Original Article

The use of surgery in a real-world clinic to diagnose and treat pulmonary cryptococcosis in immunocompetent patients

Bumhee Yang[1#], Hyun Lee[2#], Taebum Lee[3], Sun-Hyung Kim[4], Min Young Kim[5], Byeong-Ho Jeong[4], Sumin Shin[6], Seonwoo Kim[7], Kyung Soo Lee[5], O. Jung Kwon[4], Hojoong Kim[4]

[1]Division of Pulmonology, Center of Lung Cancer, National Cancer Center, Goyang, Korea; [2]Division of Pulmonary Medicine and Allergy, Department of Internal Medicine, Hanyang University College of Medicine, Seoul, Korea; [3]Department of Pathology and Translational Genomics, [4]Division of Pulmonology and Critical Care Medicine, Department of Medicine, [5]Department of Radiology, [6]Department of Thoracic and Cardiovascular Surgery, [7]Statistics and Data Center, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Contributions: (I) Conception and design: B Yang, H Lee, KS Lee, H Kim; (II) Administrative support: T Lee, SH Kim; (III) Provision of study materials or patients: B Yang, H Lee, MY Kim, S Kim, KS Lee, H Kim; (IV) Collection and assembly of data: B Yang, H Lee, MY Kim, S Kim, KS Lee, H Kim; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Hojoong Kim, MD, PhD. Division of Pulmonary and Critical Care Medicine, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea. Email: hjk3425@skku.edu.

Background: We evaluated the role played by surgery in the diagnosis and treatment of pulmonary cryptococcosis (PC) in immunocompetent subjects.

Methods: We retrospectively studied 53 immunocompetent patients who were pathologically diagnosed with PC between January 2000 and December 2016 in a tertiary referral center. We compared the radiological presentations of, and diagnostic modalities used to evaluate, patients diagnosed both surgically and non-surgically. We also compared the treatment outcomes of patients who underwent surgical resection alone and those who received additional antifungals following surgical resection.

Results: Of the 53 patients, 30 (57%) were diagnosed via non-surgical modalities including percutaneous needle biopsy (PCNB) (n=29) and transbronchial lung biopsy (TBLB) (n=1); and 23 (43%) were diagnosed by surgical modalities including video-assisted thoracoscopic wedge resection (n=22) and lobectomy (n=1). An initial clinical suspicion of a lung malignancy was associated with the use of surgical diagnostic approaches (P<0.001). Whereas undetermined locations were associated with the use of surgical diagnostic approaches, radiological findings such as clustered nodular patterns (P<0.001), cavities (P=0.005), air bronchograms (P<0.001), and peripheral lesions (P<0.001) were associated with the use of non-surgical diagnostic approaches. Of the 30 non-surgically diagnosed patients, 21 (70%) were treated with antifungals and 9 (30%) were followed-up without treatment. Of the 23 patients who underwent surgical treatment, 8 received additional antifungals. The proportion of patients who had radiological improvement was significantly higher in surgically diagnosed patients than non-surgically diagnosed patients (100% *vs.* 73%; P=0.007). However, there was no significant difference in disease progression between patients who underwent surgical resection alone and those who additionally received antifungals (P=0.999).

Conclusions: Surgical resection was required in some patients to diagnose PC. An initial suspicion of a lung malignancy was associated with use of surgical diagnostic approaches. Surgical resection not only afforded reliable diagnoses but also effectively treated PC. There was no need for additional antifungals after complete surgical resection.

Keywords: Pulmonary cryptococcosis (PC); surgery; diagnosis; treatment; antifungal

Submitted Jul 28, 2018. Accepted for publication Mar 26, 2019.
doi: 10.21037/jtd.2019.04.17
View this article at: http://dx.doi.org/10.21037/jtd.2019.04.17

Introduction

Pulmonary cryptococcosis (PC) is a fungal infection caused by inhalation of spores of *Cryptococcus neoformans* and *C. gattii*, which can trigger pulmonary involvement (1). Inhalation of cryptococcal particles can cause pulmonary infection, and subsequent hematogenous dissemination may trigger central nervous system infection, especially in immunocompromised patients (2). Although PC is more common in immunocompromised patients, including acquired immune deficiency syndrome (AIDS) patients, solid-organ transplant recipients, those with hematological malignancies, and patients on chronic corticosteroids or other immunosuppressive therapies (3-5), PC is occasionally seen in immunocompetent patients (6). The incidence of PC in such patients is increasing, most of whom have no apparent underlying disease (7,8).

