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ORIGINAL REPORT

Stage-Specific Outcomes of Patients With Uterine Leiomyosarcoma: A Comparison of the International Federation of Gynecology and Obstetrics and American Joint Committee on Cancer Staging Systems

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ABSTRACT

Purpose
Uterine leiomyosarcoma (LMS) is staged by the modified International Federation of Gynecology and Obstetrics (FIGO) staging system for uterine cancer. We aimed to determine whether the American Joint Committee on Cancer (AJCC) soft tissue sarcoma (STS) staging system is more accurate in predicting progression-free survival (PFS) and overall survival (OS).

Patients and Methods
Patients with uterine LMS who presented at our institution from 1982 to 2005 were staged retrospectively according to a modified FIGO staging system and the AJCC STS staging system. The predictive accuracy of the two staging systems was compared using concordance estimation.

Results
Two hundred nineteen patients had sufficient clinical and pathologic information to be staged under both systems; 132 patients were upstaged using the AJCC staging system, whereas only four were downstaged. Stage-specific PFS and OS rates for stages I, II, and III differed substantially between the two staging systems. In both systems, there was prognostic overlap between stages II and III. Thus, despite the marked stage-specific differences in 5-year PFS and OS rates for stages I, II, and III, both systems had similar concordance indices.

Conclusion
Estimates of stage-specific PFS and OS for uterine LMS were altered substantially when using the AJCC versus FIGO staging system. Adjuvant treatment strategies should be tested in patients at substantial risk for disease progression and death. Neither the FIGO nor AJCC staging system is ideal for identifying such patients, suggesting a need for a uterine LMS-specific staging system to better target patients for trials of adjuvant therapies.

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INTRODUCTION

Uterine leiomyosarcoma (LMS) is a rare uterine malignancy; with an annual incidence of 0.64 per 100,000 women,[1] it accounts for 1% of all uterine malignancies and approximately 30% of all uterine sarcomas.[2] Unlike uterine adenocarcinoma, which has a relatively favorable prognosis, uterine LMS is generally associated with a poor outcome. Currently, uterine LMS is staged according to a modified International Federation of Gynecology and Obstetrics (FIGO) staging system for endometrial adenocarcinoma.[3] Although approximately 60% of patients present with disease confined to the uterus, the local and distant failure rates are high (45% to 80%),[4-8] and long-term survival rates languish between 20% and 60%.[4,9] With the currently available staging system, the clinical course of patients with LMS is difficult to predict.

Prospective data for adjuvant treatment strategies for completely resected FIGO stage I and II uterine LMSs are limited. One prospective study of doxorubicin versus observation did not show a benefit for patients treated with doxorubicin, but the interpretation of these data is limited by the small sample size, the histologic heterogeneity of the patients enrolled, the nonrandomized use of pelvic radiation, and the lack of standard timing for imaging to detect evidence of recurrence.[4,10-14] A recently completed phase III randomized trial of

adjuvant pelvic radiation versus observation for stage I and II uterine sarcomas did not show a benefit for local control or overall survival (OS) among patients with LMS.[15] The majority of patients who present with advanced-stage uterine LMS and patients with recurrent disease after initial resection have a median survival of less than 1 year.[16]

Apart from disease stage, commonly reported prognostic factors in patients with uterine LMS include age, grade, tumor size, mitotic rate, DNA ploidy, and menopausal status,[6,9,12,13,17,18] none of which are incorporated into the FIGO staging system. The American Joint Committee on Cancer (AJCC) has developed a separate staging system for soft tissue sarcomas (STS), most recently updated in the sixth edition published in 2002, which includes the following variables: grade, tumor size and location, and the assessment of regional lymph node spread and distant metastases. The AJCC staging system differs significantly from the modified FIGO staging system by incorporating histologic grade and tumor size. Furthermore, the AJCC system does not consider involvement of the cervix or uterine serosa as a staging variable, and patients with locoregional lymph node metastases are classified as stage IV. The objective of this study was to determine whether the AJCC staging system can better predict progression-free survival (PFS) and OS in these patients compared with the FIGO staging system.

