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Optimal adjuvant therapy in clinically N2 non-small cell lung cancer patients undergoing neoadjuvant chemotherapy and surgery: The importance of pathological response and lymph node ratio

Ashwin Shinde[a], Zachary D. Horne[b], Richard Li[a], Scott Glaser[a], Erminia Massarelli[c], Marianna Koczywas[c], Loretta Erhunmwunsee[d], Karen L. Reckamp[c], Benny Weksler[e], Ravi Salgia[c], Sushil Beriwal[f], Arya Amini[a,*]

[a] Department of Radiation Oncology, City of Hope National Medical Center, Duarte, CA, USA
[b] Department of Radiation Oncology, Allegheny Health Network Cancer Institute, Pittsburgh, PA, USA
[c] Department of Medical Oncology, City of Hope National Medical Center, Duarte, CA, USA
[d] Department of Surgery, City of Hope National Medical Center, Duarte, CA, USA
[e] Department of Thoracic Surgery, Allegheny Health Network Cancer Institute, Pittsburgh, PA, USA
[f] Department of Radiation Oncology, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

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ABSTRACT

Objectives: Optimal adjuvant therapy in patients with clinically N2 (cN2) non-small cell lung cancer (NSCLC) who undergo neoadjuvant chemotherapy followed by surgery is controversial. We evaluated the impact of adjuvant chemotherapy (CT) and/or radiation (RT) in this patient population.

Materials and methods: Patients with non-metastatic, cN2 NSCLC diagnosed from 2004 to 2015 were identified from the National Cancer Database, which captures 70% of cancer cases diagnosed in the United States. Patients underwent neoadjuvant CT and surgical resection. Patients couldn't receive RT before surgery. Survival was compared using log-rank and Cox proportional hazards modeling. Subset analyses were performed based on post-chemotherapy surgical nodal staging (ypN0-2) and lymph node ratio (LNR), including 0%, 1–15%, or > 15% involvement. LNR was defined as number of nodes involved by tumor divided by number of nodes examined.

Results and conclusions: We identified 1541 patients. The percentage of patients who received adjuvant CT and RT was 18.9% and 35.7% respectively. ypN status and LNR were predictive of survival on univariate analysis, but only LNR maintained significance on multivariate analysis. There was no benefit observed for adjuvant CT or RT in the entire cohort. On subset analyses, a survival benefit was observed in ypN2 patients with receipt of CT or RT (HRs 0.77 and 0.81, respectively, $p < 0.05$). In patients with LNR > 15%, there was a significant benefit of RT (HR 0.76, $p = 0.007$) and borderline benefit of CT (HR 0.78, $p = 0.058$). Patients with cN2 disease with subsequent ypN0-1 and/or LNR < 15% following induction chemotherapy do not benefit from adjuvant therapy. Patients with persistent N2 disease and LNR > 15% who receive adjuvant CT and RT have improved survival. Aggressive consolidative therapy appears to improve survival in patients with persistent or high nodal burden disease.

1. Introduction

Multimodality therapy is the current standard of care for resectable stage III non-small cell lung cancer (NSCLC). Approximately 10% of all NSCLC cases present as stage IIIA-N2, and for these individuals, disease control and overall survival (OS) remain poor, with 5-year survival rates of 23% [1]. Based on randomized trials and a meta-analysis demonstrating improved OS with the addition of induction chemotherapy (CT) plus surgery versus surgery alone, induction chemotherapy is a reasonable option for resectable stage IIIA-N2 NSCLC [2,3]. Induction CT also appears to have similar efficacy to neoadjuvant chemoradiation (CRT) [4,5]. Nodal response after induction chemotherapy is an important prognostic factor. A study by the Swiss SAKK group led to the conclusion that patients with nodal downstaging from

* Corresponding author at: Department of Radiation Oncology, City of Hope National Cancer Center, 1500 E. Duarte Road, Duarte, CA, 91010, USA.
E-mail address: aamini@coh.org (A. Amini).

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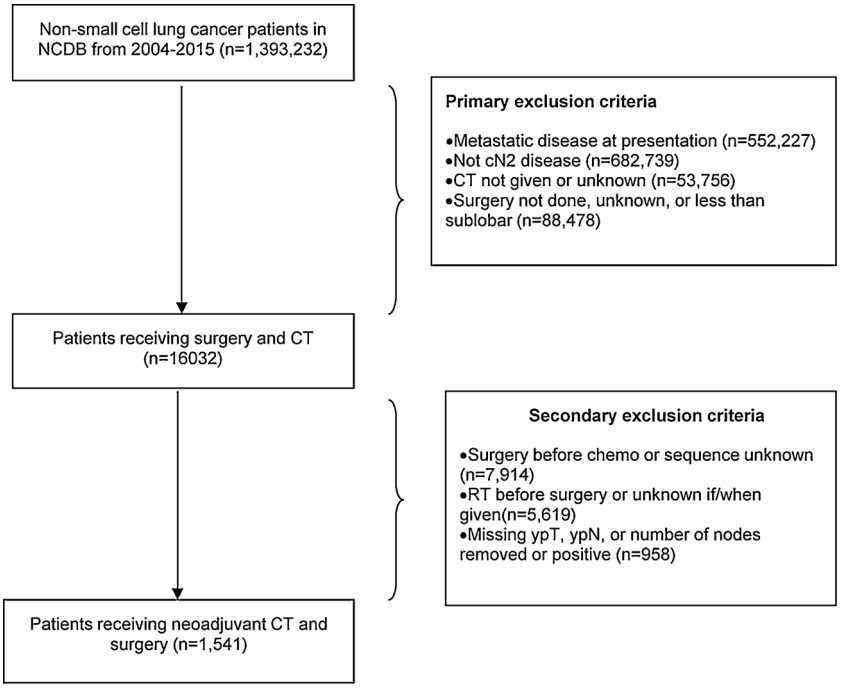

