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A Society of Gynecologic Oncology Evidence-based Review (and Recommendations)

Uterine smooth muscle tumors of unknown malignant potential: A challenging question

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HIGHLIGHTS

- Pathological features of STUMPs preclude an equivocal diagnosis of leiomyosarcoma, but do not fulfill criteria for leiomyoma.
- Genomic index seems to represent a prognostic tool for predicting the clinical outcome of patients with STUMPs.
- Surgery is the standard therapy of STUMPs, whereas there is no role for adjuvant hormone therapy or chemotherapy.
- The recurrence rate of STUMPs ranges between 0% and 36%, with a mean value of approximately 13%.
- STUMP can relapse as either STUMP or leiomyosarcoma

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ABSTRACT

Uterine smooth muscle tumors of unknown malignant potential [STUMP]s are neoplasms with pathological features that preclude an equivocal diagnosis of leiomyosarcoma, but that do not fulfill the criteria for leiomyoma or its variants, and raise concerns that the tumors may behave in a malign fashion. Total hysterectomy with or without bilateral salpingo-oophorectomy is the standard treatment if fertility is completed, whereas myomectomy alone can be taken into consideration in young patients who desire to preserve childbearing potential. A careful surveillance every 6 months for 5 years and then yearly is strongly warranted. Patients with STUMP can relapse as either STUMP or leiomyosarcoma in approximately 11–13% of the cases, and their 5-year overall survival ranges from 92 to 100%. The present paper reviews the clinicopathological features of uterine STUMPs with a particular focus on most commonly accepted histopathological criteria for the diagnosis and on biological behaviour of these controversial neoplasms.

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1. Introduction

Smooth muscle tumors of the uterus are classified as benign tumors, termed leiomyomas, or malignant tumors, termed leiomyosarcomas, on the basis of three key histopathologic features proposed from Stanford in 1994: cytologic atypia, mitotic count, and tumor cell necrosis [1]. In most cases these guidelines allow to classify a smooth muscle tumor as benign or malignant; however, some problematic lesions show intermediate morphologic features that do not completely fulfill the criteria for malignancy and are difficult to classify. Therefore, since the paper by Stanford investigators, several authors proposed a new diagnostic category: smooth muscle tumor of unknown malignant potential [STUMP] [2–4]. According to 2014 World Health Organization [WHO] classification, STUMPs are defined as neoplasms with pathological features that preclude an equivocal diagnosis of leiomyosarcoma, but that do not fulfill the criteria for leiomyoma or its variants, and raise concerns that the tumor may behave in a malign fashion, and only the outcome will confirm its benign or malignant nature [2].

The present paper aims to review the clinicopathological features of uterine STUMPs reported in the literature with a particular focus on the biological behaviour of these controversial neoplasms. Moreover, the most commonly accepted histopathological criteria for the diagnosis of STUMP are also reviewed.

2. Clinical features

At presentation, the mean/median age of patients with STUMP is 41–48 years, with a range from 20 to 75 years (Table 1) [4–10]. Tumor diameter ranges from 3 cm to approximately 30 cm, and symptoms and signs are similar to those of leiomyoma, such as abnormal uterine bleeding, anemia, dysmenorrhea, pelvic pain, pelvic mass, infertility, or complaints due to compression of adjacent organs [5–8,11–13]. For instance, Hughes et al. [13] described the case of a 20-year-old woman with menorrhagia and anemia associated with a subserosal fibroid at the fundus of the uterus measuring 20 × 18 cm. The treatment with gonadotropin-releasing hormone [GnRH] agonists for 6 month significantly reduced the size of fibroid. Then the patient underwent a myomectomy and the pathologic examination revealed a STUMP. Clauss et al. [14] presented the anecdotal case of a preterm birth at the 27th week of gestation, probably due to a chorioamnionitis, with the coincidental finding of a STUMP.

