# Malignant fibrous histiocytoma of bone

## A retrospective EMSOS study of 125 cases

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**In an effort to learn more about malignant fibrous histiocytoma (MFH) of bone and its prognosis with different treatment approaches, the European Musculo-Skeletal Oncology Society (EMSOS) initiated a retrospective survey among its members. Data requested included patient and treatment variables and outcome. The information on all patients with histologically proven, primary, localized osseous extremity MFH was analyzed if surgical tumor removal was performed and disease status was documented for at least one follow-up date. 125 such patients were evaluable (74 male, 51 female; median age 34 years; tumor site femur 81, tibia 26, humerus 12, other 6). Local treatment was surgery only (110) or surgery plus radiotherapy (15). Chemotherapy was used in 97/125. On last follow-up, 85 patients remained in remission, 33 had developed metastases, 6 a local recurrence, and 1 a combined relapse. With a median follow-up of 3.9 years for patients at risk, actuarial 5-year disease-free survival was 59%. In univariate analyses, younger age and the use of chemotherapy were associated with a more favorable outcome, as was limb-salvage surgery. 23 of 66 tumors with information on response to preoperative chemotherapy responded well (> 90% necrosis). Among these 23, only one relapsed.**

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Malignant fibrous histiocytoma (MFH) of bone, a pleomorphic spindle cell sarcoma which shares many features with certain subtypes of osteosarcoma, is a rare neoplasm. Consequently, only small patient series have been reported. This is especially true of patients treated on modern interdisciplinary regimens. Until the 1970s, treatment for MFH and for other malignant bone tumors mainly relied on ablative surgery, with or without additional radiotherapy. Distant metastases developed in most patients treated in this way, resulting in poor long-term survival of only approximately one third of patients (Spanier et al. 1975, Huvos 1976, Ghandur-Mnaymneh et al. 1982, Capanna et al. 1984) and leading many institutions to adopt adjuvant or neoadjuvant chemotherapy for their patients with MFH. Such a combined local plus systemic treatment approach, often based on existing protocols for osteosarcoma, has been associated with possible improved survival in non-randomized settings (Bacci et al. 1988, Earl et al. 1993, Yokoyama et al. 1993, Ham et al. 1996), but the numbers of patients in all reports addressing this question have been limited.

To learn more about the disease and its prognosis with different treatment approaches, the European Musculo-Skeletal Oncology Society (EMSOS) conducted a retrospective survey among its members, asking about their experience of this unusual tumor. It was believed that such a combined European effort might lead to meaningful conclusions concerning potential prognostic variables and especially to clarify the potential role of chemotherapy in the disease. We report the survey and current practice and outcomes.

## Patients and methods

### *Patient recruitment*

All members of EMSOS were asked to participate in the joint project. Data collection and evaluation were performed at the Department of Pediatric Hematology and Oncology of the University Hospital Hamburg-Eppendorf, Germany. Patients were considered evaluable for analysis if they had a histologically proven, primary, localized MFH of bone situated in an extremity for which surgical treatment was subsequently performed. Adequate information concerning the date of diagnosis and the disease status (remission or relapse) on at least one follow-up date had to be available. Patients with other malignant conditions in addition to MFH were excluded.

### *Data acquisition*

Information concerning patient, tumor, treatment and outcome variables asked for by questionnaire included patient-related data (date of birth, sex), tumor-related data (date of biopsy, tumor site, tumor size, presence or absence of pathological fracture, presence or absence and duration of tumor-related pain and swelling), laboratory values at presentation (lactate dehydrogenase (LDH) and alkaline phosphatase (AP)), information on local therapy (type of surgery, additional local irradiation), information on systemic chemotherapy, histological response to preoperative chemotherapy (more or less than 90% necrosis), and outcome (date and site of relapse, if any; date of last follow-up). Tumor volume was approximated from three-dimensional measurements by using the ellipsoid formula. The evaluation of tumor response was restricted to patients who had received preoperative chemotherapy, but not radiotherapy. A tumor was considered to have responded well to preoperative chemotherapy, if fewer than 10% viable tumor cells were reported for the resected specimen. This level accorded with current European practice for osteosarcoma (Winkler et al. 1993, Souhami et al. 1997).