Fig. 1. Diagram illustrating exclusion criteria and case selection for patient cohort. Abbreviations: NCDB = National Cancer Data Base, cN2 = Clinical N2, CT = Chemotherapy, RT = Radiation Therapy, ypT = post-chemotherapy pathological tumor staging, ypN = post-chemotherapy pathological nodal staging.

N2 to N0-1 after induction CT had improved disease-free and OS in comparison to those with persistent N2 disease [6]. A follow-up publication demonstrated local relapse rates of 30% amongst all comers with initially N2 disease, with approximately 50% of patients receiving adjuvant RT, but did not provide details about effect of RT on oncologic outcomes [7].

The current National Comprehensive Cancer Network (NCCN) guidelines suggest induction CT, with or without radiation (RT), as an appropriate option for patients with resectable stage IIIA-N2 NSCLC [8]. However, optimal adjuvant therapy is not well defined in this patient population and often left to the discretion of the treating physicians. Previous retrospective studies showed that pathological downstaging and lymph node ratio (LNR) in this clinical scenario were prognostic [9–11]. We sought to determine the importance of consolidative CT and RT with respect to OS in patients with clinical N2 (cN2) disease who undergo induction CT followed by surgery. We hypothesized that LNR and nodal response to induction CT would predict OS and predict the need for more aggressive adjuvant therapy.

2. Materials and methods

2.1. Data source

The National Cancer Database (NCDB) is a national oncology database sponsored by the American College of Surgeons and the American Cancer Society. It includes patient data from over 1500 accredited facilities and captures over 70% of newly diagnosed cancer cases in the United States [12]. The data used in the study are derived from a de-identified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology used, or the conclusions drawn from these data by the investigators.

Using the NCDB, a total of 1,393,232 patients with NSCLC were identified. Patients were excluded if they had known metastatic disease or unknown metastatic status. Patients with clinical stage IIIA-N2 disease who underwent induction chemotherapy followed by surgery were included. Surgery was required to be an oncologic resection (sublobar resection, lobectomy, or pneumonectomy); biopsy and those coded as local destruction of tumor were excluded. Patients receiving RT prior to surgery were excluded. Patients receiving brachytherapy or forms of radiation besides external beam radiation were excluded. Patients were required to have complete clinical tumor (cT) and nodal (cN) staging, as well as post-surgical pathological tumor (ypT) and nodal (ypN) staging. Given limitations of the sample size, any values with discordant data were maintained within the analysis. Fig. 1 describes the process of creating the study population.

2.2. Variable definitions

All variables were selected a priori. Demographic variables including age, year of diagnosis, race/ethnicity, insurance status, Charlson comorbidity score, distance from facility, facility type, facility location, and median income were defined according to their respective data fields in the NCDB data dictionary [13]. Race was categorized as non-Hispanic White, non-Hispanic Black, Hispanic, or other. Facility regions were grouped into Northeast, South, Midwest, and West regions. Insurance status was grouped into government (Medicare/Medicaid/other), private, or uninsured. Comorbidity was defined as per the Charlson-Deyo Comorbidity score [14]. Distance from facility was grouped at $\leq$ 10 or > 10 miles straight-line distance. Income was coded based on census tract estimates and are not patient-specific.

For pathologic factors, histology was classified as adenocarcinoma, squamous, or other using International Classification of Diseases for Oncology, 3rd edition [ICD-O-3] codes [15]. Pathologic tumor (ypT) and nodal (ypN) stages were collected, along with margin status. Lymph node ratio (LNR) was defined as the number of lymph nodes positive divided by number of lymph nodes examined. The median LNR was 0.14, or 14%, amongst all patients. Accordingly, LNR was grouped into 3 subgroups for inclusion as a covariate: 1) 0% of examined lymph nodes involved (ypN0), 2) Between 1 and 15% of examined lymph nodes involved, 3) Greater than 15% of examined lymph nodes involved. For treatment factors, surgery was defined as: 1) lobectomy, including bilobectomy, 2) pneumonectomy, including extended and radical pneumonectomy, and 3) sublobar or otherwise unspecified