The risk factors and biological events that lead to STUMP are poorly understood. Guntupalli et al. [4], who reviewed 41 patients treated between 1990 and 2005 at The University of Texas M.D. Anderson Cancer Center, found that none of them had a prior pelvic radiotherapy and only 3 (7.3%) had received prior hormone replacement therapy. The preoperative diagnosis is quite impossible, and tumor is detected at the definitive pathologic examination of hysteroscopic, D&C, myomectomy or hysterectomy specimen in a patient with suspected leiomyoma [11].

The reliability of ultrasound and diffusion-weighted [DW]-magnetic resonance imaging [MRI] for the characterization of smooth muscle uterine tumors is very limited [12,15–27]. On MRI, leiomyosarcomas and STUMPs can display high T1-weighted and T2-weighted (due to necrosis) signals, but a clear-cut distinction between these tumors and leiomyomas is not feasible because of atypical imaging features. The addition of serum lactate dehydrogenase [LDH] assay to dynamic MRI seems to offer some useful information for the differential diagnosis of leiomyosarcoma from degenerated leiomyoma of the uterus [28]. Contrast-enhanced [CE]- MRI appeared to yield both higher diagnostic accuracy (0.94 *versus* 0.52, $p < 0.05$), and higher specificity (0.96 *versus* 0.36, $p < 0.05$) compared with DW-MRI for discriminating between leiomyosarcoma/STUMP and leiomyoma, with a comparably high sensitivity (0.88 *versus* 1.00) [29]. Based on receiver operating characteristic [ROC] analysis, the area under the ROC curve [AUC] of CE-MRI in the diagnosis of leiomyosarcoma/STUMP was significantly superior to that of DW-RMI (0.92 *versus* 0.68, $p < 0.01$).

Few data are currently available about the usefulness of ^{18}F-fluorodeoxyglucose [FDG] positron emission tomography [PET]/computed tomography [CT] scan [30–33]. Zhang et al. [32] reported the case of a 42-year-old Chinese woman with intense 18F-FDG uptake in the uterus. Pathological examination of hysterectomy specimen was consistent with STUMP. A Chinese retrospective investigation assessed PET/CT findings in 21 women with rapidly growing uterine masses suspected of being malignant on ultrasound or MRI [33]. The pathologic examination of surgical specimens showed a leiomyosarcoma in 7 cases, a STUMP in one case, and a leiomyoma in 13 cases. The maximal standardized uptake values [SUV_{max}] of leiomyosarcoma/STUMP (range, 3.7–11.8) were higher compared with those of leiomyomas (range, 2.0–9.4; $p = 0.003$) despite a significant overlap, and moreover the metabolic tumor/necrosis ratio was higher in the former than in the latter ($p < 0.001$) with no significant overlaps. All leiomyosarcomas/STUMPs had a typical pattern of 18F-FDG uptake with a specific hollow ball sign, reflecting a sharp transition between necrotic and viable, well-preserved tumor cells. This sign was always absent in leiomyomas, since the hyaline necrosis occurring in leiomyomas shows a variable amount of hyalinized collagen interposed between the central degenerated region and peripheral preserved smooth muscle cells [34].

3. Clinical outcome

STUMPs are often slow growing tumors, that sometimes can relapse and metastasize as either STUMP or leiomyosarcoma [2,4,8,9,34–36]. Some patients with STUMP have a long clinical course after relapse, whereas in other cases recurrent disease has an aggressive behavior associated with multiple relapses and death [4,9,36,37]. Recurrent disease may involve different sites, such as pelvis, ovary, abdomen, omentum, retroperitoneum, liver, lung, pleura, bone, brain and spine [4,10,37–42]. Five-year overall survival [OS] of patients with STUMP is 92–100% [4,5,37]. Peters et al. [37] reported that 5-year disease-free survival [DFS] and 5-year OS were 66% and 92% respectively, among 15 patients with STUMP *versus* 28% and 40%, respectively, for 32 patients with leiomyosarcoma.

The recurrence rate ranges between 0% and 36.4%, with a mean value of 12.9% and with a median time to recurrence of approximately 51 months (range, 15 months–9 years) [3–10] (Table 2). However, the

Table 1
Smooth muscle tumor of the uterus of unknown malignant potential: age at presentation.

