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Scottish Referral Guidelines for Suspected Cancer Update – Evidence Review (Sarcomas and Bone)

The purpose of this document is to synthesise and critique evidence and insight related to referral guidelines for suspected sarcomas and bone cancer. Key themes have been determined from the literature. For each key theme e.g. symptoms, the papers are summarised separately with some high-level synthesis to provide steer on how this may impact referral guidelines. At the end of the document, a table comparing NICE NG12 and SRG guidelines can be found for reference.

This document includes evidence on the following topics:

- Symptoms
- Investigation findings
- Safety Netting
- Risk Stratification
- Other topics where the evidence base is emerging

Background

Sarcomas are a type of cancer that can appear anywhere in the body. They are generally organised into two main types, soft tissue sarcoma and bone sarcoma (also known as primary bone cancer). Within these two types, there are around 100 subtypes of sarcomas[1].

Sarcomas, including primary bone cancer, are classed as rare cancers[2], accounting for less than 1% of all new cancer cases (data from 2018, 2019 and 2021) in Scotland[3]. Soft tissue sarcomas can occur at any age, but most often in middle aged and older adults. For primary bone cancer, osteosarcoma and Ewing sarcoma are more common in children and young adults, and chondrosarcomas are more common in middle aged and elderly people.

Stage at diagnosis, survival by stage, and routes to diagnosis data for soft tissue sarcomas are not publicly available in any UK nation. Due to the heterogeneity of this group of tumours, incidence has been historically under-reported. Additionally, the classification of soft tissue

[1] Including primary cancers of the bone and cancers of the soft tissue, deep skin, fat, muscles, blood vessels, nerves, tendons, ligaments, tissues around the joints and primary cancers of the bone. Cancer Research UK. What are soft tissue sarcomas? [Internet]. Accessed 2024 Aug.
[2] ESMO (2024). "Families" and List of Rare Cancers [Internet]. ESMO. Accessed 2024 Aug.
[3] Public Health Scotland. Annual Cancer Incidence (updated 2024 May). Available from: https://www.opendata.nhs.scot/dataset/annual-cancer-incidence

sarcomas has continued to evolve over recent decades, most importantly the 2020 WHO Classification of soft tissue sarcoma and bone sarcoma codes all gastrointestinal stromal tumours (GISTs) as malignant[4], resulting in variations in incidence reporting.

For bone cancers, stage at diagnosis and survival by stage data is not publicly available in Scotland. In Wales (2019), among the 20 bone cancer cases with a recorded stage, 25% were diagnosed at stage 1, 40% at stage 2, 5% at stage 3 and 30% at stage 4[5]. 89.2% of those diagnosed at stage 2 survived their disease for 1 year or more.

Routes to diagnosis data is not publicly available for bone cancers in Scotland. Data from other nations shows that being diagnosed via emergency presentation is associated with later stage at diagnosis. In England (2018), around 450 bone cancer cases with a known route to diagnosis, 18.3% were diagnosed via emergency presentation[6]. The majority of cases are diagnosed through other outpatient routes (30.2%) or GP referral (27.1%) and 14.8% of cases are diagnosed via urgent referral for suspected cancer.

There is some evidence of inequalities in diagnosis for younger adult patients and those from more deprived backgrounds. Younger et al. (2018)[7] found that young adult sarcoma patients are more likely to experience delays to diagnosis through misattribution of symptoms and multiple consultations with their GP, whereas elderly patients were more likely to be referred for further investigation. Bacon et al. (2023)[8] noted that young adults, elderly patients, and those from more deprived areas were more likely to present via emergency routes. (See 'Safety Netting' section for more information).

Sarcomas and bone cancers can present slightly differently depending on subtype and location. Given low incidence rates, sarcomas are trickier to collect data on and research, which makes guideline development for primary care more challenging. Patients with sarcomas or bone cancers often experience delays to diagnosis. While evidence on the impact this has on outcomes is limited, it can impact patient

[4] World Health Organisation (WHO) Board. Classification of Tumours. Soft Tissue and Bone Tumours. International Agency for Research on Cancer. 2020.
[5] Cancer Research UK. Early Diagnosis [Internet]. crukcancerintelligence.shinyapps.io. Accessed 2024 Jul. Available from: crukcancerintelligence.shinyapps.io/EarlyDiagnosis/
[6] Ibid.
[7] Younger E, Husson O, Bennister L, et al. Age-related sarcoma patient experience: results from a national survey in England. BMC Cancer [Internet]. 2018 Oct [cited 2024 Jul 29];18:991. Avila
[8] Bacon A, Wong K, Fernando MS, et al. Incidence and survival of soft tissue sarcoma in England between 2013 and 2017, an analysis from the National Cancer Registration and Analysis Service. Int J Cancer [Internet]. 2023 [cited 2024 Aug 5];152(9):1789-1803.

experience[9]. Continued review and optimisation of the referral guidelines will support primary healthcare professionals achieve timelier diagnosis through the urgent referral pathway, thus ensuring people are referred along the right route at the right time.

Search Strategy

Search terms: PubMed search for combinations of the following terms: bone cancer, bone sarcoma, sarcoma, soft tissue sarcoma, prevalence, PPV, symptomatic, presentation, secondary, symptom, bone swelling, bone pain, mass, lump, lymph node enlargement, lymphadenopathy, primary care, direct access, recognition, referral, routine, urgent referral, routes to diagnosis, diagnosis, comorbidity, inequalities, safety netting, risk stratification, stage, investigation, x-ray, ultrasound.

For the purpose of this review, evidence related to soft tissue sarcomas includes site-specific evidence on head and neck sarcomas but does not include papers that summarise evidence for other anatomical sites or recurrence as this is out of scope for this review.

