Survival following lung resection in immunocompromised patients with pulmonary invasive fungal infection

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Abstract

OBJECTIVES: Pulmonary invasive fungal infections (IFIs) are associated with high mortality in patients being treated for haematological malignancy. There is limited understanding of the role for surgical lung resection and outcomes in this patient population.

METHODS: This is a retrospective cohort of 50 immunocompromised patients who underwent lung resection for IFI. Patient charts were reviewed for details on primary malignancy and treatment course, presentation and work-up of IFI, reasons for surgery, type of resection and outcomes including postoperative complications, mortality, disease relapse and survival. Analysis was also performed on two subgroups based on year of surgery from 1990–2000 and 2001–2014.

RESULTS: The median age was 39 years (range: 5–64 years). Forty-seven patients (94%) had haematological malignancies and 38 (76%) underwent haematopoietic stem cell transplantation (HSCT). Surgical indications included haemoptysis, antifungal therapy failure and need for eradication before HSCT. The most common pathogen was Aspergillus in 34 patients (74%). Wedge resections were performed in 32 patients (64%), lobectomy in 9 (18%), segmentectomy in 2 (4%) and some combination of the 3 in 7 (14%) for locally extensive, multifocal disease. There were 9 (18%) minor and 14 (28%) major postoperative complications. Postoperative mortality at 30 days was 12% (n = 6). At the time of death, 15 patients (30%) had probable or proven recurrent IFI. Causes of death were predominantly related to refractory malignancy, fungal lung disease or complications of graft versus host disease (GVHD). Patients who had positive preoperative bronchoscopy cultures had a trend towards worse survival compared with those with negative cultures (hazard ratio: 1.80, P = 0.087).

CONCLUSIONS: Surgical resection of IFI in immunocompromised patients is associated with high perioperative mortality. Long-term survival is limited by recurrent malignancy, persistent fungal infection and GVHD but has improved in recent years. Selection for surgical resection is difficult in this patient population, but should be carefully considered in those who are symptomatic, or have failed antifungal treatment.

Keywords: Fungal infection • Haematological malignancy • Immunocompromised • Surgery

INTRODUCTION

Aspergillus is a ubiquitous fungus that is commonly inhaled, but seldom affects individuals with normal host defences. It is responsible for a spectrum of infectious diseases, including invasive pulmonary aspergillosis that is the most common form of invasive fungal infection (IFI), and is associated with high mortality among patients with haematological malignancies, especially following haematopoietic stem cell transplant (HSCT) [1]. Aspergillus can invade directly into adjacent structures including blood vessels or disseminate haematogenously [2]. Other fungal organisms including Mucor and Scedosporium are also important causes of fungal lung infection associated with high mortality among immunocompromised patients [3].

The incidence of IFI in haematology patients ranges from 2 to 20% depending on the use of antifungal prophylaxis. Allogeneic HSCT, neutropenia and graft versus host disease (GVHD) are among the greatest risk factors [4]. Diagnosis and treatment of IFI
continues to be a challenge and antifungal therapy alone is frequently insufficient to eradicate IFI, or can preclude patients from receiving HSCT necessary to treat their underlying haematological disease [1, 5]. One study demonstrated a 40% IFI-related mortality for HSCT recipients with active fungal infection compared with 2.54% for HSCT recipients without history of IFI [6].

Surgical treatment of pulmonary aspergilloma is widely reported in the literature dating back to the first successful lobectomy by Gerstl et al. [7] in 1948, and recent studies support that resection of isolated lesions in otherwise healthy individuals is safe [5, 8-14]. In contrast, surgical experience with IFI in immunocompromised patients with haematological malignancies is limited to a few small series that cite variable mortality (0-31% short term at 30 days and 21-72% long term at 1 year or more) primarily due to relapsed leukaemia or lymphoma [15-19]. Even with improved tolerance and efficacy of new antifungal agents as first-line therapy (i.e. voriconazole) and prophylaxis (i.e. micafungin) [20], the mortality in these patients can be as high as 50% for neutropenic patients and 90% for post-HSCT patients [21]. Surgery serves the purposes of definitive diagnosis, salvage therapy when medical treatment has failed, treatment for haemoptysis and as the best chance for eradication of IFI before HSCT [18].

