CANCER EPIDEMIOLOGY

INTERNATIONAL JOURNAL of CANCER

Incidence and survival of soft tissue sarcoma in England between 2013 and 2017, an analysis from the National Cancer Registration and Analysis Service

Andrew Bacon[1] | Kwok Wong[1] | Malee S. Fernando[2] | Brian Rous[1,3] |
Roger J. W. Hill[1] | Shane D. Collins[1,4] | John Broggio[1] | Sandra J. Strauss[1,4]

[1]NHS Digital, National Cancer Registration and Analysis Service, Leeds, UK

[2]Department of Histopathology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK

[3]Department of Histopathology, Cambridge University Hospitals, Cambridge, UK

[4]University College London, Cancer Institute, London, UK

Correspondence
Sandra J. Strauss, UCL Cancer Institute, 72 Huntley Street, London, WC1A 6DD, UK.
Email: s.strauss@ucl.ac.uk

Funding information
Sarcoma UK, Grant/Award Number: SUK106.2018; UCLH Biomedical Research Centre

Abstract

There is a paucity of population-based data detailing the incidence and survival of patients with soft tissue sarcoma (STS), in part due to the heterogeneity of disease and changes to classification. Here, the incidence and survival of all STS subtypes registered in England between 2013 and 2017 were analysed using cancer registry data held by the National Cancer Registration and Analysis Service. Age-standardised incidence rates were calculated per 1 000 000 using the 2013 European Standard Population. Net survival was computed using Brenner's alternative method, with the Ederer II estimator. Age-specific overall survival was assessed using Kaplan-Meier. The influence of age, sex, socioeconomic deprivation and diagnostic routes on survival was assessed using Cox proportional hazards modelling. In total, 19 717 patients were diagnosed with STS, an average of 3943 patients per year and representing approximately 0.8% of malignancies. The most common histological diagnoses were Gastrointestinal Stromal Tumours (GIST), leiomyosarcoma and undifferentiated sarcoma, accounting for 20.2%, 13.3% and 12.7% of all sarcomas, respectively. Five-year net survival for all malignant STS was 65.0%; and was lowest for patients with vascular tumours at 39%. Patients from most deprived cohorts had 23% greater chance of dying within 5 years than patients in least deprived areas. This population-based study has allowed us for the first time to define the incidence and survival rates of prevalent STS subtypes in England such as GIST, liposarcoma and leiomyosarcoma, as well as rare entities and groups with inferior outcome. This data is invaluable for service provision, benchmarking and addressing inequality.

What's new?

Histological and anatomical diversity of soft tissue sarcoma (STS), along with variability in classification and reporting, present major challenges for understanding STS incidence and survival. In our study, STS incidence and outcome were analysed for an English population using the 2013 World Health Organisation classification system for soft tissue tumours and data from England's National Cancer Registration and Analysis Service. Analyses show that, on average, more than 3900 patients were diagnosed with STS in England annually from 2013 to 2017, with an overall incidence of 78 persons per million. Overall, 65% of patients with malignant STS survived 5 years with outcome varying across age groups.

1 | INTRODUCTION

Sarcomas are a heterogenous group of mesenchymal tumours with a wide anatomical distribution and more than 80 histological subtypes,[1,2] accounting for ~1% of all newly diagnosed cancers each year.[3,4] They are an important group of diseases that affect patients of all ages including children and adolescents and require complex treatment that can have a significant impact on the quality of life and with many examples of poor outcome. Attainment of accurate population-based data on the incidence and outcome of sarcomas according to the different histological subtypes has been hampered by the heterogeneity of the disease, challenges of reporting using standard pathology systems which assign tumours according to anatomic site rather than histology, as well as changes to pathology classification, and rarity of many of the defined subtypes. As a consequence, there is a paucity of data available and considerable variation in incidence reported over time and between regions or countries and dependent on the availability of expert pathology review.[5-7] Histology-specific population-based data is, however, increasingly available, including a French Nationwide analysis of sarcoma incidence made possible due to the establishment of French Reference Centre networks, and a report of German regional registry data that now reaches over 90% completeness.[8-10] To date, incidence and outcome of soft tissue sarcoma (STS) has not been reported in England. Historically, the collection of diagnostic and clinical data has been challenging for cancer registries to assess systematically, whilst ensuring the accuracy and completeness of primary data.[11] However, the establishment of the National Cancer Registration and Analysis Service in 2013, coupled with increased procurement of electronic records, has strengthened NHS Digital's ability to provide comprehensive analysis for service providers, clinicians, patients, researchers and charities on rare and less common cancers. The aim of the study was to provide an accurate population-based description of the incidence and survival of STS in England, according to clinically relevant histological parameters for the first time, to inform the clinical and research communities, as well as stakeholders in provision of care and to identify groups with inferior outcome.[12]

2 | METHODS

2.1 | Data collection

All cancer diagnoses are required to be registered in England. Patients of all ages, resident in England, diagnosed with histologically confirmed sarcoma between January 1, 2013 and December 31, 2017 were included in the analysis, including those diagnosed by death certificate only. Diagnoses were made by pathologists and recorded by specialist clinical coders on the National Cancer Data Register with diagnostic data undergoing quality control within NCRAS Cancer Data Registration system (CDRS). Classifications of disease were extracted according to the International Classification of Diseases for Oncology third edition ICDO-3, which unlike ICD-10, not only includes the anatomical site of origin, but also a morphology code detailing the specific histology and a behaviour code (benign, uncertain/intermediate behaviour or malignant). Soft tissue tumours of uncertain/intermediate and malignant behaviour are registered in the National Disease Registration Service.

To ensure consistent coding across the cohort, ICD03.1 was used. The 2013 WHO classification, which was used to ensure consistency of reporting, was published after ICDO3.1, thus some entities are missing from ICDO3.1 and could potentially be coded differently. Many of the affected tumours are considered benign so are not included the study. Malignant tumours that were introduced in the 2013 WHO classification but not explicitly listed in ICDO3.1 include low grade fibromyxoid sarcoma which was coded as a specific entity throughout the study, sclerosing epithelioid fibrosarcoma, which is coded as fibrosarcoma, NOS in the study and intimal sarcoma, coded as sarcoma, NOS in the study.

Uncertain behaviour tumours that were introduced in the 2013 WHO classification system but not explicitly listed in ICDO3.1 include dermatofibrosarcoma protuberans which is coded as behaviour 3 in ICDO3.1 so are included as well as solitary fibrous tumour, retiform haemangioendothelioma, palmar/plantar fibromatosis; glomangiomatosis; and myxoinflammatory fibroblastic sarcoma/haemosiderotic fibrolipomatous tumour, which were included through use of the matrix rule (rule F) lipofibromatosis; tenosynovial giant cell tumour,

diffuse type and melanotic schwannoma were excluded from the study.

Patient demographics are collected from NHS providers through the Cancer Outcomes and Services Dataset (COSD). Lower super output area-based deprivation measures are assigned to patients based on their postcode of residence at the time of diagnosis and are based on the income domain of the Indices of Multiple Deprivation.[13] Quintile 1 represents the most affluent quintile, and the fifth the poorest. Routes to diagnosis (RTD) are defined employing an algorithmic approach that describe patients' care pathways to diagnosis of cancer as one of eight routes. It uses Hospital Episode Statistics, a data warehouse containing details of all admissions, outpatient appointments and emergency attendances at NHS hospitals in England, which are linked to Cancer Waiting Times and data from national screening programmes.[14] RTD thus includes cancers detected via a screening programme, those reflecting the urgency of referral (emergency presentation, 2-week wait [TWW], which mandates that patients with suspected *cancer* are referred from primary to secondary care and must be seen within 2 weeks of referral, and elective GP referral), and cases where patients' diagnostic journey started in secondary care (Outpatient elective or 'Other inpatients'). The remaining two routes include cases identified based on death certificates and those with no useful record on RTD (unknowns).

Registration of death in England is compulsory through the Office of National Statistics, with registrations passing through a series of automatic validations to ensure a complete annual dataset. This analysis was performed more than 2 years from the end of the follow-up period to analysis, thus the death dataset is complete.

2.2 | Protection of cancer registration data

NHS Digital collects data for cancer registration under sections 254 (1) and 254(6) of the 2012 Health and Social Care Act following a direction of the Secretary of State for Health and Social Care.[15]

2.3 | Study design

This population-based cohort analysis includes all registrable primary tumours of malignant and intermediate behaviour for patients diagnosed with STS. Kaposi sarcoma was excluded because it is routinely managed outside of sarcoma services. STS were defined according to the 2013 WHO Classification of Tumours of Soft Tissue and Bone with 84 separate morphologies grouped within 16 subgroups.[1] Cases where the primary site was registered to bone or articular cartilage were excluded from analysis. If the patient's primary site of disease is unknown, they will have a site code of C80 attached to their morphological description. Here C80 is defined as 'unknown primary site', of which, there are 62 cases. In these instances, allocation to soft tissue was based on the morphology code.

