Ontario
Cancer Care Ontario
Action Cancer Ontario

Evidence-based Series 11-2 Version 2 – EDUCATION AND INFORMATION 2014

Adjuvant Chemotherapy Following Complete Resection of Soft Tissue Sarcoma in Adults

Members of the Sarcoma Disease Site Group

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

An assessment conducted in October 2014 put Evidence-based Series (EBS) 11-2 Version 2 in the Education and Information section. This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes. The PEBC has a formal and standardize process to ensure the currency of each document (PEBC Assessment & Review Protocol)

Evidence-based Series (EBS) 11-2 Version 2, the resulting review report, consists of the following 5 parts:

1. **Guideline Report Overview**
2. **Summary**
3. **Full report**
4. **Document Assessment and Review Tool**

and is available on the CCO Website on the PEBC Sarcoma DSG page

Report Date: October 28, 2013

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

Journal Citation (Vancouver Style): Figueredo A, Bramwell VHC, Bell R, Davis AM, Charette ML; Members of the Cancer Care Ontario Practice Guidelines Initiative Sarcoma Disease Site Group. Adjuvant chemotherapy following complete resection of soft tissue sarcoma in adults: a clinical practice guideline. Sarcoma.2002;6:5-18.

Guideline Citation (Vancouver Style): Members of the Sarcoma Disease Site Group. Adjuvant chemotherapy following complete resection of soft tissue sarcoma in adults. Ghert M, Agbassi C, reviewers. Toronto (ON): Cancer Care Ontario; 2011 Sep 15 [Education and Information 2014 Oct]. Program in Evidence-based Care Evidence-Based Series No.: 11-2 Version 2. Education and Information 2014

TABLE OF CONTENTS

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

Evidence-based Series 11-2 Version 2

Adjuvant Chemotherapy Following Complete Resection of Soft Tissue Sarcoma in Adults

Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES AND KEY CHANGES
	Search Dates	Data		
Original version Nov 2000	1996 to 2000	Full Report	Peer review publication* Web publication	Not Applicable (NA)
Update Feb 2005	2001 to 2005	New data added to original Full Report	Peer review publication Updated Web publication	NA
Version 2 Sep 2011	2005 to 2011	New data found in Document Assessment & Review Tool	Updated Web publication	2005 Guideline Recommendations ENDORSED

* Figueredo A, Bramwell VHC, Bell R, Davis AM, Charette ML and Members of the Cancer Care Ontario Practice Guidelines Initiative Sarcoma Disease Site Group. Adjuvant chemotherapy following complete resection of soft tissue sarcoma in adults: a clinical practice guideline. *Sarcoma* 2002;6:5-18.

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

Evidence-based Series 11-2 Version 2

Adjuvant Chemotherapy Following Complete Resection of Soft Tissue Sarcoma in Adults

Guideline Review Summary

Review Date: May 31, 2011

The 2005 guideline recommendations are

ENDORSED

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

OVERVIEW

Evidence-based Series History

This guidance document was originally released by the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO), in 2000 and its first update released in February 2005. In May 2011, the PEBC guideline update strategy was applied, and the new updated document released in September 2011. The Summary and the Full Report in this version are the same as February 2005 version.

Update Strategy

Using the Document Assessment & Review Tool at the end of this report, the PEBC update strategy includes an updated search of the literature, review and interpretation of the new eligible evidence by clinical experts from the authoring guideline panel, and consideration of the guideline and its recommendations in response to the new available evidence.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Questions Considered

1. What are the benefits of anthracycline-based adjuvant chemotherapy in adult patients with completely resected soft tissue sarcomas (STS), in terms of local disease control, systemic recurrence, and overall survival?
2. When these benefits are assessed in the context of expected toxicities, in what circumstances should adjuvant chemotherapy be recommended?

3. Are there any advantages in using combination versus single-agent anthracycline-based chemotherapy in adjuvant setting?

Literature Search and New Evidence

The new search (February 2005 to March 2011) yielded three new meta-analysis publications. Brief results of these publications are shown in the Document Assessment & Review Tool at the end of this report.

Impact on Guidelines and Its Recommendations

The new data supports existing recommendations for Guideline (adjuvant chemotherapy following complete resection of STS in adults). Therefore, the Sarcoma DSG ENDORSED the 2005 recommendations on adjuvant chemotherapy following complete resection of STS in adults.

program in evidence-based care
a cancer care ontario program

programme de soins fondé sur des preuves
un programme de action cancer ontario

Adjuvant Chemotherapy Following Complete Resection of Soft Tissue Sarcoma in Adults

Practice Guideline Report #11-2

A Figueredo, VHC Bramwell, R Bell, AM Davis, ML Charette, and members of the Sarcoma Disease Site Group.

Please see the EBS 11-2 Version 2 Guideline Review Summary and the Document Assessment & Review Tool for the summary of updated evidence published between 2005 and 2011.

February 2005

SUMMARY

Guideline Questions

1. What are the benefits of anthracycline-based adjuvant chemotherapy in adult patients with completely resected soft tissue sarcomas, in terms of local disease control, systemic recurrence, and overall survival?
2. When these benefits are assessed in the context of expected toxicities, in what circumstances should adjuvant chemotherapy be recommended?
3. Are there any advantages in using combination versus single-agent anthracycline-based chemotherapy in the adjuvant setting?

Target Population

The recommendations apply to adult patients with resected soft tissue sarcoma.

Recommendations

- It is reasonable to consider anthracycline-based adjuvant chemotherapy in patients who have had removal of a sarcoma with features predicting a high likelihood of relapse (deep location, size >5 cm, high histological grade). These features correspond to International Union Against Cancer (UICC) stage III.[*]
- Although the benefits of adjuvant chemotherapy are most apparent in patients with extremity sarcomas (7% risk difference [RD] for overall survival at 10 years), patients with high-risk tumours at other sites should also be considered for such therapy.

[*] Sobin LH, Wittekind Ch, eds. *International Union Against Cancer. TNM Classification of Malignant Tumours.* 5th ed. New York: Wiley-Liss; 1997.

Qualifying Statements

- There is insufficient evidence on patients with retroperitoneal sarcomas or stromal tumours of the bowel to make recommendations for adjuvant chemotherapy. The risk of serious toxicity in retroperitoneal sarcomas when chemotherapy is combined with radiation therapy is of major concern. Similarly, the data on uterine sarcomas come from a single trial with negative results; therefore, no specific recommendations can be made about these tumours.
- Risks of severe persistent adverse effects of adjuvant chemotherapy, such as cardiomyopathy, should be carefully evaluated and balanced against the expected benefit, particularly in patients aged 70 years or older and those with significant co-morbidity.
- There are insufficient data to determine whether single-agent doxorubicin or combination chemotherapy with doxorubicin should be recommended. This decision should take into account issues such as patient preference/convenience, likely adverse effects, costs, and available resources. Meta-analyses of trials evaluating adjuvant chemotherapy with single-agent doxorubicin and doxorubicin-based combination regimens, both compared with observation, showed similar results for mortality and recurrence. Many of the doxorubicin-based combination chemotherapy regimens examined in the trials are not considered every effective today. New regimens using high-dose ifosfamide and epirubicin have reported significant advantages in small trials. These results will require confirmation in larger trials.

Methods

Entries to MEDLINE (1996 to January Week 4, 2005), EMBASE (1996 to Week 6, 2005), CANCERLIT (1996 through August 2002), and Cochrane Library (2005, Issue 1) databases and abstracts published in the proceedings of the 1997-2002 annual meeting of the American Society of Clinical Oncology (ASCO) were systematically searched for evidence relevant to this practice guideline report.

Evidence was selected and reviewed by one member of the Practice Guidelines Initiative Sarcoma Cancer Disease Site Group and methodologists. This practice guideline report has been reviewed and approved by the Sarcoma Cancer Disease Site Group, which comprises medical oncologists, radiation oncologists, surgeons, a pathologist, a methodologist, and community representatives.

External review by Ontario practitioners is obtained for all practice guidelines through a mailed survey. Final approval of the guideline report is obtained from the Practice Guidelines Coordinating Committee.

The Practice Guidelines Initiative has a formal standardized process to ensure the currency of each guideline report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Key Evidence

- Considering all resected soft tissue sarcoma patients, doxorubicin-based adjuvant chemotherapy significantly reduces all recurrences, with an absolute benefit of 10% (95% confidence interval, 5% to 15%; p=0.0001) at 10 years. There is only a non-significant effect for survival, with an absolute benefit of 4% at 10 years (95% confidence interval, -1% to 9%). Considering only patients with soft tissue sarcoma of the extremities, the benefit of adjuvant chemotherapy is 7% at 10 years (p=0.001). Most chemotherapy regimens produce significant toxicity.

Update

- The final results of the small trials evaluating new regimens have since been fully published. One of the small randomized studies, which used a new regimen of high-dose epirubicin and ifosfamide in large high grade extremity sarcomas, showed improved disease free (p=0.04) and overall survival (p=0.03).

Future Research

Patients should be encouraged to participate in clinical trials comparing adjuvant chemotherapy versus observation to further characterize benefits.

For further information about this practice guideline report, please contact Dr. Shailendra Verma, Chair, Sarcoma Cancer Disease Site Group, 503 Smyth Road, Ottawa, Ontario, K1H 1C4; TEL (613) 737-7700 Ext. 56792; FAX (613) 247-3511.

The Practice Guidelines Initiative is sponsored by:
Cancer Care Ontario & the Ontario Ministry of Health and Long-term Care.

Visit http://www.cancercare.on.ca/
for all additional Practice Guidelines Initiative reports
.

PREAMBLE: About Our Practice Guideline Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle.[1] The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis, and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee, whose membership includes oncologists, other health providers, patient representatives, and CCO executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network that is expected to consult with relevant stakeholders, including CCO.

Reference:

[1] Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

For the most current versions of the guideline reports and information about the PEBC, please visit the CCO Web site at:
http://www.cancercare.on.ca
For more information, contact our office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775
E-mail: ccopgi@mcmaster.ca

Disclaimer

Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the practice guideline is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

program in evidence-based care
a cancer care ontario program

programme de soins fondé sur des preuves
un programme de action cancer ontario

Adjuvant Chemotherapy Following Complete Resection of Soft Tissue Sarcoma in Adults

Practice Guideline Report #11-2

A Figueredo, VHC Bramwell, R Bell, AM Davis, ML Charette, and members of the Sarcoma Disease Site Group.

Please see theEBS 11-2 Version 2 Guideline Review Summary and the Document Assessment & Review Tool for the summary of updated evidence published between 2005 and 2011.

February 2005

FULL REPORT

I. QUESTIONS

1. What are the benefits of anthracycline-based adjuvant chemotherapy in adult patients with completely resected soft tissue sarcomas, in terms of local disease control, systemic recurrence, and overall survival?
2. When these benefits are assessed in the context of expected toxicities, in what circumstances should adjuvant chemotherapy be recommended?
3. Are there any advantages in using combination versus single-agent anthracycline-based chemotherapy in the adjuvant setting?

II. CHOICE OF TOPIC AND RATIONALE

Soft tissue sarcomas (STS) include a variety of malignant tumours affecting mesenchymal tissues of the extremities, trunk, head and neck, and viscera. These tumours are rare, comprising less than 1% of all malignancies (1). In Canada, the estimated incidence is 650 new cases per year (2). Regionalized multi-disciplinary units have been recommended to provide for the best management of these patients. While wide surgical resection of tumours remains the most effective treatment, 30% to 50% of patients develop local recurrences and/or distant metastases, many of which eventually lead to death (1,3,4). Predictors of disease relapse include high histological grade, size >5 cm, and deep location. These factors indicate stage III in the International Union Against Cancer (UICC) classification (5) (please see Appendix I for staging information). To reduce the chances of disease relapse after surgery, adjuvant radiotherapy and chemotherapy have been advocated. However, results of individual trials have been inconclusive (1,3,4). Recently, several quantitative overviews of doxorubicin-based adjuvant chemotherapy trials have been published (6-9). The Sarcoma Disease Site Group (DSG) of the Cancer Care Ontario Practice Guidelines Initiative (CCOPGI) deemed it necessary to investigate whether doxorubicin-based adjuvant

chemotherapy should be recommended as part of the management of adult patients with resected STS. This guideline did not consider non-anthracycline-based chemotherapy regimens or neoadjuvant chemotherapy.

