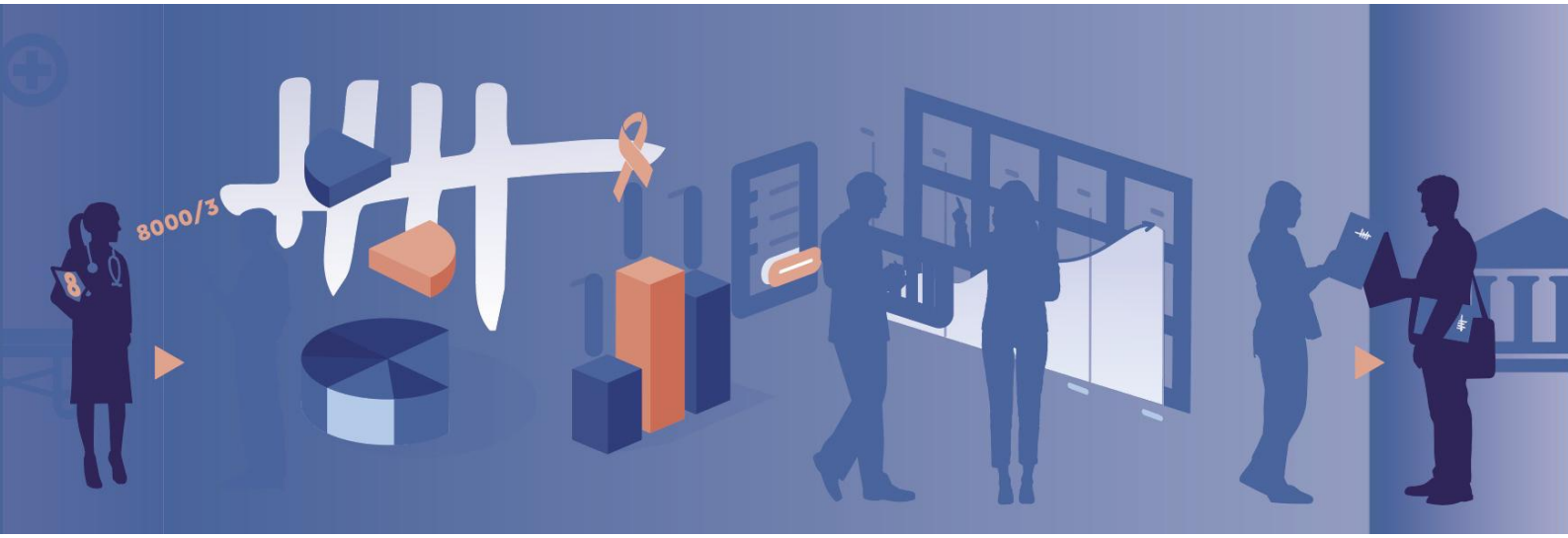
Belgian Cancer Registry

Volume-outcome relationship in cancer care:

SARCOMA – LITERATURE OVERVIEW



Belgian Cancer Registry

Colophon

TITLE: Volume-outcome relationship in cancer care: Sarcoma – Literature overview

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Sarcoma

1. Sarcoma epidemiology in Belgium

The Belgian Cancer Registry published an epidemiological report on sarcoma in Belgium (Belgian Cancer Registry, 2022). The main objective was to describe the incidence of malignant bone and soft tissue sarcoma (STS) in Belgium between 2004 and 2019, with a specific focus on the ten most recent years. This report provided the first complete overview of the sarcoma incidence in Belgium. A concise overview of the epidemiology in Belgium is shown below, including subtyping according to tumour location and histology.

Sarcomas constitute a very rare and heterogeneous group of tumours, consist of around 100 different subtypes and make up 1.7% of all cancer diagnoses in Belgium. On average, in the period 2010-2019, there were 1114 new sarcoma diagnoses per year in Belgium. 90% of sarcomas arise in soft tissues and organs (viscera), whereas 10% originate in bones, joints and articular cartilage. Age-specific incidence rates are shown in figures below.

Figure 2 All sarcomas: age-specific incidence rates (N/100,000) by primary tumour location, Belgium 2004-2019

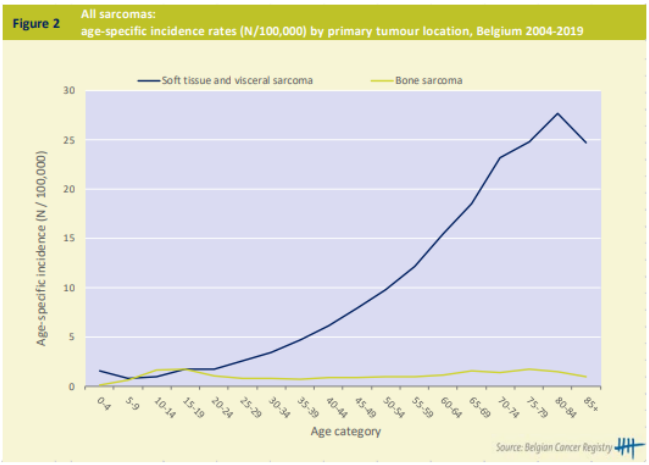
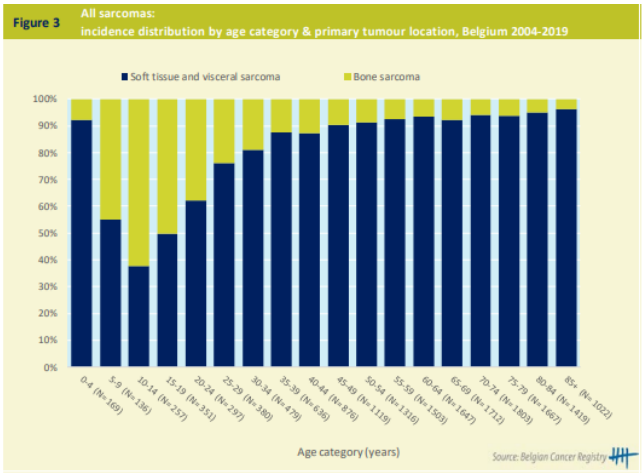
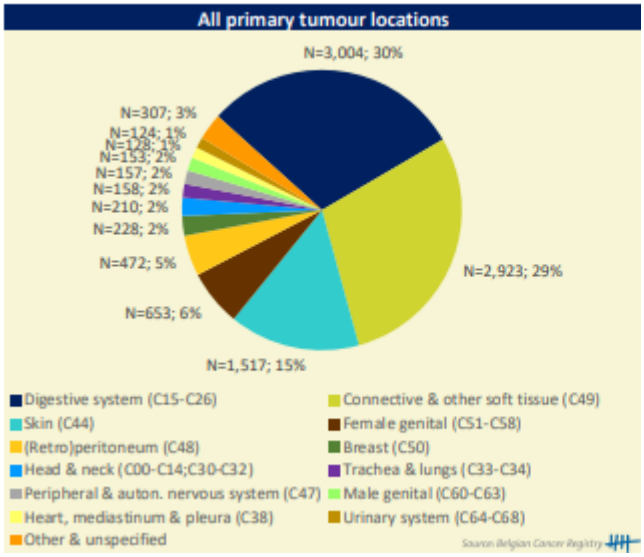


Figure 3 All sarcomas: incidence distribution by age category & primary tumour location, Belgium 2004-2019



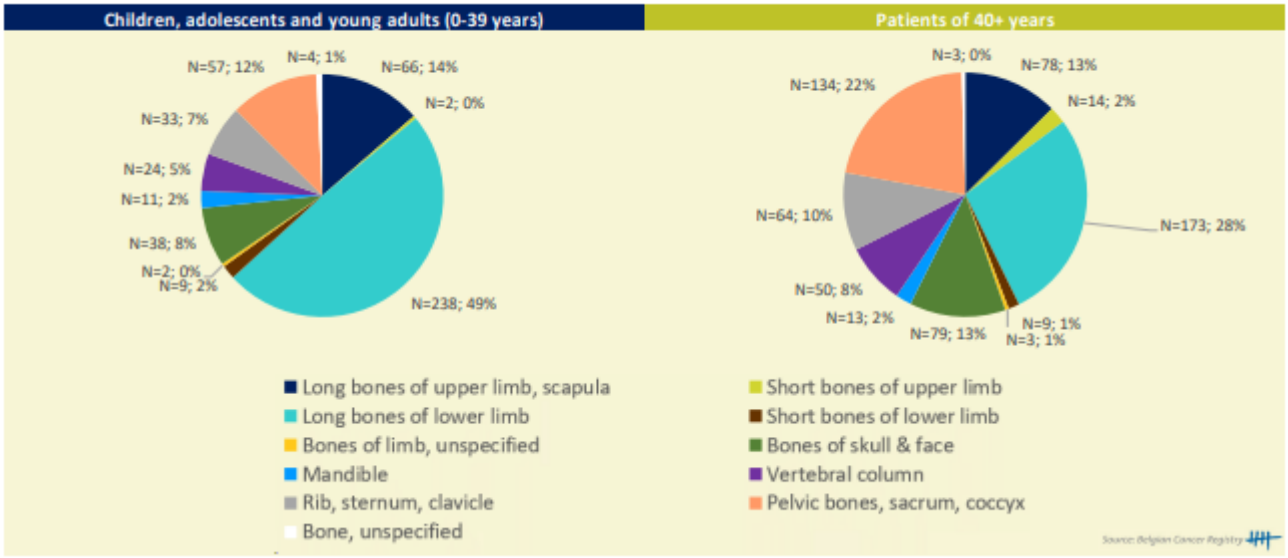
The incidence depends on the **tumour location**, with the most frequent locations for **soft tissue and visceral sarcomas** being the digestive system, connective and other soft tissue sarcomas (STS) and the skin.

Figure 2 Soft tissue and visceral sarcoma: Incidence distribution by primary tumour location*, Belgium 2010-2019



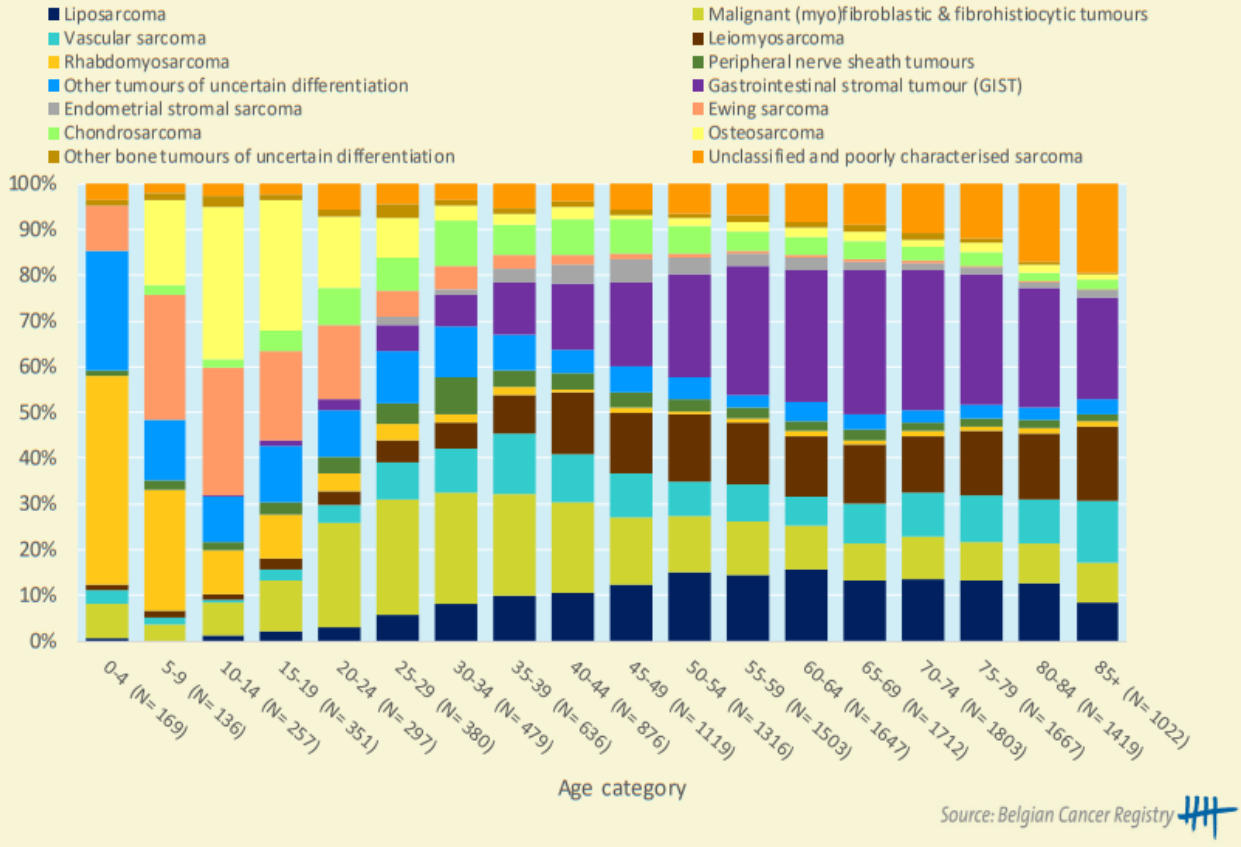
For **bone sarcomas** the main primary **tumour locations** are the long bones of the leg, of the arm together with the scapula, and unspecified bones of a limb.

Figure 2 Bone sarcoma: Incidence distribution by primary tumour location, Belgium 2010-2019



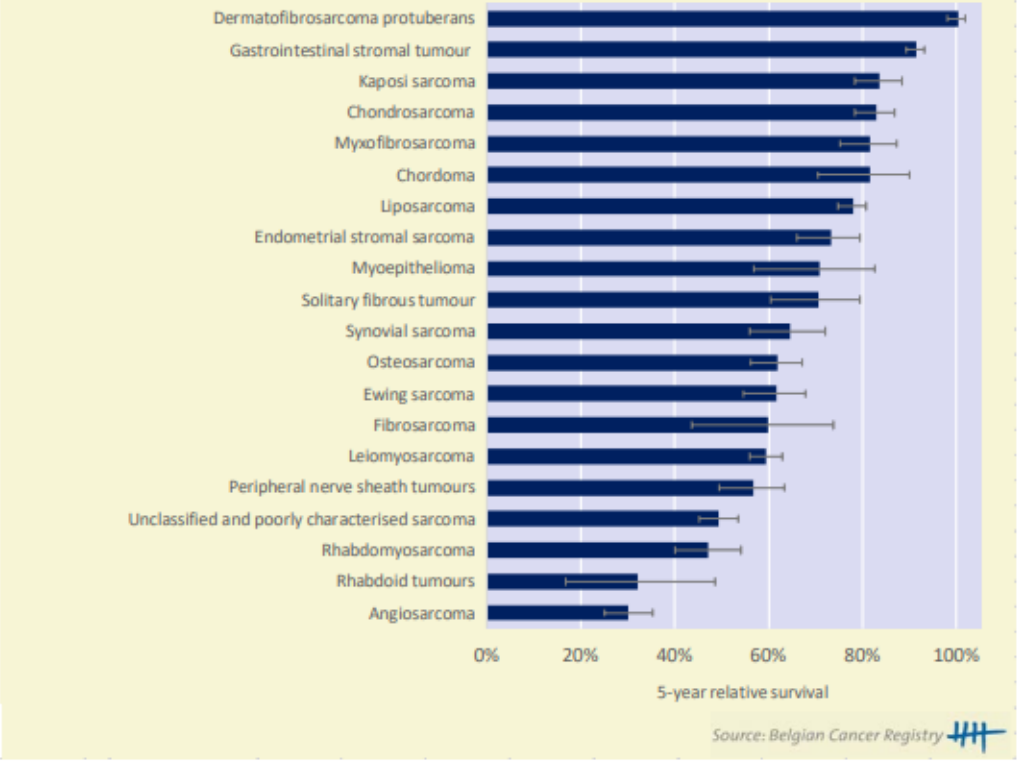
Sarcoma classification according to **histological type**: Overall, gastro-intestinal stromal tumours (GIST) are the most frequently occurring sarcomas (23%) followed by liposarcoma in males (14%) and leiomyosarcoma in females (16%).