Authors	Patients (n.)	Age (years)
Gantupalli [4]	41	Mean = 43 (range 25–75)
Ng [5]	18	Median = 44.6 (range, not reported)
Dańska-Bidzińska [6]	10	Mean = 41 (range, 25–56)
Dell' Asta [7]	5	Median = 48 (range, 44–51)
Bacanakgil [8]	6	Mean = 42 (range, 24–52)
Basaran [9]	21	Mean = 43 (range, 20–64).
Gupta [10]	22	Median = 45.3 (range, 31.9–51.8)

Table 2
Smooth muscle tumor of the uterus of unknown malignant potential: recurrence rates.

Author	Patients (n.)	Follow-up time (months)	Patients who recurred
Ip [3]	16	Median = 51.5 (range, 21–192)	2 (12.5%)
Gantupalli [4]	41	Mean = 45 (range, 1–171)	3 (7.3%)
Ng [5]	18	60[a]	0 (0%)
Dańska-Bidzińska [6]	10	Mean = 16 (range, 4–29)	0
Dall' Asta [7]	5	Median = 35 (range, 6–81)	0
Bacanakgil [8]	6	Median = 38 (range, 11–120)	1 (16.7%)
Basaran [9]	21	Mean = 65.9 (range, 10–154)	4 (19.0%)
Gupta [10]	22	Median = 74.5 (range, 26–166)	8 (36.4%)
	–		–
	139		18 (12.9%)

[a] All 18 patients were disease- free after 5 years.

true recurrence rates are difficult to be assessed, given the different diagnostic criteria, the limited number of patients and the different follow-up time periods reported in the literature.

A retrospective chart review of the oncology database of a tertiary referral center in Singapore between 1970 and 2006 detected 18 cases of STUMP and 72 cases of leiomyosarcoma. No leiomyosarcoma had a prior diagnosis of STUMP, and all 18 patients with STUMP were disease-free after 5 years [5]. Similarly, none of the 10 patients assessed in a polish study [6] and none of the 5 patients evaluated in an Italian investigation [7] developed recurrent disease.

Three (7.3%) of the 41 patients treated at Anderson Cancer Center relapsed after 13 months, 47 months, and 68 months, respectively, and one of these was found to have a leiomyosarcoma at the time of failure [4]. All the three patients with relapse were alive with no evidence of disease at a mean follow-up of 121 months. The mean age of the patients who recurred was 34 years, whereas the mean age of the patients who did not was 44 years ($p = 0.09$).

Two of the 16 patients (12.5%) with STUMP analyzed by Ip et al. [3] recurred after 15 and 51 months, respectively, and both patients were still alive 40 and 74 months later, respectively.

Bacanakgil et al. [8] reported that only one of 6 (16.7%) patients recurred 11 months after surgery, and that the relapse was not related to mitotic count, degree of atypia and necrosis.

Four of 21 patients (19.0%) treated at two tertiary Turkish centers relapsed and one of these (4.8%) died [9]. Recurrent tumors were leiomyosarcomas in 3 cases (75.0%). There was no age difference between patients who failed and those who did not.

In the series of Gupta et al. [10] disease relapsed in 8 (36.4%) of 22 patients with STUMP treated at the Brigham and Women's Hospital between 1994 and 2009. Local recurrence occurred in 4 patients, 2 of whom were initially treated with myomectomy and two of whom were treated with hysterectomy. Metastatic disease occurred in the remaining 4 patients, all of whom initially underwent hysterectomy.

Some authors failed to detect a relationship between the risk of recurrence and the clinical features such as patient age, ethnicity, smoking habit, type of surgery (hysterectomy *versus* myomectomy) [4,9].

4. Treatment strategy and surveillance

Although there are no National Comprehensive Cancer Network Clinical Practice Guidelines established for STUMP, surgery is commonly accepted as the standard therapy whereas there is no role for adjuvant hormone therapy or chemotherapy [3,4,7,11,12,37]. Total hysterectomy with or without bilateral salpingo-oophorectomy, by vaginal, abdominal, or mini-invasive approach, is the gold standard definitive treatment if fertility is completed, whereas myomectomy alone can be taken into consideration in young patients who desire to preserve childbearing potential [4,6,7,9,12,13,43]. Morcellation must be avoided to prevent the risk of diffuse peritoneal implants, which can be benign or malignant [42,44,45]. Patients with surgically removed STUMP should undergo a baseline chest, abdomen and pelvic CT scan to rule out subclinical lesions [12].

