The management of myxofibrosarcoma – a ten-year experience in a single specialist centre

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INTRODUCTION

Soft tissue sarcomas (STS) are uncommon malignant tumours of extra-skeletal connective tissue, accounting for approximately 1% of adulthood malignancies in the United Kingdom. Myxofibrosarcoma, previously known as myxoid variant of malignant fibrous histiocytoma (19), was first described as an independent disease by the World Health Organisation (WHO) in 2002 (4). Although myxofibrosarcoma is a common form of STS, it is a rare tumour that poses a challenge to clinicians primarily due to its high rate of aggressive local recurrence independent of grade and optimal surgery (10). Myxofibrosarcoma is more common in elderly patients and typically presents as a slow growing painless mass either deep within limb musculature or superficially (10,16). Diagnosis is based on histological characteristics including myxoid stroma, cytologic atypia and pleomorphism (17). Myxofibrosarcoma can be graded according to the Trojani system (1,9), in which grade I tumours are locally aggressive, but grade II and III tumours have metastatic potential (20) (Table I).

Treatment aims to prolong survival, prevent local recurrence, maximise function and minimise morbidity. Radical, limb salvage surgery with clear
the management of myxofibrosarcoma is essential and adjuvant treatment involving radiotherapy is advised. In order to obtain a radical excision, tissue reconstruction may be required following resection rather than direct wound closure, hence the level of soft tissue resection needs to be carefully planned. Where local control is not achieved, amputation is recommended (12).

Local recurrence (LR) for myxofibrosarcoma is quoted between 18-54% and documented up to 21 years following initial resection (11,13,18). Certain disease characteristics predispose to local recurrence (Table II) (10,11,14). Locally recurrent, initially low grade disease may return as a higher grade tumour (5) increasing the likelihood of metastasis. Metastasis occurs in approximately 15% of patients within 5 years (18). The five year survival of patients has been quoted as 62-84% (3,16,18). Prognosis is dependent on grade as the degree of myxoid change is inversely related to metastatic disease (10).

We aim to demonstrate recent and long-term results of the treatment for myxofibrosarcoma in a single specialist Soft Tissue Sarcoma centre. And assess whether resection margin, tumour size or grade impact local recurrence, metastasis or death.

### PATIENTS AND METHODS

A retrospective cohort study was designed to assess the management of myxofibrosarcoma within our centre. 38 patients diagnosed with myxofibrosarcoma, between January 2003 and July 2012, were identified using a database of histological specimens including both biopsy samples and resected specimens. All patients were discussed at a multidisciplinary meeting following referral and a management strategy formulated. Eight patients were excluded: two were transferred to palliative care due to metastatic disease on presentation, four were found to have a different histological diagnosis of the resected specimen and two had incomplete medical records at the time of case note review.

Details regarding the initial referral, investigations, multidisciplinary team discussions and operative data for the remaining 30 patients were collected via case note analysis by a single clinician using a standardised proforma. All excised tumours were reviewed by an expert sarcoma histopathologist and graded according to the Trojani system. Data was collated using Microsoft Excel.

All patients underwent initial limb salvage surgery, with 27 patients also receiving adjuvant treatment in the form of radiotherapy. Statistical analysis was performed using IBM SPSS software. Margin and size were analysed against recurrence, metastasis and death using a non-parametric comparison of group medians. Grade was analysed against recurrence, metastasis and death using a linear test of association. Fisher’s exact test was used to assess the association between local recurrence and metastasis.

### RESULTS

Thirty patients (13 male, 17 female) with a mean age of 65.8 years (median 67.5 years, range 21-91 years) received surgical management for a
diagnosis of myxofibrosarcoma between January 2003 and July 2012. Twenty five patients (83.3%) were treated for primary disease. All tumours were located in the extremities, with 22 patients treated for lower limb tumours and the remaining 8 patients treated for upper limb tumours (Table III). The mean time from referral to discussion within the multi-disciplinary meeting was 9.7 days (median 8 days, range 1-41 days).