Figure 4 All sarcomas: incidence distribution by histological subtype and age category, Belgium, 2004-2019



The 5-year relative survival for all sarcomas is very similar between males (73%) and females (74%). The prognosis of sarcoma patients differs to a great extent between the histological subtypes, with the best 5-year relative survival for patients with dermatofibrosarcoma protuberans (100%), followed by GIST (91%), and the worst for patients with angiosarcoma (30%) and rhabdoid tumours (32%).

Figure 8 All sarcomas: 5-year relative survival (%) by histological subtype in Belgium, 2010-2019



The relative survival values are represented with 95% Confidence Intervals

Figure 7 on page 220 of the 2022 sarcoma report shows that survival depends on the tumour location, with retroperitoneal sarcomas (RPS) having the worst 5-year relative survival (< 50% for the period 2000-2007). RPS, a less frequent subset of STS, is usually very large at diagnosis and intimately related to major retroperitoneal structures, making its management and surgery very challenging. Note that in 2009 two papers were published which changed the RPS surgical policy to compartmental resection, improving survival, and that this policy was adapted worldwide as the new surgical guideline for RPS in 2012 (Bonvalot et al., 2009; Gronchi et al., 2009).

More information, data and figures are available in the BCR publication "Bone & soft tissue tumour epidemiology in Belgium, 2004-2019" (Belgian Cancer Registry, 2022).

2. Aims and scope of the current literature study

The aim of this literature study was to evaluate evidence for a volume/outcome association in the cancer care of sarcoma.
The literature search was performed in February 2025, in the databases PubMed and Cochrane Library. The goal was to put together a general overview of available evidence in literature, focussing whenever possible on studies summarizing the evidence, including (systematic) reviews and meta-analyses. A systematic literature review was not within scope of the current study.

In addition, some criteria were agreed upon. For outcome, the main focus was on post-treatment mortality and survival. Evidence on concentration for the full oncologic care trajectory was searched, so no treatment type-specific searches. For the organisation of sarcoma care in other countries, the focus was on evidence from study populations that are most relevant for Belgium, so European and Northern American studies.

3. (Systematic) reviews volume/outcome association for sarcoma

Since evidence for a volume/outcome association for sarcoma care may have been summarised before, firstly a search was performed for existing systematic reviews and meta-analyses concerning this subject. Four such reviews were found, for which the main findings are listed in the following subsections 3.1-3.4 (two extensive, two concise). No meta-analyses were found. Also, the subsection 3.5 was added with an overview of studies analysing the effects of travel bias.

3.1 Centralized and Interdisciplinary Therapy Management in the Treatment of Sarcomas (Strönisch et al., 2023)

- Systematic search **until 12 July 2022** (search performed according to the 2020 PRISMA guidelines)
  - Conducted in PubMed, EMBASE, Ovid Medline, ClinicalTrials.gov and Cochrane Library databases
  - Subject: the centralised treatment of adult sarcoma patients (>18y) at expert centres and the use of interdisciplinary tumour boards (soft tissue and bone sarcoma)
  - Results: **20 studies** concerning **centralised treatment at Expert Centres (EC)** vs. Non-Expert Centres (NEC) (see Table 2 in the Strönisch paper, 'patient outcome analysis', for detailed information)
- Main findings: **At EC** compared to NEC, diagnostic procedures were more adequately performed, and treatment was associated with better outcomes in the majority of studies. **Patients treated at EC benefited from:**
  - **longer survival, lower local recurrence rates and a better postoperative outcome**.
- All studies conducted an outcome analysis of interdisciplinary and centralised sarcoma treatment. A risk of bias assessment was performed for every study using the Risk of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool.
- All results are listed in detail per study in Table 2 (see printscreen below for 1 study). (Strönisch et al., 2023)
- No standard definition was used to define an expert centre (EC).

Table 2. 'Group I—patient outcome analysis': The table summarizes the study and patient's characteristics, results on the treatment site and the interdisciplinary tumour board and other relevant results. Outcome analysis is reported in three sections for overall survival, recurrence and surgical outcome. Abbreviations: DSS (disease-specific survival), DFS (disease-free survival), E (expert), EC (expert centre), HR (hazard ratio), ITB (interdisciplinary tumour board), LR (local recurrence), LRFS (local recurrence-free survival), MD (metastatic disease), N/A (not available), NEC (non-expert centre), OS (overall survival), PFS (progression-free survival), OR (odds ratio), RFS (recurrence-free survival), S (surgeon).

Author	Year	Type of Trial	n	Median Age (Years)	Sex Ratio (Female:Male in %)	Sarcoma Type	Treatment Site	Interdisciplinary Tumour Board	Treatment and Other	Median Follow Up (Range)	Overall Survival	Recurrence	Surgical Outcome
Blay et al. [10]	2017	Retrospective data base study, multicentric, prospectively obtained data	12,528 (9646 for survival analysis)	18–101 (61)	51.1:49.6	Soft tissue sarcoma	N/A	Primary tumour imaging ($p < 0.001$) with tumour board 87.9% w/o tumour board 60.4% Diagnostic biopsy ($p < 0.001$) with tumour board 87.7% w/o tumour board 41.9%	N/A	26 months	N/A	Treatment before tumour board presentation 2 year-LRFS ($p < 0.001$) before 65.4% after 76.9% 2 year-RFS ($p < 0.001$) before 46.6% after 51.7% multivariate analysis LRFS Treatment before tumour board HR 1.8 ($p < 0.001$) RFS Treatment before tumour board HR 1.3 ($p < 0.001$)	R0-status at primary surgery ($p < 0.001$) with tumour board 52.6% w/o tumour board 32.2% Re-excision ($p < 0.001$) with tumour board 6.0% w/o tumour board 17.4%

- In the table on the next page, the main findings are summarised for these 20 studies regarding overall survival (column 5) and recurrence(-free survival) (column 6). The colour code for the results is: statistically significant better outcome at EC in dark green, indication for better outcome at EC or other benefit in light green, no significant difference in orange.

Summary 20 studies from systematic review Strönisch et al., 2023:

First author, Year	Ref nr	Sarcoma type	N pts (country/database, study period)	Overall survival	Recurrence	Remarks
Blay et al., 2017	10	STS and visceral	12528 (survival: 9646), (FR NetSarc = 26 EC's, 2010-2014)	N/A	MDTB before Tx start: LRFS and RFS sign. ↑ vs after Tx start (UV & MV analysis)	26 EC's included
Jagodzińska-Mucha et al., 2020	11	Ewing	180 (Poland, 2000-2018)	If referred to EC <3 months post-diagnosis: 5y OS ↑ (>3m HR 1.6, 95% CI 0.97-2.76, p=0.066)	If referred to EC <3 months post-diagnosis: 5y PFS sign. ↑ (28% vs 14% if >3m, p<0.001)	1 EC included (for 50 pts Tx start outside of EC, of which 23 pts Tx start >3m post-diagnosis)
Gilg et al., 2020	12	Myxofibrosarcoma	109 (Austria, 1990-2014)	DSS NS different (EC vs. NEC, OR 0.27, 95% CI: 0.05-1.44, p=0.13)	LRFS NS diff. (OR 0.4 [0.07-2.07], p =0.26) Primary surgery at EC: sign. ↑ R0 margins (85% vs. 12% at NEC, p<0.001); and LRFS ↓ if R1/2-status at primary surgery: OR 8.5 (95% CI 1.59–49.79) (p = 0.01).	Monocentric study (all diagnoses at the EC): 62% primary surgery at EC, 38% at external NEC. Survival: only MV analyses (factors: tumour depth, grade, R status, EC vs. NEC).
Venigalla et al., 2018	13	localised STS	9205 (US NCDB, 2004-2013)	5y OS sign. ↑ when Tx at EC (72.2% vs. 57.1% at NEC, p < 0.001) (MV analysis: HR = 0.81, 95% CI: 0.72 – 0.90, p ≤ 0.001)	N/A	Treatment at EC 17%, NEC 83% EC = high-V of 79-252 cases/10y study period
Marec-Bérard et al., 2020	14	All sarcomas	140, age 13-25 y old (FR Rhône-Alpes region, 2000-2005)	Adolescents and Young Adults (AYA) not the subject of this literature overview	Adolescents and Young Adults (AYA) not the subject of this literature overview	Adult hospital N=43, paediatric hospital N=79, mixed N=18 --> NS difference in vital status
Snow et al., 2018	15	RPS	88 (Australia, 2008-2016)	NS different	primary surgery at EC: trend recurrence rate ↓ (p=0.055)	Monocentric study (EC) 88 pts with surgery (of which 29.5% surgery at NEC)
Kreyer et al., 2018	16	Ewing	481 (Germany, 2006-2009)	OS ↓ for non-compliance to EC tumour board (MDTB) recommendation (vs. compliance to MDTB): p=0.003	N/A	MDTB discussion at 1 EC, MDTB request by various centres, MDTB recommendations were followed or not (so not really EC vs. NEC)
Bonvalot et al., 2019	17	localised RPS	2945 (FR NetSarc = 26 EC's, 2010-2017)	Surgery at EC: 2y OS ↑ (87% vs 70%, p<0.001) MV analysis: surgery at EC independent predictor of OS (HR 0.49)	Surgery at EC: 2y LPFS and PFS ↑ (p<0.001) (LPFS: 75% vs. 55%) MV analysis: both p<0.001 (LPFS EC OR 0.530 | PFS EC OR 0.604)	36.6% surgery in EC, 63.4% surgery in NEC. Median N of surgeries per centre in study period in EC's = 23, in NEC's = 1
Bhangu et al., 2004	18	STS (no H&N or RPS)	260 (survival: 231) (UK region, 1994-1996)	MV analysis: Tx at EC: 5y OS ↑ (p = 0.048) (NEC HR 1.7, 95% CI 1.01–2.8)	LR (p = 0.001) EC 19%, NEC 39%	Tx at EC 37%, NEC 63%. N EC's = 1; N NEC's = 38
Martin-Broto et al., 2019	19	localised STS, non-visceral	622 (Spain, 2004-2011)	EC: 3y OS sign. ↑ (p=0.003, 82% vs. 70.4%) (MV analysis NS)	Recurrences in EC's = 44%, NEC's 56%. 3y RFS EC 66%, NEC 46.4% (p=0.019) (MV analysis NS)	Tx at EC 46%, NEC 54% N EC's = 2; N NEC's = 29
Sandrucci et al., 2018	20	RPS	72 (Italy region, 2006-2011)	R0/1-status at EC with high surgeon case V: sign. ↑ (80% vs. 49% at EC with low surgeon case V, p=0.013)	N/A	Tx at EC 52.2% (= high-volume, >100 sarcomas observed/year,

				And 5y OS ↑ if R0/1-status (65% vs 31% for R2-status, p < 0.001)		N=2 centres), NEC 47.8% (= low-volume, <100, N=20) NEC excluded from analysis (prognostic data freq. unavailable)
Ray-Coquard et al., 2004	21	localised STS	100 (FR Rhône-Alpes region, 1999-2001)	N/A	UV analysis: local relapse: sign. ↓ if MDTB, surgery at EC and management at cancer network centre vs. university hospital (p=0.02 each), metastatic relapse: sign. ↓ if MDTB and management at cancer network (p=0.04 and p=0.01) MV analysis: conformity to clinical practice guidelines ↑ if MDTB before surgery (OR=30.7, CI 6-144), surgery at EC (OR=11.5, CI 2-57) and management at cancer network centre (OR=13.9, CI 1.1-170)	2 EC's (1 university hospital outside of cancer network, 1 comprehensive cancer network centre), 50 pts/centre. Surgery N=95 (at EC N=44, at NEC N=51)
Keung et al., 2018	22	localised RPS	6950 (US NCDB, 1998-2011)	Surgery at EC vs. NEC: 5y OS ↑ (58% vs 52%, p<0.001) MV analysis: surgery at EC: HR 0.77 (95% CI 0.65–0.91, p=0.003)	N/A	EC definition: > 10 RPS cases/y (= 4/1131 hospitals, treating ± 10% of pts)
Alvarez et al., 2021	23	Ewing | Osteosarcoma	531 | 959 (US California Cancer Registry, 2000-2014)	MV analysis: All Tx at EC: 5y OS sign. ↑ vs. part/none Ewing: HR 0.49 (CI 0.37-0.67) Osteos. HR 0.78 (CI 0.63-0.97)	N/A	All vs part or none of the Tx at an EC
Ipach et al., 2012	24	Clear cell sarcoma	11 (Germany, 2000-2011)	Tx at EC: OS ↑ (death after mean of 58.4 months (range 5-127), NEC: 26.8 months (range 13-41)	Tx at EC: metastases after mean of 18 months (range 9-27), NEC: 9 months (range 4-15)	Monocentric study, surgery at the EC N=6, surgery at a NEC N=5. No statistical analysis.
Abellan et al., 2009	25	localised extremity STS	174 (Spain, 1983-2006)	NS different (p>0.05)	pts referred to EC only after local relapse: DSS ↓ (28% vs. 73% and 76%, p<0.001), metastases ↑ (51% vs. 22% and 16%, p<0.001)	Monocentric study, referred directly to EC (57%), after inadequate primary surgery (22%) or after local relapse (21%).
Melo Mateus et al., 2023	26	All	1962 (Portugal, 2016-2019)	MV analysis: All Tx at EC: OS ↑ vs. never Tx at EC (HR 0.60, 95% CI 0.46-0.79, p<0.05)	N/A	5 adult EC sarcoma centres in Portugal (status 2023). All Tx at EC (43% of pts), no Tx at EC (53%).
Sobiborowicz et al., 2021	27	Perivascular epithelioid cell tumours	27 (Poland, 1999-2019)	NS different (p=0.16)	Surgery at EC: 5y LRFS ↑ (p<0.005), 5y DFS ↑ (100% vs 14% (95% CI 2-80%), p<0.001)	1 EC (national sarcoma reference centre). Surgery at EC N=13, referred to EC after first surgery N=14.
Blay et al., 2019	28	All	25851 (FR NetSarc = 26 EC's, 2010-2018)	MV analysis: primary surgery at EC: OS ↑ (HR 0.68, CI 0.62–0.75, p < 0.001)	MV analysis: primary surgery at EC: LRFS ↑ (HR 0.65, CI 0.61–0.70, p<0.001) DFS ↑ (HR 0.84, CI 0.80–0.89, p<0.001)	primary surgery at EC (33.7%), NEC (54.8%), no surgery (12.4%)
Pollock & Stalley, 2004	29	Musculoskeletal tumours	142 (77 malignant) (Australia, 2002)	N/A	N/A	Biopsy at EC vs. biopsy at NEC prior to referral to EC. NEC: more radical Tx in 25%

CI: (95%) confidence interval; DFS: disease-free survival; DSS: disease-specific survival; EC: expert centre; HR: hazard ratio; LR: local recurrence; MDTB: multidisciplinary tumour board (presentation); MV (analysis): multivariate analysis; N: number; N/A: not applicable; NCDB: National Cancer DataBase; NEC: non-expert centre; NS: not significant; OR: odds ratio; OS: overall survival; (L)PFS: (local) progression-free survival; pts: patients; R: resection margins; (L)RFS: (local) recurrence-free survival; Ref nr: reference number in the Strönisch paper; RPS: retroperitoneal soft tissue sarcoma; sign.: significant; STS: soft tissue sarcoma; Tx: treatment; UV (analysis): univariate analysis; V: volume; vs: versus; y: year.

