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Preoperative Histopathological Grading and Clinical Staging versus Surgico-Pathological Grading and Surgical Staging in Endometrial Carcinoma Patients: A Single Centre Retrospective Study

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Results: Endometrioid adenocarcinoma was the most common histological subtype with an agreement of 75.3% (61/81) on final pathology. The overall concordance rate between pre- and postoperative histological grade was 65.4% (53/81). 25.9% (21/81) patients had been upgraded while 8.6% (7/81) had been downgraded. The accuracy of clinical and surgical staging was 64.2% (52/81) with 22.2% (18/81) patients had been upstaged and 13.6% (11/81) down-staged.

Conclusion: Tumor histology and grade, as well as the clinical staging, are only moderate predictors of the final surgical pathological outcome and surgical staging.

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Conclusion: Tumor histology and grade, as well as the clinical staging, are only moderate predictors of the final surgical pathological outcome and surgical staging. The highly aggressive serous and clear cell carcinomas have been missed on endometrial samplings. Preoperative grade 1 and clinical stage II tumors had the lowest agreement when compared postoperatively. Cautious planning and patient counseling must be required regarding the surgical approach to endometrial cancer.

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I. Introduction

Endometrial cancer tops the list among tumors of the female genital tract in developed countries (1). In China, endometrial cancer ranks in second place behind cervical cancer as the most prevalent gynecological malignancy. It has been associated with reproductive factors, late menopause and high usage of exogenous hormone (2). Based on clinical and histopathologic features, endometrial carcinoma is classified as Types I (mainly endometrioid) and II (non-endometrioid). Type I endometrial carcinomas are generally endometrioid adenocarcinomas making 80-90% of all cases. Type II cancers comprise the remaining 10-20% and include uterine papillary serous carcinoma and clear cell carcinoma (3, 4).

Tumor grade and subtype are crucial parameters that dictate the extent of surgery, adjuvant therapy and prognosis (5). These have been determined by histological examination of an endometrial sample obtained by dilation and curettage (D & C) or Pipelle endometrial biopsy or hysteroscopic biopsy (6). The tumor is graded according to the percentage of solid non-squamous growth as follows: Grade 1 ≤ 5%; Grade 2: 6-50%; Grade 3: ≥ 50% solid growth (7).

From its introduction in 1958 until 1988 endometrial carcinoma had been clinically staged by the International Federation of Gynecology and Obstetrics (FIGO) (8). Inaccuracies in clinical staging (9) and results of Gynecologic Oncology Group (GOG) 33 contributed its alteration to surgical staging in 1988 (10). The latter has been lastly revised in 2009 (11). Endometrial carcinoma is distinct from other gynecologic cancers in that it has a double staging system: clinical and surgical staging (12) which are shown below in tables 1 and 2 (13, 14). Clinical staging has been based on pelvic examination, endometrial biopsy and imaging studies (12). Surgical staging-either by laparotomy or minimally invasive techniques (15)-involves inspection of the abdomen and pelvis, the collection of pelvic washings, hysterectomy, bilateral salpingo-oophorectomy (BSO) and pelvic and para-aortic lymphadenectomy (16). It has to be noted that pelvic washings no longer form part of FIGO 2009 surgical staging but are still collected at the time of hysterectomy (17).

Comprehensive surgical staging allows precise diagnosis of the disease and its extent, identification of high-risk patients for recurrence, tailoring of patients for adjuvant therapy to decrease the relapse risk and

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determination of the prognosis (18, 19). Despite these advantages, surgical staging has, clinical staging still holds significant importance in several instances. Firstly, it is valuable for patients who are not candidates for a hysterectomy due to morbid obesity or cardiopulmonary dysfunction that render surgery or anesthesia too risky (20). Adjuvant therapy has to be prescribed based solely on clinical staging and potential risk. This treatment plan adds to cost of medical care and increased morbidity for the patients (21). Secondly, clinical staging is applicable for young women desiring complete preservation of fertility. The endometrial lesions need to be excised and hormone therapy initiated (22). Thirdly, patients with clinical stage II disease who cannot undergo a radical hysterectomy due to associated co-morbidities may have to be treated by neoadjuvant radiotherapy followed by simple hysterectomy (23).

