

Management and outcome of acral soft tissue sarcoma

Abstract

Aim

The aim of this study was to evaluate the surgical management and outcomes of patients with acral (peripheral extremity hand or foot) soft tissue sarcomas.

Methods and Patients

We identified 63 patients with acral soft tissue sarcomas who presented to a tertiary referral sarcoma service (27 hands and 36 feet). Mean age was 49 (35 males and 28 females). The commonest sarcoma subtypes were epithelioid in the hand (8 patients) and synovial in the foot (11 patients).

Results

In 41 patients (65%) the tumour size was less than 5cm in its largest dimension (median size 3cm). 27 patients (43%) were diagnosed after inadvertent excision prior to their referral to the specialist sarcoma unit. After biopsy and staging, primary surgical intervention at the sarcoma unit was excision and limb salvage in 43 (68%), partial (digit or ray) amputation in fourteen (22%) and more proximal amputation in six (10%). At final follow up, local recurrence had been treated by one partial amputation and six amputations, resulting in a partial amputation rate of 24%, and the proximal amputation rate to 19%.

The rate of local recurrence was 19% and the 5 year survival was 82%. Patients who underwent inadvertent excision demonstrated no statistically significant difference in survival or local recurrence, but underwent a higher rate of amputation ($p=0.008$). Large tumour size ($>5\text{cm}$) was associated with lower survival ($p=0.04$) and a higher risk of local recurrence ($p=0.009$).

Conclusions

The majority of acral soft tissue sarcomas are smaller than 5cm at presentation, indicating that whilst size can be a useful prognostic factor, it should not be used as a diagnostic threshold for referral. Increased tumour size is associated with a higher rate of local recurrence and reduced survival. Sarcoma excision with limb preservation does not result in an increased risk of local recurrence.

Key words

Sarcoma; soft tissue; acral; prognosis; inadvertent

Clinical relevance

- The majority of acral soft tissue sarcomas are less than 5cm in size

- Inadvertent excision is associated with a higher rate of all amputations
- Survival and local recurrence were not influenced by a prior inadvertent excision
- Limb salvage surgery can be achieved in the majority of patients

Introduction

Sarcomas represent only 1% of all cancer diagnosis in the UK¹. Soft tissue sarcomas of the hand and foot (acral) are rare as they comprise only a small proportion of all sarcomas. Their rarity and varied presentation means that diagnosis is frequently overlooked, delayed, and often only becomes apparent after inadvertent excision. The recognition of these challenges led to the development of national guidelines with specialist services providing the multi-disciplinary management of suspected sarcomas in the UK. National Institute for Health and Care Excellence (NICE) guidance has previously stated²:

“Any patient with a soft tissue mass that is increasing in size, or has a size more than 5 cm, whether or not it is painful, should either be referred for an urgent ultrasound scan, or referred directly to a sarcoma diagnostic centre.”

There is a paucity of evidence relating to the management of acral soft tissue sarcomas. Historically, wide excision maintaining an adequate margin often resulted in amputation. In the early 1980s, the initial rate of limb sacrificing amputation was over 30%³. Other studies have reported amputation rates of 10% for the hand⁴ and around 30% for the foot^{5,6}. A clear margin of excision has been shown to be important in avoiding local recurrence⁴. Studies have also shown that increased tumour size and grade are associated with a poorer survival^{4,5,7-10}. Advances in medical imaging, histological assessment, careful tumour resection and improved reconstructive options have aided preservation of the affected limb. Consequently, current treatment protocols generally include tumour excision with a clear margin preserving the limb where possible, in order to preserve life, function and quality of life^{8,11}.

The multi - disciplinary team (MDT) management of acral sarcoma involves local imaging (X-ray, whole limb MRI and ultrasound or CT guided tissue biopsy. Once a diagnosis of sarcoma is made from histological analysis of the tissue biopsy, systemic staging (namely PET CT scan) is performed.

Primary sarcomas require an excision with a clear margin. This may entail simple resection and primary closure, wide local resection and reconstruction, partial amputation with or without reconstruction or a limb sacrificing amputation. Inadvertent excision patients are treated with the same principle of complete clearance of tumour with clear margins. All patients are assessed for the consideration of adjuvant therapy. Radiotherapy is considered for limb sparing resections but rarely for limb sacrificing amputation. Chemotherapy is used for chemo-sensitive tumours namely synovial sarcomas and rhabdomyosarcomas.

This study aims were to evaluate the surgical outcomes of acral soft tissue sarcomas. The size of tumour at presentation, the number of diagnoses that followed inadvertent excision, the management and how this relates to patient outcomes including local recurrence, metastasis and survival is discussed.