In immunocompetent hosts, PC often mimics a lung malignancy, or a chronic inflammatory or infectious disease such as tuberculosis. On imaging, single or multiple nodular lesions or mass-like consolidations are apparent (9,10). Therefore, the diagnostic approach varies widely depending on the initial presumed diagnosis and radiological findings. If the presumed diagnosis is benign, physicians may prefer to use non-surgical modalities, such as percutaneous needle biopsy (PCNB) or transbronchial lung biopsy (TBLB), for definitive diagnosis. If the presumed diagnosis is malignant, more invasive diagnostic modalities such as video-assisted thoracoscopic surgery (VATS) are employed, especially when the lesions are not peripheral. However, previous studies have simply described the diagnostic modalities employed; the factors that influence the diagnostic approaches chosen remain unclear.

Various PC treatment options are available, including surgical resection, antifungal agents, and observation (11,12). However, as surgical resection is required for the diagnosis of many PC cases, treatment options should be determined on the basis of the need for such resection. No specific recommendations for the treatment of PC diagnosed by surgical resection are available and it is unclear whether such patients require additional antifungals. Also, the natural disease course in such patients has not been well-documented. Thus, we evaluated the role for surgery in PC diagnosis and treatment in a real-world clinic, and the need (or otherwise) for additional antifungals after surgical resection of PC.

Methods

Patients

The medical records of 53 immunocompetent patients diagnosed with PC in Samsung Medical Center (a 1,979-bed referral hospital) in Seoul, South Korea, between January 2000 and December 2016, were retrospectively reviewed. All patients had pathologically confirmed PC; biopsy specimens were obtained via non-surgical modalities such as PCNB (n=29, 55%) and TBLB (n=1, 2%) and a surgical modality (VATS) (n=23, 43%) (*Figure 1*). The study was approved by the Institutional Review Board of Samsung Medical Center. The need for written patient consent was waived because the study was retrospective in nature (IRB no. 2017-06-142-011).

Image definition and interpretation

Thoracic computed tomography (CT) images were evaluated for the presence of lung abnormalities (nodules, masses, and consolidations). All radiological data were retrospectively reviewed by the three co-authors (B Yang, MY Kim, and KS Lee). Nodules were defined as round or oval opacities <3 cm in the greatest diameter; larger opacities were termed masses. A consolidation was defined as a parenchymal non-nodular opacity that obscured the underlying pulmonary architecture and that was often accompanied by an air bronchogram. Each pattern was classified as predominantly central, peripheral, undetermined, or multiple. Undetermined means predominantly lesion defined as lesion between central and peripheral, and multiple is defined as involve of more than two of peripheral, central, and undetermined. Cavitations within nodules or masses were noted. After assessment of lung parenchymal abnormalities, all lesions were further classified into six patterns: solitary pulmonary nodules, solitary pulmonary masses, scattered nodules, clustered nodules, a bronchopneumonic pattern, and a mixed pattern. Solitary pulmonary nodes and masses were defined when the lung lesions consisted of a single nodule or a single mass. The clustered nodular pattern was defined when the lesions consisted of multiple nodules of various sizes in segments of the same lobe (*Figure 2A*). The scattered nodular pattern was defined when the lesions consisted of multiple nodules of various sizes in segments of the same lung (*Figure 2B*).

