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Preoperative predictors of endometrial carcinoma in patients undergoing hysterectomy for endometrial intraepithelial neoplasia

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Abstract

Objective Patients undergoing surgery for endometrial intraepithelial neoplasia (EIN) have a high likelihood of concurrent endometrial cancer (EC). Lymph node dissection (LND) may be required during the operation. Our aim was to predict the presence of cancer and identify which patients might require lymph node dissection preoperatively.

Materials and methods This study included 172 patients diagnosed with EIN and operated on by gynecologic oncology surgeons between June 2020 and December 2024. Demographic data, imaging findings, examination notes, surgical details, and pathology results were recorded. Initial associations with progression to EC were analyzed using two-sample t-tests and Mann-Whitney U tests for continuous covariates, and odds ratios (OR) with 95% confidence intervals (CI) for categorical covariates. The relationships between Mayo criteria and either LND or endometrial thickness(ET) were evaluated using Fisher's exact test. All *p*-values were two-sided.

Results A total of 172 patients were eligible for inclusion. Final pathology revealed EIN in 101 patients (58.7%) and EC in 71 patients (41.3%) after hysterectomy. The likelihood of EC increased with age (< 50 vs. ≥50 years: OR = 3.94, 95% CI: 2.00–7.79, $p < 0.001$). Diabetes (OR: 2.35, 95% CI: 1.15–4.78, $p = 0.019$) and hypertension (OR: 2.54, 95% CI: 1.36–4.74, $p = 0.004$) were more frequently observed in patients with EC compared to those with EIN. Univariate analysis identified age ≥ 50, body mass index (BMI) ≥ 35 kg/m^2, postmenopausal status, diabetes, hypertension, and ET ≥ 14 mm as variables associated with occult EC. Patients with ET ≥ 14 mm had a fourfold increased likelihood of concurrent EC (aOR: 4.06, 95% CI: 1.89–8.75). Forty-four (62%) patients with endometrial cancer met the Mayo criteria, indicating a need for lymph node dissection.

Conclusion Age ≥ 50, postmenopausal status, presence of diabetes and hypertension, BMI ≥ 35 kg/m^2, and ET ≥ 14 mm are strong predictors of concurrent endometrial cancer. These patients should be referred to gynecologic oncology, as they may require lymph node assessment, including lymphadenectomy or sentinel lymph node biopsy.

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Keywords Endometrial intraepithelial neoplasia, Endometrial cancer, Lymph node dissection, Endometrial thickness, Gynecologic oncology

Introduction

Endometrial intraepithelial neoplasia (EIN), also known as atypical hyperplasia (AH), was first classified by the World Health Organization (WHO) in 1994, dividing endometrial hyperplasias into four main categories: simple hyperplasia without atypia, complex hyperplasia without atypia, simple atypical hyperplasia, and complex atypical hyperplasia. This classification posed diagnostic challenges for pathologists and management difficulties for clinicians. In 2000, pathologists introduced the EIN classification, which categorized lesions into benign endometrial hyperplasia and EIN. In 2014, the WHO adopted the current two-tier system: hyperplasia without atypia and atypical hyperplasia (endometrial intraepithelial neoplasia) [1, 2].

Histologically, EIN is characterized by abnormal proliferation of endometrial glands and an increased gland-to-stroma ratio compared to proliferative endometrium, along with cytological atypia, representing a neoplastic process [3]. The risk of concurrent endometrial cancer (EC) in patients undergoing hysterectomy for EIN or AH can be as high as 43% [4]. Risk factors for EIN closely resemble those for EC, primarily involving prolonged unopposed estrogen exposure. These include advanced age, early menarche, late menopause, nulliparity, polycystic ovary syndrome (PCOS), obesity, diabetes, and use of estrogen-containing medications [5, 6].

Diagnosis is typically made through endometrial biopsy in an outpatient setting. Other diagnostic methods include dilation and curettage (D&C), with or without hysteroscopy [7]. International organizations have published various guidelines to reduce disparities in clinical practice. In 2020, ESGO, ESTRO, and ESP (European Society of Gynaecological Oncology– European Society for Radiotherapy and Oncology– European Society of Pathology) updated their management guidelines by incorporating recent advances in surgical procedures and molecular biology [8, 9]. Hysterectomy remains the standard treatment for EIN due to the risk of concurrent or future malignancy. This approach allows for comprehensive pathological evaluation and provides advanced opportunities for both diagnosis and treatment.

In patients who are surgically eligible, minimally invasive techniques are recommended. For postmenopausal women, bilateral salpingo-oophorectomy is advised as part of surgical management. In premenopausal patients, the decision for salpingo-oophorectomy should be individualized based on risk factors and fertility considerations [10–13]. Although conservative medical treatment may be an option in selected cases, hysterectomy remains the standard of care for patients with EIN due to the risk of concurrent or future malignancy [11, 14, 15].

