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Original Article

Hysteroscopy-Guided Endometrial Sampling Diagnostic Performance in Endometrial Intraepithelial Neoplasia Patients

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ABSTRACT **Objective:** To compare the diagnostic performance of hysteroscopy-guided versus blind sampling in detecting concurrent endometrial carcinoma in patients with endometrial intraepithelial neoplasia (EIN) and to identify factors associated with missing cancer diagnosis.

Design: This is a retrospective cohort study.

Setting: Integrated academic and community healthcare system in Minnesota and Wisconsin, USA, January 1, 2018, and January 1, 2023.

Participants: This included 151 patients diagnosed with EIN during endometrial sampling who underwent a hysterectomy within 3 months. Patients with concurrent cancer diagnoses were excluded.

Interventions: Patients diagnosed with EIN using hysteroscopy-directed biopsy were compared to those diagnosed with blind-sampling methods using the pathology results of the subsequent hysterectomy specimen as the gold standard comparator to analyze rates of missed endometrial cancer (EC) diagnosis.

Measurements and Main Results: The primary outcome was a reduced risk of unanticipated concurrent EC on the final hysterectomy pathology result for patients diagnosed with endometrial intraepithelial hyperplasia via a hysteroscopy-directed biopsy (odds ratios [OR] = 0.44, 95% confidence intervals [CI] = 0.20−0.95, p = .033). In multivariate analysis, body mass index ≥30 and patient age >60 were associated with an elevated risk of EC on final pathology (OR = 4.17, 95% CI = 1.51−11.51, p = .004; OR = 5.56, 95% CI = 1.22−35.21, p < .001), respectively, and diabetes mellitus was the only independent variable associated with a higher risk of EIN on final hysterectomy pathology (OR = 7.01, 95% CI = 1.40 −35.04, p = .018). Age, body mass index, and endometrial thickness on pre-biopsy ultrasound were not associated with an increased risk of overlooking concurrent endometrial carcinoma on final hysterectomy pathology on univariate and multivariate analyses.

Conclusion: Hysteroscopy-directed biopsy may reduce the risk of missing a concurrent endometrial malignancy during endometrial sampling in women with EIN. The results affirm the superior diagnostic accuracy of hysteroscopy-directed endometrial evaluation. Journal of Minimally Invasive Gynecology (2025) 32, 725−730. © 2025 AAGL. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

Keywords: Endometrial intraepithelial neoplasia; Endometrial hyperplasia; Endometrial cancer; Hysteroscopy

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Introduction

Uterine cancer is the most common gynecologic malignancy, with a rising incidence of 1% in White patients and >2% in other diverse ethnic minorities [1−3]. Since endometrial intraepithelial neoplasia (EIN) is a precursor lesion that, if treated early, may result in the prevention of progression to endometrial cancer (EC), The Centers for Disease Control and Prevention highlighted opportunities for early diagnosis as a priority [4].

For patients diagnosed with EIN, the risk of encountering concurrent undiagnosed endometrial carcinoma at the time of hysterectomy ranges from 32% to 62.5%, with an 11% risk of deep myometrial invasion and a 3.3% risk of nodal involvement [5−8]. Due to these risks, management strategies are individualized based on the patient's comorbidities and desire for future fertility. The standard of care is total hysterectomy, and for poor surgical candidates or those who desire to maintain fertility, uterine-sparing, and hormonal therapeutic options may be offered [9]. At our institution patients are referred to gynecologic oncologists to complete surgical treatment that may involve sentinel lymph node dissection if specific high-risk criteria are fulfilled (Table 1) [10]. This referral paradigm impacts access to care, especially for patients who live in rural counties and may be unable or refuse to travel to seek subspecialty care, which was noted to worsen their survival [11].

