

Late Recurrences in Soft Tissue Sarcomas - A Review

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ABSTRACT

Sarcomas are malignant tumors that arise from the connective tissue. Soft tissue is part of connective tissue and includes fat, muscle, nerves, tendons, and blood and lymph vessels. Soft tissue sarcomas (STS) account for 1 percent of all adult cancers in the U.S. Leiomyosarcoma (LMS) is a type of STS that grows in smooth muscles. LMS accounts for 7-11% of all cases of STS. Generally, STS are treated with wide margin surgical resection and some patients are offered radiation and/or chemotherapy to decrease recurrence. Recurrences generally happen in the first two years and late recurrence is defined as appearance of original cancer after 5 years following initial treatment and being disease free. Late recurrences can be in the local area of the initial site or at a distant location. A patient with LMS in the left upper arm was treated with a curative intent with radiation and surgery in Kentucky in 2016. He relocated to Fort Worth, TX recently and was found to have the same LMS in the stomach in 2022, more than 5 years after his initial curative treatment. This prompted us to do literature review of late recurrences in STS. We found that late recurrences happen in 6-15% of patients with STS even if they survived 5 years without cancer following original cancer treatment. LMS accounts for 12% of all late recurrences. Only 27-36% of all STS patients are expected to be alive at 5 years from diagnosis of late distant recurrences.

Introduction

Sarcomas are malignant solid tumors that arise from connective tissue. Soft tissue is part of connective tissue and includes fat, muscle, nerves, tendons, and blood and lymph vessels. Soft tissue sarcomas (STS) account for 1% of all adult cancers in the U.S [1]. Leiomyosarcoma (LMS) is a type of STS that grows in smooth muscles. LMS accounts for 7-11% of all cases of STS [2]. The American Cancer Society (ACS) estimates that about 13,190 new STS cases will be diagnosed in 2022. Also, according to ACS about 5,130 people are expected to die of this disease in 2022 [3].

STS are generally treated with wide margin surgical resection and some patients are offered radiation and/or chemotherapy to decrease recurrence [4]. Recurrences generally happen in the first two years. Though there is no formal definition for late recurrence, it is generally accepted that late recurrence is an appearance of original cancer after 5 years following initial treatment and being disease free according to National Cancer Institute (NCI) [5]. Late recurrences can be in the local area of the initial site or at a distant location.

Patient Case

A 37-year-old male with LMS in the left arm was treated with neoadjuvant radiation and then surgery with complete resection of an 80 mm tumor in July 2016 in Kentucky. He underwent guideline recommended surveillance for 5 years and then relocated to Texas in 2021. The patient was admitted to John Peter Smith hospital in Fort Worth, Texas in February 2022 for abdominal pain. He was found to have iron deficiency anemia. Computed tomography (CT) showed a gastric mass in region of gastric fundus measuring about 78.5 mm x 45.8 mm in axial plane (Fig. 1). No other areas of disease were detected.

Endoscopy showed a large mass in the proximal stomach biopsy. Strong smooth muscle actin and myosin staining indicated smooth muscle differentiation, favoring a diagnosis of LMS. He underwent robotic total gastrectomy with roux-en-y esophagojejunostomy. On gross pathology, tumor was found to be located within the body of the stomach along the greater curvature. The tumor measured 80 mm x 60 mm x 60 mm. On microscopy it was grade 2 and all margins were negative. None of the 13 lymph nodes that were removed had cancer (Fig. 2).

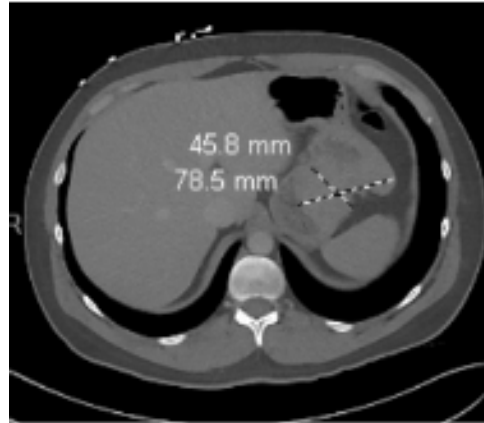


Figure 1. A 78.5 mm x 45.8 mm gastric mass in the region of gastric fundus in axial plane detected by CT scan



Figure 2. Endoscopy picture showing the tumor arising from the gastric wall and partially obstructing the lumen

Methods

Search Strategy

An electronic search of the PubMed database was performed to obtain key literature on STS from the year 2000, using the following search terms: "soft" AND "tissue" AND "sarcomas" AND "late" AND "recurrence". The PubMed database was chosen as it is the most widely used peer-reviewed resource for medical literature. This search resulted in 93 studies.

