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The effect of radiotherapy and surgery on stage IIIA/B NSCLC patients treated with chemotherapy

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► ***Original article***

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ABSTRACT

Background: The combination of radiotherapy and surgery is used to treat locally advanced non-small cell lung cancer (NSCLC). The aim of this study was to analyze IIIA/B NSCLC patients treated with chemotherapy from the Surveillance, Epidemiology, and End Results (SEER) database to clarify whether patient prognosis correlated with surgery and radiotherapy. ***Materials and Methods***: The IIIA/B NSCLC patients were selected from the SEER database and classified into IIIA (N0-1), IIIA (N2), IIIB (N2), and IIIB (N3). Cox analyses and Kaplan–Meier method were used to estimate the prognostic factors and lung cancer specific survival (LCSS) curves. ***Results***: We divided 7933 cases into IIIA (N0-1), IIIA (N2), IIIB (N2), and IIIB (N3). Cox regression showed that age, sex, primary site, grade, treatment, T stage, and marriage were independent risk factors for IIIA (N0-1); age, sex, treatment, and T stage had prognostic significance for IIIA (N2); age, sex, primary site, grade, treatment, and T stage were prognostic factors for IIIB (N2); and age and primary site had effect on the prognosis of IIIB(N3). The effect of chemotherapy-surgery was better than that of chemotherapy-preoperative radiotherapy-surgery and chemotherapy-surgery-postoperative radiotherapy for IIIA (N0-1). In IIIA (N2) and IIIB, radiotherapy did not improve the LCSS. ***Conclusion***: Surgery offered more survival benefits for IIIA (N0-1) patients. Radiotherapy did not improve the LCSS of IIIA (N2) and IIIB patients.

INTRODUCTION

Non-small cell lung cancer is currently a leading cause of cancer-related deaths worldwide [(1)]. Non-small cell lung cancer (NSCLC) comprises 85% of all lung cancers, and approximately one third of these patients are diagnosed with stage IIIA/IIIB [(2, 3)]. Stage IIIA/IIIB, a locally advanced NSCLC, has a higher risk of local relapse and distant metastasis and a poorer prognosis [(4, 5)].

Surgery, radiotherapy and chemotherapy are the most common treatment options. The standard surgical pattern for lung cancer is lobectomy plus systemic mediastinal lymph node dissection [(6)]. A plethora of level I evidence show that adjuvant chemotherapy can improve the overall and disease-free survival [(7)]. However, there is currently no consensus on the role of radiotherapy in locally advanced NSCLC.

Complete surgical resection plus mediastinal lymph node dissection are recommended for stage IIIA (N0-1) NSCLC, and platinum-based adjuvant chemotherapy is the standard treatment for patients [(8)]. IIIA (N0-1) NSCLC patients generally does not need radiotherapy, but radiotherapy is often used clinically, and its specific prognostic effect has not been studied [(9, 10)].

Postoperative radiotherapy is recommended as an alternative therapy for resectable stage III (N2) in the National Comprehensive Cancer Network (NCCN) guidelines [(11-13)]. However, the American Society for Radiation Oncology and American Society of Clinical Oncology (ASCO) guidelines held a point of view that postoperative radiotherapy did not improve the survival time [(14, 15)]. It is controversial about the use of preoperative radiotherapy. Some studies have shown that preoperative radiotherapy can improve survival, but other studies have confirmed that preoperative chemotherapy alone is sufficient prior to surgery in III (N2) patients [(16)].

Definitive concurrent chemoradiotherapy (CCRT) has become the standard treatment strategy for IIIB N3-positive stage NSCLC. However, large-sample studies have not been performed to explore the prognostic effects of radiotherapy in IIIB N3 patients who have received surgery [(17)].

During clinical practice, surgical resection and radiotherapy are commonly used to treat locally advanced NSCLC simultaneously. However, the relationship between prognosis and different treatment patterns has not been clarified. The prognostic effect of postoperative or preoperative radiotherapy

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remains to be explored. To date, large-sample studies have not been performed to explore the effect of preoperative and postoperative radiotherapy on the prognosis of IIIA (N0-1), IIIA (N2), IIIB (N2), and IIIB (N3). The basic information of locally advanced NSCLC patients treated with concomitant chemotherapy was downloaded from the SEER database in this study. Having analyzed the prognostic factors associated with locally advanced NSCLC, we sought to determine whether radiotherapy should be recommended for locally advanced NSCLC and what is the appropriate time for radiotherapy.

