Follow-Up Surveillance of Soft Tissue Sarcoma

Effective Date: May, 2014

The recommendations contained in this guideline are a consensus of the Alberta Provincial Sarcoma Tumour Team synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

BACKGROUND

Sarcomas are rare tumours that develop from certain tissues, commonly bone or muscle. The two main types of sarcomas are bone sarcomas and soft tissue sarcomas (STSs). In the United States 11,410 new adult cases of STS are expected in 2013 with an additional 4,390 deaths.[1] Soft tissue sarcomas are malignant tumors that arise in any of the mesodermal tissues of the extremities (50%), trunk and retroperitoneum (40%), or head and neck (10%). The reported international incidence rates range from 1.8 to 5 per 100,000 per year.[2] In Canada, in 2007, there were 1116 new cases of STS. STSs account for approximately 1% of adult cancers.

Follow-up surveillance strategies for STSs have not been well researched and most guideline recommendations are based on a consensus of experts as opposed to a review of high quality clinical trials. Oftentimes surveillance strategies are based on a combination of tumour-specific biology, tumour location, intent of treatment, clinical experience and data on patterns of recurrence after STS resection. A 2002 study of 2,123 patient records examined patterns of STS relapse and found that approximately two-thirds of STS recurrences occur within two years, 15% of recurrences occur in the third year and 18% of recurrences occur after 3 years; 9% of which occur after 5 years.[3] This highlights two important things: 1) that surveillance strategies should opt for more frequent and aggressive surveillance immediately after resection and 2) that surveillance strategies should be implemented long-term as a significant portion of relapses occur after 5 years. As STSs can present in a range of types it is difficult to create rigid recommendations in respect to follow-up. The rarity of STSs makes recruitment into the high quality RCTs that would provide best-evidence for follow-up protocols difficult. In this guideline we will discuss new research and previously existing guidelines pertaining to the post-treatment follow-up of individuals with STS.

GUIDELINE QUESTIONS

- What are the appropriate follow-up protocols for the surveillance of post-treatment STS?

DEVELOPMENT AND REVISION HISTORY

This guideline was reviewed and endorsed by the Alberta Provincial Sarcoma Tumour Team. Members of the Alberta Provincial Sarcoma Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Sarcoma Tumour Team and a Knowledge Management Specialist from the Guideline Utilization Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Utilization Resource Unit Handbook.

This guideline was originally developed in April 2014.

SEARCH STRATEGY

Medical journals were searched using the Medline (1950 to February 2014), PubMed (1946 to February 2014) and Google Scholar databases. The search terms included: follow-up, surveillance, soft tissue sarcoma, Sarcoma [MeSH]. The references and bibliographies of articles identified through these

searches were scanned for additional sources. Articles were excluded from the review if they: had a non-English abstract or if they were not available through the library system.

A search of clinical practice guidelines was also conducted, and yielded four published guidelines by the following organizations: the British Columbia Cancer Agency (BCCA), the National Comprehensive Cancer Network (NCCN), the European Society for Medical Oncology (ESMO), and the UK Sarcoma Specialists Consensus Guideline.

TARGET POPULATION

The recommendations outlined in this guideline apply to adults over the age of 18 years. Different principles may apply to pediatric patients.

RECOMMENDATIONS

1. For low risk, low grade sarcomas, clinical examination and chest X-ray should be conducted every 6 months for the first 2 years then annually for 5 years after surgical resection. Annual surveillance for up to 10 years can be considered but will be left to the discretion of the responsible physician. Local imaging may be appropriate if physical examination is deemed unreliable.

2. For high risk, moderate or high grade sarcomas, clinical examination and chest X-ray should be conducted every 4 months for the first 2 years following surgical resection, then every 6 months for the third year, and q 6 to 12 months for years 4 &5 after surgical resection. Annual surveillance for up to 10 years should be considered but remains at the discretion of the physician.

3. Baseline post resection imaging obtained no earlier than 3 months after surgery should be considered for all patients particularly those felt to be at higher risk of recurrence or where physical examination of the local tissue is felt to be unreliable. For superficial tumours subsequent clinical examination will suffice. For those cases where local imaging is deemed necessary for accurate surveillance, the imaging schedule should coincide with the regular follow-up visit whenever possible.

4. Local imaging modality may include Ultrasound, CT or MRI depending on resource availability, reliability and tumour location. Unless otherwise indicated a similar modality for subsequent surveillance should be used where possible in order to improve serial interpretation. Cross sectional imaging should be performed in all cases when local recurrence is suspected. Routine use of CT for pulmonary imaging is not recommended but should be considered when improved imaging sensitivity is required.