Date: 2015 – present. In the table summaries, the only papers included from pre-2015 are those that are relevant for explaining differences in Scottish Referral Guidelines (SRG) and NICE NG12 guidelines. These have been gathered from NICE NG12 Evidence Review document.

Peer-reviewed literature

Note: grey rows in the table represent studies that have already been summarised earlier in the document.

Topic: Symptoms
Summary: Evidence supports the symptoms for bone sarcoma (BS), and partly support the symptoms for soft-tissue sarcoma (STS), included in the current guidelines. There is limited evidence reporting the PPV of symptoms for BS and STS with one of the largest studies (Paper 1) reporting that no PPV of symptoms exceeded 1%. Bone cancer / bone sarcomas:

[9] Soomers V, van der Graaf W, Zaidi S, Kaal S, Hayes A, Schreuder B, et al. The route to diagnosis of sarcoma patients: Results from an interview study in the Netherlands and the United Kingdom. PLoS ONE. 2020; 15(12): e0243439.

Across the studies, bone pain was the most common presenting symptom for bone cancers. The frequency of bone pain at presentation ranged from 29% (of 63 patients) in Paper 2 to 81.4% (of 102 patients) in Paper 6. This symptom is currently included in SRG guidelines. (NICE NG12 guidelines do not provide any specific symptoms for bone sarcomas and instead recommends a suspected cancer pathway referral if x-ray suggests the possibility of bone sarcoma. It is unclear from the available data how many referrals are made from primary care versus radiology).

Soft tissue sarcomas:

Across the studies, lump/mass or painless lump/mass was the most common presenting symptom for soft tissue sarcomas. The frequency of this symptom at presentation ranged from 29% (of 373 patients) in Paper 2 to 68% (of 377 patients) in Paper 4. This is in partial agreement with current guidelines which further characterises a lump based on size, depth, recurrence and lymph node enlargement, and in general agreement with NG12.

Paper 8 regarded size of lump >5cm, increasing size, and lump deep to the fascia as the best predictors of a malignant mass. (See 'Investigation Findings' for more information). There is some evidence to suggest that the size of a suspicious mass that warrants urgent investigation could be lowered. Paper 8 found that reducing the size threshold from >5cm to >4cm improved diagnostic sensitivity from 76% to 89% and Paper 7 found that the average size of a head and neck soft tissue sarcoma at presentation to the sarcoma unit following a referral was 45mm.
It is unclear from the evidence base if there is a standardised method for accurately measuring lump size in primary care and is likely a combination of clinical experience/assessment, patient description and measurement tools in primary care.

There was limited evidence to support lymph node enlargement as a symptom for STS and only reported in 1% of patients diagnosed in Paper 2.

Paper number	Study	Cancer	Summary	Notes
1	Dommett R, Redaniel M, Stevens M, Hamilton W, and Martin R. Features of cancer in teenagers and young adults in primary	BS and STS	This study aimed to investigate the association of symptoms and consultation frequency in primary care for teenagers and young adults with cancers.	Population-based case-control study using data from the Clinical Practice Research Datalink (UK) between 1988-2010.

	care: A population-based nested case-control study. British Journal of Cancer. 2013;108:2329-2333.		• Lump mass swelling, musculoskeletal symptoms, chest pain, and ≥3 consultations were independently associated with BS and STS. • Lump mass swelling below neck not including abdomen had a PPV of 0.0415% (95% CI; 0.0124-0.1392). • Musculoskeletal symptoms had a PPV of 0.0093% (95% CI; 0.0058-0.0151). • ≥3 primary care consultations (for any symptom) had a PPV: 0.003% (95% CI; 0.0024-0.0037). • Chest pain had a PPV of 0.0027% (95% CI; 0.1-0.77).	N=1,064 cancer cases of teenagers and young adults aged 15-24 years matched to 13,206 controls. 196 cases were for BS & STS. **Limitations:** This study did not distinguish between bone and soft tissue sarcoma and so was not able to analyse PPV of each symptom for each sarcoma. The study was carried out in adolescents and young adults for which BS is more common and STS is less common than in adults. This may affect the accuracy of PPV findings that would be representative of an adult population.
2	Zakkak N, Barclay ME, Swann R, McPhail S, Rubin G, Abel GA, et al. The presenting symptom signatures of incident cancer: evidence from the English 2018 National Cancer Diagnosis Audit. British Journal of Cancer [Internet]. 2024 Feb 1 [cited 2024 July 30];130(2):297–307.	BS and STS	This study aimed to (1) examine the relative frequency of presenting symptoms by cancer site, and (2) to examine the relative frequency of cancer sites by presenting symptom, among incident cancer cases. The proportion of patients with sarcoma cancers (defined as ICD-10 codes C40-41 and C48-49) presenting with the following symptom groups was: • Lump/mass/lymph node: 29% • Non-specific: 18% • Lower abdominal: 18% • None recorded: 15%	Data from the National Cancer Diagnosis Audit 2018 (England) was analysed. N=55,122. 54% were men and 39% were 60-74 years old. For 20% of patients, no presenting symptoms were recorded. 63 patients were diagnosed with BS. 373 patients were diagnosed with STS. **Limitations:** this is a case-only analysis (only patients with diagnosis of cancer were included), and so cannot make inferences about PPV. For BS particularly,

			• Musculoskeletal: 13% • Upper abdominal: 7% • Ulceration & Respiratory: 4% • Urological & Skin Lesion: 3% • CNS & Breast: 1% <u>For bone sarcoma:</u> Mean number of symptoms: 1.2 15 different symptoms were reported in >1% of the cohort. There were no symptoms reported in >50% of the cohort. The most common symptoms, and the proportion of patients diagnosed that experienced these symptoms, were as follows: • Bone pain: 29% • Back pain: 19% • Sarcomatous (soft tissue) lump & Other: 11% <u>For connective and soft tissue sarcomas:</u> Mean number of symptoms: 1.4 26 different symptoms were reported in >1% of the cohort. There were no symptoms reported in >50% of the cohort. The most common symptoms, and the proportion of patients diagnosed that experienced these symptoms, were as follows: • Sarcomatous (soft tissue) lump: 29%	cohort sizes are small relative to other cancer site cases, which may limit the accuracy of findings.

