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ORIGINAL ARTICLE

Thoracoscopic radical resection in the treatment of NSCLC patients (stage IIIA) after neoadjuvant chemotherapy

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Summary

Purpose: *We aimed to investigate the efficacy and safety of thoracoscopic radical resection of lung cancer in the treatment of patients with stage IIIA non-small cell lung cancer (NSCLC) after neoadjuvant chemotherapy.*

Methods: *A total of 132 NSCLC patients (stage IIIA) were collected. Among them, 66 received preoperative neoadjuvant chemotherapy and thoracoscopic radical resection of lung cancer (NACT group), and 66 underwent thoracoscopic radical resection of lung cancer directly (control group). Next, the downstaging of the tumor was analyzed after neoadjuvant chemotherapy, and the R0 resection rate, surgical conditions, postoperative complications, and changes in the levels of serum tumor markers were compared between the two groups of patients.*

Results: *The response rate of neoadjuvant chemotherapy was 51.5% (34/66), and the overall downstaging rate was 53.0% (35/66) after neoadjuvant chemotherapy, with 34 cases of T downstaging and 35 cases of N downstaging. The operative time was clearly shorter in the NACT group than that in control group. The R0 resection rate in the NACT group was prominently higher than that in the the control group. The follow-up results uncovered that the 3-year overall survival (OS) and 3-year progression-free survival (PFS) rates were 50.0% and 21.2% in the NACT group, and 36.4% and 6.1% in the control group, respectively. Based on the results of log-rank test, the OS and PFS of patients in the NACT group were markedly better than those in the control group.*

Conclusions: *Neoadjuvant chemotherapy benefits patients with NSCLC (stage IIIA), and it is capable of effectively leading to pathological down-staging, elevating the R0 resection rate, significantly improving the survival of patients and considerably repressing the progression of the disease.*

Key words: *neoadjuvant chemotherapy, NSCLC, stage IIIA, radical resection of lung cancer, efficacy*

Introduction

Primary lung cancer is the most common malignancy in the world. In China, a country with a high incidence of lung cancer, its annual prevalence rate is about 130.2 per 100,000 people, of which about 75-80% are non-small cell lung cancer (NSCLC) patients [1,2]. NSCLC is mainly treated through surgery. However, the overall efficacy and prognosis are poor since radical excision is hard to be attained by simple surgery in most patients already with locally advanced or metastasized tumors at the time of presentation [3].

The concept of neoadjuvant chemotherapy has been proposed in recent years. Many clinical studies on neoadjuvant chemotherapy for stage IIIA NSCLC have manifested that neoadjuvant chemotherapy is able to reduce tumor size, lead to downstaging of NSCLC, increase surgical resection rate and eliminate distant micrometastases, thus prolonging the survival time of patients [4,5]. It is currently recognized that the best course of neoadjuvant chemotherapy for NSCLC is 2-3 cycles. An insufficient cycle of chemotherapy will

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greatly suppress the treatment effect, while over 3 cycles of chemotherapy will increase the risk of surgery and promote the incidence of complications. Besides, chemotherapy will also lead to the decline in the physical state, thereby raising the risk of infection and making the healing of wounds more difficult [6,7]. In this study, the clinical data of 132 patients with stage IIIA NSCLC were retrospectively analyzed, and the efficacy and safety of surgery combined with preoperative neoadjuvant chemotherapy (NACT) and simple surgery were analyzed, hoping to provide a reasonable reference for decision-making in the cinic.

Methods

Study subjects

A total of 132 stage IIIA NSCLC patients were selected, including 88 males and 44 females aged 24-73 years (median 59.5). Before sugery, both groups of patients were definitely diagnosed with NSCLC according to the results of bronchoscopic biopsy and computed tomography (CT)-guided percutaneous lung puncture biopsy, and the clinical stage was confirmed to be stage IIIA (T1-2N2M0, T3N1-2M0 and T4N0-1M0) based on the results of pathological examinations including chest CT enhanced scan examination, abdominal color Doppler ultrasound examination, head magnetic resonance imaging examination and whole body nuclide bone scan and the internationally accepted TNM staging system (7th edition, 2009) by the Union Internationale Contre le Cancer (UICC). Patients with contraindications to chemotherapy and surgery or with a history of malignant tumors were excluded. The patients enrolled were divided into two groups according to different treatment methods to receive preoperative NACT combined with thoracoscopic radical resection of lung cancer (NACT group, n=66) and simple thoracoscopic radical resection of lung cancer (control group, n=66). The clinical baseline data like age, gender, tumor pathological type, site and stage showed no statistically significant differences between the two groups (p>0.05) (Table 1). All patients enrolled were informed and signed the informed consent in accordance with *Declaration of Helsinki*. This study was approved by the Ethics Committee of Binzhou People's Hospital.

