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Clinical and reproductive outcomes of uterine smooth muscle tumor of uncertain malignant potential (STUMP): A tertiary center experience

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Abstract

Some smooth muscle tumors do not meet the histologic criteria for definite benign-malignant distinction and this rare group is thus classified as smooth muscle tumors of uncertain malignant potential (STUMP). Due to the high heterogeneity, there are no standard guidelines for the diagnosis, treatment, and follow-up of uterine STUMPs. So, we aimed to evaluate the treatment modalities in patients with/without fertility desires. The size, mitotic count, presence of necrosis and atypia of tumors were obtained from the final pathology reports. Patients were followed up with electronically merged records via telephone until October 2022. Recurrence, time to recurrence, and recurrence histopathology were included in the study. Myomectomy was performed in 50% of the patients. Frozen section was not considered necessary in 57.1% of all patients and 50% of the patients who underwent frozen section were reported as benign. The median follow-up was 64.5 months. Tumor necrosis was observed in 14.3% of patients. The median mitosis count was calculated as 2.5 (1-9) per 10 high-power fields. The recurrence rate was calculated to be 7.2%. The accuracy of a frozen section diagnosis may not always be reliable, it is often confirmed after the final pathology has been reported. Patients who desire fertility can be supported. Our research indicates that recurrence rates could be lower in centers where experienced pathologists are making the diagnosis.

Keywords: fertility, leiomyoma, leiomyosarcoma, mitotic count, necrosis, recurrence

1. Introduction

The most common tumor of the female genital tract is smooth muscle cell tumors, affecting approximately 75% of women (1, 2). Histopathologically, structures that are non-infiltrative, contain spindled cells with no atypia, show fewer than five mitotic figures per 10 high-power fields (HPFs) and no necrosis are defined as leiomyomas (3, 4). Occasionally, a uterine mass presumed to be a leiomyoma may later receive a diagnosis of a leiomyoma variant or leiomyosarcoma (LMS). Although there is a wide range of leiomyoma variants, some may demonstrate a single histologic feature associated with LMS, such as an increased mitotic index or severe cytologic atypia, but are histologically benign. Some smooth muscle tumors do not meet the histologic criteria for definite benign-malignant distinction and this rare group is thus classified as having uncertain malignant potential (5, 6).

Smooth muscle tumors of uncertain malignant potential (STUMP) were first described in 1973 (7). These tumors do not meet the histological criteria for leiomyoma variants and leiomyosarcomas, but raise concerns that they may have malignant potential. The World Health Organization defined uterine STUMPs as smooth muscle tumors with features that preclude a definitive diagnosis of leiomyosarcoma (4). Due to the high heterogeneity, there are no standard guidelines for the diagnosis, treatment, and follow-up of uterine STUMPs. Its pathogenesis, risk factors, and prognostic features remain unsolved. Therefore, in this study, we analyzed the histopathological features of STUMP cases in detail. We aimed to evaluate the treatment modalities and the recurrence of the disease in patients with or without fertility desires.

2. Materials and Methods

This study, which includes the clinical and pathological results of 14 patients reported as uterine STUMP between September 2013 and August 2022, has also been approved by the Local Research Ethics Committee of our hospital (Approval No:

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114/2022). The study adhered to the tenets of the Declaration of Helsinki and we obtained informed consent from all participants before surgery. Patients' ages, menopausal status, fertility desires, surgical procedure information, intraoperative frozen section and final pathology results were obtained from hospital records.

Uterine STUMP was diagnosed according to the diagnostic criteria defined by Bell et al. (8) and Ip et al. (9). All specimens were examined by gynecopathologists with more than ten years of experience in gynecology. All pathological blocks were re-evaluated, and diagnoses were checked. The size, mitotic count, presence of necrosis and atypia of tumors were obtained from the final pathology reports. Patients were followed up with electronically merged records via telephone until October 2022. Postoperative delivery status and need for hysterectomy were questioned in patients who underwent myomectomy. In addition, recurrence, time to recurrence, and recurrence histopathology were included.

