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Uterine Leiomyosarcoma Management, Outcome, and Associated Molecular Biomarkers: A Single Institution's Experience

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Abstract

Background—Uterine leiomyosarcoma (ULMS) is an aggressive, rapidly progressive tumor lacking clinical and molecular predictors of outcome.

Methods—ULMS patients (n = 349) were classified by disease status at presentation to MDACC as having intra-abdominal (n = 157) or distant metastatic disease (n = 192). Patient, tumor, treatment, and outcome variables were retrospectively retrieved. Formalin-fixed, paraffin-embedded tumor and control tissues from these patients (n = 109) were assembled in a tissue microarray and evaluated for hormone receptors and markers of angiogenesis, cell-cycle progression and survival. Patient, tumor, and treatment variables were correlatively analyzed.

Results—The 5- and 10-year disease-specific survival (DSS) for the cohort was 42 and 27 %, respectively. Patients with primary intra-abdominal tumors had better outcomes than those with

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recurrent intraperitoneal tumors. Whites had a more favorable prognosis. In patients with intra-abdominal tumors, only mitotic count >10M/10HPF portended poorer prognosis. Patients with pulmonary metastasis had improved outcomes with "curative" metastasectomy. ULMS samples exhibited loss of ER and PR expression, overexpressed Ki-67, and altered p53, Rb, p16, cytoplasmic β-catenin, EGFR, PDGFR-α, PDGFR-β, and AXL levels. Metastatic tumors had increased VEGF, Ki-67, and survivin expression versus localized disease. Survivin and β-catenin expression were associated with intraperitoneal recurrence; high bcl-2 expression predicted longer DSS.

Conclusions—Analysis of both clinicopathologic factors and immunohistochemical biomarkers in ULMS identified several prognostic clinical and molecular factors, suggesting that further study may lead to improved ULMS understanding and treatment.

Uterine leiomyosarcoma (ULMS) comprises 1–3 % of uterine cancers. Poor 5-year ULMS survival rates of 30–65 % account for their contribution to ~25 % of uterine cancer-related deaths.[1–5] Surgical excision is the therapeutic mainstay for localized and isolated metastatic ULMS. Despite aggressive surgery, intraperitoneal recurrence (IPR), and/or distant metastasis occur in more than 50 % of cases, resulting in poor overall survival of 28.4 months for IPR disease and 12.5 months for distant metastases.[3–8] Neither adjuvant chemotherapy/radiotherapy nor investigative molecular therapeutics have shown better than modest survival effects in high-risk localized and metastatic disease.[9–11]

The search for theragnostically relevant ULMS biomarkers has failed to yield consistent results. In small patient cohort retrospective reviews, the only consistent reported prognostic factor is disease stage at diagnosis, while age and mitotic count have been variably reported as prognostic indicators.[5,12–14] No definitive therapeutic biomarkers have been confirmed, although many promising candidates have been proposed, including factors involved in apoptosis (p53, MDM2, Bcl-2), cell-cycle regulation (Rb, p16), invasion (MMP-2, MMP-9), metastasis, and growth factor/angiogenic signaling (PDGF, PDGFR, VEGF, etc.).[10,15]

An increased understanding of leiomyosarcoma biology is needed to improve therapeutics. We assembled a large, single-institution ULMS patient database and annotated tissue microarray (TMA) in order to identify theragnostic biomarkers relevant to ULMS patients.

MATERIALS AND METHODS

Clinical Database

Records of 349 ULMS patients evaluated at the University of Texas MD Anderson Cancer Center (UTMDACC) between January 1989 and April 2011 were reviewed after Institutional Review Board approval. A clinical database was constructed including patient, tumor, and treatment variables and outcome data. Patients were not routinely staged because many presented with recurrent disease or after resection of primary disease. For our purposes, IPR was defined as any intra-abdominal recurrence, including both local recurrence at the site of prior resection and peritoneal spread due to tumor seeding, due to the impossibility in many cases of distinguishing an implant caused by peritoneal adhesions to a large primary tumor from those caused by tumor cell seeding due to disruption of tumor capsule.

