Chemotherapy combined with intermittent microwave ablation in the treatment of oligometastatic non-small cell lung cancer

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Summary

Purpose: To observe the role of chemotherapy combined with microwave ablation in the treatment of oligometastatic non-small cell lung cancer (NSCLC).

Methods: 68 oligometastatic NSCLC patients were enrolled in this comparative study and randomly received chemotherapy with intermittent CT guided microwave ablation or chemotherapy only. The efficacy and the adverse effects were evaluated at 1, 3, and 6 months after treatment.

Results: Patients in the experimental group received microwave ablation after chemotherapy (n=34), complete remission (CR) was found in 8 cases (23.53%), partial remission (PR) in 16 cases (47.06%), and the total effective rate (CR+PR) was 70.59%. Microwave ablation with concurrent chemotherapy was performed in patients of the control group (n=33) and there were 0 patients of CR (0%), 12 patients of PR (36.36%), and the total effective rate (CR+PR) was 36.36% ($\chi^2=7.890, p<0.01$). The score of Karnofski performance status (KPS) in the experimental group was significantly higher ($p<0.05$). The median progression-free survival (PFS) in the control group and the experimental group was 3.6±0.2 months and 5.4±0.1 months ($\chi^2=42.731, p<0.01$). The incidence of pneumothorax and bloody sputum in the experimental group was higher than that in the control group ($\chi^2=6.031, p<0.05$). However, no evident differences were found regarding other common complications of microwave ablation and chemotherapy.

Conclusion: Chemotherapy combined with intermittent microwave ablation is superior to chemotherapy alone in improving the disease control rate and the quality of life of patients, as well as prolonging the PFS of patients.

Key words: chemotherapy, intermittent, microwave ablation, oligometastic, non-small cell lung cancer

Introduction

In recent years, the incidence and mortality of lung cancer in the world have shown an obvious upward trend, and have become the leading cause of death of malignant tumors [1]. Surgical treatment is still the first choice for radical treatment of primary bronchogenic carcinoma. However, due to the relatively low diagnostic level for lung cancer in the early phase, the high grade of malignancy of lung cancer and its complex biological characteristics and other reasons, most of the patients are diagnosed with lung cancer in the middle and advanced stages, and have lost the chance of surgical treatment [2]. Chemotherapy is the main treatment for advanced lung cancer patients [3]. Nevertheless, the mortality of advanced lung cancer is relatively high because of the side effects and drug resistance [4]. Since the concept of oligometastatic NSCLC has raised, the therapeutic strategies for oligometastatic NSCLC have changed over the last decade from palliative to curative intent [5].

Later, the development of minimally invasive tumor ablation therapy in malignant tumors guid-
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ed by B ultrasound or CT has attracted more and more attention [6-8]. At present, microwave ablation is widely used in the treatment of liver cancer at home and abroad, which can achieve the effect of killing cancer tissue in situ without surgery [9]. Microwave ablation therapy has its unique safety, minimally invasive and effective advantages in the treatment of malignant tumors. Microwave ablation combined with chemical therapy has gradually become one of the important means of clinical treatment of NSCLC [10].

According to the National Comprehensive Cancer Network (NCCN) guidelines, oligometastatic NSCLC can be treated locally with surgery or radiotherapy for local control, and combined with systemic chemotheraphy [3]. However, there are no related studies of chemotherapy combined with intermittent microwave ablation in the treatment of oligometastatic NSCLC.

Methods

Study population

Patients with advanced NSCLC confirmed by clinical, imaging and pathological examinations who were able to tolerate interventional therapy and chemotherapy were enrolled in Rizhao People’s Hospital affiliated to Jining Medical College from September 2012 to August 2013. The main symptoms were chest pain, hemoptysis, cough, expectoration, fatigue, anorexia, weight loss, etc. All patients signed the informed consent and volunteered to participate in this study. All the patients were randomly divided into the control group and the experimental group. Microwave ablation with concurrent chemotherapy was adopted in patients of the control group, and patients in the experimental group received microwave ablation after chemotherapy.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Inclusion criteria

1: Pathological diagnosis of lung cancer patients, also including patients with initial treatment; 2: Pulmonary solitary lesions with observable evaluation; with wild-type EGFR/ALK/ROS1; 3: Stage IV NSCLC with hepatic solitary metastasis only; 4: Patients without radiotherapy, chemotherapy, or molecular targeted therapy 3 weeks before treatment; 5: Normal function of heart and lung; 6: 18-70 years old regardless of gender; 7: The survival time was expected to be over 3 months; 8: Good physical condition, Karnofsky performance scale (KPS) score >70 points; 9: Patients with no serious diabetes or coagulopathy; 10: Routine examination showed no interventional treatment and chemotherapy contraindication; 11: Informed consent was signed by the patient and/or the family.

