Invasive pulmonary aspergillosis secondary to microwave ablation: a multicenter retrospective study

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ABSTRACT
Purpose: Invasive pulmonary aspergillosis (IPA) is a life-threatening complication of microwave ablation (MWA) during the treatment of primary or metastatic lung tumors. The purpose of this study was to investigate the clinical, radiological and demographic characteristics and treatment responses of patients with IPA after MWA.

Materials and methods: From January 2011 to January 2016, all patients who were treated by MWA of their lung tumors from six health institutions were enrolled in this study. Patients with IPA secondary to MWA were identified and retrospectively evaluated for predisposing factors, clinical treatment, and outcome.

Results: The incidence of IPA secondary to lung MWA was 1.44% (23/1596). Of the 23 patients who developed IPA, six died as a consequence, resulting in a high mortality rate of 26.1%. Using computed tomography (CT), pulmonary cavitation was the most common finding and occurred in 87.0% (20/23) of the patients. Sudden massive hemoptysis was responsible for one-third of the deaths (2/6). Most patients (22/23) received voriconazole as an initial treatment, and six patients with huge cavities underwent intracavitary lavage. Finally, 17 patients (73.9%) achieved treatment success.

Conclusions: Lung MWA may be an additional host risk factor for IPA, particularly in elderly patients with underlying diseases and in patients who have recently undergone chemotherapy. Early and accurate diagnosis of IPA after MWA is critical for patient prognosis. Voriconazole should be given as the first-line treatment as early as possible. Bronchial artery embolization or intracavitary lavage may be required in some patients.

Introduction
Microwave ablation (MWA) has been developed over the past decade as a new image-guided percutaneous thermal ablation technique for the treatment of primary and metastatic lung tumors [1]. MWA, with an electromagnetic field frequency ranging from 900–2450 MHz, utilizes dielectric hysteresis to generate energy that heats tumor tissues to lethal temperatures. Heating is based on agitation of polar molecules (primarily H2O) with an oscillating electric field to induce cell death by coagulation necrosis [2]. MWA offers some advantages, such as a larger ablation zone, shorter ablation duration, lower heatsinking effect and synergistic action of multiple antennas [3]. Furthermore, microwaves propagate effectively through air-filled lungs that are characterized by a high impedance, low electrical conductivity and low thermal transfer [4]. Based on the above merits, MWA has been increasingly applied to various stages of pulmonary primary and metastatic tumors [5–13].

Despite being a minimally invasive procedure, MWA can cause major complications [5–7,13]. Invasive pulmonary aspergillosis (IPA), a life-threatening and common complication secondary to MWA, was rarely reported previously [14]. The goals of this retrospective multicenter study were to investigate the incidence and clinical and radiologic manifestations of IPA in patients who underwent MWA and to analyze the treatment outcomes, mortality rate and possible risk factors.

Materials and methods
This was a retrospective, multicenter review of patients included in a comprehensive lung MWA database was formed by six health institutions in China. From January 2011 to January 2016, all patients who were treated by MWA of their lung tumors were enrolled in this study. Patients with IPA secondary to MWA were identified and retrospectively evaluated for predisposing factors, clinical treatment and...
outcome. Approval from each institutional review board and written informed consent from the patients were obtained for the analysis of lung tumor MWA.

**Percutaneous microwave ablation procedure**

Immediate preoperative computed tomography (CT; Lightspeed 16; GE Healthcare, Waukesha, WI) was used to design individualized treatment plans considering the tumor location, size and adjacent structures. The MTC-3C microwave ablation system (Qi Ya Research Institute of Microwave Electronic, Nanjing, China. Registration standard: YZB/country 1408–2003. No: SFDA (III) 20073251059) or the ECO-2450B microwave ablation system (ECO Microwave Electronic Institute, Nanjing, China. Registration standard: YZB/country 1475–2013. No: SFDA (III) 20112251456) was used for MWA.