Therapeutic methods

NACT was conducted using the chemotherapy regimens for NSCLC recommended by the National Comprehensive Cancer Network (NCCN) guidelines [8]. Gemcitabine-cisplatin (GP) regimen was applied in patients with squamous lung carcinoma as follows: Gemcitabine was intravenously infused at 1,000 mg/m^2 on

Table 1. Baseline characteristics of the studied patients

Characteristics	*NACT group (n=66)* *n (%)*	*Control group (n=66)* *n (%)*	*p value*
Age (years)	60.3±8.9	58.8±9.3	0.346
Gender			0.356
Male	47 (71.2)	41 (62.1)	
Female	19 (28.8)	25 (37.9)	
Pathological type			0.293
Squamous cell carcinoma	38 (57.6)	29 (43.9)	
Adenocarcinoma	25 (37.9)	33 (50.0)	
Adenosquamous carcinoma	3 (4.5)	4 (6.1)	
Smoking history			0.368
Yes	39 (59.1)	44 (66.7)	
No	27 (40.9)	22 (33.3)	
Tumor location			0.375
Central	37 (56.1)	42 (63.6)	
Peripheral	29 (43.9)	24 (36.4)	
TNM staging			0.551
T1N2M0	7 (10.6)	4 (6.1)	
T2N2M0	28 (42.4)	32 (48.5)	
T3N1M0	28 (42.4)	29 (43.9)	
T4N1M0	3 (4.5)	1 (1.5)	
KPS score (points)			0.293
70-80	40 (60.6)	34 (51.5)	
80-90	26 (39.4)	32 (48.5)	

NACT: neoadjuvant chemotherapy; TNM: tumor, node, metastasis; KPS: Karnofsky performance status

days 1 and 8, and cisplatin was intravenously infused at 30 mg/m^2 on days 1-3, with 21 days as a cycle. Docetaxel-cisplatin (TP) regimen was given to patients with lung adenocarcinoma. Specifically, docetaxel was intravenously infused at 75 mg/m^2 on day 1, and cisplatin was intravenously infused at 30 mg/m^2 on days 1-3, with 21 days as a cycle. Following 2 cycles of NACT, surgery was performed after 4-6 weeks of rest. During chemotherapy, adjuvant therapies including hydration therapy, diuretic therapy, antiemetic therapy, and liver protection therapy were routinely carried out. In the control group, the patients were treated directly with surgery. Thoracoscopic surgery was conducted in both groups.

Before surgery, patients were subjected to auxiliary examinations such as electrocardiography, chest+abdominal enhanced CT, head MRI, whole body bone scan, blood routine tests, biochemical routine tests, blood coagulation function examination and tumor marker examination to comprehensively assess their general condition and tumor burden. After excluding surgical contraindications, an appropriate surgical approach was chosen from wedge resection, pulmonary lobectomy, sleeve lobectomy and total pneumonectomy based on tumor invasion degree, adhesion degree, tumor range and lymph node metastasis. Hilar and mediastinal lymph node dissection was applied in the two groups of patients.

In accordance with the general condition of patients, adjuvant chemotherapy was given from 14-28 days after surgery. According to the NCCN guidelines, all patients enrolled continued to undergo 4 cycles of adjuvant chemotherapy after surgery based on the GP and TP regimens.

