International Orthopaedics (SICOT) (2008) 32:381–384
DOI 10.1007/s00264-007-0319-8

ORIGINAL PAPER

Retrospective analysis of the impact of symptom duration on prognosis in soft tissue sarcoma

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Received: 15 November 2006 / Revised: 8 December 2006 / Accepted: 12 December 2006 / Published online: 22 March 2007

Abstract The objective was to assess whether time to diagnosis is influenced by patient/tumour-related factors and whether or not duration of symptoms has any impact on survival in soft tissue sarcoma. The study was an analysis of prospectively collected data for patients treated at our centre over a 20-year period. Risk factors were assessed by Kaplan–Meier analysis and the Cox proportional hazards model. Of 1,508 patients, 159 had metastatic disease at diagnosis and were excluded from analyses. In the remaining 1,349 patients overall 5-year survival was 60%. Duration of symptoms had a significant impact on survival (p=0.0037) with each additional week of symptoms reducing the monthly hazard rate by 0.2%. Patient and tumour-related factors significantly associated with longer symptom duration were low-grade, subcutaneous tumours, and epithelioid or synovial sarcoma. Symptom duration was not associated with age/gender or tumour size. Patients with long symptom durations tend to have low-grade disease and a more favourable outcome than patients who experience short symptom durations.

Résumé Le but de l'étude est de mettre en évidence l'influence du diagnostic précoce et son effet sur la survie des patients affectés de sarcomes des tissus mous. Une analyse prospective de recueil des données a été réalisée sur une période de 20 ans en utilisant la méthode de Kaplan–Meier. Sur 1,508 patients, 159 ont été exclus de l'analyse car ils présentaient déjà des métastases au moment du diagnostic. Sur les 1,349 patients restant, la survie moyenne à 5 ans a été de 60%. La précocité du diagnostic a un impact significatif sur la survie (p=0.0037) et, chaque semaine additionnelle améliore le score. Les facteurs significatifs pour une évolution relativement longue sont les tumeurs de bas grade, les tumeurs sous-cutanées épithélioides ou synoviales. La longueur de l'évolution et la symptomatologie ne sont pas en relation avec l'âge, le sexe ou la taille de la tumeur. Les patients qui ont présenté une longue évolution des signes cliniques ont plutôt une tumeur de bas grade et leur avenir est plus favorable que les patients don't l'évolution symptomatique est très courte.

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Introduction

Data from the National Survey of NHS Patients has identified significant delays in the diagnosis of six common cancers (lung, breast, etc.) and it has been suggested that this may partly explain why cancer patients in the UK are diagnosed at a more advanced stage compared with their European counterparts [1]. It is well known that soft tissue sarcomas (STS) often present late, the average size at presentation being 10 cm, but the effect of the delay in diagnosis on outcome is not known. There are a number of reasons for the delay in diagnosis and these include the fact that STS are rare and have varied clinical and histological presentations. There are about 2,000 new cases per year in the UK and STS account for less than 1% of all adult and 7–10% of paediatric malignancies [2].

Soft tissue sarcomas usually present with a painless lump. Patient delays arise because STS are not always associated with symptoms that may trigger a patient to seek medical attention such as pain, functional deficit or rapid growth [2, 4]. Doctor delay usually occurs because of misdiagnosis based on clinical examination leading to no or inadequate investigation. Attempts to improve the time to diagnosis have been made by producing guidelines for

urgent referral that have been widely circulated in the UK [7]. These guidelines suggest that anyone with a lump with any of the following features should be referred for investigation for suspected malignancy:

- Greater than 5 cm
- Increasing in size
- Deep to the deep fascia
- Painful

However, there is no evidence to show that those patients who are diagnosed and treated earlier are conferred a prognostic advantage. In fact it has been suggested that those patients who present earlier tend to have high-grade disease and have a less favourable outcome [9].

The aim of this paper is to assess whether symptom duration has any impact on patient survival, and also whether or not patient and tumour-related factors are related to the duration of symptoms prior to presentation.

