk for nodal involvement. Years after a 2001 American College of Surgeons Patient Care Evaluation revealed underuse of mediastinoscopy, we show persistent underuse of invasive nodal staging in a population-based cohort. Invasive staging was associated with significantly better survival.

See Commentaries on pages 1230 and 1232.

Curative-intent resection is considered the optimal treatment for patients with early-stage non–small cell lung cancer (NSCLC).¹ Because of its major prognostic effect, thorough nodal evaluation is recommended at key steps of

the care process, including preoperative radiologic studies and invasive nodal sampling, nodal retrieval at resection, and careful examination of all specimens by the pathology team.² Preoperative staging is used to triage patients with evidence of clinical mediastinal nodal involvement away from primary surgical resection.^{3,4}

A 2001 American College of Surgeons Patient Care Evaluation revealed use of preoperative mediastinoscopy in only

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Abbreviations and Acronyms

CT	= computed tomography
EBUS	= endobronchial ultrasonography
EUS	= endoscopic ultrasonography
MS-QSR	= Mid-South Quality of Surgical Resection cohort
NSCLC	= non-small cell lung cancer
PET-CT	= positron-emission tomography
TBNA	= transbronchial needle aspiration

27% of patients, but did not evaluate the survival implications of lack of preoperative invasive staging.⁵ In the same report, <50% of procedures provided lymph node material for pathologic examination. Since that report, minimally invasive mediastinal nodal staging, with endobronchial ultrasonography (EBUS) and endoscopic ultrasonography (EUS), has become a highly recommended complement to mediastinoscopy before curative-intent resection.^{3,4,6} Invasive mediastinal staging is recommended when the risk of mediastinal nodal involvement exceeds 10%. There is consensus on the need for preoperative histologic evaluation of radiographically abnormal mediastinal lymph nodes. Patients with radiographically normal-appearing mediastinal lymph nodes who have centrally located tumors, radiographically suspected N1 disease, and solid tumors >3 cm have been reported to have risk for occult mediastinal nodal disease >20%.^{3,7}

We examined the use and performance characteristics of invasive nodal staging in a multi-institutional population-based cohort of surgically resected NSCLC. Our objectives were to evaluate how invasive staging practices have evolved since the 2001 Patient Care Evaluation, and the effects on patient survival. We hypothesized that a decade or more later, adoption and performance characteristics of invasive mediastinal nodal staging would have improved significantly, and appropriate use would be associated with improved survival.

METHODS**The Mid-South Quality of Surgical Resection Cohort**

With the approval of each participating hospital's institutional review board, we conducted a population-based observational cohort study involving surgical resections for NSCLC from 2009 to 2018 at all 11 eligible hospitals in 4 contiguous Dartmouth Hospital Referral Regions: Jonesboro, Ark; Memphis, Tenn; Oxford, Miss, and Tupelo, Miss. Hospital Referral Regions are geographic units of analysis developed by the Dartmouth Atlas of Health Care to delineate regional health care markets in the United States. Each is composed of ZIP code areas grouped together based on the referral patterns for tertiary care for Medicare beneficiaries. There are 306 Hospital Referral Regions and their boundaries often cross state lines.⁸ For example, the Memphis, Tenn, Hospital Referral Region includes parts of eastern Arkansas, northern Mississippi, and West Tennessee. These states have the second, third, and fourth highest lung cancer

incidence and mortality rates in the United States.⁹ All hospitals with an annual volume of at least 5 curative-intent resections are included in the Mid-south Quality of Surgical Resection cohort (MS-QSR). For this analysis, we excluded patients who received neoadjuvant chemotherapy or radiation, which confound the comparison of clinical and pathologic nodal stage.

Indications for Invasive Mediastinal Nodal Staging

Based on practice guidelines, we identified the following indications: tumor size ≥ 3 cm/clinical T2-T4; clinical N1-N3 by computed tomography (CT) short-axis lymph node diameter ≥ 1 cm, or positron-emission tomography-CT (PET-CT) scan describing any lymph node with a standardized uptake value ≥ 2.5 .^{3,4,6,10} The database did not allow identification of proximal tumor location, another frequently-cited indication.

