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Preoperative predictors of endometrial cancer at time of hysterectomy for endometrial intraepithelial neoplasia or complex atypical hyperplasia

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Abstract

Background: Endometrial intraepithelial neoplasia (EIN), also known as complex atypical hyperplasia (CAH), is a precancerous lesion of the endometrium associated with a 40% risk concurrent endometrial cancer at the time of hysterectomy. While a majority of endometrial cancers (EC) diagnosed at the time of hysterectomy for endometrial intraepithelial neoplasia are low-risk, low-stage, approximately 10% of patients ultimately diagnosed with EC will have high-risk disease that would warrant lymph node assessment to guide adjuvant therapy decisions. Given these risks, some physicians choose to refer patients to a gynecologic oncologist for definitive management. Currently, little data exists regarding preoperative factors that can predict the presence of concurrent endometrial cancer in patients with endometrial intraepithelial neoplasia. Identification of these factors may assist in the preoperative triaging of patients to general gynecology or gynecologic oncology.

Objective(s): 1) To determine if preoperative factors can predict the presence of concurrent endometrial cancer at time of hysterectomy in patients with endometrial intraepithelial neoplasia; 2) To describe the ability of preoperative characteristics to predict which patients may be at a higher risk of lymph node involvement requiring lymph node assessment at the time of hysterectomy.

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The authors report no conflicts of interest.

Study Design: We conducted a retrospective cohort study of women undergoing hysterectomy for pathologically-confirmed endometrial intraepithelial neoplasia from January 2004 to December 2015. Patient demographics, imaging, pathology, and outcomes were recorded. The “Mayo criteria” were used to determine patients requiring LND. Unadjusted associations between covariates and progression to endometrial cancer were estimated through two-sample *t*-tests for continuous covariates and by logistic regression for categorical covariates. A multivariable model for endometrial cancer at the time of hysterectomy was developed using logistic regression with 5-fold cross-validation.

Results: Of the 1055 charts reviewed, 169 patients were eligible and included. Eighty-seven (51.5%) patients had a final diagnosis of endometrial intraepithelial neoplasia/other benign disease while eighty-two (48.5%) were ultimately diagnosed with endometrial cancer. No medical comorbidities were found to be strongly associated with concurrent endometrial cancer. Patients with endometrial cancer had a thicker average endometrial stripe compared to the patients with no endometrial cancer at time of hysterectomy (15.7 mm (SD = 9.5) vs 12.5 mm (SD = 6.4), $p=0.01$). Endometrial stripe of ≥ 2 cm was associated with 4.0 times the odds of concurrent endometrial cancer (95% CI: (1.5–10.0)), controlling for age. 87% of endometrial cancer cases were stage T1a (Nx or N0). Approximately 44% of patients diagnosed with endometrial cancer and an endometrial stripe ≥ 2 cm met the “Mayo criteria” for indicated lymphadenectomy compared to 22% of endometrial cancer patients with an endometrial stripe < 2 cm.

Conclusions: Endometrial stripe thickness and age were the strongest predictors of concurrent endometrial cancer at time of hysterectomy for endometrial intraepithelial neoplasia. Referral to a gynecologic oncologist may be especially warranted in endometrial intraepithelial neoplasia patients with an endometrial stripe of ≥ 2 cm given the increased rate of concurrent cancer and potential need for lymph node assessment.

Condensation:

Endometrial stripe thickness on preoperative ultrasound is predictive of concurrent uterine adenocarcinoma at time of hysterectomy for endometrial intraepithelial neoplasia.

Keywords

Endometrial hyperplasia; endometrial intraepithelial neoplasia; precancerous lesion; endometrial cancer; transvaginal pelvic ultrasound; endometrial stripe

Introduction:

Endometrial intraepithelial neoplasia (EIN), formally known as complex atypical hyperplasia (CAH), is a premalignant lesion of the endometrium that is of clinical significance due to an approximately 30% risk of progression to endometrial adenocarcinoma (EC)(1–3). Furthermore, the prevalence of concurrent EC in patients diagnosed with EIN undergoing hysterectomy approaches 43% (4). Risk factors for the development of EIN include obesity, anovulation, nulliparity, and diabetes (5, 6). A diagnosis of EIN can be made by outpatient endometrial biopsy or by dilation and curettage with or without hysteroscopy (D&C)(7, 8). Given the high risk of concurrent adenocarcinoma and the risk of progression, the standard treatment of EIN is surgical

management with hysterectomy with or without bilateral salpingo-oophorectomy (BSO). This treatment protocol allows for full pathologic evaluation, assessment of concurrent cancer, and provides definitive therapy (4, 9). Nonsurgical management may be appropriate for patients desiring future fertility or for those patients with comorbidities precluding surgical management (10).

