Uterine smooth muscle tumors with uncertain malignant potential: analysis following fertility-saving procedures

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ABSTRACT

Objective The aim of this study was to analyze the clinical and reproductive outcomes of patients treated with myomectomy who were histologically diagnosed with uterine smooth muscle tumor of uncertain malignant potential (STUMP).

Methods Patients who were diagnosed with STUMP and underwent a myomectomy at our institution between October 2003 and October 2019 were identified. Variables of interest obtained from the institution’s database included patient age, relevant medical history, pre-operative appearance of the tumor on ultrasound, parameters of the surgical procedure, histopathological analysis of the tumor, post-operative clinical course, and course of follow-up, including reinterventions and fertility outcomes.

Results There were a total of 46 patients that fulfilled the criteria of STUMP. The median patient age was 36 years (range, 18–48 years) and the mean follow-up was 47.6 months (range, 7–149 months). Thirty-four patients underwent primary laparoscopic procedures. Power morcellation was used for specimen extraction in 19 cases (55.9% of laparoscopic procedures). Endobag retrieval was used in nine patients and six procedures were converted to an open approach due to the suspicious peri-operative appearance of the tumor. Five patients underwent elective laparotomy due to the size and/or number of tumors; three patients had vaginal myomectomy; two patients had the tumor removed during planned cesarean section; and two underwent hysteroscopic resection. There were 13 reinterventions (five myomectomies and eight hysterectomies) with benign histology in 11 cases and STUMP histology in two cases (4.3% of all patients). We did not observe any recurrence as leiomyosarcoma or other uterine malignancy. We did not observe any deaths related to the diagnosis. Twenty-two pregnancies were recorded among 17 women, which resulted in 18 uncomplicated deliveries (17 by cesarean section and one vaginal), two missed abortions, and two pregnancy terminations.

Conclusions Our study found that uterus-saving procedures and fertility-preservation strategies in women with STUMP are feasible, safe, and seem to be associated with a low risk of malignant recurrence, even while maintaining the mini-invasive laparoscopic approach.

WHAT IS ALREADY KNOWN ON THIS TOPIC
⇒ There is a lack of sufficient information regarding the oncological behavior of uterine smooth muscle tumors of uncertain malignant potential (STUMP) and the long-term outcome of patients who underwent fertility-saving procedures.

WHAT THIS STUDY ADDS
⇒ Our study suggests that uterus-saving procedures are a viable and safe option for all patients with STUMP, especially those with reproductive plans.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY
⇒ Patients with a STUMP diagnosis may not require hysterectomy and can pursue pregnancy if pathology is confirmed in expert centers.

INTRODUCTION

Uterine fibroids are primarily diagnosed among women in their 30s and 40s. In recent years, reproductive and social behavior have evolved, with women of more advanced ages expressing fertility desires. Due to this shift, demand for uterus-saving management is growing. Surgical removal of the tumor — myomectomy — remains a standard curative approach with the best reproductive prognosis; furthermore, it provides the opportunity to obtain a specimen for histological analysis, giving it an advantage over less invasive methods, such as focused ultrasonography (US) or uterine artery embolization.

Uterine tumors are classified according to their histopathological structures. Generally, when uterine leiomyoma cannot be determined as a standard/variant leiomyoma, adenomyoma, or leiomyosarcoma it is labeled as uterine smooth muscle tumor of uncertain malignant potential (STUMP). Due to its rare occurrence, lack of sufficient data regarding its biological behavior and long-term outcome, and heterogeneity of histopathological features, women with STUMP ought to be studied. Our study focused on the oncological safety of uterus-saving treatment, reproductive outcomes, and the influence of such an approach on the overall outcomes.
METHODS

This was a retrospective study of prospectively collected data with the approval of the ethics committee of the General University Hospital, Prague (220/20 S-IV). Patients who underwent myomectomy as a fertility-saving procedure and were diagnosed with STUMP at our institution between October 2003 and October 2019 were enrolled. The following data were obtained from our database with the patients’ consent: age at the time of diagnosis, relevant data from patient history, detailed pre-operative description of the uterine tumor using vaginal and abdominal US, parameters of the procedure (surgical approach, peri-operative description, size and number of tumor(s), mode of specimen extraction, blood loss, complications, reason for laparoscopy), post-operative clinical course, course of follow-up focused on clinical symptoms, US findings, recurrences, and reproductive outcomes.