Given the high likelihood of concurrent EC in patients undergoing hysterectomy for EIN or AH, intraoperative frozen section evaluation by an experienced pathologist may be considered to guide intraoperative decision-making. The frozen section result can guide the need for additional surgical procedures [11, 16, 17]. Although most EC cases detected in this setting are early-stage, some patients may require lymph node dissection (LND). Depending on the clinical scenario, either sentinel lymph node mapping or full surgical staging may be appropriate. This has led to ongoing debate about whether all patients with an EIN diagnosis should be operated on by a gynecologic oncologist [18, 19].

Identifying patients at risk for carcinoma before surgery could aid in determining the most appropriate treatment strategy. Decisions regarding the addition of bilateral salpingo-oophorectomy or lymph node dissection can be made preoperatively, and in resource-limited settings, such evaluation can help determine which patients should be referred to a gynecologic oncology specialist. Several studies have investigated preoperative factors predictive of endometrial carcinoma, including patient age, endometrial thickness(ET) on transvaginal ultrasound (TVUS), body mass index (BMI), and biopsy method [20, 21].

In this study, we aimed to determine whether preoperative clinical characteristics could predict the presence of concurrent carcinoma in patients with EIN. Our goal was to identify which patients might require oncologic surgery and should be referred to gynecologic oncology prior to hysterectomy.

Materials and methods

This study was approved by the Ethics Committee of Başakşehir Çam and Sakura City Hospital (Approval Number: E-96317027-514.10-263703971) and conducted in accordance with the principles of the Declaration of Helsinki. The study was conducted at Başakşehir Çam and Sakura City Hospital, a tertiary care center located in Turkey. Patients who were diagnosed with EIN or AH based on endometrial sampling between June 2020 and December 2024 and who underwent hysterectomy with bilateral salpingo-oophorectomy and intraoperative frozen section analysis were retrospectively reviewed. All surgeries were performed by gynecologic oncology surgeons. Laparoscopic and robotic approaches were primarily preferred. Laparotomy was reserved for patients who were not eligible for minimally invasive procedures.

Patients with a known history of cancer, incomplete medical records, or those who declined surgery were excluded from the study. Demographic characteristics, pathology reports, imaging findings, and surgical records were obtained and recorded from the hospital's electronic medical system.

Patient height and weight data were retrieved from preoperative hospital admission records. Transvaginal ultrasonography measurements were taken at the time patients presented with pathology results. Serum CA125 values were documented based on laboratory tests performed during the initial patient evaluation. Hemogram values (including hemoglobin, leukocyte, platelet, neutrophil, and lymphocyte counts) were collected from blood tests performed within seven days prior to surgery. The neutrophil-to-lymphocyte ratio (NLR) was calculated by dividing the neutrophil count by the lymphocyte count, and the platelet-to-lymphocyte ratio (PLR) was calculated by dividing the platelet count by the lymphocyte count.

All patients underwent intraoperative frozen section analysis performed by pathologists. If frozen section results were indicative of endometrial carcinoma, lymph node dissection was performed during the same operation by gynecologic oncology surgeons. Final pathology results were also retrieved from the hospital records.

To determine which patients required lymph node dissection, the Mayo criteria were applied. According to these criteria, lymph node dissection is recommended in the following cases:

- Grade 1 or 2 endometrioid adenocarcinoma with tumor size ≥ 2 cm and > 50% myometrial invasion,
- Grade 3 endometrioid adenocarcinoma,
- Any grade of non-endometrioid histology (e.g., serous, clear cell carcinoma) [19, 21]. Patients who met these criteria were classified as high-risk for endometrial carcinoma.

Statistical analyses were performed using IBM SPSS Statistics (Version 27). Descriptive statistics (counts, frequency, mean, and standard deviation) were reported. Initial associations with progression to EC were made by two-sample t-tests and Mann-Whitney U test for continuous covariates and by the estimation of odds ratios (OR), and 95% confidence intervals (CI), for categorical covariates. Cut-off value are determined by Roc curve analysis and Youden's Index for continuous covariates. A predictive multivariable logistic model for progression to EC was developed by with variables with $p < 0.05$. 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.

Since the effect size in similar studies was not known, a post-hoc power analysis was performed using G*Power version 3.1.9.7 (Faul et al., 2007). The analysis, based on a sample size of 86, demonstrated a power of 99.9% with an alpha error of 0.05 and an effect size (Cohen's h) of 0.87.

Results

A total of 172 patients were eligible to be included in the study. 101 (%58,7) patients had a final diagnosis of EIN and 71 (%41,3) patients were diagnosed with endometrial cancer by final pathology at time of hysterectomy.

Demographics and clinical characteristics of patients are reported in Table 1 by final pathologic diagnosis. The average age of patients diagnosed with EC at time of hysterectomy was 57 years (SD: 9.2), compared to 50 years (SD: 9.4) for those with EIN. As women aged, they were more often diagnosed with EC (< 50 yrs vs. ≥50: OR = 3.94, 95% CI:2.00–7.79, $p < 0,001$). The presence of diabetes (OR:2.35 CI:1.15–4.78 p:0.019)and hypertension (OR:2.54 CI: 1.36–4.74 p:0.004) were found to be more frequent in patients with EC compared to patients with EIN.

