Treatment options for pulmonary multifocal ground glass opacity type adenocarcinoma: Surgery combine thermal ablation?

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ABSTRACT

Objectives: To retrospectively analyze the clinical results of the treatment of pulmonary multifocal adenocarcinoma presenting as ground glass opacity (GGO) by surgery and thermal ablation.

Methods: 87 GGO-type pulmonary adenocarcinomas of 48 patients (14 males and 34 females; mean age: 59.7 years old ± 9.9, range: 33–79 years old) had been treated from March 2015 to March 2019. Treatment means included 43 wedge resections, 7 segmentectomy, 17 lobectomies, and 20 thermal ablations. The indication selected for treatment means, safety, and local tumor progression rate were evaluated.

Results: No operation-related death occurred in all patients. 42 times of surgery were performed and 67 carcinomas were resected in 42 patients. 23 times of single-port Video-assisted thoracoscopic surgery (VATS), 8 times of two-port VATS and 11 times of three-port VATS were performed in total. There were 2 cases of air leak (exceeding 1 week), 1 case of chylothorax and 1 case of massive pleural effusion. Time duration of surgery was between 60 and 300 mins (mean: 167 mins). Intra-operative blood loss was between 5 and 300 mL (mean: 44 mL). Time of chest drainage was between 2 and 23d (mean 4.9d). Chest drainage volume was between 14 and 4633 mL (mean: 872 mL). Post-operation LOS (length of stay) was between 3 and 25d (mean: 6.2d). 15 times of thermal ablation were performed (1 case of air leak) and 20 carcinomas were ablated in 14 patients. The ablation time was between 30 and 120 min (mean: 43 min); post-operation LOS was between 1 and 10d (mean: 3.5d). During the mean follow-up period (16 months ± 13) (range: 5–60 months), no local tumor progression occurred.

Conclusions: Surgery and thermal ablation are safe and effective options for the treatment of pulmonary multifocal GGO-type adenocarcinoma.

1. Introduction

In 1996, the Fleischner Society proposed the concept of pulmonary ground-glass opacity (GGO), which referred to the slightly increased-density shadows of bronchial and vascular markings shown on high-resolution computed tomography (CT) images. Its pathogenic factors included tumor, infection, local hemorrhage, and interstitial fibrosis. Based on the existence of the solid components in GGO, it is generally classified into pure GGO (pGGO) and mixed GGO (mGGO). pGGO and mGGO are also known as subsolid nodules. The common pathological types of GGO-type tumor include atypical adenomatous hyperplasia (AAH), adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), and invasive adenocarcinoma.

In recent years, a number of pulmonary multifocal GGO cases have increased significantly, and approximately 20%–30% of the resected GGO samples have been accompanied by other multiple intrapulmonary small GGO focuses. Studies suggested that these nodules had multicentric origins rather than being categorized as T3 or T4 stage using the tumor-node-metastasis (TNM) staging system. Moreover, these nodules should be treated as multiple primary lung cancers. The current main treatment methods for pulmonary multifocal GGO are forming a troika including the following: surgery, stereotactic body radiation therapy (SBRT), and thermal tumor ablation (including radiofrequency ablation, microwave ablation, and cryoablation). The prognosis after the surgical resection of pulmonary multifocal GGO is satisfactory, and postoperative 5-year disease-free survival rate is comparable to that of single stage I pulmonary adenocarcinoma. Prognosis will not be affected even if sub-lobectomy is performed. SBRT has a limitation in determining the targeted volume and difficulty in repeated treatments; hence, this surgical treatment is being challenged by thermal tumor ablation. Through the retrospective analysis of clinical results of the treatment for pulmonary multifocal GGO-type adenocarcinoma by surgery and thermal ablation, this paper preliminarily investigates the basic principles for the selection of treatment options.

