

Likelihood of incidental finding of gynecological cancer in women undergoing hysterectomy for benign indications

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Summary

Objective: The aim of this study was to determine the incidence of unexpected gynecological malignancy (UGM) after hysterectomy performed for benign indications. **Methods:** We analysed patient sample data extracted from a medical database between 1 January 2007 and 10 August 2019 for 2740 women who underwent a hysterectomy for benign indications. The Kolmogorov-Smirnov test, Kruskal-Wallis test and Chi-square test were performed. Statistical significance was reached if $p < 0.05$. **Results :** The most common primary indications for hysterectomy were leiomyomata (1403, 51%), abnormal uterine bleeding (784, 28.61%), and pelvic organ prolapse (504, 18.39%). A laparotomic, laparoscopic or vaginal hysterectomy was performed in 1452 (53%), 836 (30.5%) and 452 (16.5%) women, respectively. unexpected gynecological malignancy after hysterectomy was diagnosed in 22 (0.80%) women. The incidence of unexpected uterine malignancies (UUM), unexpected endometrial cancer, and unexpected uterine malignancies without endometrial cancer was 0.54%, 0.40% and 0.14% respectively. Mean ages were not significantly different for abdominal, laparoscopic and vaginal hysterectomy groups (51.75 ± 9.83 , 51.32 ± 9.51 , 51.39 ± 10.04 years respectively, $p = 0.299$). No significant difference in the incidence of unexpected gynecological malignancy was noted between the groups [laparotomy 0.47%, laparoscopy 0.22%, vaginal 0.11%, $p = 0.066$]. The incidence of unexpected leiomyosarcoma [laparotomic 0.11%, laparoscopic 0.03%, vaginal 0.0%] and unexpected endometrial carcinoma [laparotomic 0.26%, laparoscopic 0.11%, vaginal 0.03%] was significantly higher in abdominal and laparoscopic hysterectomy groups than the vaginal hysterectomy group and no significant difference was observed between the abdominal and laparoscopic hysterectomy groups ($p = 0.037$, $p = 0.028$, $p = 0.108$, respectively). **Conclusion:** The incidence of unexpected gynecological malignancy diagnosed after hysterectomy performed for benign conditions was very low, if the correct indications were selected.

Key words: Hysterectomy; Uterine malignancy; Unexpected malignancy; Benign indication; Unexpected gynecologic malignancy.

Introduction

Hysterectomy is the most common major surgery with about 400,000 cases for benign conditions performed in the United States annually [1]. Uterine leiomyomas, abnormal uterine bleeding and uterovaginal prolapse are the most common indications for hysterectomy [2]. In various studies, it was reported that 0.12-2.7% of patients who underwent hysterectomy with benign indications had unexpected endometrial cancer, 0.22-0.39% uterine sarcoma and 0.19-2.7% unexpected gynecologic malignancies [2-5]. Risk estimates from the U.S. Food and Drug Administration (FDA) and American College of Obstetricians and Gynecologists range from 1 in 352 to 1 in 500, respectively, for women undergoing surgery for presumed myomas [6]. Unexpected risk of cancer leads to fear of minimally invasive approaches, especially in patients with a large uterus that may need to be removed [7].

Compared with abdominal hysterectomy, minimally invasive approaches provide a lower risk of perioperative complications and faster recovery [8]. However, smaller incisions present the difficulty of removing large samples. The use of electromechanical morcellators has facilitated tissue removal during endoscopic procedures [9]. How-

ever, concerns have been raised with the use of a morcellator for the inadvertent spreading of hidden malignancies of assumed benign tissues [10]. If an unexpected malignancy is detected after surgery using a morcellator, it may worsen the prognosis of the malignancy and may require additional treatment [11]. This has led the FDA to issue a safety communication “discouraging the use of power morcellation” and has resulted in changes in surgical practice [12-13].

To guide patient counseling and clinical practice, determining the accurate incidence of unexpected gynecological malignancies (UGM) will be clinically important.

