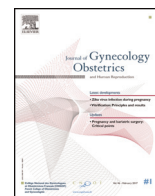




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Original Article

Incidence of occult malignancies identified during hysterectomies performed for benign indications



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ARTICLE INFO

Article history:

Received 9 April 2019

Received in revised form 12 July 2019

Accepted 14 August 2019

Available online 23 August 2019

Keywords:

Occult gynaecologic malignancy

Hysterectomy

Benign indications

ABSTRACT

Objective: Hysterectomy is a commonly performed gynaecological procedure worldwide. Although most hysterectomies are performed for benign indications, the possibility of an unexpected malignancy in the final pathology results should be considered. The aim of our study was to investigate the evaluation and management of patients who underwent hysterectomy for benign reasons but were diagnosed with a malignancy in the final pathology results.

Methods: We retrospectively examined the medical records of patients who underwent hysterectomy for benign indications between 2011 and 2017, and recorded the information obtained from these patient files.

Results: In total, 1050 patients who underwent hysterectomy for benign indications were included in the study. Among these patients, 127 underwent hysterectomy for uterine prolapse, 230 for uterine myoma, 223 for treatment-resistant menometrorrhagia, 150 for treatment-resistant menometrorrhagia and uterine myoma, 61 for endometriosis, 108 for ovarian cysts, 45 for endometrial polyps, and 106 for treatment-resistant menometrorrhagia and ovarian cysts. In 13 of these patients, malignancy was unexpectedly identified via the final pathology results. Seven of these patients had sarcoma, three had cervical cancer, two had ovarian cancer, and one had metastasis of a haematological malignancy.

Conclusion: Malignancy was identified in 13 of the 1050 patients included in our study. The incidence of unexpected malignancy in these patients who underwent hysterectomies performed for benign indications was determined to be 1.23%. Seven of these 13 patients had sarcoma. Our results demonstrate the absence of reliable data for preoperative detection of sarcoma.

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Introduction

Hysterectomy is one of the most frequently performed gynaecological surgeries, and approximately 90% of all hysterectomies are performed for benign reasons. The most common indications for hysterectomy are leiomyoma and abnormal uterine bleeding [1,2]. Hysterectomy can be performed abdominally, laparoscopically, robotically, or vaginally. The vaginal approach is thought to be most suitable because it is associated with a

shorter hospital stay, faster mobilisation, and less bleeding compared with other methods (abdominal, laparoscopic, robotic) [3]. Using a morcellator during laparoscopic hysterectomy facilitates the removal of material from large uteri. Compared with the abdominal approach, it also reduces morbidity and the duration of hospital stay [4]. However, using a morcellator in the presence of an underlying occult malignancy can increase the likelihood of a malignant tumour spreading inside the abdomen [2,5]. Although sarcomas represent <1% of all gynaecological malignancies, they are still rather aggressive tumours [6,7]. In postmenopausal women with rapidly growing uterine myomas, the possibility of sarcoma should definitely be considered [8]. The incidence of unexpected sarcoma in patients who undergo hysterectomies is between 0.09% and 0.049%, and that of unexpected endometrial cancer in patients who undergo hysterectomies is between 0.13% and 0.45% [9,10]. The aim of our study was to discuss and evaluate, in light of the current literature, the

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issues that merit attention during preoperative evaluation when an occult malignancy is identified in a patient undergoing hysterectomy for a benign indication.

Materials and methods

Patients who had undergone hysterectomy for benign indications at our clinic between 2011 and 2017 were included in our study, and the records of these patients were examined retrospectively. As preparation for surgery, complete blood count, coagulation tests, tumour marker and hepatitis marker assessments, and blood chemistry tests had all been routinely performed. Electrocardiography and posterior–anterior chest radiography were performed on all patients. Prior to surgery, consultation was conducted with the anaesthesiology clinic for all patients. The patients were admitted to their wards 2 days before surgery, and the most suitable surgical procedure for each patient was determined based on a physical examination performed before surgery. The patients underwent vaginal, laparoscopic, or abdominal hysterectomy depending on which technique was most suitable. All patients were older than 40 years of age and underwent surgery owing to treatment-resistant menometrorrhagia (TRM); all had endometrial biopsy pathology results in their files (normal endometrial biopsy results that were obtained through a biopsy performed either at our clinic or at a location outside our clinic during the past 6 months). Patients reported to have complex atypical hyperplasia during preoperative assessment, those who underwent postpartum hysterectomy for obstetric reasons, those with a malignancy detected following the frozen section procedure applied during surgery, and those with premalignant lesions with a CIN 2 or higher malignancy potential detected after cervical biopsy were excluded from the study. The medical records of 1050 patients who had hysterectomies for benign indications were examined. The patients' age, preoperative surgery indications, final pathology, and method of surgery were

all evaluated via their medical records. Among the 1050 patients whose files were examined, 13 patients were found to have a final pathology of sarcoma, ovarian cancer, or cervical cancer, and none had incidental endometrial cancer.