Gynecologic oncology resources are far scarcer in underserved communities and communities with people of color, and ethnic minorities. This, in and of itself, may not explain all the disparities and poorer outcomes in these groups, yet longer waiting times have been correlated with additional morbidities in this patient population [12−14]. Additionally, the already scarce gynecologic oncology resources are further challenged with the added burden of benign complex gynecologic referrals [15].

While referral of patients with EIN to gynecologic oncologists was found cost-effective based on earlier studies [16], that recommendation may have to be reevaluated now with increased uptake of hysteroscopic diagnostic modalities that offer higher sensitivity and lower risk of missing consequential pathology. The role of hysteroscopy-directed endometrial sampling in evaluating abnormal uterine bleeding has been proven superior to blind approaches due to its higher agreement with the final pathology [17,18]. In a large retrospective study by Ceci et al [19], hysteroscopy showed a diagnostic sensitivity of 98%, a specificity of 95%, and a negative predictive value of 98%.

Our study aims to assess the comparative diagnostic performance of hysteroscopy-guided endometrial sampling compared to blind sampling (BS) in patients diagnosed with EIN. The literature on this specific pathology is limited. We hypothesize that hysteroscopy-directed sampling (HDS) will lead to a lower risk of unanticipated concurrent endometrial carcinoma during a hysterectomy performed for surgical management of EIN.

Table 1

Description of Mayo risk stratification criteria for predicting lymphatic dissemination in endometrial cancer

Mayo Criteria	
Low risk	TD ≤ 2 cm, MI < 50%, grade 1 or 2 MI = 0%, any TD or grade
Low-intermediate risk	TD > 2 cm or unknown, grade 1 or 2, MI < 50% Grade 3, MI < 50%
High-risk	Grade 1 or 2, MI ≥ 66% Grade 3, MI ≥ 50%, adnexal metastasis

MI = myometrial invasion; TD = tumor diameter.
Kilts et al. *Gynecol Oncol*. 2019;155:21−26.

Materials and Methods

The local Institutional Review Board (IRB approval # 22-013217) deemed this study exempt. This retrospective cohort study only included patients diagnosed with endometrial hyperplasia with atypia or EIN who later underwent a hysterectomy for definitive surgical management in the Mayo Clinic enterprise within 3 months of diagnosis between January 1, 2018, and March 1, 2023. Exclusion criteria included subjects who were "highly suspected," "bordering on," or diagnosed with concurrent EC at the time of their pre-hysterectomy biopsy, as well as those receiving progesterone therapy at the time of sampling or hysterectomy. Patients diagnosed with EIN in outside institutions and whose slides were not reviewed by a Mayo Clinic pathologist were also excluded.

Subjects were identified using an electronic medical record search of the ICD-10 diagnosis code for EIN (N85.02) as well as a hysterectomy CPT code following the EIN diagnosis.

Both HDS (using graspers or resectoscopes) and hysteroscopy-assisted global resection using mechanical morcellation devices were grouped under the HDS category. Patients diagnosed using BS methods, including disposable vacuum-assisted aspiration catheters (e.g., Pipelle, Endosampler) or dilation and curettage, were grouped under BS regardless of whether diagnostic hysteroscopy preceded or followed sampling.

Demographic data abstracted from the medical record included: race, age, body mass index (BMI), gravidity, parity, menopausal status, hormonal medications., preoperative ultrasound-reported endometrial thickness, pathological diagnosis, and comorbidities such as diabetes mellitus (DM) and hypertension. Surgical data of interest included details surrounding lymph node dissection at the time of the hysterectomy, final pathological diagnosis, and, if applicable, the stage of EC.

