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Original Article

Clinicopathologic evaluation of uterine smooth muscle tumors of uncertain malignant potential (STUMP): A single center experience

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ABSTRACT

Objective: To investigate the clinical outcomes and histopathological features of uterine smooth muscle tumors of uncertain malignant potential (STUMP).
Methods: The study analysed cases diagnosed with uterine STUMP in a tertiary center, between January 2003 and September 2018. We investigated the clinical, operative and histopathologic data of the cases. Follow-up information and clinical outcomes were also examined.
Results: 28 cases with uterine STUMP were studied. The mean age of the patients was 44.5 ± 9.0 years and the median parity was 2 (0–6). The mean tumor diameter was 6.3 cm (range 2–27 cm) and most (78.6%) of the tumors were located intramurally. In 25% of the cases diagnosis was after myomectomy, while in the others diagnosis was after hysterectomy. Of the patients who wanted to preserve the uterus and their fertility and who did not therefore undergo a subsequent hysterectomy, one patient became pregnant without any complication. One case with a history of myomectomy, presented as STUMP. The median follow-up time was 45.4 months (range 5–180). Recurrence occured in one case (3.7%) 33 months after diagnosis. Distant metastasis occurred in the lungs and the pathology of the biopsy was liposarcoma, and the patient died of the disease 62 months after diagnosis.
Conclusion: Uterine STUMP is a rare condition, and diagnosis can be difficult, often with unusual combinations of findings. Prognosis for the patient is unclear and their is a risk of recurrence with the tumors. To reduce mortality, regular follow-up and a centralised approach are recommended.

Introduction

Uterine leiomyomas are the most common form of gynecologic tumor [1]. Surgery is predominantly involved in existing management strategies, but the choice of treatment is decided based on the patient's age and desire to desire fertility [1]. As diagnosis can only occur after surgical removal of the uterine masses, the results of histopathology may give rise to a less frequent diagnosis of a leiomyoma variant or uterine sarcoma. Leiomyoma variants are classified as benign or malignant according to their histological characteristics [2]. The presence of abundant mitoses (>10 High Power Fields{HPF}), nuclear atypia, and tumor cell necrosis define the diagnosis as a malignant smooth muscle tumor [2]. The tumors that have some sarcoma properties but do not meet all the diagnostic criteria for sarcoma are defined as smooth muscle tumors of uncertain malignant potential (STUMP) [3].

STUMP is a rare neoplasm and is generally diagnosed in patients in their forties [4]. Diagnosis of STUMP can be difficult as there are unusual combinations of findings and the accuracy of diagnoses can vary from one pathologist to another given the different diagnostic criteria used and the subjective nature of the diagnostic process [5]. While most STUMP patients have good outcomes, unexpected aggresive behaviour can be seen in some of the tumors [5]. Because of the neoplasm's rarity, the etiology, prognostic factors, clinical outcomes and recurrence risks of the tumor are poorly defined.

In this study, we evaluated the clinical and histopathological characteristics of 28 patients with uterine STUMP in a single instution.

Material and methods

Our initial evaluation was of 30 patients who were operated on in the tertiary center İzmir Tepecik Education and Research

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Table 1
Clinical and Pathological Features of The Patients.

