Radiotherapy and Oncology 131 (2019) 75–80

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Addition of chemotherapy improves overall survival in patients with T2N0M0 non-small cell lung cancer undergoing definitive radiation therapy: An analysis of the SEER database

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ARTICLE INFO

Article history:
Received 5 September 2018
Received in revised form 27 November 2018
Accepted 2 December 2018
Available online 31 December 2018

Keywords:
The Surveillance, Epidemiology, and End Results (SEER)
Non-small cell lung cancer
The American Joint Committee on Cancer (AJCC)
Radiation
Chemotherapy

ABSTRACT

Objectives: Despite recommendations by clinical guidelines, an advantage of adding systemic chemotherapy to definitive radiation in patients with early stage non-small cell lung cancer (NSCLC) has never been demonstrated by randomized or large-scale studies. This study evaluates the role of chemotherapy in T2N0M0 NSCLC patients who did not undergo surgical resection.

Materials and methods: Using the Surveillance, Epidemiology, and End Results (SEER) database, we screened for patients with T2N0M0 NSCLC who received radiation therapy without surgical resection from 2004 to 2015. T-staging was defined according to the American Joint Committee on Cancer (AJCC) 6th (Year 2004+) and 7th (Year 2010+) versions. Overall survival based on chemotherapy status was assessed by univariate and multivariate analyses.

Results: A total of 6075 and 3138 patients were identified for AJCC 6th (T2; 3–7cm) and 7th (T2a; 3–5 cm, T2b; 5–7 cm) version, respectively. Administration of chemotherapy was associated with younger age, male sex, non-adenocarcinoma, and high pathologic grade. Kaplan–Meier's estimates demonstrated that the chemotherapy group had a statistically significant longer five-year overall survival than the non-chemotherapy group in patients with AJCC 6th T2 (19.9% vs 15.8%, $p = 0.0023$) and AJCC 7th T2b (5–7 cm, 20.9% vs 13.6%, $p = 0.0046$) but not those with AJCC 7th T2a (3–5 cm, 24.3% vs 21.1%, $p = 0.4369$). Multivariate analyses also revealed that the use of chemotherapy was an independent prognostic factor in AJCC 6th T2 and AJCC 7th T2b.

Conclusions: This study strongly suggests that chemotherapy may benefit non-adenocarcinoma patients with primary tumor larger than 5 cm (AJCC 8th T3) undergoing chest radiation.

Lung cancer is the most common cause of cancer mortality in developed nations [1]. Despite recent developments in new systemic and local treatment modalities, survival of patients with advanced stage disease remains very poor. Those who achieve long-term survival are primarily limited to node negative, localized disease that can be surgically resected [2]. Adjuvant chemotherapy in early stage non-small cell lung cancer was shown to improve five-year overall survival by approximately 5% and became standard in routine practice for patients with positive lymph nodes or primary tumors larger than 4 cm [3–5].

However, the median age of NSCLC patients at diagnosis is 70 years old [2]. In real-world practice, these patients tend to have underlying comorbidities that limit options in cancer management. Guidelines recommend radiation therapy including stereotactic beam radiation therapy (SBRT) for early stage NSCLC patients who cannot tolerate or refuse surgical resection [3]. Data extrapolation from patients who received adjuvant chemotherapy for resected early stage NSCLC has led to recommendations for the addition of chemotherapy after radiation for patients with high risk features such as primary tumor larger than 4 cm [3]. This relatively weak recommendation is not based on any controlled clinical trial or even large-scale retrospective studies focusing on early stage (stage I–II). Verma et al. conducted a retrospective analysis using National Cancer Database (NCDB) to define the role of adjuvant chemotherapy in the setting of SBRT [6]. Although their analysis showed adjuvant chemotherapy improved survival in patients who underwent SBRT for primary tumor larger than 5 cm, the retrospective study identified only 30 patients who were treated with adjuvant chemotherapy [6]. All the other retrospective studies included fewer patients than did the NCDB analysis [7,8].

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https://doi.org/10.1016/j.radonc.2018.12.004
0167-8140/

In recent years retrospective research tools with large patient databases became available for cancer researchers. They include the Surveillance, Epidemiology, and End Results (SEER) which covers approximately a quarter of US cancer population [9]. More recently, information about chemotherapy became available for public SEER researchers so that they can assess its role in various cancer types. In this study, we investigated if chemotherapy can influence long-term outcome in early stage NSCLC who underwent radiation therapy without surgical resection.

