One-year mortality in patients with bone and soft tissue sarcomas as an indicator of delay in presentation

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ABSTRACT

INTRODUCTION For many cancers, one-year mortality following diagnosis is a reflection of either advanced stage at diagnosis, multiple co-morbidities and/or complications of treatment. One-year mortality has not been reported for soft tissue or bone sarcomas. This study reports 1-year sarcoma mortality data over a 25-year period, investigates prognostic factors and considers whether a delay in presentation affects 1-year mortality.

METHODS A total of 4,945 newly diagnosed bone sarcoma and soft tissue sarcoma patients were identified from a prospectively maintained, single institution oncology database. Of these, 595 (12%) died within 1 year of diagnosis. Both patient factors and tumour characteristics available at diagnosis were analysed for effect.

RESULTS There was significant variation in one-year mortality between different histological subtypes. There has been no significant change in mortality rate during the last 25 years (mean: 11.7%, standard deviation: 2.8 percentage points). Soft tissue sarcoma patients who survived over one year reported a longer duration of symptoms preceding diagnosis than those who died (median: 26 vs 20 weeks, $p < 0.001$). Prognostic factors identified in both bone and soft tissue sarcomas mirrored those for mid to long-term survival, with high tumour stage, large tumour size, metastases at diagnosis and increasing age having the greatest predictive effect.

CONCLUSIONS One-year mortality in bone and soft tissue sarcoma patients is easy to measure, and could be a proxy for late presentation and therefore a potential performance indicator, similar to other cancers. It is possible to predict the risk of one-year mortality using factors available at diagnosis. Death within one year does not correlate with a long history but is associated with advanced disease at diagnosis.

KEYWORDS

Sarcoma – Symptoms – Diagnosis – Mortality – Prognostic factors – One-year

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Death within one year of cancer diagnosis is a devastating outcome for patients, families and healthcare professionals. Fortunately, among the major cancer types, there has been a consistent increase in one-year survival. In England between 1985 and 2004, one-year survivorship for colorectal cancer improved from 65.1% to 71.9%, for female breast cancer from 88.9% to 95.0% and for male prostate cancer from 79.0% to 95.8%.¹ Although data on one-year survival for patients with sarcomas have not been reported, there has been no change in five-year survivorship since the introduction of chemotherapy, the ability to downgrade tumours pre-operatively and the advent of limb salvage surgery.^{2,5}

One-year mortality is now a proxy for early/late stage at diagnosis for major cancer groups, where improvements in one-year mortality reflect increasing proportions of patients having an earlier diagnosis.¹ Late diagnosis is considered a key reason for inferior sarcoma survival rates in England compared with Europe, with strategies employed to reduce

symptom duration by enhancing diagnostic services and raising public awareness.⁴ Domain 1 of the National Health Service outcomes framework aims to prevent people from dying early.⁴ It emphasises the need to treat people in an appropriate and timely fashion. Establishing how far advanced the disease is at the point of diagnosis (risk stratification) helps to tailor treatments to the individual.

Sarcomas are a rare heterogeneous group of tumours that often present late with large size at diagnosis and long symptom duration. Early diagnosis, to reduce size at presentation and decrease the incidence of synchronous metastasis, is fundamental to improving prognosis, with superior resection margins and reduced surgical complications in smaller tumours.^{5,6} Delays in diagnosis of both bone and soft tissue sarcomas are common and multifactorial; they are often due to public and professional low awareness as well as the non-specific nature of many symptoms.^{7,8}

Reducing one-year mortality is an important issue following the publication of national guidelines, where the performance of cancer services are under increasing scrutiny.^{9,10} Early diagnosis and identification of high risk patients is a large facet of this work. Established prognostic factors for mid to long-term survival are reported to include patient age, tumour size, depth, stage and histological subtype, metastasis at diagnosis and response to treatment.^{7,11,12}

This study reports mortality data and factors affecting 1-year survival in patients with bone and soft tissue sarcomas, and determines whether there have been any changes over a 25-year period. It also investigates whether death within one year of sarcoma diagnosis could be due to delay in presentation and its validity as a proxy for advanced stage at diagnosis.

