Surgical management of invasive fungal infections in adult leukemia patients: experience from a large tertiary center in Southeast-Asia

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Abstract

Objectives: Invasive fungal infections (IFIs) are a major cause of morbidity and mortality in acute leukemia patients undergoing chemotherapy or hematopoietic stem cell transplantation (HSCT). Surgical interventions may be necessary to improve the survival outcomes of these patients. The aim of this study is to report a single-center experience using surgical intervention as adjunctive treatment for IFI in adult leukemia patients.

Methods: A retrospective review was conducted to obtain clinical characteristics and outcomes of surgically managed IFI patients diagnosed between January 2005 and December 2015 in our center.

Results: Nineteen acute leukemia patients, median age 46 years (range 19–65), underwent 20 surgical procedures as management for IFI. Three patients had proven IFI diagnoses prior to surgery. Sixteen patients underwent surgery for both diagnostic and therapeutic purposes. Post-surgery, the diagnostic yield for proven IFI increased by a factor of 5, and 15 patients had definitive IFI diagnoses. Surgical complications included 2 pleural effusions, 4 pneumothoraxes, and 1 hydropneumothorax. The median duration of hospitalization for patients with complications was 9 days (range 3–64). Thirteen patients benefited overall from the procedure, 3 had temporary clinical benefits, and 2 had progression of IFI. After surgery, the 3-month and 2-year overall survival rates were 89.5% and 57.9%, respectively. The median time from surgery to resumption of chemotherapy or HSCT was 25 days.

Conclusions: Surgical interventions for IFI are feasible in selected leukemia patients, as they yield valuable information to guide antifungal therapy or enable therapeutic outcomes with acceptable risk, thereby allowing patients to proceed with curative chemotherapy and HSCT.

Keywords: Invasive fungal infection, Leukemia, Surgical management

1. INTRODUCTION

Invasive fungal infections (IFIs) are a major cause of morbidity and mortality in immunocompromised patients. Risk factors for IFI include prolonged neutropenia, inherited or acquired immunodeficiency, immunosuppressant use, allogeneic hematopoietic stem cell transplant (HSCT), and solid organ transplantation.[1–3] According to a large-scale study, the prevalence of IFI in hematological patients was 4.6%, and IFI-related mortality was 39%.[4] Based on local data, the prevalence of proven and probable IFI in Singapore General Hospital for patients with acute leukemia on induction and salvage chemotherapy is 11% for acute lymphocytic leukemia (ALL) and 8.5% for acute myeloid leukemia (AML) with antifungal prophylaxis.[5]

In patients with hematological malignancy, the most common etiological agent of IFI is *Aspergillus*, which frequently affects the lungs, followed by *Candida*. Other pathogens such as *Fusarium* and *Mucorales* are less common.[6] Currently, diagnostic investigations such as galactomannan antigen and B-D-glucan, medical imaging, and antifungal drugs are generally the mainstay in the diagnosis and treatment of IFI in acute leukemia patients, while surgery largely plays an adjunctive role.[7,8]

However, multiple studies have concluded that medical management of IFI in leukemia patients may not always yield optimal results.[9–11] One such study suggests that the failure rate of medical IFI treatment may reach up to 50% in invasive aspergillosis (IA). This was further associated with a 12-week overall death rate exceeding 30% in both IA and invasive candidiasis.[7] As such, surgical intervention may be necessary in selected patients for both diagnostic and therapeutic purposes. Surgery may play a role in emergency settings to prevent massive hemoptysis, as well as in elective settings to improve the control of fungal disease and patient survival.[12–16]

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Due to the nature of the disease and surrounding circumstances, data on surgical interventions may be difficult to obtain, and existing evidence is usually from small cohorts. There is hence a need for further data to help us develop optimal guidelines regarding the benefits and risks of surgery for IFI in leukemia patients. The aim of this study is to report the experience of a large tertiary center in using surgical interventions as adjunctive treatment for IFI in adult leukemia patients. We discuss the patient profile, feasibility, and survival outcomes of these surgical interventions for IFI.

