

# Different Patterns of Pneumothorax in Patients With Soft Tissue Tumors Treated With Pazopanib

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## Research article

**Keywords:** chemotherapy, pazopanib, pneumothorax, soft tissue sarcoma

**Posted Date:** December 1st, 2020

**DOI:** <https://doi.org/10.21203/rs.3.rs-115852/v1>

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# Abstract

**Background:** To investigate the patterns of pneumothorax in pazopanib treatment, focusing on the positional relationship between the visceral pleura and metastatic lung tumor.

**Methods:** We examined 20 patients with advanced soft tissue tumor who developed lung metastases before pazopanib treatment during 2012–2019. Pneumothorax was classified into two types based on the location of the metastatic lesion around the visceral pleural area before pazopanib treatment: subpleural type, within 5 mm from the pleura; central type, > 5 mm from the pleura. We investigated the rates of pneumothorax and the risk factors.

**Results:** Overall, 5 patients experienced pneumothorax (3 subpleural and 2 central type). Cavitation preceded pneumothorax in 80% of the patients and led to connection of the cavitated cyst of the metastatic lesion to the chest cavity in a shorter term in those with the subpleural type. Conversely, a more gradual increase in cavity and sudden cyst rupture were observed in the central type. The risk factors for pneumothorax were cavitation after the initiation of pazopanib and previous intervention before pazopanib including ablation or surgery. The locations of metastatic lesion were not risk factor for the occurrence of pneumothorax.

**Conclusion:** Pneumothorax is an adverse event of pazopanib treatment. Therefore, attention must be paid to the predisposing factors such as the formation of cavitation after pazopanib initiation and previous interventions on the lungs. Moreover, as the subpleural pneumothorax tends to occur earlier than the central type, the different time course can be anticipated based on the positional relationships of the metastatic lesions to the visceral pleura.

## Background

Pazopanib, a multi-channel kinase inhibitor, has been approved for the treatment of soft tissue tumors in 2012 based on the results of a phase III clinical trial. While pneumothorax was not a common adverse event in this trial, with an incidence of only 3.3% [1], subsequent real-world studies indicated a higher incidence of 7–15% [2, 3]. Because this critical adverse event interrupts treatment and may even require its cessation [2], management of pneumothorax is essential in the clinical setting. Based on our clinical experience, we identified two types of pneumothorax in patients treated with pazopanib from two different metastatic lesions: *subpleural type* and *central type*. This study aimed to investigate the patterns of pneumothorax. We proposed different types of pneumothorax focusing on the positional relationship between metastatic lesions and pleura and presented their clinical features. We also proposed the appropriate treatment strategy for pneumothorax developing after pazopanib treatment.

## Methods

Patients and pazopanib protocol

From 2014 to 2018, 32 patients with advanced soft tissue tumors were treated with pazopanib at the Nagoya City University Hospital. All patients received at least one cycle of an anthracycline-containing regimen. All patients had a performance status (PS) of 0–2 before pazopanib treatment, and the inclusion criteria in the package insert [4] were followed. None of these patients had a past medical history of cavity lung lesions, infection (e.g., tuberculosis, non-tuberculous mycobacterial infection, aspergilloma), sarcoidosis, primary lung cancer, etc. After excluding 4 patients with extra-pulmonary metastases, a total of 19 patients were included in the analysis. The baseline characteristics, including age, sex, PS, pathological diagnosis, the number of lung lesions, and pretreatment history of lung disease, were reviewed. The initial pazopanib dose was 800 mg (once daily; orally), and the dose was reduced based on the occurrence of adverse events (e.g., diarrhea, nausea, loss of appetite, hypertension, hand-foot syndrome) or patient status.

### Radiographic analysis and definition of pneumothorax

Chest computed tomography (CT, 2-mm slice) was performed before the initiation of pazopanib and repeated at every visit for 3–6 months to monitor metastatic lesions. All metastatic target lesions were evaluated by a single observer (HA) who classified the target lesions as subpleural (i.e., located within 5 mm or attached to visceral pleura) or central (i.e., located over 5 mm from the visceral pleura) based on the images before the initiation of pazopanib treatment. Measurements were evaluated at the point where the distance between the visceral pleura and tumor-ridge was tangentially minimized in axial-CT images. In addition, cavitation, defined as a degenerated change of metastatic lesion into a cyst storing air after pazopanib [5], was carefully observed as it preceded the pneumothorax.

### Treatment of pneumothorax

The severity of pneumothorax was categorized based on the Common Terminology Criteria for Adverse Events CTCAE 5.0 and the size of collapse. The size was evaluated by measuring the length from the lung margin to the chest wall on chest radiography [6]. “Small” pneumothorax was defined as “small rim of air around the lung (< 2 cm),” “moderate” as “collapsed about halfway to the heart,” and “complete” as “airless lung or separation from the diaphragm.” Treatment was according to the American College of Chest Physicians or British Thoracic Society guidelines [6]. Asymptomatic patients or those with small pneumothorax were only closely monitored and/or administered oxygen therapy. Further, pazopanib administration was discontinued for 3 to 4 weeks until recovery of pneumothorax. Meanwhile, symptomatic patients or those with moderately sized to complete pneumothorax (> 2 cm) were primarily treated with drainage or aspiration using one-way valve or water seal devices for 5–7 days. Meanwhile, pleurodesis with 5–10 KE of picibanil (Chugai Pharmaceutical, Japan) was considered for repeated or refractory pneumothorax. Video-associated thoracoscopic surgery (VATS) was performed only for the removal of resilient blebs/bullae or fistula.

