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Evidence-Based Series 11-10 EDUCATION AND INFORMATION 2015

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

Appropriate Surgical Margins and Proper Handling of Soft Tissue Sarcoma of the Extremities

R. Kandel, N. Coakley, J. Werier, J. Engel, S. Verma, and the Sarcoma DSG

Report Date: September 7, 2012

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Section 1: Guideline Recommendations
Section 2: Evidentiary Base
Section 3: Development, Recommendations, & External Review Process

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Evidence-Based Series 11-10: Section 1

Appropriate Surgical Margins and Proper Handling of Soft Tissue Sarcoma of the Extremities: Guideline Recommendations

R. Kandel, N. Coakley, J. Werier, J. Engel, S, Verma, and the Sarcoma DSG

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

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QUESTIONS

1. In limb salvage surgery for extremity soft tissue sarcoma (STS), what is considered an adequate surgical margin, in the context of the following:
   a. Surgery alone?
   b. Surgery in combination with adjuvant or neoadjuvant radiation and/or chemotherapy?

2. What would be the appropriate number of surgical resection specimens to obtain?

3. What is the appropriate handling technique for surgical resection specimens?

TARGET POPULATION

Patients with STS of the extremities who are candidates for limb-sparing surgery and whose treatment objectives are to obtain local control and overall survival.

INTENDED USERS

This guideline is targeted to surgeons performing extremity STS surgery, oncologists (radiation and medical) who treat these patients, and pathologists examining the resection specimens from these patients.

RECOMMENDATIONS AND KEY EVIDENCE

RECOMMENDATION 1

In limb salvage surgery for STS, surgery should be planned with the objective of achieving a clear margin. However, in order to preserve functionality, surgery may result in a close or even microscopically positive margin. Based on the consensus opinion of the Sarcoma Disease Site Group, a 'close' margin is considered to be <1cm following formalin fixation. In the circumstance of a close or microscopically positive margin, the use of preoperative or postoperative radiation may be considered.

Key Evidence 1

Twenty-eight studies provided evidence on margin status and recurrence rates (1-28). Local recurrence rates ranged from 3%-24% for patients with negative margins and from 6%-53% for positive margins.

Two studies (1,2) provided recurrence free survival rates for extremity STS treated with surgery alone. They both concluded that positive margin status was associated with increased recurrence rate.

Twenty-four studies evaluated the use of radiotherapy in addition to the resection of STS (4-27). Of those studies, three provided separate results for radiotherapy (RT) versus no radiotherapy. Two of these studies demonstrated no difference in local recurrence rates between the groups (5,9), and the third showed that RT decreased the frequency of local recurrence (16).

Only one study provided results for the use of chemotherapy in addition to surgery and radiation in patients with marginal excisions (incisions through the pseudocapsule or reactive zone) (28). No significant benefit was observed.

Qualifying Statements

In limb-sparing surgery for STS, an adequate margin for surgical treatment alone or for surgery with RT cannot be defined as the studies did not definitively identify an appropriate margin distance. Intact fascia (which can be measured in millimeters) is considered an adequate margin by some.

A microscopic positive margin in STS of the limb treated with surgery and radiation may have an increased rate of local recurrence. This suggests that every effort should be made to achieve a negative margin.

In the event that limb function will be compromised, surgeons and patients may wish to discuss the benefits and risks of accepting a very close margin that may even be microscopically positive and the importance of preoperative or postoperative RT.

Local recurrences have been observed even when negative margins are achieved with surgery and with surgery and radiation, suggesting that tumour characteristics other than margin status are important. Further study is required.

At this time, there is no evidence to support the use of postoperative chemotherapy in soft tissue tumours of the extremity that have undergone intralesional or marginal excisions.

RECOMMENDATION 2
For the histological assessment of margins, no definitive recommendations can be made for the appropriate number of margin samples that are required.

Key Evidence 2
Three guidelines (29-31) and one protocol (32) addressed this question but did not provide any evidence that could be used for recommendations.

RECOMMENDATION 3
It is not possible to make evidence-based recommendations as to the appropriate handling of surgical resection specimens to assess the adequacy of excision. Guidelines, where mentioned, endorse inking margins and sampling them perpendicular to (and not enface to) the margin.

In the absence of evidence-based recommendations, the Sarcoma Disease Site Group (DSG) recommends the following, based on the expert opinion of the Working Group and consensus of the DSG members:

- **The specimen should be received fresh with orientation indicated by the surgeon.**
- **The specimen and the tumour should be measured in three dimensions.**
- **The distances from all six margins should be measured and the location of the tumour (superficial or deep) and the relationship to fascia, if present, indicated.**
- **All margins should be sampled perpendicular to the margin, and at least 2 samples taken from the closest margin and 1-2 sections from all other margins.**
- **More extensive margin sampling should be considered for tumours such as angiosarcoma, epithelioid sarcoma, and chondrosarcoma.**

Key Evidence 3
Because no evidence was identified to inform these recommendations, they are based on the expert opinion and consensus of the Sarcoma DSG and are consistent with current guidelines (29-31).

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Updating
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Evidence-Based Series 11-10: Section 2

Appropriate Surgical Margins and Proper Handling of Soft Tissue Sarcoma of the Extremities: Evidentiary Base

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QUESTIONS

1. In limb salvage surgery for extremity soft tissue sarcoma (STS), what is considered an adequate surgical margin, in the context of the following:
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INTRODUCTION

Sarcomas are a heterogenous group of mesenchymal malignancies that arise in soft tissue and bone. They affect all age groups and can arise in any part of the body. They are relatively rare, comprising approximately 2% of adult tumours and 15% of pediatric malignancies (1). In Ontario, approximately 700 new adult sarcoma cases per year are registered. STS are the more common sarcomas, and these tumours occur most frequently in the extremities. Treatment is often multimodal and complex, and these patients can experience significant morbidity and mortality as a consequence of the treatment or the disease. The goals of sarcoma management include both a cure for and the functional preservation of involved tissues and adjacent critical structures.

Surgery is the primary treatment for extremity STS. In the past, surgery consisted of amputation, but several studies have now demonstrated the efficacy of limb-sparing surgical techniques combined with preoperative or postoperative radiation in achieving acceptable local control and equivalent overall survival. The combination of radiation therapy (RT) with surgery allows for limb salvage by using radiation to biologically 'sterilize' microscopic extensions of disease and sparing neurovascular and osseous structures. Developments in

cross-sectional imaging, (including computed tomography [CT] and magnetic resonance imaging [MRI]), as well as improved treatment planning processes such as CT simulation, have greatly improved the targeting of tissues at risk for tumour involvement. The use of adjuvant chemotherapy in STS, except for rhabdomyosarcoma and Ewing's sarcoma (PNET), continues to be controversial.

Surgical excision is the primary treatment for extremity STS, and, although necessary for cure, recurrence and metastases can occur in the presence of complete resection. This raises the question as to what is an adequate margin, a question complicated by the type of tissue at the margin, e.g., fascia versus fat. In addition, there is evidence that a planned positive microscopic margin (2) such as that against a neurovascular bundle does not result in a worse outcome. As well, how do we define adequate assessment (gross assessment and number of histological samples) of resection margins?

To answer these questions, and provide guidance for clinicians the Sarcoma Disease Site Group (DSG) (Appendix A) decided to prepare a clinical practice guideline on this topic, based on a systematic review of the available evidence. This section presents the systematic review.

METHODS

This evidentiary base was developed using the following planned two-stage method:

1. Search and evaluation of existing systematic reviews: If one or more existing systematic reviews are identified that address the research questions and are of reasonable quality, then those systematic reviews would form the core of the evidentiary base.
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.

The resulting evidentiary base and related recommendations are intended to promote evidence-based practice in Ontario, Canada. 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.

Literature Search Strategy

The MEDLINE (1975 to June 2011), EMBASE (1975 to June 2011), and Cochrane Library (2011, Issue 2) databases were searched for published practice guidelines, technology assessments, systematic reviews, clinical trials, and studies. Reference lists of papers and review articles were scanned for additional citations. The Canadian Medical Association Infobase (http://www.cma.ca/index.cfm/ci_id/54316/la_id/1.htm), the National Guidelines Clearinghouse (http://www.guideline.gov/), and other websites were searched for existing evidence-based practice guidelines. The American Society of Clinical Oncology (ASCO) Conference proceedings from 2007-2010 were searched. Search terms indicative of sarcoma, surgical margins, and handling of specimens were used, with the full search strategy available in Appendix B.

