Original Study

The Role of Postoperative Radiation Therapy for pN2 Non–small-cell Lung Cancer

Nikhil P. Mankuzhy,[1,2] Muayad F. Almahariq,[1] Zaid A. Siddiqui,[1] Andrew B. Thompson,[1] Inga S. Grills,[1] Thomas M. Guerrero,[1] Kuei C. Lee,[1] Craig W. Stevens,[1] Thomas J. Quinn[1]

Abstract

The role of postoperative radiation therapy for locally advanced lung cancer remains controversial. We conducted a propensity score and inverse probability of treatment weighting retrospective cohort analysis using the Surveillance, Epidemiology, and End Results database. After accounting for baseline characteristics and receipt of chemotherapy, postoperative radiation therapy improved overall survival among a subset of patients with a positive to sampled lymph node ratio ≥ 50%.

Background: The role for postoperative radiation therapy (PORT) for patients with non–small-cell lung cancer (NSCLC) with mediastinal lymph node (LN) involvement (pN2 disease) is controversial. We compared surgery alone with PORT among patients with pN2 NSCLC. We then performed subset analyses to better delineate patients that might benefit from PORT. **Patients and Methods:** We conducted a propensity score (PS)-matched, inverse probability of treatment weighting (IPTW) Surveillance, Epidemiology, and End Results (SEER) analysis of patients with pN2 disease from 1989 to 2016 with surgery alone or PORT. Multiple imputation with chained equations was used for missing LN data. **Results:** A total of 8631 patients were included in this analysis; 4579 underwent surgery alone, and 4052 underwent PORT. Following PS matching and IPTW, there was no difference in overall survival (OS) (hazard ratio [HR], 0.99; $P = .76$). However, PORT improved OS among a subset of patients with a LN positive to sampled ratio $\geq$ 50% (HR, 0.90; $P = .01$). Moreover, there was a trend towards improved OS among this subset, even with chemotherapy (HR, 0.91; $P = .09$). **Conclusion:** PORT is not associated with an improvement or detriment in OS for all patients with pN2 NSCLC. However, patients with a positive to sampled LN ratio $\geq$ 50% may benefit, regardless of chemotherapy status. Nevertheless, PORT will remain the standard of care as we await the results of the ongoing LUNG ART trial.

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Introduction

Lung cancer is the leading cause of cancer death in the United States, comprising almost one-quarter of the estimated cancer deaths in men and women.[1] Over 80% of lung cancer cases are non–small-cell lung cancer (NSCLC), with the vast majority being locally advanced.[2,3] For patients who undergo resection, there is a plethora of level 1 evidence that supports the use of adjuvant chemotherapy, with improvement in both overall survival (OS) and disease-free survival.[4] However, the role for postoperative radiation therapy (PORT) remains controversial as studies demonstrate conflicting results regarding improvement in OS and locoregional control. Recent evidence-based clinical practice guidelines indicate no high-level evidence for routine implementation of PORT; however, its use in patients with positive margins (R1 resection), gross residual disease (R2 resection), or mediastinal lymph node (LN) involvement (pN2 disease) may bolster locoregional control and potentially OS.[5]

The PORT meta-analysis, conducted initially in 1998[6] and updated in 2016,[7] consistently demonstrated an overall adverse effect of PORT on OS (hazard ratio [HR], 1.18), with a 2-year absolute survival detriment of 5%. However, among patients with pN2 disease, there was no clear evidence of worse outcomes, warranting continued investigation to determine the potential

[1]Department of Radiation Oncology, Beaumont Health, Royal Oak, MI
[2]Oakland University William Beaumont School of Medicine, Rochester, MI

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Address for correspondence: Thomas J. Quinn, MD, Department of Radiation Oncology, Beaumont Health, 3601 W 13 Mile Rd, Royal Oak, MI 48073
E-mail contact: thomas.quinn@beaumont.org

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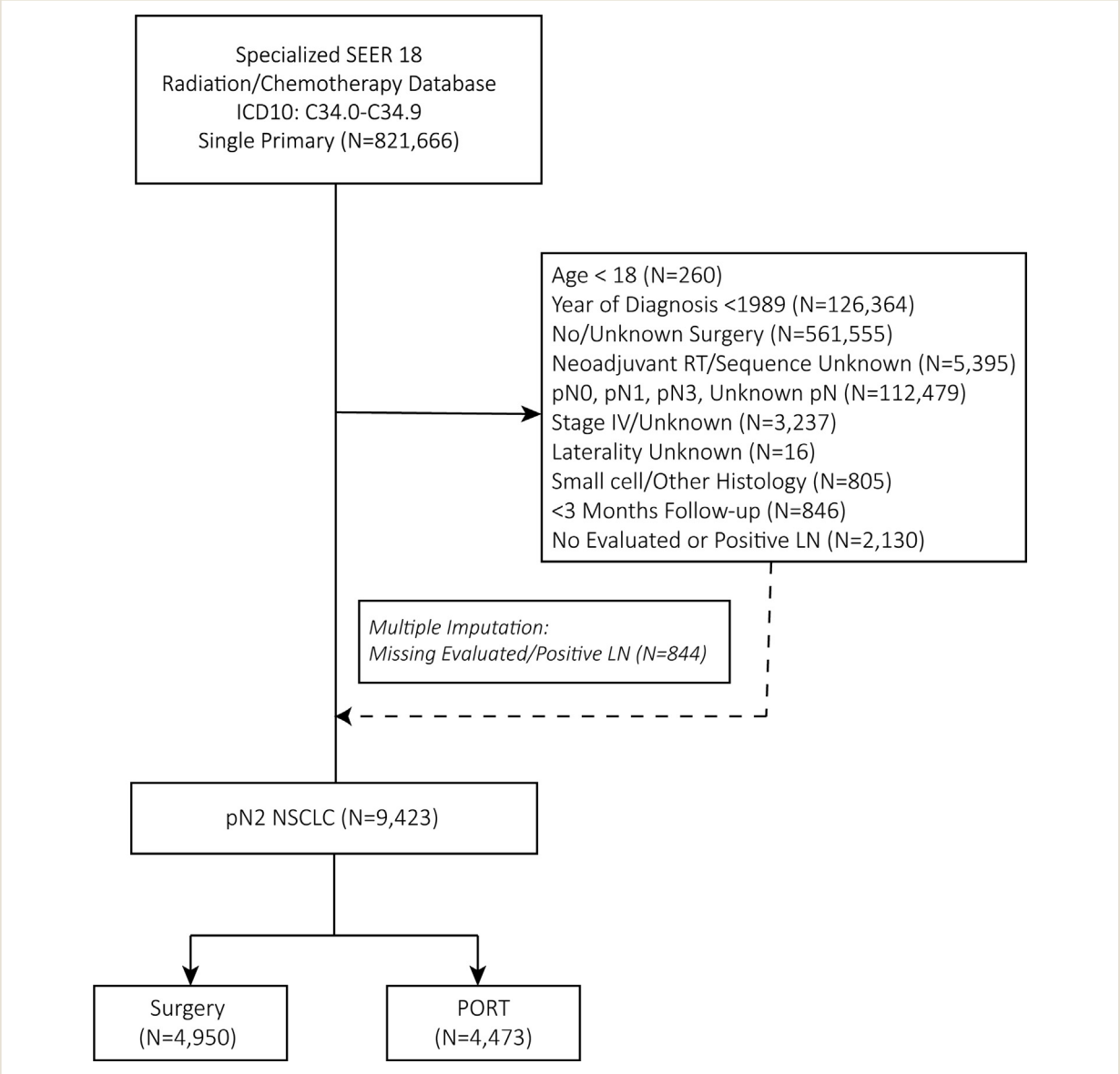
benefit of PORT for mediastinal nodal disease. Of note, in their findings, the overall detriment to locoregional recurrence (LRR)-free survival was less than what was observed for OS, and that LRR-free survival was largely influenced by survival with deaths accounting the majority of events.[7] As such, the adverse effect of PORT could be attributable to other factors rather than inferior tumor control or adverse treatment effects. Given significant advances in radiotherapy (RT) techniques and contemporary staging with better surgical techniques and positron emission tomography-computed tomography scans, a modern analysis is necessary to further elucidate the effect of PORT in pN2 NSCLC.[8] Ongoing phase III trials are also evaluating the utility of PORT in patients with pN2 disease (NCT00410683).[9] Recent institutional retrospective and database registry analyses support the use of PORT in pN2 disease, but these studies are limited in generalizability.[10-12]

