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Clinical utility of sentinel lymph node biopsy in atypical endometrial hyperplasia: A multicenter cohort study

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HIGHLIGHTS

- 47% of preoperative atypical hyperplasia cases had occult endometrial cancer (EC).
- Sentinel Lymph Node (SLN) biopsy detected 4.7% nodal metastases in occult EC.
- SLN assessment guided adjuvant therapy in 50% of treated EC in the SLN cohort.
- Beyond metastasis detection, SLN biopsy may refine staging and treatment decisions.

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ABSTRACT

Objective. To evaluate the clinical impact of Sentinel Lymph Node (SLN) biopsy in women with preoperative diagnosis of Atypical Endometrial Hyperplasia/Endometrial Intraepithelial Neoplasia (AEH/EIN), focusing on surgical safety and feasibility and adjuvant treatment decisions.

Methods. Multicenter retrospective study which included 411 patients with preoperative diagnosis of AEH/EIN who underwent total hysterectomy between 2014 and 2025. Demographic, preoperative, surgical, pathological and adjuvant treatment data were collected from prospectively maintained databases and outcomes were compared between patients who underwent SLN biopsy and those who did not. Descriptive statistics were used.

Results. Occult endometrial cancer (EC) was diagnosed in 47% of overall patients at final pathology; of whom 16% was classified within the intermediate to high-risk cases. SLN mapping was associated with slightly longer operative time. SLN metastases were found in 4.7% of patients with EC. SLN assessment modified treatment decisions in 11 of 22 patients (50%) receiving adjuvant therapy within the SLN cohort. Positive SLN findings led to chemotherapy escalation in 5 patients, while negative SLN status supported chemotherapy omission in 6 high to intermediate risk cases. No patients in the non-SLN group received chemotherapy.

Conclusion. SLN biopsy in AEH/EIN is a feasible and safe procedure that provides staging information in the subgroup with occult EC. Regardless of metastasis frequency, SLN status provides actionable prognostic information. Whether positive or negative, SLN findings refine risk stratification and may guide the escalation or de-escalation of adjuvant therapy, supporting the consideration of SLN biopsy in AEH/EIN patients.

1. Introduction

Accurate surgical staging by total hysterectomy with bilateral adnexectomy and lymph node assessment is crucial to guide postoperative management in endometrial cancer (EC) patients [1–3]. For this

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purpose, sentinel lymph node (SLN) biopsy has emerged as a less invasive alternative to systematic pelvic lymphadenectomy. This technique offers high sensitivity and negative predictive value for nodal metastasis with minimal surgical morbidity, which allowed recommending this technique in all apparently early-stage EC [4–6].

Atypical endometrial hyperplasia, also known as endometrial intraepithelial neoplasia (AEH/EIN), is a precursor of endometrioid EC. When preoperatively diagnosed, AEH/EIN has been associated with a 36–44% risk of concurrent EC on final pathology and up to a 29% risk of progression to invasive EC if untreated [1,7–9]. Among these patients with a postoperative diagnosis of EC, most have low-risk, early-stage disease; however, a non-negligible minority presents with intermediate- to high-risk features [8,10]. On this basis, a growing body of literature is investigating the use of SLN biopsy even in patients with preoperative AEH/EIN, with complication rates and operative times comparable to hysterectomy alone [11–13]. Nonetheless, International Guidelines still do not currently recommend SLN biopsy as a standard surgical procedure in case of preoperative AEH/EIN diagnosis. The main reason is that the overall incidence of nodal metastasis in women with preoperative diagnosis of AEH/EIN and occult EC is approximately 2% [14].

To further investigate the role of SLN biopsy in patients with AEH/EIN, we performed a retrospective multicenter study to assess its clinical impact in these patients. Indeed, the purpose of SLN biopsy is not simply the identification of metastasis but providing a global information on the lymph node status regardless of whether positive or negative. Therefore, in addition to investigate surgical safety and diagnostic accuracy of SLN biopsy in AEH/EIN, we specifically assessed in which extend the information of lymph node status provided by SLN biopsy in these patients guided the subsequent management, particularly focusing on the adjuvant treatment choice.

