# Assessment of Bone Disease in Multiple Myeloma Patients After Autologous Stem Cell Transplant

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## ABSTRACT

***Background :*** Detection of lytic bone lesions is crucial in the workup for multiple myeloma (MM) and very often dictates the decision to start treatment. Modern imaging techniques such as MRI, PET, and CT offer superior detection of myeloma bone disease and extramedullary manifestations of plasma cell dyscrasias. Autologous stem cell transplant (ASCT) is regarded as frontline therapy in candidate patients. Recent advances in understanding of myeloma bone disease showed that the receptor activator of nuclear factor kappa-B ligand (RANKL) and osteoprotegerin (OPG) system plays a key role in this regard.

***Objectives :*** to assess the response of bone disease in patients with multiple myeloma using whole body low dose CT (WBLD CT) scan after different modalities of treatment including autologous stem cell transplant.

***Patients and method :*** This is a prospective cohort study in which patients with multiple myeloma had baseline WBLD CT scan with basic evaluation. They were then received induction chemotherapy with and then grouped into two groups according to the modality of consolidation (ASCT vs no ASCT). Both groups had second WBLD CT and were compared for the osteolytic lesions concerning size and site.

***Results :*** 20 patients were included in the study (12 males, 8 females), 8 treated with chemotherapeutic protocols (mainly bortezomib based) (group A) while 12 patients underwent ASCT during their course of treatment (group B). The improved score was found only in two patients, one in each group.

***Conclusion :*** myeloma bone disease needs to be assessed initially and promptly prevented and treated since it increases morbidity and mortality. Using newer imaging modalities like WBLD CT, MRI, PET scan is encouraged over conventional X ray skeletal survey.

***Keywords :*** bone disease , multiple myeloma , autologous stem cell transplant .

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# تقييم الافات الغظمية لدى مرضى النقيوم المتعدد بعد زراعة الخلايا الجذعية الذاتية

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## الخلاصة

**الخلفية :** إن الكشف عن الآفات المحللة للعظم أمر بالغ الأهمية فى العمل على مرض الورم النقوى العظمى (MM) وغالبًا ما تملى قرار بدء العلاج. توفر تقنيات التصوير الحديثة مثل التصوير بالرنين المغناطيسى ، والتصوير المقطعى بالإصدار لبوزيترونى ، والتصوير المقطعى المحوسب كشفًا فائقًا عن مرض الورم النقوى العظمى والمظاهر خارج النخاع لخلل التنسج فى خلايا البلازما. يعتبر زرع الخلايا الجذعية الذاتية بمثابة علاج فى الخطوط الأمامية للمرضى المرشحين.أظهرت التطورات لحديثة فى فهم مرض الورم النخاعى العظمى أن منشط مستقبلات العامل النووى كابا- بى لجند ونظام osteoprotegerin يلعب دو ًرا رئيسيًا فى هذا الصدد.

**الأهداف :** تقييم استجابة مرض العظام لدى مرضى الورم النقوى المتعدد باستخدام التصوير المقطعى المحوسب منخفض الجرعة لكامل الجسم بعد طرق مختلفة من العلاج بما فى ذلك زرع الخلايا الجذعية الذاتية.

**المرضى والطريقة :** هذه دراسة جماعية محتملة حيث كان المرضى الذين يعانون من الورم النخاعى العظمى قد خضعوا لفحص لتصوير المقطعى المحوسب منخفض الجرعة لكامل الجسم الأساسى مع التقييم الأساسى. ثم تم تلقيهم العلاج الكيميائى مع ثم تجميعهم فى مجموعتين وفقًا لطريقة العلاج المتممةASCT مقابل عدمASCT . خضعت كلتا المجموعتين للتصوير المقطعى المحوسب منخفض الجرعة لكامل الجسم ثانية وتم مقارنتها للآفات المحللة للعظم فيما يتعلق بالحجم والموقع.
**النتائج :** تم تضمين ٢٠مريضًا فى الدراسة ١٢ذكور و ٨إناث ، ٨تم علاجهم ببروتوكولات العلاج الكيميائى (المعتمدة على بورتيزوميب) (المجموعة أ) بينما خضع ١٢مريضًا للعلاج بزرع الخلايا الجذعية الذاتية خلال مسار العلاج (المجموعة ب.) تم العثور على النتيجة المحسنة فى مريضين فقط ، واحد فى كل مجموعة.
**الاستنتاج :** يجب تقييم مرض الورم النقوى العظمى فى البداية وعلى وجه السرعة للوقاية منه ومعالجته لأنه يزيد من معدلات المراضة والوفيات باستخدام طرائق التصوير الحديثة مثل ، MRI،WBLD CTيتم تشجيع فحصPET على المسح التقليدى لهيكل العظمى بالأشعة السينية .

