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Evaluating the Impact of Surveillance Follow-Up Intervals in Patients Following Resection of Primary Well-Differentiated Liposarcoma of the Retroperitoneum

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Abstract

Background.—Resection of recurrent retroperitoneal well-differentiated liposarcoma (RP-WDLPS) is unlikely to result in cure. Thus, most clinicians delay surgery after recurrence until symptom intolerance or increasing rate of disease progression. The aim of this study was to determine whether longer surveillance intervals in this population would impact outcomes or delay treatment in those who recur.

Methods.—A retrospective review of patients with primary RP-WDLPS who underwent resection between April 1996 and April 2017 and surveillance at MDACC ($n = 91$) was performed.

Results.—Median age at diagnosis of primary RP-WDLPS was 61 years; median tumor size was 30 cm. Complete resection was achieved in 85 (93.4%) patients. Among patients who underwent complete resection, recurrence occurred in 53 (60.2%) with median time to recurrence of 27.0 months. Thirty-six (69.6%) of these patients underwent resection of recurrent disease at a median 40.2 months from primary tumor resection. Surveillance imaging at 4-month (vs 3-month) intervals would not have impacted recurrence management in 84 (95.5%) patients; imaging at 6-month (vs 3-month) intervals would not have impacted management of recurrence in 80 (90.9%).

Conclusions.—Recurrence was common, often occurring beyond the early postoperative period following primary RP-WDLPS resection. More frequent surveillance imaging (q3–4 vs q6 months) in the first 2 years following primary RP-WDLPS resection may not significantly impact timing of surgery or systemic therapy for recurrence. If longer surveillance intervals were shown to be safe with equivalent outcomes in prospective studies, the resulting change in practice could lead to decreased anxiety and cost for patients and healthcare systems.

Well-differentiated liposarcoma (WDLPS) is the most common histologic subtype of soft tissue sarcoma occurring in the retroperitoneum (RP) and for which complete macroscopic

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surgical resection is the recommended treatment. Although retroperitoneal WDLPS (RP-WDLPS) has negligible potential for distant metastasis, and overall survival (OS) of patients following resection of RP-WDLPS is generally better than other soft tissue sarcoma subtypes, locoregional recurrences are common, occurring in up to 60% of patients at 5 years, and are the cause of most RP-WDLPS related deaths.[1] Regular follow-up and routine surveillance imaging to detect locoregional recurrences is the standard of care following surgical resection of primary RP-WDLPS. The decision regarding when to operate for RP-WDLPS recurrence is often a difficult one. Surgical "cure" following locoregional RP-WDLPS recurrence is unlikely and many surgical oncologists will defer surgery for recurrent disease until development of symptoms, an increase in rate of disease progression, or concern for dedifferentiation.[2] However, it is unclear whether earlier detection of locoregional RP-WDLPS recurrence improves patient outcomes.[3]

Clinicians caring for patients with RP-WDLPS have available a number of postoperative surveillance guidelines for soft tissue sarcoma. Unfortunately, these recommendations are often vague, lack supporting evidence, and/or differ from each other, resulting in significant variability in timing of postoperative surveillance between institutions and even amongst sarcoma physicians within the same institution.[1,4,5] The National Comprehensive Cancer Network (NCCN) Soft Tissue Sarcoma treatment guidelines,[5] which is the most common reference for surgeons practicing in the United States, recommends assessment with imaging with CT and/or MRI with chest X-ray (CXR) or chest CT every 3–6 months for 2–3 years, then every 6 months until year 5 and then annually. The European Society of Medical Oncology (ESMO) clinical practice guidelines recommend assessment of low-grade sarcoma patients every 4–6 months with CT scan and CXR in the first 3–5 years, then annually.[4] Although the French National Cancer Institute has similar surveillance recommendations as those from ESMO for grade 1 sarcomas, they do not recommend prolonged follow-up after 5 years.[6] The approach of the Transatlantic Australasian Retroperitoneal Sarcoma Working Group (TARPSWG), comprised of clinicians from over 35 European and North American sarcoma centers, emphasizes the need for ongoing surveillance beyond 5 years in patients who have undergone retroperitoneal sarcoma resection; for histologies that have a more indolent clinical course, such as WDLPS, it recommends surveillance with CT imaging every 6 months for 3 years followed by annual assessment.[1]

