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Soft tissue sarcoma in Italy: From epidemiological data to clinical networking to improve patient care and outcomes

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ABSTRACT

Sarcomas are rare malignant neoplasms that develop from mesenchymal cells and include a heterogeneous and large group of histological subtypes that may occur at any anatomical site. Soft tissue sarcomas (STS), the focus of this review, account for ≈70–80% of sarcomas and represent < 1% of all cancers. The heterogeneity of STS applies to both their topography and morphology, and 5-year survival can vary widely depending on disease stage and the complex interplay between anatomical site and histology for different STS subtypes. The rarity and heterogeneity of STS, together with other factors, such as the lack of clinical expertise often lead to difficulties and delays in making an accurate diagnosis and to the inappropriate management of each STS subtype. Therefore, this group of cancers requires special attention and approaches to diagnosis and treatment. Epidemiological data on STS are limited, and concerns have been raised regarding accurate registration of STS in cancer registries, including issues related to details of the histotypes. This review provides an overview of the epidemiology of STS in Italy, focusing on data from the Italian Association of Cancer Registries (AIRTUM), and compares findings with those from other European countries. Based on these data, and considering that STS is among the most common group of rare cancers, the relevance of multidisciplinary care for STS patients through reference centres, clinical networks and collaborative disease-specific groups is discussed.

1. Introduction

Sarcomas are rare malignant neoplasms that develop from mesenchymal cells; they represent approximately 1% of all cancers and include a heterogeneous group of more than 70 different histological subtypes that may arise at any anatomical site [1–7]. Therefore, both topography and morphology contribute to the heterogeneity of sarcomas. In most cases, risk factors for sarcoma are unclear, although exposure to ionising radiation has increased the risk of soft tissue sarcoma (STS) [8]. Current estimates suggest that radiotherapy-associated sarcomas account for only 3–6% of all sarcomas [9–11]. Primary radiation-related STS, rather than sporadic disease, has been associated

Abbreviations: AIRTUM, Italian Association of Cancer Registries; CIR, crude incidence rates; CONTICANET, Connective Tissue Cancer Network; ECCO, European CanCer Organisation; EURACAN, European Reference Network for Rare Adult Solid Cancers; FAP, familial adenomatous polyposis; GIST, gastrointestinal stromal tumours; IR, incidence rate; NetSarc, Clinical Reference Network for Sarcomas-GIST-Desmoids; RARECARE, Surveillance of Rare Cancers in Europe; RARECAREnet, Information Network on Rare Cancers; RITA, rare cancers in Italy; RRePS, Reference Network for Pathology of Soft Tissue-GIST-Desmoid-Visceral Sarcomas; STS, soft tissue sarcoma; WHO, World Health Organisation

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Table 1
Expert-panel recommendations for strategies required to enhance sarcoma care. Table adapted from The Sarcoma Policy Checklist [3].

- Assigned and certified reference centres for sarcoma in each European region
- Improved professional training for all healthcare professionals involved in sarcoma care
- A multidisciplinary approach to patient care
- Increased incentives for research and innovation
- Faster patient access to effective therapies

with significantly worse disease-specific survival [12]. Other potential risk factors for sarcomas include chemical exposure to herbicides (e.g. phenoxyacetic acids), wood preservatives (e.g. those containing chlorophenols), chronic lymphedema (Stewart–Treves syndrome) and inherited conditions such as neurofibromatosis-1, retinoblastoma and Li-Fraumeni syndrome [6,10].

STS comprise ≈70–80% of sarcomas [1,3] and are one of the main groups of cancers among rare cancers [13]. The significant anatomical and histological heterogeneity of STS means it is often difficult for healthcare professionals to acquire the levels of expertise required for appropriate management of each different STS subtype [14]. In addition, epidemiological data on specific STS subtypes are limited, and there are concerns about data quality regarding STS subtype in population-based cancer registries. The difficulties in making an exact diagnosis by pathologists, together with possible registration bias, could lead to a high proportion of poorly specified STS histological subtypes, which in turn could lead to a possible underestimation of the incidence of specific STS subtypes [15]. Published articles focusing on STS epidemiology in Italy are lacking. Thus, an important aim of this review is to bring together all data available in Italy and other EU countries to provide more accurate epidemiological data to healthcare policy makers and other stakeholders in Italy and elsewhere, and to provide a synthesis of these data, which may lead to improved patient care and clinical outcomes. Additional, definitive aims of the review are to raise awareness about STS and the importance of registries, and to focus on the importance of multidisciplinary management in referral centres. These aims are also in line with expert-panel recommendations, such as those from the Sarcoma Policy Checklist (Table 1) [3]. The review compares epidemiological data from the population-based Italian Association of Cancer Registries (AIRTUM) [1] with data from population-based studies from Europe: the Connective Tissue Cancer Network (CONTICANET) [7], the Surveillance of Rare Cancers in Europe (RARECARE) Working Group [6], the Information Network on Rare Cancers (RARECAREnet) [16,17], and rare cancers in Italy (RITA) [18].