Exclusion criteria

1: Patients with pathologically diagnosed small cell lung cancer; 2: Patients with stage I-IIIA by TNM stage who were able to undergo surgical resection; 3: Patients who had been treated with chemotherapy or radiotherapy or surgery; 4: Senile and weak patients who were not expected to tolerate interventional therapy and chemotherapy and were expected to survive for <6 months; 5: KPS score <60 points; 6: Patients with heart, liver, kidney and other serious dysfunctions, or combined with diabetes and coagulopathy; 7: Pregnant and lactating women and all unmarried young patients.

Therapeutic treatment plan

All the patients were randomly divided into the control group and the experimental group. Control group: 6 cycles of chemotherapy alone. Experimental group: CT guided microwave ablation for hepatic metastasis after 2 cycles of chemotherapy, then, 2 cycles of chemotherapy were performed and CT guided microwave ablation was used to treat the pulmonary lesions, followed by another 2 cycles of chemotherapy.

Chemotherapy protocol

1: The GP protocol was used in NSCLC patients with squamous cell carcinoma confirmed histologically: Gemcitabine, 1000 mg/m² d1, d8; Cisplatin, 75 mg/m² (total dose) d1-3; or DP protocol: Docetaxel, 75 mg/m² d1; Cisplatin, 75 mg/m² (total dose) d1-3; 21 days for 1 cycle, in a total of 6 cycles.

2: The AP protocol was used in NSCLC patients with adenocarcinoma confirmed histologically: Pemetrexed, 500 mg/m² d1; Cisplatin, 75 mg/m² (total dose) d1-3; or DP protocol: Docetaxel, 75 mg/m² d1; Cisplatin, 75 mg/m² (total dose) d1-3; 21 days for 1 cycle, in a total of 6 cycles.

Microwave ablation

Instrument and equipment:

1: 16-slice spiral CT (Siemens, Germany); 2: Cool-tip microwave therapeutic apparatus (Fuzhong Medical High-Tech Co., Ltd); 3: Cool-tip microwave knife (Fuzhong Medical High-Tech Co., Ltd).

Preoperative preparation

1: Improvement of the heart and lung function, lung function could be tested in patients with suitable condition. Patients were given sedatives and cough medicines if they had cough, and hemostatic treatment was adopted if there was hemoptysis and bloody sputum; 2: The patient or the family members signed the informed consent prior to the operation as well as the informed consent for cool-tip microwave tumor ablation; 3: Before treatment all patients were subjected to laboratory tests including routine blood tests, blood coagulation time, liver and kidney function, blood sugar and biochemical tests, six serum hepatitis B markers and HIV tests.

Ablation procedure

CT scan was performed firstly, and the puncture point, the angle and the depth of the needle were deter-
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mined according to the scanning results. The approach of percutaneous access was determined by tumor size, morphology, location, adjacent structures, and process pathways. After local anesthesia with 5 ml 2% lidocaine, the microwave needle was inserted according to the designed angle and depth. Then, the CT scan was repeated to confirm the point of the needle to its intended position, and the long axis of the tumor was tried to be prolonged. The microwave needle was inserted to the far side of the tumor. Following the verification of the position of the needle tip, the puncture needle was fixed near the skin, and normal saline inlet pipe and the microwave tube were connected. Then, the water circulation system was opened, followed by the selection of the power according to the size of the lesion, the surrounding tissue and organ condition. 40-80 W were used generally.

