Clinical Practice Guidelines for Management of Sarcoma – Series 1

Technical Report

13th April 2022

Table of Contents

Scope of the technical report

This technical report refers to the development of Clinical Practice Guidelines for Management of Sarcoma (Series 1). The following clinical questions are addressed in this series.

1. Does radiotherapy at specialised sarcoma centre improve outcomes?
   Population: Adult and Paediatric patients with bone and soft tissue sarcoma
   Intervention: Multidisciplinary team, radiotherapy
   Comparison: Treatment at non-specialised centre
   Outcomes: Local control, overall survival, wound complication, radiotherapy toxicity

2. Does surgery at specialised sarcoma centre improve outcomes?
   Population: Adult and Paediatric patients with bone and soft tissue sarcoma
   Intervention: Multidisciplinary team, surgery
   Comparison: Treatment at non-specialised centre
   Outcomes: Limb salvage rate, local control, overall survival, postoperative mortality

3. Does delayed surgical resection of the primary tumour impact on the outcome of pelvic Ewing sarcoma?
   Population: pelvic Ewing Sarcoma
   Intervention: delayed surgical resection of the primary tumour
   Comparison: surgery at time point of recommended local control in protocol
   Outcomes: Overall survival

This report includes a description of the systematic review methodology, drafting of the guidelines, search strategy, evidence summary, quality assessment and evidence statement for each clinical question.

Systematic review methodology

The topic lead and research librarian decided on the search strategy. The systematic review management software Covidence is used to facilitate systematic review. The studies identified by search strategy are imported into Covidence for review and data extraction. Duplicates are firstly removed automatically by Covidence. Each study undergoes title and abstract screening for eligibility for full text screening by two independent reviewers as per the PICO model, inclusion, and exclusion criteria. The full text of each study is then assessed for eligibility by two independent reviewers. A reason for exclusion is assigned to each excluded study. Any conflicts between the two reviewers are resolved by the lead of the clinical question.

Quantitative and qualitative data extraction for each study are performed in Covidence using a custom template by a member of the guidelines working party. The extracted data of all the studies are then exported into a single Excel file.

The quality of each study is assessed by two independent reviewers using the NHMRC Evidence Hierarchy, Newcastle-Ottawa Quality Assessment Form for Cohort Studies or Cochrane Collaboration's tool for assessing risk of bias for randomised trial. A final score for the quality assessment is assigned to each study. Finally, an evidence table which summarises the systematic assessment and critical appraisal of all studies that meet the inclusion criteria is created.

Drafting of the guidelines

The topic leads write the first draft of the guidelines. Each member of the working party for the clinical question is provided with the following for critical appraisal:

- access to Covidence which has all studies included in the title/abstract screening, full text screening, the Prisma diagram, the pdf of all studies that meet the inclusion criteria and the data extraction
- an excel file with evidence table, which summarises the systematic review and critical appraisal of all studies that meet the inclusion criteria
- final quality assessment (NHMRC Evidence Hierarchy, Newcastle-Ottawa Quality Assessment Form for Cohort Studies, Cochrane Collaboration's tool for assessing risk of bias for randomised trial) for each study that meet the inclusion criteria
- a draft guideline with evidence summary, recommendations and practice points at prior to topic working party meeting

Clinical question 1: Does radiotherapy at specialised sarcoma centre improve outcomes?

The first clinical question and its PICO model addressed by the guideline is:

1. Does radiotherapy at specialised sarcoma centre improve outcomes?
   Population: Adult and Paediatric patients with bone and soft tissue sarcoma
   Intervention: Multidisciplinary sarcoma team, radiotherapy at specialised sarcoma centre
   Comparison: Treatment at non-specialised centre
   Outcomes: Local control, overall survival, wound complication, radiotherapy toxicity

A systematic search for evidence performed by a research librarian were undertaken in February 2021 and updated in February 2022 in the following electronic databases:

- Ovid Medline, Ovid Embase, Cochrane CENTRAL (Wiley).

Date of coverage was restricted to 1990 onwards and searches were limited to articles in English only.

In Medline, the search strategy consisted of a combination of exploded subject headings (MESH) and various keywords to identify the literature.

Subject headings applied in Ovid Medline included: “Sarcoma”, “Radiotherapy”, “Patient Care team”, “Hospitals, Special”, “Referral and consultation”, “Hospitals, high-volume”. These were combined in their associated cluster groups with keywords such as: “osteosarcoma”, “liposarcoma”, “radiation”, “sarcoma centre”, Multidisciplinary team”, “specialist unit” and more. Please refer to the search strategy for a complete list of terms used. All word variations (including spelling) were searched and adjacency searching was applied in some instances that linked words in proximity to one another.
The “AND” was applied to all separate concepts in order to yield relevant citations.
The “NOT” command was used to exclude results in correspondence with the criteria.

Due to the high number of results and concern about relevancy after the initial search, a decision was made to include subjects and keywords representing outcomes in the strategy for this question, e.g., “treatment outcome”, “survival rate”, “effectiveness”, “limb salvage”, “toxicity” and more.

The search in Ovid Embase followed a similar format to the Medline search with variations according to its subject thesaurus (Emtree). In Cochrane CENTRAL, keyword combinations were used. Please see below for the complete search strategy.

The research question is aimed at patients with sarcoma of all backgrounds and ages. There is no specific risk factor for development of sarcoma therefore the population (adult and paediatric patients with bone and soft tissue sarcoma) specified in the search strategy

include all population subgroups. The focus of this research question is on the benefit of radiation therapy at highly specialised sarcoma centres which only exist in metropolitan areas. The outcomes of the systematic review will provide useful data to lobby for better support of rural patients.

The inclusion and exclusion criteria used to select studies for appraisal are described below:

Inclusion criteria:

- Studies that cover the research question in regard to their PICO
- Contains comparison between specialised/MDT/academic and non-specialised/community centres
- Population of the study covers adult and paediatric patients with bone and soft tissue sarcoma
- Investigates Intervention of Multidisciplinary team and radiotherapy
- Compares the difference of treatment at non-specialised centre
- Outcomes of the study includes limb salvage rate, local control, overall survival, functional outcome, wound complication, radiotherapy toxicity

Exclusion criteria:

- Non sarcoma
- Excluded Sarcoma Types (Kaposi Sarcoma, gastrointestinal stroma; tumour, Dermatofibrosarcoma protuberans, Adenosarcoma, Carcinosarcoma, Endometrial stromal tumours, Phyllodes tumour, gliosarcoma, uterine sarcoma)
- Review article or editorial
- Case report/series
- Conference abstract
- No comparison with specialised and non- specialised centre
- Studies that was not relevant to research question

Figure 1. PRISMA flow chart from Covidence showing the flow of information through the different phases of this systematic review for this clinical question.

Preferred Reporting Items for Systematic Reviews and Meta-Analyse (PRISMA) flow chart shows the different screening phase for question 1 (Figure 1). A total of 3,76 records were identified from the search strategy and imported into Covidence for screening. The inter-rater reliability for the title and abstract screening was 97.2% and full text review was 77.6%. The selection process yielded a final number of 21 studies for the systematic review. Please see Appendix 1 for list of the 21 studies.

Quantitative and qualitative data were extracted with a custom template within Covidence for each study. The data extraction was then exported from Covidence into the Excel file. An evidence table is created with information on study design, inclusion and exclusion criteria, number of patients/hospitals, outcomes, level of evidence, quality assessment, critical appraisal, and other relevant information. Please see Appendix 2 &3. for Evidence Summary tables and quality assessments “T1Q1_Evidence Summary and Quality Assessments”.

Not all 21 studies address the outcome endpoints defined by the PICO model. Therefore, for each outcome in the PICO model, a separate evidence table is created for appraisal. After extensive review of the studies, evidence summary and recommendations were created for the two endpoints: local recurrence and wound complication/radiation toxicity (Please see

Appendix 4. Evidence Summary tables for Local Recurrence and Wound Complication). The outcome overall survival attributable to radiotherapy treatment alone at specialised sarcoma centre could not be determined due to the nature of multidisciplinary treatment for sarcoma (often a combination of surgery, radiotherapy, and chemotherapy). Most studies identified in this search reported the outcome by overall treatment at specialised sarcoma centre rather than radiotherapy at specialised centre.

For each recommendation, an evidence statement is created and graded using a NHMRC approved method. This statement documents the synthesis and evaluation of the body of evidence to determine the grade of each recommendation. Please see below for the evidence statement form for each of the outcomes covered by the clinical question 1.

Search strategy

Search strategy for clinical question 1.

Database: Ovid MEDLINE(R) ALL <1946 to February 08, 2021>

Search Strategy:

---

1 exp sarcoma/ (139721)

2 (sarcoma* or adamantinoma* or aneurysmal bone cyst* or angiosarcoma* or atypical lipomatous or chondroblastoma* or chondromyxoid fibroma* or chondrosarcoma* or chordoma* or dermatofibrosarcoma* or desmoid-type fibromatos* or desmoid tumo?r* or desmoplastic round cell or desmoplastic small round cell or desmoplastic fibroma* or epithelioid hemangioendothelioma* or epithelioid h?emangioma* or ewing* or fibrosarcoma* or giant cell tumo?r* or inflammatory myofibroblastic or neurofibrosarcoma* or hemangiosarcoma* or malignant fibrous histiocytoma* or leiomyosarcoma* or liposarcoma* or lymphangiosarcoma* or malignant peripheral nerve sheath tumo?r* or mesenchymoma* or mesodermal mixed or myosarcoma* or myxofibrosarcoma* or myxosarcoma* or osteoblastoma* or osteosarcoma* or pecoma* or pec tumo?r* or perivascular epithelioid cell or primitive neuroectodermal tumo?r* or rhabdomyosarcoma* or solitary fibrous or spindle cell or tenosynovial giant cell).mp. (234963)

3 1 or 2 (240923)

4 exp radiotherapy/ (188879)

5 radiotherapy.fs. (193868)

6 (radiotherap* or radiation or irradiat* or imrt or xrt or 3dcrt or 3d crt).mp. (904960)

7 4 or 5 or 6 (917689)

8 3 and 7 (30528)

9 exp patient care team/ or exp hospitals, special/ or exp "referral and consultation"/ or exp hospitals, high-volume/ (205114)

10 ((sarcoma* or speciali?ed or specialist or specialty or specialization or centrali?ed or multidisciplinary or multi-disciplinary or mdt* or designated or cancer or tumo?r or oncology or managed clinical or high* volume) adj3 (center or centers or centre* or centres or team* or care or hospital* or facility or facilities or unit or units or clinic or clinics or network* or approach or referral)).mp. (204888)

11 9 or 10 (385245)

12 8 and 11 (1617)

13 surgery.fs. (2023341)

14 (surgery or surgeries or surgical or surgeon* or resection or resectable or excision).mp. (3280928)

15 13 or 14 (3280928)

16 3 and 15 (67242)

17 11 and 16 (3052)

18 exp treatment outcome/ or exp survival rate/ or exp survival analysis/ (1365516)

19 (outcome* or survival or effectiveness or advantage* or benefit* or efficacy or success* or limb salvage or local control or wound* or toxicity).mp. (6695396)

20 18 or 19 (6734096)

21 12 and 20 (1243)

22 limit 21 to (english language and yr="1990 -Current") (1047)

23 17 (3052)

24 limit 23 to (english language and yr="1990 -Current") (2513)

25 exp bone neoplasms/ or exp soft tissue neoplasms/ or exp sarcoma/ (250757)

26 (((bone* or soft tissue) adj3 (Cancer* or neoplasm* or tumo?r*)) or bstt* or sarcoma*).mp. (207991)

27 25 or 26 (311699)

28 ((second or 2nd or pathology or central* or consultative) adj2 (opinion* or review*)).mp. (9675)

29 ((diagnostic or histopatholog*) adj2 (concordance* or discordance* or discrepanc* or agreement*)).mp. (2683)

30 expert pathologist*.mp. (498)

31 28 or 29 or 30 (12739)

32 27 and 31 (432)

33 limit 32 to (english language and yr="1990 -Current") (383)

34 exp animals/ not exp humans/ (4785640)

35 ((animal* or rat or rats or swine or mouse or mice or dog or dogs) not human*).mp. (4737872)

36 34 or 35 (5035439)

37 22 not 36 (1035)

38 24 not 36 (2495)

39 33 not 36 (379)

****

Searches re-run On Feb 09 2022 to include any recent literature.

Evidence Statement Forms for each outcome

Outcome 1: Local Recurrence		
Component	Rating	Description
1. Evidence Base	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
2. Consistency	A	All studies consistent
3. Clinical Impact	B	Moderate - 2 of 4 studies did not perform multivariate analysis. There might be some unknown factors affecting the outcomes.
4. Generalisability	B	Evidence directly generalisable to target population with some caveats- only soft tissue sarcoma, mostly extremity/trunk primary, only the Ray-Coquard included 8 cases of retroperitoneal primary
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats - only one Australian study, 89 patients, two sarcoma centres, Large geographic landscape,? feasibility to deliver RT only in sarcoma centre, currently minimal patient support
Outcome 2: Wound Complication		
Component	Rating	Description
1. Evidence Base	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
2. Consistency	NA	Only one study
3. Clinical Impact	B	Moderate - In the multivariate analysis, treatment at community centre is a significant factor for postoperative wound complication.
4. Generalisability	B	Evidence directly generalisable to target population with some caveats - only in patients with soft tissue sarcoma extremity/trunk primary received preoperative RT
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats - Different definition of community centre in Australian health care setting

Clinical question 2: Does surgery at specialised sarcoma centre improve outcomes?

The second clinical question and the PICO model addressed by the guidelines is:

Does surgery at specialised sarcoma centre improve outcomes?

Population: Adult and Paediatric patients with bone and soft tissue sarcoma
Intervention: Multidisciplinary team, surgery
Comparison: Treatment at non-specialised centre
Outcomes: Limb salvage rate, local control, overall survival, functional outcome, wound complication

A systematic search for evidence were undertaken and the search strategy is documented below, including the search terms and databases searched. Advanced literature searches were conducted in late March 2021 and run in the following electronic databases: Ovid Medline, Ovid Embase, Cochrane CENTRAL (Wiley). Date of coverage was restricted to 1990 onwards and searches were limited to articles in English only.

In Medline, the search strategy consisted of a combination of exploded subject headings (MESH) and various keywords to identify the literature.

Subject headings applied in Ovid Medline included: "Sarcoma", "Patient Care team", "Hospitals, Special", "Referral and consultation", "Hospitals, high-volume". These were combined in their associated cluster groups with keywords such as: "osteosarcoma", "liposarcoma", "sarcoma centre", Multidisciplinary team", "specialist unit" and all relevant surgery terms ("surgical", "resection", "excision", etc). Please refer to the search strategy for a complete list of terms used.

All word variations (including spelling) were searched and adjacency searching was applied in some instances that linked words in proximity to one another. The "AND" was applied to all separate concepts in order to yield relevant citations. The "NOT" command was used to exclude results in correspondence with the criteria.

To reduce the number of results for this topic, the decision was made to exclude case reports, reviews, and editorials. Conference proceedings were also excluded from the Embase results. The search in Ovid Embase followed a similar format to the Medline search with variations according to its subject thesaurus (Emtree). In Cochrane CENTRAL, keyword combinations were used. See below for the complete search strategy for clinical question 2.

The research question is aimed at patients with sarcoma of all backgrounds and ages. There is no specific risk factor for development of sarcoma therefore the population (adult and paediatric patients with bone and soft tissue sarcoma) specified in the search strategy include all population subgroups. The focus of this research question is on the benefit of surgery at highly specialised sarcoma centres which only exist in metropolitan areas. The outcomes of the systematic review will provide useful data to lobby for better support of rural patients.

The inclusion and exclusion criteria are used to select study for appraisal:

Inclusion criteria:

- Studies that cover the research question and PICO model
- Contains comparison between specialised/MDT/academic and non-specialised/community centres
- Population of the study covers adult and paediatric patients with bone and soft tissue sarcoma
- Investigates Intervention of Multidisciplinary team and surgery
- Compares the difference of treatment at non-specialised centre
- Outcomes of the study includes Limb salvage rate, local control, overall survival, functional outcome, wound complication

Exclusion criteria:

- Irrelevant cancer types
- Review studies
- Case report/ series
- Not Sarcoma
- Review article/ Case reports Case Study unless the studies specifically compare the results with another centres
- No comparison with specialised and non- specialised centre
- Studies that was not relevant to research question
- Excluded Sarcoma Types (Kaposi Sarcoma, gastrointestinal stromal tumour, dermatofibrosarcoma protuberans, adenosarcoma, carcinosarcoma, endometrial stromal tumours, phyllodes tumour, gliosarcoma, uterine sarcoma)

Figure 2. PRISMA flow chart from Covidence showing the flow of information through the different phases of this systematic review for question 2.

The PRISMA flow chart shows the different screening phase for question 2 (Figure 2). A total of 3,387 studies were identified from the search strategy and imported into Covidence for screening. The inter-rater reliability for the title and abstract screening was 97.8% and full text review was 76.7%. The selection process yielded a final number of 66 studies for the systematic review (Please see Appendix 5 for full list of studies).

Quantitative and qualitative data were extracted with a custom template within Covidence for each study. The data extraction was then exported from Covidence into the Excel file. An evidence table is created with information on study design, inclusion and exclusion criteria, number of patients/hospitals, outcomes, level of evidence, quality assessment, critical appraisal, and other relevant information. Please see Appendix 6 & 7 for Evidence Summary Table and Quality assessment.

Not all 66 studies address the outcome endpoints defined by the PICO model. After critical appraisal of the 66 studies by the working party, the following four outcomes are addressed by the guidelines:

1. overall survival

2. local control rate
3. short term surgical mortality
4. limb salvage rate

For each outcome, a separate evidence table is created for appraisal (see appendix 8). For each recommendation, an evidence statement is created according to an NHMRC-approved method. This statement documents the synthesis and evaluation of the body of evidence to determine the grade of each recommendation. Please see below for the evidence statement form each of the outcomes covered by the clinical question 2.

Search strategy

Complete search strategy for clinical question 2

Database: Ovid MEDLINE(R) ALL <1946 to March 22, 2021>

Search Strategy:

---

1 exp sarcoma/ (140219)

2 (sarcoma* or adamantinoma* or aneurysmal bone cyst* or angiosarcoma* or atypical lipomatous or chondroblastoma* or chondromyxoid fibroma* or chondrosarcoma* or chordoma* or dermatofibrosarcoma* or desmoid-type fibromatos* or desmoid tumo?r* or desmoplastic round cell or desmoplastic small round cell or desmoplastic fibroma* or epithelioid hemangioendothelioma* or epithelioid h?emangioma* or ewing* or fibrosarcoma* or giant cell tumo?r* or inflammatory myofibroblastic or neurofibrosarcoma* or hemangiosarcoma* or malignant fibrous histiocytoma* or leiomyosarcoma* or liposarcoma* or lymphangiosarcoma* or malignant peripheral nerve sheath tumo?r* or mesenchymoma* or mesodermal mixed or myosarcoma* or myxofibrosarcoma* or myxosarcoma* or osteoblastoma* or osteosarcoma* or pecoma* or pec tumo?r* or perivascular epithelioid cell or primitive neuroectodermal tumo?r* or rhabdomyosarcoma* or solitary fibrous or spindle cell or tenosynovial giant cell).mp. (235606)

3 1 or 2 (241574)

9 exp patient care team/ or exp hospitals, special/ or exp "referral and consultation"/ or exp hospitals, high-volume/ (206007)

10 ((sarcoma* or speciali?ed or specialist or specialty or specialization or centrali?ed or multidisciplinary or multi-disciplinary or mdt* or designated or cancer or tumo?r or oncology or managed clinical or high* volume) adj3 (center or centers or centre* or centres or team* or care or hospital* or facility or facilities or unit or units or clinic or clinics or network* or approach or referral)).mp. (206398)

11 9 or 10 (387447)

13 surgery.fs. (2032933)

14 (surgery or surgeries or surgical or surgeon* or resection or resectable or excision).mp. (3295976)

15 13 or 14 (3295976)

16 3 and 15 (67597)

17 11 and 16 (3084)

23 17 (3084)

24 limit 23 to (english language and yr="1990 -Current") (2544)

34 exp animals/ not exp humans/ (4803234)

35 ((animal* or rat or rats or swine or mouse or mice or dog or dogs) not human*).mp. (4747093)

36 34 or 35 (5046730)

38 24 not 36 (2527)

45 (case reports or review or systematic review or editorial).pt. (5398166)

46 case report*.ti,ab. (388476)

47 45 or 46 (5473314)

48 38 not 47 (1597)

Evidence Statement Forms for each outcome

Outcome 1: Local control		
Component	Rating	Description
1. Evidence Base	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
2. Consistency	A	All studies consistent
3. Clinical Impact	A	Very large
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	A	Evidence directly applicable to Australian healthcare context
Outcome 2: Overall Survival		
Component	Rating	Description
1. Evidence Base	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
2. Consistency	B	B, (most studies consistent and inconsistency can be explained)
3. Clinical Impact	A	Very Large
4. Generalisability	B	Evidence directly generalisable to target population with some caveats - The data on soft tissue sarcoma are strong and consistent but little data on primary bone tumour and paediatric population. Given the more subspecialise nature of primary bone tumour surgery, we can probably reliably generalise the result to primary bone tumour
5. Applicability	A	Evidence directly applicable to Australian healthcare context
Outcome 3: 30-day, 90-day surgical mortality		
Component	Rating	Description
1. Evidence Base	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
2. Consistency	B	Most studies consistent and inconsistency can be explained
3. Clinical Impact	A	Very large
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	A	Evidence directly applicable to Australian healthcare context/ B, with few caveats
Outcome 4: Limb salvage rates		
Component	Rating	Description
1. Evidence Base	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
2. Consistency	B	B, (most studies consistent and inconsistency can be explained)
3. Clinical Impact	B	Moderate
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	A	Evidence directly applicable to Australian healthcare context

Clinical question 3: Does delayed surgical resection of the primary tumour impact on the outcome of pelvic Ewing sarcoma?

The third clinical question and its PICO model addressed by the guideline is:

Does delayed surgical resection of the primary tumour impact on the outcome of pelvic Ewing sarcoma?

- Population: Pelvic Ewing Sarcoma
- Intervention: Delayed surgical resection of the primary tumour
- Comparison: Surgery at time point of recommended local control in protocol
- Outcomes: Overall survival

A systematic search for evidence were undertaken and the search strategy is documented below, including the search terms and databases searched.

Advanced literature searches were conducted in late July 2021 and run in the following electronic databases: Ovid Medline, Ovid Embase, Cochrane CENTRAL (Wiley). Date of coverage was restricted to 1990 onwards and searches were limited to articles in English only.

In Medline, the search strategy consisted of a combination of exploded subject headings (MESH) and various keywords to identify the literature.

Subject headings applied in Ovid Medline included: “Sarcoma, Ewing” and “Time factors”. These were combined in their associated cluster groups with keywords such as: “ewing”, “timing”, “surgery”, “delay”, “postpone” and more. Please refer to the search strategy for a complete list of terms used.

All word variations (including spelling) were searched, and adjacency searching was applied in some instances that linked words in proximity to one another. The “AND” was applied to all separate concepts to yield relevant citations. The “NOT” command was used to exclude results in correspondence with the criteria. Case reports, reviews and editorials were excluded from the results.

The search in Ovid Embase followed a similar format to the Medline search with variations according to its subject thesaurus (Emtree). In Cochrane CENTRAL, keyword combinations were used. Please see below for the search strategy for clinical question 3.

There is no specific risk factor for development of Ewing sarcoma therefore the population specified in the search strategy applied to all population subgroups. The guideline recommendations are applicable to patients of all backgrounds and ages.

The inclusion and exclusion criteria used to select studies for appraisal are:

Inclusion criteria:

- Studies that cover the research question in regards to its PICO model
- Contains information on delayed resection of pelvic Ewing sarcoma

- Population of the study covers adult or paediatric patients with ewing sarcoma
- Investigates Intervention of surgery at time point of recommended local control in protocol
- Outcomes of the study includes local recurrence rate, overall survival, EFS, surgical complications

Exclusion criteria:

- Irrelevant cancer types
- Excluded Sarcoma that are not Ewing sarcoma
- Studies that do not include any primary pelvic Ewing sarcoma (studies with both pelvic primary and other primary site are not excluded)
- Review/editorial studies
- Case report/series
- Conference abstract with no further publication
- No comparison with surgery timing
- Studies that was not relevant to research question

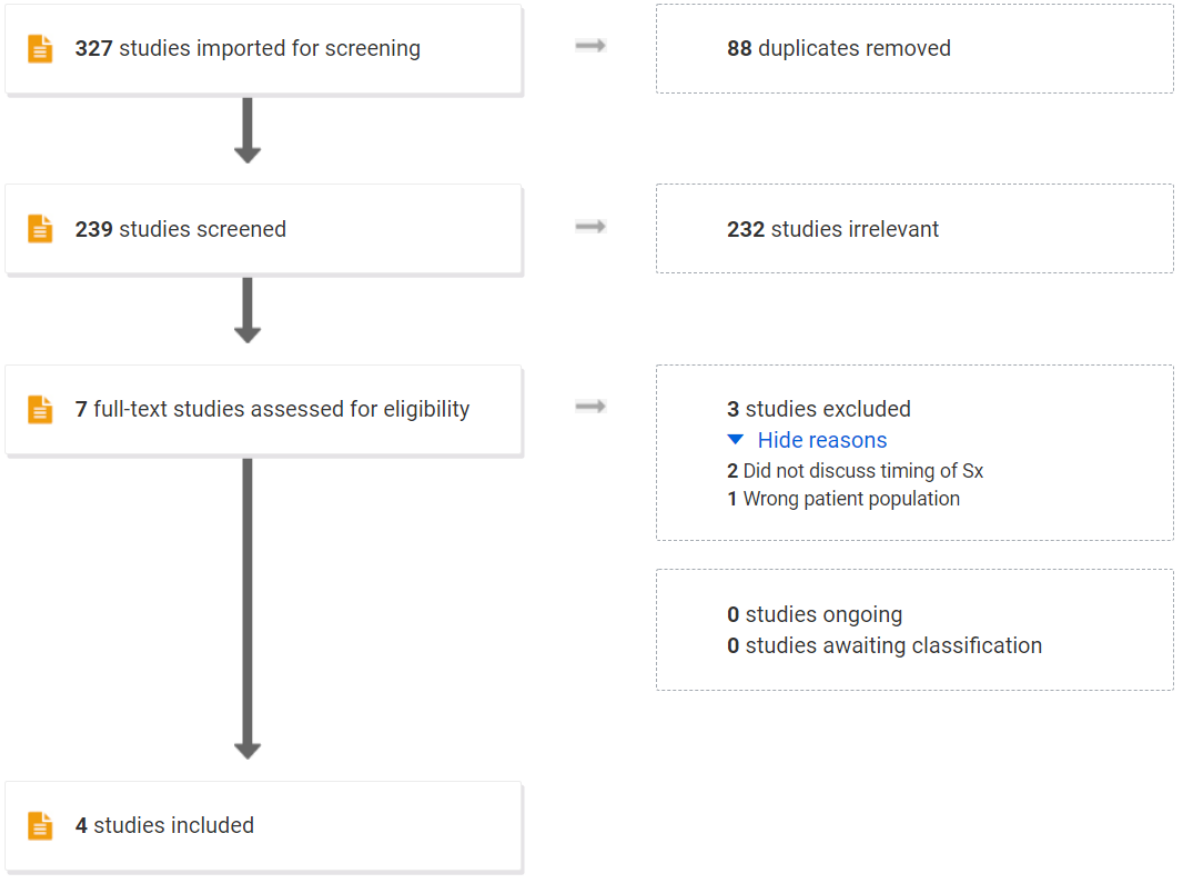

Figure 3. PRISMA flow chart from Covidence showing the flow of information through the different phases of clinical question 3.

