

Uterine smooth muscle tumours of uncertain malignant potential: single-centre experience and review of the literature

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Abstract

Introduction: Uterine smooth muscle tumours of uncertain malignant potential (STUMPs) are a rare histologically heterogeneous group of uterine smooth muscle tumours (SMTs). Their malignant potential and clinical differentiation between leiomyoma and leiomyosarcoma remain uncertain prior to surgical removal.

Aim of the study: To investigate the patients and tumour characteristics of patients with STUMPs and to propose algorithms for optimal diagnosis, treatment, and follow-up management.

Material and methods: This was a single-centre retrospective cohort study of all patients who underwent surgery for a preoperative diagnosis of uterine myoma at the University Hospital "Dr. Georgi Stranski", Pleven, Bulgaria during a period of 33 months (from January 2013 until October 2015). Data were obtained from the medical history records. We performed descriptive analysis to characterise the patient population (e.g. demographics, age, contraceptive use, and complaints that led to the diagnosis) and the tumour characteristics. Last data were obtained prior May 2019.

Results: A total of 320 medical records were retrospectively evaluated. The preoperative diagnosis of myoma was confirmed in 279 of the cases (89.4%). In 27 (8.3%) cases the final histological result was completely different. In 14 (2.3%) a histological postoperative diagnosis of STUMP was identified. All 14 STUMP lesions were intramural with a median size of 7.5 cm (range 3.5 to 15 cm). The median age at diagnosis of STUMP was 45.4 years (range 36 to 52 years), and 92.9% ($n = 13$) of the patients were premenopausal. Ultrasound data of a rapidly growing myoma were a reason for diagnosis in only three patients (25%), whereas 92.9% of the patients ($n = 13$) presented with heavy menstrual bleeding with or without anaemia. After surgery, none of the patients with STUMP experienced a relapse of the disease within the median follow-up time of 48 months ($R = 40-78$).

Conclusions: STUMP tumours are rare tumours, predominantly diagnosed in premenopausal women. They define a group of patients with very good long-term prognosis. Therefore, longer follow-up is needed to allow for conclusions on recurrence rate and survival.

Key words: myoma, smooth muscle tumours with uncertain malignant potential, leiomyosarcoma, operative treatment.

Introduction

Uterine smooth muscle tumours are divided into benign (leiomyoma) or malignant (leiomyosarcoma). This differentiation is based on histological criteria such as the presence of tumour cell necrosis, cytological atypia, and mitotic activity of the tumour cells [1]. The term uterine smooth muscle tumours of uncertain malignant

potential (STUMP) was used for the first time in 1973 by Kempson [2]. It relates to an intermediate group of tumours, which cannot be histologically diagnosed as unequivocally benign or malignant [1]. No particular risk factors or prognostic features have been identified yet, and their aetiology is not fully understood. STUMPs are rare and most frequently affect women in their mid-forties. Their diagnosis is most often histological

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and made after surgery. In most cases the indication for surgery is the presence of uterine leiomyoma. After hysterectomy or myomectomy, STUMP has been identified with a frequency of 0.01% [3].

Clinically, STUMP may present as either a benign or malignant tumour: there have been reports in the literature of locoregional recurrence or distant metastases [1]. The absence of adequate data about the risk of relapse or metastasis of STUMP leads to a discussion about the best surgical approach: laparoscopic or by laparotomy – as well as about the extent of the surgery: hysterectomy or myomectomy. Ovarian preservation is also debatable. The postoperative management of patients with STUMP as well as the follow-up recommendations remain highly variable, depending mostly on local standards and practices.

Material and methods

This was a single-centre, retrospective cohort study of all patients who underwent surgery for a preoperative diagnosis of uterine myoma at the University Hospital “Dr. Georgi Stranski”, Pleven, Bulgaria during a period of 33 months (from Jan 2013 until Oct 2015). Data were obtained from the medical history records; all files of women who underwent gynaecological surgery (hysterectomy or myomectomy) with a preoperative diagnosis of myoma were evaluated in order to identify the incidence rate of STUMP.

