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Descriptive epidemiology of sarcomas in Europe: Report from the RARECARE project

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Abstract Sarcomas are a heterogeneous group of malignant neoplasms arising from mesenchymal cells which encompass dozens of histological types and can occur in virtually any anatomic site. They form one of the principal groups of rare cancers in Europe as defined in the RARECARE project. We analysed 45,568 incident cases diagnosed during 1995–2002 and registered by 76 population-based cancer registries. Total crude incidence was 5.6 per 100,000 per year with an estimated 27,908 new cases per year in the EU27 countries, of which 84% were soft tissue sarcomas and 14% were bone sarcomas. Gastrointestinal stromal tumours (GIST) were only widely recognised as an entity in the late 1990s and consequently were under-registered. Their true incidence is believed to be about 1.5 per 100,000. Age-standardised incidence of soft tissue sarcomas ranged from 3.3 per 100,000 in Eastern Europe to 4.7 per 100,000 in Northern Europe. About 280,000 persons were estimated to be alive at the beginning of 2003 with a past diagnosis of sarcoma, of which 83% were soft tissue sarcomas and 16% were bone sarcomas. Five-year relative survival for 2000–2002 by the period was 58% for soft tissue sarcomas and 62% for bone sarcomas. The diversity and rarity of sarcomas combined with the quite large number of people affected by them mean that they provide a classic example of the importance of networking in diagnosis, therapy and research for rare cancers.

1. Introduction

Sarcomas are a heterogeneous group of malignant neoplasms arising from mesenchymal cells. They can be split up into dozens of histological categories, and they can occur in virtually any anatomic site. This gives rise

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to a huge number of possible combinations of histology and primary site which are of clinical importance. For example, a well differentiated liposarcoma of a limb has a completely different prognosis, and radically different therapeutic implications, from a histologically identical tumour arising from the retroperitoneum, where surgery is much more challenging. At the same time, a retroperitoneal liposarcoma is clinically different from a leiomyosarcoma of the same region. The complex interplay in sarcomas between anatomic site and histology, both highly relevant from the clinical standpoint, adds to the difficulties that are due to the overall rarity of this family of tumours. For many clinical presentations, medical knowledge and clinical research face major challenges because the numbers are extremely low.

Also from the epidemiological point of view, little information is readily available on patterns of incidence and survival for sarcomas. Fewer than half of all soft tissue sarcomas arise from a connective tissue primary site,[1] and in many primary sites they are outnumbered by carcinomas. Therefore they are not visible in publications in which tumours are grouped according to the International Classification of Diseases topography codes. In Europe in 1995–1999, 5-year relative survival rates of adults with cancers of the bone and cartilage and cancers of soft tissue were 55% and 59% respectively, somewhat higher that the 50% relative survival for all malignant neoplasms.[2]

The causes of most sarcomas are unknown. Ionising radiation, especially in the form of radiotherapy for a previous cancer, is the only exogenous factor to account for more than a handful of cases.[3] Other risk factors include occupational exposure to certain chemicals, including herbicides such as phenoxyacetic acids and wood preservatives containing chlorophenols. Several heritable syndromes are associated with increased risk of sarcomas. Those which account for the largest numbers of cases are probably neurofibromatosis 1 (nerve sheath tumours), heritable retinoblastoma (osteosarcoma and various soft tissue sarcomas) and Li-Fraumeni syndrome (soft tissue sarcomas and osteosarcoma).[4] Paget disease is a risk factor for osteosarcoma in older adults. In a recent study of the SEER Program, 91% of cases of osteosarcoma in people aged 60 years and over were associated with Paget disease, while 24% of cases in this age group were a second or later primary cancer.[5]

The aim of this paper is to describe incidence, prevalence and survival for sarcomas in Europe, based on a large population-based series of data collected from 89 European cancer registries in the framework of the EC funded project 'Surveillance of rare cancer in Europe' (RARECARE).

2. Materials and methods

RARECARE gathered data on cancer patients diagnosed from 1978 to 2002 and archived in 89 population-based CRs, all of which had vital status information available up to at least 31st December 2003. In the present paper we considered data from 76 CRs, excluding CRs which did not classify cancers according to the third edition of the International Classification of Diseases for Oncology (ICD-O-3) and also those which collected data on childhood cancers only.

The incidence analysis only considered cases incident from 1995 to 2002 and excluded specialised registries. Thus, the incidence analyses were restricted to 64 CRs. Incidence rates were estimated as the number of new cases occurring in 1995–2002 divided by the total person-years in the general population (male and female) in the CR areas considered, over the same period. For age-standardised rates, the European population was used.

The prevalence per 100,000 was estimated at the index date of 1st January 2003. The counting method,[6] based on CR incidence and follow-up data, was applied to CR data from 1988 to 2002. Only data from 22 registries, covering the whole 15-year period, were used for prevalence estimation. The completeness index method,[7] was used to estimate complete prevalence, and involved adding the estimated surviving cases diagnosed prior to 1988 to those counted in 1988–2002.

Completeness indices provide an estimate of the 'unobserved' prevalence fraction for a given cancer and registration time length, and are based on statistical modelling of incidence and relative survival functions. In this application incidence was modelled as a logistic exponential or polynomial function on age.

The expected number of new cases per year and of prevalent cases in Europe (EU27) were estimated multiplying the crude incidence rate and prevalence to the 2008 European population (497,455,033) provided by EUROSTAT. In providing sarcomas burden estimates, we assumed that the population covered by our CRs was representative of the population of the EU27 as a whole.

We estimated observed survival by the actuarial method. We also estimated relative survival, by the Hakulinen method,[8] as the ratio of observed survival to the expected survival in the general population of the same age and sex. Observed and relative survival refer to the period 2000–2002 and were estimated by the period approach.[9] Parametric mixture cure models[10] were fitted to relative survival data[8] on patients diagnosed in 1988–1999. This type of models allow to disentangle cancer patients population in a fraction 'cured' (C) – i.e. exposed to the same mortality rates of the general population – and in a fraction of 'fatal cases' (1 − C) – who will die of the disease. The proportion of patients who can be considered cured, C, was derived by applying these models to relative survival long-term trends.

