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Invasive Pulmonary Aspergillosis in Patients with Solid Tumors: Risk Factors and Predictors of Clinical Outcomes

Short running title: Pulmonary aspergillosis in patients with solid tumors

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Key Messages:

- Invasive pulmonary aspergillosis should be considered in patients with solid tumors, particularly those with underlying lung disease, lung cancer, and those who received chest radiotherapy.

- Most of the patients with invasive pulmonary aspergillosis and solid tumors presented with nonspecific symptoms and signs as well as nonspecific CT findings. Unlike patients with hematologic malignancies, fever and hemoptysis were not predominant symptoms and the classical halo sign and the air-crescent sign were not described

- Independent risk factors for 12-week mortality included receiving steroids within 30 days of diagnosis and chest radiotherapy. In multivariate analysis, a positive fungal stain was associated with lower odds of a successful response to antifungal therapy, whereas voriconazole treatment was associated with higher odds.

ABSTRACT

Background: The characteristics and management of invasive pulmonary aspergillosis (IPA) in patients with hematologic malignancies are well known, but IPA in patients with solid tumors is not well described.

Methods: We retrospectively reviewed all Aspergillus-positive cultures at a tertiary cancer center during 2004-2017. We identified 101 patients with IPA and solid tumors. We analyzed the association between clinical features and treatment and 12-week mortality and response to antifungal therapy.

Results: Fifty-one patients had lung cancer, 77 had underlying lung disease, 47 received chest radiation, and 33 had chronic obstructive pulmonary disease. A. fumigatus was the most common type isolated (71%); 68 patients (70%) were treated with voriconazole monotherapy. Independent risk factors for 12-week mortality included receiving steroids within 30 days of diagnosis (hazard ratio 2.2, 95% confidence interval [CI], 1.1-4.6; P=0.03) and chest radiotherapy (hazard ratio 2.6, 95% CI, 1.2-5.5; P=0.01). In multivariate analysis, a positive fungal stain was associated with lower odds of a successful response (odds ratio 0.2; 95% CI, 0.05-0.75; P=0.02), whereas voriconazole treatment was associated with higher odds (odds ratio 10.1; 95% CI, 2.1-48.5; P<0.01).

Conclusions: IPA should be considered in patients with solid tumors, particularly those with underlying lung disease.

Key Words: Invasive Pulmonary Aspergillosis; Solid Tumors; Clinical Outcomes

Introduction

Invasive aspergillosis is the leading cause of invasive fungal disease in immunocompromised patients, mostly reported in patients with hematologic malignancies, stem cell, and solid organ transplant recipients [1]. Invasive pulmonary aspergillosis (IPA), acquired by inhalation of fungal spores into the lungs, is often not considered in patients with solid tumors, which can lead to delay in diagnosis and treatment and potentially worse outcomes [2].

The European Organization for Research and Treatment of Cancer and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) established the definitions for confirmed, probable, and possible invasive fungal disease [3]. Patients with IPA may not have one of the classical aspergillosis-associated host factors [4]. Multiple other risk factors have been associated with IPA, including patients with chronic obstructive pulmonary disease (COPD) [5], and critically ill patients without underlying malignancy [6, 7]. Furthermore, patients with IPA can present with nonspecific signs, symptoms, and radiographic findings. In addition, confirmatory lung tissue biopsy is often difficult to perform. The so-called Bulpa criteria were established to diagnose IPA in patients with COPD [8, 9]. Other criteria were developed to facilitate diagnosis of IPA in patients with critical illness [10]. In a study of patients with IPA who were admitted to the intensive care unit, immunocompetent patients were significantly more likely than immunocompromised patient to have diabetes mellitus, to have a history of alcohol abuse, and to have end-stage renal disease at the time of diagnosis [11].

There are limited studies on IPA in patients with solid tumors. Given this knowledge gap, we sought to identify risk factors for IPA, the clinical presentation of IPA, and predictors of poor clinical outcomes and mortality from IPA in patients with solid tumors.