Evaluation of Invasive Mediastinal Nodal Staging

The primary exposure variable was preoperative invasive mediastinal nodal staging. In the primary analysis of invasively staged patients and those not so staged, we compared clinical indications for invasive mediastinal staging, thoroughness of nodal staging, clinical-to-pathologic nodal upstaging rates, and survival. In secondary analyses, we evaluated the invasive staging cohort by subsets: recipients of minimally invasive staging procedures (EBUS, EUS, or transbronchial needle aspiration [TBNA]) only; minimally invasive procedures and mediastinoscopy; and mediastinoscopy only.

Clinical Stage

In the cohort with invasive mediastinal nodal staging, the final clinical stage was based on the results of the invasive staging procedure, except when the stage-defining radiologically suspicious mediastinal lymph node was not sampled. In such patients, clinical stage was based on the radiology findings if those were more advanced. Because the indications for invasive staging are based on radiologic appearance (tumor size and location, nodal enlargement, or fluorodeoxyglucose avidity), we used the radiologic stage to stratify the survival analysis. For the clinical-to-pathologic nodal stage comparisons (upstaging and downstaging rates), we used the final clinical stage, which incorporated findings from the invasive staging test.

Covariates

We used patient-, surgeon-, and institution-level variables to evaluate differences between the comparison groups. Patient-level variables included age, sex, race, insurance, clinical and pathologic stage, histology, chest CT scan, PET-CT scan, specific invasive mediastinal staging (mediastinoscopy, EBUS, EUS, or TBNA), and brain magnetic resonance imaging or CT scan. We treated these variables as categorical, except for age. Surgeon-level variables indicated type of board certification (obtained from the American Board of Medical Specialties), whether or not surgical practice was dedicated thoracic, service years, and annual case-volume. Institution-level variables were presence of a teaching program, rurality, number of beds, annual lung cancer surgery volume, and proportion of underinsured (Medicaid or uninsured) lung cancer surgery patients. We treated service year of surgeon, annual lung cancer case-volume, and number of beds as continuous.

Survival

Mortality information in the MS-QSR is obtained from hospital tumor registry records and updated every 6 months. Disease recurrence information was not reliably reported in the database and therefore not analyzed. We measured overall survival from the date of surgery to the date of death or data censoring. Our primary analyses exclude the 9 invasively staged patients with preoperative, histologically proven mediastinal nodal metastasis. In sensitivity analyses that included such patients, and additional

analyses that also excluded patients with stage IV disease, there was no significant difference in our results (data not shown).

Propensity Matching

We used a 1-to-1 matched propensity score analysis to address the potential for confounding or other imbalances in the use and nonuse of any invasive mediastinal nodal staging.¹¹ Potential confounders included patient's age at surgery, sex, race, insurance, smoking status, radiologic tumor-node-metastasis stage, use of PET or CT scan, surgeon board certification, hospital teaching status, hospital bed size, hospital rurality, and hospital case volume. Propensity scores were calculated based on logistic regression, modeling any invasive staging as a function of the potential confounders outlined above, as detailed in [Appendix E1](#).

Statistical Analysis

Continuous variables were summarized with the mean $\pm$ standard deviation or median (interquartile range [IQR]), and categorical variables were presented as number (%). Differences between continuous variables were evaluated with the *t* test or Wilcoxon-Mann-Whitney test. The χ^2 test or Fisher exact test was used for categorical variables. Hospital annual lung cancer case volumes were categorized into 3 groups: <17, 17 to 35.5, or >35.5 cases.¹² The Cochran-Armitage test was used to evaluate trends in invasive staging practices by year. Survival was estimated with the Kaplan-Meier method, compared between groups using the log-rank test. Statistical significance was based on a testwise type-I error rate of 0.05, with no adjustments for multiple comparisons.¹³ All analyses were conducted using SAS version 9.4 (SAS Institute Inc, Cary, NC) or R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Analytic Cohort