US examinations were performed by a level III ultrasonographer.8 If a uterine tumor was present, we focused on signs indicative of malignancy/abnormality. These markers were established based on the current literature and included: non-uniformity, mixed echogenicity, cystic structures, ill-defined borders, absence of fan-shaped shadowing, and moderate-to-rich inner vascularization, Figure 1.10–12

All surgical procedures were performed by consultant surgeons who specialized in mini-invasive reproductive surgeries. The tumor removal technique was similar for all open, laparoscopic, and vaginal approaches. After vertical incision of the uterine serosa and musculature with monopolar energy, the tumor was reached, and by traction and countertraction was enucleated while eliminating blood loss with bipolar coagulation and/or ligation. The pseudocapsule was preserved, and a multilayer running suture of the myometrium was performed using atraumatic 1–0 absorbable polyglactin stitches (coated vicryl 1–0; Johnson & Johnson, Ethicon US, LLC).13 Hysteroscopic tumor resection was performed using a resectoscope (VersaPoint-Bipolar Resectoscopic System, Gynecare, Ethicon, Inc., Menlo Park, CA, USA) with 0.9% normal saline as the distension medium and a bipolar loop.

During the procedure the following parameters of the tumor were recorded: margins (clear vs poorly defined), texture (solid, homogenous, firm, or rubbery vs soft and/or crumbling), and vascularity (limited to the area of pseudocapsule vs abnormally high, throughout the tumor), Figure 2.14 15 In cases in which the laparoscopic approach was employed, power morcellation was used for extraction of the specimen when both pre-operative US and peri-operative macroscopic appearance of the tumor were non-suspicious (tumor appearing on ultrasound as a well-defined, round lesion with fan-shaped shadowing and circumferential flow, on surgery with clear defined margins, solid texture, and vascularity limited to the area of pseudocapsule).10 14 15 In all other cases we used morcellation in an endoscopic retrieval bag or converted to an open approach. We continued to apply this strategy even after the 2014 Food and Drug Administration (FDA) warning.16

Histopathological classification was performed according to modified Bell et al and WHO criteria.6 All cases were reviewed by an experienced gynecopathologist. The classification of lesions was based on mitotic count, type of necrosis, cytologic atypia, and assessment of cell type. Tumors that showed morphological features, which were either equivocal or exceeded the criteria for usual leiomyoma (and leiomyoma subtypes) but did not fulfill the criteria for leiomyosarcoma, were classified as STUMP. Equivocal features included uncertain cellular types (spindle cell vs epithelioid), mitotic count, and type of necrosis. Other categories of spindle smooth muscle tumor classified as STUMP included tumors with significant (moderate or high-grade) atypia and mitotic count in the range 6–9/10 high power field (HPF), tumors without significant nuclear atypia with coagulative (tumor-type) necrosis and <10 mitoses/10 HPF, and tumors without significant nuclear atypias or coagulative necrosis with ≥15 mitoses/10 HPF. Figure 3

The follow-up regimen comprised consultation, vaginal and abdominal US examination (to exclude recurrence in/outside pelvis), and clinical examination 1 month post-surgery and then every 6 months. Reoperation was planned for patients with recurrence of a tumor exceeding 2 cm in and/or showing any markers suggestive of abnormality/malignancy. The diameter threshold was established based on empirical experience. The same US parameters were...
used to evaluate the image of the lesion as on the pre-operative US. These reinterventions were performed with respect to reproductive plans; in patients with no further pregnancy plans hysterectomy was indicated, while a uterus-sparing procedure was preferred in all other patients.

RESULTS

The medical records of 46 patients with a histologically confirmed diagnosis of STUMP who underwent uterus-saving surgery were reviewed. Median patient age was 36 years (range, 18–48 years). Median diameter (according to pre-operative US) of the largest extracted myoma was 6 cm (range, 1–30 cm) with a median weight of 121 g (range, 5–11 000 g). The 1 cm myoma was extracted during a planned cesarean section.

In 34 patients (73.9 %) a laparoscopic procedure was chosen as the primary surgical approach. Power morcellation was used for specimen extraction in 19 cases (59.5% of laparoscopic procedures). We used an endoscopic retrieval bag in nine cases and converted to an open myomectomy in six cases due to the suspicious peri-operative appearance of the tumor. Five patients underwent elective open procedures due to the size and/or number of tumors; two had the tumor extracted during cesarean section; three had vaginal myomectomy due to cervical localization of the tumor, and two underwent hysteroscopic resection. For a more detailed description of the pre-operative and peri-operative appearance in the subgroups see Table 1. The frequencies of the histopathological features of STUMP are summarized in Table 2.