While we await the results of ongoing clinical trials, further investigation into the impact of PORT will provide guidance for clinicians. In this paper, we used the Surveillance, Epidemiology, and End Results (SEER) database to determine the impact of PORT on survival in patients with pN2 NSCLC. This is the largest retrospective study addressing this question and the first SEER analysis to take into account the use of systemic therapy, which was only recently added to SEER.

Figure 1 CONSORT Diagram Demonstrating the Inclusion and Exclusion Criteria Use to Select Cases With pN2 NSCLC



Abbreviations: ICD-10 = International Classification of Diseases, Tenth Edition; LN = lymph node; NSCLC = non–small-cell lung cancer; PORT = postoperative radiotherapy; RT = radiotherapy; SEER = Surveillance, Epidemiology, and End Results.

Patients and Methods

Data Source

The SEER Program collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 34% of the United States population. The specialized Radiation/Chemotherapy Database (SEER 18 Custom Data, November 2018 Submission) was used as it contains information on radiation therapy, sequence of radiation with respect to surgery, and chemotherapy. Of note, the chemotherapy field is coded either as yes or none/unknown.

Cohort Analyzed

The SEER 18 Custom Data registries were queried for International Classification of Disease C34.0-C34.9, with histologic confirmation of malignancy, corresponding to malignant neoplasms of the lung. Patients were excluded as detailed in the CONSORT diagram (Figure 1). From 1989 to 2016, a total of 8631 patients with pN2 NSCLC were identified; 4579 underwent surgical resection and 4052 underwent combined surgical resection with PORT.

Statistical Analysis

Baseline patient characteristics were assessed pre- and post-matching with χ^2 analysis and standard mean difference, where a standard mean difference > 0.1 was considered unbalanced.[13] Univariate analysis (UVA) of patient characteristics impact on OS was performed using the Kaplan-Meier (KM) method, with the log rank method to assess for significance.[14] Multivariable analysis (MVA) of patient characteristics and OS was performed using Cox proportional hazards regression modeling. Covariates included in the MVA model were selected if they were significant in the UVA model.

Multiple imputation by chained equations was used to replace missing data.[15] Specifically, multiple imputations were performed for the SEER parameters Regional nodes examined (1988+) and Regional nodes positive (1988+). A propensity score (PS)-matched analysis was performed to account for indication bias. PS were estimated using binary logistic regression modeling for receipt of surgery alone or PORT.[16] Next, inverse probability of treatment weights (IPTW) were calculated as 1/PS and 1/(1-PS).[17] Stabilization of the IPTWs was performed by multiplying the standard IPTWs by the probability of undergoing treatment that each patient received.[18] Finally, IPTW-adjusted UVA and doubly robust, IPTW-adjusted MVA were performed. A landmark survival time of 3 months was utilized in order to take immortal time bias into account.[19] Exploratory subgroup analyses were conducted and evaluated for heterogeneity using the fixed effects model as the subgroups assessed are presumed to have been subjected to similar conditions.[20] Quantification of heterogeneity was assessed with the I^2 statistic and the Cochran Q test.[21]

All statistics were completed using SEER*Stat (v8.3.5, The Surveillance Research Program of the Division of Cancer Control and Population Sciences, National Cancer Institute) and RStudio (v1.2.1335). Furthermore, all statistical analyses were performed as 2-sided with $P < .05$ considered statistically significant. R markdown for all analyses are available upon request.

Results

Patient Characteristics

The majority (71%) of patients included in this analysis were 60 years or older with median age at diagnosis of 66 years (interquartile range [IQR], 58-72 years). A majority of patients had adenocarcinoma (65%) or squamous cell carcinoma (23%). Most patients were stage IIIA (87%). The majority of patients underwent lobectomy (75%) and received chemotherapy (61%), whereas just under 50% of patients underwent PORT (47%). A total of 13.6% and 15% of patients analyzed were missing total number of LNs evaluated and LNs positive, respectively. Therefore, multiple imputation by chained equations was performed to account for missing data. Furthermore, SEER does not provide a breakdown of the number of LNs evaluated from each nodal station (N1, N2, or N3); therefore, only the total number of sampled LNs could be assessed. The median number of LNs evaluated was 9 (IQR, 5-15), and the median number of positive LNs was 2 (IQR, 1-5), of which at least 1 came from the N2 station. Most (65%) patients had a positive to sampled LN ratio of $< 50\%$. The median follow-up time for the entire cohort was 24 months (IQR, 12-49 months).

Baseline characteristics were significantly unbalanced when stratifying the population by receipt of PORT (Table 1). Patients who received PORT tended to be slightly younger (64 vs. 67 years old; $P < .001$) and tended to be treated at earlier time periods ($P < .001$). Patients who received PORT were more likely to undergo a limited resection (12% vs. 8.4%; $P < .001$) and were documented as having received chemotherapy (71% vs. 51%; $P < .001$). In addition, patients undergoing PORT had fewer LNs evaluated (9 vs. 10; $P < .001$), more LNs positive (3 vs. 2; $P < .001$), and a higher positive to sampled LN ratio (36% vs. 29%; $P < .001$). However, after PS matching and IPTW, all baseline characteristics were well-balanced between treatment arms ($P \geq .05$) (Table 1).