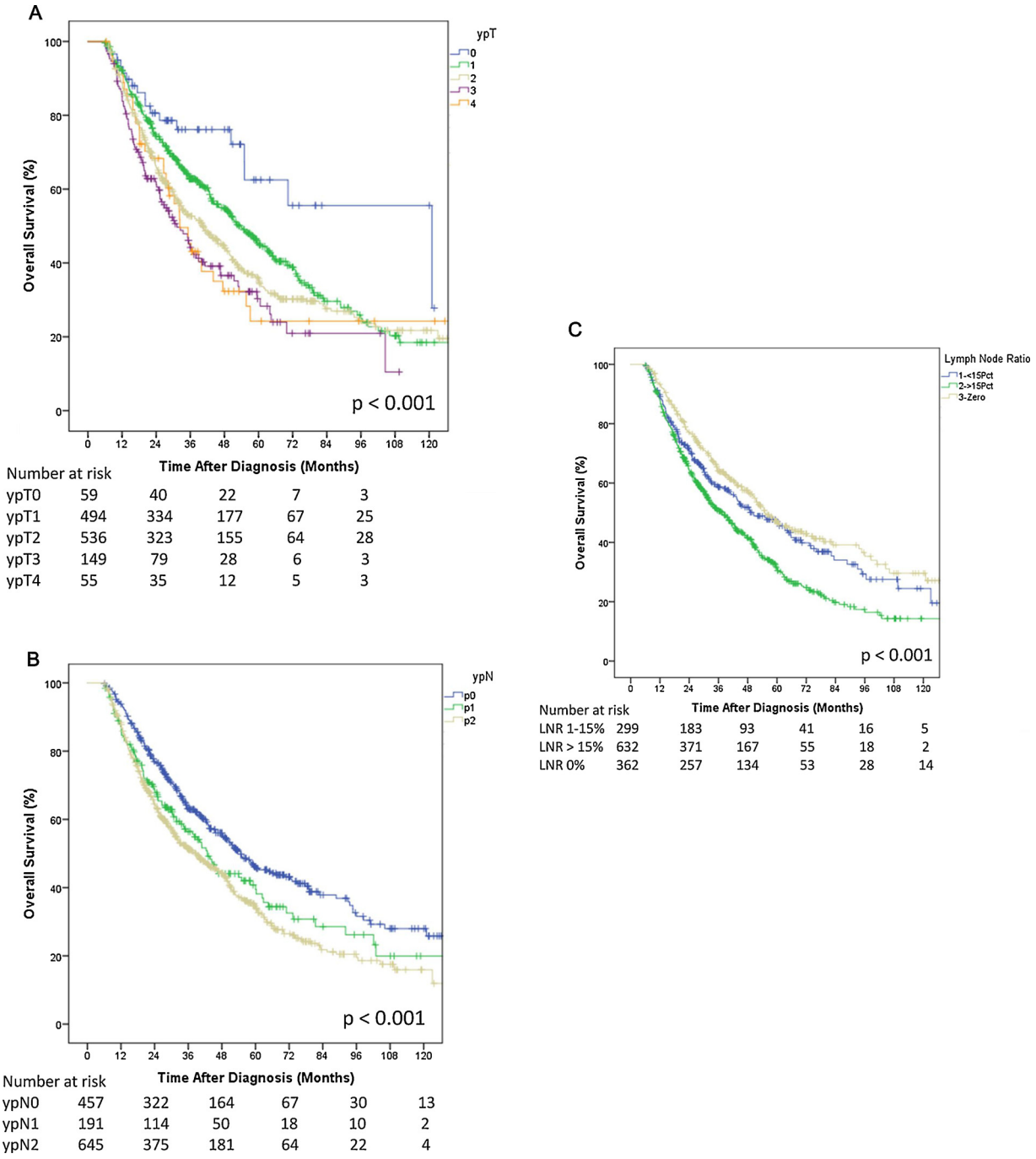

Fig. 2. Survival analysis in all patients based on **A)** ypT, **B)** ypN, and **C)** Lymph Node Ratio Abbreviations: ypT = post-chemotherapy pathological tumor staging, ypN = post-chemotherapy pathological nodal staging.

surgery. Receipt of RT was collected as a covariate. Information on receipt of adjuvant CT was obtained by those coded as receiving CT both prior to and after surgery. Patients with this variable not coded were defined as unknown receipt of adjuvant CT.

2.3. Statistical analysis

Survival analyses were performed using the log-rank test for univariate analysis (UVA) and Cox proportional hazards regression for multivariate analysis (MVA). Initial variable selection included all variables discussed previously. The final parsimonious multivariate Cox regression model was formed by using multivariate hierarchical backwards selection of variables at a significance level of $p < 0.10$. The proportional hazards assumption was assessed for all variables in the final multivariate analysis and was not violated [16]. To account for length of time required to complete all potentially planned therapy, all patients were required to have a minimum of 6 months of follow-up, to avoid immortal time bias. Planned subset analyses included stratification based on ypN stage and lymph node ratio. Stratification based on ypN was chosen as decisions for adjuvant CT and/or RT in patients not receiving neoadjuvant CT are primarily dependent on post-surgical pathological nodal status [8]. LNR was chosen as a planned subset analysis due to evidence of prognostic value of LNR in NSCLC, with or without neoadjuvant chemotherapy [11,17]. MVA was performed for the subset analyses by splitting the file by the stratification variable (either ypN or LNR), and reperforming multivariate hierarchial

Table 1
Multivariable Cox Proportional Hazard Models for Overall Survival in all patients.

