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PRACTICE GUIDELINE

Surgical margins and handling of soft-tissue sarcoma in extremities: a clinical practice guideline

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ABSTRACT

Questions

1. In limb salvage surgery for extremity soft-tissue sarcoma (STS), what is an adequate surgical margin?
2. What is the appropriate number of samples to take from the margins of a surgical resection specimen?
3. What is the appropriate handling of surgical resection specimens?

Background

Surgery is the primary treatment for extremity STS. The combination of radiotherapy with surgery allows for limb salvage by using radiation to biologically "sterilize" microscopic extensions of tumour and to spare neurovascular and osseous structures. Adjuvant chemotherapy in STS—except for rhabdomyosarcoma and Ewing sarcoma—continues to be controversial.

Methods

The MEDLINE and EMBASE databases (1975 to June 2011) and the Cochrane Library were searched for pertinent studies. The Web sites of the main guideline organizations and the American Society of Clinical Oncology conference proceedings (2007–2010) were also searched.

Results and Conclusions

Thirty-three papers, including four guidelines, one protocol, and one abstract, were eligible for inclusion.

The data suggest that patients with clear margins have a better prognosis, but no prospective studies have indicated how wide margins should be. In limb-salvage surgery for extremity STS, the procedure should be planned to achieve a clear margin. However, to preserve functionality, surgery may result in a very close (<1 cm) or even microscopically positive margin. In this circumstance, the use of preoperative or postoperative radiation should be considered.

No studies described the optimal number of tissue sections required to assess adequacy of excision nor the appropriate handling of surgical resection specimens. The Sarcoma Disease Site Group made its recommendations based on expert opinion and consensus.

KEY WORDS

Clinical practice guideline, handling, soft-tissue sarcoma, extremity, surgical margins, systematic review

1. QUESTIONS

1. In limb salvage surgery for extremity soft-tissue sarcoma (STS), what is considered an adequate surgical margin, in the context of
   (a) surgery alone?
   (b) surgery in combination with adjuvant or neoadjuvant radiotherapy (RT) or chemotherapy, or both?
2. What is the appropriate number of samples to take from the margins of a surgical resection specimen?
3. What is the appropriate handling of surgical resection specimens?

2. 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 tumours in adults and 15% of pediatric malignancies[1]. Soft-tissue sarcomas (STSS) are the more common type, and these tumours occur most frequently in the extremities. Treatment is often multimodal and complex, and patients can experience significant morbidity and mortality as a consequence of treatment or the disease. The goals of sarcoma management include both a cure and 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, alone or combined with preoperative or postoperative radiation, in achieving acceptable local control and equivalent overall survival. The combination of RT with surgery allows for limb salvage by using radiation to biologically "sterilize" microscopic extensions of disease and to spare neurovascular and osseous structures. Developments in cross-sectional imaging (including computed tomography and magnetic resonance imaging) and in treatment planning processes such as computed tomography simulation, have greatly improved the targeting of tissues at risk for tumour involvement. The use of adjuvant chemotherapy in localized STS—except for rhabdomyosarcoma and Ewing sarcoma—continues to be controversial, especially in sarcomas resected with negative margins (R0)[2,3].

Surgical excision is the primary treatment for extremity STS, and although surgery is necessary for cure, recurrence and metastases can occur in the presence of what is considered complete resection, raising the question of what is an adequate margin. This question is complicated by the type of tissue at the margin—for example, fascia or fat. In addition, there is evidence that a planned positive microscopic margin[4]—such as that against a neurovascular bundle—does not result in a worse outcome, although a recent preliminary re-review of the issue has suggested otherwise[5]. As well, how is adequate assessment of resection margins (gross assessment and number of histologic samples) to be defined?

To answer those questions and to provide guidance for clinicians, the Sarcoma Disease Site Group (DSG) of Cancer Care Ontario's Program in Evidence-Based Care (PEBC) decided to prepare a clinical practice guideline on this topic, based on a systematic review of the available evidence.

3. METHODS

3.1 Guideline Development

The guideline was developed using the methods of the practice guidelines development cycle[6], and the core methodology was the systematic review. Evidence was selected and reviewed by the working group, which included four Sarcoma DSG members (RK, JW, JE, SV) and a methodologist from the PEBC (NC). The resulting evidentiary base and related recommendations are intended to promote evidence-based practice in Ontario, Canada.