### *Evaluable patients*

Collaborators from 16 institutions (see appendix) contributed and returned questionnaires concerning 125 eligible patients with MFH of bone diagnosed between 10/79 and 7/92 to the data center (Table 1). 12 of the 36 patients included from the Rizzoli Institute have been reported (Bacci et al. 1996). The decades of life with the highest rate of affected patients were the second to fourth, with a second lower peak in the sixth decade (Figure 1). The primary tumor was situated in a metaphysis in 107 patients (86%), around the knee in 85 (68%). Information on presenting symptoms was reported for less than half of all patients. In these, pain was the leading symptom (53; 88%), with local swelling in only half of the patients (34/59). If present, local swelling preceded the diagnosis of MFH by a median of 4 (1–36) weeks, pain by a median of 12 (5–32) weeks. Information on tumor volume, LDH, and AP was incomplete (Table 1).

Table 1. Patient and tumor characteristics at presentation

| | Total | Treatment | |
|---|---|---|---|
| | | Local only | Local and systemic |
| All patients | 125 | 28 | 97 |
| Sex | | | |
| Male | 74 | 22 | 52 |
| Female | 51 | 6 | 45 |
| Age | | | |
| Years median | 34 | 60 | 30 |
| Range | 8–80 | 18–80 | 8–71 |
| ≤ 40 years | 76 | 8 | 68 |
| > 40 years | 49 | 20 | 29 |
| Tumor-site | | | |
| Femur | 81 | 19 | 62 |
| Tibia | 26 | 4 | 22 |
| Humerus | 12 | 2 | 10 |
| Other | 6 | 3 | 3 |
| Pathological fracture | | | |
| Yes | 15 | 5 | 10 |
| No | 110 | 23 | 87 |
| Tumor-volume | | | |
| Not reported | 71 | 10 | 61 |
| Reported | 54 | 18 | 36 |
| $cm^3$ median | 86 | 75 | 97 |
| Range | 2–1500 | 2–1000 | 12–1500 |
| LDH | | | |
| Not reported | 56 | 19 | 37 |
| Reported | 69 | 9 | 60 |
| IU/L median | 188 | 213 | 187 |
| Range | 104–933 | 140–360 | 104–933 |
| AP | | | |
| Not reported | 46 | 16 | 30 |
| Reported | 79 | 12 | 67 |
| IU/L median | 136 | 142 | 133 |
| Range | 20–636 | 52–297 | 20–636 |

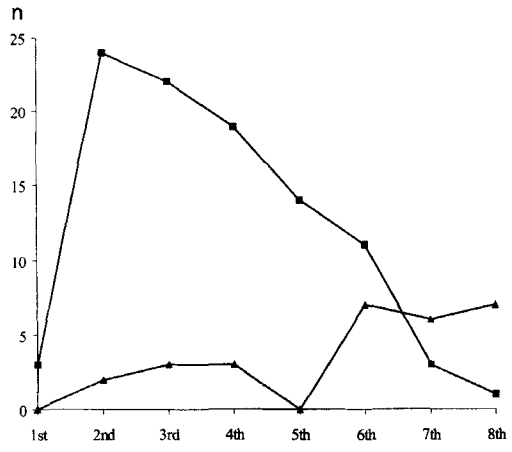


Figure 1. Age distribution of 125 evaluable patients with MFH of bone by decade of life, divided according to whether chemotherapy was given (■) or not (▲).

### *Treatment*

By definition, all 125 eligible patients underwent definitive surgery for their primary limb tumor: ablative surgery (amputation or disarticulation) in 30, limb-saving resections in 94 and rotation plasty in 1. Among 54 tumors where the volume was documented, this was median 60 (2–455) $cm^3$ with limb-salvage (41 patients) and median 260 (60–1050) $cm^3$ with ablative surgery (13 patients).

97 patients (78%) received chemotherapy in addition to local treatment (Tables 1 and 2). Patients younger than 41 years at diagnosis and females received chemotherapy more often than older patients and males. Information about which agents had been given was available for 94. Doxorubicin was the drug most frequently given (90), followed by cisplatin (78), methotrexate (70), ifosfamide (43), cyclophosphamide (26), vincristine (25), actinomycin D (20), bleomycin (17), dacarbacine (14), carboplatin (2), and etoposide (1).

### *Statistics*

Chi-square analysis was used to compare unrelated probabilities. Actuarial disease-free survival (DFS) was calculated from the date of biopsy until the date of first relapse by using the Kaplan-Meier method. The log-rank test was used to compare survival curves.