III. METHODS

Guideline Development

This practice guideline report was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario's Program in Evidence-based Care, using methods of the Practice Guidelines Development Cycle (10). Evidence was selected and reviewed by one member of the PGI's Sarcoma Cancer Disease Site Group (Sarcoma DSG) and methodologists. Members of the Sarcoma DSG disclosed potential conflict of interest information.

The practice guideline report is a convenient and up-to-date source of the best available evidence on adjuvant chemotherapy following complete resection of soft tissue sarcoma in adults, developed through systematic reviews, evidence synthesis and input from practitioners in Ontario. The body of evidence in this report is primarily comprised of mature randomized controlled trial data; therefore, recommendations by the DSG are offered. The report is intended to promote evidence-based practice. The PGI is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

External review by Ontario practitioners is obtained for all practice guideline reports through a mailed survey consisting of items that address the quality of the draft practice guideline report and recommendations, and whether the recommendations should serve as a practice guideline. Final approval of the original guideline report is obtained from the Practice Guidelines Coordinating Committee.

The PGI has a formal standardized process to ensure the currency of each guideline report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Literature Search Strategy

The recently published exhaustive reviews of the literature and clinical trial registries form the basis for the present overview (6-9). MEDLINE (Ovid) (1996 – August 2000), CANCERLIT (Ovid) (1996 – June 2000), and the Cochrane Library (Issue 3, 2000) were searched for additional trials published since the latest overview using the terms: "sarcoma" (Medical Subject Heading [MeSH]), "soft tissue sarcomas" (text words), "postoperative" (text word), "adjuvant therapy" (text word), and "adjuvant chemotherapy" (MeSH and text word). These terms were then combined with the search terms for the following publication types and study designs: practice guidelines, systematic reviews or meta-analyses, reviews, randomized controlled trials, and controlled clinical trials.

In addition, conference proceedings of the 1997-2000 annual meeting of the American Society of Clinical Oncology (ASCO) were searched for abstracts of relevant trials. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) and the National Guidelines Clearinghouse (http://www.guideline.gov/index.asp) were also searched for existing evidence-based practice guidelines.

Relevant articles and abstracts were selected and reviewed by three reviewers and the reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles.

Update

The original literature search has been updated using MEDLINE (to January Week 4, 2005), EMBASE (1996 to Week 6, 2005), CANCERLIT (through August 2002), the Cochrane Library (Issue 1, 2005), and the 2001-2004 proceedings of the annual meeting of ASCO.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

1. Randomized controlled trials (RCTs) comparing anthracycline-based adjuvant chemotherapy to observation in patients with completely resected STS.
2. Patients were at least 15 years of age.
3. Data provided on outcomes of overall and disease-free survival.
4. Abstracts of trials were considered.

Exclusion Criteria

1. Phase I and II studies were not considered for inclusion in this report because of the availability of RCTs.
2. Letters and editorials were not considered.
3. Papers published in a language other than English were not considered.

Synthesizing the Evidence

The major outcomes reported in the meta-analyses are disease relapse and survival. A published figure from the Sarcoma Meta-Analysis Collaboration (SMAC) (9) has been used to provide data on disease relapse and survival (Figure 1). To investigate outcome results versus type of therapy (single-agent versus combination chemotherapy), the data were reanalyzed by the Sarcoma DSG using the software package Metaanalyst$^{0.098}$ (provided by J. Lau, Boston, MA, USA). To estimate overall effects, and to maintain uniformity with previous meta-analyses, the odds ratio (95% confidence intervals) is reported according to the fixed effects model of Mantel-Haenzel and Peto. Estimates for odds ratios (OR) >1.0 favour the control group (observation) whereas OR <1.0 favour the treatment group (adjuvant chemotherapy). In addition, the individual published trials have been analyzed for chemotherapy toxicity and compliance.

Update

Because the SMAC meta-analysis (9) was performed using individual patient data, and this level of data is not available for the new trials identified through updating activities (1u-3u), a new meta-analysis incorporating these trials has not been done. Overall, the results of these new trials are consistent with the results of the trials examined by the SMAC.

IV. RESULTS

Literature Search Results

Four meta-analyses (6-9) and 16 RCTs (11-30) met the inclusion criteria and were reviewed. Fourteen of the RCTs were included in the overview by the SMAC (11-28) which also included updated individual patient data. Two RCTs, reported in abstract form (29,30), were published after the SMAC meta-analysis and are discussed in this overview. The chemotherapy regimens used in the RCTs have been described in Appendix II.

Update

Three RCTs (1u-3u) were found during review and updating activities. Two of the three papers (1u,2u) are fully published reports of abstracts previously included in the original guideline report (29,30). The third paper is a fully published report of a trial comparing epirubicin and ifosfamide to observation after surgery (3u).

Meta-analyses of RCTs Comparing Adjuvant Chemotherapy to Observation

Initial Meta-analyses

The first quantitative overview by Jones et al (6) was literature-based and reported in abstract form only. It included 13 published trials of doxorubicin-containing adjuvant

chemotherapy in resected STS at any location. Eligible trials compared adjuvant chemotherapy to observation. Statistically significant benefits favouring adjuvant chemotherapy were observed for overall survival (9% absolute benefit; p=0.016), time to local recurrence (p=0.0003) and metastases (p=0.0016). There was also a suggestion of increased survival benefit for combination chemotherapy versus doxorubicin alone, and of decreased local recurrence when chemotherapy was combined with radiation therapy. The authors found that reporting of outcomes was variable and suggested a centralized registry with standardized reporting of results for individual patient data assessment.

The second literature-based meta-analysis by Zalupski et al (7) was limited to nine published trials of adjuvant chemotherapy in patients with STS of the extremities. Adjuvant chemotherapy improved the overall survival rate by 10% and disease-free survival rate by 15% compared to observation. Both analyzed end-points gave significant results.

Finally, the third literature-based meta-analysis by Tierney et al (8) included 15 published trials comparing adjuvant chemotherapy to no chemotherapy in resected STS of any location (11,14,16,18,20-28). A significant improvement in overall survival (12% at 5 years; p=0.0002) was noted for the treated patients. Because of concerns with potential biases in published data and the inability to investigate patient subgroups, a meta-analysis with individual patient data was proposed and undertaken by the SMAC.

The Sarcoma Meta-analysis Collaboration (SMAC) (9)

This overview performed by European and North American investigators was conducted after three previous literature-based meta-analyses (6-8) had suggested significant improvements in overall survival, disease-free survival and local recurrence with the use of adjuvant chemotherapy. The conclusions of these initial analyses were weakened by the possibility of publication biases and relatively short follow-up times in the published results. Therefore, the collaborative effort was to include both published and unpublished results as well as updated individual patient data, in order to obtain more reliable results and to enable subgroup analyses.

The search for data was broad; it included the MEDLINE, CANCERLIT and EMBASE databases for published material, the UK Committee on Cancer Research of Clinical Trials and the US Physicians Data Query of Clinical Protocols for unpublished trials. The search extended from 1966 to 1996. The terms used in the search were not described. Reference lists of publications were also examined. Eligible studies randomly assigned patients with localized resectable STS to receive adjuvant chemotherapy or no chemotherapy. Potential biases were avoided by including published and unpublished results and by individual patient data updated by the original investigators. The methods for combining data were clearly reported and appeared appropriate. Heterogeneity of results was investigated. The conclusions were supported by the data analysis, including clinically relevant subgroup analyses.

The overall sample included 1568 patients in 14 RCTs of doxorubicin-based adjuvant chemotherapy (11-28). The published studies are described in Table 1. One unpublished trial by the Swiss Group for Clinical Cancer Research (SAKK) was also included in the SMAC meta-analysis. The chemotherapy regimens have been described in detail in Appendix II. The majority of patients (74%) were 15 to 60 years of age, and 54% were female. Seventy-four percent of patients had primary tumours, and 11% had resected recurrent tumours. The disease affected the extremities in 58% of patients, the trunk in 12%, the uterus in 17% and other sites in 10%. The most common histological types of tumours were malignant fibrous histiocytoma (20%), leiomyosarcoma (12%), synovial sarcoma (10%) and liposarcoma (9%). The histologic type was not available in 18% of cases. Most tumours (67%) were of high-grade malignancy, but in 28% of cases grade was not available. Complete tumour resections were

done in 76% of patients, marginal resections were performed in 15% of the cases and assessment was not available in 9% of cases. Radiotherapy was used in 47% of cases.

The adjuvant chemotherapy consisted of doxorubicin alone in six RCTs comprising 727 patients, and of doxorubicin combined with other drugs in eight RCTs comprising 844 patients. The drugs added to doxorubicin were cyclophosphamide in seven trials, vincristine in four trials, dacarbazine in three trials, methotrexate in three trials, actinomycin D in two trials and ifosfamide in a single small unpublished trial (SAKK) (Table 1).

All reported results are given as odds ratios (OR), hazard ratios, or as risk differences (RD) with 95% confidence intervals (CI) using the fixed effects model of Peto. Potential heterogeneity of results was explored and no significant ($p<0.10$) values were observed. One study (13) recorded recurrence, but did not distinguish between local and distant recurrence and therefore was not included in the analyses of these outcome measures (9).

In patients receiving adjuvant chemotherapy, there was a non-significant trend for increased overall survival (Figure 1 and Table 2) with a RD of 4% (95% CI, -1% to 9%) when compared with patients who received no adjuvant chemotherapy. Disease-free survival was significantly increased in treated patients with an absolute RD of 10% (95% CI, 5% to 15%; $p=0.0001$) at 10 years. This difference was mostly due to patients who were free of metastases, in whom there was a 10% difference (95% CI, 5% to 15%; $p=0.0003$) (Table 2). The difference for local recurrence was smaller, but still statistically significant (RD, 6%; 95% CI, 1% to 10%; $p=0.016$). These pooled results were not changed by excluding patients younger than 15 years of age, the presence of local recurrence or metastases, nor whether patients received induction chemotherapy.

Although tests of the overall data did not show significant statistical heterogeneity ($p<0.10$), there was evidence of clinical heterogeneity, indicated by the wide range of age groups, tumour location, tumour size, types and grade of malignancy, surgical treatment, and use of adjuvant radiation therapy and regimens of chemotherapy. The results of these subgroup analyses were difficult to interpret. The SMAC authors state "For overall survival, there was no clear evidence to suggest that any subgroup benefited more or less from adjuvant chemotherapy... There was some suggestion that men benefited more than women from chemotherapy [*but this was felt to be biologically implausible*]. Among patients with lesions of the extremities (376 deaths, 886 patients), the hazard ratio was 0.80 ($p=0.029$), equivalent to a 7% absolute benefit at 10 years. This group had the clearest evidence of a treatment effect on survival. The wide confidence intervals for the other sites reflect the small numbers, and there was no clear evidence that the results differed from those for extremity sarcomas ($p=0.58$)." There was no evidence of a differential effect of chemotherapy for any of the subgroups considered for relapse-free survival.

The conclusion of the SMAC project was that doxorubicin-based adjuvant chemotherapy, following resection of STS, is associated with a significant prolongation of the disease-free interval (mostly due to delay in metastases) and a trend for increased survival. The largest benefit in survival was in the subgroup of patients with extremity sarcomas, with an absolute 7% benefit at 10 years. Converting the risk difference to the number needed to treat (NNT) resulted in a value of 14 patients requiring treatment with adjuvant chemotherapy to delay one death.

Additional RCTs Published After the SMAC Overview

A search for trials published after the SMAC overview uncovered two RCTs reported in abstract form (29,30). Investigators at the University Hospital in Vienna randomized 59 patients to radiation therapy (RT) alone (51 Gy hyperfractionated), or to the same RT plus chemotherapy with doxorubicin, dacarbazine and ifosfamide supported by granulocyte-colony stimulating factor (G-CSF) after wide or marginal resection (29). After a mean observation

period of 41 ± 19.7 months, the percentage of patients free of disease was increased in the arm receiving adjuvant chemotherapy, but the difference was not significant. In the subgroup of patients with grade 3 lesions, disease-free survival was significantly improved in patients receiving adjuvant chemotherapy, compared with patients receiving RT alone (p=0.03). Grade 3/4 toxicity, mostly neutropenia, occurred in 26% of cases. One patient in each treatment arm experienced late local complications.

