Clinical outcomes and survival following treatment of bone metastases from uterine leiomyosarcoma: A report of 6 cases

Zehra Öztürk Başarır1, Mustafa Onur Karaca2, Kamil Balaban1, Kerem Başarır2

1Clinic of Gynecology and Obstetrics, Ankara City Hospital, Ankara, Turkey
2Department of Orthopedics and Traumatology, Ankara University, School of Medicine, Ankara, Turkey

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ABSTRACT
Objective: This study aimed to analyze the patient-reported outcomes and survival following surgical treatment of bone metastases from uterine leiomyosarcoma.

Methods: A retrospective review of six patients undergoing surgical procedures for metastatic uLMS over seven years was conducted at a single center. All patients were reviewed for their primary malignancy and characteristics of bone metastasis during follow-up. Clinical presentation of bone metastasis, modality, and the type of treatment related to musculoskeletal involvement were also analyzed. The visual analog pain scale (VAS) and Eastern Cooperative Oncology Group (ECOG) performance status scale were used pre- and postoperatively to evaluate the patient-reported outcome.

Results: Four patients had solitary bone metastases, whereas multiple bone metastases were diagnosed in two. Of those who had solitary bone metastasis, all of them were treated with wide resection. One of the two patients with multiple bone metastases was also treated with wide resection, and the other was treated with intralesional curettage. Four patients died from primary disease, and two were alive without evidence of disease recurrence. The median survival time following a diagnosis of bone metastasis was 15.0 months (95% CI, 0.6 to 29.4 months). The mean VAS scores for all six patients improved. However, the improvement in ECOG performance status was seen in only four patients.

Conclusion: Although the prognosis of uLMS patients with bone metastasis seems poor, wide resection of the solitary bone metastasis may help prolong the overall survival. Performing orthopedic surgeries for the bone metastasis from uLMS in case of intractable pain after palliative radiotherapy, impending or pathological fracture, or solitary disease has been shown to decrease the pain significantly and improve the performance status in the majority.

Level of Evidence: Level IV, Therapeutic Study

Introduction
Cancer is a leading cause of premature death and disability, particularly in women. Gynecological cancers annually took the lives of more than half a million women worldwide.1 Death usually occurs because of advanced disease and metastasis. The lymphatics and hematogenous spread being the main route for metastasis in gynecological cancers.2 In contrast to endometrial carcinomas, uterine leiomyosarcoma (uLMS) metastasizes commonly through hematogenous spread to the lung, liver, and bone at most. However, direct invasion of bone from the adjacent soft tissue lesions also plays an important role.2

Bone metastasis was associated with poor prognosis as a sign of distant spread.3 Cancer after bone metastasis is rarely cured and is associated with morbidities including pain, increased risk of fracture, and hypercalcemia.4 Bone metastasis from uLMS is quite rare and mostly reported as case reports.5

Solitary or oligometastasis of bone necessitates a different treatment algorithm than multiple metastases. Oligometastasis is defined as a stage of metastatic cancer that has clinically or radiologically proven tumor sites limited by the number of 1-3 or 1-5. It would not be rapidly spreading to more regions.6 Radical treatment modalities rather than palliation, such as wide resection of the solitary or oligo-metastases of bone, may provide a better survival in patients with different cancer types like renal cell carcinoma and thyroid cancer.7,8

Musculoskeletal metastasis poses a great challenge in the management of gynecological cancers. Especially for uLMS, considering the lack of literature and the limited number of patients in those studies, we designed this study to better understand the role of orthopedic surgery in patients with bone metastasis. Accordingly, we investigated the clinical features and prognosis by focusing on quality of life, local tumor control, and survival.