1.1. Specifics of STS

Since the current review focuses on data from Italy, it is noteworthy that AIRTUM included in the STS group, sarcomas arising from various anatomical sites (e.g. STS of head and neck, STS of limbs, STS of superficial trunk, STS of viscera); thus AIRTUM data are not based only on the topography code of the International Classification of Diseases for Oncology (ICD-O) code for soft tissue sarcomas C49 but combine the different ICD morphology codes for STS in different sites. Bone sarcomas, Kaposi sarcoma and gastrointestinal stromal tumours (GIST) were considered separate categories of sarcoma distinct from STS [1]. This is also in line with RARECARE [13] and RARECAREnet data since RARECARE proposed and RARECAREnet revised the list of rare cancers used by the AIRTUM. In the current review, we include all STS regardless of primary site, excluding specific sarcoma subtypes such as Kaposi sarcoma and GIST. The classification of STS has been updated by the World Health Organisation *Classification of Tumours of Soft Tissue and Bone* [2]. Although several entities in this revised classification system are now better defined and have been re-classified, it is unlikely to generate any discrepancies between different research papers and population-based cancer registries discussed in the current review because these data refer to periods of diagnosis prior to the revised 2013 classification. For example, data from AIRTUM [1] include patients diagnosed between 2000 and 2010. In addition, this review will focus mainly on STS and not on specific STS subtypes. There might be major differences between research articles and population-based data with respect to specific STS subtypes.

2. Incidence and prevalence of STS in Italy compared with other European countries

Incidence, which quantifies the number of new cases with sarcoma and therefore is a good proxy of the disease burden posed by patients requiring first-line treatment, is considered a more appropriate indicator of tumour rarity than prevalence. Indeed, incidence can be used to indicate the number of patients with a specific condition that may be relevant for statistical design considerations in clinical trials. Although any threshold for definition of tumour rarity should be regarded as indicative only, the RARECARE expert group defined rare cancers as those occurring with an annual incidence of fewer than six cases per 100,000 [1,6,13]. Overall, rare cancers account for approximately 24% of all cancers in Europe [1,13,17]. STS represent < 1% of all cancers [3,19] but are among the rare cancers with the highest incidence [13].

In Italy, AIRTUM presented comprehensive epidemiological data about the incidence (and prevalence) of STS and the associated survival of those affected [1]. The distribution of cancer registries in Italy covers most of the regions where expert centres are available, other than Bologna. In addition, the AIRTUM cancer registries cover only 52% of the Italian population. Nevertheless, a total of 4072 new cases of STS was estimated for the entire country in 2015. Thus, STS accounted for ≈80% of all sarcomas (4072 of 4957), with the remainder being 499 cases of bone sarcoma and 386 cases of GIST, although the incidence of GIST is likely an underestimate. Crude incidence rates (CIR; the number of all new STS occurring in 2000–2010 divided by the overall population at risk) for STS according to anatomic localisation are shown in Table 2 and ICD-O-3 topography and morphology codes for AIRTUM [1] and RARECAREnet [20] are provided in a Supplementary table. An important limitation is that AIRTUM did not provide incidence data according to STS histological subtype, as this was not the purpose of the AIRTUM report. Such data are now urgently needed in the field of STS research. However, concerns have been raised about the accurate registration of STS and other rare cancers in cancer registries, primarily related to the need for correct morphologic specification which depends on the pathological diagnosis and how it is reported in the pathological report [6,15]. For example, when a morphology code is unspecified, usually due to genuine difficulties for the pathologist in assigning a specific morphologic category, it is not possible to assign the case to a specific rare cancer entity defined based on the morphology, resulting in an underestimation of the incidence for that entity [15].