2. Methods

This multicenter, retrospective, study was conducted in Italy at the University Hospital of Verona, the National Institute of Tumor (INT) of Milan, the St. Chiara Hospital of Trento, the St Croce and Carle Hospital of Cuneo and the University Hospital of Varese. We retrospectively reviewed the prospectively maintained registers of gynecologic oncologic cases treated at the five study centers between January 2014 and February 2025. Adult (≥ 18 years) patients with a preoperative diagnosis of AEH/EIN on endometrial sampling who underwent total hysterectomy were identified and included regardless of the final pathology (i.e., EC, AEH/EIN, or benign histology).

Data on patient demographics, medical history, preoperative assessment, operative details, final pathology, and adjuvant treatment were extracted from the prospectively maintained registers and the medical records by trained investigators. Extracted data were collected in an anonymized database. Intraoperative and postoperative complications were summarized using the Clavien-Dindo classification. EC cases were classified into low-, intermediate-, high to intermediate-, and high-risk groups according to the ESGO/ESTRO/ESP Endometrial Guidelines available at the time of surgery.

The study was approved by the Institutional Review Board of all study centers, and written informed consent for collecting and using data for research purposes was obtained from all patients.

2.1. Statistical analysis

Demographic characteristics, peri- and operative details and final pathological outcomes were compared between patients who underwent SLN biopsy and those who did not, both in the overall cohort and in the subgroup with EC at final pathology. In the EC subgroup, we additionally compared adjuvant treatment patterns between patients who underwent SLN biopsy and those who did not.

Descriptive statistics were used to summarize the characteristics of the study cohort as appropriate. Comparisons between continuous variables were performed using the Wilcoxon rank-sum test; categorical variables were compared using the $\chi 2$ test or Fisher's exact test, as appropriate. A two-tailed p-value <0.05 was deemed statistically significant. Associations with binary outcomes were examined using univariable and multivariable logistic regression, with results expressed as odds ratios (ORs) and 95% confidence intervals (CIs).

3. Results

A total of 411 women with a preoperative diagnosis of AEH/EIN underwent total hysterectomy at one of the five study centers between January 2014 and February 2025 (Table 1). Occult EC was diagnosed in 47% of patients, with a higher incidence in the SLN group (53% vs 38%). SLN mapping was performed in 239 patients (58%). Those who underwent SLN mapping were older (median age 61 vs 58 years), and myometrial infiltration was more frequently suspected on preoperative imaging in the SLN group, regardless of final pathology (Table 2). In the EC subgroup, no statistically significant differences were observed in preoperative findings between the two cohorts of patients. (Table 4).

3.1. Surgical outcomes and SLN assessment

Among all patients, 68% underwent minimally invasive approach by conventional laparoscopy (LPS), with robot-assisted LPS implemented in 99 cases of the SLN cohort. Operative time was slightly longer when the SLN mapping was performed (138.5 vs 109.5 min, $p < 0.05$), while estimated blood loss (EBL) and length of stay did not differ ($p = 0.05$ and $p = 0.06$, respectively) (Table 3). Intraoperative complications were observed in 0.8% of cases in the SLN group vs 0.6% in those who did not undergo the SLN assessment ($p > 0.99$). Similarly, no differences were observed in early (7.5% vs 5.2%, $p = 0.2$) and late postoperative complications (<1% in both cohorts, $p > 0.99$), which were mostly Clavien–Dindo grade I–II. For patients who underwent SLN mapping, early postoperative complications included isolated cardiologic events, minor bleeding or hematomas, vaginal cuff dehiscence, urinary tract infection, and fever. Only two cases required repeat surgery for hemoperitoneum, and one patient developed sepsis, all of which resolved with appropriate treatment. None of these complications were related to the SLN procedure. Postoperative complications in the

Table 1
Overall population's baseline characteristics.

