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Guideline 11-6 Version 2

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Optimal Treatment Strategies for Localized Ewing's Sarcoma of Bone after Neoadjuvant Chemotherapy

The Expert Panel on Localized Ewing's Sarcoma of Bone after Neoadjuvant Chemotherapy

February 14, 2022

An assessment conducted in November 2025 deferred the review of Guideline 11-6 Version 2. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

Guideline 11-6 Version 2 is comprised of 6 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/31731

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Werier J, Yao X, Caudrelier JM, di Primio G, Ghert M, Gupta A, et al. Evidence-based guideline recommendations on treatment strategies for localized Ewing's sarcoma of bone following neo-adjuvant chemotherapy. Surg Oncol. 2016 Jun;25(2):92-7.

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Guideline Document History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES and KEY CHANGES
	Search Dates	Data		
Original Dec 2015	2000 to 2015	Full Report	Peer review publication. Web publication.	N.A.
Version 2	2015 to Jul 2021	New data found in Section 6: Document Assessment and Review	Updated web publication	2015 recommendations are ENDORSED

Optimal Treatment Strategies for Localized Ewing's Sarcoma of Bone after Neoadjuvant Chemotherapy

Section 1: Recommendations

This section is a quick reference guide and provides the guideline recommendations only. For key evidence associated with each recommendation, see Section 2.

GUIDELINE OBJECTIVES

- To make recommendations regarding the choice of surgery, radiation therapy (RT), or the combination of surgery plus RT for survival and local control in patients with localized Ewing's sarcoma of bone following neoadjuvant chemotherapy.
- To determine the appropriate surgical planning imaging (pre-chemotherapy magnetic resonance imaging [MRI] or post-chemotherapy MRI) to identify optimum resection margins in patients with localized Ewing's sarcoma who undergo surgery following neoadjuvant chemotherapy.

TARGET POPULATION

- Patients of any age diagnosed with localized Ewing's sarcoma of bone who have completed neoadjuvant chemotherapy for the first objective
- Patients of any age diagnosed with localized Ewing's sarcoma of bone who will undergo surgical management following neoadjuvant chemotherapy for the second objective

INTENDED USERS

General surgeons, orthopaedic oncology surgeons, medical oncologists, radiation oncologists, pathologists, radiologists, and other clinicians who are involved in the treatment of the target patients in the province of Ontario.

RECOMMENDATIONS

Recommendation 1
In patients with localized Ewing's sarcoma of bone following neoadjuvant chemotherapy: • Either surgery alone or RT alone is a reasonable treatment option; the combination of surgery plus RT is not recommended as an initial treatment option. • The local treatment for an individual patient should be decided by a multidisciplinary tumour board together with the patient after consideration of the following: 1) patient characteristics (e.g., age, tumour location, tumour size, response to neoadjuvant chemotherapy, and existing comorbidities), 2) the potential benefit compared with the potential complications from surgery and/or toxicities associated with RT, and 3) patient preference.

Qualifying Statements for Recommendation 1

- If complete tumour resection is impossible, RT alone may be the optimal choice.
- RT may be a treatment option postoperatively in patients who have residual tumours or positive margins.
- The optimal RT dose has not been determined. The reported RT doses in this document ranged from 55 to 60 Gray for RT alone (except one study published in 1999) and from 35 to 60 Gray for RT as an adjuvant to surgery.

Added to the 2022 Endorsement:

- One retrospective data analysis of patients in the Euro-EWING99 trial treated with induction chemotherapy reported that a combination of RT and surgery decreased local recurrence more than RT alone in patients with non-sacral tumours of the pelvis. This evidence requires corroboration from further studies to warrant a review of or change to the current recommendation. See Section 6 for details.

Recommendation 2
In patients with localized Ewing's sarcoma who will undergo surgery: • Both pre-chemotherapy and post-chemotherapy MRI scans should be taken into consideration for surgical planning. In certain anatomic locations with good chemotherapy response, the post-chemotherapy MRI may be the appropriate imaging modality to plan surgical resection margins.

Optimal Treatment Strategies for Localized Ewing's Sarcoma of Bone after Neoadjuvant Chemotherapy

Section 2: Guideline – Recommendations and Key Evidence

GUIDELINE OBJECTIVES

- To make recommendations regarding the choice of surgery, radiation therapy (RT), or the combination of surgery plus RT for survival and local control in patients with localized Ewing's sarcoma of bone following neoadjuvant chemotherapy.
- To determine the appropriate surgical planning imaging (pre-chemotherapy magnetic resonance imaging [MRI] or post-chemotherapy MRI) to identify optimum resection margins in patients with localized Ewing's sarcoma who undergo surgery following neoadjuvant chemotherapy.

TARGET POPULATION

- Patients of any age diagnosed with localized Ewing's sarcoma of bone who have completed neoadjuvant chemotherapy for the first objective
- Patients of any age diagnosed with localized Ewing's sarcoma of bone who will undergo surgical management following neoadjuvant chemotherapy for the second objective

INTENDED USERS

General surgeons, orthopaedic oncology surgeons, medical oncologists, radiation oncologists, pathologists, radiologists, and other clinicians who are involved in the treatment of the target patients in the province of Ontario.

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

Recommendation 1

In patients with localized Ewing's sarcoma of bone following neoadjuvant chemotherapy:

- Either surgery alone or RT alone is a reasonable treatment option; the combination of surgery plus RT is not recommended as an initial treatment option.

The local treatment for an individual patient should be decided by a multidisciplinary tumour board together with the patient after consideration of the following: 1) patient characteristics (e.g., age, tumour location, tumour size, response to neoadjuvant chemotherapy, and existing comorbidities), 2) the potential benefit compared with the potential complications from surgery and/or toxicities associated with RT, and 3) patient preference.

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- If complete tumour resection is impossible, RT alone may be the optimal choice.
- RT may be a treatment option postoperatively in patients who have residual tumours or positive margins.
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Added to the 2022 Endorsement:

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pelvis. This evidence requires corroboration from further studies to warrant a review of or change to the current recommendation. See Section 6 for details.

Key Evidence for Recommendation 1

The recommendations are based on eight retrospective comparative studies [1-8]. Six studies [1,2,4-6,8] stated that patients in the RT alone group had unresectable tumours, were unable to achieve adequate surgical margins, or refused to have surgery. Patients in the surgery plus RT group had residual tumour or positive margins after surgery. The range of patient age from all the included studies was 0.7 to 46 years, and 51% to 64% were male. Based on the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach, the risk of bias for each eligible study was "serious," and the aggregate quality of each comparison for any outcome was "very low" (details in **Section 4 Evidence Review**).

- RT alone versus surgery alone: Only one paper [5], which included patients with all tumour sites of disease, reported overall survival (OS) and showed no statistically significant difference between the two groups (n=362; hazard ratio [HR], 1.38; 95% confidence interval [CI], 0.84 to 2.27). A meta-analysis combining two papers [1,5] showed that surgery alone resulted in a higher event-free survival (EFS) than RT alone in any location (HR, 1.50; 95% CI, 1.12 to 2.00; p=0.007). One paper [2] in patients with Ewing's sarcoma of the humerus supported this point, but another paper [8] describing patients with pelvic disease did not find a statistically significant difference between these two groups (n=56). When considering local control as the outcome, surgery alone was better than RT alone for local control in one paper (n=362; HR, 2.39; 95% CI, 1.20 to 4.74; p=0.01) [5], but not in another two papers (n=100 combined) [2,8]. Only one paper [2] described patient-reported outcomes and showed that 100% of patients in the RT group had ≥75% functional score but 15% of patients in the surgery alone group had a score of 50% to 75% (higher scores indicate better function).
- RT alone versus surgery plus RT: Two studies [2,8] found no statistically significant difference for EFS and local control in 63 pelvic patients and 28 humerus patients. One study [2] reported that all the 28 humerus patients in the two groups had a functional score of ≥75%.
- RT alone versus surgery with or without RT: Compared with RT alone, surgery with or without RT led to a better OS (HR, 4.85, p=0.026) and disease-free survival (DFS) (HR, 5.06; 95% CI, 1.39 to 18.43; p=0.014) in 53 pelvic patients [3], a better EFS (HR, 2.92; 95% CI, 1.16 to 7.35; p=0.02) in 56 pelvic patients [4], and a better local control (rate at five years 25% versus 61%; p<0.02) in 54 mixed-location patients [7].
- Surgery plus RT versus surgery alone: Only one paper [5] reported OS and showed no statistically significant difference between the two groups in mixed location patients (n=344, HR, 1.35; 95% CI, 0.83 to 2.19). A meta-analysis combining two papers [1,5] did not demonstrate a statistically significant difference for EFS between the two groups in mixed-location patients (HR, 1.21; 95% CI, 0.90 to 1.63); another two papers also did not find a statistically significant difference between groups in pelvic and humerus patients, respectively [2,8]. Three papers reported no statistically significant difference for local control outcome [2,5,8]. Only one paper [2] reported patient-reported outcomes and showed that all the patients in the surgery plus RT group had ≥ 75% functional score but 15% of patients in the surgery alone group had a score of 50% to 75%.
- Toxicities/complications: One study [7] reported three (8%) fractures, three (8%) skin necroses, two (5%) functional changes, and two (5%) serious suppurations at 30 to 132 months of follow-up in mixed-location patients with RT alone or surgery plus RT. One study [8] did not demonstrate any second malignancies after RT at a median of 4.4

years of follow-up in 75 pelvic patients with RT alone, surgery alone, or surgery plus RT although this may just reflect the limited follow-up period. The third study [2] reported one (6%) radiotherapy-induced osteosarcoma at six years and two (12%) pathologic fractures after RT alone; three (11%) mechanical failures that needed reoperation after surgery alone occurred in humerus patients.

Interpretation of Evidence for Recommendation 1

- There was strong agreement among the Working Group members that OS, EFS/DFS, local control, and toxicities/complications were critical outcomes for recommendation development. Patient-reported outcomes were considered an important outcome of interest.
- The overall aggregate quality of each comparison for any outcome was very low. A very low quality according to GRADE means that "we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect" [9]. Also, from the above key evidence, the desirable anticipated effects are uncertain among RT alone, surgery alone, and the combination of RT and surgery (some papers found a statistically significant difference between two treatment options and some did not; some papers mixed patients under surgery alone and patients under surgery plus RT into one group, or mixed patients under RT and patients under surgery plus RT into one group).
- The toxicities from RT alone and the complications after surgery alone are not small. The combination of surgery plus RT will have more potential toxicities than single treatment alone. Therefore, after balancing desirable and undesirable effects, the Working Group made the following recommendation: the combination of surgery plus RT is not recommended as an initial treatment approach.
- Since the eight eligible papers included patients ranging in age from 0.7 to 46 years and most papers reported outcomes in mixed-location patients, the Working Group concluded that evidence was generalizable to patient population of any age diagnosed with localized Ewing's sarcoma of bone.

Recommendation 2

In patients with localized Ewing's sarcoma who will undergo surgery:

- Both pre-chemotherapy and post-chemotherapy MRI scans should be taken into consideration for surgical planning. In certain anatomic locations with good chemotherapy response, the post-chemotherapy MRI may be the appropriate imaging modality to plan surgical resection margins.

Key Evidence for Recommendation 2

- No eligible studies were found regarding the second objective.
- The Bone Cancer National Comprehensive Cancer Network (NCCN) 2015 consensus guideline [10] stated that "disease should be restaged with an MRI of the lesion and chest imaging following neoadjuvant chemotherapy".

Interpretation of Evidence for Recommendation 2

- Although there was no eligible evidence identified to answer this research question, the Working Group members believe the statement of the Bone Cancer NCCN 2015 consensus guideline for this specific area as it is appropriate at present, given standard clinical practice in Ontario. The desirable effect is that the results from post-chemotherapy MRI will clearly inform surgical oncologists of the tumour characteristics after neoadjuvant chemotherapy just before surgery. Well-designed prospective comparative studies are required to address these issues.

IMPLEMENTATION CONSIDERATIONS

The Working Group members consider these recommendations to be feasible to implement and will not affect current health inequities. The outcomes valued by the clinicians in this guideline will align with the outcomes valued by the patient and most patients will view these recommendations as acceptable; the interpretation of the evidence will align with the interpretation of most clinicians in Ontario and the recommendations will probably be accepted by most providers for their implementation. They also believe that these recommendations will not require additional training for the providers or a significant change to the current system. There will be no additional costs to implement these recommendations.

Optimal Treatment Strategies for Localized Ewing's Sarcoma of Bone after Neoadjuvant Chemotherapy

Section 3: Guideline Methods Overview

This section summarizes the methods used to create the guideline. For the systematic review, see Section 4.

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) [11]. The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle [11,12]. PEBC guidelines include an evidence review (typically a systematic review), an interpretation of and consensus agreement on the evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

BACKGROUND FOR GUIDELINE

For patients diagnosed with Ewing's sarcoma of bone, chemotherapy is the standard of care for primary treatment. Following neoadjuvant chemotherapy, all patients require local management, followed by the completion of adjuvant chemotherapy. In this regard, some patients undergo surgical treatment alone, others are treated with radiation therapy alone, and some are offered both. There has been great debate over which approach is optimal for overall survival and local control in patients with localized Ewing's sarcoma of bone following neo-adjuvant chemotherapy. It is also unclear whether post-chemotherapy magnetic resonance imaging (MRI) is better than pre-chemotherapy MRI to determine the appropriate surgical planning imaging in patients with localized Ewing's sarcoma who undergo surgical resection following neo-adjuvant chemotherapy.