The overall incidence of STS in the AIRTUM population was 6.27 per 100,000 per year. The incidence in women (6.58 per 100,000 per year) was slightly greater than that in men (5.95 per 100,000 per year) because of gynaecological sarcomas (most often occurring in the uterus) and breast sarcomas. Among STS overall, the most frequently affected sites were limbs (1.27 per 100,000 per year), skin (0.78), uterus (0.69), and superficial trunk (0.69). The CIR of STS increased with age: 0–54 years, 3.49 per 100,000 per year; 55–64 years, 9.23 per 100,000 per year; and ≥65 years, 13.97 per 100,000 per year [1].

The RARECAREnet project collected data from 94 population-based cancer registries in 27 European countries, including Italy; 19 were national registries covering the entire population in specific countries. Italy and seven other countries were covered by regional cancer registries partially representing the population of their country. Overall, during the period 2000–2007, the RARECAREnet project covered a total population of approximately 208 million (48% of the population of the participating countries). Within the current EU 28, 46% of the total population was covered. For the RARECAREnet data listed in

Table 2
Incidence rates from Italy [1] and Europe [16,17] for soft tissue sarcoma (STS) according to anatomical site of origin. Number of cases corresponds to the number of cases observed by the cancer registries in the period of each analysis.

Type of sarcoma	Italy AIRTUM data[a]	Europe RARECAREnet data[b]	
	CIR (per 100,000 per year) [95% CI] (no. of cases)	CIR (per 100,000 per year) [95% CI] (no. of cases)	Age-adjusted IR (per 100,000 per year)[c] [95% CI] (no. of cases)
STS (overall)	6.27 [6.17, 6.38] (13,914)	4.71 [4.68, 4.74] (73,795)	4.15 [4.10, 4.19] (35,043)
STS of head and neck	0.31 [0.29, 0.33] (683)	0.26 [0.25, 0.27] (4087)	0.21 [0.21, 0.23] (1925)
STS of limbs	1.27 [1.23, 1.32] (2823)	1.10 [1.08, 1.11] (17,178)	0.96 [0.94, 0.99] (8300)
STS of superficial trunk	0.69 [0.65, 0.72] (1526)	0.50 [0.49, 0.51] (7813)	0.44 [0.43, 0.46] (3834)
STS of mediastinum	0.04 [0.03, 0.04] (79)	0.03 [0.03, 0.03] (465)	0.03 [0.02, 0.03] (221)
STS of heart	0.01 [0.01, 0.02] (32)	0.01 [0.01, 0.02] (216)	0.01 [0.01, 0.02] (106)
STS of breast	0.24 [0.22, 0.27] (543)	0.18 [0.18, 0.19] (2865)	0.15 [0.14, 0.16] (1279)
STS of uterus	0.69 [0.65, 0.72] (1525)	0.55 [0.54, 0.56] (8657)	0.50 [0.48, 0.52] (4094)
STS of genitourinary tract	0.27 [0.25, 0.29] (596)	0.20 [0.19, 0.21] (3160)	0.18 [0.17, 0.19] (1486)
STS of viscera	0.53 [0.50, 0.56] (1,183)	0.38 [0.37, 0.39] (6004)	0.32 [0.31, 0.33] (2807)
STS of paratestis	0.05 [0.04, 0.06] (120)	0.03 [0.03, 0.04] (510)	0.03 [0.02, 0.03] (244)
STS of retroperitoneum and peritoneum	0.54 [0.51, 0.57] (1198)	0.31 [0.30, 0.32] (4911)	0.27 [0.26, 0.28] (2320)
STS of pelvis	0.21 [0.19, 0.23] (463)	0.20 [0.19, 0.20] (3090)	0.17 [0.16, 0.17] (1415)
STS of skin[d]	0.78 [0.74, 0.82] (1731)	0.30 [0.29, 0.31] (4737)	0.30 [0.29, 0.31] (2519)
STS of paraorbital site	< 0.01 [0.00, 0.01] (8)	0.01 [0.01, 0.01] (117)	0.01 [0.01, 0.01] (56)
STS of brain and other parts of nervous system	0.14 [0.13, 0.16] (318)	0.17 [0.17, 0.18] (2723)	0.16 [0.15, 0.17] (1283)

CI, confidence interval; CIR, crude incidence rate; IR, incidence rate; ND, no data.