A review of the literature by Vilos et al. [43] reported that 71 of 76 patients (93.4%) with STUMP treated with myomectomy alone experienced no recurrent disease with a follow-up ranging from 1 to 216 months, and that residual tumor was found in 2 (14.3%) of the 14 patients in whom initial myomectomy was followed by hysterectomy. No hysterectomized patient developed recurrent disease with a follow-up ranging from 6 months to 18.9 years.

A few cases of successful pregnancy following conservative surgery for STUMP are reported in the literature [46,47]. An accurate evaluation to rule out the presence of recurrent disease should be performed before pregnancy is attempted and a delayed hysterectomy should be recommended once childbearing is completed.

Although there is lack of consensus regarding follow-up protocols in patients with STUMP, women treated with hysterectomy should undergo periodical controls, including medical history, clinical and gynecologic examination and abdominal-pelvic ultrasound, every 6 months and whole body CT scan every year, whereas those women treated with fertility- sparing surgery should undergo clinical and ultrasound evaluation every 6 months and pelvic MRI plus chest X-ray yearly for 5 years [7,11–13]. Afterwards, follow-up controls could be performed with longer intervals.

The treatment of choice of recurrent disease is surgical excision, when feasible, followed by additional therapy such medroxyprogesterone acetate [MPA], Gn-RH agonists, and chemotherapy, although very few data are currently available about the efficacy of these agents [4,36,38,39]. For instance of the 3 patients with recurrent disease treated at the Anderson Cancer Center, the one with a pelvic mass and a pulmonary nodule underwent resection of the pelvic lesion and pulmonary lobectomy [4]. The pathologic examination of surgical specimens was consistent with STUMP. The patient received MAP daily for 10 years and the Gn-RH agonist leuprolide acetate monthly and she was alive with no evidence of disease after 157 months from the initial diagnosis. The second patient developed a retroperitoneal pelvic mass extending to the upper abdomen associated with multiple peritoneal nodules that were completely resected during cytoreductive surgery. The pathologic examination showed that all surgical specimens were STUMP, and the patient was alive and free of disease after 106 months. The third patient developed a huge retroperitoneal mass, extending from the pelvis to the level of the pancreas that was resected. The pathologic examination was consistent with leiomyosarcoma. The patient, who received postoperative doxorubicin/cisplatin-based chemotherapy, was alive with no evidence of disease after 150 months. Kotsopoulos et al. [39] reported the case of a 51-year-old woman with multiple bilateral pulmonary lesions 3 years after hysterectomy. Lung biopsy through video-assisted thoracic surgery was consistent with metastatic STUMP. She underwent multiple cycles of chemotherapy with different combination regimens, including ifosfamide, epidoxorubicin, docetaxel, gemcitabine, bevacizumab, cisplatin, cyclophosphamide and vincristine, but died 11 months later.

Atkins et al. [38] reported 3 cases of metastatic disease following STUMP. The first patient, who developed peritoneal and lymph node metastases, underwent debulking surgery followed by progesterone and remained disease-free for 3 years, whereas the other 2 patients developed liver metastases, which were treated surgically.

Shapiro et al. [36] reported the case of a solitary recurrence in the humerus 51 months after subtotal hysterectomy for a STUMP. A bone biopsy revealed a leiomyosarcoma consistent with the uterine origin. The patient underwent wide excision of the proximal humerus and reconstruction with proximal humeral endoprosthesis without any additional treatment, but she developed multiple lung metastases 12 months later.

