Adjuvant chemotherapy, not radiotherapy, prolongs survival for node-negative non–small cell lung cancer with positive surgical margins

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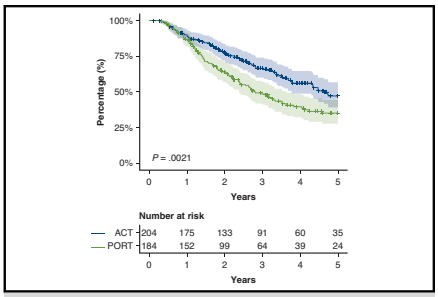
ABSTRACT

Objective: The study objective was to determine differences in survival depending on adjuvant therapy type, timing, and sequence in node-negative disease with positive margins after non–small cell lung cancer resection.

Methods: The National Cancer Database was queried for patients with positive margins after surgical resection of treatment-naöve cT1-4NoMo pNo non–small cell lung cancer who underwent adjuvant radiotherapy or chemotherapy from 2010 to 2016. Adjuvant treatment groups were defined as surgery alone, chemotherapy alone, radiotherapy alone, concurrent chemoradiotherapy, sequential chemotherapy then radiotherapy, and sequential radiotherapy then chemotherapy. The impact of adjuvant radiotherapy initiation timing on survival was evaluated using multivariable Cox regression. Kaplan–Meier curves were generated to compare 5-year survival.

Results: A total of 1713 patients met inclusion criteria. Five-year survival estimates differed significantly between cohorts: surgery alone, 40.7%; chemotherapy alone, 47.0%; radiotherapy alone, 35.1%; concurrent chemoradiotherapy, 45.7%; sequential chemotherapy then radiotherapy, 36.6%; and sequential radiotherapy then chemotherapy, 32.2% ($P = .033$). Compared with surgery alone, adjuvant radiotherapy alone had a lower estimated survival at 5 years, although overall survival did not differ significantly ($P = .8$). Chemotherapy alone improved 5-year survival compared with surgery alone ($P = .0016$) and provided a statistically significant survival advantage over adjuvant radiotherapy ($P = .002$). Compared with radiotherapy-inclusive multimodal therapies, chemotherapy alone yielded similar 5-year survival ($P = .066$). Multivariable Cox regression showed an inverse linear association between time to adjuvant radiotherapy initiation and survival, but with an insignificant trend (10-day hazard ratio, 1.004; $P = .90$).

Conclusions: In treatment-naöve cT1-4NoMo pNo non–small cell lung cancer with positive surgical margins, only adjuvant chemotherapy was associated with a survival improvement compared with surgery alone, with no radiotherapy-inclusive treatment providing additional survival benefit. Delayed timing of radiotherapy initiation was not associated with a survival reduction. (JTCVS Open 2023;14:472-82)



ACT significantly improves survival compared with PORT.

CENTRAL MESSAGE

The inclusion of ACT appears to have a stronger impact on survival than PORT in patients with node-negative NSCLC with positive margins after surgery.

PERSPECTIVE

The efficacy of adjuvant therapy focusing on node-negative disease requires greater evidence to support the role of PORT in the context of positive surgical margins. The findings from this study raise a potential paradigm shift and reevaluation of the routine practice of using radiotherapy in the care of patients who have positive margins after resections for NSCLC.

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Abbreviations and Acronyms

ACT = adjuvant chemotherapy
AJCC = American Joint Commission on Cancer
cCRT = concurrent chemoradiotherapy
CI = confidence interval
HR = hazard ratio
IQR = interquartile range
NCDB = National Cancer Database
NSCLC = non–small cell lung cancer
PORT = adjuvant radiotherapy
PSM = propensity score matching
SA = surgery alone
sCRT = sequential chemotherapy then radiotherapy
sRTC = sequential radiotherapy then chemotherapy

For medically operable patients with early stage non–small cell lung cancer (NSCLC), curative intent complete surgical resection is considered the standard treatment.[1] A small proportion of surgical resections can be associated with positive surgical margins, which can be classified as microscopic or macroscopic residual disease.[2] For patients with positive surgical margins, re-resection of the tumor or postoperative radiotherapy (adjuvant radiotherapy [PORT]) is thought to be indicated, whereas adjuvant chemotherapy (ACT) is often recommended for more advanced stages.[1,2]

PORT has been associated as an avenue of treatment for positive margins after surgical resection, but there are limited data that detail the optimal time to initiate PORT. In the LungART trial, study participants were advised to start PORT 4 weeks after surgery at the earliest, but there was no indication of the timing associated with best outcomes.[3] By using a cutoff point analysis, a time to radiotherapy of 8 weeks or more with sequential chemotherapy in margin-negative N2 disease has been associated with improved survival.[4]

In early-stage disease, although PORT has been shown to reduce local recurrence, the impact of PORT on overall survival remains uncertain with some studies suggesting that PORT may have a detrimental effect on survival.[5,6] Hancock and colleagues[7] demonstrated that the administration of both chemotherapy and radiotherapy is associated with improved survival in patients with microscopically positive margins but that chemotherapy or radiotherapy alone was less consistently associated with improved outcomes. Although these recommendations pertain to the population level, there is limited guidance on the specific treatment of node-negative disease and the timing of PORT. Additional clarity is also needed on the relative efficacy of unimodal versus combination treatment modalities. For example, the appropriate sequence of multimodal therapy—concurrent versus sequential chemoradiotherapy—is not known and has been debated, with published evidence supporting both options.[8,9]

Much of the existing literature comparing the efficacy of various adjuvant therapies focuses on lymph node–positive N2, margin-negative disease, neoadjuvant-inclusive, or otherwise multimodal therapies. More data are needed to support the role of radiotherapy in the context of positive surgical margins either with or without ACT. The objective of this study was to identify the most effective adjuvant therapy and the optimal timing for PORT specifically for patients with positive margins in treatment-naïve node-negative disease using a national cancer registry.