DISCUSSION

Guidelines regarding the optimal follow-up strategy for soft tissue sarcoma (STS) are primarily based on expert consensus. Wherever possible, enrolling patients in clinical trials investigating optimal STS follow-up strategies is strongly recommended. STSs are rare cancers, severely limiting the amount of high quality evidence available to guide follow-up strategies.

Recommendations from other Clinical Practice Guidelines

The British Columbia Cancer Agency (BCCA)'s most recent guideline related to follow-up management of STS was released in June 2010[5]. The BCCA recommend a combination of clinical examinations and chest x-rays every 4 months for years 1-2, every 8 months for years 3-5 and every 12 months thereafter, after surgical excision. They recommend limiting chest x-rays for follow-up to 10 years, however, they do not recommend limiting yearly clinical examinations. Furthermore, the BCCA recommends local imaging with either CT or MRI from baseline up to 3-6 months after treatment.

The European Society for Medical Oncology (ESMO) updated their guideline in October 2012[6]. ESMO divides their recommendations on the basis of low grade or intermediate/high grade STSs. In both cases, they state that clinical assessment of the primary site with regular chest x-rays is more cost-effective than regular use of MRI or CT. For low grade STSs, they recommend follow-up every 4-6 months for the first 3-5 years and annually thereafter following surgical excision. For intermediate/high grade STSs ESMO recommends follow-up every 3-4 months for the first 2-3 years, every 6 months up to 5 years and annually thereafter following surgical excision.

The National Comprehensive Cancer Network (NCCN) updated their follow-up management of STS guideline in March 2014 and is, therefore, the most recently updated guideline on this topic[7]. Like the ESMO guideline, the NCCN divides recommendations into low and intermediate/high grade STSs. For low grade STSs, the NCCN recommends follow-up every 3-6 months for the first 2-3 years and then annually thereafter following surgery. They suggest considering postoperative baseline and periodic imaging of the primary site based on estimated risk of locoregional recurrence with MRI, CT or ultrasound. They also suggest considering chest imaging every 6-12 months. For intermediate/high grade STSs, the NCCN recommends follow-up (plain radiograph or chest CT) every 3-6 months for 2-3 years, every 6 months for the next 2 years and then annually thereafter following surgery. The NCCN guideline recommends all follow-up appointments include a physical examination, and they suggest physicians should considering obtaining postoperative baseline and periodic imaging of the primary site with MRI, CT, or ultrasound).

One of the more comprehensive consensus guidelines on follow-up surveillance of STS was developed by the UK Sarcoma Specialists Consensus Guideline in 2010.[8] This group suggests that, due to the possibility of late relapse; follow-up should be continued for a minimum of 8 years for high grade tumours and longer for low grade tumours. Standard follow-up consultations should consist of a clinical history, a clinical examination to focus on local recurrence with follow-up ultrasound or MRI where indicated by clinical suspicion, and chest X-ray with subsequent CT for investigating suspicious lesions. In general, the UK Sarcoma Specialists recommend that frequency of follow-up consultations should be as described in ESMO's guidelines with the additional recommendation of monitoring late adverse effects of treatment.

The Alberta Sarcoma Tumour Team has reached consensus, and after taken into consideration the recommendations from other guideline sources, has optimized follow-up strategies for Albertans. The Sarcoma Tumour Team recommends clinical exam and chest X-ray every 6 months for 2 years, then annually thereafter following resection of a low grade STS. The Sarcoma Tumour Team recommends clinical exam and chest X-ray every 4 months for 2 years, then every 6 months for year 3, then annually thereafter following resection of high grade STS. They recommend considering postoperative imaging of the primary site approximately 3 months after surgery. The team recommends considering MRI, CT, or ultrasound if worrisome symptoms present at follow-up.

Use of Imaging Modalities in Follow-Up Surveillance of STS

A retrospective study with 141 participants by Brian *et al.* in 2000 evaluated the effectiveness of follow-up testing for detecting local and distant recurrences of extremity STS and remains one of the key studies examining follow-up surveillance strategies of STS[9]. A review by Whooley *et al.* published in 1999 discussed the same results[10]. Patients were observed every 3 months for 2 years, every 4 months in the third year, every 6 months in the fourth and fifth years, and every year thereafter. Each visit consisted of a patient history, physical examination, complete blood count, blood chemistry panel and chest X-ray. Of the 141 participants, 29 developed local recurrence and 57 developed distant recurrence within a median follow-up interval of 69 months. All but 1 of the local recurrences was detected by physical examination. Of the 29 identified local recurrences, 25 were surgically resected. Of the 57 identified distant recurrences, 21 were detected because of symptoms. Of the 36 asymptomatic lung recurrences, 30 were detected by follow-up chest X-ray. 24 of the 36 asymptomatic patients with lung recurrence underwent metastasectomy. It is worth noting that laboratory testing never led to the detection of any recurrence. The cost per non-quality adjusted life year (NQALY) (which describes the cost and number of years of life saved by a health intervention to be described) was $30,000 in 1997 US dollars. The authors argue that this compares favourably to other cost-effective ratios for medical interventions, and therefore recommend chest X-ray should be included with physical examination as part of follow-up in patients with extremity STS . The authors do not recommend CT and MRI scanning of the chest as a typical surveillance technique because of the high accuracy of chest X-ray in recurrence detection. The authors do recommend CT and MRI as tools to evaluate local recurrences in patients who were treated with adjuvant radiotherapy, or in deeply situated tumours.