Materials and methods

Patient selection

To screen candidates, we selected the SEER-18 dataset which includes cancer registry data from Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Utah, Los Angeles, San Jose-Monterey, Rural Georgia, Alaska Natives, Greater California, Greater Georgia, Kentucky, Louisiana, and New Jersey [9]. NSCLC Patients who were clinically staged T2N0M0 according to the American Joint Commission on Cancer (AJCC) 6th or 7th staging [10] and underwent radiation therapy without surgical resection were selected. Disease sites and corresponding ICD-O-3 codes are Main bronchus, C34.0; Upper lobe lung, C34.1; Middle lobe lung, C34.2; Lower lobe lung, C34.3; Overlapping lesion of lung, C34.8; Lung Not Otherwise Specified (NOS), C34.9. NSCLC cases were defined by removing small cell lung cancer: 8041/3, Small cell carcinoma, NOS; 8042/3, Oat cell carcinoma; 8043/3, Small cell carcinoma, fusiform cell; 8044/3, Small cell carcinoma, intermediate cell; 8045/3, Combined small cell carcinoma. Publicly available SEER stat v.8.3.5 software was used for data extraction [11].

Study analysis

The AJCC 6th and 7th version staging data are available since 2004 and 2010, respectively, and analyzed separately. T2a ($3 < T \leq 5$ cm) vs T2b ($5 < T \leq 7$ cm) subclassification is available only by the AJCC 7th version. Basic patient characteristics collected were chemotherapy administration (yes vs no/unknown), age (20–69 vs 70+), year of diagnosis (2004–2010 vs 2011–2015), sex (male vs female), histology (adenocarcinoma vs others), reason for no surgery (not recommended vs others), and histologic grade (III or IV vs Others). Calendar year of diagnosis was not assessed for the AJCC 7th data due to short follow-up time. Information regarding timing of chemotherapy in relation to radiation was not available.

Statistics

The association between chemotherapy administration and other clinical characteristics were determined by chi-squared test. Kaplan–Meier's curves and estimated overall survival according to chemotherapy status were determined by Log-rank test. Both univariate and multivariate analyses were conducted for the AJCC 6th (T2), 7th T2a, and 7th T2b groups. All the statistical analyses were performed using JMP software version 13 (SAS Institute, Cary, NC), and significance was achieved when $p < 0.05$.

Results

Correlation of characteristics with chemotherapy status

A total of 6075 and 3138 patients were identified for the AJCC 6th and 7th versions, respectively (Tables 1 and 2). Among the AJCC 7th version cases 2386 and 752 cases were T2a and T2b, respectively. Of note, patients in the AJCC 6th T2 group included those in 7th T2a and T2b groups. Administration of chemotherapy was performed in 2218 (37%), 522 (22%), and 347 (46%) of patients with the AJCC 6th (T2), 7th T2a, and 7th T2b groups, respectively. In the AJCC 6th T2 group, the use of chemotherapy was associated with younger age, early calendar year of diagnosis, male sex, histology other than adenocarcinoma, and high histologic grade (all $p < 0.0001$, Table 1). Similar trends were seen in the AJCC 7th T2a and T2b groups (Table 2).

Survival analysis

Univariate survival analysis showed that patients who received chemotherapy had significantly longer overall survival in the AJCC 6th T2, AJCC 7th T2b, but not in the AJCC 7th T2a group (Fig. 1A, C, B, $p = 0.0023$, 0.0046, 0.6045, respectively). Five-year overall survival rates according to chemotherapy status (yes vs no/unknown) were 19.9% vs 15.8%, 24.3% vs 21.1%, and 20.9% vs 13.6% in the AJCC 6th T2, AJCC 7th T2a, and T2b group, respectively (Table 3). Subgroup analyses for AJCC 6th T2 and AJCC 7th T2b groups demonstrated that survival benefit from chemotherapy is primarily observed in non-adenocarcinoma group (Fig. 2). Other clinical characteristics with significantly prolonged survival by univariate analyses were younger age, late calendar year of diagnosis, female sex, non-adenocarcinoma histology, other reason for no surgery, or other histologic grade in the AJCC 6th T2 group, female sex, non-adenocarcinoma histology, or other reason for no surgery in the AJCC 6th T2a group, and younger age, or non-adenocarcinoma histology in the AJCC 7th T2b group (Table 3).