Study Selection Criteria

Inclusion Criteria

Articles were eligible for inclusion in this systematic review of the evidence if they reported on studies that met the following criteria:

- The definition of what was considered to be a negative or positive margin through measurements or detailed descriptions was reported.

- They included adult patients with extremity (arms and legs) STS and limb-sparing surgery was the primary treatment.
- They reported on at least one of the following outcomes: local recurrence, recurrence free survival, overall survival, or disease free survival.
- For Questions 2 and 3, they reported on an outcome resulting from the handling techniques for STS specimens.

Exclusion Criteria

Studies were excluded if they:

- Were published in a language other than English as translation capabilities were not available.
- Included patients with other types of sarcoma and the results for STS were not specifically reported.
- Did not specify what constituted a negative or positive surgical margin.
- Were retrospective studies with less than 100 subjects.

Quality Appraisal of Evidence

The Appraisal of Guidelines Research and Evaluation (AGREE) tool (3) was used by four independent methodologists (NC and others) to evaluate the quality of the identified evidence-based guidelines. While all the scoring domains of the AGREE tool were considered in the evaluation of guidelines, the Rigour of Development domain, describing the rigour of systematic methods in identifying and evaluating evidence, along with the Overall Rating, were considered to be most relevant in application for this systematic review. The AGREE Tool scoring results can be found in Appendix C.

Synthesizing the Evidence

Data was not pooled in a meta-analysis due to the absence of randomized trial (RCT) data and the heterogeneity of the included studies. Very few eligible studies reported hazard ratios (HR) of primary outcomes such as overall survival, and in many studies the appropriate data were not available to estimate HR.

Statistical heterogeneity would be calculated using the x^2 test for heterogeneity and the I^2 percentage. A probability level for the x^2 statistic less than or equal to 10% ($p \leq 0.10$) and/or an I^2 greater than 50% would be considered indicative of statistical heterogeneity.

RESULTS

Literature Search Results

Articles were selected for consideration in this systematic review of the evidence if they were published reports of studies of <u>any design</u> that reported on aspects on surgical margins for STS of the extremities. Studies including patient data on other sarcoma sites were included if the results for the extremities were listed separately. Because no systematic reviews were found, this guideline focuses on the results of the primary literature search. The quality of literature was poor due to the fact that the studies were most commonly retrospective cohort studies. Furthermore, most studies did not describe how tumours were sampled or margins were evaluated. In some papers statistical analysis was lacking, and in other studies analyses were done in the presence of mixed treatment groups, e.g., RT ± chemotherapy.

Thirty-three papers, including four guidelines, one protocol, and one abstract, were eligible for inclusion in this systematic review. Four guidelines that assessed the criteria for positive margins in STS or provided information on proper handling of specimens were considered relevant to this guideline (4,5,6,7). Only the European Society for Medical

Oncology (ESMO) Guideline defined what is considered a proper surgical margin. The National Comprehensive Cancer Network (NCCN) and the Dutch Working Group on Soft Tissue Sarcoma Guideline defined only the margin criteria for when chemotherapy or radiation should be administered. The guidelines from the Association of Directors of Anatomic and Surgical Pathology (ADASP) addressed the proper handling of surgical specimens. The protocol from the College of American Pathologists (CAP) also described proper handling techniques. The Dutch Association of Comprehensive Cancer Centres (ACCC) stated that their guideline was evidence-based. However, the methods were not available in English, and so this assertion could not be verified (7). The other guidelines were consensus-based documents (4,5,6).

Thirty-two studies addressed the question of the negative versus positive criteria for surgical margins. Out of these, only three were prospective studies (8,9,10). The rest were retrospective studies using collected patient data (4,5,6,7,11–35).

There were three guidelines (5,6,7) and one protocol (36) that described the handling of surgical specimens. A table summarizing the literature search results can be found in Appendix D.

Outcomes

1. In limb salvage surgery for extremity soft tissue sarcoma what is considered an adequate surgical margin?

Thirty-three papers provided a definition of what was considered negative and positive surgical margins. While some papers did not quantitate margin distance, they did state that a clear margin was one with no residual microscopic disease left at the tumour site. As evident in the Tables 1-5, there is no agreement on what is an adequate margin. The range cited is between negative for tumour at the inked margin and 5 cm.

Surgery Alone

Two studies addressed the question of an adequate surgical margin with surgery alone. (see Table 1). The criteria of a clear margin in one study was less than 2.5cm (13) and in the other was described as being "all normal tissue surrounding the specimen" (8). In terms of local recurrences, the studies by Enneking et al and Berlin et al (8,13) showed that they were reduced in patients with negative margins. A potential bias in the surgery-alone group is that these tumours are usually superficial (11,23,29).

Table 1. Surgery alone.

Study	N	Clear margin criteria	Recurrence free Survival	Overall Survival
Enneking 1981 (8)	40	Intralesional: leaves macroscopic residual lesions, satellites and skips. Marginal: May leave both microscopic satellites in the reactive zone and skips in the surrounding tissue. Wide: Potentially leaves only microscopic skips associated with high grade lesions in the remaining surrounding normal tissues. Radical: All the normal tissue of the compartment involved encases the specimen.	Local Recurrence Marginal procedures 50% (2/4) Wide 25% (3/12) Radical 4% (1/24)	NR

Berlin 1990 (13)	137	Intralesional: leaves macroscopic residual lesions, satellites and skips. Marginal: May leave both microscopic satellites in the reactive zone and skips in the surrounding tissue. Wide: Potentially leaves only microscopic skips associated with high grade lesions in the remaining surrounding normal tissues. Radical: All the normal tissue of the compartment involved encases the specimen.	Local Recurrence Wide local excision: 10/76 (13%) Marginal local excision: 16/25 (64%)	NR

Abbreviation: NR = not reported.

Surgery in Combination with Adjuvant or Neoadjuvant Chemotherapy and/or Radiation Treatment

Most of the studies that addressed margin criteria were done in combination with adjuvant or neoadjuvant chemotherapy and/or radiation. Chemotherapy was given in 17 studies (9,10,12,14,16-19,22,24-28,31,32) and discussed in two guidelines. However, not all the studies provided detailed results for the patients receiving chemotherapy.

The two guidelines reported on what clinical situations warranted the administration of chemotherapy. The ACCC recommends that chemotherapy only be given in the context of a clinical trial (7). The ESMO guideline which is a consensus document states that adjuvant chemotherapy is not standard treatment in adult STS, but it can be used on certain high risk patients with deep tumours (5).

Only one study, a randomized trial (10), provided results for patients receiving chemotherapy (Table 2). In this study, the patients were randomized after surgery to doxorubicin or control groups. The adjuvant postoperative chemotherapy consisted of doxorubicin 60 mg/m^2 intravenously on day 1, the cycle length was 28 days, and nine cycles were given. The postoperative treatment with doxorubicin did not influence the risk of local recurrence, although those with a marginal excision also received radiotherapy. The width of the surgical margin did not influence the outcome. (10).

Table 2. Results of patients receiving chemotherapy in addition to surgery.

Study	N	Clear margin criteria	Recurrence free Survival	Overall survival
Alho 1989 (10)	185	Compartmental: the tumour was resected *en bloc* Wide excision: an adequate margin of 2.5cm of healthy tissue is included with the specimen Marginal excision: the knife cuts close to the tumour through the pseudocapsule or reactive zone in one area or more.	All patients received chemotherapy. Local recurrence free survival at 3 years Compartmental n=24, recurrences n=1 (96%) Wide local excision n=84, recurrences n=7 (92%) Marginal local excision +radiotherapy n=21, recurrences n=2 (90%) Reclassified marginal excision n=19, recurrences n=7 (63%)	Compartmental n=24, survival at 3 years 75% Wide local excision n=84, survival at 3 years 78% Marginal local excision +radiotherapy n=21, survival at 3 years 78% Reclassified marginal excision n=19, survival at 3 years 60%

Twenty-five studies and four guidelines reported on outcomes following surgery and radiation therapy and provided information about the surgical margin width as well.

