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Pathologic nodal clearance and complete response following neoadjuvant chemoradiation for clinical N2 non-small cell lung cancer: Predictors and long-term outcomes

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ABSTRACT

Purpose: From prospective studies, pathologic nodal clearance (PNC, ypN0) and pathologic complete response (pCR, ypT0N0) correlate with overall survival (OS) following neoadjuvant chemoradiation for cN2 non-small cell lung cancer (NSCLC). Contemporary cooperative group trials attempt to increase radiation doses to achieve nodal clearance and/or pCR. However, long-term comparative outcomes of dose-escalated neoadjuvant chemoradiation are lacking. The goal of this study was to evaluate rates of PNC and pCR in a large population of cN2 NSCLC, predictors thereof, and long-term outcomes thereafter.

Methods: The National Cancer Database was queried (2004–2015) for histologically-confirmed cT1-4N2M0 NSCLC undergoing neoadjuvant chemoradiation followed by lobectomy. Statistics included multivariable logistic regression, Kaplan-Meier OS analysis before and following propensity matching, Cox proportional hazards modeling, and sensitivity analysis when varying neoadjuvant radiation dose.

Results: Of 1750 patients, the pCR and PNC rates were 17% and 37%, respectively. Radiation dose > 54 Gy independently predicted for pCR. Patients achieving pCR experienced significantly higher OS than non-pCR cases ($p < 0.001$) and ypT + ypN0 cases ($p < 0.001$). In the subset of non-PNC patients, there was a trend towards higher OS in patients in whom ypT0 was achieved ($p = 0.059$). On sensitivity analysis, when separating the cohort into doses of 45.0–50.4 Gy, 50.5–54.0 Gy, 54.1–59.4 Gy, and > 59.4 Gy, 30-day mortality rates in the respective groups were 2.9%, 1.8%, 1.2%, and 3.4%.

Conclusions: Although neoadjuvant dose-escalation increases pCR rates, there is no OS benefit with dose-escalation, and high dose-escalation (i.e., > 59.4 Gy) was associated with numerically higher mortality rates, indicating the importance of careful multidisciplinary discussion.

1. Introduction

Non-small cell lung cancer (NSCLC) commonly presents as locally advanced disease, which may be managed using several different paradigms. One such approach involves trimodality therapy, consisting of neoadjuvant chemoradiotherapy (CRT) followed by resection and nodal dissection [1]. This paradigm was tested in a number of prospective trials, including the phase III Intergroup 0139 trial [2]. In that trial, consisting of cT1-3N2 disease, pathologic nodal clearance (PNC, ypN0) predicted a significantly higher survival. Those findings validated multiple prior studies [3–6], and importantly, indicated that local control may exert an effect on survival. Moreover, pCR as well as PNC following induction chemotherapy alone has also been demonstrated to be associated with improved overall survival (OS) and event free survival [7].

Following induction chemoradiation, PNC is estimated to occur in 20–50% of patients [2–6], and pathologic complete response (pCR) rates vary from 8%–48% [2,8–13]. There are several factors that may influence PNC and pCR; one modifiable parameter is radiotherapy (RT) dose, which the National Comprehensive Cancer Network (NCCN) recommends in the range of 45–54 Gy for the neoadjuvant setting [1]. This recommendation is based on a study that demonstrated that patients receiving 45–54 Gy neoadjuvantly has superior OS when compared to patients receiving a dose either < 45 Gy or > 54 Gy [14]. In efforts to increase local control and promote both nodal sterilization and pCR, dose-escalation in the neoadjuvant setting has been explored.

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A study of 19 consecutive patients receiving a median of 61.8 Gy (all but three of which received concurrent chemotherapy) demonstrated a pCR rate of 42% [8]. Moreover, of the 12 initially cN2 patients, 10 (83%) developed PNC. Four (21%) patients had postoperative complications, the mean length of postoperative hospitalization was 8 days, and no perioperative mortality occurred.

These encouraging results led to the construction of the phase II Radiation Therapy Oncology Group (RTOG) 0229 trial, whose primary endpoint was to measure PNC and pCR rates [9]. Analysis at 24.4 months (median) showed a 63% rate of PNC, which met the primary endpoint. For all patients, the median OS was 27 months; 2-year OS was 75% for patients with no residual mediastinal nodal disease, as compared to 52% with residual disease ($p = 0.002$). Of 57 analyzed patients, there were 16 instances of pulmonary complications (all grades 1–3).

In the absence of long-term results from this trial or comparative data from large retrospective studies, long-term outcomes of dose-escalated neoadjuvant CRT are lacking. The goal of this study was to evaluate rates of OS for patients with N2 NSCLC undergoing neoadjuvant CRT when stratifying by RT dose, as well as PNC and pCR rates and their impact on long term OS.

