Original Investigation

Clinical Observations and Molecular Variables of Primary Vascular Leiomyosarcoma

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IMPORTANCE Vascular leiomyosarcomas are a rare subtype of leiomyosarcomas that most commonly affect the inferior vena cava and account for 5% of all leiomyosarcomas. These tumors are aggressive malignant tumors for which adjuvant modalities have not shown increased efficacy compared with surgery.

OBJECTIVES To evaluate the outcomes of patients with vascular leiomyosarcoma and the association between vascular leiomyosarcomas and immunohistochemical molecular markers, to determine their potential prognostic and therapeutic utility.

DESIGN, SETTING, AND PARTICIPANTS Retrospective medical record review of a cohort of 77 patients who presented to the University of Texas MD Anderson Cancer Center in Houston during the period from January 1993 to April 2012. Data were analyzed during the period from November 2012 to May 2015. All of the patients received a confirmed diagnosis of vascular leiomyosarcoma. Immunohistochemical studies for biomarkers were performed on a tissue microarray that included 26 primary specimens of vascular leiomyosarcoma.

MAIN OUTCOMES AND MEASURES Demographic and clinical factors were evaluated to assess clinical course, patterns of recurrence, and survival outcomes for patients with primary vascular leiomyosarcoma. A univariate Cox proportional hazards model was used to correlate disease-specific survival and time to recurrence with potential prognostic indicators.

RESULTS Sixty-three patients with localized disease who underwent surgical resection formed the study population, and their data were used for subsequent outcomes analysis. The median age at diagnosis was 58 years (range, 22-78 years). The majority of patients were female (41 patients [65%]) and white (51 patients [81%]). The 5-year disease-specific survival rate after tumor resection was 65%. The median time to local recurrence was 43 months, the median time to distant recurrence was 25 months, and the median time to concurrent local and distant recurrences was 15 months (P = .04). Strong expressions of cytoplasmic β-catenin (hazard ratio, 5.33 [95% CI, 0.97-29.30]; P = .06) and insulinlike growth factor 1 receptor (hazard ratio, 2.74 [95% CI, 1.14-6.56]; P = .02) were associated with inferior disease-specific survival.

CONCLUSIONS AND RELEVANCE Vascular leiomyosarcomas are aggressive malignant tumors, with high recurrence rates. Expressions of β-catenin and insulinlike growth factor 1 receptor were associated with poor disease-specific survival. Prospective studies should evaluate the clinical and therapeutic utility of these molecular markers.

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Leiomyosarcomas are the most common malignant tumors affecting the vascular system and are characterized by smooth muscle differentiation and complex genomics with evidence of genetic instability.[1,2] Vascular leiomyosarcomas more commonly arise from the venous, rather than arterial, vessels. The inferior vena cava (IVC) is the most commonly involved vein and the site of origin in more than 50% of cases.[3,4] Currently, the published literature predominately consists of small, single-institution retrospective studies focused on leiomyosarcomas involving the IVC, with reported survival rates ranging from 31% to 62%[3,5-12] and 10-year survival rates as low as 22%.[13] Incomplete resection correlates with a poor prognosis.[7] While other retroperitoneal sarcomas are plagued by local recurrences, vascular leiomyosarcomas most often recur at distant sites, with reported metastatic rates of approximately 50%,[3,5-10,14] with the lung and liver being the most common sites. Factors relating to mortality vary among the published studies, and there is no standardized therapeutic approach for this complex and rare malignant tumor.

Surgical resection remains the mainstay of treatment for vascular leiomyosarcomas. Unfortunately, the benefits of systemic therapy remain to be defined, and only minimal advancement in the treatment of this disease has been made over the past 2 decades. For retroperitoneal sarcoma, the benefit of adjuvant chemotherapy following resection is unclear, with conflicting results in multiple randomized trials.[15,16] A recent meta-analysis suggested that anthracycline/ifosfamide-containing regimens may have some benefit, although this analysis did not include several European studies with differing results.[17] Therefore, there is a need for greater understanding of the molecular biology of vascular leiomyosarcomas to provide insight into novel approaches to systemic treatment in the future.

