ORIGINAL ARTICLE

The Discrepancy between Preoperative Endometrial Pathology and Final Surgical Staging Endometrial Specimens in Endometrial Carcinoma Patients

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Objective: 1) To establish the discrepancy between the histological results of preoperative endometrial pathology and the final surgical staging endometrial pathology for endometrial carcinoma. 2) To determine risk factors for upgrading histology after surgical staging.

Materials and Methods: The present study was a retrospective study that enrolled patients who were preoperatively diagnosed with endometrial carcinoma. Endometrial tissue was derived from various methods, such as endometrial aspiration, fractional curettage, and hysteroscopic resection. Thereafter, all patients underwent surgical staging at Siriraj Hospital, Thailand. Pathological reports and other informative data were collected and analyzed.

Results: Three hundred twenty patients were enrolled. There were 34.7% discrepancies between preoperative pathology and final pathology. Seventy-four patients (23.1%) had upgraded preoperative endometrial pathology compared with the final surgical staging endometrial pathology. The kappa correlation value between preoperative endometrial pathology and final surgical staging endometrial pathology was 0.62.

Conclusion: The correlation between preoperative and postoperative pathology was good. Preoperative endometrial pathology can predict the final surgical staging of endometrial pathology. However, surgeons must be aware of risk factors that influence the upgrading of grade1 or 2 endometrioid histology, such as myometrial invasion.

Keywords: Endometrial carcinoma; Upgrading; Preoperative pathology; Postoperative pathology

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Endometrial carcinoma is the most common gynecologic cancer worldwide[1]. The most commonly used treatment is surgical staging followed by adjuvant radiation or chemotherapy based on pathological findings. The staging consists of hysterectomy and bilateral salpingo-oophorectomy.

Lymphadenectomy may or may not also be performed[2]. However, if undertaken, it led to accurate staging and yield therapeutic benefits[3]. The international Federation of Gynecology and Obstetrics (FIGO) suggest removing enlarged or suspicious lymph nodes in all endometrial cancer patients. However, high-risk patients such as endometrioid grade 3, serous, clear cell carcinoma, deep myometrial invasion, and cervical extension were recommended to perform complete pelvic lymph node dissection and enlarged para-aortic lymph node resection[4]. However, lymphadenectomy can cause serious complications, such as vascular injuries, nerve injuries, lymphocysts, or lymphedema[5]. The decision to undertake lymphadenectomy depended on two factors, intraoperative findings, and preoperative endometrial pathology. A more objective interpretation is provided by preoperative endometrial pathology, either from endometrial aspiration or fractional curettage. Nevertheless, differences between preoperative endometrial pathology and final surgical staging endometrial pathology can lead to the wrong decision to perform lymphadenectomy. The intraoperative findings such as tumor size, myometrial invasion, and extrauterine disease, may

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not be accurate due to subjective interpretation by the naked eye[6].

A precise grade of histology is essential for the decision of pelvic and para-aortic lymphadenectomy. A previous study showed 16% to 40% of upgrading histology in endometrial cancer patients[7]. The primary objective of the present study was to determine the upgrade between preoperative endometrial pathology and final surgical staging endometrial pathology in patients with endometrial carcinoma. Another objective was to determine the risk factors contributing to upgrading pathology.

Materials and Methods

After receiving approval from the Siriraj Institutional Review Board, protocol SI798/2021, the authors started the present study. The sample size was calculated by using an infinite population proportion. A two-sided type 1 error of 0.05 was used, resulting in the inclusion of 320 patients needed for the present study. Patients with endometrial carcinoma that underwent surgical staging at Siriraj Hospital between 2011 and 2017 were enrolled. Medical records were retrospectively reviewed. Patients previously treated with radiotherapy, chemotherapy, or hormonal therapy were excluded. Patients with missing data were also excluded. The decision of the lymphadenectomy procedure followed FIGO guidelines. Gynecologic pathologists reviewed all of the specimens. The data from medical records were baseline characteristics, preoperative endometrial pathology, the technique for obtaining endometrial tissue, date of surgery, intraoperative findings, surgical staging procedure, pathology of surgical staging specimen, adjuvant treatments, and date of recurrence. Statistical analyses were conducted with IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). Baseline characteristics were calculated as descriptive statistics (frequency, mean, median, and standard deviation). Kappa and McNemar's statistics were used to analyze the correlation between preoperative histology and final surgical staging pathology. A p-value less than 0.05 was defined as statistically significant.

