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The value of low-dose whole body CT in the management of patients with multiple myeloma and precursor states

F. Joseph Simeone¹, Joel P. Harvey¹, Andrew J. Yee², Elizabeth K. O'Donnell², Noopur S. Raje², Martin Torriani¹, and Miriam A. Bredella¹

¹Division of Musculoskeletal Imaging and Intervention, Department of Radiology, Massachusetts General Hospital and Harvard Medical School, 55 Fruit Street, Boston, MA 02114

²Division of Hematology-Oncology, Massachusetts General Hospital and Harvard Medical School, 55 Fruit Street, Boston, MA 02114

Abstract

Objective.—To determine the value of low-dose whole-body CT (WBCT) in the management of patients with multiple myeloma (MM) and precursor states.

Materials and Methods.—The study group comprised 116 patients (mean age: 68±11 years, 48% women) who underwent WBCT for the work-up or surveillance of MM or MM precursor disease. WBCTs were reviewed for presence of MM-related bone disease and incidental findings requiring therapy. The medical records, results from bone marrow aspirations and biopsies and follow-up imaging studies were reviewed to assess the influence of WBCT on patient management.

Results.—WBCT led to a change in management in 32 patients (28%). Of those, 17 patients with MM precursor disease were found to have MM-related bone disease, 13 patients had progression of MM, requiring a change in treatment, in one patient hepatocellular carcinoma was diagnosed, requiring a change in therapy, and one patient had a rib lesion requiring intervention. In 65 patients (56%) WBCT was performed for surveillance of MM precursor disease or stable treated MM, and did not detect new lesions, thereby providing reassurance to the hematologist on disease status and management. In 15 patients (13%) WBCT was performed as a new baseline prior to a change or new therapy. In 4 patients (3%) WBCT was performed for a change in symptoms but did not detect lesions that would lead to a change in management.

Conclusion.—WBCT provides important information for disease monitoring and detection of incidental findings thereby improving the management of patients with MM.

Corresponding author: Miriam A. Bredella, MD, Professor of Radiology Massachusetts General Hospital, Yawkey 6E, 55 Fruit Street, Boston, MA 02114, Phone: 617-726-7717, Fax: 617-726-5282, mbredella@mgh.harvard.edu.

Compliance with Ethical Standards

Conflict of Interest: The authors declare that they have no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent: Informed consent was waived for this retrospective study.

Keywords

low-dose whole body computed tomography (WBCT); multiple myeloma; monoclonal gammopathy of undetermined significance (MGUS); smoldering myeloma

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Introduction

Multiple myeloma is a hematological malignancy characterized by the clonal proliferation of plasma cells [1]. Multiple myeloma is consistently preceded by monoclonal gammopathy of undetermined significance (MGUS), a premalignant plasma cell proliferative disorder, characterized by the absence of hypercalcemia, renal failure, anemia, and bone lesions (CRAB features) [2]. The rate of progression of MGUS to multiple myeloma is about 1% per year [3]. Smoldering multiple myeloma is an intermediate clinical stage between MGUS and multiple myeloma with a risk of progression to malignant disease at about 10% per year [3]. The diagnosis of multiple myeloma is defined by the International Myeloma Working Group (IMWG) criteria which include bone marrow plasma cells of $\geq 60\%$ on bone marrow biopsy, clonal bone marrow plasma cells $\geq 10\%$, serum involved to uninvolved free light chain ratio of ≥ 100 or biopsy-proven bony or extramedullary plasmacytoma and any of the CRAB features (hypercalcemia, renal failure, anemia, and bone lesions) [4].

Imaging plays a critical role in the staging and management of patients with multiple myeloma and multiple myeloma precursor disease, since the presence of bone lesions establishes the diagnosis of active multiple myeloma and necessitates therapy [5]. Imaging features of multiple myeloma-related bone disease include generalized osteopenia, focal lytic lesions, and rarely sclerotic lesions in the setting of POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, Skin changes) [6]. The absence of bone lesions on imaging is important to distinguish multiple myeloma from MGUS or smoldering myeloma [7]. Historically, radiographic skeletal surveys have been used to demonstrate lytic lesions or pathologic fractures from multiple myeloma. However, radiographs are limited in detecting small lytic lesions, esp. of the axial skeleton and rib cage, given that at least 30% of trabecular bone must be destroyed to be visible on radiographs [8]. Advances in cross-sectional imaging allow more accurate diagnosis and staging of multiple myeloma [5]. Whole-body magnetic resonance imaging (MRI) and positron emission tomography (PET) have been found to be more accurate in detecting multiple myeloma-related bone disease, compared to radiographs [9–12]. Computed tomography (CT) has been found to be the most sensitive modality in detecting small osteolytic lesions of <5 mm [13, 14]. However, CT is limited by ionizing radiation exposure. Advances in CT technology allow low-dose assessment of the whole body with doses comparable to a whole body radiographic skeletal survey [15], and, given its widespread availability and short acquisition time compared to radiographic skeletal survey, lytic bone lesions (≥ 5 mm) on whole-body CT (WBCT) have been integrated into the latest diagnostic criteria of the IMWG [4]. However, besides more accurate staging, the use of low-dose WBCT in the management of patients with multiple myeloma and its precursor states has not been emphasized in the radiology literature.

