Postoperative antifungal treatment of pulmonary cryptococcosis in non-HIV-infected and non-transplant recipient patients: a report of 110 cases and literature review

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Abstract

To explore the efficacy of postoperative antifungal treatment for preventing the recurrence of pulmonary cryptococcosis (PC) and occurrence of cryptococcal meningitis (CM).

A retrospective study was conducted in 112 hospitalized PC patients with or without antifungal treatment following surgery. The treatment failure rate, PC recurrence rate, and CM incidence were compared. Additionally, the effectiveness of postoperative antifungal therapy was assessed by gathering and analyzing the published literature.

The failure rate ($P=0.054$) and recurrence rate ($P=0.178$) were similar in the two groups, but the incidence of CM was lower in the group that received postoperative antifungal treatment ($P=0.039$). This study did not show any difference in the PC recurrence rate and failure rate in the different treatment duration groups. Thus, a shorter antifungal treatment course of 2 months may be an optional treatment. In addition, upon review of the literature, no case of CM occurrence was reported among the 169 cases given postoperative antifungal treatment.

Keywords: pulmonary cryptococcosis; surgery; antifungal therapy; cryptococcal meningitis
Introduction

Pulmonary cryptococcosis (PC) is an opportunistic infection resulting from the inhalation of the contaminated fungal organism. Although most PC studies have focused on immunocompromised hosts, such as HIV-infected patients and transplant recipients, interest in the occurrence of PC in other patients has increased recently [1]. The Infectious Disease Society of America (IDSA) 2010 Clinical Practice Guidelines for the management of cryptococcosis outlined three key populations at risk for the disease: (1) HIV-infected individuals, (2) transplant recipients, and (3) HIV negative/ non-transplant recipients [1]. Because there are no typical symptoms in non-HIV-infected and non-transplant recipient PC patients and the most common imaging abnormality is a lung mass, it is difficult to differentiate PC from lung cancer, tuberculosis, or pneumonia by chest X-ray and computed tomography (CT). False-positive 18FDG-PET examinations often lead to initial clinical misdiagnosis of cancer [2]. Thus, these patients often undergo segment resection and are diagnosed with PC by histopathological examination [3,4,5].

At present, there are no specific recommendations for additional antifungal treatment for postoperative PC patients. Revised guidelines for cryptococcal infection were developed by the IDSA in 2010, but the need for postoperative antifungal therapy has not been confirmed [1,6,7,8,9,10]. Some investigators believe that non-HIV-infected and non-transplant recipient PC patients may not need postoperative antifungal therapy, if they are asymptomatic after resection of the lesion and have no clinical, serological or radiographic evidence of extra pulmonary disease [11,12]. For example, Kishi et al. reported no reoccurrence of PC in 8 immunocompetent patients treated only by surgical resection, implying that the additional antifungal treatment might not be essential [3]. Nevertheless, the evidence is scarce and remains controversial [3, 5, 6, 7].
In addition, surgical resection can only remove PC lesions other than treat dormant infections outside lesions. In most cases, cryptococcal lung disease is thought to be caused by reactivation of dormant infections, and infectious vegetative bodies have been acquired long before the diagnosis of cryptococcosis. Recurrence of PC and occurrence of CM may be caused by incomplete treatment of dormant infections outside lesions. And the central nervous system (CNS) is easily infected through the spread of the residual pathogens from the lung. Although the incidence of postoperative cryptococcal meningitis (CM) is rare, the mortality rate is as high as 20% \(^1\), and even 30% in some studies \(^{13,14}\). However, few efforts have been made by early studies to investigate the occurrence of postoperative CM. In the present study, we attempted to answer the urgent questions of whether postoperative antifungal treatment is indispensable for preventing PC recurrence as well as the occurrence of CM.

