Sequential Versus Concurrent Chemoradiation Therapy by Surgical Margin Status in Resected Non–Small Cell Lung Cancer

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Abstract

Background: Postoperative chemoradiotherapy (CRT) for non–small cell lung cancer (NSCLC) can be delivered sequentially (sCRT) or concurrently (cCRT). Without high-volume data, current guidelines recommend either option for patients with negative margins (M–) and cCRT for those with positive margins (M+). In this study, survival was compared between sCRT versus cCRT for M– and M+ disease; survival in patients who underwent sCRT was also assessed with chemotherapy-first versus radiotherapy (RT)-first. **Methods:** The National Cancer Database was queried for patients with primary NSCLC undergoing surgery followed by CRT. Patients were excluded if they received neoadjuvant chemotherapy or RT. Both M– and M+ (including R1 and R2) subcohorts were evaluated. Multivariable logistic regression ascertained factors associated with cCRT delivery. Kaplan-Meier analysis evaluated overall survival (OS); Cox proportional hazards modeling determined variables associated with OS. Propensity score matching aimed to address group imbalances and indication biases. **Results:** Of 4,921 total patients, 3,475 (71%) were M–, 1,446 (29%) were M+, 2,271 (46%) received sCRT, and 2,650 (54%) underwent cCRT. Median OS among the sCRT and cCRT groups in patients who were M– was 54.6 versus 39.5 months, respectively ($P < .001$); differences persisted following propensity score matching ($P < .001$). In the overall M+ cohort, outcomes for sCRT and cCRT were 36.3 versus 30.5 months ($P = .011$), but showed equipoise following matching ($P = .745$). In the R1 and R2 subsets, no differences in OS were seen between cohorts ($P = .368$ and $.553$, respectively). When evaluating the sCRT population, there were no OS differences between chemotherapy-first and RT-first after matching ($P = .229$). **Conclusions:** Postoperative sCRT was associated with improved survival compared with cCRT in patients with M– disease, with statistical equipoise in those with M+ disease. Differential sequencing of sCRT does not appear to affect survival.

J Natl Compr Canc Netw 2018;16(5):508–516
doi: 10.6004/jnccn.2018.7007

Despite continual efforts to improve prognosis and decrease treatment-related toxicities, non–small cell lung cancer (NSCLC) remains a major health epidemic worldwide. NSCLC is commonly treated with upfront surgery with or without prior induction chemotherapy, followed by postoperative radiotherapy (PORT) or chemoradiotherapy (CRT).¹ PORT has been controversial since the results of a meta-analysis showed a survival detriment associated with its use²; however, this study was heavily

criticized regarding the patient population, inclusion of outdated radiotherapy (RT) techniques, and allowance of high RT doses (both total and fractional). Further definition of optimal PORT subgroups occurred with a pivotal publication showing benefit for patients with pN2 disease and those with pN1 disease not receiving chemotherapy³; this has since been corroborated by large-volume retrospective studies.^{4,5} PORT is also indicated for suspected or involved surgical margins.^{1,6,7}

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Submitted October 20, 2017; accepted for publication January 23, 2018.

Dr. Lin has disclosed that he has received research funding from Elekta, STCube Pharmaceuticals, Peregrine, Bayer, and Roche/Genentech; has served as a consultant for AstraZeneca; and has received honorarium from US Oncology and ProCure. The remaining authors have disclosed that they have no financial interests, arrangements, affiliations, or

commercial interests with the manufacturers of any products discussed in this article or their competitors.

Author contributions: Study concept: Verma, Moreno, Fang. Statistical analysis: Moreno, Haque. Supervision: Lin. Manuscript preparation and approval: All authors.

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However, what remains unclear in light of these data is optimal sequencing of postoperative RT and chemotherapy. Randomized studies have not shown a benefit in local control or survival for postoperative CRT versus PORT alone.⁸ Although clear evidence in unresected NSCLC shows that concurrent CRT (cCRT) produces improved outcomes at the expense of greater toxicities,^{9,10} phase II studies of postoperative cCRT have observed encouraging toxicity profiles.^{11,12} Sequential CRT (sCRT) remains theoretically appealing given the relative fragility of the postoperative setting, during which serious toxicities could develop if cCRT is delivered.