3.2 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 Web sites were searched for existing evidence-based practice guidelines. The American Society of Clinical Oncology conference proceedings from 2007 to 2010 were searched. Search terms indicative of sarcoma, surgical margins, and handling of specimens were used.

3.3 Study Selection Criteria

3.3.1 Inclusion Criteria

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

- The definition of what was considered to be a negative or positive margin through measurements or detailed descriptions was reported.
- The study included adult patients with extremity (arm and leg) STS, and limb-sparing surgery was the primary treatment.
- The study 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, the study reported an outcome resulting from the handling techniques for STS specimens.

3.3.2 Exclusion Criteria

Studies were excluded if they

- were published in a language other than English (because translation capacity was not available).
- included patients with other sarcoma types and the results for STS were not specifically reported.
- did not specify what constituted a negative or positive surgical margin.
- were retrospective studies with fewer than 100 subjects.

4. RESULTS

4.1 Literature Search Results

Thirty-three papers, including four guidelines, one protocol, and one abstract, were eligible for inclusion in the systematic review[7–39]. Four guidelines that assessed the criteria for positive margins in STS or that provided information on proper handling of specimens were considered relevant to the present guideline[7–10]. Only the European Society for Medical Oncology (ESMO) guideline defined what is considered a proper surgical margin. The National Comprehensive Cancer Network and the Dutch

Working Group on Soft Tissue Sarcoma guidelines defined the margin criteria only when chemotherapy or radiation should be administered. The guideline from the Association of Directors of Anatomic and Surgical Pathology addressed the proper handling of surgical specimens. The protocol from the College of American Pathologists also described proper handling techniques. The Dutch Association of Comprehensive Cancer Centres stated that their guideline was evidence-based. However, the methods were not available in English, and so that assertion could not be verified[10]. The other guidelines were consensus-based documents[7–9]. The quality of literature was poor because 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 others, analyses were done in the presence of mixed treatment groups (for example, RT with or without chemotherapy).

Thirty-two studies addressed the question of negative compared with positive criteria for surgical margins. Of those studies, only three were prospective[11–13]. The rest were retrospective studies using collected patient data[14–38].

Three guidelines[8–10] and one protocol[39] described the handling of surgical specimens. Table I summarizes the literature search results.

4.2 Question 1

Thirty-three papers provided a definition of what were considered negative and positive surgical margins. Some papers did not quantify margin distance, but did state that a clear margin had no residual microscopic disease left at the tumour site. No agreement on what is an adequate margin could be discerned. The published range runs from "negative for tumour at the inked margin" to 5 cm.

TABLE I Literature search results (1975 to June 2011)

Search stage	*Articles found*
MEDLINE, EMBASE, and Cochrane Library initial search	573
Ordered for full publication	187
Abstracts from conference proceedings	1
Articles found in hand-search of reference lists	1
Articles included in this report	33
Articles and guidelines that outline margin criteria (question 1)	32 (28 studies, 4 guidelines)
Articles and guidelines that describe proper handling of specimens (question 1)	4 (3 guidelines, 1 protocol)

4.2.1 Surgery Alone

Two studies addressed the question of an adequate surgical margin with surgery alone. The criteria of a clear margin in one study was less than 2.5 cm[16]; in the other, a clear margin was described as being "all normal tissue surrounding the specimen"[11]. The studies by Enneking *et al.* and Berlin *et al.*[11,16] showed that local recurrences were reduced in patients with negative margins. A potential bias in the surgery-alone group is that the tumours so treated are usually superficial[14,26,32].

4.2.2 Surgery in Combination with Adjuvant or Neoadjuvant Chemotherapy, or with RT, or Both

Most of the studies that addressed margin criteria involved surgery in combination with adjuvant or neoadjuvant chemotherapy, or with radiation, or both. Chemotherapy was given in seventeen studies[12,13,15,17,20–23,25,27–32,35,36] and was discussed in two guidelines. However, not all the studies provided detailed results for the patients receiving chemotherapy.