Materials and Methods

We analysed patient samples retrospectively after approval from the University of Abant İzzet Baysal University (AİBU) local ethics committee. All cases of hysterectomy performed for benign gynecologic indications from 1 January 2007 to 10 August 2019 at AİBU hospital and Bolu İzzet Baysal State Hospital were identified from a retrospectively maintained departmental billing database. The database is maintained with quality assurance by a database specialist and is searchable through International Classification of Disease codes, using Current Procedural Termi-

Table 1. — Distribution of ages and number in patients who underwent hysterectomy from 2007 to 2019.

Variables	One-sample T test					
	N / %	Mean (years)	Std. Deviation	Std. Error Mean	95% Confidence Interval	
					Lower	Upper
TAH	1452 / 52.99	51,746	9,834	0,258	51,326	52,325
TLH	836 / 30.51	51,327	9,511	0,328	50,776	52,239
VH	452 / 16.49	51,389	10,043	0,472	47,593	49,959
AUB	784 / 28.61	49,574	8,519	0,304	48,414	49,465
Leiomyoma uteri	1403 / 51.20	51,295	9,620	0,256	50,792	51,799
Endometriosis	4 / 0.14	46,466	4,613	0,557	42,055	50,878
UVP	504 / 18.39	51,354	9,618	0,429	50,390	52,117
PID	45 / 1.64	49,133	7,356	1,096	46,923	51,343
total	2740 / 100	50,671	9,166	0,175	50,226	50,898

Data are expressed as n (%). TAH total abdominal hysterectomy, TLH total laparoscopic hysterectomy, VH vaginal hysterectomy, AUB abnormal uterine bleeding, UVP utero vaginal prolapse, PID pelvic inflammatory disease.

nology. The database was queried for all hysterectomies performed during this time period. Cases performed for obstetric purposes and for malignancy or suspected malignancies were excluded.

For all gynecologic cancer and sarcoma cases, data regarding clinical presentation, preoperative evaluation, intraoperative findings and pathology were systematically reviewed from the medical record. Unexpected gynecologic cancers were defined as cases in which gynecologic cancer was confirmed on surgical pathology, but did not have clinical preoperative suspicion or indication of malignancy. Relevant clinical and pathological data were collected from the medical record, including symptoms, family history of cancer, preoperative diagnosis, imaging studies, surgeon subspecialty, surgical procedure, pathological findings, further treatment and/interventions, and survival status.

The term of indication of hysterectomy for a benign condition was associated with diagnoses of leiomyoma uteri, abnormal uterine bleeding, simple endometrial hyperplasia without atypia, adenomyosis, pelvic inflammatory disease, chronic pelvic pain, endometrial polyp and uterovaginal prolapse. Patients with endometrial hyperplasia with atypia and complex endometrial hyperplasia, endometrial intraepithelial neoplasia, cervical intraepithelial neoplasia 2 and 3, ovarian tumors and pre-existing gynecological cancer, family history of gynecological malignancies, or high blood levels of CA 125 and CA19-9 were not included in the study.

Types of hysterectomy in the study were recorded as laparoscopic hysterectomy, vaginal hysterectomy, and abdominal hysterectomy.

Statistical analysis

The data management and analysis were performed using the Statistical Package for Social Sciences version 23.0 (SPSS Inc. USA). The suitability of the data for normal distribution was determined by the Kolmogorov-Smirnov

test. Since $p = 0,000 < \alpha = 0.05$, the data were not suitable for normal distribution. For this reason, the Kruskal-Wallis test was performed. The chi-square test was used to compare the rate of malignancy of each group. The outcomes were assessed within a 95% confidence interval and statistical significance was considered if $p < 0.05$.

Results

Two thousand seven hundred forty hysterectomies for benign gynecologic indications were performed during this time period, including abdominal (1452, 52.99%), laparoscopic (836, 30.51%) and vaginal approaches (452, 16.49%). Table 1 provides an overview of the characteristics of these women. The mean age of the women who underwent a hysterectomy was 50.67 ± 9.16 years. The most common primary indications for hysterectomy were leiomyomata (1403, 51%), abnormal uterine bleeding (784, 28.61%), and pelvic organ prolapse (504, 18.39%). The total number of women diagnosed with UGM after a hysterectomy was 22 (0.80 %). These malignancies included four (0.14%) leiomyosarcomas (LMS), four (0.14%) endometrial stromal sarcomas (ESS), one (0.03%) insitu cervix squamous cell carcinoma, two (0.07%) vagina squamous cell carcinoma and eleven (0.40%) endometrium endometrioid type adenocarcinoma (Table 2).