2. Materials & methods

The NCDB is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society, which consists of de-identified information regarding tumor characteristics, patient demographics, and survival for approximately 70% of the US population [15]. All pertinent cases are reported regularly from CoC-accredited centers and compiled into a unified dataset, which is then validated. The NCDB contains information not included in the Surveillance, Epidemiology, and End Results (SEER) database, including details on radiation dose. The data used in the study were derived from a de-identified NCDB file (2004–2015). The American College of Surgeons and the CoC have not verified and are neither responsible for the analytic or statistical methodology employed nor the conclusions drawn from these data by the investigators. As all patient information in the NCDB database is de-identified, this study was exempt from institutional review board evaluation.

Inclusion criteria for this study were people age $\geq$ 18 with newly-diagnosed, histologically confirmed cT1-4 cN2 cM0 NSCLC treated with neoadjuvant CRT followed by lobectomy. The stage-based criteria mirrored those of RTOG 0229; however, cN3 patients were not evaluated herein owing to the virtual lack of representation in RTOG 0229 [9], and cT4 patients were allowed given that it does not equate with unresectable disease [1]. RT referred to a minimum dose of 45 Gy per NCCN recommendations [1]. Receipt of pneumonectomy also constituted exclusion, based on the findings of Intergroup 0139 [2]. Patients were also excluded if there was incomplete information on pathologic stage and/or vital status. In accordance with the variables in NCDB files, information collected on each patient broadly included demographic, clinical, and treatment data.

All statistical tests were two-sided, with a threshold of $p < 0.05$ for statistical significance, and were performed using STATA (version 14, College Station, TX). Multivariable logistic regression modeling determined characteristics associated with development of pCR. Survival analysis was performed per the Kaplan-Meier method, and groups were compared with the log-rank test. OS referred to the interval between the date of diagnosis and the date of death, or censored at last contact. Univariate analysis determined factors associated with overall survival; subsequently, Cox multivariate analysis was performed and included variables that were either significant or showed a strong trend to statistical significance on univariate analysis. The proportional hazards assumption was checked graphically using log-log plots.

To account for indication bias, propensity score matching was used to compare patients between groups. Propensity matching is a method

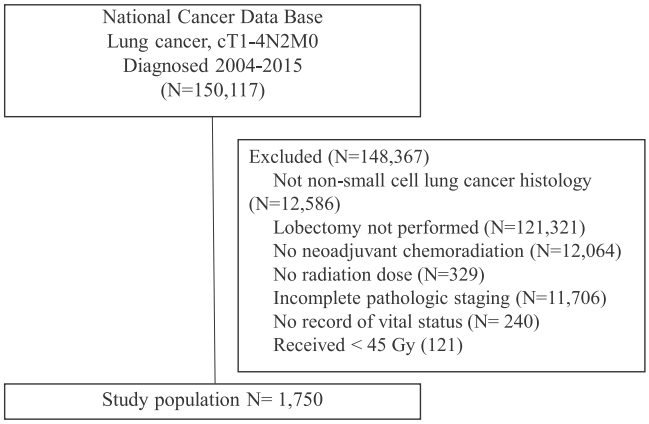

Fig. 1. Patient selection diagram.

that creates quasicase/control pairs using a retrospective cohort in an effort to account for the recorded and unrecorded confounding variables [16–18]. Propensity scores were calculated by use of a multivariable logistic regression model with the dependent variable being OS and the independent variables being those that were statistically significant for correlation with OS on multivariate analysis. Patients were matched 1:1 without replacement to avoid potential bias from many-to-one matching. Standardized differences were assessed in order to ensure balance between each of the variables included in calculating the propensity score of the matched cohorts with a value < 0.1 signifying an inconsequential imbalance [19]. Pearson's $\chi 2$ test was subsequently performed between the matched cohorts to confirm balance amongst the variable. Survival rates were then compared between the matched groups with the log-rank test.

3. Results

A complete flow diagram of patient selection is provided in Fig. 1. In total, 1750 patients met study criteria (Table 1). Of these, 289 (17%) achieved pCR and 1461 (83%) did not. Of note, the overall PNC rate was 37% (642/1750 patients).

Multivariable logistic regression analysis (Table 1) revealed several predictors of pCR. These included younger age (< 65 vs. 65–74), African-American race, Charlson-Deyo score of 1 (vs. 0), and non-adenocarcinoma histologies ($p < 0.05$ for all). Of note, when utilizing RT dose as a binary cutoff based on the upper limit recommended by the NCCN (54 Gy), higher doses were significantly associated with higher pCR rates ($p = 0.001$).

Median follow-up was 56.0 months (interquartile range, 36.7–79.2 months). Median OS for the pCR cohort was 72.2 months, versus 39.6 months for those without a pCR ($p < 0.001$, Fig. 2A); these findings persisted following propensity matching ($p < 0.001$, Fig. 2B).

