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COMPARISON OF QUALITY OF LIFE (QOL) IN PATIENTS WITH METASTATIC BONE DISEASE (MBD) BEFORE AND AFTER BISPHOSPHONATE THERAPY BASED ON CALCIUM LEVELS

Fachrizal Arfani Prawiragara[1]*, Hilmia Fahma2, Debrina Kusuma Devi3, Leonardo Tedjaprasadja[4]
[1]Department of Orthopaedic and Traumatology, Faculty of Medicine, Universitas Pembangunan Nasional Veteran Jawa Timur, Indonesia
[2]Department of Psychiatric, Faculty of Medicine, Universitas Pembangunan Nasional Veteran Jawa Timur, Indonesia
[3]Department of Internal Medicine, Faculty of Medicine, Universitas Pembangunan Nasional Veteran Jawa Timur, Indonesia
[4]Department of Public Health, Faculty of Medicine, Universitas Pembangunan Nasional Veteran Jawa Timur, Indonesia

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Corresponding Author:
E-mail: fachrizalortho.fk@upnjatim.ac.id

ABSTRACT

Background: Metastatic bone disease (MBD) is a frequent complication in advanced cancer, often resulting in pain, limited mobility, and reduced QoL. Bisphosphonates are effective in minimizing skeletal-related events by suppressing osteoclast activity. **Objective:** To assess the impact of bisphosphonate therapy on serum calcium levels and QoL in patients with metastatic bone disease. **Methods:** A retrospective cohort study was conducted involving 228 MBD patients treated at Dr. Soetomo General Hospital from 2015 to 2020. Surgical eligibility was determined using the Abdurrahman Score. Pre- and post-treatment data on serum calcium levels and Karnofsky Scores were collected and analyzed using paired t-tests. **Results:** In the surgical group, the mean Karnofsky Score improved from 46.67 ± 12.69 to 77.67 ± 9.35 ($p < 0.001$), while serum calcium levels decreased from 10.1 ± 1.20 to 7.3 ± 1.01 ($p < 0.001$). In the non-surgical group, Karnofsky Scores increased from 36.67 ± 12.22 to 49.35 ± 13.15, and calcium levels declined from 10.2 ± 1.18 to 7.6 ± 1.33 (both $p < 0.001$). **Conclusion:** Bisphosphonate therapy significantly enhances QoL and reduces serum calcium levels in patients with metastatic bone disease. The combination of surgical management and bisphosphonate therapy yields superior functional outcomes compared to non-surgical treatment.

BACKGROUND

Metastatic bone disease (MBD) represents a frequent and debilitating complication of advanced malignancies, particularly those originating from the breast, prostate, and lungs[1,2]. The skeletal system ranks as the third most common site of metastasis after the lungs and liver, often causing severe pain, decreased mobility, pathological fractures, and a decline in QoL[3,4].

Approximately 65–75% of patients with advanced breast or prostate cancer develop bone metastases during the course of their illness[5]. The pathophysiological mechanism is driven by tumor-derived factors, including parathyroid hormone-related protein (PTHrP) and receptor activator of nuclear factor kappa-B ligand (RANKL), which promote osteoclast activation, resulting in excessive bone resorption and hypercalcemia[6–8]. This disruption in bone homeostasis not only causes local skeletal complications but also contributes to systemic symptoms like hypercalcemia, fatigue, and neuromuscular impairment[9].

Bisphosphonates are synthetic analogues of pyrophosphate that strongly bind to bone mineral and inhibit osteoclast-mediated bone resorption[10]. Their use in MBD management is well established and has been shown to reduce skeletal-related events (SREs) and potentially improve patient outcomes[11,12].

In addition to pharmacologic management, surgery may be indicated in patients with impending or completed pathological fractures, spinal instability, or intractable pain. To guide surgical eligibility, the Abdurrahman Score has been developed as a multidimensional tool that includes parameters such as

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pain severity (based on VAS), tumour focality, pathological fracture presence, decubitus ulcers, and ASA physical status[13]. A total score ≥25 suggests appropriateness for surgical intervention.

This study aims to evaluate the effects of bisphosphonate therapy on serum calcium levels and quality of life (QoL), as measured by the Karnofsky Score, in patients with metastatic bone disease (MBD). It also compares outcomes between surgically and non-surgically treated patients, categorized according to the Abdurrahman Score.