## Statistical analysis

All values are presented either as mean  $\pm$  standard deviation or median with range, depending on the distribution. The chi-square test was used to compare categorical variables. All statistical analyses were conducted using SPSS version 24 (IBM, Chicago, IL), and  $P < 0.05$  was considered significant.

## Results

The mean patient age was 56.3 ( $\pm$  18.8) years, and 14 patients were men and 6 were women (Table 1). The histological subtypes included undifferentiated pleomorphic sarcoma in 9 patients, leiomyosarcoma in 3 patients, and others in 8 patients. Multiple metastatic lesions (over 10 lesions) were observed in 9 patients. The median pazopanib treatment period was 3.5 months (range, 1–51 months). At the end of the study, 16 patients died of the disease, while 4 patients were alive with the disease. The details of the patients' characteristics are shown in the Additional Table 1.

Table 1  
Chi-square analysis of the several characteristics affecting the incidence of pneumothorax

Characteristics		Incidence of pneumothorax	p-value
Sex	Male	3/14	0.848
	Female	2/6	
Histology	UPS	2/8	1.0
	Others	3/12	
Previous interventions to lungs before pazopanib administration	Yes	$\frac{3}{4}$	0.010
	No	2/16	
Cavitation of the metastatic lesion after pazopanib treatment	Yes	5/5	0.0001
	No	1/15	
Treatment response to pazopanib	PR	4/9	0.069
	SD or PD	1/11	
Presence of subpleural lesions	Yes	4/16	1.0
	No	1/4	
Initial dose of pazopanib (mg/day)	800	4/7	0.015
	Under 800	1/13	
Abbreviations: UPS, undifferentiated pleomorphic sarcoma; PR, partial response; SD, stable disease.			

Incidence of pneumothorax

Five patients were diagnosed with pneumothorax. The percentage was 15.6% (5/32) considering all patients and 25.0% (5/20) considering patients with lung metastasis. The median time to the first pneumothorax from the initiation of pazopanib was 3 months (range, 2 weeks to 20 months). In total, 3 and 2 patients developed subpleural and central pneumothorax, respectively. First pneumothorax occurred at 2 weeks, 3 weeks, and 8 months after initiation of pazopanib in the 3 patients with the subpleural type and at 3 months and 20 months in the 2 patients with the central type. Representative cases are shown in Figs. 1 and 2. Pazopanib treatment was restarted in 3 of the 5 patients after recovery from pneumothorax only if there were no other drug choices, but pneumothorax recurred in all 3 patients. Overall, the total incidents of pneumothorax were 15 times in 5 patients. Of these, pneumothorax was multi-recurrent (4 or 5 times).

With respect to the location of metastatic lung lesions, 285 lesions (14.3 [ $\pm$  12.9] lesions per patient) were detected before induction of pazopanib. Of these, 171 lesions (8.6 [ $\pm$  9.3] lesions per patient) were subpleural and 114 lesions (5.7 [ $\pm$  4.5] lesions per patient) were central. Twelve cases of pneumothorax, including recurrence, were observed from subpleural lesions (7.0%, 12/171) and 3 cases of pneumothorax (2.6%, 3/114) from central lesions. There was no difference in the incidence of pneumothorax according to tumor location (chi-square,  $p = 0.104$ ).

## Treatment

For the subpleural type, asymptomatic patients or those with small size pneumothorax (2 incidents in 2 patients) were administered conservative treatment, while a chest drainage tube was inserted in patients with moderately sized or complete pneumothorax (10 incidents in 3 patients). In total, the treatment efficacy of the chest tube insertion was 60% (6/10). For resistant cases, pleurodesis was performed; however, it resulted in remission in all cases.

All cases of central type pneumothorax involved a complete pneumothorax (3 incidents in 2 patients). The pneumothorax was uncontrollable in all cases using a chest tube; thus, pleurodesis or VATS was performed, depending on the recovery after re-expansion of the lung and the estimated size of the fistula.

## Factors associated with pneumothorax

Cavitation after the initiation of pazopanib was observed in 30% (6/20) of the patients, preceding the first pneumothorax in all patients (5/5), while 6.6% (1/15) of the patients without pneumothorax also developed cavitation ( $p = 0.0001$ , in chi-square analysis). With respect to classification according to treatment response, 45% (9/20) and 55% (11/20) were evaluated as partial responders and poor responders (stable disease or progressive disease). Of these, cavitation of the lung lesion was seen in 50% (5/10) patients with partial responders and 10% (1/10) in patients with inadequate responders (stable disease or progressive disease), but there was no significant association between treatment response to pazopanib and cavitation ( $p = 0.051$ ). Likewise, pneumothorax occurred in 44% (4/9) of partial responders and 9% (1/11) of inadequate responders (stable disease or progressive disease), but there was no significant association between treatment response to pazopanib and cavitation ( $p = 0.069$ ).