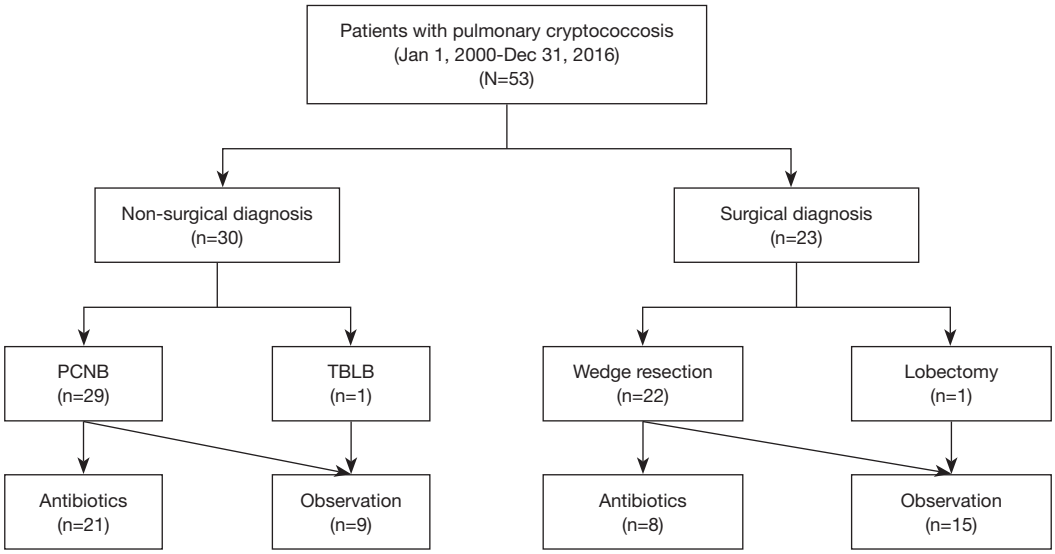

Figure 1 Diagnostic and treatment flow.

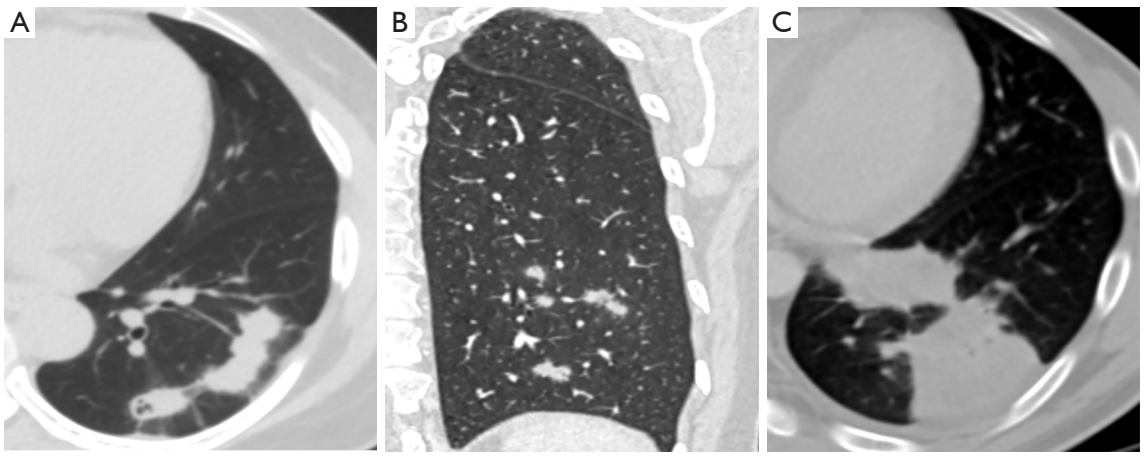

Figure 2 Radiological findings of *Cryptococcus*. (A) Clustered nodular pattern in a 52-year old female patient who was diagnosed via PCNB; (B) scattered nodar pattern in a 53-year old female who was diagnosed via surgical resection; (C) bronchopneumonic pattern in a 45-year old male who was diagnosed via PCNB. PCNB, percutaneous needle biopsy.

The bronchopneumonic pattern (*Figure 2C*) was defined when lung lesions were comprised of areas of lobular, subsegmental, or segmental consolidation, when the lesions featured ill-defined small centrilobular nodules (4–10 mm in diameter, reflecting peribronchiolar consolidation), or when the lesions had a "tree-in-bud" appearance (small centrilobular nodules with branching nodules within secondary pulmonary lobules) (13).

Pathologic diagnosis of Cryptococcus

In immunocompetent patients, the host response to *Cryptococcus* is predominantly granulomatous inflammation or granuloma, which is accompanied by various degrees of fibrosis and necrosis (14). The histologic diagnosis of *Cryptococcus* was based on its typical morphology of narrow-based budding yeasts (4–10 μm in size) with a thick

