

## DEMOGRAPHIC AND MORPHOLOGIC CHARACTERISTICS OF BONE METASTASES – 11 YEARS SINGLE CENTER EXPERIENCE

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### Abstract

This is an epidemiological study of bone metastasis (BM) diagnosed and treated in a period of 11 years. Age and sex distribution of BM, localization, origin of primary malignancy, plain radiography appearance, therapeutic options and survival of the patients were evaluated. Of 86 patients, 52 were female and 34 male, ranging in age from 44 to 87 years. The most common site of BM was femur, followed by spine and humerus, and the most common primary malignancies were in the breast, lung, kidney and prostate, respectively. Almost one third of patients were with unknown primary malignancy at the time of BM diagnosis. The analysis of patients' plain radiographies revealed that most BM were osteolytic lesions.

Bisphosphonate therapy was applied in only 41.86% of patients, radiotherapy was applied in only 2.33% of patients and combination of bisphosphonates and radiotherapy received 8.14% of patients. The rest of the patients, 47.67%, were treated with symptomatic and/or with systemic therapy according to their primary malignancy. The survival analysis did not show statistically significant influence of any of the analyzed parameters in this study on the survival of the patients. Only 26.74% of patients survived 24 months and the high 73.26% survived 1 to 24 months.

**Keywords:** bone metastases, localization, primary malignancy, radiographic appearance, survival.

### Introduction

Bone metastases (BM) are an expression of a systemic neoplastic disease, usually associated with shortened survival [1], negative impact on quality of life, increased risk of serious bone complications [1,2] and are associated with large economic impact [3,4]. In adults, bone metastases are much more common than primary bone neoplastic lesions [1], and after lung and liver, the skeleton is the third most frequent site of metastases [1,3].

Bone metastases are most often found in axial skeleton, followed by pelvic bones, femur, humerus, ribs and skull [2,3], which is correlated with red bone marrow (RBM) content of the respective bone [2,5].

The frequency of BM varies among cancers [1,3,6]. Up to 70% of all skeletal metastases are due to prostate and breast cancer [1,2,6-8] followed by thyroid cancer, cancers of the lung, urinary bladder, renal cell carcinoma and melanoma [1,8].

Dysregulation of tightly orchestrated osteoclast-mediated bone resorption and osteoblast-mediated bone deposition by tumor cells leads to either osteoblastic or osteolytic radiographic appearance of metastases [1,7].

The great majority of breast cancers, multiple myeloma, renal cell carcinoma, melanoma, non-small cell lung cancer, non-Hodgkin lymphoma, thyroid cancer or Langerhans-cell histiocytosis are prototypes of tumors that have a predilection to form osteolytic lesions in the skeleton [1,5].

The osteoblastic lesions are less common, and prostate cancer, carcinoid, small cell lung cancer, Hodgkin lymphoma and medulloblastoma usually present osteoblastic lesion radiologically [1].

Some patients, especially those with gastrointestinal, squamous cancers and 15-20% of women with breast cancer, have both osteolytic and osteoblastic (mixed) lesions [1].

The aim of this study was to present demographic and some morphological characteristics of bone metastases and to determine their influence on patient's survival.

### **Materials and methods**

We analyzed 86 consecutive patients with histologically proven bone metastatic disease diagnosed and treated at the University Clinic for Traumatology, Orthopedic Diseases, Anesthesia, Reanimation, Intensive Care and Emergency Centre in Skopje (TOARILUC), due to bone cancer symptoms in the period from 2009 to 2019.

Operative materials of all 86 patients were analyzed at the Institute of Pathology, Faculty of Medicine in Skopje. We used medical history files, plain radiography, computed tomography images (CT), bone scintigraphy, magnetic resonance images (MRI) archive paraffin blocks, slides, and pathology reports. Additional information about postoperative follow-up of the patients was provided by the University Clinic for Radiotherapy and Oncology in Skopje.

