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13 Year Retrospective Analysis of Tumors Metastasizing to Bone

Kemiğe Metastaz Yapan Tümörlerin 13 Yıllık Retrospektif Analizi

Gamze Erkilinc[1], Ayca Tan[2], Hakan Koray Tosyali[3], Peyker Temiz[2]

[1]Izmir Bakircay University Faculty of Medicine, Department of Medical Pathology, Izmir, Türkiye
[2]Manisa Celal Bayar University, Faculty of Medicine, Department of Medical Pathology, Manisa, Türkiye
[3]Manisa Celal Bayar University, Faculty of Medicine, Department of Orthopedics and Traumatology, Manisa, Türkiye

ÖZET

Amaç: Kemik, onkolojik hastalarda primer tümörün metastazının sık görüldüğü bir dokudur. Çalışmamızda histopatolojik olarak kemik metastazı saptanan hastaların klinik ve patolojik özelliklerini, sağ kalım durumlarını değerlendirmek amaçlanmıştır.

Gereçler ve Yöntem: Patoloji anabilim dalımızda 2010-2023 yılları arasında kemikte metastatik tümör tanısı alan 107 hastaya ait materyallerin hematoksilen-eozin ve immünohistokimyasal boyalı preparatları retrospektif olarak değerlendirildi. Hastaların yaş, cinsiyet, sağ kalım, klinik sonuçları hastane kayıtlarından elde edildi. Primer odak, tümörün lokalizasyonu, tümörün histopatolojik özellikleri, hastaların sağ kalım durumu retrospektif olarak değerlendirildi.

Bulgular: 107 hastanın yaşları 36 ile 84 arasında değişmekte olup; 61'i erkek, 46'sı kadındı. Kemiğe en sık metastaz yapan tümör akciğer malignitesi (%32.7; n=35) olup onu meme malignitesinin (%22.4; n=24) takip ettiği izlendi. Hastaların % 35.5'inin (n=38)ilk tanısını metastaz ile aldığı tespit edildi. En çok femur kemiğine (%65.4) metastaz izlendi. Beş yıllık sağ kalım analizinde tükrük bezinin adenoid kistik karsinomunun metastazında sağkalımın en kısa (12 ay) olduğu, kolorektal, prostat ve tiroid tümörlerinde en uzun (60 ay) olduğu görüldü.

Sonuç: Kemikte en sık metastazın femurda görüldüğünü ve nadiren atipik bölgelerde de metastaz olabileceği, metastazın en sık adenokarsinom morfolojisinde olmakla birlikte karsinosarkom gibi farklı bir morfolojide de olabileceği saptandı. Hastaların bir kısmının ilk tanısını metastaz ile aldığı ve nadiren primer odağın belirlenemediği gözlendi. Tümör içeren kemik materyalleri değerlendirilirken, metastazların çok çeşitli lokalizasyon ve morfoloji ile karşımıza çıkabileceği akılda tutulmalıdır.

Anahtar Kelimeler: Kemik, metastaz, histopatoloji, malign tümör

ABSTRACT

Aim: Bone is a tissue in which metastasis of the primary tumor is common in oncological patients. In our study, we aimed to evaluate the clinical and pathological features and survival status of patients with histopathological bone metastases.

Materials and Methods: Hematoxylin-eosin and immunohistochemical stained preparations of materials belonging to 107 patients diagnosed with metastatic tumors in bone between 2010 and 2023 in our pathology department were evaluated retrospectively. Age, gender, survival, and clinical outcomes of the patients were obtained from hospital records. Primary focus, localization of the tumor, histopathological features of the tumor, and survival status of the patients were evaluated retrospectively.

Results: The ages of 107 patients ranged from 36 to 84; 61 of them were men and 46 were women. The tumor that most frequently metastasized to the bone was lung malignancy (32.7%; n=35), followed by breast malignancy (22.4%; n=24). It was determined that 35.5% of the patients (n = 38) were initially diagnosed with metastasis. Metastasis was mostly observed in the femur bone (65.4%). In the five-year survival analysis, survival was observed to be shortest (12 months) in metastasis of adenoid cystic carcinoma of the salivary gland and longest (60 months) in colorectal, prostate and thyroid tumors.

