Uterine Smooth Muscle Tumors of Uncertain Malignant Potential (STUMP): A Retrospective Study in A Single Center

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Research Article

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Abstract

Purpose: Uterine smooth muscle tumors of uncertain malignant potential (STUMP) is a heterogeneous group of tumors with histological and biological diversity that cannot be defined as a benign leiomyoma or malignant leiomyosarcoma. The study aims to investigate the diagnostic methods, treatment management and prognosis of STUMP patients in a 13-year period.

Methods: We retrospectively reviewed the clinicopathologic information of 31 STUMP patients in Peking University People's Hospital. Statistical analyses were conducted to compare the difference of clinical characteristics between the women in myomectomy group and those in hysterectomy group.

Results: The most common clinical presentation was menstrual disorder. The tumors were mainly manifested as hypoechoic, non-cystic nodules with low blood flow signal by pelvic doppler ultrasonography. Most tumors carried Ki-67 index ranging from 10% to 30%. Immunohistochemical markers such as ER, PR, p16 and Desmin was positively expressed in tumors. At the first operation, 21 cases underwent myomectomy and 10 cases underwent hysterectomy. The patients in myomectomy group were younger than those in hysterectomy group. In the follow-up period, two cases experienced a relapse in the form of STUMP within 36 months. One case died of cardiovascular accident while the other cases were alive. Six of 21 women in myomectomy group desired pregnancy and two healthy live births were recorded.

Conclusion: The diagnosis of STUMP primarily depends on histopathologic features. Fertility-sparing surgery may be a treatment selection for patients with fertility desire. Patients with STUMP, especially in the case of myomectomy, should be informed of recurrence risk and monitored closely.

Introduction

Uterine smooth muscle tumors (SMTs) are categorized as benign leiomyoma (LM) or malignant leiomyosarcoma (LMS) regarding the presence of tumor cytologic atypia, proliferative activity and cell necrosis. Uterine LM is the most frequent benign neoplasm in the reproductive tract of women. LMS is the most common uterine sarcoma accounting for nearly 8% of all uterine malignancies [1], which has greatly contributed to uterine cancer deaths. The diagnosis of uterine SMTs, in most cases, is unequivocal. However, a rare type of uterine SMTs called uterine smooth muscle tumor of uncertain malignant potential (STUMP) shows intermediate phenotypic features and defies easy classification. According to the 2014 World Health Organization (WHO) version, uterine STUMP is a smooth muscle tumor with characteristics that preclude an definite diagnosis of LMS and do not confirm with the criteria for LM. Moreover, STUMP may have behaviors similar to malignancy [2].

Females with LM, STUMP, or LMS may present the same symptoms such as menstrual disorder and pelvic mass, and therefore, preoperative diagnosis is challenging. Furthermore, it is difficult to histologically diagnose STUMP after operation owing to the lack of standard diagnostic criteria. In 1994, Bell *et al.* proposed the intermediate category for SMTs [3]. On the basis of Bell's study [3] and the 2014 WHO guidelines [2], we employed the criteria for the diagnosis of STUMP in this study as follow: (i) suspected tumor cell necrosis in irregular shape, any mitotic index with or without atypia; (ii) no tumor cell necrosis and tumors with diffuse, moderate–severe atypia, up to 10 mitoses per 10 high-power fields (HPFs); (iii) tumors with no necrosis or atypia, but with ≥ 15 mitoses per 10 HPFs; (iv) epithelioid or myxoid leiomyomas with atypia, or nuclear mitotic figure intermediate between their benign and malignant counterparts; (v) suspected but not confirmed the presence of epithelioid or myxoid differentiation characteristics in tumors. Given the high degree of heterogeneity, there are no standard guidelines for the diagnosis, treatment and follow-up of women with STUMP which poses challenges to the management of the disease. In addition, the pathogenesis, risk factors, prognostic features of STUMP remain to be unraveled. Our study presents a thorough analysis of the demographic data, clinicopathologic characteristics, oncologic outcomes and fertility outcomes using the 13-year experience of a single institution, adding to the understanding of STUMP.

Materials And Methods

Data collection

A retrospective review was conducted to screen women histologically diagnosed with STUMP who were treated in the Department of Obstetrics and Gynecology, Peking University People's Hospital from January 2008 to January 2021. The characteristics of the women's age at diagnosis, the main clinical symptom or sign, assistant examination, histopathological types, treatment and prognosis were analyzed. The women were followed up by electronic records combined with telephone until January 2021.