There were 93 patients diagnosed with BM in the evaluated period, but 7 of them were excluded from the study, due to lack of important data.

We evaluated the following data: gender, age, localization of bone metastasis, presence of multiple bone metastases, primary malignancy, type of radiographic appearance of the metastasis (osteosclerotic, osteolytic, mixed), postoperative therapy and survival.

All of the patients complained to local pain, swelling (different degree) and functional difficulties, including fifty-one (59.30%) patients who had a pathological fracture. All of them were evaluated by plain radiography, bone scintigraphy and CT, and patients with pelvic and spine metastases were evaluated with magnetic resonance imaging (MRI) and positron emission tomography (PET) in the last three years.

All of the patients with known primary malignancy underwent appropriate systemic therapy for their primary neoplasm.

All of the patients were surgically treated by mass reduction, bone resection and most of them with intramedullary rod osteosynthesis. Four patients had multiple metastases and in these cases the metastasis with pathologic fracture was treated surgically.

Two postoperative therapeutic options for the metastases were evaluated in our study: bisphosphonates and radiotherapy.

Patients were followed up from the date of BM diagnosis for 24 months.

Statistical analysis was made by the use of the statistical software package Statistica 7.1 for Windows and SPSS Statistics 23.0, applying descriptive statistics and Kaplan Meier analysis.

### **Results**

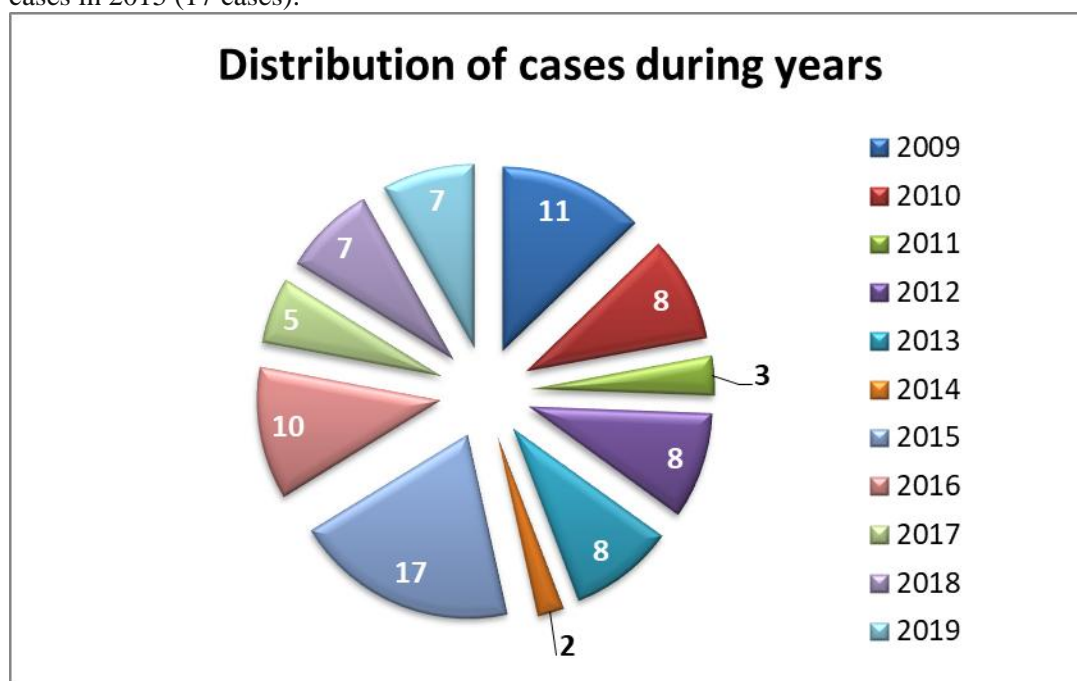
The study included 86 patients with BM, 52 (60.47%) females and 34 (39.53%) males, with female to male ratio 3:2, ranging in age from 44 to 87 years, median age  $65 \pm 9.85$ .