Tissue Microarray

The ULMS TMA has been previously described and contains 208 available archived formalin-fixed, paraffin-embedded ULMS tissues from 109 patients, including primary (n = 18), IPR (n = 66), and metastatic ULMS (n = 124).[16,17] The 35 controls included

gastrointestinal smooth muscle (n = 10), healthy myometrium (n = 15), and benign leiomyoma (n = 10).

Immunohistochemistry

Immunohistochemistry was performed using commercially available antibodies (Supplementary Table 1), following standard automated and manual protocols (Supplementary Table 2). Horseradish-peroxidase labeled secondary antibodies or biotinylated systems (4 plus system Biocare Medical, Concord, CA) were used. Scoring was performed by 3 independent investigators (AJL, EGD, and KBS). ER, PR, Ki67, and cyclin D were scored by percent nuclear expression, as low (<10 % of positive tumor nuclei/sample), or high (≥10 % positive tumor nuclei), regardless of stain intensity. All other markers were scored on intensity as 0 (absent), 1 (weak), 2 (moderate), or 3 (strong). For statistical consideration of intensity expressions, samples were grouped 0–1 (“weak”), and 2–3 (“strong”).

Statistical Analysis

Correlations between TMA biomarker expression and tumor or disease status were calculated using the Fisher exact test. In cases with multiple TMA cores, only the paired cores with the highest grade area were considered for biomarker analysis (n = 208). In order to predict disease progression and poor outcomes in early-stage disease, the earliest occurring intraperitoneal tumor on the TMA was used (n = 57) for biomarker outcomes analysis. Univariable and multivariable Cox proportional hazards model were used to analyze disease-specific survival (DSS), recurrence-free survival (RFS), and metastasis-free survival (MFS). All computations were completed with SAS for Windows (release 9.2; SAS Institute, Cary, NC). DSS was defined as death due to disease according to medical records or death certificate, or death within 1 year of disseminated disease when specific records were not available. RFS survival was determined by the date of IPR, and MFS by the date of distant metastatic lesion diagnosis.

RESULTS

The median age of 349 study patients was 52 years (range 19–83 years); 157 (45 %) had intra-abdominal disease, and 192 patients (55 %) had distant metastases. The median follow-up was 35.5 months (range 18–16.7 years); survivors had a median follow-up of 46.4 months (range 1 month–16.7 years). The 5- and 10-year DSS for all patients was 42 and 27 %, respectively (Fig. 1a).

Intra-abdominal Tumors—Patient, Tumor, Treatment Variables

Clinicopathologic features of patients with intra-abdominal disease are presented in Table 1. Intra-abdominal tumors were either primary (71 %) or recurrent (29 %). Patients were typically white (74 %) with a history of pregnancy (80 %); a minority (28 %) received hormone replacement therapy (HRT) prior to diagnosis. Mean tumor diameter was 10.6 cm (range 1–60 cm) for primary tumors and 9.6 cm (range 2–30 cm) for recurrences. Primary tumors had a mean mitotic activity of 21 mitoses/10 high-power fields (M/10HPF) (range 1–83).

All primary tumors and 36 IPR (80 %) were treated with surgical resection. Of these, 96 patients underwent tumor resection prior to UTMDACC referral, and 50 were resected at UTMDACC. The 9 recurrences were not excised because of unresectability (n = 8) or prohibitive medical comorbidities (n = 1). Margin status was negative in 72 of 148 (49 %) and positive (gross or microscopic) in 24 %.

Only 16 % of patients with intra-abdominal disease were treated with radiation therapy. There were 4 patients who received neoadjuvant radiotherapy (1 with a primary tumor and the remaining 3 with IPR). A total of 21 patients received postoperative radiation: 19 of 112 primaries and 2 of 25 IPR; 1 patient received intraoperative radiotherapy. Postoperative treatment information was unavailable on 2 patients due to lapsed follow-up. Due to the limited number of patients who received radiation therapy, further analysis was not performed on this cohort.