Two patients were lost to follow-up, and four were seen only by their outpatient gynecologist. According to their statement, these patients have shown no clinical or US signs of recurrence and have not required reintervention to date. There were 13 surgical reinterventions (28.3%) including eight hysterectomies. Two women underwent the procedure for recurrence of uterine tumor after 78 months (abdominal hysterectomy with bilateral salpingectomy) and 96 months (laparoscopically-assisted vaginal hysterectomy with bilateral salpingectomy) after the primary procedure, with benign leiomyomas as their final histology. Six patients underwent total laparoscopic hysterectomy with bilateral salpingectomy at their own request. Four of these patients with no further fertility desires underwent the procedure 2–5 months after the primary intervention: three with conventional leiomyomas, and one with epithelioid leiomyoma as final histology. Two patients underwent hysterectomies after finalizing their reproductive plans 23 and 50 months post-procedure with cellular leiomyoma and conventional leiomyoma plus adenomyosis, respectively, as final histology.

Five patients desiring fertility underwent laparoscopic re-myomectomy for uterine tumor recurrence. Knowing the history of STUMP, we extracted the specimen using an endobag. Histology showed benign lesions in three patients: one conventional, one cellular leiomyoma, and one adenomyoma. In two patients the extracted tissue was histologically classified as STUMP for moderate-to-high-grade atypia and epithelioid cellular type. Both women underwent hysterectomy. One had planned peripartum hysterectomy during her second cesarean section (both pregnancies occurred after laparoscopic re-myomectomy) with leiomyoma with bizarre nuclei as the final histology. The other patient had a total laparoscopic hysterectomy with bilateral salpingectomy and resection of a 3 cm tumor from the area of the left iliac vessels 5 years after the primary procedure. Histology revealed a conventional leiomyoma of the uterine body and adenomyosis in the distant mass.

Forty patients underwent follow-up conducted exclusively in our hospital. The mean follow-up period was 47.6 months (median, 30; range, 7–149 months). We continued with follow-up, even in patients who underwent hysterectomy. Nine patients returned to the care of their outpatient gynecologists after a mean follow-up of 76.2 months (median, 78; range, 23–149 months). One patient was released from our care after 23 months because she moved out of the country. We did not observe any uterine malignancy or deaths related to the diagnosis.

Of 42 patients with unfinished reproductive plans, 22 pregnancies were recorded among 17 women (40.5%), which resulted in 18 uncomplicated deliveries. One patient delivered vaginally at the 35th gestational week, and 17 underwent cesarean section (due to previous surgery of the uterus and nulliparity): 15 at term and two late preterm (35w1d, 36w3d). There were two first-trimester missed abortions and two terminations for unwanted pregnancy.

There were two elective hysterectomies after pregnancy; both showed benign histologies. The remaining 15 patients had stable (four women with solitary myoma up to 2 cm and typical US features) or negative US on follow-up and no clinical symptoms. The mean follow-up period of women who became pregnant was 68 months (range, 7–149 months) after myomectomy and 45 months (range, 11–137 months) after the first trimester of the first pregnancy following the primary procedure.

DISCUSSION

Summary of Main Results

According to our analysis, patients diagnosed with STUMP may not require a hysterectomy immediately. In particular, in patients with unfinished reproductive plans, a uterus-preservation strategy seems feasible and safe, and efforts to conceive can be encouraged.
Results in the Context of Published Literature

The symptoms of STUMP are non-specific and do not differ from those of benign leiomyomas or leiomyosarcomas. The pre-operative diagnostic process is also same with US as the first-line imaging technique. It is difficult to reliably distinguish STUMP from other uterine musculature tumors. According to the Morphological Uterus Sonographic Assessment (MUSA) criteria, there are no ultrasonographic findings typical of STUMP.