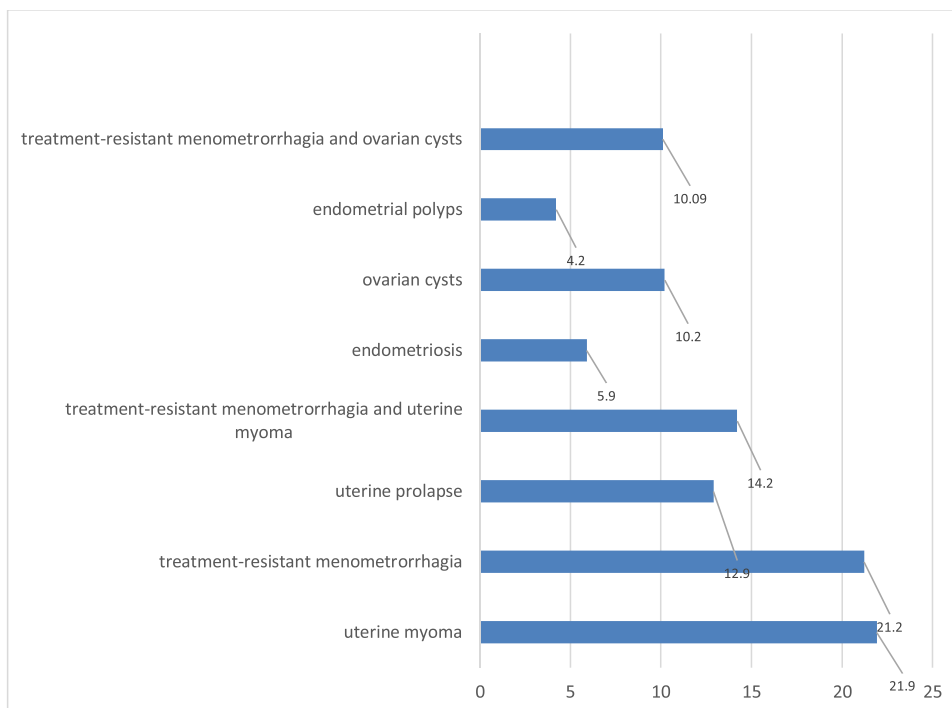
The Statistical Package for the Social Sciences (ver. 15, SPSS, Inc., Chicago, IL, USA) software was used to evaluate the findings. Results are presented as means \pm standard errors or percentages.

Results

We retrospectively examined data from 1050 patients who underwent hysterectomy for benign indications. The operation was performed using an abdominal, laparoscopic, or vaginal method. The mean patient age was 50 ± 7 years, body mass index was 29.4 ± 6.5 (kg/m^2), gravida was 3.7 ± 2.5 , and parity was 2.6 ± 1.8 . Of the 1050 patients, 230 (21.9%) underwent hysterectomy for uterine myoma, 223 (21.2%) for TRM, 127 (12.09%) for uterine prolapse, 150 (14.2%) for TRM and uterine myoma, 61 (5.9%) for endometriosis, 108 (10.2%) for ovarian cysts, 106 (10.09%) for TRM and ovarian cysts, and 45 (4.2%) for endometrial polyps (Table 1). Uterine myoma was the most frequent indication for hysterectomy.

Unexpected malignancy was identified in 13 (1.23%) of the 1050 patients. The mean age of these patients was 61 ± 4 years. All patients who underwent the procedure due to abnormal uterine bleeding had preoperative endometrial biopsies that were reported as normal. Among the 13 patients identified with unexpected malignancies, 7 (0.66%) had sarcoma, 3 (0.28%) had cervical cancer, 2 (0.19%) had ovarian cancer, and 1 had metastasised acute myeloblastic leukaemia. Endometrial cancer was not detected in any of the patients. Magnetic resonance imaging (MRI) was performed on five of the patients who underwent hysterectomy for uterine myoma but had sarcoma identified in their final pathology; no myometrial retention was observed in these patients. Preoperative endometrial pathology

Table 1
Indications for hysterectomy.