To further evaluate the effect of primary versus nodal downstaging, subgroup analyses were performed. First, the singular effect of primary tumor clearance was examined, regardless of nodal sterilization, demonstrating a strong trend towards higher OS in patients with ypT0 ypN + disease, as compared to ypT + ypN+ ($p = 0.059$, Fig. 2C). Next, patients with nodal clearance only (ypT + ypN0) were compared to lack thereof (ypT + ypN+); regardless of primary tumor status, ypN0 cases experienced higher OS ($p < 0.001$, Fig. 2D). Finally, patients with nodal clearance were subdivided into those with additional primary tumor clearance (pCR) versus nodal clearance only (ypT + ypN0), and OS differences between groups revealed superior OS for the pCR group ($p < 0.001$, Fig. 2E).

To further delve into the degree of nodal and primary downstaging, OS analysis was performed between (initially cN2) patients that remained ypN2, versus those that were downstaged to ypN1 and ypN0 (Fig. 3A). Although OS was similar between ypN2 and ypN1 disease

Table 1
Demographics and multivariable logistic regression analysis for factors predictive of pathologic complete response.

Parameter	No pCR (N = 1461)	pCR (N = 289)	Multivariable Logistic Regression	
			OR (95% CI)	*p*-value
Radiation dose				
≤ 54 Gy	953 (65.2%)	154 (53.3%)	1 (reference)	
> 54 Gy	508 (34.8%)	135 (46.7%)	1.575 (1.193-2.080)	0.001
Age				
< 65	867 (59.3%)	199 (68.9%)	1 (reference)	
65-74	490 (33.5%)	72 (24.9%)	0.534 (0.347-0.820)	0.004
> 74	104 (7.1%)	18 (6.2%)	0.591 (0.311-1.123)	0.108
Sex				
Male	697 (47.7%)	161 (55.7%)	1 (reference)	
Female	764 (52.3%)	128 (44.3%)	0.905 (0.684-1.197)	0.483
Race				
White	1296 (88.7%)	242 (83.7%)	1 (reference)	
African American	120 (8.2%)	38 (13.2%)	1.566 (1.008-2.434)	0.046
Other	45 (3.1%)	9 (3.1%)	1.178 (0.529-2.625)	0.688
Charlson/ Deyo score				
0	971 (66.5%)	178 (61.6%)	1 (reference)	
1	372 (25.5%)	87 (30.1%)	1.532 (1.135-2.067)	0.005
> 2	118 (8.1%)	24 (8.3%)	0.681 (0.394-1.180)	0.171
Insurance				
Medicaid	101 (6.9%)	27 (9.3%)	1 (reference)	
Private	710 (48.6%)	146 (50.5%)	0.919 (0.554-1.524)	0.744
Medicare	583 (39.9%)	100 (34.6%)	1.045 (0.573-1.907)	0.886
Not recorded/ Other	67 (4.6%)	16 (5.5%)	1.079 (0.511-2.281)	0.842
Income				
< $46,000	758 (51.9%)	171 (59.2%)	1 (reference)	
≥ $46,000	648 (44.4%)	110 (38.1%)	0.789 (0.592-1.052)	0.106
Not recorded	55 (3.8%)	8 (2.8%)	0.752 (0.336-1.683)	0.487
Facility				
Academic	566 (38.7%)	129 (44.6%)	1 (reference)	
Non academic	895 (61.3%)	159 (55.0%)	0.838 (0.635-1.106)	0.211
Not recorded	0 (0.0%)	1 (0.4%)	–	–
Histology				
Adenocarcinoma	847 (58.0%)	91 (31.5%)	1 (reference)	
Squamous cell carcinoma	401 (27.5%)	139 (48.1%)	3.693 (2.678-5.092)	< 0.001
NSCLC Other/ NOS	213 (14.6%)	59 (20.4%)	2.445 (1.661-3.597)	< 0.001
Tumor grade				
Well differentiated	51 (3.5%)	6 (2.1%)	1 (reference)	
Moderately differentiated	344 (23.6%)	37 (12.8%)	0.843 (0.326-2.176)	0.724
Poorly differentiated/ anaplastic	687 (47.0%)	101 (35.0%)	1.102 (0.444-2.739)	0.834
Not recorded	379 (25.9%)	145 (50.2%)	2.964 (1.199-7.330)	0.019
Clinical T stage				
T1	396 (27.1%)	65 (22.5%)	1 (reference)	
T2	656 (44.9%)	117 (40.5%)	1.003 (0.702-1.431)	0.989
T3	275 (18.8%)	76 (26.3%)	1.471 (0.989-2.187)	0.056
T4	134 (9.2%)	31 (10.7%)	0.982 (0.585-1.646)	0.944
Lymph nodes examined				
< 10	608 (41.6%)	108 (37.4%)	1 (reference)	
≥ 10	544 (37.2%)	111 (38.4%)	1.228 (0.900-1.675)	0.195
Not recorded	309 (21.2%)	70 (24.2%)	1.067 (0.745-1.529)	0.724