MATERIALS AND METHODS

Data Source

The National Cancer Database (NCDB) is a hospital-based clinical oncology tumor registry maintained as a joint effort of the American College of Surgeons and the American Cancer Society. The NCDB contains more than 34 million historical records of patients with cancer obtained from more than 1500 Commission of Cancer–accredited facilities, representing approximately 70% of patients diagnosed annually with cancer. The NCDB maintains that "the data used in the study are derived from a de-identified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator."[10] The Institutional Review Board or equivalent ethics committee of the University of Southern California approved the study protocol and publication of data (Number HS-16-00,906; approval date: December 19, 2016). Patient written consent for the publication of the study data was waived by the Institutional Review Board because this study is not considered human subjects research.

Study Population

The NCDB Participant User Data File was used to identify treatment-naïve patients (ie, no preoperative therapy) with clinical stage T1-4N0M0 and eventual pathologic N0 NSCLC who underwent surgical resection from 2010 to 2016, were found to have positive margins, and received PORT or ACT. Only patients who underwent lobectomy, extended lobectomy, pneumonectomy, extended pneumonectomy, or extended radical pneumonectomy within 180 days after diagnosis were included. Patients with clinical T descriptors missing or T0 or with metastatic disease (M1) were excluded. Only clinical node-negative and pathological node-negative patients were included. Patients whose PORT lasted greater than 60 days or who received radiotherapy dosages less than 4500 cGy or greater than 7000 cGy were excluded to ensure guideline-concordant care. Only radiotherapy of chest/lung and lung (limited) and the following radiotherapy modalities were included: external beam not otherwise specificed, photons (6-10 MV), photons (mixed energies), intensity-modulated radiotherapy, conformal or 3-dimensional therapy, or proton therapy. Patients receiving single-agent ACT were excluded as were those with unknown sequence of adjuvant therapy (Figure 1).

Variables and Outcomes

Demographic variables included sex, age, race, income, education, insurance type, urban-rural, facility type, and distance from nearest facility. Tumor and clinical specific variables included histology, Charlson-Deyo score, American Joint Commission on Cancer (AJCC) clinical TNM stage, AJCC pathological TNM stage, tumor size (≤3 cm, 3-5 cm, 5-7 cm, and

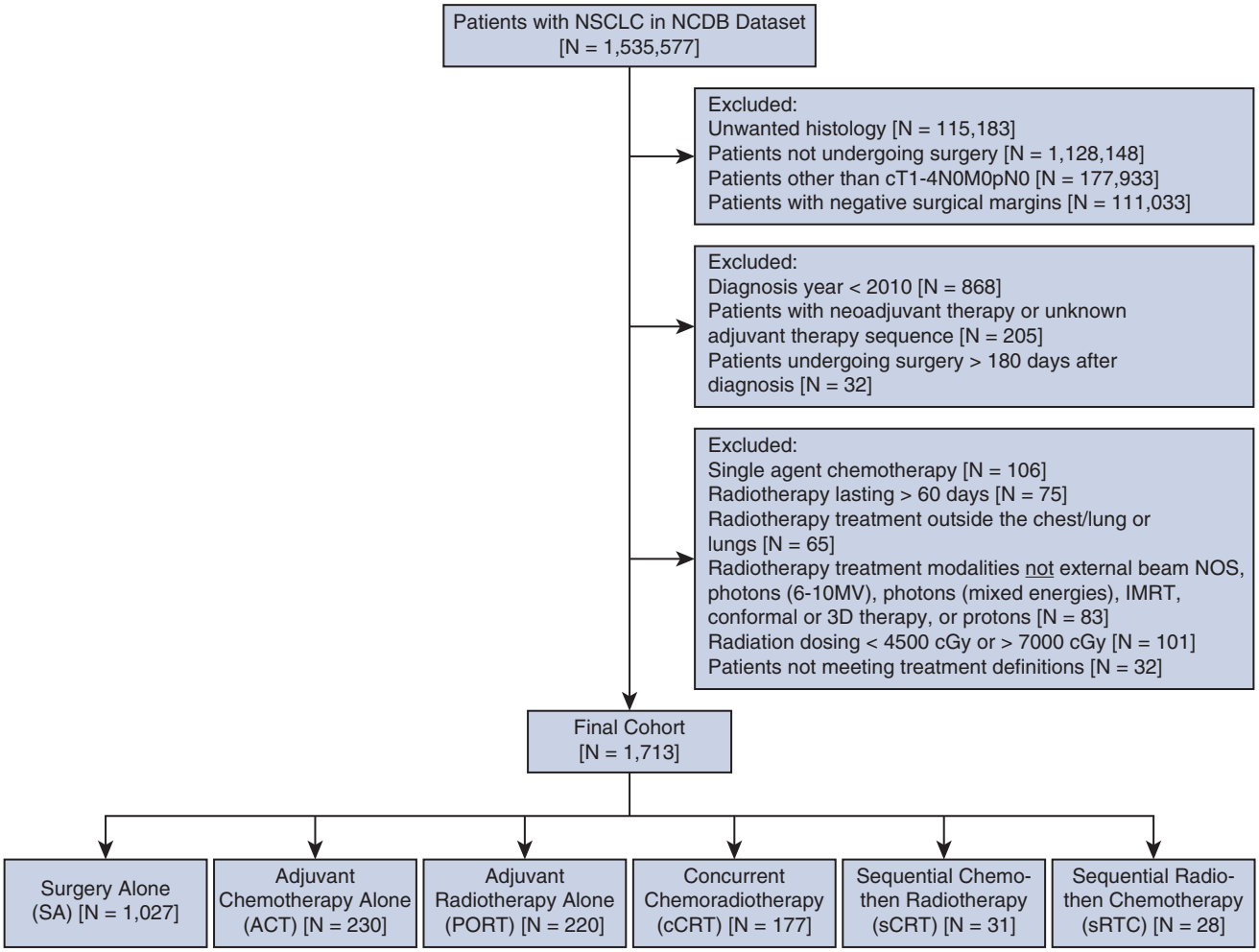

FIGURE 1. Schematic diagram showing the cohort selection process. The final cohort contained 1713 patients who were categorized into 6 separate cohorts based on the adjuvant therapy administered. *NSCLC*, Non–small cell lung cancer; *NCDB*, National Cancer Database.