2.4 | Statistical analysis

Age-standardised rates (ASR) are reported per 1 000 000 and standardised using European Standard Population (ESP) from 2013. Logistic regression was used to assess the significance of incidence across multiple deprivation quintiles and styled routes to diagnosis.

Net survival with Ederer II estimator using Brenner's alternative weighting was utilised to assess survival. This is a novel method for measuring survival against the expected survival of the population (background mortality) that enables net survival to be calculated with small cohort size numbers and limited data within certain age groups.[16] As STS are rare cancers with very small numbers within age groups this method was deemed most appropriate. Survival estimates were age standardised using the international cancer survival standard.[17] Background mortality is accounted for using life tables of all-cause mortality rates for the general population in England. Life tables used were produced by NHS Digital and are available via the Cancer-Data website (https://www.cancerdata.nhs.uk/). The second International Cancer Survival Standard (ICSS2) weighting was used to categorise net survival measures for all subtypes according to five broad age groups at diagnosis as follows: 15-44; 45-54; 55-64; 65-74; ≥75 years. Data was suppressed where there was <1 patient per ICSS age group. Results are shown with 95% confidence intervals (CIs) according to WHO classification of sarcoma subtypes. Children were excluded from Net survival analyses as the death of a child within 10 years of a cancer diagnosis is almost always due to their cancer diagnosis and not other causes, thus comparisons to the general population are not needed. Kaplan-Meier survival was used to calculate overall survival for all patients according to age including children.

Time at risk began at the date of diagnosis and continued until the point of embarkation, death or the end of the follow-up period on the December 31, 2017. A total of 65 patients (0.3%) were excluded because the only information available on diagnosis was from the death certificate and an additional 38 were removed for having synchronous tumours. For Kaplan-Meier survival analysis a further 7 patients were excluded for being outside of the age parameters (0-99). Net survival excluded an additional 540 patients for being outside of the age parameters (15-99) and 158 patients were ineligible due to data incompleteness. A total of 202 patients were lost to follow up.

Cox proportional hazards modelling was used to assess the impact morphology, age, sex, deprivation and routes to diagnosis on survival.[18] Variables were assessed for time dependency using Schoenfeld's residual test and adjusted for using polynomials or adding in time dependent variables. All tests were conducted at the 5% level of significance. Analysis was performed using Stata 15 (Station College, Texas TX; Computing Resource Centre, Santa Monica, CA).

3 | RESULTS

3.1 | Incidence

Between 2013 and 2017, 19 717 cases of STS in England were recorded, with a combined incidence of 78 persons per million; ~12

TABLE 1 Incidence of all soft tissue sarcomas diagnosed in England per million, per year between 2013 and 2017

Morphological description	Total diagnosed	Median age	Average per year	Persons				Males				Females			
				Crude	ASR	LCI	UCI	Crude	ASR	LCI	UCI	Crude	ASR	LCI	UCI
All soft tissue sarcomas	19 717	65	3943	72.00	78.36	77.25	79.47	74.36	84.91	83.24	86.61	69.70	71.80	70.37	73.25
Gastrointestinal stromal tumour (GIST)	3976	68	795	14.52	15.95	15.46	16.46	15.24	17.50	16.75	18.28	13.82	14.41	13.77	15.07
Gastrointestinal stromal tumours (intermediate behaviour)	2792	69	558	10.20	11.22	10.80	11.64	10.33	11.94	11.32	12.59	10.06	10.49	9.94	11.06
Gastrointestinal stromal tumours (malignant)	1184	67	237	4.32	4.74	4.47	5.02	4.91	5.56	5.14	6.00	3.76	3.92	3.59	4.27
Leiomyosarcoma	2627	64	525	9.59	10.46	10.06	10.88	8.15	9.45	8.89	10.03	11.00	11.48	10.91	12.07
Epithelioid leiomyosarcoma	59	64	12	0.22	0.23	0.18	0.30	0.13	0.14	0.08	0.22	0.30	0.32	0.23	0.44
Leiomyosarcoma NOS	2541	64	508	9.28	10.13	9.73	10.53	7.98	9.26	8.71	9.83	10.55	11.00	10.44	11.58
Myxoid leiomyosarcoma	27	59	5	0.10	0.10	0.07	0.15	0.04	0.05	0.02	0.11	0.15	0.16	0.10	0.24
Undifferentiated sarcoma	2501	74	500	9.13	10.54	10.12	10.96	12.00	14.62	13.90	15.36	6.34	6.45	6.03	6.90
Fibrous histiocytoma, malignant	230	78	46	0.84	1.03	0.89	1.17	1.34	1.69	1.45	1.96	0.35	0.36	0.27	0.48
Undifferentiated pleomorphic sarcoma/giant cell sarcoma	1097	77	219	4.01	4.77	4.49	5.07	5.91	7.37	6.86	7.91	2.16	2.18	1.94	2.44
Spindle cell sarcoma	867	69	173	3.17	3.54	3.30	3.79	3.43	4.13	3.77	4.51	2.92	2.99	2.71	3.29
Undifferentiated round cell sarcoma[a]	28	49	5	0.10	0.11	0.07	0.16	0.13	0.15	0.09	0.24	0.07	0.07	0.03	0.13
Undifferentiated sarcoma	279	70	56	1.02	1.13	1.00	1.28	1.04	1.24	1.04	1.47	1.00	1.02	0.86	1.21
Liposarcoma	2270	65	454	8.29	9.15	8.77	9.54	10.86	12.30	11.67	12.95	5.78	6.00	5.59	6.43
Dedifferentiated liposarcoma	533	68	107	1.95	2.20	2.02	2.40	2.63	3.08	2.76	3.42	1.28	1.33	1.14	1.54
Fibroblastic liposarcoma	6	53	1	0.02	0.02	0.01	0.05	0.04	0.04	0.01	0.09	0.01	0.01	0.00	0.04
Liposarcoma, NOS; fibroliposarcoma	572	67	114	2.09	2.31	2.12	2.51	2.72	3.11	2.79	3.44	1.48	1.51	1.31	1.73
Liposarcoma, well differentiated	548	65	110	2.00	2.20	2.02	2.39	2.45	2.75	2.46	3.06	1.56	1.64	1.43	1.88
Mixed liposarcoma	9	64	2	0.03	0.03	0.02	0.06	0.04	0.05	0.02	0.10	0.02	0.02	0.00	0.06
Myxoid liposarcoma; myxoliposarcoma	360	46	72	1.31	1.38	1.24	1.53	1.73	1.81	1.59	2.06	0.91	0.94	0.78	1.12
Pleomorphic liposarcoma[a]	230	70	46	0.84	0.93	0.81	1.06	1.14	1.42	1.22	1.64	0.56	0.56	0.45	0.70
Round cell liposarcoma	12	40	2	0.04	0.04	0.02	0.08	0.04	0.04	0.02	0.10	0.04	0.05	0.02	0.10
Other malignant soft tissue tumours	1925	71	385	7.03	7.77	7.42	8.13	6.68	8.04	7.52	8.59	7.37	7.49	7.04	7.97
Adenosarcoma	226	61	45	—	—	—	—	—	—	—	—	1.63	1.70	1.48	1.93
Angiomyoliposarcoma	5	47	1	0.02	0.02	0.01	0.04	0.02	0.02	0.00	0.06	0.01	0.01	0.00	0.05
Extraskeletal chondrosarcoma	117	62	24	0.43	0.45	0.38	0.55	0.52	0.56	0.44	0.71	0.34	0.35	0.25	0.46
Extraskeletal clear cell chondrosarcoma	1	28	0	0.00	0.00	0.00	0.02	0.01	0.01	0.00	0.04	0.00	0.00	—	—
	6	49	1	0.02	0.02	0.01	0.05	0.01	0.02	0.00	0.06	0.03	0.03	0.01	0.08

TABLE 1 (Continued)