All patients with primary disease underwent a staging CT, biopsy and surgical assessment prior to surgery. Twenty-three of 25 patients (92%) were treated with radiotherapy, with 20 treated with adjuvant radiotherapy and the remaining three with neo-adjuvant radiotherapy. None received adjuvant chemotherapy. Four patients (13.3%) had a positive margin on resection; one patient underwent further resection showing no evidence of tumour and the remaining three undergoing post-operative radiotherapy. Ten of 25 patients were found to have a grade III tumour according to the Trojani system (Table IV). Grading was not possible for all three patients treated with neo-adjuvant radiotherapy as all three tumours showed a tumour necrosis of 98-100% on histological examination.

Patients with secondary disease were also all treated with initial limb salvage surgery following staging CT and multidisciplinary discussion. However, two of the 5 patients had positive margins on resection, with one patient undergoing further resection and one patient declining further surgery. Four of the 5 patients underwent adjuvant radiotherapy.

The mean maximum tumour dimension for all tumours treated in our centre was 7.9 cm (median 7.25 cm, range 2.5-17 cm), and a mean resection margin of 2.6 mm (range 0-10 mm) was achieved. In total, five patients (16.7%) suffered a wound complication, four requiring antibiotic treatment and one patient requiring VAC therapy due to an infected skin graft. No patients returned to theatre following a wound complication.

Four patients treated with primary disease (19.2%) and four patients with secondary disease (80%) developed local recurrence. Seven patients with lower limb tumours developed local recurrence, of which six ultimately required above knee amputation, one patient declined further surgery. One further patient with an upper limb tumour also developed local recurrence, requiring above elbow amputation. The linear association between grade and local recurrence approached but did not reach clinical significance (p = 0.053). Tumour size and the margin of resection did not have a significant effect on the rate of local recurrence.

Metastasis occurred in five patients, four of which were treated for primary disease (Fig. 1). Two patients with metastatic disease also had a local recurrence. Three patients developed pulmonary metastasis, one developed metastatic lymphadenopathy of the groin and one developed femoral and scalp

<table>
<thead>
<tr>
<th>Upper Limb</th>
<th>Lower Limb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper Arm</td>
<td>Buttock</td>
</tr>
<tr>
<td>Elbow</td>
<td>Thigh</td>
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<tr>
<td>Forearm</td>
<td>Knee</td>
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<td>Lower Leg</td>
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<tr>
<td></td>
<td>Ankle</td>
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<tr>
<td></td>
<td>Foot</td>
</tr>
</tbody>
</table>

Table III. — Distribution of Tumours Observed between 2003-2012

<table>
<thead>
<tr>
<th>Grade</th>
<th>Number Patients</th>
<th>Mean Largest Dimension (cm)</th>
<th>Recurrence</th>
<th>Metastasis</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
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<td>8</td>
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<td>1</td>
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<td>10</td>
<td>10.4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
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<td>5</td>
<td>6.4</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Recurrent</td>
<td>5</td>
<td>6.4</td>
<td>4</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Table IV. — Grading of Tumours Resected between 2003-2012

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the management of myxofibrosarcoma
tumour diameter of 8.4 cm compared to 7.9 cm, and
with a high proportion of high grade tumours. This
implies that our study population is a representative
sample of the wider patient population diagnosed
with myxofibrosarcoma. Although our sample size
is smaller than in other studies, we have shown
comparable results to the literature with regards to
local recurrence, metastasis and patient survival.
We have also differentiated the outcome of patients
with primary and secondary disease, which is not
commonly noted within the literature.

Local recurrence of myxofibrosarcoma is quoted
between 17-61% (3,11,13,18,19) and occurs more
commonly with myxofibrosarcoma than other forms
of STS (8). To date, four patients with primary dis-
ease (16%) and eight patients in total (26.7%) de-
veloped a local recurrence which is comparable to
current literature. Although our results showed that
an increase in tumour grade could potentially be as-
sociated with an increased likelihood of developing
local recurrence (p = 0.053), we did not demon-
strate an increase in patient mortality for those who
developed local recurrence, a similar finding to that
of Dewan (3). However these results may be due to
the small sample size, as more recent work by
Daigler (2) demonstrated that local recurrence is a
prognostic indicator in the management of STS. We
also displayed that, once local recurrence had
occurred, repeat resection in our patients resulted in
further local recurrence in four of five patients.
Furthermore, seven of eight patients with local
recurrence during this study ultimately
required an
amputation of the affected limb. We therefore advo-
cate limb salvage surgery for primary disease but
amputation in recurrent disease.

