Review

Quantitative Imaging and Radiomics in Multiple Myeloma: opportunity or hype?

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Abstract: Multiple Myeloma (MM) is the second most common type of hematological disease and, although it is rare among patients under 40 years of age, its incidence rises in elderly subject. MM manifestations are usually known with the abbreviation CRAB (hyperCalcemia, Renal failure, Anaemia, and lytic Bone lesions). In particular, the extent of the bone disease is negatively related to a decreased patients' quality of life and, in general, bone disease in MM increases both morbidity and mortality. The detection of lytic bone lesions on imaging, especially CT and MRI, is becoming crucial from the clinical viewpoint to separate asymptomatic from symptomatic MM patients and the detection of focal lytic lesion in these imaging data is becoming relevant even when no clinical symptoms are present. Therefore, radiology is pivotal in the staging and accurate management of patients with MM even in early phases of the disease. In this review we describe the opportunities offered by quantitative imaging and radiomics in multiple myeloma. At present time there is still high variability in the choice between various imaging methods to study MM patients and high variability in image interpretation with suboptimal agreement among readers even in tertiary

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centres. Therefore, the potential of medical imaging for patients affected by MM is still to be completely unveiled. In the next years, new insights to study MM with medical imaging will derive from artificial intelligence (AI) and radiomics usage in different bone lesions and from the wide implementations of quantitative methods to report CT and MRI. Eventually, medical imaging data can be integrated with the patient's outcomes with the purpose to find radiological biomarkers for predicting the disease prognostic flow and its therapeutic response.

Keywords: multiple myeloma; computed tomography; artificial intelligence; radiomics; prognosis; imaging; diagnosis

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Abbreviations

AI: artificial intelligence

MM: multiple myeloma

MGUS: monoclonal gammopathy of undetermined significance

CRAB: hyperCalcemia, Renal failure, Anaemia, and lytic Bone lesions

MRI: Magnetic Resonance Imaging

WBLCDCT: whole-body low-dose CT

IMWG: International Myeloma Working Group

sMM: smoldering MM

RSNA: Radiological Society of North America

DICOM: Digital Imaging and COmmunications in Medicine

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1. Introduction

Multiple Myeloma (MM) is the second most common type of hematological disease and, although it is rare among patients under 40 years of age, its incidence rises in elderly subject [1]. This hematological malignant disease is characterized by the autonomous monoclonal proliferation of plasma cells in the bone marrow [2]. More specifically, MM is a cytogenetically heterogeneous disorder of clonal plasma cells in which an excessive production of either monoclonal intact immunoglobulin molecules or immunoglobulin free light chains kappa or lambda is crucial for development of clinical features [3–7]. Many risk factors for MM are known, including male sex, radiation exposure and monoclonal gammopathy of undetermined significance (MGUS) [1, 6, 8].

MM manifestations are usually known with the abbreviation CRAB (hyperCalcemia, Renal failure, Anaemia, and lytic Bone lesions). In particular, in MM the normal myeloproliferation is replaced by a pathological one, with important clinical impact leading to an increasing risk of pathological fractures [2]. This is the main reason why, in 2003, the International Myeloma Working Group (IMWG) replaced the Durie-Salmon system with a revised version (Durie-Salmon system plus), where the diagnostic role of radiography in identifying bone marrow involvement is overtaken by the increased sensitivity of Magnetic Resonance Imaging (MRI) and hybrid Positron Emission Tomography (PET) and Computerized Tomography (CT) data with FDG as tracer (FDG PET/CT) [7, 9, 10]. Indeed, the extent of the bone disease is negatively related to a decreased patients' quality of life and, in general, bone disease in MM increases both morbidity and mortality [2, 4, 11–13]. Therefore, the detection of lytic bone lesions on imaging, especially CT and MRI, is becoming crucial from the clinical viewpoint to separate asymptomatic from symptomatic MM patients and the detection of focal lytic lesion is becoming relevant even when no clinical symptoms are present [14].