PATIENTS AND METHODS

After obtaining institutional review board approval, we used the prospectively maintained Department of Surgery sarcoma database at the Memorial Sloan-Kettering Cancer Center to identify all patients with uterine LMS treated at our institution from July 1982 to June 2005. Data were extracted for age at diagnosis, surgical procedure, tumor size (≤ 5 or > 5 cm), histologic grade (high or low grade), depth (superficial or deep), lymph node metastases, postoperative treatment, date and site of first recurrence or progression of disease, and date of death or last follow-up. Stage was retrospectively assessed for every patient based on a modified FIGO staging system for endometrial adenocarcinoma (Table 1)[3] and the sixth edition of the AJCC STS staging system (Tables 2 and 3). Patients were excluded if they had insufficient information for staging for either staging system. A subset of patients presented at our institution with local or systemic recurrence, having received prior treatment at an outside institution. These patients were included only if the initial pathology was reviewed and classified as LMS at our institution and sufficient data were available regarding staging for both staging systems, primary treatment, and date and site of first recurrence. We separately analyzed patients who presented at our institution with the primary diagnosis to avoid the potential impact of referral bias on patient outcome when including patients who presented with the diagnosis of first recurrence. Patients who presented at our institution with second or later recurrences after initial treatment at outside institutions were not included.

Table 1. Modified International Federation of Gynecology and Obstetrics Staging System for Uterine Leiomyosarcoma

Stage	Definition
I	Tumor confined to the uterus
II	Tumor involving the cervix
III	Invasion of serosa, spread to pelvic organs, positive cytology, lymph node metastases
IV	Distant metastases

Table 2. American Joint Committee on Cancer Staging System for Soft Tissue Sarcomas

Primary Tumor	Definition
T1	Tumor ≤ 5 cm in greatest dimension
T1a	Superficial tumor*
T1b	Deep tumor†
T2	Tumor > 5 cm in greatest dimension
T2a	Superficial tumor
T2b	Deep tumor

*Superficial tumor is located exclusively above the superficial fascia without invasion of the fascia.

†Deep tumor is located either exclusively beneath the superficial fascia, superficial to the fascia with invasion through the fascia, or both superficial yet beneath the fascia. Retroperitoneal, mediastinal, and pelvic sarcomas are classified as deep tumors.

Because, according to the AJCC staging system, all retroperitoneal, mediastinal, and pelvic sarcomas are classified as deep tumors, all uterine LMSs are, per definition, deep tumors. Tumor size was defined as the maximum diameter of the tumor at pathologic analysis. LMSs were classified on the basis of the degree of cellularity, presence of atypia, degree of differentiation, number of mitoses per high-power field, amount of stromal necrosis, and degree of vascularity.[19,20] The majority of patients were treated with surgical excision. Some patients received adjuvant chemotherapy, radiation therapy, or a combination of both.

OS was defined as the time interval from date of initial diagnosis to the date of death or last follow-up. PFS was defined as the time interval from date of initial diagnosis to the date of the documented first recurrence or progression of disease. If there was no documented recurrence or progression of disease, PFS was calculated as the time interval from the date of initial diagnosis to the date of last follow-up or death, whichever occurred first. We acknowledge that, per definition, staging systems are developed to predict OS as a primary end point. Therefore, the stage-specific PFS analysis in this study was exploratory in nature. OS and PFS rates were estimated using the Kaplan-Meier method. The univariate *P* value in survival analysis was obtained using the log-rank test.

The predictive accuracy of the two staging systems was compared using the concordance indices, and the corresponding CIs were obtained by bootstrapping, as previously described.[21,22] Two randomly selected patients are concordant in stage and survival if the patient with the higher stage has a shorter survival. The probability of concordance is estimated by analyzing all possible pairs of patients and determining whether they are concordant (value of 1.0) or discordant (value of 0.0). A value of 0.5 indicates that of two randomly selected patients, there is a 50% chance that the patient with the higher stage will have a shorter survival (coin flip). The overall probability of concordance is the sum of the values divided by the total number of data pairs. The resulting concordance indices can range from perfect concordance (1.0) to perfect discordance (0.0). All tests were performed using SAS 9.1 (SAS Institute, Cary, NC) or library Proportional Hazards Concordance Probability Estimate in R 2.5.