Characteristics – Total population (N = 411)	Mean/N (%)
Age	58 (30–93)
⁻BMI	29 (16–55)
AEH/EIN* – surgical indication	
Yes	411 (100%)
No	0 (0%)
Preoperative endometrial thickness	10 (1–51)
Surgical approach	
ΩLPS	279 (68%)
Robot – assisted	112 (27%)
Vaginal	4 (1%)
©LPT	16 (4%)
Final pathology report	
Bening	22 (5%)
Hyperplasia without atypia	38 (9%)
*AEH/EIN	158 (39%)
¶EC	193 (47%)
SLN procedure	
No	172 (42%)
Yes	239 (58%)
SLN pathology analysis N = 219	
Ultra staging	194 (89%)
ᵅOSNA	4 (2%)
ΣN.d.	21 (9%)

*AEH/EIN: Atypical Endometrial Hyperplasia/Endometrial Intraepithelial Neoplasia; ¶EC: Endometrial Cancer; SLN: Sentinel Lymph Node; ᴬOSNA: One Step Nucleic Acid Amplification; ΣN.d: not determined, ΩLPS: Laparoscopy, ©LPT: Laparotomy, ⁻BMI: Body Mass Index.

Table 2
Pre – operative assessment divided per procedure performed.

Characteristics	SLN not performed (N = 172)	SLN performed (N = 239)	P
Age	58 (30–93)	61 (30–93)	**<0.05**
±BMI (Kg/m^2)	31 (16–55)	29 (16–55)	0.152
Endometrial thickness (mm)	11.3 (1–51)	12.3 (1–51)	0.805
n.d.	27	9	
Endometrial aspect			0.061
Homogeneous	44 (26%)	57 (24%)	
Inhomogeneous	61 (35%)	125 (52%)	
Polyp	42 (24%)	50 (21%)	
n.d.	25 (15%)	7 (3%)	
*Myometrial infiltration			**<0.05**
Yes	5 (3%)	29 (12%)	
No	144 (84%)	204 (85%)	
Σn.d	23 (13%)	6 (3%)	

±BMI: Body Mass Index, *At imaging, Σn.d, ±SLN: Sentinel Lymph Node.

non-SLN group were mainly minor and conservatively managed, including isolated febrile episodes, small pelvic or abdominal collections, and superficial wound dehiscence. Two patients required surgical reintervention, one for a pelvic collection causing ureteral compression and another for adhesive bowel obstruction, both with favorable recovery. We registered one late postoperative complication that consisted of a vesical-vaginal fistula requiring surgical repair.

Among the 239 patients who underwent SLN mapping, the overall SLN detection rate (DR) was 94% at the patient level, with successful bilateral and unilateral mapping in 87% and 13% of cases, respectively. Empty node packets were reported in 1.3% cases. Indocyanine green (ICG) was used as the primary tracer in 98% of procedures. SLN mapping was performed via intracervical injection of 2 mL of ICG in 98% of procedures, administered both deeply and superficially. No side-specific lymphadenectomy was performed when mapping was unsuccessful.

3.2. Definitive pathology

After hysterectomy, low-grade early stage endometrioid EC was the most frequent subtype, with comparable distributions of histology and clinicopathologic features between the two cohorts (Table 4). Low-risk disease, according to the risk stratification system available at the time of surgery, was predominant in both patient cohorts, with a similar incidence of intermediate- and high to intermediate risk groups. No high-risk patients were identified in the non-SLN group compared to 5.5% among those who underwent SLN biopsy.

The vast majority of SLN specimens were analyzed with ultra-staging protocol. Nodal metastases were identified in 4.7% of EC cases undergoing SLN biopsy, corresponding to 2.7% of the overall AEH/EIN cohort. Detected metastases included three macro metastases, two micro metastases, and one isolated tumor cell (ITC) Table 3.

3.3. Adjuvant treatment

Overall, 32 patients received adjuvant therapy, which was administered to 22 cases out of 126 (17%) in the SLN cohort and in 10 cases out of 67 (15%) in the non–SLN group (Table 4).

Adjuvant treatment modalities included: chemotherapy ($n = 7$), external beam radiation therapy (EBRT, $n = 9$), brachytherapy (BT, $n = 13$) and EBRT + BT ($n = 3$), with no significant difference in treatment distribution between patients who underwent SLN biopsy and those who did not (Table 4).

To assess whether SLN biopsy impacted treatment decisions, we compared adjuvant chemotherapy rates between the two cohorts of patients. Within the SLN group, 7 patients received chemotherapy, whereas none of the 67 patients without SLN biopsy received systemic therapy ($p = 0.06$).

Table 3
Surgical details divided per procedure performed.

