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Journal of Oncology Research
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ARTICLE

Postoperative Radiotherapy and N2 Non-small Cell Lung Cancer Prognosis: A Retrospective Study Based on Surveillance, Epidemiology, and End Results Database

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ARTICLE INFO

Article history
Received: 3 August 2021
Accepted: 9 August 2021
Published Online: 20 August 2021

Keywords:
Non-small cell lung cancer
Radiotherapy
Postoperative
Prognosis

ABSTRACT

The purpose of this study is to clarify the significance of postoperative radiotherapy for N2 lung cancer. This study aimed to investigate the effect of postoperative radiotherapy on the survival and prognosis of patients with N2 lung cancer. Data from 12,000 patients with N2 lung cancer were extracted from the Surveillance, Epidemiology, and End Results database (2004-2012). Age at disease onset and 5-year survival rates were calculated. Survival curves were plotted using the Kaplan-Meier method. The univariate log-rank test was performed. Multivariate Cox regression were used to examine factors affecting survival. Patients' median age was 67 years (mean 66.46 ± 10.03). The 5-year survival rate was 12.55%. Univariate analysis revealed age, sex, pathology, and treatment regimen as factors affecting prognosis. In multivariate analysis, when compared to postoperative chemotherapy, postoperative chemoradiotherapy was better associated with survival benefits (hazard ratio [HR]= 0.85, 95% confidence interval [CI]: 0.813-0.898, P <0.001). Propensity score matching revealed that patients who had received postoperative chemoradiotherapy had a better prognosis than did patients who had received postoperative chemotherapy (HR=0.869, 95% CI: 0.817-0.925, P <0.001). Female patients and patients aged <65 years had a better prognosis than did their counterparts. Patients with adenocarcinoma had a better prognosis than did patients with squamous cell carcinoma. Moreover, prognosis worsened with increasing disease T stage. Patients who had received postoperative chemoradiotherapy had a better prognosis than did patients who had received postoperative chemotherapy. Postoperative radiotherapy was an independent prognostic factor in this patient group.

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 DOI: https://doi.org/10.30564/jor.v3i2.3513

1. Introduction

Lung cancer is a common cancer type and the leading cause of cancer-related deaths worldwide [1]. In 2018, there were 2.1 million new lung cancer cases and 1.8 million lung cancer-related deaths, accounting for 18.4% of all cancer-related deaths [2]. Non-small cell lung cancer (NSCLC) accounts for about 85% of lung cancer cases [3], among which adenocarcinoma and squamous cell carcinoma are the predominant types. Surgery is the standard treatment for NSCLC. Currently there are no guidelines on adjuvant treatment for patients with postoperative pathological N2 disease stage. Adjuvant chemotherapy is the standard treatment for patients with positive lymph node metastasis after operation, but there was a significant difference in whether adjuvant radiotherapy was performed.

2. Methods

The Surveillance, Epidemiology, and End Results (SEER) database was examined for data from lung cancer patients with a pathological diagnosis of NSCLC confirmed during 2004-2012. (Figure 1). Patients were included in the present study if they met the following criteria: (1) Their postoperative stage was N2M0; (2) Squamous cell carcinoma or adenocarcinoma was confirmed by pathology testing; (3) Postoperative treatment involved chemotherapy alone; (4) Diagnosis was confirmed during 2004-2012.

Patients were excluded from the present study if they met any of the following criteria: (1) Unclear pathology results or confirmed diagnosis of a cancer type other than squamous cell carcinoma or adenocarcinoma; (2) Confirmed metastasis; (3) Intraoperative or preoperative treatment with radiotherapy; (4) No postoperative chemotherapy; (5) Confirmed multiple primary tumors; (6) Incomplete data.

