Safety and effectiveness of localized lung resection combined with neoadjuvant chemotherapy in the treatment of stage I-II non-small cell lung cancer

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Abstract. This study was conducted to evaluate the safety and effectiveness of localized lung resection combined with neoadjuvant chemotherapy in the treatment of stage I-II non-small cell lung cancer (NSCLC). A total of 88 patients, who were admitted to our hospital for first diagnosis and treatment, were selected. The patients were divided into control group (n=40 cases) and observation group (n=48 cases) according to the last digit of the admission number. The control group was treated with minimally invasive localized lung resection by thoracoscope. The observation group underwent the same procedure combined with two cycles of systemic neoadjuvant chemotherapy before the surgery was adopted in the observation group. The effects of both treatments were compared. The operation time, intraoperative blood loss and postoperative drainage volume of observation group were significantly lower than those of the control group (P<0.05). The surgical resection rate and margin negative rate of observation group were higher than those of control group, while the occurrence rate of complications was lower than that of control group; results were statistically significant (P<0.05). The serum neutrophil gelatinase associated lipocalin (lipocalin-2/NGAL), matrix metalloproteinase-9 (MMP-9) and carcinoembryonic antigen (CEA) levels of two groups after the treatment were lower than those before; however, levels in the observation group exhibited a distinct decrease. The difference has statistical significance (P<0.05). The follow-up time of two groups was 3-38 months and the median time was 20.5 months. The tumor survival period of observation group was not prolonged, however, the survival rate and quality rate of life were enhanced; the difference has statistical significance (P<0.05). Localized lung resection combined with neoadjuvant chemotherapy can effectively improve the surgical effect of stage I-II NSCLC, prolong the survival period, enhance the survival rate, decrease the occurrence rate of complications and reduce the tumor related factors lipocalin-2, MMP-9 and CEA levels.

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Introduction

Lung cancer has become one of the most important malignant tumors which threatens the health of the world population. Lung cancer has a high incidence and mortality rate and the 5-year survival rate is low (1). Non-small cell lung cancer (NSCLC) accounts for 80% of all lung cancers. Although surgical resection is the main method of treatment, a majority of patients that have a definite diagnosis are in the progressive stage with no radical indication of surgery. Whether or not the surgical resection can be performed is the most important factor that affects the prognosis (2). Therefore, early screening and treatment is the key to improve survival prognosis. Neoadjuvant chemotherapy can induce systemic or local chemotherapy before surgery or radiotherapy, which is proven to improve the resection rate, reduce tumor size and prolong the survival period (3). Preoperative adjuvant chemotherapy of localized lung resection in middle and advanced NSCLC can effectively reduce tumor pathological stage, increase the scope of resection, reduce the recurrence and metastasis rate, and enhance the clinical benefit rate of cancer and long-term survival quality (4). Postoperative adjuvant chemotherapy can help stage II-IIIa NSCLC patients by increasing survival, but the curative effect and safety of localized lung resection combined with neoadjuvant chemotherapy in patients of stage I NSCLC has not received a unified understanding (5,6). Therefore, this study conducted a summary analysis for the treatment project which was carried out in our center, in order to provide reference basis for reasonable choice of therapies.

Materials and methods

General data. A total of 88 patients with stage I-II (TNM staging) NSCLC, who were admitted to our hospital for first

diagnosis and treatment from January 2013 to January 2016, were continuously selected and examined by CT, bronchoscope, sputum cytology or tissue puncture and surgical removal of the tumor for pathological diagnosis. Patients with diseases including pulmonary metastases, primary malignant tumor of other organs, primary lung diseases such as pulmonary tuberculosis, pulmonary infection, chronic obstructive pulmonary disease, respiratory failure, basic diseases such as heart, kidney, brain and other organs dysfunction, chemotherapy and drug allergies, were excluded due to their inability to complete the course of chemotherapy.