**Materials and Methods**

**Patients and data collection**

The clinical data of 112 PC patients hospitalized in Fuzhou city of Fujian province of China from January 2008 to December 2017 were retrospectively analyzed. The inclusion criterion was PC diagnosed by surgical biopsy and histopathological examination. Cryptococcal granulomas were found in all cases based on the positive results of periodic acid Schiff (PAS) and periodic acid-silver methenamine (PASM) staining. The PC lesions and all nodules were surgically removed completely, and the clean margins were verified by a pathologist. In immunocompetent patients, the host response to Cryptococcus is predominantly granulomatous inflammation or granuloma, which is accompanied by various degrees of fibrosis and necrosis. The histologic diagnosis of Cryptococcus was based on its typical morphology of narrow-based budding yeasts (4–10 μm in size) with a thickmucicarmine positive capsule. All the cases in our study were performed GMS (Gomori
Methenamine-Silver), PAS (Periodic Acid Schiff) and mucicarmine staining. The Fontana Masson stain was performed in those cases with less amount of characteristic capsule, to discriminate the other yeasts with the similar size, such as candida or histoplasma. The characteristic of this staining was that only cryptococci, which contain melanin, is positive, so we could distinguish cryptococci from other yeasts. According to the 2010 consensus reached by the IDSA and Chinese experts on the diagnosis and treatment of PC, these postoperative patients did or did not receive 400 mg oral fluconazole daily \(^1\). This study was approved by the institutional review board (IRB) and Regional Ethics Committee of Fujian Provincial Hospital. The ethics committee waived the requirement for written informed patient consent, because this was a retrospective study based on the assessment of medical records.

**Follow-up**

The follow-up procedures included chest CT examination at 3–6 months post-surgery followed by annual CT examinations for 5 years. Liver function, renal function, and electrolyte laboratory tests were conducted once a month to monitor the occurrence of adverse effects of fluconazole. The duration of follow-up was at least 6 months following surgery and antifungal therapy. All included postoperative patients were divided into antifungal treatment and non-antifungal treatment groups. Depending on the duration of the postoperative treatment courses, the antifungal treatment patients were further divided into two groups: 2 months, and >2 months. These treatment course cut-offs were established according to the 2010 consensus reached by Chinese experts, which recommends at least 2 months’ treatment after surgery \(^15\). Treatment failure was defined as postoperative recurrence of PC and/or CM occurrence. CT detection of relapse of a lung mass was regarded postoperative recurrence, confirmed by a transbronchial lung biopsy and absorption of the lesions after antifungal treatment. The treatment failure rate, PC recurrence rate, and CM incidence after surgery were compared between the antifungal therapy group and the non-antifungal
treatment control group. In addition, the treatment failure rate and PC recurrence rate after surgery were compared among the three groups that received anti-fungal treatment for different durations.

Statistical analysis

IBM SPSS Statistics package (version 23.0) was used to analyze the patient data, including gender, age, lifestyle, clinical manifestations, immunocompromising diseases, lesion locations and sizes, presence of single or multiple nodules, types of surgery, and administration of anti-fungal treatment and the corresponding regimen. Continuous variables with a normal distribution were presented as the means±standard deviation (SD) and compared by Student’s t-test or variance analysis. Proportional variables were analyzed by the Fisher's exact test. P values less than 0.05 were considered significant.

Literature review

Our literature review scope included literature published in the PubMed, CENTRAL and Embase databases before December 19, 2018, identified by searching titles and abstracts with the following keywords: “surgical treatment/sublobar resection/lobectomy/segmentectomy/wedge resection/ pulmonary cryptococcosis”. The effects of postoperative antifungal treatment, including the treatment failure rate, PC recurrence rate, and CM incidence, were evaluated by collecting and analyzing the published data from the relevant literature.

Results

Effects of postoperative antifungal treatment
During the follow-up, 2 of the 112 patients were lost to follow-up, leaving 110 patients who were successfully followed-up with a median duration of 47.70 months (range, 14 to 116 months) by December 2018. These cases included 22 cases not given antifungal treatment, 30 cases that received 2 months of antifungal treatment, 60 cases that received >2 months of treatment. None of these 110 patients had CNS symptoms. According to the cryptococcal infection guidelines\[1\], routine lumbar puncture is usually unnecessary for patients without CNS symptoms to assess the pulmonary nodule or infiltrate for normal hosts. Among the 22 patients not given antifungal treatment, three suffered therapy failure with one case of PC recurrence, one case of CM, and one case with both PC recurrence and CM occurrence. Of the 90 cases that received postoperative antifungal treatment, 2 cases were lost during follow-up, leaving 88 patients who all received oral fluconazole at a dose of 400 mg per day. Of these, there were two cases of relapse but no cases of CM. These patients were diagnosed with PC recurrence by surgical biopsy and histopathological examination. The failure rate did not differ significantly between the antifungal and non-antifungal treatment groups (2 of 88 vs 3 of 22, \( P=0.054 \)), nor did the PC recurrence rate (2 of 88 vs 2 of 22, \( P=0.178 \); Figure 1). However, the incidence of CM in the postoperative antifungal treatment group was significantly less than in the non-antifungal treatment group (0 of 88 vs 2 of 22, \( P=0.039 \); Figure 1). Furthermore, statistical comparisons between the groups for all other clinical characteristics revealed a significant difference only in nodule location (Table 1), which was excluded by the subsequent risk factor analysis (Table 3). The failure rate did not differ significantly between the patients underwent local excision and standard lobectomy (3 of 86 vs 2 of 24, \( P=0.316 \)).