2. METHODOLOGY

An Institution Review Board (IRB)-approved retrospective review of the leukemia database was conducted to obtain clinical characteristics and outcomes of surgically managed IFI patients diagnosed between January 2005 and December 2015. Patients who fulfilled all the following criteria were included in our study:

1. acute leukemia diagnosed in the defined time period,
2. underwent intensive chemotherapy (patients on best supportive care were excluded)
3. with diagnosis of possible/probable/proven IFI by the EORTC/MSG criteria,[17] and
4. underwent surgical intervention for the IFI.

Indications for surgery were classified as either diagnostic or therapeutic. Clinical data on patients, type and duration of antifungal therapy, type of surgery, and postoperative complications were obtained from our IRB-approved database. Due to the observational nature of this study, the need for informed consent was waived.

2.1. Definitions

The classification of IFI was determined postoperatively according to EORTC/MSG 2008 diagnostic criteria.[17] Diagnostic indication for surgery refers to instances in which the preoperative diagnosis of IFI was possible or probable, and a definitive diagnosis was sought. Therapeutic indication refers to instances when surgery was performed as a treatment for the IFI to enable recovery from it (e.g., drainage of an abscess or arresting massive hemoptysis). It is possible that surgery served both diagnostic and therapeutic purposes.

Itraconazole and posaconazole were used as primary prophylaxis. Empirical antifungal treatment was started after 48 h of fever refractory to broad spectrum antibiotics. Antifungal treatment was administered as a monotherapy, combination therapy, or tandem therapy using various antifungal agents. These included caspofungin, liposomal amphotericin, voriconazole, anidulafungin, and other azoles.

The outcome of surgical treatment was defined as follows: overall benefit refers to surgery resulting in complete resolution of IFI (no recurrence of any radiological or clinical features of IFI), the ability to proceed with further invasive chemotherapy, or a change in antifungal treatment; temporary benefit refers to clear radiological or clinical improvements post-surgery allowing further leukemia treatment, followed by recurrence of radiological or clinical features with or without confirmatory evidence of IFI; and no benefit refers to a lack of clear improvement post-surgery with or without further confirmation of IFI. These definitions were formulated by hematologists from our institution, in consultation with experienced Infectious Diseases clinicians. Early postoperative complications are defined as complications occurring within 3 months postoperatively, whereas late postoperative complications refer to complications occurring at least 3 months after the surgery.[8]

2.2. Statistical analysis

Overall survival (OS) analyses were performed using the Kaplan–Meier method. Percentage, median, and range were used as appropriate to describe continuous and categorical variables.

3. RESULTS

3.1. Clinical characteristics

Among 795 acute leukemia patients diagnosed during this period, a total of 85 IFI occurred in 82 patients. Of these 82 patients, 59 had AML and 26 had ALL. Three patients had 2 IFI each. Fifty-four patients had IFI after induction or consolidation chemotherapy (40 AML, 14 ALL). Ten patients developed IFI after chemotherapy for relapse of leukemia (6 AML, 4 ALL). Twenty-one patients developed IFI after allogenic HSCT (13 AML, 8 ALL). Overall, the incidence of IFI was 8.5% after induction or consolidation chemotherapy, 12.5% after chemotherapy for relapse, and 8.7% after HSCT.

Nineteen patients with IFI, 9 males and 10 females, with a median age of 46 years (range 19–65) underwent surgical interventions. These were preselected fit patients, with most having no major comorbidities. Of these patients, 12 had AML and 7 had ALL. Only 4 out of 19 patients with IFI who underwent surgical procedures had preexisting comorbidities.

Prior to the operation, 3 patients had proven IFI, 5 had probable IFI, and 11 had possible IFI. Postoperatively, 15 patients had proven IFI, 1 had probable IFI, and 3 had possible IFI. At the time of IFI, 12 patients were on induction chemotherapy, 3 were on consolidation chemotherapy, 1 was between consolidation chemotherapy and transplant, and 3 patients had received allogeneic HSCT. Lung involvement was present in 15 patients: 11 patients had isolated lung involvement while 4 had concurrent involvement of one or multiple organs. For 3 other patients, there was a single infection in either the soft tissue or the sino–nasal area. One patient had concurrent infections in both the sino–nasal area and soft tissue.