The objective of this study is to describe our experience with surgical resection of pulmonary IFI at a high volume HSCT centre where most patients have haematological malignancies, and underwent HSCT before or after surgery. We seek to describe our selection process for surgery and to analyse the outcomes of surgical resection including postoperative complications and short-term and long-term survival.

**PATIENTS AND METHODS**

We conducted a retrospective review of all immunocompromised patients who had lung resection for IFI between December 1986 and August 2014 at a National Cancer Institute-designated comprehensive cancer centre. Nine patients who underwent open incisional lung biopsy and 1 patient who had an aborted surgery for haemoptysis in the setting of disseminated fungal disease were excluded. Another patient had two occurrences of IFI for which he underwent pulmonary resection 6 years apart, but only the first incidence was included in our analysis. Patients with multifocal IFI were included when resection was performed. Figure 1 details the selection process used to create the cohort of 50 patients who underwent curative surgery for IFI between 1990 and 2014. The patients were further divided into two subgroups based on year of surgery (1990-2000 and 2000-2014) to analyse the effect of time on outcomes.

A majority of the patients were treated before the criteria of certainty of possible, probable or proven invasive aspergillosis were created in 2002, and updated in 2008 by the European Organization for Research in Treatment of Cancer-Invasive Fungal Infection Cooperative Group and National Institute of Allergy and Infectious Diseases Mycoses Study Group. Nevertheless, IFI was suspected based on clinical history and computed tomography (CT) findings, and most patients had probable or proven infection from positive bronchoscopy and bronchoalveolar lavage (BAL) or trans-bronchial/transthoracic biopsy results. All patients were treated with antimicrobial agents before surgery, including various combinations of amphotericin B and azoles as well as broad spectrum antibiotics. Patients who developed IFI after allogeneic HSCT had been maintained on routine antifungal prophylaxis that consisted of low-dose amphotericin in early years and then micafungin after 2005. Those who received autologous HSCT received fluconazole whereas patients with GVHD on high doses of immunosuppressants received posaconazole for prophylaxis. For patients with a history of fungal disease, secondary prophylaxis was initiated with either higher doses of micafungin, amphotericin B or voriconazole (in the last 10 years).

The medical record was reviewed for surgical indications that included failed antifungal therapy, haemoptysis and need for diagnosis and definitive treatment of discrete lesions before receiving HSCT. Patients were not surgical candidates if they had significant comorbidities, advanced or multifocal disease, or were ineligible for HSCT. Surgical outcomes including postoperative complications, microbiology results and final pathology were reviewed. Surgical complications were graded using the Clavien-Dindo classification and Grade I and II complications were considered as minor while Grade III and IV complications were considered as major. Endpoints were fungal relapse, primary disease relapse and short-term and long-term mortality defined as death at 30 days and death at 1 or more years, respectively. The follow-up time was defined as time from surgery to date of death or to the last follow-up recorded in the chart. One patient moved out of the country, and was lost to follow-up before 5 years.

Discrete variables were expressed as counts (percentages) and continuous variables as means with standard deviations or medians with interquartile ranges. Subgroups were analysed for comparability using the $\chi^2$ test or Fisher’s exact test where appropriate. Survival was calculated using the Kaplan-Meier method. Forward stepwise univariate analysis of predetermined potential predictors of survival was performed using Cox proportional hazards modelling. Variables with $P < 0.10$ were selected for multivariate analysis. A P-value of <0.05 was considered significant. Variables of interest included age, sex, haematological malignancy type, timing of HSCT relative to surgery, positive preoperative BAL culture, reasons for surgery, fungal species and lesion size.