Most of the cases at the time of presentation were in the seventh decade (37.2%) and the smallest number of patients were younger than 50 years (2.32%) (Table 1).

**Table 1.** Distribution of patients with bone metastases according to age groups

Age group	Number of patients	Percentage (%)
< 50	2	2.32558
51-55	7	8.13953
56-60	17	19.76744
61-65	18	20.93023
66-70	14	16.27907
71-75	6	6.97674
76-80	14	16.27907
>80	8	9.30233
Total	86	100

Distribution of cases over years evaluated in our study is presented in Figure 1 with the highest number of cases in 2015 (17 cases).



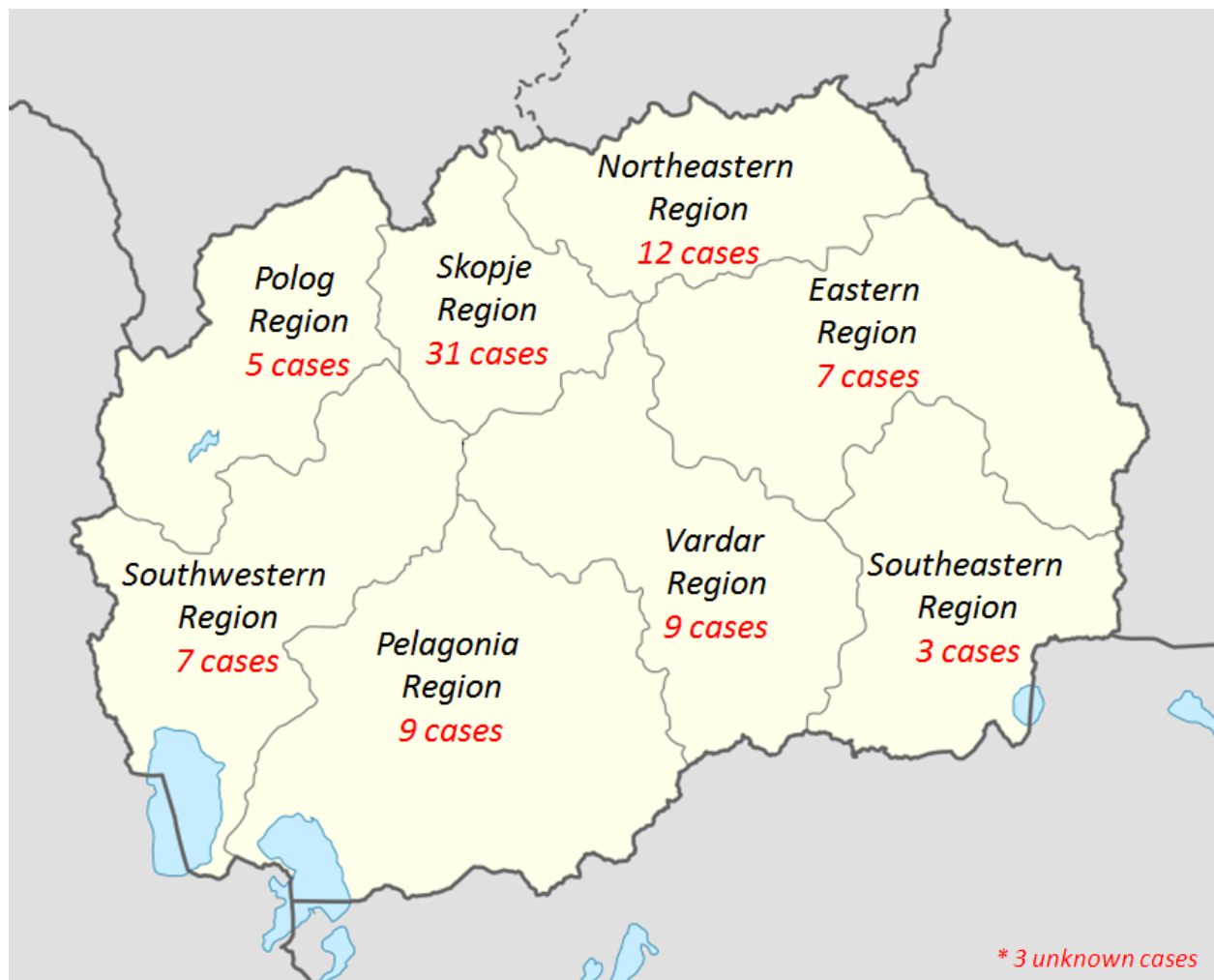
**Figure 1.** Distribution of patients with bone metastases according to occurrence by year