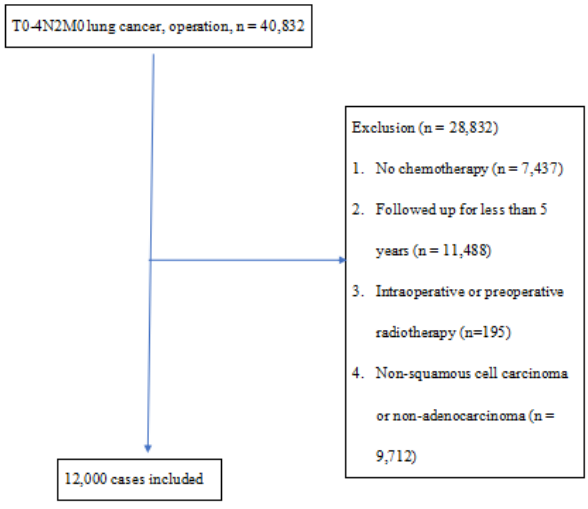

Figure 1. schematic illustration

Statistical analysis

IBM SPSS statistics version 25 was used for statistical analysis. Chi-square test was used to analyze categorical variables. Survival curves were plotted using the Kaplan-Meier method, and log-rank test was performed to analyze the differences in variables among groups. Differential variables were subjected to propensity score matching (PSM) in the postoperative chemoradiotherapy and postoperative chemotherapy group, and differences among groups were examined after matching. Univariate analysis was applied to compute models that included sex, stage, pathology, age, and treatment regimen. The variables that were significant in univariate analysis were included in multivariate analysis. Cox proportional hazards model was used for multivariate analysis. P-values <0.05 were considered statistically significant.

3. Results

Descriptive statistics

Among the 12,000 included patients. The age range was 19-95 years, with a median of 67 years (mean 66.46 ± 10.03 years). There 6127 cases (51.06%) were T0-2, 5873 cases (48.94%) were T3-4 (Table 1).

Table 1. Demographic and clinical characteristics of patients with squamous cell carcinoma and adenocarcinoma included in the Surveillance, Epidemiology, and End Results (SEER) database

Group	Cases	Percentage (%)
Sex		
Male	7119	59.33
Female	4881	40.67
Stage		
T0	66	0.55
T1	1640	13.67
T2	4421	36.84
T3	1842	15.35
T4	4031	33.59
Pathology		
Squamous cell carcinoma	6652	55.43
Adenocarcinoma	5348	44.57
Age		
≤ 65 years	5344	44.53
> 65 years	6656	55.47
Treatment		
Postoperative chemoradiotherapy	2606	21.72
Postoperative chemotherapy	9394	78.28

Univariate analysis

Kaplan-Meier curves were plotted according to sex,

DOI: https://doi.org/10.30564/jor.v3i2.3513

stage, pathology, age, and treatment regimen, revealing differences between groups. Women had a better prognosis than did men; patients aged 65 years and younger had a better prognosis than did patients older than 65 years; patients with adenocarcinoma had a better prognosis than did patients with squamous cell carcinoma; however, the prognosis worsened with increasing T stage. The prognosis of patients who had received postoperative chemoradiotherapy was better than that of patients who had received postoperative chemotherapy. There were statistically significant differences in gender, stage, pathology, age and treatment plan between groups ($P < 0.01$) (Figure 2).

Multivariate analyses

Multivariate analyses are carried out on the variables with significance of univariate analysis. Gender, T stage, pathology, age and treatment were included in the multivariate analysis. T stage was divided intoTt0-2 group and T3-4 group ,as shown in Table 2.

Table 2. Univariate and multivariate analyses

Group	Univariate analysis			Multivariate analysis		
	P	OR	95% CI	*P*	HR	95% CI
Sex	< 0.001	1.434	1.236-1.663	< 0.001	1.131	1.085-1.178
Stage	< 0.001	0.722	0.654-0.796	< 0.001	0.820	0.788-0.854
Pathology	< 0.001	1.348	1.158-1.569	< 0.001	1.142	1.085-1.178
Age	< 0.001	0.808	0.697-0.933	< 0.001	0.887	0.852-0.923
Treatment	< 0.001	0.807	0.697-0.934	< 0.001	0.855	0.813-0.898

