Clinical Practice Guidelines for Management of Sarcoma – Series 2

Technical Report

May 2023

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Scope of the technical report

This technical report refers to the development of Clinical Practice Guidelines for Management of Sarcoma (Series 2). The following five clinical questions are addressed in this series.

Topic 2 – Retroperitoneal Sarcomas

1. **What is the role of radiation therapy in the management of primary retroperitoneal sarcomas?**
    a. Population - Adult patients with primary localised retroperitoneal sarcoma
    b. Intervention – Surgical resection with neoadjuvant or adjuvant radiation therapy
    c. Comparator – Surgical resection alone
    d. Outcomes – abdominal recurrence free survival, recurrence free survival perioperative morbidity, overall survival

2. **Does multi-visceral resection improve outcomes for patients with primary retroperitoneal sarcoma outcomes?**
    a. Population - Adult patients with primary retroperitoneal sarcoma
    b. Intervention - multi-visceral resection (including adjacent organs uninvolved on preoperative imaging)
    c. Comparator – simple surgical resection
    d. Outcomes – Overall survival, abdominal recurrence free survival, recurrence free survival, perioperative morbidity

3. **Role of Biopsy in retroperitoneal sarcoma? Safety, accuracy?**
    a. Population - Adult patients with retroperitoneal sarcomas
    b. Intervention – Preoperative biopsy
    c. Comparator – no biopsy
    d. Outcomes – biopsy tract seeding, recurrence free survival, overall survival

4. **Role of chemotherapy in primary retroperitoneal sarcoma**
    a. Population - Adult patients with primary retroperitoneal sarcomas
    b. Intervention – Surgical resection with neoadjuvant or adjuvant chemotherapy
    c. Comparator – Surgical resection without chemotherapy
    d. Outcomes – Recurrence free survival, overall survival, post-operative complication

Topic 3 - Paediatric and AYA Sarcoma:

4. **Does the addition of high-dose chemotherapy have an impact on outcome of Ewing sarcoma and rhabdomyosarcoma compared to standard chemotherapy alone? in first line (a)? In relapse (b)?**
    a. Population: Ewing sarcoma and rhabdomyosarcoma
    b. Intervention: high-dose/myeloablative chemotherapy with autologous stem cell rescue
    c. Comparison: standard chemotherapy

d. Outcomes: Overall Survival, Event-Free Survival, Treatment Related Mortality and toxicity

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 worked together to decide 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 together with the main systematic reviewer writes the first draft of the guidelines. Each member of the working party for the clinical question are then 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 prior to topic working party meeting

Over virtual or face to face meetings, the working group provides feedback on the above and a consensus is reached on the evidence summary, guideline recommendations and practice points.

Topic 2, Clinical question 1: What is the role of radiation therapy in the management of primary retroperitoneal sarcomas?

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

What is the role of radiation therapy in the management of primary retroperitoneal sarcomas?

Population - Adult patients with primary retroperitoneal sarcoma
Intervention – Surgical resection with neoadjuvant or adjuvant radiation therapy
Comparator – Surgical resection alone
Outcomes – abdominal recurrence free survival, recurrence free survival
perioperative morbidity, overall survival

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

Advanced literature searches were conducted in April 2021 (with the search updated in March 2023 to include studies up to 31st December 2022) 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: “Retroperitoneal neoplasms”, “Sarcoma” and “Radiotherapy”. These were combined in their associated cluster groups with keywords such as: “retroperitoneal sarcoma”, “retroperitoneal liposarcoma”, “retroperitoneal leiomyosarcoma” and all relevant radiotherapy keywords such as “radiation”, “irradiation”, “xrt”, 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.

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
- Population of adult patients with primary retroperitoneal sarcoma
- Investigates Intervention of Surgical resection with neoadjuvant or adjuvant radiation therapy
- Compares surgical alone treatment
- Outcomes of the study includes abdominal recurrence free survival, recurrence free survival perioperative morbidity, overall survival

Exclusion criteria:

- Case Reports
- Conference Abstract Only
- Not Sarcoma
- Excluded Sarcoma Type: Kaposi Sarcoma, GIST, Dermatofibrosarcoma protuberans (DFSP), Adenosarcoma,
- Carcinosarcoma, Endometrial stromal tumours, Phyllodes tumour, gliosarcoma, uterine sarcoma)
- Not Retroperitoneal Sarcoma
- No Surgery alone comparator
- Not Relevant to research question
- Review article

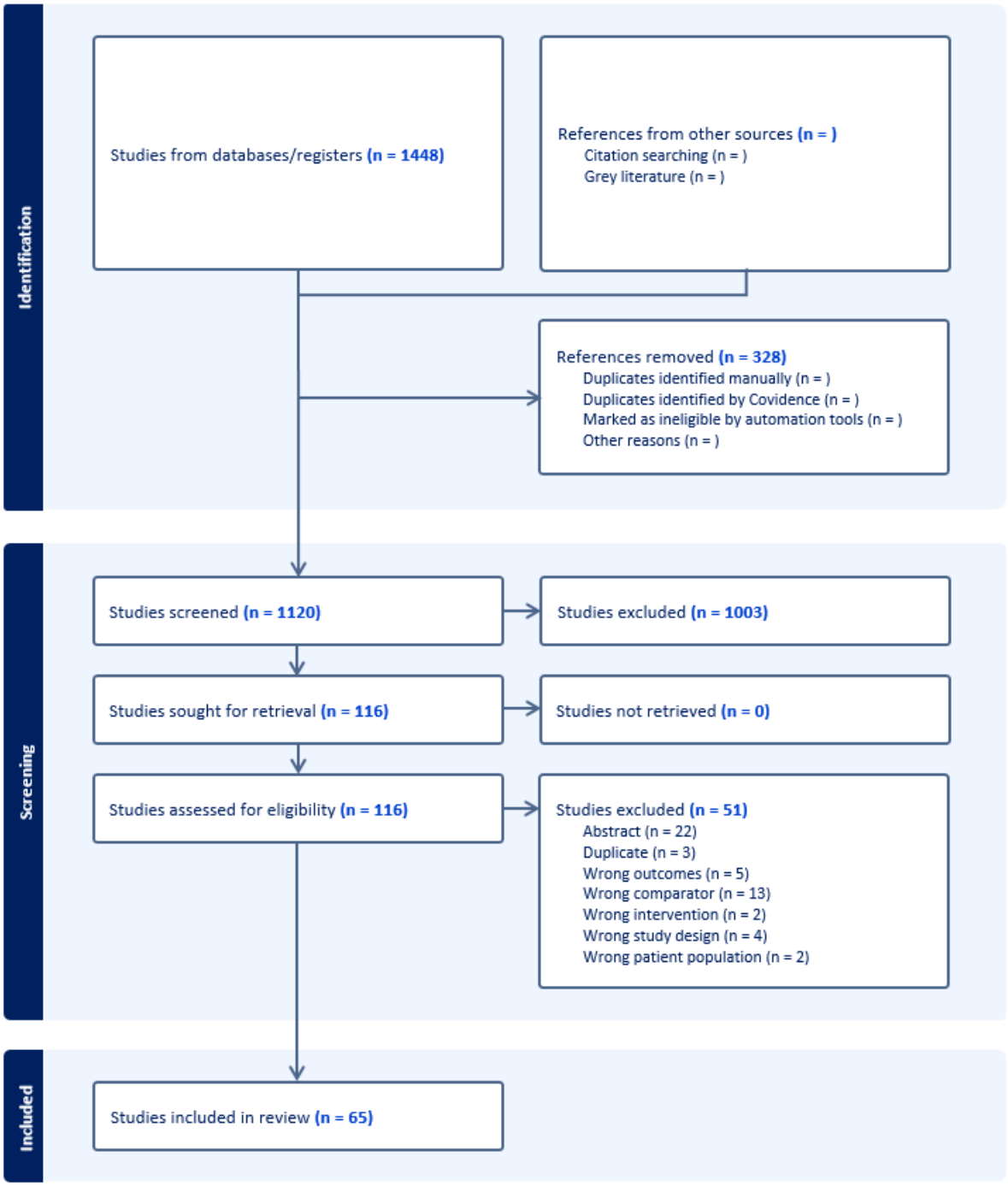

Figure 1. PRISMA flow chart from Covidence showing the flow of information through the different phases of this systematic review for Topic 2, Clinical Question 1.

Preferred Reporting Items for Systematic Reviews and Meta-Analyse (PRISMA) flow chart shows the different screening phase for Topic 2, Clinical Question 1 (Figure 1). A total of 1448 records were identified from the search strategy and imported into Covidence for screening. The inter-rater reliability for the title and abstract screening was 98.25% and full text review was 88.1%. The selection process yielded a final number of 66 studies for the systematic review. Please see Appendix 1 for list of the 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 was 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 the outcomes summary and quality assessments for Topic 2 Question 1.

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 search strategy used and evidence statement form for each of the outcomes covered by Topic 2 Question 1.

Search strategy Topic 2 Question 1

Search strategy for Topic 2 clinical question 1.

Database: Ovid MEDLINE(R) ALL <1946 to December 31, 2022>

Search Strategy:

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1 exp Retroperitoneal Neoplasms/ (9408)

2 exp sarcoma/ (140705)

3 1 and 2 (2414)

4 ((retroperitone* adj3 (sarcoma* or liposarcoma or leiomyosarcoma*)) or rpls).mp. (2179)

5 3 or 4 (3306)

6 exp radiotherapy/ (191053)

7 radiotherapy.fs. (195662)

8 (radiotherap* or radiation or irradiat* or imrt or xrt or 3dcrt or 3d crt).mp. (912403)

9 6 or 7 or 8 (925426)

10 5 and 9 (690)

11 limit 10 to (english language and yr="1990 -Current") (481)

35 exp animals/ not exp humans/ (4820145)

36 (animal* or rat o rats or swine or mouse or mice or dog or dogs or canine*).mp. (7211555)

37 (case reports or systematic review or editorial).pt. (2886720)

38 (case report* or systematic review*).ti,ab. (588234)

39 35 or 36 or 37 or 38 (10144751)

40 11 not 39 (341)

Evidence Statement Form Topic 2 Question 1

Outcome 1: Abdominal recurrence free survival endpoint		
Component	Rating	Description
1. Evidence Base	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
2. Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
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
Outcome 2: Recurrence free survival endpoint		
Component	Rating	Description
1. Evidence Base	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
2. Consistency	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	B	Evidence applicable to Australian healthcare context with few caveats
Outcome 3: Perioperative morbidity endpoint		
Component	Rating	Description
1. Evidence Base	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
2. Consistency	B	Most studies consistent and inconsistency can be explained
3. Clinical Impact	C	Slight
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats
Outcome 4: Overall survival endpoint		
Component	Rating	Description
1. Evidence Base	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
2. Consistency	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	B	Evidence applicable to Australian healthcare context with few caveats

Topic 2, Clinical question 2: Does multi-visceral resection improve outcomes for patients with primary retroperitoneal sarcoma outcomes?

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

Does multi-visceral resection improve outcomes for patients with primary retroperitoneal sarcoma outcomes?

- Population - Adult patients with primary localised retroperitoneal sarcoma
- Intervention - multi-visceral resection (including adjacent organs uninvolved on preoperative imaging)
- Comparator – simple surgical resection
- Outcomes – abdominal recurrence free survival, recurrence free survival, perioperative morbidity, overall survival

Literature searches were conducted in May 2021 (with the search updated 5th May 2022) 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: “Retroperitoneal neoplasms” and “Sarcoma”. (there isn’t a MESH to adequately describe “multi-visceral”).
These were combined in their associated cluster groups with keywords such as: “retroperitoneal sarcoma”, “retroperitoneal liposarcoma”, “retroperitoneal leiomyosarcoma” and all relevant multi-visceral keywords such as “mvr”, “complete resection”, “compartmental surgery”, 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.

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 patients with primary retroperitoneal sarcoma
- Investigates Intervention of multi-visceral resection (including adjacent organs uninvolved on preoperative imaging)
- Compares the difference of treatment of simple surgical resection
- Outcomes of the study includes abdominal recurrence free survival, recurrence free survival, perioperative morbidity, overall survival

Exclusion criteria:

- Case Reports
- Conference Abstract Only
- Not Sarcoma
- Excluded Sarcoma Type (Kaposi Sarcoma, GIST, Dermatofibrosarcoma protuberans (DFSP), Adenosarcoma, Carcinosarcoma, Endometrial stromal tumours, Phyllodes tumour, gliosarcoma, uterine sarcoma)
- Not Retroperitoneal Sarcoma
- Not Relevant to research question
- Review

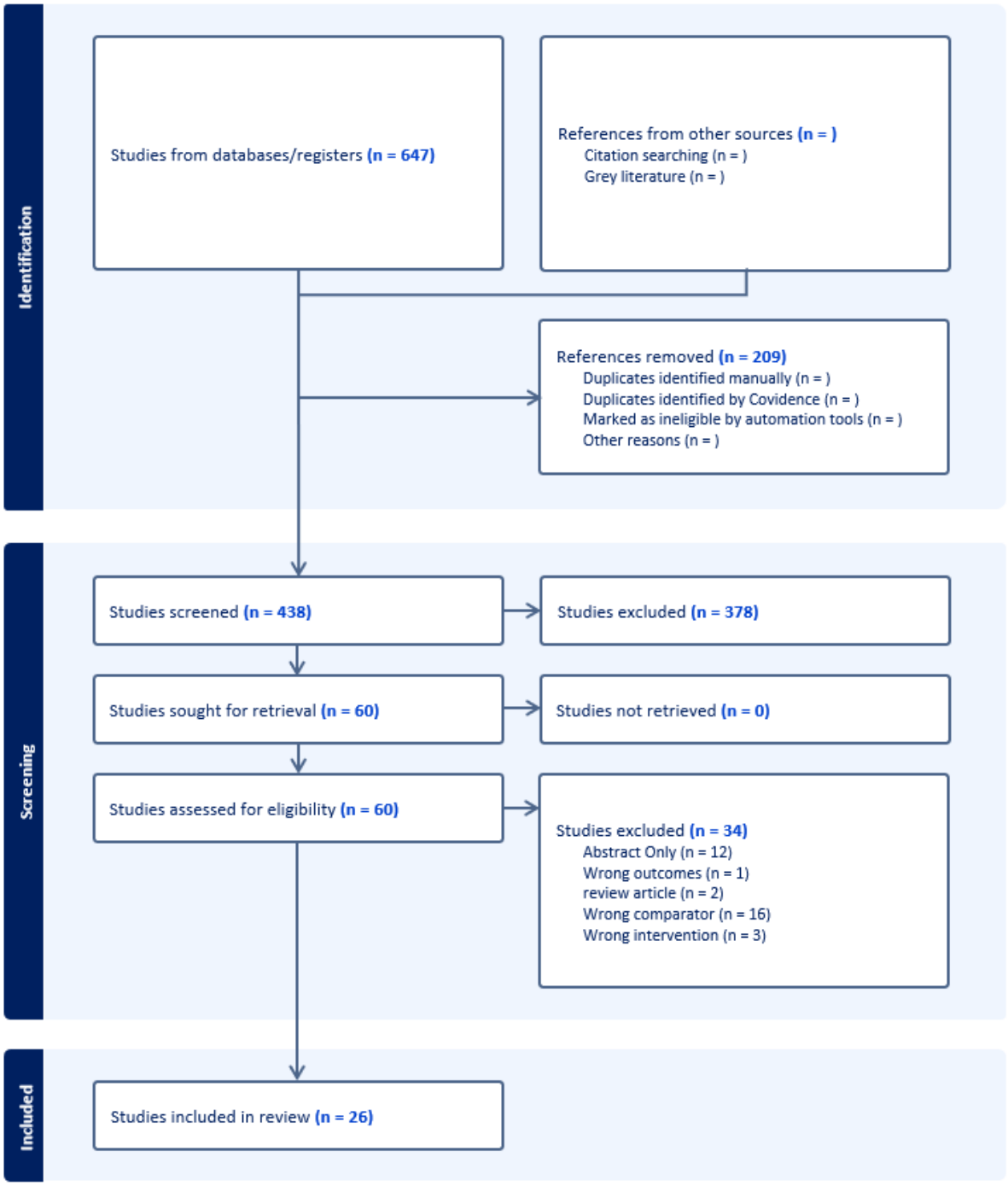

Figure 2. PRISMA flow chart from Covidence showing the flow of information through the different phases of this systematic review for Topic 2, Clinical Question 2.

The PRISMA flow chart shows the different screening phase for Topic 2, Clinical Question 2 (Figure 2). A total of 647 studies were identified from the search strategy and imported into Covidence for screening. The inter-rater reliability for the title and abstract screening was 88.7% and full text review was 86.3%. The selection process yielded a final number of 26 studies for the systematic review (Please see Appendix 3 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 4 & 5 for Evidence Summary Table and Quality assessment.

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 for each of the outcomes covered.

Search strategy Topic 2 Question 2

Complete search strategy for clinical question 2

Database: Ovid MEDLINE(R) ALL <1946 to May, 2022>

Search Strategy:

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1 exp Retroperitoneal Neoplasms/ (9416)

2 exp sarcoma/ (140856)

3 1 and 2 (2419)

4 ((retroperitone* adj3 (sarcoma* or liposarcoma or leiomyosarcoma*)) or rpls).mp. (2186)

5 3 or 4 (3314)

12 (multi-visceral or multivisceral or mvr or extended resection* or compartmental resection* or compartmental surg* or complete* adj2 resection* or complete surg*).mp. (24136)

13 5 and 12 (312)

14 limit 13 to (english language and yr="1990 -Current") (244)

36 (animal* or rat o rats or swine or mouse or mice or dog or dogs or canine*).mp. (7221056)

37 (case reports or systematic review or editorial).pt. (2892347)

38 (case report* or systematic review*).ti,ab. (590940)

39 35 or 36 or 37 or 38 (10160509)

41 14 not 39 (182)

Evidence Statement Form Topic 2 Question 2

Outcome 1: Overall Survival		
Component	Rating	Description
1. Evidence Base	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
2. Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
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
Outcome 2: Recurrence Free Survival, Cumulative Recurrence Free Survival		
Component	Rating	Description
1. Evidence Base	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
2. Consistency	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	B	Evidence applicable to Australian healthcare context with few caveats
Outcome 3: Perioperative Morbidity		
Component	Rating	Description
1. Evidence Base	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
2. Consistency	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	B	Evidence applicable to Australian healthcare context with few caveats

Topic 2, Clinical question 3: Role of Biopsy in retroperitoneal sarcoma? Safety, accuracy?

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

Role of Biopsy in retroperitoneal sarcoma? Safety, accuracy?
- Population - Adult patients with retroperitoneal sarcomas
- Intervention – Preoperative biopsy
- Comparator – no biopsy
- Outcomes – biopsy tract seeding, recurrence free survival, overall survival

Literature searches were conducted in September 2021 (with the search updated June 2022) 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: “Retroperitoneal neoplasms”, “Sarcoma” and “Biopsy”.
These were combined in their associated cluster groups with keywords such as: “retroperitoneal sarcoma”, “retroperitoneal liposarcoma”, “retroperitoneal leiomyosarcoma” and all biopsy keywords such as “core”, “pre-operative diagnosis”, etc. A few adjustments were made to this particular strategy in regards to rpls keywords in order to bring in gold papers that were otherwise missed.
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.

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
- Population of the study covers adult patients with primary retroperitoneal sarcoma
- Investigates intervention of surgical resection with preoperative biopsy
- Compares above outcomes to surgical resection without biopsy
- Outcomes of the study includes biopsy tract seeding, recurrence free survival, overall survival

Exclusion criteria:

- Case Reports
- Conference Abstract Only
- Not Sarcoma
- Excluded Sarcoma Type (Bone primary sarcomas, Kaposi Sarcoma, GIST, Dermatofibrosarcoma protuberans (DFSP), Adenosarcoma, Carcinosarcoma, Endometrial stromal tumours, Phyllodes tumour, gliosarcoma, uterine sarcoma)
- Not Retroperitoneal Sarcoma
- Paeditric cases
- Not Relevant to research question
- Review articles

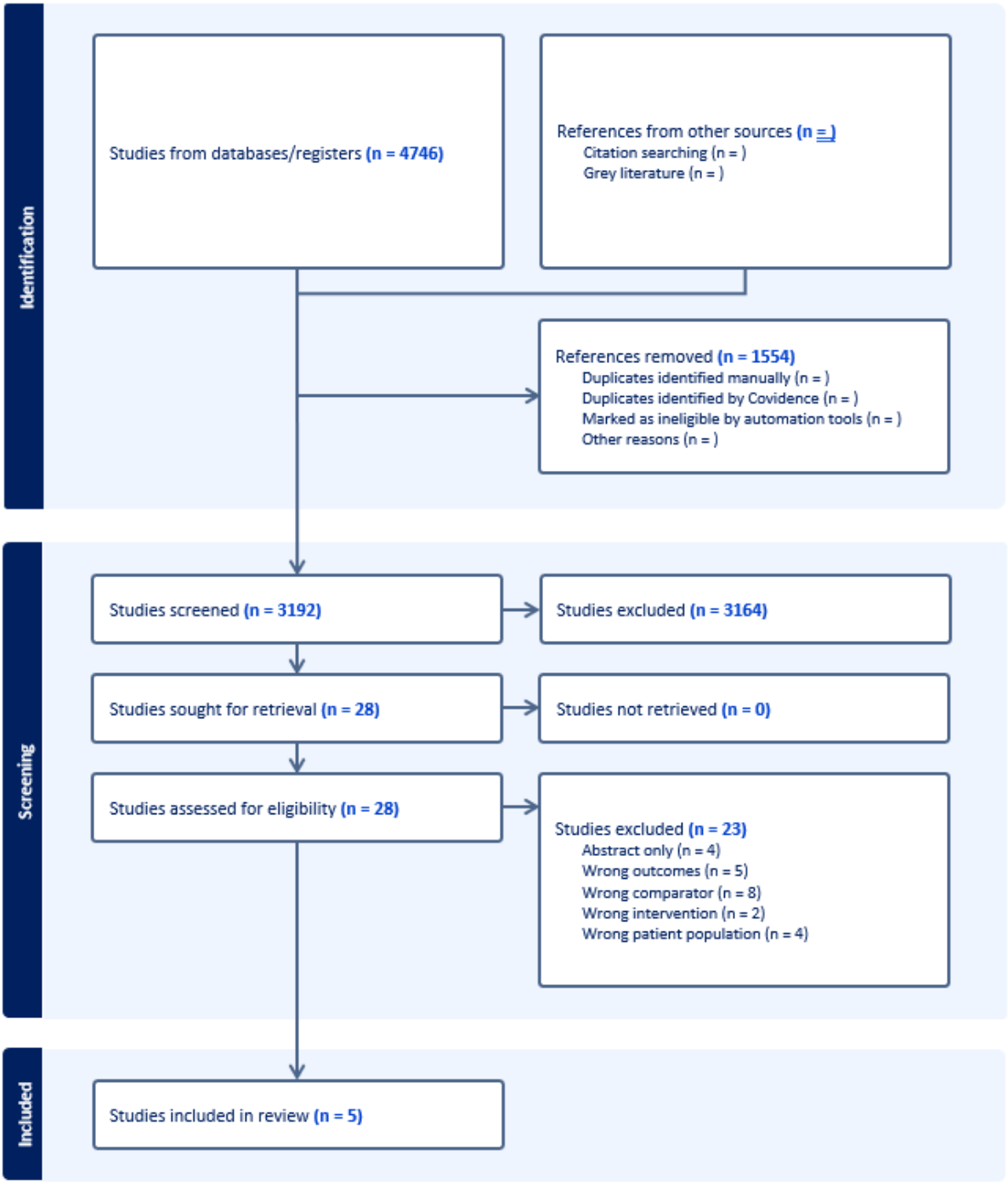

Figure 3. PRISMA flow chart from Covidence showing the flow of information through the different phases of Topic 2, Clinical Question 3.

The PRISMA flow chart shows the different screening phase for Topic 2, Clinical Question 3 (Figure 3). A total of 4746 studies were identified from the search strategy and imported into Covidence for screening. The inter-rater reliability for the title and abstract screening was 94.6% and full text review was 82.5%. The selection process yielded a final number of 5 studies for the systematic review (Please see Appendix 7 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 8 & 9 for Evidence Summary Table and Quality assessment.

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 Topic 2 Question 3

Complete search strategy clinical question 3

Database: Ovid MEDLINE(R) ALL <1946 to June 28, 2022>

Search Strategy:

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1 exp Retroperitoneal Neoplasms/ (9496)

2 exp sarcoma/ (142585)

3 1 and 2 (2460)

15 exp Biopsy/ (293831)

16 (biops* or core or pre-operative diagnosis or preoperative diagnosis).mp. (876107)

17 15 or 16 (907217)

35 exp animals/ not exp humans/ (4881960)

36 (animal* or rat o rats or swine or mouse or mice or dog or dogs or canine*).mp. (7309956)

37 (case reports or systematic review or editorial).pt. (2951287)

38 (case report* or systematic review*).ti,ab. (612428)

39 35 or 36 or 37 or 38 (10303806)

45 ((retroperitone* adj3 (sarcoma* or liposarcoma or tumo?r*)) or leiomyosarcoma* or rpls).mp. (17817)

46 3 or 45 (18542)

47 17 and 46 (2145)

48 limit 47 to (english language and yr="1990 -Current") (1525)

49 48 not 39 (542)

Evidence Statement Form Topic 2 Question 3

Outcome 1: Biopsy Tract Seeding		
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	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
Outcome 2: Local recurrence		
Component	Rating	Description
1. Evidence Base	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
2. Consistency	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	B	Evidence applicable to Australian healthcare context with few caveats
Outcome 3: Overall survival		
Component	Rating	Description
1. Evidence Base	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low 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

Topic 2, Clinical question 4: Role of chemotherapy in primary retroperitoneal sarcoma

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

Role of chemotherapy in primary retroperitoneal sarcoma

Population - Adult patients with primary retroperitoneal sarcomas
Intervention – Surgical resection with neoadjuvant or adjuvant chemotherapy
Comparator – Surgical resection without chemotherapy
Outcomes – Recurrence free survival, overall survival, post-operative complication

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

Advanced literature searches were conducted in July 2021 (with the search updated June 2022) 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: “Retroperitoneal neoplasms”, “Sarcoma” and “Drug therapy”. These were combined in their associated cluster groups with keywords such as: “retroperitoneal sarcoma”, “retroperitoneal liposarcoma”, “retroperitoneal leiomyosarcoma” and all relevant chemotherapy keywords such as “antineoplastic”, “pharmacotherapy”, “drug treatment”, 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.

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
- Population of the study covers adult patients with primary retroperitoneal sarcoma
- Investigates intervention of surgical resection with neoadjuvant or adjuvant chemotherapy
- Compares above outcomes to surgical resection without chemotherapy
- Outcomes of the study includes recurrence free survival, toxicity, overall survival

Exclusion criteria:

- Case Reports
- Conference Abstract Only
- Not Sarcoma
- Excluded Sarcoma Type (Kaposi Sarcoma, GIST, Dermatofibrosarcoma protuberans (DFSP), Adenosarcoma, Carcinosarcoma, Endometrial stromal tumours, Phyllodes tumour, gliosarcoma, uterine sarcoma)
- Not Retroperitoneal Sarcoma
- Not Relevant to research question
- Review articles

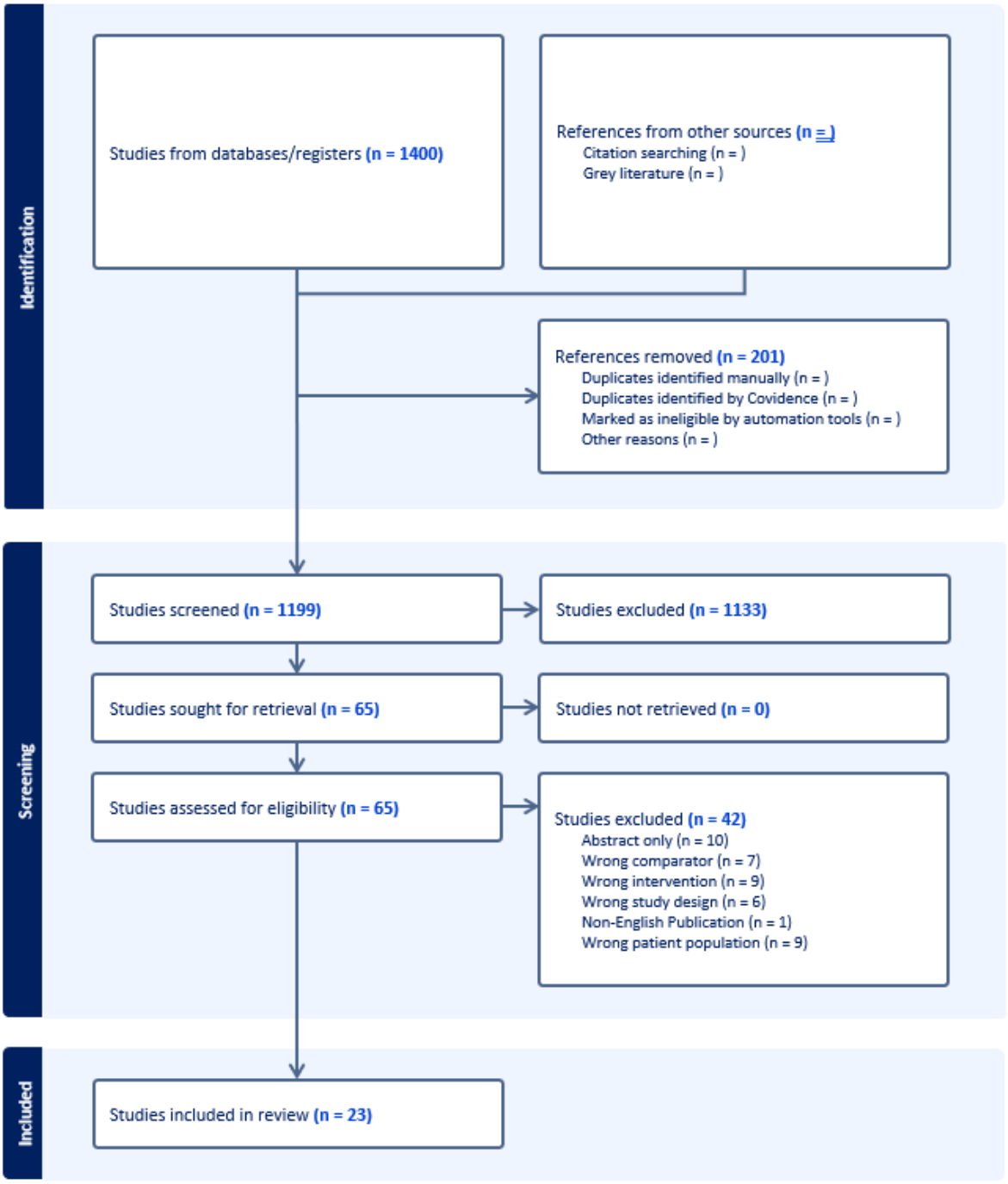

Figure 3. PRISMA flow chart from Covidence showing the flow of information through the different phases of Topic 2, Clinical Question 4.

The PRISMA flow chart shows the different screening phase for Topic 2, Clinical Question 4 (Figure 3). A total of 1400 studies were identified from the search strategy and imported into Covidence for screening. The inter-rater reliability for the title and abstract screening was 95.8% and full text review was 93.6%. The selection process yielded a final number of 23 studies for the systematic review (Please see Appendix 10 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 11 & 12 for Evidence Summary Table and Quality assessment.

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 Topic 2 Question 4

Complete search strategy clinical question 4

Database: Ovid MEDLINE(R) ALL <1946 to June 28, 2022>

Search Strategy:

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1 exp Retroperitoneal Neoplasms/ (9466)

2 exp sarcoma/ (141953)

3 1 and 2 (2445)

4 ((retroperitone* adj3 (sarcoma* or liposarcoma or leiomyosarcoma*)) or rpls).mp. (2208)

5 3 or 4 (3338)

20 exp drug therapy/ (1415593)

21 (antineoplastic or chemotherap* or chemotreatment* or pharmacotherap* or chemoimmunotherap* or chemoimmunoradiotherap* or chemoradiation or chemoradiotherap* or radiochemotherap* or drug therap* or drug treatment*).mp. (2883770)

22 20 or 21 (3504087)

23 5 and 22 (695)

24 limit 23 to (english language and yr="1990 -Current") (478)

35 exp animals/ not exp humans/ (4862047)

36 (animal* or rat o rats or swine or mouse or mice or dog or dogs or canine*).mp. (7274095)

37 (case reports or systematic review or editorial).pt. (2927343)

38 (case report* or systematic review*).ti,ab. (603194)

39 35 or 36 or 37 or 38 (10244337)

43 24 not 39 (229)

50 43 not Reversible Posterior Leukoencephalopathy Syndrome.mp. (222)

Evidence Statement Form Topic 2 Question 4

Outcome 1: Recurrence free survival		
Component	Rating	Description
1. Evidence Base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	A	All studies consistent
3. Clinical Impact	D	Restricted
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats
Outcome 2: Overall survival		
Component	Rating	Description
1. Evidence Base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	A	All studies consistent
3. Clinical Impact	D	Restricted
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats
Outcome 3: Postoperative 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 was available
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

Topic 3, Clinical Question 4: Does the addition of high-dose chemotherapy have an impact on outcome of Ewing sarcoma and rhabdomyosarcoma compared to standard chemotherapy alone? in first line (a)? In relapse (b)?

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

4. Does the addition of high-dose chemotherapy have an impact on outcome of Ewing sarcoma and rhabdomyosarcoma compared to standard chemotherapy alone? in first line (a)? In relapse (b)?
Population: Ewing sarcoma and rhabdomyosarcoma
Intervention: high-dose/myeloablative chemotherapy with autologous stem cell rescue
Comparison: standard chemotherapy
Outcomes: Overall Survival, Event-Free Survival, Treatment Related Mortality and toxicity

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

Advanced literature searches were conducted in November 2021 (an updated search in October 2022) 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 “Transplantation, autologous”. These were combined in their associated cluster groups with keywords such as: “ewing”, “high dose”, “dose intensity”, “dose escalation”, “chemotherapy”, “stem cell rescue” 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.

