ELSEVIER

European Journal of Cancer 40 (2004) 2280–2286

European Journal of Cancer

www.ejconline.com

Symptom interval in young people with bone cancer

S. Goyal [a], J. Roscoe [a], W.D.J. Ryder [b], H.R. Gattamaneni [a], T.O.B. Eden [a,b,*]

[a] *Young Oncology Unit, Christie Hospital, Wilmslow Road, Manchester M20 4BX, UK*
[b] *Academic Unit of Paediatric Oncology, Medical Statistics, Christie Hospital NHS Trust, Wilmslow Road, Manchester M20 4BX, UK*

Received 6 January 2004; received in revised form 13 May 2004; accepted 19 May 2004
Available online 2 July 2004

Abstract

Symptom interval (SI), the time from first symptom/sign to diagnosis and initiation of treatment, appears to be principally influenced by tumour biology. Whether the age of the patient, patient delay, professional delay and access to health professionals influences the SI in bone tumours was investigated in this study.

115 patients with newly diagnosed osteosarcoma and Ewing's sarcoma were retrospectively reviewed. The median total SI for all bone tumours was 3.8 months (range 1–46 months). Patients older than 12 years had a longer SI ($P = 0.05$) and more patient delays ($P = 0.02$). Total SI and professional delays were longer if the General Practitioner was first seen compared with an Accident and Emergency Consultant ($P = 0.02$ and 0.02, respectively). However, SI did not influence overall and event-free survival in this series. Bone tumour patients have long SIs that are significantly affected by age and local health-care support systems. Early referral to specialists would help to alleviate anxiety and distress to the patient and family, even if currently delay does not influence outcome.

Keywords: Patient delay; Professional delay; Health-care systems; Bone tumours; Symptom interval

1. Introduction

The symptoms and signs of childhood malignancies are frequently similar to much more common and less serious childhood illnesses. As a consequence, many children who have cancer may be symptomatic for a period of time prior to being accurately diagnosed. Whether this has any significant impact on outcome remains unclear.

Symptom interval (SI) or lag time is defined as the time from first onset of symptoms or signs to a definitive diagnosis and initiation of treatment. This has two components, patient delay and professional delay. Patient delay is defined as the period from onset of first symptom to when the patient first seeks medical help. Professional delay is the time period from that first consultation to definitive diagnosis and initiation of treatment. Flores and colleagues [1] reported that brain tumours appeared to have long SIs, especially in younger children. Edgeworth and colleagues [2] suggested that non-specificity of presenting features with a high incidence of associated behavioural symptoms might account for this. Halperin and colleagues [3] reported that for 122 children with medulloblastoma, those with low stage disease had a significantly longer SI than high staged patients (8 vs. 4 weeks; $P = 0.01$). Two other studies also examined the influence of lag time in childhood cancer and found it to be strongly associated with age and tumour type [4,5]. Pratt and colleagues [4] in their study of children with head and neck rhabdomyosarcoma suggested that early diagnosis might improve survival provided the same multidisciplinary treatment was made available to all patients. However, Saha and colleagues [5] found no correlation between lag time and outcome for any tumour in their study of 184 patients with a variety of tumour types.

The impact of patient and professional delay has not been systematically analysed separately for the different types of cancer though a study by Goddard and colleagues [6] in patients with retinoblastoma reported that type of health professional initially consulted significantly influenced SI. Analysis of the

* Corresponding author. Tel.: +44-161-446-3094; fax: +44-161-446-3092.
E-mail address: tim.eden@man.ac.uk (T.O.B. Eden).

0959-8049/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejca.2004.05.017

components of any delay might help to assess whether any preventative measures could be introduced e.g.: education about ways of presentation of childhood tumours for primary care/emergency room professionals. Even if delays do not influence outcome significantly, patient and parental anxiety is certainly alleviated by rapid diagnosis.

Bone tumours are likely to have long SIs due to their frequently slower rate of growth and older age at peak incidence [7]. This study was undertaken to analyse the influence of the component parts of SI and to assess the impact, if any, of demographic factors and tumour characteristics on it, for young people with bone tumours. We also examined the relationship between SI and survival.