Comparison of the number of unexpected uterine malignancy (UUM) among abdominal, laparoscopic and vaginal hysterectomy is shown in Table 3. Mean ages were insignificantly different between abdominal hysterectomy, laparoscopic and vaginal hysterectomy groups (51.75 ± 9.83 , 51.32 ± 9.51 , 51.39 ± 10.04 years respectively, $p = 0.299$). No significant difference in the number of women diagnosed with UUM after hysterectomy was observed between the laparotomic, laparoscopic and vaginal hysterectomy groups (laparotomy, 9 [0.36 %]; laparoscopy, 5 [0.18 %]; vaginal, 1 [0.03%] $p = 0.066$). The incidence of UUM after hysterectomy was 0.54% (15 / 2740 patients). The in-

Table 2. — Distribution of unexpected gynecological malignancies after hysterectomy from 2007 to 2019.

Gynecological malignancies	TAH	TLH	VH	total	<i>p</i> ^a
Leiomyosarcoma	3 (0.11)	1 (0.03)	0 (0)	4 (0.14)	0.037
Endometrium Endometrioid ca	7 (0.26)	3 (0.11)	1 (0.03)	11(0.40)	0.028
Endometrial stromal sarcoma	2 (0.07)	2 (0.07)	0 (0)	4 (0.14)	
İnsitu Cervix Ca	1 (0.03)	0 (0)	0 (0)	1 (0.03)	
Squamöz cell ca (vagina ca)	0 (0)	0 (0)	2 (0.07)	2 (0.07)	
Total	13 (0.47)	6 (0.22)	3 (0.11)	22 (0.80)	0.066

Data are expressed as n (%). ^a Chi-Square test TAH total abdominal hysterectomy, TLH total laparoscopic hysterectomy, VH vaginal hysterectomy, Ca carcinoma

Table 3. — Incidence of uterine malignancy in women who underwent hysterectomy from 2007 to 2019.

Patients undergoing hysterectomy	Laparotomy	Laparoscopy	<i>p</i>	Vaginal	<i>p</i>	Total
Number of patient	1452	836		452		2740
Mean age (years)	51.75 ± 9.83	51.32 ± 9.51	0.299 ^b	51,39 ± 10,04	0.299 ^b	50.67
UUM after hysterectomy n (%)	9 (0.36)	5 (0.18)	0.108 ^a	1 (0.03)	0.066 ^a	15 (0.57)
Endometrial cancer n (%)	7 (0.25)	3 (0.11)	0.108 ^a	1 (0.03)	0.028 ^a	10 (0.39)
Non-endometrial cancer n (%)	2 (0.07)	2 (0.07)	1 ^a	0	0.108 ^a	4 (0.14)

Data are expressed as n (%) or mean ± standard deviation. UUM unexpected uterin malignancy ^a Chi-Square test, ^bKruskal-Wallis test

incidence of unsuspected endometrial cancer after hysterectomy was 0.40% (11 / 2740 patients); and the incidence of UUM other than endometrial cancer after hysterectomy was 0.14 % (4 / 2740 patients) and the incidence of unsuspected LMS after hysterectomy was 0.14% (4 / 2740). The incidence of unexpected LMS [laparatomic 0.11%, laparoscopic 0.03%, vaginal 0.0%] and unexpected endometrial carcinoma [laparatomic 0.26%, laparoscopic 0.11%, vaginal 0.03%] were significantly higher in abdominal and laparoscopic hysterectomy groups than vaginal hysterectomy group, and an insignificant difference between abdominal and laparoscopic hysterectomy groups ($p = 0.037$, $p = 0.028$, $p = 0.108$, respectively) was observed. The endometrium was the most common location (11/15, 73.3 %) of all UUM after hysterectomy. In the cohort of women with occult unexpected uterine malignancy, hysterectomy was performed as a primary indication for abnormal bleeding (68.18%) and leiomyomas (18.18%).