The cancers described in this article include all soft tissue sarcomas including those in organ-specific sites (ICD-O-3 M codes 8800–8935, 8910, 8920, 8940, 8950–8959, 8963–8964, 8990–8991, 9020–9044, 9120–9133, 9150,

9170, 9180, 9231, 9240, 9251, 9260, 9364–9372, 9540, 9560–9571, 9580–9581 combined with all ICD-O-3 T codes except C40.0–41.9), malignant bone tumours (M codes 8800–8920, 9040–9044, 9120–9133, 9150, 9170, 9180–9250, 9260–9261, 9310, 9364, 9370, 9540–9581 combined with T codes C40.0–41.9) and gastro-intestinal stromal sarcoma or malignant gastrointestinal stromal tumour (GIST) (M code 8936 combined with any T code).

The present analyses are based on the new list of cancer types provided by RARECARE. The list is organised into three tiers. Tier 3 corresponds to the WHO ICD-O. Tier 3 entities have been grouped into tier 1 and 2 entities, which, on a consensus basis, were felt to be homogeneous form the clinical standpoint. In the case of soft tissue sarcomas, tier 2 is defined by the anatomical primary tumour site, differently from most other families of tumours, in which tier 2 is defined by histology. This renders the clinical importance of both anatomic site of origin (by distinguishing, say, soft tissue sarcomas of limbs from those of the uterus) and histology in these tumours.

The analyses presented here were carried out on 45,568 cases of the entities listed above that were diagnosed during 1995–2002. The numbers of registrations and main data quality indicators are presented in Table 1. Less than 0.7% of cases in each tier 1 entity were DCO. Less than 1% of cases in each tier 1 entity were diagnosed at autopsy. Microscopic verification was present in more than 95% of cases overall and in each tier 1 entity. The proportion of cases diagnosed during 1995–1998 that were censored before 5 years was below 2% for all tier 1 entities.

3. Results

3.1. Incidence

Table 2 shows the crude incidence rates overall and by sex and age group, together with the expected annual number of cases diagnosed in the EU27 countries. Total crude incidence was 5.6 per 100,000 per year, with 27,908 new diagnoses per year, of which 84% were soft tissue sarcomas and 15% were bone sarcomas. The most common tier 1 entity considered here was soft tissue sarcoma, with total crude incidence of 4.7 per 100,000 per year, followed by bone sarcoma (0.8). Soft tissue sarcoma overall had slightly higher incidence in females (5.0) than in males (4.4). This was entirely due to rates among females of 1.0 per 100,000 for sarcomas of the uterus and 0.4 per 100,000 for sarcomas of the breast, whereas paratesticular sarcomas had a rate of only 0.1 per 100,000 in males. For all other tier 2 entities within soft tissue sarcoma, males had rates that were similar to or slightly higher than those for females. Incidence of soft tissue sarcoma overall and for all sites except the heart and paraorbital region increased with age. Among the histological categories, embryonal rhabdomyosarcoma was most frequent at age 0–14, while alveolar rhabdomyosarcoma and Ewing sarcoma family of tumours (ESFT) were most frequent at ages 0–14 and 15–24. The overall age incidence pattern for bone sarcoma was bimodal, with peaks at ages 15–24 and 65+. Of the three most frequent subtypes, osteosarcoma and ESFT had their highest incidence at age 15–24 and incidence of chondrogenic sarcomas was greatest at age 65+. GIST had highest incidence at age 65+.

Table 3 shows age-standardised incidence rates by European region. Age-standardised incidence of soft tissue sarcomas was highest in Northern, Central and Southern Europe (4.5–4.7 per 100,000), lower in the UK and Ireland (3.8) and lowest in Eastern Europe (3.3). The limbs were the most common primary site for soft tissue sarcoma in all five regions. Incidence of the other entities varied relatively little between regions.

Among soft tissue sarcomas, the most frequent morphology was leiomyosarcoma, accounting for 20% of registrations for all sarcomas. This was followed by unspecified sarcomas (18%) and liposarcoma (10%). Among liposarcoma, 22% were specified as well differentiated or dedifferentiated, 23% as myxoid or round cell liposarcoma and 9% as pleomorphic. Malignant fibrous histiocytoma (MFH) accounted for 8% of all sarcomas. No other morphology, including synovial sarcoma, malignant peripheral nerve sheath tumours, vascular sarcomas (angiosarcoma, haemangioendothelioma, haemangiopericytoma and lymphangiosarcoma) and other rare soft tissue sarcomas such as clear cell sarcomas, solitary fibrous tumours, alveolar soft part sarcoma and epithelioid sarcoma accounted for more than 5% of cases.

Leiomyosarcoma was the most frequent type of sarcoma of the uterus (56%), other genitourinary sites (30%), other visceral sites (46%), peritoneum (28%) and head and neck (20%). Liposarcoma was the most frequent in the limbs (23%), phyllodes tumour was the most frequent in breast (66%), and peripheral nerve sheath tumours were the most frequent in the peripheral nerves and autonomic nervous system (67%). Liposarcoma and unspecified sarcoma each accounted for 23% of superficial trunk sarcomas.

Some morphological groups could occur in bone and extraosseous primary sites, but the Ewing sarcoma family was the only one to have more than 5% in each category: 71% bone and 29% extraosseous.

3.2. Prevalence

Table 4 shows the observed prevalence proportion for sarcomas at 2, 5 and 15 years and the estimated complete prevalence in Europe (index data 1st January 2003). About 280,000 persons were estimated to be alive at the beginning of 2008 with a past diagnosis of sarcoma. Of these, 14% and 31% were diagnosed within 2 and 5 years before the prevalence date respectively. The 17% difference between these proportions represents

Table 1
Data quality indicators of rare sarcomas cancers diagnosed in all RARECARE cancer registries, cases diagnosed 1995–2002.