Conclusion: It was determined that the most common metastasis in bone was in the femur, and rarely in atypical areas. Although metastasis was most common in adenocarcinoma morphology, it could also be in a different morphology such as carcinosarcoma. It was observed that some of the patients were initially diagnosed with metastasis and rarely the primary focus could not be determined. When evaluating tumor-containing bone materials, it should be kept in mind that metastases can present with a wide variety of localizations and morphologies.

Keywords: Bone, metastases, histopathology, malignant tumor

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Sorumlu Yazar/Corresponding Author: Gamze Erkilinc, Izmir Bakircay University, Faculty of Medicine, Department of Medical Pathology, Izmir, Türkiye
e-mail: gamzecirak@gmail.com

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INTRODUCTION

One of the most frequent locations for primary tumor metastases in cancer patients is the bone. Metastatic bone cancers are more common than primary bone tumors. Every year, at least 100,000 people are diagnosed with bone metastases. However, the precise number is unknown (1, 2). Ninety percent of cancer-related fatalities globally are attributable to metastasis, with over 1.5 million people experiencing bone metastases (3). Additionally, in cases with unknown primary cancers, it may be identified as the sole finding (4). The prognosis is mainly determined by the histological characteristics of the initial tumor; however, the presence of bone metastases is a poor prognostic indication (4).

Similar to other organs, bone metastasis is a complex situation where tumor cells travel to the surrounding tissues singly or in groups before entering the circulatory or lymphatic system and eventually finding their way to the bone (5).

Bone metastases are more typically seen in the latter stages of breast cancer in women and prostate cancer in men. Epithelial malignancies often spread to the bone (5). Lung, thyroid cancers, melanoma, and kidney tumors also frequently spread to the bone (2, 6). Hematological cancers like lymphoma and myeloma can spread to the bone (2). The lung, liver and bone are the first three areas that should be considered in cases of metastatic cancer. Commonly affected areas are the femur, humerus, skull, vertebrae, ribs and pelvis (7).

Our study aimed to evaluate the clinical findings, histopathological features and survival status of patients with tumors that metastasized to the bone.

MATERIALS AND METHODS

The study included patients who were histopathologically diagnosed with metastatic tumors in the bone within 13 years and came to our Department of Medical Pathology between 2010 and 2023 and whose bone materials were available. The research excluded patients with hematolymphoid malignancies and primary bone cancers. The ethics committee at our university gave its approval for this retrospective study (21.06.2023/20.478.486/1904).

The hospital automation system provided information on the patients' ages, genders, presenting complaints, the bone or bones the tumor metastasized to, other metastatic foci, and their survival status. The patient's bone tissue samples were cut to 3–4 micrometers thick, fixed with 10% buffered formalin, and then stored in a 10% nitric acid solution for decalcification. Slides were then stained with standard hematoxylin and eosin and any additional immunohistochemically stained preparations that were thought necessary or desirable were retrospectively collected based on clinicopathological findings.

Statistical analysis

The normality of continuous data distribution was tested using the Kolmogorov-Smirnov test or the Shapiro-Wilk test. Continuous data were compared using the independent sample t test or the Mann-Whitney U test. The SPSS ver. 21 software package (IBM Corp., Armonk, NY, USA) was used for statistical analysis. The measurement of overall survival (OS) was conducted from the initiation of primary therapy to the occurrence of death or the last follow-up. The analysis of associations was conducted using either Chi-square or Fisher's exact test. The Kaplan-Meier method was employed to estimate survival curves, and the log-rank test was utilized to calculate p-values. The study also included Cox proportional hazards regression models to investigate the association between survival and variables in both univariate and multivariate models. Significance was attributed to values of $p < 0.05$.

RESULTS

The ages of the patients diagnosed with metastases in a total of 107 bones ranged between 36 and 84 years (median 62). The male/female ratio of the patients, 61 of whom were male and 46 of whom were female, was 1.32. The distribution of patients according to gender of primary focus is given in Table 1. The youngest patient was a 36-year-old female patient diagnosed with ductal adenocarcinoma metastasis of the breast. The oldest patient was an 84-year-old man with cutaneous squamous cell carcinoma metastases. It was determined that most of the patients (84, 78.5%) applied