Methods

Using the institutional surgical and histological database searches, sixty three patients were identified between the years 2000 and 2016 with a histological diagnosis of soft tissue sarcoma of the hand or foot. Only patients with soft tissue sarcomas distal to the radiocarpal joint or distal to the ankle joint were included. All skin sarcomas were excluded. A standardised data entry spreadsheet was completed which included age, presenting symptoms, date of presentation, duration of symptoms, prior inadvertent surgery, histological tumour type and grade, date and type of definitive surgery, details regarding surgical margins and details of any subsequent surgery or adjuvant treatment, and outcomes. The size of tumour at presentation in its largest dimension was recorded, from MRI where possible or other detailed imaging; if size was not determined based on imaging then details were obtained from the relevant musculoskeletal pathology reports.

Amputations were classified into partial i.e. ray or digital amputation, or full amputation ie. below knee or below elbow. Outcomes recorded were local recurrence, subsequent metastatic disease and death. All surviving patients were followed up annually for a minimum period of 5 years, consisting of four times a year for the first two years and then bi-annually for three years. This also includes local and systemic radiological assessment on an annual basis.

Statistics

Statistical analysis was carried out using GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego California USA, www.graphpad.com). Histograms for all data sets were analysed. Data was normally distributed unless otherwise stated. Results are expressed as mean \pm SD unless otherwise stated. Unpaired t-tests and Mann Whitney U-tests were used to test for differences between two groups for parametric and non-parametric data respectively. Fisher's exact test was used to test for differences between two categorical variables. Overall survival and the rate of local recurrence were calculated using the Kaplan-Meier method and the impact of prognostic factors was assessed using the log rank test. Statistical significance was set at a level of $p < 0.05$.

Results

Patient demographics and tumour characteristics are shown in Table 1. The most common sub-types of sarcoma were epithelioid and synovial (13 patients each). The most common sarcoma sub-type was epithelioid in the hand (8 patients) and synovial in the foot (11 patients). The majority of tumours were high grade (42 of 63, 67%). The median tumour size was 3cm (See Figure 1).

Table 1 – Patient demographics and histological types

	Hand	Foot	Combined
Patient number	26	37	63
Age	50 +/- 24	47 +/-19	49 +/- 21
Sex	15M 11F	20M 17F	35M 28F

Median duration of symptoms (months) (IQR)	12 (6-16)	8 (4-12)	8 (5-12)
Histological type	Epithelioid (8) Synovial (2) Myxofibrosarcoma (4) Leiomyosarcoma (3) Pleomorphic (2) Others (7)	Epithelioid (5) Synovial (11) Myxofibrosarcoma(5) Leiomyosarcoma (4) Rhabdomyosarcoma(3) Spindle cell (3) Others (6)	Epithelioid(13) Synovial (13) Myxofibrosarcoma(9) Leiomyosarcoma(7) Rhabdomyosarcoma(3) Spindle cell(3) Pleomorphic(2) Others(12)
Histological grade	9 low 2 intermediate 15 high	4 low 6 intermediate 27 high	13 low 8 intermediate 42 high
Median size (cm) (IQR)	2.7 (1.5-4.3)	4.6 (2.5-7)	3 (2-6)
Number of inadvertent excisions (%)	12 (46%)	15 (41%)	27 (43%)
Median time to final follow up (years)(IQR)	4.9 (2.9-5.8)	5.4 (3.1-7.1)	4.8 (3.1-6.6)

The nature of treatment and outcome is detailed in Table 2. Primary surgery at the specialist sarcoma unit most frequently involved wide local excision and free flap reconstruction (41%). Radiotherapy was the most common adjuvant treatment (29 patients). The partial (digit or ray) amputation rate was 24%. The limb sacrificing amputation rate was 19%. The 5 year rate of local recurrence was 19% and overall 5 year survival was 82%.

Tables 3 and 4 demonstrate the effect of inadvertent excision and tumour size on outcome respectively. A higher rate of partial and limb sacrificing amputations was seen in the inadvertent excision group. There was no statistically significant difference in local recurrence, metastases or mortality in this group.

Figures 2 and 3 depict survival and the rate of local recurrence over time, showing no difference between the inadvertent excision group and others, although there is a trend for better local control when intentional excision is compared to initial inadvertent excision (see Figure 3). Larger tumour size was associated with a higher rate of proximal amputation and local recurrence. Figures 4 and 5 show the significantly lower survival and higher rate of local recurrence with large tumour size (>5cm). Table 5 shows the numbers at risk at each year in the different groups as depicted in the survival plots (Figures 2,3,4 and 5).

Limb preserving surgery did not increase the local recurrence rate (8 of 36 patients undergoing primary limb salvage experienced local recurrence, 2 of 6 patients undergoing primary limb sacrificing amputation experienced local recurrence, $p=0.616$ Fisher's exact test).