Appropriate body placement, puncture sites on the body surface, puncture trajectory, and antenna number were confirmed. The following drugs were administered prior to MWA as preemptive analgesia: 10 mg of morphine via subcutaneous injection, 10 mg of diazepam via intramuscular injection and 50 mg of flurbiprofen axetil via intravenous injection [15]. In addition, 2% lidocaine was injected as a local anesthesia. After achieving satisfactory anesthesia, the MWA procedure was performed by inserting the antenna (14–15G external diameter, 100–180 mm length with a 3-cm active tip and water-circulation cooling system) in the proper position along the planned trajectory. Then, a coaxial cable was used to connect the MW antenna to an MW generator with a water-circulation cooling system, and MWA was performed. The ablation power and duration were determined with reference to the manufacturers’ recommendations. Thereafter, the MW antenna was extracted, and the puncture wound was disinfected with iodine volts and then bandaged. Vital signs were monitored continuously for 6 h after the patients’ safe return to the ward. Prophylactic cefazolin sodium (4 g intravenously every 12 h) was administered starting 12 h before and discontinued 3 days after ablation. Unenhanced chest CT was performed 24–48 h post-MWA to assess the scope of ablation and to monitor for major complications. Patients were discharged 3–5 days after MWA if they recovered well. Changes in clinical condition were monitored via a follow-up CT examination, symptom enquiry, physical examination and laboratory testing.

**Case definitions of IPA (Table 1)**

IPA was defined according to the criteria of the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group [16] and was classified into one of three groups: proven, probable and possible. Proven IPA required proof demonstrating the presence of fungal elements in diseased tissue by microscopic analysis or by the culture of sterile material. Probable IPA required the presence of a host factor, a clinical criterion and a mycological criterion. Cases fulfilling the criteria for a host factor and a clinical criterion but that lacked a mycological criterion were considered possible IPA. In accordance with the guidelines, IPA assumes a diagnostic certainty of proven or probable cases [16,17]. In the present study, only patients with proven or probable IPA were included.

The response to antimycotic treatment was assessed using criteria established by the Mycoses Study Group and European Organization for Research and Treatment of Cancer [18]. Treatment success was defined as a ≥25% reduction in the diameter of radiological lesions, plus patient survival, improvement of disease-related symptoms, and documented clearance of infected sites. Treatment failure was defined as patient survival with no/minor improvement in disease-related symptoms plus a 0–25% reduction in lesion diameter.

| Category      | Type of criteria                           | Criteria                                                                 |
|---------------|--------------------------------------------|--------------------------------------------------------------------------|
| Proven IPA    | Microscopic analysis: sterile material      | Histopathologic or cytopathologic examination showing hyphae from needle aspiration or biopsy specimen with evidence of associated tissue damage |
|               | Culture: sterile material                   | Positive culture result for a sample obtained by sterile procedure from normally sterile and clinically or radiologically abnormal site consistent with infection |
| Probable IPA  | Host factors                                | Underlying disease, including chronic liver disease, COPD, and/or DM Neutropenia after perioperative chemotherapy Malnutrition Fever refractory to appropriate broad-spectrum antibacterial treatment |
|               | Clinical criteria (signs on CT)             | Dense, well-circumscribed lesion(s) with or without a halo sign Air-crescent sign Cavity |
|               | Mycological criteria                        | Aspergillus in sputum or bronchoalveolar lavage fluid indicated by 1 of the following: Presence of fungal elements indicating Aspergillus Recovery by culture of Aspergillus Galactomannan antigen detected in plasma, serum, or bronchoalveolar lavage fluid |

COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus.
deteriorating disease-related clinical symptoms plus new sites of disease or radiological exacerbation of preexisting lesions, persistent isolation of mold species from infected sites, or patient death during the prespecified period of evaluation.