**الكلمات المفتاحية :** الافات العظمية ، نقيوم متعدد ، زراعة الخلايا الجذعية الذاتية .

## INTRODUCTION

Multiple myeloma (MM) is a malignant plasma cell tumor that can build up in the bone marrow and cause bone loss and marrow failure.

Specific aspects are addressed in the development and activation of osteoclasts (OCs) and decreased osteoblastic activity (OBs). The osteoprotegerin (OPG) and receptor activator of nuclear factor kappa-B ligand (RANKL) systems are crucial in the mechanism of myeloma bone disease (MBD)[1].

The whole body x ray (WBXR) and whole body low dose CT scan (WBLD CT) findings for MM are substantially same, despite the WBLD CT being considerably better described like lytic lesions, extraosseous involvement, cortical disruption, neoplastic and osteoporotic fractures, widespread osteopenia, and endosteal scalloping.[1]

Imaging data from MRI and PET are crucial for determining the severity and prognosis of disease. WBLD CT is already the accepted imaging method for use in patients with MM in many European institutions due to various benefits over WBXR.[2,3]

As long as a patient is eligible, high-dose chemotherapy followed by ASCT is still regarded as standard of care because to its enhanced PFS and OS in numerous randomized trials.[4]

In the single transplant group, the chance of EFS for 7 years following diagnosis was 10%, whereas in the double transplant group, the chance was 20%. Patients who did not obtain a complete CR or VGPR within 3 months of the initial transplant appeared to benefit from a second transplant, according to a subset study. [5]

## AIM OF THE STUDY

The study aimed to assess the response of bone disease in patients with MM using WBLD CT scans after different modalities of treatment, including autologous stem cell transplant (ASCT).

## PATIENTS AND METHOD

### Patients

This is a prospective cohort study in which 20 patients (12 male, 8 female) diagnosed with active or relapsed active MM since a period ranging from 3-28 months were included.

They had baseline WBLD CT [ Toshiba Aquilion 128 multislice CT ] together with other blood tests ( complete blood count , ESR , renal function tests , liver function tests , serum calcium , serum albumin , beta 2 microglobulin , serum protein electrophoresis with immunofixation)[ in teaching lab./medical city complex].

We divided the study patients into two groups according to ASCT status (8 vs 12) and we compared both groups in terms of age , number of CRAB features (Calcium, Renal, Anemia, Bone ) that were present at diagnosis, percentage of plasma cells in bone marrow aspiration (BMPC%) at diagnosis, the level of M protein at diagnosis, ESR, risk status, and follow-up period.

The study was approved by the ethical and scientific committee in the Iraqi council of medical specialties.

They were then given an induction chemotherapy protocol based on the treating physician's recommendation (3-6 cycles of bortezomib-based protocols) and reassessed after achieving stringent complete response (sCR), complete response (CR), or at least very good partial response (VGPR).[6,7]

Some of these patients had undergone the second WBLD CT before starting consolidation, others after consolidation by autologous bone marrow transplant.

The decision of whom to go for ASCT or not depends on eligibility determined by the scientific committee in the bone marrow transplant center/medical city complex.

The two WBLD CTs were compared, and the osteolytic lesions less than 5 mm in diameter were excluded from counting in a newly formulated numerical scoring system where bony sites were given a number (table 1). The sum of these numbers is calculated and used to assess the improvement in bone disease.

This novel scoring system is based on a simple concept: each bone on both sides of the body counts as two, while those on one side count as one.

Inclusion criteria symptomatic multiple myeloma ,the patient is 14 years old or older, had completed the induction phase of chemotherapy , in remission at the time of the second assessment.

Exclusion criteria plasmacytoma and smoldering myeloma ,younger than 14 years ,patients who are not taking a bisphosphonate or a RANK-L antagonist during the induction period.

Table 1 the scoring system for patients with myeloma bone disease.

| Anatomical site | Score |
|---|---|
| **Skull** | 2 |
| **All cervical spines** | 1 |
| **All dorsal spines** | 1 |
| **All lumber spines** | 1 |
| **Pelvis** | 2 |
| **Others (each site)** | 1 |

## RESULTS

This study included 20 patients (12 males and 8 females), with 8 patients treated with chemotherapeutic protocols (mostly bortezomib-based) (group A), and 12 patients treated with ASCT during their treatment (group B).

