The outcome of pulmonary resection for invasive fungal infection complicating haematological malignancy†

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Abstract

OBJECTIVES: The aim of this study was to clarify clinical outcomes of pulmonary resection of invasive fungal infection (IFI) complicating haematological malignancy.

METHODS: Between 1985 and 2010, 28 patients underwent 31 pulmonary procedures for IFI complicating haematological malignancy. Retrospective chart review was performed. Seventeen patients underwent therapeutic resection and 11 patients underwent diagnostic biopsy. Survival and progression of fungal infection were analysed with the Kaplan–Meier method and prognostic factors were analysed with the Cox proportional hazards model.

RESULTS: The median follow-up was 9.5 months (range 0–139 months). The rate of operative complications is significantly higher in the therapeutic resection group (P = 0.036) in multivariate analysis. Median survival was 12 and 5 months in the diagnostic and therapeutic group, respectively. In the diagnostic group, 10 patients (91%) survived surgery and were cured of fungal infection; the management was changed based on biopsy in 3 patients (27.3%), and preoperative anaemia (P = 0.044) adversely affected survival in multivariate analysis. In the therapeutic group, anaemia (P = 0.018) and perioperative transfusion (P = 0.038) adversely affected survival following therapeutic resection in univariate analysis. The rate of fungal progression in the therapeutic group was 29.4%. In multivariate analysis, only presence of bilateral lesions (P = 0.0005) was a significant factor of fungal progression after therapeutic resection.

CONCLUSIONS: Diagnostic biopsy contributes to good diagnostic yield with long-term cure from fungal infection. The long-term outcome (overall survival) of diagnostic and therapeutic patients relied on the severity of anaemia, which appears related to underlying haematological diseases. Presence of bilateral lesions was a significant factor of fungal progression after therapeutic resection.

Keywords: Haematology • Fungi • Infection • Lung

INTRODUCTION

Less than 5% of patients with haematological malignancies develop invasive fungal infection (IFI), but overall IFI-associated mortality is very high. Sixty-nine percent of the IFIs occurred in patients with acute myeloid leukaemia. Regarding fungal species, Aspergillus species are the most common pathogens, while the highest IFI-attributable mortality rates were associated with zygomycosis. It is often difficult to obtain a definitive diagnosis based on clinical and radiographic findings alone. Negative bronchoalveolar lavage (BAL), transbronchial lung biopsy or negative computed tomography (CT)-guided lung biopsy does not exclude fungal infection. Surgical lung biopsy plays an important role in obtaining a definitive diagnosis. When the fungal lesion is localized and resistant to antifungal agents, therapeutic pulmonary resection is indicated. The aim of this study was to clarify the clinical outcomes of therapeutic and diagnostic pulmonary resections for IFI complicating haematological malignancy.

MATERIALS AND METHODS

This study was approved by the institutional review board of the Mayo Clinic, Rochester. The requirement for patient consent was waived. From January 1985 to March 2010, 28 patients underwent pulmonary resection for IFI complicating haematological malignancy in the Mayo Clinic, Rochester. Retrospective chart review was performed. Because diagnostic biopsy and therapeutic resection are quite different with regard to clinical situation and type of operation, they are analysed and discussed separately in our study. Preoperative patient characteristics are given in Table 1, comparing diagnostic patients with therapeutic patients.

Diagnostic biopsy was defined as pulmonary resection for tissue diagnosis. It is usually an incomplete resection of radiologically diffuse lesions. In terms of risks and benefits, diagnostic resection is...
performed in clinically stable cases. An emergency diagnostic biopsy was performed on an as-needed basis, but not in unstable cases or respiratory failure.

Therapeutic resection was defined as surgical resection of lesions that are resistant to medical treatment. Therapeutic resection aimed at complete resection of localized lesions. The diagnosis of IFI before therapeutic resection is based on clinical history, radiological findings and microbiological investigation such as BAL. One had allogenic bone marrow transplant before IFI, while 2 patients did after therapeutic resection. The interval between radiological investigation (CT) and therapeutic resection ranged from 0 to 18 days (median: 5 days).