Pathologic analysis

All samples were fixed with 4% neutral formaldehyde and embedded with paraffin. The slides were 4 μm in thickness and stained with hematoxylin and eosin. Histological features such as cellularity, cytological atypia, mitotic activity, and necrosis were analyzed in all cases. Immunohistochemistry staining was conducted in 25 cases, with assessments of Ki-67, p16, p53, Desmin, estrogen receptor (ER) and progesterone receptor (PR) expression. All slides were evaluated by two independent and experienced gynecological pathologists.

Statistical methods

Statistical analyses were conducted using the SPSS version 24.0 statistical software (IBM Corp., Armonk, NY, USA). Normality was tested using the Kolmogorov-Smirnov test. In a normal distribution, the data were presented as the mean ± standard deviation (SD). The non-normal distribution parameters were expressed in median and range for continuous variables. Categorical variables were presented in number and percentage. Difference between two

independent groups were evaluated using t-test. Categorical variables were assessed using the $\chi 2$ test or Fisher's exact test. *P*-values <0.05 was considered statistically significant.

Ethical approval

The institutional ethics committee of Peking University People's Hospital approved this research and a written informed consent was obtained from each case.

Results

Clinical characteristics

We reviewed the medical records of 31 women with STUMP. The women' characteristics are shown in Table 1. The average age of the women was 42.52 ± 11.26 years old. Median gravida was 2 (range 0-4), and median parity was 1 (range 0-2). Of the women, two cases (6.45%) were postmenopausal and 29 cases (93.55%) were premenopausal at the time of diagnosis. Thirteen cases (41.94%) had the symptom of menstrual disorder, and 12 cases (38.71%) had no obvious discomfort. Other less common symptoms are pollakiuria (two cases, 9.68%), abdominal or pelvic mass (two cases, 6.45%) and abdominal distension (one case, 3.22%). Median time of follow-up after surgery was 80 months (range 6-156).

Preoperative evaluation

All women received transvaginal color doppler sonography examination before surgery (Table 2). The tumor lesion was detected as single in 12 cases (38.71%) and multiple in 19 cases (61.29%). As for tumor echogenicity, two cases (6.45%) were defined as mixed, and 29 cases (93.55%) as hypoechoic. Non-cystic tumors (n = 25, 80.65%) were more common than cystic tumors (n = 6, 19.35%). The blood flow signal was detected within or around the tumor in 29 cases. Resistance index (RI) values were < 0.45 in 29.03% women (n = 9), while ≥ 0.45 in 64.52% women (n = 20) . Free fluid was detected in only three cases (9.68%). Abdominopelvic computed tomography (CT) was performed in three cases, and two cases were considered to be uterine malignancy. Of the five cases who had abdominopelvic magnetic resonance imaging (MRI), three cases were suggested with uterine fibroid degeneration and two cases without abnormal findings. There were 16 cases with known preoperative serum CA-125 values, and only one case was CA-125 high. The average serum CA-125 value was 19.08 ± 8.77 U/mL.