After anonymisation of personal data, descriptive statistics was used to characterise the patient population: data about patients' demographics (age at diagnosis), surgical management (myomectomy vs. hysterectomy), tumour characteristics (histological features, size, etc.), and postoperative management and follow-up were recorded. Pathological tumour size and morphological characteristics such as tumour cell necrosis, cytological atypia, and mitotic activity of the tumour cells were also recorded. Patients were followed up until May 2019.

Results

We evaluated 320 medical records of patients submitted to gynaecological surgery for uterine myoma. Patients' characteristics are shown in Table 1.

In 89.4% of all 320 patients ($n = 279$) the preoperative diagnosis of myoma was confirmed by postoperative histology, and in 8.3% ($n = 27$) the diagnosis was completely different: 17 patients were diagnosed with an ovarian tumour, seven patients with sarcoma, and three with endometrial cancer. In 14 cases a histological postoperative diagnosis of STUMP was given, describing a 2.3% incidence rate. In all patients the tumour lesion was single and intramural with a median size of

7.5 cm (ranges 3.5 to 15 cm). 92.9% ($n = 13$) of all patients were diagnosed prior to menopause, with a median age at diagnosis of STUMP of 45.4 years (36-52 years). History of hormone use (in particular, progestogen and contraceptive pill) was present in 83.3% ($n = 10$) for a median of 2 years (range 0.5 to 7 years). Heavy and prolonged menstrual periods were symptoms present in all patients with STUMP, and in 83.35% ($n = 10$) there was additionally a secondary anaemia. Rapidly growing myoma was a symptom in only in 25% ($n = 3$). In 85.7% of all patients with STUMP ($n = 12$) hysterectomy was the surgical procedure, with ovarian preservation in 58.3% of the cases ($n = 7$). Open hysterectomy was done in 66.7% ($n = 8$) and laparoscopy was used in 33.3% of the cases ($n = 4$). Open surgery myomectomy was the method of surgery in 14.3% ($n = 2$). The surgical approach and the extent of surgery in all cases of STUMP are shown in Table 2.

Median time of follow-up after surgery was 48 months (range: 40-78).

Discussion

Unlike uterine leiomyoma, which is the most common neoplasm of the uterus [4], STUMP is a rare, poorly defined subcategory of uterine smooth muscle tumours (SMTs), which cannot be unequivocally classified as be-

Table 1. Patients' characteristics ($n = 320$)

Investigated factor	<i>n</i>	Percentage
Age in years (median)		
Up to 40	147	45.9
40-65	151	47.2
Over 65	22	6.9
Menopausal status		
Premenopausal	257	80.3
Postmenopausal	63	19.7
Type of surgery		
Laparotomy	199	62.2
Laparoscopy	121	37.8
Type of operation		
Myomectomy	85	26.6
Hysterectomy	235	73.4
Histologic type		
Ovarian tumours	17	5.3
Sarcoma	7	2.2
Endometrial cancer	3	0.9
STUMP	14	4.4
Myoma	279	87.2

Table 2. Patients' characteristics in all cases of STUMP

Investigated factor	n	Percentage
Age in years (median)		
Premenopausal at diagnosis	13	92.9
Postmenopausal at diagnosis	1	7.1
Type of surgery		
Laparotomy	10	71.4
Laparoscopy	4	28.6
Type of operation		
Myomectomy	2	16.7
Hysterectomy	12	85.7
Local recurrences	0	0
Alive until May 2019	14	100

nign or malignant histologically [1]. The incidence of STUMP is not well documented, varying around 0.01% of all women undergoing gynaecological surgery for a presumed preoperative diagnosis of uterine myoma [3]. STUMP is diagnosed more often in premenopause, at an average age of 44 years. As seen in our cohort of patients, the most frequent chief complaint, leading to surgery and postoperative diagnosis of STUMP, is heavy menstrual bleeding with or without development of anaemia [5]. The clinical presentation of STUMP does not differ from other SMTs such as leiomyoma or leiomyosarcoma – pelvic pain, pelvic mass, abnormal uterine bleeding, compression of adjacent organs and secondary anaemia, infertility, dysmenorrhoea, and abnormal vaginal discharge may all be present [6-10], thus rendering non-specific symptoms in all these histologically and clinically different conditions. In our study, only one patient was diagnosed in menopause at the age of 52 years with clinical amenorrhoea two years prior to the diagnosis of STUMP. The chief complaint that led to the diagnosis in this patient was a rapidly growing fibroid mass detected by ultrasound, which underlines the fact that detection by ultrasound may be more relevant in menopause.

