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ORIGINAL ARTICLE

Effects of postoperative adjuvant radiotherapy on stage IIIA-N2 non-small cell lung cancer and prognostic analysis

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Summary

Purpose: *We aimed to explore the efficacy and safety of postoperative adjuvant radiotherapy in the treatment of non-small cell lung cancer (NSCLC) (stage IIIA-N2), and to analyze the influencing factors for the prognosis of patients.*

Methods: *A total of 142 patients with NSCLC (stage IIIA-N2) were collected for retrospective analysis. Postoperative adjuvant radiotherapy was performed in 71 cases (Radiotherapy group), while it was not conducted in the remaining 71 cases (Control group). The survival status of patients was recorded during follow-up. Moreover, the possible influencing factors for the prognosis of patients were analyzed.*

Results: *The median survival time was 34.7±5.4 months and 31.9±4.9 months, the 5-year overall survival (OS) rate was 32.4% and 26.8%, and the 5-year progression-free survival (PFS) rate was 25.4% and 12.7%, respectively, in the Radiotherapy group and the Control group. The 5-year OS was significantly correlated with smoking history, tumor T stage, ratio of positive lymph nodes, number of cycles of postoperative chemotherapy, and whether postoperative adjuvant radiotherapy was combined. Moreover, tumor T stage, ratio of positive lymph nodes and whether adjuvant radiotherapy was combined were independent influencing factors for postoperative OS of patients. The lower tumor T stage, lower ratio of positive lymph nodes and adjuvant radiotherapy combined corresponded to the higher OS rate.*

Conclusions: *Postoperative adjuvant radiotherapy is safe and feasible in the treatment of NSCLC (stage IIIA-N2), which can increase the survival of patients and the local control rate of tumors. Patients with a lower tumor T stage and a lower ratio of positive lymph nodes have higher survival rates.*

Key words: *non-small cell lung cancer, postoperative radiotherapy, efficacy, prognosis*

Introduction

Non-small cell lung cancer (NSCLC) (stage IIIA-N2) refers to NSCLC with ipsilateral mediastinal lymph node metastasis and/or subcarinal lymph node metastasis, accounting for approximately 20% of the total [1]. The 5-year survival rate of patients pathologically diagnosed with stage N2 NSCLC and undergoing complete resection is 7-34% [2]. According to high-level clinical evidence, postoperative chemotherapy can improve the overall survival (OS) of patients [3]. However, it is reported in the relevant literature that the local failure rate is still as high as 40% despite complete resection and aggressive postoperative adjuvant chemotherapy [4]. Postoperative radiotherapy (PORT), as a local treatment method, can theoretically increase the local control rate and improve the survival of patients [5]. However, Stewart et al [6] pointed out that PORT fails to ameliorate the survival status of

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patients in stage IIIA-N2. In 2005, a metaanalysis data were updated by PORT Group, but the updated data still did not confirm that PORT is conducive to improving the OS of patients in stage N2 [7]. With the rapid development of radiotherapy techniques, PORT has been increasingly applied in the clinic in recent years. The literature showed that PORT can raise the local control rate in patients in stage IIIA-N2, but its effect on the survival remains controversial [8,9]. In the present study, the clinical data of 142 patients with stage IIIA-N2 NSCLC admitted in our hospital from January 2014 to June 2015 were retrospectively analyzed, the efficacy and safety of PORT in the treatment of stage IIIA-N2 NSCLC were explored, and the influencing factors for the prognosis of patients were analyzed

Methods

Objects of study

The clinical data of patients pathologically diagnosed with stage IIIA-N2 NSCLC admitted to our hospital from January 2014 to June 2015 were collected. The inclusion criteria were as follows: 1) patients without systemic metastasis confirmed by preoperative systemic examination (whole-body CT, bone scan, *etc.*); 2) those undergoing lobectomy or total pneumonectomy and mediastinal lymph node dissection; 3) those with a Karnofsky performance status score ≥70 points; and 4) those with an estimated survival time >3 months. The exclusion criteria were as follows: 1) patients with a history of radiotherapy, chemotherapy, targeted therapy or other anti-tumor therapies; 2) those with severe dysfunction in the heart, lung, liver or kidney; 3) those with underlying lung diseases (chronic obstructive pulmonary disease, asthma, bronchiectasis, *etc.*); or 4) those complicated with other malignant tumors.

