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Risk and benefit of neoadjuvant therapy among patients undergoing resection for non-small-cell lung cancer†

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Abstract

OBJECTIVES: Neoadjuvant therapy has emerged as a favoured treatment paradigm for patients with clinical N2 disease undergoing surgical resection for non-small-cell lung cancer. It is unclear whether such a treatment paradigm affects perioperative outcomes. We sought to examine the National Cancer Database (NCDB) to assess the impact of neoadjuvant therapy on perioperative outcomes and long-term survival in these patients.

METHODS: All patients with a history of non-small-cell lung cancer undergoing anatomical resection between 2004 and 2014 were included. Thirty-day and 90-day mortality of all patients having neoadjuvant therapy versus those who did not were compared. In addition, the impact of neoadjuvant therapy on the overall survival of patients with clinical N2 disease was examined.

RESULTS: Of the 134 428 selected patients, 9896 (7.4%) patients had neoadjuvant chemotherapy. Patients undergoing neoadjuvant therapy had a higher 30-day (3% vs 2.6%; $P < 0.01$) and 90-day mortality (6.5% vs 4.9%; $P < 0.01$). This association remained after adjusting for covariates. Among patients with clinical N2 disease ($n = 10\,139$), 42.3%, 35.3% and 22.4% of patients had neoadjuvant, adjuvant and no chemotherapy, respectively. Univariable, multivariable and propensity score-weighted analyses indicated no difference in survival between patients receiving neoadjuvant and adjuvant chemotherapy.

CONCLUSIONS: Neoadjuvant therapy may adversely affect perioperative outcomes without providing a survival advantage compared with adjuvant therapy in clinical N2 stage patients. Randomized controlled trials need to be conducted to examine this issue further.

Keywords: Neoadjuvant • Adjuvant • Lung cancer • Lobectomy • Pneumonectomy

INTRODUCTION

Multimodality treatment has proved to be beneficial to patients with non-small-cell lung cancer beyond Stage I. Adjuvant therapy is clearly beneficial for non-small-cell lung cancer (NSCLC) beyond Stage I as demonstrated by the International Adjuvant Lung Trial as well as other studies [1–3]. The role of neoadjuvant therapy is more controversial. Early randomized controlled studies suggested a significant benefit of the neoadjuvant approach. [4–6]. Two follow-up multicentre randomized controlled trials were then performed [7, 8], with unclear conclusions.

Since the introduction of these trials, several paradigm shifts have occurred in the surgical management of lung cancer. Minimally invasive approaches to lung resection have become popular and increasingly accepted, even for central tumours and those requiring pneumonectomy [9–11]. In addition, investigators have reported that patients undergoing minimally invasive resection can more reliably tolerate adjuvant therapy [12]; this finding weakens one of the main arguments favouring neoadjuvant versus adjuvant therapy. Also, increasingly, there is an emphasis on 90-day mortality as the real cost of surgery, instead of simply relying on 30-day mortality [13], and this may be higher in patients undergoing neoadjuvant therapy [14, 15]. This decision-making is brought to a head in a situation where the surgeon has already made the requisite incisions for the resection and finds involvement of N2 lymph nodes. Several approaches to this situation have been advocated and vary depending on local training and treatment paradigms [16].

Given these paradigm shifts, we sought to assess the impact of neoadjuvant therapy on perioperative mortality of patients undergoing surgical resection. We also sought to examine the impact of the different modes of neoadjuvant therapy

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(chemotherapy versus chemoradiation) on survival after resection of clinical N2 NSCLC. These questions were the subjects of analyses using the National Cancer Database (NCDB).

METHODS

The NCDB was queried for all patients with NSCLC undergoing lobectomy or greater surgical resection. This cohort was further restricted to those patients who had lung cancer as the first cancer and with known 30-day and 90-day outcomes. To assess the impact of neoadjuvant therapy on perioperative mortality, all patients having neoadjuvant therapy prior to their surgical resection were selected. Thirty-day and 90-day mortality was compared between patients undergoing neoadjuvant therapy versus who did not. This was further subclassified into patients undergoing neoadjuvant chemotherapy alone versus neoadjuvant chemoradiation. This comparison was then repeated after adjusting for covariates including age, gender, Charlson–Deyo score (CDS), summary stage of disease and extent of surgery (lobectomy versus pneumonectomy) using logistic regression analysis. Associations between treatment groups and demographic variables were analysed using the Pearson's χ^2 test for categorical variables and Wilcoxon rank-sum test for continuous variables.