The purpose of our study was to determine the value of low-dose WBCT in the management of patients with multiple myeloma and its precursor states. We hypothesized that low-dose WBCT provides critical information for disease monitoring and detection of significant incidental findings, thereby improving the management of patients with multiple myeloma and its precursor states.

Materials and Methods

Our study was IRB approved and complied with HIPAA guidelines with exemption status for individual informed consent.

A retrospective search was performed of all low-dose WBCTs acquired from 7/24/17 to 6/5/2018, since the introduction of low-dose WBCT for the workup of patients with multiple myeloma at our institution.

Low-dose whole body CT (WBCT)

CT examinations were performed without administration of intravenous or oral contrast on multidetector CT scanners in helical mode (SOMATOM Force or SOMATOM Flash, Siemens, Forchheim, Germany; GE Discovery, GE Revolution or GE Lightspeed VCT, Boston, MA). Patients were positioned supine, head first, with the arms straight beside the body and hands placed over the upper thighs, in order to be able to assess bone changes in the upper extremities. The field of view was adapted to the patient's circumference. Detector coverage was 80 mm, rotation time 0.5 and pitch of approximately 1. The tube voltage was 120 kV and the tube current time product was between 40 and 70 mAs based on scanner noise index settings and patient weight. The scan extended from the vertex of the skull to 2 cm below the knee joint. The table speed/rotation was 24 mm. Thin collimation made whole-body coverage along the z-axis in one helical acquisition possible.

Images were reconstructed with at least two different convolution kernels including bone and soft tissue weighted kernels. Multiplanar reformatted images (MPR) were obtained to facilitate image analysis. The effective slice thickness was 2.5mm and the reconstruction increments 1.25 mm for MPR scans. The following MPR images were created, transferred to the picture archiving and communication system (PACS), and reviewed: coronal images from the head through the iliac crests in bone and soft tissue kernels, coronal images from the iliac crests through the proximal tibia in bone and soft tissue kernels, and sagittal images of the head and entire spine in bone and soft tissue kernels (Figure 1). Average radiation dose was 4.8 +/- 1.5 mSv (range 3.5–7 mSv).

Image Analysis and Patient Management

The WBCTs were reviewed for the presence or absence of multiple myeloma-related bone disease in consensus by two musculoskeletal radiologists with 6 years and 13 years of experience, respectively. Criteria for multiple-myeloma related bone disease included focal well-defined lytic lesions (≥ 5 mm) with no sclerotic margins, focal or nodular areas of asymmetric increased bone marrow density within long bones or pelvis, and sclerotic lesions in case of POEMS syndrome using established criteria [4]. In addition, incidental findings, such as fractures or other neoplasms were recorded. Multiple myeloma-related bone disease

was confirmed by tissue diagnosis and/or or clinical/imaging follow-up. The medical records, including results from bone marrow aspirations, biopsies and follow-up imaging studies were reviewed to assess the influence of WBCT on patient management and four categories were determined. 1. Change in management: a change in management included a) change in staging from MGUS or smoldering myeloma to multiple myeloma due to multiple myeloma-related bone disease detected on WBCT; b) worsening bone disease on WBCT requiring a change in therapy; c) impending fracture or fracture requiring intervention; d) detection of other neoplasm, requiring new therapy/intervention. 2. Surveillance: WBCT performed for surveillance of MGUS or smoldering myeloma or treated multiple myeloma with no new bone lesions detected on WBCT. 3. New baseline: change in therapy or new therapy was planned due to clinical symptoms and WBCT was ordered prior to the initiation of therapy as a new baseline. 4. No change in therapy: WBCT was ordered because of clinical symptoms but did not lead to a change in management.

