Evaluating the British sarcoma referral form

MA Smolle¹, A Leithner¹, RJ Grimer²

¹Medical University of Graz, Austria

²Royal Orthopaedic Hospital NHS Foundation Trust, UK

ABSTRACT

INTRODUCTION This study investigated the accuracy of general practitioner (GP) referrals under the two-week wait pathway for soft tissue sarcomas and whether the current National Institute for Health and Care Excellence criteria should be refined.

METHODS All patients referred under the two-week wait system to one centre over the course of one year were reviewed. Comparison was made between the criteria identified by the GP and those confirmed by the centre to assess the accuracy of the referrals, and to identify what criteria predicted malignancy.

RESULTS Overall, 135 patients were referred to our unit with a mean age of 56.4 years. Of these, 45 (33%) were found to have a malignant tumour. Factors identified by the GP were accurate in 74% of cases. The best predictor of malignancy was 'size >5cm' (76% sensitivity) while 'pain' was the least useful (27% sensitivity). Lowering the threshold for concern to a size of >4cm increased sensitivity to 89%. Although 106 patients had undergone some form of imaging prior to referral, this did not increase the likelihood of malignancy being detected. The combination of factors most likely to predict malignancy was a size of >5cm, increase in size, deep location and no pain (10 out of 13 referrals, 77% accuracy).

CONCLUSIONS Based on the results of this study, we recommend an adaption of the existing features for concern. The new feature for concern should be 'size >4cm' and the factor 'pain' should be removed from the urgent referral form.

KEYWORDS

Soft tissue sarcoma – Two-week wait – Clinical features

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CORRESPONDENCE TO

Robert Grimer, E: robert.grimer@nhs.net

The two-week wait referral pathway was introduced in 2000 by the Department of Health with the aim of achieving earlier diagnosis and treatment for the most common cancers. The guidelines were adapted by the National Institute for Health and Care Excellence (NICE) in 2005, including four parameters that predict malignancy for soft tissue swellings.¹ These guidelines suggest that any soft tissue lumps presenting with a size larger than 5cm, that are painful to touch, increasing in size or lying deep to the fascia should be referred urgently to a specialist centre.

Soft tissue sarcomas (STSs) constitute a rare malignancy as they account for only 1% of all human cancers; there were 3,272 new diagnoses in the UK in 2010.² Taking into account that from more than 100 soft tissue masses, only 1 is likely to be revealed as a sarcoma, an accurate detection of the malignant mass is crucial.³ The five-year survival rate for STS varies between 50% and 90%, depending on histological subtype, grade, size and depth.^{4,5} Metastasis free patients have a better prognosis than patients with tumour spread at diagnosis and the age of the patients also influences overall survival rates, with better outcome in younger individuals.^{6,7} Furthermore, elevated levels of C-reactive protein measured prior to treatment indicate a poor prognosis.⁸

Previous studies have challenged the effectiveness of the two-week wait system as the average size of the STS at time of diagnosis has not changed significantly since the introduction of the guidelines in 2000.^{9,10} The following study was therefore performed with the aim to investigate:

- > How trustworthy is the general practitioner's (GP's) interpretation of the four features (size, pain, increase in size, depth) compared with the actual findings at a special unit for STSs?
- > Which of the four features is most predictive of malignancy?
- > How could the four parameters be improved to optimise the two-week wait pathway?
- > Should the 'worrying' size at diagnosis be reduced from 5cm to 4cm?

Methods

Between August 2013 and July 2014, 135 patients were referred to the Royal Orthopaedic Hospital NHS Foundation Trust (ROH) by GPs through the two-week wait pathway with the suspicion of STS. Another 27 patients referred within the two-week wait system were excluded because they were already known to have a sarcoma.

