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ORIGINAL ARTICLE

The functional and clinical outcomes of primary and metastatic malignancies of the elbow

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Elbow tumors are rare, accounting for approximately 1% of all bone neoplasms, and primary bone tumors, metastatic disease and soft tissue tumors in the elbow and surrounding area are rare.[1] Their diagnosis and management pose a challenge to the orthopedic oncologists. Elbow tumors are surgically challenging due to their association with dense neurovascular structures, requiring careful preoperative planning and evaluation of different resection and reconstruction techniques depending on tumor size and location.[2] The complex nature of the elbow region leads to a higher rate of residual disease and local recurrence.[3] The main goal of treatment is to preserve of limb function through wide resection of tumor tissue (Figure 1). A successful reconstruction of the elbow joint would result in a more satisfactory functional outcome than an amputation.

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ABSTRACT

Objectives: This study aims to investigate the etiological distribution of primary and metastatic malignancies around the elbow and the effect of surgical and adjuvant treatments on clinical outcome.

Patients and methods: Between January 2006 and December 2020, medical records of a total of 33 patients with elbow neoplasm (15 males, 18 females; median age: 55 years; range, 39 to 71 years) who underwent surgical treatment and with or without clinical treatment were retrospectively analyzed. The outcomes and frequencies of the elbow metastatic and primary malignancies were evaluated. Data were collected from patients' medical and radiological documents, and a dedicated archive was created for this study.

Results: Most tumors occurred on the right side and were intra-articular or distal to the humerus. A total of 75.8% (25/33) of the patients had tumors of any diameter ≥5 cm. Most patients were treated with extensive resection. A total of 81.8% (27/33) of the patients had wide resected tumor margins, and 18.2% (6/33) had intralesional tumor margins. The median follow-up was 42 (range, 1 to 83) months. Synovial sarcoma and malignant peripheral nerve sheath tumors were the most common soft tissue sarcomas, and pulmonary adenoma and multiple myeloma were found in metastatic lesions.

Conclusion: Elbow surgery is particularly challenging due to the interrelationship of major neurovascular structures. Synovial sarcoma and malignant peripheral nerve sheath tumors are the most common soft tissue sarcomas, and pulmonary adenoma and multiple myeloma are found in metastatic lesions. Limb-sparing surgery is the gold-standard method recently.

Keywords: Elbow, limb-sparing surgery, malignant bone tumors, soft tissue sarcoma, wide resection.

A thorough history, comprehensive physical examination, and imaging studies such as plain radiographs are usually sufficient to suspect malignancy. Infection, trauma, and inflammatory processes should be considered in the differential diagnosis. The most common symptoms are pain and

