







Investigation of the radiological techniques to detect osteolytic lesions, fractures, and osteoporosis in multiple myeloma patients

Multiple myelom hastalarında osteolitik lezyon, fraktür ve osteoporoz tespitinde kullanılan radyolojik yöntemlerin incelenmesi

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ABSTRACT

Aim: Multiple myeloma is a malignancy of clonal plasmacytes. Osteolytic lesions represent a criterion for symptomatic myeloma and are associated with bone loss, pathological fractures, and osteoporosis. Skeletal surveys with other sophisticated techniques and dual-energy x-ray absorptiometry (DEXA) are used to screen lytic lesions, and bone mineral loss, respectively. Here, we aimed to investigate the rates of detection regarding osteolytic lesions and bone mineral loss by several imaging techniques.

Materials and Methods: The study was carried out in Aydın Adnan Menderes University Hospital/Turkey, between the years 2004- 2020. Three-hundred and ten symptomatic myeloma patients were screened retrospectively. The results of radiological techniques were recorded. The detection rate of osteolytic lesions, fractures, and plasmacytomas by imaging techniques, as well as the detection rate of bone mineral loss with DEXA were recorded. Also, the relationship between the detected lytic lesions and gender, myeloma type, and the sensitivity and specificity of DEXA to detect osteoporosis in cases with lytic lesions were investigated.

Results: Skeletal survey and PET-CT detected lytic lesions in 71.3% and 81.2% of patients, respectively. PET-CT had a sensitivity of 96.1% and specificity of 90.6% to detect lytic lesions. MRI was only used for patients with suspicious fractures and detected them for all patients who underwent MRI. The osteoporosis rate was 83.1% for 113 patients who underwent DEXA. No association was detected between lytic lesions and gender/myeloma type. The sensitivity and specificity of BMD-DEXA to detect osteoporosis among patients who have lytic lesions were 85.3% and 23.5%, respectively.

Conclusion: Our study demonstrated that osteolytic lesions are not correlated with gender or myeloma type. PET-CT is a sensitive and specific method for detecting osteolytic lesions. Although DEXA is sensitive, its specificity is limited in patients with lytic lesions.

Keywords: Bisphosphonates; multiple myeloma; osteoclasts; osteoporosis; bone loss.

ÖZ

Giriş: Multipl myelom, klonal plazma hücrelerinin bir malignitesidir. Osteolitik lezyon varlığı, semptomatik myelom için bir tanı kriteri olarak kabul edilmektedir. Ayrıca, kemik kaybı, patolojik kırıklar ve osteoporoz ile ilişkilidir.

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Litik lezyon varlığı ve kemik mineral kaybını saptamak için çeşitli görüntüleme yöntemleri ve çift enerjili x-ışını absorpsiyometrisi (DEXA) kullanılır. Bu çalışmada görüntüleme yöntemleri ve DEXA ile osteolitik lezyonların ve kemik mineral kaybının saptanma oranlarının araştırılması amaçlanmıştır.

Gereç ve Yöntem: Bu çalışma 2004-2020 yılları arasında Aydın Adnan Menderes Üniversitesi Hastanesi/Türkiye'de gerçekleştirildi. Üç yüz on semptomatik myelom hastası retrospektif olarak incelendi. Osteolitik lezyon, fraktür ve plazmasitomların görüntüleme yöntemleriyle tespit oranı ve ayrıca DEXA ile kemik mineral kaybı saptama oranı kaydedildi. Ayrıca tespit edilen litik lezyonlar ile cinsiyet, myelom tipi arasındaki ilişki ve litik lezyon saptanan olgularda DEXA'nın osteoporozu saptama duyarlılığı ve özgüllüğü araştırıldı.

Bulgular: Litik lezyonlar, direkt grafi ve PET-BT ile hastaların sırasıyla %71,3'ünde ve %81,2'sinde saptadı. PET-BT'nin litik lezyonları saptamada duyarlılığı %96,1 ve özgüllüğü %90,6 idi. MR görüntülemesine, sadece fraktür şüphesi olan hastalarda başvuruldu ve MR çekilen tüm hastalarda fraktür tespit edildi. DEXA çekilen 113 hastada osteoporoz oranı %83,1 idi. Litik lezyon varlığı ile cinsiyet/myelom tipi arasında herhangi bir ilişki saptanmadı. Osteolitik lezyon saptanan olgularda DEXA'nın osteoporozu saptamadaki duyarlılığı %83,3, özgüllüğü %23,5 olarak bulundu.