Overall Survival

For the entire cohort of pN2 NSCLC, the median OS, after adjusting for imbalances in baseline characteristics, was 28 months (IQR, 27-29 months), with corresponding 2- and 5-year point estimates of 54.8% (95% confidence interval [CI], 53.8%-55.9%) and 26.8% (95% CI, 25.9%-27.9%), respectively. Prior to PS matching, there was no significant difference in OS when stratified by receipt of PORT (HR, 1; 95% CI, 0.97-1.1; $P = .65$) (Figure 2A). Similarly, after matching, there was no significant difference in OS (median 28 vs. 27 months; HR, 0.99; 95% CI, 0.95-1; $P = .76$) (Figure 2B). The corresponding 2-year (55.3% vs. 54.3%; $P = .99$) and 5-year (26.9% vs. 26.8%; $P = .82$) OS point estimates were not statistically different.

Subgroup Analysis

An exploratory analysis was conducted to identify a subset of patients for whom PORT might provide a benefit as shown in the forest plot in Figure 3. Prior to PS matching and IPTW, there was low heterogeneity ($I^2 = 27\%$; 95% CI, 0%-51.1%; Q = 64; $P = .051$), but after IPTW adjustment, heterogeneity was eliminated ($I^2 = 0\%$; Q = 42; $P = .67$). There were several subgroups with possible improved survival with PORT. Prior to matching, patients who were diagnosed between 2005 and 2016 (HR, 0.92; 95% CI,

Table 1 Baseline Patient Characteristics

	Unadjusted			IPTW Adjusted		
	Surgery Alone (N = 4579)	PORT (N = 4052)	*P* Value[a]	Surgery Alone (N = 4779.13)	PORT (N = 4269.32)	*P* Value[a]
Age at diagnosis, y (range)	67 (59-74)	64 (57-71)	<.001	66 (58-72)	65.8 (58-72)	.264
Gender			.088			.521
Female	2493 (50)	2173 (49)		2396.4 (50.1)	2109.4 (49.4)	
Male	2457 (50)	2300 (51)		2382.7 (49.9)	2159.9 (50.6)	
Race			>.9			.911
Caucasian	4055 (82)	3665 (82)		3912.0 (81.9)	3482.0 (81.6)	
African-American	489 (9.9)	432 (9.7)		476.4 (10.0)	421.6 (9.9)	
Other	401 (8.1)	372 (8.3)		386.6 (8.1)	362.7 (8.5)	
Unknown	5 (0.1)	4 (<0.1)		4.2 (0.1)	3.1 (0.1)	
Insurance			<.001			.784
Insured	2192 (44)	1575 (35)		1923.8 (40.3)	1674.8 (39.2)	
Medicaid	263 (5.3)	202 (4.5)		227.2 (4.8)	200.6 (4.7)	
Uninsured	46 (0.9)	34 (0.8)		40.7 (0.9)	34.3 (0.8)	
Unknown	2449 (49)	2662 (60)		2587.4 (54.1)	2359.6 (55.3)	
Marital status			<.001			.853
Single	563 (11)	438 (9.8)		509.9 (10.7)	425.8 (10.0)	
Married	2886 (58)	2916 (65)		2939.6 (61.5)	2664.7 (62.4)	
Divorced	579 (12)	465 (10)		523.5 (11.0)	473.6 (11.1)	
Widowed	764 (15)	536 (12)		667.3 (14.0)	586.5 (13.7)	
Unknown	158 (3.2)	118 (2.6)		138.8 (2.9)	118.8 (2.8)	
Median income			.01			.829
<$50,000	894 (18)	888 (20)		891.0 (18.6)	819.1 (19.2)	
$50,000-64,999	2080 (42)	1754 (39)		1968.7 (41.2)	1742.6 (40.8)	
$65,000+	1976 (40)	1831 (41)		1919.4 (40.2)	1707.7 (40.0)	
Year of diagnosis			<.001			.191
1989-1994	289 (5.8)	648 (14)		438.8 (9.2)	439.2 (10.3)	
1995-2004	1547 (31)	1698 (38)		1650.6 (34.5)	1493.1 (35.0)	
2005-2016	3114 (63)	2127 (48)		2689.7 (56.3)	2337.0 (54.7)	
Primary tumor location			<.001			.932
Upper lobe	2756 (56)	2716 (61)		2777.9 (58.1)	2519.5 (59.0)	
Middle lobe	202 (4.1)	209 (4.7)		205.9 (4.3)	189.9 (4.4)	
Lower lobe	1703 (34)	1316 (29)		1534.4 (32.1)	1325.2 (31.0)	
Main bronchus	72 (1.5)	67 (1.5)		63.0 (1.3)	60.6 (1.4)	
Overlapping lesion	133 (2.7)	107 (2.4)		120.6 (2.5)	109.2 (2.6)	
Lobe, NOS	84 (1.7)	58 (1.3)		77.3 (1.6)	64.8 (1.5)	
Laterality			.2			.504
Right	2635 (53)	2446 (55)		2553.7 (53.4)	2313.9 (54.2)	
Left	2315 (47)	2027 (45)		2225.4 (46.6)	1955.4 (45.8)	
Tumor histology			.8			.898
Adenocarcinoma	3181 (64)	2907 (65)		3108.4 (65.0)	2752.9 (64.5)	
Adenosquamous carcinoma	187 (3.8)	170 (3.8)		180.4 (3.8)	172.6 (4.0)	
NSCLC	428 (8.6)	391 (8.7)		412.4 (8.6)	364.2 (8.5)	
Squamous cell carcinoma	1154 (23)	1005 (22)		1077.9 (22.6)	979.6 (22.9)	

Table 1 Continued

	Unadjusted			IPTW Adjusted		
	Surgery Alone (N = 4579)	PORT (N = 4052)	*P* Value[a]	Surgery Alone (N = 4779.13)	PORT (N = 4269.32)	*P* Value[a]
Tumor grade			.007			.923
Well-differentiated (I)	252 (5.1)	174 (3.9)		214.8 (4.5)	178.4 (4.2)	
Moderately differentiated (II)	1825 (37)	1643 (37)		1750.7 (36.6)	1596.6 (37.4)	
Poorly differentiated (III)	2306 (47)	2098 (47)		2241.1 (46.9)	1994.9 (46.7)	
Anaplastic (IV)	177 (3.6)	208 (4.7)		192.7 (4.0)	170.9 (4.0)	
Unknown	390 (7.9)	350 (7.8)		379.8 (7.9)	328.5 (7.7)	
Pleural involvement			<.001			.912
PL 0	872 (18)	711 (16)		795.7 (16.7)	722.7 (16.9)	
PL 1	142 (2.9)	102 (2.3)		124.6 (2.6)	108.6 (2.5)	
PL 2	153 (3.1)	95 (2.1)		130.4 (2.7)	103.8 (2.4)	
PL 3	45 (0.9)	28 (0.6)		35.8 (0.7)	28.2 (0.7)	
Unknown	3738 (76)	3537 (79)		3692.6 (77.3)	3306.1 (77.4)	
Type of surgery			<.001			.636
Lobectomy	3782 (76)	3322 (74)		3601.7 (75.4)	3218.1 (75.4)	
Limited resection	414 (8.4)	554 (12)		485.2 (10.2)	456.2 (10.7)	
Pneumonectomy	754 (15)	597 (13)		692.2 (14.5)	595.1 (13.9)	
Pathologic stage			.007			.493
IIIA	4346 (88)	3842 (86)		4164.1 (87.1)	3697.4 (86.6)	
IIIB	604 (12)	631 (14)		615.0 (12.9)	571.9 (13.4)	
Number of LNs sampled	10 (6-16)	9 (5-15)	<.001	9 (5-15)	9 (5-15)	.534
Number of LNs positive	2 (1-5)	3 (1-5)	<.001	2 (1-5)	2 (1-5)	.625
Ratio of positive to sampled LNs	0.29 (0.15-0.53)	0.36 (0.20-0.67)	<.001	0.33 (0.17-0.60)	0.33 (0.17-0.60)	.304
Positive LN ratio stratified			<.001			.37
<50%	3389 (68)	2692 (60)		3086.9 (64.6)	2715.6 (63.6)	
≥50%	1561 (32)	1781 (40)		1692.2 (35.4)	1553.7 (36.4)	
Chemotherapy			<.001			.089
No/unknown	2404 (49)	1313 (29)		1913.7 (40.0)	1625.6 (38.1)	
Yes	2546 (51)	3160 (71)		2865.4 (60.0)	2643.7 (61.9)	
Follow-up time, mos	24 (11-49)	23 (12-49)	.11	24 (11-49)	23 (12-49)	.178