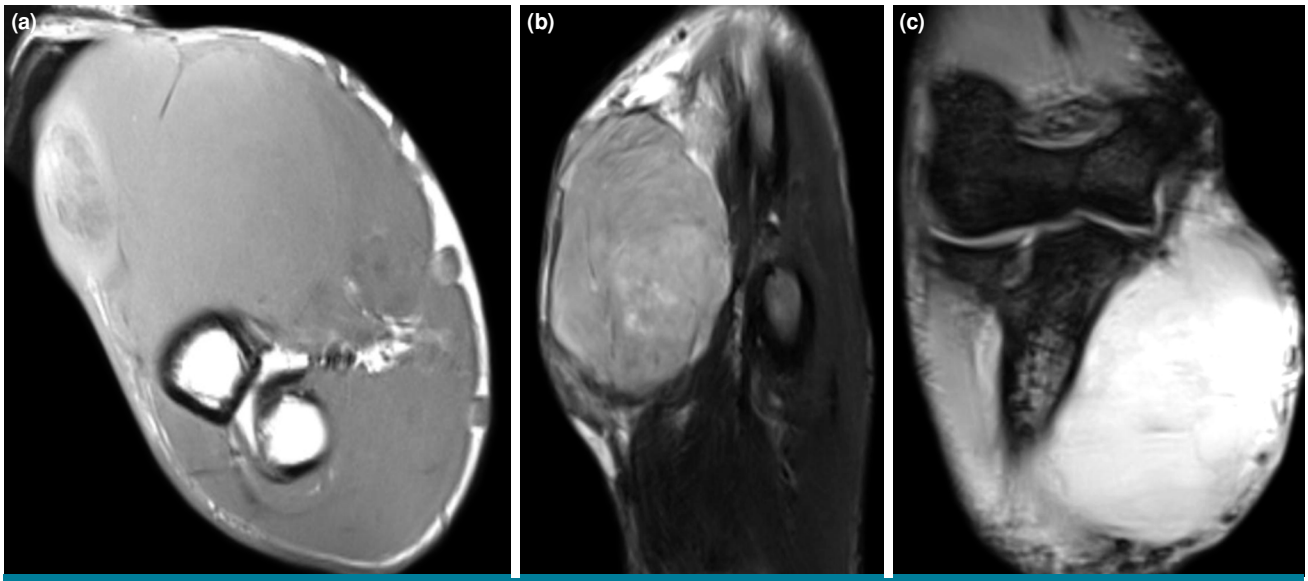


FIGURE 1. (a) Transverse, **(b)** sagittal and **(c)** coronary sections of magnetic resonance imaging of a malignant peripheral nerve sheath tumor demonstrating the proximity of neurovascular structures.

the presence of a palpable mass. However, these are not specific findings. To evaluate the mass locally, its size, the characteristics of the neoplastic tissue, and its relationship with nearby neurovascular structures, magnetic resonance imaging (MRI) is required.[3]

Limb salvage surgery has become the preferred treatment in recent years. However, its impact on function, survival, recurrence and metastasis has not been fully understood yet. There are also uncertainties about metastatic tumors.[4] In the present study, we aimed to investigate the outcomes of primary and metastatic tumors of the elbow, as well as the effectiveness of radiotherapy and chemotherapy.

PATIENTS AND METHODS

This single-center, retrospective cohort study was conducted at Gazi University Faculty of Medicine and Abdurrahman Yurtaslan Training and Research Hospital, Departments of Orthopedics and Traumatology between January 2006 and December 2020. A total of 33 cases of elbow malignancy (15 males, 18 females; median age: 55 years; range, 39 to 71 years), selected from a total of 1,404 cases of malignancy, were included in the study. The outcomes of metastatic and soft tissue tumors of the elbow were evaluated. Data were collected from the patients' medical and imaging records and a database was created specifically for this study.

The first survey collected patient characteristics, including baseline patient features (age, sex, time of diagnosis, side of the lesion, location in the region (elbow, distal humerus, radial head, olecranon), size of tumor, type of operation (Figure 2), resected tumor margins (categorized as R0, R1 and R2 for primary tumors), pathological diagnosis, histopathological grade, Tumor, Node, Metastasis (TNM) staging (7th Edition American Joint Committee on Cancer [AJCC][5]), surgical data (type of surgery, and existence of extra surgery for complications) and information about neoadjuvant/adjuvant therapy (including chemotherapy, radiation therapy). The Musculoskeletal Tumor Society (MSTS) score was used to assess functional status of the affected limb. The Mayo Elbow Performance Score (MEPS) was used to evaluate the form of disability associated with elbow injuries. In addition, plain radiography, computed tomography (CT) and/or MRI were used to define radiological features. These imaging techniques are typically used to investigate the presence of pathological fracture, lytic lesion in bone, soft tissue invasion and contrast uptake difference separately in primary sarcoma and metastatic tumors, and to attempt to determine different points in the radiological prediagnosis.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 25.0 software (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was used to determine

