# Fever after Lung Radiofrequency Ablation: Prospective Evaluation of its Incidence and Associated Factors

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**Abstract**

**Purpose:** To prospectively investigate the incidence of post-lung radiofrequency (RF) ablation fever as well as its associated factors, according to the grade of fever.

**Materials and Methods:** A total of 56 patients who underwent 67 lung RF sessions were analyzed. Post-ablation fever (≥37.0°C) was graded according to the Common Toxicity Criteria of Adverse Events v. 4.0. Fever ≥37.0°C and <38.0°C was defined as grade 0 fever. The 67 RF sessions were divided into two groups according to the presence of post-ablation fever, and the factors associated with fever were determined using univariate and multivariate analyses. Subsequently, the RF sessions accompanied by post-ablation fever were further divided into two groups according to the grade of fever (grade 0 vs. grade ≥1), and the factors associated with the grade of fever were determined.

**Results:** Grade 0, 1, and 2 fever accompanied 36 (54%), 11 (16%), and 2 (3%) sessions, respectively. Post-ablation fever was significantly associated with larger ablated parenchymal volume ($P = 0.001$) and development of pulmonary infiltration ($P = 0.004$). Additionally, development of pulmonary infiltration ($P = 0.048$) was also significantly and independently associated with higher grade of fever in the multivariate analysis.

**Conclusions:** The incidences of grade 0, 1, and 2 post-ablation fever were 54%, 16%, and 3%, respectively. Larger ablated parenchymal volume and development of pulmonary infiltration were found to be associated with the development of post-ablation fever, with the latter being an independent factor associated with higher grade of fever.

**Keywords**

Lung

Radiofrequency ablation

Fever

Pulmonary infiltration

## 1. Introduction

After radiofrequency (RF) ablation, patients commonly develop a fever, which is assumed to be a part of the so-called post-ablation syndrome, resulting from an inflammatory response to the necrotic tissue along with cytokine production [1, 2]. The reported incidences of fever after RF ablation in the abdomen are quite variable, ranging from 7–42% [1-5], with the incidence of fever >38°C reported to be as low as 3% in one previous study [6]. Similarly, the reported incidences of fever after RF ablation in the lung also vary, ranging from 7–73% [7-11]. Based on our 10-year experience of lung RF ablation, we noticed that the post-ablation fever occurred more frequently and at a higher grade than that after RF ablation in the abdominal solid organs. Indeed, a retrospective study by our group [11] showed that the incidences of fever >37.0°C and >38.0°C after lung RF ablation were 73% and 28%, respectively. However, there are only limited prospective studies investigating the incidence of post-RF ablation fever according to the grade. Another retrospective study by Nomura et al. [12] showed that larger tumor size and previous external-beam radiotherapy were significantly associated with increased C-reactive protein (CRP) levels after RF ablation of lung tumors. However, prospective studies investigating the factors associated with post-ablation fever are currently lacking. Therefore, this study was conducted to prospectively investigate the incidence of, and factors associated with, post-lung RF ablation fever, according to the grade of fever.

## 2. Materials and methods

This study was a prospective study, designed and approved by the relevant institutional review board (approval number, 1082), and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

### *2.1. Inclusion and Exclusion Criteria and Study Population*

During the study period (May 2011 to September 2012), 72 consecutive RF ablation sessions were performed in 60 patients at our institution. The inclusion criterion for this study was patients who agreed to participate in this study. The exclusion criteria included patients with body temperature ≥37.0°C, CRP level >1 mg/dL, and/or a white blood cell count >8500/μL before RF ablation, as preexisting infection and/or inflammation would make it difficult to evaluate the presence of post-ablation fever. Of the total 60 patients (72 sessions), four patients (five sessions) were excluded from the study: two patients (two sessions) owing to a CRP level >1 mg/dL before RF ablation and two patients (three sessions) who refused to provide consent. Finally, the study included 56 patients (32 men and 24 women; mean age, 63.1 years) who underwent 67 RF sessions. The characteristics of the study population are summarized in Table 1.

*2.2. Study Endpoint*

The endpoint of this study was fever after lung RF ablation. The incidence of post-ablation fever according to the grade was calculated. Subsequently, the factors associated with the presence and grade of fever were evaluated.

*2.3. RF Ablation Techniques*

RF ablation was performed for patients who were considered not to be candidates for surgery or who refused to undergo surgery, and for whom the treatment of lung cancer was expected to contribute to prolonged survival. The procedure was not performed in patients with leukopenia, thrombopenia, coagulation disturbances, substantial organ dysfunction, or poor general condition. For example, patients with a leucocyte count < 3,000 cells/μL, platelet count <50,000/μL, prothrombin time-international ratio >1.5, poor pulmonary function (predicted forced respiratory volume in 1 s ≤ 1000 mL), poor cardiac function (New York Heart Association Class ≥ III), uncontrollable diabetes (HbA1c >7.0), and/or performance status ≥2 were not candidates for RF ablation.

All patients received lung RF ablation on an inpatient basis. The details of the RF ablation techniques used at our institution have been previously described [13]. Briefly, the procedure was performed percutaneously using computed tomography (CT) fluoroscopy under local anesthesia alone or under local plus epidural anesthesia, along with conscious sedation. A multitined expandable electrode (LeVeen; Boston Scientific, Natick, MA) or an internally cooled electrode (Cool-tip; Covidien, Mansfield, MA) was used. Although the former was preferred for lung RF ablation, the latter was used for cases in which the use of a multitined expandable electrode was deemed dangerous, such as those where the tumor was located close to large vessels or the heart. The aim of the procedure was to achieve ablation of the tumor with a margin of at least 5 mm. Whenever necessary, multiple overlapping ablations were performed. Immediately after the procedure, chest CT images were obtained to assess the ablation zone and potential complications.

*2.4. Examination Protocol*

Pre-ablation examinations included complete blood count, biochemical tests, blood coagulation tests, chest radiography, chest CT, and pulmonary function tests. Furthermore, serum sialylated carbohydrate antigen, Krebs von den Lungen-6 (KL-6) and surfactant protein D (SP-D) were also measured. KL-6 is a mucinous high-molecular weight glycoprotein expressed on type II pneumocytes [14], while SP-D is a hydrophilic glycoprotein produced mainly by Clara cells and type 2 pneumocytes [15]; these markers are used for evaluating the activity of interstitial pneumonia [14, 15].

Complete blood count, biochemical tests, and chest radiography were performed 1 and 2 days after RF ablation, and chest CT and serum KL-6 and SP-D measurements were performed 2 days after RF ablation. The patients stayed in the hospital for at least 2 days after RF ablation and were discharged after any potential symptoms, including fever, and/or complications subsided. In addition, a complete blood count, biochemical tests, and chest CT were performed 1 month after RF

ablation on an outpatient basis.

