

# Predicting Outcome After Lung Resection for Invasive Pulmonary Aspergillosis in Patients With Neutropenia\*

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**Study objectives:** To investigate the factors that predict survival after lung resection for invasive pulmonary aspergillosis (IPA) in patients with neutropenia, in order to assist the selection of patients who are most likely to have a successful outcome.

**Design:** Retrospective single-center study.

**Setting:** University hospital hemato-oncologic isolation unit and division of thoracic surgery.

**Patients:** Forty-one patients with hematologic disease and suspected IPA who underwent lung resection.

**Interventions:** Lobectomy (n = 23), wedge resection (n = 16), and enucleation (n = 2).

**Results:** Mortality within 30 days was 10% (4 of 41 patients). Major perioperative complications occurred in 10%. One death was possibly related to surgery (pleural aspergillosis). Of the patients with proven aspergillosis, 87.1% were cleared of infection, but fungal relapse occurred in 10%. Overall survival was 65% at 6 months, 58% at 12 months, and 40% at 5 years after surgery. Baseline characteristics and intraoperative data did not differ significantly between survivors and nonsurvivors at 6 months or 12 months after surgery. Perioperative complications did not significantly influence the outcome. Multivariate analysis of 12-month survival revealed that the variables, progression, or recurrence of the underlying hematologic disease (relative risk [RR], 4.64; 95% confidence interval [CI], 3.51 to 5.77;  $p < 0.0001$ ), fungal relapse (RR, 5.06; 95% CI, 3.83 to 6.28;  $p < 0.0001$ ), and to a minor extent the type of the underlying hematologic disease ( $p < 0.018$ ) were the most important predictors of patient survival.

**Conclusions:** Lung resection for IPA is feasible with an acceptable operative risk. While at 10%, the perioperative mortality is considerable; the nonsurgical mortality is reported to be between 30% and 90%. Fungal infection is cleared in > 80% of patients. Mid- to long-term survival can be achieved if the underlying hematologic disease is under control. It is not yet possible to define a group of patients with IPA who are most likely to benefit from lung resection.

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**Key words:** fungal infection; hematologic disease; invasive pulmonary aspergillosis; surgery

**Abbreviations:** BMT = bone marrow transplantation; CI = confidence interval; IPA = invasive pulmonary aspergillosis; RR = relative risk; SCT = stem-cell transplantation

Invasive pulmonary aspergillosis (IPA) is a life-threatening infectious complication in patients with neutropenia. In patients undergoing myeloablative chemotherapy or stem-cell transplantation (SCT), who are at the highest risk of acquiring IPA, the incidence ranges from 5 to 15%.<sup>1–4</sup> Despite

adequate medical treatments, such as amphotericin B or voriconazole, the prognosis of IPA remains poor; reports of mortality range from 30 to 90%.<sup>1,5–7</sup> Antifungal drugs are often insufficient, and the frequency of complete response after weeks of therapy is low.<sup>8</sup> However, the rapid and effective treat-

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ment of IPA is of particular importance, as most patients need subsequent therapy for the underlying hematologic disease as soon as possible. Lung resection in combination with antifungal drugs is a controversial approach to therapy that is undertaken by only a few centers. Neutropenia and low platelet

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count may increase perioperative morbidity and mortality, and the redeeming benefit of this approach remains questionable. Several studies<sup>9–14</sup> have shown the feasibility of lung resection in these high-risk patients. There is some evidence that the combination of antifungal drugs and lung resection results in a better outcome than medical treatment alone.<sup>9–14</sup> We therefore undertook this study of outcomes after lung resection for IPA in order to assist the selection of those patients most likely to profit most from a surgical approach.