Table 3. American Joint Committee on Cancer Staging System for Soft Tissue Sarcomas

Stage	Grade	Tumor	Lymph Node	Metastasis
I	Low	T1a-b, T2a-b	N0	M0
II	High	T1b, T2a	N0	M0
III	High	T2b	N0	M0
IV	Any grade	Any T	N1	M0
	Any grade	Any T	Any N	M1

Table 4. Demographics and Clinical Characteristics of Patients With Uterine Leiomyosarcoma

Characteristic	No. of Patients (N = 219)	%
Age, years		
Median	51	
Range	23-81	
Tumor grade		
High	194	89
Low	25	11
Tumor size, cm		
≤ 5	37	17
5-10	93	42
> 10	83	38
Unknown	6	3
Tumor depth		
Deep	219	100
Primary treatment at MSKCC		
Yes	131	60
No	88	40
Surgical resection		
Performed	209	95
Not performed	10	5
Lymph node sampling		
Performed	53	24
Not performed	166	76
Lymph node status		
Positive	8	15
Negative	45	85
Patient status		
Alive without disease	37	17
Alive after recurrence	22	10
Dead of disease	149	68
Dead, not disease related	1	0.5
Dead of unknown cause	10	4.5

Abbreviation: MSKCC, Memorial Sloan-Kettering Cancer Center.

RESULTS

Of 315 identified patients with uterine LMS, 219 met inclusion criteria and had sufficient pathologic and clinical information to be assigned a stage under both the FIGO and AJCC staging systems. Ninety-six patients were excluded based on the following reasons: did not meet inclusion criteria secondary to LMS of nonuterine origin (n = 25), insufficient information for staging based on missing or imprecise documentation of tumor size and/or tumor grade (n = 69), or a combination of both (n = 2). The clinical characteristics of the study population are listed in Table 4. The majority of patients (131 of 219 patients, 60%) presented at our institution at the time of initial diagnosis of uterine LMS, and 88 patients (40%) presented after primary treatment at outside institutions. Surgical resection was performed on 209 patients (95%) and most often included a total abdominal hysterectomy and bilateral salpingo-oophorectomy. In addition, more extensive procedures, including small and large bowel resection, combined liver or lung resections, or cytoreductive procedures, were performed in 28 patients (13%).

Table 5 outlines patient distribution by stage for both staging systems for all patients (n = 219). Patients staged by the FIGO staging system were generally upstaged in the AJCC staging system. One hundred thirty-two patients (60%) were upstaged using the AJCC staging system, whereas only four patients were downstaged. Of the 119 patients classified as stage I according to the FIGO system, only 19 patients (16%) remained stage I according to the AJCC system. The majority of patients were upstaged to stage III (n = 80, 67%) because their tumor diameter was larger than 5 cm. Similarly, 11 (92%) of 12 patients who were classified as stage II in the FIGO system were upstaged to stage III in the AJCC system because their tumor size was larger than 5 cm, and AJCC does not consider cervical involvement as a stage-specific characteristic. Of 39 patients with stage III disease according to FIGO criteria, 21 (54%) were upstaged to stage IV disease according to the AJCC system. Four patients were downstaged. The remaining 14 patients (36%) who were classified as stage III according to the FIGO system remained stage III in the AJCC system.

We separately analyzed the subset of patients (n = 131) who presented at Memorial Sloan-Kettering Cancer Center at the time of initial diagnosis (Table 5). In the subgroup analysis, a similar shift toward higher stages was observed when compared with the entire cohort.

Table 5. Stage-Specific Distribution of Patients With Uterine Leiomyosarcoma Stratified According to the FIGO and AJCC Staging Systems

AJCC Stage	FIGO Stage (No. of patients) I	II	III	IV	Total No. of Patients
All patients (N = 219)					
I	19	0	1	0	20
II	20	1	3	0	24
III	80	11	14	0	105
IV	0	0	21	49	70
Total	119	12	39	49	219
Patients who presented at MSKCC at the time of initial primary diagnosis (n = 131)					
I	4	0	0	0	4
II	11	1	1	0	13
III	42	7	8	0	57
IV	0	0	16	41	57
Total	57	8	25	41	131

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; AJCC, American Joint Committee on Cancer; MSKCC, Memorial Sloan-Kettering Cancer Center.

The median follow-up time for the surviving patients of the entire cohort (n = 219) was 7.0 years (range, 0.6 to 22.8 years). Of the 219 patients, 197 (90%) experienced progression. The median time to progression was 1.1 year (95% CI, 0.9 to 1.3 years).

The median OS time for all patients was 3.6 years (95% CI, 2.7 to 4.8 years). One hundred sixty patients (73%) died during the study period. Figure 1 displays the estimated stage-specific PFS and OS rates according to both the FIGO and AJCC staging systems. Table 6 lists the estimated 5-year PFS and OS rates for both staging systems. Stage-specific PFS and OS rates for patients with stage I, II, and III disease differed substantially between the FIGO and AJCC staging systems.

