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RADIOLOGIC DIAGNOSIS OF BONE CHANGES IN MULTIPLE MYELOMA

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Abstract. Multiple myeloma (MM) is a clonal plasma cell neoplasm frequently accompanied by destructive bone disease, which constitutes a major source of morbidity through pain, pathologic fractures, hypercalcemia, and spinal cord compression. Bone involvement results from uncoupled remodeling characterized by heightened osteoclast activity and suppressed osteoblast function, producing purely osteolytic lesions without sclerotic reaction. This cross-sectional study assessed the spectrum of radiologic bone changes in 68 patients with newly diagnosed or suspected MM at a tertiary medical center in Tashkent, Uzbekistan. Conventional skeletal survey identified bone abnormalities in 72.1% of cases, with classic "punched-out" lytic lesions most prevalent in the skull (55.9%), vertebrae (50.0%), and pelvis (41.2%). Whole-body low-dose CT (WBLDCT), performed in a subset of 42 patients, detected additional osteolytic lesions in 21.4% of those with negative or equivocal skeletal surveys. MRI demonstrated focal or diffuse marrow infiltration patterns in 80% and 40% of examined cases, respectively, often before overt cortical destruction. A significant positive correlation was observed between the number of lytic lesions and Durie-Salmon stage ($r = 0.54$, $p < 0.01$), as well as negative correlations with hemoglobin levels ($r = -0.58$, $p < 0.01$) and positive correlations with β2-microglobulin ($r = 0.51$, $p < 0.01$). These results emphasize the limitations of traditional skeletal survey and the superior sensitivity of modern whole-body imaging techniques (WBLDCT and MRI) for accurate detection and staging of bone disease in MM. Early radiologic diagnosis using advanced modalities is critical for risk stratification, prevention of skeletal-related events, and optimization of therapeutic strategies, particularly in resource-variable settings.

Keywords: Multiple myeloma, osteolytic bone lesions, punched-out lesions, skeletal survey, whole-body low-dose CT, magnetic resonance imaging, bone marrow infiltration, myeloma bone disease

Introduction. Multiple myeloma (MM) represents approximately 10% of all hematologic malignancies and is defined by the clonal proliferation of malignant plasma cells within the bone marrow, resulting in monoclonal protein production and end-organ damage. The clinical presentation is classically summarized by the CRAB criteria: hyperCalcemia, Renal failure, Anemia, and Bone lesions. Bone disease is one of the most frequent and debilitating manifestations, affecting 70–90% of patients at the time of diagnosis and approaching 100% during the disease course. It contributes significantly to reduced quality of life through

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intractable bone pain, pathologic fractures, vertebral collapse with spinal cord compression, hypercalcemia, and increased mortality risk.

The underlying pathophysiology involves profound disruption of normal bone remodeling. Myeloma cells secrete cytokines such as RANKL, DKK-1, and other factors that stimulate osteoclastogenesis while simultaneously inhibiting osteoblast differentiation and activity. This uncoupling produces purely osteolytic lesions without accompanying sclerosis or periosteal reaction—a radiographic hallmark that distinguishes MM bone disease from many metastatic processes. Lesions typically require 30–50% trabecular bone loss before becoming visible on conventional radiographs, explaining the historical underestimation of disease burden by skeletal survey.

For decades, the conventional skeletal survey (plain radiography of the axial skeleton and proximal long bones) served as the standard imaging modality. However, its low sensitivity, prolonged acquisition time, patient discomfort, and inability to detect early marrow infiltration have prompted a paradigm shift. Current International Myeloma Working Group (IMWG) recommendations advocate whole-body low-dose CT (WBLDCT) as the preferred first-line modality for detecting osteolytic lesions (≥5 mm), with MRI reserved for cases without clear myeloma-defining events to identify focal marrow lesions, and PET/CT for assessing disease activity and treatment response.

Despite these advances, dedicated radiological studies describing the full spectrum of bone changes in MM cohorts, especially comparing conventional and advanced modalities in the same population, remain limited in many regions. This study aimed to (1) characterize the prevalence and patterns of radiologic bone changes in patients with MM using conventional skeletal survey, WBLDCT, and MRI; (2) evaluate the incremental diagnostic yield of advanced imaging over traditional radiography; and (3) correlate imaging findings with clinical parameters of disease severity, including anemia and staging. By highlighting these radiologic patterns, the study seeks to underscore the importance of modern imaging in timely diagnosis, accurate staging, and prevention of skeletal complications in MM.