Another trial was reported by investigators at the Rizzoli Institute and Italian collaborators (30). The abstract presents the results of the first 104 patients with resected, high-grade, primary or recurrent STS of the extremities and girdles randomized to either observation or intensive adjuvant chemotherapy with epirubicin and ifosfamide supported by G-CSF. After a median follow-up of 36 (range 4 to 73) months, there were significant improvements in disease-free (p<0.02) and overall survival (p=0.01) favouring patients on chemotherapy. No toxicity data were reported.

Update

The fully published reports of the University Hospital in Vienna and Rizzoli Institute trials were found during updating activities (1u,2u). In addition, a fully published report of a RCT evaluating a new regimen of high dose epirubicin and ifosfamide was also found (3u).

Brodowicz et al updated their report of 59 patients recruited into an RCT between 1992-99 that was stopped because of poor accrual (1u). These patients had mostly STS of the extremities, grade II or III, and had wide or marginal resection. Post-operatively, the patients were randomized to RT alone (51 Gy hyperfractionated), or to the same RT plus dose-intensive chemotherapy with ifosfamide, dacarbazine and doxorubicin, with the support of G-CSF after wide or marginal resection (1u). After a mean observation period of 41 ± 19.7 months, there was a non-significant decrease in local relapses, all relapses and death for the group of patients receiving adjuvant chemotherapy. In the subgroup of patients with grade III tumours, disease-free survival (but not overall survival) was significantly improved by chemotherapy (p=0.03).

The updated results of the Frustaci et al trial were reported for 104 patients with resected, high-grade, primary or recurrent STS of the extremities and girdles randomized to either observation or five courses of intensive adjuvant chemotherapy with epirubicin and ifosfamide supported by G-CSF. After a median follow-up of 59 months, an intention to treat analysis showed median disease free survival times of 48 versus 16 months (p=0.04) and median overall survival times of 75 versus 46 months (p=0.03) for chemotherapy and control groups, respectively. At 4 years the overall disease free survival was 50% for the chemotherapy arm and 37% for the control arm (p=0.19), with a hazard ratio (HR) of 0.59 (95% CI: 0.36-0.99, p=0.04). Overall survival at 4 years was 69% versus 50% for the chemotherapy and control arms, respectively (p=0.04), with a HR of 0.52 (95% CI: 0.29-0.93, p=0.03). Of interest, although there is a delay in distant relapse in the chemotherapy arm, at four years the distant relapse rates are the same between the arms (44% and 45%). An updated analysis at a median follow-up of 89.6 months has not disclosed a significant difference in disease free survival or overall survival for the chemotherapy and control groups. A difference in time to progression of 31.2 months for chemotherapy versus control patients was observed. However caution must be exerted as this is a relatively small study involving a typically heterogeneous population and a large study may result in no significant difference.

Another Italian group from Siena performed an adjuvant chemotherapy trial on 88 patients randomized after surgery to observation (43 patients) or chemotherapy (45 patients) (3u). This trials was prematurely closed due to poor patient accrual and its excessive duration (1985 to 1996). Chemotherapy consisted of epirubicin during the first half of the study (first 26 patients), and epirubicin combined with ifosfamide for the rest of the study

(subsequent 19 patients). After a median follow-up of 94 months, patients on adjuvant chemotherapy had improved five-year disease-free survival (69% versus 44%; p=0.01) and a trend for overall survival (72% versus 47%; p=0.06) compared to patients not receiving chemotherapy. It should be noted that only 19 patients received an intensive epirubicin/ifosfamide combination; the remainder in the chemotherapy arm received single agent epirubicin. The relapse rate was higher in the control arm (46%) compared to the adjuvant chemotherapy arm (29%), however the difference was not statistically significant (p=0.1).

Outcomes

Treatment Effects of Single-agent Doxorubicin versus Combination Chemotherapy with Doxorubicin

All of the adjuvant chemotherapy regimens investigated by the SMAC contained doxorubicin, but seven of them also included other drugs (Table 1). The dose of doxorubicin ranged from 50 to 90 mg/m^2 per course, with total cumulative doses between 400 mg/m^2 and 550 mg/m^2. A dose-response relationship was investigated but not detected in any of the meta-analyses (6-9). The effect of treatment with doxorubicin alone versus doxorubicin combined with other drugs was investigated with data from the SMAC (9). For patients treated with single-agent doxorubicin versus patients who received no adjuvant chemotherapy, the mortality OR was 0.80 (95% CI, 0.60 to 1.07), compared with 0.89 (95% CI, 0.67 to 1.18) for patients on combined chemotherapy versus those randomized to observation. The OR for recurrence for patients treated with single-agent doxorubicin versus those who received no adjuvant chemotherapy was 0.71 (95% CI, 0.53 to 0.96), similar to the OR for patients receiving doxorubicin-containing combination adjuvant therapy versus patients randomized to no adjuvant chemotherapy (OR, 0.69; 95% CI, 0.51 to 0.94).

Table 1. Randomized trials of doxorubicin-based adjuvant chemotherapy in resected soft tissue sarcomas in adults (data from 13 published studies included in SMAC meta-analysis).

Trial (ref.)	Disease Sites	Chemotherapy					#Patients assigned to each group (entered/evaluable)	
		Chemo.	Dose per course*	Dose Intensity†	Total Dose‡	RT	Control	Dox.
GOG (11)	Ut	Dox	60	20	480	no	112 / 81	113 / 75
DFCI (12)	Ex,RP, HN,Tr	Dox	90	30	450	yes	22 / 22	20 / 20
ECOG (13)	Ex,RP, HN,Tr	Dox	70	23.3	490	no	NA / 13	NA / 17
SSG (14)	Ex, HN, Br, Tr, Abd	Dox	60	15	540	some	119/88	121/93
Rizzoli (15,16)	Ex	Dox	75	25	450	some	35/35	24/24
IGSG (18,19)	EX,RP, HN,Tr	Dox	70-90	23.3-26.7	450	some	NA / 43	NA / 39
MDAH (20)	Ex	VACAR	60	15	420	yes	24 / 23	22 / 20
Mayo (21,22)	Ex,Tr	VAC/VAD	50	8.3	200	no	NA / 31	NA / 30
NCI (23,24)	Ex	AC/MTX	50-70	12.5-15.6	550	yes	28 / 28	39 / 37
NCI (25,26)	HN,Tr,Br	AC/MTX	50-70	12.5-15.6	550	yes	14 / 27	17 / 30
NCI (25,26)	RP	AC/MTX	50-70	12.5-15.6	550	yes	7 / 16	8 / 21
EORTC (27)	Ex,RP, Tr,HN,Ut	CYVADIC	50	12.5	400	yes	234 / 172	234 / 145
Bergonié (28)	Ex,RP, HN,Tr	CYVADIC	50	8.33	500	yes	NA / 28	NA / 31

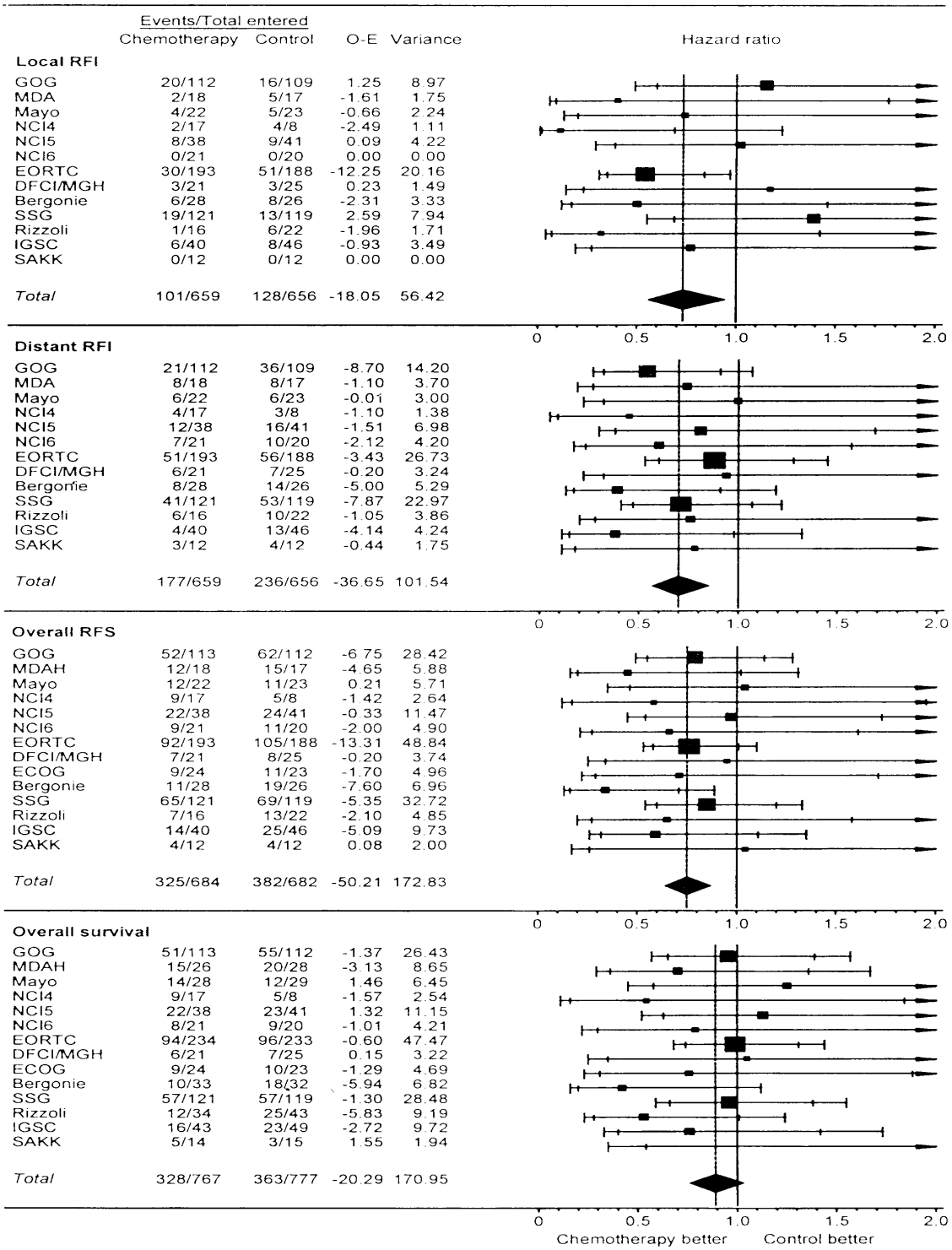
NOTE: Abd=abdominal; AC=doxorubicin + cyclophosphamide; Br=breast; Chemo. = chemotherapy; CYVADIC= cyclophosphamide + vincristine + doxorubicin + dacarbazine; Dox=doxorubicin; Ex=extremities; HN=head and neck; MTX=methotrexate + leucovorin; NA = data not available; RP=retroperitoneal; RT = radiation therapy; Tr=trunk; Ut=uterine; VAC=vincristine + cyclophosphamide + actinomycin D; VACAR=vincristine + doxorubicin + cyclophosphamide + actinomycin D; VAD=vincristine + doxorubicin + dacarbazine

* Dose per course in mg/m^2.

† Dose intensity in mg/m^2/week considering only the first 4 courses of chemotherapy.

‡ Total dose in mg/m^2.

Figure 1. Meta-analysis of the effects of adjuvant chemotherapy versus observation.



Used with permission: Sarcoma Meta-analysis Collaboration. Adjuvant chemotherapy for localized resectable soft-tissue sarcoma of adults: meta-analysis of individual data. *Lancet* 1997;350:1647-54.

Squares represent hazard ratios; area is proportional to amount of information available in trial; bars = 95% Confidence Interval (CI) (inner limit) and 99% CI (outer limit). Diamonds = overall hazard ratios for results of all trials combined - extremes of diamond give 95% CI; O-E = observed – expected; RFI = recurrence-free interval; RFS = recurrence-free survival.

NOTE: Statistical heterogeneity was p>0.10 in all four analyses: local recurrence-free interval, p=0.17; distant recurrence-free interval, p=0.86; overall recurrence-free survival, p=0.75; overall survival, p=0.54.