Methods

All consecutive patients with a newly diagnosed bone sarcoma (BS) or soft tissue sarcoma (STS) were identified from a single institution's prospectively maintained database between 1985 and 2010. Our unit is a tertiary referral centre serving a population of 18 million for BS and 5 million for STS patients. Data extracted for analysis focused on patient demographics, tumour characteristics, treatment factors, complications and survival. Patients with local recurrence at presentation were excluded from the study.

Patients were all staged at diagnosis to identify the presence of metastatic disease and had treatment according to national or international guidelines. Patients were followed up routinely in the outpatient clinic for ten years, with a schedule of three-monthly visits following treatment for two-years, then every six months to five-years and then annually thereafter. For patients who fail to attend follow-up appointments, data were obtained from their general practitioner or from the West Midlands Cancer Intelligence Unit (now Public Health England) on date and cause of death.

For STS patients, chest radiography was performed at each visit. Patients with BS also had radiography of the bone treated. Distant metastasis and local recurrence were treated on an individual basis; resection and adjuvant chemo/radiotherapy was offered where appropriate. Dates and cause of death recorded on the database were verified by Public Health England, which records clinical and mortality data for all patients with sarcomas in England. The causes of death were classified into: primary cancer (local recurrence, metastatic disease), treatment related (either postoperative or following adjuvant chemo/radiotherapy), other unrelated causes and unknown causes.

Symptom duration was defined as the patient's subjective recollection of the duration of symptoms in weeks prior to his or her first clinic attendance. The date of diagnosis was defined as the date of confirmed histological diagnosis, with patients categorised into STS or BS. STS cases were further divided into superficial or deep tumours relative to the deep fascia. Extremity tumours distal to the shoulder or hip girdles were regarded as distal, at the shoulder girdle as proximal upper, at the pelvic girdle as

proximal lower and truncal when affecting the thorax or abdomen.

For analysis purposes, tumour size was recorded as the maximum dimension in any plane on computed tomography or magnetic resonance imaging at the time of diagnosis. Patients were subdivided accordingly into large size (>8cm for BS and >5cm for STS) or small size (as defined by the TNM [tumour, lymph node, metastasis] system).¹³ In cases where a previous inadvertent excision had been carried out, the pathology report indicated the size. Tumour grade and TNM stage were recorded following radiological and histological investigations and multidisciplinary discussion.

Statistical analysis

Individual variables were analysed to assess the effect on overall mortality at one-year, comparing the prevalence of factors in patients dying within one-year with those surviving. Statistical analysis was carried out using SPSS® version 20 (IBM, New York, US). For comparison purposes of overall survival, patients alive at one year from date of diagnosis were censored in comparison with those who had died, who were uncensored. Statistical methods for non-parametric data such as duration of symptoms used the Mann-Whitney U test, with a *p*-value of <0.05 defining statistical significance. Nominal data were assessed using odds ratio (OR) and chi-squared analysis to infer differences in prevalence of factors.

Results

The study included 4,945 consecutive patients, 2,668 (54%) of whom had a BS and 2,277 (46%) a soft tissue sarcoma, reflecting the population served. Overall, 595 patients (12%) died within one year of diagnosis. Individual histological subtype mortality rates are reported in Table 1, with variation in outcome between histological subtypes in STS and BS. Tumours were located in the distal extremities in 2,424 cases (49.0%), in the proximal upper extremity in 461 cases (9.3%), in the proximal lower extremity in 1,800 cases (36.4%) and in the trunk in 257 cases (5.2%).

The median duration of symptoms varied most significantly with the grade of the tumour. Patients with high grade tumours had a significantly shorter duration of symptoms than those with lower grade tumours and this was most marked for bone tumours (Table 2). Older patients with a BS (but not a STS) also had a longer duration of symptoms prior to diagnosis (*p*<0.05).

STS patients who died within one year tended to have a shorter duration of symptoms, even when this was stratified by stage (*p*<0.001). This was not the case for BS cases, where duration of symptoms did not affect survival. For STS, this pattern of improved survival at one year with longer duration of symptoms was consistent across all histological subtypes apart from the patients with rhabdomyosarcoma, where the reverse was true. For BS, there was a mixed picture.