The guidelines listed in Table 3 vary only slightly in their recommendations (see also Table 4). The ESMO guideline does not state a margin size but recommends that radiation be given to tumours over 5 cm. The ACCC, the National Comprehensive Cancer Network, and the ADASP both recommend radiation should be given with margins <1 cm in the fixed state and <2cm in the fresh state. Only the ACCC provided a recommendation on the width of the field that should be radiated around the tumour. They suggested 5-10 cm depending on the tumour type.

In eight studies the most common reason for giving radiation treatment was a positive margin (11,14,20,21,23,24,29,31). In three studies radiation treatment was given on the basis of a discussion between the surgeon and radiation oncologist (16-18). In two studies all the patients received radiation treatment (2,25). In three studies patients with positive margins were given a boost (2,25,34). Radiation treatment was given based on the size of the tumour in two studies (14,26) and the grade of the tumour in one study (31). Six studies did not provide reasons for radiation treatment (12,15,19,27,28,32). Six studies also provided details regarding the width of the field irradiated around the tumour site, and all treated five or more centimetres (7,14,24,25,29,31).

Table 3. Comparison of guideline criteria for giving radiotherapy and margin for radiation.

Study	Recommended clear margin	Criteria for giving radiation	Margin irradiated
The Dutch Association of Comprehensive Cancer Centres (7)	NR	Radiation is recommended for tumours with margins that are <2 cm fresh or <1 cm fixed	5-10 cm depending on the type of sarcoma 2 cm for boost
ESMO (5)	1 cm but in some areas with anatomical barriers the margins may be minimal.	Radiation is standard for tumours >5 cm	NR
NCCN (4)	Negative margins should be used, but close margins may be necessary to preserve uninvolved critical neurovascular structures.	<1 cm or microscopically positive on bone or major blood vessel or major nerve	NR
Association of Directors of Anatomic and Surgical Pathology guideline 1999 (6)	Recommends that margins should be 2 cm or more if possible.	Surgical margins of less than 1.5-2 cm predispose to an increase in local recurrence and further surgery or radiation should be undertaken. If the surgical margin is bounded by an unbreached layer of fascia or periosteum this risk probably does not apply.	NR

Abbreviation: NR = not reported.

Table 4 Comparison of criteria for giving radiotherapy and margin for radiation.

Study	N	Criteria for giving radiation	Margin irradiated
Azzarelli 1993 (11)	444	Marginal margins received radiotherapy	NR
Al Yami (2010) (34)	216	Boost after surgery and positive margin. Preoperative radiation was also given	NR
Bonvalot 2010 (33)	450	Criteria not stated (published as abstract only)	NR
Bell 1989 (12)	100	-	NR
Davis 1997 (14)	239	Location and size of tumour, dissection on a neurovascular bundle leaving positive margins, surgeon deemed it necessary	5 cm
Dickinson 2006 (15)	324	Not stated definitively	NR
Gerrand 2001 (2)	566	All patients received radiotherapy. Patients with positive margin received a post-operative boost.	NR
Gronchi 2005 (16)	911	No prospectively selected criteria were used, only when the surgeon and radiation oncologist thought there was a higher chance of recurrence	NR
Gronchi 2007 (17)	1017	No prospectively selected criteria were used, only when the surgeon and radiation oncologist thought there was a higher chance of recurrence	NR
Gronchi 2010 (18)	997	No prospectively selected criteria were used, only when the surgeon and radiation oncologist thought there was a higher chance of recurrence	NR
Heslin 1996 (19)	168	NR	NR
Jebsen 2008 (20)	1093	Not stated, however given pre-operatively and post-operatively if intra-lesional and marginal resection, if the surgical margin was intra-lesional additional radiotherapy (10-20Gy) was given	NR
Karakousis 2002 (21)	114	Surgical margin less than 2 cm	NR
Keus 1994 (23)	156	Margins less than 1cm and any residual macroscopic tumour	NR
Khanfir 2003 (24)	133	Patients with residual tumour cells and marginal margin (<10mm)	5 cm
Kim 2008 (25)	150	All patients received radiotherapy, patients with positive margins an additional boost	5-8 cm
Koea 2003 (26)	951	Dependant on the size and type of tumour	NR
Liu 2010 (35)	181	Given at discretion of clinician Adjuvant radiotherapy was given to fewer patients with margins >10 mm than those with margins <10 mm	NR
Matsumoto 2002 (9)	18	NR	NR
McKee 2004 (27)	111	NR	NR
Pisters 1996 (28)	1041	Given at discretion of surgeon	NR
Popov 2000 (29)	130	Surgical margin < 2.5 cm	5 cm
Sadoski 1993 (30)	132	Grades 2 and 3 sarcomas (pre-operative; post-operative boost for positive margins)	NR
Sampo 2008 (31)	270	In cases of marginal margins where re-operation was not possible or intra-lesional, post-operative boost for positive margin	5 cm
Stojadinovic 2002 (32)	2123	NR	NR

NR = not reported.

Twenty-five studies provided results for patients treated surgically and receiving radiation treatment and in some way characterized the width of the surgical margin (Table 5). Twenty-one studies demonstrated that positive margins had an unfavourable effect on local recurrence rates (2,9,11,12,14,16-18,20,21,23,25-33,35). One study reported there was no difference in local recurrence rates between positive and negative margins (24). Another study only had patients with positive margins, and the addition of a local radiation boost did not alter the recurrence rate (34).

The rate of developing distant metastasis was analyzed in nine studies. A positive margin was associated with a greater rate of distant metastasis in six studies (12,17,27,29,32,35), while in three studies there was no difference (2,18,28).

Overall survival was examined in four studies. Only the Popov et al study found that margin status was related to overall survival (29). The other three studies found no difference in overall survival and margin status with at least a three-year follow-up (2,24,27).

In most of the studies the results from patients who received radiotherapy were combined with the patients who did not receive radiotherapy. There were three studies that reported local control outcome data pertaining to radiotherapy and margins (19,24,29). The studies by Heslin et al, Khanfir et al and Popov et al showed that there was no difference in local control between the groups that had radiation and the groups that did not, although the study by Heslin et al analyzed those with positive margins and is further complicated by the fact that certain patients received chemotherapy (19). However, since the three studies were retrospective studies not RCTs, more clinically aggressive patients might be in the radiotherapy group and could confound the results.

Table 5. Results of radiation treatment.

Study	N	Clear margin criteria	Grade	Local recurrence Metastasis rate	Overall survival
Bell 1989 (12)	100	Positive: foci of tumour at the margin of resection or if the tumour had been exposed during surgical treatment and then further normal tissue had been excised.	Low grade N=27 High grade N=73	Local recurrences at 14 months Negative margin 4/52 (8%) Positive margin 24/48 (50%). Distant Metastasis at 23 months Negative margin 11/52 (21%) Positive margin 24/48 (50%) p=0.08	NR
Azzarelli 1993 (11)	444	Adequate: no tumour at margin and at least wide margins (according to Enneking) Marginal: acceptable only when marginality is minimal and followed by radiation therapy.	Low grade N=148 High grade 284	Local recurrence Adequate margins 24% Marginal operations, 47% (p< 0.001)	NR
Sadoski 1993 (30)	132	Negative 1: cells <1 mm from the inked margins Negative 2:cells >1 mm from the inked margin Positive: not defined.	grade 1 N= 11 grade 2 N= 62 grade 3 N= 59	5 year rates for local control negative margins 97% positive margins 82% (p=0.02). Patients with <1 mm had local control rates of 94% and >1 mm had rates of 97%	NR
Keus 1994 (23)	156	Wide local excision: 2 cm Marginal excision: <2 cm	grade 1 N= 49 grade 2 N= 22 grade 3 N= 61	Local recurrence at 3 years Wide excision 6/26 (23%) (surgery only) Narrow surgery 5/64 (8%) (surgery plus radiation)	NR
Heslin 1996 (19)	168	Positive: when tumour was identified at the margin of resection. Negative: tumours that were close (within 1 mm) but did not	High grade	Results only for 42 positive margin patients local recurrence Radiation n=27 No radiation n=15	NR