Distribution of patients with bone metastases by place of residence is shown in Table 2 and Figure 2.

**Table 2.** Distribution of patients with bone metastases according to region and place of residence

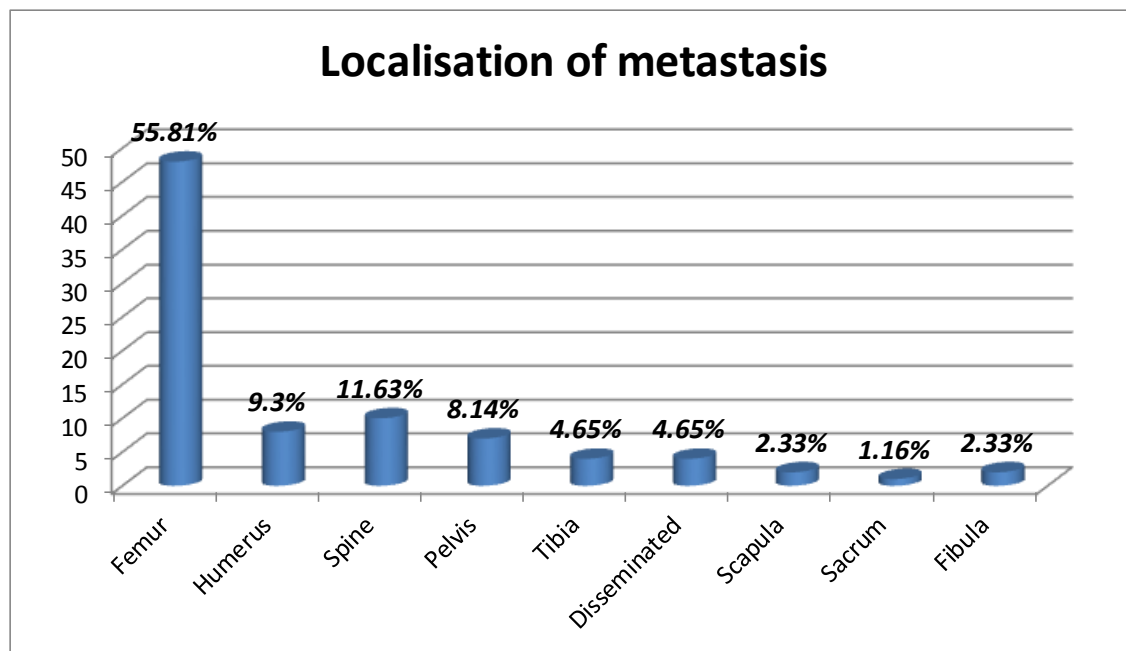
Table 2. Distribution of patients with bone metastases according to region and place of residence

Regio	Cases by region	Municipalities	Cases by municipality
<i>Polog</i>	5	<i>Tetovo</i>	3
		<i>Gostivar</i>	1
		<i>Jagunvce</i>	1
<i>Skopje</i>	31	Skopje	31
<i>Northeastern</i>	12	Kumanovo	9
		Kriva Palanka	2
		Kratovo	1
<i>Eastern</i>	7	Berovo	2
		Probištip	1
		Kočani	1
		Štip	3
<i>Southeastern</i>	3	Strumica	1
		Gevgelija	1
		Valandovo	1
<i>Vardar</i>	9	Veles	2
		Negotino	2
		Kavadarci	5
<i>Pelagonia</i>	9	Bitola	4
		Prilep	4
		Kruševo	1
<i>Southwestern</i>	7	Kičevo	2
		Ohrid	1
		Struga	2
		Debar	1
		Makedonski Brod	1
<i>Unknown</i>	3		



