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Adjuvant chemotherapy following stereotactic body radiotherapy for early stage non-small-cell lung cancer is associated with lower overall: A National Cancer Database Analysis

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ABSTRACT

Objectives: Adjuvant chemotherapy is routinely offered post-surgical resection for early stage non-small-cell lung cancer (NSCLC) ≥4 cm; however, its role following definitive stereotactic body radiotherapy (SBRT) has not been well defined. We investigated the association between receipt of adjuvant chemotherapy post-SBRT and overall survival (OS) for patients with T1-T3N0M0 NSCLC in the National Cancer Database (NCDB).

Materials and Methods: The NCDB was queried for patients with T1-T3N0M0 NSCLC treated with definitive SBRT from 2004 to 2014. The association between non-randomized receipt of adjuvant chemotherapy and OS was analyzed for all patients (n = 24,011) and a propensity-matched cohort (n = 608) using Kaplan-Meier methods and Cox proportional hazard models. A subset analysis was performed for patients with tumors ≥4 cm (n = 2,323).

Results: There were 24,011 patients in the cohort with a median follow-up of 32.5 months. Of these, 322 (1.3%) received adjuvant chemotherapy. Three-year OS was 41.3% with adjuvant chemotherapy compared to 50.6% without adjuvant chemotherapy (p = 0.001). On multivariate analysis, adjuvant chemotherapy was independently associated with higher overall mortality (hazard ratio:1.22, 95% confidence interval:1.06–1.40, p = 0.005). For tumors ≥4 cm, 3-year OS was 38.2% with adjuvant chemotherapy (n = 80) compared to 33.0% without adjuvant chemotherapy (p = 0.81). After propensity-score matching, there was a persistent association between lower OS and adjuvant chemotherapy with those receiving adjuvant chemotherapy (n = 322) having 3-year OS of 41.3% compared to 60.9% without adjuvant chemotherapy (p < 0.0001).

Conclusion: Adjuvant chemotherapy following definitive SBRT for T1-3N0M0 NSCLC is associated with lower OS and is not associated with a survival benefit for patients with tumors ≥4 cm.

1. Introduction

Lung cancer is the leading cause of cancer-related death in the United States with an estimated 234,030 new cases and 154,050 deaths from this disease in 2018 [1]. Of new non-small-cell lung cancer (NSCLC) diagnoses, an estimated 20% or less will be localized to the lung parenchyma without regional or distant metastases; however, this proportion may increase with the adoption of low-dose computed tomography screening for high-risk populations [2]. Standard of care treatment for early stage NSCLC includes lobectomy with mediastinal

Abbreviations: NSCLC, non-small-cell lung cancer; SBRT, stereotactic body radiotherapy; OS, overall survival; CALGB, Cancer and Leukemia Group B; NCDB, National Cancer Database; AJCC, American Joint Committee on Cancer; HR, hazard ratio; CI, confidence interval; IQR, interquartile range; CT, computed tomography

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lymph node sampling; however, many patients may not be suitable candidates for surgical management due to prohibitive medical comorbidities. For such individuals, stereotactic body radiotherapy (SBRT) represents a curative treatment option associated with favorable 5-year local control and overall survival (OS) of 93% and 40%, respectively [3]. Furthermore, emerging evidence suggests that SBRT and definitive surgical management may be associated with similar outcomes for patients with medically operable, early stage NSCLC [4].

While SBRT represents an attractive noninvasive treatment strategy, drawbacks include a relatively high 5-year locoregional failure rate of 38% primarily attributed to late in-lobe and regional recurrences and a high 5-year distant failure rate of 31% [3]. A logical approach to decrease these risks includes incorporation of systemic therapy into the treatment paradigm by offering adjuvant chemotherapy following SBRT. Although the Lung Adjuvant Cisplatin Evaluation Collaborative Group did not find a significant survival benefit for cisplatin-based adjuvant chemotherapy following surgical resection of stage I A/B NSCLC [5], adjuvant paclitaxel/carboplatin was associated with a 31% reduction in overall mortality for patients with tumors measuring ≥4 cm in the Cancer and Leukemia Group B (CALGB) 9633 trial suggesting a preferential benefit for patients with large primary tumors [6]. Despite these data in the setting of surgical resection, the role of adjuvant chemotherapy following definitive SBRT remains undefined in current treatment guidelines [7–10]. Moreover, there have been sparse retrospective reports published to date on this topic [11–14]. Herein, we report the impact of adjuvant chemotherapy on survival following SBRT for patients with T1-3N0M0 NSCLC in the National Cancer Database (NCDB) with subgroup analyses for propensity-score matched and large-tumor (≥4 cm) cohorts.