The decrement in points of the previously mentioned scoring system was seen just in 2 patients (one in group A and one in group B) (P value 0.5), while no change in score points was seen in the rest of the study sample. (table 2,3)(figure 1)

Table 2 descriptive table of study sample

| Patient number | Age | risk status | CRAB | BMPC% | M spike | ESR | induction protocol | ASCT | Baseline score | 2nd score | follow up period |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 36 | High | 4 | 85 | 58.4 | 90 | VCD | no | 6 | 6 | 6 |
| 2 | 52 | High | 2 | 30 | 76.2 | 154 | VCD | no | 3 | 3 | 20 |
| 3 | 32 | intermediate | 1 | 10 | 7 | 30 | VCD | no | 2 | 2 | 6 |
| 4 | 41 | Good | 2 | 30 | 49 | 35 | VRD | no | 3 | 3 | 7 |
| 5 | 52 | intermediate | 3 | 30 | 52 | 150 | VRD | no | 1 | 1 | 4 |
| 6 | 60 | intermediate | 2 | 40 | 10.6 | 75 | VTD | no | 2 | 2 | 3 |
| 7 | 55 | High | 4 | 65 | 26 | 90 | VRD | no | 7 | 7 | 3 |
| 8 | 49 | intermediate | 2 | 80 | 5 | 140 | VCD | no | 6 | 3 | 8 |
| 9 | 58 | High | 3 | 60 | 58 | 150 | VCD | yes | 4 | 4 | 20 |
| 10 | 65 | intermediate | 2 | 33 | 18 | 63 | VCD | yes | 2 | 2 | 12 |
| 11 | 44 | Good | 1 | 12 | 15.9 | 34 | VRD | yes | 2 | 2 | 4 |
| 12 | 40 | High | 4 | 40 | 45 | 155 | VRD | yes | 5 | 5 | 8 |
| 13 | 60 | Good | 2 | 30 | 8.5 | 111 | VCD | yes | 2 | 1 | 18 |
| 14 | 62 | High | 4 | 40 | 44.5 | 55 | VCD | yes | 2 | 2 | 11 |
| 15 | 54 | Good | 2 | 9 | 52 | 63 | VCD | yes | 1 | 1 | 5 |
| 16 | 48 | High | 2 | 50 | 16.6 | 29 | VCD | yes | 8 | 8 | 18 |
| 17 | 39 | intermediate | 2 | 25 | 30 | 150 | CTD | yes | 1 | 1 | 28 |
| 18 | 43 | intermediate | 2 | 9 | 11 | 72 | VRD | yes | 3 | 3 | 11 |
| 19 | 47 | intermediate | 2 | 55 | 7.5 | 150 | VTD | yes | 2 | 2 | 20 |
| 20 | 63 | intermediate | 2 | 30 | 7.9 | 60 | VRD | yes | 3 | 3 | 20 |

Table 3 shows the mean of parameters studied between group A and B with their standard deviation and significance.

| *Parameter* | *Mean A* | *SD* | *Mean B* | *SD* | *P value* |
|---|---|---|---|---|---|
| *Age* | 47.63 | 9.694 | 53.33 | 9.557 | .210 |
| *CRAB* | 2.50 | 1.069 | 2.33 | 0.888 | .709 |
| *BMPC%* | 46.25 | 27.091 | 32.75 | 17.253 | .188 |
| *M spike* | 35.525 | 26.9607 | 26.242 | 18.7666 | .374 |
| *ESR* | 95.50 | 48.996 | 91.00 | 48.821 | .842 |
| *Follow up period (months)* | 7.13 | 5.515 | 14.58 | 7.204 | .023 |

(CRAB calcium , renal , anemia , bone ; % PC in BMA : percent of plasma cells in bone marrow ;M spike : monoclonal spike ; SD : standard deviation)