**Figure 2.** Distribution of patients with bone metastases according to regions in Republic of North Macedonia

The most common site of metastasis in our series was femur in 48 patients (55.81%), followed by spine in 10 patients (11.63%) and humerus in 8 patients (9.3%). In 4 (4.65%) patients lesions were disseminated to multiple bones (Figure 3).



**Figure 3.** Distribution of patients with bone metastases according to affected bone

Of 86 patients, almost one third of them, 28 (32.57%), were with unknown primary malignancy at the time of bone metastasis diagnosis. The most common origin in cases with known primary malignancy was breast (34.88%), lung, kidney and prostate, respectively (Table 3).

**Table 3.** Distribution of patients according to origin of primary carcinoma

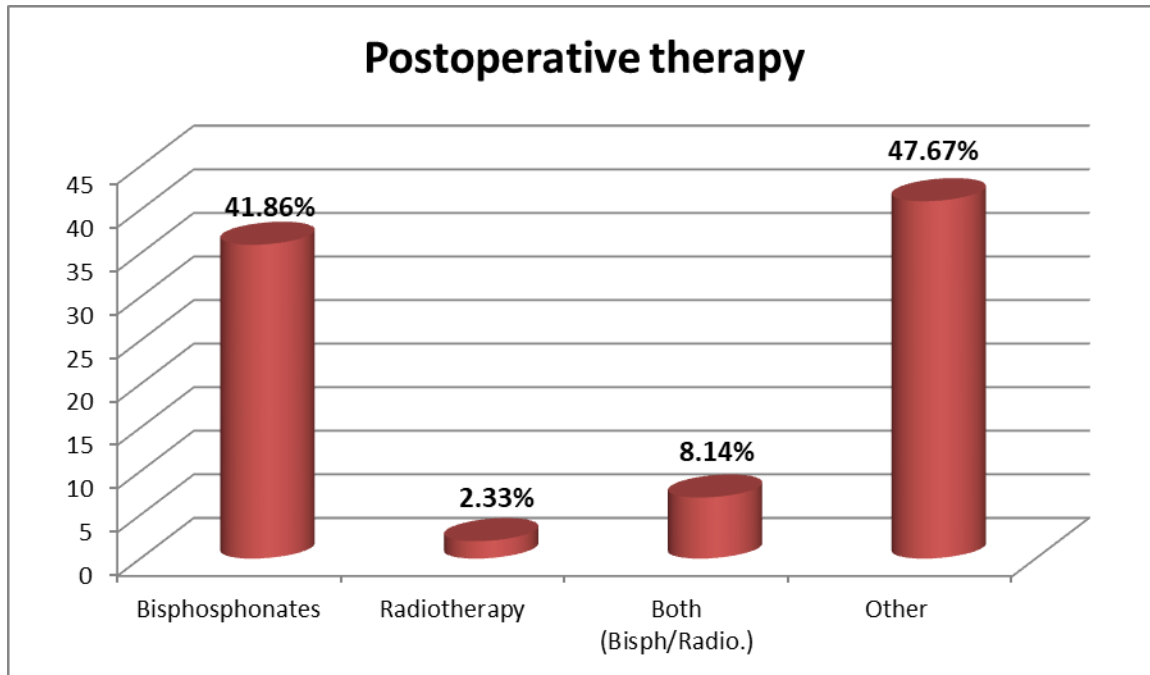
	Origin of primary neoplasm	Number of patients	Percentage (%)
1	Breast	30	34.88372
2	Lung	17	19.76744
3	Prostate	3	3.48837
4	Unknown	28	32.55814
5	Thyroid gland	1	1.16279
6	Urinary bladder	1	1.16279
7	Kidney	5	5.81395
8	Male genital system	1	1.16279
	Total	86	100

Analysis of patients' plain radiographies revealed that 65 (75.58%) patients had osteolytic bone lesion, 6 (6.97%) patients had osteoblastic and 15 (17.44%) patients had mixed osteolytic/osteoblastic lesion.