Results

The present study enrolled 329 patients. Their mean age was 59.24 years. The method of obtaining preoperative endometrial tissue was mostly fractional curettage with 59.4%, followed by endometrial aspiration (35.9%) and hysteroscopy (1.9%). Nine patients (2.8%) underwent other procedures. Four patients had cervical biopsy and five patients had tissue biopsy of prolapsed endometrial polyps prolapsed from the endometrium. More than half of the patients (62.2%) were in stage I. There were no significant differences in the demographic data of the non-upgrading and upgrading groups, except for tumor size and myometrial invasion (Table 1).

Regarding endometrial pathology, the most common preoperative and final surgical staging endometrial pathology was grade 1 endometrioid carcinoma at 43.1% and 35.6%, respectively. There was a 34.7% discrepancy between preoperative and final surgical pathology. The correlations between preoperative endometrial pathology and final surgical staging endometrial pathology are listed in Table 2. Seventy-four patients (23.1%) and 37 patients (11.6%) had upgraded and downgraded preoperative endometrial pathology compared with the final surgical staging endometrial pathology, respectively. The correlations between preoperative endometrial pathology and final surgical staging endometrial pathology were calculated using the kappa coefficient. The kappa correlation value between preoperative endometrial pathology and final surgical staging endometrial pathology was 0.62.

Univariate and multivariate analyses calculated the potential factors correlated with upgrading pathology (Table 3). The factor associated with upgrading pathology was a myometrial invasion (OR 1.50, 95% CI 1.18 to 2.27, p=0.012) on multivariable analyses.

In the present study, seven cases were grade 3 endometrioid or non-endometrioid carcinoma in the final surgical staging endometrial pathology, whereas, the related preoperative endometrial pathology before surgical staging was grade 1 endometrioid carcinoma. Fortunately, five of these patients had systematic lymphadenectomy. One patient underwent systematic lymphadenectomy due to a tumor size of 4 cm and invasion through the uterine serosa. However, at 14 months, she had recurrent cancer. Another patient underwent systematic lymphadenectomy due to an 11 cm tumor with more than 50% myometrial invasion. She had no evidence of recurrent cancer. The remaining three patients had systematic lymphadenectomy for complete staging as well as possible therapeutic benefit. They also showed no signs of recurrent cancer. The other two patients did not have systematic lymphadenectomy. Fortunately, no cancer recurrence had been found in this group of patients.

Table 1. Baseline characteristics

	Upgrading		p-value
	Yes (n=74)	No (n=246)	
Age (year); mean [SD]	57.31 [11.95]	59.82 [9.80]	0.068
BMI (kg/m^2); mean [SD]	26.88 [6.77]	26.55 [4.79]	0.641
Previous cesarean section; n (%)			0.745
No	68 (91.89)	223 (90.65)	
Yes	6 (8.11)	23 (9.35)	
Previous normal labor; n (%)			0.760
No	37 (50.00)	128 (52.03)	
Yes	37 (50.00)	118 (47.97)	
Uterine size (g); mean [SD]	169.32 [169.85]	161 [155.07]	0.731
Tumor size (cm); mean [SD]	4.74 [2.90]	3.94 [2.32]	0.015
Method for preoperative diagnosis; n (%)			0.210
Endometrial aspiration	21 (28.38)	94 (38.21)	
Fractional curettage	50 (67.57)	140 (56.91)	
Hysteroscopy	0 (0.00)	6 (2.44)	
Other	3 (4.05)	6 (2.44)	
Stage; n (%)			0.284
I	40 (54.06)	159 (64.63)	
II	8 (10.81)	17 (6.91)	
III	23 (31.08)	67 (27.24)	
IV	3 (4.05)	3 (1.22)	
Interval between operations (days); mean [SD]	67.97 [39.14]	63.35 [31.03]	0.297
Myometrial invasion; n (%)			0.024
No myometrial invasion	7 (9.46)	71 (28.86)	
Myometrial invasion <50%	36 (48.65)	88 (35.77)	
Myometrial invasion >50%	25 (33.78)	77 (31.30)	
Uterine serosa	6 (8.11)	10 (4.07)	
LVSI; n (%)			0.098
No	50 (67.57)	194 (78.86)	
Yes	24 (32.43)	52 (21.14)	
Cervical involvement; n (%)			0.229
No	55 (74.32)	195 (79.27)	
Yes	19 (25.68)	51 (20.73)	
Adnexal involvement; n (%)			0.180
No	65 (87.84)	225 (91.46)	
Yes	9 (12.16)	21 (8.54)	