Case	Age (yr)	Parity	BMI	CA125	Endication	Localisation	Initial Surgery	Secondary Surgery	Tumor Size (cm)	Increased Cellularity	Atypia	Atypic Mitoses	MI	Necrosis	Recurrence	**Follow-up time (mo)**
1	53	6	31.0	5.6	PM	SS	TAH + BSO	–	27 and 12	–	Mild, focal	–	1	(+)	–	44
2	58	6	33.3	16.5	AUB	IM	TAH + BSO	–	4	Mild	Moderate, focal	–	2-3	–	–	6
3	46	2	33.2	14.3	AUB	IM	TLH + BSO	–	5.5	–	Moderate, focal	–	8-9	–	–	8
4	75	4	44.4	46.4	PM	SS	TAH + BSO + MASS EXC + RS COLON REZ	–	12	High	Moderate, focal	–	4-5	(+)	–	12
5	40	1	24.6	23.3	PM	SM	RAD HİS + LND	–	16	High	Mild, focal	–	1	–	–	12
6	35	2	23.0	28.0	AUB	IM	MYM	–	5	–	Mild, focal	–	2	–	–	14
7	43	2	24.7	18.2	PM	SS	MYM	TAH + BSO	11	–	Mild, focal	–	1-2	(+)	–	17
8	50	3	28.0	24	AUB	SS	TAH + BSO	–	8	Mild	Mild, focal	–	2-3	–	–	18
9	40	0	28.0	135	PM	IM	TAH	–	12	–	Mild, focal	(+)	5	–	–	48
10	52	2	27.3	5.5	PM	IM	TLH + BSO	–	9	Mild	Mild, focal	(+)	1-2	–	–	61
11	42	2	31.1	8.5	AUB	IM	MYM	TAH + BSO	8.5	–	Mild, diffuse	–	3	–	–	47
12	43	2	24.8	15.3	AUB	IM	TAH	–	7	High	Mild, focal	–	8	–	–	24
13	54	3	55.3	13.4	AUB	IM	TAH + BSO	–	8	–	Moderate, focal	–	1-2	(+)	(+) (33 mo)	62 (DoD)
14	29	1	20.3	33.1	AUB	IM	MYM	–	10	–	Mild, focal	–	4	(+)	–	39
15	48	2	26.7	10.6	PM	IM	TAH + BSO	–	6	–	Moderate, focal	–	2-3	–	–	6
16	41	2	30.8	18.1	AUB	IM	TLH	–	2	–	Mild, focal	(+)	8-9	–	–	48
17	39	2	22.0	12.4	AUB	IM	MYM	TAH	6	–	Moderate, focal	–	3-4	–	–	52
18	42	2	29.1	15.0	AUB	IM	TAH	–	7,5	–	Moderate, focal	–	6-7	–	–	47
19	39	2	28.5	25.9	AUB	IM	TAH	–	22	–	Moderate, focal	–	5	–	–	56
20	45	3	30.6	23.0	AUB	IM	TLH	–	5	Mild	Moderate, focal	–	1-2	–	–	23
21	46	3	34.2	12.2	AUB	IM	TAH + BSO	–	5	Mild	High, Diffuse	–	2	–	–	31
22	34	1	29.2	22.0	AUB	IM	MYM	–	5	Mild	High, Diffuse	–	3	–	–	44
23	49	1	36.9	12.5	AUB	IM	TLH + BSO	–	4	–	High, Diffuse	–	5	–	–	5
24	48	2	35.3	18.4	AUB	IM	TAH + BSO	–	5	Mild	Mild, focal	–	5	–	–	15
25	43	3	28.5	19.6	PM	IM	TAH	–	6	High	None/None	–	7	–	–	163
26	43	2	31.4	12.3	AUB	IM	TAH	–	6.5	Mild	Moderate, focal	–	3	–	–	57
27	31	2	24.1	34	PM	IM	TAH + BSO	–	4.5	High	Mild, focal	–	1	–	–	180
28	38	2	26.3	18	AUB	SS	MYM	TAH + BSO	3	High	Moderate, focal	–	3-4	–	–	131

yr: years; mo: months; BMI: Body Mass Index,kg/m^2; CA 125:Cancer Antigen 125, U/mL; PM: Pelvic Mass; AUB: Abnormal Uterine Bleeding; IM:Intramural, SM:Submucosal, SS:Subserosal; MYM:Myomectomy; TAH: Total Abdominal Hysterectomy; TAH + BSO:Total Abdominal Hysterectomy and Bilateral Salpingo Oophorectomy; TLH:Total Laparoscopic Hysterectomy; TLH + BSO: Total Laparoscopic Hysterectomy and Bilateral Salpingo Oophorectomy; RAD HİS + LND: Radical Hysterectomy and Lymph Node Disection; TAH + BSO + MASS EXC + RS COLON REZ: Total Abdominal Hysterectomy,Bilateral Salpingo Oophorectomy,Mass Excision and Rectosigmoid Resection; MI:Mitotic Index,mitoses per 10 High Power Fields; DoD: Died of Disease.