Multivariate Cox proportional hazard analysis demonstrated the use of chemotherapy was an independent prognostic factor for better survival in the AJCC 6th T2 and 7th T2b but not in 7th T2a group ($p = 0.0001$, 0.0087, 0.4213, respectively, Table 4). Analysis for cause (disease)-specific survival demonstrated no significant difference by chemotherapy status in any AJCC group (data not shown).

Discussion

For patients with NSCLC which is limited to primary location, surgical resection has been the fundamental therapy if they can tolerate the procedure. These patients, however, are often diagnosed at an advanced age with various underlying conditions. They tend to have heavy smoking histories which is associated with chronic obstructive pulmonary disease (COPD), coronary artery disease, and others. These comorbidities often complicate and affect treatment outcome, especially surgical intervention. Those who are unfit and unlikely to tolerate surgical resection have traditionally been treated with radiation therapy alone. Development of novel radiation techniques have allowed clinicians to offer hypofractionated and more dose-intensified regimen such as SBRT [8]. Over the last few decades, randomized controlled trials demonstrated that adjuvant chemotherapy improves overall survival in resected early stage NSCLC patients with positive mediastinal/hilar node or primary tumor larger than 4 cm [3,4]. However, for those who undergo radiation therapy without resection, the role of chemotherapy has never been investigated in randomized clinical trials.

Recent guidelines suggest adjuvant chemotherapy after radiation for large primary tumors without nodal disease [3]. Retrospective analysis of patients who underwent SBRT showed that relapse was primarily seen in regional or distant locations, suggesting the need of chemotherapy [12,13]. Several small case studies and database analyses suggest that adjuvant chemotherapy improves survival. A small retrospective case analysis in China showed that the chemotherapy group ($n = 17$) had significantly longer overall

Table 1
Characteristics of patients with T2N0M0 disease according to AJCC 6th version.

		Chemotherapy		
	Total	Yes	No/Unknown	*P*-value
Total	6075	2218 (37%)	3857 (63%)	
Age				
20–69	2039	1109 (54%)	930 (47%)	<0.0001
70+	4036	1109 (27%)	2927 (73%)	
Year				
2004–2010	2993	1263 (42%)	1730 (58%)	<0.0001
2011–2015	3082	955 (31%)	2127 (69%)	
Sex				
Male	3335	1339 (40%)	1996 (60%)	<0.0001
Female	2740	879 (32%)	1861 (68%)	
Histology				
Adenocarcinoma	1794	545 (30%)	1249 (70%)	<0.0001
Others	4281	1673 (39%)	2608 (61%)	
Reason for no surgery				
Not recommended	5580	2043 (37%)	3537 (63%)	0.577015
Others	495	175 (35%)	320 (65%)	
Grade				
High (III + IV)	1850	754 (41%)	1096 (59%)	<0.0001
Others	4225	1464 (35%)	2761 (65%)	

Table 2
Characteristics of patients with T2N0M0 disease according to AJCC 7th version (2010+).

Stage	T2a (3–5 cm)				T2b (5–7 cm)			
		Chemotherapy				Chemotherapy		
	Total	Yes	No/Unknown	*P*-value	Total	Yes	No/Unknown	*P*-value
Total	2386	522 (22%)	1864 (78%)		752	347 (46%)	405 (54%)	
Age								
20–69	740	263 (36%)	477 (64%)	<0.0001	279	179	100	<0.0001
70+	1646	259 (16%)	1387 (84%)		473	168	305	
Sex								
Male	1245	297 (24%)	948 (76%)	0.0146	446	218	228	0.0693
Female	1141	225 (20%)	916 (80%)		306	129	177	
Histology								
Adeno	881	161 (18%)	720 (82%)	0.0011	214	85	129	0.0258
Others	1505	361 (24%)	1144 (76%)		538	262	276	
Reason for no surgery								
NR	2197	488 (22%)	1709 (78%)	0.1778	705	323	382	0.4847
Others	189	34 (18%)	155 (82%)		47	24	23	
Grade								
High	660	168 (25%)	492 (75%)	0.0090	248	128	120	0.0348
Others	1726	354 (21%)	1372 (79%)		504	219	285	

Abbreviations: NR, not recommended.

survival than observation group ($n = 48$) among T1-3 NSCLC patients who underwent SBRT [7]. A database analysis using NCDB also investigated the role of adjuvant chemotherapy in patients who were treated with SBRT for node negative large tumor (>5cm). Although they were able to demonstrate a statistically significant improvement in overall survival with a median OS of 30.6 and 23.4 months, respectively, they identified only 30 and 171 cases that were treated with or without chemotherapy after SBRT, respectively [6].