There is no specific risk factor for development of Ewing sarcoma, or rhabdomyosarcoma 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
- Population of the study covers adolescent and adult with Ewing sarcoma or rhabdomyosarcoma
  Investigates high-dose/myeloablative chemotherapy with autologous stem cell rescue
- Compares above outcomes with standard chemotherapy
- Outcomes of the study includes Overall Survival, Event-Free Survival, Treatment Related Mortality and toxicity
-

Exclusion criteria:

- Case Reports
- Conference Abstract Only
- Not Sarcoma
- Excluded Sarcoma Type (ie not Ewings or Rhabdomyosarcoma)
- Not Relevant to research question
- Review articles
- Animal Study/in vitro study
- Editorial

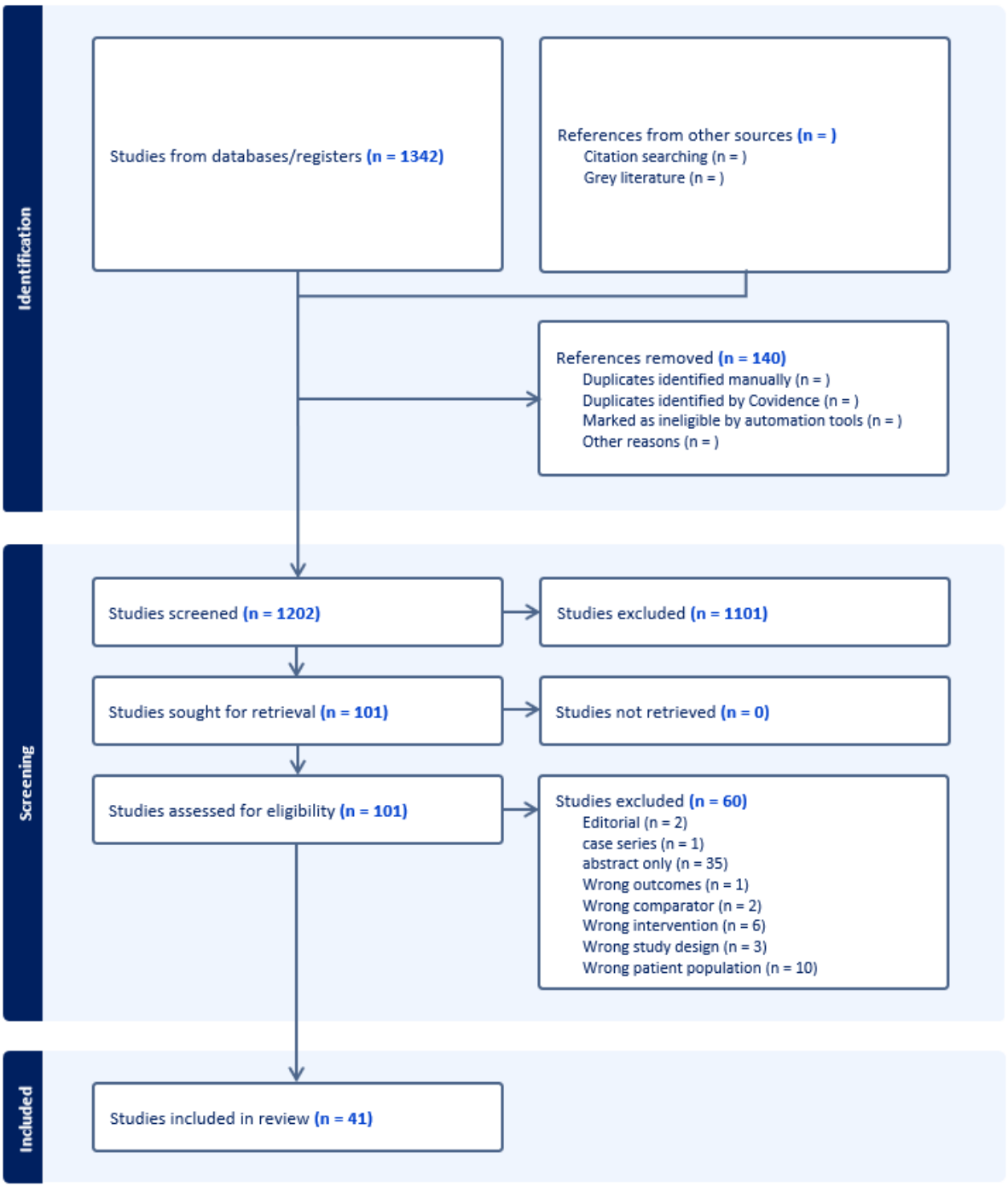

Figure 3. PRISMA flow chart from Covidence showing the flow of information through the different phases of Topic 3, Clinical Question 4.

The PRISMA flow chart shows the different screening phase for Topic 3, Clinical Question 4 (Figure 3). A total of 1342 studies were identified from the search strategy and imported into Covidence for screening. The inter-rater reliability for the title and abstract screening was 90.6% and full text review was 77.5%. The selection process yielded a final number of 41 studies for the systematic review (Please see Appendix 13 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 14 & 15 for Evidence Summary Table and Quality assessment.

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 Topic 3 Question 4

Database: Ovid MEDLINE(R) ALL <1946 to November 19, 2021>

Search Strategy:

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17 (((high dos* or myeloablative or intensive or dose intensi* or (dose adj2 escalation)) adj3 (chemotherap* or antineoplastic or chemotreatment* or pharmacotherap* or chemoimmunotherap* or chemoradiation or chemoradiotherap* or radiochemotherap* or drug*)) or hdc).mp. (22144)

18 exp transplantation, autologous/ or exp bone marrow transplantation/ or (megatherapy or (autologous adj3 transplant*) or stem cell rescue).mp. (102001)

19 17 or 18 (118388)

27 exp Sarcoma, Ewing/ or exp rhabdomyosarcoma/ (17625)

28 (ewing* or rhabdomyosarcoma*).mp. (26175)

29 27 or 28 (26175)

36 19 and 29 (697)

37 limit 36 to (english language and yr="1990 -Current") (512)

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. (4020026)

47 exp animals/ not exp humans/ (4917379)

48 (animal* or rat or rats or swine or mouse or mice or dog or dogs or canine*).mp. (7450022)

49 (case reports or systematic review or editorial).pt. (2986598)

50 (case report* or systematic review*).ti,ab. (626516)

51 47 or 48 or 49 or 50 (10465565)

52 46 or 47 or 48 or 49 or 50 (12448560)

61 37 not 52 (290)

Evidence Statement Form Topic 3 Question 4

Refractory/relapsed ES (4 comparative studies)		
Component	Rating	Description
1. Evidence Base	D	Level IV studies or Level I to III studies/SRs with a high 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
Remission status pre-transplant (4 relevant studies)		
Component	Rating	Description
1. Evidence Base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	A	All studies consistent
3. Clinical Impact	C	Slight
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats
Primary localised ES and ESFT (4 comparative studies)		
Component	Rating	Description
1. Evidence Base	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
2. Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
3. Clinical Impact	C	Slight
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats
Primary metastatic ES and ESFT (3 comparative studies)		
Component	Rating	Description
1. Evidence Base	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
2. Consistency	A	All studies consistent
3. Clinical Impact	A	Very large
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats
Primary localised or metastatic RMS and RMS-like tumours (6 comparative studies)		
Component	Rating	Description
1. Evidence Base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	D	Evidence is inconsistent
3. Clinical Impact	D	Restricted

4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats
Detailed toxicity endpoints (3 RCTs)		
Component	Rating	Description
1. Evidence Base	A	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias
2. Consistency	A	All studies consistent
3. Clinical Impact	A	Very large
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats
Refractory and relapsed RMS and RMS-like tumours (3 non-comparative studies)		
Component	Rating	Description
1. Evidence Base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	D	Evidence is inconsistent
3. Clinical Impact	D	Restricted
4. Generalisability	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability	D	Evidence not applicable to Australian healthcare context

Appendix 1. Studies included in Topic 2 Question 1 Systematic Review

Title	Authors	Published Year	Journal	Volume	Issue	Pages
Surgery and radiotherapy for retroperitoneal and abdominal sarcoma: both necessary and sufficient	Zhou, Zheng; McDade, Theodore P.; Simons, Jessica P.; Ng, Sing Chau; Lambert, Laura A.; Whalen, Giles F.; Shah, Shimul A.; Tseng, Jennifer F.	2010	Archives of surgery (Chicago, Ill. : 1960)	145	5	426-31
Prognostic factors of retroperitoneal soft-tissue sarcomas	Tansug, Tugrul; Nazli, Okay; Bozdag, Ali Dogan; Reyhan, Enver; Kara, Cemal; Derici, Hayrullah	2006	Chirurgische Gastroenterologie Interdisziplinar	22	3	179-184
Excellent local control with preoperative radiation therapy, surgical resection, and intra-operative electron radiation therapy for retroperitoneal sarcoma	Stucky, Chee-Chee H.; Wasif, Nabil; Ashman, Jonathan B.; Pockaj, Barbara A.; Gunderson, Leonard L.; Gray, Richard J.	2014	Journal of surgical oncology	109	8	798-803
Prognostic factors in retroperitoneal sarcoma: A multivariate analysis of a series of 165 patients of the French Cancer Center Federation Sarcoma Group	Coindre, Jean-Michel; Bonvalot, Sylvie; Terrier, Philippe; Kantor, Guy; Bonichon, Francoise; Bui, Binh Nguyen; Stoeckle, Eberhard	2001	Cancer	92	2	359-368
The effect of microscopic margin status on survival in adult retroperitoneal soft tissue sarcomas	Stahl, J. M.; Corso, C. D.; Park, H. S.; An, Y.; Rutter, C. E.; Han, D.; Roberts, K. B.	2017	European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology	43	1	168-174
Treatment of patients with primary retroperitoneal sarcoma: predictors of	Snow, Hayden A.; Hitchen, Tatiana X.; Head, Jessica; Herschtal, Alan; Bae, Susie; Chander,	2018	ANZ journal of surgery	88	11	1151-1157

outcome from an Australian specialist sarcoma centre	Sarat; Chu, Julie; Hendry, Shona; Ngan, Samuel Y.; Desai, Jayesh; Choong, Peter F. M.; Henderson, Michael; Gyorki, David E.					
Prognostic factors predictive of survival for truncal and retroperitoneal soft-tissue sarcoma	Singer, S.; Corson, J. M.; Demetri, G. D.; Healey, E. A.; Marcus, K.; Eberlein, T. J.	1995	Annals of surgery	221	2	185-95
Radiotherapy and extent of surgical resection in retroperitoneal soft-tissue sarcoma: multi-institutional analysis of 261 patients	Sampath, Sagus; Hitchcock, Ying J.; Shrieve, Dennis C.; Randall, R. Lor; Schultheiss, Timothy E.; Wong, Jeffrey Y. C.	2010	Journal of surgical oncology	101	5	345-50
Outcomes in a series of 103 retroperitoneal sarcomas	Choudry, U.; Ott, M. J.; Willett, C. G.; Betensky, R. A.; Souba, W. W.; Pierie, J. P. E. N.	2006	European journal of surgical oncology	32	10	1235-1241
Tissue expander placement and adjuvant radiotherapy after surgical resection of retroperitoneal liposarcoma offers improved local control	Park, Hyojun; Lee, Sanghoon; Choi, Gyu Seong; Kim, Jong Man; Park, Jae Berm; Kwon, Choon Hyuck David; Joh, Jae-Won; Kim, Sung Joo; Kim, Bokyong; Lim, Do Hoon; Choi, Yoon-La	2016	Medicine (United States)	95	32	e4435
Adjuvant radiotherapy in retroperitoneal sarcomas. A Scandinavian Sarcoma Group study of 97 patients	Nyhus, Anniken B.; Elde, Ingvild K.; Trovik, Linn H.; Monge, Odd R.; Jebsen, Nina L.; Ovrebo, Kjell; Almquist, Martin; Haugland, Hans Kristian; Eide, Johan; Rissler, Pehr; Engellau, Jacob	2014	Acta Oncologica	53	9	1165-1172
The effect of neoadjuvant radiation therapy on perioperative outcomes among patients undergoing resection of retroperitoneal sarcomas	Nussbaum, Daniel P.; Speicher, Paul J.; Gulack, Brian C.; Ganapathi, Asvin M.; Keenan, Jeffrey E.; Stinnett, Sandra S.; Kirsch, David G.; Tyler, Douglas S.; Blazer, Dan G., 3rd	2014	Surgical oncology	23	3	155-60
Long-term Oncologic Outcomes After Neoadjuvant Radiation Therapy for Retroperitoneal Sarcomas	Nussbaum, Daniel P.; Speicher, Paul J.; Gulack, Brian C.; Ganapathi, Asvin M.; Englum, Brian R.; Kirsch, David G.; Tyler, Douglas S.; Blazer, Dan G., 3rd	2015	Annals of surgery	262	1	163-70

Preoperative or postoperative radiotherapy versus surgery alone for retroperitoneal sarcoma: a case-control, propensity score-matched analysis of a nationwide clinical oncology database	Nussbaum, Daniel P.; Lane, Whitney O.; Blazer, Dan G.; Rushing, Christel N.; Peterson, Bercedis L.; Cardona, Diana M.; Kirsch, David G.	2016	The Lancet Oncology	17	7	966-975
Surgically Treated Retroperitoneal Sarcoma: A Population-based Competing Risks Analysis	Nazzani, Sebastiano; Preisser, Felix; Bandini, Marco; Marchioni, Michele; Tian, Zhe; Soulieres, Denis; Montanari, Emanuele; Ratti, Dario; Acquati, Pietro; Briganti, Alberto; Shariat, Shahrokh F.; Abdollah, Firas; Carmignani, Luca; Karakiewicz, Pierre I.	2018	European urology oncology	1	4	346-351
A contemporary analysis of radiotherapy effect in surgically treated retroperitoneal sarcoma	Nazzani, Sebastiano; Bandini, Marco; Marchioni, Michele; Preisser, Felix; Tian, Zhe; Soulieres, Denis; Montanari, Emanuele; Motta, Gloria; Acquati, Pietro; Briganti, Alberto; Shariat, Shahrokh F.; Abdollah, Firas; Carmignani, Luca; Karakiewicz, Pierre I.	2018	Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology	127	2	318-325
Surgical resection for recurrent retroperitoneal leiomyosarcoma and liposarcoma	Nathenson, Michael J.; Barysauskas, Constance M.; Nathenson, Robert A.; Regine, William F.; Hanna, Nader; Sausville, Edward	2018	World journal of surgical oncology	16	1	203
The prognostic impact of dedifferentiation in retroperitoneal liposarcoma: a series of surgically treated patients at a single institution	Mussi, Chiara; Collini, Paola; Miceli, Rosalba; Barisella, Marta; Mariani, Luigi; Fiore, Marco; Casali, Paolo G.; Gronchi, Alessandro	2008	Cancer	113	7	1657-65
Preoperative radiation therapy combined with radical surgical resection is associated with a lower rate of local recurrence when treating unifocal, primary retroperitoneal liposarcoma	Molina, George; Hull, Melissa A.; Chen, Yen-Lin; DeLaney, Thomas F.; De Amorim Bernstein, Karen; Choy, Edwin; Cote, Gregory; Harmon, David C.; Mullen, John T.; Haynes, Alex B.	2016	Journal of surgical oncology	114	7	814-820
Resectable retroperitoneal soft tissue sarcomas. The effect of extent of resection	van Doorn, R. C.; Gallee, M. P.; Hart, A. A.; Gortzak, E.; Rutgers, E. J.; van Coevorden, F.; Keus, R. B.; Zoetmulder, F. A.	1994	Cancer	73	3	637-42

and postoperative radiation therapy on local tumor control						
Neoadjuvant radiotherapy followed by surgery compared with surgery alone in the treatment of retroperitoneal sarcoma: a population-based comparison	Turner, B. T.; Hampton, L.; Schiller, D.; Mack, L. A.; Robertson-More, C.; Li, H.; Quan, M. L.; Bouchard-Fortier, A.	2019	Current oncology (Toronto, Ont.)	26	6	e766-e772
Lack of survival benefit following adjuvant radiation in patients with retroperitoneal sarcoma: A SEER analysis	Tseng, Warren H.; Martinez, Steve R.; Canter, Robert J.; Do, Ly; Tamurian, Robert M.; Borys, Dariusz	2011	Journal of Surgical Research	168	2	e173-e180
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.; French Sarcoma, Group	2014	Annals of oncology : official journal of the European Society for Medical Oncology	25	3	735-742
Evaluation of Preoperative Chemotherapy or Radiation and Overall Survival in Patients with Nonmetastatic, Resectable Retroperitoneal Sarcoma	Ma, Sung Jun; Farrugia, Mark K.; Shekher, Rohil; Iovoli, Austin J.; Singh, Anurag K.; Oladeru, Oluwadamilola T.	2020	JAMA network open	3	11	
Should adjuvant radiotherapy be administered in addition to front-line aggressive surgery (FAS) in patients with primary retroperitoneal sarcoma?	Laplanche, A.; Le Pechoux, C.; Al Mokhles, H.; Musat, E.; Baey, C.; Terrier, P.; Domont, J.; Le Cesne, A.; Bonvalot, S.	2013	Annals of Oncology	24	3	832-837
Analysis of perioperative radiation therapy in the surgical treatment of primary and recurrent retroperitoneal sarcoma	Lane, Whitney O.; Cramer, Christina K.; Nussbaum, Daniel P.; Speicher, Paul J.; Gulack, Brian C.; Czito, Brian G.; Kirsch, David G.; Tyler, Douglas S.; Blazer, Dan G., 3rd	2015	Journal of surgical oncology	112	4	352-8
Treatment Factors Associated With Overall Survival in Retroperitoneal Sarcoma: An Institutional Review	Kwong, Mei L.; Lee, Becky; Kunihira, Karissa; Sutjiadi, Brian; Reeves, Mark E.; Selleck, Matthew; Yang, Gary; Solomon, Naveenraj	2020	The American surgeon	86	10	1358-1362

Efficacy of Postoperative Radiotherapy Using Modern Techniques in Patients with Retroperitoneal Soft Tissue Sarcoma	Kim, Hyun Ju; Koom, Woong Sub; Cho, Jaeho; Kim, Hyo Song; Suh, Chang Ok	2018	Yonsei medical journal	59	9	1049-1056
Comparison of perioperative radiation therapy and surgery versus surgery alone in 204 patients with primary retroperitoneal sarcoma: A retrospective 2-institution study	Kelly, Kaitlyn J.; Dukleska, Katerina; Brennan, Murray F.; Singer, Samuel; Yoon, Sam S.; Chang, Kevin K.; Kuk, Deborah; Qin, Li-Xuan; Chen, Yen-Lin; Delaney, Thomas F.	2015	Annals of surgery	262	1	156-162
Value of combined treatment of retroperitoneal sarcomas	Kaminski, Andrzej; Strojek, Jan; Kolosza, Zofia; Pilecki, Boleslaw	2007	Polski Przeglad Chirurgiczny	79	4	534-547
Management of primary and recurrent soft-tissue sarcoma of the retroperitoneum	Jaques, D. P.; Coit, D. G.; Hajdu, S. I.; Brennan, M. F.	1990	Annals of surgery	212	1	51-9
Prognostic factors associated with long-term survival for retroperitoneal sarcoma: implications for management	Heslin, M. J.; Lewis, J. J.; Nadler, E.; Newman, E.; Woodruff, J. M.; Casper, E. S.; Leung, D.; Brennan, M. F.	1997	Journal of clinical oncology : official journal of the American Society of Clinical Oncology	15	8	2832-9
Operative management of primary retroperitoneal sarcomas: a reappraisal of an institutional experience	Hassan, Imran; Park, Saung Z.; Donohue, John H.; Nagorney, David M.; Kay, Paul A.; Nasciemento, Antonio G.; Schleck, Cathy D.; Ilstrup, Duane M.	2004	Annals of surgery	239	2	244-50
Significant benefits in survival by the use of surgery combined with radiotherapy for retroperitoneal soft tissue sarcoma	Hager, Sven; Makowiec, Frank; Henne, Karl; Hopt, Ulrich T.; Wittel, Uwe A.	2017	Radiation oncology (London, England)	12	1	29
Radiotherapy for retroperitoneal liposarcoma: A report from the Transatlantic Retroperitoneal Sarcoma Working Group	Haas, Rick L. M.; Bonvalot, Sylvie; Miceli, Rosalba; Strauss, Dirk C.; Hayes, Andrew J.; Swallow, Carol J.; Gladdy, Rebecca; Hohenberger, Peter; Jakob, Jens; van Coevorden, Frits; van Houdt, Winan J.; Rutkowski, Piotr; Szacht, Milena; Callegaro, Dario; Fiore, Marco; Gronchi, Alessandro;	2019	Cancer	125	8	1290-1300

	Honore, Charles; Fairweather, Mark; Raut, Chandrajit P.; Chung, Peter W.					
Outcomes for soft-tissue sarcoma in 8249 cases from a large state cancer registry	Gutierrez, Juan C.; Perez, Eduardo A.; Franceschi, Dido; Moffat, Frederick L., Jr.; Livingstone, Alan S.; Koniaris, Leonidas G.	2007	The Journal of surgical research	141	1	105-14
Predictors of improved survival for patients with retroperitoneal sarcoma	Giuliano, Katherine; Canner, Joseph K.; Wolfgang, Christopher L.; Ahuja, Nita; Bivalacqua, Trinity; Terezakis, Stephanie; Herman, Joseph; Nagarajan, Neeraja; Schneider, Eric B.	2016	Surgery (United States)	160	6	1628-1635
Preoperative radiotherapy in the management of retroperitoneal liposarcoma	Ecker, B. L.; Peters, M. G.; McMillan, M. T.; Sinnamon, A. J.; Zhang, P. J.; Fraker, D. L.; Levin, W. P.; Roses, R. E.; Karakousis, G. C.	2016	The British journal of surgery	103	13	1839-1846
The importance of the margin of resection and external radiation in non-lipomatous retroperitoneal sarcoma	Littau, Michael J.; Kulshrestha, Sujay; Bunn, Corinne; Agnew, Sonya; Sweigert, Patrick; Luchette, Fred A.; Baker, Marshall S.	2021	American journal of surgery	221	3	543-548
The importance of the margin of resection and radiotherapy in retroperitoneal liposarcoma	Littau, Michael J.; Kulshrestha, Sujay; Bunn, Corinne; Agnew, Sonya; Sweigert, Patrick; Luchette, Fred A.; Baker, Marshall S.	2021	American journal of surgery	221	3	554-560
Radiation Therapy for Retroperitoneal Sarcomas: Influences of Histology, Grade, and Size	Leiting, Jennifer L.; Bergquist, John R.; Hernandez, Matthew C.; Merrell, Kenneth W.; Folpe, Andrew L.; Robinson, Steven I.; Nagorney, David M.; Truty, Mark J.; Grotz, Travis E.	2018	Sarcoma	2018		7972389
Retroperitoneal liposarcoma: the role of adjuvant radiation therapy and the prognostic factors	Lee, Hong Seok; Yu, Jeong Il; Lim, Do Hoon; Kim, Sung Joo	2016	Radiation oncology journal	34	3	216-222
Role of radiation therapy for retroperitoneal sarcomas: An eight-institution study from the US Sarcoma Collaborative	Chouliaras, Konstantinos; Senehi, Rebecca; Ethun, Cecilia G.; Poultsides, George; Grignol, Valerie; Clarke, Callisia N.; Roggin, Kevin K.; Fields, Ryan C.; Schwartz, Patrick B.; Ronnekleiv-Kelly, Sean M.; D'Agostino, Ralph, Jr.; Johnson, Emily N.; Levine, Edward	2019	Journal of surgical oncology	120	7	1227-1234

	A.; Cardona, Kenneth; Votanopoulos, Konstantinos I.					
Recurrence patterns after resection of retroperitoneal sarcomas: An eight-institution study from the US Sarcoma Collaborative	Chouliaras, Konstantinos; Senehi, Rebecca; Levine, Edward A.; Votanopoulos, Konstantinos; Ethun, Cecilia G.; Cardona, Kenneth; Poultsides, George; Tran, Thuy; Grignol, Valerie; Gamblin, Thomas Clark; Roggin, Kevin K.; Tseng, Jennifer; Fields, Ryan C.; Weber, Sharon M.; Russell, Gregory B.	2019	Journal of surgical oncology	120	3	340-347
Effect of radiation therapy on survival in surgically resected retroperitoneal sarcoma: a propensity score-adjusted SEER analysis	Choi, A. H.; Barnholtz-Sloan, J. S.; Kim, J. A.	2012	Annals of oncology : official journal of the European Society for Medical Oncology	23	9	2449-2457
Outcome and prognosis in retroperitoneal soft tissue sarcoma	Catton, C. N.; O'Sullivan, B.; Kotwall, C.; Cummings, B.; Hao, Y.; Fornasier, V.	1994	International journal of radiation oncology, biology, physics	29	5	1005-10
A contemporary large single-institution evaluation of resected retroperitoneal sarcoma	Bremjit, Prashoban J.; Jones, Robin L.; Chai, Xiaoyu; Kane, Gabrielle; Rodler, Eve T.; Loggers, Elizabeth T.; Pollack, Seth M.; Pillarisetty, Venu G.; Mann, Gary N.	2014	Annals of surgical oncology	21	7	2150-8
Primary retroperitoneal sarcomas: a multivariate analysis of surgical factors associated with local control	Bonvalot, Sylvie; Rivoire, Michel; Castaing, Marine; Stoeckle, Eberhard; Le Cesne, Axel; Blay, Jean Yves; Laplanche, Agnes	2009	Journal of clinical oncology : official journal of the American Society of Clinical Oncology	27	1	31-Jul
Preoperative radiotherapy plus surgery versus surgery alone for patients with	Bonvalot, Sylvie; Gronchi, Alessandro; Fiore, Marco; Sangalli, Claudia; Le Pechoux, Cecile;	2020	The Lancet Oncology	21	10	1366-1377

primary retroperitoneal sarcoma (EORTC-62092: STRASS): a multicentre, open-label, randomised, phase 3 trial	Honore, Charles; Swallow, Carol J.; Chung, Peter; Strauss, Dirk; Miah, Aisha; Meeus, Pierre; Blay, Jean Yves; van Coevorden, Frits; Haas, Rick L.; Stoldt, Stephan; Stoeckle, Eberhard; Rutkowski, Piotr; Rastrelli, Marco; Raut, Chandrajit P.; Baldini, Elizabeth H.; Hompes, Daphne; De Paoli, Antonino; Stelmes, Jean-Jacques; Litiere, Saskia; Marreaud, Sandrine; Dei Tos, Angelo P.; Gelderblom, Hans					
Prognostic factors in primary retroperitoneal soft-tissue sarcomas	Belivacqua, R. G.; Rogatko, A.; Hajdu, S. I.; Brennan, M. F.	1991	Archives of Surgery	126	3	328-334
The Benefit of Adjuvant Radiotherapy in High-grade Nonmetastatic Retroperitoneal Soft Tissue Sarcoma: A SEER Analysis	Bates, James E.; Dhakal, Sughosh; Mazloom, Ali; Constine, Louis S.	2018	American journal of clinical oncology	41	3	274-279
Preoperative radiation for retroperitoneal sarcoma is not associated with increased early postoperative morbidity	Bartlett, Edmund K.; Roses, Robert E.; Meise, Chelsey; Fraker, Douglas L.; Kelz, Rachel R.; Karakousis, Giorgos C.	2014	Journal of surgical oncology	109	6	606-11
Long-term outcomes in treatment of retroperitoneal sarcomas: A 15 year single-institution evaluation of prognostic features	Abdelfatah, Eihab; Guzzetta, Angela A.; Nagarajan, Neeraja; Schulick, Richard; Wolfgang, Christopher L.; Pawlik, Timothy M.; Choti, Michael A.; Meyer, Christian; Thornton, Katherine; Ahuja, Nita; Montgomery, Elizabeth A.; Herman, Joseph; Terezakis, Stephanie; Frassica, Deborah	2016	Journal of surgical oncology			
Factors affecting survival in retroperitoneal sarcomas treated with upfront surgery: A real-world study by turkish oncology group	Akagunduz, B.; Telli, T. A.; Yildirim, H. C.; Goksu, S. S.; Demir, N.; Hafizoglu, E.; Ozer, M.; Cevik, G. T.; Sakin, A.; Aydin, S. G.; Samanci, N. S.; Ozyurt, N.; Atci, M. M.; Ayhan, M.; Turan, M.; Sariyar, N.; Karacin, C.; Kilickap, S.; Paydas, S.; Dogan, M.	2021	UHOD - Uluslararasi Hematoloji-Onkoloji Dergisi	31(2)		92-98
Factors associated with disease-free and abdominal recurrence-free survival in	Bredbeck, B. C.; Delaney, L. D.; Kathawate, V. G.; Harter, C. A.; Wilkowski, J.; Chugh, R.;	2022	Journal of Surgical Oncology	125	8	1292-1300

abdominopelvic and retroperitoneal sarcomas	Cuneo, K. C.; Dossett, L. A.; Sabel, M. S.; Angeles, C. V.					
Has the Outcome for Patients Who Undergo Resection of Primary Retroperitoneal Sarcoma Changed Over Time? A Study of Time Trends During the Past 15 years	Callegaro, D.; Raut, C. P.; Ng, D.; Strauss, D. C.; Honore, C.; Stoeckle, E.; Bonvalot, S.; Haas, R. L.; Vassos, N.; Conti, L.; Gladdy, R. A.; Fairweather, M.; van Houdt, W.; Schrage, Y.; van Coevorden, F.; Rutkowski, P.; Miceli, R.; Gronchi, A.; Swallow, C. J.	2021	Annals of Surgical Oncology	28(3)		1700-1709
Critical impact of radiotherapy protocol compliance and quality in the treatment of retroperitoneal sarcomas: Results from the EORTC 62092-22092 STRASS trial	Haas, R.; Stelmes, J. J.; Zaffaroni, F.; Sauve, N.; Clementel, E.; Bar-Deroma, R.; Le Pechoux, C.; Litiere, S.; Marreaud, S.; Alyamani, N.; Andratschke, N. H. J.; Sangalli, C.; Chung, P. W.; Miah, A.; Hurkmans, C.; Gronchi, A.; Bovee, Jvmg; Gelderblom, H.; Kasper, B.; Weber, D. C.; Bonvalot, S.	2022	Cancer	10		10
Low and moderate grade retroperitoneal liposarcoma: Is adjuvant radiotherapy associated with improved survival in patients undergoing R1 resection?	Littau, M. J.; Kim, P.; Kulshrestha, S.; Bunn, C.; Tonelli, C.; Abdelsattar, Z. M.; Luchette, F. A.; Baker, M. S.	2022	American journal of surgery.	10		
Comparison of comprehensive complication index and Clavien-Dindo classification in patients with retroperitoneal sarcoma	Tirotta, F.; Parente, A.; Richardson, T.; Almonib, A.; Evenden, C.; Max Almond, L.; Desai, A.; Hodson, J.; Ford, S. J.	2021	Journal of Surgical Oncology	124(7)		1166-1172
Radical Versus Non-Radical Resection for Early-Stage Retroperitoneal Sarcoma: A Propensity Score-Matched Analysis	Weng, C.; Wang, J.; Zhao, J.; Yuan, D.; Huang, B.; Wang, T.	2021	Frontiers in Oncology	11		706543
Outcome after surgical resection of multiple recurrent retroperitoneal soft tissue sarcoma	Willis, F.; Musa, J.; Schimmack, S.; Hinz, U.; Mechtersheimer, G.; Uhl, M.; Schmidt, T.; Frohling, S.; Buchler, M. W.; Schneider, M.	2021	European Journal of Surgical Oncology	47(8)		2189-2200
Cumulative Burden of Postoperative Complications in Patients Undergoing Surgery for Primary Retroperitoneal Sarcoma	Tirotta, F.; Parente, A.; Hodson, J.; Desai, A.; Almond, L. M.; Ford, S. J.	2021	Ann Surg Oncol	28	12	7939-7949

Preoperative Radiotherapy in Patients With Primary Retroperitoneal Sarcoma: EORTC-62092 Trial (STRASS) Versus Off-trial (STREXIT) Results	Callegaro, D.; Raut, C. P.; Ajayi, T.; Strauss, D.; Bonvalot, S.; Ng, D.; Stoeckle, E.; Fairweather, M.; Rutkowski, P.; van Houdt, W. J.; Gelderblom, H.; Sangalli, C.; Hayes, A.; Honore, C.; Gladdy, R. A.; Fau, M.; Haas, R.; Tzanis, D.; Miah, A. B.; Chung, P.; Baldini, E. H.; Marreaud, S.; Litiere, S.; Swallow, C. J.; Gronchi, A.	2022	Annals of Surgery	14		14
Lifelong Imaging Surveillance is Indicated for Patients with Primary Retroperitoneal Liposarcoma	Eckardt, M. A.; Graham, D. S.; Klingbeil, K. D.; Lofftus, S. Y.; McCaw, T. R.; Bailey, M. J.; Goldring, C. J.; Kendal, J. K.; Kadera, B. E.; Nelson, S. D.; Dry, S. M.; Kalbasi, A. K.; Singh, A. S.; Chmielowski, B.; Eilber, F. R.; Eilber, F. C.; Crompton, J. G.	2022	Annals of Surgical Oncology	29		29
Clinical Impact of External Beam Radiotherapy for Surgically Resected Primary Retroperitoneal Liposarcoma	Erstad, D. J.; Chiang, Y. J.; Witt, R. G.; Cope, B.; Nassif, E. F.; Scally, C. P.; Torres, K. E.; Feig, B. W.; Hunt, K. K.; Bishop, A. J.; Guadagnolo, B. A.; Roland, C. L.; Keung, E. Z.	2023	Annals of Surgical Oncology	30	2	926-940
The management of retroperitoneal sarcoma: The experience of a single institution and a review of the literature	Feki, J.; Lajnef, M.; Fourati, M.; Sakka, D.; Hassena, R. B.; Slimen, M. H.; Daoud, J.; Khanfir, A.	2023	Journal of Taibah University Medical Sciences	18	1	125-131

Appendix 2. Evidence Summary Topic 2 Question 1 Systematic Review

Outcome 1: Abdominal recurrence free survival

Study No.	Study Identifier	Country	Design	Inclusion criteria	Exclusion criteria	No. of patients	Time frame	Follow up	Local control/ abdominal recurrence free survival	Multivariate analysis	Comments
1	Abdelfatah 2016	USA	Retrospective cohort study	Primary, unifocal RPS Age > 18 John Hopkins	GIST, desmoid, lymphoma, sarcomatosis	131	1994-2010	> 5y	See MVA	RT decreased local recurrence on MVA (values not stated; HR 0.28 (95% CI 0.09-0.86, p=0.026).	RT 24% (pre op 29%, post op 48%, pre & intra op 13%, RT alone 10%). EBRT 40-50.4Gy, IORT 10-12Gy
2	Bonvalot 2009	France	Retrospective cohort study	Primary RPS		382	1985-2005	Median 4.4y (range 1-8)	Pre or post-op RT decr 3y abdo RR (34 v 49%, HR 0.64 (0.45-9), p=0.01)	RT not significant on MVA	RT 32% (pre op 9%, post op 91%). Post op median 45Gy, range 10-66Gy
3	Bonvalot 2020	USA, Canada, UK, Europe	Randomized controlled trial	Age > 18 Localised RP or infra-peritoneal spaces of pelvis Unifocal Non-metastatic Operable Suitable for RT WHO PFS 0-2	Not originating from bone structure, abdominal, or gynecological viscera	266	2012-2017	Median 43.1mo (IQR 28.8-59.2)	See MVA	No difference abdo recurrence free survival 4.5y (RT+surg) v 5y (surg alone), HR 1.01 (95% CI 0.71–1.44, p=0.95).	Neoadj RT (50%; 50.4Gy 3DCRT or IMRT) LPS subgroup had 10% absolute benefit in ARFS with addition of RT. Supplementary data: benefit of RT in 2 subgroups: well diff LPS (HR 0.69) & low grade tmrs (HR 0.73). Local relapse: 37 v 19.5% (all); 30 v 11%.