Significant Factors	All Patients (n = 1541) n (%)	Hazard of death (95% Confidence)	P Value
Age (Median [IQR])	64 (57-70)	1.011 (1.001-1.020)	0.027
Race			
Non-Hispanic White	1282 (83.2)	Reference	
Black	127 (8.2)	0.92 (0.70-1.21)	0.55
Hispanic	57 (3.7)	1.19 (0.80-1.77)	0.38
Other/Unknown	75 (4.9)	0.59 (0.40-0.89)	0.012
Insurance Status			
Government	759 (49.3)	Reference	
Private	727 (47.2)	0.90 (0.76-1.08)	0.27
Uninsured	27 (1.8)	1.81 (1.05-3.11)	0.033
Unknown	28 (1.8)	0.65 (0.34-1.27)	0.21
Median Income (Residential Area)			
< $38,000	216 (14.0)	Reference	
$38,000-$47,999	323 (21.0)	0.99 (0.77-1.28)	0.97
$48,000-$62,999	381 (24.7)	1.11 (0.87-1.41)	0.41
≥ $63,000	597 (38.7)	0.97 (0.77-1.23)	0.79
Unknown	24 (1.6)	2.34 (1.33-4.12)	0.003
Pathological Factors			
Histology			
Adenocarcinoma	929 (60.3)	Reference	
Squamous	430 (27.9)	1.12 (0.94-1.33)	0.22
Other	182 (11.8)	1.32 (1.06-1.64)	0.013
ypT stage			
T0	70 (4.5)	Reference	
T1	592 (38.4)	1.71 (1.05-2.78)	0.03
T2	627 (40.7)	2.10 (1.30-3.42)	0.003
T3	192 (12.5)	2.61 (1.56-4.37)	< 0.001
T4	60 (3.9)	2.37 (1.32-4.24)	0.004
Margin			
Negative	1410 (91.5)	Reference	
Positive	109 (7.1)	1.52 (1.18-1.96)	0.001
Unknown	22 (1.4)	1.12 (0.64-1.96)	0.68
Lymph Node Ratio			
1-15 percent	370 (24.0)	Reference	
> 15 percent	760 (49.3)	1.35 (1.11-1.64)	0.002
Zero	411 (26.7)	0.82 (0.66-1.02)	0.074
Treatment Factors			
Received adjuvant EBRT			
No	991 (64.3)	Reference	
Yes	550 (35.7)	0.86 (0.73-1.01)	0.074

backwards selection of variables at a significance level of $p < 0.10$ as stated previously, with all variables included again, except for the stratification variable.

3. Results

3.1. Patient cohort

A total of 1541 patients were included (Fig. 1). Median follow-up for the entire cohort was 3.1 years and 4.2 years for survivors. Across all patients, 3-year OS was 56.4%. The percentage of all patients who received adjuvant CT and RT was 18.9% and 35.7% respectively (Table S1). For the 1384 patients with known adjuvant CT status, 292 (21.1%) received adjuvant CT. Additional demographic, pathologic and treatment baseline characteristics are summarized in Table S1. A median number of 12 lymph nodes were examined per patient (IQR 7-20). In total, 746 patients (48.4%) received no additional adjuvant therapy, while 134 (8.7%), 346 (22.4%), and 158 (10.3%) received CT alone, RT alone and CT + RT, respectively. In patients who had a LNR > 15%, 567 (74.6%) patients had ypN2 disease. Only 122 (16.1%) of patients with LNR > 15% had ypN1 disease. The remaining 71 (9.3%) patients with documented LNR > 15% did not specify the location of lymph node involvement, as the data was discordant for this subset, with these patients listed as ypN0. Only 208 patients with ypN2 disease had a LNR 1–15%.

3.2. Factors affecting survival in all patients

On UVA, post-chemotherapy and post-surgical staging for both ypT and ypN affected OS. In patients stratified by ypT, 3-year OS for patients with ypT0/T1/T2/T3/T4 disease was 76.1%/62.8%/52.7%/44.2%/45.3%, respectively ($p < 0.001$, Fig. 2A). When stratified by ypN, 3-year OS for patients with ypN0/N1/N2 disease was 63.1%/56.4%/51.3%, respectively ($p < 0.001$, Fig. 2B). When stratified by LNR, 3-year OS for patients with LNR 0%/1–15%/ > 15% was 64.1%/58.6%/50.7%, respectively ($p < 0.001$, Fig. 2C). Receipt of CT or RT was not associated with survival on Kaplan-Meier analysis across all patients.

On MVA, residual tumor at the primary (ypT ≥ 1) was associated with worse survival (HRs 1.71–2.61, $p < 0.03$ for all, Table 1). ypN was not significantly associated with survival. Other factors that predicted for worse survival included increasing age, uninsured status, other histology, positive margins, and LNR > 15% ($p < 0.05$, Table 1). Factors that predicted for improved survival included other race, which includes Asian patients (HR 0.59, $p = 0.012$). Receipt of CT and RT did not have a statistically significant effect on OS for all patients.