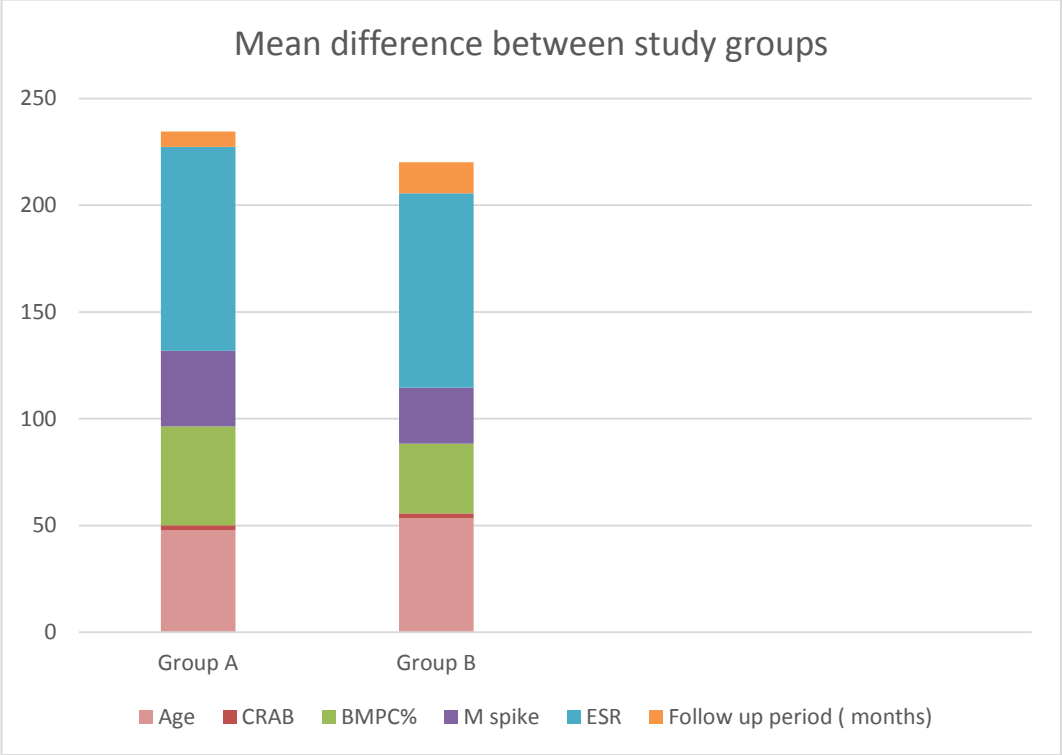


Figure 1 shows the mean difference between study groups

## DISCUSSION

The authors noticed in MM patients that there is a predilection of bone disease , in particular lytic lesions , toward specific anatomical sites but why this happened is of unknown mechanism[8].

Durie Salmon PLUS radiological classification depends on MRI finding of focal lytic lesions and/or spinal involvement [9] We have no current WBLD CT data, and it does not reflect the differences in anatomical sites, so we propose a scoring system for these lesions that converts them from descriptive to numerical pattern (as shown in table 1).

When we calculate these numbers to see if there is any improvement or not, a higher count would be considered a disease relapse and was excluded from the study.

The use of WBLD CT is more solid than skeletal survey in detecting bone lesions; it has less radiation exposure than a formal CT scan; it is rapid; it has good interpretation; and it is readily available [9].

Still MRI and PET scan is more sensitive and specific than WBLD CT specially in soft tissue situations[10] but these modalities are not so available, costly and need more time to perform. So, we choose WBLD CT as our diagnostic tool.

Reece et al. (Canadian study) compare ASCT in patients younger than 60 years and older patients[11] .His study showed fewer lytic lesions in the younger age group, but this study failed to show any statistically significant difference.

Majolino et al (Italian study) demonstrated a correlation in response post ASCT in regard to risk status and time from diagnosis[12], while the present study doesn't. It may be because their cohort depended on tandem transplant and selected all patients post induction, while we selected patients with sCR, CR, and VGPR categories and for single ASCT.

Although BMPC% had been evaluated in CR percentage post ASCT [8] , but no comparative researches on its effect on lytic lesions were found, however this study shows no significant association between them.

By definition, the M protein level should be more than 3 g/l to diagnose symptomatic multiple myeloma[8], But the amplitude of that protein does not have prognostic significance to the disease outcomes as well as bone disease, so did our study, which demonstrated a non-significant association.

Although ESR is elevated in most patient with myeloma and about one third is above 100 mm/hr [5], no match was found about their association with lytic lesions, this study shows no association between them also.

The only significance was seen in the period of follow up, as Meera Mohan et al demonstrated in her study[13] , Re-mineralization occurred mainly at cortical bone sites but was seen also in cancellous bone. The pelvic bone is a flat one that develops by membranous ossification. For example, lytic MM bony lesions, for example in the pelvis, keep their mineralizing ability, which can refurbish the bone mineral defect to near normal levels over a period.

## CONCLUSION

ASCT would not change the appearance of lytic lesions detected by CT scanning except after longer follow-up.

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