2. Materials and methods

2.1. Data source

The data used in the study are derived from a de-identified NCDB file containing demographic, treatment, and survival variables in an institutional review-board exempt study. The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. Of note, 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 investigators. The NCDB represents a hospital-based registry capturing approximately 70% of newly diagnosed cancers in the United States [15], and regularly updated data are included from > 1500 Commission on Cancer-approved centers. Treatment assignment within the NCDB is based upon the judgment of individual physicians and is not randomized.

2.2. Patient selection

All patients were required to have a diagnosis of clinical T1-3N0M0 NSCLC according to the American Joint Committee on Cancer (AJCC) 7th Edition. Since patients undergoing SBRT for definitive treatment of early stage NSCLC may have comorbidities precluding procedures necessary for histologic confirmation of malignancy, this was not a specific eligibility requirement. Treatment dates ranged from 2004 to 2014 to allow for at least 1 year of follow-up after treatment. All patients were coded as having received definitive SBRT without prior surgery or induction chemotherapy. SBRT was defined by the NCDB codes "stereotactic radiosurgery, NOS" or "linac radiosurgery" with radiation therapy delivered in 10 or fewer fractions when dose and fractionation information was available [16]. Patients were considered to have received adjuvant chemotherapy if they were assigned one of three codes including (1) "chemotherapy was administered as first course therapy, but the type and number of agents is not documented in the patient record," (2) "single-agent chemotherapy administered as first course therapy," or (3) "multiagent chemotherapy administered as first course therapy" with chemotherapy delivered between days 1 and 56 following the first fraction of SBRT (day 0). This timeframe for adjuvant chemotherapy is consistent with the time to random assignment in CALGB 9633 which was performed up to 56 days postoperatively [6]. The large tumor cohort consisted of individuals with lesions ≥4 cm.

2.3. Statistical analysis

Patient, tumor, and treatment-related characteristics were compared between groups using the chi square test. OS was estimated using the Kaplan Meier method with differences between groups assessed using the log-rank test. Multivariate analyses to identify independent predictors of OS were performed using Cox proportional hazards regression and hazard ratios (HRs) as well as 95% confidence intervals (CIs) were reported. Variables included in these analyses were significantly different between groups or have previously been associated with OS for patients with early stage NSCLC.

To account for confounding, we developed a propensity score model for the likelihood of receiving and not receiving adjuvant chemotherapy which included the following variables: year, tumor histology, T-stage, age, sex, Charlson-Deyo comorbidity score, type of treatment facility, and insurance status. A 1:1 propensity score match without replacement was then performed between the two groups with a caliper width of 0.0001, and the cohorts were then compared with a log-rank test [17]. All statistical analyses were performed using JMP statistical software, version 13.0 (SAS Institute, Cary, NC) and SPSS24 (IBM Inc, Armonk, NY).

3. Results

3.1. Population characteristics

Patient, tumor, and treatment characteristics for the study population are displayed in Table 1. The analyzed cohort was comprised of 24,011 patients with cT1-3N0M0 early stage NSCLC treated with definitive SBRT from 2004 to 2014 with 93.4% (n = 22,432 of 24,011) having histologic confirmation of malignancy including 93.4% (n = 22,115 of 23,689) in the non-adjuvant chemotherapy group and 98.4% (n = 317 of 322) in the adjuvant chemotherapy group. Median follow-up for the entire cohort was 32.5 months (interquartile range [IQR]: 22.1–49.0 months) and was 31.3 months for those receiving adjuvant chemotherapy compared to 32.6 months for those not receiving adjuvant chemotherapy. The median SBRT dose was 50 Gy delivered in a median of 4 fractions. A total of 322 patients (1.3%) also received adjuvant chemotherapy given a median of 27 days after the first day of SBRT (range: 1–56 days) with 71.7% receiving multiagent chemotherapy, 21.4% receiving single-agent chemotherapy, and the remainder receiving an unknown number of agents.