The majority of EIN patients ultimately diagnosed with EC will have early stage, low-risk disease. However, approximately 12% will have high-grade tumors with deep myometrial invasion and a 3–7% risk of lymph node involvement (4, 11–13). While the comprehensive surgical staging with lymph node assessment via full lymphadenectomy or sentinel lymph node approach for all patients with EIN would result in overtreatment in a large proportion of patients, there remains a subset of patients for which lymph node assessment as a guide to adjuvant therapy is beneficial in reducing the risk of over- or under-treatment. Additionally, hysterectomy results in disruption of the lymphatic channels making sentinel lymph node assessment impossible to perform after hysterectomy, in the event of an EC diagnosis on intraoperative or final pathology. This fact has resulted in ongoing discussions about whether or not a referral to a gynecologic oncologist is warranted in all cases of EIN (14).

Given the challenging management decisions associated with EIN, interest exists in identifying factors that may improve pre-operative risk prediction of EC. Previous studies have identified sampling method as being associated with EC risk with EIN diagnosed on office biopsy alone being more strongly associated with EC on follow up (15, 16). A retrospective study identified pathologic characteristics such as extent of EIN, or involvement of a polyp or other suspicious feature as important in the prediction of underlying cancer risk with the highest risk in patients assigned the designation of EIN suspicious (16). However, little data exists on the impact of objective preoperative factors that may be used to predict the risk of underlying EC.

The primary purpose of this study was to determine if preoperative factors, including imaging and patient characteristics, can predict the presence of concurrent EC at time of hysterectomy in patients diagnosed with EIN. A secondary outcome was to describe the ability of preoperative characteristics to predict which patients may require a lymph node dissection.

Materials and Methods:

After obtaining Institutional Review Board approval, a retrospective chart review was performed encompassing all patients undergoing hysterectomy and bilateral salpingo-oophorectomy for confirmed EIN at The Ohio State University (OSU) from January 2004 to December 2015. Confirmation of a EIN diagnosis by an OSU pathologist was required for inclusion. Lymph node assessment was performed either at the time of primary surgery or, in rare cases, in a second surgery based on intraoperative frozen section, final pathology diagnosis, and/or provider choice. Patients with no preoperative imaging or those who had undergone pre-hysterectomy endometrial ablation were excluded. Patient demographics, imaging results, pathologic data and outcomes were recorded from the medical record.

We used the widely accepted “Mayo criteria” to calculate for whom a lymph node dissection would be recommended (15). The Mayo criteria recommends a lymph node dissection for patients with; a) grade 1 or grade 2 endometrioid adenocarcinoma ≥ 2 cm and $> 50\%$ myometrial invasion, any grade 3 endometrioid adenocarcinomas, and all non-endometrioid adenocarcinomas (serous, clear cell, mixed, carcinosarcoma). Descriptive statistics (counts, frequency, mean, and standard deviation) were reported. Initial associations with progression to EC were made by two-sample *t*-tests for continuous covariates and by the estimation of odds ratios (OR), and 95% confidence intervals (CI), for categorical covariates. A predictive multivariable logistic model for progression to EC was developed by forward selection of covariates with crude association at the 10% level and 5-fold cross validation. Model discrimination was assessed by the area under the ROC curve (AUC), while model calibration was assessed using the Hosmer-Lemeshow goodness of fit test. The associations between Mayo criteria and either LND or EMS thickness were assessed using Fisher’s exact test. All reported p-values are two sided. Data were analyzed in Stata version 15.1 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

Results:

In total, 169 were eligible to be included in the study. EIN was diagnosed by endometrial biopsy in 44% of the patients, while 56% of patients were initially diagnosed by D&C. Seventy-three (43%) patients had a final diagnosis of EIN and 82 (48%) were diagnosed with endometrial cancer at time of hysterectomy while 14 (8%) had other benign disease.