The overall cohort consisted of 3096 patients, of whom 179 (6%) who had neoadjuvant therapy and 1 patient missing invasive nodal staging details were excluded to avoid confounding of the comparison between clinical and pathologic staging, providing a residual analytic cohort

of 2916. Of these patients, 632 (22%) had invasive mediastinal nodal staging, either a minimally invasive staging procedure, a mediastinoscopy, or both ([Figure 1](#)). Eighty-four percent of the invasively staged patients had only 1 staging test: 366 underwent mediastinoscopy, 161 underwent EBUS, 1 underwent EUS, and 6 underwent TBNA only. Of the 98 patients who had multiple invasive staging tests, 65 combined mediastinoscopy with EBUS, 32 underwent mediastinoscopy and TBNA, 1 underwent mediastinoscopy and EUS. No patients had more than 2 invasive staging modalities.

Clinical Indications for Invasive Mediastinal Nodal Staging

In the analytic population, 58% of patients had 1 or more of the 3 indications for invasive mediastinal nodal staging, including 98% of those who did, and 47% of those who did not, undergo a mediastinal staging procedure ([Table 1](#)). Tumor size was the most common indication in the whole population (45%), whereas detection of an enlarged lymph node by CT scan criteria was the most common indication in those who had an invasive procedure (96%). This indication was present in 11% of those who did not undergo invasive staging (9% also had a PET-CT scan indicating the presence of a suspicious lymph node). Eighty-one patients (4%) who did not receive invasive mediastinal staging had all 3 indications.

Factors Associated With Use of Invasive Staging

Time trends. Use of invasive mediastinal staging procedures increased steadily over time, from a low of 12% in 2009 and 2011 to a high of 38% in 2017 ($P < .0001$).

FIGURE 1. Consolidated standards of reporting trials diagram showing the derivation and sorting of the analytic cohort. EBUS, Endobronchial ultrasonography; EUS, endoscopic ultrasonography; TBNA, transbronchial needle aspiration.

TABLE 1. Indications for invasive nodal staging

Clinical indication	Total (N = 2916)	No invasive staging (n = 2284 [78%])	Had invasive staging (n = 632 [22%])	P value
Tumor size ≥3 cm/cT2-4	1306 (45)	927 (41)	379 (60)	<.0001
Clinical N1-N3 by CT criterion*	864 (30)	257 (11)	607 (96)	<.0001
Lymph node with SUV ≥2.5	397 (14)	212 (90)/235 (9)†	185 (94)/196 (29)†	<.0001‡
Number of high-risk features				
0	1222 (42)	1212 (53)	10 (2)	<.0001§
1	1016 (35)	829 (36)	187 (30)	
2	483 (17)	162 (7)	321 (51)	
3				
Tumor ≥3 cm/cT2-4 + clinical N1-N3 by CT criterion*		73 (45)	250 (78)	
Tumor ≥3 cm/cT2-4 + lymph node with SUV ≥2.5		27 (17)	0 (0)	
Clinical N1-N3 by CT criterion* + lymph node with SUV ≥2.5		62 (38)	71 (22)	
3	195 (7)	81 (4)	114 (18)	

Values are presented as n (%) of patients in category. CT, Computed tomography; SUV, standardized uptake value. *CT criterion was lymph node short axis diameter ≥1 cm. †Eligible patient %, column %. ‡P value for the column % (lymph node with SUV ≥2.5 vs none). §Based on χ^2 test for the number of high-risk features per patient (0, 1, 2, and 3).

This increase was driven by increased use of minimally invasive staging procedures as well as mediastinoscopy, alone and in combination (Figure 2, A). Increasing use of invasive staging was also evident in the subset of patients with any of the 3 indications, ranging from 18% in 2009 to 64% in 2017 ($P < .0001$) (Figure 2, B).