($p = 0.380$), the former was associated with inferior OS as compared to ypN0 cases ($p < 0.001$). Evaluation of primary tumor response was performed by means of evaluating the number of T stages downstaged (0, 1, or 2+, denoted by the term *a*–*b* in patients with cT*a* disease and ypT*b* disease) (Fig. 3B). This analysis demonstrated no statistical differences in OS when comparing no T downstaging to 1 ($p = 0.974$) or 2+ ($p = 0.503$) levels of T downstaging.

Sensitivity analysis was then performed by substratifying patients into more granular cohorts based on neoadjuvant RT dose and evaluating rates of PNC, pCR, and postoperative outcomes (Table 2). Patients receiving 45.0–50.4 Gy demonstrated a nodal clearance and pCR rate of 50.1% and 13.1%, respectively. Statistical comparisons between corresponding values for patients having received 50.5–54.0 Gy were 57.0% and 21.9%, along with 48.2% and 11.8% for the 54.1–59.4 Gy cohort and 58.7% and 22.5% for the > 59.4 Gy cohort. Analysis of 30- and 90-day mortality revealed that, with reference to the 45–50.4 Gy subset, the two higher-dose groups (50.5–54.0 Gy and 54.1–59.4 Gy) experienced decreased postoperative mortality. As compared to these two groups, the highest-dose group (> 59 Gy) experienced increased 30- and 90-day postoperative mortality. OS analysis between the four subcohorts showed no statistically significant differences (Fig. 3C).

In the overall cohort, there were several predictors of OS on Cox multivariate analysis (Table 3). These included advancing age, male gender, and greater comorbidities ($p < 0.05$ for all). Of note, although RT dose was not related to OS, pCR was a strong factor associated with OS ($p < 0.001$).

4. Discussion

Increasing RT dose as a means to improve PNC and pCR rates is an area of ongoing investigation but without long-term comparative data. This novel study of a contemporary national database, the largest of its kind to date, demonstrates several notable findings. Higher RT doses did not independently influence OS. However, when a binary cut-off at

