



Treatment challenges in and outside a network setting: Soft tissue sarcomas



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ABSTRACT

Patients with soft tissue sarcoma (STS) experienced better outcomes when treated according to existing clinical practice guidelines either at reference institution or dedicated treatment networks. Despite increasing evidence supporting referral to sarcoma specialised units, up to half of patients are not managed according to guidelines, particularly those in the early stage of their disease requiring surgery. Also, criteria to certify expertise of institutions, such as the treatment volume, are debated and health authorities have only recently started identification of these centres and creation of treatment networks in Europe as well as in several countries. This process have important implications for both patient outcomes and innovation of existing treatment strategies through clinical research, making improvement of clinical pathways a priority for health care authorities. This article will discuss issues with management of patients with STS, such as pathological diagnosis and adherence to guidelines, and the definition of referral centres and networks will be illustrated along with existing experiences and population-based data.

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Introduction

Soft tissue sarcoma (STS) affects about 5 new patients yearly every 100,000 people with 30,200 new cases expected every year in Europe [1–3].

These tumours, which encompass more than 50 different histology [4,5], have been recognised as rare cancer since, based on an international consensus, it was decided that incidence is more accurate than prevalence to define rare tumours, while prevalence remains the best indicator to define rare diseases [6,7]. Management of patients with STS is challenged by issues shared with other rare tumours [8]. Firstly, these rare neoplasms account for roughly one in five tumours representing a significant burden for both patients and health care system [6]. Patients with rare cancers,

including STS, did worse than those with more frequent neoplasms (49% 5-year survival for rare and 63% 5-year survival for 'common' cancers), suggesting that - beside biological factors specific to the different diseases - several issues limit care of these patients [7,9]. Treatment strategies are often suboptimal and major deviations from guidelines are identified in up to half of patients [10–18]. This unsatisfactory management is strictly linked to difficulties in access to clinical reference centre and network. Also, fewer investments exist in clinical research on rare cancer and STS leading to less innovative drugs being tested in clinical trial and eventually becoming available [8,19,20].

Management of patients with STS differs based on patient characteristics, tumour presentation, and histopathologic features, mostly sarcoma subtype and tumour grade, underlining the importance of an accurate pathological diagnosis [21–23]. More than 40% of first histological diagnosis are modified when a second opinion is requested to a pathologist with expertise in sarcoma [24]. Recently, molecular analysis is becoming a widely diffuse technique that significantly impact final diagnosis in cases where

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morphology and immunohistochemistry do not identified the correct STS histology [25,26]. Also, only one in two to three patients is managed consistently with recommendations included in clinically practice guidelines for treatment of sarcomas [12,16,18]. Surgery is burdened by the lowest quality with approximatively only half of patients receiving appropriate management of localised disease, resulting in high incidence of local recurrence and lower survival rates [12,16,18]. Conversely, patients do better when treated in referral institutions by surgeons with expertise in sarcoma [12,17,18,27,28].

All these findings support referral of patients with sarcomas to network and centres with high expertise in these tumours. However, this process has been only recently started in many countries worldwide and particularly in Europe [29]. Networks of professionals are increasing performance of second pathology opinion from expert pathologists as well as centralizations to referral units for patient treatments. More recently, the EU has launched the European Reference Networks (ERNs) which will provide highly specialised healthcare for rare or low prevalence complex diseases or conditions including rare cancers. Out of the 24 ERNs recently established, three are for rare cancers: EURACAN on all adult rare cancers, EuroBloodNet on all haematological diseases, and PaedCan on all paediatric cancers. Sarcomas of soft tissues and bone are included in EURACAN which gathers 66 Health Care Providers in 17 European countries, and 22 Associate partners (Patients Advocacy Groups, rare disease stakeholders).

This article discusses issues with management of patients with STS, with particular regards to pathological diagnosis and management according to guidelines. Challenges in the definition of referral centres and networks will be illustrated along with experiences from single institutions and national initiatives. Also, data from seven European population-based databases, which are representative of six EU countries, including Belgium, Bulgaria, Ireland, Finland, Netherlands, and Slovenia and the region of Navarra in Spain will be used to support discussion of relevant issues [3,7].