Moreover, the predisposing factor for pneumothorax was previous lung treatment (e.g., metastasectomy or radiofrequency ablation for the resection of metastatic lesions) before pazopanib administration (75% [3/4] vs 13% [2/16],  $p = 0.01$ , Table 1). Also, the initial dose of pazopanib was associated with the rate of pneumothorax (57% [4/7] vs 8% [1/13],  $p = 0.015$ , Table 1) in comparison to the maximum dose (800 mg).

## Discussion

Pneumothorax is a serious adverse event of pazopanib treatment, and there have been case reports and series on pneumothorax occurring after pazopanib treatment [2, 7–9]. In Japan, Nakano et al. reported a 10.3% incidence of pneumothorax, and the risk factor was a lung metastatic tumor measuring > 3 cm and history of pneumothorax [2]. Although the cause was unclear, this incidence rate was higher than that in the multi-center clinical trials of pazopanib (3% in the PALETTE study) [1]. In this study, we classified pneumothorax into two types: subpleural and central. In the subpleural type, the metastatic lesion was located around or attached to the visceral pleura. Typically, after cavitation of the metastatic tumor, pneumothorax occurred at the junction between the chest cavity and the ruptured cavity. In contrast, in the central type, the metastatic lesion was located at the distal part from the pleura. After cavitation, the check-valve mechanism occurred or air leaked continuously to the cavity. Finally, the high pressure caused enlargement of the cavity resulting in rupture and pneumothorax.

We hypothesized that compared with central pneumothorax, subpleural pneumothorax occurs sooner after the initiation of pazopanib and is occasionally refractory. Meanwhile, central pneumothorax is slower in onset but is sometimes intractable owing to the formation of an untreatable large fistula between the cavity and the pneumatocele (continuous massive air leakage into the cavity). Despite the limited number of cases in this study, this classification may be useful for clinicians to predict the timing and severity of pneumothorax.

We assumed that the cause of the central pneumothorax was similar to pneumatocele. Originally, pneumatocele is an air-filled cyst that develops within the lung parenchyma. It often occurs in respiratory infection, trauma, or during mechanical ventilation [10, 11]. Although the exact mechanism is unclear, it has been considered to be caused by parenchymal necrosis and check-valve bronchiolar obstruction [12]. Meanwhile, another study proposed local collections of air in the interstitial tissue [13]. In our case series, a gradually enlarging cyst was observed, and a necrotic tract from the cyst to the pleural membrane was observed on the resected specimen (Fig. 2). This finding suggested that compared with subpleural pneumothorax, central type pneumothorax is preceded by more extensive necrosis.

The actual etiology of pneumothorax after pazopanib treatment is unclear, but it is considered to be caused by air leakage from degenerated cavities. Cavitation is often caused by several angiogenic agents [14, 15] including pazopanib. In this study, cavitation of the tumor preceded pneumothorax in most cases. In contrast, secondary pneumothorax is rarely reported in kidney cancer, for which pazopanib has also been approved [16]. Thus, it was assumed that these degenerative changes might be distinct to sarcomas for unknown reasons. In addition, cavitation of lung metastases may also be associated with the

treatment response to pazopanib and the risk of pneumothorax [17], thus making the treatment challenging. In our department, re-administration of pazopanib is only considered when pazopanib is effective in controlling tumor progression or the treatment options are limited. However, all patients developed recurrence of pneumothorax; as such, re-administration of pazopanib should be carefully considered.

This study has some limitations. First, during the early phase of the study period, the new drugs for advanced soft tissue sarcoma including eribulin or trabectedin were not approved; thus, treatment options were limited. This may have increased the incidence of pneumothorax in high-risk patients (i.e., those with a previous history of pneumothorax or with degenerative cavity) and recurrence of pneumothorax. Thus, continuing or re-administering pazopanib should be carefully considered in the patients with a history of pneumothorax after pazopanib treatment, and other alternative chemotherapeutics should also be considered. Consistent with a previous study, we found that cavitation is associated with the treatment response to pazopanib [11]. Thus, a balance between pazopanib efficacy and adverse events should be maintained when planning treatment. Second, this study was performed at a single institution and a limited number of patients were included in the study, thus posing a limitation toward performing multivariate analyses and reaching a precise conclusion. Moreover, only one race (East Asian) was included in the study. Thus, these conditions might have influenced the results. Third, although the relationship between pneumothorax and the dose of pazopanib is not proven, the dose varied between patients and might have influenced the study findings. Finally, the high incidence of pneumothorax in the current study indicates the possibility of an investigation bias. Specifically, pneumothorax was diagnosed via chest radiography or computed tomography, and this increased the diagnosis rate. However, to the best of our knowledge, this is the first study to classify pneumothorax after pazopanib treatment according to its pattern.

## Conclusions

In conclusion, pneumothorax is considered to be one of the severe adverse events of pazopanib treatment. Although the precise prediction might be difficult, close attention must be paid to the predisposing factors, including the formation of cavitation after the initiation of pazopanib and previous interventions performed on the lungs. Moreover, from the viewpoint of the positional relationship where the subpleural type tends to occur earlier than central pneumothorax and since the central type may be challenging to treat owing to the larger fistula between the chest cavity and the degenerated cavity, the different behaviors can be anticipated. Thus, the location of the metastatic lesion should be considered during decision-making for the observation of such lesions in the lungs.