Data analysis was conducted using SPSS version 23. The normality of distribution was tested with Shapiro-Wilk and skewness-kurtosis tests (10). Descriptive statistics were provided for non-normally distributed variables as median (minimum-maximum), for normally distributed variables as mean ± standard deviation and for nominal variables as case number and percentage (%).

3. Results

A total of 14 patients with a diagnosis of uterine STUMP were evaluated. The prevalence of the STUMP was calculated as 0.34% among 4112 patients who underwent hysterectomy or myomectomy due to myoma uteri at this period. The mean age was 44.1 years (range 33-52) and the mean tumor diameter was 83.2 mm (22-160). Myomectomy was performed in 50% (7/14) of the patients. Among the patients who underwent myomectomy, 1 immediately after the first final report and 3 in the following years underwent hysterectomy. Frozen section was not considered necessary in 57.1% (8/14) of all patients and 50% (3/6) of the patients who underwent frozen section were reported as benign. Median follow-up was 64.5 (10-104) months. All clinical features of the patients are given in Table 1.

Table 1. Clinical characteristics of uterin STUMP patients (*N=14*)

Clinical Features	
Age [1] (years)	44.1 (33-52)
Tumor Size [1] (mm)*	83.2 (22-160)
Mitotic Count [2] (per 10 HPF)	2.5 (1-9)
Initial Surgery	
Myomectomy	7 (50.0%)
Hysterectomy	7 (50.0%)
Frozen Section	
Absent	8 (57.1%)
Benign	3 (21.4%)
Borderline	2 (14.3%)
Malign	1 (7.2%)
Hysterectomy After Initial Diagnosis	1
Need for Hysterectomy in the Following Years	3
Follow up [2] (month)	64.5 (10-104)
Recurrence	1 (7.2%)
uSTUMP	1
LMS	0

Abbreviation: u*STUMP*, Uterine Smooth Muscle Tumors of Uncertain Malignant Potential*; mm*, Millimeter; *HPF,* High Power Fields*; LMS,* Leiomyosarcoma

[1] = Mean and range values were given [2] = Median and range values were given

* = Hysteroscopic procedure was excluded

In the final pathology, only one patient (7.2%) had no atypia, one patient had mild atypia, one patient had mild-moderate atypia, and eleven patients had moderate or severe atypia. In addition, two patients (14.3%) showed tumor necrosis. In addition, tumor necrosis was observed in 2 (14.3%) patients. The median mitosis count was calculated as 2.5 (1-9) in HPFs. Detailed characteristics of the patients are summarized in Table 2.

Table 2. Clinical characteristics of uterine STUMP patients

Patients			***Surgery***			***Pathology Results***				
Case	**Age**	**Menop. Status**	**Frozen Section**	**Initial Surgery**	**Surgical Extraction Techniques**	**Atypia Distribution and Degree**	**N**	**MC**	**Subsequent Treatment**	**Recurrence**
1	43	P	*No*	*L/T Myomectomy + USO*	*Transabdominal*	*Diffuse, Moderate to Severe*	*No*	*5*	*No*	*No*
2	46	P	*No*	*L/T Myomectomy*	*Transabdominal*	*Diffuse, Mild to Moderate*	*No*	*2*	*Hysterectomy*	*STUMP*
3	52	M	*Benign*	*L/T Hysterectomy + BSO*	*Transabdominal*	*Diffuse, Severe*	*No*	*3*	*No*	*No*
4	47	P	*Benign*	*L/T Hysterectomy + BSO*	*Transabdominal*	*Diffuse, Moderate*	*No*	*5*	*No*	*No*
5	49	M	*No*	*L/S Myomectomy*	*Morcellation*	*Diffuse, Moderate to Severe*	*No*	*1*	*No*	*No*
6	42	P	*Borderline*	*H/S Myomectomy*	*Hysteroscopic*	*Diffuse, Severe*	*No*	*3*	*Hysterectomy*	*No*
7	51	M	*No*	*L/S Hysterectomy + BSO*	*Vaginally*	*Diffuse, Moderate to Severe*	*No*	*9*	*No*	*No*

