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Uterine smooth muscle tumor of uncertain malignant potential: A retrospective analysis*

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Abstract

Objective.—This retrospective study was designed to evaluate the clinicopathologic features and outcomes of a cohort of patients diagnosed with uterine smooth muscle tumor of uncertain malignant potential (STUMP) seen at a single institution.

Methods.—All patients diagnosed with uterine STUMP and seen between 1990 and 2005 at The University of Texas M. D. Anderson Cancer Center were identified using the institution's databases. Variables of interest included age at diagnosis, recurrence rate, and disease-free and overall survival.

Results.—Forty-one patients with uterine STUMP were identified and included in the study. The mean age at diagnosis was 43 years (range 25–75 years). The mean follow-up time was 45 months (range 1–171 months). Three patients (7.3%) had a recurrence during the follow-up period. One of the three patients who had recurrent disease was found to have a leiomyosarcoma at the time of recurrence. Recurrence rates were similar for women who underwent myomectomy and those who underwent hysterectomy. All three patients with recurrence were alive and disease-free at a mean follow-up time of 121 months.

Conclusion.—Our results suggest that in this cohort of patients with uterine STUMP the recurrence rate was 7%. Recurrences can be in the form of STUMP or leiomyosarcoma.

Keywords

Uterus; Smooth muscle tumors; Uncertain malignant potential; STUMP; Recurrence; Myomectomy

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Conflict of interest statement

The authors have no conflicts of interest to declare.

Introduction

Uterine smooth muscle tumors of uncertain malignant potential (STUMP) represent a poorly defined subcategory of uterine smooth muscle tumors. One way to define STUMP is by exclusion-i.e., tumors that do not fit the definition for any of the other categories of uterine smooth muscle tumors are classified as STUMP. In the most widely used classification system of uterine smooth muscle tumors proposed by Bell et al. [1], malignant conventional spindle cell smooth muscle tumors (conventional leiomyosarcomas) are defined as tumors with at least two of the following three features: (1) diffuse cytologic atypia, (2) tumor cell necrosis, and (3) ≥ 10 mitoses per 10 high-power fields. In contrast, leiomyomas are defined as tumors with a bland appearance, no tumor cell necrosis, and ≤ 4 mitoses per 10 high-power fields. Variants of leiomyoma include (1) mitotically active leiomyoma, which has >5 and <19 mitoses per 10 high-power fields, and (2) atypical or symplastic leiomyoma, which has cytologic atypia but no tumor cell necrosis and <10 mitoses per 10 high-power fields. Tumors that do not meet these definitions are classified as STUMP.

STUMP can be difficult for pathologists to diagnose and the risk factors and clinical behavior of these tumors are poorly understood. The goal of this study was to evaluate the clinicopathologic features and outcomes of a cohort of patients diagnosed with uterine STUMP and seen at a single institution. Variables of interest included race/ethnicity, tobacco use status, recurrence patterns, and disease-free and overall survival.

Materials and methods

This study was conducted with approval from the institutional review board of The University of Texas M. D. Anderson Cancer Center. We identified all patients diagnosed with uterine STUMP and seen at M. D. Anderson Cancer Center from 1990 to 2005. At the time of diagnosis all specimens were reviewed by a single team of gynecologic pathologists. All cases were spindle cell type and were defined as STUMP if they fit one of the following sets of criteria: (1) tumor cell necrosis, no atypia, and a mitotic index <10 mitoses per 10 high-power fields; (2) diffuse atypia, no tumor cell necrosis, and a mitotic index <10 mitoses per 10 high-power fields; (3) no tumor cell necrosis, no atypia, and a mitotic index >20 mf/10 HPF; (4) cellularity/hypercellularity and a mitotic index >4 mitoses per 10 high-power fields; (5) irregular margins or vascular invasion at the periphery of the tumor. These criteria were determined based on prior work published by Bell et al. [1] and our own institutional unpublished criteria. The pathology material for all patients with recurrent disease was re-reviewed by a gynecologic pathologist (AM) for this study to ensure that the original uterine tumor had not been misclassified as a STUMP when in fact it was a leiomyosarcoma. Immunohistochemical studies were not performed in the pathology specimens of these patients since their value is limited in cases of STUMP [2]. We obtained demographic data from patient charts, including age at diagnosis, race/ethnicity, tobacco use status, initial treatment, prior radiation therapy or hormonal therapy, time to recurrence, if any, and disease-free and overall survival. For patients with recurrent disease, we recorded the anatomic site involved, the pathologic features of the recurrence, the size of recurrent tumors, and treatment at recurrence. The Kaplan–Meier method was used to analyze survival

outcomes. For all tests, a P value $<.05$ was considered statistically significant. SAS/STAT software programs (Cary, NC) were used to perform all statistical analyses.

