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Discriminant analysis of prognostic factors for malignant fibrous histiocytoma in soft tissue

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Abstract We prospectively followed 32 patients with soft-tissue malignant fibrous histiocytoma (MFH). Parameters were age; sex; tumor size, location, and depth; operative method; chemotherapy; radiotherapy; and histology. Patients with recurrence or metastases due to MFH within 6 months after the initial operation were separated from those without these characteristics by discriminant analysis with statistically significant difference. The order of influential functions was histology, depth of tumor, operative method, and sex. Male patients with deep-seated storiform-pleomorphic type MFH, receiving less comprehensive surgery, had the greatest risk of local recurrence or early metastases. We have to pay particular attention to patients with these factors and perform adequate surgery, because local recurrence and metastases were found to be closely related, and to have a great influence on the prognosis of this disease. Discriminant analysis to separate patients with MFH recurrence or metastases within 6 months after the initial operation from those without these characteristics is worthwhile for prognostic assessment.

Key words Discriminant analysis · Prognostic factors · MFH · Soft tissues

Introduction

Malignant fibrous histiocytoma (MFH), the most commonly diagnosed soft-tissue sarcoma, occurs predominantly in middle-aged individuals.[6,9] Various therapeutic strategies, such as wide resection,[5] chemotherapy,[7] and radiotherapy,[16] have been employed, but satisfactory prognosis has not been achieved. For a practical choice of treatment, it is very important to know which factors affect the recurrence or metastases of MFH. Several factors, such as tumor location, size, and depth; patient age; operative procedures; and histology, are known to affect the prognosis of soft-tissue MFH.[1,6,10,11,14] Those patients who suffer MFH recurrence or early metastasis have poor survival.[1] In this study, we analyzed which factors affected such early metastases or local recurrence. Further, we looked for parameters associated with death and metastases due to soft-tissue MFH.

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Patients and methods

We retrospectively followed 32 patients (16 men and 16 women) who presented with soft-tissue MFH between June 1986 and March 1999. The mean age was 53 years (range, 25 to 73 years). The primary tumor locations were: the lower extremities in 21, the trunk in 6, and the upper extremities in 5. The size of the tumor ranged from 2 to 30 cm in largest diameter. In 8 patients, the tumors were subcutaneous, and in 24, they were in deep locations, based on whether the tumor had grown through the deep fascia. For the initial operative procedure,[8] amputation with a curative wide margin was performed in 6 patients, wide resection in 12, marginal resection in 11, and intralesional resection in 3. Chemotherapy and radiation therapy were performed for 23 and 10 patients, respectively. The agents used for adjuvant chemotherapy were: adriamycin (ADR), pirarubicin (THP), ifosfamide (IFO), cisplatin (CDDP), dacarbazine (DTIC), vincristine (VCR), and actinomycin D, administered singly or in combination. A uniform chemotherapy protocol was not employed. Most patients received more than two cycles of adjuvant chemotherapy. Radiotherapy was administered as an adjuvant to surgical resection. The technique and doses varied throughout the study, but generally included delivery of photons or electrons by external beam. Diagnosis was based on the histology derived from

Table 1. Parameters assessed in this study

Parameter	Ordering
Age	(Real numbers)
Sex	Male, 1; Female, 2
Tumor location	Distal from knee or elbow, 1; proximal from knee or elbow, 2; trunk, 3
Depth of tumor	Subcutaneous, 1; deep, 2
Operative method	Intralesional, 1; marginal, 2; wide, 3; amputation, 4
Tumor size	Major × minor axes
Chemotherapy	Not performed, 1; performed, 2
Radiotherapy	Not performed, 1; performed, 2
Histology	Myxoid, 1; storiform-pleomorphic, 2

surgical specimens. Histologically, there were 26 storiform-pleomorphic and 6 myxoid variants.