The study aims to compare the accuracy of the tumor cell type and grade in the endometrial sampling with that of the hysterectomy specimen. Clinical and surgical staging were also analyzed to determine the reliability of the pretreatment clinical assessment.

Table 1: FIGO Clinical Staging (1971)

Stage	Characteristics
Stage I	The carcinoma is confined to the corpus uteri
Stage IA	The length of the uterine cavity is ≤ 8 cm
Stage IB	The length of the uterine cavity is> 8 cm
Stage II	The carcinoma has involved the corpus and the cervix but has not extended outside the uterus
Stage III	The carcinoma has extended outside the uterus but not outside the true pelvis
Stage IV	The carcinoma has extended outside the true pelvis or has obviously involved the mucosa of the bladder or rectum. A bullous edema as such does not permit a case to be allocated to stage IV
Stage IVA	Spread of the growth to adjacent organs
Stage IVB	Spread of distant organs

Table 2: FIGO surgical staging system for endometrial cancer (2009)

Stage	Characteristics
I	Tumor confined to the corpus uteri
IA	No or less than half myometrial invasion
IB	Invasion equal to or more than half of the myometrium
II	Tumor invades cervical stroma, but does not extend beyond the uterus
III	Local and/or regional spread of the tumor
IIIA	Tumor invades the serosa of the corpus uteri and/or adnexae
IIIB	Vaginal and/or parametrial involvement
IIIC	Metastasis to pelvic and/or paraaortic lymph nodes
IIIC1	Positive pelvic nodes
IIIC2	Positive paraaortic lymph nodes with or without positive pelvic lymph nodes
IV	Tumor invades bladder and/or bowel mucosa, and/or distant metastases
IVA	Tumor invasion of bladder and/or bowel mucosa
IVB	Distant metastases, including intraabdominal metastases and/or inguinal lymph nodes

II. Materials and Methods

Following approval by the Institutional Review Board, a retrospective review had been conducted in the tumor registry of the 1st Affiliated Hospital of Chongqing Medical University to identify all patients who underwent surgery for endometrial carcinoma during January 2015 throughout December 2016.

Inclusion criteria were as follows:

1. Patients who had been adequately investigated,
2. Patients with a preoperative histopathological report suggesting endometrial cancer which had been confirmed after hysterectomy,
3. Patients who underwent both clinical and surgical staging.

Exclusion criteria included:

1. Patients in whom endometrial carcinoma was not the primary disease,
2. Patients who received neoadjuvant therapy: chemotherapy, radiation therapy, hormone therapy,
3. Patients who had been diagnosed with endometrial carcinoma postoperatively and thus had an absent initial histological grade, cell type, and clinical staging,
4. Patients who were inoperable and hence had no surgical staging.

The electronic medical records of these patients had been examined, and clinicopathological data including age, body mass index, parity, clinical staging, tumor grade and histology preoperatively and postoperatively as well as surgical staging had been extracted. Preoperative investigations were: complete blood count, fasting blood sugar, liver function tests, blood urea, creatinine, electrolytes, thyroid function tests, tumor markers and chest X-ray. All the patients underwent a sonographic examination at first, followed by dilation and curettage and lastly either abdominopelvic CT scan or MR imaging. In patients in whom endometrial cancer was being suspected, but the histopathological report was inconclusive hysteroscopy has been performed. The surgical approach for hysterectomy was either laparotomy or laparoscopy depending on the surgeon's skills and experience. Upon entering the abdomen 100ml of sterile saline were poured in the pelvis and the peritoneal washings had been collected. Then, followed a thorough intra abdominal and pelvic exploration and any suspicious areas were biopsied or excised. Next hysterectomy with bilateral salpingo - oophorectomy, pelvic lymphadenectomy, and selective para - aortic lymphadenectomy were carried out.

The statistical workouts have been performed using SPSS software version 20.

III. Results

From January 2015 to December 2016, 97 endometrial carcinoma patients had been identified. 16 of them had been excluded from the study as:

1. Four patients received neoadjuvant chemotherapy.
2. Five patients received radiation therapy preoperatively.
3. One patient - histological report revealed no cancer cell from the hysterectomy specimen.
4. Four patients-endometrial tissue sampling identified adenocarcinoma, but the hysterectomy specimens have been reported as severe endometrial hyperplasia.
5. Two patients-endometrial carcinoma was diagnosed postoperatively. These patients lacked preoperative tumor histology, grading, and clinical staging.

