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Does obesity affect pathologic agreement of initial and final tumor grade of disease in endometrial cancer patients?

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Abstract

Objectives—The objectives of this study were to compare preoperative and postoperative tumor grade to determine if surgical staging decisions for endometrial cancer based on preoperative biopsy are feasible and whether obesity affects the agreement.

Methods/Materials—A retrospective cohort study of women with endometrial cancer between 1/2010 and 12/2011 was performed. Demographics, stage of final pathology, biopsy method, pre- and postoperative tissue grade, and histology were abstracted and stratified by patient BMI (obese ≥ 30 kg/m² and non-obese < 30 kg/m²). Patients with incomplete records or uterine sarcoma were excluded. The agreement between preoperative and postoperative tumor grade for all patients and in obese and non-obese patients was determined using weighted kappa statistics.

Results—445 patients were included: 161 non-obese patients and 284 obese patients. The proportion of preoperative sampling via office biopsy and dilation and curettage (D&C) was similar in each cohort. Overall, the agreement between preoperative and postoperative pathology was only fair (weighted kappa 0.21). Stratified by BMI, the agreement between preoperative and postoperative grade remains fair in obese and slight in non-obese patients (weighted kappas 0.21 and 0.19, respectively). Substantial increases in tumor grade from preoperative to postoperative pathologic specimens occurred in both cohorts.

Conclusions—Obesity does not appear to significantly alter the correlation between preoperative biopsy and final tumor grade. With only fair correlation between pre- and postoperative pathologic evaluation, utilization of preoperative biopsy pathology results as a triage tool for surgical staging should be avoided. However, the discordance between pre- and

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postoperative pathology in favor of a higher grade on final pathology in both groups may cause some surgeons to favor staging.

Background

Endometrial cancer (EMCA) remains the most common gynecologic cancer in the United States with an estimated 54,870 new cases being diagnosed in 2015 and a continued rise in incidence of the last decade (1). Obesity is a well-recognized risk factor for type I EMCA due to excess unopposed estrogen production in over abundant adipose tissue (2-8). Recent data demonstrates 36% of women in the United States are obese with a body mass index (BMI) greater than 30 kg/m² and 8% are morbidly obese with a BMI greater than 40 kg/m² (9).

In the diagnostic workup for abnormal uterine bleeding (AUB), transvaginal ultrasound (TVUS) is often used to evaluate the endometrial cavity. Research has shown that the most cost-effective strategy for diagnosing EMCA in women with AUB is to first obtain a TVUS then an endometrial biopsy when indicated (10, 11). While an endometrial stripe thickness of 4mm is reassuring for a benign process, the quality of the images rendered by ultrasound can vary according to patient comorbidities like diabetes and obesity (10). van Doorn and colleagues noted that obesity decreased the accuracy of endometrial stripe thickness measurement on TVUS such that the authors called into question the clinical utility of ultrasound in obese women when evaluating postmenopausal bleeding (10). Most patients diagnosed with EMCA have undergone endometrial sampling via either in-office biopsy with an endometrial pipelle or dilation and curettage (D&C). While studies have demonstrated that both methods of endometrial sampling have favorable specificities for diagnosing EMCA, and that this is more accurate than a TVUS in premenopausal vs. postmenopausal women, it is unknown if there is any effect of obesity on the correlation between tumor grade on a preoperative biopsy specimen and final surgical pathology (12-16).

While total hysterectomy with bilateral salpingo-oophorectomy is the preferred therapy for EMCA management in women who have completed childbearing and who do not have other co-morbidities that would preclude surgical management, the role of surgical staging continues to be debated (17). Gynecologic oncologists utilize several approaches in order to identify EMCA patients to undergo surgical staging. Decisions for surgical staging can be based on preoperative biopsy results, intraoperative assessment of tumor size and depth of invasion, and intraoperative frozen section; however, the pre-operative decision to proceed with either full surgical staging or sentinel node biopsy are also utilized in contemporary EMCA management (18-24). Several studies have demonstrated comprehensive surgical staging in non-obese versus obese patients to have comparable safety when evaluating intraoperative and postoperative complications, ICU stays, and length of hospital stay; however, increasing BMI leads to longer operative times, higher conversion from laparoscopic to open procedures, and decreased ability to complete lymph node dissection (25-28). Since obesity has been shown to negatively affect the accuracy of the diagnostic workup of EMCA using TVUS, our goal was to determine whether histologic evaluation is affected by obesity also (10). More specifically, is the level of agreement between

preoperative and postoperative tumor grade in EMCA patients impacted by obesity? We also sought to establish if the preoperative and final surgical pathology correlate in such a way that preoperative tumor grade can be reliably used when deciding to whether to proceed with surgical staging.

