

Original Research

Retrospective Analysis on Characteristics of Uterine Smooth Muscle Tumors of Uncertain Malignant Potential—13 Years' Experience

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Abstract

Background: Benign leiomyomas (LM) and malignant leiomyosarcomas (LMS) can be distinguished by increased cellularity with mitotic activity. Uterine smooth muscle tumors of uncertain malignant potential (STUMP) are a group of rare tumors in between, for which there is still no standardized classification, nor any definitive preoperative imaging or laboratory investigations regarding the possible inclusion of STUMP in the differential diagnosis. **Methods:** In this study, we retrospectively reviewed 6 cases of STUMP, and assessed their pathogenesis, risk factors, and prognostic features. **Results:** The mean age of STUMP patients was 40.6 years old. No recurrence has been reported in all six cases after more than 3.6 years of follow-up. The mean tumor size was 9.44 cm (range 6.14–12.21). 4 cases (66.7%) with <5 mitoses, 1 case (16.7%) with 5–9 mitoses, and 1 case (16.7%) with >10 mitoses per 10 high-power fields. Immunohistochemical staining for cyclin dependent kinase inhibitor 2A (p16), tumor protein p53 (p53), and Antigen KI-67 (Ki-67) was 100% positive (2/2, 6/6, and 6/6, respectively). The estrogen receptor (ER) expression rate was 50.0% (3/6), and the progesterone receptor (PR) was 33.3% (1/3). There was no correlation between the expression of these biomarkers and mitotic counts or recurrence. **Conclusions:** The current immunohistochemical biomarkers are ineffective in determining the probability of malignancy in STUMP patients with desire of further fertility. Detection of gene expression profiles or variants using next-generation molecular techniques may aid in disease prediction, diagnosis, treatment, and prognosis.

Keywords: uterine smooth muscle tumor; STUMP; mitotic activity; malignancy potential; atypical leiomyoma; leiomyosarcoma

1. Introduction

Uterine smooth muscle tumors of uncertain malignant potential (STUMP), first discovered by Kempson [1] in 1973, is a group of unusual smooth muscle tumors with histopathological features between the diagnostic criteria for benign leiomyomas (LM) or malignant leiomyosarcomas (LMS). These tumors were characterized by three features: diffuse or multifocal atypia, tumor necrosis, and mitotic activity, and classified into the categories of recurrence, limited experience, and low malignancy potential. Then later in 1994, Kempson and his Stanford colleague Bell further investigated the clinicopathological features of 213 problematic smooth muscle neoplasms and classified into 5 groups using these features other than just mitotic indexes to predict clinical outcomes in each group. It is known as the Stanford Criteria [2–4]. In 2003, the World Health Organization classifies leiomyoma variants as benign with a low risk of recurrence, and STUMP belongs to a group of smooth muscle tumors that cannot be diagnosed reliably and solely as benign or malignant [5]. The largest study of uterine STUMP was performed by Guntupalli *et al.* [6]. They divide STUMP into five categories based on

different histological features.

Given the high heterogeneity and equivocity in clinical and pathological features as well as the overlap with LM and LMS, no definition of STUMP has been standardized and treatment strategies vary greatly [7]. The decision between myomectomy and hysterectomy remains unclear. For young patients with desire of further fertility, a balance between risks and benefits ought to be discussed. A literature review of 14 articles on myomectomy versus hysterectomy conducted by Vilos *et al.* [4] highlights therapeutic dilemmas associated with patients diagnosed with STUMP who wish to maintain fertility. Among 76 patients with STUMP treated with myomectomy solely, 5 (6.6%) experience recurrence of disease as mitotically active leiomyoma with no cellular atypia. Patient lived without complications. 71 of 76 patients (93.4%) who underwent myomectomy as the sole treatment exhibited no evidence of recurrent disease with follow-up ranging from 1 to 216 months. Of 14 patients in whom treatment initially consisted of myomectomy followed by hysterectomy, residual tumor was found in 2 (14.3%), and no residual STUMP was found in 2 (14.3%). Peters *et al.* [8], nevertheless, reported a case



Table 1. The symptoms and procedures of patients with diagnosed uterine STUMP.

Case no.	Age	Parity	Initial symptoms	Procedure	Frozen section
1	47	2	Urinary frequency & bloating	hysterectomy + LSO	Spindle cells
2	42	1	Urinary frequency & menorrhagia	hysterectomy + LSO	Not done
3	30	1	Menorrhagia	Myomectomy then hysterectomy	Not done
4	57	2	Mild abdominal pain & urinary frequency	hysterectomy + BSO	Not done
5	29	0	Incidental finding from missed abortion US	Myomectomy	Not done
6	65	2	Hematuria (referred from GU)	Hysterectomy + LSO	Not done

LSO, left salpingo-oophorectomy; BSO, bilateral salpingo-oophorectomy.