Local recurrence was frequently associated with metastatic disease at final follow up (10 of 13 patients with local recurrence had metastases at final follow up, $p=0.0001$ Fisher's exact test, and 9 patients had metastases with no local recurrence of the remaining 50 patients). Initial limb sacrificing amputation was associated with increased mortality (4 of 6 patients dead at final follow up, $p=0.032$ Fisher's exact test) but mortality was not increased with initial limb sparing amputations (6 of 17 patients dead at final follow up, $p=0.352$). The remaining 6 deaths occurred in patients without any form of amputation.

Table 2 – Nature of treatment and outcome

	Hand	Foot	Combined
Primary surgery at tumour service	1 excision biopsy (4%) 9 wide local excision (35%) 9 WLE and free flap (35%) 1 limb sparing amputation and free flap (4%) 5 limb sparing amputation (19%) 1 limb sacrificing amputation (4%)	7 wide local excision (19%) 17 WLE and free flap (46%) 2 limb sparing amputation and free flap (5%) 6 limb sparing amputation (16%) 5 limb sacrificing amputation (14%)	1 excision biopsy (2%) 16 wide local excision (25%) 26 WLE and free flap (41%) 3 limb sparing amputation and free flap (5%) 11 limb sparing amputation (17%) 6 limb sacrificing amputation (10%)
Adjuvant treatment	7 radiotherapy 1 chemotherapy	22 radiotherapy 8 chemotherapy	29 radiotherapy 9 chemotherapy
Total eventual partial amputation	9 (35%)	6 (16%)	15 (24%)
Total eventual proximal amputation	2 (8%)	10 (27%)	12 (19%)
5 year local recurrence	22%	14%	19%
Local recurrence at final follow up	5 (19%)	8 (22%)	13 (21%)
Metastases at final follow up	7 (27%)	12 (32%)	19 (30%)
5 year survival	86%	80%	82%
Death at final follow up	4 (15%)	12 (32%)	16 (25%)

Table 3 – Analysis of effect of inadvertent excision on outcome

	Inadvertent	Non inadvertent	P value
Median size (cm)(IQR)	4 (2-7)	4 (2-5.9)	0.646

All amputations	11 of 27	4 of 36	0.008**
Full amputation	7 of 27	5 of 36	0.352
Local recurrence	9 of 27	4 of 36	0.067
Metastatic disease	10 of 27	9 of 36	0.407
Death	8 of 27	8 of 36	0.566

Table 4 – Analysis of the effect of tumour size on outcome

	Size <5cm	Size ≥5cm	P value
Median duration of symptoms (months)(IQR)	8 (4-12)	12 (6-16)	0.362
Amputation	14 of 41	13 of 22	0.067
Limb sacrifice	3 of 41	9 of 22	0.002**
Local recurrence	4 of 41	9 of 22	0.007**
Metastatic disease	9 of 41	10 of 22	0.083
Death	7 of 41	9 of 22	0.066

Table 5 – Numbers at risk at different time points

Time (years)	0	1	2	3	4	5	6	7	8	9	10
Total	63	57	53	50	39	30	20	13	8	5	4
inadvertent	27	24	23	22	16	12	8	6	3	2	2
non inadvertent	36	33	30	28	23	18	12	7	5	3	2
>5cm	41	37	36	34	24	17	13	8	5	4	3
<5cm	22	20	17	16	15	13	7	5	3	1	1

Discussion

In this series the majority of acral soft tissue sarcomas are smaller than 5cm. Increased tumour size was associated with a higher rate of local recurrence and a lower survival rate. These results are consistent with those of previous studies that have shown that tumour size is a strong prognostic indicator¹². It is clear that acral soft tissue sarcomas often present when smaller than 5cm. This suggests that the use of size alone as a diagnostic threshold for acral sarcoma is hazardous, and the clinician should remain alert. This study suggests that all

suspicious solid acral lesions should be promptly investigated, regardless of size, in order to exclude a potential sarcoma.

Inadvertent excision prior to definitive treatment was common (43%), and led to a higher rate of partial amputation, and a higher rate of local recurrence (9/27 compared to 4/36) but this was not statistically significant ($p=0.067$), and there was no adverse impact on survival. Our findings are consistent with previous research^{10,13}, suggesting that underlying tumour biology may be the most important predictor of local recurrence and survival rather than method of diagnosis. Pradhan et al demonstrated that the size and grade of the tumour were factors in predicting survival, as well as remarking upon the importance of a clear margin of excision in achieving local control¹⁰. Poorer survival has been shown to be associated with higher tumour grade and larger tumour size by several previous studies^{4,5,7-10}.

