High Resolution Computed Tomography Angiography Improves the Radiographic Diagnosis of Invasive Mold Disease in Patients With Hematological Malignancies

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Background. Computed tomography pulmonary angiography (CTPA) may improve the diagnostic capabilities of CT imaging for invasive mold disease, but its performance relative to other signs (ie, halo sign, hypodense sign, pleural effusion, reversed halo sign) is unknown.

Methods. We prospectively compared the diagnostic performance of CTPA vs other CT imaging findings in 100 patients with hematological malignancies and possible invasive mold disease defined by EORTC/MSG criteria. After undergoing extensive diagnostic work-up, patients were upgraded to probable or proven mold disease based on galactomannan antigen, culture or histology; or remained as possible mold disease if an alternative diagnosis could not be established.

Results. In total, 46 /100 patients who underwent CTPA were upgraded to probable or proven mold disease. Excluding 8 CTPA cases that were nonevaluable by the radiologist, a positive occlusion sign identified by CTPA was 100% sensitive for the diagnosis of probable or proven mold disease (41/41). Among patients who could not be upgraded from the possible mold disease category (n = 51), 25 (49%) had evidence of vessel occlusion by CTPA with only one positive patient eventually reaching an alternative diagnosis (Staphylococcus aureus septic thrombosis). Intravenous and/or oral antifungal therapy was stopped earlier in patients with a negative vs positive CTPA results (P ≤ .001).

Conclusions. Vessel occlusion detected by CTPA is a more sensitive and possibly more specific radiographic sign vs other common CT findings of invasive mold disease in patients with hematological malignancies.

Keywords. aspergillosis; diagnosis; computed tomography.

Invasive mold disease is a serious infectious complication in patients with hematological malignancies [1, 2] that often delays the administration of chemotherapy resulting in lower rates of complete remission and increased mortality [3, 4]. Definitive diagnosis of invasive mold disease requires bronchoscopy and/or lung biopsy for culture or histological documentation of infection, which may be unfeasible in patients with severe thrombocytopenia. Consequently, some patients with hematological malignancies who present with fever and lung infiltrates suggestive of mold disease on radiologic exam receive weeks to months of antifungal therapy, even without a definitive diagnosis [5].

The need for prolonged empiric antifungal therapy reflects the limitations of current diagnostic tools for invasive mold disease [6]. High-resolution computed tomography (HRCT) may detect nodular infiltrates surrounded by ground glass attenuation (halo sign) in...
88%–96% of neutropenic patients the first day of invasive aspergillosis [7]. However, this finding disappears in one-third of patients within 72 hours, and in the remaining two-thirds of patients within 2 weeks [7, 8]. The halo sign is not specific for invasive aspergillosis, as other infections, neoplastic, and inflammatory processes can produce similar opacities with ground glass attenuation [9]. The serum galactomannan test for aspergillosis also has some diagnostic limitations, including lower sensitivity in the setting of antifungal prophylaxis [10, 11], and false-positive results in patients receiving piperacillin-tazobactam [12]. Recently, Duarte and colleagues reported that 13.8% of all serum galactomannan tests in asymptomatic, high-risk patients with hematological malignancies receiving posaconazole prophylaxis were false positives, making the test unreliable for screening in the setting of a low disease incidence associated with effective prophylaxis [13].

High-resolution CT pulmonary angiography (CTPA) is a complementary technique that has shown promise for distinguishing invasive mold disease from other causes of macrodense pulmonary infiltrates by virtue of detection of angioinvasion—a pathogenic hallmark of mold disease [14, 15]. The sensitivity and specificity of CTPA for diagnosis of proven or probable mold disease is reported to range from 80%–100%, with a negative predictive value exceeding 90%. However, published experience with this technique is still limited, and it is unknown whether an occluded vessel sign identified by CTPA is superior to other radiographic findings for diagnosing or ruling-out invasive mold disease.

The purpose of this prospective study was to compare the diagnostic performance of CTPA vs common HRCT findings among a cohort of patients with hematological malignancies and possible mold disease as defined according to European Organization for Research and Treatment of Cancer Mycoses Study Group (EORTC/MSG) criteria [16]. We hypothesized that a positive vessel occlusion sign identified by CTPA would be a more sensitive and specific radiographic sign for proven or probable mold disease compared to other common HRCT signs in patients with hematological malignancies.

