Review Article

Post-operative surveillance in soft tissue sarcoma: using tumor-specific recurrence patterns to direct approach

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Abstract: Significant challenges exist in creating surveillance recommendations for soft tissue sarcomas (STS) given the vast heterogeneity of recurrence patterns between histologic subtypes. Using the most recent evidence on the natural history of STS, this review will propose surveillance strategies based on tumor location and histologic subtype.

Keywords: Recurrence; soft tissue sarcoma (STS); surveillance

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Introduction

Major scientific and technological advances coupled with increased access to care have changed the perception on how various cancers exist within the population: what was once considered an acutely fatal disease in many malignancies is now viewed as a chronic condition requiring extended follow-up and surveillance. The expansion of increased access to care and screening mechanisms has led to earlier detection of malignancies which has resulted in the highest recorded prevalence of cancer survivors (1). This increase in survivorship has led to a heightened awareness of the particular issues surrounding cancer survivorship, including the challenges in coordinating long-term oncologic care (2). Although patients have benefited from the increased survival that treatment advances bring, many survivors continue to have psychosocial distress related to their status as a cancer survivor. A major cause behind these patients' anxiety is the fear of cancer recurrence (3). To ease this distress, multiple societies have crafted surveillance strategies which not only follow the natural history of each malignancy, but also are cost-effective and will not burden an already overused healthcare system (4-7). Although routine surveillance may offer several benefits including monitoring ongoing treatment, managing treatment side-effects, providing support to patients and families, and identifying other social issues, the aim of an effective surveillance program is to detect cancer recurrence at a treatable, and potentially curable, stage (8).

Surveillance in sarcoma

Although surveillance protocols have been developed in parallel with our growing knowledge of cancer biology, many of these surveillance programs lack evidence for their effectiveness in detecting local or distant recurrences at a treatable stage. This is especially true in soft tissue sarcoma (STS), where the complex heterogeneity of the disease presents particular challenges in crafting effective surveillance strategies (9). The natural history of STS is determined largely by the histologic subtype of tumor and the anatomic site of origin. To this end, national and international groups have recommended surveillance strategies that encompass the diverse tumor behaviors that STS subtypes may exhibit. For example, the National Comprehensive Cancer Network (NCCN) (v2. 2018) has

separate recommendations for extremity/superficial trunk STS and retroperitoneal sarcomas (RPS) (10). For patients with resected stage 1A/1B extremity/superficial trunk STS, postoperative surveillance includes a history and physical exam every 3 to 6 months for 2 to 3 years and then annually afterwards with a consideration for chest imaging, as well as baseline postoperative and periodic imaging of the primary site of disease based on the estimated risk of locoregional recurrence. For patients with resected stage 2 or 3A disease, surveillance includes history and physical exam every 3 to 6 months for 2 to 3 years, then every 6 months for the next 2 years, and then annually, as well as chest imaging and baseline postoperative and periodic imaging of the primary tumor site. NCCN guidelines for surveillance for resected RPS include a physical exam with cross sectional imaging every 3 to 6 months for 2 to 3 years then every 6 months for the next 2 years and annually afterwards. These guidelines differ from other prominent society recommendations, including the European Society of Medical Oncology (ESMO) and the British Sarcoma Group, which further highlights the scarcity of evidence-based practice surrounding postoperative surveillance in STS (11,12).

In an effort to better prognosticate outcomes for patients, multiple groups have developed nomograms to give a more personalized approach in predicting oncologic outcomes (13-19). These nomograms use individual clinical and pathologic characteristics to calculate prognosis based on statistical models. The benefit of using nomograms over traditional staging systems is that for rare tumors such as STS, precision and patient-centered tools can help better inform conversations between physicians and patients regarding treatment options and surveillance strategies. These nomograms however have several limitations. First, nomograms are often built on specific institutional experiences and thus they lack external validation. Second, nomograms are often constrained by the era in which they were created so as new treatments emerge in treating STS, these nomograms will have to be readjusted to maintain their applicability (20). Lastly, in informing surveillance protocols, nomograms are often limited in their efficacy in predicting location and multi-focality of tumor recurrences.