4	Bredbeck 2022	USA	Retrospective cohort study	Abdomino-pelvic & RP STS Age > 18 Curative intent	Unresectable DM GIST, visceral or abdo wall sarcoma	159	1998-2015	5.3y	Neoadj RT improved abdo recurrence free survival (5.31 v 3.23 years, p=0.029)	Significant on MVA (6.14y v 3.22y, p=0.002). Adjuvant RT no difference ARFS.	Neoadj RT 11%, adj RT 19%. Median 50.4Gy (range 45-60Gy) Subgroup anal: neoadj RT improved ARFS for LPS (8.86 v 3.11y, p<0.001) but not LMS (p=0.575)
5	Callegaro 2022	USA, Canada, Europe	Retrospective cohort study	Adult patients Curative intent surgery for RPS	STRASS trial GIST, desmoid, gynae or bone sarcoma, alveolar or embryonal RMS, Ewings Pre-op chemo	1097	2012-2017	39 months	RT assoc w/ improved ARFS in WDLPS and G1-2 DDLPS (but not G3 DDLPS or LMS)	Propensity score matching	
6	Catton 1994	Canada	Retrospective cohort study	RPS		104	1975-1988	6.3y (range 1.4- 10.4)	Decreased LRF (R0 & R1) with PORT (103 vs 30m; p = 0.06)	No MVA	RT 35% (PORT), median 40Gy. Benefit in infield relapse free rates if dose ≥35Gy (p=0.02)
7	Chouliaras *(Recurrence Patterns)* 2019	USA	Retrospective cohort study	Primary RPS Curative intent	Desmoid Multifocal, metastatic	498	2000-2016	4.3y	No difference local recurrence (neoadj RT incl in univariate analysis; values not cited)	No MVA	RT 12.4% (neoadj) Propensity score matched analyses for neo-RT vs no-RT and adj-RT vs no-RT
8	Chouliaras *(Role of RT)* 2019	USA	Retrospective cohort study	Primary RPS US Sarcoma Collaborative	Metastatic disease, sarcomatosis IORT or brachy alone	425	2000-2016	31.4mo	*Neoadj RT*: median time to LR 146mo (RT) v 96mo, p=0.58 (unadjusted); 59 v 35mo, p=0.35 (matched) *Adj RT*: median time to LR 83mo (RT) vs 96mo, p=0.99 (unadjusted); 71 v 95mo, p= 0.27 (matched)	RT not predictive of LR	RT 30% (pre op 13%, post op 18%). Higher grade tumours in RT group Propensity score matched

9	Haas 2019	USA, UK, Europe	Retrospective cohort study	Localised primary RPS Liposarcoma (well-diff or dediff) Surgical resection +/- RT		607	2002-2011	56mo	8y LR 11.8% (RT) v 39.2% (surg alone) for all groups (well diff, G1-2 dediff & G3 dediff) before but not after IPTW	No association on MVA for any groups or endpoints	RT 29% (pre & post op) Used IPTW (inverse probability of treating weighting) to account for biases due to non-random RT assignment
10	Hassan 2004	USA	Retrospective cohort study	Primary RPS	Age < 16 Primary GIT/GUT sarcoma	97	1983-1995	3y (all pts), 6y (survivor)	5y disease recurrence (local and distant) 41% (adj RT) v 45% (surg alone), p=0.76.	Histo subtype only predictor of OS on MVA	RT included pre-op (43%), intra op (28%) and post op (43%). LMS more likely to receive RT than LPS
11	Heslin 1997	USA	Retrospective cohort study	RPS, surgery	Metastatic disease Biopsy only Desmoid	48	1982-1990	Median 97mo (min 5y)	Increased local failure free survival with RT (84 v 54%, p=0.02)	Incomplete gross resection (p=0.003) only significant	RT 27% (majority PORT, few had IORT/brachy)
12	Kelly 2015	USA	Prospective cohort study	Primary RPS Gross total resection	Multifocal, recurrence Unable to have RT RT-induced tumours Active malignancy GIST	204	2003-2011	Median 30mo	Decreased LR with RT (HR 0.28, p=0.035 univariate; HR 0.26, p=0.026 MVA). Increased *LR free survival* (91 v 65%, p=0.024)	RT decreased LR and LR-free survival	RT 16% (94% pre op; 6% PORT +/- 47% IOERT if not well enough for pre op). Median 50Gy. RT group more LPS, more pelvic tumours.
13	Kim 2018	Korea	Retrospective cohort study	Primary RPS	Pre 1994 Stage IV No follow up Double primary malignancy	80	1994-2015	37.1mo (range, 5.8–207.9)	Increased 5y LFFS with RT (74 v 24%, HR 0.179, p=0.001)	Post op RT only independent prognostic factor for improved LFFS	RT 48% (post op). Median 54 Gy (range, 36.0–66.9 Gy). No correlation between RT dose & LFFS
14	Le Pechoux 2013	France	Retrospective cohort study	Primary RPS (or early re-excision after inapprop sx) >18 years PFS 0-2		110	1994-2008	4.1y (median)	No difference abdo relapse (5y 36 v 22%, HR 0.48, p=0.18)	RT increased RFS, but not abdo RR	RT 44% (PORT). RT more likely for margin pos (R1-2) & G3 tumours
15	Lee 2016	Korea	Retrospective cohort study	Primary retroperitoneal liposarcoma	Recurrence Previous RT (incl pre op RT) R2 resection	77	2000-2013	36mo (range 5-169)	No difference (3y LC 52.5 (RT) vs 59.7% (surg alone), p=0.312)	Histologic subtype (well-diff vs not) assoc with LC (HR 2.73 (CI 1.32-5.67),	RT 42% (PORT), median 54Gy RT group less well-diff LPS.

										p=0.007), as was grade (1 v 2-3). RT not SS (p=0.32)	Subgroup: trend to improved LC for: non-well diff subtypes 181(3y LC 35 v 44%, 1p=0.087) de-diff subtypes (3y LC 28 v 42%, p=0.054)
16	Molina 2016	USA	Retrospective cohort study	Primary, unifocal RPS Liposarcoma GTR (R0, R1)		41	1991-2003	51.5mo (pre op), 803mo (no RT)	5y LRFS 95.6% (RT) v 75% (surg alone), p=0.0213. HR for LR 0.11 (95% CI 0.01-0.91, p=0.04).	Not reported	RT 66% (n=16 pre op, 9 pre + IOERT, 2 pre&post op, 1 IOERT) Propensity score matched
17	Mussi 2008	Italy	Retrospective cohort study	Retroperitoneal liposarcoma (well-diff or de-diff)	Distant metastases	93	1985-2004	71mo (IQR 28-132)	5y LRFS 51.4% (RT) v 25% (surg alone), HR 0.45 p=0.044	Yes	RT 26% (20 pre op, 4 post op). Median 50Gy (range 36-65)
18	Sampath 2010	USA	Retrospective cohort study	RPS National Oncology Database Age > 18	Ewing, RMS, desmoid Recurrence Palliative R2 resection	261	1982-2003	59mo (range 0.2-186)	5y LFFS 79% (adj RT) v 64% (surg alone), HR 0.42 (95% CI 0.21, 0.86), p<0.05 (MVA).	RT significant for LFFS	RT 26% (pre op 20%, post op 2%, unk 12%) RT dose & sequence not assoc with LFFS
19	Snow 2018	Australia	Retrospective cohort study	RPS (primary or recurrent) Localised & metastatic	Visceral, gynaecologic, paediatric sarcoma, GIST, desmoid	88 (primary resectable RPS)	2008-2016	36mo	Neoadj RT increased FFLR (HR 0.33 (95% CI 0.13, 0.84), p=0.014).	No MVA	RT 26% (neoadj 88%, adj 9%, pall 3%). Higher use of neoadj RT at specialised centre (87 v 12%) LR defined as retroperitoneum or peritoneal cavity. Results reported for primary resected RPS only (n=88)
20	Stoeckle 2001	France	Retrospective cohort study	Primary RPS	Recurrence Visceral sarcoma, fibromatosis	165 (145 localised)	1980-1994	47mo (range, 3–160)	In M0 patients with complete excision, RT decreased 5y actuarial LRFI 55 v 23%, p=0.0021	RR 3.35 for no RT (95% CI 1.8, 6.3), p=0.0002	RT 56% (M0 &M1) (97% post op), median 50Gy (range 45-90)

21	Stucky 2014	USA	Retrospective cohort study	RPS (primary or recurrent) Curative intent treatment	Distant mets R2 resection	63	1996-2011	45mo	5y LC 89% (RT) v 46% (surg alone), p=0.004)	RT assoc with decr LR on MVA (HR 0.19; 95% CI 0.05-0.69, p = 0.003)	RT 59% (preop EBRT & IOERT, median 45Gy EBRT, 12.5Gy IOERT). RT pts younger, more likely local recur
22	Toulmonde 2014	France	Retrospective cohort study	Primary RPS Age >18 No active malignancy Expert path review	SFT, sarcomas of uncertain malignancy	586	1988-2008	6.5y (range 5.9-7.1)	In M0 patients with complete excision, RT decreased 5y actuarial LRFI 55 v 23%, p=0.0021	On MVA, RR 3.35 for no RT (95% CI 1.8, 6.3), p=0.0002	RT 29% (post op 74%, median 50Gy) Peri-operative RT were associated with a lower risk of LR relapse for DDLPS
23	Trovik 2014	Norway, Sweden	Retrospective cohort study	RPS Curative intent	Recurrence Distant metastases	97	1988-2009	4.7y (range 0.5-18.5)	5y LRFS 77% (RT) v 39% (surg alone), HR 0.33 (95% CI 0.17-0.64), 27p=0.001)	RT assoc with LR (HR 0.20 (95% CI 0.09-0.45), p<0.001), DMFS and OS on MVA	RT 43% (pre op 12%, post op 88%, median 50Gy (range 20-65)). RT more frequent for HG tumours (52 HG v 38% LG, p=0.132)
24	Turner 2019	Canada	Retrospective cohort study	RPS Age >18 GTR	Post op RT GI/GU origin Metastatic disease	102	1990-2014	90mo	Median LRFS 89.3mo (RT) vs 28.4mo (surg alone	RT increased LRFS on MVA (HR 0.42, 95% CI 0.24, 0.79, p=0.01).	RT 64% (neoadj)
25	Willis	Germany	Retrospective cohort study	Primary, recurrent or metastasised RPS, surgical resection	GIST, embryonal, paediatric or gynaecological RPS	201	2001-2017	36.9mo	See MVA	No difference LR free survival for all comers (p=0.860) or LPS subgroup (p=0.879) (Supplementary Data)	

Outcome 2: Recurrence free survival

Study No.	Study Identifier	Country	Design	Inclusion criteria	Exclusion criteria	Number of Patients	Time frame	Follow up	Recurrence free survival	Multivariate analysis	Comments
1	Abdelfatah 2016	USA	Retrospective cohort study	Primary, unifocal RPS Age > 18	GIST, desmoid, lymphoma, sarcomatosis	131	1994-2010	> 5y	RT not associated with RFS on MVA (HR 1.25 (CI 0.61-2.59), p=0.538)	MVA: RFS increased with positive margins (R1 margin HR 4.28, p < 0.001), tumour size >15 cm (HR 4.38, p=0.024), presence of mets (HR 6.61, p=0.003)	RT 24% (pre op 29%, post op 48%, pre & intra op 13%, RT alone 10%). EBRT 40-50.4Gy, IORT 10-12Gy
2	Akagunduz 2021	Turkey	Retrospective cohort study	RPS Curative surgery	Neoadj RT or chemo Age <18y Distant mets Neoadj CT or RT for locally advanced dx Ewing, RMS, GIST,desmoid, gyne sarcoma	197	2000-2020	33mo (range 3-209)	RFS 17mo (surg) v 35mo (surg + CT), 70mo (surg + RT), 50mo (surg + CT + RT), p=0.215	MVA: tumour size & resection margin assoc w/ RFS. RT not significant.	RT 44% (PORT)
3	Bevilacqua 1991	USA	Retrospective cohort study	Primary RPS Nil prior surgery (unless biopsy/limited excision elsewhere within 3 months of admission)	Visceral tumours	80 (62 complete resection)	1982-1988	Not stated	5y DFS 44% (RT) vs 63% (no RT), p= 'NS' (p value not cited)	NS on MVA	RT 32% (of R0 pts) (15 EBRT, 4 brachy, 1 EBRT + brachy, median 47.7Gy, range 20-65Gy)
4	Bonvalot 2020	USA, Canada, UK, Europe	Randomized controlled trial	Age > 18 Localised RP or infra-peritoneal spaces of pelvis Unifocal Non-metastatic Operable Suitable for RT WHO PFS 0-2	Not originating from bone structure, abdominal, or gynecological viscera	266	2012-2017	Median 43.1mo (IQR 28.8-59.2)	3-year metastasis-free survival 68.2% surgery v 68.3% surg + RT (HR 0.89, 95% CI 0.58-1.36, p=0·59)	N/A as RCT	Neoadj RT (50%; 50.4Gy 3DCRT or IMRT) LPS subgroup had 10% absolute benefit in ARFS with addition of RT. Benefit of RT in 2 subgroups: well diff LPS & low grade tmrs.

5	Bredbeck 2022	USA	Retrospective cohort study	Abdomino-pelvic & RP STS Age > 18 Curative intent	Unresectable DM GIST, visceral or abdo wall sarcoma	159	1998-2015	5.3y	DFS 4.66y (neoadj RT) vs 3.12y (no RT), p = 0.110	Adjusting for grade & margins, neoadj RT improved DFS (5.46y vs. 3.1y, p = 0.015	RT 30% (neoadj 11%, adj 19%). Median 50.4Gy (range 45-60Gy) Subgroup anal: neoadj RT improved ARFS for LPS (8.86 v 3.11y, p<0.001) but not LMS (p=0.575)
6	Bremjit 2014	USA	Retrospective cohort study	Primary localized RPS		132	2000-2013	31.8mo	Neoadj RT no difference PFS (p=0.565	MVA not performed as univariate negative.	RT 33% (neoadj). RT more likely for low grade (HG tumours more likely to have chemo) & large tumours (mean 20cm vs 18.5cm)
7	Callegaro 2021	USA, Canada, UK, Europe	Retrospective cohort study	Age > 16y Primary RPS Non-metastatic Curative intent surgery	Ewings, RMS, GIST, desmoid fibromatosis, gynaecologic sarcoma	1942	2002-2017	Min 37mo	See MVA	RT improved DFS (HR 0.73 (95% CI 0.58-0.90), p=0.013	Study looking at outcomes over 3 distinct time periods. RT 27% (post op 5%, pre op 22%). Decline in PORT over time.
8	Callegaro 2022	USA, Canada, Europe	Retrospective cohort study	Adult patients Curative intent surgery for RPS	STRASS trial GIST, desmoid, gynae or bone sarcoma, alveolar or embryonal RMS, Ewings Pre-op chemo	1097	2012-2017	39 months	No difference distant metastasis free survival overall or in subgroup analysis	Propensity score matching	
9	Catton 1994	Canada	Retrospective cohort study	RPS		104	1975-1988	6.3y (range 1.4-10.4)	No difference distant RFS (p value 'NS')	Not performed	RT 35% (PORT), median 40Gy. Benefit in infield relapse free rates if dose ≥35Gy (p=0.02)
10	Chouliaras 2019 *(Recurrence Patterns)*	USA	Retrospective cohort study	Primary RPS Curative intent	Desmoid Multifocal, metastatic	498	2000-2016	4.3y	No difference distant RFS (univariate)	MVA: histology predicted DM (LMS more likely to recur distantly cf well diff or mixed type LPS). RT not significant	RT 12.4% (neoadj) Propensity score-matched analyses for neo-RT vs no-RT & adj-RT vs no-RT
11	Chouliaras 2019 *(Role of RT)*	USA	Retrospective cohort study	Primary RPS	Metastatic disease, sarcomatosis IORT or brachy alone	425	2000-2016	31.4mo	Adjusted (matched) RFS 27.24 mo (adj RT) v 35.94mo (no RT), p=0.84; 33.87mo (neoadj RT) v 17.64mo (no RT), p=0.28.	Propensity score matched. No difference RFS for neoadj RT (HR 0.98, p=0.95) or adjuvant RT (HR 0.7, 0.15)	RT 30% (pre op 13%, post op 18%). Higher grade tumours in RT group Propensity score matched

12	Eckardt 2022	USA	Retrospective cohort study	Primary RPS. PFS =>10y after initial surgery	PFS < 10y after initial surgery	39	1972-2010	21y	No relationship between RT and 'recurrence'	On MVA HR 0.93 (95% CI 0.22-4.00), p=0.927	NB. Location of recur not reported (local & distant)
13	Haas 2019	USA, UK, Europe	Retrospective cohort study	Localised primary RPS Well-diff or dediff LPS Surgical resection +/- RT		607	2002-2011	56mo	No diff DM with RT (after IPTW) *Well-diff LPS*: too small *G1-2 dediff LPS*: crude cumulative incidence (CCI) of DM at 5y 9.6% (S+RT) v 9.3 (surg alone); at 8y 9.6% (S+RT) v 8.1% (surg alone). No assoc before IPTW (HR 1.17, 95% CI 0.45-3.01, p=0.749) or after IPTW (HR 1.04, 95% CI 0.15-7.34, p=0.966). *G3 DDLPS:* CCI of DM at 5y 30.1% (S+RT) v 30.6% (surg alone), 8y 35.1% (S+RT) v 30.6% (surg alone). Effect of RT not SS before (HR 0.70, 95% CI 0.36-1.36, p=0.296) or after IPTW (HR 1.30, 95% CI 0.25-6.67, p=0.750).	RT not significant	RT 29% (pre & post op) Used IPTW (inverse probability of treating weighting) to account for biases due to non-random RT assignment
14	Hager 2017	Germany	Retrospective cohort study	RPS Curative intent surgery		46	2001-2014	55.51mo (range 7-148)	5y PFS for R0 pts (n=39) 41.2% (S+RT) v 26.8% (surg alone), p=0.362 (univariate)	MVA not reported for PFS	RT 50% (pre op, post op, IOERT)
15	Hassan 2004	USA	Retrospective cohort study	Primary RPS	Age < 16 Primary GIT/GUT sarcoma	97	1983-1995	3y (all pts), 6y (survivors)	5y disease recurrence (local and distant) 41% (adj RT) v 45% (no RT), p=0.76	Not reported for RFS	RT 49% (pre-op 43%, intra op 28%, post op 43%). LMS more likely to receive RT than LPS
16	Heslin 1997	USA	Retrospective cohort study	RPS, surgery	Metastatic disease Biopsy only Desmoid	48	1982-1990	Median 97mo (min 5y)	RT not signif for distant metastasis (univariate)	MVA not reported for DM	RT 27% (majority PORT, few had IORT/brachy
17	Lane 2015	USA	Retrospective cohort study	Surgical resection RPS (primary & recurrent)	Desmoid, GIST Unresectable Prior RT	94 (n=74 primary, n=20 recur)	1990-2001	1341d (no RT), 1393d (RT)	No difference (primary RPS only), p=0.49	RT (incl. primary & recurrent) significant assoc w/ decreased recurrence (HR 0.34,	Univariate outcomes for primary only not SS, MVA included

								(range 434-2051)		p<0.01) and increased OS (HR 0.3, p=0.02) on MVA	primary & recurrence dx together RT 39% (primary), 40% (recurrent), pre & post op EBRT +/- IORT
18	Le Pechoux 2013	France	Retrospective cohort study	Primary RPS (or early re-excision after inappropriate surgery) >18 years PFS 0-2		110	1994-2008	4.1y (median)	See MVA	5y (any) RFS 60% (S+ RT) v 47% (surg alone), HR 0.43, p=0.02. Median *distant* RFS 7.8y (S+RT) v not reached (S alone) (ie. <50% pts have metastatic recur in surg alone group). Adj HR *distant* recur 0.79 (95% CI 0.33-1.90), p=0.60 (all MVA).	RT 44% (PORT). RT more likely for margin pos (R1-2) & G3 tumours, less likely for LPS. Neoadj chemo more likely in S+RT grp (included in MVA)
19	Lee 2016	Korea	Retrospective cohort study	Primary retroperitoneal liposarcoma	Recurrence Previous RT (incl pre op RT) R2 resection	77	2000-2013	36mo (range 5-169)	3y DFS 50 v 58%, p=0.285	Not reported for DFS	RT 42% (PORT), median 54Gy RT group less well-diff LPS. Subgroup: trend to improved LC for: non-well diff subtypes (3y LC 35 v 44%, p=0.087) de-diff subtypes (3y LC 28 v 42%, p=0.054)
20	Molina 2016	USA	Retrospective cohort study	Primary, unifocal RPS Liposarcoma GTR (R0 or R1)		41	1991-2003	51.5mo (pre op), 803mo (no RT)	5y distant RFS86.1% (RT) v 84.9% (no RT), p=0.90.	No MVA	RT 66% (n=16 pre op, 9 pre + IOERT, 2 pre& post op, 1 IOERT) Propensity score matched
21	Nathenson 2018	USA	Retrospective cohort study	Retroperitoneal LPS or LMS		49	2000-2013	6.9y (for pts still alive)	No difference in PFS w/ neoadj or adj RT, p=0.69 for both (only n=18)	No MVA	RT 37% 9adj & neoadj), mean 54.2Gy LMS: 2y PFS 38% (RT) v 33% (no RT) LPS 2y PFS 56% (RT) vs 49% (no RT)
22	Park 2016	Korea	Retrospective cohort study	RPS (LPS only) Complete resection ("no residual tumour on CT 2 mo post-op) Primary & recurrent tumours	Prior malignancy Failure to complete RT Metastatic disease	53	2005-2012	38.9mo (median)	See MVA	5y DFS 75% (RT + TE), 29% (RT w/out TE), 85% (no RT). Increased RFS for tissue expander + PORT v surg alone (OR 12.4, p=0.04); but not for PORT w/out expander cf. surg alone (p=0.52).	RT 49% (PORT) NB. Higher RT dose (54Gy) in grp 1 cf. group 2 (50.4Gy)

23	Pierie 2006	USA	Retrospective cohort study	Primary RPS		103	1973-1998	Not reported	See MVA	On MVA, IOERT plus EBRT assoc w/ increased absence of local and distant recurrences (HR 0.26, p = 0.048)	RT numbers not stated (pre, post & intra-op)
24	Stoeckle 2001	France	Retrospective cohort study	Primary RPS French Sarcoma Group registry	Recurrence Visceral sarcoma, fibromatosis	165 (145 = M0)	1980-1994	47mo (range 3-160)	5y metastasis free survival in M0 pts 65% (RT) v 69% (no RT), p=0.7835. No difference 5y MFS for all pts (p=0.07)	No difference on MVA	RT 56% (PORT)
25	Toulmonde 2014	France	Retrospective cohort study	Primary RPS Age >18 No active malignancy Expert path review	SFT, sarcomas of uncertain malignancy	586	1988-2008	6.5y (range 5.9-7.1)	See MVA	On MVA, RT not assoc w/ distant metastasis (p value not cited)	RT 29% (post op 74%, median 50Gy) Peri-operative RT were associated with a lower risk of LR relapse for DDLPS
26	Trovik 2014 (Nyhus)	Norway, Sweden	Retrospective cohort study	RPS Curative intent	Recurrence Distant metastases	97	1988-2009	4.7y (range 0.5-18.5)	5y DMFS 68% (RT) v 51% (no RT), p=0.207	On MVA, RT increased DMFS, HR 0.42 (95% CI 0.20-0.88), p=0.021	RT 43% (pre op 12%, post op 88%, median 50Gy (range 20-65)). RT more frequent for HG tumours (52 HG v 38% LG, p=0.132)
27	van Doorn 1994	Nether-lands	Retrospective cohort study	RPS Potentially resectable		34	1973-1990	38mo (range 2-208)	At median f/up 24mo, DFS 3/19 pts (no RT) v 6/13 pts (RT), p<0.01. Median time to recur 60mo (RT) v 24mo (no RT), p<0.01.	No MVA	RT 30% (PORT, median 56Gy, 40-62Gy)
28	Willis	German y	Retrospective cohort study	Primary, recurrent or metastasised RPS, surgical resection	GIST, embryonal, paediatric or gynaecological RPS	201	2001-2017	36.9mo	See MVA	No difference DM free survival in all comers (p=0.729). No diff PFS in LMS subgroup (p value not cited)	

Outcome 3: Perioperative morbidity

Study No	Study Identifier	Country	Study design	Inclusion criteria	Exclusion criteria	Number of Patients	Time frame	Follow up	Perioperative morbidity	Multivariate analysis	Comments
1	Bartlett 2014	USA	Retrospective cohort study	Primary RPS American College of Surgeons Registry	Not stated	696	2005-2001	Not reported	30d M&M 31 (RT) v 30% (no RT), p=0.745	RT NS for 30d M&M (OR 0.5, 95% CI 0.2–1.4)	Overweight, obese, underweight, prolonged OT time, clean-contaminated wound, increased blood

											transfusion requirement all assoc with M&M on MVA.
2	Bonvalot 2020	USA, Canada, UK, Europe	Randomized controlled trial	Age > 18 Localised RP or infra-peritoneal pelvis Unifocal Non-metastatic Operable Suitable for RT WHO PFS 0-2	Not originating from bone, abdominal, or gynecologic viscera	266	2012-2017	43.1mo (median)	OT dur'n 288 (surg) v 300min (RT) Intra-op transf'n 19 (S) v 29% (RT) LOS 12 (S) v 14d (RT) Post-op death 2% (S=RT) Re-op 11% (surg) v 12% (RT) Serious AEs 24 (RT) v 10% (surg) Pt's worst grade 'on study': G1-2 58% (surg) v 59% (RT), G3 20% (S) v 30% (RT), G4 2.3% (S) v 6.3% (RT). G5 1.6% (pre op RT only).	N/A	Neoadj RT (50%; 50.4Gy 3DCRT or IMRT)
3	Chouliaras 2019 *(Role of RT)*	USA	Retrospective cohort study	Primary RPS	Metastatic disease, sarcomatosis IORT or brachy alone	425	2000-2016	31.4mo	In hospital complication rate: 34% (no RT) v 41% (pre op RT) v 29% (post op RT), p=0.32 Re-op rates: 7.6% (no RT) v 3.6% (neoadj RT) v 1.4% (adj RT), p=0.1 Readmission rates: 10.6% (no RT) v 16.4% (neoadj RT) v 8.3% (adj RT), p=0.34	No MVA	RT 30% (pre op 13%, post op 18%). Higher grade tumours in RT group Propensity score matched
4	Ecker 2016	USA	Retrospective cohort study	Age > 18 Primary retroperitoneal LPS Non-metastatic Resection Curative intent NCDB	< 45Gy pre op Adj or intra-op RT without neoadj RT Prior palliative surg or RT	347	2004-2013	52mo	30d mort 1.5% (neoadj RT) v 1.5% (surg alone), p=0.588 (unmatched cohort) 90d mort 5.1% (neoadj RT) v 3.3% (surg alone), p=0·467 (unmatched cohort) Readmission within 30d: 6.9% (neoadj RT) v 6.3% (surg alone), p=0.309	No MVA	RT 8.4% (neoadj +/- IORT +/- EBRT)). Use increased over study period (8.5% 2004, 13.9% 2013). Median 50Gy. Prior to propensity matching, RT pts younger, lived in more pop'n dense areas, larger tumours, more recently diagnosed, tmt at academic/ research facility, smaller tumours and more likely to have had chemo.
5	Erstad 2023	USA	Retrospective cohort study	NCDB Non metastatic, primary, retroperitoneal	Distant mets Histo/grade mismatch No definitive	3911	2004-2017	4.1y	WDLPS: neoadj RT assoc w/ longer LOS; but not assoc w/ increased risk of death	No MVA for peri-op morbidity	LOS not assoc w/ OS. Propensity score matched cohorts for use of RT (n=670 WDLPS, n=X

				liposarcoma (inclwell diff G1 & dediff G2-4)	resection R2 resection IORT Systemic chemo death w/in 30d of surgery				No diff 30d readmission or 90d mortality for WDLPS or DDLPS by use of RT (any) or neoadj RT		DDLPS) and use of neoadj RT (n=208 WDLPS, n=X DDLPS)
6	Hassan 2004	USA	Retrospective cohort study	Primary RPS	Age < 16 Primary GIT/GUT sarcoma	97	1983-1995	3y	No diff post-op complications with adjuvant RT (rates and p values not reported)	No MVA	RT 49% (pre op 43%, IOERT 28%, post op 43%). RT more likely for LMS (cf LPS)
7	Kelly 2015	USA	Prospective cohort study	Primary RPS Gross total resection	Multifocal, recurrence Unable to have RT RT-induced tumours Active malignancy GIST	204	2003-2011	30mo (median)	Complications w/in 30d 41% (RT) v 17% (surg alone), p=0.004. Same length of stay (7 days). No operative/peri-operative deaths in either group.	No MVA for this endpoint	RT 16% (94% pre op RT, 6% PORT; photons, protons +/-- IOERT). RT group more pelvic tumours & different histo less LMS, less WDLS, more DDLS, MPNST & 'other')
8	Leiting 2008	USA	Retrospective cohort study	RPS NCDB	>1 site of cancer Palliative treatment	2264	2004-2012	Not reported	30d unplanned readmission 6.1% (surg alone) v 5% (RT), p<0.001	No MVA for this endpoint	RT 32% (9% pre op), median 50Gy. RT pts younger, LMS > LPS, more non-academic facilities, more chemo, smaller tmrs (15 v 19cm), more high grade, more positive margins.
9	Ma 2020	USA	Retrospective cohort study	NCDB Non metastatic, resectable RPS	Survival <6mo after diagnosis	7857	2006-2015	48.7 mo	Readmission w/in 30d 9.2% (RT) v 8.3% (no RT), p=0.84	No MVA for this endpoint	RT 10.8% (pre op)
10	Mollina 2016	USA	Retrospective cohort study	Primary, unifocal retroperitoneal liposarcoma Complete resection (R0 or R1)	Non-liposarcoma	41	1991-2003	51.5mo (pre op RT), 803mo (no RT)	No deaths 30d post op in either group	No MVA for this endpoint	

11	Nussbaum 2014	USA	Retrospective cohort study	RPS, resected	Missing data	785	2005-2011	Not reported	RT assoc w/ longer operative time (278 v 240min, p=0.014) No difference 30d mortality (2.8% both, p=0.999), major complication rate (29% RT vs 26% surg alone, p=0.787), overall complication rate (35 v 30%, p=0.498), surgical site infection, or early return to OR (5.6% RT vs 7.6%, p=0.778)	No MVA for this endpoint	RT 9% (pre op). RT pts younger. Propensity score matched.
12	Nussbaum 2015	USA	Retrospective cohort study	RPS, resected NCDB		11324	1998-2011	Not reported	LOS 6d (RT) v 5d (no RT), p=0.027 No diff 30d mortality (RT 0.9% vs. no RT 1.9%, p=0.163 propensity matched), or 30d readmission rate (RT 4.6 v 3.5%, p=0.343)	No MVA for this endpoint	RT 6.1% (neoadj). Incr in RT use during study (4% in 1998, 15% in 2011). RT pts younger, more male, more treated at academic/research facility, and thus liver further from treatment centre
13	Tirotta 2021 #1 *(CCI)*	UK	Retrospective cohort study	Primary RPS, surgery	Recurrent or metastatic disease	191	2008-2019	Not reported	RT not assoc w/ longer length of stay than surg alone (pre op p=0.583, post op p=0.403. any RT p=0.591)	MVA: RCCI, tumor size & organ weighted resection scores assoc w/ longer LOS. RT not significant	RT numbers not stated.

