Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

Research Article

J Exp Clin Med
2021; 38(4): 538-544
doi: 10.52142/omujecm.38.4.26

Is there any possibility of uterine sarcoma, STUMP and benign myoma variants in the patients operated for myoma uteri

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Received: 02.04.2021 • **Accepted/Published Online:** 03.05.2021 • **Final Version:** 30.08.2021

Abstract

Malignant pathologies may be observed in the histopathological examination of the patients who were operated with the diagnosis of myoma uteri. We aimed to investigate the rates of detection of uterine sarcoma, smooth muscle tumor of uncertain malignant potential and benign myoma variants who were operated due to myoma uteri. Patients who were operated with the diagnosis of myoma uteri between 2012-2018 were included. Patients with and without malignant pathology were compared in terms of their characteristics. The malignancy was encountered in 39 patients (1.5%) among 2583 patients. A significant difference was found between the patients with and without malignancy in terms of age, admission complaints, and cervical smear results. Patients in the malignant group were found to be older (52.5±11.0 vs 48.1±6.1, p=0.016). Postmenopausal bleeding was significantly a more common complaint in the malignant group (p=0.028). The rate of abnormal cytology in the cervical smear results in the malignant group was 5.1% (p=0.004). Pathology reports of the patients who were operated for myoma uteri may result with malignancy. In the preoperative evaluation, it is necessary to pay attention to the patients' characteristics, to evaluate the risk factors for the possibility of a malignancy.

Keywords: hysterectomy, myoma uteri, myomectomy, STUMP, uterine sarcoma

1. Introduction

Myoma uteri which is the most common benign, monoclonal tumor in the reproductive-aged women (1). It has been reported in the literature that women have myoma uteri with an incidence ranging from 5% to 40% (2). When the hysterectomy specimens are histopathologically examined, approximately 70% of the cases are found to have myoma uteri (3). The clinical symptoms and signs of myoma uteri depend on the location, size and number of myoma uteri. The most common symptoms are abnormal uterine bleeding, pelvic pain, dysmenorrhea, and infertility. The most common indication for hysterectomy is myoma uteri and 40-60% of hysterectomies are performed due to myoma uteri (4, 5).

Epidemiological factors including age, race, body mass index (BMI), heredity, reproductive factors, sex hormones, obesity, lifestyle factors (diet, caffeine and alcohol consumption, cigarette smoking, physical activity and stress), environmental factors, comorbid conditions, and genetic factors are responsible for the development of myoma uteri (6-10). Women with a history of familial myoma uteri are diagnosed at an earlier age, with more than one myoma uteri and undergo hysterectomy at an earlier age (11).

The main surgical methods in the management of myoma uteri are myomectomy and hysterectomy. Surgical treatment of myoma uteri is currently performed by laparoscopy rather than laparotomy due to the widespread use of non-invasive methods and increasing minimally invasive surgical skills of surgeons.

Pure mesenchymal tumors (sarcomas) such as leiomyosarcoma and endometrial stromal sarcoma and smooth muscle tumor of uncertain malignant potential (STUMP) are rarely diagnosed aggressive tumors and constitute approximately 3% of all malignant uterine tumors (12). Risk factors of uterine sarcomas include nulliparity, advanced age, history of pelvic radiation, number of spontaneous abortion and history of tamoxifen use. Uterine leiomyosarcoma with a similar ultrasonographic characteristics to myoma uteri is the most common uterine sarcoma (13).

There is no safe method to be used in the preoperative diagnosis of leiomyosarcoma. However, myoma uteri showing rapid change in appearance or in size in postmenopausal patients should be investigated. Furthermore, age, imaging characteristics including lacuna with necrotic spaces and

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increased central vascularization indicate increased risk of leiomyosarcoma at a relative annual incidence reported to be between 0.014-0.28% (14, 15).

