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Prognostic factors in patients with malignant fibrous histiocytoma of the extremities

Ekstremite yerleşimli malign fibröz histiyositomlu hastalarda prognostik faktörler

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Amaç: Ekstremite yerleşimli malign fibröz histiyositomlu olgularda prognostik faktörler araştırıldı.

Çalışma planı: Çalışmada ekstremite yumuşak doku malign fibröz histiyositom tanısı konan 26 hasta (22 erkek, 4 kadın; 15 hasta <60 yaş) yaş, cinsiyet, tümörün durumu (primer veya nüks), etkilenen ekstremite, tümörün yerleşimi (proksimal veya distal), boyutu, derinliği, derecesi; rezeksiyon kalitesi, adjuvan tedavi ve tanı konduğunda uzak metastaz olması gibi sağkalımı etkileyebilecek faktörler açısından değerlendirildi.

Sonuçlar: Hayatta olan 16 hastanın ortalama takip süresi 44.8 ay (dağılım 24-120 ay) idi. Tanı konmadan önceki ortalama semptom süresi yedi ay (dağılım 1-26 ay) idi. Tüm hastalara cerrahi rezeksiyon yapıldı. On yedi hastada geniş cerrahi sınır (R0) elde edildi. Toplam yedi hastada amputasyon yapıldı. On yedi hastaya adjuvan terapi, 10 hastaya radyoterapi uygulandı. Sekiz hastada lokal nüks gelişti. İki hastada tanı konduğunda uzak metastaz vardı. Takip sırasında sekiz hastada ortalama 13 ayda (dağılım 7-20 ay) uzak metastaz gelişti. Kaplan-Meier yöntemiyle hesaplanan beş yıllık sağkalım oranı %61.5 bulundu. Düşük dereceli tümörlerde beş yıllık sağkalım oranı %100 iken, yüksek dereceli tümörlerde bu oran %28.2 idi. Tekdeğişkenli (p=0.004) ve çokdeğişkenli (p=0.023) analizlerde tümör derecesi sağkalımı etkileyen tek parametre idi.

Çıkarımlar: Malign fibröz histiyositomlu hastalarda yüksek dereceli tümör olması kötü prognoz göstergesidir.

Anahtar sözcükler: Ekstremite; histiyositom, benign fibröz/tedavi; tümör metastazı; tümör nüksü, lokal; prognoz; radyoterapi, adjuvan; yumuşak doku neoplazileri/tedavi; sağkalım analizi.

Objectives: We evaluated prognostic factors in patients with malignant fibrous histiocytoma of the extremity.

Methods: The study included 26 patients (22 males, 4 females; 15 patients < age 60) with a diagnosis of malignant fibrous histiocytoma of the extremity. Clinical and pathological data were analyzed including age, gender, affected extremity, presentation status (primary or recurrent), localization (proximal or distal), size, depth, and grade of the tumor, resection quality, adjuvant therapy, and the presence of distant metastasis at the time of diagnosis.

Results: The mean follow-up of 16 patients who were alive was 44.8 months (range 24 to 120 months). The mean symptom duration before diagnosis was seven months (range 1 to 26 months). All the patients underwent surgical resection. A margin-negative R0 resection was obtained in 17 patients. Amputation was performed in seven patients. Adjuvant chemotherapy and radiotherapy were administered to 17 patients and 10 patients, respectively. Local recurrence was detected in eight patients. Two patients had distant metastasis at the time of diagnosis while eight patients developed distant metastasis within a mean of 13 months (range 7 to 20 months) postoperatively. Kaplan-Meier analysis showed an overall five-year survival rate of 61.5%, being 100% in low-grade tumors, and 28.2% in high-grade tumors. Tumor grade was the only significant parameter affecting survival in both univariate (p=0.004) and multivariate (p=0.023) analyses.

Conclusion: Patients with high-grade malignant fibrous histiocytoma have a poorer prognosis.