A total of 91 patients received chemotherapy: 25 intra-abdominal tumors received neoadjuvant chemotherapy (3 primary tumors, 22 IPR); 72 received adjuvant (14 primary tumors, 58 IPR); 7 received both neoadjuvant and adjuvant chemotherapy. Chemotherapeutic regimens were usually doxorubicin/ifosfamide (AI)-based (n = 43), gemcitabine/docetaxel (GT)-based (n = 22), or included a combination of these 2 regimens (n = 15). Only 8 of 91 patients received a regimen based neither on AI nor GT. Refractory patients received a variety of conventional cytotoxic or experimental therapeutics. No significant survival differences were seen between treatment groups (AI, GT, both or neither) (data not shown).

Intra-abdominal Tumors—Survival, Recurrence, Metastasis

DSS—Patients presenting with intra-abdominal disease had 5- and 10-year DSS of 58 and 42 % (Fig. 1b) over a median follow-up of 42.0 months (range 3 months–16.7 years) (Table 1). In univariable analysis (Table 2), white race predicted improved DSS (p = 0.002) vs. other races (black, Hispanic, Asian, and Indian), as did microscopically negative resection margins (p = 0.003) and mitotic count <10M/10HPF (p = 0.030). Increasing tumor size predicted worse DSS (p = 0.046) as a continuous variable. IPR status at (p <0.0001) or after (p = 0.003) presentation to UTMDACC were also associated with worse DSS; the latter remained an independent prognosticator on multivariable analysis (p = 0.011) when mitotic count and surgical margins were excluded for low retrievable data counts (Fig. 1c).

RFS—The overall IPR rate after presentation to UTMDACC (including those with a history of prior IPR) was 51 %, with a median time to recurrence of 24.6 months (range 1–86 months). The 5- and 10-year RFS were 42 and 40 %, respectively (Fig. 1d). Notably, patients who presented to UTMDACC with IPR had shorter median time to re-recurrence (19.9 months [range 1–47 months]) compared with those with primary lesions (median 30.0 months, range 1 month–7.2 years), as well as a higher overall rate of recurrence (69 vs. 44 %, p <0.001) (Fig. 1e).

IPR on presentation to UTMDACC (p <0.001), increasing tumor size (p = 0.001), and chemotherapy treatment (p = 0.002) predicted worse RFS in univariate analysis. Conversely, negative surgical margins were strongly associated with improved RFS (p <0.0001). However, only >2 prior recurrences remained an independent prognosticator on multivariable analysis (hazard ratio [HR] = 5.0, 95 % confidence interval [95 % CI]: 2.50–10.01; p <0.0001).

MFS—Distant metastases developed in 41 % of patients with intra-abdominal disease. Median time to metastasis was 29.9 months (range 2 months–8.3 years), with 5- and 10-year MFS of 51 and 41 %, respectively (Fig. 1f). There were no significant differences in MFS between primary and IPR. Only increasing mitotic count emerged as a significant risk factor (HR = 2.99, 95 % CI: 1.17–7.62; p = 0.0219) in univariate analysis, but did not remain independent on multivariable analysis.

Distant Metastatic Disease—Patient, Tumor, Treatment Variables

A total of 192 patients presented to UTMDACC with distant metastatic disease (Table 3). Overall demographics were similar to the local patient cohort. Concurrent intra-abdominal (primary or recurrent) tumors were present in 104 cases (54 %). Metastasis most frequently involved a single organ (80 %), especially the lungs (32 %). Other sites included bone, liver, subcutis, and solid organs (Supplementary Table 5). Most patients (90 %) received chemotherapy, typically AI-based (n = 53), GT-based (n = 34), or both (n = 78). Only 6 patients received none of these (data not shown). Less frequently dacarbazine, cisplatin, or trabectedin were used as a last-line therapy. Of the 13 patients not receiving chemotherapy, 1 died prior to treatment, 8 had no evidence of disease after complete surgical resection, 1 had prohibitive medical comorbidities; the reason was unclear for 3. Patients who received both AI and GT tended to have shorter survival than the remainder of patients treated with any other regimen (data not shown). Metastasectomy with curative intent was used for nearly 50 % of patients for sites including subcutis, lung, liver, and femur. Spinal lesions received palliative surgery or radiation therapy only.

