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Change in histological grade in locally recurrent soft tissue sarcomas

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Abstract

Histological examination of locally recurrent soft tissue sarcomas usually reveals an appearance similar to that of the original tumour. Occasionally, however, recurrent sarcomas appear more or less malignant histologically than the initial lesion. The goals of this paper were to identify the frequency with which this phenomenon occurs, factors that predict for a change in grade and to determine if this change is associated with a different prognosis from other patients with local recurrence. From a large sarcoma database, 124 patients with local recurrence were identified. These patients were distributed into groups who had no change in histological grade, increased histological grade or decreased histological grade on local recurrence. Increased grade occurred approximately 20% of the time, whereas decreased grade occurred in 7% of cases. A histological diagnosis of myxofibrosarcoma was predictive of an increase in histological grade on local recurrence. An increase in histological grade with local recurrence was not associated with a poorer survival.

Keywords: Sarcoma; Surgery; Radiation; Local recurrence; Malignant fibrous; Histiocytoma; Myxofibrosarcoma

1. Introduction

Surgical resection and adjuvant treatment of a soft tissue sarcoma carries a risk of local recurrence of the tumour of between 10 and 20% [1–7]. In most of these cases, the histological appearance of the recurrent tumour is identical to the original. However, this is not always the case [8]. Some soft tissue tumours gradually become more histologically malignant, whereas others undergo a more abrupt dedifferentiation. Rarely, tumours may undergo ''differentiation''. The factors leading to these histological changes are not known.

Morphological changes in the tumour that suggest progression of malignancy are described by histological grading, which is essential to make decisions on treatment and to predict the prognosis of patients with soft tissue sarcomas. The French Federation of Cancer Centers Sarcoma Group (FNCLCC) grading system, devised by Trojani [9,10] utilises the histological parameters of tumour differentiation, tumour necrosis and mitotic count to assign a score of 1 (low) to 3 (high) to a soft tissue sarcoma. This system has been shown to have good predictive value for distant metastasis development and mortality [10].

The goals of this study were to determine the incidence with which soft tissue sarcomas change Trojani grade histologically, to investigate possible risk factors predictive for this histological grade change, and to determine whether a change in histological grade affects patient survival.

2. Patients and methods

Criteria for inclusion in the study included a diagnosis of soft tissue sarcoma with local recurrence occurring more than 6 weeks after the initial surgical resection. It was felt that a recurrence less than 6 weeks after resection likely represented residual disease. All

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patients had their definitive initial resection done at our hospital, and the pathology of the initially resected and recurrent tumours were reviewed and graded by one of four musculoskeletal pathologists affiliated to our unit. Prior to 1997, the original Trojani grading system was used [9], but subsequent to 1997 a modification of this system was used [10]. The histology of all patients with a change in histological grade was reviewed a second time by a single pathologist to verify this change, using the modified system [10]. Patients with dermatofibrosarcoma protuberans were excluded.

A total of 124 patients that fulfilled the above criteria were identified from our prospectively collected database. Patients were divided into 3 groups – those with unchanged histological grade in the recurrent tumour (Group 1), those with increased grade (Group 2), and those with decreased grade (Group 3).

Demographic variables were compared between groups using the χ^2 test and Fisher's exact test. Continuous statistics were compared using *t*-tests between groups. Survival curves were calculated using the methods of Kaplan and Meier and compared using the log rank test.

3. Results

Of the 124 patients with local recurrence, there were 92 (74%) who had no change in the grade of their tumours (Group 1), 24 (19%) whose tumours increased in grade (Group 2), and 8 (7%) whose tumours decreased in grade (Group 3). All patients in Groups 2 and 3 were verified as having an altered histological grade at the second review. This review did not reassign any patients to Group 1. There was no variation between the various pathologists in assigning cases to the 3 Groups. The histological features of differentiation, necrosis and mitotic count all contributed to cases with changes in grade. No one specific feature of the Trojani system seemed to be associated with the altered grade.