Currently, this notion remains highly controversial. National guidelines exemplify this ambiguity, recommending either paradigm for patients with margin-negative (M-) and margin-positive (M+) R1 (microscopic) disease; cCRT is endorsed for R2 (gross residual) disease.¹ Additionally, sequencing of sCRT is also highly controversial.¹³ Chemotherapy followed by RT may allow for earlier treatment of potential micrometastases,³ but others espouse initial RT so as to deliver early local therapy to the area of greatest disease burden.¹⁴

To date, evaluation of sCRT versus cCRT by margin status, as well as optimal sequencing of sCRT, have not been studied with high-volume data. This study of a large, contemporary national database aimed to evaluate national practice patterns and outcomes addressing these important and highly applicable clinical questions.

Methods

The National Cancer Database (NCDB) is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society, and consists of deidentified information regarding tumor characteristics, patient demographics, and patient survival for approximately 70% of the US population.^{15–24} All pertinent cases are reported regularly from CoC-accredited centers and compiled into a unified data set, which is then validated. The NCDB contains information not captured in the SEER database, including details regarding use of systemic therapy. The data used in the study were derived from a deidentified NCDB file (2004–2014). The American College of Surgeons nor the CoC have not verified and neither are

responsible for the analytic or statistical methodology used or the conclusions drawn from these data by the investigators. As all patient information in the NCDB database is deidentified, this study was exempt from Institutional Review Board evaluation.

The inclusion criterion for this study was newly diagnosed, primary NSCLC treated with upfront surgery followed by postoperative chemotherapy and RT. Patients who received neoadjuvant chemotherapy and/or RT were excluded. Surgery was defined as an oncologic-quality procedure, and hence local tumor destruction/excision techniques (including laser, cryosurgery, and electrocautery) constituted exclusion. RT was defined as external-beam RT to a dose of 45 to 74 Gy.^{5,6} Per multiple other NCDB publications, concurrent therapy referred to starting chemotherapy and RT within 14 days of each other, with the remainder designated as sequential.^{25,26} Patients with an interval of >6 months from surgery to adjuvant therapy, or between adjuvant RT and chemotherapy, were excluded, per other work, in order to differentiate between potential salvage and definitive therapy.⁵ No patients were excluded who died within a certain point after surgery, similar to prior investigations⁵ and sensitivity analyses demonstrating no impact on results when this cohort was eliminated.⁶ Lastly, although PORT is recommended for pN2 disease, we allowed pN0 and pN1 disease for numerous reasons, including the lack of prospective assessment to date on whether these populations are at higher risk of locoregional recurrence; retrospective studies have suggested no differences.²⁷ We also allowed inclusion of patients with pN1, M- disease owing to the lack of direct randomized comparisons between postoperative CRT and chemotherapy alone, together with the fact that PORT is still often delivered in these patients.⁶ We also allowed patients with pN0, M- disease (which constituted a large minority of this cohort) for multiple reasons. First, postoperative CRT cannot be disregarded altogether for pT3–4, pN0 disease; these cases may still be at enough risk of locoregional failure (eg, based on extent of lymphovascular invasion, lymph node ratio, and other factors) to warrant adjuvant therapy. Additionally, many institutions make individualized decisions on adjuvant local therapy based on precise surgical findings, in light of data showing a connection between local failure and distance from tumor to ink.^{28,29}

In accordance with the variables in NCDB files, information collected on each patient broadly included demographic, clinical, and treatment data. All statistical tests were 2-sided, with a threshold of $P<.05$ for statistical significance, and were performed using STATA, version 14 (StataCorp LP). Multivariable logistic regression modeling was used to determine characteristics that were predictive for receipt of cCRT. The Kaplan-Meier method was used for survival analysis, and comparisons between groups were performed with the log-rank test. Overall survival (OS) was defined as the interval between the date of diagnosis and the date of death, or censored at last contact. Univariate analysis was performed to determine factors associated with OS, and subsequently Cox multivariate analysis was performed including