Characteristics	SLN not performed (N = 172)	SLN performed (N = 239)	P
Surgery performed			**<0.05**
ΩLPS	145 (84%)	135 (57%)	
Robot – assisted	13 (8%)	99 (41%)	
Vaginal	3 (2%)	0 (0%)	
©LPT	11 (6%)	5 (2%)	
Other procedures performed			0.459
μPLD mono-lateral	0 (0%)	2 (0.8%)	
PLD bilateral	4 (2%)	1 (0.4%)	
βPALD	0 (0%)	1 (0.4%)	
Omentectomy	0 (0%)	1 (0.4%)	
None	168 (98%)	234 (98%)	
Operative time	109.5	138.5	**<0.05**
Estimated Blood Loss	45 (0–500)	50 (0–500)	**0.053**
Intraoperative complications			>0.99
Yes	1 (0.6%)	2 (0.8%)	
No	171 (99.4%)	237 (99.2%)	
Early post-operative complications (<30 days)			0.276
Yes	9 (5.2%)	18 (7.5%)	
No	163 (94.8%)	220 (92.1%)	
Σn.d	0 (0%)	1 (0.4%)	
Late post-operative complications (>30 days)			>0.99
Yes	1 (0.6%)	1 (0.4%)	
No	167 (97.1%)	236 (99%)	
n.d.	4 (2.3%)	2 (0.6%)	
Clavien Dindo (post-operative complications N = 19)			0.342
I	2 (20%)	2 (11%)	
II	4 (40%)	13 (68%)	
III	3 (30%)	3 (16%)	
IV	1 (10%)	1 (5%)	
Post operative length of stay	3 (1–56)	3 (1−32)	0.06
Definitive histology			**<0.05**
αAEH/EIN	75 (44%)	83 (34%)	
Benign	27 (16%)	19 (8%)	
ΠEC	67 (38%)	126 (53%)	
n.d.	3 (2%)	11 (5%)	
SLN mapping			N/A
Yes		224 (94%)	
No		15 (6%)	
n.d.		0 (0%)	
Type of tracer			N/A
∞ICG		235 (98%)	
Methylen blue		4 (2%)	
n.d.		0 (0%)	
SLN mapping pattern (N = 224)			N/A
Mono-lateral		29 (13%)	
Bilateral		195 (87%)	
n.d.		0 (0%)	
Empty packet (N = 224)			N/A
Yes		3 (1.3%)	
No		220 (98.2%)	
n.d.		1 (0.5%)	
SLN involvement (N = 224)			N/A
Yes		6 (2.7%)	
No		218 (97.3%)	
Type of metastasis (N = 6)			N/A
ʃITC		1 (17%)	
Micro		2 (33%)	
Macro		3 (50%)	

*NA: not applicable, ±SLN: Sentinel Lymph Node, ΩLPS: Laparoscopy, ©LPT: Laparotomy, μPLD: Pelvic Lymph node Dissection, βPALD: Para-aortic Lymph node Dissection, ΣN.d: not determined, ΠEC: Endometrial Cancer, α AEH/EIN: Atypical Endometrial Hyperplasia/Endometrial Intraepithelial Neoplasia, ∞ ICG: Indyocianine green, ʃITC: isolated tumor cells.

Among patients who underwent SLN biopsy, treatment escalation occurred in 5 of 22 patients (23%), who received chemotherapy exclusively based on positive SLN findings. Two additional patients received chemotherapy based on high-risk characteristics, irrespective of nodal assessment. Conversely, 6 high to intermediate risk patients received

Table 4
Endometrial cancer features and adjuvant treatment modalities.