The incidence of undiagnosed leiomyosarcoma and endometrial stromal sarcoma in patients who underwent hysterectomy with a diagnosis of myoma uteri has been reported between 0.05% and 0.28% (16). In these patients, performing hysterectomy due to myoma uteri delays the diagnosis and treatment for uterine malignancies. In addition, if an endoscopic morcellation is used without an endobag, there is a risk that the underlying malignant tissues may scatter around and be implanted into the abdomen.

Our aim was to determine the incidence of malignancy depending on the histopathological results and to compare their clinical, demographic, and preoperative ultrasonographic characteristics of the patients who had been operated for myoma uteri.

2. Materials and methods

This retrospective cohort study was conducted at Health Sciences University Istanbul Kanuni Sultan Suleyman Training and Research Hospital. Approval for the study was obtained from the local ethical committee (KAEK/2018.06.14). The principles stated in the Helsinki Declaration were followed and informed consent was obtained from the participants. All patients who underwent hysterectomy and myomectomy performed via abdominal, vaginal, or laparoscopic methods due to the preliminary diagnosis of myoma uteri between January 2012 and December 2018 were included in the study. Myoma uteri was diagnosed preoperatively in all patients using transvaginal and/or transabdominal ultrasonography according to koital status. Computed tomography and magnetic resonance imaging were performed in the case of cancer susceptibility. Patients who were not operated and those who underwent myomectomy with a hysteroscopic method were excluded from the study. Patients who had missing data were also excluded. A total of 2583 patients who met the eligibility criteria for the study were included.

Demographic characteristics of the patients including age, gravity, parity, history of abortion, mode of delivery, menstruation or menopausal status, comorbid conditions, history of previous operations, complaints during the consultation, cervical cytology results, ultrasonographic findings, endometrial sampling results, route of operation, and the presence of malignancy based on the histopathological results were examined. All these characteristics were compared among the patients with and without malignancy depending on the histopathological results.

2.1. Statistical analysis

Data analyzes were done with the Statistical Package for Social Sciences 22.0 (SPSS Inc, Chicago, Illinois, USA) package program. Descriptive statistical methods (Percentage, Average, Standard Deviation) were used while evaluating the study data. Independent samples two test was used because the data was normally distributed. Chi-square test was used to compare categorical data. The significance level of $p < 0.05$ was considered statistically significant in the 95% confidence interval. Thresholds for the association of age of the patients with malign tumors were determined by initially using receiver operating characteristics (ROC) curves to ascertain the optimal cut-off value. The sensitivity, specificity, positive likelihood ratio values were presented. We used logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CI) to associate exposure variables with risk of developing malign tumors in both univariable and multivariable-adjusted models.

Table 1. Demographic and clinical characteristics of patients

Characteristics	mean±SD (min-max) or number (%)
Age (years)	48.1±6.2
Gravide	
-Nulligravid	94 (3.6)
-Multigravid	2489 (96.4)
Parity	
-Nullipar	104 (4)
-Multipar	2479 (96)
Abortus	
-Absent	1337 (51.8)
-Present	1246 (48.2)
Labor route	
-No birth	83 (3.2)
-Vaginal birth	1991 (77.1)
-Cesarean section	252 (9.8)
-Vaginal birth+cesarean section	257 (9.9)
Personal history	
-Absent	1989 (77)
-Present	594 (23)
Gynecological operation history	
-Absent	2374 (91.9)
-Present	209 (8.1)
Operation history	
-Absent	1870 (72.4)
-Present	713 (27.6)
Menstrual regularity	
-Irregular	1478 (57.2)
-Regular	711 (27.5)
-Menopause	394 (15.3)
Complaint	
-Control	103 (4)
-Menstrual irregularity	1618 (62.6)
-Pelvic pain	676 (26.2)
-Incontinence, prolapsus	76 (2.9)
-Postmenopausal bleeding	110 (4.3)

3. Results

The demographic characteristics of the patients are shown in Table 1. The mean age of the patients was 48.1±6.2 years. While 104 patients (4%) were nulliparous, 2479 patients (96%) were multiparous. Most patients gave birth vaginally (1991 patients, 77.1%). Among them, 23% of the patients had

some chronic diseases such as hypertension, diabetes mellitus, and thyroid dysfunction. In 209 patients (8.1%), there was a history of gynecological operations. Of those, 394 patients (15.3%) were postmenopausal, 1478 patients (57.2%) had irregular menstruation cycles, and 711 patients (27.5%) had regular menstruation cycles. The most common complaint of the patients (62.6%) was menstrual irregularity.