2. Patients and methods

The clinical records of a series of 115 consecutively presenting unselected patients, aged 4–22 years, referred to the Royal Manchester Children's and the Christie Hospitals with newly diagnosed Ewing's sarcoma and osteosarcoma between January 1990 and April 2002 were retrospectively reviewed. Cases treated in these centres, but excluded from the review, included; four children who were referred from overseas for part of their care, two who had received a single course of treatment in the hospital, but were normally resident elsewhere, two who had been originally misdiagnosed and four where missing data precluded meaningful analysis. This analysis reports on the remaining 103 with a verified diagnosis. The following clinical parameters were recorded in a uniform format on a computer database; gender, ethnicity, age at diagnosis, date and type of first symptom or sign, date and type of health-care professional to whom the patient first presented, action of that first health-care professional consulted, date of first referral to a specialist, date and type of specialist seen, action of specialist, date of biopsy, date of diagnosis, type of tumour, presence of metastases at diagnosis, site of tumour, date seen by cancer specialist, date treatment started, length of event-free survival from diagnosis and total survival from diagnosis. A patient was considered to be symptomatic from the day that unrelieved symptoms, directly attributable to the bone tumour, were first recorded. The total SI was calculated from the date of onset of symptoms until the date of diagnosis. The date of diagnosis was recorded as the date when the biopsy was reported. When the clinical notes did not record the precise date of diagnosis, the patient was only included in analysis of length of SI from first symptom to initial consultation (patient delay). Complete information on total SI, patient delay and professional delay was available in 96, 87 and 84 patients, respectively.

3. Statistical methods

The data was transferred into an S-Plus spreadsheet for statistical analysis. The distribution of the three lag times (patient delay, professional delay and total delay) exhibited some positive skew. For simple two group analyses, medians were calculated and compared using the Mann–Whitney U-test. Four two-level factors were considered for their influence on lag times: diagnosis (Ewing's, osteosarcoma), age ($\leqslant 12$, >12 years), site (limb, axial) and health professional first seen (General Practitioner, Accident and Emergency). Of primary interest was the impact of the last three of these factors and also whether any observed effects varied between the two diagnostic groups. Multiple regression analysis was used to perform these more in-depth analyses. In each case $\log_{10}$ (lag + 0.5) was used as the response variable in order to deal with the skewed distributions, the 0.5 term being added as a number of the lag times were zero. The transformed lag times were much more symmetrically distributed. For each response/factor combination, the following three models were considered:

1. Diagnosis * factor.
2. Diagnosis + factor.
3. Diagnosis.

Comparisons between models were made with the usual F test. The first comparison was between 1 and 2, a test for interaction to see if the effect of the factor depended on the diagnosis. If the first test was not significant then a comparison between models 2 and 3 was made to see if there was a consistent additive effect of the factor irrespective of the diagnosis. We also examined the effect of total lag time, cast into three groups, on survival for each of the diagnostic groups. Survival curves were estimated using the Kaplan–Meier method and compared using the log rank test.

4. Results

Of the 103 patients analysed, the male to female ratio was 1.2:1. Median age was 15 years (range 4–22 years), with 80% aged 10–20 years (Table 1). There were twice as many osteosarcoma as Ewing's sarcoma cases (1.9:1). More patients with Ewing's sarcoma presented with metastases (26%) than those with osteosarcoma (10%). Eighty percent were limb tumours and 20% occurred at axial sites. A higher portion of axial tumours was seen in the Ewing's group (37%) compared with osteosarcomas (12%) (Table 1).