The two guidelines reported on clinical situations warranting the administration of chemotherapy. The Dutch Association of Comprehensive Cancer Centres recommends that chemotherapy be given only in the context of a clinical trial[10]. The ESMO guideline (a consensus document) states that adjuvant chemotherapy is not standard treatment in adult STS, but can be used in certain high-risk patients with deep tumours[8].

Only one study provided results for patients receiving chemotherapy. That study was a randomized trial[13], in which, after surgery, patients were randomized to a doxorubicin or a control group. The adjuvant postoperative chemotherapy consisted of doxorubicin 60 mg/m^2 intravenously on day 1. Cycle length was 28 days, and 9 cycles were given. The postoperative treatment with doxorubicin did not influence the risk of local recurrence, although patients with a marginal excision also received RT. The width of the surgical margin did not influence outcomes[13].

Twenty-five studies and four guidelines reported on outcomes after surgery and RT, and also provided information about the surgical margin width.

The guidelines listed in Table II vary only slightly in their recommendations. The ESMO guideline does not state a margin size, but recommends that radiation be given when tumours are larger than 5 cm. The Dutch Association of Comprehensive Cancer Centres, the National Comprehensive Cancer Network, and the Association of Directors of Anatomic and Surgical Pathologists all recommend that radiation be given when margins are less than 1 cm in the fixed state and less than 2 cm in the fresh state. Only the Dutch Association of Comprehensive Cancer Centres provided a recommendation concerning the width of the field that should be radiated around the tumour. They suggested 5–10 cm depending on the tumour type.

TABLE II Comparison of guideline criteria for giving radiotherapy and for irradiated margins

Reference	*Recommended clear surgical margin*	*Criteria for giving radiation*	*Margin irradiated*
Association of Directors of Anatomic and Surgical Pathology guideline, 1999 [9]	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	Not reported
Dutch Association of Comprehensive Cancer Centres, 2004 [10]	Not reported	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
National Comprehensive Cancer Network, 2010 [7]	Negative margins should be obtained, but close margins may be necessary to preserve critical uninvolved neurovascular structures	<1 cm or microscopically positive on bone or major blood vessel or major nerve	Not reported
European Society for Medical Oncology, 2010 [8]	1 cm (but in some areas with anatomic barriers, the margins may be minimal)	Radiation is standard for tumours >5 cm	Not reported

The most common reason for giving RT was a positive margin. This factor was reported in eight studies[14,17,23,24,26,27,32,34]. The administration of RT on the basis of a discussion between the surgeon and radiation oncologist was reported in three studies[19–21]. In two studies, all patients received RT[4,28]. Patients with positive margins were given a boost in three studies[4,28,37]. In two studies, RT was given based on the size of the tumour[17,29] and, in one study, on its grade[34]. Six studies did not provide reasons for RT[15,18,22,30,31,35]. Six studies also provided details about the width of the field irradiated around the tumour site. All treated a field of 5 cm or more[10,17,27,28,32,34].

Twenty-five studies that provided results for patients treated with surgery and RT characterized the width of the surgical margin in some way. Twenty-one studies demonstrated that positive margins had an unfavourable effect on local recurrence rates[4,12,14,15,17,19–21,23,24,26,28–36,38]. One study reported that local recurrence rates did not differ for margins that were either less than 1 cm or 1 cm and greater[27]. Another study had only patients with positive margins. In that study, addition of a local postoperative radiation boost in patients who had received RT preoperatively did not alter the recurrence rate[37].

The rate of distant metastasis was analyzed in nine studies. A positive margin was associated with a greater rate of distant metastasis in six studies[15,20,30,32,35,38], but in three studies, there appeared to be no difference associated with margin status[4,21,31].

Overall survival was examined in four studies. Only the study by Popov and colleagues found that margin status was related to overall survival[32]. The other three studies found no difference in overall survival and margin status with at least 3 years of follow-up[4,27,30].