**Inclusion and exclusion criteria of IPA associated with MWA, and data collection**

Inclusion criteria were as follows: (a) patients undergoing percutaneous lung MWA during the past two months; (b) symptoms of lower respiratory tract infection (fever, cough, expectoration, hemoptysis, chest pain, dyspnea, pleural effusion); (c) confirmed signs of infection at the ablation site by imaging; (d) a positive Aspergillus result by sputum smear and culture, smear and culture of aseptic specimens derived from the ablation zone, or galactomannan antigen detection; (e) the initial exclusion of a bacterial infection; (f) poor effect of broad-spectrum antibacterial treatment; (g) proven and probable cases of IPA; (h) good efficacy of the appropriate empirical therapy against molds. Exclusion criteria were: (a) infection that occurred more than 2 months after MWA; (b) infection of a non-ablation site; (c) the absence of aforementioned mycological evidence; (d) positive bacterial cultivation results from the original specimen; (e) excellent efficacy following antibacterial treatment.

From the hospitals’ data processing systems, we extracted and examined the hospital medical records, discharge reports and radiographic results of all participants. We recorded the demographic features, smoking history, comorbidities, pulmonary function test results, lung tumor characteristics, radiotherapy or chemotherapy histories, MWA details, clinical symptoms of IPA, laboratory test results, the evolution of imaging findings, hospitalization periods, responses to treatment and outcomes. Definitive diagnosis of proven and probable IPA was established by a multidisciplinary tumor board that included a medical oncologist, respiratory and probable IPA was established by a multidisciplinary treatment and outcomes. Definitive diagnosis of proven of imaging findings, hospitalization periods, responses to ical symptoms of IPA, laboratory test results, the evolution radiotherapy or chemotherapy histories, MWA details, clin- pulmonary function test results, lung tumor characteristics, the demographic features, smoking history, comorbidities, and radiographic results of all participants. We recorded and examined the hospital medical records, discharge reports

**Continuous variables**

Continuous variables were summarized as the mean ± standard deviation (SD) and were assessed using an independent-samples t-test. Proportions were calculated for categorical variables. If a categorical variable was not fit for the χ² test because 1 or more cells in a crosstab had an expected count of less than 5, then the 2-sided Fisher exact test was adopted. A p value of less than .05 was considered statistically significant. All statistical analyses were performed using SPSS version 17.0 packaged software (SPSS, Inc, Chicago, IL).

**Results**

A total of 1596 patients underwent CT-guided percutaneous MWA of lung tumors, as shown in Table 2. Of these, 23 (1.44%) developed proven (n = 6) or probable (n = 17) IPA, including nineteen men and four women, with a mean age of 64.5 ± 7.4 (range: 50.0–79.0) years. All 23 patients with IPA had histologically confirmed primary lung cancers (11 adenocarcinomas, 10 squamous carcinomas and two indeterminate tumors) spanning all TNM stages from I to IV (2 cases of Ia, 4 cases of Ib, 2 cases of Ila, 1 case of Iib, 4 cases of IIIa, 5 cases of IIIb and 5 cases of IV).

**Tumor ablation and complications**

The characteristics of the tumor, the ablation and the complications that arose due to the ablation in the 23 patients with IPA are shown in Table 3. A total of 25 lesions were ablated including ablation of single (n = 21) and double lesions (n = 2). Single-spot ablation (one antenna) was used for tumors with a maximum diameter of ≤3.0 cm while multiple-spot ablation (two antennae) was used for tumors >3.0 cm in diameter. Complications experienced after ablation, according to the classification of the Imaging-guided Tumor Ablation International Working Group of the Society of Interventional Radiology [19], included the following: post ablation syndrome (n = 16), which was treated with nonsteroidal drugs, when necessary; pneumothorax (n = 9, of which six required catheterization for closed drainage);