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 (PSM) was used to compare patients between groups. PSM is a method that creates quasi-case/control pairs using a retrospective cohort in an effort to account for the recorded and unrecorded confounding variables.^{30–32} Propensity scores were calculated using a multivariable logistic regression model, with the dependent variable being receipt of particular treatment paradigm and the independent variables being those that were statistically significant for correlation with OS on multivariate analysis. Patients were matched 1:1 without replacement

Table 1. Cohort Characteristics and Factors Associated With Receiving Concurrent CRT

Parameter	All Patients (N=4,921)	Negative Margin (N=3,475)	Positive Margin (N=1,446)	Multivariable Logistic Regression	
				OR (95% CI)	P Value ^a
Age, y					
<65	2,642 (54%)	1,885 (54%)	757 (52%)	Ref	Ref
65–74	1,697 (35%)	1,200 (35%)	497 (34%)	0.949 (0.805–1.118)	.530
>74	582 (12%)	390 (11%)	192 (13%)	1.026 (0.821–1.281)	.824
Sex					
Male	2,613 (53%)	1,784 (51%)	829 (57%)	Ref	Ref
Female	2,308 (47%)	1,691 (49%)	617 (43%)	0.903 (0.802–1.017)	.093
Race					
White	4,271 (87%)	3,002 (86%)	1,269 (88%)	Ref	Ref
Black	497 (10%)	358 (10%)	139 (10%)	1.057 (0.868–1.288)	.581
Asian	98 (2%)	72 (2%)	26 (2%)	0.903 (0.591–1.379)	.636
Other	55 (1%)	43 (1%)	12 (1%)	1.013 (0.581–1.767)	.964
Charlson-Deyo score ^b					
0	2,693 (55%)	1,937 (56%)	756 (52%)	Ref	Ref
1	1,653 (34%)	1,135 (33%)	518 (36%)	1.123 (0.987–1.278)	.079
≥2	575 (12%)	403 (12%)	172 (12%)	0.981 (0.812–1.185)	.840
Insurance type					
Medicaid	317 (6%)	216 (6%)	101 (7%)	Ref	Ref
Private	2,076 (42%)	1,495 (43%)	581 (40%)	1.005 (0.784–1.289)	.968
Medicare	2,253 (46%)	1,572 (45%)	681 (47%)	1.123 (0.854–1.477)	.407
Uninsured	128 (3%)	88 (3%)	40 (3%)	0.968 (0.632–1.480)	.879
Other	147 (3%)	104 (3%)	43 (3%)	1.028 (0.683–1.548)	.895
Annual income					
<\$63,000	3,556 (72%)	2,496 (72%)	1,060 (73%)	Ref	Ref
≥\$63,000	1,310 (27%)	940 (27%)	370 (26%)	0.759 (0.662–0.870)	<.001
Not recorded	55 (1%)	39 (1%)	16 (1%)	–	–
Facility type					
Academic	1,277 (26%)	927 (27%)	350 (24%)	Ref	Ref
Nonacademic	3,584 (73%)	2,503 (72%)	1,081 (75%)	1.242 (1.085–1.422)	.002
Not recorded	60 (1%)	45 (1%)	15 (1%)	–	–
Distance to treating facility, miles					
≤20	3,509 (71%)	2,494 (72%)	1,015 (70%)	Ref	Ref
>20	1,359 (28%)	944 (27%)	415 (29%)	1.127 (0.959–1.289)	.080
Not recorded	53 (1%)	37 (1%)	16 (1%)	–	–
Year of diagnosis					
2004–2008	1,711 (35%)	1,207 (35%)	504 (35%)	Ref	Ref
2009–2014	3,210 (65%)	2,268 (65%)	942 (65%)	0.867 (0.765–0.983)	.026

Percentages may not add up to 100% due to rounding.
Abbreviations: CRT, chemoradiotherapy; NOS, not otherwise specified; NSCLC, non–small cell lung cancer; OR, odds ratio.
^aStatistically significant P values are in bold.
^bThe Charlson-Deyo score is a weighted score of comorbidities as defined by several medical codes.