STS remains a rare malignancy even in centers specializing in cancer care, which makes crafting effective surveillance strategies difficult (21). In this review, we will discuss single- and multi-institutional studies regarding the natural history and recurrence patterns of STS and propose histology- and site-specific postoperative surveillance recommendations.

Natural history and recurrence patterns in extremity and superficial truncal STS

Of all STS, approximately 80% of tumors occur in the extremities and superficial trunk (22). There are over 75 separate histologic subtypes, each with a distinct biological behavior. Because of this diversity, studying individual tumor types can be difficult due to their rarity, and many groups have reported oncologic outcomes by grouping STS by the location of the primary tumor site, as this is a major consideration when approaching the treatment of these tumors. There are several limitations when approaching STS this way however, including challenges in effectively relaying prognostic information to patients with less common subtypes of STS. Regardless, multiple groups have published data regarding the natural history of extremity and superficial trunk STS with large cohorts of patients over several years. A recent multi-institutional study of 1,452 patients with localized extremity STS found that the 10-year overall survival (OS) for patients was 72.9% and the incidence of distant metastasis over 10 years was 25% (15). Another study from the French Sarcoma Group which included 3,255 patients found that the incidence of death by 9 years for patients with truncal STS approached 15% and for extremity STS approached 22%, while the incidence of local relapse in 9 years was almost 40% in patients with truncal STS and 23% in patients with extremity STS (23). This data is further supported by a smaller study of 188 patients with an extremity STS at a single-institution with a mean follow up time of 5 years which found that 13% of patients experienced local recurrence and 24% experienced a distant recurrence (24).

When considering prognostic factors which may help build surveillance programs, multiple groups have reported pathologic tumor grade as one of the most predictive factors for higher rates of recurrence. In the previously mentioned series from the French Sarcoma Group, tumor grade was an independent prognostic factor for both local and distant metastatic-free survival (23). Intermediate and high-tumor grade has been associated with a 2 to 6-fold increase risk of local recurrence and a 5-fold increase risk of distant metastasis (24,25) When examining only those patients with high-grade extremity STS, local recurrence rates have been reported to be 12% at 5 years and 14% at 10 years (26). Histologic tumor grade however has limitations and thus should be used with caution when prognosticating a patient's future clinical course. A large study with over 1,000 patients from Japan noted that the predictive capability for survival of

histologic grade was only applicable in three tumor subtypes: malignant fibrous histiocytoma (MFH), leiomyosarcoma (LMS), and liposarcoma (LPS) (27). This finding is further supported an additional study of 1,240 patients from the French Federation of Cancer Centers Sarcoma Group which found that histologic grade was prognostic in MFH, unclassified sarcomas, synovial sarcomas, LMS, and LPS, but not in other STS subtypes (28). Thus, using histologic grade as the primary variable to craft surveillance programs for all 75 sarcoma subtypes should be avoided. This review will focus on the natural history of the most common histologic types in extremity and truncal STS in an effort to help build effective surveillance programs.

(I) Well-differentiated LPS (WD-LPS): patients with WD-LPS are considered to have a generally favorable overall prognosis with a 5-year disease specific survival (DSS) of 93% (17). When these tumors recur, they almost exclusively recur locally, as distant recurrences have been rarely reported. The 5-year local recurrence free survival (RFS) has been described to be anywhere between 86% and 98%, though older studies have reported this number to be as low as 70% (29-31). It is important to note however, that WD-LPS has been associated with late (>5 years) local recurrences thus suggesting the need for long-term surveillance (32).