Pathological findings

The median tumor size was 7.25 cm (range 2.5-20). 80.65% women (n = 25) had a single STUMP, and 19.35% women (n = 6) more than one STUMP. The anatomical localizations of STUMPs are shown in Table 3. The tumors of 29 cases' were intrauterine (intramural in 23 cases, subserous in two cases and submucous in four cases). The other two cases' tumors were extrauterine (one case in broad ligament and one in the vaginal stump). One case received laparoscopic assisted vaginal hysterectomy and bilateral salpingectomy because of LM. A few months later, she developed a mass, which was confirmed to be STUMP by histopathology, in the vaginal stump. As for gross pathology, the tumors generally appears to be between typical LM and LMS. There were 23 STUMPs (74.19%) with gray or white pale yellow, soft and delicate texture and unclear vortex structure, seven STUMPs (22.58%) with slightly brittle texture, and three STUMPs (9.68%) with edema, hemorrhage or cystic degeneration. Intraoperative frozen section was conducted in nine cases including seven cases shown fibroid degeneration or suspected malignancy by preoperative imaging and two cases with slightly brittle tumors. The results suggested that four cases (44.44%) were highly cellular LM, three cases (33.33%) were suspected LMS and two cases (22.23%) were suspected STUMP. It is difficult to determine the tumor boundary or growth pattern in 20 cases (64.52%) who had myomectomy. With regard to hysterectomy specimens, there are seven cases (22.58%) with clear demarcation of tumor, but the other four cases (12.90%) with unclear or invasive boundaries, among which even one case had vascular infiltration. The tumors were divided into three subtypes according to mitotic count per 10 HPF: < 5 mitoses (n = 12, 38.71%), 5-9 mitoses (n = 11, 35.48%), and ≥ 10 mitoses (n = 7, 22.58%). Atypia of the tumors was classified as none (n = 1, 3.23%), mild (n = 11, 35.48%), mild to moderate (n = 11, 35.48%), moderate (n = 6, 19.35%), and moderate to severe (n = 2, 6.45%) subtypes. Focal or multifocal necrosis islands were seen in five cases (16.13%) with STUMPs. The immunohistochemistry staining was available in 25 women. The positive rate of Desmin was 94.44% (17/18), ER 83.33% (10/12) and PR 100% (12/12). The expression rate of p53 was 38.89% (7/18), and that of p16 was 70.59% (12/17). Ki-67 proliferation index was mostly among 10%-30% with the percentage of 65.22 (15/23) (Table 3).

Oncologic Outcomes

As shown in Table 4, there was a significant difference between myomectomy and hysterectomy groups in terms of age and surgical approach ($P < 0.05$). However, there was no significant difference concerning gravida, parity, serum CA-125 values, tumor diameter, tumor number and the median follow-up time between the two groups. It seemed tumor morcellation was more often in the myomectomy group than the hysterectomy group (33.33% vs 0%), although there was no statistical significance ($P = 0.066$). Recurrent disease was seen in 2 cases (6.45%), both of which were from the myomectomy group (Table 5). One recurred 36 months after abdominal myomectomy, and the other recurred 12 months after hysteroscopic myomectomy. The recurrent pathology in the two cases was still a STUMP in the uterus. They underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy after relapse and did not receive adjuvant treatment. Except for one case who died due to cardiovascular accident, the remaining women survived with no evidence of disease at the lastest follow-up.

Reproductive Outcomes

Of 21 women who received myomectomy during initial treatment, six had fertility desire. Two of the women achieved pregnancies spontaneously and gave birth to two full-term healthy babies by cesarean section (Table 6). At the lastest follow-up, three cases were still actively trying to get pregnant, while one

case was diagnosed with cervical carcinoma and underwent radical hysterectomy.

Discussion

Uterine STUMP represents a group of rare, poorly defined borderline tumor in which pathological and clinical features of both LM and LMS overlap. STUMP is found in around 0.01% women who receiving surgery for a presumed diagnosis of uterine LM [4]. Existing literature information for STUMP is limited. Most published reports about STUMP include small sample sizes. Herein, we summarized the clinical characteristics, oncologic and obstetric outcomes of STUMP cases, which provides useful information to the body of knowledge on this disease.

STUMP generally occurs in women of reproductive age. In this study, the average age of STUMP cases was 42.52 years old and the majority of women were premenopausal, which is consistent with previous literatures [5-8]. It is difficult to identify STUMP before surgery and histopathological evaluation. As seen in our cohort of cases, the clinical presentation were stratified as menstrual disorder, pelvic mass or abdominal distension, which are lack of specificity and resemble those of LM and LMS [8]. Imaging modalities are not able to distinguish STUMP from LM and LMS [9,10]. Table 2 indicated that sonographic features with multiple tumors, hypoechoic nodules, high resistance index values, non-cystic appearance and no free fluid were more common in STUMP cases. CA-125 is a valuable biomarker for the diagnosis and prognosis of serous ovarian cancers, whereas it is not a useful indicator for STUMP [6]. We found that serum CA-125 levels in the majority of STUMP cases were in the normal range (Table 2). Therefore, to date no definite imaging techniques and biomarkers are feasible for preoperative diagnosis of STUMP.

