



National guideline concordance and outcomes for pathologic N2 disease in non-small cell lung cancer

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Background: Real-world treatment practices for positive mediastinal nodal disease in non-small cell lung cancer (NSCLC) continues to vary despite guidelines. We aim to assess national trends in the treatment of pathologic-N2 disease, and evaluate the association with clinical nodal staging and timing of systemic therapy.

Methods: The National Cancer Database was queried for patients with NSCLC who underwent lobectomy and had pathologic-N2 disease from 2010–2017. National Comprehensive Cancer Network (NCCN) guideline concordance was evaluated. cN2 patients were analyzed based on timing of systemic therapy and response. Multivariable logistic regression evaluated outcomes by type of systemic therapy. Survival analysis utilized Cox proportional hazards regression and Kaplan-Meier methods.

Results: 10,225 patients met inclusion criteria. Fifty-four percent of patients were understaged prior to surgery as either cN0 or cN1. Of clinically staged N2 patients, 56% received NCCN recommended neoadjuvant therapy. Annual guideline concordance increased until 2016 to a max of 62.9%. Neoadjuvant and adjuvant systemic therapy showed an overall survival benefit compared with no systemic therapy (HR 0.54 & 0.57), but no difference when compared against each other. Complete response after neoadjuvant therapy was associated with improved survival (5-year OS 56.1%, $P < 0.001$), while partial response, no-response, and adjuvant therapy were similar. All systemic treatment strategies improved survival compared with no systemic therapy (5-year OS 24.5%).

Conclusions: Guideline concordance for treatment of cN2 disease has been increasing, but still not followed in over 1/3 of patients. Responsiveness to neoadjuvant therapy appears to be a predictor of survival, and may become a prognostic adjunct for determining which patients would benefit from additional systemic therapy.

Keywords: Lung cancer; surgery; guidelines; lobectomy

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Introduction

The optimal treatment of patients with non-small cell lung cancer (NSCLC) with pathologic mediastinal lymph node involvement is a rapidly evolving field. While the sequence of therapy and modalities utilized continue to be

questioned, for patients who are otherwise fit for surgery and are without N3 disease, some combination of surgical therapy with systemic therapy remains the mainstay of care (1-3). While the National Comprehensive Cancer Network (NCCN) guidelines recommend against upfront

surgical resection for these patients (4) (with the specific recommendation being for induction chemotherapy plus or minus radiation therapy in potential surgical candidates), no randomized trials have been performed specifically comparing the sequence of therapy for patients with N2 disease.

Several studies utilizing datasets from the early 2000s have suggested that outcomes are similar for neoadjuvant and adjuvant chemotherapy in patients who underwent complete resection (5-8). If such a belief is increasingly held among thoracic surgeons, it may, at least in part, explain low concordance with guidelines for invasive mediastinal staging. As the primary rationale for invasive mediastinal staging is to identify patients with “occult N2” disease so that they can be treated with induction therapy, if there is no difference between neoadjuvant and adjuvant therapy, the utility of invasive staging is lower. A recent paper from the Society of Thoracic Surgeons General Thoracic Database showed overall low use of invasive mediastinal staging, with only 43% of patients with clinical stage IB or higher undergoing invasive staging (9). This may be particularly relevant for patients with a clinically negative mediastinum.

To help shed further light on these important issues, we utilized the National Cancer Database (NCDB) to better understand the association between both clinical nodal stage and timing of therapy on short and long-term outcomes in patients with pathologic N2 NSCLC who underwent anatomic surgical resection. We hypothesized that patients who were occult N2 (cN0/cN1, pN2) would have better outcomes than patients with clinically evident N2 disease. We also hypothesized that there would not be significant clinical differences between cN2 patients who underwent neoadjuvant chemotherapy, compared with those who underwent adjuvant treatment. We present the following article in accordance with the STROBE reporting checklist (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-21-1845/rc>).

Methods

Data source

The NCDB a joint project of the American Cancer Society and the American College of Surgeon's Commission on Cancer (CoC), is a nationwide facility-based oncology dataset that currently captures 70% of all newly diagnosed cancers in the United States annually reported from

approximately 1,500 hospitals with CoC-accredited cancer programs. The NCDB only includes patients treated at facilities that are continuously accredited by the CoC. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Patient selection

Utilizing the most recent data available from the NCDB, the 2017 participant user file was queried for patients with histologically confirmed N2 disease and an overall stage of IIIA. Per the American Joint Committee on Cancer 7th edition (10), this included T1, T2, and T3 disease. Patients who were clinically staged as IIIA with cN2 disease, received neoadjuvant therapy, and then were downstaged to pN0 or pN1 were also included. Only histology consistent with Adenocarcinoma, Squamous Cell Carcinoma, or Adenosquamous Carcinoma were included based on ICD-0-3 codes (11). Data was analyzed from 2010 onward, as that was when the NCDB started maintaining the most granular information regarding surgical approach. Only patients who underwent lobectomy were evaluated. Patients who had a previous primary lung malignancy, were pT4, or who received non-standard of care treatment including neoadjuvant or adjuvant radiation without chemotherapy were excluded. The patient selection flow chart can be seen in *Figure 1*.

Variables studied

The NCDB provides patient demographic, clinical, and treatment variables. Trends of treatment guideline concordance based on recommendations from the NCCN were evaluated during this time period (4). The resulting cohort of patients were first categorized by clinical nodal stage with a comparison of demographics and tumor characteristics. A sub-analysis was then performed of only clinical N2 patients separated by utilization and timing of systemic therapy. The primary outcomes were overall survival and guideline concordance. Secondary outcomes included 30-day readmission and 30- and 90-day mortality. This cohort of clinical N2 patients was then further divided based on timing of systemic therapy and nodal response, with overall survival as the primary outcome evaluated.