**RESULTS**

Tables 1 and 2 detail patient characteristics and clinical presentations of IFI including relevant diagnostic data. The most common underlying malignancy was acute leukaemia in 33 patients (66%) followed by chronic leukaemia and lymphoma in 4 patients (8%) each. Less common haematological disorders were aplastic anaemia, multiple myeloma and myelodysplastic syndrome, each with 2 patients (4%). Three patients had solid tumours: choriocarcinoma, primitive neuroectodermal tumour and lung cancer.

Thirty-eight patients (76%) received HSCT. Of these, 18 (47%) had transplant before surgery, 17 (45%) had transplant after surgery and 3 (8%) had transplant before and after surgery. Six patients (12%) had GVHD preoperatively. Persistent fever was the most common presenting symptom in 34 patients (68%) followed by cough in 29 patients (58%), chest pain in 21 patients (42%) and haemoptysis in 6 patients (12%). Neutropenia defined as an absolute neutrophil count of $< 1.0 \times 10^9/l$ was found in 34 patients (68%) at the time of surgery. The median duration of preoperative neutropenia was 20 days (interquartile range, 16–23 days).

On diagnostic CT chest scan, 22 patients (44%) had pleural effusion, the same number had cavitation and 12 patients (24%) had identifiable pleural or chest wall involvement. All patients had bronchoscopy with BAL and 21 (42%) yielded positive histopathology or culture results. In addition, 19 patients (38%) underwent...
transthoracic or trans-bronchial biopsy with 12 positive results (63%). Following surgical resection, 37 patients (74%) had proven IFI on histopathology or culture. The median lesion size was 3.00 cm (interquartile range, 1.65–4.38 cm). All but 4 patients had a specific fungal pathogen identified by bronchoscopy, transthoracic/transbronchial biopsy or surgical pathology. *Aspergillus* was the most common in 34 patients (74%) followed by *Mucor* in 6 patients (13%) and *Scedosporium* in 4 patients (9%). When no organism could be identified on final culture, the most common histopathology findings were fibrosis, abscess and granuloma.

Surgery details are summarized in Table 3. The median time between diagnosis of IFI and surgery was 18 days (interquartile range, 7–37 days). Failure of antifungal therapy was the main reason for surgery in 24 patients (48%). Twenty patients (40%) underwent resection of a localized lesion suspected to be IFI on imaging before planned HSCT. There were 6 patients (12%) for whom surgery was intended to treat haemoptysis. Lung resection was performed open in 36 patients (72%) and thorascopically in 14 patients (28%). Twenty-two (44%) patients underwent single and 10 (20%) patients had multiple wedge resections. We performed 9 (18%) lobectomies, 2 (4%) segmentectomies and 1 bilobectomy (2%). Six patients underwent a combination of wedge resection and lobectomy or segmentectomy for extensive or multifocal lesions. One patient had involvement of the pericardium and left phrenic nerve that required resection and pericardial window. Another patient had extensive local invasion, necessitating debridement and chest wall resection. Both patients had *Mucor* isolated on surgical pathology.

Major postoperative complications occurred in 14 patients (28%), and are listed in Table 3. The most severe complications resulting in postoperative death were refractory fungal pneumonia (n = 3) and acute respiratory distress syndrome (ARDS), n = 3. Two patients developed fatal pulmonary haemorrhage from unrelenting IFI: one upon readmission nearly 4 weeks after surgery and the other following a complicated 7-week postoperative course. Multisystem organ failure (MSOF) and sepsis led to postoperative hospital
death in 2 patients. The first patient succumbed to overwhelming neutropenic sepsis and MSOF following induction chemotherapy 3 weeks after surgery. The second patient survived more than 4 months following surgery before similarly succumbing to sepsis and MSOF. Emergent reintubation for respiratory failure occurred in 2 patients who survived hospitalization, although 1 required tracheostomy for prolonged ventilation. Other non-fatal major complications included renal failure requiring haemodialysis (n = 2) and singular cases of haemothorax requiring chest tube drainage, anaemia requiring transfusion and severe malnutrition treated with total parenteral nutrition.