HR=hazard ratio

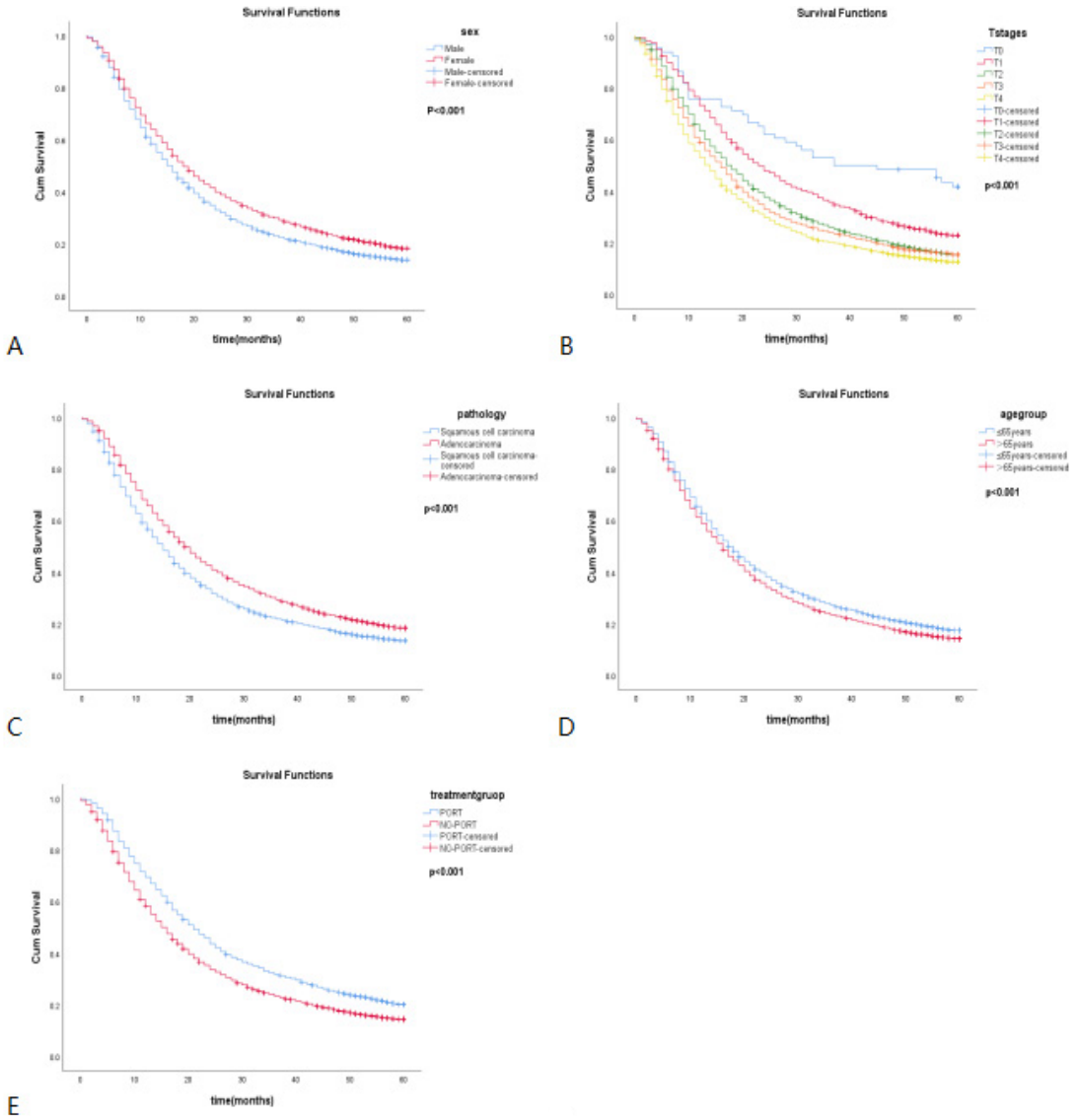

Figure 2. Kaplan-Meier curves of overall survival according to different groups. Survival difference of patients in group was statistically significant (p<0.001).

 DOI: https://doi.org/10.30564/jor.v3i2.3513

Propensity score matching

After matching on sex, stage, pathology findings, and age, a total of 4,842 patients were included and divided evenly between the postoperative chemoradiotherapy (n=2421) and postoperative chemotherapy group (n = 2421). The sample included 2,779 men and 2,063 women in. There were 21 cases at T0 stage, 1,091 cases at T1 stage, 1,922 cases at T2 stage, 556 cases at T3 stage, and 1,252 cases at T4 stage. There were 2,185 cases of squamous cell carcinoma and 2,657 cases of adenocarcinoma. There were 2,300 patients aged 65 years or younger and 2,542 patients older than 65 years. The age range was 19-90 years, with a median of 66 years (mean 65.66 ± 9.72). The 5-year survival rate and median survival time before and after matching are presented in Table 2. Before matching, the median survival time was 17 months, and the 5-year survival rate was 12.55%; after matching, the median survival time was 19 months, and the 5-year survival rate was 18.5%. The prognosis of patients who had received postoperative chemoradiotherapy was significantly better than that of patients who had received postoperative chemotherapy alone (hazard ratio [HR]=0.869, 95% confidence interval [CI]: 0.817-0.925, P <0.001). Treatment regimen was an independent prognostic factor for lung cancer patients (Table 3, and Figure 3 and 4).