Statistical analysis

Continuous variables were compared using Student's *t*

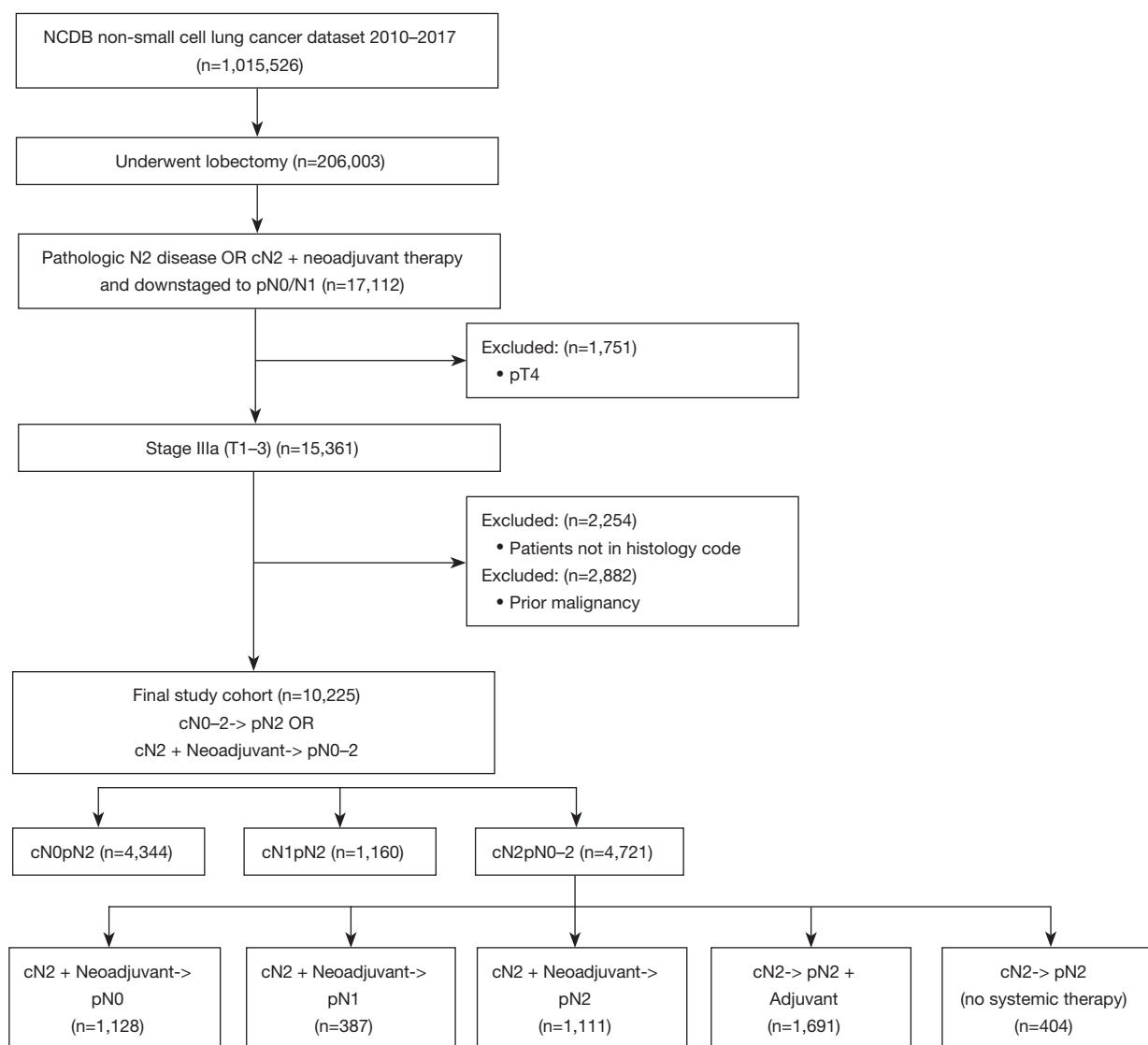


Figure 1 Patient selection flowchart.

tests, and categorical variables were compared using χ^2 and ANOVA tests. Multiple comparisons were made using the Tukey-Kramer method test for ANOVA and log-rank tests, while the Bonferroni correction was used for chi-square tests. Kaplan-Meier methods with log-rank tests were used to analyze overall survival in our cohort. Multivariable survival analysis was performed using Cox Proportional Hazards regression. Statistical analyses were performed using SAS 9.4 statistical software (SAS Institute, Cary, NC, USA). All tests were two-sided, and a P value less than 0.05 was considered statistically significant.

Results

A total of 10,225 Stage IIIA NSCLC patients with pathologic N2 disease and ultimately received surgical lobectomy were included in this study. This included both pT1–3 pN2 patients, and cT1–3 cN2 who received neoadjuvant therapy and were downstaged to pN0 or pN1. Patient demographics and tumor characteristics for each clinical nodal stage cohort are presented in *Table 1*. Patients with cN2 disease were more likely to have private insurance (cN0 33%, cN1 34%, cN2 41%, $P<0.0001$) and be treated at an academic center (cN0 34%, cN1 36%, cN2 42%),

Table 1 Demographics, tumor characteristics, and outcomes based by clinical stage