Patient demographic and clinical characteristics. Demographic characteristics were similar between the patients, except for race (Table 2). Proportionately more African Americans had invasive mediastinal nodal staging (26% vs 18%; $P = .0001$). Radiologic staging was more thorough in the invasively staged cohort, with 87% versus 81% undergoing a PET-CT scan ($P = .0004$) and 45% versus 25% undergoing brain imaging ($P < .0001$). The invasively staged cohort had significantly higher proportions of patients with squamous cell and other histology and fewer with adenocarcinoma ($P < .0001$).

Surgeon and institutional characteristics. At the surgeon level, patients who underwent invasive staging were more likely to have been operated on by a surgeon who was board certified in cardiothoracic surgery ($P = .0070$), had a thoracic-focused practice ($P < .0001$), or had a higher annual case volume ($P < .0001$); there was no significant difference in the number of years in practice ($P = .2300$). Teaching institutions were more likely to perform preoperative invasive nodal staging procedures than nonteaching institutions (66% vs 53%; $P < .0001$), but institutional rurality did not significantly influence the likelihood of preoperative invasive mediastinal staging.

Performance Characteristics of Invasive Nodal Staging Tests

Stage comparisons and nodal stage shifts. Clinical T, N, and aggregate stage distributions were more advanced in patients who underwent invasive mediastinal nodal staging ($P < .0001$) (Table 3). After invasive staging, there was a

striking downshift in proportion of clinical N2 and N3 disease, from 78% to 11%. Other than 9 patients with histologically identified N2 disease who nevertheless underwent primary resection, these residual clinical N2 or N3 cases were patients in whom a histologic specimen was not retrieved from the stage-defining radiologically abnormal anatomic nodal station. Only 6% of noninvasively staged patients were staged as clinical N2 or N3.

Pathologic stage was also more advanced in the invasive staging group ($P < .0001$). In particular, the pN1 proportions were 20% versus 9% and the pN2 proportions were 10% versus 8%. Clinical-to-pathologic nodal stage shift was significantly more likely in the invasively staged cohort ($P < .0001$). Nodal stage was unchanged in 69% of the invasive staging cohort, compared with 80% of the noninvasively staged patients; both upstaging and downstaging rates were higher in the invasive staging group (Table 3).

Thoroughness of invasive nodal staging tests. The median (IQR) number of mediastinal lymph node stations examined from any invasive staging, mediastinoscopy only, minimally invasive staging only, and both mediastinoscopy and minimally invasive staging was 2 (IQR, 0-3), 2 (IQR, 0-3), 1 (IQR, 0-2) and 3 (IQR, 1-4), respectively ($P < .0001$). In 122 patients who had an invasive staging procedure (19%), no lymph node material was delivered for examination, including 63 of 366 mediastinoscopies performed alone (17%) and 50 of 161 EBUS performed alone (31%). Five of 98 patients (5%) who had combined invasive staging modalities had no lymph node material delivered.

Invasive staging and pathologic nodal staging quality. In the whole cohort, 155 patients (5%) were pathologic NX, including 142 (6%) of those without invasive staging (meaning they had no histologic evaluation of lymph nodes at any point pre- or intraoperatively) and 13 (2%) of the

FIGURE 2. Trends in preoperative use of invasive mediastinal nodal staging procedures showing low, but increasing, overall use of invasive staging tests. A, All patients. B, Patients with 1 or more high-risk features (tumor size ≥ 3 cm/clinical T2-T4; clinical N1-N3 by computed tomography short axis lymph node diameter ≥ 1 cm, or positron-emission tomography-computed tomography scan describing any lymph node with a standardized uptake value ≥ 2.5).

invasively staged patients (Table 3). Furthermore, 18% of the whole cohort had no pathologic mediastinal lymph node examination, including 450 patients (20%) in the non-invasively staged cohort (meaning they had no evaluation of mediastinal nodes at any point in their care) and 67 patients (11%) in the invasively staged cohort ($P < .0001$). Sixty-four patients who had invasive staging had pathologic N2 disease, of whom 9 were detected by preoperative invasive staging. Therefore, 55 of 632 invasively staged patients (9%) had unexpected N2 disease.