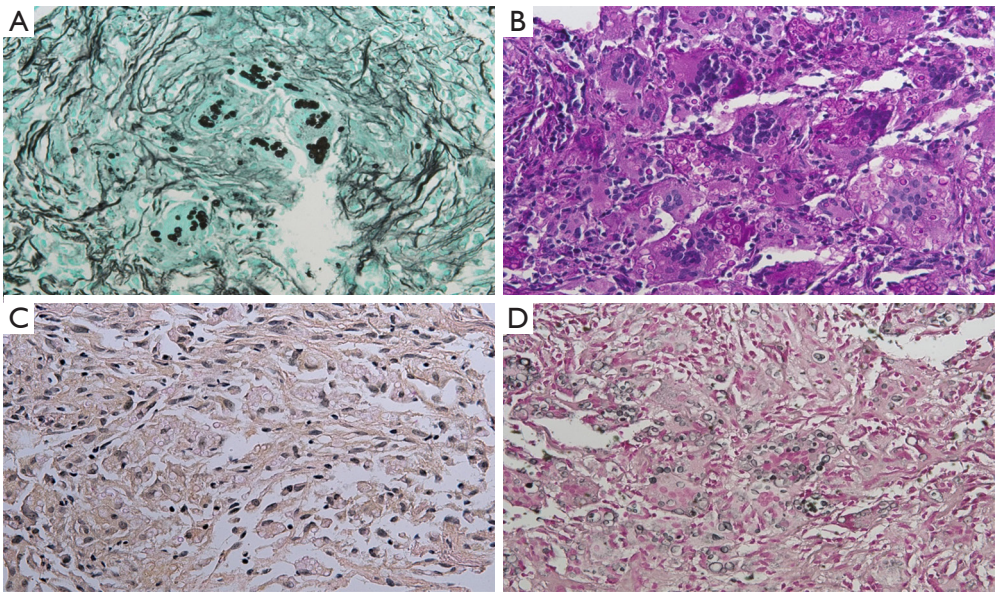

Figure 3 Histologic diagnosis of *Cryptococcus* (×400). (A,B) Narrow-based budding yeasts (4–10 μm in size) are positive in GMS and PAS stains, and (C) mucicarmine stain is positive in capsule. (D) Fontana Masson stain positivity helps to differentiate *Cryptococcus* from other similar yeasts. GMS, Gomori Methenamine-Silver; PAS, Periodic Acid Schiff.

mucicarmine positive capsule *(Figure 3A,B,C)*. All cases of our study were performed GMS (Gomori Methenamine-Silver), PAS (Periodic Acid Schiff) and mucicarmine staining. In some case with lesser amount of characteristic capsule, the Fontana Masson stain was performed to discriminate other yeasts of similar size, such as candida or histoplasma. The characteristic of this stain was that only cryptococci, which contain melanin, showed positive, so we could distinguish cryptococci from other yeasts *(Figure 3D)*.

Treatments and responses

After PC diagnosis, the treatment modalities were applied at the discretion of the attending physicians. Generally, patients who were diagnosed non-surgically were given antifungals or followed-up without specific treatment, while patients who were diagnosed surgically were further treated with antifungals or followed-up without additional antifungal treatment. After initial treatment, patients were usually followed-up at 1-month intervals for 3 months, and 3-month intervals thereafter, via chest X-ray or CT in addition to laboratory tests. The treatment responses were categorized as complete or partial, stable disease, or progressive disease, as described previously. A complete response was defined as complete disappearance of all clinical symptoms and radiological findings. A partial response was defined as partial resolution of the chest CT lesion, regardless of clinical improvement. No change was defined as no imaging change and progressive disease was defined as progression evident on chest CT (15).

Statistical analysis

All data are presented as medians with interquartile ranges (IQRs) for continuous variables, and as numbers with percentages for categorical variables. Data were compared using the Mann-Whitney U test for continuous variables and the Pearson χ^2 test or Fisher's exact test for categorical variables. The one-sample proportion test was used to derive P values for the radiological findings. A two-sided $P<0.05$ was considered to reflect statistical significance in all analyses. All statistical analyses were performed using SPSS statistical software (ver. 23.0; IBM Corp., Armonk, NY, USA) and R (ver. 3.2.3; R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients

The baseline characteristics of the 53 PC patients are

Table 1 Baseline characteristics of 53 patients with PC

Baseline characteristics	Total (n=53, 100%)	Non-surgical diagnosis (n=30, 57%)	Surgical diagnosis (n=23, 43%)	P
Age, years	57 [47–66]	52 [43–63]	64 [53–69]	0.239
Sex, male	35 [66]	22 [73]	13 [57]	0.200
Current or ex-smoker	28 [53]	16 [53]	12 [52]	0.921
Comorbidities				
Diabetes mellitus	15 [28]	6 [20]	9 [39]	0.125
Hypertension	20 [38]	6 [20]	14 [61]	0.002
History of tuberculosis	5 [9]	2 [7]	3 [13]	0.431
Malignancy	15 [28]	3 [10]	12 [52]	0.001
Clinical symptoms				
Cough	14 [26]	10 [33]	4 [17]	0.192
Sputum	10 [19]	7 [23]	3 [13]	0.342
Hemoptysis	2 [4]	1 [3]	1 [4]	0.848
No symptoms	36 [68]	18 [60]	18 [78]	0.158

Data are presented as number [%] or as median [interquartile range]. PC, pulmonary cryptococcosis.

summarized in *Table 1*. They included 35 males (66%), and the median patient age was 57 years (IQR: 47–66 years). Twenty-eight patients (53%) were current or ex-smokers. The most common comorbidities were hypertension (n=20, 38%), a malignancy (n=15, 28%), diabetes mellitus (n=15, 28%), and a previous history of tuberculosis (n=5, 9%). In terms of symptoms at the time of PC diagnosis, 36 patients (68%) had no symptoms, 14 (26%) had cough, 10 (19%) exhibited sputum production, and 2 (4%) exhibited hemoptysis.