This study obtained approval of the Ethics Committee of The Second Affiliated Hospital of Chongqing Medical University and gained written informed consent right of patients or their families. The patients were randomly divided into control group (n=40 cases) and observation group (n=48 cases). In the control group, there were 24 males and 16 females; aged between 48-72 years, with an average of 60.7±12.5. There were 13 smokers and 10 cases of stage I and 30 cases of stage II; the maximum diameter of the tumor ranged from 0.5 to 3.0 cm, with an average of 1.3±0.4 cm. The average number of tumors was 1.1±0.3. In the observation group, there were 26 males and 22 females; aged between 49-71 years, with an average of 62.1±13.4. There were 15 smokers, and 15 cases of stage I and 33 cases of stage II. The maximum diameter of tumor ranged from 0.6 to 3.5 cm, with an average of 1.5±0.7 cm; the average number of tumors was 1.2±0.5. The comparison of general data of the two groups had no significant difference (P>0.05).

Treatment method. This entire study was completed by one surgical and nursing team, according to the standard medical procedure. The control group was treated with minimally invasive localized lung resection by thoracoscope, while the observation group had the surgery combined with neoadjuvant chemotherapy.

Neoadjuvant chemotherapy. Preoperative neoadjuvant chemotherapy was administered for 21 days in the observation group. The specific medication was gemcitabine hydrochloride for injection (Chinese medicine standard H20163144; specifications, gemcitabine 0.2 g as count; Shandong New Times Pharmaceutical Co. Ltd., Shandong, China), with intravenous infusion on day 1 and 8, 1,000 mg/m^2, 30 min/time; cisplatin for injection (Chinese medicine standard H21020212; specifications, 20 mg; Jinzhou Jiutai Pharmaceutical Co. Ltd., Jinzhou, China), with intravenous infusion on day 1, 75 mg/m^2. The conventional hydration, elevating white blood cells, prevention of infection and other symptomatic treatment were administered during the chemotherapy period. Ondansetron (Chinese medicine standard H19980117; specifications, C18H19N30 8 mg as count; Shanghai Shangyao Chinese and Western Pharmaceutical Co. Ltd., Shanghai, China) was used to prevent nausea. Routine blood tests and liver and kidney function were regularly administered and examined.

Surgical method. The perfect preoperative preparation, establishment of vein channel, clinostatism of uninjured side, general anesthesia of double lumen endotracheal intubation, one-lung ventilation and vital signs monitoring were performed. The three-hole method was used for operating. The observation hole was at the seventh to eighth intercostal space of midaxillary line, with a length of 1.0 to 1.5 cm. The auxiliary operating hole was at the seventh to eighth intercostal space of posterior line axillary, with a length of 1.5 to 2.0 cm. The main operating hole was at the third to fourth intercostal space, with the length of 2.0 to 3.5 cm. Firstly, the lesion was be explored, and then the following steps were performed: i) Dissociated anatomy of corresponding lung segment; ii) exposure of artery-vein and bronchus of pulmonary segment; iii) segment artery-vein and segment bronchus; and iv) the utilization of thoracoscope cut stitching instrument for the occlusion of segment bronchus. The anesthetist confirmed the resected corresponding lesion of pulmonary segments and exposed intersegmental fissure. When the lung segment of lesions collapsed, and with the full expansion of the normal lung tissues around the boundary of lung segments needing resection were confirmed. The intersegmental fissure was resected by thoracoscope cut stitching instrument. The lymph nodes of group 12 and 13 were regularly probed in the operation, along with the intraoperative pathologic examination of lung segments which were resected. The operation method of localized lung resection of the two groups was the same.

Table I. Comparison of operation time, intraoperative blood loss and postoperative drainage volume.