Demographics for the study population are reported in Table 1 by final pathologic diagnosis. The average age of patients diagnosed with EC at time of hysterectomy was 56 years (SD: 10.0), compared to 54 years (SD: 10.0) for those with EIN/other benign disease. As women aged, they were more often diagnosed with EC (≥ 65 yrs vs. < 50 : OR=2.7, 95% CI: (1.1, 6.8), $p=0.08$). In both groups, most patients were Caucasian/White, postmenopausal, and had never used hormone replacement therapy. The most commonly noted medical comorbidity in both groups was obesity (83% in both groups). Median BMI was 39.5 (min, max: 21.0, 64.3) for those progressing to EC and 41.5 (min, max: 19.9, 69.2) in those who did not. The rate of hypertension, diabetes, and breast cancer were similar between the two groups.

The final multivariable model (Figure 1) found preoperative transvaginal ultrasound endometrial stripe thickness (EMS) and age group to be strongly associated with an increased odds of EC. The final predictive model had reasonable discrimination (AUC: 0.64, 95% CI: (0.56, 0.72)) and calibration (Hosmer-Lemeshow goodness of fit test p-value: 0.41). Those with EC at time of hysterectomy had an average EMS of 15.7 (SD = 9.5) mm compared to those with EIN/other benign disease 12.5 (SD = 6.4). Patients with an EMS of ≥ 2 cm or greater had 4.0 times the odds of concurrent EC (OR 4.0, 95% CI: 1.6, 10.1), controlling for age (Table 1). An increased odds of EC is also suggested for those patients with increased age, 65 years and older (aOR: 2.3, 95% CI: 0.9, 5.9), compared to those patients 50 and younger, controlling for EMS thickness (Table 1).

Table 2 describes the characteristics of those who were diagnosed with EC at time of hysterectomy. The majority of EC cases were early stage as defined as T1a (Nx or N0) (87%), had low risk pathologic features such as grade 1 disease (92%), endometrioid histology (96%) and lack of lymphovascular space invasion (89%). However, 10% of patients had greater than 50% myometrial invasion; these patients are considered stage IB or higher. Fifteen percent of the EC cohort received adjuvant therapy, most commonly with vaginal brachytherapy. Approximately 24% (n=20) of EC cases underwent lymphadenectomy (LND); 7 of these (35%) met Mayo criteria. Twenty-three of 82 patients with endometrial cancer met Mayo criteria (28%). Ten (44%) patients with an EMS of 2 cm or greater met Mayo criteria on final pathology compared to 13 (22%) of those with EMS less than 2 cm, indicating that a lymph node dissection would be warranted. Of the patients with EMS $\geq$ 2 cm and EC diagnosis, 20 (87.0%) had grade 1, 2 (8.7%) had grade 2, and 1 (4.4%) had grade 3; 2 (8.7%) had non-endometrioid histology, 4 (17.4%) had $>50\%$ myometrial invasion, and 3 (13.0%) had LVSI.

There were two instances of stage III disease. One patient had a dedifferentiated carcinoma at time of hysterectomy and subsequently underwent imaging as she did not undergo lymph node assessment at time of hysterectomy. Her imaging demonstrated lymphadenopathy that was biopsied and found to be consistent with metastatic disease. She then received systematic chemotherapy without complete lymphadenectomy and had no evidence of disease at 17 months. The other patient had stage IIIC disease of endometrioid histology, grade 3, and was noted to have an EMS of 13.5 mm prior to hysterectomy.

In the entire cohort there was a single recurrence after a median follow up time of 2.4 years. This patient had stage IA, grade I endometrioid EC with negative lymphovascular space invasion (LVSI). She did not undergo LND and did not receive adjuvant therapy. She was found to have pelvic and nodal recurrences 12 months after hysterectomy. She declined any additional therapy in favor of hospice placement and died from disease within two months.

Discussion:

Principal findings:

Our study demonstrates that patients with a preoperative diagnosis of complex endometrial hyperplasia and an EMS of 2 cm or greater, have 4.0 (95% CI: 1.6, 10.1) times the odds of endometrial cancer at the time of hysterectomy, controlling for age. Furthermore, 44% (n=10) of patients with an EMS $\geq$ 2 cm would have required lymph node dissection based on Mayo criteria.

Clinical implications:

Management of EIN continues to be a complex issue especially when deciding on referral to a gynecologic oncologist. Previous studies exploring the prediction of the risk of concurrent EC in patients with EIN have focused on factors such as sampling method and histologic characteristics such as type and extent of EIN (16). For the first time, we have demonstrated that the preoperative endometrial stripe (EMS) thickness determined by preoperative transvaginal ultrasound (TVUS) is associated with increased odds of EC, while controlling

for age. These results may be particularly relevant to women and their gynecologists who are in settings that may be a distance away from the gynecologic oncologist. Applying this assessment may assist in making the decision/plan for referral.