Tier	Entity	Data quality indicators				
		Number of malignant cancers 1995–2002	Death certificate only	Autopsy	Microscopic verification	Cases 1995–1998 censored before 5 years
		N	(%)	(%)	(%)	(%)
	Sarcomas					
1	Soft tissue sarcoma	38,526	0.6	0.5	96.7	1.4
2	Soft tissue sarcoma of head and neck	2338	0.0	0.1	96.7	1.6
2	Soft tissue sarcoma of limbs	8323	0.3	0.1	96.9	1.5
2	Soft tissue sarcoma of superficial trunk	3748	0.6	0.7	96.5	1.4
2	Soft tissue sarcoma of mediastinum	214	1.4	1.4	93.9	0.0
2	Soft tissue sarcoma of heart	122	0.8	4.1	94.3	0.8
2	Soft tissue sarcoma of breast	1526	0.0	0.0	98.1	1.7
2	Soft tissue sarcoma of uterus	4011	0.6	0.4	96.8	1.3
2	Other soft tissue sarcomas of genitourinary tract	1954	0.4	0.8	97.1	1.5
2	Soft tissue sarcoma of viscera	4169	0.7	1.5	96.4	1.0
2	Soft tissue sarcoma of paratestis	263	0.0	0.0	98.9	1.5
2	Soft tissue sarcoma of retroperitoneum and peritoneum	2322	0.9	0.6	95.7	1.2
2	Soft tissue sarcoma of pelvis	116	0.0	0.0	95.7	0.9
2	Soft tissue sarcoma of skin	2473	0.0	0.0	99.6	1.3
2	Soft tissue sarcoma of paraorbit	54	1.9	0.0	92.6	3.7
2	Soft tissue sarcoma of brain and other parts of nervous system	1560	1.1	0.4	94.8	1.3
2	Embryonal rhabdomyosarcoma of soft tissue	511	0.0	0.0	99.0	0.8
2	Alveolar rhabdomyosarcoma of soft tissue	264	0.0	0.0	97.3	0.8
2	Ewing's family tumours of soft tissue	433	0.2	0.7	98.4	1.8
2	Other soft tissue sarcoma	4636	1.3	0.6	95.3	1.3
1	Bone sarcoma	6494	0.6	0.2	95.5	1.5
2	Osteosarcoma	1838	0.8	0.2	95.6	1.7
2	Chondrogenic sarcomas	1969	0.6	0.1	96.4	1.4
2	Chordoma	352	0.9	1.1	94.0	2.0
2	Vascular sarcomas	26	0.0	0.0	96.2	0.0
2	Ewing's family tumours	1053	0.7	0.0	96.2	1.2
2	Epithelial tumours (adamantinoma)	70	0.0	0.0	92.9	5.7
2	Other high grade sarcomas (fibrosarcoma, malignant fibrous histiocytoma)	147	0.7	0.0	97.3	0.0
2	Other bone sarcoma	1039	0.5	0.5	93.1	1.6
1	Gastrointestinal stromal sarcoma	548	0.0	0.5	99.6	0.0

cases in the third to fifth years following diagnosis, presumably undergoing clinical follow-up. The remaining 69% represents long-term survivors, among whom 108,000 (38% of the total) had survived more than 15 years after diagnosis.

The most prevalent sarcomas were soft-tissue sarcomas (233,000 cases) followed by bone sarcomas (46,000 cases). The distribution of prevalence by time since diagnosis was fairly similar for the different cancers.

3.3. Survival

Table 5 shows period survival estimates for the years 2000–2002 for tier 1 entities of sarcomas. Fig. 1 shows 5-year relative survival for tier 1 and tier 2 entities. Five-year relative survival of tier 1 entities was 58% for soft tissue sarcoma, 62% for bone sarcoma and 68% for GIST. Soft tissue sarcomas of the skin (mainly dermatofibrosarcoma protuberans) had the highest survival rate, 90% or above, while soft tissue sarcoma of the mediastinum and heart had survival rates below 15%. Five-year survival from sarcoma of the uterus was 49% overall but was 65% for tumours of stromal histology (mainly endometrial stromal tumour) and 42% for other types (predominantly leiomyosarcoma and sarcoma NOS). Leiomyosarcoma had 5-year relative survival of 49% for all sites combined. Survival from leiomyosarcoma varied between the most frequent primary sites: 43% (95% confidence interval (95% CI) 39–47%) for uterus, 55% (95% CI 46–64%) for stomach, 52% (95% CI 43–61%) for small intestine, 32% (95% CI 25–40%) for retroperitoneum and 55% (95% CI 51–59%) for soft tissue. Among bone sarcomas, the highest

Table 2
Observed cases. Crude incidence rates per 100,000 and standard errors (SE) in Europe. rates and SE by sex and age and estimated incident cases arising in Europe per year.