Materials and methods

The study is an analysis of prospectively collected data for all patients diagnosed or treated with an STS at our centre over a 25-year period. Patients referred with local recurrence or another previous malignancy were excluded from the analyses. Information regarding when the patients first experienced symptoms was entered into the unit's oncology database at their first consultant–outpatient appointment. Symptom duration was defined as time in weeks from the first symptoms experienced by the patient to the time of diagnosis. The size/symptom ratio has been used as a very approximate surrogate of the rate of growth of the lesions [9].

The R statistics software was used for data analysis [8]. Five-year overall survival was calculated for those patients who were treated with curative intention (i.e. those who did not have metastatic disease at diagnosis). Risk factors were assessed by Kaplan–Meier analysis and the Cox proportional hazards (Cph) model. The later models were checked for the proportional hazard assumption (Schoenfield residuals), influential observations (Cook's D) and non-linearity (martingale residuals). Statistical significance was determined using 95% confidence intervals where appropriate. Student's *t* test was used for comparing duration means; where multiple levels were involved Tukey's HSD was used.

Results

Tumour characteristics

The study population comprised 1,508 patients. The mean age at diagnosis was 52.6 years (range 1.0–94.0) with a male:female ratio of 1.4:1. The mean tumour diameter was 10.6 cm (range 0.3–42.0) with deep tumours averaging 11.7 cm and superficial tumours 6.4 cm. High-, intermediate and low-grade tumours accounted for 53%, 26% and 21% of the study population. Seventy-eight percent of tumours were deep and 22% were subcutaneous. The percentage of deep and subcutaneous tumours that were high grade was 51.0% and 49.8% respectively. The percentage of high-grade tumours in patients under the age of 50 was 42.7%.

Factors' association with symptom duration

The mean symptom duration within our study was 70.1 weeks (range 1–1,560). Although those patients with metastatic disease at diagnosis had a shorter mean symptom duration than those without, this was not statistically significant (metastasis at diagnosis 52.8 weeks, no metastasis at diagnosis 72.2 weeks, mean difference 19.4, 95% CI −2.5 to 41.4).

Table 1 shows the association of patient and tumour-related factors with symptom duration. Tumour depth and grade were found to be significant, but linear regression did not imply that symptom duration was dependent on tumour size, patient age or the presence of metastases at diagnosis. Many patients with epithelioid and synovial sarcomas had a prolonged duration of symptoms prior to diagnosis and when lumped together these two tumour types were significantly different from all the other diagnoses.

Survival

One hundred and fifty-nine patients (11%) had metastatic disease at diagnosis and overall 5-year survival in this group was 14%. In view of this poor prognosis, these patients were excluded from further analyses of survival except where stated. In the remaining 1,349 patients the overall 5-year survival was 60%. The Kaplan–Meier analysis of survival in the non-metastatic patients produced a median of 104 months (95% CI=90–137) derived from 1,207 cases (142 missing observations). A Cph model (n= 12,06) showed that duration of symptoms has a significant positive impact on survival (p=0.0038) with a hazard ratio of 0.998 (95% CI=0.997–0.999), implying that an additional week of symptoms improves the monthly survival rate by 0.2%. In those patients with metastatic disease at diagnosis, symptom duration did not have any significant impact on survival (hazard ratio 0.998, 95% CI 0.995–1.000).

The size/symptom duration ratio may give an approximation of the tumour growth rate. We divided the tumour size by duration of symptoms to provide an estimate of the rate of growth per month. We found that the mean monthly

Table 1 A comparison of symptom duration (weeks) with patient and tumour-related factors for the non-metastatic cases

Group	Number	Mean	Range	Mean difference	95% CI
Sex					
Male	564	76.7	1–1,040		
Female	785	65.9	1–1,560	10.8	−24.8–3.2
Depth					
Subcutaneous	309	98.1	2–1,300		
Deep	1,000	62.6	1–1,560	35.4	16.5–54.4
Grade					
High	626	45.8	1–1,040	High, intermediate 29.6	8.9–50.3
Intermediate	322	75.4	2–1,300	High, low 61.4	39.8–83.0
Low	283	107.2	2–1,560	Intermediate, low 31.8	7.2–56.4
Histology					
Epithelioid/synovial	149	125.4	1–1,040		
All others	1,200	65.6	1–1,560	59.8	29.9–89.8