| Table 2. Demographic and clinical characteristics of patients. | Patients undergoing MWA (n = 1596) | Patients with IPA (n = 23) | P value |
|---|---|---|---|
| Gender | | | .037 |
| Male | 984 (61.7) | 19 (82.6) | |
| Female | 612 (38.3) | 4 (17.4) | |
| Smoking history | | | | |
| Yes | 587 (36.8) | 19 (82.6) | <.001 |
| Smoking index >400 | 381 (23.9) | 15 (65.2) | <.001 |
| Underlying disease | | | | |
| COPD | 97 (6.1) | 13 (56.5) | <.001 |
| Cardiovascular disease | 286 (17.9) | 7 (30.4) | .175 |
| Malnutrition | 153 (9.6) | 4 (17.4) | .260 |
| DM | 113 (7.1) | 2 (8.7) | 1.000 |
| HBV | 74 (4.6) | 1 (4.3) | 1.000 |
| Lung tumours | | | <.001 |
| Primary | 931 (58.3) | 23 (100.0) | |
| Metastatic | 665 (41.7) | 0 (0.0) | |
| Perioperative chemotherapy | 716 (44.9) | 15 (65.2) | .027 |

Data are presented as number (%) or mean ± SD, unless stated otherwise.

HBV: hepatitis B virus infection.
Table 3. Tumor, ablation, and complication characteristics of 25 lesions in 23 patients with IPA.

| Characteristics                        | Lesion (25) |
|----------------------------------------|-------------|
| Mean size of tumor (cm)                | 3.85 ± 1.50 (1.8–7.2) |
| Site of tumor                          |             |
| Right upper lobe                       | 10 (40.0)   |
| Right middle lobe                      | 1 (4.0)     |
| Right lower lobe                       | 5 (20.0)    |
| Left upper lobe                        | 7 (28.0)    |
| Left lower lobe                        | 2 (8.0)     |
| Power of ablation                      |             |
| 50 W                                   | 1 (4.0)     |
| 60 W                                   | 5 (20.0)    |
| 70 W                                   | 19 (76.0)   |
| Number of antennae                     |             |
| One                                    | 10 (40.0)   |
| Two                                    |             |
| Mean time of ablation (min)            | 13.70 ± 6.63 (4.0–28.0) |
| GGO size 24–48 hours after ablation (cm)| 6.44 ± 1.76 (2.9–9.8) |
| Complication related to ablation       |             |
| Postablation syndrome                  | 16 (69.6)   |
| Pneumothorax                           | 9 (39.1)    |
| Pleural effusion                       | 10 (43.3)   |
| Hemoptysis                             | 3 (13.0)    |
| Atelectasis                            | 3 (13.0)    |

Data are presented as number (%) or mean ± SD (range), unless stated otherwise. GGO: ground-glass opacity.

pleural effusion (n = 10, of which five underwent thoracentesis); hemoptysis (n = 3, which was managed with the appropriate administration of hemostatic drugs); and atelectasis (n = 3, which required no special treatment).

Clinical characteristics, diagnosis, treatment and prognosis of patients with IPA

The clinical characteristics of patients with IPA including symptoms and laboratory and radiological findings are shown in Table 4. It should be noted that the sputum of most patients was characterized as being smoke gray in color and containing a flocc. Of the six cases of proven IPA, one was verified by visualization of the hyphae via direct microscopy and five were verified by positive culture of intracavitary drainage under sterile conditions.

Regarding antifungal treatment, 22 cases initially received intravenous voriconazole while one case received itraconazole. Once clinical improvement was demonstrated with intravenous voriconazole, patients were discharged with oral itraconazole (n = 5) or oral voriconazole (n = 17). Six patients required intracavitary lavage due to necrotic liquefaction and five required thoracic drainage due to pleural effusion and bronchopleural fistula. Both procedures were performed via percutaneous catheterization. Bronchial artery embolization was performed in one patient to manage severe hemoptysis. Six patients (26.1%) died before completion of treatment and their treatment responses were categorized as failures.