Materials and Methods

Study design and patient population

We retrospectively reviewed the microbiological data of all patients with a positive culture for *Aspergillus* at The University of Texas MD Anderson Cancer Center between March 2004 and September 2017. We included patients who met all of the following criteria: 18 years of age or older; *Aspergillus* in a culture of a respiratory sample (bronchoalveolar lavage, expectorated sputum, endotracheal aspirate, pleural fluid, or lung tissue); and underlying solid tumor. Duplicate patients, patients with no underlying malignancy, with concomitant solid and hematologic malignancies, and patients who had undergone hematopoietic stem cell or solid organ transplant were excluded.

Study variables

We extracted from medical records the following data: demographic variables, underlying comorbidities, primary solid tumor, and cancer treatment modalities. The revised response evaluation criteria in solid tumors were used to assess cancer status [12]. We collected information on IPA presenting signs and symptoms, laboratory data, and antifungal treatment. Neutropenia was defined as an absolute neutrophil count of less than 500 cells/μL at the onset of infection. Results of serum galactomannan (GM) enzyme immunoassay for *Aspergillus* antigen were documented when available; a serum GM level of at least 0.5 ng/mL was used as a cut-off for positivity. *Aspergillus* species were identified using standard phenotypical techniques. Also documented were the presence of other significant bacterial co-infection in respiratory cultures; and findings on high-resolution computed tomography (CT) at diagnosis, follow-up, and end of therapy.

Diagnostic criteria

We used the clinical algorithm that has been applied for the diagnosis of IPA in critically ill patients [10]. This algorithm, similarly to the EORTC/MSG criteria, defines proven IPA as the presence of fungal elements in diseased tissue by histological testing or a positive culture of a sample obtained from a sterile site by aseptic techniques, excluding bronchoalveolar lavage. Probable IPA diagnosis requires the fulfillment of 4 criteria: (1) *Aspergillus*-positive culture of lower respiratory tract sample; (2) signs and symptoms suggestive of IPA; (3) abnormal chest radiograph or CT scan of the lungs; and (4) host risk factor (neutropenia, hematologic or solid malignancy, prednisone intake equivalent to more than 20 mg/day [600 mg in 30 days], or congenital or acquired immunodeficiency). A positive culture was considered to indicate colonization if the patient did not meet the above criteria for proven or probable IPA or if the patient had resolution of symptoms and signs without antifungal therapy.

Study outcomes

The primary outcome of the study was 12-week overall survival for all patients [13]. A secondary outcome was the response to antifungal therapy at 12-week follow-up, reported as success (complete response or partial response and survival) or failure (stable disease, progression of disease, or death) [14]. For this analysis, we excluded patients who did not receive therapy for at least 7 days and patients lacking follow-up data.

Statistical analysis

Descriptive statistics were used to summarize patient data. Frequency and percentage were used to report categorical variables. Median and interquartile range were used to report continuous variables. We analyzed the association between host factors, clinical and

microbiologic variables with the defined outcomes by univariate analysis first. Chi-square or Fisher's exact tests were used for categorical variables. Wilcoxon rank sum test was used for continuous variables. Cox regression model was used to identify the independent predictors of 12-week mortality. Logistic regression analysis was used to identify the independent predictors of the response to antifungal therapy (success vs failure). In both multivariate analyses, factors with a *P* value ≤ 0.2 in univariate analysis were included in each initial multivariate model and then the full model was reduced to the final model by backward variable elimination procedure. A *P* value of less than 0.05 was considered statistically significant. Statistical analysis was performed using the SPSS software program (version 24; IBM Corporation, Armonk, NY).

This study was conducted in accordance with the amended Declaration of Helsinki. The study was approved by the MD Anderson Cancer Center Institutional Review Board, which waived the requirement for informed consent.

Results

Study population and underlying risk factors

Of 1,121 *Aspergillus*-positive cultures documented from March 2004 through September 2017, 669 cases were excluded on the basis of the predefined inclusion and exclusion criteria (Figure 1). A further 351 cases were classified as indicating colonization. This left in the final analysis 101 consecutive adult patients with IPA and solid tumors, of whom 10% had proven IPA and 90% fulfilled the criteria for probable IPA.