To examine the potential benefit of neoadjuvant therapy, a defined stage-specific cohort was used, which was patients with clinical N2 disease. Overall survival (OS) was defined as the time (in months) from diagnosis to death from any cause. Patients alive at the date of last follow-up were censored. In this cohort, the OS of patients having neoadjuvant chemotherapy was compared to those patients with adjuvant chemotherapy and patients getting no chemotherapy at all. Patients getting adjuvant therapy in addition to neoadjuvant therapy were included in the neoadjuvant arm. The analyses were repeated after further separating patients having neoadjuvant chemotherapy and those having neoadjuvant chemoradiation. The univariable analysis that was performed by the Kaplan–Meier methods was followed by multivariable analyses using Cox proportional hazards methods performing the same comparison after adjusting for age, gender, race, stage, grade, CDS and extent of resection. To adjust for bias in a different way, a propensity score-matched comparison of OS in patients with clinical N2 disease undergoing neoadjuvant versus adjuvant therapy was performed. An inverse probability of treatment weight model was used after accounting for gender (male/female), CDS, analytical stage group, histology, surgery (pneumonectomy and lobectomy) and age (continuous). The propensity weights were obtained from the multivariable logistic regression model for the probability of any neoadjuvant therapy (reference: adjuvant therapy). Patients who did not receive chemotherapy were excluded from the model. The probabilities were used to calculate the inverse probability of treatment weight. These were then used to weight the observations in the proportional hazards model to account for potential confounding factors [17].

In addition, to assess the impact of pneumonectomy on these results, the impact of mode of therapy on outcome was analysed in patients with clinical N2 disease having only a lobectomy. All analyses were conducted using SAS v9.4 (SAS Inc., Cary, NC, USA) at a significance level of 0.05.

Table 1: Study population selection from the NCDB

Selection criteria	Patient number
All patients with NSCLC from 2003 to 2014	1 284 846
Patients with lobectomy or pneumonectomy	283 897
Patients in whom this cancer was the first	193 003
Patients in whom the radiation–surgery sequence and the chemotherapy–surgery sequence was known	155 411
Exclude patients with unknown 30-day and 90-day mortality	134 428
Patients with clinical N2 disease	10 139

NCDB: National Cancer Database; NSCLC: non-small-cell lung cancer.

Table 2: Comparison of patients undergoing surgical resection lobectomy or greater and neoadjuvant therapy versus those who did not

Variables	Neoadjuvant	No neoadjuvant	*P*-value
Overall count, *n* (%)	9896 (7.4)	124 532 (92.6)	<0.001
Age (years), mean (SD)	60.9 (9.8)	65.9 (10.6)	<0.001
Gender, *n* (%)			
Male	5320 (53.8)	60 094 (48.3)	0.111
Female	4576 (46.2)	64 438 (51.7)	
Race, *n* (%)			
White	8607 (87)	109 042 (87.6)	<0.001
Black	879 (8.9)	10 812 (8.7)	
Other	410 (4.1)	4678 (3.8)	
Histology, *n* (%)			
Squamous	3201 (32.3)	33 449 (26.9)	<0.001
Adeno	4890 (49.4)	77 415 (62.2)	
Others	1805 (18.2)	13 668 (11.0)	
Stage, *n* (%)			
I	2292 (23.2)	73 875 (59.3)	<0.001
II	2486 (25.1)	25 813 (20.7)	
III	4170 (42.1)	16 449 (13.2)	
IV	583 (5.9)	3190 (2.6)	
Unknown	225 (2.3)	4914 (3.9)	
Grade, *n* (%)			
I/II	2705 (27.3)	69 537 (55.8)	<0.001
III/IV	4743 (47.9)	45 286 (36.4)	
Unknown	2448 (24.7)	9709 (7.8)	
Surgery, *n* (%)			
Lobectomy	8164 (82.5)	115 988 (93.1)	<0.001
Pneumonectomy	1732 (17.5)	8544 (6.9)	
CDS, *n* (%)			
0	6498 (65.7)	65 241 (52.4)	<0.001
1	2640 (26.7)	42 947 (34.5)	
2	758 (7.7)	16 344 (13.1)	
Preoperative therapy, *n* (%)			
Chemotherapy	3765 (38)	None	
Chemoradiation	6131 (62)		
30-day mortality	298 (3.0)	3239 (2.6)	0.014
90-day mortality	640 (6.5)	6086 (4.9)	<0.001

CDS: Charlson–Deyo score; SD: standard deviation.

RESULTS

Table 1 summarizes the selection criteria and the numbers of patients selected at each step. For the first analysis, 134 428 patients qualified. For the second analysis, 10 139 patients qualified for the criteria. The results of each set of analyses are summarized below.