[a] AIRTUM cancer registries covered more than 30 million people, or ≈51% of the Italian population in 2013; data shown are for the period 2000–2010 (CIR). Number of cases corresponds to the number of cases observed by the AIRTUM cancer registries in the period 2000-2010.

[b] The RARECAREnet data covered the period 2000–2007 and collated data from the pool of 83 RARECAREnet cancer registries in 27 European countries, including Italy. In 19 countries, cancer registries covered the entire national population, whereas regional cancer-registry data were collected for other countries. For the period 2000–2007, data represented a 48% coverage of the population of all participating countries. With the current EU 28, 46% of the total population was covered. The 95% CI values for CIR data are from Gatta et al. [17], which in some cases vary slightly from those reported in RARECAREnet [16]. Incidence analyses are based on data from 83 cancer registries.

[c] Data (2003–2007) calculated from the pool of 42 RARECAREnet cancer registries with available incidence data for all cancer types between 1995 and 2007 (RARECAREnet [16]). Age-adjusted incidence rates were calculated to estimate time trends, and therefore included fewer cancer registries (with data for each time period) than analyses to estimate crude rates.

[d] Excludes Kaposi sarcoma.

Table 2, CIR (2000–2007) are based on the pool of 83 cancer registries [16,17]. Importantly, in comparison of AIRTUM with RARECAREnet data, the overall CIR of STS in Italy versus Europe was greater (6.27 [95% CI 6.17, 6.38] vs 4.71 [95% CI 4.68, 4.75] cases per 100,000 per year). However, comparison based on CIR should be interpreted with caution because differences could be related to potential differences in the age distribution in Italy versus the population of the countries included in RARECAREnet. AIRTUM aimed to present the burden of rare cancers and therefore did not provide age-adjusted rates, which limits data comparisons. Considerable AIRTUM–RARECAREnet discrepancies were also evident regarding CIRs of STS at the following body sites: retroperitoneum and peritoneum (CIR [95% CI]: 0.54 [0.51, 0.57] vs 0.31 [0.30, 0.32] cases per 100,000 per year); and skin (0.78 [0.74, 0.82] vs 0.30 [0.29, 0.31]) [1,16,17]. Much of the excess in rates for AIRTUM versus RARECAREnet was accounted for by these two sites.

However, the diagnostic misclassification of STS might be another explanation for differences between AIRTUM and RARECAREnet data, considering that diagnostic discrepancy between pathologists may occur in up to 30% of cases [4]. Additionally, some of this difference may have resulted from variation in registration practices for skin cancers. Also of note is that RARECAREnet reported some inter-regional variability in age-standardised incidence rates of STS: rates were greatest in southern Europe (including Italy; 4.26 cases per 100,000 per year), central Europe (4.18), and Ireland and the UK (4.03) and lowest in northern Europe (3.89) and eastern Europe (3.78) [16].

CONTICANET was a population-based prospective study that collected epidemiological data about sarcomas over 2 years from two regions in France and one in Italy (2005–2006 in Rhone-Alpes and 2007–2008 in Aquitaine and Veneto), and included more than 26 million person-years of observation [7]. Patients had to be residents in the region and were identified by the regional network of pathologists, although experts in second opinions for sarcoma in each region supported the study and reviewed the diagnoses of local pathologists. Thus, while AIRTUM [1] and RARECAREnet [16,17] provide population-based registry data, CONTICANET [7] does not. More importantly, whereas AIRTUM and RARECAREnet used the same anatomical sites and ICD-O-3 morphology, CONTICANET did not use the same anatomical sites. Therefore, methodological differences make meaningful comparison of data from CONTICANET with those from AIRTUM and RARECAREnet difficult. For example, in CONTICANET, 968 of 1558 cases (62%) were defined as STS and 590 (38%) were defined as visceral sarcomas. The CIR for overall STS (regardless of site of origin) in CONTICANET was 5.76 per 100,000 per year [7]; overall STS CIRs for Italy [1] and Europe [16,17] were 6.27 and 4.71 per 100,000 per year, respectively.