The aims of our study were (1) to describe the natural history and clinical outcome of primary vascular leiomyosarcoma in a cohort of 63 patients treated at a tertiary cancer center in order to identify clinical and pathologic factors relating to prognosis, patterns of recurrence/metastasis, and information on survival; and (2) to identify molecular targets commonly deregulated in human specimens of vascular leiomyosarcoma using a tissue microarray to inform potential future therapeutic options.

Methods

Clinical Database

With the approval of the institutional review board of the University of Texas MD Anderson Cancer Center in Houston, we identified all patients who received a diagnosis of primary leiomyosarcoma during the period from January 1993 to April 2012. For the patients included in the tissue microarray, written informed consent was obtained. For the patients in which only clinical data were analyzed, the data were retrospectively collected under a waiver of consent/authorization approved by the institutional review board. A clinical database was constructed including patient, tumor, treatment, and outcome data. The diagnosis of vascular leiomyosarcoma was confirmed by a sarcoma pathologist at the University of Texas MD Anderson Cancer Center and in the context of multidisciplinary tumor board review. All leiomyosarcomas included in our study originated from vascular structures. In addition, to avoid including cases of vascular IVC that could represent the metastatic spread from a uterine primary tumor site, all patients with a history of surgery for another tumor or a hysterectomy were excluded. Local recurrence was considered as any recurrence at the primary site without metastasis. Clinicopathologic variables included (1) patient characteristics such as age at diagnosis (≤55 or >55 years); (2) tumor characteristics such as site, microscopic margins (R0/R1 vs R2), grade (low, intermediate, or high), and size (<5 or ≥5 cm); (3) surgical procedure; and (4) use of chemotherapy or radiation treatment. Tumor location within the IVC was described using the previously published segmental classification[3,13]: level I (infrarenal), level II (interrenal and suprarenal up to but not including the main suprahepatic veins), or level III (suprahepatic with possible intracardiac extension).

Tissue Microarray Construction and Immunohistochemical Studies

Immunohistochemical studies were performed on a previously constructed tissue microarray containing 50 vascular leiomyosarcoma specimens from 39 patients.[18] For the survival analysis, only primary tumor tissue was used for analysis (26 patients). Commercially available antibodies (eTable 1 in the Supplement) were used following standard protocols (eTable 2 in the Supplement). Horseradish-peroxidase–labeled secondary antibodies or biotinylated systems (4 plus system; Biocare Medical) were used. Scoring was performed by 2 independent pathologists (A.J.L. and E.G.D.). The biomarkers included in our microarray analysis were selected owing to their known importance in apoptosis and cell death (Bcl-2, p53, and survivin), cell survival and stress response (epidermal growth factor receptor, insulinlike growth factor 1 receptor [IGF-1R], mesenchymal epithelial transition factor, platelet-derived growth factor a, platelet-derived growth factor b, platelet-derived growth factor receptor β, β-catenin, and AXL), proliferation (Ki-67), cell cycle regulation (cyclin D1, p16, and Rb), tumor microenvironment (metalloproteinase 2 and metalloproteinase 9), and angiogenesis (vascular endothelial growth factor). Estrogen receptors, progesterone receptors, Ki67, and cyclin D1 were scored by percent nuclear expression, as low (<10% of positive tumor nuclei per sample) or high (≥10% positive tumor nuclei per sample), regardless of stain intensity. All other markers were scored on intensity as 0 (absent, or staining in <10% of tumor cells), 1 (low), 2 (moderate), or 3 (high). Samples were grouped based on expression intensity (0-1 [low] and 2-3 [high]) for statistical consideration. If the scores were discordant by only 1 category (0 vs 1 or 2 vs 3), then the scores were averaged. If they were discordant by 2 or more categories (0 vs 3, 0 vs 2, or 1 vs 3), then both pathologists looked at them together to come to an accommodation.