## MATERIALS AND METHODS

Between 1983 and 2002, 41 consecutive patients underwent lung resection for suspected IPA. The underlying hematologic disease was leukemia (mainly acute and chronic myeloid) in 27 patients, severe aplastic anemia in 7 patients, myelodysplastic syndrome in 4 patients, non-Hodgkin lymphoma in 2 patients, and multiple myeloma in 1 patient. Immunosuppressive therapy, before invasive aspergillosis was suspected, consisted of high-dose chemotherapy in 27 patients, and bone marrow transplantation (BMT) or SCT in 8 patients. Six patients with aplastic anemia had received antilymphocyte globulin. The mean age of the 15 female patients (37%) and 26 male patients was 39.8 years (range, 9 to 68 years). Symptoms before surgery were fever in 34 patients (83%), chest pain in 7 patients (17%), and cough in 3 patients (7%). IPA was suspected if, in addition to antibiotic resistant fever, chest radiograph and thoracic CT scans showed the development of localized infiltrates. Bronchoscopy with BAL was not performed routinely because of its low diagnostic sensitivity.<sup>15</sup>

Pulmonary infiltrates were located unilaterally in 34 patients (83%) and bilaterally in 7 patients (17%). Given the fact that, with conservative treatment alone, mortality is high, we operated on those patients who had one to two infiltrates and were not in very poor physical condition. Lung resection was undertaken the day after, or no more than a few days after establishing clinical and radiologic suspicion of IPA. If pulmonary infiltrates were bilateral, video-assisted thoracic surgery was performed on the side with the smaller lesion, and the open procedure was done on the opposite side. Low platelet count was not a contraindication for surgery. However, patients generally received transfusions to increase the platelet count up to  $40 \times 10^9/\text{L}$  preoperatively. Nevertheless, platelet counts ranged from 5 to  $388 \times 10^9/\text{L}$  on the day of operation due to the underlying hematologic disease. No WBCs were given, but patients occasionally received RBCs preoperatively. All patients were treated perioperatively by the hemato-oncologic isolation unit under standardized conditions according to defined protocols for hematologic disease or severe aplastic anemia.

We reviewed in detail all of the hospital records focusing on baseline characteristics, operation protocols, perioperative mor-

bidity and mortality, and short-term and long-term outcomes. For comparison of continuous and categorical variables, the Mann-Whitney *U* test,  $\chi^2$ , or Fisher Exact Tests were used, as appropriate. Survival was calculated using the Kaplan-Meier estimator. To adjust for effects of perioperative variables on the short-term and long-term outcomes, a Cox proportional hazard regression model was fitted with forward stepwise variable entry.

## RESULTS

Lung resection consisted of lobectomy in 23 patients (56%), single or multiple wedge resection in 16 patients (39%), and enucleation in 2 patients (5%). All patients underwent phases of neutropenia (neutrophil count  $< 0.5 \times 10^9/\text{L}$ ) prior to surgery. On the day of operation, 29 patients (71%) were neutropenic; the mean hemoglobin count was 10.0 g/dL (range, 7.3 to 12.2 g/dL), and the mean platelet count was  $43.0 \times 10^9/\text{L}$  (range, 5 to  $388 \times 10^9/\text{L}$ ). All patients were treated with broad-spectrum antibiotics and had received amphotericin B or voriconazole preoperatively. The duration of lung resection ranged from 30 to 210 min (mean, 110 min). The mean intraoperative blood loss was 293 mL (range,  $< 50$  to 1,000 mL). All patients but one were extubated immediately in the operating theater.

Major postoperative complications occurred in four patients (10%): one patient had a persistent air leakage, acquired pleural aspergillosis, and died at day 56, probably of IPA (autopsy was rejected by the relatives); another patient needed reoperation for bronchial stump dehiscence; one patient acquired life-threatening liver bleeding, resulting from preoperative CT-guided marking of a pulmonary lesion, and needed emergency laparotomy a few hours after lung resection; and one patient presented with a reversible ARDS. All except the one patient who acquired pleural aspergillosis recovered and were discharged home after a few weeks. Minor complications included the following: pleural effusion ( $n = 6$ ), seroma ( $n = 2$ ), and prolonged air leakage ( $n = 2$ ). There were no deep wound infections or empyema necessitating reoperation.