When patients were categorised by TNM stage, 76% of those dying within one year had a tumour of stage 3 or greater (ie large and high grade, with or without metastases) whereas only 39% of those surviving at one year had

Table 1 One-year mortality rates and duration of symptoms (DOS) of individual sarcoma subtypes in bone and soft tissue sarcomas

	Subtype	Alive	Dead	Mortality rate	Median DOS	
					Alive	Dead
Soft tissue sarcomas	Alveolar soft part sarcoma	13	0	0%	52 wks	–
	Clear cell sarcoma	26	4	13%	63 wks	52 wks
	Epithelioid sarcoma	25	4	14%	52 wks	59 wks
	Fibrosarcoma	38	3	7%	52 wks	12 wks
	Leiomyosarcoma*	181	26	13%	26 wks	16 wks
	Liposarcoma	237	24	9%	26 wks	16 wks
	Malignant fibrous histiocytoma	152	22	13%	28 wks	6 wks
	Rhabdomyosarcoma*	34	6	15%	16 wks	52 wks
	Synovial sarcoma	220	7	3%	52 wks	26 wks
	Other	1,064	191	15%		
	Total	1,990	287	13%	26 wks	20 wks
Bone sarcomas	Chondrosarcoma*	469	47	9%	52 wks	36 wks
	Ewing's sarcoma	437	39	8%	20 wks	16 wks
	Malignant fibrous histiocytoma	62	9	13%	8 wks	50 wks
	Osteosarcoma*	977	127	12%	10 wks	12 wks
	Other	415	86	17%		
	Total	2,360	308	12%	16 wks	16 wks

* $p<0.05$

such a tumour (OR: 5.0, 95% confidence interval [CI]: 3.9–6.3, $p<0.0001$) (Fig 1). The risk of dying within one year increased steadily as the stage increased, from 0% for stage 1A tumours to 30% for stage 4 bone tumours and 40% for stage 4 STS cases.

Tables 3 and 4 report other factors that affected the chance of survival significantly at one year, including tumour location (trunk and pelvis have worst survival), increasing age, extracompartmental tumours and inability to completely excise the tumour with even a marginal margin. Over half (53%) of all sarcoma patients who died within one year suffered with pelvic girdle tumours (OR 3.91, (95% CI: 3.28–4.68, $p<0.001$). For BS, additional factors indicating a poor prognosis were the presence of a pathological fracture and amputation as a primary treatment while for STS, a deep location of the tumour was also an indicative factor.

There was a striking difference in the size of STS between those who died within one year (median: 12cm) and those who survived (median: 8cm) ($p<0.001$). Similarly, survivors at one year tended to be younger (median: 55 years) than those who died (median: 66 years) ($p<0.001$) and this was also true for BS, where survivors at one year had a median age of 21 years at diagnosis compared with 43 years for those who did not survive ($p<0.001$). The

difference in the size of BS was also noticeable between those who died within one year (median: 12cm) and those who survived (median: 9.5cm, $p<0.001$).

One hundred and ninety-four (32%) of all sarcoma patients presenting with synchronous metastases died within one year of diagnosis, with a larger OR in STS than in BS (7.08 vs 3.37). The incidence of synchronous metastasis was correlated positively to increasing tumour size (Fig 2).

Patients undergoing an inadvertent excision of a STS prior to the referral procedure were statistically less likely to die within one year than those referred directly ($p<0.0001$). However, these patients tended to have smaller, lower grade and more superficial tumours. Patients with deeper tumours had poorer outcomes, with larger size at presentation.