Fungal progression was defined as a new or aggravated pulmonary lesion of fungal infection in an ipsilateral or contralateral side in the postoperative period.

For comparisons of continuous and categorical variables, the Mann–Whitney U, χ² or Fisher’s exact tests were used as appropriate. Overall survival following diagnostic biopsy, overall survival and fungal progression following therapeutic resection were calculated from the date of the surgical procedures and analysed with the Kaplan–Meier method. Overall survival was compared between diagnostic biopsy patients and therapeutic resection patients, using the log-rank method. Potential prognostic factors of overall long-term survival in diagnostic biopsy and therapeutic resection patients and those of fungal progression in therapeutic resection patients were analysed with the Cox proportional hazards model. P-values < 0.05 were considered statistically significant. If the P-values was under 0.15 in univariate analysis, it was included in multivariate analysis. We used JMP Version 8.0.1 (copyright 2008 SAS Institute, Inc.) for statistical analysis.

### RESULTS

**Risk factor analysis for perioperative complications for all patients**

In univariate analysis, type of procedures (diagnostic biopsy vs therapeutic resection, \( P = 0.0584 \)) showed a tendency for perioperative complications and preoperative oxygen use \( (P = 0.0374) \) was a significant factor, while none of the factors of age \( (P = 0.394) \), gender \( (P = 0.548) \), symptomatic \( (P = 0.585) \), smoking history \( (P = 1.0) \), preoperative chemotherapy \( (P = 0.17) \), preoperative radiotherapy \( (P = 0.33) \), preoperative forced expiratory volume in 1 s (FEV1) predicted \( (P = 0.40) \), preoperative bone

### Table 1: Preoperative patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Diagnostic ( n = 11 )</th>
<th>Therapeutic ( n = 17 )</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range of age (median)</td>
<td>15–66 (median; 38)</td>
<td>22–75 (median; 58)</td>
<td>0.068</td>
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<tr>
<td>Female gender</td>
<td>3 (27.2%)</td>
<td>3 (17.6%)</td>
<td>0.55</td>
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<tr>
<td>Symptomatic</td>
<td>6 (54.5%)</td>
<td>14 (82.3%)</td>
<td>0.21</td>
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<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>4 (36.4%)</td>
<td>13 (76.5%)</td>
<td>0.29</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>0</td>
<td>1 (5.88%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Cough</td>
<td>1 (9.1%)</td>
<td>0</td>
<td>0.23</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>1 (9.1%)</td>
<td>0</td>
<td>0.32</td>
</tr>
<tr>
<td>Haematological diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>1 (9.1%)</td>
<td>10 (58.8%)</td>
<td>0.0053</td>
</tr>
<tr>
<td>ALL</td>
<td>2 (18.2%)</td>
<td>3 (17.6%)</td>
<td>0.55</td>
</tr>
<tr>
<td>CML</td>
<td>1 (9.1%)</td>
<td>0</td>
<td>0.17</td>
</tr>
<tr>
<td>CLL</td>
<td>3 (27.2%)</td>
<td>3 (17.6%)</td>
<td>0.55</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>3 (27.2%)</td>
<td>1 (5.88%)</td>
<td>0.031</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>1 (9.1%)</td>
<td>0</td>
<td>0.17</td>
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<td>Haematological profiles (median values)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>9.0</td>
<td>10.5</td>
<td>0.29</td>
</tr>
<tr>
<td>White blood cell (K/mm³)</td>
<td>9.6</td>
<td>5.6</td>
<td>0.39</td>
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<tr>
<td>Neutrophil (K/mm³)</td>
<td>2.0</td>
<td>0.8</td>
<td>0.27</td>
</tr>
<tr>
<td>Platelet (K/mm³)</td>
<td>1350.0</td>
<td>1185.0</td>
<td>0.33</td>
</tr>
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<td>Laterality of lesions</td>
<td></td>
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<tr>
<td>Unilateral</td>
<td>4 (36.4%)</td>
<td>13 (76.5%)</td>
<td>0.23</td>
</tr>
<tr>
<td>Bilateral</td>
<td>7 (63.6%)</td>
<td>4 (23.5%)</td>
<td>0.23</td>
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<tr>
<td>BAL performed</td>
<td>8 (72.7%)</td>
<td>12 (70.6%)</td>
<td>0.84</td>
</tr>
<tr>
<td>TBLB performed</td>
<td>3 (27.2%)</td>
<td>3 (17.6%)</td>
<td>0.21</td>
</tr>
<tr>
<td>Positive smoking history</td>
<td>6 (54.5%)</td>
<td>5 (29.4%)</td>
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<tr>
<td>Preoperative oxygen use</td>
<td>2 (18.2%)</td>
<td>2 (11.8%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Median preoperative %FEV1 predicted</td>
<td>81</td>
<td>80</td>
<td>0.78</td>
</tr>
<tr>
<td>Cavitary lesion on CT</td>
<td>2 (18.2%)</td>
<td>10 (58.8%)</td>
<td>0.034</td>
</tr>
<tr>
<td>Emergent procedure</td>
<td>1 (9.1%)</td>
<td>0</td>
<td>0.21</td>
</tr>
<tr>
<td>Preoperative antifungal</td>
<td>8 (72.7%)</td>
<td>14 (82.3%)</td>
<td>0.61</td>
</tr>
<tr>
<td>Preoperative bone marrow transplant</td>
<td>3 (27.2%)</td>
<td>2 (11.8%)</td>
<td>0.34</td>
</tr>
<tr>
<td>Preoperative chemotherapy</td>
<td>5 (45.5%)</td>
<td>15 (88.2%)</td>
<td>0.047</td>
</tr>
<tr>
<td>Preoperative radiotherapy</td>
<td>0</td>
<td>1 (5.88%)</td>
<td>0.33</td>
</tr>
</tbody>
</table>