Patients were included in the analyses until the time of death or until their last date of follow-up evaluation. The mean follow-up period was 41 months (range, 6 to 105 months). The parameters assessed were age; sex; tumor size, location, and depth; operative method; chemotherapy; radiotherapy; and histology (Table 1). Tumor locations were numbered as follows: trunk, 3; proximal extremities from the elbow or knee, 2; and distal extremities, 1. The depth was assessed as subcutaneous or deeper regions. Operative procedures were numbered as follows: amputation with curative wide margin, 4; wide resection, 3; marginal resection, 2; and intralesional resection, 1. Tumor size was calculated by multiplying values for the major and minor axes. Chemotherapy and radiotherapy were assessed as performed or not performed.

With these nine parameters mentioned above, discriminant analysis was conducted to assess whether patients with recurrence or metastases due to MFH within 6 months after the initial operation could be separated from those without these characteristics. In addition, two more parameters, local recurrence and secondary surgery, ordered as for the initial operation, were assessed for outcome. Finally, we determined the influence of the parameters on mortality.

Results

The local recurrence rates in this study were 100% (3/3) for intralesional resection, 72% (8/11) for marginal resection, 17% (2/12) for wide resection, and 0% (0/6) for amputation with curative wide margin. The local recurrence rate with radiation therapy was 60% (6/10), while that without radiation therapy was 36% (8/22). Local recurrence or metastatic rate with chemotherapy was 74% (15/23), while the rate was 44% (4/9) in patients without chemotherapy. In the assessment of whether patients with recurrence or metastases due to MFH within 6 months after the initial operation could be separated from those without these characteristics, discriminant analysis demonstrated a statistically significant difference, with $F = 2.8811$ and degrees of freedom (df) = (5, 26) (Fig. 1; $\alpha = 0.05$).

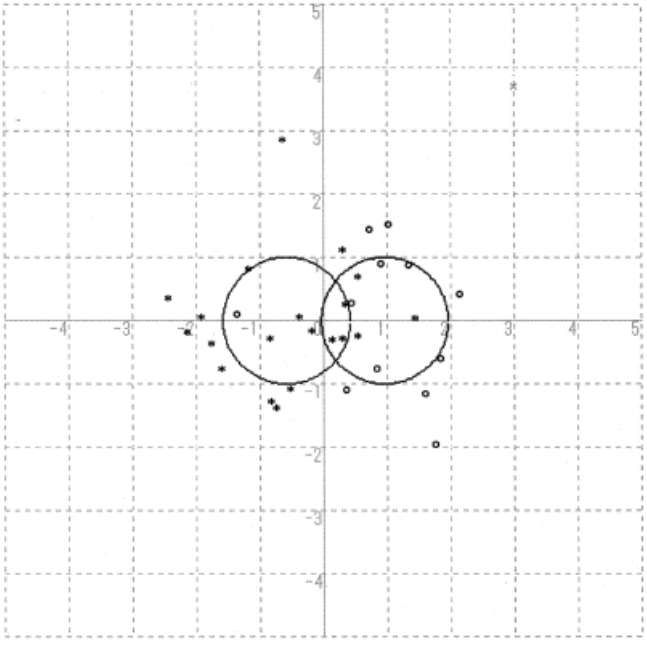

Fig. 1. Canonical coordinates for local recurrence or metastases. Patients with recurrence or metastases of malignant fibrous histiocytoma (MFH) within 6 months after the initial operation (*open circles*) were separated from those without such recurrence or metastasis (*asterisks*) by discriminant analysis

Table 2. Discriminant analysis for local recurrence or metastases

Parameter	Partial F value
Histology	6.63
Depth of tumor	2.56
Operative method	2.84
Sex	2.19