>7 cm), surgical margin, and procedure type (Table 1). Histology was subdivided into adenocarcinoma, squamous cell carcinoma, and other. The tumor size cutoffs were chosen in accordance with the Eighth Edition TNM NSCLC staging classification.

Patients were grouped into 6 cohorts based on their adjuvant therapy sequence: surgery alone (SA), surgery followed by ACT only, surgery followed by PORT only, surgery followed by concurrent chemoradiotherapy (cCRT; defined as chemotherapy and radiotherapy starting within 14 days of each other), surgery followed by sequential radiotherapy then chemotherapy (sRTC; defined as chemotherapy starting after completion of radiotherapy), and surgery followed by sequential chemotherapy then radiotherapy (sCRT; defined as readiotherapy starting at least 100 days after initiation of chemotherapy, per guidelines used in the ANITA and Lung ART trials[3,11]). The primary outcome of interest was 5-year overall survival, defined as the interval from the date of surgery to the date of last contact or last vital status.

Statistical Analysis

Descriptive analysis was used to report frequencies and percentages for all categorical variables for each cohort. Demographic and clinical characteristics (Table 1) were compared using a chi-square test or Fisher exact test when appropriate. The log-rank test with Bonferroni adjustment for *P* values was used to compare the overall 5-year survival of groups, with Kaplan–Meier estimators calculated for the 5-year time point. Cox regression was used for the association of days between surgery and radiotherapy initiation to 5-year overall survival. Days between surgery and radiotherapy were evaluated as a continuous variable. Tumor size, age, binary gender, quartile of median income, facility location, histology, and surgical margin were included in the time to radiotherapy model as covariates. Proportional hazard assumptions were evaluated using Schoenfeld residuals. TNM clinical staging was omitted because a test based on scaled Schoenfeld residuals showed that the proportional hazards assumption was not supported. All analyses were conducted using R version 4.1.2 (R Foundation for Statistical Computing).

Propensity Matching Survival Analysis

A propensity score matching (PSM) method (nearest-neighbor matching without replacement, using a logistic propensity model and a caliper of 0.2) was used to control for age (in terciles), sex, pathologic stage group (0, 1, 2, 3, or 4), and tumor size (discretized into 4 levels according to Eighth Edition AJCC). Clinical stage group was also viewed as a possible confounder, but was not selected due to moderate rank correlation with pathologic stage group. More complex propensity models, which would have allowed controlling for more variables, were not supported. The

TABLE 1. Demographics and clinical characteristics of National Cancer Database patients

Characteristic	SA (N = 1027)		PORT (N = 220)		ACT (N = 230)		cCRT (N = 177)		sCRT (N = 31)		sRTC (N = 28)		*P* value
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	
Sex													.29
Male	547	53.3	131	59.5	116	50.4	102	57.6	19	61.3	17	60.7	
Female	480	46.7	89	40.5	114	49.6	75	42.4	12	38.7	11	39.3	
Age, y													<.0001
≤61	195	19.0	42	19.1	79	34.3	63	35.6	7	22.6	10	35.7	
61-68	209	20.4	59	26.8	70	30.4	40	22.6	9	29.0	9	32.1	
68-75	293	28.5	56	25.5	56	24.3	52	29.4	9	29.0	6	21.4	
>75	330	32.1	63	28.6	25	10.9	22	12.4	6	19.4	3	10.7	
Race													.73
Missing	3	0.3	1	0.5	0	0	0	0	0	0	0	0	
Black	88	8.6	16	7.3	20	8.7	12	6.8	2	6.5	0	0	
Other	30	2.9	7	3.2	5	2.2	3	1.7	2	6.5	0	0	
White	906	88.2	196	89.1	205	89.1	162	91.5	27	87.1	28	100	
Histology													.46
Adenocarcinoma	537	52.3	102	46.4	134	58.3	89	50.3	17	54.8	12	42.9	
Other	34	3.3	8	3.6	10	4.3	7	4	1	3.2	2	7.1	
Squamous cell	456	44.4	110	50	86	37.4	81	45.8	13	41.9	14	50	
Charlson-Deyo Score													.006
0	469	45.7	91	41.4	115	50	96	54.2	16	51.6	12	42.9	
1	359	35	77	35	90	39.1	63	35.6	10	32.3	11	39.3	
2	138	13.4	30	13.6	19	8.3	16	9	3	9.7	5	17.9	
≥3	61	5.9	22	10	6	2.6	2	1.1	2	6.5	0	0	
Income													.19
Missing	3	0.3	0	0	1	0.4	1	0.6	0	0	0	0	
≥$38,000	813	79.2	176	80	193	83.9	133	75.1	28	90.3	21	75	
<$38,000	211	20.5	44	20	36	15.7	43	24.3	3	9.7	7	25	
Education													.2
Missing	3	0.3	0	0	1	0.4	1	0.6	0	0	0	0	
<20.9% no high school	834	81.2	187	85	202	87.8	143	80.8	25	80.6	24	85.7	
>21% no high school	190	18.5	33	15	27	11.7	33	18.6	6	19.4	4	14.3	
Insurance													<.0001
Missing	6	0.6	3	1.4	4	1.7	1	0.6	0	0	0	0	
Not insured	11	1.1	5	2.3	12	5.2	1	0.6	0	0	0	0	
Private insurance/managed care	218	21.2	65	29.5	90	39.1	60	33.9	12	38.7	11	39.3	
Medicaid	59	5.7	8	3.6	9	3.9	15	8.5	3	9.7	1	3.6	
Medicare	721	70.2	133	60.5	114	49.6	95	53.7	15	48.4	15	53.6	
Other government	12	1.2	6	2.7	1	0.4	5	2.8	1	3.2	1	3.6	
Urban/rural													.9
Missing	25	2.4	2	0.9	4	1.7	3	1.7	0	0	0	0	
Metro	803	78.2	168	76.4	181	78.7	132	74.6	25	80.6	22	78.6	
Urban	177	17.2	45	20.5	40	17.4	35	19.8	6	19.4	6	21.4	
Rural	22	2.1	5	2.3	5	2.2	7	4	0	0	0	0	
Facility type													.06
Missing	3	0.3	0	0	0	0	1	0.6	0	0	0	0	
Community cancer program	79	7.7	22	10	24	10.4	16	9	3	9.7	1	3.6	
Comprehensive community cancer program	466	45.4	101	45.9	106	46.1	97	54.8	16	51.6	18	64.3	
Academic/research program	330	32.1	66	30	68	29.6	34	19.2	4	12.9	7	25	
Integrated network cancer program	149	14.5	31	14.1	32	13.9	29	16.4	8	25.8	2	7.1	

