# Routine Pre- and Post-Hematopoietic Stem Cell Transplant Computed Tomography of the Abdomen for Detecting Invasive Fungal Infection Has Limited Value

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A B S T R A C T

The diagnostic utility of obtaining chest and abdomen computed tomography (CT) to evaluate for invasive fungal infection (IFI) before and after hematopoietic stem cell transplant (HSCT) remains unclear. The study was conducted as a quality improvement project. Chest and abdomen CT of patients who underwent an allogeneic HSCT over a 13-month period were reviewed. Scans included those performed pretransplant in all patients and days 0 to 100 post-transplant in selected patients. Sixty-six patients had chest and abdomen CT scans pretransplant. Chest CT was suggestive of IFI in 9 patients (13.6%), including 3 patients with prior history of IFI. After transplant, 37 patients had an initial chest CT and 14 patients an initial abdominal CT. The first chest CT post-transplant was suggestive of IFI in 3 patients; all had an abnormal CT pretransplant. After the initial post-transplant evaluation, 15 patients had 28 additional CT scans of the chest and 12 patients 19 additional CT scans of the abdomen. An abnormal chest CT with proven evidence of IFI was seen in only 1 patient. None of the 99 abdominal CT scans performed pre- or post-transplant had evidence of IFI. There is little benefit in obtaining abdominal CT scans in HSCT patients for detecting IFI either pre- or post-transplant.


## INTRODUCTION

Radiation risk from computed tomography (CT) imaging is cumulative and in an unselected population increases the risk of subsequent solid tumors, particularly in younger patients, girls, and in those who undergo CT imaging of the abdomen and pelvis [1]. A radiation-induced solid tumor is projected to result from every 300 to 390 abdomen/pelvis scans for girls [1]. The risk of leukemia in children is estimated at .8 to 1.0 cases per 10,000 abdomen/pelvis CT scans [1]. The Childhood Cancer Survivor Study reported the 30-year cumulative incidence of secondary malignant neoplasms in 14,359 5-year survivors of childhood cancer to be 20.5% [2]. The radiation risk of CT imaging may be higher in those who have undergone an allogeneic hematopoietic stem cell transplant (HSCT) because of more frequent imaging, exposure to chemotherapy, and radiation therapy in some patients.

In 1982, Bartley et al. [3] reported the results of CT scanning to diagnose hepatic and systemic invasive fungal infections (IFIs) in children undergoing treatment for leukemia at St. Jude Children's Research Hospital in Memphis, Tennessee. Subsequently, CT imaging of the abdomen was incorporated as part of routine screening in patients with unexplained prolonged fever with neutropenia and as part of pre-HSCT evaluation studies. In the present era of prophylactic antifungal therapy, we hypothesize that the diagnostic benefit of this approach is limited, may be outweighed by the radiation risk of CT imaging, and, when considered together with the risks of sedation and contrast administration, represents poor utilization of resources with limited benefit for the patient.

## METHODS

The study was conducted as a quality improvement project and approved by the St. Jude Children's Research Hospital institutional review board. Two senior pediatric radiologists at our institution (S.C.K. and R.A.K.) reviewed the CT scans of chest and abdomen (CAF) to look for evidence of IFI in all children who underwent allogeneic HSCT between September 1, 2012 and September 30, 2013. Scans reviewed included those performed pre-HSCT in all patients as part of routine pretransplant evaluation and days 0 to 100 post-HSCT in those with signs and symptoms suggestive of IFI or with unexplained prolonged fever with neutropenia, obtained at the discretion of the requesting physician.