METHODS

Study Design

This study employed a retrospective cohort design using a database review of patients with metastatic bone disease who were treated at Dr. Soetomo General Hospital between 2015 and 2020. The available medical record data consisted of two clinical groups:

1) A non-surgical group who received therapy without surgical intervention, and
2) A surgical group who received therapy following surgery.

A separate untreated of placebo control group was not available in the existing hospital records. However, to minimize potential selection and information bias, the study compared two clinically relevant treatment pathways within the same patient population. Consistent inclusion and exclusion criteria were applied across both groups to ensure comparability and strengthen the internal validity of the analysis.

Study Population and Sample

The study population consisted of patients diagnosed with metastatic bone disease (MBD) who received treatment at Dr. Soetomo General Hospital, Surabaya, Indonesia. The study sample included patients identified in the institutional database who were treated between 2015 and 2020. Patient data were obtained through a review of the electronic medical records from the Department of Orthopedics and Traumatology, Faculty of Medicine, Universitas Airlangga/Dr. Soetomo General Hospital.

The primary cancers most frequently associated with MBD in this cohort were breast cancer (the most common) and lung cancer (the second most common). The duration of MBD prior to therapy ranged from 6 to 24 months, with an average duration of approximately 12 months (±1 year). All patients who met the eligibility criteria recorded in the database were included in the analysis. The inclusion criteria were:

1. Patients diagnosed with metastatic bone disease;
2. Patients with an Abdurrahman score ≥25 or <25 who underwent therapy;
3. Patients willing to undergo examination and interview;
4. Patients with available pre- and post-therapy laboratory data, including albumin, liver function tests, hemoglobin, and renal function tests;
5. Patients with complete medical records and no prior therapy before the study period.

The exclusion criteria were:

1. Patients receiving strong opioid analgesics;
2. Patients with comorbidities unrelated to metastatic bone disease;
3. Patients who refused participation or data collection; and
4. Patients who had previously undergone chemotherapy prior to inclusion.

Patients were grouped based on their Abdurrahman Score:

- Surgical group: score ≥25,
- Non-surgical group: score <25.

The Abdurrahman Score assigns values based on:

- Pain severity using the Visual Analog Scale (VAS),
- Tumour focality (unifocal/multifocal),
- Presence of pathological fracture,
- Presence of decubitus ulcers,
- ASA physical status.

Biphosphonate Administration

Bisphosphonate therapy was administered as part of the standard treatment protocol for patients with metastatic bone disease. The commonly used bisphosphonates in this study were zoledronic acid and pamidronate, depending on drug availability at the hospital. Each medication was prepared as a sterile intravenous infusion solution under aseptic conditions according to institutional procedures.

The dosage regimen followed standard clinical practice. Zoledronic acid was administered at a dose of 4 mg intravenously every four weeks, whereas pamidronate was given at a dose of 90 mg intravenously every three to four weeks. The dose was adjusted based on each patient's renal function, since

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bisphosphonates are primarily excreted through the kidneys.

Both agents were administered via the intravenous route through a large vein. Zoledronic acid infusions were delivered slowly over 15–30 minutes, while pamidronate was infused over approximately two hours. The controlled infusion rate aimed to prevent acute infusion reactions and minimize the risk of renal impairment.

Bisphosphonate therapy was given periodically every three to four weeks for a minimum of six months, depending on the patient's clinical condition, bone pain response, calcium levels, and disease progression. In the context of this study, treatment duration and outcomes were evaluated before and after bisphosphonate administration by assessing serum calcium levels and quality of life parameters, including the Karnofsky Performance Score and Visual Analogue Scale (VAS) for pain.

Data Collection

The sampling technique employed in this study was consecutive sampling. All patients diagnosed with metastatic bone disease (MBD) who met the inclusion criteria were included, encompassing both those who underwent operative and non-operative therapy. The study was conducted retrospectively in 2020, utilizing patient data collected from 2015 to 2020 at Dr. Soetomo General Hospital, Surabaya, Indonesia.