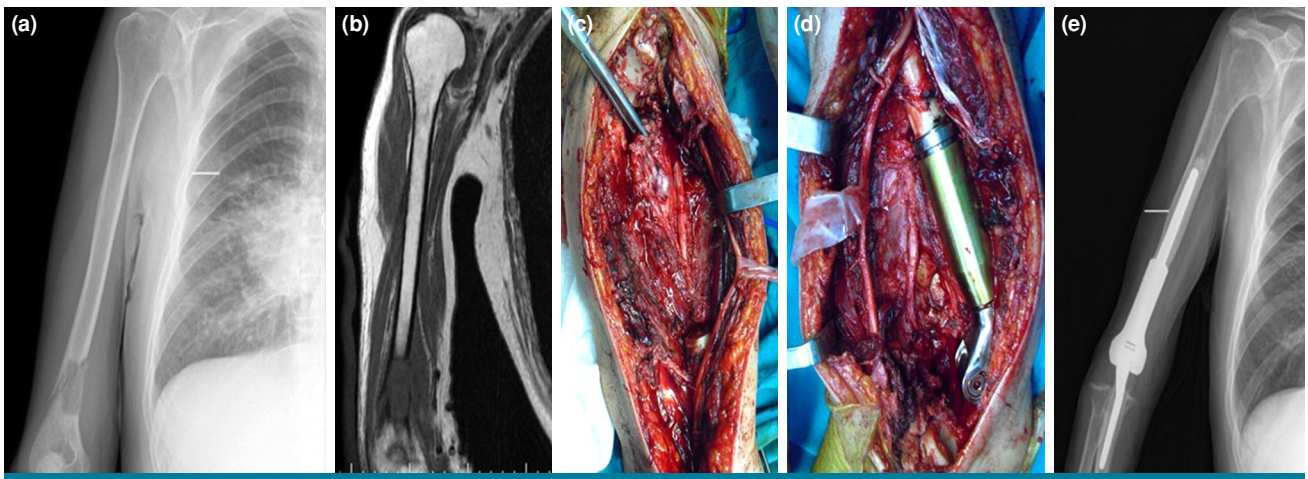


FIGURE 2. (a) Preoperative X-ray example of distal humerus pathological fracture (pulmonary adenocarcinoma metastasis), **(b)** preoperative magnetic resonance imaging coronal image, **(c)** intraoperative imaging before prosthesis, **(d)** intraoperative imaging before prosthesis, **(e)** postoperative humerus distal tumor resection arthroplasty.

whether variables were normally distributed. Continuous data were expressed in median and interquartile range (IQR) (25^{th}-75^{th} percentile), while categorical data were expressed in number and frequency. Numerical variables were compared using the Mann-Whitney U test for non-parametric variables. The chi-square test with Yate's correction and Pearson chi-square were used to compare categorical data. The Kaplan-Meier survival analysis was used to estimate the duration of the survival. A p value of <0.05 was considered statistically significant.

RESULTS

Compared to all orthopedic oncology patients undergoing surgery of our archives, the rate of all elbow malignancies was 2.3%, the rate of primary sarcomas alone was 0.9%, and the rate of metastatic tumors was 2.84%. Most of the tumors were located in the right side and in the elbow or distal humerus. A total of 75.8% (25/33) of the patients had a tumor with ≥5 cm in diameter. In addition, 81.8% (27/33) of the patients had wide resected tumor margins, and 18.2% (6/33) had intralesional tumor margins

TABLE I
Demographic features, side, and location of tumors of the patients (n=33)

	All patients				Soft tissue tumors (n=13)				Osseous tumors (n=20)				
	n	%	Median	IQR	n	%	Median	IQR	n	%	Median	IQR	*p*
Age (year)			55.0	39.0-71.5			50.0	24.5-71.5			63.5	40.8-72.3	0.456
Sex													0.948
Male	15	45.5			6	46.2			9	45.0			
Female	18	54.5			7	53.8			11	55.0			
Side of lesion													0.567
Right	21	63.6			7	53.8			6	30.0			
Left	12	36.4			6	46.2			14	70.0			
Localization of the tumor													
Elbow	16	48.5			11	84.6			5	25.0			
Distal humerus	13	39.4			2	15.4			11	55.0			
Radial head	1	3.0			-	-			2	10.0			
Olecranon	1	3.0			-	-			1	5.0			
Size of tumor (in any diameter (cm)													
<5 cm	8	24.2			2	15.4			6	30.0			
≥5 cm	25	75.8			11	84.6			14	70.0			

IQR: Interquartile range.

TABLE II
Type of operation, type of resected tumor margin, and pathological diagnosis, follow-up duration and recurrence ratio of the patients (n=33)

