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SCIENTIFIC ARTICLE

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

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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 the 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 Whole-body CT 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 before 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 Whole-body CT provides important information for disease monitoring and detection of incidental findings, thereby improving the management of patients with MM.

Keywords Low-dose whole-body computed tomography · WBCT · Multiple myeloma · Monoclonal gammopathy of undetermined significance · MGUS · Smoldering myeloma

Introduction

Multiple myeloma (MM) is a hematological malignancy characterized by the clonal proliferation of plasma cells [1]. MM 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 MM is about 1% per year [3]. Smoldering MM is an intermediate clinical stage between MGUS and MM, with a risk of progression to malignant disease at about 10% per year [3]. The diagnosis of MM is defined by the International Myeloma Working Group (IMWG) criteria, which include bone marrow plasma cells of ≥60% on bone marrow biopsy, clonal bone marrow plasma cells ≥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 MM and MM precursor disease, as the presence of bone lesions establishes the diagnosis of active MM and necessitates therapy [5]. Imaging features of MM-related bone disease include generalized osteopenia, focal lytic lesions, and rarely sclerotic lesions in the setting of

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polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes (POEM) syndrome [6]. The absence of bone lesions on imaging is important to distinguish MM from MGUS or smoldering myeloma [7]. Historically, radiographic skeletal surveys have been used to demonstrate lytic lesions or pathological fractures from MM. However, radiographs are limited in detecting small lytic lesions, especially 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 MM [5]. Whole-body magnetic resonance imaging (MRI) and positron emission tomography (PET) have been found to be more accurate in detecting MM-related bone disease, compared with 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 with a whole-body radiographic skeletal survey [15], and, given its widespread availability and short acquisition time compared with 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 MM 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 MM and its precursor states. We hypothesized that low-dose WBCT provides critical information for disease monitoring and the detection of significant incidental findings, thereby improving the management of patients with MM 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 24 July 2017 to 5 June 2018, since the introduction of low-dose WBCT for the workup of patients with MM at our institution.

Low-dose whole-body CT

Computed tomography examinations were performed without administration of intravenous or oral contrast medium 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, USA). Patients were positioned supine, head first, with the arms straight beside the body and hands placed over the upper thighs, 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 it possible to obtain whole-body coverage along the z-axis in one helical acquisition.

Images were reconstructed with at least two different convolution kernels, including bone and soft-tissue weighted kernels. Multiplanar reformatted (MPR) images were obtained to facilitate image analysis. The effective slice thickness was 2.5 mm and the reconstruction increments were 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 (Fig. 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 MM-related bone disease in consensus by two musculoskeletal radiologists with 6 years and 13 years of experience respectively. Criteria for MM-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 the case of POEMS syndrome using established criteria [4]. In addition, incidental findings, such as fractures or other neoplasms, were recorded. MM-related bone disease was confirmed by tissue diagnosis and/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, including:

    a) A change in staging from MGUS or smoldering myeloma to MM secondary to MM-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