All patients were treated with radical surgery, and postoperative adjuvant chemotherapy. Postoperative adjuvant radiotherapy was performed in 71 cases (Radiotherapy group), while it was not conducted in the remaining 71 cases (Control group). There were 94 males and 48 females aged 45-71 years (median 55.7). The baseline data had no statistically significant differences between the two groups, and they were comparable (Table 1, p>0.05). This study was approved by the Ethics Committee of Tangdu Hospital, Air Force Medical University. Signed written informed consents were obtained from all participants before the study entry.

Preoperative evaluation and operation methods

All patients underwent thoracoscopic radical resection, including 122 cases of lobectomy, and 20 cases of one-side total pneumonectomy. R_0 resection was achieved in all patients.

Platinum-based postoperative adjuvant chemotherapy lasted for 2-6 courses, including 38 cases of VP regimen (vinorelbine combined with cisplatin), 26 cases of GP regimen (gemcitabine combined with cisplatin), 34 cases of TP regimen (paclitaxel combined with cisplatin), 18 cases of PP regimen (pemetrexed combined with cisplatin), 16 cases of EP regimen (etoposide combined with cisplatin), and 9 cases of TC regimen (paclitaxel combined with carboplatin). The chemotherapy was performed for <4 cycles in 44 cases, and ≥4 cycles in 98 cases.

During radiotherapy, the patient was fixed with a vacuum phantom in supine position. After simulated positioning with spiral CT, the patient kept breathing calmly and CT scan was performed (slice thickness: 5 mm) from 5 cm above the inlet of thorax to 5 cm below the base of lung. The CT scan images were transmitted through the local area network to the treatment planning system. Three-dimensional conformal radiotherapy technique was adopted, and the clinical target volume was delineated in the treatment planning system, including subcarinal, ipsilateral mediastinal, and ipsilateral hilar lymph node drainage regions. The radiotherapy dose was 1.8-2.0 Gy/fraction, once a day, and 45-54 Gy in total.

Table 1. Baseline demographic and clinical characteristics of the studied patients

Parameters	*Radiotherapy group (n=71)* *n (%)*	*Control group (n=71)* *n (%)*	*p value*
Age, years	56.26±10.31	54.89±9.43	0.410
Gender			0.375
Male	50 (70.4)	44 (62.0)	
Female	21 (29.6)	27 (38.0)	
Smoking history	48 (67.6)	54 (76.1)	0.351
Tumor location			0.697
Left lung	16 (22.5)	19 (26.8)	
Right lung	55 (77.5)	52 (73.2)	
KPS score			0.358
70-80	24 (33.8)	18 (25.4)	
80-90	47 (66.2)	53 (74.6)	

KPS: Karnofsky performance status

Observation indexes

The operation-related indexes, including operation methods, number of lymph nodes dissected, ratio of positive lymph nodes and postoperative pathology, were compared between the two groups. The incidence of treatment-related adverse reactions was evaluated in accordance with the Common Terminology Criteria for Adverse Events v3.0. All patients were followed up through clinical examination and imaging every 3 months within the first 2 years after operation. Chest CT and serum tumor marker examinations were routinely performed, and head CT/MR, abdominal B ultrasound and bone scan were further conducted at an interval of 1 follow-up cycle or when the patient had clinical symptoms. The recurrence and metastasis during the follow-up period were confirmed by definite imaging or pathological diagnosis. OS was defined as the duration from the first operation to death or the last follow-up. Progression-free survival (PFS) was defined as the duration from the first operation to the first postoperative event (recurrence, metastasis or death).

Statistics

SPSS 22.0 software (IBM, Armonk, NY, USA) was used for statistical analyses. Measurement data were expressed as mean±standard deviation, and t-test was performed for intergroup comparison. Enumeration data were expressed as rates (%), and x^2 test was performed for intergroup comparison. The survival curves were plotted using the Kaplan-Meier method. The influence of the patient's age, gender, tumor site, operation method, pathological T stage, pathological N stage and postoperative adjuvant chemotherapy on the prognosis of patients were compared through log-rank test. The above variables were incorporated into the Cox proportional hazard regression model for multivariate analysis, based on which the independent risk factors affecting prognosis were obtained. $P<0.05$ suggested statistically significant difference.