Characteristics	EC* - SLN not performed (N = 67)	EC - SLN performed (N = 126)	P
Age	58 (30–93)	58 (30–93)	0.46
±BMI (Kg/m^2)	29 (16–55)	29 (16–55)	0.74
Endometrial thickness (mm)	10 (1–51)	12.3 (1–51)	0.9
n.d.	6	9	
Endometrial aspect			0.288
Homogeneous	12 (18%)	18 (14%)	
nhomogeneous	32 (48%)	80 (63%)	
Polyp	17 (25%)	26 (21%)	
n.d.	6 (9%)	2 (2%)	
~Myometrial infiltration			0.068
Yes	4 (6%)	20 (16%)	
No	58 (87%)	104 (82%)	
Σn.d	5 (7%)	2 (2%)	
Histological subtype			0.546
Endometrioid	66 (99%)	124 (98%)	
Other	0 (0%)	2 (2%)	
°n.d.	1 (1%)	0 (0%)	
Histological grading			0.166
G1	48 (72%)	82 (65%)	
G2	18 (27%)	39 (31%)	
G3	0 (0%)	5 (4%)	
n.d.	1 (1%)	0 (0%)	
ϛLVSI involvement			0.338
Yes	2 (3%)	9 (7%)	
No/focal	63 (94%)	117 (93%)	
n.d.	2 (3%)	0 (0%)	
Myometrial invasion			0.995
No	33 (49%)	64 (51%)	
<50%	22 (33%)	44 (35%)	
≥50%	9 (13%)	18 (14%)	
n.d.	3 (5%)	0 (0%)	
Cervical stromal invasion			1.00
Yes	2 (3%)	3 (2.4%)	
No	62 (92.5%)	123 (97.6%)	
n.d.	3 (4.5%)	0 (0%)	
P53 abnormal			0.567
Yes	0 (0%)	3 (2%)	
No	29 (43%)	80 (64%)	
n.d.	38 (57%)	43 (34%)	
§MSI			1.00
Yes	4 (6%)	12 (10%)	
No	28 (42%)	72 (57%)	
n.d.	35 (52%)	42 (33%)	
POLe mutant			>1.00
Yes	2 (3%)	33 (26%)	
No	10 (15%)	1 (1%)	
n.d.	55 (82%)	92 (73%)	
FIGO stage 2009			0.459
IA	50 (75%)	105 (83%)	
IB	7 (10%)	13 (10%)	
II	2 (3%)	3 (3%)	
IIIB	0 (0%)	0 (0%)	
IIIC1	0 (0%)	5 (4%)	
IIIC2	0 (0%)	0 (0%)	
IV	0 (0%)	0 (0%)	
n.d.	8 (12%)	0 (0%)	
Risk group – molecular classification unknown			0.252
Low	50 (74.5%)	104 (83%)	
Intermediate	6 (9%)	8 (6%)	
High to Intermediate	3 (4.5%)	7 (5.5%)	
High	0 (0%)	7 (5.5%)	
n.d.	8 (12%)	0 (0%)	
Adjuvant therapy			1
No	49 (73%)	104 (83%)	
Yes	10 (15%)	22 (17%)	
n.d.	8 (12%)	0 (0%)	
Type of adjuvant therapy			
CHT[1]	0 (0%)	7 (32%)	0.06
EBRT[2]	3 (30%)	6 (27%)	0.208
BT[3]	6 (60%)	7 (32%)	
EBRT + BT	1 (10%)	2 (9%)	

EC*: Endometrial cancer, ~ preoperative findings, SLN: Sentinel Lymph node, °n.d.: not determined, ϛLVSI: Lymph vascular space invasion, §MSI: Microsatellite instability, CHT[1]: Chemotherapy, EBRT[2]: External Beam Radiation Therapy, BT[3]: Brachytherapy.

Table 5
Pre-operative predictors of concurrent endometrial cancer (EC) after surgery.

Variable	Univariable OR (95% CI)	P	Multivariable OR (95% CI)	P
*BMI	1.01 (0.98–1.04)	0.71		
Suspected myometrial invasion	2.52 (1.20–5.67)	**0.018**	1.63 (0.73–3.85)	0.25
Endometrial thickness	1.04 (1.01–1.07)	**0.010**	1.02 (0.98–1.05)	0.25
Endometrial aspect				
Non homogeneus	3.32 (1.96–5.71)	**<0.05**	2.75 (1.57–4.91)	**<0.05**
Polyp	1.92 (1.05–3.55)	**<0.05**	1.76 (0.93–3.36)	0.082

*BMI: Body Mass Index.

adjuvant therapy without chemotherapy following negative SLN results. Overall, SLN assessment modified adjuvant treatment allocation in 11 of 22 patients (50%). This corresponded to 9% of all EC patients undergoing SLN biopsy (11/126) and 6% of the overall EC population (11/193). In the non-SLN cohort, 3 high to intermediate risk patients received adjuvant therapy without chemotherapy, despite meeting guideline-based criteria for chemotherapy consideration.