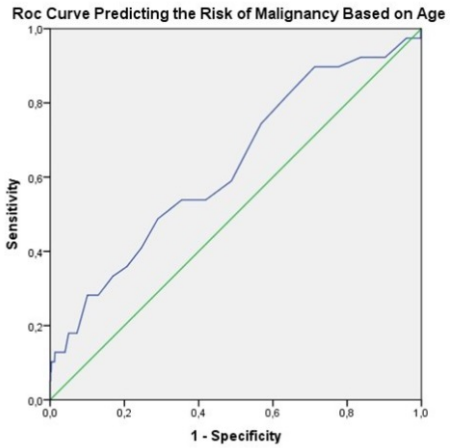
Table 2. Preoperative and postoperative clinical characteristics of patients

Characteristics	Mean±SD (min-max) or number (%)
Cervical smear results	
-Absent	318 (12.3)
-Normal	2228 (86.3)
-Preinvasive lesion	37 (1.4)
Adnexial pathology	
-Absent	2307 (89.3)
-Present	276 (10.7)
Myoma size (cm)	5.3±3.3
Endometrial thickness (mm)	11.4±5.2
Endometrial sampling result	
-Absent	1143 (44.3)
-Normal	1006 (38.9)
-Polyp	345 (13.4)
-Hyperplasia	89 (3.4)
Operation route	
-Abdominal	2013 (77.9)
-Laparoscopic	493 (19.1)
-Vaginal	77 (3.0)
Pathology	
-Myoma uteri	1902 (73.6)
-Adnexial mass	31 (1.3)
-Endometriosis	91 (3.5)
-Myoma uteri+endometriosis	520 (20.1)
-Cancer	39 (1.5)
Malignity	
-Absent	2544 (98.5)
-Present	39 (1.5)

The findings of detailed physical and gynecological examination preoperatively are presented in Table 2. While cervical smear was not performed in 318 patients (12.3%), 2228 patients (86.3%) had normal cervical smear results, and 37 patients (1.4%) had preinvasive lesion which were managed using additional diagnostic tests such as colposcopy and no cervical and/or vaginal malignant lesion was detected. The mean size of myoma uteri and endometrial thickness were 5.3±3.3 cm and 11.4±5.2 mm, respectively. Preoperative endometrial sampling was not performed in 1143 patients (44.3%). In most of the patients, the operation was performed abdominally (77.9%). When the postoperative histopathological results were evaluated, the diagnosis of myoma uteri was confirmed in 1902 patients (73.6%), while malignancy including uterine sarcoma, and STUMP was detected in 39 patients (1.5%).

The comparison of patients with and without malignancy depending on their demographic and clinical characteristics is shown in Table 3. There was significant difference between the groups regarding age (52.5±11.0 vs 48.1±6.1 years, p=0.016). When the gestational history of the patients was compared, no significant difference was found. It was determined that 5.1% of the patients with malignancy were nulligravid while this rate was 3.6% in benign cases (p=0.617). It was also determined that 5.1% of the cases having malignancy were nulliparous whereas 4% of benign cases were nulliparous (p = 0.724). It was observed that complaint of postmenopausal bleeding was more common in the malignant group compared to the benign group (12.8% vs 4.1%, p=0.028).