Table 2. Parameters related to surgery and pathological details

Parameters	*Radiotherapy group (n=71)* *n (%)*	*Control group (n=71)* *n (%)*	*p value*
Surgical method			0.470
Lobectomy	59 (83.1)	63 (88.7)	
Left/right total pneumonectomy	12 (16.9)	8 (11.3)	
Pathological type			0.669
Squamous cell carcinoma	36 (50.7)	31 (43.7)	
Adenocarcinoma	24 (33.8)	27 (38.0)	
Adenosquamous carcinoma	6 (8.5)	7 (9.9)	
Large cell carcinoma	5 (7.0)	6 (8.5)	
T stage			0.493
T1	11 (15.5)	9 (12.7)	
T2	23 (32.4)	18 (25.4)	
T3	37 (52.1)	44 (62.0)	
Number of lymph nodes dissection			0.136
1-20	24 (33.8)	16 (22.5)	
≥20	47 (66.2)	55 (77.5)	
Positive lymph nodes			0.397
≤50	33 (46.5)	28 (39.4)	
>50	38 (53.5)	43 (60.6)	
Postoperative chemotherapy regimens			0.558
VP	21 (29.6)	17 (23.9)	
GP	11 (15.5)	15 (21.1)	
TP	18 (25.4)	16 (22.5)	
PP	8 (11.3)	10 (14.1)	
EP	9 (12.7)	7 (9.9)	
TC	3 (4.2)	6 (8.5)	
Postoperative chemotherapy cycles			0.276
<4	25 (35.2)	19 (26.8)	
≥4	46 (64.8)	52 (73.2)	

VP: Vinorelbine+Cisplatin, GP: Gemcitabine+Cisplatin, TP: Taxol+Cisplatin, PP: Pemetrexed+Cisplatin, EP: Etoposide+Cisplatin, TC: Taxol+Carboplatin

Results

Comparison of operation conditions and tumor pathological characteristics between the two groups

In the Radiotherapy group and Control group, 59 cases and 63 cases underwent lobectomy, and the remaining 12 and 8 cases underwent one-side total pneumonectomy, respectively. R_0 resection was achieved in all patients. According to the postoperative pathological results, there were 36 cases (50.7%) and 31 cases (43.7%) of squamous cell carcinoma, 24 cases (33.8%) and 27 cases (38.0%) of adenocarcinoma, 6 cases (8.5%) and 7 cases (9.9%) of adenosquamous carcinoma, and 5 cases (7.0%) and 6 cases (8.5%) of large cell carcinoma, respectively, in the Radiotherapy and Control group. In terms of postoperative pathological T stage, 11 cases (15.5%) and 9 cases (12.7%) were in stage T1, 23 cases (32.4%) and 18 cases (25.4%) in stage T2, and 37 cases (52.1%) and 44 cases (62.0%) in stage T3, respectively, in the Radiotherapy and Control group. The number of lymph nodes dissected was <20 in 24 cases (33.8%) and 16 cases (22.5%), and ≥20 in 47 cases (66.2%) and 55 cases (77.5%), respectively, in the Radiotherapy and Control group. The ratio of positive lymph nodes was ≤50% in 33 cases (46.5%) in the Radiotherapy group and 28 cases (39.4%) in the Control group, and it was >50% in 38 cases (53.5%) in the Radiotherapy group and 43 cases (60.6%) in the Control group. There were no statistically significant differences in the above indexes between the two groups (p>0.05) (Table 2).

Comparison of incidence of adverse reactions between the two groups

Grade III-IV hematological toxicity occurred in 5 cases (7.0%) and 3 cases (4.2%), and grade III-IV gastrointestinal reactions occurred in 6 cases (8.5%) and 5 cases (7.0%), respectively, in the Radiotherapy and Control group. In the Radiotherapy group, there were 2 cases (2.8%) of radiation esophagitis (grade III-IV), and no radiation pneumonia grade III-IV occurred. All adverse reactions were improved after symptomatic treatment, and no other grade III-IV adverse reactions were found.

Follow-up results of patient survival

All patients were followed up for 6-60 months. The median survival time was 34.7±5.4 months and 31.9±4.9 months, respectively, in the Radiotherapy and Control group. In the Radiotherapy and Control group, the 1-, 3- and 5-year OS rates were 97.2% (69/71) *vs.* 91.5% (65/71), 49.3% (35/71) *vs.* 42.3% (30/71), and 32.4% (23/71) *vs.* 26.8% (19/71), while the 1-, 3- and 5-year PFS rates were 87.3% (62/71) *vs.* 81.7% (58/71), 40.8% (29/71) *vs.* 28.2% (20/71), and 25.4% (18/71) *vs.* 12.7% (9/71), respectively. The OS curves of patients were plotted by Kaplan-Meier method (Figure 1) and log-rank test showed that both OS and PFS in the Radiotherapy group were significantly superior to those in the Control group, showing statistically significant differences (p=0.042, p=0.013).