Multiparous patients were predominant in both groups. Mean PLR and NLR values were similar between the two groups and statistically insignificant, respectively (146.34 ± 45.46 vs. 138.09 ± 46.96 p:0.252, 2.29 ± 0.79 vs. 2.47 ± 0.98 p:0.219). Ca125 levels were not significantly different in both groups (EIN vs. EC: OR = 2.65 CI:0.74–9.42 p:0.203) and were mostly below the threshold of 35 (%96 vs. %90,1).

The univariable analysis revealed that the variables associated with occult endometrial carcinoma were age ≥ 50, a body mass index greater than 35 kg/m2, Menopausal status, presence of diabetes and hypertension, endometrium thickness ≥ 14 mm(Table 1).

The multivariable analysis determined that body mass index ≥ than 35 kg/m2, Menopausal status and ET ≥ 14 mm were independent predictors of occult carcinoma. The final predictive model had reasonably good discrimination (AUC: 0.78), and calibration (Hosmer-Lemeshow goodness of fit test p-value: 0.77). Those with EC at time of hysterectomy had an average ET of 15 (SD = 97.5) mm compared to those with EIN 9.3 (SD = 5.0). Patients with an ET of 14 mm or greater had 4 times the odds of concurrent EC (aOR 4.06, 95% CI: 1.89–8.75). An increased odds of EC is also suggested for those patients with BMI ≥ 35 kg/m2 (aOR: 2.62, 95% CI:1.28–5.37) and postmenopausal patients compared to premenopausal patients (aOR: 3.09, 95% CI: 1.50–6.39) (Table 1).

The tumor characteristics of the 71 patients diagnosed with EC are presented in Table 2 at time of hysterectomy.

Table 1 Baseline patient characteristics and predictive factors for endometrial carcinoma in patients with endometrioid intraepithelial neoplasia who underwent hysterectomy

		EİN (*n* = 101), n (%)	EC (*n* = 71) n (%)	OR (95% CI)	*P* value	aOR (95% CI)	*P* value
Age	< 50	54 (53,5)	16 (22,5)	Reference			
	≥ 50	47 (46,5)	55 (77,5)	3.94 (2.00–7.79)	< 0,001		
BMI (kg/ m^2)	< 35	75 (74,3)	33 (46,5)	Reference		Reference	
	≥ 35	26 (25,7)	38 (53,5)	3.32 (1.74–6.33)	< 0,001	2.62 (1.28–5.37)	0.008
Parity	Nulliparous	5 (5,0)	8 (11,3)	Reference			
	multiparous	96 (95,0)	63 (88,7)	0.41 (0.12–1.31)	0.148		
Menopausal status	premenopausal	65 (64,4)	19 (26,8)	Reference		Reference	
	postmenopausal	36 (35,6)	52 (73,2)	4.94 (2.54–9.60)	< 0,001	3.09 (1.50–6.39)	0.002
Hypertension	No	67 (66,3)	31 (43,7)	Reference			
	Yes	34 (33,7)	40 (56,3)	2.54 (1.36–4.74)	0.004		
Diabetes mellitus	No	83 (82,2)	47 (66,2)	Reference			
	Yes	18 (17,8)	24 (33,8)	2.35 (1.15–4.78)	0.019		
endometrium thickness	< 14	85 (84,1)	33 (46,5)	Reference		Reference	
	≥ 14	16 (15,9)	38 (53,5)	6.11 (3.01–12.43)	< 0,001	4.06 (1.89–8.75)	< 0.001
Ca125 (U/mL)	< 35	97 (96)	64 (90,1)	Reference			
	≥ 35	4 (4)	7 (9,9)	2.65 (0.74–9.42)	0.203		

Abbreviations: EIN, endometrial intraepithelial Neoplasia; aOR, EC, endometrium carcinoma; OR, odds ratio; aOR, adjusted odds ratio; CI, confidence interval; BMI, body mass index

Table 2 Clinicopathological characteristics of patients diagnosed with endometrial carcinoma at time of final pathology

		Endometrial carcinoma (*n* = 71) n (%)
myometrial invasion	<%50	62 (87,3)
	≥%50	9 (12,7)
Lymph-vascular space invasion	Negative	60 (84,5)
	Positive	11 (15,5)
Grade	1	45 (63,4)
	2	21 (29,6)
	3	5 (7)
tumor size	< 2 cm	29 (40,8)
	≥ 2 cm	42 (59,2)
histology	Endometrioid	67 (94,4)
	Mixed pattern	1 (1,4)
	Serous	3 (4,2)
meets mayo criteria	No	27(38)
	Yes	44 (62)
Lymph node metastasis	No	69 (97,2)
	Yes	2 (2,8)

The majority of EC cases had endometrioid histology (94.4%) and negative of lymphovascular space invasion (84.5%). 7% of patients had high-grade disease (Grade 3). 12.7% of patients had greater than 50% myometrial invasion. 44 (62%) of the patients with endometrial cancer met the Mayo criteria, indicating that a lymph node dissection would be required. Systematic lymph node dissection was performed in 51 patients who met the Mayo criteria on frozen section and had suspected lymph node involvement.