Survival. Using invasive mediastinal nodal staging procedures to select patients for surgical resection was

associated with improved survival in radiologically defined high-risk subsets of patients. The survival effect was greatest in the patients with the highest-risk features, based on radiologic evidence of advanced nodal stage (Figure 3, A-D). The specific approach to invasive staging did not appear to alter the survival effect, although our study design was not optimized for such analysis (data not shown). In the propensity-matched analysis, patients who had invasive mediastinal nodal staging had a significantly better survival than those who did not ($P = .0157$) (Figure 4). Risk stratification by number of indications for invasive staging revealed significantly worse survival in the noninvasively

TABLE 2. Comparison of patient-, surgeon-, and institution-level demographic and clinical characteristics between lung cancer resection patients without and with invasive mediastinal nodal staging

Characteristic	No invasive staging (n = 2284 [78%])	Invasive staging (n = 632 [22%])	P value
Patient level			
Age (y)	67.1 ± 9.5	67.2 ± 9.3	.8805
Sex			.0775
Male	1149 (50)	343 (54)	
Female	1135 (50)	289 (46)	
Race			.0001
White	1845 (81)	463 (73)	
African American	412 (18)	162 (26)	
Other	27 (1)	7 (1)	
Insurance			.1358
Medicare	1035 (45)	259 (41)	
Medicaid	328 (14)	107 (17)	
Commercial	860 (38)	244 (39)	
Uninsured	61 (3)	22 (3)	
Chest CT scan			.2026
No	183 (8)	41 (6)	
Yes	2101 (92)	591 (94)	
PET-CT scan			.0004
No	431 (19)	81 (13)	
Yes	1853 (81)	551 (87)	
Brain imaging such as MRI or CT			<.0001
No	1702 (75)	346 (55)	
Yes	576 (25)	286 (45)	
Histology			<.0001
Adenocarcinoma	1191 (52)	258 (41)	
Squamous	678 (30)	220 (35)	
Other	415 (18)	154 (24)	
Surgeon level			
Board certification			.0070
Cardiothoracic surgery	2164 (95)	615 (97)	
General surgery	120 (5)	17 (3)	
Dedicated thoracic			<.0001
No	1507 (66)	314 (50)	
Yes	775 (34)	318 (50)	
Service years	30.7 ± 9.2	28.3 ± 11.1	.2300*
Annual cases	28.0 ± 24.2	32.3 ± 25.0	<.0001*
Institution level			
Teaching program			<.0001
No	1075 (47)	215 (34)	
Yes	1209 (53)	417 (66)	
Rurality			.1060
No	1855 (81)	531 (84)	
Yes	429 (19)	101 (16)	
Number of beds	617 (339-793)	617 (315-793)	.9492*
Annual surgical volume	60.2 ± 42.5	62.0 ± 46.6	.8414*

Values are presented as mean ± standard deviation, n (%), or median (interquartile range). CT, Computed tomography; PET, positron emission tomography; MRI, magnetic resonance imaging. *Based on Wilcoxon test on median.

staged cohort with 1 or more risk factors, but not in the invasively staged cohort (Figure E1, A and B).