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Concurrent vs Sequential CRT in NSCLC

Table 1. Cohort Characteristics and Factors Associated With Receiving Concurrent CRT (cont.)

Parameter	All Patients (N=4,921)	Negative Margin (N=3,475)	Positive Margin (N=1,446)	Multivariable Logistic Regression	
				OR (95% CI)	P Value ^a
Histology					
Adenocarcinoma	2,479 (50%)	1,916 (55%)	563 (39%)	Ref	Ref
Squamous cell carcinoma	1,498 (30%)	914 (26%)	584 (40%)	1.134 (0.985–1.307)	.081
Adenosquamous carcinoma	169 (3%)	102 (3%)	67 (5%)	1.012 (0.732–1.401)	.941
NSCLC, NOS	233 (5%)	149 (4%)	84 (6%)	1.616 (1.199–2.176)	.002
NSCLC, other	542 (11%)	394 (11%)	148 (10%)	1.130 (0.927–1.378)	.228
Primary tumor location					
Upper lobe	3,025 (62%)	2,158 (62%)	867 (60%)	Ref	Ref
Middle lobe	220 (5%)	149 (4%)	71 (5%)	1.032 (0.776–1.373)	.829
Lower lobe	1,353 (27%)	978 (28%)	375 (26%)	0.879 (0.768–1.006)	.060
Main bronchus	72 (2%)	32 (1%)	40 (3%)	1.004 (0.606–1.665)	.986
Overlapping regions	121 (3%)	75 (2%)	46 (3%)	0.726 (0.497–1.061)	.098
Not specified	130 (3%)	83 (2%)	47 (3%)	0.675 (0.468–0.974)	.036
Tumor grade					
Well-differentiated	227 (5%)	162 (5%)	65 (5%)	Ref	Ref
Moderately differentiated	1,881 (38%)	1,368 (39%)	513 (36%)	0.890 (0.667–1.187)	.428
Poorly differentiated	2,467 (50%)	1,698 (49%)	769 (53%)	0.898 (0.675–1.195)	.462
Not recorded	346 (7%)	247 (7%)	99 (7%)	0.976 (0.684–1.392)	.891
Pathologic T classification					
T1	1,061 (22%)	901 (26%)	160 (11%)	Ref	Ref
T2	1,945 (40%)	1,475 (43%)	470 (33%)	0.879 (0.752–1.027)	.105
T3	1,115 (23%)	656 (19%)	459 (32%)	1.007 (0.834–1.215)	.944
T4	509 (10%)	260 (7%)	249 (17%)	1.236 (0.981–1.559)	.073
Not recorded	291 (6%)	183 (5%)	108 (8%)	0.834 (0.570–1.219)	.349
Pathologic N classification					
N0	1,099 (22%)	602 (17%)	497 (34%)	Ref	Ref
N1	1,062 (22%)	658 (19%)	404 (28%)	0.890 (0.741–1.068)	.210
N2	2,308 (47%)	1,924 (55%)	384 (27%)	0.692 (0.587–0.817)	<.001
N3	41 (1%)	33 (1%)	8 (1%)	2.358 (1.150–4.835)	.019
Not recorded	411 (8%)	258 (7%)	153 (11%)	1.619 (1.156–2.268)	.005
Surgical margin status					
Negative	3,475 (71%)	3,475 (100%)	0 (0%)	Ref	Ref
Positive	1,446 (29%)	0 (0%)	1,446 (100%)	1.750 (1.526–2.007)	<.001
Postoperative CRT					
Sequential	2,271 (46%)	1,780 (51%)	491 (34%)	–	–
Concurrent	2,650 (54%)	1,695 (49%)	955 (66%)	–	–

Percentages may not add up to 100% due to rounding.

Abbreviations: CRT, chemoradiotherapy; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; OR, odds ratio.

^aStatistically significant *P* values are in bold.