The goal of the first analysis is to assess the impact of neoadjuvant therapy on 30-day and 90-day mortality after surgical

Table 3: Univariable and multivariable analyses of variables associated with perioperative mortality

Variables	Reference	Univariable model estimate (95% CI)	Multivariable model estimate (95% CI)
30-day mortality			
No neoadjuvant	Neoadjuvant	0.86 (0.76–0.97)	0.81 (0.71–0.92)
Neoadjuvant chemoradiation	Neoadjuvant chemotherapy	1.46 (1.13–1.88)	1.72 (1.33–2.22)
No neoadjuvant		1.10 (0.89–1.36)	1.15 (0.92–1.43)
Female	Male	0.50 (0.47–0.54)	0.58 (0.54–0.62)
CDS 1	CDS 0	1.28 (1.19–1.38)	1.23 (1.14–1.33)
CDS 2		1.93 (1.76–2.11)	1.74 (1.59–1.91)
Stage			
II	I	1.32 (1.21–1.43)	1.11 (1.01–1.21)
III		1.44 (1.31–1.57)	1.19 (1.08–1.31)
IV		1.73 (1.45–2.05)	1.72 (1.44–2.06)
Unknown		1.14 (0.95–1.36)	1.30 (1.08–1.56)
Pneumonectomy	Lobectomy	3.20 (2.94–3.49)	3.58 (3.27–3.93)
Age (years)		1.05 (1.05–1.05)	1.06 (1.06–1.06)
90-day mortality			
No neoadjuvant	Neoadjuvant	0.74 (0.68–0.81)	0.74 (0.68–0.81)
Neoadjuvant chemoradiation	Neoadjuvant chemotherapy	1.53 (1.28–1.82)	1.81 (1.51–2.16)
No neoadjuvant		0.98 (0.85–1.14)	1.08 (0.93–1.26)
Female	Male	0.49 (0.47–0.52)	0.57 (0.54–0.60)
CDS 1	CDS 0	1.25 (1.18–1.32)	1.22 (1.15–1.29)
CDS 2		1.89 (1.76–2.02)	1.75 (1.63–1.87)
Stage			
II	I	1.47 (1.38–1.56)	1.28 (1.20–1.36)
III		1.77 (1.66–1.89)	1.53 (1.43–1.64)
IV		2.83 (2.54–3.16)	2.99 (2.67–3.36)
Unknown		1.23 (1.08–1.40)	1.44 (1.25–1.64)
Pneumonectomy	Lobectomy	2.96 (2.77–3.15)	3.00 (2.80–3.23)
Age (years)		1.05 (1.05–1.05)	1.06 (1.06–1.06)

CDS: Charlson–Deyo score; CI: confidence interval.

resection of NSCLC. Table 2 summarizes the demographic and clinical characteristics of the 134 428 selected patients. Of these, 9896 (7.4%) patients had neoadjuvant chemotherapy. The majority of these patients (6131; 62%) had neoadjuvant chemoradiation. Patients undergoing neoadjuvant therapy were significantly younger (60.9 years vs 65.9 years) and had better functional status (lower CDS) compared to those who did not. This is in keeping with neoadjuvant therapy being considered for patients who are fit enough for tolerating a more aggressive treatment paradigm. Also, a greater proportion of patients having neoadjuvant therapy had pneumonectomy (17.5% vs 6.9%), probably due to larger central tumours being typically selected for such an approach. Although the 30-day mortality of the neoadjuvant approach (unadjusted) was slightly higher than those without (3% vs 2.6%; $P = 0.014$), there was a clinically significant difference in the 90-day mortality (6.5% vs 4.9%; $P < 0.001$). This difference better estimates the mortality cost of an intensive regimen. Univariable analyses (Table 3) also confirm the expected association of age, gender, CDS and pneumonectomy on the 30-day and 90-day mortality. In addition, the results suggest that neoadjuvant chemoradiation was associated with a higher 30-day and 90-day mortality when compared with neoadjuvant chemotherapy (odds ratio 1.46 and 1.53, respectively; $P < 0.01$). Multivariable analysis again confirms the known impact of age, gender, CDS and pneumonectomy on these outcomes. Interestingly, although the non-neoadjuvant group as a whole showed a lower 30-day and 90-day mortality when compared with those who received neoadjuvant therapy (odds ratio 0.81 and 0.74, respectively; $P < 0.01$), this difference was primarily driven by the higher mortality of patients in the chemoradiation group.

While the above comparison provides a backdrop of the relative risk of neoadjuvant therapy in general, an appropriate clinical context is provided by selecting only patients with clinical N2 disease. Clinical N status and not pathological N status provides a better comparison because of potential pathological N downstaging by neoadjuvant therapy. Table 4 summarizes the demographic and clinical characteristics of the 10 139 patients who were included for this analysis. Of these patients, 4289 (42.3%) had neoadjuvant therapy, 3582 (35.3%) had adjuvant therapy and 2268 (22.4%) had neither. Of note, the last group was older and had a higher CDS pointing to the reason for not using a multimodality treatment in these patients. The higher comorbidity index probably also accounts for the high 30-day and 90-day mortality (9% and 16.4%, respectively) in this subgroup. The adjuvant and neoadjuvant groups were more equivalent in mean age (62.9 and 60.8 years, respectively) and comorbidity index (CDS). With these being equivalent, the raw 30-day and 90-day mortality was different (3.1% vs 0.3% and 6.4% vs 1.8% respectively), confirming the first analysis with respect to the increased perioperative cost of a neoadjuvant strategy. In all, 8.4% of the patients with neoadjuvant therapy also had adjuvant therapy and these patients were grouped with the neoadjuvant arm.