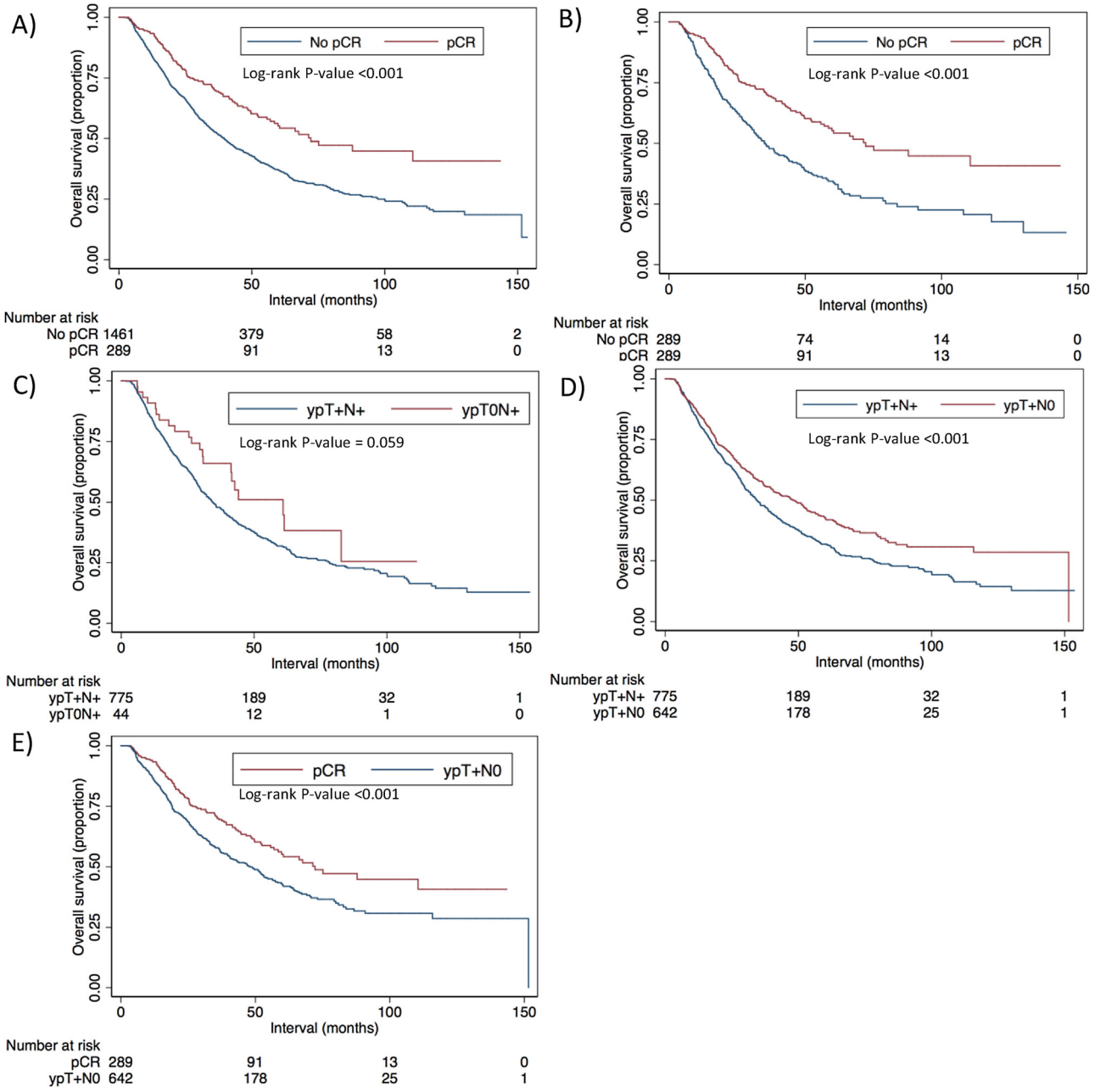

Fig. 2. Kaplan-Meier curves comparing overall survival for A) patients having achieved pathologic complete response versus lack thereof, B) the aforementioned comparison in propensity matched cohorts, C) ypT0N + vs. ypT + N+ patients, D) ypT + N0 vs ypT + N+ patients, E) ypT + N0 vs ypT0N0 patients.

54 Gy was used, higher neoadjuvant RT doses were associated with higher pCR rates, and pCR was associated with higher OS. The results also imply that, although nodal clearance is more associated with OS, clearance of the primary tumor may be important (even in the context of nodal sterilization). Lastly, postoperative mortality was not increased with moderate increases in RT dose, but higher degrees of dose-escalation (i.e., > 59 Gy) did display numerically higher postoperative mortality.

When taking neoadjuvant dose into account, the overall rates of PNC and pCR herein are comparable to existing data [2–13]. Of note, the dose-escalated patients' rates were similar to the 63% PNC in RTOG 0229, but numerically higher than the 8% pCR in that trial [9]. Additionally, it is important to note that one series [10] showed an association between PNC (but not pCR) and OS. Although that may be contradictory to these data (showing the association between pCR and OS), the correlation between PNC and pCR likely results in some level of congruity.

Subgroup evaluation also brings forth several salient conclusions. Based on these data, PNC seems to be more "important" to OS than primary tumor clearance. This concept is similar to the paradigm of response following neoadjuvant chemotherapy in breast cancer [20]. However, there could be a benefit to additional sterilization of primary tumor disease. In this study, patients with pCR were associated with higher OS than those patients with nodal clearance only, and there was also a trend towards higher OS in patients with primary tumor clearance in the absence of nodal clearance. To that end, further studies must be conducted, with the caveat that primary tumor sterilization occurs less often, given the sheer bulkiness of primary disease in many cases.

The findings on sensitivity analysis with relation to response rates and postoperative outcomes were also noteworthy. It is unclear why mortality rates were higher in the 45–50.4 Gy cohort than the