- The 20 identified studies are: (Abellan et al., 2009; Alvarez et al., 2021; Bhangu et al., 2004; J.-Y. Blay et al., 2017, 2019; Bonvalot et al., 2019; Gilg et al., 2020; Ipach et al., 2012; Jagodzińska-Mucha et al., 2020; Keung et al., 2018; Kreyer et al., 2018; Marec-Bérard et al., 2020; Martin-Broto et al., 2019; Melo Mateus et al., 2023; Pollock & Stalley, 2004; Ray-Coquard et al., 2004; Sandrucci et al., 2018; Snow et al., 2018; Sobiborowicz et al., 2021; Venigalla et al., 2018)
    - Bonvalot 2019 and Keung 2018 are frequently-cited key papers.
    - 2 studies were not within the scope of this overview (reasons: AYA population and no survival or relapse analysed) (Marec-Bérard et al., 2020; Pollock & Stalley, 2004).
- Main findings:
    - Diagnosis: diagnostic procedures were more frequently and adequately performed in expert centres (for more information, see Strönisch paper section 3.1.2).
    - In **almost all studies (14/17 studies)** that conducted a survival analysis, patients benefited from an **improvement** in **overall or recurrence-free survival** when **treated at an expert centre** (or treated conform the EC MDTB recommendations (Kreyer et al., 2018)). This was reflected in the results of large database analyses on all sarcomas combined, and in small cohort studies on specific sarcoma subtypes.
        - The 3/17 studies that did not find a direct significant benefit had small patient populations of a specific sarcoma type (range 72-109) (Gilg et al., 2020; Sandrucci et al., 2018; Snow et al., 2018). Gilg et al. (2020) did find significantly more R0 resections after myxofibrosarcoma surgery at an EC vs. a NEC.
        - The 3/20 studies not included are the 2 studies outside the scope (Marec-Bérard et al., 2020; Pollock & Stalley, 2004) and 1 study that did not calculate survival, only relapse rates (Ray-Coquard et al., 2004).

      For more information, see Strönisch paper section 3.1.3.
    - Surgical outcome: all studies on resection margins (13 studies) showed higher rates of complete tumour resec-tion (R0) when surgery was done at an EC (for details per study, see Strönisch paper Table 2 and section 3.1.4).
- Other findings:
    - The implementation of an inter/multidisciplinary tumour board (MDTB) was associated with slightly discrepant results. In a greater number of studies, it was associated with a lower local relapse rate, better overall survival and surgical outcome. On the other hand, the review implied that two studies found a shorter survival. However, only one study actually compared MDTB versus no MDTB (studies not specified, but probably the Blay studies below). For more information, see Strönisch paper Table 2 and section 3.2.
        - (J.-Y. Blay et al., 2019):
            - NetSarc France, 26 EC's, N=25851 sarcoma patients operated (of which 56% discussed at an EC MDTB before treatment) including N=9954 patients operated at an EC (of which 64% discussed at an EC MDTB before treatment), 2010-2018.
        - Presentation to a MDTB was associated with improved LRFS (HR 0.67) and event-free survival (HR 0.80), but correlated to a worse OS (HR 1.56) (all three $p<0.001$). The OS was particularly poor for patients discussed at an EC MDTB but not operated in an EC, which could point to the importance of experienced surgical teams for more complex patient populations.(J.-Y. Blay et al., 2017):
            - Comparison was treatment start before vs. after MDTB (but the review did not clearly state the comparator group, whereby this could be interpreted as poorer survival after MDTB). But actually, all patients were discussed in a MDTB, so it was not MDTB vs. no MDTB.
            - NetSarc France, 26 EC's, 9646 sarcoma patients (31% MDTB before treatment, 69% after), 2010-2014.
            - MV analysis: Treatment start before MDTB was a negative prognostic factor for LRFS and RFS (compared to treatment after MDTB: HR: 1.80 and 1.26, respectively; both $p<0.001$). This underlines the importance of MDTBs before the start of treatment. OS was not assessed.
    - In the studies included in this review, neoadjuvant therapy or multimodal treatment was more frequently carried out at expert centres.
- Main limitations:
    - The authors indicate that due to subjectively selected search terms (which may not guarantee the topic's comprehensiveness) and differences in spelling, the search might have been not entirely complete.
    - Many studies had a severe bias risk according to the ROBINS-I tool (options: low, moderate, serious, critical). However, this tool has limitations in evaluating retrospective studies (see Strönisch paper Table 4).
    - Patients with metastatic disease seem underrepresented in the literature concerning centralisation and interdisciplinary therapy. Many studies focussed on patients with a localised tumour stage.

- Increasing role of targeted therapy and the implementation of a molecular tumour board not addressed

For more information, see Strönisch paper section 4.2.

3.2 Surgery at specialised sarcoma centres improves patient outcomes - A systematic review by the Australia and New Zealand sarcoma association clinical practice guidelines working party (Hong et al., 2023)

See also: https://sarcoma.org.au/does-surgery-at-a-specialised-sarcoma-centre-improve-outcomes

- Systematic search **until March 2021**
  - Conducted in Ovid Medline, Ovid Embase, and Cochrane Central (Wiley)
  - Subject: **Adult and paediatric patients with bone and soft tissue sarcoma**, undergoing **surgery** in a specialist sarcoma centre (high-volume or expert centre (EC)) compared with non-specialist centre; evaluation of local control, limb salvage rate, 30-day and 90-day surgical mortality and overall survival.
  - Results: 66 studies
    (see Hong paper Suppl. Table 4 for surgical mortality and Suppl. Table 5 for better overall survival in MV analysis)
- Main findings: **Definitive surgery performed at specialised sarcoma centres** was associated with a **higher limb conservation rate** and improved local control as defined by **higher rate of negative surgical margins (= complete tumour resections, R0), lower rate of local relapse and improved local recurrence free survival.** Available evidence shows a favourable pattern of **lower 30-day and 90-day post-operative mortality rates, and greater overall survival** when surgery was performed in specialist sarcoma centres compared with non-specialised centres.
- No standard definition was used to define a specialised sarcoma centre (expert centre, EC) = a high-volume centre.

- All results are listed in detail per study in Suppl. file "Suppl. mmc2" (Hong et al., 2023), see printscreen below for 1 example:

Study Identifier	Country	Design	Type of Sarcoma (bone, soft tissue etc)	Inclusion criteria	Exclusion criteria	Definition of high volume/specialised centre	Number of hospital/centres	Study period
Abarca 2018	USA	Retrospective cohort study	Extremity STS	Extremity STS, age >18		To define treating facilities as either high- or low-volume, the authors investigated each center's annual volume of STS patients from 1998 to 2012. Those with an average annual sarcoma volume of 10 or more(22 facilities, 2%) as high-volume, and those that treated less than 10(1178 facilities, 98%) as low-volume	1200 facilities	1998 to 2012

Total number of patients in the study	Group differences	Endpoint	endpoint	2 yr OS	5 yr OS	10 yr OS	Multivariate analysis
The initial study population consisted of 7874 cases of STS that fit the study criteria	RT use 55% vs 52%, p =0.108	positive margins 12% v 17%, p<0.001	30 day readmissom 7% v&%, p=NS	87% vs84%, p=0.003	72.7% vs 68.1%, p=0.001	57.6% vs 53.3%, p=0.001	High Vol=1, increased mortality. Low vol. 2yr HR 1.25, 5 yr HE 1.24, 10 Hr 1.22

MORTALITY (see Hong paper section 3.3 and Supplementary Table 4)

- In the next table, the main findings are summarised for 30-day and 90-day mortality in high-V vs low-V sarcoma centres for the 12 identified studies. In this table, the terms high-volume (V) centre and expert centre (EC) are used as synonyms. The colour code for the results is: significantly better at EC in dark green, other benefit in light green, no significant difference in orange.

- The 12 identified studies are: (Adam et al., 2019; Bagaria, Chang, et al., 2018; Bagaria, Neville, et al., 2018; Berger et al., 2018; Gutierrez et al., 2007; Kalaiselvan et al., 2019; Keung et al., 2018; Lazarides et al., 2019; Schmitz et al., 2019; Stiles et al., 2018; Villano et al., 2019; Villano, Zeymo, Chan, Shara, et al., 2020)

Summary 12 studies from systematic review Hong et al., 2023 with mortality results:

Ref nr	First author, Year	Sarcoma type	N pts (country/ database, study period)	30d and/or 90d post-surgery mortality	Definition high volume/ EC centre	Remarks
9	Adam, 2019	RPS localised	5340 (US NCDB, 1998-2012)	Sign. ↓ in high-V MV: 90d: OR=0.25, p=0.02	≥10 cases/y	909 hospitals, EC's treating 5.2% of pts
10	Bagaria, Chang, 2018	Localised extra-abdominal STS	13684 (US NCDB, 2003-2007)	Sign. ↓ in high-V: 30d: 0.4% vs 1.2%, p<0.001. MV: 30d NS, OR 0.49, CI 0.16-1.31 (p=0.12)	>10 cases/y low-V: ≤ 3 /y	1158 hospitals (high-V N=44, low-V N= 934)
11	Bagaria, Neville, 2018	RPS	3803 (US NCDB 2004-2013)	Sign. ↓ in high-V MV: 30d: low-V OR=4.66 95% CI:2.26-9.63, p<0.001; 90d: sign. difference (no details)	>10 cases/y low-V: ≤ 4 /y	3 EC's/678 hospitals, treating 10.5% of pts
13	Berger, 2018	RPS localised	2762 (US NCDB, 2004-2013)	NS 30d and 90d; high-V 90d: 6.2% vs 6.4% in low-V; p=0.809. (no MV) Note: the EC's mean surgery V for the 10y period was only: 8.6 ± 15.3 vs 2.3 ±2.9, p<0.001.	>500 annual cancer cases	192 EC's/682 hospitals (high general cancer V ≠ high sarcoma V per se)
27	Kalaiselvan, 2019	RPS	72 (UK region, 2004-2017)	NS 90d after centralisation (p=0.677), despite more complex surgeries	Centralisation to 1 EC MDTB	72 pts (of which 59 pts post-centralisation)
28	Keung, 2018	RPS localised	6950 (US NCDB, 1998-2011)	Sign. ↓ in high-V 30d and 90d; 90d: 3.2% vs 5.7%, p=0.007 (no MV)	> 10 cases/y	4 EC's/1131 hospitals, treating ± 10% of pts
31	Lazarides, 2019	Extremities STS	25406 (US NCDB, 1998-2012)	Sign. ↓ in high-V; 30d: 0.3% vs. 0.4%, p=0.018 (no MV)	≥ 20 cases/y	9 EC's/1272 hospitals
50 =57	Schmitz, 2019	RPS	2599 (US NCDB, 1998-2012)	Sign. ↓ in high-V; 30d: 1.2% vs. 2.8%, p = 0.0026. (no MV)	≥10 cases/y	high-V N pts=1250
51	Gutierrez, 2007	STS (extremity and RPS)	4205 (US Florida, 1981-2001)	Sign. ↓ in high-V, 30d and 90d. 90d: 1.6% vs. 3.6%, p<0.001; MV: low-V OR 2.26, CI:1.42-3.59, p<0.001.	Top 1/3 of pts = >5 cases/y	7 EC's/256 hospitals, treating 1/3 of pts
55	Stiles, 2018	Desmoplastic small round cell	125 (74 surgery) (US NCDB, 2004-2014)	NS 30d and 90d; high-V 90d: 0% vs 4.7%; p=0.507. (no MV)	≥5 cases/10y = ≥0.5 cases/y	2 EC's/97 hospitals, treating 12% of pts (N=15)
56	Villano, 2019	RPS localised	8721 (US NCDB, 2004-2015)	NS 30d and 90d; high-V 90d: 2.3% vs 3.7%, p=0.102 (no MV) Sign. ↓ in high-V (if inclusion of V pancreatic cancer surgery) compared to high-V only RPS, 30d and 90d, p<0.001	> 10 cases/y low-V: <5/y	6 EC's/356 hospitals Treating 9.6% of pts (EC N pts = 840)
47	Villano, Zeymo, Chan, Shara, 2020	RPS localised	8721 (US NCDB, 2004-2015)	NS 90d; high-V: 2.1% vs 3.7%, p=0.145 (no MV) Statistical model 90d: >8 cases/y: HR 0.93, 95% CI 0.88-0.94	≥ 13 cases/y (identified via modelling survival benefit)	(EC N pts=385)

CI: (95%) confidence interval; d: day; EC: expert centre; HR: hazard ratio; MDTB: multidisciplinary tumour board (presentation); MV (analysis): multivariate analysis; N: number; NCDB: National Cancer DataBase; NS: not significant, OR: odds ratio; pts: patients; Ref nr: reference number in the Hong paper; RPS: retroperitoneal sarcoma; Sign.: significant; STS: soft tissue sarcoma; V: volume; vs: versus; y: year.

- Main findings:
  - 7 studies: significant better (lower) 30-day and/or 90-day mortality post-surgery in high(er)-volume centres: 4 studies on retroperitoneal, 2 on extra-abdominal/extremity STS and 1 on both RPS and extremity sarcoma.
  - 3 studies: no difference (Berger et al., 2018; Kalaiselvan et al., 2019; Stiles et al., 2018), however this can be partly explained by:
    - Small patient populations for rare tumours (N= 72 and 74) for long study periods (11 and 14 years)
    - High-volume definition not specific to sarcoma but all cancer cases, leading to a mean cut-off of only 0.86 RPS surgeries/year (Berger et al., 2018)
  - 2 studies: These 2 studies used the same RPS patient population but with different high-volume definitions. They both found no difference in mortality in high- vs low-volume centres per se, but did find other statistically significant evidence pointing to a beneficial volume-outcome result (see table for details) (Villano et al., 2019; Villano, Zeymo, Chan, Shara, et al., 2020).
    Note: There was no significant mortality difference, despite the high-V centres having significantly more complex surgeries, advanced-stage and high-grade disease. In a way, this also speaks to the advantage of centralisation.
- Note: Studies had various definitions of high-V and low-V centres! A frequently used definition was ≥10 surgeries/y for either RPS or extra-abdominal/extremity STS.
- Note: 11/12 studies were based on US data. Only 1 study concerned European data, but only from one specific UK region.

OVERALL SURVIVAL (see Hong paper section 3.4 and Supplementary Table 5)

- Hong et al. states that **34 studies report overall survival** according to surgery at a specialised sarcoma centre or not. They are listed in Supplementary Table 1 of the Hong paper (a long list stated to include 66 papers but in fact it is only 64), but they are not named specifically. For the purpose of this literature overview, all studies were re-evaluated and a **selection of 36 studies was made** that reported overall survival.
- In the next table, the main findings are summarised for overall survival in specialised sarcoma/expert/high-volume centres versus non-specialised/low-volume centres for all these 36 identified studies. In this table, the terms high-volume (V) centre and expert centre (EC) are used as synonyms. The colour code for the results is: significantly better at EC in dark green, other benefit in light green, no significant difference in orange, significantly worse at EC in red.

