Refer prior to biopsy of suspected appendicular soft tissue sarcoma

Robert S J Elliott, Michael Flint, Gary French

Abstract

**Aim** Appendicular soft tissue tumours are rare and inappropriate investigation can result in unnecessary loss of limb or life. We reviewed the investigation and referrals of patients to our institution.

**Method** This is a review of prospectively collected data stored in a tumour registry database. We included all patients (126) referred to the service for investigation and management with a primary soft tissue tumour in 2006 and 2007.

**Results** There was a highly significant association (RR=6.2) between pre referral procedures (PRPs) and suffering a complication (P<0.0001) in comparison to non-biopsied referrals (NBRs). Those referred by general surgeons were more likely (RR=2.6) to have undergone PRP (p<0.0017). The median interval between referral and senior author review was 8 days for the PRP group and 10 days for the NBR group (P=0.2574).

**Conclusion** Biopsy of suspected appendicular soft tissue sarcoma should be performed by a tumour specialist or in prior consultation with, to minimise adverse outcomes. There was minimal delay till review by an orthopaedic tumour specialist at Middlemore Hospital and achieving a tissue diagnosis does not expedite this.

Sarcomas of the limbs (appendages) are rare. They represent less than 1% of all malignancy. Benign appendicular soft tissue masses occur 150 times more frequently.\(^1\)

Limb salvage surgery has replaced amputation over the last 30 years, but relies on appropriate diagnostic workup and biopsy technique. It achieves comparable survival but maintains function, and it is thought to be possible in over 90% of cases.

Errors may necessitate amputation or greatly complicate a limb salvaged procedure. These errors include technical issues such as type of biopsy, approach, sample inadequacy, infection and bleeding. Accurate diagnosis should involve a multidisciplinary team including a musculoskeletal radiologist, sarcoma surgeon and a musculoskeletal pathologist.

The risk of incorrect diagnosis is greater in centres that do not employ this approach. Previous studies have highlighted the increased risk of adverse outcomes when invasive investigations are performed without input from a sarcoma surgeon and the associated multidisciplinary team.

New Zealand is a sparsely populated country and has four orthopaedic tumour surgeons which is in keeping with the recommended ratio of 1:1,000,000. Consequently some patients find themselves long distances from tertiary tumour centres. This study reviews the investigation and referrals of patients to the Bone and...
Soft Tissue Tumour Service at Middlemore Hospital, and compares the short-term outcomes between those who had undergone an invasive procedure prior to referral and those who had not.

Materials and Methods

We reviewed the charts of all patients (126) with a soft tissue tumour referred to the senior authors from 1/1/2006 to 31/12/2007 to allow a minimum 2-year follow-up. The information was stored in a prospective Tumour Registry Database. Where information was not available in records kept at our institution, the referring institution was contacted. We excluded any patient who had an established diagnosis and treatment instigated by an Orthopaedic Tumour specialist, and those with a known primary malignancy elsewhere as we wanted to focus on primary investigation of masses of unknown origin.

Demographics, symptoms and examination findings were recorded. Data was collected on interval from referral to first letter from tumour service, type of investigations performed prior to referral and those performed subsequent. Biopsy diagnosis and final diagnosis and outcome at 2 years post presentation was recorded where possible.

Complications were recorded. Broadly these comprised procedural issues such as incorrect biopsy approach, uncontrolled bleeding, infection, wound breakdown and incomplete excision and diagnostic errors such as inadequate sample and incorrect diagnosis by pathologist.

Management under our service involves reviewing plain films and MRI for localised staging with a dedicated musculoskeletal radiologist prior to invasive procedure. Most biopsies are performed open by the tumour surgeon at our institution.

Radiologist biopsies are performed under instruction to avoid contaminating tumour naïve compartments. On occasion the service would request the referring institution perform a biopsy under specific instruction. Systemic staging is performed with a CT thorax.

Biopsied tissue was reviewed with a multidisciplinary team including the musculoskeletal pathologist, radiologist and sarcoma surgeon.

Data was analysed with the Graphpad InStat software program. All P values were two sided. Fisher’s exact test was used for categorical association, and Welch unpaired T-test was used to compare the waiting times between groups given its nonparametric distribution. The establishment of the database and the use of its data for research has received Ethics Board approval.