The PRISMA flow chart shows the different screening phase for question 3 (Figure 3). A total of 239 studies were identified from the search strategy and imported into Covidence for screening. The inter-rater reliability for the title and abstract screening was 96.7% and full text review was 100%. The selection process yielded a final number of four studies for the

systematic review (Please see Appendix 9 for full list of studies). The only outcome endpoint in the PICO model that is addressed by these four studies is overall survival. The evidence summary, recommendation and practice point are created to address the overall survival endpoint only (see Appendix 10 & 11 for table summary and quality assessments).

An evidence statement form is provided which documents the synthesis and evaluation of the body of evidence to determine the grade of the recommendation, according to an NHMRC-approved method. Please see below for Evidence Statement Form.

Search Strategy

Complete search strategy clinical question 3

Database: Ovid MEDLINE(R) ALL <1946 to July 23, 2021>

Search Strategy:

---

8 exp Sarcoma, Ewing/ (7226)

9 ewing*.mp. (11908)

10 8 or 9 (11908)

14 (exp time factors/ or timing.mp.) and (surgery or surgeries or surgical or surgeon* or resect* or excision).mp. (213872)

15 ((delay* or postpone* or defer* or local control) adj3 (surgery or surgeries or surgical or resect* or excision)).mp. (11765)

16 14 or 15 (222938)

34 10 and 16 (214)

35 limit 34 to (english language and yr="1990 -Current")

46 (melanoma* or kaposi* or glioma* or carcinoma* or renal cell or brain or leuk?emia* or cell line* or "in vivo" or "in vitro").ti,ab. (3953955)

47 exp animals/ not exp humans/ (4864720)

48 (animal* or rat or rats or swine or mouse or mice or dog or dogs or canine*).mp. (7362254)

49 (case reports or systematic review or editorial).pt. (2929761)

50 (case report* or systematic review*).ti,ab. (604288)

51 47 or 48 or 49 or 50 (10323155)

52 46 or 47 or 48 or 49 or 50 (12271310)

60 34 not 52 (151)

Evidence Statement Form

Evidence Statement Form		
Component	Rating	Description
1. Evidence Base	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
2. Consistency	A	All studies consistent
3. Clinical Impact	B	Moderate
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats (absence of Australian data, but there is no reason to the overseas data are not applicable in Australia)

Appendix 1. Studies included in Clinical Question 1

Title	Authors	Published Year	Journal	Volume	Issue	Pages
Impact of radiation therapy facility volume on survival in patients with cancer	Tchelebi, L. T.; Shen, B.; Wang, M.; Gusani, N. J.; Walter, V.; Abrams, R.; Verma, V.; Zaorsky, N. G.	2021	Cancer	127	21	4081-4090
Preoperative Radiation Performed at a Nonsarcoma Center May Lead to Increased Wound Complications Following Resection in Patients With Soft Tissue Sarcomas	Ellison, C.; King, D; Neilson, J.; Wooldrife, A.; Charlson, J.; Hackbarth, D.; Johnstone C,; Bedi, M.	2021	Am J Clin Oncol	44		619-623
Improved survival for extremity soft tissue sarcoma treated in high-volume facilities	Abarca, Tyler; Gao, Yubo; Monga, Varun; Tanas, Munir R.; Milhem, Mohammed M.; Miller, Benjamin J.	2018	Journal of surgical oncology	117	7	1479-1486
Conformity to clinical practice guidelines, multidisciplinary management and outcome of treatment for soft tissue sarcomas	Ray-Coquard, I.; Thiesse, P.; Ranchere-Vince, D.; Chauvin, F.; Bobin, J. Y.; Sunyach, M. P.; Carret, J. P.; Mongodin, B.; Marec-Berard, P.; Philip, T.; Blay, J. Y.	2004	Annals of oncology : official journal of the European Society for Medical Oncology	15	2	307-15
Should soft tissue sarcomas be treated at high-volume centers? An analysis of 4205 patients	Gutierrez, Juan C.; Perez, Eduardo A.; Moffat, Frederick L.; Livingstone, Alan S.; Franceschi, Dido; Koniaris, Leonidas G.	2007	Annals of surgery	245	6	952-8
Monitoring referral and treatment in soft tissue sarcoma: study based on 1,851 patients from the Scandinavian Sarcoma Group Register	Bauer, H. C.; Trovik, C. S.; Alvegard, T. A.; Berlin, O.; Erlanson, M.; Gustafson, P.; Klepp, R.; Moller, T. R.; Rydholm, A.; Saeter, G.; Wahlstrom, O.; Wiklund, T.	2001	Acta orthopaedica Scandinavica	72	2	150-9
Relevance of Reference Centers in Sarcoma Care and Quality Item Evaluation: Results from the Prospective Registry of the Spanish	Martin-Broto, J.; Hindi, N.; Cruz, J.; Martinez-Trufero, J.; Valverde, C.; De Sande, L. M.; Sala,	2019	Oncologist	24	6	e338-e346

Group for Research in Sarcoma (GEIS)	A.; Bellido, L.; De Juan, A.; Rubio-Casadevall, J.; Diaz-Beveridge, R.; Cubedo, R.; Tendero, O.; Salinas, D.; Gracia, I.; Ramos, R.; Bague, S.; Gutierrez, A.; Duran-Moreno, J.; Lopez-Pousa, A.					
Trends in practice patterns and outcomes: A decade of sarcoma care in the United States	Song, Yun; Ecker, Brett L.; Tang, Rebecca; Maggino, Laura; Roses, Robert E.; DeMatteo, Ronald P.; Fraker, Douglas L.; Karakousis, Giorgos C.	2019	Surgical oncology	29		168-177
The European study on centralisation of childhood cancer treatment	Gatta, G.; Botta, L.; Comber, H.; Dimitrova, N.; Leinonen, M. K.; Pritchard-Jones, K.; Siesling, S.; Trama, A.; Van Eycken, L.; van der Zwan, J. M.; Visser, O.; Zagar, T.; Capocaccia, R.	2019	European Journal of Cancer	115		120-127
Soft Tissue Sarcoma of the Extremities: What Is the Value of Treating at High-volume Centers?	Lazarides, Alexander L.; Kerr, David L.; Nussbaum, Daniel P.; Kreulen, R. Timothy; Somarelli, Jason A.; Blazer, Dan G., 3rd; Brigman, Brian E.; Eward, William C.	2019	Clinical orthopaedics and related research	477	4	718-727
Overcoming a travel burden to high-volume centers for treatment of retroperitoneal sarcomas is associated with improved survival	Schmitz, Robin; Adam, Mohamed A.; Blazer, Dan G., 3rd	2019	World journal of surgical oncology	17	1	180
Soft tissue sarcoma - a population-based, nationwide study with special emphasis on local control	Sampo, Mika M.; Ronty, Mikko; Tarkkanen, Maija; Tukiainen, Erkki J.; Bohling, Tom O.; Blomqvist, Carl P.	2012	Acta oncologica (Stockholm, Sweden)	51	6	706-12
The clinical prognostic factors and treatment outcomes of adult patients with Ewing sarcoma	Jagodzinska-Mucha, P.; Lugowska, I.; Switaj, T.; Kosela-Paterczyk, H.;	2020	International journal of clinical oncology	25	11	2006-2014

	Wagrodzki, M.; Kozak, K.; Falkowski, S.; Morysinski, T.; Goryn, T.; Dawidowska, A.; Rutkowski, P.					
Adherence to Guidelines for Adult (Non-GIST) Soft Tissue Sarcoma in the Netherlands: A Plea for Dedicated Sarcoma Centers	Hoekstra, Harald J.; Haas, Rick L. M.; Verhoef, Cornelis; Suurmeijer, Albert J. H.; van Rijswijk, Carla S. P.; Bongers, Ben G. H.; van der Graaf, Winette T.; Ho, Vincent K. Y.	2017	Annals of surgical oncology	24	11	3279-3288
Is Treatment at a High-volume Center Associated with an Improved Survival for Primary Malignant Bone Tumors?	Malik, Azeem Tariq; Alexander, John H.; Khan, Safdar N.; Scharschmidt, Thomas J.	2020	Clinical orthopaedics and related research	478	3	631-642
Patterns of care of superficial soft tissue sarcomas: it is not always just a lump	Tan, Mark Ting Le; Thompson, Stephen R.; Schipp, Diane; Bae, Susie; Crowe, Philip J.	2018	Asia-Pacific journal of clinical oncology	14	5	e472-e478
Association of cancer center type with treatment patterns and overall survival for patients with sacral and spinal chordomas: An analysis of the National Cancer Database from 2004 to 2015	Wright, C. H.; Wright, J.; Cioffi, G.; Hdeib, A.; Kasliwal, M. K.; Kruchko, C.; Barnholtz-Sloan, J. S.; Sloan, A. E.	2020	Journal of Neurosurgery: Spine	32	2	311-320
Impact of centralization in primary retroperitoneal sarcoma treatment: analysis using hospital-based cancer registry data in Japan	Kimura, T.; Kawai, K.; Kandori, S.; Nitta, S.; Kojo, K.; Nagumo, Y.; Negoro, H.; Okuyama, A.; Higashi, T.; Kojima, T.; Nishiyama, H.	2020	International journal of clinical oncology	25	9	1687-1694
Does facility volume influence survival in patients with primary malignant bone tumors of the vertebral column? A comparative cohort study	Lazarides, Alexander L.; Kerr, David L.; Dial, Brian L.; Steele, John R.; Lane, Whitney O.; Blazer, Dan G., 3rd; Brigman, Brian E.; Mendoza-Lattes, Sergio; Erickson, Melissa M.; Eward, William C.	2020	The spine journal : official journal of the North American Spine Society	20	7	1106-1113
Relationship between treatment center case volume and survival for localized Ewing sarcoma: The role of radiotherapy timing	Lin, Timothy A.; Ludmir, Ethan B.; Liao, Kai-Ping; McAleer, Mary Frances; Bishop,	2020	Pediatric blood & cancer	67	11	e28685

	Andrew J.; Grosshans, David; McGovern, Susan; Woodhouse, Kristina D.; Paulino, Arnold C.; Yeboa, Debra Nana					
Association Between Treatment at High-Volume Facilities and Improved Overall Survival in Soft Tissue Sarcomas	Venigalla, Sriram; Nead, Kevin T.; Sebro, Ronnie; Guttmann, David M.; Sharma, Sonam; Simone, Charles B., 2nd; Levin, William P.; Wilson, Robert J., 2nd; Weber, Kristy L.; Shabason, Jacob E.	2018	International journal of radiation oncology, biology, physics	100	4	1004-1015

Appendix 2. Summary table Clinical Question 1 all studies

First Author	Year	Country	Patient source	Study period	Design	Definition of Specialised centre	Inclusion	Overall No. pt	Overall no. of centres	Specialised No.	Non specialised no.	RT Use (specialised v other)	Endpoints	Endpoints	2 year OS	5 yr OS	10 yr OS	Multivariate analysis	Comments
Abarca	2018	USA	NCDB	1998-2012	Retrospective cohort study	High vol=≥10 sarcoma per year	Extremity STS, age >18	7874	1200	2437 (31%)	5437 (69%)	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	No difference in limb salavge rate, RT rate but more Chemo in high Vol. Can't separate specific data for RT (quality, dose, toxicity). Data For OVERALL specialised
Bauer	2001	Sweden, Norway	Scandinavian Sarcoma Gorup	1986-1997	Retrospective cohort study	MDT sarcoma centre (referral before sx or not)	age 16, STS extremity/trunk wall	1851	8	1173 (68%)	563 (32%)	for intralesional or marginal excision: 54% vs 21% , P: not reported	5 yr Local recurrence: 20% v 70%, P=not reported	wide/compartmental margin: 66% v 11%, P=Not reported	–	–	–	–	LR comparsion is potentially biased as those treated at local centre without recurrence will not be referred to SSG sarcoma centre
Gatta	2019	6 European countries	RARECAREnet project	2000-2007	Retrospective cohort study	By case no.	age <15	4415 (16 childhood Ca), 429 Sarcoma	–	high vol. vs low	–	No details	–	–	–	–	–	adjusted risk of dying (RR).Bone sarcoma:Belgium, RR 0.81 (0.26-2.56) 0.72. Ireland RR 0.34 (0.11-1.04), 0.06. STS : No difference	No treatment details (Sx, RT, Chemo), General conclusion to support centralisation of childhood Ca treatment (17% lower risk fo dying for all childhood ca treated in high vol. centre. .Bone and STS no difference in survival by high or low vol, no RT/SX/chemo details. Follow up time and lost to follow up not reported
Gutierrez	2007	USA	Florida Cancer Database study	1981-2001	Retrospective cohort study	facilities grouped into 3 balanced percentile ranges by surgical volume. Top 1/3 vs 2/3	Soft tissue (1st presentation for Sx), extremity and RPS	4205	256	7 hospitals performed 1504 cases (32.2%)	3169 cases	43% v 24.2% (p<0.001)	30 & 90 day mortality 0.7% v 1.5% (p 0.028), 1.%v 3.6% (p<0.001)	Amputation rate 9.4% v 13.8% (p=0.048)	–	37.4% v 33.2% (p=0.002)	15.9% v 11.6% (p=0.002)	Overall survival: high vol=1, low Vol RR of death 1.292 (1.003-1.663, p= 0.047)	high RT use in high vol. centre. No LR data. High Volume centres: younger, more high grade, more >10cm, more extremity, more RT and chemo use. Treatment at a HVC was an independent predictor of good outcome. Better OS for treatment (Sx/RT/Chemo) at high vol centre, no specific RT endpoint by volume.
Hoekstra	2017	Netherlands	Netherlands Cancer Registry	2006-2011	Retrospective cohort study	high-volume >= 10 sarcoma resections annually	age >18, STS	3317	96	5 sarcoma centres. 12% of hospitals accounted for 50% resection	–	40% had RT. High RT use when Sx was performed in high vol, academic and sarcoma centers. No difference in RT after R1 resection netween academic and general centres after adjustment for case mix	following adjustment for case mix factors, resection without prior pathological confimation was considerably higher in low-vol, general hospitals and no sarcoma research	–	–	No % given but reported no difference in OS between hospital categories	–	following adjustment for case mix factors, high vol centres less R2 resection, adjusted OR 0.54)	Higher RT use in high vol but no LR details. The odds for sarcoma patients to receive radiotherapy appeared higher when surgery was performed in high-volume hospitals, academic hospitals, and sarcoma research centers. The same was true regarding adjuvant radiotherapy following R1 resection, although this effect was no longer significant between academic and general hospitals after adjustment for case mix factors. No details on follow up period/lost to follow up, hence one star on outcome
Jagodzinska-Mucha	2020	Poland	Maria Sklodowska-Curie National Research Institute of Oncology	2008-2018	Retrospective cohort study	Initial treatment at referral center or within 3 months from biopsy v > 3 months	adult, Ewing	180	1	157	23	81% had RT as combination therapy (no breakdown)	5 yr PFS 28% v 14%, p=0.001	–	–	–	–	Cox proportional hazard model: treatment <3 months from Biopsy. HR 1.625 (0.969-2.759, p=0.066)	treatment at sarcoma centre with 3 months v > 3months. No RT/Sx/chemo details. NO local recurrence details. Can only conclude early referral to sarcoma has better PFS
Kimura	2020	Japan	Hospital based cancer registry	2008-2015 (cohort A 2008-2009, cohort B 2012-2015)	Retrospective cohort study	high volume >=3 patients/year	RPS	2391	541	2 hospitals had >10 pts /year, 95% <3 pts/yr	–	higher RT use in high volume centre (cohort A, 13.2% v 9%, cohort B 9.1% v 6.2%)	–	–	–	69.2% v 55.5%, p=0.38	–	–	only survival data in Cohort A, No RT details, No Multivariate analysis, poor quality
Lazarides	2019	USA	NCDB	1998-2012	Retrospective cohort study	High vol.≥20 pts per year	STS extremity	25406	1270 (9=high vol.)	3310 (13%)	22096 (87%)	50% v 49%, p=0.23. More preop RT:40.5% v 21.7%, p<0.001. OR 1.62 (1.39-1.88, p<0.001) after controlling for grade, size and margin status. Days to RT 73 days v 77 days, p=0.023	positive margin 10% v 17%, p<0.001. No difference in amputation (5%v 5%). More radical resection in high vol 65% v 45%, p<0.001.	30-day mortality 0.3% v 0.4%, p=0.018	–	better OS seen in all grades	–	lower risk of death in high vol. HR 0.81, 0.75-0.88, p<0.001	No RT quality details, no local recurrence data
Lazarides	2020	USA	NCDB	1998-2012	Retrospective cohort study	High vol. ≥5 pts over study period	primary malignant bone tumours of the vertebral column	733	–	327 (44.6%)	406 (55.4%)	48% v 42% , p=0.1316	more likely to have Sx: 91% v 80%, p<0.001. en bloc resection more likely in high vol, centres: OR 2.11 (1.5-2.96, p<0.001, 48% v 30%, P<0.0001)	no difference in margin status, positive margin 32% v 35%, p=0.15		all histologies:71% v 58% , p<0.0001. Osteosarcoma 50% v 29%, p=0.0112. Chordoma 78% v 63%, p=0.0007. Chondrosarcoma 72% v 67%, p=0.33		better survival at high vol. centre: HR 0.75 (0.5800.97, p=0.0289)	No RT details, no local recurrence data
Lin	2020	USA	NCDB	2004-2014	Retrospective cohort study	mean case vol into quartiles (0.19, 0.54, 1.09, 2.11 per year)	Localised Ewing treated by Chemo + RT	391	171	Q1 76, Q2 52, Q3 28, Q4 15.	–	Delayed RT (≥16 wks from chemo) in Q1-4: 42.2%, 31.7%, 31%, 30.9%	–	–	–	Worse 5yr OS Q1 v Q2-4: 60% v 72.4%, p=0.024. For Q2-4: 5yr OS Q4 79.4% v Q2-3 69.1%, p=0.024	–	–	–	Lowest OS in Q1 centre, partly explained by highest rates of delayed RT. Treatment at highest vol centres had better OS but appears independent of RT timing. No local recurrence data. No RT quality.
Malik	2020	USA	NCDB	2004-2015	Retrospective cohort study	high-volume = at least 20 patients per throughout study period	Bone sarcoma of extremity or pelvis	14039	840	2115 (15%)	11924 (85%)	High vol 13% vs low vol 17%, p<0.001	Positive margin: high vol 4% v low vol. 8%, P<0.001	–	–	High vol 65% v 61%, p=0.003	–	more limb salvage surgery OR 1.34 (1.14-1.59, p=0.001). Lower mortality (HR 0.85, 0.77-0.93, P<0.001)	No RT quality details, no local recurrence data. SB: Very similar to Lazarides 2019 paper; only 15% of pts managed at LVC (simialr to STS-E), ?okay to apply this to Australian context? Very different medicare structure, quite surprising that substantial proportions of patients with ewing sarcoma and osteosarcoma being managed at LVC (this is less likely to happen in Aus, I thought?)
Martin-Broto	2019	Spain	Registry of the Spanish Group for Research in Sarcomas (GEIS)	2004-2011	Prospective cohort study	Research Centre = multidisciplinary team experienced in sarcoma + weekly operative sarcoma committee, minimum of 70 patients with STS/ year, and at least a defined regional referral policy	Soft tissue sarcoma extremity or trunk wall	622	31	2 centres, 285 pts (46%)	337 (54%)	no difference b/w research centres v others, 80% for stage 3	trend for better median RFS 63.3 months v 39.6 months (p=0.1). 3 yr RFS better for biopsy in research centre 66% v 46.4%, p=0.019	for pts with mets at Dx, pts on research centre had better median OS 30.5 months v 18.5 months (p=0.036)	–	3 yr acturial OS: 82% v 70.4% , p=0.003	–	Not done	High local recurrence in research centre but referral bias as ot with local recurrence were referred to research centre and registered under research centre. NO RT details; can't intrepret local recurrence data
Ray-Coquard	2004	France	Rhone-Alpes region	1999-2001	Retrospective cohort study	Conformity to clinical practice guidelines	age >18, localized or locally advanced soft tissue sarcomas	100	2	MDT 69, Cancer network 67	No MDT 31, no cancer network 33	Rate of conformaity with COG of RT=81%	Local relapse by conformity of RT to CPG: yes 30% v no 63%, p=0.007	–	–	–	–	pre Sx MDT discussion, management in reference centre and within cancer network independently predicted conformity to CPG.	RT: conformity to CRG less local relapse, reference centre predicts for conformity to CPG.
Sampo	2012	Finland	Finnish Cancer Registry	1998-2001	Retrospective cohort study	high volume centres = centres treating 2/3 of the patients (of the final surgeries) during the study period intermediate-volume centres = hospitals treating 3-17 patients during the study period low-volume centres = hospitals treating 1-2 patients during the study period	age >18, STS extremity and trunk	219	24 (3 high vol, 5 intermediat e, 16 low)	153	intermediate 40, low 22	RT use: HVC 75.2%, IVC 56.3%, LVC 31.6%, p<0.0001	5 year Local recurrence free rate: HVC 82%, IVC 61%, LVC 69%, p=0.046. Local recurrence rate decreased as surgical bol of the centre increased: RR per 10 pts 0.914 (0.851-0.97, p=0.006). Wide reseaection 31.4% v 17.5% c14.2%, p=0.004	sarcoma specific survival HVC 71%, IVC 59%, LVC 66%, p=0.237. Metastaese free survival 67%v 61%v 78%, p=0.283	–	–	–	Not done	Higher RT use in high vol centre, better 5 year local control at high vol centre (NB 5year 82% is lower than expected)
Schmitz	2019	USA	NCDB	1998-2012	Retrospective cohort study	low-volume centre = median annual case volume of 1 case/year, high-volume centre = median annual case volume of 10 cases/year	RPS	2599	–	long distance/high volume 1250	short distance/low volume 1309	LT/HV 29% vs ST/LV 25%, p=0.044	30 day mortality LT/HV 1.2% v 2.8%, p=0.0026	R2 resection LT/HV2.6% v 4.4%, p=0.003	–	LT/HV 63% v 53%, p<0.0001	–	OS: long distance/high vol HR 0.726 (0.601-0.878, p=0.0009)	NCDB: No RT details, NO local recurrence data