Study	N	Clear margin criteria	Grade	Local recurrence Metastasis rate	Overall survival
		involve the fascia		Distant Metastasis 42 Positive margin patients Distant metastasis Radiation n=27 No radiation n=13	
Pisters 1996 (28)	1041	Microscopic positive: tumour present within less than 1 mm from inked margin.	High grade = 678 (65%) low grade = 363 (35%)	Microscopically positive margin was adverse factor in local control (RR=1.8; 95% CI,1.3-2.5) Median time to local recurrence was 17 months Margins were not significant for developing metastases (p=0.13) Median time to distant recurrence was 13 months.	NR
Davis 1997 (14)	239	Positive: tumour found at the inked margin.	low grade = 47 (19.7%) high grade = 192 (80.3%)	Time to local recurrence decreased with margin positive surgery (x^2=18.30, p<0.00001.	NR
Popov 2000 (29)	130	Compartmental: the tumour was resected *en bloc* Wide: ≥ 2.5 cm or less than 2.5 but an intact anatomical barrier Intralesional: if visible tumour tissue was left in the operation area or tumour was cut through during operation Marginal: less than wide but more than intralesional	Low grade =28 high grade = 77 unclassified = 1	Local control at 5 years Wide or compartmental operations without RT 83% Marginal resections with RT 84%. Metastasis-free survival at 5 years Wide or compartmental operations without RT 88% Marginal operations with RT 60%	Overall survival at 5 years was 88% in wide or compartmental operations without RT and 68% in marginal operations with RT
Gerrand 2001 (2)	566	Positive margin: tumour presence at the margin of resection or intraoperative exposure of the tumour. Grossly positive: when the surgeon or pathologist could identify tumour at the margin of resection. Microscopic positive margin: inspection of the margin did not reveal tumour, but was identified at histological examination.	Grade available for positive margin patients only grade 1 = 27 grade 2 = 23 grade 3 = 37	Margin positive patients divided into 4 groups based on grade. Group 1 and 2 were low risk with negative or microscopic margins n=52 Group 3 and 4 were the high risk with positive margins n=35 Rate of local recurrence differed significantly between the low (4.2% and 3.6%) and the high-risk groups (31.6% and 37.5%) Number of local recurrences Group 1: 1 (4.2%) Group 2: 1 (3.6%) Group 3: 6 (31.6%) Group 4: 6 (37.5%) Mean time to local recurrence group 1: 4 months; group 2: 2 months; group 3: 35 months; group 4: 25 months Number of distant recurrences Group 1: 0/24 (0%) Group 2: 11/28 (39%) at a mean of 1.6 years Group 3: 6/19 (32%) at a mean of 3.1 years Group 4: 6/16 (25%) at a mean of 2 years	Alive, without disease at 5 years Group 1: 24/24 Group 2-12/28 Group 3- 9/19 Group 4: 8/16
Karakousis 2002 (21)	114	Adequate/wide: >2 cm	Grade 3 = 114	In patients with tumours Adequate wide margins 22%	NR

Study	N	Clear margin criteria	Grade	Local recurrence Metastasis rate	Overall survival
		or <2 cm, but considered adequate if the lateral margin consisted of a strong fascial barrier. Narrow surgical margin: <2cm within a compartment		Narrow Margins 19% but these received radiotherapy	
Matsumoto 2002 (9)	18	Curative: ≥5 cm from the reactive zone. Wide: not sufficiently to be curative. Marginal: passes through the reactive zone. Intralesional: margin present within a lesion.	NR	One local recurrence at 6 years was a marginal margin 1/18 (5.6%)	NR
Stojadinovic 2002 (32)	2123	Microscopically negative: no tumour at the inked margin. Microscopically positive: tumour present at the inked margin	NR	For extremity STS a positive margin was associated with developing a local recurrence (p<0.001) -For extremity STS a positive margin was associated with developing a distant recurrence p=0.03	NR
Khanfir 2003 (24)	133	Minimal: if margins in one section were less than 1 cm Optimal: if margins were ≥1 cm all around the tumour	grade 1= 25 (19%) grade 2= 51 (38%) grade 3=53 40%) unknown=4 (3%)	Local recurrence free rate Minimal n=62, 5 year -80%, 10 year 77% p=0.53 Optimal n=71, 5 year 76%, 10 year 68%. No significant difference in optimal patients between the radiotherapy group and no radiotherapy group. 10-year local recurrence rate for No radiation was 35% (95% CI 48-78%) For radiation 23% (95% CI 50-92%) p=0.19 For minimal margins the 10-year local recurrence rate for no radiation treatment was 53% (95% CI 25-75%) and with radiation treatment 17% (95% CI 8-32%) p=0.005	Tumour margins not significant in multivariate analysis. 5- and 10-year survival were 69%(95% CI 56-79%) and 63% (95% CI 49-75%) for minimal margins and 85% (95% CI 74-91%) and 72% (95% CI 58-84%) for optimal margins. p<0.04 Radiation had no influence on survival. 5- and 10-year overall survival rates in the no radiation group were 76% and 65% and in the radiation group 78% and 70% p=0.93
Koea 2003 (26)	951	Microscopically positive: 1 mm from inked margin.	Low grade = 311 (33%) high grade = 640 (67%)	Negative n=787 5 year local recurrence free survival 87% Positive n=163, 5 year local recurrence free survival 78% p<0.001 (RR=2.0; 95% CI,1.3-2.9)	NR
McKee 2004 (27)	111	microscopically positive: 0 mm close: 1-9 mm clear ≥10 mm	Low grade = 16 (14%) high grade = 95 (86%)	Local recurrence free survival for 5 years ≥ 10 mm 85% (95% CI, 74-79) 1-9 mm 58% (95% CI, 40-74) 0 mm 58% (95% CI, 30-86) p=0.04 Distant metastases free survival at 5 years	Median overall survival for ≥10 mm >88 months (range 6-251 months 1-9 mm 66 months (range 4-165 months)

Study	N	Clear margin criteria	Grade	Local recurrence Metastasis rate	Overall survival
				≥10 mm 72% (95% CI, 60-84) 1-9 mm 37% (95% CI, 2-51) 0 mm 56% (95% CI, 26-86) p=0.0684% some patients received chemotherapy or radiation	0 mm 41 months (range 3-167 months) p=0.09
Gronchi 2005 (16)	911	Positive: tumour within 1mm from inked surface. Negative: absence of tumour within 1mm from the inked surface.	grade 1 = 255 (28%) grade 2 = 226 (25%) grade 3 = 430 (47%)	Local relapse free survival median time 15 months positive vs. negative margin tumours was HR=1.94 (95% CI, 1.37-2.73) p=0.0002 Metastasis free survival Median time 14 months positive vs. negative margin tumours was HR=1.1 (95% CI, 0.8-1.6) p=0.495	NR
Dickinson 2006 (15)	279	Wide contaminated <1 mm Wide 1-4 mm Wide 5-9 mm Wide 10-19 mm Wide+2 cm No residual tumour Radical resection Margins not defined	NR	Relative Local recurrence rate Wide contaminated - n=36, RR=3.76; 95% CI, 0.96-14.83 <1 mm - n=59, RR=3.76; 95% CI, 0.64-7.64 1-4 mm - n=61, RR=0.52; 95% CI, 0.11-2.42 5-9 mm - n=33, RR=0.62; 95% CI, 0.10-3.65 10-19 mm - n=51, RR=1.00 referent category +2 cm - n=12 No recurrences P=0.023 There was no information for 22 patients. Relative Metastatic Rate Wide contaminated - n=36, RR=2.14; 95% CI, 0.40-11.29 <1 mm - n=59, RR=1.87; 95% CI, 0.40-8.76 1-4 mm - n=61, RR=4.17; 95% CI, 0.87-18.82 5-9 mm - n=33, RR=2.80; 95% CI, 0.57-14.02 10-19 mm - n=51, RR=2.46, 95% CI, 0.49-11.26 +2 cm - n=12, 1.00 Referent category No residual tumour n=10 NA for metastasis rate Radical resection n=8 6.17; 95% CI, 0.84-45.59 Margins not defined n=24, RR=1.99; 95% CI, 0.35-11.42 p=0.335	There was a significant association between overall survival and positive surgical margins (x^2 test statistics = 14.7, p=0.043) but not between 1 mm and ≥2 cm.
Gronchi 2007 (17)	1017	Positive: tumour within 1 mm from inked surface. Negative: absence of tumour within 1 mm from the inked surface.	grade 1 = 268 grade 2 = 259 grade 3 = 449	Local relapse Positive margins had an unfavourable effect for local relapse (HR=2.60; 95% CI, 1.82-3.7, p<0.001) Distant Metastasis Margin status not significant HR=1.27; 95% CI, 0.91-1.78,	NR