Figure 1. Microwave ablation procedure in primary cancer. Plain CT scan was performed before puncture procedure to map the tumor size and location (A). For large mass, contrast-enhanced CT clearly showed vessels in the tumor to avoid bleeding caused by puncture damage. B: The step-by-step puncture procedure is shown in (C, D). Repeat ablation was performed to ensure complete ablation (E, F). Plain CT scan was performed after ablation procedure to exclude aerothorax and bleeding (G, H).

Figure 2. Microwave ablation procedure in cancer metastatic to the liver. Plain CT scan was performed before puncture procedure to map the tumor size and location (A). The step-by-step puncture procedure is shown in (B, C). Repeat ablation was performed to ensure complete ablation (D, E, F). Plain CT scan was performed after ablation procedure to exclude bleeding (G). MRI was performed in follow-up time to observe the recurrence in the ablation site (H).
and the treatment time was 12-20 min on the basis of the power size and local blood supply of the lesion. At the end of treatment, the patient was instructed to hold breath, the needle was pulled out in the course of treatment to prevent bleeding and needle track implantation. After therapy, CT scanning was performed to observe the changes of lesions and the occurrence of complications such as pneumothorax and hemothorax. The patients were instructed to stay in bed, in combination with the anti-infective treatment, hemostasis, relieving cough and pain. Intensive monitoring was performed to see if there were any surgical complications or other complications (Figure 1 and 2).

**Postoperative treatment**

1. The patients were transported back to the ward using oxygen bags and nasal catheters for oxygen inhalation, and were escorted by special medical staff.

2. The patients were transported to the ICU for 4 h and then transferred to the general ward when the situation was stable.

3. Chest radiographs were taken for patients 24 h or 48 h after surgery, to find secondary pneumothorax and hemothorax.

4. All the patients were given hemostatic drugs to prevent bleeding. The usage of antibiotics was determined according to the situation after operation to prevent infection.

**Evaluation criteria**

Patients in the control and the experimental group were evaluated with follow-up every 2 cycles of chemotherapy. Chest CT was conducted 1 month after microwave ablation, and whole abdominal and chest CT were reviewed at 1, 3, and 6 months after treatment. Simultaneously, CT enhanced scan was used to evaluate the activity of the lesions, and the efficacy was evaluated objectively according to the modified Response Evaluation Criteria in Solid Tumors (mRICIST) [10].

**Follow-up**

The effective rate was (CR+PR)/100*100%. For PD and dead patients, follow-up was terminated and PD patients received additional treatment. The PFS of the two groups was counted and the adverse reactions were observed in both groups at the same time.

**Statistics**

The data were analyzed by SPSS 16.0 software. Measurement data were compared using t test, and the χ² test was used in the comparison of enumeration data. Kaplan-Meier method and Log Rank test were applied for comparison of PFS between groups. The difference was statistically significant when p<0.05.

**Results**

**Clinical features**

A total of 67 patients were studied: 33 in the control group and 34 in the experimental group. The treatment program was successfully completed in both groups. Qualitative data including

<table>
<thead>
<tr>
<th>Variables</th>
<th>Treatment group (n=34)</th>
<th>Control group (n=33)</th>
<th>p value</th>
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<td>Patient related factors</td>
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<td>KPS (%)</td>
<td>81.18±7.29</td>
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<td>14 (42.4)</td>
<td></td>
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<tr>
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<td>0</td>
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<tr>
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<tr>
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<td>15</td>
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<tr>
<td>SCC</td>
<td>20</td>
<td>18</td>
<td></td>
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<tr>
<td>Lung tumor size (cm)</td>
<td>3.8±1.2</td>
<td>3.9±1.3</td>
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</table>

**Follow-up**

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**Results**

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A total of 67 patients were studied: 33 in the control group and 34 in the experimental group. The treatment program was successfully completed in both groups. Qualitative data including
gender, histopathology, and clinical stage were not statistically significant in the two groups at baseline (p>0.05). In addition, no obvious statistical difference was also found regarding quantitative data of age, tumor diameter, and KPS score at baseline (p>0.05) (Table 1).

KPS scoring improvement

There was no significant difference in KPS scores between the experimental group and the control group before the microwave ablation (p>0.05). The KPS scores at 1 months and 5 months after operation were significantly different between the experimental group and the control group, indicating statistical difference (p<0.05) (Table 2).