Our large database study suggests that chemotherapy improves overall survival in T2N0M0 NSCLC patients who are treated with radiation, and that survival benefit is primarily in the AJCC 7th T2b (larger than 5 cm) patients, supporting the result of the previous small studies. This study is also consistent with a SEER-Medicare analysis on the role of chemotherapy in elderly patients with stage I–II NSCLC who were treated with thoracic radiation [14]. The study demonstrated that survival benefit was observed when non-complexity radiation (i.e., conventional radiation) instead of complexity radiation (e.g., SBRT) was used for stage I NSCLC. The study also showed chemotherapy improved survival in stage II NSCLC regardless of type of chest radiation. Their study suggests that chemotherapy has little role if the disease is well controlled by local therapy such as SBRT, which is in line with the lack of benefit in adjuvant chemotherapy for stage I disease with $T < 4$ cm.

In contrast to surgically staged patients, these patients are clinically staged without extensive nodal staging. Larger primary tumors such as T2 with clinically negative node are more likely to be under-staged than smaller disease [15]. A recent retrospective large study in Netherlands reported the concordance rates between clinical and pathological staging for clinical T1 and T2 were only 66.7% and 48.8%, respectively [15]. Given that surgical patients with positive nodes have longer survival with adjuvant chemotherapy [4], the benefit of chemotherapy in those undergo-

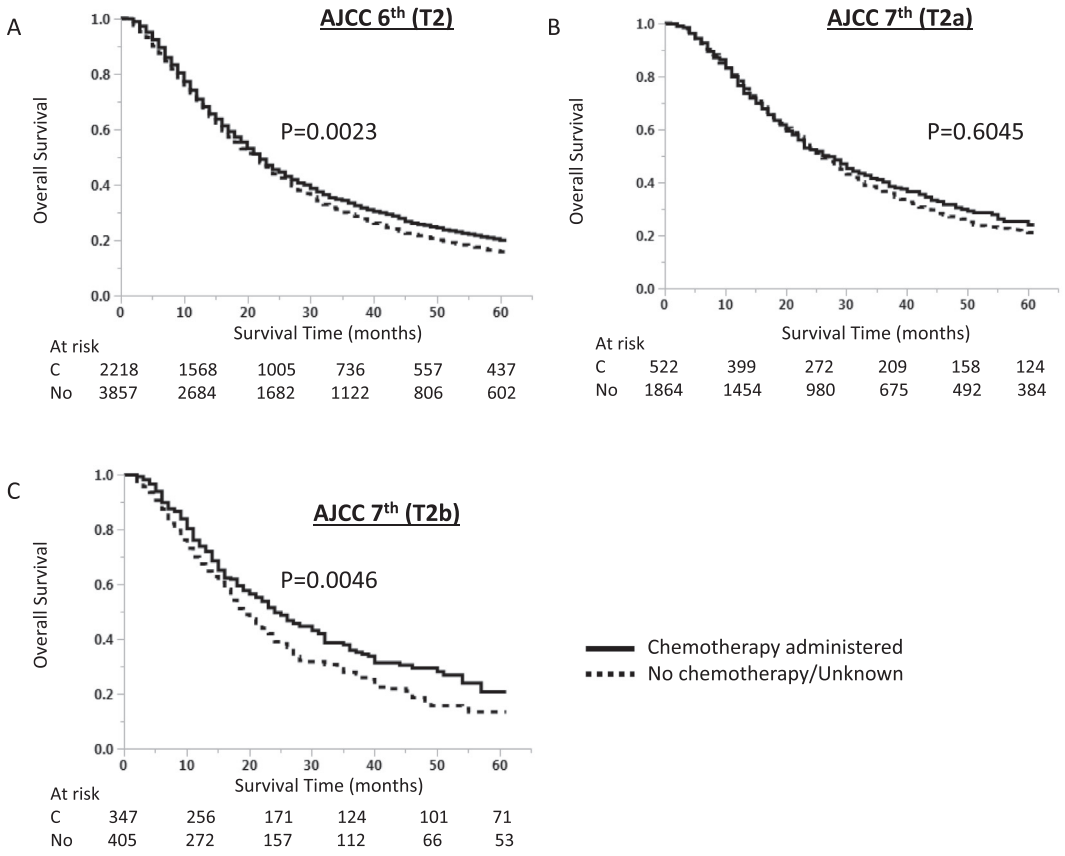

Fig. 1. Overall survival of patients with AJCC 6th T2 (A), 7th T2a (B), and 7th T2b (C) according to chemotherapy status. Survival curves were generated by Kaplan–Meier's method. Log-rank test was used for statistical analysis.