Histological diagnosis

Histological diagnosis of STS represents a challenge for pathologists with frequent inaccuracies requiring need for expert pathology review [30,31]. A prospective population-based study had specifically addressed the issue of second pathology opinion in STS analysing sarcoma diagnoses performed over a two-year period in three European Regions [24,32]. In this study, all cases underwent central pathology review and differences between initial diagnosis and second opinion were scored as follow: 1) no agreement between first and final pathology report on either benign vs malignant or sarcoma vs non-mesenchymal tumour diagnosis; 2) partial agreement, when there was lack of agreement on histopathological grade or histology; and 3) agreement. No agreement and partial agreement were observed in 8% and 35% of patients, respectively, resulting in an overall lack of concordance in 44% of patients. In case of partial agreement, tumour grade was not reported by 57% of pathology report, and in 19% of cases diagnosed as G1 tumours at first pathology evaluation were upgraded to G2-G3 after second opinion. Sarcoma histology was the other source of major variations in 22% of cases. Another important finding is that when a pathologist requested a second opinion the diagnosis was accurate in 50% of cases, while when second opinion was done without been requested by the pathologist who first diagnosed a case, a scenario that represents the majority of cases included in this study, 30% of the histology diagnoses were significantly inaccurate.

Diagnostic inaccuracies and difference between primary diagnosis and second opinion are expected at the population level. However, the magnitude of this difference is remarkably high and

calls for implementation of second opinion in routine practice. Pathology review is already part of standard management of patients with STS in some countries, such as the UK, where it is recommended by the NICE [33]. Wide diffusion of this diagnostic approach is limited by apparently increased costs of performing the same procedure twice.

Complexity of performing an adequate pathological diagnosis for STS is also increased by the need for molecular testing. A further study was conducted on the same cases examining also the value of molecular analysis [26]. Three categories of tumours were considered: suspicious GIST, sarcomas suspected to harbour a translocation, and cases where an atypical lipomatous tumour or a well-differentiated/dedifferentiated liposarcomas was suspected. In GIST molecular analysis was useful for reaching the correct diagnosis in 4% of all analysed patients and necessary only in less than 1% of cases. In translocated sarcomas, molecular analysis modified diagnosis in 16% of patients with probable diagnosis ($n = 12/77$), and allowed diagnosis in 22% of cases when the initial diagnosis of a translocated sarcoma was only possible ($N = 19/87$). In the latter case, molecular analysis changed diagnosis in 10 cases when the initial diagnosis was probable ($n = 10/76$), and when the initial diagnosis was only possible it enabled final diagnosis in 18% of cases ($n = 9/50$) thus resulting useful in 19 cases (9%). These data underline the role of performing molecular analysis in STS and furtherly reinforce the need of centralised diagnosis where facilities for performing molecular analysis of a wide spectrum of diseases requiring different and specific markers are needed.

This evidence favours routine second pathology opinion for sarcoma diagnosed by pathologists lacking in specific expertise for soft tissue tumours and there is a large need to gain recognition for this process. For instance, this has been standard practice in the UK since 2006 [33] and it has been estimated that this process has increased yearly employment cost, which includes an additional clinical scientist, biomedical scientist and secretary, by approximatively 80,000 pounds at each of the four existing cytogenetic/molecular pathology laboratories. Unfortunately, in many national and regional health care systems this process is not part of the common clinical pathway and patients are charged for cost of second opinion. Some units and institutions tackle this issue through supporting directly the cost related with second pathology opinion.

The centralised pathology review has also relevant implications for clinical research beyond its clinical value [8,34]. In the light of the above mentioned findings, about one in three patients enrolled in clinical trials investigating soft tissue sarcomas is at risk of being non-eligible [35]. Currently, most research collaborative groups, such as the European Organization for Research and Treatment of Cancer (EORTC) reviewed patient slides centrally [35]. However, this process is particularly challenging for material transfer agreement issues across institutions and nations. As a result, pathology review is performed after randomization increasing the chances that a patient is erroneously enrolled. For instance an EORTC study investigating adjuvant treatment in high-risk STS after enrolled 2% of a non-mesenchymal tumours and sarcoma histologies supposed to be excluded as well as 6% of tumours were downgraded from high to low grade of malignancy, findings that would have made these patients not eligible if detected before randomization [36]. This risk is even greater considering that current trials investigating STS are focusing on specific histology and molecular characteristics. Contemporary trials, such as the IST-1001, has overcome this issue through centralization of second pathology opinion [37].

Network of pathologists have pivotal roles for treatment and research in STS. Surely, patients managed within a network can benefit from high-quality diagnosis with second opinion requested for difficult cases. A network offers opportunities for organizing

meetings of pathologists and other professionals involved in sarcoma to discuss diagnostic challenges for the identification of different STS histologies, offering also education opportunities for trainees and young consultants. Also, centres belonging to a network can deliver high quality clinical trials. Finally, an established network of soft tissue pathologists can serve also to centres outside this network which can refer cases for histological and molecular diagnosis.