3.3. Role of adjuvant chemotherapy and/or radiation in patient subsets

The benefit of CT differed depending on patient ypN. In ypN0 patients, there were no significant differences in 3-year OS with CT compared to without (63.1% vs 62.0%; $p = 0.88$); ypN1 patients had a similar pattern with no significant difference in 3-year OS with or without CT (61.1% vs 57.5%; $p = 0.83$). However, in ypN2 patients, adjuvant CT improved survival (3-year OS 49.3% vs 58.3%, $p = 0.020$, Fig. 3A). When stratifying by LN ratio, patients with a LNR of 0% or 1–15% did not benefit from CT (3-year OS 63.4% vs 66.7%, $p = 0.86$ and 57.0% vs 58.0%, $p = 0.92$, respectively). In patients with LNR > 15%, CT improved OS (3-year OS 49.3% vs 58.6%, $p = 0.036$, Fig. 3B).

The addition of RT demonstrated a similar survival pattern to CT. On UVA, the addition of adjuvant RT demonstrated no significant OS benefit in ypN0 or ypN1 patients. Adjuvant RT was associated with improved OS in ypN2 patients (3-year OS 48.8% vs 53.5%, $p = 0.015$, Fig. 4A). When stratified by LNR, there was only a benefit in LNR > 15% patients (3-year OS 48.9% vs 52.6%, $p = 0.004$, Fig. 4B).

On MVA stratified by ypN status, adjuvant CT and RT did not affect OS for ypN0 or ypN1 patients (Table S2A, S2B). In ypN2 patients, adjuvant CT and RT both maintained significant benefits (HRs 0.77 and 0.81, respectively, $p < 0.05$, Table 2A). When stratified by LNR, there was no benefit of adjuvant CT or RT in patients with LNR < 15% (Table S2C). In patients with LNR > 15%, there was a significant benefit of adjuvant RT (HR 0.76, $p = 0.007$, Table 2B). Adjuvant chemotherapy reached borderline significance in regards to improving survival (HR 0.78, $p = 0.058$, Table 2B)

To determine whether both ypN2 and LNR > 15% were independent predictors, exploratory analyses were performed on the low numbers of ypN1/LNR > 15% and ypN2/LNR 1-15 % patients. In ypN1/LNR > 15% patients, UVA of CT and RT did not show significant differences in OS ($p = 0.21$ and 0.072, respectively). In ypN2/LNR 1-15 % patients, UVA of CT and RT did not show significant differences in OS ($p = 0.94$ and 0.64, respectively).

4. Discussion

Current adjuvant therapy recommendations are unclear in the NCCN guidelines for patients with cN2 disease receiving neoadjuvant CT followed by surgery. Our study demonstrates both persistent N2 disease and nodal ratio positivity were significant determinants of survival. On univariate analyses, we demonstrate an approximately