*2.5. Evaluation of Post-ablation Fever*

During the hospital stay, body temperature was measured at least twice a day after the RF ablation. After discharge, the body temperature was investigated using a questionnaire. The maximal value of body temperature in the first month after RF ablation was used for the subsequent analyses. Post-ablation fever was deemed present when the maximum body temperature was ≥37.0°C. Fever was graded according to the Common Toxicity Criteria of Adverse Events (CTCAE) v. 4.0. Because fever <38.0°C is not graded in this version of the CTCAE, fever ≥37.0°C and <38.0°C was defined as grade 0 fever in this study. Other clinical adverse events (e.g., cough, dyspnea, malaise, and nausea) were also investigated and graded according to the CTCAE v. 4.0. The worst grade of those events in the first month after RF ablation was adopted.

To determine the factors associated with post-ablation fever, multiple variables were analyzed, including patient-related factors (e.g., age, gender, presence of pulmonary emphysema, history of previous radiation, and the KL-6, SP-D, and pulmonary function values before RF ablation), lesion-related factors (e.g., cancer type, distance from the pleura to the tumor, and tumor volume), and procedure-related factors (e.g., type of electrode used, maximum RF power, RF application time, ablated parenchymal volume, and development of pulmonary infiltration after RF ablation).

Pulmonary emphysema was deemed present when bullae, blebs, or centrilobular or panlobular emphysema were observed anywhere in the lungs upon chest CT images. With regard to the distance from the pleura, the shortest distance to the nearest pleura from the tumor was used for the analyses. When multiple tumors were treated during a session, the RF application time was defined as the sum duration of the RF energy application for all treated tumors. The tumor and ablation zone volumes were calculated using the following formula: $\pi/6 \times$ maximum diameter $\times$

diameter perpendicular to the maximum diameter × diameter in the craniocaudal direction. The diameters of the ablation zones were measured on CT images obtained 2 days after RF ablation. The ablated parenchymal volume was calculated by subtracting the tumor volume from the ablation zone volume. When multiple tumors were ablated, the sum of the tumor volume and the ablated parenchymal volume were used.

A representative case showing no development of pulmonary infiltration is shown in Fig. 1. On the CT images on day 2 after RF ablation, the ablation zone became denser and clearer but was similar in size and distribution compared with that immediately after RF ablation, as reported previously [16]. On the other hand, pulmonary infiltration was deemed to have developed when infiltrative opacities became apparent on the CT images on day 2 after RF ablation, beyond and/or away from the ablation zone on the CT images obtained immediately after RF ablation (Fig. 2 and 3). Development of pulmonary infiltration was evaluated with the consensus of a chest radiologist and an interventional radiologist.

For the analyses, the 67 RF sessions were first divided into two groups according to the presence or absence of post-ablation fever. To determine the factors associated with development of fever, the above-mentioned variables were compared between the two groups using univariate analyses. Student's *t* test was used to analyze numerical values, and the $\chi^2$ test or Fisher's exact test was used to analyze categorical values. Subsequently, variables that were significant in the univariate analyses were subjected to multivariate logistic regression analysis to determine the independent factors associated with fever development. Moreover, the sessions accompanied by post-ablation fever were further divided into two groups according to the grade of fever: grade 0 vs. grade ≥1 fever, and similar univariate and multivariate analyses were performed to determine the factors associated with the grade of fever.

*2.6. Steroid Therapy*

Considering that corticosteroids are potent inhibitors of inflammation [17], patients who fulfilled at least two of the following criteria were treated with steroid therapy: 1) maximum temperature of ≥38°C until day 2, 2) a CRP level of ≥10 mg/dL on day 2, 3) pulmonary infiltration apparent on CT on day 2. Intravenous administration of methylprednisolone 125 mg, along with a prophylactic oral antibiotic, was initiated on day 2 and continued for 3 days.

*2.7. Pulmonary Infiltration*

For cases in which pulmonary infiltration developed after RF ablation, the distribution of the pulmonary infiltration on the CT images was noted, and the incidence of pulmonary infiltration was calculated according to the grade of post-ablation fever. Further, the KL-6 and SP-D values after RF ablation in the cases of pulmonary infiltration were compared with those before RF ablation using a paired *t* test.

*2.8. Statistical Analysis*

For all analyses, $P < 0.05$ was considered statistically significant. Analyses were performed using the Statistical Package for the Social Sciences (SPSS) software (version 19.0; IBM, Armonk, NY).

## 3. Results

*3.1. Post-ablation Fever*

Grade 0, 1, and 2 fever occurred after 36 (54%), 11 (16%), and 2 (3%) sessions, respectively, while no fever was seen after 18 (27%) sessions. Table 2 shows clinical findings according to the grade of fever. Mean CRP values on day 2 were 0.95 mg/ dl, 3.3 mg/dl, 12.1 mg/dl, and 20.1 mg/dl in the patients with no, grade 0, 1, and 2 fever, respectively. The 49 patients with fever were accompanied with a total of 19 events of grade 1 cough, 3 events of grade 1 or 2 dyspnea, 24 events of grade 1 malaise, and 6 events of grade 1 nausea. There were no grade 3 or more events.

No patient developed lung abscess or sepsis. Steroid therapy was prescribed for 15 cases. Among those, 10 cases showed fever ≥38°C until day 2.

Table 3 shows the results of the univariate and multivariate analyses to identify the factors associated with the development of post-ablation fever. Univariate analyses showed that larger ablated parenchymal volume ($P = 0.001$) and development of pulmonary infiltration ($P = 0.004$) were significantly associated with the development of fever. However, neither of these factors remained significant in the multivariate analysis.

Table 4 shows the results of the univariate and multivariate analyses to identify the factors associated with the grade of post-ablation fever. The univariate analyses showed that the presence of pulmonary emphysema ($P = 0.004$), larger ablated parenchymal volume ($P = 0.016$), and development of pulmonary infiltration ($P = 0.001$) were significantly associated with grade 1 or 2 fever. Among those, development of pulmonary infiltration ($P = 0.048$; odds ratio, 10.1) was the only significant independent factor in the multivariate analysis.

*3.2. Pulmonary Infiltration*

Pulmonary infiltration appeared after 27 (40%) out of 67 sessions. In these cases, infiltrative opacities were evident in the surrounding parenchyma contiguous with the ablation zone, and the opacities tended to exhibit a nonsegmental and gravity-dependent distribution (Fig. 2 and 3). In all 27 cases, the opacities were no longer apparent on CT one month after RF ablation.

Pulmonary infiltration developed in 11% (2/18), 36% (13/36), 83% (10/12), and 100% (2/2) of the sessions accompanied by no fever, grade 0, grade 1, and grade 2 fever, respectively. In the cases of pulmonary infiltration, the mean KL-6 and SP-D values were 306.8 U/mL and 55.6 ng/mL, respectively, before RF ablation, while the corresponding values after RF ablation were 274.9 U/mL and 43.0 ng/mL, respectively, showing significant decreases ($P < 0.001$ for KL-6 and $P = 0.001$ for SP-D).