			• Other: 12% • Abdominal pain & Distension: 8% • Bone pain: 6% 1% experienced local lymphadenopathy.	
3	Younger E, Husson O, Bennister L, et al. Age-related sarcoma patient experience: results from a national survey in England. BMC Cancer [Internet]. 2018 Oct [cited 2024 Jul 29];18:991.	BS and STS	This study aimed to understand age- and tumour-related differences in sarcoma patients' experiences. The study investigated presentation, route to diagnosis, treatment, and post-treatment experiences. • For STS, the most common presenting symptom was a 'painless lump' (41%). • For bone sarcoma, the most common presenting symptom was bone pain (31%).	Cross-sectional study of adult sarcoma patient respondents to the National Cancer Patient Experience Surveys in England for 2012-2014. N=558 survey responders. 75% of responders were diagnosed with STS and 25% were diagnosed with BS. **Limitations:** Survey response rate was higher in middle-aged (40-64 years) patients which means findings may not be representative of the general sarcoma patient population. The study relies on patient recall and does not use medical records to validate responses which may affect the accuracy of the findings.
4	Rafiq M, de Boer J, Mar J, et al. Clinical activity in general practice before sarcoma diagnosis: an Australian cohort study. British Journal of General Practice [Internet]. 2024	BS and STS	The study aimed to examine pre-diagnostic GP clinical activity before a sarcoma diagnosis to identify whether there are opportunities to expedite the diagnosis of sarcoma in general practice. • Patients with STS were more likely to present with a painless mass (68%) than BS patients (34%).	Retrospective cohort study of newly diagnosed sarcoma patients between 1 Jan 2002 – 31 July 2021 in the ACCORD dataset (Australia). N=441. 377 patients were diagnosed with STS and 64 with BS.

	Aug [cited 2024 Jul 29] ;74(745):e508-e516.		• Patients with BS were more likely to present with pain (70%) than STS patients (36%)	**Limitations:** Particularly for BS, cohort sizes were small which may limit the reliability of the findings. The study uses Australian data which limits the applicability of findings to a UK setting.
5	Martin S, Clark S, Gerrand C, et al. Patients' Experiences of a Sarcoma Diagnosis: A Process Mapping Exercise of Diagnostic Pathways. Cancers [Internet]. 2022 Mar [cited 2024 Jul 29] ;14(5):1273.	BS and STS (incl. H&N)	The study aimed to describe patients' experiences of pre-diagnostic signs and symptoms of sarcomas and pathways to diagnosis. • Main presenting symptom for BS was pain (66.7%) and for STS was lump/swelling (33.3%). • Presenting symptoms for H&N was very varied.	Mixed-methods study involving quantitative, qualitative and inductive thematic secondary analysis of interviews with sarcoma patients across England and Scotland. N=78. 21 were diagnosed with BS, 41 with STS, 9 with head and neck sarcoma, and 7 with gastrointestinal stromal tumour. **Limitations:** Each sarcoma cohort had a small sample which limits the reliability and applicability of findings. Self-selection recruitment for the study means participants may not be representative of the general sarcoma population. The study relies on patient recall and does not use medical records to validate responses which may affect the accuracy of the findings.
6	Goedhart L, Gerbers J, Ploegmakers J, Jutte P. Delay in Diagnosis and Its Effect on Clinical	BS	The study aimed to investigate delay in diagnosis by both patients and doctors, and to evaluate its effect on outcomes.	Retrospective study of BS patients diagnosed between October 2020 – 2012 in the Netherlands. N=102

	Outcome in High-grade Sarcoma of Bone: A Referral Oncological Centre Study. Orthopaedic Surgery [Internet]. 2016 Jul [cited 2024 Jul 29] ;8(2):122-128.		• Pain was the most common symptom for patients with bone sarcomas and was present in 81.4% osteosarcoma patients, 68.9% Ewing sarcoma patients, and 68.4% chondrosarcomas patients.	54 patients were diagnosed with osteosarcoma, 29 with Ewing sarcoma, and 19 with chondrosarcoma. **Limitations:** the study's small sample size limits the reliability and applicability of findings. The study was based in the Netherlands which limits the applicability of findings to a UK setting.
7	Jaly A, Thway K, Touska P, et al. Imaging Soft-tissue Sarcomas of the Head and Neck: A Tertiary Soft-tissue Sarcoma Unit Experience. Anticancer Research [Internet]. 2019 Nov [cited 2024 Jul 29];39(11): 6223–6230.	STS (H&N)	This study aimed to describe imaging features of head and neck (H&N) soft tissue sarcomas. • Head and neck sarcomas often present as a large, superficial mass with no lymph node involvement. • Average size of primary tumour at presentation to the sarcoma unit (following a referral) was 45mm.	Retrospective study looking at referrals to the Royal Marsden Sarcoma Unit (England) between Jan 2011 – May 2015. N=62. The majority of STSs analysed were angiosarcomas as this is most common in the head and neck. **Limitations:** the small sample size limits the reliability and applicability of findings.
8	Smolle MA, Leithner A, and Grimer RJ. Evaluating the British sarcoma referral form. The Annals of The Royal College of Surgeons of England [Internet]. 2015 Aug [cited 2024 Jul 29];97(6):434-438.	STS	This study aimed to investigate concordance of GP referrals with NICE 2005 guidelines for STS, and whether the guidelines should be refined. • 'Size >5cm' had a 76% sensitivity and 66% specificity for diagnosis of STS. • Through their own analysis, lowering the threshold for concern to 'size >4cm' increased sensitivity to 89%.	Study evaluating the two-week wait referral pathways to a single centre in England between Aug 2013 – Jul 2014. N=135. This study refers to the NICE 2005 guidelines before the update in 2015. The 2005 guidelines are very similar to current SRG.