Effects of different antifungal treatment duration
As shown in Table 2, there was one case of PC recurrence in the group that received 2 months of antifungal treatment and one case in the group that received more than 2 months of treatment. The PC recurrence rate and failure rate did not differ significantly between the two groups with differing durations of antifungal treatment ($P=1.000$). Additionally, there was no difference in the incidence of liver dysfunction between the two groups ($P=1.000$), and the liver damage rates were 2 of 30, and 4 of 58, respectively. No other adverse effects of fluconazole were observed between the two groups. Except for the expected differences in the medication cost ($266±112$, and $518±188$ respectively, $P<0.05$), no other significant differences were found between the two groups with differing antifungal treatment duration (Table 2). Taken together, these results indicated that there were no differences in the clinical characteristics of patients between the two groups.

**Review of the literature on postoperative antifungal treatment of PC**

Our literature search identified 18 articles$^{[2,5,6,9,16-29]}$ containing 286 cases that met our search criteria (Figure 2; Table3). Studies were rated according to the level of evidence provided according to the criteria of the Centre for Evidence-Based Medicine in Oxford, UK$^{[30]}$. The methodological quality of retrospective studies was assessed by the modified Newcastle-Ottawa scale$^{[31]}$, which consists of three factors: patient selection, comparability of the study groups, and assessment of outcome. A score of 0–9 (allocated as stars) was allocated to each study. Observational studies achieving six or more stars were considered to be of high quality. Agreement between the two reviewers was 96% in study selection and 93% in quality assessment. The characteristics of the included studies, which ranged from 6 to 7 stars by the grading systems, are summarized in Table 3, and the effectiveness of postoperative antifungal treatment was evaluated. However, the quality of the literature...
evidence was generally low. Matching of criteria such as underlying diseases, lifestyles, symptoms, nodule sizes, imaging characteristics, lesion locations, and types of surgery was not possible, because this information was not clearly described in all studies. Among them, treatment failure events occurred in both antifungal (1/169) and non-antifungal treatment (4/117) groups. However, no CM incidence was reported among patients given postoperative antifungal treatment. In contrast, three CM cases were reported among patients without postoperative antifungal treatment. Nevertheless, because postoperative treatment failure is rare and the number of related articles is limited, a meta-analysis was almost impossible.

Case 1

The patient had an immunocompromising disease, and the PC was diagnosed by surgical biopsy and histopathological examination. Both smear and culture test of sputum and alveolar lavage fluid were negative. No postoperative treatment was administered, and PC relapse and CM occurred 1 year after surgery. The complications of type I respiratory failure and cerebrospinal fluid abnormalities were cured after treatment. This case was reported by Lan et al. in 2016 with 3 years of follow-up [27].

Case 2

A patient with an APACHE II score of 0-9 was diagnosed with mild PC by surgical biopsy and histopathological examination. Immunoassay showed the cryptococcus capsular polysaccharide antigen titer was negative (≤1:4). After surgery, this patient did not receive any treatment until the PC relapsed and the conditions were improved by further therapy. This case was reported by Wang et al. in 2014 with continued follow-up [25].

Case 3
A patient with an APACHE II score of 10-20 was also reported by Wang et al. in 2014 and was diagnosed with severe PC by surgical biopsy and histopathological examination. After postoperative antifungal treatment for 3–12 months, PC still relapsed, although the conditions were finally improved by further therapy. This case was still in further follow-up when the article was published [25].

Case 4

A 63-year-old immunocompetent male was admitted with a right lung mass accidentally found after trauma. PC was diagnosed by surgical biopsy and histopathological examination. He did not receive any postoperative treatment, and the CM developed 5 months after surgery and was cured by further therapy. This case was reported by Hu et al. in 2006 with 30 months of follow-up [18].

