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Research article

Differentiating diffuse from focal pattern on Computed Tomography in multiple myeloma: Added value of a Radiomics approach

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ABSTRACT

Purpose: Focal pattern in multiple myeloma (MM) seems to be related to poorer survival and differentiation from diffuse to focal pattern on computed tomography (CT) has inter-reader variability. We postulated that a Radiomic approach could help radiologists in differentiating diffuse from focal patterns on CT.

Methods: We retrospectively reviewed imaging data of 70 patients with MM with CT, PET-CT or MRI available before bone marrow transplant. Two general radiologist evaluated, in consensus, CT images to define a focal (at least one lytic lesion > 5 mm in diameter) or a diffuse (lesions < 5 mm, not osteoporosis) pattern. N = 104 Radiomics features were extracted and evaluated with an open source software.

Results: The pathological group included: 22 diffuse and 39 focal patterns. After feature reduction, 9 features were different ($p < 0.05$) in the diffuse and focal patterns (n = 2/9 features were Shape-based: MajorAxisLength and Sphericity; n = 7/9 were Gray Level Run Length Matrix (Glrlm)). AUC of the Radiologists versus Reference Standard was 0.64 (95 % CI: (0.49–0.78) p = 0.20. AUC of the best 4 features (MajorAxisLength, Median, SizeZoneNonUniformity, ZoneEntropy) were: 0.73 (95 % CI: 0.58–0.88); 0.71 (95 % CI: 0.54–0.88); 0.79 (95 % CI: 0.66–0.92); 0.68 (95 % CI: 0.53–0.83) respectively.

Conclusion: A Radiomics approach improves radiological evaluation of focal and diffuse pattern of MM on CT.

1. Introduction

Abnormal production of monoclonal immunoglobulin M component of plasma cells and bone marrow increase of plasma cells is the typical characteristic of multiple myeloma (MM). The bone lesions of myeloma are caused by the proliferation of tumor cells from a single clone and the activation of osteoclasts that destroy the bone [1]. Indeed, bone disease reduces patients' quality of life increasing both morbidity and mortality, therefore the role of imaging is crucial in the management of patients with MM. Imaging is important to detect bone lesions requiring immediate start of therapy of follow-up after treatment, to predict the risk of early progression from smoldering MM (SMM) to active disease, to identify sites of extra-medullary disease and to identify sites of bone disease at potential risk of pathologic fractures or neurologic complications [2]. According to recent staging systems for MM, in patients with newly diagnosis, a correct treatment approach and evaluation of prognostic factors rely also on focal lesion identification on Magnetic Resonance Imaging (MRI), Computed Tomography (CT) or PET/CT [3]. Indeed, the role of conventional radiography, the standard of care for many years, is going to be replaced by more sensitive methods. Compared to conventional radiography, PET/CT [4] and whole-body low-dose CT (WBLDCT) are able to detect the presence of active disease in up to 25 %–40 % of cases, according to large retrospective studies [4]. It was demonstrated that the presence of at least one lytic lesion is a negative prognostic factor for patients with MM [5]. In 2014, the International Myeloma Working Group (IMWG) updated the definition of MM including in the definition the presence of at least one lytic lesion detected not only by conventional radiography but also by one of the novel morphologic imaging techniques, such as CT, WBLDCT, or PET/CT; and the presence of more than one FL on MRI [6]. At diagnosis the incorporation of new imaging modalities

(WBLDCT and PET/CT) for accurate diagnostic purposes is recommended with a grade A recommendation [2]. However, there is still considerable heterogeneity in clinical practice regarding imaging usage

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in MM [2] and, as for every radiological techniques, variability among readers could reduce the diagnostic efficacy due to difficulties in differentiating small lesion of approximately 5 mm in diameter typical of a focal pattern with a worse prognosis [3]. Even among expert, agreement in detecting lytic lesions on PET/CT for staging using the Italian myeloma criteria for PET USe (IMPeTUs) criteria was 0.54 (0.41_0.68) using Krippendorff's alpha for lesions probably > 5 mm in diameter [7]. The cutting-edge research topic of Radiomics analysis aim to extract complex data from clinical images to help radiologists and clinicians in both diagnosis and prognosis. [8–10]. We made the hypothesis that Radiomics analysis could help radiologists to unveil imaging characteristic on CT specific of a MM pattern, especially to identify lytic lesions. Therefore, the aim of this study was to assess if a Radiomics approach could improve radiological accuracy in differentiating a focal pattern from a diffuse pattern on CT.

