The sarcoma diagnostic interval: a systematic review on length, contributing factors and patient outcomes

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ABSTRACT

Sarcomas are rare and heterogeneous mesenchymal tumours of soft tissue or bone, making them prone to late diagnosis. In other malignancies, early diagnosis has an impact on stage of disease, complexity of therapeutic procedures, survival and health-related quality of life (HRQoL). Little is known about what length of diagnostic interval should be considered as delay in patients with bone (BS) or soft tissue sarcomas (STS). To quantify total interval (defined as time from first symptom to histological diagnosis) and its components, identify contributing factors to its length and determine the impact on patients' outcome in terms of mortality and HRQoL. A systematic review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Seventy-six articles out of 2310 met the predefined inclusion criteria. Total intervals, varied broadly; 9–120.4 weeks for BS and 4.3–614.9 weeks for STS. Older age and no initial radiological examinations were contributing factors for a long interval in BS, while in STS results were conflicting. The impact of length of total interval on clinical outcomes in terms of survival and morbidity remains ambiguous; no clear relation could be identified for both BS and STS. No study examined the impact on HRQoL. The length of total interval is variable in BS as well as STS. Its effect on outcomes is contradictory. There is no definition of a clinically relevant cut-off point that discriminates between a short or long total interval. Prospero: CRD42017062492.

INTRODUCTION

Sarcomas are a rare group of solid malignant mesenchymal tumours, which comprise more than 70 histological subtypes. They have considerable heterogeneity with respect to age of onset, anatomic location, tempo of progression and outcome. Approximately 80% of sarcomas originate in soft tissue, the remainder in bone. Sarcomas form a typical example of rare cancers, with an estimated European incidence averaging 4–5 per 100 000 per year.[1] Patients with rare cancers have a higher mortality rate than those with common cancers because of delays to accurate diagnosis and subsequent suboptimal or inadequate treatment, fewer developments in novel therapies and reduced opportunities to participate in clinical trials.[2]

Early and accurate diagnosis of cancer is important to optimise patient outcomes in terms of local disease control, overall survival and health-related quality of life (HRQoL).[3,4] The absence of a typical and uniform sarcoma presentation, the lack of public awareness, and the limited experience of primary and secondary healthcare professionals with sarcomas can result in a prolonged total interval and late referral to specialist sarcoma centres. The total interval is the time between first symptoms and (preferably histological) diagnosis (figure 1).[5] To date, the impact of late referrals on sarcoma patient outcomes has been understudied and reports have been contradictory.

To inform interventions that shorten the total interval, better insights are needed into the determinants of each component of the total interval, such as sociodemographic, clinical, psychological and healthcare factors. The aim of this systematic review is to examine the total interval of sarcoma patients by quantifying its length, identifying contributing factors and determine the impact on patients' outcome in terms of mortality and HRQoL.

MATERIAL AND METHODS
Search strategy

We conducted a systematic review according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[6]

A computerised search of the literature through PubMed (1946–present), MEDLINE (1950–present), EMBASE (1974–present), Web of Science (1945–present) and Cochrane Library was carried out with the help of a librarian of the Radboudumc by two researchers (vs and OH) on 28 February 2019.
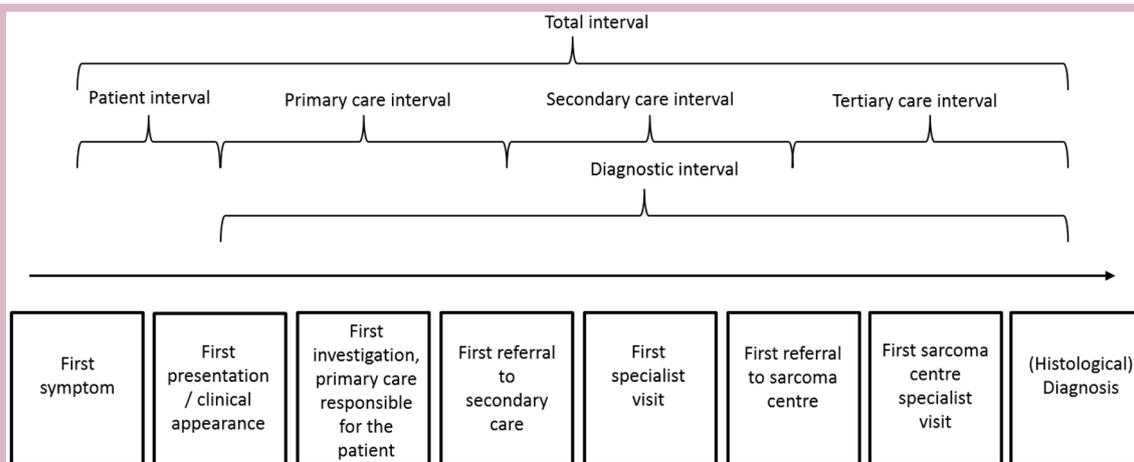
Figure 1 Time intervals in the route from first symptom until start of treatment. Adapted from Olesen *et al*[5] 2009. Total interval: from first symptom to diagnosis; patient interval: from the date the patient first noticed a sarcoma-related symptom until the first presentation to a doctor with this symptom; Diagnostic interval: from first presentation to a doctor until diagnosis; primary care interval: from first presentation to a general practitioner until first referral to secondary care (if applicable) or to a specialist sarcoma centre; secondary care interval: from referral to secondary care until referral to tertiary care (a specialist sarcoma centre); tertiary care interval: from referral to a specialist sarcoma centre until the date of (histological) diagnosis.

The search strategy combined terms related to 'sarcoma', 'delayed diagnosis', 'early diagnosis' or 'referral'. The search string is presented in online supplementary material A.

Selection criteria

Studies were included if they met the following criteria: (1) study participants had a proven diagnosis of sarcoma; (2) the total interval or any of its components as defined in figure 1 were available and (3) the full-text paper was available in English. Reviews were excluded because they did not contain original data and single case reports were excluded to limit selection bias.

Definition

The following definition was used: the total interval, defined as time between first symptoms and (histological) diagnosis, which includes both a patient and diagnostic interval; the latter can be further divided into a primary, secondary and tertiary care interval. The intervals and their associated time points are illustrated in figure 1. This figure was adapted from Olesen *et al*[5 7] by adding a tertiary interval, consistent with centralised sarcoma care pathways.

Data extraction and synthesis

Study design, inclusion period, study population, length of total interval and its components, and effect of total interval on outcomes, such as metastases at diagnosis, overall survival and HRQoL, were extracted from included articles. Factors influencing length of total interval or its components were extracted and organised as tumour-specific factors (eg, histology), patient specific (eg, age) or healthcare related (eg, available imaging studies). Based on our clinical experience, previous reports and different healthcare providers treating these

groups of patients, we expected to find different results for bone sarcoma (BS) and soft tissue sarcoma (STS), and data were thus presented in separate tables. Due to the heterogeneity of inclusion criteria and methods, it was not possible to conduct a meta-analysis, so results were reported descriptively.

RESULTS

Included articles

Our search yielded 2304 unique hits. The reference lists of relevant articles were searched for additional studies which resulted in six additional publications versus and OH screened titles and abstracts of these 2310 publications, 109 studies met the inclusion criteria. After careful independent full-text screening by versus and OH, 62 studies were included in this review. The flow chart of this selection procedure is presented in figure 2.

Bone sarcomas

Length of total interval

Thirty-four studies involving a total of 17 258 patients investigated the total interval in BS (table 1)[8–41]; five of these studies prospectively collected follow-up data. A broad range in the length of the total interval was found, which varied from 9 to 120.4 weeks.

Components of the total interval

The impact of patient intervals was measured in 19 studies (mean 4.1–34.1 weeks), eight studies measured the primary care interval (mean 5–32.3 weeks), whereas the secondary (mean 2.3–7.1 weeks) and tertiary care intervals (mean 2–17.4 weeks) were measured in two and three studies respectively (table 1).
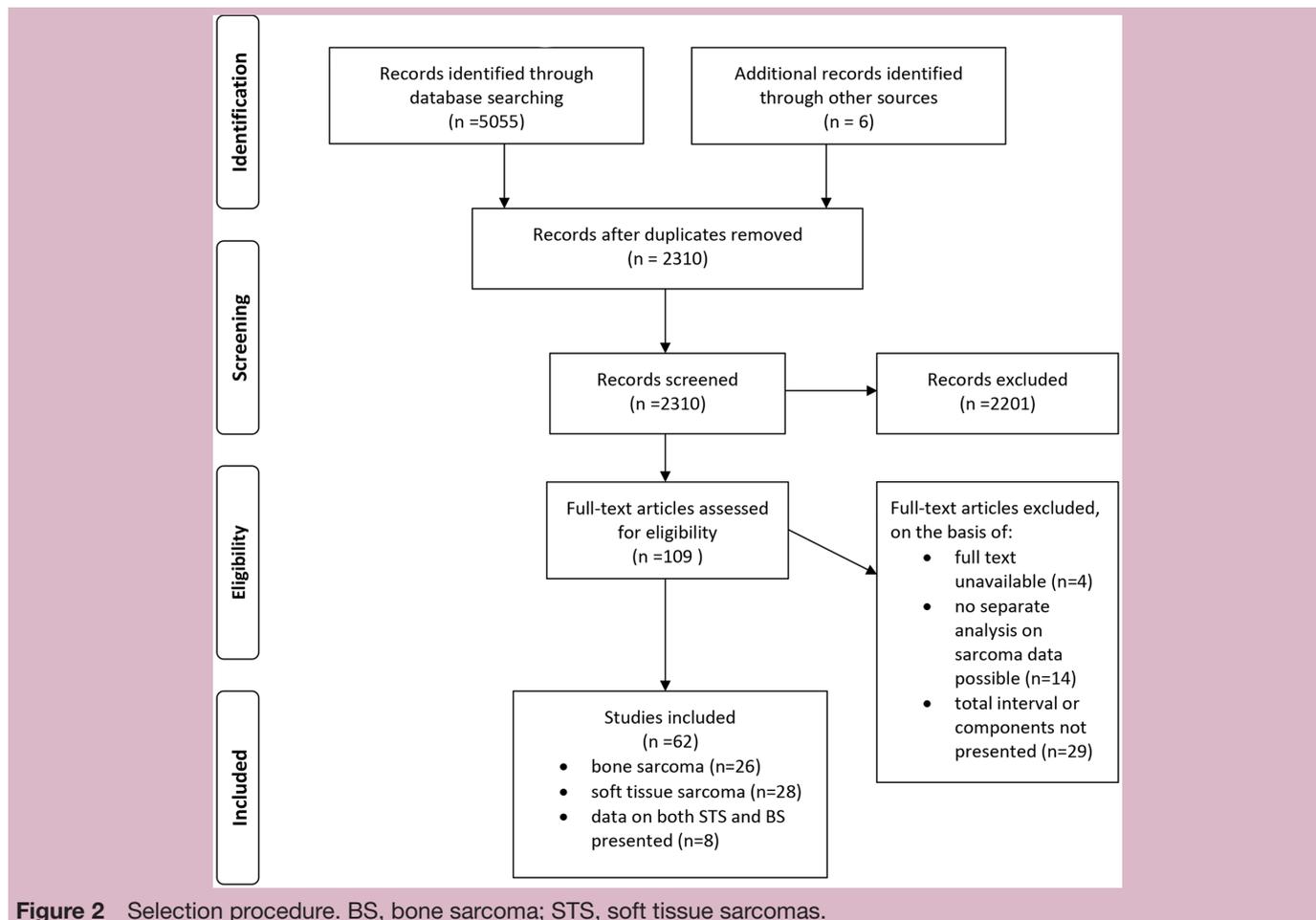
Figure 2 Selection procedure. BS, bone sarcoma; STS, soft tissue sarcomas.

Effect of tumour-specific factors

Several factors were studied as determinants of the length of the total interval. Interestingly, tumour-specific factors such as tumour size or grade did not appear to influence the length of total interval.[22 26 27 41] Patients with sarcomas located in the trunk were shown to have a longer interval than those who have sarcomas in the extremities (29 vs 14 weeks; p<0.001) by Lawrenz et al (n=1792).[41]

Tumour histology was found to be of influence on the total interval. Goedhart et al performed a retrospective study among 102 patients with high-grade BS and reported a significantly longer patient interval and secondary care interval for chondrosarcoma versus Ewing sarcoma and osteosarcoma,[21] which resulted in a significantly longer total interval, with a mean of 98.3 weeks for chondrosarcoma, versus 22.9 and 23.3 weeks for Ewing sarcoma and osteosarcoma, respectively.

Four other studies reported similar results on total intervals for Ewing sarcoma and osteosarcoma; all had a trend towards a longer diagnostic pathway for patients with Ewing sarcoma.[12 14 26 40] In a study by Widhe et al (n=106), the longer diagnostic pathway in Ewing sarcoma was a result of both a longer patient and primary care component[12] whereas a study by Sneppen et al (n=124), reported a four times longer diagnostic interval for Ewing sarcoma than for osteosarcoma patients despite similar patient intervals.[26] Lawrenz et al illustrated that intermediate-grade tumours had a longer diagnostic interval (52 weeks) compared with high-grade BS (12 weeks; p<0.001).[41] In contrast, a study focusing only on BS of the foot (n=32) presented opposite results: a median total interval of 32.3 weeks for chondrosarcoma, vs 64.5 weeks and 77.4 weeks for osteosarcoma and Ewing sarcoma, respectively.[15] Another small study (n=6) reported that half of patients with osteosarcoma of the foot had a considerable patient delay, resulting in a mean total interval of 120.4 weeks.[16]

Effect of patient-specific factors

Gender was not associated with the length of the total interval in four studies,[12 26 39 40] however, there was evidence that patient age was a factor. Six studies reported a significantly longer total interval for older teenagers, adolescents or adults compared with younger children or (younger) teenagers (<12 vs ≥12–22 years[1122]; <20 vs ≥20–86 years[26]; <22 vs ≥22 years[27]; 0–14 vs 15–19 vs 20–29 years[40]; <12 versus ≥12 years[11]). Furthermore, Desandes et al found young adults were more at risk for a longer total interval than patients in puberty (15–19 vs 20–24 years; 10.1 vs 21.4 weeks respectively; p=0.04).[35] Lawrenz et al (n=1792) investigated age (mean 30.7 years) as a continuous variable and reported every additional year of age was associated with a 1.3 weeks longer total

3

Table 1 Diagnostic intervals in bone sarcoma

Author; year	Study design, inclusion period and country	Study population	Age (years)	Patient interval in weeks	Primary care interval in weeks	Secondary care interval in weeks	Tertiary care interval in weeks	Diagnostic interval in weeks	Total interval in weeks
Kammerer 2012[8]	Retrospective 1972–2010 Germany	36 osteosarcoma of jaw	33.9 (2-81)*†	15.9 (4.3–103.2)*†	NR	NR	NR	NR	NR
Pan 2010[9]	Retrospective 2003–2008 Malaysia	30 osteosarcoma around the knee joint	17 (9–34)*†	10 (0–49)*†	5*	5 (0–24)*†	2*	NR	17 (4–55)*†
Widhe 2010[10]	Retrospective 1980–2002 Sweden	106 chest wall chondrosarcoma	57*	12.9 (0–507.4)‡†	19.35 (0.43–847.1)‡†	NR	NR	NR	34.4 (4.3–855.7)‡†
Goyal 2004[11]	Retrospective 1990–2002 UK	103 bone sarcoma	15 (4–22)‡†	4.3‡	NR	NR	NR	6.88‡	16.34 (4.3–197.8)‡†
Widhe 2007[13]	Retrospective 1981–2000 Sweden	26 Ewing sarcoma of the rib	16 (6–26)‡†	10.75 (0–43)‡†	12.9 (0–43)‡†	NR	NR	NR	NR
Widhe [12]	Retrospective 1983–1995 Sweden	102 osteosarcoma	15.8 (5.5–29.5)*†	6 (1–26)*†	9 (1–52)*†	NR	NR	NR	15 (2–75)*†
		47 Ewing sarcoma	15.4 (2.5–26.0)*†	15 (1–100)*†	19 (1–72)*†	NR	NR	NR	34 (3–150)*†
Guerra 2006[14]	Retrospective 1985–2001 Brazil	198 osteosarcoma	15.7*	NR	NR	NR	NR	NR	22.6*
		55 Ewing sarcoma	12.8*	NR	NR	NR	NR	NR	34.8*
Brotzmann 2013[15]	Retrospective 1969–2008 Switzerland	32 bone sarcoma of the foot	NR	NR	NR	NR	NR	NR	43‡
		15 chondrosarcoma	NR	NR	NR	NR	NR	NR	32.3‡
		9 osteosarcoma	NR	NR	NR	NR	NR	NR	64.5‡
		8 Ewing sarcoma	NR	NR	NR	NR	NR	NR	77.4‡
Biscaglia 1998[16]	Retrospective 1983–1999 Italy	12 osteosarcomas of the foot	33 (17–64)*†	50%§	NR	NR	NR	NR	120.4 (6–48)*†
Bacci 1999[17]	Retrospective 1979–1997 Italy	618 Ewing sarcoma	NR	13*	NR	NR	4*	4*	18*
Bacci 2000[19]	Retrospective 1983–1999 Italy	965 high-grade osteosarcoma of the extremity	NR	5.2*	NR	NR	NR	4.8*	10.5 (1–59)*†
		810 localised		6.0*	NR	NR	NR	NR	10.7*
		155 metastasized disease		4.1* (p<0.00017)	NR	NR	NR	NR	9.0* (p<0.016)
Bacci 2002[18]	Retrospective 1980–1999 Italy	1071 high-grade osteosarcoma of the extremity	<15: n=501¶ ≥15: n=570¶	NR	NR	NR	NR	NR	NR
		891 localised disease		NR	NR	NR	NR	NR	10.9*
		180 metastasized disease		NR	NR	NR	NR	NR	9.3* (p<0.0002)
Bacci 2007[20]	Retrospective 1983–2006 Italy	888 Ewing sarcoma family tumour	<12: n=160¶ ≥12: n=728¶	NR	NR	NR	NR	NR	75%§

Continued

Table 1 Continued

Author; year	Study design, inclusion period and country	Study population	Age (years)	Patient interval in weeks	Primary care interval in weeks	Secondary care interval in weeks	Tertiary care interval in weeks	Diagnostic interval in weeks	Total interval in weeks
Goedhart 2016[21]	Retrospective 2000–2012 The Netherlands	102 high-grade bone sarcoma	30.0 (5-89)*†	NR	NR	NR	NR	NR	NR
		19 chondrosarcoma		34.9* (p<0.05)	28.2*	7.1* (p<0.05)	5*	NR	98,3*
		29 Ewing sarcoma		5.9*	14.8*	2.3*	3.5*	NR	22.9* (p<0.01)
		54 osteosarcoma		6.4*	8.3*	2.4*	3.8*	NR	23.3* (p<0.01)
Brasme 2014[22]	Prospective 1988–2000 France	436 Ewing sarcoma	12‡	NR	NR	NR	NR	NR	10‡
Kim 2009[23]	Retrospective 1985–2005 Korea	26 osteosarcoma and doctor delay >45 days	30.2 (4–67)*†	NR	NR	NR	NR	45.2*	NR
Simpson 2005[24]	Retrospective 1965–2005 Scotland	19 Ewing sarcoma of upper limb	19 (3–57)*†	25.8 (4.3–774)‡†	NR	NR	NR	5 (1–128)‡†	35 ‡
Wurtz 1999[25]	Retrospective 1975–1995 USA	68 bone sarcoma of pelvic girdle	41 (8–82)‡†	NR	NR	NR	NR	NR	43³ 25.8 (4.3–206.4)‡†
Sneppen 1984[26]	Retrospective 1962–1979 Denmark	84 osteosarcoma	28 (8–86)*†	6.9*	NR	NR	NR	7.3*	27.5 (8.6–154.8)*†
		40 Ewing sarcoma	17 (2–62)*†	6.5*	NR	NR		32.3*	41.3 (4–206.4)*†
Nandra 2015[27]	Retrospective 1985–2010 UK	2360 bone sarcomas	22‡	NR	NR	NR	NR	NR	16 ‡
Vadillo 2011[28]	Retrospective 1952–2007 Peru	135 bone sarcomas of the jaw	31 (1–80)*†	13*	19.7*	NR	17.4*	NR	50.1*
Ashwood 2003[29]	Prospective 1997–1998 UK	100 tumour service	36.3*	63.6 (0–111.8)*†	NR	NR	NR	58 (2,3–516)*†	NR
		49 malignant disease: 47 sarcoma	NR	32.7 (2.2–47.3)*†	32.3 (0–55.9)*†	NR	NR	NR	NR
George 2012[30]	Retrospective 2011 UK	107 sarcoma of which	≥18*	4.3‡	NR	NR	NR	13.7‡	NR
		41 bone sarcoma		6.5 (0–309‖)‡†	16.8 (1.5–211.6)‡†	NR	NR	NR	NR
Martin 2007[31]	Retrospective 2001–2003 USA	235 patients;	22.2 (15–29)*†	NR	NR	NR	NR	NR	10.7*
		66 with sarcoma		NR	NR	NR	NR	NR	20.3*
		30 bone sarcoma		NR	NR	NR	NR	NR	15.7*
Smith 2011[32]	Prospective 1985–2009 UK	2568 bone sarcomas	25‡	NR	NR	NR	NR	NR	16‡
Grimer 2006[33]	Prospective 1986–2006 UK	1460 bone sarcoma	NR	NR	NR	NR	NR	NR	16‡
Lawrenz 2018[41]	Retrospective 1990–2014 UK	bone sarcoma: 1446 non-metastatic 346 metastatic	30.7*	NR	NR	NR	NR	NR	16‡ 45.8* vs 29.9*

Continued

Table 1 Continued

Author; year	Study design, inclusion period and country	Study population	Age (years)	Patient interval in weeks	Primary care interval in weeks	Secondary care interval in weeks	Tertiary care interval in weeks	Diagnostic interval in weeks	Total interval in weeks
Balmant 2018[40]	Retrospective 2007–2011 Brazil	1257 osteosarcoma and Ewing sarcoma	0–29¶	NR	NR	NR	NR	NR	NR
			0–14¶ (46%)	NR	NR	NR	NR	1.1‡	NR
			15–19¶ (33%)	NR	NR	NR	NR	1.3‡	NR
			20–29¶ (21%)	NR	NR	NR	NR	1.9‡	NR
Bielack 2002[39]	Retrospective 1980–1998 German/Austrian/Swiss	1702 high-grade osteosarcomas	16.7†	NR	NR	NR	NR	9.9‡	NR
Chen 2017[34]	Retrospective 2004–2012 USA	364 malignancies of which 30 bone sarcoma	16.5‡	NR	NR	NR	NR	NR	12.4‡
Desandes 2018[35]	Retrospective 2012–2013 France	993 malignancies of which 48 bone sarcoma	NR	NR	NR	NR	NR	NR	NR
			15–19 (n=33)¶	NR	NR	NR	NR	NR	10.1‡
			20–24 (n=15)¶	NR	NR	NR	NR	NR	21.4‡
Petrilli 2006[36]	Prospective 1987–1996 Brazil	209 high-grade osteosarcomas	14 (2.4–24.5)*†	NR	NR	NR	NR	NR	18.4*
Yang 2009[37]	Retrospective 1994–2005 Hong Kong	51 osteosarcoma	13 (3–20)‡†	4.3 (0–51.4)‡†	NR	NR	NR	3 (0–50)‡†	8.7 (0–51.6)‡†
Younger 2018[38]	Retrospective 2015 UK	558 sarcoma of which 140 bone sarcoma	64.1 (18–96)*†	56.7%§	NR	NR	NR	NR	NR

*Mean.
†Range within brackets.
‡Median.
§% of delays attributed to this interval.
¶Included age group.
NR, not reported.

interval (p<0.00).[41] In contrast Guerra *et al* (n=253) found no significant relationship between age (range 0–30 years) and the length of the total interval.[14] Younger *et al* found no relationship between age and patient interval nor diagnostic interval.[38]

The presenting symptom did not predict the length of the total interval in four studies.[12 13 22 26] Study results (n=4) on the influence of pain symptoms on the total interval are contradictory, with some studies suggesting a shortening of the interval, no influence or even a longer total interval.[12 13 22 26]

Effect of healthcare system-related factors

The influence of the year of first presentation was studied in five studies. None showed evidence of shortening total intervals over the past 30–50 years,[10 14 22 26 41] despite advances in healthcare models including the introduction of cancer pathways and dedicated specialist sarcoma centres.

The location of first presentation to a healthcare professional was investigated among patients with Ewing sarcoma. The diagnostic interval was significantly longer when presenting to a general practitioner (GP) compared with the accident & emergency department (p=0.04).[11]

The influence of radiology and pathology investigations on the diagnostic interval were reported in two studies.[10 12] When no imaging studies were ordered at the patient's first contact with a healthcare professional, a longer diagnostic interval was observed. When imaging was incorrectly interpreted as normal, which was the case in 35% of patients with chondrosarcoma at non-specialist centres, this resulted in an even longer diagnostic interval (21 vs 9.5 months). At non-specialist centres, only 26% (n=39) of chondrosarcomas biopsied were correctly diagnosed as malignant, while at specialist sarcoma centres, 94% (n=34) were correctly diagnosed.[10] A descriptive study by Ashwood *et al* highlighted how imaging studies performed prior to referral to a specialist centre often had to be repeated because they did not provide all the required information, and biopsies or surgeries performed by the referring teams often complicated the patient's subsequent management.[29]

A qualitative study in Malaysia by Pan *et al* (n=30) demonstrated the multifactorial nature of diagnostic delay, which was dependent on the patient perception of symptoms and complaints, the influence of traditional healers and the proximity of health clinics.[9] A Brazilian study with 1257 BS patients found differences in diagnostic intervals between geographic regions, possibly explained by the availability of CT scan equipment and the difference in number of hospital beds per region.[40]

Relationship between total interval and outcomes

The influence of delay on clinical outcomes of BS patients has been investigated in 20 of the 34 included BS studies (table 2).[10 11 15 17–25 27 28 31 33 36 37 39 41]

In 12 of these studies (n=7414), no significant association between length of the total interval (mean total interval between 8.7 and 50.1 weeks) and overall survival was found.[11 15 19 21 22 25 27 28 33 36 37 39] However, one of these studies (n=1702) found that patients with a longer total interval more often had metastatic disease at diagnosis than those with a short total interval.[39]

One study of 965 high-grade osteosarcomas of the extremities diagnosed between 1983 and 1999, identified an inverse relationship between the total interval and the stage of disease[19]; the patient interval was significantly shorter in patients with metastatic disease compared with patients with localised disease (4.1 vs 6.0 weeks), ultimately resulting in a shorter total interval (9.0 vs 10.7 weeks). The total interval was significantly shorter in patients who later relapsed than in patients who remained free of disease after 5 years. However, this difference lost significance when patients were analysed according to disease stage at presentation. In a secondary analysis of this patient population, including patients diagnosed between 1980 and 1983 (n=1071),[18] patients with a diagnostic interval <2 months were significantly more likely to have metastases at diagnosis than those with a longer interval (56.1% vs 45.2%; p<0.0009).

Two other studies by the same research group in patients with Ewing sarcoma and Ewing sarcoma family of tumours (ESFT), both demonstrated that a diagnostic interval <2 months was associated with an increased likelihood of metastases at diagnosis (table 2),[17 20] impact on overall survival was not reported.

A study with 1792 BS patients showed that a longer duration of symptoms was associated with longer survival (HR 0.996, 95% CI 0.994 to 0.998).[41] This continuous association was lost when patients were compared in categories (<or >4 months; HR 0.935 95% CI 0.743 to 1.177).

In contrast, four studies with a combined number of 386 patients with chondrosarcoma, osteosarcoma and Ewing sarcoma, and mean total intervals between 10.7 and 35 weeks, reported a negative impact of a long total interval on stage and survival.[10 23 24 31]

No study has reported on the association between length of the total interval on patient-reported outcomes including HRQoL.

Soft tissue sarcoma

Length of total interval

Thirty-six studies investigated the total interval for STS (table 3).[27 30–35 38 42–69] A combined total of 16 845 patients were included and, reflecting STS heterogeneity, the total interval varied tremendously; between 4.3 and 614.9 weeks.

Components of the total interval

Eleven studies examined the length of one or more components of the total interval.[30 38 44 47 50–52 54 58 59 63] Patient intervals varied between a median of 1.3–17.2 weeks, the primary care interval lasted 0.1–13.3 weeks, the secondary care interval varied between 1.1 and 6.9 weeks and the tertiary care interval was 2.1–7.9 weeks.

Table 2 The effect of diagnostic interval on stage or metastases at diagnosis, or overall survival (OS) for bone sarcomas

Author; year	Study design, inclusion period and country	Study population	Age (years)	Total interval in weeks	Stage of disease or metastases at diagnosis	OS
Widhe 2010[10]	Retrospective 1980–2002 Sweden	106 chest wall chondrosarcoma	57*	34.4 (4.3–855.7)†‡	NR	Patients who died from chondrosarcoma had interval >8 months (p<0.05)
Goyal 2004[11]	Retrospective 1990–2002 UK	103 bone sarcoma	15 (4–22)†‡	16.34 (4.3–197.8)†‡	NR	No association
Brotzmann 2013[15]	Retrospective 1969–2008 Switzerland	32 bone sarcoma of the foot	NR	43†	No association	No association
Bacci 1999[17]	Retrospective 1979–1997 Italy	618 Ewing sarcoma	NR	18 ‡	Stage: no association Interval <2 months, more metastases (32 vs 12% p<0.0001)	
Bacci 2000[19]	Retrospective 1983–1999 Italy	965 high-grade osteosarcoma extremity	NR	10.5 (1–59)*‡	NR	No association
Bacci 2002[18]	Retrospective 1980–1999 Italy	High-grade osteosarcoma extremity 891 localised disease 180 metastasized disease	<15: n=501§ ≥15: n=570§	10.9* 9.3* (p<0.0002)	45.2% diagnostic interval <2 months 56.1% diagnostic interval <2 months (p<0.0009)	NR
Bacci 2007[20]	Retrospective 1983–2006 Italy	888 Ewing sarcoma family tumour	<12: n=160§ ≥12: n=728§	<2 months: n=215§ ≥2 months: n=658§	35.5% metastatic disease 15.9% metastatic disease (p<0.0001)	NR NR
Goedhart 2016[21]	Retrospective 2000–2012 The Netherlands	19 chondrosarcoma 29 Ewing sarcoma 54 osteosarcoma	30.0 (5–89)*‡	98.3* 22.9* (p<0.01) 23.3* (p<0.01)	**Metastatic disease** 10.5% 37.9% 24.1%	**5 years OS** 60.9% 49% 67%
Brasme 2014[22]	Prospective 1988–2000 France	436 Ewing sarcoma	12†	10†	No association	No association
Kim 2009[23]	Retrospective 1985–2005 Korea	26 osteosarcoma and doctor delays >45 days	30.2 (4–67)*‡	NR	NR	**5 years OS: 26% 10 years OS: 10%**
Simpson 2005[24]	Retrospective 1965–2005 Scotland	19 Ewing sarcoma of upper limb	19 (3–57)*‡	35†	A higher Enneking stage resulted in greater mortality (p=0.02)	NR
Wurtz 1999[25]	Retrospective 1975–1995 USA	68 bone sarcoma of pelvic girdle	41 (8–82)*‡	43‡	No association	No association

Continued

Table 2 Continued

Author; year	Study design, inclusion period and country	Study population	Age (years)	Total interval in weeks	Stage of disease or metastases at diagnosis	OS
Nandra 2015[27]	Retrospective 1985–2010 UK	2668 bone sarcoma	22†	16†	No association	No association
Vadillo 2011[28]	Retrospective 1952–2007 Peru	135 bone sarcoma of the jaw	31 (1–80)*‡	50.1*	NR	No association
Martin 2007[31]	Retrospective 2001–2003 USA	30 bone sarcoma	22.2 (15–29)*‡	15.7*	Osteosarcoma: diagnostic interval 259 days longer for patients with advanced stage disease than those with localised disease (p<0.01)	NR
Grimer 2006[33]	Prospective 1986–2006 UK	1460 bone sarcoma	NR	16†	NR	No association
Lawrenz 2018[41]	Retrospective 1990–2014 UK	Bone sarcoma 1446 non-metastatic 346 metastatic	30.7*	16† 45.8* vs 29.9*	No association P=0.009	Non-metastatic cohort: longer interval, better survival (HR 0.996). No association >or < 4 months.
Bielack 2002[39]	Retrospective 1980–1998 German/Austrian/Swiss	1702 high grade osteosarcoma	16.7*	9.9†	Longer diagnostic interval: more primary metastases (p=0.007)	No association
Petrilli 2006[36]	Prospective 1987–1996 Brazil	209 high grade osteosarcoma	14 (2.4–24.5)*‡	18.4*	No association	No association
Yang 2009[37]	Retrospective 1994–2005 Hong Kong	51 osteosarcoma	13 (3–20)†‡	8.7 (0–51.6)†‡	No association	No association

*Mean.
†Median.
‡Range within brackets.
§Included group.

Table 3 Length of diagnostic intervals for STS

Author; year	Study design, time period and country	Study population	Age (years)	Patient interval (weeks)	Primary care interval (weeks)	Secondary care interval (weeks)	Tertiary care interval (weeks)	Diagnostic interval (weeks)	Total interval (weeks)
Gofman 2007[61]	Retrospective 1991–2004 Israel	73 synovial sarcoma	38 (8–82)*†	NR	NR	NR	NR	NR	77.4 (8.6–202.1)*†
Amant 2003[62]	Retrospective 1990–2002 Belgium	6 endometrial stromal sarcoma	34*	NR	NR	NR	NR	NR	614.9 (103.2–1754.4)*†
Nakamura 2011[63]	Retrospective 2001–2009 Japan	100 STS, referred for additional resection	57 (0–89)‡*	12.9 (4.3–309.6)*†	NR	NR	NR	15%§	25.8 (4–310)*†
Pawlik 2003[64]	Retrospective 1975–2002 USA	29 angiosarcoma of the scalp	71*	NR	NR	NR	NR	NR	21.9 (0–73.5)*†
Rougraff 2012[65]	Retrospective 1992–2007 USA	381 grade 3 STS of extremity or flank	NR	NR	NR	NR	NR	NR	66.6‡ 20*
Rougraff 2006[69]	Retrospective 1992–2003 USA	624 sarcoma: 382 soft-tissue sarcoma / 278 high-grade STS / 104 low-grade STS	NR	NR	NR	NR	NR	NR	73.3 (0.25–362.8)‡‡ 127.4 (0.25–256)‡‡†
Singla 2014[66]	Retrospective 1990–2011 USA	72 angiosarcoma	65 (19–93)*†	NR	NR	NR	NR	NR	0–154.8† 41%§
Ferrari 2010[67]	Retrospective 1977–2005 Italy	575 STS	≤21¶	NR	NR	NR	NR	NR	8.6 (1–258)*†
Pratt 1978[42]	Retrospective 1962–1976 USA	46 rhabdomyosarcoma of head or neck	5.9 (0.3–20.5)*†	NR	NR	NR	NR	NR	4.3–19.3*
Bandyopadhyay 2016[43]	Retrospective 1991–2010 USA	391 primary pulmonary artery sarcoma	52 (14–94)*†	NR	NR	NR	NR	NR	14.3*
Brouns 2003[44]	Retrospective 1999–2001 Belgium	100 STS	50.5 (3–88)*†	17.2 (8.6–1032)*†	NR	NR	NR	25.8 (8.6–339.7)*†	NR
Chandu 2003[45]	Retrospective 1955–1999 Scotland	109 STS	33.4 (10–77)‡‡	NR	NR	NR	NR	86‡	NR
Clark 2005[46]	Prospective 2003–2004 UK	31 STS with referral >3 months (19.5%)	59 (34–84)‡‡	NR	NR	NR	NR	94.6 (17.2–412.8)‡‡	NR
Johnson 2008[47]	Prospective/recall 2005 UK	162 STS	53 (16–88)‡‡	1.3* 28.6‡	2.4*	6.9*	NR	25.0* 83.1‡	40.4* 112.3‡
Lawrence 1986[48]	Retrospective 1977–1978 and 1983–1984	2355 STS and 3457 STS	>18¶	NR	NR	NR	NR	4.3*	17.2*
Park 2010[49]	Retrospective 1997–2008 Korea	18 grade 3 STS of the extremity with delay >1 year	44.8 (15–79)‡‡	NR	NR	NR	NR	NR	(51.6–154.8)†
Seinen 2010[50]	Retrospective 2003–2009 Sweden	33 retroperitoneal sarcoma (1 GIST)	66 (21–86)‡‡	3.3 (0–73.1)*†	2.1 (0–34.9)*†	5.1 (0.3–160)*†	1.1 (0.1–69)*†	13.4 (4.3–172)*†	NR
Bruun 1976[51]	Retrospective 1962–1974 Denmark	7 oral sarcoma	29 (10–81)‡‡	6.9‡	NR	NR	NR	15.9‡	NR
Cooper 1996[52]	Retrospective 1984–1993 Ireland	18 STS interval >4 weeks	43 (2–89)*†	36%§	23%§	11%§	NR	28*	NR

Continued

Table 3 Continued

Author; year	Study design, time period and country	Study population	Age (years)	Patient interval (weeks)	Primary care interval (weeks)	Secondary care interval (weeks)	Tertiary care interval (weeks)	Diagnostic interval (weeks)	Total interval (weeks)
Antillon 2008[53]	Retrospective 2000–2007 Guatemala	47 rhabdo-myosarcoma / 33 non-rhabdo-myosarcoma	6 (1–17)*† / 11 (2–17)*†	NR	NR	NR	NR	NR	8.6 (2–51.6)*† / 25.8 (3–154.8)*†
Chotel 2008[54]	Retrospective 1985–2006 UK	33 synovial sarcoma	12.3 (3–16)‡‡	43 (0–156)‡‡	NR	NR	NR	50 (0–362)‡†	98 (2–364)‡†
Durve 2004[55]	Retrospective 1980–2000 UK	14 rhabdo-myosarcoma of ear and temporal bone	4.5 (1.0–8.6)‡‡	NR	NR	NR	NR	NR	21 (4–78)‡‡
Watson 1994[56]	Retrospective 1985–1992 Australia	40 STS of extremity	59 (14–87)*†	NR	NR	NR	NR	NR	16 weeks (2–104)*†
Monnier 2006[57]	Retrospective 1982–2002 France	66 dermatofibrosarcoma protuberans	43 (8–81)‡‡	NR	NR	NR	NR	NR	520.1 (8.3–2115.6)‡†
Dyrop 2013[60]	Retrospective 2007–2010 Denmark	258 STS	NR	NR	NR	NR	2007: 4* 2010: 2.6*	NR	NR
Buvarp Dyrop/ 2016[59]	Retrospective 2014–2015 Denmark	545 referred patients of which: 102 sarcoma patients (88 soft tissue 14 bone)	55 (0–93)*‡	NR / 11*	NR / 2.4*	NR / 4.1*	NR / 2.4*	NR	NR / 25.1*
George 2012[30]	Retrospective 2011 UK	66 STS	≥18¶	4.3 (0–516)*‡	13.3 (1.7–154.8)*‡	NR	NR	NR	NR
Martin 2007[31]	Retrospective 2001–2003 USA	38 STS	22.2 (15–29)‡‡	NR	NR	NR	NR	NR	24.9‡
Smith 2011[32]	Prospective 1985–2009 UK	2366 STS	57*	NR	NR	NR	NR	NR	26*
Grimer 2006[33]	Prospective 1986–2006 UK	1460 STS	NR	NR	NR	NR	NR	NR	26*
Chen 2017[34]	Retrospective 2004–2012 USA	364 malignancies of which 18 STS	14*	NR	NR	NR	NR	NR	7.2*
Nandra 2015[27]	Retrospective 1985–2010 UK	2277 STS	57*	NR	NR	NR	NR	NR	26*
Desandes 2018[35]	Retrospective 2012–2013 France	993 malignancies of which 43 STS	NR / 15–19† / 20–24†	NR	NR	NR	NR	NR	22.9[a] / 15.4* / 48.7*
Smolle 2019[68]	Retrospective 1982–2014 UK	248 synovial sarcomas	37† / <16¶ / ≥16¶	NR	NR	NR	NR	NR	52* / 49.8* / 52*
Younger/ 2018[38]	Retrospective 2015 UK	558 sarcoma of which 418 STS	64.1 (18–96)‡‡	46.8%§	NR	NR	NR	NR	NR

Continued

Author; year	Study design, time period and country	Study population	Age (years)	Patient interval (weeks)	Primary care interval (weeks)	Secondary care interval (weeks)	Tertiary care interval (weeks)	Diagnostic interval (weeks)	Total interval (weeks)

Table 3 Continued

*Median.
†Range within brackets.
‡Mean.
§Included age group.
¶% of delays attributed to this interval.
GIST, gastrointestinal stromal tumour; STS, soft tissue sarcomas.

Effect of tumour-specific factors

Three studies found no relationship between tumour size and length of the total interval,[27 54 69] one study (n=575) in children and adolescents found that larger tumours were associated with a longer total interval (both for tumours <5 vs ≥5 cm and <10 vs ≥10 cm),[67] while a study in adults (n=162) reported that smaller tumours (median 8 cm) were associated with a longer total interval.[47]

Five studies reporting on the influence of tumour localisation have yielded contradictory results. Chotel *et al* (n=33) reported that synovial sarcoma of the knee or elbow had a longer total interval than tumours at other sites[54] and Smolle *et al* found synovial sarcomas located superficially had a longer interval than deeply located tumours (n=248; 2 years vs 12 months).[68] However, two other studies found no relationship between tumour site and total interval.[47 69] In children and adolescents, Ferrari *et al* (n=575) reported a longer total interval for STS of the extremities compared with tumours at other sites[67]; the authors attributed this difference to the underlying tumour histology, which for extremity tumours was more likely to consist of non-rhabdomyosarcomas and thus to encompass a broad spectrum of tumour biologies including low-grade STS. There are limited data specifically exploring the relationship between tumour histology and total interval, but Nandra *et al* (n=2 277) identifed that low-grade sarcomas were associated with a longer total interval.[27]

Effect of patient-specific factors

Patient gender, level of education and measures of social deprivation were not associated with length of total interval.[47 67] The effect of patient age was examined in five studies. Ferrari *et al* (n=575) established that children over 10 years old had a longer total interval than those younger than 10 years old.[67] Desandes *et al* (n=43) found the same result when comparing age groups 15–19 vs 20–24 years (15.4 vs 48.7 weeks; p=0.04).[35] Smolle *et al* found no difference for patients with synovial sarcoma older or younger than 16 years old.[68] A large retrospective study of almost 5000 sarcoma patients found no difference in total interval in patients older and younger than the median study age of 57 years.[27] A Sarcoma UK survey (n=558) established no association between age and patient interval or total interval.[38]

Two studies in children examined the effect of presenting symptoms on the total interval. The first (n=575) found no significant difference in the length of total interval between patients presenting with a swelling or with a specific symptom (eg, urethral obstruction).[67] The second in 33 patients with synovial sarcoma found the presence of a lump led to a shorter doctor interval, while a periarticular location or presence of a joint contracture led to both a longer patient and a longer doctor interval.[54]

Effect of healthcare system-related factors

The influence of the year of first presentation was studied in two publications, which did not find an improvement in total interval over the past 30–40 years.[54 67]

In a study of 162 STS patients surveyed in 2005, the median patient interval was just 1.3 weeks, while the median primary care interval was 25.0 weeks[47]; if patients were reassured by the first medical professional they consulted (eg, their GP), it took twice as long to be referred on to an appropriate specialist centre.

Another single centre study of 545 patients with suspected sarcoma referred to a specialist clinic in Denmark reported a median total interval of 25.1 weeks[59]; 102 patients (19%) had a sarcoma (88 soft tissue, 14 BS), 68 patients (12%) had another malignancy.[58] Patients referred to the centre with prior investigations in their local hospital had a longer total interval than those with investigations in the sarcoma centre (median 13.3 vs 23.7 weeks). Synovial sarcoma patients with an unplanned resection had a longer diagnostic interval than those referred directly to a sarcoma centre (24 vs 12 months; p=0.001).[68]

Relationship between total interval and patient outcomes

The influence of the length of total interval on clinical outcomes in STS patients has been reported in 10 retrospective studies (table 4).[27 43 54 61–63 65 67–69]

Five of these studies observed no effect on survival.[54 61 65 68 69] One study (n=2 277) reported that patients with STS treated between 1985 and 2010 with a longer total interval (26 vs 20 weeks) had a significantly improved survival rate, even when stratified by disease stage.[27] This pattern was consistent for all histological subtypes apart from rhabdomyosarcoma where survival was significantly better with a short total interval (n=34, 16 vs 52 weeks total interval). Furthermore, patients undergoing unplanned resections prior to specialist referral had a lower 1-year mortality rate than patients referred directly. These patients tended to have small, superficial, low-grade tumours, which are associated with a better prognosis.

Three studies reported that patients with a shorter total interval had improved overall survival rates.[43 63 67] Ferrari et al analysed the risk of death for 575 children at different time intervals and found worse survival with increased diagnostic interval and with diagnostic intervals <1 month vs 1–3 months (HR 1.4 (95% CI 0.7 to 2.6)) and <1 month vs >12 months (HR 3.6 (95% CI 1.7 to 8.0)), respectively.[67] Bandyopadhyay et al (n=391) reported that the odds of death increased by 46% for every doubling of the diagnostic interval.[43]

No study has investigated the influence of the length of the total interval on patient-reported outcomes.

DISCUSSION

To the best of our knowledge, there is no published systematic review on the sarcoma total diagnostic interval.

Analysis of the length of the total interval is complex, as it is influenced by many different factors. In sarcomas, assessment of the total interval is further challenged by the heterogeneity of the disease, the rarity of the group and the presence of 70+ subtypes.

Focusing on the patient interval, it might be anticipated that patients who consult a doctor early have a reason for doing so (eg, worrying, severe symptoms or evidence of rapid progression), which would result in a quicker referral for investigation and a shorter diagnostic interval[16 21] and vice versa.[12 13 26 54] However, some aspecific symptoms such as pain have given contradictory results.[22 26]

Both patient and doctor intervals might be influenced by the biological behaviour of the sarcoma. The usually indolent chondrosarcomas had a longer total interval than the more aggressive osteo and Ewing sarcomas,[12 14 21 26] and non-rhabdomyosarcoma STS had a longer total interval than rhabdomyosarcomas or soft tissue ESFT.[67]

Furthermore, tumour location influences the length of the total interval, with atypical tumour presentations increasing the difficulties in diagnosis and prolonging the diagnostic interval.

There are two main findings from studies of the primary and secondary care intervals. First, if at initial presentation the assessing clinician is falsely reassured or makes an incorrect diagnosis, the diagnostic interval is severely prolonged.[47 62] Second, patients undergoing an unplanned resection prior to referral to a specialist centre have a lower 1-year mortality rate than those referred directly to a specialist centre.[27] This finding may be due to selection bias, as patients undergoing unplanned resections have smaller, superficial and lower grade tumours, which are known factors associated with a better prognosis.