Table 2. Histopathological features of uterine STUMP patients.

Case no.	Tumor Size (cm)	Margin	Atypia	Mitosis	Necrosis	IHC stains	Recurrence
1	11 × 9 × 8 intramural	tumor involvement	moderate	2	none	p16+, p53+, ER–, PR+, Ki-67 low, HIF+	none at 12.8 y
2	12 × 11 × 6 intramural	free	mild	7	none	p53 focally weak+, ER+, PR–, Ki-67 moderate	none at 8.5 y
3	12.5 × 11 × 12 subserosal	free	moderate to severe	20–25	presence (hemorrhagic)	p16+, p53+, ER–, PR–, Ki-67 moderate	none at 8.0 y
4	7 × 9 × 8 intramural	free	mild	3	none	p53 focally+, ER+, Ki-67 moderate	none at 5.9 y
5	7 × 6 × 5.5 subserosal	tumor involvement	moderate	3	none	p53+, ER–, Ki-67 moderate	none at 5.4 y
6	14 × 13 × 10 intramural	free	mild	1–2	presence	p53 focally+, ER+, Ki-67 moderate	none at 3.6 y

p16, cyclin dependent kinase inhibitor 2A; p53, tumor protein p53; Ki-67, Antigen KI-67; ER, estrogen receptor; PR, progesterone receptor; +, positive; –, negative; HPF, high power fields.

of peritoneal recurrence of STUMP after extensive hysterectomy and adjuvant chemotherapy, and unfortunately still died 12 months after treatments. A meta-analysis published by Rizzo *et al.* [9] showed that the use of adjuvant chemotherapy did not reduce the recurrence rate of early LMS. It is to confirm that, the recurrence and disease outcomes do not depend solely on treatment modalities and that morphological variant of the disease defers on individual basis. It is the best to consider patient's age, fertility desire, tumor size, histological features, and patient's preference when confronting with STUMP.

Since there are no standard guidelines for the diagnosis, treatment, and follow-up of patients with uterine STUMP, the pathogenesis, risk factors, and prognostic features of STUMP remain to be elucidated. Our study deepens understanding of STUMP with a retrospective analysis using 13 years of experience at a single institution.

2. Materials and Methods

2.1 Study Design, Population, and Ethical Approval

A case series study was conducted from September 2008 to September 2021 in Cardinal Tien Hospital, Main branch, a Class 1 regional teaching hospital. A total of six cases of uterine STUMP with complete data were recruited and studied retrospectively. The ethical approval was ob-

tained from the Institutional Review Board of Cardinal Tien Hospital (No. CTH-111-3-5-018).

2.2 Data Collection

We describe a case series of 6 women with initial symptomatic myomas or abnormal uterine bleeding from Cardinal Tien Hospital. The patients' initial clinical presentation, fertility desire, type of surgery received, imaging, histopathological and immunochemical staining, follow-up, and recurrence were recorded retrospectively.

3. Results

Of all the six cases we recruited in our study shown in Tables 1,2 cases (33.3%) were postmenopausal, and the other 4 cases (66.6%) were premenopausal. The mean age was 40.6 years old. We re-evaluated preoperative sonographic images of patients, and discovered that almost all had well-defined margins. All 6 cases (100%) showed heterogeneity with partly hyperechoic regions, 2 cases (33.3%) had cystic degeneration of the tumor, 1 case (16.6%) showed tumor calcification, 2 cases (33.3%) had posterior enhancement and 2 cases (33.3%) had lobulated nodules of various sizes. Three of them (50.0%) underwent endometrial aspiration prior to surgical intervention, which revealed simple hyperplasia without atypia. Frozen

section was requested in only one case (16.6%) since the preoperative imaging (computed tomography) showed cystic cavities with irregular walls. All these atypical features prompted physicians to order an intraoperative frozen section under the suspicion of endometrial stromal sarcoma, undifferentiated endometrial sarcoma, or other malignant stromal malignant tumors rather than a simple benign leiomyoma. The other case was a 30-year-old female who had completed childbearing and was diagnosed with STUMP after a regularly scheduled myomectomy. After a thorough explanation of the disease nature, the patient preferred to undergo a subsequent hysterectomy 4 days following myomectomy while she was still in postoperative recovering.