^bThe Charlson-Deyo score is a weighted score of comorbidities as defined by several medical codes.

to avoid potential bias from many-to-one matching. Standardized differences were assessed to ensure balance between each of the variables included in calculating the propensity score to the matched cohorts, with a value <0.1 signifying an inconsequential imbalance.³³ Pearson chi-square test was subsequently performed between the matched cohorts to confirm balance among the variable. Survival rates were then compared between the matched groups using the log-rank test.

Results

A complete flow diagram of patient selection is provided in supplemental eFigure 1 (available with this article at JNCCN.org). A total of 4,921 patients met study analysis criteria (Table 1). Of these, 3,475

(71%) were M– and 1,446 (29%) were M+; 2,271 (46%) received sCRT and 2,650 (54%) underwent cCRT. Multivariable logistic regression analysis revealed that independent predictors of cCRT delivery included lower income, treatment at a nonacademic facility, diagnosis at earlier periods (2004–2008), histology of NSCLC not otherwise specified, and M+ disease (*P*<.05 for all). The association with pathologic nodal classification is more difficult to interpret; with pN0 as the reference, patients with pN2 disease were less likely to receive cCRT (*P*<.001), but the very few patients who were evidently pN3 more often underwent cCRT (*P*=.019).

Median follow-up was 30 months (interquartile range, 17–52 months). In all patients, median OS for patients who underwent sCRT was 50 versus 37 months for cCRT (*P*<.001) (supplemental

eFigure 2A. When separating these patients by margin status, sCRT displayed a higher OS in the M– (55 vs 40 months; $P<.001$) and M+ groups (36 vs 31 months; $P=.011$) (Figure 2A,B). Following PSM (supplemental eTables 1–3), these findings persisted among all patients (50 vs 39 months; $P=.001$; supplemental eFigure 2B) and in the M– group (55 vs 40 months; $P<.001$; Figure 2C), but showed equivalence in the M+ group (36 vs 33 months; $P=.745$; Figure 2D).

Given that not all patients with M+ disease had available data on extent of resection, when substratifying them according to resection status and evaluating sCRT versus cCRT, both groups experienced similar OS in R1 (38 vs 37 months; $P=.368$) and R2 resections (25 vs 21 months; $P=.553$) (Figure 3A, B). These populations, namely the patients with R2 resections, were too small to reliably undergo PSM.

When analyzing the sCRT subset only, patients who received chemotherapy followed by RT experienced improved OS compared with those receiving RT followed by chemotherapy (53 vs 39 months; $P=.002$; Figure 3C). Following PSM (supplemental eTable 4), statistical equipoise remained between groups (46 vs 40 months; $P=.229$; Figure 3D).

In the overall cohort, there were several predictors of OS on univariate analysis (Table 2). After multivariate adjustment for potential confounding factors (Table 2), factors independently associated with poorer OS included advancing age, male sex, high comorbidity index, Medicaid insurance, treatment at a non-academic facility and at earlier periods (2004–2008), adenosquamous histology, differentiation status, lower lobe location, T and N classification, surgical margin status, and receipt of cCRT ($P<.05$ for all).

Discussion

Our study of a contemporary national database most notably demonstrates that sCRT is associated with improved outcomes for patients with M– disease, and statistical equipoise for those with M+ disease. Additionally, sCRT performed in a chemotherapy-first manner produced statistically equivalent survival as administering RT-first. Collectively, these hypothesis-generating data do not imply causation (as discussed further) and should ideally be tested prospectively, but do illustrate comparative outcomes between sCRT and cCRT (and sequencing of sCRT) for the first

Figure 1. Kaplan-Meier overall survival curves comparing sequential chemoradiotherapy (gray) versus concurrent chemoradiotherapy (black) in patients with (A) margin-negative disease and (B) margin-positive disease, and in propensity score-matched patients with (C) margin-negative disease and (D) margin-positive disease.