Results

Forty-one patients met the criteria for uterine STUMP and were followed at M. D. Anderson Cancer Center during the study period (Table 1). The mean age of the patients at diagnosis was 43 years (range 25–75 years). Twenty-three patients were Caucasian (56%), 11 were Hispanic (27%), 5 were African American (12%), 1 was Asian (3%), and 1 was classified as other (2%). Twelve patients (29%) had a history of smoking. Five patients (12%) had a total abdominal hysterectomy alone as their initial surgical intervention, 20 patients (48%) had a total abdominal hysterectomy with bilateral salpingo-oophorectomy, 10 patients (24%) had a myomectomy, and 6 patients (14%) had a total abdominal hysterectomy with a unilateral salpingo-oophorectomy. None of the 10 patients who underwent a myomectomy as their initial surgery underwent a completion hysterectomy. None of the patients had a history of irradiation of the pelvis prior to being diagnosed with uterine STUMP. Three patients (7%) had received hormone replacement therapy prior to being diagnosed with uterine STUMP. After surgery, each patient had baseline chest radiography done and was then followed with semi-annual pelvic exams and yearly Pap smears. None of the patients received chemotherapy or radiation therapy after the initial diagnosis of uterine STUMP. The mean follow-up time for all patients was 45 months (range 1–171 months).

Of the 41 patients studied, 3 patients (7.3%) developed recurrent disease—one at 13 months, one at 47 months, and one at 68 months. The mean disease-free interval was 42 months. The mean age of the patients who had a recurrence was 34 years, whereas the mean age of the patients who did not have a recurrence was 44 years ($P=.09$) (Table 1). Race/ethnicity was not predictive of recurrence ($P=.79$); neither was tobacco use status ($P=.48$) or type of initial surgery (total abdominal hysterectomy alone vs. total abdominal hysterectomy and bilateral salpingo-oophorectomy vs. total abdominal hysterectomy and unilateral salpingo-oophorectomy vs. myomectomy) ($P=.9$).

One of the patients with recurrent disease was originally diagnosed with uterine STUMP after undergoing a total abdominal hysterectomy and unilateral salpingo-oophorectomy. A right parametrial synchronous STUMP was also detected. She presented 13 months after the initial diagnosis of uterine STUMP with complaints of a cough and pelvic pain, which prompted chest radiography and computed tomography of the chest, abdomen, and pelvis. The patient was found to have a pelvic mass and a pulmonary nodule. The patient underwent resection of the pelvic mass and was found to have no other evidence of disease in the abdomen or pelvis. In addition, the patient also underwent pulmonary lobectomy. The final pathology review from these surgeries revealed recurrent STUMP. The patient was then started on medroxyprogesterone acetate. She was given 40 mg 4 times daily for 7 years, then 40 mg twice daily for another 3 years and 7.5 mg leuprolide acetate by injection once per month. The patient continues to have surveillance with annual pelvic exams and chest X-rays. She has been followed for 157 months since the initial diagnosis with STUMP and remains without evidence of recurrence.

The second patient with recurrent STUMP was originally diagnosed with uterine STUMP after undergoing a total hysterectomy and bilateral-salpingo-oophorectomy. She presented 68 months after the original diagnosis of uterine STUMP with a palpable abdominal mass. The patient was found to have a retroperitoneal pelvic mass extending to the upper abdomen and compressing the right renal vessels. The patient was taken to the operating room, where the retroperitoneal mass was confirmed and the patient was also found to have multiple peritoneal nodules. All tumors were resected. All surgical specimens removed revealed recurrent STUMP. No information was available about whether this patient was treated postoperatively. The patient was disease-free 106 months after the initial diagnosis of uterine STUMP.

The third patient with recurrent STUMP was originally diagnosed with uterine STUMP after undergoing a total abdominal hysterectomy. She presented 47 months after the original diagnosis of uterine STUMP with pelvic pain. At that time, the patient underwent computed tomography of the abdomen and pelvis, which revealed a large retroperitoneal mass extending from the pelvis to the level of the pancreas. The patient subsequently underwent bilateral salpingo-oophorectomy and resection of the retroperitoneal mass. The final pathology review from that surgery showed that the right ovarian mass and the retroperitoneal mass were consistent with leiomyosarcoma. The patient was treated with doxorubicin and cisplatin postoperatively. At last follow-up, 150 months after the initial diagnosis of uterine STUMP, the patient was alive without evidence of disease. For the three patients with recurrence, the overall survival rate was 100% with a mean follow-up time of 128 months from the initial diagnosis of uterine STUMP.

None of the patients who underwent myomectomy suffered a recurrence, therefore one may suggest that patients diagnosed with a STUMP at the time of a myomectomy may be managed expectantly; however, due to the small number of patients in our study it is difficult to make a definitive statement regarding the safety of such approach. In the 3 patients with recurrences, one patient underwent a bilateral salpingo-oophorectomy at the time of the original surgery, a second patient underwent a unilateral salpingo-oophorectomy, and a third patient only underwent a hysterectomy at the time of initial surgery.

