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Surgical margins do not affect prognosis in high grade myxofibrosarcoma

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Abstract

Introduction: Myxofibrosarcoma (MFS) is one of the most common soft tissue sarcomas (STS) in elderly patients and it primarily affects the extremities. The aim of this retrospective analysis is to understand the natural history of MFS and whether adequate treatment influence prognosis.

Patients and methods: We reviewed 129 adult patients with primary, localized, FNCLCC grade 3 MFS of the extremities operated at Istituto Ortopedico Rizzoli, Bologna. Sarcoma specific survival (SS), local recurrence (LR) and distant metastasis (DM) were analyzed.

Results: Among excised MFS (119), 106 (89.9%) had R0 margins, 13 (10.1%) R1 margins. No significant correlation between margins adequacy and tumor depth, location and size was found. Estimated SS was 73.2% at 5 years and 66.3% at 10 years, with a better SS in superficial MFS ($p = 0.011$). Local recurred MFS had a worse SS ($p = 0.049$). Local recurrence-free rate was 74.3% at 5 and 10 years. Even if not significant, a better outcome in term of LR was observed in superficial MFS and R0 margins. Distant metastasis-free survival was 75.6% at 5 years and 72.9% at 10 years, with a better outcome in superficial MFS ($p = 0.012$).

Discussion: Myxofibrosarcoma remain a debated entity with specific behavior features. Myxofibrosarcoma tends to local recur due to its infiltrative grow pattern making difficult to achieve "safe margins". To date, surgical margins as classified for other STS are not predictive of LR and patients' survival. Tumor grade and depth are still the most important prognostic factors.

Keywords: Extremity sarcoma; Myxofibrosarcoma; Surgical margins

Introduction

Myxofibrosarcoma (MFS) is one of the most common soft tissue sarcomas (STS) in elderly patients. It primarily affects the extremities and girdles, especially in the lower limbs.[1] Considering the prevalence of this sarcoma in late age, the incidence of this neoplasia is expected to increase in our aging society.

A characteristic clinical feature of MFS is its propensity for local recurrence (LR). The incidence of LR ranges from 32% to 60%[2,3] and is more frequent than other STS, even in the case of low grade lesions and lesions widely excised.[4] A possible explanation for the LR is the characteristic infiltrative growth pattern of MFS, leading tumors to extend along vascular and fascial planes when deeply seated[5,6] or to infiltrate the dermis when superficial.[7] This biological behavior has a direct impact on surgical treatment. In most STS, surgeons can excise with "safe margins" quite easily,[8–10] but it remains unclear whether standard margins assessment is adequate for MFS.

Preoperative tumor evaluation with magnetic resonance imaging (MRI) or computerized axial tomography scan (CAT-scan) has been shown to be difficult as well, leading

Abbreviations: MFS, myxofibrosarcoma; STS, soft tissue sarcoma; SS, sarcoma specific survival; LR, local recurrence; DM, distant metastasis; EBRT, external beam radiation therapy; CT, chemotherapy; MRI, magnetic resonance imaging; CT-scan, computerized axial tomography scan.

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to frequent underestimation of tumor extension due to the specific infiltrative pattern of MFS.[11,12]

For these reasons and because of its frequent superficial presentation, MFS represents one of the most frequently "unplanned" excised STS.[13]

Furthermore, radiation therapy represents a real challenge in the attempt to ensure that all potential microscopic disease is encompassed in the planning target volume.[14]

In addition, 15–38% of locally recurrent MFSs progress to a higher-grade disease with an attendant increase in metastatic potential.[1]

Nevertheless, the prognosis of MFS is relatively good compared to other STS, with a risk of distant metastases (DM) ranging between 20% and 25%[2] and a disease-specific survival of 83%.[15]

In an effort to improve the current understanding of the natural history and treatment outcomes of primary, localized, high grade MFS, we conducted a retrospective analysis of patients treated at a single Institution (Istituto Ortopedico Rizzoli, Bologna, Italy).