Fifty percent of patients initially presented to their General Practitioner (GP), 36% to Accident and Emergency Departments (A&E), 5% directly to a consultant and 2% to other professionals, one to a rheumatologist and one to a physiotherapist. In seven patients, there

Table 1
Basic demographic details of cohort analysed

	Osteosarcoma ($n = 68$)	Ewing's sarcoma ($n = 35$)
Gender	M 40 (59%) F 28 (41%)	M 17 (49%) F 18 (51%)
Age at diagnosis (years)		
$\leqslant 12$	14 (21%)	13 (37%)
>12	54 (79%)	22 (63%)
Primary site		
Axial	8 (12%)	13 (37%)
Limb	60 (88%)	22 (63%)
Metastases at diagnosis	7 (10%)	9 (26%)

M, male; F, female.

was no information on type of health professional first consulted (Table 2). Of the 77 cases where the precise action of the first clinician was recorded, 61% carried out imaging studies, whereas in nearly a quarter of cases (23%) antibiotics and/or analgesics were initially prescribed for symptomatic relief. Only 14 % of the first clinicians seen immediately referred the patient to another professional. Of these referrals, the two most likely specialists to be consulted were orthopaedic consultants (40%) and bone cancer specialists (43%). Eight percent were referred directly to oncologists and a further 9% saw other consultants including cardiothoracic, spinal or neurosurgeons. No information on first specialist referral was available for two patients. Seventy eight percent of orthopaedic consultants initially referred their patients to another specialist, for example a bone cancer specialist, whereas 93.2% of bone cancer specialists carried out imaging and biopsy themselves. Inevitably, the number of specialists seen will lead to some delay in definitive diagnosis and commencement of treatment (Table 2).

The median total SI for all bone tumours was 3.8 months (range 1–46 months), 3.4 months for osteosarcoma (range 1–15 months) and 5.7 months for Ewing's sarcoma (range 1–46 months). Though Ewing's sarcoma had a significantly longer total SI, overall the component patient and professional delays between the two tumours were not significantly different. This could, in part, be due to the absence of complete cohort data. The date of first presentation was missing in some patients, which precluded calculation of the patient and professional delays without affecting estimation of the total SI. From Table 3, it is evident that older age at diagnosis prolonged the total SI significantly, irrespective of the diagnostic group ($P = 0.05$), but patient delays for older patients were significantly longer only for Ewing's sarcoma patients (2.4 vs. 0.4 months) (Fig. 1). Axial site of origin prolonged both the total SI (7 vs. 3.3 months) and professional delays (4.7 vs. 1.4 months). However, on regression analysis this effect was significant ($P = 0.002$) only for professional delays (Table 4) and was present irrespective of the diagnostic group (Fig. 2).

The type of health professional initially consulted also made a significant difference with the median total SI for those presenting to a GP being 4.3 vs. 2.8 months for A&E presenters. On regression analysis, this effect was additive ($P = 0.02$) (Table 4). Patient delays were longer when presenting to a GP for osteosarcoma patients (1.3 vs. 0.9 months). Although there was no evidence for an interaction with Ewing's sarcoma, the additive effect was significant i.e. patient delays were longer irrespective of the diagnostic group ($P = 0.04$) (Table 4). Professional delays were significantly longer when presenting to a GP in patients with Ewing's sarcoma (2.8 vs. 1.3 months) ($P = 0.02$) (Fig. 3). This difference was further reinforced for axial tumours where the GP professional delay was prolonged although the analysis was on a smaller number of patients (Fig. 4).

Asian patients showed a trend for longer total SI in both tumour types, but this was not significantly different from the total series ($P = 0.87$). The presence of metastases at diagnosis did not significantly affect the total SI or its component parts.

There was no significant difference found between total and event-free survival times by SI (grouped into <3 months, 3–6 months and >6 months) when both tumours were grouped together or when analysed separately (Figs. 5 and 6).

Table 2
Initial professional consulted and first specialist seen

	Type of health professional first consulted					First specialist seen				
	GP	A&E	Consultant	Other[a]	NA	Orthopaedic consultant	Bone cancer specialist	Oncologist	Other[b]	NA
Osteosarcoma ($n = 68$)	36	24	3	2	3	24	37	1	4	2
Ewing's sarcoma ($n = 35$)	16	13	2	0	4	17	7	6	5	0
Total ($n = 103$)	52	37	5	2	7	41	44	7	9	2

GP – General Practitioner; A&E – Accident and Emergency; NA – data not available.
[a] This was a rheumatologist and physiotherapist.
[b] Other consultants including cardiothoracic, spinal and neurosurgeons.