Entity	EU overall			Sex				Age								Estimated number of cases arising in EU per year
				Male		Female		0–14 years		15–24 years		25–64 years		65+ years		
	Observed cases 1995–2002	Rate	SE	Rate	SE	Rate	SE	Rate	SE	Rate	SE	Rate	SE	Rate	SE	
Sarcomas																
Soft tissue sarcoma	38,127	4.7	<0.1	4.4	<0.1	5.0	<0.1	0.9	<0.1	1.3	<0.1	4.4	<0.1	13.1	0.1	23,574
Soft tissue sarcoma of head and neck	2314	0.3	<0.1	0.4	<0.1	0.2	<0.1	0.1	<0.1	0.1	<0.1	0.2	<0.1	1.0	<0.1	1431
Soft tissue sarcoma of limbs	8287	1.0	<0.1	1.1	<0.1	1.0	<0.1	0.1	<0.1	0.3	<0.1	0.9	<0.1	3.0	<0.1	5124
Soft tissue sarcoma of superficial trunk	3731	0.5	<0.1	0.5	<0.1	0.4	<0.1	0.1	<0.1	0.1	<0.1	0.4	<0.1	1.4	<0.1	2307
Soft tissue sarcoma of mediastinum	209	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	0.1	<0.1	129
Soft tissue sarcoma of heart	120	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	0.0	a	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	74
Soft tissue sarcoma of breast	1499	0.2	<0.1	<0.1	<0.1	0.4	<0.1	<0.1	<0.1	<0.1	<0.1	0.2	<0.1	0.4	<0.1	927
Soft tissue sarcoma of uterus	3989	0.5	<0.1	0.0	a	1.0	<0.1	<0.1	<0.1	<0.1	<0.1	0.6	<0.1	1.0	<0.1	2466
Other soft tissue sarcomas of genitourinary tract	1919	0.2	<0.1	0.2	<0.1	0.3	<0.1	0.1	<0.1	<0.1	<0.1	0.2	<0.1	0.7	<0.1	1187
Soft tissue sarcoma of viscera	4070	0.5	<0.1	0.6	<0.1	0.5	<0.1	<0.1	<0.1	<0.1	<0.1	0.4	<0.1	1.8	<0.1	2517
Soft tissue sarcoma of paratestis	262	<0.1	<0.1	0.1	<0.1	0.0	a	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	0.1	<0.1	162
Soft tissue sarcoma of retroperitoneum and peritoneum	2295	0.3	<0.1	0.3	<0.1	0.3	<0.1	<0.1	<0.1	<0.1	<0.1	0.3	<0.1	0.9	<0.1	1419
Soft tissue sarcoma of pelvis	115	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	0.1	<0.1	71
Soft tissue sarcoma of skin	2465	0.3	<0.1	0.3	<0.1	0.3	<0.1	<0.1	<0.1	0.1	<0.1	0.3	<0.1	0.7	<0.1	1524
Soft tissue sarcoma of paraorbit	54	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	33
Soft tissue sarcoma of brain and other parts of nervous system	1531	0.2	<0.1	0.2	<0.1	0.2	<0.1	0.1	<0.1	0.1	<0.1	0.2	<0.1	0.3	<0.1	947
Embryonal rhabdomyosarcoma of soft tissue	493	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	0.25	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	305
Alveolar rhabdomyosarcoma of soft tissue	261	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	0.1	<0.1	0.1	<0.1	<0.1	<0.1	<0.1	<0.1	161
Ewing's family tumours of soft tissue	426	0.1	<0.1	0.1	<0.1	<0.1	<0.1	0.1	<0.1	0.1	<0.1	<0.1	<0.1	<0.1	<0.1	263
Bone sarcoma	6474	0.8	<0.1	0.9	<0.1	0.7	<0.1	0.7	<0.1	1.2	<0.1	0.7	<0.1	1.2	<0.1	4003
Osteosarcoma	1835	0.2	<0.1	0.3	<0.1	0.2	<0.1	0.3	<0.1	0.5	<0.1	0.1	<0.1	0.2	<0.1	1135
Chondrogenic sarcomas	1965	0.2	<0.1	0.3	<0.1	0.2	<0.1	<0.1	<0.1	0.1	<0.1	0.3	<0.1	0.5	<0.1	1215
Chordoma	352	<0.1	<0.1	0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	0.1	<0.1	218
Vascular sarcomas	26	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	0.0	a	<0.1	<0.1	<0.1	<0.1	16
Ewing's family tumours	1046	0.1	<0.1	0.2	<0.1	0.1	<0.1	0.3	<0.1	0.4	<0.1	0.1	<0.1	<0.1	<0.1	647
Epithelial tumours (adamantinoma)	69	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	43
Other high grade sarcomas (fibrosarcoma, malignant fibrous histiocytoma)	146	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	90
Gastrointestinal stromal sarcoma	535	0.1	<0.1	0.1	<0.1	0.1	<0.1	0.0	a	<0.1	<0.1	0.1	<0.1	0.2	<0.1	331

[a] Statistic could not be calculated.

Table 3
Age standardised incidence rates per 100,000 and standard errors (SE) by European region for the period 1995–2002. Tier 1 entities and tier 2 entities with EU overall ASR of at least 0.1 per 100,000.

Entity	European region										EU overall	
	Northern Europe		Central Europe		Eastern Europe		Southern Europe		UK and Ireland			
	Adj. Rate	SE	Adj. Rate	SE	Adj. Rate	SE	Adj. Rate	SE	Adj. Rate	SE	Adj. Rate	SE
Sarcomas												
Soft tissue sarcoma	4.7	0.1	4.5	0.1	3.3	0.1	4.5	0.1	3.8	<0.1	4.2	<0.1
Soft tissue sarcoma of head and neck	0.2	<0.1	0.3	<0.1	0.2	<0.1	0.2	<0.1	0.2	<0.1	0.2	<0.1
Soft tissue sarcoma of limbs	1.0	<0.1	1.0	<0.1	0.7	<0.1	0.8	<0.1	0.9	<0.1	0.9	<0.1
Soft tissue sarcoma of superficial trunk	0.6	<0.1	0.4	<0.1	0.3	<0.1	0.4	<0.1	0.4	<0.1	0.4	<0.1
Soft tissue sarcoma of breast	0.1	<0.1	0.2	<0.1	0.1	<0.1	0.2	<0.1	0.2	<0.1	0.2	<0.1
Soft tissue sarcoma of uterus	0.6	<0.1	0.4	<0.1	0.5	<0.1	0.5	<0.1	0.4	<0.1	0.5	<0.1
Other soft tissue sarcomas of genitourinary tract	0.2	<0.1	0.2	<0.1	0.2	<0.1	0.2	<0.1	0.2	<0.1	0.2	<0.1
Soft tissue sarcoma of viscera	0.6	<0.1	0.4	<0.1	0.3	<0.1	0.5	<0.1	0.4	<0.1	0.4	<0.1
Soft tissue sarcoma of retroperitoneum and peritoneum	0.2	<0.1	0.3	<0.1	0.2	<0.1	0.4	<0.1	0.2	<0.1	0.3	<0.1
Soft tissue sarcoma of skin	0.5	<0.1	0.3	<0.1	0.1	<0.1	0.5	<0.1	0.2	<0.1	0.3	<0.1
Soft tissue sarcoma of brain and other parts of nervous system	0.2	<0.1	0.2	<0.1	0.2	<0.1	0.1	<0.1	0.2	<0.1	0.2	<0.1
Ewing's family tumours of soft tissue	0.1	<0.1	0.1	<0.1	<0.1	<0.1	0.1	<0.1	0.1	<0.1	0.1	<0.1
Bone sarcoma	0.8	<0.1	0.9	<0.1	0.7	<0.1	0.8	<0.1	0.7	<0.1	0.8	<0.1
Osteosarcoma	0.3	<0.1	0.3	<0.1	0.2	<0.1	0.2	<0.1	0.2	<0.1	0.2	<0.1
Chondrogenic sarcomas	0.3	<0.1	0.3	<0.1	0.2	<0.1	0.2	<0.1	0.2	<0.1	0.2	<0.1
Ewing's family tumours	0.1	<0.1	0.1	<0.1	0.1	<0.1	0.2	<0.1	0.2	<0.1	0.1	<0.1
Gastrointestinal stromal sarcoma	0.1	<0.1	0.1	<0.1	<0.1	<0.1	0.1	<0.1	<0.1	<0.1	0.1	<0.1