Study	N	Clear margin criteria	Grade	Local recurrence Metastasis rate	Overall survival
				p=0.157	
Jebsen 2008 (20)	1093	Intralesional: the plane of the excision in any part of the tumour, passed through the tumour, leaving microscopic or macroscopic tissue behind Marginal margin: when the plane of excision passed outside the tumour, but in any part too close to the tumour to merit a wide margin. Wide margin: when the excised tumour was surrounded by a cuff of healthy tissue or uninvolved fascia Compartmental: when the entire compartment containing the tumour was removed	grade 1=226 (2%) grade 2=145 (14%) grade 3=332 (31%) grade 4= 585 (53%)	5 year local control rate Intralesional vs. wide HR=6.3; 95% CI, 3.6-10.9 Marginal vs. Wide HR=2.6; 95% CI, 1.7-4.0	NR
Kim 2008 (25)	150	Positive microscopic: tumour within less than 1 mm from the inked margin. Close margin – tumour within less than 10 mm from inked margin Negative margin: an inked margin being greater than 1 cm away from the tumour Group A: negative margins + radiation Group B: positive margins plus radiation	Low grade = 63 high grade = 87	5-year local failure between groups Group A 7/38 (18%) Group B 20/73 (27%)	NR
Sampo 2008 (31)	270	Compartmental: if an intracompartmental tumour and the whole muscle compartment was excised en bloc. Wide: If the tumour was excised with a smallest microscopic margin of 2.5 cm. Marginal: less than 2.5 cm wide with only microscopic residual tumour. Intralesional: macroscopic tumour left.	Low grade = 78 high grade = 189	Estimated 5-year Local control Margins of <-0.4 cm n=68 (78.1%) 0.4-2.0 cm -(79%) >2.0 cm -(85%) p= 0.003 Margins of at least 1 cm yielded a 5-year local control rate of 83.3% 2 cm=85.9% and 2.5 cm=89.2%	NR
Bonvalot 2010 (33) (abstract)	450	Clear median minimum margin was 2 mm (range 0.5 to 35 mm).	grade 1 = 21% grade 2 = 33% grade 3 = 47%	Absence of clear margins was significantly predictive of local recurrence (p<0.001)	NR
Al Yami (2010) (34)	216	Microscopically positive: tumour cells at the inked margin Grossly positive: if the tumour was exposed intraoperatively or was visible on gross pathologic examination.	grade 1 = 68 (31.4%) grade 2 = 58 (26.8%) grade 3 = 90 (41.7%)	All 216 patients had positive margins Local recurrence Preoperative radiation with post-operative boost 9/41 -5 year local recurrence survival was 73.8% Preoperative radiation and no boost 6/52 5-year local recurrence survival was 90.4% p= 0.13	NR

Study	N	Clear margin criteria	Grade	Local recurrence Metastasis rate	Overall survival
				5-year estimated Metastasis-free survival Preoperative plus boost 67.3% Preoperative radiation only 69.1% (p = 0.95).	
Gronchi 2010 (18)	997	Positive R1: tumour within 1mm from inked surface. Negative R0: absence of tumour within 1mm from the inked surface.	grade 1 = 304 (30.5%) grade 2 = 267 (26.8%) grade 3 = 426 (42.7%)	Local recurrence R0 120/874 (14%) R1 44/117 (38%) Local relapse free survival p<0.001 HR=2.67 (95% CI, 1.74-4.11) Distant Metastasis R0 - 227/874 (26%) R1 – 36/117 (31%) Distant Metastasis Free Survival p=0.979 HR=0.99 (95% CI, 0.66-1.50)	NR
Liu 2010 (35)	181	Microscopically positive: 0–1 mm 1–4 mm, 5–9 mm, 10–19 mm, 20–29 mm, and ≥30 mm	77.3% were high grade	Local recurrence free survival Margins <10mm vs. margins >10mm HR=23.74; 95% CI, 5.77-97.73 p<0.001 Distant metastasis free survival Margins <10 mm vs. Margins >10 mm HR=11.40; 95% CI, 4.13-31.50, p<0.001	NR

Abbreviations: RR = relative risk, CI = confidence interval, RT = radiation therapy, HR = hazard ratio, NR = not reported, vs. = versus.

2. What is the appropriate number of sections from a surgical specimen that should be taken to assess surgical margins?

Three guidelines and one protocol addressed this question (5,6,7,36). No evidence-based data are available as to how to adequately assess margins or whether the assessment should be done on fresh or fixed resection specimens.

ADASP and CAP advocate the use of perpendicular (rather than enface) blocks from margins in STS (6,36).

ADASP recommends that any margin macroscopically more than 5 cm should be considered clear and need not be sampled, except in cases of epithelioid sarcoma and angiosarcoma, which are prone to subclinical proximal or satellite spread (6). However, there is no recommendation as to the number of sections that should be taken.

The Dutch guideline states that margins in millimetres should be provided but offers no guidance on how that assessment should be accomplished. On one page the guideline states that margin distances should be based on the gross assessment of the specimen, and on the next page it states that it should be assessed microscopically.

The NCCN states that both the surgeon and pathologist should assess margins and the margin distances should be provided in the surgical report but gives no advice on how to assess margin adequacy.

3. What is the appropriate handling of surgical resection specimens?

Three guidelines and one protocol addressed this question (5,6,7,36). The guidelines written by the ADASP, ACCC and CAP outline recommendations for handling resection specimens. The recommendation is that resections arrive in the pathology lab unfixed as soon as possible after excision (6,7,36). The Dutch guideline further recommends that the specimens arrive preferably on gauze moistened with physiological salt solution. In addition they recommend storing representative tissue and freezing it for later testing as needed (7). The ADASP and the ESMO guidelines recommend that whenever possible the orientation of a resection specimen be verified with the operating surgeon (5,6).

ONGOING TRIALS

Protocol id and NLM identifier	Sponsor	Estimated enrolment	Patients' age	Purpose
NCT00870701	Institut Claudius Regaud	570	18 Years and older	Randomised Multicentric Phase III Study Comparing Observation Versus Post-Surgery Radiotherapy After Complete Exeresis With Margins Greater Than or Equal to 1 cm in Soft Tissue Sarcoma.
NCT00346164	National Cancer Institute	400	Up to 29 years	This phase III trial is studying observation to see how well it works compared with radiation therapy, combination chemotherapy, and/or surgery in treating patients with STS.

DISCUSSION

Although there have been many studies on what constitutes an appropriate margin, there are no randomized trials or prospective studies that assess surgical margins and outcomes for STS of the extremities. Most of the available evidence is from retrospective reviews of charts and databases. The studies are confounded by differences in treatments as some patients received preoperative and others postoperative radiotherapy and/or chemotherapy. Many other studies had to be excluded since they did not categorize their results by the type of sarcoma; for example, bone and soft tissue were analyzed together or truncal and extremity sarcomas were grouped together. When the clinical groupings are not uniform, it is difficult to interpret the results since one cannot tell if a treatment is effective or if it is the location, type, size, and/or grade of sarcoma that is influencing the results.

There is a need for guidance as to what constitutes an adequate surgical margin with respect to the management of this condition. There is no standard of care, and different surgeons have different definitions of what constitutes an adequate margin. The Working Group (Appendix A) recommends that, after the extensive review of the data, the goal should be to obtain negative margins. Local recurrences have been observed even when negative margins are achieved with surgery and surgery and radiation, suggesting that tumour characteristics other than margin status are important. It would seem that the width of the margin obtained should be influenced by the subsequent effect on functionality. A close margin or even a planned microscopically positive margin may be acceptable, given the study by Gerrand et al (2). In cases with close margins (<1 cm as measured in the fixed state by the pathologist), consideration should be given to the administration of postoperative radiotherapy. Clearly there are other factors, such as tumour type, grade, and biology or even the type of tissue (e.g., fascia) at the margin, that affect the rate of both local and

systemic recurrence. The topic needs further investigation, and ongoing molecular studies may provide insight into other relevant tumour characteristics that influence outcome.

There were no studies that addressed how many sections needed to be taken of the resection margins.

No evidence was located concerning how many sections should be taken from a surgical specimen to assess the adequacy of excision. Very few studies mentioned how the specimens in their studies were sampled or the number of sections taken. These inconsistencies make it difficult to compare results from study to study. There is a great need for evidence-based standardization of the process of sampling tumours.