Table 3
Univariate analysis for OS according to chemotherapy status.

	AJCC 6th (T2)		*P*-value	AJCC 7th (T2a)		*P*-value	AJCC 7th (T2b)		*P*-value
Variable	N	5-year OS%	(Log-rank)	N	5-year OS%	(Log-rank)	N	5-year OS%	(Log-rank)
Age									
20–69	2039	20.7%	<0.0001	740	21.6%	0.097	279	19.6%	0.0096
70+	4036	15.8%		1626	22.1%		473	15.4%	
Year									
2004–2010	2993	20.2% (4 years)	<0.0001	NA			NA		
2011–2015	3082	26.8% (4 years)		NA			NA		
Sex									
Male	3335	14.1%	<0.0001	1245	15.8%	<0.0001	446	15.0%	0.2613
Female	2740	21.5%		1141	28.4%		306	19.0%	
Histology									
Adeno	1794	19.7%	<0.0001	881	25.0%	0.0016	214	18.1%	0.0208
Others	4281	16.5%		1505	20.3%		538	16.4%	
Reason									
NR	5580	16.9%	0.0001	2197	21.1%	0.0211	705	16.3%	0.2919
Others	495	23.7%		189	29.7%		47	29.3%	
Grade									
High	1850	15.7%	0.0004	660	18.4%	0.0850	248	21.0%	0.4737
Others	4225	18.2%		1726	23.4%		504	15.3%	
Chemotherapy									
Yes	2218	19.9%	0.0023	522	24.3%	0.4369	347	20.9%	0.0046
No/Unknown	3857	15.8%		1864	21.1%		405	13.6%	

Abbreviations: NR, not recommended; NA, not available; OS, overall survival.

ing radiation might be driven by clinically negative but understaged (microscopic) nodal disease. This concept of chemotherapy for relatively more advanced disease (i.e., cT2b with potential microscopic nodal involvement) is consistent with historical clinical trials for unresectable stage III NSCLC which demonstrated that addition of chemotherapy to radiation improved survival as well [16,17].

We acknowledge there are limitations in this study. SEER started collecting chemotherapy data in 2004 but currently provides researchers with only dichotomous information (i.e., pres-