2. Methods

The study was performed in accordance with the current version of the Declaration of Helsinki and the International Conference on Harmonization of Good Clinical Practice Guidelines. Approval from the institutional review board was obtained (003REG2019). According to our standard procedure, all patients signed a written informed consent form, encompassing the use of anonimized data for retrospective research purposes, before CT examination. Radiomic analysis was applied to CT data collected in the clinical workup and did not influence patient care in any way. According to the nature of the study, STARD checklist was followed as appropriate [11].

2.1. Study design, inclusion criteria

Our retrospective study included 70 consecutive patients (mean age, 60 years ± 9.2 [standard deviation]; range, 35–88 years) admitted to the IRCCS Policlinico San Martino Hospital (Genoa, Italy) because they were suspected of having MM in the last five years. Inclusion criteria were pre-transplant total-body CT available and retrievable from the Hospital Picture archiving and communication system (PACS) or available from outpatient clinic with minimal technical standard. Minimal and standard technical inclusion parameters for CT are reported in Table 1.

All CT scans were read in consensus by two groups of radiologists.

The first group included two general radiologists (G.S. 15 years of experience, A.C. 1 year of experience) one of them, the senior, with extensive track record in CT reporting and musculoskeletal radiology. The two general radiologists were blinded to the diagnosis of the patients and they were asked to assess if the CT pattern was diffuse or focal (Fig. 1).

The second group included two experienced radiologists (A.T. 12 years of experience, F.R. 5 years of experience) expert in musculoskeletal Radiology and bone image interpretation, one of them with European Diploma and Member of tumour sub-committee of the European Society of Musculoskeletal Radiology. After six months to avoid biases, the two expert radiologists worked in consensus aware of the diagnosis of MM and able to check follow-up radiological evaluation to assess if the pattern on CT had to be considered diffuse or focal, and their consensus was the reference standard of our study. Considering that biopsy is not available for all suspicious area identified on CT, radiologists' consensus could be considered the best feasible reference standard, as already done in literature [12].

2.2. Test methods

2.2.1. Index test1 - Computed Tomography

Diffuse bone marrow infiltration in the skeleton was recorded according to the criteria proposed by Staebler (lesions < 5 mm, not osteoporosis) [13,14]. Focal pattern was defined as the presence of at least one > 5 mm of focal or lytic lesion in the axial skeleton (ie, spine and sacral bone) or extra-axial skeleton (ie, all other parts of the skeleton). Soft tissue lesions were not considered because outside the scope of the study. Lesions in typical locations for degenerative changes and osteoporotic changes were not counted. The presence of at least one focal or lytic lesion was considered clinically relevant because it is a highly significant adverse prognostic factors for patients with MM, and recored [5].

2.2.2. Index test2 - radiomics analysis

Radiomics analysis was performed on all CT images suspected of having pathology within

manually selected regions of interest (ROIs) including all the bone of axial and extra-axial skeleton on single slices where the bone was visually judged different from a normal bone by radiological assessment. All images were read and processed in the raw Digital Imaging and Communications in Medicine (DICOM) format. Raw imaging data underwent pre-processing to discriminate the signal from the noise. ROIs were placed by two researchers (A.T. and F.R.) expert in quantitative image analysis (9 and 3 years of experience). Theoretically, ROIs placement would have been independent from the kind of bone lesion present on CT. From CT images, we extracted 104 image features using an open-source software platform for medical image informatics, image processing, and three-dimensional visualization (3D Slicer 4.10; www.slicer.org) built over two decades through support from the National Institutes of Health and a worldwide developer community and largely used in literature [15]. 3D-Slicer can be employed for quantitative image feature extraction and image data mining research in large patient cohorts [15]. Definitions, descriptions and subdivisions into classes of Radiomics features are available in literature [16]. We computed a total of n = 104 features per patient. This feature initial pool was subjected to the selection procedure. From the total of n = 104 features, z-score normalization was applied making the range of the features more uniform and removing features that had high similarity with other features. Therefore, we selected strongly correlated features (P value below 0.05) and eliminated the redundancies as normally done in literature [17].

Mean time for single patient Radiomics analysis was calculated with a commercially available stopwatch, including the time to download images, perform image adjustment and analysis and finally data collection in the database. Radiologists were well trained in the usage of Radiomics tools and probably reduced the reading time.*Statistical*

Table 1
Minimal* and standard Computed Tomography Technical parameters for inclusion.