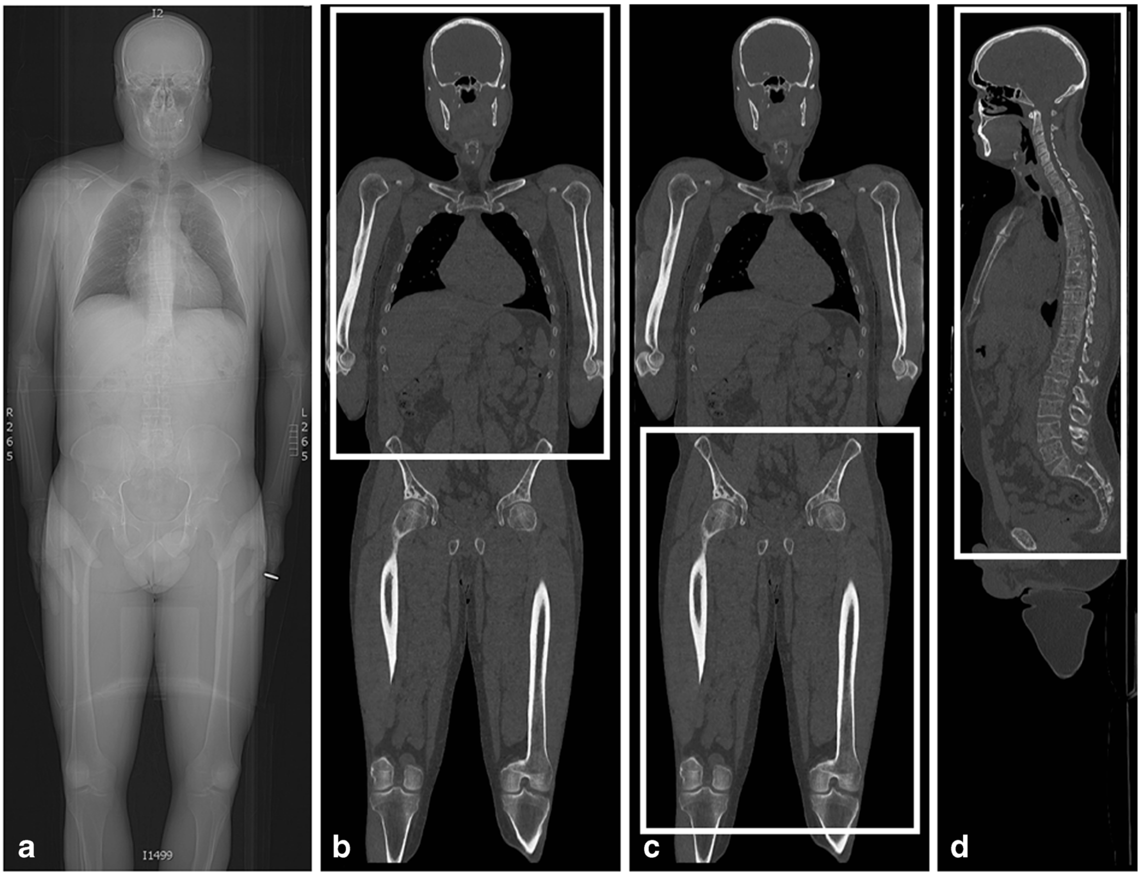

Fig. 1 A 46-year-old man with multiple myeloma. **a** Frontal CT scout image demonstrates patient positioning for whole-body CT (WBCT) myeloma survey with arms down and hands over the pelvis or upper thighs. **b** Coronal reconstructed image of the entire body from the same patient showing the field of view (*white boxes*) used for the coronal images from the head through the iliac crests and **c** coronal images from the iliac crests through the proximal tibia. **d** *White box* overlying sagittal image of the entire body shows field of view for images of the head and entire spine

2. Surveillance: WBCT performed for surveillance of MGUS or smoldering myeloma or treated MM with new bone lesions detected on WBCT
3. New baseline: change in therapy or new therapy was planned owing to clinical symptoms and WBCT was ordered before 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. Before WBCT, 25 patients were diagnosed with MGUS, 15 patients with smoldering myeloma, 5 with plasmacytoma, 1 patient with POEMS syndrome, and 70 patients with MM, 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 MM-related bone disease and 13 patients had progression of MM, requiring a change in treatment (Fig. 2). In one patient with MM, a previously undiagnosed hepatocellular carcinoma was detected on WBCT and subsequently confirmed (Fig. 3). In one patient with MM, 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 MM precursor disease or stable treated MM, and did not detect new lesions, thereby providing reassurance to the hematologist with regard to disease status and management.

In 15 patients (13%), WBCT was performed as a new baseline before a change in therapy or new therapy, which was planned because of clinical symptoms before WBCT.

