The efficacy and safety of radiofrequency ablation in the treatment of inoperable patients with pulmonary malignant nodules

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Research Article

Keywords: Radiofrequency ablation, Pulmonary malignant nodules, Efficacy, Safety.

Posted Date: November 30th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-2317899/v1

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Abstract

Objective: Radiofrequency ablation (RFA) has been recently applied as an alternative treatment in the patients with pulmonary malignancies. The aim of our study was to assess the incidence of complications and survival rate of RFA for malignant lung nodules, and evaluate the efficacy and safety of RFA in the treatment of inoperable patients with pulmonary malignant nodules.

Methods: The clinical data of 50 patients (34 men and 16 women) aged 74.2 (range 65-84) years with primary (n=42) and metastatic (n=8) lung malignant nodules treated with RFA from June 2015 and July 2017 in Hebei General Hospital were considered for this study, and the characteristics and clinical data of these patients were analyzed. Complications, progression-free survival, and overall survival at 1, 2 and 5 years of these patients were evaluated.

Results: Following the procedure. There were no major complications and deaths during the operation. 26 (52%) patients presented mild-to-moderate chest pain that was easily controlled by analgesic drugs. 8 (16%) patients with pneumothorax, 4 (8%) haemoptysis, 6 (12%) pneumonia, 7 (14%) pleural effusion, and 1 (2%) postoperative bronchopleural fistula. Needle-track implantation was observed in 2 (4%) patients. Median progression-free survival (PFS) was 24.6 months (range, 6.8-60 months). The PFS at 1, 2, 5 years was 76%, 52%, and 20% respectively. Median overall survival (OS) was 35.5 months (range 10.2-60 months). The OS at 1, 2, and 5 years was 80%, 58%, and 32%, respectively.

Conclusion: RFA is a safe and effective alternative treatment for the inoperable patients with primary or metastatic pulmonary malignant nodules. The clinical impact and long-term results of RFA need to be further confirmed in a larger series of patients, and RFA should ideally be compared with surgery.

Introduction

There are about 600,000 new lung cancer cases worldwide every year. As a malignant tumor with the highest mortality, lung cancer has posed a serious threat to people's life safety[1]. Surgical resection is still the standard treatment in resectable patients with primary pulmonary cancer or pulmonary solitary metastatic nodule and offers the best chance of cure[2]. However, approximately two-thirds of all non-small cell lung cancer (NSCLC) patients are ineligible for curative resection due to cardiopulmonary comorbidities, concomitant extrapulmonary diseases and/or advanced age[3]. The lung is also the second most frequent organ of metastasis. Local treatment may be useful in patients with pulmonary solitary metastatic lesion[4].

Imaging-guided radiofrequency ablation (RFA) has been proved to be effective in the treatment of liver tumors[5–7]. More recently, it has been used to treat renal, adrenal, thyroid, and breast neoplasms [8–11]. RFA is a technique that relies on the delivery of RF energy through an electrode inserted in the tumor mass to generate a localised high temperatures field that heats the target tissue, causing necrosis [12]. During the past few years, Computed tomography (CT)-guided RFA has been evaluated as an alternative minimally invasive treatment option for these nonsurgical lung malignant nodule candidates [12–15].
The main advantage of CT-guided RFA is shorter hospital stay, lower cost, and fewer complications to the patients [16].

The clinical safety and efficacy of RFA are still under discussion for lung cancer patients [12], the aim of our study was to assess the incidence of complications and survival rate of RFA for malignant lung nodules, and evaluate the efficacy and safety of RFA in the treatment of inoperable patients with pulmonary malignant nodules.

**Materials And Methods**

Between June 2015 and July 2017, 50 patients (34 men and 16 women) aged 65–84 (mean 74.2) years underwent CT-guided RFA of pulmonary nodules at the Department of Thoracic Surgery of the Hebei General Hospital in China. All patients had primary or secondary pulmonary malignant nodules and were considered inoperable due to poor cardiopulmonary status, the presence of other extrapulmonary diseases, patient refusal of surgery or advanced age. As for comorbidities, 32 patients with chronic obstructive pulmonary disease (COPD), 22 patients with severe emphysema, 16 patients with heart failure, 18 patients with coronary heart disease, and 8 patients with extrapulmonary malignancy. The characteristics of the enrolled patients were shown in Table 1. The data were obtained from the Department of Medical Record Statistics of Hebei General Hospital.