GUIDELINE DEVELOPERS

This guideline was undertaken by the PEBC at the request of the Sarcoma DSG. The Sarcoma DSG comprised of three medical oncologists, three radiation oncologists, five surgeons, two pathologists, two radiologists, and one methodologist for this guideline (see Appendix 1). The project was led by a small working committee of the group, referred to as the Working Group from this point forward, whose members were responsible for creating the evidence base, drafting the first version of the recommendations and leading the response to the external review. The Working Group members are noted in Appendix 1. All the Sarcoma DSG members

contributed to the final interpretation of the evidence, refinement of the recommendations, and approval of the final version of the document. Competing interests in the areas of receiving financial support as a consultant or principal investigator from a relevant business entity were declared; Appendix 1 provides further detail. Individuals with competing interests were not allowed to participate as a member of the Working Group unless otherwise stated.

GUIDELINE DEVELOPMENT METHODS

The PEBC uses the AGREE II as its organizational methodological framework. Beginning with a project plan, systematic methods of evidence synthesis and/or adaptation, consensus of interpretation of evidence (see **Section 4 Evidence Review**), drafting and contextualization of recommendations (see **Section 2 Guideline**), and external review (see **Section 5 Internal & External Review**) of the draft guideline define key steps in the process. The PEBC's processes and methods are described in more detail in the PEBC Handbook on the CCO website *PEBC Handbook.*

A search for existing guidelines based on a systematic review for adaptation or endorsement was conducted using the following sources from 2011 to July 2014:

- Practice guideline databases: the Standards and Guidelines Evidence Directory of Cancer Guidelines (http://www.cancerview.ca/sage), National Guideline Clearinghouse (http://www.guideline.gov/), and Canadian Medical Association Infobase (https://www.cma.ca/En/Pages/SearchPage.aspx?k=guidelines).
- Guideline developer websites: National Institute for Health and Care Excellence (https://www.nice.org.uk/guidance), Scottish Intercollegiate guidelines Network (http://www.sign.ac.uk/guidelines/index.html), American Society of Clinical Oncology (http://www.instituteforquality.org/practice-guidelines), and National Health and Medical Research Council (Australia) (http://www.nhmrc.gov.au/guidelines/publications/subject/Clinical%20practice%20guidelines).
- MEDLINE and EMBASE were searched by using "Ewing Sarcoma" or "bone Sarcoma" with their alternatives AND "guideline" with its alternatives.

A search for existing guidelines for adaptation or endorsement did not yield an appropriate source document. A search of the primary literature was required (see **Section 4 Evidence Review**). Using this evidence, recommendations were drafted and approved by the Sarcoma DSG. The draft document was circulated for internal review to an independent committee of the PEBC and for external review to experts in the field (see **Section 5 Internal & External Review**). Refinements to the document were made in response to the feedback received and final recommendations approved by the guideline group. To achieve approval of the draft document and final document, a consensus of 75% of the members of the Sarcoma DSG was required, with dissenting opinions noted, where appropriate.

Focus

The primary focus of this guideline is on the clinical evidence. Other features related to the implementation of recommendations such as costs, human resources, unique requirements for special or disadvantaged populations, development and measurement of quality indicators are addressed by other divisions at CCO. The perspective of the Sarcoma DSG on these issues is described in the **Section 2 Guideline** under "Implementation Considerations".

ACKNOWLEDGEMENTS

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- Melissa Brouwers, Laurie Elit, Donna Maziak, Sheila McNair, Hans Messersmith, for providing feedback on draft versions.
- Crystal Su for conducting a data audit.
- Sara Miller for copyediting.

A complete list of the members of the Sarcoma DSG for this guideline and the Working Group, with their affiliations and conflict of interest information, is provided in Appendix 1 after **Section 5 Internal & External Review**.

Optimal Treatment Strategies for Localized Ewing's Sarcoma of Bone after Neoadjuvant Chemotherapy

Section 4: Systematic Review

INTRODUCTION

Ewing's sarcoma is a highly malignant, small, round cell tumour and it is the second most common primary bone cancer in children, adolescents, and young adults [13]. The incidence is approximately one to three per million population every year [14]. Ewing's sarcoma occurs more frequently in Caucasians than in Asians, and males are affected more than females, with a ratio of approximately 1.5:1 [14]. The most common primary bony sites include the long bones (47%), pelvis (26%), chest wall (16%) and spine (6%) [14]. Chemotherapy is considered a standard treatment to reduce the tumour size before further local control management, but after neo-adjuvant chemotherapy, it is unclear whether radiation therapy (RT) alone, surgery alone, or both is the best approach for local control [2]. Also, for the patients who are qualified and are willing to have surgical treatment, it is not clear if pre-chemotherapy magnetic resonance imaging (MRI) or post-chemotherapy MRI is appropriate to plan an optimal resection. Thus, the Working Group (the guideline authors including two surgical oncologists, two medical oncologists, one radiation oncologist, one radiologist, one pathologist, and one methodologist) of the Sarcoma Disease Site Group (DSG) in association with the Program in Evidence-Based Care (PEBC) of Cancer Care Ontario (CCO), conducted a systematic review to summarize the relevant papers from the medical literature to develop a clinical guideline. Based on the objectives of the guideline, the Working Group derived the research questions outlined below. The systematic review had been registered on the website of the International prospective register of systematic reviews (www.crd.york.ac.uk/prospero) as CRD42015013600.

The PEBC is supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ministry.

RESEARCH QUESTIONS

1. Among the options of surgery alone, RT alone, and the combination of RT plus surgery, which is the optimum treatment strategy to improve clinical outcomes (i.e., overall survival [OS], relapse-free survival [RFS]/progression-free survival [PFS]/event-free survival [EFS]/disease-free survival [DFS]/local control, toxicities/complications, and patient-reported outcomes) in patients with localized Ewing's sarcoma of bone following neoadjuvant chemotherapy?
2. Between pre-chemotherapy MRI and post-chemotherapy MRI, which surgical planning imaging is the most appropriate to plan an optimal resection (e.g., negative margins) in patients with localized Ewing's sarcoma of bone who undergo surgical resection following neoadjuvant chemotherapy?

METHODS

This evidence review was developed using a planned two-stage method, summarized here and described in more detail below.

1. Search and evaluation of existing systematic reviews: If one or more existing systematic reviews were identified that address the research questions and were of reasonable quality, then those systematic reviews would form the core of the evidence review.
2. Systematic review of the primary literature: This review would focus on those areas not covered by existing reviews if any are located and accepted.

Search for Existing Systematic Reviews

The MEDLINE, EMBASE, and Cochrane Database of Systematic Reviews databases were searched from January 2007 to February 11, 2015 to identify existing relevant systematic reviews and meta-analyses. Search terms for indicative of "Ewing Sarcoma" or "bone Sarcoma" with their alternatives, AND "systematic review" or "meta-analysis" with their alternatives were used.

Search for Primary Literature

If no eligible systematic reviews were identified, a primary search of the literature was performed and described below.

Literature Search Strategy

MEDLINE, EMBASE, and Cochrane library were searched from 1999 onwards to find full publications; and the American Society of Clinical Oncology (ASCO) Annual Meeting Abstracts and Connective Tissue Oncology Society (CTOS) Annual Meeting Abstracts were checked for abstracts that met the following study selection criteria. The search strategies are reported in Appendix 2.

Study Selection Criteria and Process

Inclusion Criteria

An article was eligible for inclusion if it met all the following preplanned criteria:

1. It was a full-text report published in the period from 1999 to February, 2015 for the first research question (Q1) and from 2004 to February 11, 2015 for the second research question (Q2) or a conference/meeting abstract published from 2012 to 2014 for either question.
2. For a full-text report, it reported on a randomized controlled trial (RCT), or comparative study that controlled for the baseline confounders (like multivariable analysis, etc.) or showed no significant difference for the patient characteristics between treatment groups for Q1 and Q2, or prospective single-arm study for Q2 only.
3. For a conference/meeting abstract, it reported on an RCT for Q1 and there is no study design limitation for Q2.
4. Analyzed sample size should be ≥30 patients.
5. It investigated surgery, RT, or combination of surgery and RT in patients with localized Ewing's sarcoma of bone following neo-adjuvant chemotherapy for Q1 or investigated surgical planning imaging (pre-chemotherapy MRI or post-chemotherapy MRI) for optimal resection (e.g., negative margins) in patients with localized Ewing's sarcoma of bone for Q2.
6. For an existing systematic review, it should describe database search methods (including database names and search date) and study selection criteria; and it should have at least one eligible article that met the above inclusion criteria.

Exclusion Criteria

An article or abstract was excluded if it met any of the following preplanned criteria:

1. It was published in a language other than English.
2. It was published in the form of a letter, animal study, editorial, or commentary.
3. Studies reported the outcomes on mixed patients of >10% metastatic, non-osseous, without neoadjuvant chemotherapy, or non-Ewing's sarcoma patients but without subgroup analysis for patients with localized Ewing's sarcoma of bone following neoadjuvant chemotherapy.

A review of the titles and abstracts that resulted from the search was performed by one reviewer (XY). For those that warranted full-text review, XY reviewed each article and discussed with the other Working Group members (JC, GDP, MG, RG, AG, RK, SV, JW) to confirm the final study selections.

Data Extraction and risk of Bias Assessment

Data extraction was performed by XY. All extracted data and information were audited by an independent auditor (CS).

Study quality and potential for bias for each study were assessed by the modified Cochrane Collaboration tools for randomized studies [15] and for non-randomized controlled studies (ACROBAT-NRSI) [16].

Synthesizing the Evidence

The GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) method for assessing the quality of aggregate evidence was used for each comparison using the GRADEpro Guideline Development Tool [9,17]. The outcomes were rated for their importance for decision-making by the Working Group in Appendix 3. Only those outcomes that were considered critical or important were included in the GRADE evidence tables. Five factors were assessed for each outcome in each comparison, and they included the risk of bias, inconsistency, indirectness, imprecision, and other considerations (e.g., publication bias).

If there was no clinical heterogeneity for patient characteristics and intervention for each outcome from two or more trials, a meta-analysis was conducted using the Review Manager software (RevMan 5.3) provided by the Cochrane Collaboration [18]. A hazard ratio (HR) <1.0 indicates improved efficacy for the experimental arm and a HR >1.0 indicates improved efficacy for the control arm.

Any subgroup analyses from the original studies for which denominators are less than 30 should be considered carefully, because they usually have large 95% confidence intervals (CIs) that are unlikely to be statistically significant. A two-sided significance level of α=0.05 was assumed.

RESULTS

Search for Existing Systematic Reviews

No clinical practice guidelines based on a systematic review were found. Two systematic reviews [19,20] were relevant and met the preplanned inclusion criteria. Since neither of them used the same preplanned selection criteria of this review, we did not use any of them as a base to start a systematic review and these two reviews were not discussed further. However, the included studies in these two systematic reviews were reviewed as potentially eligible studies for this systematic review.

Search for Primary Literature

Literature Search Results

A total of 6010 English papers were identified. Two hundred forty-six were selected for full-text review. Of these, eight met the pre-defined eligibility criteria for this systematic review and their reference lists were hand-searched and no further eligible papers were found [1-8]. A check of conference abstracts did not yield any abstract that met the pre-planned study selection criteria. The PRISMA flow diagram (http://www.prisma-statement.org/statement.htm) of studies considered in the systematic review was modified and shown in Appendix 4.

Study Design and Quality

The eight eligible studies were all retrospective comparative studies (Table 4-1). The risk of bias for each study was assessed using the modified Cochrane Collaboration tool: ACROBAT-NRSI [16] in Appendix 5. For each study, if one domain was judged as having serious risk, the overall risk of bias for the study was marked as serious risk. Six studies [1,3-7] performed multivariable analysis to control for potential baseline confounders and two studies [2,8] showed no significant difference for patient characteristics between treatment groups at baseline; therefore, all eight eligible studies had moderate risk of bias for confounding and patient selection domains, respectively. Because of the retrospective nature of the studies, measurement of intervention and departures from intervention domains were moderate risks. In all studies, only patients who had data for outcomes were chosen; thus, there was no information for the missing data domain but serious bias in selection of the reported result domain. In this systematic review, except for OS, which was unlikely to be influenced by the knowledge of the intervention received by study participants, other outcome measures were subjective and had serious risk of bias. Overall, the risk of bias for each eligible study was serious.

Table 4-1. Study design and patients characteristics.