## 4. Discussion

Carrafiello et al. [1] showed that fever (≥37.5℃) occurred in six (11%) of 53 patients undergoing RF ablation of abdominal tumors, Wah et al. [2] showed that 15 (42%) of 36 patients developed low-grade fever (≥37°C) after RF ablation of hepatic or renal tumors, and Dodd et al. [3] showed that fever occurred after 16 (32%) of 50 RF ablation sessions for hepatic tumors. In addition, two groups showed that fever after RF ablation of liver metastases occurred in 7% and 8% of the cases [4, 5], while Rossi et al. showed that the rate of fever >38°C after RF ablation of small hepatic cancer was 3% [6]. On the other hand, this prospective study showed that the incidences of post-ablation fever ≥37.0°C and ≥38.0°C were 73% and 19%, respectively, which were similar to those shown in our previous retrospective study [11]. Of note, in this study, post-ablation fever appeared to be more frequent and of a higher grade than that after RF ablation in the abdomen reported in previous studies. Although the incidence of grade 2 fever was 3%, this result may be underestimated because of application of steroid therapy to selected cases.

Dodd et al. [3] reported that the tumor volume, ablated tissue volume, ablated hepatic parenchymal volume, and post-ablation aspartate aminotransferase levels were significantly related to post-ablation syndrome after RF ablation for hepatic tumors, and Nomura et al. [12] showed that large tumor size and previous external-beam radiotherapy were associated with increased CRP levels after RF ablation of lung tumors. In the present study, while tumor volume or previous radiation therapy did not significantly correlate with the presence or grade of fever, ablated parenchymal volume was a significant factor for the development of post-ablation fever in this study. Moreover, development of pulmonary infiltration was also found to be significantly associated with the development of fever, and it was the only independent factor for higher grade of fever in the multivariate analysis. The risk of developing post-ablation fever and grade 1 or 2 fever was 4.5 times

and 10 times higher for patients with development of pulmonary infiltration than those without it. Further, the incidence of pulmonary infiltration increased along with the grade of post-ablation fever, and we speculate that this lung-specific phenomenon may be one of the reasons for fever being more frequent and of a higher grade after lung RF ablation compared to after RF ablation in the abdomen.

In a subset of cases, bronchiolitis obliterans organizing pneumonia (BOOP)-like reactive pneumonitis [18], interstitial pneumonia [12], and aspiration pneumonia [19] may develop after lung RF ablation, with reported incidences of 0.4%, 0.6%, and 1%, respectively. Lee et al. [20] described a case of acute respiratory distress syndrome, and Okuma et al. [21] reported a case of acute deterioration of interstitial pneumonia; however, the distribution of the pulmonary infiltration in this study appeared different from that of BOOP-like reactive pneumonitis and aspiration pneumonia. Based on the CT findings and background and time course of the patients, acute respiratory distress syndrome, acute deterioration of interstitial pneumonia, and interstitial pneumonia were deemed unlikely in the cases of pulmonary infiltration. Further, the KL-6 and SP-D values did not increase after RF ablation in these cases. Therefore, we suggest that the pulmonary infiltration in this study showed different etiology from the previously reported cases of pneumonia. Yamamoto et al. [22] investigated the time course of histopathological changes in an ablated region in a normal porcine lung. The ablated zone at 3 days post-ablation consisted of three layers: the outermost layer showed severe congestion accompanied by hemorrhage, neutrophil infiltration, and fibrin deposition; the intermediate layer comprised alveolar spaces filled with exudates; and the innermost layer comprised necrotic tissue. We speculate that the pulmonary infiltration seen in our cases was primarily caused by exudates distributed from the ablation zone to the surrounding parenchyma through the pores of Kohn and canals of Lambert. This assumption is supported by the nonsegmental and gravity-dependent distribution of the infiltrative opacities. We further presume that cytokines, induced by proinflammatory mediators in the exudates, were dispersed into vessels of the

parenchyma affected by the pulmonary infiltration, followed by systemic spreading, and this may explain the observed association between pulmonary infiltration and post-ablation fever. As previously reported [16], pulmonary infiltration may result from hemorrhage and/or edema. Although we suggest that the main mechanism of pulmonary infiltration was not hemorrhage or edema, given the association with post-ablation fever, it should be noted that we did not investigate the etiology and mechanism of pulmonary infiltration in this study, which did not include histopathological analyses, and this is a major limitation of the present study. Accordingly, future studies focusing on this point are warranted.

Our study may give some suggestions to manage the patients who undergo lung RF ablation. First, prophylactic use of anti-inflammatory drugs may be considered especially for the patients at a high risk of high fever (i.e., those with pulmonary emphysema or in whom marginal parenchyma is extensively ablated). As a matter of course, however, it should be decided on a case-by-case basis, taking into account general condition and comorbidities of the patient. Second, given that post-ablation fever was rarely accompanied with severe clinical symptoms, other causal complications such as sepsis and abscess should be ruled out for the patients who develop severe symptoms along with high fever. Such complications after lung RF ablation have been described in literature [10-12, 23].

## 5. Conclusion

The incidences of grade 0, 1, and 2 fever after lung RF ablation were 54%, 16%, and 3%, respectively. Larger ablated parenchymal volume and development of pulmonary infiltration were identified as significant factors associated with the development of fever. Further, development of pulmonary infiltration was also found to be an independent factor associated with higher grade of fever.

**References**

[1] Carrafiello G, Laganà D, Ianniello A, et al. Post-radiofrequency ablation syndrome after percutaneous radiofrequency of abdominal tumours: one centre experience and review of published works. Australas Radiol 2007; 51:550–4.

[2] Wah TM, Arellano RS, Gervais DA, et al. Image-guided percutaneous radiofrequency ablation and incidence of post-radiofrequency ablation syndrome: prospective survey. Radiology 2005; 237:1097–102.

[3] Dodd GD 3rd, Napier D, Schoolfield JD, Hubbard L. Percutaneous radiofrequency ablation of hepatic tumors: postablation syndrome. AJR Am J Roentgenol 2005; 185:51–7.

[4] Van Tilborg AA, Meijerink MR, Sietses C, et al. Long-term results of radiofrequency ablation for unresectable colorectal liver metastases: a potentially curative intervention. Br J Radiol 2011; 84:556–65.

[5] Lencioni R, Goletti O, Armillotta N, et al. Radio-frequency thermal ablation of liver metastases with a cooled-tip electrode needle: results of a pilot clinical trial. Eur Radiol 1998; 8:1205–11.

[6] Rossi S, Buscarini E, Garbagnati F, et al. Percutaneous treatment of small hepatic tumors by an expandable RF needle electrode. AJR Am J Roentgenol 1998; 170:1015–22.

[7] Lee JM, Jin GY, Goldberg SN, et al. Percutaneous radiofrequency ablation for inoperable non-small cell lung cancer and metastases: preliminary report. Radiology 2004; 230:125–34.