The 30-day all-cause postoperative mortality was 12% due to refractory IFI (n = 3), ARDS (n = 2), and neutropenic sepsis (n = 1) as detailed previously. The median follow-up time for survivors was 35 months (interquartile range, 8–102 months) and median survival was 12 months. Twenty-nine patients (58%) had relapse of their primary malignancy while 15 patients (30%) had recurrent pulmonary IFI and 17 patients (34%) had chronic GVHD. At 5 years after pulmonary resection for surgery, fungal speciation and lesion size did not reveal any significant difference in the timing of surgery relative to HSCT or the surgical indication. However, as seen in Table 4, more patients in the early group had Aspergillus (85%, n = 23) identified compared with those in the later group (58%, n = 11) and all patients found to have Mucor had surgery in later years (P = 0.007). While there was no significant difference in the occurrences of major or minor complications or cause of death over time, the median survival of the earlier group was 5 months compared with 24 months in those receiving treatment in recent years (P = 0.046).

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Pulmonary IFI in the setting of immunosuppression after treatment of haematological malignancy is associated with high mortality and the role and outcomes of surgical resection are not well defined. Moreover, there is relatively little described about the long-term prognosis of haematology patients who undergo pulmonary resection for IFI. Our institution, a high volume HSCT...
centre, has accumulated nearly 25 years of experience in the surgical management of IFI in this patient population. From 1986 to 2014, there were 10,648 HSCTs performed at our hospital and 5,791 (54%) were autologous transplants and 4,857 (46%) were allogeneic transplants (unpublished from the City of Hope Department of Hematology database). During the same period, 769 probable or proven cases of IFI (7.2%) developed in this patient population (unpublished, personal communication from Dr Tegtmeier) and 50 (6.5%) underwent surgical resection. Our experience differs from most institutional series on pulmonary IFI that focus on tuberculosis-associated aspergillomas or populations with a minority of immunosuppressed patients with relatively short follow-up [5, 8–14]. Twenty-eight percent of patients in our series had major postoperative complications and overall 30-day surgical mortality was 12%. This is comparable with what is reported in other studies in similar patient populations, although higher than in lung resections for malignancy [15–19]. Five-year overall survival was only 19%. The most common causes of death were malignancy, fungal relapse and GVHD.

Although the main causes of death did not change significantly when comparing the earlier and later cohorts, the median survival was notably better in patients who were treated during or before 2000 than in those who were treated during or before 2000 (5 months vs 24 months, P = 0.046). A number of things may account for this significant decrease in mortality over time including advances in more effective antifungal therapy, more sensitive imaging modalities, improved critical care management of sepsis and MSOF, more effective systemic treatment of malignancy and earlier recognition and treatment of GVHD. Furthermore, the analysis of IFI over time demonstrates that *Aspergillus* is significantly less prevalent now than it was before and other opportunistic pathogens like *Mucor* are becoming more common. In addition, the experience of the initial decade of managing these patients allowed for better patient selection for surgical resection in later years, which may have also contributed to improved survival.

The relatively high postoperative mortality rates and poor long-term survival underscore the technical challenges of surgical resection of IFI and the management of these patients postoperatively. Many patients are thrombocytopenic and neutropenic at the time of diagnosis, increasing the likelihood of postoperative blood transfusions, infection and wound healing problems. Patients with GVHD that affect various organ systems may experience chronic pain. The combination of thrombocytopenia and chronic pain poses a challenge for postoperative pain control due to inability to use epidural anaesthesia and non-steroidal anti-inflammatory medications. Intraoperatively, tissue planes are often destroyed by infection and chest wall invasion can occur leading to technical challenges.