Mean age was 51.4 years (range 3–88 years) in Group 1, 57.6 years (range 19–83 years) in Group 2 and 68 years (range 48–81 years) in Group 3. There were 42 males (46%) and 50 females (54%) in Group 1, 16 males (67%) and 8 females (33%) in Group 2 and 5 males (63%) and 3 females (38%) in Group 3. In Group 1, 60(65%) tumours were in the lower extremities, 23 in the upper extremities (25%) and 9 in the trunk area (10%). In Group 2, 17 were in the lower extremities (71%), 4 in the upper extremities (17%) and 3 in the trunk area (13%). In Group 3, there were 4 lower and 4 upper extremity tumours (50%).

The distribution of histological subtypes among the different groups is shown in Table 1. For those with myxofibrosarcoma (myxoid variant of malignant fibrous histiocytoma – (MFH)), a higher proportion had an increase in grade (10/24) compared with the group with no change in grade (15/92). This difference was statistically significant ($P = 0.008$). There were no cases where the histological diagnosis of the tumour changed with local recurrence.

The mean time to local recurrence for Group 1 was 20.9 months (range 2–171 months); for Group 2 this was 24.3 months (range 2–69 months) and for Group 3 this was 23.4 months (range 5–41 months). There was no significant difference between the groups with respect to the time to local recurrence. The patients were then divided into groups with local recurrence less than and greater than 12 months and 24 months to see whether earlier or later recurrence was associated with an increased risk of a change in grade. We could demonstrate no difference between the groups.

Radiation therapy has been mentioned as a possible factor leading to an increase in histological grade in locally recurrent tumours. A total of 15 patients (16%) were treated with pre-operative or, most commonly

Table 1
Histological diagnoses of recurrent sarcomas

Histological diagnosis	Group 1 unchanged	Group 2 increased grade	Group 3 decreased grade
Malignant fibrous histiocytoma (MFH)	18	3	2
Myxofibrosarcoma	15	10	
Liposarcoma	10	4	2
Synovial sarcoma	11	1	
Leiomyosarcoma	14	2	1
Rhabdomyosarcoma	6		
Fibrosarcoma	2		
Malignant peripheral nerve sheath tumour (MPNST)	7	2	2
Clear cell sarcoma	1	1	
Epithelioid sarcoma	1		
Soft tissue Ewing's sarcoma	1		
Soft tissue osteosarcoma	1		
Myofibroblastic sarcoma	2		1
Malignant mesenchymoma	3	1	

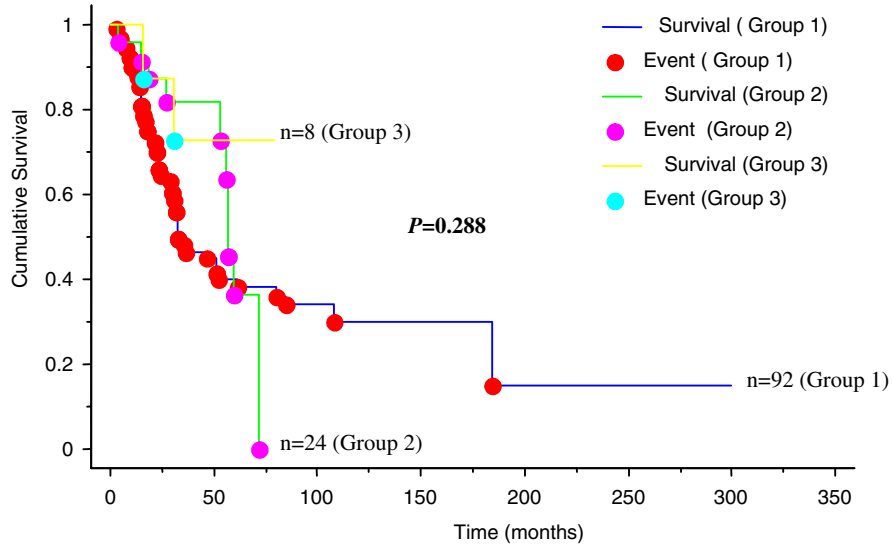

Fig. 1. Kaplan–Meier cumulative survival – Groups 1–3.