**PATIENTS AND METHODS**

**Patient Population**

This study was performed in patients admitted to the Institute of Hematology “Lorenzo e Ariosto Seràgnoli,” S.Orsola-Malpighi Hospital, University of Bologna (Bologna, Italy) from March 2008 to June 2014. The study design was approved by the Institutional Research Committee in accordance with principles outlined in the Declaration of Helsinki.

Consecutive adult hematology patients with fever for >72 hours receiving empiric antibacterial therapy with a clinical suspicion of invasive mold disease were referred for chest HRCT. Patients with a history of allergy to contrast agents, or at high risk for contrast-exacerbated acute renal injury were excluded. Patients were included in the study if they met radiological criteria and proceeded to CTPA as described below. Thirty-six patients were reported in a previous pilot study [14], but the diagnostic performance of their exam had not been analyzed in relation to other CT findings.

**Computed Tomography**

All patients referred for HRCT were examined by the radiologist with a multidetector CT scanner (Lightspeed 16 and Lightspeed VCT 64, GE, Milwaukee, Wisconsin; Brilliance iCT 128, Philips Healthcare, Cleveland, Ohio). CTPA was recommended after review of the basal scan by the radiologist (1–1.25 mm slice thickness, 1 mm reconstruction interval, bone kernel). Patients proceeded to CTPA if they had at least 1 macrodense infiltrate with a circumference larger than 10 mm (or larger than 12–15 mm in the peripheral, apex, or base lung). The decision to perform CTPA was made irrespective of the presence of a halo sign. CTPA was not considered for patients with cavitating infiltrates.

CTPA was performed after IV administration of 70–80 mL of nonionic contrast media at a flow rate of 3–3.5 mL/second, with a dedicated starting-delay for pulmonary angiography varying between 12 and 15 seconds under control of the scanning software. Contrast administration was followed by a 30–40 mL saline flush at the same flow rate. Scanning was performed using 1–1.25 mm slice thickness, 1 mm reconstruction interval, standard kernel. The CT images were transferred to a dedicated workstation (Advantage 4.3–4.5, GE, Milwaukee, Wisconsin), and 2-dimensional (2D) reconstructions were performed using multiplanar reformattting programs. The CTPA axial images and the 2D maximum intensity projection reconstructed images in coronal, sagittal, and oblique planes were analyzed for the presence of vascular occlusion. Vascular occlusion was defined according to criteria proposed by Sonnet et al [15], as an interruption of a vessel at the border of a focal lesion without depiction of the vessel inside the lesion or peripheral to the lesion. If a certain feature was present at least once in a patient, the patient was designated as “CTPA positive.”

All images were evaluated by 2 expert radiologists blinded to the clinical course and patient diagnosis. In the case of disagreements, the radiologists discussed the findings and reached a consensus interpretation. In addition to CTPA, the radiologist noted the number and characteristics of other infiltrates (number, size, morphology), the presence of absence of halo sign, and other HRCT findings suggestive of invasive mold disease, including the hypodense sign, reversed halo sign, and pleural effusion, bronchial occlusion, and “crazy paving.” CTPA results were communicated to physicians involved in the care of the patient.

**Diagnostic Assessment**

All patients met EORTC/MSG criteria of possible invasive mold disease at the time CTPA was performed [16]. Additionally, all
patients underwent an extensive diagnostic and microbiologic workup to establish the cause of infection within 90 days of CTPA, or an alternative diagnosis if the patient did not meet mycological criteria for proven or probable mold disease [16]. The majority (97%) of patients were screened 2–3 times weekly using the serum galactomannan assay (Plateia, Bio-Rad Laboratories, Hercules, California and Bio-Rad, Marnes-la-Coquette, France), with an optical density index ≥0.5 on 2 consecutive tests considered positive. When bronchoscopy was performed, lavage fluid was tested for galactomannan in conjunction with cultures or histology using the same positive index cut-off for a single test.

The risk for invasive mold disease was estimated individually for each patient at the time of initial HRCT using a validated institutional mold risk score [17]. Microbiological or histological data, underlying malignancy status and treatment, and infection outcomes were prospectively collected for up to 90 days following the initial CTPA test. To ensure consistency in case assessment, cases were reviewed by 2 hematologists, 2 radiologists, and infectious diseases specialist before recording the final clinical diagnosis.

**Safety**

Serum creatinine was recorded within 24 hours of HRCT scan (baseline) and at 1, 3, and 7 days after the administration of contrast. Contrast-associated nephropathy was defined as an increase in serum creatinine of at least 0.5 mg/dL or a 25% relative increase within 72 hours of contrast administration according the Acute Kidney Injury Network (AKIN) guidelines [18].