			This translated to 6 more malignancies (out of 45) being detected from size alone. • 'Pain' was the least useful predictor of malignancy and had 27% sensitivity and 66% specificity for diagnosis of STS. • 'Increase in size' had 73% sensitivity and 51% specificity for diagnosis of STS. • 'Deep to the fascia' had 57% sensitivity and 68% specificity for diagnosis of STS. • Soft tissue masses with the combination of size >5cm, no pain, an increase in size, and deep location were most predictive of malignancy.	**Limitations:** This study includes patients already referred to secondary care, so therefore are already a higher-risk cohort than those presenting with symptoms in primary care. This may therefore reduce the applicability of these findings to a primary care setting. This study evaluates the referral pathways of a single institution in England which may limit the generalisability of the results to the wider UK landscape.
9	Buvarp Dyrop H, Vedsted P, Rædkjær M , Safwat A, Keller Johnny. Routes to Diagnosis for Suspected Sarcoma: The Impact of Symptoms and Clinical Findings on the Diagnostic Process. Sarcoma [Internet]. 2016 Dec [cited 2024 Jul 29]; 2016(1):8639272.	STS	The study aimed to the examine the association between presenting symptoms and time intervals for suspected sarcoma. • Most frequent reason for seeking medical care for the total patient population was pain (20%). • There was no statistical difference in the proportion of patients with pain between those with benign conditions and those with sarcoma (59.2% vs 55.9% respectively). • The most frequent reported initial symptoms for patients diagnosed with	Prospective study of patients who were referred for suspected sarcoma between September 2014 to August 2015 to a single centre (Denmark). The study uses both questionnaires and medical records to validate findings. N=545. 102 were diagnosed with sarcoma. **Limitations:** Patients (N=56) and GPs (N=42) who chose to opt-out / did not participate may have introduced a participation bias which could affect the

			sarcoma was 'noticed lump' (65.7%) and 'pain' (26.5%).	reliability of the findings. The study was based in the Denmark which may limit the applicability of findings to a UK setting.

Topic: Investigation findings				
Summary: This section includes papers on the use of ultrasound for investigation and diagnosis. While the use of ultrasound is largely completed in secondary care, NG12 recommends direct access to ultrasound for STS investigation. Additionally, the British Sarcoma Group have produced guidance[10] to help primary care practitioners and ultrasonogrpahers identify which masses on ultrasound need referral to a sarcoma unit, and those which can be managed by local services. <u>Bone sarcoma / bone cancer</u> If there is clinical suspicion for sarcoma in primary care based on symptoms e.g. bone pain, it is recommended in SRG to refer for an x-ray for further investigation prior to completing an urgent suspected cancer referral. There is general clinical consensus that x-ray imaging should be used for investigation[11]. NG12 also recommends the use of x-ray for symptom investigation. <u>Soft tissue sarcoma</u> Current SRG do not recommend a specific investigation for symptoms of STS. Evidence shows that the use of ultrasound imaging of soft tissue lumps can aid in the identification of malignancy[12]. Paper 10 and 11 show that ultrasound have a diagnostic accuracy of 86% and 77% respectively. NG12 recommends the use of ultrasound for symptom investigation. The scarcity of evidence is reflected in the limited number of papers represented in this section, including international studies.				
Paper number	Study	Cancer	Summary	Notes

[10] BSG. Ultrasound screening of soft tissue masses in the trunk and extremity: a British Sarcoma Group guide for ultrasonographers and primary care. British Sarcoma Group; 2019.
[11] Gerrand C, Athanasou N, Brennan B, et al. UK guidelines for the management of bone sarcomas. Clin Sarcoma Res. 2016;6(7).
[12] Lakkaraju A, Sinha R, Garikipati R, Edward S, Robinson P. Ultrasound for initial evaluation and triage of clinically suspicious soft-tissue masses. Clin Radiol. 2009 Jun;64(6):615-21.

10	Shu H, Ma Q, Li A, Wang P, Gao Y, Yao Q, Hu Y, Ye X. Diagnostic Performance of US and MRI in Predicting Malignancy of Soft Tissue Masses: Using a Scoring System. Frontiers in Oncology [Internet]. 2022 Apr [cited 2024 Jul 30]; 12:853232.	STS	This study aimed to assess the diagnostic performance of ultrasound and MRI in predicting malignancy of soft tissue masses using a scoring system developed for this study based on B-mode US and MRI parameters. • The scoring system based on US parameters had a 92% sensitivity, 72% specificity, and 86% accuracy (AUC) with the cutoff value of 3.5. Margin, maximum diameter (>50.5mm), echogenicity, and vascular density were independent factors in differentiating malignancy. • The scoring system based MRI parameters had an 87% sensitivity, 76% specificity, and 89% accuracy (AUC) with the cutoff value of 2.5. Margin, maximum diameter (>45.5mm), and affected peripheral soft tissue were independent factors in differentiating malignancy. • Performance of ultrasound and MRI are comparable. The findings support ultrasound use as an initial examination for soft tissue masses.	Retrospective study of patients with a pathological diagnosis of soft tissue masses between January 2018 and May 2021 at a single institution (China). N=120 **Limitations:** The study was based in China so may not be applicable to a UK setting. Patients included in the study have been referred to secondary care, so therefore are already a higher-risk cohort than those presenting with symptoms in primary care. This reduces the applicability of these findings to a primary care setting.