Table 2. Therapy and outcome

| | Total | Treatment | |
|---|---|---|---|
| | | Local only | Local and systemic |
| All patients | 125 | 28 | 97 |
| Local therapy | | | |
| Surgery only | 110 | 24 | 86 |
| Surgery and radiotherapy | 15 | 4 | 11 |
| Ablative surgery | 30 | 8 | 22 |
| Limb-sparing surgery [a] | 95 | 20 | 75 |
| Chemotherapy | | | |
| Preoperative only | 7 | – | 7 |
| Postoperative only | 10 | – | 10 |
| Pre- and postoperative | 80 | – | 80 |
| None | 28 | 28 | – |
| Follow-up, median (range) | | | |
| All patients, years | 2.3 (0.1–11.4) | 1.3 (0.2–8.6) | 2.6 (0.1–11.4) |
| Patients at risk, years | 3.9 (0.5–11.4) | 2.5 (1.1–8.6) | 3.9 (0.5–11.4) |
| followed at 1 year | 95 | 16 | 79 |
| 2 years | 67 | 9 | 58 |
| 3 years | 47 | 5 | 42 |
| 4 years | 33 | 2 | 31 |
| 5 years | 23 | 1 | 22 |
| 10 years | 1 | 0 | 1 |
| Outcome | | | |
| No relapse | 85 | 14 | 71 |
| Relapse | 40 | 14 | 26 |
| local/combined | 7 | 5 | 2 |
| systemic | 33 | 9 | 24 |

[a] The only rotation plasty was included among the limb-sparing procedures

## Results

After a median follow-up of 3.9 (0.5–11.4) years for patients at risk, the actuarial 5-year disease-free survival probability of all 125 evaluable patients was 59% (Figure 2). Altogether 40/125 tumors relapsed. 6 patients suffered an isolated local recurrence as first relapse, 1 a local recurrence simultaneously with pulmonary metastases, and 33 distant metastases without local recurrence (lung 27, bone 5, not specified 1) (Table 2). No metastases to lymph nodes were reported.

While there was no significant correlation between patient sex or tumor site and disease-free survival, patients aged 40 years or less had a better prognosis than older patients (Figure 3). In 54 patients with data on tumor volume available, this could not be defined as a predictor of disease-free

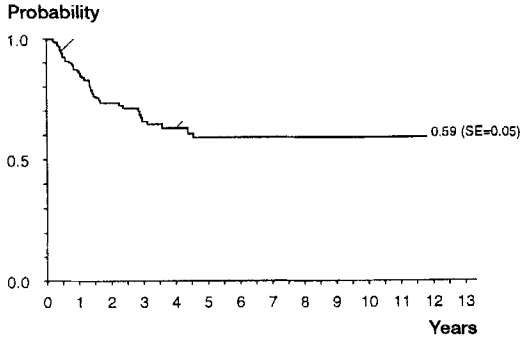


Figure 2. Disease-free survival of all 125 evaluable patients. Tick marks indicate median follow-up for patients still at risk and for the latest patient entered, respectively. SE standard error.

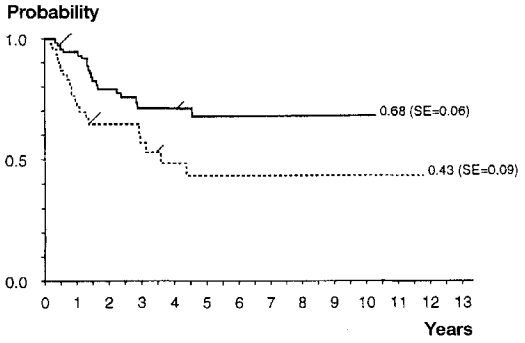


Figure 3. Disease-free survival of patients older than 40 years (hatched line; n 76; in continuous clinical remission (CCR) 57) at diagnosis, compared to that of younger patients (solid line; n 49; in CCR 28; p = 0.01, log-rank test). Tick marks, see Figure 2.

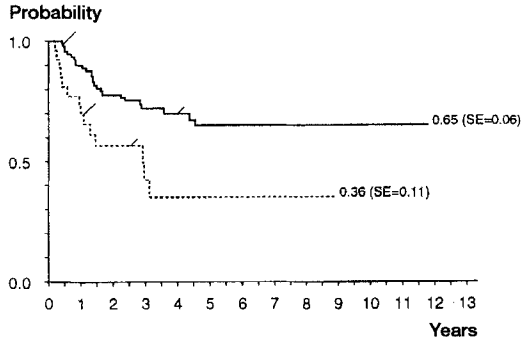


Figure 4. Disease-free survival of patients treated with local plus systemic therapy (solid line; n 97; in CCR 71) compared to that of patients treated with local therapy only (hatched line; n 28; in CCR 14; p = 0.003, log-rank test). Tick marks, see Figure 2.