3. Histological subtypes of STS

In the CONTICANET project, the most frequent histotypes of STS were liposarcoma (26.2% of cases), leiomyosarcoma (16.1%), and dermatofibrosarcoma protuberans (10.1%); the CIR for liposarcoma was 0.94 cases per 100,000 population per year, with dedifferentiated liposarcoma being the most common subset (0.24 cases per 100,000 per year) [7]. In males, the most frequent STS histotypes were liposarcoma (22%) and leiomyosarcoma (11%); in females, the most frequent STS histotypes were leiomyosarcoma (21%) and liposarcoma (13%) [7]. Interestingly, in the Rhone-Alpes region, data revealed a younger peak age incidence for well-differentiated liposarcoma (60–69 years) than dedifferentiated liposarcoma (80–89 years) [21]. In the RARECARE project, the most frequent STS histotypes were leiomyosarcoma, which accounted for 20% of all sarcomas, then unspecified sarcoma (18%), and liposarcoma (10%) [6]. Although these results may be somewhat unexpected in that liposarcoma was not the most frequent STS histotype, these findings may be explained by several factors [6]. The female STS population included a large proportion of uterine leiomyosarcomas. Overall, 24% of leiomyosarcomas arose in the uterus, which highlights a pressing need for pathological reclassification of uterine

sarcomas. In addition, not all GIST diagnosed as leiomyosarcomas may have been recorded as originating from the gastrointestinal tract, as some cases may have been reported as retroperitoneal or pelvic in origin. Also, some leiomyosarcomas may now be classified as pleomorphic sarcomas with a myogenic differentiation that is insufficient to make them true leiomyosarcomas. RARECARE also had a relatively high proportion of unspecified sarcomas (18%), which would have contributed to a lower incidence of specific histological subtypes of STS [6].

Of note, in France, the Reference Network for Pathology of Soft Tissue-GIST-Desmoid-Visceral Sarcomas (RRePS) has undertaken the systematic histopathologic review of all newly diagnosed cases of sarcoma, GIST, and desmoid tumours and estimated the following distribution of STS by histotype: liposarcoma (25.2% of cases), undifferentiated pleomorphic sarcoma (21.8%), leiomyosarcoma (17.1%), myxofibrosarcoma (5.8%), angiosarcoma (5.0%), rhabdomyosarcoma (5%), synovial sarcoma (4.2%), malignant peripheral neural sheath tumours (2.6%) and others (13.3%) [22,23].

From the clinical standpoint, identification of histological subtype is essential for surgical planning, and this is the first thing an expert centre or a network of reference centres treating STS ensure. In France, for example, patients with retroperitoneal STS managed outside the Clinical Reference Network for Sarcomas-GIST-Desmoids (NetSarc) were five times less likely to have a histological diagnosis before definitive surgery, three times less likely to have a case discussion by a multidisciplinary team, and four times less likely to have relevant preoperative imaging [22]. This preparation is important because, with appropriate adherence to diagnostic and therapeutic guidelines and with better initial identification of histological subtype, patients with retroperitoneal STS in France in 2014 were reported to have median overall survival of 96 months and a 5-year overall survival rate of 66%, which appeared to be an improvement on the 5-year overall survival rate of ≈50% generally reported for retroperitoneal STS [24].

4. Survival data by anatomical site

Overall, the 5-year survival for STS can vary widely depending on disease stage [3] and the complex interplay between anatomical site and histology for different STS subtypes [6]. For example, the prognosis and therapeutic implications are very different for a well-differentiated liposarcoma of a limb compared with a well-differentiated liposarcoma arising from the retroperitoneum, where surgery is more difficult [6].

Five-year relative survival for STS in Italy (AIRTUM data) was generally similar to that in Europe (Table 3) [1,17]. No survival data were available in Italy regarding heart and paraorbital sites because of the limited number of cases observed, and a survival difference of > 5% was noted in Italy versus Europe for STS arising at the following anatomical sites: genitourinary tract (56.1 vs 50.4%), viscera (49.6 vs 42.1%), and pelvis (55.3 vs 47.4%) [1,17]. The significantly smaller sample size of the AIRTUM compared with the RARECAREnet database cannot solely explain such divergent survival [1,17]. However, these are descriptive statistics that are not age standardised or corrected for factors that could affect survival, such as different case and stage mix; thus, these results should be interpreted with caution.