Song	2019	USA	NCDB	2005-2014	Retrospective cohort study	HVH = Hospitals that exceeded the 90th percentile in the number of patients treated per year	extra-abdominal soft tissue sarcoma	55212	577	57 centers	520 centers	resected stage 1-3: 2005-2009: preop RT HVH 35.9% v 19%, 2010-2014 HVH 43.2% v 28.2%	–	–	–	3 yr OS High vol 69.5% v 63.2%, p<0.001	–	High vol: 8% hazard reduction in all cause death (HR 0.92, 0.89-0.95, p<0.001). Only vol, not academic status was associated with OS. High vol: higher R0 resection HR 1.27, 1.2-1.15,	More RT use for stage 1-3 in HVC. NCDB: no RT details, no local recurrence
Tan	2018	Australia	Two sarcoma centres	1995-2013	Retrospective cohort study	initial management at sarcoma centres vs elsewhere, all had further Rx at sarcoma centres	age >18, superficial soft tissue sarcoma	89	2	31 (35%)	58 (65%)	61% v 10%, P<0.0005	more than one operation: 26% v 78%, p<0.0005. final clear margins: 77% v74%, p 0.62	Local recurrence 6.5% v 24%, p=0.038	–	–	–	–	location of initial management for predictor for local recurremce, distant mets and disease specific survivlal	small no., didn't analyse data by RT use.
Venigalla	2018	USA	NCDB	2004-2013	Retrospective cohort study	Facilities in top 1 percentile (99th percentile) by case volume (79-252 cases) over the study period	age>18, Non-metastatic STS treated with definitive surgery and either pre-op or post-op EBRT. Both Sx and RT at the reporting facility (pts treated at multiple centres were excluded)	9025	973	1578 (17%)	7447 (83%)	Preop RT: high vol 37% v low vol 19%. Postop RT: high vol 63% v 81%, p<0.001	Negative margin: high vol 81% v low vol 72%, p<0.001	–	–	72.2% v 67.4%	57.1% v 49%, p<0.001	propensity-score matching. HV v LV, imporved overall survival, HR 0.87, 0.8-0.95, P=0.001. test for interaction b/w HV and academic centes, Non significant.i.e OS benefit assooiated with HV was not modified bu treatment at academic centres	All had definitive Sx and RT at one centre, probably can generalise the data to RT (NCDB, no RT details, No local recurrence data)
Wright	2020	USA	NCDB	2004-2015	Retrospective cohort study	Community cancer program (CCP): 100-500 ca cases/yr. Comprehensive community cancer program (CCCP): 100-500 cases/yr. Academic research program (ARP): postgraduate eductaion in4+ specialites+ >5- cancer cases. Integrated network cancer program (INCP): multiple facilities provdiign integrated cancer care and comprehensive services	vertebral column and sarcal chordoma	1266	–	ARP: 56.2, INCP:9.2%	CCP: 3.4%. CCCP: 18.1%	No difference in RT use and time to RT by centres	CCP and CCCP were less likely to have Sx.	–	Adjusted median survival: 131 months v 124 months v 109 months v 79 months	ARP 76.08% v INCP 70.3% V CCCP 61.5% v CCP 52.7%	–	ARP: 1, CCP HR 1.98 p0.018, CCCP HR 1.29 p=0.089, INCP HR 1.19 p=0.425	ARP is associated with increased odds of treatment associated with improved OS. No difference in odds of receiving RT/time to RT. NCDB (No RT details/location, No local recurrence)
Ellison	2021	USA	single centre	2000-2016	Retrospective cohort study	all had Sx at Medical College of Wisconsin, RT some at academic centre (>500 all Ca cases/yr, postgraduate education > 4 areas) and some at community cancer centre (100-500 Ca cases/ yr, no post graduate program). None at comprehensive community cancer centre.	Soft tissue sarcoma extremity or trunk wall	191	1	117	74	117 (61.3%, of those 29% IMRT) at academic centre and 74 (38.7%, of those 38% IMRT) at community centers.	Postop wound complication: academic 21% vs community cancer centre 39%, p=0.009	IMRT did not significantly impact wound complications at academic institutions (P= 0.08), however, in the community, the use of IMRT significantly decreased wound complication (59% v 7%, p<0.0001) from 59% versus 7% (P<0.0001).	–	–	–	both location of tumor (P= 0.0012, 95% CI: 0.03-0.45, OR: 0.13) and RT performed at a community center (P= 0.02, 95% CI: 1.13-4.48, OR: 2.25) remained significant in correlation with postoperative wound complication	retrospective single Sx centre. No local recurrence/survival data
Tchelebi	2021	USA	NCDB	2004-2013	Retrospective cohort study	by volume, low, intermediate, high and very high	soft tissue sarcoma treated by Rt with curative intent	2678	814	high: 717, very high:236	Low: 628, intermediate:618	all had RT	–	–	–	Neoadjuavnt and adjuavant RT: facility had no impact on OS.	–	adjust for age, gender, clinical stage, insurance but not size, Grade, histology	

Appendix 3. Quality Assessment Clinical Question 1

Study	Title	NHMRC Level of Evidence	Risk of Bias (Newcastle Ottawa scale for cohort study)			
			Selection	Comparability	Outcome	Overall
Abarca 2018	Improved survival for extremity soft tissue sarcoma treated in high-volume facilities	III-3	4	1	3	Good Quality
Bauer 2001	Monitoring referral and treatment in soft tissue sarcoma: study based on 1,851 patients from the Scandinavian Sarcoma Group Register	III-3	2	1	3	Fair Quality
Gatta 2019	The European study on centralisation of childhood cancer treatment	III-2	2	0	1	Poor Quality
Gutierrez 2007	Should soft tissue sarcomas be treated at high-volume centers? An analysis of 4205 patients	III-2	4	1	2	Good Quality
Hoekstra 2017	Adherence to Guidelines for Adult (Non-GIST) Soft Tissue Sarcoma in the Netherlands: A Plea for Dedicated Sarcoma Centers	III-3	4	1	1	Poor Quality
Jagodzinska-Mucha 2020	The clinical prognostic factors and treatment outcomes of adult patients with Ewing sarcoma	III-3	4	2	3	Good Quality
Kimura 2020	Impact of centralization in primary retroperitoneal sarcoma treatment: analysis using hospital-based cancer registry data in Japan	III-3	4	0	1	Poor Quality
Lazarides 2019	Soft Tissue Sarcoma of the Extremities: What Is the Value of Treating at High-volume Centers?	III-3	4	2	3	Good Quality
Lazarides 2020	Does facility volume influence survival in patients with primary malignant bone tumors of the vertebral column? A comparative cohort study	III-3	4	2	3	
Lin 2020	Relationship between treatment center case volume and survival for localized Ewing sarcoma: The role of radiotherapy timing	III-3	4	1	2	Good Quality
Malik 2020	Is Treatment at a High-volume Center Associated with an Improved Survival for Primary Malignant Bone Tumors?	III-3	4	2	2	Good Quality
Martin-Broto 2019	Relevance of Reference Centers in Sarcoma Care and Quality Item Evaluation: Results from the Prospective Registry of the Spanish Group for Research in Sarcoma (GEIS)	III-2	4	0	2	Poor Quality
Ray-Coquard 2004	Conformity to clinical practice guidelines, multidisciplinary management and outcome of treatment for soft tissue sarcomas	III-3	4	1	3	Good Quality
Sampo 2012	Soft tissue sarcoma - a population-based, nationwide study with special emphasis on local control	IV	4	0	2	Poor Quality
Schmitz 2019	Overcoming a travel burden to high-volume centers for treatment of retroperitoneal sarcomas is associated with improved survival	III-3	4	2	3	Good Quality
Song 2019	Trends in practice patterns and outcomes: A decade of sarcoma care in the United States	III-3	4	2	3	Good Quality
Tan 2018	Patterns of care of superficial soft tissue sarcomas: it is not always just a lump	III-3	4	2	2	Good Quality
Venigalla 2018	Association Between Treatment at High-Volume Facilities and Improved Overall Survival in Soft Tissue Sarcomas	III-3	4	2	3	Good Quality
Wright 2020	Association of cancer center type with treatment patterns and overall survival for patients with sacral and spinal chordomas: An analysis of the National Cancer Database from 2004 to 2015	III-3	4	2	1	Poor Quality
Ellison 2021	Preoperative Radiation Performed at a Nonsarcoma Center May Lead to Increased Wound Complications Following Resection in Patients With Soft Tissue Sarcomas	III-3	4	2	3	Good Quality
Tchelebi 2021	Impact of radiation therapy facility volume on survival in patients with cancer	III-3	4	1	3	Fair Quality

Appendix 4. Clinical Question 1 Outcomes Summary Tables

Outcome 1: Local Recurrence

First Author	Year	Country	Patient source	Study period	Design	Definition of Specialised centre	Inclusion	Overall No. pt	Overall no. of centres	Specialised No.	Non specialised no.	RT Use (specialised v other)	Endpoints	Endpoints
Bauer	2001	Sweden, Norway	Scandinavian Sarcoma Gorup	1986-1997	Retrospective cohort study	MDT sarcoma centre (referral before sx or not)	age 16, STS extremity/trunk wall	1851	8	1173 (68%)	563 (32%)	for intralesional or marginal excision: 54% vs 21% , P: not reported	5 yr Local recurrence: 20% v 70%, P=not reported	wide/compartmental margin: 66% v 11%, P=Not reported
Ray-Coquard	2004	France	Rhone-Alpes region	1999-2001	Retrospective cohort study	Conformity to clinical practice guidelines	localized or locally advanced soft tissue sarcomas	100	2	MDT 69, Cancer network 67	No MDT 31, no cancer network 33	Rate of conformaity with COG of RT=81%	Local relapse by conformity of RT to CPG: yes 30% v no 63%, p=0.007 u	–
Sampo	2012	Finland	Finnish Cancer Registry	1998-2001	Retrospective cohort study	high volume centres = centres treating 2/3 of the patients (of the final surgeries) during the study period intermediate-volume centres = hospitals treating 3-17 patients during the study period low-volume centres = hospitals treating 1-2 patients during the study period	STS extremity and trunk	219	24 (3 high vol, 5 intermediate, 16 low)	153	intermediate 40, low 22	RT use: HVC 75.2%, IVC 56.3%, LVC 31.6%, p<0.0001	5 year Local recurrence free rate: HVC 82%, IVC 61%, LVC 69%, p=0.046. Local recurrence rate decreased as surgical bol of the centre increased: RR per 10 pts 0.914 (0.851-0.97, p=0.006). Wide reseaection 31.4% v 17.5% c14.2%, p=0.004	sarcoma specific survival HVC 71%, IVC 59%, IVC 66%, p=0.237. Metastaese free survival 67%v 61%v 78%, p=0.283
Tan	2018	Australia	Two sarcoma centres	1995-2013	Retrospective cohort study	initial management at sarcoma centres vs elsewhere, all had further Rx at sarcoma centres	superficial soft tissue sarcoma	89	2	31 (35%)	58 (65%)	61% v 10%, P<0.0005	more than one operation: 26% v 78%, p<0.0005. final clear margins: 77% v74%, p 0.62	Local recurrence 6.5% v 24%, p=0.038

Outcome 2: Wound Complication

First Author	Year	Country	Patient source	Study period	Design	Definition of Specialised centre	Inclusion	Overall No. pt	Overall no. of centres	Specialised No.	Non specialised no.	RT Use (specialised v other)	Endpoints	Endpoints	2 year OS	5 yr OS	10 yr OS	Multivariate analysis	Comments
Ellison	2021	USA	single centre	2000-2016	Retrospective cohort study	all had Sx at Medical College of Wisconsin, RT some at academic centre (>500 all Ca cases/yr, postgraduate education > 4 areas) and some at community cancer centre (100-500 Ca cases/ yr, no post graduate program). None at comprehensive community cancer centre.	Soft tissue sarcoma extremity or trunk wall	191	1	117	74	117 (61.3%, of those 79% IMRT) at academic centre and 74 (38.7%, of those 38% IMRT) at community centers.	Postop wound complication: academic 21% vs community cancer centre 39%, p=0.009	IMRT did not significantly impact wound complications at academic institutions (P= 0.08), however, in the community, the use of IMRT significantly decreased wound complication (59% v 7%, p<0.0001) from 59% versus 7% (P<0.0001).	–	–	–	both location of tumor (P= 0.0012, 95% CI: 0.03-0.45, OR: 0.13) and RT performed at a community center (P= 0.02, 95% CI: 1.13-4.48, OR: 2.25) remained significant in correlation with postoperative wound complication	retrospective single Sx centre. No local recurrence/survival data

Appendix 5 . List of studies for Clinical Question 2

Title	Authors	Published Year	Journal	Volume	Issue	Pages
Overcoming a travel burden to high-volume centers for treatment of retroperitoneal sarcomas is associated with improved survival	Schmitz, R.; Adam, M. A.; Blazer, D. G.	2019	World Journal of Surgical Oncology	17	1	180
Conformity to Clinical Practice Guidelines at Initial Management in Adult Soft Tissue and Visceral Tumors since the Implementation of the NetSarc Network in Eastern France	Gantzer, Justine; Di Marco, Antonio; Fabacher, Thibaut; Weingertner, Noelle; Delhorme, Jean-Baptiste; Brinkert, David; Bierry, Guillaume; Ghnassia, Jean-Pierre; Jegu, Jeremie; Kurtz, Jean-Emmanuel	2019	The oncologist	24	8	e775-e783
Improving Long-Term Outcomes for Patients with Extra-Abdominal Soft Tissue Sarcoma Regionalization to High-Volume Centers, Improved Compliance with Guidelines or Both?	Bagaria, Sanjay P.; Chang, Yu-Hui; Gray, Richard J.; Ashman, Jonathan B.; Attia, Steven; Wasif, Nabil	2018	Sarcoma	2018		8141056
Overall survival after resection of retroperitoneal sarcoma at academic cancer centers versus community cancer centers: An analysis of the National Cancer Data Base	Berger, N. G.; Silva, J. P.; Mogal, H.; Clarke, C. N.; Bedi, M.; Charlson, J.; Christians, K. K.; Tsai, S.; Gamblin, T. C.	2018	Surgery (United States)	163	2	318-323
The Volume-Outcome Relationship in Retroperitoneal Soft Tissue Sarcoma: Evidence of Improved Short- and Long-Term Outcomes at High-Volume Institutions	Bagaria, S. P.; Neville, M.; Gray, R. J.; Gabriel, E.; Ashman, J. B.; Attia, S.; Wasif, N.	2018	Sarcoma	2018		3056562
Hospital volume threshold for the treatment of retroperitoneal sarcoma	Adam, M. A.; Moris, D.; Behren, S.; Nussbaum, D. P.; Jawitz, O.; Turner, M.; Lidsky, M.; Blazer, D.	2019	Anticancer research	39	4	2007-2014
Surgery in reference centers improves survival of sarcoma patients: a nationwide study	Blay, J. Y.; Honore, C.; Stoeckle, E.; Meeus, P.; Jafari, M.; Gouin, F.; Anract, P.; Ferron, G.; Rochwerger, A.; Ropars, M.; Carrere, S.; Marchal, F.; Sirveaux, F.; Di Marco, A.; Le Nail, L.	2019	Annals of oncology	30	7	1143-1153

	R.; Guiramand, J.; Vaz, G.; Machiavello, J. C.; Marco, O.; Causeret, S.; Gimbergues, P.; Fiorenza, F.; Chaigneau, L.; Guillemin, F.; Guilloit, J. M.; Dujardin, F.; Spano, J. P.; Ruzic, J. C.; Michot, A.; Soibinet, P.; Bompas, E.; Chevreau, C.; Duffaud, F.; Rios, M.; Perrin, C.; Firmin, N.; Bertucci, F.; Le Pechoux, C.; Le Loarer, F.; Collard, O.; Karanian-Philippe, M.; Brahmi, M.; Dufresne, A.; Dupre, A.; Ducimetiere, F.; Giraud, A.; Perol, D.; Toulmonde, M.; Ray-Coquard, I.; Italiano, A.; Le Cesne, A.; Penel, N.; Bonvalot, S.					
Predictors of surgical quality for retroperitoneal sarcoma: Volume matters	Maurice, M. J.; Yih, J. M.; Ammori, J. B.; Abouassaly, R.	2017	Journal of Surgical Oncology	116	6	766-774
Primary retroperitoneal sarcomas: A multivariate analysis of surgical factors associated with local control	Bonvalot, S.; Rivoire, M.; Castaing, M.; Stoeckle, E.; Le Cesne, A.; Blay, J. Y.; Laplanche, A.	2009	Journal of clinical oncology	27	1	31-37
Desmoplastic small round cell tumor: A nationwide study of a rare sarcoma	Stiles, Z. E.; Dickson, P. V.; Glazer, E. S.; Murphy, A. J.; Davidoff, A. M.; Behrman, S. W.; Bishop, M. W.; Martin, M. G.; Deneve, J. L.	2018	Journal of Surgical Oncology	117	8	1759-1767
Evaluation of clinical outcomes and prognostic factors for synovial sarcoma arising from the extremities	Sakabe, T.; Murata, H.; Konishi, E.; Takeshita, H.; Ueda, H.; Matsui, T.; Horie, N.; Yanagisawa, A.; Kubo, T.	2008	Medical Science Monitor	14	6	CR305-CR310
Local recurrences after the treatment of soft tissue malignant fibrous histiocytoma (unclassified pleomorphic sarcoma) of the limbs	Lytvynenko, O. O.; Konovalenko, V. F.; Ryzhov, A. Y.	2019	Wiadomosci lekarskie (Warsaw, Poland : 1960)	72	8	1523-1526

Tumor-associated mortality and prognostic factors in myxofibrosarcoma - A retrospective review of 109 patients	Gilg, M. M.; Sunitsch, S.; Leitner, L.; Bergovec, M.; Szkandera, J.; Leithner, A.; Liegl-Atzwanger, B.	2020	Orthopaedics and Traumatology: Surgery and Research	106	6	1059-1065
Influence of unplanned excisions on the outcomes of patients with stage III extremity soft-tissue sarcoma	Traub, F.; Griffin, A. M.; Wunder, J. S.; Ferguson, P. C.	2018	Cancer	124	19	3868-3875
Retroperitoneal sarcomas: Patterns of care at diagnosis, prognostic factors and focus on main histological subtypes: A multicenter analysis of the French Sarcoma Group	Toulmonde, M.; Bonvalot, S.; Meeus, P.; Stoeckle, E.; Riou, O.; Isambert, N.; Bompas, E.; Jafari, M.; Delcambre-Lair, C.; Saada, E.; Le Cesne, A.; Le pechoux, C.; Blay, J. Y.; Piperno-Neumann, S.; Chevreau, C.; Bay, J. O.; Brouste, V.; Terrier, P.; Ranchere-Vince, D.; Neuville, A.; Italiano, A.	2014	Annals of oncology	25	3	735-742
Soft tissue sarcoma of the hand: Is unplanned excision a problem?	Lans, Jonathan; Yue, Kai-Lou C.; Castelein, Rene M.; Chen, Neal C.; Lozano-Calderon, Santiago A.	2019	European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology	45	7	1281-1287
Identifying the Minimum Volume Threshold for Retroperitoneal Soft Tissue Sarcoma Resection: Merging National Data with Consensus Expert Opinion	Villano, A. M.; Zeymo, A.; Chan, K. S.; Shara, N.; Al-Refaie, W. B.	2019	Journal of the American College of Surgeons			
Textbook outcomes among patients undergoing retroperitoneal sarcoma resection	Moris, D.; Cerullo, M.; Nussbaum, D. P.; Blazer, D. G.	2020	Anticancer research	40	4	2107-2115
A need for clarity on surgical management of breast sarcoma: Scottish sarcoma network guidelines and regional audit	Lo, S.; Foster, N.; Campbell, L.; White, J.; Nixon, I.; Mansell, J.; McCleery, M.; Whyte, L.; Cowie, F.	2020	Journal of Plastic, Reconstructive and Aesthetic Surgery			

Clinical outcome of recurrent giant cell tumor of the extremity in the era before molecular target therapy: The Japanese Musculoskeletal Oncology Group study	Takeuchi, A.; Tsuchiya, H.; Ishii, T.; Nishida, Y.; Abe, S.; Matsumine, A.; Kawai, A.; Yoshimura, K.; Ueda, T.	2016	BMC musculoskeletal disorders	17	1	306
Management of Sarcoma in Adolescents and Young Adults: An Australian Population-Based Study	White, V. M.; Orme, L. M.; Skaczkowski, G.; Pinkerton, R.; Coory, M.; Osborn, M.; Bibby, H.; Nicholls, W.; Conyers, R.; Phillips, M. B.; Harrup, R.; Walker, R.; Thompson, K.; Anazodo, A.	2019	Journal of Adolescent and Young Adult Oncology	8	3	272-280
Surgical treatment is decisive for outcome in chondrosarcoma of the chest wall: A population-based Scandinavian Sarcoma Group study of 106 patients	Widhe, B.; Bauer, H. C. F.	2009	Journal of thoracic and cardiovascular surgery	137	3	610-614
An analysis of factors related to recurrence of myxofibrosarcoma	Kikuta, K.; Kubota, D.; Yoshida, A.; Suzuki, Y.; Morioka, H.; Toyama, Y.; Kobayashi, E.; Nakatani, F.; Chuuman, H.; Kawai, A.	2013	Japanese Journal of Clinical Oncology	43	11	1093-1104
Soft tissue sarcoma in children, adolescents and young adults: Outcomes according to compliance with international initial care guidelines	Collignon, C.; Carton, M.; Brisse, H. J.; Pannier, S.; Gauthier, A.; Sarnacki, S.; Tilea, B.; Savignoni, A.; Helfre, S.; Philippe-Chomette, P.; Cardoen, L.; Boccara, O.; Pierron, G.; Orbach, D.	2020	European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology	46	7	1277-1286
Practice referral patterns and outcomes in patients with primary retroperitoneal sarcoma in British Columbia	Merchant, S.; Cheifetz, R.; Knowling, M.; Khurshed, F.; McGahan, C.	2012	American Journal of Surgery	203	5	632-638
Should Soft Tissue Sarcomas be Treated at a Specialist Centre?	Bhangu, A. A.; Beard, J. A. S.; Grimer, R. J.	2004	Sarcoma	8	1	1-Jun
Biopsies in the Community Lead to Postoperative Complications in Soft Tissue Sarcomas	Bedi, Meena; King, David M.; Hackbarth, Donald A.; Charlson, John A.; Baynes, Keith; Neilson, John C.	2015	Orthopedics	38	9	e753-9

Survival impact of centralization and clinical guidelines for soft tissue sarcoma (A prospective and exhaustive population-based cohort)	Derbel, Olfa; Heudel, Pierre Etienne; Cropet, Claire; Meeus, Pierre; Vaz, Gualter; Biron, Pierre; Cassier, Philippe; Decouvelaere, Anne-Valerie; Ranchere-Vince, Dominique; Collard, Olivier; De Laroche, Eric; Thiesse, Philippe; Farsi, Fadila; Cellier, Dominic; Gilly, Francois-Noel; Blay, Jean-Yves; Ray-Coquard, Isabelle	2017	PLoS ONE	12	2	e0158406
Treatment-related prognostic factors in managing osteosarcoma around the knee with limb salvage surgery: A lesson from a long-term follow-up study	Hu, J.; Zhang, C.; Zhu, K.; Zhang, L.; Cai, T.; Zhan, T.; Luo, X.	2019	BioMed Research International	2019		3215824
Impact of early access to multidisciplinary care on treatment outcomes in patients with skull base chordoma	Freeman, J. L.; DeMonte, F.; Al-Holou, W.; Gidley, P. W.; Hanna, E. Y.; Kupferman, M. E.; Su, S. Y.; Raza, S. M.	2018	Acta Neurochirurgica	160	4	731-740
Impact of specialist management on survival from radiation-associated angiosarcoma of the breast	Feinberg, L.; Srinivasan, A.; Singh, J. K.; Parry, M.; Stevenson, J.; Jeys, L.; Grimer, R.; Peart, F.; Warner, R.; Ford, S.; Gourevitch, D.; Hallissey, M.; Desai, A.	2018	The British journal of surgery	105	4	401-409
Improved survival using specialized multidisciplinary board in sarcoma patients	Blay, J. Y.; Soibinet, P.; Penel, N.; Bompas, E.; Duffaud, F.; Stoeckle, E.; Mir, O.; Adam, J.; Chevreau, C.; Bonvalot, S.; Rios, M.; Kerbrat, P.; Cupissol, D.; Anract, P.; Gouin, F.; Kurtz, J. E.; Lebbe, C.; Isambert, N.; Bertucci, F.; Toumonde, M.; Thyss, A.; Piperno-Neumann, S.; Dubray-Longeras, P.;	2017	Annals of oncology : official journal of the european society for medical oncology	28	11	2852-2859

	Meeus, P.; Ducimetiere, F.; Giraud, A.; Coindre, J. M.; Ray-Coquard, I.; Italiano, A.; Le Cesne, A.					
Survival Benefit of the Surgical Management of Retroperitoneal Sarcoma in a Reference Center: A Nationwide Study of the French Sarcoma Group from the NetSarc Database	Bonvalot, S.; Gaignard, E.; Stoeckle, E.; Meeus, P.; Decanter, G.; Carrere, S.; Honore, C.; Delhorme, J. B.; Fau, M.; Tzanis, D.; Causeret, S.; Gimbergues, P.; Guillois, J. M.; Meunier, B.; Le Cesne, A.; Ducimetiere, F.; Toulmonde, M.; Blay, J. Y.	2019	Annals of surgical oncology	26	7	2286-2293
Increased survival of non low-grade and deep-seated soft tissue sarcoma after surgical management in high-volume hospitals: a nationwide study from the Netherlands	Vos, M.; Blaauwgeers, H. G. T.; Ho, V. K. Y.; van Houdt, W. J.; van der Hage, J. A.; Been, L. B.; Bonenkamp, J. J.; Bemelmans, M. H. A.; van Dalen, T.; Haas, R. L.; Grunhagen, D. J.; Verhoef, C.	2019	European journal of cancer	110		98-106
Liposarcoma: outcome based on the Scandinavian Sarcoma Group register	Engstrom, K.; Bergh, P.; Gustafson, P.; Hultborn, R.; Johansson, H.; Lofvenberg, R.; Zaikova, O.; Trovik, C.; Wahlstrom, O.; Bauer, H. C.	2008	Cancer	113	7	1649-1656
Biopsy of musculoskeletal tumours - Beware	Pollock, R. C.; Stalley, P. D.	2004	ANZ Journal of Surgery	74	7	516-519
Variations in retroperitoneal soft tissue sarcoma outcomes by hospital type: A national cancer database analysis	Villano, A. M.; Zeymo, A.; Chan, K. S.; Unger, K. R.; Shara, N.; Al-Refaie, W. B.	2020	JCO Oncology Practice	16	9	E991-E1003
Nonreferral of possible soft tissue sarcomas in adults: A dangerous omission in policy	Abellan, J. F.; Lamo De Espinosa, J. M.; Duart, J.; Patino-Garcia, A.; Martin-Algarra, S.; Martinez-Monge, R.; San-Julian, M.	2009	Sarcoma	2009		827912
Processes and outcomes of care for soft tissue sarcoma of the extremities	Paszat, L.; O'Sullivan, B.; Bell, R.; Bramwell, V.; Groome, P.;	2002	Sarcoma	6	1	19-26