Methods

Following Institutional Review Board approval, a retrospective cohort study was performed for women undergoing surgical management for diagnosed complex atypical hyperplasia (CAH) or EMCA between January 2010 and December 2011. Medical records were abstracted to obtain age at diagnosis, race, BMI, preoperative endometrial sampling method, histology, tumor grade, surgical approach, final pathology, and adjuvant chemotherapy or radiation therapy. Final pathologic evaluation included histologic cell type, depth of myometrial invasion, lymphovascular space invasion, and nodal disease. Patients were excluded from analysis if they had incomplete medical records or if preoperative pathology revealed uterine sarcoma or carcinosarcoma.

Preoperative biopsy pathology was not reviewed for all patients as a large number of these evaluations were done at outside facilities and slides were not available for review. Pathologists specializing in gynecologic oncology pathology reviewed all final surgical pathology specimens and the histologic grade was determined by International Federation of Gynecology and Obstetrics criteria. Intraoperative frozen section was not performed out of concern for reliable results at our institution. Gynecologic oncologists at a large academic center performed all surgical procedures removing the tissues evaluated on final pathology.

A comparison of preoperative and postoperative tumor grade was made in all patients. Patients were then stratified by BMI into an obese group with a BMI ≥ 30 kg/m² and non-obese group with a BMI <30 kg/m². Weighted kappa coefficients were used to compare preoperative and postoperative tumor grade in both groups. Differences in baseline characteristics between the obese and non-obese groups were compared using Chi-square and Fisher's Exact tests. Chi-square tests were used to compare the preoperative and final tumor grade and histology between the obese and non-obese groups. SAS version 9.2 (SAS Institute, Cary, NC) was utilized to perform all analyses.

Results

526 women met study inclusion criteria of which 81 patients were excluded: 63 had incomplete records and on preoperative biopsy 18 had either uterine sarcoma or carcinosarcoma. Of the total 445 women included in this study, 161 were identified as non-obese with a BMI <30 and 284 were obese with a BMI ≥ 30 . Patient demographics are listed in Table 1. Notably the mean BMI was 25.5 (± 3.5) in the non-obese group. 90 patients (55.9%) underwent a preoperative endometrial biopsy, 69 patients (42.9%) had a D&C, while 2 patients (1.2%) underwent sampling that was not explicitly stated. In the obese cohort, the mean BMI was 39.6 (± 7.8). 145 patients (51.1%) had an endometrial biopsy, 137 patients (48.2%) had a D&C, and it is unknown how 2 of the patients (0.7%) were sampled. The obese and non-obese groups were similar in baseline characteristics with a few

exceptions: in the non-obese group, the patients were older and in the obese group there were more black women (Table 1).

The preoperative and final tumor grade and histology for both cohorts are displayed in Table 2. Based on preoperative biopsy, the majority of patients had cancer (N=403, 90.6%). The most common histology was endometrial adenocarcinoma-NOS (N=320, 71.9%). No statistically significant differences were noted between the cohorts in terms of preoperative tumor grade, although both CAH (N=30, 10.6% versus N=12, 7.5%) as well as grade 2 disease were more common in obese (N=117, 41.2%) compared to non-obese patients (N=57, 35.4%), while both grade 1 (N=26, 16.1% versus N=40, 14.1%) and grade 3 (N=66, 41% versus N=97, 34.1%) were more common in the non-obese group (p=0.329). Similar to grade, there was not a statistically significant difference in histology between the obese and non-obese groups (p=0.701).

On final pathology, endometrioid adenocarcinoma was the most common histology (N=372, 83.6%). The differences in histology between the two cohorts were not statistically significant (p=0.457). Grade 1 disease was more common in the obese cohort (N=47; 16.5%) than the non-obese cohort (N=19; 11.8%). Interestingly, the majority of patients in both the obese (N=142; 50.0%) and non-obese groups (N=100, 62.1%) had grade 3 disease, which was a substantial increase in the proportion of patients with grade 3 tumors as compared to preoperative biopsy results. The difference for tumor grade between the two groups was not statistically significant (p=0.086).