Patient data were obtained from the institutional medical records. Eligibility for inclusion was assessed based on the completeness of laboratory data, particularly pre- and post-therapy serum calcium levels, to ensure accurate group classification. Patients were then categorized into the appropriate study groups according to their treatment modality.

The Karnofsky Performance Status (KPS) and Visual Analogue Scale (VAS) scores following therapy were extracted from the patients' medical records. For cases in which the postoperative KPS data were not fully documented, telephone follow-up was conducted to assess the patients' functional status after therapy. This approach ensured that updated and reliable information was obtained while maintaining methodological consistency in evaluating post-treatment outcomes.

Comparative analyses were then performed between pre- and post-therapy calcium levels, as well as between pre- and post-intervention quality of life indicators, to assess the clinical effectiveness of palliative surgical management in patients with metastatic bone disease.

Statistical Analysis

The study results were presented descriptively in tables to compare patients who underwent surgery and those who did not. Prior to statistical analysis, data normality was tested using the Shapiro-Wilk test. Because the comparison involved two independent groups, patients who received surgical treatment and those who did not, an independent *t*-test was used to evaluate differences in serum calcium levels before and after bisphosphonate therapy between these groups. Statistical analyses were performed using SPSS Software Version 22.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Patient Demographics

In this study, data were obtained from a total of 228 patients with metastatic bone disease who received treatment at Dr. Soetomo General Hospital. The majority of the patient were male for 30 individuals (30.5%), while the remaining 198 patients (69.5%) were female (**Table 1**).

Table 1. Characteristics of Patients with Metastatic Bone Disease

Gender Characteristics	Number of patients
Male	30 (30.5%)
Female	198 (69.5%)

Karnofsky Score

Karnofsky score results are presented in **Table 2**. A total of 30 patients were included in this analysis, consisting of 15 patients who underwent surgical therapy and 15 who received non-surgical therapy, making the groups equivalent in number. The analysis revealed that patients with metastatic bone disease who underwent surgical treatment demonstrated a better survival rate compared to those who did not undergo surgery. The mean Karnofsky score before surgery was 46.67, which increased to 77.67 after surgical intervention. In the non-surgical group, the mean score before treatment was 36.67 and increased to 49.35 after therapy. Evaluation of the Karnofsky scores showed a statistically significant variation

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between the pre-treatment and post-treatment assessments ($p < 0.001$). The higher post-treatment Karnofsky score observed in the surgical group indicates an improvement in patients' functional status and overall quality of life (QoL).

Table 2. Comparison of Karnofsky Scores (Pre- and Post-Therapy) in Surgical and Non-Surgical Groups

Group	Pre-Therapy Mean ± SD	Post-Therapy Mean ± SD	95% CI	p-value
Surgical	46.67 ± 12.69	77.67 ± 9.35	31.00 (24.9-37.1)	<0.001
Non-Surgical	36.67 ± 12.22	49.35 ± 13.15	12.68 (5.7-19.7)	<0.001

Serum Calcium Levels

The next analysis compared patients who underwent surgical treatment and those who did not, as measured by pre- and post-therapy serum calcium levels. The results of serum calcium levels are presented in **Table 3**. In the surgical group, the mean preoperative calcium level was 10.1 ± 1.20, while the postoperative mean was 7.3 ± 1.01. Among patients who did not undergo surgical intervention, the mean pre-therapy calcium level was 10.2 ± 1.18, and the post-therapy mean was 7.6 ± 1.33. A statistically significant difference was found in the mean serum calcium levels between the pre-treatment and post-treatment measurements ($p < 0.001$). Serum calcium levels were notably lower following surgical intervention.

Table 3. Comparison of Serum Calcium Levels (Pre- and Post-Therapy) in Surgical and Non-Surgical Groups

Group	Pre-Therapy Mean ± SD	Post-Therapy Mean ± SD	95% CI	p-value
Surgical	10.1 ± 1.20	7.3 ± 1.01	2.8 (2.2-3.4)	<0.001
Non-Surgical	10.2 ± 1.18	7.6 ± 1.33	2.6 (1.9-3.3)	<0.001

DISCUSSION

This study supports the effectiveness of bisphosphonates in improving both functional status and biochemical profiles in patients with metastatic bone disease (MBD). Significant improvements were observed in the Karnofsky Performance Status (KPS) and reductions in serum calcium levels post-therapy, with better outcomes seen in patients eligible for surgery. Bisphosphonates exert their therapeutic effect by inhibiting osteoclast activity, thereby reducing skeletal destruction and serum calcium release[10–12]. The decline in calcium levels observed in this study reflects successful suppression of the pathological bone resorption process typically seen in bone metastases[6–8].