Variable	All, N (%)	cN0, N (%)	cN1, N (%)	cN2, N (%)	P value
Total patients, N	10,225	4,344	1,160	4,721	
Demographics					
Age, years [mean ± SD]	65±10	66±10	66±10	64±10	<0.0001 ^{ab}
Sex					0.0016 ^{ac}
Female	5,450 (53.3)	2,402 (55.3)	588 (50.7)	2,460 (52.1)	
Male	4,775 (46.7)	1,942 (44.7)	572 (49.3)	2,261 (47.9)	
Race					0.184
Caucasian	8,367 (81.8)	3,531 (81.3)	957 (82.5)	3,879 (82.2)	
African American	985 (9.6)	410 (9.4)	102 (8.8)	473 (10.0)	
Hispanic	345 (3.4)	169 (3.9)	42 (3.6)	134 (2.8)	
Asian/Pacific Islander	396 (3.9)	180 (4.1)	44 (3.8)	172 (3.6)	
Other/unknown	132 (1.3)	54 (1.2)	15 (1.3)	63 (1.3)	
Insurance status					<0.0001 ^{ab}
Private	3,727 (36.4)	1,416 (32.6)	392 (33.8)	1,919 (40.6)	
Medicare	5,388 (52.7)	2,455 (56.5)	656 (56.6)	2,277 (48.2)	
Medicaid/other government	833 (8.1)	346 (8.0)	87 (7.5)	400 (8.5)	
None/other	277 (2.7)	127 (2.9)	25 (2.2)	125 (2.6)	
Income					0.0026 ^a
<\$38,000	1,497 (14.6)	642 (14.8)	182 (15.7)	673 (14.3)	
\$38,000–\$62,999	4,631 (45.3)	1,994 (45.9)	527 (45.4)	2,110 (44.7)	
≥\$63,000	2,977 (29.1)	1,191 (27.4)	322 (27.8)	1,464 (31.0)	
Unknown	1,120 (11.0)	517 (11.9)	129 (11.1)	474 (10)	
Location					0.0134 ^a
Metro/Suburban	8,206 (80.3)	3,495 (80.5)	919 (79.2)	3,792 (80.3)	
Urban	1,463 (14.3)	640 (14.7)	169 (14.6)	654 (13.9)	
Rural	197 (1.9)	85 (2.0)	31 (2.7)	81 (1.7)	
Unknown	359 (3.5)	124 (2.9)	41 (3.5)	194 (4.1)	
Facility type					<0.0001 ^{ab}
Non-academic	6,363 (62.2)	2,876 (66.2)	745 (64.2)	2,742 (58.1)	
Academic/research program	3,862 (37.8)	1,468 (33.8)	415 (35.8)	1,979 (41.9)	
Distance to facility, miles, median [Q1–Q3]	12 [5–28]	11 [5–27]	12 [5–28]	12 [5–28]	0.8710
Charlson-Deyo comorbidity					<0.0001 ^{ab}
0	5,866 (57.4)	2,324 (53.5)	652 (56.2)	2,890 (61.2)	
1	2,974 (29.1)	1,334 (30.7)	348 (30.0)	1,292 (27.4)	
≥2	1,385 (13.5)	686 (15.8)	160 (13.8)	539 (11.4)	

Table 1 (continued)

Table 1 (continued)

Variable	All, N (%)	cN0, N (%)	cN1, N (%)	cN2, N (%)	P value
Tumor characteristics					
Clinical T stage					<0.0001 ^{abc}
1	4,349 (42.5)	2,296 (52.9)	472 (40.7)	1581 (33.5)	
2	4,430 (43.3)	1,698 (39.1)	541 (46.6)	2,191 (46.4)	
3–4	1,446 (14.1)	350 (8.1)	147 (12.7)	949 (20.1)	
Pathologic T stage					<0.0001 ^{abc}
1	3,551 (34.7)	1,332 (30.7)	304 (26.2)	1,915 (40.6)	
2	4,954 (48.4)	2,313 (53.2)	603 (52.0)	2,038 (43.2)	
3	1,720 (16.8)	699 (16.1)	253 (21.8)	768 (16.3)	
Tumor size, cm, median [Q1–Q3]	3.2 [2.3–4.8]	3.0 [2.2–4.4]	3.4 [2.4–5.1]	3.5 [2.4–5.0]	<0.0001 ^{ac}
Tumor size (cm)					<0.0001 ^{abc}
<2.0	1,684 (16.5)	790 (18.2)	143 (12.3)	751 (15.9)	
2.0–3.9	4,672 (45.7)	2,167 (49.9)	542 (46.7)	1,963 (41.6)	
4.0–5.9	2,259 (22.1)	878 (20.2)	260 (22.4)	1,121 (23.7)	
≥6.0	1,529 (15)	497 (11.4)	213 (18.4)	819 (17.3)	
Unknown	81 (0.8)	12 (0.3)	2 (0.2)	67 (1.4)	
Histology					<0.0001 ^{ac}
Adenocarcinoma	7,528 (73.6)	3,371 (77.6)	836 (72.1)	3,321 (70.3)	
Squamous cell carcinoma	2,365 (23.1)	809 (18.6)	289 (24.9)	1,267 (26.8)	
Adenosquamous carcinoma	332 (3.2)	164 (3.8)	35 (3.0)	133 (2.8)	
Treatment					
Chemotherapy					<0.0001 ^{abc}
None	1,485 (14.5)	872 (20.1)	209 (18.0)	404 (8.6)	
Neoadjuvant	2,831 (27.7)	115 (2.6)	90 (7.8)	2,626 (55.6)	
Adjuvant	5,909 (57.8)	3,357 (77.3)	861 (74.2)	1,691 (35.8)	
Radiation	5,339 (52.2)	1,796 (41.3)	527 (45.4)	3,016 (63.9)	<0.0001 ^{abc}
Diagnosis to first treatment, days, median [Q1–Q3]	32 [16–52]	34 [15–55]	34 [20–52]	30 [15–49]	<0.0001 ^{ab}
Diagnosis to surgery, days, median [Q1–Q3]	51 [25–110]	36 [17–59]	41 [25–64]	104 [41–140]	<0.0001 ^{abc}
Surgery to adjuvant treatment, days, median [Q1–Q3]	61 [43–132]	64 [43–135]	61 [43–131]	57 [42–120]	<0.0001 ^a
Surgical approach					<0.0001 ^{ac}
Open	5,350 (52.3)	2,174 (50.0)	618 (53.3)	2,558 (54.2)	
Minimally invasive	3,252 (31.8)	1,558 (35.9)	357 (30.8)	1,337 (28.3)	
Unknown	1,623 (15.9)	612 (14.1)	185 (15.9)	826 (17.5)	

Table 1 (continued)

Table 1 (continued)