survival rate was for the rare adamantinomas (83%) and the lowest was for vascular sarcomas (34%). Survival of osteosarcoma and Ewing sarcoma was about 53%.

Survival rates were generally similar for males and females. Survival was consistently lower for persons aged 65+ than for younger age groups.

Fig. 2 shows 5-year relative survival for tier 1 entities of sarcomas by EU regions. Five-year relative survival from soft tissue sarcoma was 54% in Eastern Europe and the UK and Ireland and 59–61% in the other three European regions. Survival varied more markedly between regions for bone sarcomas: 49% in Eastern Europe, 58% in the UK and Ireland and 62–66% in the other regions.

3.4. Estimated proportion of cured patients

There were only sufficient data to calculate estimates for two diagnostic groups. The estimated proportions of patients diagnosed during 1988–99 who were cured were 47.9% for soft tissue sarcoma and 50.9% for bone sarcoma.

4. Discussion

The results presented in this paper give for the first time a comprehensive account of the descriptive epidemiology of sarcomas throughout Europe. The data are from population-based cancer registries and have been subjected to uniform, stringent validation procedures. Data sets were only accepted if they had been originally coded in, or converted to, the current edition of ICD-O. The information in this paper should therefore be accurate and up to date, assuming that there have been no major changes in incidence or survival since the study period. The principal limitation of the study is that, because it is based on data that are historical, albeit quite recent, certain diagnostic subgroups may be systematically under- or over-represented. For example, many tumours that appear in the data set as fibrosarcoma or MFH would be reassigned to other categories if their pathology could be reviewed.[11]

Sarcomas of all types had a combined incidence of about 6 per 100,000, with 28,000 new cases per year in Europe. Incidence overall and for most tier 1 entities increased with age. About 280,000 people were estimated to be alive in Europe with a past diagnosis of sarcoma in 2008. More than three quarters of incident and prevalent cases were soft tissue sarcomas.

Population-based data on incidence of soft tissue sarcoma in the United States was investigated in a study from SEER Program,[1] covering more than 26,000 tumours diagnosed during 1978–2001. As in the present study, incidence increased with age and fewer than 50% of cases had a primary site that was in connective tissue (C49). Males, however, had slightly higher incidence than females. There were only minor differences between the two studies in the list of tumour types included. The SEER data included a higher proportion of fibrohistiocytic tumours (28%) than RARECARE (13%), with the difference being greater for dermatofibrosarcoma protuberans (11% versus 4%) than for

Table 4
Observed prevalence proportion × 100,000 and standard errors (SE) by duration (2, 5, 15-years) and estimated complete prevalence in Europe. Tier 1 entities and tier 2 entities with at least 1000 prevalent cases.

Entity	Duration						EU complete prevalence 1st January 2003		
	2 Years		5 Years		15 Years				
	Prop.	SE	Prop.	SE	Prop.	SE	Prop.	SE	No. of cases
Sarcomas									
Soft tissue sarcoma	6.8	0.1	14.4	0.2	28.6	0.2	46.9	0.4	233,097
Soft tissue sarcoma of head and neck	0.4	<0.1	0.9	<0.1	1.8	0.1	2.9	0.1	14,628
Soft tissue sarcoma of limbs	1.7	0.1	3.8	0.1	7.5	0.1	11.6	0.2	57,837
Soft tissue sarcoma of superficial trunk	0.6	<0.1	1.2	<0.1	2.3	0.1	4.0	0.1	20,003
Soft tissue sarcoma of breast	0.3	<0.1	0.7	<0.1	1.4	<0.1	2.2	0.1	10,994
Soft tissue sarcoma of uterus	0.7	<0.1	1.5	<0.1	3.1	0.1	4.9	0.1	24,295
Other soft tissue sarcomas of genitourinary tract	0.3	<0.1	0.7	<0.1	1.2	<0.1	2.2	0.1	10,746
Soft tissue sarcoma of viscera	0.7	<0.1	1.3	<0.1	2.1	0.1	2.6	0.1	13,145
Soft tissue sarcoma of paratestis	0.1	<0.1	0.1	<0.1	0.3	<0.1	0.3	<0.1	1511
Soft tissue sarcoma of retroperitoneum and peritoneum	0.4	<0.1	0.7	<0.1	1.0	<0.1	1.2	0.1	6192
Soft tissue sarcoma of skin	0.5	<0.1	1.3	<0.1	2.7	0.1	4.5	0.2	22,582
Soft tissue sarcoma of paraorbit	<0.1	<0.1	<0.1	<0.1	0.1	<0.1	0.2	<0.1	1166
Soft tissue sarcoma of brain and other parts of nervous system	0.3	<0.1	0.7	<0.1	1.2	<0.1	2.1	0.1	10,527
Embryonal rhabdomyosarcoma of soft tissue	0.1	<0.1	0.2	<0.1	0.5	0.0	1.7	0.2	8307
Ewing's family tumours of soft tissue	0.1	<0.1	0.2	<0.1	0.3	<0.1	0.5	<0.1	2713
Bone sarcoma	1.2	<0.1	2.7	0.1	5.8	0.1	9.3	0.2	46,193
Osteosarcoma	0.3	<0.1	0.7	<0.1	1.7	0.1	3.2	0.1	15,834
Chondrogenic sarcomas	0.4	<0.1	0.9	<0.1	2.0	0.1	3.6	0.1	17,691
Chordoma	0.1	<0.1	0.2	<0.1	0.3	<0.1	0.4	<0.1	1959
Ewing's family tumours	0.2	<0.1	0.4	<0.1	0.9	<0.1	2.3	0.2	11,381
Gastrointestinal stromal sarcoma	a	a	a	a	a	a	a	a	a