rate of growth was 0.182 cm/month, but that there was a wide range (0.0005 cm/month to 6.0 cm/month). There was a significant difference in the size/symptom duration ratio between patients with deep and and those with superficial tumours (means of 0.213 cm/month vs. 0.072 cm/month respectively, $p<0.0001$) and also a small difference between patients with different grades of tumour (mean of 0.219 cm/month for high grade vs. 0.165 cm/month for low grade, $p=0.02$). The size/symptom duration ratio had a highly significant ($p<0.0001$) impact on overall survival in a Cph model, with an increasing size/symptom ratio producing a hazard ratio of 1.40 (95% CI 1.19–1.65). There was no significant difference in the size/symptom duration ratio between patients with and those without metastases.

We finally investigated whether duration of symptoms had any effect on survival when we tried to rule out other likely confounding factors—size, grade, depth and presence of metastases at diagnosis. When we looked at patients with deep, high-grade tumours greater than 5 cm in diameter and without metastases at diagnosis ($n=411$), we were unable to show that symptom duration had any effect on survival (hazard ratio 1.0).

Discussion

The management of STS is highly topical. The National Institute for Health and Clinical Excellence has produced guidelines for improving outcomes for people with sarcomas and a recent editorial reiterated the current Department of Health guidelines, stating that any patient with a lesion causing concern should be seen by a specialist centre within 2 weeks in order to allow earlier diagnosis and improve prognosis [5, 6]. Although delay in presentation to a medical professional and subsequent delay in referral to a specialist centre have been described in the literature, there have been no large studies looking at the influence of specific tumour- and patient-related factors on symptom duration (time to diagnosis) or on the effect of diagnostic delay on outcome [3]. The aim of this paper has been to determine these factors and also to determine whether symptom duration influences overall survival.

The rarity of STS leads to considerable delay in diagnosis. We have shown that those patients who present early, and therefore have a shorter duration of symptoms, have a less favourable overall survival. This is probably a reflection of the poor prognosis conferred by high-grade disease, which we have demonstrated to be associated with significantly shorter symptom durations than those experienced by patients with intermediate or low-grade disease. We have been unable to demonstrate any significant survival benefit associated with shorter symptom durations, even when the effect of more aggressive tumours (i.e. those with faster growth rates) is accounted for in multivariate analysis.

The size/symptom duration ratio is a crude approximation of the rate of growth of the tumour and is clearly subject to recall bias by the patient when reporting symptom duration and also inter- and intra-observer bias by the clinician when determining the maximum tumour diameter. It was first described as a prognosticator in patients with high-grade STS by Ruka et al. [9]. The rate of growth appears to be a highly significant factor in survival, with an increased rate of growth leading to a worse outlook.

It is surprising to note that patients with subcutaneous lesions present significantly later than those with deep lesions. One possible explanation for this is that superficial lumps and bumps are common and in the absence of pain or rapid growth may not trigger a patient to seek medical attention. One can certainly imagine a patient being more concerned by a large deep lump, which they suddenly

notice, than a slow-growing, superficial one. The evidence for this is that mean size/symptom duration ratio (or approximate rate of growth) is significantly higher in deep compared with subcutaneous lesions (deep 0.21 cm/month, subcutaneous 0.07 cm/month, $p<0.0001$). However, most deep lumps will not be appreciated until they have reached at least 5 cm and many will be bigger than this (average size 11 cm in this series) and thus will by definition have a high size/symptom ratio.

Conclusions

We have been unable to demonstrate a prognostic advantage in patients with a shorter duration of symptoms found to have a soft tissue sarcoma, but we have shown that many patients are content to leave lumps and bumps while they get bigger and size in itself is known to be one of the most important prognostic factors for survival of patients with STS [10]. We have shown that patients who have very long symptom durations have a more favourable prognosis and this is probably due to the association of longer symptom durations with low-grade, superficial tumours, which confer a more favourable outcome.

We have been unable to demonstrate that a shorter duration of symptoms improves outcome, probably because of the highly significant impact of grade on both prognosis and duration of symptoms. However, it stands to reason that if a tumour is diagnosed earlier it will be smaller and this may well improve outcome. Early referral of any patient fitting any of the criteria for a suspicious lump will improve the chances of diagnosing STS at an earlier stage.

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