Between groups receiving adjuvant chemotherapy or not receiving adjuvant chemotherapy, there were no significant differences in gender, Charlson-Deyo comorbidity score, or race (all $p > 0.05$). The adjuvant chemotherapy group was significantly more likely to have lower T-stage (55.3% vs. 75.2% with T1 disease, $p < 0.001$ for all T-stages), younger age (9.6% age 80+ vs. 31.8%, $p < 0.001$ for all age categories), a histologic confirmation of diagnosis (98.4% vs. 93.4%, $p = 0.0003$), a higher proportion with squamous cell histology (37.0% vs. 34.8%, $p = 0.033$ for all tumor histologies), a higher proportion of Hispanic patients (2.5% vs. 1.1%, $p = 0.042$), a lower proportion of patients with Medicare (74.8% vs. 79.9%, $p = 0.043$ for all insurance types), a lower proportion of patients treated at an academic research program (32.9% vs. 40.5%, $p = 0.047$ for all facility types), and more patients diagnosed in 2004–2009 (29.8% vs. 19.7%, $p < 0.0001$).

Population characteristics were also compared as a function of tumor size as displayed in Table 1. A total of 2323 patients had tumors ≥4 cm with concordant T-stage information according to the AJCC 7th

Table 1
Patient characteristics of clinical T1-3N0M0 non-small cell lung cancer patients treated with stereotactic body radiation therapy.

Characteristic	All patients (n = 24,011)	Patients not receiving adjuvant chemotherapy (n = 23,689)	Patients receiving adjuvant chemotherapy (n = 322)	P	Patients with tumor ≥4 cm not receiving adjuvant chemotherapy (n = 2243)	Patients with tumors ≥4 cm receiving adjuvant chemotherapy (n = 80)	P
Clinical factors							
Gender				0.733			0.439
Male	46.3	46.3	45.3		54.4	50.0	
Female	53.7	53.7	54.7		45.6	50.0	
Comorbidity score				0.455			0.011
0	58.0	58.0	54.9		58.1	40.0	
1	26.4	26.4	29.5		25.6	33.8	
2+	15.6	15.6	15.5		16.3	26.3	
T-stage				< .0001			0.015
T1	74.9	75.2	55.3		—	—	
T2	22.2	22.0	35.4		91.6	83.8	
T3	2.9	2.8	9.3		8.4	16.3	
Age at diagnosis (years)				< .0001			< .0001
18-59	6.0	5.9	12.4		3.3	10.0	
60-69	21.9	21.7	31.7		15.9	28.8	
70-79	40.6	40.6	46.3		38.1	52.5	
80+	31.5	31.8	9.6		42.8	8.8	
Histologic confirmation of diagnosis							
Yes	93.4	93.4	98.4	0.0003	96.7	97.5	0.693
No	6.6	6.6	1.6		3.3	2.5	
Histology				.033			0.054
Adenocarcinoma	41.1	41.1	40.4		31.9	33.8	
NSCLC (NOS)	16.3	16.3	14.9		15.3	13.8	
Squamous	34.8	34.8	37.0		43.5	47.5	
Large cell	0.9	0.9	2.5		1.2	3.8	
Socioeconomic factors							
Race				0.293			0.639
White	90.4	90.4	87.3		90.3	86.3	
Black	7.6	7.5	14.9		7.3	10.0	
Other	1.4	1.4	1.6		1.3	2.5	
Ethnicity				0.042			0.572
Hispanic	1.1	1.1	2.5		1.3	0.0	
Insurance status				0.043			0.051
Not insured	0.7	0.7	1.2		0.4	0.0	
Private insurance/ managed care	12.3	12.2	16.4		9.7	16.3	
Medicaid	2.8	2.7	4.3		2.2	6.3	
Medicare	79.9	79.9	74.8		82.5	75.0	
Other government	3.3	3.3	2.5		1.2	2.5	
Institutional factors							
Facility type				0.047			0.198
Community cancer program	3.1	3.1	4.0		3.3	5.0	
Comprehensive community cancer program	42.6	42.5	46.9		44.0	52.5	
Academic research program	40.4	40.5	32.9		39.0	27.5	
Year of diagnosis				< .0001			0.741
2004-2009	19.9	19.7	29.8		23.4	25.0	
2010-2014	80.1	80.2	70.2		76.6	75.0	

Abbreviations: NOS = not otherwise specified; NSCLC = non-small cell lung cancer.