Nowadays, radiology is pivotal in the staging and accurate management of patients with MM even in early phases of the disease. Medical imaging is used not only to detect bone lesions but also to predict the risk of early progression from smouldering MM (SMM) to active MM and to identify extra-medullary disease [2, 12, 14]. CT in particular is useful to identify the sites of either possible pathologic fractures or neurologic complications and to score bone damage quantitatively [7, 12]. Further, compared to conventional radiography, PET/CT and whole-body low-dose CT (WBLDCT) are able to detect the presence of active disease in up to 25% to 40% of cases negative at conventional radiography [2]. Following this strictly evidence-based approach, a grade A recommendation has been therefore assigned to the incorporation of these new imaging modalities (WBLDCT and PET/CT) [7, 9, 10].

Yet, the diagnostic and prognostic capabilities of medical imaging in MM are still under investigation and development. In fact, significant variability in image-based prognostic scores is present among different centres and in clinical practice [5, 11, 13, 15]. Further, although the updated version of the IMWG criteria accepts the use of CT, WBLDCT and PET/CT to diagnose lytic bone disease in MM, there is still a lack of reliable computational tools for increasing the prognostic value of these modern imaging modalities. In the present review, we will briefly describe the role of new radiological achievements to increase diagnostic potential of medical imaging, with specific focus on CT.

2. Quantitative evaluation of bone CT and reader's experience

As illustrated by a vast amount of scientific literature, daily clinical practice presents a wide usage of CT data for the diagnosis and follow-up of patients with MM, but, at the same time, there is high variability in image interpretation due to different factors [3–5, 11–14, 16, 17]. By instance, it is not always possible to obtain WBLDCT in every patient and often patients with MM receive standard

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total body CT including thorax and abdominal evaluation. However, after standard reporting of thorax and abdominal findings, in patients affected by MM the focus should be given to small lytic lesion [3–5, 18]. Further, the largest number of CT examinations of patients affected by MM is performed in the elderly, which implies that multiple degenerative bone changes are likely to influence the radiological report reducing the agreement among readers in CT image interpretation to detect even clinically significant small lytic lesions [6,8,10,11].

In order to quantitatively evaluate the status of bone damage, risk of fracture and instability in MM, to reduce reader's variability, and to assess CT data with good agreement, radiologists and clinicians have developed the Myeloma Spine and Bone Damage Score (MSBDS)[19].

The MSBDS scoring system present several nice aspects:

- On a series of 70 patients with total body CT available and acquired at the same centre, the MSBDS criteria resulted to be fast, reproducible and easy to integrate in daily clinical practice.

- MSBDS resulted to be useful not only for Radiologists specifically trained to assess the musculoskeletal system, but also for clinicians with no formal training in radiology [19].

- MSBDS correlated well with other quantitative evaluation systems such as the MY-RADS score, supporting the reliability of the MSBDS criteria and suggesting that this scoring system could be reliable for total-body CT in MM patients.

- MSBDS has the unique feature that it has been specifically designed and tailored on MM patients while, on the contrary, previously published scoring systems developed mainly in orthopaedic environments were designed for spinal assessment in metastatic patients [20].

- MSBDS not only evaluates the bones to look for spinal instability, but the lytic bony damage is considered with prognostic target. Specific items of MSBDS are dedicated to the proximal femur involvement and to lytic lesions.

- MSBDS could be far more reliable and diffuse than other scores used for MM patients such as the MY-RADS score and the IMPeTUs criteria for PET or PET/CT [13].

- At a very practical level, MSDBS can be used on CT images that are far more available than MR images, is very fast and easily reproducible and requires the scoring of a low number of parameters.