AML: acute myelogenic leukaemia; ALL: acute lymphocytic leukaemia; CML: chronic myelogenic leukaemia; CLL: chronic leukocytic leukaemia; BAL: bronchoalveolar lavage; TBLB: transbronchial lung biopsy; FEV1: forced expiratory volume in 1 s.
marrow transplant (P = 0.88), preoperative haemoglobin (P = 0.188), white cell count (P = 0.60), platelet (P = 0.997), cavitary lesion (P = 0.315), emergent procedure (P = 0.312), lobectomy (P = 0.90), thoracotomy (P = 0.517), fungal species (P = 0.282) was significant or showed a tendency for complications. In multivariate analysis, type of procedures (therapeutic resection, P = 0.036) and preoperative oxygen use (P = 0.049) were significant. Based on the above analysis, diagnostic biopsy and therapeutic resection are discussed separately.

**Diagnostic biopsy**

Fungal diagnosis. Fungal diagnoses were as follows: Aspergillus in 6 patients (1 with acute myelogenic leukaemia, 2 with acute lymphocytic leukaemia, 1 with chronic leukocytic leukaemia, 1 with malignant lymphoma and 1 with multiple myeloma), Rhizopus in 1 patient with chronic myelogenic leukaemia, Histoplasma in 1 patient with chronic leukocytic leukaemia, Blastomyces in 1 patient with malignant lymphoma and Cryptococcus in 1 patient with chronic leukocytic leukaemia.

Surgical procedure. All diagnostic biopsies were done under general anaesthesia using a double-lumen tracheobronchial tube. Four patients underwent video-assisted thoracoscopic surgery and 7 patients underwent a limited thoracotomy. All patients underwent wedge resection with endoscopic linear staplers. Samples were sent to microbiological and pathological analysis. Just before the surgical procedures, platelets were transfused in 2 patients based on their haematological profiles. One patient showed neutropenia (<0.5 × 10⁹ cell/l) and received a granulocyte-stimulating factor in the perioperative period. Two patients underwent bilateral sequential diagnostic wedge biopsies because the radiographic appearances were different, but both patients had an interval of >5 months. The median day of postoperative pleural drainage was 3 days.