Study	Country	Design	N; Mean/median age (range), y	Male	Tumour Site
Carrie 1999 [3]	France	Retrospective comparative	53[a]; 13 (3-28)	51%	Pelvis: 100%
Shankar 1999 [6]	United Kingdom	Retrospective comparative	191; 12 (1-27)	55%	Extremity: 50%, Pelvis: 18%, Others: 32%
Sokolov 2000 [7]	Bulgaria	Retrospective comparative	54; 15 (4-43)	59%	Extremity: 83%, Pelvis: 17%
Bacci 2006 [1]	Italy	Retrospective comparative	453[b]; 17 (1.5-40)[c]	64%	Extremity: 64%, Central: 36%
Yock 2006[d] [8]	United States	Retrospective comparative	75; NR (all pts ≤30, 83% of them <18)	52%	Pelvis: 100%
Donati 2007[e] [4]	Italy	Retrospective comparative	56; 18 (6-46)	57%	Pelvis: 100%
Bacci 2009[f] [2]	Italy	Retrospective comparative	55; 18 (3-40)	62%	Humerus: 100%
DuBois 2015[g] [5]	United States	Retrospective comparative	465; 12 (0.7-33)	54%	Extremity: 53%, Pelvis: 21%, Others: 26%

Abbreviations: N = sample size, NR = not reported, pts = patients, y = years.
[a]This information came from 59 patients; 53 of them had final outcomes.
[b]It showed 453 patients with neoadjuvant chemotherapy in Table 2 but 454 in Table 1 in its original paper.
[c]This information came from 512 patients in the study; only 453 of them had neochemotherapy.
[d]About 50% of patients in this study were included in the DuBois paper; Patient data in this study were retrospectively collected from a randomized clinical trial (INT-0091), and focused on localized pelvic Ewing's sarcoma patients from both chemotherapy groups.
[e]Most patients in this paper were included in the Bacci 2006 paper.
[f]Approximately 80% of patients in this study were included in the Bacci 2006 paper.

[g]Patient data in this study were retrospectively collected from three clinical trials (INT-0091, INT-0154, and AEWS0031), and focused on localized Ewing's sarcoma of bone from the standardized chemotherapy group and not the experimental chemotherapy group.

Outcomes

1. **Research question 1. Among the options of surgery alone, RT alone, and the combination of RT plus surgery, which is the optimum treatment strategy to improve clinical outcomes (i.e., OS, RFS/EFS/DFS/local control, toxicities/complications, and patient-reported outcomes) in patients with localized Ewing's sarcoma of bone following neoadjuvant chemotherapy?**

All eight eligible papers attempted to answer this research question. Six of them [1,2,4-6,8] stated that patients in the RT alone group had unresectable tumours, were unable to achieve adequate surgical margins, or refused to have surgery; patients in the surgery alone group had complete surgical excision with clear margins; patients in the surgery plus RT group had residual tumours or positive margins after surgery. The other two papers [3,7] stated that the decision for local treatment was made by clinicians based on individual patient circumstance. The outcomes of OS, RFS/PFS/EFS/DFS/local control, and toxicities/complications were rated as "CRITICAL" and patient-reported outcomes were rated as "IMPORTANT" by the Working Group (Appendix 3). All outcomes are summarized in Table 4-2. The aggregate quality for each comparison with any outcome is very low based on the GRADE approach (Tables 4-3 to 4-7). The range of mean/median patient age from all the included studies was 12 to 18 years, and 51% to 64% were male patients (Table 4-1). The RT dose for RT alone was 55 to 60 Gray in six papers [1-5,8], 40 to 60 Gray in one paper [6], and 35 to 60 Gray for RT alone or surgery with RT in one paper [7]. The range of RT dose for RT after surgery was 35 to 60 Gray in the eight papers. Only the Donati study included 10 preoperative patients with RT dose of 40 to 45 Gray [4].

For the six studies [1,3-7] that conducted multivariable analysis to control for potential confounders, the variables in the multivariable analysis model and the variables that were identified to significantly relate to the local control rate are listed in Appendix 6. Local treatment (surgery alone or surgery plus RT) in five studies [1,3-5,7], good response to neoadjuvant chemotherapy in four studies [1,3,5,7], age (not consistent for younger or older patients) in three studies [1,5,6], tumour size (≤150 mm^3 or ≤200 mm^3) in two studies [1,3], and tumour site (extremity) in two studies [5,6], were associated with better OS, EFS, or local control.

Table 4-2. Main outcomes of surgery versus RT versus surgery plus RT in Ewing's sarcoma of bone.

Study		Intervention (dose)	N	OS		DFS/EFS		LC		Toxicity/complication
				HR (95% CI) or survival rate	p-value	HR (95% CI) or survival rate	p-value	HR (95% CI) or LC rate	p-value	
Carrie 1999 [3]	Tumour size not in model	RT (60 Gy) vs. Surg/Surg+RT (35-60 Gy)	27 vs. 26	HR: 2.59[a] (NR)	0.059	HR for DFS: 2.64 (1.01-6.92)[a]	0.048	NR		NR
	Tumour size in model	RT (60 Gy) vs. Surg/Surg+RT (35-60)	NR (total N =36)	HR: 4.85[a] (NR)	0.026	HR for DFS: 5.06 (1.39-18.43)[a]	0.014	NR		NR
Shankar 1999 [6]		Surg vs. RT (40-60 Gy)/Surg+RT (35-55 Gy)	115[b] vs. 76	At 5 years: 75% (65-82) vs. 70% (57-79); At 10 years: 68% (57-77) vs. 70% (57-79)	0.70	NR		At 5 y: 90% (82-94) vs. 88% (77-94)	0.60	NR
Sokolov 2000 [7]		RT(NR) vs. Surg±RT (35-60 Gy)	14 vs. 40	NR		NR		At 5 y: 25% (2-48)[c] vs. 61% (46-76)[c]	0.02	RT: 3 (8%) fracture, 3 (8%) skin necrosis, 2 (5%) functional changes, 2 (5%) suppurations at 30-132 months
Bacci 2006[a] [1]		RT (60 Gy) vs. Surg	147 vs. 191	NR		HR for EFS: 1.6 (1.1-2.5)	0.015	NR		NR
		Surg+RT (44.8-60 Gy) vs. Surg	115 vs. 191	NR		HR for EFS: 1.3 (0.9-2.1)	0.11	NR		NR
Yock 2006[d] [8]	Large tumour (≥8cm)	RT (55.8 Gy) vs. Surg vs. Surg+RT (45-55.8 Gy)	17 vs. 6 vs. 15	NR		At 5 y: 59% (35-82) vs. 50% (10-90) vs. 40% (15-65)	0.52	At 5 y: 76% (56-97) vs. 83% (51-100) vs. 87% (69-100)	0.76	No second malignancies during median follow-up of 4.4 (0.6-11.4) y
	Small tumour (<8cm)	RT (55.8 Gy) vs. Surg vs. Surg+RT (45-55.8 Gy)	27 vs. 6 vs. 4	NR		At 5 y: 49% (30-67) vs. 33% (0-71) vs. 75% (33-100)	0.54	At 5 y: 74% (57-91) vs. 67% (22-100) vs. NR	0.50	
Donati 2007[e] [4]		RT (55-60 Gy) vs. Surg±RT (40-60 Gy)	33 vs. 23	NR		HR for EFS: 2.92 (1.16-7.35)	0.02	NR		NR
Bacci 2009[f] [2]		RT (55-60 Gy) vs. Surg vs. Surg+RT (35-40 Gy))	17 vs. 27 vs. 11	NR		At 5 y: 35% (12-58)[c] vs. 74% (57-91)[d] vs. 54% (25-83)[c]	0.04	At 5 y: 82% vs. 93% vs. 81%	NS	RT alone: 1 pt (6%) radiotherapy-induced osteosarcoma at 6 years, 2 pts (12%) pathologic fracture Surg: 3 pts (11%) mechanical failure that needed re-surgery
DuBois 2015[g] [5]		RT (55.8 Gy[h]) vs. Surg	121 vs. 241	HR: 1.38 (0.84-2.27)	0.20	HR for EFS: 1.40 (0.93-2.12)	0.11	2.39 (1.20-4.74)	0.01	NR
		Surg+RT(45-50.4 Gy[i]) vs. Surg	103 vs. 241	HR: 1.35 (0.83-2.19)	0.22	HR for EFS: 1.13 (0.75-1.71)	0.55	0.96 (0.40-2.27)	0.92	

Abbreviation: CI = confidence interval, DFS = disease-free survival (defined as any disease recurrence including local, regional, or distant, but death is not included), EFS = event-free survival (events defined as disease progression, death from any cause, or second malignant neoplasm), Gy = Gray, HR = hazard ratio, LC = local control, N = sample size, NR = not reported, NS = not significant, OS = overall survival, post-op = post-

operative, pre-op = pre-operative, PRO = patient-reported outcomes, QOL = quality of life, RT = radiation therapy, Surg = surgery, vs. = versus, y = years.

[a]The original authors reported relative risk in their Cox proportional hazard analysis. It should be hazard ratio. We have contacted authors to confirm this point but there is no response.

[b]One of 115 patients did not have any treatment.

[c]It was calculated from the data provided in the paper.

[d]About 50% of the patients from this study was included in the DuBois 2015 study.

[e]The original authors reported relative risk in their Cox proportional hazard analysis and they confirmed that relative risk should be hazard ratio; Most patients in this paper were included in the Bacci 2006 paper.

[f]About 80% of the patients from this study was included in the Bacci 2006 study.

[g]This study conducted several logistic regression models and the results were similar. We chose and presented the results in our table from the model that included most variables (surgical and radiation propensity scores, age, tumour site, and tumour size).

[h]The information of doses of radiation therapy were from references 4-6 in this paper (Study INT-0091 [21], INT-0154 [22], and AEWS0031 [23]).

Table 4-3. RT alone versus surgery alone in patients with localized Ewing's sarcoma of bone[a].

Quality assessment							Summary of findings	Quality	Importance
№ of studies (sample size)	Study design/ tumour location	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HR (95% CI) or survival rate (95% CI)		
Overall survival									
1 (362) [5]	Observational study/whole body	Serious [1]	Not serious	Not serious	Serious [2]	None	HR 1.38 (0.84 to 2.27), NS	⊕◯◯◯ VERY LOW	CRITICAL
Event-free survival									
2 (700) [1,5]	Observational studies/whole body	Serious [1]	Not serious	Not serious	Serious [2]	None	Pooled HR 1.50 (1.12 to 2.00), p=0.007	⊕◯◯◯ VERY LOW	CRITICAL
1 (56)[b] [8]	Observational study/pelvis	Serious [1]	Not serious	Not serious	Serious [2]	None	Large tumour (≥8cm) at 5 y: 59% (35-82) vs. 50% (10-90), NS[c]; Small tumour (≥8cm) at 5 y: 49% (30-67) vs. 33% (0-71), NS[c]	⊕◯◯◯ VERY LOW	CRITICAL
1 (44)[d] [2]	Observational study/ humerus	Serious [1]	Not serious	Not serious	Serious [2]	None	At 5 y: 35% (12-58) vs. 74% (57-91), p=0.01[c]	⊕◯◯◯ VERY LOW	CRITICAL
Local control									
1 (362) [5]	Observational studies/whole body	Serious [1]	Not serious	Not serious	Serious [2]	None	HR 2.39 (1.20-4.74), p=0.01; Bacci 2009 (n=44):	⊕◯◯◯ VERY LOW	CRITICAL
1 (44)[d] [2]	Observational study/ humerus	Serious [1]	Not serious	Not serious	Serious [2]	None	At 5 y: 82% (64-100) vs. 93% (83-100) at 5 y, NS[c]	⊕◯◯◯ VERY LOW	CRITICAL
1 (56)[b] [8]	Observational study/pelvis	Serious [1]	Not serious	Not serious	Serious [2]	None	Large tumour (≥8cm) at 5 y: 76% (56-97) vs. 83% (51-100), NS[c]; Small tumour (≥8cm) at 5 y: 74% (57-91) vs. 67% (22-100), NS[c]	⊕◯◯◯ VERY LOW	CRITICAL
Patient-reported outcomes									
1 (44)[d] [2]	Observational study/ humerus	Serious [1]	Not serious	Not serious	Serious [2]	None	Function score[e]: 100% of pts ≥75% vs. 15% of pts between 50-75% and 85% of pts ≥75%	⊕◯◯◯ VERY LOW	IMPORTANT

Abbreviations: CI = confidence interval, HR = hazard ratio, NS = nonsignificant, pts = patients, RT = radiation therapy, vs = versus, y = years.
[a]GRADE Working Group grades of evidence [9]:

High quality = We are very confident that the true effect lies close to that of the estimate of effect.
Moderate quality = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality = Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality = We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[1] All the included studies were found to have serious risk.

[2]The sample size was less than 2,000 [24].

[b]About 50% of patients in this paper were included in the DuBois 2015 paper.

[c]P-value was calculated from the data provided in the paper.

[d]About 80% of patients in this paper were included in the Bacci 2006 paper.

[e]Function score ranged from 0% to 100% (higher scores indicate better functions).

Table 4-4. RT alone versus surgery plus RT in patients with localized Ewing's sarcoma of bone[a].

Quality assessment							Summary of findings	Quality	Importance
№ of studies (sample size)	Study design/ tumour location	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Survival rate (95% CI)		
Event-free survival									
1 (63) [8]	Observational study/pelvis	Serious [1]	Not serious	Not serious	Serious [2]	None	Large tumour (≥8cm) at 5 y: 59% (35-82) vs. 40% (15-65), NS[b]; Small tumour (≥8cm) at 5 y: 49% (30-67) vs. 75% (33-100), NS[b]. Bacci 2009	⊕◯◯◯ VERY LOW	CRITICAL
1 (28) [2]	Observational study/ humerus	Serious [1]	Not serious	Not serious	Serious [2]	None	At 5 y: 35% (12-58) vs. 54% (25-83), NS[b]		
Local control									
1 (63) [8]	Observational study/pelvis	Serious [1]	Not serious	Not serious	Serious [2]	None	Large tumour (≥8cm) at 5 y: 76% (56-97) vs. 87% (69-100), NS[b]	⊕◯◯◯ VERY LOW	CRITICAL
1 (28) [2]	Observational study/ humerus	Serious [1]	Not serious	Not serious	Serious [2]	None	At 5 y: 82% (64-100) vs. 81% (58-100) at 5 y, NS[b]		
Patient-reported outcomes									
1 (28) [2]	Observational study/ humerus	Serious [1]	Not serious	Not serious	Serious [2]	None	Function score: 100% of pts ≥75% vs. 100% of pts ≥75%, NS[b]	⊕◯◯◯ VERY LOW	IMPORTANT

Abbreviations: CI = confidence interval, HR = hazard ratio, NS = nonsignificant, pts = patients, RT = radiation therapy, vs = versus, y = years.