Determining the potential tumor malignancy prior to surgery is crucial for deciding the surgical approach and type of specimen extraction. The low pre-operative (US) and peri-operative correct detection of STUMP lesions in our group confirms the difficult diagnosis of these tumors. There is ongoing research into identifying the tools to differentiate between benign and potentially malignant uterine tumors. A study by Cotrino et al offers new specific characteristics of STUMP identifiable on US. These tumors appear heterogeneous, without calcifications, without shadowing and regular borders, with internal microcystic anechoic areas, and with both circumferential and intralesional vascularization. A study by Ho et al stated that using fluorodeoxyglucose-PET prior to surgery can safely distinguish leiomyosarcoma or STUMP from benign leiomyoma. Suzuki et al proposed a new MRI grading system for fibroids, focusing on variant leiomyomas and STUMP. Based on MRI characteristics, uterine fibroids were categorized into five subgroups, determining two subgroups unsuitable for morcellation, and proposing hysterectomy in women with fulfilled fertility desires. Despite these new findings, US remains the first-line examination method, due to lower cost, better accessibility, and comparable yield, even more in centers with expert US facilities.

Laparoscopic myomectomy is associated with less pain, lower blood loss, shorter hospital stays, faster recovery, and decreased incidence of post-operative adhesions than the open approach. Until the 2014 high-profile case of occult sarcoma after uterine morcellation and its subsequent ban, power morcellation was the method of choice for specimen extraction. Cell dissemination during morcellation is suspected to cause parasitic leiomyomas, iatrogenic adenomyosis, disseminated leiomyomatosis, or spread and upstage undetected uterine sarcoma. In a systematic review by Van der Meulen et al the overall incidence of parasitic myomas after laparoscopy via morcellation was reported to be between 0.12% and 0.95%. We had one case (2.17%) of iatrogenic adenomyosis that was resected from the left iliac vessel during total laparoscopic hysterectomy in a patient who underwent two laparoscopic myomectomies 5 years prior, the first one with use of morcellation and the second with endobag specimen extraction.

In a meta-analysis by Pritts et al, the risk of occult leiomyosarcoma found during surgery for presumed benign fibroids was approximately 1 in 2000. When the meta-analysis was restricted to only prospective studies, the result was 1 leiomyosarcoma per 8300 surgeries, which is less frequent than previously estimated. There has been a return to open procedures and abrupt development of new specimen extraction techniques such as contained morcellation. However, recent studies report the detection of leiomyoma cells in peritoneal washings after open myomectomy and even after the use of in-bag morcellation. New methods for decreasing the risk of dissemination during power morcellation are currently being studied. A study by Yu et al suggested that rigorous irrigation with up to 3 L of saline solution reduced the risk of dissemination. Because of the rare occurrence and indolent nature of STUMP tumors, we can only speculate on the incidence of iatrogenic peritoneal implants and their potential biological consequences.

Table 1  Types of procedure and frequency of tumor abnormalities on pre-operative ultrasound or peri-operatively

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>LM</th>
<th>OM</th>
<th>VM</th>
<th>CM</th>
<th>HM</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (n)</td>
<td>28</td>
<td>11†</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>46‡</td>
</tr>
<tr>
<td>Abnormal tumor appearance on US (but normal peri-operative appearance)</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Abnormal peri-operative tumor appearance (but normal on US)</td>
<td>2</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Abnormal peri-operative and US tumor appearance</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>No abnormalities</td>
<td>19</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>27</td>
</tr>
<tr>
<td>Reintervention</td>
<td>9</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>13</td>
</tr>
</tbody>
</table>

*Six of these procedures started laparoscopically and were converted to open myomectomy.
†During the study period 2206 patients underwent fertility-saving procedures for uterine fibroids at our institution of which 46 had a histologically verified uterine smooth muscle tumor of uncertain malignant potential (STUMP).
CM, cesarean myomectomy (performed during cesarean section); HM, hysteroscopic myomectomy; LM, laparoscopic myomectomy; OM, open myomectomy; US, ultrasonography; VM, vaginal myomectomy.

Table 2  Histopathological analysis of the specimens from 46 patients with uterus-saving procedures and diagnosed with uterine smooth muscle tumor of uncertain malignant potential (STUMP)

<table>
<thead>
<tr>
<th>Histological features of STUMP</th>
<th>All patients (n (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None present</td>
</tr>
<tr>
<td>Coagulative necrosis</td>
<td>13 (28.3)</td>
</tr>
<tr>
<td>Cytologic atypia</td>
<td>27 (58.7)</td>
</tr>
<tr>
<td>High cellularity</td>
<td>38 (82.6)</td>
</tr>
<tr>
<td>Epithelioid cellular type</td>
<td>38 (82.6)</td>
</tr>
<tr>
<td>Mitotic count &gt;5 over 10 HPF</td>
<td>34 (73.9)</td>
</tr>
</tbody>
</table>