The histologic distinction between benign and malignant uterine SMTs remains challenging. In accordance with the literature [11], our data showed that none were definitely diagnosed as STUMP by the intraoperative frozen section analysis, which may be of limited value in differential diagnosis of such a complex disease in a short time. The pathological diagnosis criteria for STUMP are controversial in some settings. However, all the authors emphasized the three criteria including mitotic index, cytological atypia, and coagulative tumor cell necrosis. The current diagnostic criteria for STUMP may need further refinement. Gupta M et al. proposed that histological parameters, such as atypical mitoses, epithelioid differentiation, infiltrative/irregular margins and vascular intrusion, which raised an alarm for adverse outcomes, should be included in the diagnostic system of STUMP [12]. To aid in the triage of uterine SMTs, immunohistochemical markers including Ki-67, p53, p16 and PR have been employed in reports, in which the profile of STUMP generally defined as being much closer to LM than LMS [13-15]. An obvious increase of Ki-67 proliferation index may be conducive in differential diagnosis of STUMP [13]. Petrović D et al. indicated that Ki-67 expression was negative in all LM and higher than 5% in STUMP and LMS cases [14]. Mutations in the p53 gene, which always participates in the invasion process, is ubiquitous in malignancy. The p16 gene is a tumor suppressor gene involved in the regulation of cell proliferation. The p53 [14-15] and p16 gene [15] are generally highly expressed in LMS, and has a certain expression in STUMP, but rarely expressed in LM. On the contrary, expression of PR was found in LM and STUMP, but not in LMS [14]. In this study, we found that most cases carried Ki-67 proliferation index ranging from 10% to 30%. More than 80% women had expression of PR, ER and Desmin. About 2/3 cases had p16 positive and 1/3 cases had p53 positive.

Although no standard principles for the management of women with STUMP have been approved, surgery seems to be the primary treatment for STUMP (regardless of surgical approach - abdominal, laparoscopic or hysteroscopic). For STUMP cases who do not desire pregnancy, hysterectomy with or without bilateral salpingo-oophorectomy is considered the gold standard. If fertility preservation is a problem of concern, myomectomy may be a treatment option after balancing the risk of recurrence and fertility preservation. The recurrence rate of is similar for women in myomectomy group and hysterectomy group [6,7,16], and the surgical approach seems to have no influence on the recurrence rate [6]. It is worth emphasizing that morcellation of the tumor is not a good choice because it increased risk of metastasis and relapse suggested by existing evidence [17,18]. In our study, morcellation was used in seven cases of myomectomy group and none of hysterectomy group. The reported recurrence rate for STUMP is 8.7%-11% [19]. Recurrences could be in the form of STUMP or LMS [16]. Our data showed that 6.45% (2/31) cases recurred with the histopathology of STUMP 12-36 months after myomectomy. And one of the two cases who suffered a relapse received morcellation at the first surgery. Some studies explored the relevant factors of recurrence. An interesting finding is that younger women were more likely to recur [16,20]. Sahin H et al. found that the risk of recurrence was higher for subserosal tumors than intramural and submucosal counterparts [7], while the result from another literature [6] did not support the conclusion. Statistical analyses indicated that mitosis on pathology was the only independent risk factor for recurrence in the event of STUMP [6]. Expression of immunohistochemical markers such as Ki-67 [6], p53 [6,20], and p16 [6,20] may be useful in the prediction of the recurrence of STUMP. Recently, Croce S et al. analyzed the genomic profiling by array-comparative genomic hybridization comparing LM, STUMP and LMS cases and proposed that tumors with a genomic index <10 were categorized as nonrecurring STUMPs and those with a genomic index >10 indicated STUMPs with recurrences and unfavorable outcomes [21]. Further, they reported that genomic index with a cut-off = 35 might be a hint for poor overall survival [22]. The treatment choice for recurrence is surgery with or without adjuvant therapy including chemotherapy, radiotherapy and gonadotropin-releasing hormone analogue according to the pathologic type of recurrence. But the truth may be that the therapeutic strategy is mostly determined by the physician's preferences [19].

It has been reported that the time to recurrence for STUMP cases ranged from 2 to 194 months [19], and the five-year overall survival is 92-100% [16,23]. Therefore, a long-term follow-up program deserves to be considered for STUMP cases in spite of favorable prognosis. Especially, close surveillance should be mandatory in the case of myomectomy, and these women should be informed about potential morbidity and mortality of the tumor. No definitive conclusions regarding implementation of follow-up protocols has been achieved. Ip PP et al. suggested that a postoperative evaluation should be conducted every 6 months in the first 5 years and an annual follow-up visit for the next 5 years [20]. Physical examinations and imaging tests including chest radiography, pelvic ultrasound, MRI and/or CT scan are recommended to detect recurrences.