The percentage of patients in each of the four patient management categories was determined. Mean and standard deviations of patient characteristics are presented.

Results

We identified 116 patients (mean age: 68 ± 11 years, 56 women, 50 men) who underwent low-dose WBCT. Prior to WBCT, 25 patients were diagnosed with MGUS, 15 patients with smoldering myeloma, five with plasmacytoma, one patient with POEMS syndrome, and 70 patients with multiple myeloma, based on IMWG criteria [4]. All WBCTs were of diagnostic quality.

Low-dose WBCT led to a change in management in 32 patients (28%). Of those, 10 patients with a history of MGUS, 4 patients with smoldering myeloma, and 3 patients with plasmacytoma were found to have multiple myeloma-related bone disease and 13 patients had progression of multiple myeloma, requiring a change in treatment (Figure 2). In one patient with multiple myeloma, previously undiagnosed hepatocellular carcinoma was detected on WBCT and subsequently confirmed (Figure 3). In one patient with multiple myeloma, a rib lesion was detected on WBCT which was subsequently treated with cryoablation for pain control.

In 65 patients (56%) low-dose WBCT was performed for surveillance of multiple myeloma precursor disease or stable treated multiple myeloma, and did not detect new lesions, thereby providing reassurance to the hematologist on disease status and management.

In 15 patients (13%) WBCT was performed as a new baseline prior to a change in therapy or new therapy which was planned due to clinical symptoms prior to WBCT.

In 4 patients (3%) WBCT was ordered because of a change in clinical symptoms but did not detect lesions that would lead to a change in management.

Discussion

Our study showed that low-dose WBCT provides critical information for disease monitoring and detection of significant incidental findings, thereby improving the management of patients with multiple myeloma and its precursor states.

Multiple myeloma is a fatal malignancy of plasma cells, accounting for approximately 13% of hematological malignancies and 2% of all cancers in the US [1, 16, 17]. The survival of patients with multiple myeloma has improved since the advent of novel therapies such as autologous stem cell transplantation, immunomodulatory drugs, and proteasome inhibitors [18–20], requiring sensitive techniques for early diagnosis and accurate staging. Imaging plays a critical role for the early diagnosis and surveillance of patients with multiple myeloma since the presence of multiple myeloma-related bone disease indicates the necessity of therapy [5].

Multiple myeloma is consistently preceded by MGUS, a precursor disease characterized by the absence of bone lesions and organ or tissue impairment. The life-long risk of MGUS to progression to multiple myeloma is about 1 % per year [2, 4, 7]. Smoldering multiple myeloma is an intermediate clinical stage between MGUS and multiple myeloma, also characterized by the absence of bone lesions, with a risk of progression to malignant disease at about 10% per year [3]. Given the fact that nearly all multiple myeloma cases are preceded by MGUS or smoldering myeloma, it is of clinical importance to detect bone involvement to rule out disease progression, which would require the initiation of therapy. Moreover, in patients with multiple myeloma, bone involvement is a major cause of morbidity and mortality and an important indicator of prognosis [4].

Radiographic skeletal surveys have been traditionally used to demonstrate lytic lesions from multiple myeloma or pathologic fractures. However, radiographs are relatively insensitive and nonspecific for detecting myeloma-related bone disease, esp. in anatomically complex areas such as the axial skeleton or rib cage, or in patients with reduced bone mineral density [21–23]. In fact, at least 30% of trabecular bone must be destroyed to be visible on radiographs [8]. However, underestimation of multiple myeloma-related bone disease could lead to misclassification of multiple myeloma patients into a precursor state, thereby preventing the initiation of necessary therapy. In fact, in the updated IMWG diagnostic criteria lesions measuring 5 mm on CT or MRI are now included in the diagnosis of multiple myeloma [4]. This highlights the need for more accurate imaging techniques to diagnose bone involvement in multiple myeloma.

Advances in cross-sectional imaging allow more accurate diagnosis and staging of multiple myeloma [5]. Whole body magnetic resonance imaging (MRI) and 18F-fluorodeoxyglucose positron emission tomography (PET) with computerized tomography (PET/CT) have been found to be more accurate than radiographs in detecting multiple myeloma-related bone disease [9–12, 24]. A main advantage of whole body MRI is the lack of ionizing radiation while limitations include costs and availability. FDG-PET/CT has been found to be accurate in monitoring therapy in multiple myeloma and in the setting of relapse. In addition, FDG-

PET/CT provides independent prognostic information at time of diagnosis and following therapy [25–31] but is limited by ionizing radiation, costs and availability.