MATERIALS AND METHODS

Patients

The SEER database of the NCI collects data on cancer diagnosis, treatment, and survival for 30% of the American population. Since patients with stage IIIA/B NSCLC are routinely treated with chemotherapy, our study included the patients who had received chemotherapy to eliminate the influence of confounding factors. We downloaded relevant data from the SEER database of patients with single primary lung cancer and screened out IIIA and IIIB NSCLC patients who were not lost to follow-up and had complete basic information from 2004 to 2015. The treatment methods of patients were based on the information of 'Radiation sequence with surgery', 'Reason no cancer-directed surgery', and 'Radiation recode' from the SEER database. A total of 7,933 patients treated with chemotherapy were enrolled in this study, and they were divided into three groups based on the N stage: IIIA (N0-1), IIIA (N2), IIIB (N2), and IIIB (N3). Patients' information was revised based on the eighth edition of lung cancer stage classification developed by the American Joint Committee on Cancer. The following categories were classified as non-marital status: separated, single (never married), unmarried or domestic partner, and widowed by the SEER database interpretation file. Time of LCSS was counted from the date of diagnosis to the date of death due to lung cancer. We abbreviated chemotherapy-surgery as Chemo-Sur, chemotherapy-radiotherapy as Chemo-Radio, chemotherapy-preoperative radiotherapy-surgery as Chemo-Preo-Sur, and chemotherapy-surgery-postoperative radiotherapy as Chemo-Sur-Posto in the following description.

Statistical analysis

We use using SPSS (24.0; SPSS) to finish all statistical analyses. LCSS analysis was analyzed by Kaplan–Meier method. We used univariate and multivariate analyses to evaluate the correlation between the clinical factors and LCSS. We used the hazard ratio and 95% confidence interval to report the results. P values less than 0.05 were considered statistically significant and all p values were two-sided. X-tile software was used to calculate the cut-off value of age.

RESULTS

Univariate analysis and multivariate analysis of stage IIIA (N0-1) NSCLC

A total of 2097 stage IIIA (N0-1) NSCLC patients with pathological confirmation identified from the SEER database were included in the univariate Cox regression analysis to examine the effect of each clinical variable on LCSS. On univariate analysis of IIIA (N0-1) NSCLC patients, age, pathology, sex, primary site, grade, treatment, T stage, and marriage were associated with the prognosis ($p < 0.05$, table 1). Multivariate Cox analysis of LCSS showed that age (64-74 years and ≥ 75 years), sex (male), primary site (main bronchus and inferior lobe), grade, T stage (T4), marriage, and treatment (Chemo-Radio, Chemo-Preo-Sur, and Chemo-Sur-Posto) were independent poor prognostic factors of survival in LUAD patients ($p<0.05$, table 1).

Univariate analysis and multivariate analysis of stage IIIA (N2) NSCLC

A total of 3270 stage IIIA (N2) NSCLC patients with complete information from the SEER database were included in univariate Cox regression analysis to explore the effect of each clinical variable on LCSS. On univariate analysis of LCSS of patients, age, pathology, sex, laterality, treatment, and T stage were associated with the prognosis ($p < 0.05$, Table 2). Multivariate Cox analysis of LCSS showed that age (62-75 years and ≥ 76 years), sex (male), treatment (Chemo-Radio), and T stage (T2) were independent poor prognostic factors of survival in LUAD patients ($p<0.05$, table 2).

Univariate analysis and multivariate analysis of stage IIIB (N2) NSCLC

2059 stage IIIB (N2) NSCLC patients were analyzed by univariate and multivariate analysis. Age, pathology, sex, primary site, grade, treatment, and T stage were associated with the prognosis of stage IIIB (N2) NSCLC patients on univariate analysis ($p<0.05$, table 3). Age, sex, primary site, grade, treatment, and T stage were associated with the prognosis of stage IIIB (N2) NSCLC patients on multivariate analysis ($p<0.05$, table 3).

Univariate analysis and multivariate analysis of stage IIIB (N3) NSCLC

507 stage IIIB (N3) NSCLC patients were analyzed by univariate and multivariate analysis. Univariate and multivariate analyses showed that age and primary site were associated with the prognosis of stage IIIB (N3) NSCLC patients ($p<0.05$, table 4). Surgery and radiotherapy no longer had a positive

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influence on the prognosis of patients.