**Statistical Analysis**

Baseline demographic characteristics were analyzed as absolute numbers and their relative frequencies and compared by Fisher exact test. Continuous variables were expressed as mean ± standard deviation (SD) if normally distributed, or as median and interquartile range (IQR) if nonnormally distributed and compared using Student t or Mann–Whitney U test according to their distribution.

The diagnostic accuracy of the CTPA-identified vessel occlusion sign was compared to other HRCT findings on a per-patient basis using 2 × 2 tables (ie, patient classified as positive if they ever had a positive test). The sensitivity, specificity, positive and negative likelihood ratio, and diagnostic odds ratio and corresponding 95% confidence intervals were calculated for each sign (or combination of signs) analyzed as a binary variable. In a secondary analysis, patients not upgradable to EORTC/MSG probable or proven disease were analyzed using classification trees ($\chi^2$ automatic interaction detection) to examine the concordance of CTPA with final diagnosis of pulmonary infiltrates. For the safety analysis, serum creatinine levels were compared at each timepoint using repeated-measures analysis of variance with Bonferroni correction. All analysis was performed with STATA version 13 (Stata Corp, College Station, Texas) and SPSS 22 (IBM, New York, New York).

**RESULTS**

**Patient Characteristics**

CTPA was performed in 100 of 750 patients with hematological malignancies referred for HRCT during the timeperiod. The most common reason for not performing CTPA was the lack of an evaluable lesion during the basal HRCT scan. Eight CTPA exams could not be evaluated by the radiologist because of nonvisible vessels. The distribution of final EORTC/MSG or clinical diagnosis in the study cohort is depicted in Figure 1.

Characteristics of the study population are presented in Table 1. The most common underlying malignancies included acute myeloid leukemia/ myelodysplastic syndrome (55%), followed by acute lymphocytic leukemia (19%) and lymphoma (16%). Most patients were receiving consolidation or salvage chemotherapy at the time of the CTPA imaging (45%), whereas nearly one-third (31%) of patients had received an allogeneic hematopoietic stem cell transplant.

The median mold infection risk score in the study population was 7 (IQR 6–7) corresponding to an estimated baseline mold disease risk rate of approximately 10% [17]. One-third of all patients were receiving mold-active prophylaxis at the time of imaging.

**Diagnostic Outcome**

A total of 41/92 evaluable patients (44%) were eventually upgraded to EORTC/MSG criteria for probable or proven invasive mold disease. Five of the 8 CTPA nonevaluable patients had a positive serum galactomannan (including 1 patient with *Fusarium* spp. isolated in blood culture) and were classified as probable-proven mold disease. CTPA was positive in 41/41 (100%) of evaluable patients with probable or proven mold disease (Table 2). If unreadable cases were included in the analysis and considered as a “negative” CTPA result, CTPA was positive in 41/46 (89%) patients with probable or proven mold disease.

The distribution of the 41 cases of probable or proven mold disease are shown in Figure 1, which included 39 cases of aspergillosis and 2 cases of mucormycosis. Serum galactomannan tests were positive in 36/67 (54%) of CTPA positive and 2/22 (9%) of CTPA-negative patients. Bronchoalveolar lavage galactomannan was positive in 9/13 (69%) CTPA-positive and 0/6 (0%) of CTPA-negative patients. Receipt of mold-active antifungal prophylaxis was associated with a significantly lower rate of serum galactomannan (27% vs 51%, $P = .0002$) but not CTPA positivity (64% vs 69%, $P = .09$).

The halo sign was present overall in 48/67 (72%) of CTPA positive and 8/25 (32%) of CTPA-negative patients. Similarly, the hypodense sign was present 28/67 (42%) of CTPA-positive
and 1/24 (4%) of CTPA-negative patients. All other signs (pleural effusion, reverse halo, bronchial occlusion crazy paving) occurred relatively infrequently among patients with proven or probable mold disease (Table 2).