As shown in *Figure 1*, 30 patients (57%) were diagnosed using non-surgical modalities including PCNB (n=29) and TBLB (n=1), and 23 were diagnosed using surgical modalities including VATS wedge resection (n=22) and VATS lobectomy (n=1). As shown in *Table 1*, there was no significant difference in age, sex, smoking history, the frequency of comorbidities such as diabetes mellitus, history of previous tuberculosis, or clinical symptoms between patients diagnosed surgically and non-surgically. However, the frequency of malignancy was significantly higher in patients diagnosed surgically [52% (12/23) *vs.* 10% (3/30); P=0.001].

As shown in *Figure 4*, the initial presumed clinical diagnosis in surgically diagnosed patients was more commonly lung malignancy versus those who were non-surgically diagnosed [70% (16/23) *vs.* 17% (5/30); P<0.001 for initial clinical diagnosis].

Radiological findings

The thoracic CT findings are summarized in *Table 2*. In terms of radiological patterns, the scattered nodular pattern was the most common (n=16, 30%), followed by the solitary nodular pattern (n=15, 28%), the clustered nodular pattern (n=10, 19%), the multiply clustered nodular pattern (n=4, 8%), the bronchopneumonic pattern (n=4, 8%), and the mixed pattern (n=2, 3%). Cavitation was found in 13 patients (25%), and air bronchograms was seen in 15 (28%). Of all lung lesions, 66% (n=35) were peripheral. Radiological characteristics of 15 cryptococcosis patients with a solitary pulmonary pattern show in *Table S1*. There was no difference of the radiological characteristics in the choice of diagnosis modality among patients with solitary pulmonary nodules. Also, the initial clinical diagnosis and radiological findings according to the diagnostic approach were showed in *Table S2*.

As shown in *Table 2*, for the diagnosis of PC, surgical modality was more frequently used than non-surgical modality in patients with the following radiologic patterns; clustered nodular pattern (79% *vs.* 21%; P<0.001), cavities

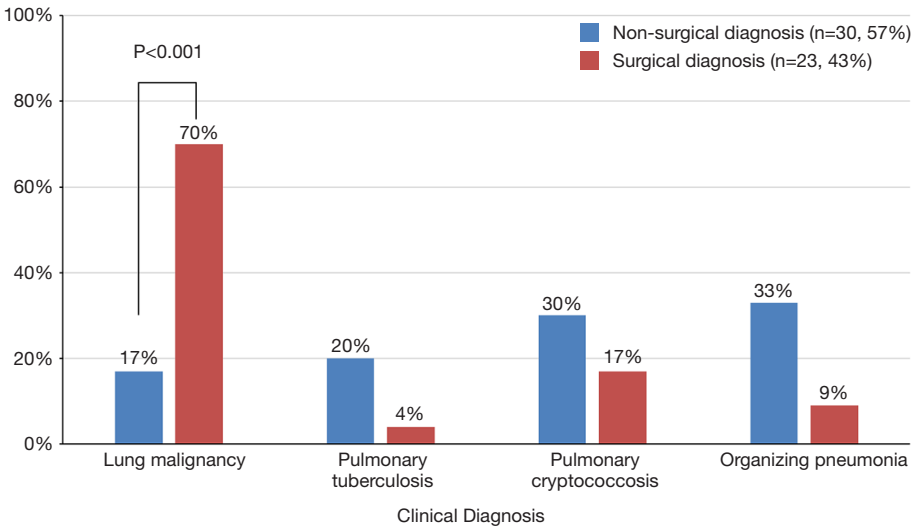

Figure 4 Initial presumed clinical diagnosis in patients with PC. PC, pulmonary cryptococcosis.