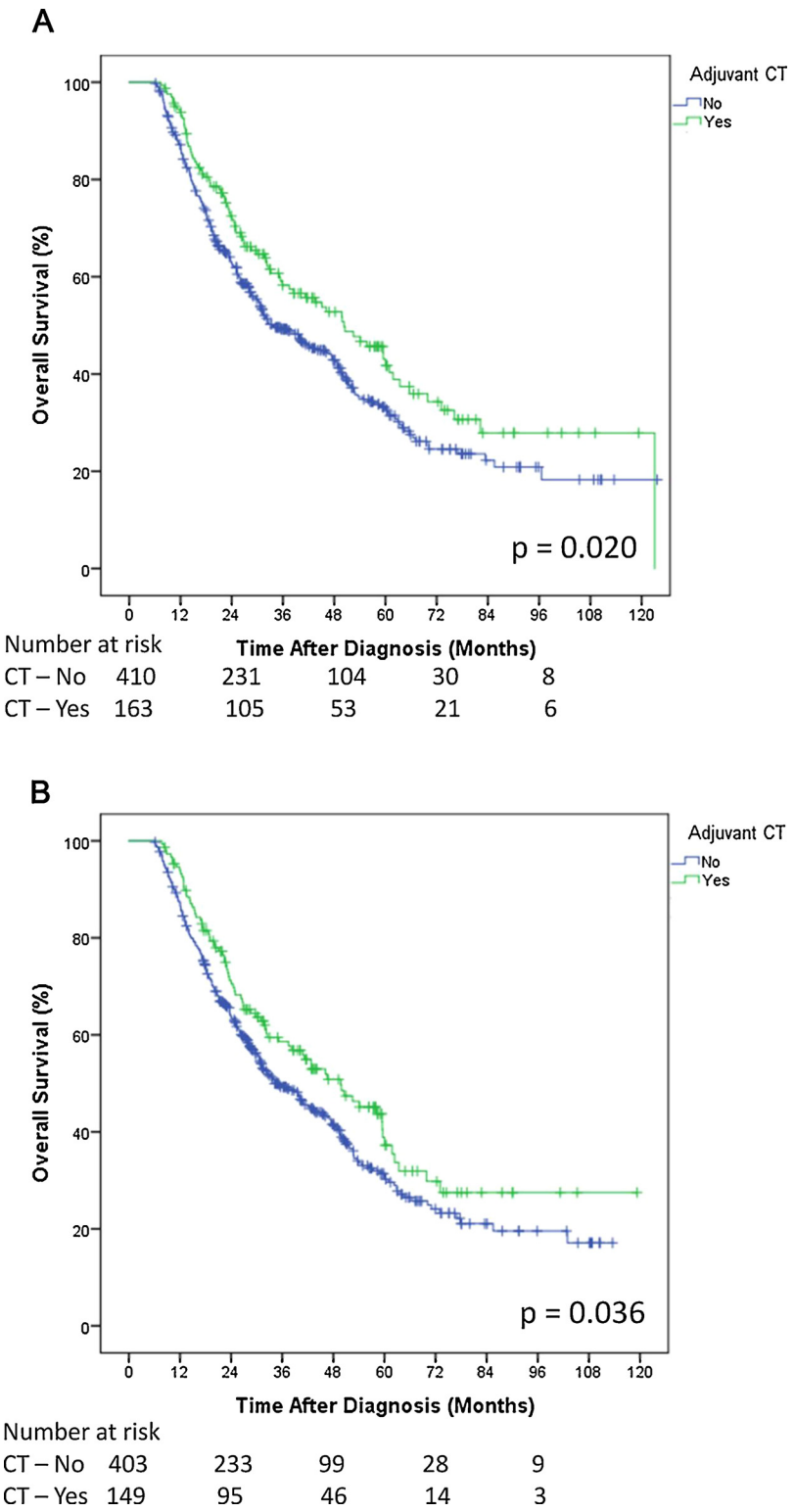

Fig. 3. Survival analysis based on receipt of adjuvant CT in patients with **A)** ypN2 disease and **B)** Lymph Node Ratio > 15%. Abbreviations: CT = Chemotherapy, ypN = post-chemotherapy pathological nodal staging.

10% absolute decrease in survival for every increase in ypT from ypT0 until ypT3. Similar results were seen when stratified by ypN, with a 10% relative decrease in survival for every increase in ypN. Higher LNR also negatively influenced survival with a cut-off of 15% in our cohort.

In ypN0 and ypN1 patients, there was no significant benefit to either adjuvant CT or RT in this patient cohort. Similarly, in patients with a LNR < 15%, there was no benefit of adjuvant CT or RT. However, in patients with ypN2 disease and a LNR > 15%, there appeared to be an approximately 20% relative benefit in OS on MVA with both CT and RT. Both ypN2 status and higher LNR following neoadjuvant chemotherapy are suggestive of more aggressive disease. While the NCDB does not record patterns of failure, one may speculate the survival benefit observed with adjuvant therapy for patients with persistent nodal disease or higher nodal ratio is due to RT and CT reducing risk of local and