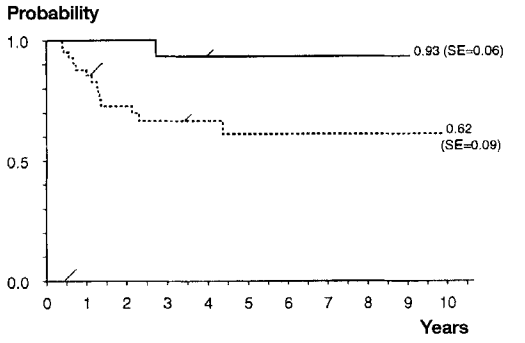


Figure 5. Disease-free survival as a function of tumor response to preoperative chemotherapy. A good response (< 10% viable tumor; solid line; n 23; in CCR 22) was associated with a more favorable prognosis than a poor response (hatched line; n 43; in CCR 29; p = 0.01, log-rank test). Tick marks, see Figure 2.

survival probability (DFS 55% for volumes < 100 $cm^3$, 61% for volumes ≥ 100 $cm^3$, p = 0.07).

As for therapy-associated variables, patients who had received chemotherapy had a better prognosis than did those who had not (Figure 4). Information on histological tumor response was available for 66 of 77 patients treated with preoperative chemotherapy but not preoperative radiotherapy. A good response was achieved in one third (23/66). 15/45 tumors whose preoperative treatment included doxorubicin, 20/59 whose preoperative treatment included cisplatin, 20/49 whose preoperative treatment included methotrexate, and 4/16 whose preoperative treatment included ifosfamide responded. Information on the duration of preoperative chemotherapy was available for 20 good and 33 poor responders. In these, the median duration was 6 (1–11) and 5 (3–18) weeks, both less than generally prescribed by osteosarcoma protocols.

Patients whose tumors responded well to preoperative chemotherapy had a better prognosis than those whose tumors responded poorly (Figure 5). As only 10 patients had received postoperative chemotherapy only (Table 2), a meaningful comparison between adjuvant and neoadjuvant chemotherapy was not feasible. Moreover, the database did not permit a detailed evaluation of the impact which individual agents or their dose-intensity might have had on outcome.

Overall, limb-sparing surgery could not be defined as a risk factor for relapse. On the contrary, DFS was 64% after resections (95 patients: 7 local/combined failure, 19 distant metastases), but

only 43% after ablative surgery (30 patients: 0 local/combined failure, 14 distant metastases) ($p = 0.02$). Information on surgical margins was not available. 1 local relapse occurred among 15 patients who had received local radiation therapy in addition to surgery, and 6 among 110 who had not. None of the 23 tumors with a documented good response to preoperative chemotherapy relapsed locally.

## Discussion

This EMSOS survey represents clinical experience of the largest contemporary series of patients with malignant fibrous histiocytoma of bone. The aims of the survey were to gather information on the presentation, current treatment, and outcome of this rare tumor. In view of the paucity of available data, and especially the lack of even moderately large prospective trials, it was felt that such a retrospective survey, with all its many inherent limitations, might help to point out possible interactions between patient, tumor, or treatment-related variables and outcome. We placed special emphasis on effects which might be associated with systemic (preoperative) chemotherapy.

Complete surgery of all malignant foci is rarely achieved with tumors of the axial skeleton or primary metastatic disease. As patients without adequate local control are highly unlikely to be long-term survivors, regardless of other risk factors or treatment (Little and McCarthy 1993, Yokoyama et al. 1993), we restricted our analysis to patients with localized extremity MFH, whose tumors were surgically removed.

Patient and tumor characteristics in the EMSOS series, including presenting signs and symptoms, patient age and sex, tumor-site and laboratory values, were similar to those reported by others (Spanier et al. 1975, Huvos 1976, McCarthy et al. 1979, Huvos et al. 1985, Kumar et al. 1990, Nishida et al. 1997), suggesting that the study population was, indeed, representative for MFH of bone. As in those other published series, we found patients with osseous MFH to be older than the average patient with osteosarcoma. The rate of pathologic fractures in our series—15/125—, while probably higher than would be expected for osteosarcoma, is lower than the 9/11 or 13/23 reported by Spanier et al. (1975) or Feldman and Lattes (1977), respectively, but is in the same range as the 20% reported for 90 patients from the Rizzoli Institute (Capanna et al. 1984).

MFH of bone is believed to disseminate rapidly (Malawer et al. 1997). In one report from the pre-chemotherapy era, 9 of 11 patients died of the tumor after an average disease-free interval of only 6 months (Spanier et al. 1975). A review of the literature up to 1982, including 74 patients, reported a cumulative 5-year survival rate of 37% (Ghandur-Mnaymneh et al. 1982). Our survey, like other reports (Dahlin and Unni 1977, Maeyama 1984, Huvos et al. 1985, Bacci et al. 1998), suggests that outcome might be somewhat more favorable. More than three quarters of all relapses in our series occurred as distant metastases to the lung. In contrast to earlier observations by Spanier et al. (1975), no lymph node metastases were reported. However, due to our restriction of evaluability to patients with localized extremity lesions, a direct comparison to other series, which had broader entry criteria, is not feasible.