Standardized CAF were obtained using 3.75-mm (in children weighing $\leq$ 11.5 kg) and 5-mm (in children weighing $>$ 11.5 kg) collimated helical images through the chest and abdomen, reconstructed in standard (soft tissue) and lung algorithm, and reformatted in coronal and sagittal planes. All scans were reviewed at lung, soft tissue, and bone window/levels. Weight-based dose modulation was used for all patients weighing at least 31.5 kg; patients under 31.5 kg were imaged at 100 kVp, whereas patients $\geq$ 31.5 kg were imaged at 120 kVp. The noise index for patients weighing up to 11.5 kg was 12.35 (chest) and 9.88 (abdomen) and for patients weighing over 11.5 kg was 11.57 and 9.83, respectively. Forty percent adaptive statistical iterative reconstruction (ASiR, General Electric Healthcare, Waukesha, WI) was used for all studies on all patients. All CAF studies were performed during i.v. administration of 2.0 mL/kg iodixanol 270 mg-I/mL to a maximum of 150 mL. All studies were performed on a LightSpeed VCT XTe 64 detector scanner (General Electric Healthcare, Waukesha, WI).

Transplant-related variables were abstracted from a prospectively collected database that included patient demographics, underlying diagnosis, remission status, donor and product type, conditioning regimen, symptoms and signs suggestive of IFI if present, grades II to IV graft-versus-host disease, and pre-HSCT absolute neutrophil count (ANC). Screening on

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whole blood for galactomannan was performed pre-HSCT and once weekly post-HSCT on all patients. Galactomannan index value ≥ .5 was considered positive. Microbiologic records were reviewed to identify patients with IFI defined according to accepted criteria [4]. Changes to antifungal therapy based on CT scan findings were noted.

***Statistical Analysis***

The first evaluation date of CT scan before and after transplant was used for analysis. CT scans whose evaluation date exceeded 100 days post-transplant were not considered. Descriptive statistics such as frequencies/percentages for categorical variables and mean, median, range, and standard deviation for continuous variables were provided for pre- and post-transplant data. Fisher's exact test (for categorical variables) and Wilcoxon rank sum test (for quantitative variables) were used to compare patients with and without IFI as suggested by chest CT pre- and post-transplant. McNemar's exact test was used to compare patients with and without IFI as suggested by chest CT pre- and post-transplant. Clinical variables tested included age at transplant, gender, underlying disease, remission status, transplant and product type, receipt of total body irradiation (TBI), presence of symptoms and signs of IFI, ANC, and galactomannan test if positive. All reported *P* values are 2-sided and are considered significant if <.05. Statistical analyses were performed with SAS software, version 9.3 (SAS Institute, Cary, NC).

## RESULTS

Sixty-six patients had CAF pretransplant. Demographics of these patients are presented in Table 1. Seven patients had a history of proven IFI in the lung (n = 4), extremity (1), sinus (1), and blood (1) (Figure 1). All patients tested negative for galactomannan in whole blood pretransplant. Of these 66 patients, pretransplant chest CT was abnormal in a patient who had a focal nodule in the right lower lobe, which was completely resected with positive culture for *Aspergillus fumigatus* (1), in a patient with a nodular opacity in the left upper lobe with history of *Candida parapsilosis* fungemia (patient 2), and in a third patient with proven *Aspergillus* spp. infection in a previous HSCT with resolving opacities before the current transplant (patient 3). The remaining 4 patients had complete resolution of their IFI pretransplant.

Six patients had no prior history of IFI but had small unilateral or bilateral pulmonary nodules not amenable to biopsy. Galactomannan in whole blood and testing for endemic mycoses were negative in all patients. The 7 patients with prior history of IFI and 6 asymptomatic patients with pulmonary nodules received empiric antifungal therapy post-transplant. None of the 66 patients studied had evidence of IFI on abdominal CT scan.

Thirty-seven patients CT imaging post-transplant. Demographics of these patients are presented in Table 1. Indications for performing scans for the first evaluation post-transplant included prior history of IFI or evidence thereof in pretransplant CT with or without a history of unexplained fever with prolonged neutropenia (7 patients), unexplained fever with prolonged neutropenia (14 patients), increased respiratory rate and hypoxia (8 patients), abnormal pulmonary function tests (2 patients), *C. albicans* fungemia (1 patient), assessment of response in patients with solid tumor receiving an allogeneic HSCT (2 patients), and other causes, including rising Epstein-Barr virus DNA in blood (3 patients). An abnormal chest CT suggestive of IFI was seen in 3 patients, all of whom had an abnormal chest CT pretransplant: 1 patient (patient 2) had widespread nodular opacities post-transplant, whereas 2 patients had nodules on chest CT with no prior history suggestive of IFI and developed fever and more nodular opacities post-transplant. Galactomannan was negative and the nodules were not amenable to biopsy. Antifungal therapy was modified with addition of liposomal amphotericin for 1 patient (patient 2) and voriconazole for the other 2 patients. Three patients had positive galactomannan post-transplant with a normal chest CT. Two of these patients had chest CT suggestive of IFI pretransplant. An abdominal CT was performed with the chest CT in 14 patients. None had findings suggestive of IFI.