As shown in Table 2, the anatomical localizations of STUMPs were intramural 4 cases (66.7%) and subserosal in 2 cases (33.3%). Intraoperative frozen section was conducted in all six cases. The mean tumor size was 9.44 cm (range 6.14–12.21). Two STUMPs had tumor involved margin (33.3%). As for pathology, these tumors appeared to be between typical LM and LMS generally. According to mitotic count per 10 high-power fields (HPFs), there were 4 cases (66.7%) with <5 mitoses, 1 case (16.7%) with 5–9 mitoses, and 1 case (16.7%) with >10 mitoses. Three cases (50.0%) were mild atypia, one (16.6%) was moderate atypia, one (16.6%) had central necrosis, one (16.6%) had severe necrosis with massive hemorrhage, and one (16.6%) had bizarre giant cells and marked ischemic change. The immunohistochemistry staining was available in all 6 cases. The expression rate of p16, p53 and Ki-67 was 100% (2/2, 6/6, and 6/6, respectively). The positive rate of ER was 50.0% (3/6), and that of PR was 33.3% (1/3). Of all the patients, the youngest one (case no. 5) was a 29-year-old married female with gravida 2, para 0, abortion 1, whose STUMP was found incidentally during a myomectomy after her prior dilation and curettage (D&C). A fundal wall myoma was discovered during her miscarriage under sonography. No recurrence was found during postoperative follow-up up to 5.4 years. She is currently onto her second pregnancy at 20 + 5/7 gestational weeks. None of the patients displayed any sign of recurrence at the 5-year follow-up.

We found no correlation between tumor size, mitotic count, atypia, necrosis, and recurrence. Although it is not rare to find recurrence and metastasis years after surgery reported by other medical facilities, no recurrence has been reported in all six cases so far. Some studies reported recurrence rates STUMP as high as 7.3–26.7% [6,8–12], especially higher in some cases with nuclear atypia, frequently associated with adverse outcomes.

Even though no recurrence or death was found in our 5-year follow-up of STUMP patients who underwent surgery from 2008 to 2022, it could be the result of our scant of case number compared to other multi-disciplinary medical centers. As a matter of fact, patients who were diagnosed and operated on STUMP should be followed up for

a longer term.

4. Discussion

It is crucial to differentiate benign leiomyomas from uterine sarcomas or leiomyosarcomas since the latter poses great morbidity and mortality worldwide and account for nearly 15% of all female cancers [10]. However, we are confronted with a group of smooth muscle tumors that also originates from uterus itself but yet its malignant potential cannot be precisely predicted with our current understandings. STUMP shares phenotypic features between benign myoma and malignant leiomyoma, which makes the differentiation challenging for gynecologists and pathologists preoperatively and even postoperatively [11]. Precautionary measures are usually taken whenever there is suspicion of STUMP, but are they really necessary? Excessive measures such as hysterectomy and bilateral lymphadenectomy do lead to scarring, irreversible infertility, possible infection and lymphedema, and rarely, limb numbness as result of nerve damage. So far experts have not reached a consensus on treatment modality for STUMP, again, owing to its ambiguous nature.

The clinical presentation, laboratory, and radiological findings vary greatly among our patients with STUMP. There are no specific symptoms and signs of STUMP, and it can occur in all age groups. According to literatures and our own analysis, the initial presenting symptoms of STUMP coincide with those of uterine leiomyoma and even some, with uterine leiomyosarcoma. STUMP also shares some common symptoms with those of LM and LMS, such as abnormal uterine bleeding, pelvic pain, bearing down pressure, which makes the preoperative discrimination challenging. Simple diagnostic criteria like poorly defined tumor margin, absence of acoustic shadow, non-myometrial tumors, and moderate to high signal intensity under T1 or T2 sequences of magnetic resonance imaging (MRI), can question the diagnosis of simple benign uterine fibroids but inclusion of malignant entity is not definitive when, often is the case, not all the malignant features are present [12]. Currently, the definitive diagnosis still relies on histopathological confirmation. The management of individual cases may be modified based on preoperative sonographic findings (e.g., tumor margins, presence of suspicious cystic change, and areas of heterogeneity) and clinicopathologic prognostic factors (e.g., size, mitotic activity, age, and presence or absence of vascular invasion). Since STUMP cannot be diagnosed preoperatively and the recurrence is unpredictable, treatment approaches and follow-ups remain controversial. To the best of current knowledge, radical resection is considered to be the only curative treatment. For those who have fertility desire, fertility-sparing approach such as myomectomy and local tumor excision may be recommended, with more prompt follow-ups. However, the oncological outcome of STUMP remains unknown due to limited experience and data. For those who are menopausal

or have completed childbearing, hysterectomy is highly recommended. Surprisingly, Rizzo *et al.* [7] found that a greater portion of those who relapsed were younger regardless of the disease's indolent behavior and protracted survival. According to some studies, STUMP patients are found to relapse after a mean of 51 months, and they have a mean life expectancy of 61 months and a 5-year overall survival of 92% [7,9].