CONCLUSIONS

The optimal adequate surgical margin for patients with STS of the extremities cannot be established because of the lack of evidence-based literature. There was great heterogeneity across studies with respect to margin width, tumour size, treatment modalities, and demographics. However, the data suggest that patients with clear margins have a better prognosis and that patients with close or positive margins should be considered for post-operative radiation.

In limb salvage surgery for extremity STS, the surgery should be planned to achieve a clear margin. However, in order to preserve functionality, surgery may result in a very close or even microscopically positive margin. In this circumstance, the use of preoperative **or** postoperative radiation may be considered.

There was also no agreement on the optimum number of sections required to assess the adequacy of the excision. There was very little information pertaining to the appropriate sampling of surgical resection margins.

Because no evidence-based conclusions could be drawn from the literature published to date, the Working Group made recommendations based on expert opinion and consensus.

CONFLICT OF INTEREST

Information regarding conflict of interest declarations can be found at the end of Section 3.

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Appendix A. Members of the Working Group and the Sarcoma DSG.

The Working Group members

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Dr. Joel Werier, Surgical Oncologist, Department of Orthopaedic Surgery, The Ottawa Hospital Regional Cancer Centre, Ottawa, Ontario
Dr. Jay Engel, Surgical Oncologist, Department of Surgical Oncology, Cancer Centre of Southeastern Ontario, Kingston, Ontario.
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The Sarcoma DSG members

Dr. Jordi Cisa, Surgical Oncologist, Department of Orthopaedic Surgery, Laurentian Hospital, Sudbury, Ontario.
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Dr. Abha Gupta, Medical Oncologist, Division of Haematology/Oncology, The Hospital for Sick Children, Toronto, Ontario
Carol Swallow, Surgical Oncologist, Department of Surgical Oncology, Princess Margaret Hospital, Toronto, Ontario
Dr. Jawaid Younus, Medical Oncologist, London Regional Cancer Care Program, London Health Sciences Centre, London, Ontario

Appendix B. Literature search strategy.

MEDLINE -Surgical Margins
1. exp "Neoplasms, Connective and Soft Tissue"/
2. sarcoma$.tw.
3. sarcoma/di
4. sarcoma/su
5. sarcoma/pa
6. soft tissue neoplasm/ surgery*
7. extremity.mp.
8. 6 and 7
9. specimens.mp.
10. specimen.mp.
11. 9 or 10
12. 1 or 2 or 3 or 4 or 5 or 6
13. 11 and 12
14. limit 13 to (english language and humans)
15. resection.mp.
16. 14 and 15
17. margin.mp.
18. 14 and 17
19. limit 18 to (english language and humans)

Embase -Surgical Margins
1. exp "Neoplasms, Connective and Soft Tissue"/
2. sarcoma$.tw.
3. sarcoma/di
4. sarcoma/su
5. sarcoma/pa
6. soft tissue neoplasm/ surgery*
7. specimens.mp.
8. specimen.mp.
9. 1 or 2 or 3 or 4 or 5 or 6
10. margin.mp.
11. 9 and 10
12. limit 11 to (human and english language)
13. sarcoma.mp.
14. 9 and 13
15. 10 and 14
16. limit 15 to (human and english language)
17. letter.pt.
18. editorial.pt.
19. comment.pt.
20. news.pt.
21. review.pt.
22. 17 or 18 or 21

MEDLINE and EMBASE Handling of specimens
1. exp "Neoplasms, Connective and Soft Tissue"/
2. sarcoma/di
3. sarcoma/su
4. sarcoma/pa
5. soft tissue neoplasm/ surgery*
6. exp *Sarcoma/cl, di, pa, su [Classification, Diagnosis, Pathology, Surgery]

7. exp *Specimen Handling/ae, cl, is, mt, st, td, ut [Adverse Effects, Classification, Instrumentation, Methods, Standards, Trends, Utilization]
8. Adult/ or extremeties.mp.
9. specimen handling/mt
10. exp Pathology, Surgical/cl, mt, st, td [Classification, Methods, Standards, Trends]
11. recommendations.ti.
12. reporting.ti.
13. 1 or 2 or 3 or 4 or 5 or 6
14. 7 or 9 or 10 or 11 or 12
15. 13 and 14
16. limit 15 to english language
17. limit 16 to human
18. limit 17 to humans
19. remove duplicates from 18
20. limit 19 to yr="2010 - 2011"

Appendix C. Results of AGREE Tool quality rating of evidence-based guidelines.

Guideline	AGREE Domain Scores						
	Scope and Purpose (%)	Stakeholder Involvement (%)	Rigour of Development (%)	Clarity and Presentation (%)	Applicability (%)	Editorial Independence (%)	Overall Rating
Dutch Working Group on Soft Tissue Tumours	51.3	22.2	30.7	65.2	37.5	4.1	Recommended for adoption or discussion
Association of Directors of Anatomic and Surgical Pathology	69.4	33.3	14.5	63.8	19.7	0	Recommended for adoption or discussion
ESMO	47.2	31.9	26.5	59.7	13.5	37.4	Recommended for adoption or discussion
NCCN	61.5	41.1	29.5	74	21.5	51.3	Recommended for adoption or discussion

Abbreviations: ESMO= European Society for Medical Oncology; NCCN – National Comprehensive Cancer Network

Appendix D. Literature search results (1975-June 2011).

Stages of search	Number of articles
MEDLINE, EMBASE, and Cochrane Library initial search	573
Number ordered for full publication	187
Number of abstracts from conference proceedings	1
Number of articles found from hand searching reference lists	1
Number of articles included in this report	33
Total number of articles and guidelines included outlining margin criteria **(question 1)**	32 (28 studies and 4 guidelines)
Total number of articles and guidelines included describing proper handling of specimens. (**questions 2 and 3**)	4 (3 guidelines, 1 protocol)

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program in evidence-based care | programme de soins fondé sur des preuves

Evidence-Based Series 11-10: Section 3

Appropriate Surgical Margins and Proper Handling of Soft Tissue Sarcoma of the Extremities: Development, Recommendations, & External Review Process

R. Kandel, N. Coakley, J. Werier, J. Engel, S. Verma, and the Sarcoma DSG

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

Report Date: September 7, 2012

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) (1). 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 care.

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 is produces evidence-based and evidence-informed guidelines, known as Evidence-based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that 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.

This EBS is comprised of the following sections:

- *Section 1: Guideline Recommendations*. Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.

- *Section 2: Evidentiary Base*. Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.
- *Section 3: Development Methods, Recommendations Development, and External Review Process*. Summarizes the EBS development process, the recommendations development process and the results of the formal external review of the draft version of the EBS.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This EBS was developed by the Sarcoma DSG of the CCO PEBC. The Sarcoma DSG consists of surgeons, pathologists, and medical and radiation oncologists (Section 2: Appendix A).

Where evidence was not available or was not sufficient to reach a conclusion for the recommendations the Working Group made recommendations based on expert opinion.

Report Approval Panel Review and Approval

Prior to the submission of this EBS draft report for External Review, the report was reviewed and approved by the PEBC Report Approval Panel, a panel that includes oncologists and whose members have clinical and methodological expertise. Key issues raised by the Report Approval Panel included the following (with arrowhead bullet indicating the Working Group response):

1. The title indicates that this guideline is for soft tissue sarcomas of the extremities, but this is not explicitly defined in the document. Also, the abbreviation STS is used without prior definition (minor point)
   - ➢ This has now been changed in the document.
2. There is no listing of who the members are and from what field of medicine. There is in Section 3 page 2, a reference to a website but it would be preferable to be mentioned in section 1 &/or 2.
   - ➢ Section 2, Appendix A provides this information.
3. The guideline should target radiation and medical oncologists as they care for these patients.
   - ➢ The guideline will now be sent to medical oncologists, radiation oncologists, and surgeons who treat sarcoma.
4. One of the exclusion criteria was retrospective studies under 100 pts but there are 2 studies in the tables with <100 pts.
   - ➢ Those with less than 100 patients were prospective studies. There was no cap on the number of patients in prospective studies.
5. The methods section should be changed to reflect the new template.
   - ➢ This has now been changed in the document.
6. The discussion is very brief. You could have included more detail since for 2 of the 3 questions, the conclusion was that there wasn't enough evidence to make recommendations, despite the fact that over 30 papers were included.
   - ➢ There was no evidence in any of the 30 papers, and so no recommendations could be made for any of the 3 questions. The authors feel the discussion is sufficient.
7. Two comments were made on who provided the "expert opinion" for the recommendations.
   - ➢ The members of the Working Group provided the expert opinion. This has been changed in the document.