The agreement between preoperative and postoperative tumor grade among all patients included in this study was fair as the weighted kappa was 0.21. When stratified by BMI, the agreement between preoperative and postoperative grade remains only fair in obese and slight in non-obese patients with weighted kappas of 0.21 and 0.19 respectively, p=0.77 (Table 3). When the discordance between preoperative and postoperative histology is broken down further, we found that, overall, substantial increases in tumor grade from preoperative to postoperative pathologic specimens occurred. In the non-obese cohort, grade 1 disease was upgraded to grade 2 disease in 10 patients and grade 3 disease in 8 patients. In addition, grade 2 disease was upgraded to grade 3 disease in 34 patients and CAH was upgraded to grade 2 disease in 6 patients and grade 3 in 3 patients. Some histology was downgraded as 10 patients with grade 3 disease were found to have grade 2 disease on final pathology. There was even more upgrading in the obese cohort as CAH was upgraded to grade 1 disease in 15 patients, grade 2 disease in 12 patients, and grade 3 disease in 3 patients. In patients with grade 1 disease initially, final pathology found grade 2 disease in 15 patients and grade 3 disease in 4 patients. 55 patients with grade 2 disease were upgraded to grade 3 disease. Final pathologic evaluation downgraded 11 patients from grade 2 to grade 1 disease and 13 patients from grade 3 to grade 2 disease. The difference between the number of upgrades for each pathologic grade within the non-obese and obese groups were statistically significant (p=0.0003 and p<0.0001 respectively) (Table 4).

Discussion

Type I EMCAs are directly linked to obesity due to excess estrogen exogenously produced in adipose tissue, which then stimulates proliferation of the endometrium (6-8). Newer studies have found relationships between not only obesity but also insulin resistance and increased androgen levels in the pathogenesis of endometrial cancer due to inflammatory mediators, adiponectin, leptin, plasminogen activator inhibitor-1, and insulin-like growth factor-1 (29-31). While data supports equivalent specificities between endometrial sampling via either in-office biopsy or D&C, no studies have investigated whether obesity affects the correlation between preoperative biopsy and final pathologic tumor grade (12-16). Since obesity has been shown to affect some aspects of preoperative diagnostic workup, preoperative information such as preoperative biopsy which reliably predicts final tumor grade could be invaluable to surgeons trying to decrease the morbidity of an operation that has been shown to be higher when full staging is performed on obese women (10, 24-27). In our study, we found that changes in tumor grade were more pronounced (and more frequent) in obese women than in a similar group of non-obese women.

Full surgical staging for EMCA includes a total hysterectomy and bilateral salpingo-oophorectomy with a pelvic and para-aortic lymphadenectomy despite the fact that studies have shown there is a low-risk of nodal metastases in patients with early stage disease (32, 33). Two randomized trials found no difference in overall survival or progression free survival in patients who underwent surgical staging in clinically early stage EMCA with or without lymphadenectomy supporting the potential limitation of staging as a part of initial surgical management (34-36). Pelvic and para-aortic lymph node dissections can also lead to significant morbidity including lower extremity lymphedema, lymphocele formation, neurovascular damage, and increased risk of thrombotic events (37-41).

Surgeons rely on many different approaches including preoperative biopsy data, intraoperative frozen pathologic section, depth of myometrial invasion, size of the tumor, and also preoperative tumor grade to help decide which patients are at risk of nodal metastases and therefore need lymphadenectomy. Despite studies validating the low-risk of nodal metastases in early stage EMCA patients using these different triage techniques and considering the potential added morbidity following pelvic and para-aortic lymph node dissection, there is not complete consensus within the Gynecologic Oncology community as to the best way to identify patients who need operative lymph node evaluation (18-24, 37-41).

Definitive decisions based on retrospective evaluations warrant caution when attempting to apply them to clinical practice. Nonetheless, our series is a large series of endometrial cancer patients treated in a similar fashion during a two-year period at a large National Comprehensive Cancer Network Cancer Center with dedicated gynecologic pathologists reviewing all final pathology. While it is almost certain that a preoperative review and official pathologic interpretation of all diagnostic slides would improve agreement and correlation, previous work by the Gynecologic Oncology Group (GOG) and others has clearly demonstrated, both in complex atypical endometrial hyperplasia and endometrial adenocarcinoma, a lack of diagnostic correlation even with experienced pathologists (42,

43). These discrepancies may be due to inadequate tumor volume on pipelle biopsies, incorrect reporting of initial pathology, dedifferentiation of tumors as they invade the myometrium, procedural difficulties encountered in the obese patient and/or inadequate immunohistochemistry. Moreover, our findings may have implications at smaller volume institutions without dedicated gynecologic pathology support. We believe this lack of formal review of outside hospital preoperative biopsy pathology more accurately represents what occurs at many hospitals on a day-to-day basis where formal review of all pathologic specimens by gynecologic pathologists is not always possible.