The final sample constituted of 81 patients. The characteristics of the study group have been summarized in Table 3.

Table 3: Demographic characteristics of the patients in the study group

Characteristics		(N= 81, 100%)
Age	< 50 years	31 (38.3%)
	≥ 50	50 (61.7%)
Gravida	Nulligravida	4 (4.9%)
	Primigravida	11 (13.6%)
	Multigravida	66 (81.5%)
Parity	Nulliparous	6 (7.4%)
	P1	42 (51.9%)
	P2	26 (32.1%)
	P≥3	7 (8.6%)
BMI	< 18.5	3 (3.7%)
	18.5-24.9	36 (44.4%)
	25.0-29.9	37 (45.7%)
	≥30	5 (6.2%)

These women had a mean age of 53.6 years (range 35-76 years). 81.5% of the cohort were multigravida (range G0-G10), and 51.9% were primipara (range P0-P5). The median body mass index (BMI) was 25.1 kg/m^2 (range 17.7-37.2 kg/m^2).

Table 4: Comparison of the histologic types at dilation and curettage and hysterectomy

		Hysterectomy Specimen					Total
		Endometrioid carcinoma	Serous carcinoma	Clear cell carcinoma	Mucinous carcinoma	Mixed carcinoma	
Dilation and curettage	Endometrioid carcinoma	56	3	2	0	0	61
	Serous carcinoma	1	2	0	0	0	3
	Clear cell carcinoma	0	0	1	0	0	1
	Mucinous carcinoma	0	0	0	1	0	1
	Mixed carcinoma	0	0	0	0	1	1
	Adenocarcinoma	12	0	0	1	1	14
	Total	69	5	3	2	2	81

Table 4 shows the results of histological analysis of the preoperative curettage samples and the hysterectomy specimens.

a) Preoperative Cell Type

According to the histologic examination of the endometrial tissue samplings, endometrioid carcinoma was the most common pathology (61/81 = 75.3%) followed by adenocarcinoma (14/81 = 17.3%). The remaining 6 cases (7.4%) have been read as follows: Three serous carcinoma, one clear cell carcinoma, one mucinous carcinoma and one mixed carcinoma.

b) Postoperative Cell Type

From the postoperative specimens, the adenocarcinoma subtype has been ultimately assigned as endometrioid carcinoma (12/14 = 85.7%), mucinous carcinoma (1/14 = 7.1%), mixed carcinoma (1/14 = 7.1%).

8.2% (5/61) of endometrioid carcinoma have been reviewed to serous carcinoma (3 cases) and clear cell carcinoma (2 cases) in the final histological report.

1 patient with serous carcinoma has been diagnosed as endometrioid carcinoma on the final histology.

As a result, the tumors were finally distributed as endometrioid (69/81= 85.2%), serous (5/81= 6.2%), clear cell (3/81=3.7%), mucinous (2/81=2.5%) and mixed carcinoma (2/81=2.5%).

c) Overall Agreement

The overall concordance between the preoperative and postoperative subtypes was 75.3% (61/81). Diagnoses of fifty six endometrioid carcinomas, two serous carcinomas, one mucinous carcinoma, one clear cell carcinoma and one mixed carcinoma corresponded with their original subtypes.

Table 5: Comparison between preoperative and postoperative histologic grade

		Postoperative			Total
		Grade 1	Grade 2	Grade 3	
Preoperative	Grade 1	10 (45.5%)	9 (40.9%)	3 (13.6%)	22 (27.2%)
	Grade2	4 (9.3%)	30 (69.8%)	9 (20.9%)	43 (53.1%)
	Grade 3	1 (6.2%)	2 (12.5%)	13 (81.3%)	16(19.7%)
Total		15 (18.5%)	41 (50.6%)	25 (30.9%)	81 (100%)

Table 5 summarizes the comparison of the histologic grades between the preoperative samplings and the surgical specimens.

d) Preoperative Tumor Grade

Based on initial pathological analysis of endometrial curettage, 43/81 (53.1%) cases of endometrial carcinoma have been mostly read as Grade 2 tumors, 22/81 (27.2%) as Grade 1 tumors and 16/81 (19.7%) as Grade 3 tumors.