Statistics

Local recurrence–free survival was calculated as the time from the initial treatment to recurrence. Deaths due to disease were

treated as a disease-specific survival (DSS) end point; other deaths were considered as censored observations. The distributions of local recurrence-free survival and DSS were estimated using the Kaplan-Meier method and compared using the log-rank test. A univariate Cox proportional hazards model was used to correlate DSS and time to distant recurrence with potential prognostic indicators. $P < .05$ was considered statistically significant. All computations were performed using SPSS Statistics software, version 22 (IBM Corp).

Results

Patient and Tumor Characteristics

Seventy-seven patients presented to the MD Anderson Cancer Center with vascular leiomyosarcoma during the period from 1993 to 2012. Of these, 12 patients presented with synchronous metastatic disease, and 2 patients were found to have metastatic disease at the time of referral to our institution; all 14 patients were excluded from further analysis. The remaining 63 patients with localized disease who underwent surgical resection formed the study population, and their data were used for subsequent outcomes analysis (**Table 1**). The median age at diagnosis was 58 years (range, 22-78 years). The majority of patients were female (41 patients [65%]) and white (51 patients [81%]).

The vascular leiomyosarcomas were most often large and high-grade tumors, with 96% (46 of 48 patients for whom size was documented) being 5 cm in size or larger and 89% (24 of 27 patients for whom grade was documented in the pathology report) considered intermediate/high-grade tumors. The most common anatomic site involved was the IVC (42 patients [67%]) with 9 tumors arising from the saphenous or femoral veins, 4 from the renal vein, 3 from upper-extremity veins, and 5 from other sites (including the inferior mesenteric vein, aorta, and pulmonary artery) (Table 1).

Treatment

Treatment patterns and surgical management were assessed for the 63 patients who presented with localized disease and underwent surgical resection (Table 1). Of the 42 patients with vascular leiomyosarcomas involving the IVC, 12 (29%) underwent ligation of the IVC, whereas 30 (71%) underwent reconstruction of the IVC with primary repair, vein patch, or graft. Of the 63 patients, 15 (24%) underwent preoperative/neoadjuvant therapy, including systemic chemotherapy alone (n = 6), radiation (n = 2), or combined chemoradiation therapy (n = 7). An additional 16 patients (25%) received postoperative adjuvant therapy, including chemotherapy alone (n = 7), radiation alone (n = 7), or combined chemoradiation (n = 2). Neoadjuvant chemotherapy was used for patients for whom the possibility of R0/R1 resection was questionable, whereas postoperative chemotherapy was used for patients at high risk of recurrence (large tumors, high-grade sarcomas, or close margins [<1 cm]). Eighteen patients received radiation therapy (for a total of 10 extremity lesions and 8 intra-abdominal lesions). For the purposes of statistical analyses, adjuvant and neoadjuvant therapies were included as 1 group. The