Edition. These patients had a median follow-up of 30.9 months (IQR: 20.3–46.2 months) and received a median SBRT dose of 50 Gy in a median of 5 fractions. Of these, 80 (3.4%) received adjuvant chemotherapy. Patients with large tumors receiving adjuvant chemotherapy were more likely to have a higher Charlson-Deyo comorbidity score (26.3% with Charlson-Deyo comorbidity score 2+ vs. 16.3%, $p = 0.011$ for all Charlson-Deyo comorbidity score categories), higher T-stage (16.3% T3 vs. 8.4%, $p = 0.015$ for all T-stages), and younger age (8.8% age 80+ vs. 42.8%, $p < 0.0001$ for all age categories).

3.2. Survival

Kaplan-Meier curves displaying OS for the entire cohort as a function of receipt of adjuvant chemotherapy are displayed in Fig. 1. OS was significantly lower for patients receiving adjuvant chemotherapy (HR: 1.26, 95% CI: 1.09–1.44, $p = 0.001$) with those patients having a median OS of 28.0 months (95% CI: 24.9–30.8) compared to 36.5 months (95% CI: 35.9–37.2) for those not receiving adjuvant chemotherapy. Multivariate analysis identifying variables independently associated with OS for the entire cohort is displayed in Table 2. Adjuvant chemotherapy (HR 1.22, 95% CI: 1.06–1.40, $p = .005$) remained independently associated with lower OS while other independent prognostic factors included gender (HR 0.79, 95% CI: 0.77-0.82 for female gender, $p < 0.0001$), higher T-stage (HR 1.54, 95% CI: 1.40–1.70 for T3, $p < 0.0001$ for all T-stages), age at diagnosis (HR 1.47, 95% CI: 1.34–1.60 for age 80+, $p < 0.0001$ for all age categories), tumor histology (HR 1.26, 95% CI: 1.21–1.31 for squamous

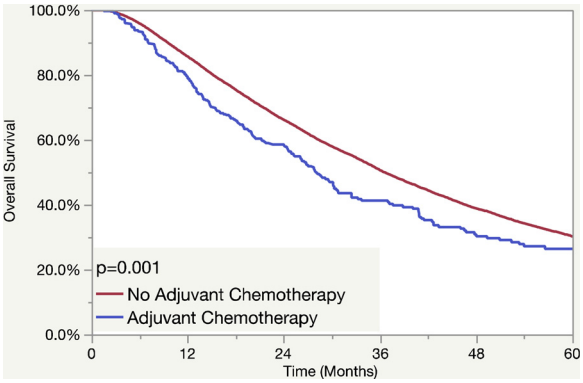

Fig. 1. Overall survival for patients with clinical T1-3N0M0 non-small cell lung cancer treated with stereotactic body radiotherapy from 2004 to 2014 in the National Cancer Database.

histology, $p < 0.0001$ for all histologies), race (HR 0.91, 95% CI: 0.85-0.98 for black compared to white race, $p = 0.02$ for all race categories), ethnicity (HR 0.91, 95% CI: 0.77–1.08 for Hispanic ethnicity, $p = 0.046$), and facility type (HR 1.05, 95% CI: 0.94–1.16 for comprehensive community cancer program, $p = 0.02$ for all facility types). When including histologic confirmation of diagnosis in the same multivariate analysis, this variable was not independently associated with OS (HR: 1.02, 95% CI: 0.95–1.11, $p = 0.55$) while receipt of adjuvant systemic therapy remained significantly associated with lower OS (HR: 1.22, 95% CI: 1.06–1.40, $p = 0.005$). A sensitivity analysis was performed for patients receiving chemotherapy < 29 days from the first fraction of SBRT ($n = 174$) and suggested that chemotherapy administration in this group was similarly associated with lower OS although this association did not reach significance (HR: 1.16, 95% CI: 0.88–1.52, $p = 0.30$).