e) Postoperative Tumor Grade

However, in the postoperative specimens Grade 2 tumors were still the most common diagnosis but in lesser amount 41/81 (50.6%). This decline also mirrored Grade 1 tumors 15/81 (18.5%). Compared with the initial grading, Grade 3 tumors have been increased to 25/81 (30.9%) in the final pathology report.

f) Overall Agreement

The accuracy between the different preoperative and postoperative tumor grades has been highlighted in light green in table 5. As the tumor grades were increasing, the discrepancy between the endometrial tissue samplings and the hysterectomy specimens decreased. The results show the highest concordance of 81.3% (13/16) in Grade 3 tumors and lowest concordance in Grade 1 tumors, 45.5% (10/22). In Grade 2 tumors 30/81 (69.8%) of the preoperative grading coincided with the final one. Therefore the overall concordance rate was 53/81 (65.4%)

g) Upgrading and Downgrading

34.6% (28/81) of the patients had a revision in their tumor grade. 21/81(25.9%) had been upgraded while only 7/81 (8.6%) had been downgraded.

12/22 (54.5%) of Grade 1 tumors were upgraded: 9/22 (40.9%) to Grade 2 and 3/22 (13.6%) to Grade 3.

Out of the 43 Grade 2 tumors, 9/43 (20.9%) were upgraded to Grade 3 while 4/43 (9.3%) had been downgraded to Grade 1.

Of the 16 Grade 3 tumors, 2/16 (12.5%) were being downgraded to Grade 2, and 1/16 (6.2%) had been downgraded to Grade 1.

Table 6: Comparison between clinical staging and surgical staging

	Surgical Staging			
	Stage I	Stage II	Stage III	Total
Clinical Stage I	44 (78.6%)	7 (12.5%)	5 (8.9%)	56 (69.1%)
Stage II	11 (47.8%)	6 (26.1%)	6 (26.1%)	23 (23.4%)
Stage III	0	0	2 (100%)	2 (2.5%)
Total	55 (67.9%)	13 (16.05%)	13 (16.05%)	81 (100%)

Table 6 shows the outcome of clinical and surgical staging in the study cohort.

h) Clinical Staging

Regarding clinical staging, 69.1 % (56/81) were stage I, 23.4% (23/81) were stage II and 2.5% (2/81) were stage III.

i) Surgical Staging

According to FIGO 2009 classification, 67.9% (55/81) had been surgically diagnosed as stage 1, 16.05% (13/81) as stage II and 16.05% (13/81) as stage III.

j) Discordances

The discrepancy between clinical stage I and surgical stage I was 21.4% (12/56). 7 cases (12.5%) had been upstaged to surgical stage II and 5 cases (8.9%) to surgical stage III.

Among 23 cases which were assigned clinical stage II, the inaccuracy in their diagnoses was 74.9% (17/23) after surgical staging. 11 cases (47.8%) were down-staged to the surgical stage I and 6 cases (26.1%) had been upstaged to surgical stage III.

2 cases (100%) with clinical stage III had been confirmed as surgical stage III.

Based on these results, the highest discrepancy rate has been noted in clinical stage II. i.e., 74.9%. The light blue values in table 6 indicate concordance rate between clinical and surgical staging.

k) Upstaging and Down-Staging

The above modifications led to an overall change in staging in 29/81 cases (35.8%). 18 cases (22.2%) had been upstaged while the remaining 11 (13.6%) were down-staged. Highest upstaging and down-staging rate have been observed in clinical stage II.

IV. Discussion

Endometrial cancer is of multifactorial etiology. In all, increasing body mass index and obesity is a well-established risk factor for endometrial cancer incidence, both in premenopausal and postmenopausal women (24, 25).Before menopause estrogen is primarily derived from the ovaries. However, after menopause adipose tissue becomes the principal source of estrogen. In response to advancing age and excess adiposity, the level of aromatase enzyme increases. Aromatase causes peripheral aromatization of and rostenedione to estrone and estradiol. Simultaneously overweight/ obesity decreases the level of sex hormone binding globulin (SHBG) that binds estrogens (24). This biologic model is especially evident in postmenopausal women (26). The net result is an increased level of unopposed estrogens that stimulate endometrial proliferation, a prerequisite for endometrial tumorigenesis (27). Other well-known risk factors include low parity, early menarche, late menopause, use of tamoxifen or exogenous estrogens without progestins, physical inactivity, diabetes, hypertension, and Lynch syndrome (28-32).