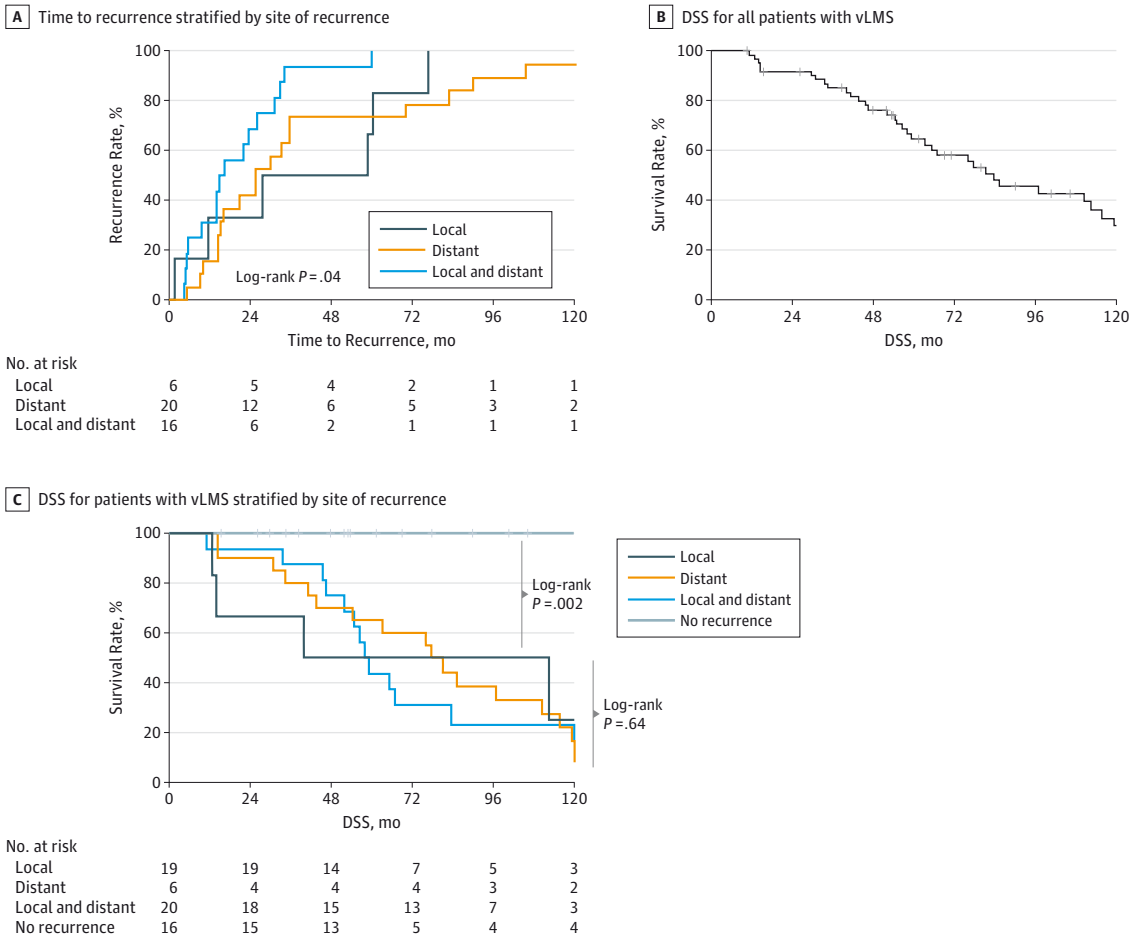
Table 1. Characteristics of Patients With Localized Disease at Presentation and Patients Included in the Tissue Microarray (TMA) With Vascular Leiomyosarcoma (vLMS)