Key words: Extremities; histiocytoma, benign fibrous/therapy; neoplasm metastasis; neoplasm recurrence, local; prognosis; radiotherapy, adjuvant; soft tissue neoplasms/therapy; survival analysis.

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Soft-tissue sarcomas account for approximately 1% of adult malignancies, and of these, 60% occur in the extremities.[1] In adults, the most common subtype of soft-tissue sarcoma is malignant fibrous histiocytoma (MFH). In addition to soft tissue, MFH can also occur in bones as a primary intraosseous tumour.[2,3] MFH most commonly presents as an enlarging painless mass. MFH is slightly more common in men than in women, but the cause of this tumour is not clearly understood.[4] It has been reported in patients of all age groups; however, it is generally seen in patients who are more than 50 years old.[5] Tumours in the lower extremity are more common than those in the upper extremity.[1,6,7] They most frequently metastasize to lung.[5]

Histologically, in the classic appearance of MFH the cells are arranged in a whorled or cartwheel-like pattern, in the shape of high grade spindle cell sarcoma. In addition to this, the appearance can be quite variable. In the tumour, benign or malignant-appearing multinuclear cells, histiocyte-like cells (having large indented nuclei and abundant, well-identified cytoplasm), cells having foamy cytoplasm, inflammatory cells and fibrosis in varying amounts can be seen. MFH is characterized by its lack of osteoid production.[8] The tumour has a broad range of histological appearances, and five subtypes have been described: storiform–pleomorphic, myxoid, giant cell, inflammatory and angiomatoid.[9] Pleomorphic MFH is the most common variant, accounting for more than 65% of cases.[10] The angiomatoid form is generally observed in patients under 20 years of age.[5]

The primary mode of therapy for MFH is surgical excision with adjuvant chemotherapy. The rate of local recurrence in MFH has been reported to be between 16 and 31%.[6,11,12] Distant metastases are a major problem in the management of this tumour. The reported five-year survival rate for patients with MFH has ranged from 59% to 66.7%.[1,11,12] Advanced age, tumour size, tumour grade, local recurrence, resection quality, tumour depth, and adjuvant chemotherapy have been reported to affect survival rate in patients with MFH.[1,6,11,13] However, predictors of survival rate in patients with MFH remain controversial.

In this retrospective study, we investigated the clinical and pathological factors associated with overall survival rate in patients with soft-tissue MFH in their upper or lower extremities.

Patients and methods

This study investigated retrospectively the patients in our hospital who were diagnosed as having MFH in the soft tissue of an extremity during the period March 1986 - May 2006. The inclusion criteria were as follows: presence of a soft-tissue MFH in an extremity (upper or lower), minimum postoperative follow-up of more than 24 months, and at least 18 years of age. Of the 32 patients (23 male, 9 female; mean age 58 years; range 16-78 years) diagnosed with MFH in the study period, 26 met these inclusion criteria.

In all patients, regional lymph nodes were carefully palpated and evaluated by ultrasonography for metastases. Imaging methods used at the time of diagnosis included radiographs, computerized tomography, and magnetic resonance imaging (MRI), with the latter being available only for patients in the last 15 years of the study period. Preoperative surgical planning was based on the results of fine needle aspiration biopsy or tru-cut biopsy. After the resection of the lesion this preoperative diagnosis was confirmed pathologically.

The parameters that were examined for their potential association with survival rate included patients' age and gender, presentation status (primary or recurrent), involved extremity (upper or lower), tumour location (proximal or distal), tumour size, tumour depth, tumour grade, resection quality, use of radiotherapy, use of adjuvant chemotherapy and presence of distant metastasis at diagnosis (Table 1). Survival times were calculated from the time of definitive resection. All parameters were investigated via univariate and multivariate analyses.