Table 1. Metastatic Tumor Distribution by Main Focus and Gender

Primary Tumor Focus	Male, n(%)	Female, n(%)	Total n(%)
Lung	30 (85.7)	5 (14.3)	35 (32.7)
Breast	0 (0)	24(100)	24 (22.4)
Prostate	9 (100)	0(0)	9(8.4)
Not found	6 (66.7)	3 (33.3)	9 (8.4)
Kidney	5 (55.6)	4 (44.4)	9 (8.4)
Upper gastrointestinal	5 (71.4)	2 (28.6)	7 (6.5)
Thyroid	0 (0)	4 (100)	4 (3.7)
Cutaneous	1 (33.3)	2 (66.7)	3 (2.8)
Hepatopancreaticobiliary	2 (66.7)	1 (33.3)	3 (2.8)
Colorectal	1 (100)	0 (0)	1 (0.9)
Bladder	1 (100)	0 (0)	1 (0.9)
Uterus	0 (0)	1 (100)	1 (0.9)
Salivary gland	1 (100)	0 (0)	1 (0.9)
Total	61 (57)	46 (43)	107 (100)

to the hospital with complaints of pain. It was observed that the most frequently metastasized cancer was lung adenocarcinoma, followed by ductal adenocarcinoma of the breast. Macroscopic images of the patients materials are presented in figure 1. The following macroscopic images show colon adenocarcinoma metastases to the hand's distal phalanx (A), Lung adenocarcinoma metastases to the tibia bone (B), Squamous cell carcinoma of the lung metastases to the fibula bone (C), Breast ductal adenocarcinoma metastases to the femur bone (D), Lung adenocarcinoma metastasis to the femur bone (E), Clear cell renal cell carcinoma metastases to the humerus bone (F), Metastatic prostate cancer to the femur bone (G), Metastatic thyroid cancer to the femur bone (H), Metastasis of lung squamous cell carcinoma to the humerus bone (I)

The most commonly involved bone in metastasis is the femur (n=71, 60.5%), followed by the humerus (n=13, 15.8%), vertebrae (n=8, 7.4%), tibia (n=6, 5.6%) and pelvis (n=6, 5.6%), forearm (n=2, 1.8%), scapula (n=1, 0.9%) and distal phalanx of the hand (n=1, 0.9%).

Most of primary tumors metastasizing to the femur 81.7% (n=58) have adenocarcinoma morphology, followed by squamous cell carcinoma 7% (n=5), malignant epithelial tumor (Unable to determine specific subtypes) 7% (n=5), and small cell carcinoma of the lung n=3 (4.2%). It was noted