Materials and Methods
The study was approved by the Ethical Committee of Ankara University School of Medicine by the approval number of i5-311-20. We retrospectively reviewed all patients from orthopedic database who had been treated for bone metastasis due to gynecologic cancer with a multidisciplinary approach based...
on a decision of the Bone and Soft Tissue Tumors Council of Ankara University Faculty of Medicine Hospital between January 2011 and December 2018. Patients with bone metastases from uLMS and with a minimum of 12 months of follow-up were included in this study. Patients with incomplete medical archive data and who were lost to follow-up were excluded from the study. The confirmation of uLMS metastasis was made by bone biopsy for patients with solitary metastasis and confirmed by a review of the pathology database for all patients after orthopedic surgery. For the pathological grading, uLMS is classified with a 2-tiered grading system as either low-grade or high-grade tumor grade according to 3 histological parameters in the microscopic analysis which were mitotic rate, cytological atypia, and cell necrosis. We documented the FIGO (The International Federation of Gynecology and Obstetrics) stage which was recorded after the diagnosis of uLMS in all 6 patients. It was commonly used to state the disease stage without uncertainty among clinicians and to predict patients’ outcomes and prognosis for gynecologic cancers, including uLMS. FIGO stages define the tumor’s current status or spread. If it is limited to the uterus, it is represented by stage I which is also called IA or IB according to its size greater or smaller than 5 cm. In stage II, the tumor extends beyond the uterus within the pelvis. If it invades abdominal tissues, it is called stage III. In stage IVA or IVB, either the tumor invades the bladder and/or rectum or there is distant metastasis.

Data on patient characteristics, tumor characteristics, clinical presentation of bone metastasis, modality, and the type of treatment related to musculoskeletal involvement, follow-up, and clinical outcome were collected. There were 3 types of treatment modalities that were chemotherapy, radiation therapy, and surgery defined as “yes” or “no.”

The clinical and functional outcome was defined as improvement in the pain and performance status, which were measured using the visual analog pain scale (VAS) and the Eastern Cooperative Oncology Group (ECOG) performance status scale, respectively. These patient-reported outcomes were evaluated preoperatively and 1 month after surgery. The ECOG performance status scale describes the patient’s level of functioning in terms of their ability to care for themselves, daily activity, and physical ability. This scale has scores ranging from 0 to 5, where 0 represents fully active, 4 signifies completely disabled, which means totally confined to a bed or chair, and 5 means death. We only emphasized the analysis of immediate preoperative and 1-month-after assessment for avoiding the impact of cancer recurrence on the patient’s outcome.

All statistical analysis was conducted with use of Statistical Package for the Social Science (SPSS) software (SPSS Inc, Chicago, Ill, USA). A comparison of parametric variables was performed using a paired t-test, and P values less than .05 were considered statistically significant. Patient survival was estimated by the Kaplan-Meier method.

### Results

In the orthopedic database, 8 patients who were surgically treated for bone metastasis of uLMS were found. Two of the patients were excluded from the study due to incomplete medical archive data, leaving 6 patients to be included in the cohort. Demographics and characteristics of primary tumor for these 6 patients are summarized in Table 1. The median age at diagnosis was 53 years (range: 35-69 years), and patients were followed for an average period of 16 months (range: 12-45 months). In 5 of the patients, uLMSs were operated with gynecological surgeries whereas only 1 patient (patient no. 2) received chemotheraphy instead of gynecological surgery due to multiple visceral organ metastases. Patient no. 3 and 6 had no other metastases other than the bone. Visceral organ metastasis was seen in rest of the 4 patients in addition to bone, and the lung was the most frequent one.

Characteristics of bone metastasis, data on orthopedic surgery, patients’ outcomes, and follow-up are summarized in Table 2. The mean interval from the primary diagnosis of uterine cancer to the detection of bone metastasis was 53.83 months (range: 0-192 months). Curative treatment (33.3%), intractable pain after radiotherapy (33.3%), and impending or pathological fracture (33.3%) were indications for orthopedic surgery. The orthopedic surgery margin was wide resection in 5 patients and intralesional in only 1. Two patients of those who had wide resection of the bone lesion had resection arthroplasty. Both of two metastases were localized to the proximal femur. (Figure 1)

After data collection was completed, 4 patients died on an average of 40.5 months (range: 16-207 months) after diagnosis of the primary disease, and 2 patients were alive without evidence of disease recurrence. Two patients (patients no. 1 and 4) had new bone metastasis detected during their follow-up and had no other orthopedic surgery for them. Patient no. 4 had developed clavicle and scalpula metastasis accompanying the tibia lesion after intralesional curettage followed by internal fixation and was managed with additional radiotherapy due to the patient’s wish for no further surgery. Patient no. 1, on the other hand, did not receive any additional intervention, including radiotherapy, despite the presence of multiple metastases due to her poor general condition. All the 6 patients were given bisphosphonate treatment after surgery.