Table 2. Pooled results of adjuvant chemotherapy in adult patients with resected soft tissue sarcomas (data from the Sarcoma Meta-analysis Collaboration).

Survival Rate	# Trials	# Pts	Odds Ratio (95% CI)	p value	Risk Difference (95% CI)†
Overall	14	1544	0.89 (0.76 to 1.03)	0.12	-0.04 (-0.09 to -0.01)
Overall‡	12	886	0.80 (NA)	0.029	-0. 07 (NA)
Disease-free	14	1366	0.75 (0.64 to 0.87)	0.0001	-0.10 (-0.15 to -0.05)
Without Local Recurrence	13*	1315	0.73 (0.56 to 0.94)	0.016	-0.06 (-0.10 to 0.01)
Without Metastases	13*	1315	0.70 (0.57 to 0.85)	0.0003	-0.10 (-0.15 to -0.05)

Note: CI = confidence interval; NA = data not available; pts = patients.
* ECOG trial (13) not included; data not available.
† A minus (-) sign in front of the risk difference indicates a decrease in risk for treated patients versus controls.
‡ Only patients with extremity sarcomas.

Adverse Effects

Among the 14 trials included in the SMAC, toxicity data were not available for one unpublished study (SAKK) and for one published trial (20). Reporting of adverse effects in the other trials was not standardized. Some trials reported mostly qualitative assessments of toxicity (11-13,15,21,28), while others reported quantitative data according to standard toxicity grading scales (14,17,23-27). Adverse effects frequently consisted of alopecia, fatigue, anorexia, nausea and vomiting, leucopenia or neutropenia, thrombocytopenia, infections, mucositis and cardiotoxicity. Alopecia was considered significant in 50% (27) to 90% (13,21,25) of patients. Nausea and vomiting was mild to moderate in some trials; it was considered severe in 22% to 50% of patients in other trials (13,14,17,19). Various degrees of nadir or treatment day leucopenia or neutropenia were described in all trials, but neutropenic sepsis was uncommon and only a single patient was reported as dying due to infection (27). Severe thrombocytopenia was rare but it contributed to death in one patient with concurrent neutropenic sepsis and multiple organ failure (27). Cardiotoxicity was generally reported and consisted of arrhythmias and congestive heart failure, the latter leading to death in six patients (14,19,21,25,26). While the reported adverse effects could be attributed to doxorubicin, there were other side-effects associated with other drugs. Severe peripheral neuropathy induced by vincristine was reported in four (3.2%) of 126 patients treated with cyclophosphamide, vincristine, doxorubicin and dacarbazine (27). Cystitis was noted in four (7.8%) patients treated with doxorubicin, cyclophosphamide, methotrexate and leucovorin and concurrent RT (25,26); another patient had reduced creatinine clearance on high-dose methotrexate (26). Diarrhea occurred in two (8%) of 30 patients receiving vincristine, doxorubicin, cyclophosphamide and actinomycin D (21).

The available quantitative toxicity data has been tabulated for toxic deaths and major toxic events such as severe infections and cardiotoxicity (Table 3). The overall rate of toxic

deaths was nine in 523 patients (1.7%), and was similar for patients treated with single-agent doxorubicin (1.7%) or doxorubicin combined with other drugs (1.7%). The overall rate of cardiotoxicity was 25 cases among 494 patients (5.1%). Those receiving doxorubicin alone had a 5.6% cardiotoxicity rate, while the cardiotoxicity rate for doxorubicin combined with other drugs was 4.4%. Severe infections occurred more commonly in patients receiving multiple drug chemotherapy with a rate of 3.1% (7 of 226 patients) versus 0.4% (1 of 251 patients) in those receiving only doxorubicin (Table 3).

Overall, no correlation was found between chemotherapy toxicity and the use of radiation therapy (RT) (data not shown). Only three trials did not use RT (11,13,21) and another omitted the use of doxorubicin during RT (28). Of note, however, is that one trial of combined RT and chemotherapy versus RT alone in patients with retroperitoneal sarcomas was terminated because of poor results and toxicity in the combined treatment group (25).

Update

All three reports of the most recent trials (1u-3u) provided toxicity data. The Brodowicz et al trial (1u) described toxicity as moderate with no fatalities and no episodes of neutropenic sepsis or cardiomyopathy. One patient in the RT group and three patients in the RT plus chemotherapy group had local complications related to the underlying bone. Frustaci et al (2u) noted that the toxicity observed in their trial was mainly hematologic: 35% of patients had grade 4 leucopenia, 33% developed neutropenic sepsis, 24% required packed red blood cell transfusions, and 4% had grade 4 thrombocytopenia. No cardiotoxicity was observed using ventricular ejection fraction measurements. Petrioli et al (3u) reported that no patient experienced any grade 4 adverse event. The following grade 3 adverse events were reported among 45 patients receiving adjuvant chemotherapy: leucopenia, 15.6%; nausea and/or vomiting, 6.7%; stomatitis, 4.4%. Of significance among these newer trials is the high rate of neutropenic sepsis in the Frustaci et al trial (2u) in spite of the use of G-CSF rescue after chemotherapy.

Table 3. Severe toxicity of adjuvant chemotherapy in adult patients with resected soft tissue sarcomas (data from published papers).

Trial (Ref.)	Chemotherapy*	# Evaluable Patients	# Toxic Deaths (%)	# Pts Infec. (%)	# Pts Cardiotoxic (%)
GOG (11)	Dox	75	0	0	6 (8.0%)
DFCI (12)	Dox	20	1 (5.0%)	1(5.0%)	2 (10.0%)
ECOG (13)	Dox	17	0	NA	0
SSG (14)	Dox	93	3 (3.2%)	0	4 (4.3%)
Rizzoli (15,16)	Dox	24	0	0	1 (4.2%)
ISG (18,19)	Dox	39	NA	0	2 (5.1%)
All Dox alone	Dox	268	4/229 (1.7%)	1/251 (0.4%)	15/268 (5.6%)
MDAH (20)	VACAR	20	NA	NA	NA
Mayo (21,22)	VAC/VAD	30	1(3.3%)	1 (3.3%)	0
NCI (23,24)	AC/MTX	37	0	NA	NA
NCI (25,26)	AC/MTX	30†	1(3.3%)	2 (6.7%)	5 (16.7%)
NCI (25,26)	AC/MTX	21‡	2 (9.5%)	3 (14.3%)	3 (14.3%)
EORTC (27)	CYVADIC	145	1 (0.7%)	1 (0.7%)	2 (1.4%)
Bergonié (28)	CYVADIC	31	0	NA	NA
All Dox+other	Dox + other	314	5/294 (1.7%)	7/226 (3.1%)	10/226 (4.4%)
All	Dox +/- other	582	9/523 (1.7%)	8/477 (1.7%)	25/494 (5.1%)

Note: #Pts= number of patients; Infec.= severe infections; NA = Data not available.
* Chemotherapy: Please see footnote of Table 1.
† Includes 13 patients treated outside the randomized trial.
‡ Includes 13 patients treated outside the randomized trial.

Compliance with Chemotherapy

Compliance data were not reported in six trials (12,13,17,20,25,26), reported in a limited manner in three trials (15,21,28), and investigated in more detail and correlated with major outcomes in four other trials (11,14,24,27). Compliance data were not available for the unpublished trial included in the SMAC meta-analysis (SAKK). In Table 4, we have tabulated compliance with chemotherapy according to whether patients received any treatment, or had minor or major reductions of chemotherapy. We considered patients receiving at least four courses of chemotherapy as having a minor reduction of treatment.

Overall compliance with treatment was similar for both single-agent doxorubicin and doxorubicin combined with other drugs. Of 276 patients randomized to receive doxorubicin alone, data were not available for 76 patients. Of the data available for 200 patients, 107 (53.5%) received full dose treatment and 177 (88.5%) received at least four courses of treatment. Among 314 patients randomized to receive doxorubicin combined with other drugs data were only available for 243 patients. Of these 243 patients, 143 (58.8%) received full treatment and 184 (75.7%) received at least four courses of chemotherapy (Table 4).

Update

Compliance was reported as high in both fully published trials (1u,2u) and not well-documented in the trial reported by Petrioli et al (3u). Brodowicz et al (1u) noted that chemotherapy was discontinued in two of 31 (6%) patients due to impaired healing but that

the remainder of patients received all planned chemotherapy with delays of <2 weeks in 12%. Frustaci et al (2u) reported that seven patients did not receive the prescribed chemotherapy and four patients did not complete treatment due to toxicity after two, three, four and five courses of treatment. The level of compliance in these two trials (1u,2u) is similar to that found in the trials reviewed previously. Petrioli et al (3u) reported that two patients in the adjuvant therapy arm did not begin chemotherapy and that a further two patients (one each in the control and adjuvant therapy arms) were lost to follow-up immediately after surgery.

Table 4. Compliance with adjuvant chemotherapy (data from published papers).

Trial (Ref.)	Chemotherapy*	Total # Pts	# No Treatment (%)	# Major Treatment Reduction (%)	# Minor Treatment Reduction (%)	# Full Treatment (%)
GOG (11)	Dox	83	8 (9.6%)	6 (7.2%)	14 (16.9%)	55 (66.3%)
DFCI (12)	Dox	20	NA	NA	NA	NA
ECOG (13)	Dox	17	NA	NA	NA	NA
SSG (14)	Dox	93	NA	10 (10.8%)	54 (58.1%)	29 (31.2%)
Rizzoli (15,16)	Dox	24	0	0	2 (8.3%)	23 (95.8%)
ISG (18,19)	Dox	39	NA	NA	NA	NA
All Dox-alone	Dox	276	8/107 (7.5%)	16/200 (8.0%)	70/200 (35.0%)	107/200 (53.5%)
MDAH (20)	VACAR	20	NA	NA	NA	NA
Mayo (21,22)	VAC/VAD	30	0	5 (16.7%)	2 (6.7%)	23 (76.7%)
NCI (23,24)	AC/MTX	37	0	0	3 (8.1%)	34 (91.9%)
NCI (25,26)	AC/MTX	30†	NA	NA	NA	NA
NCI (25,26)	AC/MTX	21‡	NA	NA	NA	NA
EORTC (27)	CYVADIC	145	19 (13.1%)	34 (23.5%)	16 (11.0%)	76 (52.4%)
Bergonié (28)	CYVADIC	31	0	1 (3.2%)	20 (64.5%)	10 (32.3%)
All Dox + other	Dox +other	314	19/243 (7.8%)	40/243 (16.5%)	41/243 (16.9%)	143/243 (58.8%)

Note: # = number; NA = Data not available; pts = patients.
* Chemotherapy: please see footnote in Table 1.
† Includes 13 patients treated outside the randomized trial.
‡ Includes 13 patients treated outside the randomized trial.

V. INTERPRETIVE SUMMARY

Despite some variation in the results of individual trials, all meta-analyses have shown that in patients with resected STS of any type, doxorubicin-based adjuvant chemotherapy significantly prolongs disease-free survival. The 10% absolute increase in disease-free survival at 10 years shown in the SMAC individual patient data overview is due both to reduced distant metastases and local recurrences. In spite of this reduction of relapses, there is only a trend for increased survival for the entire group of sarcoma patients (Table 2).

Although the data are consistent with modest survival benefits across all sarcomas examined, there are clues as to potential patient subgroups which are more likely to benefit. In the SMAC meta-analysis, a statistically significant survival benefit associated with doxorubicin-based chemotherapy (7% absolute increase in survival at 10 years) was found in 886 patients with extremity sarcomas. The next two largest groups are those of uterine and trunk sarcomas with 263 and 182 patients respectively. Few retroperitoneal sarcomas are included, and the main contributing study (26) was terminated early because of an adverse effect of chemotherapy and substantial toxicity. Only 30 patients in the SMAC meta-analysis

had abdominal sarcomas (14). Furthermore, only 24% of patients in the database were above age 60. Many of the trials excluded patients above age 65, or in some cases 70. Thus, it is difficult to generalize the beneficial results detected in the SMAC overview to patients with retroperitoneal tumours, or those above age of 70 years. Finally, there was no difference in the reduction of mortality or disease recurrence between single-agent or combination adjuvant therapy with doxorubicin.