(Continued)

TABLE 1. Continued

Characteristic	SA (N = 1027) No.	SA (N = 1027) %	PORT (N = 220) No.	PORT (N = 220) %	ACT (N = 230) No.	ACT (N = 230) %	cCRT (N = 177) No.	cCRT (N = 177) %	sCRT (N = 31) No.	sCRT (N = 31) %	sRTC (N = 28) No.	sRTC (N = 28) %	*P* value
Distance													.49
Missing	4	0.4	0	0	0	0	0	0	0	0	0	0	
>12.5 miles	551	53.7	127	57.7	133	57.8	95	53.7	19	61.3	19	67.9	
≤12.5 miles	472	46	93	42.3	97	42.2	82	46.3	12	38.7	9	32.1	
AJCC Clinical T													<.0001
c1	465	45.3	81	36.8	41	17.8	29	16.4	4	12.9	6	3.6	
c2	386	37.6	96	43.6	108	47.0	68	38.4	13	41.9	16	57.1	
c3	140	13.6	37	16.8	68	29.6	64	36.2	10	32.3	2	7.1	
c4	36	3.5	6	2.7	13	5.7	16	9	4	12.9	4	14.3	
AJCC Pathologic T													<.0001
p1	315	30.7	55	25.0	8	3.5	9	5.1	1	3.2	1	3.6	
p2	413	40.2	81	36.8	94	40.9	35	19.8	10	32.3	11	39.3	
p3	249	24.2	72	32.7	108	47	102	57.6	16	51.6	12	42.9	
p4	45	4.4	11	5	20	8.7	30	16.9	4	12.9	4	14.3	
pIS	3	0.3	0	0	0	0	0	0	0	0	0	0	
pX	2	0.2	1	0.5	0	0	1	0.6	0	0	0	0	
Tumor size													<.0001
≤3 cm	461	51.9	76	41.8	52	25.6	42	28.2	4	14.3	5	21.7	
3-5 cm	240	27.0	70	38.5	66	32.5	53	35.6	7	25.0	12	52.2	
5-7 cm	108	12.1	26	14.3	40	19.7	29	19.5	12	42.9	5	21.7	
>7 cm	80	9.0	10	5.5	45	22.2	25	16.8	5	17.9	1	4.3	
Surgical margins													.22
Residual tumor, NOS	411	40	78	35.5	99	43	73	41.2	12	38.7	6	21.4	
Microscopic	578	56.3	139	63.2	122	53	96	54.2	19	61.3	21	75	
Macroscopic	38	3.7	3	1.4	9	3.9	8	4.5	0	0	1	3.6	
Procedure type													.34
Lobectomy or bilobectomy	976	95	212	96.4	212	92.2	169	95.5	31	100	27	96.4	
Pneumonectomy	51	5	8	3.6	18	7.8	8	4.5	0	0	1	3.6	

SA, Surgery alone; *PORT*, adjuvant radiotherapy; *ACT*, adjuvant chemotherapy; *cCRT*, sequential chemotherapy then radiotherapy; *sCRT*, sequential chemotherapy then radiotherapy; *sRTC*, sequential radiotherapy then chemotherapy; *AJCC*, American Joint Commission on Cancer; *NOS*, not otherwise specified.

log-rank test was used to compare the entire survival experiences of the samples resulting from the PSM procedure. With the same PSM samples, a bootstrap method (the ordinary method, with 10,000 replicates) was used with Kaplan–Meier estimators at 5 years to estimate ratios of 5-year survival probabilities and calculate 95% confidence intervals (CIs).

RESULTS

Of the 114,313 patients with cT1-4N0 pN0 NSCLC, 3280 (3%) had positive margins and 1713 (1%) met the cohort-specific inclusion criteria for treatment-naïve surgical intervention from 2010 to 2016. Of those 1713, 60.0% (1027) underwent SA and 40.0% (686) received some form of adjuvant therapy. For those patients receiving adjuvant therapy, 13.4% (230) underwent ACT, 12.8% (220) underwent PORT, 10.3% (177) underwent cCRT, 1.8% (31) underwent sCRT, and 1.6% (28) underwent RTC.

Evaluating Survival Across Cohorts

ACT yielded the greatest survival, whereas sRTC yielded the lowest estimated 5-year survival probability: ACT, 47.0%; cCRT, 45.7%; sCRT, 36.6%; PORT, 35.1%; sRTC, 32.2%; and SA, 40.7% ($P = .033$) (Figure 2). Compared with SA, the 5-year survival of PORT was not significantly different ($P = .8$) (Figure 3, *A*), although PORT was associated with an estimated 5-point reduction in 5-year survival probability. Between the 2 unimodal therapies, ACT provided a significant improvement in survival over PORT ($P = .0021$) (Figure 3, *B*), which remained significant after correcting for multiple testing ($P = .032$). ACT was the only adjuvant treatment group that improved 5-year survival compared with SA ($P = .0016$) (Figure 3, *C*); this statistical difference remained significant after multiple-testing correction ($P = .024$).