Conclusion

In conclusion, the category and management of STUMP continues to be progressed. The diagnosis for STUMP mainly depends on the histopathological manifestations. No single marker has proved robust enough to incorporate into clinical practice in separating STUMP from other variants, especially for an individual case. However, it would be beneficial to analyze immunohistochemical panel such as PR, ER, Ki-67, p16 and p53. A future perspective may investigate the molecular characteristics of STUMP using the state-of-the-art molecular biology techniques. For women with fertility desire, myomectomy may remain a treatment option. Whether fertility is preserved or not, regular and long-term follow-up through clinical evaluation and imaging examinations is highly recommended for women with STUMP regarding the potential risk of recurrence as LMS.

Declarations

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Conflicts of interest

Not applicable.

Availability of data and material

Data will be provided if necessary.

Code availability

Not applicable.

Authors' contributions

CZ: case information collection, statistical analyses and manuscript writing; JG: clinical profiles collection, follow-up work; SSL: pathological sections review and interpretation; YLZ: pathological sections review and interpretation; HLZ: design study, data analyses, manuscript editing.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

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Tables

Table 1. Demographic and clinical characteristics of patients (n=31)		
Characteristics		Values
Age (mean ± SD, years)		42.52 ± 11.26
Gravida (median)		2 (0-4)
Parity (median)		1 (0-2)
Menopausal state		
	Postmenopause	2 (6.45%)
	Premenopause	29 (93.55%)
Complaint		
	Menstrual disorder	13 (41.94%)
	Pollakiuria	3 (9.68%)
	abdominal or pelvic mass	2 (6.45%)
	Abdominal distension	1 (3.22%)
	No obvious symptoms	12 (38.71%)
Surgical procedure		
	TAH	7 (22.58%)
	TAH + BSO	3 (9.68%)
	TAH + USO	1 (3.23%)
	Abdominal myomectomy	11 (35.48%)
	Laparoscopic myomectomy	6 (19.35%)
	Hysteroscopic myomectomy	3 (9.68%)
Surgical approach		
	Open	21 (67.74%)
	Non-open	10 (32.26%)
Morcellation		
	No	24 (77.42%)
	Yes	7 (22.58%)
Recurrence rate		2 (6.45%)
	After hysterectomy	0 (0%)
	After myomectomy	2 (6.45%)
Recurrent pathology		
	STUMP	2 (100%)
	LMS	0 (0%)
Follow-up (median, months)		80 (6-156)
Abbreviations: SD, standard deviation; TAH, total abdominal hysterectomy; TAH+BSO/USO, total abdominal hysterectomy+bilateral salpingo-ophorectomy/unilateral salpingo-oophorectomy; STUMP, uterine smooth muscle tumors of uncertain malignant potential; LMS, leiomyosarcoma.		

Table 2. Preoperative evaluation of patients (n=31)		
Characteristics		Values
Sonographic findings		
Number of tumor/myoma		
	Single	12 (38.71%)
	Multiple	19 (61.29%)
Echogenicity		
	Mixed	2 (6.45%)
	Hypoechoic	29 (93.55%)
RI values of tumors		
	< 0.45	9 (29.03%)
	≥ 0.45	20 (64.52%)
	Unknown	2 (6.45%)
Cystic appearance		
	No	25 (80.65%)
	Yes	6 (19.35%)
Free fluid		
	No	28 (90.32%)
	Yes	3 (9.68%)
Serum CA-125 (median, U/mL)		
≥ 35		1 (3.22%)
< 35		15 (48.39%)
Unknown		15 (48.39%)

Abbreviations: RI, resistance index.