Patients who were classified as stage I, II, or III by the FIGO system had lower 5-year PFS rates compared with similarly staged patients according to the AJCC staging system. Patients with stage IV disease according to the FIGO and AJCC systems had a low estimated 5-year PFS rate of 4% and 6%, respectively. As expected, after excluding the patients who presented at our institution with a recurrence, the PFS rates for the majority of patients (stages II and III) compared favorably with the entire cohort (data not shown).

The 5-year OS rate was 57% for patients with FIGO stage I disease and 95% for patients with AJCC stage I disease. There was prognostic overlap between stages II and III in both the FIGO and AJCC staging systems. Patients with stage III disease had a favorable outcome when compared with patients with lower, stage II disease. The 5-year OS rate was 16% for patients with FIGO stage IV disease and 18% for patients with AJCC stage IV disease.

The AJCC staging system was more accurate in identifying patients with a better prognosis, whereas the FIGO staging system was better at detecting patients with a worse prognosis. This phenomenon of stage migration is also known as the Will Rogers phenomenon. AJCC upstages patients with a worse prognosis, which leads to the migration of these patients to higher stages. Removing them from the lower stage increases the median survival of the patients remaining in that stage. Likewise, the migrated patients have a better prognosis than the patients in the higher stages. Adding them to the patients with a worse prognosis increases the median survival of the higher stage as well.[23]

The concordance indices for both staging systems with regard to PFS and OS are listed in Table 7. The two staging systems had identical concordance estimates for PFS (concordance index = 0.60). The results were comparable to the subgroup of patients who presented at time of initial diagnosis (n = 131; concordance index = 0.62 for the FIGO system and 0.59 for the AJCC system). The concordance estimates of OS for all patients were 0.62 for the FIGO system and 0.63 for the AJCC system. Again, the results were comparable to the subgroup of patients who presented at initial diagnosis (concordance index = 0.63 for the FIGO system and 0.62 for the AJCC system).