Short-term effects

In the control group (n = 33) the short-term effect was followed up for 6 months and there were 0 patients of CR (0%), 12 patients of PR (36.36%), and the total effective rate (CR+PR) was 36.36%. In the experimental group (n = 34) the short-term effect was followed up for 6 months, complete remission (CR) was found in 8 cases (23.53%), partial remission (PR) in 16 cases (47.06%), and the total effective rate (CR+PR) was 70.59%. The difference between the two groups was statistically significant (χ²=7.890, p<0.01), which was significantly lower in the control group than that in the experimental group.

Progression free survival (PFS)

The median PFS in the control group and the experimental group was 3.6±0.2 months and 5.4±0.1 months, and the difference was significant between groups (χ²=42.731, p<0.01). The corresponding median PFS was significantly shorter in the control group than the experimental group. The cumulative PFS curve is shown in Figure 3.

Figure 3. Kaplan-Meier method and Log Rank test were applied for comparison of PFS between groups. The difference was statistically significant (p<0.00043).
Adverse events

There were 5 cases (17.65%) of pneumothorax in the experimental group, which were obviously higher than that in the control group (0%), with statistical difference (p<0.05). The pulmonary compression accounted for 30% of the patients with pneumothorax after microwave ablation, and all patients were cured after oxygen inhalation or thoracic puncture and aspiration. The incidence of bloody sputum in the experimental group was higher than that in the control group (χ²=6.031, p<0.05); however, no evident differences were found regarding other common complications of microwave ablation and chemotherapy, including fever, chest pain, and myelosuppression (p>0.05), which are illustrated in Table 3.

Discussion

The quality of life of cancer patients attracts more and more attention, especially for the elderly patients. The treatment should not merely prolong the patient’s survival, but also consider the quality of life of the patient. In this study, statistical difference (p<0.05) was observed regarding the KPS score of the experimental group which was higher than that of the control group 1 month after treatment although there was no significant difference in preoperative KPS score between the two groups (p<0.05), indicating that microwave ablation may delay the deterioration in quality of life. We believe that microwave ablation can nearly completely kill tumor tissue, and some patients can even achieve the equivalent of surgical results, which help reduce the tumor burden and achieve tumor free survival, thereby improving the quality of life and mental state of the patients.

In the study conducted by Ronot et al [10], advanced NSCLC was treated with chemotherapy combined with microwave ablation, and it was estimated that the overall objective effective rate was 74.4%, median PFS was 8.7 months, and overall survival was 21.3 months, which was significantly better than that of the single chemotherapy group. Xu et al performed a clinical trial to compare the effect of microwave ablation combined with concurrent chemoradiotherapy and concurrent chemoradiotherapy for locally advanced NSCLC, the results of which showed that the ratio of effective rates were 85.1% versus 80.4% for mediastinal lymph node (p=0.843) and 83.0% versus 100% for pulmonary tumors (p=0.503), respectively, for the RT and ablation groups. Kaplan-Meier analysis demonstrated 2-year OS rate of NSCLC patients in the ablation group was higher than in the RT group, but without statistical difference (log-rank, p=0.297) [11]. In the present study, the evaluation criteria for clinical effect were divided into two aspects. Considering short-term effect, follow-up 6 months later showed that the effective rates of the experimental group and the control group were 70.59% and 36.36%, respectively. The effective rate of the experimental group was higher than that of the control group, and the difference between the two groups was statistically significant (χ²=7.890, p<0.01). The mean PFS in the control group and the experimental group was 3.6±0.2 months and 5.4±0.1 months, respectively, and the difference was significant (χ²=42.731, p<0.01). Previous studies have shown that microwave ablation has synergistic effects with systemic chemotherapy [12-14]. A possible reason may be that chemotherapy can kill G1-S tumor cells, while microwave can kill tumor cells in different phases without distinction. Microwave can effectively kill local tumor tissue, while systemic chemotherapy can kill tumors of the circulatory system and metastasis. At the same time, microwave can enhance the immune function of the organism and help reverse the immune suppression caused by chemotherapy. Therefore, it is speculated that microwave ablation therapy has some synergistic effects with chemotherapy.