[a] This entity definition is too recent for prevalence estimation.

MFH (17% versus 9%). For MFH, the lower proportion in RARECARE is consistent with the data relating to a more recent period when this diagnosis was less frequently used.[11] Currently, MFH refers to undifferentiated pleomorphic sarcomas or pleomorphic varieties of other sarcomas.

The most frequent histological type in this study was leiomyosarcoma, whereas it is well known that the most common histology among soft tissue sarcomas is liposarcoma. One should notice that in females there is the big group of uterine leiomyosarcomas. Many GIST were previously classified as leiomyosarcomas and leiomyomas (and the like). In addition, not all GIST diagnosed as leiomyosarcomas may have been recorded as originating from the gastrointestinal tract, since sometimes the origin was felt to be retroperitoneal or pelvic. Also, 24% of all leiomyosarcomas arose in the uterus, and there is an urgent need for pathological reclassification of uterine sarcomas. Finally, some leiomyosarcomas may now be classified as pleomorphic sarcomas with a myogenic differentiation which is not sufficient to make them true leiomyosarcomas. All this may explain why liposarcoma was not appreciated as the most frequent histology in the soft tissue sarcoma family by cancer registries.

The lower proportion of dermatofibrosarcoma protuberans might be due to rigorous exclusion from some contributing registries not just of skin carcinomas but of all non-melanoma skin cancers, among them dermatofibrosarcoma protuberans and other sarcomas of the skin.

RARECARE had a higher proportion of unspecified sarcomas (18%) than SEER (13%). RARECARE has undertaken a study on data quality for selected groups of cancers, in which the main issue for sarcoma was the proportion of sarcoma NOS. A random sample of about 2000 cases of sarcoma NOS was selected from 30 cancer registries participating in this study, representing 12% of all sarcomas contributed by these registries. The registries were invited to revise the morphology based on the pathological reports in order to confirm or change the diagnosis and report the new morphology code (the revision did not include a review of the pathological sample). After the revision, 79% were confirmed as sarcoma NOS and 12% had a more precisely defined morphology (mainly GIST). Thus the revision allowed registries to reduce the number of cases registered as sarcoma NOS, supporting the idea that more attention should be paid to diagnostic coding when registering sarcomas. However, in several cases even expert pathologists can well give a diagnosis of sarcoma NOS. In other words, adult-type soft tissue sarcomas are properly diagnosed as sarcoma NOS in a substantial proportion of cases. The fact that the majority of cases reviewed were confirmed as sarcoma NOS after review of the pathological reports tends to support the relative good quality of cancer registry data in the RARECARE database for tumours whose diagnosis was problematic.

Table 5
Observed survival rates (%), estimated relative survival rates and standard errors (SE) by one and 5 years, and number of cases analysed. Period survival analysis 2000–2002. Tier 1 entities.

Entity	Duration						
	1 Year			5 Years			
	Observed	Relative		Observed	Relative		Cases analysed
	%	%	SE	%	%	SE	*N*
Sarcomas							
Soft tissue sarcoma	75.1	77.1	0.4	50.4	57.8	0.5	12,693
Bone sarcoma	82.8	83.9	0.9	57.3	61.6	1.2	2093
Gastrointestinal stromal sarcoma	81.4	83.5	2.1	58.8	67.8	4.0	355