Hospital, in the period between January 2003 and September 2018. Of this group, two patients with vaginal STUMP were excluded. Our diagnoses of uterine STUMP were based on the criteria defined by Bell et al. [2] and Ip et al. [5]: 1)focal or multifocal tumors with moderate-severe atypia, ≤10 mitosis/10 HPFs and no tumor cell necrosis (TCN), 2)diffuse, moderate-severe atypia, ≤10 mitosis/10 HPFs and no TCN, 3) no atypia, ≤10 mitosis/10 HPFs and presence of TCN, 4)no atypia, >20 mitosis/10 HPFs, and no TCN, 5)no atypia, ≤10 mitosis/10 HPFs, uncertain type of necrosis. All specimens were examined by pathologists with more than ten years experience in gynecology. Follow-up patients were included. The clinical, radiological, operative and patholologic data of the cases were investigated by a multidiciplinary tumor board. Patients' data was obtained from hospital records. The age, parity, body mass index, menopausal status, preoperative CA 125 level, hormone replacement and pelvic radiation history, operative results, postoperative findings and follow-up time were all noted. The histopathologic findings were examined. Increased cellularity was classified as mild and high. In mild cellularity, the tumors had most nuclei with overlapping of nuclear membranes; in high cellularity, most nuclei were more extensively crowded with overlapping of nuclear membranes and scant intervening stroma. Cytologic atypia was considered when tumor cells show grade 2 and 3 nuclear atypia as described by Bell et al. [2]. If this feature was in most sections, it was defined as diffuse; if it was in occasional section, it was defined as focal. Mitotic activity was assessed using the highest count method and only definite mitotic figures. The mitotic figures were defined when absence nuclear membrane and presence of hairy extensions of chromatin extending from a central clot-like dense mass of chromosomes, either singularly or separated. The number of mitotic figures were counted in 10 HPFs. Necrosis was noted if present. Hyaline necrosis was defined as a region of collagen or granulation tissue intervening between tumors that are viable and non-viable, with common bleeding and less prominent cellular lines. Immunohistochemical stainings were performed in our hospital's laboratory using current procedures. They were obtained using an automated immuno-stabilizer with a primary incubation. The antibodies that were used: p16 (Clone IHC016, dilution 1:200, GeneAb); p53 (Clone DO-7, dilution 1:500, Cell Marque); Ki-67 (Clone 30-9, prediluted, Ventana); estrogen receptor (Clone SP1, dilution 1:500, Ventana) progesterone receptor (Clone PgR636, dilution 1:150, Dako Corporation); panCK (Clone AE1&AE3, dilution 1:500, Cell Marque); actin, smooth muscle (SMA) (Clone 1A4, prediluted, Cell Marque); desmin (Clone DE-R-11, prediluted, Ventana); CD-10 (Clone NCL-L-CD10-270, dilution 1:100, Leica); caldesmon (Clone E89, prediluted, Cell Marque); vimentin (Clone Vim-3B4, prediluted, Ventana); HMB-45 (Clone HMB-45, dilution 1:500, Cell Marque); Melan-A (Clone A103, dilution 1:500, Cell Marque); and S-100 (Clone E-140, dilution 1:500, Spring). Each patient each received follow-up that included pelvic examination, pelvic ultrasonography and Chest X-Ray (6-monthly) and pelvic and thoracic computed tomography if needed (annually). Across the data, the recurrence status, time to recurrence, recurrence histopathology, disease-free status and overall survival rates were also analysed. This retrospective study was approved by the institutional review board.

Statistical analyses were made using SPSS Software (Ver.22; SPSS Inc.Chicago). $P < 0,05$ was considered as statistically significant. Numbers and percentages were used for categorical variables, and mean, standart deviation, median, minimum and maximum were used for numerical variables. The independent *t*-test and Mann Whitney U test were used for comparing means. The Kaplan Meier survival analysis was used for survival analysis.

Results

28 patients with uterine STUMP were investigated. Clinical and pathologic results are shown in Table 1. The mean age of the patients at the time of diagnosis was 44.5 ± 9.0 years (range: 29–75). The median parity was 2 (0–6). 57% of the patients were postmenopausal. In only one patient (3.5%), preoperative serum CA 125 was above the cut-off level of 35 with a level of 135 U/mL (Case 9). No patients had a history of pelvic radiation or hormon replacement. The median body mass index (BMI) was 28.8 kg/m^2 (range: 20.3–55.3). In 42.9% of the cases obesity was recorded (BMI > 30).