Analysis of prognostic factors

The 5-year OS rate was 25.0% and 34.8%, respectively, in patients aged <60 years old and those aged ≥60 years old, and the difference was not statistically significant (p=0.169). The 5-year OS rate was 29.8% and 29.2%, respectively, in male and female patients, indicating that the survival was not significantly correlated with gender (p=0.609). 102 smokers and 40 non-smokers had a 5-year OS rate of 20.6% and 52.5%, respectively, and the dif-

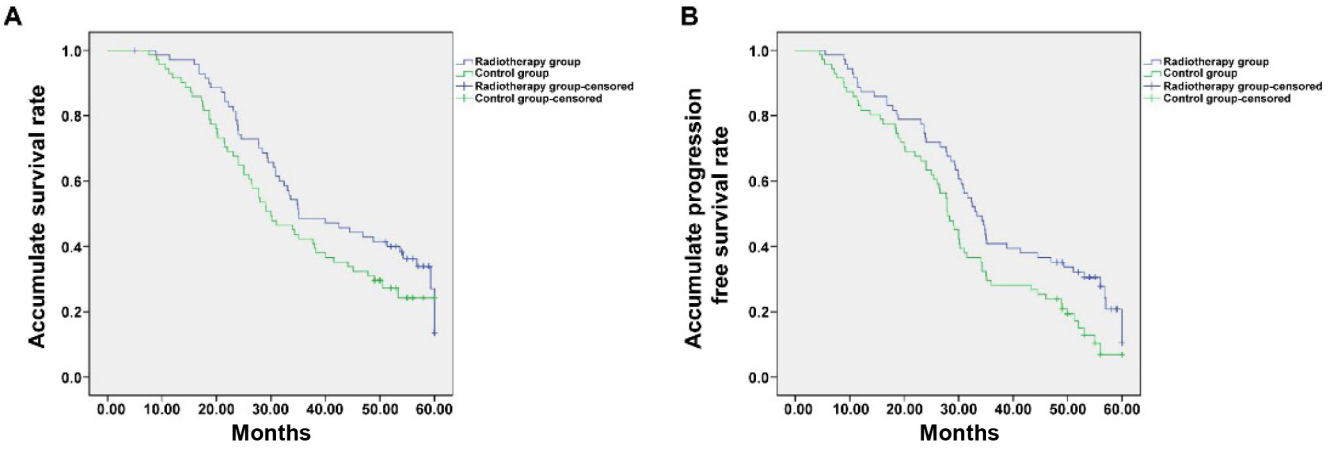

Figure 1. Kaplan-Meier survival curves of patients in Radiotherapy group and Control group. **A:** The overall survival rate of patients in Radiotherapy group was significantly higher than that of Control group (p=0.042). **B:** The progression-free survival rate of patients in Radiotherapy group was significantly higher than that of Control group (p=0.013).

Table 3. Univariate analysis of predictors for 5-year overall survival rate in patients with IIIA-N2 non-small cell lung cancer

Parameters	*Total (n=142) n (%)*	*5-year overall survival rate %*	x^2	*p value*
Age, years			0.805	0.169
<60	76 (53.5)	25.0		
≥60	66 (46.5)	34.8		
Gender			0.463	0.609
Male	94 (66.2)	29.8		
Female	48 (33.8)	29.2		
Smoking history			4.738	0.011
Yes	102 (71.8)	20.6		
No	40 (28.2)	52.5		
Surgical method			0.588	0.497
Lobectomy	122 (85.9)	28.7		
Left/right total pneumonectomy	20 (14.1)	35.0		
Pathological type			0.737	0.634
Squamous cell carcinoma	67 (47.2)	25.4		
Adenocarcinoma	51 (35.9)	31.4		
Adenosquamous carcinoma	13 (9.2)	38.5		
Large cell carcinoma	11 (7.7)	36.4		
T stages			18.561	0.006
T1	20 (14.1)	45.0		
T2	41 (28.9)	36.6		
T3	81 (57.0)	22.2		
Number of lymph nodes dissection			0.196	0.763
1-20	40 (28.2)	32.5		
>20	102 (71.8)	28.4		
Positive lymph nodes			2.979	0.039
≤50	61 (43.0)	36.1		
>50	81 (57.0)	24.7		
Postoperative chemotherapy regimens			3.074	0.558
VP	38 (26.8)	31.6		
GP	26 (18.3)	26.9		
TP	34 (23.9)	26.5		
PP	18 (12.7)	44.4		
EP	16 (11.3)	20.0		
TC	9 (6.3)	22.2		
Postoperative chemotherapy cycles			15.670	0.009
<4	44 (31.0)	15.9		
≥4	98 (69.0)	35.7		
Postoperative adjuvant radiotherapy			3.656	0.042
Yes	71 (50.0)	32.4		
No	71 (50.0)	26.8		