Within the cohort diagnosed with concurrent EC, the majority of cases were early stage with low risk pathologic features such as grade 1 or endometrioid histology. In fact, almost half of these cases were confined to the endometrium. There was a lower rate of high-risk disease in our cohort (grade 2/3 disease or outer 50% myoinvasion) compared to previously studied cohorts (4, 18). This may reflect demographic differences, such as a higher proportion of Caucasian patients and a higher BMI in our cohort, both of which are associated with the development of type I endometrial cancers (19). Type I endometrial cancers are most often estrogen-dependent and are associated with lower grades and rates of myoinvasion, LVSI, and lymph node involvement compared to type II endometrial cancers (20).

The major advantage in referring patients with EIN to a gynecologic oncologist is gynecologic oncologist's ability to perform comprehensive staging including lymph node assessment when needed. While the impact of routine lymphadenectomy on survival is controversial, the benefit of lymph node assessment lies within determining which patients need adjuvant therapy (21). Previously, full lymphadenectomy was performed as part of comprehensive surgical staging but was associated with increased lymphedema(20). Interest then turned to defining low-risk patients in which full lymph node dissection could be avoided. Mariani et al. defined a low-risk population consisting of patients with grade 1 or 2 endometrioid adenocarcinoma with less than 50% myometrial invasion and a tumor less than 2 cm in diameter (20 23). A prospective study utilizing these criteria demonstrated a <1% risk of lymph node involvement in these low-risk patients compared to 16% in those not meeting the criteria. Notably, in our cohort, 44% of patients with an EMS $\geq$ 2 cm would have required lymph node dissection using the criteria described above.

Most recently, sentinel lymph node (SLN) mapping has been introduced into the surgical management of endometrial cancer with the intention to reduce morbidity associated with a full lymphadenectomy (e.g. lymphedema, lymphocele). SLN mapping in EC involves injecting the cervix with ICG, a fluorescent dye, with or without a colorimetric dye or radioactive tracer, and has been shown to be a reliable and safe alternative to full lymphadenectomy with a low false negative rate (24–28). It is important to note that ability to perform SLN mapping in EC depends on intact, unobstructed lymphatic channels originating from the uterine corpus and cervix and cannot be performed after hysterectomy. EIN patients diagnosed with endometrial cancer with high-risk features at time of hysterectomy alone would then subsequently require a full lymphadenectomy. This results in the patient being exposed to additional anesthesia risks and surgical risks associated with lymphadenectomy.

One alternative approach to management of EIN in the era of SLN mapping is to offer SLN dissection to all patients with EIN. This would allow for a less-morbid, yet reliable, lymph node assessment and avoidance of a second surgical procedure and its associated risks in the event of an endometrial cancer diagnosis. Based on our study, the risk of meeting Mayo criteria (indicating need for lymphadenectomy) in patients with EIN/CAH was 28%. SLN

mapping should be considered for all patients with EIN/CAH, especially for patients with an endometrial stripe >2 cm on preoperative pelvic ultrasound. Knowledge of lymph node status in patient with high intermediate uterine risk factors would allow a more tailored recommendation for postoperative therapy or surveillance, with possible omission of external beam radiation therapy and/or chemotherapy for those at low risk of recurrence (29, 30).

Strengths and limitations:

Limitations of this study include its retrospective nature and potential lack of measured confounders. Additionally, the rate of concurrent EC at time of hysterectomy is slightly higher in this cohort (48.5%) than in the prospective GOG 167 cohort, which demonstrated a concurrent EC risk of 43% (4). This may be explained by the fact that we are a tertiary referral center and thus receive referrals from many different centers with varying degrees of pathologist expertise. Although the preoperative diagnosis was not centrally reviewed for all cases, this does reflect the “real-world” of gynecologic care. Strengths of this study include the large cohort, final pathology review at a single-institution, and inclusion of objective variables to better predict the risk of underlying cancer at time of hysterectomy for EIN.