Of all patient and tumor characteristics assessable at diagnosis, only patient age correlated with outcome, younger patients doing better than older ones. Similar observations have been published by others (Huvos et al. 1985, Little and McCarthy 1993). Naka et al. (1995) evaluated the outcome in 20 cases of MFH of bone in patients older than 40 years of age and found a 5-year survival rate of only 22%. In our series and in others, however, age was not independent of treatment-related variables—for example, older patients were less likely to receive chemotherapy. The retrospective design of our survey does not allow us to draw definitive conclusions as to whether age per se or treatment was the dominant factor.

The failure to detect an effect of tumor-volume on prognosis—which has been reported for osteosarcoma (Bieling et al. 1996)—may well have been due to the fact that the number of patients for whom information on volume was reported was far from complete. The same holds true of some other variables, such as AP and LDH, prohibiting definitive statements about these factors.

As for treatment-associated variables, patients who received chemotherapy in addition to local

therapy had a significantly lower relapse risk than patients who did not (whose 5-year disease-free survival rate of 36% still seems higher than reported for osteosarcoma treated with surgery only (Link 1993)). However, the two groups were not comparable for age and sex, and the comparatively younger age of those patients who received chemotherapy may have contributed to the observed difference in outcome. On the other hand, our results correspond well to previous observations in smaller groups of patients with osseous MFH given chemotherapy in addition to surgery (Urban et al. 1983, den Heeten et al. 1985, Huvos et al. 1985, Bacci et al. 1988, 1990, 1996, Earl et al. 1993, Yokoyama et al. 1993, Ham et al. 1996). Several earlier reports from the Rizzoli Institute (Bacci et al. 1988, 1990, 1996), which was also a major contributor to the EMSOS series, and another paper on 17 patients (Yokoyama et al. 1993) have retrospectively compared surgery only with surgery plus additional chemotherapy and suggested an improved outcome with chemotherapy. In very small series of less than 20 patients with rather short follow-up, survival rates of up to 80% and more have been reported, using this approach (Earl et al. 1993, Ham et al. 1996). On the other side of the spectrum, Huvos et al. (1985), when analyzing the Memorial Hospital experience from 1927–1984, noted only an insignificant improvement in survival for 66 patients treated after modern chemotherapy became available at the institution, compared to patients treated earlier, but gave no details as to whether all eligible patients had actually received chemotherapy.

In our series, the response rate to preoperative chemotherapy—approximately only one third—was lower than that achieved in osteosarcoma and lower than that which others reported for small series of osseous MFH (den Heeten et al. 1985, Huvos et al. 1985, Ham et al. 1996). However, it is in agreement with reports by Earl et al. (1993) and Bacci et al. (1996). Note that the very high response rate for high-dose methotrexate-based regimens recently reported by Ham et al. (1996) could not be confirmed by our survey.

The prognosis for 23 patients whose MFH responded well to preoperative chemotherapy was excellent, with only 1 of them developing metastases and none a local recurrence. One reasonable interpretation of this finding would be that some patients with MFH of bone benefit from systemic chemotherapy. If so, the beneficial effect of chemotherapy seems to extend from the prevention of systemic relapses to the prevention of local recurrence after surgery, again mirroring the situation in osteosarcoma (Picci et al. 1994, Bielack et al. 1996).

Limb salvage was not associated with a higher relapse risk than ablative surgery. Indeed, it appeared to have a better prognosis (95 patients: DFS 64%, 7 local/combined failure, 19 distant metastases) than the latter (30 patients: DFS 43%, 0 local/combined failure, 14 distant metastases). This difference was due only to a lower rate of distant metastases in patients treated by limb salvage, which more than compensated the higher rate of local failure associated with this type of procedure. The observation might be attributable to selection bias, with limb salvage surgery substituting as a marker for less advanced locoregional disease. Unfortunately, information on surgical margins was not available.

In conclusion, the results of this EMSOS survey show that the prognosis of patients with localized, operable malignant fibrous histiocytoma of an extremity bone need not always be poor. Our findings agree with previous suggestions that chemotherapy in addition to surgery may have a role in treating osseous MFH. A good response to preoperative chemotherapy seems to be associated with an excellent prognosis. Prospective trials are needed to determine the optimal treatment. Such studies in this rare disease require international collaboration.

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