DISCUSSION

Proper patient selection for curative-intent surgery requires optimal clinical staging, including invasive evaluation of mediastinal lymph nodes in patients deemed to be at risk for nodal metastasis. Such patients, when confirmed, are usually triaged to nonsurgical or neoadjuvant therapy.^{4,14,15} A 2001 American College of Surgeons Patient Care Evaluation revealed use of mediastinoscopy in only 27% of NSCLC resections performed in Commission on Cancer-accredited institutions, with only 47% of these providing lymph node material for pathologic examination.⁵ A subsequent report from a single National Cancer Institute-designated Comprehensive Cancer Center revealed lymph node yield in 100% and sampling of at least 2 mediastinal nodal stations in 98% of mediastinoscopy procedures performed by 2 general thoracic surgeons from 1997 to 2013.¹⁶ Current guidelines recommend use of the minimally invasive mediastinal nodal staging techniques EBUS or EUS, followed by mediastinoscopy when negative in residually high-risk patients before resection.^{3,4,6,17} Accepted indications for invasive preoperative mediastinal nodal staging include large or proximally located tumors, and radiologic evidence of possible nodal metastasis.^{3,4,6}

In the MS-QSR—a contemporary, population-based, predominantly community-level cohort from a high lung cancer incidence and mortality region of the United States—invasive mediastinal nodal staging was used in only 22% of patients (mediastinoscopy was used in 16%), even lower than the 2001 Patient Care Evaluation. The low mediastinoscopy utilization rate is not attributable to a generally low-risk population—47% of noninvasively staged patients had at least 1 indication—nor was it attributable to greater reliance on less invasive mediastinal staging procedures, use of which was only 9% in this cohort. Combined use of minimally invasive mediastinal staging and mediastinoscopy was least frequent (3%). Others have reported similar persistent underuse of invasive nodal staging, including mediastinoscopy.^{18,19} However, we also found a significant increasing trend toward use of preoperative invasive mediastinal nodal staging procedures, which increased from 12% to 38% over time, and even more so in high-risk patients.

A key finding from our analysis is the size of the opportunity to improve patient selection for surgery: invasive staging was used in only 37% of patients with at least 1 indication; 19% of procedures failed to provide sufficient material for histologic evaluation. Although this seems

TABLE 3. Stage comparison between resected lung cancer patients without and with preoperative invasive mediastinal nodal staging

Stage	No invasive staging (n = 2284 [78%])	Invasive staging (n = 632 [22%])	P value
Clinical T category			
1	1307 (57)	254 (40)	<.0001
2	496 (22)	187 (30)	
3	202 (9)	101 (16)	
4	158 (7)	62 (10)	
Insufficient record	121 (5)	28 (4)	
Clinical T category distribution of clinical N0 patients			
1	1204 (59)	9 (36)	.0053
2	422 (21)	5 (20)	
3	158 (8)	6 (24)	
4	132 (7)	1 (4)	
Insufficient record	111 (5)	4 (16)	
Clinical N category by CT or PET-CT criteria			<.0001
0	2027 (89)	25 (4)	
1	120 (5)	116 (18)	
2	121 (5)	483 (76)	
3	16 (1)	8 (1)	
Clinical N category after invasive staging*			<.0001
0	2027 (89)	487 (77)	
1	120 (5)	75 (12)	
2	121 (5)	61 (10)	
3	16 (1)	9 (1)	
Clinical M category			.1365
0	2229 (98)	610 (97)	
1	55 (2)	22 (3)	
Clinical stage before invasive staging			<.0001
IA	1182 (52)	9 (1)	
IB	310 (14)	4 (1)	
IIA	101 (4)	0 (0)	
IIB	252 (11)	97 (15)	
IIIA	250 (11)	465 (74)	
IIIB	14 (1)	7 (1)	
IV	55 (2)	22 (3)	
Insufficient records	120 (5)	28 (4)	
Clinical stage after invasive staging*			<.0001
IA	1182 (52)	202 (32)	
IB	310 (14)	87 (14)	
IIA	101 (4)	46 (7)	
IIB	252 (11)	128 (20)	
IIIA	250 (11)	111 (18)	
IIIB	14 (1)	8 (1)	
IV	55 (2)	22 (3)	
Insufficient records	120 (5)	28 (4)	

(Continued)