(II) Dedifferentiated LPS (DD-LPS): recent advances in immunohistochemistry and molecular profiling have reclassified many tumors previously labeled as MFH as DD-LPS (16). For this review, clinical outcomes for MFH reported in older studies will be referenced with more recent series reporting outcomes specific for DD-LPS, though the older classification also included a more diverse tumor population which encompassed 4 to 5 different types of sarcomas thus making the ability to summarize recurrence patterns for this particular subtype especially difficult. Patients with DD-LPS have a 5-year OS rate between 44% and 70% and a 10-year OS rate between 38% and 43% (17,33-35). Patients with DD-LPS recur both locally and at distant sites with local recurrence rates of 22-31% and distant metastasis rates of 10–33% (33-36).

(III) Pleomorphic LPS: pleomorphic LPSs are generally aggressive tumors which frequently recur both locally and distantly. Previous groups have reported a 5-year OS rate of 40–63%, and a 5-year DSS of 53–81% (37-41). Patients with pleomorphic sarcoma have a 10-year local recurrence rate of up to 45% and a 10-year distant recurrence rate of up to 50%. It is important to note that for pleomorphic sarcoma, the most common site for distant recurrence is the lung (30).

(IV) Myxoid LPS: myxoid LPSs is subdivided into two groups: pure myxoid LPS and myxoid/round cell LPS. Patients with myxoid LPS generally have favorable outcomes with 5-year DSS rates of 88–100% and 10-year DSS rate of up to 93% (17,29,30,37). Tumor recurrences are more frequently locoregional, with an overall 5-year RFS rate of 75% and a 5-year and 10-year local RFS rate of 84–86% and 84%, respectively; and a 5-year and 10-year distant RFS rate of 96-100% and 95%, respectively (15,17,29,37). On the other hand, patients with myxoid/round cell LPS tend to have worse outcomes in the presence of a greater than 5% round cell component placing patients at an increased risk for metastasis and death (37). For myxoid/round cell LPS, 5-year DSS rates are 74–87% and 10-year DSS are as low as 77% (17,37). Five-year and 10-year local RFS rates are 86% and 78%, respectively and 5-year and 10-year distant RFS are both 78% (37). As opposed to pleomorphic LPS, the majority of distant metastases in myxoid LPS are extra-pulmonary—with abdominopelvic metastasis occurring quite frequently. The patterns of recurrence for these tumors often involve metastatic spread to the spine (30–74% of extrapulmonary metastases), the retroperitoneum (18–71% of extrapulmonary metastases), and the abdominal and thoracic wall (up to 9% of extrapulmonary metastases) although metastases to other sites including intraabdominally have been reported (37,42-45). Thus, surveillance strategies should include imaging these sites with appropriate cross-sectional imaging, which may include MRI.

(V) Malignant Peripheral Nerve Sheath Tumor (MPNST): MPNSTs are rare tumors which can be associated with neurofibromatosis type 1 (NF-1) or occur sporadically. The presence of a hereditary tumor syndrome has questionable association with worse prognosis as one series of 205 patients showed no difference in recurrence rates between those patients with and without NF-1, and an overall disease specific mortality of 43% at 10 years

and disease-free survival of 40% at 10 years (46). In a separate series of 140 patients however, 10-year DSS was 35% for patients with NF-1 while it was 50% for patients without NF-1 (47). Even considering these differences in survival, patients with MPNST have recurrence rates of up to 50% at 5 years which mandates strict surveillance protocols for these patients (46-48).

(VI) Myxofibrosarcoma: Although these tumors overall have a fair prognosis with 5-year OS rates between 75% and 77% (30,49), these tumors tend be locally aggressive and infiltrative and thus can have local recurrences quite often. The 5-year local RFS rate for myxofibrosarcoma is 69–86% and the distant metastasis free survival rate is 68–83% (30,49-51). Distant metastases most commonly occur in the lung in patients with myxofibrosarcoma.