<table>
<thead>
<tr>
<th>Patients’ characteristics</th>
<th>Number of patients (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Average 74.2 ± 3.7</td>
</tr>
<tr>
<td></td>
<td>Range 65–84</td>
</tr>
<tr>
<td>Gender</td>
<td>Male 34 (68%)</td>
</tr>
<tr>
<td></td>
<td>Female 16 (32%)</td>
</tr>
<tr>
<td>Tumor type</td>
<td>NSCLC 42 (84%)</td>
</tr>
<tr>
<td></td>
<td>Pulmonary metastasis 8 (16%)</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>Present 32 (64%)</td>
</tr>
<tr>
<td>Severe emphysema</td>
<td>Present 22 (44%)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Present 16 (32%)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>Present 18 (36%)</td>
</tr>
<tr>
<td>Extrapulmonary malignancy</td>
<td>Present 8 (16%)</td>
</tr>
</tbody>
</table>
The study protocol, which was concordant with the principles of the Helsinki Declaration, was approved by the Institutional Ethics Committee (ID: 706409, Hebei General Hospital, Shijiazhuang, China). This study was a retrospective study of medical records and the ethics committee waived the requirement for informed consent. A total of 50 patients with malignant lung nodules were enrolled into our study, of which 42 patients (84%) were primary lung cancer and 8 patients (16%) were metastases from extrapulmonary diseases. The 8 metastatic tumors were diagnosed at pathologic biopsy (4 patients) or development of new pulmonary lesions in patients with known metastatic disease elsewhere (4 patients). The primary malignancies were as follows: colorectal carcinoma, 4 patients; and one patient each with endometrial carcinoma, renal cell carcinoma, gallbladder carcinoma, and breast carcinoma. The mean diameter of pulmonary malignant nodules was 1.8 cm (range 0.9–2.7 cm). The diagnosis of all enrolled patients were confirmed by cytology or histology.

The following were done before the operation: physical examination and medical history taking; enhanced chest CT; electrocardiography; pulmonary function testing. Laboratory tests including blood routine, liver and kidney function, tumor markers, blood gas analysis, coagulation panel were also performed before the operation. Water deprivation was used 2 hours before treatment.

Before CT-guided RFA, all enrolled patients underwent an accurate clinical and anesthesiological assessment and signed informed consent. Continuous cardiac, blood pressure and oxygen saturation monitoring were performed throughout the procedures. RFA was performed by thoracic surgeons. The patient was prepped in the prone, lateral, or supine ecubitus position, depending on the preselected electrode insertion tract (a straight line passing from the skin surface through an intercostals space to the centre of the nodules). The pathway chosen represented the shortest and most direct path to the tumor that did not intersect any major airways or blood vessels. Patients were given morphine as analgesic therapy before the RFA operation. The best insertion position was selected under CT scan guidance. After disinfecting the skin at the needle entry site, local anesthesia was performed with 15 ml of 2% lidocaine layer by layer, the 22-gauge Chiba needle was inserted into the deepest part of the nodule under CT scan guidance through the chest wall and part of lung tissue. The RF generator was started and power was progressively increased until impedance reached values that blocked further energy delivery. Because increased impedance is an effect of necrosis in the target area, energy is only delivered until complete necrosis of the target tissue is achieved. CT scans were performed during the procedure to assess both the results of the ablation – typically manifested as a perilesional ground-glass opacity – and the extent of possible pneumothorax or haemorrhage. The tine was retracted and the needle path was ablated simultaneously.

Follow-up CT was obtained immediately postprocedure then follow-up CT evaluations were conducted every 3 months up to 2 years and every 6 months up to 5 years after the procedure. The mean follow-up for all patients was 37.8 months (range, 10.2–60 months).

**Statistical analysis**
Continuous data were presented as the mean ± standard deviation (SD). Categorical data were expressed as number (percentage). All statistical analyses were performed using IBM SPSS Version 21 (SPSS Statistics v21, IBM Corporation, Somers, NY, USA).

Results

The CT-guided percutaneously RFA was successfully performed in all enrolled 50 patients. Each of the 50 lung nodules was treated in a single RFA session and received a single electrode insertion. There were no major complications and deaths during the operation. None of the patients experienced severe pain following operation. Mild-to-moderate chest pain was complained by 26 patients (52%) after RFA, which lasted for 3–12 h and was easily controlled by analgesic drugs. Post-treatment CT scan revealed pneumothorax in 8 cases (16%), among which 3 patients were self-limiting and 5 patients required closed thoracic drainage. Other minor complications included: four patients (8%) developed haemoptysis which was relieved by conservative treatment; 6 patients (12%) complained of fever due to pneumonia which was successfully treated by prolonging antibiotic therapy. Pleural effusion was occurred in 7 patients (14%), among whom 4 cases (9.5%) were self-absorption without special treatment and other 3 patients required drainage. Needle-track implantation was observed in 2 (4%) patients, 4–6 months after RFA. One patient (2%) developed postoperative bronchopleural fistula which was cured by prolonging closed thoracic drainage. The perioperative complications of all enrolled patients were shown in Table 2.

