

Evaluation of occult uterine *leiomyosarcomas*

Emrah Beyan¹, Ahkam Göksel Kanmaz¹, Abdurrahman Hamdi İnan², Volkan Karataşlı¹,
Sadettin Oğuzhan Tutar³, Murat Alan¹, Emrah Töz¹, Muzafer Sancı¹

¹Health Sciences University, Tepecik Education and Research Hospital, Department of Gynecology and Obstetrics, İzmir, Turkey

²Ministry of Health İzmir Provincial Health Directorate Bornova Türkan Özilhan State Hospital, İzmir, Turkey

³Ministry of Health Ardahan Provincial Health Directorate Ardahan State Hospital, Turkey

ABSTRACT

Objectives: To determine the frequency of occult uterine leiomyosarcomas following hysterectomies and myomectomies performed for benign reasons at our clinic and to draw comparisons with similar studies in the literature.

Material and methods: All hysterectomies and myomectomies that have been performed for benign reasons at our clinic between 2010 and 2017 were retrospectively examined via the hospital's information system and the patients that were found to have *leiomyosarcomas* were analysed. The incidence of occult uterine *leiomyosarcoma* per 1000 surgeries at our clinic was calculated using the Wilson score interval.

Results: A total of 6,173 hysterectomies were performed, and occult uterine *leiomyosarcoma* was identified in 5 patients. The incidence of occult uterine *leiomyosarcoma* was calculated to be 0.08% (95% CI 0.03–0.018%). Only 1 of the 771 patients who underwent myomectomy was identified with occult uterine *leiomyosarcoma*, making its incidence in myomectomy 0.12% (95% CI 0.02–0.073%). When all the patients are considered, occult uterine *leiomyosarcoma* was identified in 6 of the 6,944 patients, and the general incidence of occult uterine *leiomyosarcoma* was calculated as 0.08% (95% CI 0.03–0.018%).

Conclusions: In our study, the incidence of occult uterine *sarcoma* following myomectomy and hysterectomy was found to be lower than that reported in the literature. The reason for this lower incidence includes not only genetic causes and racial differences but also preoperative imaging, endometrial and cervical sampling that is performed on every patient.

Key words: *leiomyosarcoma*; hysterectomy; myomectomy; myoma

Ginekologia Polska 2019; 90, 8: 433–437

INTRODUCTION

Hysterectomy is a commonly performed surgery in gynaecology, and it is reported that approximately 600,000 hysterectomies are performed annually in the South Korea, which is roughly similar to the number of such surgeries performed annually in the United States [1, 2]. A study conducted in Turkey in 2017 on secondary care hospitals affiliated with the Ministry of Health revealed that the total number of hysterectomies performed annually was more than 15,000 [3]. The large majority of hysterectomies are performed for benign reasons worldwide. According to a society-wide study carried out in the United States, the indications for hysterectomy include uterine fibroids in 51.4% of the cases, abnormal uterine bleeding in 41.7%, endometriosis in 30% and uterine prolapse in 18.2% [4]. Another study in the United States determined that approximately 43,000 myomectomies are performed annually due to uterine fibroids, which is the most common reason for hysterectomy, whereas this figure is approximately 9,412 for Turkey [3, 5].

Uterine *sarcomas* reportedly account for 1% of all gynaecological cancers, and 3–7% of uterus-related cancers [6]. According to their histological classification, 40% of uterine sarcomas are *carcinosarcomas*, 40% are *leiomyosarcomas*, 10–15% are endometrial stromal *sarcomas* and 5–10% are undifferentiated *sarcomas* [7]. *Leiomyosarcomas*, listed in this classification, show clinical findings similar to those of uterine fibroids, which leads to certain difficulties in the preoperative diagnosis and treatment of patients [7–9]. Although they are not specific, *leiomyosarcomas* are associated with several risk factors that are different from those associated with uterine fibroids, such as being from the black community, being diagnosed above the age of 60 years, use of tamoxifen or exposure to pelvic radiation, and retinoblastoma in childhood [10–13].

In recent years, there has been an increase in the number of hysterectomies and myomectomies performed worldwide through minimally invasive methods for indications of uterine fibroids, leading to a greater need for the morcella-

Corresponding author:

Emrah Beyan

Health Sciences University, Tepecik Education and Research Hospital, Department of Gynecology and Obstetrics, 35100 İzmir, Turkey

e-mail: emrahbeyan@gmail.com

tion of specimens. In this context, the U.S. Food and Drug Administration (FDA) 2014 has drawn attention to the possibility of occult gynaecological cancers, particularly uterine *sarcomas* that are associated with uterine fibroids [14]. Based on the possibility of uncontrolled spread within the abdomen in gynaecological cancers that could not be identified preoperatively, have been conducted following the aforementioned FDA report for determining the frequency of occult uterine *sarcomas*. A review of the literature shows that the frequency of occult uterine *sarcomas* tends to vary in the range of 0–0.89% [5, 15].