Figure 3 charts 1-year mortality rates at our institution, which have not changed significantly over the past 25 years (mean: 11.7%, standard deviation: 2.8 percentage points, range: 5–17%). Of the 595 patients who died within one year, 470 (79%) died from the primary sarcoma, most owing to metastases. Similar trends have been found in another study.¹⁴ Of these patients with metastasis, 70% were pulmonary, 15% having multiple metastasis. Seventeen patients (3%) died as a direct complication of treatment, including sepsis following chemotherapy. Non-tumour related causes

Table 2 Median duration of symptoms in soft tissue and bone sarcomas influenced by patients' age category, tumour size and the presence of metastasis at diagnosis

	Variable	Duration of symptoms	Interquartile range
Soft tissue sarcomas	All soft tissue sarcomas	26 wks	12–52 wks
	Younger than median age (57 yrs)	26 wks	12–64 wks
	Older than median age (57 yrs)	26 wks	12–52 wks
	Smaller than median size (9cm)	26 weeks	12–78 wks
	Larger than median size (9cm)*	26 weeks	12–52 wks
	Low grade	44 weeks	16–104 wks
	Intermediate grade	32 weeks	16–78 wks
	High grade*	20 weeks	12–52 wks
	No metastasis at diagnosis	26 weeks	12–52 wks
	Metastasis at diagnosis	26 weeks	12–52 wks
Bone sarcomas	All bone sarcomas	16 weeks	8–14 wks
	Younger than median age (22 yrs)	12 weeks	6–20 wks
	Older than median age (22 yrs)*	28 weeks	12–75 wks
	Smaller than median size (10cm)	16 weeks	8–40 wks
	Larger than median size (10cm)	20 weeks	8–44 wks
	Low grade	52 weeks	26–125 wks
	High grade*	12 weeks	8–30 wks
	No metastasis at diagnosis	16 weeks	8–40 wks
	Metastasis at diagnosis	18 weeks	8–32 wks

* $p < 0.05$ **Figure 1** The distribution of cancer stage in patients alive (A) and those dead (B) at one year

Table 3 Soft tissue sarcoma one-year mortality rates influenced by tumour and patient variables at the time of diagnosis

Characteristic	Variables	Alive	Dead	Mortality rate	OR	95% CI	p-value
Sex	Female	848	118	12.22%	1.06	0.83–1.37	0.631
	Male	1,142	169	12.89%			
Location of tumour	Trunk	162	24	12.90%	1.72	1.31–2.26	0.0001
	Proximal upper	128	12	8.57%			
	Proximal lower*	836	157	15.81%			
	Distal**	862	94	9.83%			
	Unknown	2	0				
Age	Younger than median age (57 yrs)	1,070	100	8.55%	2.17	1.68–2.82	<0.0001
	Older than median age (57 yrs)	920	187	16.89%			
Tumour size	<5cm	510	15	2.86%	4.07	2.29–7.25	<0.0001
	5–9.99cm	518	62	10.69%			
	10–14.99cm**	400	91	18.53%			
	15–19.99cm*	190	31	14.03%			
	20cm	139	42	23.20%			
	Unknown	233	46				
Relation to fascia	Superficial	527	36	6.39%	2.52	1.75–3.62	<0.0001
	Deep	1,461	251	14.66%			
	Unknown	0	2				
Relation to compartments	Intracompartmental	538	35	6.11%	1.64	1.11–2.42	0.0133
	Extracompartmental	1,097	117	9.64%			
	Unknown	355	135				
Histological grade	Low**	372	9	2.36%	8.52	4.31–16.75	<0.0001
	Intermediate	507	49	8.81%			
	High*	1,111	229	17.09%			
Metastasis at diagnosis	None	1,840	182	9.00%	7.08	5.28–9.48	<0.0001
	Present	150	105	41.18%			
Cancer stage	1A	106	0	0.00%	8.13	2.55–25.87	0.0004
	1B	22	1	4.35%			
	2A**	161	3	1.83%			
	2B	363	12	3.20%			
	2C	180	22	10.89%			
	3	786	119	13.15%			
	4A*	93	71	43.29%			
	4B	61	38	38.38%			
	Unknown	218	21				
Inadvertent excision	No	1,412	235	4.78%	0.31	0.19–0.47	<0.0001
	Yes	438	22	14.27%			
	Unknown	140	30				

OR = odds ratio; CI = confidence interval; TNM = tumour, lymph node, metastasis
*variable tested; **control

Table 4 Bone sarcoma one-year mortality rates influenced by tumour and patient variables at the time of diagnosis