[a]Grades of evidence from GRADE system [9]:

High quality = We are very confident that the true effect lies close to that of the estimate of effect.

Moderate quality = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality = Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low quality = We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[1] All the included studies were found to have serious risk.

[2] The sample size was less than 2,000 [24].

[b]P-value was calculated from the data provided in the paper.

Table 4-5. RT alone versus surgery alone or surgery plus RT in patients with localized Ewing's sarcoma of bone[a].

Quality assessment							Summary of findings	Quality	Importance
№ of studies (sample size)	Study design/ tumour location	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HR (95% CI) or survival rate (95% CI)		
Overall survival									
1 (53) [3]	Observational study/pelvis	Serious [1]	Not serious	Not serious	Serious [2]	None	When tumour size not in regression model (n=53): HR 2.59[b], p=0.059; When tumour size in regression model (n=36): HR 4.85[b], p=0.026	⊕◯◯◯ VERY LOW	CRITICAL
Disease-free survival									
1 (53) [3]	Observational study/pelvis	Serious [1]	Not serious	Not serious	Serious [2]	None	When tumour size not in regression model (n=53): HR 2.64 (1.01-6.92)[b], p=0.048; When tumour size in regression model (n=36): HR 5.06 (1.39-18.43)[b], p=0.014	⊕◯◯◯ VERY LOW	CRITICAL
Event-free survival									
1 (56) [4]	Observational study/pelvis	Serious [1]	Not serious	Not serious	Serious [2]	None	HR 2.92 (1.16-7.35)[c], p=0.02	⊕◯◯◯ VERY LOW	CRITICAL
Local control									
1 (54) [7]	Observational study/whole body	Serious [1]	Not serious	Not serious	Serious [2]	None	Sokolov 2000: 25% (2-48) vs. 61% (46-76) at 5 years, p<0.02[d]	⊕◯◯◯ VERY LOW	CRITICAL

Abbreviations: CI = confidence interval, HR = hazard ratio, RT = radiation therapy.

[a]Grades of evidence from GRADE system [9]:

High quality = We are very confident that the true effect lies close to that of the estimate of effect.

Moderate quality = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality = Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low quality = We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[1] The included studies were found to have serious risk.

[2] The sample size was less than 2,000 [24].

[b]The original authors reported relative risk in their Cox proportional hazard analysis. It should be a hazard ratio. We have contacted the authors to confirm this point but there is no response.

[c]The original authors reported relative risk in their Cox proportional hazard analysis and they confirmed that relative risk should be hazard ratio; Most patients in this paper were included in the Bacci 2006 paper.

[d]P-value was calculated from the data provided in the paper.

Table 4-6. Surgery plus RT versus surgery alone in patients with localized Ewing's sarcoma of bone[a].

Quality assessment							Summary of findings	Quality	Importance
№ of studies (sample size)	Study design/ tumour location	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HR (95% CI) or survival rate (95% CI)		
Overall survival									
1 (344) [5]	Observational study/whole body	Serious [1]	Not serious	Not serious	Serious [2]	None	HR 1.35 (0.83-2.19), NS	⊕◯◯◯ VERY LOW	CRITICAL
Event-free survival									
2 (650) [1,5]	Observational studies/whole body	Serious [1]	Not serious	Not serious	Serious [2]	None	Pooled HR 1.21 (0.90-1.63), NS	⊕◯◯◯ VERY LOW	CRITICAL
1 (31)[b] [8]	Observational study/pelvis	Serious [1]	Not serious	Not serious	Serious [2]	None	Large tumour (≥8cm) at 5 y: 40% (15-65) vs. 50% (10-90), NS[c]; Small tumour (<8cm) at 5 y: 75% (33-100) vs. 33% (0-71), NS[c]	⊕◯◯◯ VERY LOW	CRITICAL
1 (38)[d] [2]	Observational study/ humerus	Serious [1]	Not serious	Not serious	Serious [2]	None	At 5 y: 54% (25-83) vs. 74% (57-91), NS[c]	⊕◯◯◯ VERY LOW	CRITICAL
Local control									
1 (344) [5]	Observational study/whole body	Serious [1]	Not serious	Not serious	Serious [2]	None	HR 0.96 (0.40-2.27), NS	⊕◯◯◯ VERY LOW	CRITICAL
1 (21)[b] [8]	Observational study/pelvis	Serious [1]	Not serious	Not serious	Serious [2]	None	Large tumour (≥8cm) at 5 y: 87% (69-100) vs. 83% (51-100), NS[c]	⊕◯◯◯ VERY LOW	CRITICAL
1 (38)[d] [2]	Observational study/ humerus	Serious [1]	Not serious	Not serious	Serious [2]	None	At 5 y: 81% (58-100) vs. 93% (83-100), NS[c]	⊕◯◯◯ VERY LOW	CRITICAL
Patient-reported outcomes									
1 (38)[d] [2]	Observational study/ humerus	Serious [1]	Not serious	Not serious	Serious [2]	None	Function score[e]: 100% of pts ≥75% vs. 15% of pts between 50-75% and 85% of pts ≥75%	⊕◯◯◯ VERY LOW	IMPORTANT

Abbreviations: CI = confidence interval, HR = hazard ratio, NS = nonsignificant, pts = patients, RT = radiation therapy, vs = versus, y = years.

[a]Grades of evidence from GRADE system [9]:
High quality = We are very confident that the true effect lies close to that of the estimate of effect.
Moderate quality = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality = Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality = We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[1] All the included studies were found to have serious risk.

[2] The sample size was less than 2,000 [24].

[b]About 50% of patients in this paper were included in the DuBois 2015 paper.
[c]P-value was calculated from the data provided in the paper.
[d]About 80% of patients in this paper were included in the Bacci 2006 paper.
[e]Function score ranged from 0% to 100% (higher scores indicate better functions).

Table 4-7. Surgery alone versus RT alone or surgery plus RT in patients with localized Ewing's sarcoma of bone[a].

Quality assessment							Summary of findings	Quality	Importance
№ of studies (sample size)	Study design/ tumour location	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Survival rate (95% CI)		
Overall survival									
1 (191) [6]	Observational study/whole body	Serious [1]	Not serious	Not serious	Serious [2]	None	At 5 y: 75% (65-82) vs. 70% (57-79), NS; At 10 y: 68% (57-77) vs. 70% (57-79), NS	⊕◯◯◯ VERY LOW	CRITICAL
Local control									
1 (191) [6]	Observational study/whole body	Serious [1]	Not serious	Not serious	Serious [2]	None	At 5 y: 90% (82-94) vs. 88% (77-94), NS	⊕◯◯◯ VERY LOW	CRITICAL

Abbreviations: CI = confidence interval, NS = nonsignificant, RT = radiation therapy, vs = versus, y = years.
[a]Grades of evidence from GRADE system [9]:
High quality = We are very confident that the true effect lies close to that of the estimate of effect.
Moderate quality = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality = Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality = We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

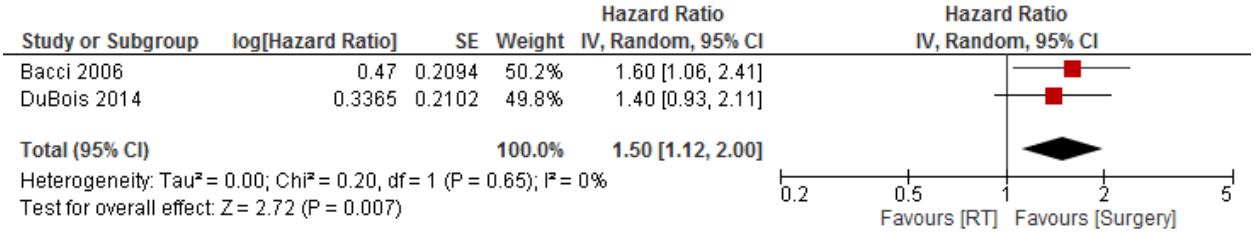
[1] The included studies were found to have serious risk.
[2] The sample size was less than 2,000 [24].

A. RT alone versus surgery alone

Four papers compared RT alone with surgery alone [1,2,5,8]. All the patients in the four papers who underwent surgery alone had negative surgical margins. Only the DuBois 2015 paper [5] reported OS and showed no statistically significant difference between the two groups (HR, 1.38; 95% CI, 0.84 to 2.27) in Table 4-3.

All four papers reported EFS (event was defined as disease progression, death from any cause, or second malignant neoplasm). The Yock 2006 paper [8] focused on patients with pelvic Ewing's sarcoma and the Bacci 2009 paper [2] focused on patients with humerus Ewing's sarcoma; and both the Bacci 2006 paper [1] and the DuBois 2015 paper [5] included patients with localized Ewing's sarcoma of bone in all the body parts. Approximately 50% of patients in the Yock 2006 paper were included in the DuBois 2015 paper [5] and approximately 80% of patients in the Bacci 2009 paper [2] were included in the Bacci 2006 paper [1]. Thus, a meta-analysis with data from the Bacci 2006 [1] and the DuBois 2015 papers [5] was performed and showed that surgery alone resulted in a higher EFS than RT alone (HR, 1.50; 95% CI, 1.12 to 2.00; p = 0.007) in 700 mixed location patients (Figure 1). The Bacci 2009 [2] favoured the surgery alone group in 44 humerus patients (Table 4-3). The Yock 2006 paper [8] did not find a statistically significant difference between these two groups in both subgroups of large tumour (≥8 cm, n=23) and small tumour (<8 cm, n=33) in pelvic patients (Table 3).

Figure 1. Event-free survival for radiation therapy (experimental) versus surgery (control) in localized Ewing's sarcoma of bone.



For the outcome of local control, surgery alone was better than RT alone in the DuBois 2015 papers in 362 mixed location patients (HR, 2.39; 95% CI, 1.20 to 4.74; p=0.01) [5], but no statistically significant difference was found in 56 pelvic patients in Yock 2006 [8] and in 44 humerus patients in the Bacci 2009 papers [2] in Table 4-3.

Only the Bacci 2009 paper reported patient-reported outcomes [2]. All the patients (n=17) in the RT group had a score of ≥75% (higher scores indicate better function); but 85% of patients (n=27) in the surgery-alone group had a score of >75% and the rest of 15% had a score of 50% to 75% (Table 4-3).

B. RT alone versus surgery plus RT

Both the Yock 2006 and Bacci 2009 papers [2,8] found that there were no statistically significant differences between RT alone and surgery followed by RT for EFS and local control in 91 patients (63 pelvic patients and 28 humerus patients) in Table 4-4.

The Bacci 2009 [2] reported that all the 28 humerus patients in the two groups had a function score of ≥75%.

C. RT alone versus surgery without or with RT

For this comparison, three studies [3,4,7] with a sample size of 53 to 56 for each study reported four outcomes and each outcome was reported by one study only. Compared with RT alone, surgery with or without RT led to better OS (HR, 4.85; p=0.026) and DFS (HR, 5.06; 95%

CI, 1.39 to 18.43; p=0.014) in 53 pelvic patients [3], EFS (HR, 2.92; 95% CI, 1.16 to 7.35; p=0.02) in 56 pelvic patients [4], and local control (rate at five years 25% versus 61%; p<0.02) in 54 mixed-location patients [7] (Table 4-5). However, none of them had a subgroup analysis for RT alone versus surgery, or RT alone versus surgery plus RT. Hence, we do not know whether these effects came from surgery alone, surgery plus RT, or both. Thus, it is not possible to determine relative treatment effects from these data.

D. Surgery plus RT versus surgery alone

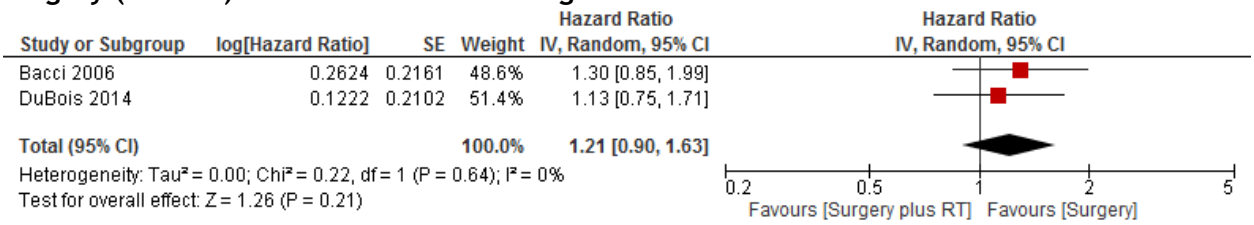
Four papers reported outcomes for this comparison [1,2,5,8]. The Dubois 2015 and the Bacci 2006 papers conducted multivariable analysis; thus, surgical margin should not impact their results [1,5]. However, all the patients who underwent surgery alone had negative margins in the Bacci 2009 and the Yock 2006 papers [2,8]. Again, only the DuBois 2015 paper [5] reported OS and showed no statistically significant difference between the two groups in 344 mixed-location patients (HR, 1.35; 95% CI, 0.83 to 2.19) in Table 4-6.