Conformity to guidelines, sarcoma centre/network and prognosis

Roughly half of patients with STS are not managed consistently with recommendations included in clinical practice guidelines [10–18]. Surgery is burdened by the highest incidence of deviation from guidelines underlying that patients with early stage STS, the clinical scenario where surgery is the primary standard treatment option with a direct impact on the cure rate, are often managed outside referral centres and sarcoma networks [12,18]. Unplanned initial excision for STS of extremities and trunk wall are performed in up to 40% of patients, particularly for small and superficial tumours in young patients [38]. Some authors reported a higher risk of disease progression and death after unplanned excision also when compared to high-risk STS (e.g. AJCC stage III tumours) [39]. Others suggested this association being related to prognostic negative tumour features, including tumour excision margins, and not to unplanned surgery [38,40]. In a large retrospective single centre series, patients who were re-excised after unplanned surgery and those who were primarily resected had non-statistically significant adjusted 10-year cumulative incidences of local relapse (18.7% vs 16.4%), metastasis (17.6% and 20.2), and mortality (20.4% and 22.4) [40]. Surely, unplanned surgery, also called ‘whoops surgery’, has implications for the subsequent management of patients as plastic reconstructions are frequently needed at re-excision [38]. Second surgery is also burdened by an estimated extra cost of 3700 US dollars compared to primary excision after adjusting for several confounders, including tumour size, American Society of Anesthesiologists (ASA) status, grade, and tumour site [41]. Even more importantly this lack of a preoperative plan affects also outcomes of patients with sarcomas seated in the abdomen and retroperitoneal space, which represents a challenge for surgical oncologists [42,43] and are often treated at general surgery department with no specific expertise in these tumours and are sometimes referred for persistent disease after index surgery [44]. These patients are at higher risk of early post-operative mortality, subsequent recurrence and death compared to patients who have a complete resection of their tumours at a referral institution [45]. Interestingly, patients with a primary retroperitoneal sarcoma treated at referral centres belonging to the *Trans-Atlantic Retroperitoneal Sarcoma Working Group* (TARPSWG) showed longer overall survival (5-year overall survival: 67%, [46]) compared to patients included in population-based database such as the Surveillance, Epidemiology, and End Results (SEER, 5-year overall survival: 47% [47] Fig. 1). Series from surgical referral units for retroperitoneal sarcoma which has adopted an extended resection approach suggested also greater chances for achieving R0/R1 resections and better tumour local control beyond patient survival [48–50].

Radiotherapy (20%) and chemotherapy (5%) have lower incidence of undertreatment than surgery [12,18]. Patients are more likely to undergo a proper treatment strategy when their case is presented in a multidisciplinary tumour (MDT) meeting, and management occurs at a reference centre or a network for sarcoma [12]. Also, patients with early stage STS having a tumour with a diameter of >5 cm, deeply seated, of high malignancy grade, or having a positive resection margin after surgery are more likely to be undertreated [16]. In these patients, the high risk of disease

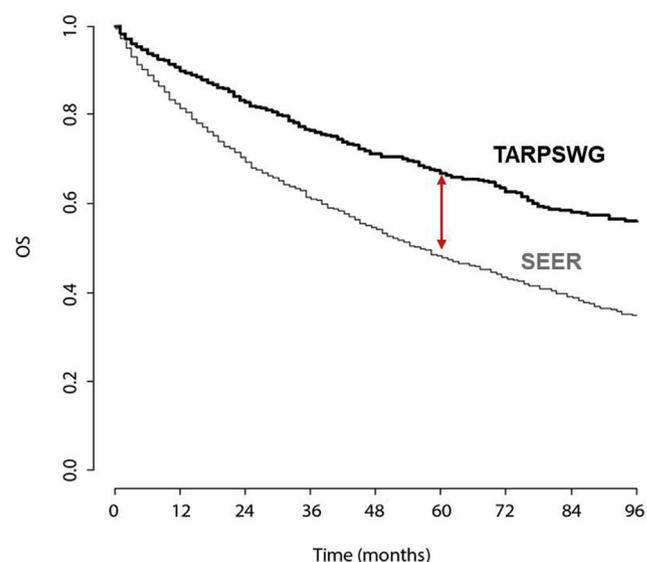


Fig. 1. Indirect visual comparison of overall survival (OS) curves of data from patients gathered in the database of the *Trans-Atlantic Retroperitoneal Sarcoma Working Group* (TARPSWG, N = 1007 patients, 5-year overall survival: 67% - black colored line [46]) and in the Surveillance, Epidemiology, and End Results (SEER) database (N = 1365 patients, 5-year overall survival: 47% - gray colored line [47]).

progression associated to tumours' adverse prognostic factors is increased by the chances of not being treated properly and has been reported as high as four-five folds considering all early stage sarcoma subtypes [16]. Lack of adherence to guidelines in a prospective study was more likely in patients at non-referral units compared to referral centres (57% vs 20%) [18]. Interestingly, also patients treated at reference centres survived longer when managed according to guidelines compared to patients who received treatments non-adherent to guidelines, a clinical scenario that exists also at units with specific sarcoma expertise. This difference cannot be detected for patients managed outside referral centres, who did worse than patients receiving appropriate treatments at referral centres regardless the quality of treatment they had received [18].