Morphological description	Total diagnosed	Median age	Average per year	Persons Crude	ASR	LCI	UCI	Males Crude	ASR	LCI	UCI	Females Crude	ASR	LCI	UCI
Extraskeletal dedifferentiated chondrosarcoma															
Embryonal sarcoma[a]	11	11	2	0.04	0.04	0.02	0.07	0.03	0.03	0.01	0.07	0.05	0.05	0.02	0.10
Giant cell tumour of soft part, NOS[a]	6	48	1	0.02	0.02	0.01	0.05	0.01	0.01	0.00	0.05	0.03	0.03	0.01	0.07
Malignant tumour, giant cell type	2	N/A	0	0.01	0.01	0.00	0.03	0.00	0.00	—	—	0.01	0.01	0.00	0.05
Malignant tumour, spindle cell type	23	72	5	0.08	0.10	0.06	0.15	0.10	0.12	0.06	0.20	0.07	0.07	0.04	0.14
Mesenchymal chondrosarcoma[a]	11	26	2	0.04	0.04	0.02	0.07	0.03	0.03	0.01	0.07	0.05	0.05	0.02	0.10
Mesenchymoma, malignant	19	62	4	0.07	0.07	0.04	0.12	0.07	0.08	0.04	0.15	0.06	0.07	0.03	0.13
Myosarcoma	4	58	1	0.01	0.01	0.00	0.04	0.01	0.01	0.00	0.04	0.02	0.02	0.00	0.06
Extraskeletal osteosarcoma, NOS[a]	47	65	9	0.17	0.19	0.14	0.25	0.19	0.21	0.14	0.32	0.16	0.16	0.10	0.25
Sarcoma, NOS	1430	74	286	5.22	5.88	5.57	6.20	5.68	6.94	6.45	7.46	4.78	4.82	4.46	5.20
Stromal sarcoma	17	58	3	0.06	0.06	0.04	0.10	0.01	0.01	0.00	0.05	0.12	0.12	0.07	0.19
Myxoid fibroblastic sarcomas	967	68	193	3.53	3.88	3.63	4.13	4.09	4.71	4.32	5.12	2.98	3.05	2.76	3.36
Low-grade fibromyxoid sarcoma[a]	79	49	16	0.29	0.29	0.23	0.37	0.33	0.34	0.25	0.46	0.25	0.24	0.17	0.34
Myxofibrosarcoma	888	69	178	3.24	3.58	3.35	3.83	3.76	4.37	3.99	4.77	2.74	2.80	2.53	3.10
Vascular tumours	948	70	190	3.46	3.78	3.54	4.03	2.85	3.37	3.03	3.72	4.06	4.19	3.85	4.56
Angiomyosarcoma	39	68	8	0.14	0.16	0.11	0.21	0.15	0.16	0.10	0.25	0.14	0.15	0.09	0.23
Epithelioid haemangioendothelioma, malignant[a]	68	53	14	0.14	0.16	0.11	0.21	0.15	0.16	0.10	0.25	0.14	0.15	0.09	0.23
Glomus tumour, malignant glomus tumour[a]	8	41	2	0.03	0.03	0.01	0.06	0.02	0.02	0.00	0.07	0.04	0.03	0.01	0.08
Haemangioendothelioma, malignant[a]	13	64	3	0.05	0.05	0.03	0.09	0.05	0.06	0.02	0.12	0.04	0.05	0.02	0.10
Haemangiosarcoma, angiosarcoma of soft tissue	820	71	164	2.99	3.29	3.06	3.52	2.43	2.92	2.61	3.26	3.54	3.65	3.34	3.99
Soft tissue tumours of intermediate behaviour	955	53	191	3.49	3.63	3.41	3.87	3.46	3.66	3.33	4.01	3.52	3.61	3.29	3.94
Abdominal fibromatosis	143	39	29	0.52	0.53	0.44	0.62	0.29	0.30	0.21	0.41	0.75	0.75	0.61	0.91
Angiomatoid fibrous histiocytoma[a]	35	18	7	0.13	0.12	0.08	0.17	0.13	0.12	0.07	0.19	0.13	0.13	0.07	0.20
Atypical lipomatous tumours	516	61	103	1.88	2.04	1.87	2.23	2.26	2.48	2.21	2.78	1.52	1.61	1.40	1.84
Giant cell fibroblastoma	6	30	1	0.02	0.02	0.01	0.05	0.03	0.03	0.01	0.07	0.01	0.01	0.00	0.05
Giant cell tumour of soft parts (morphologic abnormality)[a]	117	48	23	0.43	0.44	0.36	0.52	0.27	0.28	0.20	0.38	0.58	0.59	0.47	0.74
Glomangiomatosis (pericytic tumours)	12	59	2	0.04	0.05	0.02	0.08	0.06	0.06	0.03	0.12	0.03	0.03	0.01	0.08

(Continues)

TABLE 1 (Continued)

Morphological description	Total diagnosed	Median age	Average per year	Persons Crude	Persons ASR	Persons LCI	Persons UCI	Males Crude	Males ASR	Males LCI	Males UCI	Females Crude	Females ASR	Females LCI	Females UCI
Haemangioendothelioma, NOS[a]	36	13	7	0.13	0.12	0.09	0.17	0.12	0.11	0.06	0.18	0.14	0.14	0.08	0.21
Myofibromatosis, NOS	26	1	5	0.09	0.08	0.05	0.12	0.10	0.09	0.05	0.14	0.09	0.08	0.04	0.14
Myxoinflammatory fibroblastic sarcoma[a]	29	59	6	0.11	0.11	0.07	0.16	0.07	0.08	0.04	0.15	0.14	0.14	0.08	0.22
Pleomorphic hyalinizing angiectatic tumour (PHAT)	6	64	1	0.02	0.02	0.01	0.05	0.02	0.02	0.00	0.07	0.02	0.02	0.00	0.06
Plexiform fibrohistiocytic tumour	21	13	4	0.08	0.07	0.05	0.11	0.07	0.06	0.03	0.12	0.09	0.09	0.04	0.15
Retiform haemangioendothelioma	8	38	2	0.03	0.03	0.01	0.06	0.02	0.02	0.00	0.07	0.04	0.04	0.01	0.08
Dermatofibrosarcoma protuberans	734	44	147	2.68	2.75	2.55	2.96	2.49	2.58	2.31	2.87	2.86	2.92	2.64	3.23
Fibrosarcomatous dermatofibrosarcoma protuberans	—	—	—	N/A				—	—	—	—				
Endometrial stromal sarcoma	394	55	79	—	—	—	—	—	—	—	—	2.84	2.96	2.67	3.27
Endometrial stromal sarcoma[a]	241	58	48	—	—	—	—	—	—	—	—	1.74	1.81	1.59	2.06
Endometrial stromal sarcoma, low grade[a]	153	50	31	—	—	—	—	—	—	—	—	1.10	1.15	0.97	1.34
Synovial	397	42	79	1.45	1.47	1.33	1.62	1.57	1.59	1.38	1.82	1.33	1.35	1.16	1.56
Synovial sarcoma, biphasic	48	39	10	0.18	0.18	0.13	0.24	0.19	0.19	0.12	0.28	0.16	0.17	0.10	0.25
Synovial sarcoma, epithelioid cell	2	47	0	0.01	0.01	0.00	0.03	0.00	0.00	—	—	0.01	0.02	0.00	0.06
Synovial sarcoma, NOS	277	42	55	1.01	1.02	0.90	1.15	1.06	1.07	0.90	1.26	0.97	0.97	0.81	1.15
Synovial sarcoma, spindle cell	70	43	14	0.26	0.26	0.20	0.33	0.30	0.31	0.22	0.43	0.21	0.21	0.14	0.30
Rhabdomyosarcoma	559	16	112	2.04	1.94	1.78	2.11	2.24	2.09	1.86	2.35	1.85	1.79	1.58	2.03
Alveolar rhabdomyosarcoma[a]	156	15	31	0.57	0.53	0.45	0.62	0.59	0.53	0.42	0.66	0.55	0.53	0.41	0.66
Embryonal rhabdomyosarcoma[a]	180	7	36	0.66	0.58	0.50	0.67	0.75	0.64	0.52	0.78	0.56	0.52	0.41	0.65
Mixed type rhabdomyosarcoma	3	20	1	0.01	0.01	0.00	0.03	0.01	0.01	0.00	0.04	0.01	0.01	0.00	0.05
Pleomorphic rhabdomyosarcoma[a]	70	70	14	0.26	0.29	0.23	0.37	0.27	0.33	0.23	0.46	0.24	0.25	0.17	0.35
Rhabdomyosarcoma, NOS; rhabdosarcoma	121	42	24	0.44	0.43	0.36	0.52	0.47	0.45	0.34	0.57	0.42	0.42	0.32	0.54
Spindle cell rhabdomyosarcoma[a]	29	19	6	0.11	0.10	0.07	0.15	0.15	0.14	0.08	0.21	0.06	0.07	0.03	0.13
Tumours of uncertain differentiation	425	46	85	1.55	1.57	1.42	1.73	1.75	1.80	1.57	2.04	1.36	1.35	1.16	1.56
Alveolar soft part sarcoma[a]	28	27	6	0.10	0.10	0.07	0.14	0.10	0.10	0.05	0.16	0.11	0.10	0.06	0.17
Clear cell sarcoma (except of kidney M8964/3)[a]	44	33	9	0.16	0.16	0.11	0.21	0.16	0.15	0.09	0.23	0.17	0.17	0.10	0.25
Clear cell sarcoma of kidney[a]	14	3	3	0.05	0.04	0.02	0.07	0.07	0.06	0.03	0.11	0.04	0.03	0.01	0.07
Desmoplastic small round cell tumour[a]	59	23	12	0.22	0.21	0.16	0.27	0.30	0.29	0.21	0.40	0.13	0.13	0.08	0.21

TABLE 1 (Continued)