The Durie Salmon System and the International Staging System are still the standard of care in patients with MM for staging. However, the increasing number of patients with MM evaluated with CT needs a thorough evaluation with reliable and quantitative parameters as suggested by recent advancement in precision medicine [21, 22]. The MSDBS is ready for immediate clinical application and improves current methods of scoring bone lesions in MM (**Figure 1**). We also point out that MSBDS is only an option to quantitatively score MM bone involvement and it should represent a starting point to correctly evaluate the patient's impairment not only in clinical practice but also in the medico-legal field (e.g.: private health insurances). Every quantitative criteria and potential imaging biomarker has to be validated in large trials. At the present time, a prospective clinical validation of MSBDS criteria is underway and results will be available as soon as negative effects of COVID-19 pandemic will be less severe on radiological research [23]

Another important issue in medical imaging related to MM is concerned with the reader's experience. Radiology is a wide field where different subspecialties are present. For example, the European Society of Radiology, who promotes and coordinates the scientific, philanthropic, intellectual and professional activities of radiology, have several affiliated subspecialty reflecting great heterogeneity in radiological profession [24]. For MM, the interpretation of bony lesion is

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straightforward in most cases due to the fact that lesions are lytic. However, in some cases, lesion could be numerous, well circumscribed and could punch out lucencies, raindrop skull, endosteal scalloping and sometimes generalized osteopenia [25,26]. In these cases, it is likely that a sub-speciality with experience in reading CT and MRI data will enhance the role of CT and MRI for MM [27, 28]. In many centers, consultation and second-opinion interpretation of medical images by subspecialty radiologists are routinely performed [5, 29–33]. A recent study was done with the aimto improve the radiological detection and characterization of clinically significant lytic lesions using standard CT (**Figure 2**). Discrepancy rates up to 15% have been reported describing reports by radiologists at different levels of training and radiologists at different clinical settings, while the discrepancy rate in interpreting a clinically important abnormality (e.g., interpreting the presence of a lytic lesion >5 mm) reached 21% [5]. A clinical benefit of a subspecialty second-opinion consultation in MM CT has been demonstrated particularly for lytic lesions. Indeed, a lytic lesion in MM is sometimes difficult to detect, especially when the diameter is between 5 and 10 mm and when it is located in an osteoporotic and degenerated vertebral body. Particularly for these patients, dedicated musculo-skeletal (MSK) radiologists could solve difficult and uncertain cases [28, 32, 34]. The expertise of a dedicated reader is also crucial because reference standard is difficult to achieve in MM since bone biopsy could not be obtained in small lesions and in every anatomical location.

3. Radiomics in MM

Multiple myeloma (MM) is a genetically complex disease that evolves from pre-malignant stages such as M-GUS and SMM and progresses to symptomatic MM [35].

In MM the development of the disease is very complex and a progression with clonal sweeps in the early phase and a regional evolution in advanced disease have been recently confirmed [6]. Therefore, the analysis of multiple bone lesions could be done using computer algorithms supporting the use of radiomics. By instance, a recent application of radiomics in MM showed that, in clinical practice, radiomics is able to improve the radiological evaluation of focal and diffuse pattern of MM on CT by improving the Area Under the Curve (AUC) of radiologists [3]. Specifically, accuracy in terms of the AUC of radiologists compared to the reference standard was lower (64%) than accuracy computed using a radiomics approach, which obtained a maximum value of 79%. Further, using a radiomics approach it is possible to increase the reading accuracy of radiological characterization of focal and diffuse pattern of MM on standard CT [3].

With specific reference to CT data, the use of artificial intelligence (AI) for the assessment of MM radiomics typically relies on the two-step process illustrated in **Figure 3**:

1. Pattern recognition and property extraction algorithms [36, 37] is applied to either specific bone lesions or the whole skeleton asset in order to extract quantitative descriptors of the impact of the disease on the MM bone structure.

2. Machine learning [38, 39], in either its unsupervised or supervised version, is applied against the descriptors extracted by step 1 in order to both stratify the MM patients on the basis of their CT data characteristics and predict the disease outcome as far as post-transplantation relapse is concerned.

Preliminary results obtained by means of this kind of approach [39] show that MM is associated to an extension of the intra-bone volume for the whole body and that machine learning can identify CT image properties mostly correlating with the disease evolution.