Statistics presented: median (IQR); n (%)

Abbreviations: IPTW = inverse probability of treatment weighting; LN = lymph node; NOS = not otherwise specified; NSCLC = non–small-cell lung cancer; PL 0 = no evidence of visceral pleural invasion, tumor does not completely traverse the elastic layer; PL 1 = invasion beyond the visceral elastic pleura, but limited to the pulmonary pleura, tumor extends through the elastic layer; PL 2 = invasion to the surface of the pulmonary pleura, tumor extends to the surface of the visceral pleura; PL 3 = tumor extends to the parietal pleura; PORT = postoperative radiotherapy.

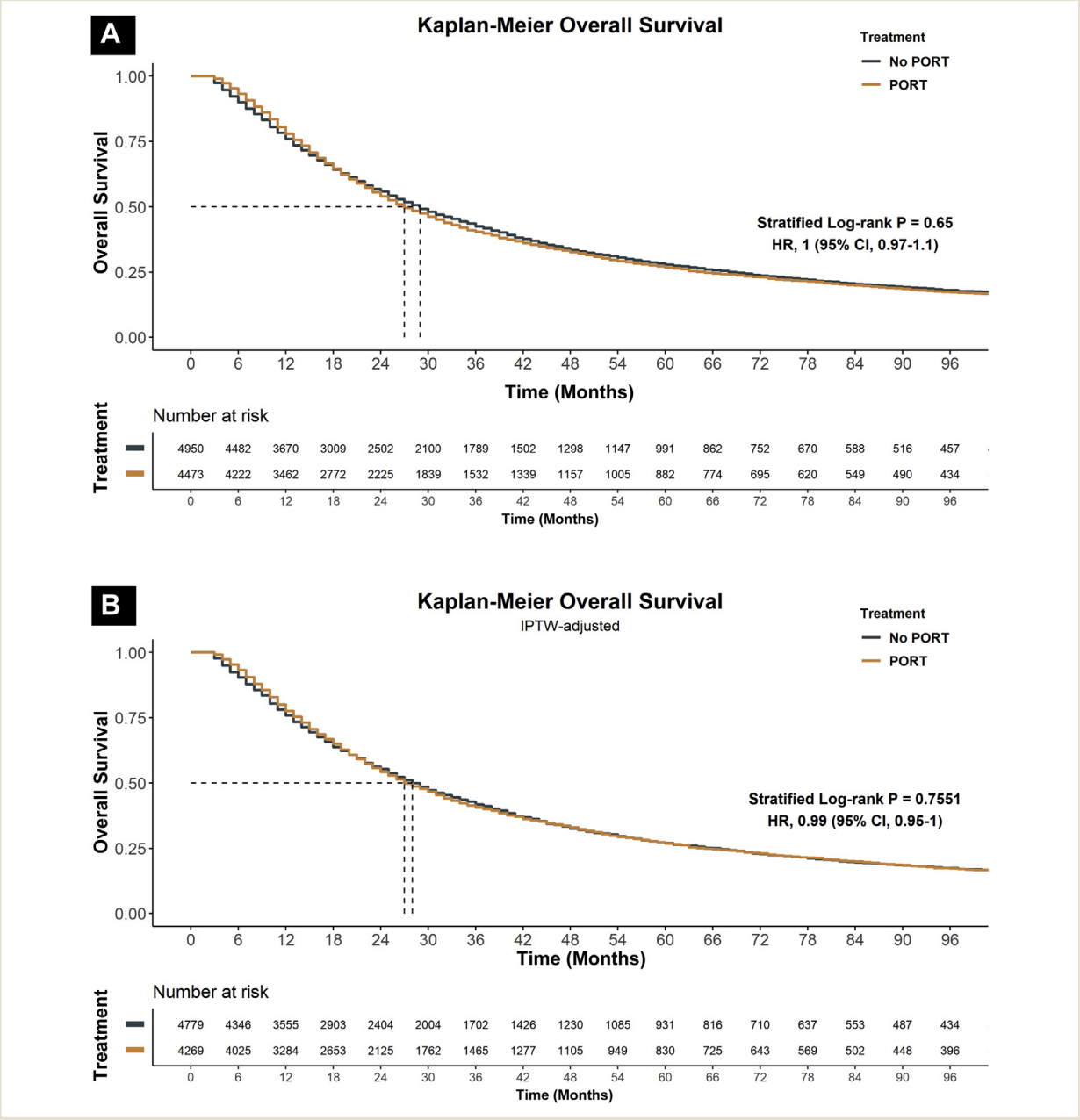
[a]Statistical tests performed: Wilcoxon rank-sum test; χ^2 test of independence; Fisher exact test.

0.85-0.99; $P = .02$), had insurance (HR, 0.91; 95% CI, 0.84-0.99; $P = .04$), or had an LN-positive ratio ≥ 50% (HR, 0.91; 95% CI, 0.84-0.98; $P = .01$) all appeared to benefit from PORT (Figure 3A). However, following IPTW adjustment (Figure 3B), the subgroup that appeared to benefit the most from PORT were patients with LN-positive ratio ≥ 50% (HR, 0.90; 95% CI, 0.84-0.97; $P = .01$), whereas male patients had a less robust benefit of PORT (HR, 0.94; 95% CI, 0.88-1.0; $P = .04$). In contrast, after matching, widowed patients seemed to do worse with PORT (HR, 1.16; 95% CI, 1.02-1.31; $P = .02$).