Outcome 4: Overall survival

Study No.	Study Identifier	Country	Design	Inclusion criteria	Exclusion criteria	Number of Patients	Time frame	Follow up	Overall survival	Multivariate analysis	Comments
1	Abdelfatah 2016	USA	Retrospective cohort study	Primary, unifocal RPS Age > 18	GIST, desmoid, lymphoma, sarcomatosis	131	1994-2010	> 5y	See MVA	Margins (R1 margin HR 4.28, p < 0.001), tumour size >15 cm (HR 4.38, p=0.024), presence of mets (HR 6.61, p=0.003) assoc w/ OS. RT not significant (HR 0.57, 95% CI 0.28-1.16, p=0.122).	RT 24% (pre op post op 48%, p intra op 13%, RT 10%)

2	Akagunduz 2021	Turkey	Retrospective cohort study	RPS Curative surgery	Neoadj RT or chemo Age <18y Distant mets Neoadj CT or RT for locally advanced dx Ewing, RMS, GIST,desmoid, gyne sarcoma	197	2000-2020	33mo (range 3-209)	OS 100mo (surg), 95mo (surg + CT), not reported (surg + RT), 74mo (surg + CT + RT), p=0.421	MVA: tumour size & resection margin assoc w/ OS. RT not significant (p=0.421)	RT 44% (POR
3	Bates 2018	USA	Retrospective cohort study	RPS Age > 18 SEER	RMS, endometrial stromal sarcoma, adenosarcomas, GIST No surgery	480	1973-2010	300mo	OS 27mo (surg alone) v 36mo (RT), HR 0.79, p=0.023.	On MVA, adj RT remained significant (HR = 0.80; 95% CI, 0.65-0.98), p= 0.029).	RT 30% (POR Subgroup: only benefit for fibror sarcomas (HR (p=0.036) & male 0.72, p=0.03 NB. OS benefit m at median f/up converged by 8 f/up
4	Bevilacqua 1991	USA	Retrospective cohort study	Primary RPS Nil prior surgery (unless biopsy/limited excision elsewhere w/in 3 mo of admission)	Visceral tumours	80	1982-1988	Not stated	5y OS 57% (RT) v 59% (no RT), p= 'NS' (values not cited).	NS on MVA	RT 32% (of R0 pt EBRT, 4 brachy, 1 + brachy, med 47.7Gy, range 20
5	Bonvalot 2009	France	Retrospective cohort study	Primary RPS		382	1985-2005	Median 4.4y (range 1-8)	See MVA	RT not predictive of OS. High grade, tumour rupture, gross residual disease & positive margins predictive of poor OS	RT 37% (pre op IOERT 5%, pos 29%), PORT me 45Gy (10-66(
6	Bonvalot 2020	USA, Canada, UK, Europe	Randomized controlled trial	Age > 18 Localised RP or infra-peritoneal spaces of pelvis Unifocal Non-metastatic Operable Suitable for RT WHO PFS 0-2	Not originating from bone structure, abdominal, or gynecological viscera	266	2012-2017	Median 43.1mo (IQR 28.8-59.2)	5y OS 79.4% (surg) v 76.7% (RT). Median OS not reached in either group (HR 1.16, 95% CI 0.65-2.05, p=0.62)	N/A	Neoadj RT (50 50.4Gy 3DCRT or LPS subgroup ha absolute bene ARFS with addit RT. Benefit of R subgroups: well d & low grade tr
7	Bremjit 2014	USA	Retrospective cohort study	Primary localized RPS		132	2000-2013	31.8mo	No difference OS with neoadj RT (HR 0.7 (95% CI 0.3-1.6), p=0.3726).	MVA not performed as univariate negative.	RT 33% (neoadj more likely for L tumours more lik have chemo) & tumours (mean vs 18.5cm)

8	Callegaro 2022	USA, Canada, Europe	Retrospective cohort study	Adult patients Curative intent surgery for RPS	STRASS trial GIST, desmoid, gynae or bone sarcoma, alveolar or embryonal RMS, Ewings Pre-op chemo	1097	2012-2017	39 months	No difference overall survival (nor in subgroup analysis)	Propensity score matching	
9	Callegaro 2021	USA, Canada, UK, Europe	Retrospective cohort study	Age > 16 years Primary, non-metastatic RPS Curative intent surgery	Ewings, RMS, GIST, desmoid fibromatosis, gynaecologic sarcoma	1942	2002-2017	37 months (min)	See MVA	RT assoc w/ improved OS (HR 0.79 (95% CI 0.66-0.95), p=0.042)	Study looking outcomes ove distinct time pe
910	Catton 1994	Canada	Retrospective cohort study	RPS		104	1975-1988	6.3y (range 1.4-10.4)	No difference OS (values not cited, p value 'NS')	Not performed	RT 35% (PORT), r 40Gy. Benefit in relapse free ra dose ≥35Gy (p=
11	Choi 2012	USA	Retrospective cohort study	RPS Curative intent surgery SEER	Metastatic disease Unknown details for matching	618	1988-2006	Not stated	See MVA	No difference OS (p=0.10) No difference DSS with RT HR 1.17 (no RT) 95% CI 0.87-1.56), p=0.30 (propensity score matched)	RT 27% (pre, p IOERT). RT more for younger pts, in Midwest. Prop score matche
12	Chouliaras 2019 *(Role of RT)*	USA	Retrospective cohort study	Primary RPS	Metastatic disease, sarcomatosis IORT or brachy alone	425	2000-2016	31.4mo	Adjusted (matched) OS 76.85mo (adj RT) vs 72.74mo (no RT); 77.24mo (neoadj RT) vs 39.1mo (no RT).	No difference OS on MVA for neoadj RT (HR 1.14, p=0.69) or adj RT (HR 0.8, p=0.4)	RT 30% (pre op post op 18%). H grade tumours group Propensity sc matched
13	Derici 2006	China	Retrospective cohort study	RPS	Metastatic Visceral GU/GI sarcoma, lymphoma, carcinoid, desmoid, fibromatosis	27	1992-2005	34mo (range 1-125)	Median OS 71mo (surg) v 14mo (adj RT), p=0.0967	Not significant	RT 52% (POR
14	Ecker 2016	USA	Retrospective cohort study	Age > 18 Primary retroperitoneal LPS Non-metastatic Resection Curative intent NCDB	< 45Gy pre op Adj or intra-op RT without neoadj RT Prior palliative surg or RT	347	2004-2013	52mo	*Unmatched cohort*: 5y OS 67.4% (neoadj RT) v 62.25% (surg alone), p=0.062 (NS) *Matched cohort*: mOS 129.2mo (neoadj RT) v 84.3mo (surg alone), HR 1.54 (95% CI 1.01-2.36) p=0.046. Same results for 1y OS (89.9 v 91.7%) & 5y OS (60.4 v 67·4%)	No difference on MVA	RT 8.4% (neoad IORT +/- EBRT)) increased over (8.5% 2004, 13 2013). 208 (unmatched 347 (propensity matched)

15	Erstad 2023	USA	Retrospective cohort study	NCDB Non metastatic, primary, retroperitoneal LPS	Distant mets Histology/grade mismatch No definitive resection Incomplete gross resection (R2) IORT Systemic chemo death w/in 30d of surgery	3911	2004-2017	4.1y	WDLPS: no diff OS with RT (HR 1.06 (95% ICI 0.76-1.48, p=0.737) or specifically neoadj RT (HR 1.67, 95% CI 0.95-3.42, p=0.067) DDLPS: no diff OS by any RT (p=0.089) or neoadj RT (p=0.688)	NS on MVA	Propensity sc matched cohor use of RT (n= WDLPS, n=X DD and use of neoa (n=208 WDLPS DDLPS)
16	Feki 2023	Tunisia	Retrospective cohort study	Treatment for RPS at Habib Bourguiba University Hospital in Sfax Surgical treatment	GIST, germinal tumours, lymphoma, bone tumours	19	1999-2016	Not reported	RT assoc w/ improved OS on MVA (p=0.031)	Yes	
17	Gutierrez 2007	USA	Retrospective cohort study	Fibrosarcoma, LPS, MFH, LMS, GIST Extremity, trunk & RPS Florida Cancer Registry	Recurrence	967	1981-2004	Not reported	See MVA	Improved OS for retroperitoneal tumours: 27mo (RT) v 20mo (no RT), p=0.041 (NB. Intent not known – curative vs palliative)	RT 27% (timing intent not stated = 967/9642 pts (a
18	Haas 2019	USA, UK, Europe	Retrospective cohort study	Localised primary RPS Well-diff or dediff LPS Surgical resection +/- RT 8 high volume sarcoma centres (FNCLCC)		607	2002-2011	56mo	No difference OS with RT (after IPTW). No difference by subgroups (well diff, G1-2 dediff, G3 dediff LPS)	No association on MVA for any groups or endpoints	RT 28% (pre & Po IPTW to accour biases due to r random RT assig
19	Hassan 2004	USA	Retrospective cohort study	Primary RPS	Age < 16 Primary GIT/GUT sarcoma	97	1983-1995	3y (all pts), 6y (survivors)	RT not significant (numbers not reported)	RT not significant (numbers not reported)	RT 49% (pre op IOERT 28%, pos 43%). RT more lik LMS (cf LPS
20	Heslin 1997	USA	Retrospective cohort study	RPS, surgery	Metastatic disease Biopsy only Desmoid	48	1982-1990	Median 97mo (min 5y)	No difference (values not stated)	Incomplete resection assoc w/ worse OS (p=0.003). RT not significant	RT 27% (majority few had IORT/b
21	Jaques 1990	USA	Retrospective cohort study	Age > 16y RPS (primary &		114	1982-1987		No difference (p value not reported)	Not performed	RT 27% (incl prim recurrent)

				recurrent) Surg at MSK							
22	Kaminski 2007	Poland	Retrospective cohort study	RPS		37	1992 - 2005	Not reported	5y OS 80% (adj RT) v 34.8% (no RT) v 72.9% (adj RT after 2nd surgery at recurrence), p=0.44.	Not performed	RT 41% (PORT +/
23	Kim 2018	Korea	Retrospective cohort study	Primary RPS	Pre 1994 Stage IV No follow up Double primary malignancy	80	1994-2015	37.1mo (range, 5.8–207.9)	5y OS 71.6% (PORT) v 70.6% (no RT), p=0.604	RT not significant	RT 48% (post Median 54 Gy (r 36.0–66.9 G
24	Kwong 2020	USA	Retrospective cohort study	Age >18 RPS (incl. palliative, recurrent)		695	2000-2017	41.6 months (median)	No difference	Not reported	RT 26% (pre & po "Median OS 36m sig diff in survival Sx alone vs Sx neoadj or adj th figure 1C"
25	Lane 2015	USA	Retrospective cohort study	Surgical resection RPS (primary & recurrent)	Desmoid, GIST Unresectable Prior RT	94 (n=74 primary, n=20 recur)	1990-2001	1341d (no RT), 1393d (RT) (range 434-2051)	No difference OS with RT for primary disease (p=0.23). Subgroup: 5y OS 40.4% (EBRT) v 42.8% (EBRT + IORT), NS	MVA: improved OS w/ RT for primary & recurrent dx (adjusted HR for risk of death 0.3 (95% CI 0.11-0.80), p=0.016).	Univariate outc for primary only MVA included pr & recurrence together RT 39% (primary (recurrent), pre op EBRT +/- IO
26	Le Pechoux 2013	France	Retrospective cohort study	Primary RPS (or early re-excision after inappropriate surgery) >18 years PFS 0-2		110	1994-2008	4.1y (median)	See MVA	5y OS 71% (RT) v 77%, p=0.84. mOS 10y (S+RT) vs not reached (surg alone), adjusted HR of death 0.91 (95% CI 0.34-1.39), p=0.84	RT 44% (PORT more likely for n pos (R1-2) & tumours
27	Lee 2016	Korea	Retrospective cohort study	Primary retroperitoneal liposarcoma	Recurrence Previous RT (incl pre op RT) R2 resection	77	2000-2013	36mo (range 5-169)	3y OS 75 v 94%, p=0.393.	Not reported for OS	RT 42% (PORT), r 54Gy RT group less we LPS.
28	Leiting 2018	USA	Retrospective cohort study	RPS NCDB	>1 site of cancer Palliative treatment	2264	2004-2012	Not reported	See MVA	Increased OS (HR mortality 0.72, 95% CI 0.62–0.84, p < 0.001) Subgroups: RT assoc w/ prolonged mOS for HG RPS (64.3 vs. 43.6mo, p < 0.001), tumours < 15 cm (104.1 vs. 84.2mo, p = 0.007), & LMS (104.8 vs. 61.8mo,	RT 32% (9% pre median 50Gy. R younger, LMS > more non-acad facilities, more c smaller tmrs (19cm), more h

										p<0.001). No impact of RT on OS for well-diff or de-diff LPS	grade, more po margins.
29	Littau 2021 #1 (all)	USA	Retrospective cohort study	RPS Complete resection NCDB	Age < 18y Metastatic disease IORT Neoadj AND adj RT Delayed surgery (>30 weeks b/w diagnosis & OT)	4018	2004-2016	Not reported	See MVA	*By tumour size*: Pre-op RT not assoc w/ improved OS p=0.37 small, p=0.84 int, p=0.61 large) PORT assoc w/ improved OS for large (>10cm) tumours (OR 0.76, 95% CI 0.64-0.90, p=0) *Large tumours, stratified by tumour grade*: Pre op RT not assoc with OS (low p=0.71, int p=0.77, high p=0.11) PORT assoc w/ increased OS for high (OR 0.73, 95% CI 0.59-0.90, p=0.00) but not low (p=0.39) or int grade (p=0.63)	RT 24.2% (pre & op)
30	Littau 2021 #2 (Non-lipomatous)	USA	Retrospective cohort study	Non-lipomatous primary RPS Complete resection NCDB	Age < 18y Metastatic disease Neoadj RT, IORT Delayed surgery (>30 weeks b/w diagnosis & OT)	3394	2004-2016	Not reported	See MVA	Improved OS for: *Small tumours:* Adj RT HR 0.67 (95% CI 0.46, 0.99), p=0.04 *Int tumours:* Neoadj RT HR 0.67 (95% CI 0.46, 0.98), p=0.04 Adj RT HR 0.61 (95% CI 0.50, 0.76), p=0.00 *Large tumours*: OS benefit Neoadj RT HR 0.50 (95% CI 0.37, 0.68), p=0.00 Adj RT HR 0.56 (95% CI 0.47, 0.69), p=0.00	RT 36% (pre and op)
31	Littau 2022	USA	Retrospective cohort study	Primary RPS Mod or well-diff LPS R1 resection Tumours > 5cm	Metastatic dx High grade (poorly diff or undiff) Neoadj RT, IORT, adjuvant chemo	421	2004-2016	Not reported	No difference (HR 1.31, 95% CI 0.82-2.10, p=0.258)	Not reported	RT 24% (POR Academic centre likely to use RT (reduction)
32	Ma 2020	USA	Retrospective cohort study	NCDB Non metastatic, resectable RPS	Survival <6mo after diagnosis	7857	2006-2015	48.7 mo (27.6-76.8)	OS at 60mo: 27.6% (surg alone) vs. 29% (pre op RT), HR 0.83 (95% CI 0.72-0.97), p=0.02.	On MVA (matched pair analysis) improved OS with preop RT (HR 0.88, p=0.03)	RT 10.8% (pre
33	Nathenson 2018	USA	Retrospective cohort study	Retroperitoneal LPS or LMS		49	2000-2013	6.9y (for pts still alive)	No diff OS w/ neoadj or adj RT, p=0.65 (only n=18) LMS: 2y OS 88% (RT) v 53% (no RT)	No MVA	RT 37% 9adj & n mean 54.2G LMS: 2y PFS 38% 33% (no RT LPS 2y PFS 56% (49% (no RT

									LPS: 2y OS 90% (RT) vs 88% (no RT)		
34	Nazzani 2018 #1 (Surgically Treated RPS)	USA	Retrospective cohort study	SEER RPS Surgery	Metastatic Age < 20	1226	2004-2014	33mo	5y non-disease specific mortality 5.9% (RT) v 7.2% (no RT), HR 0.8 (95% CI 0.5-1.4), p=0.5	Age only predictor for NDSM. RT not significant.	RT 30% (timing stated) 5y *disease spe* mortality 29.4% 25.7% (no RT), H (95% CI 0.6=0; p=0.037 (MV
35	Nussbaum 2015	USA	Retrospective cohort study	RPS, resected NCDB		11324	1998-2011	Not report ed	See MVA	5y OS 52.3% (neoadj RT) v 57.8% (no RT), p=0.254 (before propensity matching) 5y OS 53.2% (neoadj RT) vs 54.2% (no RT), p=0.695 (after propensity matching) Subgroup anal: no diff OS for LMS Exploratory anal: RT assoc w/ improved OS for high grade tumours (5y OS 49.1% v 46.2%, p=0.022)	RT 6.1% (neoadj in RT use during (4% in 1998, 15 2011). RT pts yo more male, m treated at academic/rese facility, and thus further from tmt
36	Nussbaum 2016	USA	Case-control study	Adults Primary RPS NCDB	Desmoids, DFSP Recurrence Died w/in 30d of surgery Distant metastasis IORT, both pre & post-op RT	9068	2003-2011	42mo	mOS 110mo (pre op RT) v 66mo (no RT), HR 0.70 (95% CI 0.59-0.82), p<0.0001 mOS 89mo (post op RT) v 64mo, HR 0.78 (95% CI 0.71-0.85), p<0·0001	N/A (propensity score matched)	RT 44% (pre & po Propensity sc matched Post-hoc anal sh RT benefit n dependent on m status
37	Singer 1995	USA	Retrospective cohort study	Primary or locally recurrent truncal & RPS		389 (total), 83 (RPS)	1970-1994	95mo (range 3.5-285)	No difference	RT not assoc w/ OS (p=0.287). Subgroup: PORT assoc w/ OS for truncal sarcoma (HR 0.42, p=0.03) but not RPS (RR and p values not reported)	RT numbers not
38	Snow 2018	Australia	Retrospective cohort study	RPS (primary or recurrent) Localised & metastatic	Visceral, gynaecologic, paediatric sarcoma, GIST, desmoid	88 (primary resectabl e RPS)	2008-2016	36mo	No OS difference with neoadj RT (HR 1, 95% CI 0.40-2.7), p=0.93)	No MVA	RT 73% (pre & po NB. Results for p resected RP
39	Stahl 2017	USA	Retrospective cohort study	RPS R0 or R1 NCDB	Age < 18 Distant metastases Non-adult sarcoma histology Diagnosis in 2012 (insufficient f/up) Prior malignancy	4015	1998-2012	67mo	RT use assoc w/ OS (HR 0.81, 95% CI 0.70-0.93, p=0.016 (MVA). But, no SS diff with RT on OS in R0 and R1 pts separately (p=0.143, 0.069)	Yes	RT 28% (pre & in median 50.4

40	Stoeckle 2001	France	Retrospective cohort study	Primary RPS French Sarcoma Group registry	Recurrence Visceral sarcoma, fibromatosis	165	1980-1994	47mo (range 3-160)	5y OS for M0 patients 52% (post op RT) v 44% (no RT), p=0.0363 (univariate).	No difference on MVA	RT 56% (M0 &M1 post op), median (range 45-9
41	Stucky 2014	USA	Retrospective cohort study	RPS (primary or recurrent) Curative intent treatment	Distant mets R2 resection	63	1996-2011	45mo	5y OS 60% (for surg & S+RT), p=0.95	Not performed as univariate NS	RT 59% (pre & in
42	Tirotta 2021 #2 (Cumulative Burden Postop Comp)	UK	Retrospective cohort study	Primary RPS Surgery	Recurrence Distant metastases	191	2008-2019	38mo (IQR 18-67)	RT not assoc w/ OS (pre op HR 0.77, p=0.662; post op HR 1.45, p=0.474	Not performed (NS on univariate)	RT 12% (pre & po
43	Toulmonde 2014	France	Retrospective cohort study	Primary RPS Age >18 Expert path rv	SFT, sarcomas of uncertain malignancy Active malig	586	1988-2008	6.5y (range 5.9-7.1)	See MVA	RT not assoc w/ OS (p value not cited).	RT 29% (post op median 50G
44	Trovik 2014	Norway, Sweden	Retrospective cohort study	RPS Curative intent	Recurrence Distant metastases	97	1988-2009	4.7y (range 0.5-18.5)	5y OS 71% (RT) v 52% (no RT), p=0.019	On MVA, RT assoc w/ increased OS, HR 0.36 (95% CI 0.18-0.72), p=0.004.	RT 43% (POR
45	Tseng 2011	USA	Retrospective cohort study	SEER RPS Surgery	Age < 18y Metastatic disease	1535	1988-2004	31mo (range 1-203mo)	Median OS 60mo (with or without RT), p=0.59 *By grade:* OS benefit to RT for int grade (105 v 55mo, p=0.01), but not low grade (p=0.83) or high grade (p=0.13) *By histology:* RT improved OS for MFH (51 v 16mo, p=0.002) Median DSS 86mo (RT) vs 117 mo (surg alone), p=0.84 *By grade:* trend to improved DSS at 5y for intermediate grade (68 v 52%, p=0.06) *By histology:* RT improved DSS for MFH (62 v 35mo, p=0.01)	RT not assoc w/ OS (HR 0.92, 95% CI 0.78-1.09) RT not assoc w/ DSS (HR 0.96, 95% CI 0.78–1.17) MVA: younger age, female, low & it grade, LPS, tmrs 5-10cm, complete resection all assoc w/ better OS & DSS	RT 24% (pre & po
46	Turner 2019	Canada	Retrospective cohort study	RPS Age >18 GTR	Post op RT GI/GU origin Metastatic disease	102	1990-2014	90mo	See MVA	RT increased OS (HR 0.42 (95% CI 0.19, 0.9), p=0.03)	RT 64% (neoa

47	Weng 2021	China	Retrospective cohort study	SEER Stage I RPS (radical & non-radical resection)	Recurrent or multiple tumours	886 (316 radical intent)	2004-2015	4.58y	RT assoc w/ decreased overall mortality in pts undergoing radical resection (HR 0.52, 95% CI 0.30-0.91; P = 0.02)	MVA (propensity matching): RT assoc w/ decreased overall mortality (adjusted HR 0.56, 95% CI 0.32-0.98; p= 0.04) MVA: no diff RPS-specific mortality b/w radical & non-radical resections in pts who receive peri-op RT (AHR 0.71, 95% CI 0.33-1.53, p=0.39)	RT 27% (radi resection; timin stated)
48	Willis 2021	Germany	Retrospective cohort study	Primary, recurrent or metastasised RPS Resection	GIST, embryonal, pediatric or gynecological RPS	201 (primary)	2001-2017	36.9m o (13.1-81.3)	See MVA	No benefit of RT (EBRT vs no RT, IORT vs no RT, EBRT + IORT vs no RT), p=0.864 (primary tmrs) No benefit in subgroups: LPS (p=0.808) or LMS (p=0.107)	RT 46.3% (for n primary tmrs: p post op).
49	Zhou 2010	USA	Retrospective cohort study	SEER Age>18 Primary RPS or abdo (non-visceral) sarcoma	Visceral or GI origin, GIST, Kaposi, multiple hemorrhagic sarcomas	2504 (1901 locoregional)	1988-2005	2y	See MVA	Add'n of RT to surgery increased OS for stage I (additional 50.8% RR; multivariate HR 0.49 (95% CI, 0.25-0.96, p=0.04), but no SS benefit for add'n of RT for st II-III dx (HR, 0.78; 95% CI, 0.58-1.06; p=0.11)	RT 24% (post locoregional dx

Appendix 3. Quality Assessment for Topic 2 Question 1

Study	Title	Reviewer	NHMRC Level of Evidence	Risk of Bias (Newcastle Ottawa scale for cohort study)			
				Selection	Comparability	Outcome	Overall
Abdelfatah 2016	Long-term outcomes in treatment of retroperitoneal sarcomas: A 15 year single-institution evaluation of prognostic features	1	III-2	4	2	3	Good Quality
		2	III-2	4	2	2	Good Quality
		Final	III-2	4	2	3	Good Quality
Akagunduz 2021	Factors affecting survival in retroperitoneal sarcomas treated with upfront surgery: A real-world study by turkish oncology group	1	III-2	4	2	3	Good Quality
		2	III-2	4	2	3	Good Quality
		Final	III-2	4	2	3	Good Quality
Bartlett 2014	Preoperative radiation for retroperitoneal sarcoma is not associated with increased early postoperative morbidity	1	III-2	4	1	2	Good Quality
		2	III-2	4	1	3	Good Quality
		Final	III-2	4	1	3	Good Quality
Bates 2018	The Benefit of Adjuvant Radiotherapy in High-grade Nonmetastatic Retroperitoneal Soft Tissue Sarcoma: A SEER Analysis	1	III-2	4	2	3	Good Quality
		2	III-2	4	2	3	Good Quality
		Final	III-2	4	2	3	Good Quality
Belivacqua 1991	Prognostic factors in primary retroperitoneal soft-tissue sarcomas	1	III-2	4	2	3	Good Quality
		2	III-2	4	1	1	Poor Quality
		Final	III-2	4	1	1	Poor Quality
Bonvalot 2009	Primary retroperitoneal sarcomas: a multivariate analysis of surgical factors associated with local control	1	III-2	4	2	3	Good Quality
		2	III-2	4	2	3	Good Quality
		Final	III-2	4	2	3	Good Quality
Bredbeck 2022	Factors associated with disease-free and abdominal recurrence-free survival in abdominopelvic and retroperitoneal sarcomas	1	III-3	4	2	3	Good Quality
		2	III-2	4	2	3	Good Quality

		Final	III-2	4	2	3	Good Quality
Bremjit 2014	A contemporary large single-institution evaluation of resected retroperitoneal sarcoma	1	III-2	3	1	2	Good Quality
		2	III-2	4	2	3	Good Quality
		Final	III-2	4	1	3	Good Quality
Callegaro 2021	Has the Outcome for Patients Who Undergo Resection of Primary Retroperitoneal Sarcoma Changed Over Time? A Study of Time Trends During the Past 15 years	1	III-3	3	1	2	Good Quality
		2	III-2	3	1	2	Good Quality
		Final	III-2	3	1	2	Good Quality
Catton 1994	Outcome and prognosis in retroperitoneal soft tissue sarcoma	1	III-2	4	0	3	Poor Quality
		2	III-2	4	1	2	Good Quality
		Final	III-2	4	0	2	Poor Quality
Choi 2012	Effect of radiation therapy on survival in surgically resected retroperitoneal sarcoma: a propensity score-adjusted SEER analysis	1	III-2	4	1	2	Good Quality
		2	III-2	4	2	3	Good Quality
		Final	III-2	4	2	2	Good Quality
Choudry 2006	Outcomes in a series of 103 retroperitoneal sarcomas	1	III-3	3	1	3	Good Quality
		2	III-2	4	2	2	Good Quality
		Final	III-2	4	1	2	Good Quality
Chouliaras 2019 (1)	Recurrence patterns after resection of retroperitoneal sarcomas: An eight-institution study from the US Sarcoma Collaborative	1	III-2	4	2	3	Good Quality
		2	III-2	3	0	2	Poor Quality
		Final	III-2	4	1	2	Good Quality
Chouliaras 2019 (2)	Role of radiation therapy for retroperitoneal sarcomas: An eight-institution study from the US Sarcoma Collaborative	1	III-2	4	2	3	Good Quality
		2	III-2	3	1	1	Poor Quality
		Final	III-2	3	1	1	Poor Quality
Coindre 2001	Prognostic factors in retroperitoneal sarcoma: A multivariate analysis of a series of 165 patients of the French Cancer Center Federation Sarcoma Group	1	III-2	4	1	2	Good Quality
		2	III-2	4	1	3	Good Quality
		Final	III-2	4	1	3	Good Quality
Ecker 2016	Preoperative radiotherapy in the management of retroperitoneal liposarcoma	1	III-2	4	2	3	Good Quality

		2	III-2	4	2	3	Good Quality
		Final	III-2	4	2	3	Good Quality
Giuliano 2016	Predictors of improved survival for patients with retroperitoneal sarcoma	1	III-2	4	2	3	Good Quality
		2	III-2	4	1	2	Good Quality
		Final	III-2	4	1	2	Good Quality
Gutierrez 2007	Outcomes for soft-tissue sarcoma in 8249 cases from a large state cancer registry	1	III-2	4	2	2	Good Quality
		2	III-2	4	2	2	Good Quality
		Final	III-2	4	2	2	Good Quality
Haas 2019	Radiotherapy for retroperitoneal liposarcoma: A report from the Transatlantic Retroperitoneal Sarcoma Working Group	1	III-2	4	2	3	Good Quality
		2	III-2	4	2	3	Good Quality
		Final	III-2	4	2	3	Good Quality
Hager 2017	Significant benefits in survival by the use of surgery combined with radiotherapy for retroperitoneal soft tissue sarcoma	1	IV	4	1	2	Good Quality
		2	III-2	4	1	2	Good Quality
		Final	III-2	4	1	2	Good Quality
Hassan 2004	Operative management of primary retroperitoneal sarcomas: a reappraisal of an institutional experience	1	III-3	4	0	3	Poor Quality
		2	III-2	4	1	3	Good Quality
		Final	III-3	4	0	3	Poor Quality
Heslin 1997	Prognostic factors associated with long-term survival for retroperitoneal sarcoma: implications for management	1	III-2	4	0	3	Poor Quality
		2	III-2	3	0	2	Poor Quality
		Final	III-2	3	0	2	Poor Quality
Jaques 1990	Management of primary and recurrent soft-tissue sarcoma of the retroperitoneum	1	III-3	4	0	2	Poor Quality
		2	III-2	4	0	2	Poor Quality
		Final	III-2	4	0	2	Poor Quality
Kaminski 2007	Value of combined treatment of retroperitoneal sarcomas	1	IV	4	0	2	Poor Quality
		2	III-2	4	0	2	Poor Quality
		Final	III-3	4	0	2	Poor Quality

Kelly 2015	Comparison of perioperative radiation therapy and surgery versus surgery alone in 204 patients with primary retroperitoneal sarcoma: A retrospective 2-institution study	1	III-2	4	2	3	Good Quality
		2	III-2	4	2	3	Good Quality
		Final	III-2	4	2	3	Good Quality
Kim 2018	Efficacy of Postoperative Radiotherapy Using Modern Techniques in Patients with Retroperitoneal Soft Tissue Sarcoma	1	III-2	4	2	3	Good Quality
		2	III-2	4	2	3	Good Quality
		Final	III-2	4	2	3	Good Quality
Kwong 2020	Treatment Factors Associated With Overall Survival in Retroperitoneal Sarcoma: An Institutional Review	1	III-2	4	2	3	Good Quality
		2	III-2	4	0	2	Poor Quality
		Final	III-2	4	0	2	Poor Quality
Lane 2015	Analysis of perioperative radiation therapy in the surgical treatment of primary and recurrent retroperitoneal sarcoma	1	III-2	4	2	3	Good Quality
		2	III-2	4	2	3	Good Quality
		Final	III-2	4	2	3	Good Quality
Laplanche 2013	Should adjuvant radiotherapy be administered in addition to front-line aggressive surgery (FAS) in patients with primary retroperitoneal sarcoma?	1	III-2	4	1	2	Good Quality
		2	III-2	4	0	3	Poor Quality
		Final	III-2	4	1	3	Good Quality
Lee 2016	Retroperitoneal liposarcoma: the role of adjuvant radiation therapy and the prognostic factors	1	III-2	4	2	3	Good Quality
		2	III-2	4	2	3	Good Quality
		Final	III-2	4	2	3	Good Quality
Leiting 2018	Radiation Therapy for Retroperitoneal Sarcomas: Influences of Histology, Grade, and Size	1	III-2	4	2	3	Good Quality
		2	III-2	3	2	3	Good Quality
		Final	III-2	3	2	3	Good Quality
Littau 2021	The importance of the margin of resection and radiotherapy in retroperitoneal liposarcoma	1	III-2	4	2	3	Good Quality
		2	III-2	4	2	1	Poor Quality
		Final	III-2	4	2	1	Poor Quality
Littau 2021	The importance of the margin of resection and external radiation in non-lipomatous retroperitoneal sarcoma	1	III-2	4	1	3	Good Quality

		2	III-2	4	1	3	Good Quality
		Final	III-2	4	1	3	Good Quality
Littau 2022	Low and moderate grade retroperitoneal liposarcoma: Is adjuvant radiotherapy associated with improved survival in patients undergoing R1 resection?	1	III-2	4	2	3	Good Quality
		2	III-2	4	2	3	Good Quality
		Final	III-2	4	2	3	Good Quality
Ma 2020	Evaluation of Preoperative Chemotherapy or Radiation and Overall Survival in Patients with Nonmetastatic, Resectable Retroperitoneal Sarcoma	1	III-2	4	2	3	Good Quality
		2	III-2	4	2	3	Good Quality
		Final	III-2	4	2	3	Good Quality
Molina 2016	Preoperative radiation therapy combined with radical surgical resection is associated with a lower rate of local recurrence when treating unifocal, primary retroperitoneal liposarcoma	1	III-2	4	1	2	Good Quality
		2	III-2	4	0	3	Poor Quality
		Final	III-2	4	1	3	Good Quality
Mussi 2008	The prognostic impact of dedifferentiation in retroperitoneal liposarcoma: a series of surgically treated patients at a single institution	1	III-2	4	2	3	Good Quality
		2	III-2	4	2	3	Good Quality
		Final	III-2	4	2	3	Good Quality
Nathenson 2018	Surgical resection for recurrent retroperitoneal leiomyosarcoma and liposarcoma	1	III-2	4	0	3	Poor Quality
		2	III-2	4	0	3	Poor Quality
		Final	III-2	4	0	3	Poor Quality
Nazzani 2018 (1)	Surgically Treated Retroperitoneal Sarcoma: A Population-based Competing Risks Analysis	1	III-3	4	1	3	Good Quality
		2	III-2	4	2	3	Good Quality
		Final	III-2	4	2	3	Good Quality
Nazzani 2018 (2)	A contemporary analysis of radiotherapy effect in surgically treated retroperitoneal sarcoma	1	III-2	4	2	3	Good Quality
		2	III-2	4	2	3	Good Quality
		Final	III-2	4	2	3	Good Quality
Nussbaum 2014	The effect of neoadjuvant radiation therapy on perioperative outcomes among patients undergoing resection of retroperitoneal sarcomas	1	III-2	4	2	3	Good Quality