All four papers reported EFS. The results from the Bacci 2006 [1] and the DuBois 2015 [5] were pooled and no difference was found between the two groups in 650 mixed-location patients (HR, 1.21; 95% CI, 0.90 to 1.63) (Figure 2). The Bacci 2009 [2] and the Yock 2006 paper [8] also did not show a statistically significant difference between these two groups in 38 humerus and 31 pelvic patients, respectively (Table 4-6).

Three papers reported the outcome of local control, and all showed no statistically significant difference between the two groups [2,5,8] in Table 4-6.

Only the Bacci 2009 paper reported functional score in 44 humerus patients [2]. All patients (n=11) in the surgery plus RT group had a score of ≥75% but 15% of patients (n=27) in the surgery-alone group had a score of 50% to 75% (Table 4-6).

Figure 2. Event-free survival for surgery plus radiation therapy (experimental) versus surgery (control) alone in localized Ewing's sarcoma of bone.



E. Surgery alone versus RT alone or surgery plus RT

One study [6] investigated this comparison and showed no statistically significant difference between the two groups for OS at five and 10 years, and local control at five years in 191 mixed-location patients (Table 4-7). However, because they mixed patients who had RT alone and who had surgery plus RT together, we do not know whether there is no difference for the real effect between surgery alone and RT alone or between surgery alone and surgery plus RT from this table. Therefore, it is not possible to determine relative treatment effects from these data.

F. Toxicities/complications

Three studies reported RT toxicities and/or surgery complications in Table 4-2. The Sokolov study reported the following severe RT toxicities (including patients with RT alone and patients with post-operative RT) three (8%) fractures, three (8%) skin necroses, two (5%) functional changes, and two (5%) serious suppurations at 30 to 132 months [7]. The Yock 2006 study did not find any second malignancies during the median 4.4-year follow-up [8]. The Bacci 2009 study [2] demonstrated that one patient (6%) developed RT-induced osteosarcoma at six

years and two patients (12%) had pathologic fracture after RT alone; three patients (11%) had mechanical failure that needed reoperation after surgery alone.

Research question 2. Between pre-chemotherapy MRI and post-chemotherapy MRI, which surgical planning imaging is appropriate for optimal resection (e.g., negative margins) in patients with localized Ewing's sarcoma of bone who undergo surgical resection following neoadjuvant chemotherapy?

No eligible studies were found to answer this research question. That guideline—Bone Cancer, from the U.S. National Comprehensive Cancer Network (version 1.2015) [10]—provided recommendations on MRI to determine the appropriate surgical planning imaging. The quality of the guideline was assessed by using the AGREE II instrument (Table 4-8) [25], and adopted from the Standards and Guidelines Evidence Inventory of Cancer Guidelines developed by the Canadian Partnership Against Cancer (Available at: http://cancerguidelines.ca/Guidelines/inventory/index.php).

Table 4-8. Results of AGREE II quality rating for the NCCN version 1.2015 guideline[a].

Guideline	AGREE II Domain Score					
	Scope and Purpose	Stakeholder Involvement	Rigour of Development	Clarity and Presentation	Applicability	Editorial Independence
NCCN 2015	72.2%	58.3%	37.5%	80.6%	39.6%	87.5%

Abbreviation: NCCN, National Comprehensive Cancer Network.
[a]These results were adopted from the Standards and Guidelines Evidence Inventory of Cancer Guidelines developed by the Canadian Partnership Against Cancer. Available at: http://cancerguidelines.ca/Guidelines/inventory/index.php

Ongoing, Unpublished, or Incomplete Studies

The National Cancer Institute Clinical Trials Database (http://www.clinicaltrials.gov/) was searched on March 15, 2015 for potential trials meeting the selection criteria for this systematic review. There are two ongoing, unpublished, or incomplete trials that would be eligible for inclusion in the update of this guideline in the future (Appendix 7).

DISCUSSION

This systematic review showed inconsistent results for the first research question. When RT alone was compared with surgery alone, three papers [1,2,5] supported that surgery alone might lead to a better EFS, but one paper [8] did not find a difference between two groups; one paper supported that surgery alone might lead to a better local control [5] , but another two papers [2,8] did not support this result. Compared with RT alone, surgery plus RT was not associated with better clinical outcomes [2,8]. Compared with surgery alone, combined therapy with surgery plus RT also did not result in better clinical outcomes [1,2,5,8]. The undesirable effect could be happened from either surgical treatment (such as re-surgery needed or physical dysfunction) or RT (such as fractures, skin necroses, functional changes, and/or serious suppurations, etc.).

For the second research question, no evidence that met our preplanned study selection criteria was found. The Bone Cancer NCCN (National Comprehensive Cancer Network) 2015 consensus guideline [10] stated that "disease should be restaged with an MRI of the lesion and chest imaging following neo-adjuvant chemotherapy". The Working Group believed that the post-chemotherapy MRI strategy from the NCCN 2015 guideline is reasonable in patients with

localized Ewing's sarcoma of bone to allow orthopaedic oncologists to plan optimal pre-operative strategies on patients who would undergo surgical resection following neoadjuvant chemotherapy, given the standard clinical practice in the Ontario context.

There are several limitations in the existing literature regarding the first research question. First, the aggregate quality of evidence is very low from the GRADE approach for each comparison. Due to the variability of location of disease, institutional preferences, and specific details of decision-making in each patient, there are no relevant RCTs. In order to keep comparability, the Working Group only included studies that controlled for the baseline confounders or showed no significant difference of patient characteristics between the treatment groups, but not all the studies controlled the same confounders. One study [5] used logistic regression to generate propensity and performed several multivariable analyses; two studies [1,4] stated that the variables that proved significant in the univariable analysis were investigated in the multivariable analysis model; and other three studies did not clarify why the variables in the multivariable analysis model were chosen. The variables that were not significant in the univariable analysis might be significant in the multivariable analysis model [26]. Thus, some potential confounders might have been missed in the multivariable models in some studies, which could render the estimation uncertain. Second, except for the Donati 2007 study [4] that included 10 patients with preoperative RT, no study investigated the effect of pre-operative RT. Thus, the effect of pre-operative RT remains untested. Third, among the eight eligible papers reporting five different comparisons, patients in three papers overlapped [1,2,4] and patients in another two papers also overlapped [5,8]. Four papers reported outcomes in patients with tumours in various sites, while four papers reported outcomes from tumours present only in the pelvis or humerus. These differences make subgroup analyses in specific anatomic location (such as pelvic or extremity) impossible for each comparison. Fourth, the sample size from most included papers was small (less than 100 patients in six of eight papers). Due to limited eligible papers and heterogeneity, it was impossible to perform meta-analyses to increase power for all comparisons. Hence, any possible difference that may exist between the treatment options may be more difficult to identify. Fifth, patient-reported outcomes are lacking, which indicates the need for long-term functional studies.

CONCLUSIONS

The existing evidence shows that, in patients with localized Ewing's sarcoma of bone following neoadjuvant chemotherapy, either surgery alone **(**if complete surgical excision with clear margin can be reached) or RT alone may be a treatment option; if complete tumour resection is impossible, RT alone may be the optimal choice; and for patients who had residual tumours or positive margins after surgery, surgery followed by RT may be another reasonable treatment. The optimal local treatment for an individual patient should be decided by consideration of patient characteristics (e.g., age, tumour location, tumour size, response to neochemotherapy, and existing morbidities), the potential desirable and undesirable effects, and patient preference. Post-chemotherapy MRI may be reasonable to allow for optimal pre-operative planning in patients who undergo surgical resection following neo-adjuvant chemotherapy. Well-designed prospective comparative studies are required to better answer these research questions.

CONFLICT OF INTEREST

Information regarding conflict of interest declarations can be found in Appendix 1.

Optimal Treatment Strategies for Localized Ewing's Sarcoma of Bone after Neoadjuvant Chemotherapy

Section 5: Internal and External Review

INTERNAL REVIEW

Program in Evidence-Based Care (PEBC) guidelines are reviewed by a panel of content experts—Expert Panel and a methodology panel—Report Approval Panel (RAP). Both panels must approve the document. The Working Group was responsible for incorporating the feedback and required changes of both of these panels. The details of these reviews and actions taken are described below. Appendix 1 provides a list of members of the Working Group, RAP and Expert Panel and summarizes conflict of interest declarations for all members. The PEBC conflict of interest policy is available on the website of Cancer Care Ontario (CCO): https://archive.cancercare.on.ca/common/pages/UserFile.aspx?fileId=103568

Expert Panel Review and Approval

The Sarcoma Disease Site Group (DSG) acted as the Expert Panel for this document. For approval of the guideline document, 75% of the Sarcoma DSG membership must cast a vote or abstain, and of those that voted, 75% must approve the document. At the time of the voting, Sarcoma DSG members could suggest changes to the document, and make their approval conditional on those changes. In those cases, the Working Group was responsible for considering the changes, and if those changes could be made without substantially altering the recommendations, the altered draft would not need to be resubmitted for approval.

Of the eight members of the Sarcoma DSG (except the guideline authors), seven members voted and one abstained, for a total of 87.5% response. Of seven members who voted and whose expertise is in this area, all of them approved the document (100%). The main comments from the Expert Panel and the Working Group's modifications/actions/responses taken in response are summarized in Table 5-1.

Table 5-1. Modifications/actions/responses regarding main comments from the Expert Panel.

Main comments	Modifications, actions, or responses
1. In Qualifying Statements for Recommendation 1, you stated "The reported RT doses in this document have ranged from 40 to 60 Gray for RT alone and from 35 to 60 Gray for RT as an adjuvant to surgery". Except one study, all other studies used a dose minimum of 55 Gray for RT alone.	We have modified that sentence as: "The reported RT doses in this document ranged from 55 to 60 Gray for RT alone (except one study published in 1999) and from 35 to 60 Gray for RT as an adjuvant to surgery."
2. In my opinion, it would be easier to read/understand if the paragraphs were sorted as follows . RT alone vs surgery alone . RT alone versus surgery plus RT . RT alone vs surgery alone/surgery plus RT . Surgery plus RT versus surgery alone . Surgery alone versus RT alone/surgery plus RT We will have the three groups RT alone vs surgery ± RT and then surgery groups. As it is sorted now, it is a little bit difficult to follow what has been evaluated in different studies and how they compared with each other.	We have reorganized the orders to present the outcomes in **Sections 2 and 4** based on the reviewer's comments.

3. The following paper seems to be eligible but just misses the literature cut-off: Choi Y, Lim DH, Lee SH, Lyu CJ, Im JH, Lee YH, et al. Role of Radiotherapy in the Multimodal Treatment of Ewing Sarcoma Family Tumors. Cancer Res Treat. 2015 Feb 16 [epub].	The Choi 2015 paper was published after our literature search date (Feb 11, 2015). However, we will not include it in our future update because it is not a randomized controlled trial and does not have multivariable analysis to control the potential confounders at the baseline. It does not meet our study selection criteria.
4. I wonder if there might be consideration to answer the question(s) about radiation management (similar to Q2 in this review) in further projects.	This is a good idea. We can consider that point in the future projects.

Report Approval Panel Review and Approval

Three RAP members reviewed and approved this document in August 2015. The summary of main comments from the RAP and the Working Group's modifications/actions/responses taken in response are showed in Table 5-2.

Table 5-2. Modifications/actions/responses regarding main comments from the RAP.

Main comments	Modifications, actions, or responses
1. The second recommendation has no evidence; maybe it would be best to include it in the discussion only.	It seems that it would be very hard to find evidence even in the future to answer the second research question. Thus, the Working Group members believe the statement from the Bone Cancer National Comprehensive Cancer Network 2015 consensus guideline is appropriate at present for this specific area, given standard clinical practice in Ontario. The other Sarcoma DSG members (Expert Panel Review) have approved this Recommendation. This guideline will have External Review. All the Ontarian doctors in the PEBC database who may use this guideline potentially will receive an invitation to review this guideline. We will reconsider this recommendation if we receive any comments from External Review against this recommendation.
2. I like Appendix 3, but it is not clear if this external input is reflected in the document.	We summarized this report in the first paragraph under Outcomes in **Section 4** on page 14. We also mentioned it under Interpretation of Evidence for Recommendation 1 in **Section 2** on Page 4.
3. I do not understand why the specific dates were selected for each of the three searches on page 10.	We did not select any search dates. The three search dates were the time when we did the three database searches.
4. Why did you think the second research question was important? This is not explicitly stated.	We have added several sentences to explain this point under INTRODUCTION in **Section 4** on page 9.
5. The age of these recommendations is broad. I get it and it is justified. Does Pediatric Oncology Group of Ontario (POGO) have a guideline on this topic? If yes, we need to make sure both our recommendations and theirs align. If POGO does not have one, we should let POGO know about this document.	The POGO does not have a guideline on this topic. We will inform POGO of this guideline after it is published on the CCO website.