The most common symptom of the patients was abnormal uterine bleeding (60.7%). In 22 (78.6%) of the patients the tumor was located in intramurally. Myomectomy was performed in 7 (25%) of the patients, while the remaining 21 (75%) patients received hysterectomy as the initial surgical intervention. One patient (Case 5) had an intraoperative mass in the isthmic region of the uterus, sitting on the douglas cavity, as large as 16 cm, with an increase in vascularity. In addition, due to the heterogeneous internal structure in preoperative Magnetic Resonance Imaging (MRI), the mass was thought to be at risk of malignancy. Therefore, the patient received radical hysterectomy and pelvic/paraaortic lymphadenectomy. In all myomectomy specimens, all surgical margins of the samples were negative from STUMP. The mean age of the patients who were initially treated with myomectomy was 37.1 ± 4.9; and the mean age of the group with hysterectomy was 47.0 ± 8.8 (p = 0.01). Of the patients who underwent myomectomy initially, 4 (57.1%) of them subsequently received hysterectomy. No residual tumors were detected in the hysterectomy specimens.

The median tumor size was 6.3 cm (range; 2–27). In 50% of the patients there were additional uterine masses that were excised and reported as leiomyomas. In the hysterectomy specimen of one patient (Case 1) two gross masses (27 and 12 cm) were diagnosed as STUMP. One patient (Case 9) had a history of myomectomy, occurring 10 years before the surgery of our study period. One patient (Case 4) had received myomectomy, which had been reported as cellular leiomyoma 30 months prior to our study, without morcellation, but via pfannenstiel incision. In the secondary operation, we resected the tumor along with her rectosigmoid colon because the tumor had invaded her rectosigmoid colon serosa. A retroperitoneal 10 cm mass could not be optimally desected. She received follow-up at 12 months when the remaining mass was observed to be the same size and she received no adjuvant treatment.

Mild atypia was present in 13 cases (46.4%), and high atypia was reported in 3 cases (10.7%). No increase in cellularity was detected in 14 cases (50%). The mean mytotic index was calculated as 3–4 (in 10 HPF) (range: 1–9). Nine of the cases (32.1%) had ≥ 5 mitoses/10 HPFs. Necrosis was reported in 18% of the cases and all of the necrosis types were hyalin necrosis. Lymphatic or vascular involvement were not observed in any cases. The immunohistochemistry analyses and receptors are shown in Table 2. Fourteen cases were immunreactive for p53 and 8 cases for p16. The tumors showed progesteron receptor expression in 16 cases and estrogen receptor in 4 cases. ≥10% Ki-67 positivity was observed in four cases and 13 cases had SMA staining positivity. In recurrent patient (Case 13), the atypic cells showed p16, desmin and caldesmon positivity; the progesterone receptor and staining with p53 were negative. The tumor showed 10–15% positivity with Ki-67 in recurrent case.

The median follow-up time in the study group was 45.4 months (range: 5–180). The patients did not receive any adjuvant treatment after the diagnosis of STUMP.

Of the 28 patients in this study, recurrence occured in only one patient (3.6%) (Case 13), observed 33 months after undergoing

Table 2
Receptors and Immunochemical Study of Reported Cases.

Case	P16	P53	PR	ER	PanCK	Actin	Desmin	Ki-67 (%)	CD10	SMA	Caldesmon	Vimentin	HMB45	MelenA	S-100	WT1	CD34	Bcl-2	Follow-up (mo)	Outcome
1	Focal (+)	10%	+	+	–	+	+	2-3	–										44	ANED
2		–	+			+	+	2-3	–										6	ANED
4	Diffuse (+)	10%	+		–		+	10-15	–	+	+								12	ANED
5		–	+					5											12	ANED
6		3%	+					1-2	–										14	ANED
7		–	+	+	–	+	+	2-3	–			+	–	–	–	–	–		17	ANED
8		+						0											18	ANED
9		3%						5											48	ANED
10		10%					+	2-3	–	+									61	ANED
11		5%	+				+	5		+									47	ANED
12	+	–	+	+			+	1	–	+	+							–	24	ANED
13	+	–	–				+	10-15		+	+				–				33/62	Recurrence; DoD
14		–	+				+	1-2	–	+									39	ANED
15	+	4-5%	+		–		+	1-2	–	+	+		–	–	–				6	ANED
16		–	+					0	–	+	+								48	ANED
17		–					+	4-5	–	+									52	ANED
18		+	+				+	10	–	+									47	ANED
19								10		+			–		–				56	ANED
20		–						–											23	ANED
21	Focal (+)	+	+					5-10						–			–		31	ANED
22		+	+				+	3-4	–	+				–					44	ANED
23	Focal (+)	+						3-4											5	ANED
24		+	+					5											15	ANED
26	Focal (+)	10%	+	+	–		+	5-7	Focal (+)	+	+							+	57	ANED
28						+													131	ANED