Observation indexes

After two cycles of NACT in the observation group, the efficacy was evaluated according to the RECIST 1.1 and the results of CT examinations at 4-6 weeks: complete remission (CR): all target lesions disappeared, and the short diameter of metastatic lymph nodes was less than 10 mm, partial remission (PR): the total length of target lesions was reduced by ≥30%, stable disease (SD): the total length of target lesions was reduced, but did not reach the level in PR, or it was increased, but lower than the level in PD, and progressive disease (PD): the total length of target lesions was increased by ≥20%, and the measured value was increased by ≥5 mm, or a new lesion appeared. Objective response rate=(CR cases + PR cases) / total cases × 100%.

The main adverse reactions of patients undergoing NACT were recorded, including gastrointestinal reaction, bone marrow depression, and mild liver and renal function impairment. Indexes such as operative time, intraoperative blood loss, R0 resection rate, thoracic drainage volume within 24 h after surgery, length of postoperative hospital stay, and incidence rate of postoperative complications of the two groups of patients were recorded. Besides, the levels of serum cytokeratin 19 fragment (CYFRA21-1) and carcinoembryonic antigen (CEA) were measured through radioimmunoassay 1 day before chemotherapy, 1 day after chemotherapy and 7 days after surgery.

All patients were followed up to record their survival. Overall survival (OS) referred to the time interval from treatment to death or last follow-up. Progression-free survival (PFS) was defined as the time interval from treatment to disease progression or recurrence and metastasis. The last follow-up time was December 31, 2019.

Statistics

SPSS 22.0 statistical package (IBM, Armonk, NY, USA) was utilized for statistical analyses. Measurement data were expressed as mean ± standard deviation, and t-test was employed for the comparison between two groups. Enumeration data were expressed as ratio (%), and x^2 test was used for comparison among groups. Survival curves were plotted via Kaplan-Meier method, and Log-rank test was adopted for survival analysis. $P<0.05$ indicated that the difference was statistically significant.

Table 2. Comparison of surgery parameters and complications of patients in the two studied groups

Parameters	*NACT group (n=66)*	*Control group (n=66)*	*p value*
Operation time (min)	185.2±27.3	202.5±30.4	0.001
Blood loss (ml)	278.7±30.8	288.3±33.9	0.091
Thoracic drainage volume 24h after surgery (ml)	296.1±110.5	282.9±126.7	0.525
Postoperative hospital stay time (day)	9.4±3.6	10.3±3.9	0.171
Complications, n (%)			
Incision infection	2 (3.0)	1 (1.5)	0.559
Pulmonary infection	10 (15.2)	4 (6.1)	0.090
Pulmonary atelectasis	3 (4.5)	2 (3.0)	0.648
Respiratory failure	0 (0)	1 (1.5)	0.316
Bronchopleural fistula	0 (0)	0 (0)	1.000
Arrhythmia	4 (6.1)	3 (4.5)	0.698
Hydrothorax	32 (48.5)	28 (42.4)	0.484
Pneumothorax	20 (30.3)	16 (24.2)	0.434

NACT: neoadjuvant chemotherapy

Results

Short-term efficacy of neoadjuvant chemotherapy and incidence of adverse reactions

In NACT group, GP was administered to 57.6% (38/66) of the patients, and TP to 42.4% (28/66) of the patients. After NACT in the 66 patients, there were 2 cases of CR, 32 cases of PR, and 32 cases of SD, with a response rate of 51.5% (34/66). The major adverse reactions after NACT were gastrointestinal reactions, bone marrow depression, mild liver and renal function impairment, which were alleviated after symptomatic treatment. The incidence rate of adverse reactions was 34.8% (23/66).

Comparisons of surgical indexes between the two groups of patients

Surgical treatment was performed in both groups. Surgical conditions are shown in Table 2. The operative time was clearly shorter in the NACT group than that in the control group (185.2±27.3 min *vs.* 202.5±30.4 min, p<0.001), whereas the intraoperative blood loss (278.7±30.8 mL *vs.* 288.3±33.9 mL, p=0.091), thoracic drainage volume within 24 h after surgery (296.1±110.5 mL *vs.* 282.9±126.7/mL, p=0.525) and average length of postoperative hospital stay (9.4±3.6 days *vs.* 10.3±3.9 days, p=0.171) had no statistically significant differences between the two groups of patients (p>0.05). The major postoperative complications observed in the two groups of patients included incision infection, pulmonary infection, pulmonary atelectasis, respiratory failure, bronchopleural fistula, arrhythmia, hydrothorax and pneumothorax. There were no statistically significant differences in the incidence rates of pulmonary infection [15.2% (10/66) *vs.* 6.1% (4/66)], hydrothorax [48.5% (32/66) *vs.* 42.4% (28/66)] and pneumothorax [30.3% (20/66) *vs.* 24.2% (16/66)] between the two groups (p>0.05).