We were unable to identify significant predictors of outcome among patients in this cohort because of the heterogeneity of malignancies, timing of resection relative to HSCT and indications for surgery. Nevertheless, there were several important observations from our experience. First, the most common reasons for surgical resection of pulmonary IFI in our institution were failure of medical management, the presence of probable or proven IFI before HSCT and haemoptysis. The Infectious Disease Society of America, which published guidelines for the treatment of invasive aspergillosis, recommended surgical evaluation for haemoptysis, fungal lesions invasive of great vessels, pericardium, or chest wall and solitary lesions found on work-up for HSCT. Selection for surgery including the type and extent of resection as well as the timing remains at the surgeon’s discretion [22]. No specific criteria have been established for failure of medical management although we consider persistent or progressive disease on clinical or radiographic examination after a therapeutic course of antifungal therapy to be sufficient to prompt surgical evaluation.

The consequences of not proceeding with resection for the outlined indications involve high mortality from inability to treat the underlying haematological malignancy due to IFI or, when HSCT is performed in the setting of active pulmonary IFI, from persistent post-transplant fungal infection [6]. Historical data show poor survival for salvage therapy in patients with pulmonary IFI who failed antifungal treatment, had haemoptysis or were planning to undergo HSCT [4, 20]. Our data are useful when counselling all patients with resectable IFI, including those with mucormycosis, for understanding potential complications associated with surgery and long-term survival typical of these diseases.

Diagnosis of IFI remains difficult despite the use of CT imaging and identification of pathognomonic halo or crescent signs [23]. The use of diagnostic modalities such as bronchoscopy (30–50% sensitivity) and percutaneous or endoscopic biopsy (35–80% sensitivity) is useful but limited [24, 25]. Our experience demonstrated 42 and 63% sensitivity for bronchoscopy and transthoracic needle biopsy, respectively. The highest diagnostic yield was from surgical resection with 74% sensitivity. In 26% of patients, the surgical pathology revealed only fibrosis, abscess or granuloma. This may represent complete or near-complete response to antifungal therapy, although the persistence of a lesion on imaging after medical treatment led to surgical resection prior to immunosuppressant systemic therapy. Unfortunately, in the absence of better
prooperative diagnostic tools, there was no way to prevent these patients from undergoing surgical resection. Nebiker et al. [15] demonstrated a similar rate of negative pathology of 27% (n = 19) in a larger cohort of 71 immunocompromised patients. While these benign findings question the necessity of surgical resection, the consequences of under-treating pulmonary IFI in this challenging patient population, especially before HSCT, can be disseminated IFI and death.

This study had a number of limitations. First was the selection bias involved with determining surgical candidates. Despite having one of the main indications for surgery, patients with advanced disseminated IFI, multiple comorbidities or incurable haematological disease were excluded from surgery. These selection criteria favour surgical outcomes by eliminating patients with expected poor outcomes. If all patients were to have surgery, the outcomes might have been similar to those reported with medical therapy alone. Secondly, we did not analyse haematology patients who developed IFI but did not undergo surgical resection for comparison. This would have given context to the indications for surgery and may have allowed us to compare the length of antifungal treatment in both groups and long-term outcomes. Another limitation of this study was the small size and heterogeneity of the patient sample, which greatly limited our ability to analyse predictors of survival. Despite the limitations, this is one of the largest series of surgical resection of pulmonary IFI that focuses on patients with haematological malignancy. Further investigation is needed to determine potential predictors of surgical mortality, such as the importance of timing of resection relative to HSCT, underlying haematological disorder, type of fungus and the presence of limited multifocal fungal disease. Pooling of data through collaboration among high-volume HSCT centres may lead to a better understanding of these predictors and better refine patient selection. Future directions for improving IFI management include discovering better diagnostic tools and developing more effective antifungal agents for treatment and prophylaxis of IFI in these susceptible patients.

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