Characteristic	No./Total No. (%)	
	Patients With Localized vLMS (n = 63)	TMA Patients With vLMS (n = 26)
Age at diagnosis, median (range), y	58 (22-78)	55 (22-77)
Sex		
Male	22/63 (35)	9/26 (35)
Female	41/63 (65)	17/26 (65)
Race		
White	51/63 (81)	18/26 (69)
African American	7/63 (11)	5/26 (19)
Hispanic	5/63 (8)	3/26 (12)
Tumor size, cm		
<5	12/58 (21)	1/26 (4)
≥5	46/58 (79)	25/26 (96)
Tumor grade		
Low	3/27 (11)	1/9 (11)
Intermediate	7/27 (26)	2/9 (22)
High	17/27 (63)	6/9 (67)
Location		
Inferior vena cava	42/63 (67)	17/26 (65)
Segment I	13/63 (21)	11/26 (42)
Segment II	26/63 (41)	6/26 (23)
Segment III	3/63 (5)	0/26 (0)
Vein		
Saphenous/femoral	9/63 (14)	2/26 (8)
Renal	4/63 (6)	4/26 (15)
Upper-extremity	3/63 (5)	0/26 (0)
Other	5/63 (8)	3/26 (12)
Primary surgery		
At outside institution	37/63 (59)	26/28 (93)
At MDACC	26/63 (41)	2/28 (7)
Resection status		
R0/R1	37/46 (80)	21/25 (84)
R2	9/46 (20)	4/25 (16)
Treatment		
Surgery alone	33/63 (52)	11/26 (42)
Surgery and chemotherapy	13/63 (21)	9/26 (35)
Preoperative	6/63 (10)	3/26 (12)
Postoperative	7/63 (11)[a]	7/26 (27)
Surgery and radiation	9/63 (14)	0/26 (0)
Preoperative	2/63 (3)	0/26 (0)
Postoperative	7/63 (11)	0/26 (0)
Surgery, chemotherapy, and radiation	9/63 (14)	6 (23)
Multivisceral resection	16/63 (25)	
Kidney	13/63 (21)	8/26 (31)
Adrenal gland	11/63 (17)	5/26 (19)
Liver	1/63 (2)	1/26 (4)
Intestine	2/63 (3)	1/26 (4)
Recurrence		
Local only	6/63 (10)	3/26 (12)
Distant only	16/63 (25)	6/26 (23)
Local and distant	20/63 (32)	6/26 (23)

Abbreviation: MDACC, MD Anderson Cancer Center.

[a] One patient received preoperative and postoperative chemotherapy.

Figure 1. Kaplan-Meier Estimate of Time to Recurrence and Sarcoma-Specific Survival Stratified by Recurrence Type



DSS indicates disease-specific survival; vLMS, vascular leiomyosarcoma.

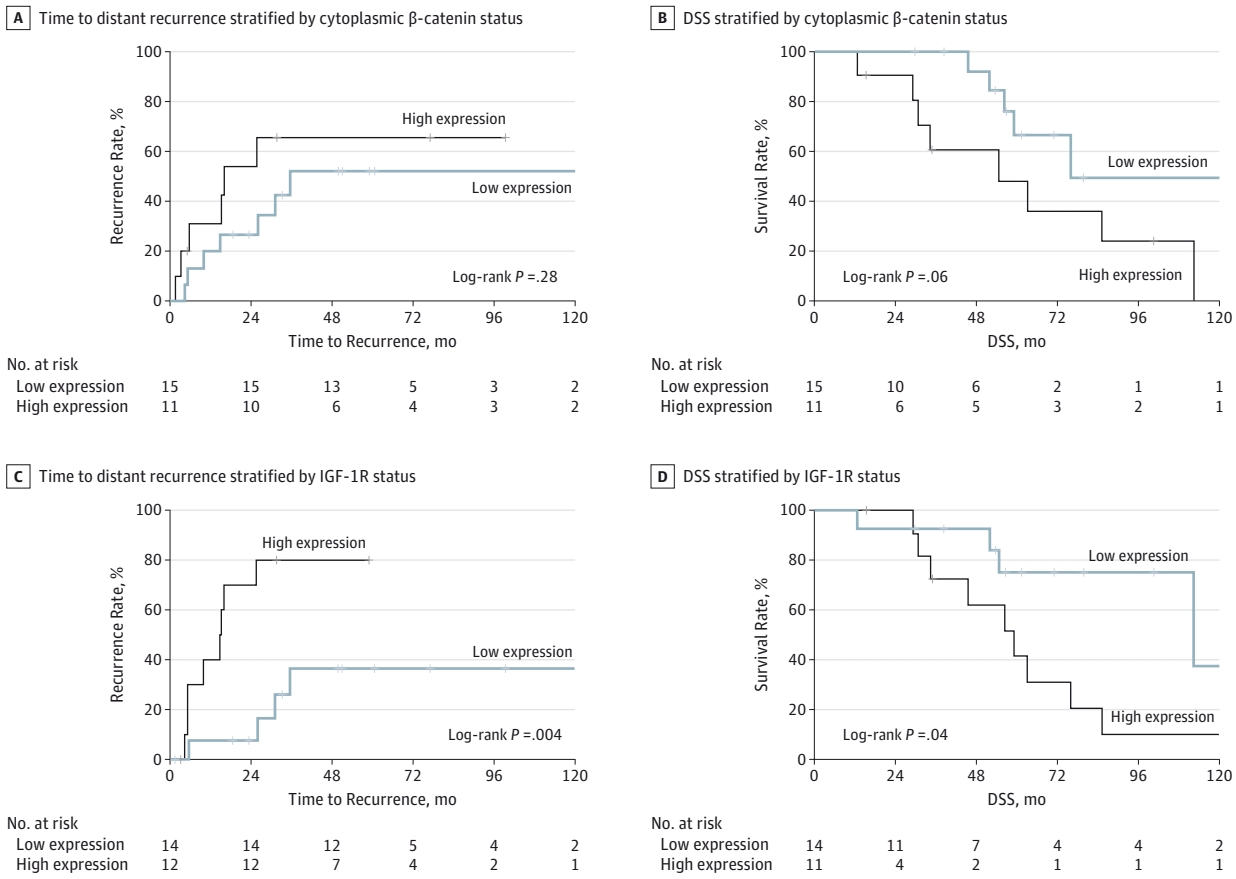
chemotherapy regimens varied; 9 of 22 patients (41%) were treated with some combination of doxorubicin hydrochloride and ifosfamide, and 7 of 22 patients (32%) were treated with gemcitabine hydrochloride and docetaxel.