Benefits in preventing disease relapse and improving survival are achieved at the cost of a significant degree of toxicity, including a 5% rate of life-threatening drug-induced events and a 2% toxic fatality rate. Although most toxicity is acute (nausea and vomiting, infections, cardiac arrhythmias, etc.), other events, such as cardiomyopathy, have long-term consequences. All these untoward effects have a major impact on treatment compliance (Table 4) and will affect patient's quality of life, which unfortunately has not been specifically measured.

Update

The three new trials (1u-3u) confirm the observations seen in the previous trials of adjuvant chemotherapy an advantage in terms of time-to-progression for the high dose combined chemotherapy regimen used in the Frustaci et al trial (2u). As median survival for the treatment group has not been reached further follow-up is required to discern whether there is a survival advantage.

VI. ONGOING TRIALS

The National Cancer Institute's clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) was searched for reports of new or ongoing trials.

Protocol ID	Title and details of trial
EORTC-62931, CAN-NCIC-SR3	Phase III randomized study of adjuvant high-dose doxorubicin and ifosfamide plus filgrastim (G-CSF) versus no adjuvant chemotherapy and G-CSF after definitive surgery in patients with high-grade soft tissue sarcoma. Outcomes: local disease control, overall survival, relapse-free survival, toxicity. Projected accrual: 340 evaluable patients within 3.5 years. Status: closed. Summary last modified: December 22, 2003. Accessed: August 17, 2004. Available at: http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=64132&version=HealthProfessional&protocolsearchid=1093567.

VII. DISEASE SITE GROUP CONSENSUS

The benefits in preventing disease relapse and improving patient survival, especially in patients with resected STS of the extremities, although modest, compare favourably with results for adjuvant chemotherapy in early breast cancer (31,32) and stage III colon cancer (33), where adjuvant therapy is considered standard care. The SMAC database used to draw these conclusions is, however, much smaller than similar databases for the other common tumours. With this limitation, doxorubicin-based adjuvant chemotherapy can be reasonably considered for adult patients with resected STS of the extremities at high risk of recurrence (deep high grade tumours >5 cm in size) and at low risk of adverse effects (no underlying diseases, particularly cardiovascular).

The information related to the effect of chemotherapy on local control should be interpreted with some caution. In the SMAC meta-analysis, 15% of patients treated with chemotherapy experienced local recurrence (101 of 659 cases), compared with 19% (126 of

656 cases) in the control group. These relatively high rates of local recurrence are of concern. Local treatment is most important in the initial management of sarcomas. In extremity sarcomas, wide surgical excision, supplemented by radiation in cases where tumour size or location limits the procedure, can achieve local control in over 90% of cases (34-37). However, the meta-analysis did not separately assess the local recurrence rate for extremity sarcomas. The higher rate of local recurrence reported may be explained by the inclusion of non-extremity sarcomas, which are known to have a higher rate of local failure (34).

The consideration of doxorubicin-based adjuvant chemotherapy for patients with STS at non-extremity locations is more problematic. There are limited data about these tumours, and the available trials are inconclusive as to benefits with respect to disease relapse or survival. Due to the fact that there are few trials investigating patients with retroperitoneal sarcomas, and the observed adverse effect of chemotherapy on survival (when combined with RT), doxorubicin-based adjuvant chemotherapy cannot be recommended for retroperitoneal sarcomas. The data on uterine sarcomas are based mostly in a single trial with negative results; therefore, no specific recommendation can be made about these tumours. Gastrointestinal stromal tumours (GIST) should now be considered separately from other STS; most GIST constitutively express a cKIT receptor and are responsive to imatinib mesylate (38). The role of this drug as adjuvant therapy is currently being evaluated in clinical trials. The Sarcoma DSG is in the process of developing an evidence summary on the use of imatinib mesylate as palliative treatment for patients with unresectable or metastatic GIST expressing cKIT.

The search should continue for more effective adjuvant therapies (39). It was not possible to demonstrate a larger benefit for doxorubicin-based combination chemotherapy compared with single-agent doxorubicin. This may be due to the fact that some of the combination regimens in the SMAC database are not considered useful today. On the other hand, combination chemotherapy with ifosfamide (the second most active drug in advanced STS) is only represented by a small study with 31 patients (9). The significant results of the second Rizzoli trial (30) using intensive epirubicin and ifosfamide supported by G-CSF should be pursued in future clinical trials. Strategies for reducing anthracycline-induced cardiotoxicity should be investigated. This approach may have limitations, as the use of doxorubicin by infusion compared with the drug given by bolus reduced not only cardiotoxicity but also disease-free and overall survival (40). Because of problems with toxicity and drug compliance, patient quality of life should be investigated and reported. As the meta-analyses have shown, a large number of patients will be required to demonstrate significant differences in outcomes, and these trials will require international cooperation.

VIII. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

This section describes the external review activities undertaken for the original guideline report. For a description of external review activities of the new information presented in the updated sections of this report, please refer to Update below.

Draft Recommendations

Based on the evidence described in the original report above, the Sarcoma DSG drafted the following recommendations:

Target Population

These recommendations apply to adult patients with resected soft tissue sarcoma.

Draft Recommendations

- Overall, doxorubicin-based adjuvant chemotherapy after resection of STS in adults

significantly improves disease-free survival. There is only a non-significant trend for increased overall survival with doxorubicin-based adjuvant chemotherapy, with an absolute benefit of 4% at 10 years. Most regimens of chemotherapy produce significant toxicity. Thus, it is reasonable to consider such therapy only in patients who have removal of a sarcoma with features predicting a high likelihood of relapse (deep location, size >5 cm, high histological grade). These features correspond to International Union Against Cancer (UICC) stage III.

- Although the benefits of adjuvant chemotherapy are most apparent (7% risk difference [RD] for overall survival at 10 years) in patients with extremity sarcomas, patients with high-risk tumours at other sites should also be considered for such therapy. There is not sufficient evidence available on patients with retroperitoneal sarcomas and stromal tumours of the bowel to make recommendations for adjuvant chemotherapy. The risk of serious toxicity in retroperitoneal sarcomas when chemotherapy is combined with radiation therapy is of major concern.
- Risks of severe persistent adverse effects, such as cardiomyopathy, should be carefully evaluated and balanced against the expected benefit, particularly in patients aged 70 years or more and those with significant co-morbidity.
- There are insufficient data to determine whether single-agent doxorubicin or combination chemotherapy should be preferred. This decision should take into account issues such as patient preference/convenience, likely adverse effects, costs and available resources.
- Patients should be encouraged to participate in clinical trials comparing adjuvant chemotherapy versus observation to further characterize benefits.

Practitioner Feedback

Based on the evidence contained in the original report and the draft recommendations presented above, feedback was sought from Ontario clinicians.

Methods

Practitioner feedback was obtained through a mailed survey of 78 practitioners in Ontario (26 medical oncologists, 14 radiation oncologists, 32 surgeons, two pathologists and four gynecologists). The survey consisted of 21 items evaluating the methods, results and interpretive summary used to inform the draft recommendations outlined and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The results of the survey have been reviewed by the Sarcoma DSG.

Results

Key results of the practitioner feedback survey are summarized in Table 5. Forty-six (61%) surveys were returned. Thirty-two respondents (70%) indicated that the report was relevant to their clinical practice and they completed the survey. In addition, one respondent indicated that the report was not relevant to his/her practice, but went on to answer the other questions in the questionnaire. This practitioner has been included in the analysis below, for a total of 33.

Table 5. Practitioner responses to eight items on the practitioner feedback survey.

Item	Number (%)		
	Strongly agree or agree	**Neither agree nor disagree**	**Strongly disagree or disagree**
The rationale for developing a clinical practice guideline, as stated in the "*Choice of Topic*" section of the report, is clear.	31 (94)	1 (3)	1 (3)
There is a need for a clinical practice guideline on this topic.	25 (76)	6 (18)	2 (6)
The literature search is relevant and complete.	29 (88)	4 (12)	0 (0)
The results of the trials described in the report are interpreted according to my understanding of the data.*	30 (91)	1 (3)	1 (3)
The draft recommendations in this report are clear.*	30 (91)	1 (3)	1 (3)
I agree with the draft recommendations as stated.*	29 (88)	1 (3)	2 (6)
This report should be approved as a practice guideline.	23 (70)	6 (18)	4 (12)
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?*	**Very likely or likely**	**Unsure**	**Not at all likely or unlikely**
	24 (73)	4 (12)	4 (12)

* Percentages do not add up to 100 because data from one practitioner was missing.

Summary of Written Comments

Six (18%) respondents provided written comments. The main points are summarized below.

1. One practitioner commented that uterine sarcomas have traditionally been treated somewhat differently than other STS, rightly or wrongly. It was the opinion of this practitioner that the effectiveness of the guideline could be improved by addressing this distinction and adopting one of the following strategies: 1. providing a rationale for including uterine STS in the current analysis and draft recommendations, 2. excluding uterine sarcomas from the analysis, or 3. making specific comments in the document about these tumours.
2. Another practitioner commented that assessing tumour grade and its role in tumour responsiveness should be considered.

Modifications/Actions

1. As a result of this comment, a statement regarding uterine sarcomas was added to the Interpretive Summary, the Disease Site Group Consensus Process and one of the Qualifying Statements of the Practice Guideline.
2. No changes were made to the guideline document to address this comment.

Approved Practice Guideline Recommendations

These practice guideline recommendations reflect the integration of the draft recommendations with feedback obtained from the external review process. They have been approved by the Sarcoma DSG and the Practice Guidelines Coordinating Committee.

Recommendations

- It is reasonable to consider doxorubicin-based adjuvant chemotherapy in patients who have had removal of a sarcoma with features predicting a high likelihood of relapse (deep location, size >5 cm, high histological grade). These features correspond to International

Union Against Cancer (UICC) stage III.[*]
- Although the benefits of adjuvant chemotherapy are most apparent in patients with extremity sarcomas (7% risk difference [RD] for overall survival at 10 years), patients with high-risk tumours at other sites should also be considered for such therapy.

Qualifying Statements
- There is insufficient evidence on patients with retroperitoneal sarcomas or stromal tumours of the bowel to make recommendations for adjuvant chemotherapy. The risk of serious toxicity in retroperitoneal sarcomas when chemotherapy is combined with radiation therapy is of major concern. Similarly, the data on uterine sarcomas come from a single trial with negative results; therefore, no specific recommendations can be made about these tumours.
- Risks of severe persistent adverse effects of adjuvant chemotherapy, such as cardiomyopathy, should be carefully evaluated and balanced against the expected benefit, particularly in patients aged 70 years or older and those with significant co-morbidity.
- There are insufficient data to determine whether single-agent doxorubicin or combination chemotherapy with doxorubicin should be recommended. This decision should take into account issues such as patient preference/convenience, likely adverse effects, costs and available resources. Meta-analyses of trials evaluating adjuvant chemotherapy with single-agent doxorubicin and doxorubicin-based combination regimens, both compared with observation, showed similar results for mortality and recurrence. Many of the doxorubicin-based combination chemotherapy regimens examined in the trials are not considered very effective today. New regimens using high-dose ifosfamide and epirubicin have reported significant advantages in preliminary trials. These results will require confirmation in larger trials.

IX. PRACTICE GUIDELINE

This practice guideline reflects the most current information reviewed by the Sarcoma DSG.

Target Population

The recommendations apply to adult patients with resected soft tissue sarcoma (STS).

Recommendations

- It is reasonable to consider anthracyline-based adjuvant chemotherapy in patients who have had removal of a sarcoma with features predicting a high likelihood of relapse (deep location, size >5 cm, high histological grade). These features correspond to International Union Against Cancer (UICC) stage III.[*]
- Although the benefits of adjuvant chemotherapy are most apparent in patients with extremity sarcomas (7% risk difference [RD] for overall survival at 10 years), patients with high-risk tumours at other sites should also be considered for such therapy.

Qualifying Statements

- There is insufficient evidence on patients with retroperitoneal sarcomas or stromal tumours of the bowel to make recommendations for adjuvant chemotherapy. The risk of serious toxicity in retroperitoneal sarcomas when chemotherapy is combined with radiation therapy is of major concern. Similarly, the data on uterine sarcomas come from

[*] Sobin LH, Wittekind Ch, eds. *International Union Against Cancer. TNM Classification of Malignant Tumours.* 5th ed. New York: Wiley-Liss; 1997.

a single trial with negative results; therefore, no specific recommendations can be made about these tumours.