Groups	Operation time (min)	Intraoperative blood loss (ml)	Postoperative drainage volume (ml)
Observation	110.8±23.6	214.6±40.7	523.6±86.3
Control	145.7±32.4	390.5±51.3	754.2±75.4
t-test	4.326	4.638	4.857
P-value	0.033	0.030	0.026

Observation index. The operation time, intraoperative blood loss, postoperative drainage volume, surgical resection rate, margin negative rate, occurrence rate of perioperative complications, serum neutrophil gelatinase associated lipocalin (lipocalin-2/NGAL), matrix metalloproteinase-9 (MMP-9), carcinoembryonic antigen (CEA) levels, follow-up of no tumor survival period, survival rate and quality of life of two groups were compared. ELISA method was used to test lipocalin-2, MMP-9 and CEA levels. Five milliliters of fasting elbow venous blood was collected and centrifuged at 1500 x g for 30 min. The supernatant was taken, stored at -20˚C and centralized for inspection. The kit was purchased from Sigma-Aldrich (St. Louis, MO, USA), and the microplate reader was purchased from Beijing Liuyi Instrument Factory (Beijing, China) with instruction steps were strictly followed. The progress of the disease was judged by the means of CT for regular re-examination in 1, 6 and 12 months after operation. The improvement in quality of life was evaluated by reference to the quality of life scale for tumor patients, with the full marks of 60 points, and the rate of bonus points of more than 75% means the quality of life has improved.

Table II. Comparison of surgical resection rate, margin negative rate and occurrence rate of perioperative complications [n (%)].

Groups	n	Surgical resection rate	Margin negative rate	Infection	Lung dysfunction	Bronchial or pleural fistula	Others[a]	Occurrence rate of complications
Observation	48	46 (95.8)	45 (93.8)	1	1	1	1	4 (8.3)
Control	40	32 (80.0)	31 (77.5)	2	3	3	2	10 (25.0)
χ^2		3.972	4.892					4.530
P-value		0.046	0.027					0.033

[a]Malnutrition, pressure sores, acute dysfunction of heart, liver, kidney and other organs.

Table III. Comparison of serum lipocalin-2, MMP-9 and CEA levels.

Groups	Lipocalin-2 (pg/ml)		MMP-9 (pg/ml)		CEA (μg/l)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation	0.13±0.04	0.05±0.01	50.4±8.7	24.3±9.6	6.8±1.4	3.1±0.5
Control	0.12±0.03	0.07±0.02	48.6±7.5	32.5±8.3	6.7±1.5	5.2±0.6
t-test	0.063	4.235	0.152	4.629	0.325	4.758
P-value	0.869	0.036	0.627	0.024	0.527	0.018

MMP-9, matrix metalloproteinase-9; CEA, carcinoembryonic antigen.

Statistical analysis. SPSS 19.0 software was used for data statistics (IBM SPSS, Armonk, NY, USA). Measurement data were expressed as mean ± standard deviation, independent sample t-test was applied for comparison between groups, and paired t-test was adopted for comparison in each group; the data were expressed as ratio, while the (correction) χ^2 test was used for comparison between groups. P<0.05 was considered to indicate a statistically significant difference.

Results

Comparison of operation time, intraoperative blood loss and postoperative drainage volume. The operation time, intraoperative blood loss and postoperative drainage volume of observation group were evidently lower than those of control group; the differences were statistically significant (Table I) (P<0.05).

Comparison of surgical resection rate, margin negative rate and occurrence rate of perioperative complications. The surgical resection rate and margin negative rate of observation group were higher than those of the control group while the occurrence rate of complications was lower than that of control group; the differences were statistically significany (Table II) (P<0.05).

Comparison of serum lipocalin-2, MMP-9 and CEA levels. The serum lipocalin-2, MMP-9 and CEA levels of two groups after the treatment were lower than those before, while the observation group had a more distinct decrease; the difference was statistically significant (Table III) (P<0.05).

Table IV. Comparison of follow-up of no tumor survival period, survival rate and quality of life.