11	Griffith J, Yip S, Hung E, Wong R, Leung J, Ng A, Tong C, Lee R. Accuracy of ultrasound in the characterisation of deep soft tissue masses: a prospective study. European Radiology [Internet]. 2020 Jun [cited 2024 Jul 30];(30)5894–5903.	STS	The study aimed to investigate the accuracy of ultrasound in characterising the likelihood of malignancy in soft tissue masses. • Ultrasound for identifying malignancy had a sensitivity of 97%, specificity of 85%, PPV of 67% and NPV of 99%. • For all masses with histology (n=134), the first ultrasound diagnosis was correct for 77% of masses. • Clinical examination had a 47% accuracy for diagnosis of mass type and 61% accuracy for detecting malignancy.	Prospective study analysing discrete, deep soft tissue masses on ultrasound located in any body area except for the face, neck and breast on cases between Oct 2013 – June 2019 (Hong Kong). N=579. 134 masses had confirmed histology to compare ultrasound performance against. 38 masses were malignant. **Limitations:** The study was based in Hong Kong so may not be applicable to a UK setting. As masses that had already undergone imaging were excluded from the study, the masses included in the study were a lower-risk cohort. This reduces the applicability of these findings to a primary care setting.

Topic: Safety Netting
Summary: The low incidence rate of soft tissue sarcomas and bone cancer mean that a full time GP is unlikely to make more than one diagnosis during their entire career, which makes identifying possible malignancies challenging for GPs. Evidence suggests that the majority of patients who develop BS or STS will present with symptoms to their GP, providing opportunities for recognition and referral of these cancers along a managed route. However, it also suggests many will often present to their GP multiple times prior to referral. Multiple appointments ahead of referrals were frequently reported in the evidence and there may be opportunities to reduce these and potentially improve patient outcomes, health care experience and quality of life. Understanding the frequency of presentation and rate of onward referral has useful implications for safety netting approaches and the development of better decision tools and diagnostic pathways.

Paper number	Study	Cancer	Summary	Notes
-	Younger E, Husson O, Bennister L, et al. Age-related sarcoma patient experience: results from a national survey in England. BMC Cancer [Internet]. 2018 Oct [cited 2024 Jul 29];18:991. Paper also summarised above. See paper 3.	BS and STS	This study aimed to understand age- and tumour-related differences in patients' experiences. • 27% of patients waited >3 months after first developing symptoms before seeking a medical professional. 10% waited >1 year. • 80% of patients sought advice from their GP about their symptoms. 72% of these patients were referred for further investigation. Of the 28% that were not referred for further investigation, 8.6% were treated for another condition, 8.4% were told their symptoms were not serious but to return if they persisted, and 8.1% were not advised to return. • 22% presented to the emergency department. • Adolescent and young adult patients (18-39 years) were more likely to be treated for another condition or advised their symptoms were not serious, whereas elderly patients (65+ years) were more likely to be referred for further investigation.	See above.

12	Mendonca S, Abel G, Lyratzopoulos G. Pre-referral GP consultations in patients subsequently diagnosed with rarer cancers: a study of patient-reported data. British Journal of General Practice [Internet]. 2016 Mar [cited 2024 Jul 30]; 66(644):e171-e181.	BS and STS	This study aimed to examine the frequency and predictors of repeat pre-referral consultations with GPs in patients with cancers. • 41.3% of patients diagnosed with BS, and 31.9% of patients diagnosed with STS had ≥3 pre-referral consultations with their GP.	A study of patient reported data. Data was analysed from three waves of the English National Cancer Patient Experience Survey (2010, 2013, 2014). N=95,582. 196 patients diagnosed with BS and 508 diagnosed with STS presented to their GP at least once. **Limitations:** relies on patient recall and what they categorise as a consultation linked to their subsequent diagnosis which may limit the accuracy of findings. No detail about the circumstances of the consultations and reasons for not being referred in initial consultations are provided so we cannot understand the decision-making process and possible safety-netting steps being made by the GP.
13	Soomers V, Husson O, Young R, Desar I, Van der Graaf W. The sarcoma diagnostic interval: a systematic review on length, contributing factors and patient outcomes. ESMO Open [Internet]. 2020 Feb [cited 2024 Jul 30];5(1):e000592.	BS and STS	This review aimed to examine the total interval of sarcoma patients from first symptoms to diagnosis by quantifying its length, identifying contributing factors, and determining the impact on patients' outcomes. • The mean primary care interval for BS patients was 5-32.3 weeks.	In this systematic review 8 studies were included investigating BS primary care interval, and 5 studies were included investigating STS primary care interval. Primary care interval was defined as the interval between first presentation to a GP until first referral to secondary care or specialist sarcoma centre.