However, the use and validation of radiomics for prognostic purposes in MM is still in progress and several factors have to be considered before assuming radiomics results completely reliable, repeatable and feasible in clinical practice. In general, medical imaging is capable of generating imaging biomarkers, while acquisition and analysis processes are different from frequently used

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comparators like blood or urine biomarkers. This difference is related to the methodology for obtaining the sample. In radiology the acquisition of the sample (i.e., the data set of images) is heterogeneous by design, since complex equipment from different vendors is clinically used. Even with multiple human and technological efforts, standardization of image quality as an input for different imaging biomarkers analysis is difficult and it is not yet clear whether a complete standardization can be realized. Several scientific societies such as the European Society of Radiology and the Radiological Society of North America (RSNA) tried to provide standards for the best possible standardisation at the acquisition level and the minimum requirements for the image analysis software used in imaging biomarkers qualification [22, 23, 40–44]. However, more sophisticated corrective measures could be done by artificial intelligence (AI) based approaches to let complex and deep neural networks learn from the lack of homogeneity in the collected images, both in the DICOM metadata and in the pixel information and adjust the imaging parameters to be analyzed.

3. Conclusions

There is still high variability in the choice between various imaging methods to study MM patients and high variability in image interpretation with suboptimal agreement among readers even in tertiary centres. Therefore, the potential of medical imaging for patients affected by MM is still to be completely unveiled. In the next years, new insights to study MM with medical imaging will derive from AI and radiomics usage in different bone lesions and from the wide implementations of quantitative methods to report CT and MRI. Eventually, medical imaging data can be integrated with the patient's outcomes, with the purpose to find radiological biomarkers for predicting the disease prognostic flow and its therapeutic response.

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Figure 1: MSBDS (Myeloma Spine and Bone Damage Score). Interpretation: High-risk: >10: immediate surgical or radiation oncologist consultation. Medium risk: ≥ 5-10: possible instability and medium risk of pathologic fracture. Low-risk: <5. * Bone abnormalities not sufficient to give high risk scores, if isolated. **1 point for every segment according to MY-RADS (from: Tagliafico AS, Belgioia L, Bonsignore A, Signori A, Formica M, Rossi F, Piana M, Schenone D, Dominietto A. Development and definition of a simplified scoring system in patients with multiple myeloma undergoing stem cells transplantation on standard computed tomography: myeloma spine and bone damage score (MSBDS). Cancer Imaging. 2020 Apr 28;20(1):31. doi: 10.1186/s40644-020-00306-1. PMID: 32345379; PMCID: PMC7189746.)

Location	Points
Junctional Spine (C0-C2, C7-T2,T11-L1,L5-S1)	3
Mobile Spine (C3-C6, L2-L4)	2
Collapse/involvement >50%	3
Collapse < 50%*	2
Posterolateral (facet, pedicle) involvement monolateral	2
Posterolateral (facet, pedicle) bilateral monolateral	3
Spinal Canal involvement	5
Trochanteric region focal lesions <10 mm	2
Femoral neck or entire trochanteric region	5
More 2/3 of bone diameter	3
Focal lesion > 5mm at any site*	1
Diffuse Pattern	1**

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Figure 2: Example of minimal Computed Tomography Technical parameters for lytic lesion detection in multiple myeloma (from: Tagliafico AS, Belgioia L, Bonsignore A, et al. Subspecialty Second-Opinion in Multiple Myeloma CT: Emphasis on Clinically Significant Lytic Lesions. Medicina (Kaunas). 2020;56(4):195. Published 2020 Apr 23. doi:10.3390/medicina56040195)

Number of detector rows*	16 or more up to 128
Minimum Scan coverage*	Skull base to femur
Tube voltage(kV)/time-current product (mAs)	120/50–70, adjusted as clinically needed
Reconstruction convolution kernel	Sharp, high-frequency (bone) and smooth (soft tissue). Middle-frequency kernel for all images are adjusted by the radiologist as deemed necessary
Iterative reconstruction algorithms	Yes (to reduce image noise and streak artefacts)
Thickness*	≤5 mm
Multiplanar Reconstructions (MPRs)	Yes (sagittal, coronal and parallel to long axis of proximal limbs)
Matrix, Rotation time, table speed, pith index	128x128, 0.5 s,24mm per gantry rotation, 0.8