Short-term (<30 days) operative mortality and morbidity. The only mortality was that of acute respiratory distress syndrome associated with pulmonary aspergillosis (1 patient, 9.1%). The only morbidity was postoperative atrial arrhythmia (1 patient, 9.1%). Antifungal agent (Amphotericin B) was started prior to surgery in 7 patients (63.6%), which apparently did not impair diagnostic yield. Postoperative antifungal agents were continued in all cases and the time frame was decided upon by the haematology service. Regarding both patients undergoing bilateral procedures, one side was diagnosed as fungal infection while the other side proved to be a non-infectious process in either case.

**Long-term survival after diagnostic biopsy.** Ten of 11 patients survived in perioperative periods and all of them were cured of fungal infection with antifungal agents. Survival after diagnostic biopsy is shown in Fig.1 (median; 12.0 months). The causes of death are as follows: underlying haematological malignancy in 5 patients, sepsis in 1 patient and unknown in 1 patient. In univariate analysis, gender (P = 0.0026), bilateral lesions (P = 0.0117) and postoperative complications (P = 0.0285) were significant factors for improved survival after diagnostic biopsy; smoking history (P = 0.088) and preoperative haemoglobin (P = 0.054) showed tendencies for worse survival; while none of the factors of age (P = 0.92), preoperative chemotherapy (P = 0.40), preoperative FEV1% predicted (P = 0.92), preoperative oxygen use (P = 0.85), bone marrow transplant (P = 0.53), preoperative white cell count (P = 0.30) and preoperative platelet (P = 0.33) was significant or showed a tendency for perioperative complications. In multivariate analysis, only preoperative haemoglobin (P = 0.0439) was a significant factor, while neither gender (P = 0.393) nor presence of bilateral lesions (P = 0.17) was significant.

The influence of diagnostic biopsy on antifungal management. While 8 patients continued the same antifungal agent after surgery at the discretion of haematological disease services, in 3 patients (27.6%) of the diagnostic group, the management was changed after the pathological diagnosis (from no antibiotic to an antifungal agent for one, from an antibacterial to an antifungal for another and from an antifungal agent to another antifungal for the third).

**Therapeutic resection cases**

Fungal diagnosis. Fungal diagnoses were as follows: Aspergillus in 8 patients (4 with acute myelogenic leukaemia, 2 with acute...
lymphocytic leukaemia, 2 with chronic lymphocytic leukaemia),
Mucor in 6 patients (4 with acute myelogenic leukaemia, 1 with
acute lymphocytic leukaemia, 1 with malignant lymphoma),
Rhizopus in 2 patients with acute myelogenic leukaemia) and
Histoplasma in 1 patient with chronic lymphocytic leukaemia.

Surgical procedure. All therapeutic resections were performed
with a standard posterolateral thoracotomy. Four patients (23.5%)
underwent wedge resection, 5 patients (29.4%) underwent
segmentectomies and 8 patients (46.1%) underwent lobectomies.
Of the 8 lobectomy patients, 4 patients had a bronchial stump
reinforcement (pericardial fat pad: 1, serratus anterior muscle: 2,
lattissimus dorsi muscle: 1). The median day of postoperative
pleural drainage was 4 days.