Effect of the treatment pattern on prognosis

In stage IIIA (N0-1) patients, Chemo-Sur offered more survival benefits compared to Chemo-Radio (HR 2.699; 95% CI: 2.316-3.145; p<0.001), Chemo-Preo-Sur (HR 1.282; 95% CI: 1.010-1.628; p=0.041), and Chemo-Sur-Posto (HR 1.359; 95% CI: 1.139-1.621; p=0.001) (table 1). In stage IIIA (N2) patients, the difference among Chemo-Sur, Chemo-Preo-Sur (HR 1.035; 95% CI: 0.854-1.256; p=0.725), and Chemo-Sur-Posto (HR 1.005; 95% CI: 0.880-1.149; p=0.939) was not significant, although these three treatment methods were better than Chemo-Radio (HR 1.984; 95% CI: 1.773-2.220; p<0.001) (table 2). In stage IIIB (N2) patients, Chemo -Preo-Sur (HR 1.767; 95% CI: 0.584-1.008; p=0.057) and Chemo-Sur-Posto (HR 1.073; 95% CI: 0.889-1.297; p = 0.462) cannot assist Chemo-Sur to prolong the survival time of patients (table 3). In stage IIIB (N3) patients, any treatment no longer had a positive effect on patient outcomes (table 4). The analysis of Kaplan–Meier method showed that different treatment methods were associated with different survival timepoints for stage IIIA (N0-1), IIIA (N2), and IIIB (N2) NSCLC. Further, Chemo-Sur, Chemo-Radio, Chemo-Preo-Sur, and Chemo-Sur-Posto no longer provided a positive impact on stage IIIB (N3) NSCLC (figure 1). The Kaplan–Meier method was used to further compare the prognostic effects of surgery and radiotherapy by comparing Chemo-Sur, Chemo-Radio, Chemo-Preo-Sur, and Chemo-Sur-Posto (figure 2). In stage IIIA (N0-1) NSCLC, Chemo-Sur was superior to Chemo-Radio, Chemo-Preo-Sur, and Chemo-Sur-Posto. In patients with stages IIIA (N2), IIIB (N2), and IIIB (N3) NSCLC, there was no difference among Chemo-Sur, Chemo-Preo-Sur, and Chemo-Sur-Posto. In other words, we could conclude that surgery was associated with longer survival, and radiotherapy could not improve the survival benefit for stages IIIA and IIIB NSCLC patients treated with chemotherapy.

Table 1. The study collected and screened stage IIIA (N0-1) NSCLC patients who had received chemotherapy from the SEER database. Table 1 presents the results of univariate and multivariate Cox analyses to show the prognostic effect of Chemo-Sur, Chemo-Radio, Chemo-Preo-Sur, and Chemo-Sur-Posto.

Variables	n	LCSS			
		Univariate analysis		Multivariate analysis	
		HR(95%CI)	HR p Value	HR(95%CI)	HR p Value
Age	2097		<0.001		<0.001
≤63	865	1	-	1	-
64-74	856	1.203(1.060-1.366)	0.004	1.227(1.079-1.395)	0.002
≥75	376	1.632(1.400-1.901)	<0.001	1.415(1.208-1.657)	<0.001
Race	2097		0.251		
White	1726	1	-		
Black	202	0.929(0.766-1.127)	0.456		
Other	169	0.841(0.675-1.048)	0.122		
Pathology	2097		<0.001		
Adenocarcinoma	1010	1	-		
Squamous cell carcinoma	1087	1.337(1.194-1.496)	<0.001		
Sex	2097		0.001		0.001
Male	1256	1	-	1	-
Female	841	0.827(0.737-0.929)	0.001	0.825(0.732-0.929)	0.001
Primary Site	2097		<0.001		0.007
Upper lobe	1471	1	-	1	-
Middle lobe	69	0.711(0.497-1.018)	0.062	0.872(0.607-1.253)	0.459
Inferior lobe	466	1.084(0.946-1.241)	0.246	1.236(1.074-1.423)	0.003
Main bronchus	91	1.731(1.339-2.236)	<0.001	1.291(0.994-1.678)	0.056
Laterality	2097		0.808		
left	959	1	-		
right	1138	0.986(0.881-1.104)	0.808		
Grade	2097		0.023		0.018
Grade I	76	1	-	1	-
Grade II	832	0.937(0.683-1.285)	0.684	1.018(0.741-1.399)	0.913
Grade III	1157	1.125(0.824-1.537)	0.457	1.227(0.896-1.681)	0.203
Grade IV	32	1.070(0.616-1.859)	0.81	1.117(0.641-1.944)	0.697
Treatment	2097		<0.001		<0.001
Chemo-Sur	742	1	-	1	-
Chemo-Radio	766	3.028(2.635-3.480)	<0.001	2.699(2.316-3.145)	<0.001
Chemo-Preo-Sur	182	1.293(1.028-1.625)	0.028	1.282(1.010-1.628)	0.041
Chemo-Sur-Posto	407	1.407(1.187-1.668)	<0.001	1.359(1.139-1.621)	0.001
T stage	2097		<0.001		0.010
T3	1711	1	-	1	
T4	386	1.889(1.590-2.244)	<0.001	1.282(1.061-1.549)	
Marriage	2097		0.001		<0.001
Marital status	1228	1	-	-	-
Non-marital status	869	1.218(1.088-1.364)	0.001	1.283(1.142-1.442)	<0.001