Positive to Evaluated LN Ratio Subgroup Analysis

We further explored the impact of PORT in patients with a LN-positive ratio ≥ 50%. A total of 3342 patients were identified within this subgroup, of whom 1977 received chemotherapy as part of their treatment. Patients with LN-positive ratio ≥ 50% had improved outcomes both before (HR, 0.91; 95% CI, 0.84-0.98; $P = .01$) (Figure 4A) and after PS matching with IPTW (HR, 0.9; 95% CI, 0.84-0.97; $P = .01$) (Figure 4B). However, among those patients with a LN-positive ratio ≥ 50% and who received chemotherapy, there was no improvement in OS prior to matching

Figure 2 Overall Survival, Stratified by Receipt of PORT, for Patients With pN2 Non–small-cell Lung Cancer before (A) and after Propensity Score-matching With Inverse Probability of Treatment Weighting Adjustment (B)



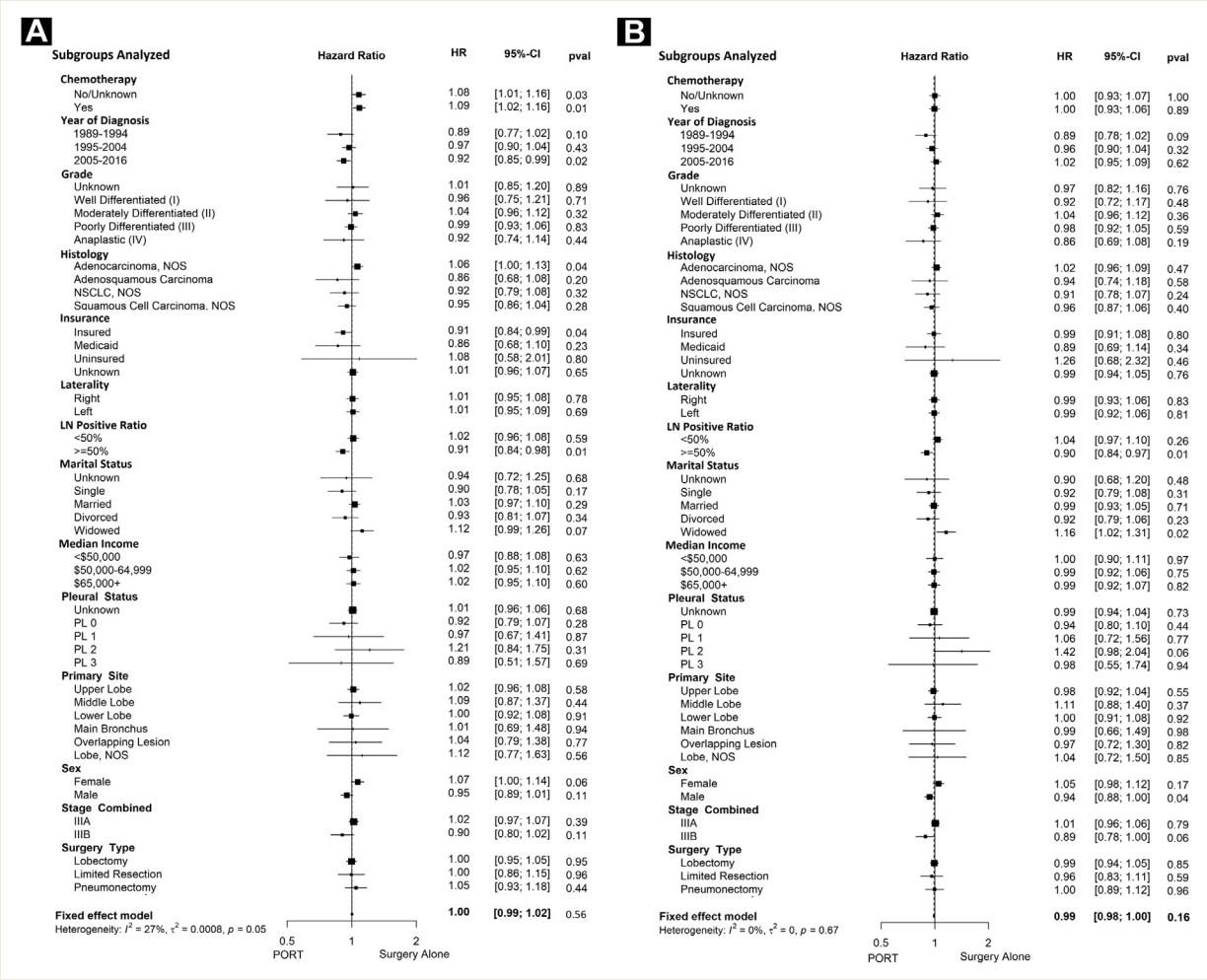
Abbreviations: CI = confidence interval; HR = hazard ratio; IPTW = inverse probability of treatment weighting; PORT = postoperative radiation therapy.

(HR, 0.97; 95% CI, 0.88-1.1; $P = .61$) (Figure 4C). However, after accounting for baseline imbalances, PORT trended towards improved OS (HR, 0.91; 95% CI, 0.82-1; $P = .09$) (Figure 4D).

Univariate Analysis

We performed UVA to correlate baseline, tumor-, and treatment-related characteristics with OS among the entire cohort of patients with pN2 disease (Table 2). After PS matching, higher median income (HR, 0.83; $P < .001$), year of diagnosis 1995 to 2004 (HR, 0.8; $P < .001$), year of diagnosis 2005 to 2016 (HR, 0.55; $P < .001$), and increased number of LNs sampled (HR, 0.99; $P < .001$) were associated with improved OS. In contrast, age as a continuous variable (HR, 1.02; $P < .001$), male gender (HR, 1.28; $P < .001$), lower lobe tumor location (HR, 1.1; $P < .001$), grade 2 disease (HR, 1.18; $P = .01$), grade 3 disease (HR, 1.35; $P < .001$), grade 4 disease (HR, 1.51; 95% CI, 1.2-1.9; $P < .001$), tumor extension to parietal pleura (PL 3) (HR, 2.5; $P < .001$), adenosquamous (HR, 1.24; $P < .001$), NSCLC, not otherwise specified (HR, 1.15;

Figure 3 Exploratory Subgroup Analysis of Patient-, Tumor-, and Treatment-Related Characteristics before (A) and after Inverse Probability of Treatment Weighting Adjustment (B). HR < 1 Favors Postoperative Radiation Therapy and HR > 1 Favors Surgery Alone



Abbreviations: CI = confidence interval; HR = hazard ratio; LN = lymph node; NOS = not otherwise specified; NSCLC = non–small-cell lung cancer; PORT = postoperative radiation therapy.

$P = .001$), and squamous histology (HR, 1.18; $P < .001$) were associated with worse OS.

Patients with positive LN ratio $\geq$ 50% had worse OS (HR, 1.5; $P < .001$). In terms of other treatment-related factors, limited resection (HR, 1.31; $P < .001$) and pneumonectomy (HR, 1.29; $P < .001$) were associated with worse OS. In contrast, the receipt of chemotherapy (HR, 0.7; $P < .001$) was associated with improved OS.