Table 2 Radiological findings of 53 patients with PC

Radiologic findings*	Total (n=53, 100%)	Non-surgical diagnosis (n=30, 57%)	Surgical diagnosis (n=23, 43%)	P
Main pattern				
Nodular pattern				
Scattered nodular	16 [30]	7/16 [44]	9/16 [56]	0.230
Clustered nodular	14 [26]	11/14 [79]	3/14 [21]	<0.001
Solitary pulmonary nodular	15 [28]	8/15 [53]	7/15 [47]	0.407
Solitary pulmonary mass	2 [4]	1/2 [50]	1/2 [50]	0.500
Bronchopneumonic pattern	4 [8]	3/4 [75]	1/4 [25]	0.051
Mixed pattern	2 [4]	0/2 [0]	2/2 [100]	–
Other signs				
Cavity	13 [25]	9/13 [69]	4/13 [31]	0.005
Mediastinal lymphadenopathy	1 [2]	0/1 [0]	1/1 [100]	–
Air bronchogram	15 [28]	11/15 [73]	4/15 [27]	<0.001
Location				
Peripheral	36 [68]	24/36 [67]	12/36 [37]	<0.001
Central	1 [2]	0/1 [0]	1/1 [100]	–
Undetermined	13 [25]	4 /13 [31]	9/13 [69]	0.005
Multiple	3 [6]	2/3 [67]	1/3 [33]	0.255
Number of lobes involved	2 [1–6]	4 [1–6]	1 [1–6]	0.069

Data are presented as number [%] or as median [interquartile range]. *, one sample proportion test was used for P values for radiologic findings. PC, pulmonary cryptococcosis.

Table 3 Comparison of treatment responses between non-surgically diagnosed patients and surgically diagnosed patients

Outcomes	Total (n=53, 100%)	Non-surgical diagnosis (n=30, 57%)	Surgical diagnosis (n=23, 43%)	P
Treatment outcome				
Improvement	45 [85][a]	22 [73]	23 [100]	0.007[d]
Partial response or no change	7 [13]	7 [23][b]	0 [0]	
Progression	1 [2]	1 [4][c]	0 [0]	
Follow-up duration	29.4 [15.5–53.0]	23.2 [13.3–59.0]	33.1 [19.3–53.3]	0.210

[a], one patient with clustered nodular pattern who was followed-up without treatment had spontaneous remission; [b], radiologic patterns included solitary pulmonary nodular pattern (n=4) and solitary pulmonary mass or nodule (n=3); [c], radiologic pattern included clustered nodular pattern (n=1); [d], Pearson χ^2 test comparing proportion of patients with improvement.

(69% *vs.* 31%; P=0.005), air bronchograms (73% *vs.* 27%; P<0.005), and peripheral location (67% *vs.* 33%; P<0.001).

Treatments and responses

Comparison of treatment responses between non-surgically diagnosed patients and surgically diagnosed patients

Of the 30 patients who were non-surgically diagnosed, 21 were treated with antifungals including fluconazole (n=19) and itraconazole (n=2) for a median of 6.3 months (IQR, 3.6–6.5 months) and 9 were followed-up without treatment. In comparison, of 23 patients who were surgically diagnosed, 8 were treated with antifungals including fluconazole (n=7) and itraconazole (n=1) for a median of 5.6 months (IQR, 3.0–7.0 months) (*Figure 1*). As shown in *Table 3*, During a median of 29.4 months follow-up duration, the proportion of patients who had improvement were significantly higher in patients who were surgically diseased than those who were non-surgically diagnosed [100% (23/23) *vs.* 73% (22/57); P=0.007]. There were no casas with recurrent PC after complete improvement. Also, none of those who underwent surgical resection had post-operative complications.

Comparison of clinical characteristics and treatment responses between patients diagnosed surgically who did and did not receive additional antifungal treatment

As shown in *Table 4*, there was no significant difference in age, sex, smoking history, comorbidity status, or radiological findings between patients who did and did not receive antifungals after surgical resection (*Table 4*). Regardless of antifungal treatment status, no patient who underwent surgical resection developed progressive disease.

Discussion

In this study, most PC cases were found incidentally, and thus in the absence of specific symptoms, in most immunocompetent subjects. The diagnostic approach was affected by several factors including the initial presumed clinical diagnoses and the radiological patterns. Surgical resection was required to diagnose PC in 43% of patients. The proportion of patients with an initial presumed diagnosis of lung malignancy was significantly higher among surgically diagnosed than non-surgically diagnosed patients. Whereas undetermined location was more common in surgically diagnosed patients, radiologic findings including clustered nodular pattern, cavities, air bronchograms, and peripherally located lesions were more common among non-surgically diagnosed patients. Additionally, we found that antifungals were not necessary to prevent PC recurrence after complete surgical resection.