	All patients				Primary sarcoma (n=13)				Metastatic tumors (n=20)				
	n	%	Median	IQR	n	%	Median	IQR	n	%	Median	IQR	*p*
Type of operation													
Wide resection	15	45.4											
Tumor resection prosthesis	7	21.2											
Curettage, cement augmentation, and internal fixation	4	12.1											
Curettage, cement augmentation	2	6.1											
Transhumeral amputation	3	9.1											
Curettage and internal fixation	1	3.0											
Cryopreservation	1	3.0											
Type of resected tumor margin													
Wide	27	81.8			13	100.0			14	70.0			
Intralesional	6	18.2			-	-			6	30.0			
Surgical margin													0.041
R0	13	86.7			13	86.7			-	-			
R1	2	13.3			2	13.3			-	-			
R2	0	0			0	0			-	-			
Pathological diagnosis													
Pulmonary adenocarcinoma metastasis	4	12.1											
Multiple myeloma	4	12.1											
Pulmonary squamous cell carcinoma metastasis	3	9.1											
Mammary adenocarcinoma metastasis	3	9.1											
Synovial sarcoma	3	9.1											
Malign peripheric nerve sheath tumor	2	6.1											
Pleomorphic sarcoma	2	6.1											
Hodgkin lymphoma	1	3.0											
Neuroendocrine tumor metastasis	1	3.0											
Dermatofibrosarcoma protuberans	1	3.0											
Embryonal rhabdomyosarcoma	1	3.0											
Epithelioid sarcoma	1	3.0											
Ewing sarcoma	1	3.0											
Fibromyxoid sarcoma	1	3.0											
Non-Hodgkin lymphoma	1	3.0											
Colon adenocarcinoma metastasis	1	3.0											
Metastatic leiomyosarcoma	1	3.0											
Myxoid liposarcoma	1	3.0											
Plasmacytoma	1	3.0											
Follow-up duration after the operation (month)			42.0	13.0-69.6			32.0	10.5-57.5					0.094
Recurrence	2	6.1			2	15.4			-	-			0.317

IQR: Interquartile range.

TABLE III
Clinical features of the patients associated with malignancy and type of neoadjuvant treatments

	All patients				Primary sarcomas (n=13)				Osseous metastasis (n=20)				
	n	%	Median	IQR	n	%	Median	IQR	n	%	Median	IQR	*p*
Chemotherapy history	23	67.6			6	46.2			17	85.0			**0.018**
Chemotherapy cures			4. 0	3.0-5.0			0.0	0.0-3.0			3.5	2.0-5.5	**0.022**
Radiotherapy history	17	51.5			8	61.5			9	45.0			0.481
Bone marrow transplantation	1	3.0			-	-			1	5.0			
Complications	4				2				2				
MSTS score		23.48											
MEPS score		73.6											
Grade of cancer													0.919
1	6	18.2			2	15.4			4	20.0			
2	14	42.4			6	46.2			8	40.0			
3	13	39.4			5	38.1			8	40.0			
Stage of cancer (TNM)													
I	6	18.2			2	15.4			4	20.0			
II	7	21.2			3	23.1			4	20.0			
III	6	18.2			6	46.2			-	-			
IV	14	42.4			2	15.4			12	60.0			
Stage of cancer (AJCC)													
IA	5	15.2			1	7.7			4	20.0			
IB	1	3.0			1	7.7			-	-			
IIA	2	6.1			1	7.7			1	5.0			
IIB	5	15.29			2	15.4			3	25.0			
III	6	18.2			6	46.2			-	-			
IVA	1	3.0			-	-			1	5.0			
IVB	13	39.4			-	-			11	55.0			
Status of patients													
Alive	18	54.5			11	73.3			7	87.5			0.739
Deceased	15	45.5			4	26.7			1	12.5			0.913

IQR: Interquartile range; MSTS: Musculoskeletal Tumor Society; MEPS: Mayo Elbow Performance Score; TNM: Tumor, node, metastasis; AJCC: American Joint Committee on Cancer.

(curettage + cementing in metastatic carcinomas). The median follow-up was 42.0 (range, 13.0 to 69.6) months, with a minimum of 1.0 and a maximum of 83.0 months (Table I). The recurrence rate after the operation was 6.1% (2/33). The median MSTS score was 23.48 (range, 10 to 30). The median MEPS score was 73.6 (range, 25 to 95). The MSTS functional scores were low and MEPS functional scores were fair as expected in patients who underwent prosthetic surgery.

For primary sarcomas, 10 out of 15 patients (66.7%) had a tumor size greater than 5 cm, while five patients (33.3%) had a tumor size less than 5 cm. Analysis of the effect of tumor size on surgical margin recurrence and survival showed a statistically significant association with surgical margin (p=0.041). However, no effect was observed on recurrence and survival (p=0.317, p=0.739). When the surgical margins of the primary sarcomas were analyzed, 13 out of 15 patients had an R0 margin, 2 had an R1 margin and none had an R2 margin. In terms of the relationship between surgical margin and recurrence, no statistically significant relationship was found (p=0.506). There was also no significant relationship when analyzing the relationship between recurrence and the addition of chemotherapy/radiotherapy with survival (p=0.365, p=0.913).