TABLE 3. Continued

Stage	No invasive staging (n = 2284 [78%])	Invasive staging (n = 632 [22%])	P value
Pathologic T category			<.0001
In situ/0	12 (1)	3 (0.5)	
1	1093 (48)	222 (35)	
2	880 (39)	261 (41)	
3	262 (11)	122 (19)	
4	37 (2)	24 (4)	
Pathologic N category			<.0001
0	1745 (76)	426 (67)	
1	216 (9)	129 (20)	
2	181 (8)	64 (10)	
X	142 (6)	13 (2)	
Pathologic stage			<.0001
0	12 (1)	2 (0.3)	
IA	966 (42)	181 (29)	
IB	524 (23)	117 (18)	
IIA	82 (4)	27 (4)	
IIB	353 (15)	140 (22)	
IIIA	261 (11)	123 (19)	
IIIB	56 (2)	26 (4)	
IV	30 (1)	16 (3)	
Clinical vs pathologic nodal staging†			<.0001
No change	1816 (80)	436 (69)	
Upstaged	300 (13)	117 (19)	
Downstaged	168 (7)	79 (12)	

Values are presented as n (%). CT, Computed tomography; T, tumor; N, nodal; M, metastasis; PET, positron emission tomography. *Final clinical stage, reflecting findings at invasive staging if done. †Identical to radiologic stage for the no invasive staging cohort.

better than the Patient Care Evaluation findings, there is clearly room for further improvement. Combined-modality invasive staging was relatively infrequent and a large subset of minimally invasive staging was TBNA, which is a very limited staging modality. The enormity of the quality improvement opportunity is further emphasized by the finding that patients who were not invasively staged were also at greater risk for suboptimal pathologic nodal staging: 6% had no histologic evaluation of any lymph nodes at any time before, during, or after curative-intent surgery for lung cancer, and 20% had no mediastinal lymph nodes examined at any point in their care. Risk-based selection of patients for invasive staging was associated with improvement in survival, the magnitude of which was greatest in those with radiologic evidence of nodal metastasis, especially mediastinal nodal metastasis. Noninvasively staged patients with 1 or more indications for invasive staging had significantly worse survival than those with no indication (Figure E1, A).

FIGURE 3. Survival of sequentially higher-risk subsets of patients with and without preoperative invasive mediastinal nodal staging procedures, showing the benefit of using invasive staging tests to select patients for curative-intent surgical resection. A, All patients. B, Patients with at least 1 of 3 indications: tumor size ≥ 3 cm/clinical T2-T4, clinical N1-N3 determined by lymph node enlargement by computed tomography (CT) criterion or positron emission tomography (PET)-computed tomography criterion (fluorodeoxyglucose-avid lymph node with standardized uptake value ≥ 2.5). C, Patients with clinical N1-N3 by CT or PET-CT criteria. D, Patients with suspected mediastinal lymph node involvement (N2-N3) by CT or PET-CT criterion.

Our analysis is susceptible to all the limitations of a retrospective study design. We have only included patients who received primary resection, thus patients who were appropriately triaged to nonsurgical therapy are not available in this surgical resection database. This unknown denominator problem renders impossible a formal calculation of the performance characteristics such as the sensitivity, specificity, and predictive values of the invasive mediastinal nodal staging procedures in our cohort.²⁰ Whether or not tumor size >3 cm is an indication for invasive mediastinal nodal staging has been debated, with evidence available for and against.^{7,21} But current guidelines such as those of the National Comprehensive Cancer Network support this

indication.⁴ Other potential indications for invasive mediastinal nodal staging, such as proximal tumor location, are not reliably identified. This arguably biased our analysis toward underestimation of the extent of underuse of invasive mediastinal staging, because a proportion of those who did not undergo invasive nodal staging who had none of our 3 indications may have had a proximally located tumor; for example, a significant proportion of the 678 patients who had squamous cell histology, which tends to be more proximally located.