OS was also estimated using the Kaplan-Meier method for the subset of patients with tumors ≥4 cm as displayed in Fig. 2. Among these patients with large tumors, there was no significant association between receipt of adjuvant chemotherapy and OS (HR: 0.97, 95% CI: 0.74–1.24, $p = 0.81$) with those receiving adjuvant chemotherapy having a median OS of 26.8 months (95% CI: 20.0–30.8) compared to 22.8 months (95% CI: 21.8–24.1) for those not receiving chemotherapy. Among these patients, multivariate analysis displayed in Table 3 identified gender (HR 0.78, 95% CI 0.71-0.86 for female gender, $p < 0.0001$), higher Charlson-Deyo comorbidity score (HR 1.34, 95% CI 1.17–1.53 for Charlson-Deyo comorbidity score 2+, $p = 0.0002$ for all Charlson-Deyo comorbidity score categories), higher T-stage (HR 1.19, 95% CI: 1.00–1.40 for T3, $p = 0.041$ for all T-stages), older age at diagnosis (HR 1.38, 95% CI: 1.02–1.87 for age 80+, $p = 0.0004$ for all age categories), and non-adenocarcinoma histology (HR 1.28, 95% CI: 1.14–1.44 for squamous histology, $p = 0.0001$ for all histology categories) as being independently associated with OS. This same multivariate analysis additionally including histologic confirmation of diagnosis showed no association between OS and histologic confirmation of diagnosis (HR: 1.10, 95% CI: 0.83–1.47, $p = 0.49$) or receipt of adjuvant chemotherapy (HR: 0.97, 95% CI: 0.74–1.26, $p = 0.82$).

3.3. Propensity-score matching

Propensity-score matching was performed to limit the influence of potentially confounding patient and treatment-related factors disproportionately represented in groups receiving or not receiving adjuvant chemotherapy. After propensity-score matching, a cohort of 608 patients were well-matched for year of diagnosis ($p = 0.55$), tumor histology ($p = 0.75$), T-stage ($p = 0.15$), age at diagnosis ($p = 0.69$), gender ($p = 0.88$), Charlson-Deyo comorbidity score ($p = 0.95$), facility type ($p = 0.85$), and insurance status ($p = 0.79$) as determined using chi square analysis. Within the propensity-score matched cohort, median follow-up was 34.4 months (IQR: 23.7–55.2 months) with 322 (53.0%) receiving adjuvant chemotherapy. There was a stronger association between lower OS and receipt of adjuvant chemotherapy after propensity-score matching on univariate analysis (HR: 1.60, 95% CI: 1.30–1.98, $p < 0.0001$) as displayed in Fig. 3. Those who received adjuvant chemotherapy following SBRT had a median OS of 28.0 months (95% CI: 24.9–30.8) compared to 47.7 months (95% CI: 40.0–56.8) for those not receiving adjuvant chemotherapy. Propensity-score matching was also performed for a cohort of 148 patients with tumors ≥4 cm ($n = 74$ receiving adjuvant chemotherapy) after which OS continued to be statistically similar between groups (HR: 1.22, 95% CI: 0.83–1.82, $p = 0.31$). Patients in this cohort receiving adjuvant chemotherapy had a median OS of 27.9 months (95% CI: 20.2–40.9) compared to 29.6 months (95% CI: 18.5–44.1) for those not receiving adjuvant chemotherapy. When performing propensity-score matching

Table 2
Multivariate Cox proportional hazard models predicting overall survival among T1-3N0M0 non-small cell lung cancer patients treated with stereotactic body radiation therapy (n = 24,011).