- The 36 identified studies are: (Abarca et al., 2018; Adam et al., 2019; Bagaria, Chang, et al., 2018; Bagaria, Neville, et al., 2018; Berger et al., 2018; Bhangu et al., 2004; J.-Y. Blay et al., 2019; Bonvalot et al., 2019; Dilday et al., 2021; Feinberg et al., 2018; Gutierrez et al., 2007; Hoekstra et al., 2017; Hu et al., 2019; Kalaiselvan et al., 2019; Keung et al., 2018; Lans et al., 2019; Lazarides et al., 2019, 2020; Lo et al., 2021; Malik et al., 2020; Martin-Broto et al., 2019; Maurice et al., 2017; Merchant et al., 2012; Paszat et al., 2002; Schmitz et al., 2019; Song et al., 2019; Stiles et al., 2018; Stiller et al., 2006; Toulmonde et al., 2014; Traub et al., 2018; Venigalla et al., 2018; Villano, Zeymo, Chan, Shara, et al., 2020; Villano, Zeymo, Chan, Unger, et al., 2020; Vos et al., 2019; Widhe & Bauer, 2009; Wright et al., 2020)

- Main findings:
    - 31 studies included surgery at specialised sarcoma centre as a variable in multivariable analysis
        - 23 studies: significantly better overall survival (OS) after surgery at a specialised sarcoma centre
            - See green background in penultimate column
            - Per country:
                - 16 US (15 US NCDB database + 1 Florida)
                - 7 other: 2 UK, 2 France (NetSarc), 1 Sweden, 1 Canada, 1 China
            - Per sarcoma type:
                - 1 sarcoma in general
                - 16 STS: 7 RPS, 4 extremity STS, 1 RPS + extremity STS, 2 STS in general, 1 STS (non-RPS, non-head & neck), 1 STS (extra-abdominal)
                - 6 bone: 1 bone in general, 1 bone vertebral column, 1 osteosarcoma + Ewing sarc., 1 osteosarcoma knee, 1 chondrosarcoma chest wall, 1 chordoma spine and sacrum
        - 8 studies: non-significant difference in OS after surgery at a specialised sarcoma centre versus not
            - See orange in penultimate column (some had smaller patient numbers: 64, 82, 500, 511)
            - See remarks in last column for possible explanations e.g. presence of other benefits.
        - According to the Hong paper, 16 studies showed surgery at a specialised sarcoma centre as a predictive factor for better overall survival in multivariate analyses (see green background in second column).
    - 5 studies with no MV analysis (no colour in penultimate column). Smaller patient numbers: 36, 41, 72, 125, 622.

Summary studies from systematic review Hong et al., 2023 with overall survival (OS) results:

First author, Year	Ref nr Hong	N pts	country/ database, study period	Sarcoma type	OS significantly better in high-V/expert centre (EC) in UV analysis?	OS sign. better in MV analysis?	Remarks
(Abarca et al., 2018)	7	7874	US NCDB 1998-2012	Extremity STS	2, 5, 10y OS (def. = 10 cases/y)	yes	2% of hospitals treated 31% of patients
(Adam et al., 2019)	9	5340	US NCDB 1998-2012	RPS	10y OS	yes	
(Bagaria, Chang, et al., 2018)	10	13684	US NCDB 2003-2007	Extra-abdominal STS	5y OS	NS (HR=0.92, CI 0.82-1.02)	MV: adherence to NCCN guidelines, irrespective of hospital V, is associated with improved OS (HR=0.79, CI 0.73-0.87, p<0.001). High-V more NCCN adherence (p=0.03).
(Bagaria, Neville, et al., 2018)	11	5407	US NCDB 2004-2013	RPS	5y OS	yes	
(Berger et al., 2018)	13	2762	US NCDB 2004-2013	RPS	10y OS	NS (HR 0.91, CI 0.79-1.04, p=0.17)	EC def.: >500 annual cancer cases. EC: more R0 resections and more radical resections. (high general cancer V ≠ high sarcoma V per se)
(Bhangu et al., 2004)	14	260	UK 1994-1996	STS, no H&N or RPS	5y OS (MV analyses only)	yes	
(Blay et al., 2019)	15	25851	FR NetSarc 2010-2018	All sarcoma's	OS (HR 0.681, p<0.001)	yes	Surgery at EC (33.7%) vs out-of-network centre
(Bonvalot et al., 2019)	16	2945	FR NetSarc 2010-2017	RPS	2y OS (OR 0.496, p=0.001)	yes	Surgery at EC (36.6%) vs out-of-network centre
(Dilday et al., 2021)	58	15886	US NCDB 1998-2012	Extremity STS	10y	yes	
(Feinberg et al., 2018)	21	36	UK 1998-2015	Radiation-assoc. breast angiosarcoma	NS (EC OS: (months) median 75.4 vs 48.8, p=0.112)	no MV (or NS; no full text)	Sign. better DSS and local recurrence rate.
(Gutierrez et al., 2007)	51	4205	US Florida CDS 1981-2001	Extremity STS, RPS	10y	yes	
(Hoekstra et al., 2017)	25	3317	Netherlands NCR 2006-11	STS, no GIST	5y OS NS (HR=1.12)	NS (HR=1.15, CI 0.99-1.34)	high V (≥10 cases/y): less macroscopic residual disease (R2 resection; adjusted OR: 0.54)
(Hu et al., 2019)	59	182	China, 2004-2013	Osteosarcoma knee	10y OS	yes	Biopsy/surgery at EC (N=151) vs not (N=31)
(Kalaiselvan et al., 2019)	27	72	UK NW coast 2004-2017	RPS	5y OS NS before vs after centralisation (60% vs 46%, p=0.575) (despite more complex surgeries after centralisation)	no MV	Before vs after centralisation to 1 EC MDTB (95 surgeries for 72 pts, 79 after centralisation) 5y OS: sign. difference in EC vs national average (60% vs 40.6%) OR 2.26 (1.23-3.91), p=0.0027.
(Keung et al., 2018)	28	6950	US NCDB 1998-2011	RPS	5y OS (def. = 10/y)	yes	
(Lans et al., 2019)	52	64	US 1 centre database 1971-1992	STS hand	5y OS worse when Tx start at EC (60% vs. 89% Tx start at NEC, p=0.021)	NS (HR: 1.5, CI 0.96-2.4, p=0.078, incl. tumour size)	81% Tx start NEC (mostly unplanned excisions). EC: larger tumour size (p=0.069)
(Lazarides et al., 2019)	31	25406	US NCDB 1998-2012	Extremity STS	5y OS (def. = 20/y) (HR 0.81, p<0.001)	yes	
(Lazarides et al., 2020)	30	733	US NCDB 2004-2015	Vertebral column bone tumour	5y OS (def. = 5/study period)	yes	V def. based on N overall Tx, not only surgery.
(Lo et al., 2021)	32	41	UK W-Scotland 2007-2019	Breast	NS (p=0.43)	no MV	N=21 initial surgery at EC, N=20 at NEC
(Malik et al., 2020)	34	14039	US NCDB 2004-2015	Bone tumours	5y OS (def. = 20/y)	yes	V def. based on N overall Tx, not only surgery.
(Maurice et al., 2017)	35	2198	US NCDB 2004-2014	RPS	NS (def. = 5/y) High-V: median OS 71.1 months vs 68.9 months in low-V (p=0.341)	NS	Insufficient FU time + maybe confounders not sufficient to cover higher complexity pts in EC's High-V: more R0: OR 1.79, p<0.001; and R0: better OS: HR 0.68, p<0.001).
(Martin-Broto et al., 2019)	no	622	Spain 2004-2011	STS, non-visceral	3y OS	no MV	
(Merchant et al., 2012)	36	82	Canada 2000-2009	RPS	Referral before: median 10y OS 94 months vs after: 54.2, p=0.062. RFS sign. better before: p=0.04.	NS (before: HR 0.53, CI 0.2-1.2, p=0.115)	Referral before vs after surgery (referral before = 82.9% surgery by surgical oncology surgeon, vs. 0% for referral after)
(Paszat et al., 2002)	37	1467	Canada 1987-1996	Extremity STS	NS 5y OS (by case V 1st hospital)	NS (V 1st hospital)	high-V/EC def.: A) case V of 1st hospital, >50/ study period; B) cancer centre in 3m post-Dx

					Yes 5y OS (if attended cancer centre)	yes (if attended cancer centre)	(based on all Tx; N= 893 pts with surgery)
(Schmitz et al., 2019)	50	2599	US NCDB 1998-2012	RPS	5y OS (def. = 10 cases/y)	yes	
(Song et al., 2019)	42	55212	US NCDB 2005-2014	Extra-abdominal STS	3y OS	yes	high-V def.: >90th percentile in V STS pts treated
(Stiles et al., 2018)	55	125	US NCDB 2004-2014	Desmoplastic small round cell tumour	NS (high-V OS: median 59.1 months vs 28.0 m in low-V, p = 0.135)	no MV	74 surgery (high-V def.: ≥5 cases/10y) 2 EC's/97 hospitals, treating 12% of pts (N=15)
(Stiller et al., 2006)	no	849 | 1349	UK 1980-1994	Ewing | Osteosarcoma	5y OS	yes	Ages 0-39y
(Toulmonde et al., 2014)	45	511	France (12 centres French Sarcoma Group) 1988-2008	RPS	10y OS NS (specialised surgeon vs not)	NS (no details)	43.5% surgery by specialised surgeon from EC EC surgeon: independently associated with locoregional relapse & abdominal sarcomatosis
(Traub et al., 2018)	54	500	Canada 1989-2010	Extremity STS stage III	5y OS NS (50.1% after planned resection vs 54% initial unplanned resection, p=0.3)	NS (no details)	Monocentric, 94/500 pts referred to EC after inadequate excision in NEC; re-excision group sign. more plastic reconstruction & amputation
(Venigalla et al., 2018)	46	9025	US NCDB 2004-2013	STS	10y OS	yes	
(Villano, Zeymo, Chan, Shara, et al., 2020)	47	8721	US NCDB 2004-2015	RPS	5y OS (def.: 13 cases/y)	yes	13/y threshold statistically defined in the study
(Villano, Zeymo, Chan, Unger, et al., 2020)	60	10113	US NCDB 2004-2015	RPS	5y OS (EC = academic centre)	yes	analysis by hospital type: risk of death at community centres increased significantly as surgical volume ↑ (HR 1.26; CI 1.03-1.53)
(Vos et al., 2019)	48	5282	Netherlands 2006-2015	STS	10y OS sign worse in high-V (68% vs 76% in low-V, p<0.001)	NS (p=0.91)	high-V: ≥20/y (51% of pts); low-V: <10/y (42%) high-V: ↑ low-grade, large, deep-seated tumours
		1222		STS non low-grade and deep-seated	10y OS (high-V vs low-V)	yes	
(Widhe & Bauer, 2009)	49	97	Sweden 1980-2002	Chondrosarcoma chest wall	10y OS sarcoma centres vs not (related to better surg. margins)	yes	
(Wright et al., 2020)	61	1266	US NCDB 2004-2015	Chordoma spine and sacrum	5y OS (academic vs community cancer program)	yes	

Green/orange background penultimate column: significantly/NS better OS after surgery at an EC. Green background second column: surgery at an EC is a predictive factor for better OS in MV analyses, according to the Hong paper.

CI: (95%) confidence interval; def.: definition (of high-volume or expert centre); DSS: disease-specific survival; Dx: diagnosis; EC: expert centre; FU: follow-up; HR: hazard ratio; MDTB: multidisciplinary tumour board (presentation); MV (analysis): multivariate analysis; N: number; NCDB: National Cancer DataBase; NEC: non-expert centre; NS: not significant; OR: odds ratio; OS: overall survival; pts: patients; R: resection margins; RFS: recurrence-free survival; Ref nr: reference number in the Hong paper; RPS: retroperitoneal soft tissue sarcoma; sign.: significant; STS: soft tissue sarcoma; Tx: treatment; UV: univariate; V: volume; vs: versus; y: year.

- Note: Studies had various definitions of high-V (or specialised sarcoma/expert centres) and low-V centres!
  - Frequently used: ≥10 surgeries/y for either RPS or extra-abdominal/extremity STS; 2 studies used 20 surgeries/year (Lazarides et al., 2019; Vos et al., 2019).
  - For RPS one study used a statistical model: Overall mortality risk was reduced by 4% per additional procedure (HR 0.96, 95%CI 0.95-0.98) up to a threshold of 13 procedures/year; no further reduction was observed over 13 (HR 0.99, 95% CI 0.97-1.01). (Villano, Zeymo, Chan, Shara, et al., 2020)
- Note: (Villano, Zeymo, Chan, Unger, et al., 2020) discussion:
  - This analysis demonstrates that community centres may garner a higher risk of death with progressively increasing RPS surgical volume. So simply increasing this volume at such sites to improve outcomes can be questioned. These findings further reinforce the call for performance of RPS surgery at high-V hospitals.
  - Note that within this nationally representative US cohort, no community centre actually performed >2-3 procedures per year on average.
  - There are 'structure of care' factors that can be different between academic and community centres that likely contribute significantly to the observed effect of hospital type. Namely, variables such as number of beds, intensive care unit (ICU) setting, nursing:patient ratio, availability of a multidisciplinary team, interventional radiology capabilities, expertise of adjunct departments (radiation oncology, medical oncology), etc., all likely play a multifactorial role.

- Note: (Vos et al., 2019):
    - Non low-grade and deep-seated tumours (i.e. tumours that require more complex surgery and more multidisciplinary treatment) have poorer prognostic characteristics = more referral to high-V centres. Low-grade STS patients will most probably not die from their STS = more frequent at the low-V centres.
    - Conclusion: We plea for stricter referral guidelines, stating that all patients with suspected/confirmed STS should at least be discussed in an expertise centre.

- General conclusion Hong systematic review:
    - Despite the heterogeneity of studies and lack of randomised data, there is a fairly consistent large body of evidence showing surgery at specialised sarcoma centres is associated with improved patient outcomes in terms of local control, limb salvage rates, 30-day and 90-day post-operative mortality, and overall survival.
    - It is recommended that patients with suspected sarcoma be referred early to a specialised sarcoma centre for multidisciplinary management, which includes planned biopsy and definitive surgery.
- Limitations:
    - Available evidence is predominantly limited by the usual limitations of retrospective, registry, and non-randomised data including potential for selection bias.
    - Bias because patients with favourable prognosis may not be referred to EC's, while those with more advanced disease, prognostically negative characteristics or complex treatment requirements may be more likely to be referred to specialist centres/EC's. In the MV analyses, however, this could be partly accounted for by the inclusion of these factors as prognostic variables.
    - On the other hand, there could also be a 'healthy traveller bias', as more therapy-compliant or healthier patients may be more motivated to travel to an EC. See section 3.5 for more information on travel bias in sarcoma care.

Some studies did not analyse high- vs low-volume centres or (overall) survival, or they made other comparisons without a clear link with volume. These were therefore not included in the current overview table (for more details and full list, see Supplementary Table 1 of the Hong paper). Some examples:

- (Abellan et al., 2009): 3 referral pattern groups in monocentric study (referred directly to EC, after inadequate primary surgery, after local relapse) in 174 patients with extremity STS in Spain, diagnoses 1983-2006: OS NS different between groups. Group referred only after local relapse: lower disease-specific survival and higher rate of metastases ($p<0.001$).
- (Bauer et al., 2001): STS of the extremities or trunk wall, 8 sarcoma centres in Norway and Sweden, diagnoses 1986-1997, 1851 patients, overview results in general after centralisation of care. No analyses between different groups for OS.
- (J.-Y. Blay et al., 2017): STS and visceral sarcoma patients discussed in 26 French NetSarc centres MDTB before vs after treatment start, 2010-2014, 9646 patients in survival analysis: LRFS and RFS significantly higher when MDTB before treatment start (UV and MV analyses), OS not determined.
- (Collignon et al., 2020): French monocentric study with 127 patients with localised STS, 2006-2015, of which 59 patients with surgery, investigated the following of 5 main care guideline criteria (age group: 0-25 years. Small age = outside literature study scope). OS was NS better if 5/5 criteria were followed vs. ≤4/5: OS 93.6% (85.5-100%) vs. 79.5% (68.9-91.8%; p= 0.11). Loco-regional relapse-free survival was significantly better (p=0.047).
- (Decanter et al., 2019): Re-excision study STS France, NS difference in 5y-OS if re-excision at EC or not (after initial surgery at a NEC).
- (Derbel et al., 2017): Study in the Rhone Alpe region of France, STS 2005-2007, which showed how surgery adherent to clinical practice guidelines was statistically associated with a better OS only if performed in an expert referral centre.