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Table 2. The study collected and screened stage IIIA (N2) NSCLC patients who had received chemotherapy from the SEER database. Table 2 presents the results of univariate and multivariate Cox analyses to show the prognostic effect of Chemo-Sur, Chemo-Radio, Chemo-Preo-Sur, and Chemo-Sur-Posto.

Variables	n	LCSS			
		Univariate analysis		Multivariate analysis	
		HR(95%CI)	HR p Value	HR(95%CI)	HR p Value
Age	3270		<0.001		<0.001
≤61	1137	1	-	1	-
62-75	1596	1.277(1.159-1.407)	<0.001	1.189(1.078-1.311)	0.001
≥76	537	1.833(1.615-2.080)	<0.001	1.569(1.379-1.785)	<0.001
Race	3270		0.073		
White	2651	1	-		
Black	338	0.856(0.740-0.990)	0.036		
Other	281	0.915(0.784-1.069)	0.263		
Pathology	3270		<0.001		
Adenocarcinoma	1923	1	-		
Squamous cell carcinoma	1347	1.383(1.268-1.509)	<0.001		
Sex	3270		<0.001		<0.001
Male	1756	1	-	1	-
Female	1514	0.782(0.717-0.852)	<0.001	0.834(0.764-0.910)	<0.001
Primary Site	3270		0.108		
Upper lobe	1993	1	-		
Middle lobe	152	1.031(0.835-1.272)	0.777		
Inferior lobe	1001	1.091(0.992-1.199)	0.074		
Main bronchus	124	1.248(0.997-1.562)	0.054		
Laterality	3270		0.019		
left	1338	1	-		
right	1932	1.111(1.017-1.213)	0.019		
Grade	3270		0.142		
Grade I	175	1	-		
Grade II	1358	1.258(1.021-1.550)	0.031		
Grade III	1705	1.279(1.040-1.573)	0.02		
Grade IV	32	1.254(0.775-2.028)	0.357		
Treatment	3270		<0.001		<0.001
Chemo-Sur	804	1	-	1	-
Chemo-Radio	1512	2.154(1.930-2.404)	<0.001	1.984(1.773-2.220)	<0.001
Chemo-Preo-Sur	238	1.016(0.839-1.231)	0.871	1.035(0.854-1.256)	0.725
Chemo-Sur-Posto	716	0.985(0.862-1.126)	0.828	1.005(0.880-1.149)	0.939
T stage	3270		<0.001		0.005
T1	2506	1	-	1	
T2	764	1.386(1.255-1.530)	<0.001	1.159(1.046-1.284)	0.005
Marriage	3270		0.450		
Marital status	1916	1	-		
Non-marital status	1354	1.034(0.948-1.128)	0.450		