Table 5 summarizes the impact of demographic, clinical and treatment strategy on the long-term outcomes of patients with clinical N2 disease undergoing surgical resection. As is well known, increasing age, stage, comorbidity (CDS) and extent of resection (pneumonectomy) were associated with a worse OS in

Table 4: The characteristics of patients with clinical N2 disease who had surgical resection

Variables	Neoadjuvant	Adjuvant	None	*P*-value
Overall count, *n* (%)	4289 (42.3)	3582 (35.3)	2268 (22.4)	
Age (years), mean (SD)	60.8 (9.6)	62.9 (9.7)	67.5 (10.7)	<0.001
Gender, *n* (%)				
Male	2154 (50.2)	1848 (51.6)	1289 (56.8)	<0.001
Female	2135 (49.8)	1734 (48.4)	979 (43.2)	
Race, *n* (%)				
White	3731 (87.0)	3063 (85.5)	1963 (86.6)	0.008
Black	359 (8.4)	380 (10.6)	209 (9.2)	
Other	199 (4.6)	139 (3.9)	96 (4.2)	
Histology, *n* (%)				
Squamous	1271 (29.6)	997 (27.8)	761 (33.6)	<0.001
Adeno	2322 (54.1)	2106 (58.8)	1211 (53.4)	
Others	696 (16.2)	479 (13.4)	296 (13.1)	
Stage, *n* (%)				
I	864 (20.1)	199 (5.6)	616 (27.2)	<0.001
II	545 (12.7)	430 (12.0)	362 (16.0)	
III	2643 (61.6)	2704 (75.5)	1133 (50.0)	
IV	159 (3.7)	226 (6.3)	139 (6.1)	
Unknown	14 (0.3)	18 (0.5)	15 (0.7)	
Grade, *n* (%)				
I/II	1149 (26.8)	1467 (41.0)	1031 (45.5)	<0.001
III/IV	1976 (46.1)	1815 (50.7)	1023 (45.1)	
Unknown	1164 (27.1)	300 (8.4)	214 (9.4)	
Surgery, *n* (%)				
Lobectomy	3612 (84.2)	3030 (84.6)	1911 (84.3)	0.892
Pneumonectomy	677 (15.8)	552 (15.4)	357 (15.7)	
CDS, *n* (%)				
0	2863 (66.8)	2075 (57.9)	1150 (50.7)	<0.001
1	1128 (26.3)	1140 (31.8)	727 (32.1)	
2	298 (6.9)	367 (10.2)	391 (17.2)	
Preoperative therapy, *n* (%)				
Chemotherapy	1362 (31.8)			
Chemoradiation	2927 (68.2)			
Adjuvant chemotherapy, *n* (%)	847 (8.4)	3582 (100)	None	
30-Day mortality, *n* (%)	132 (3.1)	10 (0.3)	205 (9.0)	<0.001
90-Day mortality, *n* (%)	275 (6.4)	64 (1.8)	373 (16.4)	<0.001

CDS: Charlson Deyo score; SD: standard deviation.

Table 5: Univariable and multivariable analyses of variables associated with overall survival of patients with clinical N2 NSCLC undergoing resection

Variables	Reference	Univariable model estimate (95% CI)	Multivariable model estimate (95% CI)
No chemotherapy	Neoadjuvant	1.50 (1.40–1.60)	1.52 (1.38–1.67)
Adjuvant chemotherapy		1.05 (0.99–1.11)	0.99 (0.90–1.08)
Neoadjuvant chemoradiation	Neoadjuvant chemotherapy	1.08 (0.99–1.18)	0.87 (0.69–1.10)
Female	Male	0.77 (0.73–0.81)	0.80 (0.76–0.84)
CDS 1	CDS 0	1.17 (1.10–1.24)	1.13 (1.06–1.19)
CDS 2		1.43 (1.31–1.55)	1.31 (1.21–1.43)
Stage			
II	I	1.25 (1.13–1.39)	1.30 (1.17–1.44)
III		1.40 (1.29–1.51)	1.53 (1.41–1.66)
IV		2.43 (2.14–2.74)	2.74 (2.42–3.11)
Unknown		1.60 (1.12–2.30)	1.56 (1.08–2.23)
Histology			
Adenocarcinoma	Squamous cell	0.91 (0.86–0.97)	1.01 (0.94–1.07)
Other		0.99 (0.91–1.07)	1.08 (1.00–1.18)
Pneumonectomy	Lobectomy	1.39 (1.30–1.49)	1.47 (1.37–1.58)
Age (years)		1.02 (1.02–1.02)	1.02 (1.02–1.03)