[8] Rossi S, Dore R, Cascina A, et al. Percutaneous computed tomography-guided radiofrequency thermal ablation of small unresectable lung tumours. Eur Respir J 2006; 27:556–63.

[9] Kang S, Luo R, Liao W, Wu H, Zhang X, Meng Y. Single group study to evaluate the feasibility and complications of radiofrequency ablation and usefulness of post treatment position emission tomography in lung tumours. World J Surg Oncol 2004; 2:30.

[10] Yasui K, Kanazawa S, Sano Y, et al. Thoracic tumors treated with CT-guided radiofrequency

ablation: initial experience. Radiology 2004; 231:850–7.

[11] Sano Y, Kanazawa S, Gobara H, et al. Feasibility of percutaneous radiofrequency ablation for intrathoracic malignancies: a large single-center experience. Cancer 2007; 109:1397–405.

[12] Nomura M, Yamakado K, Nomoto Y, et al. Complications after lung radiofrequency ablation: risk factors for lung inflammation. Br J Radiol 2008; 81:244–9.

[13] Hiraki T, Gobara H, Mimura H, et al. Radiofrequency ablation of lung cancer at Okayama University Hospital: a review of 10 years of experience. Acta Med Okayama 2011; 65:287–97.

[14] Kobayashi J, Kitamura S. KL-6: a serum marker for interstitial pneumonia. Chest 1995; 108:311–5.

[15] Honda Y, Kuroki Y, Matsuura E, et al. Pulmonary surfactant protein D in sera and bronhioalveolar lavage fluids. Am J Respir Crit Care Med 1995; 152:1860–6.

[16] Goldberg SN, Gazelle GS, Compton CC, McLoud TC. Radiofrequency tissue abation in the rabbit lung: efficacy and complications. Acad Radiol 1995; 9:776–84.

[17] Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids--new mechanisms for old drugs. N Engl J Med. 2005; 353:1711–23.

[18] Hiraki T, Gobara H, Kato K, Toyooka S, Mimura H, Kanazawa S. Bronchiolitis obliterans organizing pneumonia after radiofrequency ablation of lung cancer: report of three cases. J Vasc Interv Radiol 2012; 23:126–30.

[19] Soga N, Yamakado K, Gohara H, et al. Percutaneous radiofrequency ablation for unresectable pulmonary metastases from renal cell carcinoma. BJU Int 2009; 104:790–4.

[20] Lee JM, Jin GY, Goldberg SN, et al. Percutaneous radiofrequency ablation for inoperable non-small cell lung cancer and metastases: preliminary report. Radiology 2004; 230:125–34.

[21] Okuma T, Matsuoka T, Hamamoto S, Nakamura K, Inoue Y. Percutaneous computed tomography-guided radiofrequency ablation of lung tumors complicated with idiopathic interstitial

pneumonia. Ann Thorac Surg 2009; 87:948–50.

[22] Yamamoto A, Nakamura K, Matsuoka T, et al. Radiofrequency ablation in a porcine lung model: correlation between CT and histopathologic findings. AJR Am J Roentgenol 2005; 185:1299–306.

[23] Fernando HC, De Hoyos A, Landreneau RJ, et al. Radiofrequency ablation for the treatment of non-small cell lung cancer in marginal surgical candidates. J Thorac Cardiovasc Surg. 2005; 129:639–44.

**Figure captions**

**Fig. 1.** A representative case of grade 0 fever after radiofrequency (RF) ablation of a pulmonary metastasis, showing no pulmonary infiltration.

(a) Computed tomography (CT) fluoroscopic image obtained during RF ablation showing the multitined expandable electrode (arrow) deployed to the tumor (arrowhead), with the patient in the prone position.

(b) CT image immediately after RF ablation showing ground-glass opacities (arrows), suggesting an ablation zone surrounding the tumor. Note that the image was obtained with the patient in the prone position but was turned upside down in order to facilitate a comparison with image (c). Arrowheads indicate pneumothorax.

(c) CT image obtained 2 days after RF ablation showing that the ablation zone has become denser and clearer but is similar in size and distribution, compared with that immediately after RF ablation

**Fig. 2.** A representative case of grade 1 fever after radiofrequency (RF) ablation of a pulmonary metastasis.

(a) CT fluoroscopic image obtained during RF ablation showing the multitined expandable electrode (arrow) deployed to the tumor (arrowhead).

(b) CT image immediately after RF ablation showing ground-glass opacities (arrows), suggesting an ablation zone surrounding the tumor. The arrowheads indicate a drainage chest tube for the pneumothorax.

(c) CT image obtained 2 days after RF ablation showing infiltrative opacities beyond the ablation zone. Note that the opacities tend to exhibit a gravity-dependent distribution. The arrowhead indicates a chest tube.

**Fig. 3.** A representative case of grade 1 fever after radiofrequency (RF) ablation of a pulmonary metastasis.

(a) Computed tomography (CT) image obtained before RF ablation showing a small nodule (arrow) in the right upper lobe.

(b) CT image obtained immediately after RF ablation showing ground-glass opacities (arrows), suggesting an ablation zone.

(c) CT image obtained 2 days after RF ablation showing infiltrative opacities (arrows) beyond the ablation zone. Note that the opacities tend to exhibit a gravity-dependent distribution.

## Tables

Table 1. Characteristics of Patients, Lesions, and Procedures

| Variable | | Value |
|---|---|---|
| Patient characteristics (n = 56) | | |
| Age (y) | Mean ± SD (Range) | 63.1 ± 10.6 (31–81) |
| Gender | Male/Female | 32/24 |
| Emphysema | Yes/No | 12/44 |
| Previous radiation | Yes/No | 3/53 |
| Lesion characteristics (n = 67) | | |
| Cancer type | Primary/Secondary | 6/61 |
| Laterality of the lung | Right/Left | 36/31 |
| Tumor size (mm) | Mean ± SD (Range) | 12.2 ± 8.3 (4–55) |
| Distance from pleura (mm) | Mean ± SD (Range) | 11.4 ± 12.4 (0–41) |
| Procedure characteristics (n = 67) | | |
| Electrode | Multitined expandable | 58 |
| | Internally cooled | 8 |
| | Both | 1 |

SD = standard deviation.

Table 2. Clinical findings according to the grade of fever.

| | | Post-ablation fever (no. of sessions) | | | |
|---|---|---|---|---|---|
| | | No (n = 18) | Grade 0* (n = 36) | Grade 1 (n = 11) | Grade 2 (n = 2) |
| CRP value (mg/dl)** | Mean ± SD | 0.95 ± 0.66 | 3.3 ± 5.7 | 12.1 ± 7.9 | 20.1 ± 7.0 |
| Cough | Absent/Grade 1/Grade 2 | 15/3/0 | 26/10/0 | 4/7/0 | 0/2/0 |
| Dyspnea | Absent/Grade 1/Grade 2 | 18/0/0 | 34/2/0 | 10/0/1 | 2/0/0 |
| Malaise | Absent/Grade 1/Grade 2 | 11/7/0 | 21/15/0 | 3/8/0 | 1/1/0 |
| Nausea | Absent/Grade 1/Grade 2 | 17/1/0 | 32/4/0 | 9/2/0 | 2/0/0 |

CRP = C-reactive protein, SD = standard deviation

*Grade 0 fever is defined as fever ≥37.0°C and <38.0°C.