Sudden massive hemoptysis was responsible for a third of the deaths (2/6). Based on clinical and radiological improvement, 17 patients (73.9%) achieved treatment success, including five who died from tumor recurrence or metastasis, rather than IPA. In patients with treatment success, the mean duration of treatment was 44.6 days (vs. 18.5 days in those with treatment failure). Also of note, secondary bacterial infections developed in eight patients during antifungal treatment (Table 5).

Discussion

Aspergillus, a saprophytic fungus, is a ubiquitous, hardy organism that grows best on organic debris and in humid environments while its natural ecological niche is the soil [20]. Aspergillus releases thousands of airborne conidia into the atmosphere that can easily be inhaled into the distal airways and alveoli. In immunocompetent hosts without underlying lung disease, these conidia are normally eliminated by mucociliary clearance and innate immune mechanisms [21]. MWA destroys tumors and a small amount of the surrounding normal lung tissue. Necrotic tissue debris in ablation sites offers excellent conditions for germination of dormant spores. Although hundreds of Aspergillus species have been identified, few have been implicated in human disease. A. fumigatus is the most common pathogenic species, accounting for 90% of the pulmonary aspergillosis cases. Although less common, A. terreus, A. flavus and A. niger also contribute to the pulmonary aspergillosis incidence [22], as demonstrated in the present study.