In patients with proven IFI, diagnostic confirmation was performed by histology, culture, both histology and culture, or PCR. The identified fungal pathogens included *Aspergillus*, *Fusarium*, Mucor, *Candida*, and other unspecified moulds (Table 1). Details of the demographic and clinical data are reflected in Table 1.

3.2. Surgical management

Twenty surgical procedures were recorded in 19 patients. Of these patients, 16 underwent surgery for both diagnostic and therapeutic indications, while 3 underwent surgery for therapeutic purposes only. One patient underwent 2 procedures for different IFI (aspergillosis and fusariosis). The surgical procedures performed are outlined in Table 2. The median interval between the clinical-radiological diagnosis of IFI and surgery was 10 days, with a range of 0 to 356 days. All surgeries were scheduled electively and none were conducted under emergency conditions. Surgical data including the type of surgical interventions and antifungal treatment are summarized in Table 2.

In all cases, prior to surgery, antifungal drugs were administered. This was given as monotherapy in 10 patients (53%), combination therapy in 4 patients (21%), and tandem therapy in 3 patients (16%). Details of these therapies are found in Table 3.

Table 1

Demographic and clinical data on patients who underwent surgical intervention for IFI.

	n = 19
Female gender (%)	10 (53%)
Median age in years at IFI diagnosis (range)	46 (19–65)
Underlying disease	AML–12 (63%)
	ALL–7 (37%)
Patient comorbidities	Hypertension–1(5%)
	Hypertension, bladder cancer–1 (5%)
	Prior acute promyelocytic leukemia–1 (5%)
	Idiopathic thrombocytopenia–1 (5%)
Classification of IFI by EORTC/MSG criteria (postoperatively)	Proven–15 (79%)
	Probable–1 (5%)
	Possible–3 (16%)
Phase of treatment at diagnosis of IFI	Induction–12 (63%)
	Consolidation–3 (16%)
	Between consolidation and post-transplant–1 (5%)
	Post-transplant–3 (16%)
Organ involvement	Isolated pulmonary/pleural–11 (58%)
	Pulmonary and pericardial–2 (11%)
	Pulmonary and splenic–1 (5%)
	Pulmonary, skin, joints, and bone–1 (5%)
	Sino–nasal–2 (11%)
	Soft tissue–1 (5%)
	Sino–nasal and soft tissue–1 (5%)
Diagnostic confirmation	Histology alone–7 (37%)
	Culture alone–2 (11%)
	Histology and culture–5 (26%)
	PCR (*Aspergillus*)–1 (5%)
Type of fungi in proven cases	*Aspergillus*–5 (26%)
	Fusarium–2 (11%)
	Mucor–1 (5%)
	Candida–1 (5%)
	Unspecified molds–5 (26%)
	Dual (mold in lung tissue and *Candida* in blood)–1 (5%)

3.3. Hematological parameters before surgery

Most of the procedures were conducted after recovery of blood counts, but in a single case, the patient was neutropenic. The median preoperative neutrophil count prior to surgery was 2.96×10^9/L (range 0.08–17.52×10^9/L). Red blood cell transfusions were required by 6 out of 19 patients, and 8 patients required platelet transfusions. The median preoperative hemoglobin was 9 g/dL (range 7.1–12.8 g/dL), and the median preoperative platelet count was 64×10^9/L (range 6–379×10^9/L). These parameters are reflected in Table 2.

3.4. Early and late outcomes

A total of 7 patients experienced early postoperative complications, and no patients experienced late postoperative complications. Complications were observed in 7 cases after lung resection. These were 2 pleural effusions, 4 pneumothoraxes, and 1 hydropneumothorax (Fig. 1). There were no major complications such as bronchopleural fistulas, nonhealing bronchial stumps, or severe hemorrhage. No repeat surgeries were required. The median duration of hospitalization post-surgery for patients with complications was 9 days (range 3–64).