Discussion

To our knowledge, this is the largest study to date of clinicopathologic factors, recurrence rates and long-term outcomes in patients with uterine STUMP. Of note, we did not find race/ethnicity to differ significantly between patients who did and did not develop a recurrence. This contrasts with the results of previous studies that have addressed the same question in patients with leiomyosarcomas. Toro et al. [3] compared the incidence of leiomyosarcoma between Caucasian and African American women and found that the incidence in African American women was 1.7 times that in Caucasian women.

We also did not find tobacco use status to differ between patients with and without recurrence. Previous studies have found that smoking in particular and tobacco use in general may decrease the risk of uterine leiomyoma and leiomyosarcoma. In a multicenter case-control study, Lumbiganon et al. [4] examined 910 patients with symptomatic uterine

leiomyomas and 2709 controls and found that smoking was associated with a decrease in the relative risk of developing uterine leiomyoma. Schwartz et al. [5] examined this same question in 58 patients with leiomyosarcoma and 210 controls and also found that smoking reduced the risk of developing leiomyosarcoma (odds ratio=0.6).

In contrast to previous studies of leiomyomas and leiomyosarcomas, previous studies of STUMP have been mainly case reports and case series examining only a small number of patients. In 1994, Peters et al. [6] compared the outcomes of 15 patients with STUMP to those of 22 patients with leiomyosarcomas. They found that the recurrence rate was 27% for STUMP and 69% for leiomyosarcomas and that the overall survival rate at 5 years was 92% for patients with STUMP and 40% for patients with leiomyosarcomas. However, that report does not specify the histology of the recurrent tumors (STUMP vs. leiomyosarcoma). In addition, there was no mention in that report as to whether patients with leiomyosarcoma at recurrence had their original pathology slides reviewed to ensure that the original uterine tumor had not been misclassified as a STUMP when in fact it was a leiomyosarcoma. More recently, Berretta et al. [7] published a report of three cases of patients with STUMP. During the follow-up, one patient developed diffuse lung metastases. Histologic examination indicated the presence of STUMP-induced lung metastases. This recurrence was diagnosed 9 years from the original diagnosis. The patient was then treated with gonadotropin-releasing hormone agonists and an aromatase inhibitor. There is limited data on whether STUMP tumors are hormone sensitive. Unfortunately, most studies that have performed immunohistochemistry analysis of STUMP tumors focusing on progesterone and estrogen receptor expression have been hindered by the fact that the number of patients with STUMP tumors is very small.

The tumor most closely related to STUMP that has been examined in detail is the mitotically active leiomyoma, which is defined as a tumor with a high mitotic index (>5 and <19 mitoses per high-power field). Prayson and Hart [8] studied 15 patients with mitotically active leiomyomas and found that there were no recurrences at a mean follow-up time of 30 months. O'Conner and Norris [9] found similar results in a group of 73 women with mitotically active leiomyomas, with a mean follow-up time of 84 months. Only 1 recurrence as a mitotically active leiomyoma was noted in that study, with no recurrence as an overt malignancy or metastases outside of the pelvis. Our finding that STUMP may recur as leiomyosarcoma indicates that STUMP, unlike mitotically active leiomyoma, should not be strictly considered a benign variant of leiomyoma.

The strengths of our study include the fact that it is the largest series on uterine STUMP reported to date, the long follow-up time, and the fact that all pathology slides were reviewed by a single team of gynecologic pathologists. We recognize that although this is the largest series reported to date, the limited number of patients and recurrent events and the variety of treatment approaches make it difficult to draw definitive conclusions regarding risk factors or treatment options for patients with this diagnosis.

On the basis of our findings, we propose that patients with STUMP should be counseled regarding the potential for recurrence as leiomyosarcoma. The ideal criteria for follow-up remain elusive. Patients with STUMP may require closer surveillance than a yearly

examination and may need a consultation with a gynecologic oncologist. More studies are encouraged to determine the true recurrence rate of STUMP tumors along with the clinical behavior of this rare entity.

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Table 1

Demographic differences between nonrecurrence and recurrence groups

Characteristic	Nonrecurrence group (N = 38)	Recurrence group (N = 3)	P value
Mean age	43.9 years	33.7 years	.09
Prior treatment			
Hormone replacement therapy	3(7)	0	
Pelvic radiation therapy	0	0	
Race/ethnicity			.792
Caucasian	22 (57)	1 (33)	
African American	4(11)	1 (33)	
Hispanic	10 (26)	1 (33)	
Asian	1 (3)	0	.484
Other	1 (3)	0	
Tobacco use	11 (26)	1 (33)	
Follow-up time	39 months	128 months	
Alive with no evidence of disease at last follow-up	38 (100)	3 (100)	
Type of surgery			.90
TAH	4(11)	1 (33)	
TAH-BSO	19 (50)	1 (33)	
TAH-USO	5 (14)	1 (33)	
Myomectomy	10 (25)	0	

Values in table are number of patients (percentage) unless otherwise indicated.