2. Methods

2.1. Patient population

A total of 87 GGO-type pulmonary adenocarcinomas of 48 patients...
(14 men and 34 women; mean age, 59.7 years ± 9.9; range, 33–79 years) were treated between March 2015 and March 2019 (see Table 1). There were 30, 4, 8, 29, and 14 focuses in the right upper lung, right middle lobe, right lower lobe, left upper lobe, and left lower lobe, respectively. These focuses included 52 pGGOs and 35 mGGOs. The pathology of 2 focuses was not obtained, and in the remaining focuses, there were 7 AAHs, 27 AISs, 19 MIAs, and 32 adenocarcinomas, all without lymph node metastasis.

2.2. Treatment

Surgery or thermal ablation can be considered based on the anatomical position, size, and quantity of GGO.

Surgery: the incision option includes single-port, two-port, and three-port video-assisted thoracoscopic surgery (VATS). Regarding the range of resection, wedge resection, segmentectomy, or lobectomy can be selected according to the focus size, position, and distribution. Focuses are distributed bilaterally; thus, the one-stage or two-stage surgery is selected.

Thermal ablation: radiofrequency ablation, microwave ablation, or cryoablation can be selected. Ablation range is defined as the inactivation of target tumor and surrounding 0.5–1 cm normal tissues with GGO as the target. One-stage or two-stage ablation can be used for ≤3 unilateral pulmonary GGOs or ≤5 bilateral pulmonary GGOs.

All patients underwent chest CT approximately 4 weeks after treatment (baseline) and subsequently repeated chest CT once every 3 months. Comparison with baseline CT was made to observe whether local progression or relapse occurred.

2.3. Statistical analyses

The Statistical Package for the Social Sciences version 23.0 statistical package was used to establish database and input data. The numerical variables conforming to normal distribution are represented by \( \bar{x} \pm \text{SD} \), and the independent samples t-test was used to compare the differences between the two groups. The numerical variables that do not conform to normal distribution are represented by \( M (Q_{25}, Q_{75}) \), and the rank-sum test was used to compare the differences between the two groups. Two independent samples were subjected to the Mann–Whitney U test. Multiple independent samples were subjected to the Kruskal–Wallis test.

Table 1

| Item                        | Sex Male: 14 | Female: 34 |
|-----------------------------|-------------|------------|
| Age                         | 59.7 years ± 9.9 (range, 33–79 years) |            |
| Position                    | Right upper lobe: 30 | Right middle lobe: 4 | Right lower lobe: 29 | Left upper lobe: 14 | Left lower lobe: 8 |
| Size                        | 1.16 cm ± 0.78 (range, 0.40–4.3 cm) |            |
| Operation                   | Surgery: 34 | Surgery + thermal ablation: 8 |
| Thermal ablation            | 6 |

Table 2

| Item                        | Thermal ablation (n = 15) | Surgery (n = 42) | P value |
|-----------------------------|--------------------------|-----------------|---------|
| Age (years)                 | 59.67 ± 9.92             | 59.36 ± 8.81    | 0.917   |
| Blood loss (mL)             | 0                        | 44 ± 53         | 0.000   |
| Operation time (min)        | 43 ± 25                  | 167 ± 67        | 0.000   |
| Drainage volume (mL)        | 59 ± 230                 | 821 ± 1015      | 0.000   |
| Extubation time (day)       | 2.3 ± 2.7                | 4.9 ± 3.6       | 0.013   |
| Postoperative LOS (day)     | 3.5 ± 3.0                | 6.2 ± 3.7       | 0.016   |
| Expense (yuan)              | 34,524 ± 15,709          | 67,480 ± 29,143 | 0.000   |

3. Results

No operation-related death and severe complication were observed in all patients.