Variable	All, N (%)	cN0, N (%)	cN1, N (%)	cN2, N (%)	P value
MI converted to open	522 (16.1)	221 (14.2)	65 (18.2)	236 (17.7)	0.0202 ^a
Outcomes					
Length of stay, days, median [Q1–Q3]	5 [3–7]	5 [3–7]	5 [3–7]	5 [3–7]	0.2767
30-day mortality	154 (1.7)	52 (1.4)	18 (1.8)	84 (2.0)	0.1065
90-day mortality	346 (3.9)	126 (3.4)	36 (3.7)	184 (4.4)	0.0573
30-day readmission	399 (4.0)	185 (4.3)	51 (4.5)	163 (3.5)	0.1037
Lymph node harvest, median [Q1–Q3]	11 [7–17]	11 [7–17]	12 [8–18]	11 [7–17]	<0.0001 ^{bc}
Lymph node harvest					<0.0001 ^{abc}
≤ 5	1,449 (15.4)	595 (14.6)	128 (11.8)	726 (17.0)	
6–15	5,132 (54.4)	2,295 (56.5)	576 (52.9)	2,261 (52.8)	
>15	2,853 (30.2)	1,172 (28.9)	385 (35.4)	1,296 (30.3)	
Number of positive nodes, median [Q1–Q3]	3 [1–5]	2 [1–4]	3 [2–6]	3 [1–5]	<0.0001 ^{abc}
Resection					0.0002 ^{bc}
R0	9,276 (95.0)	3,978 (95.3)	1,009 (92.4)	4,289 (95.3)	
R1	475 (4.9)	195 (4.7)	78 (7.1)	202 (4.5)	
R2	18 (0.2)	3 (0.1)	5 (0.5)	10 (0.2)	
Any positive margins	829 (8.2)	319 (7.4)	139 (12.1)	371 (8.0)	<0.0001 ^{bc}

^a, cN2 vs. cN0, P<0.05; ^b, cN2 vs. cN1, P<0.05; ^c, cN1 vs. cN0, P<0.05.

P<0.0001). Clinical T-Stage correlated with N-Stage, with cN2 having the highest rates of T3–T4 tumors (20% for cN2 vs. 8% for cN0 and 13% for cN1). There was significant understaging of T-stage, regardless of nodal stage. Excluding patients that received neoadjuvant therapy who may have been downstaged, all clinically staged nodal groups had a substantial increase in the T-stage of the tumors after surgery. For this entire cohort, 10% of patients were cT3–4, while after surgery, 17.0% were pT3–4 (Table S1).

Despite a final pathologic stage of N2 in the entire cohort, 20% of the cN0 group and 18% of the cN1 group did not receive any systemic therapy. This is compared to just 9% of the cN2 cohort. Positive margins were highest in the cN1 group (12%), and this group ultimately also had the worst overall survival (median 3.7 years, 5-year OS 40%) (Figure 2, Table 2).

Analysis of clinical N2 patients

A total of 4,721 patients were found to have clinical N2 disease. Of this cohort, 404 patients received no systemic therapy (8%), 2,626 received neoadjuvant (56%), and 1,691 received adjuvant (36%). Patient demographics and tumor characteristics of the cN2 group are seen in Table 3. Patients with neoadjuvant therapy were more likely to have an R0 resection than patients undergoing upfront surgery. 30-day and 90-day mortality rates were similar among patients receiving neoadjuvant therapy (2.3%, 4.9%) vs. patients undergoing upfront surgery, regardless of systemic therapy (1.6%, 3.8%). However, patients who received no systemic therapy had a much higher 30-day and 90-day mortality (7.8%, 17.2%) compared with patients who received neoadjuvant therapy and those patients who received adjuvant systemic therapy (0.2%, 0.7%).

The NCCN Guidelines recommend neoadjuvant systemic therapy prior to lobectomy for clinical N2 NSCLC. During this time period, the rate of guideline concordance rose from 48% in 2010 to 63% in 2016. In 2017, only 52% of cN2 patients received neoadjuvant therapy (Figure 3). For this group, being treated at an academic center was correlated with receiving neoadjuvant therapy versus upfront lobectomy for cN2 disease (academic 64% vs. non-academic 50%, $P < 0.0001$). Survival differed based on receipt and timing of systemic therapy. In univariate analysis, median survival was 2.0 years for no systemic therapy, 5.0 years for neoadjuvant, and 3.9 years for adjuvant ($P < 0.0001$). Five-year survival was 25%, 50%, and 43% respectively.

On multivariable analysis, both neoadjuvant and adjuvant systemic therapy showed an overall survival benefit

compared with no systemic therapy (HR 0.54, $P < 0.0001$ for neoadjuvant, and HR 0.57, $P < 0.0001$ for adjuvant). There was no difference in survival when comparing adjuvant vs. neoadjuvant (Table 4).

Timing and response to systemic therapy in cN2 patients

A survival analysis was performed based on receipt, timing, and nodal response to systemic therapy. Patients were divided into one of five groups: (I) complete response: cN2-> neoadjuvant-> pN0; (II) partial response: cN2-> Neoadjuvant-> pN1; (III) no response: cN2-> Neoadjuvant-> pN2; (IV) adjuvant: cN2-> pN2-> adjuvant; (V) no systemic therapy: cN2-> pN2. Complete responders showed a significantly improved survival compared to the rest of the group, while those without any systemic therapy showed a significantly worse survival (median survival: complete 6.2 years, partial 4.7 years, no response 4.2 years, adjuvant 3.9 years, no systemic therapy 2.0 years, $P < 0.0001$) (Figure 4, Table 5).

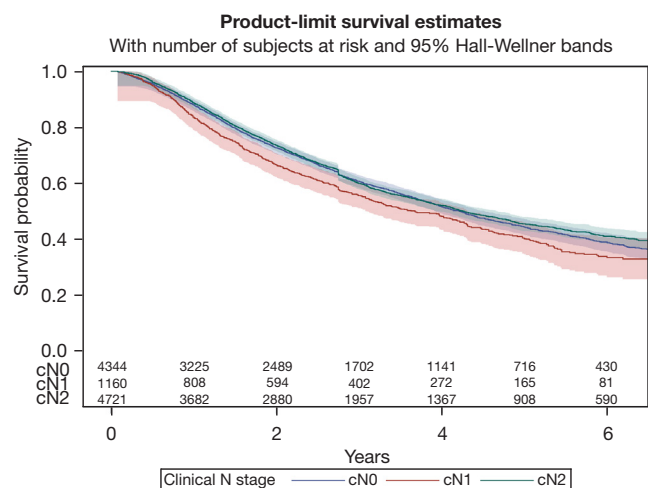


Figure 2 Overall survival separated by clinical nodal stage (cN0, cN1, cN2).