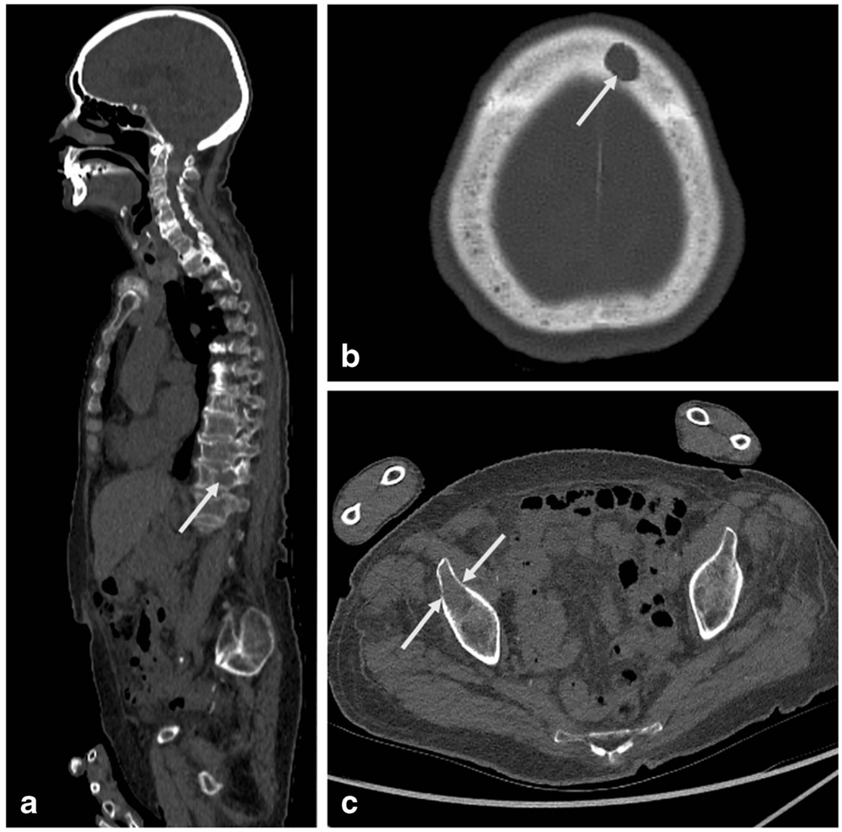

Fig. 2 A 91-year-old woman with monoclonal gammopathy of undetermined significance (MGUS) upstaged to multiple myeloma after lytic lesions were detected on WBCT. **a** Multiple lytic lesions are seen throughout the skeleton including on a sagittal CT reformatted image of the spine, **b** axial CT image of the skull, and **c** axial CT image of the right acetabulum (*arrows*). Note pathologic compression fracture of the involved lower thoracic vertebral body in **a** (*arrow*)

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 MM 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 USA [1, 16, 17]. The survival of patients with MM 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 MM because the presence of MM-related bone disease indicates that therapy is necessary [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 progressing to MM is about 1% per year [2, 4, 7]. Smoldering MM is an intermediate clinical stage between MGUS and MM, 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 MM 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 MM, 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 MM or pathological fractures. However, radiographs are relatively insensitive and nonspecific for detecting myeloma-related bone disease, especially 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 MM-related bone disease could lead to misclassification of MM 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 MM [4]. This highlights the need for more accurate imaging techniques to diagnose bone involvement in MM.

Advances in cross-sectional imaging allow more accurate diagnosis and staging of MM [5]. Whole-body magnetic