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 artifacts)
Thickness*	≤ 5 mm
Multiplanar Reconstructions (MPRs)	Yes (sagittal, coronal and parallel to long axis of proximal limbs)
Matrix, Rotation time, table speed, pith index	128 × 128, 0.5 s,24 mm per gantry rotation, 0.8

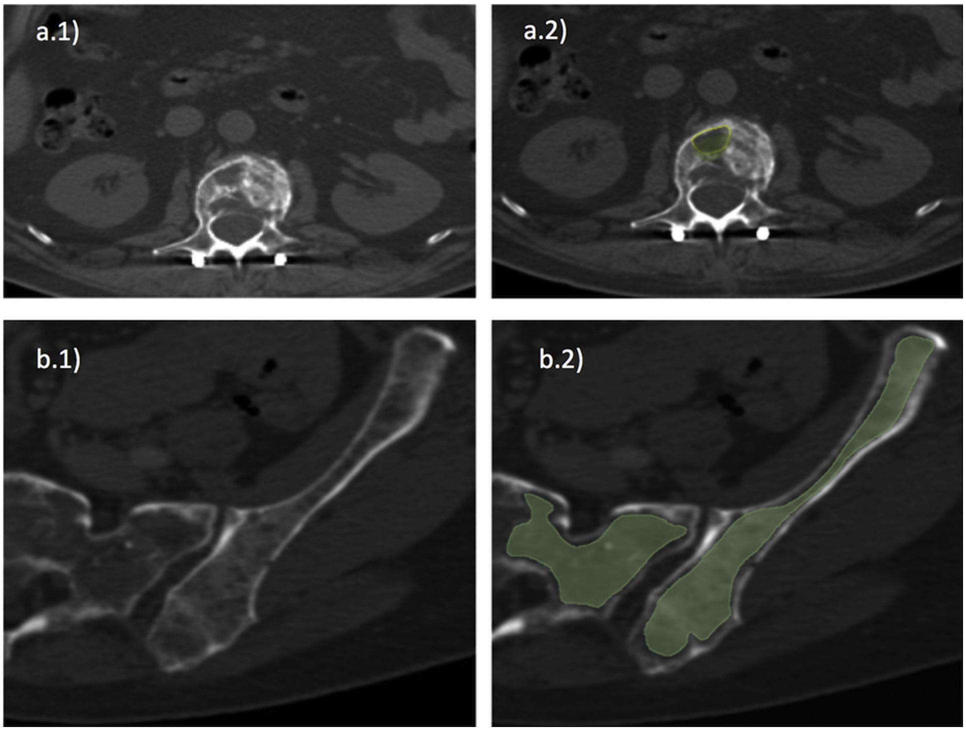

Fig. 1. Examples of focal and diffuse bone patterns on CT.
In a.1) graphical example of focal lytic lesion (> 5 mm) of the spine on CT. In a.2) the same lesion with manually selected regions of interest (ROIs) in green using 3D Slicer 4.10. In b.1) graphical example of diffuse bone pattern lesion of the left hemi-sacrum and left iliac bone. In b.2) the same lesion with manually selected regions of interest (ROIs) in green using 3D Slicer 4.10.

Analysis

Inter-observer agreement in differentiating diffuse from focal pattern was estimated among the two groups of radiologists to confirm the need of more accurate (Radiomics) measurements to improve CT interpretation. For research purposes Cronbach's alpha was considered acceptable if between 0.7 and 0.8. Comparison of Radiomics features of diffuse and focal pattern was done with non-parametric tests (Mann-Whitney *U* test for unpaired data with 1000 bootstraps samples) considering a p value of 0.05 as statistically significant; then feature reduction was done to avoid over-fitting. Accuracy was measured using receiver operating characteristic (ROC) analyses to estimate the area under the curve (AUC) and compare Radiologists and Radiomics evaluation against reference standard using statistical software, p values below 0.05 were considered statistically significant.

Kaplan–Meier analysis was performed to generate progression and survival curves according to diffuse or focal pattern. Time to event and survival between groups was compared with the two-tailed log-rank test. Statistical tests were done using statistical software (STATA MP, StataCorp, 4905 Lakeway Dr, College Station, TX, USA and MedCalc).

Table 2
Summary of n = 16/104 Radiomics features resulted to be different in focal and diffuse pattern. P values < 0.05 are considered statistically significant.