The type of postoperative therapy is shown in Table 3.

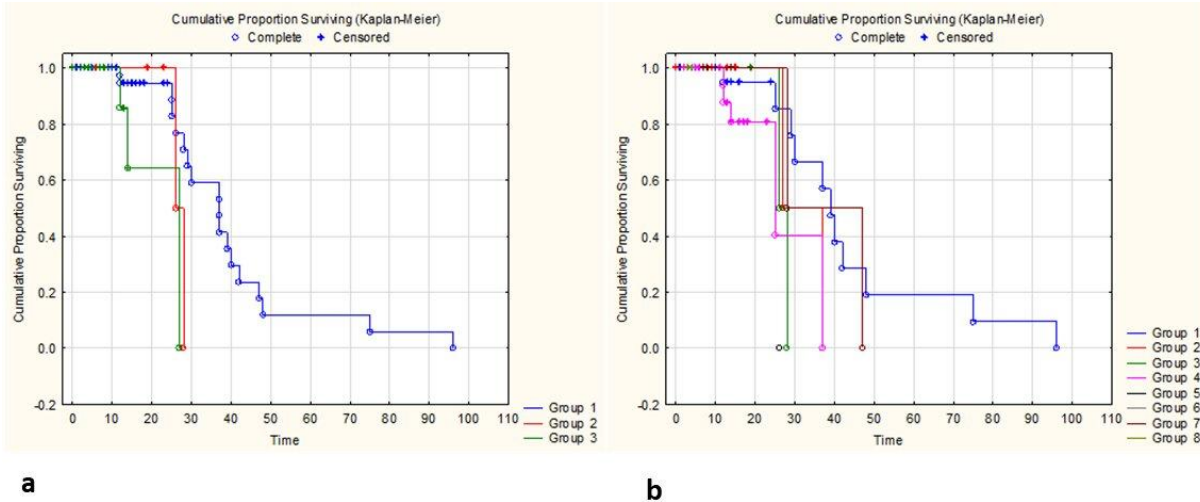
Bisphosphonate therapy was applied in only 41.86% of patients, radiotherapy was applied in only 2.33% patients and combination of bisphosphonates and radiotherapy received 8.14% patients.

The rest of the patients, 47.67%, were treated with symptomatic or systemic therapy according to their primary malignancy, or with combination of both.



**Figure 4.** Type of postoperative therapy in patients with bone metastases and percentage of patients in whom the therapy was applied

Only 26.74% of patients survived 24 months and high 73.26%, almost  $\frac{3}{4}$  of patients, survived 1 to 24 months. The survival analysis did not show statistically significant influence of any of analyzed parameters in this study on the survival of the patients (Figure 5).



\*a) 1-osteolytic lesion, 2-osteoblastic lesion, 3-mixed  
 b) See table 3.

**Figure 5.** Kaplan-Meier curves showing insignificant difference in survival rate according to plain radiography appearance of the lesions,  $p < 0.16$  (a) and the origin of primary malignancy,  $p < 0.60$  (b).

### Discussion

Survival from cancer has increased during the last few decades, so the incidence of bone metastases has increased, too [9]. Bones are one of the most common sites of metastases for many types of solid cancers and many studies have shown that the prevalence of bone metastases is more than 70% in patients with metastatic breast and prostate cancer, and approximately 30% in metastatic renal cell carcinoma [10]. The bone is the third common site of metastatic disease and only the lung and the liver have higher metastatic rate than skeleton [11]. In patients over 50 years of age, they are even more common than all primary bone malignancies together [12].