Characteristic	Hazard ratio	95% Confidence Interval	*p*-Value
Clinical factors			
Gender			< .0001
Male	1.0 (ref)		
Female	0.79	0.77-0.82	
Comorbidity score			< .0001
0	1.0 (ref)		
1	1.10	1.06-1.15	
2+	1.36	1.30-1.42	
T-stage			< .0001
T1	1.0 (ref)		
T2	1.44	1.39-1.50	
T3	1.54	1.40-1.70	
Age at diagnosis (years)			< .0001
18-59	1.0 (ref)		
60-69	1.11	1.02-1.22	
70-79	1.26	1.16-1.38	
80+	1.47	1.34-1.60	
Histology			< .0001
Adenocarcinoma	1.0 (ref)		
NSCLC (NOS)	1.17	1.11-1.23	
Squamous	1.26	1.21-1.31	
Large cell	1.34	1.15-1.57	
Socioeconomic factors			
Race			0.02
White	1.0 (ref)		
Black	0.91	0.85-0.98	
Other	0.87	0.75-1.02	
Ethnicity			0.046
Non-Hispanic	1.0 (ref)		
Hispanic	0.91	0.77-1.08	
Insurance status			0.06
Not insured	1.0 (ref)		
Private insurance/managed care	0.96	0.77-1.20	
Medicaid	1.07	0.84-1.36	
Medicare	1.04	0.83-1.30	
Other government	0.99	0.78-1.26	
Institutional factors			
Facility type			0.02
Community cancer program	1.0 (ref)		
Comprehensive community cancer program	1.05	0.94-1.16	
Academic research program	1.00	0.90-1.11	
Year of diagnosis			0.20
2004-2009	1.0 (ref)		
2010-2014	0.97	0.94-1.01	
Treatment received			.005
No adjuvant chemotherapy	1.0 (ref)		
Adjuvant chemotherapy	1.22	1.06-1.40	

Abbreviations: NOS = not otherwise specified; NSCLC = non-small cell lung cancer.

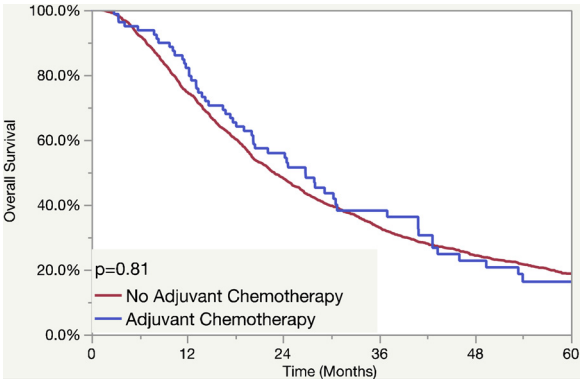

Fig. 2. Overall survival for patients with clinical T2-3N0M0 non-small cell lung cancer and tumors ≥4 cm treated with stereotactic body radiotherapy from 2004 to 2014 in the National Cancer Database.

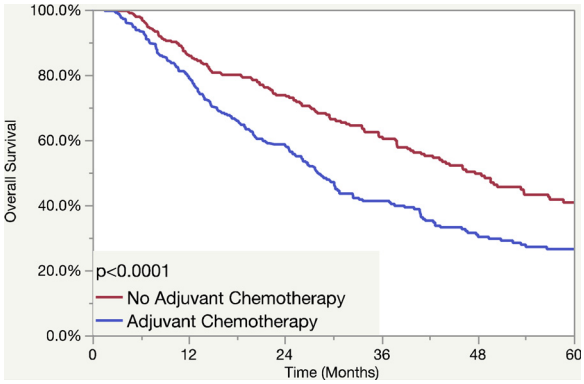

Fig. 3. Overall survival for propensity-score matched patients with clinical T1-3N0M0 non-small cell lung cancer treated with stereotactic body radiotherapy from 2004 to 2014 in the National Cancer Database.

Table 3
Multivariate Cox proportional hazard models predicting overall survival among T1-3N0M0 non-small cell lung cancer patients with tumors ≥4 cm treated with stereotactic body radiation therapy (n = 2,323).