IPA primarily occurs in severely immunocompromised patients such as those with a hematologic malignancy, inherited immune deficiencies, connective tissue disease, or that are undergoing immunosuppressive therapy or have had a solid organ transplant [16]. Recent studies have revealed additional risk factors including critical illness, malnutrition, end-stage liver disease, alcoholic hepatitis, COPD, chemotherapy and DM [23–25]. In COPD patients that are heavy smokers, decreased mucociliary clearance of the airway delays the elimination of Aspergillus spores and long-term use of an inhaled corticosteroid weakens the local immunity thereby increasing the incidence of IPA. In this study, the IPA incidence after
| IPA Certainty | Risk factor                  | Chest CT                        | Type of specimen | Species       | Co-infection | Antifungal drug | Adjuvant therapy | Treatment response | Outcome      |
|---------------|------------------------------|--------------------------------|------------------|---------------|--------------|-----------------|------------------|--------------------|--------------|
| 1 Proven      | COPD                         | Cavitation                      | Intracavitary fluid, Sputum | A. fumigatus  | None         | Voriconazole, Itraconazole | Intracavitary lavage | success         | alive        |
| 2 Probable    | Chronic liver disease COPD   | Consolidation, Infiltration, BRF| Sputum            | A. fumigatus  | K. pneumoniae| Voriconazole    | Thoracic drainage  | failure          | dead (infection)|             |
| 3 Proven      | COPD                         | Cavitation                      | Histopathological examination, Sputum | A. fumigatus  | A. baumannii, S. aureus | Voriconazole    | Intracavitary lavage | success         | alive        |
| 4 Probable    | Chemo, DM                    | Cavitation, Nodules, Infiltration | Sputum            | A. fumigatus  | None         | Voriconazole    | Thoracic drainage  | success          | alive        |
| 5 Probable    | Chemo, COPD                  | Cavitation, BRF                 | Sputum            | A. fumigatus  | None         | Voriconazole, Itraconazole | Thoracic drainage  | success          | alive        |
| 6 Probable    | Chemo, COPD                  | Cavitation                      | Sputum            | A. fumigatus  | None         | Voriconazole, Itraconazole | Thoracic drainage  | success          | alive        |
| 7 Proven      | malnutrition                 | Cavitation, Infiltration, BRF   | Intracavitary fluid, Sputum | A. fumigatus  | None         | Voriconazole    | Intracavitary lavage | failure          | dead (infection)|             |
| 8 Probable    | Chemo                        | Cavitation, Nodules, Infiltration | Sputum            | A. fumigatus  | None         | Voriconazole    | Bronchial artery embolization | success         | alive        |
| 9 Proven      | Chemo, COPD                  | Cavitation                      | Intracavitary fluid, Sputum | A. fumigatus  | K. pneumoniae, Viridans Streptococci | Voriconazole | Intracavitary lavage | success         | dead (cancer)|             |
| 10 Probable   | Chemo malnutrition           | Cavitation, Consolidation, Infiltration | Sputum            | A. fumigatus  | S. aureus, E. coli | Voriconazole | None             | failure          | dead (infection)|             |
| 11 Probable   | Chemo, COPD                  | Cavitation                      | Sputum            | A. fumigatus  | None         | Itraconazole    | None             | success          | alive        |
| 12 Probable   | Chemo, COPD, DM              | Cavitation, Infiltration         | Sputum            | A. fumigatus  | None         | Voriconazole    | None             | failure          | dead (infection)|             |
| 13 Probable   | Proven malnutrition          | Cavitation, Consolidation        | Sputum            | A. fumigatus  | None         | Voriconazole, Itraconazole | Thoracic drainage  | success          | alive        |
| 14 Proven     | Chemo                        | Cavitation, Nodules              | Intracavitary fluid, Sputum | A. fumigatus  | None         | Voriconazole, Itraconazole | Intracavitary lavage | success         | dead (cancer)|             |
| 15 Probable   | Chemo                        | Cavitation                      | Sputum            | A. fumigatus  | None         | Voriconazole    | None             | success          | alive        |
| 16 Probable   | Chemo, COPD                  | Cavitation                      | Sputum            | A. fumigatus  | None         | Voriconazole    | None             | success          | alive        |
| 17 Probable   | COPD                         | Cavitation                      | Sputum            | A. fumigatus  | None         | Voriconazole, Itraconazole | None             | success          | alive        |
| 18 Proven     | COPD                         | Cavitation, Nodules, Infiltration | Intracavitary fluid, Sputum | A. fumigatus  | Acinetobacter Iwofii | Voriconazole | None             | success         | alive        |
| 19 Probable   | COPD                         | Cavitation                      | Sputum            | A. fumigatus  | K. pneumoniae| Voriconazole    | None             | failure          | dead (hemothysis)|             |
| 20 Probable   | Chemo                        | Consolidation                   | Sputum            | A. fumigatus  | E. coli      | Voriconazole    | None             | success          | alive        |
| 21 Probable   | malnutrition, COPD           | Cavitation, Consolidation        | Sputum            | A. fumigatus  | Viridans Streptococci, N. pneumoniae | Voriconazole | None             | success          | dead (hemothysis)|             |
| 22 Probable   | COPD                         | Cavitation                      | Sputum            | A. terreus   | None         | Voriconazole    | None             | success          | alive        |
| 23 Probable   | Chemo                        | Cavitation, Nodules              | Sputum            | A. fumigatus  | None         | Voriconazole    | None             | success          | alive        |

Chemo: chemotherapy.
MWA was significantly increased in patients with COPD and in those that smoke \((p < .05)\). In addition, chemotherapy is known to lead to neutropenia and to a decline in systemic immunity, thus facilitating the occurrence of IPA. These observations were also found to be consistent with our findings.