6. Neoadjuvant chemotherapy is standard. There was no question about doing nothing afterwards. It is unclear why patients need surgery or/and RT after chemotherapy.	We have added more words to make this point clear on page 9 in Introduction in Section 4: "Chemotherapy is considered a standard treatment to reduce the tumour size before further local control management".

EXTERNAL REVIEW
External Review by Ontario Clinicians and Other Experts

Targeted Peer Review

Six targeted international peer reviewers who are considered to be clinical and/or methodological experts on the topic were identified by the Working Group. Three agreed to be the reviewers (Appendix 1). Three responses were received. Results of the feedback survey are summarized in Table 5-3. The comments from targeted peer reviewers and the Working Group's responses are summarized in Table 5-4.

Table 5-3. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=3)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.				1	2
2. Rate the guideline presentation.					3
3. Rate the guideline recommendations.			1		2
4. Rate the completeness of reporting.				1	2
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?				1	2
6. Rate the overall quality of the guideline report.				1	2
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.			1	1	1
8. I would recommend this guideline for use in practice.			1		2
9. What are the barriers or enablers to the implementation of this guideline report?	--- Institutional biases/preferences given lack of level 1 data. --- None as recommendations are in line with what is known and in place in daily practice. --- Local experience may be limited in smaller centres. Even in the United Kingdom, there are only 80 new cases of Ewing's sarcoma a year. As a result, four years ago, we established a National Ewing's Multi-Disciplinary Team, which meets once a fortnight via a Wa bex teleconference. All new cases are discussed and local treatment agreed. We are just				

	auditing this. With such a rare tumour there may be a case for a similar set-up in Canada.

Table 5-4. Responses to main comments from targeted peer reviewers.

Comments	Responses
1. It was restricted to English literature only	Due to resource limitation, all the PEBC documents are restricted to English literature.
2. This guideline identifies the relative lack of evidence in this area and it is based on published papers. In the United Kingdom, we have come up with a very different decision: We have become much more aggressive treatment in local control. We held a European consensus conference in Birmingham in approximately 2006, and the conclusion of which was that "all of the pre-chemotherapy volume needs to be sterilized, ideally by surgery or if not by the combination of radiotherapy and surgery". This is now confirmed in the latest consensus guidelines: local control guidelines (EuroEwing 2012) and the British Sarcoma Group national guidelines.	The CCO PEBC guidelines are evidence-based guidelines. Consensus-based guidelines are appreciated, but may not be developed based wholly on evidence.
3. Consensus guidelines from other countries were not included, such as local control guidelines (EuroEwing 2012) and in the British Sarcoma Group national guidelines.	Again, the CCO PEBC guidelines are evidence-based guidelines. Thus, in general, we do not search or include consensus guidelines if we can find evidence from medical literature. However, for the second research question in this guideline regarding pre-chemotherapy MRI or post-chemotherapy magnetic resonance imaging (MRI) or post-chemotherapy MRI, we are unable to find any evidence from medical literature, and that is why we looked at consensus guidelines. There is no relevant content in the British Sarcoma Group national guidelines.

Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. All oncologists in the PEBC database who showed their interest on sarcoma were contacted by email to inform them of the survey. Fifty-five professionals were contacted; 52 practice in Ontario versus three who practice outside Ontario. Thirteen (24%) responses were received. Seven stated that they did not have interest in this area or were unavailable to review this guideline at the time. The results of the feedback survey from six people are summarized in Table 5-5. The main comments from the consultation and the Working Group's responses are summarized in Table 5-6.

Table 5-5. Responses to four items on the professional consultation survey.

	Number (%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.			1 (17%)	3 (50%)	2 (33%)
	Strongly Disagree	(2)	(3)	(4)	Strongly Agree

	(1)				(5)
2. I would make use of this guideline in my professional decisions.	1 (17%)			2 (33%)	3 (50%)
3. I would recommend this guideline for use in practice.				2 (33%)	4 (67%)
4. What are the barriers or enablers to the implementation of this guideline report?	---As this matches current practice, I do not anticipate problems with implementation. ---Barriers: The assumption of this guideline is that "neoadjuvant chemotherapy" is equally effective in all patients despite patients had been accrued over a long time interval; the eligible studies in this guideline had mediocre data and low sample size; Enablers: At least a framework to start examining what we do. Hopefully it will encourage people to examine the same parameters when they review their data so that we can have a clearer direction in the future - as there never will be a randomized trial. ---This is a very practical guideline and should be implemented: (1) Adequate education to ensure all surgeons, radiologists, oncologists, and other healthcare personnel fully understand and follow the guideline; (2) Close follow-up to monitor the changes in each centre. CCO needs to set up a regular follow-up plan with detailed indicators; (3) All patients' data need to be centralized; (4) Evaluate the impact of this guideline on patient outcomes: CCO should collect and analyze pre- and post-implementation data to determine if there is an improvement in Ewing's sarcoma patient outcomes. It may be challenging at the initial phase.				

Table 5-6. Modifications/actions taken/responses regarding main written comments from professional consultants.

Comments	Responses
1. Thorny issue. I don't disagree with anything said since there is a lot of suggestive language in the guideline. For Q2, I would vote pre-chemotherapy MRI because I am not convinced that we, medical oncologists, can wipe out everything in the bulk area. Some surgical specimens have left us surprised.	This recommendation is not based on evidence, and therefore is only qualified as a suggestion. From a surgical oncology standpoint, the consensus of the group was that both pre- and post-chemotherapy MRIs should be taken into consideration for surgical planning. In certain anatomic locations with good chemotherapy response, the post-chemotherapy MRI may be the appropriate imaging modality to plan surgical resection margins.
2. Quality of recommendations is limited by available data.	Although available data are limited, the guideline group members do our best to make useful recommendations for Ontarians.

CONCLUSION

The final guideline recommendations contained in Section 2 and summarized in Section 1 reflect the integration of feedback obtained through the external review processes with the document as drafted by the DSG Working Group and approved by the DSG Expert Panel and the PEBC RAP.

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Appendix 1. Members of the Working Group, Sarcoma Disease Site Group, and Report Approval Panel, and Targeted peer reviewers with their conflict of interest declaration.

1. Members of the Working Group

Name	Affiliation	Declarations of interest
Joel Werier, Orthopaedic Oncologist	Division of Orthopaedic Surgery, The Ottawa Hospital Regional Cancer Centre, Ottawa, Ontario	None declared
Xiaomei Yao, Health Research Methodologist	Program in Evidence-Based Care, Cancer Care Ontario, Department of Oncology, McMaster University, Hamilton, Ontario	None declared
Jean-Michel Caudrelier, Radiation Oncologist	Division of Radiation Oncology, The Ottawa Hospital Regional Cancer Centre, Ottawa, Ontario	None declared
Gina Di Primio, Radiologist	Division of Radiology St. Joseph's Healthcare Hamilton, Hamilton, Ontario,	None declared
Michelle Ghert, Orthopaedic Oncologist	Division of Orthopaedic Surgery, Juravinski Cancer Centre, Hamilton, Ontario	None declared
Abha Gupta, Medical Oncologist	Division of Haematology/Oncology, The Hospital for Sick Children, Toronto, Ontario	None declared
Rita Kandel, Pathologist	Department of Pathology & Laboratory Medicine, Mount Sinai Hospital, Toronto, Ontario	None declared
Shailendra Verma, Medical Oncologist	Department of Medical Oncology, The Ottawa Hospital Regional Cancer Centre, Ottawa, Ontario	None declared

2. Other Sarcoma Disease Site Group members for this guideline

Name, Expertise	Affiliation	Declarations of interest
Charles Catton, Radiation Oncologist	Division of Radiation Oncology, The Princess Margaret Hospital, Toronto, Ontario	I treat Ewing's sarcoma as part of my employment
Thomas Corbett, Radiation Oncologist	Division of Radiation Oncology, Juravinski Cancer Centre, Hamilton, Ontario	None declared
Jay Engel, Surgical Oncologist	Department of Surgical Oncology, Cancer Centre of	None declared

	Southeastern Ontario, Kingston, Ontario	
Rebecca Gladdy, Surgical Oncologist	Department of Surgical Oncology, Mount Sinai Hospital, Toronto, Ontario	None declared
Barb Heller, General Surgeon	Department of Surgery, McMaster University, Hamilton, Ontario	None declared
Naveen Parasu, Radiologist	Department of Radiology, Juravinski Cancer Centre, Hamilton, Ontario	None declared
Snezana Popovic, Pathologist	Department of Pathology and Molecular Medicine, McMaster University, Hamilton, Ontario	None declared
Richard Tozer, Medical Oncologist	Department of Medical Oncology, Juravinski Cancer Centre, Hamilton, Ontario	None declared

3. Members of the Report Approval Panel

Name, Expertise	Affiliation	Declarations of interest
Laurie Elit, Gynecologist	Juraviniski Cancer Centre, Hamilton, Ontario, Canada	None declared
Melissa Brouwers, Director of Program in Evidence-Based Care	Cancer Care Ontario, Toronto, Ontario, Canada McMaster University, Hamilton, Ontario, Canada	None declared
Donna Maziak, Surgical Oncologist	Ottawa General Hospital, Ottawa, Ontario, Canada	None declared

4. Members of the Targeted Peer Reviewers

Name, Expertise	Affiliation	Declarations of interest
Robert Grimer, Orthopaedic Oncologist	Royal Orthopaedic Hospital, Northfield, Birmingham, United Kingdom	None declared
Lor Randall, Orthopaedic Oncologist	The University of Utah's Huntsman Cancer Institute and Primary Children's Medical Center, Salt Lake City, Utah, United State	I received ≥$5000 in a single year in the past five years for presentations given at Biomet meetings in Japan and for institutional support to program for participation on their board in Musculoskeletal Transplant Foundation. I have also received an OREF Young Investigator grant and an OMEGA Fellowship grant.
Robert Turcotte, Orthopaedic Oncologist	Montreal General Hospital and Montreal Children's	I am an employee of McGill University; I was a Chair of

	Hospital, Montreal, Quebec, Canada	the orthopaedic surgery residency program in 2014.

Appendix 2. Literature search strategies

Database(s): **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)** 1946 to Present

Search Strategy:

#	Searches
1	(ewing$ or ESFT$ or (bone adj2 sarcoma$)).mp.
2	(presurger$ or pre-surger$ or preoperat$ or pre-operat$ or postsurger$ or post-surger$ or postoperat$ or post-operat$).mp.
3	(surger$ or radiotherap$ or radiation$ or operat$ or surgical$ or irradiat$ or amputat$ or resect$ or excision$).mp.
4	exp Ewing sarcoma/rt, su, th [Radiotherapy, Surgery, Therapy]
5	(adjuvant adj3 therapy).mp.
6	or/2-5
7	Animal/ not Human/
8	(comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
9	or/7-8
10	(1 and 6) not 9
11	limit 10 to (english language and yr="1999 -Current")
12	remove duplicates from 11

Database(s): **Embase** 1996 to 2015 Week 06

Search Strategy:

#	Searches
1	(ewing$ or ESFT$ or (bone adj2 sarcoma$)).mp.
2	(presurger$ or pre-surger$ or preoperat$ or pre-operat$ or postsurger$ or post-surger$ or postoperat$ or post-operat$).mp.
3	(surger$ or radiotherap$ or radiation$ or operat$ or surgical$ or irradiat$ or amputat$ or resect$ or excision$).mp.
4	adjuvant therapy.mp. or exp adjuvant therapy/
5	or/2-4
6	exp Ewing sarcoma/rt, su, th [Radiotherapy, Surgery, Therapy]
7	(editorial or note or letter or erratum or short survey).pt. or abstract report$/ or letter$/ or case stud$/
8	Animal/ not Human/
9	or/7-8
10	((1 and 5) or 6) not 9
11	limit 10 to (english language and yr="1999 -Current")

Appendix 3. Classification of important outcomes

Research Question 1: Three comparisons for surgery vs. RT, surgery vs. surgery plus RT, or RT vs. surgery plus RT in patients with localized Ewing's sarcoma of bone following neoadjuvant chemotherapy

RFS/EFS/PFS/LC, toxicity/complication, PRO

	OS	RFS/EFS/PFS/LC	Toxicity/complication	PRO
J. Werier	9	8	6	5
X. Yao	9	8	8	6
J. Caudrelier	5	9	9	7
G. Di Primio	No response			
M. Ghert	7	9	7	6
A.A. Gupta	9	9	9	9
R. Kandel	9	9	9	5
S. Verma	9	8	9	6
Average score	**8.1**	**8.6**	**8.1**	**6.3**
Importance[a]	**CRITICAL**	**CRITICAL**	**CRITICAL**	**IMPORTANT**

Abbreviations: EFS = event-free survival, LC = local control, LF = local failure, OS = overall survival, PFS = progression-free survival, PRO = patient-reported outcomes (including quality of life), RFS = relapse-free survival, RT = radiation therapy, vs. = versus.

[a]GRADE (Grading of Recommendations Assessment, Development and Evaluation) specifies three categories of outcomes according to their importance for decision-making: 7, 8, or 9 scores represent CRITICAL; 4, 5, or 6 scores represent IMPORTANT; 1, 2, or 3 scores represent NOT IMPORTANT.