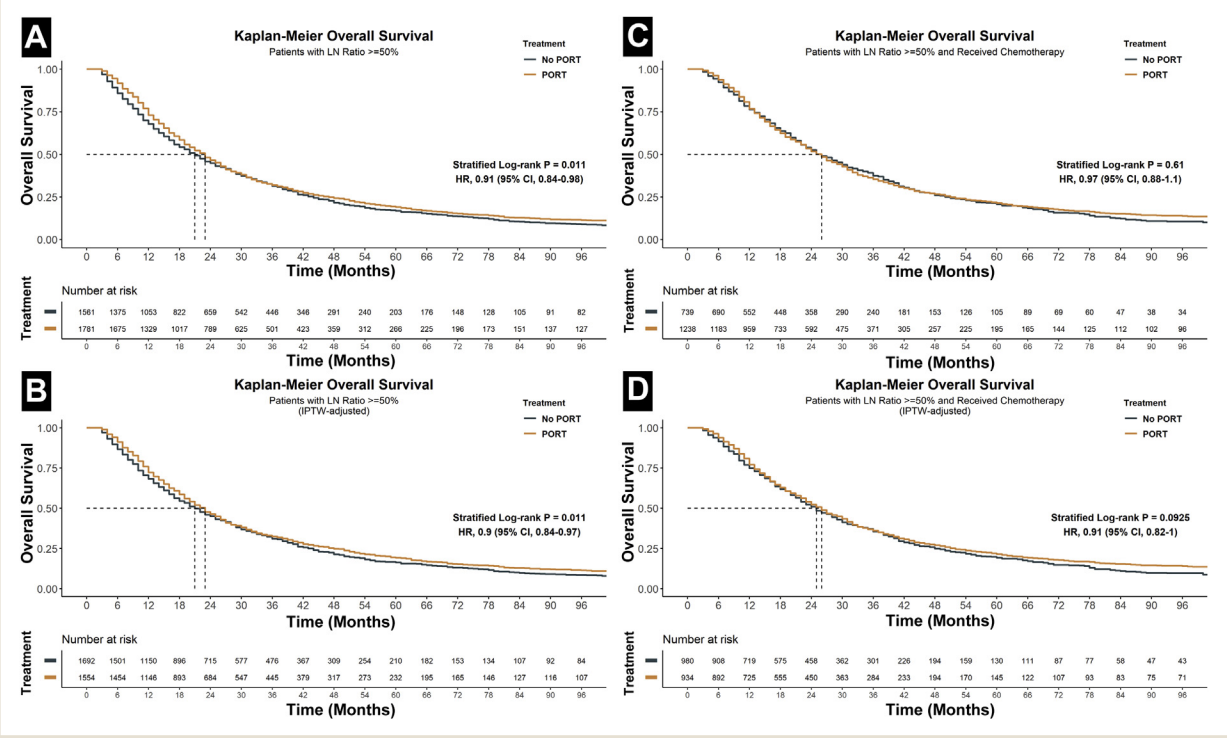
Multivariable Analysis

MVA of factors that were significant on UVA was performed among the entire cohort of patients with pN2 disease (Table 3). Similar to UVA, female gender, year of diagnosis, and higher median income were associated with improved OS in the unadjusted MVA and doubly robust MVA. Similarly, age at diagnosis, PL 2 and PL 3 disease, stage IIIB disease, and grade 2/3/4 disease were associated with worse OS in both MVA models. In terms of surgical management, limited resection and pneumonectomy remained associated with worse OS as did having a $\geq$ 50% positive LN ratio. Finally, the receipt of chemotherapy was protective in both models with the doubly robust MVA demonstrating an HR of 0.88 ($P < .001$).

Discussion

In this large SEER analysis of patients treated from 1989 to 2016, we found that PORT for pN2 NSCLC was not associated with an improvement in OS. An exploratory subgroup analysis identified patients with a ratio of positive to sampled LNs of $\geq$ 50% may benefit the most from PORT. Moreover, this particular factor was highly statistically significant as a predictor for worse OS in both the PS-matched and IPTW UVA and MVA. The benefit of PORT trended towards significance among the subgroup of patients receiving chemotherapy. To our knowledge, this is the first SEER analysis to account for the use of chemotherapy.

Figure 4 Subgroup Analysis of Overall Survival, Stratified by Receipt of Postoperative Radiation Therapy, for Patients With pN2 NSCLC and Lymph Node Positive Ratio ≥ 50% (A) and after Propensity Score Matching With Inverse Probability of Treatment Weighting Adjustment (B). Subgroup Analysis of Overall Survival, Stratified by Receipt of Postoperative Radiation Therapy, for Patients With pN2 NSCLC, Receiving Chemotherapy, and Lymph Node-positive Ratio ≥ 50% (C) and after Propensity Score Matching With Inverse Probability of Treatment Weighting Adjustment (D)



Abbreviations: CI = confidence interval; HR = hazard ratio; IPTW = inverse probability of treatment weighting; LN = lymph node; NSCLC = non–small-cell lung cancer; PORT = postoperative radiation therapy.

The updated PORT meta-analysis included 2343 patients from 14 trials conducted between 1966 and 1998, comparing surgery alone with surgery and adjuvant RT. Results indicated that although PORT was detrimental to OS for all patients, there was improved local control of disease and adverse survival effect among patients with N2 disease.[7] Our findings suggest that the benefit of PORT is limited to individuals with at least a 1:2 ratio of positive to sampled LNs, and not to all pN2 patients, regardless of systemic therapy use. Patients with an adequate LN sampling with a low number of positive mediastinal LNs may not benefit from PORT.

Several prior SEER analyses have investigated the impact of PORT in patients with pN2 disease treated in earlier periods.[22-25] Overall, these analyses were in favor of PORT in this subset of patients. One analysis in particular did find a benefit for PORT in patients with > 50% positive LN ratio.[25] However, these studies either did not adjust for baseline characteristics, used 1:1 matching, which excluded nearly 50% of patients, or were not able to account for the receipt of chemotherapy. These factors likely confounded the results and explain the discrepancy with our analysis, which did not find a benefit for PORT in patients with pN2 disease overall. Another potential explanation is that our analysis is the most up-to-date and includes a large percentage of patients treated with modern RT. A SEER analysis investigating intercurrent heart disease after PORT demonstrated a reduction of heart disease mortality when comparing periods of treatment of 1983 to 1998 with 1989 to 1993.[26] This highlights a potential benefit of improved RT planning and delivery techniques in sparing the heart and reducing radiation-related cardiac mortality.