**Diagnostic Performance**

Vessel occlusion identified by CTPA had greater diagnostic sensitivity for proven or probable mold disease compared to the halo or hypodense sign, or combinations of these signs with a pleural effusion (Table 3). Excluding unreadable cases, CTPA was 100% sensitive test. The specificity of CTPA was calculated at 51% because nearly half of patients with possible mold disease had a positive vessel occlusion sign but did not reach mycological criteria to upgrade their diagnosis to probable or proven disease. When possible cases (n = 51) were adjudicated to a final clinical diagnosis, CTPA was positive in 25/26 (96%) of patients who retained a clinical diagnosis of possible mold disease and was negative in 14/15 (93%) cases of bacterial pneumonia. A single false-positive CTPA result occurred in a patient with disseminated *S. aureus* infection with septic thrombosis to the lungs. A possible false negative-CTPA result occurred in a 49 year-old patient with AML who died from his underlying malignancy without microbiologic evidence of mold disease or clinical response to antifungal therapy. All other causes of macrodense opacities (ie, lymphoma, viral pneumonia, multimicrobial pneumonia, bronchiolitis obliterans organizing pneumonia, tuberculosis) were associated with a negative CTPA result. The presence of a halo sign (*P* = .03) or vessel occlusion by CTPA (*P* < .0001) differentiated patients with a final diagnosis of possible mold disease vs other causes (Supplementary Figure 1).

If the remaining possible cases of invasive mold disease (no alternative diagnosis established) are included with proven or probable cases, the sensitivity and specificity of CTPA was superior to all other radiographic signs for the diagnosis of invasive mold disease with the highest calculated diagnostic odds ratio (Table 3).

**Safety**

No patients developed contrast-associated nephropathy within 48 hours based on AKIN criteria [18]. Mean creatinine levels

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**Figure 1.** Study design flowchart. Abbreviations: CT, computed tomography; CTPA, computed tomography pulmonary angiography; EORTC, European Organization for Research and Treatment of Cancer; MSG, Mycoses Study Group.
did not differ significantly from baseline vs 1, 3, or 7 days after contrast administration, \((P \geq .35\) all comparisons; Supplementary Figure 2). However, serum creatinine did increase by >0.5 mg/dl in 2 patients 7 days after contrast administration with the receipt of other nephrotoxic therapies (cyclosporine, liposomal amphotericin B, furosemide) and/or onset of septic shock.
Impact of CTPA on Systemic Antifungal use

Details concerning intravenous or oral mold-active antifungal use after CTPA results are presented in Table 4. Despite similar baseline risk scores for mold disease and HRCT findings suggestive of mold disease, patients with negative CTPA test had shorter treatment courses of both intravenous (median 0 vs 13 days, \(P < .0001\)) and oral (median 0 vs 14, \(P < .0001\)) antifungal therapy compared to patients with a positive occlusion sign.

DISCUSSION

Our data suggest that CTPA was the most sensitive and possibly most specific radiographic sign associated with the diagnosis of invasive mold disease in patients with hematological malignancies. Even if unreadable CTPA exams are conservatively assumed to represent a “negative” result, vessel occlusion remained the most sensitive radiographic sign corresponding to probable or proven mold disease (Table 3). If unreadable cases (8/100) are excluded, vessel occlusion identified by CTPA was 100% sensitive for the diagnosis of probable or proven mold disease.

Assessing the diagnostic performance of CTPA for invasive mold disease is challenging, as definitive histological or microbiological evidence of infection is often lacking. Culture and galactomannan antigen lack the sensitivity to rule out mold disease based on a single negative test, especially if a patient is receiving mold-active prophylaxis [11,18,19]. In our study nearly one-half (25/51, 49%) of possible invasive mold disease cases were CTPA positive. After extensive diagnostic workup, only 1 patient had a false-positive CTPA (S. aureus septic thrombosis), and 1 patient had possibly false-negative result, which

Table 3. Diagnostic Performance of CTPA vs Other CT Findings

<table>
<thead>
<tr>
<th>CT Findings</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Pos LR (95% CI)</th>
<th>Neg LR (95% CI)</th>
<th>Diagnostic OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC/MSG proven or probable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halo sign</td>
<td>0.63 (.48–.77)</td>
<td>0.44 (.31–.59)</td>
<td>1.13 (.81–1.58)</td>
<td>0.83 (.51–1.33)</td>
<td>1.36 (.57–3.31)</td>
</tr>
<tr>
<td>Hypodense sign</td>
<td>0.46 (.31–.61)</td>
<td>0.83 (.71–.92)</td>
<td>2.73 (1.43–5.40)</td>
<td>0.65 (.47–.85)</td>
<td>4.13 (1.53–11.94)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>0.56 (.41–.71)</td>
<td>0.74 (.60–.85)</td>
<td>2.18 (1.32–3.70)</td>
<td>0.59 (.40–.83)</td>
<td>3.67 (1.48–9.43)</td>
</tr>
<tr>
<td>Halo sign + pleural effusion</td>
<td>0.41 (.27–.57)</td>
<td>0.91 (.80–.97)</td>
<td>4.46 (1.91–10.88)</td>
<td>0.64 (.48–.81)</td>
<td>6.75 (2.13–25.82)</td>
</tr>
<tr>
<td>Hypodense sign + pleural effusion</td>
<td>0.32 (.20–.48)</td>
<td>0.94 (.84–.99)</td>
<td>5.87 (1.98–18.20)</td>
<td>0.71 (.56–.86)</td>
<td>8.07 (2.05–46.87)</td>
</tr>
<tr>
<td>CTPA (including unreadable cases as negative results)</td>
<td>0.89 (.76–.96)</td>
<td>0.52 (.38–.67)</td>
<td>1.85 (1.40–2.55)</td>
<td>0.21 (.09–.47)</td>
<td>8.63 (2.81–32.32)</td>
</tr>
<tr>
<td>CTPA (excluding unreadable cases)</td>
<td>1.00 (.86–1.0)</td>
<td>0.51 (.37–.65)</td>
<td>2.04 (1.60–2.80)</td>
<td>(\infty)</td>
<td>(\infty)</td>
</tr>
</tbody>
</table>