Figure 1. Macroscopic images of the patients materials

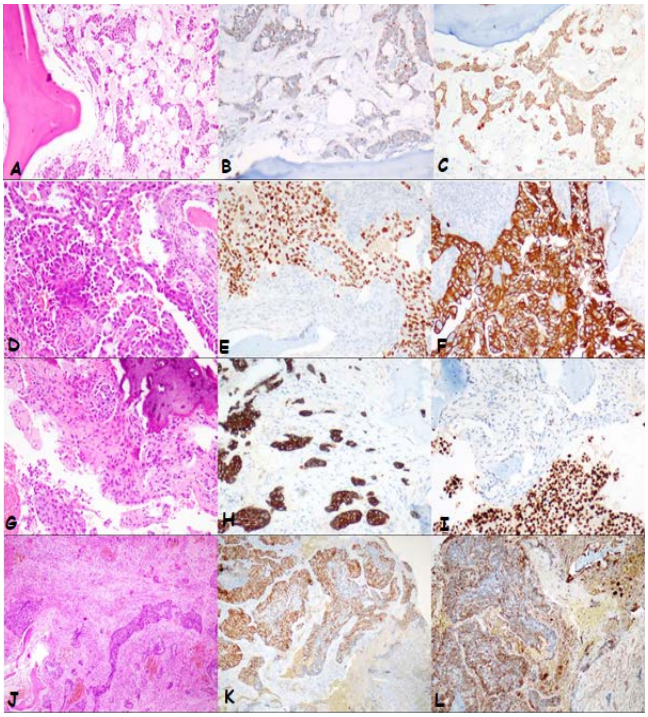

Figure 2. Microscopic findings of the metastatic tumors

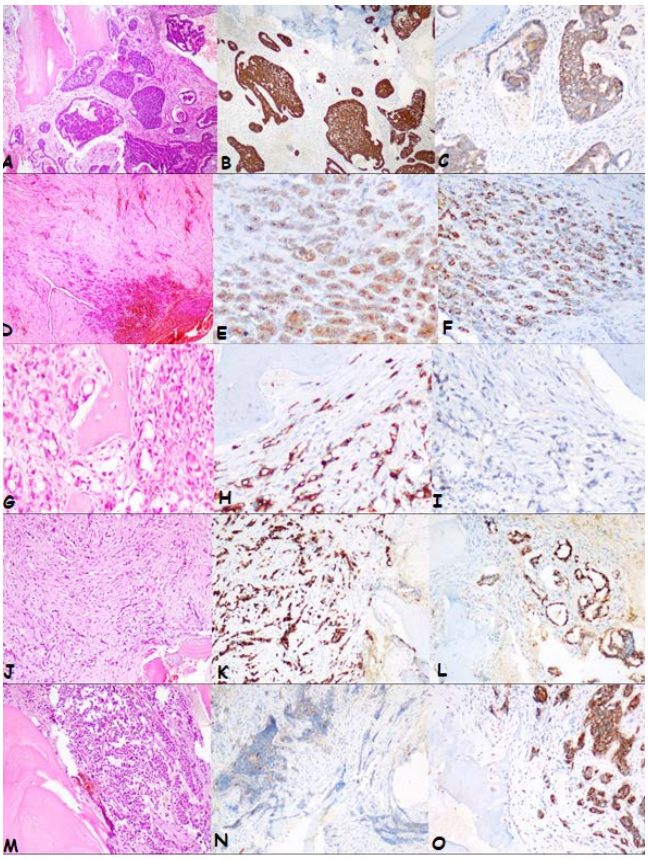

Figure 3. Microscopic findings of the metastatic tumors

Table 2. Tumor histopathological subtypes of metastatic patient

Tumor Histopathology	n	%	Total (%)
Adenocarcinoma	85	86.9	77.6
Squamous cell carcinoma	10	9.3	86.9
Malignant epithelial tumor (Unable to determine specific subtypes)	7	6.5	93.5
Small cell carcinoma	4	3.7	99.1
Carcinosarcoma	1	0.9	100.0
Total n (%)	107	100.0	100.0

that 32.4% (n=23) of primary tumors that metastasized to the femur were diagnosed with metastasis. The most common primary focus is lung in 29.6% (n=21), breast in 22.5% (n=16), renal cell carcinoma of the kidney in 11.3% (n=8), prostate in 9.9% (n=7), upper gastrointestinal (GI) system in 8.5% (n=7). =6), thyroid 4.2% (n=3), not found 7% (n=5), pancreaticobiliary 2.8% (n=2), salivary gland 1.4% (n=1) (Table 2). Microscopic findings of the cases are shown in figure 2 and 3. Metastatic prostate adenocarcinoma: (A) Epithelial island-like tumor cell groups following bone trabeculae (H&E x100); (B) Positivity of tumor cells with PSAP (x100), (C) Positivity of tumor cells with PanCK (x100). Metastatic lung adenocarcinoma: (D) Infiltration of epithelial cells in the papillary architecture adjacent to the bone trabeculae (H&E x100), (E) Positivity of tumor cells with TTF-1 (x100), (F) Positivity of tumor cells with CK7 (x100), Metastatic urothelial carcinoma: (G) Epithelial cell groups adjacent to bone trabeculae (H&E x100), (H) Positivity of tumor cells with CK7 (x100), (I) Positivity of tumor cells with GATA3 (x100), Metastatic carcinosarcoma: (J) Metastatic foci where epithelial and mesenchymal components are observed together between bone trabeculae (H&E x40), (K) Positivity of tumor cells with estrogen receptor (x40), (L) Positivity of tumor cells with vimentin (x40) and Metastatic adenoid cystic carcinoma: (A) Epithelial tumor islands adjacent to bone trabeculae (H&E x40), (B) Positivity of tumor cells with CK7 (x40), (C) Positivity of tumor cells with CD117 (x100), Metastatic thyroid carcinoma: (D) Epithelial tumor cell groups in a relatively follicular pattern with occasional overlap between bleeding areas adjacent to millimetric bone trabeculae (H&E x40), (E) Positivity of tumor cells with thyroglobulin (x200), (F) Positivity of tumor cells with TTF-1 (x100), Metastatic gastric signet ring cell carcinoma: (G) Intracytoplasmic mucin accumulation between bone trabeculae, sometimes glandular, sometimes scattered individual malignant epithelial cell infiltration (H&E x200), (H) Pale focal positivity of tumor cells with CDX2 (x200), (I) Positivity of tumor cells with CK7 (x200), Metastatic breast ductal adenocarcinoma: (J) Epithelial cell infiltration adjacent to bone trabeculae (H&E x100), (K) CK7 positivity of tumor cells (x100), (L) GATA 3 positivity of tumor cells (x100), Metastatic small cell neuroendocrine carcinoma: (M) Tumor cell infiltration adjacent to bone trabeculae (H&E x100), (N) Pale punctate positivity of tumor cells with PanCK (x100), (O) Positivity of tumor cells with chromogranin (x100)