Literature review. Multiple myeloma (MM) is a clonal plasma cell neoplasm characterized by bone marrow infiltration, monoclonal protein production, and frequent end-organ damage, with bone disease representing one of the most common and debilitating features. Bone involvement occurs in 70–90% of patients at diagnosis and approaches nearly 100% during the disease course, manifesting as severe bone pain, pathologic fractures, vertebral collapse with spinal cord compression, hypercalcemia, and increased mortality risk. The pathophysiology of myeloma bone disease involves profound uncoupling of normal bone remodeling: malignant plasma cells and the bone marrow microenvironment secrete factors such as RANKL, MIP-1α, and DKK-1 that markedly stimulate osteoclast activity while simultaneously inhibiting osteoblast differentiation and function through Wnt pathway suppression. This results in purely osteolytic lesions without reactive sclerosis or periosteal new bone formation—a radiographic hallmark that distinguishes MM from many other metastatic bone diseases.

For decades, the conventional skeletal survey (whole-body plain radiography) served as the standard imaging modality for detecting bone lesions in MM. Typical findings include multiple well-defined “punched-out” lytic lesions, most commonly affecting the axial skeleton (skull with “raindrop” or “pepper-pot” appearance, vertebrae, pelvis, and ribs), endosteal scalloping, cortical thinning or breakthrough, and diffuse osteopenia with pathologic fractures. However, conventional radiography has well-documented limitations: it requires 30–50% trabecular bone mineral loss before a lesion becomes detectable, leading to low sensitivity (false-

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negative rates of 30–70%), prolonged acquisition time, patient discomfort, and frequent underestimation of disease burden, particularly in the spine and pelvis.

Advances in cross-sectional imaging have largely superseded skeletal survey. The International Myeloma Working Group (IMWG) now recommends whole-body low-dose computed tomography (WBLDCT) as the preferred first-line modality for detecting osteolytic bone lesions (≥5 mm in size) due to its superior sensitivity, rapid acquisition (30–40 seconds), wide availability, and ability to evaluate the entire skeleton with radiation doses comparable to or only slightly higher than skeletal survey. Multiple studies demonstrate that WBLDCT detects significantly more osteolytic lesions than conventional radiography, identifying additional lesions in 20–25% of patients previously classified as having negative or equivocal skeletal surveys and reclassifying up to 22% of smoldering MM cases as active MM.

Magnetic resonance imaging (MRI), particularly whole-body or spine/pelvis protocols using T1-weighted, T2-weighted fat-suppressed, and STIR sequences, offers the highest sensitivity for early bone marrow infiltration before cortical destruction occurs. MRI can reveal focal lesions (≥5 mm), diffuse marrow replacement (low T1 signal), or variegated "salt-and-pepper" patterns. It is especially valuable for assessing spinal complications, differentiating benign from malignant vertebral fractures, and evaluating patients with suspected smoldering MM when WBLDCT is negative. Studies show MRI detects bone involvement in 40–50% of patients with normal skeletal surveys and provides superior detection of diffuse marrow patterns compared with CT.

18F-FDG PET/CT combines metabolic and anatomic information and is particularly useful for assessing disease activity, extramedullary involvement, and treatment response, though it requires lytic destruction visible on the CT component to fulfill IMWG myeloma-defining event criteria. Current IMWG consensus guidelines advocate a stepwise approach based on availability and resources: WBLDCT as first-line for bone lesion detection, with MRI or PET/CT as second-line when WBLDCT is negative or inconclusive, or for specific clinical questions such as smoldering disease risk stratification or response assessment.

Despite these technological advances, dedicated radiological studies comprehensively describing the spectrum of bone changes using both conventional and modern modalities in the same patient cohort remain relatively limited, especially in diverse geographic settings. The present study addresses this gap by systematically evaluating conventional skeletal survey, WBLDCT, and MRI findings in patients with confirmed or suspected MM, with the aims of characterizing prevalence and patterns of radiologic bone involvement, quantifying the incremental diagnostic yield of advanced imaging, and correlating imaging features with clinical and laboratory markers of disease severity.