In our study, the most common soft tissue sarcomas were synovial sarcoma and malignant peripheral nerve sheath tumors, and metastatic lesions were found to be pulmonary adenoma and multiple myeloma. The type of operation, type of resected tumor margin, and pathological diagnosis, follow-up duration and recurrence ratio of the patients are shown in Table II.

Clinical features of the patients associated with malignancy and the time to the last visit after the operation are in Table III. Almost two-thirds of the patients had a chemotherapy history, and nearly one-half had a radiotherapy history. The grade of cancer was 1 in 18.2% (6/33), 2 in 42.4% (14/33), and

3 in 39.4% (13/33) of the patients. The frequency of chemotherapy history and cure number were significantly higher in the osseous metastasis group (p=0.018, p=0.022). The frequency of radiation history and grade of cancer was similar between the groups (p>0.05). Four complications were observed; two of them were infections after comprehensive resection surgery. Patients were treated with debridement surgery. One of the complications was the loosening of the prosthesis. The patient followed, as there was a complaint. One of the complications was radial nerve neuropraxia treated with medical interventions.

Comparing the radiological characteristics of the two groups, the pathological fracture rate was not statistically different (p=0.051). However, pathological fracture was significantly more common in metastatic lesions (p=0.035), soft tissue invasion and contrast uptake difference were significantly more common in primary sarcomas (p<0.01, p=0.002), and lytic lesions in bone were more common in metastatic lesions (p<0.01).

During follow-up, the mortality rate was 54.5% (18/33). The Kaplan-Meier survival analysis showed that mean survival was 47 months with a standard error (SE) of 7.925 (range, 31.467 to 62.533) at 95% confidence interval (CI) (Figure 3). The median cumulative survival rate in the first year was 55.7% with an 8.9% SE, while it was 41.1% with a 9.2% standard error at five years. The median cumulative survival rate in the first year for soft tissue metastasis (n=13) is 76.9% with 11.7% SE versus 40.3% with 11.6% SE for osseous metastasis (n=20). The median cumulative survival rate at five years for soft tissue metastasis was 57.7% with a 15.0% SE error, while 28.8% with a 10.8% SE for osseous metastasis patients. Regarding survival rate, no significant difference between soft tissue metastasis and osseous metastasis groups was found (p=0.094).

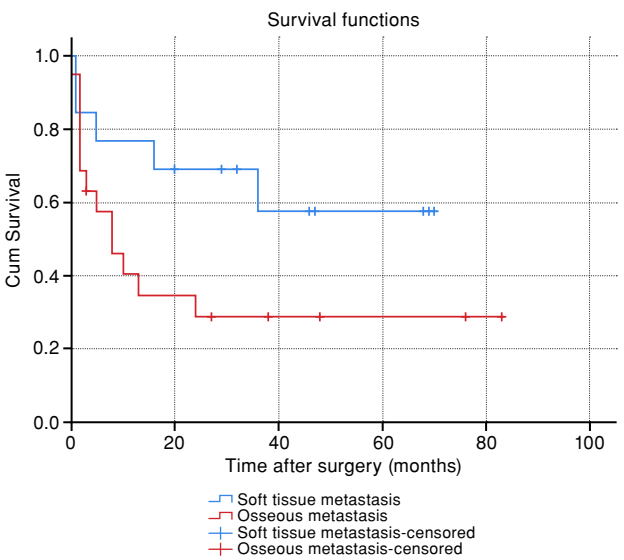


FIGURE 3. Kaplan-Meier survival analysis of soft tissue sarcomas and metastatic tumors.

DISCUSSION

Compared with other parts of the body, primary and metastatic malignancies of the elbow are rare.[6,7] A study of metastases in the upper extremities found that the most common sites of metastases were the humerus, the scapula and the clavicle, but the elbow was not evaluated.[8] There is a limited number of literature data on malignancies of the elbow. In the present study, the primary sarcoma rate was found to be 0.9% and the metastatic tumor rate was 2.84%, which is consistent with the literature. Physicians must be aware of the characteristics of the lesion to accurately evaluate and refer any patient with suspected elbow neoplasm to a reference center to prevent misdiagnosis and misinterpretation of the lesion, ensuring appropriate treatment.[9]

The most common elbow malignancies are metastatic and hematological. Multiple myeloma and renal cell carcinoma metastasis were the most common malignancies with a rate of 21% in the case series by Kruckeberg et al.[10] In our case series, multiple myeloma and lung carcinoma metastasis were 12% and 21% respectively and were the most common histological subtypes in this analysis. Although rare, metastases and soft tissue sarcomas should be kept in mind, when a swelling is seen in the elbow region. Our case series revealed that soft tissue involvement and contrast uptake difference were primarily seen in primary sarcomas when examined radiologically, while metastatic lesions exhibited more lytic lesions and pathological fracture features. Although periosteal reaction was associated with pathological fracture in metastatic lesions, there was one case of metastatic adenocarcinoma that invaded soft tissue in addition to bone (Figure 4).