In most of the studies, the results for patients who received RT were combined with the results for patients who did not receive RT. Three studies reported local control outcomes data pertaining to RT and margins[22,27,32]. The studies by Heslin *et al.,* Khanfir *et al.,* and Popov *et al.* showed no difference in local control between the groups that received radiation and the groups that did not, although the study by Heslin and colleagues analyzed only patients with positive margins. The Heslin *et al.* study was further complicated by the fact that some patients received chemotherapy[22]. However, given that those three studies were retrospective and not randomized controlled trials, patients with more clinically aggressive disease might be in the RT group, potentially confounding the results.

4.3 Question 2

Three guidelines and one protocol addressed the question of the appropriate number of samples to take from the margins of a surgical resection specimen[8–10,39]. No available evidence-based data addressed how to adequately assess margins or whether the assessment should be done using fresh or fixed resection specimens.

The Association of Directors of Anatomical and Surgical Pathology and the College of American Pathologists advocate the use of perpendicular (rather than *en face*) blocks from margins in STS[9,39].

The Association of Directors of Anatomical and Surgical Pathology recommends that any margin macroscopically more than 5 cm be considered clear and that it need not be sampled except in cases of epithelioid sarcoma and angiosarcoma, which are prone to subclinical proximal or satellite spread[9]. However, no recommendation about the number of sections that should be taken is made.

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

The National Comprehensive Cancer Network guideline states that the surgeon and the pathologist should both assess the margins and that the margin distances should be provided in the surgical report. However, the guideline gives no advice on how to assess margin adequacy.

4.4 Question 3

Three guidelines and one protocol addressed the appropriate handling of surgical resection specimens[8–10,39]. The guidelines written by the Association of Directors of Anatomic and Surgical Pathology, The Dutch Association of Comprehensive Cancer Centres, and the College of Pathologists all recommend that resections arrive in the pathology lab unfixed as soon as possible after excision[9,10,39]. The Dutch guideline further recommends that the specimens arrive preferably on gauze moistened with physiologic salt solution. In addition, the Dutch guideline recommends storing representative tissue and freezing it for later testing as needed[10]. The Association of Directors of Anatomic and Surgical Pathology and the ESMO guidelines recommend that, whenever possible, the orientation of a resection specimen be verified with the operating surgeon[8,9].

5. DSG CONSENSUS PROCESS

The draft guideline was circulated to the Sarcoma DSG for review and discussion. The group approved the document and agreed that no major changes were necessary.

6. REVIEW AND APPROVAL BY THE PEBC REPORT APPROVAL PANEL

The final report was also reviewed and approved by the PEBC report approval panel, which consists of three members, including two oncologists with expertise in clinical and methodology issues, and the PEBC director. Key issues raised by the Report Approval Panel included the lack of a discussion of health benefits and side effects, of an explicated definition of STS, and of any comment on the type or quality of radiation administered in the studies.

The Sarcoma DSG received and responded to all comments. The discussion section was expanded to address most of the concerns and to provide additional context and commentary.

7. EXTERNAL REVIEW

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

7.1 Methods

7.1.1 Targeted Peer Review

During the guideline development process, 4 targeted peer reviewers from Canada (considered clinical or methodology experts on the topic) were identified by the guideline authors. Three reviewers agreed to participate, and the draft report and a questionnaire were sent by e-mail for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and questions about whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent on June 12, 2012. Follow-up reminders were sent at 2 weeks and at 4 weeks. All the targeted peer reviewers were required to complete a conflict of interest form. Two reviewers completed their questionnaires; one reviewer joined the professional consultation.

7.1.2 Professional Consultation

The guideline authors identified 60 potential participants. Feedback was obtained through a brief online survey of these health care professionals who are the intended users of the guideline. Participants were asked to rate the overall quality of the guideline recommendations and whether they would use and recommend them. Written comments were invited. Participants were contacted by e-mail and directed to the survey Web site, where they were provided with access to the survey. The notification message was sent June 11, 2012. Two follow-up reminders were sent on June 25 and July 9, 2012.

7.2 Results

7.2.1 Summary of Written Comments from the Targeted Peer Review

The main concerns raised were

- that "preoperative radiation" should be added in recommendation 1 ("the use of postoperative radiation should be considered").

- that the intent of the guideline was to provide clinicians with guidance on the definition of an adequate surgical margin, but the document did not provide any clinically useful guidance on how to proceed.
    - The poor quality of many of the studies and the lack of a randomized controlled trial made providing such guidance difficult. The authors inserted a recommendation based on the consensus opinion of the expert panel.