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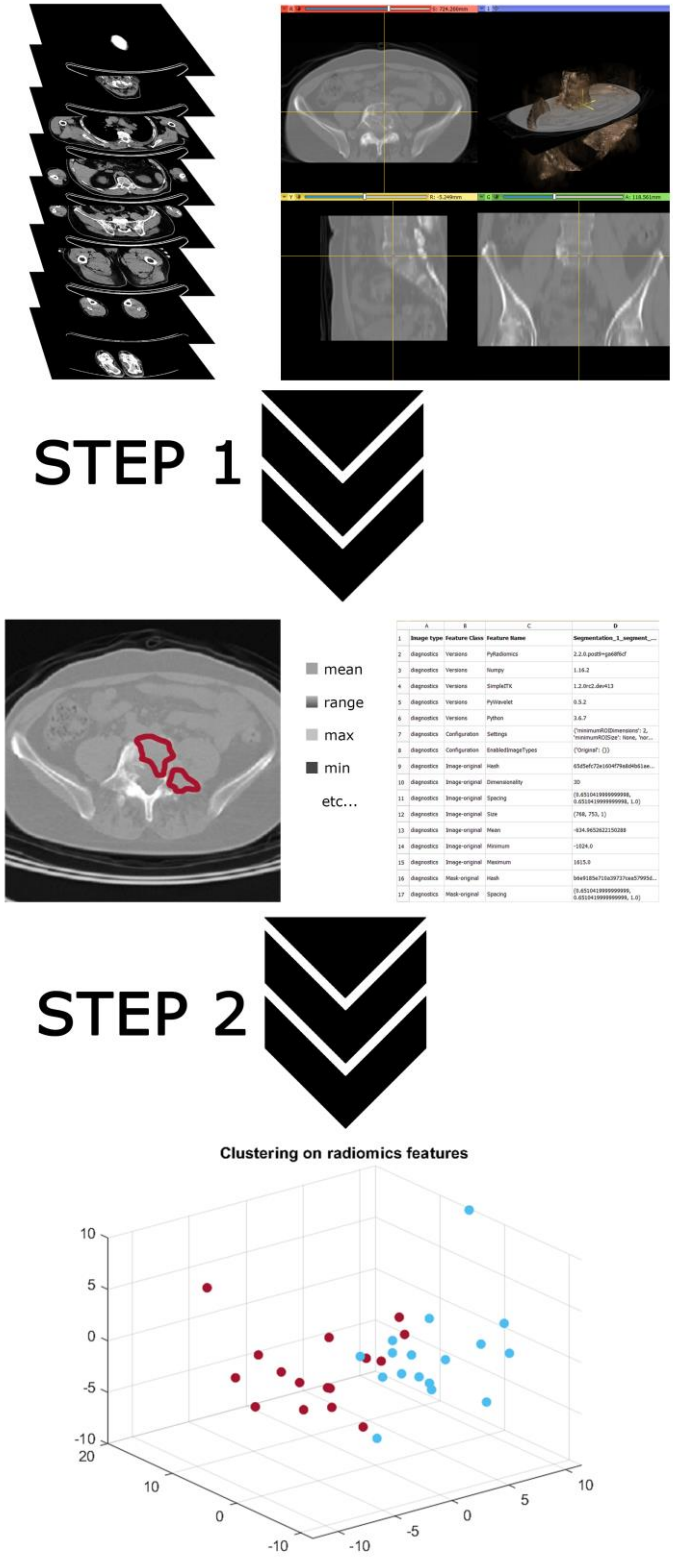
Figure 3. The two-step process of AI-based radiomics. The input data (first row) are fed into a property exctraction algorithm to obtain a set of image features (second row). These features are fed into a machine learning algorithm to obtain patients' stratification (third row).



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