Of the 135 patients included in our study, 74 (55%) were male and 61 (45%) female, with a mean age of 56.4 years (range: 3–92 years). Two-thirds ($n=90$, 67%) had a benign lesion and the rest ($n=45$, 33%) presented with a malignancy. The most common benign diagnosis was lipoma ($n=20$) whereas the most frequent malignant one was spindle cell sarcoma ($n=9$). Thirty-five patients had a STS. Ten patients were found to have a non-sarcomatous soft tissue tumour or borderline lesion (five metastases, two lymphomas and three fibromatoses), all of which required urgent treatment so they were included in our study in the total number of malignancies.

All patients were assessed at our unit with imaging (if they had not been imaged already) and diagnosis confirmed by biopsy if the imaging was not diagnostic. The presence or absence of the four features reported by the GP on the referral form was also noted.

Statistical analysis

Accuracy for the four parameters was calculated with a chi-squared test (Table 1). Statistical significance was measured using Fisher's exact test. Correlation of size estimates was tested by linear regression analysis and size estimates were compared using the t-test for paired samples.

Results

Table 2 shows the frequency of the identified features of concern, both by GPs and the actual findings at the ROH. Of the 135 patients included in the study, 106 had undergone prior imaging (mostly magnetic resonance imaging) arranged by the GP, which had raised the possibility of malignancy. In 23 cases, some information regarding one or more of the features of concern was missing (from either the GPs or the ROH).

Size

For all urgently referred soft tissue swellings, the mean size when examined and documented by the GPs was 5.6cm (standard deviation [SD]: 4.7cm) for benign lesions and 7.6cm (SD: 4.3cm) for malignancies. At the specialist centre, the mean size for benign swellings was 5.4cm (SD: 4.3cm) whereas it was 8.6cm (SD: 5.9cm) for sarcomas. Size estimates by GPs and experts showed a high correlation on

Table 1 The four features of concern for soft tissue sarcoma: correlation of findings of general practitioners (GPs) and specialists at the Royal Orthopaedic Hospital (ROH)

Features	ROH +		ROH -		Accuracy
	GP +	GP -	GP +	GP -	
Size >5cm	60	13	12	50	82%
Pain	31	10	27	62	72%
Increase in size	56	16	24	31	69%
Deep	38	13	16	61	77%

Table 2 Frequency of identified features of concern observed by general practitioners (GPs) and at the Royal Orthopaedic Hospital (ROH). Accuracy compares assessment by GPs and with that by the ROH. Sensitivity and specificity with respect to malignancy are based on observations made at the ROH.

Features	GPs	ROH	Accuracy	Sensitivity	Specificity
Size >5cm	72	73	82%	76%	66%
Pain	58	41	72%	27%	66%
Increase in size	80	72	69%	73%	51%
Deep	54	51	77%	57%	68%

linear regression analysis ($r^2=0.798$, $p<0.01$) (Fig 1) and there was no significant difference between the estimates (t-test for paired values, $p>0.05$). There was also no significant difference in the mean size of the lump in patients who had undergone prior imaging (6.5cm with imaging and 6.8cm without imaging, $p=0.7$).

A chi-squared test was used to compare GPs' measurements with the findings at the ROH (Table 1). Sixty soft tissue swellings were found being positive for 'size >5cm' by both GPs and ROH specialists. In another 50 cases, they concurred about this parameter being negative. These results led to an accuracy of 82% for the feature 'size >5cm' ($p<0.001$).

From the 45 cases with malignancy, 34 (76%) were larger than 5cm and only 11 sarcomas (24%) had smaller dimensions. This feature had the highest sensitivity (76%) and the second highest specificity (66%) of all four parameters (Table 2).

If the critical size were lowered from 5cm to 4cm, then 40 of the 45 malignancies would have been referred purely because their size was larger than 4cm, leading to a sensitivity of 89% with a specificity of 48%. As a result, 11 malignancies may not have been detected if the size of concern is set at 5cm, compared with only 5 malignant tumours when the cut-off is set at 4cm.

Pain

A total of 62 soft tissue swellings were detected as being painless both by GPs and the specialist centre, and in 31 cases, both agreed on the presence of pain, resulting in 72% accuracy ($p<0.001$). Of the 45 malignancies in our study, only a quarter ($n=12$) were associated with pain while the remaining malignancies ($n=33$) were non-tender to touch. Sensitivity (27%) and specificity (66%) of pain was therefore rather poor.