Case 5

This immunocompetent patient was diagnosed with PC by surgical biopsy and histopathological examination. No cryptococcosis was detected by bronchoscopic examination. The patient did not receive any postoperative treatment, and PC relapse and CM development occurred after surgery. The conditions were improved by further therapy. The case was reported by Liu et al. in 2006 with continued follow-up until the article was published [17].

Discussion

In this report, our retrospective review of 110 cases revealed no significant differences in the PC recurrence rate between groups with and without antifungal treatment. Therefore, in consideration of the limited sample size in the present study, we cannot definitively conclude that postoperative antifungal treatment is dispensable. On the other hand, the postoperative
CM incidence among 88 cases in the antifungal treatment group was significantly less than that in the non-antifungal treatment group. In addition, no CM incidence has been reported in 169 postoperative antifungal treatment cases described in the published literature. Taken together, these results strongly support the idea that the hematogenous spread of cryptococci to the CNS after surgery can be prevented by early vigorous antifungal treatment.\(^7\)

For PC patients with mild-to-moderate symptoms, the present antifungal treatment scheme includes oral fluconazole (400 mg per day orally) for 6–12 months\(^1\). However, the specific postoperative treatment and optimal duration of therapy have not been precisely elucidated. In our retrospective study, the PC recurrence rate and failure rate did not differ significantly between two groups with different antifungal treatment durations. There also was no difference in the incidence of liver dysfunction among the two groups. Therefore, in consideration of the high cost, the effect of extended antifungal treatment after surgery is limited, and a shorter treatment course of 2 months may be an optional treatment. At the same time, similar PC recurrence and CM occurrence rates were found between the groups that underwent two types of surgery \((P=0.316)\), indicating that standard lobectomy may not be needed if local excision can remove lesions completely. Considering these findings together, we propose that a regimen of 2 months oral fluconazole treatment following lung local wedge resection is economical and optional for preventing PC recurrence and CM occurrence.

There were some limitations in the current study. For example, in our study, lumbar puncture was not performed to rule out asymptomatic CNS involvement, although according to the cryptococcal infection guidelines\(^1\), routine lumbar puncture is usually unnecessary for patients without CNS symptoms to assess the pulmonary nodule or infiltrate for normal hosts. And the PC diagnosis tests also include pathogen culture, smear slides, and cryptococcal latex agglutination test, the results of these laboratory tests were not fully available for this retrospective study. Whether fluconazole was given or not is based on the experience of
the governing physician, it may lead to selection bias. The canavanine-glycine-bromothymol blue assay and genome sequencing were not applied, making it difficult to distinguish cases of infection by C. neoformans from C. gattii\cite{32,33}. Moreover, antibiotic resistance can reduce the effectiveness of anti-fungal therapy. Nevertheless, in our clinical laboratory, cryptococcosis pathogen identification (ID) and antibiotic susceptibility test (AST) are not available. Therefore, we cannot exclude the possibility that the presence of resistant strains may have contributed to the postoperative therapy failure. If the antifungal drug can be selected based on a drug susceptibility test, the postoperative treatment failure rate will be further reduced. Second, this retrospective study had a follow-up length of less than 9 years, whereas cryptococcosis may recur decades later when triggered by other conditions. Furthermore, the sample size was relatively small, and the treatment sites were limited to three hospitals in a local region of China. In summary, a prospective, large-sample case-control study is needed to validate and reinforce our conclusions.

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**Conflict of Interest:** All authors declare they have no conflict of interest.
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Figure Legends

Figure 1 Comparison of the treatment failure rate, PC recurrence rate, and CM incidence after surgery between the antifungal therapy group and the non-antifungal treatment control group.

- Treatment failure rate $P=0.054$
- PC recurrence rate $P=0.178$
- CM recurrence rate $P=0.039$
Figure 2 Flow diagram of identification of relevant literature reports.