**value on day 2

Grades of cough, dyspnea, malaise and nausea are the worst grades until 1 month.

Table 3. Results of Univariate and Multivariate Analyses of Multiple Variables to Determine the Factors associated with Post-ablation Fever

| Variable | | Univariate analysis | | | Multivariate analysis | |
|---|---|---|---|---|---|---|
| | | Post-ablation fever (no. of sessions) | | | | |
| | | Yes (n = 49) | No (n = 18) | *P* value | Odds ratio (95% CI) | *P* value |
| Age(y) | Mean ± SD | 61.5 ± 10.7 | 65.6 ± 9.7 | 0.16 | | |
| Gender | Male/Female | 28/21 | 12/6 | 0.58 | | |
| Emphysema | Yes/No | 11/38 | 4/14 | 1.00 | | |
| Previous radiation | Yes/No | 3/46 | 1/17 | 1.00 | | |
| KL-6 before RF ablation (U/mL) | Mean ± SD | 294 ± 123 | 262 ± 157 | 0.40 | | |
| SP-D before RF ablation (ng/mL) | Mean ± SD | 61.0 ± 40.4 | 63.5 ± 49.8 | 0.83 | | |
| FEV(L) | Mean ± SD | 2.42 ± 0.78 | 2.16 ± 0.83 | 0.23 | | |
| FVC(L) | Mean ± SD | 3.15 ± 0.95 | 3.00 ± 0.91 | 0.54 | | |
| $FEV_1$(%) | Mean ± SD | 76.8 ± 8.3 | 70.9 ± 12.7 | 0.08 | | |
| Cancer type | Primary/Secondary | 4/45 | 2/16 | 0.66 | | |
| Distance from pleura (mm) | Mean ± SD | 10.4 ± 11.7 | 14.2 ± 14.3 | 0.27 | | |
| Tumor volume ($cm^3$) | Mean ± SD | 1.73 ± 5.43 | 2.26 ± 7.48 | 0.75 | | |
| Electrode* | Multitined expandable/Internally cooled | 42/6 | 16/2 | 0.62 | | |
| Max power (w) | Mean ± SD | 62.3 ± 27.6 | 61.7 ± 33.8 | 0.94 | | |
| Radiofrequency application time (min) | Mean ± SD | 29.3 ± 16.4 | 25.1 ± 13.3 | 0.33 | | |
| Ablated parenchymal volume ($cm^3$) | Mean ± SD | 29.1 ± 18.9 | 17.1 ± 8.2 | 0.001 | 1.05 (0.99-1.12) | 0.13 |
| Development of pulmonary infiltration | Yes/No | 25/24 | 2/16 | 0.004 | 4.51 (0.82-24.8) | 0.083 |

SD = standard deviation, KL-6 = Krebs von den Lungen-6, SP-D = surfactant protein D, RF = radiofrequency, FEV = forced expiratory volume, FVC = forced vital capacity, $FEV_1$ = forced expiratory volume in 1 s to forced vital capacity, CI = confidence interval

*One session with both multitined expandable and internally cooled electrodes is excluded from the analysis.

Table 4. Results of Univariate and Multivariate Analyses of Multiple Variables to Determine the Factors associated with the Grade of Post-ablation Fever

| Variable | | Univariate analysis | | | Multivariate analysis | |
|---|---|---|---|---|---|---|
| | | Post-ablation fever (no. of sessions) | | | | |
| | | Grade1 or 2 (n = 13) | Grade 0** (n = 36) | *P* value | Odds ratio (95% CI) | *P* value |
| Age(y) | Mean ± SD | 63.5 ± 9.4 | 60.7 ± 11.2 | 0.42 | | |
| Gender | Male/Female | 9/4 | 19/17 | 0.35 | | |
| Emphysema | Yes/No | 7/6 | 4/32 | 0.004 | 3.50 (0.50-24.8) | 0.21 |
| Previous radiation | Yes/No | 0/13 | 3/33 | 0.56 | | |
| KL-6 before RF ablation (U/mL) | Mean ± SD | 329 ± 127 | 281 ± 121 | 0.23 | | |
| SP-D before RF ablation (ng/mL) | Mean ± SD | 51.1 ± 37.0 | 64.6 ± 41.4 | 0.31 | | |
| FEV(L) | Mean ± SD | 2.52 ± 0.57 | 2.38 ± 0.85 | 0.59 | | |
| FVC(L) | Mean ± SD | 3.35 ± 0.76 | 3.08 ± 1.01 | 0.39 | | |
| $FEV_1$(%) | Mean ± SD | 75.6 ± 6.56 | 77.3 ± 8.84 | 0.53 | | |
| Cancer type | Primary/Secondary | 0/13 | 4/32 | 0.56 | | |
| Distance from pleura (mm) | Mean ± SD | 13.9 ± 14.7 | 9.1 ± 10.4 | 0.20 | | |
| Tumor volume ($cm^3$) | Mean ± SD | 1.10 ± 0.92 | 1.96 ± 6.32 | 0.63 | | |
| Electrode* | Multitined expandable/Internally cooled | 13/0 | 29/6 | 0.13 | | |
| Max power (w) | Mean ± SD | 59.6 ± 19.8 | 63.3 ± 30.1 | 0.69 | | |
| Radiofrequency application time (min) | Mean ± SD | 29.0 ± 10.0 | 29.4 ± 18.3 | 0.94 | | |
| Ablated parenchymal volume ($cm^3$) | Mean ± SD | 44.1 ± 26.0 | 23.7 ± 11.9 | 0.016 | 1.03 (0.97-1.09) | 0.32 |
| Development of pulmonary infiltration | Yes/No | 12/1 | 13/23 | 0.001 | 10.1 (1.025-100.3) | 0.048 |

SD = standard deviation, KL-6 = Krebs von den Lungen-6, SP-D = surfactant protein D, RF = radiofrequency, FEV = forced expiratory volume, FVC = forced vital capacity, FEV1 = forced expiratory volume in 1 s to forced vital capacity, CI = confidence interval

*One session with both multitined expandable and internally cooled electrodes is excluded from the analysis.