Similar conclusions regarding the routine use of CT imaging were drawn by Kane in an expert opinion statement published in 2004[11]. Like the authors above, Kane argues that the use of routine chest CT would be costly and provide little additional benefit if risk of lung metastases is low. These views are echoed by Van Rijswijk *et al.* in 2007 who argued that intense MRI surveillance of STS does not add to clinical assessment in detecting local recurrence; although there may be use for MRI in cases of recurrent, locally aggressive fibromatosis[12]. In their study, pulmonary metastases were effectively detected using conventional chest radiographs. In a 2008 review by James *et al.*, baseline MRI was deemed useful 6-8 weeks following surgical resection although few studies looking at cost-effectiveness of such regimes have been conducted[13]. The authors noted that some studies suggest more frequent MR imaging as a means of surveillance[14] although several studies[10, 12, 13] have determined this to not be cost-effective. The authors themselves state that MR imaging in their institution is reserved for those cases considered at particularly high risk of developing a local recurrence. Other groups feel similarly about routine CT imaging, recommending routine CT only for those individuals at high risk of relapsing[15,16].

Cost-Effectiveness of STS Follow-Up

Cost-effectiveness of interventions is commonly cited in studies on surveillance strategies for STS; however, limited studies have examined the actual costs of follow-up surveillance. A review by Goel *et al.* in 2004 summarized literature on the topic from the years 1982 to 2003[17]. They found 34 articles discussing 54 follow-up strategies. Variations in cost in 2003 US dollars ranged from $485 for follow-up of low grade sarcoma to $21,235 for high-grade sarcomas – a 42.8-fold difference. The average cost of the 54 strategies was $6,401 and physical examinations and chest X-rays were the most commonly used screening modalities. The authors state that the scientific literature has yet to reflect the consensus in many clinical practice guidelines, including the NCCN guidelines discussed above.

Surveys of Current Practice Patterns

As evidence-based guidelines for the follow-up surveillance of STS are limited and primarily based on expert consensus, practice patterns can vary considerably. Gerrand *et al.* conducted a survey with 121 physicians involved in the care of patients with STS in the UK[18]. For patients with trunk or extremity tumours at low risk of relapse, they found that most clinicians followed them for up to 5 or 10 years. For patients with high risk of relapse, however, the majority of clinicians followed-up for up to 10 years. Clinic visits and chest X-rays were the most common tests at follow-up and 83% of clinicians thought regular follow-up was of benefit. The authors urged for more RCTs to determine optimal surveillance strategies. Beitler *et al.* reported similar results in an earlier study[19]. They found that frequency of follow-ups increased with tumour size and grade and decreased with post-operative year. Similar results were reported in another study[20]. Complete blood count and liver function tests were the most commonly ordered blood tests although many respondents did not order blood tests routinely. A third study by Johnson *et al.* in 2005 looked at practice patterns of members of the Society of Surgical Oncology.[21] The survey was administered to 1,592 people of whom 716 responded and 318 indicated involvement in long-term follow-up of patients with STS. Like the previous two studies, clinic visits and chest X-rays were the most commonly performed interventions. The authors found considerable variability in post-operative surveillance strategies among surgeons and believed lack of evidence supporting any particular strategy was most likely responsible for this variability. As in previous studies, the authors urged for more high quality studies on optimal strategies.

In 2002 and 2003 Sakata *et al.* published two articles[20, 22] based on the survey results of the Society of Surgical Oncology also used by Johnson *et al.* In both studies 318 physicians responded to the survey and were involved in the follow-up care of patients with STS. In one study they were examining the influence of surgeon's age on the STS surveillance strategy employed[22]. They found that although minor variations existed between age groups, post-operative surveillance strategies were only minimally affected by surgeon's age. In a second study, published as an abstract at the 2002 ASCO Annual Meeting and as a paper in 2003, Sakata *et al* examined whether tumour grade and size accounted for variation in follow-up surveillance of STS[20]. The authors found that office visits, complete blood count, liver function tests, chest X-rays, chest CT imaging, extremity CT imaging, and extremity MRI were ordered significantly ($p<0.05$) more frequently with increasing tumour size and grade.