	Mackillop, W.; Bartfay, E.; Holowaty, E.					
Treatment at low-volume hospitals is associated with reduced short-term and long-term outcomes for patients with retroperitoneal sarcoma	Keung, Emily Z.; Chiang, Yi-Ju; Cormier, Janice N.; Torres, Keila E.; Hunt, Kelly K.; Feig, Barry W.; Roland, Christina L.	2018	Cancer	124	23	4495-4503
Management of primary malignant bone and soft tissue tumors of foot and ankle: Is it worth salvaging?	Ozger, H.; Alpan, B.; Aycan, O. E.; Valiyev, N.; Kir, M. C.; Agaoglu, F.	2018	Journal of Surgical Oncology	117	2	307-320
Disparities in Amputation Rates for Non-metastatic Extremity Soft Tissue Sarcomas and the Impact on Survival	Dilday, J. C.; Nelson, D. W.; Fischer, T. D.; Goldfarb, M.	2021	Annals of surgical oncology	28	1	576-584
Regionalization of retroperitoneal sarcoma surgery to high-volume hospitals: Missed opportunities for outcome improvement	Villano, A. M.; Zeymo, A.; McDermott, J.; Barrak, D.; Unger, K. R.; Shara, N. M.; Chan, K. S.; Al-Refaie, W. B.	2019	Journal of Oncology Practice	15	3	E247-E261
Soft tissue sarcoma of the upper extremity: Descriptive data and outcome in a population-based series of 108 adult patients	Gustafson, P.; Arner, M.	1999	Journal of Hand Surgery	24	4	668-674
Oncological outcome and prognostic factors in the therapy of soft tissue sarcoma of the extremities	Ipach, Ingmar; Wingert, Tobias; Kunze, Beate; Kluba, Torsten	2012	Orthopedic reviews	4	4	e34
Different quality of treatment in retroperitoneal sarcomas (RPS) according to hospital-case volume and surgeon-case volume: A retrospective regional analysis in Italy	Sandrucci, S.; Ponzetti, A.; Gianotti, C.; Mussa, B.; Lista, P.; Grignani, G.; Mistrangelo, M.; Bertetto, O.; Di Cuonzo, D.; Ciccone, G.	2018	Clinical sarcoma research	8	1	3
Watch and Wait Approach for Re-excision After Unplanned Yet Macroscopically Complete Excision of Extremity and Superficial Truncal Soft Tissue Sarcoma is Safe and Does Not Affect Metastatic Risk or Amputation Rate	Decanter, Gauthier; Stoeckle, Eberhard; Honore, Charles; Meeus, Pierre; Mattei, Jean Camille; Dubray-Longeras, Pascale; Ferron, Gwenael; Carrere, Sebastien; Causeret, Sylvain; Guilloit, Jean-Marc; Fau, Magali; Rosset, Philippe; Machiavello, Jean-	2019	Annals of surgical oncology	26	11	3526-3534

	Christophe; Delhorme, Jean Baptiste; Regenet, Nicolas; Gouin, Francois; Blay, Jean-Yves; Coindre, Jean-Michel; Penel, Nicolas; Bonvalot, Sylvie					
Patterns of care and survival for patients aged under 40 years with bone sarcoma in Britain, 1980-1994	Stiller, C. A.; Passmore, S. J.; Kroll, M. E.; Brownbill, P. A.; Wallis, J. C.; Craft, A. W.	2006	British Journal of Cancer	94	1	22-29
Impact of centralization of services on outcomes in a rare tumour: Retroperitoneal sarcomas	Kalaiselvan, R.; Malik, A. K.; Rao, R.; Wong, K.; Ali, N.; Griffin, M.; Chandrasekar, C. R.; Fenwick, S. F.; Poston, G. J.; Malik, H.	2019	European journal of surgical oncology	45	2	249-253
Soft tissue sarcoma should be treated at a tumor center: A comparison of quality of surgery in 375 patients	Gustafson, P.; Dreinhofer, K. E.; Rydholm, A.	1994	Acta Orthopaedica Scandinavica	65	1	47-50
Patterns of care of superficial soft tissue sarcomas: it is not always just a lump	Tan, M. T. L.; Thompson, S. R.; Schipp, D.; Bae, S.; Crowe, P. J.	2018	Asia-Pacific Journal of Clinical Oncology	14	5	e472-e478
Adherence to Guidelines for Adult (Non-GIST) Soft Tissue Sarcoma in the Netherlands: A Plea for Dedicated Sarcoma Centers	Hoekstra, H. J.; Haas, R. L. M.; Verhoef, C.; Suurmeijer, A. J. H.; van Rijswijk, C. S. P.; Bongers, B. G. H.; van der Graaf, W. T.; Ho, V. K. Y.	2017	Annals of surgical oncology	24	11	3279-3288
Association of cancer center type with treatment patterns and overall survival for patients with sacral and spinal chordomas: An analysis of the National Cancer Database from 2004 to 2015	Wright, C. H.; Wright, J.; Cioffi, G.; Hdeib, A.; Kasliwal, M. K.; Kruchko, C.; Barnholtz-Sloan, J. S.; Sloan, A. E.	2020	Journal of Neurosurgery: Spine	32	2	311-320
Association Between Treatment at High-Volume Facilities and Improved Overall Survival in Soft Tissue Sarcomas	Venigalla, S.; Nead, K. T.; Sebro, R.; Guttmann, D. M.; Sharma, S.; Simone, C. B.; Levin, W. P.; Wilson, R. J.; Weber, K. L.; Shabason, J. E.	2018	International journal of radiation oncology biology physics	100	4	1004-1015
Trends in practice patterns and outcomes: A decade of sarcoma care in the United States	Song, Y.; Ecker, B. L.; Tang, R.; Maggino, L.; Roses, R. E.; DeMatteo, R. P.; Fraker, D. L.; Karakousis, G. C.	2019	Surgical Oncology	29		168-177

Soft tissue sarcoma - A population-based, nationwide study with special emphasis on local control	Sampo, M. M.; Ronty, M.; Tarkkanen, M.; Tukiainen, E. J.; Bohling, T. O.; Blomqvist, C. P.	2012	Acta Oncologica	51	6	706-712
Conformity to clinical practice guidelines, multidisciplinary management and outcome of treatment for soft tissue sarcomas	Ray-Coquard, I.; Thiesse, P.; Ranchere-Vince, D.; Chauvin, F.; Bobin, J. Y.; Sunyach, M. P.; Carret, J. P.; Mongodin, B.; Marec-Berard, P.; Philip, T.; Blay, J. Y.	2004	Annals of oncology	15	2	307-315
Relevance of Reference Centers in Sarcoma Care and Quality Item Evaluation: Results from the Prospective Registry of the Spanish Group for Research in Sarcoma (GEIS)	Martin-Broto, J.; Hindi, N.; Cruz, J.; Martinez-Trufero, J.; Valverde, C.; De Sande, L. M.; Sala, A.; Bellido, L.; De Juan, A.; Rubio-Casadevall, J.; Diaz-Beveridge, R.; Cubedo, R.; Tendero, O.; Salinas, D.; Gracia, I.; Ramos, R.; Bague, S.; Gutierrez, A.; Duran-Moreno, J.; Lopez-Pousa, A.	2019	Oncologist	24	6	e338-e346
Does facility volume influence survival in patients with primary malignant bone tumors of the vertebral column? A comparative cohort study	Lazarides, A. L.; Kerr, D. L.; Dial, B. L.; Steele, J. R.; Lane, W. O.; Blazer, D. G.; Brigman, B. E.; Mendoza-Lattes, S.; Erickson, M. M.; Eward, W. C.	2020	Spine Journal	20	7	1106-1113
Soft tissue sarcoma of the extremities: What is the value of treating at high-volume centers?	Lazarides, A. L.; Kerr, D. L.; Nussbaum, D. P.; Kreulen, R. T.; Somarelli, J. A.; Blazer, D. G.; Brigman, B. E.; Eward, W. C.	2019	Clinical orthopaedics and related research	477	4	718-727
Time to Treatment Initiation and Survival in Adult Localized High-Grade Bone Sarcoma	Lawrenz, J. M.; Featherall, J.; Curtis, G. L.; George, J.; Jin, Y.; Anderson, P. M.; Shepard, D. R.; Reith, J. D.; Rubin, B. P.; Nystrom, L. M.; Mesko, N. W.	2020	Sarcoma	2020		2984043
Should soft tissue sarcomas be treated at high-volume centers? An analysis of 4205 patients	Gutierrez, J. C.; Perez, E. A.; Moffat, F. L.; Livingstone, A.	2007	Annals of surgery	245	6	952-958

	S.; Franceschi, D.; Koniaris, L. G.					
The European study on centralisation of childhood cancer treatment	Gatta, G.; Botta, L.; Comber, H.; Dimitrova, N.; Leinonen, M. K.; Pritchard-Jones, K.; Siesling, S.; Trama, A.; Van Eycken, L.; van der Zwan, J. M.; Visser, O.; Zagar, T.; Capocaccia, R.	2019	European journal of cancer	115		120-127
Monitoring referral and treatment in soft tissue sarcoma: study based on 1,851 patients from the Scandinavian Sarcoma Group Register	Bauer, H. C.; Trovik, C. S.; Alvegard, T. A.; Berlin, O.; Erlanson, M.; Gustafson, P.; Klepp, R.; Moller, T. R.; Rydholm, A.; Saeter, G.; Wahlstrom, O.; Wiklund, T.	2001	Acta Orthopaedica Scandinavica	72	2	150-9
Improved survival for extremity soft tissue sarcoma treated in high-volume facilities	Abarca, T.; Gao, Y.; Monga, V.; Tanas, M. R.; Milhem, M. M.; Miller, B. J.	2018	Journal of Surgical Oncology	117	7	1479-1486
Is Treatment at a High-volume Center Associated with an Improved Survival for Primary Malignant Bone Tumors?	Malik, A. T.; Alexander, J. H.; Khan, S. N.; Scharschmidt, T. J.	2020	Clinical orthopaedics and related research	478	3	631-642

Appendix 6. Summary tables Clinical Question 2 all studies

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	Total number of patients in the study	Group differences	Endpoint	endpoint	2 yr OS	5 yr OS	10 yr OS	Multivariate analysis	Comments
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	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	No difference in limb salavge rate, RT rate but more Chemo in high Vol. Can't separate specific data for RT (quality, dose, toxicity). Data For OVERALL specialised
Abellan 2009	Spain	Retrospective cohort study	soft tissue of extremity	minimum follow up of 2 years extremity soft tissue	extraskeletal Ewing mets at diagnosis	single sarcoma centre pts where divided into 3 groups: A. direct referral to and first diagnosed at the centre (n=99) B. Whoops cases, immediate referral after initial inadequate excision (n=38) c. local recurrence (one or more) after treatment elsewhere (n=37)	1	1983-2006	174	Local recurrenco: group A (10%), Group B (13%), Group c (59%). A vs B p=0.608, A+B vs C (p<0.0001) highest rate in group C independent of depth and grade Metastasis: Group A (22%), Group B (16%), Group c (51%). A vs B p=0.403, A+B vs C (p<0.001). highest rate in group C independent of depth and grade	**Local recurrence** Group A vs Group B/C 10% vs 13%/59%	DFS: Group A = 73% Group B = 76% Group C= 28%. OS Mean for the 3 groups = 69.9%. No difference between the groups.	_	_	_	Multivariate analysis between groups A and B showed that only tumour size statistically influenced both overall and disease-free survival (P = .024).	Though the survival b/w group A and B were similar there was a higher norbidity rate in Group B (whoops procedure was performed in a different centre)
Adam 2019	USA	Retrospective cohort study	retroperitoneal sarcoma	Non-metastatic RPS, received surgery, ≥•18 years of age	Metastatic disease, additional malignancies, treated at multiple hospitals.	>10 cases/year	909	1998-2012	5340	Compared to low volume, high volume hospitals more often had patients with high-grade and larger tumors. Adjusted 90-day mortality was significantly lower in high-vs.low-volume hospitals(odds ratio(OR)=0.25,p=0.02).With adjustment, treatment in high-vs.low-volume hospitals was associated with lower odds of margin positivity (OR=0.58,p=0.001),and improved overall survival (hazard ratio(HR)=0.61,p=0.002).	**30 Day Readmission** similar = 3.8 % vs 5.4% P = NS **Length of stay** 8 vs 7 p <0.0001. Positive margins - On receipt of surgical Rx Adjusted OR = 0.58 was lower in high volume centres for positive margins. 90 day - Mortality 2% vs 6 % p = 0.04.	Adjusted survival following surgical Rx was higher in high volume centre HR = 0.61 p=0.002	_	_	unadjusted 35% vs 33%	_	
Bagaria 2018	US	Retrospective cohort study	soft tissue	STS of extremities, trunk and head/neck Stage I - III Curative intent surgery only all treatment at reporting hospital Histologies: liposarcoma, histiocytoma, myxofibrosarcoma, malignant peripheral nerve sheath tumor, NOS	St IV palliative surgery	a priori determination of hospitals according to mean annual STS surgery volume divided into 3 equal terciles (1T, 2T, and 3T) with mean volume = total volume of STS surgery cases divided by number of years a hospital reported to the NCDB Thus high volume (3T) was >= 11 cases per year 2T was 3.2 - <11 cases per year 1T was =< 3 cases per year	1158 (1T = 934, 2T = 180, 3T = 44)	2003-2007	13684	hospitals stratified by volume of STS surgeries per year --> divided into 3 terciles. High volume (3T) vs low volume (1T) 53% vs 50%. Most pronounced for For stage III cancers 59% vs 49%	R0 Margin Negative resection (3T vs 1T) 90% vs 83% p < 0.001 **30 day - Mortality** 0.4%(3T) vs 1.2%(1T) p<0.001 **90 day - Mortality** 32.4% vs 35.8% (p = 0.003)	_	_	71.5% vs 68.5% p <0.001 NCCN guideline compliant vs noncompliant patients 72.4% vs 67.2% (p < 0.001) No difference between the centres (1T,2T,3T) when compliant with NCCN	_	"71.5% vs 68.5% p <0.001 NCCN guideline compliant vs noncompliant patients 72.4% vs 67.2% (p < 0.001) No difference between the centres (1T,2T,3T) when compliant with NCCN"	
Bagaria 2018	USA	Retrospective cohort study	retroperitoneal sarcoma	Retroperitoneal sarcoma	GIST extra-abdominal sarcoma	Average annual volume/hospital of curative intent surgery for RPS was calculated by dividing the total number of surgical resections performed at a hospital by the number of years that data were reported to the NCDB. low volume (<5 cases/year), medium volume (5,Ä¿10 cases/year),and high volume (>10 cases/year)	3694	2004-2013	5407	Two patient cohorts were created. 1. all patients diagnosed with RPS irrespective of whether they underwent surgery or not. 2. subset of group 1comprising only of patients who underwent curative intent surgery. In the multivariable analysis for overall survival. After controlling for patient and tumor variables, patients who were treated at a low-volume hospital had a 52% greater risk of all-cause long-term mortality compared to those treated at a high-volume hospital (HR 1.56, 95% CI1.16,Ä¿2.11;p<0.0032).	Positive margins High volume - 16.3% Intermediate volume - 31.8% Low volume - 26.3% 30 day - Mortality 0.5% vs 2.4% Log regression analysis - 4 fold increase in a low volume centre OR =4.66 90 day - Mortality 1.2% vs 5.3%	_	_	Overall 66% vs 56% P<0.001. Patients undergoing curative intentive surgery 69% vs 57%	_	for R0 margin rate; low-volume centers were less likely to achieve R0 margin status compared to high-volume centers (OR 0.46, 95% CI 0.31-0.70;P=0.0003). Patients undergoing RPS surgery at a low-volume hospital had a greater than 4 fold increase in the risk of dying within 30 days if surgery compared to patients undergoing surgery at a high-volume hospital (OR=4.66; p<0.001). 90-day mortality rates followed a similar trend for absolute and adjusted risk of post-operative mortality. patients who were treated at a low-volume hospital had a 52% greater risk of all-cause long-term mortality compared to those treated at a high-volume hospital (HR 1.56, 95% CI 1.16–2.11; p = 0.0032).	"High-volume centers were more likely to treat patients whose tumors were larger (17.5 cm versus 15 cm) and of higher grade (58% versus 47%) than low-volume centers. "
Bauer 2001	Scandinavia	Retrospective cohort study	STS of extremity or trunk wall	STS of extremity or trunk wall	Sarcoma - Head and neck, RPS, viscera, kaposi sarcoma, Dermatofibrosarcoma Protrubens	Not defined. All patients recorded in the SSG were treated in the sarcoma centre	8	1986-1997	1851	**RT post marginal or intralesional excision** (54 % vs 21%). 4/10 patients were untouched before referral to specialised centre	**Local recurrence** 0.2 vs 0.7	**R0 Margin negative resection** 66% vs 11%	_	51% in the specialised centre	_	_	
Bedi 2015	USA	Retrospective cohort study	soft tissue	soft tissue sarcoma of extremity or body wall who had percutaneous biopsy preop RT followed by Surgery	age <18 Mets at diagnosis recurrent disease small subcutaneous tumour no preop RT rhabdomyosarcoma, PNET, Kaposi angiosarcoma , fibromatosis follow up <6 months missing medical report/path report/treatment information postop RT No RT	pts were grouped by percutaneous biopsy at the sarcoma centre vs outside prior to referral to the sarcoma centre	one sarcoma centre	2000-2010	92	pts were grouped as biopsy outside vs biopsy at sarcoma centre, no further details of other inventions	Increased wound complication rates following percutaneous biopsies performed by nonmusculoskeletal trained physicians vs musculoskeletal specialists (50% vs 18%, P=.01) and at nonacademic centers compared with academic centers (34% vs 25%, P=.36) following priv-op RT	_	_	_	_	Multivariate analysis showed that lower-extremity soft tissue sarcomas (P=.03; 95% confidence interval, 0.005-0.740; odds ratio, 0.06) led to a lower rate of wound complications and that biopsies performed in the community setting (P=.01; 95% confidence interval, 1.58-21.15; odds ratio, 5.79) led to increased wound complications postoperatively.	
Berger 2018	US	Retrospective cohort study	retroperitoneal	Stage I to III nonmetastatic retroperitoneal sarcoma Histology: pleomorphic sarcoma, fibrosarcoma, liposarcoma, and leiomyosarcoma Curative resection	Stage IV, lymph node involvement or evidence of metastases operative biopsy only	Academic cancer centers (ACC) = annual cancer volume > 500 new cancer diagnoses and affiliation with training programs Community cancer centers (CCC) = all other facilities	192 ACCs, 490 CCCs	2004-2013	2762	"Neoadjuvant RT (13% vs 5.2%) P<0.01 Adjuvant RT after resection (15.2% vs 26.9%, P < .001)"	Radical resection (60.3% vs 43.3%). R0 resection (55.9% vs 47.0) P< .001. Greater mean volume of resectors in specialized centres (8.6 ± 15.3 vs 2.3 ± 2.9, P < .001)	**30 day readmission and 90-Day mortality** - No difference	_	Unadjusted OS after RPS resection was improved at ACCs compared to CCCs median OS (84.2 months vs 70.1 months P = .014)	_	factors predictive of positive resection margins after RPS resection were age at diagnosis (OR - 1.12), tumour size (OR - 1.01) . factors that decrease odds for positive margins were Neoadjuvant RT (OR- 0.67) and resection at ACCs (OR - 0.83)	
Bhangu 2004	UK	Retrospective cohort study	soft tissue sarcoma	soft tissue sarcoma	Head and neck GIST RPS	pts were identified from the Cancer Intelligence Unit database only one hospital in the health region had sarcoma MDT	38	1/1/1994-31/12/1996	96 sarcoma centre 164 non sarcoma centre		**adequate excision margins (wide or radical margin)** (39% vs 35%) **Local recurrence LR** (19% vs 39%) P value = 0.0011. Positive margin conferred a 45% risk of LR at DGH vs 32% at SC	_	_	58% not significantly different between the two centres	_	grade, depth, size of tumour and treatment centre to be the most significant in Overall survival	
Blay 2017	France	Prospective cohort study	Soft tissue sarcoma visceral sarcoma	Soft tissue sarcoma visceral sarcoma age>15	Bone sarcoma desmoid	Comparison between presentation at one of the NETSARC MDT board before (n=5181, 42.2%) or after (n=7247, 57.8%) primary treatment	NETSARC (26 reference centres) vs other	1 Jan 2010- 31 Dec 2014	n=12528 survival analysis on 9646 pts without mets at Dx	In Multivariable analysis, presentation to a MDTB before treatment, was associated with the highest risk ratio for LRFS and was also a strong independent negative prognostic factor for RFS (Table3). Overall survival was too early to assess given the median follow-up,	**NETSARC MDTB before vs after treatment: 2 yr Local relapse free survival** 76.9% vs 65.4% P <0.001 . **2 yr Relapse Free survival** 51.7% vs 46.6% P<0.001	**NETSARC MDTB before vs after treatment Quality of first surgery** **R0** 1436 (52.6%) vs 1968 (32.2%) **<0.001** **R1** 845 (30.9%) vs 1965 (32.1%) **R2** 204 (7.1%) vs 1148 (18.8%) **NE** 246 (9.1%) vs 1032 (16.9%) **Resection after first surgery** 165 (6.0%) vs 1065 (17.4%) **Quality of final surgery** **R0** 1571 (57.5%) vs 2845 (46.5%) **<0.001** **R1** 773 (28.3%) vs 1529 (25.0%) **R2** 141 (5.1%) vs 707 (11.5%) **NE** 246 (9.1%) vs 1032 (16.9%)	_	_	_	presentation to a MDTB before treatment,was associated with the highest risk ratio for LRFS and was also a strong independent negative prognostic factor for RFS (Table3). Overall survival was too early to assess given the median follow-up,	
Blay 2019	France	Prospective cohort study	Bone and ST	Confirmed sarcoma diagnosis	None	Multidisciplinary tumour board	26	01/01/2020-01/05/2018	35784	In multivariable analysis, Surgery in a NETSARC center was found consistently associated with a reduction in the risk of locainelapse, progression, and death, with hazard ratio of 0.64, 0.83, and0.68 for LRFS, EFS, and OS.	Initial R0 resection (53% vs 19.6%) R1 resection (24% vs 20.2%) R2 resection (4.2% vs 8.5%) Unknown (18.8% vs 50%). Reoperation 6.2% vs 15.7%. Final R0 resection (56.7% vs 29.5%) R1 resction (21.8% vs 15.7%) R2 resection (3.0% vs 6.2%)	_	_	_	_	Local relapse free survival - NETSARC MDT before treatment HR = 0.670 P , Surgery in a NETSARC center HR = 0.654. Disease free survival Surgery in a NETSARC center HR = 0.843 NETSARC MDT before treatment HR 0.800 Overall survival NETSARC MDT before treatment HR 1.563, Surgery in a NETSARC center HR= 0.681"	