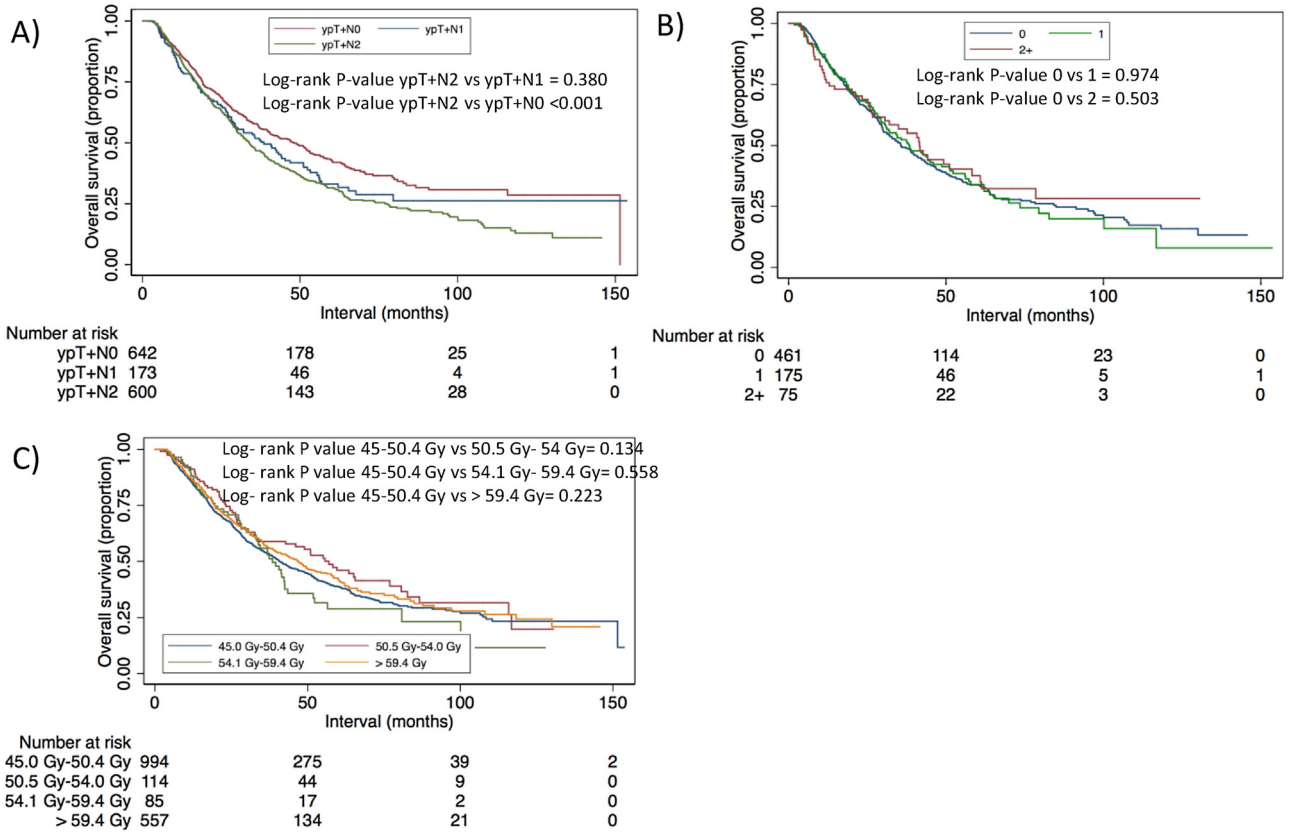

Fig. 3. Kaplan-Meier overall survival based on A) degree of nodal downstaging, B) degree of primary tumor downstaging, C) neoadjuvant radiotherapy dose.

50.5–54 Gy and 54.1–59.4 Gy cohorts, although explanations include the smaller sample sizes in the latter, as well as differences in facility volume and/or surgical techniques. Nevertheless, there was a numeric increase in 30- and 90-day mortality when comparing the groups receiving either 50.5–54.1 Gy or 54.1–59.4 Gy to those receving > 59.4 Gy groups, indicating that high dose escalation should be performed with caution and based on patient tolerance as well as careful multidisciplinary discussion. Additionally, it is unclear why despite the higher rates of pCR and PNC with neoadjuvant dose escalation, no improvement in OS was observed with the increased dose. One possible explanation of this is that any clinical improvement with the greater response to higher dose was precluded by the worse 30- and 90- day mortality observed amongst patients receiving higher neoadjuvant RT doses. Of note, it is unclear what the causes of postoperative mortality were, because the NCDB does nor record specific types of complications or causes of death.

There are several strategies that may be utilized going forward to increase PNC and pCR rates. These include dose escalation by means of more safer techniques, such as proton beam therapy (PBT). PBT-mediated dose-escalation in the definitive setting has been prospectively tested [21], with encouraging findings despite the detriment in survival from RTOG 0617 [22]. Because PBT offers a method to safely dose-escalate, a concept that was almost certainly not performed safely with three-dimensional conformal RT in RTOG 0617, the concept of safe dose-escalation remains an unresolved notion. Second, focal dose-escalation in the definitive setting has also been evaluated prospectively by means of stereotactic RT in multiple studies [23,24]; this concept could be applied to the neoadjuvant setting in the future. Third, the RTOG 1106 study is evaluating positron emission tomography to guide adaptive dose-escalated RT to areas that persist in fluorodeoxyglucose avidity following initial RT [25]. This concept could also be applied to novel indicators of aggressive tumor biology at risk of

Table 2
Sensitivity analysis of radiation dose and influence on nodal clearance rate, pathologic complete response, and postoperative outcomes.