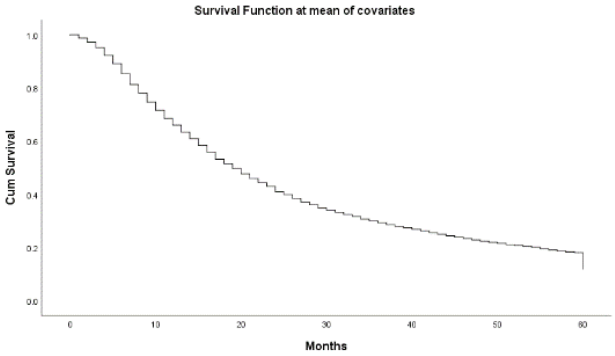

Figure 3. Survival curve at mean of covariates

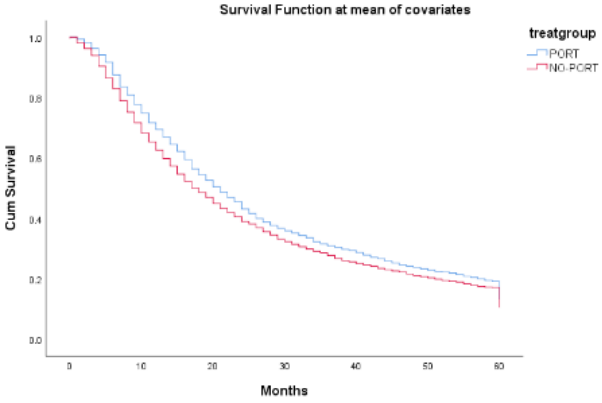

Figure 4. Significant difference survival curve of between after-matching PORT and NO-PORT (p<0.001).

Table 3. Survival outcomes for lung cancer patients included in the Surveillance, Epidemiology, and End Results (SEER) database, before and after propensity score matching

Group	Before matching				After matching			
	Cases	Percentage (%)	5-year survival rate (%)	Median survival time (months)	Cases	Percentage (%)	5-year survival rate (%)	Median survival time (months)
Sex								
Male	7119	59.33	11.14	16	2779	57.39	15.87	17
Female	4881	40.67	14.61	18	2063	42.61	22.06	22
Stage								
T0	66	0.55	30.30	37	21	0.43	38.10	28
T1	1640	13.67	19.02	23	1091	22.53	24.01	24
T2	4421	36.84	12.12	18	1922	39.69	18.21	20
T3	1842	15.35	12.87	16	556	11.48	16.19	11
T4	4031	33.59	9.95	14	1252	25.88	14.86	15
Pathology								
Squamous cell carcinoma	6652	55.43	10.34	15	2185	45.13	15.56	16
Adenocarcinoma	5348	44.57	15.30	19	2657	54.87	20.93	21
Age								
≤ 65 years	5344	44.53	14.20	17	2300	47.50	20.04	20
> 65 years	6656	55.47	11.22	16	2542	52.51	17.11	18
Treatment								
Postoperative chemotherapy + radiotherapy	2606	21.72	16.58	21	2421	50	20.12	21
Postoperative chemotherapy	9394	78.28	11.43	16	2421	50	16.89	17

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4. Discussion

NSCLC is a common type of lung cancer, of which adenocarcinoma and squamous cell carcinoma are the predominant subtypes. At the time of diagnosis, 30%-40% of patients have been reported to have disease at a locally advanced stage, accompanied by metastasis of cancer cells [4]. There are differences in the treatment of patients with N2 stage disease with mediastinal lymph node metastasis. Although comprehensive treatment is regarded as a standard regimen for N2 patients with resectable NSCLC, the optimal combination therapy regimen remains unclear [5]. Chemotherapy is required to treat resectable NSCLC [6,7]. Treatment regimens include radical concurrent chemoradiotherapy, induction chemotherapy or chemoradiotherapy, and postoperative chemotherapy or chemoradiotherapy. It remains unclear which regimen is optimal, but 5-year survival rate for any regimen is 20-45% [8]. Moreover, 5-year overall survival rates associated with micro-single-station, micro-multi-station, macro-single-station, and macro-multi-station involvement of mediastinal N2 lymph nodes have been reported as 34%, 11%, 8%, and 3%, respectively [9]. Surgery alone is insufficient, and the survival rate of patients with operable locally-advanced NSCLC is not high [10]. It is increasingly believed that patients with N2 disease stage should not be treated with surgery alone. In fact, evidence from randomized trials shows that adjuvant therapy is better than resection alone [11,12]. The guidelines on NCCN (National Comprehensive Cancer Network) treatment recommend that adjuvant chemotherapy or adjuvant chemoradiotherapy be performed for patients with disease stage N2. The present study examined differences in survival rates between patients with pN2 disease stage treated with chemotherapy alone and chemoradiotherapy.