Bonvalot 2009	France	Retrospective cohort study	retroperitoneal sarcoma	primary retroperitoneal sarcoma		By number of treated pts at centre: >30, 10-30, <10	all hospitals in French	Jan 1985- June 2005	382		**Patients undergoing Compartmental resection - centre dependant** Specialised centre (> 30 patients per year) -76% (10 - 30 patients per year) - 16%/ Others (<30 patients per year) - 13% (P= .0001). **Tumour rupture during surgical procedure inversley proportional to Level of centre** Specialised centre (> 30 patients per year) -9% (10 - 30 patients per year) - 22% Others (<30 patients per year) - 35%	_	_	_	_	_	lindependent predictive factors associated with better local control were low grade (P<.0001), compartmental surgery(P=0.04), and a high number of patients undergoing operation perc enter (P=.0002).	
Bonvalot 2019	France	Prospective cohort study	retroperitoneal sarcoma	surgery for non metastatic retroperitoneal sarcoma age> 15	desmoid GIST	a clinical network for sarcoma (NetSarc), 26 reference centres	a clinical network for sarcoma (NetSarc), 26 reference centres	1 Jan 2010-1 Jan 2017	Total 2945 1st surgery at Referral centres (n=1078, 36.6%) 1st surgery at outside centres(n=1867, 63.4%)		**NSC (Specialised centre) vs others,** **2 yr Local progression free survival (LPFS)** 75% vs 55% P <0.001	**NSC (Specialised centre) vs others,** R0 resections (41.9%) vs. (12.3%) fewer R2 resections (4.5%) vs. (9.2%) fewer piecemeal resections with nonevaluable or unknown margins (19.7%) vs.(60.7%) (p =0.001)	87% vs 70%	_	_	In the multivariate analysis, surgery in an NSC was an independent predictor of OS, with a two fold lower odds ratio of death than that for surgery outside NetSarc (OR: 0.49(≤0.001)	
Callignon 2020	French	Retrospective cohort study	soft tissue sarcoma	age <25 soft tissue sarcoma or intermediate grade tumour limb, trunk, head and neck	No distant mets	Institut Curie and RCPPI vs other	Institut Curie and RCPPI vs other	2006-2015	127	_	**1. Compliance with criteria stastitically significant in Expert centers (RCPPI + Institut Curie) 77 cases as compared to Other general centres 50 cases** -Imaging before biopsy 72 vs 33 p < 0.0001 -Biopsy beforetreatment 63 vs 25 p < 0.0001 -MTD before biopsy 69 vs 8 p < 0.0001 -Somatic molecular biology available 66 vs 33 p = 0.009. 2. **Reoperation rate inversely related to the** **number of criteria(CPGs)** **6%** - 5 CPGs criteria **25%** - 3-4 CPGs criteria **56%** - <//>2 CPGs criteria . **3. Immediate re-operation was inversely related to the** **number of criteria** (0% when 5 criteria vs. 14% for 3/4, 46% if < 2; P < 0.001)**:**	Loco regional relapse free survival (LRRFS) at 5 years is 79.6%. For malignant tumors, outcome was better when 5 criteria were reached - 5 year EFS 90.8% vs. 71.6 < 4 criteria; p < 0.033), OS 93.6% vs. 79.5% < 4 criteria; p < 0.11), and LRFFS 90.6% vs. 73.1% p < 0.047)	_	OS at 5 yrs = 88.4% There was no statistical significant difference according to the number of CPG criteria fulfilled for all tumours though on stratification it was significant when considered tumour size > 5cm or malignant tumours.	_	" After stratification on tumor size, there was a significant difference on OS and EFS according to the number of CPG criteria fulfilled for large tumors . >5 cm tumour size: 5 criteria vs 4 criteria, 5 year OS 100% vs 72.5%, p=0.002, 5year EFS 89.3% vs 56.2%, p=0.0077, 5year Local regional relapse free survival 89.3% vs 61.6%, p=0.012 The endpoints of this study do not fit with our PICO. Data suggest better guidelines compliance at expert center, and better compliance is associated with better OS and EFS for >5cm tumour."	The endpoints of this study do not fit with our PICO. Data suggest better guidelines compliance at expert center, and better compliance is associated with better OS and EFS for >5cm tumour.
Decanter 2019	France	Retrospective cohort study	soft tissue of extremity or truncal	soft tissue sarcoma arising in the limbs or superficial truncal initially operated outside of community centers	surgical biopsies, R2 or piecemeal resections, non-amenable to curative-intent surgery (e.g.multifocal disease, presence of node involvement, or presence of distant metastasis)	Sarcoma reference centres in France Group A. Patients who underwent systematic re-excision in sarcoma reference centers after referral. Group B. Patients who underwent re-excision outside of community centers, which had already been performed at referral. Group C Patients without systematic re-excision, grouping together patients who could have had re-excision but did not undergo surgery intentionally and patients for whom radiotherapy was chosen over surgery due to the potential morbidity of re-excision	ConticaBase prospective database, all consecutive patients with STS arising in the limbs or superficial truncal initially operated outside of community centers and then referred to 1 of 18 participating sarcoma reference centers in France	1 January 2007 and 31 December 2013	Total 576	R0 resection and (neo)adjuvant radiotherapy were regarded as confounding factors for LRFS. Tumor over 50 mm in size, deep tumor, and (neo)adjuvant radiotherapy were associated with MRFS and were regarded as confounding factors.	For local recurrence, amputation as a second procedure - None in Group A(0) and in Group B/C(6.6%)	After RE, the R0 resection rate was higher in Group A compared with Group B.	_	5-year OS was 88.4%, 87.3%, and 88% in Groups A, B, and C, respectively (p = 0.22), while 5-year MFRS (Metastsic relapse free survival) was 85.4%, 86.2%, and 84.9%, respectively (p = 0.938). Overall statistically no significant difference.	_	Group A patients showed significantly improved LRFS (p = 0.0001) after taking into account confounding factors such as R0 resection and (neo)adjuvant radiotherapy. Multivariate analysis also showed that RE in SRCs did not influence MFRS (p = 0.367) after taking into account confounding factors such as tumor size, deep tumor, and (neo)adjuvant radiotherapy	
Derbel 2017	French	Retrospective cohort study	soft tissue	adults with a newly diagnosed primary sarcoma documented by any public or private pathology laboratory in the RA region soft tissue only		expert center was identified as a structure seeing a high volume of sarcoma, with dedicated multidisciplinary sarcoma team and high level of molecular analysis, histological and radiologic second opinion activity adherence to clinical guideline 2004 version	French RA region (43 pathology labs, and 158 pathologists)	March 2005- March 2007	472	RT adherence to CPG 85%. Chemo adherence to CPG 96%	Expert vs General Hospitals **Global dherence to CPGs(Diagnosis to post treatment survey)** - 57.1 % vs 19.5 % P (<0.001) **Pre-op MDT assessment** - 36.6% vs. 9.7% (p<0.001).	OS - influenced by adherence to CPGs for surgery and organizational setting (66% reduction when both adhered to CPG and in expert centre) in pts. With localised STS.	_	_	_	Adherence to CPGs for surgery and treatment in an expert center for sarcoma are independent positive factors affecting PFS and OS in STS patients.	
Dilday 2021	USA	Retrospective cohort study	soft tissue	soft tissue sarcoma of the extremity	metastatic disease	Academic >10 extremity sarcomas each year, Community for 5- 0 cases per year Other <5 cases/year	1500 Cancer-accredited facilities and captures more than 70% of all newly diagnosed malignancies in the United States annually.	1998-2012	15886		**Overall amputaion rates - 4.7%** High volume vs moderate/low volume centre (5.6% vs 3.4% / 3.3%; p<0.001). Academic centres vs community hospitals (5.4% vs 3.7%;p< 0.001) In older adults amputations significantly less in community facility (OR-0.75)	_	_	66% for extremity STS with an amputation. At higher volume centers (HR 0.83, CI 0.74–0.94) had a decreased risk of death at 10 years.	females (HR 0.83, 95%CI 0.78-0.89) and those treated at higher volume centers (HR 0.83, 95%CI 0.74-0.94) had a decreased risk of death at 10 years.	
Engstrom 2008	Norway and Sweden	retrospective cohort study	Liposarcoma	Liposarcoma extremity and superficial trunk	metastatic disease complete local excision not feasible	not clear definition sarcoma centres vs others	5 sarcoma centers in Sweden 3 sarcoma centers in Norway	1 March 1986-31 December 1998	237 177 (75%) referral to sarcoma centres vs 60 not referred prior to first surgery		No pre-operative microscopic diagnosis Sarcoma centre (9%) vs Others(40%)	Wide marginal excisions (Sarcoma centre vs Others) - 45% vs 0% Overall intralesional margins - 67% Overall marginal surgical margins - 43%	_	_	_	primary surgery outside a sarcoma center correlated independently with local recurrence. (HR 2.43, 95%CI 1.17-5.05, p=0.018). primary surgery outside a sarcoma center was not a factor associated with risk of metastasis"	
Feinberg 2018	UK	Retrospective cohort study	Radiation associated angiosarcoma of breast	Radiation associated angiosarcoma of breast	extensive disease not suitable for surgery	sarcoma service (n-26)	1 sarcoma centre vs other	February 1998 -December 2015	36 sarcoma service (n=26) local hospital (n=10)		**Local recurrence** - (9 of 26 versus 8 of 10); P =0 015. M**edian local recurrence-free interval** greater for pts managed in Sarcoma service (20.9 vs 5.5 months). **Metastatic rate** - no difference. **Disease specific survival** Sarcoma service vs others (months) Median (91.1 vs 48.8)	**Complete histological excision** (BSG guidelines) - No difference Sarcoma service vs locally (18 of 26 versus 5 of 10) respectively P= 0.456. **Complete excision** based on the Milan criteria 28 (excision margin at least 1 mm) no difference b/w Sarcoma service vs others **Salvage procedures** (4 vs 0). All 4 referred from local centres	_	Overall survival Sarcoma service vs others (months) **Median** (75.4 vs 48.8) P= 0.112	_	Binary logistic regression analyses showed no association between proximity of the closest resection margin and metastasis (odds ratio 0 88, 95 per cent c.i. 0 47 to 1 62; P =0 673).	
Freeman 2018	USA	Retrospective cohort study	skull base chordoma	Skull base chordoma	_	Patients were separated into two cohorts 1) those presenting with persistent/progressive disease after prior biopsy or prior surgery elsewhere (n= 30) 2/ those who received treatment for initial disease at MDACC (n=21)	MDACC (1) vs others	1993-2014	51		Recurrence higher in the PD group compared to ID group (57% vs 47 %) .	Significantly high PFS - Initial management in a multidisciplinary center vs initial surgery with or without (XRT) other setting (64 vs 25 months, p = 0.035) Median PFS without XRT (64 vs 16 months)	_	_	_	"Prior surgery outside of a multidisciplinary setting significantly increased the risk of recurrence on univariate (HR, 2.3; 95%CI 1.13-4.6, p=0.022) and multivariate analysis (HR, 2.8; 95%CI 1.4-5.9, p= 0.006), respectively. "	
Gantzer 2019	France	Retrospective cohort study	soft tissue/visceral tumour	soft tissue or visceral tumour suspected to be sarcoma at initial presentation	bone or Kaposi's sarcoma, GIST	not specified	_	January 1 2010- December 31 2016	643 (248 reference center, 393 nonexpert center)	reference vs nonexpert centers	Adherence to composite criteria: Global conformity of the initial management, 31.7% v 7%		_	_	_	Type of centre (non expert centre) predicts for nonconformity to imaging criterion (4.89 (3.12–7.84), <.001), Biopsy criterion (3.62 (2.46–5.37) <.001) and pathology criterion (1.47 (1.01–2.13) α=0.05)	Does not address the PICO endpoints
Gatta 2019	6 European countries	Retrospective cohort study	All Sarcoma	age <15	_	by case number	_	2000-2007	4415 (16 childhood Ca), 429 Sarcoma		_	_	_	_	_	adjusted risk of dying (RR).Bone sarcoma:Belgium, RR 0.81 (0.26-2.56) 0.72. Ireland RR 0.34 (0.11-1.04), 0.06. STS : No difference	No treatment details (Sx, RT, Chemo), General conclusion to support centralisation of childhood Ca treatment (17% lower risk fo dying for all childhood ca treated in high vol. centre. .Bone and STS no difference in survival by high or low vol, no RT/SX/chemo details. Follow up time and lost to follow up not reported
Gilg 2020	Austria	Retrospective cohort study	myxofibrosarcoma	myxofibrosarcoma minimum follow up of 12 months for surviving patients	metastasis at diagnosis (n=3) no follow up data (n=2) No specimen for path review (n=6)	one sarcoma centre (no clear definition) this study examined patients initially treated at the sarcoma vs initial treatment outside	one sarcoma centre covering large parts of southern Austria vs others	1990-2014	109 (68 at sarcoma centre, 41 had initial treatment elsewhere(		R0 resection 85% v 12%, p<0.001	_	_	_	_	sarcoma centre v non sarcoma centre: DFS OR 0.27 (0.05-1.44, p 0.13), Local recurrence free survival OR 0.4 (0.07-2.07, p=0.26). Distant mets free survival OR 0.3 (0.06-1.71, α=0.19)	
Gustafson 1994	Sweden	Retrospective cohort study	soft tissue	adult soft tissue sarcoma of extremity and trunk minimum follow up 3 years	not operated mets at Diagnosis	Group A: referred before Sx Group B: referred after Sx GRO	1 university of Lund Population based database for Sweden health care region, 1.5M population	1970-1989	375		Crude local recurrence rate 19% v 21% v 62% (p= not reported)	amputation rate: 9% v 15% v 6% (P=not reported). Crude death rate: 26% v 23% v31% (P=NR)	_	_	_	Not done	
Gustafson 1999	Sweden	Prospective cohort study	soft tissue sarcoma of the upper extremity	age >16 soft tissue sarcoma of the upper extremity	shoulder location	Lund University centre vs others	Southern Swedish health care region (1.5m population)	1964-1993	108 Lund University centre (n=72) vs others (n=32)	In the univariate and multivariate analyses, treatment centre was not included as a variable. I think this is a prospective cohort as "compulsory reporting of all malignancy, and no one lost to follow up".	Adequate local treatment: Lund University centre 81.9% v other 46.9%, p=not reported)	local recurrence: Lund University centre 17.4% v other 51.2% (p=not reported)	_	_	_	In the univariate and multivariate analyses, treatment centre was not included as a variable	

Gutierrez 2007	USA	Retrospective cohort study	Soft tissue (1st presentation for Sx), extremity and RPS	Soft tissue (1st presentation for Sx), extremity and RPS		facilities grouped into 3 balanced percentile ranges by surgical volume. Top 1/3 vs 2/3	256	1981-2001	4205		30 & 90 day mortality 0.7% v 1.5% (p 0.028), 1.%v 3.6% (p<0.001)	Amputation rate 9.4% v 13.8% (p=0.048)		37.4% v 33.2% (p=0.002)	15.9% v 11.6% (p=0.002)	Overall survival: high vol=1, low Vol RR of death 1.292 (1.003-1.663, p= 0.047)	high RT use in high vol. centre. No LR data. High Volume centres: younger, more high grade, more >10cm, more extremity, more RT and chemo use. Treatment at a HVC was an independent predictor of good outcome. Better OS for treatment (Sx/RT/Chemo) at high vol centre. no specific RT endpoint by volume.
Hoekstra 2017	Netherlands	retrospective cohort study	soft tissue sarcoma	age >18, STS	_	high-volume >= 10 sarcoma resections annually	96	2006-2011	3317		following adjustment for case mix factors; resection without prior pathological confimation was considerably higher in low-vol, general hospitals and no sarcoma research	_	_	No % given but reported no difference in OS between hospital categories	_	following adjustment for case mix factors, high vol centres less R2 resection, adjusted OR 0.54)	Higher RT use in high vol but no LR details. The odds for sarcoma patients to receive radiotherapy appeared higher when surgery was performed in high-volume hospitals, academic hospitals, and sarcoma research centers. The same was true regarding adjuvant radiotherapy following R1 resection, although this effect was no longer significant between academic and general hospitals after adjustment for case mix factors. No details on follow up period/lost to follow up, hence one star on outcome
Hu 2019	China	Retrospective cohort study	osteosarcoma around the knee	Osteosarcoma around the knee limb salvage surgery	Mets at Diagnosis limb amputation as primary procedure age >60 incomplete follow up (n=13)	Biopsy/tumour resection at the sarcoma centre (n=151) vs elsewhere (n=31)	1	Jan 2004-Dec 2013	182		5 year local recurrence free survival 9% v 58.1%, P<0.001	_	_	_	_	For overall survival, the risk factor biopsy/tumor resection performed by different centers (HR 2.8, 1.5-5.2, P=0.001). For local recurrence, in the multivariate analysis, only biopsy/tumor resection performed by different centers was independent predictors of local recurrence (HR 4.099(1.649-10.192). P=0.002).	Did not report intervention details by centers
Ipach 2012	Germany	Retrospective cohort study	soft tissue	soft tissue sarcoma of extremity minimum follow up 12 months	_	one sarcoma centre vs external hospitals	1 sarcoma centre + external hospitals	1990-2008	118	Patients pre-treated at an external hospital had, compared with those who underwent primary surgery at our institution, twice the risk of local tumour recurrence (HR 1.955, 95% CI 2.26-3.04, P<0.003).	Preop Biopsy perfomred: 98.2% v 8.1%. R0 resection: 82.4% v 18.4%	Local recurrence sarcoma v other: 1 yr 9.1% v 17.2%m 3 years 12.5% v 32.5%, 5 year 21.2% v 45.7% (p=<0.013)	_	_	_	Patients pre-treated at an external hospital had, compared with those who underwent primary surgery at our institution, twice the risk of local tumour recurrence (HR 1.955, 95% CI 2.26-3.04, P<0.003).	No follow up data could be collected in every tenth case.
Kalaiselvan 2019	UK	Retrospective cohort study	RPS	surgery for RPS		centralization of RPS (one MDT at Royal Liverpool, 3.9 M population) v pre centralization	North West Costal region of UK	1/1/2004-30/11/2017	72 (13 pre centralization, 59 post centralization)	In addition there was an increase in multi-visceral resections (p<0.0006) between the two time points (pre and post centralization of RPS) .This in turn may reflect on the local recurrence rates, which has improved from 38.5% to 16% before and after centralization respectively. Despite the increased complexity of surgery with centralization, there was no difference in 90-day mortality between the two time periods, (p=0.677.)The 5-year survival for all primary resections post-centralization was 60% compared to 46% pre-centralization (p=0.575). The overall survival at 5-yr for resected primary RPS within the national registry over the time period of this study was 40.6%. The 5-year survival, post centralization, in our series is 60%. This compare favorably with the national results, p=0.0027: Odds ratio 2.262 (1.226-3.911)	Local recurrence: precentralisation 31.2% v post centralization 12.7%	_	_	Despite the more radical nature of surgerypost-centralization, there was no difference in 5-year survival for RPS patients when compared to pre-centralization, p\u0.57	_	Not done	
Keung 2018	USA	Retrospective cohort study	retroperitoneal sarcoma	retroperitoneal sarcoma	paediatric No surgery CNS or bone primary incomplete information	High volume: >10 cases per year Low volume: <= 10 cases per year	National Cancer Data Base (NCDB)	1998-2011	6950 High volume: 680 (9.8%) Low Volume: 6270 (90.2%)	Additional analyses have suggested a dose effect associated with increasing hospital case volume and better patient outcomes and found progressive improvements in patient outcome with increasing hospital case volume (0-5 cases/year, 6-10 cases/year, and >10 cases/year).	R2 resections: 1.6% v 4.5% (p=0.001)	**30 day readmission** (1.8% v 3.4%, p=<0.001). **30 day mortality** (1.9% v 3.1%, p=<0.004). **90 day mortality** 3.2% v 5.7% p=0.007	_	57.7% v 52%, p=0.003	_	treatment at an HVH was found to be associated with a reduced risk of death compared with treatment at an LVH (HR, 0.77; 95% confidence interval, 0.65-0.93; P=.003) Similar results when separate analyses were performed that were limited to patients for whom a Charlson-Deyo Score was available in the NCDB (2003-2011; 3524 patients).	RT use: 17.2% v 27.9%, p<0.001. Multivariate analysis, RT was associated with better OS (HR 0.8, 95%CI 0.73-0.88, p<0.001). BUT no RT fractionation details/toxicity
Kikuta 2013	Japan	Retrospective cohort study	Myxofibrosarcoma	Myxofibrosarcoma		*This study reported outcome of first operation :unplanned surgery at non specialised centre vs primary wide resection at one sarcoma centre. All patients were ultimately treated at the one sarcoma centre, National cancer centre hospital.	One specialised centre vs others for the first surgery	1999-2008	100	Primary unplanned re-section was significantly related to the 5-year disease free survival rate (P=0.0401) *	5 year recurrence free survival 89% v 55%, p=0.0001	_	_	_	_	primary unplanned resection at a previous non-specialised hospital was the only factor significantly correlated with the recurrence free survival (RR 5.35, p=0.0011).	
Lans 2019	USA	Retrospective cohort study	Soft tissue sarcoma of hand	Soft tissue sarcoma of hand age =>18	insufficient data (n=6) rejected standard surgical treatment (n=1) adequate oncological treatment outside (n=4)	single centre (Mass General hospital) vs other non oncological centre	1 vs others	1971-1992	64	Patients treated initially at an oncology center had worse overall survival, 60% 5-years survival, compared to patients treated initially at non-oncology center, 89% 5-year survival (p=0.021) .	Final Margin (positive) 12% v 25%, p=0.36	Amputation 33% v 42%, p=0.25	_	Patients treated initially at an oncology center had worse 5yr OS 60% compared to patients treated initiallyat non-oncology center, 89% I (p=0.021) However, there was no association when multivariable Coxregression was performed with corrections for tumor size (HR: 1.5,95% CI: 0.96-2.4, p=0.078_	_	no association when multivariable Cox regression was performed with corrections for tumor size (HR: 1.5, 95% CI: 0.96-2.4, p=0.078). Positive final margin was independently associated with the development of metastasis (HR: 5.4, 95% CI: 1.3-22.5,p=0.022). In multivariable Cox's regression, a positive margin (HR: 3.9, 95% CI: 1.0e14 ,p=40.048) was independently associated with worse disease-free survival.	small no.
Lazarides 2019	USA	Retrospective cohort study	soft tissue of extremity	soft tissue sarcoma of the extremity	_	High vol ≥20 pts per year	High volume 1270 (9=high vol.centres), low volume 22096 (87%)	1998-2012	25406		positive margin 10% v 17%, p<0.001. No difference in amputation (5%v 5%). More radical resection in high vol 65% v 45%, p<0.001.	30-day mortality 0.3% v 0.4%, p=0.018	_	better OS seen in all grades	_	lower risk of death in high vol. HR 0.81, 0.75-0.88, p<0.001	No RT quality details, no local recurrence data
Lazarides 2020	USA	Retrospective cohort study	primary malignant bone tumours of the vertebral column	primary malignant bone tumours of the vertebral column		High vol. ≥5 pts over study period	high volume 327 (44.6%). Low volume 406 (55.4%)	1998-2012	733		more likely to have Sx: 91% v 80%, p<0.001. en bloc resection more likely in high vol, centres: OR 2.11 (1.5-2.96, p<0.001, 48% v 30%, P<0.0001)	no difference in margin status, positive margin 32% v 35%, p=0.15	_	all histologies:71% v 58% , p<0.0001. Osteosarcoma 50% v 29%, p=0.0112. Chordoma 78% v 63%, p=0.0007. Chondrosarcoma 72% v 67%, p=0.33	_	better survival at high vol. centre: HR 0.75 (0.5800.97, p=0.0289)	No RT details, no local recurrence data
Lo 2020	UK	Retrospective cohort study	Breast sarcoma	Breast sarcoma curative surgery	breast carcinoma, sarcomas of chestwall dermal sarcomas (e.g.DermatoFibroma Sarcoma Protuberans)	sarcoma centre vs peripheral hospitals	West of Scotland Cancer Registry and pathology databases	Jan 2007 to May 2019	41 sarcoma centre (n=21) others (n=20)	_	Positive margin after initial surgery: 0% v 50%, p=0.0002, OR 43 (2.3-806.5)	_	_	_	_	The positive margin rate was significantly higher in WLE (7/8,87.5%) than with any form of mastectomy (pooled data 3/29,10.3%), p=0.0003(odds ratio 60.7, 95%CI 5.4,Â 676.9) When stratifying for tumours<5cm this trended towards improved survival at the Sarcoma Centre. No difference was noted on Kaplan Meier survival curves analysed with the logrank test ,between patients treated initially at the sarcoma centre or peripheral hospitals for overall survival (p=0.43),stratified for tumours <5cm (p=0.16) and disease-free survival (p=0.31)	small no. , follow up period not reported
Lytvynenko 2019	Ukraine	Retrospective cohort study	Malignant histiocytoma	Malignant fibrous histiocytoma	not stated	One sarcoma centre vs other	One sarcoma centre vs other	Not stated	130	_	recurrence rates 40% at specialised facility vs. 86.9% at general surgical facility	_	_	_	_	Not done	no details on treatment details by centers, study period, follow up, no multivariate analysis