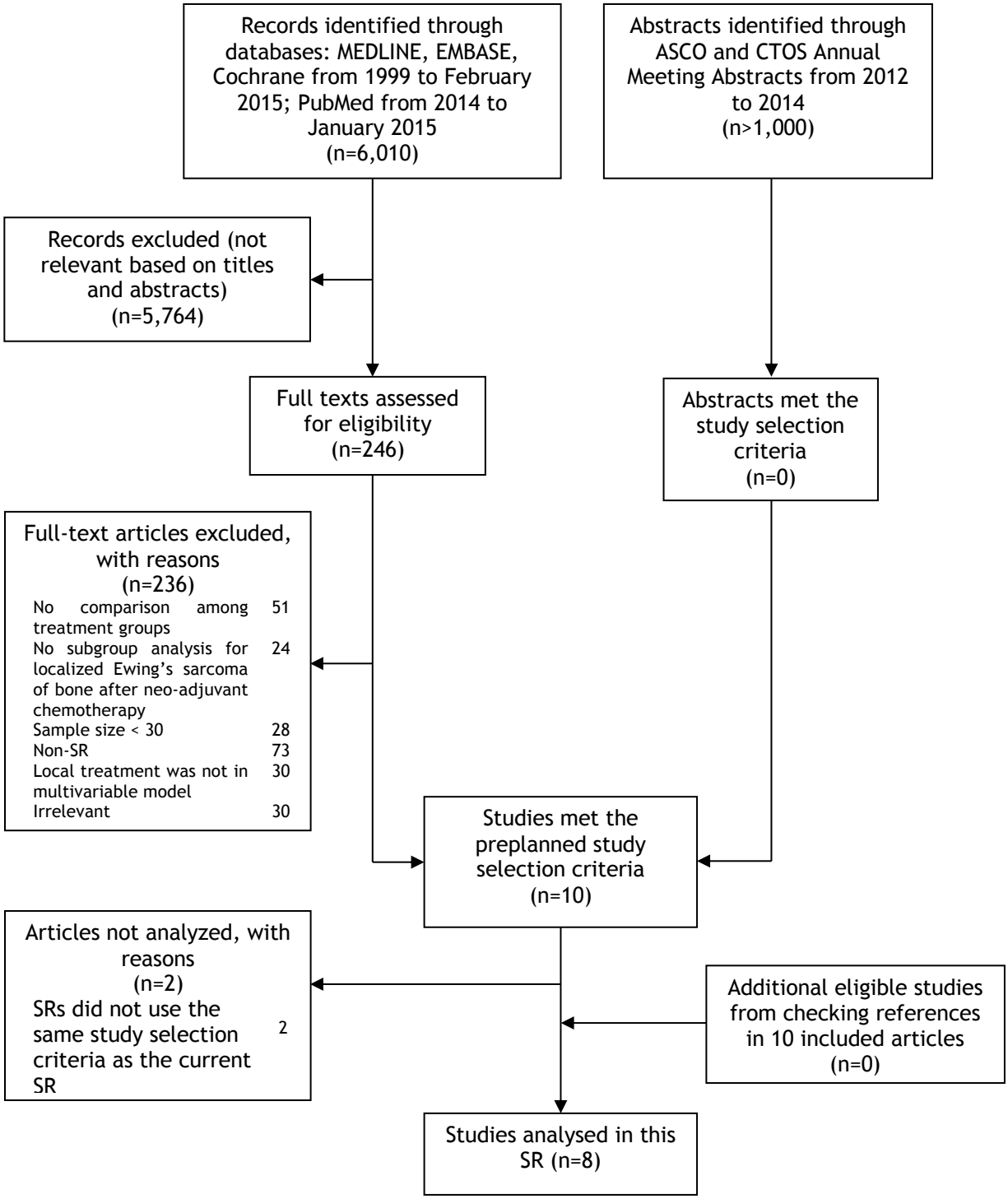
Research Question 2: Pre-chemotherapy MRI vs. post-chemotherapy MRI in patients with localized Ewing's sarcoma of bone who undergo surgical resection following neo-adjuvant chemotherapy

	Optimum resection (e.g., negative margins)	OS	PRO
J. Werier	9	7	6
X. Yao	8	9	6
J. Caudrelier	9	4	5
G. Di Primio	No response		
M. Ghert	9	9	7
A.A. Gupta	9	4	4
R. Kandel	9	9	5
S. Verma	8	9	6
Average score	**8.7**	**7.3**	**5.6**
Importance[a]	**CRITICAL**	**CRITICAL**	**IMPORTANT**

Abbreviations: MRI = magnetic resonance imaging, OS = overall survival, PRO = patient-reported outcomes (including quality of life), vs. = versus.

[a]GRADE (Grading of Recommendations Assessment, Development and Evaluation) specifies three categories of outcomes according to their importance for decision-making: 7, 8, or 9 scores represent CRITICAL; 4, 5, or 6 scores represent IMPORTANT; 1, 2, or 3 scores represent NOT IMPORTANT.

Appendix 4. Modified PRISMA flow diagram.



Abbreviations: ASCO = American Society of Clinical Oncology, CTOS = Connective Tissue Oncology Society, SR = systematic review.

Appendix 5. Risk of bias assessment table.

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in measurement of interventions	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Funding[a]	Overall
Carrie 1999	Moderate risk	Moderate risk	Moderate risk	Moderate risk	No information	Low risk for OS; serious bias for other outcomes	Serious risk	No information	Serious risk
Shankar 1999	Moderate risk	Moderate risk	Moderate risk	Moderate risk	No information	Low risk for OS; serious bias for other outcomes	Serious risk	Low risk	Serious risk
Sokolov 2000	Moderate risk	Moderate risk	Serious risk	Moderate risk	No information	Serious risk	Serious risk	No information	Serious risk
Bacci 2006	Moderate risk	Moderate risk	Moderate risk	Moderate risk	No information	Serious risk	Serious risk	No information	Serious risk
Yock 2006	Moderate risk	Moderate risk	Moderate risk	Moderate risk	No information	Serious risk	Serious risk	Low risk	Serious risk
Donati 2007	Moderate risk	Moderate risk	Moderate risk	Moderate risk	No information	Serious risk	Serious risk	No information	Serious risk
Bacci 2009	Moderate risk	Moderate risk	Moderate risk	Moderate risk	No information	Serious risk	Serious risk	No information	Serious risk
DuBois 2015	Moderate risk	Moderate risk	Moderate risk	Moderate risk	No information	Low risk for OS; serious bias for other outcomes	Serious risk	Low risk	Serious risk

Abbreviations: OS = overall survival.
[a]Low risk = non-industry funding.

Appendix 6. Significant factors in multivariable analysis from eligible papers.

Study	Rules for variables into multivariable model	Variables in the multivariable analysis	Statistically significant variables associated with a better outcome
Carrie 1999	NR	**Model 1 for OS or EFS:** Age (<12 y vs. ≥12 y); Tumour site (iliac wing vs. other pelvic locations); Response to neo-adjuvant chemotherapy (SD vs. CR/PR); Neoadjuvant chemotherapy protocol I[a] (EW84 vs. EW93); Neoadjuvant chemotherapy protocol II[a] (EW88 vs. EW93); Local treatment (RT alone vs. Surg±RT) **Model 2 for OS or EFS:** Age (<12 y vs. ≥12 y); Tumour site (iliac wing vs. other pelvic locations); Tumour size (>200 mm^3 vs. ≤200 mm^3) Response to neoadjuvant chemotherapy (SD vs. CR vs. PR); Neoadjuvant chemotherapy protocol II (EW88 vs. EW93); Local treatment (RT alone vs. Surg±RT)	**Model 1:** Local treatment (Surg±RT) **Model 2:** Tumour size (≤200 mm^3); Response to neo-adjuvant chemotherapy (CR/PR); Local treatment (Surg±RT)
Shankar 1999	NR	**Model 1 for OS or local control:** Age (0-4 y vs. 5-9 y vs. 10-14 y vs. ≥15 y); Gender (male vs. female); Tumour site (extremity vs. other sites); Surgery (non-Surg vs. incompleted Surg vs. completed Surg); RT (RT±Surg vs. Surg) **Model 2 for local control:** Age (0-4 y vs. 5-9 y vs. 10-14 y vs. ≥15 y); Gender (male vs. female); Tumour site (Long bone vs. other sites); Surgery (non-Surg vs. incompleted Surg vs. completed Surg); RT (RT±Surg vs. Surg)	**Model 1:** Age (younger); Gender (male); Tumour site (extremity) **Model 2:** Tumour site (extremity)
Sokolov 2000	**NR**	**Model for local control:** Preoperative chemotherapy (4 drugs [VACA] vs. 6 drugs [VACA+Endoxan+adriamycine]); Local treatment (RT alone vs. Surg±RT); Other variables were age, gender, tumour site, and tumour size (no details)	Preoperative chemotherapy (6 drugs); Local treatment (Surg±RT)

Bacci 2006	Only the variables that proved significant in the variable analysis were investigated in multivariable model.	**Model for EFS:** Age (≤14 y vs. >14 y); Gender (male vs. female); Serum LDH value (normal vs. elevated); Tumour size (≤150 mL vs. >150 mL); Local treatment (Surg alone vs. Surg±RT and Surg alone vs. RT alone); Surgical margins (adequate vs. inadequate); Histologic response to chemotherapy (grade III vs. grade II and grade III vs. grade I)	Age (>14 y); Serum LDH value (normal); Tumour size (≤150 mL); Local treatment (Surg along when comparing with RT alone); Surgical margins (adequate); Histologic response to chemotherapy (grade III)
Donati 2007	Only the variables that proved significant in the univariable analysis were investigated in multivariable model.[b]	**Model for EFS:** Gender (male vs. female); Local treatment (RT alone vs. Surg±RT)	Local treatment (Surg±RT)
DuBois 2015	They performed several multivariate models with different variables, and all the multivariable models showed similar results.[c]	**Model for OS, EFS, or local control:** Age (<12 y vs. ≥12 y); Tumour site (distal extremity vs. proximal extremity vs. pelvis vs. chest wall vs. spine); Clinical trial (INT-0091 vs. INT-0154 vs. AEWS0031); Surgical and radiation propensity scores	Age; Tumour site; Clinical trial; Surgical and radiation propensity scores

Abbreviations: CR = complete response, EFS = event-free survival, NR = not reported, OS = overall survival, PR = partial response, RT = radiation therapy, SD = stable disease, Surg = surgery, VACA = vincristine, dactinomycin, adriamycin, and cyclophosphamide, vs = versus, y = years.
[a]There were no details for EW84, EW88, and EW93 chemotherapy protocols in the paper.
[b]The univariable analysis included following variables: gender, age, tumour site, tumour volume, different chemotherapy, histologic response, surgical margin, and local treatment.
[c]The model that included the most variables is shown.

Appendix 7. Ongoing trials.

Investigator (country)	Title	Study design, sample size (age)	Protocol ID	Estimated study completion date
Mohamed Zaghlol (Egypt)	Post-operative radiotherapy in poor responders Ewing's sarcoma patients	RCT, 150 (<18 y)	NCT01734863	December 2022
Jaume Mora Graupera (Spain)	Study of intensive chemotherapy, surgery and radiotherapy to treat Ewing's sarcoma in children and young adults	Non-RCT, 43 (≤40 y)	NCT01696669	December 2015

Abbreviations: RCT = randomized controlled trial, y = years.

Ontario Health
Cancer Care Ontario

Evidence-Based Series 11-6 Version 2: Section 6

Optimal Treatment Strategies for Localized Ewing's Sarcoma of Bone after Neoadjuvant Chemotherapy

Document Review Summary

J. Werier, C. Arinze, and Members of the Expert Panel on Localized Ewing's Sarcoma of Bone after Neoadjuvant Chemotherapy

February 14, 2022

The 2015 guideline recommendations are

ENDORSED

This means that the recommendations are still current and relevant for decision making

OVERVIEW

The original version of this guidance document was released by Cancer Care Ontario's Program in Evidence-based Care in 2015.

In December 2020, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist conducted an updated search of the literature. A clinical expert (JW) reviewed and interpreted the new eligible evidence and proposed the existing recommendations could be endorsed. The Expert Panel on Localized Ewing's Sarcoma of Bone after Neoadjuvant Chemotherapy endorsed the recommendations found in Section 1 of the Clinical Practice Guideline in February 2022.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Questions Considered

1. Among the options of surgery alone, RT alone, and the combination of RT plus surgery, which is the optimum treatment strategy to improve clinical outcomes (i.e., overall survival [OS], relapse-free survival [RFS]/progression-free survival [PFS]/event-free survival [EFS]/disease-free survival [DFS]/local control,

toxicities/complications, and patient-reported outcomes) in patients with localized Ewing's sarcoma of bone following neoadjuvant chemotherapy?

2. Between pre-chemotherapy MRI and post-chemotherapy MRI, which surgical planning imaging is the most appropriate to plan an optimal resection (e.g., negative margins) in patients with localized Ewing's sarcoma of bone who undergo surgical resection following neoadjuvant chemotherapy?

Literature Search and New Evidence

The new search (2015 to June 2021) yielded no new publications of RCTs. However, one network meta-analysis and four retrospective studies that compared RT alone to surgery alone or to a combination of RT and surgery, following neoadjuvant therapy, were identified. An additional search for ongoing studies on Clinicaltrials.gov yielded no relevant ongoing RCTs. Brief results of these searches are shown in the Document Review Tool.

A 2020 network meta-analysis met inclusion criteria [1], however, among the 11 studies in that publication, seven were included in the original 11-6 guideline, two were retrieved in the literature search for this review, and two did not meet inclusion criteria. Therefore, the results of the meta-analysis are not considered for this review.