			• Primary care interval for STS patients had a median range of 0.1-13.3 weeks. • Patient gender, level of education and measures of social deprivation were not associated with length of total interval. • There was some evidence that older adolescents and young adults (range: 12-29 years) were more likely to have longer total intervals than adolescents and children. • More aggressive sarcomas had shorter total interval. • Two studies in BS found that when imaging studies were not ordered at patients first contact with a HCP, there was a longer diagnostic interval. • There was no association between length of total interval and survival for BS patients. For STS patients, the evidence was conflicting.	Total interval was defined as the interval between first symptom to (histological) diagnosis. **Limitations:** Studies span a large time frame (50 years) in which diagnostic techniques and pathways have evolved so findings may not be applicable to current context. Furthermore, this review included analysis of international studies which have different population settings and healthcare systems. This may limit the applicability of findings to a UK context.
-	Rafiq M, de Boer J, Mar J, et al. Clinical activity in general practice before sarcoma diagnosis: an Australian cohort study.	BS and STS	The study aimed to examine pre-diagnostic GP clinical activity before a sarcoma diagnosis to identify whether there are opportunities to expedite the diagnosis of sarcoma in general practice.	See above. **Limitations:** The study does not include information on the indications for investigation, imaging results or referral

	British Journal of General Practice [Internet]. 2024 Aug [cited 2024 Jul 29] ;74(745):e508-e516. Paper also summarised above. See paper 4.		• 55% of STS patients and 48% of BS patients were referred to a specialist by their GP. • Patients had a median 3-4 GP visits in the 6 months prior to diagnosis, and 6 GP visits in the year prior to diagnosis. • Cases showed increased clinical activity (imaging, blood tests, visits, prescriptions) in primary care in the 6 months prior to diagnosis.	details so we cannot understand the decision-making process and possible safety-netting steps being made by the GP. The study uses Australian data which limits the applicability of findings to a UK setting.
14	Herbert A, Lyratzopoulos G, Whelan J, Taylor R, Barber J, Gibson F, Fern L. Diagnostic timeliness in adolescents and young adults with cancer: a cross-sectional analysis of the BRIGHTLIGHT cohort. The Lancet Child and Adolescent Health [Internet]. 2018 Mar [cited 2024 Jul 30];2(3):180–190.	BS and STS	This study aimed to investigate diagnostic timeliness in adolescents and young adults with incident cancers. • Patients with BS and STS had longer symptom onset-to-diagnosis intervals compared to other cancer sites. • Median symptom onset-to-diagnosis intervals were longest for BS. • Patients with BS were more likely to have 3+ GP consultations pre-referral.	Cross-sectional analysis of BRIGHTLIGHT cohort (aged 13-24 years with a new primary cancer diagnosis across England) between July 2012 and April 2015. N=748 for symptom onset-to-diagnosis interval analysis. 68 were diagnosed with BS, 41 with STS. N=701 for GP prereferral analysis. 63 were diagnosed with BS, 39 with STS. **Limitations:** This study relies on patient recall which may limit the accuracy of findings.
-	Martin S, Clark S, Gerrand C, et al. Patients' Experiences of a Sarcoma Diagnosis: A Process		The study aimed to describe patients' experiences of pre-diagnostic signs and symptoms of sarcomas and pathways to diagnosis.	See above.

	Mapping Exercise of Diagnostic Pathways. Cancers [Internet]. 2022 Mar [cited 2024 Jul 29] ;14(5):1273. Paper also summarised above. See paper 5.		• Misattribution of symptoms in primary care occurred in 33.3% of BS and mostly in males (5M : 2F), in 22% of STS and mostly in females (2M : 7F), and 33.3% of head and neck sarcomas.	
15	Holthuis E, van der Graaf W, Drabbe C, et al. The prediagnostic general practitioner care of sarcoma patients: a real-world data study. Journal of Surgical Oncology [Internet]. 2024 Jun [cited 2024 Jul 30]; 130(2):265-275.	BS and STS	The study aimed to explore GP visit patterns and GP recorded diagnoses in the 12 months preceding a sarcoma diagnosis. • BS and STS cases showed a significant rise in monthly GP visits 2 months and 4 months respectively leading to diagnosis. • For BS cases, GPs most frequently documented diagnoses of musculoskeletal neoplasm (42.8%), knee symptoms/complaints (9.7%) and shoulder symptoms/complaints (9.7%). • For STS cases, GPs most frequently recorded diagnoses of musculoskeletal neoplasm (26.6%), uncomplicated hypertension (15.6%) and cystitis/UTI (12.2%). • Many STS cases were diagnosed with nonspecific symptoms which highlights the diversity of its clinical	Real world data study of adult sarcoma cases (ICD-10-GM codes C40, C41 and C49) diagnosed from 2010 to 2020 identified through the Netherlands Cancer Registry and matched (age ±5 years, sex, GP practice, registration years in GP practice) to cancer-free controls in GP data. N=188 BS patients N=787 STS patients **Limitations:** This study relies on GP coded data, which may lead to under-representation of conditions and symptoms impacting the accuracy of findings. Analysis is based on Dutch data and so findings which limits the applicability of findings to a UK setting.

			presentation and the difficulty in distinguishing between common complaints.	
16	Soomers V, van der Graaf W, Zaidi S, et al. The route to diagnosis of sarcoma patients: Results from an interview study in the Netherlands and the United Kingdom. PLoS ONE [Internet]. 2020 Dec [cited 2024 Jul 30]; 15(12): e0243439	BS and STS	This study aimed to investigate the route to diagnosis experienced by sarcoma patients, the impact route to diagnosis had on quality of life and care satisfaction, and the differences observed between English and Dutch patients' experiences. • The main trigger for help-seeking was interference of symptoms with daily life. • Diagnostic interval was prolonged (relatively) if the symptoms were misattributed to a differential diagnosis, there were inefficiencies in the investigation and reporting processes, there were long waiting times following referral, or there was a lack of lead clinician. • Factors related to lack of lead clinician were more evident in the English cohort. • To improve diagnostic pathways, patients recommended an increase in awareness amongst patients and HCPs, empowering patients, and having one clinical lead.	Qualitative interview analysis including 7 Dutch and 8 English patients over the age of 18 and who had been diagnosed within the past 4 months. N=15 Lack of lead clinician referred to patients being repeatedly referred to different specialists or where continuity of care was not with the same doctor. **Limitations:** Results rely on patient recall and interview responses may have been influenced by their diagnosis or point at treatment. This limits the reliability of the findings and results cannot be generalised to all sarcoma patients.