The only significant difference between the groups in terms of preoperative clinical characteristics of the patients was cervical smear results (5.1% vs 1.4%, p=0.004) (Table 4). While the mean size of myoma uteri were similar between the groups, the endometrial thickness was found to be thicker in the malignant group (5.3±3.4 vs 5.3±3.3 cm, p=0.979; 12.9±7.9 vs 11.3±5.2 mm, p=0.070; respectively). The most common route of operation was found to be the abdominal route in both groups (84.6% vs 77.8%, p=0.429). Although no statistical significance was detected in the logistic regression analysis, presence of comorbid conditions and previous history of gynecological operations increased the risk of malignancy (RR=1.77 (0.91-3.44), p=0.095; RR=1.32 (0.45-3.90), p=0.611) (Table 5).



Cut-off value for age	Area under curve	Sensitivity (%)	Specifity (%)	Positive likelihood ratio	p
49.5	0.63	53.8	64.6	1.52	0.005

Fig.1. The receiver operating characteristics (roc) curve predictand the risk of malignancy based on age

When the age-based roc curve was drawn to predict the risk of malignancy, statistical significance was found (p=0.005) (Fig. 1). The risk of malignancy increased with cut-off values for age more than 49.5 years. The sensitivity and specificity of that age to detect malignancy were 53.8% and 64.6%, respectively.

Table 3. Comparison of the patients regarding their demographic and clinical characteristics

Characteristics	Malignity		p
	Absent (n=2544)	Present (n=39)	
Age (years)	48.1±6.1	52.5±11.0	**0.016**
Gravide			
-Nulligravid	92 (3.6)	2 (5.1)	0.617
-Multigravid	2452 (96.4)	37 (94.9)	
Parity			
-Nullipar	102 (4)	2 (5.1)	0.724
-Multipar	2442 (96)	37 (94.9)	
Abortus			
-Absent	1318 (51.8)	19 (48.7)	0.702
-Present	1226 (48.2)	20 (51.3)	
Labor route			
-No birth	82 (3.2)	1 (2.6)	0.109
-Vaginal birth	1955 (76.8)	36 (92.3)	
-Cesarean section	250 (9.8)	2 (5.1)	
-Vaginal birth+cesarean section	257 (10.1)	0	
Personal history			
-Absent	1964 (77.2)	25 (64.1)	0.054
-Present	580 (22.8)	14 (35.9)	
Gynecological operation history			
-Absent	2339 (91.9)	35 (89.7)	0.617
-Present	205 (8.1)	4 (10.3)	
Operation history			
-Absent	1842 (72.4)	28 (71.8)	0.933
-Present	702 (27.6)	11 (28.2)	
Menstrual regularity			
-Irregular	1458 (57.3)	20 (51.3)	0.189
-Regular	702 (27.6)	9 (23.1)	
-Menopause	384 (15.1)	10 (25.6)	
Complaint			
-Control	103 (4)	0	**0.028**
-Menstrual irregularity	1591 (62.5)	27 (69.2)	
-Pelvic pain	669 (26.3)	7 (17.9)	
-Incontinence, prolapsus	76 (3)	0	
-Postmenopausal bleeding	105 (4.1)	5 (12.8)	

Data are presented as mean±SD or number (%), $p<0.05$ accepted as statistically significant