Age and gender distribution of BM varies from study to study depending on regions and analyzed groups, but they are rare in patients under 40 years and sex distribution generally depends on the primary malignancy type [1,12-14].

Clinically, bone metastasis can be asymptomatic in 5% to 25% of the patients [14]. However, most of the patients are symptomatic and present with variety of skeletal-related events: severe pain, impaired mobility, pathologic fractures, spinal cord compression, bone marrow aplasia and hypercalcemia [1,2,10,12,15]. Renal cell carcinoma metastases are most commonly associated with symptoms in patients [16]. It is considered that bone metastases lead to increase of mortality and morbidity of patients and seriously impair quality of life [10].

Pain is the most common presentation of skeletal metastasis [1,2,14], and it was noticed in all of our patients. Bone pain, especially in later phase of the disease, is constant, poorly localized and may be worse at night and during activity [2]. Bone pain with characteristics mentioned above may alert to a threatening pathological bone fracture [1].

Pathological fractures are a consequence of tumor-mediated bone destruction and typically occur when more than 50% of the cortex is destroyed [14]. In the study carried by Zacharia *et al.* [14] 27% of patients had a pathological fracture. In our study all of the analyzed patients presented with pain and more than half (59.3%) had a pathological fracture.

Radiography is considered insensitive to screen for asymptomatic metastases, but plain radiography is recommended as an initial imaging study in patients with bone pain, and hybrid techniques



which fuse morphological and functional data are the most sensitive and specific for BM [17]. Radiographic evaluation of BM can show osteolytic, osteoblastic or mixed pattern of presentation [1].

Osteolytic lesions in the skeleton are usually associated with breast cancers, renal cell carcinoma, melanoma, non-small cell lung cancer, non-Hodgkin lymphoma and thyroid cancer [1]. Destruction of the normal bone, as a main characteristic of osteolytic lesions, is thought to be a result of secretion of pro-osteoclastogenic cytokines that increase bone resorption. This microenvironment rich with parathyroid hormone-related peptide (PTHrP) interleukin-1 (IL-1), IL-6, macrophage colony-stimulating factor (M-CSF), RANKL stimulate osteoclast precursors and osteoclast activity with consecutive excessive bone resorption [1,6,8].

Mechanisms of excessive new bone formation with a poor quality in osteoblastic lesions are not fully understood [1]. Some tumor-derived factors lead to osteoblast proliferation, differentiation, and bone formation [9]. PSA and tumor-derived peptide endothelin-1 (ET-1) are seemed to be the major contributors in prostatic cancer bone metastases [1,18,19]. Additionally, carcinoid, small cell lung cancer, Hodgkin lymphoma and medulloblastoma can have this pattern of presentation [1].

Treatment of bone metastasis should be multidisciplinary, including combination of surgery, external radiotherapy, radionuclide therapy, ablation, accompanied by denosumab, bisphosphonate, chemotherapy, hormone and immunotherapy [2, 1, 4].

According to Shibata et al. [4] surgery is strongly suggested for pain relief and functional improvement in metastasis of long bones, and it is also beneficial in cases of spinal cord involvement or compression of peripheral nerve.

Bisphosphonates inhibit bone demineralization and promote osteoclast apoptosis, have not fully understood direct apoptotic effects on tumor cells (via modulation of activity of proapoptotic genes in tumor cells) and enhance immune surveillance against malignant cells [1]. In bone oncology they are widely used for treatment of tumor-induced hypercalcemia and bone pain [1, 4]. Shibata *et al.* [4] emphasized the benefit of using zoledronic acid and denosumab in patients with lung, breast and prostate cancer with a significantly decreased rate of skeletal-related events.

External radiotherapy provides a rapid pain relief in 80-90% of patients with localized metastatic bone pain [1].