Concurrent vs Sequential CRT in NSCLC

Figure 2. Kaplan-Meier overall survival curves comparing sequential chemoradiotherapy versus concurrent chemoradiotherapy in patients with (A) R1 resection and (B) R2 resection. Comparison of the sequential chemoradiotherapy cohort with receipt of (C) chemotherapy-first versus radiotherapy-first, and (D) after propensity score matching.

time in a large population. To this extent, although the standard of care from prospective data supports adjuvant chemotherapy in both pN1 and pN2 disease (with additional RT in the latter), this study does not support the routine administration of cCRT.

In the absence of prospective data, it is readily acknowledged that retrospective selection biases may limit interpretation of this work. Notably, the cCRT group consisted of higher-risk disease (illustrating adherence to national guidelines), thus likely necessitating more aggressive therapy. These patients may have also likely received suboptimal chemotherapy doses if concurrent RT was delivered. PSM is a powerful tool to control for many of these biases, but only the variables available in the NCDB can be controlled. Although equipoise between both groups was demonstrated for M+ disease, it is entirely possible that cCRT offers a real benefit to higher-risk patients (as observed by examining both R1 and R2 subgroups). However, that benefit is not enough to overcome multiple poor-prognostic factors when comparing to the sCRT group. A converse argument, however, is that delivering aggressive cCRT after lung resection may incur substantially more treatment-related morbidities, some of which may predispose toward earlier mortality, and that the increased toxicity from cCRT could diminish oncologic benefit (potentially even in the higher-risk patient population). Because the NCDB does not record other end points such as locoregional control, cancer-specific survival, or toxicities, it is unclear whether OS differences are cancer-related or morbidity-related. There is less reason to believe both groups experienced similar postoperative or 30-day mortality, given the similar initial slopes of the Kaplan-Meier curves in both groups, without a drastic decline in either group. Nevertheless, single- or multi-institutional data may be able to provide further insight, albeit at the cost of much smaller sample sizes. For instance, Kim et al³⁴ demonstrated an increase in locoregional recurrence-free survival, but no differences in OS, with cCRT in M– cases (n=68).

Likewise, the finding of statistically similar OS for chemotherapy-first and RT-first sCRT can be biased in either direction, especially in the absence of locoregional control as an end point in the NCDB. A major shortcoming of the NCDB is the absence of information on number of received chemotherapy cycles; although all patients received full-dose RT, those who received initial RT may not have tolerated optimal postoperative chemotherapy, thus compromising outcomes. This

group may also have had larger-volume residual disease and/or rapid postoperative recurrence, neither of which is captured by the NCDB. However, the counterargument is the principal rationale for why chemotherapy is most commonly delivered first: namely, that virtually all postoperative patients who warrant combined-modality therapy are at high risk of distant failure, for which early chemotherapy administration is most necessary.

Based on these unavoidable biases in this and other similar NCDB studies,^{5,6} we posit a conservative interpretation of these data: there may not be a benefit to routinely delivering cCRT in patients with M– and M+ disease, but well-selected patients may very well benefit from this approach. It is more intuitive that the relative benefit to concurrent therapy is greater with the larger amount of postoperative disease remaining. Although the NCDB does not code for size/volume of gross residual disease, it is still reasonable to consider cCRT or RT-first sCRT for larg-

er-volume gross residual disease, or potentially even in patients with rapid growth following surgery. Although, most commonly chemotherapy was administered before PORT in patients undergoing sCRT, select patients may very well have an initially higher risk of local/regional failure instead of distant failure.¹⁴ We recommend that decision-making should continue to be made judiciously, while assessing the balance between oncologic benefit and potential adverse events. Factors such as age, performance status, and tolerance of concurrent therapy (along with tolerance of surgery and/or any postoperative events) are essential to consider when determining optimal postoperative management, and despite these data, we highly advocate for individualized management in this circumstance.