**Grade 0 fever is defined as fever ≥37.0°C and <38.0°C.

Fig. 1a

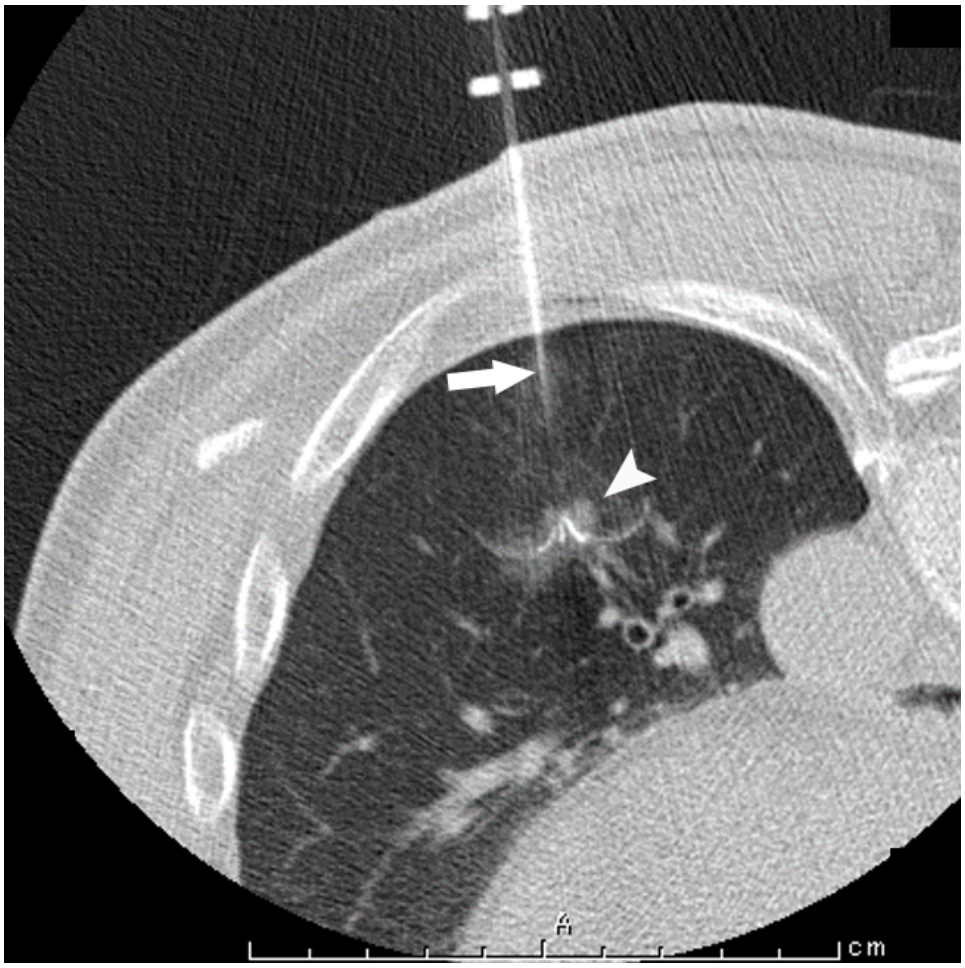

Fig. 1b

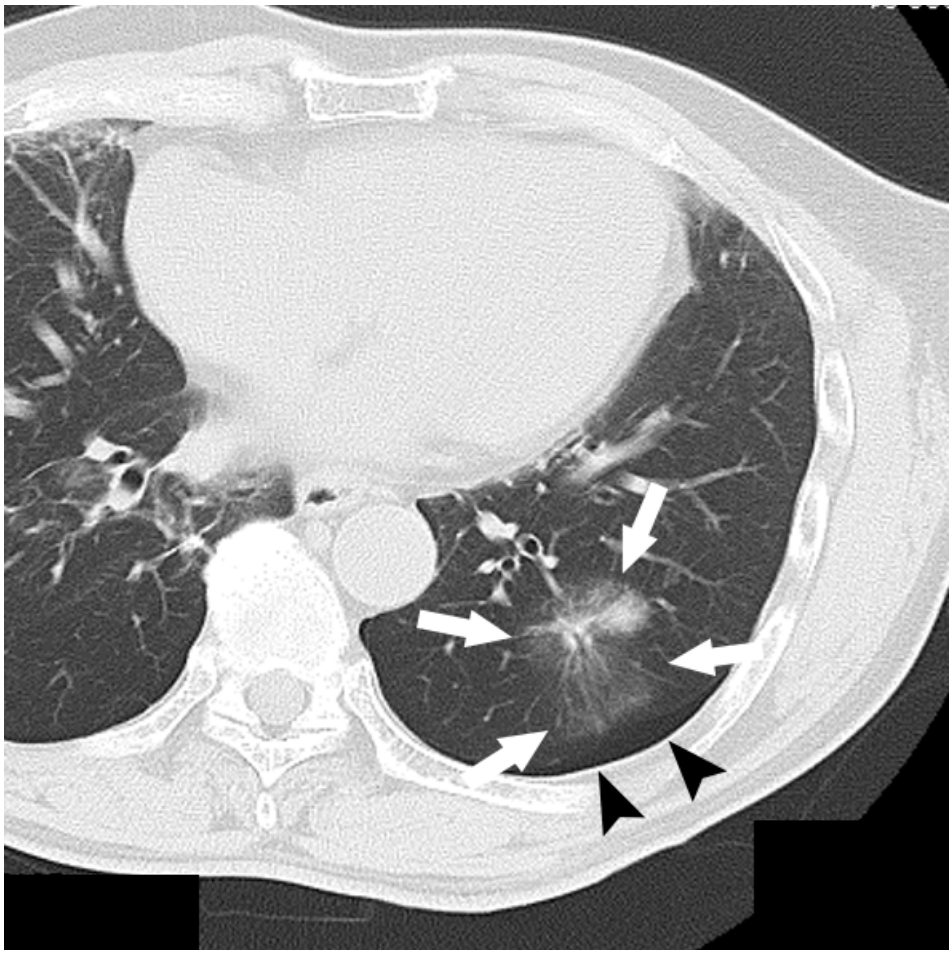