The primary outcome of interest was the percentage of patients diagnosed with endometrioid EC at the time of the

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hysterectomy in the HDS and BS cohorts using the hysterectomy specimen as the gold standard (reference). Statistical analysis was based on frequency data and diagnostic agreement of the procedures. Quantitative variables were expressed as means and standard deviations or medians as appropriate. Qualitative variables were expressed as absolute and relative frequencies. The open-source statistical software Jamovi (version 2.3.21) was utilized for the statistical analyses. Initial associations for diagnosing EC were utilized with a Chi-square test for categorical covariates by estimating odds ratios (OR) and 95% confidence intervals (CIs). The parametric one-way ANOVA and nonparametric Kruskal−Wallis test were utilized to identify potential confounding variables. By performing binary logistic analysis, ORs and 95% CIs were estimated for all significant parameters found in the univariate analysis during the multivariable analyses. Statistical power was set at 80%, with the alpha value set at 0.05 for type I error. The analysis considered the rate of missing cancer in the BS to be 47%, and the assumption was that HDS had at least a 20% better detection rate. Sample size assessment required 150 patients with 1:1 allotment, assuming a 1-sided significance of 5% (based on a Chi-square test using nQuery Advisor 7.0).

Results

Table 2 summarizes the demographic characteristics of the two study cohorts. The mean age of patients for the HDS group ($n = 76$) was 60.45 ± 11.48 (years ± SD), compared to 63.95 ± 10.73 (years ± SD) with the BS group ($n = 75$). The majority of patients in both groups were postmenopausal (76.8%) and White (92%). In both groups, the two most reported medical comorbidities were obesity (66.8%) and hypertension (43.5%), with no notable differences in the rates of comorbidities, menopause, or hormonal therapy. Similarly, there were no statistically significant differences in BMI or preoperative endometrial thickness by ultrasound assessment between the groups.

Upon pathological examination of hysterectomy specimens, 37 out of 114 patients (25%) were diagnosed with EC. The concurrent EC rate at the time of hysterectomy for the HDS and BS groups was 17% and 32%, respectively ($p < .05$), with a reduced risk of unanticipated concurrent EC in the HDS group (OR = 0.44, 95% CI = 0.20−0.95, p = .033). The BS group included patients evaluated using blind vacuum aspiration ($n = 50$) and patients with hysteroscopic visualization before BS ($n = 25$). Sixty-nine out of 76 (90.8%) of patients diagnosed via HDS were sampled using a mechanical morcellation device that assisted in global sampling and resection of the endometrium. The frequency of missing EC diagnosis was higher in the blind Pipelle group alone compared to sequential hysteroscopy and BS (36% and 24%, respectively, p = .25). Interestingly, none of the patients evaluated via HDS were found to have advanced EC, while 5% of the patients evaluated by BS techniques had advanced disease.

Table 3 outlines the characteristics of subjects who went on to have confirmed diagnosis of EIN versus EC. In univariate analysis (data not shown), BMI ≥ 30 was associated with an elevated risk of EC on final pathology (OR = 4.17, 95% CI = 1.51−11.51, p = .004). The risk of diagnosing EC was higher in patients >60 years of age (OR = 5.56, 95% CI = 1.22−35.21, $p < .001$). In multivariate analysis, DM was the only independent variable associated with a higher risk of EIN on final hysterectomy pathology (OR = 7.01, 95% CI = 1.40−35.04, p = .018). Endometrial thickness on pre-biopsy ultrasound was not associated with concurrent

Table 2

Patient demographics

	Blinded-Bx ($n = 75$)	95% CI	Directed-Bx ($n = 76$)	95% CI	p-Value
Age, yr ± SD	60.45 ± 11.48	57.8−63.1	63.95 ± 10.73	61.5−66.4	.14
Body mass index	34.8 ± 8.69	32.8−36.8	35.93 ± 10.13	33.6−38.2	.59
Endometrial thickness	12.5 ± 8.13	10.5−14.5	13.24 ± 6.3	11.7−14.8	.96
Hypertension	31		35		.56
Diabetes	15		16		.87
Nulligravidity	15		26		.051
Nulliparity	17		20		.41
Menopause	21		14		.14
Hormone replacement	7		9		.88
Breast cancer	3		5		.48
Tamoxifen	1		3		.32
EIN	51		63		
Endometrial cancer	24		13		.033
Stage 1a	20		13		.30
Stage 1b	3		0		
Stage 2b	1		0		

Bx = biopsy; CI = confidence interval; EIN = endometrial intraepithelial neoplasia; SD = standard deviation.