For multimodal combination therapies, cCRT and [sRTC + sCRT] yielded statistically similar 5-year survival ($P = .88$) when compared with each other. Because of their small sample sizes, sRTC and sCRT were grouped into a single sequential adjuvant therapy cohort for the purposes of statistical analysis. In comparison with unimodal therapy options, neither cCRT nor [sRTC + sCRT] was associated

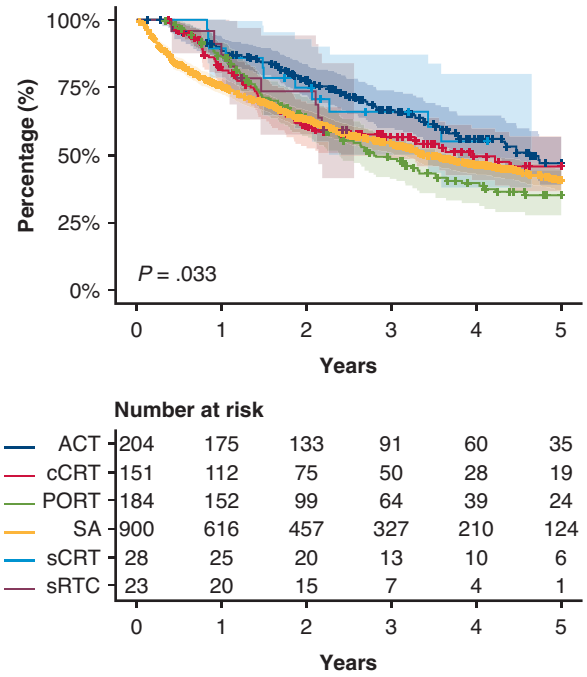

FIGURE 2. Kaplan–Meier survival analysis demonstrating 5-year overall survival of patients with positive margins for all adjuvant therapy treatments with 95% CIs. Overall survival was highest for patients receiving ACT (47.0%) and lowest for those undergoing sRTC (32.2%) ($P = .033$). *ACT*, Adjuvant chemotherapy; *cCRT*, sequential chemotherapy then radiotherapy; *PORT*, adjuvant radiotherapy; *SA*, surgery alone; *sCRT*, sequential chemotherapy then radiotherapy; *sRTC*, sequential radiotherapy then chemotherapy.

with a significant survival advantage over PORT ($P = .33$ and $P = .41$, respectively) or ACT ($P = .089$ and $P = .23$, respectively). ACT did not differ from the radiotherapy-inclusive combination therapies (cCRT + sRTC + sCRT) in prolonging survival ($P = .066$) (Figure 3, *D*). Additionally, there were no 30-day or 90-day mortalities for any of the 5 adjuvant treatment cohorts.

Subgroup Analyses

To confirm the relative effectiveness of ACT, a propensity-matched analysis was performed. Controlling for age, sex, pathological stage group, and tumor size, ACT provided a statistically significant survival advantage over PORT (unadjusted $P < .001$; 95% CI, 1.74 [1.15-2.64]) and statistically equivalent survival compared with cCRT (unadjusted $P = .29$; 95% CI, 1.05 [0.73-1.48]) (Table 2), both of which are consistent with the prior results.

The relative adjuvant treatment efficacy across individual clinical T stages yielded no significant survival differences for the cT1 subgroup, with SA (51.9%) yielding the highest survival. In cT2 patients, ACT (57.5%) had the highest 5-year survival and provided statistically significant survival advantage over cCRT (50.5%), cCRT + sRTC + sCRT (44.4%), SA (36.5%), and PORT (30.8%) (unadjusted $P = .03$, $P = .03$, $P < .01$, $P < .01$, respectively). For cT3 + cT4 (combined due to small cT4 sample size), sCRT + sRTC (40.4%), cCRT (37.6%), and ACT (30.3%) individually provided significant survival benefit compared with SA (22.6%) (unadjusted $P = .04$, $P < .01$, $P < .01$, respectively). However, no therapy proved more statistically effective than the others (all $P > .64$).

As a proxy for disease-specific survival, a subgroup analysis was performed for those patients with Charlson-Deyo score equal to 0 whereby the only statistically significant comparison was ACT (45.3%) versus SA (42.4%) (unadjusted $P = .047$), with no significant differences between the different adjuvant treatment groups (ie, cCRT, 45.2%; PORT, 41.7%; sCRT + sRTC, 37.6%).

Time to Adjuvant Radiotherapy

To evaluate the relationship between PORT timing and survival, a multivariable Cox model was fitted using the PORT and cCRT cohorts combined. The sRTC and sCRT cohorts were excluded because of small sample size and likelihood that the 100-day minimum before initiation of radiotherapy would skew the analysis, respectively. Using time as a continuous variable and the log of the hazard ratios (HRs) derived from the Cox model, a negative, statistically nonsignificant linear relationship was observed between time to PORT initiation and survival (10-day HR, 1.004, 95% CI, 0.949-1.062, $P = .90$) (Figure 4); thus, the data did not support a significant association between delayed start to PORT and survival. Replicating this analysis with PORT and cCRT treatment cohorts individually yielded the same outcome, with no estimated survival benefit associated with PORT initiation timing (10-day HR, 1.000, 95% CI, 0.937-1.068, $P = .99$ for PORT; 10-day HR, 1.018, 95% CI, 0.897-1.157, $P = .78$ for cCRT). Given the linear relationship between time and the log HR, time to radiotherapy initiation was neither dichotomized according to a single cut-point nor evaluated within discrete time intervals.

The median time to PORT initiation was 49.0 days (interquartile range [IQR], 42-67) for the combined PORT + cCRT group. For PORT, the median time was 55.5 days (IQR, 42-75); for cCRT, the median time was 48.0 days (IQR, 39-61).

DISCUSSION

The current study of 1713 patients from the NCDB with treatment-naïve cT1-4N0M0 pN0 NSCLC and positive margins addresses a current gap in knowledge in which there is a paucity of data to support current therapeutic recommendations. Across the entire cohort, ACT alone was the only treatment statistically associated with an improvement in survival compared with SA. ACT also provided a significant survival benefit compared with PORT (Figure 5).