5. Historical evolution in the pathologic diagnosis

The term STUMP was first proposed in 1973 by Kempson to describe tumors with a malignant clinical behaviour that were difficult to classify as sarcomas by using the histological criteria available at the time [48]. Years later, in the Stanford study, Bell et al. [1] performed a retrospective analysis of 213 problematic uterine smooth muscle tumors. In this article, the term 'STUMP' was not used; however, the authors delineated four histological categories of uterine smooth muscle tumors with an uncertain malignant potential: 1) '*atypical leiomyoma with limited experience' (AL-LE)*, tumor showing focal or multifocal moderate-severe atypia, no tumor cell necrosis and a mitotic count equal or less to 10 mitoses per 10 high power fields [HPF]; 2) '*smooth muscle tumor with low malignant potential' (SMT-LMP)*, characterized by tumor cell necrosis, with absent or minimal atypia and <10 mitoses/10 HPF; *3) 'atypical leiomyoma with low risk of recurrence' (AL-LRR)*, tumor displaying diffuse moderate-to-severe atypia, no tumor cell necrosis and a mitotic count <10/10 HPF; 4) *'mitotically active leiomyoma with limited experience' (MAL-LE)*, tumor characterized by an increased mitotic activity, equal

or greater to 20/10 HPF, but with no evidence of atypia and tumor cell necrosis. In the same paper, the authors also delineated the three most prognostically relevant features in spindle cell smooth muscle tumors: diffuse cytologic atypia, tumor cell necrosis, and ≥ 10 mitoses/10 HPF, suggesting thus that tumors showing at least two of the these three features should be interpreted as conventional leiomyosarcomas. On the other hand, leiomyomas were defined as tumors with a mitotic count <4/10 HPF, without atypical cells and with no tumor cell necrosis.

Successively to the categories proposed by Bell et al. [1], the WHO classification introduced the definition of STUMP for tumors showing worrisome histological features that raise concerns for a malignant behavior, but do not satisfy all the Stanford diagnostic criteria for leiomyosarcoma [2].

To date the largest published series on STUMPs is provided by Guntupalli et al. [4], which reported the pathological features and outcomes of 41 patients with a pathologically confirmed diagnosis of STUMP [4]. In this paper, based on authors institutional criteria and on the work published by Bell et al. [1], five pathological categories of STUMP were identified: 1) neoplasms showing tumor cell necrosis, no atypia, and a mitotic index <10/10 HPF; 2) tumors characterized by diffuse atypia, no tumor cell necrosis, and a mitotic index <10/10 HPF; 3) tumors showing a mitotic index >20/10 HPF but without atypia or tumor cell necrosis; 4) tumors with increased cellularity with a mitotic index >4/10 HPF; 5) tumors showing irregular margins or vascular invasion at the periphery of the tumor. Interestingly, only 3/41 patients (7.3%) showed a recurrence during the follow-up period. Moreover, one patient with histologically confirmed uterine STUMP, was found to have a leiomyosarcoma in the recurrence site. Despite the innovative suggestions presented in this paper, such as the hypercellularity, the presence of irregular margins and the vascular invasion, which were not included in the original Stanford criteria, the authors have not described the histological features seen in those cases with recurrence. In 2010 D' Angelo and Prat [49] proposed the following histological parameters for the diagnosis of STUMP: 1) tumor cell necrosis in a typical leiomyoma; 2) necrosis of uncertain type with a mitotic count ≥10/10 HPFs, or marked diffuse atypia; 3) marked diffuse or focal atypia with a borderline mitotic count; 4) necrosis difficult to classify (Fig. 1). Moreover, the authors suggested that pathologist should make every effort to classify a smooth muscle tumor as benign or malignant, since most tumors diagnosed as STUMP are associated with favourable outcome.