Overall mortality within 30 days postoperative was 10% (4 of 41 patients): 2 patients died of bacterial septicemia, and 2 patients died probably due to disseminated IPA under persistent neutropenia (autopsy was rejected by the relatives). One death, that of the patient who acquired pleural aspergillosis, may have been related to surgery. Fungal infection was confirmed by histologic examination in 31 patients (76%). Pathology revealed nonspecific fibrosing alveolitis in seven patients (17%), lung infarction in two patients (5%), and bacterial abscess in one patient (2%). The infection was definitively cleared in 87% of patients with proven IPA. Four patients with histologically proven IPA had ongoing or relaps-

ing fungal infections; two of them died probably due to disseminated IPA (autopsy was rejected by the relatives). Overall survival was 65%, 58%, 47%, and 40% at 6 months, 12 months, 3 years, and 5 years, respectively (Fig 1). There was no statistical significant difference in the survival between patients with (n = 31) and without (n = 10) histologically proven IPA (p = 0.26; Fig 1).

Univariate analysis of baseline characteristics showed no significant differences between survivors and nonsurvivors at 6 months or 12 months; 12-month data are given in Table 1. Intraoperative and postoperative factors did not differ significantly between survivors and nonsurvivors at 6 months and 12 months; 12-month data are given in Table 2. In contrast, progression or reoccurrence of the underlying hematologic disease and fungal relapse were found in nonsurvivors at 6 months and 12 months; 12-month data are given in Table 2. Multivariate analysis of 6-month and 12-month survival revealed that the variables, progression, or reoccurrence of the underlying hematologic disease, fungal relapse, and to a minor extent the type of hematologic malignancy were the most important predictors of outcomes; 12-month analysis is given in Table 3 (Fig 1, 2). In patients with histologically proven IPA (n = 31), the multivariate analysis of 12-month survival showed the same significant variables: progression or reoccurrence of the underlying hematologic disease (relative

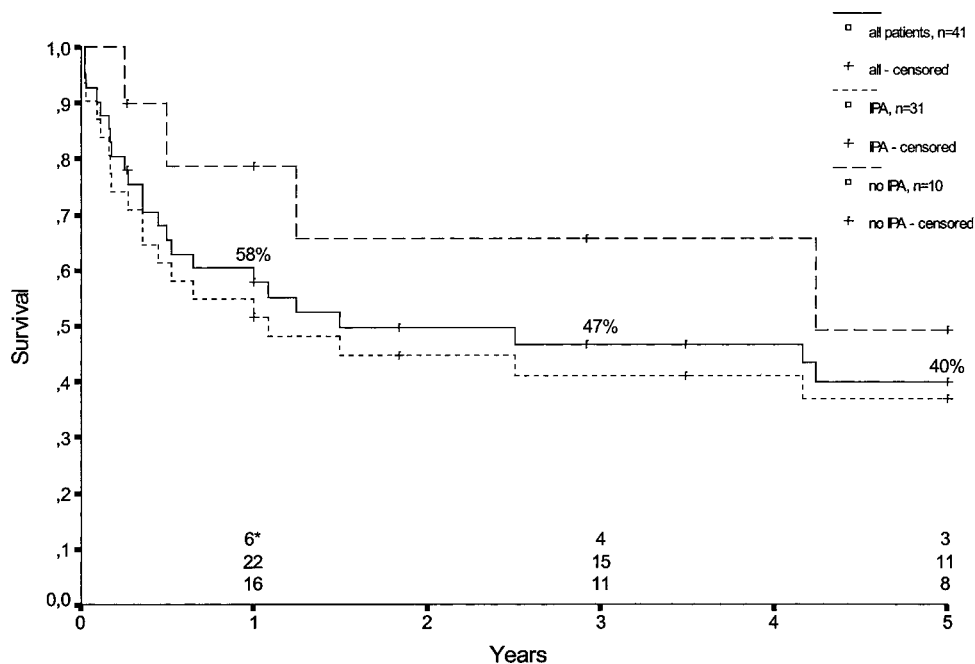
**Table 1—Baseline Characteristics of Survivors and Nonsurvivors at 12 Months After Surgery\***