-	Goedhart L, Gerbers J, Ploegmakers J, Jutte P. Delay in Diagnosis and Its Effect on Clinical Outcome in High-grade Sarcoma of Bone: A Referral Oncological Centre Study. Orthopaedic Surgery [Internet]. 2016 Jul [cited 2024 Jul 29] ;8(2):122-128. Paper also summarised above. See paper 6.	BS	The study aimed to investigate delay in diagnosis by both patients and doctors, and to evaluate its effect on outcomes. • Mean patient-related interval was 83.2 days (SD 208.1 days). • Most doctor related delays occurred at the GP / pre-hospital stage. • Mean overall pre-hospital doctor-related delay was 101.5 days (SD 189.7 days). • There was no association between length of delay and patient outcomes.	See above. Delay in diagnosis was defined as the period between initial clinical symptoms and histopathological diagnosis. Short delays were <4 months, prolonged delays were >4 months.
-	Buvarp Dyrop H, Vedsted P, Rædkjær M, Safwat A, Keller Johnny. Routes to Diagnosis for Suspected Sarcoma: The Impact of Symptoms and Clinical Findings on the Diagnostic Process. Sarcoma [Internet]. 2016 Dec [cited 2024 Jul 29]; 2016(1):8639272. Paper also summarised above. See paper 9.	STS	The study aimed to the examine the association between presenting symptoms and time intervals for suspected sarcoma. • 87.3% of sarcoma patients first presented to their GP. • GPs initially suspected malignancy (tentative diagnosis) in 32.9% of sarcoma cases and 30.6% of benign cases. • There was a trend towards a higher number of GP consultations for sarcoma patients compared to patients with benign conditions (not significant).	See above.

-	Smolle MA, Leithner A, Grimer RJ. Evaluating the British sarcoma referral form. The Annals of The Royal College of Surgeons of England [Internet] 2015 Aug [cited 2024 Jul 29] ;97(6):434-438. Paper also summarised above. See paper 8.	STS	This study aimed to investigate concordance of GP referrals with NICE 2005 guidelines for STS, and whether the guidelines should be refined. • GPs accuracy for features of concern for STS were: 82% for 'size >5cm' 77% for 'deep to the fascia' 72% for 'pain' 69% for 'increase in size'. • 'Increase in size' feature was the least accurate of GP interpretations. This could be caused by suggestiveness of questions asked while taking patient history and patient recall.	See above.
17	Bacon A, Wong K, Fernando MS, et al. Incidence and survival of soft tissue sarcoma in England between 2013 and 2017, an analysis from the National Cancer Registration and Analysis Service. *Int J Cancer* [Internet]. 2023 [cited 2024 Aug 5];152(9):1789-1803.	STS	This study aimed to provide a population description of incidence and survival of STS in England according to clinically relevant histological parameters. • For routes to diagnosis, 39% of patients presented via GP referrals, 22.1% via the 2-week wait, 16.1% via emergency presentation and 15.5% via other outpatient appointments. • Children and young adults, those aged 75+ years, and those in more deprived areas are more likely to	Population-based cohort study describing histologically confirmed STS diagnosis between 2013 to 2017 from the National Cancer Data Register (England). N = 19,717 **Limitations:** The study refers back to English data between 2013 – 2017 which may limit applicability to current Scottish context.

			present through an emergency route.	

Topic: Risk Stratification				
Summary: For some types of bone cancer, younger people have a higher risk. Osteosarcoma and Ewing sarcoma are more common in children and young adults, and chondrosarcomas are more common in middle aged and elderly people. For soft-tissue sarcomas, risk factors include age (≥65 years), radiation exposure, previous radiotherapy treatment, and rare genetic conditions and predispositions. Infection with Epstein Barr virus and Human Herpes Virus 8 have been linked to leiomyosarcoma and Kaposi's sarcoma respectively and mostly affects those with lowered immunity. Previous cancer treatment has been associated with increased risk for developing subsequent malignant neoplasms. Radiotherapy treatment, particularly for adults after breast cancer[13], has been associated with developing sarcoma[14], and both radiotherapy and chemotherapy treatment for children with cancer have been linked to risk of primary bone cancer and sarcomas[15] [16]. Cancer Research UK has published information on risk factors associated with soft-tissue sarcomas and bone cancer. Paper 28 reported that soft tissue sarcomas are most likely to occur on limbs, and when considering anatomical location in women, in the uterus.				
Paper number	Study	Cancer	Summary	Notes

[13] Snow A, Ring A, Struycken L, Mack W, Koç M, Lang JE. Incidence of radiation induced sarcoma attributable to radiotherapy in adults: A retrospective cohort study in the SEER cancer registries across 17 primary tumor sites. Cancer Epidemiology [Internet]. 2021 Feb [cited 2024 Jul 30];70:101857.
[14] Berrington de Gonzalez, A., Kutsenko, A. & Rajaraman, P. Sarcoma risk after radiation exposure. Clin Sarcoma Res. 2012;2(18).
[15] Teepen J, van Leeuwen F, Tissing W, et al. Long-Term Risk of Subsequent Malignant Neoplasms After Treatment of Childhood Cancer in the DCOG LATER Study Cohort: Role of Chemotherapy. JCO. 2017;35(20):2288-2298.
[16] Fidler M, Reulen R, Winter D, et al. Risk of Subsequent Bone Cancers Among 69 460 Five-Year Survivors of Childhood and Adolescent Cancer in Europe, JNCI. 2017;110(2):183–194.