With the relative widespread availability of MDCT scanners, whole-body MDCT has been increasingly used in the screening of the skeleton in patients with multiple myeloma and several studies have shown that WBCT is accurate in detecting multiple myeloma-related bone disease [12–14, 21–23, 32–35], however, CT is limited by ionizing radiation exposure. Advances in CT technology allow low-dose assessment of the whole body and WBCT has been integrated into the latest diagnostic criteria of the IMWG [4, 33]. In fact, the updated IMWG diagnostic criteria now include 5 mm lesions on CT or MRI, which were previously not counted towards the diagnosis of myeloma, supporting to role of advanced cross-sectional imaging in the staging of patients with multiple myeloma. As a result, WBCT has replaced radiographic skeletal surveys in many institutions, mainly in Europe. Horger et al [22] used WBCT to assess therapy response in patients with multiple myeloma and WBCT was more reliable than conventional, laboratory-based follow-up [22]. Ippolito et al [36] focused on the value of WBCT in lesion detection in patients with multiple myeloma. WBCT was a reliable method for lesion detection and staging [36]. However, besides more accurate lesion detection and staging, the use of low-dose WBCT in the management of patients with multiple myeloma is has not been studied.

The aim of our study therefore was to assess the value of low-dose WBCT in management of patients with multiple myeloma and its precursor states. We used a dedicated low-dose whole body protocol which was of diagnostic quality in all cases. Axial images and multiplanar reformations in the coronal and sagittal planes were used to assess for multiple-myeloma-related bone disease, lesions at risk for pathologic fracture and incidental findings which might affect management. The mean radiation dose of our protocol of 4.8 mSv is comparable to other low-dose WBCT protocols reported in the literature [21, 34, 36]. The radiation dose for a radiographic skeletal survey is about 2.5 mSv [15]. Lambert et al recently published a low-dose WBCT protocol with a radiation dose of 2.7 mSv [15], demonstrating that WBCT can obtain diagnostic images at doses comparable to a radiographic skeletal survey.

In our study, low-dose WBCT was able to provide important information on patient management in 97% of cases. In almost one third of our patients, low-dose WBCT either led to a change in staging from multiple myeloma precursor disease to multiple myeloma or progression of multiple myeloma, requiring a change in therapy. Moreover, low-dose WBCT was able to detect critical incidental findings in one patient (hepatocellular carcinoma), which required a change in management. In one patient a rib lesion was detected which was subsequently treated with cryoablation. An important aspect in the management of patients with treated multiple myeloma and its precursor states is surveillance and detection of conversion to multiple myeloma or relapse. More than half of our low-dose WBCTs were performed for surveillance of either multiple myeloma precursor disease or stable treated multiple myeloma, and did not detect disease progression. Although not directly changing management, the WBCT provided reassurance to the hematologist on disease status and management.

Our study was limited by the retrospective study design and short-term follow-up. Advantages of our study include the large number of patients scanned using a uniform low-dose protocol, dedicated for the work-up of patients with multiple myeloma and precursor disease, detailed information of bone marrow aspirations and biopsies and follow-up imaging.

In conclusion, low-dose WBCT provides critical information for disease monitoring and detection of incidental findings thereby improving the management of patients with multiple myeloma.

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Figure 1:

46-year-old man with multiple myeloma. Frontal CT scout image (a) demonstrates patient positioning for WBCT myeloma survey with arms down and hands over the pelvis or upper thighs. Coronal reconstructed image of the entire body from the same patient showing the field of view (white boxes) used for the coronal images from the head through the iliac crests (b) and coronal images from the iliac crests through the proximal tibia (c). White box overlying sagittal image of the entire body (d) shows field of view for images of the head and entire spine.

Figure 2:

91-year-old woman with MGUS upstaged to multiple myeloma after lytic lesions were detected on WBCT. Multiple lytic lesions are seen throughout the skeleton including on sagittal CT reformatted image of the spine (a), axial CT image of the skull (b) and axial CT image of the right acetabulum (c) (arrows). Note pathologic compression fracture of the involved lower thoracic vertebral body in (a) (arrow).

Figure 3:

63-year-old woman with multiple myeloma and incidentally found hepatocellular carcinoma. Axial CT image from WBCT (a) demonstrates a low attenuation mass in the right lobe of the liver (arrow). Subsequent post contrast liver MRI image (b) shows an enhancing mass, concerning for hepatocellular carcinoma, later confirmed on needle biopsy (c) (arrows).