Table 3
Median SIs (in months) and component parts for both osteosarcoma and Ewing's sarcoma, separately and together

Tumour type		Age group (years)		Site		First health professional seen	
		⩽12	>12	Axial	Limb	GP	A&E
Osteosarcoma and Ewing's sarcoma	Total SI	2.7 (0.6, 46.2)	4.2 (1.0, 27.1)	7.0 (2.2, 13.6)	3.3(0.6, 46.2)	4.3 (1.0, 46.2)	2.8 (0.6, 27.1)
	Patient delay	0.5 (0.0, 10.1)	1.6 (0.0, 12.0)	1.0 (0.0, 6.1)	1.0 (0.0, 12.0)	1.0 (0.0, 12.0)	0.9 (0.0, 6.1)
	Professional delay	2.7 (0.3, 7.3)	1.7 (0.1, 13.6)	4.7 (0.2, 8.4)	1.4 (0.1, 13.6)	1.8 (0.3, 13.6)	1.3 (0.1, 9.7)
Osteosarcoma	Total SI	2.6 (0.8, 13.3)	3.8 (1.0, 14.6)	6.6 (2.2, 12.9)	3.3 (0.8, 14.6)	3.5 (1.0, 14.6)	2.8 (0.8, 9.7)
	Patient delay	1.0 (0.0, 10.1)	1.0 (0.0, 12.0)	1.5 (0.4, 3.0)	1.0 (0.0, 6.0)	1.3 (0.0, 12.0)	0.9 (0.0, 3.4)
	Professional delay	1.1 (0.4, 4.4)	1.7 (0.2, 13.6)	5.6 (0.2, 6.3)	1.4 (0.2, 13.6)	1.5 (0.3, 13.6)	1.7 (0.4, 9.7)
Ewing's sarcoma	Total SI	3.7 (0.6, 46.2)	6.3 (2.1, 27.1)	7.3 (3.2, 13.6)	3.6 (0.6, 46.2)	6.3 (2.4, 46.2)	3.0 (0.6, 27.1)
	Patient delay	0.4 (0.0, 2.0)	2.4 (0.1, 6.1)	1.0 (0.0, 6.0)	1.9 (0.0, 5.0)	1.0 (0.0, 5.0)	1.0 (0.0, 6.1)
	Professional delay	1.9 (0.3, 7.3)	1.7 (0.1, 8.4)	4.2 (0.6, 8.4)	1.4 (0.1, 7.1)	2.8 (1.2, 7.9)	1.3 (0.1, 8.4)

SI – Symptom interval; GP – General Practitioner; A&E – Accident and Emergency.

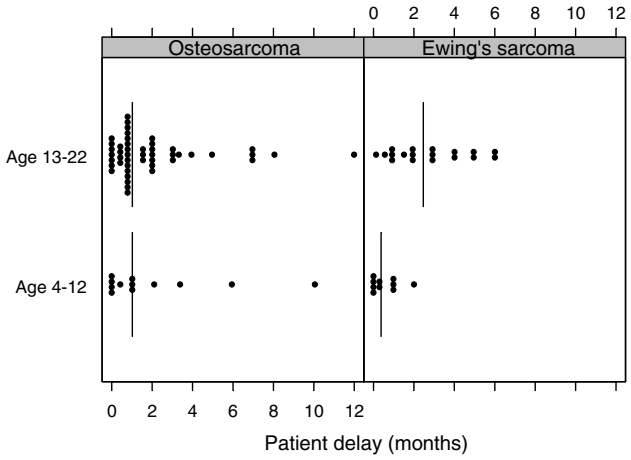

Fig. 1. Dot plot of patient delay by age and diagnosis. Vertical lines represent median values.