Short-term (<30 days) operative mortality and morbidity. The
total mortalities were four patients (23.5%). Of the 4 patients, 2
patients had bilateral lesions. These patients with bilateral lesions
were planned to undergo surgical resection for the contralateral
lesions. In both patients, fungal infection progressed to systemic
infection. The other mortalities were due to aspiration pneumonia
(1 patient, 5.9%) and acute respiratory distress syndrome associated
with bacterial pneumonia (1 patient). Morbidities included post-
operative haemothorax (1 patient), chylothorax (1 patient),
abdominal fungal abscess (1 patient), surgical site infection (1 patient)
and paroxysmal supraventricular tachycardia (1 patient). Only the
patient with the haemothorax required a surgical intervention
(thoracoscopic drainage of haemothorax). Postoperative antifungal
agents were typically given either intravenously or orally at the
discretion of the haematology service. In univariate analysis, only
preoperative oxygen use showed a tendency for short-term operative
complications (mortality or morbidity) \((P = 0.069)\). No other factor
such as age \((P = 0.77)\), gender \((P = 0.45)\), symptomatic \((P = 0.45)\),
preoperative chemotherapy \((P = 0.17)\), preoperative radiotherapy
\((P = 0.17)\), underlying haematological disease \((P = 0.55)\), smoking
history \((P = 0.464)\), preoperative FEV1 predicted \((P = 0.21)\),
preoperative lower haemoglobin \((P = 0.47)\), preoperative lower white
cell count \((P = 0.384)\), preoperative lower platelet \((P = 0.959)\),
preoperative bone marrow transplant \((P = 1.0)\), cavity lesions on CT
\((P = 0.77)\) and presence of bilateral lesions \((P = 0.30)\) was statistically
significant or showed a tendency for complications.

Long-term survival after therapeutic resection. Overall survival
following therapeutic resection is shown in Fig. 1 (median; 5
months). There was no significant difference in overall survival
between diagnostic patients and therapeutic patients \((P = 0.472)\).
The median progression-free survival is 4 months. Excluding 5
patients due to operative mortality, 7 of 12 patients had died in
the follow-up. The causes of death were as follows: aggravation
of underlying haematological malignancy (3 patients), progression
of fungal infection in the lung (2 patients), others (2 patients).
Preoperative lower haemoglobin (anaemia) \((P = 0.018)\) and
perioperative transfusion \((P = 0.038)\) were significant factors of
survival after therapeutic resection in univariate analysis; presence
of bilateral lesions \((P = 0.066)\), preoperative radiotherapy
\((P = 0.094)\) and preoperative lower white cell count \((P = 0.08)\) were
tendencies for poor survival. In multivariate analysis, no significant
factor was identified, but the presence of bilateral lesions
\((P = 0.086)\) was a tendency for poor survival. Anaemia \((P = 0.398)\),
perioperative transfusion \((P = 0.413)\), preoperative radiotherapy
\((P = 0.276)\) and lower white cell count \((P = 0.769)\) were not a
significant factor nor showed a tendency for complications in
multivariate analysis.

Fungal progression after therapeutic resection. The
progression-free survival is shown in Fig. 2. We had 5 patients
with postoperative fungal progression following therapeutic
resection. Three patients experienced lethal fungal progression
within 30 days of therapeutic resection and in two patients of the
three the contralateral lesions became aggravated postoperatively.
One patient had a slow fungal progression in the long term, and
apparently died from hepatic failure before the fungal infection
progressed to systemic infection. Preoperative lower haemoglobin
(anaemia) \((P = 0.025)\) and presence of bilateral lesions \((P = 0.0015)\)
were significant prognostic factors of progression of fungal
infection after therapeutic resection in univariate analysis, while
only presence of bilateral lesions \((P = 0.0027)\) was a significant
factor in multivariate analysis.

DISCUSSION

Diagnosis of and treatment for infection in haematological patients
are very important because infection is the most common cause

Figure 2: The Kaplan–Meier curve for progression-free survival following therapeutic pulmonary resection for invasive fungal infection.
of death in haematological patients and pulmonary infection is highly associated with death. However, diagnosis of fungal infection in haematological patients is not straightforward. Radiological investigation plays an important role in diagnosis processes, but that alone is seldom diagnostic. Although cavitory lesions and halo signs in CT are highly suggestive of IFI in haematological patients with neutropenia, diffuse infiltrates are non-specific and will also include possibilities of non-infectious processes such as haemorrhage, congestive heart failure or haematological lesions [1].