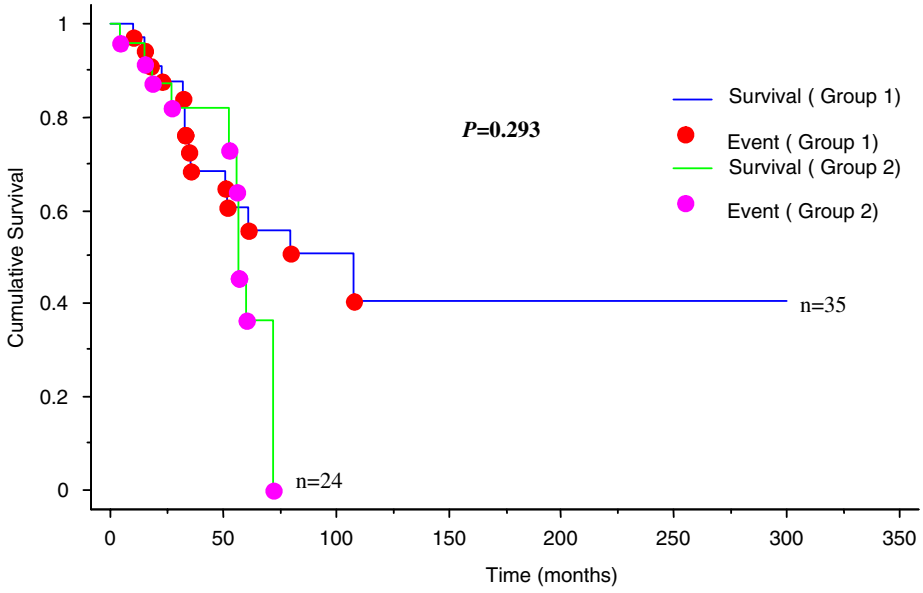

Fig. 2. Kaplan–Meier Survival – Groups 1 and 2 with Grade 3 eliminated.

post-operative irradiation in Group 1. Seven patients (29%) in Group 2 and one (13%) in Group 3 underwent similar radiotherapy treatment. In order to determine whether radiotherapy increased the risk of a subsequent increase in grade, we compared Group 2 with Groups 1 and 3 combined. There was no difference between the Groups with respect to the incidence of a change in grade ($P = 0.15$).

Sixteen patients (17%) in group 1 were treated with adjuvant chemotherapy, whereas no patients were given such chemotherapy in Groups 2 or 3. This is to be expected, as only the patients in Groups 1 and 3 could present with initial tumours of Trojani grade 3. This was the case for 57 patients in Group 1 and 3 patients in Group 3.

In Group 1, the mean tumour size was 9.6 cm (median 10 cm, range 1.5–30 cm), in Group 2 it was 11.3 cm (median 9 cm, range 1–25 cm) and in Group 3 it was 13.4 cm (median 10.5 cm, range 7–24 cm). These differences were non-significant. Sixty-six percent of tumours in Group 1 were larger than 5 cm in diameter, whereas 79% in Group 2 and 100% of those in Group 3 were larger than 5 cm. There was no significant difference between the Groups.

Of the tumours in Group 1, 79% were deep and 21% were superficial. In Group 2, 65% of tumours were deep

and 35% were superficial. Eighty-three percent of tumours in Group 3 were deep and 17% were superficial. Once again, there was no significant difference between the Groups.

The adequacy of the surgical margin was assessed as a possible associated factor. In Group 1, 38% had negative margins (no histological or gross extension of tumour to resection margins) and 62% had either microscopic or gross-positive margins. In Group 2, 33% had negative margins and 67% had positive margins. Fifty percent of the patients in Group 3 had negative margins and 50% had positive margins.