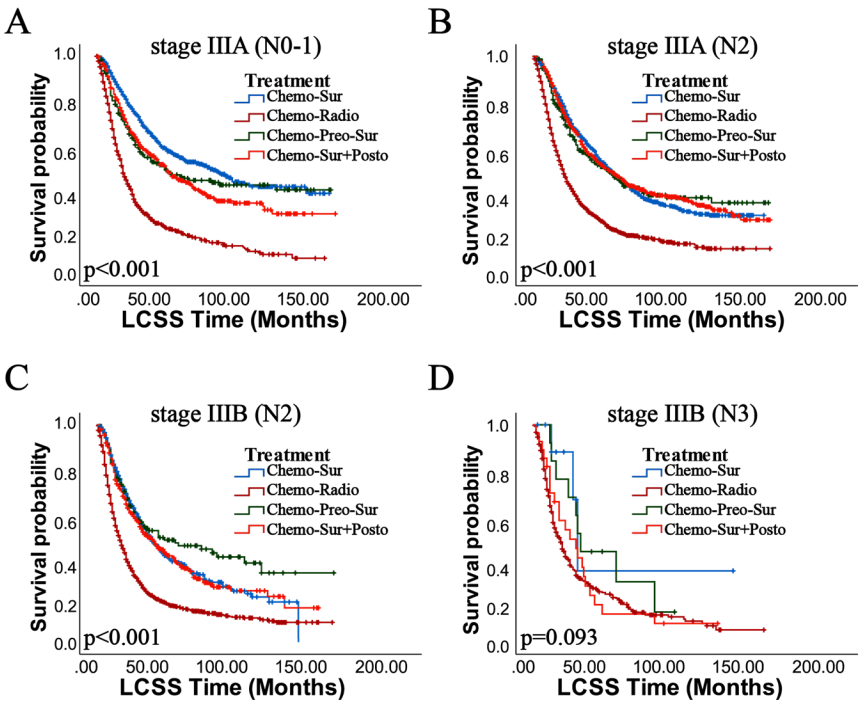

Figure 1. The Kaplan–Meier method of stage IIIA/B NSCLC. The study collected and screened stage IIIA/B NSCLC patients who had received chemotherapy from the SEER database. These patients were divided into four groups according to the N status. The Kaplan–Meier method was used to explore the significance of treatment. **(A)** The Kaplan–Meier curve of stage IIIA (N0-1) NSCLC ($p < 0.001$). **(B)** The Kaplan-Meier curve of stage IIIA (N2) NSCLC ($p < 0.001$). **(C)** The Kaplan–Meier curve of stage IIIB (N2) NSCLC ($p < 0.001$). **(D)** The Kaplan-Meier curve of stage IIIB (N3) NSCLC ($p = 0.093$).

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Table 3. The study collected and screened stage IIIB (N2) NSCLC patients who had received chemotherapy from the SEER database. Table 3 presents the results of univariate and multivariate Cox analyses to show the prognostic effect of Chemo-Sur, Chemo-Radio, Chemo-Preo-Sur, and Chemo-Sur-Posto.

Variables	n	LCSS			
		Univariate analysis		Multivariate analysis	
		HR(95%CI)	HR p Value	HR(95%CI)	HR p Value
Age	2059		0.001		0.004
≤60	704	1	-	1	-
61-67	517	1.125(0.983-1.289)	0.088	1.126(0.982-1.291)	0.088
≥68	838	1.264(1.121-1.425)	<0.001	1.229(1.087-1.389)	0.001
Race	2059		0.462		
White	1651	1	-		
Black	210	1.056(0.892-1.251)	0.527		
Other	198	0.914(0.765-1.092)	0.320		
Pathology	2059		<0.001		
Adenocarcinoma	1026	1	-		
Squamous cell carcinoma	1033	1.366(1.232-1.514)	<0.001		
Sex	2059		<0.001		<0.001
Male	1197	1	-	1	-
Female	862	0.752(0.676-0.835)	<0.001	0.752(0.676-0.836)	<0.001
Primary Site	2059		<0.001		<0.001
Upper lobe	1361	1	-	1	
Middle lobe	71	0.971(0.728-1.294)	0.839	1.146(0.858-1.530)	0.355
Inferior lobe	493	1.143(1.012-1.291)	0.032	1.352(1.193-1.532)	<0.001
Main bronchus	134	1.650(1.355-2.010)	<0.001	1.320(1.082-1.612)	0.006
Laterality	2059		0.304		
left	859	1	-		
right	1200	1.057(0.951-1.173)	0.304		
Grade	2059		0.004		0.004
Grade I	91	1	-	1	-
Grade II	813	0.935(0.727-1.203)	0.603	0.928(0.721-1.194)	0.560
Grade III	1124	1.141(0.891-1.461)	0.298	1.135(0.885-1.455)	0.318
Grade IV	31	0.910(0.553-1.499)	0.711	0.998(0.605-1.647)	0.994
Treatment	2059		<0.001		<0.001
Chemo-Sur	337	1	-	1	-
Chemo-Radio	1209	1.969(1.695-2.288)	<0.001	1.728(1.474-2.027)	<0.001
Chemo-Preo-Sur	131	0.832(0.635-1.088)	0.179	1.767(0.584-1.008)	0.057
Chemo-Sur-Posto	382	1.026(0.850-1.239)	0.787	1.073(0.889-1.297)	0.462
T stage	2059		<0.001		<0.001
T3	571	1	-	1	
T4	1488	1.768(1.560-2.005)	<0.001	1.459(1.272-1.675)	<0.001
Marriage	2059		0.368		
Marital status	1226	1	-		
Non-marital status	833	1.049(0.945-1.166)	0.368		