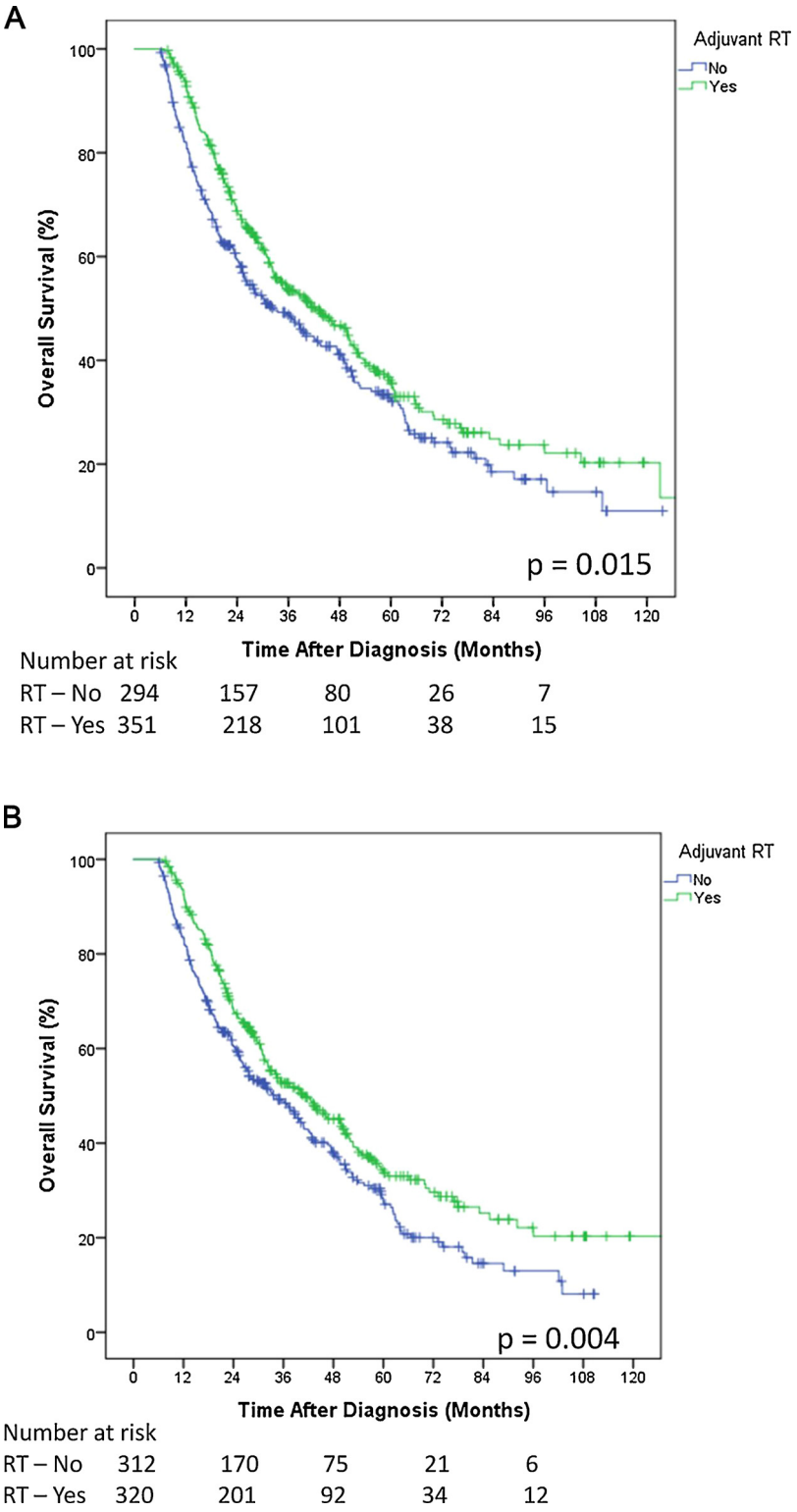

Fig. 4. Survival analysis based on receipt of adjuvant RT in patients with **A)** ypN2 disease and **B)** Lymph Node Ratio > 15%. Abbreviations: RT = Radiation Therapy, ypN = post-chemotherapy pathological nodal staging.

distant recurrence respectively, which contribute to overall survival as appreciated in smaller retrospective series [10].

Previous studies have shown the prognostic significance of pathologic treatment response in patients undergoing neoadjuvant CT [18–20]. LNR has also been shown to be prognostic in this clinical scenario [11,17]. On MVA in our study, for all patients, the primary drivers of outcome were pathological T downstaging, and lymph node ratio. While there is overlap between patients with LNR > 15% and those with ypN2 disease, LNR was prognostic on multivariate analysis while nodal clearance was not in our patient cohort. This suggests that residual LNR may be a more prognostic factor than nodal staging.

Haager et al used a LNR cut-off of 0.33 (> 33% involvement) in patients undergoing neoadjuvant CT, showing a difference in median OS of 39.3 vs 14.7 months [11]. In a patient population not receiving

Table 2
Multivariable Cox Proportional Hazard Models for Overall Survival in **A)** N2 patients, and **B)** Patients with LN ratio > 15.

A) N2

Significant Factors	All Patients (n = 785) n (%)	Hazard of death (95% Confidence)	P Value
Age (Median [IQR])	64 (57-70)	1.012 (1.001-1.023)	0.028
Pathological Factors			
Histology			
Adenocarcinoma	538 (68.5)	Reference	
Squamous	159 (20.3)	1.47 (1.16-1.87)	0.002
Other	88 (11.2)b	1.25 (0.93-1.69)	0.15
Lymph Node Ratio			
1-15 percent	208 (26.5)	Reference	
> 15 percent	567 (72.2)	1.40 (1.10-1.79)	0.006
Treatment Factors			
Received adjuvant EBRT			
No	371 (47.3)	Reference	
Yes	414 (52.7)	0.81 (0.66-0.995)	0.044
Received adjuvant CT			
No	518 (66.0)	Reference	
Yes	192 (24.5)	0.77 (0.60-0.99)	0.040
Unknown	75 (9.6)	1.25 (0.94-1.66)	0.12

B) LN Ratio > 15%

Significant Factors	All Patients (n = 760) n (%)	Hazard of death (95% Confidence)	P Value
Insurance Status			
Government	362 (47.6)	Reference	
Private	370 (48.7)	0.81 (0.66-0.996)	0.046
Uninsured	14 (1.8)	1.67 (0.81-3.46)	0.17
Unknown	14 (1.8)	0.87 (0.35-2.13)	0.76
Median Income (Residential Area)			
< $38,000	109 (14.3)	Reference	
$38,000-$47,999	146 (19.2)	1.05 (0.74-1.49)	0.80
$48,000-$62,999	183 (24.2)	1.31 (0.94-1.82)	0.11
≥ $63,000	311 (40.9)	1.1 (0.80-1.52)	0.54
Unknown	10 (1.3)	3.17 (1.49-6.76)	0.003
Pathological Factors			
Histology			
Adenocarcinoma	507 (66.7)	Reference	
Squamous	165 (21.7)	1.24 (0.97-1.60)	0.085
Other	88 (11.6)	1.40 (1.05-1.88)	0.024
ypT stage			
T0	23 (3.0)	Reference	
T1	272 (35.8)	2.28 (0.92-5.68)	0.075
T2	334 (43.9)	2.81 (1.13-6.97)	0.026
T3	101 (13.3)	2.74 (1.07-7.02)	0.036
T4	30 (3.9)	3.33 (1.23-9.02)	0.018
Treatment Factors			
Received adjuvant EBRT			
No	390 (51.3)	Reference	
Yes	370 (48.7)	0.76 (0.62-0.93)	0.007
Received adjuvant CT			
No	504 (66.3)	Reference	
Yes	173 (22.8)	0.78 (0.60-1.008)	0.058
Unknown	83 (10.9)	1.29 (0.98-1.69)	0.072