8. Health benefits and side effects were not discussed.
   - This was covered by the discussion on positive versus negative margins.
9. The box structure of the recommendations was hard to follow.
   - The boxes around the recommendations have been reformatted to make it easier to follow.
10. For question 1, the recommendation is somewhat vague. There is no specific recommendation for what a clear margin should be, even though a number of studies were reviewed. If it is based on consensus/expert opinion, it would be helpful to commit to a definition, eg 'no tumour at the cut margin", etc.
    - This is a very difficult question and the Group struggled with it. In the absence of any data, the group is satisfied with their recommendation and its wording.
11. There is a recommendation to consider radiation in the setting of positive margins, but no comment on the type of radiation/quality of radiation administered in the studies.
    - This was not one of the research questions in this guideline to be addressed, so the literature related to this was not reviewed. Thus no recommendations can be made related to the type of radiation/quality of radiation administered
12. Suggest that Key evidence for first question be slightly revised. Currently written as "28 studies provided evidence on negative margins and recurrence rates". I think what is meant is ". provided evidence on margin status and recurrence rates"
    - This has been changed in the document.
13. Is keeping functionality just common sense?
    - Changes have been made to the document for clarity.
14. Several comments were made about the tables.
    - The Sarcoma DSG does understand that the tables can be difficult to understand. Many attempts have been made to clarify the data. Many studies did not present complete and clear data, and that is reflected in the tables.

External Review by Ontario Clinicians and Other Experts

The PEBC external review process is two pronged and includes a targeted peer review intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following the review and discussion of Section 1: Guideline Recommendations and Section 2: Evidentiary Base of this EBS and the review and approval of the report by the PEBC Report Approval Panel, the guideline authors circulated Sections 1 and 2 to external review participants for review and feedback. Box 1 shows the section 1 draft recommendations and supporting evidence developed by the guideline authors before External Review.

RECOMMENDATIONS AND KEY EVIDENCE

RECOMMENDATION 1

In limb salvage surgery for STS, surgery should be planned with the objective of achieving a clear margin. However, in order to preserve functionality, surgery may result in a very close or even microscopically positive margin. In this circumstance, the use of postoperative radiation should be considered.

Key Evidence 1

Twenty-eight studies provided evidence on margin status and recurrence rates. Local recurrence rates ranged from 3%-24% for patients with negative margins and from 6%-53% for positive margins.

Two studies provided recurrence free survival rates for extremity STS treated with surgery alone. They both concluded that positive margin status was associated with increased recurrence rate.

Twenty-four studies evaluated the use of radiotherapy in addition to the resection of STS. Of those studies, three provided separate results for radiotherapy (RT) versus no radiotherapy. Two of these studies demonstrated no difference in local recurrence rates between the groups, and the third showed that RT decreased the frequency of local recurrence.

Only one study provided results for the use of chemotherapy in addition to surgery and radiation in patients with marginal excisions (incisions through the pseudocapsule or reactive zone). No significant benefit was observed.

Qualifying Statements
In limb-sparing surgery for STS, an adequate margin for surgical treatment alone or for surgery with RT cannot be defined as the studies did not definitively identify an appropriate margin distance. Intact fascia is considered an adequate margin by some.

A microscopic positive margin in STS of the limb treated with surgery and radiation has an increased rate of local recurrence. This suggests that every effort should be made to achieve a negative margin.

In the event that limb function will be comprised, surgeons and patients may wish to discuss the benefits and risks of maintaining a microscopically positive margin and the role of postoperative RT.

Local recurrences have been observed even when negative margins are achieved with surgery and with surgery and radiation, suggesting that tumour characteristics other than margin status are important. Further study is required.

At this time, there is no evidence to support the use of postoperative chemotherapy in soft tissue tumours of the extremity that have undergone intralesional or marginal excisions

RECOMMENDATION 2
For the histological assessment of margins, no definitive recommendations can be made for the appropriate number of margin samples that are required.

Key Evidence 2
One guideline and one protocol addressed this question but did not provide any evidence that could be used for recommendations.

RECOMMENDATION 3
It is not possible to make evidence-based recommendations as to the appropriate handling of surgical resection specimens to assess the adequacy of excision. Guidelines, where mentioned, endorse inking margins and sampling them perpendicular to (and not enface to) the margin. **In the absence of evidence-based recommendations, the Sarcoma Disease Site Group (DSG) recommends the following, based on the expert opinion of the Working Group and consensus of the DSG members:**

- **The specimen should be received fresh with orientation indicated by the**

surgeon.
- **The specimen and the tumour should be measured in three dimensions.**
- **The distances from all six margins should be measured and the location of the tumour (superficial or deep) and the relationship to fascia, if present, indicated.**
- **All margins should be sampled perpendicular to the margin, and at least 2 samples taken from the closest margin and 1-2 sections from all other margins.**
- **More extensive margin sampling should be considered for tumours such as angiosarcoma, epithelioid sarcoma, and chondrosarcoma.**

Key Evidence 3
Because no evidence was identified to inform these recommendations, they are based on the expert opinion and consensus of the Sarcoma DSG and are consistent with current guidelines.

Methods
Targeted Peer Review: During the guideline development process, four targeted peer reviewers from Canada considered clinical and/or methodological experts on the topic were identified by the guideline authors. Several weeks prior to the completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Three reviewers agreed, and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on June 12, 2012. Follow-up reminders were sent at two weeks and at four weeks. All the targeted peer reviewers were required to complete the conflict of interest form. Two reviewers (WT and TN) finished their questionnaires and one reviewer (JW) joined *Professional Consultation* below.

Professional Consultation: Sixty potential participants were identified by the guideline authors. Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. Participants were asked to rate the overall quality of the guideline (Section 1) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1) and the evidentiary base (Section 2). The notification email was sent on June 11, 2012. Two follow-up reminders were sent on June 25 and July 9, 2012.

Results
Targeted Peer Review: Responses were received from two of three reviewers: WT from Calgary, Alberta and TN from Vancouver, British Columbia. The key results of the feedback survey are summarized in Table 1. The written comments by targeted peer reviewers and the modifications/actions/responses taken by the authors are summarized in Table 2.

Table 1. Responses to nine items on the targeted peer reviewer questionnaire.

Question	Reviewer Ratings (n=2)				
	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.	0	0	0	1	1
2. Rate the guideline presentation.	0	0	0	1	1
3. Rate the guideline recommendations.	0	1	0	1	0

4. Rate the completeness of reporting.	0	1	0	1	0
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?	0	1	1	0	0
6. Rate the overall quality of the guideline report.	0	1	0	1	0
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.	1	0	0	0	1
8. I would recommend this guideline for use in practice.	1	0	0	0	1
9. What are the barriers or enablers to the implementation of this guideline report?	• Subspecialists will implement as guidelines are a close fit to current practice and the process is impressive. Practitioners at hospitals doing low volume work will be unlikely to read and implement.				

Table 2. Summary of written comments by targeted peer reviewers and the modifications/actions/responses regarding written comments.