	45-50.4 Gy n = 994 (%)	50.5- 54 Gy n = 114 (%)	54.1- 59.4 Gy n = 85 (%)	> 59.4 Gy n = 557 (%)	P value
Pathologic complete response					
No	864 (86.9%)	89 (78.1%)	75 (88.2%)	433 (77.7%)	< 0.001
Yes	130 (13.1%)	25 (21.9%)	10 (11.8%)	124 (22.3%)	
Complete nodal clearance					
No	496 (49.9%)	49 (43.0%)	44 (51.8%)	230 (41.3%)	< 0.001
Yes	498 (50.1%)	65 (57.0%)	41 (48.2%)	327 (58.7%)	
30- day postoperative mortality					
Dead	29 (2.9%)	2 (1.8%)	1 (1.2%)	19 (3.4%)	< 0.001
Alive	963 (96.9%)	110 (96.5%)	83 (97.7%)	520 (93.4%)	
Not reported	2 (0.2%)	2 (1.8%)	1 (1.2%)	18 (3.2%)	
90- day posoperative mortality					
Dead	71 (7.1%)	2 (1.8%)	3 (3.5%)	36 (6.5%)	< 0.001
Alive	921 (92.7%)	108 (94.7%)	81 (95.3%)	503 (90.3%)	
Not reported	2 (0.2%)	2 (1.8%)	1 (1.2%)	18 (3.2%)	

Table 3
Univariate and multivariate analysis for factors predictive of overall survival.

	Univariate analysis			Multivariate analysis		
Characteristic	Hazard ratio	95% Confidence interval	P value	Hazard ratio	95% Confidence interval	P value
Pathologic complete response						
Yes	**1 (reference)**			**1 (reference)**		
No	**1.745**	**1.431-2.128**	**< 0.001**	**1.739**	**1.424-2.125**	**< 0.001**
Radiation dose						
≤ 54 Gy	1 (reference)			–	–	–
> 54 Gy	0.953	0.835-1.088	0.476	–	–	–
Age						
< 65	**1 (reference)**			**1 (reference)**		
65-74	**1.399**	**1.222-1.602**	**< 0.001**	**1.273**	**1.045-1.550**	**0.016**
> 74	**1.618**	**1.284-2.038**	**< 0.001**	**1.538**	**1.162-2.035**	**0.003**
Sex						
Male	**1 (reference)**			**1 (reference)**		
Female	**0.778**	**0.686-0.883**	**< 0.001**	**0.777**	**0.684-0.884**	**< 0.001**
Race						
White	1 (reference)			–	–	–
African American	0.862	0.683-1.089	0.213	–	–	–
Other	1.034	0718-1.488	0.859	–	–	–
Charlson/ Deyo score						
0	**1 (reference)**			**1 (reference)**		
1	**1.069**	**0.924-1.238**	**0.369**	**1.083**	**0.934-1.256**	**0.292**
≥ 2	**1.412**	**1.137-1.754**	**0.002**	**1.323**	**1.063-1.653**	**0.012**
Insurance						
Medicaid	**1 (reference)**			**1 (reference)**		
Private	**1.093**	**0.835-1.431**	**0.518**	**1.054**	**0.804-1.382**	**0.705**
Medicare	**1.470**	**1.122-1.927**	**0.005**	**1.131**	**0828-1.545**	**0.438**
Not recorded/ Other	**1.149**	**0.75-1.705**	**0.489**	**1.046**	**0.703-1.557**	**0.824**
Income						
< $46,000	1 (reference)			–	–	–
≥ $46,000	0.944	0.830-1.074	0.383	–	–	–
Not recorded	1.122	0.807-1.449	0.495	–	–	–
Facility						
Academic	1 (reference)			–	–	–
Non academic	1.098	0.965-1.250	0.154	–	–	–
Histology						
Adenocarcinoma	1 (reference)			–	–	–
Squamous cell carcinoma	1.081	0.937-1.248	0.285	–	–	–
NSCLC Other/ NOS	1.049	0.881-1.248	0.590	–	–	–
Tumor grade						
Well differentiated	1 (reference)			–	–	–
Moderately differentiated	1.226	0.843-1.782	0.287	–	–	–
Poorly differentiated/ anaplastic	1.102	0.766-1.585	0.602	–	–	–
Not recorded	0.827	0.569-1.201	0.318	–	–	–
Clinical T stage						
T1	1 (reference)			–	–	–
T2	1.085	0.928-1.270	0.307	–	–	–
T3	1.080	0.893-1.305	0.428	–	–	–
T4	1.190	0.942-1.504	0.145	–	–	–
Lymph nodes examined						
< 10	1 (reference)			–	–	–
≥ 10	0.879	0.762-1.014	0.077	–	–	–
Not recorded	0.953	0.808-1.123	0.565	–	–	–

requiring dose-escalation, such as radiomic parameters [26,27]. Finally, there are several biologic factors that may have an impact on the response of the tumor to therapy. NSCLC with EGFR mutations present may have greater sensitivity to tyrosine kinase inhibitors (TKIs), though this has not been demonstrated to have an impact in the neoadjuvant setting [28]. It is possible that use of TKIs in the neoadjuvant setting along with CRT may further improve pCR rates in patients with EGFR mutated NSCLC. Additionally, SNPs and many candidate miRNAs have been identified that may be associated with radio- and/or chemosensitivity [29], and there is a prospective trial in Europe that is seeking to create a predictive molecular signature for response of NSCLC to chemotherapy (NCT00864266).