Another important contribution in expanding the histological parameters for the diagnosis of STUMP was provided by Gupta et al. [10] which reported the clinicopathological features of 22 uterine STUMPs. In this study the authors adopted the following subcategories for the diagnosis of STUMP: 1) neoplasms in which tumor necrosis is ambiguous and difficult to classify; 2) tumors with diffuse or multifocal atypia and a borderline mitotic count (8–9 mitoses/10 HPF); 3) tumors without atypia or necrosis but with a mitotic index >15/10 HPF; 4) tumors showing coagulative/ischemic necrosis in multifocal or irregularly-shaped foci; 5) tumors with epithelioid morphology and myxoid smooth muscle tumors showing atypia or increased proliferative activity; 6) myometrial invasion in the absence of other histological features of malignancy; and 7) atypical mitotic figures in the absence of other histological features of malignancy. In this paper, recurrent disease was observed in 8 (36.4%) cases and the most common histological features encountered in cases with adverse outcome included moderate-severe nuclear atypia, epithelioid features, infiltrative or irregular margins, atypical mitoses, and vascular invasion. Therefore, authors suggested

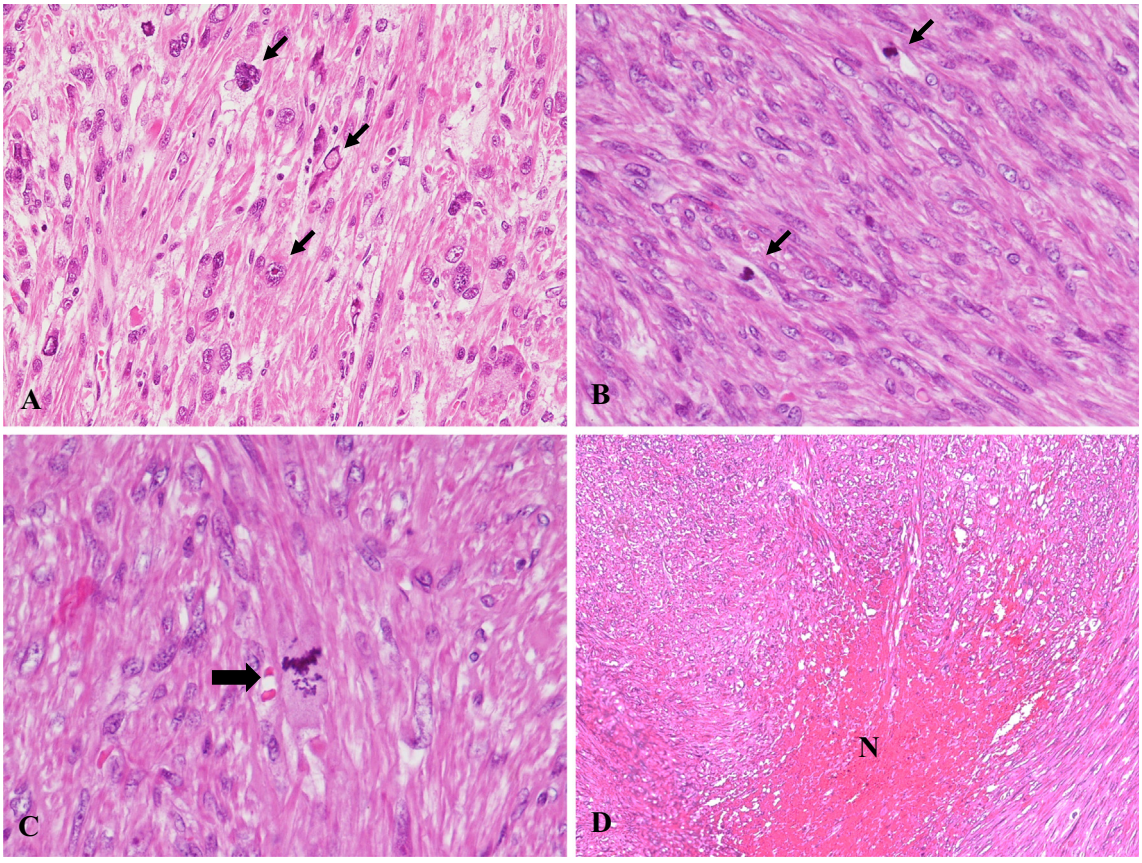

Fig. 1. Histopathological features of STUMP. Haematoxylin and eosin stained sections illustrating the typical histopathological features of STUMPs. A) Moderate to severe cytological atypia (arrows); B) Increased mitotic activity (arrows); C) Atypical mitotic figure (arrow); D) Ambiguous tumor cell necrosis.