3.4. Predictors of occult EC and SLN involvement

Univariable analysis identified endometrial thickness, non-homogeneous endometrium, suspected endometrial polyp, and suspected myometrial invasion on preoperative imaging as predictors of occult EC at final pathology. However, in the multivariable model, only a non-homogeneous endometrium was an independent risk factor for occult EC ($p < 0.05$) Table 5.

No preoperative factors were identified as predictors of SLN involvement at univariable analysis. Regarding pathological variables, univariate analysis showed that high tumor grade, lymph-vascular space invasion (LVSI), and deep myometrial invasion were associated with nodal metastasis ($p < 0.05$). In contrast, tumor diameter on final pathology demonstrated a borderline association ($p = 0.05$). However, after multivariable adjustment, none of these variables retained independent significance ($p > 0.05$) Table 6.

4. Discussion

4.1. Summary of main results

In this large multicenter cohort, SLN biopsy in patients with preoperative AEH/EIN demonstrated high feasibility and safety, but more importantly provided clinically relevant information that influenced adjuvant treatment decisions in patients upstaged to EC. In our study, nearly half of patients with a preoperative diagnosis of AEH/EIN were found to have endometrial cancer following hysterectomy, and 16% of these cases were classified as intermediate- to high-risk disease. SLN mapping demonstrated high DR and safety, with a nodal metastasis rate of 4.7%. Beyond metastasis identification, SLN biopsy provided staging information, influencing adjuvant treatment decisions bidirectionally: chemotherapy escalation in the presence of positive SLN findings and omission of systemic therapy in selected high to intermediate risk patients with negative SLN results. The clinical value of SLN biopsy in this setting does not primarily lie in identifying nodal metastases, which remain infrequent, but in refining postoperative risk stratification and guiding treatment decisions. On the other hand, a substantial proportion of patients ultimately had benign pathology, raising concerns regarding potential overtreatment when SLN biopsy is systematically applied in AEH/EIN.

Table 6
Predictors of lymph node involvement.

Variable	Univariable OR (95% CI)	P	Multivariable OR (95% CI)	P
Pre-operative factors				
Age	0.95 (0.87–1.03)	0.27		
*BMI	0.85 (0.62–1.06)	0.22		
Preoperative endometrium thickness	0.98 (085–1.08)	0.77		
Post-operative factors				
Grading	7.83 (2.16–18.9)	**<0.05**	11.7 (0.74–15.12)	0.26
°LVSI	6.53 (2.64–35.9)	0.08		
Tumor diameter	1.06 (1–1.13)	0.05		
Postoperative myometrial invasion	8.64 (2.37–56)	**<0.05**	0.96 (0.80–1.07)	0.068

*BMI: Body Mass Index, °LVSI: Lymph vascular space invasion.

4.2. Results in the context of published literature

The 47% incidence of occult EC at final pathology in our AEH/EIN population aligns with published literature, reporting rates between 30% and 50% [15]. Consistent with previous studies, the majority of concurrent EC cases were low-grade (G1–2) early-stage endometrioid adenocarcinoma, with low-risk disease accounting for 80% of the entire EC population [16]. However, a non-negligible proportion of our patients (16%) presented with intermediate to high-risk features, comparable to reported rates of 3–36% in similar cohorts [17,18].

The high DR of SLN biopsy in our study, with no differences in complication rate compared to the non–nodal assessment cohort of patients, confirms the safety and feasibility of this procedure, as previously demonstrated in other studies [4,19,20]. However, as shown in the study by Bogani et al., performing SLN biopsy is statistically correlated with an increased operative time (109.5 min compared to 138.5 min), without a significant impact on length of hospital stay or estimated blood loss [21].

SLN metastasis rate was 4.7% within patients with concurrent EC who underwent SLN biopsy. This is consistent with Kim et al.'s report of 5.9% SLN positivity in G1-G2 endometrioid EC with <50% of myometrial invasion and falls within the expected range for predominantly low risk-disease of less than 3% [22].