Of the 19 patients, 13 benefited overall from the procedure, 3 had temporary clinical benefits, 2 had progression of IFI, and in 1 patient no definite conclusions could be drawn due to lack of information (Fig. 2). Of the 15 patients with proven IFI diagnoses, 9 benefited overall, 3 had temporary clinical benefits, 2 had progression of IFI, and in 1 patient no definite conclusions could be drawn. Of the 9 patients who benefited overall, 7 were alive at the time of data collection and 2 had died. The 3 patients with temporary clinical benefits succumbed 2 to 6 months post-surgery due to unrelated septic events.

The patient with a probable IFI diagnosis benefited overall from the procedure, being able to proceed with further chemotherapy but succumbing to central nervous system (CNS) leukemia 8 months later. The 3 patients with a diagnosis of possible IFI also benefited overall. Two were able to proceed with HSCT and 1 with chemotherapy post-surgery, but all eventually succumbed to leukemia and/or unrelated septic events.

After 3 months from IFI diagnosis, 17 patients were alive and 2 had died, 1 due to mycosis. The 3-month OS was 89.5%. Two years after diagnosis, 11 patients were alive, whereas 6 had died from progression of underlying hematological disease, 1 died of pneumonia unrelated to IFI, and 1 died of unknown causes. The 2-year OS was 57.9%. Median survival from date of diagnosis was 12 months, with a median follow-up duration of 12 months (range 4.8–120.6). The Kaplan–Meier curve of OS is presented as Figure 3. The median time from surgery to resumption of chemotherapy or HSCT was 25 days (range 9–314) (Fig. 4). The surgical complications and outcomes are summarized in Table 2.

4. DISCUSSION

Despite recent advances in therapy, IFI still represents a major complication in severely immunocompromised hosts undergoing chemotherapy or HSCT for acute leukemia. Previous studies show that the most frequently involved organ is the lung,[18,19] similar to our findings. Table 1 shows a breakdown of the pathogens involved in the 15 proven IFI. In agreement with published observations,[20] we noted a rising trend in non-*Aspergillus* moulds, with only 5 patients diagnosed with pulmonary aspergillosis, and a significant number of other opportunistic pathogens such as *Fusarium* and *Mucor*. There were thus a sizable number of non-galactomannan-positive cases where surgery was performed for diagnostic and therapeutic indications.

Clinicians have acknowledged the importance of early diagnosis and treatment with appropriate antifungals to optimise patient outcomes.[21] A number of trials have shown that timely surgical intervention in conjunction with medical management has resulted in better outcomes than antifungal therapy alone.[12–14]

According to guidelines from the Infectious Diseases Society of America (IDSA),[22] surgery for aspergillosis should be considered for localized disease that is easily accessible to debridement, such as invasive fungal sinusitis. The benefit of surgery for IA in other settings, such as in the treatment of endocarditis, osteomyelitis, or focal CNS disease, appears rational. Other indications are less clear and require consideration of the patient's immune status, comorbidities, confirmation of a single focus, and the risks of surgery.

In general, surgical treatment of IFI is considered feasible in patients who are fit for the procedure, where the underlying hematological disease is sufficiently stable and nonprogressive, where the fungal infection is resectable, and there are indications for surgery in accordance with IDSA guidelines.[17] In these patients, surgery can yield valuable information to guide antifungal therapy or enable therapeutic outcomes with acceptable risk, allowing patients to proceed with curative chemotherapy and HSCT.

Table 2

Details of surgical interventions.