Despite the availability of published (albeit somewhat disparate) guidelines, a number of survey-based studies polling surgeons treating sarcoma patients have reported highly variable surveillance practices with respect to both follow-up intervals, surveillance imaging modalities used, and cost.[7–10] Reasons underlying practice variations were multifactorial and included the perceived recurrence risk but also surgeon specific factors such as surgeon age and training.[9]

The current consensus of the multidisciplinary sarcoma group at our institution is to examine and image patients following primary RP-WDLPS resection every 3 months for the first 2 years postoperatively. The aim of the present study was to investigate whether longer surveillance intervals (every 4 or 6 months vs 3 months) might be feasible in patients after

resection of primary RP-WDLPS without detriment to patient outcomes or delaying treatment in those who recur.

METHODS

Study Design

We performed a retrospective review of all patients with primary retroperitoneal well-differentiated liposarcoma (RP-WDLPS) who underwent surgical resection at the University of Texas MD Anderson Cancer Center (MDACC) between April 1996 and April 2017 and who received follow-up care and surveillance at MDACC. This study was approved by the Institutional Review Board of MDACC.

Data Source and Study Population

The electronic medical records of all patients with primary RP-WDLPS who underwent surgical resection between April 1996 and April 2017 were identified and reviewed. Of the records reviewed, only patients who also received follow-up care and surveillance at MDACC were included in the final study cohort ($n = 91$). Patients whose primary liposarcoma contained both well-differentiated and dedifferentiated components were excluded. Variables collected included date of diagnosis of primary RP-WDLPS, patient age at diagnosis, gender, and primary tumor characteristics including tumor size, and multifocality. Factors associated with surgical treatment of primary RP-WDLPS were collected and included number of organs resected en bloc and surgical margins (R0/R1 macroscopic complete resection vs R2 macroscopic incomplete resection).

Patient outcomes of interest included length of hospital stay (LOS) following surgical resection of primary RP-WDLPS, postoperative complications within 30 days after surgery, death within 90 days after surgery, local recurrence-free survival (LRFS), distant recurrence-free survival (DMFS), and overall survival (OS). For patients who developed recurrent disease and who underwent surgical resection, presence of multifocality and histologic subtype of recurrence were noted and time to recurrence following primary RP-WDLPS resection was determined.

The postoperative surveillance strategy for each patient was queried and documented. Variables of interest included date and time to first postoperative outpatient follow-up as well as frequency of surveillance imaging. For those patients who developed local or distant recurrence, time to recurrence was calculated from date of surgical resection of primary RP-WDLPS to date of diagnosis of recurrence. Additionally, it was noted whether the surveillance strategy, including a change in imaging interval, was shortened following diagnosis of liposarcoma recurrence. All modalities utilized for treatment of recurrent disease were documented and included whether and when the patient received systemic or radiation therapy and/or underwent surgical resection of recurrent disease.

Statistical Analysis

Descriptive statistics were used to show the distribution of variables in the study cohort.

RESULTS

Patients and Primary RP-WDLPS Characteristics

Ninety-one patients underwent resection of primary RP-WDLPS between April 1996 and April 2017 and had surveillance for disease recurrence at MDACC (Table 1). Median age at diagnosis of primary RP-WDLPS was 61 years (range, 32–83 years) with a slight male preponderance (52.7%). Median primary tumor size was 30 cm (range, 6–100 cm) and most tumors were unifocal (82.4%). All patients were treated with surgery alone, with the majority undergoing macroscopic complete resection of their primary RP-WDLPS (R0/R1 resection 93.4%). Most patients had no additional organs resected with the primary RP-WDLPS, although 13 (14.3%) had 1 organ resected, 7 (7.7%) had 2 organs resected, 8 (8.8%) patients had 3 organs resected, and 9 (9.9%) patients had 4 or more organs resected. There was no difference in number of additional organs resected with the primary RP-WDLPS between patients who underwent surgery before January 2011 ($n = 54$) and those who underwent surgery after January 2011 ($n = 39$); median number of organs resected was 0 (range, 0–5) in both time periods.