Malik 2020	USA	Retrospective cohort study	Osteosarcoma Chondrosarcoma Ewing‚Äôs sarcoma Chordoma Others	1.Primary malignant bone tumors of the extremities (C40.0-C40.3, C40.8, and C40.9) undergoing treatment (surgery, chemo-therapy, and/or radiotherapy) 2.Registered in National Cancer Database between 2004 to 2015	1. Primary malignant spinal osseous tumors 2. Benign tumours	high-volume (at least 20 patients per year) low-volume (fewer than 20 patients per year)	835 (High volume centres - 6, Low volume centre - 829)	2004 - 2015	14039 (high volume:2215, 15%. Low volume: 11924, 85%)	RT use: High vol 13% vs low vol 17%, p<0.001	for the 40% of pts who commenced treatment with combined modality treatment in specialised centre, there were no recurrences	–	–	High vol 65% v 61%, p=0.003	–	more limb salvage surgery OR 1.34 (1.14-1.59, p=0.001). Lower mortality (HR 0.85, 0.77-0.93, P<0.001)	No RT quality details, no local recurrence data. SB: Very similar to Lazarides 2019 paper; only 15% of pts managed at LVC (similar to STS-E), Tokay to apply this to Australian contex? Very different medicare structure, quite surprising that substantial proportions of patients with ewing sarcoma and osteosarcoma being managed at LVC (this is less likely to happen in Aus, I thought?)
Martin-Broto 2019	Spain	Prospective cohort study	soft tissue sarcoma extremity or trunk wall	Soft tissue sarcoma extremity or trunk wall	lack of essential data, visceral sarcoma	Research Centre = multidisciplinary team experienced in sarcoma + weekly operative sarcoma committee, minimum of 70 patients with STS/ year, and at least a defined regional referral policy	31	2004-2011	622 (specialised centre: 2 centers, 285 pt, 46% v non specialised 337, 54%)		trend for better median RFS 63.3 months v 39.6 months (p=0.1). 3 yr RFS better for biopsy in research centre 66% v 46.4%, p=0.019	for pts with mets at Dx, pts on research centre had better median OS 30.5 months v 18.5 months (p=0.036)	–	3 yr acturial OS: 82% v 70.4% , p=0.003	–	Not done	High local recurrence in research centre but referral bias as ot with local recurrence were referred to research centre and registered under research centre. NO RT details; can't intrepret local recurrence data
Maurice 2017	USA	Retrospective cohort study	Retroperitoneal sarcoma	Retroperitoneal sarcoma	Metastatic disease unknown N or M stage (n=1929) unknown surgery status (n=7) prior or concurrent cancer status	Hospital volume was classified based on the average number of retroperitoneal sarcoma cases managed at the hospital per year (for actual years that the hospital reported to the NCDB) as low (<5) or high (=>5), with high-volume centers corresponding to the top 10th percentile.	not clear	2004-2013	3141 (329 high volume vs 2812 low volume)	–	R0/R1 margin: High vol 97.4% v Low vol 92.4%, p=0.002	–	–	Median OS 71.1months v 68.9 months, p=0.341	–	high-volume centers had 1.9-fold higher odds of undergoing surgical management (P< 0.001), 2.5-fold higher odds of receiving a R0/R1 resection (P= 0.026), and 1.8-fold higher odds of an R0 resection (P< 0.001). Academic setting predicted use of surgical management (P< 0.001) and R0/R1 resection (P= 0.015) but not R0 resection (P= 0.882). R1 (HR 0.56, 95%CI 0.43-0.72,P< 0.001) and R0 resection (HR 0.68,95%CI 0.57-0.81,P< 0.001) were strong independent predictors of improved OS.	
Merchant 2012	Canada	Retrospective cohort study	Retroperitoneal sarcoma	age 18 resectable disease malignant neoplasm of the retroperitoneum Pts had been referred to tertiary care and had undergone a surgical resection.	mets at Dx unresectable disease those who were never referred to the tertiary centre had all their surgeries outside British Columbia autopsy only cASE	Referral to a tertiary care center was defined as being referred to either the BCCA or to a surgical oncologist (6 mBC)	Cancer Registry study	1 Jan 2000- 31 Dec 2009	82, 41 referral before Sx, 41 referral after Sx	–	R1/R1 resection: Referral before 97.6% v 65.9%, p=0.0002	initial surgery performed by a surgical oncologist had a more favorable median OS (94.0 months, 95% CI, 53.7–100.0]) compared with those who had their surgery performed by a non surgical oncologist (median OS 54.2 months, 95% CI, 30.4–120.2,P=0.0328).	–	Median OS: referal before Sx 94 months v 54.2 mont, (p=0.06)	–	Overall survival: Referral before surgery is associated with higher rates of complete resection and the use of adjuvant radiation; furthermore, it is associated with prolonged survival in the univariate but not in the multivariate analysis (HR 0.529. 95% CI 0.2-1.2, p=0.115). Relapse free survival; in multivariate analysis, referral group did not affect RFS.	
Moris 2020	USA	Retrospective cohort study	retroperitoneal sarcoma	age 18 retroperitoneal sarcoma	–	By case volume per 3-year period. 1. 2 or less cases 2. 3-5 cases 3. 6-10 cases 4. >10 cases	–	2004-2015	11302		surgery at high-volume centers was associated with a higher probability of a textbook outcomes (p=0.009). textbook outcomes were associated with significantly longer overall survival (p<0.001).	Textbook outcomes were associated with 81.6% longer survival (95%CI 1.508-2.188, P<0.001).	–	–	–	Not done	did not report baseline characteristic or intervention by case volume
Ozger 2018	Turkey	Retrospective cohort study	Bone and soft tissue tumours of foot or ankle	Primary malignant bone and soft tissue tumours of foot and ankle Surgery at single institution by single surgeon	Insufficient data (n=7)	Not defined (single institution study), initial management at the one specialised centre vs initial management elsewhere	1	1992-2015	42	Not reported	Survival rates were not affected by tumor volume, osteoarticular involvement, biopsy type, preoperative RT, neoadjuvant chemo, unplanned resections,and surgical margin according to Cox regression analysis.	–	–	–	–	Not done	small .no. single center
Paszat 2002	Canada	Retrospective cohort study	soft tissue sarcoma extremity	age >17 soft tissue sarcoma extremity		135 hospitals admitted fewer than 20 new cases of STSE during the 10 years, 11 admitted between 20 and 50 cases, and one hospital admitted more than 50 cases	147 hospitals	1 Jan 1987-31 Dec 1996	n=1467	–	RT use increased with: increasing case load of the hospital of first admission (p<0.0001), and ncreasing attendance rates at acancer centre within 3 months of diagnosis (p<0.0001)	–	–	–	–	The adjusted relative risk of amputation at any time following diagnosis was 3.5 (95% CI (1.63, 7.46) among cases not attending a cancer centre. For cases not attending a cancer centre within 3 months of Dx, The adjusted relative risk of death was 1.4 95% CI (1.1. 1.7).	
Pollock 2004	Australia	Retrospective cohort study	all musculoskeletal tumour	all musculoskeletal tumour	bony mets	Biopsy by senior sarcoma surgeon (Stalley, n=113) vs biopsy by referring surgeon outside the sarcoma centre (n=29)	1	2002	142	–	Amputation: Bx by Stalley 7% v 25%, p=0.03. Suboptimal biopsy hindering definitive treatment: 1.8% v 38%, p<0.0001	Adquate diagnostic material: 97% v 72%, p=0.0001. Adjuvant RT: 5.3% v 20%, p=0.05	–	–	–	did not adjust for other factors such as age gender, tumour factor. Hence 0 star for comparability on the Ottawa scale	single surgeon, no mutlivariate anlaysis but Australian data
Rey-Coquard 2004	France	Retrospective cohort study	localised or locally advanced soft tissue sarcomas	localised or locally advanced soft tissue sarcomas		Conformity to clinical practice guidelines	2	1999-2001	100 (MDT 69, Cancer network 67, No MDT 31, no cancer network 33		Local relpase by conformity of RT to CPG: yes 30% v no 63%, p=0.007 u	Rate of conformaity with COG of RT=81%	–	–	–	pre Sx MDT discussion, management in reference centre and within cancer network independently predicted conformity to CPG.	RT: conformity to CRG less local relapse, reference centre predicts for conformity to CPG.
Sakabe 2008	Japan	Retrospective cohort study	synovial sarcoma	Synovial sarcoma extremities at least 2 year follow up for alive patients		one sarcoma center vs others	1 vs others	Sept 1979-April 2005	17		inadequate Initial surgical margin 0% v 57.1%. Metastatic rate 20% v 57.1%	A statistically significant factor in the log-rank test with regard to tumour-related death was the item underwent initial surgical resection at other hospitals (p=0.02).	–	–	–	Not done	very small number no details on intervention difference by center No multivariate analysis
Sampo 2012	Finland	Retrospective cohort study	STS extremity and trunk	STS extremity and trunk		high volume centres = centres treating 2/3 of the patients (of the final surgeries) during the study period intermediate-volume centres = hospitals treating 3-17 patients during the study period low-volume centres = hospitals treating 1-2 patients during the study period	24 (3 high vol, 5 intermediate, 16 low)	1998-2001	219 (153 specilised, 40 intermediate, 22 low)	RT use: HVC 75.2%, IVC 56.3%, LVC 31.6%, p<0.0001	**5 year local recurrence free rate**: HVC 82%, IVC 61%, LVC 69%, p=0.046. Local recurrence rate decreased as surgical bol of the centre increased: RR per 10 pts 0.914 (0.851-0.97, p=0.006). **Wide reseaection 31.4% v 17.5% c14.2%, p=0.004**	sarcoma specific survival HVC 71%, IVC 59%, IVC 66%, p=0.237. Metastasea free survival 67%v 61%v 78%, p=0.283	–	–	–	Not done	Higher RT use in high vol centre, better 5 year local control at high vol centre (NB 5year 82% is lower than expected)
Sandrucci 2018	Italy	Retrospective cohort study	Retroperitoneal sarcoma	retroperitoneal sarcoma No mets at diagnosis patients were identified from pathology report		HVCCC, a high-volume cancer center with a sarcoma-committed surgical team (high CCV and SCV > 20 surgeries per year) and a regular RPS-multidisciplinary board (RMB) HVTCA, a high-volume tertiary care academic hospital without a sarcoma-committed surgical team (high CCV and SCV ‚Ä≥5-20 cases per year for each involved surgeon) and a formalized RMB LVSCH, a group of low volume hospitals (low CCV and SCV < 5 RPS surgeries per year) without a formalized RMB	22 hospitals, two regions of northern Italy, Piedmont and Aosta Valley (with a total amount of 4.5 million of inhabitants),	2006-2011	138 HVTCA (n=47, 34.7%) HVCCC (n=25, 18.1%) LVSCH (n=66, 47.8%)	–	R0: HVCCC 40% v HVTCA 21%, p=0.001. R1 40% v28%, R2 12% v 32%	–	–	65% for R0/1 and 31% for R2 patients (P < 0.001) without differences between HVCCC and HVTCA cases (P = 0.06)	–	In both logistic regression models concerning intact specimen and surgical margins, only the "care center" item demonstrated a statistically significant correlation (i.e. HVCCC versus HVTCA) (P= 0.03, adjusted effects).	improved surgical outcomes with high vol. centre
Schmitz 2019	USA	Retrospective cohort study	retroperitoneal sarcoma	Retroperitoneal sarcoma		low-volume centre = median annual case volume of 1 case/year, high-volume centre = median annual case volume of 10 cases/year	–	1998-2012	2599 (long distance/high volume 1250, short distance/low volume 1309)	LT/HV 29% vs ST/LV 25%, p=0.044	30 day mortality LT/HV 1.2% v 2.8%, p=0.0026	R2 resection LT/HV2.6% v 4.4%, p=0.003	–	LT/HV 63% v 53%, p<0.0001	–	OS: long distance/high vol HR 0.726 (0.601-0.878, p=0.0009)	NCDB: No RT details, NO local recurrence data
Song 2019	US	Retrospective cohort study	extra-abdominal soft tissue sarcoma	extra-abdominal soft tissue sarcoma		High vol hospital = exceeded the 90th percentile in the number of patients treated per year	57700%	2005-2014	55212 (57 High vol, 520 low vol)		resected stage 1-3: 2005-2009: preop RT HVH 35.9% v 19%, 2010-2014 HVH 43.2% v 28.2%	–	–	3 yr OS High vol 69.5% v 63.2%, p<0.001	–	High vol: 8% hazard reduction in all cause death (HR 0.92, 0.89-0.95, p<0.001). Only vol, not academic status was associated with OS. High vol: hither R0 resection HR 1.27, 1.2-1.35.	More RT use for stage 1-3 in HVC. NCDB: no RT details, no local recurrence
Stiles 2018	USA	Retrospective cohort study	Desmoplastic small round cell tumor peritoneal cavity and retroperitoneum	age 0-39 Desmoplastic small round cell tumor peritoneal cavity and retroperitoneum	–	Facility identification codes were grouped into two groups based on the volume of DSRCT cases reported at the facility over the course of the study period (2004-2014): low (<5cases reported for study period), and high (‚Ä•5 cases reported for study period).	97 centers Low: 110 pts, 95 centers High 15 patients- 2 centers	2004-2014	125	–	Postoperative mortality: 30 day 0% v 1.6%, p=0.706), 90-day 0% v 4.7%, p=0.507	Median length of stay: 9 days v 7 days (p=0.136)	–	median OS: High vol v Low 59.1 vs 28.8 months (p=0.135)	–	adjuvant chemotherapy was associated with a reduced risk of mortality (HR 0.3,P= 0.073) and residual macroscopic disease after resection correlated with increased risk of mortality (HR 5.3,P= 0.071).	NCBD: no local recurrence details

Stiller 2006	UK	Retrospective cohort study	Bone	age <40 primary malignant bone cancer		BTS: the two supra-regional Bone Tumour Services in London and Birmingham; UKCCSG: the 20 paediatric oncology centres affiliated to the UK Children,ÂÔs Cancer Study Group (from 1990, some London BTS patients were registered with the UKCCSG but for all the analyses presented here they have been counted as BTS) Other teaching hospitals: the remaining 26 hospitals in geographical proximity to and attached to medical schools; Non teaching hospitals: the remaining 82 hospitals treating study patients	National Registry of Childhood Tumours for age <15 age 15-39 Regional cancer registry in Ok, national cancer registries of Scotland and Wales	1980-1994	2843	–	–	Osteosarcoma 5yr OS. 1980-1984 (P=0.009) BTS 50%, UKCCSG 51%, Other teaching 28%, non teaching 37%. 1985-1989 (p=0.07) BTS 54%, UKCCSG 58%, Other teaching 54%, non teaching 37%1990-1994 (p=.49) BTS 49%, UKCCSG 55%, Other teaching 55%, non teaching 44%	–	Ewing: 1980-1984 (p=0.0003), BTS 33%, UKCCSG 40%, other teaching 31%, non teaching 21%. 1985-1989 (p<0.0001) BTS 57%, UKCCSG 52%, Other teaching 36%, non teaching 22%. 1990-1994 (p<0.0001) BTS 57%, UKCCSG 59%, other teaching 42%, non teaching 11%	–	1985 – 1994: age, sex, primary site, surgical treatment centre, the results relating to main treatment centre for both OS and ES retained significance. For both OS and ES diagnosed since 1985, patients whose main treatment centre was a non specialist hospital had a lower survival rate.	
Takeuchi 2016	Japan	Retrospective cohort study	giant cell tumour	giant cell tumour extremities no medical treatment	axial site recurrence in soft tissue lack of info on grade	primary treatment at one of the Japanese Musculoskeletal Oncology Group centre (n=91) vs treatment elsewhere then referral to sarcoma centres at recurrence (n=12)	20 cancer centers and university hospitals that participate in the Japanese Musculoskeletal Oncology Group (JMOG) network	1980-2008	103 (91 at sarcoma cnetres, 12 elsehwere)	–	Recurrence free survival: sarcoma centre 68.2% v initial treatment elsewhere 56.3%, p=0.002	–	–	–	–	recurrence free survival: 1st treatment elsewhere RR 5.078 (95% (1.92-13.4), p<0.001)	did not report baseline characteristics and intervention by treatment centres
Tan 2018	Australia	Retrospective cohort study	superficial soft tissue sarcoma	superficial soft tissue sarcoma		initial management at sarcoma centres vs elsewhere, all had further Rx at sarcoma centres	2 sarcoma centres v initial management elsewhere	1995-2013	89 (31 sarcoma centres v 58 elsewhere)	RT use 61% v 10%, P<0.0005	more than one operation: 26% v 78%, p<0.0005. final clear margins: 77% v74%, p 0.62	Local recurrence 6.5% v 24%, p=0.038	–	–	–	location of initial management for predictor for local recurrence, distant mets and disease specific survival	small no., didn't analyse data by RT use.
Toulmonde 2014	France	Retrospective cohort study	retroperitoneal sarcoma	age >18 primary retroperitoneal sarcoma	fibrous solitary tumor	Specialised surgeons vs non specialised surgeons	12 sarcoma centres	Jan 1998- December 2008	586 (43.5% sarcoma surgeon, 56.5% non sarcoma surgeon)	Among the 511 patients who underwent surgery for a localized RPS, factors significantly associated with R2 resection in multi-variate analyses were DDLPS and ,ÂôOther,Âõ histologies, multi-focality, adjacent organ involvement, type of surgery and and nonspecialization of the surgeon.	abdominal sarcomatosis: surgeon by sarcoma sugeons HR 0.5 (0.3-0.96, P=0.04)	Local recurrence: surgery by sarcoma surgeon HR 0.5 (0.4-0.7, p=0.001)	–	–	–	Among the 511 patients who underwent surgery, factors significantly associated with R2 resection iwere DDLPS and ,"other" histologies, multi-focality, adjacent organ involvement, type of surgery and and non specialization of the surgeon. For local regional relapse: male gender, adjacent organ involvement,specialization of the surgeon and piecemeal resectionand perioperative radiotherapy remained independent factors. Specialisation of sarcoma not a factor for OS.	
Traub 2018	Canada	Prospective cohort study	soft tissue	Stage 3 (>5cm, deep, high grade) soft tissue sarcoma extremity minimum follow up 24 monmths	metastatic disease	planned excision vs unplanned excision elsewhere (all had further treatment at sarcoma centers)	2 (Mount Sinai Hospital and Princess Margaret Cancer Center), unplanned excision elsewhere before referral vs planned excision at these 2 centers	1986-2010	500 (406 planned excision, v 94 unplanned)	–	5 year Local recurrence free rate: planned excision 90.1% v 88.3%, p-0.42	amputation: planned 10.1% v 18.1%, p0.03. Postop complication requiring Sx: No difference	–	Planned excision 50.1% v unplanned 54%, p=0.3	–	unable to identify any parameter that increased the risk of overall, metastasis-free, and local recurrence-free survival rates.	whoops sx but all had final treatment at sarcoma centres. Authors: Unplanned excision leads to an unfavorable clinical course and necessitates more extensive surgery. As a result of aggressive re-excision and multidisciplinary treatment, a negative effect on oncologic outcomes cannot be confirmed.
Venigalla 2018	USA	Retrospective cohort study	soft tissue	age>18, Non-metastatic STS treated with definitive surgery and either pre-op or post-op EBRT. Both Sx and RT at the reporting facility (pts treated at multiple centres were excluded)	–	Facilities in top 1 percentile (99th percentile) by case volume (79-252 cases) over the study period	973	2004-2013	902S [high vol:1578 (17%), low vol; 7447 (83%)]	Preop RT: high vol 37% v low vol 19%. Postop RT: high vol 63% v 81%, p<0.001	–	–	–	72.2% v 67.4%	57.1% v 49%, p<0.001	propensity-score matching. HV v LV, improved overall survival, HR 0.87, 0.8-0.95, P=0.001. test for interaction b/w HV and academic centes, Non significant.i.e OS benefit associated with HV was not modified by treatment at academic centres	All had definitive Sx and RT at one centre, probably can generalise the data to RT (NCDB, no RT details, No local recurrence data)
Villano 2019	USA	Retrospective cohort study	retroperitoneal sarcoma	age 18 retroperitoneal sarcoma	age >90 unknown ethnicity (n=169), unknown insurance (n=250), lack of postoperative follow-up (n=5) stage 4 (n=815) GIST	High volume (>=13 procedures per year), n=385 Low volume (<13 procedures per year), n=8336	National Cancer Database It captures approximately 70% of all cancer incidences in the US and spans all regions of the country, totalling more than 34 million hospital records.	2004-2015	8721 (high vol 385, low vol 8336)	RT use: high vol 15.3% v low vol 37.8%, <0.001	Multivisceral resection: 39.2% v 27%, p<0.001. Negative margin: high vol 81% v low vol 72%, p<0.001. R0/R1 resection: 93.8% v 84.6%, p<0.001	30 day admission: 5.5% v 4.6%, p=0.496. 90 day mortality: 2.1% v 3.7%, p=0.145. Mean length of stay 8.8 days v 6.3 days, P<0.001	–	Overall survival, however, was significantly longer atHVHs (74.6% vs 60.9%, p<0.001).	–	Overall mortality risk was reduced by 4% per additional case (HR 0.96, 95%CI 0.95 to 0.98) up to a threshold of 13 cases/year; no further reduction was observed over 13(HR 0.99, 95% CI 0.97 to 1.01).	By vol. not centres or surgeon. There are THREE RPS papers by Villano using the NCDB RPS cases from the same study period.
Villano 2020	USA	Retrospective cohort study	Retroperitoneal sarcoma	Retroperitoneal sarcoma treated with surgery	unknown age unknown race unknown insurance status Mets at diagnosis No postoperative follow up (n=1230) missing facility (n=997)	by surgical volume, procedure per year (0-1, 1-3, 3.1-5, 6-10, >10) or by facility type (community, comprehensive community, integrated network, Academic research) community: The facility accessions more than 100 but fewer than 500 newly diagnosed cancer cases each year." comprehensive community; The facility accessions 500 or more newly diagnosed cancer caseseach year. integrated network: The organization owns, operates, leases, or is part of a joint venture with multiple facilities providing integrated cancer care and offers comprehensive services Academic research: The facility participates in postgraduate medical education in at least four program areas, including internal medicine and general surgery	NCDB represents a collaborative effort administered by the American Cancer Society and American College of Surgeons. The database comprises registry information on patients treated at 1,500 Commission on Cancer(CoC),Âaccredited hospitals, which span approximately70% of all cancer cases in the United States.	2004-2015	10113	–	R0/1 margin: academic research 87.6% v integrated network 84.7% v comprehensive community 80.1% v community 78.3%	–	18 months OS academic research 82.7% v integrated network 81.3% v comprehensive community 80.6% v community 82.1%	academic research 60.1% v integrated network 58.1% v comprehensive community 56% v community 55.5%	academic research 41.8% v integrated network 36.7% v comprehensive community 39.8% v community 37.1%	Among hospital-level factors, only annual hospital surgical volume was significant, whereby increasing annual surgical volume yielded improved risk of death in a dose-dependent manner (HR, 0.92; 95% CI, 0.89 to 0.95).	There are THREE RPS papers by Villano using the NCDB RPS cases from the same study period.
Vos 2019	Netherlands	Retrospective cohort study	soft tissue	soft tissue sarcoma	GIST, Kaposi's sarcoma, age <18	High Volume: >=20 resection per year Medium volume: 10-19 resection per year Low volume: 1-9 resection per year	76 hospital	2006-2015	5282 Low=2196 Medium=407 High=2679	–	multiple procedures varied from 29% in high-volume hospitals and in medium-volume hospitals to 36% in low-volume hospitals (p<0.01)	potential 'whoops' resection was lower as the annual surgical volume increased: 62% in low-volume hospitals, 44% in medium-volume hospitals and 29% in high-volume hospitals (p<0.01)	–	–	High vol 68% v medium vol 68% v low vol 76%	surgery in a high-volume hospital showed a significant and beneficial effect on net survival compared with surgery in a low-volume hospital (RR 1.3, 95% CI 1.02-1.6,p=0.03). The same impact was observed in comparison with medium-volume hospitals, although this failed to reach statistical significance (RR 1.3, 95% CI 0.98-1.8,p=0.07) .	
White 2019	Australia	Retrospective cohort study	any sarcoma	age 15-24 sarcoma	giant cell tumour of bone	paediatric centre (n=48) vs youth dedicated centre/specialist sarcoma centre (n=203) vs non specialist adult (n=67)	22	1 Jan 2007 - 31 Dec 2012	318	aim: whether care differs by type of hospital attended and whether treatment and outcomes differ between these types of hospitals. Type of treatment center was not associated with overall survival for any sarcoma type after adjusting for disease chracteristics, age, gender, chemotherapy.	–	–	–	–	–	**OS: STS** Paediatric centre HR 1, AYA sarcoma centre HR 2.39 (0.71-8.02, p=0.159), other adult HR 1.48 (0.2-5.51, p0.563). **Bone sarcoma** Paediatric centre HR 1, AYA sarcoma centre HR 1.4 (0.27-7.3, p=0.693), other adult HR 0.8 (0.17-4.78, p=0.774). **Ewing Paediatric centre HR 1, AYA sarcoma centre HR 2.81 (0.91-8.72, p=0.07), other adult HR 2.51 (0.8-7.95, p=0.116)**	authors: After adjusting for disease and patient characteristics, survival was not associated with treatment center type forany diseaase type. (no RT/ sx details)
Widhe 2009	Sweden	Retrospective cohort study	chondrosarcoma of chest wall	Chondrosarcoma chest wall (ribs and sternum) curative treatment	clavicle as not flat bone	orthopaedic sarcoma centre vs others	19 3 orthopaedic sarcoma centres (n=55) 16 thoracic/general surgery (n=42)	1980-2002	97		Wide margin: sarcoma centres 45.5% v non sarcoma centres 4.8% (p<0.001). Marginal: 47.2% v 42.8%, intralesional: 7.3% v 52.4%.	Local recurrence: sarcoma centres 16.4% v non sarcoma centres 57.1%, p<0.001. Metastasis: sarcoma centres 21.8% v non sarcoma 16.7%, p=0.05	–	–	sarcoma centres 75% v non sarcoma centres 59%, p=0.04	prognostic factors for local recurrence: surgical margin, grade. prognostic factors for metastasis: grade, local recurrence and tumour size Patients operated with wide surgical margins resulted in fewer local recurrences and better overall survival.	
Wright 2020	USA	Retrospective cohort study	vertebral column and sarcal chordoma	vertebral column and sarcal chordoma		Community cancer program (CCP): 100-500 ca cases/yr. Comprehensive community cancer program (CCCP): 100-500 cases/yr. Academic research program (ARP): postgraduate eductaion in4+ specialities+ >5-- cancer cases. Integrated network cancer program (INCP): multiple facilities providign integrated cancer care and comprehensive services	CCP: 3.4%, CCCP: 18.1%, ARP: 56.2, INCP: 9.2%	2004 - 2015	1266	No difference in RT use and time to RT by centres	CCP and CCCP were less likely to have Sx.	–	Adjusted median survival: 131 months v 124 months v 109 months v 79 months	ARP 76.08% v INCP 70.3% V CCCP 61.5% v CCP 52.7%	–	ARP: 1, CCP HR 1.98 p0.018, CCCP HR 1.29 p=0.089, INCP HR 1.19 p=0.425	ARP is associated with increased odds of treatment associated with improved OS. No difference in odds of receiving RT/time to RT. NCDB (No RT details/location, No local recurrence)