EORTC/MSG proven, probable or possible*

<table>
<thead>
<tr>
<th>CT Findings</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Pos LR (95% CI)</th>
<th>Neg LR (95% CI)</th>
<th>Diagnostic OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halo sign</td>
<td>0.69 (.57–.79)</td>
<td>0.65 (.46–.82)</td>
<td>2.00 (1.26–3.52)</td>
<td>0.47 (.31–.74)</td>
<td>4.16 (1.55–11.85)</td>
</tr>
<tr>
<td>Hypodense</td>
<td>0.39 (.28–.52)</td>
<td>0.93 (.78–.99)</td>
<td>5.72 (1.72–21.13)</td>
<td>0.65 (.52–.82)</td>
<td>8.64 (1.91–80.76)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>0.45 (.33–.57)</td>
<td>0.72 (.53–.87)</td>
<td>1.63 (.91–3.20)</td>
<td>0.75 (.56–1.07)</td>
<td>2.13 (.78–6.38)</td>
</tr>
<tr>
<td>Halo sign + pleural effusion</td>
<td>0.32 (.22–.45)</td>
<td>0.97 (.82–1.00)</td>
<td>9.39 (1.82–54.07)</td>
<td>0.70 (.58–.85)</td>
<td>13.20 (1.92–572.4)</td>
</tr>
<tr>
<td>Hypodense sign + pleural effusion</td>
<td>0.24 (.15–.36)</td>
<td>0.97 (.82–1.00)</td>
<td>6.94 (1.32–40.38)</td>
<td>0.79 (.67–.94)</td>
<td>8.69 (1.23–381.31)</td>
</tr>
<tr>
<td>CTPA (including unreadable cases as negative results)</td>
<td>0.90 (.81–.96)</td>
<td>0.90 (.73–.98)</td>
<td>8.71 (3.70–25.23)</td>
<td>0.11 (.05–.22)</td>
<td>72.55 (16.76–470.47)</td>
</tr>
<tr>
<td>CTPA (excluding unreadable cases)</td>
<td>0.98 (.81–.96)</td>
<td>0.89 (.71–.98)</td>
<td>8.86 (3.5–25.6)</td>
<td>0.02 (.003–.09)</td>
<td>406.40 (45.1–21,316.1)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CT, computed tomography; CTPA, computed tomography pulmonary angiography; EORTC, European Organization for Research and Treatment of Cancer; MSG, Mycoses Study Group; Neg LR, negative likelihood ratio; OR, odds ratio; Pos LR, positive likelihood ratio.

* EORTC possible cases where patients responded to antifungal therapy without isolation of other pathogens or establishment of an alternative diagnosis.

Table 4. Patterns of Antifungal Use in Evaluable CTPA-positive vs CTPA-negative Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CTPA Positive, n = 67</th>
<th>CTPA Negative, n = 25</th>
<th>(P) Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous antifungal therapy, no. (%)</td>
<td></td>
<td></td>
<td>.03</td>
</tr>
<tr>
<td>Liposomal amphotericin B</td>
<td>30 (45)</td>
<td>5 (20)</td>
<td></td>
</tr>
<tr>
<td>Voriconazole</td>
<td>10 (15)</td>
<td>0 (0)</td>
<td>.06</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>2 (3)</td>
<td>2 (6)</td>
<td>.3</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>2 (3)</td>
<td>2 (6)</td>
<td>.3</td>
</tr>
<tr>
<td>Combination therapy</td>
<td>13 (19)</td>
<td>0 (0)</td>
<td>.02</td>
</tr>
<tr>
<td>Median-days (IQR)</td>
<td>13 (6–20)</td>
<td>0 (0–8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Oral antifungal therapy, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voriconazole</td>
<td>28 (42)</td>
<td>2 (8)</td>
<td>.007</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>11 (16)</td>
<td>1 (4)</td>
<td>.75</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>1 (1)</td>
<td>1 (4)</td>
<td>.06</td>
</tr>
<tr>
<td>Median-days (IQR)</td>
<td>14 (0–42)</td>
<td>0 (0–0)</td>
<td>.003</td>
</tr>
</tbody>
</table>