| Variables                                    | Survivors<br>(n = 25) | Nonsurvivors<br>(n = 16) | p Value |
|----------------------------------------------|-----------------------|--------------------------|---------|
| Age, yr                                      | 39.5 ± 17.4           | 40.3 ± 17.1              | 0.9     |
| Female gender                                | 7 (28)                | 8 (50)                   | 0.2     |
| Disease                                      |                       |                          | 0.4     |
| Acute leukemia                               | 15 (60)               | 7 (44)                   |         |
| Chronic leukemia                             | 2 (8)                 | 3 (19)                   |         |
| Aplastic anemia                              | 5 (20)                | 2 (12)                   |         |
| Others†                                      | 3 (12)                | 4 (25)                   |         |
| Treatment of the<br>underlying disease       |                       |                          | 0.9     |
| High-dose<br>chemotherapy                    | 16 (64)               | 11 (69)                  |         |
| BMT and SCT                                  | 5 (20)                | 3 (19)                   |         |
| Antilymphocyte<br>globulin                   | 4 (16)                | 2 (12)                   |         |
| Pulmonary infiltrates                        |                       |                          | 0.2     |
| Unilateral                                   | 19 (76)               | 15 (94)                  |         |
| Bilateral                                    | 6 (24)                | 1 (6)                    |         |
| Duration of neutropenia<br>before surgery, d | 17.1 ± 20.9           | 30.4 ± 49.6              | 0.2     |

\*Data are presented as mean ± SD or No. (%).

†Myelodysplastic syndrome (n = 4), non-Hodgkin lymphoma (n = 2), multiple myeloma (n = 1).

risk [RR], 4.09; 95% confidence interval [CI], 2.95 to 5.23; p = 0.0003), fungal relapse (RR, 4.62; 95% CI, 3.37 to 5.87; p = 0.0002), and the type of the hematologic disease (p = 0.036).



**FIGURE 1.** Overall survival of patients operated for suspected IPA (n = 41); and overall survival of patients with (n = 31) and without (n = 10) histologically proven IPA (p = 0.26). \*No. of patients included in the Kaplan-Meier curves.

**Table 2—Intraoperative and Postoperative Data of Survivors and Nonsurvivors at 12 Months\***

| Variables                                          | Survivors<br>(n = 25) | Nonsurvivors<br>(n = 16) | p Value  |
|----------------------------------------------------|-----------------------|--------------------------|----------|
| Type of operation                                  |                       |                          | 0.3      |
| Lobectomy                                          | 12 (48)               | 11 (69)                  |          |
| Wedge resection                                    | 11 (44)               | 5 (31)                   |          |
| Enucleation                                        | 2 (8)                 | 0                        |          |
| Laboratory data at operation, × 10 <sup>9</sup> /L |                       |                          |          |
| Hemoglobin                                         | 9.8 ± 1.3             | 9.7 ± 1.0                | 0.9      |
| Platelets                                          | 75.7 ± 95.3           | 83.1 ± 98.5              | 0.8      |
| Transfusions (concentrates)                        |                       |                          |          |
| Erythrocytes (0–7 d after surgery)                 | 4.2 ± 2.4             | 5.3 ± 2.5                | 0.15     |
| Platelets (0–7 d after surgery)                    | 2.5 ± 1.9             | 3.7 ± 3.8                | 0.2      |
| Duration neutropenia after surgery, d              | 15.8 ± 25.7           | 14.4 ± 17                | 0.8      |
| Postoperative complications                        |                       |                          | 0.3      |
| Major                                              | 1 (4)                 | 3 (19)                   |          |
| Minor                                              | 6 (24)                | 4 (25)                   |          |
| Reoccurrence of the hematologic disease            | 0                     | 11 (69)                  | < 0.0001 |
| Patients with fungal relapse                       | 0                     | 4 (25)                   | 0.02     |

\*Data are presented as No. (%) or mean ± SD.