-	Martin S, Clark S, Gerrand C, et al. Patients' Experiences of a Sarcoma Diagnosis: A Process Mapping Exercise of Diagnostic Pathways. Cancers [Internet]. 2022 Mar [cited 2024 Jul 29] ;14(5):1273. Paper also summarised above. See paper 5.	BS and STS	The study aimed to describe patients' experiences of pre-diagnostic signs and symptoms of sarcoma and pathways to diagnosis. • BS was mostly diagnosed in males (67.7%), and those aged 25-39 (47.6%). • STS was mostly diagnosed in females (56.1%) and those aged 40-64 (46.3%) • Head and neck sarcoma was mostly diagnosed in females (66.7%%) and those aged 40-64 (55.6%)	See above.
-	Bacon A, Wong K, Fernando MS, et al. Incidence and survival of soft tissue sarcoma in England between 2013 and 2017, an analysis from the National Cancer Registration and Analysis Service. *Int J Cancer* [Internet]. 2023 [cited 2024 Aug 5];152(9):1789-1803. Paper also summarised above. See paper 17.	STS	This study aimed to provide a population description of incidence and survival of STS in England according to clinically relevant histological parameters. • Median age at diagnosis was 65 years. • Sarcomas were more common in females between ages 40 to 60 years and more common in males over 60 years. • Increased incidence of STS was described in more affluent areas compared to more deprived areas (22% vs 16%).	See above.

18	Bhatt N, Deady S, Gillis A, et al. Epidemiological study of soft-tissue sarcomas in Ireland. *Cancer Medicine* [Internet]. 2016 [cited 2024 Aug 5]; 5(1):129-135.	STS	The study aimed to describe current incidence and survival of STS in Ireland. • The most frequent site for developing STS was the limbs (20%), the uterus (16%) and the skin (10%). • Peak incidence of STS was in the age group 75-79 years. • Incidence rates of STS were higher in females than in males (0.837M : 1F). • STS in females was most commonly found in the uterus, and in males in the limbs.	Retrospective population study on data from the National Cancer Registry of Ireland between 1994 to 2012. N=3339 STS cases **Limitations:** Classification of sarcomas evolved considerably over the study period which could affect reported incidence rates. This study used the RARECARE group classification system which may not reflect the same classification system used in the UK, limiting the applicability of findings.
19	Weskamp P, Ufton D, Drysch M, Wagner JM, Dadras M, Lehnhardt M, Behr B, Wallner C. Risk Factors for Occurrence and Relapse of Soft Tissue sarcoma. Cancers [Internet]. 2022 Mar [cited 2024 Jul 30]; 14(5):1273.	STS	This study aimed to determine if there are reliable risk factors for developing STS as well as prognostic indicators for recurrence free survival. • The combination of smoking, genetic predisposition, toxins and chronic inflammation together is associated with an overall significantly increased risk for STS. • Each risk factors alone was not found to be statistically significant.	Systematic meta-analysis of 24 studies published between 1993 and 2019. N=6452 patients. **Limitations:** Some of the risk factors analysed are quite broad and non-specific which limits the applicability of findings for a clinical setting.

Emerging Topics

AI models in imaging for diagnosis

Machine learning models are being developed to improve the detection and efficiency of identifying bone and soft tissue malignancy in diagnostic imaging. These tools aim to reduce the need of time-consuming expert manual review and provide computer-aided diagnostic tools to clinicians. Many of these tools are still in the development and testing phase and more evidence will be needed before it can be implemented.

Suspected Cancer Referral Guidelines: NG12 and SRG

	NG12	SRG
	https://www.nice.org.uk/guidance/ng12/evidence/full-guideline-pdf-2676000277	https://www.cancerreferral.scot.nhs.uk/sarcomas-and-bone-cancers/

Bone	Bone sarcoma in adults
	Consider a **suspected cancer pathway referral (28 days)** for adults if an **X-ray** suggests the possibility of bone sarcoma.
		Investigation of suspected bone cancer
		An **X-ray** of the appropriate area should be requested on patients who have:
		• **unexplained bone pain or tenderness**, which is:
		  ○ persistent
		  ○ increasing
		  ○ non-mechanical
		  ○ nocturnal or at rest
		If x-ray is suggestive of bone tumour, refer **as urgent suspicion of cancer** to sarcoma service.
		
		Good Practice Points
		• Sarcomas of the long bones are usually excluded by normal x-ray but further investigation may be required for spine, pelvis, ribs or scapula.
		• If symptoms persist but x-ray is normal, repeat x-ray (following discussions with radiologist) and consider referral

		• Suspected spontaneous or low impact fracture should raise suspicion of underlying malignancy

Soft tissue sarcoma	<u>Soft tissue sarcoma in adults</u>
	Consider an **urgent, direct access ultrasound scan** (to be done within 2 weeks) to assess for soft tissue sarcoma in adults with an unexplained lump that is **increasing in size**.
	
	Consider a **suspected cancer pathway referral (28 days)** for adults if they have ultrasound scan findings that are suggestive of soft tissue sarcoma or if ultrasound findings are uncertain and clinical concern persists.
		<u>Urgent suspicion of cancer referral</u> <u>(soft tissue sarcoma)</u>
		• Soft tissue mass with **one or more** of the following characteristics:
		  ○ size **>5cm**
		  ○ **increasing in size**
		  ○ **deep to fascia, fixed or immobile**
		  ○ **recurrence** after previous excision
		  ○ **regional lymph node enlargement**