The most influential function in this analysis was histology (partial $F = 6.63$), followed by depth of tumor (partial $F = 2.56$), operative method (partial $F = 2.84$), and sex (partial $F = 2.19$; Table 2). In the assessment of whether patients with early metastases due to MFH could be separated from those without these characteristics, discriminant analysis demonstrated a statistically significant difference, with $F = 5.1873$ and df = (7, 24) (Fig. 2; $\alpha = 0.01$). The most influential function was local recurrence within 6 months after the initial operation (partial $F = 9.41$), followed by depth of tumor (partial $F = 5.61$), sex (partial $F = 3.11$), histology

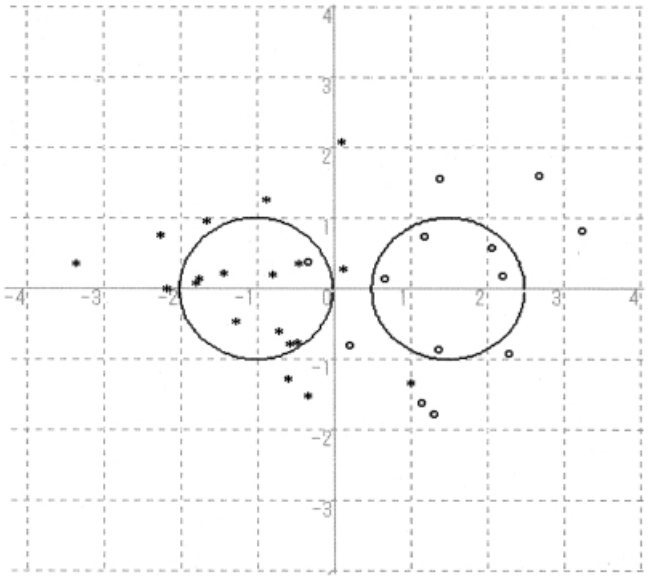

Fig. 2. Canonical coordinates for metastases due to MFH. Patients with metastases of MFH (*open circles*) and those without such metastasis (*asterisks*) could be completely separated by discriminant analysis

Table 3. Discriminant analysis for metastases due to MFH

Parameter	Partial F value
Recurrence within 6 months of original operation	9.41
Depth of tumor	5.61
Sex	3.11
Histology	2.27
Radiotherapy	2.46
Chemotherapy	1.61

MFH, malignant fibrous histiocytoma

(partial F = 2.27), radiotherapy (partial F = 2.46), and chemotherapy (partial F = 1.61; Table 3).

In the assessment of mortality, discriminant analysis demonstrated a statistically significant difference from survival, with F = 10.1990 and df = (8, 23) (Fig. 3; α = 0.01). The most influential function was whether or not metastases were present within 6 months after the initial operation (partial F = 22.04), followed by sex (partial F = 9.85), operative method for local recurrence (partial F = 6.15), depth of tumor (partial F = 3.61), operation for metastases (partial F = 3.51), local recurrence within 6 months (partial F = 2.72), radiotherapy (partial F = 2.48), and age (partial F = 2.02; Table 4).

Discussion

Analyses of prognostic factors in soft-tissue MFH have been the subject of several reports,[1,6,10,11,14] with tumor size, histology, and location; patient age; and surgical procedures being found to be related to the prognosis. Recurrence within 1 year was a risk factor,[1] and an association has been observed between local recurrence and metastasis in soft-tissue sarcomas.[13] When we initially treat patients with soft-tissue MFH, it is very important to determine which factors we need to focus on to prevent early local recurrence or metastases, because early local recurrence or metastases results in poor prognosis. We therefore analyzed factors that affected local recurrence or metastases due to soft-tissue MFH within 6 months after the initial operation, and found that discriminant analysis allowed distinction.