## List Of Abbreviations

CT, computed tomography; PS, performance status; VATS, video-associated thoracoscopic surgery.

## Declarations

### *Ethics approval and consent to participate*

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (The ethical committee of the Nagoya City University Hospital, No. 60-19-0029, approved on May 28, 2019) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The written consents were obtained from study participants.

### *Consent for publication*

Informed consents for publication were obtained from the study participants.

### *Availability of data and materials*

The datasets supporting the conclusion of this article are included within the article. The underlying datasets are available from the author on reasonable request.

### *Competing interests*

The authors declare that they have no competing interests.

### *Funding*

This research received no funding support.

### *Authors' contributions*

Conception; HA, HM, SY, HO, KH, SM, YK, SS, ST, TT, RN and HM. Design of the work; HA, SY. Acquisition, analysis, or interpretation of data; HA, HK, SM. Creation of new software used in the work; HA. Drafted the work or substantively revised it, HA, HM, SY, HO, KH, SM, YK, SS, ST, TT, RN and HM. All authors have read and approved the manuscript.

### *Acknowledgements*

We thank the staff members of the Division of Pathology of Nagoya City University Hospital for evaluating the histological specimens and the staff members of the Department of Radiology of Nagoya City University Hospital for evaluating the radiological images.

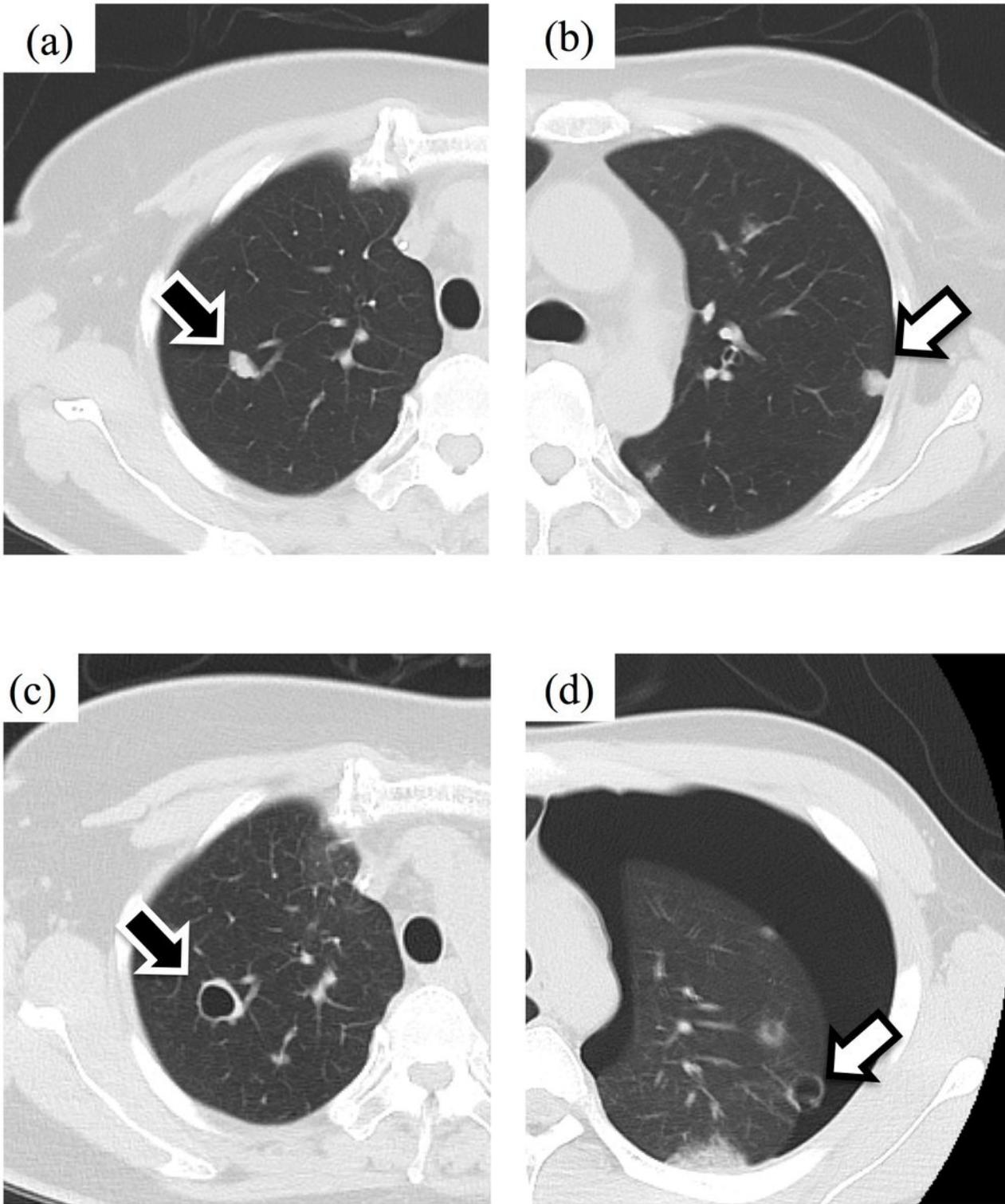
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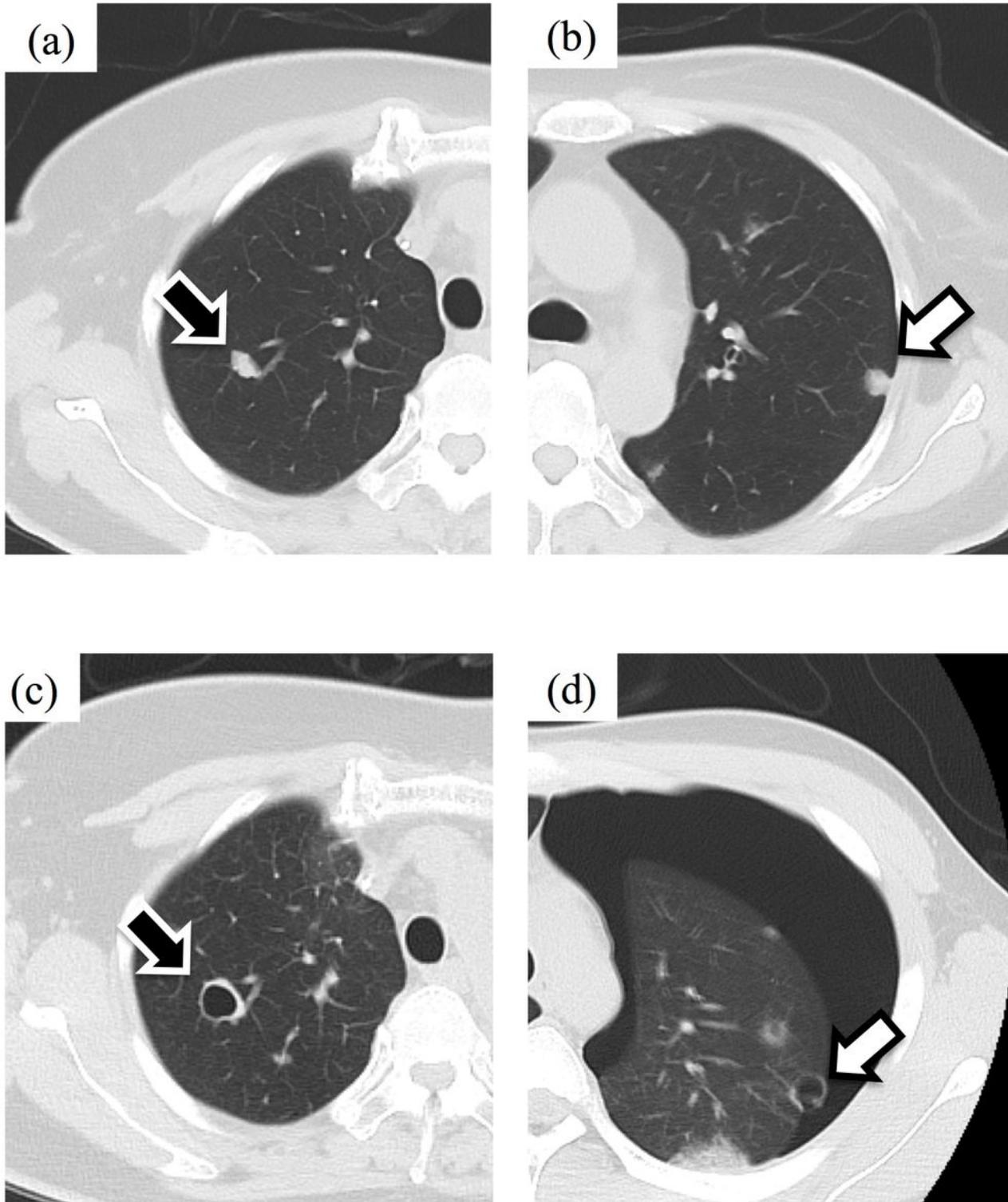
## Figures