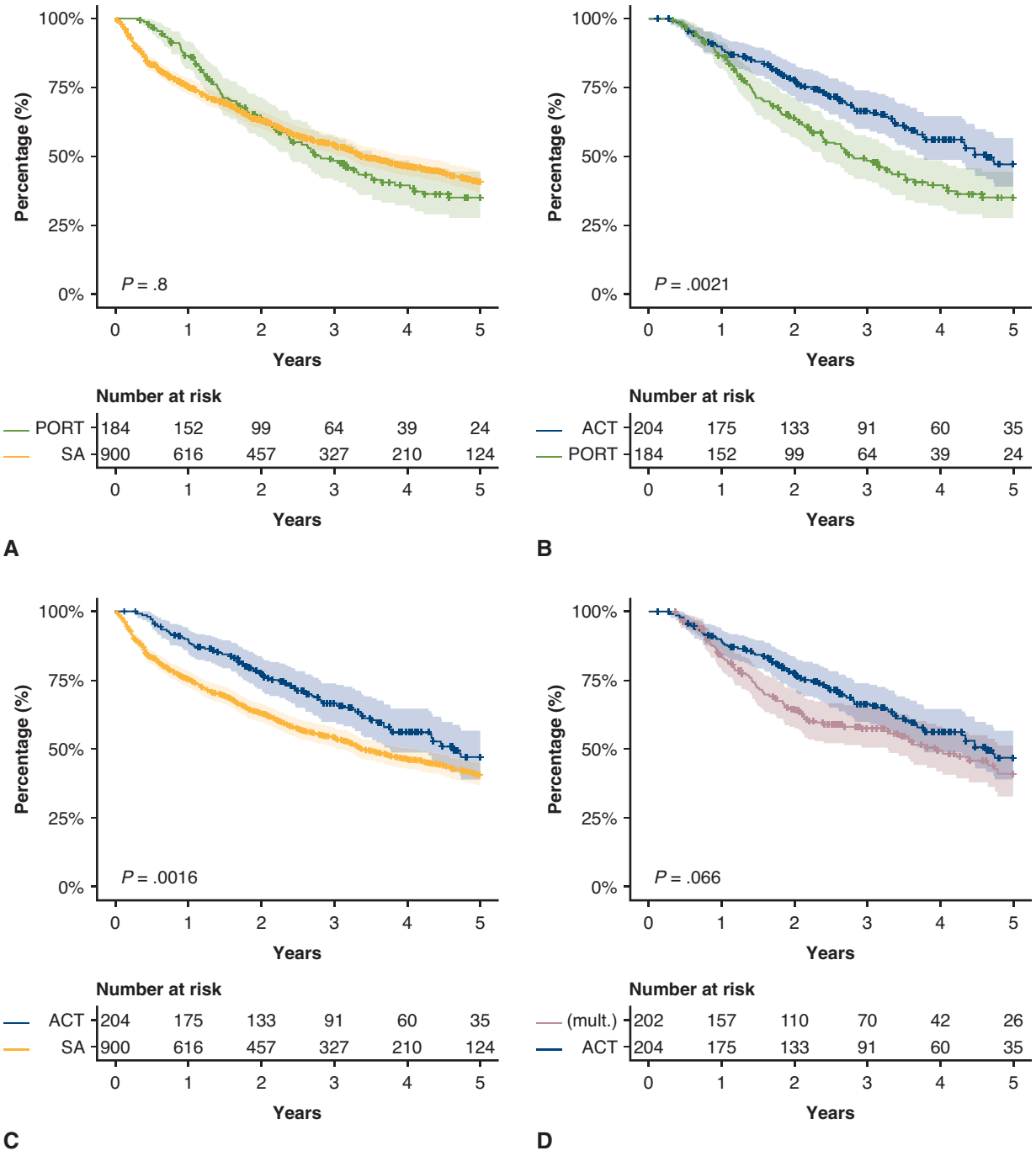

FIGURE 3. Kaplan–Meier survival analysis demonstrating 5-year overall survival of patients with positive margins with 95% CIs according to different adjuvant therapy treatments for (A) PORT and SA; (B) ACT and PORT; (C) ACT and SA; and (D) ACT and the 3 radiotherapy-inclusive combination therapies of cCRT and sCRT and sRTC. *PORT*, Adjuvant radiotherapy; *SA*, surgery alone; *ACT*, adjuvant chemotherapy.

Further, there was no evidence that radiotherapy-inclusive treatment provided any additional survival benefit compared with SA or ACT. For combination adjuvant radiotherpay and chemotherapy modalities, neither concurrent nor sequential therapies were found to be superior. These results were reinforced by the propensity-matched analyses, demonstrating overall equivalence between ACT and cCRT, and clinical T-stage analyses, whereby ACT was equivalent to radiotherapy-inclusive treatment in cT1 and cT3+cT4 and at least equivalent, if not better, in cT2

TABLE 2. Output from propensity-matched analysis

Comparison	PSM sample size	PSM log-rank test *P* value	PSM bootstrap ratio of 5-y survival probabilities (95% CI)
ACT vs PORT	132 + 132 = 264	<.001	1.74 (1.15-2.64)
ACT vs cCRT	127 + 127 = 254	.290	1.05 (0.73-1.48)
PORT vs cCRT	104 + 104 = 208	.027	1.60 (0.97-2.58)

PSM, Propensity score matching; *CI*, confidence interval; *ACT*, adjuvant chemotherapy; *PORT*, adjuvant radiotherapy; *cCRT*, concurrent chemoradiotherapy.

disease. This suggests that tumor size impacted survival for ACT. Although not the same tumor dimensions (ie, 3-5 cm), these results harken to the CALGB 9633 trial that identified strong overall survival signals favoring ACT for tumors greater than 4 cm.[12,13]

In this analysis, the use of PORT alone was not associated statistically with any survival benefit compared with SA, and in fact was estimated to lead to a worse 5-year survival. If confirmed by a future study with a larger sample, this lack of efficacy would be inconsistent with many studies that have recommended the use of PORT in the settings of margin-negative and incompletely resected N0-2 disease.[6,14] However, the current study is consistent with other literature in not showing a statistically significant survival impact of PORT in both margin-positive and node-negative disease.[5,15-17] Although the findings regarding the relative efficacies of PORT and ACT might challenge the existing National Comprehensive Cancer Network guidelines, which do not recommend ACT alone for any margin-positive patients,[2] they do support both Hancock and colleagues[7] and Smeltzer and colleagues,[18] who concluded that ACT alone can be more effective compared with PORT alone. The current study goes further with individual comparisons of the different adjuvant treatments, especially unimodal versus multimodal, and survival analysis segmentation by clinical T stage. Taken altogether, these results highlight that chemotherapy has more consistently shown better overall survival than PORT, even in N0 patients.