BMI=body mass index; LVSI=lymphovascular space invasion; SD=standard deviation

Table 2. Correlations between preoperative and final pathology

Preoperative pathology	Final pathology; n (%)			
	Grade 1 endometrioid	Grade 2 endometrioid	Grade 3 endometrioid	Non-endometrioid
Grade 1 endometrioid	89 (27.8)	42 (13.1)	3 (0.9)	4 (1.3)
Grade 2 endometrioid	24 (7.5)	64 (20.0)	16 (5.0)	6 (1.9)
Grade 3 endometrioid	0 (0.0)	8 (2.5)	10 (3.1)	3 (0.9)
Non-endometrioid	1 (0.3)	4 (1.3)	3 (0.9)	43 (13.4)

Kappa 0.6228; 95% CI 0.5545 to 0.6911

Table 3. Univariable and multivariable analyses of upgrading pathology

	Univariable analysis			Multivariable analysis		
	Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value
BMI (kg/m^2)	1.01	0.96 to 1.06	0.640			
Previous cesarean section	0.86	0.33 to 2.18	0.744			
Previous normal labor	1.08	0.65 to 1.82	0.759			
Uterine size (g)	1.00	0.99 to 1.00	0.731			
Tumor size (cm)	1.13	1.02 to 1.25	0.164			
Method for preoperative diagnosis	1.59	0.90 to 2.83	0.210			
Interval between operations (days)	1.00	0.99 to 1.01	0.297			
Myometrial invasion	3.99	1.67 to 9.51	0.002	1.50	1.18 to 2.27	0.012
LVSI	1.64	0.92 to 2.92	0.093			
Cervical involvement	1.45	0.79 to 2.64	0.223			
Adnexal involvement	1.76	0.79 to 3.96	0.168	1.91	0.79 to 4.39	0.136

BMI=body mass index; LVSI=lymphovascular space invasion; CI= confidence interval

Discussion

Various histological types were found in the present study, both endometrioid and non-endometrioid. Overall, the kappa correlation between preoperative endometrial pathology and final surgical staging endometrial pathology in the present study was good at 0.62. This result was consistent with the previous studies[7,8]. The rates of upgrading and downgrading pathology between preoperative endometrial pathology and final surgical staging endometrial pathology were 23.1% and 11.6%, respectively. In the present study, only myometrial invasion was found to be a factor in pathology upgrading.

When there was a discrepancy in the severity of the endometrial pathology, patients received surgery and adjuvant therapy based on the most severe pathological result.

The previous study showed insufficient tissue sampling at 15% to 60% in preoperative histology[8]. Another factor was the precise selection of tissue. Hysteroscopic resection is the only endometrial biopsy method that provides clear preoperative tissue visibility. The agreement rate for endometrial preoperative and postoperative histology was 98.1% using the hysteroscopic technique[9]. The present study found no upgrading histology in patients that underwent hysteroscopic resection. However, the number of these patients was too small to find relevance. The present study also found relevance between upgrading histology and myometrial invasion, which is the same as other studies[7,10]. As GOG-33, the myometrial invasion was a prognostic factor for pelvic and para-aortic lymph node metastasis. It was one of the significant factors in predicting high-risk endometrial cancer. The incidence of middle and deep myometrial invasion was commonly found in grade 2 to 3 endometrioid carcinoma[6]. Thus, patients who had myometrial invasion with a preoperative diagnosis of grade 1 endometrioid carcinoma may have a higher chance of having an upgraded pathology on the final pathology. This finding alerted the surgeon to the need for additional nodal dissection in patients with low-grade pathology and myometrial invasion.