In the cohort of women found to have an unanticipated uterine malignancy at the time of hysterectomy, the median age at diagnosis was 51 years (range 47–62). All of unsuspected endometrial malignancy cases were detected as endometrioid type adenocarcinomas, nine of them were stage 0 and two of them were stage 1A. All of the sarcoma cases were detected stage 1A leiomyosarcoma and none were post-menopausal. All leiomyosarcoma cases were determined to have undergone hysterectomy for uterine leiomyoma. Preoperative endometrial sampling and Cancer Antigen 125 levels were determined to be normal in these patients. Endometrial stromal sarcoma (ESS) cases were found to have undergone hysterectomy for endometrial polyp disease associated with postmenopausal bleed-

ing. All ESS cases were detected as stage 1A. The insitu cervix squamous cell carcinoma case was 47 years old and preoperative cervical smear result was normal. All of UUM patients did not receive any additional surgery or treatments outside of observation. Vaginal squamous cell carcinoma cases were detected from pathologic specimen of the vagina who underwent vaginal hysterectomy. All of them were stage 1 and radiotherapy was applied after diagnosis.

Discussion

Our study found that the incidence of UUM, unexpected endometrial cancer, and UUM without endometrial cancer was 0.54, 0.40, and 0.14 %, respectively. Considering that these incidence rates were reported to be 0–1.24, 0–1.02, and 0.07–0.40 %, respectively, in previous studies (Table 4), the current results were comparable but were in the middle range. Ethnic characteristics may also have a significant impact on this difference because it has previously been reported that Korean women have a lower incidence of uterine cancer [3, 19, 20, 22, 27]. The endometrium was the most common location (11/15, 73.3 %) of all UUM after hysterectomy. In the cohort of women with occult unexpected uterine malignancy, the median age at diagnosis was 51 years (range 47–62), hysterectomy was performed as a primary indication for abnormal bleeding (68.18%) and leiomyomas (18.18%). Similar to other studies, endometrial cancer was more common in patients with post-menopausal abnormal uterine bleeding [18].

In our study, the incidence of unsuspected LMS after hysterectomy was found 0.14 percent. All leiomyosarcoma cases were determined to undergo hysterectomy for uterine leiomyoma. Preoperative endometrial sampling and Cancer

Table 4. — Comparison of the studies on unexpected uterine malignancy after hysterectomy.