Dissemination of guidelines and promotion of education symposia have been effective strategies to improve quality of care in common cancers [51] and were also implemented for rare cancers, including STS to improve compliance to guidelines [15]. However, a prospective population-based study demonstrated that these measures were only partially successful [52]. Following dissemination of STS guidelines, patients with extremity and trunk wall sarcomas were more likely to undergo preoperative multidisciplinary discussion and being diagnosed with negative resection margins. Conversely, no improvements were observed for visceral and retroperitoneal tumours, underlying the challenges of managing these complex cases. These data also support the conclusion of better care for patients treated within reference centres and networks, where up-to-date treatment options exist and specific expertise are offered to patients. Despite the evidence supporting centralization of care for patients with STS within reference centres and dedicated networks, agreement of requirements to define a sarcoma centre is lacking and creation of sarcoma network is in its infancy.

Key elements for a sarcoma centre and network

Several measures have been identified by national and international societies to define a sarcoma centres and characterised a network [53–55]. Quality indicators includes several domain of STS

treatment, such as the performance of preoperative imaging, the rate of patients with a complete and incomplete microscopic tumour resection, the rate of re-excision following incomplete surgery, availability of MDT, and treatment volume. The implementation of the latter two indicators, although widely recognised for the identification of a sarcoma-specific unit, raise relevant issues.

Defining a sarcoma centre: the volume effect

Volume of managed patients has been suggested as one of the key characteristic to identify a hospital with better outcomes in several tumours [56–58]. The Accreditation and Designation Program (A&D) of the Organization for European Cancer Institutes (OEI), which was aimed at improving the quality of care in Cancer Centres and designate Comprehensive Cancer Centres in Europe, stated that the most important feature of a reference institution is an high enough workload certifying medical expertise, technical adequacy, and access to clinical trials [59]. Early results of this program were analysed investigating volumes of several domains of care, research, and education. Volume is meant to account for medical expertise, technical adequacy, and access to clinical trials. Variations in these functions and activities were detected across institutions, although their impact on patient outcomes as well as the added value of this program is to be investigated. However, data regarding optimal number of patients with STS to be managed to define a reference sarcoma unit is lacking.

The Italian Society of Surgical Oncology (SICO) conducted a survey to assess the value of several criteria in the definition of expertise in STS within an institution [55]. A questionnaire was circulated among members of this scientific society who are mainly surgical oncologists and general surgeons dealing with cancer patients in their practice. This questionnaire investigated the following domains: expertise in STS, documented good clinical practice and outcomes, quality of human resources, organization and governance, existing diagnostic and therapeutic facilities, educational activities, networking, and access to web-based platforms for case discussion. There was a wide consensus on considering volume as an indicator of expertise in STS. Other features were considered to identify a referral unit beyond volume, including established diagnostic and therapeutic clinical pathways, availability of a MDT, routinely performance of second pathology opinion when first diagnosis is performed by a pathologist not experienced in STS, and availability of surgical subspecialties other than general surgery. Additionally availability of research facilities, such as a prospective patient database, and clinical trials were thought to be important in defining a sarcoma referral centre. The RARECAREnet project also identified a list of quality criteria for centres of expertise for STS which was agreed within a groups of experts, from European cancers societies/associations and includes: diagnostic procedures, availability of an experts pathologist, adherence to clinical guidelines, quality of the surgery and of the pathological report after surgery, availability of MDT and participation in clinical and translational research. The SICO followed recommendations for optimal volume for a sarcoma centre established by the National Institute for Health and Care Excellence (NICE) Improving Outcomes Guidance (IOG) in 2006 in the UK [33]. The minimum number of new patients with sarcoma to be treated at a single centre yearly was 100 for STS and 50 for bone sarcoma. Similar indications are suggested also by other organization. For instance, the European CanCer Organization (ECCO), which recently released essential requirements for quality cancer care in adult-type STS and bone sarcomas, suggests that 100 new patients with STS and bone sarcomas should be treated yearly at each referral centre, reflecting a less centralised referral pathways in Europe compared to the UK [53]. Also, surgeons should performed at least 30–40 procedures a year for sarcomas and they

must participate in sarcoma MDT and meetings [53]. This ECCO document also underlines the importance of considering whether or not a reference centre is part of a network when identifying optimal target volume for defining expertise of a centre acknowledging that both the structure of a network and the distribution of expertise can significantly influence the suggested threshold for treatment volume [53]. Another example is the Sarcoma Alliance in the US, which defined that a sarcoma referral centre should treat 50 new patients yearly [60]. Although these definitions are based on sensible patient volumes representing 1–2 new patients with sarcoma to be treated weekly, data on a clear association between volume and patient outcomes are not currently available. In this regard, some authors agreed on limitations of patient volume as a characteristics reflecting expertise and support creation of treatment networks [29].