Distant Metastatic Disease—DSS

The median follow-up for the metastatic cohort (Table 3) was 32.3 months (range 1 month–15.1 years). The 5- and 10-year DSS were 30 and 15 %, respectively. Negative prognosticators on univariable analysis (Table 4) included: presence of multiple tumors, including synchronous intra-abdominal lesions (p = 0.01); multiple lesions within a single organ (p = 0.03); multiple organs with lesions (p = 0.002); and the presence of pulmonary metastases alone (p = 0.005). As with local tumors, treatment with chemotherapy portended worse DSS (p = 0.02). Both white race and surgery with curative intent were associated with improved DSS (p = 0.014 and p <0.0001, respectively). On multivariable analysis, pulmonary metastases (p = 0.02) and surgery with curative intent (p <0.0001) remained independent predictors of survival.

Biomarker Analysis

Immunohistochemical staining of the ULMS TMA revealed differential expression of a number of biomarkers compared to non-neoplastic controls (Supplementary Table 3, Supplementary Fig. 1), including loss of ER (p <0.0001), PR (p = 0.003), and PDGF-A (p = 0.0001) and overexpression of Ki-67 (p <0.0001), nuclear survivin (p = 0.007), p53 (p = 0.0006), Rb (p = 0.004), p16 (p <0.0001), cytoplasmic β-catenin (p <0.0001), EGFR (p = 0.023), PDGFR-α (p <0.0001), PDGFR-β (p = 0.0127), PDGF-B (p = 0.0036), and Axl (p = 0.01). Interestingly, KIT and MET, previously suggested to be involved in LMS, were not commonly expressed.[18,19]

Advanced tumors (IPR and distant metastatic) demonstrated increased expression relative to primary tumors of proliferation markers Ki-67 (78 vs. 50 %; p = 0.0035) and p16 (84 vs. 56 %; p = 0.019), as well as elevated VEGF (75 vs. 54 %; p = 0.015).

Biomarker Association with Outcome

To identify potential prognostic biomarkers, correlation of expression with outcome was performed in intra-abdominal tumors (n = 57) (Supplementary Table 4). Poor RFS was predicted by elevated cytoplasmic (HR = 3.78, p = 0.002) and nuclear (HR = 2.35, p = 0.0144) survivin expression, cytoplasmic (HR = 1.58, p = 0.0369) and nuclear (HR = 5.81, p = 0.001) β-catenin expression, and PDGF-B expression (HR = 2.12, p = 0.0193). In contrast, elevated MMP-9 (HR = 0.57, p = 0.0251) and PDGF-B expression (HR = 0.30, p = 0.0439) predicted reduced MFS, while improved DSS was related to high Bcl-2 expression (HR = 0.61, p = 0.0284).

DISCUSSION

Our study represents one of the largest reported ULMS experiences and demonstrates similar clinicopathologic features and poor outcomes as prior series.[4–6] It was hoped that the large size of our series would enable improved insight into prognostic biomarkers of disease progression. However, we were ultimately able to confirm only a few critical prognosticators. It may be that the complexity and genetic diversity of ULMS requires deeper data mining to identify specific subsets of cases with distinct patterns of behavior.

Demographically, only white race was identified as a (positive) prognosticator for DSS. Similarly, the 2008 SEER analysis also implicated race, with African American patients demonstrating worst survival compared with their non-African-American counterparts.[12] However, in our analysis, race was not significant in multivariable analysis, implying that it was not an independent prognosticator in either intraperitoneal or metastatic disease. It may be, then, that white patients are predisposed to less aggressive tumors or may overall receive different therapy. Further investigation into biological correlates with respect to race might address these queries.

Localized tumors at high risk for intra-abdominal recurrence were large, incompletely resected, treated with chemotherapy, and often had a history of previous IPR—all factors likely indicative of poor local control or widespread peritoneal seeding. In contrast, only high mitotic activity (an indicator of aggressive tumor growth) predicted MFS. DSS was predicted by a combination of these factors with the addition of race, initially suggesting that both local and distant spread impacted survival. This was confirmed on multivariate analysis for DSS, where, after exclusion of mitotic counts and margins (due to an incomplete data set) only prior history of IPR remained an independent predictor of survival, highlighting the importance of complete surgical resection by an experienced surgeon at the time of initial operation.