4. Discussion

Our aim was to investigate the detection rates of uterine sarcoma, STUMP and benign myoma variants in the patients who had been operated with the indication of myoma uteri. In our population, 39 patients (1.5%) were found to have malignancy according to their histopathological evaluation. We detected significant differences between the benign and malign cases in terms of age, complaint during the consultation, and cervical smear results. Myoma uteri, which affects 70-80% of reproductive-aged women, is the most common indication for hysterectomy, constituting 40-60% of all hysterectomy indications (4, 5, 12). The most common symptoms are abnormal uterine bleeding, pelvic pain, dysmenorrhea, and infertility. Myomectomy and hysterectomy are the main surgical approaches in the management of myoma uteri. With the increase of minimally invasive surgical skills of surgeons and the development of instruments used in laparoscopic surgeries, electromechanical morcellators have been developed, thus enabling hysterectomy with endoscopic methods even in the patients with large myoma uteri. The incidence of undiagnosed uterine sarcoma in the patients who underwent hysterectomy with a diagnosis of myoma uteri has been reported between 0.05% and 0.28% (16). The incidence of leiomyosarcoma was reported as 1/8300 in prospective studies, and 1/1700 in retrospective studies (17). The prevalence of malignant neoplasms was 0.34% according to a comprehensive study who underwent laparoscopic hysterectomy. However, histology of uterine malignant neoplasms was not reported in this study (18). In our study, 39 patients (1.5%) had malignancy in their histopathological results. The reason for higher incidence compared to other studies is that we deal with complicated cases at a tertiary referral center. Advanced age was determined as a predictor for uterine sarcoma according to our results. This supports the fact that advanced age is among the risk factors for uterine malignancy. In the most comprehensive study about this topic, it was concluded that the risk of malignancy was associated with increasing age (18). In a population-based study including uterine sarcomas, the rate of undetected uterine sarcoma was reported as 0.36% (19). In this study, the risk was found to be associated with older age. Adjusted relative risk was 2.5 times more between 50 and 59 years of age, compared to women aged younger than 50, and more than 12.8 times for older than 60 years of age. The risk of malignancy increased also significantly in the patients older than 49.5 in our results.

Table 4. Comparison of the patients regarding their preoperative and postoperative clinical characteristics

Characteristics	Malignity		p
	Absent (n=2544)	Present (n=39)	
Cervical smear result			
Absent	308 (12.1)	10 (25.6)	**0.004**
Normal	2201 (86.5)	27 (69.2)	
Preinvasive lesion	35 (1.4)	2 (5.1)	
Adnexial pathology			
Absent	2273 (89.3)	34 (87.2)	0.664
Present	271 (10.7)	5 (12.8)	
Myoma size (cm)	5.3±3.3	5.3±3.4	0.979
Endometrial thickness (mm)	11.3±5.2	12.9±7.9	0.070
Endometrial sampling result			
Absent	1129 (44.4)	14 (35.9)	0.111
Normal	990 (38.9)	16 (41)	
Polyp	340 (13.4)	5 (12.8)	
Hyperplasia	85 (3.3)	4 (10.3)	
Operation route			
Abdominal	1980 (77.8)	33 (84.6)	0.429
Laparoscopic	487 (19.1)	6 (15.4)	
Vaginal	77 (3)	0	

Data are presented as mean±SD or number (%), Used independent samples t-test or chi-square test; p<0.05 accepted as statistically significant

Black race has been reported to be another risk factor for both myoma uteri and uterine sarcoma with a 2-3 times higher risk than in white women (20). Other risk factors of uterine sarcomas include long-term tamoxifen use (5 years or more), pelvic irritation, history of childhood retinoblastoma, hereditary leiomyomatosis, and renal cell carcinoma syndrome (16). It was not possible to perform such an analysis in our study because we included only the patients from white race population and there were no patients having other risk factors listed above. Early menarche and nulliparity are accepted as risk factors for myoma uteri (16). It was shown in the literature that the risk of myoma uteri decreases with each pregnancy (21-23). However, the relationship of the parity with uterine sarcoma has not yet been proven. Although there was no significant difference in our population, the risk of malignancy increased in nulligravid and nulliparous patients when this possibility was compared between the groups.

Table 5. Results of logistic regression analysis

Risk factors	RR (95% CI)	p
Personal history	1.77 (0.91-3.44)	0.095
Gynecological operation history	1.32 (0.45-3.90)	0.611
Operation history	0.99 (0.48-2.06)	0.985
Adnexial pathology	1.28 (0.49-3.32)	0.609
Cervical smear result	0.53 (0.25-1.15)	0.107

Used binary logistic regression analysis, p<0.05 accepted as statistically significant RR, risk ratio; CI, confidence interval

Since abnormal uterine bleeding, pelvic pain, and pelvic mass can be a complaint of admission for both uterine myoma and sarcoma, it is not possible to use them in differential diagnosis (24, 25). In our study, although the main complaint was abnormal uterine bleeding in both groups, postmenopausal bleeding was significantly more common in the malignant group.