Of the primary tumors that metastasized to the humerus, 30.8% (n=4) were lung and breast, 7.7% (n=1) could not be found, and 1 (7.7%) patient each had metastasis from the uterus and thyroid. The first diagnosis of malignancy were reported 46.2% (n=6) of the metastatic patients. It was observed that most of the metastases, 69.2% (n=9), had adenocarcinoma morphology. It was noted that 1 (7.7%) patient had carcinosarcoma. Among these metastatic tumors, one of them (12.5%) was originated from prostate and 37.5% (n=3) of them from breast.

Adenocarcinoma was the most prevalent metastatic tumor (77.6%; n = 83), with lung metastases accounting for 26.9% of cases (n = 7). Of the patients, 70 (65.4%) had multiple bone metastases. Hematoxylin and eosin-stained sections were used to identify the significant focus in 79 (73.8%) of the tumors, coupled with further immunohistochemistry slide targeted at the primary focus. Based on histopathological analysis, adenocarcinomas accounted for 23 (65.7%) of the tumors that metastasized from the lung to the bone, squamous cell carcinomas for 9 (25.7%), and small cell carcinomas for 3 (8.6%). Diagnoses were established by immunohistochemistry using the following done: p63, synaptophysin, chromogranin, CDX-2, CK7, TTF-1, HMWCK, CD56, CK19, EMA, NAPSIN A, PanCK, and synaptophysin. The most common site of metastasis in bone was the femur (n=21).

According to histopathology, the tumor that spread from the colorectal area to the bone had an adenocarcinoma-like appearance. It was determined that CK7, CDX-2, CK20, CEA, CK19, SATB2 positive or negative slides were used immunohistochemically to make the diagnosis. If the 24 tumors that spread from the breast to the bone, 22 (91.6%) had ductal adenocarcinoma-like histopathology, whereas the remaining 2 (8.4%) had lobular adenocarcinoma-like morphology. Immunohistochemistry was used to identify GCDFP15, GATA3, Mamaglobin, CK7, Estrogen, Progesterone, and e-cadherin slides as positive or negative. A tumor exhibiting carcinosarcoma morphology on histopathology metastasized from the uterus to the bone. It was discovered that the vimentin, PanCK, EMA, and CK5/6 slides that were immunohistochemically positive or negative were used to make the diagnosis. Noted was metastasis to the humerus bone.

Nine tumors with an acinar-type adenocarcinoma morphology were found to have metastasized from the prostate to the bone. By employing immunohistochemistry, it was discovered that the diagnosis was achieved in cases of positive or negative findings using the slides PSA, HMWCK, NKX3.1, AMACR, CK7, CK20, and PSAP. The most prevalent locations for bone metastases were seven femurs (77.7%), one pelvic (11.1%), and one vertebral (11.1%). Histopathologically, four tumors with a follicular pattern papillary carcinoma

Table 3. Primary foci of tumors that metastasize to bone and their diagnosis based on metastasis

Primary Tumor Focus	Diagnosed with Known, n(%)	Diagnosed with Metastasis, n(%)	Total Percentage n(%)
Colorectal	1 (100)	0(0)	1 (0.9)
Lung	23 (65.7)	12 (34.3)	35 (32.6)
Upper gastrointestinal	3 (42.9)	4 (57.1)	7 (6.4)
Breast	22 (91.7)	2 (8.3)	24 (22.4)
Cutaneous	2 (66.7)	1 (33.3)	3 (2.7)
Hepatopancreaticobiliary system	2 (66.7)	1 (33.3)	3 (2.7)
Kidney	5 (55.6)	4 (44.4)	9 (8.4)
Prostate	8 (88.9)	1 (11.1)	9 (8.4)
Thyroid	2 (50)	2 (50)	4 (3.7)
Not found	0 (100)	9 (100)	9 (8.4)
Bladder	0(0)	1 (100)	1 (0.9)
Uterus	1 (100)	0 (0)	1 (0.9)
Salivary gland	1 (100)	0 (0)	1 (0.9)
Total	70 (62.6)	37 (37.4)	107 (100)