STS prognosis is also affected by adherence to clinical practice guidelines and by the expertise of the treating centre. Indeed, a side study of the CONTICANET project, which included 151 patients with sarcoma who were prospectively enrolled in the Veneto region of Italy, revealed that patients not treated according to clinical practice guidelines had a significant, 5-fold increase in the risk of local relapse ($p < 0.001$) and a significant, 4-fold reduction in sarcoma-specific survival ($p < 0.001$), irrespective of tumour stage [25]. Several other studies also support the benefits of adherence to clinical guidelines in STS, including a prospective population-based cohort study conducted in the Rhone-Alpes region of France [26].

Table 3
Five-year relative survival from Italy [1] and Europe [17] for soft tissue sarcoma (STS) according to anatomical site of origin.

Type of sarcoma	5-year relative survival (%)	
	AIRTUM data[a]	RARECAREnet data[b]
STS (overall)	62	57
STS of head and neck	61	60
STS of limbs	72	68
STS of superficial trunk	52	48
STS of mediastinum	20	23
STS of heart	ND	14
STS of breast	78	75
STS of uterus	56	52
STS of genitourinary tract	56	50
STS of viscera	50	42
STS of paratestis	92	87
STS of retroperitoneum and peritoneum	44	39
STS of pelvis	55	47
STS of skin	91	90
STS of paraorbital site	ND	63
STS of brain and other parts of nervous system	54	55

ND, no data.

[a] AIRTUM cancer registries covered more than 30 million people, or ≈51% of the Italian population in 2013; data shown are for the period 2000–2008 (5-year relative survival). Specific values were reported for STS overall and STS of paratestis, skin, uterus and mediastinum; other values were estimated from a graph.

[b] The RARECAREnet data covered the period 2000–2007 and collated data from 27 European countries, including Italy. In 19 countries, cancer registries covered the entire national population, whereas regional cancer-registry data were collected for other countries. For the period 2000–2007, data represented a 46% coverage of the European population.

5. The emerging importance of Italian and European reference centres and networks

One of the major benefits of cancer registries is the creation of large databases for data analyses, with important implications for clinical research into rare tumours. Indeed, registries provide significant sources of information for researchers and clinicians and, in some cases, facilitate the creation of control groups for clinical trials. Expertise of the treating centre is one of the most significant factors affecting survival in STS: treatment within specialised multidisciplinary teams is crucial, since expertise in all areas of diagnosis and treatment (dedicated radiologist, pathologist, surgeon/s, radiotherapist, and medical oncologist) is required to manage STS appropriately. Moreover, conformity to approved treatment guidelines is clearly improved when patients are treated by a multidisciplinary team in a reference centre [5]. Results of the previously mentioned prospective population-based cohort study conducted in the Rhone-Alpes region between 2005 and 2007 demonstrated a beneficial impact of treatment in regional expert centres, not only on adherence to clinical practice guidelines but also on survival of patients with STS [26]. The study authors noted that a possible reason for the improved adherence to clinical practice guidelines may be related to a consistent use of multidisciplinary assessments and treatment planning in expert centres compared with other institutions [26]. Interestingly, data from 1431 adults with STS revealed that almost half of all patient treatment programmes deviated from clinical practice guideline recommendations. This underscores the importance of promoting increased adherence to relevant guidelines, with the attendant likelihood of reduced treatment costs and improved sarcoma care [27].

Many of these themes are also discussed in a recent review clearly supporting centralisation and a multidisciplinary team approach in the diagnosis and management of patients with STS [28]. The review highlights the importance of an accurate pathological diagnosis and the need for expert pathology review, the high rate of suboptimal adherence to clinical practice guidelines in STS (especially in surgery),

and the greater likelihood that patients undergo an appropriate treatment strategy when their case is presented in a multidisciplinary team setting and when management occurs within a reference centre or network for sarcoma [28].

Reference centres and clinical networks have potentially pivotal roles in reducing delays in diagnosis, increasing patient participation in clinical trials, addressing the age-specific needs of patients, and investigating factors relating to tumour biology [29]. It is clearly necessary to raise awareness about reference centres for STS management, not only in the general population but also among general practitioners and other physicians, so that patient referral to such centres can be expedited. Indeed, centralisation of STS management in high-volume reference centres appears to improve outcomes [14]. For example, the French National Cancer Institute established a national network of 26 reference centres for patients with sarcoma diagnosis. About two-thirds of the 26,883 patients included in this NetSarc database had STS. For patients without a case discussion by a NetSarc multidisciplinary tumour board before initial treatment, the risk of local, metastatic, or overall relapse was significantly elevated compared with patients who had such a discussion (hazard ratio 1.9; $p < 0.001$) [14]. Furthermore, 1007 patients with a diagnosis of retroperitoneal sarcoma managed at six European and two North American reference centres had a 10-year overall survival of 46%; the corresponding 10-year crude cumulative incidence of local recurrence was 35%, and that of distant metastasis was 22% [30]. The study authors noted that the 10-year overall survival rate observed in their study (from 2002 to 2011) was about 20% higher when compared with relevant population-based results (from 1988 to 2005) [30]. However, the different time periods may have been a confounding factor and it is unclear whether the comparison allowed for different age structures of the two data sets.