27 (61%) patients with an ET of 14 mm or greater met Mayo criteria on final pathology compared to 17 (39%) of those with ET less than 14 mm. Of the patients with ET ≥ 14 mm and EC diagnosis, 21 (55.0%) had grade 1, 14 (37%) had grade 2, and 3 (8%) had grade 3; 3 (8%) had non-endometrioid histology, 5 (13%) had > 50% myometrial invasion, and 5 (13.0%) had LVSI.

Discussion

Due to the risk of concurrent endometrial cancer in patients with endometrial intraepithelial neoplasia or complex atypical hyperplasia, there is ongoing debate about whether these patients should be managed by general obstetricians/gynecologists or referred to gynecologic oncologists. Some patients may be diagnosed with EC, raising the concern of incomplete surgical staging if treated outside of oncology settings. If carcinoma is present, lymph node dissection may be required for surgical

staging. Therefore, careful evaluation is necessary to determine which patients should be referred to a gynecologic oncologist. This study evaluates risk factors to assist in identifying patients at higher risk for carcinoma who may benefit from specialized management.

In our study, the prevalence of concurrent endometrial cancer was found to be 41.3%. This is consistent with prior reports ranging from 25 to 50% [4, 19, 22–24]. Variations in prevalence may be influenced by factors such as sample size, ethnic background, and patient demographics. Since our institution is a tertiary referral center with expertise in gynecologic oncology, the higher proportion of cancer cases is likely related to referral bias involving patients with suspected malignancy.

We observed that patients with EC had a significantly higher mean age, with cancer risk increasing approximately 3.94 times in women aged ≥ 50 years. Similarly, Abt et al. reported increasing age as a significant risk factor for cancer [25], and a 2020 study by Gianella et al. identified age over 60 as a predictor [26]. The presence of diabetes and hypertension was also more common among EC patients in our cohort. Matsuo et al. found diabetes to be an independent risk factor [20], and a study by Erdem et al. with 227 patients identified both diabetes and hypertension as predictive [22]. However, Vetter et al. did not find these comorbidities significant in their analysis of 169 patients, possibly due to ethnic or population differences [19].

Obesity is a well-known risk factor for endometrial cancer and is also associated with poorer outcomes [27]. In our study, a BMI ≥ 35 kg/m² was a significant risk factor for carcinoma. Shree et al. similarly showed an increasing risk of EC with rising BMI [28], and findings from Gianella et al. were consistent with ours, showing increased EC prevalence with obesity [29]. Our study also observed a higher risk of EC in postmenopausal women, aligning with Liang et al., who reported menopause as a predictive factor [30].

Recent studies have demonstrated a significant relationship between ET and the risk of EC. Our findings revealed that ET ≥ 14 mm was associated with a fourfold increase in the risk of concurrent EC. Preoperative transvaginal ultrasound may thus be useful for identifying patients at risk. Vetter et al. reported a fourfold increased risk with an ET ≥ 20 mm [19]. Abt et al. also found that preoperative ET ≥ 20 mm was associated with a twofold increase in EC risk on final pathology (RR 2.0, 95% CI: 1.3–2.9) [25]. In a 2024 study, Shree et al. identified ET ≥ 9 mm as predictive of malignancy (OR: 3.13, $p = 0.05$) [28]. Burrows et al. showed that patients with ET > 1.1 cm had a 6.1-fold increased likelihood of EC diagnosis (95% CI: 1.32–27.68) [31]. In contrast, Thongsang et al., in a 2025 study of 113 patients (36 with EC), found no significant difference in ET between groups, likely due to their smaller sample size [32].

Having surgery performed by a gynecologic oncologist is important for proper lymph node assessment in EIN patients. According to certain criteria, some of these patients may require lymph node dissection, which enables full surgical staging and helps guide the need for adjuvant therapy [19]. In our study, 44 (62%) of the patients diagnosed with EC met the Mayo Clinic criteria for lymphadenectomy. As all surgeries were performed by gynecologic oncologists, lymphadenectomy was performed during the same procedure, preventing the need for reoperation and facilitating timely referral for adjuvant treatment.

Recently, sentinel lymph node (SLN) mapping has emerged as an alternative to full lymphadenectomy to reduce surgical morbidity. An additional advantage of sentinel lymph node mapping is its ability to identify low-volume metastases, such as micrometastases or isolated tumor cells, through ultrastaging [33, 34]. However, there is no consensus on which EIN patients should undergo SLN mapping. In selected cases, SLN biopsy may provide useful information for adjuvant treatment planning [17, 30]. Rosati et al. reported that SLN biopsy provided prognostic and therapeutic information in 60.8% of cases with a 47.2% EC rate [35]. Bell et al. found SLN mapping to be more cost-effective than frozen section evaluation in patients with preoperative ET ≥ 20 mm [36]. Vieira-Serna et al. reported an SLN metastasis rate below 2% in patients undergoing surgery for EIN, suggesting that routine SLN mapping may not be necessary [37]. The question of which EIN patients should undergo SLN mapping remains open and requires further research. In our study, patients with ET ≥ 14 mm were more likely to meet Mayo criteria for high-risk disease, suggesting that these patients could be considered for SLN mapping.