Table 4. Univariate and Multivariate analysis results of tumors according to histopathological types

	Univariate		Multivariate	
Tumor Histopathology	**OR (95% CI)**	**p value**	**OR (95% CI)**	**p value**
Adenocarcinoma	Reference		Reference	
Squamous cell carcinoma	2.65 (1.33-5.27)	0.005	2.60 (1.28-5.30)	0.008
Malignant epithelial tumor (Unable to determine specific subtypes)	0.71 (0.30-1.66)	0.431	0.75 (0.28-1.98)	0.564
Small cell carcinoma	1.99 (00.61-6.47)	0.260	1.90 (0.56-6.43)	0.302
Carsinosarcoma	9.64 (1.24-74.78)	0.030	9.88 (1.24-78.60)	0.030
Diagnosis with metastasis				
Yes	Reference		Reference	
No	1.12 (0.72-1.74)	0.625	1.18 (0.71-1.98)	0.492
Number of metastatic focus				
Soliter	Reference		Reference	
Multible	1.28 (0.82-2.00)	0.275	1.27 (0.78-2.08)	0.335
Gender				
Male	Reference		Reference	
Female	0.72 (0.47-1.12)	0.147	0.93 (0.58-1.50)	0.778

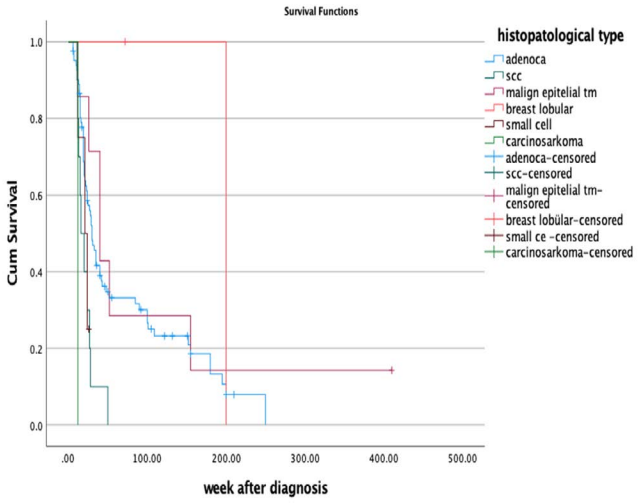

Figure 4. Carcinosarcomas have a much lower survival duration than other types

morphology had spread from the thyroid to the bone. It was discovered that in cases of positive or negative thyroglobulin, TTF-1, CK7, and CK20 slides, immunohistochemistry was used to make the diagnosis. 25% (n=1) of the cases of metastasis were found in the humerus and 75% (n=3) in the femur.

According to histopathology, three tumors with cutaneous-to-bone metastases were squamous cell carcinomas. It was discovered that immunohistochemistry was used to make diagnoses in cases where the findings of the PanCK, P63, P40, HMB45, and MelanA slides were either positive or negative. Nine tumors that spread from the kidney to the bone exhibited clear cell carcinoma of the kidney in terms of histopathology. It was discovered that CK7, CK20, AMACR, CD10, RCC, CA IX, vimentin, and PAX8 slides that were immunohistochemically positive or negative were used to make the diagnosis. Eight patients (88.9%) had metastases to their femur malignancy, whereas one patient (11.1%) had metastases to their forearm. Histopathologically, the tumor that spread from the bladder to the bone appeared to be papillary urothelial carcinoma.

It was discovered that CK7, CK20, GATA 3, and AMACR slides that were immunohistochemically positive or negative were used to make a diagnosis. The primary focus could not be determined with immunohistochemical results in 9 (8.4%) of the patients (Table 3). Of the patients, 69 (64.5%) had a primary diagnosis that was confirmed during follow-up, and 38 (35.5%) had metastases at the time of diagnosis (Table 3). Of the patients having metastases at admission, twenty-five (65.8%) and thirteen (34.2%) were female. Of the 69 patients with a recognized diagnosis, thirty-three (47.8%) were male and thirty-six (52.2%) were female. For 41% of male patients and 28.3% of female patients, the first diagnosis of metastasis was made.