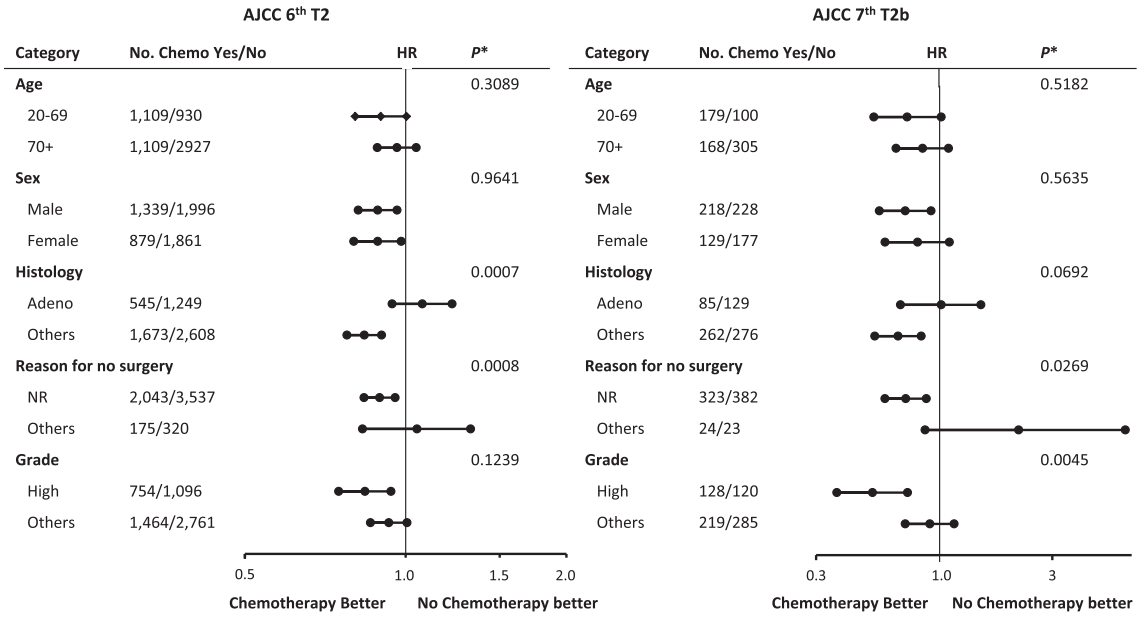

Fig. 2. Forest plot analysis on overall survival of patients with AJCC 6th T2 and 7th T2b according to chemotherapy status. Each horizontal bar indicates a hazard ratio and 95% confidence interval. *, probability of interaction trend test; NR, not recommended; HR, hazard ratio.

Table 4
Multivariate Cox proportional Hazard analyses for OS.

Variable	AJCC 6th T2 HR (95% CI)	*P*	AJCC 7th T2a HR (95% CI)	*P*	AJCC 7th T2b HR (95% CI)	*P*
Chemotherapy (Yes vs No/unknown)	0.88 (0.82–0.94)	0.0001	0.94 (0.82–1.09)	0.4213	0.76 (0.62–0.93)	0.0087
Age (20–69 vs 70+)	0.86 (0.81–0.93)	<0.0001	0.88 (0.77–1.00)	0.0472	0.79 (0.64–0.98)	0.0297
Year (2011–2015 vs 2004–2010)	0.78 (0.73–0.84)	<0.0001	NA		NA	
Sex (Female vs Male)	0.80 (0.75–0.85)	<0.0001	0.78 (0.69–0.87)	<0.0001	0.89 (0.73–1.09)	0.2726
Histology (Adeno vs Others)	0.83 (0.77–0.89)	<0.0001	0.85 (0.75–0.96)	0.0083	0.73 (0.58–0.91)	0.0060
Reason for no surgery (Others vs NR)	0.78 (0.70–0.88)	<0.0001	0.79 (0.62–0.98)	0.0332	0.78 (0.50–1.21)	0.2720
Grade (Others vs High)	0.90 (0.85–0.97)	0.0035	0.93 (0.82–1.06)	0.2633	0.88 (0.72–1.08)	0.2323

Abbreviations: NR, not recommended; HR, hazard ratio; NA, not available; OS, overall survival.

ence or absence of its administration). Information about chemotherapy agent, dose, number of cycles, and timing in relation to radiation are not available. This means that there may be patients who received chemotherapy prior to radiation. Based on routine practice and guideline recommendations, we assume most patients in this study underwent radiation prior to chemotherapy.

We are also aware that lack of information in SEER database about performance status, co-morbidities, and others might affect interpretation of the study. Those who underwent radiation instead of surgery likely have underlying disease and poor performance status which influence prescription of chemotherapy. Patients in the chemotherapy group may have better survival partly due to lack of such severe co-morbidities.

Detail for radiation regimens is also currently lacking in this database. In recent years, SBRT became available and commonly used for oncology practice. This study is unable to define type of radiation (e.g., SBRT), fractionation, or doses. Regardless of whether SBRT or standard thoracic radiation is utilized, however, it does not address micrometastases that are invisible at diagnosis. Completion of local therapy systemic chemotherapy is expected to treat micrometastasis or residual disease at the primary site. Therefore, it seems quite reasonable to offer chemotherapy for patients with cT2bN0 disease following completion of radiation therapy.

Contrary to the clinical trials in resected early stage NSCLC where histology had no impact on adjuvant chemotherapy [4], this study unexpectedly showed that chemotherapy benefited primarily patients with nonadenocarcinoma histology. Squamous cell carcinoma accounts for most of the histology and are more commonly located in proximity to central airway [2]. Discrepancy between clinical and pathologic staging, however, does not seem to differ between adenocarcinoma and squamous cell carcinomas [18,19]. We think it is unlikely that chemotherapy agents primarily for squamous cell carcinoma (e.g., gemcitabine) was commonly used for the entire groups. This finding cannot be easily explained and require further investigation.

Our analysis encompasses thousands of patients and is expected to assist clinicians in decisions regarding adjuvant chemotherapy for NSCLC patients undergoing radiation therapy.

Specifically, our results suggest that addition of adjuvant chemotherapy will extend survival for patients with large primary tumors undergoing radiation therapy

Financial support

None

Disclosure

All authors declared there is no conflict of interest.

Acknowledgements

We thank Dr. Michael Mirro's team at Mirro Center for Research and Innovation for administrative support.

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