Patient characteristics are summarized in Table 1. Of the 101 patients included in the final analysis, 89% were white, and 53% were female. The median age at cancer diagnosis was 60 years (interquartile range [IQR], 55 - 65), and the median age at IPA diagnosis was 63 years

(IQR, 58 -70). The median time from cancer diagnosis to IPA diagnosis was 1.6 years (IQR, 0.6 - 4.5).

The most common underlying solid tumors diagnosed before IPA were lung cancer (51%), head and neck cancer (19%), gastrointestinal cancer (13%), and breast cancer (11%), 57% had progressive disease, and 43% had a disease that was in remission or stable. In this cohort of patients, during the 30 days before IPA diagnosis, 30% of the patients received chemotherapy, 10% received immunotherapy, 31% received corticosteroids (19 of whom (61%) received a cumulative dose equivalent of ≥ 600 mg of prednisone), and 10% received fluconazole antifungal prophylaxis. In addition, 47 patients (47%) received radiation therapy to the chest at some time before IPA diagnosis. Only 2 patients had neutropenia at IPA diagnosis.

Two patients were known to be HIV positive, 3 had end-stage renal disease, 16 had diabetes mellitus, and 33 had COPD. The severity of COPD was not documented in most patients and thus was not included in this analysis. The majority of patients (76%) had some form of underlying lung disease, most commonly secondary to tumor involvement as primary lung cancer or metastasis (41%), radiation pneumonitis (13%), and other structural lung diseases (22%).

Clinical presentation

Eighty-one percent of the patients with IPA presented with respiratory symptoms, whereas only 20% presented with fever, 16% with hemoptysis, and 11% with pleuritic chest pain (Table 1). Most of the positive cultures were from bronchoalveolar lavage samples (75%) or endotracheal aspirates or expectorated sputum samples (17%). *A. fumigatus* was the most common *Aspergillus* type isolated (71%), followed *A. terreus* (11%), *A.flavus* (7%), and other *A.*

species (11%). Calcofluor fungal stain was positive by microscopy in 21% of the cases. Lung tissue biopsy was done in 21 patients, of whom 10 (48%) had a positive culture or evidence of fungal elements on histopathologic examination. Serum GM was positive in 23 patients (40% of the 57 who had serum GM assay performed). The CT findings at presentation were nodular lesions in 41% of patients, cavitary lesions in 14%, mixed nodular and cavitary lesion in 11%, and consolidative lesions in 17%.

Antifungal therapy

Among the 97 patients with available data on primary antifungal therapy, 70% were treated with voriconazole monotherapy, 9% with a combination of voriconazole and a second antifungal (echinocandin or amphotericin B), 6% with posaconazole, 5% with itraconazole, 4% with echinocandin monotherapy, and other antifungal combination therapy 6%. The median duration of primary antifungal therapy was 8 weeks (IQR, 3-16). Twenty-one patients (21%) received antifungal salvage therapy because of inadequate response to treatment; the salvage therapy was posaconazole monotherapy in 6 patients (29%), voriconazole in 4 (19%), amphotericin B in 3 (14%), and combination therapy in 3 (14%).

Study outcomes

Among the 101 patients in the overall cohort, the overall survival rate at 12 weeks was 69% and the survival rate after one year was reduced to 42%. Results of univariate and multivariate analysis of predictors of overall survival at 12 weeks are summarized in Table 2. Patients who died were more likely to be male (68% vs. 37%, $P<0.01$), to have underlying lung disease (90% vs. 70%, $P=0.03$), to have progressive underlying solid tumor (84% vs. 46%, $P<0.01$), to have received chest radiation therapy (63% vs. 40%, $P=0.03$), and to have received

steroids (45% vs. 24%, *P*=0.04). Patients alive at 12 weeks were more likely to have breast cancer (16% vs. 0% *P*=0.02). In multivariate analysis, receiving radiation therapy (hazard ratio 2.6; 95% CI, 1.2-5.5; *P*=0.01) and receiving steroids within 30 days before IPA diagnosis (hazard ratio 2.2; 95% CI, 1.1-4.6; *P*=0.03) were independent risk factors for mortality (Figure 2).