**Figure 1**

Representative case of pneumothorax from a subpleural type lesion. (a-b) A 57-year-old woman was diagnosed with unclassified pleomorphic sarcoma in the right lower leg with multiple lung metastases. Before initiation of pazopanib (800 mg), both central- (black arrow) and subpleural-type (white arrow) metastases without cavitation were observed;(c) cavitation of the metastatic lesion are observed at the lung parenchyma (central type, black arrow) and around the subpleural lesion after 2 weeks; (d) one

month after the initiation, pneumothorax occurred from the subpleural type lesion (white arrow), but the central type was not ruptured.



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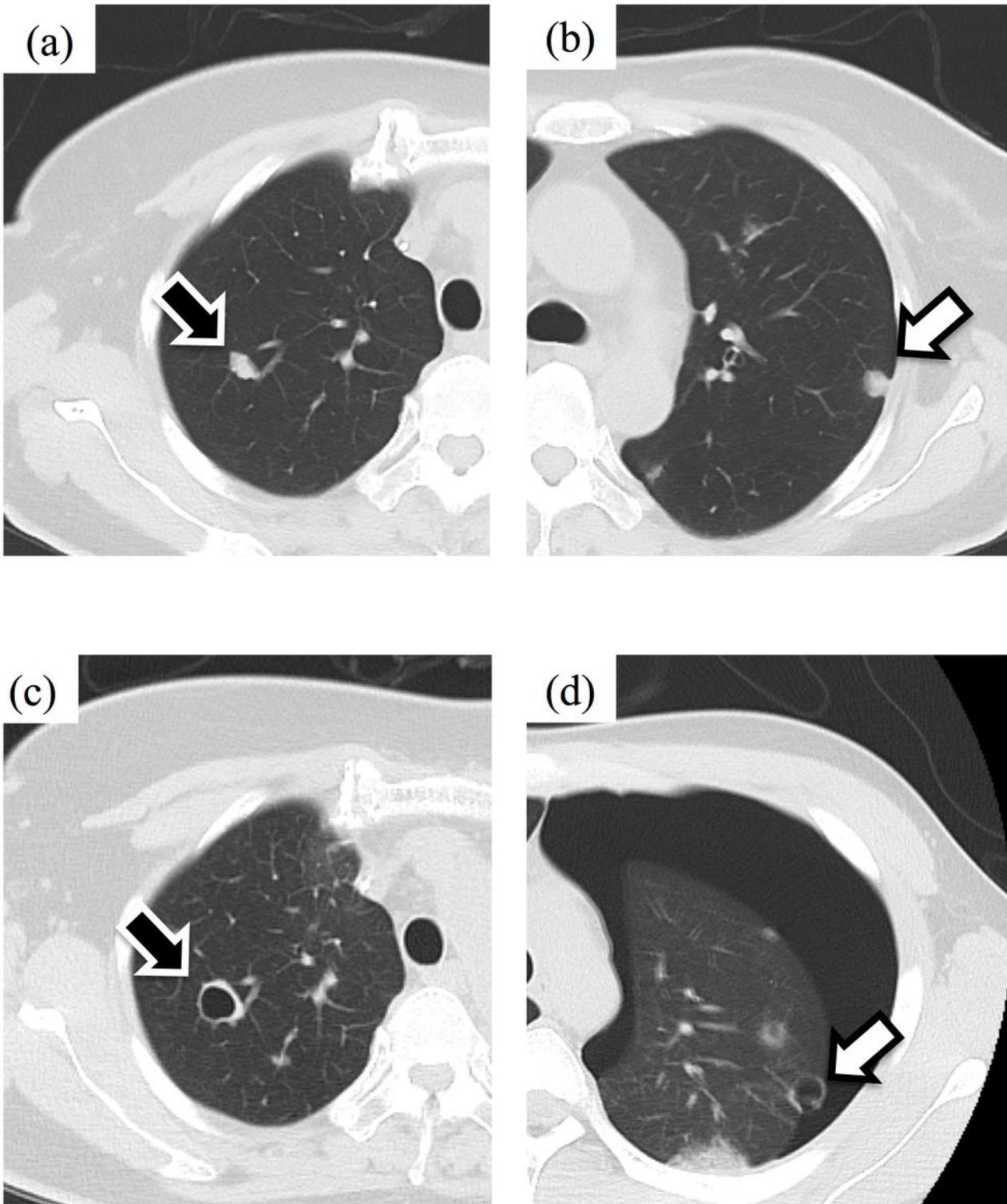
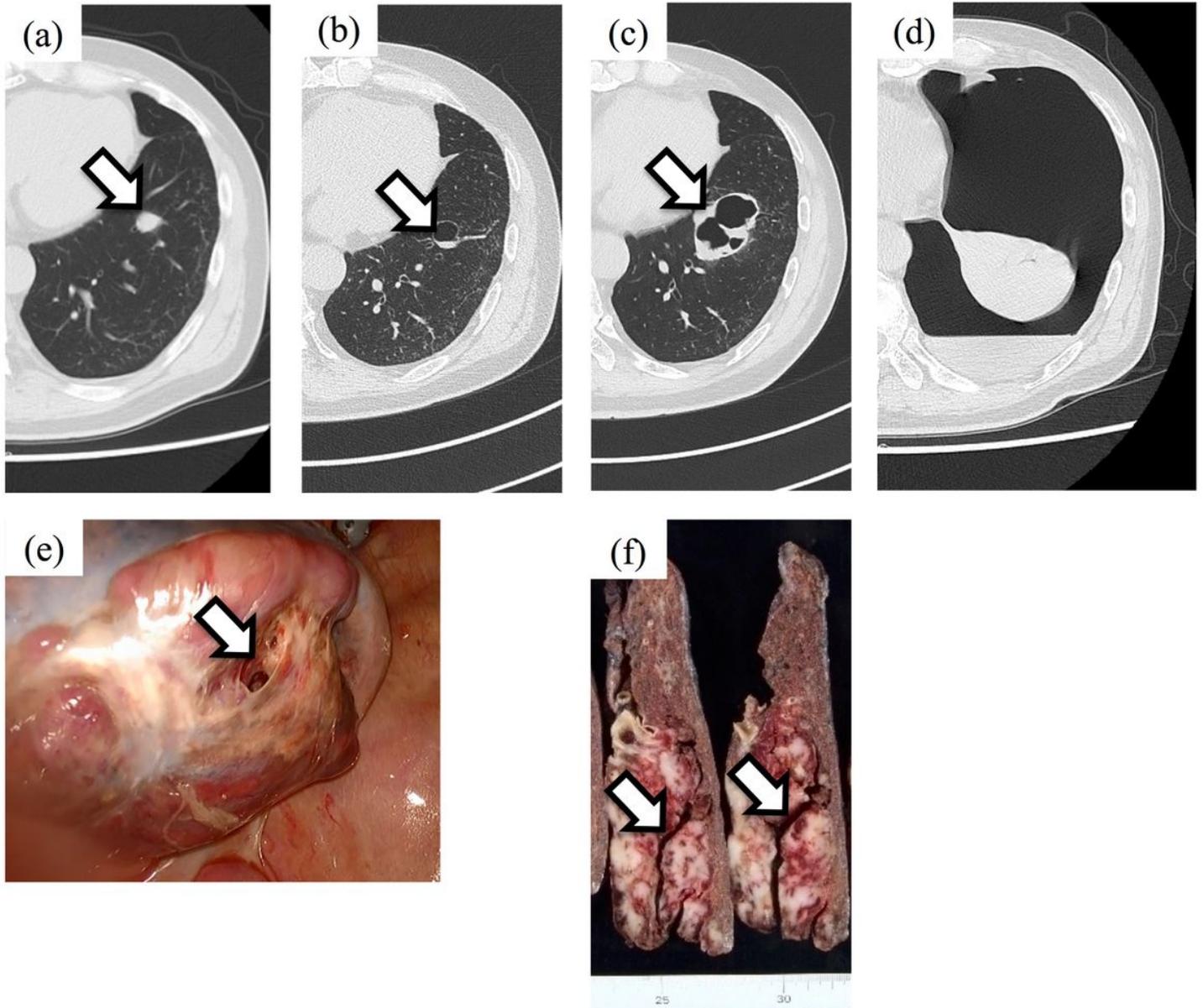