neoadjuvant CT, Chiappetta et al used a LNR cut-off of 40%. In an attempt to avoid overfitting the data, we decided to proceed with a cut-off near the median LNR of our group, at 15%. Currently, number of lymph nodes positive is an important aspect of staging in many cancers. Similarly, thoroughness of lymph node dissection, represented by number of lymph nodes examined, is critical in breast, colorectal, esophageal, and lung cancers [21–24]. LNR is a simplified way to combine both concepts into one evaluable variable and may be worth considering in future American Joint Committee on Cancer (AJCC) staging criteria for lung cancer.

Previous studies evaluating adjuvant therapy in this clinical scenario have been limited by sample size, retrospective nature, and variable results. Patients with ypN2 disease often are offered post-operative radiation therapy (PORT) based on data from the ANITA trial and additional retrospective series [9,11,25]. Our study justifies current practices of PORT in the ypN2 population. There are several series evaluating the role of adjuvant therapy in upfront N2 patients. In a retrospective study performed at MD Anderson, 179 patients with persistent ypN2 disease underwent PORT with or without adjuvant CT. In the 25% of patients who received adjuvant CT, mostly given concurrently with RT, there was both a distant failure and overall survival benefit [9]. A similar analysis in those who were pathologically downstaged to ypN0 or ypN1, who did not receive PORT, demonstrated that adjuvant CT did not improve distant failure or OS [10]. Our results are similar: only ypN2 patients appear to benefit from adjuvant CT. The primary benefit of adjuvant CT may be that these ypN2 are at highest risk for distant metastatic failure, and even if neoadjuvant CT did not result in complete pathologic clearance of the mediastinum, it may remain active at suppressing sites of distant metastatic failure.

Previously published research on the value PORT has been in patients undergoing upfront surgical resection, a different cohort than the current one, patients undergoing neoadjuvant chemotherapy. Published meta-analyses have shown that patients with pN0 or pN1 disease have a survival detriment with use of PORT, while the value was unclear in patients with pN2 disease [26,27]. More recently, results from the ANITA trial demonstrated that patients with pN1 disease who underwent chemotherapy should not receive PORT due to a survival detriment; however, all patients with pN2 disease and patients with pN1 disease not receiving chemotherapy demonstrated a survival benefit with addition of PORT [25]. Given that this was a post-hoc analysis of the ANITA trial, a currently ongoing trial, LungART, is randomizing patients undergoing upfront surgical resection who demonstrate pN2 disease to PORT versus observation (Clinicaltrials.gov # NCT00410683).

Our study is limited by the standard limitations of retrospective analysis and database studies, such as inclusion of only 70% of the population treated in CoC-accredited facilities and lack of smoking status as a variable of interest. We attempted to mitigate as much bias as possible by adjusting for potentially measured confounders and including all variables into our multivariable model. There is also potential for unmeasured confounders or missing data to introduce bias into the results. There is also an issue of some data discordance when evaluating multiple variables that specify similar data points in large databases; this was seen with 9% of patients with a calculated LNR of > 15% being coded as ypN0 disease. The total sample size was small compared to most NCDB studies, given our goal of having a dataset minimizing unknown variables, potentially resulting in insufficient power for evaluating benefit of CT and RT in small subset analyses. With this small sample size, propensity score matching or adjustment based on predictors of utilization of CT and/or RT would diminish statistical power further. Further, dose of RT is incomplete and often miscoded, and therefore was not incorporated in the study. CT agents and number of cycles given are not recorded in the NCDB. There could be confounding, as patients who received 3–4 cycles of CT pre-operatively may be less likely to receive adjuvant CT, as compared to patients who received only 1–2 cycles pre-operatively. Lastly, the NCDB does not contain data on cause-specific survival and thus only overall survival can be evaluated.

In the absence of randomized data, clinicians may want to consider observation for patients with either ypN0 or N1 disease, or LNR < 15%. However, in patients with both ypN2 disease and a LNR > 15%, consideration of adjuvant CT and RT should be given based on the results of this patient cohort, in order to reduce the higher risks for local and distant recurrence which impact OS. These results are primarily hypothesis generating, and future trials are necessary to determine optimal adjuvant therapy combinations including the incorporation of more modern targeted agents in addition to immunotherapy.

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Disclosures

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2019.05.020.

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