5. Discussion

Although lag times in bone tumours have been studied as a component part of 'all solid tumours' in childhood [5,7], the impact, if any, of the different components of the health support systems on lag time in bone tumours has not previously been analysed. The median SI for osteosarcoma and Ewing's sarcoma was 3.4 and 5.7 months, respectively. These values are higher than those observed by Pollock and colleagues [7] (osteosarcoma median 8 weeks; Ewing's sarcoma median 10 weeks). Saha and colleagues [5] also showed a median lag time of 8 weeks for all bone tumours in their group of patients. The longer SI in our patients may be a reflection of geographical variation in health-care access or in patient response to symptoms/signs. Our findings corroborate those of Pollock and colleagues [7] in that Ewing's sarcoma had a longer SI than osteosarcoma largely due to its greater propensity for growth in the axial skeleton (37% vs. 12%) in our series. Age was significantly shown to affect the total SI, a finding similar to that reported both by Saha and colleagues and Pollock and colleagues [5,7]. However, when the component parts of SI were analysed separately for both tumour groups combined patient delay was longer in older patients (>12 years), but professional delay was not.

Since the two tumours had significantly different median SIs, they were analysed separately to identify other factors that may influence them independently. Patient delay was significantly longer for older patients with Ewing's sarcoma, but not osteosarcoma. This could have resulted from a greater propensity of Ewing's sarcoma occurring at axial sites where symptoms such as chest pain and backache without an obvious visible mass were more likely to be ignored or put down as for example muscle strain/growing pains, especially in fit

Table 4
Multiple regression analysis exhibiting influence of demographic features on lag times for the two diagnostic groups (values in bold are significant)

	Age ($\leqslant$12 years, 12 years)		Site (limb, axial)		Health professional (GP, A&E)	
	Interaction	Additive	Interaction	Additive	Interaction	Additive
Total SI	0.90	**0.05**	0.68	0.08	0.19	**0.02**
Patient delay	**0.02**	–	0.46	0.62	0.35	**0.04**
Professional delay	0.70	0.39	0.30	**0.002**	**0.02**	–

SI – Symptom interval; GP – General Practitioner; A&E – Accident and Emergency.

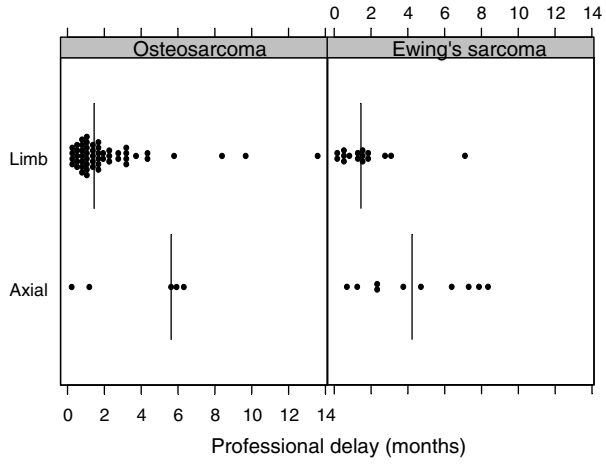

Fig. 2. Dot plot of professional delay by disease site and diagnosis. Vertical lines represent median values.

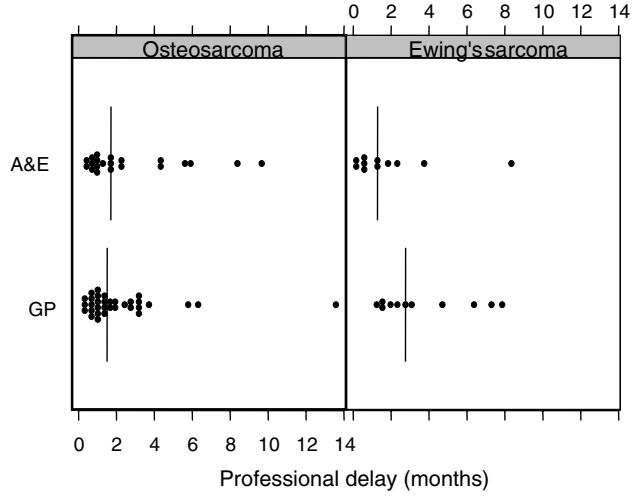

Fig. 3. Dot plot of professional delay by disease and health professional initially seen. Vertical lines represent median values.

young people active in sport. In addition, self-reporting predominates in adolescents compared with parental reporting in younger children. Osteosarcoma appears to be reported earlier because it arises from more easily visible bones of the extremities, where pain is more often than not associated with an observed mass.