3.3 The benefit for radiotherapy at specialised sarcoma centres: A systematic review and clinical practice guidelines from the Australia and New Zealand Sarcoma Association (Hong et al., 2022)

See also: https://sarcoma.org.au/does-radiotherapy-at-a-specialised-sarcoma-centre-improve-outcomes

- A systematic literature search was performed from **1990 to February 2022** (using the PICO model)
    - Conducted in Medline, Embase, Cochrane Central databases
    - Subject: local control, survival and toxicity of radiotherapy (RT) at specialised sarcoma centres
    - Results: **21 studies** were included (17 cancer registry studies, 4 retrospective comparative studies)
- Main findings:
    - 4 studies (with RT as part of limb conservation treatment) showed better conformity to clinical practice guidelines and an improved local recurrence free survival when RT treatment is supported through, but may not be necessarily delivered at a specialised sarcoma centre. (Hong reference numbers 17-20). Patient cohorts were generally grouped into management by sarcoma centres versus not, generally defined as the location of surgery, not specifically RT. The exact treatment location of RT was not clearly identified in most studies.

  - 1 retrospective study only analysed toxicity specifically and demonstrated that patients who received preoperative RT at community centres compared to RT at a specialised sarcoma centre were more likely to develop a major wound complication. (Ellison et al., 2021)
    - 204 patients (with localised resectable STS, pre-operative radiotherapy (RT) and limb-sparing resection), 73.5% received the RT at an specialist (academic) sarcoma centre.
    - Multivariate analysis: if RT in non-specialist centre: patients 2.25 times more likely to develop a major wound complication compared to specialist sarcoma centre (OR: 2.25, 95 % CI: 1.13–4.48, p = 0.02).
  - 14 studies reported overall survival; 12 showed significantly better 5-year overall survival for patients managed at specialised sarcoma centres, however the specific impact of RT delivered at sarcoma centres could not be determined. (Hong reference numbers 4-16 and 21)
    - 10 studies utilised the US NCBD database, which captures overall survival, but not local recurrence, which is the more relevant endpoint for RT in sarcoma.
- Conclusion:
  - It was **not possible to determine the specific effect of RT at specialised sarcoma centres** on local control and survival, **as the studies reported the outcome of overall treatment** at specialised sarcoma centres, generally defined as the location of surgery, **not specifically RT**.
  - Evidence-based recommendation Grade B: Patients with soft tissue sarcoma requiring radiotherapy should be **managed through a specialised sarcoma centre to reduce local recurrence and rate of major wound complication**.
- Other remarks:
  - The overall benefit of treatment at sarcoma centres is likely due to the expertise of the multidisciplinary team including radiation oncology.
  - There were various definitions of a specialised sarcoma centre in these studies. Most were defined either by case number per year or by percentile of the total cases diagnosed in the region.
  - Extensive literature shows better outcomes with treatment at high volume RT centres for other malignancies.
  - Mentioned in discussion: When RT in a specialised centre is not practical for patients, close collaboration between the specialised and non-specialised sarcoma radiation oncology teams is needed.
- See Supplementary Table 2 for details on the 21 studies.

3.4 The volume effect in paediatric oncology: a systematic review (Knops et al., 2013)

- Only short discussion because paediatric oncology actually falls outside the scope of the current literature overview.
- A systematic literature search was performed from **1966 to November 2010**:
  - Conducted in databases of Medline/PubMed and The Cochrane Library + expert supply
  - Subject: effect of provider case volume on the quality of care or survival in childhood cancer
  - Results: **3 studies** that concerned sarcoma (Knops reference numbers 15,16,21) (14 studies for all tumour types)
- Main findings:
  - It is likely that children with osteosarcoma or Ewing's sarcoma have a better survival in high-volume hospitals. High-volume/specialised centres were defined as 5-9 osteosarcoma patients/year or > 10 Ewing's sarcoma patients/year.
  - There are indications that rhabdomyosarcoma patients have a better survival in specialised hospitals.
- More information in supplementary File S2 (results per study) and S3 (results per tumour type; see print screen below):

Tumour Type	Studies	Comparison	Level of Research	Highest level of Conclusion	Results
Osteosarcoma	Stiller 2006 [21] Craft 1987 [15] Stiller 1988 [16]	Hospital volume Specialised hospitals	A2 B B	2	• It is likely that survival is better in specialised paediatric oncology high volume centres (5-9pt/centre/year) [21].
Ewing's sarcoma	Stiller 2006 [21] Stiller 1988 [16]	Hospital volume Specialised hospitals	A2 B	2	• There are indications that survival in paediatric oncology centres is better compared to other hospitals [16]. • It is likely that survival in high volume hospitals is better compared to low volume hospitals. This applies especially to patients aged 10-14 years in hospitals treating over 10 patients per year [21].
Rhabdomyo-sarcoma	Stiller 1988 [16]	Specialised hospitals	B	3	• There are indications that survival is better in paediatric oncology centres compared to other hospitals [16].

3.5 Travel bias

Travel bias: patients who are willing or able to travel (often farther) to a high-volume/expert centre may differ in important ways from those treated locally at low-volume centres (e.g. health status, tumour characteristics, socio-demographics).

- Healthy traveller bias (subtype of travel bias): people who travel tend to be healthier, younger and more health-conscious than the general population. This is often used in a more international setting and for example studies of vaccines.
- Referral bias (separate bias type but can interact with travel): Patients referred to expert centres can differ systematically from those who aren't referred. For example: severe cases may be more likely to be referred. Travel can influence referral bias, for example: patients willing or able to travel farther may be more often referred.

Some of the apparent outcome benefit of high-volume centres may come from these differences or biases rather than purely the effect of volume or experience. Multivariate analyses try to correct for these differences as much as possible by using adjustment factors such as age, overall health, comorbidities, tumour size, cancer stage, etc., but cannot exclude residual confounding by factors uncontrolled for.

Some examples of studies that examined the link between travel distance, hospital volume and outcome:

(Abarca et al., 2018)
- US NCDB, **extremity STS**, 1998-2012, 7874 patients (MV analyses seemed not to include travel distance)
- High-V (≥ 10 cases/y): mean travel distance was substantially farther than low-V (< 10 cases/y): 84 vs. 39 miles ($p < 0.001$).

(Schmitz et al., 2019)
- US NCDB, **RPS**, 1998-2012, 2599 patients
- Travel distance and V were divided in quartiles. 2 groups were made: long travel to high-V centre (median 56 miles and 10 cases/y) vs. short travel to low-V centre (median 14 miles and 3 cases/y):
    - Long & high-V: Younger and more often white ($p < 0.01$). More comorbidities, higher tumor grade, and more often radical resections and radiotherapy (all $p < 0.05$). Less R2 resections ($p=0.003$).
    - Long & high-V: sign. ↓ 30d mortality (1.2% vs. 2.8%, $p=0.003$) and ↑ 5-y survival (63% vs. 53%, $p<0.001$).
    - MV analyses: long & high-V: 27% improvement in overall survival (HR 0.73, $p<0.001$).
- Conclusion: Travelling to high-V centres for RPS treatment confers a significant short- and long-term survival advantage.

(Malik et al., 2020)
- US NCDB, **bone tumours**, 2004-2015, 14039 patients
- High-V (≥ 20 cases/y): median travel distance was substantially farther than low-V (< 20 cases/y): 77 vs. 23 miles ($p < 0.001$).
- Sign. higher 5-year OS in high-V centres. MV analysis: Treatment at high-V centres was significantly associated with a lower risk of mortality (HR 0.85 [0.77-0.93], $p<0.001$), but travel distance was not associated with overall survival.

(Moten et al., 2020)
- US NCDB, **extremity STS**, 2006-2015, 21763 patients
- Travel ≥ 15 miles (vs. < 15 miles) (both patient groups stratified by tumour size):
    - More undifferentiated tumours, more stage II than I disease, more surgery, more R0 resection margins.
    - Facility type (academic or non-academic): more academic (67.3%) (vs. < 15 miles: 45.8% academic, $p<0.001$).
    - MV analyses: no difference in 5-year OS (HR=1.00, 95% CI: 0.94-1.07) for all stages, nor for each stage separately.
        - MV model included relevant adjustment factors (e.g. age, sex, tumour size, grade, stage, facility type)
- Limitations:
    - No information on hospital volume was available nor included in the analyses! Facility type was an adjustment factor in the MV analysis (no information on its significance in the model). Since academic centres tend to have higher volumes, this could serve as a proxy for hospital volume.
    - Only 2 groups were compared (cut-off 15 miles ≈ 24.1 km), which might not adequately capture substantive differences in travel distance.
- Conclusion: Greater distance travelled is associated with comparable survival, despite patients having more advanced disease. Major limitation is that hospital volume was not taken into account.

(Vidri et al., 2021)
- US NCDB, **extremity STS stages I-III**, 2004-2015, 11979 patients
- Divided in quartiles: travel distance (<8, 8-17, 18-49, >49 miles ≈ 78.9 km) and volume (<3, 3-5, 6-12, >12 cases/year):
    - Higher-V centres: larger, less differentiated tumours, higher clinical stage.
    - MV analyses: Volume but not travel distance was associated with improved survival (HR 0.65, CI 0.52-0.83) and rate of R0 resection (HR 1.87, CI 1.4-2.5). There were many relevant adjustment factors (tumour, treatment and patient characteristics, including race, insurance status, income, education).
    - MV sub-analyses long travel to high-V centre (>12 cases/year) vs. short travel to low-V centre (<3 cases/year): long & high-V: have a survival advantage (higher OS (HR 0.45 [0.29-0.69], $p<0.001$) and increased odds of R0 resections: 87.4% vs. 77.4% (OR 2.07 [1.23-3.49], $p=0.006$).
- Discussion: The effects of distance on survival and odds of obtaining R0 resections generally disappear when hospital volume is introduced into the model. This demonstrates that the suggested effects described by Moten et al. of distance travelled to a treatment facility are mostly mediated by hospital volume.
- Conclusion: Overall survival seems unaffected by travel distance. Higher hospital case volume is consistently associated with a survival advantage. You can control for travel (or referral) bias by including hospital V in MV analyses.

(Lazarides et al., 2019)
- US NCDB, **extremity STS**, 1998-2012, 25406 patients
- Volume in 2 groups: high-V (≥ 20 cases/y) vs. low-V (<20 cases/y). Distance in quartiles (short <6 vs. long travel >42 miles):
    - High-V centres: larger, higher-grade tumours (both p<0.001), longer travel distance (136 vs. 37 miles, p<0.001).
    - MV analyses:
        - High-V: overall lower mortality risk (HR 0.81, p<0.001), less likely positive margins (OR 0.59, p<0.001)
        - Independent predictors for mortality: High-V centre (HR 0.79) and travel distance above median (HR 1.09; both p<0.001): both shorter travel and higher sarcoma V appeared to improve survival
    - Sub-analyses: long travel to high-V vs. short travel to low-V centre: higher OS (HR 0.80 [0.71-0.90], p<0.001)
- Discussion: The small apparent survival benefit of shorter travel distance was attributed to improved FU or monitoring, but greater importance was given to the sub-analysis showing that long travel to a high-volume centre improved survival.

(Fujiwara, Ogura, et al., 2021):
- US NCDB, **STS**, 2004-2016, 34528 patients
- MV analyses: reduced mortality risk was associated with longer (vs. short, < 10 miles) travel distance (>100 miles: HR=0.877) and with management at academic/research (vs. non-academic/research) centres (HR = 0.857; both P≤0.001).
- Increased travel distance was associated with superior survival, which was attributable to a higher proportion of patients receiving sarcoma care at distant academic/research centres, regardless of tumour stage.
- Conclusion: These data support centralised STS care. Overcoming referral and travel barriers may enable more patients to be treated at specialised centres and may further improve survival rates, even when it imposes an increased travel burden.

(Fujiwara et al., 2022)
- US NCDB, **bone sarcoma**, 2004-2015, 8432 patients
- Distance travelled in tertiles: ≤ 10 (=16.1 km), 11-49, ≥ 50 miles (=80.5 km). Hospital V in tertiles: ≤ 5, 6-19, ≥ 20 cases/year.
- Mortality risk was lower for patients who travelled ≥50 miles vs. ≤10 miles (HR 0.69 [95% CI 0.63-0.76]) and for high-volume facilities (≥20 cases/year) vs. low (≤5 cases/year) (HR 0.72 (95% CI 0.66-0.80).
- Worse survival for short travel to low-V vs. long travel to high-V centre, underlying the importance of Tx at high-V centres.
- Conclusion: Greater travel burden was associated with higher survival rates, which was attributable to patients travelling to receive care at high-V facilities.

(Gazendam et al., 2025)
- 1 Canadian expert centre, **STS**, 2010-2021, 1570 surgical patients
- Travel distance: ≤ 50 km (mean travel distance 24.8 km) vs. > 50 km (mean travel distance 176 km)
    - No differences in disease or treatment characteristics, nor in overall survival (OS) (p=0.29)
    - MV: sign. predictors of worse OS: age, higher tumour grade & depth, lower income; not: distance travelled.

In summary, patients who travel farther are more likely to be treated at high-V centres, which generally achieve better outcomes, suggesting some degree of travel bias. However, some studies noted that despite better outcomes at high-volume centres, those centres also saw larger/higher-grade tumours (i.e., worse baseline) so it is not a perfect bias in favour. Altogether, even after adjusting for travel distance and other confounding factors, higher hospital volume remains independently associated with improved outcomes, indicating a true volume effect beyond biases such as travel bias. It should be noted that there may be logistic or health-system factors and regional differences that affect generalizability, such as the density of expert centres in the territory under study.

4. Organisation sarcoma care in other countries, including targeted search of recent studies

The organisation of sarcoma treatment in networks of reference centres was proposed first by the Scandinavian sarcoma group in Scandinavian countries. (Bauer et al., 2001) Since then, several countries have organised national sarcoma groups and/or reference centres and networks. In most countries, such as France, the diagnosis and treatment of patients with sarcoma can be carried out in any oncology facility. In others, such as Scandinavian countries or the UK, the management of sarcoma patients must be carried out in dedicated reference centres. (J. Y. Blay et al., 2024)

In this section the organisation of sarcoma care in a number of different countries is discussed, based on some key publications. Countries not included in this overview, but that could also be informative are: Scandinavian countries (Trovik et al., 2017), Portugal (Melo Mateus et al., 2023), Spain (Martin-Broto et al., 2019) and Italy (Sandrucci et al., 2018).

Also, studies have been done with data from different countries pooled together:
- (Callegaro et al., 2023): For 8 specialist sarcoma reference centres (6 Europe, 2 North America) a study was performed titled "New Sarculator Prognostic Nomograms for Patients With Primary Retroperitoneal Sarcoma - Case volume does matter":

  - Centres were divided in low- and high-volume (cut-off 13 cases/y), RPS surgery, study period 2010-2017
  - N pts=857 in high-volume centres and N pts=244 in low-volume centres, the cut-off used for high- vs low-volume (13 cases/year) was based on (Villano, Zeymo, Chan, Shara, et al., 2020).
  - High-volume centres had better 5-year disease free survival (54% vs 40%, p < 0.001), better 5-year overall survival (71% vs 63%, p = 0.012) and on multivariate analysis that centre volume significantly predicted overall survival.
- (Gorostidi et al., 2023): "Impact of Hospital Case Volume on Uterine Sarcoma Prognosis: SARCUT Study Subanalysis"
  - First study to analyse the impact of hospital uterine sarcoma case volume on overall and progression-free survival.
  - Europe, 44 centres, 2001-2007, high-V definition: ≥ 10 gynaecologic sarcoma/y, 966 patients (213 in high-V)
  - Overall survival significantly better in high-V (HR=0.57, CI 0.42-0.78, p<0.001)
  - Remained statistically significant after adjustment for other variables e.g. FIGO stage (Cox hazard regression model)

4.1 France

Current status: 3 reference networks (https://netsarc.sarcomabcb.org/):

- NetSarc: French clinical reference network for soft tissue and visceral sarcomas, implemented in 2010 (26 centres).
- ResOs: French reference network for bone (Fr: réseau os) sarcoma & rare bone tumours, implemented in 2013 (14 centres).
- These 2 networks work jointly with the French sarcoma pathological reference network (RRePS) which insures a second expert pathological review of every suspected case.