Recent studies have demonstrated that, in cases of EIN, not only clinical features but also integrated histological parameters may play a significant role in predicting concurrent endometrial cancer. In a 2024 study, Raffone et al. showed that patients could be stratified into prognostically relevant groups based on histological characteristics. This approach suggests that preoperative evaluation can be informed not only by clinical data but also by histopathological findings. Combining clinical features with histological parameters may contribute to more individualized treatment planning [38].

In recent years, molecular classification has gained significant importance in determining prognosis and guiding adjuvant treatment in endometrial cancer. Risk stratification based on molecular markers such as p53 abnormal (p53abn), mismatch repair deficient (MMRd), Polymerase Epsilon (POLE) mutated, and non-specific molecular profile (NSMP) can help personalize

postoperative management. Although our study focused on preoperative clinical predictors, advanced risk assessment based on molecular classification may further enhance treatment planning in cases diagnosed with concurrent endometrial carcinoma [39].

Conclusion

There is ongoing debate regarding which patients diagnosed with EIN or AH should be referred to gynecologic oncology. In our study, age over 50 years, postmenopausal status, presence of diabetes and hypertension, BMI ≥ 35 kg/m², and endometrial thickness ≥ 14 mm were identified as strong predictors of concurrent endometrial cancer. Referral to gynecologic oncology should be considered for these patients, as they may require lymphadenectomy or sentinel lymph node dissection. This approach may help avoid the need for a second surgery and ensure timely initiation of adjuvant treatment when necessary.

Limitations

This study has several limitations. First, being conducted at a tertiary referral center may limit the generalizability of the findings to primary and secondary healthcare settings. In addition, the fact that all surgeries were performed by gynecologic oncology surgeons in a center where intraoperative frozen section analysis is routinely available may not reflect the standard practice in all institutions. To validate the results and assess their applicability to a broader patient population, multicenter prospective studies are needed.

Abbreviations

AH	Atypical Hyperplasia
BMI	Body Mass Index
EC	Endometrial Carcinoma
EIN	Endometrial Intraepithelial Neoplasia
ET	Endometrial Thickness
LND	Lymph Node Dissection
NLR	Neutrophil-to-Lymphocyte Ratio
PCOS	Polycystic Ovary Syndrome
PLR	Platelet-to-Lymphocyte Ratio
TVUS	Transvaginal Ultrasound

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Author contributions

Conceptualization: NÇÇ, HÖÇ, İTYData Collection: NÇÇ, MY, İYStatistical Analysis: NÇÇ, MY, GGManuscript Writing: NÇÇ, HÖÇCritical Review and Editing: NÇÇ GG, İTY, İYSupervision: NÇÇ, İTY, HÖÇAll authors reviewed and approved the final version of the manuscript.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Başakşehir Çam and Sakura City Hospital (Approval Number: E-96317027-514.10-263703971). According to Turkish legislation and the institutional ethics committee policies of our hospital, obtaining informed consent from patients is not required for retrospective studies.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