Appendix 7. Quality Assessment Clinical Question 2

Study	Title	NHMRC Level of Evidence	Risk of Bias (Newcastle Ottawa scale for cohort study)			
			Selection	Comparability	Outcome	Overall
Abellan 2009	Nonreferral of possible soft tissue sarcomas in adults: A dangerous omission in policy	III-2	4	1	2	Good Quality
Adam 2019	Hospital volume threshold for the treatment of retroperitoneal sarcoma	III-3	4	2	2	Good Quality
Bagaria 2018 (1)	Improving Long-Term Outcomes for Patients with Extra-Abdominal Soft Tissue Sarcoma Regionalization to High-Volume Centers, Improved Compliance with Guidelines or Both?	III-2	4	2	2	Good Quality
Bagaria 2018 (2)	The Volume-Outcome Relationship in Retroperitoneal Soft Tissue Sarcoma: Evidence of Improved Short- and Long-Term Outcomes at High-Volume Institutions	III-2	4	2	3	Good Quality
Bedi 2015	Biopsies in the Community Lead to Postoperative Complications in Soft Tissue Sarcomas	III-3	4	2	2	Good Quality
Berger 2018	Overall survival after resection of retroperitoneal sarcoma at academic cancer centers versus community cancer centers: An analysis of the National Cancer Data Base	III-2	4	2	2	Good Quality
Bhangu 2004	Should Soft Tissue Sarcomas be Treated at a Specialist Centre?	III-2	4	2	2	Good Quality
Blay 2017	Improved survival using specialized multidisciplinary board in sarcoma patients	III-2	4	2	2	Good Quality
Blay 2019	Surgery in reference centers improves survival of sarcoma patients: a nationwide study	III-2	4	2	2	Good Quality
Bonvalot 2009	Primary retroperitoneal sarcomas: A multivariate analysis of surgical factors associated with local control	III-3	4	2	3	Good Quality
Bonvalot 2019	Survival Benefit of the Surgical Management of Retroperitoneal Sarcoma in a Reference Center: A Nationwide Study of the French Sarcoma Group from the NetSarc Database	III-2	4	2	2	Good Quality
Collignon 2020	Soft tissue sarcoma in children, adolescents and young adults: Outcomes according to compliance with international initial care guidelines	III-2	4	2	3	Good Quality
Decanter 2019	Watch and Wait Approach for Re-excision After Unplanned Yet Macroscopically Complete Excision of Extremity and Superficial Truncal Soft Tissue Sarcoma is Safe and Does Not Affect Metastatic Risk or Amputation Rate	III-2	4	2	3	Good Quality
Derbel 2017	Survival impact of centralization and clinical guidelines for soft tissue sarcoma (A prospective and exhaustive population-based cohort)	III-3	4	1	3	Good Quality
Dilday 2021	Disparities in Amputation Rates for Non-metastatic Extremity Soft Tissue Sarcomas and the Impact on Survival	III-2	4	2	3	Good Quality
Engstrom 2008	Liposarcoma: outcome based on the Scandinavian Sarcoma Group register	III-2	4	2	3	Good Quality
Feinberg 2018	Impact of specialist management on survival from radiation-associated angiosarcoma of the breast	III-2	4	2	3	Good Quality
Freeman 2018	Impact of early access to multidisciplinary care on treatment outcomes in patients with skull base chordoma	III-3	4	1	2	Good Quality
Gantzer 2019	Conformity to Clinical Practice Guidelines at Initial Management in Adult Soft Tissue and Visceral Tumors since the Implementation of the NetSarc Network in Eastern France	III-2	4	2	2	Good Quality
Gilg 2020	Tumor-associated mortality and prognostic factors in myxofibrosarcoma - A retrospective review of 109 patients	III-2	4	2	3	Good Quality
Gustafson 1994	Soft tissue sarcoma should be treated at a tumor center: A comparison of quality of surgery in 375 patients	III-2	4	0	3	Poor Quality
Gustafson 1999	Soft tissue sarcoma of the upper extremity: Descriptive data and outcome in a population-based series of 108 adult patients	III-2	4	0	3	Poor Quality
Hu 2019	Treatment-related prognostic factors in managing osteosarcoma around the knee with limb salvage surgery: A lesson from a long-term follow-up study	III-2	4	2	2	Good Quality
Ipach 2012	Oncological outcome and prognostic factors in the therapy of soft tissue sarcoma of the extremities	III-2	4	2	3	Good Quality
Kalaiselvan 2019	Impact of centralization of services on outcomes in a rare tumour: Retroperitoneal sarcomas	III-2	4	1	2	Good Quality
Keung 2018	Treatment at low-volume hospitals is associated with reduced short-term and long-term outcomes for patients with retroperitoneal sarcoma	III-2	4	2	3	Good Quality
Kikuta 2013	An analysis of factors related to recurrence of myxofibrosarcoma	III-2	4	2	3	Good Quality
Lans 2019	Soft tissue sarcoma of the hand: Is unplanned excision a problem?	III-2	4	2	2	Good Quality
Lo 2020	A need for clarity on surgical management of breast sarcoma: Scottish sarcoma network guidelines and regional audit	III-2	4	1	2	Fair Quality
Lytvynenko 2019	Local recurrences after the treatment of soft tissue malignant fibrous histiocytoma (unclassified pleomorphic sarcoma) of the limbs	III-2	4	0	2	Poor Quality
Maurice 2017	Predictors of surgical quality for retroperitoneal sarcoma: Volume matters	III-2	4	2	3	Good Quality
Merchant 2012	Practice referral patterns and outcomes in patients with primary retroperitoneal sarcoma in British Columbia	III-2	4	1	3	Good Quality
Moris 2020	Textbook outcomes among patients undergoing retroperitoneal sarcoma resection	III-2	4	2	3	Good Quality
Ozger 2018	Management of primary malignant bone and soft tissue tumors of foot and ankle: Is it worth salvaging?	III-3	4	0	3	Poor Quality
Paszat 2002	Processes and outcomes of care for soft tissue sarcoma of the extremities	III-2	4	2	2	Good Quality
Pollock 2004	Biopsy of musculoskeletal tumours - Beware	III-3	4	0	3	Poor Quality
Sakabe 2008	Evaluation of clinical outcomes and prognostic factors for synovial sarcoma arising from the extremities	III-3	4	0	3	Poor Quality

Sandrucci 2018	Different quality of treatment in retroperitoneal sarcomas (RPS) according to hospital-case volume and surgeon-case volume: A retrospective regional	III-2	4	1	3	Good Quality
Stiles 2018	Desmoplastic small round cell tumor: A nationwide study of a rare sarcoma	III-2	4	2	3	Good Quality
Stiller 2006	Patterns of care and survival for patients aged under 40 years with bone sarcoma in Britain, 1980-1994	III-2	4	2	3	Good Quality
Takeuchi 2016	Clinical outcome of recurrent giant cell tumor of the extremity in the era before molecular target therapy: The Japanese Musculoskeletal Oncology	III-2	4	1	2	Good Quality
Toulmonde 2014	Retroperitoneal sarcomas: Patterns of care at diagnosis, prognostic factors and focus on main histological subtypes: A multicenter analysis of the French Sarcoma Group	III-2	4	2	3	Good Quality
Traub 2018	Influence of unplanned excisions on the outcomes of patients with stage III extremity soft-tissue sarcoma	III-2	4	2	3	Good Quality
Villano 2019	Identifying the Minimum Volume Threshold for Retroperitoneal Soft Tissue Sarcoma Resection: Merging National Data with Consensus Expert Opinion	III-2	4	2	3	Good Quality
Villano 2019	Regionalization of retroperitoneal sarcoma surgery to high-volume hospitals: Missed opportunities for outcome improvement	III-2	4	2	3	Good Quality
Villano 2020	Variations in retroperitoneal soft tissue sarcoma outcomes by hospital type: A national cancer database analysis	III-2	4	2	3	Good Quality
Vos 2019	Increased survival of non low-grade and deep-seated soft tissue sarcoma after surgical management in high-volume hospitals: a nationwide study	III-2	4	2	2	Good Quality
White 2019	Management of Sarcoma in Adolescents and Young Adults: An Australian Population-Based Study	III-2	4	2	3	Good Quality
Widhe 2009	Surgical treatment is decisive for outcome in chondrosarcoma of the chest wall: A population-based Scandinavian Sarcoma Group study of 106 patients	III-2	4	2	2	Good Quality
Abarca 2018	Improved survival for extremity soft tissue sarcoma treated in high-volume facilities	III-3	4	1	3	Good Quality
Bauer 2001	Monitoring referral and treatment in soft tissue sarcoma: study based on 1,851 patients from the Scandinavian Sarcoma Group Register	III-3	2	1	3	Fair Quality
Gatta 2019	The European study on centralisation of childhood cancer treatment	III-2	2	0	1	Poor Quality
Gutierrez 2007	Should soft tissue sarcomas be treated at high-volume centers? An analysis of 4205 patients	III-2	4	1	2	Good Quality
Hoekstra 2017	Adherence to Guidelines for Adult (Non-GIST) Soft Tissue Sarcoma in the Netherlands: A Plea for Dedicated Sarcoma Centers	III-3	4	1	1	Poor Quality
Lazarides 2019	Soft Tissue Sarcoma of the Extremities: What Is the Value of Treating at High-volume Centers?	III-3	4	2	3	Good Quality
Lazarides 2020	Does facility volume influence survival in patients with primary malignant bone tumors of the vertebral column? A comparative cohort study	III-3	4	2	3	Good Quality
Malik 2020	Is Treatment at a High-volume Center Associated with an Improved Survival for Primary Malignant Bone Tumors?	III-3	4	2	2	Good Quality
Martin-Broto 2019	Relevance of Reference Centers in Sarcoma Care and Quality Item Evaluation: Results from the Prospective Registry of the Spanish Group for Research in Sarcoma (GEIS)	III-2	4	0	2	Poor Quality
Ray-Coquard 2004	Conformity to clinical practice guidelines, multidisciplinary management and outcome of treatment for soft tissue sarcomas	III-3	4	1	3	Good Quality
Sampo 2012	Soft tissue sarcoma - a population-based, nationwide study with special emphasis on local control	IV	4	0	2	Poor Quality
Schmitz 2019	Overcoming a travel burden to high-volume centers for treatment of retroperitoneal sarcomas is associated with improved survival	III-3	4	2	3	Good Quality
Song 2019	Trends in practice patterns and outcomes: A decade of sarcoma care in the United States	III-3	4	2	3	Good Quality
Tan 2018	Patterns of care of superficial soft tissue sarcomas: it is not always just a lump	III-3	4	2	2	Good Quality
Venigalla 2018	Association Between Treatment at High-Volume Facilities and Improved Overall Survival in Soft Tissue Sarcomas	III-3	4	2	3	Good Quality
Wright 2020	Association of cancer center type with treatment patterns and overall survival for patients with sacral and spinal chordomas: An analysis of the National Cancer Database from 2004 to 2015	III-3	4	2	1	Poor Quality

Appendix 8. Clinical Question 2 Outcomes summary tables

Outcome: 30, 90 day mortality

Ref	Author	Year	Sarcoma	No. of patients	30-day Mortality	90-day Mortality	Notes
4384	Adam	2019	PRS	5,340		2% HVH vs 6% LVH (p = 0.04)	HVH > 10 cases/year; LVH < 5 cases/year)
4056	Bagaria	2018	STS	13684	3T hospital not associated with lower risk of 30-ay mortality (OR 0.7)		High volume (3T) > 11 cases/year
4054	Bagaria	2018	PRS	5407 (HiVH 563, LVH 4471)	0.5% HVH vs 2.4% LVH (p = 0.027)	1.2% HVH vs 5.3% LVH (p = 0.0012)	High volume > 10 cases/year, low volume < 5)
4533	Berger	2018	PRS	CCC 1120 vs ACC 1642		6.2% (CCC) vs 6.4% (ACC) (p = 0.809)	community cancer centre (CCC) vs acadamic cancer centre (ACC). ACC status if annual volume of > 500 new cancer diagnoses
3172	Gutierrez	2007	STS	4205	0.7% (HVC) vs 1.5% (LVC) (p = 0.028)	1.6% (HVC) vs 3.6% (LVC) (p = 0.001)	Separated into tertiles based on volume. HVC repressented top tercile 5 - 24 cases/year; LVC represented bottom two tertiles (< 4 cases/year)
2558	Kalaiselvan	2019	PRS	72		No difference between pre- and post-centralisation	
2455	Keung	2018	PRS	6950	1.9% vs 3.1% (p < 0.004)	3.2% vs 5.7% (p = 0.007)	HVH > 10 cases/year. "failure to rescue" following perioperative complication - differences noted between high volume and low volume hospitals for other major surgery. Cannot identify cause for increased mortality
2242	Lazarides	2019	STS	HVC 3310 LVC 22,096	HVC 0.3% vs LVC 0.4% (p = 0.018)		HVC > 20 cases/year
871	Schmitz	2019	PRS	2599	1.2% (LT/HV) vs 2.8% (ST/LV) (p = 0.0026)		long travel (56 miles) to high volume (> 10 cases per year) vs short travel burden (4 miles) to low volume (1 case/year)
1012	Stiles	2018	Desmoplastic small round cell tumour	HVH 15; LVH 110	0% HVH vs 1.6% LVH (p = 0.706)	0% HVH vs 4.7% LVH (p = 0.507)	NOT STATISTICALLY SIGNIFICANT. Desmoplastic small round cell tumour; HVH > 5 cases between 2004 and 2014
618	Villano	2019	PRS	HVH 840, LVH 6701	0.7% (HVH) vs 1.5% (LVH) (p = 0.138)	2.3% (HVH) vs 3.7% (LVH) (p = 0.102)	NOT STATISTICALLY SIGNIFICANT. HVH > 10 cases/year; LVH < 5 cases/year)
624	Villano	2019	PRS	LVH 8336; HVH 385		2.1% (HVH) vs 3.7% (LVH)	HVH > 13 cases; LVH < 13 cases

Outcome: Limb Salvage

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	Total no: of patients	Group differences	Endpoint	endpoint	2 yr OS	5 yr OS	10 yr OS	Multivariate analysis	Comments
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	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 7%, 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	No difference in limb salvage rate, RT rate but more Chemo in high Vol. Can't separate specific data for RT (quality, dose, toxicity). Data For OVERALL specialised
Decanter 2019	France	Retrospective cohort study	soft tissue of extremity or truncal	soft tissue sarcoma arising in the limbs or superficial truncal initially operated outside of community centers	surgical biopsies, R2 or piecemeal resections, non-amenable to curative-intent surgery (e.g.multifocal disease, presence of node involvement, or presence of distant metastasis)	Sarcoma reference centres in France Group A. Patients who underwent systematic re-excision in sarcoma reference centers after referral. Group B. Patients who underwent re-excision outside of community centers, which had already been performed at referral. Group C Patients without systematic re-excision, grouping together patients who could have had re-excision but did not undergo surgery intentionally and patients for whom radiotherapy was chosen over surgery due to the potential morbidity of re-excision	ConticaBase prospective database, all consecutive patients with STS arising in the limbs or superficial truncal initially operated outside of community centers and then referred to 1 of 18 participating sarcoma reference centers in France	1 January 2007 and 31 December 2013	Total 576	RD resection and (neo)adjuvant radiotherapy were regarded as confounding factors for LRFS. Tumor over 50 mm in size, deep tumor, and (neo)adjuvant radiotherapy were associated with MRFS and were regarded as confounding factors.	For local recurrence, amputation as a second procedure - None in Group A(0) and in Group B/C(6.6%)	After RE, the RD resection rate was higher in Group A compared with Group B.	_	5-year OS was 88.4%, 87.3%, and 88% in Groups A, B, and C, respectively (p = 0.22), while 5-year MFRS (Metastsic relapse free survival) was 85.4%, 86.2%, and 84.9%, respectively (p = 0.938). Overall statistically no significant difference.	_	Group A patients showed significantly improved LRFS (p = 0.0001) after taking into account confounding factors such as RD resection and (neo)adjuvant radiotherapy. Multivariate analysis also showed that RE in SRCs did not influence MFRS (p = 0.367) after taking into account confounding factors such as tumor size, deep tumor, and (neo)adjuvant radiotherapy	
Dilday 2021	USA	Retrospective cohort study	soft tissue	soft tissue sarcoma of the extremity (All patients)	metastatic disease	Academic >10 extremity sarcomas each year, Community for 5- 0 cases per year Other <5 cases/year	1500 Cancer-accredited facilities and captures more than 70% of all newly diagnosed malignancies in the United States annually.	1998-2012	15886		**Overall amputaion rates - 4.7%** High volume vs moderate/low volume centre (5.6% vs 3.4% / 3.3%; p<0.001). Academic centres vs community hospitals (5.4% vs 3.7%;p< 0.001) In older adults amputations significantly less in community facility (OR-0.75)	_	_	_	66% for extremity STS with an amputation. At higher volume centers (HR 0.83, CI 0.74–0.94) had a decreased risk of death at 10 years	females (HR 0.83, 95%CI 0.78-0.89) and those treated at higher volume centers (HR 0.83, 95%CI 0.74-0.94) had a decreased risk of death at 10 years.	
Gustafson 1994	Sweden	Retrospective cohort study	soft tissue	adult soft tissue sarcoma of extremity and trunk minimum follow up 3 years	not operated mets at Diagnosis	Group A: referred before Sx Group B: referred after Sx Group C: not referred	1 university of Lund Population based database for Sweden health care region, 1.5M population	1970-1989	375		Crude local recurrence rate 19% v 21% v 62% (p= not reported)	amputation rate: 9% v 15% v 6% (P=not reported). Crude death rate: 26% v 23% v31% (P=NR)	–	_	_	Not done	
Gutierrez 2007	USA	Retrospective cohort study	Soft tissue (1st presentation for Sx), extremity and RPS	Soft tissue (1st presentation for Sx), extremity and RPS		facilities grouped into 3 balanced percentile ranges by surgical volume. Top 1/3 vs 2/3	256	1981-2001	4205		30 & 90 day mortality 0.7% v 1.5% (p 0.028), 1.%v 3.6% (p<0.001)	Amputation rate 9.4% v 13.8% (p=0.048)		37.4% v 33.2% (p=0.002)	15.9% v 11.6% (p=0.002)	Overall survival: high vol=1, low Vol RR of death 1.292 (1.003-1.663, p= 0.047)	high RT use in high vol. centre. No LR data. High Volume centres: younger, more high grade, more >10cm, more extremity, more RT and chemo use. Treatment at a HVC was an independent predictor of good outcome. Better OS for treatment (Sx/RT/Chemo) at high vol centre, no specific RT endpoint by volume.
Lans 2019	USA	Retrospective cohort study	Soft tissue sarcoma of hand	Soft tissue sarcoma of hand age =>18	insufficient data (n=6) rejected standard surgical treatment (n=1) adequate oncological treatment outside (n=4)	single centre (Mass General hospital) vs other non oncological centre	1 vs others	1971-1992	64	Patients treated initially at an oncology center had worse overall survival, 60% 5-years survival, compared to patients treated initially at non-oncology center, 89% 5-year survival (p=0.021) .	Final Margin (positive) 12% v 25%, p=0.36	Amputation 33% v 42%, p=0.25	_	Patients treated initially at an oncology center had worse 5yr OS 60% compared to patients treated initially at non-oncology center, 89% l (p=0.021) However, there was no association when multivariable Cox regression was performed with corrections for tumor size (HR: 1.5,95% CI: 0.96-2.4, p=0.078_	_	no association when multivariable Cox regression was performed with corrections for tumor size (HR: 1.5, 95% CI: 0.96-2.4, p=0.078). Positive final margin was independently associated with the development of metastasis (HR: 5.4, 95% CI: 1.3-22.5,p=0.022). In multivariable Cox's regression, a positive margin (HR: 3.9, 95% CI: 1.0e14.8,p=0.048) was independently associated with worse disease-free survival.	small no.
Lazarides 2019	USA	Retrospective cohort study	soft tissue of extremity	soft tissue sarcoma of the extremity	–	High vol.≥20 pts per year	High volume 1270 (9=high vol.centres), low volume 22096 (87%)	1998-2012	25406		positive margin 10% v 17%, p<0.001. No difference in amputation (5%v 5%). More radical resection in high vol 65% v 45%, p<0.001.	30-day mortality 0.3% v 0.4%, p=0.018	–	better OS seen in all grades	_	lower risk of death in high vol. HR 0.81, 0.75-0.88, p<0.001	No RT quality details, no local recurrence data
Malik 2020	USA	Retrospective cohort study	Osteosarcoma Chondrosarcoma Ewing,Ads sarcoma Chordoma Others	1.Primary malignant bone tumors of the extremities (C40.0-C40.3, C40.8, and C40.9) undergoing treatment (surgery, chemo-therapy, and/or radiotherapy) 2.Registered in National Cancer Database between 2004 to 2015	1. Primary malignant spinal osseous tumors 2. Benign tumours	high-volume (at least 20 patients per year) low-volume (fewer than 20 patients per year)	835 (High volume centres - 6, Low volume centre - 829)	2004 - 2015	14039 (high volume:2215, 15%. Low volume: 11924, 85%)	RT use: High vol 13% vs low vol 17%, p<0.001	for the 40% of pts who commenced treatment with combined modality treatment in specialised centre, there were no recurrences	_	_	High vol 65% v 61%, p=0.003	_	more limb salvage surgery OR 1.34 (1.14-1.59, p=0.001). Lower mortaility (HR 0.85, 0.77-0.93, P<0.001)	No RT quality details, no local recurrence data. SB: Very similar to Lazarides 2019 paper; only 15% of pts managed at LVC (similar to STS-6), ?okay to apply this to Australian context? Very different medicare structure, quite surprising that substantial proportions of patients with ewing sarcoma and osteosarcoma being managed at LVC (this is less likely to happen in Aus, I thought?)
Paszat 2002	Canada	Retrospective cohort study	soft tissue sarcoma extremity	age >17 soft tissue sarcoma extremity		d	147 hospitals	1 Jan 1987-31 Dec 1996	n=1467	–	RT use increased with: increasing case load of the hospital of first admission (p<0.0001), and increasing attendance rates at acancer centre within 3 months of diagnosis (p<0.0001)	_	_	_	_	The adjusted relative risk of amputation at any time following diagnosis was 3.5 (95% CI (1.63, 7.46) among cases not attending a cancer centre. For cases not attending a cancer centre within 3 months of Dx, The adjusted relative risk of death was 1.4 95% CI (1.1, 1.7).	
Pollock 2004	Australia	Retrospective cohort study	all musculoskeletal tumour	all musculoskeletal tumour	bony mets	Biopsy by senior sarcoma surgeon (Stalley, n=113) vs biopsy by referring surgeon outside the sarcoma centre (n=29)	1	2002	142	–	Amputation: Bx by Stalley 7% v 25%, p=0.03. Suboptimal biopsy hindering definitive treatment: 1.8% v 38%, p=0.0001	Adquate diagnostic material: 97% v 72%, p=0.0001. Adjuvant RT: 5.3% v 20%, p=0.05	–	_	_	did not adjust for other factors such as age gender, tumour factor. Hence 0 star for comparability on the Ottawa scale	single surgeon, no mutlivariate anlaysis but Australian data
Traub 2018	Canada	Retrospective cohort study	soft tissue	Stage 3 (>5cm, deep, high grade) soft tissue sarcoma extremity minimum follow up 24 monmths	metastatic disease	planned excision vs unplanned excision elsewhere (all had further treatment at sarcoma centers)	2 (Mount Sinai Hospital and Princess Margaret Cancer Center), unplanned excision elsewhere before referral vs planned excision at these 2 centers	1986-2010	500 (406 planned excision, v 94 unplanned)	–	5 year Local recurrence free rate: planned excision 90.1% v 88.3%, p-0.42	amputation: planned 10.1% v 18.1%, p0.03. Postop complication requiring Sx: No difference	–	Planned excision 50.1% v unplanned 54%, p=0.3	_	unable to identify any parameter that increased the risk of overall, metastasis-free, and local recurrence-free survival rates.	whoops sx but all had final treatment at sarcoma centres. Authors: Unplanned excision leads to an unfavorable clinical course and necessitates more extensive surgery. As a result of aggressive re-excision and multidisciplinary treatment, a negative effect on oncologic outcomes cannot be confirmed.

Outcome: Local Recurrence

Ref	Author	Year	Sarcoma	No. of patients	Local recurrence (Sarcoma centre vs non)	Incomplete resection (Sarcoma centre vs non)	Local recurrence-free survival (Sarcoma centre vs non)	Notes
281	Toulmonde	2014	PRS	586	Hazard ratio 0.5 if performed by specialist surgeon (multivariate analysis)	Harard ratio 2.9 for piecemeal resection		
4056	Bagaria	2018	STSE	13,684		3T higher rate margin negative vs 1T [90% vs 83%)		3rd Tertile > 11 cases/year; 1st Tertile < 3 cases/year
3046	Hoekstra	2017	STSE	3317		Less R2 resections in high volume centres (odds ratio 0.54)		Higher rates of R1 resection in higher volume may be due to marginal resection to preserve function
423	Tan	2018	STS	89	6.5% vs 24%	77% vs 74%		
3174	Gustafson	1994	STS	195 patients referred before surgery vs 102 referred after surgery vs 78 not referred	18% in patients referred before surgery vs 1.7 x higher for patients referred after surgery vs 2.4 x higher for patients not referred			
2373	Malik	2020	Bone	2115 high volume (at least 20 cases/year) vs 11,924 low volume (< 20 cases/year)	4% margin positive vs 8%			high volume centres with lower margin positive rates, but also lower amputation rates
4668	Abarca	2018	STSE	7874		12% vs 17%		High volume centres with fewer positive surgical margins
4574	Bauer	2001	STS	1851	5 year cumulative local recurrence rate 0.2 (sarcoma centre) vs 0.7	negative margin 66% in sarcoma centre vs 11%		
2242	Lazarides	2019	STSE	25,406: 3310 in high-volume centre (> 20 cases/year) vs 22,096 in low volume centres (< 20 patients/year)		High volume centres less likely to have positive margins (odds ratio 0.59)		
871	Schmitz	2019	PRS	2599		ST/LV ssignificantly more R2 resections (4.4% vs 2.6%)		long travel (56 miles) to high volume (> 10 cases per year) vs short travel burden (4 miles) to low volume (1 case/year)
1264	Ray-Coquard	2004	STS	100	21% cancer centre vs 49% for other	R2 resection higher in general hospital (61%) vs cancer hospital (27%)		
1356	Sampo	2012	STS	219			5 year LRFS 82% (high volume) vs 61% (intermediate) vs 69% (low)	
2244	Lazarides	2020	bone - vertebral column	733			No difference in margin status between high and low volume facilities	
3457	Ipach	2012	STS	118	9.1% vs 17.2% in first year; 12.5% vs 32.5% after 3 years; and 21.2% vs 45.7% after 5 years			
620	Villano	2020	PRS	10,113		academic centres more R0/R1 (87.6% vs 78.3%)		
4407	Bonvalot	2019	PRS	2945		41.9% first resections were R0 at NetSarc facility vs 12.3%	2 year local progression-free survival 75% at NetSarc facility vs 55%	
2890	Feinberg	2018	RAAS	36	patients managed locally had higher rate of local recurrence (8 out of 10) vs at sarcoma serivce (9 of 26)	No significant difference	20.9 months (sarcoma service) vs 5.5 months	
1482	Paszat	2002	STSE	1467	Increasing STSE case volume associated with increased proportion of definitive surgery - i.e. no revisions			
4533	Berger	2018	PRS	2762		Academic centres more R0 55.9% vs 47.0%; lesser odds of positive margin 0.83	1	
2603	Gantzer	2019	STS	643		R0/R1 higher in reference centres 48.6% vs 32%		higher rates of R0 resection in referral centre
1079	Song	2019	STS	55212		R0 higher in high volume (78.5% vs 72%)		high volume > 90th percentile number of patients treated per year
640	Venigalla	2018	STS	9025: 1578 high volume vs 7447 low volume		treatment at high volume facility decreased likelihood of positive margins (odds ratio 0.72)		high volume (top 1% by case volume 79 - 252 cases)
2558	Kalaiselvan	2019	PRS	72	12.7% (post-centralisation of referrals) vs 21.2%			
189	Widhe	2009	Chondrosarcoma	106 patients; 97 surgeries with curative intent	treatment at sarcoma centre 9/55 recurrences vs 24/42 in those treated at nonspecialty centres	4/55 sarcoma centre resections were intralesional vs 22/42		