Objectives

The present study aimed to determine the frequency of occult uterine *leiomyosarcomas* following hysterectomies and myomectomies performed for benign reasons at our clinic and to draw comparisons with similar studies in the literature.

MATERIAL AND METHODS

All hysterectomies and myomectomies that have been performed at Izmir University of Health Sciences Tepecik Training and Research Hospital between 2010 and 2017 were retrospectively examined via the hospital's information system. The preoperative diagnoses of all patients were examined. The study included patients who were operated for benign reasons, such as pelvic pain, leiomyoma, endometriosis, abnormal uterine bleeding and uterovaginal prolapse. For the past 10 years, our clinic has been collecting cervical smear samples for endometrial sampling purposes from all patients who have planned hysterectomy surgeries, with sample collection being performed at least 1 month before the date of surgery. Therefore, all patients included into the study had their preoperative assessment done according to these principles.

Patients with planned operations for diagnosed gynaecological or non-gynaecological cancers, patients with dysplasia or atypical endometrial hyperplasia, patients with prior surgeries performed for staging purposes, patients with suspicions of malignancy in their medical history and patients with hysterectomies performed for obstetric reasons were excluded from the study. The cases of uterine *sarcomas* that were initially not detected during preoperative examination but were subsequently identified as a result of postoperative histopathological examinations performed following hysterectomy and myomectomy surgeries were classified based on the guidelines of the World Health Organisation [16], and the patients that were found to have *leiomyosarcomas* were analysed.

The information of patients identified with occult uterine *leiomyosarcomas* was examined in detail through the hospital's information system and patient files. An analysis

was performed on the patients' demographic characteristics, preoperative findings, primary surgical indication and type, weight of specimen, final pathology results, postoperative conditions and treatments and patient survival. The incidence of occult uterine *leiomyosarcoma* per 1000 surgeries at our clinic was calculated using the Wilson score interval.

Simultaneously, our results on occult uterine *leiomyosarcoma* were compared with those of suitable studies found by performing searches on PubMed using the MeSH terms 'Hysterectomy'; 'Myomectomy'; 'Adenosarcoma'; 'Leiomyosarcoma' and 'Carcinosarcoma'.

Statistical analysis

The data were statistically analysed using SPSS 22.0 (SPSS Inc., Chicago, Illinois) software. The normality distribution of continuous variables was evaluated with a normality test that was suitable to the number of data collected. Mean \pm standard deviation or median (min. and max.) were used for descriptive continuous variables. The Mann–Whitney U test was used for the comparison of variables lacking normal distribution, whereas the Student's t-test was used for the comparison of variables with normal distribution. Categorical variables were presented as number of cases and percentages. A value of $p < 0.05$ was considered to be significant. EpiTools epidemiologic calculators (<http://epitools.ausvet.com.au>) were used for the Wilson score interval.

RESULTS

A total of 6,173 hysterectomies were performed at our clinic over 7 years, and occult uterine *leiomyosarcoma* was identified in 5 patients. The incidence of occult uterine *leiomyosarcoma* was calculated to be 0.08% (95% CI 0.03–0.018%). Only 1 of the 771 patients who underwent myomectomy was identified with occult uterine *leiomyosarcoma*, making its incidence in myomectomy 0.12% (95% CI 0.02–0.073%). When all the patients are considered, occult uterine *leiomyosarcoma* was identified in 6 of the 6,944 patients, and the general incidence of occult uterine *leiomyosarcoma* was calculated as 0.08% (95% CI 0.03–0.018%), which is similar to its incidence in patients undergoing hysterectomy. Among the patients included in the study, 4,572 (65.8%) underwent abdominal hysterectomy, 1,022 (14.7%) underwent total laparoscopic hysterectomy, 579 (8.3%) underwent vaginal hysterectomy and 771 (11.1%) underwent myomectomy.

The most common indication of the patients who underwent abdominal and laparoscopic hysterectomy was symptomatic leiomyoma (39%), whereas their second most common indication for hysterectomy was treatment-resistant menometrorrhagia (23%). The most common indication of patients who underwent vaginal hysterectomy was pelvic organ prolapse (64%).

Among the patients included in our study, the primary surgical indication of those identified with occult uterine *leiomyosarcoma* was for symptomatic leiomyoma in all of them. Moreover, 2 patients also had an indication for treatment-resistant menorrhagia in addition to symptomatic leiomyoma.