Number of surgical procedures	20
Reason for surgery	Therapeutic only–3 patients (16%) Diagnostic and therapeutic–16 patients (84%)
Type of surgery (20 procedures in 19 patients)	• Open thoracotomy (wedge resections, lobectomies or pericardial window)–6 (30%) • Open thoracotomy with decortication–2 (10%) • Video-assisted thoracoscopic surgery–5 (25%) (four upper lobe wedge resections, one lower lobe wedge resections) • Functional endoscopic sinus surgery (FESS)–4 (20%) • Splenectomy–1 (5%) • Abscess drainage and debridement–1 (5%) • Arthrotomy with radial reaming and drainage–1 (5%)
Interval between initial diagnosis of IFI and surgery (median + range in days)	10 (0–356)
Type of antifungal prophylaxis	Itraconazole[*]–10 (53%) Posaconazole[†]–9 (47%)
Type of antifungal therapy before surgery	Monotherapy–10 (53%) Combination therapy–4 (21%) Tandem therapy–3 (16%)
Hematological parameters before surgery	
Hb (g/dL)	Median: 9 (range 7.1–12.8) Six patients required red blood cell transfusions
Neutrophils ($\times 10^9$/L)	Median: 2.96 (range 0.08–17.52)
Neutrophils $<0.5 \times 10^9$/L	1 (0.05%)
Platelets ($\times 10^9$/L)	Median: 64 (range 6–379) Eight patients required platelet transfusions
Platelets $<50 \times 10^9$/L (%)	8 (42.1%)
Complications	Pleural effusion–2 (11%) Pneumothorax–4 (21%) Hydropneumothorax–1 (5%)
Surgical outcomes	Overall benefit–13 (68%) Temporary benefit–3 (16%) Progression of IFI–2 (11%) Data inconclusive–1 (5%)
Overall survival	89.5% at 3 months 57.9% at 2 years
Median time to resumption of chemotherapy or HSCT (n = 13)[‡]	25 days

[*] Itraconazole prophylaxis: Syrup 200 mg Q12 h × 15 doses, then capsule 200 mg Q8 h.

[†] Posaconazole prophylaxis: Suspension 200 mg TDS.

[‡] Six patients did not have any chemotherapy or HSCT postoperatively.

Early diagnosis is important to enable prompt treatment with targeted antifungals. However, diagnosis of fungal infection is difficult, as patients frequently present with nonspecific symptoms such as pyrexia of unknown origin. Furthermore, nonsurgical investigative modalities, such as serological tests, have the disadvantages of low sensitivity and specificity, presenting diagnostic challenges for clinicians.[21] A study showed that bronchoalveolar lavage was only able to culture fungus in 40% of patients with pulmonary IFI.[23] In contrast, surgical biopsies and resected specimens often yield confirmed diagnoses with high accuracy.[8]

In our study, only 3 patients had proven IFI diagnoses prior to surgery, and 16 patients underwent surgery for both diagnostic

Table 3

Antifungal therapies given prior to surgery.

Antifungal treatment	Antifungal agents	Number of patients
Monotherapy	Caspofungin	1
	Liposomal Amphotericin	6
	Azoles	3
Combination therapy	Liposomal amphotericin + azoles	2
	Caspofungin + Voriconazole	1
	Anidulafungin + Voriconazole	1
Tandem therapies	Caspofungin → Liposomal Amphotericin	1
	Caspofungin → Voriconazole	1
	Liposomal amphotericin → Voriconazole	1
Information unavailable	NA	2