Morphological description	Total diagnosed	Median age	Average per year	Persons				Males				Females			
				Crude	ASR	LCI	UCI	Crude	ASR	LCI	UCI	Crude	ASR	LCI	UCI
Epithelioid sarcoma[a]	97	49	19	0.35	0.36	0.29	0.44	0.41	0.42	0.32	0.55	0.30	0.31	0.22	0.41
Mixed tumour NOS, malignant[a]	12	69	2	0.04	0.05	0.03	0.09	0.07	0.08	0.04	0.15	0.01	0.01	0.00	0.05
Myoepithelial carcinoma[a]	64	66	13	0.23	0.26	0.20	0.33	0.22	0.26	0.17	0.37	0.25	0.25	0.17	0.35
Extraskeletal myxoid chondrosarcoma[a]	69	62	14	0.25	0.27	0.21	0.34	0.29	0.31	0.22	0.42	0.22	0.22	0.15	0.32
Rhabdoid sarcoma (extra-renal rhabdoid tumour)	38	1	8	0.14	0.13	0.09	0.17	0.14	0.13	0.08	0.20	0.14	0.12	0.07	0.19
Myofibrosarcomas and other fibroblastic sarcomas	391	61	78	1.43	1.53	1.38	1.69	1.51	1.67	1.45	1.92	1.35	1.39	1.20	1.60
Fibrosarcoma, NOS	62	64	12	0.23	0.24	0.19	0.31	0.28	0.31	0.22	0.42	0.17	0.18	0.11	0.27
Haemangiopericytoma	28	60	6	0.10	0.11	0.07	0.16	0.10	0.11	0.06	0.19	0.10	0.10	0.06	0.17
Infantile fibrosarcoma; congenital fibrosarcoma[a]	15	0	3	0.05	0.04	0.02	0.07	0.07	0.05	0.02	0.10	0.04	0.04	0.01	0.08
Inflammatory myofibroblastic tumour[a]	78	51	16	0.28	0.30	0.24	0.38	0.27	0.30	0.21	0.42	0.30	0.30	0.21	0.41
Malignant tenosynovial giant cell tumour[a]	18	45	4	0.07	0.07	0.04	0.11	0.07	0.07	0.03	0.13	0.06	0.06	0.03	0.12
Solitary fibrous tumour, NOS	190	65	38	0.69	0.77	0.66	0.89	0.71	0.83	0.67	1.01	0.68	0.71	0.57	0.87
Malignant peripheral nerve sheath tumours (MPNST)	359	49	72	1.31	1.36	1.22	1.51	1.45	1.53	1.32	1.76	1.17	1.19	1.01	1.39
Granular cell tumour, malignant	7	46	1	0.03	0.03	0.01	0.06	0.03	0.03	0.01	0.08	0.02	0.02	0.00	0.07
MPNST with rhabdomyoblastic differentiation	29	35	6	0.11	0.11	0.08	0.16	0.16	0.17	0.10	0.26	0.06	0.06	0.02	0.11
Malignant peripheral nerve sheath tumour, NOS	257	50	51	0.94	0.97	0.85	1.10	1.01	1.06	0.89	1.26	0.86	0.88	0.73	1.05
Malignant schwannoma; neurilemoma, malignant	59	50	12	0.22	0.22	0.17	0.29	0.24	0.26	0.18	0.36	0.19	0.19	0.12	0.28
Perineurioma, malignant; perineural MPNST	5	50	1	0.02	0.02	0.01	0.04	0.01	0.01	0.00	0.04	0.03	0.03	0.01	0.08
Rhabdomyosarcoma with ganglionic differentiation	2	2	0	0.01	0.01	0.00	0.02	—	—	—	—	0.01	0.01	0.00	0.04
Phyllodes tumour	289	56	58	—	—	—	—	—	—	—	—	2.08	2.18	1.93	2.45
Phyllodes tumour, malignant[a]	—	—	—	N/A											

Note: Incidence is presented according to the European Standard Population.

Abbreviations: ASR, age standardised rate; LCI, lower confidence interval; UCI, upper confidence interval.

[a]Ultra-rare soft tissue sarcomas.
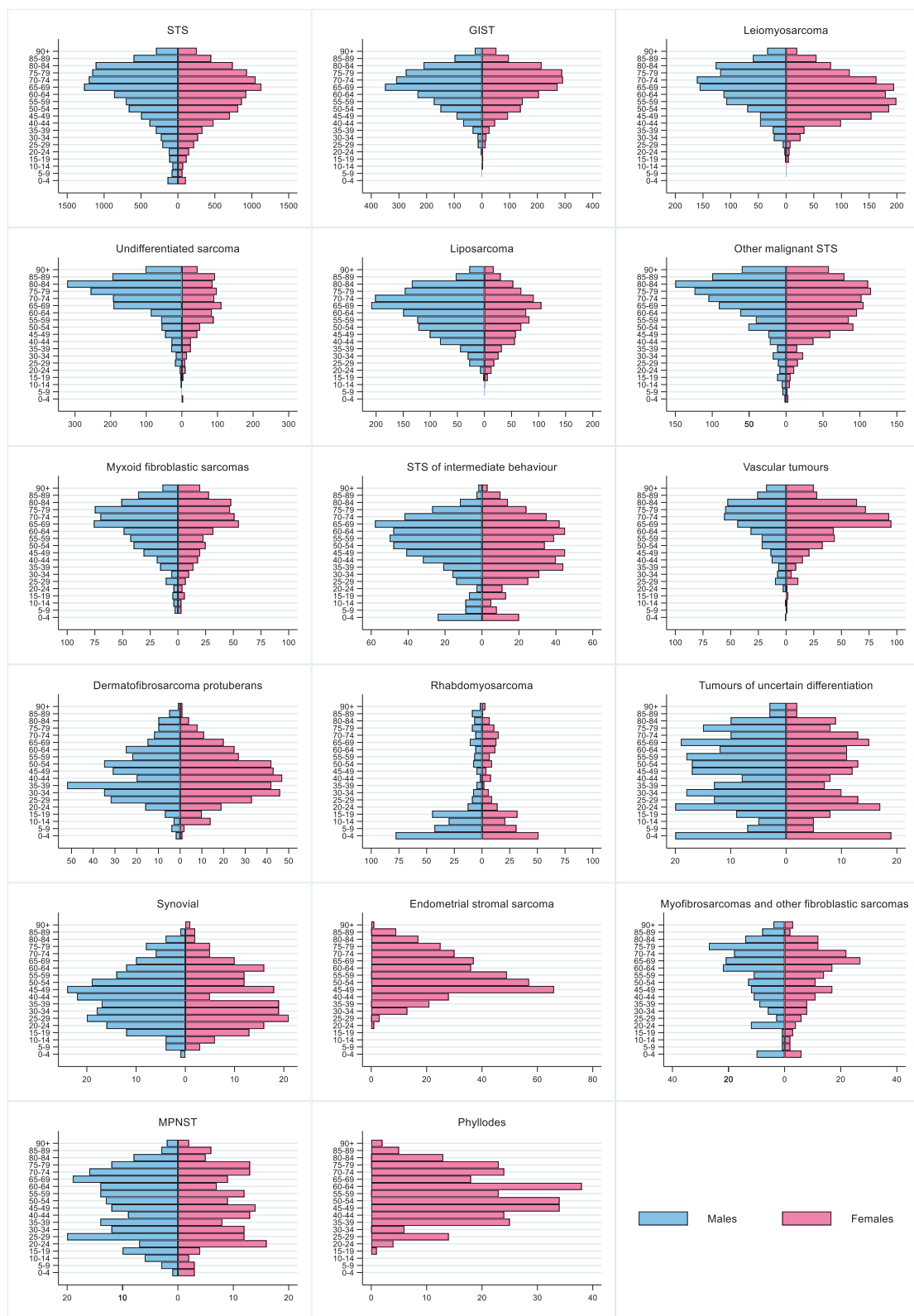
* STS – Soft Tissue Sarcoma; GIST – Gastrointestinal Stromal Tumours; MPNST – Malignant Peripheral Nerve Sheath Tumours

FIGURE 1 Age distribution according to 5-year age band for all sarcoma subtypes for male and female patients diagnosed in England between 2013 and 2017. Sarcoma subtypes are listed in order of their frequency

new diagnoses a day (Table 1). On average 3943 cases (range: 3873-4123) were registered annually and account for 0.8% of all newly diagnosed malignant neoplasms and tumours of intermediate behaviour. As all cancer diagnoses are required to be registered in England with data completeness established as being over 98% complete within a year and reaching 100% after 5 years of diagnosis, this analysis offers an accurate population-based incidence of sarcoma in England.

Incidence of STS remained stable across all subtypes, with no considerable increase identified between 2013 and 2017 (Figure S1). Gastrointestinal stromal tumours (GIST) have the highest annual incidence of 16.0 per million; however, as only tumours of malignant and intermediate behaviour are registered in the national disease registration service, and previous WHO GIST classifications recorded tumours as benign, intermediate behaviour or malignant, this number may be an underrepresentation. Leiomyosarcoma, undifferentiated sarcoma and liposarcoma make up the next largest tumour groups, with an incidence of 10.5, 10.5 and 9.2 per million, respectively (Table 1). Incidence of less common and rare subtypes is also described; malignant peripheral nerve sheath tumours (MPNST) have an incidence of 1.4 per million and 1.5 per million persons for synovial sarcoma. We were also able to describe the incidence of many sarcomas that fall within the recent definition of 'ultra-rare' sarcomas.[19] These include alveolar soft part sarcoma, desmoplastic round cell tumours, low grade fibromyxoid sarcoma and inflammatory myofibroblastic tumour with incidences of 0.1, 0.2, 0.3 and 0.3 per million respectively. Overall, there is a preponderance for males compared to females, although, females have a greater incidence of vascular tumours, dermatofibrosarcoma protuberans and leiomyosarcomas.