The limitation of the present study was the lack of preoperative imaging in the routine practice. There were many methods to assess myometrial invasion in endometrial cancer patients preoperatively. Transvaginal ultrasound (TVS) was the first option in developing countries. TVS had sensitivity and specificity to detect deep myometrial invasion at 82% and 81%, respectively[11]. Magnetic resonance imaging (MRI) was another option for preoperative assessment for myometrial invasion. The study in Sweden showed that the accuracy for detecting deep myometrial invasion in TVS and MRI was 75.8% and 73.8%, respectively[12]. There was no scientific difference between MRI and intraoperative frozen section in assessment for myometrial invasion[13]. The intraoperative frozen section required many resources. It is, therefore, not recommended, as it cannot be reproduced. Ultimately, the myometrial invasion was examined during the operation. For patients with myometrial invasion, further nodal dissection should be considered as it was correlated with upgraded pathology.

Adnexal involvement was a prognostic factor for pelvic lymph node metastasis, whereas it had no statistically significant correlation with upgrading

histology[6]. The present data confirmed that adnexal involvement is not correlated with an upgraded pathology. According to FIGO staging, adnexal involvement changed the patient's stage to IIIA independent of grading.

Obesity was another predicting factor for upgrading histology in a previous study[14]. Obesity caused a hyper-estrogenic stage followed by greater endometrial thickness. Inadequate tissue sampling may occur. Unfortunately, there was no statistically significant data indicating obesity-related higher-grade pathology in the present study.

The present study did not measure the volume of the specimens. There were no relevant data demonstrating the relationship between biopsy volume and the grading of the tumor.

Long waiting times for surgery may decrease the survival of the patient. If the diagnosis to surgery interval was more than 12 weeks, five years survival was decreased[15]. The correlation of upgrading in a patient with a long diagnosis to surgery interval was insignificant in the present study. Long waiting times and poor prognosis may contribute to disease transmission but do not alter grade.

Despite the benefits of accurate staging and better prognoses, pelvic and para-aortic lymph-adenectomies did not improve the recurrence rate[16,17]. However, lymphadenectomy is still indicated in those with a high risk of lymph node metastasis. The high risk of lymph node metastasis in FIGO guideline 2021 was endometrioid grade 3 or non-endometrioid, deep myometrial invasion, and cervical extension[4]. If preoperative histology guided pelvic lymphadenectomy, 23% of patients in the present study would be undertreated by abandoning pelvic lymphadenectomy.

Although precise preoperative endometrial pathology is required, unfortunately, it cannot be achieved in all cases. Performing a sentinel lymph node biopsy can replace pelvic and para-aortic lymphadenectomies. The detection rate is high, with a low false negative rate[18,19]. It can assess lymph node status while reducing complications from lymphadenectomy. It also guides the postoperative adjuvant treatment. There was no statistically significant difference in survival between systemic lymphadenectomy and sentinel lymph node biopsy for patients with non-bulking positive lymph nodes[20].

Accurate non-surgical staging is also necessary for patients for whom surgical staging might not be the optional treatment choice, such as those with fertility desires. In such cases, providing counseling on the risk of upgrading is essential. Molecular classification for preoperative histology may help in the decision of lymphadenectomy but needs further study.

In conclusion, preoperative endometrial pathology and final surgical staging endometrial pathology has a good correlation. Importantly, pathology upgrading should be considered in patients who have myometrial invasion. The value of the present study is demonstrating the potential of pathology upgrading, especially in patients with myometrial invasion. As a result, systematic lymphadenectomy should be considered in this situation.

What is already known on this topic?

The correlation between preoperative endometrial pathology and final surgical staging of endometrial pathology was good (kappa=0.62). Preoperative endometrial pathology can predict the final surgical staging of endometrial pathology

What this study adds?

Despite a good correlation between preoperative and final pathology, there was a 23.1% upgrade in pathology in this study. These results could lead to suboptimal treatment for lymphadenectomy.

The present study results warn the physicians to consider both preoperative pathology and intra-operative myometrial invasion findings to justify lymph node dissection.

Conflicts of interest

The authors declare no conflict of interest.

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