Figure 1

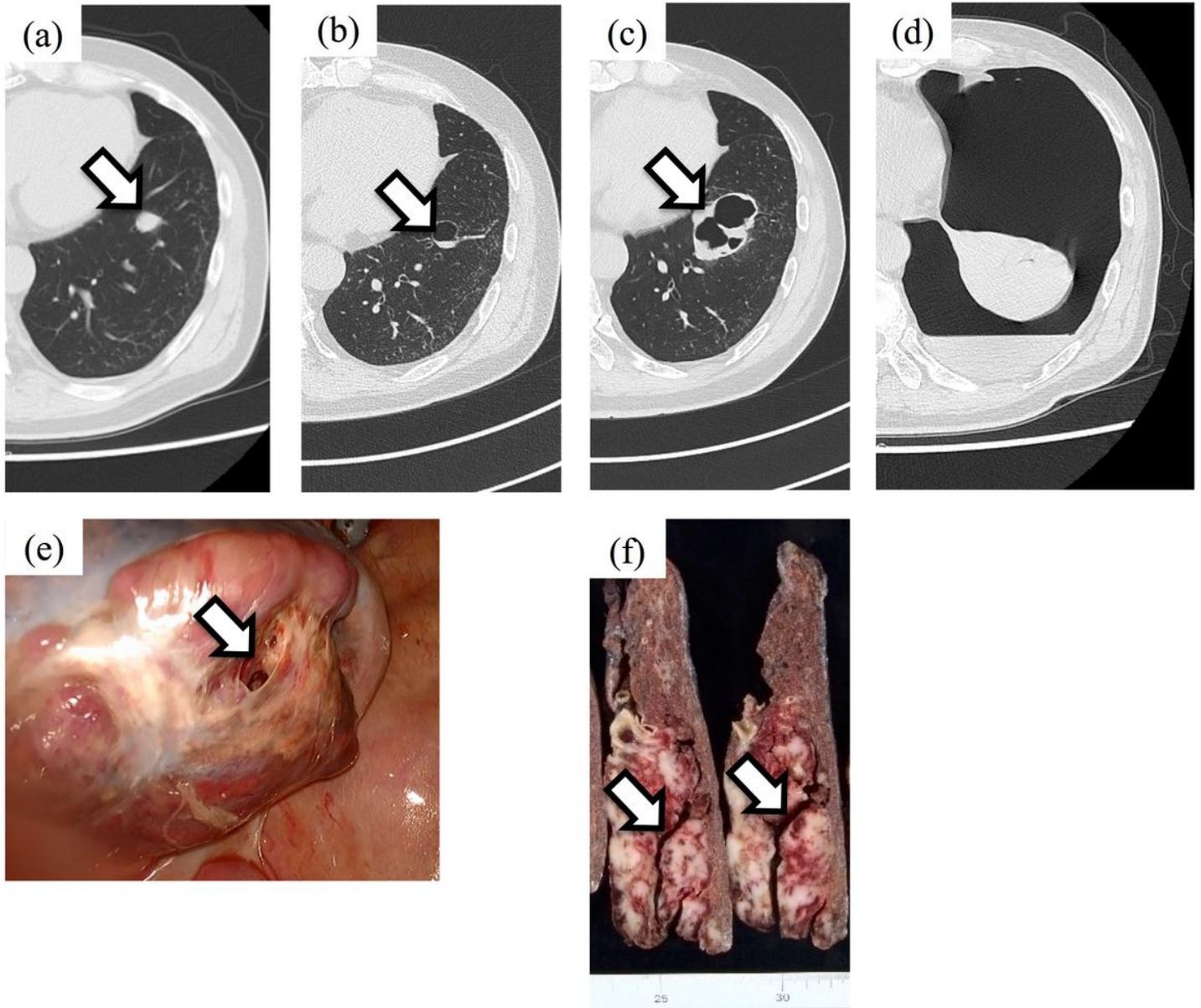
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**Figure 2**