3.1. Surgery

Surgery was performed 42 times, and 67 carcinomas were resected in 42 patients. Single-port, two-port, and three-port VATS were performed 23, 8, and 11 times in total, respectively. The treatments included 43 wedge resections, 7 segmentectomies, and 17 lobectomies. There were 2 cases of air leak (exceeding 1 week), 1 case of chylothorax, and 1 case of massive pleural effusion. Time duration of surgery was between 60 and 300 min (mean, 167 min). Intraoperative blood loss was between 5 and 300 mL (mean, 44 mL). Time of chest drainage was between 2 and 23 days (mean, 4.9 days). Chest drainage volume was between 14 and 4653 mL (mean, 872 mL). Postoperative length of stay (LOS) was between 3 and 25 days (mean, 6.2 days).

3.2. Thermal ablation

Thermal ablation (radiofrequency ablation or microwave ablation) was performed (1 case of air leak) 15 times, and 20 carcinomas were ablated in 14 patients. The ablation time was between 30 and 120 min (mean, 43 min), and postoperative LOS was between 1 and 10 days (mean, 3.5 days).

3.3. Comparison between surgery and thermal ablation

Thermal ablation and VATS showed statistical differences in blood loss volume (\( t = 5.314, P = 0.000 \), operation time (\( t = 10.458, P = 0.000 \)), drainage volume (\( t = 4.912, P = 0.000 \)), drainage time (\( t = 3.061, P = 0.010 \)), LOS (\( t = 2.832, P = 0.014 \)), and expense (\( t = 4.635, P = 0.000 \) (Table 2)).

Thermal ablation and VATS based on different ports showed statistical differences in blood loss volume (\( F = 8.211, P = 0.000 \)), operation time (\( F = 18.187, P = 0.000 \)), drainage volume (\( F = 3.837, P = 0.015 \)), and expense (\( F = 6.375, P = 0.001 \)). Further variance analysis (LSD test) revealed that the blood loss volumes of thermal ablation and single-port VATS were significantly lesser than those of two-port (\( P = 0.000 \)) and three-port VATS (\( P = 0.000 \)). Thermal ablation time was significantly shorter than the duration of single-port (\( P = 0.000 \)), two-port (\( P = 0.000 \)), and three-port VATS (\( P = 0.000 \)). Drainage volume of thermal ablation was significantly lesser than those of single-port (\( P = 0.020 \)), two-port (\( P = 0.003 \)), and three-port VATS (\( P = 0.038 \)). Extubation time of thermal ablation was significantly lesser than that of single-port VATS (\( P = 0.035 \)). Expense of thermal ablation was significantly lesser than those of single-port (\( P = 0.001 \)), two-port (\( P = 0.000 \)), and three-port VATS (\( P = 0.011 \) (Table 3)).

During the mean follow-up period (16 months ± 13) (range, 5–60 months), no local tumor progression was observed.

Considering the fact that each patient can have multiple operations performed, we did not analyze the effect of operations on perioperative results and local recurrences.

4. Discussion

Each focus of pulmonary multifocal GGO is independent. Some argue that the main focus would influence prognosis, whereas others believe
that not only the main focus but also the size of secondary focuses and consolidation should also be taken into consideration, specifically the change of consolidation. The International Association for the Study of Lung Cancer Staging Commission suggests that the prognosis of multifocal GGO/lepidic growth pulmonary adenocarcinoma largely depends on the highest T stage of the main focus in the TNM staging system.1 Furthermore, a Japanese study of 246 patients with multifocal GGO demonstrated that both main focus and secondary focus influence the survival rate.2 In a retrospective study of 67 patients undergoing surgical resection (39 complete resections) of pulmonary multifocal GGO, Shimada3 found that unresected GGOs only showed 8% change, and 23% of patients had a new focus. Multivariate analysis revealed that the main focus size and consolidation were associated with prognosis, and secondary or residual focus and their growth condition or formation of a new focus had no influence on prognosis. Other studies also demonstrated that a patient’s prognosis will not be affected after the resection of the main focus regardless if secondary focuses continuously grow, a new focus is formed, or residual focuses are not treated.4 Therefore, it is necessary to preferentially treat the main focus and also take secondary focuses into consideration. Considering the group in this study, secondary focuses were small pGGOs; hence, only main focuses of 13 patients were treated. No change was detected in the observation of secondary focuses. Among patients who had nodules within the same pulmonary lobe, 8 patients underwent wedge resection plus wedge resection and 2 underwent lobectomy. Among patients who had nodules within the ipsilateral different pulmonary lobes, 6 patients underwent wedge resection plus wedge resection, 5 underwent segmentectomy plus wedge resection, and 3 underwent lobectomy plus wedge resection. For nodules located bilaterally, patients’ physical conditions should be considered in addition to the above principles: one-stage operation (2 cases of wedge resection plus thermal ablation and 1 case of thermal ablation plus lobectomy) or two-stage operation (3 cases of lobectomy then thermal ablation, 1 case of wedge resection plus wedge resection then thermal ablation, and 1 case of wedge resection then thermal ablation). In all cases of two-stage operation, the interval was longer than 1 month. A short interval between two operations is not beneficial to a patient’s recovery after surgery and may increase the risk of thermal ablation.