Discussion

Using the most recent National Cancer Database registry data, we find that 54% of all patients with pathologic N2 disease were initially understaged as cN0 or cN1 and discovered to have involved mediastinal nodes after surgical resection. Of those that were clinically staged as N2 and who underwent lobectomy, only 56% received neoadjuvant therapy. This is despite clear NCCN recommendations for induction chemotherapy, plus or minus radiation, in cN2 patients (4). While there has been literature promoting upfront surgical resection for single station N2 disease (12,13), it is a rare entity and there is no consensus guideline advocating for surgery followed by adjuvant

Table 2 Overall survival by clinical stage

Variable	All	cN0	cN1	cN2	P value
Follow-up months, median [Q1-Q3]	30 [13-51]	29 [12-50]	26 [10-46]	32 [15-53]	<0.0001 ^{abc}
Overall survival					0.0002 ^{bc}
Median years (Q1-Q3)	4.2 (1.8-9.2)	4.2 (4.0-4.4)	3.7 (3.2-4.2)	4.3 (1.9-9.2)	
1 year	87.8%	88.0%	83.6%	88.7%	
3 years	59.7%	60.7%	55.6%	59.9%	
5 years	44.4%	44.3%	40.2%	45.4%	

^a, cN2 vs. cN0, $P < 0.05$; ^b, cN2 vs. cN1, $P < 0.05$; ^c, cN1 vs. cN0, $P < 0.05$.

Table 3 Demographics, tumor characteristics, and outcomes of cN2 patients by timing of systemic therapy

Variable	All, N (%)	No therapy, N (%)	Neoadjuvant, N (%)	Adjuvant, N (%)	P value
Total patients, N	4,721	404	2,626	1,691	
Demographics					
Age, years [mean ± SD]	64±10	71±10	62±9	65±9	<0.0001 ^{abc}
Sex					0.0020 ^a
Female	2,460 (52.1)	177 (43.8)	1,397 (53.2)	886 (52.4)	
Male	2,261 (47.9)	227 (56.2)	1,229 (46.8)	805 (47.6)	
Race					0.00061 ^c
Caucasian	3,879 (82.2)	329 (81.4)	2,166 (82.5)	1,384 (81.8)	
African American	473 (10.0)	36 (8.9)	251 (9.6)	186 (11.0)	
Hispanic	134 (2.8)	15 (3.7)	66 (2.5)	53 (3.1)	
Asian/Pacific Islander	172 (3.6)	10 (2.5)	113 (4.3)	49 (2.9)	
Other/Unknown	63 (1.3)	14 (3.5)	30 (1.1)	19 (1.1)	
Insurance Status					<0.0001 ^{abc}
Private	1,919 (40.6)	83 (20.5)	1,229 (46.8)	607 (35.9)	
Medicare	2,277 (48.2)	283 (70.0)	1,111 (42.3)	883 (52.2)	
Medicaid/other government	400 (8.5)	23 (5.7)	218 (8.3)	159 (9.4)	
None/other	125 (2.6)	15 (3.7)	68 (2.6)	42 (2.5)	
Income, USD					<0.0001 ^{abc}
<\$38,000	673 (14.3)	76 (18.8)	327 (12.5)	270 (16.0)	
\$38,000–\$62,999	2,110 (44.7)	198 (49.0)	1,114 (42.4)	798 (47.2)	
≥\$63,000	1,464 (31.0)	99 (24.5)	910 (34.7)	455 (26.9)	
Unknown	474 (10)	31 (7.7)	275 (10.5)	168 (9.9)	
Location					<0.0001 ^{bc}
Metro/Suburban	3,792 (80.3)	314 (77.7)	2,141 (81.5)	1,337 (79.1)	
Urban	654 (13.9)	70 (17.3)	324 (12.3)	260 (15.4)	
Rural	81 (1.7)	11 (2.7)	27 (1.0)	43 (2.5)	
Unknown	194 (4.1)	9 (2.2)	134 (5.1)	51 (3.0)	
Facility type					<0.0001 ^{bc}
Non-academic	2,742 (58.1)	271 (67.1)	1,361 (51.8)	1,110 (65.6)	
Academic/research program	1,979 (41.9)	133 (32.9)	1,265 (48.2)	581 (34.4)	
Distance to facility, miles, median [Q1–Q3]	12 [5–28]	12 [5–30]	12 [6–30]	11 [5–26]	0.0089 ^b
Charlson-Deyo comorbidity					<0.0001 ^{abc}
0	2,890 (61.2)	210 (52.0)	1,728 (65.8)	952 (56.3)	
1	1,292 (27.4)	123 (30.4)	652 (24.8)	517 (30.6)	
≥2	539 (11.4)	71 (17.6)	246 (9.4)	222 (13.1)	

Table 3 (continued)

Table 3 (continued)