Methods Study Design and Setting. This prospective cross-sectional study was conducted at a tertiary multi-profile medical center in Tashkent, Uzbekistan, between January 2025 and December 2025. The institutional review board approved the protocol, and written informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

Participants Sixty-eight adult patients (aged 40–75 years) with confirmed or highly suspected MM according to the International Myeloma Working Group (IMWG) criteria were consecutively enrolled. Inclusion required bone marrow plasmacytosis ≥10% (or biopsy-proven plasmacytoma) plus monoclonal protein detection and/or evidence of end-organ damage. Patients with solitary plasmacytoma, monoclonal gammopathy of undetermined significance (MGUS), smoldering MM without imaging evaluation, or prior anti-myeloma therapy were excluded.

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Radiological Assessment All patients underwent a standardized conventional skeletal survey comprising digital radiographs of the skull, entire spine, pelvis, chest, humeri, and femora. In 42 patients, whole-body low-dose CT (WBLDCT) was performed using a standardized low-dose protocol (120 kVp, 40–60 mAs, slice thickness 2–3 mm). MRI of the spine and pelvis (or whole-body MRI when feasible) was conducted in 35 patients on a 1.5T or 3T scanner with T1-weighted, T2-weighted fat-suppressed, and STIR sequences.

Two board-certified radiologists with experience in oncologic imaging, blinded to clinical and laboratory data, independently reviewed all studies. Key diagnostic criteria included:

- **Punched-out lytic lesions**: well-defined, round or ovoid lucent areas ≥5 mm in diameter without sclerotic margins
- **Endosteal scalloping**, cortical thinning, or breakthrough
- **Diffuse osteopenia** with or without vertebral compression fractures
- **Raindrop or pepper-pot skull** appearance
- On MRI: focal lesions (≥5 mm), diffuse marrow replacement (low T1 signal), or variegated ("salt-and-pepper") patterns

Lesion number, size, distribution (axial vs. appendicular), and complications (pathologic fractures, soft-tissue extension, spinal instability) were documented. Interobserver agreement was quantified using Cohen's kappa coefficient.

Clinical and Laboratory Data Demographic information, presenting symptoms (bone pain, fatigue, neurologic deficits), and laboratory parameters—including hemoglobin, serum calcium, creatinine, serum/urine protein electrophoresis, free light chain ratio, β2-microglobulin, and bone marrow biopsy results—were recorded. Disease staging was performed using the Durie-Salmon system.

Statistical Analysis Data were analyzed using SPSS version 26.0. Continuous variables are expressed as mean ± standard deviation; categorical variables as frequencies and percentages. Associations between radiological findings and disease severity parameters were evaluated using chi-square tests, independent t-tests, and Pearson's correlation coefficients. A p-value < 0.05 was considered statistically significant.

Results. The study cohort comprised 39 males (57.4%) and 29 females (42.6%), with a mean age of 58.3 ± 9.7 years. Bone pain was the most common presenting symptom (76.5%), followed by fatigue (82.4%). Laboratory abnormalities included anemia in 82.4%, hypercalcemia in 29.4%, and renal impairment in 36.8%. According to Durie-Salmon staging, 22.1% were Stage I, 33.8% Stage II, and 44.1% Stage III.

Conventional skeletal survey revealed radiologic evidence of bone involvement in 49 patients (72.1%). The predominant pattern was multiple punched-out osteolytic lesions, with the highest frequency in the skull (raindrop appearance in 38 patients, 55.9%), vertebrae (50.0%, often with compression fractures), pelvis (41.2%), and ribs (32.4%). Diffuse osteopenia with fractures was noted in 47.1%, and endosteal scalloping or cortical destruction in 39.7%.

WBLDCT, performed in 42 patients, identified additional or more numerous lytic lesions in 9 cases (21.4%) where the skeletal survey was negative or equivocal, particularly in the spine, pelvis, and scapulae. MRI, available for 35 patients, showed focal marrow lesions in 28 cases (80.0%) and diffuse infiltration in 14 cases (40.0%), including several patients with normal or subtle radiographic findings.