CI: confidence interval; NSCLC: non-small-cell lung cancer.

both univariable and multivariable analyses. Also, female patients have a better OS compared with their male counterparts. In univariable analyses, patients having no neoadjuvant therapy fare worse than patients having neoadjuvant therapy. Also, there was no difference in survival of patients having a neoadjuvant approach versus an adjuvant approach (Fig. 1). Separating the neoadjuvant approach into patient having neoadjuvant chemotherapy versus neoadjuvant chemoradiation, the OS was not statistically different between both groups (Fig. 2A). These findings were reiterated on multivariable analyses, where no statistically significant differences were seen in patients having neoadjuvant therapy versus those having adjuvant therapy. In addition, no differences were seen in patients having neoadjuvant chemoradiation versus those having neoadjuvant chemotherapy alone.

Adjusting for bias using a different technique, propensity score-weighted analyses were performed to compare patients with clinical N2 disease having neoadjuvant chemotherapy versus those having adjuvant therapy (Fig. 2B). In this analysis, there is a statistically significant (although clinically non-significant) advantage of adjuvant therapy over neoadjuvant therapy (hazard ratio 0.93, 95% confidence interval 0.87–0.99; $P = 0.02$).

In addition, to assess the impact of pneumonectomy on the comparisons in the multivariable analyses, some of the main analyses were repeated in the lobectomy population alone. Table 6 summarizes the results of these comparisons. As shown, the exclusion of pneumonectomy patients did not affect the OS of the patients with respect to the administration of neoadjuvant versus adjuvant therapy.

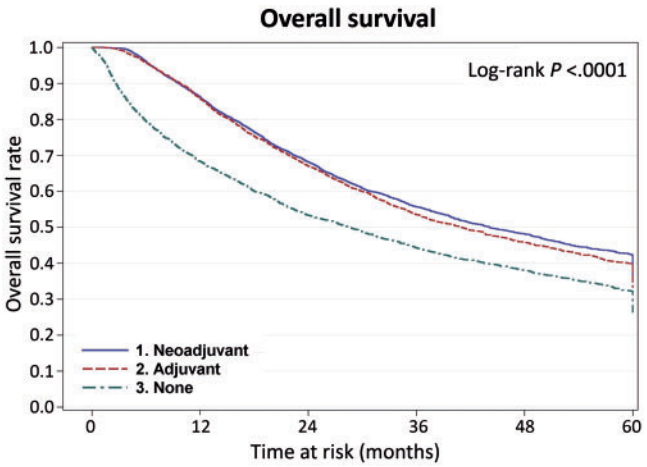

Figure 1: Univariable analysis comparing the overall survival after neoadjuvant, adjuvant and no chemotherapy in non-small-cell lung cancer patients with clinical N2 disease undergoing surgical resection. The null hypothesis for the log-rank test is that no differences exist between the 3 comparison groups. No differences are seen between overall survival of patients with neoadjuvant and adjuvant therapy.

DISCUSSION

The current paradigm of neoadjuvant therapy for the treatment of Stage IIIA N2 disease is based on 2 small randomized trials [5, 6]. Follow-up trials on this concept has led to unclear conclusions. The EORTC 08941, a negative trial, randomized patients between definitive chemoradiation and neoadjuvant chemotherapy followed by surgery. The INT 0139 trial randomized patients between neoadjuvant chemoradiation followed by surgery and definitive chemoradiation. An unplanned subset analysis of patients undergoing a lobectomy revealed an OS benefit. Also, increased progression-free survival for the entire cohort was seen. Even though these trials did not show a clear benefit, neoadjuvant therapy came to be liberally used for the management of patients with N2 disease. The reasons for the adoption of neoadjuvant therapy are 3-fold. The first is that many patients undergoing thoracotomy for resection of a large central tumour are not fit enough to tolerate adjuvant therapy due to delayed recovery, hampering the delivery of multimodality therapy. Neoadjuvant therapy provides a method of delivering at least 2–3 cycles of chemotherapy to these patients with greater reliability. The second is that neoadjuvant therapy can be considered a biological 'stress test', where the response of the tumour to chemotherapy can be tested. Tumours that respond to chemotherapy with down-staging of N2 disease have a higher long-term survival, justifying surgical resection. The third is an avoidance of futile surgery by weeding out those patients in