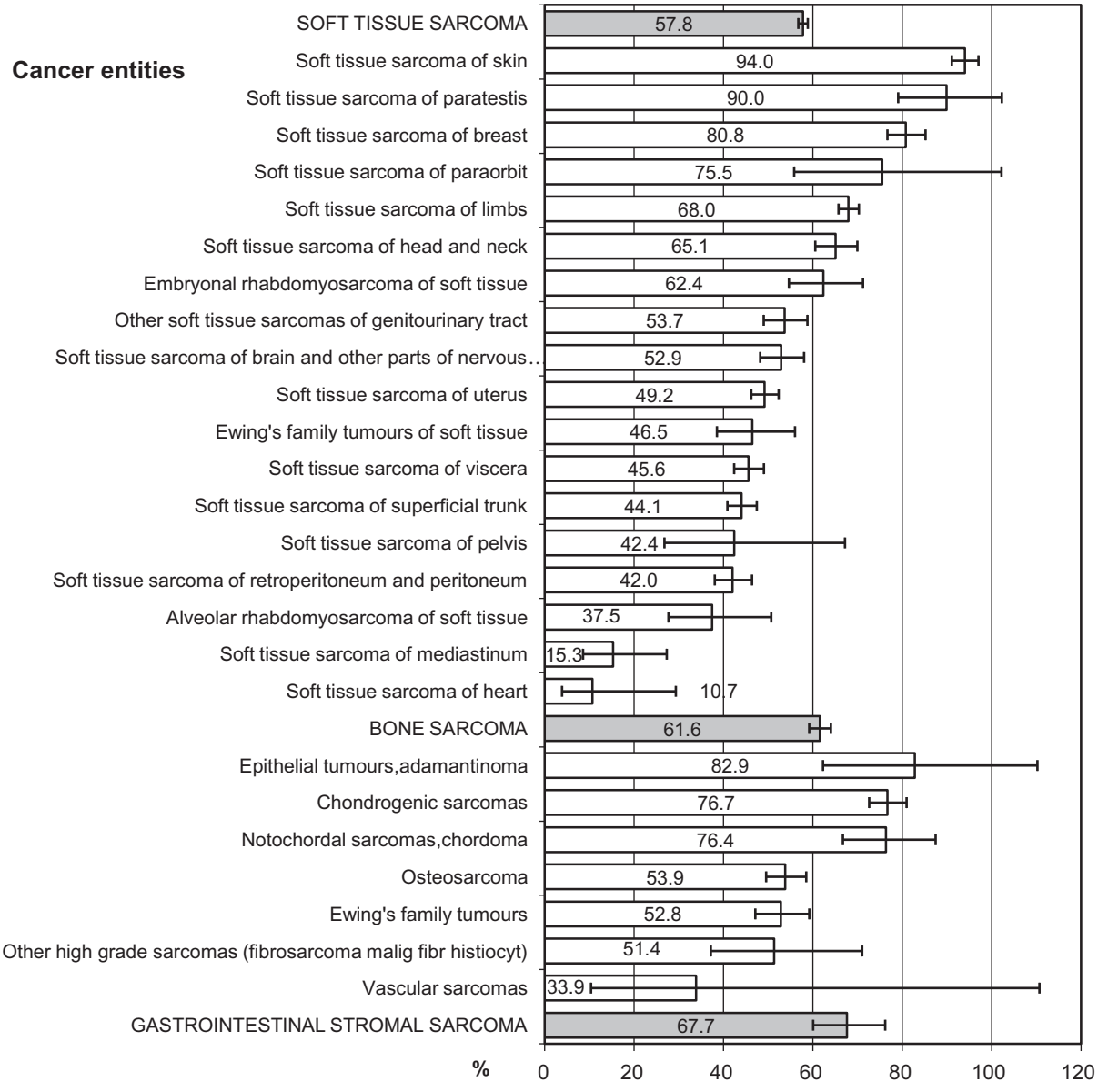

Fig. 1. Period analysis – 5-year relative survival (%) by sarcoma entities.

In contrast to most other tier 1 entities, the age incidence curve for bone sarcomas was bimodal with a first peak in the 15–24 age group. The first peak is due to osteosarcoma and Ewing sarcoma, while the second peak is due to chondrosarcomas. The pattern for osteosarcoma, including lower rates in the middle age range,

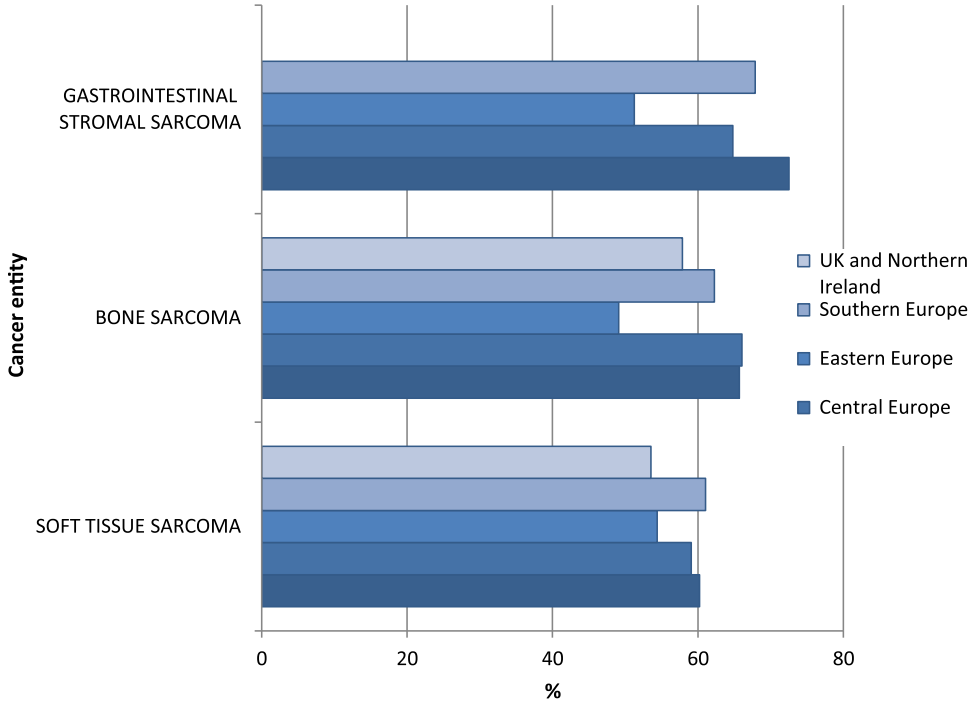

Fig. 2. Five years relative survival of sarcomas (tier 1 entities) by EU regions.

was similar to those observed in populations of industrialised countries in other continents.[5,12] The incidence peak of Ewing sarcoma at age 15–24 and the steadily increasing incidence of chondrosarcoma with age were also observed in the United States SEER registries.[13]

GIST is now recognised as the most common non-epithelial tumour of the digestive tract, but it was acknowledged as a separate entity only in the 1990s.[14] In a population-based study in Western Sweden with diagnostic review of all potential cases diagnosed during 1983–2000, only 28% of cases had GIST as their original histological diagnosis and the remainder were first diagnosed as leiomyoma, leiomyosarcoma and other types of mesenchymal tumour.[15] Because specific codes for GIST were only introduced in the third edition of ICD-O, we also analysed incidence in RARECARE for the years 2001–02. Of the 535 cases diagnosed in 1995–2002, 243 were diagnosed in 2001–02. For those two most recent years the incidence was 0.15 per 100,000 (SE 0.01). Population-based studies with pathology review in several European countries have estimated the incidence of GIST to be in the range 1.0–1.5 per 100,000.[15–19]