Increase in size

In 56 cases, GPs and specialists agreed there was an increase in size of the soft tissue mass and in an additional 31 cases, they both agreed there was no history of recent growth. However, the accuracy of GPs' interpretation (69%) was the lowest out of all four features ($p<0.001$).

Figure 1 Comparison of measurements for 135 soft tissue masses taken by general practitioners (GPs) and specialists at the Royal Orthopaedic Hospital (ROH)

Two-thirds ($n=30$, 67%) of malignancies were positive for 'increase in size', compared with less than half ($n=43$, 48%) of the benign lesions. Consequently, this parameter was found to be sensitive in 73% and specific in 51% of cases.

Depth

GPs and specialists at the ROH concurred that 61 soft tissue swellings were located superficially and 38 were deep, leading to an accuracy of 77% ($p<0.001$). Of the 45 malignancies, 25 (56%) were located deep to the fascia. Only 27 (30%) of the 90 benign lesions were deep. For the parameter 'deep to fascia', sensitivity was 57% and specificity 68%.

Combination of criteria

According to our results from seven cases in which all four features, only three (43%) turned out to be malignant (Table 3). For soft tissue swellings with only one positive parameter (either size, pain, increase in size or depth), 18% were malignant, compared with an average 35% chance of malignancy once two features were positive. Additionally, as

soon as three parameters were fulfilled, the risk of malignancy was elevated to a mean 62%.

In our study, the combination of factors most predictive of malignancy were positivity for size, depth and increase in size, and negativity for pain. Of the 13 patients presenting with this constellation, 10 (77%) were diagnosed with a malignancy.

Of the 106 patients who had undergone imaging prior to referral, 33 (31%) turned out to have a malignant lesion compared with 12 (41%) of the 29 who were referred on clinical grounds alone.

Discussion

Over 500,000 patients are diagnosed annually with cancer in the UK; about 3,000 of these suffer from STS.² They constitute a rare but aggressive tumour entity, with overall survival rates of approximately 56%, depending on different prognostic factors such as histological subtype, size, grade and stage.^{4,5,11} There has been no refinement of the criteria for early diagnosis of STS since 2000 although

Table 3 Combination of features of concern cases observed at the Royal Orthopaedic Hospital

	Number of features present															
	0	1			2							3				4
Size		✓			✓	✓	✓					✓	✓	✓		✓
Pain			✓		✓				✓	✓		✓	✓		✓	✓
Increase in size				✓			✓		✓		✓	✓		✓	✓	✓
Deep					✓			✓		✓	✓		✓	✓	✓	✓
Malignant	3	2	1	3	0	0	5	4	0	0	3	3	1	10	1	3
Benign	11	9	3	11	4	4	7	2	4	2	3	3	3	3	0	4
Total	14	11	4	14	4	4	12	6	4	2	6	6	4	13	1	7
Malignant	21%	18%	25%	21%	0%	0%	42%	67%	0%	0%	50%	50%	25%	77%	100%	43%

several studies have reported that pain is not a useful indicator of malignancy, and may in fact delay referral and therefore the chances of cure.¹⁰

The results of this study show that GPs have become more precise in detecting STS compared with previous studies.¹⁰ From 135 urgent referrals to the ROH within a 1-year time period, 45 (33%) were identified as STS whereas Pencavel *et al* only found STS in 2 (2%) of their series of 102 patients.¹⁰

Size

In our cohort, the average size for benign swellings examined by the GPs was nearly identical to the actual dimensions evaluated at the special unit, as shown by a high linear correlation between both estimates ($r^2=0.798$). The average size for malignancies evaluated by the GPs was 7.6cm (SD: 4.3cm) although they actually measured about 8.6cm (SD: 5.9cm). This is a little less than the usual size for STS at initial presentation over the past 25 years.⁶ Nevertheless, while benign soft tissue tumours are approximately 5cm in size, sarcomas are most often clearly positive for the parameter 'size >5cm'. As size correlates directly with chances of survival for patients with STS, it is crucial to diagnose them at an early stage.¹²