VP: Vinorelbine+Cisplatin, GP: Gemcitabine+Cisplatin, TP: Taxol+Cisplatin, PP: Pemetrexed+Cisplatin, EP: Etoposide+Cisplatin, TC: Taxol+Carboplatin

Table 4. Univariate analysis of predictors for overall survival rate in patients with IIIA-N2 non-small cell lung cancer

Parameters	*Wald value*	*RR*	*95% CI*	*p value*
Smoking history	1.535	0.994	0.795-1.424	0.668
T stage	10.462	6.515	2.896-19.265	0.019
Positive lymph nodes (%)	3.918	2.714	1.781-5.093	0.034
Postoperative chemotherapy cycles	1.767	1.461	0.910-1.807	0.285
Postoperative adjuvant radiotherapy	4.479	0.863	0.544-0.939	0.027

RR: Relative risk, CI: Confidence interval

ference was statistically significant (p=0.011). The 5-year OS rate was 28.7% and 35.0%, respectively, in patients undergoing lobectomy and left/right total pneumonectomy, and there was no statistically significant difference (p=0.497). The patients with squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma and large cell carcinoma had a 5-year OS rate of 25.4%, 31.4%, 38.5% and 36.4%, respectively, and the differences were not statistically significant (p=0.634). The 5-year OS rate was 45.0%, 36.6% and 22.2%, respectively, in patients in stage T1 (n=20), stage T2 (n=41) and stage T3 (n=81), showing statistically significant differences (p=0.006). Besides, no statistically significant difference was found in the 5-year OS rate (32.5% *vs.* 28.4%) in the case of the number of lymph nodes dissected <20 (n=40) and ≥20 (n=102) (p=0.763). There was a statistically significant difference in the 5-year OS rate (36.1% *vs.* 24.7%) in the case of the ratio of positive lymph nodes ≤50% (n=61) and >50% (n=81) (p=0.039). The 5-year OS rate displayed no statistically significant difference among patients receiving different postoperative chemotherapy regimens (p=0.558). Forty four cases and 98 cases underwent postoperative chemotherapy for <4 cycles and ≥4 cycles, respectively, and their 5-year OS was 15.9% and 35.7%, respectively, displaying a statistically significant difference (p=0.009). The patients undergoing PORT had a markedly higher 5-year OS than those undergoing no PORT (32.4% *vs.* 26.8%, p=0.042). According to the results of univariate analysis, the 5-year OS was not correlated with age, gender, operation methods, pathological types, number of lymph nodes dissected and postoperative chemotherapy regimens, but was significantly correlated with smoking history, tumor T stage, ratio of positive lymph nodes, number of cycles of postoperative chemotherapy, and whether adjuvant radiotherapy is combined (p=0.011, p=0.006, p=0.039, p=0.009, p=0.042). The results of multivariate analysis revealed that tumor T stage, ratio of positive lymph nodes and whether adjuvant radiotherapy is combined were independent influencing factors for postoperative OS of patients. The lower tumor T stage, lower ratio of positive lymph nodes and adjuvant radiotherapy combined corresponded to the higher OS rate (p=0.010, p=0.034, p=0.027) (Tables 3 and 4).

Discussion

Radical resection is one of the most important treatment means for patients with operable stage IIIA-N2 NSCLC, but the postoperative survival remains low, and the 3- and 5-year survival rates are about 45.3-51.7% and 28.1-47% [10,11]. Local recurrence or distant metastasis is the main reason for failure of operation in patients with stage IIIA-N2 NSCLC, and the local recurrence and distant metastasis are 28-47% and 39-67%, respectively [12]. Therefore, postoperative adjuvant treatment appears to be particularly important. Postoperative chemotherapy can kill postoperative residual micrometastases and subclinical lesions to some extent, thereby lowering the risks of recurrence and metastasis. At present, the subgroup analysis of multiple large-sample phase III clinical trials in the world has shown that postoperative chemotherapy can benefit patients with stage IIIA-N2 NSCLC, which confirms the therapeutic value of postoperative adjuvant chemotherapy for stage IIIA-N2 NSCLC [13,14]. However, the local or regional recurrence rate is still high after postoperative chemotherapy. According to relevant studies, PORT can reduce the local recurrence rate and raise the survival rate of patients with stage IIIA-N2 NSCLC after surgery [15]. However, whether PORT is needed for patients with stage IIIA-N2 NSCLC after R_0 resection remains currently controversial.