1. Emons G, Beckmann MW, Schmidt D, Mallmann P, Uterus commission of the Gynecological Oncology Working Group (AGO). New WHO classification of endometrial hyperplasias. Geburtshilfe Frauenheilkd. 2015;75(2):135–6. https://doi.org/10.1055/s-0034-1396256. PMID: 25797956; PMCID: PMC4361167.
2. Raffone A, Travaglino A, Saccone G, Insabato L, Mollo A, De Placido G, Zullo F. Endometrial hyperplasia and progression to cancer: which classification system stratifies the risk better? A systematic review and meta-analysis. Arch Gynecol Obstet. 2019;299(5):1233–42. https://doi.org/10.1007/s00404-019-05103-1. Epub 2019 Feb 27. PMID: 30810881.
3. Sanderson PA, Critchley HO, Williams AR, Arends MJ, Saunders PT. New concepts for an old problem: the diagnosis of endometrial hyperplasia. Hum Reprod Update. 2017;23(2):232–54. https://doi.org/10.1093/humupd/dmw042. PMID: 27920066; PMCID: PMC5850217.
4. Trimble CL, Kauderer J, Zaino R, Silverberg S, Lim PC, Burke JJ 2nd, Alberts D, Curtin J. Concurrent endometrial carcinoma in women with a biopsy diagnosis of atypical endometrial hyperplasia: a Gynecologic Oncology Group study. Cancer. 2006;106(4):812-9. https://doi.org/10.1002/cncr.21650. PMID: 16400639.
5. Wise MR, Gill P, Lensen S, Thompson JM, Farquhar CM. Body mass index Trumps age in decision for endometrial biopsy: cohort study of symptomatic premenopausal women. Am J Obstet Gynecol. 2016;215(5):598.e1-598.e8 https://doi.org/10.1016/j.ajog.2016.06.006. Epub 2016 Jun 8. PMID: 27287687.
6. Giannella L, Paganelli S. Abnormal uterine bleeding in premenopausal women and the role of body mass index. Am J Obstet Gynecol. 2017;216(5):533. https://doi.org/10.1016/j.ajog.2016.12.012. Epub 2016 Dec 19. PMID: 28007435.
7. Clark TJ, Mann CH, Shah N, Khan KS, Song F, Gupta JK. Accuracy of outpatient endometrial biopsy in the diagnosis of endometrial cancer: a systematic quantitative review. BJOG. 2002;109(3):313– 21. https://doi.org/10.1111/j.1471-0528.2002.01088.x. PMID: 11950187.
8. Restaino S, Paglietti C, Arcieri M, Biasioli A, Della Martina M, Mariuzzi L, Andreetta C, Titone F, Bogani G, Raimondo D, Perelli F, Buda A, Petrillo M, Greco P, Ercoli A, Fanfani F, Scambia G, Driul L, Vizzielli G. The Udine hospital Gynecological-Oncological tumor board group. Management of patients diagnosed with endometrial cancer: comparison of guidelines. Cancers (Basel). 2023;15(4):1091. https://doi.org/10.3390/cancers15041091. PMID: 36831434; PMCID: PMC9954548.
9. Restaino S, Buda A, Puppo A, Capozzi VA, Sozzi G, Casarin J, Gallitelli V, Murgia F, Vizzielli G, Baroni A, Corrado G, Pasciuto T, Ferrari D, Novelli A, Berretta R, Legge F, Vizza E, Chiantera V, Ghezzi F, Landoni F, Scambia G, Fanfani F. Anatomical distribution of sentinel lymph nodes in patients with endometrial cancer: a multicenter study. Int J Gynecol Cancer. 2022;32(4):517–524. https://doi.org/10.1136/ijgc-2021-003253. PMID: 35110375.
10. The American College of Obstetricians and Gynecologists Committee Opinion no. 631. Endometrial intraepithelial neoplasia. Obstet Gynecol.