Results

Of the 126 included patients, 35 were primary referrals comprising 34 from general practitioners (GPs) from within the catchment area of our institution and 1 directly from a radiologist subsequent to performing an ultrasound at the request of a GP. The remainder (91) were tertiary referrals from other specialists which included orthopaedic surgeons (55), general surgeons (28), plastic surgeons (5), oncologists (2) and a physician (1). Referrals were received from Whangarei to Invercargill, with the majority (123) being from the North Island.

The majority (20) of the primary referrals did not have any imaging, 6 had plain films, 5 had ultrasound scans (USSs) and 4 had magnetic resonance imaging (MRI).

Of the 91 tertiary referrals 79 presented with a MRI and 1 patient was contraindicated for MRI due to cochlear implants. Localised computed tomography (CT) was performed for 7 patients, 11 had USS, 5 had plain films and 11 had staging CT thorax scans. Four of the tertiary referrals did not have any accompanying imaging.

Thirty-three of the referrals had a histology report resulting from a total of 36 invasive pre-referral procedures (PRPs). All PRPs were tertiary referrals from secondary clinicians.
Two of these patients had an incomplete excision performed by their GP prior to referral to the secondary clinician. Fifteen of these resulted from excisional biopsy, 8 from open biopsy, 7 from needle biopsy, and 3 were from image guided biopsy. The 13 of 15 excisional biopsies had positive margins. Therefore 13 of 33 (39%) resulted from inadvertent excision.

Patients were more likely to have undergone PRP when referred by general surgeons (RR=2.6, p<0.0017) when compared with orthopaedic surgeon referrals (Table 1).

Table 1. Referral source and rate of pre-referral procedure

<table>
<thead>
<tr>
<th>Specialty</th>
<th>Referrals</th>
<th>Procedures</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>General surgeon</td>
<td>28</td>
<td>16</td>
<td>0.57</td>
</tr>
<tr>
<td>Orthopaedic</td>
<td>55</td>
<td>12(2) †</td>
<td>0.22</td>
</tr>
<tr>
<td>GP</td>
<td>34</td>
<td>2</td>
<td>0.06</td>
</tr>
<tr>
<td>Plastic surgeon</td>
<td>5</td>
<td>2</td>
<td>0.4</td>
</tr>
<tr>
<td>Oncologist</td>
<td>2</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Physician</td>
<td>1</td>
<td>1(1)</td>
<td>1</td>
</tr>
</tbody>
</table>

†: (x) is radiology guided procedures

The interval between referral and first review by one of the senior authors was not recordable in 29 patients of which 26 were tertiary referrals. Another patient repeatedly failed to attend her appointment. Of the remaining 96 patients the mean interval was 16 days for all referrals, with a median of 10 and a range of 0 to 215 days.

The patient who waited 215 days had symptoms of swelling for 10 years and had already undergone an MRI suggesting a schwannoma, which it proved to be. Of the 65 Tertiary referrals with known interval the median wait was 9 days with a mean of 13 and range of 0 to 110 days.

The patient who waited 110 days had symptoms for 4 years and an MRI which was suggestive of organising haematoma, which it proved to be. The number of days between referral and first review by a senior author was compared between the PRP group and those who were Non-Biopsied Referrals (NBR).

The interval was not known for eight of the 33 PRP group and 18 of the 58 NBR group. The PRP median wait was 8 days, while the NBR group median was 10 days. This is not clinically or statistically significant (two-sided P value=0.2574, Welch unpaired t test).

In the NBR group two patients waited longer than 30 days. A patient with a lipoma waited 40 days whilst another with an organising haematoma waited 110 days; both of which had MRI prior to referral.

The majority of these patients presented with an MRI and there was a trend toward patients with malignancy being seen earlier but this was not statistically significant (P=0.20, Chi-squared) [Figure 1].
There were 21 complications relating to these 36 procedures affecting 18 (55%) patients. There were 13 incomplete excisions, 2 infections, 2 histology reports which differed to subsequent diagnosis following excision, 2 specimens were deemed to be non diagnostic (both blind fine needle aspirates), 1 episode of incorrect approach, and a case where a histology report was not acted upon for 4 months. Seventeen of the 18 patients eventually were found to have malignancy.