Vascular Leiomyosarcoma–Specific Recurrence, Metastasis, and Survival

At a median follow-up of 5.1 years (range, 0.87-13.9 years), 42 of 63 patients (66%) developed recurrent disease (local and/or distant) at a median time to recurrence of 33 months. Six patients developed a local recurrence only, 16 patients developed distant recurrences only, and 20 patients developed synchronous local and distant recurrences (Table 1). The median time to local recurrence was 43 months, and the median time to distant recurrence was 25 months (**Figure 1**A). Interestingly, patients who presented with synchronous local and distal disease had a median time of 15 months (P = .04) (Figure 1A). The majority of distant metastases were to the lung (15 of 36 patients [42%]), liver (11 of 36 patients [31%]), bone (8 of 36 patients [22%]), abdomen (6 of 36 patients [17%]), and other sites (7 of 36 patients [19%]), including brain and soft tissue.

The estimated DSS rate for the 63 patients who presented with localized disease was 96% at 1 year and 65% at 5 years (Figure 1B). Patients without recurrent disease demonstrated improved sarcoma-specific survival compared with patients with recurrent disease (Figure 1C). However, the estimated DSS rates were similar regardless of the type of recurrence (local vs distant). The estimated 2-year DSS rate was 100% for patients with no recurrence, 66.7% for patients with local recurrence, 90% for patients with distant recurrence, and 93.7% for patients with local and distant recurrence, and the estimated 5-year DSS rate was 100% for patients with no recurrence, 50% for patients with local recurrence, 65% for patients with distant recurrence, and 43.7% for patients with local and distant recurrence. Univariate analyses of patient, tumor, and treatment characteristics failed to demonstrate any significant difference in the estimated DSS rates, although there was a trend toward improved survival in the patients who underwent surgery and radiation (hazard ratio, 0.43 [95% CI, 0.19-1.01]; P = .05). The limited number of patients in each group precluded any definite conclusion regarding the site of origin. Therefore, the subset analysis based on site or origin was omitted.

Figure 2. Kaplan-Meier Estimate of Time to Recurrence and Sarcoma-Specific Survival Stratified by Protein Expression Levels



DSS indicates disease-specific survival; IGF-1R, insulinlike growth factor 1 receptor.