Representative case of pneumothorax from a central type lesion. A 63-year-old man was diagnosed with unclassified pleomorphic sarcoma in the right thigh without any metastasis. The patient developed a single metastasis after 1 year; thus, lobectomy with video-associated thoracoscopic surgery was performed. (a) A single metastasis of the left lobe (central lesion, white arrow) was observed; thus,

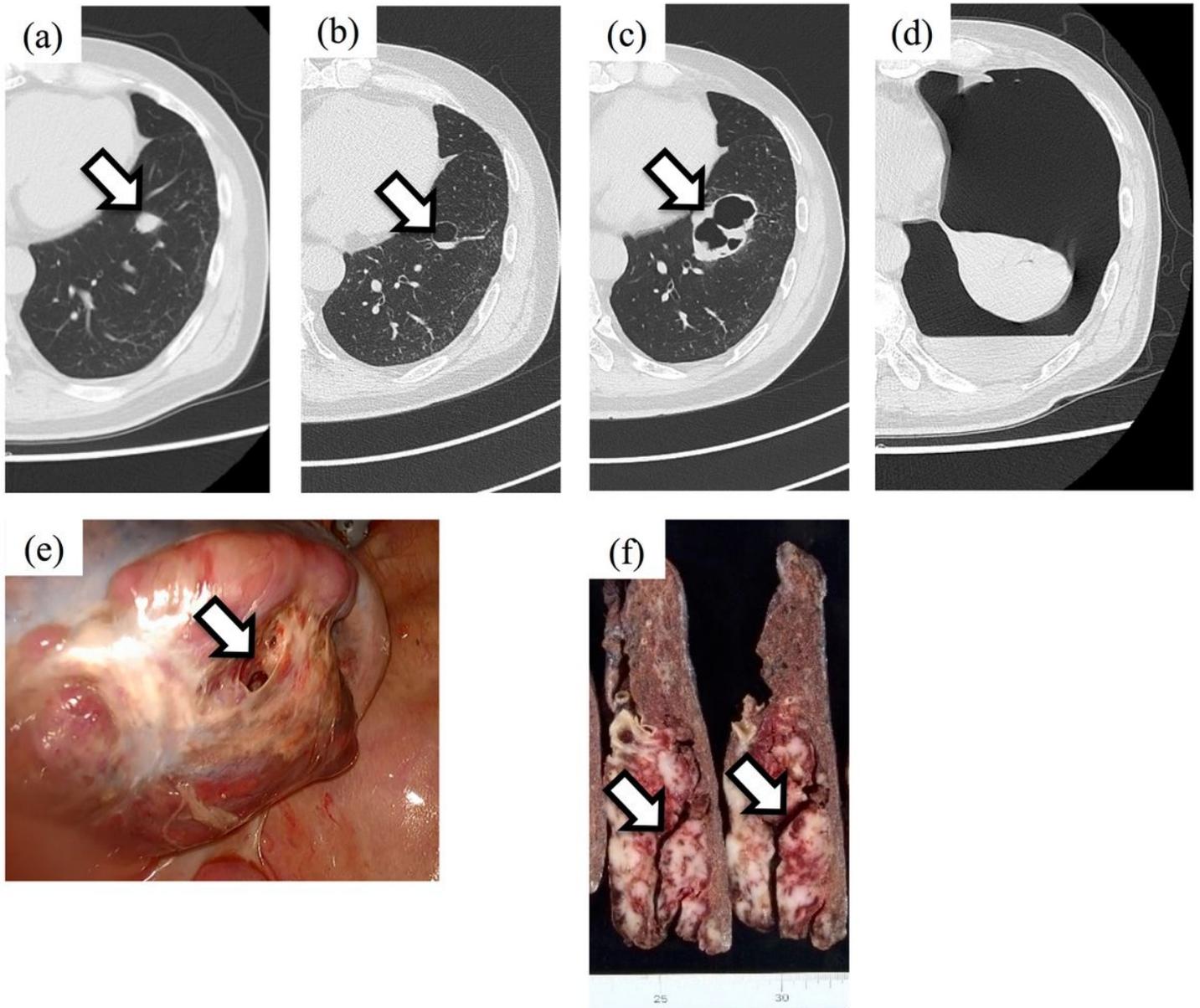
pazopanib 600 mg was initiated; (b) after 2 months, cavitation of the metastatic lesion was observed (white arrow); (c) the cavitation increased gradually; (d) after 6 months, the patient developed dyspnea and was then diagnosed with severe pneumothorax with a mediastinal shift; (e) a chest drainage was performed, but the patient's status did not improve; thus, lobectomy with fistula (white arrow) was performed; (f) macroscopic image of the resected specimen indicating a massive necrotic area (white arrow) along the fistula to the degenerative cavity.



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