Sonuç: Çalışmamız, osteolitik lezyonların cinsiyet veya myelom tipi ile korele olmadığını göstermiştir. PET-BT, osteolitik lezyonları saptamak için hassas ve spesifik bir yöntemdir. DEXA, osteoporozu saptamada duyarlı bir yöntem olmasına rağmen; özgüllüğü, litik lezyonları olan hastalarda sınırlı bir değere sahiptir.

Anahtar Sözcükler: Bisfosfonatlar; multipl myelom; osteoklast; osteoporoz; kemik kaybı.

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INTRODUCTION

Multiple myeloma (MM) is a malignancy of clonal plasma cells, accumulating in the bone marrow and/or extramedullary tissues. It is a disease of the elderly and the median age of patients at initial diagnosis is 65(1). Osteolytic bone lesions are considered a myeloma-defining event and are thought to occur due to the imbalance between the activity of osteoclasts and osteoblasts. Osteoclast activation is a result of clonal plasma cell-osteocyte interactions, which causes the stimulation of the NOTCH signaling pathway and an increase in the receptor activator of NFκB ligand (RANKL) / Osteoprotegerin(OPG) ratio (1, 2). Ninety percent of patients develop bone lesions over the course of the disease (3). Osteolysis is a significant issue in MM because it causes fractures, spinal cord compression, and hypercalcemia (4) Conventional radiography (CR) is the most common and easy modality with a relatively low sensitivity to detect osteolytic bone lesions. Recently, to increase detection capacity; sophisticated cross-sectional techniques such as 18F-fluorodeoxyglucose positron emission tomography integrated with computed tomography (PET-CT), whole-body low-dose computed tomography (WBLD-CT), and whole-body magnetic resonance imaging (WB-MRI) are being used in many centers (2). On the other hand, bone mineral density- dual energy x-ray absorptiometry (BMD-DEXA) is a widely-used

technique to detect osteoporosis, which is a common long-term outcome for MM patients. Here, we aimed to present our radiological and BMD-DEXA findings in our newly diagnosed MM patients.

MATERIALS and METHODS

Three hundred and ten patients who were being followed up at the Hematology Department XXXX Hospital between the years of 2004-2020 were enrolled in the study. Only symptomatic MM patients, who were diagnosed according to the International Myeloma Working Group 2016 criteria were included (5). The study was designed to be single-center, retrospective, multidisciplinary, analytic, and cross-sectional. Skeletal survey (posteroanterior view of the chest, anteroposterior and lateral views of the cervical spine, thoracic spine, lumbar spine, humerus, and femur, anteroposterior and lateral views of the skull, and anteroposterior view of the pelvis) was performed in all patients. PET-CT was selected for all eligible patients and those with suspected extramedullary plasmacytoma. Also, an MRI of the suspicious area was performed in selected patients to indicate the mass or fracture. No radiological scans, including MRI or PET-CT, were used to investigate bone marrow involvement. Lytic lesion presence on the skeletal survey was described as at least one lesion with a characteristic sharply defined,

spheroid punched-out appearance. WBLD-CT or WB-MRI techniques were not used for any patient. Before initiating bisphosphonates therapy (usually preferred as zoledronic acid, 4 mg per month, intravenously); BMD-DEXA was performed in all eligible patients to detect osteopenia/osteoporosis. The associations between osteolytic bone lesions and gender and Ig type as well as the sensitivity and specificity of imaging techniques to detect radiological lesions were investigated.

Statistical Analysis

SPSS 26.0 (IBM Corporation, Armonk, New York, United States) software program was used for the statistical analysis. Qualitative data were given as numbers and percentages while quantitative data were given as mean \pm standard deviation. The Chi-square or Fisher's exact test was used to determine an association between categorical variables. The sensitivity (specificity) was calculated as the number of diseased (non-diseased) that were correctly classified, divided by all diseased (non-diseased) individuals. A p-value below 0.05 was considered significant.

RESULTS

One-hundred and sixty-six male and 144 female patients were included in the study. The mean age of the patients was 65.1 ± 10.5 . Regarding

MM subtypes; 171 patients (55.2%) were IgG, 61 (19.7%) were IgA, 62 (20%) were light chain and 16 (5.2%) were other types (IgM, IgD, biconal, non-secretory). Regarding the radiological screening at initial diagnosis; all patients were evaluated with CR and 186 patients (60 %) were also screened with PET-CT. MRI was performed on 111 patients (35.8 %). Osteolytic lesion(s) ($1 \leq$) were detected in 221 (71.3 %) of the patients, who were screened with CR and in 151 (81.2 %) of 186 patients who also underwent PET-CT. Extramedullary plasmacytoma at diagnosis or during the course of the disease was detected in 59 patients (19% of all patients) by PET-CT and/or MRI. Fractures and accompanying hypointense lesions were detected in 107 (96.4 %) patients who underwent MRI, whereas 4 (3.6 %) patients did not have hypointense lesions on the floor of the fracture. BMD-DEXA was performed in 136 patients (43.9%) before initiating a bone resorption inhibitor such as zoledronic acid. Findings consistent with osteoporosis (T score below - 2, 5) were found in 113 (83.1 %) patients who underwent BMD-DEXA imaging. In 34% of these patients, the Z score was also below -2, supporting that it is associated with myeloma-related secondary osteoporosis (6).