Among the 239 patients who underwent SLN biopsy, 53% were upstaged to endometrial cancer at final diagnosis, whereas patients with definitive benign histology were potentially subjected to overtreatment.

In accordance with current Guidelines, SLN biopsy for staging purposes is recommended for all patients with a diagnosis of endometrial cancer, irrespective of their risk category [23]. Consequently, all 126 patients with a final diagnosis of EC in our cohort who underwent SLN biopsy were appropriately staged per contemporary standards. In contrast, the 67 patients with the same final histology who did not undergo SLN biopsy lacked complete nodal evaluation, potentially leading to suboptimal adjuvant treatment planning, including both over- and undertreatment [23].

Although the difference did not reach statistical significance, likely reflecting the small number of events, our findings demonstrate that SLN biopsy provided clinically relevant information beyond simple metastasis detection, informing individualized adjuvant treatment allocation. These results are consistent with those reported by Matanes et al., who, in a retrospective cohort of 162 patients with a preoperative diagnosis of EIN undergoing surgery with SLN mapping, found that 9.25% harbored intermediate-high or high-risk disease on final pathology, and that SLN status directly guided adjuvant treatment decisions, potentially avoiding surgical re-staging or empirical adjuvant therapy [1]. Conversely, among high to intermediate risk patients who did not undergo SLN biopsy, three cases meeting guideline-based criteria for chemotherapy consideration, based on stage II disease and substantial lymph vascular space invasion, did not receive systemic therapy. While exploratory, this observation may reflect the limitations of risk stratification in the absence of nodal assessment and suggests a potential risk of under-treatment [6].

Notably, the 2023 FIGO staging system has shifted EC classification to an integrated morpho-molecular model, including histological subtype, LVSI and molecular classification into stage assignment [24]. The 2025 ESGO/ESTRO/ESP Guidelines have subsequently adopted this staging system as the reference framework for risk stratification and adjuvant treatment decision – making. Within this evolving paradigm, lymph node assessment remains clinically relevant, as surgical staging retains independent prognostic significance across molecular subgroups [23,25]. Moreover, recent evidence has demonstrated substantial variability in lymph node involvement according to molecular subtype, ranging from 3.0% in POLE – mutated tumors to 16.5% in p53 abnormal tumors [26]. Importantly, lymph node status maintains direct implications for adjuvant treatment decision – making, complementing rather than being superseded by molecular classification [25]. Accordingly, these considerations may reinforce the rationale for performing SLN biopsy at the time of hysterectomy in patients with AEH/EIN, as occult EC cases will require accurate staging within the current molecular-anatomic framework, enabling more precise risk stratification and increasingly individualized adjuvant treatment strategies.

Importantly, omitting SLN biopsy eliminates the possibility of performing surgical staging through SLN biopsy, as uterine removal disrupts lymphatic channels required for the procedure itself. Consequently, nodal assessment can thereafter only be performed through bilateral pelvic lymphadenectomy, which carries a higher complication rate compared with SLN biopsy but becomes necessary for accurate postoperative risk stratification [27].

Consistent with previous studies, an inhomogeneous endometrial aspect emerged as an independent preoperative predictor of concurrent endometrial cancer in our cohort [17].

4.3. Strengths and weaknesses

This study benefits from its large, multicentric design and represents one of the most extensive series on this topic to date. However, several limitations should be acknowledged. First, the retrospective nature of the analysis could lead to indication bias. Indeed, SLN biopsy was more frequently performed in patients with suspicious preoperative features, such as suspected myometrial invasion on imaging, which likely contributed to baseline differences between groups. Additionally, we were unable to incorporate molecular classification, as recommended in current guidelines, because data were missing for a subset of patients due to changes in clinical practice during the prolonged recruitment period. Furthermore, adjuvant treatment decisions in our cohort were guided by the 2020 ESGO/ESTRO/ESP guidelines, which adopted a clinicopathologic risk-stratified approach without integrating molecular classification into staging or treatment allocation. Since the 2025 Guidelines recommend SLN mapping for all patients with uterine-confined disease, regardless of risk category, and integrate molecular subtyping into both staging and adjuvant therapy decisions, the treatment patterns observed in our study may not fully reflect current clinical practice, and this should be considered when interpreting our findings [23]. We were also unable to confirm endometrial thickness as an independent preoperative predictor of occult endometrial cancer, as previously reported by Rosati et al. [17]. Similarly, no preoperative predictors of lymph node involvement were identified in our cohort.