Material and methods

From January 1990 to June 2015, a total of 319 patients affected by high grade MFS underwent surgical excision at a single Institution (Istituto Ortopedico Rizzoli, Bologna, Italy).

All cases were histologically revised and classified according to the 2013 World Health Organization classification of STS[16] by experienced sarcoma pathologists of our Institute.

Diagnosis of MFS was based on the presence of alternating hypocellular, myxoid areas and hypercellular, fibrous areas, pleomorphism and aggregation of neoplastic cells around curvilinear vessels. Immunostains were used to exclude other entities that may mimic MFS. A 3-step system (FNCLCC) was used to assess MFS grade.[17]

One hundred and twenty nine adult patients (>18 years) with primary localized high grade MFS (FNCLCC grade 3) of the extremities (hand and foot excluded) were selected from the patient population in order to analyze a clinically homogenous group.

Tumor size was assessed on surgical specimens using the larger diameter as a reference and depths were divided into superficial (above the muscle fascia) and deep (below the muscle fascia), according to preoperative imaging (CAT-scan or MRI). All patients underwent operation in order to obtain limb-sparing, function-sparing surgery with negative surgical margins, according to the residual tumor (R) classification.[10] The use of plastic surgery was recorded.

The use of external beam radiotherapy (EBRT) and chemotherapy (CT) was decided at the discretion of a multidisciplinary team (orthopedic surgeon, radiotherapist and oncologist).

Radiation therapy was administrated according to STS guidelines.[18]

Anthracycline-based drug regimen was used and in most patients incorporated ifosfamide.

Patients' characteristics are presented by frequencies and percentages for categorical variables, median and range for continuous variables.

The Kaplan–Meier method was used to estimate overall sarcoma specific survival (SS), LR-free survival and DM-free survival.

Local recurrence-free survival and DM-free survival intervals were defined as the time between surgery and the first LR or DM, respectively, or last follow up available, whichever came first. Similarly, SS interval was defined as the time between surgery and death or last follow up, whichever came first. Patients who died of other causes were censored. Differences in survival rates were assessed by the log-rank test.

Multivariable analysis of LR were based on cause-specific hazards and therefore carried out by Cox regression models. P values <0.05 were considered significant.

The following prognostic factors were studied: tumor size and depth, surgical margins, RT and CT.

All analysis was completed using the Statistical Package for Social Science (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.).

Results

Median age at the time of surgery was 69 years (range, 34–91); 73 patients (57%) were male, 55 (43%) were female.

One hundred MFS (78%) were localized in the lower limb, 15 (12%) in the upper limb, 5 (4%) in the pelvic girdle and 9 (7%) in the shoulder girdle.

Eighteen (14%) were small (<5 cm) and 111 (86%) were large (>5 cm); 68 (61%) of these were >10 cm.

Twenty-three MFS (18%) were superficial, 106 (82%) were deep with a significant positive correlation ($p < 0.001$) between depth and size (deep tumors tent to be larger) (Table 1).

In 119 (92%) patients excision was possible, whereas in 10 (8%) patients amputation was necessary.

Among excised MFS, 106 (89.9%) had R0 margins, 13 (10.1%) R1 margins.

No significant correlation between margins adequacy and tumor depth (superficial/deep), location (girdle/extremities) and size (<5 cm/>5 cm) was found.

Plastic surgery was necessary in 15 cases (6 pedicle muscle flaps, 6 fascio cutaneous flaps, 2 free flaps and 1 skin graft), particularly in superficial MFS (35% vs. 9%) ($p = 0.03$). The use of plastic surgery did not correlate with a negative surgical margin.

Overall, adjuvant or neoadjuvant EBRT was mostly used in deep and large MFS. In deep and large MFS with R0 margins 12 patients had adjuvant EBRT, 3 had neoadjuvant EBRT and 6 had combined neoadjuvant and adjuvant