Of the 33 referrals with histology on presentation, 28 were diagnosed as malignant. Three patients underwent amputation and one 78 year old patient who had undergone an intralesional excision was recommended an amputation but declined it. There were 5 known deaths at 2 years post referral. One patient required buttonhole excision of the previous biopsy tract that had compromised a tumour naïve compartment.

Biopsy was performed on 47 patients once reviewed by the tumour specialist at this institution. This includes two patients where biopsy was repeated as the histology result was deemed to be non diagnostic. This comprised 34 open biopsies, five ultrasound guided fine needle aspirates (FNAs), three Trucut biopsies and one excisional biopsy. Four other biopsies were performed at the base hospital under the detailed instruction of one of the tumour specialists.

There were four complications affecting four patients of 47 (9%). There was one infection, one case of excessive bleeding, a wound breakdown and a non diagnostic sample.

Of the 47 NBR patients who underwent biopsy once reviewed, 26 proved to be malignant. Ten of these patients were known to have died at 2 years, 2 had local recurrence and 1 had pulmonary metastases. One patient underwent amputation.
A broad spectrum of sarcoma and other malignancies were diagnosed with the most common being malignant fibrous histiöytoma (12), leiomyosarcoma (9), liposarcoma (8) and synovial sarcoma (5).

The majority of complications occurred in patients who were found to have malignancy. In fact, only one complication in each group (PRP and NBR) occurred to patients who had benign histology.

The NBR group was biased as it had a large number of referrals that proved to be benign. The majority of the PRP group were malignant, hence their referral. Therefore, to compare the rates of complication between the groups, those with benign histology were excluded.

There were 28 malignancies in the PRP group which suffered 20 complications. The NBR group had 26 malignancies with three complications. There was an highly significant association between PRPs and suffering a complication (P=<0.0001). The relative risk of complication was 6.2 (C.I. 2.0–18.4). [Table 2]

### Table 2. Incidence of complications

<table>
<thead>
<tr>
<th>Referral type</th>
<th>Sarcomas</th>
<th>Complications</th>
<th>Amputations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post procedure</td>
<td>28</td>
<td>20</td>
<td>3(+1)*</td>
</tr>
<tr>
<td>Pre biopsy</td>
<td>26</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>&lt;0.0001</td>
<td>0.35</td>
</tr>
</tbody>
</table>

*Amputation recommended but declined.

If inadvertent excision is excluded, the PRP group suffered 7 complications in 15 patients with a relative risk of 4.55 (C.I. 2.1-9.7, P=0.001).

**Discussion**

Biopsy of suspected malignant soft tissue tumour is essential for an accurate diagnosis, and although it is a relatively minor procedure in its own right, has significant complications. This study demonstrated that 55% of patients who had undergone an invasive procedure prior to referral suffered at least one complication. There were 21 complications in 36 procedures at a rate of 0.58 complication/procedure.

By contrast, of the 47 patients biopsied by the musculoskeletal tumour team, the complication rate was 0.09. Errors in diagnosis, non representative samples and biopsy site complications resulting in alterations in treatment or outcome have been shown to be between 2–12 times greater when the biopsy is performed at the referring institution rather than the Orthopaedic Tumour Centre.\(^2\)\(^-\)\(^5\) This study replicated those results with a relative risk of 6.2.

In 1982, 56.5% of patients referred were pre biopsy in Mankin’s report. Despite this publication and the documentation of unacceptably high adverse outcome associated with biopsy in the referring institution the pre biopsy referral rate fell to 52.8% in their repeat study of 1996. A 2001 paper by the Scandinavian Sarcoma Group reported a 67% pre biopsy referral rate within their series.
In our study 74% of all referrals were pre biopsy. There were two patients who had undergone an invasive procedure by their general practitioners (GP) who proved to have malignancy. The majority of GPs do not perform such procedures.

Including their figures biases our result in favour of increased NBR. Of the tertiary referrals there were 31 PRP patients out of a total of 91, meaning 66% were NBR, showing our practice is comparable to that of Scandinavia.