Seventy-seven patients received antifungal therapy and had a known end-of-therapy outcome. Results of univariate and multivariate analysis of predictors of therapy success versus failure are summarized in Table 3. Patients with therapy failure were more likely to be male (60% vs. 30%, *P*=0.01), to have underlying progressive malignancy (73% vs. 36%, *P*<0.01), to have received chest radiation therapy (66% vs. 38%, *P*=0.02), and to have a fungal stain positive for *Aspergillus* on respiratory samples (40% vs. 15%, *P*=0.01) and less likely to have breast cancer (3% vs. 21%, *P*=0.04). Patients with successful outcomes were more likely to be treated with voriconazole as compared to those who failed therapies (89% vs. 63%, p <0.01). In multivariate analysis, a positive fungal stain was associated with lower odds of therapy success (odds ratio 0.2; 95% CI, 0.05-0.75; *P*=0.02), and treatment with voriconazole was associated with higher odds of therapy success (odds ratio 10.1; 95% CI, 2.1-48.5; *P*<0.01).

Discussion

We herein present what we believe is the largest series of patients with solid tumors and IPA reported to date. Our findings showed that a substantial proportion of patients who developed IPA had lung cancer, underlying lung disease, or COPD. Radiation therapy to the chest and steroid therapy during the 30 days before IPA diagnosis were associated with death by 12 weeks, and positive fungal stain was associated with failure of antifungal therapy whereas voriconazole therapy was associated with successful outcomes.

Many studies have shown that invasive aspergillosis does occur in critically ill patients and patients with other non-traditional risk factors [15, 16]. The algorithm for the diagnosis of critically ill patients [10] was more useful than the EORTC/MSG criteria in this setting [3, 17]. Our current study is not the first to recognize lung malignancy, COPD, and critical illness as risk factors for IPA, but none of the previous studies showing these associations focused on patients with solid tumors [18, 19, 20]. Ohmagari, et al. published a case series of 13 patients with solid tumors and invasive aspergillosis diagnosed between 1999 and 2003 and reported that the lung was the most common site of infection [21]. In the literature and in our current study, most of the patients with IPA and no underlying hematologic malignancy presented with nonspecific symptoms and signs as well as nonspecific CT findings. Fever and hemoptysis were not predominant symptoms and the classical halo sign and the air-crescent sign were not described [22, 23]. Studies done among critically ill patients have suggested combining 1,3-β-d-Glucan in the serum and GM from bronchoalveolar lavage to improve diagnostic accuracy for IPA [24, 25, 26].

In our study, the most important predictors of response to antifungal therapy were voriconazole therapy and fungal stain positive for *Aspergillus*. The higher response rate and survival in patients treated with voriconazole have been well established in patients with hematologic malignancy [27, 28, 29]. However, to our knowledge, our study is the first to show similar benefits of voriconazole in patients with solid tumors. Our study shows an additional prognostic value of positive fungal stain which could represent a marker of higher fungal load.

The 12-week overall survival rate was high in our cohort. Not surprisingly, patients with underlying progressive malignancy had higher mortality rates. However, other factors associated

with increased mortality in patients with underlying solid tumors were not previously known. We identified two factors unrelated to underlying cancer progression that were predictive of 12-week mortality: radiation therapy to the chest and receipt of steroids in the 30 days before IPA diagnosis. There was no significant difference between patients who received high-dose and those who received low-dose steroids. The steroid dose threshold to be considered a risk for invasive aspergillosis varies significantly across published studies. Palmer et al. explained that the dose of steroids required to affect the patient's immune response and put the patient at risk for invasive aspergillosis appears to depend on many host factors [30]. Other important findings in our study are the associations between positive serum GM and positive fungal stain and higher 12-week mortality. Although these findings were not statistically significant, probably because of small sample size, a larger study but in more heterogeneous cohort showed that positive serum GM could be a strong predictor of mortality [17].