624	Villano	2019	PRS	840 at high volume hospitals; 1180 at medium volume; and 6701 at low volume		92.7% R0 (HVH) vs 83% R0 (LVH)		high volume > 13 procedures/year
3319	Gilg	2020	Myxofibrosarcoma	109: 68 sarcoma centre, 41 non-sarcoma centre		adeuate margins significantly more common if primary resection at sarcoma centre	5 year LRFS OR 0.4 (p 0.26)	Local recurrece occurred more commonly in patients who underwent primary resection with inadequate margins (OR 8.5); R1 status at primary resection was an independent risk factor for decreased local recurrence free survival
1350	Sandrucci	2018	PRS	138		Multivariate analysis: high volume comprehensive cancer centre better quality macroscopic margins (R0/R1) and higher rate of intact tumour resection. HVCCC 80% R0/R1 vs high volume tertiary centre 60% R0/R1	1	HVCCC: dedicated surgical team (> 20 surgeries/year) and regular MDT; HVTCA: no dedicated team < 5 cases per year; but. Formal MDT)
4647	Abellan	2009	STSE	174	Group A 10%, Group B 13%, Group C 59%			group A (virgin STS) 57%, group B (whoops cases - referred after excision) 22%, group C (referred after recurrence) 21%; "whoops" case = inadequate initial excision (IIE)
1965	Merchant	2012	PRS	82		R0 /R1 97.6% if referred before surgery vs 65.9% if referred after initiial resection	LRFS significantly affected by referral group (p 0.04) in univariate but not multivariate	
954	Sakabe	2008	Synovial Sarcoma	17	4/7 (57.1%) treated initially at other hospital vs 5.9% at referral centre			
2422	Lytvynenko	2019	malignant fibrous histiocytoma	130	86.9% recurrence if primary treatment in centre with only general surgical facilities vs 40% in specialised oncological centre			
4069	Collignon	2020	STS paeds	127			LRRFS for malignant tumours improved with ESMO CPG compliance (89.3% vs 61.1%)	
430	Takeuchi	2016	Recurrent GCT bone	103	re-recurrence: treatment elsewhere 8/12 vs 24/91 at specialist centre		5 year LRFS 0.563 for initial treatment elsewhere vs 0.682 at specialist institution (p 0.002)	
4421	Blay	2019	STS	35784		R0 53.0% first ssurgery in NetSARC vs 19.6% outside	Surgery in NetSARC centre HR 0.654	
4054	Bagaria	2018	PRS	5407		R0 81.5% (high volume) vs 68.2%; R2 2.4% (high volume) vs 5.4% (p 0.0001)		High volume > 10 cases/year, low volume < 5)
4384	Adam	2019	PRS	5,340		high volume vs low volume OR 0.58 for margin positivity		
594	Vos	2019	STS	5282		"whoops" resection lower as annual surgical volume increased (62% low volume vs 29% high volume)		
2013	Maurice	2017	PRS	3141		high volume centre 1.8 -fold higher odds of R0 resection	1	
2089	Lo	2020	Breast	46		incomplete excision rate 0% at sarcoma centre vs 50% at peripheral hospitals		
2455	Keung	2018	PRS	6950		R2 resection higher in low volume hospital (< 10 cases) 4.5% vs 1.6%		
2308	Kikuta	2013	Myxofibrosarcoma	100		1	multivariate analysis - correlation with 5 year LRFS: primary unplanned resection at another facility 55% vs 89%	can die from local recurrence without metastasis
4399	Bonvalot	2009	PRS	382	multivariate analysis: higher number of operations per centre correlates with decreased abdominal recurrence and better local control (p 0.002)			
3540	Decanter	2019	STSE	Group A 300; Group B 71; Group C 251	28/300 group A, 15/71 group B, 80/251 group C		5 year LRFS 83% group A, 73.5% group B, 63.8% group C; Group A hazard ratio 0.43 (p 0.00001)	Group A (systematic re-excision at sarcoma referral centre); Group B (systematic re-excision outside of community centres); Group C (without re-excision)
4491	Bhangu	2004	STS	260	39% at district hospitals vs 19% at specialist centre p 0.0011			Rate of local recurrence related to centre of treatment but not tumour size, depth or grade

3771	Engstrom	2008	Liposarcoma	237	univariate analysis: primary surgery at outside centre p 0.0033; multivariate analysis: primary surgery outside sarcoma centre p 0.018	45% treated at sarcoma centre had wide margin vs 0 if treated outside		

Outcome: Overall Survival

Study Identifier	Country	Design	Type of Sarcoma (bone, soft tissue etc)	Inclusion criteria	Exclusion criteria	No. of pts	Definition of high volume/specialised centre	Endpoint	endpoint	2 yr OS	5 yr OS	10 yr OS	Multivariate analysis	Comments
Bagaria 2018	USA	Retrospective cohort study	retroperitoneal sarcoma	Retroperitoneal sarcoma	GiST extra-abdominal sarcoma	5407	Average annual volume/hospital of curative intent surgery for RPS was calculated by dividing the total number of surgical resections performed at a hospital by the number of years that data were reported to the NCDB. low volume (<5 cases/year), medium volume (5,Ä¡10 cases/year),and high volume (>10 cases/year)	Positive margins High volume - 16.3% Intermediate volume - 31.8% Low volume - 26.3% 30 day - Mortality 0.5% vs 2.4% Log regression analysis - 4 fold increase in a low volume centre OR =4.66 90 day - Mortality 1.2% vs 5.3%	_	_	Overall 66% vs 56% P<0.001. Patients undergoing curative intentive surgery 69% vs 57%	_	for R0 margin rate; low-volume centers were less likely to achieve R0 margin status compared to high-volume centers (OR 0.46, 95% CI 0.31-0.70;P=0.0003). Patients undergoing RPS surgery at a low-volume hospital had a greater than 4 fold increase in the risk of dying within 30 days if surgery compared to patients undergoing surgery at a high-volume hospital (OR=4.66; p<0.001). 90-day mortality rates followed a similar trend for absolute and adjusted risk of post-operative mortality. patients who were treated at a low-volume hospital had a 52% greater risk of all-cause long-term mortality compared to those treated at a high-volume hospital (HR 1.56, 95% CI 1.16–2.11; p = 0.0032).	"High-volume centers were more likely to treat patients whose tumors were larger (17.5 cm versus 15 cm) and of higher grade (58% versus 47%) than low-volume centers. "
Bhangu 2004	UK	Retrospective cohort study	soft tissue sarcoma	soft tissue sarcoma	Head and neck GiST RPS	360	pts were identified from the Cancer Intelligence Unit database only one hospital in the health region had sarcoma MDT	**adequate excision margins (wide or radical margin)** (39% vs 35%) **Local recurrence LR** (19% vs 39%) P value = 0.0011. Positive margin conferred a 45% risk of LR at DGH vs 32% at SC	_	_	58% not significantly different between the two centres	_	grade, depth, size of tumour and treatment centre to be the most significant in Overall survival	
Blay 2019	France	Prospective cohort study	Bone and ST	Confirmed sarcoma diagnosis	None	29497	Multidisciplinary tumour board	Initial R0 resection (53% vs 19.6%) R1 resection (24% vs 20.2%) R2 resection (4.2% vs 8.5%) Unknown (18.8% vs 50%). Reoperation 6.2% vs 15.7%. Final R0 resection (56.7% vs 29.5%) R1 resction (21.8% vs 15.7%) R2 resection (3.0% vs 6.2%)	_	_	_	_	Local relapse free survival - NETSARC MDT before treatment HR = 0.670 P , Surgery in a NETSARC center HR = 0.654. Disease free survival Surgery in a NETSARC center HR = 0.843 NETSARC MDT before treatment HR 0.800 Overall survival NETSARC MDT before treatment HR 1.563, Surgery in a NETSARC center HR= 0.681"	
Bonvalot 2019	France	Prospective cohort study	retroperitoneal sarcoma	surgery for non metastatic retroperitoneal sarcoma age> 15	desmoid GiST	2945	a clinical network for sarcoma (NetSarc), 26 reference centres	**NSC (Specialised centre) vs others, 2 yr Local progression free survival (LPFS)** 75% vs 55% P <0.001	**NSC (Specialised centre) vs others,** R0 resections (41.9%) vs. (12.3%) fewer R2 resections (4.5%) vs. (9.2%) fewer piecemeal resections with nonevaluable or unknown margins (19.7%) vs.(60.7%) (p =0.001)	87% vs 70%	_	_	In the multivariate analysis, surgery in an NSC was an independent predictor of OS, with a two fold lower odds ratio of death than that for surgery outside NetSarc (OR: 0.496,p0.001)	
Dilday 2021	USA	Retrospective cohort study	soft tissue	soft tissue sarcoma of the extremity	metastatic disease	15886	Academic >10 extremity sarcomas each year, Community for 5- 0 cases per year Other <5 cases/year	**Overall amputaion rates - 4.7%** High volume vs moderate/low volume centre (5.6% vs 3.4% / 3.3%; p<0.001) Academic centres vs community hospitals (5.4% vs 3.7%;p< 0.001) In older adults amputations significantly less in community facility (OR-0.75)	_	_	_	66% for extremity STS with an amputation. At higher volume centers (HR 0.83, CI 0.74–0.94) had a decreased risk of death at 10 years	females (HR 0.83, 95%CI 0.78-0.89) and those treated at higher volume centers (HR 0.83, 95%CI 0.74-0.94) had a decreased risk of death at 10 years.	
Hu 2019	China	Retrospective cohort study	osteosarcoma around the knee	Osteosarcoma around the knee limb salvage surgery	Mets at Diagnosis limb amputation as primary procedure age >60 incomplete follow up (n=13)	182	Biopsy/tumour resection at the sarcoma centre (n=151) vs elsewhere (n=31)	5 year local recurrence free survival 9% v 58.1%, P<0.001	_	_	_	_	For overall survival, the risk factor biopsy/tumor resection performed by different centers (HR 2.8, 1.5-5.2, P=0.001). For local recurrence, in the multivariate analysis, only biopsy/tumor resection performed by different centers was independent predictors of local recurrence (HR 4.099(1.649-10.192), P=0.002).	Did not report intervention details by centers
Keung 2018	USA	Retrospective cohort study	retroperitoneal sarcoma	retroperitoneal sarcoma	paediatric No surgery CNS or bone primary incomplete information	6950	High volume: >10 cases per year Low volume: <= 10 cases per year	R2 resections: 1.6% v 4.5% (p=0.001)	**30 day readmission** (1.8% v 3.4%, p=0.001). **30 day mortality** (1.9% v 3.1%, p=0.004). **90 day mortality** 3.2% v 5.7% p=0.007	_	57.7% v 52%, p=0.003	_	treatment at an HVH was found to be associated with a reduced risk of death compared with treatment at an LVH (HR, 0.77; 95% confidence interval, 0.65-0.91 [P=.003]) Similar results when separate analyses were performed that were limited to patients for whom a Charlson-Deyo Score was available in the NCDB (2003-2011; 3524 patients).	RT use: 17.2% v 27.9%, p<0.001. Multivariate analysis, RT was associated with better OS (HR 0.8, 95%CI 0.73-0.88, p<0.001). BUT no RT fractionation details/toxicity
Lazarides 2019	USA	Retrospective cohort study	soft tissue of extremity	soft tissue sarcoma of the extremity	_	25406	High vol.≥20 pts per year	positive margin 10% v 17%, p<0.001. No difference in amputation (5%v 5%). More radical resection in high vol 65% v 45%, p<0.001.	30-day mortality 0.3% v 0.4%, p=0.018	_	better OS seen in all grades	_	lower risk of death in high vol. HR 0.81, 0.75-0.88, p<0.001	No RT quality details, no local recurrence data
Maurice 2017	USA	Retrospective cohort study	Retroperitoneal sarcoma	Retroperitoneal sarcoma	Metastatic disease unknown N or M stage (n=1929) unknown surgery status (n=7) prior or concurrent cancer status	3141	Hospital volume was classified based on the average number of retroperitoneal sarcoma cases managed at the hospital per year (for actual years that the hospital reported to the NCDB) as low (<5) or high (=>5), with high-volume centers corresponding to the top 10th percentile.	R0/R1 margin: High vol 97.4% v Low vol 92.4%, p=0.002	_	_	Median OS 71.1months v 68.9 months, p=0.341	_	high-volume centers had 1.9-fold higher odds of undergoing surgical management (P< 0.001), 2.5-fold higher odds of receiving a R0/R1 resection (P= 0.026), and 1.8-fold higher odds of an R0 resection (P< 0.001). Academic setting predicted use of surgical management (P< 0.001) and R0/R1 resection (P= 0.015) but not R0 resection (P= 0.882). R1 (HR 0.56, 95%CI 0.43-0.72,P< 0.001) and R0 resection (HR 0.68,95%CI 0.57-0.81,P< 0.001) were strong independent predictors of improved OS.	
Paszat 2002	Canada	Retrospective cohort study	soft tissue sarcoma extremity	age >17 soft tissue sarcoma extremity		1467	135 hospitals admitted fewer than 20 new cases of STSE during the 10 years, 11 admitted between 20 and 50 cases, and one hospital admitted more than 50 cases	RT use increased with: increasing case load of the hospital of first admission (p<0.0001), and increasing attendance rates at acancer centre within 3 months of diagnosis (p<0.0001)	_	_	_	_	The adjusted relative risk of amputation at any time following diagnosis was 3.5 (95% CI (1.63, 7.46) among cases not attending a cancer centre. For cases not attending a cancer centre within 3 months of Dx, The adjusted relative risk of death was 1.4 95% CI (1.1, 1.7).	
Schmitz 2019	USA	Retrospective cohort study	retroperitoneal sarcoma	Retroperitoneal sarcoma		2599	low-volume centre = median annual case volume of 1 case/year, high-volume centre = median annual case volume of 10 cases/year	30 day mortality LT/HV 1.2% v 2.8%, p=0.0026	R2 resection LT/HV2.6% v 4.4%, p=0.003	_	LT/HV 63% v 53%, p<0.0001	_	OS: long distance/high vol HR 0.726 (0.601-0.878, p=0.0009)	NCDB: No RT details, NO local recurrence data
Venigalla 2018	USA	Retrospective cohort study	soft tissue	age>18, Non-metastatic STS treated with definitive surgery and either pre-op or post-op EBRT. Both Sx and RT at the reporting facility (pts treated at multiple centres were excluded)	_	9025	Facilities in top 1 percentile (99th percentile) by case volume (79-252 cases) over the study period	_	_	_	72.2% v 67.4%	57.1% v 49%, p<0.001	propensity-score matching. HV v LV, imporved overall survival, HR 0.87, 0.8-0.95, P=0.001. test for interaction b/w HV and academic centes, Non significant.i.e OS benefit asscoiated with HV was not modified bu treatment at academic centres	All had definitive Sx and RT at one centre, probably can generalise the data to RT (NCDB, no RT details, No local recurrence data)
Villano 2019	USA	Retrospective cohort study	retroperitoneal sarcoma	age 18 retroperitoneal sarcoma	age >90 unknown ethnicity (n=169), unknown insurance (n=250), lack of postoperative follow-up (n=5) stage 4 (n=815) GiST	8721	High volume (>=13 procedures per year), n=385 Low volume (<13 procedures per year), n=8336	Multivisceral resection: 39.2% v 27%, p<0.001. Negative margin: high vol 81% v low vol 72%, p<0.001. R0/R1 resection: 93.8% v 84.6%, p=0.001	30 day admission: 5.5% v 4.6%, p=0.496. 90 day mortality: 2.1% v 3.7%, p=0.145. Mean length of stay 8.8 days v 6.3 days, P<0.001	_	Overall survival, however, was significantly longer atHVHs (74.6% vs 60.9%, p<0.001).	_	Overall mortality risk was reduced by 4% per additional case (HR 0.96, 95%CI 0.95 to 0.98) up to a threshold of 13 cases/year; no further reduction was observed over 13(HR 0.99, 95% CI 0.97 to 1.01).	By vol. not centres or surgeon. There are THREE RPS papers by Villano using the NCDB RPS cases from the same study period.

Villano 2020	USA	Retrospective cohort study	Retroperitoneal sarcoma	Retroperitoneal sarcoma treated with surgery	unknown age unknown race unknown insurance status Mets at diagnosis No postoperative follow up (n=1230) missing facility (n=997)	10113	by surgical volume, procedure per year (0-1, 1.1-3, 3.1-5, 6-10, >10) or by facility type (community, comprehensive community, integrated network, Academic research) community: The facility accessions more than 100 but fewer than 500 newly diagnosed cancer cases each year." comprehensive community; The facility accessions 500 or more newly diagnosed cancer caseseach year. integrated network: The organization owns, operates, leases, or is part of a joint venture with multiple facilities providing integrated cancer care and offers comprehensive services Academic research: The facility participates in postgraduate medical education in at least four program areas, including internal medicine and general surgery	R0/1 margin: academic research 87.6% v integrated network 84.7% v comprehensive community 80.1% v community 78.3%	–	18 months OS academic research 82.7% v integrated network 81.3% v comprehensive community 80.6% v community 82.1%	academic research 60.1% v integrated network 58.1% v comprehensive community 56% v community 55.5%	academic research 41.8% v integrated network 36.7% v comprehensive community 39.8% v community 37.1%	Among hospital-level factors, only annual hospital surgical volume was significant, whereby increasing annual surgical volume yielded improved risk of death in a dose-dependent manner (HR, 0.92; 95% CI, 0.89 to 0.95).	There are THREE RPS papers by Villano using the NCDB RPS cases from the same study period.
Vos 2019	Netherlands	Retrospective cohort study	soft tissue	soft tissue sarcoma	GIST, Kaposi's sarcoma, age <18	5282	High Volume: >=20 resection per year Medium volume: 10-19 resection per year Low volume: 1-9 resection per year	multiple procedures varied from 29% in high-volume hospitals and in medium-volume hospitals to 36% in low-volume hospitals (p<0.01)	potential 'whoops' resection was lower as the annual surgical volume increased: 62% in low-volume hospitals, 44% in medium-volume hospitals and 29% in high-volume hospitals (p<0.01)	–	–	High vol 68% v medium vol 68% v low vol 76%	surgery in a high-volume hospital showed a significant and beneficial effect on net survival compared with surgery in a low-volume hospital (RR 1.3, 95% CI 1.02-1.6,p=0.03). The same impact was observed in comparison with medium-volume hospitals, although this failed to reach statistical significance (RR 1.3, 95% CI 0.98-1.8,p=0.07) .	
Wright 2020	USA	Retrospective cohort study	vertebral column and sarcal chordoma	vertebral column and sarcal chordoma	–	1266	Community cancer program (CCP): 100-500 ca cases/yr. Comprehensive community cancer program (CCCP): 100-500 cases/yr. Academic research program (ARP): postgraduate eductaion in4+ specialites+ >5-- cancer cases. Integrated network cancer program (INCP): multiple facilities provdiign integrated cancer care and comprehensive services	CCP and CCCP were less likely to have Sx.	–	Adjusted median survival: 131 months v 124 months v 109 months v 79 months	ARP 76.08% v INCP 70.3% V CCCP 61.5% v CCP 52.7%	–	ARP: 1, CCP HR 1.98 p0.018, CCCP HR 1.29 p=0.089, INCP HR 1.19 p=0.425	ARP is associated with increased odds of treatment associated with improved OS. No difference in odds of receiving RT/time to RT. NCDB (No RT details/location, No local recurrence)

Appendix 9. List of Studies for Clinical Question 3

Title	Authors	Published Year	Journal	Volume	Issue	Pages
Impact of treatment protocol on outcome of localized Ewing's sarcoma	Nasaka, Srividya; Gundeti, Sadashivudu; Ganta, Ranga; Arigela, Ravi; Maddali, Lakshmi; Linga, Vijay	2016	South Asian journal of cancer	5	4	194-195
Timing of Local Therapy Affects Survival in Ewing Sarcoma	Lin, Timothy A.; Ludmir, Ethan B.; Liao, Kai-Ping; McAleer, Mary Frances; Grosshans, David R.; McGovern, Susan L.; Bishop, Andrew J.; Woodhouse, Kristina D.; Paulino, Arnold C.; Yeboa, Debra Nana	2019	International journal of radiation oncology, biology, physics	104	1	127-136
Clinical prognostic factors in pediatric Ewing sarcoma	Ali, Bilal Abou; Nader, Ralph; Muwakkit, Samar; Abboud, Miguel; El Solh, Hassan M. B.; Saab, Raya Hamad	2013	Journal of clinical oncology	31	15 SUPPL. 1	
Clinical outcome of children and adults with localized Ewing sarcoma: impact of chemotherapy dose and timing of local therapy	Gupta, Abha A.; Pappo, Alberto; Saunders, Natasha; Hopyan, Sevan; Ferguson, Peter; Wunder, Jay; O'Sullivan, Brian; Catton, Charles; Greenberg, Mark; Blackstein, Martin	2010	Cancer	116	13	3189-94

Appendix 10. Summary table Clinical Question 3 all studies

First Author	Year	Country	Patient source	Study period	Design	Decision on timing of surgery	Inclusion	Overall No. pt	Overall no. of centres	Pelvic primary	Intervention	Delay in surgical resection and outcome	Primary Endpoints	Secondary Endpoints	3-year OS	5 yr OS	3-yr EFS	5y EFS	Multivariate analysis	Comments
Ali	2014	Lebanon	single centre	1999-2012	Retrospective cohort study	Not discussed. Reasons for delays included delays in procurement of prosthesis (3), scheduling delays (5), delays in multidisciplinary discussions (n=3), attempts at better chemoreduction (n=2), and no documented reasons (n=4)	EWS	39	1	?	No delay in local control (surgery and/or radiation) beyond week 15 (n=22, 56%) vs delay (n=17, 44%)	Delay in local control beyond week 15 for 17 patients (44%) - with worse 5y OS of 36% compared to 93% for no delay (p<0.001). 5y-EFS 38% and 69% respectively (p-value 0.002)	OS/EFS	-	-	5 y OS **HR 16.123**, 95% CI (1.99-130.23) p=0.009	-	HR 5.0, 95% CI (1.65-15.13), p=0.004	No multivariate	Delays in local control mostly in patients with RT alone (8/12) compared to surg (7/27) + more delays in metastatic disease (75%) vs localised (35%). Small single center study. No multivariate analysis. No specific results for pelvic Ewing. Country with emerging economy.
Gupta	2010	Canada	2 centres	1990-2005	Retrospective cohort study	At the discretion of the multidisciplanary treating team. Time to local therapy=time from chemo to radiation or surgery	Newly diagnosed localised EWS	53	2	8	Time to local therapy shorter in pediatric vs adult (3.38mo (0.85-14.9) vs 7.63mo (3.68-20.9); p0.0003)	Median time to local therapy in patients with recurrence/PD = 6.2mo (2-21mo) vs 3.75mo (3.75-9.07) in patients in remission (HR 1.13; 95%CI 1.04-1.23; p=0.003)	OS/EFS	Median time to disease recurrence, median time to local therapy	Ped 81%+/-7.7%; adult 59+/-12% (p0.02)	–	Ped 70%+/-9%; adult 43+/-13% (P0.1)	–	Primary pelvic tumor site (HR 4.26; p0.018) and **time to local therapy (HR 1.19; 95%CI 1.1-1.31; p=0.02**) significant for EFS	Large tertiary centers but small number of patients. No specific results for pelvic disease. No specific results for surgery.
Lin	2019	USA	National Cancer database	2004-2014	Retrospective cohort study	Time to local therapy=time from chemo to RT or surgery	Newly diagnosed localised EWS	1318	multiple	?	2 patient groups by time to first definitive local therapy (ie. Surgery or RT or surg+RT): 6-15 weeks (954 patients) vs 16+ weeks (364p). For surg only: 536 vs 182 (718)	For patients treated with surgery alone, 5y OS trended higher from 6-15w compared to ≥16w (p0.092). No differences in the time to local therapy were found with respect to tumor size, primary tumor site, or comorbidity score.	OS	–	–	For local control 6-15w, 5y and 10y OS 78.7% and 70.3% vs for ≥16w 70.4% and 67.1% (p<0.01). For surgery alone: 5y OS 6-15w 81.6% vs ≥16w 79.4% (p0.092)	–	–	In the multivariable Cox proportional hazards regression model , age>21 years (P<.001; HR, 1.65;95% CI, 1.28-2.12), tumor size>8cm(P=0.016; HR,1.38; 95% CI, 1.06-1.80), and **time to first definitive local therapy≥16 weeks (P=0.005; HR, 1.41; 95% CI, 1.11-1.80)** were associated with reduced overall survival.	Large database with high number of patients but no specific results for pelvic disease
Nasaka	2016	India	single centre	2002-2012	Retrospective cohort study	Not discussed.	Localised EWS	73	1	45 (axial primary)	3 patients groups - group 1, non ifosfamide regimens, group 2 VDC/IE for 12 cycles, group 3 VDC/IE 17 cycles - compared for characteristics and outcome	Time to local therapy <4mo was associated with better outcome on univariate analysis (median RFS 36.8 vs 27.9mo; p0.004; median OS 42.5 vs 32.6; p0.0004).	Relapse-free survival (RFS)	OS	35%, 45% and 70% for group 1,2,3	-	3y RFS 17%, 31% and 60% for group 1, 2 and 3. For axial primary, 3y RFS 42% for XRT, 75% for surgery (p=0.01)	-	Nil multivariate.	45 axial primary - 35 (77.8%) received XRT and 10 surgery (22.2%). Small single centre study. No multivariate analysis. No specific results for pelvic disease

Appendix 11. Quality Assessment Clinical Question 3

Study	Title	Reviewer	NHMRC Level of Evidence	Risk of Bias (Newcastle Ottawa scale for cohort study)			
				Selection	Comparability	Outcome	Overall
Ali 2014	Outcome of Ewing sarcoma in a multidisciplinary setting in Lebanon	Final	III-3	4	2	2	Good Quality
Nasaka 2016	Impact of treatment protocol on outcome of localized Ewing's sarcoma	Final	III-3	4	1	2	Good Quality
Lin 2018	Timing of Local therapy affects survival in Ewing sarcoma	Final	III-3	4	2	3	Good Quality
Gupta 2010	Clinical outcome of children and adults with localized Ewing sarcoma	Final	III-3	4	2	2	Good Quality