Characteristic	Variables	Alive	Dead	Mortality rate	OR	95% CI	p-value
Sex	Female	993	122	10.94%	1.13	0.88–1.45	0.3236
	Male	1,367	186	11.98%			
Location of tumour	Trunk	64	7	9.86%	3.24	2.49–4.22	<0.0001
	Proximal upper	284	37	11.53%			
	Proximal lower*	647	160	19.83%			
	Distal**	1,364	104	7.08%			
	Unknown	1	0				
Age	Younger than median age (22 yrs)	1,252	112	8.21%	1.99	1.56–2.55	0.0001
	Older than median age (22 yrs)*	1,108	196	15.03%			
Tumour size	<5cm	126	6	4.55%	1.19	0.93–2.64	0.0897
	5–9.99cm	493	28	5.37%			
	10–14.99cm**	370	33	8.19%			
	15–19.99cm*	151	18	10.65%			
	20cm	66	18	21.43%			
	Unknown	1,154	205				
Relation to compartments	Intracompartmental	151	6	3.82%	2.24	0.97–5.16	0.0578
	Extracompartmental	1,606	143	8.18%			
	Unknown	603	159				
Histological grade	Low	216	5	2.26%	4.06	1.63–9.90	0.0025
	High	1,560	145	8.50%			
	Unknown	584	158				
Pathological fracture	No fracture	2,055	243	10.57%	1.80	1.34–2.43	0.0001
	Present at diagnosis	305	65	17.57%			
Metastasis at diagnosis	None	2,106	219	9.42%	3.37	2.55–4.45	<0.0001
	Present	254	89	25.95%			
Cancer stage	1A	77	0	0.00%	9.50	5.09–17.73	<0.0001
	1B	80	2	2.44%			
	2A**	353	13	3.55%			
	2B	527	49	8.51%			
	3	28	10	26.32%			
	4A*	180	63	25.93%			
	4B	66	28	29.79%			
	Unknown	1,049	143				
Amputation procedure	Limb salvage surgery	2,051	254	11.02%	1.41	1.03–1.94	0.033
	Amputation	309	54	14.88%			

OR = odds ratio; CI = confidence interval; TNM = tumour, lymph node, metastasis
*variable tested; **control

Figure 2 Effect of size on incidence of synchronous metastasis at diagnosis

of death accounted for 65 cases (11%). In 43 patients, the cause of death could not be identified.

Discussion

This study uniquely reports the 1-year mortality of STS and BS over a 25-year period as well as the factors that affect 1-year survival following diagnosis. These factors are largely the same as those known to be important in predicting overall survival.^{2,12,15} Patients with advanced tumours at diagnosis (ie large, high grade and with metastases) have the worst prognosis, particularly when coupled with increasing age and proximal location. Additionally, our findings show that an increased duration of symptoms does not correspond with increased one-year mortality. This may not be surprising as previous work has demonstrated that a long duration of symptoms in STS patients is related to lower grade, which in turn has a better survival.¹⁶

Study limitations

A significant limitation of this study is that no assessment of co-morbidity was made. Although 11% of the patients

who died within one year died of other causes, most deaths were attributed to the primary tumour and subsequent metastasis. Co-morbidity has not been shown to relate to overall survival for STS.¹⁷ Another limitation was incomplete or missing data, which in particular affected factor analysis. For instance, analysis of median duration of symptoms was limited by the small sample size once divided into diagnosis subtype. This could not be avoided with the institution's database, which includes data from over 25 years ago. However, this dataset was collected using consistent definitions over this time period and uniform disease assessment. Histological necrosis after chemotherapy, resection margins and local recurrence were excluded from our study as they are not parameters that are available at diagnosis.

Our routine follow-up imaging for STS includes a chest x-ray and BS patients also have bone radiography. More comprehensive cross-sectional imaging would be useful to identify recurrence but it is not feasible or ethical to do this for a large group of patients and it would not have been possible for patients treated in the 1980s.