All three were merged in 2018 within the NETSARC+ network, which aims to improve the outcome of sarcoma patients (and which also manages the common database: sarcomabcb.org). This database gathers all cases of sarcomas with confirmed pathological diagnosis after central expert review, all cases presented in multidisciplinary tumour boards (MDTBs) within the network, and describes their diagnosis, patient and tumour characteristics, therapeutic management, and outcome. (J. Y. Blay et al., 2024) The database is considered close to exhaustive, which offers the opportunity to evaluate the real-life impact of the organisation of reference centres on patient survival at a nationwide level. Exhaustivity is ensured by the mandatory pathology review.

Reference centres must have:

- A dedicated multidisciplinary team (with expert pathologists, radiologists, surgeons, radiation oncologists, medical oncologists, nuclear medicine specialists, molecular biologists and paediatricians)
- Participation to the educational and research activities of the French Sarcoma Group is requested
- Weekly MDTBs dedicated to sarcomas
- A threshold level of activity (e.g. number of incident patients) is not requested in NETSARC+.

Since 2010, second pathological review is mandatory for sarcoma patients nationwide and presentation to a specialised MDTB before treatment is recommended. (J.-Y. Blay et al., 2019; Bonvalot et al., 2019) Note that the diagnosis and treatment of patients with sarcoma can thus be carried out in any oncology facility. (J. Y. Blay et al., 2024)

Several publications have been made concerning retroperitoneal sarcoma or all sarcomas (see tables in the previous section).
In a study by Blay and colleagues from 2017, a comparison was made between a group of STS patients who were presented to a tumour board before versus after the start of treatment. This showed that the guidelines were better followed in patients who were discussed beforehand. The operation quality was also higher (52.6% R0 resection vs. 32.2%, p<0.001), as was the recurrence-free survival (LRFS HR 1.804, p<0.001 / RFS HR 1.263, p<0.001). (J.-Y. Blay et al., 2017), see also p.8 for study details.

Key publication:
Blay et al., 2024, Improved nationwide survival of sarcoma patients with a network of reference centres: (J. Y. Blay et al., 2024)

- Aim: Compare the survival of patients in three periods: 2010-2012 (non-exhaustive), 2013-2015, and 2016-2020 (last two considered as close to exhaustive)
- Patient population: N=43975 (sarcomas, GISTs and connective tissue tumours of intermediate malignancy
- Results:
  - Main: The implementation of the national reference network for sarcoma was associated with an improvement of overall survival and compliance to guidelines nationwide in sarcoma patients.
  - Detailed:
    - Overall survival was significantly superior in the period 2016-2020 versus 2013-2015 versus 2010-2012 for the entire population, for patients >18 years of age, and for both metastatic and non-metastatic patients in univariate and multivariate analyses (P < 0.0001).
      - 2016-2020 versus 2013-2015: HR = 0.82 [95% CI: 0.77-0.87]
      - At 12 months from diagnosis, survival rates were 92.7% in the 2016-2020 period versus 90.4% in the 2013-2015 period, i.e. a 24% reduction of the relative risk of death for 2016-2020.
      - In multivariate analysis, the most recent period (2016-2020) was an independent favourable prognostic factor compared to the period 2010-2015: HR = 0.78 [95% CI: 0.73-0.83]

- Over the three periods, we observed a significantly improved compliance to clinical practice guidelines (CPGs) nationwide: the proportion of patients biopsied before surgery increased from 62.9% to 72.6%; the percentage of patients presented to NETSARC MDTBs before first surgery increased from 31.7% to 44.4% (P < 0.0001).
- The proportion of patients with R0 resection on first surgery increased (from 36.1% to 46.6%), while R2 resection rate decreased (from 10.9% to 7.9%).
- The overall quality of surgery is significantly superior in the NETSARC centres versus non-reference centres, with two times more R0 resections and six times less R2 resections.
- Discussion: The better survival is likely to result from a general improvement in standard therapeutic practices as recommended by CPGs. Of note, the magnitude of improvement was larger in the metastatic patient population, as well as in the population of patients without documented surgery, possibly because of the increase in the number of therapeutic options for advanced patients in the last years, with new cytotoxics, targeted treatment, and local treatments [cryoablation, radiotherapy, and high-intensity focused ultrasound for metastatic lesions]. The authors interpreted this global improvement as a consequence of the 10 years of regular training and communication to the primary care physicians, radiologists, and surgeons, along with university courses in medical schools.

The conclusions of the most referenced French studies are:

- (J.-Y. Blay et al., 2017) (12528 patients with STS and visceral sarcoma, 2010-2014) :
  The compliance to clinical practice guidelines and relapse-free survival of sarcoma patients are significantly better when the initial treatment is guided by a pre-therapeutic specialised MDTB.
- (J.-Y. Blay et al., 2019) (25851 patients with all types of sarcoma and surgery (33.7% at reference centre), 2010-2018): Surgical treatment in a reference centre reduces the risk of relapse and death.
- (Bonvalot et al., 2019) (2945 patients with retroperitoneal sarcoma and surgery (36.6% at reference centre), 2010-2017): Surgery for primary RPS within an NSC was associated with a better OS.

Also, the medico-economic analysis of NETSARC indicates the cost-effectiveness of the central pathology review and the reduction of re-operations for patients operated in reference centres. (Perrier et al., 2018)

AYA's are outside the scope of this review, so only a quick mention: a Netsarc study on 3227 sarcoma patients (diagnosis 2010-2017) showed that overall survival was not different, but locoregional recurrence-free and progression-free survival were significantly better in AYA's treated at reference sarcoma centres versus non-reference centres (HR 0.58 and 0.83, respectively). (Kubicek et al., 2023)

4.2 UK

Overview of centralisation efforts for sarcoma care, and specifically RPS, in UK (Desai & Hayes, 2025):

- Efforts started in 1984 (see Desai & Hayes, 2025 for more information)
- 2006: National Institute for health and Clinical Excellence (NICE) guidelines (Fujiwara, Grimer, et al., 2021), see also chapter 5:
  - Recommendation for urgent referral to a specialist centre for patients with a soft-tissue sarcoma
  - The Sarcoma MDT was established as central to the management of patients with bone or soft-tissue sarcoma
    - Min. criteria: STS MDT: 100 new patients with STS/y; bone MDT: 50 new patients with bone sarcoma/y
- 2019: NHS England publication of the National Service Specification for the provision of care for patients with sarcoma (National Health Service (NHS) England, 2019):
  - Specialist Sarcoma MDT should manage a minimum of 100 new soft tissue sarcomas per year --> 12 specialist sarcoma centres
  - 5 specialist bone centres, with a minimum required volume of 50 new bone sarcomas per year
  - Centres treating RPS should perform surgical resection of minimally 24 cases of primary RPS per year (only recommendation in 2019)
- 2023: Compelling data (Callegaro et al., 2023; Kamarajah et al., 2023; Tirotta et al., 2023), presented to UK sarcoma community led to difficult discussions how to reduce inequalities in care for RPS patients. In particular, the survival difference seen between the top three centres by volume in England and the other centres was particularly striking (Tirotta et al., 2023). More information on these compelling studies:
  - Callegaro study: see chapter 4 introduction on p.17 (8 specialist sarcoma reference centres: 6 Europe, 2 US)
  - Kamarajah study: see subsection 'US' on p.23.
  - Tirotta study: see 'key publication' in next paragraph
- 2024: Consensus within sarcoma community that RPS patients would be better served by a smaller number of higher volume centres: reduce number of RPS centres in the UK from 12 to 5 or 6 (then each centre has at least 24 resections of primary RPS per year)
- 2025: Meetings with all existing RPS centres to discuss next steps. The 2019 Service Specification will be revised to reflect the published data which will provide a regulatory and financial mechanism to effect these changes.

Key publication:
Tirotta et al., 2023: Better survival in specialist centres retroperitoneal sarcoma (Tirotta et al., 2023)

- Aim: compare outcomes for UK RPS patients undergoing surgery in high-volume specialist sarcoma centres (N=3), low-volume specialist sarcoma centres (N=12) and non-specialist sarcoma centres (N not mentioned).
- Patient population: 1120 UK surgically treated RPS patients with primary RPS diagnosis in 2013-2018 (39% in high-volume, 37% in low-volume and 24% in non-specialist sarcoma centres)
- Results:
    - High-volume centres operated on an average of 24 patients per year (range: not mentioned-46), for low-volume centres this was 6 per year (range: 1-13). Non-specialist centres performed a mean of <1 resection per year (range: 0-4).
    - Patients undergoing surgery for RPS in a high-volume specialist centre had a 5-year OS of 62.8% vs. 51.7% in a low-volume specialist centre (HR: 0.78, 95% CI: 0.62-0.96, p<0.05). Both were significantly higher than the 42.0% in non-specialist centres (p<0.01).
    - Overall, patients were 20% and 10% more likely to be alive at 5 years if operated on at a high-volume vs. a non- and low-volume specialist centre, respectively.

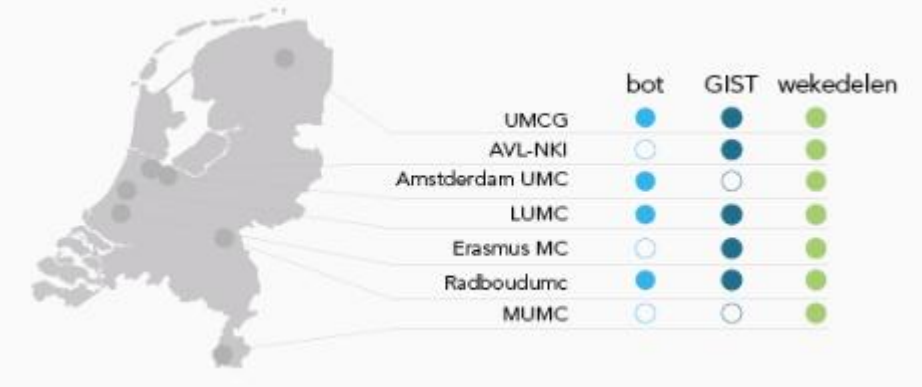
Other studies:

- (Kalaiselvan et al., 2019)
    - Aim: Analyse impact of centralisation (merger of 3 sarcoma networks in May 2011 in the North-West costal region of England) on patient outcomes
    - Patient population: 72 RPS patients (2004-2017) that underwent 95 operations (including 91 with curative intent). This included 23 re-resections for 14 patients with recurrent RPS; 20 of these 23 occurred post-centralisation.
    - Results:
        - Post- vs. pre-centralisation: increase in resection rates (12.2 vs. 2.5 yearly) and more complex multi-visceral resections (63.3% vs 12.5%), without compromising R0/1 resection rates (data not provided); peri-operative mortality (90-day p=0.677) or overall survival (5-year survival: 60% vs. 46%, p=0.575).
    - Editorial comment: small patient number to constitute a specialist centralised service (Tirotta et al., 2020)
- (Fujiwara, Grimer, et al., 2021)
    - Aim: determine impact of the NICE guidelines from 2006 on the disease-specific survival of patients with STS
    - Patient population: 2427 patients with STS referred to a supra-regional centre in the ten-year periods before (n = 1,386) and after (n = 1,041) the issue of the NICE guidelines
    - Results: post-NICE vs pre-NICE:
        - Mean tumour size significantly smaller at diagnosis (9.1 cm (SD 6.2) post-NICE vs 10.3 cm (SD 6.5) pre-NICE; p < 0.001)
        - Number of patients who had undergone an inadvertent excision ('whoops procedure') significantly decreased (20% (n = 204) post-NICE vs 28% (n = 389) pre-NICE; p < 0.001)
        - 5-year DSS was 63% in the pre-NICE and 71% in post-NICE groups (p < 0.001). The improved survival was more significant for those with a high-grade tumour (pre-NICE 48% vs post-NICE 68%; p < 0.001).
        - In those with a high-grade tumour, the mean size of the tumour (11.6 cm (SD 6.2) vs 9.6 cm (SD 5.8); p<0.001) and the number of patients with metastasis at the time of diagnosis (15% (N=124) vs 10% (N=80); p=0.007) significantly decreased in the post-NICE group.
    - Conclusion: An improvement in survival was seen after the introduction of the NICE guidelines, especially in patients with a high-grade STS. More patients were referred at an earlier stage, indicating a clearer pathway after the issue of national policy for the management of STS in the UK.

4.3 Netherlands

Current state of centralisation in centres of expertise (iKNL, no date):

- There are centres of expertise recognised by the government for the diagnosis (including biopsy) and treatment of bone sarcoma (4 centres), soft tissue sarcoma (7 centres) and GIST (5 centres).
- In practice, this is a recommendation (not mandatory), so not all patients are treated in these expert centres. In 2017-2018 the following % of patients was operated in a designated expert centre: 87% of bone sarcoma, 51% of STS and 31% of GIST. (iKNL, 2020) This is partly explained by the so-called 'whoops' resections.
- All general hospitals should organise a MDT meeting once a week to discuss all patients before treatment with a centre of expertise or refer the patient to such an expert centre. (SONCOS - Platform Oncologie, 2025)



(iKNL, no date): https://iknl.nl/kankersoorten/bot-en-wekedelenkanker

In the Netherlands, the SONCOS "normeringsrapport" is published annually, in which the (pre)conditions for good oncological care are multidisciplinary defined. They continuously strive to improve the care for oncology patients. After publication of new standards, the oncological centres have one year of implementation time to comply with the new standards, unless otherwise stated in the report. The latest report dates from 2025 (SONCOS - Platform Oncologie, 2025). It states the minimum volumes for an expertise centre for soft tissue sarcoma:

- Surgical treatment of 20 patients with STS (previously this was 10)
- MDT discussion of 100 patients with STS and/or GIST

In the report "Sarcomenzorg in Nederland" an overview is given for sarcoma in adults by the Netherlands Comprehensive Cancer Organisation for the period 2009-2018. (iKNL, 2020) Sarcoma care has been increasingly centralised since around 2011. Expertise centres either provide the care themselves or share their knowledge and experience about sarcomas with collaborating hospitals. A joint MDT meeting is hereby essential. However, almost a third of patients with a soft tissue sarcoma is not discussed with a centre of expertise. In practice, both diagnosis and treatment of soft tissue sarcomas take place in almost all hospitals in the Netherlands. This is partly because many more patients are seen with a non-malignant soft tissue tumour than a malignant one. Direct referral of every patient suspected of having a soft tissue sarcoma to an expert centre was therefore neither considered necessary nor desirable. (iKNL, 2020)

Key publication:

- (Vos et al., 2019) = on behalf of the Dutch Sarcoma Study Group (DSSG)
    - Aim: evaluate centralisation of **soft tissue sarcoma** surgery and its effect on survival
    - Patient population: 5282 operated patients with primary STS, 2006-2015, data from Dutch cancer registry
    - 3 hospital categories based on **yearly resection number**: low- (<10), medium- (10-19) or **high-volume (≥20)**
    - Results:
        - 42% was treated in low-volume hospitals, 7.7% in medium- and 51% in high-volume hospitals
        - A significant trend over time towards treatment in a high-volume hospital ($p < 0.01$)
        - Case-mix: In low-V hospitals, more patients with low-grade, small and superficial tumours were treated than in high-V hospitals.
        - Univariate analysis: significantly better survival for patients treated in low-V hospitals (10-year net survival 76%) vs. medium-V (68%, $p=0.001$) and high-V (68%, $p<0.001$)
            - Multivariate analysis (= with adjustment for prognostic factors age, STS subtype, grade, depth and size): no impact of surgical V
        - Subgroup analysis: patients with **non low-grade and deep-seated tumours** (= more complex surgery and more multidisciplinary treatment required, were more frequently referred to high-V hospitals): a **benefit from treatment in a high-volume hospitals** with a higher 10-year net survival rate of 54% (high-volume) versus 49% (low-volume) and 42% (medium-volume).
            - Multivariate analysis: relative rate of survival of 1.3 in high-V vs. low-V hospitals (95% CI 1.02-1.6, $p = 0.03$). High-V vs. medium-V had a trend towards significance: RR 1.3 (95% CI 0.98-1.8, $p=0.07$).
    - The researchers advocate for stricter referral guidelines, where patients suspected of or confirmed soft tissue sarcoma should at least be discussed in an expertise centre and referred to a high-volume hospital for an imaging biopsy prior to treatment if they are suspected of high-grade or deep-seated soft tissue sarcoma.