The SI and professional delay were longer for axial tumours than limb tumours. Overall, the patient delay

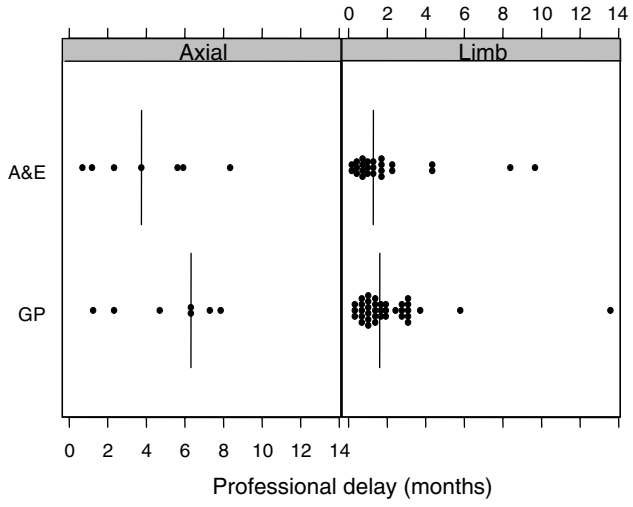

Fig. 4. Dot plot of professional delay by site and type of professional first seen.

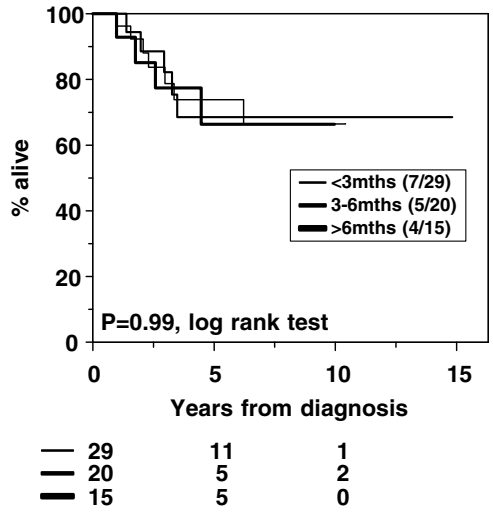

Fig. 5. Osteosarcoma: survival by symptom interval (SI) (the numbers beneath the curves represent deaths/patients initially at risk and those at the bottom the ongoing numbers at risk). mths, months.

was not significantly affected by site probably because symptoms arising in axial tumours prompt the patient to seek a consultation with a doctor as they do for limb tumours, but the same symptoms in the absence of an obvious 'visible mass' do not seem to alert the suspicion

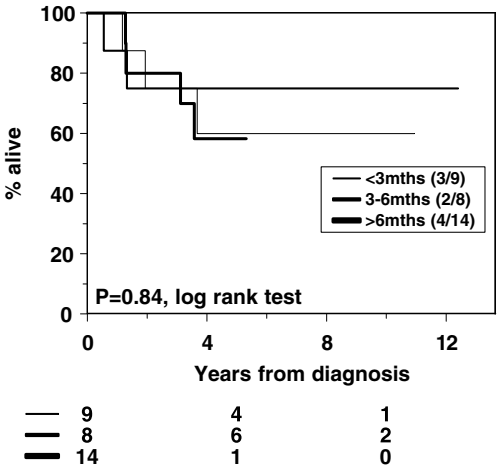

Fig. 6. Ewing's sarcoma: survival by symptom interval (SI) (the numbers beneath the curves represent deaths/patients initially at risk and those at the bottom the ongoing numbers at risk).

of the health professional in the same way that limb symptoms do.

The SI was significantly longer if the health professional first seen was a GP. Presentation to A&E much more commonly led to immediate X-rays than with a GP consultation. For axial tumours, in the absence of visible masses X-rays are essential to recognise a tumour. These patients may also be more acutely ill at presentation. The overall likelihood of being X-rayed was similar whether presenting to a GP (46%) or A&E (51%), although the time required, and hence delay, was much shorter with the latter. The median interval between first presentation to a health professional and seeing a specialist was 0.9 months if presenting to a GP compared with 0.4 months if presenting to A&E. This appears to be because the time required for an orthopaedic consultation after seeing the GP is likely to be longer than that from the A&E. Goddard and colleagues [6] also found significant delays in diagnosis if health visitors were the first primary health-care professionals consulted in their series of 100 patients with retinoblastoma. This is not a reflection on health visitors or GPs, but the inherent delays in referral from professional to professional.