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Table 4. The study collected and screened stage IIIA (N3) NSCLC patients who had received chemotherapy from the SEER database. Table 4 presents the results of univariate and multivariate Cox analyses to show the prognostic effect of Chemo-Sur, Chemo-Radio, Chemo-Preo-Sur, and Chemo-Sur-Posto.

Variables	n	LCSS			
		Univariate analysis		Multivariate analysis	
		HR(95%CI)	HR p Value	HR(95%CI)	HR p Value
Age	507		0.027		0.046
≤67	273	1	-	1	-
68-75	133	1.159(0.908-1.480)	0.236	1.154(0.903-1.475)	0.253
≥76	101	1.426(1.103-1.843)	0.007	1.389(1.072-1.798)	0.013
Race	507		0.288		
White	393	1	-		
Black	50	0.882(0.627-1.242)	0.473		
Other	64	0.785(0.570-1.082)	0.139		
Pathology	507		0.149		
Adenocarcinoma	265	1	-		
Squamous cell carcinoma	242	1.160(0.948-1.420)	0.149		
Sex	507		0.905		
Male	301	1	-		
Female	206	0.988(0.806-1.211)	0.905		
Primary Site	507		0.004		0.006
Upper lobe	322	1	-	1	-
Middle lobe	21	1.091(0.666-1.787)	0.729	1.059(0.644-1.739)	0.822
Inferior lobe	141	1.502(1.196-1.886)	<0.001	1.464(1.164-1.840)	0.001
Main bronchus	23	1.523(0.983-2.361)	0.060	1.560(1.006-2.419)	0.047
Laterality	507		0.521		
left	221	1	-		
right	286	0.936(0.963-1.146)	0.521		
Grade	507		0.288		
Grade I	16	1	-		
Grade II	190	0.679(0.391-1.178)	0.168		
Grade III	297	0.765(0.446-1.314)	0.332		
Grade IV	4	1.420(0.407-4.954)	0.582		
Treatment	507		0.123		
Chemo-Sur	10	1	-		
Chemo-Radio	459	2.963(0.950-9.243)	0.061		
Chemo-Preo-Sur	12	1.791(0.484-6.628)	0.383		
Chemo-Sur-Posto	26	2.671(0.799-8.930)	0.111		
T stage	507		0.113		
T1	352	1	-		
T2	155	1.191(0.959-1.480)	0.113		
Marriage	507		0.128		
Marital status	319	1	-		
Non-marital status	188	1.175(0.955-1.446)	0.128		