Patient Outcomes Following Primary RP-WDLPS Resection

Median length of follow-up in this cohort was 66.8 months (range, 11.2–283.5 months). Median postoperative LOS was 8 days (range, 5–37 days). Among patients who underwent macroscopic complete (R0/R1) resection ($n = 88$), 53 (60.2%) patients developed recurrent disease (Table 2) with overall median recurrence-free survival of 41.5 months (range, 2.0–283.5 months). Median time to recurrence was 27.0 months (range, 2.0–123.6 months) (Table 3). Of 53 recurrences, 30 (56.6%) were diagnosed beyond 2 years following primary RP-WDLPS resection and of these 9 (17.0%) were diagnosed beyond 5 years following primary RP-WDLPS resection. Fifty-one (96.2%) patients developed local recurrences, while 1 developed both local and distant (pulmonary) recurrences and 1 developed sarcomatosis at the time of recurrence. Thirty-six (67.9%) patients ultimately underwent surgery for first recurrence. Among patients who underwent macroscopic complete (R0/R1) resection ($n = 88$), median OS was 67.2 months (range, 11.2–283.5 months).

Patterns of Postoperative Surveillance

We next examined patterns of postoperative follow-up and surveillance in this cohort of 91 patients who underwent surgical resection of primary RP-WDLPS. During the study period, there was no consistent pattern with respect to surveillance frequency during the first 2 years following primary tumor resection, or algorithm for decreasing the frequency of surveillance (Table 1). Overall, the median time from primary RP-WDLPS resection to the first postoperative follow-up visit was 3 months (range, 0.2–14.5 months). In the first 2 years following resection of primary RP-WDLPS, most patients underwent cross-sectional imaging every 3 or 4 months [35 (38.5%) and 27 (29.7%) patients, respectively], although a significant number of patients underwent surveillance imaging more (11, 12.1%) or less frequently (18, 19.8%).

Among the 53 patients who developed recurrent liposarcoma following macroscopic complete (R0/R1) primary RP-WDLPS, the median time from resection of primary RP-

WDLPS to resection of recurrent liposarcoma was 40.2 months (range, 8.7–118.5 months) (Table 3). Diagnosis of disease recurrence was associated with an increase in frequency of surveillance imaging, occurring in 22 (61.1%) of 36 patients who ultimately underwent surgery for recurrent disease. Among these 36 patients, the median time from diagnosis of recurrence to surgery for recurrence was 6.1 months (range, 0.9–58 months) and the median number of scans between diagnosis of recurrence and surgery for recurrence was 2 scans (range, 0–13 scans) (Table 3).

Potential Impact of Postoperative Surveillance Interval on Management of Recurrent Liposarcoma

We next evaluated whether surveillance intervals of 4 or 6 months compared to 3 months would have impacted the management of patients in the first 24 months following macroscopic complete (R0/R1) resection of primary RP-WDLPS ($n = 88$) (Table 4). Frequency of surveillance imaging would not have impacted management or outcomes of the 35 (39.8%) patients who did not recur, nor of 30 (34.1%) patients who recurred after 2 years following primary tumor resection.

The remaining 23 (26.1%) patients of the initial 88 patients in this study were diagnosed with liposarcoma recurrence within the first 2 years following macroscopic complete (R0/R1) resection of primary RP-WDLPS. Among these 23 patients, 1 was found to have recurrent disease at first surveillance imaging 2.5 months after primary surgery and was initiated on systemic therapy (Adriamycin, ifosfamide, mesna) shortly thereafter. For this particular patient, surveillance imaging at 4 or 6 months would have resulted in a later diagnosis of recurrent liposarcoma and delayed initiation of systemic therapy. Four additional patients did not receive any further therapy for recurrent liposarcoma and therefore surveillance imaging every 4 or 6 months versus 3 months would not have impacted their liposarcoma management.