Table 2: Analysis of patients’ perioperative complications

<table>
<thead>
<tr>
<th>Complications</th>
<th>N = patients(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain</td>
<td>26(52%)</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>8(16%)</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>4(8%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>6(12%)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>7(14%)</td>
</tr>
<tr>
<td>Needle-track implantation</td>
<td>2(4%)</td>
</tr>
<tr>
<td>Bronchopleural fistula</td>
<td>1(2%)</td>
</tr>
<tr>
<td>Major cardiopulmonary complications</td>
<td>0(0%)</td>
</tr>
<tr>
<td>Perioperative death</td>
<td>0(0%)</td>
</tr>
</tbody>
</table>

All 50 patients underwent chest CT scan at the first month after operation as baseline assessment. And then follow-up CT evaluations were conducted every 3 months up to 2 years and every 6 months up to 5 years after the procedure. The lesion was larger or more than at baseline, indicating the progression of the disease. The median follow-up was 37.8 months (range, 10.2–60 months). Median progression-free
survival (PFS) was 24.6 months (range, 6.8–60 months). Median overall survival (OS) was 35.5 months (range 10.2–60 months). The PFS at 1, 2, 5 years was 76%, 52%, and 20% respectively. The OS at 1, 2, and 5 years was 80%, 58%, and 32%, respectively. 23 (67.6%) patients died of cardiopulmonary failure or advanced age and not related to malignant lung nodules. 11 (32.4%) patients died of progression of primary lung cancer or metastasis from extrapulmonary cancer. The prognostic outcome of RFA was shown in Table 3.

Table 3: Outcome of RFA in 50 patients assessed at 1, 2 and 5 years

<table>
<thead>
<tr>
<th>Variables</th>
<th>1-year</th>
<th>2-years</th>
<th>5-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression-free survival rate (PFS%)</td>
<td>38 (76%)</td>
<td>40 (80%)</td>
<td>10 (20%)</td>
</tr>
<tr>
<td>Overall survival rate (OS%)</td>
<td>26 (52%)</td>
<td>29 (58%)</td>
<td>16 (32%)</td>
</tr>
</tbody>
</table>

Discussion

In the present study, we conducted CT-guided percutaneously RFA in 50 pulmonary malignant nodules. The overall survival rate in 1, 2 and 5 years were 80%, 58%, and 32%, respectively. 23 (67.6%) patients died of cardiopulmonary failure or advanced age and not related to malignant lung nodules. The results of the current study indicated that RFA maybe a safe and effective alternative for local control of NSCLC and pulmonary metastatic nodules for patients who were ineligible for curative surgery due to cardiopulmonary comorbidities, concomitant extrapulmonary diseases and/or advanced age.

The imaging-guided percutaneously RFA introduced in 1990 for the treatment of hepatic tumors has been widely used as the preferred ablative technique in the treatment of renal, adrenal, thyroid, lung and breast neoplasms throughout the world[17]. RFA was a recognized technique for treating various kinds of solid tumor because of its minimally invasive procedure and maximum function reserved [18]. Since it was performed in lung tumor in 2000, however the clinical safety and efficacy of RFA has become the main concern due to its wide application [19]. Reports from Caroline et al showed that 30-day mortality related to the CT-guided RFA was 0.4–2.6% [20, 21]. In our study, There were no major fatal complications and deaths within 30 days after operation. All these results demonstrated that RFA is a safe procedure in clinical practice. Lencioni et al. [22] conducted the first prospective, intention-to-treat, multi-center clinical trial with the aim of evaluating the feasibility, safety, and effectiveness of RFA in the treatment of lung malignancies in 2008. Overall survival was 70% at 1 year and 48% at 2 years in patients with NSCLC. Baere et al. [23] reported their experience of RFA in treating lung metastases in 566 patients with 1,037 metastases In 2015. They found the 4-year PFS was 44.1%. In the present study, the overall survival (OS) rate and progression free survival (PFS) rate for patients with pulmonary malignant nodules were 80% and 76% at 1 year, 58% and 52% at 2 years and 32% and 20% at 5 years, which was consistent with previous study. A total of 32 patients (64%) died of various causes during the 60-month follow-up in our study, among which 23 (67.6%) patients died of cardiopulmonary failure or advanced age and not related to malignant lung nodules. 11 (32.4%) patients died of progression of primary lung cancer or metastasis.
from extrapulmonary cancer. Therefore, the CT-guided RFA should only be performed under suitable patients’ election criteria and following adequate guidance and training.