(VII) Undifferentiated pleomorphic sarcoma (UPS): as with DD-LPS, many patients with UPS were previously classified as MFH, but with current improvements in molecular profiling, more specific and recent studies for UPS are summarized in this review. Patients with UPS have been described to have a 5-year DSS of 60–63%, 5-year local RFS rates of 73–81%, and a 5-year distant metastasis-free survival of 57–70% (30,52). Because of the high propensity of these tumors to recur both locally and distantly, surveillance imaging should focus on both the primary tumor site and the lungs in these patients.

Natural history and recurrence patterns in retroperitoneal STSs

The tumor diversity seen in extremity and superficial trunk STS, although to a lesser extent, has also been described in RPSs and, as in extremity and superficial trunk STS, these subtypes can exhibit vastly different recurrence patterns from one another. Fortunately, in the current era of sarcoma treatment, the Trans-Atlantic RPS Working Group (TARPSWG) was formed to better characterize this rare cohort of malignancies by compiling data from several high-volume sarcoma centers (53,54). The TARPSWG found that for all RPS, the 5-year local recurrence rate was 26% and 10-year local recurrence rate was 35%. This data stresses the importance of ongoing surveillance for late recurrences which may occur in RPS, an observation reported by other groups as well (19,32). A few select histologic subtypes of RPS comprise the majority of tumors seen and we will focus on these:

(I) Well-Differentiated LPS: WD-LPS is the most commonly occurring histologic subtype of RPS, with an OS rate of up to 80% at 8 years (19,53,55). Local recurrence rates are between 19% and 58% at 5 years and up to 60% at 15 years, with over one-third of these local recurrences being multi-focal recurrences (19,55-57). Tseng *et al.* reported that up to 18% of these multifocal, locoregional recurrences are remote from the original resection field, in a compartment remote from the index tumor resection (58). As in the extremity, WD-LPS in the retroperitoneum has practically a 0% distant metastasis rate.

(II) Dedifferentiated LPS: as in the extremity and superficial trunk, DD-LPS has the worst overall prognosis of LPS subtypes. The 5-year OS rates range between 37% and 44%, with the incidence of local recurrences being between 58% and 82% by 5 years and distant recurrences between 9% and 44% (19,53,55-57). Similar to WD-LPS, a large proportion of DD-LPS local recurrences are multifocal with up to 28% outside the original resection field, though in DD-LPS recurrences occur sooner and more frequently (55,58). Grade also has prognostic importance in DD-LPS. Grade 3 tumors are the most aggressive type and have significantly worse outcomes compared to grade 2 tumors with lower 8-year OS (30% *vs.* 50%) and higher 8-year distant metastasis risk (30% *vs.* 10%), though local recurrence risks are similar between grades (53).

(III) LMS: LMS represents the second most common histologic subtype of retroperitoneal STS and is associated with a low local recurrence rate (6–16% at 5 years). LMS is however associated with a high distant metastasis rate of up to 58% at 5 years (19,53,56,57). These tumors also warrant extended surveillance for recurrences as they are associated with a 3-fold higher risk for late (greater than 5 years) metastatic recurrence (32).

(IV) Solitary fibrous tumor (SFT): patients with SFT have a generally favorable prognosis given the low-malignant potential and indolent nature of these tumors. Survival at 8 years is as high as 75% and these tumors have low local recurrence rates between 4% and 8%, although more aggressive

variants of SFT do exist which tend to recur distantly at rates of up to 41% at 5 years (19,53,56). A recent study from Memorial Sloan Kettering Cancer Center of 219 patients with SFTs found 5-year and 10-year disease specific death rates of 9% and 11%, 5-year and 10-year local recurrence rates of 4% and 7%, and 5-year and 10-year distant recurrence rates of 13% and 16%, though late local and distant recurrences have been reported at up to 16 years after presentation (59).