		2	III-2	4	2	3	Good Quality
		Final	III-2	4	2	3	Good Quality
Nussbaum 2015	Long-term Oncologic Outcomes After Neoadjuvant Radiation Therapy for Retroperitoneal Sarcomas	1	III-2	4	2	3	Good Quality
		2	III-2	4	1	3	Good Quality
		Final	III-2	4	1	3	Good Quality
Nussbaum 2016	Preoperative or postoperative radiotherapy versus surgery alone for retroperitoneal sarcoma: a case-control, propensity score-matched analysis of a nationwide clinical oncology database	1	III-2	4	2	3	Good Quality
		2	III-2	4	2	3	Good Quality
		Final	III-2	4	2	3	Good Quality
Nyhus 2014	Adjuvant radiotherapy in retroperitoneal sarcomas. A Scandinavian Sarcoma Group study of 97 patients	1	III-2	4	2	3	Good Quality
		2	III-2	4	2	3	Good Quality
		Final	III-2	4	2	3	Good Quality
Park 2016	Tissue expander placement and adjuvant radiotherapy after surgical resection of retroperitoneal liposarcoma offers improved local control	1	IV	4	1	3	Good Quality
		2	III-2	4	1	3	Poor Quality
		Final	III-2	4	1	3	Poor Quality
Sampath 2010	Radiotherapy and extent of surgical resection in retroperitoneal soft-tissue sarcoma: multi-institutional analysis of 261 patients	1	III-2	4	2	3	Good Quality
		2	III-2	4	2	3	Good Quality
		Final	III-2	4	2	3	Good Quality
Singer 1995	Prognostic factors predictive of survival for truncal and retroperitoneal soft-tissue sarcoma	1	III-2	3	1	3	Good Quality
		2	III-2	3	2	1	Good Quality
		Final	III-2	3	2	1	Poor Quality
Snow 2018	Treatment of patients with primary retroperitoneal sarcoma: predictors of outcome from an Australian specialist sarcoma centre	1	III-2	4	0	3	Poor Quality
		2	III-2	4	1	3	Good Quality
		Final	III-2	4	1	3	Good Quality
Stahl 2017	The effect of microscopic margin status on survival in adult retroperitoneal soft tissue sarcomas	1	III-2	4	1	2	Good Quality
		2	III-2	3	1	2	Good Quality

		Final	III-2	3	1	2	Good Quality
Stucky 2014	Excellent local control with preoperative radiation therapy, surgical resection, and intra-operative electron radiation therapy for retroperitoneal sarcoma	1	III-2	3	1	2	Good Quality
		2	III-2	4	2	3	Good Quality
		Final	III-2	4	2	2	Good Quality
Tansug 2006	Prognostic factors of retroperitoneal soft-tissue sarcomas	1	IV	4	0	2	Poor Quality
		2	III-2	3	0	3	Poor Quality
		Final	IV	3	0	3	Poor Quality
Tirotta 2021	Comparison of comprehensive complication index and Clavien-Dindo classification in patients with retroperitoneal sarcoma	1	III-2	4	2	3	Good Quality
		2	III-2	4	2	3	Good Quality
		Final	III-2	4	2	3	Good Quality
Tirotta 2021 (2)	Cumulative Burden of Postoperative Complications in Patients Undergoing Surgery for Primary Retroperitoneal Sarcoma	1	III-2	4	2	3	Good Quality
		2	III-2	4	0	3	Poor Quality
		Final	III-2	4	2	3	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	1	III-2	4	2	3	Good Quality
		2	III-2	4	2	3	Good Quality
		Final	III-2	4	2	3	Good Quality
Tseng 2011	Lack of survival benefit following adjuvant radiation in patients with retroperitoneal sarcoma: A SEER analysis	1	III-2	4	1	2	Good Quality
		2	III-2	4	2	2	Good Quality
		Final	III-2	4	2	2	Good Quality
Turner 2019	Neoadjuvant radiotherapy followed by surgery compared with surgery alone in the treatment of retroperitoneal sarcoma: a population-based comparison	1	III-2	4	1	2	Good Quality
		2	III-2	4	2	3	Good Quality
		Final	III-2	4	2	3	Good Quality
vanDoorn 1994	Resectable retroperitoneal soft tissue sarcomas. The effect of extent of resection and postoperative radiation therapy on local tumor control	1	IV	3	0	3	Poor Quality
		2	III-2	4	0	3	Poor Quality
		Final	III-2	4	0	3	Poor Quality

Weng 2021	Radical Versus Non-Radical Resection for Early-Stage Retroperitoneal Sarcoma: A Propensity Score-Matched Analysis	1	III-3	4	2	3	Good Quality
		2	III-2	4	2	3	Good Quality
		Final	III-2	4	2	3	Good Quality
Willis 2021	Outcome after surgical resection of multiple recurrent retroperitoneal soft tissue sarcoma	1	III-3	4	2	3	Good Quality
		2	III-2	4	2	3	Good Quality
		Final	III-3	4	2	3	Good Quality
Zhou 2010	Surgery and radiotherapy for retroperitoneal and abdominal sarcoma: both necessary and sufficient	1	III-2	4	2	3	Good Quality
		2	III-2	4	2	1	Poor Quality
		Final	III-2	4	2	1	Poor Quality
Eckardt 2022	Lifelong Imaging Surveillance is Indicated for Patients with Primary Retroperitoneal Liposarcoma	1	III-2	4	1	2	Good Quality
		2	**III-2**	**4**	**2**	**3**	**Good Quality**
		Final	**III-2**	**4**			**Good Quality**
Feki 2023	The management of retroperitoneal sarcoma: The experience of a single institution and a review of the literature	1	III-3	2	0	2	Poor Quality
		2	**III-2**	**4**	**2**	**2**	**Good Quality**
		Final				**2**	
Callegaro 2022	Preoperative Radiotherapy in Patients With Primary Retroperitoneal Sarcoma: EORTC-62092 Trial (STRASS) Versus Off-trial (STREXIT) Results	1	III-2	4	2	3	Good Quality
		2	**III-2**	**4**	**2**	**3**	**Good Quality**
		Final	**III-2**	**4**	**2**	**3**	**Good Quality**
Erstad 2023	Clinical Impact of External Beam Radiotherapy for Surgically Resected Primary Retroperitoneal Liposarcoma	1	III-2	4	2	3	Good Quality
		2	**III-2**	**4**	**2**	**3**	**Good Quality**
		Final	**III-2**	**4**	**2**	**3**	**Good Quality**

Study	Title	Reviewer	NHMRC Level of Evidence	Cochrane Collaboration's tool for randomised trial (low risk, unclear, high risk)					
				Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias

Bonvalot 2020	Preoperative radiotherapy plus surgery versus surgery alone for patients with primary retroperitoneal sarcoma (EORTC-62092: STRASS): a multicentre, open-label, randomised, phase 3 trial	Final	II	Low risk	High risk	High risk	Low risk	Low risk	Low risk

Appendix 4. Studies included in Topic 2 Question 2 Systematic Review

Title	Authors	Published Year	Journal	Volume	Issue	Pages
Outcome following resection of retroperitoneal sarcoma	Smith, H. G.; Panchalingam, D.; Hannay, J. A. F.; Smith, M. J. F.; Thomas, J. M.; Hayes, A. J.; Strauss, D. C.	2015	The British journal of surgery	102	13	1698-709
Histologic Subtype and Margin of Resection Predict Pattern of Recurrence and Survival for Retroperitoneal Liposarcoma		2003	Annals of surgery	238	3	358-3
Predictors of disease-free and overall survival in retroperitoneal sarcomas: A modern 16-year multi-institutional study from the United States sarcoma collaboration (USSC)	Schwartz, Patrick B.; Vande Walle, Kara; Winslow, Emily R.; Abbott, Daniel E.; Ethun, Cecilia G.; Cardona, Kenneth; Tran, Thuy B.; Poultsides, George; Tseng, Jennifer; Roggin, Kevin; Grignol, Valerie; Howard, John Harrison; Krasnick, Bradley A.; Fields, Ryan C.; Mogal, Harveshp; Clarke, Callisia N.; Senehi, Rebecca; Votanopoulos, Konstantinos	2019	Sarcoma	2019		53951
Patient outcome after complete surgery for retroperitoneal sarcoma	Rossi, Carlo Riccardo; Varotto, Andrea; Pasquali, Sandro; Campana, Luca Giovanni; Mocellin, Simone; Sommariva, Antonio; Montesco, Maria Cristina; Rastrelli, Marco; Vecchiato, Antonella; Pilati, Pierluigi; Nitti, Donato	2013	Anticancer research	33	9	4081-7
Tumor biology remains the main determinant of prognosis in retroperitoneal sarcomas: a 14-year single-center experience	Ng, Deanna Wan Jie; Tan, Grace Hwei Ching; Chia, Claramae Shulyn; Chee, Soo Khee; Quek, Richard; Farid, Mohamad; Teo, Melissa Ching Ching	2017	Asia-Pacific journal of clinical oncology	13	5	e458-e465
Extended resection including adjacent organs and Ki-67 labeling index are prognostic factors in patients with retroperitoneal soft tissue sarcomas	Morizawa, Yosuke; Miyake, Makito; Hori, Shunta; Nakai, Yasushi; Anai, Satoshi; Tanaka, Nobumichi; Fujimoto, Kiyohide; Shimada, Keiji; Tatsumi, Yoshihiro; Konishi, Noboru	2016	World journal of surgical oncology	14	1	43
Prognostic factors predicting survival in the treatment of retroperitoneal sarcoma	Kiviniemi, H.; Laitinen, S.; Makela, J.	2000	European Journal of Surgical Oncology	26	6	552-5

Retroperitoneal soft tissue sarcoma: effect of hyperthermic total abdominal perfusion	Eroglu, A.; Kocaoglu, H.; Demirci, S.; Akgul, H.	1999	Tumori	85	4	259-6
Morbidity, mortality and temporal trends in the surgical management of retroperitoneal sarcoma: An ACS-NSQIP follow up analysis	Judge, Sean J.; Lata-Arias, Kathleen; Yanagisawa, Mio; Darrow, Morgan A.; Monjazeb, Arta M.; Kirane, Amanda R.; Bold, Richard J.; Canter, Robert J.; Canter, Daniel J.	2019	Journal of surgical oncology	120	4	753-7
Concomitant organ resection does not improve outcomes in primary retroperitoneal well-differentiated liposarcoma: A retrospective cohort study at a major sarcoma center	Ikoma, Naruhiko; Roland, Christina L.; Torres, Keila E.; Chiang, Yi-Ju; Mann, Gary N.; Hunt, Kelly K.; Cormier, Janice N.; Feig, Barry W.; Wang, Wei-Lien; Somaiah, Neeta	2018	Journal of surgical oncology	117	6	1188-1194
Differences between en bloc resection and enucleation of retroperitoneal sarcomas	Gonzalez Lopez, Jose Antonio; Artigas Raventos, Vicente; Rodriguez Blanco, Manuel; Lopez-Pousa, Antonio; Bague, Silvia; Abellan, Miriam; Trias Folch, Manel	2014	Cirugia espanola	92	8	525-3
Clinical benefit and residual kidney function of en bloc nephrectomy for perirenal retroperitoneal sarcoma	Cho, Chan Woo; Lee, Kyo Won; Park, Hyojun; Kim, Hyung Joon; Park, Jae Berm; Choi, Yoon-La; Yu, Jeong Il; Lee, Su Jin; Choi, Dong Il; Kim, Sung Joo	2018	Asia-Pacific journal of clinical oncology	14	5	e465-e471
Primary and recurrent retroperitoneal soft tissue sarcoma: Prognostic factors affecting survival	Bertani, Emilio; Biffi, Roberto; Luca, Fabrizio; Crotti, Cristiano; Testori, Alessandro; Lazzaro, Gianluca; Ugo, Pace; Andreoni, Bruno; Zbar, Andrew P.; De Pas, Tommaso; Chiappa, Antonio	2006	Journal of surgical oncology	93	6	456-4
Aggressive Surgical Approach for Treatment of Primary and Recurrent Retroperitoneal Soft Tissue Sarcoma	Chiappa, Antonio; Bertani, Emilio; Pravettoni, Gabriella; Zbar, Andrew Paul; Foschi, Diego; Spinoglio, Giuseppe; Bonanni, Bernardo; Polvani, Gianluca; Ambrogi, Federico; Cossu, Maria Laura; Ferrari, Carlo; Venturino, Marco; Crosta, Cristiano; Bocciolone, Luca; Biffi, Roberto	2018	The Indian journal of surgery	80	2	154-1
Primary retroperitoneal sarcomas: a multivariate analysis of surgical factors associated with local control	Bonvalot, Sylvie; Rivoire, Michel; Castaing, Marine; Stoeckle, Eberhard; Le Cesne, Axel; Blay, Jean Yves; Laplanche, Agnes	2009	Journal of clinical oncology : official journal of the American Society of Clinical Oncology	27	1	31-Jul

A retrospective, single-center cohort study on 65 patients with primary retroperitoneal liposarcoma	Wu, Yi-Xi; Liu, Jun-Yan; Liu, Jia-Jia; Yan, Peng; Tang, Bo; Cui, You-Hong; Zhao, Yong-Liang; Shi, Yan; Hao, Ying-Xue; Yu, Pei-Wu; Qian, Feng	2018	Oncology letters	15	2	1799-1810
Resectable retroperitoneal soft tissue sarcomas. The effect of extent of resection and postoperative radiation therapy on local tumor control	van Doorn, R. C.; Gallee, M. P.; Hart, A. A.; Gortzak, E.; Rutgers, E. J.; van Coevorden, F.; Keus, R. B.; Zoetmulder, F. A.	1994	Cancer	73	3	637-4
Neoadjuvant radiotherapy followed by surgery compared with surgery alone in the treatment of retroperitoneal sarcoma: a population-based comparison	Turner, B. T.; Hampton, L.; Schiller, D.; Mack, L. A.; Robertson-More, C.; Li, H.; Quan, M. L.; Bouchard-Fortier, A.	2019	Current oncology (Toronto, Ont.)	26	6	e766-e772
Contiguous organ resection is safe in patients with retroperitoneal sarcoma: An ACS-NSQIP analysis	Tseng, Warren H.; Martinez, Steve R.; Chen, Steven L.; Bold, Richard J.; Canter, Robert J.; Tamurian, Robert M.	2011	Journal of surgical oncology	103	5	390-3
Postoperative Morbidity after Radical Resection of Primary Retroperitoneal Sarcoma	Swallow, Carol J.; Macneill, Andrea J.; Gronchi, Alessandro; Callegaro, Dario; Fiore, Marco; Miceli, Rosalba; Barretta, Francesco; Bonvalot, Sylvie; Hohenberger, Peter; Jakob, Jens; Van Coevorden, Frits; Rutkowski, Piotr; Szacht, Milena; Hayes, Andrew J.; Strauss, Dirk C.; Honore, Charles; Fairweather, Mark; Raut, Chandrajit P.; Cannell, Amanda; Haas, Rick L.; Casali, Paolo G.; Pollock, Raphael E.	2018	Annals of surgery	267	5	959-9
Long-term outcomes in treatment of retroperitoneal sarcomas: A 15 year single-institution evaluation of prognostic features	Abdelfatah, Eihab; Guzzetta, Angela A.; Nagarajan, Neeraja; Schulick, Richard; Wolfgang, Christopher L.; Pawlik, Timothy M.; Choti, Michael A.; Meyer, Christian; Thornton, Katherine; Ahuja, Nita; Montgomery, Elizabeth A.; Herman, Joseph; Terezakis, Stephanie; Frassica, Deborah	2016	Journal of surgical oncology			
Postoperative Outcomes of Distal Pancreatectomy for Retroperitoneal Sarcoma Abutting the Pancreas in the Left Upper Quadrant	Kim, K. D.; Lee, K. W.; Lee, J. E.; Hwang, J. A.; Jo, S. J.; Kim, J.; Lim, S. H.; Park, J. B.	2021	Frontiers in Oncology	11		79294

Oncological outcomes after major vascular resections for primary retroperitoneal liposarcoma	Spolverato, G.; Chiminazzo, V.; Lorenzoni, G.; Fiore, M.; Radaelli, S.; Sanfilippo, R.; Sangalli, C.; Barisella, M.; Callegaro, D.; Gronchi, A.	2021	European Journal of Surgical Oncology	47	12	3004-3010
Aggressive surgery in retroperitoneal soft tissue sarcoma carried out at high-volume centers is safe and is associated with improved local control	Bonvalot, Sylvie; Miceli, Rosalba; Berselli, Mattia; Causeret, Sylvain; Colombo, Chiara; Mariani, Luigi; Bouzaiene, Hatem; Le Pechoux, Cecile; Casali, Paolo Giovanni; Le Cesne, Axel; Fiore, Marco; Gronchi, Alessandro	2010	Annals of surgical oncology	17	6	1507-
Predictors of outcomes in patients with primary retroperitoneal dedifferentiated liposarcoma undergoing surgery	Keung, Emily Z.; Hornick, Jason L.; Bertagnolli, Monica M.; Baldini, Elizabeth H.; Raut, Chandrajit P.	2014	Journal of the American College of Surgeons	218	2	206-1
Variability in Patterns of Recurrence After Resection of Primary Retroperitoneal Sarcoma (RPS): A Report on 1007 Patients From the Multi-institutional Collaborative RPS Working Group	Gronchi, Alessandro; Strauss, Dirk C.; Miceli, Rosalba; Bonvalot, Sylvie; Swallow, Carol J.; Hohenberger, Peter; Van Coevorden, Frits; Rutkowski, Piotr; Callegaro, Dario; Hayes, Andrew J.; Honore, Charles; Fairweather, Mark; Cannell, Amanda; Jakob, Jens; Haas, Rick L.; Szacht, Milena; Fiore, Marco; Casali, Paolo G.; Pollock, Raphael E.; Raut, Chandrajit P.	2016	Annals of surgery	263	5	1002-9

Appendix 5. Evidence Summary Topic 2 Question 2 Systematic Review

Outcome 1: Overall Survival

First Author; Year of Publication	Country	Study Period	Design	Population	Sample Size	Survival Outcome	Endpoints
MacNeil; 2018	Europe; North America	2002-11	Retrospective cohort study	Primary retroperitoneal sarcoma	1007	5-year overall survival 68.10% (64.80-71.50). 10-year overall survival 46.70% (40.50%-53.80%)	
Abdelfatah; 2016	USA	1994-2010	Case series	Primary retroperitoneal sarcoma	115	Median survival 62.7 months	Number of resected organs >5 vs 0, Median Survival HR 6.25 (p=0.005). R0-1 vs R2, Median survival 73.5 mths vs 10.1 mths (p<0.001). Low/intermediate grade vs high grade, Median survival HR 2.01 (p=0.032)
Bonvalot; 2009	France	1985-2005	Retrospective cohort study	Primary retroperitoneal sarcoma	382	5-year overall survival 57% (51-62)	Histologic margins R0 vs R1, Overall survival HR 1.7 (95% CI 1.07-2.72, p=0.03). Gross residual disease R0-1 vs R2, Overall surviva HR3.14 (95%CI 1.67-5.92, p=0.0004).
Chiappa; 2006 and 2018	Italy	1994-2015	Case series	Primary and recurrent retroperitoneal sarcoma	83	5-year survival 51% (41-63)	High grade vs low grade, 5- year survival 14% vs 57% (p=0.0004) Complete resection (R0-1) vs incomplete resection, 5-year survival 63% vs 17% (p=0.003) Recurrence vs no recurrence, 5-year survival 26% vs 100% (p=0.003)

Cho; 2017	Korea	1996-2015	Retrospective cohort study	Primary peritoneal sarcoma	114	5-year cancer specific survival	Nephrectomy vs no nephrectomy, 5-year cancer specific survival 75% vs 71% (p=0.554). Grade 2 tumours, nephrectomy vs no nephrectomy, 5-year cancer specific survival 88% vs 43% (p=0.077).
Eroglu; 1999	Turkey	1990-96	Case series	Retroperitoneal sarcoma	33	Median 5-year overall survival 58 months. 5-year overall survival 49% (48-73).	Low-grade (G1) vs high-grade (G2-3), 5-year survival HR 11.1 (95% CI 2.5-48.8, p=0.0014).
Ikoma; 2017	USA	1995-2011	Retrospective cohort study	Primary WDLPS retroperitoneal sarcoma	83	Median overall survival 11.3 years. 86% 5-year survival.	No statistically significant predictors of OS.
Lopez; 2014	Spain	2000-10	Retrospective cohort study	Retroperitoneal sarcoma	56	Median overall survival	Group A (Enucleation) vs Group B (En bloc resection), overall survival 47.9 vs 57.3 (p=0.08).
Makela; 2000	Finland	1977-96	Case series	Primary retroperitoneal sarcoma	32	5-year overall survival 31%. 10-year overall survival 19%.	High grade tumour vs low grade tumour, median survival 10 months vs 42 months. Radical resection (R0-R1) versus other resection (R2), median survival 70 months vs 20 months (palliative) and 10 months (other) (p=0.0118)
Morizawa; 2016	Japan	2002-14	Retrospective cohort study	Retroperitoneal sarcoma	23	3-year overall survival 50%.	Simple resection vs extended resection (contiguous organs), overall survival HR 3.80 (95% CI 1.25-16.59, p=0.04). Simple resection vs extended resection, 3-year survival 0% vs 78%.
Ng; 2017	Singapore	2000-14	Case series	Primary and recurrent retroperitoneal sarcoma	85	Median overall survival 45 months	R0 vs R1, overall survival 11 months vs 36 month (p=0.04, HR 2.04).

							Tumour adherent to adjacent organs vs invasive into the contiguous organ, overall survival 143 months vs 71 months (p=0.02).
Rossi; 2013	Italy	1989-2010	Case series	Primary and recurrent retroperitoneal sarcoma	43	5-year overall survival 70% (primary disease)	Primary disease vs recurrent disease, 5-year overall survival 70% vs 36% (p=0.002). R0 vs R1, 5-year overall survival 93% vs 45%(p=0.013).
Schwartz; 2019	USA	2000-16	Case series	Primary retroperitoneal sarcoma	571	Median overall survival 81.6 months (66.3-96.8)	High grade tumour (Grade 2-3) vs low grade tumour (Grade 1), overall survival HR 2.44 (95% CI, 1.6-3.74, p<0.01). Positive margins (R2) vs negative macroscopic margins (R0-1), overall survival HR 2.41 (95% CI, 1.57-3.69, p<0.01).
Singer; 2003	USA	1982-2001	Retrospective cohort study	Primary retroperitoneal sarcoma	177	Median disease-specific survival 83 months (74-169). 3-year disease-specific survival 73% (66.3-96.8).	DD histology vs WD histology, disease-specific survival HR 6.0 (95% CI, 3.3-10.9, p<0.0001). Gross positive margins (R2) vs negative margins (R0), disease-specific survival HR 3.80 (95% CI, 2-7.4, p<0.0001). Contiguous organ resection yes vs no, disease-specific survival HR 1.9 (95% CI 1.01-3.5, p=0.05).
Smith; 2015	UK	2005-2014	Case series	Primary retroperitoneal sarcoma	362	3-year disease-specific survival 81.2% (75.60-85.70).	Grade 1 vs Grade 3, 3-year DSS, HR 0.03 (95% CI 0.01-0.12, p<0.001). Grade 2 vs Grade 3, 3-year DSS, HR 0.28 (95% CI 0.16-0.5, p<0.001). Organs resected >3 vs 0, HR 2.18 (95% CI 0.91-5.18, p=0.079).
Spolverato; 2021	Italy	2002-19	Retrospective cohort study	Primary retroperitoneal sarcoma	425 (24)	5-year overall survival 69% (64-75)	Vascular resection vs no vascular resection (propensity matched analysis), 5-year survival 60% vs 81% (p=0.05). Vascular resection vs no vascular resection, HR 5.17 (95% CI 1.41-18.99, p=0.013).

Turner; 2019	Canada	1990-2014	Retrospective cohort study	Primary and recurrent retroperitoneal sarcoma	102	Overall survival	Grade 2 vs grade 1, overall survival HR 4.00 (95% CI 1.21-13.17, p=0.02) Grade 3 vs grade 1, overall survival HR 3.30 (95% CI 1.09-9.96, p=0.03).
van Doorn; 1994	Netherlands	1973-90	Case series	Retroperitoneal sarcoma	34	Median overall survival 53 months (16-198)	No statistically significant predictors of survival.
Wu; 2018	China	2005-15	Case series	Primary retroperitoneal liposarcoma	51	Median overall survival 43.3 months.	Low grade vs high grade, DSS 53.3 months vs 24.9 months (p<0.001). Contiguous organ resection vs palliative surgery, DSS 42.7 months vs 19.4 months (p=0.008).
Kim; 2021	South Korea	2001-2020	Retrospective cohort study	Retroperitoneal sarcoma	86	Overall survival	Distal pancreatectomy vs no distal pancreatectomy, overall survival 1-, 5-, 10-years, 84.8%, 45.8%, 25% vs 90.5%, 59.3%, 32.1% (p=0.145).
Bonvalot; 2010	France; Italy	France 2000-8; Italy 2002-10	Retrospective cohort study	Primary retroperitoneal sarcoma	249	5-year overall survival 65.4%(95% CI 56.8%-72.7%)	
Gronchi; 2016	Europe; North America	2002-11	Retrospective cohort study	Primary retroperitoneal sarcoma	1007	5-, 8-, 10-year overall survival were 67% (95% CI 63-70), 56% (95% CI 52-61), 46% (95% CI 40-53)	Tumour size 30cm vs 13 cm (HR 1.34, 95% CI 1.05-1.70, p=0.011) Completeness of resection R2 vs R0/R1 (HR2.36, 95% CI 1.45-3.84, p=0.001) FNCLCC Grade III vs I (HR 6.47, 95% CI 3.70-11.30 p<0.001) Multifocality yes vs no (HR 1.85, 95% CI 1.30-2.63, p=0.001)

Keung; 2014	USA	1998-2008	Retrospective cohort study	Primary retroperitoneal dedifferentiated liposarcoma	119	5-year overall survival 42%. Median OS 59 months (95% CI 51.8-66.2 months)	Median survival 63.2 months (95% CI 55.8-83.3 months) in R0/R1 vs 17.8 months (95% CI 10.0-41.5 months) in R2 (p<0.001). Intermediate-grade FNCLCC vs high-grade (HR 1.83, 95% CI 1.04-3.21, p=0.037). R0/R1 vs R2 (HR 4.00, 95% CI 1.50-10.67, p=0.006). Intact tumour specimen vs fragmented specimen (HR 2.20, 95% CI 1.02-4.74, p=0.045).

Outcome 2: Recurrence Free Survival

First Author; Year of Publication	Country	Study Period	Design	Population	Sample Size	Recurrence Outcome	Endpoints
Abdelfatah; 2016	USA	1994-2010	Case series	Primary retroperitoneal sarcoma	115	Median recurrence free interval 20 months	R1 vs R0, local recurrence HR 3.82(p=0.006). Organs resected 0 vs 1-2 vs 3-4 vs >5, overall recurrence, 70.1 vs 17.5 vs 16.1 vs 14.7 (p=0.083). R0 vs R1, overall recurrence 35.9 months vs 18.2 months (p=0.042).
Bonvalot; 2009	France	1985-2005	Retrospective cohort study	Primary retroperitoneal sarcoma	382	5-year abdominal recurrence rate, 49% (0.42-0.56).	Grade 3 vs grade 1, abdominal recurrence HR 2.57 (95% CI 1.48-4.45, p=0.0008). Simple resection vs compartmental resection, abdominal recurrence HR 1.99 (95% CI 1.03-3.84, p=0.04). Contiguously involved organs vs compartmental resection, abdominal recurrence HR 2.17 (95% CI 1.19-3.94, p=0.01). R1 vs R0, abdominal recurrence HR1.18 (95% CI 1.18-2.98, p=0.008).

Cho; 2017	Korea	1996-2015	Retrospective cohort study	Primary peritoneal sarcoma	114		Grade 2 histopathology, nephrectomy vs no nephrectomy, recurrence 55% vs 63% (p=0.048).
Ikoma; 2017	USA	1995-2011	Retrospective cohort study	Primary WDLPS retroperitoneal sarcoma	83	5-year disease-free survival	Unifocal disease vs multifocal disease, DFS HR 0.250 (95% CI 0.113-0.551, p<0.001).
Lopez; 2014	Spain	2000-10	Retrospective cohort study	Retroperitoneal sarcoma	56	Disease free survival	Enucleation vs en bloc resection, DFS en bloc resection stated to be significant in text p<0.01. R0 vs R1-2, DFS en bloc resection stated to be significant in text p=0.05.
Ng; 2017	Singapore	2000-14	Case series	Primary and recurrent retroperitoneal sarcoma	85	Overall recurrence, 59%.	Descriptive analysis. Local recurrence 80%, distant recurrence 10%, local and distant recurrence 10%.
Rossi; 2013	Italy	1989-2010	Case series	Primary and recurrent retroperitoneal sarcoma	43	Local disease-free survival, 60%.	LMS vs other histology, 5-year local disease-free recurrence 62% vs 93% (p=0.003).
Schwartz; 2019	USA	2000-16	Case series	Primary retroperitoneal sarcoma	571	Median DFS 35.3 months (27.6-43.0).	High grade tumour (Gr 2-3) vs low grade tumours (Gr 1), DFS HR 2.66 (95% CI 1.88-3.77, p<0.01). En bloc resection 3-4 organs vs 0 organs, DFS HR 1.56 (1.03-2.37, p=0.04).

Singer; 2003	USA	1982-2001	Retrospective cohort study	Primary retroperitoneal sarcoma	177	Median local recurrence, 45 months (30-61).	DDLPS vs WDLPS, local recurrence HR 3.6 (95% CI 2.2-6, p<0.0001). Contiguous organ resection yes vs no, local recurrence HR 1.7 (95% CI 1.02-2.8, p=0.04). DDLPS vs WDLPS, distant recurrence HR 15 (p<0.0001) Contiguous organ resection yes vs no, distant recurrence HR 3 (p=0.02).
Smith; 2015	UK	2005-2014	Case series	Primary retroperitoneal sarcoma	362	Local and distant recurrence.	Grade 1 vs grade 3, local recurrence HR 0.09 (95% CI 0.04-0.2, p<0.001). Grade 2 vs Grade 3, local recurrence HR 0.35 (95% CI 0.22-0.56, p<0.001). R2 vs R0-1, local recurrence HR 2.64 (95% CI 1.36-5.14, p-0.004). Grade 1 vs grade 3, distant recurrence HR 0 (95% CI 0.00-0.42, p=0.02).
Spolverato; 2021	Italy	2002-19	Retrospective cohort study	Primary retroperitoneal sarcoma	425 (24)	Local recurrence 31% (26-36). Distant recurrence 9% (6-12).	Vascular resection vs no vascular resection (propensity matched analysis), local recurrence 45% vs 24% (p=0.05). Vascular resection vs no vascular resection, distant recurrence 20% vs 0% (p=0.04). Vascular resection vs no vascular resection, recurrence-free survival HR 6.60 (95% CI 2.16-20.15, p<0.001).
van Doorn; 1994	Netherlands	1973-90	Case series	Retroperitoneal sarcoma	34	Median time to local recurrence (with or without distant disease) 14 months (1-145).	No statistically significant results.
Kim; 2021	South Korea	2001-2020	Retrospective cohort study	Retroperitoneal sarcoma	86	Local recurrence-free survival	DP vs N-DP, 1-, 5-, 10-year local RFS 74.8, 37.5, 18.8 vs 76.1, 39.7, 18.9 (p=0.807). Resection of the pancreas was not associated with LR. Primary tumour, R2 resection and high grade (Gr 3) tumours were associated with LR.

Bonvalot; 2010	France; Italy	France 2000-8; Italy 2002-10	Retrospective cohort study	Primary retroperitoneal sarcoma	249	CCI local recurrence 22.3% (95% CI 16.5-30.2%). CCI distant recurrence 24.2% (95% CI 18.4-31.9%)	Abdominal recurrence, FNCLCC grade II vs grade I (HR 4.36, 95% CI 1.70-11.19, p=0.005). Distant recurrence, LMS vs LPS (HR 3.53, 95% CI 1.56-7.96, p=0.023). Distant recurrence, FNCLCC grade II vs I (HR 11.16, 95% CI 1.43-87.30, p<0.001).
Gronchi; 2016	Europe; North America	2002-11	Retrospective cohort study	Primary retroperitoneal sarcoma	1007	CCI LR at 5-, 8-, 10-years were 25.9% (23.1-29.1), 31.3% (27.8-35.1), 35% (30.5-40.1). Median time to first local recurrence was 39 months. CCI distant mets at 5-, 8-, 10-years were 21% (18.4-23.8), 21.6% (19.0-24.6), 21.6 (19.0-24.6). Median time to DM 14 months.	LR, tumour size 30cm vs 13cm (HR 1.38, 95% CI 1.07-1.78, p=0.045). LR, completeness of resection R2 vs R0/R1 (HR 2.81, 95% CI 1.76-4.49, p<0.001). LR, FNCLCC grade III vs I (HR 4.58, 95% CI 2.62-8.00, p<0.001). LR, tumour rupture yes vs no (HR 1.67, 95% CI 1.09-2.57, p=0.019). LR, multifocality yes vs no (HR 2.05, 95% CI 1.43-2.94, p<0.001). DM, FNCLCC grade III vs I (HR 4.83, 95% CI 2.74-8.49, p<0.001). DM, multifocality yes vs no (HR 1.94, 95% CI 1.27-2.97, p=0.002).
Keung; 2014	USA	1998-2008	Retrospective cohort study	Primary retroperitoneal dedifferentiated liposarcoma	119	5-year local recurrence-free survival 15%. Median LRFS 21.5 months (14.5-28.5).	LRFS, single tumour vs multifocal disease (HR 1.89, 95% CI 1.1-3.23, p=0.021). DRFS, R0/R1 resection vs R2 resection (HR 3.18 (95% C 1.32-7.64, p=0.010.