- Risks of severe persistent adverse effects of adjuvant chemotherapy, such as cardiomyopathy, should be carefully evaluated and balanced against the expected benefit, particularly in patients aged 70 years or older and those with significant co-morbidity.
- There are insufficient data to determine whether single-agent doxorubicin or combination chemotherapy with doxorubicin should be recommended. This decision should take into account issues such as patient preference/convenience, likely adverse effects, costs and available resources. Meta-analyses of trials evaluating adjuvant chemotherapy with single-agent doxorubicin and doxorubicin-based combination regimens, both compared with observation, showed similar results for mortality and recurrence. Many of the doxorubicin-based combination chemotherapy regimens examined in the trials are not considered very effective today. New regimens using high-dose ifosfamide and epirubicin have reported significant advantages in small trials. These results will require confirmation in larger trials.

Future Research

Patients should be encouraged to participate in clinical trials comparing adjuvant chemotherapy versus observation to further characterize benefits.

X. JOURNAL REFERENCE

Figueredo A, Bramwell VHC, Bell R, Davis AM, Charette ML and Members of the Cancer Care Ontario Practice Guidelines Initiative Sarcoma Disease Site Group. Adjuvant chemotherapy following complete resection of soft tissue sarcoma in adults: a clinical practice guideline. *Sarcoma* 2002;6:5-18.

XI. ACKNOWLEDGEMENTS

The Sarcoma DSG would like to thank Dr. Alvaro Figueredo, Dr. Vivien Bramwell, and Ms. Julie Makarski for taking the lead in drafting and revising this practice guideline report.

REFERENCES

1. Brennan ME, Casper ES, Harrison LB. Soft tissue sarcoma. In: DeVita VT, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology*. Philadelphia-New York: JB Lippincott; 1997:1738-88.
2. National Cancer Institute of Canada. *Canadian Cancer Statistics 1994*. Toronto, Canada; 1994:35.
3. Lewis JJ, Benedetti F. Adjuvant therapy for soft tissue sarcoma. *Surg Oncol Clin North Am* 1997;6:847-62.
4. Mertens WC, Bramwell VHC. Adjuvant chemotherapy for soft tissue sarcomas. *Hematol Oncol Clin North Am* 1995;9:801-15.
5. Sobin LH, Wittekind Ch, eds. *International Union Against Cancer. TNM Classification of Malignant Tumours*. 5th ed. New York: Wiley-Liss; 1997:106-9.
6. Jones GW, Chouinard E, Patel M. Adjuvant adriamycin (doxorubicin) in adult patients with soft-tissue sarcomas: a systematic overview and quantitative meta-analysis [Abstract]. *Clin Invest Med* 1991;14:A772.
7. Zalupski MM, Ryan JR, Hussein ME, et al. Defining the role of adjuvant chemotherapy for patients with soft tissue sarcoma of the extremities. In: Salmon SE, ed. *Adjuvant Therapy of Cancer VII*. Philadelphia: JB Lippincott; 1993:385-92.
8. Tierney JF, Mosseri V, Stewart LA, Souhami RL, Parmar MKB. Adjuvant chemotherapy for soft-tissue sarcoma: review and meta-analysis of the published results of randomized clinical trials. *Brit J Cancer* 1995;72:469-75.
9. Sarcoma Meta-analysis Collaboration. Adjuvant chemotherapy for localized resectable soft-tissue sarcoma of adults: meta-analysis of individual data. *Lancet* 1997;350:1647-54.
10. Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: A conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13:502-12.
11. Omura GA, Blessing JA, Major F, Lifshitz S, Ehrlich CL, Mangan C, et al. A randomized trial of adjuvant adriamycin in uterine sarcomas: a Gynecologic Oncology Group study. *J Clin Oncol* 1985;3:1240-5.
12. Antman K, Suit H, Amato D, Corson J, Wood W, Proppe K, et al. Preliminary results of a randomized trial of adjuvant doxorubicin for sarcomas: lack of apparent difference between treatment groups. *J Clin Oncol* 1984;2:601-8.
13. Lerner HJ, Amato DA, Savlov E, DeWys WD, Mittelman A, Urtasun RC, et al. Eastern Cooperative Oncology Group: a comparison of adjuvant doxorubicin and observation for patients with localized soft tissue sarcoma. *J Clin Oncol* 1987;5:613-7.
14. Alvegard TA, Sigurdsson H, Mouridsen H, Solheim Ø, Unsgaard B, Ringborg U, et al. Adjuvant chemotherapy with doxorubicin in high grade soft tissue sarcoma: a randomized trial of the Scandinavian Sarcoma Group. *J Clin Oncol* 1989;7:1504-13.
15. Gherlinzoni F, Bacci G, Picci P, Capanna R, Calderoni P, Lorenzi EG, et al. A randomized trial for treatment of high grade soft tissue sarcoma of the extremities: preliminary results. *J Clin Oncol* 1986;4:552-8.
16. Picci P, Bacci G, Gherlinzoni F, Capanna R, Mercuri M, Rugieri P, et al. Results of a randomized trial for the treatment of localized soft tissue sarcoma (STS) of the extremities in adult patients. In: Ryan JR, Baker LH, eds. *Recent concepts in sarcoma treatment*. Dodrecht: Kluwer Academic Publishers; 1988:144-8.
17. Antman K, Amato D, Pilepich M, Lerner H, Balcezak S, Borden E, et al. A preliminary analysis of a randomized Intergroup (SWOG, ECOG, CALGB, NCOG) trial of adjuvant doxorubicin for soft tissue sarcomas. In: Salmon SE, ed. *Adjuvant Therapy of Cancer*. Philadelphia: JB Lippincott; 1990:725-34.

18. Baker LH. Adjuvant therapy for soft tissue sarcomas. In: Ryan JR, Baker LH, eds. *Recent concepts in sarcoma treatment*. Dodrecht: Kluwer Academic Press; 1988:130-5.
19. Antman K, Ryan L, Borden E, et al. Pooled results from three randomized adjuvant studies of doxorubicin versus observation in soft tissue sarcoma: 10-year results and review of the literature. In: Salmon SE, ed. *Adjuvant Therapy of Cancer VI*. Philadelphia: JB Lippincott; 1990:529-43.
20. Benjamin RS, Terjanian TO, Fenoglio CJ, Barkley HT, Evans HL, Murphy WK, et al. The importance of combination chemotherapy for adjuvant treatment of high-risk patients with soft tissue sarcomas of the extremities. In: Salmon SE, ed. *Adjuvant Therapy of Cancer V*. Orlando: Grune and Stratton; 1987:735-44.
21. Edmonson JH, Fleming TR, Ivins JC, Burgert O, Soule EH, O'Connell MJ, et al. Randomized study of systemic chemotherapy following complete excision of nonosseous sarcomas. *J Clin Oncol* 1984;2:1390-6.
22. Edmonson JH. Systemic chemotherapy following complete excision of nonosseous sarcomas: Mayo Clinic experience. *Cancer Treat Symp* 1985;3:89-97.
23. Rosenberg SA, Tepper J, Glatstein E, Costa J, Young R, Baker A, et al. Prospective randomized evaluation of adjuvant chemotherapy in adults with soft tissue sarcoma of the extremities. *Cancer* 1983;52:424-34.
24. Chang AE, Kinsella T, Glatstein E, Baker AR, Sindelar WF, Lotze MT, et al. Adjuvant chemotherapy for patients with high-grade soft tissue sarcomas of the extremities. *J Clin Oncol* 1988;6:1491-500.
25. Glenn J, Kinsella T, Glatstein E, Tepper J, Baker A, Sugarbaker P, et al. A randomized, prospective trial of adjuvant chemotherapy in adults with soft tissue sarcomas of the head and neck, breast and trunk. *Cancer* 1985;55:1206-14.
26. Glenn J, Sindelar W, Kinsella T, Glatstein E, Tepper J, Costa J, et al. Results of multimodality therapy of resectable soft tissue sarcomas of the retroperitoneum. *Surgery* 1985;97:316-25.
27. Bramwell V, Rouesse J, Steward W, Santoro A, Schraffordt-Koops H, Buesa J, et al. Adjuvant CYVADIC chemotherapy for adult soft tissue sarcoma -reduced local recurrence but no improvement in survival: a study of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. *J Clin Oncol* 1994;12:1137-49.
28. Ravaud A, Bui NB, Coindre JM, Kantor G, Stöckle E, Lagarde P, et al. Adjuvant chemotherapy with CYVADIC in high risk soft tissue sarcoma: a randomized prospective trial. In: Salmon SE, ed. *Adjuvant Therapy of Cancer VI*. Philadelphia: JB Lippincott; 1990: 556-66.
29. Brodowicz T, Schwameis E, Widder J, Wiltschke C, Amann G, Dominkus M, et al. Significant improvement of relapse free survival as well as time to distant failure for adult grade 3 soft tissue sarcoma after adjuvant augmented chemotherapy plus adjuvant hyperfractionated accelerated radiotherapy: A prospective randomized trial of the Austrian cooperative soft tissue sarcoma study group [Abstract]. *Eur J Cancer* 1999;35 (Suppl4):S269-70. Abstract 1075.
30. Frustaci S, Gherlinzoni F, De Paoli A, Buonadonna A, Zmerly H, Fissi S, et al. Maintenance of efficacy of adjuvant chemotherapy (CT) in soft tissue sarcoma (STS) of the extremities up-date of a randomized trial [Abstract]. *Proc Am Soc Clin Oncol* 1999;18:546a. Abstract 2108.
31. Anonymous. Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. A Canadian consensus document. *Can Med Assoc J* 1998;158(Suppl 3):S43-63.
32. Early Breast Cancer Trialists' Collaborative Group. Systematic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy: 133 randomized trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. *Lancet* 1992;339:1-15,71-85.

33. Figueredo A, Fine S, Maroun J, Walker-Dilks C, Wong S, and the Provincial Gastrointestinal Disease Site Group. Adjuvant therapy for stage III colon cancer after complete resection. *Cancer Prev Control* 1997;1:304-19.
34. LeVay J, O'Sullivan B, Catton CN, Bell RS, Fornasier VL, Cummings B, et al. Outcome and prognostic factors in soft tissue sarcoma in the adult. *Int J Radiat Oncol Biol Phys* 1993;27:1091-99.
35. Wilson AN, Davis A, Bell RS, O'Sullivan B, Catton C, Madadi F, et al. Local control of soft tissue sarcoma of the extremity: The experience of a multidisciplinary sarcoma group with definitive surgery and radiotherapy. *Eur J Cancer* 1994;30A:746-51.
36. Noria S, Davis AM, Kandel RA, Levesque J, O'Sullivan B, Catton CN, et al. Residual disease following unplanned excision of a soft tissue sarcoma of an extremity. *J Bone Joint Surg Am* 1996;78A:650-5.
37. Davis AM, Kandel RA, Wunder JS, Unger R, Meer J, O'Sullivan B, et al. Unplanned excision as a predictor of local relapse in soft tissue sarcoma of the extremity. *J Surg Oncol* 1997;66:81-7.
38. Heinrich MC, Blanke CD, Druker, BJ, Corless, CL. Inhibition of KIT tyrosine kinase activity: a novel molecular approach to the treatment of KIT-positive malignancies. *J Clin Oncol* 2002; 20: 1692-1703.
39. Allen A. The cardiotoxicity of chemotherapeutic drugs. *Sem Oncol* 1992;19:529-42.
40. Casper ES, Gaynor JJ, Hajdu SI, Magill GB, Tan C, Friedrich C, et al. A prospective randomized trial of adjuvant chemotherapy with bolus versus continuous infusion of doxorubicin in patients with high-grade extremity soft tissue sarcoma and an analysis of prognostic factors. *Cancer* 1991;68:1221-9.

Update

This section includes all references obtained from review and updating activities.

1u. Brodowicz T, Schwameis E, Widder J, Amann G, Wiltschke C, Dominkus M, et al. for the Austrian Cooperative Soft Tissue Sarcoma Study Group. Intensified adjuvant IFADIC chemotherapy for adult soft tissue sarcoma: a prospective randomized feasibility trial. *Sarcoma* 2000;4:151-60.
2u. Frustaci S, De Paoli A, Bidoli E, La Mura N, Berretta M, Buonadonna A, et al. Ifosfamide in the adjuvant therapy of soft tissue sarcomas. *Oncology* 2003;65(Suppl 2):80-4.
3u. Petrioli R, Coratti A, Correale P, D'Aniello C, Grimaldi L, Tanzini G, et al. Adjuvant epirubicin with or without ifosfamide for adult soft-tissue sarcoma. *Am J Clin Oncol* 2002;25(5):468-73.