We defined IPR to include both recurrence at the site of prior surgical excision as well as intra-abdominal spread, because in many cases, large tumors were adherent to multiple peritoneal sites at the time of primary surgery, and it was not possible to distinguish true local recurrence from peritoneal seeding. Thus, in our population IPR may include more aggressive tumors than reported in other series; this could account for why IPR was not previously reported as a prognostic factor.[6] Importantly, IPR developed more rapidly than distant hematogenous metastasis (mean 24.6 vs. 29.9 months) and were prone to re-recur, thus resulting in an escalating cycle of bulky peritoneal disease.

As discussed previously, most of the factors associated with recurrence in intra-abdominal tumors can be related to tumor resectability. Size is a predictive factor in other series, with size>11 cm being an independent predictor of death (HR of 11.63) in one such study.[3,12–14] This likely reflects the difficulty in complete excision of bulky tumors in the pelvis, especially those with multiple adhesions, while positive resection margins are a well-known risk factor for IPR.[20,21]

Aggressive tumor behavior is also reflected in proliferative ability or mitotic count. Increasing mitotic count has been correlated to increased IPR and decreased DSS, with one review citing no recurrences in tumors <10M/10HPF, and up to an 80 % disease-free survival (DFS) in tumors with <10M/10HPF, compared with a 20 % DFS in tumors with >20M/10HPF.[9,12,22] We found that mitotic count (in primary tumors only) was a risk factor for poor DSS and MFS but not RFS. It was not an independent factor on multivariable analysis, likely due to the limited patient number.

Chemotherapy use correlated with worse outcomes in both intra-abdominal and metastatic cohorts in univariate analysis, reflecting a selection bias favoring chemotherapy administration for more aggressive or advanced tumors. Moreover, we found no significant survival differences between the treatment groups in intraperitoneal disease, although multiple confounders within the chemotherapeutic regimens (i.e., dose/cycle number variations, midcycle changes), render interpretation of this data problematic at best. However, the trend toward shorter survival in meta-static patients who received both AI and GT may reflect a switch of chemotherapy regimen reacting to a patient's nonresponse to the original agent and thus is already inclined to a worse outcome.

Only 13 patients with metastases did not receive chemotherapy; of these, 8 had completely resectable metastases, which may account for the association of no chemotherapy with better prognosis. Similarly, improved DSS resulted from curative metastasectomy, emphasizing the importance of definitely reducing tumor burden and supporting the findings of Burt et al.[23] that resection of pulmonary metastases leads to improved long-term survival. Furthermore, high tumor burden in the form of multiple metastases in single or multiple organs, or concurrent intra-abdominal and metastatic disease were all associated with worse DSS. Multiple lesions are less likely to be durably resected, reflecting more aggressive behavior of widely disseminated ULMS. Notably, of patients presenting with distant metastases, the survivors at 10 years all underwent surgical resection with curative intent, with disease limited to a single organ at presentation, most commonly the lung. At least 2 patients had undergone hysterectomy many years earlier, although ULMS may have only been diagnosed in retrospect, suggesting the possibility of more indolent disease and low tumor burden in these cases.

Although patients with pulmonary lesions may be resectable via wedge resection or lobectomy, in our series pulmonary disease was associated with worse DSS. While no studies specific to ULMS have reported on the prognostic importance of pulmonary metastasis, there are reports that lung metastases portend a shorter survival than metastases to other sites in univariate analysis of metastatic soft tissue sarcomas; this was not significant in multivariate analysis.[24] In contrast, no difference was found in survival between pulmonary and non-pulmonary metastasis in a study of extremity soft tissue leiomyosarcomas.[25]

Our findings could be related to a number of factors, including disease burden—wherein patients with pulmonary metastasis often had multiple synchronous lung tumors or rapidly developed additional nodules following metastasectomy or even to as-yet-unknown factors specific to ULMS. However, at the present time, such theories remain speculative only.