In this study, 34 patients in the experimental group successfully completed the operation, and no serious complications occurred during the microwave ablation. In the experimental group postoperatively, there were 5 cases (17.65%) of pneumothorax in the experimental group, which was obviously

<table>
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<th>Variables</th>
<th>Treatment group (n=34)</th>
<th>Control group (n=33)</th>
<th>p value</th>
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</thead>
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<tr>
<td>Pneumothorax</td>
<td>6 (17.65)</td>
<td>0</td>
<td>0.025</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>13 (38.24)</td>
<td>4 (12.12)</td>
<td>0.014</td>
</tr>
<tr>
<td>Fever</td>
<td>2 (5.88)</td>
<td>1 (3.03)</td>
<td>0.511</td>
</tr>
<tr>
<td>Chest pain</td>
<td>9 (26.47)</td>
<td>7 (21.21)</td>
<td>0.614</td>
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<tr>
<td>Myelosuppression</td>
<td>6 (17.65)</td>
<td>8 (24.24)</td>
<td>0.507</td>
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Table 3. Adverse events in the two groups
higher than that in the control group (0%), with statistical difference (p<0.05). The pulmonary compression accounted for 30% of the patients with pneumothorax after microwave ablation, and all patients were cured after oxygen inhalation or thoracic puncture and aspiration. The incidence of pneumothorax after CT guided percutaneous pulmonary biopsy was estimated to be about 14.4-17.87%, which was similar to that of the incidence of pneumothorax in the study [15,16]. Pneumothorax may be caused by microwave puncture for pleural lesions. Secondly, it may be correlated with the relative movement of the visceral and parietal pleura caused by respiratory movements, especially in coughing, which may cause the incision of the puncture needle to the pleura, so as to stimulate pneumothorax [17]. To reduce the incidence of pneumothorax after microwave ablation, patients should undergo meticulous breath holding training before surgery, and should be given treatment for severe cough. In addition, adequate intra-operative anesthesia could prevent the patient from severe pain.

In this study, the coagulation function was normal in both the experimental group and the control group; 13 patients (38.24%) had bloody sputum in the experimental group, which was significantly higher than in the control group (12.12%), with statistical difference (χ²=6.031, p<0.05). The main reason of bloody sputum in the experimental group was the damage of microwave puncture to lung parenchyma. To reduce the incidence of bloody sputum or bleeding after microwave ablation, enhanced scan should be performed before surgery to map the distribution and location of the surrounding vessels. Meanwhile, during the preoperative CT scan, the image should be analyzed carefully. Appropriate puncture approach should be carefully selected to avoid puncture damage to larger vessels. Besides, the frequency of punctures should be reduced as much as possible to achieve success at one puncture. At the end of the puncture operation, repeat CT scans should be performed to observe if there is dynamic bleeding at the site of the puncture. For patients with hemoptysis or bloody sputum, preoperative hemostasis should be given. At the same time, surgery should be carried out by experienced operator who has systematic training, which may help improve the safety and accuracy of microwave ablation treatment, and to reduce the incidence of pneumothorax, hemothorax and bloody sputum [18,19].

In this study, the preoperative blood routine tests and inflammatory indexes were checked in both the experimental and the control group, showing no evidence of obvious infection. There was no difference in the incidence of fever between the experimental and the control group after the microwave ablation treatment (p>0.05). In the experimental group, there were 2 cases of fever after microwave ablation, the temperature was less than 38.5°C which was considered to be absorption fever. The temperature turned to normal within 3 days without antibiotic treatment. As for the incidence of myelosuppression, there were 6 cases (17.65%) in the experimental group and 8 cases in the control group (24.24%) without significant difference between groups (p>0.05), suggesting that microwave ablation may not cause myelosuppression.

In conclusion, microwave ablation combined with chemotherapy is an effective treatment for advanced NSCLC. Ablation of the lesion during chemotherapy is more advantageous in improving PFS than after chemotherapy without significant adverse effects.

However, the sample size of this study was small, and the observation time was short due to the limitation of time, therefore the accuracy of the conclusion and its long-term effect, such as the overall survival rate of patients, should be further studied.

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Conflict of interests

The authors declare no conflict of interests.

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