Groups	n	No tumor survival period (month)	Survival rate	Quality of life
Observation	48	13.4	42 (87.5)	40 (83.3)
Control	40	10.2	28 (70.0)	26 (65.0)
χ^2		6.325	4.107	3.911
P-value		0.007	0.043	0.048

Comparison of follow-up of no tumor survival period, survival rate and quality of life. The follow-up time of two groups was 3-38 months and the median time was 20.5 months. No tumor survival period of observation group was prolonged, the survival rate and quality rate of life were enhanced, and the difference was statistically significant (P<0.05) (Table IV).

Discussion

NSCLC often presents as hidden onset as the early symptoms are often not typical. At the time of confirmed diagnosis, the condition of patients has often already developed into middle and advanced period so that the effect of surgery and postoperative radiotherapy and chemotherapy is unsatisfactory. CEA is embryonic cancer antigen and is present in low levels in normal human serum. When cancer cells lose polarity, they secrete CEA into the blood which causes CEA

serum levels to increase. Therefore, it has become one of most the widely used tumor markers with great sensitivity in lung cancer, breast cancer and liver cancer (7). Lipocalin-2 is a member of the apolipoprotein family that can regulate fat metabolism, osmotic pressure and immune response of the body. It also closely associates with proliferation, differentiation, invasion and other biological behaviors of malignant tumors (8). MMP-9 provides an extracellular microenvironment for the invasion and metastasis of tumors (9). Therefore, CEA, lipocalin-2 and MMP-9 can be used as effective observation indexes in the treatment of lung cancer.

In recent years, thoracoscopic lobectomy or sublobar resection surgery has been applied in the treatment of elderly patients with stage I NSCLC (10), the radioactive seed implantation also has been used in the treatment of early NSCLC patients who cannot receive surgery (11), which has actually led to an increase in cure rate. The pulmonary lobectomy and radiotherapy can cause greater trauma for patients, while localized lung resection has gradually become one of the stage I NSCLC radical operation instead of palliative replacement therapy. This significantly reduces the trauma and protects lung function to the utmost (12,13). Pulmonary segmental resection is the removal of the pulmonary artery and vein, the bronchial alveolar units and lymph nodes, with the same as pulmonary lobectomy that belongs to anatomical resection, conforming to principle of non-tumor treatment in surgical oncology (14). However, due to the accurate lung segment localization, better operating techniques and more experience in pulmonary resection are needed in pulmonary segmental resection. In addition, the postoperative 5-year survival rate of patients is approximately 30-60% and so the effect of a single surgical treatment is not good (15).

The neoadjuvant chemotherapy can significantly reduce the tumor mass, decrease the micro-metastasis of intraoperative tumor cells and thereby enhance the effect of surgical resection and improve long-term prognosis. Li *et al* (16) reported the results of neoadjuvant chemotherapy in the treatment of locally advanced NSCLC patients, and showed that the surgical resection rate significantly increased to 89.1%, intraoperative blood loss and operation time decreased, and the 3-year survival rate postoperatively significantly increased. Hu *et al* (17) administered neoadjuvant chemotherapy before radical resection of pulmonary carcinoma. Results indicated that the expression levels of lipocalin-2 and MMP-9 of tissues in the treatment group distinctly decreased and the total effective rate of treatment significantly increased to 91.7%. Our study implied that the operation time, intraoperative blood loss and postoperative drainage volume of observation group were evidently lower than those of control group and the surgical resection rate and margin negative rate of observation group were higher than those of control group. In addition, we demonstrated that while the occurrence rate of complications was lower than that of control group, the serum lipocalin-2, MMP-9 and CEA levels of observation group after the treatment were significantly lower than those of control group. The follow-up of no tumor survival period of observation group was prolonged, the survival rate and quality rate of life were enhanced, and the differences were statistically significant. In conclusion, localized lung resection combined with neoadjuvant chemotherapy can effectively improve the surgical effect of stage I-II NSCLC, prolong the survival period, enhance the survival rate, decrease the occurrence rate of complications and reduce the tumor related factors lipocalin-2, MMP-9 and CEA levels, which showed great safety and effectiveness of application.

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