Imaging modalities and recommendations for surveillance

Presently, there is a lack of clinical trials assessing the effectiveness of varying imaging modalities and frequencies needed for optimal surveillance for patients with extremity, superficial trunk, or retroperitoneal STS. Current guidelines are informed by retrospective studies, consensus opinions, tumor biology, and cost-effectiveness models. In regard to extremity STS, common practice for surveillance includes a clinical history and physical exam to assess for local recurrences and chest radiographs to assess for pulmonary metastases, with chest computed tomography (CT) scan reserved for suspicious lesions seen on plain films (60-63). According to the NCCN guidelines, chest X-ray can be used for chest imaging though chest CT scan without contrast is preferred. When considering cost effectiveness specifically, optimal surveillance for distant metastases for patients with intermediate to high-grade disease has been shown to be chest X-ray at longer intervals when the distant recurrence risk is less than 33% and chest CT scan when the distant recurrence risk is greater than 33% (64). Assessing for local recurrences for most patients can be done effectively with physical exam alone, as advance imaging including magnetic resonance imaging (MRI), has been shown to infrequently detect asymptomatic local recurrences (65,66). When considering RPS, contrast-enhanced CT scans of the abdomen and pelvis is the most appropriate imaging modality for surveillance of the abdomen, while non-contrast CT scan of the chest or plain radiographs can be considered depending on the risk of distant metastasis (67). Functional imaging with positron emission tomography (PET) scan is currently not recommended for routine use in STS surveillance due to the lack of data regarding its effectiveness (68).

Our recommendations for postoperative surveillance are informed by the primary tumor site, underlying tumor biology and clinical behavior of the STS being surveyed. For patients with more indolent extremity and superficial trunk STS (WD-LPS and pure myxoid LPS), we recommend a surveillance protocol consisting of a clinical history and physical exam with chest radiographs every 6 months for 3 years followed by annually thereafter. For patients with more intermediate- to aggressive-tumor histologic subtypes of extremity and superficial truck STS (myxoid/round cell LPS, pleomorphic LPS, DD-LPS, MPNST, myxofibrosarcoma, and UPS), we recommend clinical history and physical exam with chest CT scan without contrast every 3–6 months for 2–3 years, then every 6 months for 2 years, and then annually afterwards. For patients with myxoid/round cell LPS, obtaining a CT scan of the abdomen and pelvis with contrast at the time of obtaining chest imaging is also necessary as these tumors often recur in extra-pulmonary locations, and consideration of MRI imaging of the spine is suggested as these tumors frequently metastasize to bony areas. In regards to imaging of the primary tumor site in STS of the trunk or extremity, we would not routinely perform imaging if the site could be appropriately assessed clinically however we would consider MRI at the time of surveillance assessment for those sites that are unable to be adequately assessed clinically and/or if abnormal clinical findings were identified.

For RPS, we suggest routine postoperative surveillance for tumor recurrence, as selective surveillance initiated by patient symptoms may be too non-specific to effectively detect recurrences at a stage where intervention may be beneficial. Routine surveillance for more indolent RPS tumor types (WD-LPS and SFT) should consist of a clinical history and physical exam and cross-sectional imaging of the abdomen and pelvis (CT scan preferred or MRI) every 6 months for 3 years followed by annual assessment. For RPS tumor subtypes which are more aggressive (DD-LPS and intermediate- to high-grade LMS), surveillance should consist of clinical history and physical exam with cross sectional imaging of the chest, abdomen, and pelvis (CT scan preferred or MRI) every 4 months for 2 years followed by every 6 months for the next 3 years and then annually afterwards.

In designing surveillance regimens which more closely reflect tumor biology based on histologic subtype, we feel that the ability to detect local and distant recurrences at an interventional stage will improve for patients with STS. We also stress the importance of pairing these surveillance strategies with high-quality nomograms to better predict oncologic outcomes for patients.

Conclusions

Unique obstacles exist in creating surveillance strategies for STS due mainly to the diverse natural history and recurrence patterns between tumor subtypes. In recent years however, multiple groups have compiled extended follow-up data on the specific histologic subtypes of STS. In light of this data, we propose using tumor-specific protocols for postoperative surveillance centered around the histologic subtype of each tumor.

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Footnote

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