Nevertheless, it is also interesting to evaluate factors and trends associated with cCRT versus sCRT delivery. Based on results from multivariable

Table 2. Univariate and Multivariate Cox Proportional Hazards Model for Overall Survival				
Parameter	Univariate		Multivariate	
	HR (95% CI)	P Value ^a	HR (95% CI)	P Value ^a
Age, y				
<65	Ref	Ref	Ref	Ref
65–74	1.323 (1.219–1.437)	<.001	1.312 (1.177–1.462)	<.001
>74	1.598 (1.426–1.790)	<.001	1.543 (1.342–1.774)	<.001
Sex				
Male	Ref	Ref	Ref	Ref
Female	0.761 (0.706–0.821)	<.001	0.782 (0.724–0.846)	<.001
Race				
White	Ref	Ref	Ref	Ref
Black	0.948 (0.835–1.077)	.415	1.041 (0.914–1.187)	.544
Asian	0.682 (0.503–0.925)	.014	0.789 (0.580–1.075)	.134
Other	0.833 (0.562–1.236)	.364	0.843 (0.567–1.253)	.398
Charlson-Deyo score ^b				
0	Ref	Ref	Ref	Ref
1	1.121 (1.031–1.218)	.007	1.084 (0.996–1.179)	.061
≥2	1.236 (1.214–1.527)	<.001	1.296 (1.153–1.457)	<.001
Insurance type				
Medicaid	Ref	Ref	Ref	Ref
Private	0.820 (0.697–0.964)	.017	0.778 (0.660–0.918)	.003
Medicare	1.113 (0.948–1.306)	.190	0.814 (0.679–0.975)	.026
Uninsured	1.075 (0.815–1.419)	.608	1.085 (0.821–1.434)	.566
Other	1.041 (0.900–1.357)	.767	0.941 (0.720–1.230)	.656
Annual income				
<\$63,000	Ref	Ref	–	–
≥\$63,000	0.921 (0.845–1.040)	.063	–	–
Facility type				
Academic	Ref	Ref	Ref	Ref
Nonacademic	1.163 (1.065–1.271)	.001	1.143 (1.044–1.252)	.004
Distance to treating facility, miles				
≤20	Ref	Ref	–	–
>20	0.996 (0.915–1.084)	.930	–	–
Year of diagnosis				
2004–2008	Ref	Ref	Ref	Ref
2009–2014	0.863 (0.798–0.934)	<.001	0.876 (0.808–0.950)	.001

Abbreviations: CRT, chemoradiotherapy; HR, hazard ratio; NOS, not otherwise specified; NSCLC, non-small cell lung cancer.

^aStatistically significant P values are in bold.

^bThe Charlson-Deyo score is a weighted score of comorbidities as defined by several medical codes.

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Concurrent vs Sequential CRT in NSCLC

Table 2. Univariate and Multivariate Cox Proportional Hazards Model for Overall Survival (cont.)