Table 3. Pathological characteristics of patients (n = 31)		
Characteristics		Values
Macroscopy		
Tumor size (median, cm)		7.25 (2.5-20)
Tumor no.		
	Single	25 (80.65%)
	Multiple	6 (19.35%)
Tumor location		
	Intramural	23 (74.19%)
	Subserous	2 (6.45%)
	Submucous	4 (12.91%)
	Extrauterine	2 (6.45%)
Histopathology		
Degeneration		
	No	14 (45.16%)
	Yes	17 (54.84%)
Mitosis (n/10 HPFs)		
	< 5	12 (38.71%)
	5-9	11 (35.48%)
	≥ 10	7 (22.58%)
	Unknown	1(3.23%)
Atypia		
	None	1 (3.23%)
	Mild	11 (35.48%)
	Mild to moderate	11 (35.48%)
	Moderate	6 (19.35%)
	Moderate to severe	2 (6.45%)
Necrosis		
	Absent	23 (74.19%)
	Focal/multifocal	5 (16.13%)
	Suspected	2 (6.45%)
	Unknown	1 (3.23%)
Immunohistochemistry		
Ki-67(%)		
	<10	7 (30.43%)
	10-30	15 (65.22%)
	>30	1 (4.35%)
p16		
	+	12 (70.59%)
	-	5 (29.41%)
p53		

	+	7 (38.89%)
	-	11 (61.11%)
ER		
	+	10 (83.33%)
	-	2 (16.67%)
PR		
	+	12 (100%)
	-	0 (0%)
Desmin		
	+	17 (94.44%)
	-	1 (5.56%)
Note: Tumor size was analyzed as the largest measured diameter. Abbreviations: HPFs, high-power fields; ER, estrogen receptor; PR, progesterone receptor.		

Table 4. Differences between myomectomy and hysterectomy groups (n = 31)

Characteristics	Myomectomy (n = 21)	Hysterectomy (n =10)	t/χ2	*P*- value
Age (mean ± SD, years)	39.38 ± 10.54	49.10 ± 10.25	-	0.022
Gravida (median)	1 (0-4)	2 (1-3)	-	0.082
Parity			3.543	0.141
Nullipara	6 (28.57%)	0 (0%)	-	
Multipara	15 (71.43%)	10 (100%)	-	
Serum CA-125 (mean ± SD, U/mL)	17.26 ± 7.52	23.08 ± 10.86	-	0.230
Tumor size (median, cm)	7.25 (3.5-20)	7.25 (2.5-15)	-	0.791
Tumor no.			0.004	1.000
Single	17 (80.95%)	8 (80.00%)	-	
Multiple	4 (19.05%)	2 (20.00%)	-	
Surgical approach			7.029	0.012
Open	11 (52.38%)	10 (100%)	-	
Non-open	10 (47.62%)	0 (0%)	-	
Morcellation			4.306	0.066
No	14 (66.67%)	10 (100%)	-	
Yes	7 (33.33%)	0 (0%)	-	
Follow-up (median, months)	69 (6-151)	98 (20-156)	-	0.320
Recurrent rate, No. (%)	2 (9.52%)	0 (0%)	-	-
Abbreviations: SD, standard deviation.				

Table 5. Clinicopathological features and outcomes of patients with recurrence disease (n = 2)

				Initial treatment				Recurrent treatment					
No	Age (year)	Gravida	Parity	Tumor size (cm)	Morcellation	Surgery		Time to recurrence (months)	Location	Surgery	Recurrence Pathology	Outcome	Follow up (months)
1	32	1	0	7.5	No	AM	Open	36	Uterus	TAH+BSO	STUMP	ANED	129
2	51	1	1	7.5	Yes	HM	Hys	12	Uterus	TAH+BSO	STUMP	ANED	40

Abbreviations: AM, abdominal myomectomy; HM, Hysteroscopic myomectomy; Open, open abdominal; Hys, hysteroscopic; TAH+BSO: total abdominal hysterectomy with bilateral salpingo-oophorectomy; STUMP, uterine smooth muscle tumors of uncertain malignant potential; ANED, alive with no evidence of disease.

Table 6. Clinicopathological characteristics of patients with obstetrics outcomes (n = 2)

No	Age (year)	Tumor Localization	Tumor size (cm)	Tumor no.	Initial surgery	Time to pregnancy (months)	Birth type	Fertility Outcome	Follow up (months)	Oncologic outcome
1	31	Intramural	4	Single	LM	12	CS	full-term delivery	87	ANED
2	25	Intramural	3.5	Single	AM	24	CS	full-term delivery	38	ANED

Abbreviations: AM, abdominal myomectomy; LM, laparoscopic myomectomy; CS, cesarean section; ANED, alive with no evidence of disease.