The clinical symptoms and routine blood test used to diagnose IPA are often nonspecific and indistinguishable from a bacterial infection. The most common sign of IPA is a persistent fever that responds poorly to broad-spectrum antibiotic treatment [26]. Smoke-gray sputum that contains a floc is characteristic of IPA and may aid in IPA diagnosis. In this study, significant expectoration was attributed to the giant necrotic cavitation that was observed in 87.0% of the cases. Massive hemoptysis, attributable to the potent invasive ability of Aspergillus hyphae into the bronchial arterioles, was a life-threatening symptom. Chest CT provided evidence of IPA which included dense, well-circumscribed lesion(s) with/without a halo sign of ground glass attenuation, air-crescent signs and cavity formation [16,27]. A retrospective study demonstrated that macronodules (94%), a halo sign (61%), consolidation (30%), infarct-shaped nodules (27%), cavitory lesions (20%) and air crescent signs (10%) were present on chest CT imaging [28]. In our study, the most common chest CT imaging feature, cavitation with uneven walls within a mass of irregular nodules or consolidation (87.0%), was observed approximately 3–4 weeks after MWA (Figure 1). The cavity size was generally larger than that of GGO after MWA (7.36 ± 1.94 cm vs 6.44 ± 1.76 cm, \(p < .05\)), signifying the strong aggressive capability of Aspergillus. Other radiological findings included infiltration, nodules, consolidation and BRF, and these findings often coexisted (Figure 2).

In this study, clear diagnosis of IPA depended on microbiological evidence that was mainly obtained by sputum smear and culture or by intracavitary lavage smear and culture. However, negative smear cultures do not exclude IPA when it is highly suspected clinically [29], thus a serum GM test may aid IPA diagnosis. GM is released by Aspergillus spp., during hyphal growth as opposed to the conidia, hence GM testing potentially allows for differentiation between an active infection and colonization [30–32]. A positive serum GM test combined with a pathogenic culture of specimens was conducted to distinguish between the Aspergillus species and exclude colonization.

At present, there are mainly three classes of antifungal agents active against Aspergillus spp.: triazoles, polyenes and caspofungin [23,33]. Voriconazole and itraconazole are triazoles, while amphotericin B is a polyene macrolide antibiotic. Voriconazole and amphotericin B are the initial treatments of choice for invasive aspergillosis, whereas caspofungin is only approved for salvage treatment [17,23,33]. In an international, multicenter randomized open-label trial, voriconazole was compared with amphotericin B deoxycholate as an initial treatment. Voriconazole proved beneficial in terms of the response rate (53% vs. 32%), mortality rate (29% vs. 42%) and with respect to the rates of severe adverse reactions [34,35]. Hence, voriconazole is recommended for first-line treatment of IPA [17]. Voriconazole is initially dosed intravenously (6 mg/kg every 12 h for one day and then 4 mg/kg every 12 h) and is then dosed orally when clinical improvement is demonstrated. Oral itraconazole (400–600 mg/d) may serve as an alternate therapy once clinical improvement has been demonstrated with intravenous voriconazole [28].

In cases of IPA that were complicated by massive hemoptysis that threatened clinical stability, bronchial artery embolization [23] was an appropriate treatment option. In addition, intracavitary lavage by catheterization may be
appropriate for some patients with huge cavities accompanied by inadequate drainage. Voriconazole was used to lavage cavities in this study, as opposed to amphotericin [36]. In the present study, the mortality rate of IPA was attributed to massive hemoptysis and multiple organ failures that were induced by Aspergillus infection with/without secondary bacterial infection.

Conclusions
In conclusion, lung MWA may be an additional host risk factor for IPA, particularly in male patients with underlying diseases (especially COPD), heavy smokers or in patients who are undergoing perioperative chemotherapy. Early and accurate diagnosis of IPA after MWA was critical for the prognosis of patients. IPA should be considered in patients post-MWA that present with fever, cough that produces smoke-gray sputum, cavitation with/without infiltration on chest CT, positive Aspergillus culture, positive GM test results and poor response to broad-spectrum antibiotics. Furthermore, voriconazole, rather than itraconazole, should be used as the first line treatment and should be initiated as early as possible. Bronchial artery embolization or intracavitary lavage may be required. In this study, the relatively low incidence of IPA limited the analysis and identification of additional susceptibility and influencing factors. The participation of additional research institutions is required to expand the sample size. In addition, as a multicenter retrospective study, a minor bias might exist in selection of the IPA cases, which may have a slight effect on the results.

Disclosure statement
No potential conflict of interest was reported by the authors.

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