Summary of written comments	Modifications, actions, or responses
1. The authors decided to include published abstracts from ASCO, but why not other conference, such as SSO, AAOS, USCAP and (especially) CTOS. Given the relative lack of strong underlying data from the published literature, including particularly for questions 2 and 3, the report could have been improved by mining these sources.	Abstract could not provide enough data to answer the three research questions in this guideline. However, ASCO is the large and common conference source, thus it was listed on the project plan only.
2. The Dutch guidelines that claim to be evidence-based and seem to be one of the better sources for information lacked a methodology section in English. It might be worth contacting them for an English translation as the vast majority of professionals in that country are fluent in English and a translation may already exist or be easily obtained.	To keep consistence with other guidelines in PEBC CCO, we only include English publications.
3. Recommendation 1 says "the use of postoperative radiation should be considered." In cases e.g. tumor adjacent to large nerve, there may be a planned marginal excision, and pre-operative radiation would be relevant in such a case (i.e. microscopic positive margin is a preoperative expectation based on imaging rather than a postoperative finding based on pathology). Also as the authors well know an important Canadian trial supports the equivalence or in some cases superiority of preoperative over postoperative radiation. Therefore this	We have added "preoperative or" in the Recommendation 1 in Section 1 and in the corresponding sentence under Conclusion in Section 2.

	guideline should not specify postoperative radiation, and should either say "the use of pre- or postoperative..." or perhaps "the use of postoperative radiation should be considered if appropriate preoperative radiation had not already been administered." The same change is recommended to the conclusion section.	
4.	In Recommendation 3, why is chondrosarcoma specifically listed as a case needing more extensive sampling, as these are often grossly visible and lobulated tumors, as opposed to e.g. superficial spreading tumors like myxoinflammatory fibroblastic sarcoma (or indeed "poorly circumscribed superficial tumors" in general)? The tissue at the margin should be described as to its nature (fascia, muscle, fat), but there is no mention of this in the recommendation.	Chondrosarcoma is included as microscopic positive margins can occur in these tumours. There is reference to fascia and a statement has been added into the discussion related to the type of tissue at the margin.
5.	In section 2 on page 2 under Introduction: "The use of adjuvant chemotherapy in STS, except for extraosseus osteosarcoma and Ewing sarcoma, continues to be controversial." Rhabdomyosarcoma needs to be added here, whereas extraosseus osteosarcoma should be deleted. Certainly at my institution the experience with extraosseus osteosarcoma is that its response to chemotherapy is much more like that of undifferentiated sarcoma/MFH than it is like bone-based osteosarcoma, and it is controversial whether adjuvant chemotherapy is of value.	Extraosseous osteosarcoma has been changed to rhabdomyosarcoma as recommended.
6.	Evidentiary base, page 8. Paragraph 2 claims no difference in OS – length of followup time should be mentioned as this would help the reader assess the likelihood their negative result is based on adequate evidence. Paragraph 4 mentions three studies that found no difference in local control with and without radiation, but the very key caveat here – whether these patients were randomized or not – needs to be clarified. If these are nonrandomized then the sentence needs this major caveat highlighted as the data would have major confounders if the more clinically aggressive cases were the ones more likely to get radiation.	We have revised the corresponding paragraphs in Section 2 based on the reviewer's comment.
7.	In Discussion in Section 2, the support for acceptable planned positive margins in Gerrand et al. perhaps should be emphasized	Gerrand et al data are mentioned in several sites in the document.

a bit more, as it is based on local Ontario experience and is therefore obviously particularly applicable and relevant to cancer treatment in Ontario.	
8. The stated intent of the guideline is to provide clinicians with guidance on the definition of an adequate surgical margin -- this has not been achieved. The document provides a summary of select literature but does not provide any clinically useful guidance on how to proceed.	An evidence based definition of what constitutes an adequate margin could not be gleaned from the literature even though been many studies have been published correlating outcome and margin status. This is due to the poor quality of many of the studies and the lack of an RCT. The authors have inserted a recommendation as follows: Based on consensus opinion of the expert panel, a 'close' margin is considered to be <1cm following formalin fixation. This document will be reviewed in three years time to determine if it is still relevant to current practice and to ensure that the recommendations are based on the best available evidence. If new evidence becomes available that will result in changes to these recommendations before three years have elapsed, an update will be initiated as soon as possible.
9. Data on preoperative versus postoperative radiotherapy are combined in one table. These two groups of patients are inherently different. Their margin status and recurrence issues are different. This difference is not addressed at all in either the background information or the recommendations.	The main research questions did not focus on the role of radiotherapy in extremity soft tissue sarcoma in this guideline. Thus, we think it is alright to put the studies with preoperative or postoperative radiotherapy in one table. Furthermore some studies report on patient outcome as a group even though they received pre- and/or post-operative radiotherapy.
10. No levels of evidence are applied to the recommendations.	To date, PEBC CCO guidelines do not classify evidence into different levels because Cochrane Handbook pointed out that the interpretation of a summary score or level of evidence approach had potential problems and might mislead the end users.

Professional Consultation: Fifteen responses out of 60 (25%) potential participants were received. Six stated that they did not have interest in this area. The key results of the feedback survey from nine doctors are summarized in Table 3. The comments from the professional consultants and the Working Group modifications/actions taken in response are summarized in Table 4.

Table 3. Responses to four items on the professional consultation survey.

Question	Number (%)				
	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.	0%	0%	22%	67%	11%
	Strongly	(2)	(3)	(4)	Strongly

	Disagree (1)				Agree (5)
2. I would make use of this guideline in my professional decisions.	0%	0%	0%	67%	33%
3. I would recommend this guideline for use in practice.	0%	0%	0%	67%	33%
4. What are the barriers or enablers to the implementation of this guideline report?	• There should be no barriers. Lack of evidence does impact on guideline quality.				

Table 4. Summary of written comments by professional consultants and modifications/actions/responses regarding written comments.

Summary of written comments	Modifications, actions, or responses
1. Under recommendation 1, there are far more than 24 studies that evaluate the use of radiotherapy in addition to resection for STS. This includes 4 randomized trials, none of which seem have been cited. What were the criteria for selecting studies for inclusion? It is generally agreed that there is some nuance to a surgical margin, and that a planned positive margin is different from an unplanned positive margin with respect to risk of recurrence. This does not seem to have been addressed.	An evidence based definition of what constitutes an adequate margin could not be gleaned from the literature even though been many studies have been published correlating outcome and margin status. This is due to the poor quality of many of the studies and the lack of RCTs. The authors have inserted a recommendation as follows: Based on consensus opinion of the expert panel, a 'close' margin is considered to be <1cm following formalin fixation. This document will be reviewed in three years time to determine if it is still relevant to current practice and to ensure that the recommendations are based on the best available evidence. If new evidence becomes available that will result in changes to these recommendations before three years have elapsed, an update will be initiated as soon as possible.
2. In Recommendation 1, "...In this circumstance, the use of postoperative radiation should be considered." I don't think this is a strong enough statement. If the margin is not "widely" negative, then radiation should not only be considered but for close or positive margins it should generally be MANDATORY. However, this would not be the case for low grade, well differentiated, lipoma-like liposarcoma which typically should not receive adjuvant radiation even following close or positive resection margins.	We have changed "should be" to "may be" in Recommendation 1.
3. One Qualifying Statement: "A microscopic positive margin in STS of the limb treated with surgery and radiation has an increased rate of local recurrence. This suggests that every effort should be made to achieve a negative margin." This is true in general but it depends on the context of the positive margin.	We have revised this Qualifying Statement based on reviewer's comments.

For example a positive margin which results from resection of a sarcoma along a fixed critical structure such as major nerve, vessel or periosteum, and is treated with adjuvant radiation may not have any increased risk of local relapse compared to close but negative margin resections also treated with adjuvant radiation.	
4. This guideline presents very little data beyond which would be considered baseline knowledge for anyone with a specialty practice providing care for patients with extremity soft tissue sarcoma. Especially regarding surgical margins, it presents no quantitative data on which to base decision-making. In fact it does not even go so far as to make a recommendation as to what would be considered a reasonable margin surrounding a soft tissue sarcoma resected without any adjuvant therapy. In terms of a positive margin, it does not suggest what should be done if this occurs: for example, re-excision of that margin if possible, or the addition of a postoperative radiation boost if the patient received preoperative radiation. It also makes no mention of the setting of where that type of margin may be acceptable versus not or less acceptable due to risk of local relapse. Regarding tissue handling, there are only few recommendations in this report, and they would be considered minimum standard of care.	An evidence-based definition of what constitutes an adequate margin could not be gleaned from the literature even though been many studies have been published correlating outcome and margin status. This is due to the poor quality of many of the studies and the lack of an RCT. The authors have inserted a recommendation as follows: Based on consensus opinion of the expert panel, a 'close' margin is considered to be <1cm following formalin fixation. This document will be reviewed in three years time to determine if it is still relevant to current practice and to ensure that the recommendations are based on the best available evidence. If new evidence becomes available that will result in changes to these recommendations before three years have elapsed, an update will be initiated as soon as possible.

Conclusion

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the Sarcoma DSG, the Gynecology Cancer DSG, and the Working Group.

Conflict Of Interest

In accordance with the PEBC Conflict of Interest Policy, the guideline authors, the Sarcoma DSG members, and internal and external reviewers were asked to disclose potential conflicts of interest. The authors, members, and reviewers reported that they had no conflicts of interest.

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