Table-1. Imaging techniques and detection ratios.

Imaging	Detection	n(%)	Positivity rate
Conventional Radiography	Osteolytic lesion (+)	221 (71.3)	71.3%
	Osteolytic lesion (-)	89 (28.7)	
PET-CT	Osteolytic lesion (+)	151 (48.7)	81.2%
	Osteolytic lesion (-)	35 (11.3)	
	N/A	124 (40)	
BMD-DEXA	Osteoporosis (+)	113 (36.5)	83.1%
	Osteoporosis (-)	23 (7.4)	
	N/A	174 (56.1)	
MRI	Fracture, hypointense lesion (+)	107 (34.5)	100%
	Fracture, hypointense lesion (-)	4 (1.3)	
	N/A	199 (64.2)	

N/A: Not applicable

PET-CT: 18F-fluorodeoxyglucose positron emission tomography integrated with computed tomography

BMD-DEXA: Bone mineral density- Dual energy x ray absorptiometry

MRI: Magnetic resonance image

Table-2. The associations between imaging techniques and gender/MM type.

	Osteolytic lesion(s) on CR	Osteolytic lesion(s) on PET-CT	Osteolytic lesion(s) on MRI
	p value	p value	p value
Gender	0.736 †	0.588 †	0.999 ‡
MM type	0.173 †	0.123 †	0.109 †

†Calculated by the Pearson Chi-square test.

‡Calculated by the Fisher's exact test.

CR: Conventional radiography Ig: immunoglobulin

The radiological characteristics of the patients were summarized in Table-1. There was no association between osteolytic bone lesions detected by imaging techniques and gender or MM type (Table-2). PET-CT was found very sensitive (96.1%) and specific (90.6%) as a radiological imaging technique to detect osteolytic lesions. Although the sensitivity of MRI to detect fractures was high (96.9%), its specificity was only 6.7%. Also, among patients who have lytic lesions on CR, the sensitivity and specificity of BMD-DEXA to detect osteoporosis were 85.3% and 23.5%, respectively.

DISCUSSION

The importance of an osteolytic lesion at diagnosis initially comes from the Durie-Salmon staging system, which is designed to estimate disease bulk. The staging involves the criteria of absence of lytic bone lesions or osteoporosis as stage 1, and the presence of more than 3 lytic lesions as stage 3. Stage 2 is accepted as patients fitting neither stage 1 nor stage 3 (7). Osteolysis is a CRAB finding (hypercalcemia, renal failure, anemia, lytic bone lesions) and a disease-defining event, which requires the initiation of anti-myeloma therapy (1). Osteolysis and osteoporosis in MM are associated with each other and bone mineral density loss is an anticipated long-term complication of MM, with the potential of pathological bone fractures; which can be alleviated or prevented by osteoclast inhibitors such as bisphosphonates (8). Bone mineral loss is mostly expected in the vertebral body (49%). This is a location where any pathological fracture can cause compression of the spinal cord and subsequent paralysis which can be irreversible (4, 9). Therefore, focusing on bone pathology is essential not only to diagnose symptomatic MM but also to prevent these bone-related complications.

CR has been used as an imaging method due to its availability, low cost, and ease of use for many

years. Still, it is the only method available for some centers. However, there is a lack of sensitivity; because when trabecular bone loss is greater than 30%; the lesion then becomes detectable on CR (3). Also, the evaluation of pelvis and spine, and the differentiation of benign osteoporosis from osteolytic lesions are challenging points; which therefore carry the risk of overlooking lytic bone lesions (3). It is suggested that up to 20% of patients with lytic lesions cannot be detected by CR (10-12) CRs also have subjectivity for interpretation of the presence of lytic lesions. Therefore, the Durie-Salmon staging system was revised as the Durie-Salmon Plus staging system, which integrated more sensitive and objective methods than CR; such as PET-CT or WB-MRI (10-13). Currently, general opinion recommends against the use of CR, unless it is the only available method in the center (14-15).