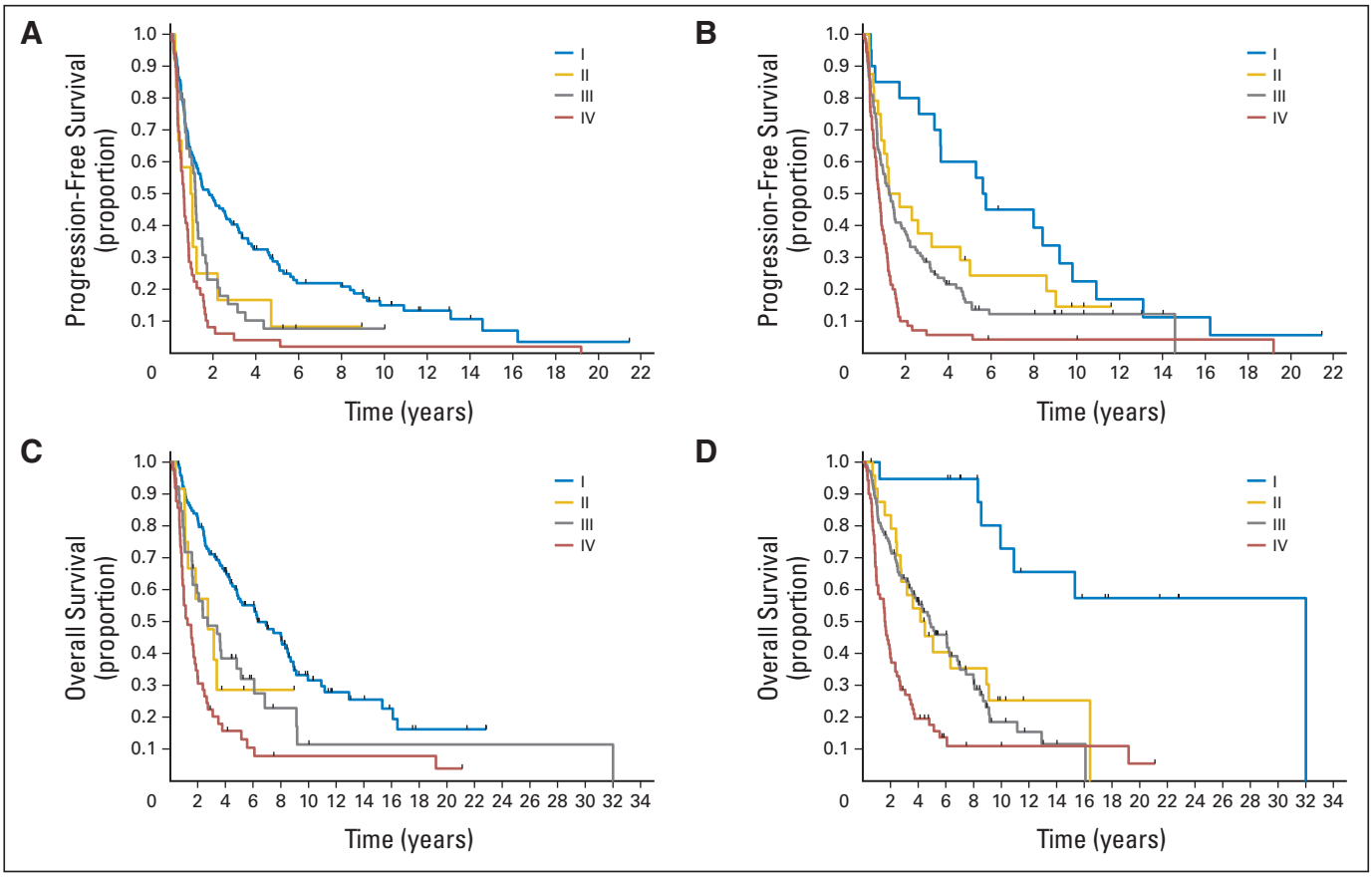

Fig 1. Progression-free survival by (A) International Federation of Gynecology and Obstetrics (FIGO) stage and (B) American Joint Committee on Cancer (AJCC) stage. Overall survival by (C) FIGO stage and (D) AJCC stage.

Table 6. Five-Year PFS and OS Rates of Patients Stratified by Stage According to the FIGO and AJCC Staging Systems

	FIGO					AJCC				
		5-Year PFS (%)		5-Year OS (%)			5-Year PFS (%)		5-Year OS (%)	
Stage	No. of Patients	PFS Rate	95% CI	OS Rate	95% CI	No. of Patients	PFS Rate	95% CI	OS Rate	95% CI
I	119	28	20 to 36	57	47 to 66	20	60	36 to 78	95	68 to 99
II	12	8	1 to 31	29	7 to 55	24	24	10 to 43	45	25 to 64
III	39	8	2 to 19	35	21 to 50	105	16	9 to 24	48	38 to 58
IV	49	4	1 to 12	16	7 to 27	70	6	2 to 13	18	10 to 28

Abbreviations: PFS, progression-free survival; OS, overall survival; FIGO, International Federation of Gynecology and Obstetrics; AJCC, American Joint Committee on Cancer.

DISCUSSION

Staging systems for patients with cancer are important for determining prognosis, guiding treatment, and identifying patients for clinical trials. The ideal staging system has the capacity to reliably characterize the behavior of the malignancy by accurately discriminating between different prognostic subgroups within a patient population, allowing clinicians to select appropriate therapies and compare clinical experiences among centers and among treatments over the continuum of time.

The rarity of uterine LMS has hampered the development of a disease-specific staging system. Consequently, gynecologic oncologists and medical oncologists use a modification of the FIGO endometrial cancer staging system, which primarily focuses on the staging of endometrial adenocarcinomas. Unlike the vastly more common adenocarcinomas, which are of epithelial origin, typically spread initially to the lymphatics, and, in early stages, are associated with a relatively favorable prognosis, uterine LMSs are characterized by a high rate of local and distant recurrences, a propensity for early hematogenous spread (often without evidence of lymphatic spread[24,25]), and an overall poor prognosis.

In the current study, a comparison between the FIGO and AJCC STS staging systems was performed involving 219 patients with uterine LMS who were treated at our institution over a period of 23 years. Estimates of stage-specific PFS and OS for uterine LMS were altered substantially between the two staging systems. A small subset of patients who met the criteria for classification as AJCC stage I (low-grade tumors regardless of size) had a markedly improved estimated 5-year PFS and OS. Uterine LMS of low grade is rare and distinguishes itself, at least theoretically, from high-grade LMS by relatively favorable clinical behavior. There is no uniform grading scheme for uterine LMS. Although some pathologists do not consider low-grade LMS a true LMS, but rather an atypical leiomyoma, others use the grading system used for extrauterine LMS.[12,17,18,20,26] In light of the excellent 5-year OS rate of 95%, our results indicate that these patients constitute a distinct group of patients with a favorable prognosis and an indolent disease pattern.