The most common lung abnormality patterns were clustered or solitary pulmonary nodules (3,10,13,16). In agreement with these findings, the most frequent lung abnormality patterns detected by CT in the present study were nodular (84%), including the scattered nodular pattern (30%), the solitary pulmonary nodular pattern (28%), and the clustered nodular pattern (26%). Extending the findings of previous studies, we also found that the chosen diagnostic approach was significantly affected by these radiological patterns. Most patients with clustered nodular patterns were diagnosed non-surgically, whereas only about half of those with scattered or solitary nodular patterns were diagnosed non-surgically. Several possible explanations for these results may be proposed. As the clustered nodular pattern is the best-known PC radiological pattern, non-surgical methods might have been preferred

Table 4 Comparison of clinical characteristics and treatment responses between patients diagnosed surgically who did and did not receive additional antibiotic treatment

Clinical characteristics	Surgical resection (n=15)	Antibiotic treatment after surgical resection (n=8)	P
Age, years	65 [55–74]	62 [50–65]	0.615
Sex, male	9 [60]	6 [70]	0.691
Current or ex-smoker	8 [53]	3 [38]	0.672
Radiologic finding (main pattern)			0.907
Solitary pulmonary nodular	5 [33]	3 [38]	
Solitary pulmonary mass	1 [7]	0 [0]	
Scattered nodular	5 [33]	4 [50]	
Clustered nodular	2 [13]	0 [0]	
Multiple clustered nodular	0 [0]	0 [0]	
Bronchopneumonic pattern	1 [7]	0 [0]	
Mixed pattern	1 [7]	1 [13]	
Treatment outcome			>0.999
Improvement	15 [100]	8 [100]	
Partial response or no change	0 [0]	0 [0]	
Progression	0 [0]	0 [0]	
Follow-up duration, months	33.9 [15.1–52.2]	45.0 [25.1–93.3]	>0.999

Data are presented as number [%] or as median [interquartile range].

because of initial suspicion of PC in 43% of patients. Also, most clustered nodular lesions were peripheral (79%), and thus easy to approach via PCNB. In contrast, the scattered nodular patterns might not have been considered suggestive of PC; PC was very rarely considered as a presumed diagnosis in such patients. Moreover, as the lesions were scattered throughout the lobes, PCNB may not have been feasible. However, in some cases, PC was successfully diagnosed using non-invasive modalities such as TBLB and PCNB. Thus, clinical suspicion of PC in cases exhibiting the scattered nodular pattern might reduce the rate of unnecessary surgical resection. In cases with solitary pulmonary nodules, the most frequent presumed clinical diagnosis was a malignancy. Therefore, some cases, especially those exhibiting high-level FDG uptake, may have undergone surgical resection under a high suspicion of malignancy. Also, radiological findings such as cavities and air bronchograms were associated with the use of non-surgical diagnostic approaches.

PC treatment in immunocompetent patients remains controversial. Treatments include simple observation, medical treatment, and surgical resection. A few reports (15,17,18) found that PC in symptom-free immunocompetent patients was indolent and resolved spontaneously. However, in our study, of nine patients who were followed-up without specific treatment, only one exhibited a complete response, no changes were evident in seven, and one progressed. Therefore, we suggest that even patients who were previously healthy (thus without underlying disease) should be treated rather than simply observed to prevent unnecessary patient concern and the inevitable radiological exposure associated with close follow-up.

In terms of surgical resection, a significant proportion of patients required diagnostic resection, as is also true in patients with pulmonary actinomycosis (19) and pulmonary MALT lymphoma (20,21), which mimic lung cancer. However, as is also true of these rare diseases, no guidelines for PC treatment diagnosed by surgical resection are available. Several studies (6,15) have reported complete or partial responses to fluconazole after PC diagnosis via surgical resection or PCNA. A recent study (22) recommended that patients with proven or probable PC,

whether symptomatic or not, should receive a single course of antifungal therapy. However, no study has yet evaluated the role played by antifungal treatment after surgical resection. Thus, the fact that antifungals are not required constitutes new and useful information; this is also the case with other rare diseases (19-21).

Our study had several limitations. First, the work was retrospective in nature and was performed in a single center. Second, although we showed that complete resection prevented PC recurrence without the need for antifungals after surgical resection, the number of patients in the two groups was relatively small. Nevertheless, we suggest that complete surgical resection prevents recurrence in immunocompetent patients with localized lesions compatible with PC. In such cases, surgical resection not only allows accurate diagnosis, but also successful management (and thus a high probability of complete response). However, further studies with longer-term follow-up are needed. Third, we did not have culture results. Thus, we could not identify subspecies of *Cryptococcus*. Thus, future studies are needed to evaluate whether the clinical and radiological manifestations are different according to subtypes of *Cryptococcus*.