## DISCUSSION

IPA represents a major diagnostic and therapeutic problem in patients with neutropenia. The incidence ranges from 5 to 15% in patients undergoing high-dose chemotherapy or SCT for hematologic malignancies.<sup>1–4</sup> Clinical signs of IPA are nonspecific, but often characteristic; the occurrence of fever despite appropriate broad-spectrum antibiotic therapy and new appearance of pulmonary consolidations or infiltrates on thoracic CT scan are highly suspicious of invasive aspergillosis.<sup>16</sup> Other diagnostic tools such as bronchoscopy with BAL, CT-guided percutaneous lung biopsy, or microbiological tests are of limited value.<sup>16</sup>

The optimal therapeutic management of IPA is controversial, ranging from different antifungal drugs to additional lung resection. Medical treatment of IPA is often insufficient and is reported to be associated with mortality rates ranging from 30 to 90%.<sup>1,5–7</sup> A recently published multicenter trial<sup>8</sup> showed that 3 months after starting amphotericin B or voriconazole for invasive aspergillosis, the complete response rates were 16.5% and 20.8%, and the partial response rates were 15% and 31.9%, respectively. However, rapid and effective treatment of IPA is of particular importance because most pa-

tients will need subsequent immunosuppressive therapy for the underlying hematologic disease as soon as possible.

Whether radical surgical removal of the necrotic and poorly perfused lung tissue clears IPA more quickly than do antifungal drugs is not proven but is probable. Combining medical treatment and lung resection is controversial, and is done at only a few centers. However, some studies<sup>9–14,17,18</sup> have shown that lung resection in these high-risk patients is feasible with a remarkably low morbidity and mortality: the 30-day mortality ranges from 0% in smaller series, to 31% in larger series. Our patients showed a 30-day mortality of 10%; two patients died due to bacterial septicemia, and two patients died probably as a result of relapsing aspergillosis under persistent neutropenia. Major complications occurred in 10% of patients, and one patient died as a result (from pleural aspergillosis). Lobectomy was performed in most patients, but the number of wedge resections for IPA at our institution has increased in recent years, reflecting a less invasive policy. Enucleation was done only in exceptional cases. At the outset, we thought that full lobectomy would produce less perioperative complications, but there were no more problems when only the infected parts of the lung were resected (wedge resection). It is important to note that the central vessel proximal to the infiltrate is often occluded by a fungal thrombus, so this part of the lung tissue should always be resected. Pathologists should be aware that sections of the proximal vessel must be carefully investigated to be sure not to miss the fungal infection by only looking at the specimen of the peripheral “ischemic” infiltrate. However, due to the small number of subgroups, our data does not allow independent validation of the surgical procedures. Nevertheless, we recommend wedge resection for IPA if possible.

There is some evidence that the combination of lung resection and medical treatment results in a better outcome and a reduced IPA-related mortality

**Table 3—Multivariate Analysis of 12-Month Survival in All Patients**

| Variables                                                         | RR   | 95% CI    | p Value  |
|-------------------------------------------------------------------|------|-----------|----------|
| Hematologic disease                                               |      |           | 0.018    |
| Acute leukemia                                                    | 1.00 |           |          |
| Chronic leukemia                                                  | 1.69 | 1.27–3.23 |          |
| Aplastic anemia                                                   | 0.95 | 0.88–1.08 |          |
| Others*                                                           | 1.92 | 1.27–2.44 |          |
| Progression or reoccurrence of the underlying hematologic disease | 4.64 | 3.51–5.77 | < 0.0001 |
| Fungal relapse                                                    | 5.06 | 3.83–6.28 | < 0.0001 |

\*Myelodysplastic syndrome (n = 4), non-Hodgkin lymphoma (n = 2), multiple myeloma (n = 1).