Population-based data from the six countries and the region of Navarra considered here, showed relevant variations in treatment volumes. Fig. 2 depicts the distribution of the hospitals where new incident patients with STS were treated highlighting their yearly treatment volume. The histograms have similar patterns across countries, with relatively long tails representing a wide number of centres managing less than desirable volumes. The majority of hospital treat much less than the above suggested of 50–100 new patients yearly. Consistently, number of surgical procedures performed for STS followed a similar trend (Fig. 3). Strikingly, a minimum target of 50 surgical procedures for centre yearly is reached in only one hospital among examined countries. Although, it should be acknowledged that countries described here are small and medium population countries (from 2,000,000 in Slovenia to 17,000,000 in Netherlands and the expected number of new cases/years ranges from 122 to 970, respectively). Thus, the proposed cut-off can be good for big-population country but difficult to reach in small-population countries because these cancers are rare. Thus, especially in these countries organizing care for rare cancers challenges the health care systems. Anyway accurate patient referral has been established also in countries with small population such as the Nordic Countries (see paragraph ‘Network examples’).

Defining a sarcoma centre: the MDT

National guidelines and recommendations from international scientific societies identify the MDT as one of the most important element in the clinical pathway of cancer patients, especially the case of rare cancers and STS [21,61]. The role of MDT in STS is supported by studies investigating association between conformity to guidelines and patient prognosis that have demonstrated a clear association between formulating a treatment plan within an MDT and outcomes [12,17].

It has been estimated that cancer MDT changed treatment plan formulating by patient own consultant in 2–52% of cases [62]. Tumour board were recognised as a possible improvement in oncology since 1995 in England and Wales with the so called ‘Calman-Hine report’, which addressed policy for commissioning cancer services [63]. This document suggested that previous ‘there are many elements within specialist care including [...] the multi-disciplinary team available to look after the patients [...]’. Following these suggestions, the UK National Health Service (NHS) Cancer Plan for England in 2000 recommended that ‘the care of all patients with cancer should be formally reviewed by a specialist team’, formally introducing the need for MDT in oncology. Studies have identified benefits of MDT [64], which included: improvements in the communication between health care professionals as well as consistency, continuity, coordination and cost-effectiveness of care resulting in better clinical outcomes; increased patients referral for clinical trials; greater opportunities for clinical audit and therefore service improvements; increased satisfaction and wellbeing of both