The remaining 18 (78.3%) of 23 patients who developed liposarcoma recurrence within the first 2 years following primary RP-WDLPS resection all underwent surgery for resection of recurrent disease. The median time between primary tumor resection and resection of recurrence in this group of patients was 21.3 months (range, 8.7–77.2 months). The median time from diagnosis of recurrence to surgery for recurrence was 10.1 months (range, 2.6–58 months). In this group of 18 patients, detection of recurrent disease was associated with an increase in imaging frequency in only 2 (11.1%) patients. Sixteen of the 18 (88.9%) patients underwent at least 1 additional surveillance visit with repeat imaging before proceeding to surgery for recurrence.

DISCUSSION

In this cohort of 91 patients who underwent resection of primary RP-WDLPS and who underwent surveillance for disease recurrence at MDACC, surveillance imaging at longer intervals versus shorter intervals (6 months vs q3 or 4 months) did not appear to significantly impact decision-making with respect to timing of surgery for resection of recurrent disease or utilization of systemic or radiation therapies. The different surveillance intervals also did not seem to have an impact on patient survival. Additionally, although recurrence was

common in this cohort, occurring in > 60% of patients who underwent macroscopic complete (R0/R1) resection of primary RP-WDLPS, the majority (56.6%) of recurrences occurred beyond the first 2 years after primary RP-WDLPS resection. The median time to recurrence was 27.0 months and 17.0% of recurrences occurred 5 years after primary RP-WDLPS resection. These results support further prospective and multi-institutional investigation into the optimal surveillance strategy and frequency for patients following primary RP-WDLPS resection.

The question of what is the optimal surveillance strategy for cancer patients following primary tumor resection is a complex one. The surveillance strategy should depend on primary tumor biology and behavior as well as availability of treatment options once recurrence is detected. Most sarcoma centers perform surveillance at 3- to 4-month intervals for high-grade retroperitoneal sarcomas, although with some variation in guidelines and clinician reported surveillance practices.[1,4,5] However, whether earlier diagnosis of recurrent disease affords patients a broader range of available treatment options, or improves overall survival, certainly requires further assessment for patients with retroperitoneal sarcomas.[3,11,12] In general, the possibility of cure after recurrence is considered to be low and surgeons need to carefully consider the potential morbidity of reoperation.[13] This likely explains the delay observed between diagnosis of recurrence and reoperation among patients who ultimately underwent resection of recurrent retroperitoneal liposarcoma in this cohort. A limitation of this study was that we were unable to determine indication(s) or surgical decision-making to proceed with surgery for recurrent disease in all cases, given the retrospective nature of this study.

Another question that remains to be addressed among the sarcoma community is how long should surveillance be continued for each histology following primary tumor resection? Toulmonde et al. examined the French Sarcoma Group database and identified 3369 patients who underwent macroscopically complete surgical resection for a localized soft tissue sarcoma between 1990 and 2009. Of these, 719 (21.3%) remained recurrence-free 5 years after initial diagnosis.[6] Of these 719 patients, 67 (9.3%) developed a late local recurrence and 42 (5.8%) developed a late metastatic recurrence.

There has been limited study on the value of various surveillance strategies for patients with retroperitoneal sarcoma. Also, there have been few studies examining the cost-effectiveness of imaging frequency and modalities for these patients. Therefore, this represents a significant unmet need and future efforts should evaluate surveillance strategies.[14]

Beyond the potential implications different surveillance strategies may have on diagnosis of recurrence and patient survival outcomes, studies in other populations of patients with cancer have demonstrated that routine follow-up visits and imaging can contribute to anxiety and cancer-related worry among patients.[15,16] There is a limited body of literature reporting on quality of life (QoL) and patient expectations among sarcoma patients, typically among patients with advanced/metastatic disease or in the orthopedic setting.[17,18] Importantly, a small number of studies have reported on psychological distress following diagnosis, during active treatment periods, and during follow-up in the sarcoma patient population.[19,20] Across studies, psychosocial distress levels have been shown to be markedly higher in the

postoperative period, and in one study of 202 patients with bone or soft tissue sarcoma, up to one third of patients demonstrated high levels of psychosocial distress even up to and beyond 2 years postoperatively.[19,21] These findings have implications for the surgeon in decision-making regarding appropriate circumstance and timing to offer surgery for recurrent disease.