PR: Progesterone Receptor; ER:Estrogen Receptor; SMA:Smooth Muscle Actin; ANED:Alive with No Evidence of Disease; DoD: Died of Disease.

hysterectomy, when she presented with pelvic pain. A large pelvic mass (15 cm) and distant paranchymal metastasis in her lung paranchymes were detected using a Positron Emission Computerized Tomography (PET CT) scan. The fine needle aspiration biopsy of the lungs revealed mixoid liposarcoma. Systemic chemotherapy (cisplatin and ifosfamide) was started, however the patient died of the disease 62 months after the initial diagnosis of STUMP. The age of the recurrent case was 54 at diagnosis and the mean age of the non-recurrent cases was 44.1 ± 9.0 (p = 0.294).

One patient who had received abdominal mymectomy and wanted to preserve fertility (1/3; 33.3%) became pregnant 12 months after the diagnosis (Case 22). No complications occured in this period and cesarean section was performed in the 37^{+3} gestational week without any neonatal problems.

Discussion

STUMP tumors are rare and are commonly diagnosed by histopatholological evalaution after surgical excision of the tumor. Because of this, only retrospective case studies have been reported in the previous literature [2,4,6]. Consequently, the frequency of STUMP is difficult to determine. Since there is a risk of recurrence, studies have been conducted to investigate the prognostic factors [4,7]. But it was stated that race/ethnicity, smoking and type of surgery are not indicative of recurrence [4]. In addition, optimal follow-up recommendations were not determined in studies with limited number of patients [4,7].

Although parity is known to reduce the risk of fibroid formation, only one patient (1/28) had nulliparity in the study group [1]. The majority of the patients in our study were obese. As is known, obesity increases the risk of uterine myomas [1]. In our study's one recurrent case (Case 13) and in the case with history of cellular leiomyoma (Case 4) the patients were morbidly obese. The increased estrogen levels associated with obesity seem to be also associated with STUMP. The fact that there has been a low number of recurrent cases seen in previous studies, may be a reason that the effect of obesity on recurrence is not specified.

It is known that radiological evaluation with abdominal MRI can reveal atypic lesions such as high signal intensity areas, the presence of any small high-signal areas with unenhanced pockets and suggest the need for the surgical removal of the lesion; however, no specific findings have been reported that would enable this method to distinguish STUMP from other leiomyomas [8]. That same study reported that MRI did not prove to be of an additionally use in the diagnosis of the patients before surgery. Preoperative ultrasound features of STUMPs were previously studied and singularity, solidity, hyperechogenicity, heterogeneity and features of acoustic shadowing and margins were noted as preoperative findings [9]. In our study, there were additional uterine masses that were excised other than STUMPs and reported as leiomyomas. Only one patient had two gross masses that were diagnosed as STUMP, others had singular tumors.

The clinical findings of STUMP are similar to benign uterine leiomyomas and uterine sarcomas [5]. Abnormal vaginal bleeding, pelvic pain and mass are common symptoms, as also indicated in the findings of our study.

The Stanford criteria for the diagnosis of leiomyoma variants and leiomyosarcomas is based on the assessment of three major histologic features: cellular atypia, mitotic activity and tumor cell necrosis [2]. STUMP is diagnosed when it does not meet all the criteria for leiomyosarcoma [2]. While tumor cell coaugulative necrosis has been shown to predict malignant potential, the mitotic index is also important for predicting the clinical behaviour of the tumor [10]. In our study group, no tumor cell necrosis was reported and only 32.1% of the patients' results showed an MI of >5/HPF. Central pathological review is also recommended for diagnosis of STUMP [7]. In a previous study, only 71.4% of the cases diagnosed STUMP by central pathological review later proved to be STUMP in the final diagnosis [7]. In a multicenter study of patients diagnosed with STUMP in 12 different centers, the diagnosis of STUMP was confirmed in only 24.1% of patients [11]. Therefore, consultation is recommended in experienced centers for unclear uterine smooth muscle tumors [7]. It was reported that the use of comparative genomic hybridization is useful to assist in the diagnostic challenge [11]. Furthermore, it was noted that the addition of parameters, such as epithelioid differentiation, vascular involvement and infiltrative/irregular borders, may facilitate the diagnosis [12]. In our study, we only used pathologists from a single tertiary referral center who had more than 10 years' experience in gynecologic oncology to examine the specimens.