When assessing the multimodal combination therapies, neither cCRT nor sequential therapy (ie, sCRT + sRTC, combined due to small individual sample sizes) provided any significant survival advantage over SA. Although merely a failure to reject the null hypothesis, this finding is different from some studies that identified a benefit in concurrent over sequential chemoradiotherapy[9,19-21] while also affirming others that failed to do so.[8,22,23] In the context of ACT's relative advantage or equivalent efficacy, if the focus is shifted to comparing the efficacy between multimodal and unimodal treatment modalities instead of only multimodal, then the statistically equivalent survival benefit of ACT may prompt a reconsideration to use a unimodal option moving forward.

Sura and colleagues[4] used the NCDB to define the impact of relative timing of postoperative radiotherapy on overall survival. The study focused on pN2, margin-negative disease and used a dichotomized approach in the analysis with therapy initiation defined as less than or greater than

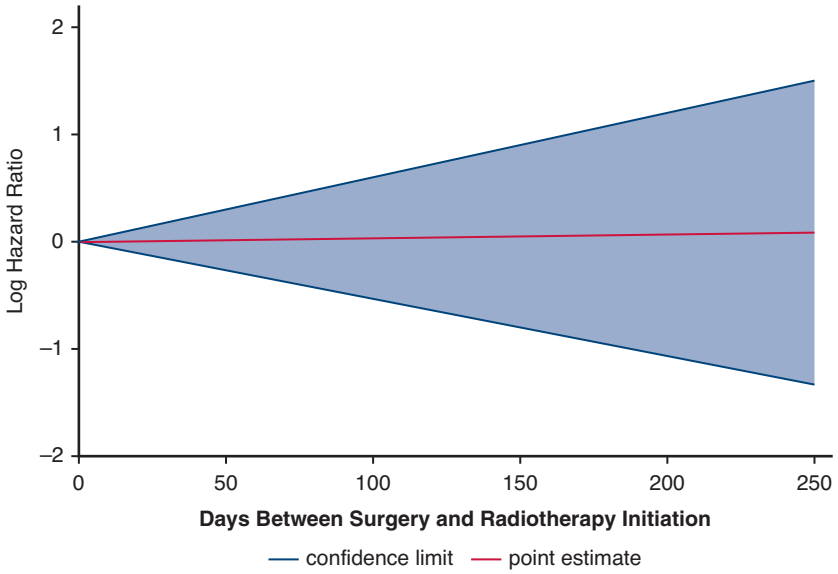

FIGURE 4. Modeling the relationship between time to initiation of PORT and mortality risk for cCRT and PORT using the log of the HRs derived from a multivariable Cox model, shown on the Y-axis. The 95% CIs of the adjusted HRs are represented by the shaded area (10-day HR, 1.004, 95% CI, 0.949-1.062, $P = .90$).

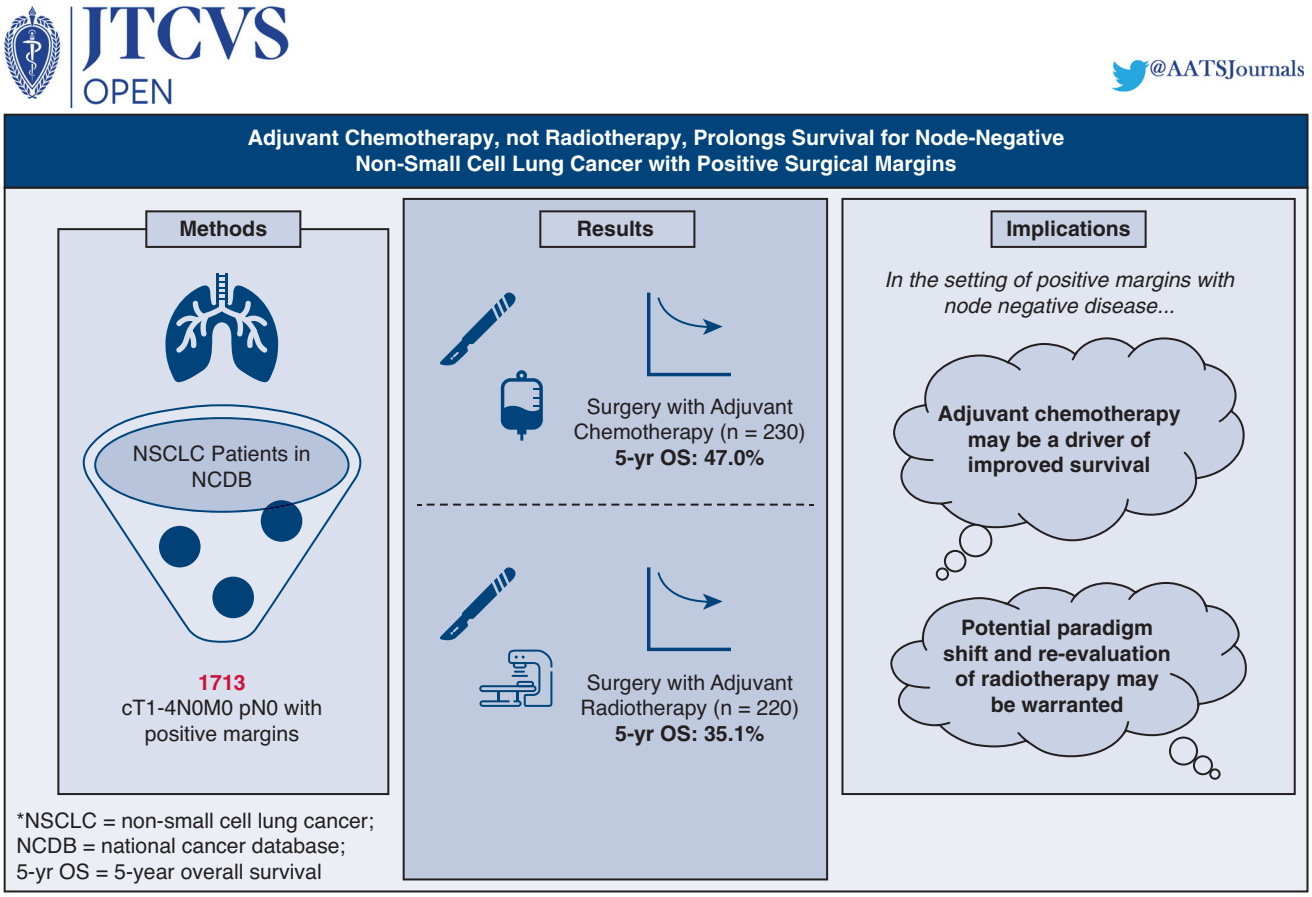

FIGURE 5. Summary of the methods, results, and implications of this study. *NSCLC*, Non–small cell lung cancer; *NCDB*, National Cancer Database; 5-yr, 5-year overall survival.