Eligibility Criteria

The search results were narrowed by selecting studies in humans that were published in English and excluded case reports which resulted in 78 studies. We then manually looked at all the 78 studies and excluded the studies that did not address the outcomes of patients and/or did not follow the patients for the full 5 years to qualify for late recurrences. After the manual screening we were left with 3 studies with about 1800 patients. We retrieved these studies for a full and detailed review.

Results

As detailed in Table 1 below we found that late recurrences happen in 6-15% of patients with STS even if they survived 5 years without cancer following original cancer curative treatment. Late distant recurrences occurred in 4-6% of patients. Only 27-36% of these patients are expected to be alive at 5 years from diagnosis of late distant recurrence. This survival rate is much less than the late local survival rate of 67-94%. LMS accounts for 12% of all late distant recurrences.

Table 1. Summary of data from almost 1,800 patients from the 3 studies discussed

Published Article	Nakamura, T. et al [6]	Toulmonde, M. et al [7]	Gibbs, JF. et al [8]
Initial Cohort (A) (time = t)	1912	3369	NA
Follow-up Cohort (B) (z = t + at least 5 years)	603	719	468
Late Total Recurrences (% of B)	38 (6%)	109 (15%)	39 (8%)
Late Distant Recurrences (C) (% of B)	24 (4%)	42 (6%)	7 (distant only) 14 (both local and distant) (4%)
Late Local Survival (time from z)	79% at 3-years 67% at 5-years	NA	94% at 5-years
Late Distant Survival (time from z)	42% at 3-years 27% at 5-years	NA	36% at 5-years
LMS Specific Cohort (z = t + at least 5 years) (% of B)	58 out of 603 (9.6%)	81 out of 719 (11%)	NA
LMS Specific Late Distant Recurrences (% of C)	4 out of 38 (12%)	10 out of 81 (12%)	NA

Discussion

Cancers can recur many years later due to awakening from dormancy [9]. During the period when cancer is not detected, the cancer cells can still be inside the body in an inactive or dormant state. Some cancer cells can disseminate from the original primary tumor, develop a home in distant organs and enter a growth arrested phase. The National Comprehensive Cancer Network (NCCN) guidelines recommend periodic scans after treatment completion based on estimated risk of locoregional recurrence. But there are no standard guidelines for imaging to identify distant metastasis other than chest imaging. Recurrences can develop and go undetected when cancer cells that were not fully eradicated by the first treatment and were too small to be detected by follow-up scans. After a while, these cells grow into tumors or cancers that are large enough to be detected in scans or cause symptoms.

This dormancy of cancer cells can be explained by several mechanisms. One is the interaction between the growth factor of cells and their adhesion signaling. This causes these cancers to be dormant because of the interruption of the G₀-G₁ phase of the cell cycle. The second way dormancy can be explained is that the cancer cell populations are unable to recruit blood vessels leading to them being inactive. Cancers can also be dormant through immunosurveillance which refers to the power of innate and adaptive immune system (cytolytic T cells and natural killer cells) to eradicate cancerous growth [10]. Preventing the awakening of dormant cancer cells is a topic of active study in numerous research laboratories around the world.

Conclusion

Patients and healthcare professionals need to be aware of the possibility of late sarcoma recurrences. More research and awareness campaigns are needed on this topic to improve overall outcomes. Professional organizations such as NCCN, ACS and NCI should develop improved guidelines that address this issue.

Limitations

Our search term “recurrence” might have inadvertently excluded some articles that may have used some other term to discuss STS disease recurrence.

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