Unfortunately, despite meticulous planning, surprises in histology will always occur and it highlights the importance of always sending excised tissue for examination. Previous studies have documented inadvertent incomplete excision as comprising 19%-53% of referrals to sarcoma centres. This study showed a rate of 13/91 (14%).

Mankin has previously demonstrated that soft tissue masses are more likely to be biopsied prior to referral than bony lesions and often by non-orthopaedic surgeons. This study has demonstrated a significant difference in referral practice between general surgeons and orthopaedic surgeons. This perhaps reflects the fact that general surgeons encounter tumours on a much more frequent basis and therefore are more willing to perform invasive investigative procedures in aid of diagnosis.

Mankin’s message has been widely disseminated in orthopaedic literature, but the ramifications of a poorly executed biopsy on limb salvage surgery may not be as well appreciated amongst other specialities. Injudicious biopsy or inadvertent excision compromises tissue planes and increases the likelihood of local recurrence. Local recurrence is an independent predictor of mortality.

The New Zealand Guidelines Group (2007) recommended early referral for suspected sarcoma without delay for investigations and that biopsy should be avoided. Ultrasound scan, or MRI where possible, should be requested in the interim.

It has been shown that high volume centres treating sarcomas achieve better outcomes. Limb salvage surgery has become the standard of care over the last 30 years and is achievable in >90% of patients in combination with neoadjuvant and adjuvant therapy. It requires meticulous planning from a multidisciplinary team to ensure margins are clear and reconstruction is functional and safe.

Moffat et al looked at a series of 4025 patients treated in Florida. They defined high volume as being above the 67th centile for number of patients treated for sarcoma. These centres saw an average of 5–24 cases per year (c.f. our institution=27/yr). Their results were significantly better, with significantly less complications in comparison to low volume centres.

The mean number of days from referral to review by the senior author was 16 days, although some patients were subject to delay (up to 7 months). Significant doctor delay (time from first consultation to final diagnosis) has previously been defined as >1 month by Brouns et al (Netherlands) who reported a rate of 27%. We were unable to determine when the patients were first seen by the referring clinician. Instead we calculated the wait till review by a senior author from the time of referral. There were 8 of 96 patients (8%) who waited more than 31 days (32–215 days).

A United Kingdom paper defined doctor delay as >3months and reported a rate of 19.5%. Under this criterion we had 2 of 96 (2%). Our interval is not comparable with the definition of doctor delay, but interval till review post referral is low with no
significant difference between those presenting with histological sample and those without.

The majority (88%) of tertiary referrals presented with MRI imaging. This is the imaging modality of choice for local staging. Multiplanar images provide information on size, location, substance and relationship to adjacent structures.

MRI can accurately identify benign soft tissue masses but has limited success of 25-50% accuracy when identifying tissue diagnosis of sarcomas.\(^{13,14}\) Whilst still needing to proceed to biopsy to achieve diagnosis; MRI has allowed triaging of referrals.

Of the NBR group there were no cases of malignant tumour waiting more than 30 days for review by a senior author. The trend suggesting malignant masses were reviewed earlier was not statistically significant.

This is not a population based study. Referrals to the service are done so on clinician preference basis.

Considerable numbers of patients were lost to follow up so conclusions were not drawn on morbidity and mortality beyond the perioperative period. There were increased amputations in the PRP group, but this was not statistically significant.

The deaths were mentioned to highlight the threat that these tumours pose. The mortality rate would certainly have been higher than what is suggested by these results. The interval between referral and senior author review was not known in 24% of PRP and 31% of NBR group.

**Conclusions**

Patients with malignancy are more likely (RR 6.2) to suffer complications or compromise of local therapy when they undergo an invasive procedure prior to referral to a Specialist tumour centre.

Patients are more likely to have undergone an invasive procedure when referred to the service by general surgeons.

Patients who had a histological diagnosis confirming malignancy were not seen significantly earlier than those who did not.

MRI is the gold standard for localised imaging and no patients referred with MRI who proved to have malignancy waited more than 30 days till review by a senior author.

Any suspected malignant soft tissue tumour of the limbs should be referred to a tumour surgeon from a regional sarcoma multidisciplinary team prior to any invasive procedure. If this is not possible due to geographical difficulties, discussion with a tumour specialist should precede any invasive procedure.

**Competing interests:** Nil.

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References: