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.

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. 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.

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). 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). 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. 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.
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 al57 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 2.5–7.1 weeks) and tertiary care intervals (mean 2–17.4 weeks) were measured in two and three studies respectively (table 1).
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 20 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 component12 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 years11 22; <20 vs ≥20–86 years36; <22 vs ≥22 years27; 0–14 vs 15–19 vs 20–29 years40; <12 versus ≥12 years11). 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 interval.41
| 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 | 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 | 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 | 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 | 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 | 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)*† |
| Guerra 2006 | Retrospective 1985–2001 Brazil | 198 osteosarcoma | 15.7* | NR | NR | NR | NR | NR | 22.6* |
| Brotzmann 2013 | Retrospective 1969–2008 Switzerland | 32 bone sarcoma of the foot | NR | NR | NR | NR | NR | NR | 43* |
| Bacci 1999 | Retrospective 1979–1997 Italy | 618 Ewing sarcoma | NR | 13* | NR | NR | NR | NR | 120.4 (6–48)*† |
| Bacci 2000 | Retrospective 1983–1999 Italy | 965 high-grade osteosarcoma of the extremity | NR | 5.2* | NR | NR | NR | 4.8* | 10.5 (1–59)*† |
| Bacci 2002 | Retrospective 1980–1999 Italy | 1071 high-grade osteosarcoma of the extremity | <15: n=501¶ ≥15: n=570¶ | NR | NR | NR | NR | 10.7* | 9.0* (p<0.016) |
| Bacci 2007 | Retrospective 1983–2006 Italy | 888 Ewing sarcoma family tumour | <12: n=160¶ ≥12: n=728¶ | NR | NR | NR | NR | NR | 75%§ |

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 | Retrospective 2000–2012 The Netherlands | 102 high-grade bone sarcoma | 30.0 (5–89)† | NR | NR | NR | NR | NR | NR |
| Brasme 2014 | Prospective 1988–2000 France | 436 Ewing sarcoma | 12‡ | NR | NR | NR | NR | NR | 10‡ |
| Kim 2009 | Retrospective 1985–2005 Korea | 26 osteosarcoma and doctor delay >45 days | 30.2 (4–67)† | NR | NR | NR | NR | NR | 45.2‡ |
| Simpson 2005 | Retrospective 1965–2005 Scotland | 40 Ewing sarcoma of upper limb | 19 (3–57)† | 25.8 (4.3–774)‡† | NR | NR | NR | NR | 35‡ |
| Wurtz 1999 | Retrospective 1975–1995 USA | 68 bone sarcoma of pelvic girdle | 41 (5–82)† | NR | NR | NR | NR | NR | 43 (25.8 (4.3–206.4)† |
| Sneppen 1984 | Retrospective 1962–1979 Denmark | 84 osteosarcoma | 28 (8–86)† | 6.9* | NR | NR | NR | 7.3* | 27.5 (8.6–154.8)† |
| Nandra 2015 | Retrospective 1985–2010 UK | 2360 bone sarcomas | 22‡ | NR | NR | NR | NR | NR | 16‡ |
| Vadillo 2011 | Retrospective 1952–2007 Peru | 135 bone sarcomas of the jaw | 31 (1–80)† | 13* | 19.7* | NR | NR | NR | 50.1* |
| Ashwood 2003 | Prospective 1997–1998 UK | 100 tumour service | 36.3* | 63.6 (0–111.8)† | NR | NR | NR | NR | 58 (2.3–516)*† |
| George 2012 | Retrospective 2011 UK | 107 sarcoma of which: 47 sarcoma | 32.1 (2.2–47.3)† | 32.3 (0–55.9)† | NR | NR | NR | NR | NR |
| Martin 2007 | Retrospective 2001–2003 USA | 235 patients; 66 with sarcoma | 22.2 (15–29)‡† | NR | NR | NR | NR | NR | 10.7* |
| Smith 2011 | Prospective 1985–2009 UK | 2568 bone sarcomas | 25‡ | NR | NR | NR | NR | NR | 16‡ |
| Grimer 2006 | Prospective 1986–2006 UK | 1460 bone sarcoma | NR | NR | NR | NR | NR | NR | 16‡ |
| Lawrenz 2018 | Retrospective 1990–2014 UK | bone sarcoma: 1446 non-metastatic 346 metastatic | 30.7* | NR | NR | NR | NR | NR | 54.8* vs 29.9* |
| 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| Retrospective 2007–2011 Brazil           | 1257 osteosarcoma and Ewing sarcoma | 0-29¶      | NR                       | NR                            | NR                            | NR                            | NR                       | NR                   |
|             |                                          |                 | 0-14¶ (46%) | NR                       | NR                            | NR                            | NR                            | NR                       | NR                   |
|             |                                          |                 | 15–19¶ (33%) | NR                       | NR                            | NR                            | NR                            | NR                       | NR                   |
|             |                                          |                 | 20–29¶ (21%) | NR                       | NR                            | NR                            | NR                            | NR                       | NR                   |
| Bielack 2002| Retrospective 1980–1998 German/Austrian/Swiss | 1702 high-grade osteosarcomas | 16.7†      | NR                       | NR                            | NR                            | NR                            | NR                       | 9.9‡                 |
| Chen 2017   | Retrospective 2004–2012 USA              | 364 malignancies of which 30 bone sarcoma | 16.5‡      | NR                       | NR                            | NR                            | NR                            | NR                       | 12.4‡                |
| Desandes 2018| 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                       | NR                   |
|             |                                          |                 | 20–24 [n=15] | NR                       | NR                            | NR                            | NR                            | NR                       | 10.1‡                |
| Petrilli 2006| Prospective 1987–1996 Brazil           | 209 high-grade osteosarcomas | 14 (2.4–24.5)*† | NR                       | NR                            | NR                            | NR                            | NR                       | 18.4*                |
| Yang 2009   | 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| 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). 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.10

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 13 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   | Retrospective 1980–2002 Sweden            | 106 chest wall chondrosarcoma | 57*        | 34.4 (4.3–855.7)†‡     | NR                                         |     |
| Goyal 2004   | Retrospective 1990–2002 UK                | 103 bone sarcoma   | 15 (4–22)†‡ | 16.34 (4.3–197.8)†‡   | NR                                         |     |
| Brotzmann 2013 | Retrospective 1969–2008 Switzerland       | 32 bone sarcoma of the foot | NR         | 43†                    | No association                             |     |
| Bacci 1999   | Retrospective 1979–1997 Italy             | 618 Ewing sarcoma  | NR         | 18 ‡                   | Stage: no association                       |     |
| Bacci 2000   | Retrospective 1993–1999 Italy             | 965 high-grade osteosarcoma extremity | NR         | 10.5 (1–59)*‡        | No association                             |     |
| Bacci 2002   | Retrospective 1980–1999 Italy             | High-grade osteosarcoma extremity 891 localised disease 180 metastasized disease | <15: n=501§ ≥15: n=570§ | 10.9*                       | 45.2% diagnostic interval <2 months          | NR |
| Bacci 2007   | 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 |
| Goedhart 2016 | Retrospective 2000–2012 The Netherlands    | 19 chondrosarcoma   | 30.0 (5–89)*‡ | 98.3*                       | Metastatic disease                         | 5 years OS |
|              |                                          | 29 Ewing sarcoma   | 22.9* (p<0.01) | 23.3* (p<0.01)           |                                           |     |
|              |                                          | 54 osteosarcoma    |             |                         |                                           |     |
| Brasme 2014  | Prospective 1988–2000 France              | 436 Ewing sarcoma  | 12†        | 10†                    | No association                             |     |
| Kim 2009     | Retrospective 1985–2005 Korea             | 26 osteosarcoma and doctor delays >45 days | 30.2 (4–67)*‡ | NR                       | NR                                         |     |
| Simpson 2005 | 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   | Retrospective 1975–1995 USA               | 68 bone sarcoma of pelvic girdle | 41 (8–82)*‡ | 43†                    | 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 |
| Pettrilli 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.
| 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) |
|-------------|-------------------------------------|------------------|-------------|------------------------|-----------------------------|-----------------------------|-----------------------------|--------------------------|------------------------|
| Golman 2007 | Retrospective 1991-2004 Israel       | 73 synovial sarcoma | 38 (8-82)† | NR                     | NR                          | NR                          | NR                          | NR                       | 77.4 (8.6–202.1)†       |
| Amant 2003  | Retrospective 1990-2002 Belgium      | 6 endometrial stromal sarcoma | 34* | NR                     | NR                          | NR                          | NR                          | NR                       | 614.9 (103.2–1754.4)*†   |
| Nakamura 2011 | Retrospective 2001-2009 Japan        | 100 STS, referred for additional resection | 57 (0–89)‡* | 12.9 (4.3–309.6)*† | NR                          | NR                          | NR                          | NR                       | 15%§                   |
| Pavlik 2003  | Retrospective 1975-2002 USA          | 29 angiosarcoma of the scalp | 71* | NR                     | NR                          | NR                          | NR                          | NR                       | 21.9 (0–73.5)*†          |
| Rougraff 2012 | Retrospective 1992-2007 USA         | 381 grade 3 STS of extremity or flank | NR  | NR                     | NR                          | NR                          | NR                          | NR                       | 66.6‡                   |
| Rougraff 2006 | Retrospective 1992-2003 USA         | 624 sarcoma: 382 soft-tissue sarcoma | NR  | NR                     | NR                          | NR                          | NR                          | NR                       | 73.3 (0.25–362.8)‡†      |
| Ferrari 2010 | Retrospective 1977–2005 Italy        | 575 STS | ≤21† | NR                     | NR                          | NR                          | NR                          | NR                       | 8.6 (1–258)†             |
| Pratt 1978   | 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*               |
| Bandopadhay 2016 | Retrospective 1991–2010 USA        | 391 primary pulmonary artery sarcoma | 52 (14–94)*† | NR                     | NR                          | NR                          | NR                          | NR                       | 14.3*                  |
| Brouns 2003  | Retrospective 1999–2001 Belgium      | 100 STS | 50.5 (3–88)*† | 17.2 (8.6–1032)*† | NR                          | NR                          | NR                          | NR                       | 25.8 (8.6–339.7)*†       |
| Chaudu 2003  | Retrospective 1955–1999 Scotland     | 109 STS | 33.4 (10-77)‡† | NR                     | NR                          | NR                          | NR                          | NR                       | 86‡                    |
| Clark 2005   | Prospective 2003–2004 UK             | 31 STS with referral >3 months (19.5%) | 59 (34–84)*† | NR                     | NR                          | NR                          | NR                          | NR                       | 94.6 (1.72–412.8)‡‡       |
| Johnson 2008  | Prospective/recall 2005 UK           | 162 STS | 53 (16–88)*† | 1.3*                  | 28.4‡†                     | 2.4*                        | 6.9*                       | 25.0*                   | 40.4*                  |
| Lawrence 1986 | Retrospective 1977–1978 and 1983–1984 | 2355 STS and 3457 STS | >18‡ | NR                     | NR                          | NR                          | NR                          | NR                       | 4.3*                   |
| Park 2010    | 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  | 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   | Retrospective 1962–1974 Denmark      | 7 oral sarcoma | 29 (10-81)*† | 6.9‡† | NR                     | NR                          | 15.9†                       | NR                       |
| Cooper 1996  | Retrospective 1984–1993 Ireland      | 18 STS interval >4 weeks | 43 (2-89)*† | 36%§               | 23%§                       | 11%§                       | NR                         | NR                       | 28*                    |

Continued
| Author; year | Study design, time period and country | Study population | Age (years) | Patient interval (weeks) | Primary care interval (week) | Secondary care interval (week) | Tertiary care interval (week) | Diagnostic interval (week) | Total interval (week) |
|-------------|--------------------------------------|------------------|------------|-------------------------|-----------------------------|-----------------------------|-----------------------------|---------------------------|--------------------------|
| Antillon 2008 | Retrospective 2000–2007 Guatemala | 47 rhabdo-myosarcoma | 6 (1–17)† | NR | NR | NR | NR | 8.6 (2–51.6)† | 25.8 (3–154.8)† |
| | 33 non-rhabdo-myosarcoma | 11 (2–17)† | 43 (0–156)† | NR | NR | NR | NR | 50 (0–362)† | 98 (0–364)† |
| Chotel 2008 | Retrospective 1985–2006 UK | 33 synovial sarcoma | 12.3 (3–16)† | NR | NR | NR | NR | 21 (4–78)† | 16 weeks (2–104)† |
| Durve 2004 | Retrospective 1980–2000 UK | 14 rhabdo- myosarcoma of ear and temporal bone | 4.5 (1.0–8.6)† | NR | NR | NR | NR | NR | NR |
| Watson 1994 | Retrospective 1985–1992 Australia | 40 STS of extremity | 59 (14–87)† | NR | NR | NR | NR | NR | 520.1 (8.3–2115.6)† |
| Monnier 2005 | Retrospective 1982–2002 France | 66 dermatofibrosarcoma protuberans | 43 (8–81)† | NR | NR | NR | NR | NR | NR |
| Dyrop 2013 | Retrospective 2007–2010 Denmark | 258 STS | NR | NR | NR | NR | NR | 2007: 4* | 2010: 2.6* |
| Buvarp Dyrop 2016 | Retrospective 2014–2015 Denmark | 545 referred patients of which: 102 sarcoma patients (88 soft tissue 14 bone) | 55 (0–93)† | NR | NR | NR | NR | NR | NR |
| George 2012 | Retrospective 2011 UK | 66 STS | ≥18† | 4.3 (0–516)† | 13.3 (1.7–154.8)† | NR | NR | NR | NR |
| Martin 2007 | Retrospective 2001–2003 USA | 38 STS | 22.2 (15–29)† | NR | NR | NR | NR | NR | 24.9† |
| Smith 2011 | Prospective 1985–2009 UK | 2366 STS | 57* | NR | NR | NR | NR | NR | 26* |
| Griner 2009 | Prospective 1986–2006 UK | 1460 STS | NR | NR | NR | NR | NR | NR | 26* |
| Chen 2017 | Retrospective 2004–2012 USA | 364 malignancies of which 18 STS | 14* | NR | NR | NR | NR | NR | 7.2* |
| Nandra 2015 | Retrospective 1985–2010 UK | 2277 STS | 57* | NR | NR | NR | NR | NR | 26* |
| Desandes 2018 | Retrospective 2012–2013 France | 993 malignancies of which 43 STS | NR | NR | NR | NR | NR | NR | 22.9* |
| Smolle 2019 | Retrospective 1982–2014 UK | 248 synovial sarcomas | 37† | NR | NR | NR | NR | NR | 52* |
| Younger 2018 | Retrospective 2015 UK | 558 sarcoma of which 418 STS | 64.1 (18–96)† | NR | NR | NR | NR | NR | NR |

Continued
Effect of tumour-specific factors

Three studies found no relationship between tumour size and length of the total interval, 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), while a study in adults (n=162) reported that smaller tumours (median 8 cm) were associated with a longer total interval.

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 and Smolle et al found synovial sarcomas located superficially had a longer interval than deeply located tumours (n=248; 2 years vs 12 months). However, two other studies found no relationship between tumour site and total interval.

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; 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=277) identified that low-grade sarcomas were associated with a longer total interval.

Effect of patient-specific factors

Patient gender, level of education and measures of social deprivation were not associated with length of total interval. 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. 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). Smolle et al found no difference for patients with synovial sarcoma older or younger than 16 years old. 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. A Sarcoma UK survey (n=558) established no association between age and patient interval or total interval.

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 (e.g., urethral obstruction). 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.
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.66

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;59 120 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.43 61–63 65–67 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.21 43 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 osteosarcoma 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 65 67 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 do 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     | 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      | Retrospective 1990–2002 Belgium       | 15 endometrial stromal sarcoma | 34‡        | NR                     | 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   | Retrospective 2001–2009 Japan         | 100 STS, referred for additional resection | 57 (0–89)‡† | 25.843–17)*‡           | NR                                            | 5 years survival: 54.4% (66.8% without metastases, 5.9% with metastases) |
|                       |                                      |                  |             |                        |                                               | 12/43 metastases vs 6/51 metastases (p=0.04) |
|                       |                                      |                  |             |                        |                                               | 77% (48 patients without metastases) |
| Rougraff et al 2012   | Retrospective 1992–2007 USA           | 381 grade 3 STS of extremity or flank | NR         | 66.6 20†              | No association                                | No association        |
| Rougraff et al 2007   | Retrospective 1992–2003 USA           | 624 sarcoma: 382 soft tissue sarcoma | NR         | No association         | No association                                | No association        |
|                       |                                      | 278 high-grade STS | 73.3 (0.25–362.8)†† | No association         | No association                                | No association        |
|                       |                                      | 104 low-grade STS | 127.4 (0.25–256)†† | No association         | No association                                | No association        |
| Ferrari et al 2010    | 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 | 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     | Retrospective 1985–2006 UK            | 33 synovial sarcoma | 12.3 (3-16)‡† | 98 (2–364)‡†          | NR                                            | No association        |
| Nandra et al 2015     | 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     | Retrospective 1982–2014 UK            | 248 synovial sarcomas | 37‡        | 52*                   | NR                                            | No association (<1 year versus >1 year) |

Continued
litigation in sarcoma cases in the USA. 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. 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. 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. 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.
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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Contributors All authors have contributed to this manuscript and have agreed to submit the manuscript to ESMO open for publication.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES
1 Stillcr CA, Trama A, Serrano D, et al. Descriptive epidemiology of sarcomas in Europe: report from the RARECARE project. Eur J Cancer 2013;49:684–95.
2 Blay J-Y, Coindre J-M, Ducimetière F, et al. The value of research collaborations and consortia in rare cancers. Lancet Oncol 2016;17:e62–9.
3 DeSantis CE, Kramer JL, Jemal A. The burden of rare cancers in the United States. CA Cancer J Clin 2017;67:261–72.
4 McPhail S, Johnson S, Greenberg D, et al. Stage at diagnosis and early mortality from cancer in England. Br J Cancer 2015;111:Suppl 1:S108–15.
5 Olesen F, Hansen RP, Vedsted P. Delay in diagnosis: the experience in Denmark. Br J Cancer 2009;101 Suppl 2:S5–8.
6 Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.
7 Weller D, Vedsted P, Rubin G, et al. The Aarhus statement: improving design and reporting of studies on early cancer diagnosis. Br J Cancer 2012;106:1262–7.
8 Kämmner PW, Shabazfar N, Vorkshori Makoei N, et al. Clinical, therapeutic and prognostic features of osteosarcoma of the jaws – experience of 36 cases. J Craniofac Surg 2012;24:541–8.
9 Pan KL, Chan WH, Chia YY. Initial symptoms and delayed diagnosis of osteosarcoma around the knee joint. J Orthop Surg 2010;18:55–7.
10 Widhe B, Bauer HCF. Diagnostic difficulties and delays with chest wall chondrosarcoma: a Swedish population based Scandinavian sarcoma group study of 106 patients. Acta Oncol 2011;50:435–40.
11 Goyal S, Roscoe J, Ryder WDJ, et al. Symptom interval in young people with bone cancer. Eur J Cancer 2004;40:2280–6.
12 Widhe B, Widhe T. Initial symptoms and clinical features in osteosarcoma and Ewing sarcoma. Journal of Bone & Joint Surgery - American Volume (Research Support, Non-U. S. Gov’t) 2000;82:667–74.
13 Widhe B, Widhe T, Bauer HCF. Ewing sarcoma of the rib—initial symptoms and clinical features: tumor missed at the first visit in 21 of 26 patients. Acta Orthop 2007;78:840–4.
14 Guerra RB, Testa MD, Mistry A, LdaC, et al. Comparative analysis between osteosarcoma and Ewing’s sarcoma: evaluation of the time from onset of signs and symptoms until diagnosis. Clinics 2015;61:99–106.
15 Bro tzmann M, Hefti F, Baumhoer D, et al. Do malignant bone tumors of the foot have a different biological behavior than sarcomas at other skeletal sites? Sarcoma 2013;2013:1–8.
16 Biscaglia R, Gasbarrini A, Böhl ing T, et al. Osteosarcoma of the bones of the Foot—an easily misdiagnosed malignant tumor. Mayo Clin Proc 1998;73:842–7.
17 Bacci G, Di Fiore M, Rimondini S, et al. Delayed diagnosis and tumor stage in Ewing’s sarcoma. Oncol Rep 1999;6:465–6.
18 Bacci G, Ferrari S, Longhi A, et al. High-grade osteosarcoma of the extremity: differences between localized and metastatic tumors at presentation. J Pediatr Hematol Oncol 2002;24:27–30.
19 Bacci G, Ferrari S, Longhi A, et al. Delay in diagnosis of high-grade osteosarcoma of the extremities, has it any effect on the stage of disease? Tumor 2000;86:204–6.
20 Bacci G, Balladelli A, Forini C, et al. Ewing’s sarcoma family tumours - Differences in clinicopathological characteristics at presentation between localised and metastatic tumours. J Bone Joint Surg Br 2007;89B:1229–33.
21 Goedhart LM, Gerbers JG, Ploegmakers JWW, et al. Delay in diagnosis and its effect on clinical outcome in high-grade sarcoma of bone: a referral oncological centre study. Orthop Surg 2016;8:122–8.
22 Brasseme JF, Chartrousse M, Obertin A, et al. Time to diagnosis of Ewing tumors in children and adolescents is not associated with metastasis or survival: a prospective multicenter study of 436 patients. Journal of Clinical Oncology (Multicenter Study Research Support, Non-U. S. Gov’t) 2014;32:1935–40.
23 Kim MS, Lee S-Y, Cho WH, et al. Prognostic effects of doctor-associated diagnostic delays in osteosarcoma. Arch Orthop Trauma Surg 2009;129:1421–5.
24 Simpson PMS, Reid R, Porter D. Ewing’s sarcoma of the upper extremity: presenting symptoms, diagnostic delay and outcome. Sarcoma 2005;9:15–20.
25 Wurtz LD, Peabody TD, Simon MA. Delay in the diagnosis and treatment of primary bone sarcoma of the pelvis. J Bone Joint Surg Am 1999;81:317–25.
26 Sneepen O, Hansen LM. Presenting symptoms and treatment delay in osteosarcoma and Ewing’s sarcoma. Acta radiol 1984;23:159–62.
27 Nandra R, Hwang N, Matharu GS, et al. One-Year mortality in patients with bone and soft tissue sarcomas as an indicator of delay in presentation. Annals 2015;97:425–33.
28 Vadillo RM, Contreras SJS, Canales JCG. Prognostic factors in patients with jaw sarcomas. Braz Oral Res 2011;25:421–6.
29 Ashwood N, Witt JD, Hallam PJ, et al. Analysis of the referral pattern to a supraglottic bone and soft tissue tumour service. Ann R Coll Surg Engl 2003;85:272–6.
30 George A, Grimer R. Early symptoms of bone and soft tissue sarcomas: could they be diagnosed earlier? Annals 2012;94:261–6.
31 Martin S, Ulrich C, Munsell M, et al. Delays in cancer diagnosis in underinsured young adults and older adolescents. Oncologist (Research Support, N. I. H., Extramural Research Support, Non-U.S. Gov’t) 2007;12:816–24.
32 Smith GM, Johnson GD, Grimer RJ, et al. Trends in presentation of bone and soft tissue sarcomas over 25 years: little evidence of earlier diagnosis. Annals 2011;93:542–7.
33 Grimer RJ. Size matters for sarcomas! Annals 2006;88:519–24.
34 Chen J, Muller CA. Patterns of diagnosis and misdiagnosis in pediatric cancer and relationship to survival. J Pediatr Hematol Oncol 2017;39:e110–5.
Desandes E, Brugière L, Moliné F, et al. Adolescent and young adult oncology patients in France: heterogeneity in pathways of care. *Pediatr Blood Cancer* 2018;65:e27235.

Petrelli AS, de Camargo B, Filho VO, et al. Results of the Brazilian osteosarcoma treatment group studies III and IV: prognostic factors and impact on survival. *J Clin Oncol* 2006;24:1161–8.

Yang JYK, Cheng FWT, Wong KC, et al. Initial presentation and management of osteosarcoma, and its impact on disease outcome. *Hong Kong Med J* 2009;15:434–9.

Younger E, Husson O, Bennister L, et al. Age-Related sarcoma patient experience: results from a national survey in England. *BMC Cancer* 2018;18:991.

Bielack SS, Kempf-Bielack B, Delling G, et al. Prognostic factors in high-grade osteosarcoma of the extremities or trunk: an analysis of 1,702 patients treated on the German cooperative osteosarcoma Study Group protocols. *J Clin Oncol* 2002;20:776–90.

Balmant NV, de Paula Silva N, de OSM deSSR, et al. Delays in the health care system for children, adolescents, and young adults with bone tumors in Brazil. *J Biol Pediatria* 2018.

Lawrenz JM, Stryon JP, Parry M, et al. Longer duration of symptoms at the time of presentation is not associated with worse survival in primary bone sarcoma. *Bone Joint J* 2018;100-B:652–61.

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. *Pediatrics* 1978;61:30–4.

Bandyopadhyay D, Panchabhai BS, Bajaj NS, et al. Primary pulmonary artery sarcoma: a close associate of pulmonary embolism—20—year observational analysis. *J Thorac Oncol* 2016;6:2992–601.

De Silva MVC, Barrett A, Reid R. Premonitory pain preceding swelling: a distinctive clinical presentation of synovial sarcoma which may prompt early detection. *Sarcoma* 2003;7:131–5.

Clark MA, Thomas JM, Delay in referral to a specialist soft-tissue sarcoma unit. *Eur J Surg Oncol* 2005;31:443–8.

Johnson GD, Smith G, Dramis A, et al. Delays in referral of soft tissue sarcomas. *Sarcoma* 2008;2008:1–7.

Lawrence W, de Camaro J, Collins D, et al. Adult soft tissue sarcomas. A pattern of care survey of the American College of surgeons. *Annals of Surgery* 1986;205:349–59.

Park JH, Kang CH, Kim CH, et al. Sarcoma of the extremity with a delayed diagnosis. *Am J Surg* 1986;205:349–59.

Chavanne W, Donegan WL, Natarajan N, et al. Factors leading to delay in diagnosis of soft tissue sarcomas. *Sarcoma* 2017;8:2592–601.

Seinen J, Almquist M, Styring E, et al. Delays in the management of retroperitoneal sarcomas. *Sarcoma* 2010;2010:1–4.

Bruun JP. Time lapse by diagnosis of oral cancer. *Oral Surgery, Oral Medicine, Oral Pathology* 1976;42:139–49.

Cooper TM, Sherman M, Collins D, et al. Soft tissue sarcoma of the extremity. *Ann R Coll Surg Engl* 1996;78:453–6.

Antillon F, Castellanos M, Valverde P, et al. Treating pediatric soft tissue sarcomas in a country with limited resources: the experience of the Unidad Nacional de Oncologia Pediatria in Guatemala. *Pediatr Blood Cancer* 2006;46:734–9.

Chotel F, Unnithan A, Chandrasekar CR, et al. Variability in the presentation of synovial sarcoma in children. *Bone Joint J* 2008;90-B:1090–6.

Durve DV, Kaneanagor RG, Albert D, et al. Paediatric rhabdomyosarcoma of the ear and temporal bone. *Clin Otolaryngol Allied Sci* 2004;29:32–7.

Watson DI, Coventry BJ, Langlois SL, et al. Soft-Tissue sarcoma of the extremity. experience with limb-sparing surgery. *Med J Aust* 1994;160:412–6.

Monnier D, Vidal C, Martin L, et al. Dermatofibrosarcoma protuberas: a population-based cancer registry descriptive study of 66 consecutive cases diagnosed between 1982 and 2002. *J Eur Acad Dermatol Venereol* 2006;20:1237–42.

Buvarp Dyrop H, Vedsted P, Raedkjær M, et al. Imaging and investigations before referral to a sarcoma center delay the final diagnosis of musculoskeletal sarcoma. *Acta Orthopaedica* 2017:1–6.