Variable	All, N (%)	No therapy, N (%)	Neoadjuvant, N (%)	Adjuvant, N (%)	P value
Tumor characteristics					
Clinical T stage					<0.0001 ^{bc}
1	1,581 (33.5)	146 (36.1)	808 (30.8)	627 (37.1)	
2	2,191 (46.4)	183 (45.3)	1,179 (44.9)	829 (49.0)	
3–4	949 (20.1)	75 (18.6)	639 (24.3)	235 (13.9)	
Pathologic T stage					<0.0001 ^{abc}
1	1,915 (40.6)	102 (25.2)	1,325 (50.5)	488 (28.9)	
2	2,038 (43.2)	211 (52.2)	936 (35.6)	891 (52.7)	
3	768 (16.3)	91 (22.5)	365 (13.9)	312 (18.5)	
Tumor size, cm [median (Q1–Q3)]	3.5 (2.4–5.0)	3.5 (2.5–5.0)	3.5 (2.4–5.2)	3.3 (2.3–5.0)	0.0083 ^b
Tumor size (cm)					<0.0001 ^{abc}
<2.0	751 (15.9)	49 (12.1)	429 (16.3)	273 (16.1)	
2.0–3.9	1,963 (41.6)	183 (45.3)	1,015 (38.7)	765 (45.2)	
4.0–5.9	1,121 (23.7)	97 (24.0)	635 (24.2)	389 (23.0)	
≥6.0	819 (17.3)	71 (17.6)	492 (18.7)	256 (15.1)	
Unknown	67 (1.4)	4 (1.0)	55 (2.1)	8 (0.5)	
Histology					0.0019 ^{abc}
Adenocarcinoma	3,321 (70.3)	262 (64.9)	1,859 (70.8)	1,200 (71.0)	
Squamous cell carcinoma	1,267 (26.8)	126 (31.2)	708 (27.0)	433 (25.6)	
Adenosquamous carcinoma	133 (2.8)	16 (4.0)	59 (2.2)	58 (3.4)	
Treatment					
Radiation	3,016 (63.9)	0 (0.0)	2,005 (76.4)	1,011 (59.8)	<0.0001 ^{abc}
Diagnosis to first treatment, days, median [Q1–Q3]	30 [15–49]	34 [9–61]	31 [18–47]	29 [11–50]	0.0218
Diagnosis to surgery, days, median [Q1–Q3]	104 [41–140]	37 [15–62]	132 [111–160]	35 [17–60]	<0.0001 ^{bc}
Surgery to adjuvant treatment, days, median [Q1–Q3]	57 [42–120]	–	–	61 [42–132]	–
Surgical approach					<0.0001 ^{abc}
Open	2,558 (54.2)	249 (61.6)	1,440 (54.8)	869 (51.4)	
Minimally invasive	1,337 (28.3)	130 (32.2)	744 (28.3)	463 (27.4)	
Unknown	826 (17.5)	25 (6.2)	442 (16.8)	359 (21.2)	
MI converted to open	236 (17.7)	25 (19.2)	134 (18.0)	77 (16.6)	0.7331

Table 3 (continued)

Table 3 (continued)

Variable	All, N (%)	No therapy, N (%)	Neoadjuvant, N (%)	Adjuvant, N (%)	P value
Outcomes					
Length of stay, days, median [Q1–Q3]	5 [3–7]	7 [4–10]	5 [3–7]	5 [3–7]	<0.0001 ^{ac}
30-day mortality	84 (2.0)	27 (7.8)	54 (2.3)	3 (0.2)	<0.0001 ^{abc}
90-day mortality	184 (4.4)	59 (17.2)	115 (4.9)	10 (0.7)	<0.0001 ^{abc}
30-day readmission	163 (3.5)	24 (6.0)	92 (3.6)	47 (2.8)	0.0086 ^{ac}
Lymph node harvest, median [Q1–Q3]	11 [7–17]	11 [7–16]	11 [7–18]	11 [7–17]	0.7120
Lymph node harvest					0.0055 ^{bc}
≤5	726 (17.0)	59 (15.4)	424 (18.3)	243 (15.4)	
6–15	2,261 (52.8)	223 (58.4)	1,169 (50.4)	869 (55.0)	
>15	1,296 (30.3)	100 (26.2)	727 (31.3)	469 (29.7)	
Number of positive nodes, median [Q1–Q3]	3 [1–5]	3 [1–5]	2 [1–5]	3 [2–5]	<0.0001 ^b
Resection					0.0009 ^b
R0	4,289 (95.3)	368 (95.1)	2,432 (96.4)	1,489 (93.6)	
R1	202 (4.5)	19 (4.9)	89 (3.5)	94 (5.9)	
R2	10 (0.2)	0 (0.0)	3 (0.1)	7 (0.4)	
Any positive margins	371 (8.0)	33 (8.2)	161 (6.2)	177 (10.6)	<0.0001 ^b
Reason for no chemotherapy					–
None, not part of the first course of treatment	–	192 (47.5)	–	–	
Contraindicated	–	48 (11.9)	–	–	
Died prior to planned/recommended therapy	–	10 (2.5)	–	–	
Recommended but not administered, unknown reason	–	54 (13.3)	–	–	
Recommended but patient refused	–	100 (24.8)	–	–	
Follow-up months, median [Q1–Q3]	32 [15–53]	17 [4–34]	33 [17–55]	32 [15–53]	<0.0001 ^{bc}
Overall survival					<0.0001 ^{abc}
Median years (Q1–Q3)	4.3 (1.9–9.2)	2.0 (1.7–2.3)	5.0 (2.1–8.9)	3.9 (3.5–4.2)	
1 year	88.7%	67.9%	90.7%	90.2%	
3 years	59.9%	35.3%	65.0%	57.5%	
5 years	45.4%	24.5%	50.1%	42.7%	

^a, Adjuvant vs. No Therapy, P<0.05; ^b, Adjuvant vs. Neoadjuvant, P<0.05; ^c, Neoadjuvant vs. No Therapy, P<0.05.

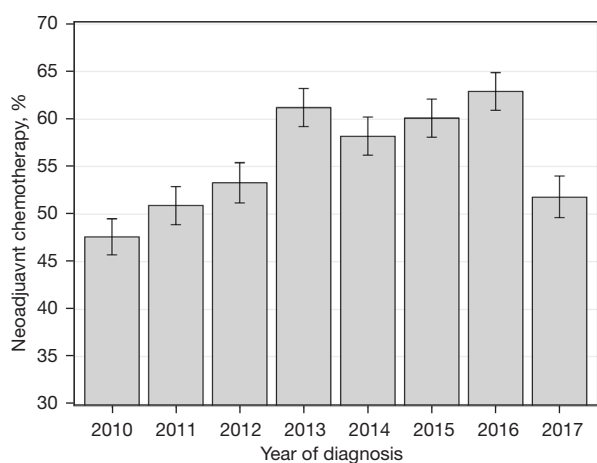


Figure 3 Guideline concordance based on NCCN recommendations (neoadjuvant systemic therapy for resectable cN2 non-small cell lung cancer patients) by year.

therapy wherein we would expect 35.8% of clinically staged N2 patients to follow that treatment algorithm, as seen in this cohort.