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Table 3

Multivariate analysis between the EC and EIN group

	EC (n = 37), n (%)	EIN (n = 114), n (%)	OR (95% CI)	p-Value
Age				
>60	32	61	5.56 (1.22−35.21)	.001
<60	5	53	Reference	
Menopausal status				
Premenopausal	6	29	Reference	
Postmenopausal	31	83	1.81 (0.68−4.77)	.22
Obesity				
BMI > 30	32	69	4.17 (1.51−11.51)	.004
BMI < 30	5	45	Reference	
Hypertension				
Yes	18	48	0.77 (0.36−1.62)	.48
No	19	66	Reference	
Diabetes				
Yes	5	26	7.01 (1.40−35.04)	.018
No	32	88	Reference	
Endometrial thickness				
>15 mm	8	39	1.55 (0.63−3.82)	0.33
<15 mm	22	69	Reference	
Nulligravida				
Yes	7	42	2.51 (1.01−6.19)	.043
No	30	72	Reference	

CI = confidence interval; EC = endometrial cancer; EIN = endometrial intraepithelial neoplasia; OR = odds ratio.
Obesity is defined as BMI > 30. Endometrial thickness was stratified in various levels as >5, >10, >20 mm (data not shown), and >15 mm, but none of those reached statistical significance.

EC on final hysterectomy pathology on univariate or multivariate analyses. On the binomial multivariate model, having EC was less likely for those who do not have DM (OR = 0.19, p = .02), those with BMI < 30 (OR = 0.89, p < .001), and for those who were <60 years of age (OR = 0.89, p = .002). The predictive measures of our model were a specificity of 26%, a sensitivity of 98%, and an area under the curve of 0.83.

A total of 44 subjects (29.14%) underwent lymph node dissection during the primary hysterectomy procedure based on the Mayo Clinic Criteria (Table 1). Twenty (45%) were later identified as having an EC diagnosis. The other 24 (55%) had EIN or other benign pathology. It was noted that 17/37 (45.95%) patients with final diagnosis commensurate with EC did not have lymph node dissection; nonetheless, all were deemed early-stage EC (Stage IA Grade 1). None of the patients diagnosed by an HDS method were noted to have more than Stage IA EC diagnosis on final pathology.

Discussion

Our study demonstrates the superior accuracy of HDS in excluding advanced EC in EIN patients, a subset that typically gets subspecialty referral and surgical management. A BMI > 30 (p = .004), and an age above 60 (p < .001) were the only two variables associated with a higher risk of EC on final pathology in univariate analysis.

The high sensitivity noted in the HDS group could be partly explained by the high utilization rate (90.8%) of mechanical morcellating devices in that cohort. A study by Dueholm et al [20] evaluated hysteroscopic resectoscopes' performance for assessment of tumor histology in patients referred for EC or atypical hyperplasia in their study, hysteroscopic resection missed an underlying cancer diagnosis only in 2.2% of atypical hyperplasia cases, none of which were advanced. Their low rate of missing EC may be due to several factors, including its prospective design with the intent of detecting EC, as well as use of resectoscope loop that is capable of deeper tissue sampling compared to the mechanical morcellators used in the majority of our study subjects. The Gynecologic Oncology Group trial reported the risk of missing cancer in EIN patients used BS techniques in their trial, resulting in rates as high as 42%, with an 11% risk of deep myometrial invasion, a trend demonstrated in our data set [6]. A systematic review by Bourdel et al [21] determined a high-risk of missed EC in BS patients, even if followed by a hysteroscopic inspection.