A large population-based study undertaken by the RARECAREnet project, which included an analysis of the extent of centralisation of rare cancer treatment, suggested that centralisation of treatment could act as a proxy for a good healthcare organisation and quality of care [17]. The study authors reported on survival improvements for some groups of rare cancer "for which multidisciplinary approaches and centralisation of treatments might take credit" [17]. The RARECAREnet project has also undertaken studies to assess quality of care in STS in several countries, including Italy, although results have not yet been published [31]. Nevertheless, based on these findings, discussions have been held in several countries and support the use of results from studies such as those undertaken by the RARECAREnet project [31].

Collaboration, at both a national and an international level, is pivotal to guarantee the optimal management of rare cancers [32]. The European CanCer Organisation (ECCO) emphasises that multidisciplinary care should be available for all patients with sarcoma [33], and the European Union is now supporting the organisation of a dedicated European Reference Network for Rare Adult Solid Cancers (EURACAN). The objective is to centralise knowledge and expertise (from > 65 reference centres in ≈18 countries) about ten families of rare cancers, with the aim of increasing opportunities for patients to be involved in clinical trials and to receive the most appropriate treatment and care through multidisciplinary teams [14,34]. European Reference Networks are still in their infancy, and some important points remain to be defined to enhance teamwork, cross-border patient transfers, and relevant reimbursement between reference centres. Nevertheless, some important advances have already been made towards these goals (Table 4). For instance, a predefined criterion for reference centres to be included in EURACAN (and a criterion of particular relevance in the management of rare cancers) was demonstration of care organisation into multidisciplinary teams [3].

From a historical perspective, the Italian Rare Cancers Network (Rete Nazionale dei Tumori Rari) was established in 1997 and compiled a database of all clinical teleconsultations and details of histological revisions obtained from contributing reference centres for rare adult solid cancers in Italy [1,3,18]. Over the years, it grew to include 100 Italian centres of medical oncology, providing centralised pathologic diagnostic reviews as well as clinical expertise in sarcomas and rare tumour diagnosis and management, but the network lacked an official certification framework [1,18]. However, a new National Rare Cancer Network with an official certification framework was approved in Italy in September 2017, and currently each Italian region is in the process of identifying participating centres [35].

Table 4
Potential advantages of European Reference Networks for rare adult solid tumours.
Table adapted from The Sarcoma Policy Checklist [3].

- Increased opportunities for patients to be involved in clinical trials and receive the most appropriate treatment and care through multidisciplinary teams and cross-border teamwork
- Clinical database establishment and joint collation of clinical-practice data to check whether treatments are provided in line with agreed standards and to support research
- Establishment of quality assurance mechanisms for laboratory testing
- Upskilling and education resources available for healthcare professionals
- Rapid exchange between reference centres of biological samples, diagnostic materials, information, radiological images, and telemedicine e-tools

Thus, while our data highlight the need for a national network of care for STS and rare cancers in general in Italy, this would also be appropriate in many other large-population countries in Europe. Such networks should be based on centres of expertise where multidisciplinary teams are essential. In Italy, we can learn from developments in other countries, such as France, where significant progress has been made. Italy and many other European countries urgently need to delineate national networks for rare cancers in order to also ensure appropriate engagement in the European Reference Network.

Alongside the pivotal need for regional, national, and international reference centres, it should not be overlooked that patients from rural and peripheral areas may have difficulty accessing such centres for sarcoma care. Moreover, patient transfer between regions may be difficult, and patients may not be reimbursed for their travel or accommodation expenses [3]. Important steps should be taken to remove any potential barriers or access restrictions so that patients can readily obtain enhanced sarcoma care. One approach advocated to ensure appropriate care for all patients regardless of where they live is the 'hub-and-spoke' model, which makes available to collaborating centres ('spokes') the expertise of reference centres ('hubs') [36].