This study has several limitations. It was a retrospective analysis performed at a single center. However, the center is a large referral center, and thus our results could be generalizable to patients with solid tumors. Despite rigorous follow-up, some patients completed therapy in a different facility or were lost to follow-up, leading to missing data, which could have affected the disease outcomes. We did not measure attributable mortality, which is difficult to determine in complex cases and autopsies are not commonly done. However, by limiting the observation period to 12 weeks and including the cancer status in multivariate analysis, we were able to identify independent risk factors for mortality. We did not test BAL GM in our study which had better sensitivity and maybe contributed to more cases, it is likely that many cases of IPA in patients with solid tumors may have been missed by using a positive culture for Aspergillus as the entry criterion. Hence, the present number of cases are likely still an underestimate.

Our findings indicate that IPA should be considered in patients with solid tumors, particularly those with underlying lung disease. Radiation therapy to the chest, recent steroid therapy, and positive fungal stain were associated with poor outcomes, while voriconazole therapy was associated with improved outcomes. Larger prospective studies are needed to evaluate the benefit of antifungal prophylaxis in higher-risk patients with solid tumors.

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Declaration of Interest

All authors have read and approved this manuscript and disclose that they have no conflicts of interest.

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Table 1: Characteristics and Treatment of IPA in Patients with IPA and Solid Tumors (N=101)

Variable	Value
Median age at IPA (IQR), yr	63 (58-70)
Sex, %	
Male	47
Female	53
Race, %	
White	89
African American	7
Asian	4
Underlying solid tumor, %[a]	
Lung cancer	51
Head and neck cancer	19
Gastrointestinal cancer	13
Breast cancer	11
Other cancer	15
Host factors, %	
Diabetes mellitus	16
ESRD	3
COPD	33
Underlying lung disease[b]	76
HIV	2
Other risk factors, %	
Prednisone therapy in the 30 days before IPA diagnosis	31
Chemotherapy in the 30 days before IPA diagnosis	30
Immunotherapy in the 30 days before IPA diagnosis	10
ANC < 500 cells/μL at time of IPA diagnosis	2
Radiation therapy to the chest before IPA diagnosis	47
Source of fungal culture	
Sputum	14
BAL	76
Endotracheal tube	3
Pleural fluid	3
Biopsy	5
Clinical presentation, %	
Respiratory symptoms (cough and/or dyspnea)	81
Fever	20
Hemoptysis	16
Pleuritic chest pain	11
Serum galactomannan positive, %[c]	40
Calcofluor fungal stain positive by microscopy for aspergillosis, %	21
CT scan findings, %	
Nodular lesions	41

Cavitary lesions	14
Nodular and cavitary lesions	11
Consolidative lesions	17
First-line antifungal therapy, %	
Voriconazole monotherapy	70
Voriconazole plus either echinocandin or liposomal amphotericin B	9
Posaconazole monotherapy	6
Itraconazole monotherapy	5
Echinocandin monotherapy	4
Other antifungal combination therapy	5
Median duration of primary antifungal therapy (IQR), weeks	8 (3-16)

[a] 13 patients (12%) had multiple cancers.
[b] primary lung cancer or lung metastasis, radiation pneumonitis, and other structural lung diseases.
[a] Galactomannan test was available for 57 cases; the percentage was calculated based on available tests
Abbreviations: ANC, absolute neutrophil count; COPD, chronic obstructive pulmonary disease; BAL, bronchoalveolar lavage; CT, computed tomography; ESRD, end-stage renal disease; IPA, invasive pulmonary aspergillosis; IQR, interquartile range.

Table 2: Univariate and Multivariate Analysis of Predictors of Overall Survival at 12-week Follow-up (N=101)[a]