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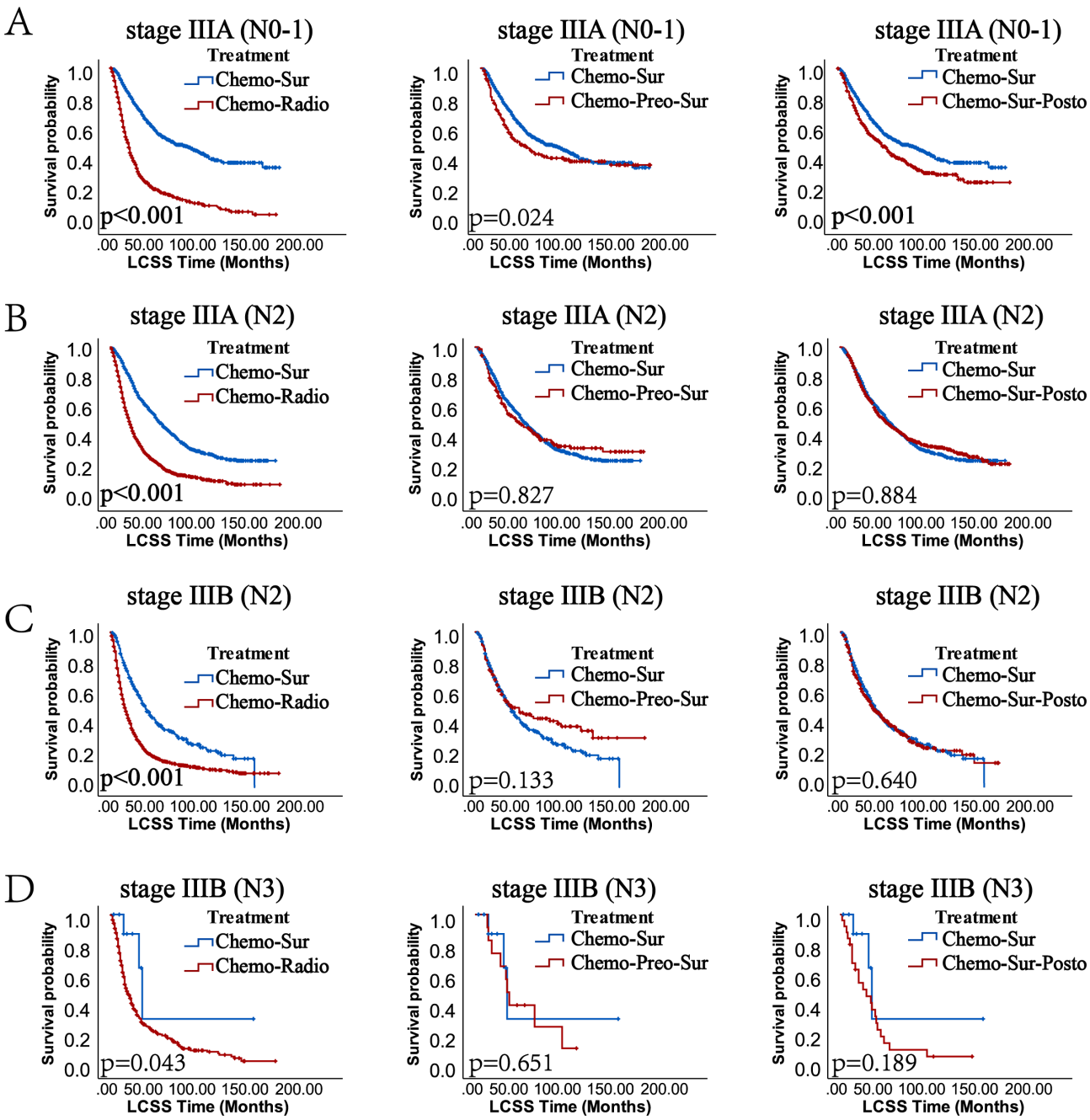

Figure 1. The Kaplan–Meier method of stage IIIA/B NSCLC. The study collected and screened stage IIIA/B NSCLC patients who had received chemotherapy from the SEER database. These patients were divided into four groups according to the N status. The Kaplan–Meier method was used to explore the significance of treatment. **(A)** The Kaplan–Meier curve of stage IIIA (N0-1) NSCLC ($p < 0.001$). **(B)** The Kaplan–Meier curve of stage IIIA (N2) NSCLC ($p < 0.001$). **(C)** The Kaplan–Meier curve of stage IIIB (N2) NSCLC ($p < 0.001$). **(D)** The Kaplan–Meier curve of stage IIIB (N3) NSCLC ($p = 0.093$).

DISCUSSION

Over the past two decades, the incidence of lung cancer has gradually increased. The mainstream approaches include surgical removal of lung lobes [18], radiotherapy [19], and chemotherapy [20]. Stages I and II NSCLC patients should be treated by complete surgical resection [21]. Multi-disciplinary therapy based on systemic therapy is more suitable for patients with stage IV disease. But previous studies have not provided consistent recommendations and treatment strategies for locally advanced lung cancer (stages IIIA and IIIB). The main point of debate was whether radiotherapy could prolong the survival time of locally advanced lung cancer patients.

Many studies have focused on exploring the optimal treatment strategies for locally advanced lung cancer. But these are some limitations for these studies. Our study aimed to systematically evaluate the effects of radiotherapy and surgery on the prognosis of patients with locally advanced NSCLC. We collected 7933 stage IIIA and IIIB NSCLC patients who had received chemotherapy from the SEER

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database, and we divided them into stage IIIA (N0-1), IIIA (N2), IIIB (N2), and IIIB (N3). The treatment patterns that we wanted to study included Chemo-Sur, Chemo-Radio, Chemo-Preo-Sur, and Chemo-Sur-Posto.