The mean age of the patients included into the analysis was 48.63 years, whereas our subgroup analysis revealed that the patients who underwent abdominal hysterectomy, total laparoscopic hysterectomy, vaginal hysterectomy and myomectomy had a mean age of 48.91, 49.20, 61.20 and 37.28 years, respectively. The mean age of patients identified with occult uterine *leiomyosarcoma* was 46.5 years, which was lower than that of other patients. The patients' body mass indices varied between 22 and 28. None of the patients identified with occult uterine *leiomyosarcoma* had any tamoxifen use prior to surgery. One patient used an oral contraceptive, whereas none of the other patients had any oral contraceptive use or received hormone replacement treatment. The uterus weight of the patients who underwent hysterectomy varied between 146 and 2500 g. The patient whose uterus weighed 2500 g was found to be obese compared with the other patients, and it was understood that this patient did not attend her routine gynaecological examinations regularly.

The findings of the patients are summarised in Table 1. Six patients identified with occult uterine *leiomyosarcoma* had no pathological findings in their preoperative cervical smear and endometrial samples. Preoperative ultrasonography examination was performed on only 5 patients, whereas patient number 4 also had a magnetic resonance imaging performed in addition to ultrasonography, although their findings were not interpreted to be indicative of malignancy.

All of the patients were operated by gynaecology specialists under suitable conditions. Five patients had oophorectomies performed in addition to hysterectomy, and 1 patient only had a myomectomy surgery performed. Morcellation was not applied in any patient. In all patients, the operated piece was removed as a single whole piece, and we observed

that, except for patient number 4, a frozen sample examination was not performed on the collected pieces, as there was no suspicion of malignancy. A frozen sample examination was performed on only 1 patient. The results of this examination were checked only according to the mitosis count, and the final pathological diagnosis of *leiomyosarcoma* was established in the final pathological examination.

Three patients identified with occult uterine *leiomyosarcoma* had stage 1c *leiomyosarcoma*, two had stage 1b *leiomyosarcoma* and one had stage 2 *leiomyosarcoma*. Combined radiotherapy plus chemotherapy was used in the secondary treatment of 4 patients, whereas 1 patient received only radiotherapy and 1 received conservative treatment. None of the patients showed recurrence during their monitoring period, and all patients were still alive at the time this article was penned. The mean disease-free survival was determined as 60 (40–86) months.

DISCUSSION

A total of 6,944 patients who underwent hysterectomy and myomectomy surgeries at our clinic for benign reasons within a seven-year period were included in the study. Occult uterine *leiomyosarcoma* was identified in 6 of the 6,944 patients, and the general incidence of occult uterine *leiomyosarcoma* was calculated as 0.08% (95% CI 0.03–0.018%). Following the FDA's notable 2014 report, which presented a prevalence of 1/498 (0.2%) for occult uterine *leiomyosarcoma*, there has been a visible increase in the literature in the frequency of studies conducted on this subject [17]. Many studies have reported the rates of occult uterine *leiomyosarcoma* at their own clinics, with incidences varying between 0% and 0.89%. A summary of these studies is provided in Table 2.

In their 2008 study that focused solely on patients who underwent myomectomy, Sinha et al. [18] determined the incidence of occult uterine *leiomyosarcoma* to be 0.40%, whereas Brohl et al. [19] identified this incidence to be 0.24%. In our analysis, the rate of occult uterine *leiomyosarcoma* following myomectomy surgery was calculated

Table 1. Information of patients with occult uterine leiomyosarcoma

Patient	Age [years]	BMI	Primary diagnosis	Primary surgery	Uterine weight [g]	Sarcoma type	Stage	Treatment	Status	Follow-up [months]
1	52	28	ULM	TAH	241	LMS	1c	RT + CT	Live	60
2	47	29	ULM + TRM	TAH	146	LMS	1b	RT + CT	Live	48
3	54	31	ULM	TAH	610	LMS	2	RT + CT	Live	40
4	47	38	ULM	TAH	2500	LMS	1c	RT	Live	60
5	47	27	ULM + TRM	TAH	469	LMS	1c	RT + CT	Live	86
6	32	22	ULM	Myomectomy	128	LMS	1b	None	Live	72

ULM — uterine leiomyoma; TRM — treatment-resistant menorrhagia; TAH — total abdominal hysterectomy; LMS — leiomyosarcoma; RT — radiotherapy; CT — chemotherapy