Table 3
Histopathological parameters for the diagnosis of STUMP according to the largest published works.

Reference	Atypia	MF/10 HPF	Necrosis	Other features
Bell [1]	Focal/multifocal moderate-severe	≥10	Absent	–
Ip [3]	Absent or minimal atypia	<10	Present	–
	Diffuse moderate-to-severe atypia	<10	Absent	–
	None	≥20	Absent	–
	None	≥10	Uncertain	–
	Diffuse/multifocal, moderate to severe	Borderline/uncertain	Absent	–
Oliva [2]	Focal/multifocal moderate-severe	<10	Absent	–
	Diffuse	<10	Absent	–
	None	<10	Present	–
	None	>15	Absent	–
Guntupalli [4]	None	<10	Present	–
	Diffuse	<10	Absent	–
	None	>20	Absent	–
	None	>4	Absent	Increased cellularity
	–	–	–	Irregular margins or vascular invasion
D' Angelo and Prat [49]	None	Any	Present	–
	None	≥10	Ambiguous/difficult to classify	–
	Marked-diffuse	<10	Ambiguous/difficult to classify	–
	Marked-diffuse/focal	Borderline (8–9)	Absent	–
Gupta [10]	–	–	Ambiguous/difficult to classify	–
	Diffuse or multifocal	Borderline (range 8–9)	Absent	–
	None	> 15	Absent	–
	–	–	–	Coagulative/ischemic necrosis in multifocal or irregularly-shaped foci
	–	–	–	Epithelioid morphology/myxoid smooth muscle tumors showing atypia
	–	–	–	Epithelioid morphology/myxoid smooth muscle tumors showing increased proliferative activity
	–	–	–	Myometrial invasion
	–	–	–	Atypical mitotic figures

the inclusion of epithelioid differentiation, atypical mitoses, vascular invasion and infiltrative/irregular margins into the diagnostic criteria for STUMP diagnosis.

The most relevant histopathological parameters for the diagnosis of STUMP according to the largest published works are summarized in Table 3.

6. Immunohistochemistry and molecular biomarkers

Immunohistochemistry is an essential diagnostic tool in the distinction of uterine smooth muscle tumors from other tumor types. Briefly, these tumors are characterized by diffuse and strong expression of markers of smooth muscle differentiation, including smooth muscle-specific actin, desmin, and h-caldesmon. However, the use of immunohistochemistry for prognostic purpose and for the distinction between benign and malignant smooth muscle tumors still remains controversial.

Recent studies have proposed potential biomarkers, including p16, p53, KI-67, p21, Twist, bcl-2, estrogen receptor [ER] and progesterone receptor [PR], to identify uterine smooth muscle tumors with a higher risk of malignant behaviour [49–51]. In our opinion, p16, p53 and KI-67 represent the most useful immunomarkers for identifying clinically aggressive smooth muscle tumors. However, the experience with these markers is still limited, and their use in diagnostic practice is not recommended at present. Moreover, immunohistochemistry for KI-67 may be of diagnostic utility in the evaluation of mitotic activity, especially in tumors with atypia but without necrosis. In fact, KI-67 may help in distinguishing pyknotic nuclei from true mitotic figures.

Molecular studies on smooth muscle tumors have identified potential prognostic biomarkers, including genomic instability (by cytogenetics), aneuploidy (by flow cytometry) and allelic imbalance (by loss of heterozygosity at microsatellites) [52–54]. These techniques, however, are not available in all laboratories, require particular expertise, and therefore their applicability is limited.

A promising molecular approach in the diagnosis of problematic smooth muscle tumors has been proposed in two recent papers by Croce et al. [55,56]. The authors analyzed by Array-Comparative Genomic Hybridization Analysis the genomic profile of a series of uterine smooth muscle lesions for which histological parameters were not conclusive and for which there was a poor interobserver agreement. Moreover, by the comparison of the genomic indices in leiomyomas and leiomyosarcomas, the authors have set a genomic index threshold of 10. Therefore tumors with a genomic index <10, characterized by a low level of chromosomal rearrangements, were classified as STUMPs with benign clinical behaviour, while tumors with a genomic index >10, harboring complex genomic profiles, represented STUMPs with unfavourable outcomes. The genomic index seemed to emerge as a prognostic tool that separates the problematic uterine smooth muscle lesions in two categories: tumors with a benign clinical course, similar to leiomyomas, and a group of malignant tumors, similar to leiomyosarcomas.