Age was considered as a categorical variable, and two age groups were defined: < 60 years and ≥ 60 years. Presentation status was defined as primary or recurrent tumour. Recurrence was noted if the tumour had recurred in the same site. Tumour location was defined as either distal (distal to knee or elbow) or proximal. Tumour size was defined as the greatest dimension at pathological examination, in two groups: ≤ 5 cm and >5 cm. Tumour depth was determined by preoperative MRI (if available at the time) and by intraoperative and histopathologic findings. Tumours were classified as deep if they invaded the muscular fascia, and superficial if they did not extend beyond subcutaneous tissue.

Table 1. Characteristics of the patients included this study

Parameter	Number of Patients	*P values*
Age		
<60	15	0.85
≥60	11	
Gender		
Male	22	0.60
Female	4	
Involved extremity		
Lower ext	17	0.21
Upper ext	9	
Location		
Proximal	17	0.64
Distal	9	
Tumour Depth		
Superficial	4	0.08
Deep	22	
Tumour Grade		
Low grade	9	0.004
High grade	17	
Chemotherapy		
Used	17	0.19
Not used	9	
Radiotherapy		
Used	10	0.48
Not used	16	
Recurrence		
Positive	8	0.94
Negative	18	
Resection Quality		
R0	17	0.19
R1	9	
Tumour size		
≤5 cm	10	0.48
>5 cm	16	
Distant metastasis at diagnosis		
Yes	2	0.06
No	24	

Tumour grade was defined histologically as low grade (G1 or G2) or high grade (G3 or G4) according to the classification proposed by the American Joint Committee on Cancer.[14] Resection quality was determined according to the R-classification described by the International Union Against Cancer: R0 = no residual tumour; R1 = microscopic residual tumour or tumour seen intraoperatively, even in the case of subsequent extended resection; and R2 = macroscopic tumour left in situ.[6] Evaluations of resection quality were based on histopathologic findings.

Chemotherapy and radiotherapy procedures were made according to the patients' situation after their evaluation by the medical oncology and radiation oncology departments. Chemotherapy was usually used in case of metastasis or high grade tumours. In chemotherapy protocols doxorubicin was used as the main agent (60 mg/m2). With this drug, in double or triple combination, ifosfamide (1500 mg/m2), methotrexate (50 mg/kg), cisplatin (100 mg/m_) or etoposide (100 mg/m2) were used for various periods according to the patient's clinical situation. After the surgical wound had healed completely, radiotherapy was applied in 2-2.5 Gray (Gy) fractions, for an average dose of 40-60 Gy. Radiation therapy was preferred in case of low quality resection or a deeply seated tumour.

Statistical analyses were performed with SPSS 11.0 statistical software (SPSS Inc., Chicago, IL). Survivorship analysis was made with the Kaplan-Meier method, with 95% confidence intervals. Standard univariate procedures were used for an initial examination of the data (i.e., t tests for continuous variables and chi-square statistics for dichotomous variables). Multiple regression analysis (logistic regression) was used for examining dichotomous outcomes such as survival at the time of study, and their potentially associated parameters. A parameter was accepted to be a risk factor if its p value was less than 0.05.

Results

The surviving 16 patients were followed up for a mean of 44.8 months (range 24 – 120 months). Table 1 shows the distribution of patients across the study parameters. All patients presented with a palpable mass. Six patients additionally complained of pain. Median duration of symptoms before presentation was 7 months (range 1 – 26 months). Tumour-related haemorrhage was seen on MRI in one patient whose tumour was in the gluteal region. Calcification was seen on computerized tomography in one patient whose tumour was in the shoulder.

All patients underwent complete gross resection of the tumour. Wide-margin resection (R0) was achieved in 17 patients. To achieve wide margins, free muscle flaps were made in three patients who had high-grade MFH in the lower extremity. Marginal

resection (R1) was performed in nine patients. R2 resection was not used in any of the patients.