3.2 | Age distribution at diagnosis

The overall median age at diagnosis was 65 years (range 0-102). Undifferentiated sarcomas present with the oldest median age at diagnosis of 74 years (range 0-102); and rhabdomyosarcoma in the youngest, with a median age of 16 years (ranges 0-94; Table 1). For most sarcoma subtypes, incidence increases with age and peaks between 65 and 69 years (Figure 1). Dermatofibrosarcoma and synovial sarcoma are more frequently described between the ages of 20 and 60 years. MPNSTs are also seen in younger patients with a median age at diagnosis of 49 years (range 1-96). Sarcomas were more common in females between ages of 40 and 60 years and more common in males over 60 years.

3.3 | Routes to diagnosis and social deprivation

In total, 39.0% of patients presented via GP referrals, 22.1% presented through TWW, 16.1% were Emergency Presentations (EP) and 15.5% through other outpatient appointments (Table 2). Patients with

TABLE 2 Proportion of patients by sarcoma subgroup according to routes to diagnosis (2013-2017)

Final route by percentage	TWW	GP referral	EP	Inpatient elective	Other outpatient	Screening	Unknown	DCO
All STS (incl. tumours of intermediate behaviour)	22.1	39.0	16.1	2.1	15.5	0.2	4.9	0.1
Gastrointestinal stromal tumour	10.1	35.9	26.4	4.0	21.2	0.0	2.3	0.1
Leiomyosarcoma	26.6	38.8	13.7	1.1	12.1	0.0	7.5	0.1
Undifferentiated sarcoma	31.6	39.1	11.3	1.6	11.6	0.0	4.7	0.0
Liposarcoma	28.1	41.7	9.2	1.5	15.2	0.0	4.4	0.0
Other malignant soft tissue sarcomas	23.6	34.4	24.0	1.2	12.0	0.0	4.5	0.3
Myxoid and other fibroblastic tumours	38.0	35.6	5.5	0.7	15.3	0.0	5.0	0.0
Soft tissue sarcoma of intermediate behaviour	5.1	58.4	6.8	2.7	20.0	0.0	6.9	0.0
Vascular tumours	20.9	38.4	20.7	0.8	14.5	0.8	3.8	0.1
Dermatofibrosarcoma protuberans	17.8	54.2	2.7	1.4	9.0	0.0	14.9	0.0
Rhabdomyosarcoma	14.0	24.5	36.3	5.5	16.8	0.0	2.9	0.0
Tumours of uncertain differentiation	21.6	34.8	16.7	3.1	18.4	0.7	4.7	0.0
Synovial sarcoma	24.4	35.8	8.1	1.3	23.4	0.0	7.1	0.0
Endometrial stromal tumour	24.4	45.2	11.7	1.5	14.2	0.0	3.0	0.0
Myofibrosarcomas and other fibroblastic sarcomas	16.1	43.5	16.1	3.1	16.1	0.3	4.9	0.0
Malignant peripheral nerve sheath tumour	13.1	42.6	15.9	1.9	24.0	0.0	2.5	0.0
Phyllodes	54.0	24.2	4.8	0.3	5.2	7.3	4.2	0.0

Abbreviations: DCO, death certificate only; EP, emergency presentations; TWW, two-week wait.
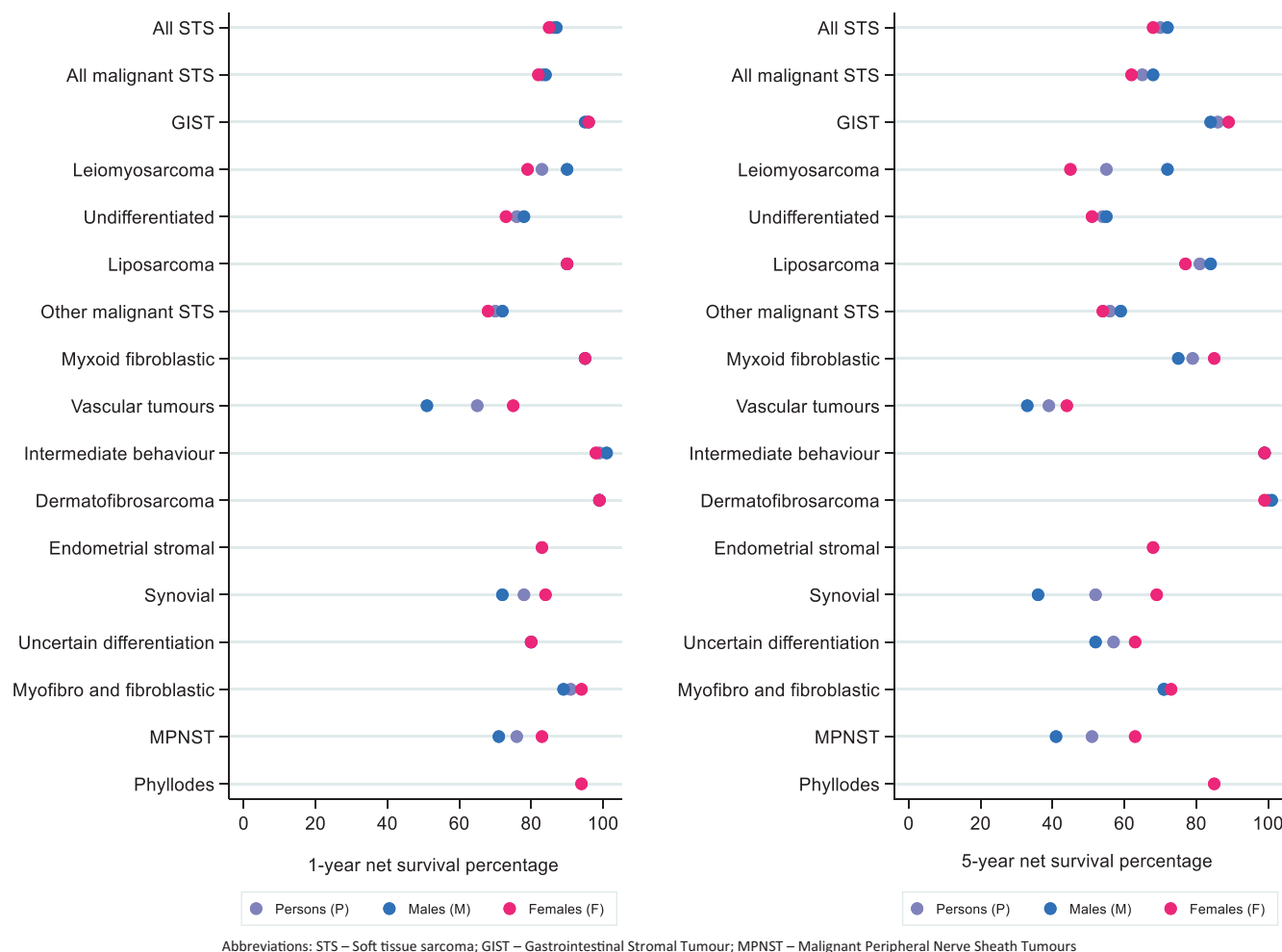
FIGURE 2 One- and five-year net survival according to morphological subtype and gender, for patients diagnosed between 2013 and 2017

Abbreviations: STS – Soft tissue sarcoma; GIST – Gastrointestinal Stromal Tumour; MPNST – Malignant Peripheral Nerve Sheath Tumours

rhabdomyosarcoma were most likely to present acutely with 36.3% presenting as an EP. For patients diagnosed with a GIST, 26.4% presented through EP. Phyllodes tumours were most likely to present through a TWW. GIST and STS of intermediate behaviour were least likely to present via TWW (Table 2). Analysis of presentation by age demonstrated children and young adults, and the oldest cohort to more frequently present via EP (Figure S4). Incidence of STS is more frequently described in the most affluent areas of the country across accounting for 22% of the cohort compared to incidence in the most deprived making up 16%. STS appears less common in more deprived areas for male patients, which is inversely proportional to the age standardised rate for females. Further detail is provided in Table S1. There was an increasing likelihood for patients to present through an emergency route as deprivation increases (Figure S4).