Table 2. Comparison of occult uterine leiomyosarcoma studies

Author	Year	Centers that include study	Operation type	Study duration	Number of patients	Rate of Occult LMS, n (per 100)
Parker et al. [26]	1994	Two	Hysterectomy, Myomectomy	1988–1992	1332	3 (0.23)
DiNapoli et al. [21]	2018	Single	Hysterectomy, Myomectomy	2010–2014	1959	4 (0.20)
Kundu et al. [20]	2017	Single	Hysterectomy, Myomectomy	2004–2014	2825	10 (0.35)
Seidman et al. [27]	2012	Single	Hysterectomy, Myomectomy	2005–2010	1091	2 (0.18)
Brohl et al. [19]	2015	Multiple	Myomectomy	2005–2014	2075	5 (0.24)
Sinha et al. [18]	2008	Single	Myomectomy	1998–2005	505	2 (0.40)
Multinu et al. [28]	2019	Multi	Hysterectomy	1999–2013	3759	4 (0.11)
Leung et al. [29]	2008	Single	Hysterectomy	1996–2005	1297	3 (0.23)
Ramm et al. [30]	2012	Multiple	Hysterectomy	2004–2009	708	1 (0.14)
Kho et al. [15]	2016	Single	Hysterectomy	2000–2014	10109	9 (0.89)
Yuk et al. [2]	2016	Multiple	Hysterectomy	2010–2012	12850	8 (0.06)
Theben et al. [31]	2013	Single	Hysterectomy	2005–2010	1584	2 (0.13)
Wright et al. [32]	2014	Multiple	Hysterectomy	2006–2012	36470	none
Wan et al. [33]	2013	Single	Hysterectomy	2003–2011	640	1 (0.16)
Current Study		Single	Hysterectomy, Myomectomy	2010–2017	6944	6 (0.08)

LMS — *leiomyosarcoma*

to be 0.12%. In addition to the specific geographical region where analyses are performed, racial and genetic differences are possibly the causes of these different results.

A review of the literature shows that while the incidence of occult uterine *leiomyosarcoma* in patients who undergo only hysterectomies can be 0.89% at the highest [15], the incidence of occult uterine *leiomyosarcoma* varies between 0.20% and 0.38% when all patients who underwent hysterectomy and myomectomy are included in the analysis [20, 21]. In our study, the incidence of *leiomyosarcoma* was calculated to be 0.08%, which is relatively lower than that reported in other studies. There are only a limited number of studies in Turkey regarding the incidence of occult *leiomyosarcoma*; however, a previous study in Turkey has reported an annual *leiomyosarcoma* incidence of 0.26% [22].

Currently, no tests that might be used to diagnose *leiomyosarcoma* preoperatively during the evaluation of patients for uterine leiomyoma are available. Unexplained pain and atypical vaginal bleeding in the presence of uterine leiomyoma along with a rapid increase in the leiomyoma's size can serve as warnings with regards to *leiomyosarcoma* [7, 23]. As vaginal bleeding independently can be observed in submucosal myomas of any additional pathology and pain can also occur following a possible degeneration in the myomas, these two symptoms — vaginal bleeding and pain — have rather low value in preoperative differential diagnosis [24, 25]. Parker et al have also reported that a rapid increase in the size of the uterus cannot be used in distinguishing *leiomyosarcomas* from leiomyomas [26].

As uterine *leiomyosarcomas* that have not been identified during preoperative differential diagnosis can possibly spread into the abdominal cavity, it is suggested that it is not suitable to perform power morcellation following minimally invasive procedures in the absence of adequate protective equipment for the intra-abdominal area [18, 20]. The major limitation of this study was its retrospective nature. The fact that the hospital's information underwent a major overhaul in the 2000s and that we could not include patients admitted prior to this period considerably restricted our ability to increase our study sample size. Nevertheless, compared with the data obtained from single-centre studies performed in Turkey and worldwide, we believe that our study makes a marked contribution to the literature with its number of patients and the rates it determined. Simultaneously, we also believe that our study serves as an important source because it illustrates the situation in Turkey based on comparisons with other studies.

CONCLUSIONS

In our study, the incidence of occult uterine *sarcoma* following myomectomy and hysterectomy was found to be lower than that reported in the literature. We believe that the underlying reason for this lower incidence includes not only genetic causes and racial differences but also preoperative imaging and preoperative endometrial and cervical sampling that is performed on every patient. Although it might not seem cost-effective when viewed solely from a cost-effectiveness standpoint, we believe that detailed

preoperative examination is useful given the possibility of medico-legal complications, additional treatment needs of patients and pain and anxiety the patients might experience. Conducting international multi-centre prospective studies on such patients will likely play a guiding role in determining the appropriate incidence of *leiomyosarcoma* and in identifying the proper measures against it.

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