						5-year distant recurrence-free survival 33%. Median DRFS 45.8 months (29.7-61.8)	

Outcome 3: Perioperative Morbidity

First Author; Year of Publication	Country	Study Period	Design	Population	Sample Size	Perioperative Morbidity	Endpoints
MacNeil; 2018	Europe; North America	2002-11	Retrospective cohort study	Primary retroperitoneal sarcoma	1007	Post-operative severe morbidity (CD≥3).	Resected organ score 4 vs 1, severe morbidity (CD≥3), OR 1.51 (95% CI 0.85-1.73, p=0.007). Resected organ score 8 vs 0, severe morbidity (CD≥3), OR 3.00 (95% CI 1.24-7.29, p=0.007).

Bonvalot; 2009	France	1985-2005	Retrospective cohort study	Primary retroperitoneal sarcoma	382	Post-operative morbidity (CD≥2), 22%. Perioperative mortality (60 days), 3%.	Descriptive analysis in text. Half of all the complications required re-operation (CD≥3).
Chiappa; 2006 and 2018	Italy	1994-2015	Case series	Primary and recurrent retroperitoneal sarcoma	83	Post-operative complications.	Descriptive analysis only.
Cho; 2017	Korea	1996-2015	Retrospective cohort study	Primary peritoneal sarcoma	114	Post-operative renal function.	Nephrectomy vs no nephrectomy, post-operative eGFR 62.3mL/min/1.73m^2 (55.3-79) vs 78.6mL/min/1.73m^2 (59-102.4), p=0.004. Nephrectomy vs no nephrectomy, acute kidney injury 52% vs 4% (p<0.001).
Ikoma; 2017	USA	1995-2011	Retrospective cohort study	Primary WDLPS retroperitoneal sarcoma	83	Post-operative complications, 14.5%	No organ resection vs concurrent organ resection, severe morbidity (CD≥3),4.4% vs 26.3% (p=0.045).

Rossi; 2013	Italy	1989-2010	Case series	Primary and recurrent retroperitoneal sarcoma	43	Post-operative complications, 12% in the primary sarcoma series.	Descriptive analysis in the text only. No statistical analysis with respect to morbidity.
Smith; 2015	UK	2005-2014	Case series	Primary retroperitoneal sarcoma	362	30-day morbidity, 15.7%. 30-day mortality, 1.4%. 90-day mortality, 3%.	Descriptive analysis only. No statistical analysis with respect to morbidity and mortality.
Spolverato; 2021	Italy	2002-19	Retrospective cohort study	Primary retroperitoneal sarcoma	425 (24)	90-day severe morbidity (CD≥3).	Vascular resection vs No vascular resection (propensity matched analysis), 54% vs 25% (p=0.002). No association with higher risk of reoperation, or death within 90 days.
Kim; 2021	South Korea	2001-2020	Retrospective cohort study	Retroperitoneal sarcoma, specifically those tumours abutting the pancreas	86	30-day overall and severe morbidity (CD≥3), 48.8% and 15.1% respectively.	DP vs N-DP, overall morbidity 57.6% vs 43.4% (p=0.26). DP vs N-DP, severe morbidity (CD≥3), 18.2% vs 13.2% (p=0.55). Grade B post-op pancreatic fistula, 18.2% in the DP group. No Grade C POPF.

Judge; 2019	USA	2012-15	Retrospective cohort study	Primary retroperitoneal sarcomas	564	30-day overall morbidity, 19%. 30-day severe morbidity (CD≥3), 9%.	MVR vs no MVR, overall morbidity 22% vs 17% (p=0.13). MVR vs no MVR, severe morbidity (CD≥3) 11% vs 8% (p=0.18). Low serum albumin (<2.5g/dL) vs Normal serum albumin (>3.5g/dL), severe morbidity OR 5.76 (1.70-19.53, p<0.01). Insufficient data to comment on mortality outcomes.
Tseng; 2011	USA	2005-07	Retrospective cohort study	Primary retroperitoneal sarcoma	156	30-day overall morbidity, 25.6%. 30-day severe morbidity (CD≥3), 11.5%. 30-day mortality, 1.3%.	Contiguous organ resection vs simple resection, severe morbidity (CD≥3) HR 0.78 (95% CI 0.05-13.18, p=0.86). ASA 3 vs ASA 1-2, severe morbidity (CD≥3) HR 3.23, (95% CI 1.33-7.84, p=0.01). Operative time (per hours increase), severe morbidity (CD≥3) HR1.38 (95% CI 1.05-1.81, p=0.02).
Bonvalot; 2010	France; Italy	France 2000-8; Italy 2002-10	Retrospective cohort study	Primary retroperitoneal sarcoma	249	Post-operative morbidity (CD≥3) 18% (95% CI 14-23). Surgical re-intervention required in 12% (8-17). Psot-operative mortality 3% (1-6).	Morbidity pattern according to number of organs resected. Severe morbidity (CD≥3) HR 2.75 (95% CI 1.32-5.74, p=0.007, where greater than three organs resected vs three or fewer. Higher ORs for severe morbidity following resection of major vein, small bowel (duodenum), stomach, and artery (ORs 2.56, 2.31, 1.99, 3.48) respectively.
Gronchi; 2016	Europe; North America	2002-11	Retrospective cohort study	Primary retroperitoneal sarcoma	1007	Post-operative complications, grade 3 12.7%, and grade 4 5.2%. Post-operative mortality at 30, 60 and 90 days was 1.8%, 2.9%, and 4.1% respectively.	

Appendix 6. Quality Assessment for Topic 2 Question 2 Systematic Review

Study	Title		NHMRC Level of Evidence	Risk of Bias (Newcastle Ottawa scale for cohort study)			
		Reviewer		Selection	Comparability	Outcome	Overall
Abdelfatah, 2016	Long-term outcomesin treatment of retroperitoneal sarcomas: A 15 year single-institution evaluation of prognostic factors.	1	IV	2	1	3	Fair Quality
		2	III-2	4	0	3	poor
		Final	III-2	4	0	3	poor
Bonvalot, 2009	Primary retroperitoneal sarcomas: A multivariate analysis of surgical factors associated with local control.	1	III-3	4	2	3	Good Quality
		2	III-2	4	2	3	good
		Final	III-2	4	2	3	Good Quality
Chiappa, 2006	Primary and recurrent retroperitoneal soft tissue sarcoma: Prognostic factors affecting survival.	1	IV	3	0	1	Poor Quality
		2	IV	4	0	1	poor
		Final	IV	4	0	1	Poor Quality
Chiappa, 2018	Aggressive surgical approach for treatment of primary and recurrent retroperitoneal soft tissue sarcoma	1	IV	3	0	1	Poor Quality
		2	III-3	4	0	1	Poor
		Final	III-3	4	0	1	poor
Cho, 2017	Clinical benefit and residual kidney function of en bloc nephrectomy for perirenal retroperitoneal sarcoma.	1	III-3	4	2	2	Good Quality
		2	III-3	4	2	2	Good
		Final	III-3	4	2	2	Good Quality

Eroglu, 1999	Retroperitoneal soft tissue sarcoma: Effect of hyperthermic total abdominal perfusion.	1	IV	2	1	2	Fair Quality
		2	IV	2	1	2	fair
		Final	IV	2	1	2	Fair Quality
Ikoma, 2017	Concomitant organ resection does not improve outcomes in primary retroperitoneal well-differentiated liposarcoma: A retrospective cohort study at a major sarcoma center.	1	III-3	4	2	3	Good Quality
		2	III-2	4	2	3	good
		Final	III-2	4	2	3	Good Quality
Judge, 2019	Morbidity, mortality and temporal trends in the surgical management of retroperitoneal sarcoma: An ACS-NSQIP follow-up analysis.	1	III-3	4	2	3	Good Quality
		2	III-2	4	2	3	good
		Final	III-2	4	2	3	Good Quality
Gonzalez Lopez, 2014	Differences between en bloc resection and enucleation of retroperitoneal sarcomas.	1	III-3	3	2	2	Good Quality
		2	III-2	3	2	2	good
		Final	III-2	3	2	2	Good Quality
MacNeill, 2018	Postoperative morbidity after radical resection of primary retroperitoneal sarcoma.	1	III-3	4	2	3	Good Quality
		2	III-3	4	2	3	Good Quality
		Final					
Makela, 2000	Prognostic factors predicting survival in the treatment of retroperitoneal sarcoma.	1	IV	3	0	2	Poor Quality
		2	IV	4	0	1	poor
		Final	IV	3	0	2	Poor Quality
Morizawa, 2016	Extended resection including adjacent organs and Ki-67 labeling index are prognostic factors in patients with retroperitoneal soft tissue sarcoma.	1	III-3	4	2	3	Good Quality

		2	III-3	4	2	3	good
		Final	III-3	4	2	3	Good Quality
Ng, 2017	Tumour biology remains the main determinant of prognosis in retroperitoneal sarcomas: a 14-year single centre experience.	1	IV	2	0	3	Poor Quality
		2	III-3	4	2	3	good
		Final	III-3	3	2	3	good
Rossi, 2013	Patient outcome after complete surgery for retroperitoneal sarcoma.	1	IV	2	2	2	Fair Quality
		2	III-2	4	2	3	good
		Final	III-2	4	2	2	good
Schwartz, 2019	Predictors of disease-free and overall survival in retroperitoneal sarcomas: A modern 16-year multi-instituional study from the United States Sarcoma Collaboration (USSC).	1	IV	3	0	3	Poor Quality
		2	III-2	4	2	3	good
		Final	III-2	4	2	3	Good Quality
Singer, 2003	Histologic subtype and margin of resection predict pattern of recurrence and survival for retroperitoneal liposarcoma.	1	III-3	4	1	3	Good Quality
		2	III-3	4	1	3	Good Quality
		Final	III-3	4	1	3	Good Quality
Smith, 2015	Outcome following resection of retroperitoneal sarcoma.	1	IV	4	1	3	Good Quality
		2	III-2	4	1	2	good
		Final	III-2	4	1	2	Good Quality
Tseng, 2010	Contiguous organ resection is safe in patients with retroperitoneal sarcoma: An ACS-NSQIP analysis.	1	III-3	4	2	3	Good Quality
		2	III-3	4	2	3	Good Quality
		Final	III-3	4	2	3	Good Quality

Turner, 2019	Neoadjuvant radiotherapy followed by surgery compared with surgery alone in the treatment of retroperitoneal sarcoma: a population-based comparison.	1	III-3	1	1	3	Poor Quality
		2	III-2	4	2	1	poor
		Final	III-2	3	2	1	Poor Quality
van Doorn, 1993	Resectable retroperitoneal soft tissue sarcomas.	1	IV	1	0	2	Poor Quality
		2	IV	1	2	2	Poor Quality
		Final	IV	1	2	2	Poor Quality
Wu, 2017.	A retrospective, single-centre cohort study on 65 patients with primary retroperitoneal liposarcoma.	1	IV	2	0	1	Poor Quality
		2	IV	3	0	1	poor
		Final	IV	3	0	1	Poor Quality
Kim, 2021	Postoperative outcomes of distal pancreatectomy for retroperitoneal sarcoma abutting the pancreas in the left upper quadrant.	1	III-3	4	2	3	Good Quality
		2	III-2	4	2	3	good
		Final	III-2	4	2	3	Good Quality
Spolverato, 2021	Oncological outcomes after major vascular resections for primary retroperitoneal liposarcoma.	1	III-3	4	2	3	Good Quality
		2	III-2	4	2	3	good
		Final	III-2	4	2	3	Good Quality
Bonvalot 2010	Aggressive surgery in retroperitoneal soft tissue sarcoma carried out at high-volume centers is safe and is associated with improved local control	1	III-3	3	2	3	Good Quality
		2	III-3	3	2	3	Good Quality
		Final	III-3	3	2	3	Good Quality
Keung 2014	Predictors of outcomes in patients with primary retroperitoneal dedifferentiated liposarcoma undergoing surgery	1	III-3	3	2	3	Good Quality

		2	III-3	3	2	3	Good Quality
		Final	III-3	3	2	3	Good Quality
Gronchi 2016	Variability in Patterns of Recurrence After Resection of Primary Retroperitoneal Sarcoma (RPS): A Report on 1007 Patients From the Multi-institutional Collaborative RPS Working Group	1	III-3	2	2	3	Fair Quality
		2	III-3	2	2	3	Fair Quality
		Final	III-3	2	2	3	Fair Quality

Appendix 7. Studies included in Topic 2 Question 3 Systematic Review

Title	Authors	Published Year	Journal	Volume	Issue	Pages
Clinical characteristics and surgical outcomes of retroperitoneal tumors: a comprehensive data collection from multiple departments	Sassa, Naoto; Yokoyama, Yukihiro; Nishida, Yoshihiro; Yamada, Suguru; Uchida, Hiroo; Kajiyama, Hiroaki; Nagino, Masato; Kodera, Yasuhiro; Gotoh, Momokazu	2020	International journal of clinical oncology	25	5	929-936
Needle tract seeding following core biopsies in retroperitoneal sarcoma	Van Houdt, W. J.; Schrijver, A. M.; Cohen-Hallaleh, R. B.; Memos, N.; Fotiadis, N.; Smith, M. J.; Hayes, A. J.; Van Coevorden, F.; Strauss, D. C.	2017	European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology	43	9	1740-1745
Percutaneous core needle biopsy in retroperitoneal sarcomas does not influence local recurrence or overall survival	Wilkinson, M. J.; Martin, J. L.; Khan, A. A.; Hayes, A. J.; Thomas, J. M.; Strauss, D. C.	2015	Annals of surgical oncology	22	3	853-8
Preoperative Biopsy in Patients with Retroperitoneal Sarcoma: Usage and Outcomes in a National Cohort	Straker, Richard J., 3rd; Song, Yun; Shannon, Adrienne B.; Marcinak, Clayton T.; Miura, John T.; Fraker, Douglas L.; Karakousis, Giorgos C.	2021	Annals of surgical oncology			
Treatment of patients with primary retroperitoneal sarcoma: predictors of outcome from an Australian specialist sarcoma centre	Snow, Hayden A.; Hitchen, Tatiana X.; Head, Jessica; Herschtal, Alan; Bae, Susie; Chander, Sarat; Chu, Julie; Hendry, Shona; Ngan, Samuel Y.; Desai, Jayesh; Choong, Peter F. M.; Henderson, Michael; Gyorki, David E.	2018	ANZ journal of surgery	88	11	1151-1157

Appendix 8. Evidence Summary Topic 2 Question 3 Systematic Review

First Author	Year	Country	Study period	Patient source	Design	Inclusion	Exclusion	Total Number of patients	No. of pt with Bx	No. of pt without Bx	Biospy method	Endpoints	Biopsy tract seeding	Early complications	Recurrence free survival	Overall survival	Multivariate analysis	Comments
Sassa	2020	Japan	January 2005 - July 2018	Nagoya University Hospital	Retrospective cohort study	All patients diagnosed with primary retroperitoneal tumours	Limb and bone sarcoma Incomplete medical information	422	180 (43%)	242 (57%)	68% needle biopsy, 32% incisional biopsy (either open laparotomy or laproscopic)	-	No recurrence along biopsy route	-	Nil comparison bx vs no bx	Nil comparison bx vs no bx.	-	Study aim to describe clinical characteristics, treatments and survival of RPS patients Included patients < 18 years age Report recurrence free survival data but do not compare biopsy to non biopsy Include all retroperitoneal tumours (benign, malignant including neurogenic origin, lymphoma, metastases) not just sarcoma Single institution
Snow	2018	Australia	October 2008 - December 2016	Peter MacCallum Cancer Centre database	Retrospective cohort study	Retroperitoneal sarcoma primary or recurrent non-metastatic and metastatic untreated patients or patients with initial surgery at others centres prior to referral to PMCC	Visceral sarcomas (including GIST), gynaecological sarcomas, paediatric sarcomas, desmoid tumours patients with inadequate follow up to establish oncologic outcomes	138	Of total cohort biopsy = 109 patients (79%) In subset, biopsy = 65 (74%)	Of total cohort, no biopsy = 29 In subset, no biopsy = 23	Core biopsy	5 yr OS, 5 yr recurrence free survival	-	-	Of 88 patients with primary, resectable RPS - 5 yr local RFS - not employing a biopsy was associated with higher LR rates, HR 2.8 [1.1, 7.0], p = 0.019	Of 88 patients with primary, resectable RPS - 5 yr OS - biopsy v no bx not significantly associated with OS, HR 1.4 [0.51, 3.6], p value = 0.55	-	Main objective to describe experience of managing RPS at an Australian specialist centre. Comparing outcomes at specialist centre vs non specialist centre Small number at risk at 5 years - median follow up 36 months, majority of patients captured in latter half of enrolment period Specialist centres more likely to use diagnostic core biopsy (92% v 31%, p <0.001) Specialist centres more likely to use neoadjuvant radotherapy (87% vs 12%, p < 0.001) Do not look at biopsy tract seeding
Straker	2021	USA	2006-2014	National Cancer Database	Retrospective cohort study	Non metastatic RPS who underwent tumor resection	Excisional biopsy Non-sarcoma histology Missing staging, treatment or survival data	2620	1110 (42.4%)	1510 (57.6%)	core needle biopsy	5 yr OS	-	-	-	Unmatched cohort - patients who underwent Bx lower 5 year OS rate (57.8% bx vs 62.6% no bx, p 0.003) Of matched cohort - no significant difference in 5 yr OS (56.5% bx vs 58.4% no bx, p = 0.247)	Bx not significantly associated with OS, HR 1.1, p value 0.07	Significant differences between Bx and no bx groups - therefore 1:1 propensity matching was performed Unmatched cohort - male patients, those with smaller tumours, those treated at HVCs and those with non-WDLPS histology signifiicantly more likely to have bx Patients who did and did not undergo Bx were compared using propensity matching Receipt of neoadjuvant radiation therapy, neoadjuvant systemic therapy, radical surgical resection and complete resection significantly associated with biopsy Bx may indirectly improve outcomes by virtue of receipt of neoadjuvant thearpy and attainment of complete tumour resection Median flu time 54.4 months Survival date in NCDB only in terms of 30- and 90- mortality and OS, does not capture local recurrence
VanHoudt	2017	UK, Netherlands	1990-2014	The Royal Marsden NHS Foundation Trust database, The Netherlands Cancer Institute (NCI)/Antoni van Leeuwenhock Hospital database	Retrospective cohort study	Resection of primary retroperitoneal sarcoma	Follow up < 1 year Benign lesions Recurrent retroperitoneal sarcomas Gastrointestinal stromal tumours Metastatic retroperitoneal sarcomas	498	255 (51.2%)	243 (48.8%)	Core needle (14-, 15- or 16-gauge needle) - route: trans-abdominal in 40%, transperitoneal in 20%, open 1 %, trans- rectal 1%, transvaginal 0%, unknown 39% - technique: coaxial 43%, non-co-axial 40%, unknown 17% - image guided: yes 74%, no 25%, unknown 2%	Needle tract recurrence, local recurrence	5 patients (2%) developed biopsy site recurrence 3 of these patients had 2 biopsy attempts as initial outside of institution non diagnostic All 5 patients biopsied trans-abdominally and not with co-axial technique Nil significant difference in occurance of NTS for route of biopsy (p=0.11) (but low number of events) Increased risk of NTS when non co-axial method used (p=0.02)	-	70 patients (29.4%) experienced LR - median time to LR 14 months. No significant difference in LR rate between patients with or without bx p =0.3 No significant difference in LR between trans-abdominal and trans-retroperitoneal route p=0.72		The biopsy route did not significantly correlate with LR rate	Latency period of 6 months - 7 years from dx to NTS Patients with liposarcoma less likely to have biopsy Short median follow up (38 months) 2 of the 5 cases presented with distant metastases around the same time as NTS
Wilkinson	2014	UK	1990-2011	Royal Marsden NHS foundation trust database	Retrospective cohort study	Patients who underwent resection of a primary retroperitoneal sarcoma (intermediate or high grade)	Low grade sarcomas (GI) Recurrent retroperitoneal sarcomas Gastrointestinal stromal tumours Metastatic retroperitoneal sarcomas	150, analysis also of two subgroups: - patients with liposarcoma n = 96 - patients who had complete macroscopic clearance	90	60	Core needle (14- or 16-gauge) freehand if easily palpable, image guided for impalpable tumours transperitoneal under LA in 43%, 48% CNB under image guidance where preferred route retroperitonal - specific info about approach not available, remaining 9% method not stated	immediate biopsy related complications, NTS, local recurrence, overall survival	n = 0 developed biopsy site recurrence (NTS)	n = 1 (1.1%) had abdominal wall rectus sheath hematoma	median LRFS 44 months (1-155) bx versus 57 (1-160) no bx. no significnat different in proportion of patients who developed LR between bx (52%) and no bx (52%) Of n =127 patients who had complete macroscopic clearance, no significant difference in LRFS between bx versus no bx (p=0.132, HR 1.19, 95% CI 0.73-1.94) No significant difference in LRFS between bx vs no bx when comparing patients with liposarcoma (n=96) seperately p =0.107, HR 1.29 95% CI 0.71-2.26)	No difference in OS between CNB and non-CNB groups (p value = 0.264, HR 1.27 95% CI 0.82-1.95) when comparing n = 150 When comparing the n = 96 patients with liposarcoma - significant decrease in OS in bx group vs no bx HR 1.84, 95% CI 1.21-3.22, p =0.01)	no significant increase in LR after bx HR 1.57 (0.91-2.72,) p = 0.101 no significant increase in OS after bx HR 1.38 (0.85-2.26) p=0.191	do not routinely perform pre-op bx of resectable RPS if imaging diagnostic of retroperitoneal liposarcoma The bx group consisted of smaller and more high grade tuomours Liposarcomas not requiring CNB less differentiated and lower grade median follow up 48 months 96 patients had liposarcoma, 29 leiomyosarcoma, 6 pleomorphic sarcoma. Only 47% of patients with liposarcoma had bx, versus 86% of patients with leiomyosarcoma, 67% pleomorphic

Appendix 9. Quality Assessment for Topic 2 Question 3 Systematic Review

Study	Title	Reviewer	NHMRC Level of Evidence	Risk of Bias (Newcastle Ottawa scale for cohort study)			
				Selection	Comparability	Outcome	Overall
Sassa 2019	Clinical characteristics and surgical outcomes of retroperitoneal tumors: a comprehensive data collection from multiple departments	R1	III-2	4	0	2	Poor Quality
		R2	III-2	4	0	3	Poor Quality
		Final	III-2	4	0	2	Poor Quality
Snow 2018	Treatment of patients with primary retroperitoneal sarcoma: predictors of outcome from an Australian specialist sarcoma centre	R1	III-2	4	1	3	Good Quality
		R2	III-2	4	1	3	Good Quality
		Final	III-2	4	1	3	Good Quality
Straker 2021	Preoperative Biopsy in Patients with Retroperitoneal Sarcoma: Usage and Outcomes in a National Cohort	R1	III-2	4	2	3	Good Quality
		R2	III-2	4	1	3	Good Quality
		Final	III-2	4	1	3	Good Quality
Van Houdt 2017	Needle tract seeding following core biopsies in retroperitoneal sarcoma	R1	III-2	4	2	3	Good Quality
		R2	III-2	4	1	3	Good Quality
		Final	III-2	4	1	3	Good Quality
Wilkinson 2014	Percutaneous core needle biopsy in retroperitoneal sarcomas does not influence local recurrence or overall survival	R1	III-2	4	2	3	Good Quality
		R2	III-2	4	1	3	Good Quality
		Final	III-2	4	1	3	Good Quality

Appendix 10. Studies included in Topic 2 Question 4 Systematic Review

Study	Title	Authors	Published Year	Journal	Volume	Issue	Pages
Akagunduz 2021	Factors affecting survival in retroperitoneal sarcomas treated with upfront surgery: A real-world study by turkish oncology group	Akagunduz, B.; Telli, T. A.; Yildirim, H. C.; Goksu, S. S.; Demir, N.; Hafizoglu, E.; Ozer, M.; Cevik, G. T.; Sakin, A.; Aydin, S. G.; Samanci, N. S.; Ozyurt, N.; Atci, M. M.; Ayhan, M.; Turan, M.; Sariyar, N.; Karacin, C.; Kilickap, S.; Paydas, S.; Dogan, M.	2021	UHOD - Uluslararasi Hematoloji-Onkoloji Dergisi	31(2)		92-98
Bredbeck 2022	Factors associated with disease-free and abdominal recurrence-free survival in abdominopelvic and retroperitoneal sarcomas	Bredbeck, B. C.; Delaney, L. D.; Kathawate, V. G.; Harter, C. A.; Wilkowski, J.; Chugh, R.; Cuneo, K. C.; Dossett, L. A.; Sabel, M. S.; Angeles, C. V.	2022	Journal of Surgical Oncology	125(8)		1292-1300
Bremjit 2014	A contemporary large single-institution evaluation of resected retroperitoneal sarcoma	Bremjit, Prashoban J.; Jones, Robin L.; Chai, Xiaoyu; Kane, Gabrielle; Rodler, Eve T.; Loggers, Elizabeth T.; Pollack, Seth M.; Pillarisetty, Venu G.; Mann, Gary N.	2014	Annals of surgical oncology	21	7	2150-8
Callegaro 2021	Has the Outcome for Patients Who Undergo Resection of Primary Retroperitoneal Sarcoma Changed Over Time? A Study of Time Trends During the Past 15 years	Callegaro, D.; Raut, C. P.; Ng, D.; Strauss, D. C.; Honore, C.; Stoeckle, E.; Bonvalot, S.; Haas, R. L.; Vassos, N.; Conti, L.; Gladdy, R. A.; Fairweather, M.; van Houdt, W.; Schrage, Y.; van Coevorden, F.; Rutkowski, P.; Miceli, R.; Gronchi, A.; Swallow, C. J.	2021	Annals of Surgical Oncology	28(3)		1700-1709
Chouliaras 2019	Role of radiation therapy for retroperitoneal sarcomas: An eight-institution study from the US Sarcoma Collaborative	Chouliaras, Konstantinos; Senehi, Rebecca; Ethun, Cecilia G.; Poultsides, George; Grignol, Valerie; Clarke, Callisia N.; Roggin, Kevin K.; Fields, Ryan C.; Schwartz, Patrick B.; Ronnekleiv-Kelly, Sean M.; D'Agostino, Ralph, Jr.; Johnson,	2019	Journal of surgical oncology	120	7	1227-1234

		Emily N.; Levine, Edward A.; Cardona, Kenneth; Votanopoulos, Konstantinos I.					
Chouliaras 2019	Recurrence patterns after resection of retroperitoneal sarcomas: An eight-institution study from the US Sarcoma Collaborative	Chouliaras, Konstantinos; Senehi, Rebecca; Ethun, Cecilia G.; Poultsides, George; Tran, Thuy; Grignol, Valerie; Gamblin, Thomas Clark; Roggin, Kevin K.; Tseng, Jennifer; Fields, Ryan C.; Weber, Sharon M.; Russell, Gregory B.; Levine, Edward A.; Cardona, Kenneth; Votanopoulos, Konstantinos	2019	Journal of surgical oncology	120	3	340-347
Datta 2017	Contemporary reappraisal of the efficacy of adjuvant chemotherapy in resected retroperitoneal sarcoma: Evidence from a nationwide clinical oncology database and review of the literature	Datta, Jashodeep; Ecker, Brett L.; Neuwirth, Madalyn G.; Geha, Rula C.; Fraker, Douglas L.; Roses, Robert E.; Karakousis, Giorgos C.	2017	Surgical oncology	26	2	117-124
Gholami 2009	The value of surgery for retroperitoneal sarcoma	Gholami, Sepideh; Jacobs, Charlotte D.; Kapp, Daniel S.; Parast, Layla M.; Norton, Jeffrey A.	2009	Sarcoma	2009		605840
Gronchi 2009	Aggressive surgical policies in a retrospectively reviewed single-institution case series of retroperitoneal soft tissue sarcoma patients	Gronchi, A.; Lo Vullo, S.; Fiore, M.; Mussi, C.; Stacchiotti, S.; Collini, P.; Lozza, L.; Pennacchioli, E.; Mariani, L.; Casali, P. G.	2009	J Clin Oncol	27	1	24-30
Gronchi 2012	Frontline extended surgery is associated with improved survival in retroperitoneal low- to intermediate-grade soft tissue sarcomas	Gronchi, A.; Miceli, R.; Colombo, C.; Stacchiotti, S.; Collini, P.; Mariani, L.; Sangalli, C.; Radaelli, S.; Sanfilippo, R.; Fiore, M.; Casali, P. G.	2012	Ann Oncol	23	4	1067-73

Gronchi 2016	Variability in Patterns of Recurrence After Resection of Primary Retroperitoneal Sarcoma (RPS): A Report on 1007 Patients From the Multi-institutional Collaborative RPS Working Group	Gronchi, A.; Strauss, D. C.; Miceli, R.; Bonvalot, S.; Swallow, C. J.; Hohenberger, P.; Van Coevorden, F.; Rutkowski, P.; Callegaro, D.; Hayes, A. J.; HonorÃ©, C.; Fairweather, M.; Cannell, A.; Jakob, J.; Haas, R. L.; Szacht, M.; Fiore, M.; Casali, P. G.; Pollock, R. E.; Raut, C. P.	2016	Ann Surg	263	5	1002-9
Kilkennylii 1996	Retroperitoneal sarcoma: The University of Florida experience	Kilkenny Iii, John W.; Bland, Kirby I.; Copeland Iii, Edward M.	1996	Journal of the American College of Surgeons	182	4	329-339
Klooster 2016	Is long-term survival possible after margin-positive resection of retroperitoneal sarcoma (RPS)?	Klooster, Brittany; Rajeev, Rahul; Chrabaszcz, Sarah; Charlson, John; Miura, John; Bedi, Meena; Gamblin, Thomas Clark; Johnston, Fabian; Turaga, Kiran K.	2016	Journal of surgical oncology	113	7	823-7
Li 2021	Adjuvant therapy for retroperitoneal sarcoma: a meta-analysis	Li, X.; Wu, T.; Xiao, M.; Wu, S.; Min, L.; Luo, C.	2021	Radiation Oncology	16	1	196
Ma 2020	Evaluation of Preoperative Chemotherapy or Radiation and Overall Survival in Patients with Nonmetastatic, Resectable Retroperitoneal Sarcoma	Ma, Sung Jun; Farrugia, Mark K.; Shekher, Rohil; Iovoli, Austin J.; Singh, Anurag K.; Oladeru, Oluwadamilola T.	2020	JAMA network open	3	11	
Meric 2000	Impact of neoadjuvant chemotherapy on postoperative morbidity in soft tissue sarcomas	Meric, F.; Milas, M.; Hunt, K. K.; Hess, K. R.; Pisters, P. W.; Hildebrandt, G.; Patel, S. R.; Benjamin, R. S.; Plager, C.; Papadopolous, N. E.; Burgess, M. A.; Pollock, R. E.; Feig, B. W.	2000	Journal of clinical oncology : official journal of the American Society of Clinical Oncology	18	19	3378-83

Miura 2015	Impact of chemotherapy on survival in surgically resected retroperitoneal sarcoma	Miura, J. T.; Charlson, J.; Gamblin, T. C.; Eastwood, D.; Banerjee, A.; Johnston, F. M.; Turaga, K. K.	2015	European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology	41	10	1386-92
Perez 2007	Retroperitoneal and truncal sarcomas: prognosis depends upon type not location	Perez, Eduardo A.; Gutierrez, Juan C.; Moffat, Frederick L., Jr.; Franceschi, Dido; Livingstone, Alan S.; Spector, Seth A.; Levi, Joe U.; Sleeman, Danny; Koniaris, Leonidas G.	2007	Annals of surgical oncology	14	3	1114-22
Saracoglu 2022	Retrospective analysis of pelvic and retroperitoneal sarcomas. Single center's experience	Saracoglu, C.; Akyuz, C.; Gulmez, M.	2022	Annali Italiani di Chirurgia	93		195-201
Schwartz 2019	Predictors of disease-free and overall survival in retroperitoneal sarcomas: A modern 16-year multi-institutional study from the United States sarcoma collaboration (USSC)	Schwartz, Patrick B.; Vande Walle, Kara; Winslow, Emily R.; Abbott, Daniel E.; Ethun, Cecilia G.; Cardona, Kenneth; Tran, Thuy B.; Poultsides, George; Tseng, Jennifer; Roggin, Kevin; Grignol, Valerie; Howard, John Harrison; Krasnick, Bradley A.; Fields, Ryan C.; Mogal, Harveshp; Clarke, Callisia N.; Senehi, Rebecca; Votanopoulos, Konstantinos	2019	Sarcoma	2019		5395131
Singer 1995	Prognostic factors predictive of survival for truncal and retroperitoneal soft-tissue sarcoma	Singer, S.; Corson, J. M.; Demetri, G. D.; Healey, E. A.; Marcus, K.; Eberlein, T. J.	1995	Annals of surgery	221	2	185-95

Stahl 2017	The effect of microscopic margin status on survival in adult retroperitoneal soft tissue sarcomas	Stahl, J. M.; Corso, C. D.; Park, H. S.; An, Y.; Rutter, C. E.; Roberts, K. B.; Han, D.	2017	European Journal of Surgical Oncology	43	1	168-174
Zhuang 2022	Prognostic Factors and Nomogram Construction for First Local Recurrent Retroperitoneal Sarcoma Following Surgical Resection: A Single Asian Cohort of 169 Cases	Zhuang, A.; Lu, W.; Fang, Y.; Ma, L.; Xu, J.; Wang, J.; Tong, H.; Zhang, Y.	2022	Frontiers in Oncology	12		856754