Many of the strategies above imply the critical need to optimally select which patients optimally benefit from dose-escalation in the neoadjuvant setting. Indeed, it is important to balance potential toxicities with oncologic benefit and recognize that many patients will not profit from measures to promote pCR or PNC. Moreover, the concept of neoadjuvant dose-escalation for purposes of nodal clearance and/or pCR must continue to be questioned. For instance, it will be essential to critically evaluate whether the proportion of cases that achieve pCR are simply the result of “favorable biology” and were thus predisposed towards better outcomes even in the absence of dose-escalation. In other words, there are likely unknown biological factors in various NSCLCs that result in differential response to chemotherapy/CRT; because genomic analysis has not elucidated these factors thus far, it may be appropriate to surmise how to select the “biologically proper” cases for more aggressive management. Moreover, it is important to note that while higher neoadjuvant radiation were associated with a higher pCR rate, higher radiation doses were not associated with an improvement in OS. It is possible that there is a biological explanation that links pCR and OS, and that the greater OS observed in patients with pCR is due to tumor biology that is sensitive to therapy. Therefore, the patients who

are found to have pCR with conventional radiation doses may have more biologically sensitive disease at both the primary site and at subclinical micrometastatic disease present at the time of diagnosis. The micrometastatic disease may be eradicated by systemic chemotherapy, leading to the observed OS benefit in patients with a pCR. Furthermore, it should be emphasized that OS is the gold standard for evaluating the efficacy of a new treatment paradigm. While the present results do show a greater pCR rate with higher neoadjuvant radiation therapy doses, no improvement in OS was observed, highlighting that further research is required before determining the optimal neoadjuvant radiation dose.

Additionally, it should be noted that trimodality treatment treatment is one of multiple appropriate management options for locally advanced NSCLC. Induction chemotherapy followed by surgery has also been demonstrated to be an effective management option for this cohort of patients. In a multi-center, international trial by Pless et al. no benefit was found with the addition of induction radiation therapy to induction chemotherapy for patients with Stage IIIA/N2 NSCLC [30]. Importantly, while the pCR rate was low (3% in the induction CRT arm vs. 0% in the induction chemotherapy arm), the rate of nodal downstaging (defined as N2- > N1 or N0) was high (64% in the induction CRT arm vs. 53% in the chemotherapy arm). Additionally, the German ESPATUE trial demonstrated no OS differences when comparing outcomes between Stage III NSCLC patients treated with either definitive chemoradiation or induction chemoradiation followed by surgery [31]. Therefore, while trimodality therapy is often used as a management option for locally advanced NSCLC, there is data to support bimodality treatment in select patients.

Although the NCDB provides a unique platform with which to study this novel clinical issue, this investigation is not without additional limitations to those discussed above [32]. First, the NCDB does not catalog RT volumes or techniques, other outcomes (e.g. LC, PFS, quality of life), or toxicities. Second, the NCDB does not record further lines of treatment (e.g. re-irradiation, further systemic and/or targeted therapy), which could influence OS. Third, although a strength of this study was accounting for number of lymph nodes dissected (which can influence the ypN status), the NCDB does not give time from CRT completion to surgery. This understudied parameter has not been reported in multiple notable publications [8,10] but must be better addressed in the future. Nevertheless, the known shortcomings of a national, large-volume database, the first of its kind to date, do not diminish the necessity for further investigation.

5. Conclusions

There has been an increase in clinical interest regarding neoadjuvant radiotherapy dose-escalation for cN2 NSCLC, in order to increase PNC and pCR rates. However, long-term outcomes of dose-escalated neoadjuvant CRT are lacking. This study of a contemporary national database, the largest to date, displayed a PNC rate of 37% and pCR rate of 17%. Predictors of pCR were detailed, including radiation doses above the NCCN-recommended 54 Gy. Patients with pCR experienced higher OS than ypT + ypN0 cases; in the subset of ypN0 patients, there was a trend towards higher OS in patients in whom ypT0 was achieved. No OS benefit observed with higher neoadjuvant RT doses. Moreover, high dose-escalation (i.e., > 59.4 Gy) was associated with numerically higher postoperative mortality, indicating that high dose escalation should be performed based on careful multidisciplinary discussion and patient tolerance.

Conflict of interest statement

The authors assert that they have no relevant financial interests to disclose.

Disclaimers

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