The median survival time for the 6 patients following a diagnosis of bone metastasis was 15.0 months (95% CI, 0.6-29.4 months) (Figure 2). The estimated 1-year survival was 66.7%. The mean preoperative VAS which was 7.1 ± 1.4 decreased significantly to 2.8 ± 0.1 month after surgery (P < .001). Pain relief was observed in all 6 patients (100%). The mean pre-and postoperative ECOG performance status grades for all 6 patients were 2.8 ± 1.3 and 2.3 ± 1.6, respectively. The paired samples t-test showed no statistically significant improvement.

### Table 1. Summary of demographic and primary tumor-related data

| Patient | Age | FIGO stage | Grade | Treatment for primary tumor | Visceral organ metastasis |
|---------|-----|------------|-------|-----------------------------|--------------------------|
| 1       | 69  | IIIC       | H-G   | Surg + chemo + RT           | Lung                     |
| 2       | 35  | IIIC       | H-G   | Chemo                       | Lung/LN/brain/adrenal gland |
| 3       | 47  | IIIC       | L-G   | Surg                        |                          |
| 4       | 58  | IIIB       | H-G   | Surg + chemo + RT           | Lung                     |
| 5       | 67  | IIIC1      | H-G   | Surg + chemo + RT           | Liver/LN                |
| 6       | 48  | IIIC       | L-G   | Surg                        |                          |

Surg, surgery; chemo, chemotherapy; LN, lymph node; H-G, high-grade; L-G, low-grade.
in ECOG performance status ($P = .5$). Improvement in performance status was seen in 4 of the 6 patients (66.6%).

We encountered a complication in only 1 patient, which was due to an infection secondary to wound dehiscence, then it was treated with debridement.

**Discussion**

Uterine leiomyosarcoma is a rare disease among malignant gynecologic tumors with a very unfavorable prognosis.\(^1\) It is estimated that up to 10% of uterine cancers present with distant metastasis.\(^2\) Five-year overall survival for distantly metastatic disease is 17.3% for uterine cancers.\(^6\) Previous studies have shown that the disease was most likely to metastasize to the lung, followed by the liver and bone.\(^7\) The most common sites for osseous metastases in gynecological cancers are the vertebrae, pelvic bones, ribs, and femur, similar to that of our series.\(^7\) Isolated metastasis to the appendicular bone is extremely rare and is thought to be a result of the hematological spread of tumor cells.\(^18\) Few previous studies have evaluated the characteristic features of bone metastasis of uLMS mostly as a part of disseminated disease.\(^19\)

Bone metastasis in gynecologic cancers has been explained by 2 possible mechanisms.\(^1\) First, direct invasion into the bone from soft tissue tumor masses is one mechanism and second, hematogenous spread through the systemic circulation or the Batson venous plexus. In the current series, 2 patients had lower-grade lesions and local metastasis and the other 4 most probably had the second mechanism for involvement. They have multiple-organ and osseous metastases. Concerning the literature, most cases of metastatic uLMS evaluated in this study are similar to what has been previously reported. Most cases had multiple metastases (~80%) and high-grade lesions within the fifth and sixth decades of life.\(^5\)

Traditionally, patients with bone metastasis have been staged as being in the most advanced phase of the disease, and radiotherapy

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**Table 2. Summary of bone metastasis and related clinical data**

| Patient | Bone metastasis | Orthopedic surgery | VAS before surgery | ECOG before surgery | Additional therapy | Follow-up | Status |
|---------|-----------------|-------------------|-------------------|-------------------|------------------|------------|--------|
| 1       | Femur/spine      | IF/PF Resection arthroplasty | 6/3 | 23 | - | 8/3 | 3/5 | DOD |
| 2       | Femur            | IPaRT Resection arthroplasty | 6/3 | 6/3 | RT | 6/3 | 2/3 | DOD |
| 3       | Pubic bone       | C Resection | 9/3 | 9/3 | - | 8/3 | 3/2 | DOD |
| 4       | Tibia/scapula    | IBKRT Curettage + IMN with cement | 36 | 36 | Cavitye, IIMN with cement | 8/3 | 3/2 | DOD |
| 5       | Ilium            | IF/PF Resection + screw with cement | - | - | - | 7/3 | 3/2 | NED |
| 6       | Pubic bone       | C Resection | 52 | 52 | - | 5/2 | 1/0 | NED |