Other studies:

- (Hoekstra et al., 2017)
  - **STS**, non-GIST, 3317 patients (89% with surgical resection), diagnosis 2006-2011, high-volume (≥10 resections/y), low-volume (<10/y)
  - For particular indicators (grade, resection status, ''whoops'' resection, and delivery of radiotherapy), outcomes were better when diagnostics and treatment occurred in high-volume hospitals, academic hospitals, and sarcoma research centres compared with other hospitals.
  - Surgery in high-volume hospitals less often resulted in R2 resections.
- (Goedhart et al., 2019)
  - **high-grade bone sarcomas** (chondro-, osteo- and Ewing sarcoma), diagnosis in the Netherlands, 2000- 2014
  - In the period 2010-2014 85% of patients was treated in one of the bone sarcoma expert centres.
  - For high-grade central osteosarcoma, treatment at a bone tumour centre was associated with better survival (HR 0.593, 95%CI: 0.414–0.850, p=0.004).
- (Van Der Horst et al., 2022)
  - **Myxofibrosarcoma STS**, Netherlands Cancer Registry, diagnosis in 2002-2019, 908 patients
  - Univariate: Surgery at sarcoma expertise centres, instead of general hospitals, was associated with better OS outcomes (median OS 156.8 months vs. 126.0 months, p=0.02).
  - Multivariate: only trend for better OS in sarcoma expertise centres (HR=1.3 (95% CI 1.0-1.6), p=0.087)
- (Melis et al., 2022)
  - Adult **STS** surgery, Netherlands Cancer Registry, diagnosis in 2016-2019, 2187 patients
  - Multivariable logistic regression: first surgery performed in a sarcoma centre was the most predominant determinant of unplanned excisions (so-called 'whoops procedures'), with unplanned resections being much more likely in non-sarcoma centres compared to first surgeries in a sarcoma centre (OR 7.77; 95% CI: 5.07-11.91).

The PhD thesis "Clinical approach towards bone sarcoma care - The impact of centralisation" of Louren Matthias Goedhart includes additional information concerning bone sarcoma centralisation and follow-up in the Netherlands. (Goedhart, 2023)

4.4 Germany

Since the end of 2018, there has been a sarcoma centre certification module from the German Cancer Society that aims to improve the quality of care for patients with sarcoma. In September 2024 there were 21 certified centres for soft tissue sarcoma in Germany of which also 14 centres certified for bone sarcoma according to the criteria of the German Cancer Society. (*Sarcoma/GIST Centers*, 2024) The certification requirements and annual reports concerning the sarcoma centres can be downloaded in German. (*Sarkomzentren*, 2024) In the annual reports it is mentioned that the number of certified sarcoma centres increased from 10 in 2019 to 14 in 2021 and to 20 in 2023.

Collecting data on a broader scale in sarcoma patients is more limited in Germany than in other countries. Therefore, Eichler and colleagues conducted a prospective cohort study in the period 2017-2020 to analyse potential predictors of MDTB utilisation. Multivariable analysis showed that patients treated at a certified cancer centre had more than 5 times higher odds of being discussed in an MDTB than those from centres without such a certification (OR = 5.39; 95% CI 3.28–8.85; p < 0.01). (Eichler et al., 2021)

Based on the first 3 years of data collection after German sarcoma care centralisation in 2018, a sarcoma-specific quality assurance scheme that includes guideline-derived quality indicators was developed. (Rückher et al., 2023)

4.5 Denmark

- 2009: introduction fast-track Cancer Patient Pathways for sarcoma (CPPs) to improve the survival of sarcoma patients by accelerating the diagnosis and treatment processes (Thorn et al., 2024)
- Centralisation of treatment since 2010 in two sarcoma centres.
- 2009: The Danish Sarcoma Database or Registry was established as a national, population-based database.
- (Thorn et al., 2024)
  - Aim: Evaluate the impact of the CPPs on the overall survival of patients with deep-seated, high-grade STS, comparing outcomes from before and after CPP implementation.
  - Patient population: high-grade STSs in the extremities or trunk wall, 712 patients, 2000-2018. 2 cohorts: pre-CPP (2000–2008, N=309) and post-CPP (2010–2018, N=403).
  - Results:
    - The five-year overall survival improved from 43% in the pre-CPP cohort to 52% post-CPP (p = 0.05).
    - Time-to-treatment was significantly reduced post-CPP, with a 3-day median decrease (18 vs. 15 days, p < 0.001).
  - Conclusion: survival has improved since the CPPs introduction and treatment delays have been reduced.
- Note: Patients still are diagnosed and sometimes treated outside the two sarcoma centres.

4.6 Switzerland

(Willburger et al., 2022)

- Treatment of soft tissue sarcomas is not centralised in Switzerland
- Patient population: surgically treated RPS, 2005-2015, Swiss hospitals
- Sarcoma centres were defined as > 50 patients with sarcoma treated/year for at least 1 year, leading to 5 sarcoma centres.
    - The overall in-hospital mortality rate was lower (3.2% vs. 9.1%) in sarcoma centres versus non-sarcoma centres (even though patients more severe and more surgical treatments). The discussion mentions non-sarcoma centres might have had more palliative care patients, but no information on this number of patients was available.
    - Higher rate of complications in sarcoma centres (55% vs. 40%) for elective hospitalisations: possibly attributed to the greater complexity of the surgical intervention and the individual patient (more comorbidities). However, no data were available on the surgery type and no multivariate analyses were performed.
    - RPS patients are treated increasingly more in sarcoma centres during 2005-2015 (from 0% to 33% in 2015, p<0.001)

(Fuchs et al., 2021): Development of a value-based healthcare delivery model for sarcoma patients

- This article describes how the value-based health care delivery principles are being adopted and fine-tuned to the care of sarcoma patients, and already partially integrated in seven major referral hospitals in Switzerland.
- The members of the SwissSarcomaNetwork (SSN; www.swiss-sarcoma.net) comprise all institutions that are willing to consecutively assess and share their transdisciplinary sarcoma data within a prospective real-world data platform (prospective RWD Sarcoma Registry of Quality).
- Together with an international advisory board, sarcoma quality indicators (work-up, weekly sarcoma MDTB, treatment complexity, outcome, PROMS/PREMS) are being defined, totalling more than 70 parameters. These quality metrics and results of their descriptive analysis are automatically generated from the registry and visualised in real-time on an interactive website for all SSN members, thereby enabling the quality management system which has been required by law in Switzerland since April 2021. (https://www.swiss-sarcoma.net/pdf/indicators_of_quality.pdf)

4.7 US

In the scientific literature, USA hospitals are called sarcoma expert centres when they have a high volume of treated patients. Many studies have investigated the relationship between patient volume and outcome, but they used different volume cut-offs to define 'high-volume' (see US studies in the tables of the previous chapter). Note that most studies retrospectively analysed data from the US National Cancer DataBase (NCDB), thereby (partly) using the same data to draw conclusions, so the evidence from these studies is partly overlapping. The NCDB captures > 70% of new cancer diagnoses annually. Note that for retroperitoneal sarcoma, for which the cut-off is often set at 10 cases per year, very few centres contributing to the NCDB actually manage more than 10 cases per year, so the label "high-volume" should be interpreted with caution. (Gronchi & Raut, 2022)

Most studies did find a volume-outcome effect (see studies in the tables of the previous chapter). Some examples:

- (Lazarides et al., 2019): 25406 patients with extremity STS diagnosed in the period 1998-2012: Found a significantly higher 5-year observed survival in hospitals that treated at least 20 cases per year.
- (Bagaria, Chang, et al., 2018): 13684 patients with extra-abdominal STS diagnosed in the period 2003-2007, the 5-year observed survival was better in high-volume centres. However, on multivariable analysis, adherence to the National Comprehensive Cancer Network (NCCN) clinical practice guidelines was associated with improved survival (HR = 0.79, CI 0.73–0.87; p < 0.001), but hospital volume was not (high-volume (≥11 cases/y) versus low-volume (<3 cases/y): HR = 0.92, CI 0.82–1.02; p = 0.12). This implies that following the guidelines is more important than volume itself.
- (Keung et al., 2018): 6950 patients with RPS, US NCDB 1998-2011: 5y overall survival was significantly better in high-volume centres, defined as ≥10 surgeries/year (also in multivariate analyses).
    - Interesting extra reading material: editorial: "A Call to Action: Why Sarcoma Surgery Needs to Be Centralized" (Raut et al., 2018)
        - "Key takeaway point: In the US, only a minority of patients with primary RPS are treated at experienced centers."
        - Editorial on invalid statistical methods used. (Putt, 2018)
- (Gutierrez et al., 2007) 4205 patients with surgery for extremity STS or RPS, US Florida CDS 1981-2001, 10y overall survival was significantly better in high-volume centres, defined as treating the upper 1/3th of patients (also in MV analyses).

Also these more recent studies were published:

- (Kamarajah et al., 2023): US NCDB, **non-metastatic RPS**, 2004-2016, surgery vs. no surgery (n patients = 11254, of which 64.1% underwent surgery)
    - Centres were divided by volume of surgery into quintiles and a clear relationship between increasing centre volume and improved survival was seen.
    - Patients were twice as likely to be offered an operation at a high-volume centre than a low-volume centre.

- (Alvarez et al., 2022): 1532 **adolescents and young adults (AYA)**, first primary STS, California Cancer Registry, 2000-2014, 40.4% received all inpatient treatments in a specialised cancer centre.
    - Overall, the 5-year survival was improved for patients who received all inpatient care at a specialised centre (59.8% ± 1.92% vs. those who received part/none, 50.7% ± 1.74%, p<0.001).
    - Multivariable regression analysis found that having all treatments at a specialised centre was associated with better overall survival (HR, 0.79, CI: 0.65–0.95) in AYAs.
- (Vidri et al., 2021): 11979 patients with **extremity STS stages I-III**, NCDB 2004-2015, volume divided in quartiles with highest volume >12 cases/year. Volume but not travel distance was associated with improved survival (HR 0.65, CI 0.52-0.83) en R0 resection (1.87, CI 1.4-2.5).
- (Ellison et al., 2021): 204 patients (with **localised resectable STS, pre-operative radiotherapy (RT)** and limb-sparing resection), 73.5% received the RT at an specialist (academic) sarcoma centre. Multivariate analysis: if RT in non-specialist centre: patients 2.25 times more likely to develop a major wound complication compared to specialist sarcoma centre (OR: 2.25, 95 % CI: 1.13–4.48, p = 0.02).
- (Lin et al., 2020): **localised Ewing sarcoma**, NCDB 2004-2014, 391 patients with **definitive RT**, quartiles based on volume
    - Treatment at the 25% lowest Ewing sarcoma volume centres is associated with reduced overall 5-y survival (60.0% vs 72.4%, p=0.024), explained partly by higher rates of delayed local definitive radiotherapy (≥16 weeks after chemotherapy initiation) (42.2% delayed RT vs 31.2%, p=0.053).
    - Treatment at the 25% highest Ewing sarcoma volume centres results in improved overall survival (compared to the 2 middle quartiles) (79.4% vs 69.1%, p=0.024), but appears independent of radiotherapy timing (delayed RT: 30.9% vs 31.4%, p=0.153).
- (Moris et al., 2020): US NCDB, **RPS** 2004-2015, 11032 patients: 54% had a 'textbook outcome' (defined as hospital length of stay<75th percentile, survival>90 days from surgery, no readmission within 30 days and grossly negative margins).
    - Undergoing surgery at high-volume centres (defined as >10 RPS surgeries per 3 years) was associated with a higher probability of a textbook outcome (p=0.009). Textbook outcomes were associated with significantly longer overall survival (p<0.001).

4.8 Canada

Healthcare in Canada is delivered on a provincial level with each province having its own regionalised healthcare system. Centralising care of patients with sarcoma in designated high-volume reference centres (as evidenced by literature) is challenging to apply to countries spanning a large geographical area or countries with a low population density, such as Canada.

(Yeo et al., 2023)

- Province of British Columbia in Canada: It is a provincial standard of care that all patients with sarcoma are discussed at least once at the provincial multidisciplinary tumour board, which occurs weekly in the high-volume centre in Vancouver. Five British Columbia cancer centres provide systemic and radiation therapy.
- Patient population: 77 Ewing sarcoma and rhabdomyosarcoma, 2000-2020, curative intent therapy in one of five cancer centres across the province, 46 patients in high-volume centres and 31 in low-volume centres.
- High-volume if ≥ 20 sarcoma cases per year; low-volume if < 20 sarcoma cases per year
- Results:
    - Patients at high-V centres were more likely to receive curative intent radiation (88% vs. 67%, p = 0.047).
    - The time from diagnosis to first chemotherapy was 24 days shorter at HVCs (26 vs. 50 days, p = 0.120).
    - There was no significant difference in overall survival by treatment centre (HR 0.850, 95% CI 0.448–1.614).
- The lack of significant difference in patient outcomes may be explained by British Columbia's existing hub-and-spoke model of care, which allows for greater consistencies in healthcare delivery across the province compared with other models. Healthcare delivery is arranged into a network of services consisting of anchoring centres (hubs) offering the full spectrum of care, complemented by secondary centres (spokes) with more limited services, allowing for an increased ease of communication, collaboration, and multidisciplinary care.
- Limitations: small patient cohort size

Other studies:

- (Gazendam et al., 2025): Contrary to previous studies, our findings suggest that **travel distance** did not influence disease presentation or survival outcomes in **STS** patients treated at a centralised sarcoma centre. This supports the effectiveness of centralised care models, even in geographically vast regions.
- (Beecroft et al., 2024): Pan-Canadian consensus recommendations for **GIST** management (as a response to the provincially rather than nationally administered Canadian healthcare system):
  We strongly advocate early **referral of patients to specialised high-volume sarcoma centres** to optimise their access to treatment options and improve outcomes. In cases where there are geographical factors that preclude regular follow-up at specialised centres, engagement of local oncologists with relevant specialist centres should be encouraged so that the

benefits of available systemic treatments can be optimised, and one-off strategies such as surgery or ablation may still be considered.

4.9 Japan

No centralisation yet, but several Japanese studies did study and/or find a volume-outcome effect:

- (Kimura et al., 2020)
  - RPS, 2008-2009 (N = 380 patients), data from Japanese HBCR database (comprises data on +/- 67% new cases in Japan)
  - When institutions were divided by hospital care volume (8 hospitals with ≥ 3 cases and 149 with < 3 cases/year), there were no statistical differences in the OS. For stage I: 5-y OS: 69.2% if ≥ 3 vs 55.5% if <3 cases/year (p=0.38)
- (Ogura, Morizane, Satake, Iwata, Toda, Muramatsu, Kobayashi, et al., 2024)
  - Bone sarcoma, NCR Japan, 2016-2019, 3755 patients (1984 with surgery)
  - Hospital volume tertiles: low (≤ 49 cases/4 years, 17.8%), medium (50–158 cases/4 years, 38.2%), or high (≥ 159 cases/4 years, 44.0%).
  - Significant associations between overall survival and hospital volume (HR low-volume centres vs high: 1.30; 95% CI 1.04-1.61; p= 0.019).
- (Ogura, Morizane, Satake, Iwata, Toda, Muramatsu, Takemori, et al., 2024)
  - STS, NCR Japan, 2016-2019, 23522 patients
  - Significant associations between overall survival and hospital volume are mentioned but no details since no full text available.
- (Nitta et al., 2024)
  - RPS, 188 patients from 106 institutions, 2008-2009, high vs low-volume defined as ≥4 vs <4 (20 vs 80% of patients), data from Japanese HBCR database
  - High-volume hospital patients had higher 10-year OS rates than low-volume (51.2% vs 23.2%, P = 0.026).
  - Multivariate analysis: treatment in low-volume hospitals was independent predictor of unfavourable survival while treatment with surgery was an independent predictor of favourable survival.