Table 7. Concordance Indices and 95% CIs for PFS and OS According to the FIGO and AJCC Staging Systems

End Point and Staging System	Concordance Index	Bootstrap 95% CI
PFS		
FIGO	0.600	0.566 to 0.641
AJCC	0.596	0.560 to 0.639
OS		
FIGO	0.620	0.586 to 0.660
AJCC	0.633	0.594 to 0.678

Abbreviations: PFS, progression-free survival; OS, overall survival; FIGO, International Federation of Gynecology and Obstetrics; AJCC, American Joint Committee on Cancer.

Despite the substantially altered and improved outcome estimates yielded by using AJCC staging for patients with stage I, II, and III disease, the AJCC staging system did not show improved overall prognostic ability, as measured by concordance index, compared with the FIGO staging system. This is likely attributable to the prognostic overlap that is seen for AJCC stages II and III and to the fact that patients with stage IV disease in both systems have a poor prognosis.

There is no commonly used test for assessing the predictive ability of a given staging system.[21,27-29] Among the available methods, we have chosen the concordance probability to measure the prognostic accuracy of the staging systems mainly because the concordance index is unaffected by the level of censoring in the data and is relatively easy to interpret. The concordance index for PFS using either the AJCC or FIGO system was 0.60, which means that for two patients with different stages, there is a 60% chance that the patient in the lower stage has a longer PFS. Likewise, the concordance index for prediction of OS was 0.63 for the AJCC staging system and 0.62 for the FIGO staging system.

Within stages II and III, the AJCC staging system failed to provide meaningful outcome estimates. Ideally, a staging system should be ordinal in nature, identifying patients with poorer prognoses as the stage categories increase. Among the relatively large group of patients with stage II and III disease, the AJCC staging system (as well as the FIGO system) predicts inferior 5-year OS rates in patients with lower stage disease. These findings suggest that tumor size (≤ 5 or > 5 cm) among the patients with high-grade LMS (the vast majority of patients with uterine LMS) does not seem to be a strong determinant of PFS and OS. Therefore, except for the small group of patients classified as stage I, AJCC was not able to discriminate between patients who are at a low risk for recurrence and death from patients who are at a high risk.

Although our study includes a limited number of patients managed over a long time period, our analysis was performed using data from a prospectively maintained surgical database with relatively long follow-up. During this time period, the diagnosis and treatment did not change significantly and should not account for differences in

outcome over time. Because of the limited number of patients, we included those patients who presented with the diagnosis of first recurrence or progression after primary treatment at an outside institution, accepting the potential selection bias toward over-representing high-risk patients. Therefore, we performed a subgroup analysis of patients who presented at our institution with the primary diagnosis of uterine LMS. The concordance indices did not differ when compared with the entire cohort.

In conclusion, the criteria of the FIGO staging system are lenient, resulting in a greater number of patients being classified as stage I compared with the AJCC staging system. Conversely, the AJCC system has the tendency to upstage patients. Thus, the strength of the AJCC staging system is to identify patients with a better prognosis, and the strength of the FIGO staging system is to detect patients with a worse prognosis. Unfortunately, the strength of one staging system is the weakness of the other. As a result, the overall predictive ability of AJCC staging was not superior to FIGO staging. Thus, for the majority of women with uterine LMS, the currently available staging systems fail to provide good estimates of PFS and OS.

The ability to provide an accurate prognosis based on patient-specific information is the goal of both patients and clinicians. In recent years, several models of prediction have been developed for the majority of cancer types. These methods include nomograms,[30-34] classification and regression trees,[35,36] and neural networks.[37] There is increasing evidence in the literature that for many cancers, alternative staging platforms such as nomograms compare favorably with the traditionally used generic staging systems.[38,39] A potential solution to address the shortcomings of the traditionally used staging systems is to develop a uterine LMS–specific nomogram that combines the stage-specific variables of both staging systems with other established clinicopathologic prognostic factors for uterine LMS. An individualized risk prediction model has the potential to improve the management of women diagnosed with uterine LMS by allowing physicians to more precisely identify patients who are at a low risk for recurrence and death and to identify those who are candidates for clinical trials of adjuvant treatment strategies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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