Grading indicates the degree of tumor aggressiveness (33). Histotype, grade, and stage are fundamental pathological elements that constitute an integral part of different risk predictive clinical models used to guide treatment (34). Preoperative grading and histologic subtype are among parameters used to determine lymphadenectomy during a hysterectomy (35). However, tumor grade following hysterectomy is frequently different from the initial endometrial sampling (36).

In a meta-analysis which included 16 previous studies that were published between 1997 and 2016 and assessed the accuracy of endometrial sampling in endometrial carcinoma, Visser et al. reported a magnitude of 67% agreement between preoperative tumor grading and final diagnosis (6). Several previous kinds of literature have shown that the rate of concordance increases with tumor grade, discrepancy being pronounced in grade 1 tumor (12, 37-40). Wang et al. compared the histological grades between curettage and hysterectomy specimen and concluded an upgrading of 50% in grade 1 tumors (41). Furthermore, Petersen et al. deduced the poorest correlation in grade 1 tumors and expressed the need for comprehensive surgical staging during hysterectomy regardless of the grade (38). These findings are consistent with those in this study. On the contrary results of analysis by Wang et al show an accuracy of 70.2%, 67.2%, and 84.4% for grades 1, 2 and 3 respectively (42). All of these studies demonstrate highest concordance rate in grade 3 tumors but figures shuffling between grades 1 and 2. A plausible

explanation for the difficulty in the distinction between grades 1 and 2 tumors has been attributed to an inter-observer agreement. Tumor grading has been based on nuclear features, and the amount of non-squamous solid tumor distinguished from the glands. It becomes very challenging for pathologists to accurately determine the 5% and 6% cutoff values in Grades 1 and 2 tumors. The overall kappa statistics for FIGO grade assignment between pathologists is 0.41-0.68 which signifies only moderate levels of inter-observer agreement. Also, when keratinization is unidentifiable, some squamous areas may be read together with the solid tumor (34, 43).

Overall the reasons for changes in tumor grade are numerous. Firstly, more tissue is available for histological analysis following hysterectomy than during curettage. Stock et al. concluded that D & C blindly scrapes less than 50% of the uterine wall in 60% of patients (44). Secondly, in the final specimen, the tumor is examined in a complete form. As a result, tissue sampling from an intact uterus for morphology increases the accuracy of the postoperative diagnosis. Thirdly, there may be a change in tumor grade from the time of D&C to hysterectomy be there a long gap for surgery. This time span is not applicable to this study as surgery has been performed within weeks after initial diagnosis. Finally, the discrepancy between grades may not be an erroneous diagnosis. In the hysterectomy specimen, there are variations in histologic type, areas of marked cellular and nuclear pleomorphism, high mitotic activity and lack of glandular differentiation. As a result, there is a heterogeneous population of cells and grade ranging from grades 1 to 3 (37). Hence, it is unlikely that the area which has been scrapped during D & C has been analyzed in the final hysterectomy specimen.

Concerning tumor histology, a concordance rate of 75.3% between prehysterectomy sample and final pathology has been found. This figure corroborates with several previous studies. Cowles et al. reported that the change between pre- and postoperative histologic subtype was 27.4% (36). Suwannee Buranawattana-choke et al. found a 25.5% change in histotype which was lower than that of Cowles et al. and Campbell et al.(40). Vorgias et al. and Filip Kisielewski et al. revealed that 67.3% and 83.75% respectively of the final histologic subtypes were similar to those found in the initial report (45, 46).