5. International recommendations/guidelines and consensus statements

The ESMO-EURACAN clinical practice guidelines are internationally highly regarded and available for 3 sarcoma categories (soft tissue/visceral, bone and GIST). Overall, they recommend that patients should be managed in sarcoma reference centres or networks (diagnosis and treatment), where multidisciplinary expertise is available and with expert pathological review/centralised diagnosis.

- (Gronchi et al., 2021): Soft tissue and visceral sarcomas: ESMO-EURACAN-GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up:
  - Management should be carried out in reference centres for sarcomas and/or within reference networks sharing multidisciplinary expertise and treating a high number of patients annually. (J.-Y. Blay et al., 2017)
  - Referral to a specialist centre should occur early at clinical diagnosis of a suspected sarcoma. This would mean referring all patients with an unexplained deep soft tissue mass, or with a superficial soft tissue lesion with a diameter ≥5 cm. Quality criteria are needed for sarcoma reference centres and, increasingly, reference networks. (Andritsch et al., 2017) = ECCO requirements
  - A pathological expert validation is required in all cases when the original diagnosis is made outside a reference centre/network. (Ray-Coquard et al., 2012)
- (Strauss et al., 2021): Bone sarcomas: ESMO-EURACAN-GENTURIS-ERN PaedCan Clinical Practice Guideline for diagnosis, treatment and follow-up:
  - The initial work-up of a suspected primary bone sarcoma tumour should be carried out at a sarcoma reference centre, and should include medical history, physical examination, radiological assessment and biopsy [IV, B].
  - Pathological diagnosis should be made by a bone tumour expert dedicated pathologist according to the 2020 WHO classification and should be supported by ancillary investigations whenever relevant [IV, A]. (expert pathological review in a sarcoma reference centre is mandatory)
  - Given their rarity and the complexity of management, the accepted standard for bone sarcoma is treatment at reference centres and/or within reference networks able to provide access to the full spectrum of care and age-specific expertise [III, A].
- (Casali et al., 2022): GIST: ESMO-EURACAN-GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up:
  - Centralisation of mutational analysis in a laboratory enrolled in an external quality assurance programme and with expertise in the disease may be useful. Centralised pathological diagnosis is more strongly recommended for GISTs without typical molecular alterations.
  - Multidisciplinary treatment planning is needed involving pathologists, radiologists, surgeons, medical oncologists, as well as gastroenterologists and nuclear medicine specialists, as applicable.

  - Management should be carried out at reference centres for sarcomas and GISTs and/or within reference networks sharing multidisciplinary expertise and treating a high number of patients annually. These centres are involved in ongoing clinical trials, in which the enrolment of GIST patients is common practice.

- (J.-Y. Blay et al., 2021): European Reference Network for rare adult solid cancers, statement and integration to health care systems of member states: a position paper of the ERN EURACAN
  - The ERN EURACAN (European Reference Network for rare Adult solid CANcers) contains 10 domains of which 1, 'connective tissue', encompasses 2 sub-thematic areas: 'STS/visceral' and 'Bone'.
  - EURACAN recommendations:
    - To create reference centres and networks for all rare cancers in all countries, and recommend a centralised pathology review and early referral to reference centres which demonstrated improved patient outcome.
    - Adoption of the EURACAN Clinical Practice Guidelines for rare cancers in all EU countries. See the ESMO-EURACAN Clinical Practice Guidelines for 1) STS/visceral, 2) GIST, and 3) Bone sarcomas.
- ECCO (European CanCer Organisation) essential requirements for quality sarcoma care (Andritsch et al., 2017) includes the following volume criteria (European consensus document):
  - A **sarcoma surgeon** should carry out at least 3–4 procedures a month (**30–40 a year**)
  - The sarcoma centre should **treat at least 100 patients** per year if the MDT manages both **bone and soft tissue sarcoma** patients (including non-surgical cases).
  - The ECCO expert group is aware that it is not possible to propose a 'one size fits all' system for all countries, but urges that access to multidisciplinary teams is guaranteed to all patients with sarcoma.
- In 2006 the National Institute for Health and Care Excellence (NICE) made recommendations in the UK for improving outcomes for people with sarcoma (see NICE document p.8 for the recommendations). (National Institute for Health and Clinical Excellence (NICE), 2006) These include the following minimum criteria:
  - Soft-tissue sarcoma MDT: should **manage** the care of at least **100** new patients with **soft-tissue sarcoma** per year
  - STS and bone sarcoma MDT: should **manage** the care of at least **50** new patients with **bone sarcoma** per year and at least **100** new patients with **STS** per year.
- The Updated Consensus Approach from the Transatlantic Australasian RPS Working Group (TARPSWG) included specific recommendations for RPS volume (Swallow et al., 2021):
  - A recent quantitative analysis of data derived from the NCDB identified 13 as the minimum annual institutional volume of RPS resections that was associated with improved long-term overall survival in the USA. (Villano, Zeymo, Chan, Shara, et al., 2020)
  - Although a clear, widely applicable threshold is still lacking, members of TARPSWG who were surveyed regarding these results concurred that a **minimum annual institutional surgical volume of 10–20 RPS cases** was appropriate for a centre to be considered one of RPS expertise.
  - Curative surgical resection is the cornerstone of treatment and should be performed in specialist centres by expert sarcoma surgeons to ensure appropriate treatment within a multidisciplinary setting.
  - Most large European centres currently contribute to the Transatlantic RPS Working Group (TARPSWG) RPS database which collects prospective data from more than 40 institutions worldwide since 2017.
- NCCN: Soft Tissue Sarcoma, NCCN Clinical Practice Guidelines in Oncology (Von Mehren et al., 2022), Bone Cancer and GIST (see website https://www.nccn.org/guidelines/category_1 to see the latest guidelines)
  - NCCN: National Comprehensive Cancer Network, a not-for-profit alliance of 33 leading cancer centres in the US.
  - All patients should be evaluated and treated (managed) by a multidisciplinary team with expertise and experience in the treatment of sarcoma and its subtypes. The team should meet on a regular basis.
  - Because soft tissue sarcoma is rare and often complex, adherence to evidence-based recommendations is particularly important. Analysis of data from 15,957 patients with soft tissue sarcoma in the National Cancer Database (NCDB) showed that NCCN Guidelines-adherent treatment was associated with improved survival outcomes. (Voss et al., 2017)
- Other additional reading material:
  - (Kasper et al., 2018): Working to improve the management of sarcoma patients across Europe: a policy checklist
  - (Gronchi & Raut, 2022):
    - They mention that a threshold of 25 cases of primary RPS cases per year also was proposed for abdominal sarcoma referral centres, but they did not include a reference for this statement.
    - Consensus exists about the need to have multidisciplinary tumour boards dedicated to RPS. Consensus also exists about the need to identify a minimum case volume. It is however less clear whether the experience of a sarcoma referral centre with high-volume expertise in certain types of sarcomas (e.g., extremity sarcoma or GIST) can automatically be translated to other types of sarcomas such as RPS.

6. Extra reading material

Literature for Belgium

- The KCE report 219 from 2014, named "Organisation of care for adults with a rare or complex cancer", mentioned soft tissue and bone sarcomas as rare and complex cancer types for which proposals should be formulated by a multidisciplinary working group to improve the quality and organisation of care in Belgium (Stordeur et al., 2014). Other cancer types included in the report are currently the subject of centralisation (preparation) initiatives in Belgium (e.g. oesophagus, pancreas, head and neck).
- Kom op tegen Kanker (KOTK) published a dossier in 2020 explaining why reference centres are needed and what these reference centres should look like according to KOTK. (Kom op tegen Kanker, 2020) These proposals were inspired by many interviews and meetings with healthcare providers, patient representatives and policy makers. Based on this dossier, KOTK made 10 specific policy proposals in 2023 for promoting better care by establishing reference centres for rare and complex cancers. (Kom op tegen Kanker, 2023)
- The Belgian Cancer Registry (BCR) published an epidemiological report on sarcoma, describing the bone and soft tissue tumour epidemiology in Belgium for the period 2004-2019. (Belgian Cancer Registry, 2022)

Expert Pathology Review:

Many studies pointed to the importance of expert pathology review for making the correct diagnosis, hereby influencing the decision for the optimal treatment plan. Some examples:

- (Crenn et al., 2024)
    - primary bone tumours, national prospective French sarcoma network database, 1075 patients, 2018-2019.
    - Early management within the expert network significantly reduced major diagnostic discrepancies and shortened the diagnosis delay by approximately a month.
    - Systematic re-readings by Resos-Netsarc + expert pathologists: 75% diagnosis readjustments (two-thirds preoperatively, thereby mitigating the consequences of mistreatment)
- (Lurkin et al., 2010)
    - Striking data from the French Rhône-Alpes region: histological data of 448 patients diagnosed with sarcoma between in the period 2005-2006 were re-assessed by an expert panel. Full concordance was reported for only 54% of cases and more than 45% of first diagnoses were declared invalid by the expert panel conducting the centralised pathological review.
- (Thway & Fisher, 2009)
    - STS, referring reports on 349 specimens, referred to 1 UK specialist centre
    - Diagnostic discrepancy: minor in 15.7% of cases, major in 10.9% of cases
    - Almost all discrepancies occurred due to differences in tumour interpretation between general or nonsoft tissue pathologists, and pathologists at the specialist unit

Quality of Life (QoL):

- (Jones & Cesne, 2018): Quality of life and patients' expectations in soft tissue sarcoma. (review)
- (Fernando-Canavan et al., 2024): Health-related quality of life in patients with extremity bone sarcoma after surgical treatment: a systematic review
- (Franzoi et al., 2023): The psychological impact of sarcoma on affected patients. (review)
- (Hassani et al., 2023): Uncovering the gaps: A systematic mixed studies review of quality of life measures in extremity soft tissue sarcoma

Patient-Reported Outcome Measures (PROMs):

- (Generaal et al., 2024): Twenty-five years of experience with patient-reported outcome measures in soft-tissue sarcoma patients: a systematic review
- (Roets et al., 2024): Patient-reported outcomes in randomized clinical trials of systemic therapy for advanced soft tissue sarcomas in adults: A systematic review

7. Conclusions

Sarcoma treatment requires a high level of expertise due to its rarity and diversity. Despite the heterogeneity of studies and lack of randomised data, there is a fairly consistent large body of evidence showing that patients with sarcoma that are managed through specialised sarcoma expert centres (EC) by multidisciplinary teams and/or are surgically treated at an EC have better oncological outcomes.

Growing evidence exists that in the **diagnostic phase**, patients benefit from an initial discussion in a **multidisciplinary tumour board (MDTB)**, to determine the most optimal, guideline-based treatment plan. Studies show that at an EC, the diagnostic procedures were more adequately performed.

Treatment in general at an EC was associated with better outcomes in the majority of studies, including a better postoperative outcome, lower local recurrence rates and longer survival. These benefits were found in large databases on sarcoma in general and in small cohort studies on specific sarcoma subtypes.

The vast majority of studies show that **surgery** at specialised sarcoma EC's is associated with improved patient outcomes in term of local control, limb salvage rates, 30-day and 90-day mortality, and overall survival. For local control this is reflected in higher rates of negative surgical margins (R0, complete tumour resection), lower rates of local relapse and improved local recurrence-free survival. Moreover, neoadjuvant therapy or multimodal treatment were more frequently carried out at EC's.
Some studies found that the benefits in EC's were associated with treatment being conform to (inter)national clinical practice guidelines (CPG) and/or EC MDTB recommendations for the treatment plan, e.g. patients that underwent CPG-adherent surgery had significantly better OS.

For **radiotherapy** (RT), the evidence is less precise since the location of RT is not clearly specified in most studies. Several studies did show significantly better OS for patients managed at specialised sarcoma centres, however the specific impact of RT delivered at sarcoma centres could not be determined. When RT is a part of the limb conservation treatment for STS, a small number of studies show better conformity to CPG and an improved local recurrence-free rate when RT treatment is supported through, but may not be necessarily delivered at a specialised sarcoma centre. Nevertheless, it is recommended in most situations that patients with STS requiring radiotherapy should be managed through a specialised sarcoma centre to reduce the probability of local recurrence and of major wound complications.

Several countries have already organised sarcoma care in reference centres or networks and are seeing important benefits for sarcoma patients. In general, the implementation of national reference centres/networks for sarcoma is associated with improved compliance to CPG's (e.g. more biopsies and MDTB discussion before treatment), an overall better quality of surgery (e.g. more R0 and less R2 resections) and a reduced risk of relapse and death. In addition, centralisation of sarcoma care has sometimes also been linked to a reduced time-to-treatment and less unplanned excisions (so-called 'whoops procedures') overall. However, effective centralised care requires that organisational and logistical barriers be addressed to minimise the risk of treatment delays. Throughout the different studies, various definitions and volume cut-offs were used for sarcoma EC's or high-volume centres, and a generally accepted definition does not yet exist.

Several types of recommendations have been formulated in the past. The **ESMO-EURACAN Clinical Practice Guidelines**, published in 2021 and 2022, state that management should be carried out in reference centres for sarcomas and/or within reference networks sharing multidisciplinary expertise and treating a high number of patients annually. Referral to a specialist centre should occur early at clinical diagnosis of a suspected sarcoma. For STS, this would mean referring all patients with an unexplained deep soft tissue mass, or with a superficial soft tissue lesion with a diameter ≥5 cm. Quality criteria are needed for sarcoma reference centres and, increasingly, reference networks. A pathological expert validation is recommended in all cases when the original diagnosis is made outside a reference centre/network (to ensure a correct diagnosis and in this way also the most optimal treatment plan).

8. Abbreviations

AYA	Adolescents and young adults
BCR	Belgian Cancer Registry
CI	(95%) Confidence interval
CPG	Clinical practice guidelines
d	Day
def.	Definition (of high-volume or expert centre
DFS	Disease-free survival
DSS	Disease-specific survival
Dx	Diagnosis
EC	Expert centre
ECCO	European CanCer Organisation
ERN	European Reference Network
ESMO	European Society for Medical Oncology
EURACAN	European Reference Network for rare Adult solid CANcers
GIST	Gastrointestinal stromal tumour
H&N	Head and Neck
HR	Hazard ratio
iKNL	Integraal Kankercentrum Nederland
KCE	Belgian Healthcare Knowledge Centre (Kenniscentrum)
KOTK	Kom op tegen Kanker
LR	Local recurrence
MDT (meeting)	Multidisciplinary team (meeting)
MDTB	Multidisciplinary tumour board (presentation)
MV (analysis)	Multivariate analysis
N	Number
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NCDB	National Cancer DataBase (US)
NEC	Non-expert centre
NetSarc	French reference network for sarcoma
NICE	National Institute for Health and Care Excellence (UK)
NS	Not significant
OR	Odds ratio
OS	Overall survival
p	P-value
(L)PFS	(local) Progression-free survival
pts	Patients
R	resection margins
Ref nr	Reference number in a specific paper
(L)RFS	(local) Recurrence-free survival
RPS	Retroperitoneal sarcoma
RT	Radiotherapy
Sign.	Significant
SONCOS	Stichting Oncologische Samenwerking (NL)
STS	Soft-tissue sarcoma
TARPSWG	Transatlantic RPS Working Group
Tx	Treatment
UV (analysis)	Univariate analysis
V	Volume
vs	Versus
y	Year

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