There is little controversy around postoperative chemotherapy as a standard postoperative treatment for N2 stage NSCLC with postoperative lymph node metastasis [13]. However, controversy surrounds administration of adjuvant radiotherapy. Based on data from the National Cancer Database (NCDB), Drake et al. have reported no difference in the median survival time between patients treated with adjuvant chemoradiotherapy and patients treated with adjuvant chemotherapy after R0 resection of disease at stage N0 and pathological N2 (3.9 years vs 3.8 years, $P = 0.705$) [14]. Moreover, Spicer et al. have conducted a retrospective analysis of data from four chest tumor centers, and compared 5-year overall survival (OS) and disease-free survival (DFS) in patients treated with N2 postoperative chemotherapy and N2 postoperative concurrent chemoradiotherapy. Their study revealed no differences in recurrence rates, recurrence mode, perioperative mortality, OS, or DFS in patients who had received preoperative invasive mediastinal staging [15].

It has been reported that postoperative radiotherapy can benefit pN2 patients. The American Thoracic Society guidelines did not support administration of adjuvant radiotherapy for occult N2 (NSCLC) after RO resection. Postoperative radiotherapy increased the local control rate but did not improve the OS rate [16]. A meta-analysis of relevant studies has shown that adjuvant radiotherapy lacked survival benefits after complete resection of NSCLC compared with operation alone. In 2006, Lally et al., using the SEER data, argued that postoperative radiotherapy improved the survival rate of N2 patients but did not benefit patients with disease stage N0 or N1 [17]. Douillard et al. have retrospectively analyzed data from pN2 patients who had received postoperative adjuvant radiotherapy, revealing that postoperative adjuvant radiotherapy generated more benefits but showed a negative effect on pN1 [18]. Based on data from the National Cancer Database, Herskovic et al. have conducted a stratified analysis to examine whether 2,691 patients with negative N2 (ⅢA) resection margin who had received adjuvant chemotherapy during 2004-2013 should receive postoperative radiotherapy. In their study, the median survival time was 27.43 months and 25.86 months ($p < 0.05$), respectively. Postoperative radiotherapy significantly prolonged survival [19]. With improvements to radiotherapy technology, the local control rate increased, and treatment toxicity decreased [20]. Moreover, Su et al. have found that 1-year, 3-year, and 5-year OS rates associated with postoperative chemoradiotherapy and postoperative chemotherapy were 98.3% vs 86.1%, 71.7% vs 53.0% and 45.7% vs 39.0%, respectively ($P = 0.019$) [21].

In summary, there have been many studies aimed at examining the efficacy of N2 postoperative treatment regimens. In the present study, which involved analysis of data from the SEER database, we have shown that age, sex, disease stage, pathology type, and treatment regimen are factors that affect the prognosis of patients with N2 lung cancer. In the present study, women and patients with adenocarcinoma had a better prognosis than did men and patients with squamous cell carcinoma. These findings suggest that targeted therapy can be considered to prolong survival. Multivariate analysis has revealed that survival associated with postoperative chemoradiotherapy was longer than survival time associated with postoperative chemotherapy alone. With the development of novel immunotherapy and targeted therapy regimens, further research is needed to identify the optimal postoperative treatment regimen for N2 lung cancer.

 DOI: https://doi.org/10.30564/jor.v3i2.3513

5. Conclusions

It can be seen from this study that the prognosis of N2 lung cancer is affected by many factors. Young, female and adenocarcinoma patients have more survival advantages. With the increase of T stage, the prognosis is worse and worse. Postoperative adjuvant radiotherapy is better than postoperative chemotherapy alone.

Acknowledgements

We would like to thank Editage (www.editage.cn) for English language editing.

Statement of Interest

There is no conflict of economic interests affecting its scientificity and credibility in this study.

Funding

Project of Hebei Medical Science Research Plan in 2021 (20210831).

National key research and development program of China (2018YFE0114100).

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