Table 2. Prognostic Factors for Leiomyosarcoma-Specific Mortality and Distant Recurrence in 26 Primary Tumors Treated With Surgical Resection

	Recurrence-Free Survival				Disease-Specific Survival		
Protein	Tumor, No.	Median Time to Recurrence, mo	HR (95% CI)	*P* Value	Median Survival, mo	HR (95% CI)	*P* Value
Cytoplasmic β-catenin							
Negative	15	35.4	1 [Reference]	.69	75.9	1 [Reference]	.06
Positive	11	15.9	1.37 (0.29-6.54)		54.6	5.33 (0.97-29.30)	
IGF-1R							
Negative	14	None reported	1 [Reference]	.02	112.2	1 [Reference]	.02
Positive	12	15.1	2.74 (1.14-6.56)		59.2	2.74 (1.14-6.56)	

Abbreviations: HR, hazard ratio; IGF-1R, insulinlike growth factor 1 receptor.

Immunohistochemical Analysis of Tissue Microarrays

The association between several biomarkers, distant recurrence, and DSS was evaluated (eTables 1 and 2 in the Supplement). The high expression of cytoplasmic β-catenin was associated with higher distant recurrence rate and reduced disease-specific survival (**Figure 2**A and B; **Table 2**). Expression of elevated levels of IGF-1R was associated with reduced sarcoma-specific survival and a shorter time to distant recurrence (Figure 2C and D; Table 2).

Discussion

The present study includes a homogeneous group of patients with vascular leiomyosarcoma treated at a single institution. The majority of patients in this cohort developed recurrent disease, most commonly distant metastases. The time to recurrence varied based on the type of recurrence, with distant recurrences occurring earlier than local recurrences (*P* = .04).

Expression of β-catenin and IGF-1R was associated with reduced sarcoma-specific survival, and high expression of IGF-1R was associated with reduced time to distant recurrence.

The population in our study is consistent with previously published studies demonstrating a preponderance of large tumors in female patients in their sixth decade and a large proportion of high-grade tumors.[10] A large majority of our patients had tumors arising in the IVC, as seen in other published series.[6,7,9] Reported 5-year survival rates range from 31% to 63%.[3,5-10] Our result were similar, with a 5-year DSS rate of 65% and a 5-year recurrence-free survival rate of 35%. Of the 63 patients who presented with localized disease, 33 (52%) were treated with surgery alone. Of patients receiving multimodality treatment, approximately half received their adjuvant treatment prior to surgical resection. There was a trend toward improved survival with the addition of adjuvant therapy (chemotherapy and/or radiation) to macroscopically margin-negative surgery (hazard ratio, 2.13 [95% CI, 0.99-4.62]; $P = .05$), which echoes the findings of other small case series.[6] However, definitive support for the routine use of radiation in this patient population is lacking, and our study was limited in its ability to establish the possible benefits of radiation therapy for patients with vascular leiomyosarcoma owing to the small sample size. These findings need to be explored in larger multi-institutional patient cohorts. Currently, the utility of preoperative radiation for patients with retroperitoneal sarcomas is being examined in the STRASS (Surgery With or Without Radiation Therapy in Treating Patients With Previously Untreated Non-metastatic Retroperitoneal Soft Tissue Sarcoma) study, which includes patients with leiomyosarcoma (NCT01344018), as well as a variety of other histologies, and seeks to address the question of the benefit of radiation for patients with these unique tumors in a randomized, prospective fashion.