Predictor	Alive at 12 Weeks (n=70)	Died Before 12 Weeks (n=31)	*P* Value	Multivariate Cox Regression Analysis	
				Hazard Ratio (95% CI)	*P* Value
Median age (IQR), yr	62 (57-70)	63 (58-71)	0.45		
Sex, male	26 (37)	21 (68)	< 0.01		
Race, white	63 (90)	27 (87)	0.86		
Type of solid tumor					
Lung cancer	34 (49)	17 (55)	0.56		
Head and neck cancer	12 (17)	5 (16)	0.90		
Breast cancer	11 (16)	0	0.02		
Gastrointestinal cancer	8 (11)	4 (13)	> 0.99		
Status of solid tumor					
Remission/stable	38 (54)	5 (16)	< 0.01	1.0 (reference)	-
Progressive	32 (46)	26 (84)		4.7 (1.8-12.4)	0.02
Chemotherapy[b]	20 (29)	10 (32)	0.71		
Prior history of chest radiation therapy	28 (40)	19/30 (63)	0.03	2.6 (1.2-5.5)	0.01
Steroids[b]	17 (24)	14 (45)	0.04	2.2 (1.1-4.6)	0.03
Steroid dose > 600 mg[c]	10 (14)	9 (29)	0.08		
Diabetes mellitus	10 (14)	6 (19)	0.56		
COPD	24 (34)	9 (29)	0.60		
Underlying lung disease[d]	49 (70)	28 (90)	0.03		
Serum GM positive at diagnosis	12/38 (32)	11/19 (58)	0.06		
Fungal stain positive for aspergillosis	11 (16)	10 (32)	0.06		
Bacterial co-infection	33 (47)	12 (39)	0.43		
CT findings					
Nodular lesions	31/67 (46)	6/23 (26)	0.09		
Cavitary lesions	10/67 (15)	3/23 (13)	> 0.99		
Nodular and cavitary lesions	7/67 (10)	3/23 (13)	0.71		

Consolidative lesions	10/67 (15)	5/23 (22)	0.52
Therapy[e]			0.09
Voriconazole-containing therapy	57/69 (83)	18/27 (67)	
Other therapy	12/69 (17)	9/27 (33)	

[a] Values in table are number of patients (percentage) unless otherwise indicated.
[b] Chemotherapy or steroid therapy within 30 days before IPA diagnosis.
[c] Cumulative steroid dose equivalent to > 600 mg prednisone in the last 30 days before IPA diagnosis.
[d] Underlying lung disease included primary lung cancer or lung metastasis, radiation pneumonitis, and other structural lung diseases.
[e] 5 patients died before receiving antifungal therapy and were excluded from analysis.
Abbreviations: CI, confidence interval; IPA, invasive aspergillosis; COPD, chronic obstructive pulmonary disease; CT, computed tomography; GM, galactomannan.

Table 3: Univariate and Multivariate Analysis of Predictors of Success vs. Failure of Antifungal Therapy (n=77)[a]

Predictor	Success (n=47)	Failure (n=30)	*P* Value	Multivariate Logistic Regression Analysis	
				Odds ratio (95% CI)	*P* Value
Median age (IQR)-yr	61 (57-70)	63 (57-67)	0.83		
Sex, male	14 (30)	18 (60)	0.01		
Race, white	42 (89)	26 (87)	> 0.99		
Type of solid tumor					
Lung cancer	19 (40)	18 (60)	0.09		
Head and neck cancer	10 (21)	4 (13)	0.38		
Breast cancer	10 (21)	1 (3)	0.04		
Gastrointestinal cancer	4 (9)	5 (17)	0.30		
Status of solid tumor					
Remission/stable	30 (64)	8 (27)	< 0.01	1.0 (reference)	-
Progressive	17 (36)	22 (73)		0.1 (0.03-0.38)	< 0.01
Chemotherapy[b]	10 (21)	12 (40)	0.08		
Prior history of chest radiation therapy	18 (38)	19/30 (66)	0.02		
Steroids[b]	10 (21)	10 (33)	0.24		
Steroid dose >600 mg[c]	6 (13)	6 (20)	0.52		
Diabetes mellitus	7 (15)	7 (23)	0.35		
COPD	17 (36)	8 (27)	0.39		
Underlying lung disease[d]	32 (68)	25 (83)	0.14		
Serum GM positive at diagnosis	11/25 (44)	9/22 (41)	0.83		
Fungal stain positive for aspergillosis	7 (15)	12 (40)	0.01	0.2 (0.05-0.75)	0.02
Bacterial co-infection	21 (45)	13 (43)	0.91		
CT findings					
Nodular lesions	19/45 (42)	14/25 (56)	0.27		
Cavitary lesions	6/45 (13)	2/25 (8)	0.70		
Nodular and cavitary lesions	5/45 (11)	4/25 (16)	0.71		
Consolidative lesions	7/45 (16)	2/25 (8)	0.47		