Characteristic	Hazard ratio	95% Confidence Interval	*p*-Value
Clinical factors			
Gender			< .0001
Male	1.0 (ref)		
Female	0.78	0.71-0.86	
Comorbidity score			.0002
0	1.0 (ref)		
1	1.09	0.97-1.23	
2+	1.34	1.17-1.53	
T-stage			.041
T2	1.0 (ref)		
T3	1.19	1.00-1.40	
Age at diagnosis (years)			.0004
18-59	1.0 (ref)		
60-69	1.04	0.77-1.44	
70-79	1.16	0.86-1.59	
80+	1.38	1.02-1.87	
Histology			.0001
Adenocarcinoma	1.0 (ref)		
NSCLC (NOS)	1.22	1.05-1.42	
Squamous	1.28	1.14-1.44	
Large cell	1.38	0.91-2.11	
Socioeconomic factors			
Race			0.60
White	1.0 (ref)		
Black	0.93	0.77-1.13	
Other	1.08	0.70-1.66	
Ethnicity			0.89
Non-Hispanic	1.0 (ref)		
Hispanic	0.93	0.59-1.47	
Insurance status			0.71
Not insured	1.0 (ref)		
Private insurance/managed care	0.61	0.28-1.30	
Medicaid	0.59	0.26-1.33	
Medicare	0.60	0.28-1.27	
Other government	0.53	0.24-1.16	
Institutional factors			
Facility type			0.86
Community cancer program	1.0 (ref)		
Comprehensive community cancer program	0.95	0.71-1.29	
Academic research program	0.95	0.70-1.28	
Year of diagnosis			0.11
2004-2009	1.0 (ref)		
2010-2014	0.91	0.81-1.02	
Treatment received			0.82
No adjuvant chemotherapy	1.0 (ref)		
Adjuvant chemotherapy	0.97	0.74-1.26	

Abbreviations: NOS = not otherwise specified; NSCLC = non-small cell lung cancer.

with the addition of histologic confirmation of diagnosis, the hazard ratios for OS were 1.14 (95% CI: 0.93–1.41, $p = 0.20$) and 1.46 (95% CI: 0.88–2.42, $p = 0.14$) for patients with tumors of all sizes ($n = 575$ with 287 receiving adjuvant chemotherapy) and patient with tumors ≥4 cm ($n = 94$ with 47 receiving adjuvant chemotherapy), respectively.

4. Discussion

SBRT represents an effective, noninvasive strategy to provide excellent management for patients with early stage NSCLC who have medical comorbidities precluding surgical treatment or have a personal preference for nonoperative intervention. Mature data from phase II studies have reported long-term local control rates of greater than 90% for medically inoperable patients [3]. Moreover, this impressive local control appears to be associated with multiple dose regimens so long as the biologic effective dose remains at least 100 Gy [18] allowing for adjustments in dose and fractionation schemes to treat even centrally located tumors safely in this medically high-risk patient population [19]. Nevertheless, late in-lobe and regional failures can affect 20% and 18% of patients, respectively, 5 years post-SBRT [3]. Given the survival benefit associated with adjuvant carboplatin/paclitaxel following resection of large, stage IB NSCLC in an exploratory analysis of CALGB 9633 [6], it is plausible that such a treatment paradigm may also improve survival for patients receiving upfront SBRT given their propensity for late out-of-field failure. Despite this logical rationale, our data using the NCDB demonstrate that the receipt of adjuvant chemotherapy within 8 weeks of the first fraction of definitive SBRT for T1-T3N0M0 NSCLC is associated with statistically lower OS with an even stronger association between adjuvant chemotherapy and lower OS within a propensity-score matched cohort. Furthermore, no survival benefit to adjuvant chemotherapy was seen for patients with tumors ≥4 cm in size.

These results add to the relatively sparse literature investigating the efficacy of adjuvant systemic therapy following definitive SBRT. For instance, a study from Chen et al. investigating 65 patients with T1-3N0M0 NSCLC treated with SBRT reported 5-year OS of 46.0% for 17 patients receiving cisplatin-based adjuvant chemotherapy compared to 31.5% for those receiving SBRT alone [12]. Additionally, Verma et al. recently reported a 7.2-month improvement in median OS for patients with node-negative, early stage NSCLC ≥ 5 cm when receiving adjuvant chemotherapy post-SBRT [13]. These and other data identifying tumor size as an independent predictor of local failure following SBRT [20] suggest that individuals with large-volume tumors are the most likely to potentially benefit from incorporation of adjuvant systemic therapy. Nevertheless, adjuvant chemotherapy was not associated with significantly higher OS in our cohort using a different definition of large

primary tumors (≥4 cm) compared to the definition used by Verma et al., implying that candidates for this approach must be selected carefully to achieve an optimal balance of risks and benefits. In fact, patients with tumors ≥4 cm who received adjuvant chemotherapy following SBRT in our report were more likely to have a Charlson-Deyo comorbidity score of 2 or greater compared to those not receiving chemotherapy (26.3% vs. 16.3%) perhaps accounting for the lack of association with OS.