The most complications after CT-guided percutaneously RFA was chest pain (52%), which might result from thermal injury to the pleural nerve. Postoperative chest pain was easily controlled by anaglesic drugs within 12 hours after operation. The incidence of pneumothorax was 16% in our study. Most pneumothorax occurred in elderly patients with emphysema, most of whom were easily handled by conservative treatment or closed chest drainage. Only one patient developed a bronchopleural fistula due to prolonged air leakage. Eventually, the duration of the chest tube drainage was more than 1 month for this patient with bronchopleural fistula. Other complications after RFA include haemoptysis, pneumonia, pleural effusion and needle-track implantation. Most patients were cured within a short period of time following operation and were discharged successfully. Based on our results, we consider RFA was a safe and well-tolerated procedure in the treatment of pulmonary malignant nodules.

A total of 34 patients passed away during up to 60 months of follow-up. 23 (67.6%) patients died of cardiopulmonary failure or advanced age and not related to malignant lung nodules. 11 (32.4%) patients died of progression of primary lung cancer or metastasis from extrapulmonary cancer. RFA has a satisfactory local control effect on malignant lung nodules from our result. On the other hand, the participants enrolled into our study were ineligible for surgery due to accompanied with cardiopulmonary comorbidities, extrapulmonary diseases and/or advanced age, which contributed to the majority patients dying from other causes during follow-up. In the Lijun Huang et al[24] study enrolled 329 patients, 78% patients showed local progression with intrapulmonary tumor after RFA treatment. The main reason of which was the patients with tumor larger than 4 cm might have a higher ratio of local progression. Wolf also [25] observed that tumor size was a predictor of recurrence after RFA. All of the patients had lesions smaller than 3cm in this study, which also led to a excellent local control rate. Based on our results, the criteria regarding eligibility of patients to RFA were as follow: 1. The patients have a single peripheral lesion surrounded completely by lung parenchymal; 2. The lesions with a maximum diameter of 3cm were not contiguous to the hilum or the main bronchial, arterial or venous branches or to mediastinal structures such as the trachea, esophagus, heart, aorta and great arteries; 3. The patient didn't have hilar and mediastinal lymph node involvement or extrapulmonary disease, or extrapulmonary disease was well controlled.

Some limitations of this study should be pointed out. First, the enrolled patients were limited, which inevitably contributed to some bias. The main reason was patients who were suitable for RFA were limited. Secondly, this study was a retrospective study, and we did not include patients who didn't receive any treatment as the control group. In the following study, a well-designed, randomized controlled trial should be conducted to comprehensively evaluate the efficacy and safety of CT-guided RFA. All these limitations should be addressed in the following study.

**Conclusion**
In conclusion, the present study indicates that RFA can be a safe and effective alternative treatment for the inoperable patients with primary or metastatic pulmonary malignant nodules. The clinical impact and long-term results of RFA need to be further confirmed in a larger series of patients, and RFA should ideally be compared with surgery.

**Abbreviations**

NSCLC: non-small cell lung cancer;

RFA: Radiofrequency ablation;

CT: Computed tomography;

COPD: chronic obstructive pulmonary disease;

SD: standard deviation;

PFS: Progression-free survival;

OS: Overall survival;

**Declarations**

**Ethics approval and consent to participate**

This study was a retrospective study and conducted after permission from the ethics committee in Hebei General Hospital, and the informed consent of patients was not required.

**Consent for publication**

Not applicable.

**Availability of data and material**

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

**Competing interests**

The authors have declared that no conflict of interest exists in this study.

**Funding**

No funding was involved in this study.

**Authors' contributions**
Peng Qie designed the study. Huien Wang and Lijun Liu performed operation for all enrolled patients, Xuejiao Xun and Xiaodong Nie collected the data, Hongshang Cui analysed the data and performed statistical analyses. Peng Qie and Qifan Yin drafted the manuscript. Peng Qie gave important intellectual contribution and critically revised the manuscript. All authors read and approved the final manuscript.

Acknowledgements

The authors would like to thank Huien Wang and Lijun Liu for their hard work in the operation and all colleagues in the Department of thoracic surgery for their support to our research.

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