According to Dewan (3), 4% of patients present
with metastatic disease and metastasis subsequently
develops in 20% of patients. In our series, these fig-
ures were 0% and 17.2% (5 patients) respectively.
The site and grade of the tumour, as well as the
margin of resection, did not affect the likelihood of
metastasis in our series, but tumour size did reach
significance (p = 0.041). We also showed that
tumour size does not correspond to tumour grade,
which emphasises the need to treat all tumours
aggressively to ensure the best patient outcome.
Previous work suggests that lower grade tumours

metastases. Resection margin, local recurrence and
grade did not significantly affect the development
of metastasis. However, using a non-parametric in-
dependent samples median test, patients with larger
tumours were significantly more likely to develop
metastasis (p = 0.041).

Our patients have been followed-up for a mean
of 49 months (range 10-122 months, median
47 months) and 22 patients remain under follow-up.
Ten patients have now been followed up for over
five years, of which 7 are still alive and 5 remain
disease-free. Five patients (three primary, two sec-
ondary) have died, of which three presented with
primary tumours and two presented with recurrent
tumours. Two patients are receiving palliative care
at local centres. One patient has been lost to follow-
up. Tumour size, resection margin and tumour grade
did not significantly affect patient survival.

**DISCUSSION**

This study assesses patients who have been diag-
osed and treated for a rare tumour in a tertiary
referral centre over a 10-year period. The largest
series published within the United Kingdom com-
prises 172 patients (3). The patient populations in
both studies are comparable, with a mean age of
67 years compared to 65.7 years, mean maximal
are more likely to develop local recurrence (3) and the mechanism for this is unclear as no relation to tumour size or margin of excision was demonstrated here. These results again may be affected by the smaller sample size than that of other studies, and there is scope for further study in this area.

The optimal use of adjuvant therapies, including radiotherapy and chemotherapy, is still under debate. Adjuvant radiotherapy has been shown to reduce local recurrence, especially in higher grade tumours as well as in tumours in close proximity to a joint or to neurovascular structures (7,21). However, one study has shown that adjuvant radiotherapy does not improve patient survival (18). Of our 30 patients, 25 received adjuvant radiotherapy with 7 patients later developing a local recurrence; of the 2 patients who did not receive radiotherapy, one later developed local recurrence. Interestingly, none of the 3 patients who received neo-adjuvant radiotherapy have developed local recurrence or metastatic disease and we demonstrated tumour necrosis of 98-100% in all resected specimens, although one patient developed a superficial would infection that was successfully treated with co-amoxiclav only. However, the follow-up for these patients is relatively short with a mean of 29 months (range 21-45 months). Neo-adjuvant radiotherapy has previously been associated with a high wound complication rate of 35% (15) but more recent research within our department has demonstrated wound complication rates at 17.7%, comparable to adjuvant radiotherapy (6). The effectiveness of neo-adjuvant radiotherapy in the treatment of myxofibrosarcoma is an area for future research.

This study is not without limitations however. We have already discussed the small sample size at several points during this discussion, which therefore means that our results have to be interpreted with caution. Another limitation is the retrospective nature of data collection, and as patients received individualised treatment strategies we do not have a set standardised management plan for all patients in this study. A prospective, multi-centre study or national register would provide more detail into the effect of tumour characteristics and patient management into the success of treating myxofibrosarcoma, along with other forms of STS.

In conclusion, we have shown that tumour size may affect the development of metastatic disease, the management of primary disease in a specialist centre had the best chance of success, and that neo-adjuvant radiotherapy may have a potential role in the routine management of myxofibrosarcoma. A prospective, multi-centre study focussing on the use of radiotherapy, as well as studying the management of secondary disease in more detail, are future areas for research. The need for a national register for sarcoma patients is also an area to explore.

Acknowledgements

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REFERENCES

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