5.1. Potential areas for improvement

Within the framework of reference centres, several potential areas exist for enhanced overall diagnosis and management of STS. Zeev Waks and colleagues conducted a 'CareGap' analysis of 1329 patients with STS in northern Italy to identify gaps in adherence to a clinical guidelines-based clinical decision-support system [37]. Adherence was reported as 70%, which was markedly greater than the 32–54% documented in previous studies [38,39]. Possible explanations for the discrepancy include methodological issues. For example, the CareGap analysis assessed adherence based on the physician prescription at the decision point, whereas the other studies quantified adherence rates based on the actual treatments given to patients. The authors of the CareGap analysis found that deviation from guidelines was substantially greater in patients with high-grade disease than in those with low-grade disease ($p < 0.0001$) and in those with metastatic versus local presentation ($p < 0.0001$), or shorter survival time. Thus, the CareGap analysis identified patients with reduced adherence to clinical practice guidelines; indeed, it can direct physicians' attention to distinct patient cohorts likely to have higher levels of deviation from these guidelines [37].

The European Society for Medical Oncology and American Society of Clinical Oncology also acknowledge the need, through a joint global curriculum, for consistency in training and upskilling medical oncologists worldwide. In STS, for example, objectives of the global curriculum are for medical oncologists to be able to "clinically suspect the

diagnosis of STS, when appropriate, and to properly refer these patients to sarcoma reference centres for biopsy and specialised multidisciplinary treatment planning" and "collaborate with a sarcoma reference centre on the medical management of STS patients, as needed, through active clinical networking" [40].

As noted, epidemiological data on STS are limited, and the quality of such data in cancer registries may not be optimal because of issues such as poorly specified histological subtypes [15]. It is important that cancer registries provide data on all sarcomas, as defined by RARECARE, in addition to details about major histological subtype groups. For example, it may be appropriate for all registries to provide data on all morphologies regardless of the site of origin, rather than focusing solely on the ICD-O topography C49. As noted, this could provide improved consistency in reporting incidence patterns. Improved collaboration between oncologists, pathologists, and registry administrators may, in turn, improve the quality of data on detailed histological subtypes, which may facilitate better clinical outcomes and the identification of current needs and potential areas for improvement. We hope that the European Reference Network and the national clinical networks in each European country will contribute to strengthening collaboration to improve STS diagnosis. This will ultimately also have an impact on the quality of data of cancer registries since they rely on the pathological report.

6. Conclusions

Rare cancers are a major public health problem in Italy. Among such cancers, STS represent a group of histologically distinct diseases, and, through the introduction and development of regional, national, and European reference centres and networks, the rate of accurate STS diagnosis will likely continue to increase and pose an even greater public health burden. However, several knowledge and treatment gaps remain for STS. In Italy, and throughout Europe, it is important to gain more accurate information about the epidemiology of STS to ensure that stakeholders, including healthcare professionals, policy makers, and payers, understand the high unmet medical needs in STS, which may lead to increased research in medical and surgical treatment. Improving the quality of data regarding histological subtypes may also lead to more precise diagnoses and improved clinical outcomes.

Meanwhile, the increasing role and availability of multidisciplinary care for STS patients, through reference centres, clinical networks, and collaborative disease-specific groups (e.g. the Italian Rare Cancer Network and EURACAN), will likely improve not only diagnostic specificity but also epidemiological data and will likely continue to drive better patient management and enhanced outcomes.

Conflicts of interest

Dr Trama, Dr Badalamenti, Dr Baldi, Dr Marrari, Dr Palmerini, and Professor Dei Tos have nothing to disclose. Dr Brunello reports personal fees from Lilly, other fees from Pharmamar, personal fees from Eisai and personal fees from Roche, outside the submitted work. Dr Drove-Ubreva and Dr Caira report other fees from Eli Lilly, outside the submitted work. Dr Grignani has participated to advisory boards of Novartis, Bayer, Eisai, Pharmamar, and Lilly. Dr Vincenzi reports personal fees from Bayer, personal fees from Eisai, grants and personal fees from Eli Lilly, grants and personal fees from Novartis, personal fees from Pfizer, grants and personal fees from Pharmamar and personal fees from Abbott, outside the submitted work.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.canep.2019.02.012.

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