Author (year)	Data source	Study period	No. of subjects	Mean age	Procedure	Incidence of UUM	Incidence of UEC	Incidence of UUS
Yuk <i>et al.</i> [3]	Multiple centers	2010–2012	12.85	47.2 ± 7.1	Hysterectomy	24 (0.19)	16 (0.12)	8 (0.06)
Mahnert <i>et al.</i> [4]	Multiple centers	2013	7499	NA	Hysterectomy	79 (1.24)	65 (1.02)	14 (0.22)
Ramm <i>et al.</i> [16]	Multiple centers	2004–2009	708	56 ± 11	Hysterectomy	5 (0.71)	4 (0.56)	1 (0.14)
Wan <i>et al.</i> [22]	Single center	2003–2011	640	64.2 (38–93)	Hysterectomy	3 (0.47)	2 (0.31)	1 (0.16)
Ouldamer <i>et al.</i> [24]	Single center	2000–2011	2179	49.5 (21–96)	Hysterectomy	9 (0.41)	7 (0.32)	2 (0.09)
Leibsohn <i>et al.</i> [28]	Single center	1983–1988	1432	(36–62)	Hysterectomy	7 (0.49)	0 (0)	7 (0.49)
Kamikabeya <i>et al.</i> [20]	Single center	1987–2008	1364	NA	Hysterectomy	3 (0.22)	2 (0.15)	1 (0.07)
Takamizawa <i>et al.</i> [19]	Single center	1983–1997	923	44.5 ± 5.2	Hysterectomy	4 (0.43)	2 (0.21)	2 (0.21))
Frick <i>et al.</i> [14]	Single center	2005–2008	644	59.7 ± 12.0	Hysterectomy	0	2 (0.3)	0
Andy <i>et al.</i> [15]	Multiple centers	1999–2010	324	56.1	Hysterectomy	0	0	0
Ackenbom <i>et al.</i> [17]	Single center	2007–2014	1196	62.3 ± 11.3	Hysterectomy	3 (0.8)	0	0
Leung <i>et al.</i> [21]	Single center	1996–2005	1297	48 (34–77)	Hysterectomy	NA	NA	3 (0.23)
Multinu <i>et al.</i> [5]	Multiple centers	1999–2013	3759	47	Hysterectomy	0	0	5 (0.13)
Rowland <i>et al.</i> [25]	Single center	2006–2011	1115	NA	LH	10 (0.90)	5 (0.45)	5 (0.45)
Theben <i>et al.</i> [23]	Single center	2005–2010	1584	45.9 (28–81)	LASH	4 (0.25)	2 (0.13)	2 (0.13)
Wright <i>et al.</i> [26]	Multiple centers	2006–2012	36.47	NA	LH	99(0.27)	NA	NA
Present study.	Multiple centers	2007- 2019	2740	51.4 ± 9.7	Hysterectomy	15 (0.57)	11 (0.39)	4 (0.14)

Data are expressed as mean ± Standard deviation, median (range), or n (%) UUM unexpected uterine malignancy, UEC unexpected endometrial carcinoma, UUS unexpected uterine sarcoma, LM laparoscopic myomectomy, LH laparoscopic hysterectomy, LASH laparoscopic-assisted supracervical hysterectomy, NA data not available

Antigen 125 levels were determined to be normal in these patients. Similarly, in other studies, LMS rates have been reported as 0–0.49. In other words, these findings were considered to be consistent with the idea that there are no reliable preoperative diagnostic tools for leiomyosarcoma [4, 5, 7, 16]. In the same context, no significant difference in the incidence of UUM after hysterectomy was noted between the laparotomic and laparoscopic hysterectomy groups in this study.

In our study, the rate of unexpected endometrial malignancy was 0.03% and vaginal squamous cell carcinoma was 0.07% in patients who underwent vaginal hysterectomy with the diagnosis of Uterovaginal Prolapse. Similarly; unexpected endometrial malignancy incidence has been reported between 0–0.54% in hysterectomies performed with the diagnosis of pelvic floor dysfunction [14–17]. Unsus-

pected vaginal cancer cases are detected in the pathology results of vaginal tissues removed during vaginal reconstruction after vaginal hysterectomy. None of the other studies reported unexpected cases of vaginal cancer. It may be because the vaginal tissue is not removed or the extracted vaginal tissues do not undergo pathological examination.

In studies with a large number of patients, it is not possible to make file reviews. Thus, such studies obtain their results by relying on ICD10 codes in the database [3, 26]. So it is not known how much of this data is accurate or how many cancer cases were not recorded. Therefore, the higher the number of patients in the studies, the lower the incidence of unexpected cancer.

The advantages of our study are that we have a relatively large number of patients (2740) and that we have not overlooked cancer cases because we examined the individual

files and pathology results of all these patients. The fact that preoperative evaluations are not standard is the limitation of our study.

Conclusion

The incidence of UGM diagnosed after hysterectomy performed for benign conditions was very low, if the indications were selected correctly, patients considering hysterectomy especially with a large uterus should be adequately counseled about the prevalence of cancerous and precancerous conditions prior to undergoing the procedure.

Authors' contributions

Conception, design and writer: M.A.Ekici. Statistic, materials: A.C.Onal. Data collection and analysis: C.Cetin.

Ethics approval and consent to participate

Data were obtained with the informed consent of all participants. The study is approved by Abant İzzet Baysal University local ethics committee with decision no:2019/214

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Conflict of interest

The authors declare no competing interests.

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