The study of Douillard et al [9] showed that the OS rate of patients with stage IIIA-N2 NSCLC is raised by PORT from 16.6% to 21.3% in observation group, and from 34.0% to 47.4% in postoperative chemotherapy group. It was also confirmed by multivariate analysis that PORT is conducive to improving both tumor-free survival and OS of patients in stage N2 [9]. According to the subgroup analysis of Lally et al [16], PORT greatly improves the OS rate of patients with stage N2 NSCLC (p=0.007), and increases the 5-year survival from 20% to 27%, indicating that PORT can ameliorate the survival condition of patients in stage IIIA-N2. Mikell et al [17] found that the survival rate of patients undergoing postoperative adjuvant chemotherapy can be increased by PORT (p=0.048). In addition, it has been proved by a number of retrospective clinical trials that PORT can improve the survival condition of patients in stage N2 [18]. Billiet et al [19] evaluated the local recurrence rate through randomized trials involving 1677 patients, and the results manifested that regardless of the irradiation source, PORT is able to greatly reduce the postoperative local recurrence rate. If only a linear accelerator is used in radiotherapy, the local control effect will be more significant (RR=0.31, p=0.01). Dai et al [20] conducted a retrospective analysis of 221 patients with stage IIIA-N2 NSCLC in the Cancer Hospital Chinese Academy of Medical Sciences. The results showed that PORT can

raise the recurrence-free and the distant metastasis-free survival, and it was found via multivariate analysis that PORT can greatly prolong survival (p=0.000). Zou et al [21] retrospectively analyzed the effects of postoperative chemoradiotherapy and PORT alone on stage IIIA-N2 NSCLC. The results showed that, compared with PORT alone, postoperative adjuvant chemoradiotherapy significantly prolongs the survival of patients receiving excision of stage IIIA-N2 NSCLC, and raises the 5-year survival from 14.4% to 30.5% (p=0.007).

In the present study, the mean survival was 34.7±5.4 months and 31.9±4.9 months, the 5-year OS was 32.4% (23/71) and 26.8% (19/71), and the 5-year PFS rate was 25.4% (18/71) and 12.7% (9/71), respectively, in the Radiotherapy and Control group. It can be seen that both OS and PFS in the Radiotherapy group were significantly superior to those in the Control group (p=0.042, p=0.013).

There are many influencing factors for the prognosis of patients with stage IIIA-N2 NSCLC. In this study, it was found that tumor T stage, ratio of positive lymph nodes and whether adjuvant radiotherapy is combined were independent prognostic factors. The TNM stage is obtained by the analysis of large-scale clinical data, which is important guidance for developing reasonable therapeutic regimens and predicting the prognosis, and gradually revised with the continuous development of diagnosis and treatment. Saito analyzed the clinical data of 214 patients undergoing radical resection of stage IIIA-N2 NSCLC, and found that pathological T stage is an independent prognostic factor [22]. Other authors also suggested that postoperative T stage is a prognostic factor affecting survival [23]. In this study, it was also confirmed that pathological T stage was an independent prognostic factor for stage IIIA-N2 NSCLC, and the higher T stage corresponded to the worse prognosis. In 2011, some authors analyzed the prognosis of 221 cases of stage IIIA-N2 NSCLC, and divided the participants into four groups based on the number of metastatic lymph nodes (1-3, 4-6, 7-9, and >10). The results manifested that the 5-year OS was 46.2%, 35.8%, 30.7% and 12.2%, respectively, in the four groups, displaying statistically significant differences [20]. In this study, it was also found that the patients with a higher ratio of positive lymph nodes had a poorer prognosis.

In this retrospective study, the sample size was limited, and the follow-up content was not comprehensive enough. In the future, the conclusion in this study needs to be confirmed by large-sample multicenter prospective randomized studies.

Conclusions

Postoperative adjuvant radiotherapy is safe and feasible in the treatment of stage IIIA-N2 NSCLC, which can increase the survival of patients and the local control of tumors. Patients with a lower tumor T stage and a lower ratio of positive lymph nodes have a higher survival.

Conflict of interests

The authors declare no conflict of interests.

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