The most common metastasis in men patients was to the femur bone (37, 60.7%); followed by humerus (6, 9.8%), pelvis (5, 8.2%), vertebrae (5, 8.2%), tibia (5, 8.2%), forearm (2, 3.3%) and hand bones (1, 1.6%). The femur (34, 73.9%) is the most often metastasized bone in female patients. Followed by humerus (7, 15.2%), vertebrae (3, 6.5%), tibia (1, 2.2%), and scapula (1, 2.2%). Male patients did not show signs of scapula metastases, whereas female patients did not show signs of metastases to the vertebrae, forearm, or hand bones. In our study, the median survival time for patients was 30 weeks for adenocarcinoma, 16 weeks for squamous cell carcinoma, 21 weeks for small cell carcinoma, 12 weeks for carcinosarcoma (Table 4). Log Rank analysis revealed a statistically significant difference ($p = 0.002$) in the survival duration between the tumors. Carcinosarcomas have a much lower survival duration than other types (Figure 4).

DISCUSSION

In our study, the relationship between the bones in which the metastatic tumor foci were localized in patients whose cancer spread to the bone, the histopathological characteristics of the tumors, the age, gender of the patients, and survival symptoms after diagnosis were investigated. Some patients may present to pathology with a preliminary diagnosis of a primary bone tumor because isolated metastases in long bones might resemble primary sarcomas (8). 40 (37.4%) of our patients had a preliminary diagnosis of bone cancer when they arrived at the clinic. Most patients with bone metastasis have been reported to be between 40 and 60 (9). In our study, the ages of the patients ranged between 36 and 84, and the median age was 62. Patients with bone metastases most often consult a doctor with bone pain. In evaluating these patients, accompanying pathological fractures can be detected (7, 10) (11). In our study, 78.5% of patients who complained of bone pain had pathological bone fractures. Pathological fractures, most commonly in the proximal femur, occur in 10–30% of patients (12). Our study noted that the primary tumor most frequently metastasized to the femur (60.5%) in the patients.

Bone metastases are primarily seen in the pelvis, sternum, femur, ribs, and vertebrae (7). In our study, the most frequently involved bone was the femur (n=71, 60.5%), followed by the humerus (n=13, 15.8%), vertebra (n=8, 7.4%), tibia (n=6, 5.6%) and pelvis (n=6, 5.6%), forearm (n=2, 1.8%), scapula (n=1, 0.9%), and distal phalanx of the hand (n=1, 0.9%). Metastasis of the male patient diagnosed with colon adenocarcinoma to the distal phalanx bone in the hand was noted. Research involving 712 individuals with bone metastases revealed metastases in various locations, including the elbow, knee and face bones (11). In our study metastasis was observed in different localizations such as hand bone, scapula and radius bone, and the distribution of these metastasis was varied according to gender. In male and female patients, the most common metastasis was observed in the femur bone (34, 73.9%) (37, 60.7%); metastases to the scapula bone were not observed in male patients and metastases to the vertebrae, forearm and hand bones were not observed in female patients.

Adenocarcinoma is the most common epithelial tumor among bone metastasis (13). In our study, the most common morphology was adenocarcinoma (77.6%), followed by squamous cell carcinoma (9.3%). The frequency of metastasis to bone is significantly affected depending on the primary focus. The rate of metastasis to bone in breast and prostate cancers is about 70%. Other primary tumors that metastasize to bone include thyroid carcinomas, malignant melanoma, and renal cell carcinoma of the kidney (6). Lung, breast and prostate was the most common metastatic malignancies according to our study. Bone metastasis has been reported at a rate of 3-15% in primary GI tract tumor malignancies (14). In our study, we observed upper GI metastases in 7 patients (6.5%) and GI metastases in 1 patient (0.9%) in 7.3% of the patients. Bone involvement can also be observed in hematological malignancies, such as lymphoma and plasma cell neoplasia (2). We did not include these patients in our study.

The primary focus cannot be detected in 3-15% of metastatic malignancies, and 5-20% of this is seen to be skeletal metastasis (9). Despite additional immunohistochemical methods in our study, the primary focus could not be detected in 9 (23.7%) patients. In a cohort study conducted in Denmark, the most common metastasizing primary cancers were prostate, breast, and lung, and 7.5% of patients showed metastasis to bone (15). In our study, the primary focus was most frequently detected in the lung, followed by breast and prostate. Metastasis to the humerus in 1 patient diagnosed with uterine carcinosarcoma was noted. A study conducted in the USA reported that patients with solid tumors had metastases to the bone more frequently in the first 2 years (9, 16). Our study detected metastases in 67 (62.6%) patients during follow-up after diagnosis. Bone is the third most common site of metastasis after lung and liver (8). There is limited data in the literature on which bone metastases occur depending on the location of the primary focus. In our study, we found that the primary tumors that metastasized to the femur were most commonly adenocarcinoma morphology (78.9%, n=56), and the primary focus was the lung (29.6%, n=21), followed by the breast (22.5%, n=16). We also observed that metastasis to the humerus bone occurred most frequently from lung and breast (30.8%, n=4). It was determined that 37.5% (n=3) of the primary tumors that metastasized to the vertebrae originated from the breast, and one patient (12.5%) originated from the prostate.