assessment was performed on all seven patients, and their pathology results were reported to be normal. The final pathology results of three of the patients revealed cervical cancer. Only one of these three patients had a colposcopic biopsy performed owing to HPV 16 positivity. The results of this biopsy showed that the patient had CIN 1, and the final pathology results revealed cervical cancer. The other two patients had hysterectomies performed because of TRM, and their preoperative smear results were normal. For one of these two patients, final pathology results revealed cervical adenocarcinoma in situ, whereas the other patient had a final pathology of squamous epithelial cell carcinoma with an invasion depth of 1 mm. Of the two cases in our study in whom ovarian cancer was identified, one had a 12-cm ovarian cyst originating from the left ovary that was visualised via MRI. The patient's preoperative serum CA 125 level was normal, and the intraoperative frozen section procedure suggested a benign cyst. However, the final pathology was reported as high-grade serous carcinoma. In the other case, the CA 125 level was normal, and MRI of the pelvis detected a 6-cm myoma and 5-cm cyst in the left ovary, which in turn prompted the decision for hysterectomy. However, this patient did not undergo the intraoperative frozen section procedure, and her final pathology results revealed that she had a granulosa cell tumour. One patient underwent hysterectomy due to a 20-cm solid mass that globally enlarged the uterus. The patient's preoperative tumour markers were within the normal range, and the endometrial biopsy samples were normal. The patient, for whom stromal tumour or lymphoma was suspected based on the results of the intraoperative frozen section procedure, was later reported to have a final pathology of metastasising haematological malignancy (Table 2).

Discussion

Hysterectomy is a frequently performed surgical procedure worldwide. The two most common indications for hysterectomy are leiomyoma and TRM [3]. Previous studies have shown the importance of preoperative assessment, especially in high-risk patient groups. MRI performed prior to surgery can help predict unexpected results of endometrial sampling, pelvic ultrasonography, and cervical cancer screening tests.

Theben et al. reported that during the preoperative evaluation phase, they applied pelvic ultrasonography, dilation and curettage,

and a cervical cancer screening program in approximately 85% of the patients they examined [9]. In a study by Ouldameer et al., all patients were subjected to cervical cancer screening, pelvic ultrasonography, and endometrial biopsy, and the ratio of unexpected endometrial cancer was 0.4% [11]. In our study, preoperative evaluation with endometrial biopsy and pelvic ultrasonography was performed in all patients who underwent hysterectomy for indications of TRM. Conversely, although pelvic ultrasonography was performed in patients who underwent hysterectomy owing to uterine myoma, endometrial biopsies were performed in only 85% of these cases. In our study, the incidence of unexpected sarcoma was 0.6%, and no cases of endometrial cancer were encountered. Sarcoma incidence is generally low in the population as a whole; thus, the relatively high incidence of unexpected sarcomas among the incidentally detected malignancies was noteworthy. We associate this finding with the difficulty of diagnosing sarcoma preoperatively. Previous studies have shown that only 30% of leiomyosarcomas are preoperatively diagnosed with endometrial biopsy [12]. In patients who have undergone hysterectomy for myomas, the incidence of sarcomas has tended to vary, with reported ratios ranging between 1/204 and 1/667 [13]. In a study of 6360 women, the incidence of occult sarcoma was 1/500 [2]. In their study in 644 patients with uterine prolapse, Frick et al. found a rate of unexpected malignancies of 2.6%, whereas the incidence of unexpected endometrial cancer was 0.3% [14]. In a study by Ramm et al., the ratio of unexpected malignancy was 0.7%; endometrial carcinoma was found in four patients, and one had leiomyosarcoma [15].

Two studies in the literature reported the incidence of sarcoma as 0.23% and 0.49%, and our results are in agreement with those studies [16,17]. Furthermore, we noticed that a morcellator had not been used in any of the cases with unexpected malignancies. This indicates that in all patients except the 13 with identified incidental malignancies, the use of a morcellator was actually of benefit. Given the benefits to patients of minimally invasive interventions (small incision, rapid healing, lower frequency of complications), and considering that the occurrence of occult cancers is very rare, morcellator use places the patient's benefit more at the forefront [18]. Thus, rather than entirely rejecting it, there is evidence to recommend morcellator use for procedures in a suitable and carefully selected patient group.

Table 2
Characteristics of the cases.

	Surgical Indication	Surgical Approach	Specimen Weight (g)	Pathology	Preoperative Diagnosis	PAP smear
1	Abnormal uterine bleeding and leiomyomas	Abdominal	156	Leiomyosarcoma	Chronic endometritis	Normal
2	Abnormal uterine bleeding and leiomyomas	Abdominal	170	Leiomyosarcoma	Estrogen-dependent bleeding	Normal
3	Endometrial polyps and cervical dysplasia	Abdominal	135	Cervical carcinoma in situ	Cervical intraepithelial neoplasia (CIN 1-2)	Hpv (+)
4	Leiomyomas and pelvic pain	Abdominal	140	Uterine sarcoma	Atrophic endometrium	Normal
5	Abnormal uterine bleeding	Abdominal	210	Cervical squamous cell carcinoma	Atrophic endometrium	Normal
6	Leiomyomas	Abdominal	375	Leiomyosarcoma	-	Normal
7	Pelvic mass	Abdominal	220	Acute myeloid leukaemia(AML) metastasis	-	Normal
8	Ovarian cyst	Abdominal	185	Ovarian squamous cell carcinoma	-	Normal
9	Abnormal uterine bleeding and submucous myomas	Abdominal	105	Uterine sarcoma	Proliferative endometrium	Normal
10	Leiomyomas	Abdominal	140	Leiomyosarcoma	Endometrial polyp	Normal
11	Abnormal uterine bleeding	Abdominal	88	Cervical adenocarcinoma in situ	Chronic endometritis	Normal
12	Abnormal uterine bleeding and leiomyomas	Abdominal	166	Leiomyosarcoma	Endometrial polyp	Normal
13	Ovarian cyst	Abdominal	185	Granulosa cell ovarian tumor	-	Normal