Fig. 1c

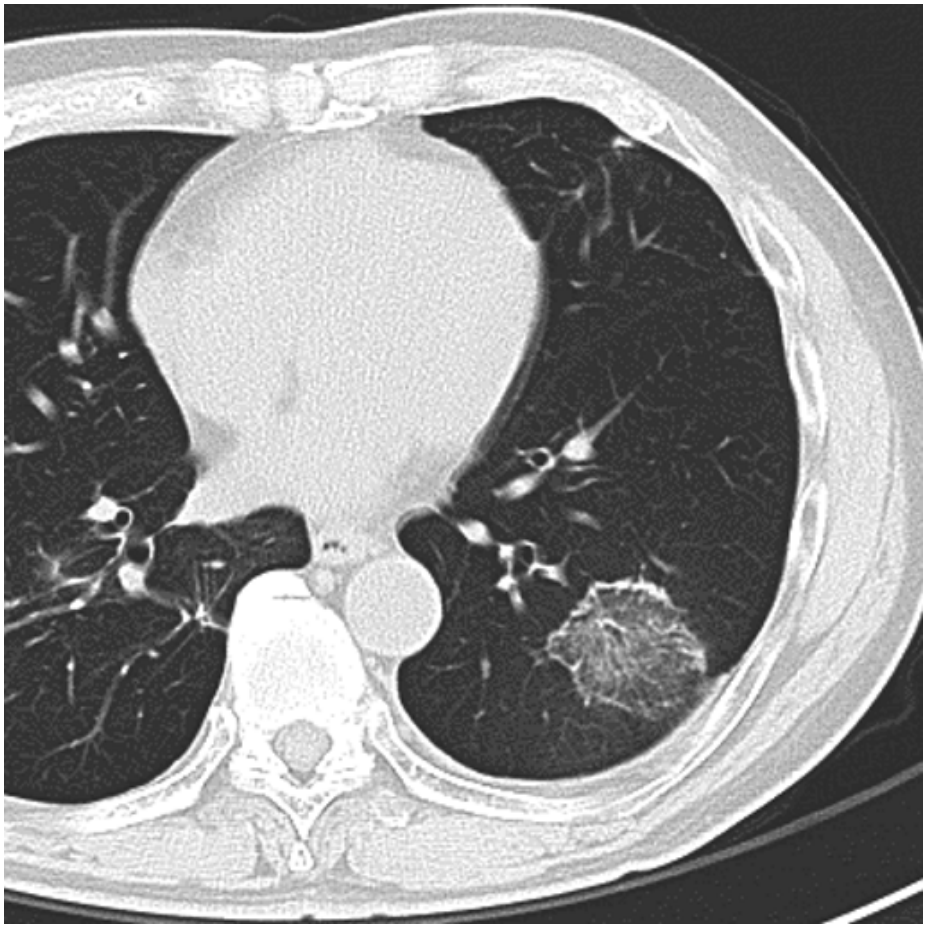

Fig. 2a

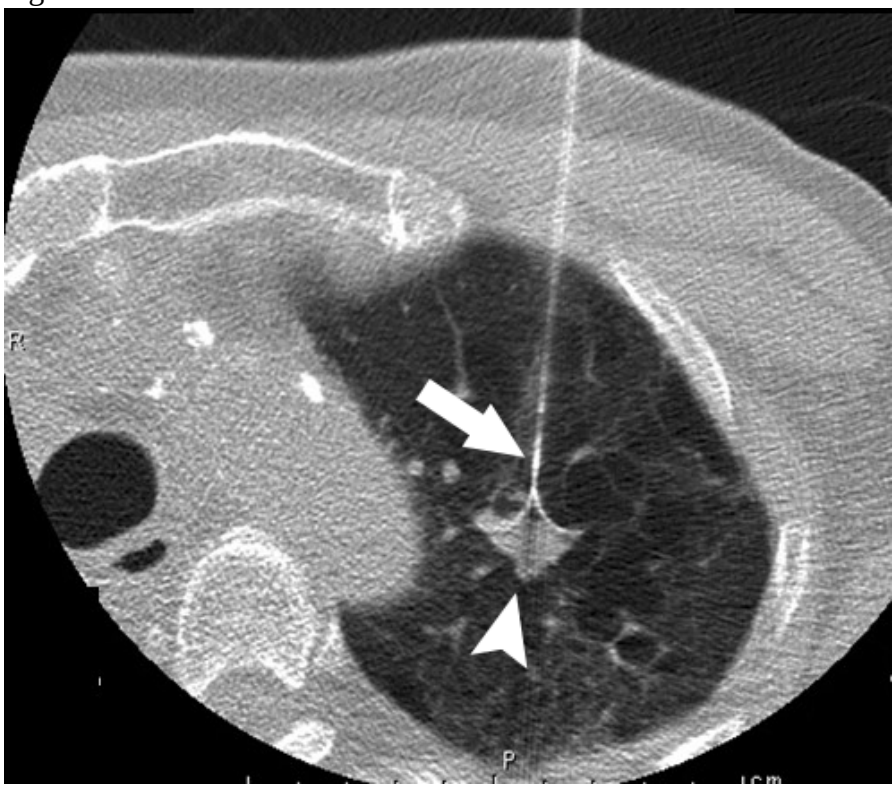

Fig. 2b

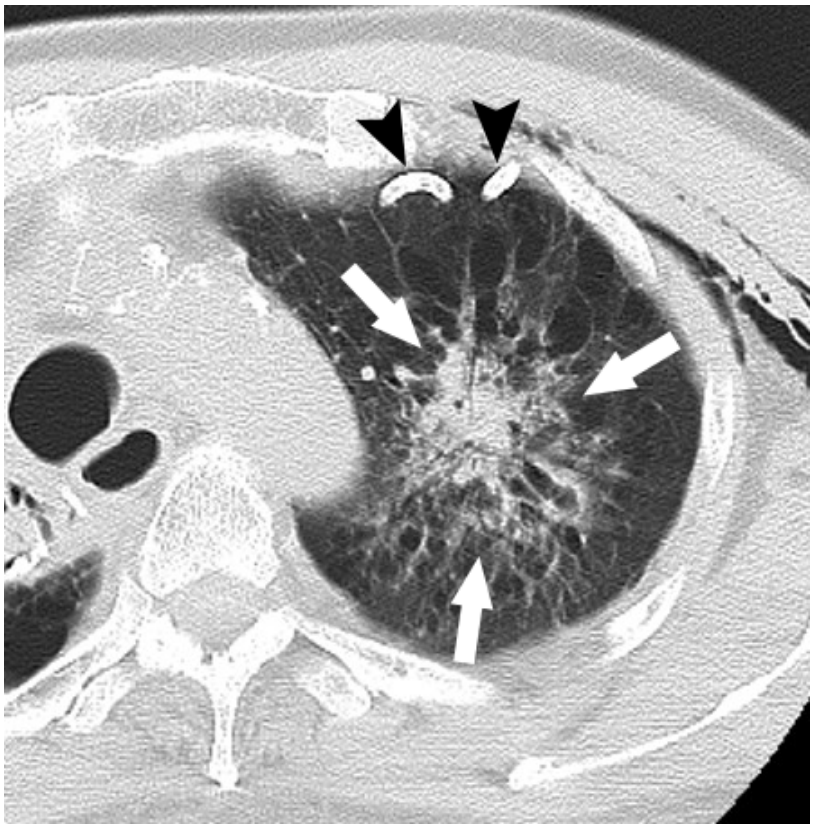