After lowering the size theoretically from 5cm to 4cm, 40 of the 45 malignancies would have been referred just because of concerning dimensions. Consequently, we recommend that the feature 'size >5cm' should be adapted to a generally valid 'size >4cm'. In a few urgent referral forms, the critical size has already been changed from 5cm to 4cm and this definition of the size parameter should definitely be preferred.¹³

Pain

Contemplating the definite diagnosis, only 12 malignancies were associated with pain. The majority of STS cases are usually painless swellings and patients are unaware of them until they increase noticeably in size.¹⁴ As shown in Table 2, positivity for pain is not a reliable prognostic factor for possible malignancy. We therefore propose removal

of 'pain' as a feature of concern since it does not appear to indicate an increasing risk of malignancy.

Increase in size

Previous studies have found out that STSs tend to increase in size over a period of a few months.¹¹ The factor 'increase in size' is rather subjective and is only based on patients' experience. The GPs recorded an increase in 70 patients whereas the ROH experts considered this parameter present in 72 cases, with rather poor accuracy. This could be partly caused by more or less suggestive questions while taking the patient's history although in this respect, the two-week time period may also play a role. However, especially in STS, a painless increase in size constitutes an important sign (and is often the only one that patients notice). These observations concur with our results as two-thirds of malignant tumours were increasing in size whereas just under half of benign lesions showed positivity for this parameter.

Depth

Previous studies have also shown that STSs are usually located deep to the fascia. This factor can cause difficulties in detection since a STS lying deep has hardly any symptoms.^{6,11} The results of our dataset match with this observation as the majority of malignancies were situated deep while benign lesions were more likely to be located subcutaneously.

Accuracy

Experience shows that with physical examination only, difficulties emerge for investigating the location of soft tissue masses. Despite this, the accuracy of GPs' interpretation for location of the lumps was 77%. This could result partly from the imaging procedures carried out by GPs in 106 of 135 cases, facilitating the localisation of soft tissue masses. In a study by Pencavel *et al*, prior imaging for all suspicious soft tissue swellings was recommended to decrease the number of non-malignant lumps referred over the two-week wait pathway to a specialist centre.¹⁰ This could

already have had an effect on the diagnostic approach of suspicious soft tissue masses at GP surgeries.

It was interesting, however, that the rate of malignancy in those patients with prior imaging (31%) was lower than in those without such imaging (41%). This does not necessarily imply that prediagnosis imaging is not helpful as the GPs may have referred patients for imaging when they had a lower threshold for concern and referred patients directly if they were more concerned. Furthermore, it is not known how many patients underwent imaging and were never referred to our unit as a benign diagnosis was confirmed. This warrants further investigation.

Study limitations

The major drawback of our study lies in the fact that the present setting is not suitable to evaluate whether the set of criteria is sufficient to identify all STS cases. Further prospective studies of non-preselected patients are therefore mandatory to assess the real sensitivity of the two-week wait referral approach.

Conclusions

This study has shown that GPs appear to have become more precise in detecting STS. Soft tissue masses with the combination of a size of >5cm, no pain, an increase in size and deep location were most likely to be malignant. The accuracy of GPs' interpretation for the concerning features compared with investigations at the special unit ranged from 69% (increase in size) to 82% (size >5cm), leading to an average accordance of 75%.

Based on the results of our study, we recommend the removal of the feature 'pain' from the main features of concern as STS tends to appear as a painless swelling. The value of prediagnostic imaging remains to be ascertained in ruling malignancy in or out. Furthermore, the threshold for size should be changed from 5cm to 4cm as the overall

survival for STS depends most on the size of the lesion. The earlier STS is diagnosed, the higher the chance of a good prognosis for the patient. Despite the results of our study, our suggested changes to the NICE guidance would benefit from assessment at other centres.

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