Table 2. Clinical characteristics of uterine STUMP patients (Continue)

Patients			*Surgery*			*Pathology Results*				
Case	**Age**	**Menop. Status**	**Frozen Section**	**Initial Surgery**	**Surgical Extraction Techniques**	**Atypia Distribution and Degree**	**N**	**MC**	**Subsequent Treatment**	**Recurrence**
9	42	P	*No*	*L/T Myomectomy*	*Transabdominal*	*Focal, Severe*	*No*	*7*	*Hysterectomy*	*No*
10	33	P	*No*	*L/T Myomectomy*	*Transabdominal*	*Diffuse, Severe*	*No*	*1*	*Hysterectomy*	*No*
11	41	P	*Borderline*	*L/T Myomectomy + USO*	*Transabdominal*	*Diffuse, Moderate*	*No*	*2*	*No*	*No*
12	36	P	*Malign*	*L/T Hysterectomy + Staging*	*Transabdominal*	*Focal, Mild*	*Yes*	*9*	*No*	*No*
13	52	M	*No*	*Vaginal Hysterectomy*	*Vaginally*	*Diffuse, Severe*	*No*	*1*	*No*	*No*
14	41	P	*Benign*	*L/T Hysterectomy + BS*	*Transabdominal*	*None*	*Yes*	*1*	*No*	*No*

Abbreviations: STUMP, Uterine smooth muscle tumors of uncertain malignant potential; P, Premenopausal; M, Menopausal; L/T, Laparotomy; L/S, Laparoscopy; H/S, Hysteroscopy; USO, Unilateral Salpingo-Oophorectomy; BSO, Bilateral Salpingo-Oophorectomy; BS, Bilateral Salpingectomy; N, Necrosis; MC, Mitotic Count

Five uterine masses were surgically removed from a 46-year-old pre-menopausal patient who had been preliminarily diagnosed with leiomyoma. The largest mass (70 mm) exhibited diffuse moderate to severe atypia and two mitoses (10 HPFs) with no necrosis. The final report declared the largest mass to be a STUMP, while the remaining four excised masses were reported as benign leiomyoma. Subsequently, one year later, the patient underwent a hysterectomy due to recurrent leiomyoma, which was reported as a STUMP in the final report. In consequence, our recurrence rate was calculated to be 7.2%.

Out of the seven patients who initially underwent myomectomy, one (42 years old) immediately proceeded to a hysterectomy upon completion of the first stage. The remaining six were followed up, one of whom gave birth via cesarean section 14 months after their initial diagnosis, and proceeded to a hysterectomy (benign) seven years later. Another one of the patients gave birth via cesarean section 24 months after their initial diagnosis, and is still being followed up. The remaining four patients did not become pregnant after their initial diagnosis of STUMP and two of them have been followed up without intervention. One of them underwent hysterectomy (benign) due to abnormal uterine bleeding three years after the initial diagnosis. The detailed characteristics of each of the patients are summarized in Table 3.

Table 3. Reproductive History of uterine STUMP patients (N=6)

Patient		**Reproductive History**		
No	**Age**	**Before Diagnosis of STUMP**	**After Diagnosis of STUMP**	**Subsequent Treatment**
1	*46*	*G0*	*No Pregnancy*	*Hysterectomy due to uterine mass one year later (STUMP)*
2	*42*	*G3P2A1L2*	*No Pregnancy*	*Hysterectomy due to AUB three year later (Benign)*
3	*49*	*G2P1A1L1*	*No Pregnancy*	*Follow Up*
4	*43*	*G4P4L4*	*No Pregnancy*	*Follow Up*
5	*33*	*G1P1L1*	*CS (14 Month later)*	*Hysterectomy due to uterine mass seven year later (Leiomyoma)*
6	*41*	*G1P1L1*	*CS (24 month later)*	*Follow Up*