One retrospective analysis of patients in the Euro-EWING99 trial treated with induction chemotherapy reported that a combination of RT and surgery decreased local recurrence more than RT alone in patients with non-sacral tumours of the pelvis [2].

Impact on the Guideline and Its Recommendations

At the time the guideline was developed in 2015, the evidence did not support a recommendation for the combination of surgery plus RT. This evidence from the Euro-EWING99 retrospective analysis requires corroboration from further studies to warrant a review of or change to the current recommendation, but it is highlighted in the qualifying statements. Hence, the Expert Panel ENDORSED the 2015 guideline on Optimal Treatment Strategies for Localized Ewing's Sarcoma of Bone after Neoadjuvant Chemotherapy.

Ontario Health
Cancer Care Ontario

Document Review Tool

Number and Title of Document under Review	11-6: Optimal Treatment Strategies for Localized Ewing's Sarcoma of Bone after Neoadjuvant Chemotherapy
Original Report Date	December 22, 2015
Date Assessed (by DSG or Clinical Program Chairs)	December 3, 2020
Health Research Methodologist	Chika Arinze
Clinical Expert	Joel Werier
Approval Date and Review Outcome (once completed)	ENDORSE February 14, 2022

Original Question(s):

1. Among the options of surgery alone, RT alone, and the combination of RT plus surgery, which is the optimum treatment strategy to improve clinical outcomes (i.e., overall survival [OS], relapse-free survival [RFS]/progression-free survival [PFS]/event-free survival [EFS]/disease-free survival [DFS]/local control, toxicities/complications, and patient-reported outcomes) in patients with localized Ewing's sarcoma of bone following neoadjuvant chemotherapy?
2. Between pre-chemotherapy MRI and post-chemotherapy MRI, which surgical planning imaging is the most appropriate to plan an optimal resection (e.g., negative margins) in patients with localized Ewing's sarcoma of bone who undergo surgical resection following neoadjuvant chemotherapy?

Target Population:

- Patients of any age diagnosed with localized Ewing's sarcoma of bone who have completed neoadjuvant chemotherapy for the first objective
- Patients of any age diagnosed with localized Ewing's sarcoma of bone who will undergo surgical management following neoadjuvant chemotherapy for the second objective

Study Selection Criteria:

Inclusion Criteria

An article was eligible for inclusion if it met all the following preplanned criteria:

1. It was a full-text report published in the period from 1999 to February 2015 for the first research question (Q1) and from 2004 to February 11, 2015 for the second research question (Q2) or a conference/meeting abstract published from 2012 to 2014 for either question.

2. For a full-text report, it reported on a randomized controlled trial (RCT), or comparative study that controlled for the baseline confounders (like multivariable analysis, etc.) or showed no significant difference for the patient characteristics between treatment groups for Q1 and Q2, or prospective single-arm study for Q2 only.
3. For a conference/meeting abstract, it reported on an RCT for Q1 and there is no study design limitation for Q2.
4. Analyzed sample size should be ≥30 patients.
5. It investigated surgery, RT, or combination of surgery and RT in patients with localized Ewing's sarcoma of bone following neo-adjuvant chemotherapy for Q1 or investigated surgical planning imaging (pre-chemotherapy MRI or post-chemotherapy MRI) for optimal resection (e.g., negative margins) in patients with localized Ewing's sarcoma of bone for Q2.
6. For an existing systematic review, it should describe database search methods (including database names and search date) and study selection criteria; and it should have at least one eligible article that met the above inclusion criteria.

Exclusion Criteria

An article or abstract was excluded if it met any of the following preplanned criteria:

1. It was published in a language other than English.
2. It was published in the form of a letter, animal study, editorial, or commentary.
3. Studies reported the outcomes on mixed patients of >10% metastatic, non-osseous, without neoadjuvant chemotherapy, or non-Ewing's sarcoma patients but without subgroup analysis for patients with localized Ewing's sarcoma of bone following neoadjuvant chemotherapy.

Search Details:

- 2017 to July 2021 Cochrane (Database of Systematic Reviews)
- January 2015 to July 2021 (Medline and Embase)
- January 2015 to August 2021 (Clinicaltrial.org for ongoing trials)

Summary of new evidence:

Out of 3011 hits from the search of Medline, Embase, and the Cochrane Database for systematic reviews, no new publications of RCTs that compared RT alone to surgery alone or a combination of RT and surgery, following neoadjuvant therapy was identified. However, one network meta-analysis and four retrospective studies were identified.

Clinical Expert Interest Declaration:

The Clinical Expert (JW) and Health Research Methodologist (CA) declared no conflict of interest.

1. Does any of the newly identified evidence contradict the current recommendations? (i.e., the current recommendations may cause harm or lead to unnecessary or improper treatment if followed)	No. The newly identified evidence does not contradict the current recommendations. However the new evidence supports the need for an additional qualifying statement.
2. Does the newly identified evidence support the existing recommendations?	Yes. However, the findings of Andreou et al (2020) suggest that a combination of surgery and RT may be beneficial in the treatment of non-sacral Ewing sarcoma of the pelvis. This new evidence should be noted in the guideline.
3. Do the current recommendations cover all relevant subjects addressed by the evidence? (i.e., no new recommendations are necessary)	Yes.
Review Outcome as recommended by the Clinical Expert	ENDORSE with an addition to the qualifying statement. Qualifying statement One retrospective data analysis of patients in the Euro-EWING99 trial treated with induction chemotherapy reported that a combination of RT and surgery decreased local recurrence more than RT alone in patients with non-sacral tumours of the pelvis. This evidence requires corroboration from further studies to warrant a review of or change to the current recommendation.
If outcome is UPDATE, are you aware of trials now underway (not yet published) that could affect the recommendations?	
DSG/Expert Panel Commentary	

Evidence Table

Author [Ref#] Study Name	**Study Design (Med F/U in Months)**	**Population and number of patients**	Result
Zhu et al (2020) [1]	Network meta-Analysis of 11 studies comparing RT surgery or a combination of surgery and RT	Patients with operable and non-metastatic Ewing sarcoma who are treated with neoadjuvant chemotherapy n = 2540	• Compared to RT only, surgery was significantly better in local recurrence [OR (95% CI) 0.48 (0.33 - 0.87) P<0.03.]. A combination of RT and surgery was also significantly better than RT alone [OR (95% CI) 0.50 (0.29 - 0.82) P<0.03]. • There was no significant survival difference between the three local control strategies.
Andreou et al (2020) [2]	Retrospective data analysis of patients in Euro-EWING99 trial treated with induction chemotherapy: VIDE	Patients with previously untreated ES Med age: 17yrs Med F/U: 54mos n = 180	• For patients with sacral tumours, 5-year local recurrence and OS rates were not statistically significantly different between those treated with combined surgery and RT and those treated with RT alone. • For non-sacral tumours, the 5 year local recurrence rate was lower in patients treated with the combination of surgery and RT than in those treated with RT alone [14% (95% CI 5 to 23) vs. 40% (95% CI 15 to 65), p = 0.018]. • Surgery and RT combination treatment for non-sacral tumours was also better than surgery alone for local recurrence [14% (95% CI 5 to 23) vs. 33% (95% CI 19 to 47), p = 0.015] and OS [72% (95% CI 61 to 83) vs. 47% (95% CI 33 to 62), p = 0.024]. • In a subgroup of non-sacral tumours with wide surgical margins and good response to induction treatment, the combination of RT and surgery resulted in higher OS [87% (95% CI 74 to 100) vs 51% (95% CI 33 to 69), p = 0.009] and EFS [83% (95% CI 68 to 98) vs 42% [95% CI 24 to 60) p = 0.015] at 5 years compared with surgery alone. • In those patients with non-sacral tumours who received surgical treatment, poor response to

			induction chemotherapy and complications from surgery were associated with lower OS.
Ahmed et al (2017) [3]	Retrospective analysis of patients treated with ifosfamide and etoposide-based chemotherapy followed by local therapy (RT or Surgery or RT + surgery)	Patients with localized skeletal or extra-skeletal ES treated on INT-0091, INT-0154, and AEWS0031protocol Med age:13yrs n = 956	• The five-year cumulative incidence of local failure in those that were treated with RT was significantly higher compared to those treated with surgery alone. [HR 4.12 (2.39 to 7.12) P <0.01]. • The significance was maintained after controlling for tumor sites. Extremity and pelvis tumors treated with RT were associated with significantly higher local failure incidence compared to those treated with surgery. [HR 6.31 (1.48-26.96) p = 0.01] • There was no difference between those treated with surgery alone and surgery plus RT [HR 1.69 (0.87-3.31) p =0.12]
Ahmed et al (2017) [4]	All patients received chemotherapy - VDC/IE	Pelvic Ewing sarcoma ES patients Med F/U: 8.3yrs n = 48	• There was no significant difference in survival and recurrence outcomes based on local control modality.
Becker et al. (2016) [5]	Retrospective analysis of patients in the Brazilian collaborative study group – EWING1 trial treated with two courses of ifosfamide/carboplatin/etoposide and two courses of vincristine/doxorubicin/cyclophosphamide followed by local control	Patients with localized bone disease Mean Age: 12.8yrs Med F/U: 4.5yrs n = 73	• 5-year EFS was significantly better in the group that had surgery alone compared to those that had RT alone or surgery + RT (71.7% vs. 64.1% vs. 30.8%; p = 0.0090). • There was no significant difference in LF rates by local control modality (p = 0.61)

EFS; Event free survival; ES: Ewings sarcoma; HR: Hazard ratio; LF: local failure; OR: odds ratio; OS: Overall survival; RT: radiotherapy; VDC/IE: vincristine, doxorubicin cyclophosphamide, ifosfamide and etoposide; VIDE: vincristine, ifosfamide, doxorubicin, and etoposide

References

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3. Ahmed SK, Randall RL, DuBois SG, Harmsen WS, Krailo M, Marcus KJ, et al. Identification of Patients With Localized Ewing Sarcoma at Higher Risk for Local Failure: A Report From the Children's Oncology Group. International Journal of Radiation Oncology Biology Physics. 2017;99(5):1286-94.
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Appendix 1. Members of the Expert Panel

Name	Affiliation	Conflict of Interest Declaration
Charles Catton	Radiation Oncologist Princess Margaret Cancer Centre, Toronto	Employment with the University Health Network.
Michelle Ghert	Orthopedic Oncologist Juravinski Cancer Centre, Hamilton	None declared.
Abha Gupta	Medical Oncologist The Hospital for Sick Children, Toronto	None declared.
Aly-Khan Lalani	Medical Oncologist Juravinski Cancer Centre, Hamilton	Ad hoc consultation for advisory meetings: AbbVie, Astellas, Bayer, BMS, Eisai, Ipsen, Janssen, Merck, Novartis, Pfizer, Roche, andTerSera. Clinical trial/research grants, all funds directed to institution: BMS (Inst), BioCanRx (Inst), Novartis (Inst), Roche (Inst), Ipsen (Inst), EMD Serrono (Inst).
Snezana Popovic	Pathologist McMaster University, Hamilton	None declared.

Appendix 2. Literature search strategies

Database(s): Embase 1996 to 2021 July 9

1. (ewing$ or ESFT$ or (bone adj2 sarcoma$)).mp.
2. (presurger$ or pre-surger$ or preoperat$ or pre-operat$ or postsurger$ or post-surger$ or postoperat$ or postoperat$).mp.
3. (surger$ or radiotherap$ or radiation$ or operat$ or surgical$ or irradiat$ or amputat$ or resect$ or excision$).mp.
4. exp Ewing sarcoma/rt, su, th [Radiotherapy, Surgery, Therapy]
5. adjuvant therapy.mp. or exp adjuvant therapy/
6. or/2-5
7. Animal/ not Human/
8. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
9. or/7-8
10. (1 and 6) not 9
11. limit 10 to (english language and yr="2015 -Current")
12. remove duplicates from 11

Database(s): Ovid MEDLINE(R) 1996 to July 9, 2021, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 2017 to July 9, 2021

1. (ewing$ or ESFT$ or (bone adj2 sarcoma$)).mp.
2. (presurger$ or pre-surger$ or preoperat$ or pre-operat$ or postsurger$ or post-surger$ or postoperat$ or postoperat$).mp.
3. (surger$ or radiotherap$ or radiation$ or operat$ or surgical$ or irradiat$ or amputat$ or resect$ or excision$).mp.
4. exp Ewing sarcoma/rt, su, th [Radiotherapy, Surgery, Therapy]
5. (adjuvant adj3 therapy).mp.
6. or/2-5
7. Animal/ not Human/
8. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
9. or/7-8
10. (1 and 6) not 9
11. limit 10 to (english language and yr="2015 -Current")
12. remove duplicates from 11

DEFINITIONS OF REVIEW OUTCOMES

1. **ARCHIVE** – ARCHIVE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is out of date or has become less relevant. The document, however, may still be useful for education or other information purposes. The document is designated archived on the CCO website and each page is watermarked with the words "ARCHIVED."

2. **ENDORSE** – ENDORSE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is still useful as guidance for clinical decision making. A document may be endorsed because the Expert Panel feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **UPDATE** – UPDATE means the Clinical Expert and/or Expert Panel recognizes that the new evidence pertaining to the guideline topic makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The Expert Panel advises that an update of the document be initiated. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making, unless the recommendations are considered harmful.