Given the fact that negative bronchoalveolar lavage or sputum culture hardly rules out infection in haematological patients with radiological abnormalities [2–4], only surgical lung biopsy will give a good diagnostic yield. Surgical biopsy, by giving us a larger specimen than sputum or bronchoalveolar lavage, will help us identify the fungal species, which leads to appropriate choice of an antifungal agent. Surgical biopsy appears to have a special value in the diagnosis of zygomycosis for multiple reasons. Its incidence in haematological patients is increasing [5], it is more difficult to culture [6] and it needs a special consideration in antifungal selection [7]. For the purpose of appropriate and quick antifungal selection, patients undergoing bone marrow transplant will benefit from surgical diagnostic biopsy because they will need more strict control of fungal infection.

As shown in our results, diagnostic biopsy should be discussed separately from therapeutic resection because the surgical indication, surgical approach and type of operation are quite different between the two types of procedures. Habicht et al. [2] and Theodore et al. [3] argued that diagnostic biopsy carries a significantly higher risk than therapeutic resection, while diagnostic biopsy in our study proved to be carried out more safely in haematological patients than therapeutic resection. Owing to relatively small numbers in previous publications and a variety of patient backgrounds, there will hardly be a consensus to risk estimation in diagnostic biopsy. More important findings of ours suggest that diagnostic biopsy contributes to a good diagnostic yield, with a cure from fungal infection.

Surgical management (therapeutic resection) vs medical management (antifungal agents) will depend on the extent of pulmonary lesions. If localized, surgery may be an option and be favoured over medical treatment [8]. Whether surgical or medical treatment for localized lesions is better is not clear, and there has been no prospective randomized study comparing medical treatment and surgical treatment in IFI in lungs. But our results have shown that therapeutic resection plays a good role in controlling local infections with an acceptable postoperative complication rate, which is consistent with previous reports [2–4, 8]. The presence of bilateral lesions is a special consideration and controversial even if each lesion is localized and can be completely resected sequentially. Bilateral lesions can be a picture of disseminated infection and if it is the case, surgical treatment is unlikely to be beneficial [9]. Habicht et al. [8] reported that bilateral lung involvement was not associated with a risk of death but most patients with bilateral lesions were treated medically alone. In our series, the benefit of surgical treatment for bilateral lesions was indeterminable and our findings suggest that patients with bilateral lesions should be treated medically first.

Even if complete resection is achieved, postoperative antifungal agents are necessary for secondary prophylaxis [2, 4], as we recommend as well.

Of interest, regardless of different patient backgrounds and different operative indications, there is no significant difference in overall survival following the surgical procedures between the therapeutic resection group and the diagnostic biopsy plus medical management group. Both groups achieved control of fungal infection with respective treatment modalities, but long-term survival of both groups relied on the severity of preoperative anaemia, which appears to reflect the severity of underlying haematological diseases as well as other conditions. During the follow-up, the most frequent cause of death both in the diagnostic biopsy group and the therapeutic resection group was aggravation of underlying haematological diseases. The finding, consistent with previous reports [4, 10], suggests that both patient groups are still at high risk even after successful treatment of IFI [11].

The limitations of our study include the retrospective study design and the small number of cases, as in other reports on IFI complicating haematological malignancy. We reviewed only the patients with the final diagnosis being IFI, excluding patients diagnosed differently. In addition, operative indications have been influenced by surgeons’ biases.

CONCLUSION

Diagnostic biopsy contributes to good diagnostic yield with a low rate of postoperative complications. The long-term outcome (overall survival) of diagnostic and therapeutic patients relied on the severity of anaemia, which appears related to underlying haematological diseases. The presence of bilateral lesions is a significant risk factor of fungal progression following therapeutic resection.

Conflict of interest: none declared.

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