The number of patients undergoing wedge resection, lobectomy, sleeve lobectomy and total pneumonectomy was 4 (6.1%), 58 (87.9%), 3 (4.5%) and 1 (1.5%) in the NACT group, respectively, and 3 (4.5%), 54 (81.8%), 6 (9.1%) and 3 (4.5%) in the control group, respectively, showing no statistically significant difference (p=0.515). The R0 resection

Table 3. Parameters related to surgery and pathological details

Parameters	*NACT group (n=66)*	*Control group (n=66)*	*p value*
Surgical method			0.515
Wedge resection	4 (6.1)	3 (4.5)	
Lobectomy	58 (87.9)	54 (81.8)	
Sleeve lobectomy	3 (4.5)	6 (9.1)	
Pneumonetomy	1 (1.5)	3 (4.5)	
Incision margin			0.048
R0	64 (97.0)	58 (87.9)	
R1	2 (3.0)	8 (12.1)	
Pretreatment T stage			0.429
T1	14 (21.2)	11 (16.7)	
T2	41 (62.1)	39 (59.1)	
T3	11 (16.7)	14 (21.2)	
T4	0 (0)	2 (3.0)	
Pretreatment N stage			0.720
N0	28 (42.4)	27 (40.9)	
N1	19 (28.8)	16 (24.2)	
N2	19 (28.8)	23 (34.8)	
Posttreatment T downstaging	34 (51.5)		
T3-T2	6 (9.1)		
T3-T1	4 (6.1)		
T2-T1	24 (36.4)		
Posttreatment N downstaging	35 (53.0)		
N2-N1	14 (21.2)		
N2-N0	3 (4.5)		
N1-N0	18 (27.3)		

NACT: neoadjuvant chemotherapy

rate was significantly higher in the NACT group than that in the control group [97.0% (64/66) *vs.* 87.9% (58/66), p=0.048)]. NACT reduced the number of patients undergoing total pneumonectomy and increased the R0 resection rate (Table 3).

Comparison of tumor stage before and after operation

Compared with the pathological stage before operation, T downstaging was found in 34 (51.5%) patients, 6 (9.1%) cases were downstaged from T3 to T2, 4 (6.1%) cases were downstaged from T3 to T1, and 24 (36.4%) cases were downstaged from T2 to T1. N downstaging was found in 35 (53.0%) patients [14 (21.2%) cases downstaged from N2 to N1, 3 (4.5%) cases downstaged from N2 to N0, and 18 (27.3%) cases downstaged from N1 to N0] after NACT. The overall downstaging rate was 53.0% (35/66) after NACT (Table 3).

Comparisons of serum tumor markers between the two groups before and after treatment

No statistically significant differences were found in the levels of serum tumor markers CYFRA21-1 and CEA between the two groups before treatment (p=0.195, p=0.150). However, after treatment, these levels were remarkably reduced in both groups, and they were obviously lower in the NACT group than in the control group (p=0.020, p=0.005) (Table 4).

Follow-up results of survival status of patients

Up to December 2019, the patients were followed up for 6-36 months (median 29.3). The 1-, 2- and 3-year OS rates in the NACT and control group were 80.3% (52/66) and 66.7% (44/66), 63.6% (42/66) and 51.5% (44/66), and 50.0% (33/66) and 36.4% (24/66), respectively. Besides, the 1-, 2- and 3-year PFS rates were 62.1% (41/66) and 37.9% (25/66), 42.4% (28/66) and 15.2% (10/66), and 21.2% (14/66) and 6.1% (4/66) in the NACT and control group, respectively. The survival curves of patients plotted via Kaplan-Meier method are shown in Figure 1. Based on the results of log-rank test, the OS and PFS of patients in the NACT group were markedly better than those in the control group (p=0.034, p<0.001).