With respect to the effect of inadvertent excision on local recurrence, the Kaplan Meier plot shows divergence suggesting an increase in the rate of local recurrence when inadvertent excision had been performed, but this was not statistically significant with our patient numbers. Table 3 demonstrates a higher rate of local recurrence in the inadvertent excision group that did not reach statistical significance ($p=0.06$). If inadvertent excision is related to increased local recurrence as the trends in our results suggest, and as other studies have shown¹⁴, and these trends occur despite the increased amputation rate seen in those tumours presenting by inadvertent excision, then this supports the recommendation for tissue biopsy to be performed prior to excision of solid acral tumours¹⁵.

The rate of an initial limb sacrificing amputation in this series is low at 10% and this was achieved by a high proportion of patients undergoing wide local excision with orthoplastic reconstruction, notably in combination with free flap coverage in 41% of cases. This reflects the modern trend towards limb salvage wherever possible in order to maintain function¹⁶, and demonstrates the importance of having a highly skilled orthoplastic surgical team as part of a specialist sarcoma service. Limb preserving surgery did not result in a higher incidence of local recurrence. In our study appropriate limb preserving surgery did not increase the risk of local recurrence or death. Proximal amputation gives no guarantee of avoiding local recurrence with 2 out of 6 initial proximal amputations still suffering local recurrence. This suggests the limb preserving approach to acral sarcoma is as safe as proximal amputation, which supports our practice of preserving the limb wherever possible. The decision as to whether limb preservation is possible and how best to do this is sometimes complex, consequently we feel that different priorities can be balanced in the patient's overall best interests by informed discussions within the MDT,

Radiotherapy was more likely to be administered in foot sarcomas (22/37) than in hand sarcomas (7/26) due to concerns regarding the effect of radiotherapy on hand function. It did not have an obvious effect on the rate of local recurrence at 5 years (22% in the hand versus 14% in the foot, $p=0.505$ Chi squared test).

Historically radiotherapy to the hands and feet was contraindicated in view of the high rate of potential soft tissue complications, notably skin desquamation and late contractures due to

fibrosis¹⁷. Subsequently with orthoplastic reconstructive surgery, after sarcoma excision the use of free flaps with post-operative radiotherapy has become our standard practice for higher grade radiosensitive disease. The regime consists of 60Gy given to the edited tumour bed, which may not fully include any free flap (50Gy given as 25 fractions (Phase 1) and then a reduced volume of 10Gy gives as five fractions). Sometimes a period of around one month non-weight bearing is required when using radiotherapy in the foot due to local discomfort. The concerns with early and late complications of radiotherapy were not seen. Only one complication of radiotherapy was seen, this involved radiotherapy related contractures in the palm.

Local recurrence was associated with metastases, with 10 out of 13 local recurrence patients also developing metastases. This is not to say that local recurrence caused metastases, but the association probably reflects the biology and behaviour of the tumour. 9 patients out of the remaining 50 had metastases without local recurrence. If patients had an initial proximal amputation then they were more likely to die of their disease than any other treatment group. The indication for proximal amputation in our unit is sarcoma of a size or with tissue involvement that requires such an extensive resection that maintaining a functional limb even after reconstruction is not possible. Given our indication for proximal amputation, the increased risk of death after such surgery probably reflects the size, extent and biology of the presenting disease.

As in previous research, we show that it is possible to successfully treat inadvertent excision by re-excision in order to achieve clear surgical margins, thereby avoiding more radical limb sacrificing amputation^{18,19}. The higher rate of partial amputations in the group of patients who had undergone inadvertent excision prior to specialist referral reflects the importance of achieving an adequate margin in the primary operation; this is rarely achieved with unplanned surgery and we found that partial amputation was more often necessary to achieve adequate margins.

This study's findings do not support size being used as a threshold for the referral or investigation of suspicious acral lesions. Revised NICE guidance states that "urgent direct access ultrasound scan, should be performed within 2 weeks, to assess for soft tissue sarcoma in adults with an unexplained lump that is increasing in size"²⁰. It is of key significance to emphasise to both patients and clinicians that a new lump's small size should not be interpreted as a reassuring feature, there is a strong argument that future guidance should make this point clearly. Cool et al have demonstrated that the chance of cure following the detection of local recurrence or metastatic disease is low²¹ and in this context it may be therefore debated how intensive follow up should be and what is recommended by future guidance in this area. The limitations to this case series include its small size and retrospective nature. This is due in part to the varied presentation and rarity of sarcoma of the extremities and the heterogeneity of the condition.

Conclusions

Many acral soft tissue sarcomas are smaller than 5cm at presentation, indicating that whilst size can be a useful prognostic factor, it should not be used as a referral or diagnostic threshold. Increased tumour size is associated with a higher rate of local recurrence and lower survival. Sarcoma excision with limb preservation does not result in increased risk of local recurrence or death. Inadvertent excision leads to a higher rate of amputation. Larger tumours necessitating amputation are associated with increased local recurrence, metastases and death.

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