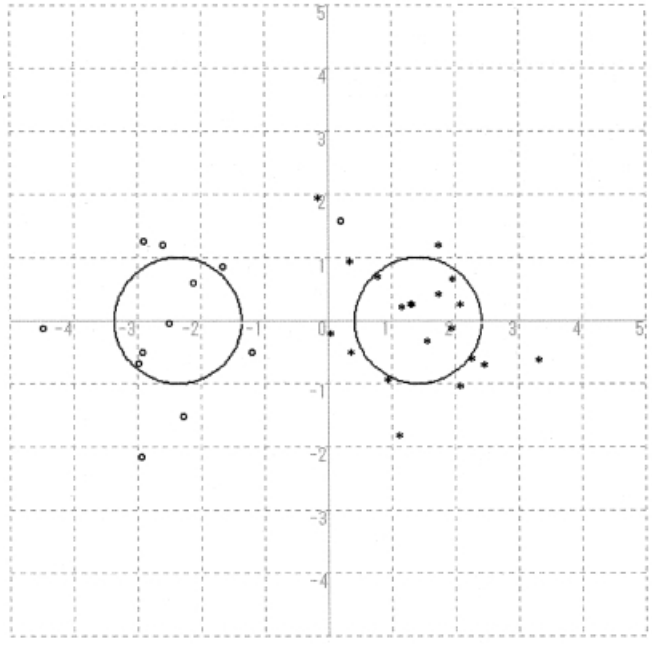

Fig. 3. Canonical coordinates for death due to MFH. Patients who died of MFH (*open circles*) could be completely separated by discriminant analysis from patients who were alive (*asterisks*)

Table 4. Discriminant analysis for death due to MFH

Parameter	Partial F value
Metastases within 6 months of original operation	22.04
Sex	9.85
Operative method for recurrence	6.15
Depth of tumor	3.61
Operation for metastases	3.52
Local recurrence within 6 months of original operation	2.72
Radiotherapy	2.48
Age	2.02

The important factors, in descending order, were: histology, tumor depth, operative procedure, and sex. Male patients with deep-seated storiform-pleomorphic type MFH, receiving less comprehensive surgery, had the greatest risk of local recurrence or early metastases. A storiform-pleomorphic histology was previously found to be associated with a poor prognosis.[6] Subcutaneous tumors has a low rate of local recurrence[2,12,13] and distant metastases,[2] while deep-seated MFH in soft tissue has a poor prognosis.[1,10,11,14] Local recurrence rates based on different operative methods were slightly higher when the operation was inadequate and similar when the operation was adequate, compared with findings in a previous report.[8] As demonstrated previously,[1,10,11,14] our study showed adequate operative procedures to be important for preventing local recurrence or metastases.

A number of studies have documented the utility of radiation therapy for soft-tissue tumors,[15,16] although such therapy was found to not prevent the local recurrence of MFH.[1] In the present series, the local recurrence rate with radiation therapy was 60%, while the rate was 36% without it. Most radiation therapy was performed for patients who did not receive adequate operative procedures. However, our data indicated that radiation therapy had little influence for this purpose, although the protocols and doses of radiotherapy varied throughout the study. Chemotherapy also was without major influence in our series, because the local recurrence or metastatic rate was 74% with chemotherapy, while it was 44% without chemotherapy. Various chemotherapy regimens have been employed for the treatment of MFH in soft tissue,[4,7] and in some patients the response was good.[3] However, as in our study, chemotheapy was not found to be an important factor in the prognosis of soft-tissue MFH on multivariate analysis.[1,14] Further investigations with a uniform chemotherapy protocol may be necessary. The partial F value was high for sex (partial $F = 2.19$). This result may have reflected the simple categorization of male and female patients as 1 and 2, respectively.

The most influential factor regarding patient mortality in this study was the presence of metastasis within 6 months after the initial operation, in line with earlier findings.[10] MFH recurrence early after the operation is linked to a higher tendency to metastasize,[1] as confirmed here.

For the practical choice of treatment, it is very important to know which factors affect early recurrence or metastases of MFH, because we can predict the coming changes of the disease and deal with them in advance. Thus, discriminant analysis which separates patients with recurrence or metastases of MFH within 6 months after the initial operation from those without these characteristics is worthwhile for prognostic assessment.

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