Therapy					
Voriconazole-containing therapy	42 (89)	19 (63)	< 0.01	10.1 (2.1-48.5)	< 0.01
Other therapy	5 (11)	11 (37)		1.0 (reference)	-

[a] Only patients who received primary antifungal therapy and had known end-of-therapy outcome were included in this analysis. Success was defined as complete response or partial response to therapy and patient alive at 12 weeks follow-up. Failure was defined as stable disease, progression of disease, or death at 12 weeks follow-up. Values in table are number of patients (percentage) unless otherwise indicated.

[b] Chemotherapy or steroid therapy within 30 days before IPA diagnosis.

[c] Cumulative steroid dose equivalent to > 600 mg prednisone in the last 30 days before IPA diagnosis.

[d] Underlying lung disease including tumor involvement as primary lung cancer or metastasis, radiation pneumonitis, and other structural lung diseases.

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; CT, computed tomography; GM, galactomannan; IPA, invasive aspergillosis.

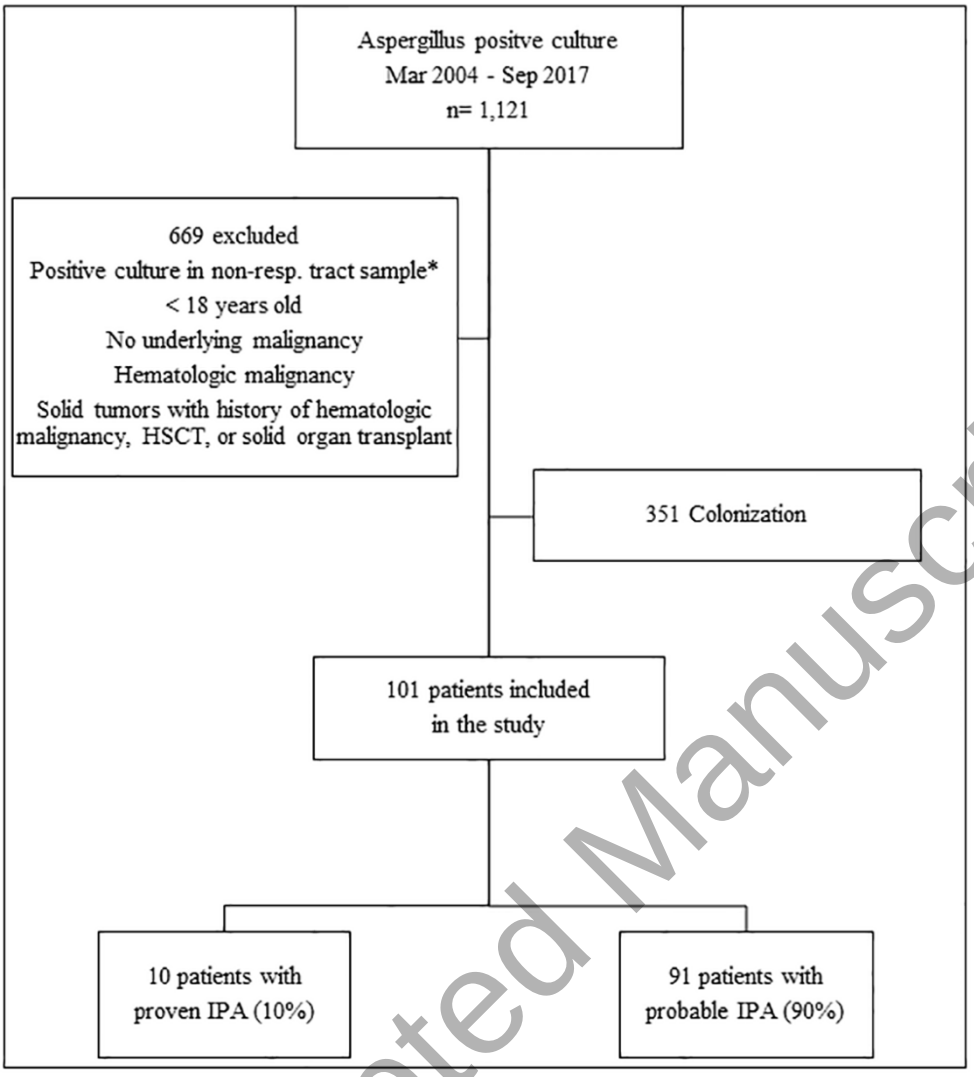
Figure Legend

Figure 1. Screening, exclusion and inclusion criteria.