Local recurrence was seen in eight patients (30.8 %), four of whom underwent amputation. The other four patients underwent repeat resection, three of whom had refused amputation. In two of these patients distant metastases subsequently developed. Amputation was applied in three patients due to the primary tumour. A total of seven patients underwent amputation (five above-knee, two above-elbow).

Two patients had metastases to distant sites at the time of diagnosis (one with metastases to lung, the other with metastases to lung and humerus). Distant metastases occurred later in eight patients (one lymph node, six pulmonary, one vertebral and pulmonary) at a median of 13 months after initial diagnosis (range 7-20 months). Neoadjuvant chemotherapy was used in six patients who had high-grade tumours. Sciatic nerve dysfunction was observed in one patient after resection of a tumour in the gluteal region.

The overall five-year survival rate for patients in the study was calculated via the Kaplan-Meier method, and was found to be 61.5% (95% CI). Survival curves for patients with low- and high-grade tumours were found to be significantly different (Figure 1). For patients with low- grade tumours, the estimated five-year survival rate was 100% (95% CI) in contrast to a rate of 28.2% (95% CI) in patients with high-grade tumours.

Histologic grade of the tumour was the only parameter in terms of which survival rates were significantly different ($p = 0.004$), as shown by univariate analysis. No significant differences were found in terms of age, gender, presentation status (primary or recurrent), tumour location, tumour depth, tumour size, presence of distant metastasis at diagnosis, resection quality or adjuvant therapy ($p > 0.05$, Table 1). The relation between survival rate and presence of distant metastasis at the time of diagnosis approached statistical significance ($p = 0.06$). Univariate ($p < 0.004$) and multivariate analysis ($p=0.023$) suggested that survival differed significantly according to tumour grade.

Discussion

MFH has been reported to be the most common sarcoma in older adults.[15] In the differential diagnosis, pleomorphic rhabdomyosarcoma, pleomorphic liposarcoma, dermatofibrosarcoma protuberans, and atypical fibroxanthoma should be considered.[5] To characterise the tumour, careful palpation of regional lymph nodes and detailed imaging studies should be performed. Older age has been reported to be associated with lower survival rates in patients with MFH.[6,15,16] Our patients' age distribution was comparable to that in other reports of patients with MFH.[5] However, advanced age was not a significant influence on survival rate in our study, and this is compatible with the findings of Salo et al. in their study of patients with MFH.[1] Gender likewise did not influence survival rate in our study, which is consistent with the findings of Peiper et al.[6]

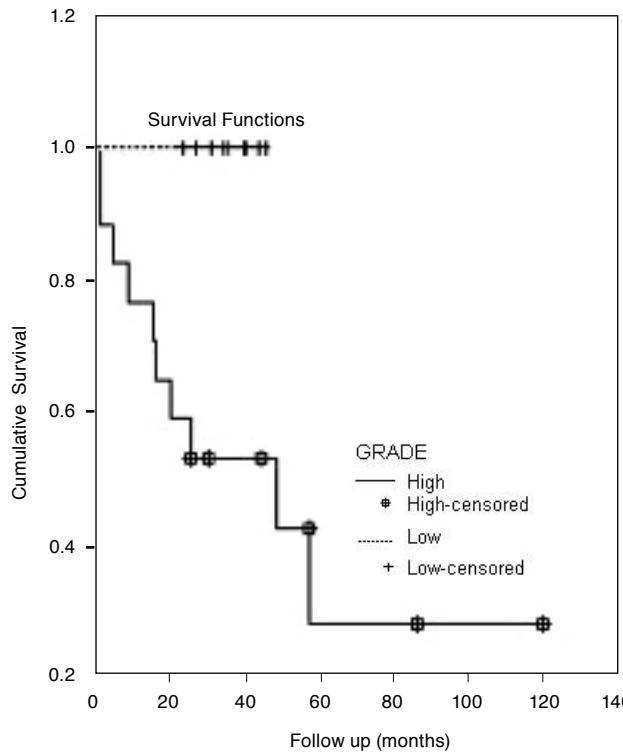

Figure 1. Kaplan-Meier survivorship analysis curve according to histological grade in 26 patients with primary malignant fibrous histiocytoma of extremities. Survivorship analysis was significantly shorter in patients with high grade.