Among all soft tissue sarcomas, sarcomas of the elbow region are less common than in other regions. The most common malignancies reported in the case series published to date are Ewing sarcoma, undifferentiated pleomorphic sarcoma, synovial sarcoma and clear cell sarcoma. In our case series, synovial sarcoma, malignant peripheral nerve sheath tumor and pleomorphic sarcoma were the most common types observed. Ewing sarcoma was

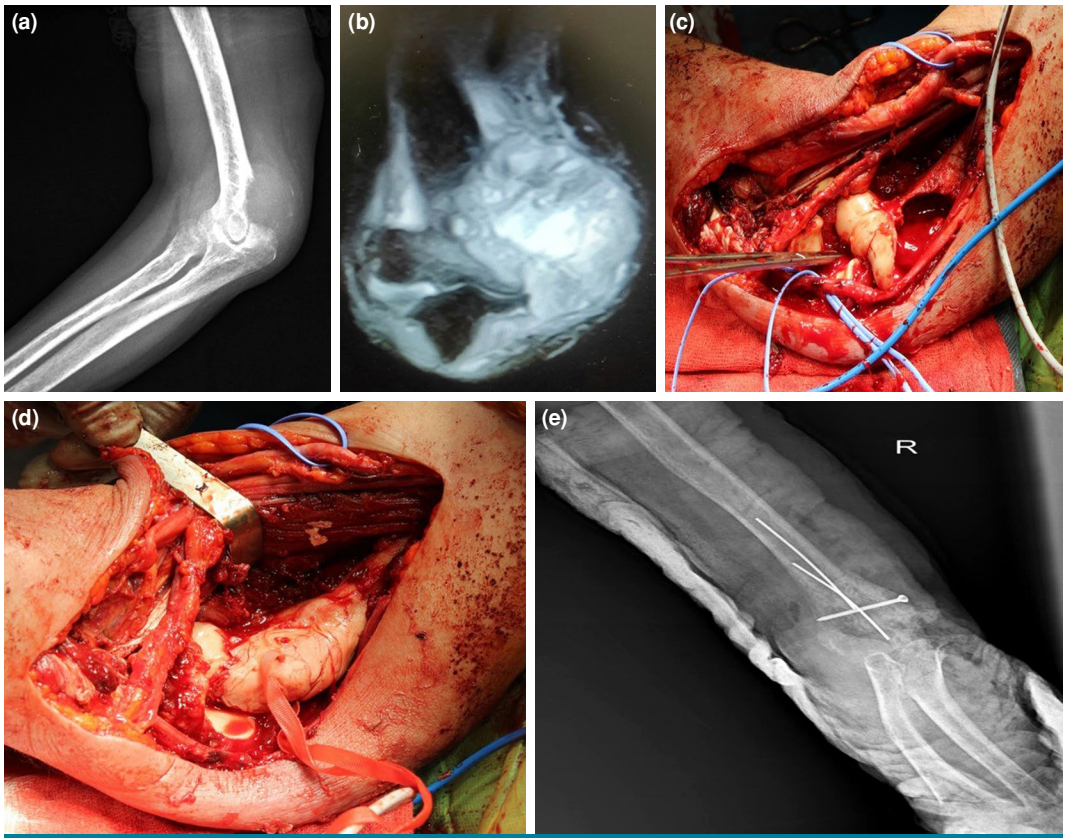


FIGURE 4. **(a)** Radiography of metastatic adenocarcinoma with lytic lesion, soft tissue invasion and contrast difference, **(b)** magnetic resonance imaging of the tumor, **(c)** intraoperative imaging of curettage of the lesion before cement + fixation, **(d)** after cement + fixation, **(e)** postoperative radiography.

seen in only one case, whereas osteosarcoma and chondrosarcoma were not observed.