Retrospective analysis revealed that GGO with a consolidation/tumor ratio (CTR) < 0.5 had no metastasis to the pulmonary hilus or mediastinal lymph node, 10% of GGOS with CTR ≥0.5 had metastasis, and AAH, AIS, MIA, and lepidic-dominant adenocarcinomas and invasive mucinous adenocarcinoma had no lymph node metastasis.12-14 These conclusions provided theoretical foundation for the treatment of pGGO and even mGGO (CTR <0.5) by thermal tumor ablation,5-14 specifically if the patient was not suitable for or refused operation, including the impossibility of reoperation due to poor pulmonary functions after main focus resection (9 case), combined cardiopulmonary diseases and advanced age (2 case), and presence of a deep focus and refusal to undergo operation (3 cases). One patient was found to have evident enlargement of two focuses (exceeding 2 mm) during follow-up. However, these two focuses were deep, and the patient refused to undergo lobectomy. After communication, pathological examination was not performed, and ablation was performed directly. However, several differences exist between the thermal ablation of GGO-type pulmonary adenocarcinoma and that of solid pulmonary nodule. First, the former is poorly defined and thus requires wider range of ablation. Second, the nodule of the former contains air, and heat sink effect is evident; thus, it is necessary to enhance the thermal transmission via intranodular saline irrigation or increased temperature. Finally, GGO or bleeding around the ablated GGO influences the evaluation of ablation effects. These factors may lead to problems including the specificity of therapeutic effect evaluation and high local progression rate. However, comparison of pre- and post-thermal ablation CT images can effectively overcome this shortcoming and reduce recurrence rate. Furthermore, thermal ablation has the following potential advantages: it is safe, conformal, and minimally invasive; has few complications, has reliable effects, and has low cost; results in rapid recovery; and can be repeated.

The present study indicates that thermal ablation is characterized by almost no hemorrhage, short operation time, short postoperative LOS, and low expenses. Compared with thermal ablation, single-port wedge resection is the more preferred treatment because it results in low blood loss volume and short operation time and can achieve complete pathology and lymph node sampling. However, if segmentectomy or lobectomy is required for the operation, thermal ablation should be considered.

5. Conclusions

In consideration of the low lymph node metastasis rate and multiple focuses of pulmonary multifocal GGO-type adenocarcinoma, surgery and thermal ablation are the safe and effective treatment options for the treatment of such type of disease. The application of thermal ablation does not exclude surgical intervention. Thermal ablation may expand the indications for hybrid surgery. However, further studies on how to combine these two methods are required.

Ethical approval

The study was approved by the ethics committee of Xuanwu Hospital, Capital Medical University. All clinical practices and observations were conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from each patient before the study was conducted.

Patient consent

Written informed consent was obtained from patients for publication of these case reports and any accompanying images.

Declaration of competing interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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