For stage IIIA (N0-1) NSCLC patients, our research found that Chemo-Sur could offer more survival benefits, and the effect of Chemo-Sur was better than that of Chemo-Radio, Chemo-Preo-Sur, and Chemo-Sur-Posto. Bryan and Donington believed that the addition of surgery to multimodality treatment appeared to improve overall survival and local control in resectable IIIA disease [22]. Gao *et al*. believed that postoperative radiotherapy was not recommended in patients with stage IIIA (N0 and N1) disease [23]. Few studies paid an attention to the role of preoperative radiotherapy in stage IIIA (N0 and N1) NSCLC. Our study extends the conclusion derived from previous studies that preoperative radiotherapy and postoperative radiotherapy do not play an important role in the prognosis of stage IIIA (N0-1) NSCLC.

For stage IIIA (N2) and IIIB (N2) NSCLC, the effect of surgery only was better than that of radiotherapy, and there was no difference between surgery and combination of radiotherapy plus surgery. But surgery and radiotherapy no longer exerted a positive impact on IIIB (N3). The same conclusions were summarized by the Kaplan-Meier method (figures 1 and 2). In other words, radiotherapy could not offer more benefits for locally advanced NSCLC patients who had received chemotherapy, and clinicians should perform surgery to improve the patients' survival without considering radiotherapy. Sara Moore and Leung B hold a point of view that combined surgery and radiotherapy appeared to provide a significant benefit above the other modalities [24]. However, the prognostic effects of surgery, postoperative radiotherapy and preoperative radiotherapy on locally advanced NSCLC have not been clearly studied. Xu *et al.* collected the IIIA (N2) NSCLC patients between 1988 to 2016 in the SEER database and explored the relationship between postoperative radiotherapy and cancer-specific mortality (CSM). The study derived the conclusion that postoperative radiotherapy could improve the survival time [25]. Chen and Wang paid attention to the role of preoperative radiation and indicated that preoperative radiation might extend the survival time by analyzing the data of IIIA (N2) NSCLC patients who either underwent preoperative radiation or did not undergo preoperative radiation [26]. Many similar studies have derived opposite conclusions. The contrary conclusions might be due to different independent prognostic factors that were included in different studies. Indeed, chemotherapy was not excluded as a confounding factor in some previous studies. For stage IIIB NSCLC patients, previous studies paid more attention to the combination of thoracic radiation and chemotherapy or multimodal therapeutic sequences based on radiation [27-29].

The study excluded the interference of chemotherapy, and systematic exploration of the effects of surgery and radiotherapy on locally advanced NSCLC made this study more valuable. However, our research also has some shortcomings. First, an inherent bias was unavoidable because our study was retrospective in nature. Future prospective studies should be considered, and more clinical characteristics should be considered to minimize bias. Second, we did not analyze the type of chemotherapeutics received by the patients with the company name and country of origin, the radiotherapy protocol for patients with daily fraction, total dose, and the radiotherapy unit used for treatment, the trade mark and country of origin of the radiotherapy unit, the timing of chemotherapy and radiation therapy, the content of chemotherapy and the dose of radiation therapy owing to the lack of record in the SEER database. Third, the classification of patients was not detailed. For example, Gao and Li performed a retrospective study based the number of lymph node metastases, and they thought that using postoperative radiotherapy should be encouraged to improve the survival time for IIIA (N2) patients (lymph nodes < 6) [30]. Wang and Ma believed that the number of lymph nodes was 3 [31]. Although their studies derived contradictory conclusions, it suggested that the studies that were based on the number of lymph nodes and treatment strategies deserved to be explored and could improve the theory of precision medicine. We hope to explore the relationship between the number of N2 lymph nodes and the prognosis of III lung cancer patients, but the SEER database did not provide clinical information about the number of N2 lymph nodes. Our future study will focus on collecting more detailed information about lung cancer patients to further explore the prognosis of lung cancer.

CONCLUSION

Surgery offered more survival benefits for chemotherapy patients with IIIA (N0-1) NSCLC. Radiation therapy did not offer benefits for locally advanced NSCLC patients or prolong their survival time. Preoperative and postoperative radiotherapy should not be recommended to treat locally advanced NSCLC.

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