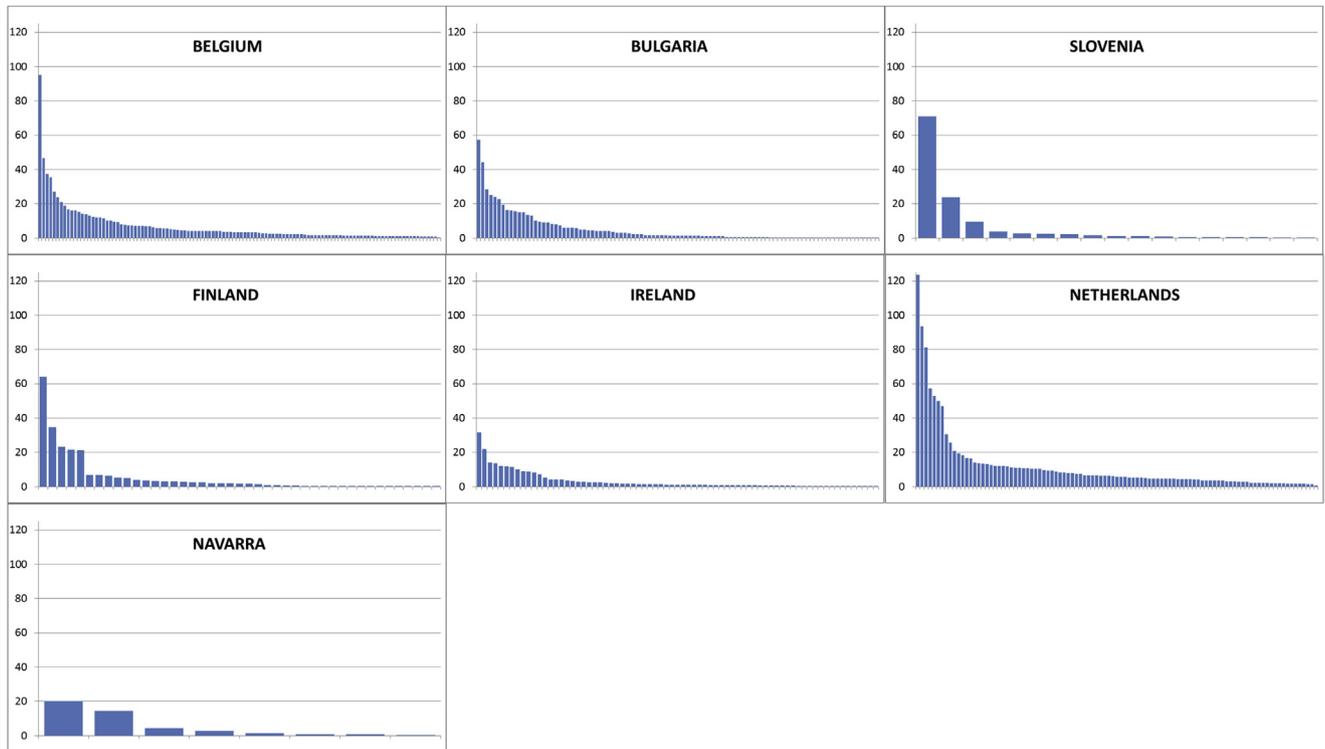


Fig. 2. Distribution of hospitals of treatment (x axis) with their treatment volume/year (Y axis) of incident STS in seven European population-based cancer registries (2000–2007). Hospital volume was calculated considering the overall number of *any* treatment delivered by the hospital on a year basis. Multiple admissions to the same hospital for the same patient were considered as a single admission. Untreated patients were assigned to the hospital of diagnosis.

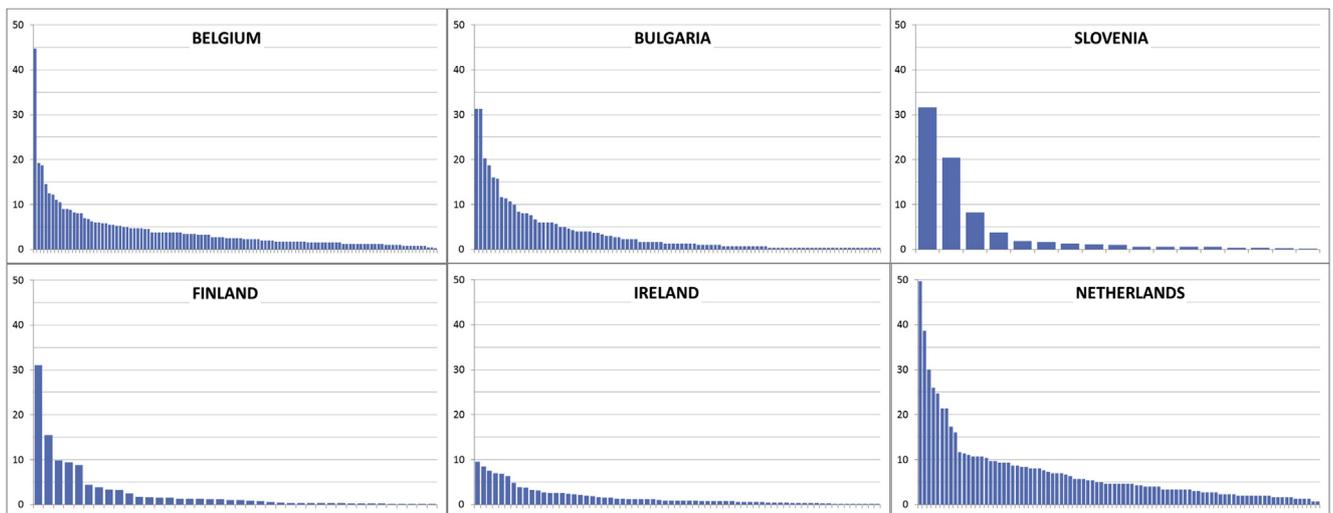


Fig. 3. Distribution of hospitals of surgery with their volume for primary STS in seven European population-based cancer registries (2000–2007). Hospital volume was calculated considering only the first surgery.

patients and health care professionals; support in the clinical decision process, particularly in conditions of uncertainty such as the case of rare tumours; and educational opportunities for health care professionals, especially those in the early stage of their careers. These advantages support conducting effective MDTs, which requires dedicated funds to support administrative management and staff time.

In several European countries STS patients are selectively discussed, based on challenges in identifying the best treatment option in a multidisciplinary fashion. Such approach, which differs

from the clinical pathways in the UK, is implemented especially in high-volume centres, where management of patients presenting with common clinical scenario is standardised and discussion of all new patients would require exceedingly long MDT time. Also, an MDT coordinator, which has a recognised role for making the MDT functional [65], is not generally available in countries outside UK.