Approximately 9% of the 4,721 cN2pN2 patients had resection without any systemic therapy. In 25% of these patients, it was due to patient refusal. Our assumption is that the remaining 75% had been planned for adjuvant systemic therapy, but were deemed either too frail or did not recover well enough from surgical resection to tolerate chemotherapy. This is partially confirmed by our data, as patients who received no systemic therapy had substantially higher 30- and 90-day mortality and 30-day readmission compared with both the neoadjuvant and adjuvant chemotherapy cohorts.

Over the 7 years of data analyzed, the rate of guideline concordance (neoadjuvant therapy for cN2 disease) slowly

Table 4 Multivariable analysis for clinical N2 patients

Variable	Survival analysis		30-day mortality		90-day mortality		30-day readmission	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age, years								
55–64 vs. <55	1.22 (1.06–1.41)	0.0046	2.33 (0.95–5.76)	0.0661	1.37 (0.76–2.48)	0.2991	0.55 (0.35–0.88)	0.0122
65–74 vs. <55	1.31 (1.12–1.55)	0.0009	3.27 (1.24–8.65)	0.0169	1.93 (1.02–3.65)	0.0445	0.86 (0.51–1.45)	0.5678
≥75 vs. <55	1.68 (1.39–2.01)	<0.0001	4.00 (1.40–11.41)	0.0096	2.14 (1.06–4.32)	0.0332	1.02 (0.55–1.88)	0.9508
Sex, male vs. female								
	1.31 (1.20–1.43)	<0.0001	1.57 (1.00–2.46)	0.0494	1.49 (1.08–2.05)	0.0145	1.27 (0.93–1.74)	0.1379
Facility type, academic/research vs. non-academic								
	0.87 (0.80–0.96)	0.0031	0.75 (0.48–1.18)	0.2120	0.62 (0.45–0.86)	0.0039	0.86 (0.62–1.18)	0.3418
Charlson-Deyo comorbidity								
1 vs. 0	1.10 (1.00–1.21)	0.0573	0.68 (0.40–1.17)	0.1615	1.04 (0.72–1.49)	0.8376	1.26 (0.89–1.79)	0.1907
≥2 vs. 0	1.30 (1.14–1.49)	<0.0001	1.14 (0.63–2.05)	0.6721	1.66 (1.09–2.51)	0.0180	1.34 (0.84–2.13)	0.2209
Tumor characteristics								
Pathologic T stage								
2 vs. 1	1.26 (1.15–1.39)	<0.0001	0.94 (0.58–1.52)	0.7959	1.22 (0.86–1.72)	0.2719	1.08 (0.76–1.53)	0.6821
3 vs. 1	1.48 (1.31–1.68)	<0.0001	1.06 (0.58–1.93)	0.8551	1.39 (0.90–2.14)	0.1330	1.28 (0.83–1.97)	0.2680
Treatment								
Treatment timing								
Neoadjuvant vs. no therapy	0.54 (0.47–0.63)	<0.0001	0.37 (0.22–0.64)	0.0003	0.40 (0.27–0.59)	<0.0001	0.75 (0.46–1.23)	0.2587
Adjuvant vs. no therapy	0.57 (0.49–0.66)	<0.0001	0.03 (0.01–0.10)	<0.0001	0.04 (0.02–0.08)	<0.0001	0.53 (0.32–0.87)	0.0131
Adjuvant vs. neoadjuvant	1.05 (0.95–1.15)	0.3285	0.09 (0.03–0.25)	<0.0001	0.10 (0.05–0.19)	<0.0001	0.70 (0.49–1.00)	0.0532

increased from 47.6% in 2010 to 62.9% in 2016. In 2017, there was a sudden dip in guideline concordance to 51.8%. We cannot provide a clear explanation why this occurred, as there were no major changes in guidelines that year. The only variation in the lung cancer landscape was the FDA approval of pembrolizumab (Keytruda, Merck and Co, Inc) in May of 2017 for metastatic non-squamous NSCLC (14,15). Overall, there is no obvious reason why guideline concordance is not higher, but it is reassuring to see the rates generally increasing.

Despite increasingly advanced diagnostic technology, the inaccuracy of clinical stage has been a continued problem for lung cancer (16,17). We specifically found that clinical accuracy of T-stage is quite poor, regardless of nodal stage.

Pathologic N2 patients are therefore also being substantially understaged by tumor characteristics, or the tumors are growing rapidly from time of clinical staging to surgery (median 35 days).

To compare the timing of therapy in similar clinical cohorts, we looked at cN2 patients only stratified by timing of systemic treatment. Patients who received neoadjuvant chemotherapy had superior 5-year overall survival (50%) compared with patients who received adjuvant treatment (43%), with a median survival difference of 1.1 years, though in multivariable analysis, there was not a significant difference in hazard ratios between these two groups. The true benefit of neoadjuvant therapy may be in the prognostic value it provides. Our data shows that tumor responsiveness to chemotherapy plays an important role in regards to survival. Clinical N2 patients receiving neoadjuvant therapy with a complete pathologic response to pN0 had the best 5-year survival of 56%. As expected, cN2 patients who received no systemic therapy before or after surgery had the worst 5-year survival of 25%. Clinical N2 patients that were either partially downstaged to pN1 by neoadjuvant therapy, remained pN2 despite neoadjuvant therapy, or had upfront surgery followed by adjuvant systemic therapy had statistically similar 5-year survivals ranging from 42.7% to 48.0%. While currently this information is merely prognostic, with new data emerging on consolidative immunotherapy and/or targeted therapy, response to neoadjuvant therapy may, in the very near future, prove predictive, helping guide who receives these additional therapies and who does not (18). Such a treatment paradigm has already been proven in the treatment of esophageal cancer (19), and a similar strategy for lung cancer is likely not far behind.