Patients with both tumours had significantly longer patient delays for those presenting to their GP compared with A&E, possibly reflecting difficulties in gaining appointments with a GP due to their heavy workload. The professional delays with osteosarcoma were no different between GP and A&E and this is probably due to the predominant location of these tumours in the limbs, which makes them more visible and easily identifiable.

No significant difference in survival was noticed in either tumour groups with increasing SIs. This is similar to the results of Butros and colleagues [8] in their analysis of patients with retinoblastoma where no definite adverse consequence of delayed diagnosis could be established despite a trend towards greater eye loss being associated with longer delays for bilateral retinoblastoma. A population-based German study [9] on breast cancer also did not find any significant difference in outcome with longer lag times, although there was an obvious tendency towards a more advanced stage of disease with patient delays of longer than one month. Such effects on survival of course relate to current treatment and overall suboptimal survival for patients with bone tumours especially osteosarcoma and axial Ewing's tumours. With significant improvements in disease control, the delay in diagnosis may be more critical.

6. Conclusions

We were unable to find a positive correlation between the total SI and outcome in the context of recent treatment schedules. We were able to demonstrate that SI is affected by tumour type and that site (axial) affects professional delay, irrespective of the diagnostic group. We have also shown that older age increases patient delay and SIs are longer in those presenting to a GP compared with A&E. The overall SI appeared longer in this series of bone tumours than previously reported.

Delay in diagnosis adds to already high levels of psychological distress and may impair the family's coping mechanisms. Education of teenagers on the importance of self-reporting symptoms could shorten patient delay. Similarly, an ongoing programme of education for primary care and A&E doctors regarding the presenting features of bone and other tumours in young people may be a useful investment of time and effort. With the development of increasingly more effective cytotoxic therapy, the speed of diagnosis may become more critical.

Acknowledgements

We are grateful to Drs. Bernadette Brennan, Eddy Estlin and Guy Makin for allowing us to use information regarding their patients for this study.

References

1. Flores LE, Williams DL, Bell BA, O'Brien M, Ragab AH. Delay in the diagnosis of paediatric brain tumours. *Am J Dis Child* 1986, **140**, 684–686.
2. Edgeworth J, Bullock P, Bailey A, Gallagher A, Crouchman M. Why are brain tumours being missed? *Arch Dis Child* 1996, **74**, 148–151.
3. Halperin EC, Watson DM, George SL. Duration of symptoms prior to diagnosis is related inversely to presenting disease stage in children with medulloblastoma. *Cancer* 2001, **91**(15), 1444–1450.

4. Pratt CB, Smith JW, Woerner S, *et al*. Factors leading to delay in the diagnosis and affecting survival of children with head and neck rhabdomyosarcoma. *Paediatrics* 1978, **61**, 30–34.
5. Saha V, Love S, Eden T, Micallef-Eynaud P, Mackinlay G. Determinants of symptom interval in childhood cancer. *Arch Dis Child* 1993, **68**, 771–774.
6. Goddard AG, Kingston JE, Hungerford JL. Delay in diagnosis of retinoblastoma: risk factors and treatment outcome. *Br J Ophthalmol* 1999, **83**, 1320–1323.
7. Pollock BH, Krischer JP, Vietti TJ. Interval between symptom onset and diagnosis of Paediatric solid tumours. *J Paediatr* 1991, **119**, 725–732.
8. Butros LJ, Abramson DH, Dunkel IJ. Delayed diagnosis of retinoblastoma: analysis of degree, cause and potential consequences. *Paediatrics* 2002, **109**(3), e45.
9. Arndt V, Sturmer T, Stegmaier C, Ziegler H, Dhom G, Brenner H, *et al*. Patient delay and stage of diagnosis among breast cancer patients in Germany – a population based study. *Br J Cancer* 2002, **86**, 1034–1040.