3.4 | Survival

Net survival for all STS was 85.8% at 1-year and 70.2% at 5-years (Table S2 and S3, respectively). For those coded as malignant

(excluding intermediate behaviour), survival was 83.1% at 1-year and 65.0% at 5-years. We defined net survival for patients with common subtypes including GISTs with a net 5-year survival of 86.0% (CI: 83.2-88.5) with a difference observed between GIST defined as intermediate and malignant grade at 92.1% and 74.6%, respectively. Net 5-year survival was 81.5% (CI: 78.6-84.1) for liposarcoma, 53.8% (CI: 50.3-57.2), for undifferentiated sarcoma and 55.3% (CI: 51.6-58.9) for leiomyosarcoma. We were also able to define outcome for rarer entities such as malignant peripheral nerve sheath tumour with a 5-year net survival of 50.7% (CI: 41.6-59.4) and synovial sarcoma with a 5-year net survival of 51.5% (CI: 41.8-60.5). Patient numbers were not sufficient to provide outcome for all ultra-rare sarcomas, but we described outcome for several of these including low grade fibromyxoid sarcoma and epithelioid sarcoma with 5-year survivals of 82.8% (CI: 63.8-94.5) and 45.3% (CI: 30.1-59.7), respectively (Figure S4). Vascular tumours have the poorest outcome with a 5-year survival of 39.0% (CI: 33.9-44.2; Figure 2; Tables S3 and S4). Overall, net survival for male STS patients was greater than females with 5-year net survival rates of 67.5% (CI: 65.66-69.4) and 62.3% (CI: 60.1-64.1) respectively, however there are notable

differences within specific subtypes (Table S4). Worse outcome was seen in males with vascular tumours (33.4% 5-year survival compared to 43.9% in females); as well as in synovial (males 35.6% compared to females 68.7%), MPNST (males 40.9% to females 62.8%) and myxoid fibroblastic sarcomas (males 74.9% to females 85.4%). Conversely, females with leiomyosarcoma, liposarcoma, other malignant soft tissue tumours and undifferentiated sarcoma had a poorer 5-year survival than males (Figure 2; Table S3). As the behaviour of endometrial stromal sarcoma (ESS) is coded as part of the ICDO3.1 definitions of disease, we were able to determine outcome for those with ow-grade ESS (8931/3) and high-grade ESS/endometrial sarcoma NOS (8930/3)

with 92.8% and 55.6% 5-year net survivals, respectively. Net survival is provided for all morphological entities in Table S4, where possible.

3.5 | Kaplan-Meier survival estimates

Kaplan-Meier survival estimates according to age, demonstrated the highest overall survival for STS to be in patients aged 25 to 44 (83.7%), falling to 49.6% for patients over 75 (Figure 3). Patients diagnosed with STS between the ages of 0 and 24 have a 5-year survival of 79.7%. Five-year survival according to age is shown in
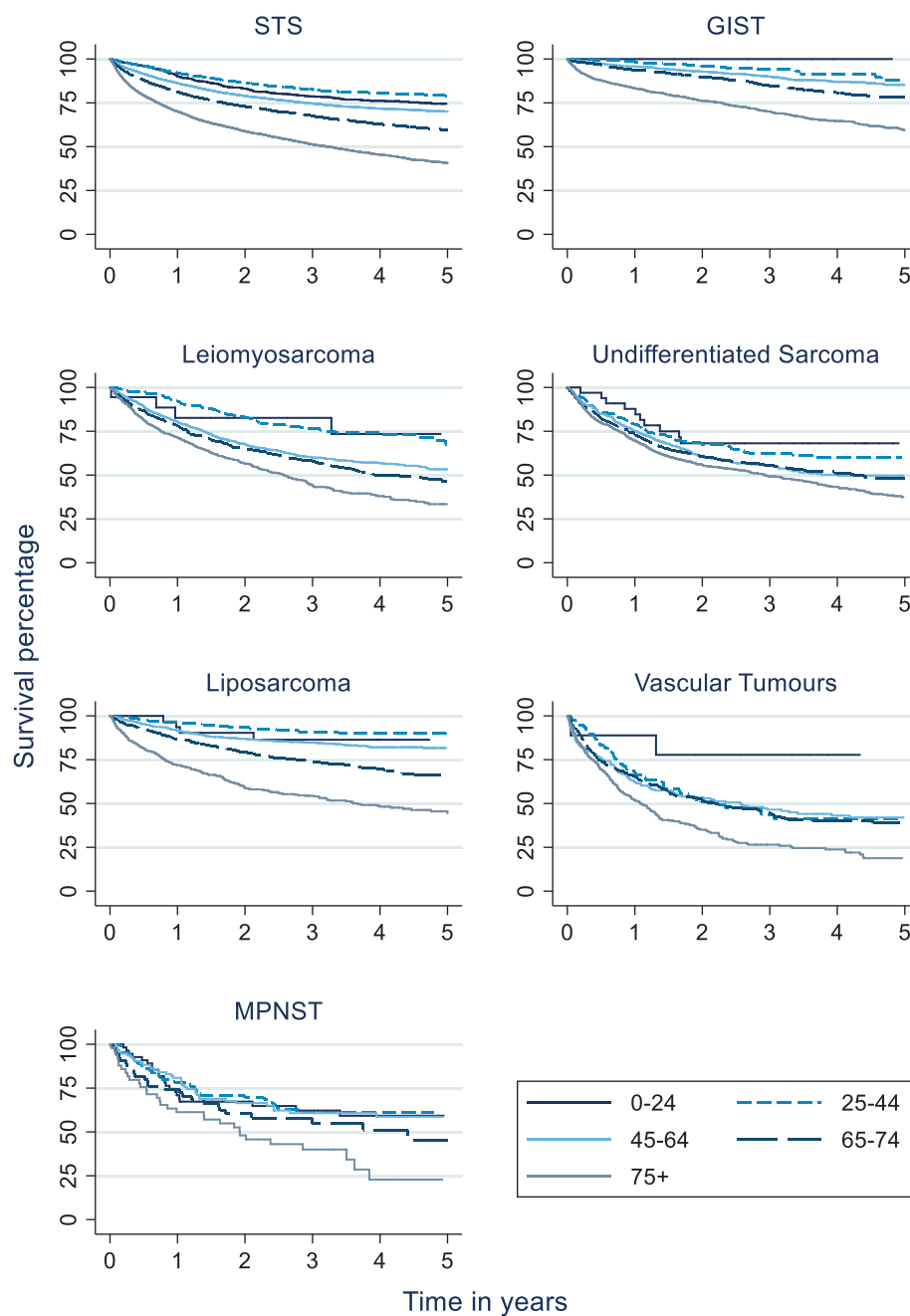
FIGURE 3 Kaplan-Meier 5-year survival estimates, between 2013 and 2017 for STS, GIST leiomyosarcoma, liposarcoma, MPNST, undifferentiated sarcoma and vascular tumours

Abbreviations: STS – soft tissue sarcoma; GIST – gastrointestinal stromal tumours; MPNST – malignant peripheral nerve sheath tumours.

	Hazard ratio	LCI	UCI	Std. Err.	Sig
Males	1.00				
Females	1.09	1.03	1.14	0.03	***
Age	1.03	1.03	1.03	0.00	***
1—Least deprived	1.00				
2	1.04	0.96	1.12	0.04	
3	1.07	0.99	1.16	0.04	
4	1.14	1.06	1.23	0.05	***
5—Most deprived	1.22	1.13	1.33	0.05	***
Two-week wait	1.00				
GP referral	0.77	0.72	0.82	0.03	***
Screening	0.87	0.47	1.62	0.28	
Inpatient elective	0.92	0.76	1.12	0.09	
Other outpatient	0.86	0.79	0.94	0.04	***
Emergency presentation	2.24	2.09	2.41	0.08	***
Unknown	0.65	0.56	0.76	0.05	***

TABLE 3 Cox regression analysis for patients diagnosed with soft tissue sarcoma between 2013 and 2017

Abbreviations: HCI, higher confidence interval; LCI, lower confidence interval; Std. Err., SE; Sig, significance.
***P < .01.

Figure 3 for seven more common subtypes; survival for all other subgroups including intermediate grade and malignant GIST are described in Figures S2 and S3.

3.6 | Cox regression

For all STS, age (HR, 1.03; CI: 1.03-1.03) and gender (HR, 1.09; CI: 1.03-1.14) are significantly associated with survival (Table 3). Patients diagnosed in the fifth deprivation quintile are 22% more likely to die of their disease than those in the reference group (deprivation 1 — least deprived) (Table 3). Outcome of patients with undifferentiated sarcoma show increasing risk as the level of deprivation increases. Patients presenting through EP have the worst outcome, most notably for patients with leiomyosarcoma, undifferentiated sarcoma and other malignant soft tissue sarcomas, with 5-year net survivals of 30.1%, 27.6% and 22.1%, respectively (Table S5). Cox regression analysis for individual soft tissue sarcoma subtypes are shown in Tables S6-S21 and Figures S5-S8.