Surveillance Frequency

There is variability in the published literature regarding the frequency of follow-up consultations after STS. Increased frequency may lead to earlier detection of recurrence and better chances of survival. However, increased frequency also increases cost and may not be the most effective use of resources. Currently, there is limited evidence to suggest early detection of recurrence has a major influence on survival[23-29] and, therefore, some authors question whether aggressive treatments upon detection of recurrence is wise[30]. Finding the optimal balance is a matter made more complicated by variations in other factors such as tumour size, location, and grade. The rarity of these cancers also makes enrolment in high quality RCTs that would allow physicians to elucidate the optimal strategy difficult.

Chou *et al.* conducted a retrospective review with 80 patients in 2012 to explore the impact of imaging frequency on disease specific survival (DSS)[16]. A total of 165 patients were assigned to three groups based on four risk factors: tumour size, depth, grade and surgical margins. Based on the number of follow-ups patients were categorized as having either more frequent surveillance (MFS) or less frequent

surveillance (LFS) as compared to the median follow-up rate. Locoregional imaging (LRI) was reserved for detection of local recurrence and chest imaging (CI) was reserved for detection of distant metastases. There were no differences in overall DSS (O-DSS) between MFS and LFS groups for LRI (p=0.279) and CI (p=0.869). Among patients with high-risk features, however, those in MFS groups for LRI or CI had significantly better O-DSS than those in the LFS groups (LRI, median 44.07 vs 27.43 months, p=0.008; CI, median 43.60 vs 36.93 months, p=0.036). The authors concluded that for individuals at high risk of relapsing, more frequent follow-ups was associated with better O-DSS. An ongoing clinical trial by Puri *et al.* offers results from an RCT with 500 patients comparing intensive follow-up protocols against cost-effective protocols for OS after bone and soft tissue sarcoma (BSTS)[31]. All patients were operated on for primary or recurrent extremity sarcomas and subsequently randomized into four groups: 1) intensive follow-up every 3 months, 2) intensive follow-up every 6 months, 3) cost-effective follow-up every 3 months, and 4) cost-effective follow-up every 6 months. Early results were presented in this abstract. The authors found that increased frequency of surveillance did not significantly impact early recognition of relapse or OS (DFS, p=0.676; OS, p=0.557) except in cases of bone sarcomas.

A recent report by oncologists at the Tom Baker Cancer Centre in Calgary, Alberta suggested the following surveillance patterns: for patients with low grade extremity/trunk/head and neck sarcoma, the authors recommended office visits and chest X-rays every 6 months for 3 years followed by once per year up until 5 years. Local imaging (including US/CT/MRI) is to be repeated only if worrisome symptoms and/or signs are noted. For patients with high grade extremity/trunk/head and neck sarcoma the authors recommended office visits and chest X-rays 3-4 times per year for the first 2 years, 2-3 times per year for the third year and every 6 months for years 4 and 5. Local imaging is only repeated if worrisome symptoms and/or signs are noted.

The Alberta Sarcoma Tumour Team has reached consensus regarding follow-up strategies for Albertans following surgical resection of a STS tumour. The group recommends clinical exam and X-ray every 6 months for 2 years, then annually thereafter following resection of a low grade STS. The Sarcoma Tumour Team recommends clinical exam and chest X-ray every 4 months for 2 years, then every 6 months for year 3, then annually thereafter following resection of high grade STS. They recommend considering postoperative imaging of the primary site approximately 3 months after surgery and the team recommends considering MRI, CT, or ultrasound if worrisome symptoms present at follow-up.

GLOSSARY OF ABBREVIATIONS

Acronym	Description
ASCO	American Society of Clinical Oncology
BCCA	British Columbia Cancer Agency
BSTS	Bone and Soft Tissue Sarcoma
CT	Computed Tomography
DFS	Disease-Free Survival
DSS	Disease Specific Survival
ESMO	European Society for Medical Oncology
LFS	Less Frequent Surveillance
MFS	More Frequent Surveillance
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
NQALY	Non-Quality Adjusted Life Year
O-DSS	Overall Disease Specific Survival
OS	Overall Survival
RCTs	Randomized Controlled Trials
STS(s)	Soft Tissue Sarcoma(s)

DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of Alberta Health Services, Cancer Care.

MAINTENANCE

A formal review of the guideline will be conducted at the next Annual Provincial Meeting in 2015. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Sarcoma Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Sarcoma Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

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