7.2.2 Summary of Written Comments from the Professional Consultation

From among the 60 participants, 15 responses were received, with 6 respondents saying that they had no interest in this area. Requests were made to change the verb "has" to "may have" in one qualifying statement ("A microscopic positive margin in STS of the limb treated with surgery and radiation has an increased rate of local recurrence").

8. PRACTICE GUIDELINE

8.1 Question 1

Recommendation: In limb-salvage surgery for STS, the operation should be planned with the objective of achieving a clear margin. However, to preserve functionality, surgery may result in a close or even a microscopically positive margin. Based on the consensus opinion of the expert panel, a "close" margin is considered to be less than 1 cm after formalin fixation. In the circumstance of a close or microscopically positive margin, the use of preoperative or postoperative radiation may be considered.

Qualifying Statements: In limb-sparing surgery for STS, an adequate margin for surgical treatment alone or for surgery with RT cannot be defined because the studies identified in the literature search did not definitively identify an appropriate margin distance. Intact fascia (which can be measured in millimetres) is considered an adequate margin by some[8,15].

A microscopically positive margin in STS of the limb treated with surgery and RT may have an increased rate of local recurrence. That possibility 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 the combination of surgery and RT, 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 an extremity that have been treated with intralesional or marginal excisions.

8.2 Question 2

Recommendation: In the histology assessment of margins, no definitive recommendations can be made concerning an appropriate required number of margin samples.

8.3 Question 3

Recommendation: It is not possible to make evidence-based recommendations concerning the appropriate handling of surgical resection specimens to assess the adequacy of excision. Where this topic is mentioned, guidelines endorse inking the margins and sampling them perpendicular to (and not *en face* to) the margin. In the absence of evidence-based recommendations, the Sarcoma 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 the orientation indicated by the surgeon.
- The specimen and the tumour should be measured in three dimensions.
- The distances from all 6 margins should be measured, and the location of the tumour (superficial or deep) and its relationship to fascia, if present, should be indicated.
- All margins should be sampled perpendicular to the margin, with at least 2 sections being 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.

9. DISCUSSION

Although many studies have considered what constitutes an appropriate margin, no randomized trials or prospective studies have assessed surgical margins and outcomes for STS of the extremities. Most of the available evidence comes from retrospective reviews of charts and databases. The studies are confounded by differences in treatments received: some patients received preoperative, and others postoperative, RT or chemotherapy, or both. Many studies had to be excluded because 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 results because it is impossible tell whether a treatment is effective or whether some combination of the location, type, size, or grade of the sarcoma is influencing the results.

There is a need for guidance concerning what constitutes an adequate surgical margin with respect to the management of STS of the extremities. There is no standard of care, and different surgeons have different definitions of what constitutes an adequate margin. After extensive review of the literature, the working group recommends that the goal should be to obtain negative margins. Local recurrences have been observed even when negative margins are achieved with surgery or with surgery and RT, 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.*[4], although even that finding is controversial[5]. In cases with close margins (<1 cm measured in the fixed state by the pathologist), consideration should be given to the administration of postoperative RT. Clearly, other factors—tumour type, grade, and biology, or even the type of tissue at the margin (for example, fascia)—affect the rate of both local and systemic recurrence. The causes of recurrence need further investigation. It may be that ongoing molecular studies will provide insight into other relevant tumour characteristics that influence outcome.

No studies addressed the number of sections that needed to be taken from the resection margins. The evidence for the number of sections that should be taken from a surgical specimen to assess adequacy of excision was nonexistent. Few studies mentioned how the specimens in their studies were sampled or how many sections were taken from margins. This lack of consistency makes it difficult to compare results study to study. There is a great need for evidence-based standardization concerning how to sample tumours.

10. PRACTICE GUIDELINE DATE

This guideline was completed in September 2012. Practice guidelines developed by the PEBC are reviewed and updated regularly. Please visit Cancer Care Ontario's Web site (https://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/sarcoma-ebs/) for the full evidence-based series report and subsequent updates.

11. ACKNOWLEDGMENTS

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12. CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest to declare.

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