We also assembled a large, clinically annotated TMA that reflected UTMDACC referral patterns, with 18 primary and more than 100 metastatic cases. Because this TMA favors advanced stage ULMS, it was expected to be useful for identifying therapeutically relevant biomarkers of aggressive disease. Surprisingly, very few of the biomarkers investigated showed significant alterations relative to primary tumors, possibly due to the small number of available primary tumors. We did show VEGF overexpression in metastatic tumors. Anti-VEGF therapies have already been used in ULMS clinical trials with modest effect.[26] Further investigation into whether this overexpressed growth factor is active in ULMS would be warranted to confirm it is a viable therapeutic target, particularly in distant metastatic tumors. Ki-67 and p16 elevations likely reflect overall increased dysregulation of survival/proliferation pathways and are probably not relevant to targeted therapy.[27,28]

The role of immunohistochemical biomarkers in prognostication remains unclear. While survivin and β-catenin expression correlated to RFS, neither the link between these factors

and clinicopathologic prognosticators nor their potential role in promoting recurrence has been fully explored. However, our findings are supported by prior reports that nuclear β-catenin overexpression is a risk factor in LMS.[29,30]

We found that elevated Bcl-2 (seen in 42 % tumors) predicted longer DSS. Expression patterns were similar to those of Zhai et al., who found Bcl-2 to be expressed in only 43 % of ULMS.[31] The role of Bcl-2 in LMS behavior is a matter of some debate. While some have found Bcl-2 expression to be a negative risk factor, we and others showed it to correlate with favorable outcomes.[32,33] Mechanisms underlying this association remain to be elucidated.

It is possible our biomarker analysis would have yielded more significant results had a larger number of primary tumors been available. As a tertiary referral center the majority of our tumor specimens consists of advanced stage tumors, which are increasingly heterogenous. In IPR too, the alterations that have rendered these tumor more aggressive have already occurred, and it is therefore difficult to select out markers within this subset that have additional prognostic value. Further analysis of a larger cohort of primary tumors would aide us in identifying prognostically relevant biomarkers for disease progression.

In conclusion, unlike prior studies, we specifically compared primary versus IPR disease in order to study factors affecting ULMS patient survival. We showed that IPR are rapidly aggressive, with poor 5-year DSS, and that synchronous intra-abdominal tumors within stage IV patients portend a worse prognosis than in patients with isolated metastatic disease in a single organ. Moreover, IPR at presentation to our tertiary care center resulted in much more rapid decline than seen in patients presenting with primary tumors. Overall, our findings suggest that 5-year prognosis is largely dependent on IPR, while long-term survival depends on metastatic potential and resectability of metastases. Our search for prognostically relevant biomarkers yielded little new insight into ULMS tumorigenesis, but did identify several markers elevated in advanced tumors, suggesting areas for further investigation that may lead to identifying these markers as possible therapeutic targets.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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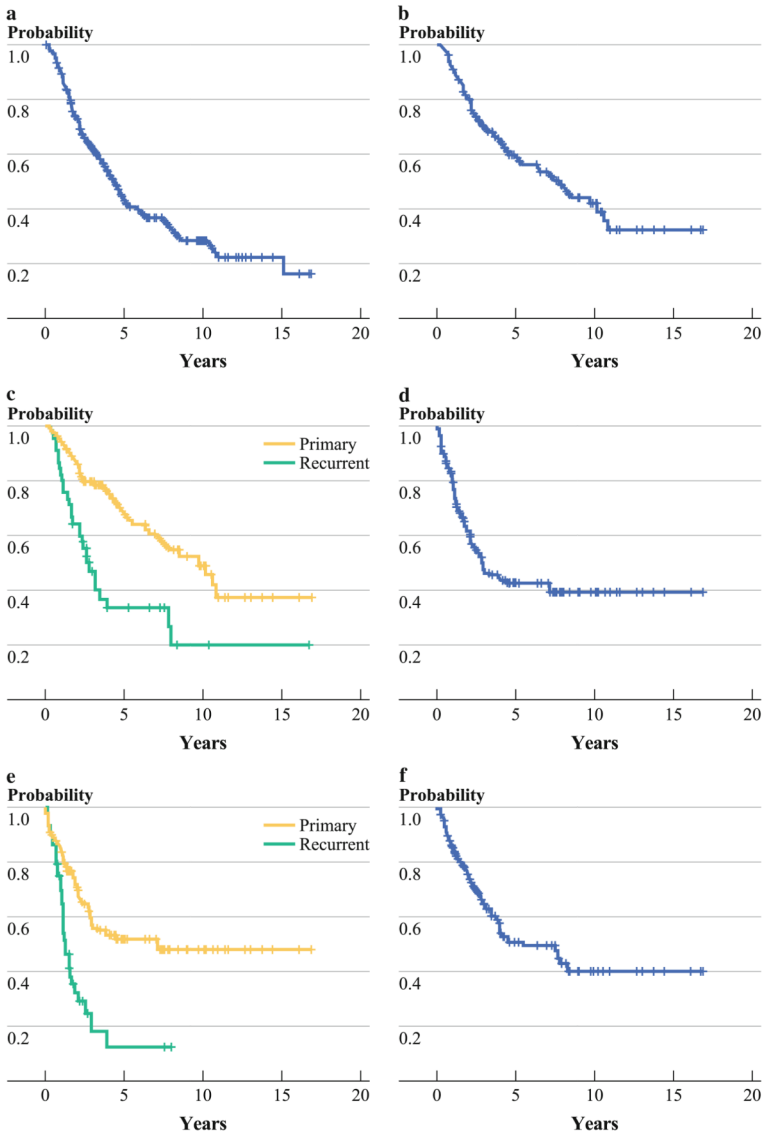