8 weeks. They found that a longer time to radiotherapy, defined as 8 weeks or more, was associated with improved survival. A similar study has been performed for ACT timing.[24] For the current study's sample, rather than dichotomizing the patient population according to a single cut-point, a continuous multivariable Cox model was created, which demonstrated that delays in PORT were not associated significantly with a survival detriment. Most mentions of radiotherapy timing are in discussions of sequencing when both ACT and radiotherapy are indicated. Although equivalence testing with a larger sample might be needed to show the absence of an effect, the possible lack of detriment to survival could provide patients the opportunity to delay their radiotherapy in accordance with a slower postoperative recovery or in the context of limited access to radiation oncology. If postoperative radiotherapy is needed, then a time constraint would not impact its efficacy.

The landscape of available treatments may soon shift now that landmark studies such as Checkmate 816, ADAURA, and IMpower010 have demonstrated the benefit of using targeted therapy and immunotherapy in both neoadjuvant and adjuvant settings. Although certainly ushering in new NSCLC treatment paradigms, the focus on disease-free survival, neoadjuvant, and margin-negative disease makes their conclusions less applicable to the current study.[25-27] Unfortunately, only a limited number of patients in the NCDB fit this study's inclusion criteria and received adjuvant immunotherapy. Thus, the relative efficacy and synergy of these new treatments could not be explored.

The observation that chemotherapy provides a consistent benefit over radiotherapy in the context of positive margins, in this sample, is somewhat counterintuitive given that positive margins represent a risk for local recurrence or invasion, which theoretically would be treated by a local therapy such as radiotherapy. In the case of postoperative locoregional recurrence, radiotherapy is widely considered standard of care. However, there is evidence suggesting that the addition of chemotherapy provides an additional survival benefit compared with radiotherapy alone, a potential explanation being that local treatments are limited by the risk of distant failure, which can be mitigated by inclusion of chemotherapy.[28] Nonetheless, the results outlined add

support for the reevaluation of current recommendations regarding adjuvant therapy.

Study Limitations

There are several limitations associated with using the NCDB for this retrospective study. The NCDB does not capture many important patient and tumor attributes regarding clinical reasoning that may have dictated the selection and sequencing of adjuvant therapy. For instance, these data could help elucidate the clinical rationale behind 1027 patients, 60.0% of this study's total sample, undergoing SA in the context of positive margins. Therefore, the assignment of patients to treatment groups may be susceptible to uncontrolled confounding factors.[29] Perhaps most limiting is that the NCDB does not capture re-resections after initial resection, which is a locoregional treatment option for many patients with positive margins.[2] The routine performance of re-resections for positive margins is unclear in the present day given the confluence of a thoracic surgical oncology era that emphasizes minimally invasive surgery and is witnessing improved systemic therapies. Although the NCDB does not capture frozen-section data that would drive re-resection at the time of the index operation, the notion of re-resection hints at the return to the operating room in a delayed fashion based on a final pathology result for a substantial operation that would likely occur with low frequency in the current epoch. In addition, the NCDB does not distinguish whether specific treatments are therapeutic or salvage in nature nor does it identify the cause of death, both of which could potentially help assess the relative benefit and underlying disease progression of each treatment group. Moreover, the NCDB lacks both disease-free and disease-specific survival data, limiting any survival analysis to overall survival only. Therefore, survival analysis may be susceptible to confounding factors such as age and underlying health. However, using a Charlson-Deyo score of 0 as a proxy for disease-specific survival, a subgroup analysis revealed no statistically significant differences in survival among the adjuvant therapy cohorts, thus decreasing the likelihood that patients' underlying health served as a confounder for the survival differences presented in this article.

Other limitations of the study pertain to the small cohort sizes, especially for the sequential therapy treatment groups. These small cohorts were accentuated when comparing adjuvant therapy cohorts sRTC and sCRT, which limited the analysis of the multimodal therapy options. With the *P* value adjustment method used (Bonferroni), the large number of treatment groups increased the risk of type I error associated with multiple comparisons, with future prospective studies needed to corroborate the findings of this study. In addition, larger sample sizes would help with using equivalence testing to detect the absence of associations or negligible associations. It is also possible for patients to undergo adjuvant therapy at a different, non-NCDB facility and thus would not be captured in this study's cohorts.

CONCLUSIONS

Chemotherapy alone was the only adjuvant therapy that consistently delivered a significant survival improvement to patients with treatment-naïve cT1-4N0M0 pN0 disease and positive surgical margins. Radiotherapy alone was not found to be significantly associated with survival benefit compared with SA. Rather, PORT may serve as an adjunct to modern systemic therapies after incomplete resection with the goal of achieving local disease control and without the expectation that PORT will impact survival. At the same time, delays to adjuvant radiotherapy initiation were not associated significantly with a reduction in survival. There was no significant statistical difference between the concurrent and sequential combination therapy cohorts, and neither provided a statistically significant survival benefit over SA. Taken together, the findings of this study suggest a potential paradigm shift in the care of margin-positive, node-negative patients, as the rapidly expanding evolution of targeted therapies and immunotherapies may also add more dimensions to consider.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: chemotherapy, margins of excision, non–small cell lung cancer, radiotherapy, surgery, timing