Conclusions:

Ultimately, the decision to refer a patient to gynecologic oncology is dependent on a discussion of risks and benefits between the patient and her provider. Patients diagnosed with EIN and an EMS of less than 2 cm should be counseled on their underlying risk of carcinoma and potential lymph node involvement. Most importantly, our results suggest that all patients with EMS thickness of 2 cm or more should be considered for referral to a gynecologic oncologist given the high odds of underlying endometrial cancer. Since almost half of the patients with an EMS $\geq$ 2 cm will meet criteria for lymph node assessment, strong consideration should be given to sentinel lymph node dissection at the time of hysterectomy for EIN. This will provide the patient with an adequate risk assessment (staging) in case of cancer diagnosis on final pathology, and would avoid a possible second surgery and/or complete lymphadenectomy.

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AJOG at a glance:

- A.** To determine if there are preoperative predictors of concurrent uterine adenocarcinoma at time of hysterectomy for endometrial intraepithelial neoplasia and need for lymph node assessment at time of surgical management.
- B.** Both preoperative endometrial stripe thickness and smoking status predicted the presence of concurrent adenocarcinoma at time of hysterectomy for endometrial intraepithelial neoplasia. Endometrial stripe thickness of ≥ 2 cm was associated with a 4-fold increase in odds of concurrent cancer compared to endometrial stripe thickness < 2 cm. 44% of patients with an endometrial stripe of ≥ 2 cm met clinical criteria for lymph node assessment.
- C.** This study suggests that referral to gynecologic oncology may be warranted for patients with endometrial intraepithelial neoplasia and especially if endometrial stripe thickness ≥ 2 cm given the increased rate of concurrent cancer and potential need for lymph node assessment.

Figure 1:
Multivariable Logistic Regression model for Endometrial Cancer

Table 1:

Baseline patient characteristics by final pathology diagnosis at time of hysterectomy.

	Endometrial carcinoma (n = 82), n (%)	Benign Pathology (n = 87), n (%)	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
EMS				
< 2 cm	59 (42.4)	80 (57.6)	Reference	Reference
≥ 2 cm	23 (76.7)	7 (23.3)	4.5 (1.8, 11.1)	4.0 (1.6, 10.1)
Smoking status				
Never smoker	55 (52.9)	49 (47.1)	Reference	
Ever smoker	25 (41.7)	35 (58.3)	0.6 (0.3, 1.2)	
Age				
≤ 50	23 (42.6)	31 (57.4)	Reference	Reference
51–64	39 (45.9)	46 (54.1)	1.1 (0.6, 2.3)	1.2 (0.6, 2.4)
≥ 65	20 (66.7)	10 (33.3)	2.7 (1.1, 6.8)	2.3 (0.9, 5.9)
Race				
Non-white	7 (53.8)	6 (46.2)	Reference	
White	75 (48.1)	81 (51.9)	0.8 (0.3, 2.5)	
Menopausal status				
Premenopausal	25 (41.0)	36 (59.0)	Reference	
Postmenopausal	56 (52.8)	50 (47.2)	1.6 (0.9, 3.0)	
Comorbidities				
BMI				
Not-obese (<30)	14 (48.3)	15 (51.7)	Reference	
Obese (≥ 30)	68 (48.6)	72 (51.4)	1.0 (0.5, 2.3)	
Hypertension				
No	25 (44.6)	31 (55.4)	Reference	
Yes	57 (50.4)	56 (49.6)	1.3 (0.7, 2.4)	
Diabetes				
No	58 (47.5)	64 (52.5)	Reference	
Yes	24 (51.1)	23 (48.9)	1.2 (0.6, 2.3)	

Note: BMI body mass index (kg/m^2). Obesity was defined as BMI ≥ 30 . Smoking status has five missing values (2 in EC group; 3 in benign pathology group). Menopausal status has two missing values (1 in EC group; 1 in benign pathology group). The adjusted odds ratio includes the variables in the final model only

Table 2:

Clinicopathological characteristics of patients diagnosed with endometrial carcinoma at time of final pathology

	Endometrial carcinoma (n = 82), n (%)
Stage	
IA	71 (86.6)
IB	4 (4.9)
II	5 (6.1)
III	2 (2.4)
Grade	
1	75 (91.5)
2	4 (4.9)
3	3 (3.7)
Histology	
Endometrioid	79 (96.3)
Mixed pattern	2 (2.4)
Dedifferentiated	1 (1.2)
LVSI	
Present	9 (11.0)
Absent	73 (89.0)
Meets Mayo Criteria	23 (28.0)
Underwent LND	20 (24.4)
Recurrence	1 (1.2)