Patient survival was analysed using Kaplan–Meier survival curves. There was no difference between the three Groups, as demonstrated in Fig. 1.

Inclusion of patients with Grade 3 tumours in this survival analysis could introduce bias towards a worse survival in the group that did not change grade. We therefore eliminated all patients with Grade 3 tumours and compared survival between Groups 1 and 2 (Fig. 2). Once again, there was no significant difference in survival between the Groups.

4. Discussion

Local recurrence is an important outcome in the management of soft tissue sarcomas. The development of a local recurrence may increase the risk of further development of locally recurrent disease [1]. With repeated surgery the function of the limb may be compromised [11]. Limb salvage may not be possible and amputation may be necessary. Many studies have investigated treatment factors that predict for the development of local recurrence. The most consistent factor is inadequate surgical margins [12]. Recent studies on outcomes of soft tissue sarcoma with modern treatments have consistently demonstrated a rate of local recurrence of between 10% and 20% [1–6]. The role of local recurrence in the development of metastatic disease is controversial. Several series have suggested that patients who develop a local recurrence have a higher risk of metastatic disease and a lower survival [3,4,13,14]. However, many other studies have found no such association [7,12,15–17]. It is likely that if an association exists it is rather weak.

Although most recurrent soft tissue sarcomas are identical to the original tumour, we have demonstrated that in approximately 20% of cases, the recurrent tumour is of a higher grade than the original, and occasionally, the recurrent tumour may even be of a lower grade. Fletcher [8] and Enzinger and Weiss [18] have described 3 patterns in which recurrent tumours may differ to the original. In the first, the tumour shows a gradual progression in grade, by becoming more necrotic, mitotically active and less differentiated. The tumours that have been reputed to follow this pattern are myxofibrosarcoma, myxoid liposarcoma, malignant peripheral nerve sheath tumour and leiomyosarcoma [8]. In our series, myxofibrosarcoma did occur more frequently in the group that had an increase in grade. This tumour, which has previously been classified as myxoid variant of MFH, is characterised by myxoid areas of variable size containing atypical spindle-shaped or multinucleate, mucin-containing vacuolated cells. Enzinger and Weiss have classified fibrohistiocytic lesions with greater than 50% myxoid stroma as myxofibrosarcoma when low grade and as myxoid MFH when high grade [18]. In a recent review of 100 cases of MFH, Fletcher and colleagues reclassified 29 cases as myxofibrosarcoma using well-defined criteria. This reclassification was found to be valuable as these tumours had a better prognosis than other types of reclassified tumours such as leiomyosarcoma [31]. Myxoid MFH, or myxofibrosarcoma, is often intermediate grade at the initial diagnosis [19] and tends to have a better prognosis than other types of MFH [20]. However, unlike initially high-grade sarcomas, an intermediate grade myxofibrosarcoma can have an increase in grade with local recurrence. When this occurs, these tumours contain a decreasing amount of myxoid matrix with local recurrence, develop increasing cellularity [21] and become more pleomorphic in appearance. This has been seen in up to 60% of this particular histological subtype of MFH [22].

In the second situation mentioned by Fletcher and Enzinger and Weiss, low-grade tumours demonstrate a sharp and abrupt transition to a high-grade sarcoma, so-called dedifferentiation. This is described most frequently for liposarcoma [23]. Only one case of liposarcoma in this series demonstrated a change from well differentiated to dedifferentiated tumour with local recurrence.

Finally, so-called ''differentiation'' has been described, most often for rhabdomyosarcomas treated with chemotherapy [24]. This phenomenon has been hypothesised to occur due to selection of chemoresistant clones, which are of a lower grade. There were no cases of rhabdomyosarcoma in our group with a decrease in grade, and, in fact, none of these patients were treated with chemotherapy.