4 | DISCUSSION

This is the first population-based study that describes the incidence and survival for all histologically described STS of intermediate and malignant behaviour, including GIST. Historically, registration of sarcoma has been a challenge, in part due to lack of expert pathology review, the evolution of classification systems and inaccurate transcribing of pathology reports to national cancer registration datasets.[20,21] In the United Kingdom, revision of National Institute for Health and Care Excellence (NICE) guidance in 2006 mandated

patients with STS be managed within specialist sarcoma centres that included expert pathology review of all new diagnoses.[22] With improvements in expert pathology review and increased availability of molecular diagnostics, 7.2% of patients were described as sarcoma NOS, which is lower than 20% described in a previous English analysis from the National Cancer Intelligence Service of STS patients diagnosed between 1996 and 2010 and the 12% observed within a European epidemiological descriptive analysis of sarcoma.[23,24]

A key strength of the data collected and held by NCRAS is the complete coverage of all people diagnosed with cancer in England making it truly population based. Internationally, there has been a paucity of comparative population-based data. An American Surveillance, Epidemiology and End Results (SEER) analysis by Toro et al, described incidence of STS between 1978 and 2001 that represented just 10% of the US population, and a more recent analysis from National Cancer Database of the American College of Surgeons representing 70% of the population.[25,26] The high case number in these analyses provide interesting insights that are valuable but lack of population-based analyses and the evolution of the histological classification systems makes comparison between datasets challenging. A descriptive epidemiological analysis of sarcomas across Europe from the RARECARE project, estimated STS to have an ASR incidence rate of 4.7 per 100 000 in Northern Europe and GIST to have an incidence of 14 per 1 000 000.[23] Other population-based studies with pathological review estimate the incidence of GIST to be in the range 1.0 to 1.5 per 100 000.[27] Here, we define the incidence of GIST inclusive of intermediate behaviour and malignant codes in England as 16 cases per 1 000 000 persons, which is higher than that observed within a recent French national study at 12.4 per million, although that was not age standardised.[9] We also defined incidence of other common subtypes of STS such as liposarcoma and leiomyosarcoma with an

ASR of 9.2 and 10.5 per million, in line with other recent population-based analyses from Switzerland and Germany.[3,10] Variation is, however, observed depending on whether tumours of intermediate malignancy are included, the recent French analysis demonstrating an incidence of liposarcoma of 12.9 per million that included atypical lipomatous tumours.[9] Analysis by specific subtype is therefore important to provide an opportunity for more accurate comparison. We were able to describe incidence of many 'ultra-rare' sarcomas, these recently defined by an international panel of experts as subtypes with an incidence of ≤1 per million.[19] These include epithelioid sarcoma, alveolar soft part sarcoma and desmoplastic small round cell which have previously been challenging to report and demonstrate an incidence of 0.4, 0.1 and 0.2 per 1 000 000, respectively, an average of just 19, 6 and 12 patients per year, and in keeping with that defined by the French Nationwide Study.[9] Interestingly two subtypes named as ultra-rare entities, phyllodes and endometrial stromal sarcoma were observed to have an incidence >1 per million in this analysis highlighting the value of provision of population-based data to the community and the need for evolving definitions as new data becomes available.

Our analysis provides incidence according to age across clinically relevant histological subtypes with increased incidence with age observed for most common subtypes of sarcoma, in keeping with previous analyses[24-26] and a higher incidence of children and adolescents with rhabdomyosarcoma. There is a male preponderance for STS and most notably, males are more likely to develop undifferentiated sarcoma and liposarcoma. Leiomyosarcoma, is most common in females due to a high proportion of patients with uterine leiomyosarcoma. Females also have a higher incidence of vascular tumours due to the development of radiation-induced breast angiosarcomas, which are described in detail in a recent analysis of breast sarcomas in England across the same time period.[28]

Net survival estimates using Brenner's alternative weighting with the Ederer II estimator was adopted to generate more disease appropriate measures for survival suitable for international comparisons. Net survival for persons diagnosed with malignant STS was 83.1% at 1-year and 65.0% at 5-years. There are very few population-based analyses with which to compare outcomes. A RARECARE analysis of patients diagnosed between 1995 and 2002 demonstrated a 5-year survival of 58% for all patients with STS using older classifications and morphological descriptions.[24] Relative survival in a Swiss study was demonstrated to be 61.6%.[3] Patients diagnosed with GIST have a 5-year survival of 86.0%, substantially higher than the 67.7% 5-year relative survival reported in the RARECARE analysis of patients diagnosed between 1995 and 2002.[23] This reflects the introduction of imatinib and other targeted therapy, based on the discovery that the disease was driven by activating mutations of c-kit and PDGF-a in the majority of cases[29] and compares favourably with an analysis from a Dutch population-based analysis of patients treated between 2009 and 2012 where a 5-year relative survival of 81.4% was observed.[30] A change in WHO classification of GISTs to include intermediate tumours, which we demonstrated to have better survival, may have also contributed to differences in outcome described. Future analyses will include tumours coded as benign potentially further influencing

the interpretation of outcome. To our knowledge, this is the first population-based analysis, using the recent WHO 2013 classification, to confidently define net survival of common STS subtypes such as liposarcoma and leiomyosarcoma with 5-year net survival of 81.5% and 55.3%, as well as undifferentiated sarcoma at 53.8%. We were also able to define outcome for rarer entities such as malignant peripheral nerve sheath tumour with a 5-year net survival of 50.7%. Patients with synovial sarcoma were demonstrated to have a 5-year net survival of 51.5% with no improvement observed since an analysis describing outcome of patients diagnosed in England between 1985 and 2009.[31] Patients diagnosed with vascular tumours have a particularly poor outcome with a 5-year net survival of 39.0%, which is little changed from the European analysis for patients diagnosed over two decades ago.[24] Our analysis was able to define net survival for patients with rarer histology's such as MPNST confirming poor outcome with a 5-year survival of 51% (95% CI: 42-59). There are no complete population-based studies with which to compare outcome, but this is in line with a 49% (95% CI: 45-53) 5-year overall survival demonstrated in a meta-analysis of 28 retrospective analyses that included over 5000 patients.[32] Patients with endometrial stromal sarcoma (ESS) had with a 5-year survival of 68.4% with no change in outcome observed since an analysis evaluated outcome of gynaecological sarcomas in England until 2008.[33] As the behaviour of ESS is coded as part of the ICDO3.1 definitions of disease, we are able to confirm excellent outcome in those with low grade disease compared to those with high grade/ESS NOS with 92.8% and 55.6% 5-year net survivals, respectively.

Multivariate cox regression analysis confirmed increasing age to be a significant prognostic factor.[34] Gender was also significant, with females 9% more likely to die from disease within 5 years of their diagnosis than their male counterparts, P < .05, which is likely to be contributed to by higher incidence in subtypes with poor outcome. For example, the difference is particularly notable in leiomyosarcoma, where males and females have a 5-year survival of 72.2% and 45.4% respectively. This is partly attributed to the high proportion of females with uterine leiomyosarcomas that continue to have a poor outcome; although females with non-gynaecological leiomyosarcoma have also been found to have a lower 5-year survival than males.[35] Further analysis to determine gender-specific impact on outcome is warranted.

An analysis of Routes to Diagnosis demonstrated an improvement in coding and an increase in patients diagnosed through TWW from 12.5% in 2006 to 2008 to 22.1%, although this is lower than more common cancers.[36,37] A significant proportion, however, continue to present as an emergency with a detrimental impact on outcome. Patient age and deprivation had an impact on route to diagnosis with children and young adults as well as elderly patients more often presenting through emergency routes and an increasing trend with increased deprivation, although an interaction of these factors on outcome remains not clear. Further work is required to identify clinical characteristics that most influence referral pathways and outcome.

Importantly, this analysis demonstrates social deprivation has a significant impact on survival with STS patients living in the most deprived quintile having a 22% greater of chance of dying within

5 years, than those in the least deprived areas. Patients with some subtypes such as MPNST fare particularly poorly and are 74% are more likely to die if they live in the poorest areas of the country. These findings appear more pronounced than analyses for more common cancers.[38] It is possible that patients from more deprived areas have poorer access to specialist sarcoma services, which has been demonstrated to impact outcome in STS[39]; this requires further evaluation, but has important implications for stakeholders with a role in addressing health inequalities.

Additional analysis of outcome according to primary site of disease and centre of diagnosis and treatment would be valuable to determine the impact of expert pathology review and specialist sarcoma services on outcome for specific anatomic sites and allow us to evaluate geographical variation and inequalities in patterns of care, work that is ongoing. Inherent to cancer registration practice, our study has limitations including data completeness for tumour size, grade and stage which although improving was insufficient for further analysis.[40]

In conclusion, this is the first comprehensive population-based analysis focused on STS in England. The analysis is based on contemporary histological classification and thereby provides detailed incidence and outcome for 84 morphological subtypes of STS within clinically relevant subgroups. The analysis provides an invaluable data source for clinicians, researchers, service providers, charities and benchmarking for international comparative studies and a basis for future studies to determine inequalities in referral and management of these challenging malignancies.

AUTHOR CONTRIBUTIONS

The work reported in the article has been performed by the authors, unless clearly specified in the text. Andrew Bacon, Kwok Wong and Sandra J. Strauss conceived the study. Andrew Bacon and Kwok Wong performed the statistical analyses. Andrew Bacon and Sandra J. Strauss drafted the article with contributions from Kwok Wong, John Broggio and Brian Rous. All other authors contributed to the interpretation of data and critically revised the article for important intellectual content. All authors have read and approved the final article for publication.