A discrepancy rate of 8.2% was seen among the endometrioid adenocarcinomas as they have been finally diagnosed as the high grade serous and clear cell carcinoma. M.H. Baek et al. reviewed 817 patients, of which 672 (82.3%) were of endometrioid cell type, with a discordance rate of 6.8% (47). Uterine papillary serous carcinoma and clear cell carcinoma are aggressive histologic subtypes with the propensity of extrauterine metastasis and have been associated with more than 50% of relapses and deaths from endometrial carcinoma (48, 49). Initial management involves a hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy and omentectomy (50). On the other hand, the primary treatment of patients with early–staged endometrial carcinoma is hysterectomy and bilateral salpingo-oophorectomy with or without lymphadenectomy (51). In a study of 349 patients with clinical stage 1, grade 1 endometrioid tumors (low-risk) Ben-Shachar et al. found that 2.5% of these patients had been ultimately diagnosed as the serous or clear cell carcinoma on final pathology (52). Based on misdiagnoses from the curettage samples in this study, five patients (8.2%) would have undergone suboptimal surgical staging which would have resulted in deleterious outcomes on overall survival of these patients. In his study, A. Di Cello et al. showed that preoperatively patients who had been positively identified as serous carcinoma erroneously diagnosed as grade 3 endometrioid adenocarcinoma is not as harmful to the patients as the reverse (53).

In this study cohort, 61.7% of patients were above 50 years. The discrepancy between initial and final histology has been explained by the fact that postmenopausal women usually have an atrophic endometrium and obtaining an adequate amount of tissue for histological diagnosis is often challenging (54). A large volume of tissue may permit more accurate evaluation of mixed endometrioid and non-endometrioid tumors (55). Lack of technical skills while performing curettage and low reproducibility between pathologists can also explain a magnitude of discrepancy between initial and final histologic subtypes (56, 57).

The tumor stage has been recognized as the chief prognostic factor for endometrial carcinoma, irrespective of histology and grade (58).Accurate preoperative staging is of clinical value to guide the surgical approach to avoid over - or under-treatment of patients, especially the elderly ones due to associated comorbidities (33). In the present study, a discordance of 35.8% between the clinical and surgical stage was found. This value coincides with other previous studies, occurring in 26.9%- 51% of patients (36, 40, 59, 60). In this study, 21.4% of patients with clinical stage 1 were upstaged following surgery. A similar outcome between 19.7% - 30.4% was reported (36, 40, 59-62). However, the highest inaccuracy had been observed in clinical stage II where 73.9% of patients were assigned a different stage postoperatively. Several authors have also evoked this in their literature with a discrepancy rate ranging between 49% - 80.5% (36, 59, 60, 62, 63). This change in staging might have been accounted by the fact that at the time of dilation and curettage lesions of an involved cervix might be omitted or an uninvolved cervix might have been wrongly diagnosed as having tumor cells (62). In this study, 8.9% and 26.1% of clinical stage I and II patients were upstaged to surgical stage III. Relying on the clinical staging these patients would have been undertreated had lymphadenectomy been

skipped. Intraoperative neurovascular injury, pelvic lymphocyst formation, and leg edema are complications of lymphadenectomy that are a serious concern to surgeons (64). Orr et al. reported that the long-term risks of lymphocyst formation were 1.3% and that of lymphedema was 0.7% (65). The benefits of lymphadenectomy outweigh the harms of the complications and provide valuable information regarding adjuvant therapy and recurrence.

Our study is limited firstly by its retrospective nature as well as a small number of patients. Secondly, hysterectomy has been performed by a team of multiple surgeons who have different levels of expertise. Thirdly, the number of lymph nodes removed at the time of hysterectomy varies. Finally, the preoperative samplings and final hysterectomy specimens have not been examined by the same pathologists. This alteration may have included bias in the reading of the histological slides. However, all the patients selected for the study were from a single center, and surgical specimens had been analyzed at that same institution which allowed a detailed discussion with the pathologists regarding the intraoperative findings. Another strength of our study is that all the preoperative specimen were obtained by D & C rather than by Pipelle endometrial biopsy as the latter has low sensitivity in the atrophic endometrium.

V. Conclusion

In short, tumor grade was similar in 65.4% of patients. 25.9% had been upgraded, and 8.6% downgraded. While 75.3% of preoperative histology corresponded with the final report, 8.3% of aggressive tumors had been missed. Concordance between clinical and surgical staging was 64.2%. 22.2% had been upstaged whereas 13.6% were down-staged. The surgeon should diligently interpret preoperative reports to plan hysterectomy and the extent of lymphadenectomy or adopt fertility-sparing surgery in endometrial cancer as the final histopathological findings and staging might change.

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Disclosures

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