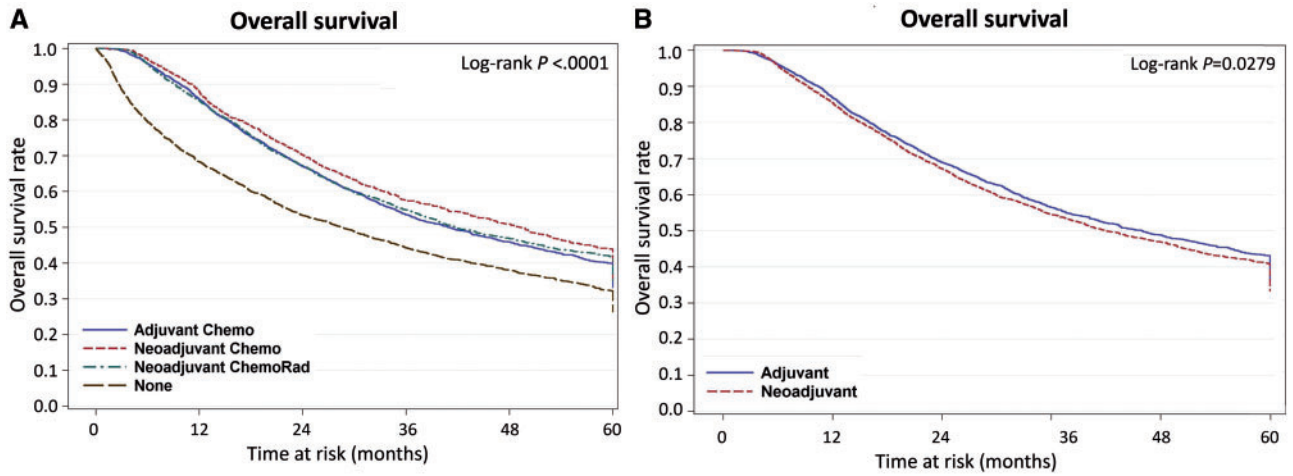

Figure 2: (**A**) Univariable analysis comparing the overall survival after neoadjuvant chemoradiation, neoadjuvant chemotherapy, adjuvant chemotherapy and no chemotherapy in non-small-cell lung cancer patients with clinical N2 disease undergoing surgical resection. The null hypothesis for the log-rank test is that no differences exist between the 4 comparison groups. (**B**) Propensity score-weighted comparison between clinical N2 disease patients having neoadjuvant versus adjuvant therapy. The null hypothesis for the log-rank test is that no differences exist between the comparison groups.

Table 6: Univariable and multivariable analyses of variables associated with overall survival of patients with clinical N2 NSCLC undergoing lobectomy alone

Variables	Reference	Univariable model estimate (95% CI)	Multivariable model estimate (95% CI)
Adjuvant	Neoadjuvant	1.09 (1.02–1.17)	0.98 (0.92–1.05)
Female	Male	0.81 (0.76–0.86)	0.82 (0.77–0.88)
CDS 1	CDS 0	1.14 (1.05–1.22)	1.11 (1.03–1.20)
CDS 2		1.33 (1.19–1.50)	1.28 (1.14–1.44)
Stage			
II	I	1.18 (1.03–1.35)	1.15 (1.00–1.33)
III		1.31 (1.18–1.45)	1.30 (1.17–1.45)
IV		2.38 (2.02–2.80)	2.57 (2.18–3.04)
Unknown		1.80 (1.09–2.97)	1.85 (1.12–3.05)
Histology			
Adenocarcinoma	Squamous cell	0.99 (0.91–1.07)	1.05 (0.97–1.14)
Other		0.99 (0.89–1.11)	1.05 (0.94–1.17)
Age (years)		1.02 (1.02–1.02)	1.02 (1.02–1.02)

CI: confidence interval; NSCLC: non-small-cell lung cancer.

whom metastatic disease is evident on restaging after neodjuvant therapy. Although these trials emphasized the impact of treatment paradigms on long-term survival, their impact on perioperative mortality was not recognized. During the time period when these trials were conducted, the main emphasis of perioperative mortality was on 30-day or in-hospital mortality, which did not seem to be impacted by a neoadjuvant treatment approach.

Our results bring into question the assumed benefit of a neoadjuvant strategy compared with an adjuvant therapy strategy for the management of NSCLC with N2 disease. Our analyses suggest that neoadjuvant therapy is associated with a higher perioperative mortality than alternative treatment approaches. This association is driven by neoadjuvant chemoradiation which is a strategy used in the majority of patients treated with neoadjuvant therapy. The higher perioperative mortality is even more evident when 90-day mortality was examined, a statistics increasingly recognized as important. Previous investigators have demonstrated several mechanisms for increased postoperative morbidity and mortality of lung resection after neoadjuvant therapy. These include a reduction in lung function and an increase in the incidence of deep venous thrombosis [18–20]. However, a head-to-head comparison of these statistics for patients undergoing neoadjuvant versus adjuvant therapy is not readily available in existing literature. In addition, nearly 30% of patients had a final analytical stage less than Stage III, even though they were considered N2 disease clinically, potentially leading to overtreatment with neoadjuvant therapy if imaging alone is used.