The lack of chemotherapy in prior analyses is likely a major confounding variable as adjuvant chemotherapy after surgery improves survival, irrespective of combination with PORT.[27] Several studies have looked at PORT in patients who received chemotherapy. A single-institution retrospective review demonstrated a trend towards improved disease-free survival at 3 years with concurrent chemoradiotherapy (CCRT) versus RT alone.[28] A secondary analysis of the Adjuvant Navelbine International Trialist Association (ANITA) phase III trial, in which PORT was not randomized but recommended per institutional preference for node-positive disease, showed PORT was detrimental to survival; however, for pN2 disease, PORT with chemotherapy and PORT with observation improved 5-year survival rates compared with chemotherapy alone and observation alone, respectively. Although PORT decreased LRR among all patients, excess death rates of "other" and "unknown" causes in the PORT group (18% with PORT and 11% without PORT) is suggestive of treatment-related adverse events.[29] Finally, a small national-level cohort study investigated radiation

Table 2 Univariate Analysis

Characteristic	Unadjusted			IPTW Adjusted		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Age at diagnosis, y	1.02	1.02-1.02	<.001	1.02	1.02-1.02	<.001
Gender						
Female	—	—		—	—	
Male	1.3	1.24-1.36	<.001	1.28	1.22-1.34	<.001
Race						
Caucasian	—	—		—	—	
African-American	0.93	0.86-1.01	.1	0.96	0.89-1.04	.3
Other	0.83	0.76-0.91	<.001	0.83	0.76-0.91	<.001
Unknown	0.42	0.14-1.31	.14	0.34	0.08-1.38	.13
Insurance						
Insured	—	—		—	—	
Medicaid	1.14	1.01-1.29	.039	1.12	0.98-1.28	.089
Uninsured	0.82	0.60-1.11	.2	0.92	0.68-1.25	.6
Unknown	1.48	1.41-1.56	<.001	1.55	1.47-1.63	<.001
Marital status						
Single	—	—		—	—	
Married	1.07	0.99-1.16	.083	1.05	0.97-1.14	.2
Divorced	1.08	0.98-1.20	.13	1.07	0.96-1.19	.2
Widowed	1.21	1.10-1.33	<.001	1.22	1.11-1.35	<.001
Unknown	1.16	0.99-1.36	.06	1.1	0.94-1.29	.2
Median income						
<$50,000	—	—		—	—	
$50,000-64,999	0.93	0.87-0.99	.032	0.92	0.86-0.98	.014
$65,000+	0.84	0.79-0.90	<.001	0.83	0.77-0.88	<.001
Year of diagnosis						
1989-1994	—	—		—	—	
1995-2004	0.81	0.76-0.88	<.001	0.8	0.74-0.86	<.001
2005-2016	0.58	0.54-0.62	<.001	0.55	0.51-0.60	<.001
Primary tumor location						
Upper lobe	—	—		—	—	
Middle lobe	1	0.89-1.12	>.9	0.97	0.86-1.09	.6
Lower lobe	1.11	1.05-1.17	<.001	1.1	1.05-1.16	<.001
Main bronchus	1.1	0.91-1.34	.3	1.07	0.88-1.32	.5
Overlapping lesion	1.2	1.04-1.39	.012	1.11	0.96-1.29	.2
Lobe, NOS	1.15	0.95-1.39	.15	1.16	0.96-1.39	.13
Laterality						
Right	—	—		—	—	
Left	1.03	0.98-1.08	.2	1.03	0.98-1.08	.2
Tumor histology						
Adenocarcinoma, NOS	—	—		—	—	
Adenosquamous carcinoma	1.23	1.09-1.38	<.001	1.24	1.10-1.40	<.001
NSCLC, NOS	1.15	1.06-1.25	<.001	1.15	1.06-1.25	.001
Squamous cell carcinoma, NOS	1.16	1.10-1.23	<.001	1.18	1.11-1.24	<.001
Tumor grade						
Well-differentiated (I)	—	—		—	—	
Moderately differentiated (II)	1.15	1.02-1.29	.027	1.18	1.04-1.34	.011
Poorly differentiated (III)	1.33	1.18-1.50	<.001	1.35	1.19-1.53	<.001
Anaplastic (IV)	1.47	1.25-1.72	<.001	1.51	1.28-1.78	<.001

Table 2 Continued

Characteristic	Unadjusted			IPTW Adjusted		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Unknown	1.26	1.09-1.45	.002	1.24	1.07-1.44	.004
Pleural involvement						
PL 0	—	—		—	—	
PL 1	1.24	1.01-1.51	.037	1.23	1.00-1.51	.054
PL 2	1.15	0.95-1.40	.2	1.27	1.04-1.55	.018
PL 3	2.29	1.72-3.03	<.001	2.5	1.86-3.36	<.001
Unknown	1.63	1.51-1.77	<.001	1.72	1.58-1.86	<.001
Type of surgery						
Lobectomy	—	—		—	—	
Limited resection	1.28	1.18-1.38	<.001	1.31	1.21-1.41	<.001
Pneumonectomy	1.28	1.21-1.37	<.001	1.29	1.21-1.38	<.001
Pathologic stage						
IIIA	—	—		—	—	
IIIB	1.33	1.24-1.42	<.001	1.34	1.25-1.43	<.001
Number of LNs sampled	0.99	0.99-0.99	<.001	0.99	0.99-0.99	<.001
Number of LNs positive	1.04	1.03-1.04	<.001	1.04	1.03-1.04	<.001
Ratio of positive to sampled LNs	2.13	1.97-2.30	<.001	2.18	2.02-2.36	<.001
Positive LN ratio stratified						
<50%	—	—		—	—	
≥50%	1.51	1.44-1.58	<.001	1.52	1.45-1.59	<.001
Chemotherapy						
No/unknown	—	—		—	—	
Yes	0.71	0.68-0.74	<.001	0.7	0.67-0.74	<.001
PORT						
No	—	—		—	—	
Yes	1.01	0.97-1.06	.6	0.99	0.95-1.04	.7

Abbreviations: CI = confidence interval; HR = hazard ratio; IPTW = inverse probability of treatment weighting; LN = lymph node; NOS = not otherwise specified; NSCLC = non–small-cell lung cancer; PL 0 = no evidence of visceral pleural invasion, tumor does not completely traverse the elastic layer; PL 1 = invasion beyond the visceral elastic pleura, but limited to the pulmonary pleura, tumor extends through the elastic layer; PL 2 = invasion to the surface of the pulmonary pleura, tumor extends to the surface of the visceral pleura; PL 3 = tumor extends to the parietal pleura; PORT = postoperative radiotherapy.

heart dose parameters in patients receiving PORT for N2 or margin-positive disease and found no association with OS.[30]

In contrast to the SEER databases, the National Cancer Database (NCDB) has comprehensive baseline characteristics and treatment-related details, including receipt of chemotherapy. Multiple NCDB analyses have demonstrated a benefit of PORT for pN2 disease. These studies looked at patients with pN2 disease, treated in 2004 to 2006[31] and 2006 to 2010,[10] evaluating patients receiving chemotherapy at any time or in the adjuvant setting, respectively. Both of these studies were conducted with advanced statistical techniques and included details on systemic therapy, and both found a benefit for PORT. Nevertheless, these NCDB studies are limited by the narrow time frame of patients included.