Appendix I. Staging system for soft tissue sarcoma.

STAGE GROUPING

Stage IA	G1,2	T1a	N0	M0
	G1,2	T1b	N0	M0
Stage IB	G1,2	T2a	N0	M0
Stage IIA	G1,2	T2b	N0	M0
Stage IIB	G3,4	T1a	N0	M0
	G3,4	T1b	N0	M0
Stage IIC	G3,4	T2a	N0	M0
Stage III	G3,4	T2b	N0	M0
Stage IV	Any G	Any T	N1	M0
	Any G	Any T	Any N	M1

TNM CLINICAL CALSSIFICATION

T-Primary Tumour

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Tumour 5 cm or less in greatest dimension
T1a	Superficial tumour*
T1b	Deep tumour*
T2	Tumour more than 5 cm in greatest dimension
T2a	Superficial tumour*
T2b	Deep tumour*

Note: *Superficial tumour is located exclusively above the superficial fascia without invasion of the fascia; deep tumour is located either exclusively beneath the superficial fascia or superficial to the fascia with invasion of or through the fascia. Retroperitoneal, mediastinal, and pelvic sarcomas are classified as deep tumours.

N-Regional Lymph Nodes

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

M-Distant Metastasis

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

G Histopathological Grading

GX	Grade of differentiation cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

Source: International Union Against Cancer. TNM Classification of Malignant Tumours, fifth edition. New York: Wiley-Liss; 1997.

Appendix II. Trial names and chemotherapy regimens used in published studies included in the SMAC overview.

GOG (11) = Gynecological Oncology Group
Regimen: doxorubicin 60 mg/m^2 IV every 3 weeks for 8 doses.
No concurrent RT.

DFCI (12) = Dana Farber Cancer Institute
Regimen: doxorubicin 90 mg/m^2 IV every 3 weeks for 5 doses.
Concurrent RT 62.5-67.5 Gy over 6.5 to 7.0 weeks, with reduced volumes after 45 GY.

ECOG (13) = Eastern Cooperative Oncology Group
Regimen: doxorubicin 70 mg/m^2 IV every 3 weeks for 7 doses.
No concurrent RT.

SSG (14) = Scandinavian Sarcoma Group
Regimen: doxorubicin 60 mg/m^2 IV every 4 weeks for 9 cycles.
Concurrent RT in patients with marginal resection, 51 Gy in 17 fractions over 24 days; for retroperitoneal tumours only 42 Gy.

Rizzoli (15,16) = Instituto Ortopedico Rizzoli
Regimen: doxorubicin 25-30 mg/m^2 IV days 1, 2 and 3, every 3 weeks for 6 cycles (or a total dose 450 mg/m^2).
Concurrent RT in patients with marginal resection, 45 Gy over 3 weeks.

Intergroup (18,19) = Intergroup Sarcoma Study Group
Regimen: doxorubicin 35 mg/m^2 (escalated to 45 mg/m^2) on days 1 and 2, every 3 weeks up to a total doxorubicin dose of 450 mg/m^2.
Concurrent RT (dose not given) for patients with "conservative resection".

MDAH (20) = M. D. Anderson Hospital
Regimen VACAR: Vincristine 2 mg every week for 9 weeks, then every 3 weeks on day 1; doxorubicin 60 mg/m^2 on day 2 (up to a total dose 420 mg/m^2, and cyclophosphamide 200 mg/m^2 orally days 3 to 5; actinomycin D 0.3 mg/m^2 iv days 1 through 5 (maximal single dose 0. mg) after doxorubicin total dose achieved. Cycles every 4 weeks while on doxorubicin, then every 8 weeks; total duration of chemotherapy 2 years.
Concurrent RT 55 Gy over 6.5 weeks plus 10 Gy to scar.

Mayo (21,22) = Mayo Clinic
Regimen VAC/VAD: 1) VAC: Vincristine 1.2 mg/m^2 days 1 and 5, cyclophosphamide 250 mg/m^2 on days 1, 3 and 5, and actinomycin D 0.325 mg/m^2 days 1 through 5; and 2) VAD: Vincristine 1.2 mg/m^2 days 22 and 26, doxorubicin 50 mg/m^2 on day 24, and DTIC 250 mg/m^2 on days 22 through 26.
All drugs given IV, in 6 week cycles, repeated 6 times.
No concurrent RT.
In addition 7 patients received MER-BCG on day 1 of each cycle of chemotherapy; then discontinued because chronic painful ulcers.

NCI (23-26) = National Cancer Institute, Bethesda, USA
Regimen AC/MTX: 1) AC: doxorubicin 50 mg/m^2 (escalated up to 70 mg/m^2) and cyclophosphamide 500 mg/m^2 Both IV day 1; cycles every 28 days until reaching a total doxorubicin dose of 550 mg/m^2.
2) MTX: Afterwards, methotrexate 50 mg/m^2 (escalated up to 250 mg/m^2) IV infusion over 6 hours on day 1, followed within 2 hours by leucovorin 15 mg IV every 6 hours for 8 doses, or more if methotrexate blood level >4 x 10^{-7}; cycles every 4 weeks up to a total methotrexate dose of 1000 mg/K.
Concurrent RT 60 Gy in 30 to 35 fractions; field size reduced after 45 Gy.
Six patients also received immunotherapy with Corynebacterium Parvum.

EORTC (27) = European Organization for Research and Treatment of Cancer
Regimen CYVADIC: Cyclophosphamide 500 mg/m^2, vincristine 1.5 mg/m^2 (maximum dose 2 mg) and doxorubicin 50 mg/m^2 on day 1, and DTIC 400 mg/m^2 on days 1through 3. All drugs given IV every 4 weeks, 8 times.
Concurrent RT in some patients, 40 Gy in 4 weeks for pelvic tumours, and 50 Gy for tumours outside the pelvis.

Bergonié (28) = Fondation Bergonié
Regimen CYVADIC: Drug doses as in EORTC regimen but cycles every 3 weeks, initially planned for 11 cycles, reduced to 9 cycles after 4 patients had major toxicity.

Concurrent RT 50 Gy in 5 weeks plus 10-15 Gy boost to tumour bed. For retroperitoneal and deep abdominal tumours RT dose decreased to 40 Gy over 5 weeks and 10 Gy boost. doxorubicin deleted during RT.

EBS 11-2 Document Assessment and Review Tool.

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

DOCUMENT ASSESSMENT AND REVIEW TOOL

Number and title of document under review	11-2: Adjuvant Chemotherapy Following Complete Resection of Soft Tissue Sarcoma in Adults
Date of current version	Feb 2005
Clinical reviewer	Michelle Ghert
Research coordinator	Chika Agbassi
Date initiated	Feb 11, 2011
Date and final results / outcomes	**May 31, 2011- ENDORSED**
Instructions. Beginning at question 1, below, answer the questions in sequential order, following the instructions in the black boxes as you go.	
1. Is there still a need for a guideline covering one or more of the topics in this document **as is**? Answer Yes or No, and explain if necessary:	1. Yes If No, then the document should be **ARCHIVED**[1] with no further action; **go to 11**. If Yes, then **go to 2**.
2. Are all the current recommendations based on the current questions **definitive**[*] or **sufficient**[§], and have less than **5 years elapsed** since the latest search? Answer Yes or No, and explain if necessary:	2. Definitive –no? Sufficient –no? Over 4 years elapsed If Yes, the document can be **ENDORSED**[2] with no further action; **go to 11**. If No, **go to 3**.
3. Is there expected or known evidence that contradicts the current recommendations, such that they may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, providing references of known evidence:	3. No If Yes, the document should be taken off the website as soon as possible. A **WARNING**[¶] should be put in its place informing a user that the document is only available by email, with a brief explanation of the reasons. If No, g**o to 4**.
4. Do current resources allow for an updated literature search to be conducted at this time? Answer Yes or No, and explain as necessary. Provide an expected date of completion of the updated search, if applicable:	4. YES • there is a designated research co-ordinator at the PEBC to carry out the literature search If No, a **DEFERRAL**[3] should be placed on the document indicating it cannot be updated at this time, but will be reviewed again on a yearly basis. If Yes, go **to 5**.
5a. **Guideline Research Questions.** Please review the original guideline research questions below and if applicable, list any MINOR changes to the questions that now must be considered. If a question is no longer relevant, it can be deleted. The Document Assessment & Review process evaluates the guideline **as is** and CANNOT accommodate significant changes to the questions or the addition of new questions introducing new patient populations or new agents/interventions because if this what is required in order to make this guideline relevant, then a brand new document should be produced and this guideline as is should be ARCHIVED (i.e., go back to Q1 of this form and answer NO).	

Original Question(s):

1. What are the benefits of anthracycline-based adjuvant chemotherapy in adult patients with completely resected soft tissue sarcomas, in terms of local disease control, systemic recurrence, and overall survival?
2. When these benefits are assessed in the context of expected toxicities, in what circumstances should adjuvant chemotherapy be recommended?
3. Are there any advantages in using combination versus single-agent anthracycline-based chemotherapy in adjuvant setting?

Target Population:
The recommendations apply to adult patients with resected soft tissue sarcoma.

5b. **Inclusion and Exclusion criteria.** List below any changes to the selection criteria in the original version made necessary by new questions, changes to existing questions, or changes in available evidence (e.g., limit a search to randomized trials that originally included non-randomized evidence).

Inclusion criteria:
Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

1. Randomised controlled trial (RCTs) comparing anthracyline-based adjuvant chemotherapy to observation in patients with completely resected STS.
2. Patients were at least 15 years of age.
3. Data provided on outcome of overall and disease-free survival.
4. Abstracts of trials were considered.
5. **Meta-analyses will also be considered**

Exclusion criteria:

1. Phase I and II studies should not be considered.
2. Letters and editorials were not considered
3. Papers published in a language other than English were not considered.

5c. Conduct an updated literature search based on that done for the current version and modified by 5a and 5b above. Report the results below.

Full Selection Criteria, including types of evidence (e.g., randomized, non-randomized, etc.):
Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

1. Randomised controlled trial (RCTs) comparing anthracyline-based adjuvant chemotherapy to observation in patients with completely resected STS.
2. Patients were at least 15 years of age.
3. Data provided on outcome of overall and disease-free survival.
4. Abstracts of trials were considered.
5. Meta-analyses will also be considered

Exclusion criteria:

1. Phase I and II studies should not be considered.
2. Letters and editorials were not considered
3. Papers published in a language other than English were not considered

Search Period:

- Feb 2005 to March 2011 (Medline March Week 3 + Embase Week 11)
- 2005 to 2010 (ASCO Annual Meeting)

Brief Summary/Discussion of New Evidence:
Of 137 total hits from Medline + Embase and 12 total hits from ASCO conference abstract searches, 3 references (one full text publication and two abstracts) representing three meta analysis were found.

Interventions	Name of RCT	Included RCTs	Population	Outcomes	Brief results	References
	Meta-analysis	18	(n=2145)	OS,DFS, LR,MFS,	Anthracycline-based chemotherapy was associated with increased **OS** [RR = 0.88: 95% CI;0.80-0.97 P=0.015], and **DFS** (p<0.001), LA (p<0.009) and **MFS** (P<0.001)	Afonso et al 2010
			(n=2170)	OS,DFS, RFS, LR,MFS	Anthracycline-based chemotherapy is beneficial in terms of 5 yrs **DFS** [Odds Ratio =0.71: 95% CI;0.54-0.85 P<0.001]; **PFS** [Odds Ratio =0.75: 95% CI;0.61-0.92 P=0.007] and **OS** [Odds Ratio =0.79: 95% CI;0.66-0.94 P=0.005]. The odds ratio for **PFS** and **OS** at 10yrs are 0.71(95%CI; 0.58-0.85 P<0.001 and 0.87 (95% CI; 0.72-1.04 P=0.12) respectively.	O'connor et al 2008
		18	Localised resectable STS (n=1953)	LR, DR,OR, Survival	RR of **LA, DR** and **OR** in the doxirubicine plus ifosfamide chemotherapy are: 0.66 (95%CI; 0.39-1.12), 0.61 (95%CI; 0.41-0.92), and 0.56 (95%CI; 0.36-0.85) respectively. A significant reduction in motarlity was observed in adjuvant doxorubicin plus ifosfamide chemotherapy HR=0.56(95%CI 0.36-0.85 P=0.01)	Pervaiz et al 2008

DFS= disease free survival; **DR**= distant recurrence; **HR**= hazard ratio; **LR**= local recurrence; **MFS**= metastatic free survival; **OR**= overall recurrence; **OS**= overall survival; **RFS**= recurrence; **RR**= relative risk.