7. Myxoid and epithelioid smooth muscle tumors

Myxoid smooth muscle tumors are defined as neoplasms containing an abundant myxoid extracellular matrix; most authors suggest a cutoff of 50% for the amount of myxoid matrix to designate the tumor as myxoid [57]. Because of the rarity of these tumors, diagnostic criteria predictive of malignancy are less well established than that for spindle cell smooth muscle tumors. The most relevant pathological features

associated with aggressive behaviour are the following: 1) mitotic count ≥2/10 HPF; 2) moderate to severe nuclear atypia; 3) tumor cell necrosis; 4) infiltrative tumor interface [57,58]. Therefore, when dealing with a myxoid smooth muscle tumor, pathologists should perform an extensive tumor sampling since the finding of any degree of cytologic atypia or mitotic activity would favor the diagnosis of leiomyosarcoma.

Epithelioid smooth muscle tumors are histologically characterized by the presence of round or polygonal cells with abundant eosinophilic cytoplasm. The following pathological features have been associated with malignant behavior in epithelioid smooth muscle tumors: 1) mitotic count ≥5/10 HPF; 2) moderate to severe nuclear atypia; 3) tumor cell necrosis; 4) infiltrative tumor interface; 5) large tumor size; 6) irregular margins or vascular invasion [58,59].

Both myxoid and epithelioid smooth muscle tumors are extremely rare neoplasms with only few reported cases in the literature. Because of their rarity, diagnostic criteria predictive of malignancy are less well defined than that for spindle cell smooth muscle tumors. Consequently, it is not clearly established in which circumstances the diagnosis of STUMP may be adequate. According to most authors, however, the diagnosis of STUMP seems appropriate for tumors with intermediate histological features between benign and malignant epithelioid/myxoid smooth muscle tumors [57–59]. In addition, a diagnosis of STUMP can be performed for atypical tumors in which the pathologist suspects, but cannot establish with confidence, that myxoid or epithelioid features are present.

8. Conclusions

If a STUMP is diagnosed at the pathologic examination of hysteroscopic, D&C or myomectomy specimen, hysterectomy is the gold standard treatment for those women who have completed their childbearing planning [12]. Otherwise, if the patient chooses a conservative approach for fertility preservation, she must be followed-up with an accurate surveillance protocol and should undergo hysterectomy after the completion of childbearing desire. Since uterine leiomyosarcomas are high grade by definition because of atypias, high mitotic count and coagulative necrosis, we can speculate that STUMPs could represent a new category of “low-grade leiomyosarcomas”. Indeed, in analogy with soft tissue sarcomas, they can recur, and in most cases, when they recur, show the same histological features observed in the primary lesion. Moreover, also in soft tissues the majority of low-grade leiomyosarcomas show a protracted clinical course without recurrences [60].

In conclusion, the limit of this article is represented by the small number of cases reported by most published series on STUMPs. Therefore, one has to question whether some of the cases reported were leiomyosarcomas and not STUMPs.

Moreover, taking into consideration the uncertain biological behaviour of these neoplasms, in our opinion, all STUMPS require a central pathology review by a pathologist with high level of expertise in the field of soft tissues gynaecological neoplasms. Moreover, all STUMP cases should be discussed in multidisciplinary tumor boards, and managed by a team of gynaecologic oncologists with high level of expertise in soft tissue sarcoma, in order to improve the outcome of these uncommon and poorly understood neoplasms.

Authors' contributions

Manuscripts concept and design: A.G.
Manuscript preparation, editing and review: A.G., GF. Z.

Declaration of Competing Interest

The authors declare no conflict of interest.

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