If there is indeed a benefit to PORT for pN2 disease, optimal sequencing of PORT with adjuvant chemotherapy remains to be determined. Lee et al conducted a retrospective single-center analysis of early PORT with and without postoperative chemotherapy, showing a 5-year OS of 40.2%, suggesting that early PORT did not worsen outcomes nor remove the benefit of adjuvant chemotherapy.[32] A small multi-center retrospective analysis of patients treated between 2008 and 2015 further illustrated a benefit of early PORT compared with late PORT with longer OS, LRR-free survival, and distant metastasis-free survival.[33] Francis et al investigated the sequencing of PORT and chemotherapy in an NCDB analysis of patients diagnosed between 2006 and 2012, which included margin status, comparing CCRT with chemotherapy followed by PORT. PS matching was utilized, and sequential chemotherapy followed by PORT provided longer median OS (56.9 months) compared with CCRT (41.5 months; $P = .019$) for patients with pN2 and negative margins. No difference was found in OS between the treatment sequences for positive margins, and no subgroup was associated with significant benefit based on sequence of therapy.[11] Some studies demonstrated a possible PORT benefit in specific patient subsets, including pN2 squamous cell cancer[34] and pN2 EGFR-mutant NSCLC.[35]

Our study has several limitations inherent in retrospective database methodology. Although we attempted to account for non-random selection of patients with PS matching and IPTW,

Table 3 Multivariable Analysis

Characteristic	MVA			Doubly Robust MVA		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Age at diagnosis, y	1.02	1.02-1.02	<.001	1.02	1.02-1.02	<.001
Gender						
Female	—	—		—	—	
Male	1.26	1.21-1.33	<.001	1.24	1.18-1.30	<.001
Median income						
<$50,000	—	—		—	—	
$50,000-64,999	0.9	0.85-0.96	.002	0.9	0.84-0.96	.001
$65,000+	0.82	0.77-0.88	<.001	0.81	0.76-0.87	<.001
Year of diagnosis						
1989-1994	—	—		—	—	
1995-2004	0.82	0.76-0.88	<.001	0.8	0.74-0.87	<.001
2005-2016	0.68	0.63-0.75	<.001	0.66	0.61-0.72	<.001
Tumor histology						
Adenocarcinoma	—	—		—	—	
Adenosquamous carcinoma	1.14	1.01-1.28	.038	1.15	1.02-1.30	.02
NSCLC	1.11	1.01-1.21	.034	1.12	1.01-1.23	.024
Squamous cell carcinoma	1.02	0.96-1.08	.6	1.03	0.97-1.10	.3
Grade						
Well-differentiated (I)	—	—		—	—	
Moderately differentiated (II)	1.16	1.03-1.31	.018	1.2	1.06-1.36	.005
Poorly differentiated (III)	1.28	1.14-1.45	<.001	1.31	1.15-1.48	<.001
Anaplastic (IV)	1.25	1.06-1.48	.009	1.29	1.08-1.53	.004
Unknown	1.21	1.04-1.39	.011	1.19	1.02-1.38	.024
Pleural involvement						
PL 0	—	—		—	—	
PL 1	1.24	1.01-1.51	.036	1.23	1.00-1.51	.051
PL 2	1.12	0.92-1.36	.3	1.25	1.02-1.52	.028
PL 3	2.11	1.59-2.80	<.001	2.31	1.72-3.10	<.001
Unknown	1.32	1.21-1.44	<.001	1.39	1.27-1.52	<.001
Type of surgery						
Lobectomy	—	—		—	—	
Limited resection	1.09	1.01-1.18	.029	1.11	1.02-1.20	.011
Pneumonectomy	1.2	1.12-1.28	<.001	1.17	1.09-1.25	<.001
Pathologic stage						
IIIA	—	—		—	—	
IIIB	1.28	1.19-1.36	<.001	1.28	1.20-1.37	<.001
Positive LN ratio stratified						
<50%	—	—		—	—	
≥50%	1.47	1.40-1.54	<.001	1.46	1.39-1.54	<.001
Chemotherapy						
No/unknown	—	—		—	—	
Yes	0.87	0.83-0.92	<.001	0.88	0.83-0.92	<.001

Table 3 Continued

Characteristic	MVA			Doubly Robust MVA		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
PORT						
No	—	—		—	—	
Yes	0.99	0.94-1.04	.7	0.98	0.93-1.02	.3

Abbreviations: CI = confidence interval; HR = hazard ratio; LN = lymph node; MVA = multivariable analysis; NSCLC = non–small-cell lung cancer; PL 0 = no evidence of visceral pleural invasion, tumor does not completely traverse the elastic layer; PL 1 = invasion beyond the visceral elastic pleura, but limited to the pulmonary pleura, tumor extends through the elastic layer; PL 2 = invasion to the surface of the pulmonary pleura, tumor extends to the surface of the visceral pleura; PL 3 = tumor extends to the parietal pleura; PORT = postoperative radiotherapy.

confounding by variables not captured in SEER may exist. Additionally, the retrospective nature of data collection limits comprehensive variable collection. Specific details on RT technique and dose are absent. We also did not have data on margin status, although our inclusion of chemotherapy and pleural involvement offers details missing in other SEER analyses. Nevertheless, our chemotherapy data is limited to inclusion in the patients' care, but sequencing with respect to neoadjuvant, adjuvant, and co-administration with RT is unknown. Moreover, the SEER database is not currently able to differentiate between no versus unknown chemotherapy receipt. Lastly, our analysis focused primarily on OS, but details regarding local recurrence, distant metastasis, and disease-free survival could have important implications for the impact of PORT in this patient population.

Conclusion

In conclusion, our data suggests that PORT does not improve or worsen OS for all patients with pN2 NSCLC; however, patients with a positive to sampled LN ratio $\geq$ 50% may benefit, regardless of chemotherapy status. Nevertheless, PORT will remain the standard of care as we await the results of the ongoing LUNG ART trial to further guide treatment recommendations.[9]

Clinical Practice Points

- There is no level 1 evidence that PORT is beneficial for patients with locally advanced NSCLC with mediastinal LN involvement.
- The SEER database recently added chemotherapy as a treatment variable.
- Prior SEER analyses demonstrated improved OS for patients with mediastinal LN disease; however, these older studies were unable to account for chemotherapy use.
- Secondary analyses of prospective trials have indicated PORT is associated with worse OS.
- We conducted an updated SEER analysis using PS matching and IPTW to account for baseline and treatment characteristics to further investigate the utility of PORT for patients with pN2 NSCLC. Furthermore, multiple imputation with chained equations was used to impute missing data for numbers of LN sampled and positive.
- PORT did not improve OS for the entire pN2 cohort (HR, 0.99; $P = .76$).
- Subset analysis revealed that PORT improved OS for patients with a positive to sampled LN ratio $\geq$ 50% (HR, 0.90; $P = .01$).
- This contemporary SEER analysis questions the routine use of PORT for all patients with pN2 disease and further explores the importance of mediastinal nodal burden as a putative indication for PORT.
- The ongoing LUNG ART trial is evaluating the role of PORT for patients with pN2 disease; however, until the results are available, the utility of PORT remains a subject of debate.

Disclosure

The authors have stated that they have no conflicts of interest.

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