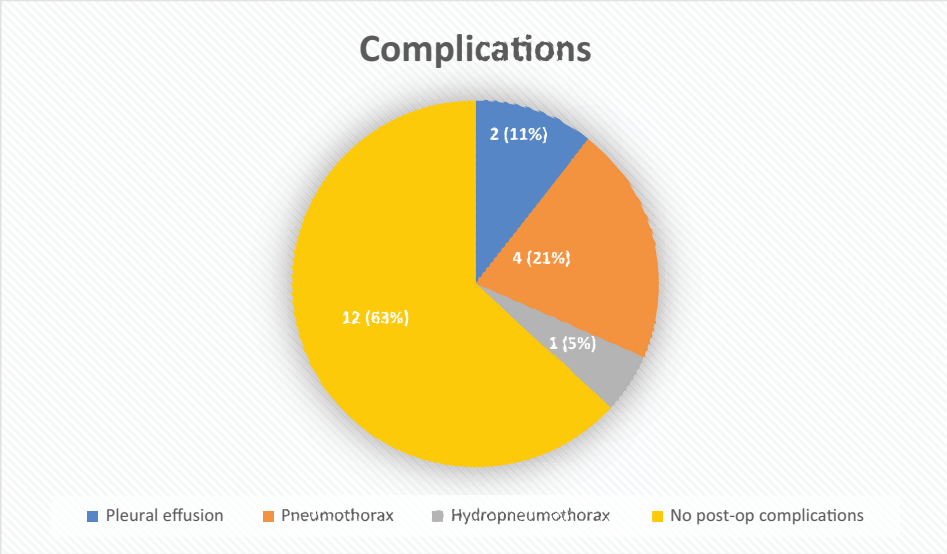

Figure 1. Complications of surgery in IFI patients (n=19).

and therapeutic purposes. Postoperatively, the diagnostic yield for proven IFI increased by a factor of 5, and 15 patients had definitive IFI diagnoses. Hence, surgical intervention was crucial in determining a diagnosis in the majority of patients. Moreover, all patients had a change of antifungal therapy postoperatively, indicating that surgically obtained specimens could guide the choice of subsequent antifungal therapy. Definitive diagnosis often results in significantly less use of empiric antifungal therapy, such as amphotericin B, reducing cost as well as the occurrence of side effects like renal toxicity.

Efficacious and timely treatment of IFI is crucial when patients are undergoing chemotherapy or awaiting HSCT, as these immunocompromised patients are at a high risk of severe complications. Recently, Chretien et al reported the single-center results of pulmonary resection in 50 hematological patients with IFI observed over a period of 22 years. Postoperatively, almost 90% of patients underwent further hematological therapy, demonstrating that surgical resection of pulmonary IFI may be safe and effective.[24]

Our study found that 13 out of 19 patients (68%) benefited overall from the surgical procedure, while another 3 (16%) benefited temporarily. In addition, the surgical procedures were well-tolerated, and no deaths were caused directly by surgery. Furthermore, there were no bleeding- or infection-related complications as a direct result of the surgeries, despite 8 patients being thrombocytopenic and 1 patient being severely neutropenic. This corroborates the findings of several published observations that lung resection can be performed with low perioperative mortality and morbidity while allowing for significant improvement in the majority of patients.[25,26] Our

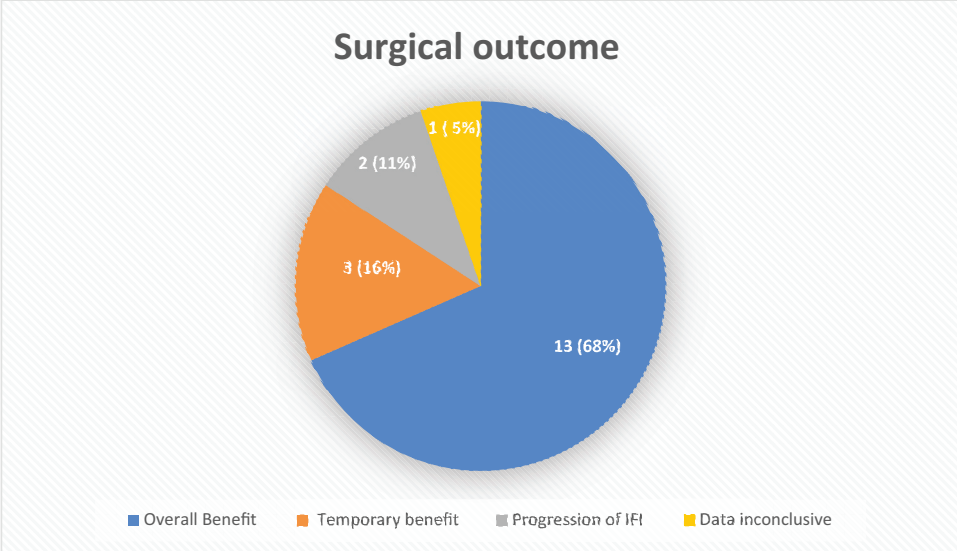

Figure 2. Surgical outcomes in IFI patients (n=19).