The marked improvement in KPS among surgical patients emphasizes the added benefit of operative stabilization in appropriate cases. In the present study, the mean KPS in the surgical group increased from 46.67 to 77.67 after treatment, while the non-surgical group improved from 36.67 to 49.35. A KPS value of ≥70 is generally considered clinically favorable, indicating that the patient is capable of self-care and daily activities with minimal assistance. Moreover, previous studies have reported that an improvement of 10–20 points in KPS represents a clinically meaningful enhancement in functional ability and quality of life. Therefore, the 31-point increase observed in the surgical group and the 12.68-point increase in the non-surgical group indicate not only statistically significant but also clinically relevant improvement, especially among surgically treated patients. These results align with previous literature reporting that surgical intervention in MBD enhances ambulation, autonomy, and overall quality of life[13].

The Abdurrahman Score also proved useful for patient stratification, enabling individualized decision-making regarding surgical intervention. Its multidimensional nature provides clinicians with a reproducible framework for identifying operable patients[14]. These findings are supported by Hansen et al., who reported improved survival and function in surgically treated patients with skeletal metastases[15]. Similarly, Chow et al. validated the Karnofsky score as a dependable indicator of quality of life in cancer patients[16].

Further analysis suggests that the combination of surgical intervention and bisphosphonate therapy provides a synergistic effect in improving patient outcomes. Surgical stabilization not only relieves pain

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and restores mobility but also reduces the risk of pathological fractures, which are major determinants of morbidity in MBD[17]. When combined with bisphosphonate therapy, which prevents further osteolysis, patients experience both structural and metabolic benefits[18]. This integrative approach underscores the multidisciplinary nature of MBD management, where orthopedic, oncologic, and palliative teams collaborate to optimize care.

The biochemical improvements observed particularly the significant reduction in serum calcium levels highlight the role of bisphosphonates as both palliative and disease-modifying agents[19]. Hypercalcemia is a frequent and potentially life-threatening complication of bone metastasis; therefore, controlling calcium metabolism is crucial for maintaining homeostasis and reducing systemic symptoms such as fatigue, nausea, and confusion[20]. The normalization of calcium levels in this study suggests that timely bisphosphonate administration can effectively mitigate these risks, improving both survival and patient comfort[21].

Limitations of this study include the absence of subgroup analyses of serum calcium levels or KPS based on gender, as the data collection was retrospective and medical record documentation was limited. Consequently, gender-related variations could not be evaluated. Future prospective studies with larger and gender-balanced samples are warranted to explore potential differences in treatment responses and functional outcomes.

CONCLUSION

The evaluation of Karnofsky score and serum calcium levels in patients with metastatic bone disease revealed that the average post-operative Karnofsky score was higher than the pre-operative score, reflecting an improvement in the patient's QoL. Furthermore, serum calcium levels decreased following the surgical procedure. These results align with existing evidence that bisphosphonate therapy effectively enhances functional status and lowers serum calcium levels in individuals with metastatic bone disease. When appropriately indicated based on the Abdurrahman Score, surgical intervention provides better outcomes, emphasizing the need to integrate pharmacological and surgical approaches for optimal palliative management of MBD.

ETHICAL APPROVAL

This research was approved by the Research Ethics Committee of Dr. Soetomo General Hospital, Surabaya (Approval No. 0332/KEPK/XII/2021) issued on December 13, 2021.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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AUTHOR CONTRIBUTIONS

Conceptualization, FAP, HF, DKD, LT; methodology, FAP, HF, DKD, LT; software, FAP, HF, DKD, LT; validation, FAP, HF, DKD, LT; formal analysis, FAP, HF, DKD, LT; investigation, FAP, HF, DKD, LT; resources, FAP, HF, DKD, LT; data curation, FAP, HF, DKD, LT; writing—original draft preparation, FAP, HF, DKD, LT; writing—review and editing, FAP, HF, DKD, LT.

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