Abbreviations: No, Number; STUMP, Uterine smooth muscle tumors of uncertain malignant potential; G, Gravidity; P, Parity (Vaginal Delivery); A, Abortions or Miscarriages; L, Live Births; CS, Caesarean Section; AUB, Abnormal Uterine Bleeding

4. Discussion

Leiomyosarcoma is encountered in approximately 200-800 hysterectomies that are performed for tumors originating from smooth muscle cells and fibroblasts of the uterus (11, 12). Of particular note is the Stanford study published in 1994, which examined 213 uterine smooth muscle tumors that did not meet all the criteria for benign leiomyomas. Bell et al. in this study defined the 'Stanford Parameters' consisting of 3 important prognostic parameters, including a high mitotic index (≥10 mitosis/10HPF), moderate-to-severe atypia, and coagulative tumor cell necrosis. They reported that the presence of at least two of these parameters indicated the presence of malignant tumors with an aggressive course, poor prognosis and high recurrence rates (8). However, in tumors that do not clearly indicate benign or malignant characteristics, the malignant potential remains undefined, and these tumors are thus classified as STUMP (13-16). The available literature for uterine STUMPs is still quite limited.

STUMP is diagnosed by the pathological evaluation of hysterectomy or myomectomy specimens. Due to the lack of standard diagnostic criteria, it is difficult to diagnose stump histologically after surgery. Gupta et al. argued that atypical mitoses, epitheloid differentiation, vascular involvement and infiltrative/irregular borders should be included in the diagnostic criteria, as they can be indicative of negative

outcomes (15). Moreover, different histological combinations such as cellularity, morphology, degree of atypia and types of necrosis make it difficult to determine the malignant potential of these lesions. Thus, predicting prognosis is also difficult (3, 4). Consequently, further research is needed to establish more comprehensive diagnostic criteria for STUMP.

The clinical presentations of STUMP are similar to those of leiomyomas and LMS (17). The majority of our patients (71.4%) were in the premenopausal period, which was consistent with the literature. Recent studies have demonstrated that STUMPs are most commonly encountered in women of reproductive age (18-20). Two studies reported the mean age of diagnosis as 41 and 42.5 years respectively (4, 20), while our study found the mean age to be 44.1 years. In one study, at least 50 mm diameter uterine masses were observed in 80% of patients (21), and another study reported a mean tumor diameter of 80 mm (8). Our study findings indicate an average tumor diameter of 83 mm, which is consistent with previous research. In a study examining the levels of the tumor marker CA-125, it was reported that the value was within the normal range (19). No imaging technique or biomarker is available for preoperative diagnosis of STUMP (4, 20, 22, 23). Moreover, it has been reported that intraoperative frozen examination is unable to provide a definitive diagnosis of STUMP (16, 20). Our study revealed that 50% of frozen patients were reported to be benign, 33.3% to be borderline, and 16.7% to be malignant; thus indicating that the accuracy of the frozen section

Following a diagnosis of STUMP, studies have recommended hysterectomy for patients with completed fertility (24). There is inadequate evidence regarding the preservation or non-preservation of the ovaries. Nevertheless, there appears to be no correlation between the type of surgical procedure, such as myomectomy or hysterectomy, and the rate of recurrence (19, 25). In our study, 50% of the patients underwent myomectomy, while the other 50% underwent hysterectomy. Additionally, one patient underwent hysterectomy following the final pathology report. Three patients subsequently underwent hysterectomy, either as a complementary procedure or due to recurrent fibroids. Overall, 78.6% of the patients underwent hysterectomies, which is consistent with the findings reported in a previous study (17).