The influence of the length of the total interval on clinical outcomes remains unclear. It might be predicted that sarcomas with more aggressive behaviour have a shorter total interval and worse survival outcomes, while sarcomas with indolent behaviour have a longer total interval and improved survival. Alternatively, it may be expected that shorter total intervals lead to earlier treatment and better outcomes. For STS, we found conflicting results, which is not surprising with over 70 histological subtypes with different clinical behaviours. Most BS studies from our review not report an association between length of total interval and survival as well. Researchers have argued that this lack of an association, often referred to as the 'waiting-time paradox', may be due to the fact that the studies have not been able to adjust for the aggressiveness of the tumour.

To date, the influence of total interval on morbidity, HRQoL and other patient-reported outcomes has not been assessed. Based on the available literature in other malignancies, improving the total interval will likely influence the level of patient satisfaction, fear and morbidity. The importance of these outcomes is demonstrated by Mesko et al who studied factors most commonly causing

Table 4 The influence of length of the total interval on outcomes for STS

Ref.	Study design, time period and country	Study population	Age (years)	Total interval (weeks)	Influence on stage or metastases at diagnosis	Influence on survival
Gofman et al 2007[61]	Retrospective 1991–2004 Israel	73 synovial sarcoma	38 (8–82)*†	77.4 (8.6–202.1)*†	NR	Total interval ≤1 year resulted in better systemic control (HR 0.3; p=0.037). No effect on overall survival.
Amant et al 2003[62]	Retrospective 1990–2002 Belgium	15 endometrial stromal sarcoma; 6 (40%) diagnosis initially missed	34‡	NR; 614.9 (103.2–1754.4)‡†	Stage 4 disease in 5/6 with missed diagnosis, compared with 1/9 in correct diagnosis group. No data on diagnostic interval in the latter group.	NR
Nakamura et al 2011[63]	Retrospective 2001–2009 Japan	100 STS, referred for additional resection	57 (0–89)‡†	25.843–17)*‡; >6 months: n=43§; ≤6 months: n=57§	NR; 12/43 metastases vs; 6/51 metastases (p=0.048)	5 years survival: 54.4% (66.8% without metastases, 5.9% with metastases); 59.7% (34 patients without metastases) (p=0.04); 77% (48 patients without metastases)
Rougraff et al 2012[65]	Retrospective 1992–2007 USA	381 grade 3 STS of extremity or flank	NR	66.6 20‡*	No association	No association
Rougraff et al 2007[69]	Retrospective 1992–2003 USA	624 sarcoma: 382 soft tissue sarcoma; 278 high-grade STS; 104 low-grade STS	NR	NR; 73.3 (0.25–362.8)‡†; 127.4 (0.25–256)‡†	No association	No association
Ferrari et al 2010[67]	Retrospective 1977–2005 Italy	575 STS	≤21§	8.6 (1–258)*†	No association	Risk of death increased the longer the diagnostic interval (p=0.002)
Bandyopadhyay et al 2016[43]	Retrospective 1991–2010 USA	391 primary pulmonary artery sarcoma	52 (14–94)*†	14.3*	NR	For every doubling diagnostic interval, the odds of death increased by 46% (p<0.001)
Chotel et al 2008[54]	Retrospective 1985–2006 UK	33 synovial sarcoma	12.3 (3–16)‡†	98 (2–364)‡†	NR	No association
Nandra et al 2015[27]	Retrospective 1985–2010 UK	2277 STS	57*	NR	No association	1-year mortality (13%), survivors longer total interval (20 vs 26 weeks)
Smolle et al 2019[68]	Retrospective 1982–2014 UK	248 synovial sarcomas	37‡; <16§; ≥16§	52*; 49.8*; 52*	NR	No association (<1 year versus >1year)

Continued

Table 4 Continued

Ref.	Study design, time period and country	Study population	Age (years)	Total interval (weeks)	Influence on stage or metastases at diagnosis	Influence on survival

*Median.
†Range within brackets.
‡Mean.
§Included group of patients.
STS, soft tissue sarcomas.

litigation in sarcoma cases in the USA.[70] In 81% of cases, a delay in diagnosis was part of the complaint, a further 7% were about misdiagnosis and 11% about unnecessary amputation. Primary care doctors and orthopaedic specialists were most common defendants in delay in diagnosis cases.

In neither BS or STS did our review identify a clear cut-off point for appropriate versus inappropriate length of total interval or its components. Apart from the contradictory results in terms of influence of the length of the interval on survival, several other factors make it difficult to draw firm conclusions. First, the design of most studies was retrospective, increasing the chance of recall bias with regard to self-reported outcomes such as dates of first symptoms. Second, many studies included a small number of heterogeneous patients, which made them unsuitable for subtype analysis. Although we excluded case reports, we included case series because they reflect the sort of research that has been done in this area, and show how heterogeneous the population is. Third, the inclusion criteria of studies differed; some studies only considered those patients who reported a diagnostic delay, which made it impossible to compare this group to the entire sarcoma population. Furthermore, diagnostic delay was defined differently throughout the literature. One of the limitations of this review is that we had to work with these different definitions,which made comparisons difficult. We propose for future reports that the date of pathological diagnosis is used as the endpoint of the diagnostic interval. Furthermore, studies included in this review were conducted over the past 50 years. During this period, radiological and histological diagnostic techniques have evolved, treatment options have improved, and, in some countries, diagnostic pathways with referrals of suspected lumps to centralised sarcoma services have developed, which may have influenced our results.

Centralised sarcoma care may improve diagnostic pathways and there is an increasing number of (inter) national guidelines for the diagnosis and management of sarcomas.[71–74] Centralising care at sarcoma centres with a multidisciplinary team improves the diagnostic interval because patients (1) do not lose time at local hospitals, (2) receive appropriate imaging for tumour staging and (3) get a higher rate of correct preoperative pathologic diagnosis.[10 12 29 30 50 58 75–79] Improvement of these factors decrease tumour size and stage at diagnosis, resulting in an increase of the quality of surgery and improvement of survival outcomes in several of these studies.[60 75 77–80] Best practices of different countries could be integrated to develop the optimal diagnostic pathway. In order for such guidelines to be successfully implemented, one needs strong political support with continuous attention to raise awareness and optimise the system by following a quality and control cycle.[60]

CONCLUSION

This review confirms the complexity of the total interval to sarcoma diagnosis. Published studies give contradictory results in terms of determinants for a long total interval as well as its influence on outcomes. The impact of a long interval on HRQoL has not been studied. To present a clinically relevant cut-off point that discriminates between a short or long interval is thus impossible. Such a cut-off point, which can differ between histological subtypes, is necessary to make guidelines more evidence based, help to guide patients and support the sarcoma diagnostic process. Furthermore, to improve care we need to understand the impact of the total interval on HRQoL of patients diagnosed with a sarcoma. Future research should include relevant outcomes for patients, as well as focus on areas where a change in management could make a difference, such as in increased public awareness, education of primary and secondary healthcare providers and improved access to specialist centres.

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