Fig. 2c

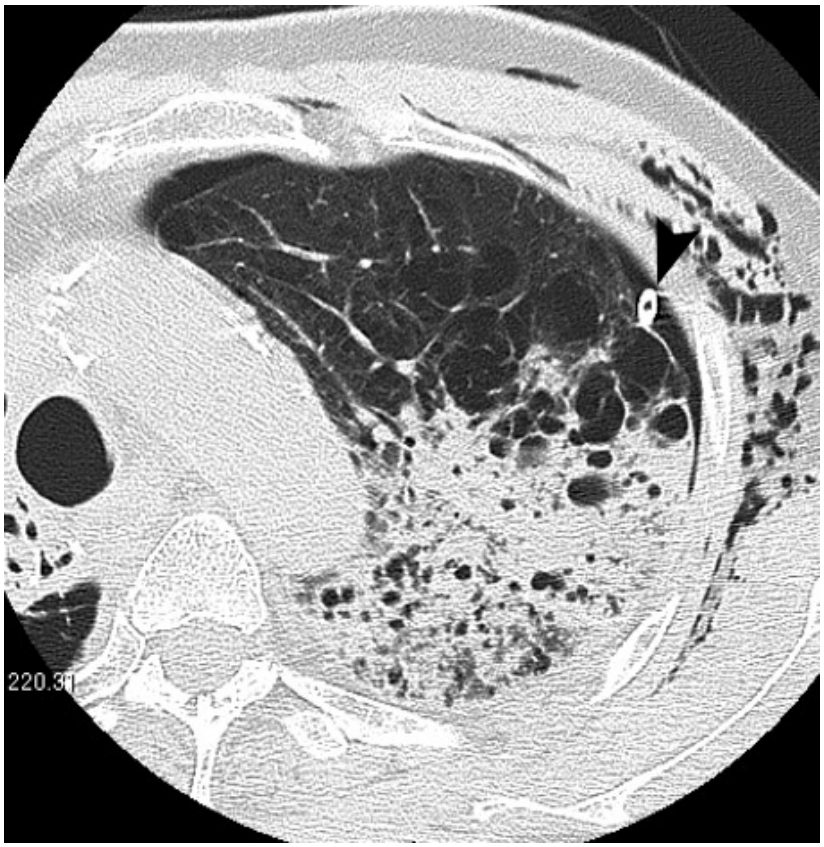

Fig. 3a

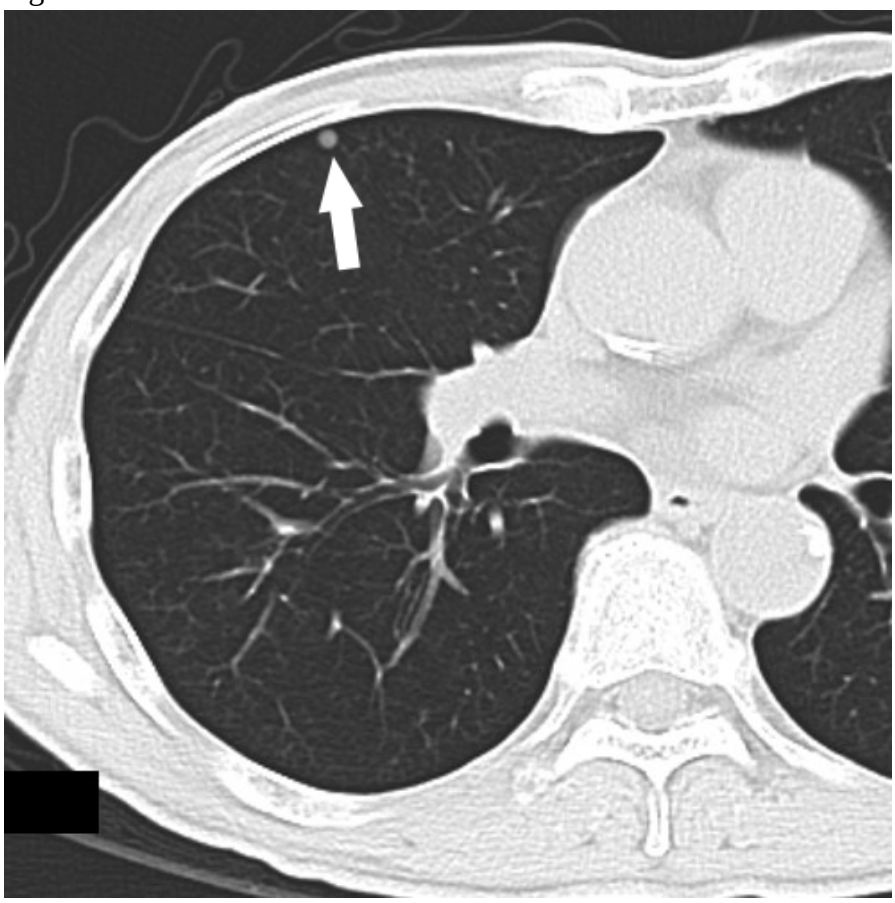

Fig. 3b

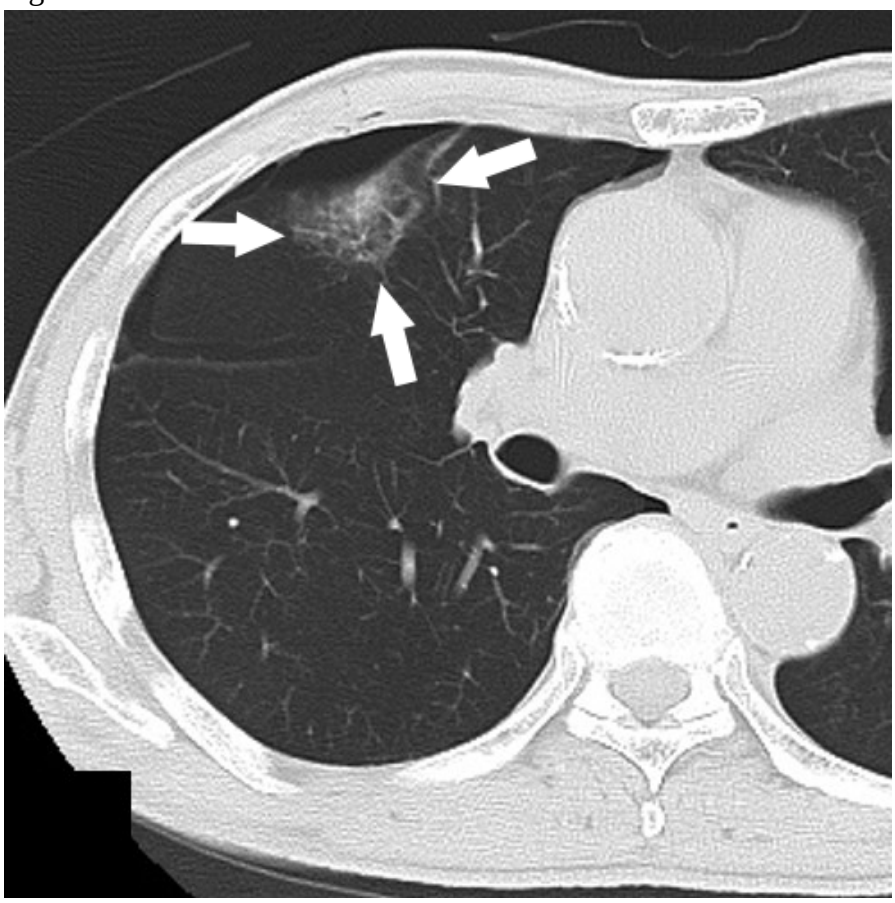

Fig. 3c