In our series of patients, as in the literature, the preoperative diagnosis was given by ultrasound (US), computer tomography (CT), or magnetic resonance imaging (MRI). However, there is no reliable method to pre-operatively differentiate between benign or malignant tumours [11]. The US examination gives only limited information on uterine SMTs and cannot distinguish STUMP from benign or malignant tumours [10]. There is some evidence in the literature that MRI may be used to distinguish benign from malignant tumours, based on data for increased signal intensity or restriction of the signal. However, to date little evidence exists to distinguish STUMP from benign conditions [12].

The definite diagnosis of SMTs comes from the pathological examination, where cytological atypia, increased mitotic rate, and the presence or absence of coagulative tumour cell necrosis (CTCN) is taken into consideration [9]. However, histological differentiation between malignant and SMTs may still be challenging. As per WHO recommendations, all SMTs that are not diagnosed categorically as benign or malignant should be classified as STUMP [5]. There are different thresholds and criteria, considered by different authors. For example, Bell *et al.* [13] divide STUMP in a separate subcategory with three groups: 1) atypical leiomyoma with low risk of recurrence – diffuse moderate-to-severe atypia, < 10 mitoses/10 high-power fields (HPF) and CTCN; 2) atypical leiomyoma but limited experience – severe atypia, < 20 mitoses/10 HPF, no CTCN; and 3) smooth muscle tumour of low malignant potential, which has CTCN, mitosis < 10/10 HPF, absent-to-mild nuclear atypia [13]. To diagnose STUMP, Guntupalli *et al.* used any of the following: tumour necrosis (+), no atypia, mitosis ≤ 10/10 HPF; diffuse atypia (+), no tumour necrosis, mitosis ≤ 10/10 HPF; no tumour necrosis, no atypia, mitosis ≥ 20/10 HPF; cellularity or hypercellularity with mitosis ≥ 4/10 HPF; and irregular margins or vascular invasion in peripheral side of tumour [7]. D'Angelo and Prat used the following criteria for diagnosis: tumour necrosis in typical leiomyoma; necrosis and ≥ 10 mitosis/10 HPF or remarkable diffuse atypia; remarkable diffuse or focal atypia and borderline mitosis; and hardly classified necrosis [14].

Most frequently in the literature, the diagnosis STUMP is made as per the histological criteria of Stanford for leiomyosarcoma – diffuse moderate-to-severe atypia, ≥ 10 mitotic figures/10 HPF and tumour cell necrosis criteria [13]. If the patient has at least two of these three criteria the diagnosis is leiomyosarcoma; if the tumour does not meet criteria for leiomyosarcoma and has combinations of Stanford's criteria, the diagnosis is STUMP; if there is absence of necrosis and atypia and ≤ 4 mitosis, the diagnosis is benign leiomyoma [5]. We also used these criteria to diagnose STUMP in our subset of 320 patients who underwent surgery for uterine fibroids.

To improve the diagnosis of STUMP, besides morphology, there are reports of the role of immunohistochemistry (IHC) as well. Several markers, such as Ki-67, p16, p53, pHH3, Bcl-2, Caveolin-1, or AT-rich interactive domain 1 α, have been tested [15, 16]. There are some preliminary reports, but the series are still too small. Some of these markers may also be discussed as prognostic variables – expression of Bcl-2 is more frequent in leiomyomas than in STUMP or leiomyosarcoma; thus, if Bcl-2 is expressed in STUMP or malignant tumours, it may have positive prognostic significance [15, 17-19]. Of interest is the fact that the expression of Caveolin-1 increases significantly from benign conditions such as

leiomyoma to STUMP and more significantly in malignant tumours such as leiomyosarcoma [20].