Although population-based, the MS-QSR cohort is not a nationally representative sample. However, findings from this region have been corroborated by analyses of nationally

FIGURE 4. Propensity-matched survival comparison between patients who had invasive versus noninvasive mediastinal nodal staging.

representative databases such as the Surveillance, Epidemiology, and End Results database.²²⁻²⁵ Furthermore, although the pattern of care in this predominantly community-based cohort may not represent the experience of higher-performing institutions such as National Cancer Institute-designated Cancer Centers and the lung cancer specialists who serve them, 85% of lung cancer surgery in the United States is performed in community-based facilities.⁵ Finally, we have only superficially and indirectly analyzed the quality of use of invasive nodal staging procedures. It is likely that the poor staging problem we describe is worse than we report, if the thoroughness of application of the procedures is factored in.^{2,4,26}

CONCLUSIONS

It appears that underuse of nodal staging for prognostication and treatment selection spans the spectrum of perioperative care for a significant proportion of patients with potentially curable NSCLC. Underuse of invasive mediastinal nodal staging and the thoroughness of nodal staging, especially in patients at high risk for nodal involvement, remain prime targets for quality improvement more than a decade after the American College of Surgeons Patient Care Evaluation highlighted this quality deficit in 2001. Interventions are needed to increase the appropriate use of invasive preoperative nodal evaluation techniques in patients with potentially curable NSCLC, especially in those with radiologically suspected nodal metastasis. In such patients, noninvasive clinical staging seems to be associated with a worse survival.

Conflict of Interest Statement

Dr Osarogiagbon has a patent for a lymph node kit used for mediastinal lymph node examination during surgery. All

other authors have nothing to disclose with regard to commercial support.

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Key Words: clinical staging, preoperative evaluation, quality of care, surgical resection, survival impact

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APPENDIX E1. PROPENSITY MATCHING

We used a 1-to-1 matched propensity score analysis to address the potential for confounding or other imbalances in the use and nonuse of any invasive mediastinal nodal staging.^{E1} Potential confounders included patient's age at surgery, sex, race, insurance, smoking status, clinical tumor-node-metastasis stage, indication of positron emission tomography (PET)/computed tomography (CT), surgeon board certification, hospital teaching status, hospital bed size, hospital rurality, and hospital case volume. Propensity scores were calculated based on logistic regression modeling any invasive staging as a function of the potential confounders outlined above. Matches were based on propensities that were most similar, defined as Mahalanobis distance,^{E2-E4} between a patient with invasive staging and a patient without. The matching was performed in R Gui software (R Foundation for Statistical Computing, Vienna, Austria) using the software package *Matching*, which automates balance optimization.^{E5-E7} The caliber, or the threshold distance for a match, was set to 0.1. To check for balance between the 2 matched samples, the package provides univariate balance statistics for all covariates included within the matching and respective *P* values (via the *MatchBalance* function) to ensure no statistical differences exist between the 2 samples. There were 2916 patients to match (2284 were no invasive staging + 632 were invasive staging), of 492 were matched. These 492 patients had similar baseline

demographic and clinical characteristics, surgeon's certification, and hospital features. The 2424 patients not matched were more often women (50% vs 45%) compared with the matched group, more likely to be white (80% vs 73%) but less likely to be African American (18% vs 26%), slightly more were receiving Medicare (45% vs 41%), there was more radiologic clinical N0 stage by computed tomography criterion or positron emission tomography-computed tomography criterion (83% vs 10%), more adenocarcinoma (50% vs 48%) but less squamous (29% vs 38%), fewer current smokers (48% vs 56%), and fewer positron emission tomography/computed tomography scans (81% vs 90%).

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FIGURE E1. Survival of patients stratified by number of high-risk features (tumor size ≥ 3 cm/clinical T2-T4; clinical N1-N3 by computed tomography (CT) short-axis lymph node diameter ≥ 1 cm, or positron-emission tomography-CT scan describing any lymph node with a standardized uptake value ≥ 2.5 , suggesting the value of using a risk-stratified approach to select patients for curative-intent surgical resection. A, Patients who did not undergo invasive staging. B, Patients who had invasive staging.