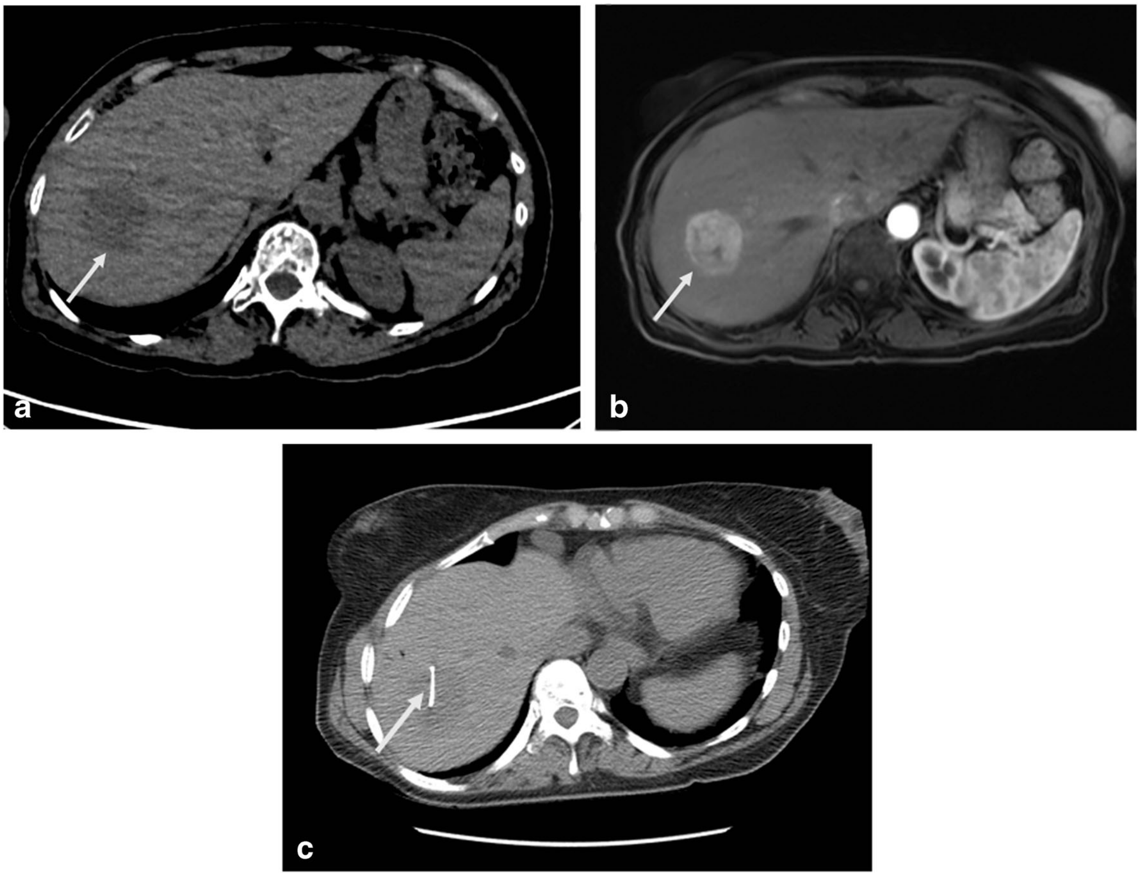

Fig. 3 A 63-year-old woman with multiple myeloma and an incidentally found hepatocellular carcinoma. **a** Axial CT image from WBCT demonstrates a low attenuation mass in the right lobe of the liver (*arrow*). **b** Subsequent post-contrast liver MRI shows an enhancing mass, a suspected hepatocellular carcinoma *(arrow)*. **c** This was later confirmed on needle biopsy (*arrow*)

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 MM-related bone disease [9–12, 24]. A main advantage of whole-body MRI is the lack of ionizing radiation and limitations include costs and availability. FDG-PET/CT has been found to be accurate in monitoring therapy in MM and in the setting of relapse. In addition, FDG-PET/CT provides independent prognostic information at the 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 MM and several studies have shown that WBCT is accurate in detecting MM-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 previously did not count toward the diagnosis of myeloma, supporting the role of advanced cross-sectional imaging in the staging of patients with MM. 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 MM 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 MM. WBCT was a reliable method for lesion detection and staging [36]. However, in addition to more accurate lesion detection and staging, the use of low-dose WBCT in the management of patients with MM has not been studied.

The aim of our study, therefore, was to assess the value of low-dose WBCT in the management of patients with MM and its precursor states. We used a dedicated low-dose whole-body protocol that was of diagnostic quality in all cases. Axial images and multiplanar reformations in the coronal and sagittal planes were used to assess for MM-related bone disease, lesions at risk for pathological fracture, and incidental findings that might affect management. The mean radiation dose of our protocol of 4.8 mSv is comparable with 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 with 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 MM precursor disease to MM or to the progression of MM, 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 that was subsequently treated using cryoablation. An important aspect in the management of patients with treated MM and its precursor states is surveillance and detection of conversion to MM or relapse. More than half of our low-dose WBCTs were performed for surveillance of either MM precursor disease or stable treated MM, 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 to the work-up of patients with MM and precursor disease, detailed information on bone marrow aspirations, and biopsies and follow-up imaging.

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

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

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

Informed consent Informed consent was waived for this retrospective study.

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