Abbreviations: CTPA, computed tomography pulmonary angiography; IQR, interquartile range.

* \(P\) values determined by Fisher’s exact test or Mann–Whitney \(U\) test.
could not be confirmed by antigen or microbiologic results. Hence, vessel occlusion may be an alternative criterion for upgrading possible cases of invasive mold disease [20, 21] to EORTC/MSG proven or probable mold disease; although further studies are needed.

Angioinvasion is recognized as a pathogenic hallmark of mold disease, although other pathogens, particularly *Pseudomonas aeruginosa* causes hemorrhage and necrosis in the lungs of neutropenic patients [9]. However, animal models and human autopsy data suggest the initial steps of invasion and thrombosis differ between these two pathogens in neutropenic patients. *Aspergillus fumigatus* invasion from the airways results in intravascular thrombosis with tissue necrosis [22], whereas *P. aeruginosa* invades from the bloodstream into the lung by toxin-mediated vasculitis and necrosis of the vessel wall, with a paucity of intraluminal bacilli and adjacent intravascular thrombi [23, 24]. These differences may explain why CTPA was positive in patients with invasive mold disease but consistently negative in our neutropenic patients *P. aeruginosa* pneumonia (n = 4 patients). Representative cases of HRCT and CTPA imaging are presented in Supplementary File 1.

The clinical utility of CTPA is ultimately defined by how it impacts patient care. Our results suggest that CTPA is a useful confirmatory diagnostic tool, but its real value may be to help rule-out invasive mold disease as a negative CTPA result was associated with a much lower negative likelihood ratio than other CT findings (Table 3). Considering proven, probable, and highly possible cases, we estimate that negative CTPA reduces the pretest probability of invasive mold disease in possible cases from 40% to 50% to a post-test probability of <5%, supporting the possible discontinuation of antifungal therapy and pursuit of alternative diagnoses [25]. In this setting, the major concern in terms of diagnostic error would be a false-negative result, which was rare in our experience but may be a greater concern if the exam was performed in patients with older lesions (ie, after several weeks) related to possible neovascularization of the lesion. Sonnet et al reported one false-negative CTPA case in a patient with pulmonary mucormycosis [15].

CTPA does carry some additional risks vs standard HRCT, which need to be weighed against its possible diagnostic benefits. Iodinated contrast media can injure the kidneys; therefore, patients with preexisting renal dysfunction or receiving multiple concomitant nephrotoxic agents may not be good candidates for the procedure. The amount of contrast administered for CTPA is roughly 60%–70% of that required for an abdominal CT, which is routinely performed in patients with hematological malignancies with persistent fever. Another possible limitation is the additional radiation required for CTPA over conventional HRCT, although a more definitive diagnosis may reduce the need for subsequent HRCT scans and offset the higher upfront costs. Moreover, advances in HRCT technology are already facilitating the use of lower radiation doses. Our recent experience with newer scanners suggest that HRCT and CTPA examinations can be adequately performed with a low-dose protocol saving more than the 80% and 35% of the dose delivered, respectively. The delivery dose for a low-dose HRCT scan is about 1.8 mGy CTDI and 68 mGy DLP. These values are equivalent to no more than 2 standard chest X-ray examinations (2 views, PA and LL) and much lower than diagnostic reference levels (LDR: for standard CT protocol 10–30 mGy CTDI, 400–650 mGy DLP).

In conclusion, CTPA improves the sensitivity, and possibly the specificity of HRCT diagnosis of invasive mold disease in patients with hematological malignancies. CTPA may be especially useful as a complementary tool to rule out invasive mold disease in patients with suspicious HRCT findings, facilitating pursuit of alternative diagnosis and earlier discontinuation of empiric antifungal therapy.

**Supplementary Data**

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyrighted. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

**Notes**

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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