STUMP is a slow-growing tumor that can recur approximately 50 months after the initial diagnosis (26). If the patient desires to give birth, fertility can be achieved prior to a hysterectomy, provided that there is close monitoring and follow-up (4, 27). However, the long-term oncological effects of this are still uncertain due to a lack of data. In our study, six patients were followed up, two of whom underwent cesarean delivery. Of these, one (50%) subsequently underwent a hysterectomy and was diagnosed with benign leiomyoma. Of the four patients who did not give birth, two required a hysterectomy and one was confirmed to have a recurrence of STUMP. Our data is invaluable for STUMP patients who desire fertility following myomectomy. Despite the limited number of cases of STUMP diagnosis that have resulted in successful pregnancies and deliveries, this information can be shared with this group to show that pregnancy is possible.

The recurrence rate of STUMPs, which may present as STUMP or LMS, is quite variable and has been reported to range from 8-11% in various studies (8, 9, 25, 28, 29). However, one study reported a recurrence rate of 14% (30). Comparatively, Guntupalli et al. reported a recurrence rate of 7.3% (25). Furthermore, about one-third of the relapse cases recur as uterine leiomyosarcomas (17). For this reason, it is advisable to conduct follow-up every 6 months for the first 5 years, and annually for the following 5 years (31). However, the time to recurrence may vary. Furthermore, the type of surgery did not appear to influence on the recurrence rate or the time to recurrence (28, 30). It has been estimated that around 60% of recurrences involve local recurrence (17). The present study revealed that the median follow-up period was 64.5 months, and a 46-year-old premenopausal patient who had initially been diagnosed with uterine fibroids underwent a hysterectomy one year after myomectomy, only to be diagnosed with STUMP once again. We did not experience any cases of relapse with LMS. The recurrence rate we calculated was 7.2%. Notably, patients who experience recurrent STUMPs have been observed to be 3-10 years younger than those who do not have recurrence (25, 31, 32). However, the age of our patient who relapsed was 46, which was above the mean age. Furthermore, the initial histopathology report of the recurred case showed mild-to-moderate atypia, 2 mitoses in 10 HPFs and there was no evidence of necrosis. Studies conducted on this subject investigated mitosis, atypia, and necrosis in recurrent and non-recurrent tumors, but no significant difference between them could be established (30). Another study discovered that the presence of atypical mitotic figures in uterine STUMP was significantly associated with atypia, but not with the risk of recurrence (33). Morcellation has been linked to an increased risk of recurrence (20, 34, 35). In our case series, one patient who underwent laparoscopic myomectomy followed by morcellation in the endobag, remained free of relapse during the 52-month follow-up period. Although there are no standardized and well-defined guidelines for treatment, surgery should be considered primarily in recurrent disease (9). There is insufficient data to adequately define treatment modalities such as post-surgical chemotherapy, radiotherapy, or endocrine approaches (8, 28).

The limitation of our study was that we were unable to provide a detailed localization of the tumor. Given the retrospective design of the study and the rarity of STUMP, the absence of guidelines for STUMP management can be regarded as a restriction. Few case reports and case series concerning fertility desire in patients with STUMP have been reported (16). We believe that the inclusion of our data on the outcomes of fertility preservation approaches will significantly

enhance the existing literature.

Uterine STUMP is a rare and complex tumor with varying histopathological combinations that can be difficult to define. The accuracy of a frozen section diagnosis may not always be reliable, it is often confirmed after the final pathology has been reported. Patients who desire fertility can be supported. Our research indicates that recurrence rates could be lower in centers where experienced pathologists are making the diagnosis.

Ethical Statement

This study has been approved by the Local Research Ethics Committee of our hospital (Approval No: 114/2022). The study adhered to the tenets of the Declaration of Helsinki and we obtained informed consent from all participants before surgery.

Conflict of interest

The authors have no conflicts of interest relevant to this article.

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None to declare.

Authors' contributions

Concept: S.A., Design: S.A., E.C., S.A., Data Collection or Processing: S.A., E.C., S.A., Analysis or Interpretation: S.A., E.C., S.A., U.K.O, M.A., Literature Search: S.A., U.K.O, M.A. Writing: S.A., U.K.O., M.A.

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