S, single; M, multiple; IPaRT, intractable pain after radiotherapy; IF/PF, impending fracture or pathological fracture; C, curettage; IMN, intermedullary nail; DOD, died of disease; NED, no evidence of disease. Interval to death from bone metastasis (month). * indicates the operation site.
is considered the first-line treatment in the management of multiple metastatic bone lesions if there is no risk of impending or existing pathological fracture. Impending or existing pathological fracture and radiotherapy-resistant pain are the most common indications for surgery. Palliation of symptoms and improvements in quality of life were a priority in these subgroups in whom cure was not achievable. In multiple metastatic patients who have bone and visceral organ metastasis such as 4 cases in our series, these indications exist, and surgery with no curative purposes and aggressive pain control were performed. This study showed a median survival time of 15.0 months after a diagnosis of bone metastasis from uLMS, but it was hard to make an implication based on such a small case series.

The oncological objective of aggressive wide excision of an osseous metastatic tumor is to achieve local tumor control. Numerous studies have shown that wide resection of solitary bone metastases from kidney or thyroid is not only safe but is also the only therapeutic modality that offers any hope of long-term survival. In this study, radical surgical intervention including wide resection of pelvic lesions was performed in 3 patients. Of the 2, patients no. 5 and 6 had excellent functional and oncological results with no signs of disease after 23 and 25 months of follow-up. However, despite the fact that uLMS was low-grade, bone metastasis was solitary, and there was no evidence of any visceral organ metastasis, patient no. 3 died 10 months after she was diagnosed with bone metastasis, showing that the natural course of uLMS with bone metastasis can be unpredictable and poor, despite the presence of possible favorable prognostic factors.

This study represents one of the largest collection of patients with bone metastases from uLMS. Most of the literature is limited to case reports. In this study, surgical intervention for treating multiple bone metastases resulted in a significant reduction in pain but not in performance status for all. Patient no. 1, who was reported to be ECOG 3 preoperatively, died 1 month after the surgery and her performance status was noted as ECOG 5. Patient no. 2 had multiple visceral organ metastases that caused a significant restriction to daily life; thus, her performance status did not get any better. This might be the reason why the surgery could not provide improvement in performance status for all patients and no statistically significant change could be observed. The results of this study are parallel with the literature and indicate that solitary bone metastases are unlike multiple metastases and require to evaluate for aggressive management.

All patients with associating lung metastasis were dead, and the mean survival of these patients was 14 months after they were diagnosed with bone metastasis, and associating lung metastasis seems to be a poor prognostic factor for the overall survival for uLMS patients with bone metastasis.

Our study has 2 major limitations. First, the number of patients included in the study was too small to have statistically significant results. Second, the retrospective, observational nature of the study was conducted at a single institution. However, our study had other strong points; initially, 2 different clinical scenarios can be clearly identified in this rare series. Additionally, the probability of a better prognosis in patients who were treated with wide resections for solitary bone metastasis may highlight the importance of our study.

The diagnosis of uLMS means a poor outcome for most of the patients affected, and complete hysterectomy with clean tumor margins is the main surgical therapy. Similarly, wide resection of solitary bone metastases from uLMS can be a good option and may help prolong survival in carefully selected patients.
In conclusion, although the prognosis of uLMS patients with bone metastasis seems to be poor in general, wide resection of the solitary bone metastasis may help in prolonging the overall survival. Performing orthopedic surgeries for the bone metastasis of uLMS in case of intractable pain after palliative radiotherapy, impending or pathological fracture, or solitary disease was shown to decrease the pain significantly and improve the performance status in majority. Associating lung metastasis seems to be a poor prognostic factor for the overall survival of uLMS patients with bone metastasis. We believe that this study gives a clinical perspective on how to manage patients who have bone metastases from uLMS with the help of being one of the largest case series including data on the primary tumor, bone metastasis, and orthopedic surgery altogether. Given the small number of patients and heterogeneity of our study population, no definite conclusions can be drawn, but future prospective studies and multi-institutional may allow for collecting more comprehensive data, helping guide clinicians in the counseling of such patients.

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