Cervical cancers constitute the second most common type of cancer among women worldwide, and HPV 16 and HPV 18 are considered the aetiological cause in approximately 70% of these cancers [19]. In the diagnosis of cervical cancer and precancerous lesions, cervical cytology and the identification and classification of HPV DNA are highly important. Cervical cancer was identified in three of the 1050 patients included in our study. Although colposcopic biopsy in a patient diagnosed with cancer owing to HPV 16 positivity gave a result of CIN 1, her final pathology results revealed that she had invasive cervical cancer. The cervical cancer screening results of the two other patients were normal, but cervical adenocarcinoma in situ was detected in one of these patients, and squamous epithelial cell carcinoma with an invasion depth of 1 mm was detected in the other. However, no HPV diagnosis or classification was performed in these two patients. Chapman et al. found that 27% of patients with occult cervical cancers identified during hysterectomy that was performed for benign reasons had normal Pap smear tests. They also determined that among 18 patients with invasive cervical cancer identified during such hysterectomies, the 5-year survival rate during follow-up was 89% [20].

The literature includes studies in which the average age of patients with occult cancers was determined to be ≥ 55 years [18]. In our study, the mean age of patients who underwent hysterectomy was 50 ± 7 years, whereas the mean age of the patients with unexpected malignancies was 61 years. This finding, which is consistent with the literature, shows that preoperative evaluation in older patients should be more comprehensive.

The diagnostic effectiveness of endometrial biopsy in patients planning to undergo hysterectomy for benign reasons has been questioned in recent years. Cakmak et al. identified no malignancies in endometrial sampling performed prior to surgery in patients slated to undergo hysterectomy for uterine myoma, and argued that endometrial sampling is unnecessary for this patient group [21]. Gebauer et al. showed that endometrial biopsy (dilation and curettage) is insufficient for diagnosing endometrial polyps [22].

Preoperative transvaginal ultrasonography may assist in identifying patients at low and high risk, and endometrial thickness measured by ultrasonography may be useful in this regard. A double layer of the endometrium that has a front-to-rear diameter $< 4\text{--}5$ mm is indicative of low risk, whereas a diameter > 5 mm is indicative of high risk [23,24]. Some reports have argued that abnormal uterine bleeding observed during the perimenopausal period requires endometrial biopsy [11].

All of these studies showcase the importance of identifying the cause of postmenopausal bleeding. However, despite this, endometrial biopsy has only a 10% success rate in detecting endometrial cancer [25]. When a pipelle is used as a biopsy tool to exclude the possibility of malignancy in women, it only samples 4% of the total endometrial surface area. Consequently, during endometrial sampling performed with a pipelle, if the tumour tissue is localised to a small area of the endometrium or on a polyp, the biopsy may falsely report a normal result [26]. Endometrial biopsy performed by dilation and curettage collects material that yields a higher chance of detecting a malignancy compared with a sample taken by pipelle. However, despite this seeming advantage, it has been reported to have a poor detection rate for focal lesions, and the failure rate in detecting malignancies varies from 100% to 38% [27]. Studies have shown that for preoperative assessment, biopsies performed in patients with suspicious lesions using hysteroscopy are more reliable. No method other than final histopathological examination of a sample can provide definitive information [11]. The diversity of approaches to endometrial cancer screening stem from the inadequacy of treatment guidelines regarding how sampling should be performed in

asymptomatic populations. Certain studies have asserted that endometrial assessment prior to hysterectomy is inadequate for women who have pelvic organ prolapse [15].

In conclusion, although the preoperative screening methods used for uterine sarcoma or ovarian cancer are limited, the cervical cancer screening program and endometrial sampling methods are still widely used, despite their low sensitivity. Abnormal perimenopausal bleeding requires endometrial biopsy; however, in cases where there is doubt or hesitation, it should be noted that sampling with a hysteroscope is also possible. In addition, it is necessary to perform a more detailed pre-surgical assessment in older adult patients. Our study indicates that even in cases that are expected to be benign, nothing should be overlooked, and detailed preoperative evaluations should be performed in all patients. For conditions with limited preoperative diagnostic methods available, such as uterine sarcoma and ovarian cancer, more sensitive screening methods must be developed.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest

Acknowledgement

None.

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