Furthermore, although oncologic outcomes comparing patients with occult EC undergoing SLN mapping versus no nodal assessment would have been clinically relevant, these data were not consistently available across participating centers, limiting the reliability of such analyses.

Finally, the higher incidence of endometrial cancer in the SLN group suggests a selection bias toward patients with more suspicious preoperative features, limiting causal inference. These limitations are likely related to the low number of these events and the intercorrelation among variables, both of which reduced the statistical power of the analysis.

4.4. Implication for practice and future research

Given the high incidence of concurrent endometrial cancer in preoperative AEH/EIN population and the demonstrated clinical utility of SLN biopsy, combined with the safety of the procedure when performed in experienced gynecologic oncology centers, SLN biopsy may be considered for these patients. Moreover, this approach aligns with 2025 ESGO/ESTRO/ESP Endometrial Cancer Guidelines which recommend SLN biopsy for all patients with endometrial cancer, regardless of risk category [27].

Importantly, confirmation of both positive and negative nodal status proved to be equally clinically relevant, as it supports the informed appropriate treatment selection and the safe omission of chemotherapy. These findings emphasize the importance of SLN biopsy not only in detecting nodal metastasis but also in its role as a staging procedure whose negative results have meaningful therapeutic implications.

However, our study was limited by sample size and did not demonstrate statistically significant differences in chemotherapy rates between cohort. Besides, as oncologic outcomes comparing the two cohorts were not available, future research with standardized oncologic follow-up and standardized management protocols are warranted to better clarify the impact of SLN assessment on long-term oncologic outcomes in this population. Key outcomes should include its impact on risk-group reclassification, adjuvant treatment decision-making, and the avoidance of overtreatment, as well as oncologic safety measured by recurrence and survival outcomes. Emphasis should be placed on identifying reliable preoperative predictors of concurrent endometrial cancer and lymph node metastasis, integrating clinical, histopathologic, and molecular factors to refine patient selection for these entities. Future large-scale studies should evaluate whether performing SLN biopsy in all patients (universal approach) is cost-effective and oncologically safe compared to performing it only in selected cases (selective approach). Furthermore, the inclusion of molecular classification may help to stratify patients more accurately and guide the extent of surgical staging. Finally, long-term follow-up studies are warranted to evaluate the prognostic impact of SLN biopsy in better defining patient risk groups, guiding more appropriate adjuvant treatment, and assessing recurrence rates and survival outcomes, ultimately contributing to a more personalized and evidence-based management of patients with AEH/EIN.

5. Conclusion

SLN biopsy is a safe and feasible procedure in patients with AEH/EIN, that may provide clinically relevant staging information in patients with occult EC. This is particularly relevant in the context of the current guidelines, which recommend SLN mapping for all patients with EC regardless of risk category. Considering its potential impact on adjuvant therapy decisions, the low morbidity associated with the procedure and the relatively high prevalence of occult EC at final pathology, SLN biopsy may represent a reasonable surgical option in patients with AEH/EIN managed at experienced gynecologic oncology centers. However, further studies are needed to better define its role and clarify whether this approach should be taken into consideration in future guideline recommendations.

CRediT authorship contribution statement

Anna Catozzo: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation. **Simone Garzon:** Writing – review & editing, Validation, Supervision, Methodology, Formal analysis, Conceptualization. **Margherita Renso:** Investigation, Data curation. **Francesco Raspagliesi:** Writing – review & editing. **Jvan Casarin:** Writing – review & editing. **Andrea Puppo:** Writing – review & editing. **Giorgio Bogani:** Writing – review & editing. **Erica Trimarchi:**

Investigation, Data curation. **Francesco Casella:** Writing – review & editing. **Carmelo Calidona:** Investigation, Data curation. **Arrigo Nozza:** Writing – review & editing. **Fabio Ghezzi:** Writing – review & editing. **Stefano Uccella:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Conceptualization.

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Declaration of competing 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 paper.

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