Cervical cytology is not a diagnostic tool for uterine sarcoma. Instead, this test is used to screen for cellular anomalies that may be associated with an increased risk of developing cervical cancer. In our clinic, cervical cytology is a screening test during preoperative examinations. The rate of abnormal cytology in our patients in the malignant group was found to be higher significantly compared to the patients in the non-malignant group. Thus, the patients having preoperative abnormal cervical cytology results should be further evaluated in terms of uterine sarcoma.

Endometrial sampling provides approximately 33% to 68% preoperative diagnosis for uterine sarcoma. There is no difference about the sensitivity between endometrial biopsy methods (26, 27). In our study, there was no significant difference in terms of endometrial sampling. This may be due to that endometrial sampling was not performed in 44.3% of the patients because of no suspicion of malignancy. However, endometrial sampling should be recommended in the patients with suspected sarcoma or whom intraperitoneal morcellation is planned (16).

There is a consensus that the presence of myoma uteri is not a risk factor for uterine sarcomas, except in rare cases. The most convincing data was obtained from the results of clinical and molecular genetic studies of a rare subset of myoma uteri with cellular or atypical histology (28-32). Sarcomas typically have complex karyotype and aneuploidy, while myoma uteri has characteristic rearrangements (33, 34).

Since rapid growth can be observed in both benign myoma uteri and sarcomas, it could not be a predictor for uterine sarcoma. In a study investigating 1332 patients who underwent myomectomy and hysterectomy due to myoma uteri, uterine sarcoma was diagnosed in 0.27% of the patients with rapid growth of uterus and 0.15% of the patients without rapid growth. Sarcoma was not detected in many premenopausal women with a rapidly growing uterus or uterine mass (32). On the other hand, the postmenopausal women having uterine mass with rapid growth or recently developed uterine mass should be evaluated in terms of malignancy. In our population, no anamnesis or physical examination about rapid growth was encountered.

In the literature, it is recommended that laboratory tests such as lactate dehydrogenase and cancer antigen 125 (CA-125) may be used for the differentiation of myoma uteri and uterine sarcoma although there was no sufficient evidence to support the clinical use of these tests. In our study, tumor markers were not examined since most patients had no suspicions of malignancy preoperatively.

The clinical prediction of uterine sarcoma is only possible by evaluating the factors together such as signs and symptoms, risk factors, non-responsiveness to treatment, magnetic resonance imaging (MRI) findings and endometrial sampling due to the difficulty of differential diagnosis preoperatively.

The investigation of morbidity rates among hysterectomy routes in the management of myoma uteri is still ongoing (35). In our study, no statistically significant difference was found in terms of hysterectomy routes between the patients with and without malignancy. We did not experience any intraoperative and short-term postoperative complications.

Retrospective design could be accepted as the limitation of our study. Despite this limitation, we contributed much to the literature. To the best of our knowledge, our study is the largest study about this topic. The analysis of all potential confounding factors, and examination of histopathology slides by the experienced pathologists' other strengths of our study.

As a conclusion, myoma uteri, the most common cause of gynecological operations, is too difficult to distinguish from uterine sarcomas. In the patients who are scheduled for operation with a diagnosis of myoma uteri, malignancy may be detected in the histopathologic examination. It is necessary to be careful about the demographic and clinical characteristics of the patients during the preoperative evaluation to determine the possibility of uterine malignancy.

Conflict of interest

The authors declare that they do not have any conflict of interest regarding this article.

Acknowledgments

The authors would like to thank the participants of this study. Approval for the study was obtained from the local ethical committee (KAEK/2018.06.14).

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