With respect to long-term survival, the superiority of multimodality therapy compared with surgery alone is again demonstrated in this cohort. However, the higher mortality in this group may be reflective of a selection bias for N2 patients not fit enough to receive multimodality therapy over and above that reflected by the CDS. Two questions then remain. The first is whether neoadjuvant chemoradiation provides a superior enough long-term outcome when compared with neoadjuvant chemotherapy alone to justify the accompanying increased perioperative mortality. Some smaller studies suggest this to be the case [21]. Other studies, including a recently published randomized control trial, suggest that the long-term outcomes of both neoadjuvant strategies are the same [22, 23]. The second question is whether a neoadjuvant therapy strategy is superior to an adjuvant therapy strategy. Currently, there are no published data supporting one strategy over the other. In the analysis presented here, adjuvant therapy has at least an equivalent long-term survival compared with neoadjuvant therapy but also has the advantage of lower perioperative risk. Our findings are consistent with a meta-analysis of 32 randomized clinical trials performed by Lim *et al.* [24], where the authors found no difference between the long-term outcomes of both approaches.

Limitations

This study has several limitations. The first limitation is that the study is retrospective and is therefore subject to several biases. Foremost among them is the selection bias of patients having a neoadjuvant versus adjuvant approach. In addition, the data are simply not granular enough to control for significant clinical factors that can affect outcomes. Particularly important in patients with clinical N2 disease is the way N2 disease was diagnosed. As the database collates information from several clinical centres with varying quality control with respect to staging practices, uniformity cannot be expected. In addition, staging algorithms have evolved over this time period. Positron emission tomography–computer tomography and endobronchial ultrasound-guided fine-needle aspiration have been more commonly used. The definition of clinical N2 disease in the database does not require histological confirmation, something that a well-designed randomized controlled trial would not accept. Also, N2 disease is heterogeneous. It could be single station, multistation, bulky, microscopic or incidentally discovered, all of which have a different prognostic importance. The details of these are not provided in a database such as the NCDB. In addition, the details of pulmonary function tests, other comorbidities and perioperative complications are not provided. Disease-free survival is not provided as well, and the OS data may not reflect oncological outcomes alone. In addition, caution should be exercised while interpreting differences when large numbers from such databases are

compared, as such analyses may show clinically non-significant differences as statistically significant. Also, while adjusting for bias was performed for existing variables with both standard multivariable analyses and propensity score weighting, analytical adjustment cannot correct for variables absent in the data. Despite these limitations, these analyses provide a real-world snapshot on the use and results of neoadjuvant strategies in a large cohort.

The significant limitations described above temper our enthusiasm to make definitive recommendations. Particularly, the authors do not encourage the widespread use of resection followed by adjuvant therapy for N2 disease diagnosed before surgery, especially for multistation or bulky N2 disease. However, if resectable, N2 disease is found at the time of surgery, and the patient is deemed to be fit enough to make the delivery of adjuvant therapy likely, and the results obtained above justify that position that the resection should be completed instead of aborting the procedure just to complete neoadjuvant therapy. In addition, the strategy of routine neoadjuvant chemoradiation should be questioned, given the significant increase in perioperative mortality.

CONCLUSION

Neoadjuvant therapy, especially neoadjuvant chemoradiation, may adversely affect perioperative outcomes without providing a survival advantage compared with adjuvant therapy in clinical N2 stage patients. These data support the development of clinical trials comparing neoadjuvant with adjuvant approaches to NSCLC patients with N2 disease.

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APPENDIX. CONFERENCE DISCUSSION

Dr D. Wood *(Seattle, WA, USA)*: This article covers a certainly a very important topic for all of us in this room. The timing and sequence of multidisciplinary management of Stage IIIA disease is certainly an area of controversy even among lung cancer experts. I have 1 comment and 2 questions. Big data is increasingly popular and increasingly presented at our scientific meetings. It is easy for all of us, myself included, to be seduced by a study like this, that analyses a 134 000 patients. Yet the strengths of large databases are also their weaknesses, often leading to potentially fatal flaws that are unintentionally deceptive. You rightly pointed out the limitations of the study related to the unknown impact of selection bias that likely results in systematic differences in the patients undergoing neoadjuvant vs adjuvant therapy. However, there are even more unmeasured and unmentioned sources of likely bias that include factors like surgeon specialization, academic versus private practice centres, National Cancer Institute (NCI)-designated cancer centres and surgeon or hospital volume. It is hard to know how these variables would influence the result, but it is actually quite possible that correction for these confounding factors might actually demonstrate the opposite conclusion from that reached in your article. One thing that appears to be a solid conclusion from your analysis is that the worst short-term outcomes with neoadjuvant therapy are driven by the patients who had both chemotherapy and radiation. In fact, when you looked at only neoadjuvant chemotherapy, the short-term outcomes were the same and the long-term survival appeared better with neoadjuvant chemotherapy compared with adjuvant chemotherapy. It might be worth going back to your figure too, just to leave that up there for people to study that difference. My first question is this: does not this seem to actually reverse your conclusion, i.e. induction chemotherapy without radiation is superior to adjuvant chemotherapy in terms of cancer survival. Would it perhaps be better to use your data to reinforce the view that neoadjuvant radiation adds morbidity but not a survival benefit to Stage IIIA patients who are having surgery as a part of their therapy. Finally, do you have a sense of what is driving the majority of patients to get both chemotherapy and radiation, rather than chemotherapy alone? Do you think that this is an actual preference of thoracic surgeons or related to multidisciplinary pressure from radiation oncologists in the multidisciplinary clinics?