As the diagnosis of STUMP is difficult, some markers such as Ki-67, p16 and p53 were used previously [6,13]. Ip et al. [6] reported that recurrent cases were strongly positive with p16 and p53. Similar to this study, the recurrent tumor in our study was immunreactive for p16, but p53 was negative. In our study, there were no cases with expressions of Ki-67 above 15%; however there were 2 cases of >10% Ki-67: in the one recurrent patient (Case 13) and in the patient with cellular leiomyoma history. Ip et al. [6] detected that all of the tumors showed immunreactivity to pregesterone receptor (PR). In accordance with this study, 94.1% (16 of 17) of STUMPs had PR expression in our study. The expression of steroid hormone receptors was reported to be not useful in predicting recurrence [6]. The recurrent case in our study had negative PR expression supporting this finding. Croce et al. [14] reported that the genome profiling is an effective tool to prevent STUMP classification of uterine smooth muscle lesions. They analyzed the genomic profile by array-comparative genomic hybridization in leiomyosarcomas, STUMPs and leiomyomas to confirm the strength of genomic index as a recurrence predictor. It was stated that the STUMP classification can be overcome using the genomic index at the cut-off of 10 and genomic profiling can be used as prognostic factors [14].

In previously reported studies, adverse outcome risks range from 5% to 30% [2,4,6]. STUMP is diagnosed after myomectomy or hysterectomy. If it is detected in the hysterectomy specimen, the patient can be followed up regularly [4,5,10]. But if it is detected after myomectomy, reports on optimal treatment and follow-up are indeterminate. Hysterectomy is recommended to minimize the risk of recurrence in patients [5]. However Guntupalli et al. [4] reported that there was no difference in the risk of recurrence between their myomectomy and hysterectomy groups. In a review of 76 patients treated only with myomectomy, recurrence occured in 6.6% of the patients. In comparison, no recurrences (0/14) occured in patients who were initially treated with myomectomy and subsequently with hysterectomy [10]. In our study, 43.7% of the cases who were diagnosed after myomectomy, wanted to preserve their uterus and their future fertility. Successful pregnancies have been reported following myomectomy for STUMP [15,16]. In our study, one patient (1/3) conceived 12 months later and live birth ocurred. It is an important observation that recurrence after myomectomy is generally isolated to the uterus [5]. So, the negative margins seem to be considerable for this group. Most of the recurrences occur as leiomyosarcomas and are frequently seen outside the pelvis [5]. In our study, there was one case of recurrent histology, occurring in the lungs as liposarcoma.

In previous studies, the range of recurrence rates was reported as between 7.3% and 26.7% [4,5,17]. But the rate varies according to the definition of STUMP that is applied [5]. In a review which included 91 patients and used only the Stanford-3-feature criteria, the recurrence rate was reported as 11% and the mean recurrence period was 51 months (range: 15–180) [5]. Late recurrences, as

much as 5 years after the diagnosis, can occur [5]. However, rapid recurrences can be observed in as short a post-diagnosis period as 6 months [18]. In our study, we calculated the recurrence risk as 3.6%. This low figure may be due to the relatively short observational period of our study. 5-year survival rates for STUMP have been reported at 92%, but it is also known that recurrences and distant metastases can occur beyond this period [17].

Uterine STUMP is a rare condition, and its diagnosis can be difficult, often with unusual combinations of findings. the condition is commonly diagnosed after an histopathological evaluation of a surgical excised tumor with myomectomy or hysterectomy. While most STUMP patients have good outcomes, unexpected aggresive behaviour can be seen in some of the tumors. Prognosis for the patient is unclear, optimal treatment is not well-defined, and tumors have a risk of recurrence. To reduce mortality, regular observation of the patient and a centralised approach to diagnosis are recommended.

Conflict of interest

The authors declare that they have no conflicts of interest.

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None.

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