Appendix 11. Evidence Summary Topic 2 Question 4 Systematic Review

First Author	Year	Country	Patient source	Study period	Design	Inclusion	Exclusion	Overall no. of patient	No. patient with chemotherapy	over 50 or 100	liz calc of chemo pt/ total patients	Neoadjuvant chemotherapy	Adjuvant chemotherapy	Overall survival	Long term survival	5 year survival	Short term survival	subtype specific survival	local	Local recurrence	Recurrence Free survival	5 year recurrence free survival	Multivariate analysis	other endpoint	Comments
Choulias (1)-RT	2019	USA	US Sarcoma Collaboration (8 centres)	2000-2016	Retrospective cohort study	Non-metastatic Retroperitoneal sarcoma, adults	intraoperative RT or brachytherapy	425	80	50	19%	21	59	Sx+NeoCx vs Sx: HR 0.9 (p=0.41), Sx+AjdCx vs Sx: HR 1.15 (p=0.66)					y	Sx+NeoCx vs Sx: HR 1.09 (p=0.88), Sx+AjdCx vs Sx: HR 0.92 (p=0.85)	Sx+NeoCx vs Sx: HR 0.75 (p=0.46), Sx+AjdCx vs Sx: HR 0.87 (p=0.59)				Role of radiation therapy
AKAGUNDUZ	2021	Turkey	10 experienced Turkish med onc departments	2000-2020	Case Series	Retroperitoneal study, curative intent resection of primary non-metastatic RPS without neoadjuvant therapy	Metastatic disease, <18 years, neoadjuvant chemotherapy or radiotherapy, ewings family sarcoma, alveolar or embyronal rhabdomyosarcoma, GIST, desmoid, gyncaecological sarcoma, patients with missing data	197	n=62 with chemo only, n=65 with chemo and RT	50	64%	0	n=62 with chemo only, n=65 with chemo and RT	CT only: median 95 months (61.1-128.9) univariate; CT+RT median 74 (62.6-128.9) univariate, overall interaction p=0.421							CT only: median 35 (24.2-45.8) univariate, CT+RT: median 50 (23.5-76.6) univariate, overall interaction p=0.215				
BREDBECK	2022	USA	Single centre	January 1998-January 2015	Case series	Sarcoma origintating within abdomen, retroperitoneum, pelvis	Unresectable based on surgeon notes. Metastatic didsease, GIST, visceral sarcoma, abdomen wall sarcoma	159	77 (37 patients had CT+RT, unclear whether combination included or was separate to systemic therapy	50	44/28% adjuvant and 33/21% neoadjuvant	33	44												No statistics reported for outcomes. One comment in results section: "Systemic Therapy was not associated with improved DFS or abdominal RFS, including adjuvant and neoadjuvant subgroups and after adjusting for grade and resection margin." It does state that "Systemic therapy was used more commonly in high-grade tumours (p<0.001). Systemi therapy was used more commonly in younger patients (P<0.0001)". "There was no difference in systemic therapy utilisation based on tumour size or location"
gronchi 2008	2008	Italy	Single centre	January 1985 - September 2007	Case series	RPS, first seen at institute for primary disease or for first relapse, who received operation	Metastatic disease	288	91	50	31.6%	Unknown	Unknown	Multivariate analysis: Sx+CT vs SX: HR 1.3 (0.86-1.97), p=0.211							Multivariate Sx+Cx vs SX: HR 1.26(0.8-1.97), p=0.314			Yes	MFS multivariate Sx+Cx vs SX: HR 0.72 (0.39-1.34), p=0.2991	

Kloosterr	2016	USA	National Cancer Database	1998-2011	Case series	Retroperitoneal sarcoma, R2, adults		395	122	100	31%	unknown	unknown	Sx+Cx vs Sx: HR 1.09 (95% CI: 0.83-1.45), p=0.51	>5 yr Sx+Cx vs Sx: HR 2.15 (95%CI 1.21-3.18, p=0.009		<3 years Sx+Cx vs Sx: HR0.69 (95% CI 0.5-0.95), p=0.024)									
Datta	2007	USA	National Cancer Database	2004-2013	Retrospective cohort study	Curative intent resection of primary non-metastatic retroperitoneal sarcoma, adults	Neoadjuvant chemotherapy, palliative treatment, death within 90 days of surgery	3892	390	100	10%	0	390	Sx+Cr vs Sx: HR 1.3 (95%CI 1.05-1.61) p=0.017; median 47.8 vs 68.9 months									Yes, see attached sheet 2 for further subgroup analysis		Data performed on propensity matched cohorts. Univariate analysis demonstrated significant differences in pa- tient and tumor features in the SA and AC cohorts (i.e., age, race, Charlson comorbidity score, insurance status, geographic region, facility type, histologic subtype, tumor size, grade, and the presence of adjacent organ invasion)
Schwartz	2019	USA	US Sarcoma Collaboration	2000-2016	Case series	Primary retroperitoneal sarcoma, surgical resection	recurrent disease	571	19 with chemo only, but 111 with chemo+RT	100	19%	Unknown	Unknown	ALL: Sx+Cx vs Sx: HR 2.65 (95%CI1.4-4.99) p<0.01; LIPOSARCOMA: neoadj p=0.10, adj p=1.00; LEIMYOSARCOMA: adj p=1.00					y		ALLL Sx+NeoCr vs S: P=0.16, Sx+AdjCx vs Sx: HR 0.64; LIPOSARCOMA - neoadj p=0.54, adj p=0.13, LEIOMYOSARCOMA - neoadj p=0.71, adj p=0.66		Yes		Unclear whether analysis included 19+111 patients with chemo
Miura 2015	2015	USA	USA National Cancer Database	1998-2011	Case series	path confirmed RPS, of named subtypes, that underwent surgical resection with curative intent	Patients with unknown chemotherapy status, presence of metastatic disease at diagnosis, pediatric sarcoma histologies (e.g.,alveolar, embryonal rhabdomyosarcoma, desmoplastic small round cell tumor), and neoplasms that were not of sarcoma histology were excluded from the analysis.	8653	1525	100	18%	163	490	unmatched: surg 68.2m, surg and chemo 40m, p 0.001; propensity matched (n=3050): surg 52.4m, surg and chemo 40m, p 0.002. multivariate: impact of chemo on survival: surg+chemo HR 1.17 (95 CI 1.04-1.31, P 0.009)									Yes, see attached sheet for further subgroup analysis		Imbalance of patient numbers; n=7128 surgery alone, n=1525 surgery+chemo.Surgery alone cohort slightly older (median age 62 v 55 years), higher % of tumours > 20cm (26.6% v 17.7%), less high grade (21.2% v 30.2% though unknown= 34.7% v 53%), less R2 (14 v 20.6%), less RT (24.8 v 30.2%); also 860 patients treatment sequence unknown (whether neoadjuvant or adjuvant)

Ma 2020	2020	USA	USA National Cancer Database	2006-2015	Case series	Non metastatic, resectable retroperitoneal sarcoma. surg alone or surgical procedure following preoperative chemotherapy or radiation.	nil recorded	6814+193; matched cohort 186+186	non matched n=193; matched n=186	100	3%	non matched n=193; matched n=186	0	non matched surg v surg+chemo (all) HR 1.55 (95 CI 1.27-1.88) P <0.01; matched surg v surg+chemo HR 1.44 (95 CI 1.07-1.94) P <0.02										Compared with preoperative radiation therapy, preoperative chemotherapy was associated with lower overall survival in 169 matched pairs (HR, 1.58; 95%CI, 1.15-2.18; P = .005)	main discrepancies very few chemo cases; is in whole cohort: n=6814 surgery alone with n= 193 surgery + chemo.
CALLEGARO	2021	International - Canada, UK, USA, Netherlands, France, Poland	10 centres	January 2002-April 2017	Case Series	>=16 years with primary (nonrecurrent), nonmetastatic RFS who underwent surgery with curative intent	Ewings family sarcoma, alveolar or embyronal rhabdomysarcoma, GIST< desmoid, gyncaelogic sarcoma	1942	293	100		Unknown	Unknown	Multivariate: SX+CT vs SX: No HR 1.27 (1.03-1.56), p=0.021									Yes	Disease specific survival multivariate Sx+CT vs SX: HR 1.33 (1.26-1.66), p=0.011	"over time, noted a drecrease in pre- and/or postoperative chemotherapy (12.5% in t3 vs 17.6% in t1, p=0.008)"
STAHL	2016	USA	National Cancer Database	1998-2012	Case Series	LPS, LMS, other more common sarcoma histologies, non metastatic, adult, RPS, no previous cancers, R0 or R1 resection	<=17 years, prior cancer, metastatic disease, surgery not performed, R2 resection, non adult sarcoma histology, diagnosis in 2012 with insufficient followup, missing values for variables of interest, nonoverlapping propensity score values	4015	445	100	11%	Unknown	Unknown	No chemo vs chemo: HR 0.74 (0.6-0.9), p=0.003, univariate									no chemo vs chemo: HR 0.82 (0.67-0.99), p=0.112	Association with R1 resection: receipt of chemotherapy vs. none (OR 1.58, 95% CI 1.27e1.95, p < .001)	"Propensity score matching produced a cohort of 1480 patients, which were well matched on all factors found to be significant predictors of final resection margin status or OS (Table S2). Propensity score matching confirmed a survival benefit based on margin status (R0 vs. R1, HR 0.74, 95% CI 0.62e0.88, p < .001)" No stats on what impact of propensity score matching for outcomes related to chemotherapy. Only 193 patients received chemotherapy with known sequence in relation to surgery. The majority of these (140/193, 72.5%) received chemotherapy after surgery

gronchi 2011	2011	Italty	Single centre	January 1985 - December 2008 (built from data in Gronchi 2008)	Case series	RPS, first seen at institute for primary disease or for first relapse, who received operation	Metastatic disease	331	109	100	33%	Unknown	Unknown	Multivariate: SX+CT vs SX: HR 1.14 (0.74-1.75), p=0.541						Multivariate Sx+Cx vs SX: HR 1.34 (0.88-2.05), p=0.1771				MFS multivariate Sx+Cx vs SX: HR 0.66 (0.36-1.2), p=0.169	
Gholami	2009	USA	Stanford Hospital and Clinics	1996 - 2007	Case series	Retroperitoneal sarcoma, adults	GIST, DSRCT	41	8	n	20%	6	3			Sx+Cx vs Sx: 43vs 30% (p=0.57)						Sx+Cx vs Sx: 12 vs 33% (p=0.87)			1 person had both Neoadjuvant and adjuvant chemo
Singer	1995	USA	Brigham and Women's Hospital and Dana Farcer Cancer institue	1970 - 1994	Case series	Truncal and retroperitoneal sarcoma, adults		183 (83 retroperitoneal only)	33 retroperitoneal	n	40%	15	18	Sx+NeoCx vs Sx: HR 1.52 (p=0.48), Sx+AdjCx vs Sx: HR 1.09 (p=0.010)	12 yr: Sx 76%, Sx+NeoCx 40%, Sx+AdjCx 38%										
Bremjit 2014	2014	USA	u. washington sarcoma unit database	2000-2013	Case series	Primary retroperitoneal sarcoma, surgical resection	nil recorded	132	28	n	21%	28	0	ALL: Sx+NACT vs Sx: HR 1.6 (95%CI 0.8-3.2) p<0.17							ALL: Sx+NACT vs Sx: HR 1.4 (95%CI 0.9-2.3) p<0.16				High-grade tumors made up a significantly greater proportion of tumors receiving neoadjuvant chemotherapy (53.6 %) than in the entire series (27.2 %). Of 132 patients identified; 28 (21.2 %) patients received neoadjuvant chemotherapy. Receipt of post operative chemotherapy was not detailed.
Choulias 2019 (2) study 801 pat recurrence	2019 (2)	USA	8 USA institutions	2000-2016	Case series	Primary retroperitoneal sarcoma, surgical resection	Patients with desmoid tumors, multifocal or metastatic disease at presentation, palliative intent resection, or incomplete survival data were excluded	498	31	n	6%	31	0						y	local recur rate after NACT= 23/31, p 0.04 (p value reflects 'more patients in the recurrence group had chemotherapy, P = .04').					very few received NACT; only 34 v 498 surg only. Study aim was to identify patterns of recurrence and its impact on OS
Kilkenny 1996	1996	USA	Uni Floria patients	1970-1994	Case series	Primary retroperitoneal sarcoma, surgical resection	Any sarcomas with an origin in the gastrointestinal tract, genitourinary system, bony tissues, or embryonic remnants were excluded. Also excluded were metastatic tumours lymphomas, desmoid tumours, and aggressive fibromatoses.	63	26	n	41%	0	chemo and ECRT n=17; adj chemo alone n=9	None of these [adjuvant] regimens gave a survival advantage'. 'table 3: effect of variables on survival; ...adjuvant therapy- 0.64 (p value)' HR not provided, appears to represent OS										grouped multiple adjuvant interventions (inc chemo+RT, RT alone)

Perez 2007	2007	USA	Tumour registries Uni Miami Sylvester Cancer Center + Jackson Memorial Hospital.	1977-2004	retrospective case series	Sarcomas of the trunk and retroperitoneum,primary and recurrence	Angiosarcomas, cystosarcomas ,desmoid tumors and Kaposi sarcomas were excluded. Tumors involving theshoulder girdle or hip joint were not included in the analysis. Patients withmissing data were excluded from each respectiveuniv ariate and multivariate analysis.	combined truncal+rps: N=189+123. RPS n=123 (surg 84, surg+chemo 38)	RPS n=38	n	31%	Unknown	Unknown	median surival RPS: surg 86m, surg + chemo 53m	see attached for median, 5-, 10-, 20-year survival of **combined truncal + RPS** (n=189/123)			see attached sheet							analyses were of sarcomas of the trunk and retroperitoneum
Meric 2000	2000	USA	MD anderson tumour registry	1991-1996	Case series	Potentially resectable primary soft tissue sarcoma	"patients with; recurrent sts; primary tumours in H+N, CNS, uterus, ovary; histological types: osteosarcoma, cytosarcoma phyllodes, post mastectomy Angiosarcomas, kaposi's sarcoma, desmond fibrzomatosis, dermatofibrosarcoma protruberans; "	RPS n=108(34 NACT+74 surg)	34	n	31%	34	0												post op morbidity outcomes, see attached tab	Review of neo adjuvant chemotherapy only and was compared with patients **who may have received post op chemo** as the purpose was to test the hypothesis that neoadjuvant chemotherapy (NeoCT) does not increase morbidity in patients undergoing radical surgery. In allcomers (extremity and retroperitoneal/vsiceral) NeoCT patients had larger tumors (median,12v8 cm), more frequently had high-grade tumors(90%v64%), and were younger (median age 47v55years).
SARACOGLU	2022	Turkey	Single centre	2011-2018	Case Series	>=18 years, RPS	Diffuse disease, <18 years, synchronous tumours, pregnancy, uncontrolled metabolic disease, gyncaecoloical/skeletal or abdominal tumours such as GIST, small round blue cell tumours, osteosarcoma, chrondosarcoma and desmoid	25	CT only n=6, CT+RT n=5	n	44%	0	CT only n=6, CT+RT n=5	CT only: mean 27.5 months +/- 9.09 SD), CT+RT: mean months 37.4 months +/- 8.02, interaction p=0.342											

ZHUANG	2022	China	Single centre	January 2011-September 2020	Case series	RPS, dedifferenciated LPS, LMS, MPNST, SFT, other histologies, first relapse, complete followup	Metastatic disease	169	17	n	10%	Unknown	Unknown	SX+CT vs SX: HR 1.047 (1.014-1.081), p=0.005 univariate							SX+CT vs SX: HR 1.025 (0.998-1.052), p=0.075 univariate		Chemotherapy not associated with RFS on multivariate analysis, however remained significant for OS (HR1.04, 10.006-1.075, p=0.020)		Used data at primary surgery as this paper was investigating prognostic factors and contructed a normogram for first local recurrent RPS following survical resection
Li	2021	China	Systematic review and meta-analysis	January 2000-December 2020	Systematic review and meta-analysis	Adjuvant therapy (chemo or RT), trials - RCT, case control, retrospective cohort) of adjuvant therapy versus surgery for RPS patients, pathological comfirmation of RPS	Letter, editorial, noncomparative sutdy; cases of groups in the study were less than 20 and 5 respectively, if HR and 95%CI could not be extracted from studies, non human studies	Overall - n=30864 (15 studies), chemotherapy studies n=9342 (n=6)	2882	100	31%			SX+CX vs SX: HR = 1.11, 95% CI 0.95–1.29; P = 0.19; Notable heterogenity in trials - sensitivity analysis indicated that patients benefited more from surgery alone than ACT (HR = 1.19, 95% CI 1.08–1.30; P = 0.0002).							SX+CX vs SX: HR = 1.30, 95% CI 0.96–1.77; P = 0.09), no statistical heterogeneity was found. Based on the two gronchi studies (with same data set)			MFS was reported by two studies in ACT versus surgery (Based on the two gronchi studies (with same data set)) 1238 participants. There was no statistical significance between the two comparisons (HR = 0.69, 95%CI 0.45–1.06; P = 0.09), no statistical heterogeneity was found	
gronchi	2016	italy	6 European and 2 North American institutions-data collected from prospectively maintained surgical databases	january 2002 and December 2011	retrospective case series	primary retroperitoneal sarcoma	Ewing sarcoma, alveolar/embryonal rhabdomyosarcomas, desmoid tumors, gynecological sarcomas, and GIST were excluded.	824	124	100	15%	Unknown	Unknown	SX+CX vs SX: HR 1.17 (95% CI 0.86, 1.57) p 0.314						SX+CX vs SX: HR 1.22 (95% CI 0.86, 1.74) p 0.271				Distant recurrence: SX+CX vs SX: HR 1.12 (95% CI 0.81, 1.55) p 0.492	demographics of chemo group not provided.

Appendix 12. Quality Assessment for Topic 2 Question 4 Systematic Review

Study	First Authors	Reviewer	NHMRC Level of Evidence	Risk of Bias (Newcastle Ottawa scale for cohort study)			
				Selection	Comparability	Outcome	Overall
216	Stahl	1	III-2	3	1	2	Good
216	Stahl	2	III-2	3	1	2	Good
		Final	III-2	3	1	2	Good
247	singer	1	III-2	3	1	2	Good
247	singer	2	III-2	3	1	2	Good
		Final	III-2	3	1	2	Good
277	schwartz	1	III-2	3	1	1	Poor
277	Schwartz	2	III-2	3	1	1	Poor
		Final	III-2	3	1	1	Poor
445	miura	1	III-2	4	1	2	Good
445	Miura	2	III-2	4	1	2	Good
		Final	III-2	4	1	2	Good
458	meric	1	III-2	4	1	2	Good
458	Meric	2	III-2	4	1	2	Good
		Final	III-2	4	1	2	Good
516	ma	1	III-2	4	1	2	Good
516	Ma	2	III-2	4	1	2	Good
		Final	III-2	4	1	2	Good
612	klooster	1	III-2	3	0	1	Poor
612	Klootser	2	III-2	3	0	1	Poor
		Final	III-2	3	0	1	Poor
669	perez	1	III-2	4	1	2	Good
669	Perez	2	III-2	4	1	2	Good
		Final	III-2	4	1	2	Good
768	datta	1	III-2	4	1	2	Good
768	Datta	2	III-2	4	1	2	Good
		Final	III-2	4	1	2	Good
799	chouliaras RT	1	III-2	3	1	1	Poor
799	CHOUL 799	2	III-2	3	1	1	Poor
		Final	III-2	3	1	1	Poor
801	chouliaras	1	III-2	3	0	2	Poor
801	CHOUL 801	2	III-2	3	0	2	Poor
		Final	III-2	3	0	2	Poor
867	bremjit	1	III-2	3	0	1	Poor
867	Bremjit	2	III-2	3	0	1	Poor

		Final	III-2	3	0	1	Poor
959	kilkenny	1	III-2	3	0	1	Poor
959	Kilkenny	2	III-2	3	0	2	Poor
		Final	III-2	3	0	2	Poor
1142	gholami	1	III-2	3	0	1	Poor
1142	gholami	2	III-2	3	0	1	Poor
		Final	III-2	3	0	1	Poor
1268	akagunduz	1	III-2	3	0	1	Poor
1268	Akagunduz	2	III-2	3	0	1	Poor
		Final	III-2	3	0	1	Poor
1276	bredbeck	1	III-2	3	1	2	Good
1276	Bredbeck	2	III-2	3	1	2	Good
		Final	III-2	3	1	2	Good
1280	Callegaro	1	III-2	3	1	2	Good
1280	Callegaro	2	III-2	3	1	2	Good
		Final	III-2	3	1	2	Good
1331	Li	1	Meta-analysis but not Level 1 evidence	NA			
1331	Li	2		NA			
		Final					
1360	Saracoglu	1	III-2	3	0	1	Poor
1360	Saracoglu	2	III-2	3	0	1	Poor
		Final	III-2	3	0	1	Poor
1396	Zhuang	1	III-2	3	0	2	Poor
1396	Zhuang	2	III-2	3	0	2	Poor
		Final	III-2	3	0	2	Poor
1398	Gronchi 2009	1	III-2	3	1	2	Good
1398	Gronchi 2009	2	III-2	3	1	2	Good
		Final	III-2	3	1	2	Good
1399	Gronchi 2012	1	III-2	3	1	2	Good
1399	Gronchi 2012	2	III-2	3	1	2	Good
		Final	III-2	3	1	2	Good
1400	Gronchi 2016	1	III-2	3	1	2	Good
1400	Gronchi 2016	2	III-2	3	1	2	Good
		Final	III-2	3	1	2	Good

Appendix 13. Studies included in Topic 3 Question 4 Systematic Review

Title	Authors	Published Year	Journal	Volume	Issue	Pages
Does consolidation with autologous stem cell transplantation improve the outcome of children with metastatic or relapsed Ewing sarcoma?	Al-Faris, N.; Al Harbi, T.; Goia, C.; Pappo, A.; Doyle, J.; Gassas, A.	2007	Pediatric Blood & Cancer	49	2	190-5
High-dose busulphan/melphalan with autologous stem cell rescue in Ewing's sarcoma	Atra, A.; Whelan, J. S.; Calvagna, V.; Shankar, A. G.; Ashley, S.; Shepherd, V.; Souhami, R. L.; Pinkerton, C. R.	1997	Bone Marrow Transplantation	20	10	843-6
Comparison of the treatment results after conventional and myeloablative chemotherapy in patients with poor prognosis Ewing's sarcoma family tumors - single center experience	Avramova, B.; Jordanova, M.; Konstantinov, D.; Hristozova, I.; Shtarbanov, I.; Bobev, D.	2011	Journal of B.U.On.	16	3	551-6
Sequential high-dose chemotherapy for children with metastatic rhabdomyosarcoma	Bisogno, G.; Ferrari, A.; Prete, A.; Messina, C.; Basso, E.; Cecchetto, G.	2009	European Journal of Cancer	45		3035â€304 1
High-dose induction chemoradiotherapy followed by autologous bone marrow transplantation as consolidation therapy in rhabdomyosarcoma, extraosseous Ewing's sarcoma, and undifferentiated sarcoma	Boulad, F.; Kernan, N. A.; LaQuaglia, M. P.; Heller, G.; Lindsley, K. L.; Rosenfield, N. S.; Abramson, S. J.; Gerald, W. L.; Small, I. N.; Gillio, A. P.; Gulati, S. C.; O'Reilly, R. J.; Ghavimi, F.	1998	Journal of Clinical Oncology	16(5)		1697-1706
European intergroup studies (MMT4-89 and MMT4-91) on childhood metastatic rhabdomyosarcoma: final results and analysis of prognostic factors	Carli, M.; Colombatti, R.; Oberlin, O.; Bisogno, G.; Treuner, J.; Koscielniak, E.; Tridello, G.; Garaventa, A.; Pinkerton, R.; Stevens, M.	2004	Journal of Clinical Oncology	22	23	4787-94

High-dose melphalan with autologous stem-cell rescue in metastatic rhabdomyosarcoma	Carli, M.; Colombatti, R.; Oberlin, O.; Stevens, M.; Masiero, L.; Frascella, E.; Koscielniak, E.; Treuner, J.; Pinkerton, C. R.	1999	Journal of Clinical Oncology	17	9	2796-803
High-dose busulfan and melphalan as conditioning regimen for autologous peripheral blood progenitor cell transplantation in high-risk ewing sarcoma patients: A long-term follow-up single-center study	Diaz, M. A.; Lassaletta, A.; Perez, A.; Sevilla, J.; Madero, L.; Gonzalez-Vicent, M.	2010	Pediatric Hematology and Oncology	27(4)		272-282
High-Dose Chemotherapy Compared With Standard Chemotherapy and Lung Radiation in Ewing Sarcoma With Pulmonary Metastases: results of the European Ewing Tumour Working Initiative of National Groups, 99 Trial and EWING 2008	Dirksen, U.; Brennan, B.; Le Deley, M. C.; Cozic, N.; van den Berg, H.; Bhadri, V.; Brichard, B.; Claude, L.; Craft, A.; Amler, S.; et al.,	2019	Journal of Clinical Oncology	37	34	3192â€320 2
Consolidation of first-line therapy with busulfan and melphalan and autologous stem cell rescue in children with Ewing sarcoma	Drabko, K.; Raciborska, A.; Bilska, K.; Choma, M.; Wojcik, B.; Zaucha-Prazmo, A.; Gorczynska, E.; Ussowicz, M.; Styczynski, J.; Skoczen, S.; Wozniak, W.; Chybicka, A.; Wysocki, M.; Gozdzik, J.; Kowalczyk, J.	2011	Bone Marrow Transplantation	1)		S88-S89
Megachemotherapy followed by autologous stem cell transplantation in children with Ewing's sarcoma	Drabko, K.; Zawitkowska-Klaczynska, J.; Wojcik, B.; Choma, M.; Zaucha-Prazmo, A.; Kowalczyk, J.; Gorczynska, E.; Toporski, J.; Kalwak, K.; Turkiewicz, D.; Chybicka, A.	2005	Pediatric Transplantation	9	5	618-21
Nonmetastatic Ewing family tumors: high-dose chemotherapy with stem cell rescue in poor responder patients. results of the Italian Sarcoma Group/Scandinavian Sarcoma Group III protocol	Ferrari, S.; Hall, K. S.; Luksch, R.; Tienghi, A.; Wiebe, T.; Fagioli, F.; Alvegard, T. A.; del Prever, A. B.; Tamburini, A.; Alberghini, M.; et al.,	2011	Annals of Oncology	22	5	1221â€122 7
Post-relapse survival in patients with Ewing sarcoma	Ferrari, S.; Luksch, R.; Hall, K. S.; Fagioli, F.; Prete, A.; Tamburini, A.; Tienghi, A.; DiGirolamo, S.; Paioli, A.; Abate, M. E.; Podda, M.; Cammelli, S.; Eriksson, M.; Brach del Prever, A.	2015	Pediatric Blood & Cancer	62	6	994-9

Myeloablative therapy with autologous stem cell rescue for patients with Ewing sarcoma	Gardner, S. L.; Carreras, J.; Boudreau, C.; Camitta, B. M.; Adams, R. H.; Chen, A. R.; Davies, S. M.; Edwards, J. R.; Grovas, A. C.; Hale, G. A.; Lazarus, H. M.; Arora, M.; Stiff, P. J.; Eapen, M.	2008	Bone Marrow Transplantation	41	10	867-72
Risk adapted chemotherapy for localised Ewing's sarcoma of bone: the French EW93 study	Gaspar, N.; Rey, A.; Berard, P. M.; Michon, J.; Gentet, J. C.; Tabone, M. D.; Roche, H.; Defachelles, A. S.; Lejars, O.; Plouvier, E.; Schmitt, C.; Bui, B.; Boutard, P.; Taque, S.; Munzer, M.; Vannier, J. P.; Plantaz, D.; Entz-Werle, N.; Oberlin, O.	2012	European Journal of Cancer	48	9	1376-85
A review of 331 rhabdomyosarcoma cases in patients treated between 1991 and 2002 in Japan	Hosoi, H.; Teramukai, S.; Matsumoto, Y.; Tsuchiya, K.; Iehara, T.; Hara, J. I.; Mitsui, T.; Kaneko, M.; Hatae, Y.; Hayashi, Y.; Mabuchi, O.; Adachi, N.; Morikawa, Y.; Nishimura, S. I.; Kumagai, M.; Takamatsu, H.; Sawada, T.; Sugimoto, T.	2007	International Journal of Clinical Oncology	12(2)		137-145
High-dose Thiotepa as Consolidation Therapy With Autologous Hematopoietic Stem Cell Transplantation for High-risk Ewing Family Tumors: Single-institution Experience	Jahnukainen, K.; Kallio, P.; Koivusalo, A.; Saarinen-Pihkala, U. M.	2015	Journal of Pediatric Hematology/Oncology	37	7	536-42
Clinical results of high-dose chemotherapy followed by autologous peripheral blood stem cell transplantation in children with advanced stage rhabdomyosarcoma	Kim, N. K.; Kim, H. S.; Suh, C. O.; Kim, H. O.; Lyu, C. J.	2012	Journal of Korean Medical Science	27	9	1066-72
Treatment of children with metastatic soft tissue sarcoma with oral maintenance compared to high dose chemotherapy: report of the HD CWS-96 trial	Klingebiel, T.; Boos, J.; Beske, F.; Hallmen, E.; Int-Veen, C.; Dantonello, T.; Treuner, J.; Gadner, H.; Marky, I.; Kazanowska, B.; Koscielniak, E.	2008	Pediatric Blood & Cancer	50	4	739-45
Primary disseminated multifocal Ewing sarcoma: results of the Euro-EWING 99 trial	Ladenstein, R.; Potschger, U.; Le Deley, M. C.; Whelan, J.; Paulussen, M.; Oberlin, O.; van den Berg, H.; Dirksen, U.; Hjorth, L.; Michon, J.; Lewis, I.; Craft, A.; Jurgens, H.	2010	Journal of Clinical Oncology	28	20	3284-91
Long-term follow up of high-dose chemotherapy with autologous	Laurence, V.; Pierga, J. Y.; Barthier, S.; Babinet, A.; Alapetite, C.; Palangie, T.; de Pinieux, G.; Anract, P.; Pouillart, P.	2005	American Journal of Clinical Oncology	28	3	301-9

stem cell rescue in adults with Ewing tumor						
Multimodality diagnostics and megatherapy in poor prognosis Ewing's tumor patients. A single-center report	Laws, H. J.; Burdach, S.; van Kaick, B.; Engel, B.; Dirksen, U.; Korholz, D.; Pape, H.; Kahn, T.; Merck, H.; Schmitz, M.; Heyll, A.; Dockhorn-Dworniczak, B.; Jurgens, H.; Gobel, U.	1999	Strahlentherapie und Onkologie	175	10	488-94
Myeloablative therapy against high risk Ewing's sarcoma: A single institution experience and literature review	Lopez, J. L.; Perez, C.; Marquez, C.; Cabrera, P.; Perez, J. M.; Ramirez, G. L.; Ordonez, R.; Praena-Fernandez, J. M.; Ortiz, M. J.	2011	Reports of Practical Oncology & Radiotherapy	16	5	163-9
Tandem high-dose chemotherapy strategy as first-line treatment of primary disseminated multifocal Ewing sarcomas in children, adolescents and young adults	Loschi, S.; Dufour, C.; Oberlin, O.; Goma, G.; Valteau-Couanet, D.; Gaspar, N.	2015	Bone Marrow Transplantation	50	8	1083-8
Megatherapy in children with high-risk Ewing's sarcoma in first complete remission	Madero, L.; Munoz, A.; Sanchez de Toledo, J.; Diaz, M. A.; Maldonado, M. S.; Ortega, J. J.; Ramirez, M.; Otheo, E.; Benito, A.; Salas, S.	1998	Bone Marrow Transplantation	21	8	795-9
The treatment of Ewing's sarcoma of bone at the University of Florida: 1969 to 1998	Marcus Jr, R. B.; Berrey, B. H.; Graham-Pole, J.; Mendenhall, N. P.; Scarborough, M. T.	2002	Clinical Orthopaedics and Related Research		397	290-297
Possible benefits of high-dose chemotherapy as intensive consolidation in patients with high-risk rhabdomyosarcoma who achieve complete remission with conventional chemotherapy	Matsubara, H.; Makimoto, A.; Higa, T.; Kawamoto, H.; Takayama, J.; Ohira, M.; Yokoyama, R.; Beppu, Y.; Takaue, Y.	2003	Pediatric Hematology and Oncology	20(3)		201-210
Impact of high-dose busulfan plus melphalan as consolidation in metastatic Ewing tumors: a study by the Societe Francaise des Cancers de l'Enfant	Oberlin, O.; Rey, A.; Desfachelles, A. S.; Philip, T.; Plantaz, D.; Schmitt, C.; Plouvier, E.; Lejars, O.; Rubie, H.; Terrier, P.; Michon, J.; Societe Francaise des Cancers de, l'Enfant	2006	Journal of Clinical Oncology	24	24	3997-4002
Primary metastatic (stage IV) Ewing tumor: survival analysis of 171 patients from the EICESS studies. European Intergroup	Paulussen, M.; Ahrens, S.; Burdach, S.; Craft, A.; Dockhorn-Dworniczak, B.; Dunst, J.; Frohlich, B.; Winkelmann, W.; Zoubek, A.; Jurgens, H.	1998	Annals of Oncology	9	3	275-81