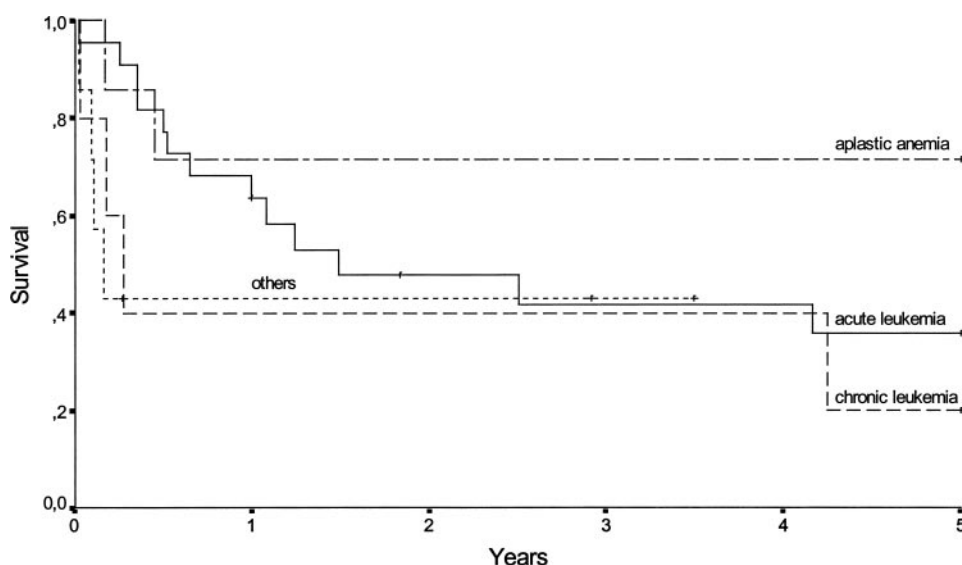


FIGURE 2. Overall survival according to the type of underlying hematologic disease: acute leukemia (n = 22), chronic leukemia (n = 5), aplastic anemia (n = 7); others are myelodysplastic syndrome (n = 4), non-Hodgkin lymphoma (n = 2), and multiple myeloma (n = 1).

compared with medical treatment alone.<sup>18</sup> However, it is not yet known which patients are at risk of perioperative death, or which patients will profit most from a surgical approach. We therefore focused our investigation on predictors of outcome after lung resection for IPA. Univariate and multivariate analysis revealed that baseline characteristics, intraoperative factors and, in particular, perioperative (surgery-related) complications did not significantly influence the outcome (Tables 1, 2). Short-term and long-term survival did not differ significantly between patients with or without histologically proven IPA (Fig 1). This could be because the management of IPA was so effective that the fungal infection no longer had a significant influence on outcomes. However, nine patients (22%) without histologic proof of IPA showed signs of nonspecific fibrosing alveolitis or embolic infarction in the resected lung tissue that we think could represent successfully treated medical patients. Unfortunately, it is not yet possible to select these patients preoperatively. It is probable that serologic studies such as the galactomannan test and the polymerase chain reaction or radiologic imaging, in the form of high-resolution, multislice CT angiography, might help to improve the selection of patients for surgery in the future.

The infection was cleared in 87.1% of patients with histologically proven IPA, a high percentage compared with results for medical treatment alone.<sup>1,5-7</sup> Factors that influenced the short-term and long-term outcomes (survival) were the progression or reoccurrence of the underlying hematologic disease, fungal relapse and, to a minor extent, the

type of the hematologic disease (Table 3). Therefore, it may be important to minimize the time for which therapy of the hematologic malignancy is discontinued. Considering the low rate of response to classical antifungal drugs,<sup>8</sup> we think that for patients for whom there is a high suspicion of IPA and only one or a few lesions in the lungs, lung resection in combination with voriconazole might be the treatment of choice. While, at 10%, the perioperative mortality is considerable, this compares favorably with the reported mortality of patients not receiving surgery of between 30% and 90%. Whether the reactivation of fungal infection under subsequent immunosuppressive therapy is decreased by a surgical approach is unproven, but this is probable. Unfortunately, however, we are not yet able to define a group of patients with IPA who are most likely to benefit from lung resection.

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