Table 4. Comparison of preoperative and postoperative serum tumor markers of patients in the two studied groups

	NACT group (n=66)	*Control group (n=66)*	*p value*
CYFRA21-1 (ng/ml)			
Pretreatment	9.52±3.38	8.69±3.78	0.186
Postoperative	5.48±3.12	6.85±3.56	0.020
CEA (ng/ml)			
Pretreatment	16.86±5.14	18.17±5.26	0.150
Postoperative	7.91±2.14	9.07±2.49	0.005

NACT: neoadjuvant chemotherapy; CYFRA: cytokeratin-19-fragment; CEA: carcinoembryonic antigen

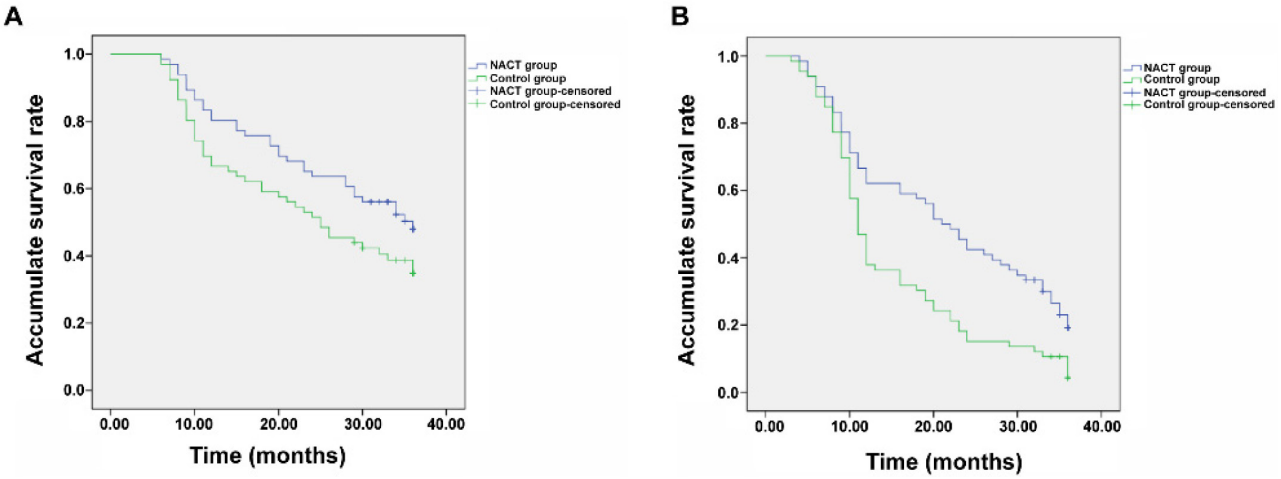

Figure 1. Kaplan-Meier survival curves of patients in the NACT and the Control group. The overall survival rate **(A)** and progression-free survival rate **(B)** of patients in the NACT group was significantly higher than that of the Control group (p=0.034, p<0.001).

Discussion

The therapeutic options for NSCLC are affected by tumor stage. Surgery is the major approach for treating the patients with early-stage localized resectable NSCLC. Postoperative adjuvant chemotherapy or preoperative NACT are applied to improve the PFS and OS of NSCLC patients [9]. In the case of stage IIIA NSCLC, lymph node metastasis is limited to ipsilateral mediastinum and carina, but it is difficult to be completely removed, especially in patients with lymph node fusion who are more prone to postoperative recurrence [10]. Recent clinical data have revealed that, in contrast with surgery alone, the combination of preoperative NACT can eliminate and control the subclinical micrometastases of NSCLC in the early stage, decreasing the size of tumors, facilitating the surgical field exposure and operation, and increasing the surgical resection rate [11].