The tumor's primary focus and histopathological subtype and the time taken for bone metastasis vary (17). In our study, the time of patients with adenocarcinoma metastasis was 30 weeks. In comparison, it was 16 weeks for patients with squamous cell carcinoma metastasis and 40 weeks for patients with malignant epithelial tumor (Unable to determine specific subtypes) metastasis. It was observed that the duration was 21 weeks for patients diagnosed with small cell carcinoma, and 12 weeks for patients diagnosed with carcinosarcoma. According to Log Rank analysis regarding survival time among tumors, it was observed that the survival time of carcinosarcomas was significantly shorter than the others.

It has been shown that the primary cannot be found in 3-15% of all patients with cancer and that 5-20% of them have skeletal metastases (9). There is a study of CK7, CK20 panel, and organ-specific/organ-restricted markers in metastatic carcinoma to suggest or confirm the primary focus of metastasis (13). For skeletal metastases of unknown primary; the primary could be identified in 85% of cases by a series of methods such as anamnesis, physical examination, laboratory tests, imaging methods of abdomen and pelvis, and finally biopsy of the most accessible bone lesion (18). Errani et al. used the immunohistochemical method to determine the primary in 52% of metastasis cases of unknown origin (19). In our study, out of 107 patients with bone metastases, different immunohistochemical panels were applied to patients whose primary diagnosis was unknown or whose primary diagnosis was known but to confirm metastasis. CEA, CK19, EMA, NAPSIN A, PanCK, p63, synaptophysin, chromogranin, CDX-2, CK7, TTF-1, HMWCK, CD56 slides for lung adenocarcinoma, CK20, CK7 CDX-2, CEA, SATB2 slides for the GI system, CK20, CK7, CDX-2, CEA, CK19, SATB2 slides for hepatopancreatic biliary system, GCDFP15, GATA3, Mamaglobin, CK7, Estrogen, Progesterone, e-cadherin slides for breast ductal adenocarcinoma, PanCK, AMACR, CK7, CK20, NKX3.1 for prostate, PSA, PSAP, HMWCK, P63, PSAP slides for the prostate, thyroglobulin, TTF-1, CK7, CK20 slides for the thyroid, PanCK, P63, P40, HMB45, MelanA slides for the cutaneous, CK7, CK20, AMACR, CD10, RCC, CA IX, vimentin, PAX8 slides for the kidney, and CK7, CK20, GATA 3, AMACR for the bladder. Unfortunately, the primary focus could not be detected in a small number of patients (n: 9, 8.4%). A situation that may cause: This situation may be due to the decalcification process (waiting with 10% nitric acid until they become cuttable) before fixation.

Metastasis to hand bones is observed very rarely. In a study conducted in 1984 by reviewing all the literature, metastases to the hand bones were detected in 0.1% of all metastatic patients (163 patients). It has been observed that metastases from the lung, breast, and kidney are the most common (20). More recently, in a study conducted in 2014, GI metastases were noted in 25% of patients (21). Our study detected colon adenocarcinoma metastasis from the hand bones to the distal phalanx in 1 patient.

CONCLUSION

Among bone metastasis the most common side was femur and rarely others. Metastasis was most commonly in the morphology of adenocarcinoma, but determined also in different morphology, such as carcinosarcoma. It was observed that some of the patients were first diagnosed with metastasis. Rarely the primary focus could not be determined. The survival rate of metastatic tumors varies, with the lowest survival rate being in salivary gland tumor metastases. When evaluating tumor-containing bone materials, it should be remembered that metastases can present with various localizations and morphologies.

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Address correspondence to: *Gamze Erkilinc, Izmir Bakircay University Faculty of Medicine, Department of Medical Pathology, Izmir, Türkiye*

e-mail: *gamzecirak@gmail.com*

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