Figure 3 One-year mortality rates at our institution for sarcoma between 1980 and 2010

Duration of symptoms

There are multiple reasons why patients present late. These include slow tumour growth, lack of pain or a palpable mass, deep location, doctor inexperience and socioeconomic factors.^{7,18} We were not able to demonstrate that a prolonged duration of symptoms (delay in presentation) led to a worse outcome at one year as patients with a long history often have slow growing, low grade tumours.¹⁹ On the contrary, patients with a longer history had better outcomes at one year, even when the effect of grade was taken into account. We suggest that patients with a longer duration of symptoms are more likely to survive beyond a year in BS and STS. This is similar to what has been concluded in studies analysing mid to long-term survival.^{18,20,21} Duration of symptoms alone does not correlate with the presence of metastasis at diagnosis, increasing tumour size or overall survival.²⁰

This study has not been able to identify whether a delay in diagnosis (for whatever reason) leads to a worse outcome as it was not possible to identify patients who had 'delay' compared with those who simply had a long history of symptoms. Medical professionals and health organisations are thought to confer the greatest source of delay in diagnosis rather than a patient's duration of symptoms. The reason is often a lack of clinical suspicion and frequent referral to non-specialist services.⁷

Predictive factors

Traditional studies use prognostic factors to estimate long-term survival. However, the validity of prognostic factors at the time of diagnosis varies with time and survival. Conditional survival taking into account response to adjunctive therapy, local recurrence and resection margins is important to long-term survival estimates.^{14,22}

At diagnosis, a number of factors are available to the clinician that can facilitate estimation of one-year mortality risk on an individual patient basis. The factors identified have been established previously in the literature when considering mid to long-term survival.^{11,12,15,22} Our results are therefore not novel but reinforce what has been described in three, five and ten-year survival studies, validating our findings.

We have confirmed that tumour size is an important factor in predicting one-year mortality and the larger the tumour at diagnosis, the worse the chances of survival. Grimer estimated that for every centimetre increase in tumour size at the time of diagnosis, there is a 3–5% reduction in overall survival for STS.¹⁹ As expected, the presence of metastases at diagnosis reduced survival and the proportion of cases with metastasis present increased almost linearly with increasing tumour size (Fig 2).¹⁹ Histological tumour grade has been shown to be the most reliable independent prognostic factor at diagnosis for mid to long-term survival^{14,25} and there was a similar magnitude of effect in our data. When combining BS and STS cases, a high grade malignancy increases the one-year mortality rate by 5.9 times compared with a low grade sarcoma and is a powerful outcome predictor.

Processing prognostic factors into a model where a single survival estimate can be obtained is more useful to the patient than ORs when counselling their expectations and making informed decisions. To date, one-year survival has not been stratified in this way although numerous authors have attempted 5–10-year models, highlighting the importance of tumour location, histological grade, tumour size, metastasis and local recurrence.^{23–25} For example, a 40-year-old patient with a large, deep, high grade synovial sarcoma of the trunk has a greater than 80% probability of sarcoma specific death within 12 years.²⁵

With increasing emphasis on early diagnosis and the use of one-year mortality as a proxy for this, we feel that further research in this area to create a nomogram for death at one year will be valuable to clinicians, patients and uniform research reporting. The use of one-year survival may be helpful in identifying early improvements in service provision and could be an indicator of earlier diagnosis.²⁶

Conclusions

We report, for the first time, one-year mortality rates for STS and BS. While we have not shown that delay in diagnosis (as measured by duration of symptoms) is a useful prognostic factor at one year for either BS or STS, this study has demonstrated that TNM stage is a useful predictor. We have also reported that tumour size at diagnosis is correlated with the incidence of synchronous metastasis. It therefore remains true that it is very important for prognosis in both BS and STS cases. The smaller the size at diagnosis, the lower the risk of the patient having metastasis and the better the chance of survival. It is disappointing that size at diagnosis for bone and soft tissue sarcomas has not changed significantly over the last 25 years¹⁹ and this has been reinforced by our demonstration that 1-year survival rates have not improved either.

Public health education to raise awareness and prompt earlier recognition of smaller tumours with lower rates of metastasis and reduced perioperative morbidity may enhance sarcoma survival. Further research is required to provide prognostic tools that can aid clinicians when guiding patients on the short-term outcome of their disease.

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