While controversy exists regarding the need and extent of lymphadenectomy during the hysterectomy in EIN or early-stage EC, lymph node pathology results may inform decision-making for adjuvant therapy [22−24]. In a retrospective review of patients diagnosed with atypical hyperplasia using BS techniques, who were later found to have EC, it was noted that the risk of lymph node involvement was 1.6% to 2.1% [25]. These patients would benefit from

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lymph node evaluation done by gynecologic oncologists. Balancing this small risk with the cost of referral and the risk of unnecessary lymph node sampling in early-stage EC (Stage IA) or EIN patients was the impetus for the decision analysis published by Chaiken et al Their analysis concluded that referring all patients with EIN diagnosis to gynecologic oncologists was cost-effective [16].

Since hysteroscopy does impose additional costs, it is reasonable to selectively offer this to patients with an increased risk of EC (such as those over 60 years of age, width obesity, or diabetes). In contrast to Vetter et al [26], who found that increased endometrial thickness (>20 mm) was associated with a 4-fold risk of concurrent carcinoma, our study found no significant difference in univariate and multivariate analysis despite considering different stratification models. This difference could be due to sample size and the fact that there were very few patients with endometrial thickness >20 mm in our subjects.

Tissue sampling methods impact sample adequacy and do enhance pathologic evaluation. The diagnosis of EIN is nuanced by the pathological criteria that have undergone several updates over the past two decades, as well as the variation of the glandular architecture and cytologic variable hormone-related features. Criteria for diagnosis of EIN were updated by the World Health Organization in 2020 to simplify management. The 1994 system categorized endometrial hyperplasia according to glandular complexity and the presence or absence of nuclear atypia [27]. Multiple studies demonstrated high intra-observer and interobserver variability in this diagnosis using the 1994 scheme [28,29]. The 2020 system stresses that the lesion must be of sufficient size so that artifact changes can be excluded, and coincident architectural and cytological alterations are evident [30].

Hysteroscopy-guided sampling's ability to obtain more tissue through a more comprehensive and guided approach may help provide an adequate specimen that would assist the pathologist in ascertaining the diagnosis more confidently.

Future work validating these findings in a broader, more diverse population would help confirm generalizability of our results. It would also be essential to assess the access to hysteroscopic evaluation resources in rural and underserved communities and their impact on referral patterns.

This study included a large sample size with a homogenous specific diagnosis of EIN. Most studies that addressed comparative hysteroscopy diagnostic performance included EIN and early EC cases due to diagnostic pitfalls. The improved diagnostic accuracy of hysteroscopy noted in our study may be partly related to the exclusion of cases that were "bordering" or "highly suggestive" of EC. One of the advantages of this work was its ability to incorporate data from multiple sites within a large enterprise with an integrated health system institution. This allows for a standardized reporting framework, which helped to minimize any performance variations in interpreting the specimens. Even though it is a strength, it is also a limitation for generalizability at institutions that do not have access to subspecialist pathologists' expertise with variable degrees of experience interpreting esoteric pathology such as EIN. Other limitations include a relatively homogeneous, non-diverse population and the retrospective design with the potential for data misclassification and selection bias. However, this would be presumed to be non-differential. Another limitation is that one-third of the blind biopsy cohort included the performance of diagnostic hysteroscopy before BS, which technically may have lowered the risk of unanticipated cancer noted in this cohort. The fact that a statistically significant difference was still noted only strengthens our findings.

Conclusion

EIN diagnosed by hysteroscopy-guided endometrial sampling methods decreases the risk of unanticipated EC diagnosis at the time of definitive hysterectomy compared to patients diagnosed by BS. When the hysteroscopic procedure includes global endometrial sampling, the risk of unanticipated advanced EC is nearly eliminated. This makes hysteroscopy-guided sampling a valuable tool for triaging patients with EIN through referral workflows that decrease patient burden, cost of care, and unnecessary subspecialty referrals that may impact access to critical cancer care.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

Data Availability Statement

Data is available from the authors upon request.

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