2015;125(5):1272–1278. https://doi.org/10.1097/01.AOG.0000465189.50026.20. PMID: 25932867.
11. Management of Endometrial Intraepithelial Neoplasia or Atypical Endometrial Hyperplasia: ACOG Clinical Consensus No. 5. Obstet Gynecol. 2023;142(3):735–744. https://doi.org/10.1097/AOG.0000000000005297. PMID: 37590985.
12. Concin N, Matias-Guiu X, Vergote I, Cibula D, Mirza MR, Marnitz S, Ledermann J, Bosse T, Chargari C, Fagotti A, Fotopoulou C, Gonzalez Martin A, Lax S, Lorusso D, Marth C, Morice P, Nout RA, O'Donnell D, Querleu D, Raspollini MR, Sehouli J, Sturdza A, Taylor A, Westermann A, Wimberger P, Colombo N, Planchamp F, Creutzberg CL. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. Int J Gynecol Cancer. 2021;31(1):12–39. https://doi.org/10.1136/ijgc-2020-002230. Epub 2020 Dec 18. PMID: 33397713.
13. Arcieri M, Paparcura F, Giorgiutti C, Taliento C, Bogani G, Driul L, Greco P, Ercoli A, Chiantera V, Fanfani F, Fagotti A, Scambia G, Mariani A, Restaino S, Vizzielli G. Robotic surgery in severely obese frail patients for the treatment of atypical endometrial hyperplasia and endometrial cancer: A Propensity-Match analysis at an ESGO-Accredited center. Cancers (Basel). 2025;17(3):482. https://doi.org/10.3390/cancers17030482. PMID: 39941849; PMCID: PMC11815858.
14. Reed SD, Voigt LF, Newton KM, Garcia RH, Allison HK, Epplein M, Jordan D, Swisher E, Weiss NS. Progestin therapy of complex endometrial hyperplasia with and without atypia. Obstet Gynecol. 2009;113(3):655–62. https://doi.org/10.1097/AOG.0b013e318198a10a. PMID: 19300331; PMCID: PMC2680496.
15. Gallos ID, Shehmar M, Thangaratinam S, Papapostolou TK, Coomarasamy A, Gupta JK. Oral progestogens vs levonorgestrel-releasing intrauterine system for endometrial hyperplasia: a systematic review and metaanalysis. Am J Obstet Gynecol. 2010;203(6):547.e1-10. https://doi.org/10.1016/j.ajog.2010.07.037. PMID: 20934679.
16. Attard Montalto S, Coutts M, Devaja O, Summers J, Jyothirmayi R, Papadopoulos A. Accuracy of frozen section diagnosis at surgery in pre- malignant and malignant lesions of the endometrium. Eur J Gynaecol Oncol. 2008;29(5):435–40. PMID: 19051807.
17. Restaino S, Arcieri M, Vizzielli G et al. Correspondence on 'Sentinel lymph node assessment in patients with atypical endometrial hyperplasia: a systematic review and meta-analysis' by Vieira-Serna. Int J Gynecol Cancer. 2024;34(4):656. https://doi.org/10.1136/ijgc-2024-005294. PMID: 38471675.
18. Touhami O, Grégoire J, Renaud MC, Sebastianelli A, Grondin K, Plante M. The utility of Sentinel lymph node mapping in the management of endometrial atypical hyperplasia. Gynecol Oncol. 2018;148(3):485–90. https://doi.org/10.1016/j.ygyno.2017.12.026. Epub 2017 Dec 28. PMID: 29290489.
19. Vetter MH, Smith B, Benedict J, Hade EM, Bixel K, Copeland LJ, Cohn DE, Fowler JM, O'Malley D, Salani R, Backes FJ. Preoperative predictors of endometrial cancer at time of hysterectomy for endometrial intraepithelial neoplasia or complex atypical hyperplasia. Am J Obstet Gynecol. 2020;222(1):60.e1-60.e7. https://doi.org/10.1016/j.ajog.2019.08.002. Epub 2019 Aug 8. PMID: 31401259; PMCID: PMC7201377..
20. Matsuo K, Ramzan AA, Gualtieri MR, Mhawech-Fauceglia P, Machida H, Moeini A, Dancz CE, Ueda Y, Roman LD. Prediction of concurrent endometrial carcinoma in women with endometrial hyperplasia. Gynecol Oncol. 2015;139(2):261–7. https://doi.org/10.1016/j.ygyno.2015.07.108. Epub 2015 Aug 1. PMID: 26238457; PMCID: PMC7521604.
21. Suh-Burgmann E, Hung YY, Armstrong MA. Complex atypical endometrial hyperplasia: the risk of unrecognized adenocarcinoma and value of preoperative dilation and curettage. Obstet Gynecol. 2009;114(3):523–529. https://doi.org/10.1097/AOG.0b013e3181b190d5. PMID: 19701030.
22. Erdem B, Aşıcıoğlu O, Seyhan NA, Peker N, Ülker V, Akbayır Ö. Can concurrent high-risk endometrial carcinoma occur with atypical endometrial hyperplasia? Int J Surg. 2018;53:350–3. https://doi.org/10.1016/j.ijsu.2018.04.019. Epub 2018 Apr 14. PMID: 29665453.
23. Giannella L, Grelloni C, Bernardi M, Cicoli C, Lavezzo F, Sartini G, Natalini L, Bordini M, Petrini M, Petrucci J, Terenzi T, Delli Carpini G, Di Giuseppe J, Ciavattini A. Atypical endometrial hyperplasia and concurrent cancer: A comprehensive overview on a challenging clinical condition. Cancers (Basel). 2024;16(5):914. https://doi.org/10.3390/cancers16050914. PMID: 38473276; PMCID: PMC10930610.
24. Taşkın S, Kan Ö, Dai Ö, Taşkın EA, Koyuncu K, Alkılıç A, Güngör M, Ortaç F. Lymph node dissection in atypical endometrial hyperplasia. J Turk Ger Gynecol Assoc. 2017;18(3):127–32. https://doi.org/10.4274/jtgga.2017.0043. PMID: 28890426; PMCID: PMC5590208.
25. Abt D, Macharia A, Hacker MR, Baig R, Esselen KM, Ducie J. Endometrial stripe thickness: a preoperative marker to identify patients with endometrial intraepithelial neoplasia who may benefit from sentinel lymph node mapping and biopsy. Int J Gynecol Cancer. 2022;32(9):1091–1097. https://doi.org/10.1136/ijgc-2022-003521. PMID: 35868657.