Future studies to determine optimal surveillance strategies should therefore weigh not only clinical implications of timing of diagnosis of recurrent disease and impact on survival outcomes but also consider patient preferences, perhaps utilizing discrete choice and best-worst scaling research methodologies,[22–25] QoL, and cost-effectiveness. If longer surveillance intervals were shown to be safe with equivalent or improved oncologic and QoL outcomes in prospective studies, the resulting change in practice patterns could result in decreased anxiety and cost for patients and the healthcare system.

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TABLE 1

Characteristics and surveillance intervals in the first 2 years of patients with primary retroperitoneal well-differentiated liposarcoma who underwent surgical resection

Patient characteristics (*n* = 91)	
Age at diagnosis, years; median (range)	61 (32–83)
Gender, *n*	
Female	43 (47.3%)
Male	48 (52.7%)
Tumor size, cm; median (range)	30 (6–100)
Multifocal, *n* (%)	
No	75 (82.4%)
Yes	16 (17.6%)
Resection type, *n* (%)	
R0/R1	85 (93.4%)
R2	3 (3.3%)
Unknown	3 (3.3%)
Number of organs resected, *n* (%)	
0	53 (58.2%)
1	13 (14.3%)
2	7 (7.7%)
3	8 (8.8%)
4 or more	9 (9.9%)
Surveillance intervals, *n* (%)	
< Every 3 months	11 (12.1%)
Every 3 months	35 (38.4%)
Every 4 months	27 (29.7%)
Every 5 months	5 (5.5%)
Every 6 months	7 (7.7%)
> Every 6 months	6 (6.6%)

R0/R1: macroscopic complete resection; R2: macroscopic incomplete resection

TABLE 2

Outcomes of patients with primary retroperitoneal well-differentiated liposarcoma who underwent macroscopic complete (R0/R1) surgical resection (n = 88)

Patient outcomes	Median (range)
Recurrence-free survival, months	41.5 (2.0–283.5)
Recurrence	53 (60.2%)
Local	51
Sarcomatosis	1
Local and distant (lung)	1
Multifocal recurrence	28 (50%)
Histology at recurrence	
WDLPS	29 (54.7%)
DDLPS + WDLPS	13 (24.5%)
Unknown	11 (20.8%)
Overall survival, months	67.2 (11.2–283.5)

DDLPS dedifferentiated liposarcoma, *WDLPS* well-differentiated liposarcoma

TABLE 3

Management of patients with disease recurrence following macroscopic complete (R0/R1) surgical resection of primary retroperitoneal well-differentiated liposarcoma (n = 88)

Recurrence characteristics (n = 53)	**Median (range)**
Time to recurrence, months	27.0 (2.0–123.6)
Resection of recurrence	36 (67.9%)
Time from resection of primary to resection of recurrence, months	40.2 (8.7–118.5)
Time from diagnosis of recurrence to resection of recurrence, months	6.1 (0.9–58.0)
Number of scans between diagnosis of recurrence and resection of recurrence	2 (0–13)

TABLE 4

Impact of surveillance imaging interval on management of liposarcoma recurrence following macroscopic complete (R0/R1) surgical resection of primary retroperitoneal well-differentiated liposarcoma (n = 88)

Impact on management of liposarcoma recurrence	Imaging frequency	
	q4 months (vs q3 months), number of patients, (%)	q6 months (vs q3 months), number of patients (%)
No impact	84 (95.5%)	80 (90.9%)
Delayed initiation of treatment (chemotherapy)	1 (1.1%)	1 (1.1%)
Unknown impact	3 (3.4%)	7 (8.0%)

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