No single morphologic feature clearly classifies uterine smooth muscle tumors into benign or malignant histological types [13]. To date, the potential malignant predisposition cannot be quantified according to the existing literatures. In recent literature reviews, immunochemical staining has emerged as one of the main diagnostic tools for the evaluation of myometrial tumors. Previous clinical studies have reported biomarker candidate factors such as cyclin E (CCNE), low molecular protein 2 (LMP2), and caveolin 1 (CAV1) for uterine mesenchymal tumors; however, no clinical link between their expression and the malignancy of STUMP has been observed [14,15]. Over the past decade, studies have also put great focuses on immunohistochemical staining for biomarkers such as epithelial growth factor receptor, vascular endothelial growth factor, galectin-3, p16, p53, Ki-67, Twist, B-cell lymphoma 2 (BCL-2), estrogen receptor, and progesterone receptor, to identify uterine smooth muscle tumors and of those with a higher risk of recurrence [16–19]. Mittal and Demopaulos used different immunochemical markers to distinguish LM, STUMP and LMS, and found that most LM and STUMP had positive PR expression whereas LMS had more ER expression [18]. Moreover, increased expression of Ki-67 and p53 and a progressive loss of steroid expression were seen more frequently in LMS compared than in LM and STUMP [19]. Positive Ki-67 expression is associated with tumor aggressiveness, clinical progression, and vascular invasion of LMS, while low Ki-67 expression is observed in patients with prolonged survival [17]. O'Neill *et al.* [19] also discovered that p16 expression seems to be much higher in LMS and its presence in STUMP suggests a worse prognosis. In another study reported by Atkins *et al.* [20], metastatic STUMP also had strong positive staining for p16. Based on these results of histochemical profile, conclusion was drawn that STUMP is much closer to LM than LSM. In this study, we found that all cases carried Ki-67 and p53 expression, about 3/6 cases had expression of ER, and 1/3 cases had PR positive. There was no correlation between the expressions of these biomarkers with the mitotic count per 10 HPFs or recurrence. This suggested that a more well-defined biomarker is required to identify this disease. With the advancement of next-generation molecular technologies, detection of gene expression profiles or variants may be useful for disease prediction, diagnosis, treatment, and prognostic assessment. Astolfi *et al.* [21] have performed a comprehensive genomic database analysis to identify mutated molecular markers of LMS,

such as p53, retinoblastoma tumor suppressor (RB1), alpha thalassemia/mental retardation syndrome X-linked (ATRX) or phosphatase and tensin homolog (PTEN). Even though these molecular markers have neither been shown to have clinical impact nor can be adequately considered in practice, bioinformatics information may give us extra strength to identify the future tendency of tumors that particularly meet with criteria of a STUMP.

Nonetheless, this study has some limitations, including the relatively small sample size of STUMP, the relatively short median follow-up time, and its retrospective design for patients who may have chosen to be followed up at other hospitals. In addition, the results of immuno-histochemical staining can be affected by differences in the selection of antibodies, staining procedures and personnel interpretation, which may cause experimental bias. However, despite these limitations, our study provides the accumulative knowledge of current discovered biomarkers and provides additional information on this topic.

5. Conclusions

In conclusion, with the understanding of the molecular expression and identifying of key biomarkers involved in tumorigenesis, we hope that independent prognostic information can be provided for individual STUMP in each clinical spectrum in the presence of these proactive molecular risks, and further construct more individualized treatment plans for each patient.

Author Contributions

YML conceived the idea, designed the study and collected the data. YML and SYH drafted the article. YML and TJL critically revised the article for important intellectual content. CKC and SWT provided administrative, technical, logistical, or material support. All authors approved the final draft of the article and provided their consent for publication.

Ethics Approval and Consent to Participate

Informed consent was not required for a retrospective study. The ethical approval was obtained from the Institutional Review Board of Cardinal Tien Hospital (No. CTH-111-3-5-018).

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Conflict of Interest

The authors declare no conflict of interest.

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