New References Identified (alphabetic order):

1. Afonso S, Ramos L, Viani G, Afonso V. Improvement in the survival for adult soft tissue sarcoma with adjuvant anthracycline chemotherapy combination: A meta analysis. ASCO Meeting Abstracts. 2010 Jun 14;28 (15 Suppl):10042.
2. O'Connor J, Chacon M, Petracci F, Chacon R. Adjuvant chemotherapy in soft tissue sarcoma: A meta-analysis. ASCO Meeting Abstracts. 2008;26 (May 20 Suppl):10526.
3. Pervaiz N, Colterjohn N, Farrokhyar F, Tozer R, Figueredo A, Ghert M. A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma [Meta-Analysis]. Cancer. 2008 Aug 1;113(3):573-81

Literature Search Strategy:

Medline

1. exp sarcoma/
2. soft tissue.tw.
3. 1 and 2
4. (adjuvant chemotherapy or adjuvant therapy).tw.
5. (200502$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$).ed.
6. 3 and 4 and 5
7. limit 6 to (human and english language)

1. Embase

1. exp sarcoma/
2. soft tissue.tw.
3. 1 and 2
4. (adjuvant chemotherapy or adjuvant therapy).tw.
5. (200506$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$).ew.
6. 3 and 4 and 5
7. limit 6 to (human and english language)

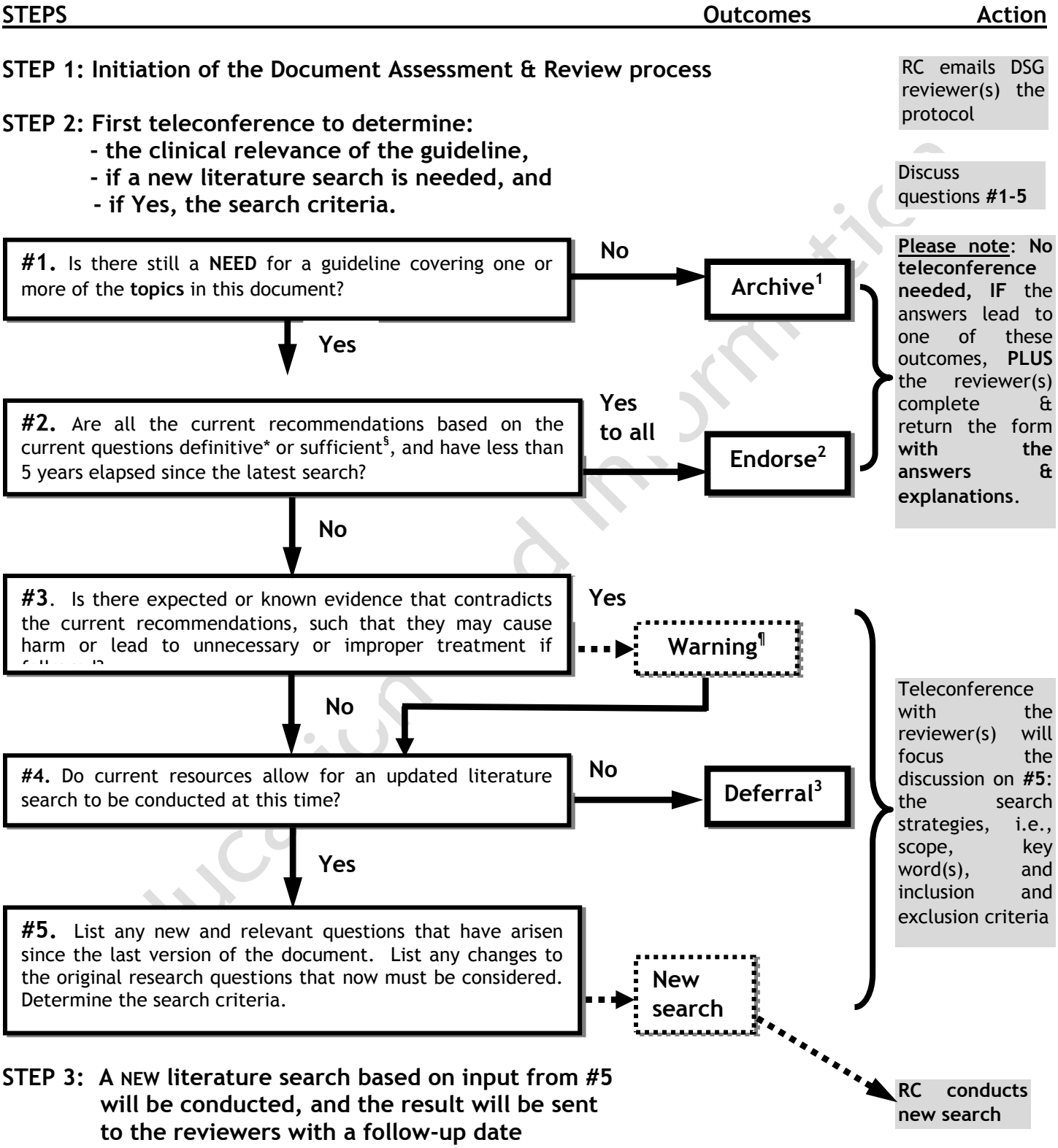
ASCO Annual Meeting – searched http://www.ascopubs.org/search with keywords: Adjuvant AND (soft tissue sarcoma).

Go to 6.

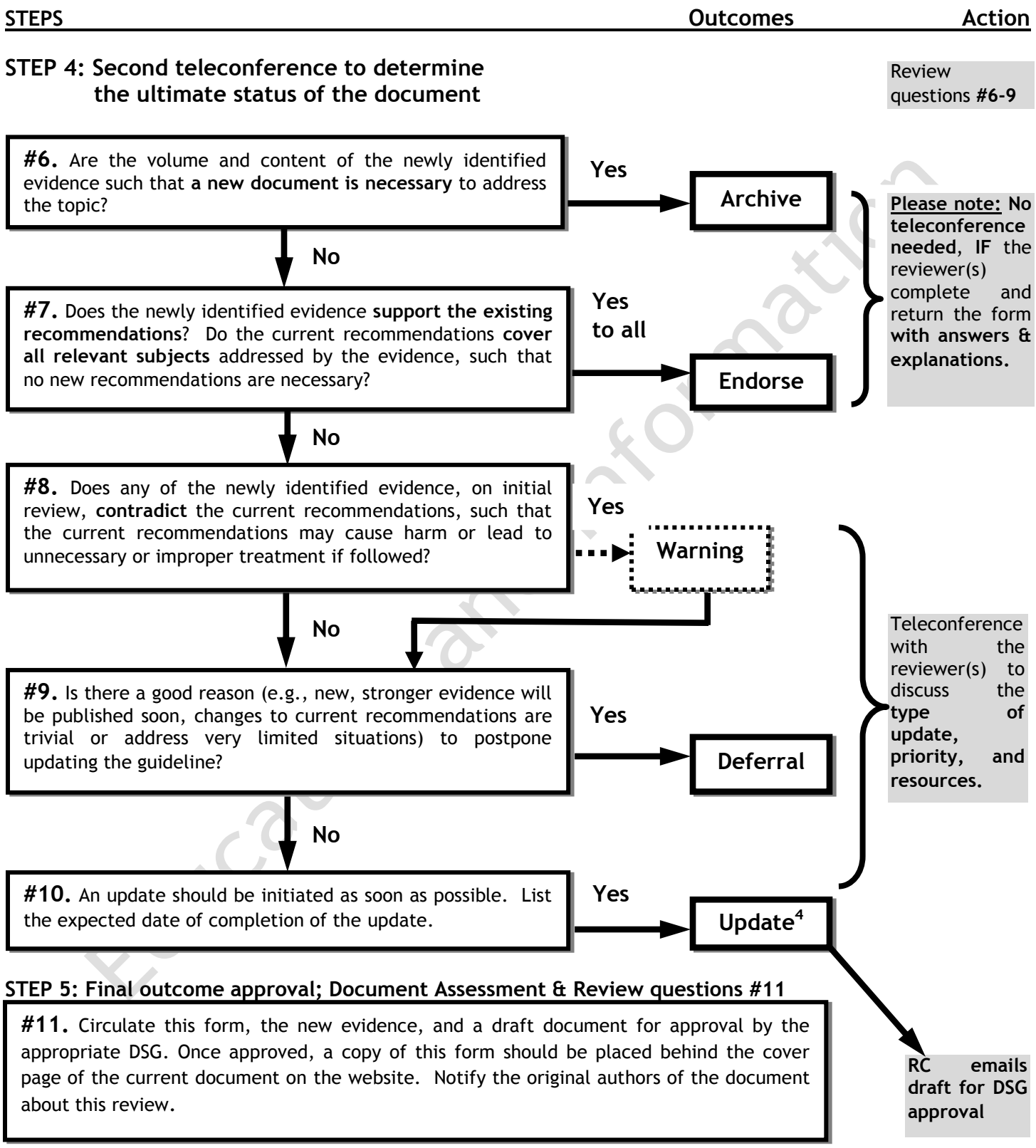
6. Is the volume and content of the new	6. No

evidence so extensive such that a simple update will be difficult?	If Yes, then the document should be **ARCHIVED** with no further action; **go to 11**. If No, **go to 7**.
7. On initial review, does the newly identified evidence support the **existing recommendations**? Do the current recommendations **cover all relevant subjects** addressed by the evidence, such that no new recommendations are necessary? Answer Yes or No, and explain if necessary:	7.Yes If Yes, the document can be **ENDORSED**. If No, **go to 8**.
8. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, citing newly identified references:	8. No If Yes, a **WARNING** note will be placed on the web site. If No, **go to 9**.
9. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary:	9. No If Yes, the document update will be **DEFERRED**, indicating that the document can be used for decision making and the update will be deferred until the expected evidence becomes available. If No, **go to 10.**
10. An update should be initiated as soon as possible. List the expected date of completion of the update:	10.Not Applicable. An **UPDATE**[4] will be posted on the website, indicating an update is in progress.
11. Circulate this form to the appropriate Disease Site Group for their approval. Once approved, a copy of this form should be placed behind the cover page of the current document on the website. Notify the original authors of the document about this review.	
DSG Approval Date:	**May 31, 2011**
Comments from DSG members:	

DOCUMENT ASSESSMENT & REVIEW 5-STEP FLOW CHART



FLOW CHART (cont.)



DOCUMENT ASSESSMENT AND REVIEW DEFINITIONS

Document Assessment and Review Terms

***DEFINITIVE RECOMMENDATIONS** – Definitive means that the current recommendations address the relevant subject area so fully that it would be very surprising to identify any contradictory or clarifying evidence.

§ SUFFICIENT RECOMMENDATIONS – Sufficient means that the current recommendations are based on consensus, opinion and/or limited evidence, and the likelihood of finding any further evidence of any variety is very small (e.g., in rare or poorly studied disease).

¶ WARNING – A warning indicates that, although the topic is still relevant, there may be, or is, new evidence that may contradict the guideline recommendations or otherwise make the document suspect as a guide to clinical decision making. The document is removed from the website, and a warning is put in its place. A new literature search may be needed, depending on the clinical priority and resources.

Document Assessment and Review Outcomes

1. **ARCHIVED** – An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of our Web site, **each page is watermarked** with the phrase "ARCHIVED".

2. **ENDORSED** – An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **DEFERRAL** - A Deferral means that the clinical reviewers feel that the document is still useful and the decision has been made to postpone further action due to a number of reasons. The reasons for deferral should be found in the Document & Assessment Review form and on the document.

4. **UPDATE** – An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.