Figure 2A. Kaplan-Meier survival curves among patients with invasive aspergillosis classified per underlying malignancy status. ($p<0.01$)

Figure 2B. Kaplan-Meier survival curves among patients with invasive aspergillosis classified per steroid intake. ($p=0.04$)

Figure 2C. Kaplan-Meier survival curves among patients with invasive aspergillosis classified per prior radiation therapy ($p=0.02$)



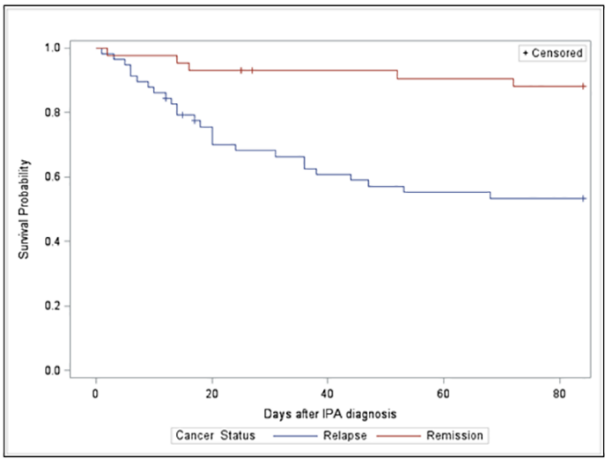


Figure 2A. Kaplan-Meier survival curves among patients with invasive aspergillosis classified per underlying malignancy status. ($p<0.01$)

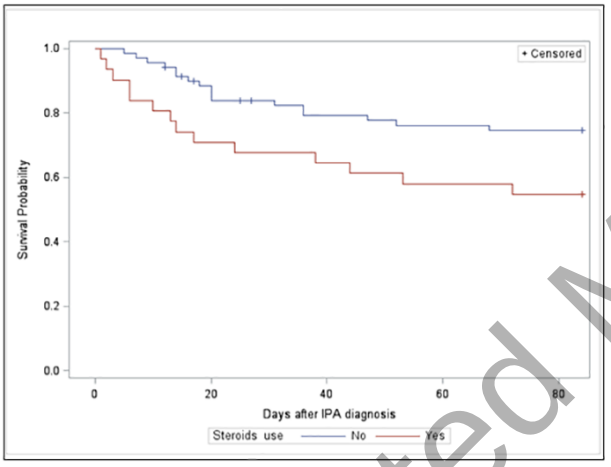


Figure 2B. Kaplan-Meier survival curves among patients with invasive aspergillosis classified per steroid intake. ($p=0.04$)

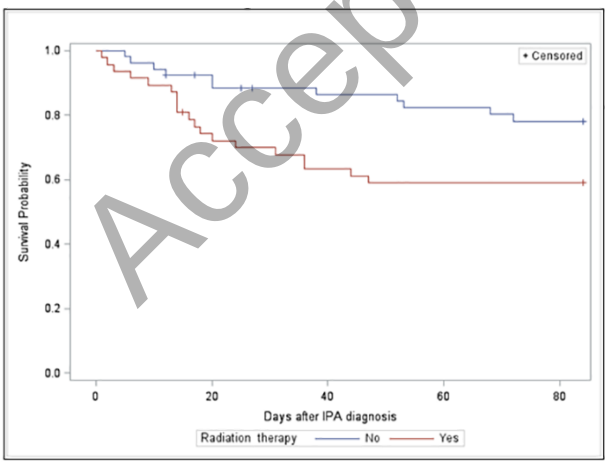


Figure 2C. Kaplan-Meier survival curves among patients with invasive aspergillosis classified per prior radiation therapy ($p=0.02$)