Pubmed: n=22
Embase: n=55
Central: n=0

Deleted duplications: n=13
Included studies: n=64

Included studies: n=18
Full-text articles: n=16
Abstracts: n=2

Excluded studies: n=46
No surgery or other surgery: n=18
CM before surgery antifungal therapy was not available: n=14
Occurrence of cryptococcal meningitis before surgery: n=4
Extrapulmonary cryptococcosis: n=1
Case reports: n=5
Abstracts data not extractable: n=4
Table Legends

Table 1 Baseline characteristics of patients.

| Factors          | Non-antifungal treatment | Antifungal treatment | P      |
|------------------|--------------------------|----------------------|--------|
| n                | 22                       | 90(88)*              |        |
| Age, years       | 49.90±10.69              | 49.47±9.16           | 0.371  |
| Gender, n (%)    |                          |                      | 0.249  |
| Male             | 10[45]                   | 52[59]               |        |
| Female           | 12[55]                   | 36[41]               |        |
| Location         |                          |                      | 0.008  |
| Left Lung        | 18[82]                   | 42[48]               |        |
| Right Lung       | 4[18]                    | 46[52]               |        |
| Diameter of nodules* |                  |                      | 0.070  |
| ≤3 cm            | 12[55]                   | 66[75]               |        |
| >3 cm            | 10[45]                   | 22[25]               |        |
| Nodule types                        |                |        |
|-------------------------------------|----------------|--------|
| Single                              | 14[64]         | 48[55] |
| Multiple nodules in a single lobe   | 8[36]          | 40[45] |

| Type of surgery                     |                |        |
|-------------------------------------|----------------|--------|
| Wedge resection                     | 18[82]         | 68[77] |
| Lobectomy                           | 4[18]          | 20[23] |

| Lifestyles                          |                |        |
|-------------------------------------|----------------|--------|
| None                                | 17[77]         | 75[85] |
| Yes                                 | 5[23]          | 13[15] |

| Clinical symptoms                   |                |        |
|-------------------------------------|----------------|--------|
| With                                | 16[73]         | 59[67] |
| Without                             | 6[27]          | 29[33] |

| Immunocompromising                  |                |        |
|-------------------------------------|----------------|--------|
| Without                             | 16[73]         | 76[86] |
| With                                | 6[27]          | 12[14] |

| Median duration of follow up        |                |        |
|-------------------------------------|----------------|--------|
|                                    | 48.91±5.01     | 47.40±1.96 | 0.087 |
|                        |     |     |            |
|------------------------|-----|-----|------------|
| Failure rate           | 3^*|13.636| 2[2.273]  |
| Recurrence of PC       | 2[9.091]|2[2.273]| 0.178     |
| Occurrence of CM       | 2[9.091]| 0[0]| **0.039** |

* 2 cases were lost to follow-up

# The longest lesion dimension was measured with a cut-off of 3 cm. According to the consensus of Chinese experts in lung nodules, \( \leq 3 \text{ cm} \) was defined as a placeholder and \( >3 \text{ cm} \) as a mass.\(^{[34]}\)

@ Damp conditions or a history of contact with pigeons or other birds.

& One case of PC recurrence, one case of CM, and one case of both.

Data are presented as number [%]
Table 2 Baseline characteristics of patient groups according to the duration of postoperative antifungal treatment

| Factors                        | 2 months | >2 months | P    |
|-------------------------------|----------|-----------|------|
| n                             | 30       | 60(58)*   | 0.426|
| Age, years                    | 50.57±9.354 | 48.91±9.097 |      |
| Gender, n (%)                 |          |           | 0.820|
| Male                          | 17[57]   | 35[60]    |      |
| Female                        | 13[43]   | 23[40]    |      |
| Location                      |          |           | 0.265|
| Left Lung                     | 13[43]   | 33[57]    |      |
| Right Lung                    | 17[57]   | 25[43]    |      |
| Nodule size                   |          | 1.000     |      |
| ≤3 cm                         | 23[77]   | 43[74]    |      |
| >3 cm                         | 7[23]    | 15[26]    |      |
| Nodule type                   |          | 0.824     |      |
| Single                        | 17[57]   | 31[53]    |      |
| Multiple nodules in a single lobe | 13[43]   | 27[47]    |      |
| Type of surgery               |          | 1.000     |      |
| Wedge resection               | 24[80]   | 44[76]    |      |
| Lobectomy                     | 6[20]    | 14[24]    |      |
| Lifestyles* | 1.000 |
|-------------|-------|
| Without     | 26[87]| 49[84] |
| With        | 4[13] | 9[16]  |
| Clinical symptoms | 0.157 |
| With        | 17[57]| 42[72] |
| Without     | 13[43]| 16[28] |
| Immunocompromising disease | 0.744 |
| Without     | 27[90]| 49[84] |
| With        | 3[10] | 9[16]  |
| Recurrence  | 1[3.333]| 1[1.724] |
| Occurrence of CM | 1.00  |
| Cost($)     | 266±112| 518±188 |
| Liver dysfunction | 2[6.667]| 4[6.897] |

* 2 cases were lost to follow-up
@ Damp conditions or a history of contact with pigeons or other birds.