Among neoadjuvant therapies, NACT for patients with stage IIIA NSCLC has been first studied in the clinic, and in accordance with the data, the overall 5-year survival rate of stage III NSCLC patients was 12.0-29.8% [12,13]. In two typical randomized controlled studies on NACT for stage IIIA NSCLC published by Roth and Rosell in 1994, a total of 60 patients with stage IIIA NSCLC were randomly divided into preoperative NACT group and simple surgery group. It was discovered that NACT group exhibited a longer median survival time than in the simple surgery group, with obvious survival benefits. These two studies have built up the position of NACT in multidisciplinary therapy for stage IIIA NSCLC [14,15]. A metaanalysis conducted by Nobuyuki Horita in 2013 included 7 clinical studies, with a total of 1,447 patients, and the results revealed that stage IIIA NSCLC patients receiving preoperative NACT had a better survival and a lower risk ratio (0.77 *vs.* 0.83) than those undergoing postoperative adjuvant chemotherapy [16]. However, questions are raised with the continuous deepening of studies despite the fact that NACT has been applied by many doctors in the treatment of stage IIIA NSCLC. Some authors believe that NACT may lead to losing the chance to undergo radical surgery due to primary drug resistance, or increase the early postoperative recurrence rate in some patients. In a multi-center prospective randomized controlled study on early NSCLC (MIP-91) reported by French DePierre, a total of 355 patients with stage I (except for T1N0), stage II and operable stage IIIA NSCLC were enrolled, and it was found that stage IIIA (N2) patients receiving preoperative chemotherapy had no significant survival advantages (p=0.85). This may be related to the choice of chemotherapy regimens [17]. Besides, a prospective randomized controlled clinical study comparing preoperative chemotherapy and simple surgery was conducted by the Japan Clinical Oncology Group. A total of 62 patients with stage IIIA/N2 NSCLC from 1993 to 1998 were included and randomly divided into NACT group and simple surgery group. The results demonstrated that NACT was not conducive to the survival time of patients with stage IIIA/N2 NSCLC [18]. The statistical power of the results was greatly reduced since the study was terminated prematurely due to a low enrollment rate. Berghmans performed a metaanalysis on 6 prospective phase III clinical studies published from 1993 to 2003, and concluded that neoadjuvant chemotherapy is beneficial to the survival of patients with NSCLC (stage IIIA), but no statistical difference is found in the survival. In addition, stage IIIA NSCLC patients should receive interventional chemoradiotherapy and other comprehensive treatments earlier than patients with stage I-II NSCLC [19]. In a metaanalysis by Nakamura, 376 patients with stage IIIA NSCLC were analyzed, and it was concluded that NACT benefits the 1-, 3- and 5-year OS of such patients, but there were no statistical differences in the 1-, 3- and 5-year OS between stage IIIA NSCLC patients undergoing NACT and those receiving surgery directly (p=0.052, p=0.108 and p=0.212) [20]. However, it was discovered in this study that NACT remarkably prolonged the OS and PFS of patients, inconsistent with the results of the previous metaanalysis. The reason may be that the time span of clinical studies included in the metaanalysis was long, the efficacy of the chemotherapy regimen used was different from that of the current recommended regimens, and the clinical staging assessment method in the previous study was limited.

In addition, the results of this study showed that NACT achieved a tumor downstaging rate of 53.0% (35/66), visibly increased the R0 resection rate of the tumor, reduced the difficulty and risk of surgery, and shortened the operative time. These results are consistent with the findings reported in the literature [21,22]. Moreover, the levels of serum tumor markers of patients were obviously lower in the NACT group than in the control group. In this study, the surgery was accomplished in all patients receiving NACT, verifying the feasibility of NACT. Furthermore, the follow-up results uncovered that the OS and PFS of patients in the NACT group were clearly better than those in the control group (p=0.034, p<0.001).

This study was retrospective and had certain shortcomings. The number of patients enrolled was limited, the chemotherapy regimen was not unique, patients who had no response to NACT and had pro-

gressive disease were not enrolled, and the content of follow-up was insufficient. In the future, it is necessary to design more rigorous multi-center large-sample prospective randomized studies to prove the conclusions of this study.

Conclusions

NACT is beneficial for patients with stage IIIA NSCLC, which can effectively achieve pathological downstaging, elevate the R0 resection rate, significantly improve the survival of patients and considerably repress the progression of disease. In addition, it results in no evident increase in the incidence rate of postoperative complications.

Conflict of interests

The authors declare no conflict of interests.

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