Although excision with good surgical margins reduces the rate of recurrence, metastasis may still occur regardless of the rate of recurrence. This phenomenon may be attributed to the high grade of the tumor.[11] Although surgical margins were positive and only two patients developed recurrence in our case series, 42.8% of patients treated for soft tissue sarcoma developed metastasis. In addition, 50% of these patients had a Grade 2 sarcoma and 35.7% had a Grade 3 sarcoma.

In the literature, the five-year survival rate of elbow sarcomas is reported to be 60 to 70%. In our case series, the survival rate for soft tissue sarcomas was 64.5%, but one of the cases died of an unrelated cause. Limb-sparing surgery was performed primarily in all soft tissue sarcomas, and transhumeral amputation was performed in only three patients after development of recurrence. Recurrence rate in our series of soft tissue sarcoma was 14%. Currently, only cases with invasion in all compartments and neurovascular structures that cannot be spared are considered indications for amputation.

The surgical management of elbow malignancies is challenging. In the past the choice between amputation and limb-sparing surgery depended on the size of the tumor, the presence of metastases, the characteristics of the tumor and the expected survival time, while limb-sparing surgery is currently more often preferred. Therefore, there is a need for the development of reconstruction techniques which are more durable. In a study of tumor resection arthroplasty carried out by Kruckeberg et al.[10] in 33 patients with metastatic carcinoma and soft tissue sarcoma, the five-year survival rate of the implant was 88% and the survival rate of the patients was 31%. In our case series of metastatic carcinoma, this rate was found to be 26%, and the majority of these patients presented with a pathological fracture of Stage IVB. In addition to resection arthroplasty, new techniques have also been under development. A case report

by Liao et al.[12] reported that a patient with clear cell carcinoma metastasis was reconstructed with a personalized design after resection using a three-dimensional (3D) printer, and functionally satisfactory results were achieved after a six-month follow-up. Although 3D-printed personalized prostheses are promising, case series of multiple patients with longer follow-up are needed.

The patients who had R1 margins had undergone adjuvant treatments and not reoperated due to the proximity of the neurovascular structures. Recent studies indicate that radiotherapy (RT) has a beneficial effect on survival and recurrence in the treatment of soft tissue sarcoma.[13] Our case series demonstrates the beneficial effect of RT on recurrence. However, the impact of RT on complications remains controversial. Whilst some studies have shown that preoperative RT is associated with an increase in wound complications,[14] improvements in RT techniques have been reported to have a reduction in these risks.[15] In our case series, three out of sixteen patients who received RT experienced wound complications. These complications were resolved through appropriate surgical procedures. It is critical to note that this information is based solely on our observations and should not be taken as a definitive conclusion.

Limb-sparing surgery is the basic surgical approach for malignant tumors of the elbow. Although this method is based on wide resection, this approach is difficult to perform due to elbow anatomy.[16] The difficulty of wide resection is increased by the proximity of functionally vital tissues, the limited soft tissue covering the joint, and the limitation of the dermis and subcutaneous fat.

Nonetheless, this study has several limitations. First, the study consisted of limited number of patients. Second, chemotherapy and radiotherapy protocols were not uniform; however, it was based on the national guidelines. Further multi-center, large-scale studies are needed to confirm these findings.

In conclusion, pathological fracture and lytic lesion in bone are more common in metastases, whereas soft tissue invasion and contrast enhancement difference are more common in primary sarcomas. Although the elbow is a rare anatomical site for metastases and soft tissue sarcomas, surgery with safe surgical margins appears to be possible; in cases where the desired surgical margin cannot be achieved or in clinically appropriate high-grade cases, the addition of radiotherapy is beneficial. Although recurrence may occur regardless of the surgical margin, limb-sparing surgery is the standard that should be performed in all possible cases. In our case series, the most common soft tissue sarcomas were synovial sarcoma and malignant peripheral nerve sheath tumors, and the most common metastatic lesions were lung cancer and multiple myeloma.

Ethics Committee Approval: The study protocol was approved by the Gazi University Ethics Committee (date: 05.10.2023, no: E-77082166-604.01.02-764631). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept: G.T.; Design: G.T., H.E.T.; Control/supervision: T.T.; Data collection and/or processing, writing the article: H.E.T.; Analysis and/or interpretation: İ.K.; Literature review, critical review: G.T., T.T.; Materials: E.A.

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