Without any clear predisposing factors, it is not known why this group of 8 patients demonstrated decreased grade in their recurrent tumours. The most likely reason is a sampling error of the initial or recurrent tumour. Interobserver variation between pathologists using the Trojani system could also explain this discrepancy. However, the reproducibility of the Trojani grading system has been examined and interobserver agreement in terms of tumour grade between 25 pathologists has been found to be 75%, even higher than agreement on histological tumour type (61%) [25]. Furthermore, a limited number of pathologists examined the histological material throughout the course of this study.

There are other possible explanations for apparent alterations in grade in the recurrent tumours. The use of newer microscopes with higher powered fields could introduce bias toward higher grade tumours with recurrence as they would be more likely to identify mitoses. A pathologist reviewing a recurrent tumour may be tempted to confirm recurrence and histological diagnosis with only a little regard for the grade. In this series, all questionable cases were reviewed and those that did have a change in grade underwent a second review. It is likely that a significant proportion of the tumours that showed an increase in grade in this study had true alterations in their histological parameters.

The use of radiotherapy has been mentioned as a possible a etiological factor for the change in grade recurrent tumours. Radiation-induced sarcomas are encountered in soft tissues and bone, and this oncogenic effect could theoretically lead to an altered morphological appearance in recurrent soft tissue sarcomas. However, radiation sarcomas are quite rare, with a reported incidence of 1% in patients receiving radiation [26] and with most occurring in patients receiving radiation for other cancers. We were unable to demonstrate a significant difference in the frequency with which the patients in each groups underwent neoadjuvant or adjuvant radiotherapy. However, there may have been a trend towards significance ($P = 0.15$) that may become significant in a higher-powered study.

It is interesting to note that in approximately 1/3 of these patients, local recurrence developed despite what appeared to be negative margins at the time of the initial surgical resection. A recent study aimed to correlate peritumoral oedema seen on magnetic resonance imaging (MRI) scans with histological features [27]. It was noted that areas separate from the main tumour mass that demonstrated oedema on MRI featured viable sarcoma cells. It is likely that resection of palpable tumour only without the oedematous surrounding tissue leaves residual viable cells behind that can lead to local recurrence. This mechanism may have played a role in some patients in our study.

The prognosis of patients who demonstrate a change in grade in locally recurrent soft tissue sarcoma has, until now, been uncertain. Because a high grade has been demonstrated repeatedly to be associated with a poorer prognosis, it seems logical to assume that those patients that developed higher-grade tumours with local recurrence would similarly have a poorer prognosis. However, unlike previous reports [8,22], these patients did not have a worse prognosis in our group, despite histological conversion to a higher grade. It is possible that in a higher-powered study a difference would have been evident. However, at five years, the survival curves are quite similar and if there is a survival disadvantage in the group that changes grade it is unlikely to be clinically significant. It is possible that this group represents a unique group of tumours, which morphologically resemble higher-grade tumours, but which behave systemically like the lower grade tumours that they originated from. As in many forms of soft tissue sarcoma, current investigation is attempting to identify specific patterns of genetic defects that may be of high prognostic significance for the development of metastatic disease, and therefore will allow targeted therapy. Specific karyotypic abnormalities have been identified that identify specific subtypes of MFH [28,29]. Specifically, the gain of a 7q32 region has been shown to predict for a worse metastasis-free survival [30]. It is possible that specific patterns of genetic alteration will be found in myxofibrosarcoma that will not be associated with a worse overall prognosis, and that altered histological appearance with local recurrence does not carry the same prognostic significance as it does in initially-identified tumours.

This study has demonstrated that the unusual phenomenon of a change in grade occurs in a significant proportion of locally recurrent soft tissue sarcoma cases. It is important for the treating clinician to be aware of this phenomenon, especially in cases of myxofibrosarcoma, as the prognosis, as reported to the patient, may not be as poor as the generally accepted histological features used to assign tumour grade according to the Trojani system may indicate.

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