Data are presented as number [%]
Table 3 Summary of literature review

| Study          | Year | Design* | Nation   | level of evidence | antifungal treatment length (months) | Patients, no. | Event | Follow-up period, years | Quality score |
|----------------|------|---------|----------|-------------------|-------------------------------------|----------------|-------|------------------------|---------------|
| Nadrous et al.[6] | 2003 | R       | 4        | 4                 | 0                                   | 6              | 0     | 1.6                    | ★★★★★★★★★★ |
| Wang et al.[16] | 2005 | R       | China    | 4                 | 0                                   | 10             | 0     |                        |               |
| Liu et al.[17]  | 2006 | R       | China    | 4                 | 6-12                                | 19             | 0     | 2-5年                  | ★★★★★★★★★★ |
|                | 2006 |         |          |                   |                                     | 0              | 6     | CM                     |               |
| Igai et al.[5]  | 2006 | R       | Japan    | 4                 | 1-2                                 | 6              | 0     | 2                      | ★★★★★★★★★★ |
| Hu et al.[18]   | 2006 | R       | China    | 4                 | 0.5-6                               | 2              | 0     | 2.5-6                  | ★★★★★★★★★★ |
|                | 2006 |         |          |                   |                                     | 0              | 5     | 1 case CM              |               |
| Kishi et al.[2] | 2006 | R       | Japan    | 4                 | 0                                   | 8              | 0     | 3.5                    | ★★★★★★★★★★ |
| Dewar et al.[9] | 2008 | R       | Canada   | 4                 | 0                                   | 2              | 0     |                        | ★★★★★★★★★★ |
| Authors       | Year | Region | n | Median Age | Follow-up Length | Ref | Comments |
|--------------|------|--------|---|------------|------------------|-----|----------|
| Sakurai et al. [19] | 2009 | Japan | 4 | NA | 4 | 0 | NA | ★★★★★★ |
| Ito et al. [20]   | 2011 | Japan | 4 | NA | 1 | 0 | NA | ★★★★★★ |
| Ye et al. [21]   | 2012 | China | 4 | NA | 26 | 0 | NA | ★★★★★★ |
| Xie et al. [22]  | 2012 | China | 4 | 1-1.5 | 51 | 0 | 3.5 | ★★★★★★★ |
| Yu et al. [23]   | 2012 | China | 4 | 1-2 | 5 | 0 | 3-11 | ★★★★★★★ |
| Peng et al. [24] | 2014 | China | 4 | 20d-4 | 14 | 0 | 0.1-3.6 | ★★★★★★ |
| Wang et al. [25] | 2014 | China | 4 | 6-12 | 8 | PC | NA | ★★★★★★ |

1 case

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| Study                | Year | Country   | Treatment Length | Death | Recovery | Duration | Treatment Type |
|----------------------|------|-----------|------------------|-------|----------|----------|----------------|
| Hayakawa et al.[26]  | 2015 | Japan     | 4 3 2 0          |       |          |          | ★★★★★         |
| Lan et al.[27]       | 2016 | China     | 4 3-6 26 0 0.3-3 |       |          |          | ★★★★★★        |
|                      | 2016 |           |                  |       |          |          |                |
| Kanjanapradit et al.[28] | 2017 | Thailand | 4 6 3 0 0.5     |       |          |          | ★★★★★         |
| WANG DX et al.[29]   | 2018 |           | 4 3 2 0          |       |          |          |                |

* R = retrospective analysis

¶NA = with antifungal treatment but the duration was not available,

Treatment length 0 = No antifungal treatment after surgery (total of 117 case)
Figure 1

- Treatment failure rate $P=0.054$
- PC recurrence rate $P=0.178$
- CM recurrence rate $P=0.039$
Figure 2

- PubMed: n=22
  - Embase: n=55
  - Central: n=0

  Excluded studies: n=46
  - No surgery or other surgery: n=18
  - CM before surgery antifungal therapy was not available: n=14
  - Occurrence of cryptococcal meningitis before surgery: n=4
  - Extrapulmonary cryptococcosis: n=1
  - Case reports: n=5
  - Abstracts data not extractable: n=4

  Deleted duplications: n=13
  Included studies: n=64
  Included studies: n=18
  Full-text articles: n=16
  Abstracts: n=2