We found that the 5-year recurrence-free survival rate for patients with local vascular leiomyosarcoma was 35%. This was slightly lower than the 5-year recurrence-free survival rate of 42% observed for patients with uterine leiomyosarcoma reported previously from our institution.[19] However, similar to other series, we observed that patients with vascular leiomyosarcoma who underwent multimodality therapy, including radical resection and radiation, had a better 10-year survival rate than patients with uterine leiomyosarcoma (41% vs 27%, respectively).[6,19]

Technical difficulties associated with complete tumor eradication by local treatment alone encourage the development of novel systemic treatment regimens for leiomyosarcomas. The use of doxorubicin for metastatic leiomyosarcoma has been associated with an improvement in progression-free survival,[20] although, in other studies of leiomyosarcomas, lower response rates to doxorubicin- or epirubicin-containing regimens have been reported.[21] In addition, gemcitabine plus docetaxel has shown some efficacy in patients with unresectable vascular leiomyosarcoma, with a 53% response rate.[22] However, given the variability in the literature and the lack of effective adjuvant treatments, there is still the need to identify new targets of therapy.

To understand the underlying molecular biology of vascular leiomyosarcomas, an immunohistochemical vascular leiomyosarcoma microarray was constructed as previously described[19] and used to analyze 26 primary tumor samples from patients who underwent surgical resection. Increased expression of cytoplasmic β-catenin within the primary tumor sample correlated with poorer disease-specific survival in univariate analysis (hazard ratio, 5.33 [95% CI, 0.97-29.3]; $P = .06$). β-Catenin is a downstream signaling protein in the canonical Wnt pathway, which is involved in both embryogenesis and oncogenesis and may also mediate effects via modulation of cell-cell adhesion through the cadherin family of transmembrane proteins.[23] Moreover, β-catenin–mediated signaling is known to play a role in other mesenchyma tumors, including desmoid fibromatosis and synovial sarcoma.[24] High levels of nuclear β-catenin and total β-catenin have been seen in a number of high-grade sarcomas, including leiomyosarcomas.[25-27] Targeted therapy against Wnt signaling is an active area of oncologic investigation,[28] and monoclonal anti-Wnt-1 antibody therapy has demonstrated cytotoxic effects in in vitro models of sarcoma.[29] There are a small number of molecules indirectly targeting the Wnt signaling pathway under evaluation for use in human disease; however, no trials of targeted therapies are ongoing in sarcoma. Further studies of the role of β-catenin in vascular leiomyosarcoma and the potential for targeted therapy in this context are required.

We found that a high level of IGF-1R expression in vascular leiomyosarcomas was associated with a shorter DSS and time to distant recurrence (Table 2). Similarly, it has been reported that about half of leiomyosarcomas involving the skin, stomach, intestine, and abdominal wall express IGF-II at a high level compared with leiomyomas involving the myometrium.[30] Taken together, these findings suggest a role for IGF-mediated signaling in the progression of leiomyosarcoma and a potential therapeutic target for aggressive tumors. Of note, several phase I and phase II clinical trials have examined the role of IGF-1R blockade in other complex karyotype soft-tissue sarcomas.[31,32] Recently, a phase I/phase II trial of combined IGF-1R antibody blockade in combination with mechanistic target of rapamycin blockade has been examined because of the complementary mechanisms of action of these targeted therapies.[33,34]

Overexpression of β-catenin in uterine leiomyosarcoma has been shown to be associated with recurrent disease.[19] In vascular leiomyosarcoma, β-catenin expression was also associated with recurrence. In vascular leiomyosarcoma and contrary to uterine leiomyosarcoma, survivin was not found to be associated with recurrence, and bcl-2 was not found to be a prognostic factor of DSS. These molecular differences may reflect subtle unique molecular variants between uterine leiomyosarcoma and vascular leiomyosarcoma.

Our study has several limitations, including the small sample size, retrospective design, long treatment interval, and the variability in the use of chemotherapy and radiation therapy. However, we feel that these limitations did not greatly affect the results of our study.

Conclusions

In conclusion, and to the best of our knowledge, we report on the largest series of patients with vascular leiomyosar-

coma. The tumors that we observed frequently behaved in an aggressive fashion with early distant metastases. Although we were unable to find significance in many treatment variables, likely owing to the disease's heterogeneity, we did find correlation between the proteins β-catenin and IGF-1R and worse outcomes, which suggests further avenues of investigation into the biology of the disease and targeted therapy.

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