Parameter	Univariate		Multivariate	
	HR (95% CI)	P Value ^a	HR (95% CI)	P Value ^a
Histology				
Adenocarcinoma	Ref	Ref	Ref	Ref
Squamous cell carcinoma	1.234 (1.133–1.345)	<.001	1.063 (0.969–1.165)	.196
Adenosquamous carcinoma	1.468 (1.208–1.784)	<.001	1.314 (1.080–1.600)	.006
NSCLC, NOS	1.281 (1.084–1.512)	.004	1.074 (0.903–1.277)	.420
NSCLC, other	1.079 (0.951–1.223)	.238	1.029 (0.904–1.172)	.663
Primary tumor location				
Upper lobe	Ref	Ref	Ref	Ref
Middle lobe	1.112 (0.927–1.334)	.254	1.138 (0.947–1.366)	.168
Lower lobe	1.130 (1.037–1.231)	.005	1.113 (1.019–1.215)	.017
Main bronchus	1.151 (0.847–1.564)	.369	0.915 (0.670–1.249)	.576
Overlapping regions	1.182 (0.944–1.479)	.145	0.978 (0.780–1.228)	.851
Not specified	0.950 (0.748–1.207)	.674	0.894 (0.701–1.139)	.363
Tumor grade				
Well-differentiated	Ref	Ref	Ref	Ref
Moderately differentiated	1.333 (1.088–1.633)	.005	1.253 (1.021–1.537)	.031
Poorly differentiated	1.397 (1.144–1.707)	.001	1.309 (1.069–1.603)	.009
Not recorded	1.401 (1.103–1.779)	.006	1.272 (0.975–1.588)	.080
Pathologic T classification				
T1	Ref	Ref	Ref	Ref
T2	1.200 (1.081–1.333)	.001	1.167 (1.049–1.198)	<.001
T3	1.244 (1.106–1.400)	<.001	1.314 (1.156–1.492)	<.001
T4	1.663 (1.450–1.807)	<.001	1.647 (1.427–1.901)	<.001
Not recorded	1.665 (1.415–1.960)	<.001	1.574 (1.255–1.976)	<.001
Pathologic N classification				
N0	Ref	Ref	Ref	Ref
N1	1.254 (1.118–1.408)	<.001	1.397 (1.238–1.576)	<.001
N2	1.156 (1.046–1.279)	.005	1.510 (1.351–1.688)	<.001
N3	1.998 (1.375–2.904)	<.001	2.363 (1.616–3.457)	<.001
Not recorded	1.468 (1.270–1.700)	<.001	1.192 (1.058–1.580)	.012
Surgical margin status				
Negative	Ref	Ref	Ref	Ref
Positive	1.373 (1.267–1.488)	<.001	1.272 (1.167–1.387)	<.001
Postoperative CRT				
Sequential	Ref	Ref	Ref	Ref
Concurrent	1.298 (1.203–1.401)	<.001	1.239 (1.144–1.340)	<.001

Abbreviations: CRT, chemoradiotherapy; HR, hazard ratio; NOS, not otherwise specified; NSCLC, non-small cell lung cancer.

^aStatistically significant P values are in bold.

^bThe Charlson-Deyo score is a weighted score of comorbidities as defined by several medical codes.

logistic regression analysis, cCRT seems to be declining in more recent periods (2009–2014), but was still more likely used at nonacademic centers. This finding could relate to the more recent publication of small series,³⁴ and to the potentially higher receptivity to evidence-based management at academic centers. Lastly, because the postoperative CRT cohort mostly comprises pN2 disease, available evidence³ has more commonly used sCRT for these circumstances, which was also observed herein. It was, however, somewhat odd that pN3 cases were more likely to receive cCRT, because surgical procedures do not routinely evaluate these areas.

The independent association between treatment at an academic facility and OS on multivariate analysis has far-reaching implications on patient counseling and management by oncologists and referring providers. There are several potential reasons for this, including greater multimodality coordination,

streamlined diagnostic processes, technical expertise, ancillary support staff for close toxicity monitoring, and potentially the availability of salvage therapies (or clinical trials). Nevertheless, this finding may impact any case of postoperative CRT and could warrant revisions in patterns of patient education.

Although the NCDB provides a unique platform with which to study this important clinical question, the present investigation has some additional limitations to those previously discussed herein. First, the NCDB does not keep track of several other factors, including chemotherapy cycles/agents, performance/functional status, lymph node ratio, lymphovascular invasion, or nature of preoperative workup (including brain MRI and PET staging). It also offers very limited or no information on RT field design, treatment volumes, or techniques. Information in technique is especially important because advanced techniques such as intensity-modulated RT can potentially reduce toxicity risk in the postoperative

setting. Second, no information is provided regarding surgeon experience, reexcision rates, and toxicity-related deaths. Third, the NCDB does not allow for an assessment of subsequent lines of treatment (eg, reirradiation, further systemic and/or targeted therapy), which could influence OS. Nevertheless, the known shortcomings of a national, large-volume database do not undermine the necessity for further prospective investigation; the ongoing LungART trial will likely help address several

unresolved PORT-related controversies (ClinicalTrials.gov identifier: NCT00410683).

Conclusions

This is the largest study to date evaluating sCRT versus cCRT in the postoperative setting. There seems to be no noticeable benefit to routinely delivering cCRT in M– or M+ disease, and sequencing sCRT with either chemotherapy-first or RT-first seemed to

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