FIG. 1.

ULMS patient (Kaplan Meier) outcome analyses. **a** 5-and 10-year DSS for all 349 patients, intra-abdominal and metastatic, was 42 and 27 %, respectively. **b** 5- and 10-year DSS of patients with intra-abdominal (n = 157) ULMS were 58 and 42 %, respectively. **c** Patients with IPR (n = 45) had a worse DSS compared with primary tumors (n = 112; p <0.001, log-rank test). **d** 5-and 10-year RFS rates for patients with intra-abdominal disease were 42 and 40 %, respectively. **e** Patients who presented with IPR had a shorter median time to subsequent recurrence compared with patients who presented with primary lesions, as well as a higher overall rate of recurrence (p <0.001, log-rank test). **f** 5-and 10-year MFS rates for patients with intra-abdominal ULMS were 51 and 41 %, respectively; no difference was observed between primary and recurrent tumor subcohorts

TABLE 1

Intra-abdominal ULMS—patient, tumor, treatment, and outcome variables

Variable	Localized (*n* = 157)
Patient variables	
Age, median years (range)	51 (19–76)
Race (white/other)	116/41
Previous HRT (yes/no) (unknown = 2)	44/111
Previous pregnancy (yes/no) (unknown = 9)	126/22
Status (primary/recurrent)	112/45
Tumor variables	
Size (mean, SD) (unknown = 21)	10.3 (7.3)
Mitotic count (mean, SD) (unknown = 22)	21 (14)
Treatment	
Surgery (yes/no)	148/9
Margins (unknown = 41)	
R0	72 (49 %)
R1	22 (15 %)
R2	13 (9 %)
Chemotherapy (yes/no)	91/66 (58 %)
Neoadjuvant	25 (30 %)
Adjuvant	72 (87 %)
Chemo alone	8
Radiotherapy (yes/no)	25/132 (16 %)
With surgery	24
Without surgery	1
Outcomes	
Median follow-up (years, SD)	3.5 (3.7)
Median follow-up for survivors (years, SD)	4.5 (3.9)
Local recurrence rate	51 %
Primary (*n* = 112)	44 %
Recurrent (*n* = 45)	69 %
Median time to recur (months, SD)	24.6 (43.4)
Primary (*n* = 112)	30.0 (47.3)
Recurrent (*n* = 45)	13.9 (18.9)
Number of recurrences (1/≥2)	51/29
Metastasis rate	41 %
Primary (*n* = 112)	45 %
Recurrent (*n* = 45)	31 %
Median time to metastasis (months, SD)	29.9 (42.5)
Sites of metastasis	
Single/multiple	59/5
Pulmonary/extrapulmonary	49/18

Variable	Localized (*n* = 157)
Disease-specific survival	
1 year	91 %
5 years	58 %
10 years	42 %