It has been suggested that female gender and IgA-type myeloma patients were more prone to develop osteolytic lesions (9). In our study, 144 women (46.5%) and 61 IgA type MM patients (19.7%) were included. Although the female sex ratio was slightly higher than the literature (F / M: 1 / 1.15 vs 1 / 1.4); IgA ratio was similar (19.7% vs 21%) (16-7). Conflicting with the literature, we have not detected any association between osteolytic lesions and gender or MM type, and the reason is unknown. The rate of detecting bone disease (osteolytic lesions and osteopenia or osteoporosis) was suggested to be 80%, while our study detected a similar rate regarding lytic lesions in PET-CT (81.2% of patients with the technique applied) (4). Another point in the study was the rate of missing osteolytic lesions by CR to be less than 20%; when the presence of lytic lesions was confirmed by PET-CT (PET-CT: 81.2 % vs CR 71.3%). Extramedullary plasmacytomas were suggested to be detected at the rate of 5-7% at initial diagnosis and up to 30% during the

course of the disease. In our study, the rate of extramedullary plasmacytomas detected by physical examination, PET-CT, and/or MRI was consistent with the literature (19%) (16, 18-19).

At initial diagnosis, Kyle R et al suggested that osteoporosis is detected in 20-25% of symptomatic MM patients and it is hypothesized that this rate increased to 80% during the course of the disease (17, 20). In our study, the osteoporosis rate prior to initiating a bisphosphonate was 83.1% (113/136), while 174 patients could not be screened with BMD-DEXA. Forty-six (33.8%) of the patients who underwent BMD-DEXA were women. This difference in osteoporosis rate could be explained by the fact that although most of the patients were screened during the diagnosis, some patients were screened with BMD-DEXA during the course of the disease, before starting bisphosphonate therapy. For the rest of the patients who underwent screening (n: 23, 16.9%), 14 patients (10.2 %) had osteopenia (T score between -1 and -2.5) and 9 patients (6%) had normal T scores (21).

In our center, we prefer PET-CT in addition to conventional radiography because of its increased sensitivity in detecting osteolytic lesions and extramedullary disease at the time of diagnosis in all eligible patients. Also, PET-CT, which contributes discriminating smoldering and active MM, combines morphological and functional imaging and represents a very useful technique for oligosecretory and nonsecretory MM (22-24). PET-CT also enables monitoring of measurable residual disease (MRD), which is usually defined as the absence of tumor plasma cells within 1.000.000 bone marrow cells. Current data suggest that PET-CT can detect hypermetabolic areas in approximately 15%-20% of patients who were considered MRD negative according to their bone marrow assessment (24). MRI is usually performed additionally for fractures and masses with potential vertebral compression in our center. Our preference for PET-CT, as opposed to MRI, is also related to monitoring treatment response, as the disappearance of bone lesions on PET-CT (but not MRI) during follow-up was found to be associated with better progression-free survival (25). Pathological and compression fractures have been reported in 20-25% of newly diagnosed MM in the literature (15). On the other hand, we detected fractures in all patients (35.8% of 310 patients) who underwent MRI due to physical examination findings supporting fracture or suspicious appearance in other imaging. This difference

(35.8% vs 20-25%) may reflect the increase in the rate of osteoporosis in the study, which facilitated fracture development.

CONCLUSION

We presented our data according to our patient registry. Compared to the literature, we found a similar osteolytic lesion rate but a higher rate of osteoporosis, which could be related to the design of the study. We have not detected any association between gender, IgA type, and osteolytic lesions. PET-CT was quite sensitive (96.1%) and specific (90.6%) as an initial radiological technique for detecting osteolytic lesions. MRI was found sensitive when the presence of a fracture was suspected, but its specificity remained low. Bone protective agents to prevent osteoclast dominant process should be initiated as soon as MM is diagnosed and osteolytic lesions are screened by highly sensitive methods which also enable disease monitoring, to prevent undesired fractures.

Limitations of the study

In our study, the interpretation of lytic lesions on CR is prone to errors due to subjectivity, similar to other studies. We have not included WBLD-CT or WB-MRI, which could have the potential to reinforce the data obtained from other techniques we used. Regarding osteoporosis, BMD-DEXA screening was performed prior to zoledronic acid initiation; however, for some patients, anti-myeloma therapy, which has the potential to alleviate bone mineral loss, has already been initiated. On the other hand, MM is not the only parameter that has an impact on osteoporosis; therefore another limitation of our study is that we have not designed our study according to other determinants.

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Ethics

This study was approved by Adnan Menderes University Rectorate, Faculty of Medicine, Non-invasive Clinical Research Ethics Committee Ethical Committee (2019-140), and it was performed in accordance with the ethical standards in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent forms were obtained from all patients for participation and publication.

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