26. Giannella L, Delli Carpini G, Sopracordevole F, Papiccio M, Serri M, Giorda G, Tsiroglou D, Del Fabro A, Ciavattini A. Atypical endometrial hyperplasia and unexpected cancers at final histology: A study on endometrial sampling methods and risk factors. Diagnostics (Basel). 2020;10(7):474. https://doi.org/10.3390/diagnostics10070474. PMID: 32668563; PMCID: PMC7400146.
27. Onstad MA, Schmandt RE, Lu KH. Addressing the role of obesity in endometrial Cancer risk, prevention, and treatment. J Clin Oncol. 2016;34(35):4225–30. https://doi.org/10.1200/JCO.2016.69.4638. Epub 2016 Nov 7. PMID: 27903150; PMCID: PMC5455320.
28. Shree Ca P, Garg M, Bhati P, Sheejamol VS. Should we prioritise proper surgical staging for patients with Atypical endometrial hyperplasia (AEH)? Experience from a single-institution tertiary care oncology centre. Eur J Obstet Gynecol Reprod Biol. 2024;303:1–8. https://doi.org/10.1016/j.ejogrb.2024.09.044. Epub 2024 Oct 3. PMID: 39393131.
29. Giannella L, Piva F, Delli Carpini G, Di Giuseppe J, Grelloni C, Giulietti M, Sopracordevole F, Giorda G, Del Fabro A, Clemente N, Gardella B, Bogani G, Brasile O, Martinello R, Caretto M, Ghelardi A, Albanesi G, Stevenazzi G, Venturini P, Papiccio M, Cannì M, Barbero M, Fambrini M, Maggi V, Uccella S, Spinillo A, Raspagliesi F, Greco P, Simoncini T, Petraglia F, Ciavattini A. Concurrent endometrial Cancer in women with atypical endometrial hyperplasia: what is the predictive value of patient characteristics?? Cancers (Basel). 2023;16(1):172. https://doi.org/10.3390/cancers16010172. PMID: 38201599; PMCID: PMC10778118.
30. Liang F, Xin W, Yang S, Wang H. Nomogram for predicting pathology upstaging in patients with EIN: is Sentinel lymph node assessment useful in these patients? J Gynecol Oncol. 2025;36(1):e1. https://doi.org/10.3802/jgo.2025.36.e1. Epub 2024 Jun 10. PMID: 38872479; PMCID: PMC11790994.
31. Burrows A, Pudwell J, Bougie O. Preoperative factors of endometrial carcinoma in patients undergoing hysterectomy for atypical endometrial hyperplasia. J Obstet Gynaecol Can. 2021;43(7):822–30. https://doi.org/10.1016/j.jogc.2021.03.009. Epub 2021 Mar 27. PMID: 33785467.
32. Thongsang W, Kuljarusnont S, Hanamornroongruang S, Ruengkhachorn I. Prevalence of occult endometrial carcinoma in patients with endometrial intraepithelial neoplasia who underwent hysterectomy. World J Surg Oncol. 2025;23(1):24. https://doi.org/10.1186/s12957-025-03677-6. PMID: 39856725; PMCID: PMC11763159.
33. De Vitis LA, Fumagalli D, Schivardi G, Capasso I, Grcevich L, Multinu F, Cucinella G, Occhiali T, Betella I, Guillot BE, Pappalettera G, Shahi M, Fought AJ, McGree M, Reynolds E, Colombo N, Zanagnolo V, Aletti G, Langstraat C, Mariani A, Glaser G. Incidence of sentinel lymph node metastases in apparent early-stage endometrial cancer: a multicenter observational study. Int J Gynecol Cancer. 2024;34(5):689–696. https://doi.org/10.1136/ijgc-2023-005173. PMID: 38514100.
34. Cucinella G, Di Donna MC, Casarin J, Schivardi G, Multinu F, Borsellino L, Buono N, Zaccaria G, Abbate A, Laganà AS, Chiantera V. Lower limb lymphedema after surgical staging for endometrial cancer: Current insights and future directions. Taiwan J Obstet Gynecol. 2024;63(4):500–505. https://doi.org/10.1016/j.tjog.2024.04.008. PMID: 39004476.
35. Rosati A, Vargiu V, Capozzi VA, Giannarelli D, Palmieri E, Baroni A, Perrone E, Berretta R, Cosentino F, Scambia G, Fanfani F. Concurrent endometrial cancer in atypical endometrial hyperplasia and the role of sentinel lymph nodes: clinical insights from a multicenter experience. Int J Gynecol Cancer. 2024;34(7):1011–1019. https://doi.org/10.1136/ijgc-2023-005202. PMID: 38431287.
36. Bell S, Smith K, Kim H, Orellana T, Harinath L, Rush S, Olawaiye A, Lesnock J. Hysterectomy with sentinel lymph node dissection in the setting of preoperative endometrial intraepithelial neoplasia and an endometrial stripe ≥ 20 mm: a cost-effectiveness analysis. Int J Gynecol Cancer. 2024;34(12):1898–1905. https://doi.org/10.1136/ijgc-2024-005658. PMID: 39107049.
37. Vieira-Serna S, Peralta J, Viveros-Carreño D, Rodriguez J, Feliciano-Alfonso JE, Pareja R. Sentinel lymph node assessment in patients with atypical endometrial hyperplasia: a systematic review and meta-analysis. Int J Gynecol Cancer. 2024;34(1):66–72. https://doi.org/10.1136/ijgc-2023-004936. PMID: 37973363.
38. Raffone A, Insabato L, Raimondo D, Del Piano I, Ricciardiello M, Cretella P, Neola D, Arciuolo D, Santoro A, Seracchioli R, Guida M, Travaglino A, Zannoni GF. Integrated histological parameters define prognostically relevant groups in atypical endometrial hyperplasia/endometrioid intraepithelial neoplasia.

Int J Gynecol Cancer. 2024;34(8):1183–8. https://doi.org/10.1136/ijgc-2024-005367. PMID: 38719279.

39. Arcieri M, Vizzielli G, Occhiali T, Giorgiutti C, Tius V, Pregnolato S, Mariuzzi L, Orsaria M, Tulisso A, Damante G, D'Elia AV, Cucinella G, Chiantera V, Fanfani F, Ercoli A, Driul L, Scambia G, Restaino S. Application of novel algorithm on a retrospective series to implement the molecular classification for endometrial cancer. Eur J Surg Oncol. 2024;50(7):108436. https://doi.org/10.1016/j.ejso.2024.108436. Epub 2024 May 23. PMID: 38820923.

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