TABLE 2

Intra-abdominal ULMS—univariable and multivariable analysis for disease-specific survival

Patient/tumor variables[a]	*N*	Univariable			Multivariable		
		Hazard ratio	**95 % CI**	***p* value**	**Hazard ratio**	**95 % CI**	***p* value**
Race (white/other)	116/41	0.46	0.28–0.75	0.0018[c]	0.42	0.19–0.92	0.0292[c]
Tumor status (recurrent/primary)	112/45	2.59	1.60–4.18	0.0001[c]	0.18	0.02–1.57	0.1212
Tumor size	136	1.03	1.00–1.07	0.0462[c]	1.02	0.97–1.07	0.3761
Microscopically clear surgical margins[b]	72/35	0.35	0.18–0.69	0.0027[c]			
Chemotherapy (yes/no)	91/66	3.52	2.04–6.08	0.00001[c]	3.61	1.60–8.13	0.0020[c]
Mitotic count[b] >10M/10HPF	90	4.91	1.17–20.59	0.0297[c]			
Local recurrence post-MDACC	157	2.09	1.28–3.41	0.0032[c]	3.03	1.30–7.10	0.0105[c]

M/10HPF mitoses per 10 high-power fields, 95 % CI 95 % confidence interval

[a] Age, previous hormone replacement therapy, pregnancy, radiotherapy, development of systemic metastasis, and number of recurrences (0–1 vs. 2 or more) were analyzed and did not show statistical significance

[b] Mitotic count and surgical margins excluded from multivariable analysis for low retrievable data counts

[c] Statistically significant ($p < 0.05$)

TABLE 3

Metastatic ULMS—patient, tumor, treatment, outcome variables

Variable	Metastatic (*n* = 192)
Patient variables	
Age (median years, range)	57 (29–89)
Race (white/other)	149/43
Previous HRT (yes/no) (unknown = 3)	50/139
Previous pregnancy (yes/no) (unknown = 18)	147/27
Synchronous local tumors (yes/no)	104/88
Primary	69
Recurrent	35
Tumor variables	
Site (single/multiple)	154/38
Organ (pulmonary/extrapulmonary)	164/62
Treatment variables	
Surgery (yes/no) (unknown = 10)	90/92 (47 %)
Chemotherapy (yes/no) (unknown = 7)	172/13 (90 %)
Outcome variables	
Median follow-up (years, SD)	2.7 (2.6)
Median follow-up for survivors (years, SD)	4.6 (3.1)
Disease-specific survival	
1 year	89 %
5 years	30 %
10 years	15 %

HRT hormone replacement therapy

TABLE 4

Metastatic ULMS—univariable and multivariable analysis for disease-specific survival

Patient/tumor variables[a]	*N*	Univariable			Multivariable		
		Hazard ratio	**95 % CI**	***p* value**	**Hazard ratio**	**95 % CI**	***p* value**
Race (white vs. other)	149/43	0.59	0.39–0.90	0.0136[b]	0.75	0.48–1.19	0.2254
Synchronous intra-abdominal tumor (yes vs. no)	104/88	1.59	1.11–2.26	0.0105[b]	1.34	0.92–1.96	0.1320
Pulmonary metastasis	164	2.32	1.28–4.23	0.0058[b]	2.56	1.16–5.62	0.0194[b]
Tumor burden (multiple sites vs. single sites of metastases)	38/154	1.92	1.26–2.92	0.0022[b]	1.18	0.75–1.89	0.4833
Multiple metastatic lesions within 1 organ vs. single lesion	192	1.67	1.05–2.65	0.0300[b]	0.79	0.44–1.42	0.4332
Chemotherapy (yes vs. no)	173/13	2.91	1.18–7.14	0.0200[b]	1.29	0.49–3.40	0.6100
Surgery with curative intent (yes vs. no)	90/92	0.23	0.15–0.34	<0.0001[b]	0.25	0.16–0.39	<0.0001[b]

CI confidence interval

[a] Age, previous hormone replacement therapy, time from primary diagnosis to development of metastases, and extrapulmonary metastases were analyzed and did not show statistical significance

[b] Statistically significant ($p < 0.05$)