Bone metastases significantly decrease the 5-year survival rates in patients: in prostate cancer patients with and without bone metastasis at diagnosis a 5-year survival rate of 3% and 56%, respectively, was observed [20]. For breast cancer these numbers were even worse (8.3% and 75.8%, respectively, for patients with and without bone metastasis at diagnosis) [4]. The median-survival of patients with BM, from the time of diagnosis, is from 6 months in melanoma to 19-25 months in breast cancer and 48 months in thyroid cancer [1].

In our study the most common site of bone metastasis was femur, 55.81%, followed by spine 11.63%, humerus 9.3% and pelvis 8.14%. Other authors reported the most common metastasis in the spine [10, 13,14], followed by the proximal segments of the limbs.

The median age of patients was  $65 \pm 9.85$  years. The youngest patient was 44 years old and the oldest 87 years old. Most of the patients were in the seventh decade of life (37.21%), followed by patients in the sixth decade (27.9%), which was in accordance with the data reported from other authors [14] and the data showing that BM rarely occurred in patients under the age of 50 (2.33%) [12,14].

Skeletal metastases were more common in female (60.47%) than in male (39.53%) patients with ratio 3:2. This data is opposite to the results obtained in other studies [13-16], in which the ratio was 3:2, male versus female. These studies pointed to the importance of estrogens and androgens on normal bone turnover. The protective effect of estrogens on the development of BM was also reported as a major factor of the lower prevalence in females [21,22,23].

The reason for this discrepancy between our data and other authors' reports may be due to the relatively small number of patients in our group and the fact that about 1/3 of all metastases in our study originated from the breast cancer.

Regarding the origin of primary malignancy, our study showed that 34.88% of BM originated from the breast cancer, 19.77% from the lung cancer, followed by the kidney and prostate cancers. In high 32.57% of cases, the primary origin of BM was not known at the time of diagnosis, which was similar to some studies [11], but much higher than others, in which only 2% of patients were with unknown primary lesion [24].

Some authors found that metastases of unknown primary origin were predominantly found in the male population [14]; in our study both sexes were equally represented, 14 male and 14 female patients, a total of 28 cases. This result may be due to the fact that in our study the female population was more prevalent.

The analysis of plain radiography in our study revealed 75.58% osteolytic, 17.44% mixed and 6.9% pure osteoblastic appearance of BM. BM from breast cancer were osteolytic in 95.35% and only 4.65% were mixed, osteolytic/osteoblastic. Prostatic cancer BM were 100% osteoblastic. Our results corresponded to other authors' reports [1,13,15,17].

In our study, more than half of the patients received bisphosphonates alone or in combination with radiotherapy. Radiotherapy alone was applied in 10.46% of the patients.

The survival analysis did not show statistically significant influence of any of the analyzed parameters in this study on the survival of the patients. More than 24 months survived only 26.74% of patients, and the other 73.26% survived 1 to 24 months, which corresponded to most of the reported data [1,4,25].

### **Conclusion**

In this study female patients were more prevalent and the median age of analyzed patients was 65 ± 9.85 years.

The most common site of BM was femur, and the most common primary malignancies were in the breast. Almost one third of patients were with unknown primary malignancy at the time of BM diagnosis.

Plain radiographies revealed that most BMs were osteolytic lesions.

The most common applied therapies were bisphosphonates only, applied in 41.86%, and symptomatic or systemic therapy and combination of both, applied in 47.67% patients.

The survival analysis did not show statistically significant influence of any of the analyzed parameters in this study on the survival of the patients.

Only 26.74% of patients survived 24 months and high 73.26% survived 1 to 24 months.

Undetermined primary malignancies are still a diagnostic problem in our daily practice accounting for more than 32% of the patients, so a more cooperative team work is needed to disclose the final diagnosis. Hopefully, this and other similar observations will contribute to further improvement of clinical approach in these patients, especially in early identification of high-risk patients and prevention of skeletal metastasis.

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