**Table 1**
Demographics of Patients Who Had Evaluation of the Chest and Abdomen for Fungus with Computed Tomography before and Within 100 Days Post-HSCT

| Characteristic | CAF Pre-HSCT (n = 66) | CAF Days 0-100 Post-HSCT (n = 37) |
|---|---|---|
| Age, yr | | |
| Mean (SD) | 9.1 (6.4) | 9.6 (6.1) |
| Median (Range) | 8.8 (.2-20.4) | 9.1 (.6-20.4) |
| Male sex | 36 (55%) | 18 (49%) |
| Diagnosis heme malignancy | 58 (87%) | 32 (87%) |
| Remission | 28 (42%) | 20 (54%) |
| Total body irradiation | 19 (29%) | 13 (35%) |
| Product type | | |
| Bone marrow | 37 (56%) | 18 (48%) |
| Peripheral blood | 24 (36%) | 15 (41%) |
| Cord | 5 (8%) | 4 (11%) |
| History IFI | 7 (11%) | 4 (11%) |
| Positive galactomannan | 0 (0) | 3 (8%) |
| ANC, cells/μL | | |
| Mean (SD) | 1027 (1276) | 892 (1233) |
| Median (range) | 500 (0-4400) | 500 (0-4400) |
| CT chest-suggestive IFI | 9 (14%) | 3 (8%) |
| CT abdomen-suggestive IFI | 0 (0) | 0 (0) |
| Transplant order | | |
| First transplant | 50 (76%) | 27 (73%) |
| Second transplant | 15 (23%) | 10 (27%) |
| Subsequent transplant | 1 (1%) | 0 (0) |

SD indicates standard deviation.

None of the variables, including age ($P = .90$), gender ($P = .28$), transplant product ($P = .44$), TBI conditioning ($P = 1.00$), or ANC ($P = .62$), was significant in predicting abnormalities suggestive of IFI in pretransplant CT. None of the variables, including age ($P = .36$), gender ($P = 1.00$), transplant product ($P = .32$), TBI conditioning ($P = 1.00$), or ANC ($P = .26$), was significant in predicting abnormalities suggestive of IFI in post-transplant CT. Abnormal pre- and post-transplant chest CT were not statistically discordant ($P = .25$).

After the initial post-transplant evaluation, 15 patients had 28 additional CT scans of the chest and 12 patients 19 additional CT scans of the abdomen. Indications for performing these scans included fever with increased C-reactive protein (4 patients), increased respiratory rate and hypoxia (3 patients), *C. albicans* fungemia (1 patient), assessment of response in patients with solid tumor (2 patients), abdominal pain and diarrhea (2 patients), and other causes (3 patients).

An abnormal chest CT suggestive of IFI was seen in patient 4, a 1-year-old male with acute lymphoblastic leukemia who received a cord HSCT. The patient subsequently developed *C. albicans* fungemia 5 days post-HSCT that was broadly susceptible to antifungals; chest CT was normal. He responded poorly to a combination of micafungin and liposomal amphotericin and developed nodular lesions in both lungs on a follow-up chest CT with no abnormalities detected on abdominal CT (Figure 2). Biopsy of the nodules revealed budding yeast with pseudohyphae. Therapy was changed to micafungin with voriconazole, to which he responded. He succumbed to a relapse of his leukemia. None of the 12 patients with abdominal CT obtained after the first post-transplant CT had findings suggestive of IFI.