Dr S. Yendamuri *(Buffalo, NY, USA)*: I agree with you, that in general, while doing large database analysis, I think the trick is to ask the right question and not to over-reach and to temper the conclusions, because certainly, the level of evidence provided by this is modest. In terms of looking at this figure, this is a univariate analysis because you can generate this survival curves only for univariate analysis. Although it does look like neoadjuvant chemo is slightly better that adjuvant chemo, if you look at the table that shows a multivariate model, there really is no difference. That's why my conclusion still remains the same, despite this figure, because multivariate analysis after adjusting for covariates it is clear that there is no difference between both. In terms of radiation, I think the intergroup study had a lot to do with the preference for chemoradiation versus chemotherapy, and I can only speculate as to why people would use chemotherapy chemoradiation in North America. Certainly we are trained at MD Anderson to use only chemotherapy, primarily driven by doctor Roth's randomized trial, but I practice in an NCI cancer institute and we only give chemotherapy. Chemoradiation is used in various selected circumstances, like superior sulcus tumour and so on. Honestly, I cannot explain the use of chemoradiation in the NCDB. It did come as a surprise to me, because I've always given neoadjuvant chemo in my practice.

Dr A. Turna *(Istanbul, Turkey)*: You presented a huge data with clinical N2 disease. There must have been one-third of these patients with pathological N0 disease, because it is clinical N2. It has failed to predict that there must have been additional one-third of patients with clinical, pathological N0 disease after the neoadjuvant chemoradiotherapy. Did you happen to look at the pathological N0 disease in terms of adjuvant and neoadjuvant therapy?

Dr Yendamuri: When I pick patients to compare, the only fair comparison was looking at the clinical N2 disease, because if I look at path N2 disease, the proportion of patients who have been downstaged would be excluded. In order to keep the comparison fair, I had to go with clinical N2 disease. Now, in the database, we have no idea of how good the clinical staging was, what the use of PET was, how many people got mediastinoscopy, how many people got EBUS. All of these are variables that are not defined. The only hope, and it's a big assumption, that those errors were equally distributed in all the compared populations. But that's just an assumption, we don't know that.

Dr. E. Vallieres *(Seattle, WA, USA)*: When you are comparing mortality rates of patients in the induction group to those in the adjuvant group, how do you account for the patient that was planned to be in the adjuvant group but died after the surgery? The two groups don't compare, you're unfortunately missing a group of patients who never made it to the adjuvant phase of their treatment. How can you with your data account for these differences?

Dr. Yendamuri: I agree, I cannot account for it. That's a limitation of any retrospective analysis like this. That's the short answer.

Dr R. Rami Porta *(Terrassa, Barcelona, Spain)*: You have shown what you think is the situation in the real world, but I do not think so. I think there are as many real worlds as individuals in this room and outside this room. In the era when we are talking more and more often about personalized medicine, I think we also have to enlarge this concept of personalized surgery. This is a topic that is prone to multiple interpretations. I missed in your presentation, because there are no data in the database, the way the clinical N2 was diagnosed, for example; how patients and tumours were selected for induction therapy; and how these tumours and patients were selected for resection after induction therapy. We know that not all are candidates for resection after induction therapy. I think that while your general conclusions are generally discussable, I think they are not applicable to individual institutions or patients. It is like a David Hamilton picture: you see the bulk, but you do not see the details.

Dr. Yendamuri: I agree with that. I don't think that the take-home message is that people with N2 disease should not have neoadjuvant therapy. However, I have heard in many national, international meetings where surgeons have come up and said 'If I do find an incidental N2 disease when I do a VATS and do a lymph node biopsy, I'm going to stop the operation and I'm going to give neoadjuvant chemotherapy and go back and do it'. Particularly, these statements have been made even after the thoracotomy. All I would suggest is that it is not necessarily true and if you have a situation where you have an N2 disease that you have found in operation, you can finish the lobe and give adjuvant therapy and you have not hurt the patient with that strategy. Certainly, it would inform me in a situation like that. But I agree, that inherent limitations of the database preclude the strengths of conclusions that we can draw.