There are important limitations to this study. The survival comparison between the different clinical nodal

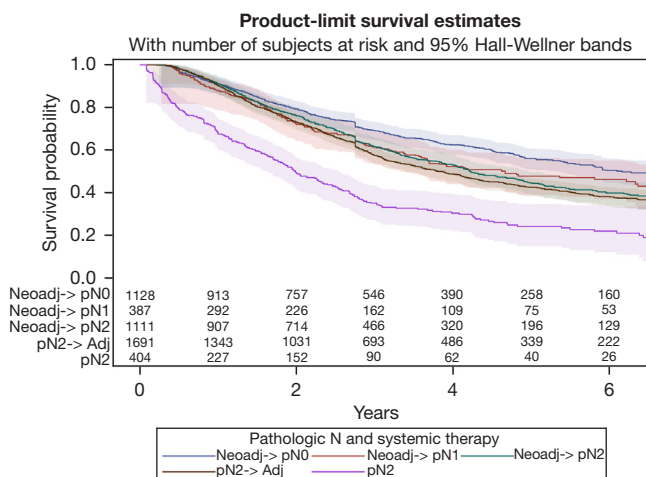


Figure 4 Overall survival by receipt and timing of neoadjuvant systemic therapy in cN2 non-small cell lung cancer patients. Separated by complete response (cN2-> pN0), partial response (cN2-> pN1), no response (cN2-> pN2), adjuvant therapy (pN2-> adjuvant) and no systemic therapy (pN2).

Table 5 Overall survival by receipt and timing of neoadjuvant systemic therapy

Variable	Neoadj-> pN0	Neoadj-> pN1	Neoadj-> pN2	pN2-> Adj	pN2	P value
Overall survival						<0.0001 ^a
Median years (Q1-Q3)	6.2 (2.4-8.6)	4.7 (1.9-6.4)	4.2 (2.1-8.9)	3.9 (1.9-8.8)	2.0 (0.8-4.8)	
1 year	91.0%	87.9%	91.3%	90.2%	67.9%	
3 years	69.3%	61.5%	61.7%	57.5%	35.3%	
5 years	56.1%	48.0%	44.7%	42.7%	24.5%	

^a, all pairwise comparisons P<0.05 except between Neoadj-> pN1 vs. Neoadj-> pN2, Neoadj-> pN1 vs. pN2-> Adj, and Neoadj-> pN2 vs. pN2-> Adj. Middle columns similar to each other, but different from outer (Neoadj-> pN0 and pN2).

stages is hard to interpret with this data. Unfortunately, the NCDB does not provide information on diagnostic mediastinal staging prior to surgical resection. We do not know how patients were clinically staged. This includes lack of information on endobronchial ultrasound (EBUS), mediastinoscopy, or even positron emission tomography (PET) scan. We therefore cannot make any valid conclusions about the accuracy of these diagnostic modalities or if patients were clinically staged appropriately. With that caveat, median and 5-year overall survival were similar between cN0pN2 and cN2pN2 patients, with most cN0 patients receiving adjuvant therapy while most cN2 patients received neoadjuvant. Both of these groups had a significant survival advantage of approximately 6 months and 5% at 5 years over the cN1pN2 patients, who like cN0, mostly received adjuvant therapy. When we performed a sub-analysis of only patients receiving adjuvant therapy, there was a moderate survival benefit for lower clinical stage. cN0 patients had a 5-year survival of 48.7%, compared with 44.9% and 42.7% for cN1 and cN2.

As it is a hospital-based study of a national dataset, granular information is not available on each individual patient. Mentioned earlier, information regarding diagnostic modality for clinical stage is not incorporated into the NCDB. While the lack of appropriate mediastinal staging likely leads to clinical understaging, it can also lead to overstaging of non-biopsy proven mediastinal disease. This would cause a false improvement in survival in the cN2pN1 and cN2pN0 cohorts, although we countered this by removing any downstaged patients who did not receive neoadjuvant therapy. Specific chemotherapy regimen, and whether a patient was planned for resection but did not make it to the operation is not included. A high percentage of patients receiving neoadjuvant chemotherapy but not making it to surgical resection would have significant implications on treatment recommendations. The lack of recurrence data and disease free survival prevent us from including them into our analysis. Finally, the NCDB does not separate bulky from non-bulky N2 disease, or single station from multi station. These are important clinical variables that play decisive roles in treatment algorithms.

Conclusions

There appears to be a high rate of clinical nodal understaging nationally. While guideline concordance is generally improving, a large number of patients with clinically involved mediastinal nodes are not receiving recommended

neoadjuvant therapy. The benefits of timing of therapy (neoadjuvant *vs.* adjuvant) on long-term survival remain unclear. What is clear is that tumor responsiveness to chemotherapy is a major predictor of survival, and may help guide additional treatment decisions. Our study indicates the need for future clinical trials incorporating effective use of diagnostic modalities for mediastinal staging and assessing specific chemotherapy regimens to help determine the best treatment strategy for lung cancer patients with clinically positive nodal disease.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-21-1845/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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Table S1 Adjuvant therapy only, t-stage progression

	All	cN0	cN1	cN2	P-value
	N (%)	N (%)	N (%)	N (%)	–
Total patients, N	5,909	3,357	861	1691	–
Tumor characteristics					
Clinical T Stage					<0.0001 ^{a,c}
1	2,804 (47.5)	1,817 (54.1)	360 (41.8)	627 (37.1)	
2	2,516 (42.6)	1,284 (38.2)	403 (46.8)	829 (49.0)	
3-4	589 (10.0)	256 (7.6)	98 (11.4)	235 (13.9)	
Pathologic T Stage					<0.0001 ^{a,c}
1	1,776 (30.1)	1,058 (31.5)	230 (26.7)	488 (28.9)	
2	3,130 (53.0)	1,789 (53.3)	450 (52.3)	891 (52.7)	
3	1,003 (17.0)	510 (15.2)	181 (21.0)	312 (18.5)	
Diagnosis to surgery, days [Median (Q1-Q3)]	35 (18-56)	34 (16-55)	37 (22-56)	35 (17-60)	<0.0001 ^{a,b}

^a, cN2 vs. cN0, P<0.05; ^b, cN2 vs. cN1, P<0.05; ^c, cN1 vs. cN0, P<0.05.