CONFLICT OF INTEREST

Sandra J. Strauss received honoraria from GSK, consulting fees from Ceridwen Oncology Ltd and travel support from Adaptimmune. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

DATA AVAILABILITYSTATEMENT

NHS Digital collects data for cancer registration under sections 254 (1) and 254(6) of the 2012 Health and Social Care Act following a direction of the Secretary of State for Health and Social Care.[15] The data that supports the findings of our study are available in the Supplementary Material of this article. Further information is available from the corresponding author upon request.

ETHICS STATEMENT

Informed consent and ethical approval was not required for the study.

ORCID

Sandra J. Strauss https://orcid.org/0000-0001-8328-0260

REFERENCES

1. Fletcher CD, Hogendoorn P, Mertens F, Bridge J. *WHO Classification of Tumours of Soft Tissue and Bone*. 4th ed. Lyon, France: IARC Press; 2013.
2. Gronchi A, Miah AB, Dei Tos AP, et al. EURACAN and GENTURIS clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2021;32(11):1348-1365.
3. Kollár A, Rothermundt C, Klenke F, et al. Incidence, mortality, and survival trends of soft tissue and bone sarcoma in Switzerland between 1996 and 2015. *Cancer Epidemiol*. 2019;63:101596.
4. Trama A, Badalamenti G, Baldi GG, et al. Soft tissue sarcoma in Italy: from epidemiological data to clinical networking to improve patient care and outcomes. *Cancer Epidemiol*. 2019;59:258-264.
5. Ducimetière F, Lurkin A, Ranchère-Vince D, et al. Incidence of sarcoma histotypes and molecular subtypes in a prospective epidemiological study with central pathology review and molecular testing. *PLoS One*. 2011;6(8):e20294.
6. Trautmann F, Schuler M, Schmitt J. Burden of soft-tissue and bone sarcoma in routine care: estimation of incidence, prevalence and survival for health services research. *Cancer Epidemiol*. 2015;39(3):440-446.
7. Mastrangelo G, Coindre J, Ducimetière F, et al. Incidence of soft tissue sarcoma and beyond. *Cancer*. 2012;118(21):5339-5348.
8. Amadeo B, Penel N, Coindre JM, et al. Incidence and time trends of sarcoma (2000-2013): results from the French network of cancer registries (FRANCIM). *BMC Cancer*. 2020;20(1):190.
9. de Pinieux G, Karanian M, Le Loarer F, et al. Nationwide incidence of sarcomas and connective tissue tumors of intermediate malignancy over four years using an expert pathology review network. *PLoS One*. 2021;16(2):e0246958.
10. Saltus CW, Calingaert B, Candrilli S, et al. Epidemiology of adult soft-tissue sarcomas in Germany. *Sarcoma*. 2018;2018:5671926.
11. Bray F, Parkin DM. Evaluation of data quality in the cancer registry: principles and methods. Part I: comparability, validity and timeliness. *Eur J Cancer*. 2009;45:747-755.
12. Dangoor A, Seddon B, Gerrand C, Grimer R, Whelan J, Judson I. UK guidelines for the management of soft tissue sarcomas. *Clin Sarcoma Res*. 2016;6:20.
13. GOV.UK. English indices of deprivation 2015; 2015. https://www.gov.uk/government/statistics/english-indices-of-deprivation-2015. Accessed July 21, 2022.
14. Elliss-Brookes L, McPhail S, Ives A, et al. Routes to diagnosis for cancer - determining the patient journey using multiple routine data sets. *Br J Cancer*. 2012;107:1220-1226.

15. https://www.legislation.gov.uk/ukpga/2012/7/section/254/enacted. Accessed July 21, 2022.

16. Brenner H, Arndt V, Gefeller O, Hakulinen T. An alternative approach to age adjustment of cancer survival rates. *Eur J Cancer*. 2004;40: 2317-2322.

17. Corazziari I, Quinn MJ, Capocaccia R. Standard cancer patient population for age standardising survival ratios. *Eur J Cancer*. 2004;40:2307-2316.

18. Cox DR. Regression models and life-tables. *J R Stat Soc Ser B*. 1972; 34:187-220.

19. Stacchiotti S, Frezza AM, Blay JY, et al. Ultra-rare sarcomas: a consensus paper from the connective tissue oncology society community of experts on the incidence threshold and the list of entities. *Cancer*. 2021;127(16):2934-2942.

20. Harris M, Hartley AL, Blair V, et al. Sarcomas in north West England: I histopathological peer review. *Br J Cancer*. 1991;64:315-320.

21. Daugaard S. Current soft-tissue sarcoma classifications. *Eur J Cancer*. 2004;40:543-548.

22. NICE. Improving outcomes for people with sarcoma; 2006. https://www.nice.org.uk/guidance/csg9/documents/improving-outcomes-for-people-with-sarcoma-all-recommendations2. Accessed January 25, 2020.

23. NCIN. Bone and soft tissue sarcomas UK incidence and survival: 1996 to 2010. http://www.ncin.org.uk/search/bone+and+soft+tissue+sarcoma+uk+incidence+and+survival. Accessed July 23, 2022.

24. Stiller CA, Trama A, Serraino D, et al. Descriptive epidemiology of sarcomas in Europe: report from the RARECARE project. *Eur J Cancer*. 2013;49:684-695.

25. Toro JR, Travis LB, Wu HJ, Zhu K, Fletcher CD, Devesa SS. Incidence patterns of soft tissue sarcomas, regardless of primary site, in the surveillance, epidemiology and end results program, 1978-2001: an analysis of 26,758 cases. *Int J Cancer*. 2006;119:2922-2930.

26. Corey RM, Swett K, Ward WG. Epidemiology and survivorship of soft tissue sarcomas in adults: a national cancer database report. *Cancer Med*. 2014;3:1404-1415.

27. Søreide K, Sandvik OM, Søreide JA, Giljaca V, Jureckova A, Bulusu VR. Global epidemiology of gastrointestinal stromal tumours (GIST): a systematic review of population-based cohort studies. *Cancer Epidemiol*. 2016;40:39-46.

28. Ahmed M, Collins S, Franks J, et al. Incidence and outcome of breast sarcomas in England (2013-2018): an analyses from the National Cancer Registration and analysis service. *Eu J Cancer*. 2022;174:1-328.

29. Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N Engl J Med*. 2001;344:1031-1037.

30. van der Graaf WTA, Tielen R, Bonenkamp JJ, Lemmens V, Verhoeven RHA, de Wilt JHW. Nationwide trends in the incidence and outcome of patients with gastrointestinal stromal tumour in the imatinib era. *Br J Surg*. 2018;105:1020-1027.

31. Brennan B, Stiller C, Grimer R, Dennis N, Broggio J, Francis M. Outcome and the effect of age and socioeconomic status in 1318 patients with synovial sarcoma in the English National Cancer Registry: 1985-2009. *Clin Sarcoma Res*. 2016;6:18.

32. Cai Z, Tang X, Liang H, Yang R, Yan T, Guo W. Prognosis and risk factors for malignant peripheral nerve sheath tumor: a systematic review and meta-analysis. *World J Surg Oncol*. 2020;18:257.

33. Francis M, Dennis NL, Hirschowitz L, et al. Incidence and survival of gynecologic sarcomas in England. *Int J Gynecol Cancer*. 2015;25(5):850-857.

34. Ferrari A, Sultan I, Huang TT, et al. Soft tissue sarcoma across the age spectrum: a population-based study from the surveillance epidemiology and end results database. *Pediatr Blood Cancer*. 2011;57:943-949.

35. Gootee J, Sioda N, Aurit S, Curtin C, Silberstein P. Important prognostic factors in leiomyosarcoma survival: a National Cancer Database (NCDB) analysis. *Clin Transl Oncol*. 2020;22:860-869. doi:10.1007/s12094-019-02196-7

36. Gerrand C, Francis M, Dennis N, et al. Routes to diagnosis for sarcoma - describing the sarcoma patient journey. *Eur J Surg Oncol*. 2015;41:1393-1399.

37. NHS Digital. Routes to diagnosis, 2018. https://digital.nhs.uk/data-and-information/publications/statistical/routes-to-diagnosis/2018. Accessed July 23, 2022.

38. McPhail S, Johnson S, Greenberg D, Peake M, Rous B. Stage at diagnosis and early mortality from cancer in England. *Br J Cancer*. 2015; 112:S108-S115.

39. Venigalla S, Nead KT, Sebro R, et al. Association between treatment at high-volume facilities and improved overall survival in soft tissue sarcomas. *Int J Radiat Oncol Biol Phys*. 2018;100(4):1004-1015.

40. Henson KE, Elliss-Brookes L, Coupland VH, et al. Data resource profile: National Cancer Registration Dataset in England. *Int J Epidemiol*. 2020;49(1):16-16h.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.