The tumour presented generally as a painless mass in our patients, and most of the lesions were in the lower extremity, as in other series.[5,11] Local recurrence was seen in eight patients (30.8%), a rate that is similar to those in other reports.[6,12] Most of our patients who had metastases had them in the pulmonary region, as in other series.[5] It has been reported that the majority of distant metastases occur within

the first two years.[17] In our series distant metastases occurred somewhat sooner, at a median of 13 months (range 7-20 months).

Tumour size and depth have been reported as factors associated with survival.[1,5] Achieving a tumour-free surgical margin is considered to be a major factor in local control.[12,18] Subfascial depth has also been associated with local failure as well as poorer overall prognosis.[6,19] In our patients we did not find these parameters to be related to prognosis and this is similar to the findings of Peiper et al. regarding tumour depth and prognosis.[6]

It has been reported that surgery with a wide margin is effective in locally controlling the neoplasm, but is not capable of preventing metastases.[5] Yurdoğlu et al.[20] reported that in patients with soft-tissue sarcoma of the extremity there was no difference in terms of survival between patients who underwent amputation and patients who underwent salvage surgery with adjuvant chemotherapy. In the extremities, distal localization of the tumour has been reported to have a better prognosis than proximal location has.[5] In our patients no effect of distal versus proximal location on survival was detected.

Regarding the presence of metastasis at initial diagnosis as an indicator of poor prognosis, in studies of prognosis in patients with soft-tissue sarcoma, patients with metastases at the time of diagnosis have tended to be excluded.[1,6,21] In our study, while this factor's effect on prognosis did not reach statistical significance, it was found to be near significance (p=0.06). This might be explained by our limited number of patients.

Yıldız et al.[22],in 40 patients with soft tissue of the extremity, found tumor grade to be the single factor that had an effect on survival. In our study also, consistent with other studies, in patients with high grade tumors the five-year survival rate was seen to be significantly lower.[1,5,12]

Preoperative radiation therapy may increase morbidity and lead to problems with wound healing,[23] and for this reason we did not use this method in our patients. It is known that tissue transfers, performed for the purpose of covering tissue defects created during surgery, provide an advantage for multidisciplinary treatment, particularly in patients with high grade disease.[24] This method was used in three patients who had high grade tumors in the lower extremity, and in the early postoperative period adjuvant therapy was applied.

Postoperative radiotherapy has been reported to improve local control of MFH.[25-27] Weitz et al.[21], however, reported that this method is not effective in providing local control. Postoperative radiation therapy was used in our patients who had a lower quality resection (R1) or a deeply seated tumour.

Adjuvant chemotherapy has also been reported to have a positive effect on survival.[13] However, the *Soft Tissue and Bone Sarcoma Group of the European Organization for Research and Treatment of Cancer* reported that adjuvant chemotherapy for adult soft tissue sarcoma reduced local recurrence but did not improve survival.[28] In our study we found that local recurrence, adjuvant radiotherapy and chemotherapy had no effect on survival. Our findings are consistent with those of Peiper et al.[6]

Occasionally in patients with MFH, peripherally located calcification may be seen on imaging studies.[5] Intralesional calcification was observed in one of our patients whose tumour was in the shoulder. At times the MFH tumour may also be extensively cystic and/or haemorrhagic, as in one of our patients whose haemorrhagic changes were detected on MRI. Haemorrhage in MFH is clinically important because the tumour can be misdiagnosed as haematoma.[5]

In conclusion, tumour grade had a significant influence on survival rate in our study, and it was seen that high-grade tumours had a poorer prognosis when compared to low grade tumours. Careful preoperative evaluation and a multidisciplinary approach are fundamental requirements in the treatment of these tumours.

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