Of note, Ernani et al. published an analysis identifying an association between lower OS and adjuvant systemic therapy for patients with early stage NSCLC receiving definitive SBRT in the NCDB [14]. Furthermore, for patients with tumors ≥4 cm and node-negative disease, adjuvant systemic therapy was associated with significantly higher OS (median OS 19 months vs. 15.9 months for SBRT alone, $p < 0.001$) in their study which differs from the insignificant association between adjuvant systemic therapy and OS reported here. There was a substantial difference in the cohort selection between the two studies, as ours included 24,001 patients compared to 11,836 patients in the Ernani analysis. Relative strengths of our report are the performance of propensity-score matching to account for potential confounding variables not recorded in the NCDB as well as the inclusion of numerous potential confounders beyond age and sex in multivariate analyses (e.g., Charlson-Deyo comorbidity score, histologic confirmation of diagnosis, tumor histology, race, ethnicity, insurance status, treating facility type, and year of diagnosis). Finally, our definition of adjuvant systemic therapy allowed for chemotherapy administration within 56 days from treatment and is consistent with the CALGB 9633 study which examined this issue. This time window for adjuvant therapy is shorter than the 90-day window in the Ernani report and could also explain the different results.

Although adjuvant chemotherapy was not associated with higher OS in this cohort of patients with T1-3N0 NSCLC receiving definitive SBRT in the NCDB, specific subsets of patients may still benefit including those who have medically operable NSCLC but decline SBRT due to preference given their likely lower medical comorbidity. Additionally, alternative approaches to adjuvant therapy may have an improved therapeutic ratio translating to improvements in oncologic outcomes. Perhaps the most promising alternative candidate adjuvant therapy post-SBRT is immunotherapy given the improved efficacy and reduced toxicity associated with this modality compared to chemotherapy in the metastatic setting [21]. Moreover, patients previously receiving radiation and later treated with pembrolizumab on KEYNOTE-001 enjoyed longer progression-free survival and OS [22], and adjuvant durvalumab following chemoradiation for stage III NSCLC has been associated with improved progression-free survival in the PACIFIC trial [23]. Other approaches such as incorporating neoadjuvant immunotherapy before SBRT holds promise as evidenced by an acceptable side effect profile and major pathological response rate of 45% in the surgical setting [24]. Otherwise, inclusion of adjuvant tyrosine kinase inhibitors for patients with targetable mutations may be successful in light of the recently reported improved disease-free survival, toxicity, and quality of life when gefitinib versus vinorelbine plus cisplatin was given adjuvantly for completely resected, *EGFR*-mutated stage II-IIIA, N1-2+ NSCLC [25].

Limitations of this study include its retrospective, non-randomized nature and reliance on data extracted from the NCDB which may be subject to errors in coding by participating facilities. Additionally, it is possible our results were influenced by selection bias including an imbalance in the proportion of patients with questionable metastatic disease counted as M0 between groups receiving or not receiving adjuvant chemotherapy. This possibility may be higher than average in a cohort such as ours wherein a low percentage of patients received the intervention of interest. Moreover, we were unable to detect differences in other endpoints beyond OS including locoregional/distant control, progression-free survival, and cancer-specific survival as these are not reported in the NCDB. Furthermore, imbalances in patient characteristics not recorded in the NCDB including the proportion of patients undergoing positron-emission tomography may have influenced treatment selection including use of adjuvant chemotherapy.

Despite these shortcomings, we have demonstrated that adjuvant chemotherapy is associated with a statistically significantly lower OS when examining a large, national cross section of patients receiving definitive SBRT for T1-3N0M0 NSCLC. The lower OS associated with adjuvant chemotherapy persisted after propensity-score matching to control for potentially confounding variables, and we discovered that even patients with large tumors ≥4 cm failed to have a significantly higher OS when receiving adjuvant systemic therapy. In conclusion, there was no benefit to adjuvant chemotherapy for patients receiving definitive SBRT for early stage NSCLC, and future clinical trials are warranted to identify more efficacious and potentially less toxic neoadjuvant or adjuvant therapeutic interventions that can improve OS for this cohort of patients who are at considerable risk for late locoregional and distant failure [3].

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