For most sarcoma categories the lowest survival rates were found in the oldest age group. A similar pattern has been observed in the United States SEER registries for soft tissue sarcoma,[20] osteosarcoma[5] and chondrosarcoma.[21]

In general, the geographical variation in survival from sarcomas was similar to that previously reported from EUROCARE for many other cancers, with higher survival in Northern, Central/Western and Southern Europe and somewhat lower survival in Eastern Europe and the British Isles. Survival varied by less than 10% between Europeans regions for soft tissue sarcoma but there was greater inter-regional variation for bone sarcomas. The pattern of substantially lower survival from bone sarcomas in Eastern Europe has been consistently observed over previous decades.[22–24] The greater inter-regional variation observed for bone sarcomas might be due to the fact that bone sarcomas need a multidisciplinary approach and thus may be more sensitive to the quality of care than soft tissue sarcomas (which mainly need surgical intervention).

Possible causes of the inequality of survival between European regions include variations in timeliness and accuracy of diagnosis and in access to appropriate treatment. All of these factors warrant investigation but cannot be studied with the data available here. There is general agreement that treatment of sarcomas should be concentrated in specialist centres with multidisciplinary expertise and knowledge of the disease, though the effect of such a policy on survival has seldom been evaluated.[25–28] As cancer registries come to collect more information on treatment, it should become relatively simple to learn whether osteosarcoma patients receive appropriate chemotherapy, but it may be much more difficult to assess the quality of multimodal treatment given to patients with high-risk soft tissue sarcomas.

The prognosis of rhabdomyosarcoma, osteosarcoma and ESFT, the principal sarcomas that affect children and young adults, was revolutionised by the introduction of chemotherapy in the 1970s. Despite their extreme rarity on a population basis, they have been a model for ‘classical’ medical oncology and have reached now a

cure rate which exceeds 60%, compared with <20% in the pre-chemotherapy era.

In the RARECARE database, the survival rates seem slightly higher than 50%, so that results of clinical studies seem to be reproduced on a population basis. Osteosarcoma and Ewing sarcoma are very rare tumours, whose treatment is often centralised to those hospitals which are involved in clinical studies. In other words, the usual disparities between trial-based and community-based patients may be mitigated in these diseases when quality of care is high overall. On the other hand, quality of care may well affect their prognosis, being so influenced by an appropriate multidisciplinary approach.

Soft tissue sarcomas of the uterus include leiomyosarcoma, endometrial stromal tumour and stromal sarcoma and sarcoma NOS. Survival was much higher for endometrial stromal sarcomas, which are usually hormone-sensitive than for other sarcomas of this site, This poorer prognosis of uterine leiomyosarcoma is well known in the clinic, and uterine sarcomas as a group are in acute need of pathologic reclassification and new therapies. In a sense, it may be worrisome that 5-year survival of endometrial stromal sarcomas did not exceed 65% at 5 years, though their natural history and their sensitivity to hormones should have brought about even better results. Today, a proportion of them would be reclassified into a high grade counterpart, the undifferentiated endometrial sarcomas, which have a dismal prognosis. However, the survival rate was still more than 10% below the 76% disease-specific survival of patients in the SEER Program diagnosed between 1988 and 2003.[29] In the SEER study survival was above 90% for grade 1 and 2 tumours and 42% for grade 3. Various terms that are synonymous with low-grade endometrial stromal sarcoma and have a malignant behaviour code in ICD-O-3 were classified as uncertain behaviour in ICD-O-2, so it is possible that some lower grade tumours were not registered and are consequently under-represented in the present study.

More recently, mesenchymal tumours have been the subject of another revolution, the introduction of molecularly targeted therapies. This first affected GIST, which is now a model of how molecularly targeted agents may work in solid cancers.[14] Because sarcomas are highly heterogeneous histologically and genomically, they present plenty of potential targets. Many studies are ongoing, therefore, on targeted agents in selected histologies within the sarcoma family. For example, there have been hints of activity of new drugs in chordomas,[30] whose prognosis has changed little over past decades. Other highly selected subgroups, such as alveolar soft part sarcomas, may benefit from targeted therapies.[31] It will be interesting to look at epidemiological data on GIST, when they become available from cancer registries in the next few years, to see how a major breakthrough involving a targeted agent can translate into prognostic improvements on a population basis in different settings. An important challenge for cancer registries will be to develop the ability to track, at the population level, the highly selective improvements resulting from this kind of 'histology-driven' or 'molecularly-driven' therapy, affecting single histologies or clinical presentations with low numbers of eligible patients. A proper pathologic diagnosis on a population basis would be crucial in this regard, and it is well known that this is still a challenge.

Collectively, the annual incidence of the tumours considered here is around 6 per 100,000, which the RARECARE project proposed as a threshold for 'rarity'. The consensus feeling was that both sarcomas and CNS tumours, which have similar incidence, need to be viewed as rare when considered as families of tumours. The main reason is that the clinical expertise needed to deal with sarcomas and CNS tumours cannot be widespread in the community. By gathering all cases recorded by participating cancer registries, the RARECARE project has shown that sarcomas make up a significant number of cases in absolute terms and are one of the main families of cancers among rare cancers. Although individually many of the sarcoma entities considered here are extremely rare, in total they contribute to 28,000 cases to the burden of newly diagnosed cancers in the EU each year. The high survival rates for many of the entities mean that the number of EU residents alive with a past diagnosis of sarcoma is about 10 times as great, in excess of 280,000 prevalent cases, many of whom will have related health problems. Many survivors of sarcoma will have undergone major surgery to a limb or organ as part of their treatment, resulting in impaired function. The diversity and rarity of sarcomas combined with the quite large number of people affected by them mean that they provide a classic example of the importance of networking in diagnosis, therapy and research for rare cancers.

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Conflict of interest statement

None declared.

Appendix A. The RARECARE Working Group

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