We acknowledge there are slightly older women in the non-obese group and more African American women in the obese group. There is, however, a similar number of women with a given histologic subtype and distribution in histologic grade of disease when comparing preoperative and postoperative histology. This suggests age and race did not affect the incidence of high-grade tumor types in this study.

In our series of nearly 450 women, there was only fair correlation between preoperative and postoperative tumor grade which was not affected by obesity. Since we noted only fair correlation between preoperative and final tumor grade, utilization of preoperative biopsy results as a triage tool to determine surgical staging decisions should be avoided. Although there were a small number of discordances between preoperative and postoperative pathologic tumor grading, the majority of these resulted in an upgrade. The most common upgrade was from grade 2 to grade 3 disease in both the non-obese and obese groups with 34 and 55 upgrades respectively. These discordances, more pronounced in the obese group, may ultimately result in some surgeons favoring surgical staging. In conclusion, while it is necessary to continue endometrial sampling for all patients with abnormal uterine bleeding concerning for underlying endometrial cancer, those results alone should not be used to reach decisions on whether to perform or omit surgical staging. More studies are needed to further assess when it is prudent to perform surgical staging in early stage EMCA patients.

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Research Highlights

- BMI does not appear to affect the correlation between preoperative biopsy and postoperative final tumor grade.
- There is only fair agreement between preoperative and postoperative tumor grade among all women with endometrial cancer.
- Tumor grade alone should not be used to determine which patients need surgical staging.

Table 1
Patient demographics based on BMI (N=445)

	Non-obese, BMI <30 N=161 (%)	Obese, BMI ≥30 N=284 (%)	
Mean Age (± SD)	66.5 (±11.8)	61.1 (±11.3)	p = 0.0001
Mean BMI (± SD)	25.5 (±3.5)	39.6 (±7.8)	p = 0.0001
Race			
White	125 (77.6)	198 (69.7)	p = 0.0626
Black	30 (18.6)	79 (27.8)	
Hispanic	4 (2.5)	2 (0.7)	
Asian/Other	2 (1.2)	5 (1.8)	
Pre-operative biopsy technique			
EMB *	90 (55.9)	145(51.1)	p = 0.4892
D&C	69 (42.9)	137(48.2)	
Unknown	2 (1.2)	2(0.7)	

* EMB = Office endometrial biopsy

Table 2
Preoperative biopsy and final pathologic evaluation

	Non-obese, BMI < 30 N=161 (%)	Obese, BMI ≥ 30 N=284 (%)	p-value
Preoperative Histology			p = 0.701
Endometrial Adenocarcinoma-NOS	122 (75.7)	198 (69.7)	
Endometrioid	18 (11.2)	42 (14.8)	
UPSC and Clear Cell	9 (5.6)	14 (4.9)	
CAH	12 (7.5)	30 (10.6)	
Preoperative Tumor Grade			p = 0.329
CAH	12 (7.5)	30 (10.6)	
1	26 (16.1)	40 (14.1)	
2	57 (35.4)	117 (41.2)	
3	66 (41.0)	97 (34.1)	
Postoperative Histology			p = 0.457
Endometrioid	134 (83.3)	238 (83.8)	
UPSC, Clear Cell, or Mixed Epithelial type	16 (9.9)	26 (9.1)	
Sarcoma/Carcinosarcoma	10 (6.2)	11 (3.9)	
CAH or NRD *	1 (0.6)	9 (3.2)	
Postoperative Tumor Grade			p = 0.086
1	19 (11.8)	47 (16.5)	
2	41 (25.5)	86 (30.3)	
3	100 (62.1)	142 (50.0)	
CAH or NRD *	1 (0.6)	9 (3.2)	

* CAH or NRD (no residual disease) includes 1 patient in the non-obese cohort without any residual disease on final pathology in tissues removed at the time of surgery. In the obese cohort, 9 patients had CAH on final pathology and no patients had NRD.

Table 3
Comparison of preoperative and postoperative tumor grade

	N	κ	p-value
Overall	445	0.21	
BMI			p = 0.77
Non-obese	161	0.19	
Obese	284	0.21	

Table 4
Comparison of the number of pathologic upgrades within each BMI group across all tumor grades

BMI	Number of pathologic upgrades*	p-value
Non-obese	61	p = <0.0001
Obese	104	p = 0.0003

* Patients with pathologic upgrades from pre-operative pathologic tumor grade compared to final surgical pathologic tumor grade.