Cooperative Ewing Sarcoma Studies						
Long-Term Follow-up of High-Dose Chemotherapy with Autologous Stem Cell Transplantation in Children and Young Adults with Metastatic or Relapsed Ewing Sarcoma: A Single-Institution Experience	Pawlowska, A. B.; Sun, V.; Calvert, G. T.; Karras, N. A.; Sato, J. K.; Anderson, C. P.; Cheng, J. C.; DiMundo, J. F.; Femino, J. D.; Lu, J.; Yang, D.; Dagis, A.; Miser, J. S.; Rosenthal, J.	2021	Transplantation and Cellular Therapy	27	1	72.e1-72.e7
The value of high-dose chemotherapy in patients with first relapsed Ewing sarcoma	Rasper, M.; Jabar, S.; Ranft, A.; Jurgens, H.; Amler, S.; Dirksen, U.	2014	Pediatric Blood & Cancer	61	8	1382-6
High-dose therapy with hematopoietic stem cell rescue in patients with poor prognosis Ewing family tumors	Rosenthal, J.; Bolotin, E.; Shakhnovits, M.; Pawlowska, A.; Falk, P.; Qian, D.; Oliver, C.; Sato, J.; Miser, J.; Forman, S.	2008	Bone Marrow Transplantation	42	5	311-8
Ewing's sarcoma family of tumors in Finland during 1990-2009: a population-based study	Serlo, J. A.; Helenius, I. J.; Sampo, M.; Vettenranta, K.; Saarinen-Pihkala, U. M.; Kivivuori, S. M.; Riikonen, P.; Kivioja, A.; Bohling, T.; Kallajoki, M.; Ristimaki, A.; Vasama, K.; Tarkkanen, M.	2013	Acta Oncologica	52	4	767-75
Outcome after relapse in an unselected cohort of children and adolescents with Ewing sarcoma	Shankar, A. G.; Ashley, S.; Craft, A. W.; Pinkerton, C. R.	2003	Medical & Pediatric Oncology	40	3	141-7
High-Dose Chemotherapy with Blood or Bone Marrow Transplants for Rhabdomyosarcoma	Stiff, P. J.; Agovi, M. A.; Antman, K. H.; Blaise, D.; Camitta, B. M.; Cairo, M. S.; Childs, R. W.; Edwards, J. R.; Gale, R. P.; Hale, G. A.; Lazarus, H. M.; Arora, M.	2010	Biology of Blood and Marrow Transplantation	16(4)		525-532
High-dose chemotherapy and blood autologous stem-cell rescue compared with standard chemotherapy in localized high-risk ewing sarcoma: Results of Euro-E.W.I.N.G.99 and Ewing-2008	Whelan, J.; Le Deley, M. C.; Dirksen, U.; Teuff, G. L.; Brennan, B.; Gaspar, N.; Hawkins, D. S.; Amler, S.; Bauer, S.; Bielack, S.; Blay, J. Y.; Burdach, S.; Castex, M. P.; Dilloo, D.; Eggert, A.; Gelderblom, H.; Gentet, J. C.; Hartmann, W.; Hassenpflug, W. A.; Hjorth, L.; Jimenez, M.; Klingebiel, T.; Kontny, U.; Kruseova, J.; Ladenstein, R.; Laurence, V.; Lervat, C.; Marec-Berard, P.; Marreaud, S.; Michon, J.; Morland, B.; Paulussen, M.; Ranft, A.; Reichardt, P.; Van Den Berg, H.; Wheatley, K.; Judson, I.; Lewis, I.; Craft, A.; Juergens, H.; Oberlin, O.	2018	Journal of Clinical Oncology	36(31)		3110-3119

Metastatic rhabdomyosarcoma: a retrospective review of patients treated at the hospital for sick children between 1989 and 1999	Williams, B. A.; Williams, K. M.; Doyle, J.; Stephens, D.; Greenberg, M.; Malkin, D.; Pappo, A. S.	2004	Journal of Pediatric Hematology/Oncology	26	4	243-7
High-dose chemotherapy and autologous peripheral blood stem cell transfusion for adult and adolescent patients with small round cell sarcomas	Yamada, K.; Takahashi, M.; Ogura, M.; Kagami, Y.; Taji, H.; Kamiya, Y.; Sugiura, H.; Morishima, Y.	2007	Bone Marrow Transplantation	39	8	471-6
High-Dose Treosulfan and Melphalan as Consolidation Therapy Versus Standard Therapy for High-Risk (Metastatic) Ewing Sarcoma	Koch, Raphael; Gelderblom, Hans; Haveman, Lianne; Brichard, Benedicte; JÃ¼rgens, Heribert; Cyprova, Sona; van den Berg, Henk; Hassenpflug, Wolf; Raciborska, Anna; Ek, Torben; Baumhoer, Daniel; Egerer, Gerlinde; Eich, Hans Theodor; Renard, Marleen; Hauser, Peter; Burdach, Stefan; Bovee, Judith; Bonar, Fiona; Reichardt, Peter; Kruseova, Jarmila; Hardes, Jendrik; KÃ¼hne, Thomas; Kessler, Torsten; Collaud, Stephane; Bernkopf, Marie; ButterfaÃŸ-Bahloul, Trude; Dhooge, Catharina; Bauer, Sebastian; Kiss, JÃ¡nos; Paulussen, Michael; Hong, Angela; Ranft, Andreas; Timmermann, Beate; Rascon, Jelena; Vieth, Volker; Kanerva, Jukka; Faldum, Andreas; Metzler, Markus; Hartmann, Wolfgang; Hjorth, Lars; Bhadri, Vivek; Dirksen, Uta	2022	Journal of Clinical Oncology			JCO.21.01942
High-dose Chemotherapy Response in Adults with Relapsed/Refractory Small Round Cell Tumours	Aykan, M. B.; Erturk, I.; Acar, R.; Yildiran, G. S.; Yildiz, B.; Karadurmus, N.	2022	Jcpsp, Journal of the College of Physicians & Surgeons - Pakistan	32	1	51-56
Survival after high-dose chemotherapy for refractory and recurrent Ewing sarcoma	Windsor, R.; Hamilton, A.; McTiernan, A.; Dileo, P.; Michelagnoli, M.; Seddon, B.; Strauss, S. J.; Whelan, J.	2022	European Journal of Cancer	170		131-139

Appendix 14. Evidence Summary Topic 3 Question 4 Systematic Review

Table 1. Studies for RMS – first line, relapse and both

Study	Design	First-line / relapse	Setting	Country	Sarcoma classifiers	High-dose chemotherapy agents	Median follow up	Median age (range)	Number of patients	Survival outcomes	Toxicity information
Bisogno 2009	Single arm trial	First-line	Not stated	Italy	Primary metastatic	Sequential HDT combinations - thiotepa/melphalan, cyclophosphamide/ thiotepa, melphalan	5 years	9.4y (0.9mo-20.9y)	70	1-year OS: 35.3% 1-year PFS: 43.6%	Detailed – 3 TRD
Carli 1999	Non-randomised trial	First-line	Multicentre	Italy	Primary metastatic	Melphalan +- other	42.8 months	7.7y (3mo-18y)	52 (HDT) / 44 (CC)	3-year OS: 29.7 vs. 19.2%, p=0.3 3-year EFS: 40% vs. 27.7%, p=0.2	Basic – TRD 1 HDT, 1 CC
Carli 2004	Retrospective cohort study	First-line	Multicentre	Italy	Primary metastatic	Melphalan	8 years	8.6y (3.2mo-18.8y)	95 (HDT) / 79 (CC)	5-year OS: 36% [95% CI 23-49%] vs. 27% [95% CI 14-41%] 5-year EFS: 29% [95% CI 16-41%] vs. 23% [95% CI 11-36%]	Basic – 6 TRD
Kim 2012	Retrospective cohort study	First-line	Single centre	Korea	Primary high risk (Group III or IV patients at diagnosis by IRS staging, Stage III or IV disease by TNM staging)	Ifosfamide + carboplatin + etoposide	7.3 years	5y (6m-15y)	13 (HDT) / 24 (CC)	5-year EFS: 41.3% (SD 17.8%) vs. 16.7% (SD 7.6%)	Basic – TRD 0 HDT, 1 CC
Williams 2004	Retrospective cohort study	First-line	Single centre	Canada	Primary metastatic	Etoposide + cyclophosphamide +- melphalan	5.5 years	Range <18y	4 (HDT) / 13 (CC)	3-year OS: 100% [95% CI 33-107%) vs. 15% [95% CI -4-35%], p=0.03 3-year FFS: 75% (95% CI 33-107%) vs. 15% (95% CI -4-35%), p=0.04	Basic, no TRM reported
Aykan 2021	Retrospective case series	Relapse	Single centre	Turkey	Primary refractory or recurrent	ICE	Not stated	26.85y	20 (ES) / 4 (RMS)	Mean PFS: 2.7 months (SD 0.97) for ES / 3.47 months (SD 0.44) for RMS 1-year OS: 44.8% (SD 14.8%) for ES vs. 75% (SD 21.7%) for RMS	Basic – 1 TRD
Matsubara 2003	Retrospective case series	Both	Single centre	Japan	(1) Clinical group III or IV disease at the primary diagnosis or (2) local relapse or distant metastasis in patient with	Hi-MEC (n=10); others	Not stated overall	8.5y (2–22)	22	5-year DFS: 36% 5-year OS: 45%	Basic – 0 TRD

					clinical group I or II disease						
Stiff 2010	Retrospective case series	Both	Multicentre	USA	All stages	Varied	78 months	14y (3-40)	62	1-year PFS: 36% [95% CI 24-48%] 3-year PFS: 29% [95% CI 18-41%] 5-year PFS: 29% [95% CI 18-41%] 1-year OS: 56% [95% CI 43-68%] 3-year OS: 39% [95% CI 28-52%] 5-year OS: 32% [95% CI 21-44%]	TRM only – 3 TRD

Table 2. Studies for RMS and RMS-like tumours – first line

Study	Design	First-line / relapse	Setting	Country	Sarcoma types	Sarcoma classifiers	High-dose chemotherapy agents	Median follow up	Median age (range)	Number of patients	Survival outcomes	Toxicity information
Boulad 1998	Single arm trial	First-line	Single centre	USA	RMS, extraosseous EWS or undifferentiated sarcoma	Primary metastatic disease or stage II or III disease at unfavourable sites (extremity, retroperitoneal, trunk, pelvic soft tissue, and perineum)	Melphalan + etoposide	62 months	14.8y (1.1 to 23).	26 (19 HDT)	1-year OS: 53% 1-year PFS: 56%	Detailed – TRD 0
Hosoi 2007	Retrospective cohort study	First-line	Multicentre	Japan	RMS, undifferentiated sarcoma	All risk groups discussed however only primary intermediate risk B and high-risk patients underwent HDT	HiMEC; TEPA/LPAM	4.3 years	5y (0–20)	63 (HDT) / 67 (CC)	5-year OS: 58.2% (high risk) vs. 18.4% (high risk) 5-year OS: 61.6% (intermediate risk group B) vs. 54.5% (intermediate risk group B)	No specific toxicity information
Klingebiel 2008	Non-randomised trial	First-line	Multicentre	Germany	RMS, other soft tissue sarcomas	Primary metastatic disease	HDT1 (cyclophosphamide and thiotepa) + HDT2 (melphalan + etoposide)	57.4 months	Range <22y	45 (HDT) / 51 (maintenance)	5-year OS: 0.27 (SD 0.13) vs. 0.52 (SD 0.14) with p=.03	TRM only – TRD 1 HDT, 0 CC

Yamada 2007	Single arm trial	First-line	Single centre	Japan	RMS, ESFT	Primary high-risk tumours (older age >15 years, presence of metastatic disease, tumour volume >100ml or axial site involvement)	Melphalan + etoposide + carboplatin (n=14); Cyclophosphamide + etoposide + carboplatin + dexamethasone (n=7)	41 months	22y (15–35)	25	Median FFS: 6 months Median OS: 41.2 months	Detailed – 1 TRD

Abbreviations: CC- conventional chemotherapy, ESFT – Ewing sarcoma family of tumour, FFS – failure-free survival, HDT – high-dose chemotherapy, OS – overall survival, PFS – progression-free survival, RMS - rhabdomyosarcoma, TRD – treatment related death, TRM – treatment related mortality, SD - standard deviation

Table 4. Studies for ESFT – first line and both

Study	Design	First-line / relapse	Setting	Country	Sarcoma classifiers	High-dose chemotherapy agents	Median follow up	Median age (range)	Number of patients	Survival outcomes	Toxicity information
Drabko 2011	Retrospective cohort study	First-line	Multicenter	Poland	Metastatic disease, localized and unresectable or large (4200ml) tumour, poor histological responders (>10% viable cells)	BuMel (n=32); TreoMel (n=3)	54 months	13.2y (1mo to 19y)	35 (HDT) / 26 (CC)	RFS at median follow-up: 66% (HDT in HR patients) vs. 27% (conventional chemotherapy in HR patients) vs. 72% (SR patients) OS at median follow-up: 71% (HDT in HR patients) vs. 31% (conventional chemotherapy in HR patients) vs. 75% (SR patients)	Minimal, TRD and secondary malignancies only
Ferrari 2011	Retrospective cohort study	First-line	Multicenter	Italy	Non-metastatic primary	BuMel	64 months	15y (3-40)	300	5-year EFS: 72% [95% CI 64-80%, HDT] vs. 33% [95% CI 11-55%, conventional chemotherapy (poor responder)] vs. 75% [95% CI 68-82%, conventional chemotherapy (good responder)]	Detailed
Gaspar 2012	Retrospective cohort study	First-line	Multicenter	France	Untreated localised primary bone tumours	BuMel	8 years	12.6y (0.5–28)	48 (high risk – HR receiving HDT) / 46 (intermediate risk - IR) / 116 (standard risk - SR)	5-year OS: 48% [95% CI 35-68%, HR regimen (HDT)] vs. 54% [95% CI 40-68%, IR regimen] vs. 70% [95% CI 61-77%, SR regimen] 5-year EFS: 48% [95% CI: 35–68%, HR regimen] vs. 54% [95% CI 40–68%, IR regimen] vs. 70% [95% CI 61–77%, SR regimen]	Basic
Laurence 2005	Retrospective case series	First-line	Monocentric	France	High-risk localised disease (bulky tumour >8 cm, inoperable tumour, or poor histologic response), metastatic disease with clinical partial or complete response and no persistent bone marrow involvement	Mel + other agents; various	7.1 years	21y (15–46)	46	5-year PFS: 47% (SD 7.6%) 5-year OS: 63% (SD 7.1%) 10-year OS: 60% (SD 8%)	Basic
Oberlin 2006	Single arm trial	First-line	Multicenter	France	Untreated metastatic bone disease	BuMel	8.2 years	12.3y (2mo to 25y)	97 (75 patients received HDTT)	1-year EFS: 47% (SD 11%, HDT) vs. 37% (SD 10%, all patients) 10-year EFS: 43% (SD 12%, HDT) 1-year OS: 38% (SD 10%, all patients)	Basic

Paulussen 1998	Retrospective cohort study	First-line	Multicenter	Germany	Primary stage IV disease	Melphalan + etoposide +- TBI +- carboplatin; others	19 months	15y (0.3-44)	171 (36 receiving HDT)	4-year EFS: 0.23% vs. 0.28%, p=0.982	Minimal
Study	**Design**	**First-line / relapse**	**Setting**	**Country**	**Sarcoma classifiers**	**High-dose chemotherapy agents**	**Median follow up**	**Median age (range)**	**Number of patients**	**Survival outcomes**	**Toxicity information**
Al-Faris 2007	Retrospective cohort study	Both	Monocentric	Canada	Metastatic/multifocal disease at diagnosis (n=26), relapsed disease (n=19)	Etoposide + cyclophosphamide + melphalan (n=17); other (n=3)	6 years (HDT) / 2 years (CC)	12.42y (3.7-16.9) in HDT, 11.75y (1.75-16.1) in CC	20 (HDT) / 25 (CC)	3-year OS: 59 vs. 34%, p=0.06 3-year EFS: 39% vs. 32%, p=0.08	Basic
Avramova 2011	Retrospective cohort study	Both	Monocentric	Bulgaria	Bulky (n=21), metastatic (n=23), early relapse (n=13)	BuMel (n=11); others	39.3 - 50.7 months	12.8y (3-30)	20 (CC between 1985 and 1997) / 22 (CC between 1997 and 2010) / 15 (HDT with ASCT)	DFS at median follow-up: 15% (conventional chemotherapy between 1985 and 1997) vs. 19% (conventional chemotherapy between 1997 and 2010) vs. 29% (HDT with ASCT) OS at median follow-up: 25% (conventional chemotherapy between 1985 and 1997) vs. 27% (conventional chemotherapy between 1997 and 2010) vs. 23% (HDT with ASCT) No significant differences in OS and DFS among the 3 groups were detected (log rank, p=0.3).	Basic
Jahnukainen 2015	Retrospective cohort study	Both	Monocentric	Finland	Metastatic disease or localized tumours of >200 mL at diagnosis, poor histological response to induction or non-radical surgery, recurrent disease	Thiotepa +- etoposide +- carboplatin; melphalan + TBI	11.8 years	10y (1 to 16)	24	10-year OS: 0.73 (SD 0.16, transplanted in 1CR) vs. 0.9 (SD 0.09)	Basic
Rosenthal 2008	Single arm trial	Both	Monocentric	USA	Metastatic bulky disease at the time of diagnosis or recurrent disease	BuMel (n=11); busulfan + carboplatin (n=9); others	2.4 years	16.24y (6.48–29.93)	20	1-year EFS: 45% [95% CI 23-65%] 3-year EFS: 45% [95% CI 25-70%] 1-year OS: 60% [95% CI 36-78%] 3-year OS: 45% CI [95% CI 22-69%]	Detailed
Serlo 2013	Retrospective cohort study	Both	Multicenter	Finland	Bone and soft tissue sarcoma at any stage	Not stated	7.0 years	17.8y	76	5-year EFS: 67% vs. 59%, p=0.817 5-year DSS (localised): 67% vs. 71%, p=0.662 5-year DSS (metastatic): 74% vs. 0%, p<0.001	No specific toxicity information

Table 5. Studies for RMS – first line, relapse and both

Study	Design	First-line / relapse	Setting	Country	Sarcoma classifiers	High-dose chemotherapy agents	Median follow up	Median age (range)	Number of patients	Survival outcomes	Toxicity information
Bisogno 2009	Single arm trial	First-line	Not stated	Italy	Primary metastatic	Sequential HDT combinations - thiotepa/melphalan, cyclophosphamide/ thiotepa, melphalan	5 years	9.4y (0.9mo-20.9y)	70	1-year OS: 35.3% 1-year PFS: 43.6%	Detailed – 3 TRD
Carli 1999	Non-randomised trial	First-line	Multicentre	Italy	Primary metastatic	Melphalan +- other	42.8 months	7.7y (3mo-18y)	52 (HDT) / 44 (CC)	3-year OS: 29.7 vs. 19.2%, p=0.3 3-year EFS: 40% vs. 27.7%, p=0.2	Basic – TRD 1 HDT, 1 CC
Carli 2004	Retrospective cohort study	First-line	Multicentre	Italy	Primary metastatic	Melphalan	8 years	8.6y (3.2mo-18.8y)	95 (HDT) / 79 (CC)	5-year OS: 36% [95% CI 23-49%] vs. 27% [95% CI 14-41%] 5-year EFS: 29% [95% CI 16-41%] vs. 23% [95% CI 11-36%]	Basic – 6 TRD
Kim 2012	Retrospective cohort study	First-line	Single centre	Korea	Primary high risk (Group III or IV patients at diagnosis by IRS staging, Stage III or IV disease by TNM staging)	Ifosfamide + carboplatin + etoposide	7.3 years	5y (6m-15y)	13 (HDT) / 24 (CC)	5-year EFS: 41.3% (SD 17.8%) vs. 16.7% (SD 7.6%)	Basic – TRD 0 HDT, 1 CC
Williams 2004	Retrospective cohort study	First-line	Single centre	Canada	Primary metastatic	Etoposide + cyclophosphamide +- melphalan	5.5 years	Range <18y	4 (HDT) / 13 (CC)	3-year OS: 100% [95% CI 33-107%) vs. 15% [95% CI -4-35%], p=0.03 3-year FFS: 75% (95% CI 33-107%) vs. 15% (95% CI -4-35%), p=0.04	Basic, no TRM reported
Aykan 2021	Retrospective case series	Relapse	Single centre	Turkey	Primary refractory or recurrent	ICE	Not stated	26.85y	20 (ES) / 4 (RMS)	Mean PFS: 2.7 months (SD 0.97) for ES / 3.47 months (SD 0.44) for RMS 1-year OS: 44.8% (SD 14.8%) for ES vs. 75% (SD 21.7%) for RMS	Basic – 1 TRD
Matsubara 2003	Retrospective case series	Both	Single centre	Japan	(1) Clinical group III or IV disease at the primary diagnosis or (2) local relapse or distant metastasis in patient with clinical group I or II disease	Hi-MEC (n=10); others	Not stated overall	8.5y (2–22)	22	5-year DFS: 36% 5-year OS: 45%	Basic – 0 TRD

Stiff 2010	Retrospective case series	Both	Multicentre	USA	All stages	Varied	78 months	14y (3-40)	62	1-year PFS: 36% [95% CI 24-48%] 3-year PFS: 29% [95% CI 18-41%] 5-year PFS: 29% [95% CI 18-41%] 1-year OS: 56% [95% CI 43-68%] 3-year OS: 39% [95% CI 28-52%] 5-year OS: 32% [95% CI 21-44%]	TRM only – 3 TRD

Table 6. Studies for RMS and RMS-like tumours – first line

Study	Design	First-line / relapse	Setting	Country	Sarcoma types	Sarcoma classifiers	High-dose chemotherapy agents	Median follow up	Median age (range)	Number of patients	Survival outcomes	Toxicity information
Boulad 1998	Single arm trial	First-line	Single centre	USA	RMS, extraosseous EWS or undifferentiated sarcoma	Primary metastatic disease or stage II or III disease at unfavourable sites (extremity, retroperitoneal, trunk, pelvic soft tissue, and perineum)	Melphalan + etoposide	62 months	14.8y (1.1 to 23).	26 (19 HDT)	1-year OS: 53% 1-year PFS: 56%	Detailed – TRD 0
Hosoi 2007	Retrospective cohort study	First-line	Multicentre	Japan	RMS, undifferentiated sarcoma	All risk groups discussed however only primary intermediate risk B and high-risk patients underwent HDT	HiMEC; TEPA/LPAM	4.3 years	5y (0–20)	63 (HDT) / 67 (CC)	5-year OS: 58.2% (high risk) vs. 18.4% (high risk) 5-year OS: 61.6% (intermediate risk group B) vs. 54.5% (intermediate risk group B)	No specific toxicity information
Klingebiel 2008	Non-randomised trial	First-line	Multicentre	Germany	RMS, other soft tissue sarcomas	Primary metastatic disease	HDT1 (cyclophosphamide and thiotepa) + HDT2 (melphalan + etoposide)	57.4 months	Range <22y	45 (HDT) / 51 (maintenance)	5-year OS: 0.27 (SD 0.13) vs. 0.52 (SD 0.14) with p=.03	TRM only – TRD 1 HDT, 0 CC
Yamada 2007	Single arm trial	First-line	Single centre	Japan	RMS, ESFT	Primary high-risk tumours (older age >15 years, presence of metastatic disease, tumour volume >100ml or axial site involvement)	Melphalan + etoposide + carboplatin (n=14); Cyclophosphamide + etoposide + carboplatin + dexamethasone (n=7)	41 months	22y (15–35)	25	Median FFS: 6 months Median OS: 41.2 months	Detailed – 1 TRD

Abbreviations: CC- conventional chemotherapy, ESFT – Ewing sarcoma family of tumour, FFS – failure-free survival, HDT – high-dose chemotherapy, OS – overall survival, PFS – progression-free survival, RMS - rhabdomyosarcoma, TRD – treatment related death, TRM – treatment related mortality, SD - standard deviation

Appendix 15. Quality Assessment for Topic 3 Question 4 Systematic Review

Study	First Authors	Reviewer	Comments	NHMRC Level of Evidence	Risk of Bias (Newcastle Ottawa scale for cohort study)			
					Selection	Comparability	Outcome	Overall
A review of 331 rhabdomyosarcoma cases in patients treated between 1991 and 2002 in Japan	Hosoi	1		III-2	4	0	1	Poor quality
		2		**III-3**	**4**	**2**	**3**	**Good**
		Final		**III-2**	**4**	**2**	**3**	**Good**
Clinical results of high-dose chemotherapy followed by autologous peripheral blood stem cell transplantation in children with advanced stage rhabdomyosarcoma	Kim	1		III-2	4	0	2	Poor quality
		2		**III-2**	**4**	**2**	**3**	**Good**
		Final		**III-2**	**4**	**2**	**3**	**Good**
Comparison of the treatment results after conventional and myeloablative chemotherapy in patients with poor prognosis Ewing's sarcoma family tumors	Avramova	1		**III-3**	**4**	**2**	**3**	**Good**
		2		III-3	3	0	2	Poor quality
		Final		III-3	4	2	3	Good
Consolidation of first-line therapy with busulfan and melphalan and autologous stem cell rescue in children with Ewing sarcoma	Drabko	1		III-2	4	0	2	Poor quality
		2		**III-2**	**4**	**2**	**3**	**Good**
		Final		**III-2**	**4**	**2**	**3**	**Good**
Does Consolidation With Autologous Stem Cell Transplantation Improve the Outcome of Children With Metastatic or Relapsed Ewing Sarcoma?	Al-Faris	1		**III-3**	**4**	**2**	**3**	**Good**
		2		III-2	4	0	1	Poor quality
		Final		III-2	4	2	3	Good
European Intergroup Studies (MMT4-89 and MMT4-91) on Childhood Metastatic Rhabdomyosarcoma	Carli M	1		**III-2**	**4**	**2**	**3**	**Good**
		2		III-2	4	0	2	Poor quality
		Final		III-2	4	2	3	Good
Ewing's sarcoma family of tumors in Finland during 1990–2009: A population-based study	Serlo	1		**III-3**	**4**	**2**	**3**	**Good**
		2		III-2	4	0	1	Poor quality
		Final		III-2	4	1	3	Good
High-dose busulfan and melphalan as condition regimen for autologous peripheral blood progenitor cell transplantation in high risk Ewing sarcaoma patients	Diaz	1		**III-3**	**3**	**2**	**3**	**Good**

		2		IV				
		Final		IV	3	0	3	Poor
High-dose busulphan/melphalan with autologous stem cell rescue in Ewing's sarcoma	Atra	1		III-3	2	1	2	Fair
		2		IV				
		Final		IV	2	0	2	Poor
High-dose chemotherapy and autologous peripheral blood stem cell transfusion for adult and adolescent patients with small round cell sarcomas	Yamada	1		IV				
		2		III-3	3	2	3	Good
		Final		**IV**	**2**	**0**	**3**	**Poor**
High-dose Chemotherapy Response in Adults with Relapsed/Refractory Small Round Cell Tumours	Aykan	1		IV				
		2		III-3	2	2	2	Fair
		Final		IV	2	0	2	Poor
High-Dose Chemotherapy with Blood or Bone Marrow Transplants for Rhabdomyosarcoma	Stiff	1		IV				
		2		III-3	3	1	3	Good
		Final		IV	3	0	3	Poor
High-dose Induction Chemoradiotherapy Followed by Autologous Bone Marrow Transplantation as Consolidation Therapy in Rhabdomyosarcoma, Extraosseous Ewing's Sarcoma, and Undifferentiated	Boulad	1		III-3	4	2	3	Good
		2		IV				
		Final		IV	3	0	3	Poor
High-dose melphalan with autologous stem-cell rescue in metastatic rhabdomyosarcoma	Carli	1		III-2	4	2	2	Good quality
		2		III-3	4	2	3	Good
		Final		III-2	4	2	3	Good
High-dose therapy with hematopoietic stem cell rescue in patients with poor prognosis Ewing family tumors	Rosenthal	1		III-3	3	1	3	Good
		2		IV				
		Final		IV	3	0	3	Poor
High-dose Thiotepa as Consolidation Therapy With Autologous Hematopoietic Stem Cell Transplantation for High-risk Ewing Family Tumors	Jahnukainen	1		III-3	4	1	3	Good
		2		III-2	4	0	3	Poor quality
		Final		III-2	4	1	3	Good
Impact of High-Dose Busulfan Plus Melphalan As Consolidation in Metastatic Ewing Tumors: A Study by the Société Franc¸aise des Cancers de l'Enfant	Oberlin	1		III-3	3	2	3	Good

		2		IV				
		Final		IV	3	0	3	Poor
Long-term follow up of high-dose chemotherapy with autologous stem cell rescue in adults with Ewing tumor	Laurence	1		IV				
		2		III-3	3	2	3	Good
		Final		IV	3	0	3	Poor
Long-Term Follow-up of High-Dose Chemotherapy with Autologous Stem Cell Transplantation in Children and Young Adults with Stem Cell Transplantation in Children and Young Adults with Metastatic or Relapsed Ewing Sarcoma: A Single-Institution Experience	Pawlowska	1		III-3	3	1	3	Good
		2		IV				
		Final		IV	3	0	3	Poor
Megachemotherapy followed by autologous stem cell transplantation in children with Ewing's sarcoma	Drabko	1		III-3	3	2	3	Good
		2		IV				
		Final		IV	3	0	3	Poor
Megatherapy in children with high-risk Ewing's sarcoma in first complete remission	Madero	1		IV	2	0	3	Poor
		2		IV				
		Final		IV	2	0	3	Poor
Metastatic rhabdomyosarcoma: a retrospective review of patients treated at the hospital for sick children between 1989 and 1999	Williams	1		III-2	4	0	2	Poor quality
		2		III-3	3	1	3	Good
		Final		III-2	3	1	3	Good
Multimodality Diagnostics and Megatherapy in Poor Prognosis Ewing's Tumor Patients	Laws	1		III-3	2	1	2	Fair
		2		IV				
		Final		IV	2	0	2	Poor
Myeloablative therapy against high risk Ewing's sarcoma: A single institution experience and literature review	Lopez, J	1		III-3	4	1	3	Good
		2		IV				
		Final		IV	3	0	3	Poor
Myeloablative therapy with autologous stem cell rescue for patients with Ewing sarcoma	Gardner	1		III-3	3	2	3	Good
		2		IV				
		Final		IV	3	0	3	Poor
Nonmetastatic Ewing family tumors: high-dose chemotherapy with stem cell rescue in poor responder patients	Ferrari	1		III-3	4	2	3	Good
		2		III-2	4	0	2	Poor quality

		Final		III-2	4	1	3	Good
Outcome after relapse in an unselected cohort of children and adolescents with Ewing sarcoma	Shankar	1		III-2	3	0	1	Poor quality
		2		III-3	2	1	3	Fair
		Final		III-2	2	1	3	Fair
Possible Benefits of High-Dose Chemotherapy as Intensive Consolidation in Patients with High- Risk Rhabdomyosarcoma Who Achieve Complete Remission with Conventional Chemotherapy	Matsubara	1		III-3	3	2	3	Good
		2		IV				
		Final		IV	3	0	3	Poor
Post-relapse survival in patients with Ewing sarcoma	Ferrari	1		III-2	4	0	2	Poor quality
		2		III-3	4	2	3	Good
		Final		III-2	4	2	3	Good
Primary disseminated multifocal Ewing sarcoma: results of the Euro-EWING 99 trial	Ladenstein	1		IV				
		2		III-3	4	1	3	Good
		Final		IV	3	0	3	Poor
Primary metastatic (stage IV) Ewing tumor: Survival analysis of 171 patients from the EICESS studies	Paulussen	1		III-3	3	1	3	Good
		2		III-2	4	0	2	Poor quality
		Final		III-2	3	1	3	Good
Risk adapted chemotherapy for localised Ewing's sarcoma of bone: The French EW93 study	Gaspar	1		III-2	4	2	3	Good
		2		III-2	4	0	3	Poor quality
		Final		III-2	4	2	3	Good
Sequential high-dose chemotherapy for children with metastatic rhabdomyosarcoma	Bisogno	1		IV				
		2		III-3	4	2	3	Good
		Final		IV	3	0	3	Poor
Survival after high-dose chemotherapy for refractory and recurrent Ewing sarcoma	Windsor	1		III-2	4	0	2	Poor quality
		2		III-2	4	2	3	Good
		Final		III-2	4	2	3	Good
Tandem high-dose chemotherapy strategy as first-line treatment of primary disseminated multifocal Ewing sarcomas in children, adolescents and young adults	Loschi	1		IV				
		2		III-3	4	2	3	Good
		Final		IV	3	0	3	Poor
The Treatment of Ewing's Sarcoma of Bone at the University of Florida: 1969 to 1998	Marcus Jr	1		III-3	4	0	1	Poor quality

		2		III-3	4	1	3	Good
		Final		III-3	4	1	3	Good
The Value of High-Dose Chemotherapy in Patients With First Relapsed Ewing Sarcoma	Rasper	1		III-2	4	0	2	Poor quality
		2		III-2	4	2	3	Good
		Final		III-2	4	2	3	Good
Treatment of children with metastatic soft tissue sarcoma with oral maintenance compared to high dose chemotherapy: report of the HD CWS-96 trial	Klingebiel	1		III-1				
		2		III-2	3	2	3	Good
		Final		III-2	3	2	3	Good

Study	First Authors	Reviewer	Comments	NHMRC Level of Evidence	Cochrane (low risk, unclear risk, High risk) for randomised trial					
					Selection	Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias
High-dose chemotherapy and blood autologous stem-cell rescue compared with standard chemotherapy in localized high-risk ewing sarcoma: Results of Euro-E.W.I.N.G.99 and Ewing-2008	Whelan	1		II	Low	Low	Low	Low	Low	NA
		2		II	Low	High	Low	Low	Low	High
		Final			Low	High	Low	Low	Low	High
High-dose Chemotherapy Compared With Standard Chemotherapy and Lung Radiation in Ewing Sarcoma With Pulmonary Metastases	Dirksen	1		II	Low	High	Low	Low	Low	Low
		2		II	Low	Low	Low	Low	Low	NA
		Final			Low	High	Low	Low	Low	Low
High-dose Treosulfan and Melphalan as Consolidation Therapy Versus Standard Therapy for High-Risk (Metastatic) Ewing Sarcoma	Koch	1		II	Low	High	Low	Low	Low	Low
		2		II	Low	Low	Low	Low	Low	NA
		Final		II	Low	High	Low	Low	Low	Low