*Only 4 (8.7%) cases with mitotic count >10.
HPF, high power field; STUMP, smooth muscle tumor of uncertain malignant potential.
The WHO defines STUMP as an entity of tumors that cannot be histologically diagnosed as unequivocally benign or malignant. According to the Stanford criteria by Bell et al, the most used classification system of fibroids, STUMPs fail to meet the definition of either leiomyosarcoma or benign leiomyomas. In a more specific categorization proposed by Guntupalli et al, the histopathological description focuses on type of tumor cell necrosis, cytological atypia, mitotic index, cellularity, tumor margins, and vascular invasion at the periphery of the tumor, forming five sets of criteria for STUMP. Other classification systems have been suggested by Gupta et al and D’Angelo and Prat. The histopathological criteria defining STUMP lack uniformity and standardization, which contributes to potential overdiagnosis of these tumors. Due to this discrepancy, we suggest central referral for these patients, and that the final diagnosis should be made by a pathologist experienced in gynecological oncology. Although our pathological samples were reviewed by the same team of pathologists, there were only 11 cases of STUMP recorded at our institution from 2003 to 2011, and 35 cases of STUMP recorded from 2012 to 2019. This could be explained by a shift in reproductive behavior, rising demand for uterus-saving procedures, the refinement of histological diagnostic criteria, and growing awareness of how to classify these lesions.

The two largest cohorts of patients with STUMP found in the literature included uterine-sparing procedures and hysterectomies. A report by Guntupalli et al included 10 myomectomies and 31 hysterectomies, with a recurrence rate of 7.3% (3/41, all after hysterectomy). Final histology from recurrent tumors classified two cases as STUMP and one as leiomyosarcoma. Sahin et al included 27 patients after myomectomy, and 30 after hysterectomy, with a recurrence rate of 14.0%. The final histology was STUMP in seven patients and leiomyosarcoma in one patient. In both studies the recurrence rate was similar in the myomectomy and hysterectomy groups, suggesting that hysterectomy does not prevent recurrence. In our cohort the reintervention rate was 28.3%. This was influenced by the uterus-preserving approach used in all patients, and by the number of patients requesting prophylactic hysterectomy after finalizing their reproductive wishes. STUMP recurrence was detected only twice (4.3%). There were no cases of uterine malignancy.

Strengths and Weaknesses
The strength of this study lies in the fact that all primary operations and reinterventions were performed by a single team of gynecological surgeons at a tertiary care center. The weakness is that follow-up of six patients (13.0%) was done outside the care of this team. Furthermore, all histological slides were reviewed by a single team of pathologists with experience in gynecopathology, although conversely there was no re-review of the slides done for the purposes of this study. To the best of our knowledge this is the largest cohort of patients diagnosed with STUMP who underwent uterus-preserving surgery. Nevertheless, due to the uncertain biological nature of STUMP tumors, patients’ desire, and recurrence of fibroids, eight patients had a hysterectomy as their final procedure. The small number of patients is also considered a study constraint. However, the main limitation of this study lies in its retrospective nature, which in turn leads to other limitations such as inconsistent surgical approach to primary procedure and unclear criteria for reintervention by hysterectomy or re-myomectomy.

Implications for Practice and Future Research
Our results suggest that uterus-preserving procedures may be a viable option for all patients with STUMP, especially those with reproductive plans. Such patients should be monitored at tertiary care centers experienced in the diagnosis and treatment of these tumors. Follow-up should consist of detailed vaginal and abdominal US. Length of surveillance and its optimal interval remain unclear. Most importantly, it seems that hysterectomy is not mandatory, and pregnancy can be encouraged in post-myomectomy patients with STUMP.

CONCLUSIONS
Our findings suggest that fertility-preserving strategies in women diagnosed with STUMP may be feasible and safe. However, it is essential that pathology is always evaluated by an expert gynecologic oncology pathologist and that patients should remain under close surveillance.

Contributors All authors contributed substantially to the study conception and design. Data acquisition was mainly done by AR, BB, ZL, and KH. AR drafted the manuscript and is the guarantor of this paper. Revisions were mainly done by MM. All the authors read the final revised manuscript and approved it for publication.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Ethics Committee of the General University Hospital, Prague (220/20 S-4). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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REFERENCES
Original research

24 Ödejmni F, Aref-Adlb M, Lioi N, et al. Rethinking the issue of power morcellation of uterine fibroids: is morcellation the real problem or is this another symptom of disparity in healthcare provision? In Vivo 2019;33:1393–401.