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Table 1 Radiological Bone Changes in Patients with Multiple Myeloma (N = 68)

Radiological Finding	Frequency n (%)	Most Common Sites	Associated with Advanced Stage (Durie-Salmon II/III) (%)
Any bone abnormality on skeletal survey	49 (72.1)	Skull, spine, pelvis	81.6
Punched-out lytic lesions	45 (66.2)	Skull (55.9%), vertebrae	84.4
Diffuse osteopenia with vertebral fractures	32 (47.1)	Thoracic and lumbar spine	75.0
Endosteal scalloping / cortical destruction	27 (39.7)	Ribs, long bones	77.8
Additional lesions detected on WBLDCT	9/42 (21.4)	Spine, pelvis, scapulae	100.0
Focal marrow lesions on MRI	28/35 (80.0)	Spine and pelvis	85.7
Diffuse marrow infiltration on MRI	14/35 (40.0)	Axial skeleton	92.9

Note. Interobserver agreement was excellent (Cohen's $\kappa = 0.89$). Advanced stage refers to Durie-Salmon Stage II or III.

Patients with a higher number of lytic lesions demonstrated significantly lower mean hemoglobin levels (9.2 ± 1.6 g/dL vs. 11.4 ± 1.3 g/dL, $p < 0.001$) and higher β2-microglobulin. Pearson correlation confirmed a moderate positive association between lesion burden and Durie-Salmon stage ($r = 0.54$, $p < 0.01$), negative correlation with hemoglobin ($r = -0.58$, $p < 0.01$), and positive correlation with β2-microglobulin ($r = 0.51$, $p < 0.01$).

Discussion. This study confirms that osteolytic bone disease is a dominant radiologic feature in multiple myeloma, detectable by conventional skeletal survey in over 70% of patients at diagnosis. The classic "punched-out" lesions without sclerotic borders or periosteal reaction reflect the unique biology of myeloma-induced uncoupled bone remodeling. Predominance in the axial skeleton aligns with sites of persistent red marrow in adults.

Conventional radiography, while widely available and low-cost, has well-documented limitations: it requires substantial bone mineral loss (30–50%) for lesion visibility and frequently underestimates disease extent, especially in the spine and pelvis. In this cohort, WBLDCT provided incremental value by identifying additional lesions in 21.4% of cases with negative skeletal surveys, consistent with multicenter data showing that 20–25% of patients classified as smoldering MM on radiography actually harbor lytic disease on CT, reclassifying them as active MM.

MRI proved highly sensitive for detecting bone marrow infiltration before cortical destruction occurs, identifying focal or diffuse patterns that guide risk stratification in early disease. These findings support current IMWG recommendations positioning WBLDCT as the first-line modality for bone disease assessment, with MRI particularly useful when no osteolytic lesions are evident on CT or when evaluating smoldering MM.

The observed correlations between radiologic lesion burden and laboratory markers of disease severity (anemia, β2-microglobulin, staging) reinforce the prognostic significance of comprehensive imaging. Early detection of bone involvement enables timely initiation of

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bisphosphonates or denosumab, radiation therapy for symptomatic sites, and surgical stabilization when indicated, potentially reducing skeletal-related events.

Conclusion. Radiologic evaluation plays a pivotal role in the diagnosis, staging, and management of bone changes in multiple myeloma. Although conventional skeletal survey remains accessible, it significantly underestimates the extent of osteolytic disease and marrow infiltration. Whole-body low-dose CT offers superior detection of lytic lesions with practical advantages in speed and patient comfort, while MRI excels at revealing early bone marrow involvement. Integrating these modern imaging techniques according to IMWG guidelines enhances diagnostic accuracy, enables precise risk stratification, and facilitates timely interventions to prevent skeletal complications. In resource-limited environments, a stepwise imaging approach—beginning with skeletal survey or WBLDCT and escalating to MRI when needed—optimizes clinical outcomes. Greater awareness and adoption of advanced radiologic modalities in the workup of suspected MM have the potential to reduce diagnostic delay, improve staging accuracy, and ultimately decrease the substantial morbidity associated with myeloma bone disease.

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