A major issue with cancer MDT is monitoring quality of the decision making process. It is expected that a functional tumour board takes correct clinical decisions leading to optimal patient management and maximization of outcomes. However, it has been

reported that 27–52% of discussed patients failed to get a treatment plan at the end of MDT discussion with also 1–16% of patients unable to stick on the proposed treatment. Shortage of dedicated time for MDT, large number of cases to be discussed, lack of participation from referring consultants, ineffective team, and poor leadership negatively impact availability of required information and ultimately lead to poor decision making [62]. Availability of patient psychosocial information and the inputs of surgeons, radiologists, pathologists, and oncologists were associated with formulation of a treatment plan, while lack of comorbidity information and nursing inputs did correlate with failure to decide on patient optimal management [66]. Also, presence of the consultant in charge of a given patient has resulted one of the most important feature to reach a decision [67]. Checklists to prepare case-based discussion and monitor quality of MDT through auditing processes can ensure properly performing MDT [68,69].

Virtually-based MDT case discussion is supposed to provide expert advice to units lacking of a specific expertise, making this option appealing for rare cancers and STS. Patients can be treated locally following treatment plan formulated at the MDT of a referral centre. This approach is the base to create treatment network and there are great expectations that this can increase overall quality of treatment. Web-based platforms and video conferences during MDT are used for performing MDT that requires discussion of cases that are managed outside the institution where the MDT takes place. The most important advantage is to involve the consultant in charge of the patient in the discussion, which ensure quality of discussion and applicability of the treatment plan provided by the MDT. Conversely, evaluation of cases non directly managed at a referral centre represents a significant extrawork for health care professionals involved in a specific MDT, which is often overbooked for discussion of institutional patients. These approaches are increasingly used for STS. For instance, the Italian professional network for rare cancer (Rete Tumori Rari, www.retetumorirari.it) gives the opportunity to consultants working outside referral centres to send patient reports and radiology images for having advice from experts, as well as pathological slides for second opinion, thus minimizing burden of travelling for patients who need consultation and treatment.

Network examples for STS

The NetSarc network

NetSarc is a network of 26 reference multidisciplinary centres in France (population: 54.5 million inhabitants), which was established in 2009 and aimed at improving quality of care for sarcoma patients at the national level with the support of the French National Cancer Institute. Remarkably, a pathology review network (RREPS) and a bone sarcoma network (RESOS) were part of NetSarc [34,70]. Results of the first five years of this project were presented at ASCO and ESMO annual meetings in 2016. Overall, 19,545 patients suspected to be affected by a sarcoma went through MDT discussion at a NetSarc centre and eventually 13,454 diagnosed with a sarcoma. RARECAREnet estimates suggest that 3200 new cases of STS are expected in France each year, suggesting that NetSarc covers the 65% of all French sarcomas [3]. Majority of these patients underwent surgery (N = 10,256) with 4304 (45%) having their surgical treatment within the NetSarc network. Remarkably, the rate of patients treated within this network increased from 41% to 48% over the study period. Twenty-six centres were part of NetSarc, with a median of 373 patients managed over five years for each centre. Three centres were identified as 'Reference centres' each managing more than a thousand new patients in the study period (range: 1187–1868) while the remaining 23 were identified as 'Expert centres' (range: 35–984). This data suggested that larger

sarcoma centres in France treated roughly 200 patients each year, a figure that compare favourably volume of largest centres in smaller counties such as The Netherlands (population: 16.3 million inhabitants) and Belgium (population: 10.5 million inhabitants, Fig. 1). There were important differences in the management of patients who had surgery within or outside NetSarc. Patients who underwent surgery in the network were more likely to have pre-operative imaging (84% vs 57%, $P < 0.001$) and tumour biopsy (77% vs 33%, $P < 0.001$, Fig. 3) comparing to hospitals outside the network. After surgery, patients whose primary surgery was performed within NETSARC centres had higher achievement of R0 resection margins (49% vs 31%) and lower R1 (27% vs 31%) and R2 resection margins (7% vs 21%). Also, approximately one in five patients treated outside NetSarc needed a second surgery compared to a much lower proportion of patients treated within NetSarc (6%). This difference in quality of surgical margins was associated with a better local relapse-free and overall survival in patients operated on within NetSarc.