Feature Name	P value
MajorAxisLength	,030
Sphericity	,012
SmallDependenceLowGrayLevelEmphasis	,032
ZoneVariance	,006
Correlation	,041
SumEntropy	,031
Skewness	,004
RunEntropy	,001
Median	,001
LowGrayLevelEmphasis	,013
Energy	,024
ShortRunLowGrayLevelEmphasis	,023
LowGrayLevelRunEmphasis	,045
SizeZoneNonUniformity	,001
LowGrayLevelZoneEmphasis	,038
SmallAreaLowGrayLevelEmphasis	,038

3. Results

N = 9/70 did not have any CT available before bone marrow transplant and were excluded, therefore the study group included 60 patients: 27 men (mean age, 59,7 years ± 9,1; range, 35–72 years) and 34 women (mean age, 61,7 years ± 9,2; range, 49–88 years).

Inter-observer agreement in differentiating diffuse from focal pattern among the two groups of radiologists resulted to be 0.57 (95 % Confidence Intervals: 0.32–0.64), $p < 0.03$.

After feature reduction and selection, n = 16/104 (15 %) of Radiomics features were different in focal and diffuse pattern (Table 2).

AUC of the radiologists' evaluation and AUC of the best four features (MajorAxisLength; Median; SizeZoneNonUniformity; ZoneEntropy) resulted to be between 0.642 (95 % Confidence Intervals: 0.494 to 0.789) and 0.790 (0.665 to 0.916) as shown in Fig. 2 and Table 3. The lowest value of AUC belonged to radiologist's evaluation.

Mean time for single patient Radiomics analysis resulted to be 1 h per patient ± 20 min. The time to read the CT scan without Radiomics was 10 min.

Kaplan-Meier plots for relapse of patients who had focal pattern compared with patients who had diffuse pattern demonstrated that the median time to progression was significantly worse for patients with a focal pattern (Fig. 3).

4. Discussion

The present study demonstrated that a Radiomics approach on standard CT images of patients with multiple myeloma acquired before transplantation strongly improves accuracy in differentiating focal from diffuse patterns. Indeed, accuracy in terms of area under the curve of Radiologists compared to the reference standard was lower (64 %) than accuracy calculated using a Radiomics approach which obtained a maximum value of 79 %. The possibility to increase diagnostic accuracy in differentiating focal from diffuse pattern on standard CT images of patients with multiple myeloma is clinically relevant for several

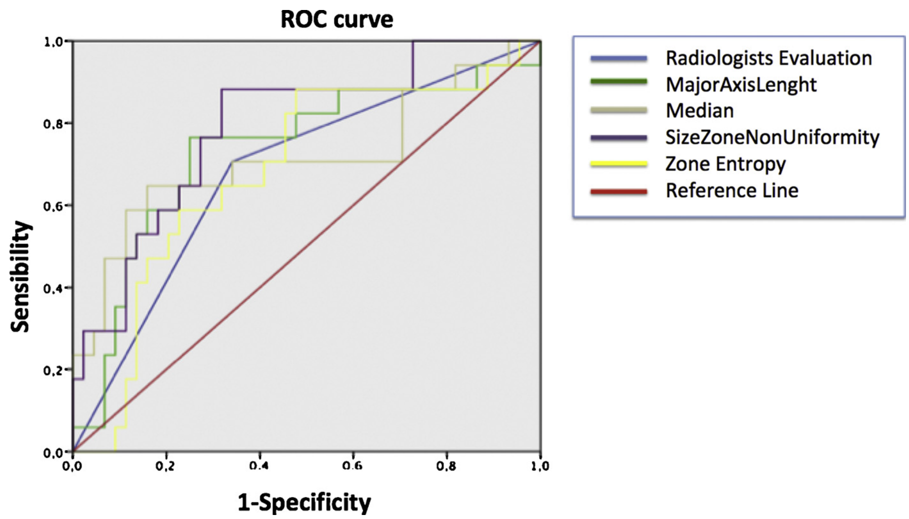

Fig. 2. The Area Under the Curve (AUC) of the radiologists' evaluation and the AUC of the best four features.

Table 3
Area Under the Curve (AUC) of the best four features. P values < 0.05 are considered statistically significant.