Because STUMP is a rare condition, there is ongoing debate in the literature about its management. Despite being considered of low malignant potential, there are reports in the literature of recurrence and metastases after diagnosis of STUMP. The local or locoregional recurrence rates are different according to different publications, generally varying between 7 and 27% [7, 15-17, 21, 22]. Distant metastases from STUMP are even rarer and represent single case reports with involvement of lungs and humerus [23, 24]. If at all, relapse of STUMP may occur late – after a median of 51 months [5], and its incidence does not depend on the type of surgical intervention – myomectomy or hysterectomy [7]. We did not find any data in the literature for different recurrence rates, depending on the surgical approach – laparoscopic or open. Nonetheless, there are some data suggesting that there might be an increase in the risk of relapse, following morcellation of the tumour [25, 26]. The five-year overall survival is reported to be 92-100% [7, 27]. In the case of recurrence, the prognosis remains relatively good because surgery remains a curative option, and there is only one case report with lethal outcome [28].

There are no treatment and follow-up guidelines for the management of patients with STUMP. Some suggestions, based on leiomyosarcoma guidelines, exist with recommendations as follows:

If a patient has been diagnosed with STUMP from biopsy or hysteroscopy, a hysterectomy should be performed (regardless of surgical method – vaginal, abdominal, or laparoscopic). Patients should get a baseline CT of the chest, abdomen, and pelvis. The follow-up consists of routine physical examination every six months for five years and thereafter annually because of the existing, but still relatively low, risk of disease recurrence or metastasis [20, 23, 29, 30].

If fertility preservation is considered, a myomectomy may also be considered. In such cases, clinical assessment with ultrasound every six months and abdominal MRI and chest X-ray annually for the first five years is recommended [1, 16, 19, 31]. When fertility is no longer of concern, a hysterectomy should be recommended because of the potential risk of recurrence [25].

Some authors discuss adjuvant therapy with progesterone or gonadotropin-releasing hormone analogues; chemotherapy may be considered for recurrent or metastatic disease [6, 22, 23]. There is no evidence of the effect of any systemic therapy for prevention of relapse or management of primary disease after surgery [7, 25, 27, 32-34].

We report a relatively large series of patients with STUMP, and despite the retrospective data there are

several key messages that we consider useful. In our study the median age of patients with STUMP was 45.4 years, which is comparable to that in the literature. Although scarce, the incidence of STUMP is reported to be much lower than in our series, which estimated it as 2.3%. A possible explanation may be the existence of several different histological criteria for diagnosis of STUMP used by different authors. A key finding from our cohort of patients is that the most frequent symptom in patients with STUMP was related to heavy menstrual bleeding and not to rapid growth of fibroids, detected clinically or by US. In our series, only three patients had fast-growing myomas whereas all premenopausal patients had heavy menstrual bleeding as a diagnostic-process triggering symptom. Most of the women with rapidly growing fibroids, after surgery were histologically proven to have usual types of uterine myomas. Our study also has limitations: the average period of follow-up was relatively short, with a median of 48 months. This may be one of the reasons for not registering any disease recurrences or systemic spread after initial surgery. No correlation or influence of the type (open vs. laparoscopic) or the extent of surgery (myomectomy vs. hysterectomy) used on recurrence could be found due to the shorter follow-up and no recurrence event until May 2019. Of importance may also be the fact that morcellation is not a method of choice in our current practice due to oncological concerns. This may also be of significance because data exist suggesting an increased risk of relapse following morcellation of the primary tumour [25, 26].

Conclusions

STUMP is a rare type of tumour, which is usually an unexpected histological diagnosis following gynaecological surgery for a preoperative diagnosis of uterine myoma in premenopausal women. Clinical preoperative discrimination from leiomyoma or leiomyosarcoma is frequently impossible, and the final diagnosis is histological. STUMP has a certain potential for relapse, independently of the surgical procedure that was used, but still the only procedure to be avoided remains morcellation because there are data about its negative prognostic influence. The patients with a diagnosis of STUMP remain on postoperative follow-up, consisting most frequently of routine physical examinations and imaging techniques twice a year for five years and thereafter annually because there is a risk, despite being low, of disease recurrence or systemic spread.

Disclosure

The authors report no conflict of interest.

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