Figure 3. Kaplan–Meier curve of overall survival from date of diagnosis.

low postoperative and surgery-related mortality rates may in fact suggest that our physicians are currently too conservative, as more patients may actually benefit from an improvement in diagnostic yield via surgery. Surgery, be it therapeutic or diagnostic, is of vital significance, as long-term survival is a function of how well-controlled the hematological disease is.[27,28]

These findings show that appropriate surgical interventions allow more rapid diagnosis and therapy for IFI, while also maintaining an acceptably low rate of perioperative morbidity. Many of our patients were able to proceed with curative chemotherapy or HSCT after surgery, eventually resulting in better outcomes. We thus suggest that physicians should adopt a mindset of being willing to utilize surgical approaches in the treatment of suitable IFI patients.

Our study has inherent biases applicable to any retrospective study. However, in this population, for the specific query regarding the role of surgery in IFI, obtaining prospective data is immensely difficult, if not impossible. A particular bias in our cohort that may be worth noting is that the selected patients were generally fit and already on intensive chemotherapy. Despite these limitations, our study shows that in clinically fit patients, surgery yields demonstrable outcomes with minimal complications. Nevertheless, prospective studies or registry-based data analysis performed on larger cohorts may provide further data

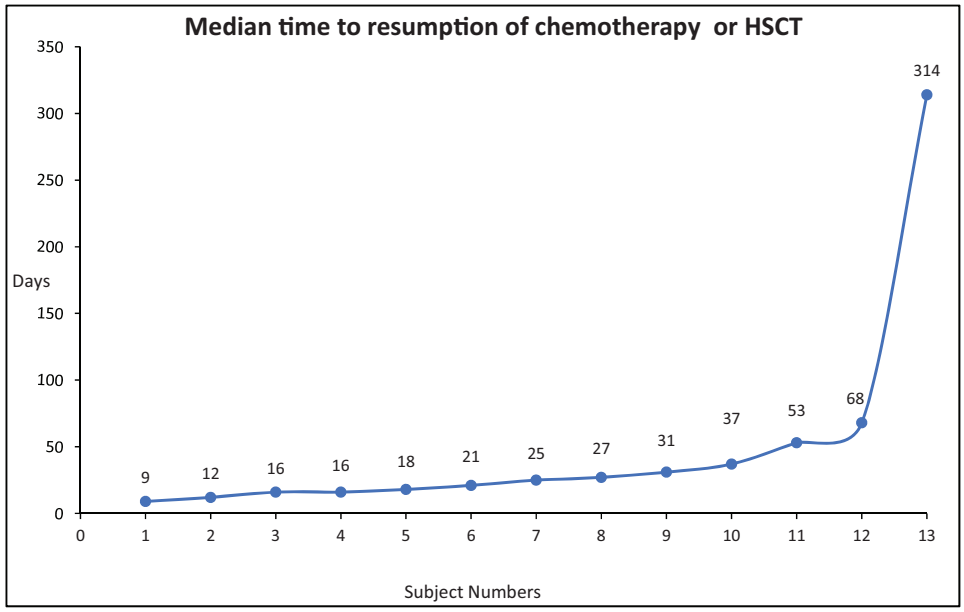

Figure 4. Time to resumption of chemotherapy or HSCT from date of surgery.

regarding the feasibility and long-term outcomes of surgical intervention for IFI.

5. CONCLUSION

This study of a large cohort of acute leukemia patients from our registry diagnosed over an 11-year period demonstrates that major surgical interventions for the management of IFI s in selected fit patients is feasible and can serve both diagnostic and therapeutic purposes. In these selected patients, surgery can yield valuable information to guide antifungal therapy or enable therapeutic outcomes with an acceptable risk, allowing patients to proceed with curative chemotherapy and stem cell transplantation.

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GCW, CN designed the research study. YCT, GCW, CN acquired the data. All authors contributed to analysis and interpretation of data. BMHK, ZXN, TTT, GCW, CN drafted the manuscript. All authors critically revised the manuscript and approved the final version for submission.
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