Conclusions

In conclusion, we found that surgical resection was diagnostically required by our PC patients. Initial clinical suspicion of a lung malignancy was associated with surgical diagnosis. Whereas undetermined location was associated with surgical diagnostic approaches, the presence of the clustered nodular pattern, cavities, air bronchograms, and peripheral lesional locations was associated with non-surgical diagnostic approaches. Surgical resection not only afforded reliable diagnoses but also effectively treated PC. Antifungals were unnecessary after complete surgical resection.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by the Institutional Review Board of Samsung Medical Center (IRB no. 2017-06-142-011). The need for written patient consent was waived because the study was retrospective in nature.

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Cite this article as: Yang B, Lee H, Lee T, Kim SH, Kim MY, Jeong BH, Shin S, Kim S, Lee KS, Kwon OJ, Kim H. The use of surgery in a real-world clinic to diagnose and treat pulmonary cryptococcosis in immunocompetent patients. J Thorac Dis 2019;11(4):1251-1260. doi: 10.21037/jtd.2019.04.17

Supplementary

Table S1 Radiological characteristics of 15 cryptococcosis patients with a solitary pulmonary pattern

Radiological characteristics	Total (n=15, 100%)	Non-surgical diagnosis (n=8, 53%)	Surgical diagnosis (n=7, 47%)	P
Solitary pulmonary nodular pattern				
Size, mm	24 [16–28]	26 [23–32]	17 [8–24]	0.017
Involved lobe				0.720
Right upper lobe	3 [20]	1 [13]	2 [29]	
Right middle lobe	0 [0]	0 [0]	0 [0]	
Right lower lobe	6 [40]	4 [50]	2 [29]	
Left upper lobe	1 [7]	1 [13]	0 [0]	
Left lower lobe	5 [33]	2 [25]	3 [43]	
Distribution				0.231
Peripheral	11 [73]	7 [88]	4 [57]	
Central	0 [0]	0 [0]	0 [0]	
Unclassified	4 [27]	1 [13]	3 [43]	
Contrast enhancement	11 [73]	4 [50]	7 [100]	0.051
SUV_{max}	4.4 [2.7–8.1]	6.9 [3.1–12.2]	3.6 [2.3–5.8]	0.103

Data are presented as number [%] or as median [interquartile range]. SUV, standardized uptake value.

Table S2 Clinical diagnosis and diagnostic approaches based on radiologic findings

Initial clinical diagnosis	Main pattern, n [%]					Other signs, n [%]			Location, n [%]			
	Nodular pattern			Mass (n=2)	Bronchopneumonic (n=4)	Mixed (n=2)	Cavities (n=13)	Air bronchograms (n=15)	Peripheral (n=36)	Central (n=1)	Undetermined (n=13)	Multiple (n=3)
	Scattered (n=16)	Clustered (n=14)	Solitary (n=15)									
Lung malignancy	7 [44]	4 [29]	8 [53]	1 [50]	0 [0]	1 [50]	3 [23]	3 [20]	11 [31]	0 [0]	9 [69]	1 [33]
Tuberculosis	0 [0]	3 [21]	1 [7]	0 [0]	1 [25]	1 [50]	3 [23]	3 [20]	5 [14]	1 [100]	0 [0]	1 [33]
Cryptococcosis	4 [25]	6 [43]	3 [20]	0 [0]	1 [25]	0 [0]	3 [23]	2 [13]	11 [31]	0 [0]	2 [15]	0 [0]
Organizing pneumonia	5 [31]	1 [7]	3 [20]	1 [50]	2 [50]	0 [0]	4 [31]	7 [47]	9 [25]	0 [0]	2 [15]	1 [33]
Diagnostic approach												
Non-surgical modality	7 [44]	11 [79]	8 [53]	1 [50]	3 [75]	0 [0]	9 [69]	11 [73]	24 [67]	0 [0]	4 [31]	2 [67]
Surgical modality	9 [56]	3 [21]	7 [47]	1 [50]	1 [25]	2 [100]	4 [31]	4 [27]	122 [33]	1 [1]	9 [69]	1 [33]
P[a]	0.230	<0.001	0.407	0.500	0.051	–	0.005	<0.005	< 0.001	–	0.005	0.255

[a], one sample proportion test was used for P values for radiologic findings.