The Scandinavian Sarcoma Group (SSC) Central Register

The Scandinavian Sarcoma Group introduce referral before surgery for patients with subcutaneous lesions larger than 5 cm in 1978 and established a Central Register for all STS in 1987 with the aim of improving existing knowledge of this rare family of tumours and monitoring of referral and treatments for STS [10,71]. Treating physicians at centres which participated in this Register have been in charge of data entry in this registry. There was an improvement in patients referred before surgery over time, starting from 52% in the first five years to 70% in the latter years [10,71]. This increased centralization mirrored the reduction of patients who need re-excision, which dropped from 29% to 19% [10,71]. Also, there was a consistent decrease in positive resection margins and local recurrence along with higher performance of radiotherapy. Metastasis-free survival also increased from 67% to 73%, although it has been stable for last 10 years. Among patients who had surgery outside designated referral units, 79% had tumours smaller than 5 cm, a condition that does not require formal referral. These results surely reflects improvements in treatment of STS over time and also underlying the increased centralization for this rare disease when guidelines and centralised treatment are established. However, this data collection lack of data from patients treated at centres which did not participate in the Central Register and authors, who acknowledged the increasing interest for service-related information from health care systems, identified the inclusion of this patients in the register as an unmet need to improve quality of treatment for STS in their countries [71].

The Danish Sarcoma Database

Case registrations is recognised as one of the main domains of a network, which requires specific funds and resources to ensure functionality as well as quality of data.

The Danish Sarcoma Database, which was established in 2009, is a national, population-based database aimed at collecting information about incidence, treatment, and prognosis of sarcomas in Denmark in order to monitor and improve the quality of sarcoma care [72]. In this Country, which has a population of almost 5700 million people, 350 new cases of STS each year are expected which are managed at two nationally recognised sarcoma units at Aarhus University Hospital, Aarhus, and Rigshospitalet/Herlev Hospital, Copenhagen. This database is endorsed by the Danish National Board of Health and consequently funded by the Danish health authorities. Case registrations is mandatory and does not require a consent process under the law of the Ministry of Health for reporting of information to clinical databases. Treatment decisions are consistently taken at weekly MDTs.

Consultants are in charge of data registration in a web-based platform for their own patients thus ensuring high quality data entering. However, dedicated personnel at each of the two referral centres cross check all uploaded information with patient medical records at the end of patient treatment.

A quality control system identifies potential pitfalls in database completion and quality. Medical record auditing can be asked to one of the two referral centres to improve patient management when possible. For instance, surgery of primary tumours resulting in positive resection margins should be less than 10% of performed operations and local recurrences within 2 years should occur in less than 20% of patients for all treated cases. Whenever these and other standards are not met, enquiries are provided to treating units with a view of improving services. Finally, this networks offer also opportunities for conducting clinical research, which employed PhD students, testing hypothesis on a prospectively collected database. Clearly, this shows also one of the main potential of treatment networks that is education to medical research.

Barriers to implementations of sarcoma clinical networks

Currently, networks such as that of NetSarc suffer from shortage of funds, although early results suggested that surgical treatment delivered to patients within a referral network is associated with higher treatment quality and better outcomes [34,70]. Also, treatments delivered in accordance to existing clinical practice guidelines lower the cost for health care systems compared to inadequate treatments [73] and networks are expected to reduce overall cost of care despite requiring dedicated resources for participants institutions and the network. Referral centres requires extra resources for patients they manage through a network and are not treated directly. For instance, cases managed at a small centre within a network may require pathology review or MDT discussion at larger and more specialised centre of the same network, which will need resources to be allocated to support work activities not directly connected to patients they directly manage. This is not to mention the need for supporting the structure of the network and its requirements, such as the prospective case registration, which is one of the most important domain in a network of centres. For instance, survival of patients with STS and other rare cancers in Europe varies between Central, South and North regions and investments, including a continuous evaluation of the progresses are needed for reducing these disparities [7]. Also, patient data and outcomes registrations can have important implications to monitor quality of care, identify pitfalls in patient clinical pathways and management. Following the above mentioned Danish database for STS as well as other example such as the American Cancer Society (ACS) national surgical quality improvement program (NSQIP) [74,75], networks should employ dedicated personnel for providing quality reports to the institution with a view of offering an audit tool that has the potential of improving care at a single institution. At the institution level the process of case registration is often conducted based on physicians interest in monitoring their quality of care and clinical research. Institutional funds are sometimes used to support this case registration, while lack of funds often left it to out of duty work for doctors and datamanagers. Despite these limitations, such efforts have translated in a significant increase in knowledge in cancer medicine and specifically in rare tumours, where understanding of tumour biology and identifying optimal treatment strategy have been often established exploiting results from retrospective non-comparative studies. However, it cannot be expected that such efforts can be reproduced at the network level, calling for support from health care providers.

Conclusions

Patients with STS experience better outcomes when treated according to guidelines either at reference centres or within treatment networks. Despite this evidence, criteria to certify sarcoma expertise of institutions are debated and health authorities have only recently started identification of these centres and creation of treatment networks in Europe as well as in several countries. Success of these initiatives will depend upon properly allocated resources and policy to limit management of patients with STS outside referral centres or treatment networks. These advances are expected to have major impact also on clinical and translational research with potentiality to furtherly improve patient outcomes.

Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Disclosure

The authors have no disclosure.

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