Feature Name	AUC	P value	95 % CI (lower limit)	95 % CI (upper limit)
MajorAxisLength	0,733	0,005	0,580	0,885
Median	0,715	0,010	0,549	0,881
SizeZoneNonUniformity	0,790	0,010	0,665	0,916
ZoneEntropy	0,682	0,029	0,531	0,833

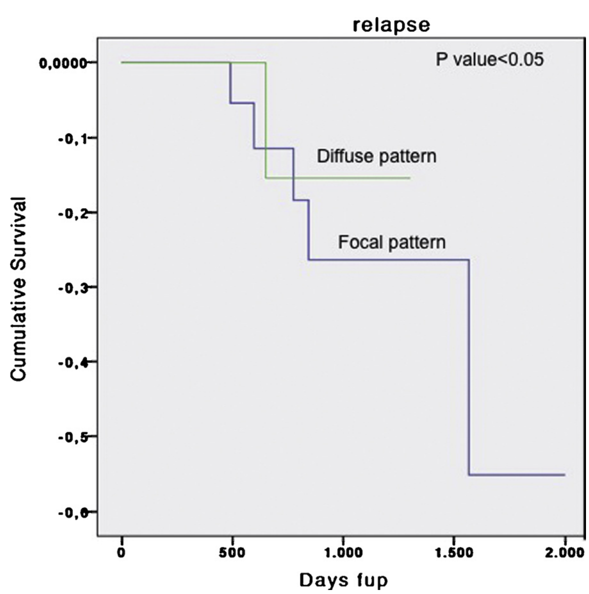

Fig. 3. Kaplan Meyer plot for relapse of patients with focal pattern (blue line) compared with patients with diffuse pattern (green line).

reasons.

First, new staging systems suggested to replace standard radiography with more sensitive methods such as CT, due to its higher capability of differentiate bone inner texture [2,7]. Therefore, more patients will undergo CT for staging of MM [2].

Second, several studies correlate pattern allocation with prognostic value [18]. Although MRI can differentiate up to five different patterns of plasma cell infiltration, including normal appearance, focal involvement, homogeneous diffuse infiltration, diffuse infiltration with additional focal lesions and variegated or salt-and-pepper pattern, CT can also identify patterns similarly to MRI [18] and CT is well suited for small (below 5 mm) focal bone lesions due to high spatial resolution capabilities [18].

Third, the low agreement between reader in staging patients affected by multiple myeloma is well known in literature [8], as confirmed by our study. Indeed, we found that the agreement among radiologists in differentiating between focal and diffuse patters was 0.57 (95 % Confidence Intervals: 0.32–0.64), $p < 0.03$ which is below the values considered acceptable for research and clinical purposes. Nanni et al. [7], calculating inter-observer variability with Krippendorff's alpha, found values of 0.56 to 0.58 indicating only moderate agreement for focal lesions. Data reported in the study by Nanni et al. [7] are consistent with our results and underlines the need of improvement to correctly identify patients with a focal pattern. In addition, the use of slight different modalities of agreement calculation such as Cronbach's alpha in the present study versus Krippendorff's alpha which automatically corrects for a casual agreement between reviewers, is not sufficient to stop seeking for better methods, such as Radiomics, to improve focal pattern recognition.

Nowadays, there is still a certain lack of agreement about the exact definition of a diffuse imaging pattern [18] In our study, we defined the presence of a focal pattern as the presence of at least one > 5 mm of focal lytic lesion in the axial skeleton or extra-axial skeleton because it has been demonstrated that the presence of more than one focal lesion could be an optimal cut-off point: indeed patients with greater than one focal lesions had significantly shorter progression-free survival than those without [5], and our results confirmed the worse prognosis for patients with focal pattern.

Concerning technical issues to be discussed, the present study has several strengths: we used clinically available CT images collected in the normal clinical workup without influencing patient care in any way and we used a free open source software for Radiomics assessment of involved bones. Finally, Radiomics assessment was made in a Radiological environment with significant expertise in quantitative imaging assessment and software development [10,19].

Concerning Radiomics feature assessment, we found that 15 % of features (16/104) were different in diffuse and focal patterns reflecting a significant difference in bone phenotype in patients with the same disease.

Among the limitations of the present study we acknowledge the retrospective nature which did not allow a perfect timing between CT acquired before transplantation and diagnosis. In addition, the evaluation of Radiomics features was made only with one software and we do not know if the usage of other software could introduce variability in feature assessment. Finally, we did not correlate CT patterns with staging before transplant, but Kaplan-Meyer results confirmed the worse prognosis for patients with focal pattern.

In conclusion, in this work we have proven that, in multiple myeloma patients, differentiation between focal and diffuse pattern on CT is difficult, but a Radiomic approach strongly improves standard radiological evaluation with implications for prognosis, patient stratification and therapeutical choices.

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